

Supplementary Information

For

Additive CHARMM Force Field
for Nonstandard Amino Acids

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S714	The calculated geometric terms of 2-acetamido-N-methyl-3-(2lambda4-triaza-1,2-dien-1-yl)propanamide.	558
S715	The calculated geometric terms of 1-propyl-2lambda4-triaza-1,2-diene.	559
S716	The calculated geometric terms of trimethyl-1H-imidazol-5-ol.	560
S717	The calculated geometric terms of 2-(4-ethyl-5-hydroxy-2-methyl-1H-imidazol-1-yl)-N-methylacetamide.	561
S718	The calculated geometric terms of [(methylsulfanyl)methyl]benzene.	563
S719	The calculated geometric terms of (3-methylbutyl)borane.	564
S720	The calculated geometric terms of ethylN-ethyl-N-methylcarbamate.	565
S721	The calculated geometric terms of 2-(2,4-dimethyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetaldehyde.	566
S722	The calculated geometric terms of 3-chloro-D-alanine.	567
S723	The calculated geometric terms of O-ethylhydroxylamine.	568
S724	The calculated geometric terms of 2-(methylsulfanyl)acetic acid.	569
S725	The calculated geometric terms of 2-ethylpropanedioic acid.	570
S726	The calculated geometric terms of 2-ethylpropanedioic acid.	571
S727	The calculated geometric terms of (2R)-2-(ethylsulfanyl)-2-hydroxyacetic acid.	572
S728	The calculated geometric terms of 2,4-dimethylphenol.	573
S729	The calculated geometric terms of 2-(ethyldisulfanyl)ethan-1-ol.	574
S730	The calculated geometric terms of 2-(methylsulfanyl)propanoic acid.	575
S731	The calculated geometric terms of 2-ethylbenzotrile.	576
S732	The calculated geometric terms of 1-ethyl-2,4-dimethylbenzene.	577
S733	The calculated geometric terms of 1,2-xylene.	578
S734	The calculated geometric terms of 4-ethylidenecyclohexa-2,5-dien-1-one.	579
S735	The calculated geometric terms of 4-ethenyl-1-methyl-1H-imidazol-5-ol.	580
S736	The calculated geometric terms of 1-(methylsulfanyl)propan-2-one.	581
S737	The calculated geometric terms of ethane-SO-thioperoxol.	582
S738	The calculated geometric terms of [(2R)-2-acetamido-2-(methylcarbamoyl)ethyl]sulfanylophosphonic acid.	583
S739	The calculated geometric terms of (ethylsulfanyl)phosphonic acid.	584
S740	The calculated geometric terms of ethanedithioperoxol.	585
S741	The calculated geometric terms of (ethylsulfanyl)sulfonic acid.	586

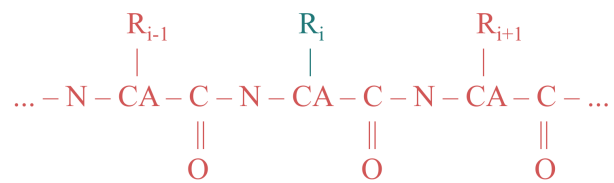
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S743	The calculated geometric terms of 3-ethyl-7-methyl-1H-indole.	588
S744	The calculated geometric terms of butan-2-ol.	589
S745	The calculated geometric terms of N-[(1S)-1-(methylcarbamoyl)ethyl]carbamate.	590
S746	The calculated geometric terms of 1-(ethylsulfanyl)propan-2-one.	591
S747	The calculated geometric terms of 2-(ethylsulfanyl)-N-methylacetamide.	592
S748	The calculated geometric terms of 1-(ethylsulfanyl)ethan-1-one.	593
S749	The calculated geometric terms of 1-(methylsulfanyl)propan-1-one.	594
S750	The calculated geometric terms of [(ethylsulfanyl)methyl]phosphonicacid.	595
S751	The calculated geometric terms of [(ethylsulfanyl)methyl]phosphonicacid.	596
S752	The calculated geometric terms of N,N,N'-trimethylguanidine.	597
S753	The calculated geometric terms of 4-methylbenzene-1,2-diol.	598
S754	The calculated geometric terms of 2,6-diboranyl-4-ethylphenol.	599
S755	The calculated geometric terms of (2S)-2,3-diacetamido-N-methylpropanamide.	600
S756	The calculated geometric terms of (2R)-2-(trimethylamino)propanamide.	602
S757	The calculated geometric terms of 2,4-dimethyl-2,3-dihydro-1H-imidazole.	603
S758	The calculated geometric terms of 2-ethyl-1H-imidazole.	604
S759	The calculated geometric terms of ethane-1,1-diol.	605
S760	The calculated geometric terms of (2Z)-3-acetamido-3-(methylcarbamoyl)prop-2-enoicacid.	606
S761	The calculated geometric terms of (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one.	607
S762	The calculated geometric terms of 1,2-difluoro-4-methylbenzene.	608
S763	The calculated geometric terms of 2-fluorobutanoicacid.	609
S764	The calculated geometric terms of (2R)-2-acetamido-2-(methylcarbamoyl)acetate.	610
S765	The calculated geometric terms of N-ethyl-N-hydroxyformamide.	611
S766	The calculated geometric terms of 2-amino-3,3,3-trifluoropropanoicacid.	612
S767	The calculated geometric terms of (2S)-2-formamido-N-methylpropanamide.	613
S768	The calculated geometric terms of 2-ethylfuran.	614
S769	The calculated geometric terms of 2-fluoro-2-methylpropane.	615
S770	The calculated geometric terms of (2S)-2-acetamido-3-fluoro-N,3-dimethylbutanamide.	616
S771	The calculated geometric terms of (Z)-methyl[1-(methylsulfanyl)ethylidene]amine.	617
S772	The calculated geometric terms of (2R,3S,4R,5R)-2-methyl-5-[(1Z)-1-(methylimino)ethyl]sulfanyloxolane-3,4-diol.	618
S773	The calculated geometric terms of (2R)-3-carbamimidamido-2-acetamido-N-methylpropanamide.	620
S774	The calculated geometric terms of N''-ethoxyguanidine.	622
S775	The calculated geometric terms of (2S)-2-hydroxypropanamide.	624
S776	The calculated geometric terms of 2-acetamido-N-([(methylcarbamoyl)methyl]carbamothioylmethyl)acetamide.	625
S777	The calculated geometric terms of N-[(methylcarbamothioyl)methyl]acetamide.	627
S778	The calculated geometric terms of N-hydroxypropanamide.	628
S779	The calculated geometric terms of 4-ethyl-1-methyl-2,3-dihydro-1H-imidazole.	629
S780	The calculated geometric terms of (5-ethyl-1H-imidazol-1-yl)phosphonicacid.	630
S781	The calculated geometric terms of 5-ethyl-1H-1,2,3-triazole.	631
S782	The calculated geometric terms of (1R)-1-(methylsulfanyl)ethan-1-ol.	632
S783	The calculated geometric terms of (1R)-1-(1H-indol-3-yl)ethan-1-ol.	633
S784	The calculated geometric terms of 2-(N-ethylacetamido)-N-methylacetamide.	634
S785	The calculated geometric terms of 2-methyl-2,3-dihydro-1H-indene.	636
S786	The calculated geometric terms of (2R)-2-(2,3-dihydro-1H-inden-2-yl)-2-acetamido-N-methylacetamide.	637
S787	The calculated geometric terms of 4-[(E)-(ethylimino)methyl]-2,5-dimethylpyridin-3-olate.	639
S788	The calculated geometric terms of 4-ethyl-2-iodophenol.	640
S789	The calculated geometric terms of (ethylsulfanyl)(pyridin-3-yl)methanone.	641
S790	The calculated geometric terms of (2E)-N-methylbut-2-enamide.	643
S791	The calculated geometric terms of pentylcarbamicacid.	644
S792	The calculated geometric terms of (2E)-2-(methyliminiumyl)propanoate.	645
S793	The calculated geometric terms of 1-(2-aminophenyl)propan-1-one.	646
S794	The calculated geometric terms of 2-methylpropane-2-thiol.	647
S795	The calculated geometric terms of 2-acetamido-N,3-dimethyl-3-sulfanylbutanamide.	648
S796	The calculated geometric terms of 1-fluoro-2-methylpropane.	650
S797	The calculated geometric terms of (2S,4S)-2-acetamido-5-fluoro-N,4-dimethylpentanamide.	651

S798	The calculated geometric terms of 2,5-dimethyl-4-[(E)-(methylimino)methyl]pyridin-3-olate.	653
S799	The calculated geometric terms of (2S)-2-acetamido-N-methylbut-3-enamide.	654
S800	The calculated geometric terms of (2S)-N-methyl-2-(methylsulfanyl)propanamide.	655
S801	The calculated geometric terms of (ethylsulfanyl)methanol.	656
S802	The calculated geometric terms of (R)-(2,2-dimethylpropyl)(methyl)-lambda3-sulfanol.	657
S803	The calculated geometric terms of trimethyl(pentyl)amine.	658
S804	The calculated geometric terms of N,N-dimethylacetamide.	660
S805	The calculated geometric terms of (2E)-2-(ethylimino)propanoate.	661
S806	The calculated geometric terms of 3-(ethylsulfanyl)-3-oxopropanoicacid.	662
S807	The calculated geometric terms of 2,3-Dimethyl-5-methylideneimidazol-4-one.	664
S808	The calculated geometric terms of N-[(1S)-1-(1-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-2-yl)ethyl]acetamide.	665
S809	The calculated geometric terms of (ethylsulfanyl)methanol.	667
S810	The calculated geometric terms of 5-ethyl-1-methyl-1H-imidazole.	668
S811	The calculated geometric terms of 5-ethyl-1-methyl-2,3-dihydro-1H-imidazole.	669
S812	The calculated geometric terms of (4-ethyl-1H-imidazol-1-yl)phosphonicacid.	670
S813	The calculated geometric terms of 4-methyl-2-nitrobenzen-1-olate.	671
S814	The calculated geometric terms of N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide.	672
S815	The calculated geometric terms of N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide.	673
S816	The calculated geometric terms of N-[(2Z)-4-(methylsulfanyl)butan-2-ylidene]acetamide.	675
S817	The calculated geometric terms of (2S)-2-acetamido-2-(methylcarbamoyl)ethylacetate.	676
S818	The calculated geometric terms of 1,1-difluoropropane.	677
S819	The calculated geometric terms of (2S)-2-acetamido-4,4-difluoro-N-methylbutanamide.	678
S820	The calculated geometric terms of (2R)-2-acetamido-2-(methylcarbamoyl)ethane-1-sulfonicacid.	679
S821	The calculated geometric terms of 2-(ethylsulfanyl)ethan-1-ol.	680
S822	The calculated geometric terms of 4-(1-hydroxyethyl)-2-methylphenol.	681
S823	The calculated geometric terms of (4-methylphenyl)(phenyl)methanone.	682
S824	The calculated geometric terms of (propanoyloxy)phosphonicacid.	683
S825	The calculated geometric terms of (propanoyloxy)phosphonicacid.	684
S826	The calculated geometric terms of 2-hydroxy-3-[2-(methylcarbamoyl)pyrrolidin-1-yl]propanoicacid.	685
S827	The calculated geometric terms of 2-[3-(2-acetamidoacetyl)-1,3-thiazolidin-4-yl]formamido-N-methylacetamide.	687
S828	The calculated geometric terms of (4R)-3-acetyl-N-methyl-1,3-thiazolidine-4-carboxamide.	689
S829	The calculated geometric terms of 1-methyl-2-nitrobenzene.	690
S830	The calculated geometric terms of 2-[1-(2-acetamidoacetyl)-2-hydroxypyrrolidin-2-yl]formamido-N-methylacetamide.	691
S831	The calculated geometric terms of (2R)-1-acetyl-2-hydroxy-N-methylpyrrolidine-2-carboxamide.	693
S832	The calculated geometric terms of (ethylsulfanyl)formamide.	694
S833	The calculated geometric terms of 2-(ethylsulfanyl)-2-[(trihydroxy-lambda4-phosphanyloxy]propanoicacid.	695
S834	The calculated geometric terms of 2,2,3,5,5-pentamethyl-2,5-dihydro-1H-pyrrol-1-ol.	697
S835	The calculated geometric terms of 3-[(methyldisulfanyl)methyl]-2,5-dihydro-1H-pyrrol-1-ol.	698
S836	The calculated geometric terms of ethoxy(methyl)phosphinicacid.	699
S837	The calculated geometric terms of ethylphenylmethanesulfonate.	700
S838	The calculated geometric terms of (dimethylamino)(ethoxy)phosphinicacid.	702
S839	The calculated geometric terms of dimethylmethylphosphonate.	703
S840	The calculated geometric terms of (nitrososulfanyl)ethane.	704
S841	The calculated geometric terms of [(1E)-prop-1-en-1-yl]benzene.	705
S842	The calculated geometric terms of 2-[(3S)-3-acetamido-2,5-dioxopyrrolidin-1-yl]-N-methylacetamide.	706
S843	The calculated geometric terms of (dimethoxyphosphoryl)dimethylamine.	708
S844	The calculated geometric terms of dimethylmethylphosphonate.	709
S845	The calculated geometric terms of 3-ethenyl-1H-indole.	710

S846	The calculated geometric terms of 2-methyl-2H-1,2,3,4-tetrazole.	711
S847	The calculated geometric terms of (2R)-2-acetamido-N-methyl-3-(2H-1,2,3,4-tetrazol-2-yl)propanamide.	712
S848	The calculated geometric terms of 1-methyl-2-(trifluoromethyl)benzene.	713
S849	The calculated geometric terms of 1,1,1-trifluoro-2-methylpropane.	714
S850	The calculated geometric terms of (2S)-2-acetamido-N-methyl-2-(thiophen-2-yl)acetamide.	715
S851	The calculated geometric terms of methylthiourea.	716
S852	The calculated geometric terms of 2-methylthiophene.	717
S853	The calculated geometric terms of 2-ethylthiophene.	718
S854	The calculated geometric terms of 3-ethyl-1H-indole-1-peroxol.	719
S855	The calculated geometric terms of cyclohex-5-ene-1,2,4-trione.	721
S856	The calculated geometric terms of 5-ethylcyclohex-5-ene-1,2,4-trione.	722
S857	The calculated geometric terms of 2-ethyl-5-hydroxycyclohexa-2,5-diene-1,4-dione.	723
S858	The calculated geometric terms of 3-ethyl-6-imino-6,7-dihydro-1H-indol-7-one.	724
S859	The calculated geometric terms of 3-methyl-1H-indol-2-ol.	725
S860	The calculated geometric terms of 3-ethyl-6,7-dihydro-1H-indole-6,7-dione.	726
S861	The calculated geometric terms of 1,2-diphenylhydrazine.	727
S862	The calculated geometric terms of 2-methylbutane-2,3-diol.	728
S863	The calculated geometric terms of (4-ethylphenyl)oxidanesulfonicacid.	729
S864	The calculated geometric terms of 4-methyl-1,3-thiazole.	730
S865	The calculated geometric terms of (ethylsulfanyl)carbonitrile.	731
S866	The calculated geometric terms of N-methyl-2-(4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide.	732
S867	The calculated geometric terms of (4Z)-1-methyl-4-(phenylmethylidene)-4,5-dihydro-1H-imidazol-5-one.	733
S868	The calculated geometric terms of (2S)-2-acetamido-N-(propan-2-ylidene)propanamide.	734
S869	The calculated geometric terms of 2-(methylsulfanyl)acetamide.	736
S870	Root Mean Square (RMSD) deviation in molecular dynamics simulations	737
S871	Selected average non-bond distances (Å) in MD simulations of proteins with the non-standard amino acids. Values in parenthesis represent the standard deviation.	737
S872	Rotatable dihedral angles observed in MD simulations and experimental structures. Standard deviations are given in parenthesis.	738

Figure S1: Regions of the non-standard amino acids represented by the CGenFF (blue) or CHARMM36 (red) atom types for the A) sidechain modified and B) backbone modified amino acids.

A)



B)

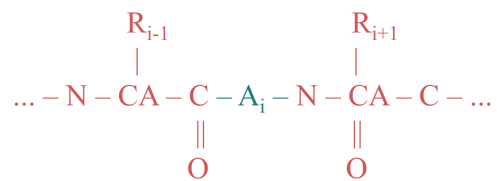
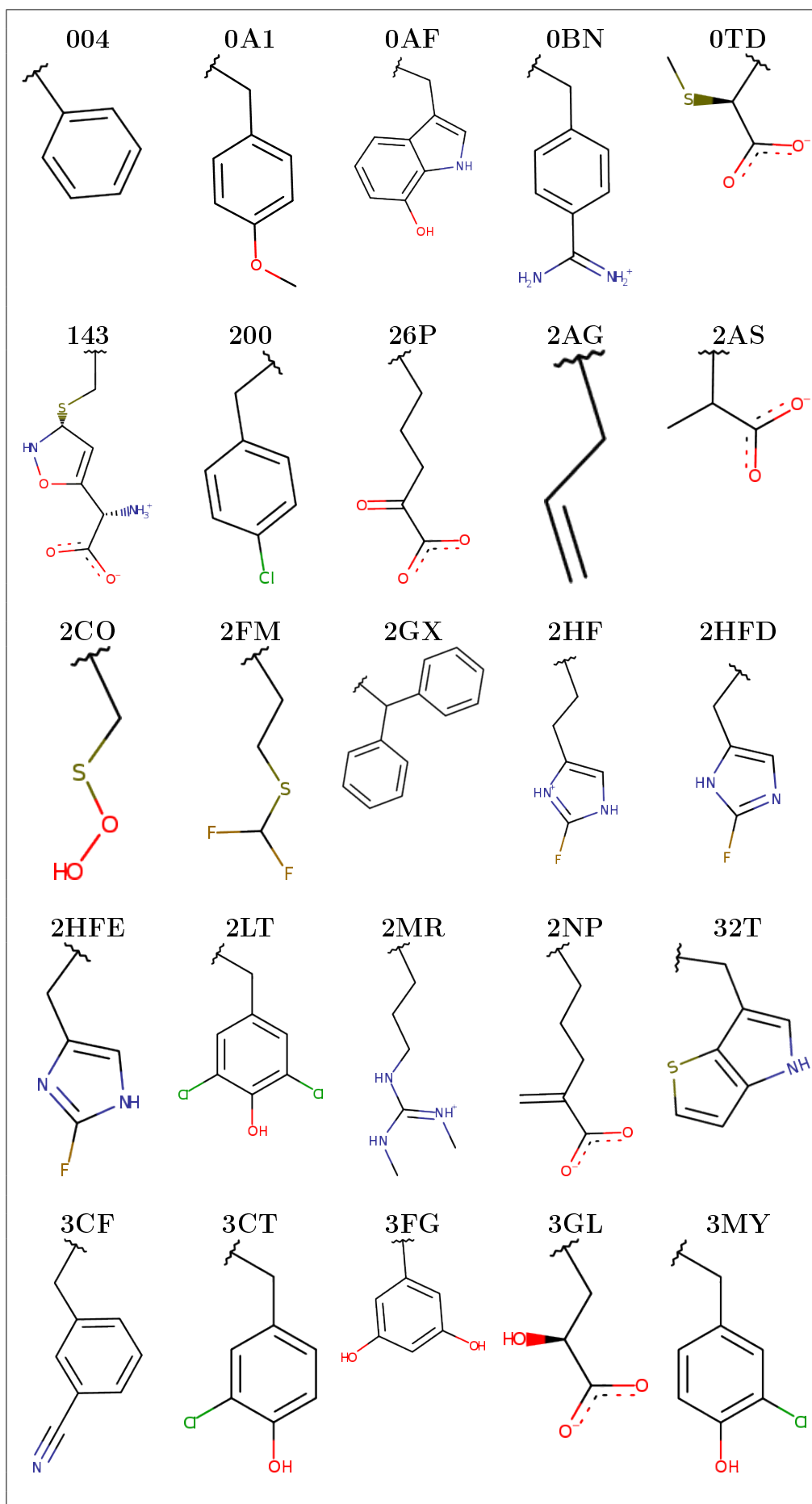
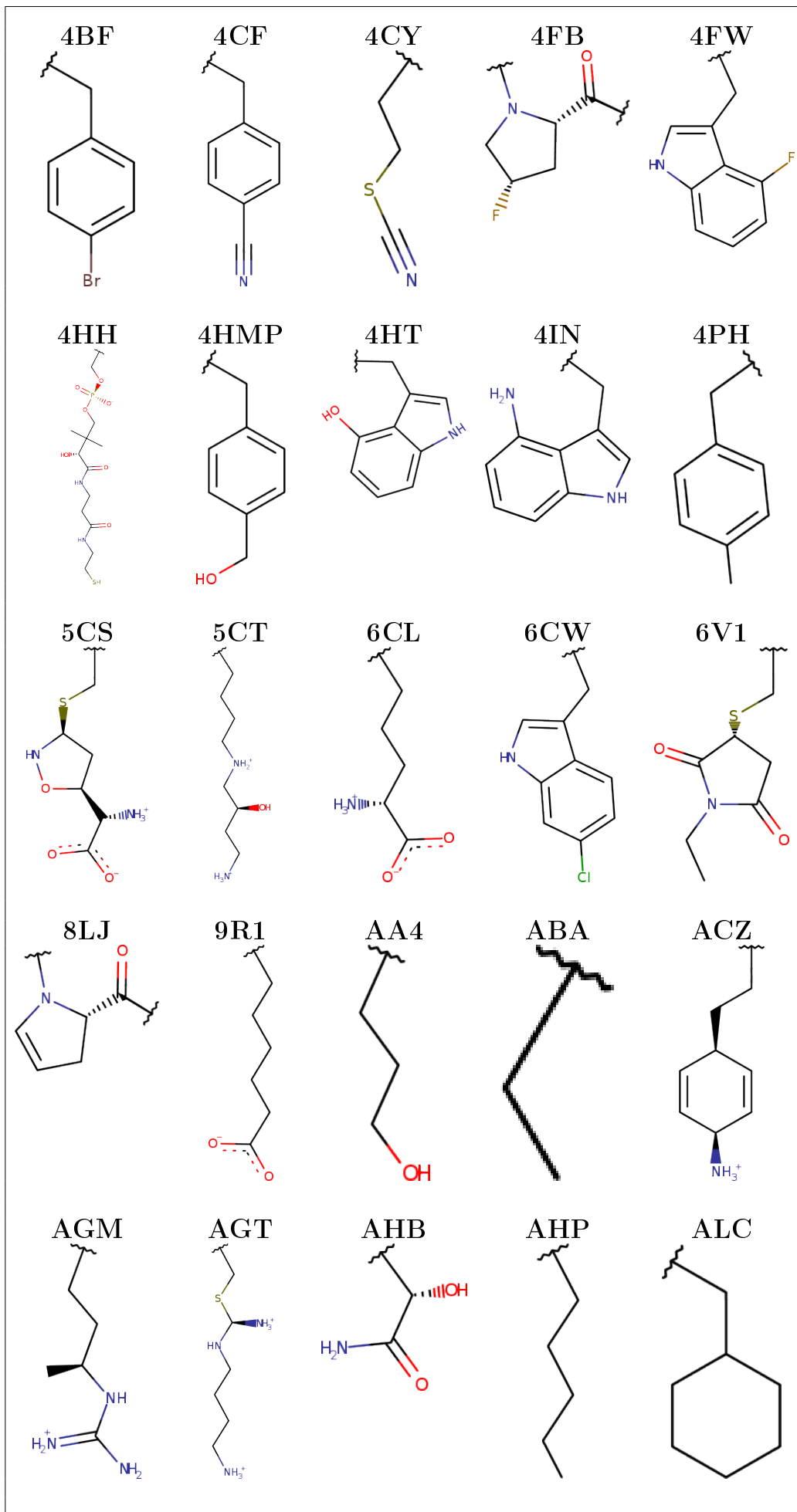
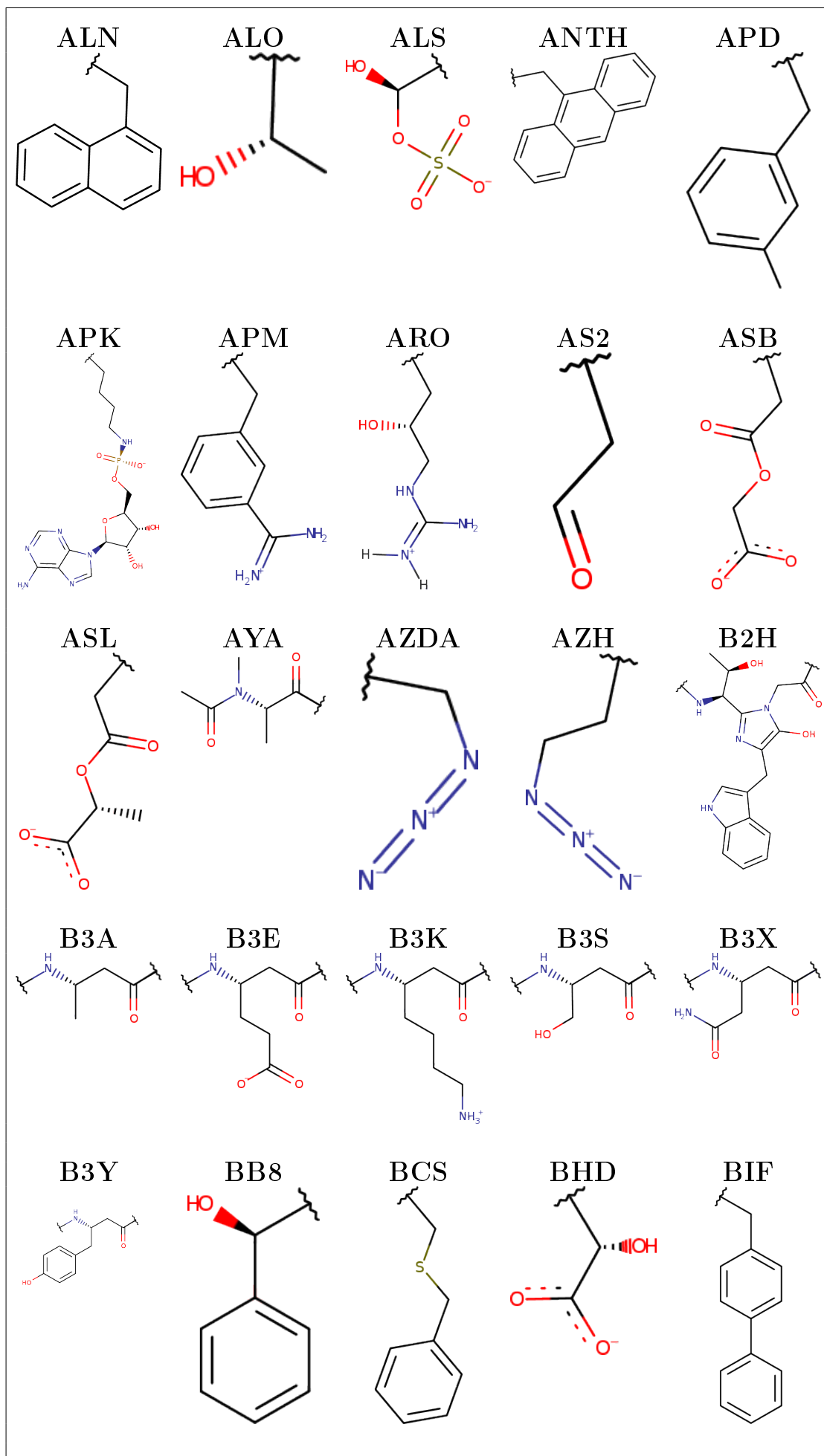
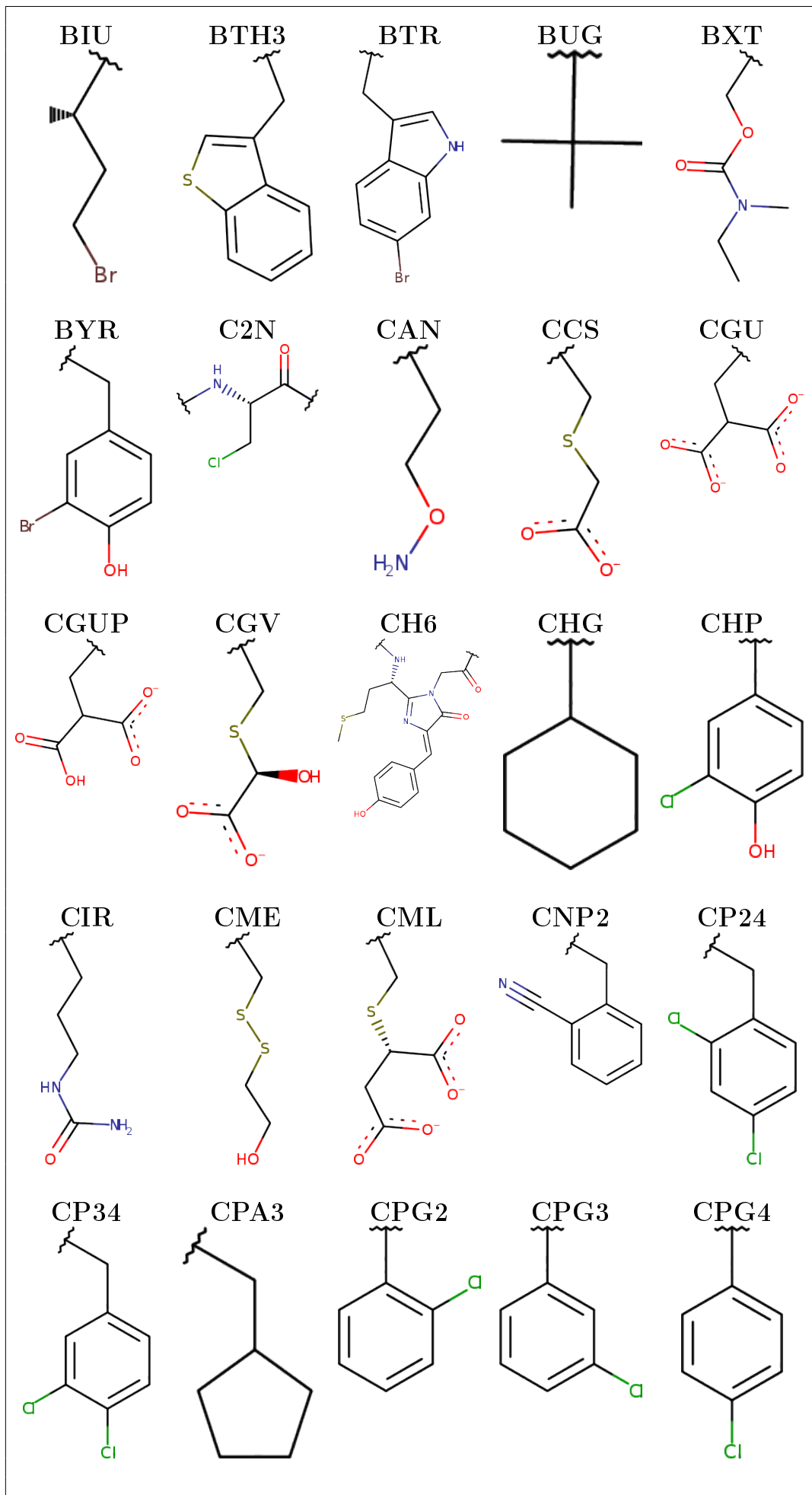


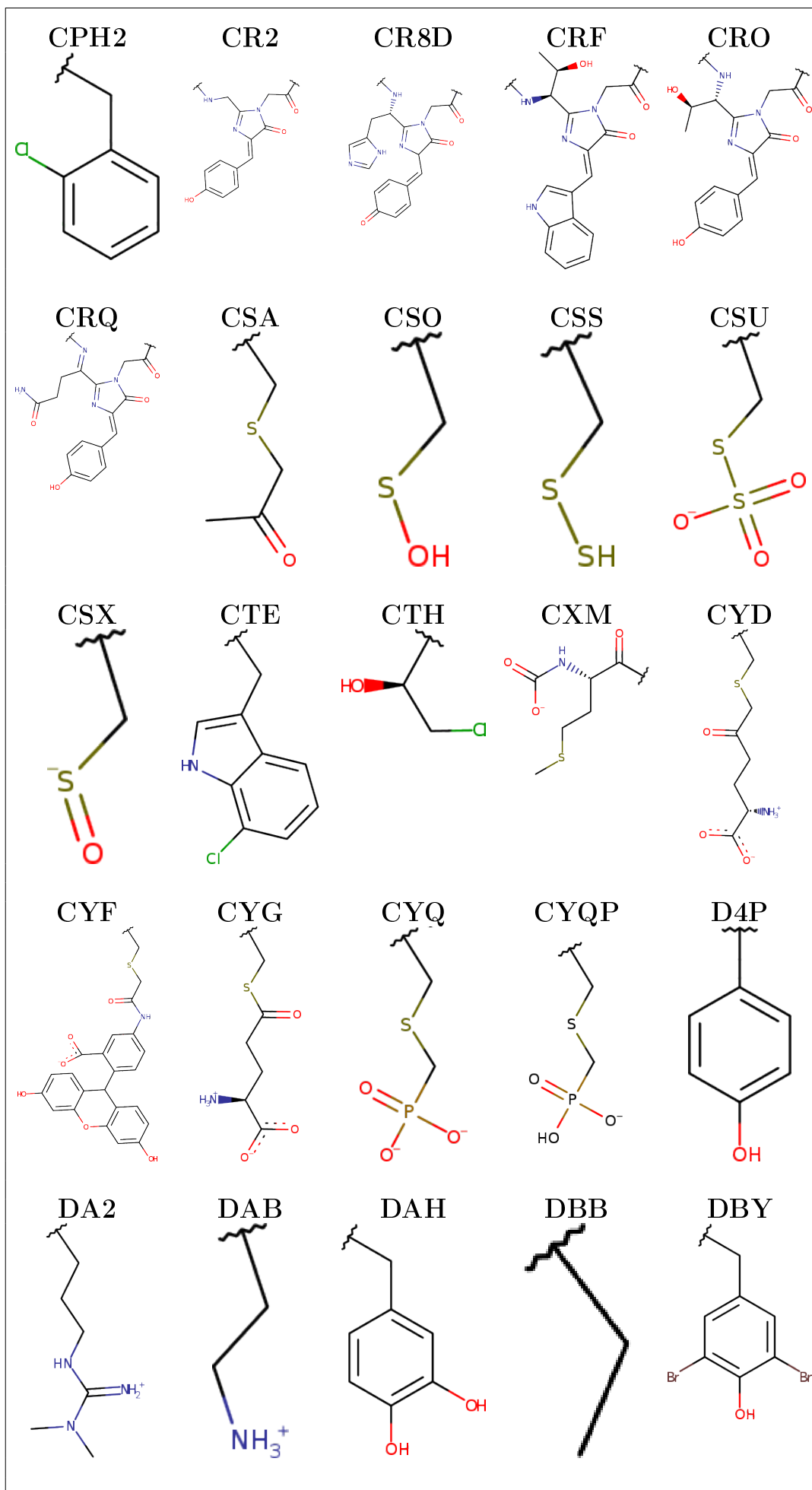
Figure S2: Chemical structures of nonstandard amino acids parametrized in this work. Sidechains and amino acids are represented for sidechain modified and backbone modified amino acids, respectively.

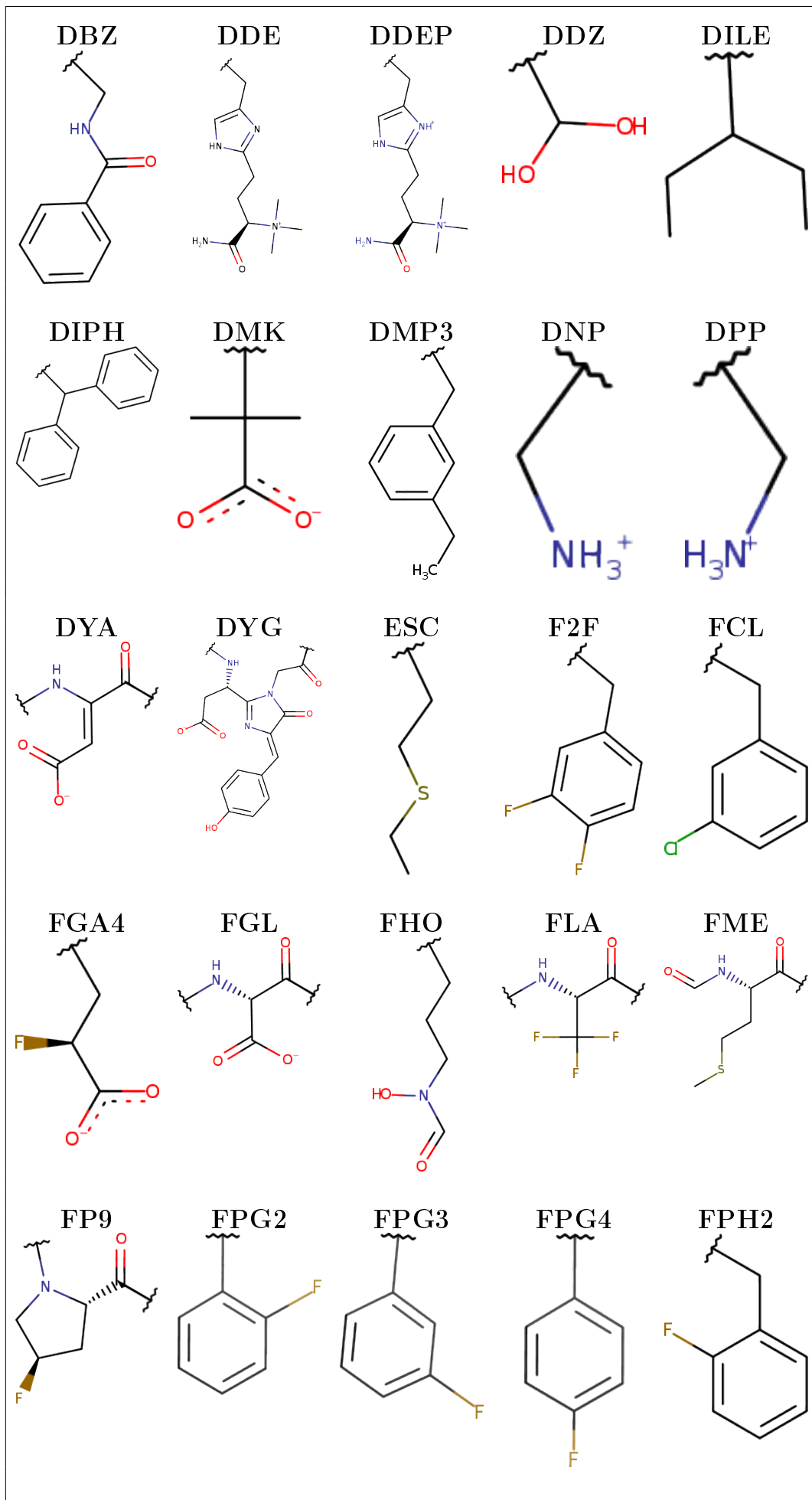


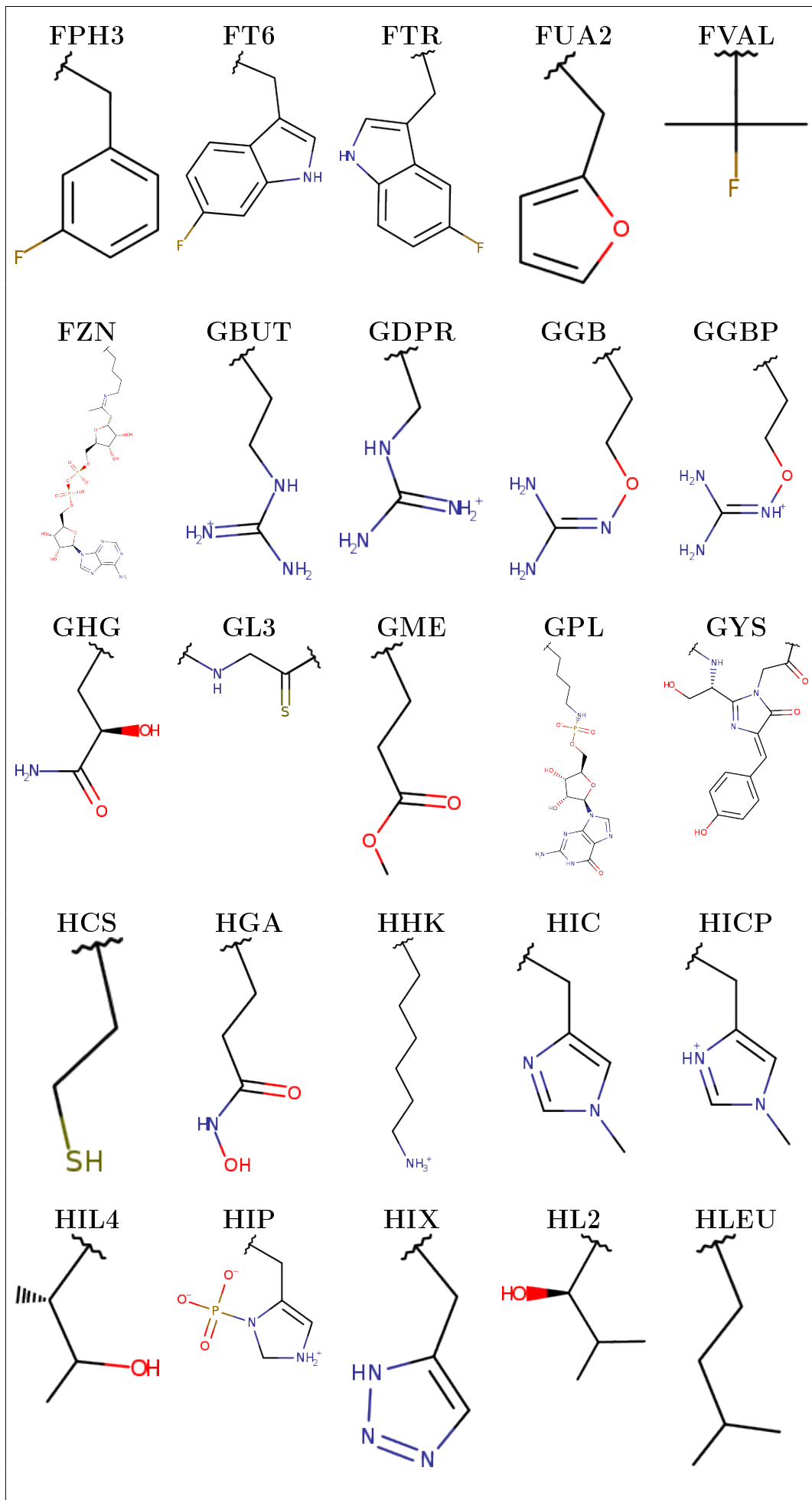


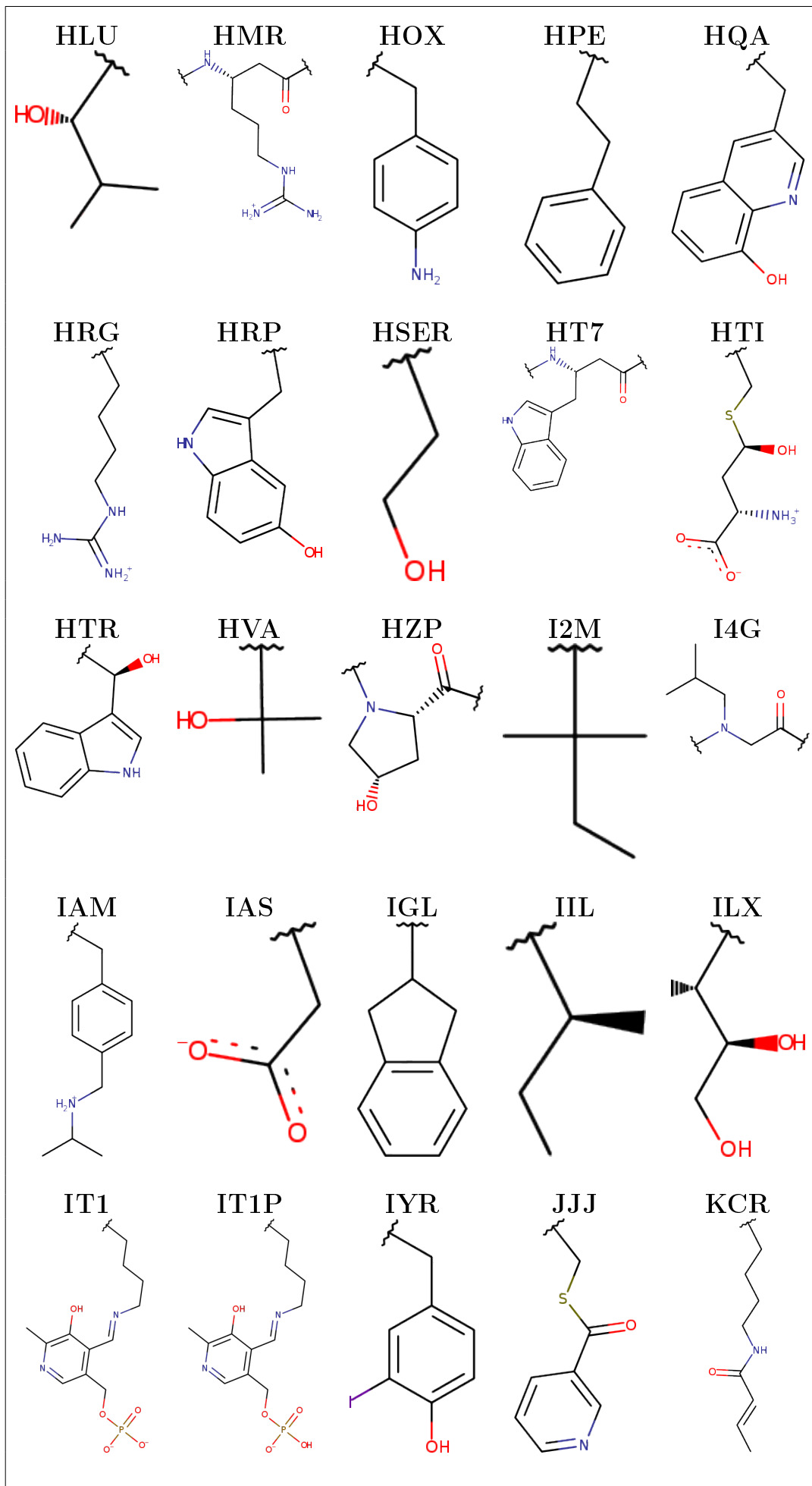


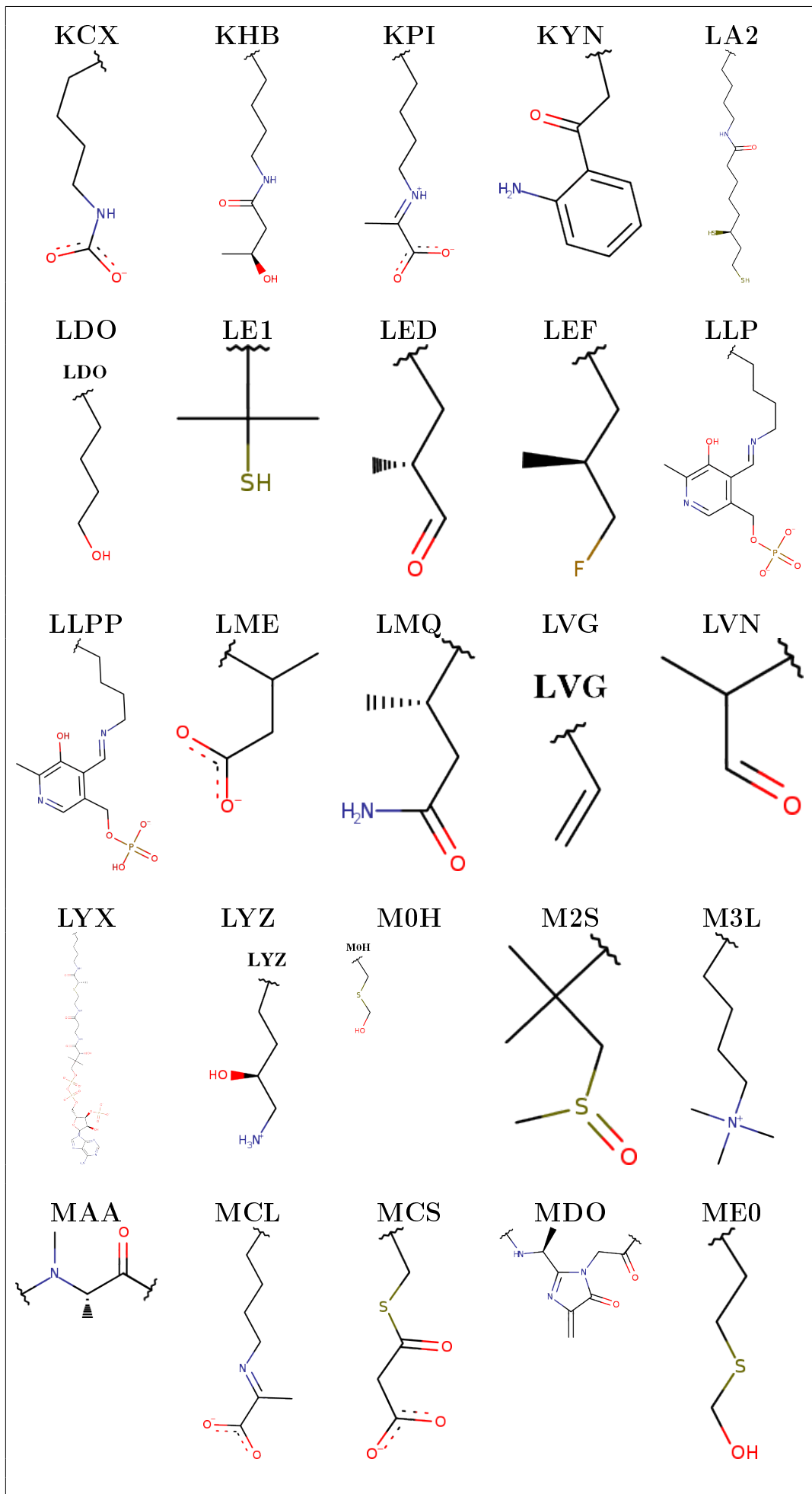


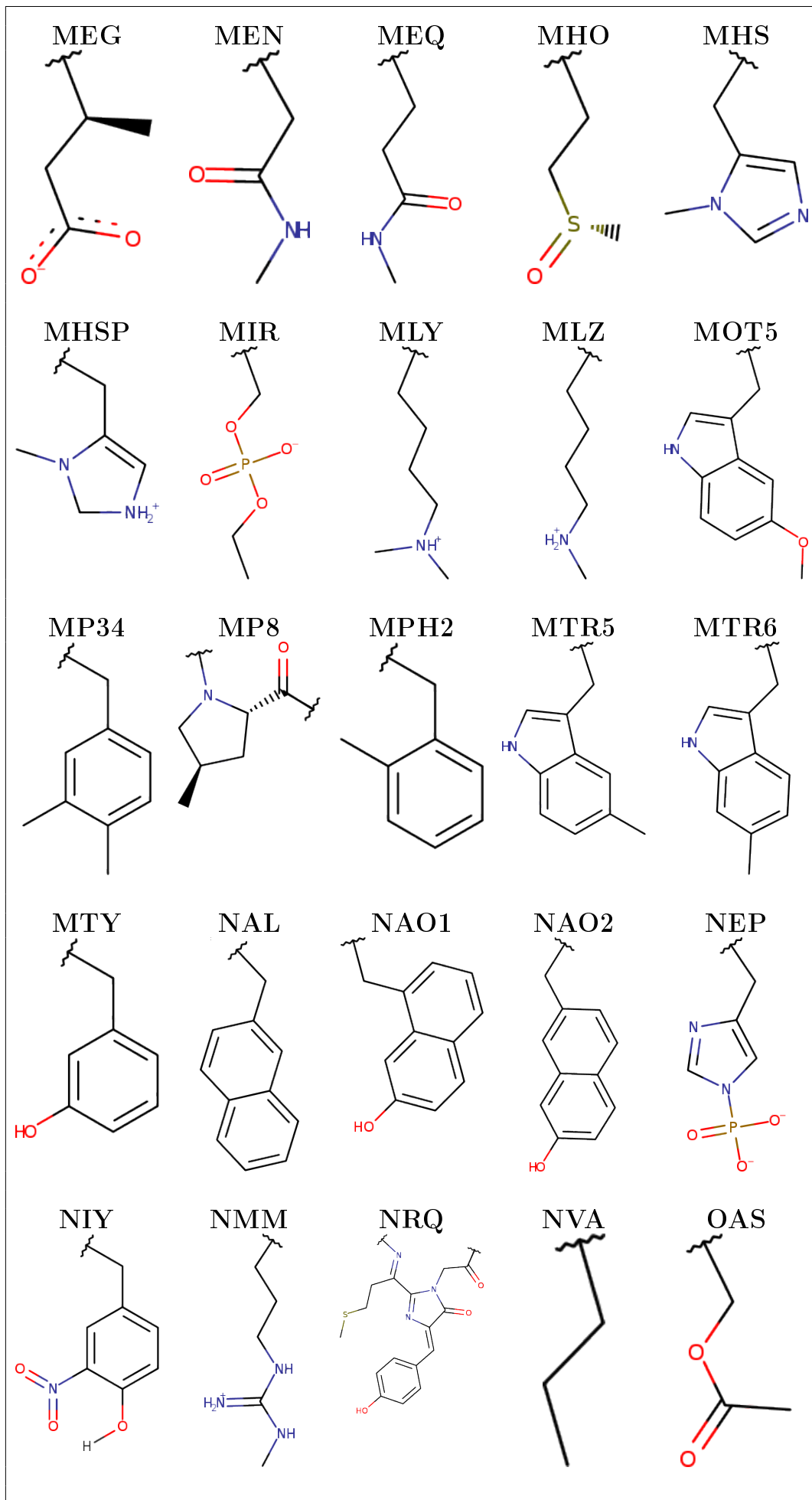


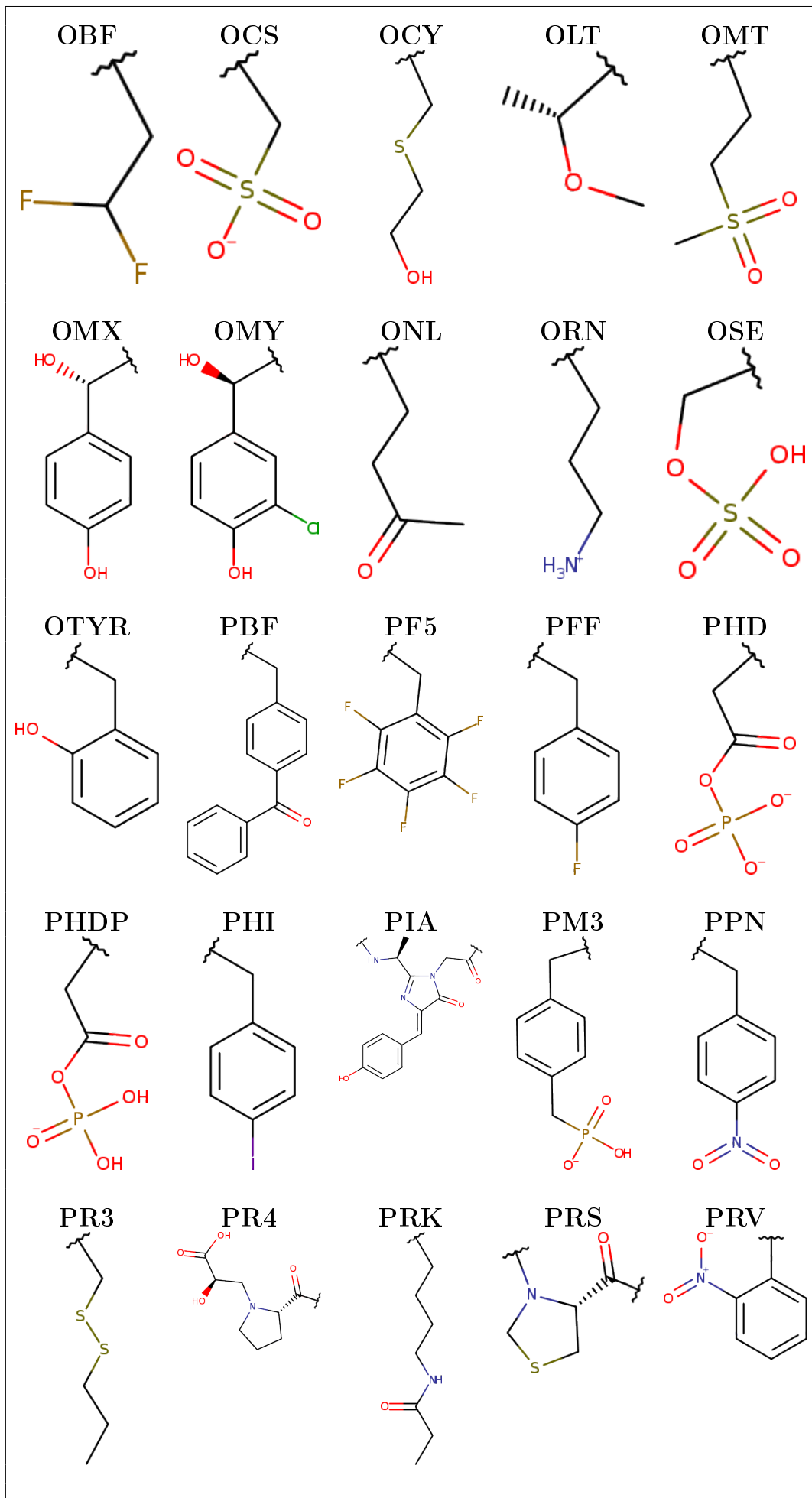


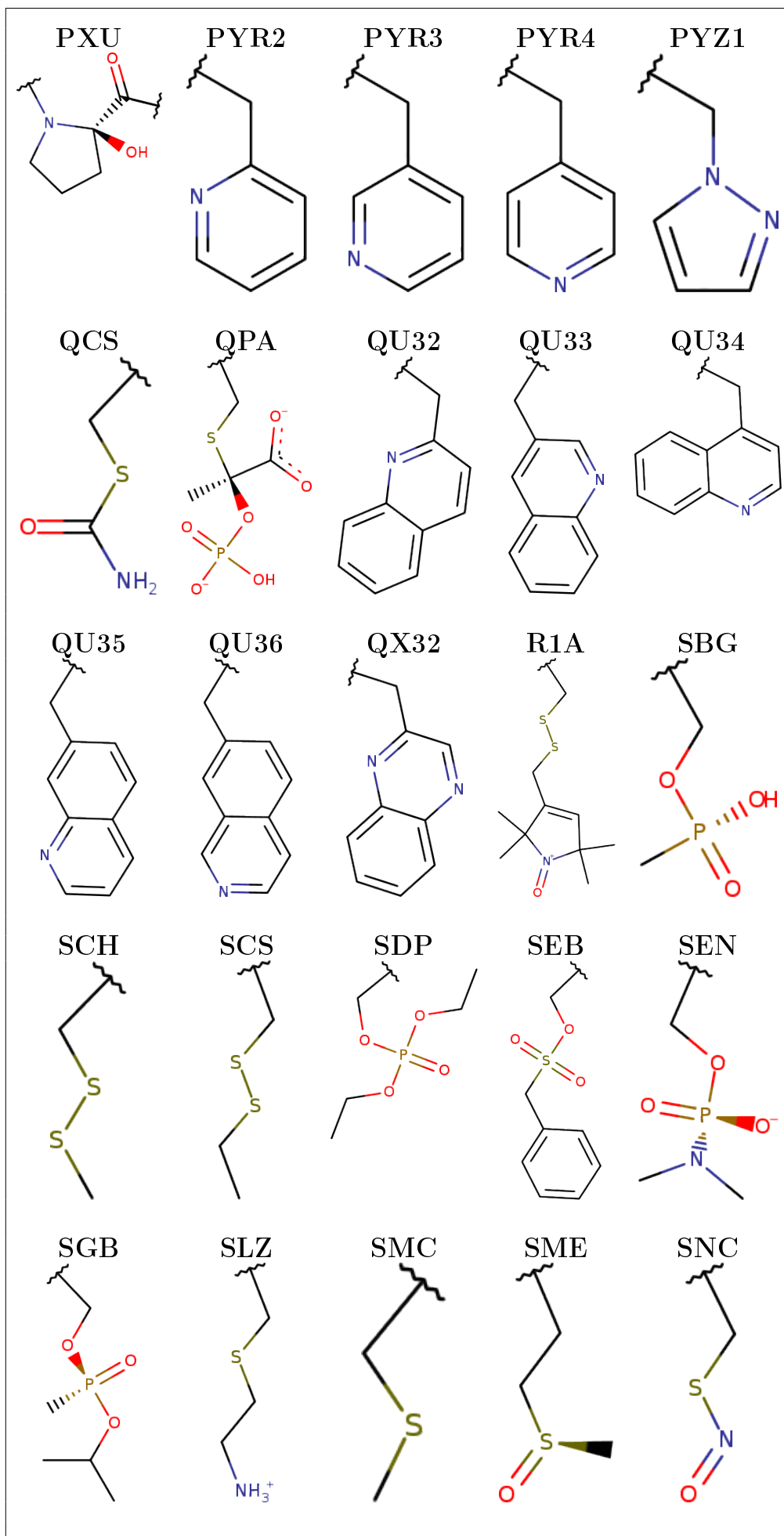


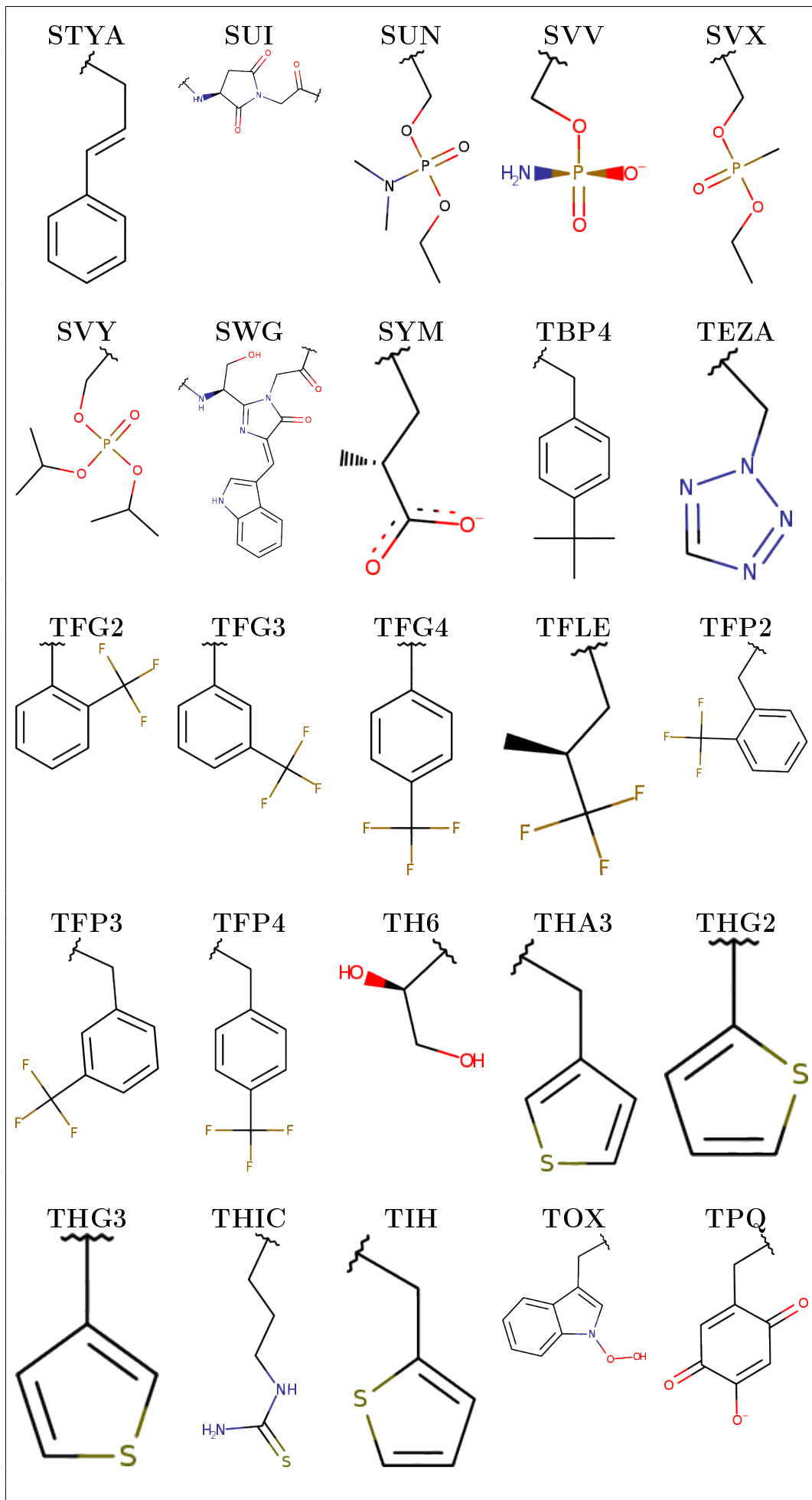












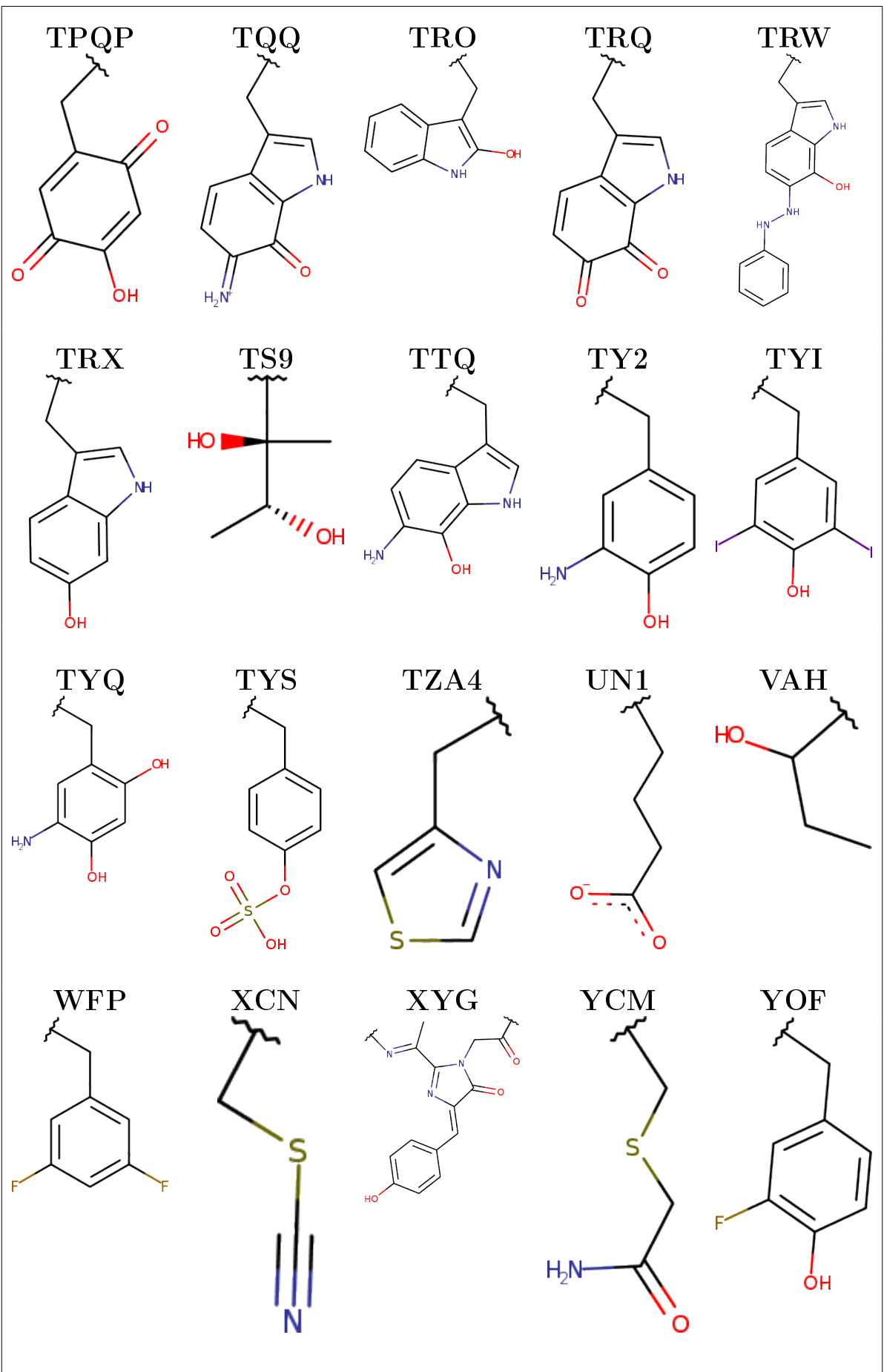


Figure S3: Percentage of molecules vs RMS deviation between *ab initio* and CHARMM electrostatic potential with A) predicted parameters and with B) optimized parameters.

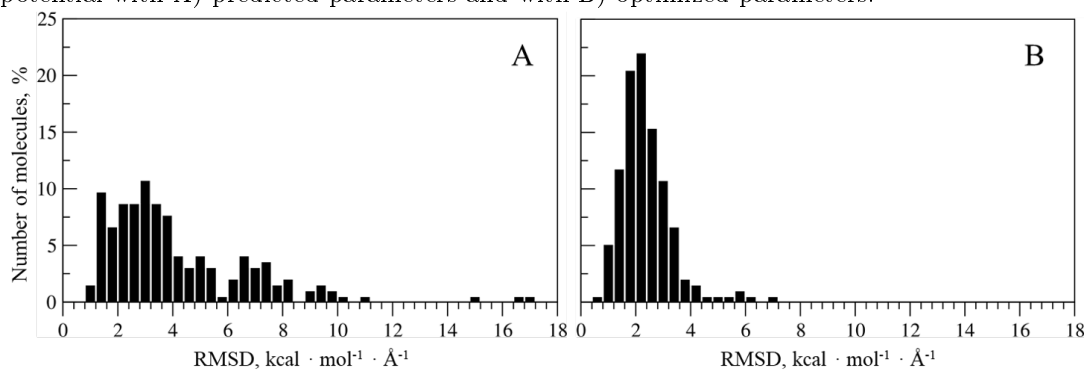


Figure S4: Percentage number of rotatable dihedrals vs RMS deviation between *ab initio* and CHARMM energy at minima points with A) predicted parameters and with B) optimized parameters.

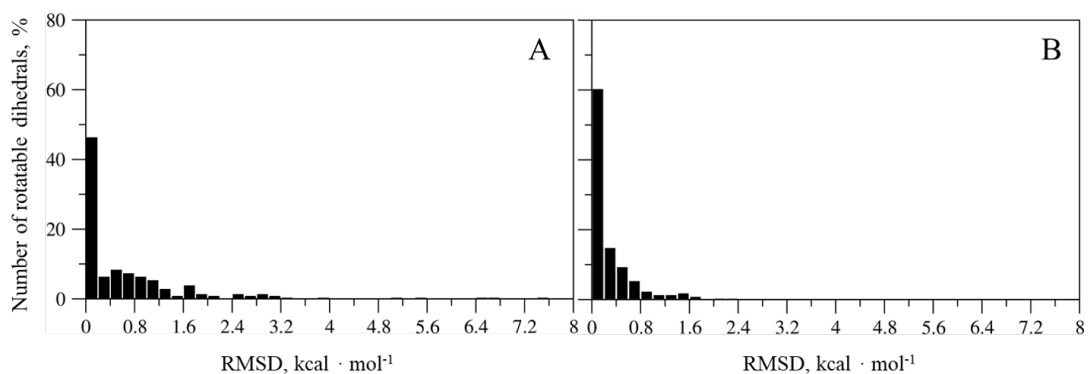


Table S1: Experimental protein structures used in this work for Molecular Dynamics simulations.

amino acid	protein	PDB ref. code	resolution (Å)	MD model
MDO	<i>Aequorea victoria</i> green fluorescent protein	1yjf (Barondeau et al. 2005)	1.35	sphere
NRQ	red fluorescent protein, eqFP611	3e5t (Nienhaus et al. 2008)	1.1	sphere
MAA	human insulin analogue	4cxn (Kosinova et al. 2014)	1.7	complete
XYG	Red fluorescent protein zRFP574	2ICR (Pletneva et al. 2007)	1.51	sphere
4FB	<i>E. coli</i> thioredoxin variant with (4S)-FluoroPro76	4hu9 (Rubini et al. 2013)	1.55	sphere
CSO	TDP2 UBA Domain Bound to Ubiquitin	6q00 (Schellenberg et al. 2020)	0.85	sphere
LE1	Designed Peptides	3h5f (Peacock, Stuckey, and Pecoraro 2009)	1.86	complete
2HF	protective antigen (PA) component of the anthrax toxin	3mhz (Wimalasena et al. 2010)	1.7	sphere
BCS	Human O(6)-alkylguanine-DNA alkyltransferase	1eh8 (Daniels et al. 2000)	2.5	sphere
GGB	Endothiapepsin in complex with fragment B53	4y4g (Huschmann et al. 2016)	1.44	sphere
PBF	<i>E. coli</i> chorismate mutase	5vht (Koh et al. 2017)	2	complete
HTI	aspartate-beta-semialdehyde dehydrogenase	1nwh (Blanco, Moore, and Viola 2003)	2	sphere
4FW	Cold Shock Protein B (CspB) containing the modified residue 4-F-Trp	6szz (Welte et al. 2020)	2.05	complete
CSS	Sulfur-substituted rhodanese	1rhs (Gliubich et al. 1998)	1.36	sphere
OCS	<i>Xanthomonas campestris</i> Peroxiredoxin Q-F6	5imv (Perkins et al. 2016)	1.05	complete
LLP	<i>Aedes aegypti</i> kynurenine aminotrasferase	1yiz (Han et al. 2005)	1.55	sphere
CME	Soybean beta-amylase	1wdr (Kang et al. 2005)	1.35	complete
KCX	Apo OXA-143 carbapenemase	5iy2 (Toth et al. 2017)	1.15	complete
SNC	S-nitroso thioredoxin	2hxx (Weichsel, Brailey, and Montfort 2007)	1.65	complete
CCS	Human DJ-1 with a natural modification on Cys-106	6e5z (Mussakhmetov et al. 2018)	1.35	complete

Complete protein and spherical protein systems were simulated using periodic boundary conditions in all cases; spherical protein systems included protein atoms within 24 Å sphere centered on the nonstandard amino acid with atoms beyond 20 Å restrained to the experimental position during MD simulations.

Table S2: List of nonstandard amino acids parametrized in this work

PDB residue	Name
004	phenylglycine
0A1	4-methoxy-phenylalanine
0AF	7-hydroxy-l-tryptophan
0BN	4-carbamimidoyl-l-phenylalanine
0TD	(3S)-3-(methylsulfanyl)-L-aspartic acid
143	S-2,3-dihydro-5-glycin-2-yl-isoxazol-3-yl-cysteine
200	4-chloro-phenylalanine
26P	2-amino-6-oxopimelic acid
2AG	2-allyl-glycine
2AS	3-methyl-aspartic acid
2CO	S-hydroperoxycysteine
2FM	s-(difluoromethyl)-homocysteine
2GX	beta-phenyl-L-phenylalanine
2HF	2-fluoro-l-histidine
2LT	3,5-dichloro-L-tyrosine
2MR	N3, N4-dimethylarginine
2NP	l-2-amino-6-methylene-pimelic acid
32T	3-(4H-thieno[3,2-b]pyrrol-6-yl)-L-alanine
3CF	3-cyano-phenylalanine
3CT	3-chloro-L-tyrosine
3FG	(2s)-amino(3,5-dihydroxyphenyl)-ethanoic acid
3GL	4-hydroxy-glutamic-acid
3MY	3-chloro-tyrosine
4BF	4-bromo-phenylalanine
4CF	4-cyano-phenylalanine
4CY	nitrilo-l-methionine
4FB	(4S)-4-fluoro-L-proline
4FW	4-fluoro-tryptophan
4HH	O-[(S)-hydroxy[(3R)-3-hydroxy-2,2-dimethyl-4-oxo-4-(3-oxo-3-[(2-sulfanylethyl)amino]propylamino)butyl]oxyphosphoryl]-L-serine
4HMP	4-hydroxymethyl-phenylalanine
4HT	4-hydroxy-tryptophan
4IN	4-amino-l-tryptophan

PDB residue	Name
4PH	4-methyl-phenylalanine
5CS	2-amino-3-(cystein-S-yl)-isoxazolidin-5-yl-acetic acid
5CT	hypusine
6CL	6-carboxyllysine
6CW	6-chloro-L-tryptophan
6V1	(2R)-2-azanyl-3-[(3R)-1-ethyl-2,5-bis(oxidanylidene)pyrrolidin-3-yl]sulfanyl-propanoic acid
8LJ	(2S)-2,3-dihydro-1H-pyrrole-2-carboxylic acid
9R1	(2S)-2-aminooctanedioic acid
AA4	2-amino-5-hydroxypentanoic acid
ABA	2-aminobutyric acid
ACZ	cis-amcilenomycin
AGM	5-methyl-arginine
AGT	S-(S)-amino[(4-aminobutyl)amino]methyl-L-cysteine
AHB	beta-hydroxyasparagine
AHP	2-aminoheptanoic acid
ALC	3-cyclohexyl-alanine
ALN	1-naphthyl-alanine
ALO	allo-threonine
ALS	(3S)-3-(sulfooxy)-L-serine
ANTH	3-(9-anthryl)-alanine
APD	3-Methyl-phenylalanine
APK	5'-O-[(S)-[(5S)-5-amino-6-oxohexyl]amino(hydroxy)phosphoryl]adenosine
APM	m-amidinophenyl-3-alanine
ARO	c-gamma-hydroxy arginine
AS2	(2r)-2-amino-4-oxobutanoic acid
ASB	aspartic acid-4-carboxymethyl ester
ASL	aspartic acid-4-carboxyethyl ester
AYA	N-acetylalanine
AZDA	azido-alanine
AZH	azidohomoalanine
B2H	Chromophore (Thr, Trp,
B3A	(3S)-3-aminobutanoic acid
B3E	(3S)-3-aminohexanedioic acid
B3K	(3S)-3,7-diaminoheptanoic acid
B3S	(3R)-3-amino-4-hydroxybutanoic acid
B3X	(3S)-3,5-diamino-5-oxopentanoic acid
B3Y	(3S)-3-amino-4-(4-hydroxyphenyl)butanoic acid
BB8	phenylserine
BCS	benzylcysteine
BHD	beta-hydroxyaspartic acid
BIF	4,4-biphenylalanine
BIU	5-bromo-L-isoleucine
BTH3	3-(3-benzothienyl)-alanine
BTR	6-bromo-tryptophan
BUG	tert-leucine
BXT	(2S)-2-azanyl-3-[ethyl(methyl)carbamoyl]oxy-propanoic acid
BYR	3-bromo-L-tyrosine
C2N	3-chloro-D-alanine
CAN	canaline
CCS	carboxymethylated cysteine
CGU	gamma-carboxy-glutamic acid
CGV	S-[(R)-carboxy(hydroxy)methyl]-L-cysteine
CH6	(4Z)-2-[(1S)-1-amino-3-(methylsulfanyl)propyl]-4-[(4-hydroxyphenyl)methylidene]-5-oxo-4-acetic 5-dihydro-1H-imidazol-1-ylacetic acid
CHG	Cyclohexylglycine
CHP	3-chloro-4-hydroxy-phenylglycine
CIR	citrulline

PDB residue	Name
CME	S,S-(2-hydroxyethyl)thiocysteine
CML	(2S)-2-[(2R)-2-amino-2-carboxyethyl]sulfanylbutanedioic acid
CNP2	2-cyano-phenylalanine
CP24	2,4-dichloro-phenylalanine
CP34	3,4-dichloro-phenylalanine
CPA3	3-cyclopentyl-alanine
CPG2	2-chloro-phenylglycine
CPG3	3-chloro-phenylglycine
CPG4	4-chloro-phenylglycine
CPH2	2-chloro-phenylalanine
CR2	(4Z)-2-(aminomethyl)-4-[(4-hydroxyphenyl)methylidene]-5-oxo-4acetic 5-dihydro-1H-imidazol-1-ylacetic acid
CR8D	2-[1-amino-2-(1H-imidazol-5-yl)ethyl]-1-(carboxymethyl)-4-[(4-oxocyclohexa-2,5-dien-1-ylidene)methyl]-1H-imidazol-5-olate
CRF	[(4Z)-2-[(1R,2R)-1-amino-2-hydroxypropyl]-4-(1H-indol-3-ylmethylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl]acetic acid
CRO	2-[(1R,2R)-1-amino-2-hydroxypropyl]-4-(4-hydroxybenzylidene)-5-oxo-5-dihydro-1H-imidazol-1-ylacetic acid
CRQ	[2-(3-carbamoyl-1-imino-propyl)-4-(4-hydroxy-benzylidene)-5-oxo-4,5-dihydro-imidazol-1-yl]-acetic acid
CSA	s-acetonylcysteine
CSO	S-hydroxycysteine
CSS	S-mercaptocysteine
CSU	cysteine-S-sulfonic acid
CSX	S-oxy cysteine
CTE	7-chloro-tryptophan
CTH	4-chloro-threonine
CXM	N-carboxymethionine
CYD	2-amino-6-(cystein-S-yl)-5-oxo-hexanoic acid
CYF	5-[2-(2-amino-2-carbamoyl-ethylsulfanyl)-acetylamino]-2-(3,6-dihydroxy-9,9a-dihydro-3h-xanthen-9-yl)-benzoic acid
CYG	2-amino-4-(amino-3-oxo-propylsulfanylcarbonyl)-butyric acid
CYQ	2-amino-3-phosphonomethylsulfanyl-propionic acid
D4P	4-Hydroxy-phenylglycine
DA2	NG,NG-dimethyl-L-arginine
DAB	diaminobutyric acid
DAH	3,4-Dihydroxy-phenylalanine
DBB	D-alpha-aminobutyric acid
DBY	3,5-dibromotyrosine
DBZ	3-(benzoylamino)-L-alanine
DDE	3-[4-(2-amino-2-carboxy-ethyl)-1H-imidazol-2-yl]-1-carbamoyl-propyl-trimethyl-ammonium
DDZ	3,3-dihydroxy-alanine
DILE	diethylalanine
DIPH	3,3-diphenylalanine
DMK	3,3-dimethyl aspartic acid
DMP3	3-ethyl-phenylalanine
DNP	3-amino-alanine
DPP	2,3-Diaminopropanoic acid
DYA	Didehydroaspartate
DYG	(3S)-3-amino-3-[(4Z)-1-(carboxymethyl)-4-[(4-hydroxyphenyl)methylidene]-5-oxo-imidazol-2-yl]propanoic acid
ESC	ethionine
F2F	3,4-difluoro-phenylalanine
FCL	3-chloro-Phenylalanine
FGA4	4-fluoro-glutamic acid
FGL	2-aminopropanedioic acid
FHO	N5-formyl-N5-hydroxy-L-ornithine

PDB residue	Name
FLA	Trifluoroalanine
FME	N-formylmethionine
FP9	(4R)-4-fluoro-L-proline
FPG2	2-fluoro-phenylglycine
FPG3	3-fluoro-phenylglycine
FPG4	4-fluoro-phenylglycine
FPH2	2-fluoro-phenylalanine
FPH3	3-fluoro-phenylalanine
FT6	6-fluoro-L-tryptophan
FTR	5-fluoro-tryptophan
FUA2	(2-furyl)-alanine
FVAL	3-fluoro-valine
FZN	(2S)-2-amino-6-[[[(1Z)-1-[[[(2R,3R,4S,5R)-5-[(R)-[(R)-[(2R,3S,4R,5R) -5-(6-amino-9H-purin-9-yl) -3,4-dihydroxytetrahydrofuran -2-yl]methoxy}(hydroxy)phosphoryl]oxy} (hydroxy)phosphoryl]oxy} methyl)-3,4-dihydroxytetrahydrofuran -2-yl]sulfanylethylidene] aminohexanoic acid
GBUT	2-amino-4-guanidinobutyric acid
GDPR	2-amino-3-guanidinopropionic acid
GGB	Canavanine
GHG	(2s,4s)-2,5-diamino-4-hydroxy-5-oxopentanoic acid
GL3	Thioglycin
GME	5-o-methyl-glutamic acid
GPL	lysine guanosine-5'-monophosphate
GYS	[(4Z)-2-(1-amino-2-hydroxyethyl)-4-(4-hydroxybenzylidene)-5-oxo-4,5-dihydro-1h-imidazol-1-yl]acetic acid
HCS	homocysteine
HGA	glutamine hydroxamate
HHK	(2s)-2,8-diaminooctanoic acid
HIC	4-methyl-histidine
HIL4	4-hydroxy-L-isoleucine
HIP	ND1-phosphonohistidine
HIX	3-(1H-1,2,3-triazol-5-yl)-L-alanine
HL2	Histidine
HLEU	homoleucine
HLU	beta-hydroxyleucine
HMR	beta-homoarginine
HOX	4-amino-L-phenylalanine
HPE	homophenylalanine
HQA	3-(8-hydroxyquinolin-3-yl)-l-alanine
HRG	Homoarginine
HRP	5-hydroxy-tryptophan
HSER	homoserine
HT7	(3S)-3-amino-4-(1h-indol-3-yl)butanoic acid
HTI	(4S)-4-[(2S)-2-amino-3-oxopropyl]sulfanyl-L-homoserine
HTR	beta-hydroxy-tryptophane
HVA	3-hydroxy-l-valine
HZP	(4S)-4-hydroxy-L-proline
I2M	3-methyl-l-alloisoleucine
I4G	N-(2-methylpropyl)glycine
IAM	4-[(isopropylamino)methyl]phenylalanine
IAS	beta-L-aspartic acid
IGL	alpha-amino-2-indanacetic acid
IIL	Allo-Isoleucine
ILX	4,5-dihydroxy-isoleucine
IT1	(2S)-2-amino-6-[[3-hydroxy-2-methyl-5-(phosphonooxymethyl)pyridin-4-yl]methylideneamino]hexanoic acid
IYR	3-iodo-tyrosine
JJJ	S-(pyridin-3-ylcarbonyl)-L-cysteine

PDB residue	Name
KCR	N-6-crotonyl-L-lysine
KCX	lysine NZ-carboxylic acid
KHB	N6-[(3S)-3-hydroxybutanoyl]-L-lysine
KPI	(2S)-2-amino-6-[(1-hydroxy-1-oxo-propan-2-ylidene)amino]hexanoic acid
KYN	kynurenine
LA2	N6-[(6R)-6,8-disulfanyloctanoyl]-L-lysine
LDO	6-hydroxy-l-norleucine
LE1	Penicillamine
LED	(4r)-5-oxo-l-leucine
LEF	(4s)-5-fluoro-l-leucine
LLP	(2S)-2-amino-6-[[3-hydroxy-2-methyl-5-(phosphonooxymethyl)pyridin-4-yl]methylideneamino]hexanoic acid
LME	(3r)-3-methyl-l-glutamic acid
LMQ	3-methyl-l-glutamine
LVG	vinylglycine
LVN	4-oxo-l-valine
LYX	N ^γ -(2-coenzyme A)-propanoyl-lysine
LYZ	5-hydroxylysine
M0H	S-(hydroxymethyl)-L-cysteine
M2S	3,3-dimethyl-methionine sulfoxide
M3L	N-trimethyllysine
MAA	N-methyl-L-alanine
MCL	NZ-(1-carboxyethyl)-lysine
MCS	malonyl cysteine
MDO	[2-((1S)-1-aminoethyl)-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl]acetic acid
ME0	hydroxy-l-methionine
MEG	(3s)-3-methyl-l-glutamic acid
MEN	n-methyl-asparagine
MEQ	n5-methyl-glutamine
MHO	s-oxymethionine
MHS	N1-methylated histidine
MIR	monoethylphosphorylserine
MLY	N-dimethyl-lysine
MLZ	N-methyl-lysine
MOT5	5-methoxy-tryptophan
MP34	3,4-dimethyl-phenylalanine
MP8	(4R)-4-methyl-L-proline
MPH2	2-methyl-phenylalanine
MTR5	5-methyl-tryptophan
MTR6	6-methyl-tryptophan
MTY	meta-tyrosine
NAL	2-naphthyl-alanine
NAO1	5-hydroxy-1-naphthalene
NAO2	6-hydroxy-2-naphthalene
NEP	N1-phosphonohistidine
NIY	meta-nitro-tyrosine
NMM	(2S)-2-amino-5-[(N-methylcarbamimidoyl)amino]pentanoic acid
NRQ	(4Z)-4-(4-hydroxybenzylidene)-2-[3-(methylthio)propanimidoyl]-5-oxo-4acetic 5-dihydro-1H-imidazol-1-ylacetic acid
NVA	norvaline
OAS	o-acetylserine
OBF	(2s)-2-amino-4,4-difluorobutanoic acid
OCS	cysteinesulfonic acid
OCY	s-(2-hydroxyethyl)-l-cysteine
OLT	o-methyl-l-threonine
OMT	methionine sulfone
OMX	(betar)-beta-hydroxy-l-tyrosine

PDB residue	Name
OMY	(betaR)-3-chloro-beta-hydroxy-L-tyrosine
ONL	5-oxo-l-norleucine
ORN	ornithine
OSE	O-sulfo-L-serine
OTYR	o-tyrosine
PBF	4-benzoyl-phenylalanine
PF5	pentafluoro-phenylalanine
PFF	4-fluoro-phenylalanine
PHD	aspartyl phosphate
PHI	4-Iodo-Phenylalanine
PIA	[(4Z)-2-[(1S)-1-aminoethyl]-4-(4-hydroxybenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl]acetic acid
PM3	2-amino-3-(4-phosphonomethyl-phenyl)-propionic acid
PPN	4-nitro-phenylalanine
PR3	S,S-propylthiocysteine
PR4	1-[(2R)-2-carboxy-2-hydroxyethyl]-L-proline
PRK	N6-propanoyl-L-lysine
PRS	Thioproline
PRV	(2R)-amino(2-nitrophenyl)ethanoic acid
PXU	2-hydroxy-L-proline
PYR2	3-(2-Pyridyl)-alanine
PYR3	3-(3-Pyridyl)-alanine
PYR4	3-(4-pyridyl)-alanine
PYZ1	3-(1-pyrazolyl)-alanine
QCS	S-carbamoyl-L-cysteine
QPA	S-[(1S)-1-carboxy-1-(phosphonoxy)ethyl]-L-cysteine
QU32	3-(2-Quinolyl)-alanine
QU33	3-(3-quinolyl)-alanine
QU34	3-(4-quinolyl)-alanine
QU35	3-(5-quinolyl)-alanine
QU36	3-(6-quinolyl)-alanine
QX32	3-(2-quinoxalyl)-alanine
R1A	3-[(2,2,5,5-tetramethyl-1-oxo-2,5-dihydro-1H-pyrrolium-3-yl)methyl]disulfanyl-D-alanine
SBG	O-[(S)-hydroxy(methyl)phosphoryl]-L-serine
SCH	S-methyl-thio-cysteine
SCS	3-(ethyl-disulfanyl)-L-alanine
SDP	2-amino-3-(diethoxy-phosphoryloxy)-propionic acid
SEB	O-benzylsulfonyl-serine
SEN	O-[N,N-dimethylphosphoramidate]-L-serine
SGB	O-[(S)-methyl(1-methylethoxy)phosphoryl]-L-serine
SLZ	thialysine
SMC	S-methylcysteine
SME	methionine sulfoxide
SNC	S-nitroso-cysteine
STYA	Styrylalanine
SUI	(3-amino-2,5-dioxo-1-pyrrolidinyl)acetic acid
SUN	O-[(R)-(dimethylamino)(ethoxy)phosphoryl]-L-serine
SVV	O-[(S)-amino(hydroxy)phosphoryl]-L-serine
SVX	O-[(R)-ethoxy(methyl)phosphoryl]-L-serine
SVY	O-[bis(1-methylethoxy)phosphoryl]-L-serine
SWG	2-[(4Z)-2-[(1R)-1-amino-2-hydroxy-ethyl]-4-(1H-indol-3-ylmethylidene)-5-oxo-imidazol-1-yl]ethanoic acid
SYM	2s,4r-4-methylglutamate
TBP4	4-tert-butyl-phenylalanine
TEZA	3-(2-tetrazolyl)-alanine
TFG2	2-(trifluoromethyl)-phenylglycine
TFG3	3-(trifluoromethyl)-phenylglycine

PDB residue	Name
TFG4	4-(trifluoromethyl)-phenylglycine
TFLE	5,5,5-trifluoro-leucine
TFP2	2-(trifluoromethyl)-phenylalanine
TFP3	3-(trifluoromethyl)-phenylalanine
TFP4	4-(Trifluoromethyl)-phenylalanine
TH6	4-hydroxy-l-threonine
THA3	3-(3-thienyl)-alanine
THG2	2-thienylglycine
THG3	3-thienylglycine
THIC	thio-citrulline
TIH	3-(2-thienyl)-alanine
TOX	1-hydroperoxy-L-tryptophan
TPQ	5-(2-carboxy-2-aminoethyl)-2-hydroxy-1,4-benzoquinone
TQQ	(S)-2-amino-3-(6,7-dihydro-6-imino-7-oxo-1H-indol-3-yl)propanoic acid
TRO	2-hydroxy-tryptophan
TRQ	2-amino-3-(6,7-dioxo-6,7-dihydro-1H-indol-3-yl)-propionic acid
TRW	TRW3-(2-amino-3-hydroxy-propyl)-6-(N'-cyclohexyl-hydrazino)octahydro-indol-7-ol
TRX	6-hydroxy-tryptophan
TS9	(2S,3S,4R)-2-amino-3,4-dihydroxy-3-methylpentanoic acid
TTQ	6-amino-7-hydroxy-l-tryptophan
TY2	3-amino-L-tyrosine
TYI	3,5-diiodotyrosine
TYQ	3-amino-6-hydroxy-tyrosine
TYS	O-sulfo-L-tyrosine
TZA4	(4-thiazolyl)-alanine
UN1	2-Aminoadipic acid
VAH	hydroxynorvaline
WFP	3,5-difluoro-phenylalanine
XCN	S-cyano-L-cysteine
XYG	[(4Z)-2-[(1Z)-ethanimidoyl]-4-(4-hydroxybenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl]acetic acid
YCM	cysteine-s-acetamide
YOF	3-fluorotyrosine

1 The Detail of Water-Compound Complexes Which Were Involved in Charge Optimization

1.1 Small molecule used for 7-hydroxy-1-tryptophan(0AF)

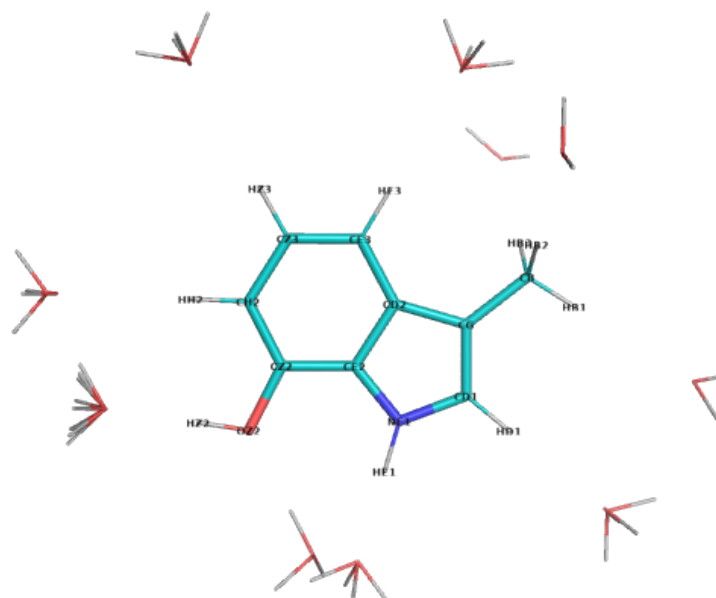


Figure S5: The molecule used for water complex calculations corresponding to 3-methyl-1H-indol-7-olate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S3: Statistics of calculated water interaction and dipole moment for 3-methyl-1H-indol-7-olate.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.72/1.45	0.10/0.27	3.305	1.18/1.13	91.47
Optimal	0.52/1.43	0.08/0.23	1.146	1.18/1.53	0.26

Table S4: The comparison list of optimized atomic charges and their initial guess for 3-methyl-1H-indol-7-olate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.278	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.070	-0.038	0.000
CD1	-0.079	-0.163	0.000
HD1	0.163	0.220	0.000
CD2	0.078	0.107	2.500
NE1	-0.431	-0.502	2.500
HE1	0.356	0.363	0.000
CE2	0.244	0.220	3.576
CZ2	0.058	0.007	3.582
OZ2	-0.536	-0.530	3.568
HZ2	0.434	0.420	0.075
CE3	-0.276	-0.259	0.000
HE3	0.177	0.201	0.000
CZ3	-0.260	-0.234	0.000
HZ3	0.174	0.196	0.000
CH2	-0.189	-0.196	0.000
HH2	0.157	0.196	0.000

Table S5: Interaction energies and geometries between probe water and selected 3-methyl-1H-indol-7-olate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.48/-0.32/-0.39	2.82/2.77/2.78
2	HB1-CB	0.0	-0.98/-0.74/-0.74	2.79/2.78/2.78
3	HB2-CB	0.0	-0.47/-0.30/-0.43	2.82/2.77/2.77
4	HD1-CD1	0.0	-1.94/-2.39/-2.66	2.52/2.29/2.25
5	HD1-CD1	90.0	-2.22/-2.51/-2.77	2.45/2.28/2.24
6	HE1-NE1	0.0	-5.45/-5.53/-4.27	1.82/1.85/1.87
7	HE1-NE1	90.0	-4.88/-5.20/-3.94	1.84/1.86/1.88
8	OZ2-CZ2	0.0	-5.70/-7.13/-7.15	1.77/1.83/1.84
9	OZ2-CZ2	90.0	-6.92/-5.79/-6.25	1.77/1.84/1.84
10	OZ2-CZ2	270.0	-6.90/-5.77/-6.23	1.77/1.84/1.84
11	HZ2-OZ2	0.0	-7.27/-7.65/-6.79	1.78/1.82/1.85
12	HZ2-OZ2	45.0	-7.78/-7.88/-7.14	1.77/1.82/1.84
13	HZ2-OZ2	90.0	-8.19/-8.09/-7.45	1.77/1.81/1.83
14	HZ2-OZ2	135.0	-7.78/-7.89/-7.14	1.77/1.82/1.84
15	HE3-CE3	0.0	-0.90/-0.76/-1.56	2.71/2.71/2.63
16	HE3-CE3	90.0	-1.07/-0.84/-1.66	2.64/2.70/2.62
17	HZ3-CZ3	0.0	-0.86/-0.70/-1.56	2.75/2.72/2.64
18	HZ3-CZ3	90.0	-1.05/-0.80/-1.69	2.68/2.71/2.63
19	HH2-CH2	0.0	-1.66/-1.90/-2.49	2.70/2.65/2.60
20	HH2-CH2	90.0	-2.24/-2.17/-2.76	2.52/2.62/2.57

1.2 Small molecule used for (3S)-3-(methylsulfanyl)-L-asparticacid(0TD)

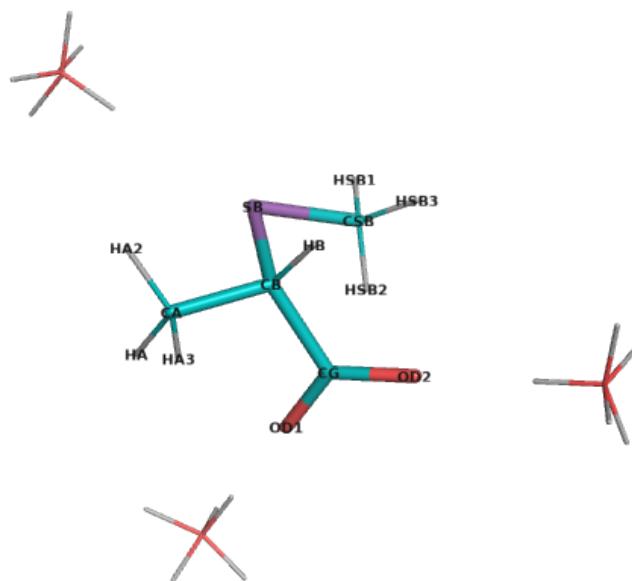


Figure S6: The molecule used for water complex calculations corresponding to 2-(methylsulfanyl)propanoic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S6: Statistics of calculated water interaction and dipole moment for 2-(methylsulfanyl)propanoic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.41/1.99	0.18/0.32	5.195	6.16/8.33	3.79
Optimal	0.22/0.34	0.22/0.39	2.714	6.16/6.34	2.06

Table S7: The comparison list of optimized atomic charges and their initial guess for 2-(methylsulfanyl)propanoic acid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.300
HA2	0.090	0.090	0.300
CA	-0.270	-0.269	0.671
HA	0.090	0.090	0.300
CB	-0.221	-0.188	17.609
HB	0.090	0.090	0.424
SB	-0.167	-0.072	17.610
CSB	-0.245	-0.220	2.563
HSB1	0.090	0.090	0.030
HSB2	0.090	0.090	0.030
HSB3	0.090	0.090	0.030
CG	0.669	0.639	4.568
OD1	-0.698	-0.760	2.500
OD2	-0.698	-0.760	2.500

Table S8: Interaction energies and geometries between probe water and selected 2-(methylsulfanyl)propanoic acid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	SB-CB	0.0	-4.61/-4.64/-3.48	2.71/2.32/2.40
2	SB-CB	90.0	-5.52/-5.64/-4.59	2.64/2.29/2.35
3	SB-CB	180.0	-5.13/-5.41/-4.32	2.69/2.29/2.36
4	SB-CB	270.0	-4.84/-4.54/-3.36	2.66/2.32/2.40
5	OD1-CG	0.0	-13.33/-13.48/-14.66	1.74/1.67/1.65
6	OD1-CG	90.0	-13.42/-13.76/-15.07	1.74/1.67/1.65
7	OD1-CG	180.0	-13.56/-13.77/-15.54	1.73/1.67/1.64
8	OD1-CG	270.0	-13.15/-13.33/-14.98	1.74/1.67/1.65
9	OD2-CG	0.0	-13.16/-12.89/-14.18	1.74/1.67/1.65
10	OD2-CG	90.0	-13.43/-13.20/-14.85	1.74/1.67/1.65
11	OD2-CG	180.0	-13.91/-13.71/-15.47	1.73/1.67/1.64
12	OD2-CG	270.0	-13.37/-13.30/-14.67	1.74/1.67/1.65

1.3 Small molecule A of S-2,3-dihydro-5-glycin-2-yl-isoxazol-3-yl-cysteine(143)

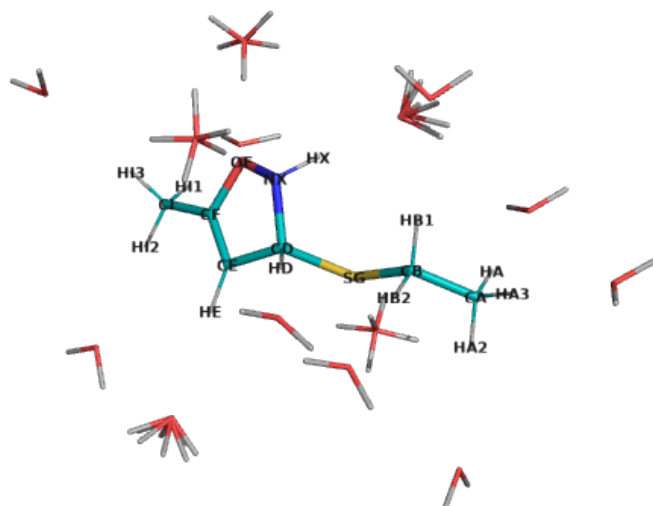


Figure S7: The molecule used for water complex calculations corresponding to (3R)-3-(ethylsulfanyl)-5-methyl-2,3-dihydro-1,2-oxazole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S9: Statistics of calculated water interaction and dipole moment for (3R)-3-(ethylsulfanyl)-5-methyl-2,3-dihydro-1,2-oxazole.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	1.48/3.08	0.25/0.54	3.654	1.12/2.13	21.59
Optimal	0.56/1.34	0.23/0.54	1.599	1.12/1.45	0.00

Table S10: The comparison list of optimized atomic charges and their initial guess for (3R)-3-(ethylsulfanyl)-5-methyl-2,3-dihydro-1,2-oxazole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA	-0.270	-0.269	0.545
HA	0.090	0.090	0.000
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CB	-0.064	-0.074	4.421
HB1	0.090	0.090	0.500
HB2	0.090	0.090	0.500
SG	-0.213	-0.201	111.156
CD	0.312	0.158	137.577
HD	0.090	0.090	6.130
NX	-0.479	-0.324	312.245
HX	0.307	0.368	4.587
CE	-0.473	-0.538	74.935
HE	0.212	0.380	3.250
OF	-0.178	-0.189	313.583
CF	0.168	0.098	105.715
CI	0.111	-0.219	90.288
HI1	0.009	0.090	2.500
HI2	0.009	0.090	2.500
HI3	0.009	0.090	2.500

Table S11: Interaction energies and geometries between probe water and selected (3R)-3-(ethylsulfanyl)-5-methyl-2,3-dihydro-1,2-oxazole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-1.13/-1.02/-1.03	2.76/2.73/2.73
2	HA2-CA	0.0	-0.59/-0.50/-0.46	2.76/2.76/2.77
3	HA-CA	0.0	-0.94/-0.63/-0.70	2.68/2.73/2.73
4	HB1-CB	0.0	-2.74/-2.46/-2.92	2.55/2.61/2.63
5	HB2-CB	0.0	-1.59/-1.87/-1.70	2.66/2.65/2.66
6	SG-CB	0.0	-1.64/-2.65/-2.94	2.88/2.34/2.33
7	SG-CB	90.0	-1.89/-2.77/-2.96	2.83/2.35/2.34
8	SG-CB	180.0	-1.60/-2.48/-2.43	2.90/2.36/2.37
9	SG-CB	270.0	-1.77/-2.43/-2.35	2.84/2.36/2.37
10	HD-CD	0.0	-1.57/-1.82/-1.57	2.63/2.65/2.69
11	NX-CD	0.0	-5.82/-4.90/-3.31	1.96/1.99/2.09
12	NX-CD	90.0	-5.80/-5.28/-4.39	1.96/1.98/2.03
13	NX-CD	180.0	-4.80/-3.76/-2.79	1.99/2.02/2.10
14	NX-CD	270.0	-4.84/-3.51/-1.94	1.99/2.03/2.15
15	HX-NX	0.0	-3.68/-3.70/-6.36	2.02/1.99/1.87
16	HX-NX	45.0	-4.46/-3.88/-6.54	1.98/1.98/1.87
17	HX-NX	90.0	-3.61/-3.49/-6.13	2.05/2.00/1.88
18	HX-NX	135.0	-2.82/-3.27/-5.90	2.12/2.02/1.89
19	HE-CE	0.0	-1.42/-1.37/-3.11	2.56/2.65/2.50
20	HE-CE	45.0	-1.42/-1.38/-3.12	2.56/2.65/2.50
21	HE-CE	90.0	-1.65/-1.47/-3.20	2.50/2.64/2.50
22	HE-CE	135.0	-1.64/-1.46/-3.20	2.51/2.64/2.50
23	OF-NX	0.0	-3.02/-2.87/-4.05	2.16/1.86/1.82
24	OF-NX	90.0	-3.87/-3.77/-4.27	2.09/1.83/1.81
25	OF-NX	180.0	-3.54/-3.79/-3.46	2.13/1.83/1.84
26	OF-NX	270.0	-3.55/-3.37/-3.75	2.11/1.84/1.82
27	HI1-CI	0.0	-1.18/-0.58/-0.11	2.59/2.73/2.78
28	HI2-CI	0.0	-1.42/-1.00/-0.84	2.67/2.74/2.79
29	HI3-CI	0.0	-1.16/-0.53/-0.08	2.59/2.73/2.78

1.4 Small molecule B of S-2,3-dihydro-5-glycin-2-yl-isoxazol-3-yl-cysteine(143)

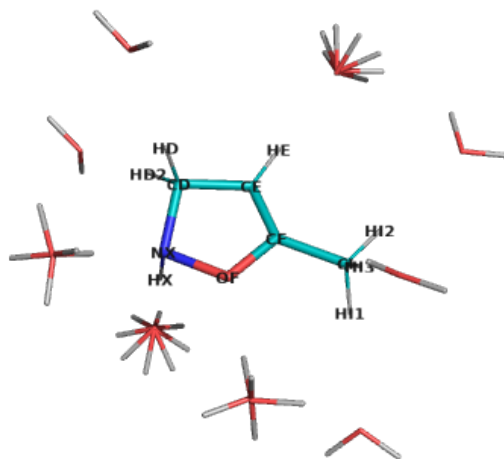


Figure S8: The molecule used for water complex calculations corresponding to 5-methyl-2,3-dihydro-1,2-oxazole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S12: Statistics of calculated water interaction and dipole moment for 5-methyl-2,3-dihydro-1,2-oxazole.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.45/2.77	0.18/0.32	5.065	2.72/3.14	37.99
Optimal	0.22/0.53	0.16/0.28	2.231	2.72/3.25	5.34

Table S13: The comparison list of optimized atomic charges and their initial guess for 5-methyl-2,3-dihydro-1,2-oxazole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HD2	0.090	0.090	2.400
CD	0.182	0.246	36.061
HD	0.090	0.090	2.400
NX	-0.595	-0.438	300.764
HX	0.346	0.368	3.466
CE	-0.479	-0.643	34.137
HE	0.233	0.329	0.207
OF	-0.162	-0.191	314.296
CF	0.219	0.098	105.686
CI	-0.194	-0.219	90.288
HI1	0.090	0.090	2.500
HI2	0.090	0.090	2.500
HI3	0.090	0.090	2.500

Table S14: Interaction energies and geometries between probe water and selected 5-methyl-2,3-dihydro-1,2-oxazole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HD2-CD	0.0	-1.54/-1.61/-2.33	2.65/2.65/2.61
2	HD-CD	0.0	-0.62/-0.59/-1.04	2.77/2.72/2.66
3	NX-CD	0.0	-6.17/-6.21/-4.14	1.95/1.94/2.02
4	NX-CD	90.0	-6.18/-6.44/-4.67	1.95/1.93/2.00
5	NX-CD	180.0	-4.99/-4.80/-2.63	1.99/1.97/2.07
6	NX-CD	270.0	-5.22/-4.86/-2.45	1.97/1.97/2.08
7	HX-NX	0.0	-3.60/-3.70/-5.67	1.99/1.91/1.85
8	HX-NX	45.0	-3.73/-3.77/-5.86	1.98/1.91/1.84
9	HX-NX	90.0	-3.57/-3.72/-5.83	1.99/1.91/1.84
10	HX-NX	135.0	-3.45/-3.65/-5.64	2.01/1.92/1.85
11	HE-CE	0.0	-1.78/-1.96/-2.30	2.42/2.62/2.57
12	HE-CE	45.0	-1.92/-2.02/-2.35	2.38/2.61/2.56
13	HE-CE	90.0	-2.00/-2.05/-2.38	2.36/2.61/2.56
14	HE-CE	135.0	-1.86/-1.99/-2.33	2.40/2.62/2.57
15	OF-NX	0.0	-3.28/-2.86/-4.20	2.14/1.87/1.82
16	OF-NX	90.0	-4.41/-4.51/-5.05	2.08/1.82/1.80
17	OF-NX	180.0	-4.71/-5.24/-4.98	2.08/1.80/1.80
18	OF-NX	270.0	-3.92/-3.70/-4.22	2.10/1.84/1.82
19	HI1-CI	0.0	-1.04/-0.91/-0.11	2.68/2.69/2.82
20	HI2-CI	0.0	-1.31/-1.36/-0.57	2.71/2.70/2.83
21	HI3-CI	0.0	-1.10/-0.81/0.03	2.61/2.67/2.79

1.5 Small molecule used for 2-amino-6-oxopimelicacid(26P)

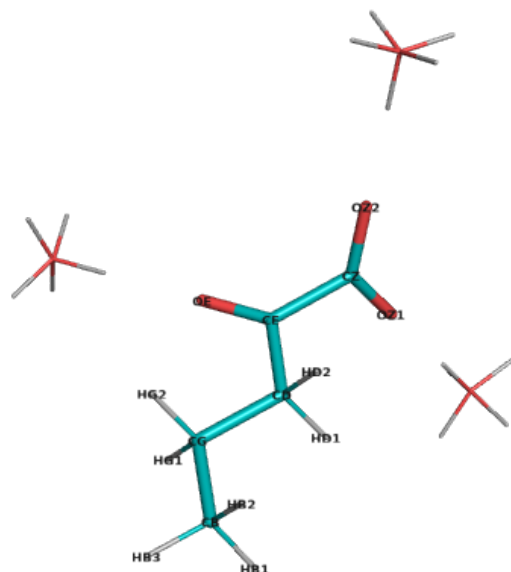


Figure S9: The molecule used for water complex calculations corresponding to 2-oxopentanoic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S15: Statistics of calculated water interaction and dipole moment for 2-oxopentanoic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.96/1.29	0.14/0.21	2.346	10.38/10.91	0.44
Optimal	0.08/0.20	0.12/0.18	3.294	10.38/9.95	1.71

Table S16: The comparison list of optimized atomic charges and their initial guess for 2-oxopentanoic acid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.270	0.045
HB2	0.090	0.090	0.000
HB1	0.090	0.090	0.000
CG	-0.180	-0.181	1.496
HG2	0.090	0.090	0.000
HG1	0.090	0.090	0.000
CD	-0.244	-0.165	16.172
HD2	0.090	0.090	1.450
HD1	0.090	0.090	1.450
CE	0.249	0.280	19.162
OE	-0.421	-0.490	0.000
CZ	0.626	0.716	20.067
OZ1	-0.695	-0.760	2.500
OZ2	-0.695	-0.760	2.500

Table S17: Interaction energies and geometries between probe water and selected 2-oxopentanoic acid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	OE-CE	0.0	-8.43/-8.23/-9.08	1.86/1.68/1.66
2	OE-CE	90.0	-9.05/-9.12/-10.14	1.86/1.68/1.65
3	OE-CE	180.0	-9.82/-9.96/-11.11	1.84/1.67/1.64
4	OE-CE	270.0	-8.97/-9.04/-10.04	1.86/1.68/1.65
5	OZ1-CZ	0.0	-12.54/-12.56/-13.27	1.75/1.68/1.66
6	OZ1-CZ	90.0	-13.08/-13.07/-14.07	1.75/1.67/1.66
7	OZ1-CZ	180.0	-13.24/-13.17/-14.18	1.74/1.67/1.65
8	OZ1-CZ	270.0	-12.55/-12.55/-13.28	1.75/1.68/1.66
9	OZ2-CZ	0.0	-12.69/-12.73/-13.55	1.75/1.68/1.66
10	OZ2-CZ	90.0	-12.49/-12.57/-13.35	1.76/1.68/1.66
11	OZ2-CZ	180.0	-13.10/-13.11/-14.10	1.75/1.67/1.66
12	OZ2-CZ	270.0	-13.08/-13.14/-14.16	1.75/1.67/1.66

1.6 Small molecule used for S-hydroperoxycysteine(2CO)

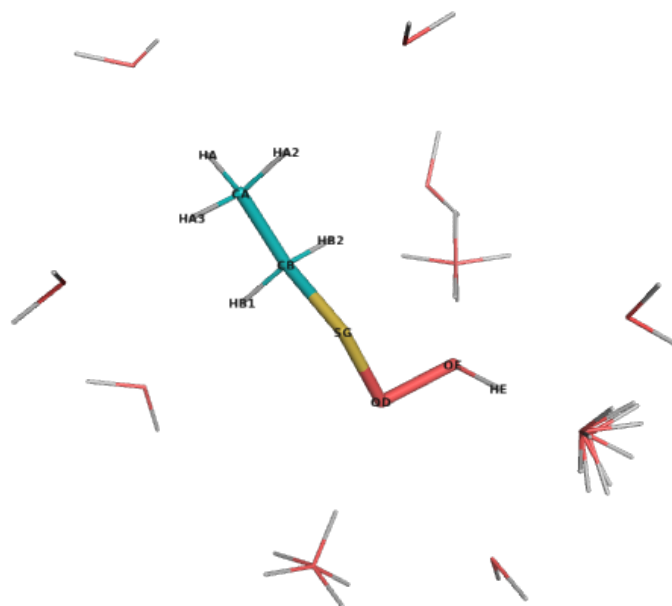


Figure S10: The molecule used for water complex calculations corresponding to (ethylsulfanyl)peroxol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S18: Statistics of calculated water interaction and dipole moment for (ethylsulfanyl)peroxol.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	1.94/4.42	1.38/6.24	5.449	1.65/3.24	25.66
Optimal	0.31/0.60	1.25/5.69	1.421	1.65/1.80	2.42

Table S19: The comparison list of optimized atomic charges and their initial guess for (ethylsulfanyl)peroxol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	2.500
HA	0.090	0.090	0.000
CB	0.023	-0.100	5.706
HB1	0.090	0.090	2.500
HB2	0.090	0.090	2.500
SG	-0.012	0.308	194.038
OD	-0.213	-0.477	388.136
OE	-0.421	-0.411	337.812
HE	0.443	0.500	27.169

Table S20: Interaction energies and geometries between probe water and selected (ethylsulfanyl)peroxol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-1.14/-1.02/-1.36	2.67/2.69/2.68
2	HA2-CA	0.0	-1.09/-0.98/-1.35	2.69/2.70/2.69
3	HA-CA	0.0	-1.39/-1.27/-1.02	2.69/2.69/2.71
4	HB1-CB	0.0	-1.22/-1.10/-0.50	2.56/2.65/2.69
5	HB2-CB	0.0	-0.80/-0.57/-0.13	2.53/2.67/2.72
6	SG-CB	0.0	-0.95/-0.39/0.25	4.40/4.75/5.00
7	SG-CB	45.0	-7.52/-7.13/-8.43	4.19/4.24/4.21
8	SG-CB	90.0	-0.52/-0.91/-1.91	4.46/4.20/3.87
9	SG-CB	135.0	-0.03/-0.17/-1.75	9.66/3.97/3.42
10	OD-SG	0.0	-3.63/-4.22/-8.04	1.98/1.80/1.67
11	OD-SG	90.0	-3.34/-3.75/-6.87	1.98/1.82/1.69
12	OD-SG	180.0	-3.52/-3.93/-6.87	1.98/1.81/1.69
13	OD-SG	270.0	-3.66/-4.25/-8.07	1.97/1.80/1.67
14	OE-OD	0.0	-3.72/-3.86/-3.59	1.94/1.95/1.97
15	OE-OD	90.0	-4.49/-4.69/-5.03	1.90/1.93/1.92
16	OE-OD	180.0	-3.60/-3.98/-4.75	1.95/1.93/1.92
17	OE-OD	270.0	-3.36/-3.41/-3.41	1.94/1.95/1.96
18	HE-OE	0.0	-7.89/-8.00/-9.29	1.70/1.76/1.73
19	HE-OE	45.0	-8.03/-7.93/-9.28	1.69/1.76/1.73
20	HE-OE	90.0	-8.00/-7.86/-9.06	1.69/1.76/1.74
21	HE-OE	135.0	-7.85/-7.93/-9.06	1.70/1.76/1.74

1.7 Small molecule used for s-(difluoromethyl)-homocysteine(2FM)

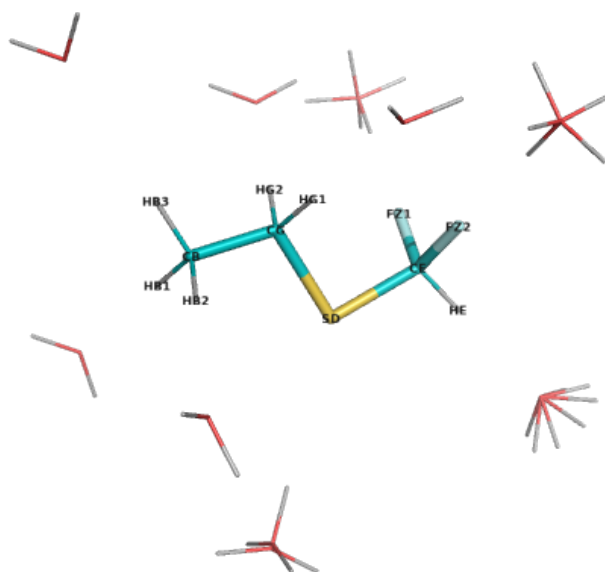


Figure S11: The molecule used for water complex calculations corresponding to [(difluoromethyl)sulfonyl]ethane, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S21: Statistics of calculated water interaction and dipole moment for [(difluoromethyl)sulfonyl]ethane.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.73/1.43	0.32/0.65	3.184	1.07/0.17	149.66
Optimal	0.31/0.59	0.31/0.56	1.372	1.07/1.32	2.97

Table S22: The comparison list of optimized atomic charges and their initial guess for [(difluoromethyl)sulfanyl]ethane, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.271	4.079
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.019	-0.065	4.459
HG1	0.090	0.090	0.600
HG2	0.090	0.090	0.600
SD	-0.124	-0.216	91.761
CE	0.011	0.290	93.470
HE	0.218	0.100	6.220
FZ1	-0.152	-0.144	17.599
FZ2	-0.152	-0.144	17.599

Table S23: Interaction energies and geometries between probe water and selected [(difluoromethyl)sulfanyl]ethane site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.34/-1.24/-0.83	2.70/2.69/2.74
2	HB1-CB	0.0	-1.12/-0.92/-0.45	2.66/2.70/2.76
3	HB2-CB	0.0	-1.13/-0.92/-0.45	2.66/2.70/2.76
4	HG1-CG	0.0	-1.20/-1.04/-0.86	2.50/2.65/2.69
5	HG2-CG	0.0	-1.19/-1.03/-0.86	2.50/2.65/2.69
6	SD-CG	0.0	-0.72/-1.20/-1.61	3.01/2.47/2.41
7	SD-CG	90.0	-0.93/-1.33/-1.94	2.93/2.45/2.38
8	SD-CG	180.0	-0.69/-1.28/-2.12	3.02/2.45/2.37
9	SD-CG	270.0	-0.93/-1.33/-1.94	2.93/2.45/2.38
10	HE-CE	0.0	-2.96/-2.62/-2.29	2.34/2.49/2.53
11	HE-CE	45.0	-2.99/-2.62/-2.27	2.33/2.49/2.53
12	HE-CE	90.0	-3.02/-2.62/-2.26	2.33/2.49/2.53
13	HE-CE	135.0	-2.99/-2.62/-2.27	2.33/2.49/2.53
14	FZ1-CE	0.0	-1.80/-1.94/-1.36	2.23/1.91/1.97
15	FZ1-CE	90.0	-1.94/-2.21/-1.37	2.22/1.90/1.97
16	FZ1-CE	180.0	-2.15/-2.48/-1.42	2.21/1.89/1.97
17	FZ1-CE	270.0	-2.04/-2.23/-1.39	2.21/1.90/1.97
18	FZ2-CE	0.0	-1.80/-1.94/-1.35	2.23/1.91/1.97
19	FZ2-CE	90.0	-2.04/-2.23/-1.39	2.21/1.90/1.97
20	FZ2-CE	180.0	-2.15/-2.48/-1.42	2.21/1.89/1.97
21	FZ2-CE	270.0	-1.94/-2.21/-1.37	2.21/1.90/1.97

1.8 Small molecule used for 2-fluoro-l-histidine(2HF)

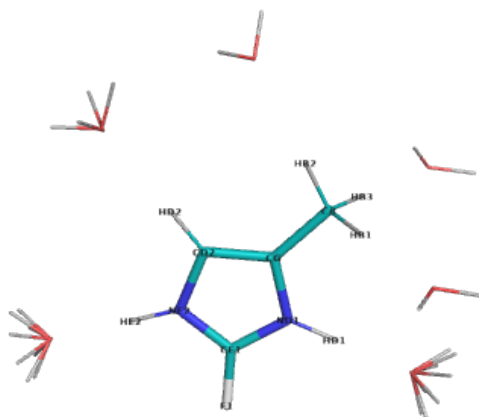


Figure S12: The molecule used for water complex calculations corresponding to 2-fluoro-4-methyl-2,3-dihydro-1H-imidazole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S24: Statistics of calculated water interaction and dipole moment for 2-fluoro-4-methyl-2,3-dihydro-1H-imidazole.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.48/0.96	0.11/0.23	3.757	0.81/1.86	9.47
Optimal	0.27/0.50	0.10/0.20	2.215	0.81/1.32	34.22

Table S25: The comparison list of optimized atomic charges and their initial guess for 2-fluoro-4-methyl-2,3-dihydro-1H-imidazole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.450
CB	-0.086	-0.227	0.891
HB1	0.090	0.090	0.450
HB2	0.090	0.090	0.450
CG	0.192	0.287	6.108
ND1	-0.534	-0.531	35.431
HD1	0.443	0.440	2.500
CD2	0.000	0.185	2.526
HD2	0.208	0.130	0.000
CE1	0.726	0.727	84.808
NE2	-0.580	-0.529	34.990
HE2	0.474	0.440	2.500
F1	-0.113	-0.192	86.487

Table S26: Interaction energies and geometries between probe water and selected 2-fluoro-4-methyl-2,3-dihydro-1H-imidazole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-6.87/-6.36/-5.91		2.32/2.51/2.54	
2	HB1-CB	0.0	-6.87/-6.36/-5.91		2.32/2.51/2.54	
3	HB2-CB	0.0	-6.99/-6.54/-6.21		2.31/2.51/2.53	
4	HD1-ND1	0.0	-16.67/-16.84/-17.10		1.71/1.73/1.73	
5	HD1-ND1	45.0	-16.98/-16.98/-17.16		1.70/1.73/1.73	
6	HD1-ND1	90.0	-17.29/-17.13/-17.22		1.69/1.73/1.73	
7	HD1-ND1	135.0	-16.98/-16.98/-17.16		1.70/1.73/1.73	
8	HD2-CD2	0.0	-9.44/-9.56/-9.68		2.13/2.15/2.16	
9	HD2-CD2	90.0	-10.16/-9.84/-9.89		2.09/2.14/2.15	
10	HE2-NE2	0.0	-16.84/-17.03/-17.17		1.70/1.72/1.73	
11	HE2-NE2	45.0	-17.14/-17.14/-17.23		1.69/1.72/1.73	
12	HE2-NE2	90.0	-17.44/-17.24/-17.29		1.68/1.72/1.73	
13	HE2-NE2	135.0	-17.14/-17.14/-17.23		1.69/1.72/1.73	

1.9 Small molecule used for 2-fluoro-l-histidine(2HFD)

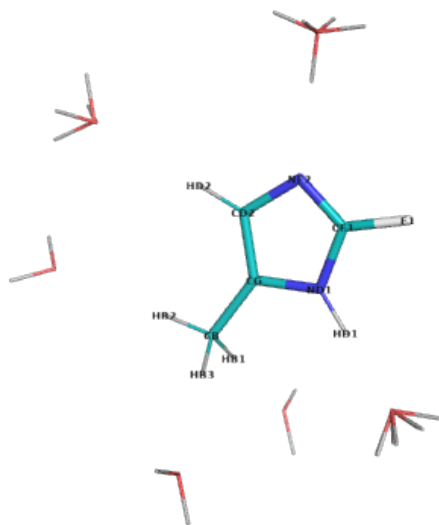


Figure S13: The molecule used for water complex calculations corresponding to 2-fluoro-5-methyl-1H-imidazole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S27: Statistics of calculated water interaction and dipole moment for 2-fluoro-5-methyl-1H-imidazole.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.46/0.92	0.18/0.32	3.140	4.51/5.50	9.59
Optimal	0.10/0.27	0.14/0.26	2.018	4.51/5.21	0.95

Table S28: The comparison list of optimized atomic charges and their initial guess for 2-fluoro-5-methyl-1H-imidazole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.163	-0.178	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.083	-0.045	2.500
CD2	0.151	0.220	2.500
HD2	0.104	0.102	0.000
ND1	-0.371	-0.385	23.567
HD1	0.348	0.338	17.781
NE2	-0.668	-0.713	15.466
CE1	0.583	0.607	76.596
F1	-0.171	-0.216	76.060

Table S29: Interaction energies and geometries between probe water and selected 2-fluoro-5-methyl-1H-imidazole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.78/-1.86/-1.95		2.65/2.65/2.64	
2	HB1-CB	0.0	-1.78/-1.86/-1.95		2.65/2.65/2.64	
3	HB2-CB	0.0	-1.83/-1.84/-2.10		2.59/2.63/2.62	
4	HD2-CD2	0.0	-1.28/-1.30/-1.86		2.59/2.35/2.31	
5	HD2-CD2	90.0	-1.37/-1.29/-1.85		2.54/2.35/2.31	
6	HD1-ND1	0.0	-7.93/-8.01/-7.63		1.80/1.83/1.84	
7	HD1-ND1	45.0	-8.02/-8.03/-7.63		1.79/1.83/1.84	
8	HD1-ND1	90.0	-8.12/-8.05/-7.63		1.78/1.83/1.84	
9	HD1-ND1	135.0	-8.02/-8.03/-7.63		1.79/1.83/1.84	
10	NE2-CD2	0.0	-6.58/-6.60/-7.16		1.96/1.93/1.92	
11	NE2-CD2	90.0	-6.51/-6.46/-6.74		1.95/1.93/1.92	
12	NE2-CD2	180.0	-6.06/-6.19/-6.22		1.97/1.94/1.93	
13	NE2-CD2	270.0	-6.51/-6.46/-6.74		1.95/1.93/1.92	
14	F1-CE1	0.0	-0.98/-0.76/-1.36		2.34/2.10/2.02	
15	F1-CE1	90.0	-1.52/-1.54/-2.16		2.30/2.04/1.98	
16	F1-CE1	180.0	-2.02/-2.29/-2.93		2.26/2.00/1.95	
17	F1-CE1	270.0	-1.52/-1.54/-2.16		2.30/2.04/1.98	

1.10 Small molecule used for 2-fluoro-1-histidine(2HFE)

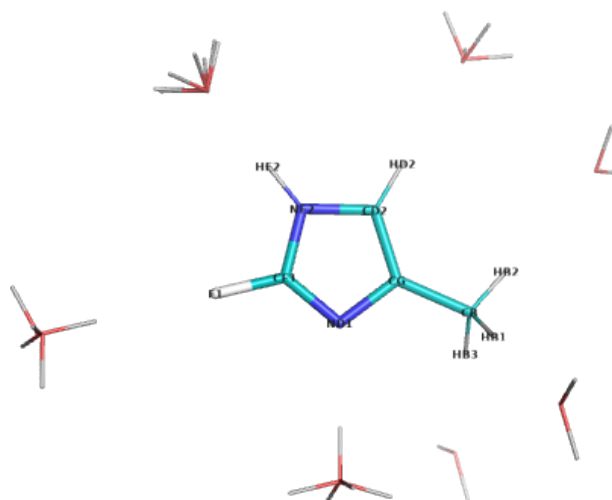


Figure S14: The molecule used for water complex calculations corresponding to 2-fluoro-4-methyl-1H-imidazole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S30: Statistics of calculated water interaction and dipole moment for 2-fluoro-4-methyl-1H-imidazole.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.41/0.90	0.16/0.32	3.127	3.91/4.72	8.86
Optimal	0.17/0.34	0.13/0.26	2.193	3.91/4.45	1.08

Table S31: The comparison list of optimized atomic charges and their initial guess for 2-fluoro-4-methyl-1H-imidazole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.450
CB	-0.270	-0.247	6.472
HB1	0.090	0.090	0.450
HB2	0.090	0.090	0.450
CG	0.297	0.305	7.285
CD2	-0.099	-0.050	2.500
HD2	0.115	0.089	0.000
ND1	-0.659	-0.710	16.437
NE2	-0.385	-0.387	23.567
HE2	0.348	0.338	17.781
CE1	0.549	0.608	76.597
F1	-0.166	-0.216	76.060

Table S32: Interaction energies and geometries between probe water and selected 2-fluoro-4-methyl-1H-imidazole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.40/-0.06/-0.23	2.78/2.79/2.75
2	HB1-CB	0.0	-0.40/-0.06/-0.23	2.78/2.79/2.75
3	HB2-CB	0.0	-1.16/-1.27/-1.53	2.76/2.71/2.68
4	HD2-CD2	0.0	-2.36/-2.49/-2.42	2.48/2.32/2.34
5	HD2-CD2	90.0	-2.69/-2.63/-2.57	2.41/2.31/2.33
6	ND1-CG	0.0	-6.65/-6.64/-7.28	1.96/1.94/1.92
7	ND1-CG	90.0	-6.50/-6.44/-6.87	1.94/1.94/1.92
8	ND1-CG	180.0	-5.96/-6.13/-6.35	1.97/1.94/1.93
9	ND1-CG	270.0	-6.50/-6.44/-6.86	1.94/1.94/1.92
10	HE2-NE2	0.0	-7.91/-8.04/-7.85	1.80/1.83/1.83
11	HE2-NE2	45.0	-8.02/-8.04/-7.83	1.79/1.83/1.83
12	HE2-NE2	90.0	-8.14/-8.04/-7.81	1.78/1.83/1.83
13	HE2-NE2	135.0	-8.02/-8.04/-7.83	1.79/1.83/1.83
14	F1-CE1	0.0	-1.94/-2.24/-2.84	2.27/2.01/1.95
15	F1-CE1	90.0	-1.47/-1.52/-2.08	2.30/2.05/1.99
16	F1-CE1	180.0	-0.96/-0.77/-1.29	2.35/2.10/2.03
17	F1-CE1	270.0	-1.47/-1.52/-2.08	2.30/2.05/1.99

1.11 Small molecule used for 1-2-amino-6-methylene-pimelicacid(2NP)

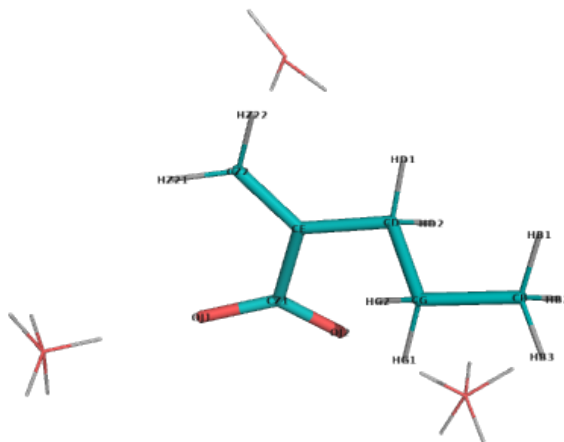


Figure S15: The molecule used for water complex calculations corresponding to 2-methylidenepentanoic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S33: Statistics of calculated water interaction and dipole moment for 2-methylidenepentanoic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.49/2.32	0.11/0.26	5.104	9.09/10.42	8.88
Optimal	0.48/1.30	0.16/0.33	2.405	9.09/9.13	1.50

Table S34: The comparison list of optimized atomic charges and their initial guess for 2-methylidenepentanoic acid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.270	0.025
HB2	0.090	0.090	0.000
HB1	0.090	0.090	0.000
CG	-0.180	-0.184	2.806
HG1	0.090	0.090	0.000
HG2	0.090	0.090	0.000
CD	-0.321	-0.256	6.589
HD2	0.090	0.090	0.425
HD1	0.090	0.090	0.425
CE	0.241	-0.015	7.839
CZ1	0.581	0.617	6.943
CZ2	-0.681	-0.422	1.329
HZ22	0.210	0.210	0.045
HZ21	0.210	0.210	0.045
OJ1	-0.710	-0.760	2.500
OJ2	-0.710	-0.760	2.500

Table S35: Interaction energies and geometries between probe water and selected 2-methylidenepentanoic acid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	OJ1-CZ1	0.0	-13.50/-13.25/-13.87	1.73/1.67/1.65
2	OJ1-CZ1	90.0	-13.76/-13.69/-14.76	1.73/1.66/1.65
3	OJ1-CZ1	180.0	-14.23/-14.26/-15.81	1.72/1.66/1.64
4	OJ1-CZ1	270.0	-13.84/-13.79/-15.03	1.73/1.66/1.65
5	OJ2-CZ1	0.0	-13.26/-13.67/-14.96	1.73/1.66/1.65
6	OJ2-CZ1	90.0	-13.61/-13.98/-15.39	1.73/1.66/1.65
7	OJ2-CZ1	180.0	-14.18/-14.36/-15.83	1.72/1.66/1.64
8	OJ2-CZ1	270.0	-13.70/-13.90/-15.27	1.73/1.66/1.65
9	CZ2-CE	0.0	-3.97/-3.54/-1.65	2.53/2.21/2.49
10	CZ2-CE	180.0	-7.45/-8.75/-8.12	2.42/2.10/2.16

1.12 Small molecule used for
3-(4H-thieno[3,2-b]pyrrol-6-yl)-L-alanine(32T)

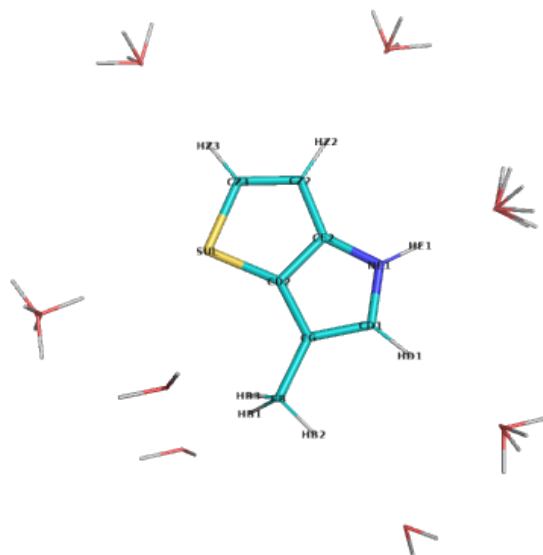


Figure S16: The molecule used for water complex calculations corresponding to 6-methyl-4H-thieno [3,2-b]pyrrole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S36: Statistics of calculated water interaction and dipole moment for 6-methyl-4H-thieno[3,2-b]pyrrole.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.59/1.04	0.27/0.54	2.167	2.68/2.14	2.21
Optimal	0.28/0.53	0.23/0.49	1.942	2.68/3.19	0.04

Table S37: The comparison list of optimized atomic charges and their initial guess for 6-methyl-4H-thieno[3,2-b]pyrrole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.244	2.526
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.060	-0.077	2.528
CD1	0.002	-0.068	0.000
HD1	0.115	0.161	0.000
CD2	-0.064	0.039	11.030
NE1	-0.345	-0.471	14.035
HE1	0.318	0.389	0.000
CE2	0.132	0.109	13.233
SUL	0.007	-0.078	9.884
CZ2	-0.235	-0.255	0.000
HZ2	0.207	0.125	0.000
CZ3	-0.266	-0.080	0.000
HZ3	0.189	0.180	0.000

Table S38: Interaction energies and geometries between probe water and selected 6-methyl-4H-thieno[3,2-b]pyrrole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.47/-0.07/-0.21	2.76/2.80/2.77
2	HB1-CB	0.0	-0.47/-0.07/-0.21	2.76/2.80/2.77
3	HB2-CB	0.0	-1.00/-0.69/-0.78	2.77/2.79/2.77
4	HD1-CD1	0.0	-1.84/-2.16/-2.33	2.55/2.32/2.30
5	HD1-CD1	90.0	-2.16/-2.29/-2.49	2.47/2.31/2.29
6	HE1-NE1	0.0	-6.07/-6.35/-6.83	1.88/1.87/1.84
7	HE1-NE1	45.0	-6.35/-6.45/-6.91	1.86/1.87/1.84
8	HE1-NE1	90.0	-6.64/-6.55/-6.98	1.85/1.87/1.84
9	HE1-NE1	135.0	-6.35/-6.45/-6.91	1.86/1.87/1.84
10	SUL-CD2	0.0	-0.94/-1.29/-1.34	3.00/2.54/2.49
11	SUL-CD2	90.0	-1.15/-1.43/-1.57	2.92/2.52/2.47
12	SUL-CD2	180.0	-0.97/-1.50/-1.69	3.00/2.51/2.45
13	SUL-CD2	270.0	-1.15/-1.43/-1.57	2.92/2.52/2.47
14	HZ2-CZ2	0.0	-1.61/-1.87/-0.76	2.61/2.62/2.79
15	HZ2-CZ2	90.0	-1.96/-2.03/-0.92	2.52/2.61/2.76
16	HZ3-CZ3	0.0	-1.71/-1.59/-2.56	2.50/2.31/2.26
17	HZ3-CZ3	90.0	-1.88/-1.65/-2.58	2.45/2.31/2.26

1.13 Small molecule used for 4-hydroxy-glutamic-acid(3GL)

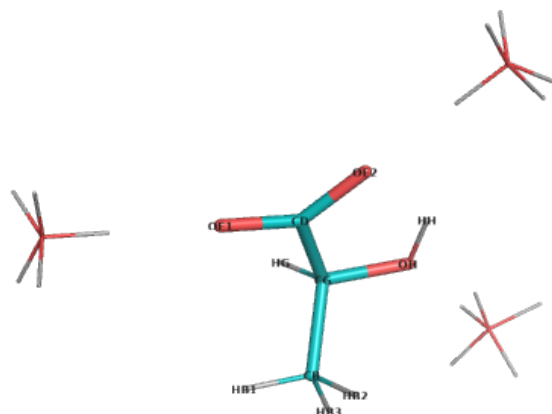


Figure S17: The molecule used for water complex calculations corresponding to 2-hydroxypropanoic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S39: Statistics of calculated water interaction and dipole moment for 2-hydroxypropanoic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.45/1.85	0.08/0.10	2.967	4.73/5.67	0.52
Optimal	0.14/0.27	0.06/0.08	2.588	4.73/4.42	7.16

Table S40: The comparison list of optimized atomic charges and their initial guess for 2-hydroxypropionic acid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.270	0.000
HB2	0.090	0.090	0.000
HB1	0.090	0.090	0.000
CG	0.035	0.060	3.837
HG	0.090	0.090	0.000
OH	-0.729	-0.613	3.613
HH	0.420	0.369	3.268
CD	0.576	0.614	3.551
OE1	-0.696	-0.760	0.250
OE2	-0.696	-0.760	0.250

Table S41: Interaction energies and geometries between probe water and selected 2-hydroxypropionic acid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	OH-CG	0.0	-10.70/-10.61/-9.03	1.81/1.80/1.84
2	OH-CG	90.0	-11.02/-10.90/-9.17	1.79/1.79/1.83
3	OH-CG	180.0	-10.78/-11.01/-9.13	1.81/1.79/1.83
4	OH-CG	270.0	-10.95/-10.85/-9.12	1.80/1.80/1.84
5	OE1-CD	0.0	-12.89/-12.63/-13.66	1.74/1.67/1.66
6	OE1-CD	90.0	-13.16/-13.16/-14.36	1.74/1.67/1.65
7	OE1-CD	180.0	-13.60/-13.74/-15.10	1.73/1.67/1.65
8	OE1-CD	270.0	-13.15/-13.16/-14.35	1.74/1.67/1.65
9	OE2-CD	0.0	-11.92/-11.86/-12.88	1.76/1.69/1.67
10	OE2-CD	90.0	-12.33/-12.35/-13.60	1.75/1.68/1.66
11	OE2-CD	180.0	-12.68/-12.91/-14.38	1.75/1.67/1.65
12	OE2-CD	270.0	-12.34/-12.43/-13.69	1.75/1.67/1.65

1.14 The dipeptide of (4S)-4-fluoro-L-proline (4FB)

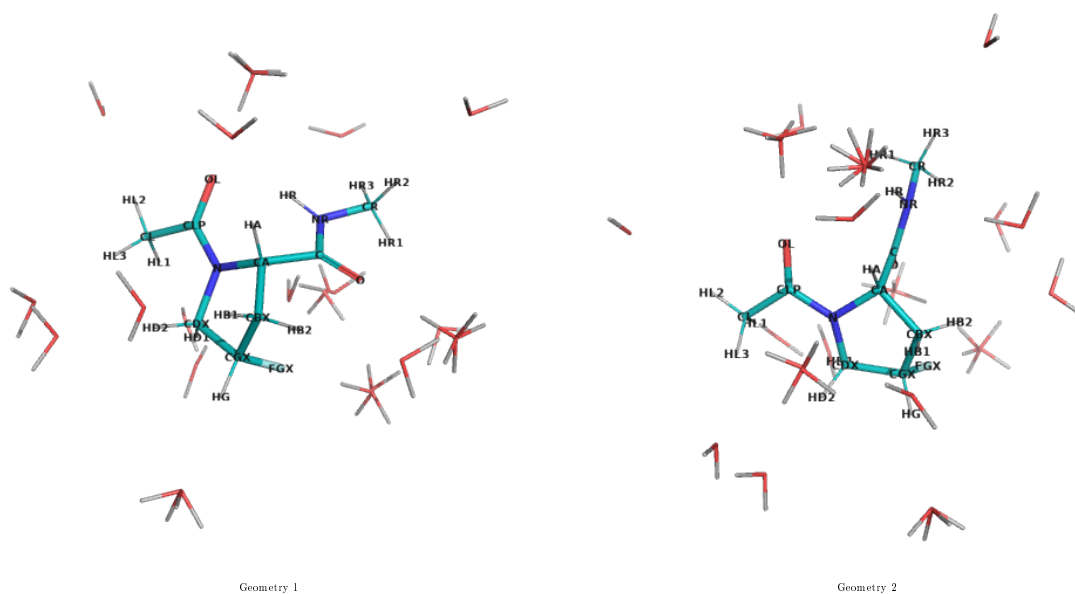


Table S42: The molecule used for water complex calculations corresponding to (4S)-4-fluoro-L-proline, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S43: Statistics of calculated water interaction and dipole moment for (4S)-4-fluoro-L-proline.

		RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
		Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Geometry 1	Initial	0.34 / 0.92	0.18 / 0.44	1.422	5.41 / 5.47	5.41
Geometry 2	Initial	0.47 / 1.35	0.11 / 0.27	1.741	3.79 / 4.25	3.79
Sum of geometries	Initial	0.42 / 1.35	0.15 / 0.44	3.163	-	-
Geometry 1	Optimal	0.35 / 0.77	0.18 / 0.44	1.369	5.41 / 5.58	5.41
Geometry 2	Optimal	0.45 / 1.11	0.11 / 0.26	1.784	3.79 / 4.39	3.79
Sum of geometries	Optimal	0.41 / 1.11	0.15 / 0.44	3.154	-	-

Table S44: The comparison list of optimized atomic charges and their initial guess for (4S)-4-fluoro-L-proline, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.270	0.000
HL1	0.090	0.090	0.000
HL2	0.090	0.090	0.000
HL3	0.090	0.090	0.000
CLP	0.510	0.510	0.000
OL	-0.510	-0.510	0.000
N	-0.265	-0.284	12.667
CA	-0.047	0.022	2.012
HA	0.090	0.090	0.000
CBX	-0.101	-0.167	2.425
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CGX	0.044	0.054	4.339
HG	0.099	0.111	0.497
FGX	-0.207	-0.220	12.335
CDX	0.027	0.033	2.383
HD1	0.090	0.090	0.000
HD2	0.090	0.090	0.000
C	0.510	0.509	0.020
O	-0.510	-0.501	0.000
NR	-0.470	-0.47	0.000
HR	0.310	0.31	0.000
CR	-0.110	-0.11	0.000
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S45: Interaction energies and geometries between probe water and selected (4S)-4-fluoro-L-proline site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
Geometry 1						
1	HL1-CL	0.0	-2.60/-2.53/-2.53		2.54/2.60/2.60	
2	HL2-CL	0.0	-1.12/-0.80/-0.80		2.58/2.68/2.68	
3	HL3-CL	0.0	-3.04/-2.88/-2.87		2.56/2.62/2.62	
4	OL-CLP	0.0	-5.24/-5.56/-5.56		1.83/1.76/1.76	
5	OL-CLP	90.0	-5.14/-5.62/-5.56		1.84/1.76/1.76	
6	OL-CLP	180.0	-4.78/-5.07/-4.93		1.85/1.78/1.78	
7	OL-CLP	270.0	-4.48/-4.81/-4.76		1.86/1.78/1.78	
8	O-C	0.0	-6.22/-6.59/-6.52		1.83/1.76/1.76	
9	O-C	90.0	-7.03/-7.40/-7.27		1.80/1.75/1.75	
10	O-C	180.0	-6.82/-7.17/-6.93		1.82/1.75/1.76	
11	O-C	270.0	-6.61/-6.79/-6.58		1.82/1.76/1.76	
12	NR-C	0.0	-3.47/-2.95/-2.76		2.23/2.24/2.26	
13	HR2-CR	0.0	-0.13/-0.17/-0.24		2.85/2.72/2.72	
14	HR3-CR	0.0	-0.91/-0.84/-0.87		2.72/2.68/2.68	
15	N-CLP	0.0	-3.28/-3.24/-3.24		3.32/3.51/3.51	
16	N-CLP	90.0	-1.21/-1.21/-1.23		3.50/3.94/3.94	
17	N-CLP	180.0	-1.10/-0.84/-0.80		3.61/3.92/3.94	
18	N-CLP	270.0	-1.37/-2.12/-2.02		3.85/3.46/3.48	
19	HA-CA	0.0	-1.45/-1.02/-1.23		2.42/2.64/2.62	
20	HB1-CBX	0.0	-2.12/-2.30/-2.09		2.61/2.63/2.65	
21	HG-CGX	0.0	-2.31/-2.23/-2.29		2.52/2.58/2.57	
22	HG-CGX	90.0	-2.35/-2.25/-2.30		2.52/2.58/2.56	
23	FGX-CGX	0.0	-4.62/-5.39/-5.54		2.08/1.83/1.82	
24	FGX-CGX	90.0	-3.22/-3.44/-3.67		2.17/1.91/1.89	
25	FGX-CGX	180.0	-2.37/-2.11/-2.32		2.20/1.95/1.93	
26	FGX-CGX	270.0	-2.70/-3.15/-3.30		2.18/1.90/1.89	
27	HD1-CDX	0.0	-2.38/-2.46/-2.43		2.52/2.60/2.60	
28	HD2-CDX	0.0	-3.16/-3.54/-3.51		2.52/2.57/2.57	
29	HA-CA	0.0	-1.45/-1.02/-1.23		2.42/2.64/2.62	
Geometry 2						
30	HL1-CL	0.0	-1.99/-1.72/-1.76		2.50/2.59/2.59	
31	HL2-CL	0.0	-0.67/-0.34/-0.35		2.64/2.71/2.71	
32	HL3-CL	0.0	-2.36/-2.30/-2.30		2.59/2.63/2.64	
33	OL-CLP	0.0	-7.78/-8.10/-8.07		1.77/1.74/1.74	
34	OL-CLP	90.0	-7.22/-6.91/-6.84		1.77/1.75/1.75	
35	OL-CLP	180.0	-4.56/-4.73/-4.57		1.84/1.78/1.78	
36	OL-CLP	270.0	-7.10/-7.17/-7.06		1.77/1.74/1.74	
37	O-C	0.0	-6.56/-7.37/-7.23		1.82/1.75/1.75	
38	O-C	90.0	-6.14/-6.98/-6.72		1.83/1.76/1.76	
39	O-C	180.0	-6.67/-7.55/-7.30		1.83/1.75/1.76	
40	O-C	270.0	-7.50/-8.31/-8.19		1.80/1.74/1.75	
41	NR-C	0.0	-2.96/-2.35/-2.07		2.09/2.13/2.15	
42	HR-NR	0.0	-4.97/-5.68/-5.90		1.91/1.89/1.89	
43	HR-NR	45.0	-4.06/-5.17/-5.41		1.95/1.90/1.90	
44	HR-NR	90.0	-5.61/-5.86/-6.12		1.88/1.88/1.88	
45	HR-NR	135.0	-6.67/-6.43/-6.67		1.84/1.87/1.87	
46	HR1-CR	0.0	-0.45/-0.27/-0.33		2.62/2.64/2.64	
47	HR3-CR	0.0	-1.16/-1.08/-1.12		2.73/2.69/2.69	
48	N-CLP	0.0	-0.83/-0.44/-0.54		2.16/2.23/2.22	
49	N-CLP	90.0	-2.23/-2.03/-1.96		2.08/2.15/2.16	
50	N-CLP	180.0	-2.75/-2.62/-2.51		2.06/2.14/2.15	
51	N-CLP	270.0	-1.36/-0.82/-0.81		2.12/2.22/2.22	
52	HA-CA	0.0	-2.22/-2.08/-2.29		2.46/2.62/2.60	
53	HB1-CBX	0.0	-2.08/-2.27/-2.06		2.59/2.63/2.65	
54	HB2-CBX	0.0	-1.17/-0.95/-0.70		2.51/2.64/2.67	
55	HG-CGX	0.0	-2.00/-2.14/-2.19		2.57/2.58/2.57	
56	HG-CGX	90.0	-2.05/-2.17/-2.21		2.56/2.58/2.57	
57	FGX-CGX	0.0	-3.72/-4.12/-4.34		2.12/1.87/1.85	
58	FGX-CGX	90.0	-2.77/-2.39/-2.64		2.17/1.93/1.91	
59	FGX-CGX	180.0	-2.91/-2.66/-2.86		2.17/1.93/1.91	
60	FGX-CGX	270.0	-4.44/-4.86/-5.00		2.08/1.84/1.83	
61	HD1-CDX	0.0	-1.07/-0.91/-0.92		2.48/2.60/2.60	
62	HD2-CDX	0.0	-2.45/-2.94/-2.95		2.58/2.59/2.59	
63	HA-CA	0.0	-2.22/-2.08/-2.29		2.46/2.62/2.60	

1.15 Small molecule used for 4-fluoro-tryptophan(4FW)

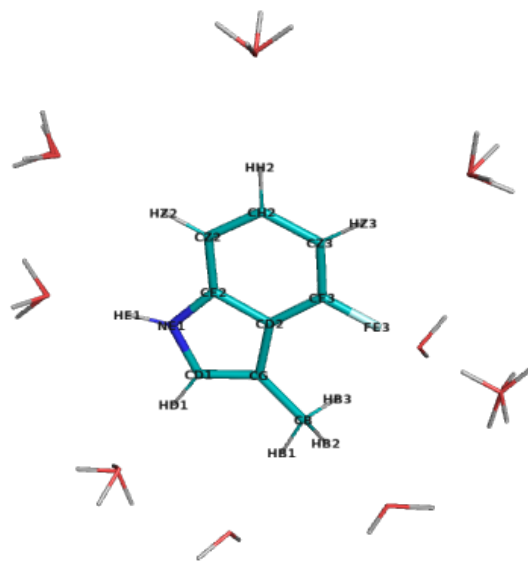


Figure S18: The molecule used for water complex calculations corresponding to 4-fluoro-3-methyl-1H-indole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S46: Statistics of calculated water interaction and dipole moment for 4-fluoro-3-methyl-1H-indole.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.75/1.70	0.16/0.25	4.213	3.42/2.98	38.48
Optimal	0.19/0.32	0.13/0.21	2.140	3.42/4.16	0.19

Table S47: The comparison list of optimized atomic charges and their initial guess for 4-fluoro-3-methyl-1H-indole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.278	0.474
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.014	-0.046	7.217
CD1	-0.058	-0.163	0.075
HD1	0.133	0.220	0.000
CD2	-0.022	-0.021	12.100
NE1	-0.381	-0.518	0.639
HE1	0.316	0.363	0.000
CE2	0.274	0.236	2.888
CE3	0.078	0.186	13.802
FE3	-0.151	-0.207	3.590
CZ2	-0.219	-0.278	0.000
HZ2	0.163	0.195	0.000
CZ3	-0.198	-0.048	11.106
HZ3	0.165	0.180	0.707
CH2	-0.295	-0.287	0.570
HH2	0.209	0.196	0.000

Table S48: Interaction energies and geometries between probe water and selected 4-fluoro-3-methyl-1H-indole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.36/-0.04/0.36	2.73/2.74/2.84
2	HB1-CB	0.0	-0.98/-0.80/-0.46	2.79/2.77/2.83
3	HD1-CD1	0.0	-2.15/-2.41/-2.66	2.50/2.31/2.25
4	HD1-CD1	90.0	-2.46/-2.54/-2.79	2.43/2.30/2.25
5	HE1-NE1	0.0	-6.33/-6.65/-5.77	1.87/1.87/1.87
6	HE1-NE1	90.0	-6.98/-6.88/-6.07	1.84/1.86/1.87
7	FE3-CE3	0.0	-2.43/-2.52/-3.05	2.17/1.97/1.93
8	FE3-CE3	90.0	-2.58/-2.70/-2.82	2.16/1.96/1.94
9	FE3-CE3	180.0	-2.60/-2.74/-2.49	2.16/1.96/1.95
10	FE3-CE3	270.0	-2.58/-2.70/-2.82	2.16/1.96/1.94
11	HZ2-CZ2	0.0	-1.55/-1.87/-1.81	2.69/2.65/2.64
12	HZ2-CZ2	90.0	-2.02/-2.09/-2.02	2.56/2.63/2.62
13	HZ3-CZ3	0.0	-1.08/-0.91/-2.78	2.59/2.48/2.37
14	HZ3-CZ3	90.0	-1.10/-0.90/-2.74	2.57/2.48/2.38
15	HH2-CH2	0.0	-1.29/-1.34/-1.80	2.64/2.65/2.63
16	HH2-CH2	90.0	-1.48/-1.43/-1.91	2.58/2.64/2.62

1.16 Small molecule A of
O-[(S)-hydroxy[(3R)-3-hydroxy-2,2-dimethyl-4-oxo-4-(3-oxo-3-[(2-sulfanylethyl)amino]propylamino)butyl]oxyphosphoryl]-L-serine(4HH)

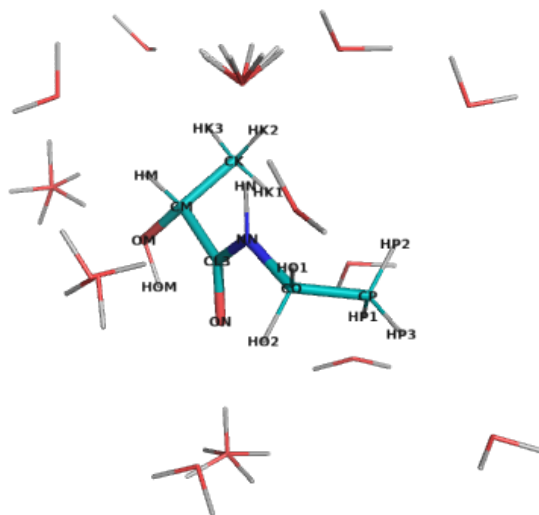


Figure S19: The molecule used for water complex calculations corresponding to (2R)-N-ethyl-2-hydroxypropanamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S49: Statistics of calculated water interaction and dipole moment for (2R)-N-ethyl-2-hydroxypropanamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.35/0.69	0.07/0.18	1.524	4.62/5.06	1.40
Optimal	0.27/0.57	0.07/0.17	2.249	4.62/5.38	2.11

Table S50: The comparison list of optimized atomic charges and their initial guess for (2R)-N-ethyl-2-hydroxypropanamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CK	-0.270	-0.268	0.000
HK1	0.090	0.090	0.000
HK2	0.090	0.090	0.000
HK3	0.090	0.090	0.000
CM	0.188	0.171	21.973
HM	0.090	0.090	0.000
OM	-0.607	-0.623	22.440
HOM	0.285	0.369	1.783
CL3	0.580	0.513	12.496
ON	-0.477	-0.501	1.525
NN	-0.568	-0.535	17.934
HN	0.312	0.312	0.000
CO	0.017	0.017	0.539
HO1	0.090	0.090	0.000
HO2	0.090	0.090	0.000
CP	-0.270	-0.265	0.359
HP1	0.090	0.090	0.000
HP2	0.090	0.090	0.000
HP3	0.090	0.090	0.000

Table S51: Interaction energies and geometries between probe water and selected (2R)-N-ethyl-2-hydroxypropanamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HK1-CK	0.0	-0.82/-0.76/-0.66	2.65/2.65/2.67
2	HK2-CK	0.0	-2.74/-2.92/-2.81	2.65/2.61/2.62
3	HK3-CK	0.0	-0.65/-0.33/-0.29	2.74/2.75/2.76
4	HM-CM	0.0	-1.71/-2.27/-2.09	2.61/2.62/2.63
5	OM-CM	0.0	-6.30/-6.49/-6.16	1.84/1.86/1.86
6	OM-CM	90.0	-6.15/-5.90/-5.76	1.82/1.86/1.87
7	OM-CM	180.0	-5.18/-5.18/-5.19	1.86/1.87/1.87
8	OM-CM	270.0	-5.97/-5.99/-5.82	1.83/1.86/1.86
9	ON-CL3	0.0	-5.16/-5.47/-5.55	1.87/1.79/1.78
10	ON-CL3	90.0	-5.17/-5.15/-5.60	1.85/1.79/1.77
11	ON-CL3	180.0	-5.04/-4.93/-5.55	1.85/1.79/1.77
12	ON-CL3	270.0	-5.38/-5.33/-5.71	1.85/1.79/1.77
13	NN-CL3	180.0	-1.70/-1.96/-2.20	2.27/2.18/2.17
14	NN-CL3	270.0	-1.12/-1.61/-1.79	2.27/2.16/2.16
15	HN-NN	0.0	-6.79/-7.23/-7.16	1.93/1.90/1.90
16	HN-NN	45.0	-7.03/-7.36/-7.29	1.91/1.90/1.90
17	HN-NN	90.0	-7.12/-7.40/-7.31	1.90/1.90/1.89
18	HN-NN	135.0	-6.83/-7.25/-7.18	1.91/1.90/1.90
19	HO1-CO	0.0	-1.71/-1.80/-1.81	2.69/2.67/2.67
20	HO2-CO	0.0	-0.39/-0.42/-0.19	2.59/2.69/2.70
21	HP1-CP	0.0	-1.02/-0.68/-0.33	2.47/2.64/2.65
22	HP2-CP	0.0	-1.14/-1.30/-1.29	2.89/2.77/2.76
23	HP3-CP	0.0	-1.05/-1.04/-1.03	2.78/2.72/2.72

1.17 Small molecule used for 4-hydroxy-tryptophan(4HT)

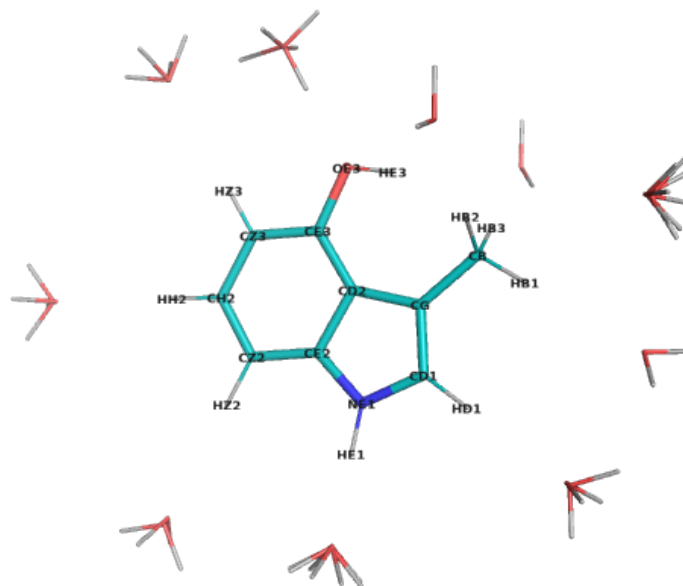


Figure S20: The molecule used for water complex calculations corresponding to 3-methyl-1H-indol-4-olate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S52: Statistics of calculated water interaction and dipole moment for 3-methyl-1H-indol-4-olate.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.37/0.88	0.09/0.27	1.934	3.61/3.40	12.46
Optimal	0.16/0.34	0.07/0.20	2.779	3.61/4.53	0.06

Table S53: The comparison list of optimized atomic charges and their initial guess for 3-methyl-1H-indole-4-olate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.278	0.000
HB2	0.090	0.090	0.000
HB1	0.090	0.090	0.000
CG	0.017	-0.046	2.500
CD1	-0.044	-0.163	0.000
HD1	0.120	0.220	0.000
CD2	0.095	0.113	3.576
NE1	-0.408	-0.518	0.000
HE1	0.322	0.363	0.000
CE2	0.244	0.236	2.500
CZ2	-0.297	-0.285	0.000
HZ2	0.177	0.195	0.000
CE3	0.030	0.041	3.582
OE3	-0.484	-0.530	3.568
HE3	0.346	0.420	0.075
CZ3	-0.300	-0.237	0.000
HZ3	0.227	0.196	0.000
CH2	-0.245	-0.193	0.000
HH2	0.200	0.196	0.000

Table S54: Interaction energies and geometries between probe water and selected 3-methyl-1H-indole-4-olate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.55/-1.48/-1.37	2.57/2.60/2.62
2	HB2-CB	0.0	-1.53/-1.47/-1.35	2.57/2.61/2.62
3	HB1-CB	0.0	-1.54/-1.42/-1.11	2.68/2.70/2.75
4	HD1-CD1	0.0	-2.19/-2.53/-3.07	2.51/2.31/2.25
5	HD1-CD1	90.0	-2.55/-2.68/-3.23	2.43/2.30/2.24
6	HE1-NE1	0.0	-6.20/-6.45/-6.05	1.88/1.87/1.87
7	HE1-NE1	45.0	-6.50/-6.56/-6.21	1.86/1.87/1.87
8	HE1-NE1	90.0	-6.82/-6.66/-6.36	1.84/1.86/1.86
9	HE1-NE1	135.0	-6.51/-6.56/-6.21	1.86/1.87/1.87
10	HZ2-CZ2	0.0	-1.25/-1.45/-1.83	2.75/2.68/2.64
11	HZ2-CZ2	90.0	-1.69/-1.67/-2.05	2.61/2.65/2.61
12	OE3-CE3	0.0	-4.58/-4.80/-4.85	1.91/1.91/1.91
13	OE3-CE3	90.0	-5.32/-5.18/-5.20	1.86/1.90/1.89
14	OE3-CE3	180.0	-4.53/-4.81/-4.78	1.92/1.91/1.90
15	OE3-CE3	270.0	-5.32/-5.18/-5.21	1.86/1.90/1.89
16	HE3-OE3	0.0	-0.68/-0.85/-0.65	5.17/5.00/5.00
17	HE3-OE3	45.0	-0.87/-0.93/-0.72	5.10/5.00/5.00
18	HE3-OE3	90.0	-1.04/-0.99/-0.77	5.06/5.00/5.00
19	HE3-OE3	135.0	-0.86/-0.92/-0.72	5.10/5.00/5.00
20	HZ3-CZ3	0.0	-0.36/-0.21/-0.35	2.70/2.68/2.68
21	HZ3-CZ3	90.0	-0.30/-0.16/-0.31	2.72/2.69/2.69
22	HH2-CH2	0.0	-0.97/-0.90/-1.47	2.69/2.68/2.63
23	HH2-CH2	90.0	-1.13/-0.98/-1.55	2.63/2.66/2.62

1.18 Small molecule used for 4-amino-l-tryptophan(4IN)

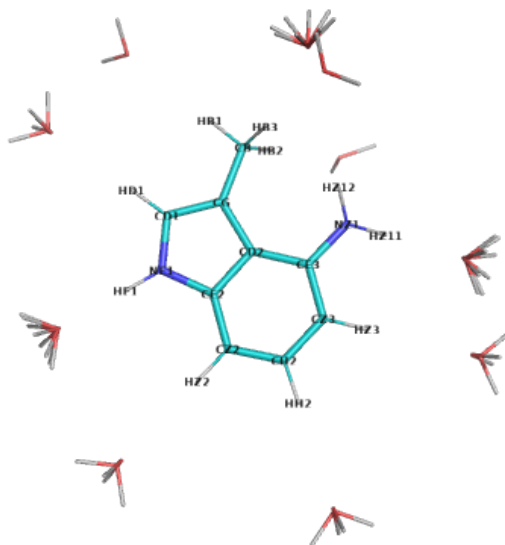


Figure S21: The molecule used for water complex calculations corresponding to 3-methyl-1H-indol-4-amine, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S55: Statistics of calculated water interaction and dipole moment for 3-methyl-1H-indol-4-amine.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.50/0.92	0.14/0.30	2.756	1.84/2.08	34.59
Optimal	0.13/0.26	0.12/0.23	1.840	1.84/2.23	2.09

Table S56: The comparison list of optimized atomic charges and their initial guess for 3-methyl-1H-indol-4-amine, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.278	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.014	-0.046	2.500
CD1	-0.098	-0.163	0.000
HD1	0.141	0.220	0.000
CD2	0.142	0.121	12.931
NE1	-0.479	-0.518	0.000
HE1	0.350	0.363	0.000
CE2	0.234	0.237	12.649
CZ2	-0.313	-0.285	0.000
HZ2	0.175	0.195	0.000
CZ3	-0.236	-0.231	0.000
HZ3	0.179	0.196	0.000
CE3	0.049	-0.013	18.759
NZ1	-0.858	-0.838	18.086
HZ11	0.365	0.382	0.075
HZ12	0.365	0.382	0.075
CH2	-0.206	-0.190	0.000
HH2	0.176	0.196	0.000

Table S57: Interaction energies and geometries between probe water and selected 3-methyl-1H-indol-4-amine site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.05/-1.30/-0.87	2.81/2.69/2.74
2	HB1-CB	0.0	-1.07/-0.97/-0.70	2.76/2.74/2.79
3	HD1-CD1	0.0	-1.83/-2.04/-2.75	2.55/2.32/2.25
4	HD1-CD1	90.0	-2.14/-2.18/-2.90	2.47/2.31/2.24
5	HE1-NE1	0.0	-5.78/-6.01/-5.78	1.89/1.87/1.87
6	HE1-NE1	45.0	-6.08/-6.11/-5.94	1.87/1.87/1.87
7	HE1-NE1	90.0	-6.37/-6.21/-6.09	1.85/1.86/1.87
8	HE1-NE1	135.0	-6.06/-6.11/-5.93	1.87/1.87/1.87
9	HZ2-CZ2	0.0	-1.06/-1.20/-1.71	2.79/2.70/2.64
10	HZ2-CZ2	90.0	-1.48/-1.41/-1.94	2.64/2.67/2.62
11	HZ3-CZ3	0.0	-0.95/-1.07/-1.47	2.81/2.69/2.65
12	HZ3-CZ3	90.0	-1.41/-1.27/-1.72	2.62/2.66/2.62
13	HZ11-NZ1	0.0	-3.72/-3.84/-4.37	2.05/1.95/1.93
14	HZ11-NZ1	45.0	-3.62/-3.81/-4.35	2.06/1.95/1.93
15	HZ11-NZ1	90.0	-4.11/-4.07/-4.69	2.02/1.94/1.91
16	HZ11-NZ1	135.0	-4.23/-4.12/-4.72	2.01/1.93/1.91
17	HZ12-NZ1	0.0	-1.22/-1.17/-0.92	3.72/3.90/3.91
18	HZ12-NZ1	45.0	-1.29/-1.20/-0.93	3.71/3.90/3.91
19	HZ12-NZ1	90.0	-1.20/-1.13/-0.87	3.68/3.91/3.92
20	HZ12-NZ1	135.0	-1.13/-1.10/-0.86	3.70/3.92/3.93
21	HH2-CH2	0.0	-0.82/-0.85/-1.49	2.74/2.70/2.63
22	HH2-CH2	90.0	-1.00/-0.94/-1.61	2.67/2.68/2.62

1.19 Small molecule used for
2-amino-3-(cystein-S-yl)-isoxazolidin-5-yl-aceticacid(5CS)

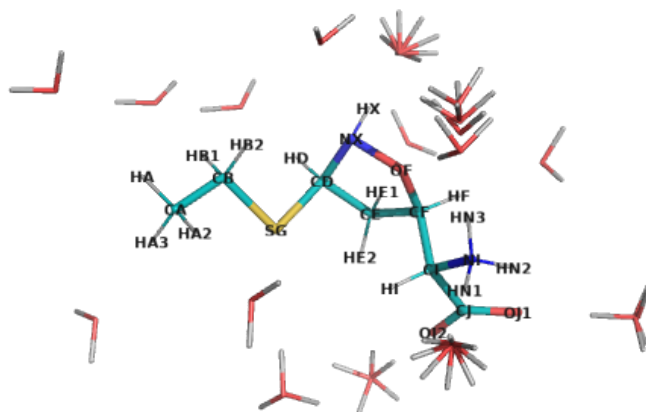


Figure S22: The molecule used for water complex calculations corresponding to 2-[3-(ethylsulfanyl)-1,2-oxazolidin-5-yl]-2-(trihydridonickelio)aceticacid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S58: Statistics of calculated water interaction and dipole moment for 2-[3-(ethylsulfanyl)-1,2-oxazolidin-5-yl]-2-(trihydridonickelio)aceticacid.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	2.58/7.15	0.41/2.09	7.048	9.49/13.29	2.60
Optimal	1.24/3.57	0.15/0.49	5.718	9.49/12.34	0.00

Table S59: The comparison list of optimized atomic charges and their initial guess for 2-[3-(ethylsulfanyl)-1,2-oxazolidin-5-yl]-2-(trihydridonickelio)acetic acid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.545
HA	0.090	0.090	0.000
CB	-0.088	-0.065	4.421
HB1	0.090	0.090	0.500
HB2	0.090	0.090	0.500
SG	-0.188	-0.209	99.339
CD	0.170	0.243	120.751
HD	0.090	0.090	6.130
NX	-0.312	-0.394	334.919
HX	0.264	0.361	4.283
OF	-0.208	-0.354	324.573
CE	-0.134	-0.207	46.322
HE1	0.090	0.090	2.648
HE2	0.090	0.090	2.648
CF	0.018	0.030	76.052
HF	0.090	0.090	4.887
CI	0.262	0.393	120.760
HI	0.090	0.090	5.902
NI	-0.162	-0.346	37.955
HN1	0.259	0.330	2.642
HN2	0.259	0.330	2.642
HN3	0.259	0.330	2.642
CJ	0.095	0.448	100.308
OJ1	-0.562	-0.760	8.256
OJ2	-0.562	-0.760	8.256

Table S60: Interaction energies and geometries between probe water and selected 2-[3-(ethylsulfanyl)-1,2-oxazolidin-5-yl]-2-(trihydridonickelio)acetic acid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.95/-0.85/-0.93	2.72/2.74/2.73
2	HA2-CA	0.0	-0.61/-0.57/-0.69	2.91/2.95/5.00
3	HA-CA	0.0	-1.20/-1.05/-1.13	2.75/2.74/2.73
4	HB1-CB	0.0	-1.50/-1.84/-2.01	2.73/2.69/2.68
5	SG-CB	0.0	-3.28/-4.10/-4.21	2.79/2.40/2.38
6	SG-CB	270.0	-1.24/-2.05/-2.56	2.82/2.34/2.31
7	HD-CD	0.0	-2.76/-3.09/-3.32	2.47/2.59/2.58
8	HX-NX	0.0	-5.89/-6.68/-8.53	1.95/1.89/1.82
9	HX-NX	45.0	-5.87/-6.66/-8.49	1.95/1.89/1.82
10	HX-NX	90.0	-5.91/-6.77/-8.61	1.95/1.89/1.82
11	HX-NX	135.0	-5.92/-6.79/-8.65	1.95/1.89/1.82
12	OF-NX	90.0	-1.98/-2.56/-5.44	1.85/1.75/1.66
13	OF-NX	180.0	-1.78/-5.34/-8.92	1.88/1.71/1.62
14	HE1-CE	0.0	-2.42/-2.22/-2.04	2.52/2.61/2.63
15	HF-CF	0.0	-2.88/-2.17/-2.35	2.35/2.57/2.55
16	HN1-NI	0.0	-11.41/-11.09/-13.52	1.71/1.78/1.74
17	HN1-NI	45.0	-11.73/-11.37/-13.83	1.70/1.78/1.74
18	HN1-NI	90.0	-11.88/-11.31/-13.84	1.70/1.78/1.74
19	HN1-NI	135.0	-11.55/-11.04/-13.53	1.70/1.78/1.74
20	HN3-NI	0.0	-4.73/-5.52/-5.68	1.97/2.28/2.20
21	HN3-NI	45.0	-3.38/-5.40/-5.33	2.23/2.32/2.25
22	HN3-NI	90.0	-1.91/-4.83/-4.44	2.62/2.36/2.32
23	HN3-NI	135.0	-2.45/-4.88/-4.66	2.28/2.34/2.28
24	OJ1-CJ	0.0	-5.18/-4.66/-6.14	1.79/1.76/1.70
25	OJ1-CJ	90.0	-7.80/-8.02/-9.93	1.73/1.71/1.66
26	OJ1-CJ	180.0	-9.91/-11.30/-13.81	1.71/1.68/1.63
27	OJ1-CJ	270.0	-8.25/-8.66/-10.86	1.73/1.70/1.65
28	OJ2-CJ	0.0	-7.58/-8.33/-10.47	1.77/1.72/1.67
29	OJ2-CJ	90.0	-8.14/-9.43/-11.84	1.75/1.70/1.66
30	OJ2-CJ	180.0	-9.57/-11.34/-13.78	1.74/1.69/1.64
31	OJ2-CJ	270.0	-8.89/-10.20/-12.34	1.75/1.70/1.66

1.20 Small molecule A of hypusine(5CT)

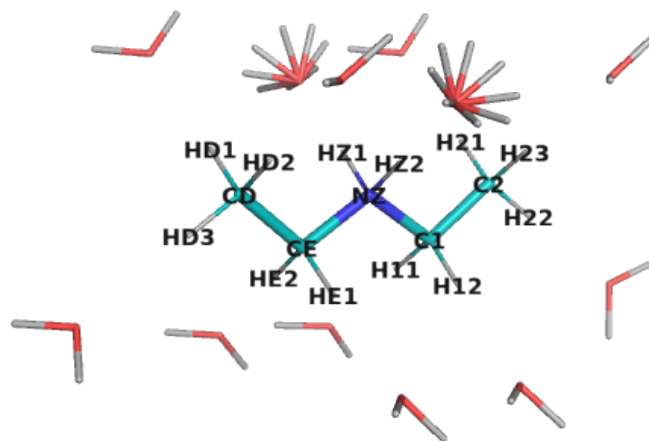


Figure S23: The molecule used for water complex calculations corresponding to diethylamine, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S61: Statistics of calculated water interaction and dipole moment for diethylamine.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.48/1.11	0.15/0.24	2.371	0.45/0.27	179.75
Optimal	0.46/1.10	0.15/0.24	2.449	0.45/0.31	179.76

Table S62: The comparison list of optimized atomic charges and their initial guess for diethylamine, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HD3	0.090	0.090	0.045
CD	-0.270	-0.270	0.709
HD1	0.090	0.090	0.045
HD2	0.090	0.090	0.045
CE	0.197	0.200	0.810
HE1	0.090	0.090	0.000
HE2	0.090	0.090	0.000
NZ	-0.394	-0.420	0.869
HZ1	0.320	0.330	0.064
HZ2	0.320	0.330	0.064
C1	0.197	0.200	0.810
H11	0.090	0.090	0.000
H12	0.090	0.090	0.000
C2	-0.270	-0.270	0.709
H21	0.090	0.090	0.045
H22	0.090	0.090	0.045
H23	0.090	0.090	0.045

Table S63: Interaction energies and geometries between probe water and selected diethylamine site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HD3-CD	0.0	-6.45/-5.34/-5.34	2.32/2.55/2.55
2	HD1-CD	0.0	-6.81/-6.32/-6.33	2.41/2.55/2.55
3	HD2-CD	0.0	-6.81/-6.32/-6.33	2.41/2.55/2.55
4	HE1-CE	0.0	-8.82/-8.52/-8.49	2.25/2.49/2.49
5	HE2-CE	0.0	-8.82/-8.52/-8.49	2.25/2.49/2.49
6	HZ1-NZ	0.0	-16.12/-16.34/-16.51	1.77/1.78/1.77
7	HZ1-NZ	45.0	-16.02/-16.32/-16.49	1.77/1.78/1.77
8	HZ1-NZ	90.0	-16.59/-16.46/-16.63	1.77/1.78/1.77
9	HZ1-NZ	135.0	-16.67/-16.48/-16.65	1.77/1.78/1.77
10	HZ2-NZ	0.0	-16.11/-16.34/-16.51	1.77/1.78/1.77
11	HZ2-NZ	45.0	-16.67/-16.48/-16.65	1.77/1.78/1.77
12	HZ2-NZ	90.0	-16.59/-16.46/-16.63	1.77/1.78/1.77
13	HZ2-NZ	135.0	-16.02/-16.32/-16.49	1.78/1.78/1.77
14	H11-C1	0.0	-8.57/-8.46/-8.43	2.27/2.49/2.49
15	H12-C1	0.0	-8.57/-8.46/-8.43	2.27/2.49/2.49
16	H21-C2	0.0	-6.78/-6.31/-6.31	2.42/2.55/2.55
17	H22-C2	0.0	-6.33/-5.28/-5.28	2.33/2.55/2.55
18	H23-C2	0.0	-6.78/-6.31/-6.31	2.42/2.55/2.55

1.21 Small molecule used for 6-carboxylysine(6CL)

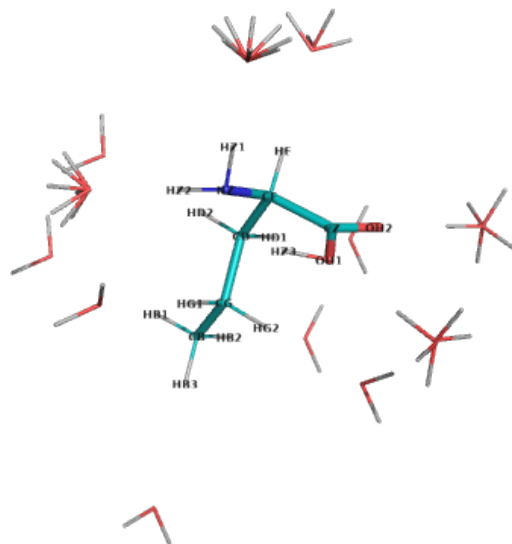


Figure S24: The molecule used for water complex calculations corresponding to 2-aminopentanoic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S64: Statistics of calculated water interaction and dipole moment for 2-aminopentanoic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	5.22/7.56	0.18/0.27	16.483	5.81/13.57	2.02
Optimal	0.44/1.12	0.09/0.18	2.920	5.81/6.79	1.97

Table S65: The comparison list of optimized atomic charges and their initial guess for 2-aminopentanoic acid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.204	0.572
HB2	0.090	0.090	0.000
HB1	0.090	0.090	0.000
CG	-0.095	-0.185	2.592
HG2	0.090	0.090	0.000
HG1	0.090	0.090	0.000
CD	-0.253	-0.195	30.356
HD1	0.090	0.090	2.500
HD2	0.090	0.090	2.500
CE	0.129	0.314	102.108
HE	0.090	0.090	3.979
CZ	0.374	0.448	99.425
NZ	-0.339	-0.368	37.376
HZ1	0.210	0.330	2.536
HZ3	0.210	0.330	2.536
HZ2	0.210	0.330	2.536
OH1	-0.448	-0.760	8.256
OH2	-0.448	-0.760	8.256

Table S66: Interaction energies and geometries between probe water and selected 2-aminopentanoic acid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.89/-0.91/-1.22	2.80/2.73/2.68
2	HB2-CB	0.0	-0.99/-0.83/-1.20	2.74/2.70/2.63
3	HB1-CB	0.0	-1.06/-1.14/-1.89	2.87/2.76/2.72
4	HG2-CG	0.0	-1.25/-0.14/1.13	2.43/2.61/2.51
5	HG1-CG	0.0	-1.61/-2.20/-3.47	2.74/2.71/2.71
6	HD1-CD	0.0	-0.33/-0.14/0.26	2.65/2.71/2.66
7	HD2-CD	0.0	-2.06/-2.15/-4.06	2.67/2.68/2.59
8	HE-CE	0.0	-1.71/-2.16/-3.36	2.57/2.62/2.55
9	HE-CE	90.0	-2.12/-2.32/-3.67	2.49/2.61/2.53
10	HZ1-NZ	0.0	-5.55/-5.89/-12.23	1.96/1.91/1.77
11	HZ1-NZ	45.0	-5.60/-5.85/-12.12	1.95/1.91/1.77
12	HZ1-NZ	90.0	-5.66/-5.99/-12.40	1.95/1.91/1.77
13	HZ1-NZ	135.0	-5.61/-6.02/-12.51	1.96/1.91/1.77
14	HZ2-NZ	0.0	-5.31/-5.79/-12.13	2.01/1.95/1.80
15	HZ2-NZ	45.0	-5.33/-5.83/-12.21	2.01/1.95/1.80
16	HZ2-NZ	90.0	-5.56/-5.81/-12.27	2.00/1.95/1.80
17	HZ2-NZ	135.0	-5.56/-5.79/-12.20	2.00/1.95/1.80
18	OH1-CZ	0.0	-3.57/-3.80/-7.50	2.00/1.86/1.73
19	OH1-CZ	90.0	-4.31/-4.85/-9.88	1.96/1.83/1.70
20	OH1-CZ	180.0	-5.60/-6.47/-13.17	1.92/1.80/1.67
21	OH1-CZ	270.0	-4.37/-4.92/-9.79	1.96/1.83/1.70
22	OH2-CZ	0.0	-5.23/-5.31/-10.60	1.88/1.80/1.67
23	OH2-CZ	90.0	-5.70/-5.96/-11.97	1.87/1.79/1.66
24	OH2-CZ	180.0	-6.26/-6.75/-13.56	1.86/1.78/1.65
25	OH2-CZ	270.0	-5.61/-6.07/-12.17	1.87/1.79/1.66

1.22 Small molecule used for (2R)-2-azanyl-3-[(3R)-1-ethyl-2,5-bis(oxidan-ylidene)pyrrolidin-3-yl]sulfanyl-propanoic acid(6V1)

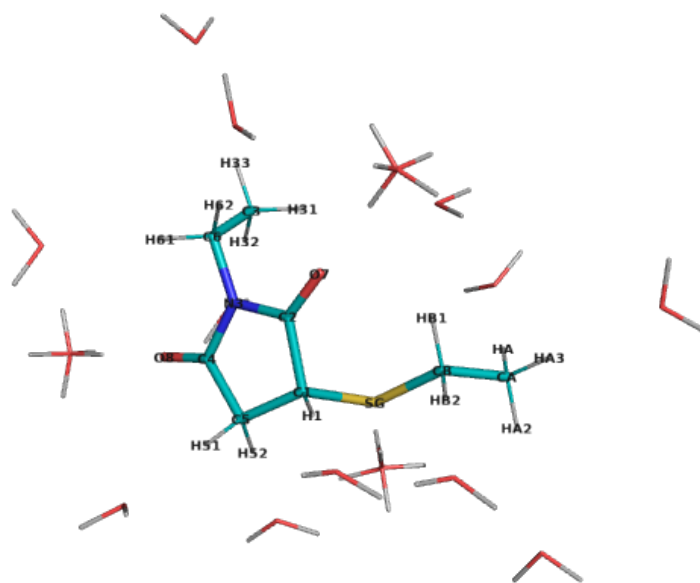


Figure S25: The molecule used for water complex calculations corresponding to (3R)-1-ethyl-3-(ethylsulfanyl)pyrrolidine-2,5-dione, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S67: Statistics of calculated water interaction and dipole moment for (3R)-1-ethyl-3-(ethylsulfanyl)pyrrolidine-2,5-dione.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.78/1.37	0.25/0.60	3.020	2.22/3.15	20.30
Optimal	0.40/0.91	0.23/0.55	2.055	2.22/2.88	0.00

Table S68: The comparison list of optimized atomic charges and their initial guess for (3R)-1-ethyl-3-(ethylsulfanyl)pyrrolidine-2,5-dione, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.545
HA	0.090	0.090	0.000
CB	-0.053	-0.065	4.421
HB1	0.090	0.090	0.500
HB2	0.090	0.090	0.500
SG	-0.149	-0.208	92.548
C1	0.014	0.159	95.619
H1	0.090	0.090	5.604
C2	0.377	0.314	10.961
O7	-0.428	-0.487	2.819
C5	-0.109	-0.028	42.610
H51	0.090	0.090	2.508
H52	0.090	0.090	2.508
C4	0.275	0.312	7.374
O8	-0.423	-0.487	0.134
N3	-0.112	-0.171	10.607
C6	0.012	0.030	9.503
H61	0.090	0.090	0.638
H62	0.090	0.090	0.638
C3	-0.304	-0.270	3.551
H31	0.090	0.090	0.050
H32	0.090	0.090	0.050
H33	0.090	0.090	0.050

Table S69: Interaction energies and geometries between probe water and selected (3R)-1-ethyl-3-(ethylsulfanyl)pyrrolidine-2,5-dione site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-1.22/-1.02/-0.89	2.71/2.71/2.72
2	HA2-CA	0.0	-0.97/-0.84/-0.69	2.71/2.73/2.76
3	HA-CA	0.0	-1.01/-0.82/-0.59	2.69/2.72/2.74
4	HB2-CB	0.0	-1.43/-1.75/-1.72	2.69/2.67/2.68
5	SG-CB	0.0	-0.90/-1.45/-1.34	3.00/2.46/2.44
6	SG-CB	90.0	-1.18/-1.73/-2.04	2.88/2.41/2.37
7	SG-CB	180.0	-0.77/-1.29/-1.72	2.96/2.42/2.36
8	SG-CB	270.0	-0.87/-1.05/-1.11	2.90/2.44/2.41
9	H1-C1	0.0	-2.51/-2.53/-3.24	2.44/2.61/2.57
10	O7-C2	0.0	-4.57/-4.35/-5.55	1.88/1.81/1.77
11	O7-C2	90.0	-4.64/-4.72/-6.01	1.88/1.80/1.77
12	O7-C2	180.0	-4.94/-4.97/-6.21	1.87/1.80/1.76
13	O7-C2	270.0	-4.99/-4.81/-5.99	1.87/1.80/1.77
14	H51-C5	0.0	-2.78/-2.11/-2.98	2.42/2.61/2.56
15	H52-C5	0.0	-2.26/-1.36/-2.12	2.34/2.63/2.57
16	O8-C4	0.0	-5.04/-5.31/-6.02	1.88/1.80/1.77
17	O8-C4	90.0	-4.84/-5.12/-5.95	1.89/1.80/1.77
18	O8-C4	180.0	-4.73/-5.11/-6.00	1.89/1.80/1.77
19	O8-C4	270.0	-4.99/-5.41/-6.22	1.89/1.80/1.77
20	H61-C6	0.0	-0.73/-0.48/-0.28	2.51/2.65/2.65
21	H62-C6	0.0	-0.63/-0.71/-0.31	2.53/2.65/2.66
22	H31-C3	0.0	-0.22/-0.45/-0.35	2.80/2.69/2.64
23	H32-C3	0.0	-1.21/-0.40/-0.41	2.46/2.62/2.60
24	H33-C3	0.0	-1.00/-0.68/-0.81	2.76/2.75/2.72

1.23 The dipeptide of (2S)-2,3-dihydro-1H-pyrrole-2-carboxylic acid (8LJ)

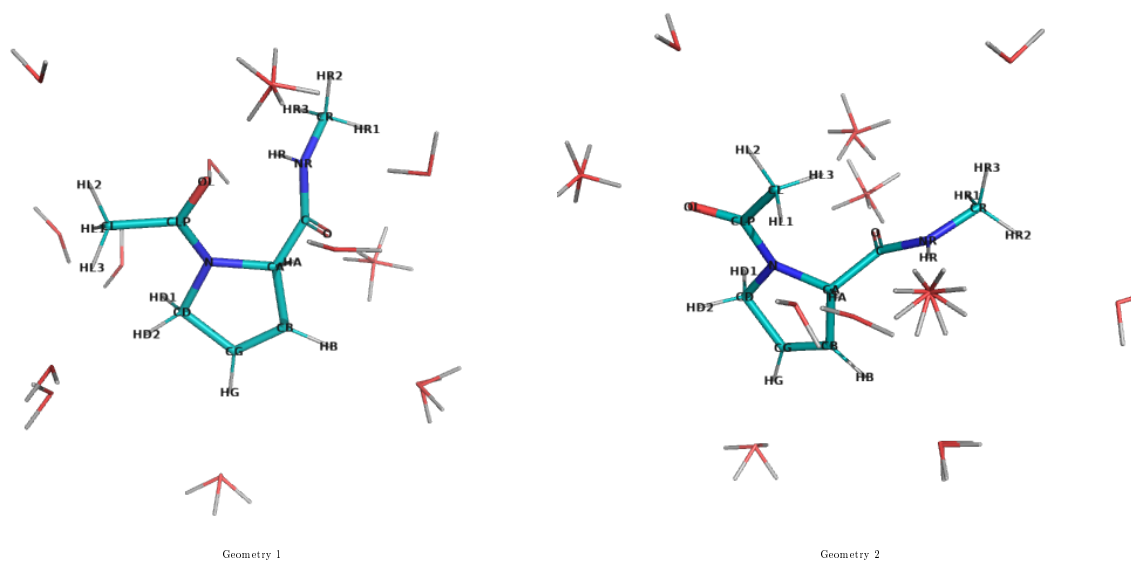


Table S70: The molecule used for water complex calculations corresponding to (2S)-2,3-dihydro-1H-pyrrole-2-carboxylic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S71: Statistics of calculated water interaction and dipole moment for (2S)-2,3-dihydro-1H-pyrrole-2-carboxylic acid.

		RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
		Energy (kcal/mol)	Distance (Å)			
Geometry 1	Initial	0.51 / 1.05	0.14 / 0.27	2.940	4.07 / 3.72	4.07
Geometry 2	Initial	0.73 / 1.41	0.13 / 0.25	2.919	6.45 / 6.75	6.45
Sum of geometries		Initial	0.64 / 1.41	5.859	-	-
Geometry 1	Optimal	0.32 / 0.83	0.15 / 0.34	2.035	4.07 / 4.00	4.07
Geometry 2	Optimal	0.60 / 1.06	0.14 / 0.29	2.054	6.45 / 6.52	6.45
Sum of geometries		Optimal	0.49 / 1.06	4.089	-	-

Table S72: The comparison list of optimized atomic charges and their initial guess for (2S)-2,3-dihydro-1H-pyrrole-2-carboxylic acid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.270	0.000
HL1	0.090	0.090	0.000
HL2	0.090	0.090	0.000
HL3	0.090	0.090	0.000
CLP	0.510	0.510	0.000
OL	-0.510	-0.510	0.000
N	-0.229	-0.245	59.884
CA	0.065	0.133	50.455
HA	0.090	0.090	0.346
CB	-0.380	-0.539	61.416
HB	0.284	0.401	36.583
CG	-0.358	-0.514	52.251
HG	0.273	0.367	33.391
CD	0.075	0.128	38.429
HD1	0.090	0.090	0.000
HD2	0.090	0.090	0.000
C	0.510	0.500	26.738
O	-0.510	-0.499	2.500
NR	-0.470	-0.47	0.000
HR	0.310	0.31	0.000
CR	-0.110	-0.11	0.000
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S73: Interaction energies and geometries between probe water and selected (2S)-2,3-dihydro-1H-pyrrole-2-carboxylic acid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
Geometry 1						
1	O-C	0.0	-6.61/-6.91/-6.83	1.81/1.75/1.75		
2	O-C	90.0	-6.80/-7.20/-7.27	1.81/1.75/1.75		
3	O-C	180.0	-6.91/-7.16/-7.09	1.81/1.75/1.76		
4	O-C	270.0	-6.78/-7.00/-6.79	1.81/1.75/1.76		
5	NR-C	0.0	-2.18/-1.99/-2.06	2.18/2.19/2.19		
6	HA-CA	0.0	-1.12/-0.87/-0.86	2.46/2.65/2.65		
7	HL1-CL	0.0	-2.30/-2.55/-2.52	2.63/2.62/2.62		
8	HL2-CL	0.0	-1.11/-0.79/-0.75	2.58/2.68/2.69		
9	HL3-CL	0.0	-2.57/-2.17/-2.07	2.50/2.61/2.61		
10	OL-CLP	0.0	-5.20/-5.61/-5.67	1.83/1.75/1.75		
11	OL-CLP	90.0	-5.19/-5.58/-5.61	1.83/1.76/1.76		
12	OL-CLP	180.0	-4.46/-4.39/-4.36	1.86/1.79/1.80		
13	OL-CLP	270.0	-4.14/-4.37/-4.39	1.86/1.78/1.78		
14	N-CLP	0.0	-2.46/-3.29/-3.51	3.12/2.89/2.85		
15	HB-CB	0.0	-1.46/-1.57/-2.52	2.30/2.57/2.50		
16	HB-CB	90.0	-1.93/-1.75/-2.73	2.22/2.56/2.49		
17	HG-CG	0.0	-2.21/-2.43/-2.96	2.34/2.57/2.52		
18	HG-CG	90.0	-2.42/-2.54/-3.10	2.29/2.56/2.52		
19	HD1-CD	0.0	-1.90/-1.96/-1.82	2.55/2.61/2.62		
20	HD2-CD	0.0	-2.49/-2.73/-2.60	2.77/2.66/2.67		
Geometry 2						
21	O-C	0.0	-6.15/-7.19/-7.26	1.84/1.75/1.75		
22	O-C	90.0	-6.36/-7.14/-7.07	1.83/1.76/1.76		
23	O-C	180.0	-5.62/-6.54/-6.42	1.84/1.76/1.77		
24	O-C	270.0	-5.84/-6.81/-6.81	1.83/1.75/1.76		
25	HR-NR	0.0	-6.67/-7.73/-7.86	1.96/1.90/1.90		
26	HR-NR	45.0	-7.22/-7.91/-8.02	1.93/1.90/1.90		
27	HR-NR	90.0	-7.48/-7.92/-8.02	1.92/1.89/1.89		
28	HR-NR	135.0	-6.94/-7.74/-7.86	1.94/1.90/1.90		
29	HR2-CR	0.0	-1.47/-1.44/-1.45	2.72/2.68/2.68		
30	HR3-CR	0.0	-1.57/-1.59/-1.60	2.70/2.67/2.67		
31	HA-CA	0.0	-3.59/-4.00/-4.00	2.64/2.61/2.61		
32	HL1-CL	0.0	-2.01/-2.20/-2.16	2.66/2.63/2.63		
33	HL2-CL	0.0	-0.61/-0.38/-0.36	2.63/2.70/2.70		
34	OL-CLP	0.0	-6.62/-6.45/-6.48	1.82/1.76/1.76		
35	OL-CLP	90.0	-6.79/-6.65/-6.67	1.82/1.76/1.76		
36	OL-CLP	180.0	-6.34/-6.12/-6.15	1.83/1.77/1.77		
37	OL-CLP	270.0	-6.34/-6.14/-6.19	1.83/1.77/1.77		
38	N-CLP	0.0	-4.49/-5.46/-5.51	3.94/3.70/3.70		
39	N-CLP	90.0	-3.30/-3.33/-3.39	4.10/3.96/3.95		
40	N-CLP	180.0	-2.92/-2.73/-2.75	4.12/4.00/4.00		
41	N-CLP	270.0	-3.37/-4.21/-4.18	4.01/3.76/3.76		
42	N-CLP	0.0	-4.49/-5.46/-5.51	3.94/3.70/3.70		
43	HB-CB	0.0	-2.18/-2.65/-3.59	2.36/2.56/2.49		
44	HB-CB	90.0	-2.59/-2.90/-3.87	2.29/2.55/2.48		
45	HG-CG	0.0	-2.21/-2.21/-2.74	2.32/2.57/2.53		
46	HG-CG	90.0	-2.39/-2.31/-2.87	2.28/2.56/2.52		

1.24 Small molecule used for cis-amclenomyin(ACZ)

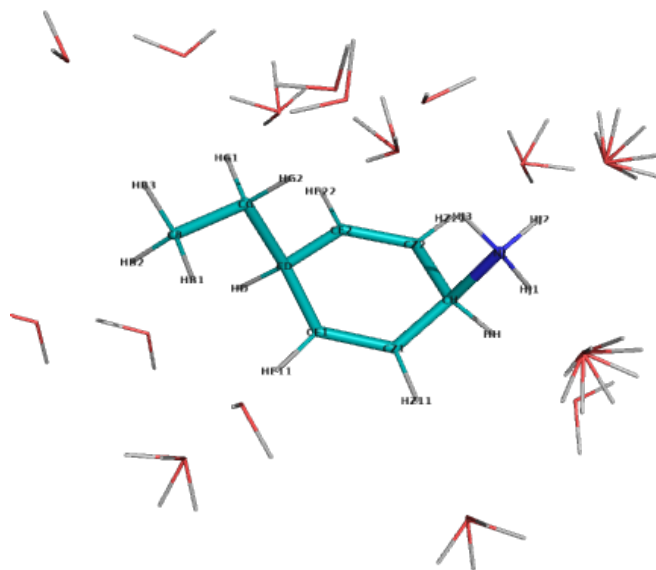


Figure S26: The molecule used for water complex calculations corresponding to (1s,4s)-4-ethylcyclohexa-2,5-dien-1-amine, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S74: Statistics of calculated water interaction and dipole moment for (1s,4s)-4-ethylcyclohexa-2,5-dien-1-amine.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.51/3.66	0.56/1.92	7.352	7.77/11.64	6.28
Optimal	0.82/3.66	0.56/1.96	1.434	7.77/8.06	1.80

Table S75: The comparison list of optimized atomic charges and their initial guess for (1s,4s)-4-ethylcyclohexa-2,5-dien-1-amine, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.269	0.424
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.180	-0.177	6.811
HG1	0.090	0.090	0.424
HG2	0.090	0.090	0.424
CD	0.155	-0.100	8.405
HD	0.090	0.090	0.735
CE1	-0.132	-0.147	8.988
HE11	0.165	0.150	0.997
CE2	-0.132	-0.147	8.988
HE22	0.165	0.150	0.997
CZ1	-0.231	-0.143	60.717
HZ11	0.127	0.150	4.413
CZ2	-0.231	-0.143	60.717
HZ22	0.127	0.150	4.413
CH	0.241	0.280	87.332
HH	0.090	0.090	5.377
NJ	-0.409	-0.374	43.451
HJ1	0.325	0.330	2.985
HJ2	0.325	0.330	2.985
HJ3	0.325	0.330	2.985

Table S76: Interaction energies and geometries between probe water and selected (1s,4s)-4-ethylcyclohexa-2,5-dien-1-amine site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-3.60/-2.99/-2.47		2.56/2.67/2.71	
2	HB1-CB	0.0	-3.70/-3.81/-2.94		2.82/2.75/2.92	
3	HB2-CB	0.0	-3.90/-3.61/-2.56		2.59/2.64/2.70	
4	HG1-CG	0.0	-4.65/-4.46/-3.27		2.53/2.62/2.70	
5	HG2-CG	0.0	-7.43/-6.26/-6.01		3.01/3.21/3.46	
6	HD-CD	0.0	-5.64/-5.34/-3.40		2.37/2.56/2.68	
7	HE11-CE1	0.0	-6.20/-5.96/-5.04		2.34/2.46/2.50	
8	HE11-CE1	90.0	-6.23/-6.03/-5.09		2.34/2.46/2.50	
9	HE22-CE2	0.0	-6.00/-5.94/-5.01		2.32/2.45/2.49	
10	HE22-CE2	90.0	-6.30/-6.03/-5.07		2.29/2.45/2.48	
11	HZ11-CZ1	0.0	-6.53/-6.22/-7.45		2.38/2.49/2.44	
12	HZ11-CZ1	90.0	-6.94/-6.38/-7.61		2.33/2.48/2.43	
13	HZ22-CZ2	0.0	-6.53/-6.25/-7.48		2.38/2.49/2.44	
14	HZ22-CZ2	90.0	-6.94/-6.41/-7.65		2.33/2.48/2.43	
15	HH-CH	0.0	-8.39/-7.41/-8.70		2.24/2.52/2.49	
16	HJ1-NJ	0.0	-16.20/-16.29/-18.08		1.75/1.75/1.74	
17	HJ1-NJ	45.0	-16.44/-16.38/-18.26		1.75/1.75/1.74	
18	HJ1-NJ	90.0	-16.52/-16.40/-18.30		1.74/1.75/1.74	
19	HJ1-NJ	135.0	-16.27/-16.30/-18.12		1.74/1.75/1.74	
20	HJ2-NJ	0.0	-16.21/-16.30/-18.10		1.75/1.75/1.74	
21	HJ2-NJ	45.0	-16.28/-16.31/-18.13		1.74/1.75/1.74	
22	HJ2-NJ	90.0	-16.53/-16.41/-18.32		1.74/1.75/1.74	
23	HJ2-NJ	135.0	-16.45/-16.40/-18.28		1.74/1.75/1.74	
24	HJ3-NJ	0.0	-5.50/-6.07/-6.29		3.33/3.70/3.65	
25	HJ3-NJ	45.0	-6.00/-6.19/-6.31		3.06/3.69/3.64	
26	HJ3-NJ	90.0	-9.88/-6.22/-6.23		1.73/3.69/3.66	
27	HJ3-NJ	135.0	-6.83/-6.10/-6.21		1.75/3.71/3.66	

1.25 Small molecule used for 5-methyl-arginine(AGM)

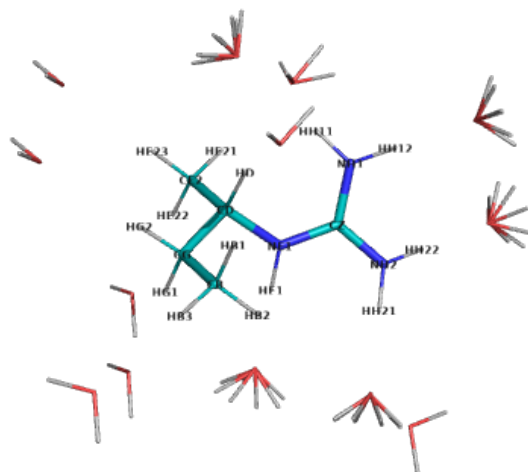


Figure S27: The molecule used for water complex calculations corresponding to N-[(2S)-butan-2-yl]guanidine, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S77: Statistics of calculated water interaction and dipole moment for N-[(2S)-butan-2-yl]guanidine.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	1.44/2.49	0.15/0.36	2.712	5.36/6.65	4.07
Optimal	0.42/1.26	0.15/0.42	1.845	5.36/5.40	6.16

Table S78: The comparison list of optimized atomic charges and their initial guess for N-[(2S)-butan-2-yl]guanidine, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.030
CB	-0.270	-0.262	3.071
HB2	0.090	0.090	0.030
HB1	0.090	0.090	0.030
CG	-0.180	-0.192	9.002
HG1	0.090	0.090	0.303
HG2	0.090	0.090	0.303
CD	0.341	0.262	15.875
HD	0.090	0.090	0.738
NE1	-0.620	-0.706	11.915
HE1	0.356	0.440	0.630
CE2	-0.263	-0.230	13.551
HE21	0.090	0.090	0.925
HE22	0.090	0.090	0.925
HE23	0.090	0.090	0.925
CZ	0.706	0.638	1.989
NH2	-0.706	-0.800	0.030
HH22	0.385	0.460	0.000
HH21	0.385	0.460	0.000
NH1	-0.706	-0.800	0.030
HH12	0.381	0.460	0.000
HH11	0.381	0.460	0.000

Table S79: Interaction energies and geometries between probe water and selected N-[(2S)-butan-2-yl]guanidine site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial		
1	HB3-CB	0.0	-4.02/-3.36/-3.16	2.51/2.64/2.65		
2	HB2-CB	0.0	-4.85/-4.79/-4.79	4.10/4.12/4.27		
3	HB1-CB	0.0	-3.76/-3.94/-3.43	2.67/2.67/2.71		
4	HG1-CG	0.0	-5.81/-5.46/-5.16	2.47/2.59/2.61		
5	HG2-CG	0.0	-5.12/-4.85/-4.38	2.46/2.59/2.61		
6	HD-CD	0.0	-6.40/-7.67/-6.85	2.57/2.57/2.61		
7	HE1-NE1	0.0	-12.41/-13.02/-14.12	1.88/1.84/1.80		
8	HE1-NE1	45.0	-12.84/-13.23/-14.33	1.87/1.83/1.80		
9	HE1-NE1	90.0	-14.04/-13.85/-15.08	1.84/1.82/1.79		
10	HE1-NE1	135.0	-13.63/-13.66/-14.89	1.85/1.82/1.79		
11	HE21-CE2	0.0	-5.42/-6.02/-5.77	2.67/2.63/2.65		
12	HE22-CE2	0.0	-4.99/-5.06/-4.80	2.54/2.59/2.60		
13	HE23-CE2	0.0	-5.18/-5.13/-4.89	2.44/2.55/2.56		
14	HH22-NH2	0.0	-13.03/-13.41/-15.23	1.83/1.80/1.77		
15	HH22-NH2	45.0	-13.03/-13.41/-15.21	1.83/1.80/1.77		
16	HH22-NH2	90.0	-14.02/-13.87/-15.79	1.80/1.80/1.76		
17	HH22-NH2	135.0	-14.00/-13.87/-15.81	1.80/1.80/1.76		
18	HH21-NH2	0.0	-12.86/-13.53/-15.35	1.84/1.80/1.77		
19	HH21-NH2	45.0	-13.20/-13.67/-15.46	1.83/1.80/1.77		
20	HH21-NH2	90.0	-14.20/-14.11/-15.99	1.80/1.79/1.76		
21	HH21-NH2	135.0	-13.85/-13.97/-15.88	1.81/1.80/1.76		
22	HH12-NH1	0.0	-13.11/-13.33/-15.15	1.83/1.81/1.77		
23	HH12-NH1	45.0	-13.14/-13.34/-15.16	1.83/1.81/1.77		
24	HH12-NH1	90.0	-14.14/-13.82/-15.77	1.80/1.80/1.76		
25	HH12-NH1	135.0	-14.10/-13.81/-15.75	1.80/1.80/1.76		
26	HH11-NH1	0.0	-7.70/-7.92/-8.18	2.32/2.74/2.68		
27	HH11-NH1	45.0	-7.48/-8.06/-8.39	2.32/2.73/2.67		
28	HH11-NH1	90.0	-7.88/-8.43/-8.71	2.35/2.71/2.65		
29	HH11-NH1	135.0	-8.22/-8.30/-8.52	2.34/2.72/2.67		

1.26 Small molecule A of
 S-(S)-amino[(4-aminobutyl)amino]methyl-L-cysteine(AGT)

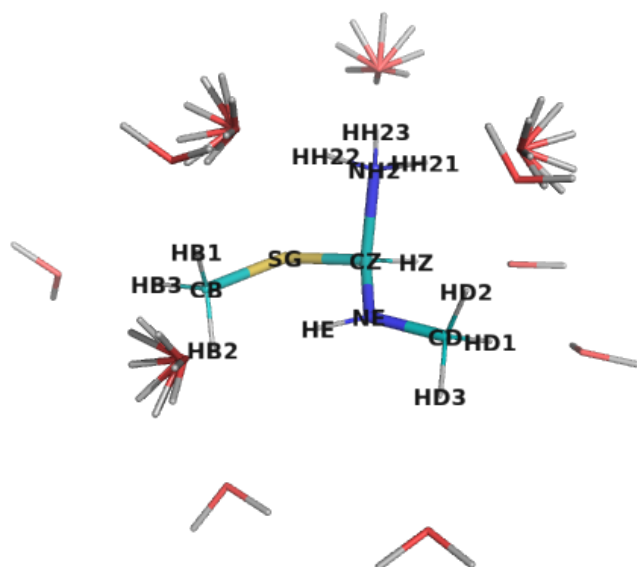


Figure S28: The molecule used for water complex calculations corresponding to [(S)-amino(methylsulfanyl)methyl](methyl)amine, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S80: Statistics of calculated water interaction and dipole moment for [(S)-amino(methylsulfanyl)methyl](methyl)amine.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	2.66/4.13	0.15/0.34	7.602	5.62/8.16	19.80
Optimal	0.51/1.57	0.13/0.31	2.106	5.62/5.89	2.75

Table S81: The comparison list of optimized atomic charges and their initial guess for [(S)-amino(methylsulfanyl)methyl](methyl)amine, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.850
CB	-0.027	-0.220	11.408
HB1	0.090	0.090	0.850
HB2	0.090	0.090	0.850
SG	-0.215	-0.076	115.754
CZ	0.424	0.484	187.553
HZ	0.159	0.090	7.361
NH2	-0.432	-0.318	54.685
HH21	0.300	0.330	3.377
HH22	0.300	0.330	3.377
HH23	0.300	0.330	3.377
NE	-0.672	-0.733	137.988
HE	0.340	0.380	7.984
CD	-0.017	-0.137	13.840
HD1	0.090	0.090	1.195
HD2	0.090	0.090	1.195
HD3	0.090	0.090	1.195

Table S82: Interaction energies and geometries between probe water and selected [(S)-amino(methylsulfanyl)methyl](methyl)amine site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial		
1	HB3-CB	0.0	-6.56/-4.99/-4.10	2.25/2.53/2.59		
2	HB1-CB	0.0	-8.20/-7.60/-7.26	2.46/2.56/2.62		
3	HB2-CB	0.0	-5.86/-5.77/-4.90	2.37/2.52/2.56		
4	HZ-CZ	0.0	-9.96/-9.08/-8.79	2.16/2.46/2.48		
5	HH21-NH2	0.0	-14.62/-14.40/-17.64	1.83/1.83/1.76		
6	HH21-NH2	45.0	-15.05/-14.84/-17.80	1.83/1.82/1.76		
7	HH21-NH2	90.0	-14.76/-14.84/-17.75	1.84/1.82/1.76		
8	HH21-NH2	135.0	-14.21/-14.38/-17.55	1.84/1.83/1.76		
9	HH22-NH2	0.0	-13.85/-14.14/-17.98	1.86/1.82/1.75		
10	HH22-NH2	45.0	-15.10/-14.82/-18.36	1.84/1.81/1.75		
11	HH22-NH2	90.0	-15.75/-15.18/-18.65	1.82/1.81/1.75		
12	HH22-NH2	135.0	-14.62/-14.53/-18.30	1.84/1.82/1.75		
13	HH23-NH2	0.0	-15.47/-15.54/-19.34	1.75/1.77/1.72		
14	HH23-NH2	45.0	-15.84/-15.64/-19.42	1.74/1.76/1.72		
15	HH23-NH2	90.0	-15.56/-15.48/-19.36	1.75/1.77/1.72		
16	HH23-NH2	135.0	-15.20/-15.39/-19.28	1.76/1.77/1.72		
17	HE-NE	0.0	-7.99/-8.01/-7.34	2.54/2.74/2.71		
18	HE-NE	45.0	-8.16/-8.10/-7.50	2.52/2.73/2.69		
19	HE-NE	90.0	-8.09/-8.40/-7.48	2.60/2.70/2.69		
20	HE-NE	135.0	-7.94/-8.31/-7.33	2.61/2.70/2.71		
21	HD1-CD	0.0	-6.55/-6.22/-5.22	2.40/2.54/2.60		
22	HD2-CD	0.0	-7.08/-6.93/-6.52	2.51/2.57/2.64		
23	HD3-CD	0.0	-5.95/-4.85/-3.86	2.35/2.56/2.62		

1.27 Small molecule used for beta-hydroxyasparagine(AHB)

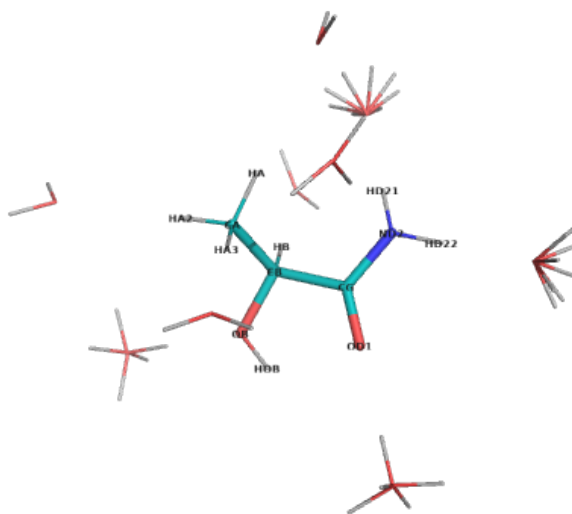


Figure S29: The molecule used for water complex calculations corresponding to (2S)-2-hydroxypropanamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S83: Statistics of calculated water interaction and dipole moment for (2S)-2-hydroxypropanamide.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.45/0.81	0.07/0.19	2.012	4.49/5.05	1.04
Optimal	0.28/0.49	0.07/0.25	2.406	4.49/5.22	1.81

Table S84: The comparison list of optimized atomic charges and their initial guess for (2S)-2-hydroxypropanamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.268	0.050
HA	0.090	0.090	0.000
CB	0.209	0.165	22.240
HB	0.090	0.090	0.050
OB	-0.609	-0.623	22.694
HOB	0.308	0.369	1.783
CG	0.495	0.540	12.508
OD1	-0.471	-0.534	1.525
ND2	-0.688	-0.629	18.343
HD21	0.333	0.310	0.262
HD22	0.333	0.310	0.262

Table S85: Interaction energies and geometries between probe water and selected (2S)-2-hydroxypropanamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.92/-0.63/-0.68		2.61/2.66/2.66	
2	HA2-CA	0.0	-0.65/-0.34/-0.28		2.75/2.75/2.77	
3	HA-CA	0.0	-2.08/-2.44/-2.44		2.72/2.66/2.66	
4	HB-CB	0.0	-2.05/-2.43/-2.31		2.58/2.62/2.63	
5	OB-CB	0.0	-6.18/-6.31/-6.15		1.84/1.86/1.86	
6	OB-CB	90.0	-5.89/-5.87/-5.84		1.83/1.86/1.86	
7	OB-CB	180.0	-5.06/-5.04/-5.15		1.86/1.88/1.87	
8	OB-CB	270.0	-5.98/-5.71/-5.68		1.83/1.87/1.87	
9	OD1-CG	0.0	-4.81/-5.19/-5.62		1.89/1.80/1.78	
10	OD1-CG	90.0	-5.03/-5.06/-5.70		1.87/1.80/1.77	
11	OD1-CG	180.0	-4.91/-4.82/-5.62		1.87/1.80/1.76	
12	OD1-CG	270.0	-5.02/-5.08/-5.76		1.87/1.79/1.77	
13	ND2-CG	0.0	-0.67/-0.27/-0.00		2.48/2.35/2.43	
14	ND2-CG	180.0	-1.42/-1.52/-1.21		2.51/2.26/2.32	
15	HD21-ND2	0.0	-7.16/-7.65/-7.44		1.88/1.87/1.88	
16	HD21-ND2	45.0	-7.25/-7.68/-7.46		1.88/1.87/1.88	
17	HD21-ND2	90.0	-7.59/-7.82/-7.58		1.86/1.87/1.88	
18	HD21-ND2	135.0	-7.51/-7.79/-7.56		1.86/1.87/1.88	
19	HD22-ND2	0.0	-6.10/-5.74/-5.49		1.84/1.87/1.88	
20	HD22-ND2	45.0	-5.90/-5.59/-5.32		1.84/1.88/1.89	
21	HD22-ND2	90.0	-5.70/-5.47/-5.19		1.85/1.88/1.89	
22	HD22-ND2	135.0	-5.88/-5.61/-5.35		1.85/1.88/1.89	

1.28 Small molecule used for (3S)-3-(sulfooxy)-L-serine(ALS)

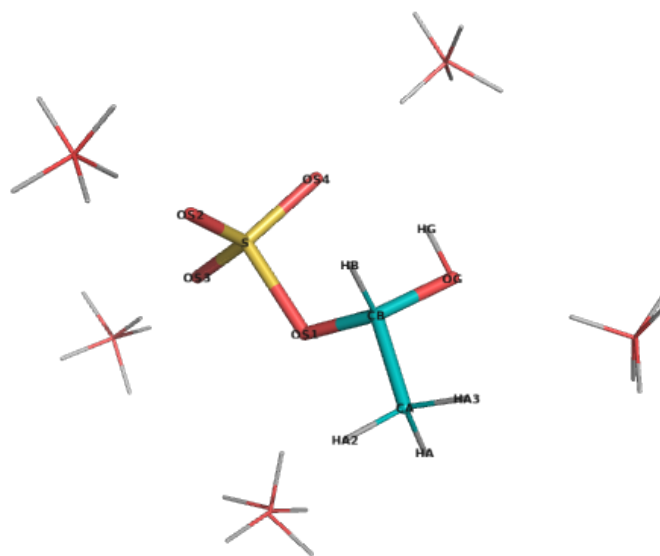


Figure S30: The molecule used for water complex calculations corresponding to [(1S)-1-hydroxyethoxy]sulfonic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S86: Statistics of calculated water interaction and dipole moment for [(1S)-1-hydroxyethoxy]sulfonic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.43/2.51	0.13/0.17	5.756	5.04/2.97	21.08
Optimal	0.27/0.58	0.15/0.28	3.583	5.04/3.54	1.72

Table S87: The comparison list of optimized atomic charges and their initial guess for [(1S)-1-hydroxyethoxy]sulfonicacid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.271	2.620
HA	0.090	0.090	0.000
CB	0.059	-0.039	8.625
HB	0.090	0.090	0.300
OG	-0.585	-0.658	9.244
HG	0.399	0.413	0.750
OS1	-0.285	-0.184	7.568
S	0.873	1.329	2.549
OS2	-0.517	-0.650	0.030
OS3	-0.517	-0.650	0.030
OS4	-0.517	-0.650	0.030

Table S88: Interaction energies and geometries between probe water and selected [(1S)-1-hydroxyethoxy]sulfonicacid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	OG-CB	0.0	-8.75/-8.50/-9.77	1.86/1.86/1.83
2	OG-CB	90.0	-8.57/-8.42/-9.88	1.85/1.85/1.82
3	OG-CB	180.0	-8.40/-8.98/-10.36	1.88/1.84/1.81
4	OG-CB	270.0	-9.22/-9.27/-10.40	1.84/1.84/1.82
5	OS1-CB	0.0	-9.95/-9.99/-7.44	2.00/1.77/1.87
6	OS1-CB	90.0	-8.12/-8.30/-6.22	2.04/1.80/1.91
7	OS1-CB	180.0	-6.29/-6.47/-4.76	2.12/1.83/1.94
8	OS1-CB	270.0	-7.56/-7.35/-5.12	2.06/1.82/1.95
9	OS2-S	0.0	-9.25/-9.63/-10.47	1.86/1.74/1.71
10	OS2-S	90.0	-9.40/-9.63/-10.67	1.86/1.74/1.71
11	OS2-S	180.0	-9.63/-9.65/-10.50	1.85/1.74/1.71
12	OS2-S	270.0	-9.64/-9.70/-10.39	1.85/1.74/1.71
13	OS3-S	0.0	-9.56/-9.91/-10.46	1.86/1.74/1.71
14	OS3-S	90.0	-9.48/-9.71/-10.37	1.86/1.74/1.71
15	OS3-S	180.0	-9.41/-9.60/-10.43	1.86/1.74/1.71
16	OS3-S	270.0	-9.54/-9.81/-10.56	1.86/1.74/1.71
17	OS4-S	0.0	-7.87/-8.28/-9.54	1.90/1.77/1.73
18	OS4-S	90.0	-8.32/-8.47/-9.23	1.85/1.74/1.71
19	OS4-S	180.0	-7.95/-8.43/-9.16	1.87/1.74/1.71
20	OS4-S	270.0	-8.14/-8.34/-9.45	1.86/1.75/1.72

1.29 Small molecule A of 5'-O-[(S)-[(5S)-5-amino-6-oxohexyl]amino(hydroxy)phosphoryl]adenosine(APK)

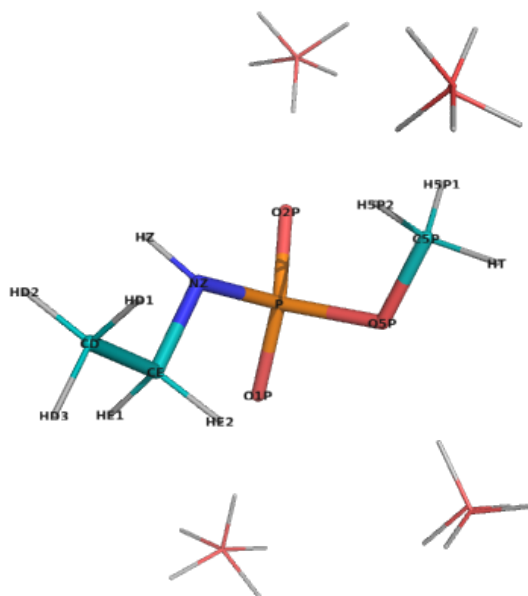


Figure S31: The molecule used for water complex calculations corresponding to (ethylamino)(methoxy)phosphinic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S89: Statistics of calculated water interaction and dipole moment for (ethylamino)(methoxy)phosphinic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.10/0.19	0.14/0.24	3.513	7.28/6.19	2.07
Optimal	0.42/0.78	0.20/0.39	3.222	7.28/6.12	2.46

Table S90: The comparison list of optimized atomic charges and their initial guess for (ethylamino)(methoxy)phosphinicacid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HD3	0.090	0.090	0.000
CD	-0.346	-0.270	1.000
HD1	0.090	0.090	0.000
HD2	0.090	0.090	0.000
CE	-0.049	-0.111	4.194
HE1	0.090	0.090	0.450
HE2	0.090	0.090	0.450
NZ	-0.746	-0.847	4.197
HZ	0.330	0.330	0.000
P	1.287	1.568	1.324
O1P	-0.785	-0.820	0.045
O2P	-0.785	-0.820	0.045
O5P	-0.463	-0.561	0.418
C5P	-0.163	-0.189	0.000
H5P1	0.090	0.090	0.000
H5P2	0.090	0.090	0.000
HT	0.090	0.090	0.000

Table S91: Interaction energies and geometries between probe water and selected (ethylamino)(methoxy)phosphinicacid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	NZ-CE	0.0	-2.96/-3.53/-2.89		4.24/3.91/4.07	
2	NZ-CE	90.0	-2.05/-2.63/-1.95		4.33/3.96/4.12	
3	NZ-CE	180.0	-2.22/-3.00/-2.26		4.31/3.92/4.07	
4	NZ-CE	270.0	-3.14/-3.84/-3.27		4.23/3.89/4.01	
5	O1P-P	0.0	-13.41/-13.73/-13.51		1.75/1.66/1.66	
6	O1P-P	90.0	-13.82/-14.00/-13.82		1.75/1.65/1.66	
7	O1P-P	180.0	-14.14/-14.40/-14.12		1.75/1.65/1.65	
8	O1P-P	270.0	-13.87/-14.25/-13.90		1.75/1.65/1.65	
9	O2P-P	0.0	-13.37/-13.49/-13.45		1.75/1.66/1.66	
10	O2P-P	90.0	-13.45/-13.70/-13.64		1.75/1.65/1.66	
11	O2P-P	180.0	-14.04/-14.21/-14.00		1.74/1.65/1.65	
12	O2P-P	270.0	-13.86/-13.95/-13.78		1.74/1.65/1.66	
13	O5P-P	0.0	-7.72/-7.25/-7.55		1.91/1.76/1.75	
14	O5P-P	90.0	-9.02/-9.33/-9.02		1.88/1.73/1.73	
15	O5P-P	180.0	-12.80/-13.29/-12.93		1.81/1.68/1.68	
16	O5P-P	270.0	-9.83/-9.78/-9.90		1.87/1.73/1.72	

1.30 Small molecule used for c-gamma-hydroxyarginine(ARO)

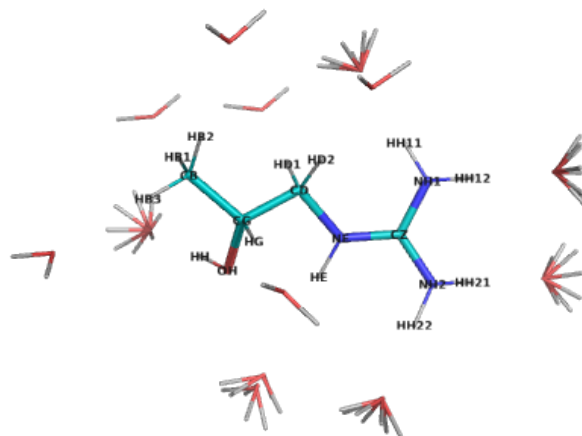


Figure S32: The molecule used for water complex calculations corresponding to N-[(2R)-2-hydroxypropyl]guanidine, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S92: Statistics of calculated water interaction and dipole moment for N-[(2R)-2-hydroxypropyl]guanidine.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.52/2.41	0.12/0.37	3.225	6.04/7.59	2.54
Optimal	0.26/0.61	0.11/0.36	1.320	6.04/5.87	2.12

Table S93: The comparison list of optimized atomic charges and their initial guess for N-[(2R)-2-hydroxypropyl]guanidine, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.300
CB	-0.270	-0.270	3.009
HB1	0.090	0.090	0.300
HB2	0.090	0.090	0.300
CG	0.273	0.139	4.744
HG	0.090	0.090	0.300
OH	-0.596	-0.645	2.500
HH	0.385	0.419	0.000
CD	0.064	0.200	4.150
HD1	0.090	0.090	0.045
HD2	0.090	0.090	0.045
NE	-0.681	-0.700	3.838
HE	0.411	0.440	0.030
CZ	0.746	0.637	0.030
NH1	-0.689	-0.800	0.000
HH11	0.377	0.460	0.000
HH12	0.377	0.460	0.000
NH2	-0.689	-0.800	0.000
HH21	0.376	0.460	0.000
HH22	0.376	0.460	0.000

Table S94: Interaction energies and geometries between probe water and selected N-[(2R)-2-hydroxypropyl]guanidine site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-4.32/-3.84/-3.30		2.45/2.59/2.62	
2	HB1-CB	0.0	-5.21/-5.15/-4.92		2.49/2.57/2.59	
3	HB2-CB	0.0	-4.52/-4.54/-4.23		2.52/2.60/2.62	
4	HG-CG	0.0	-4.77/-5.04/-4.18		2.48/2.59/2.64	
5	HH-OH	0.0	-10.17/-10.40/-10.35		1.85/1.84/1.83	
6	HH-OH	45.0	-10.32/-10.47/-10.37		1.85/1.83/1.82	
7	HH-OH	90.0	-10.65/-10.62/-10.55		1.85/1.83/1.82	
8	HH-OH	135.0	-10.54/-10.57/-10.54		1.85/1.83/1.82	
9	HD1-CD	0.0	-6.52/-6.68/-6.99		2.44/2.55/2.54	
10	HD2-CD	0.0	-6.78/-7.02/-7.18		2.42/2.56/2.55	
11	HE-NE	0.0	-4.65/-4.72/-4.39		2.69/3.05/3.06	
12	HE-NE	45.0	-3.93/-4.53/-4.15		3.01/3.10/3.14	
13	HE-NE	90.0	-4.55/-4.85/-4.51		2.93/3.06/3.08	
14	HE-NE	135.0	-5.37/-5.05/-4.76		2.65/3.01/3.02	
15	HH11-NH1	0.0	-11.38/-11.57/-13.54		1.92/1.92/1.87	
16	HH11-NH1	45.0	-11.69/-11.66/-13.67		1.91/1.92/1.87	
17	HH11-NH1	90.0	-12.32/-12.42/-14.59		1.91/1.91/1.85	
18	HH11-NH1	135.0	-12.08/-12.35/-14.48		1.91/1.91/1.85	
19	HH12-NH1	0.0	-12.97/-13.29/-15.13		1.83/1.81/1.77	
20	HH12-NH1	45.0	-13.09/-13.34/-15.19		1.83/1.81/1.77	
21	HH12-NH1	90.0	-14.11/-13.83/-15.80		1.80/1.80/1.76	
22	HH12-NH1	135.0	-13.99/-13.78/-15.74		1.80/1.80/1.76	
23	HH21-NH2	0.0	-12.86/-13.24/-15.07		1.84/1.81/1.77	
24	HH21-NH2	45.0	-12.87/-13.25/-15.07		1.84/1.81/1.77	
25	HH21-NH2	90.0	-13.87/-13.72/-15.66		1.80/1.80/1.76	
26	HH21-NH2	135.0	-13.84/-13.71/-15.66		1.80/1.80/1.76	
27	HH22-NH2	0.0	-13.14/-13.47/-15.42		1.82/1.80/1.76	
28	HH22-NH2	45.0	-13.32/-13.50/-15.39		1.81/1.80/1.76	
29	HH22-NH2	90.0	-13.94/-13.73/-15.62		1.79/1.79/1.75	
30	HH22-NH2	135.0	-13.72/-13.70/-15.64		1.80/1.79/1.75	

1.31 Small molecule used for asparticacid-4-carboxymethylester(ASB)

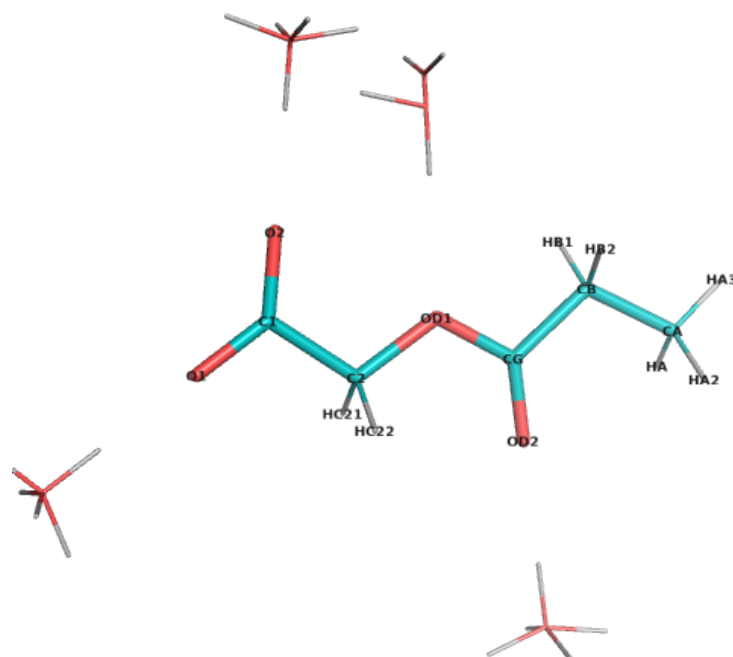


Figure S33: The molecule used for water complex calculations corresponding to 2-(propanoyloxy)acetic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S95: Statistics of calculated water interaction and dipole moment for 2-(propanoyloxy)acetic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.50/3.13	0.13/0.31	4.255	12.47/14.55	2.58
Optimal	0.59/1.28	0.11/0.25	3.110	12.47/12.17	4.51

Table S96: The comparison list of optimized atomic charges and their initial guess for 2-(propanoyloxy)acetic acid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.269	0.000
HA	0.090	0.090	0.000
CB	-0.340	-0.220	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.826	0.908	2.500
OD2	-0.550	-0.642	0.000
OD1	-0.379	-0.472	3.629
C2	-0.100	0.021	4.338
HC21	0.090	0.090	0.000
HC22	0.090	0.090	0.000
C1	0.597	0.564	4.409
O1	-0.707	-0.760	0.325
O2	-0.707	-0.760	0.325

Table S97: Interaction energies and geometries between probe water and selected 2-(propanoyloxy)acetic acid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	OD2-CG	0.0	-6.69/-6.64/-7.41		1.90/1.77/1.73	
2	OD2-CG	90.0	-7.35/-7.58/-8.52		1.90/1.76/1.73	
3	OD2-CG	180.0	-8.44/-8.75/-9.83		1.88/1.75/1.72	
4	OD2-CG	270.0	-7.34/-7.57/-8.51		1.90/1.76/1.73	
5	OD1-CG	0.0	-14.66/-15.67/-17.79		2.08/1.83/1.77	
6	OD1-CG	90.0	-6.70/-5.42/-5.52		2.55/2.55/2.52	
7	OD1-CG	270.0	-6.69/-5.40/-5.51		2.55/2.55/2.53	
8	O1-C1	0.0	-13.32/-12.76/-13.86		1.73/1.67/1.66	
9	O1-C1	90.0	-13.53/-13.25/-14.53		1.73/1.67/1.65	
10	O1-C1	180.0	-13.99/-13.83/-15.29		1.72/1.66/1.64	
11	O1-C1	270.0	-13.53/-13.25/-14.53		1.73/1.67/1.65	
12	O2-C1	0.0	-13.39/-13.63/-14.69		1.74/1.67/1.65	
13	O2-C1	90.0	-13.46/-13.78/-15.24		1.74/1.67/1.65	
14	O2-C1	180.0	-13.88/-14.11/-15.87		1.73/1.66/1.64	
15	O2-C1	270.0	-13.46/-13.78/-15.24		1.74/1.67/1.65	

1.32 The dipeptide of N-acetylalanine (AYA)

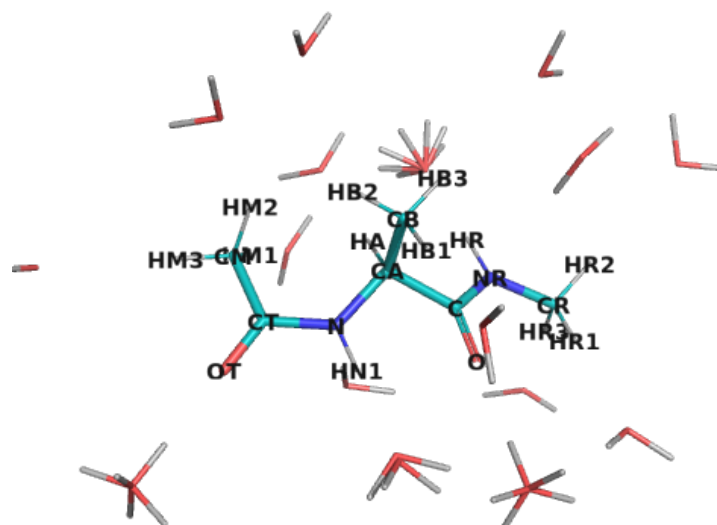


Figure S34: The molecule used for water complex calculations corresponding to (2S)-2-[(1S)-1-hydroxyethyl]amino-N-methylpropanamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S98: Statistics of calculated water interaction and dipole moment for (2S)-2-[(1S)-1-hydroxyethyl]amino-N-methylpropanamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.46/0.89	0.07/0.14	1.413	7.40/7.26	2.56
Optimal	0.43/0.83	0.07/0.14	1.379	7.40/7.24	2.16

Table S99: The comparison list of optimized atomic charges and their initial guess for (2S)-2-[(1S)-1-hydroxyethyl]amino-N-methylpropanamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CM	-0.270	-0.270	0.000
HM1	0.090	0.090	0.000
HM2	0.090	0.090	0.000
HM3	0.090	0.090	0.000
CT	0.510	0.512	0.000
OT	-0.510	-0.510	0.000
N	-0.470	-0.467	0.000
HN1	0.310	0.307	0.000
CA	0.070	0.071	0.000
HA	0.090	0.090	0.000
CB	-0.270	-0.269	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
HB3	0.090	0.090	0.000
C	0.510	0.509	0.000
O	-0.510	-0.513	0.000
NR	-0.470	-0.474	0.000
HR	0.310	0.312	0.000
CR	-0.110	-0.108	0.000
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S100: Interaction energies and geometries between probe water and selected (2S)-2-[(1S)-1-hydroxyethyl]amino-N-methylpropanamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	O-C	0.0	-5.41/-5.90/-5.97	1.86/1.77/1.77
2	O-C	90.0	-5.54/-6.04/-6.12	1.85/1.77/1.76
3	O-C	180.0	-4.91/-5.73/-5.80	1.86/1.76/1.76
4	O-C	270.0	-5.07/-5.79/-5.86	1.85/1.76/1.76
5	NR-C	0.0	-0.02/-0.27/-0.29	2.56/2.52/2.52
6	HR-NR	0.0	-6.63/-7.46/-7.48	1.94/1.90/1.90
7	HR-NR	45.0	-7.17/-7.68/-7.70	1.92/1.89/1.89
8	HR-NR	90.0	-7.64/-7.89/-7.92	1.90/1.89/1.89
9	HR-NR	135.0	-7.12/-7.68/-7.70	1.92/1.89/1.89
10	HR2-CR	0.0	-1.69/-1.61/-1.61	2.68/2.67/2.67
11	HR3-CR	0.0	-1.52/-1.46/-1.46	2.68/2.66/2.67
12	HA-CA	0.0	-3.27/-4.04/-4.06	2.79/2.69/2.69
13	N-CT	0.0	-1.50/-1.66/-1.68	2.23/2.25/2.25
14	HN1-N	0.0	-2.38/-2.10/-2.03	1.87/2.01/2.01
15	HN1-N	135.0	-0.79/-1.37/-1.30	2.00/2.05/2.06
16	HM1-CM	0.0	-2.05/-2.02/-2.04	2.61/2.67/2.66
17	HM2-CM	0.0	-1.78/-1.89/-1.91	3.21/3.21/3.21
18	HM3-CM	0.0	-0.62/-0.29/-0.30	2.63/2.72/2.71
19	OT-CT	0.0	-6.35/-6.22/-6.20	1.83/1.77/1.77
20	OT-CT	90.0	-6.51/-6.38/-6.37	1.83/1.77/1.77
21	OT-CT	180.0	-6.63/-6.47/-6.47	1.83/1.77/1.77
22	OT-CT	270.0	-6.43/-6.34/-6.33	1.83/1.77/1.77
23	HB1-CB	0.0	-1.30/-0.85/-0.84	2.47/2.61/2.61
24	HB2-CB	0.0	-2.11/-2.04/-2.05	2.79/2.76/2.76
25	HB3-CB	0.0	-1.39/-1.81/-1.81	2.79/2.68/2.68

1.33 Small molecule used for azido-alanine(AZDA)

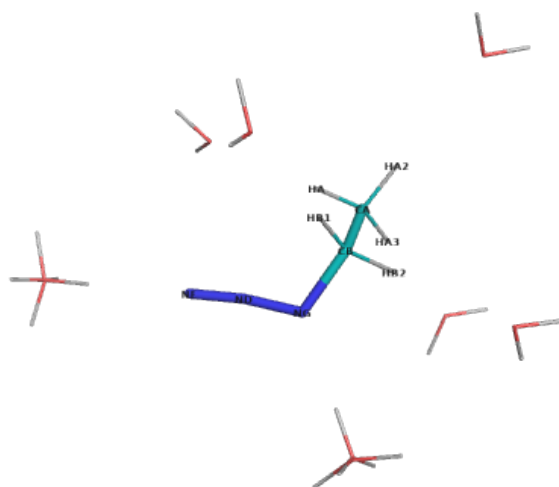


Figure S35: The molecule used for water complex calculations corresponding to 1-ethyl-2-azidoethane, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S101: Statistics of calculated water interaction and dipole moment for 1-ethyl-2-azidoethane.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	-/-	-/-	-	-/-	-
Optimal	0.18/0.33	0.10/0.17	1.626	2.40/2.79	4.73

Table S102: The comparison list of optimized atomic charges and their initial guess for 1-ethyl-2- λ -triazol-1,2-diene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	-	
HA2	0.090	-	
CA	-0.270	-	
HA	0.090	-	
CB	0.117	-	
HB1	0.090	-	
HB2	0.090	-	
NG	-0.525	-	
ND	0.489	-	
NE	-0.261	-	

Table S103: Interaction energies and geometries between probe water and selected 1-ethyl-2- λ -triazol-1,2-diene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	NG-CB	0.0	-4.49/-4.65/-		2.01/1.93/-	
2	NG-CB	90.0	-4.47/-4.45/-		1.98/1.92/-	
3	NG-CB	180.0	-3.88/-3.93/-		2.02/1.94/-	
4	NG-CB	270.0	-4.56/-4.33/-		1.98/1.93/-	
5	NE-ND	0.0	-2.02/-2.24/-		2.26/2.09/-	
6	NE-ND	90.0	-1.94/-2.02/-		2.26/2.10/-	
7	NE-ND	180.0	-1.71/-1.80/-		2.28/2.11/-	
8	NE-ND	270.0	-1.92/-2.03/-		2.26/2.10/-	
9	HA3-CA	0.0	-1.12/-0.80/-		2.68/2.70/-	
10	HA2-CA	0.0	-1.42/-1.50/-		2.71/2.68/-	
11	HA-CA	0.0	-1.51/-1.52/-		2.62/2.63/-	
12	HB1-CB	0.0	-1.73/-2.06/-		2.62/2.61/-	
13	HB2-CB	0.0	-1.46/-1.27/-		2.60/2.67/-	

1.34 Small molecule used for azidohomoalanine(AZH)

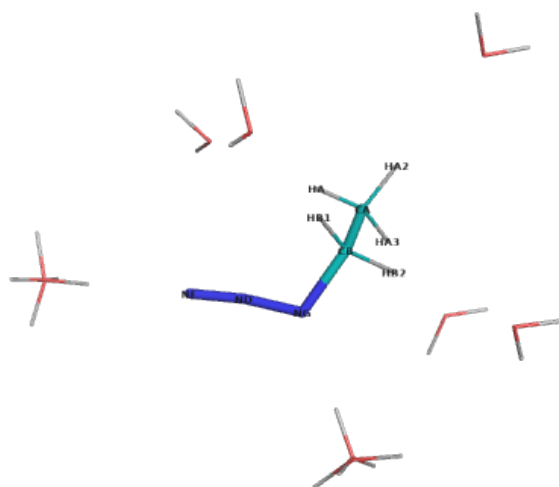


Figure S36: The molecule used for water complex calculations corresponding to 1-ethyl-2-lambda4-triazole-1,2-diene, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S104: Statistics of calculated water interaction and dipole moment for 1-ethyl-2-lambda4-triazole-1,2-diene.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	-/-	-/-	-	-/-	-
Optimal	0.18/0.33	0.10/0.17	1.626	2.40/2.79	4.73

Table S105: The comparison list of optimized atomic charges and their initial guess for 1-ethyl-2- λ -triazol-1,2-diene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	-	
HA2	0.090	-	
CA	-0.270	-	
HA	0.090	-	
CB	0.117	-	
HB1	0.090	-	
HB2	0.090	-	
NG	-0.525	-	
ND	0.489	-	
NE	-0.261	-	

Table S106: Interaction energies and geometries between probe water and selected 1-ethyl-2- λ -triazol-1,2-diene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	NG-CB	0.0	-4.49/-4.65/-		2.01/1.93/-	
2	NG-CB	90.0	-4.47/-4.45/-		1.98/1.92/-	
3	NG-CB	180.0	-3.88/-3.93/-		2.02/1.94/-	
4	NG-CB	270.0	-4.56/-4.33/-		1.98/1.93/-	
5	NE-ND	0.0	-2.02/-2.24/-		2.26/2.09/-	
6	NE-ND	90.0	-1.94/-2.02/-		2.26/2.10/-	
7	NE-ND	180.0	-1.71/-1.80/-		2.28/2.11/-	
8	NE-ND	270.0	-1.92/-2.03/-		2.26/2.10/-	
9	HA3-CA	0.0	-1.12/-0.80/-		2.68/2.70/-	
10	HA2-CA	0.0	-1.42/-1.50/-		2.71/2.68/-	
11	HA-CA	0.0	-1.51/-1.52/-		2.62/2.63/-	
12	HB1-CB	0.0	-1.73/-2.06/-		2.62/2.61/-	
13	HB2-CB	0.0	-1.46/-1.27/-		2.60/2.67/-	

1.35 Small molecule A of Chromophore(Thr, Trp, Gly)(B2H)

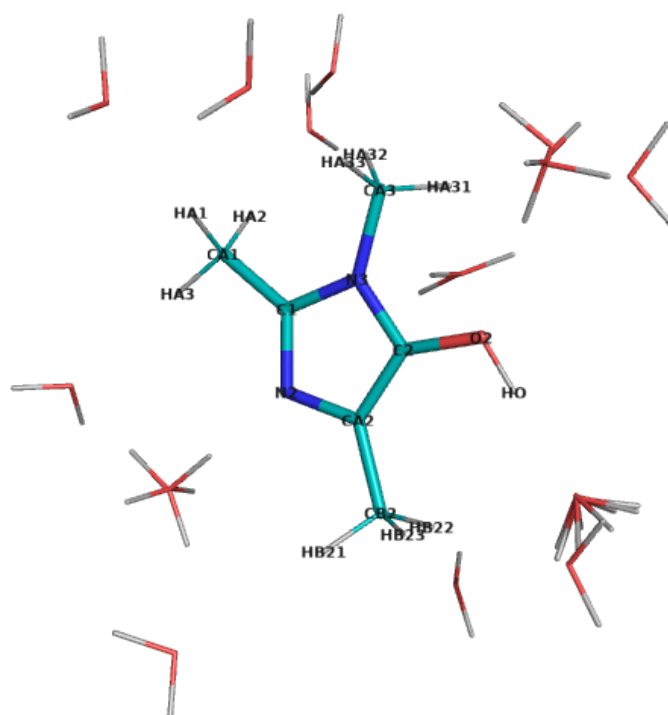


Figure S37: The molecule used for water complex calculations corresponding to trimethyl-1H-imidazol-5-ol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S107: Statistics of calculated water interaction and dipole moment for trimethyl-1H-imidazol-5-ol.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.92/1.99	0.12/0.25	3.944	2.69/1.12	16.07
Optimal	0.27/0.51	0.07/0.14	2.347	2.69/3.46	1.48

Table S108: The comparison list of optimized atomic charges and their initial guess for trimethyl-1H-imidazol-5-ol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA1	-0.229	-0.113	14.764
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
HA3	0.090	0.090	0.000
C1	0.379	0.239	26.194
N2	-0.700	-0.679	20.607
N3	-0.040	-0.042	33.417
CA2	0.165	0.325	33.412
C2	0.104	0.071	73.413
O2	-0.504	-0.554	65.809
HO	0.432	0.420	4.985
CB2	-0.270	-0.246	6.867
HB21	0.090	0.090	0.450
HB22	0.090	0.090	0.450
HB23	0.090	0.090	0.450
CA3	-0.147	-0.231	3.536
HA31	0.090	0.090	0.000
HA32	0.090	0.090	0.000
HA33	0.090	0.090	0.000

Table S109: Interaction energies and geometries between probe water and selected trimethyl-1H-imidazol-5-ol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA1-CA1	0.0	-1.45/-1.66/-1.80		2.67/2.64/2.61	
2	HA2-CA1	0.0	-1.56/-1.69/-1.84		2.63/2.64/2.61	
3	N2-C1	0.0	-7.90/-8.33/-7.36		1.89/1.89/1.90	
4	N2-C1	90.0	-8.35/-8.07/-7.42		1.86/1.89/1.90	
5	N2-C1	180.0	-7.33/-7.26/-6.73		1.91/1.91/1.91	
6	N2-C1	270.0	-8.37/-8.04/-7.40		1.86/1.89/1.90	
7	N3-C1	0.0	-0.63/-0.73/-2.25		2.56/2.47/2.31	
8	N3-C1	180.0	-1.70/-2.21/-2.59		2.48/2.37/2.31	
9	O2-C2	0.0	-3.08/-3.12/-3.61		2.05/2.19/2.17	
10	O2-C2	90.0	-2.09/-2.25/-3.34		2.20/2.22/2.18	
11	O2-C2	180.0	-1.32/-1.68/-3.31		2.33/2.25/2.17	
12	O2-C2	270.0	-3.13/-3.24/-3.96		2.07/2.17/2.15	
13	HO-O2	0.0	-6.62/-6.22/-5.38		1.87/1.97/2.04	
14	HO-O2	45.0	-6.61/-6.36/-5.67		1.84/1.96/2.02	
15	HO-O2	90.0	-6.03/-6.20/-5.59		1.87/1.97/2.02	
16	HO-O2	135.0	-5.91/-6.02/-5.28		1.91/1.98/2.05	
17	HB22-CB2	0.0	-2.22/-2.47/-2.94		2.71/2.65/2.60	
18	HB23-CB2	0.0	-0.39/-0.09/-0.75		2.84/2.80/2.69	
19	HA32-CA3	0.0	-2.00/-2.35/-1.67		2.72/2.64/2.73	
20	HA33-CA3	0.0	-1.60/-1.66/-0.80		2.61/2.62/2.71	

1.36 Small molecule B of Chromophore(Thr,Trp,Gly)(B2H)

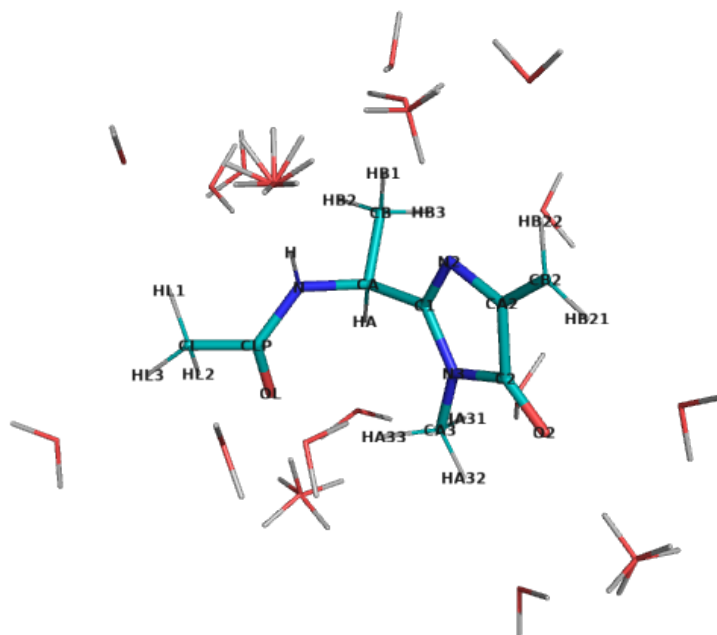


Figure S38: The molecule used for water complex calculations corresponding to N-[(1S)-1-(1-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-2-yl)ethyl]acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S110: Statistics of calculated water interaction and dipole moment for N-[(1S)-1-(1-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-2-yl)ethyl]acetamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.97/1.76	0.44/2.26	6.449	4.14/4.46	51.78
Optimal	0.51/1.11	0.08/0.19	1.846	4.14/4.25	8.20

Table S111: The comparison list of optimized atomic charges and their initial guess for N-[(1S)-1-(1-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-2-yl)ethyl]acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.270	0.000
HL1	0.090	0.090	0.000
HL2	0.090	0.090	0.000
HL3	0.090	0.090	0.000
CLP	0.510	0.513	6.342
OL	-0.510	-0.510	0.000
N	-0.470	-0.452	12.613
H	0.310	0.287	8.293
CA	0.270	0.234	17.154
HA	0.090	0.090	0.520
CB	-0.270	-0.267	2.233
HB1	0.090	0.090	0.300
HB2	0.090	0.090	0.300
HB3	0.090	0.090	0.300
C1	0.233	0.058	27.526
N2	-0.679	-0.703	41.131
N3	-0.080	-0.073	17.082
C2	0.407	0.510	20.808
O2	-0.489	-0.482	6.517
CA2	0.466	0.510	42.290
CB2	-0.593	-0.444	13.655
HB21	0.230	0.230	0.950
HB22	0.230	0.230	0.950
CA3	-0.195	-0.271	3.821
HA31	0.090	0.090	0.000
HA32	0.090	0.090	0.000
HA33	0.090	0.090	0.000

Table S112: Interaction energies and geometries between probe water and selected N-[(1S)-1-(1-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-2-yl)ethyl]acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HL1-CL	0.0	-2.68/-2.54/-2.07		2.50/2.60/2.61	
2	HL2-CL	0.0	-2.37/-1.88/-1.35		2.49/2.62/2.65	
3	HL3-CL	0.0	-1.37/-0.81/-0.56		2.53/2.68/2.69	
4	OL-CLP	0.0	-6.07/-6.66/-6.66		1.81/1.76/1.77	
5	OL-CLP	90.0	-5.68/-6.12/-6.38		1.82/1.76/1.77	
6	OL-CLP	180.0	-4.51/-4.80/-5.83		1.85/1.79/1.78	
7	OL-CLP	270.0	-4.97/-5.68/-6.34		1.85/1.78/1.77	
8	H-N	0.0	-5.97/-6.89/-4.95		1.87/1.86/1.90	
9	H-N	45.0	-5.79/-6.66/-4.68		1.87/1.86/1.91	
10	H-N	90.0	-6.64/-7.14/-5.01		1.83/1.85/1.89	
11	H-N	135.0	-6.88/-7.41/-5.31		1.83/1.84/1.88	
12	HA-CA	0.0	-1.17/-1.68/-0.23		2.81/2.73/2.82	
13	HB1-CB	0.0	-0.31/-0.41/0.11		2.74/2.72/5.00	
14	HB2-CB	0.0	-1.35/-1.76/-1.16		2.69/2.64/2.67	
15	HB3-CB	0.0	-1.43/-1.66/-0.82		2.69/2.65/2.72	
16	N2-C1	0.0	-6.44/-6.58/-6.00		1.90/1.98/1.98	
17	N2-C1	90.0	-7.30/-6.19/-6.79		1.90/1.99/1.97	
18	N2-C1	180.0	-3.96/-3.69/-5.44		2.10/2.05/2.00	
19	N2-C1	270.0	-5.92/-4.96/-5.69		1.91/2.00/1.98	
20	N3-C1	0.0	-2.09/-2.13/-2.47		2.71/2.52/2.48	
21	O2-C2	0.0	-5.35/-5.70/-5.42		1.87/1.78/1.79	
22	O2-C2	90.0	-5.52/-5.68/-4.88		1.86/1.78/1.80	
23	O2-C2	180.0	-5.44/-5.54/-4.18		1.86/1.78/1.81	
24	O2-C2	270.0	-5.48/-5.72/-4.91		1.86/1.78/1.80	
25	HB21-CB2	0.0	-1.64/-1.45/-3.39		2.32/2.47/2.41	
26	HB22-CB2	0.0	-1.38/-0.95/-2.47		2.50/2.56/2.47	
27	HA31-CA3	0.0	-1.49/-1.55/-0.63		2.65/2.64/2.73	

1.37 Small molecule used for phenylserine(BB8)

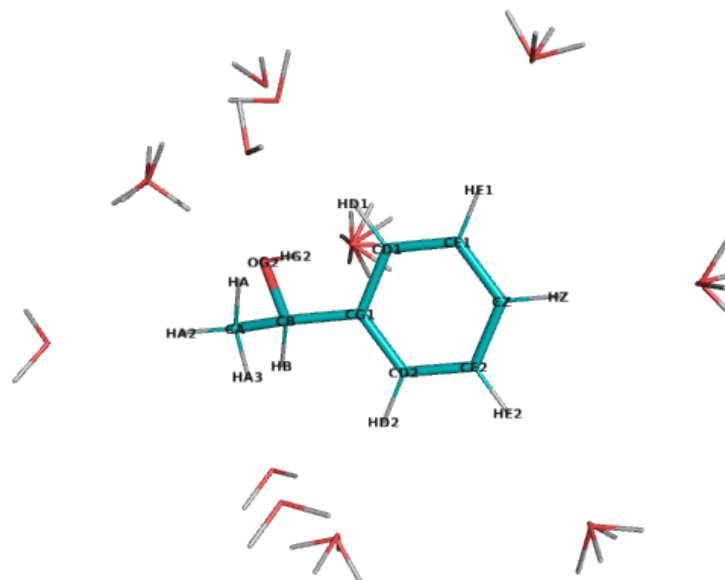


Figure S39: The molecule used for water complex calculations corresponding to (1R)-1-phenylethanol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S113: Statistics of calculated water interaction and dipole moment for (1R)-1-phenylethanol.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.41/0.97	0.07/0.23	2.021	1.67/2.48	2.26
Optimal	0.27/0.71	0.08/0.24	1.517	1.67/2.21	1.47

Table S114: The comparison list of optimized atomic charges and their initial guess for (1R)-1-phenylethan-1-ol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.269	0.000
HA	0.090	0.090	0.000
CB	0.110	0.132	3.300
HB	0.090	0.090	0.000
OG2	-0.575	-0.643	4.339
HG2	0.384	0.413	0.300
CG1	-0.037	-0.001	4.230
CD2	-0.101	-0.111	2.130
HD2	0.115	0.115	0.000
CD1	-0.101	-0.111	2.130
HD1	0.115	0.115	0.000
CE2	-0.115	-0.115	0.000
HE2	0.115	0.115	0.000
CE1	-0.115	-0.115	0.000
HE1	0.115	0.115	0.000
CZ	-0.115	-0.115	0.000
HZ	0.115	0.115	0.000

Table S115: Interaction energies and geometries between probe water and selected (1R)-1-phenylethan-1-ol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.83/-0.75/-0.85	2.73/2.73/2.72
2	HB-CB	0.0	-1.39/-1.52/-1.61	2.70/2.69/2.68
3	OG2-CB	0.0	-5.58/-5.22/-5.95	1.85/1.89/1.87
4	OG2-CB	90.0	-5.87/-5.54/-6.27	1.83/1.88/1.86
5	OG2-CB	180.0	-5.41/-5.68/-6.38	1.87/1.88/1.85
6	OG2-CB	270.0	-5.66/-5.49/-6.20	1.84/1.88/1.86
7	HG2-OG2	0.0	-5.93/-5.91/-6.29	1.79/1.83/1.82
8	HG2-OG2	45.0	-5.48/-5.67/-6.07	1.80/1.84/1.82
9	HG2-OG2	90.0	-5.91/-5.84/-6.25	1.79/1.83/1.82
10	HG2-OG2	135.0	-6.37/-6.09/-6.48	1.78/1.83/1.81
11	HD2-CD2	0.0	-1.60/-1.72/-1.82	2.64/2.66/2.65
12	HD2-CD2	90.0	-1.82/-1.77/-1.87	2.56/2.65/2.64
13	HD1-CD1	0.0	-1.08/-0.38/-0.28	2.44/2.68/2.68
14	HE2-CE2	0.0	-1.32/-1.20/-1.23	2.66/2.70/2.70
15	HE2-CE2	90.0	-1.49/-1.26/-1.29	2.60/2.69/2.69
16	HE1-CE1	0.0	-1.29/-1.07/-1.08	2.65/2.70/2.70
17	HE1-CE1	90.0	-1.42/-1.10/-1.10	2.60/2.70/2.70
18	HZ-CZ	0.0	-1.28/-1.10/-1.12	2.66/2.71/2.71
19	HZ-CZ	90.0	-1.45/-1.16/-1.18	2.61/2.70/2.70

1.38 Small molecule used for benzylcysteine(BCS)

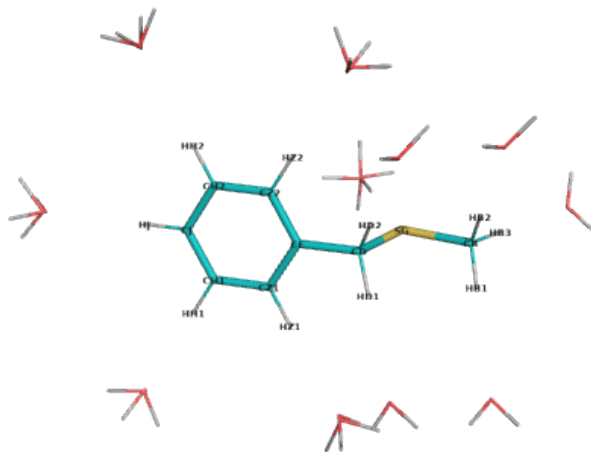


Figure S40: The molecule used for water complex calculations corresponding to [(methylsulfanyl)methyl]benzene, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S116: Statistics of calculated water interaction and dipole moment for [(methylsulfanyl)methyl]benzene.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.88/1.15	0.19/0.42	6.735	1.61/4.22	54.50
Optimal	0.44/0.94	0.23/0.51	2.306	1.61/1.93	1.74

Table S117: The comparison list of optimized atomic charges and their initial guess for [(methylsulfanyl)methyl]benzene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.268	-0.220	2.500
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
SG	-0.147	-0.058	20.033
CD	0.118	0.288	31.010
HD1	0.090	0.090	0.000
HD2	0.090	0.090	0.000
CE	-0.153	-0.364	33.323
CZ1	-0.115	-0.170	17.051
HZ1	0.115	0.115	0.000
CZ2	-0.115	-0.170	17.051
HZ2	0.115	0.115	0.000
CH1	-0.115	-0.108	0.000
HH1	0.115	0.115	0.000
CH2	-0.115	-0.108	0.000
HH2	0.115	0.115	0.000
CJ	-0.115	-0.115	0.000
HJ	0.115	0.115	0.000

Table S118: Interaction energies and geometries between probe water and selected [(methylsulfanyl)methyl]benzene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.31/-0.37/-1.34	2.60/2.78/2.67
2	HB1-CB	0.0	-1.24/-1.12/-2.27	2.71/2.73/2.63
3	HB2-CB	0.0	-1.24/-1.12/-2.27	2.71/2.73/2.63
4	HD1-CD	0.0	-1.73/-2.24/-2.87	2.58/2.60/2.56
5	HD2-CD	0.0	-1.73/-2.24/-2.87	2.58/2.60/2.56
6	HZ1-CZ1	0.0	-1.07/-1.15/-0.55	2.65/2.70/2.84
7	HZ1-CZ1	90.0	-1.52/-1.33/-0.83	2.54/2.68/2.78
8	HZ2-CZ2	0.0	-1.07/-1.15/-0.55	2.65/2.70/2.84
9	HZ2-CZ2	90.0	-1.52/-1.33/-0.83	2.54/2.68/2.78
10	HH1-CH1	0.0	-1.23/-0.84/-0.26	2.66/2.73/2.79
11	HH1-CH1	90.0	-1.41/-0.91/-0.33	2.60/2.72/2.78
12	HH2-CH2	0.0	-1.23/-0.84/-0.26	2.66/2.73/2.79
13	HH2-CH2	90.0	-1.41/-0.91/-0.33	2.60/2.72/2.78
14	HJ-CJ	0.0	-1.23/-0.84/-0.36	2.66/2.73/2.77
15	HJ-CJ	90.0	-1.40/-0.90/-0.42	2.60/2.72/2.76
16	SG-CB	0.0	-2.08/-2.81/-2.60	2.87/2.38/2.45
17	SG-CB	90.0	-1.78/-2.09/-1.11	2.87/2.43/2.62
18	SG-CB	180.0	-1.38/-1.75/-0.24	2.96/2.45/2.81
19	SG-CB	270.0	-1.78/-2.09/-1.11	2.88/2.43/2.62

1.39 Small molecule used for beta-hydroxyasparticacid(BHD)

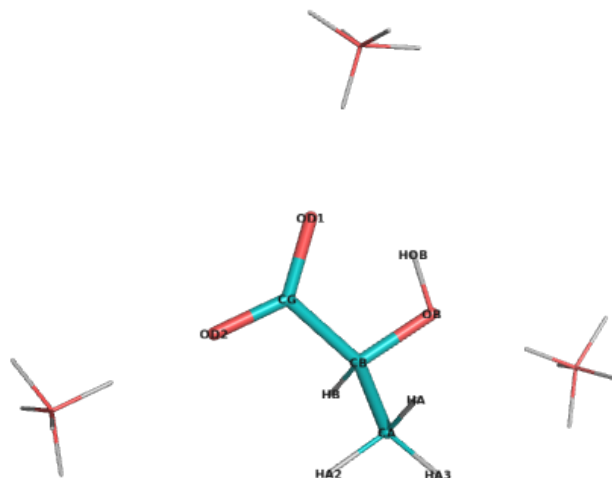


Figure S41: The molecule used for water complex calculations corresponding to 2-hydroxypropanoic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S119: Statistics of calculated water interaction and dipole moment for 2-hydroxypropanoic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.45/1.85	0.08/0.10	2.985	4.73/5.68	0.49
Optimal	0.14/0.26	0.06/0.08	2.589	4.73/4.41	7.16

Table S120: The comparison list of optimized atomic charges and their initial guess for 2-hydroxypropanoic acid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.268	0.000
HA	0.090	0.090	0.000
CB	0.035	0.058	3.837
HB	0.090	0.090	0.000
CG	0.576	0.614	3.551
OB	-0.729	-0.613	3.613
HOB	0.420	0.369	3.268
OD1	-0.696	-0.760	0.250
OD2	-0.696	-0.760	0.250

Table S121: Interaction energies and geometries between probe water and selected 2-hydroxypropanoic acid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	OB-CB	0.0	-10.70/-10.61/-9.04	1.81/1.80/1.84
2	OB-CB	90.0	-11.02/-10.91/-9.17	1.79/1.79/1.83
3	OB-CB	180.0	-10.78/-11.01/-9.13	1.81/1.79/1.83
4	OB-CB	270.0	-10.95/-10.85/-9.13	1.80/1.80/1.84
5	OD1-CG	0.0	-11.92/-11.86/-12.88	1.77/1.69/1.67
6	OD1-CG	90.0	-12.33/-12.35/-13.61	1.75/1.68/1.66
7	OD1-CG	180.0	-12.68/-12.91/-14.38	1.75/1.67/1.65
8	OD1-CG	270.0	-12.34/-12.43/-13.69	1.75/1.67/1.65
9	OD2-CG	0.0	-12.89/-12.63/-13.66	1.74/1.67/1.66
10	OD2-CG	90.0	-13.15/-13.16/-14.36	1.74/1.67/1.65
11	OD2-CG	180.0	-13.60/-13.74/-15.10	1.73/1.67/1.65
12	OD2-CG	270.0	-13.15/-13.15/-14.36	1.74/1.67/1.65

1.40 Small molecule used for 3-(3-benzothieryl)-alanine(BTH3)

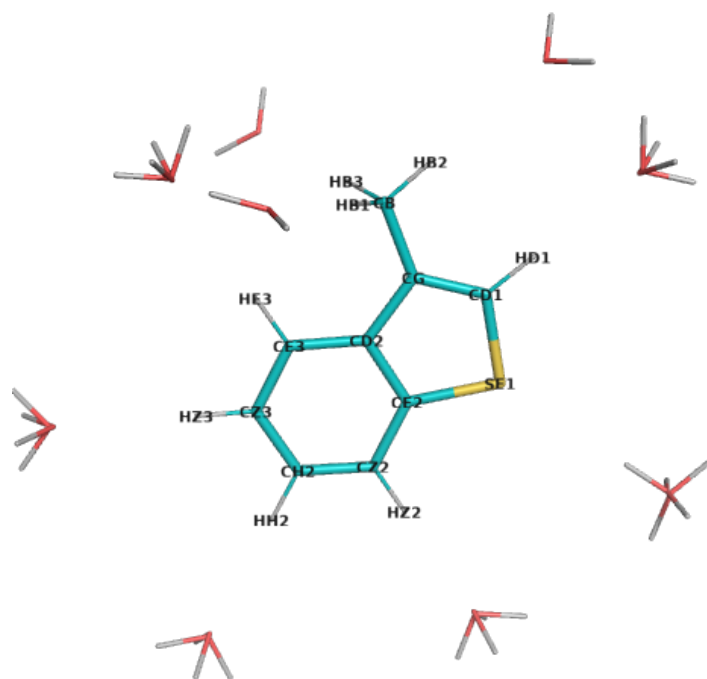


Figure S42: The molecule used for water complex calculations corresponding to 3-methyl-1-benzothiophene, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S122: Statistics of calculated water interaction and dipole moment for 3-methyl-1-benzothiophene.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.67/1.56	0.29/0.61	3.306	1.26/1.36	70.31
Optimal	0.21/0.39	0.24/0.51	1.646	1.26/1.50	0.57

Table S123: The comparison list of optimized atomic charges and their initial guess for 3-methyl-1-benzothiophene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.277	2.500
HB2	0.090	0.090	0.000
HB1	0.090	0.090	0.000
CG	0.053	-0.030	2.500
CD2	0.184	0.204	0.000
CD1	-0.233	-0.095	2.500
HD1	0.170	0.201	0.000
CE3	-0.243	-0.339	0.000
HE3	0.163	0.201	0.000
CE2	0.012	0.140	0.000
SE1	-0.031	-0.167	2.500
CZ3	-0.112	-0.236	0.000
HZ3	0.164	0.196	0.000
CZ2	-0.287	-0.208	0.000
HZ2	0.225	0.230	0.000
CH2	-0.267	-0.286	0.000
HH2	0.202	0.196	0.000

Table S124: Interaction energies and geometries between probe water and selected 3-methyl-1-benzothiophene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.06/-1.09/-0.97		2.71/2.69/2.69	
2	HB2-CB	0.0	-1.49/-1.18/-1.50		2.68/2.71/2.70	
3	HB1-CB	0.0	-1.07/-1.10/-0.91		2.70/2.69/2.70	
4	HD1-CD1	0.0	-1.97/-2.03/-3.54		2.49/2.30/2.22	
5	HD1-CD1	90.0	-2.23/-2.09/-3.57		2.42/2.30/2.22	
6	HE3-CE3	0.0	-1.61/-1.81/-1.44		2.65/2.66/2.67	
7	HE3-CE3	90.0	-1.81/-1.94/-1.55		2.62/2.64/2.65	
8	SE1-CD1	0.0	-0.72/-1.09/-1.50		3.04/2.53/2.43	
9	SE1-CD1	90.0	-0.96/-1.21/-1.66		2.94/2.51/2.41	
10	SE1-CD1	180.0	-0.76/-1.15/-1.56		3.03/2.52/2.42	
11	SE1-CD1	270.0	-0.96/-1.21/-1.66		2.94/2.51/2.41	
12	HZ3-CZ3	0.0	-1.28/-1.45/-0.87		2.66/2.65/2.69	
13	HZ3-CZ3	90.0	-1.47/-1.55/-0.97		2.60/2.64/2.67	
14	HZ2-CZ2	0.0	-1.59/-1.45/-2.08		2.54/2.61/2.56	
15	HZ2-CZ2	90.0	-1.75/-1.49/-2.08		2.48/2.61/2.56	
16	HH2-CH2	0.0	-1.34/-1.34/-1.05		2.64/2.65/2.68	
17	HH2-CH2	90.0	-1.53/-1.44/-1.15		2.58/2.64/2.66	

1.41 Small molecule used for
 (2S)-2-azanyl-3-[ethyl(methyl)carbamoyl]oxy-propanoicacid(BXT)

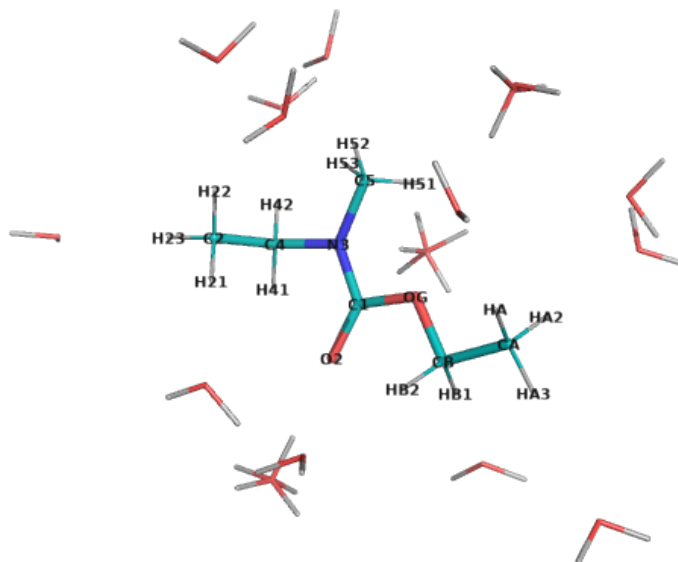


Figure S43: The molecule used for water complex calculations corresponding to ethylN-ethyl-N-methylcarbamate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S125: Statistics of calculated water interaction and dipole moment for ethylN-ethyl-N-methylcarbamate.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.72/2.30	0.19/0.52	3.181	2.47/2.29	4.70
Optimal	0.23/0.51	0.33/1.32	1.714	2.47/2.91	2.66

Table S126: The comparison list of optimized atomic charges and their initial guess for ethylN-ethyl-N-methylcarbamate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.271	0.000
HA	0.090	0.090	0.000
CB	0.007	0.160	0.497
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
OG	-0.188	-0.316	5.561
C1	0.383	0.198	11.820
O2	-0.460	-0.389	0.888
N3	-0.168	-0.236	13.936
C5	-0.135	-0.094	5.912
H51	0.090	0.090	0.181
H52	0.090	0.090	0.181
H53	0.090	0.090	0.181
C4	-0.069	0.047	7.392
H41	0.090	0.090	0.675
H42	0.090	0.090	0.675
C2	-0.270	-0.269	2.571
H21	0.090	0.090	0.050
H22	0.090	0.090	0.050
H23	0.090	0.090	0.050

Table S127: Interaction energies and geometries between probe water and selected ethylN-ethyl-N-methylcarbamate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-1.15/-0.99/-1.29	2.73/2.71/2.68
2	HA2-CA	0.0	-0.74/-0.69/-0.56	2.80/2.75/2.74
3	HA-CA	0.0	-0.70/-0.66/-0.52	2.80/2.76/2.75
4	HB1-CB	0.0	-0.82/-0.52/-0.65	2.56/2.67/2.64
5	HB2-CB	0.0	-0.78/-0.44/-0.60	2.56/2.68/2.65
6	OG-CB	90.0	-0.13/-0.27/-0.89	3.70/3.33/3.20
7	OG-CB	180.0	-0.20/-0.66/-1.29	3.78/3.27/3.16
8	OG-CB	270.0	-0.22/-0.33/-1.01	3.66/3.34/3.20
9	O2-C1	0.0	-5.93/-5.87/-5.49	1.84/1.78/1.79
10	O2-C1	90.0	-6.04/-6.15/-5.86	1.84/1.77/1.79
11	O2-C1	180.0	-6.03/-6.25/-5.93	1.84/1.77/1.79
12	O2-C1	270.0	-6.18/-6.19/-5.95	1.83/1.77/1.78
13	N3-C1	0.0	-1.37/-1.09/-1.83	2.37/2.28/2.21
14	N3-C1	90.0	-1.60/-1.44/-3.03	2.34/2.25/2.14
15	N3-C1	180.0	-2.32/-2.83/-4.63	2.32/2.18/2.08
16	N3-C1	270.0	-2.22/-2.37/-3.17	2.32/2.21/2.15
17	H51-C5	0.0	-0.41/-0.83/-0.15	4.10/2.78/4.62
18	H52-C5	0.0	-1.54/-1.65/-1.68	2.70/2.65/2.65
19	H53-C5	0.0	-1.23/-1.43/-1.04	2.71/2.65/2.67
20	H42-C4	0.0	-1.29/-1.32/-1.71	2.75/2.70/2.66
21	H22-C2	0.0	-1.10/-1.09/-1.13	2.86/2.78/2.77
22	H23-C2	0.0	-0.79/-0.63/-0.90	2.82/2.75/2.72

1.42 Small molecule A of (C12)

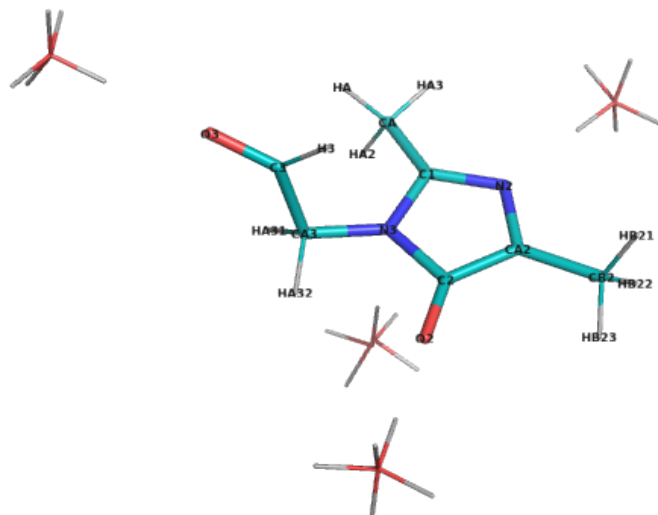


Figure S44: The molecule used for water complex calculations corresponding to 2-(2,4-dimethyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetaldehyde, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S128: Statistics of calculated water interaction and dipole moment for 2-(2,4-dimethyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetaldehyde.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	3.04/6.28	0.11/0.21	10.344	4.36/8.57	16.00
Optimal	0.17/0.48	0.07/0.13	3.178	4.36/4.01	4.79

Table S129: The comparison list of optimized atomic charges and their initial guess for 2-(2,4-dimethyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetaldehyde, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.113	14.764
HA	0.090	0.090	0.000
C1	0.220	0.334	18.884
N2	-0.705	-0.678	15.120
CA2	-0.004	0.319	31.349
C2	0.348	-0.159	78.743
O2	-0.740	-0.788	75.409
N3	-0.072	-0.465	35.013
CA3	-0.167	0.173	15.307
HA31	0.090	0.090	0.125
HA32	0.090	0.090	0.125
C3	0.284	0.215	17.419
H3	0.090	0.089	2.500
O3	-0.434	-0.401	12.965
CB2	-0.270	-0.246	6.938
HB21	0.090	0.090	0.450
HB22	0.090	0.090	0.450
HB23	0.090	0.090	0.450

Table S130: Interaction energies and geometries between probe water and selected 2-(2,4-dimethyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetaldehyde site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	N2-C1	0.0	-12.41/-12.55/-11.23	1.89/1.85/1.87
2	N2-C1	90.0	-12.16/-12.02/-10.44	1.88/1.86/1.88
3	N2-C1	180.0	-11.21/-11.28/-9.13	1.92/1.87/1.90
4	N2-C1	270.0	-12.21/-12.06/-10.57	1.88/1.86/1.88
5	O2-C2	0.0	-13.56/-13.41/-17.32	1.71/1.70/1.66
6	O2-C2	90.0	-13.29/-13.27/-17.12	1.72/1.70/1.66
7	O2-C2	180.0	-12.86/-13.10/-16.69	1.73/1.70/1.66
8	O2-C2	270.0	-13.31/-13.28/-17.14	1.72/1.70/1.66
9	N3-C1	0.0	-5.53/-5.53/-11.01	2.32/2.29/2.01
10	N3-C1	90.0	-3.54/-3.06/-4.95	2.44/2.49/2.17
11	N3-C1	180.0	-5.44/-5.55/-7.80	2.33/2.27/2.07
12	N3-C1	270.0	-7.58/-7.82/-13.85	2.24/2.19/1.96
13	O3-C3	0.0	-6.99/-7.08/-6.25	1.91/1.79/1.81
14	O3-C3	90.0	-6.90/-7.06/-6.74	1.92/1.79/1.80
15	O3-C3	180.0	-6.95/-6.88/-6.50	1.91/1.79/1.80
16	O3-C3	270.0	-6.94/-6.95/-6.04	1.92/1.79/1.81

1.43 Small molecule used for 3-chloro-D-alanine(C2N)

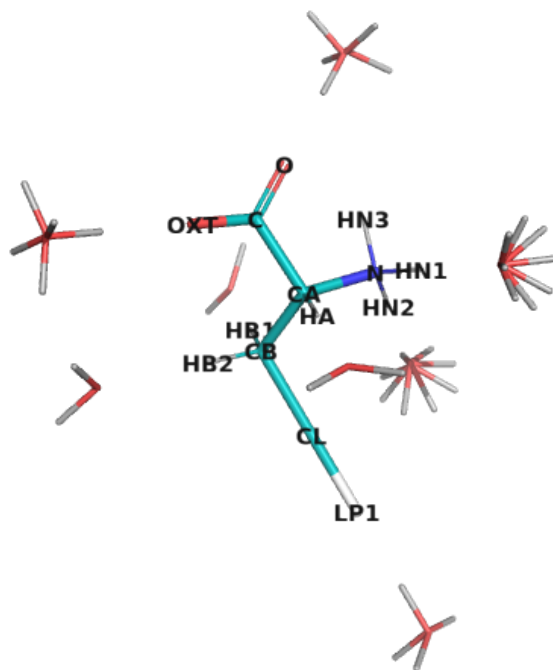


Figure S45: The molecule used for water complex calculations corresponding to 3-chloro-D-alanine, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S131: Statistics of calculated water interaction and dipole moment for 3-chloro-D-alanine.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	2.97/4.82	0.11/0.22	10.904	8.95/14.10	10.10
Optimal	0.55/1.10	0.08/0.23	5.904	8.95/11.40	2.23

Table S132: The comparison list of optimized atomic charges and their initial guess for 3-chloro-D-alanine, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
N	-0.162	-0.358	39.263
HN1	0.259	0.330	2.536
HN2	0.259	0.330	2.536
HN3	0.259	0.330	2.536
CA	0.293	0.181	104.048
HA	0.090	0.090	4.186
CL	-0.151	-0.151	15.677
LP1	0.050	0.050	-
CB	-0.168	0.090	35.711
HB1	0.090	0.090	2.500
HB2	0.090	0.090	2.500
C	0.119	0.448	99.425
OXT	-0.514	-0.760	8.256
O	-0.514	-0.760	8.256

Table S133: Interaction energies and geometries between probe water and selected 3-chloro-D-alanine site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HN1-N	0.0	-12.82/-12.31/-13.60	1.70/1.78/1.75
2	HN1-N	45.0	-12.44/-12.10/-13.36	1.71/1.78/1.75
3	HN1-N	90.0	-12.61/-12.07/-13.31	1.70/1.78/1.75
4	HN1-N	135.0	-12.99/-12.28/-13.55	1.69/1.78/1.75
5	HA-CA	0.0	-3.38/-3.33/-3.48	2.33/2.56/2.55
6	OXT-C	0.0	-6.99/-7.23/-10.18	1.79/1.74/1.67
7	OXT-C	90.0	-8.09/-8.32/-12.22	1.77/1.73/1.65
8	OXT-C	180.0	-9.01/-9.55/-13.75	1.76/1.72/1.64
9	OXT-C	270.0	-7.82/-8.47/-11.76	1.78/1.73/1.66
10	O-C	0.0	-4.18/-3.08/-5.95	1.82/1.80/1.70
11	O-C	90.0	-7.36/-7.09/-10.54	1.75/1.73/1.65
12	O-C	180.0	-9.24/-9.82/-14.06	1.73/1.70/1.63
13	O-C	270.0	-7.21/-6.64/-10.45	1.75/1.73/1.66

1.44 Small molecule used for canaline(CAN)

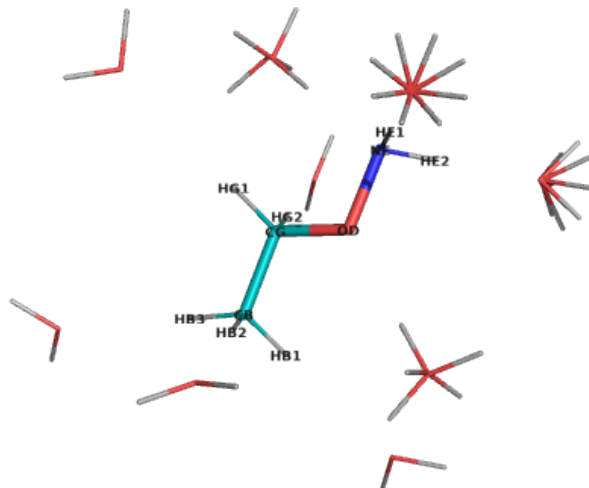


Figure S46: The molecule used for water complex calculations corresponding to O-ethylhydroxylamine, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S134: Statistics of calculated water interaction and dipole moment for O-ethylhydroxylamine.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.62/0.83	0.14/0.26	1.526	0.52/0.48	21.06
Optimal	0.25/0.66	0.15/0.28	1.899	0.52/0.09	129.06

Table S135: The comparison list of optimized atomic charges and their initial guess for O-ethylhydroxylamine, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.270	1.950
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.060	-0.011	5.264
HG1	0.090	0.090	1.950
HG2	0.090	0.090	1.950
OD	-0.224	-0.177	26.724
NE	-0.704	-0.684	35.462
HE1	0.344	0.346	24.150
HE2	0.344	0.346	24.150

Table S136: Interaction energies and geometries between probe water and selected O-ethylhydroxylamine site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.80/-0.92/-0.70	2.82/2.72/2.75
2	HB1-CB	0.0	-0.35/-0.24/-0.14	2.86/2.80/2.83
3	HB2-CB	0.0	-0.35/-0.24/-0.14	2.86/2.80/2.83
4	HG1-CG	0.0	-0.46/-0.44/-0.21	2.86/2.77/2.82
5	HG2-CG	0.0	-0.46/-0.44/-0.21	2.86/2.77/2.82
6	OD-CG	0.0	-4.06/-4.06/-3.32	2.08/1.80/1.84
7	OD-CG	90.0	-4.61/-4.38/-3.82	2.04/1.79/1.82
8	OD-CG	180.0	-4.55/-4.38/-4.03	2.07/1.79/1.81
9	OD-CG	270.0	-4.61/-4.38/-3.82	2.04/1.79/1.82
10	NE-OD	0.0	-5.41/-5.42/-4.82	2.02/1.98/2.01
11	NE-OD	90.0	-5.25/-4.94/-4.62	2.04/1.99/2.01
12	NE-OD	180.0	-4.40/-3.74/-3.92	2.11/2.02/2.03
13	NE-OD	270.0	-5.24/-4.94/-4.61	2.04/1.99/2.01
14	HE1-NE	0.0	-3.53/-3.75/-4.25	2.02/1.89/1.87
15	HE1-NE	45.0	-3.55/-3.72/-4.21	2.02/1.89/1.87
16	HE1-NE	90.0	-3.31/-3.59/-4.09	2.04/1.90/1.88
17	HE1-NE	135.0	-3.30/-3.61/-4.12	2.04/1.89/1.88
18	HE2-NE	0.0	-3.53/-3.74/-4.24	2.02/1.89/1.87
19	HE2-NE	45.0	-3.30/-3.61/-4.12	2.04/1.89/1.88
20	HE2-NE	90.0	-3.31/-3.59/-4.09	2.04/1.90/1.88
21	HE2-NE	135.0	-3.55/-3.72/-4.21	2.01/1.89/1.88

1.45 Small molecule used for carboxymethylatedcysteine(CCS)

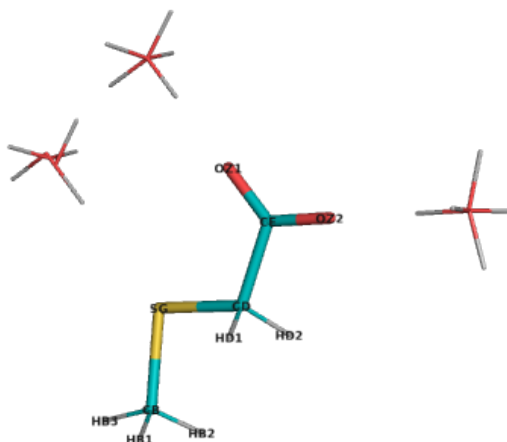


Figure S47: The molecule used for water complex calculations corresponding to 2-(methylsulfanyl)acetic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S137: Statistics of calculated water interaction and dipole moment for 2-(methylsulfanyl)acetic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.59/2.62	0.19/0.36	5.570	9.62/11.68	5.23
Optimal	0.62/1.13	0.20/0.36	3.011	9.62/8.82	2.33

Table S138: The comparison list of optimized atomic charges and their initial guess for 2-(methylsulfanyl)aceticacid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.327	-0.220	2.500
HB2	0.090	0.090	0.000
HB1	0.090	0.090	0.000
SG	-0.102	-0.045	13.516
CD	-0.217	-0.258	13.516
HD2	0.090	0.090	0.000
HD1	0.090	0.090	0.000
CE	0.590	0.593	4.482
OZ1	-0.697	-0.760	2.500
OZ2	-0.697	-0.760	2.500

Table S139: Interaction energies and geometries between probe water and selected 2-(methylsulfanyl)aceticacid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	OZ1-CE	0.0	-13.58/-13.96/-15.05	1.75/1.67/1.65
2	OZ1-CE	90.0	-13.16/-13.80/-15.37	1.75/1.67/1.65
3	OZ1-CE	180.0	-13.24/-13.92/-15.86	1.75/1.67/1.64
4	OZ1-CE	270.0	-13.16/-13.80/-15.37	1.75/1.67/1.65
5	OZ2-CE	0.0	-13.40/-12.77/-14.29	1.73/1.67/1.65
6	OZ2-CE	90.0	-13.77/-13.34/-15.00	1.73/1.67/1.65
7	OZ2-CE	180.0	-14.33/-13.97/-15.77	1.72/1.66/1.64
8	OZ2-CE	270.0	-13.77/-13.34/-15.00	1.73/1.67/1.65
9	SG-CB	0.0	-8.36/-9.49/-9.54	2.62/2.25/2.27
10	SG-CB	90.0	-4.97/-4.85/-4.24	2.80/2.45/2.55
11	SG-CB	180.0	-3.20/-2.21/-1.35	2.93/2.69/3.29
12	SG-CB	270.0	-4.97/-4.84/-4.24	2.80/2.45/2.55

1.46 Small molecule used for gamma-carboxy-glutamic acid (CGU)

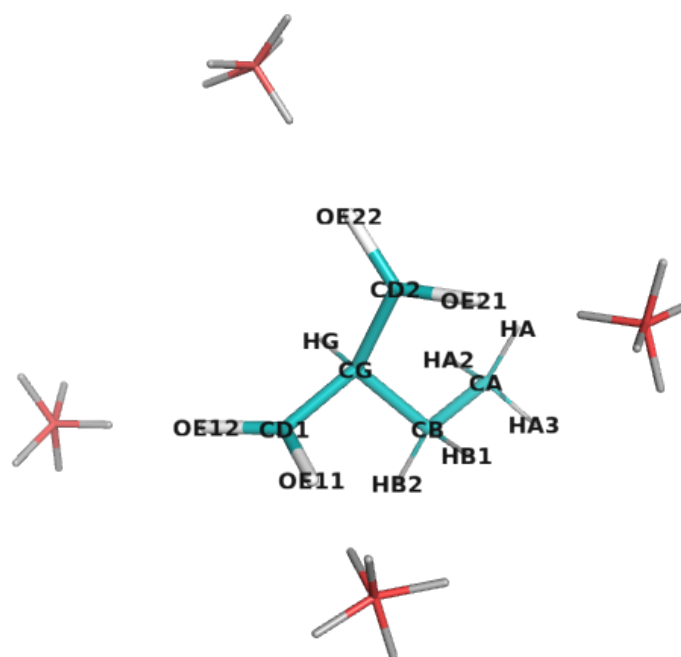


Figure S48: The molecule used for water complex calculations corresponding to 2-ethylpropanedioic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S140: Statistics of calculated water interaction and dipole moment for 2-ethylpropanedioic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.36/2.03	0.03/0.04	3.936	8.34/9.27	1.17
Optimal	0.53/0.92	0.05/0.06	3.825	8.34/9.75	2.80

Table S141: The comparison list of optimized atomic charges and their initial guess for 2-ethylpropanedioic acid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.277	0.507
HA	0.090	0.090	0.000
CB	-0.202	-0.169	0.064
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.380	-0.414	48.124
HG	0.090	0.090	0.000
CD1	0.890	0.680	41.904
OE12	-0.867	-0.760	2.350
OE11	-0.867	-0.760	2.350
CD2	0.890	0.680	41.904
OE22	-0.867	-0.760	2.350
OE21	-0.867	-0.760	2.350

Table S142: Interaction energies and geometries between probe water and selected 2-ethylpropanedioic acid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	OE12-CD1	0.0	-19.26/-18.48/-17.49		1.66/1.62/1.64	
2	OE12-CD1	90.0	-18.30/-17.38/-16.27		1.67/1.63/1.65	
3	OE12-CD1	180.0	-18.72/-18.08/-16.82		1.66/1.62/1.64	
4	OE12-CD1	270.0	-19.45/-19.10/-17.95		1.66/1.62/1.64	
5	OE11-CD1	0.0	-19.72/-20.21/-19.13		1.67/1.62/1.64	
6	OE11-CD1	90.0	-19.03/-19.59/-18.50		1.68/1.62/1.64	
7	OE11-CD1	180.0	-17.61/-17.29/-16.13		1.68/1.63/1.65	
8	OE11-CD1	270.0	-17.56/-17.28/-16.20		1.69/1.63/1.65	
9	OE22-CD2	0.0	-19.48/-19.15/-18.19		1.67/1.62/1.64	
10	OE22-CD2	90.0	-19.24/-19.27/-18.18		1.67/1.62/1.64	
11	OE22-CD2	180.0	-18.16/-17.66/-16.46		1.67/1.63/1.65	
12	OE22-CD2	270.0	-17.88/-17.21/-16.16		1.68/1.63/1.65	
13	OE21-CD2	0.0	-19.02/-19.48/-18.38		1.67/1.62/1.64	
14	OE21-CD2	90.0	-17.68/-17.55/-16.46		1.68/1.63/1.65	
15	OE21-CD2	180.0	-18.00/-18.22/-16.99		1.67/1.62/1.64	
16	OE21-CD2	270.0	-19.18/-20.03/-18.81		1.67/1.62/1.64	

1.47 Small molecule used for gamma-carboxy-glutamic acid (CGUP)

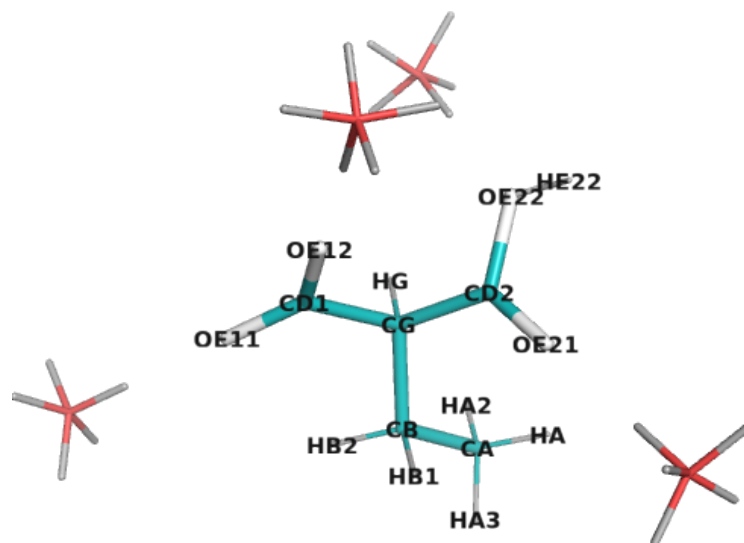


Figure S49: The molecule used for water complex calculations corresponding to 2-ethylpropanedioic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S143: Statistics of calculated water interaction and dipole moment for 2-ethylpropanedioic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.42/2.46	0.10/0.13	5.471	7.75/10.25	6.14
Optimal	0.22/0.47	0.09/0.12	2.391	7.75/7.81	1.43

Table S144: The comparison list of optimized atomic charges and their initial guess for 2-ethylpropanedioic acid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.286	1.687
HA	0.090	0.090	0.000
CB	-0.298	-0.166	2.361
HB1	0.090	0.090	0.125
HB2	0.090	0.090	0.125
CG	-0.206	-0.269	37.703
HG	0.090	0.090	0.436
CD1	0.677	0.625	30.570
OE12	-0.694	-0.760	2.150
OE11	-0.694	-0.760	2.150
CD2	0.744	0.846	40.123
OE22	-0.561	-0.631	4.829
OE21	-0.528	-0.568	4.482
HE22	0.290	0.429	0.262

Table S145: Interaction energies and geometries between probe water and selected 2-ethylpropanedioic acid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	OE12-CD1	0.0	-12.37/-12.58/-13.54		1.76/1.68/1.66	
2	OE12-CD1	90.0	-12.52/-12.54/-14.45		1.76/1.68/1.65	
3	OE12-CD1	180.0	-12.93/-12.87/-15.38		1.75/1.68/1.65	
4	OE12-CD1	270.0	-13.00/-13.00/-14.91		1.75/1.68/1.65	
5	OE11-CD1	0.0	-12.40/-12.52/-14.01		1.75/1.68/1.65	
6	OE11-CD1	90.0	-12.84/-12.95/-14.67		1.75/1.67/1.65	
7	OE11-CD1	180.0	-13.25/-13.18/-15.33		1.74/1.67/1.64	
8	OE11-CD1	270.0	-12.74/-12.67/-14.64		1.75/1.68/1.65	
9	OE22-CD2	0.0	-4.46/-4.48/-3.72		2.03/1.94/1.96	
10	OE22-CD2	90.0	-4.84/-4.37/-3.69		2.00/1.95/1.96	
11	OE22-CD2	180.0	-7.29/-7.74/-8.14		2.01/1.92/1.91	
12	OE22-CD2	270.0	-8.01/-8.20/-8.53		1.94/1.89/1.89	
13	OE21-CD2	0.0	-8.73/-9.05/-9.15		1.87/1.75/1.74	
14	OE21-CD2	90.0	-7.59/-7.41/-7.13		1.89/1.77/1.76	
15	OE21-CD2	180.0	-7.51/-7.39/-7.06		1.89/1.77/1.77	
16	OE21-CD2	270.0	-8.92/-9.19/-9.38		1.87/1.75/1.74	

1.48 Small molecule used for
S-[(R)-carboxy(hydroxy)methyl]-L-cysteine(CGV)

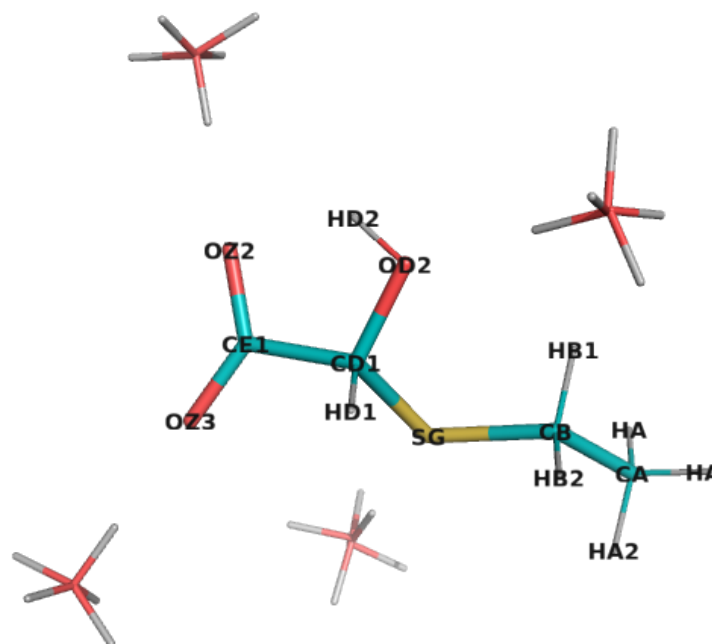


Figure S50: The molecule used for water complex calculations corresponding to (2R)-2-(ethylsulfanyl)-2-hydroxyaceticacid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S146: Statistics of calculated water interaction and dipole moment for (2R)-2-(ethylsulfanyl)-2-hydroxyaceticacid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.51/2.37	0.22/0.43	3.976	9.59/11.50	3.41
Optimal	0.34/1.04	0.20/0.40	3.134	9.59/8.99	6.19

Table S147: The comparison list of optimized atomic charges and their initial guess for (2R)-2-(ethylsulfanyl)-2-hydroxyaceticacid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.075
HA	0.090	0.090	0.000
CB	-0.181	-0.065	3.549
HB1	0.090	0.090	0.030
HB2	0.090	0.090	0.030
SG	-0.139	-0.200	32.582
CD1	0.052	0.113	32.478
HD1	0.090	0.090	0.424
OD2	-0.603	-0.604	18.795
HD2	0.363	0.363	4.115
CE1	0.544	0.643	5.786
OZ2	-0.653	-0.760	2.512
OZ3	-0.653	-0.760	2.512

Table S148: Interaction energies and geometries between probe water and selected (2R)-2-(ethylsulfanyl)-2-hydroxyaceticacid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	SG-CB	0.0	-6.75/-7.78/-8.50	2.69/2.29/2.26
2	SG-CB	90.0	-4.43/-4.64/-4.74	2.79/2.40/2.39
3	SG-CB	180.0	-3.00/-2.58/-2.27	2.89/2.50/2.51
4	SG-CB	270.0	-4.64/-4.71/-4.85	2.77/2.39/2.38
5	OD2-CD1	0.0	-8.80/-8.46/-8.77	1.86/1.90/1.89
6	OD2-CD1	90.0	-8.80/-8.66/-8.77	1.85/1.89/1.89
7	OD2-CD1	180.0	-8.73/-8.89/-7.80	1.89/1.89/1.90
8	OD2-CD1	270.0	-8.34/-8.74/-7.98	1.91/1.90/1.90
9	OZ2-CE1	0.0	-10.94/-11.03/-12.58	1.79/1.70/1.67
10	OZ2-CE1	90.0	-11.64/-11.69/-13.55	1.77/1.69/1.66
11	OZ2-CE1	180.0	-11.86/-12.05/-14.18	1.77/1.68/1.65
12	OZ2-CE1	270.0	-11.40/-11.45/-13.31	1.77/1.69/1.66
13	OZ3-CE1	0.0	-12.31/-12.21/-13.85	1.77/1.69/1.66
14	OZ3-CE1	90.0	-11.97/-12.14/-14.01	1.77/1.69/1.66
15	OZ3-CE1	180.0	-12.43/-12.68/-14.80	1.76/1.68/1.65
16	OZ3-CE1	270.0	-12.50/-12.67/-14.58	1.77/1.68/1.65

1.49 Small molecule A of (4Z)-2-[(1S)-1-amino-3-(methylsulfonyl)propyl]-4-[(4-hydroxyphenyl)methylidene]-5-oxo-4acetic5-dihydro-1H-imidazol-1-ylaceticacid(CH6)

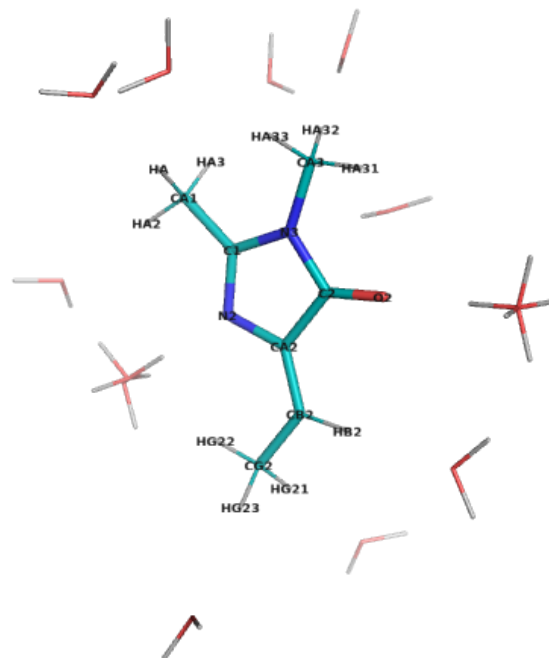


Figure S51: The molecule used for water complex calculations corresponding to (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S149: Statistics of calculated water interaction and dipole moment for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.92/1.64	0.10/0.25	6.526	3.17/0.45	27.81
Optimal	0.49/1.31	0.09/0.22	3.053	3.17/3.55	14.34

Table S150: The comparison list of optimized atomic charges and their initial guess for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA1	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
HA2	0.090	0.090	0.000
HA3	0.090	0.090	0.000
C1	0.233	0.074	23.781
N2	-0.679	-0.703	41.871
N3	-0.080	-0.079	15.706
C2	0.407	0.509	24.002
O2	-0.489	-0.482	6.710
CA2	0.288	0.516	47.153
CB2	-0.105	-0.135	25.469
HB2	0.150	0.150	3.270
CG2	-0.270	-0.274	15.277
HG21	0.090	0.090	1.175
HG22	0.090	0.090	1.175
HG23	0.090	0.090	1.175
CA3	-0.195	-0.271	3.821
HA31	0.090	0.090	0.000
HA32	0.090	0.090	0.000
HA33	0.090	0.090	0.000

Table S151: Interaction energies and geometries between probe water and selected (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA-CA1	0.0	-2.17/-2.61/-1.51		2.59/2.58/2.65	
2	HA2-CA1	0.0	-0.97/-0.86/0.05		2.58/2.64/2.77	
3	HA3-CA1	0.0	-2.55/-2.73/-1.57		2.52/2.57/2.64	
4	N2-C1	0.0	-4.99/-6.30/-5.60		2.09/2.01/2.02	
5	N2-C1	90.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
6	N2-C1	180.0	-5.35/-5.42/-6.38		1.95/2.01/1.99	
7	N2-C1	270.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
8	N3-C1	0.0	-0.26/-0.82/-0.78		2.74/2.52/2.49	
9	O2-C2	0.0	-5.51/-5.57/-5.00		1.85/1.78/1.80	
10	O2-C2	90.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
11	O2-C2	180.0	-5.92/-5.61/-4.27		1.84/1.78/1.81	
12	O2-C2	270.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
13	HB2-CB2	0.0	-1.40/-1.60/-2.82		2.32/2.47/2.44	
14	HG21-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
15	HG23-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
16	HA32-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	
17	HA33-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	

1.50 Small molecule B of (4Z)-2-[(1S)-1-amino-3-(methylsulfonyl)propyl]-4-[(4-hydroxyphenyl)methylidene]-5-oxo-4acetic5-dihydro-1H-imidazol-1-ylaceticacid(CH6)

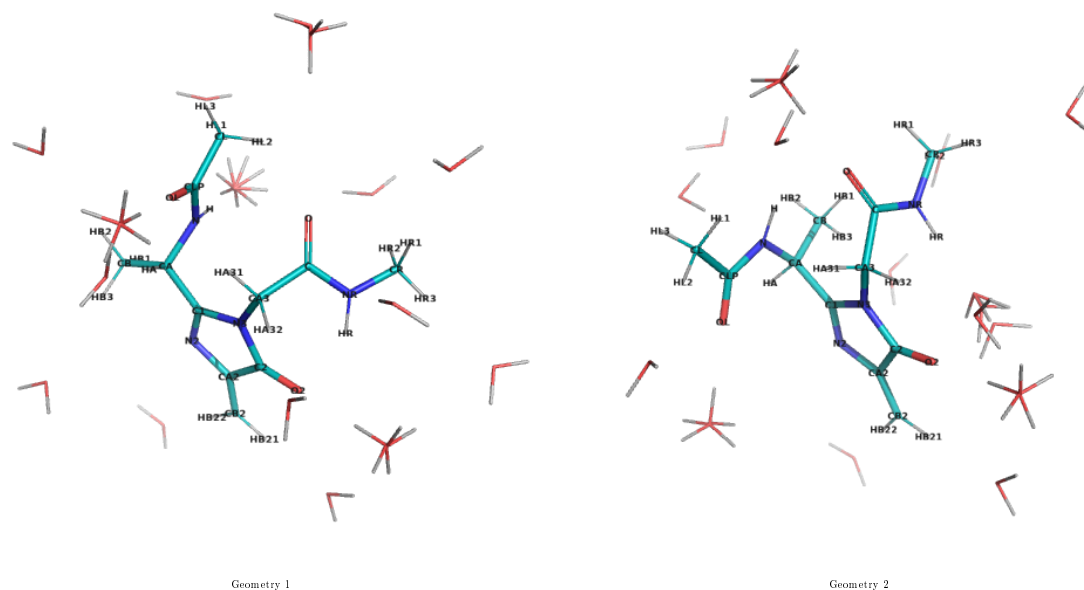


Table S152: The molecule used for water complex calculations corresponding to N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S153: Statistics of calculated water interaction and dipole moment for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide.

		RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
		Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Geometry 1	Initial	0.86 / 2.05	0.07 / 0.17	6.601	1.19 / 4.07	1.19
Geometry 2	Initial	1.02 / 2.07	0.09 / 0.23	6.126	6.37 / 4.43	6.37
Sum of geometries	Initial	0.95 / 2.07	0.08 / 0.23	12.727	-	-
Geometry 1	Optimal	0.36 / 0.81	0.07 / 0.16	2.460	1.19 / 1.37	1.19
Geometry 2	Optimal	0.51 / 0.91	0.08 / 0.19	2.701	6.37 / 7.25	6.37
Sum of geometries	Optimal	0.45 / 0.91	0.08 / 0.19	5.161	-	-

Table S154: The comparison list of optimized atomic charges and their initial guess for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
C1	0.233	0.164	24.002
N2	-0.679	-0.703	41.104
N3	-0.031	-0.499	22.994
C2	0.407	0.613	23.378
O2	-0.489	-0.482	6.517
CA2	0.466	0.512	42.773
CB2	-0.593	-0.444	13.655
HB21	0.230	0.230	0.950
HB22	0.230	0.230	0.950
CA3	-0.154	0.043	13.461
HA31	0.090	0.090	0.177
HA32	0.090	0.090	0.177
C	0.510	0.499	10.097
O	-0.510	-0.517	3.479
NR	-0.470	-0.442	6.773
HR	0.310	0.299	0.000
CR	-0.110	-0.108	0.239
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S155: Interaction energies and geometries between probe water and selected N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
Geometry 1				
1	O-C	0.0	-5.45/-5.47/-6.22	1.84/1.77/1.76
2	O-C	90.0	-6.01/-6.48/-6.53	1.83/1.75/1.76
3	O-C	180.0	-5.96/-6.64/-6.64	1.83/1.75/1.75
4	O-C	270.0	-5.67/-5.94/-6.62	1.84/1.76/1.75
5	NR-C	0.0	-1.32/-1.50/-1.08	2.24/2.20/2.22
6	HR2-CR	0.0	-1.10/-1.26/-1.09	2.71/2.66/2.67
7	HR3-CR	0.0	-1.39/-1.22/-1.32	2.66/2.67/2.67
8	N2-C1	0.0	-5.74/-6.45/-6.04	1.95/1.92/1.92
9	N2-C1	90.0	-6.51/-6.37/-7.24	1.90/1.92/1.90
10	N2-C1	180.0	-5.60/-5.66/-7.65	1.96/1.93/1.90
11	N2-C1	270.0	-6.64/-6.59/-7.43	1.90/1.91/1.89
12	O2-C2	0.0	-3.88/-3.93/-3.54	1.88/1.80/1.81
13	O2-C2	90.0	-4.94/-5.15/-4.46	1.84/1.77/1.79
14	O2-C2	180.0	-4.95/-5.20/-4.05	1.84/1.77/1.79
15	O2-C2	270.0	-3.93/-4.12/-3.39	1.87/1.79/1.81
16	HB21-CB2	0.0	-1.84/-1.64/-3.47	2.32/2.48/2.42
17	HB22-CB2	0.0	-1.82/-1.01/-2.42	2.42/2.54/2.46
18	HA31-CA3	0.0	-2.08/-2.47/-1.68	2.70/2.69/2.70
19	HA-CA	0.0	-2.47/-2.76/-1.19	2.49/2.56/2.66
Geometry 2				
20	O-C	0.0	-6.06/-6.90/-7.24	1.86/1.76/1.75
21	O-C	90.0	-5.25/-6.15/-7.32	1.87/1.77/1.75
22	O-C	180.0	-4.71/-5.63/-6.52	1.88/1.77/1.76
23	O-C	270.0	-5.56/-6.46/-6.85	1.86/1.76/1.76
24	HR-NR	0.0	-7.09/-7.67/-7.53	1.93/1.90/1.90
25	HR-NR	45.0	-7.71/-7.90/-7.71	1.91/1.89/1.89
26	HR-NR	90.0	-7.79/-7.84/-7.79	1.90/1.89/1.89
27	HR-NR	135.0	-7.18/-7.62/-7.61	1.92/1.90/1.89
28	HR1-CR	0.0	-0.71/-0.04/0.30	2.50/2.69/2.67
29	HR2-CR	0.0	-1.54/-1.44/-1.38	2.68/2.66/2.66
30	HR3-CR	0.0	-1.84/-1.82/-1.70	2.68/2.67/2.66
31	N2-C1	0.0	-6.46/-6.98/-6.58	1.93/1.91/1.91
32	N2-C1	90.0	-6.88/-6.47/-7.35	1.89/1.91/1.89
33	N2-C1	180.0	-5.73/-5.60/-7.60	1.95/1.93/1.90
34	N2-C1	270.0	-7.31/-7.09/-7.94	1.88/1.91/1.89
35	N3-C1	0.0	-0.22/0.03/-2.15	2.60/2.67/2.17
36	O2-C2	0.0	-4.96/-5.34/-4.95	1.88/1.79/1.80
37	O2-C2	90.0	-5.32/-5.37/-4.66	1.87/1.78/1.80
38	O2-C2	180.0	-5.74/-5.89/-4.71	1.87/1.78/1.81
39	O2-C2	270.0	-5.94/-6.25/-5.51	1.85/1.77/1.79
40	HB21-CB2	0.0	-1.43/-1.20/-3.03	2.33/2.48/2.41
41	HB22-CB2	0.0	-1.29/-0.66/-2.05	2.47/2.56/2.47
42	HA31-CA3	0.0	-3.71/-4.08/-3.49	2.50/2.57/2.57
43	HA-CA	0.0	-2.67/-3.45/-1.93	2.59/2.58/2.69

1.51 Small molecule used for citrulline(CIR)

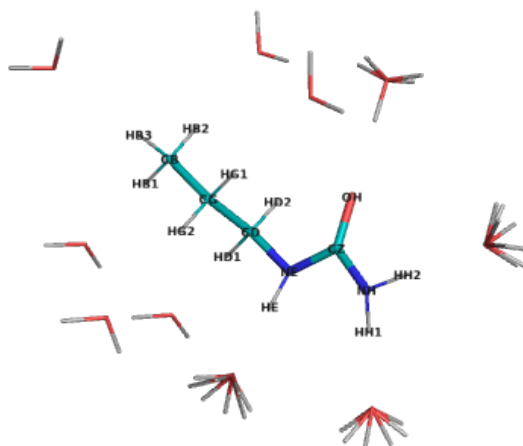


Figure S52: The molecule used for water complex calculations corresponding to propylurea, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S156: Statistics of calculated water interaction and dipole moment for propylurea.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.39/0.71	0.07/0.16	2.728	3.59/4.17	11.01
Optimal	0.28/0.57	0.05/0.13	2.469	3.59/4.19	0.72

Table S157: The comparison list of optimized atomic charges and their initial guess for propyl urea, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.286	3.464
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.180	-0.182	2.854
HG2	0.090	0.090	0.000
HG1	0.090	0.090	0.000
CD	-0.037	0.080	5.289
HD1	0.090	0.090	0.000
HD2	0.090	0.090	0.000
NE	-0.309	-0.404	7.397
HE	0.267	0.272	5.020
CZ	0.284	0.375	6.124
OH	-0.450	-0.484	0.000
NH	-0.525	-0.681	5.894
HH1	0.295	0.340	0.050
HH2	0.295	0.340	0.050

Table S158: Interaction energies and geometries between probe water and selected propylurea site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.66/-0.49/-0.52	2.84/2.77/2.77
2	HB1-CB	0.0	-0.77/-0.80/-1.00	2.88/2.77/2.75
3	HB2-CB	0.0	-0.52/-0.33/-0.53	2.77/2.72/2.71
4	HG2-CG	0.0	-0.98/-1.01/-1.17	2.90/2.77/2.74
5	HD1-CD	0.0	-1.19/-1.39/-1.90	2.76/2.69/2.64
6	HE-NE	0.0	-4.98/-5.30/-4.90	1.95/1.93/1.94
7	HE-NE	45.0	-5.70/-5.61/-5.26	1.91/1.91/1.92
8	HE-NE	90.0	-5.76/-5.69/-5.31	1.91/1.91/1.92
9	HE-NE	135.0	-5.05/-5.39/-4.97	1.95/1.92/1.94
10	OH-CZ	0.0	-6.14/-6.58/-6.73	1.83/1.77/1.76
11	OH-CZ	90.0	-6.38/-6.71/-7.09	1.82/1.77/1.75
12	OH-CZ	180.0	-6.40/-6.52/-7.02	1.82/1.77/1.76
13	OH-CZ	270.0	-6.38/-6.55/-6.88	1.82/1.77/1.76
14	HH1-NH	0.0	-5.66/-5.92/-5.88	1.92/1.90/1.89
15	HH1-NH	45.0	-5.83/-6.08/-6.04	1.91/1.89/1.88
16	HH1-NH	90.0	-5.29/-5.84/-5.80	1.94/1.90/1.89
17	HH1-NH	135.0	-5.10/-5.67/-5.64	1.95/1.91/1.89
18	HH2-NH	0.0	-4.66/-4.30/-4.39	1.88/1.90/1.88
19	HH2-NH	45.0	-4.30/-4.10/-4.19	1.90/1.90/1.89
20	HH2-NH	90.0	-3.93/-3.88/-3.96	1.92/1.91/1.90
21	HH2-NH	135.0	-4.27/-4.06/-4.15	1.90/1.91/1.89

1.52 Small molecule used for S,S-(2-hydroxyethyl)thiocysteine(CME)

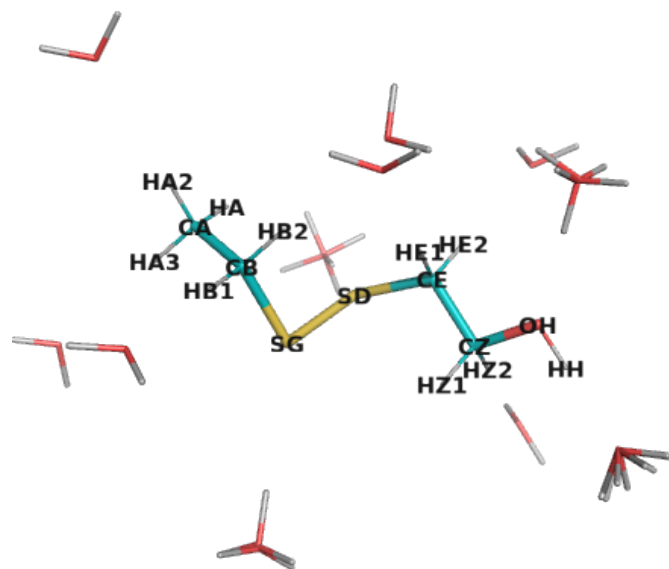


Figure S53: The molecule used for water complex calculations corresponding to 2-(ethyldisulfanyl)ethan-1-ol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S159: Statistics of calculated water interaction and dipole moment for 2-(ethyldisulfanyl)ethan-1-ol.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.41/0.98	0.29/0.53	2.928	1.23/1.19	57.65
Optimal	0.60/1.43	0.34/0.63	1.495	1.23/1.43	2.97

Table S160: The comparison list of optimized atomic charges and their initial guess for 2-(ethyldisulfanyl)ethan-1-ol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.000
HA	0.090	0.090	0.000
CB	-0.026	-0.099	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
SG	-0.136	-0.081	0.045
SD	-0.215	-0.091	21.353
CE	0.071	-0.088	21.695
HE1	0.090	0.090	0.000
HE2	0.090	0.090	0.000
CZ	-0.004	0.048	14.547
HZ1	0.090	0.090	0.050
HZ2	0.090	0.090	0.050
OH	-0.650	-0.649	2.300
HH	0.420	0.420	0.000

Table S161: Interaction energies and geometries between probe water and selected 2-(ethyldisulfanyl)ethan-1-ol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.84/-0.55/-0.51	2.71/2.73/2.75
2	HA2-CA	0.0	-1.05/-1.01/-0.80	2.78/2.72/2.74
3	HB1-CB	0.0	-1.61/-1.23/-0.93	2.57/2.68/2.72
4	HB2-CB	0.0	-2.56/-2.52/-1.91	2.67/2.71/2.73
5	SG-CB	0.0	-1.27/-2.02/-1.27	2.92/2.35/2.42
6	SG-CB	90.0	-1.09/-1.48/-1.03	2.89/2.38/2.44
7	SG-CB	180.0	-1.13/-1.81/-1.48	2.94/2.37/2.42
8	SG-CB	270.0	-1.60/-2.37/-1.76	2.85/2.34/2.39
9	SD-SG	0.0	-1.03/-2.11/-1.35	2.96/2.34/2.44
10	SD-SG	90.0	-1.40/-2.53/-1.44	2.88/2.31/2.42
11	SD-SG	180.0	-1.31/-2.73/-1.59	2.92/2.30/2.41
12	SD-SG	270.0	-1.16/-2.25/-1.42	2.90/2.32/2.43
13	HE1-CE	0.0	-1.13/-1.27/-0.75	2.93/2.87/2.94
14	HE2-CE	0.0	-1.37/-0.91/-0.39	2.52/2.66/2.73
15	HZ2-CZ	0.0	-0.94/-1.19/-1.36	2.73/2.67/2.66
16	OH-CZ	0.0	-5.65/-6.09/-5.94	1.84/1.85/1.86
17	OH-CZ	90.0	-5.74/-5.96/-6.07	1.83/1.85/1.86
18	OH-CZ	180.0	-4.72/-4.87/-5.59	1.88/1.87/1.86
19	OH-CZ	270.0	-5.56/-5.66/-5.89	1.83/1.85/1.86
20	HH-OH	0.0	-6.38/-6.50/-6.56	1.80/1.82/1.82
21	HH-OH	45.0	-6.47/-6.53/-6.60	1.79/1.82/1.82
22	HH-OH	90.0	-6.58/-6.56/-6.65	1.79/1.82/1.82
23	HH-OH	135.0	-6.49/-6.54/-6.61	1.79/1.82/1.82

1.53 Small molecule used for
 (2S)-2-[(2R)-2-amino-2-carboxyethyl]sulfanylbutanedioic acid(CML)

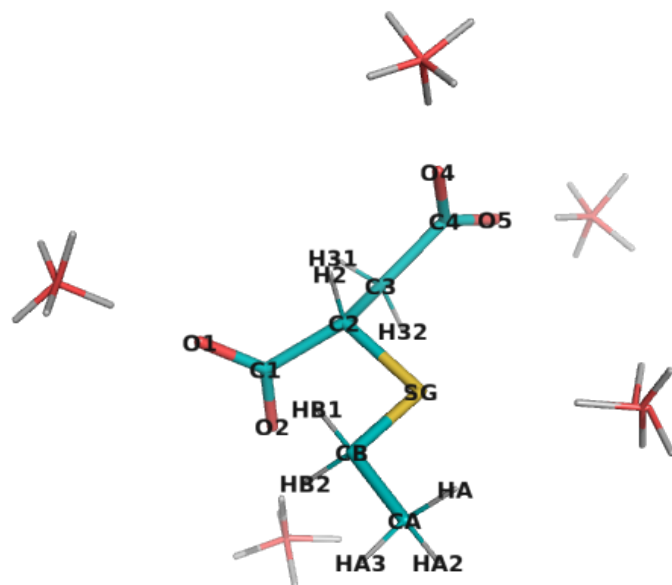


Figure S54: The molecule used for water complex calculations corresponding to 2-(ethylsulfanyl)butanedioic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S162: Statistics of calculated water interaction and dipole moment for 2-(ethylsulfanyl)butanedioic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.74/1.65	0.17/0.38	4.739	10.13/12.41	3.62
Optimal	0.45/1.18	0.18/0.41	2.449	10.13/10.35	3.26

Table S163: The comparison list of optimized atomic charges and their initial guess for 2-(ethylsulfanyl)butanedioicacid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.075
HA	0.090	0.090	0.000
CB	-0.203	-0.066	3.154
HB1	0.090	0.090	0.030
HB2	0.090	0.090	0.030
SG	-0.226	-0.197	18.760
C2	0.016	-0.136	18.900
H2	0.090	0.090	0.424
C1	0.714	0.645	4.583
O1	-0.803	-0.760	2.500
O2	-0.803	-0.760	2.500
C3	-0.219	-0.277	7.209
H31	0.090	0.090	0.300
H32	0.090	0.090	0.300
C4	0.738	0.621	2.564
O4	-0.832	-0.760	0.000
O5	-0.832	-0.760	0.000

Table S164: Interaction energies and geometries between probe water and selected 2-(ethylsulfanyl)butanedioicacid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	SG-CB	0.0	-10.99/-12.17/-12.65		2.60/2.24/2.23	
2	SG-CB	90.0	-6.93/-7.15/-7.08		2.71/2.33/2.34	
3	SG-CB	180.0	-4.08/-3.03/-2.61		2.85/2.44/2.51	
4	SG-CB	270.0	-6.19/-6.08/-6.13		2.74/2.35/2.36	
5	O1-C1	0.0	-17.26/-16.91/-16.85		1.69/1.64/1.65	
6	O1-C1	90.0	-16.82/-16.58/-16.66		1.69/1.64/1.64	
7	O1-C1	180.0	-16.34/-16.03/-15.66		1.69/1.64/1.65	
8	O1-C1	270.0	-16.27/-16.05/-15.46		1.70/1.64/1.65	
9	O2-C1	0.0	-17.57/-17.65/-17.60		1.70/1.64/1.64	
10	O2-C1	90.0	-16.12/-16.54/-15.86		1.71/1.64/1.65	
11	O2-C1	180.0	-15.82/-16.00/-15.62		1.70/1.64/1.65	
12	O2-C1	270.0	-16.55/-16.74/-16.89		1.70/1.64/1.64	
13	O4-C4	0.0	-17.94/-18.26/-18.06		1.69/1.63/1.64	
14	O4-C4	90.0	-17.19/-17.50/-16.91		1.69/1.63/1.64	
15	O4-C4	180.0	-16.22/-16.43/-15.80		1.69/1.63/1.65	
16	O4-C4	270.0	-16.44/-16.75/-16.44		1.70/1.63/1.65	
17	O5-C4	0.0	-17.86/-17.28/-16.84		1.68/1.63/1.64	
18	O5-C4	90.0	-17.26/-16.86/-16.31		1.68/1.63/1.65	
19	O5-C4	180.0	-17.49/-17.20/-16.42		1.67/1.63/1.64	
20	O5-C4	270.0	-17.76/-17.45/-16.76		1.68/1.63/1.64	

1.54 Small molecule A of (4Z)-2-(aminomethyl)-4-[(4-hydroxyphenyl)methylidene]-5-oxo-4acetic5-dihydro-1H-imidazol-1-ylaceticacid(CR2)

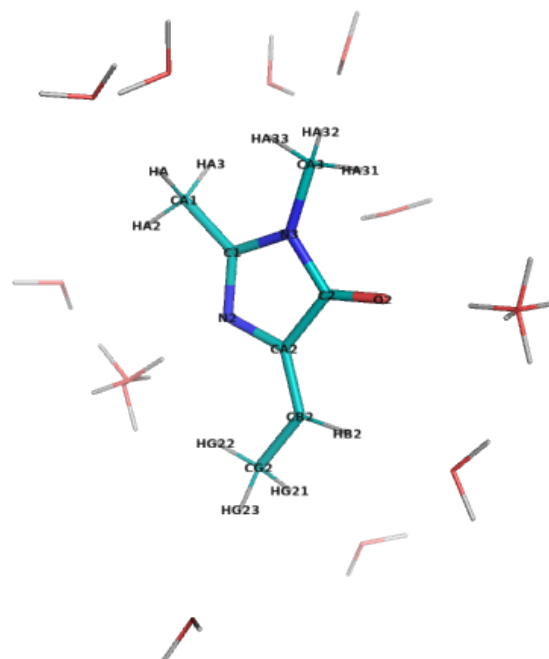


Figure S55: The molecule used for water complex calculations corresponding to (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S165: Statistics of calculated water interaction and dipole moment for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.92/1.64	0.10/0.25	6.526	3.17/0.45	27.81
Optimal	0.49/1.31	0.09/0.22	3.053	3.17/3.55	14.34

Table S166: The comparison list of optimized atomic charges and their initial guess for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA1	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
HA2	0.090	0.090	0.000
HA3	0.090	0.090	0.000
C1	0.233	0.074	23.781
N2	-0.679	-0.703	41.871
N3	-0.080	-0.079	15.706
C2	0.407	0.509	24.002
O2	-0.489	-0.482	6.710
CA2	0.288	0.516	47.153
CB2	-0.105	-0.135	25.469
HB2	0.150	0.150	3.270
CG2	-0.270	-0.274	15.277
HG21	0.090	0.090	1.175
HG22	0.090	0.090	1.175
HG23	0.090	0.090	1.175
CA3	-0.195	-0.271	3.821
HA31	0.090	0.090	0.000
HA32	0.090	0.090	0.000
HA33	0.090	0.090	0.000

Table S167: Interaction energies and geometries between probe water and selected (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA-CA1	0.0	-2.17/-2.61/-1.51		2.59/2.58/2.65	
2	HA2-CA1	0.0	-0.97/-0.86/0.05		2.58/2.64/2.77	
3	HA3-CA1	0.0	-2.55/-2.73/-1.57		2.52/2.57/2.64	
4	N2-C1	0.0	-4.99/-6.30/-5.60		2.09/2.01/2.02	
5	N2-C1	90.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
6	N2-C1	180.0	-5.35/-5.42/-6.38		1.95/2.01/1.99	
7	N2-C1	270.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
8	N3-C1	0.0	-0.26/-0.82/-0.78		2.74/2.52/2.49	
9	O2-C2	0.0	-5.51/-5.57/-5.00		1.85/1.78/1.80	
10	O2-C2	90.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
11	O2-C2	180.0	-5.92/-5.61/-4.27		1.84/1.78/1.81	
12	O2-C2	270.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
13	HB2-CB2	0.0	-1.40/-1.60/-2.82		2.32/2.47/2.44	
14	HG21-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
15	HG23-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
16	HA32-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	
17	HA33-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	

1.55 Small molecule B of (4Z)-2-(aminomethyl)-4-[(4-hydroxyphenyl)methylidene]-5-oxo-4,5-dihydro-1H-imidazol-1-ylacetic acid (CR2)

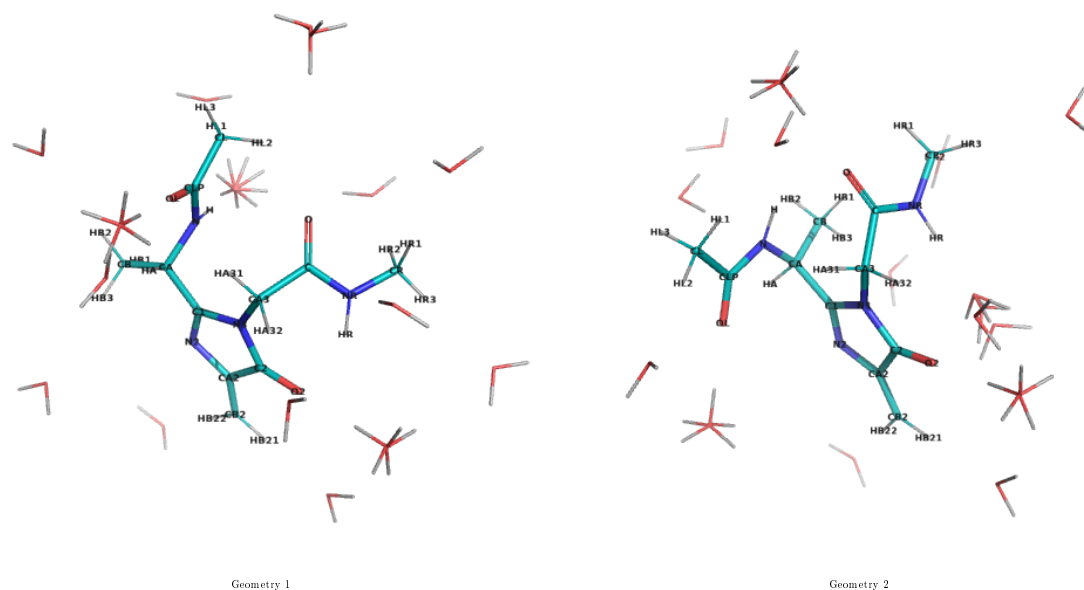


Table S168: The molecule used for water complex calculations corresponding to N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S169: Statistics of calculated water interaction and dipole moment for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide.

		RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
		Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Geometry 1	Initial	0.86 / 2.05	0.07 / 0.17	6.601	1.19 / 4.07	1.19
Geometry 2	Initial	1.02 / 2.07	0.09 / 0.23	6.126	6.37 / 4.43	6.37
Sum of geometries	Initial	0.95 / 2.07	0.08 / 0.23	12.727	-	-
Geometry 1	Optimal	0.36 / 0.81	0.07 / 0.16	2.460	1.19 / 1.37	1.19
Geometry 2	Optimal	0.51 / 0.91	0.08 / 0.19	2.701	6.37 / 7.25	6.37
Sum of geometries	Optimal	0.45 / 0.91	0.08 / 0.19	5.161	-	-

Table S170: The comparison list of optimized atomic charges and their initial guess for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
C1	0.233	0.164	24.002
N2	-0.679	-0.703	41.104
N3	-0.031	-0.499	22.994
C2	0.407	0.613	23.378
O2	-0.489	-0.482	6.517
CA2	0.466	0.512	42.773
CB2	-0.593	-0.444	13.655
HB21	0.230	0.230	0.950
HB22	0.230	0.230	0.950
CA3	-0.154	0.043	13.461
HA31	0.090	0.090	0.177
HA32	0.090	0.090	0.177
C	0.510	0.499	10.097
O	-0.510	-0.517	3.479
NR	-0.470	-0.442	6.773
HR	0.310	0.299	0.000
CR	-0.110	-0.108	0.239
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S171: Interaction energies and geometries between probe water and selected N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
Geometry 1				
1	O-C	0.0	-5.45/-5.47/-6.22	1.84/1.77/1.76
2	O-C	90.0	-6.01/-6.48/-6.53	1.83/1.75/1.76
3	O-C	180.0	-5.96/-6.64/-6.64	1.83/1.75/1.75
4	O-C	270.0	-5.67/-5.94/-6.62	1.84/1.76/1.75
5	NR-C	0.0	-1.32/-1.50/-1.08	2.24/2.20/2.22
6	HR2-CR	0.0	-1.10/-1.26/-1.09	2.71/2.66/2.67
7	HR3-CR	0.0	-1.39/-1.22/-1.32	2.66/2.67/2.67
8	N2-C1	0.0	-5.74/-6.45/-6.04	1.95/1.92/1.92
9	N2-C1	90.0	-6.51/-6.37/-7.24	1.90/1.92/1.90
10	N2-C1	180.0	-5.60/-5.66/-7.65	1.96/1.93/1.90
11	N2-C1	270.0	-6.64/-6.59/-7.43	1.90/1.91/1.89
12	O2-C2	0.0	-3.88/-3.93/-3.54	1.88/1.80/1.81
13	O2-C2	90.0	-4.94/-5.15/-4.46	1.84/1.77/1.79
14	O2-C2	180.0	-4.95/-5.20/-4.05	1.84/1.77/1.79
15	O2-C2	270.0	-3.93/-4.12/-3.39	1.87/1.79/1.81
16	HB21-CB2	0.0	-1.84/-1.64/-3.47	2.32/2.48/2.42
17	HB22-CB2	0.0	-1.82/-1.01/-2.42	2.42/2.54/2.46
18	HA31-CA3	0.0	-2.08/-2.47/-1.68	2.70/2.69/2.70
19	HA-CA	0.0	-2.47/-2.76/-1.19	2.49/2.56/2.66
Geometry 2				
20	O-C	0.0	-6.06/-6.90/-7.24	1.86/1.76/1.75
21	O-C	90.0	-5.25/-6.15/-7.32	1.87/1.77/1.75
22	O-C	180.0	-4.71/-5.63/-6.52	1.88/1.77/1.76
23	O-C	270.0	-5.56/-6.46/-6.85	1.86/1.76/1.76
24	HR-NR	0.0	-7.09/-7.67/-7.53	1.93/1.90/1.90
25	HR-NR	45.0	-7.71/-7.90/-7.71	1.91/1.89/1.89
26	HR-NR	90.0	-7.79/-7.84/-7.79	1.90/1.89/1.89
27	HR-NR	135.0	-7.18/-7.62/-7.61	1.92/1.90/1.89
28	HR1-CR	0.0	-0.71/-0.04/0.30	2.50/2.69/2.67
29	HR2-CR	0.0	-1.54/-1.44/-1.38	2.68/2.66/2.66
30	HR3-CR	0.0	-1.84/-1.82/-1.70	2.68/2.67/2.66
31	N2-C1	0.0	-6.46/-6.98/-6.58	1.93/1.91/1.91
32	N2-C1	90.0	-6.88/-6.47/-7.35	1.89/1.91/1.89
33	N2-C1	180.0	-5.73/-5.60/-7.60	1.95/1.93/1.90
34	N2-C1	270.0	-7.31/-7.09/-7.94	1.88/1.91/1.89
35	N3-C1	0.0	-0.22/0.03/-2.15	2.60/2.67/2.17
36	O2-C2	0.0	-4.96/-5.34/-4.95	1.88/1.79/1.80
37	O2-C2	90.0	-5.32/-5.37/-4.66	1.87/1.78/1.80
38	O2-C2	180.0	-5.74/-5.89/-4.71	1.87/1.78/1.81
39	O2-C2	270.0	-5.94/-6.25/-5.51	1.85/1.77/1.79
40	HB21-CB2	0.0	-1.43/-1.20/-3.03	2.33/2.48/2.41
41	HB22-CB2	0.0	-1.29/-0.66/-2.05	2.47/2.56/2.47
42	HA31-CA3	0.0	-3.71/-4.08/-3.49	2.50/2.57/2.57
43	HA-CA	0.0	-2.67/-3.45/-1.93	2.59/2.58/2.69

1.56 Small molecule A of
 2-[1-amino-2-(1H-imidazol-5-yl)ethyl]-1-(carbOymethyl)-4-[(4-Oocycl
 ohexa-2,5-dien-1-ylidene)methyl]-1H-imidazol-5-olate(CR8D)

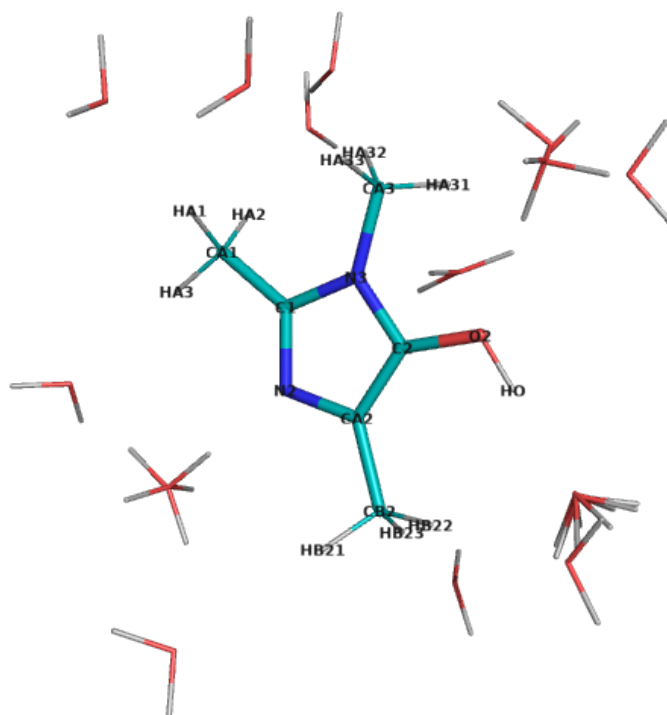


Figure S56: The molecule used for water complex calculations corresponding to trimethyl-1H-imidazol-5-ol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S172: Statistics of calculated water interaction and dipole moment for trimethyl-1H-imidazol-5-ol.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.92/1.99	0.12/0.25	3.944	2.69/1.12	16.07
Optimal	0.27/0.51	0.07/0.14	2.347	2.69/3.46	1.48

Table S173: The comparison list of optimized atomic charges and their initial guess for trimethyl-1H-imidazol-5-ol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA1	-0.229	-0.113	14.764
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
HA3	0.090	0.090	0.000
C1	0.379	0.239	26.194
N2	-0.700	-0.679	20.607
N3	-0.040	-0.042	33.417
CA2	0.165	0.325	33.412
C2	0.104	0.071	73.413
O2	-0.504	-0.554	65.809
HO	0.432	0.420	4.985
CB2	-0.270	-0.246	6.867
HB21	0.090	0.090	0.450
HB22	0.090	0.090	0.450
HB23	0.090	0.090	0.450
CA3	-0.147	-0.231	3.536
HA31	0.090	0.090	0.000
HA32	0.090	0.090	0.000
HA33	0.090	0.090	0.000

Table S174: Interaction energies and geometries between probe water and selected trimethyl-1H-imidazol-5-ol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA1-CA1	0.0	-1.45/-1.66/-1.80		2.67/2.64/2.61	
2	HA2-CA1	0.0	-1.56/-1.69/-1.84		2.63/2.64/2.61	
3	N2-C1	0.0	-7.90/-8.33/-7.36		1.89/1.89/1.90	
4	N2-C1	90.0	-8.35/-8.07/-7.42		1.86/1.89/1.90	
5	N2-C1	180.0	-7.33/-7.26/-6.73		1.91/1.91/1.91	
6	N2-C1	270.0	-8.37/-8.04/-7.40		1.86/1.89/1.90	
7	N3-C1	0.0	-0.63/-0.73/-2.25		2.56/2.47/2.31	
8	N3-C1	180.0	-1.70/-2.21/-2.59		2.48/2.37/2.31	
9	O2-C2	0.0	-3.08/-3.12/-3.61		2.05/2.19/2.17	
10	O2-C2	90.0	-2.09/-2.25/-3.34		2.20/2.22/2.18	
11	O2-C2	180.0	-1.32/-1.68/-3.31		2.33/2.25/2.17	
12	O2-C2	270.0	-3.13/-3.24/-3.96		2.07/2.17/2.15	
13	HO-O2	0.0	-6.62/-6.22/-5.38		1.87/1.97/2.04	
14	HO-O2	45.0	-6.61/-6.36/-5.67		1.84/1.96/2.02	
15	HO-O2	90.0	-6.03/-6.20/-5.59		1.87/1.97/2.02	
16	HO-O2	135.0	-5.91/-6.02/-5.28		1.91/1.98/2.05	
17	HB22-CB2	0.0	-2.22/-2.47/-2.94		2.71/2.65/2.60	
18	HB23-CB2	0.0	-0.39/-0.09/-0.75		2.84/2.80/2.69	
19	HA32-CA3	0.0	-2.00/-2.35/-1.67		2.72/2.64/2.73	
20	HA33-CA3	0.0	-1.60/-1.66/-0.80		2.61/2.62/2.71	

1.57 Small molecule B of
 2-[1-amino-2-(1h-imidazol-5-yl)ethyl]-1-(carbOymethyl)-4-[(4-Oocycl
 ohexa-2,5-dien-1-ylidene)methyl]-1h-imidazol-5-olate(CR8D)

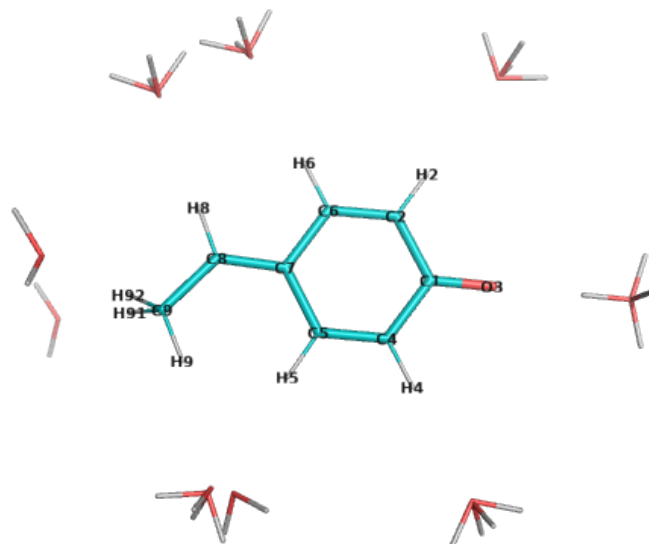


Figure S57: The molecule used for water complex calculations corresponding to 4-ethylidenecyclohexa-2,5-dien-1-one, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S175: Statistics of calculated water interaction and dipole moment for 4-ethylidenecyclohexa-2,5-dien-1-one.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.64/1.14	0.10/0.15	4.864	6.34/3.76	7.20
Optimal	0.43/0.99	0.08/0.15	2.506	6.34/6.76	5.10

Table S176: The comparison list of optimized atomic charges and their initial guess for 4-ethylidenecyclohexa-2,5-dien-1-one, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
C9	-0.270	-0.270	0.000
H9	0.090	0.090	0.000
H91	0.090	0.090	0.000
H92	0.090	0.090	0.000
C8	-0.021	-0.153	0.000
H8	0.150	0.150	0.000
C7	0.084	0.015	4.010
C5	-0.159	-0.159	20.897
H5	0.150	0.150	2.456
C6	-0.159	-0.159	20.897
H6	0.150	0.150	2.456
C2	-0.144	-0.082	12.094
H2	0.150	0.150	2.500
C4	-0.144	-0.082	12.094
H4	0.150	0.150	2.500
C1	0.198	0.311	17.406
O3	-0.405	-0.441	0.247

Table S177: Interaction energies and geometries between probe water and selected 4-ethylidenecyclohexa-2,5-dien-1-one site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	H9-C9	0.0	-3.17/-2.69/-2.03	2.78/2.84/2.92
2	H91-C9	0.0	-1.84/-1.58/-0.78	2.62/2.68/2.76
3	H92-C9	0.0	-1.84/-1.58/-0.78	2.62/2.68/2.76
4	H8-C8	0.0	-2.64/-3.63/-2.22	2.53/2.48/2.56
5	H8-C8	90.0	-3.17/-3.80/-2.42	2.44/2.47/2.54
6	H5-C5	0.0	-2.40/-2.24/-1.99	2.75/2.72/2.73
7	H5-C5	90.0	-3.02/-2.42/-2.11	2.64/2.70/2.71
8	H6-C6	0.0	-2.20/-2.84/-2.51	2.55/2.53/2.53
9	H6-C6	90.0	-2.73/-3.08/-2.68	2.45/2.50/2.51
10	H2-C2	0.0	-1.14/-0.91/-1.78	2.51/2.57/2.52
11	H2-C2	90.0	-0.93/-0.80/-1.66	2.55/2.59/2.53
12	H4-C4	0.0	-1.20/-0.83/-1.70	2.51/2.57/2.52
13	H4-C4	90.0	-0.98/-0.72/-1.57	2.55/2.59/2.53
14	O3-C1	0.0	-6.27/-6.42/-6.02	1.84/1.69/1.69
15	O3-C1	90.0	-6.25/-6.51/-6.11	1.84/1.69/1.69
16	O3-C1	180.0	-6.24/-6.45/-6.05	1.84/1.69/1.69
17	O3-C1	270.0	-6.25/-6.51/-6.11	1.84/1.69/1.69

1.58 Small molecule A of
 [(4Z)-2-[(1R,2R)-1-amino-2-hydroxypropyl]-4-(1H-indol-3-ylmethylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl]acetic acid(CRF)

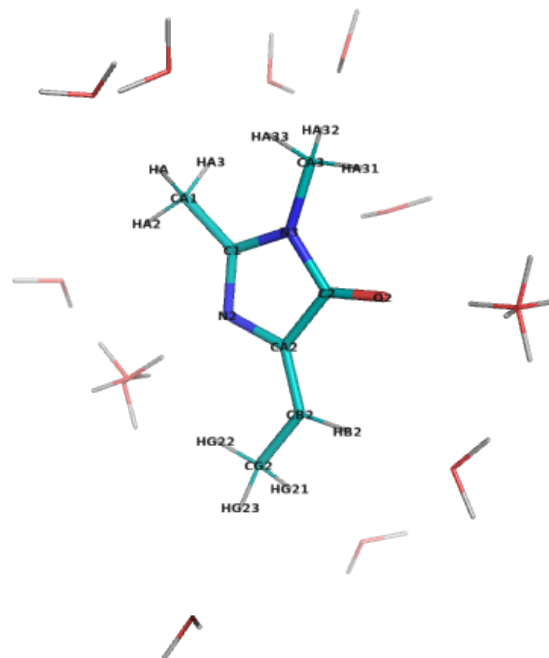


Figure S58: The molecule used for water complex calculations corresponding to (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S178: Statistics of calculated water interaction and dipole moment for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.92/1.64	0.10/0.25	6.526	3.17/0.45	27.81
Optimal	0.49/1.31	0.09/0.22	3.053	3.17/3.55	14.34

Table S179: The comparison list of optimized atomic charges and their initial guess for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA1	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
HA2	0.090	0.090	0.000
HA3	0.090	0.090	0.000
C1	0.233	0.074	23.781
N2	-0.679	-0.703	41.871
N3	-0.080	-0.079	15.706
C2	0.407	0.509	24.002
O2	-0.489	-0.482	6.710
CA2	0.288	0.516	47.153
CB2	-0.105	-0.135	25.469
HB2	0.150	0.150	3.270
CG2	-0.270	-0.274	15.277
HG21	0.090	0.090	1.175
HG22	0.090	0.090	1.175
HG23	0.090	0.090	1.175
CA3	-0.195	-0.271	3.821
HA31	0.090	0.090	0.000
HA32	0.090	0.090	0.000
HA33	0.090	0.090	0.000

Table S180: Interaction energies and geometries between probe water and selected (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA-CA1	0.0	-2.17/-2.61/-1.51		2.59/2.58/2.65	
2	HA2-CA1	0.0	-0.97/-0.86/0.05		2.58/2.64/2.77	
3	HA3-CA1	0.0	-2.55/-2.73/-1.57		2.52/2.57/2.64	
4	N2-C1	0.0	-4.99/-6.30/-5.60		2.09/2.01/2.02	
5	N2-C1	90.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
6	N2-C1	180.0	-5.35/-5.42/-6.38		1.95/2.01/1.99	
7	N2-C1	270.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
8	N3-C1	0.0	-0.26/-0.82/-0.78		2.74/2.52/2.49	
9	O2-C2	0.0	-5.51/-5.57/-5.00		1.85/1.78/1.80	
10	O2-C2	90.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
11	O2-C2	180.0	-5.92/-5.61/-4.27		1.84/1.78/1.81	
12	O2-C2	270.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
13	HB2-CB2	0.0	-1.40/-1.60/-2.82		2.32/2.47/2.44	
14	HG21-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
15	HG23-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
16	HA32-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	
17	HA33-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	

1.59 Small molecule B of
[(4Z)-2-[(1R,2R)-1-amino-2-hydroxypropyl]-4-(1H-indol-3-ylmethylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl]acetic acid(CRF)

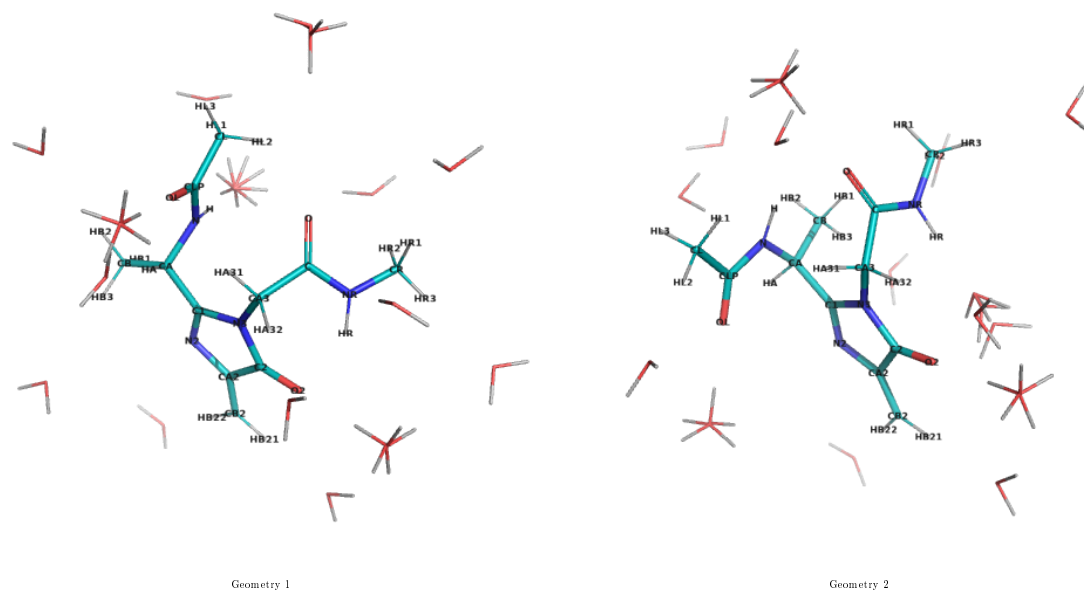


Table S181: The molecule used for water complex calculations corresponding to N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S182: Statistics of calculated water interaction and dipole moment for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide.

		RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
		Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Geometry 1	Initial	0.86 / 2.05	0.07 / 0.17	6.601	1.19 / 4.07	1.19
Geometry 2	Initial	1.02 / 2.07	0.09 / 0.23	6.126	6.37 / 4.43	6.37
Sum of geometries	Initial	0.95 / 2.07	0.08 / 0.23	12.727	-	-
Geometry 1	Optimal	0.36 / 0.81	0.07 / 0.16	2.460	1.19 / 1.37	1.19
Geometry 2	Optimal	0.51 / 0.91	0.08 / 0.19	2.701	6.37 / 7.25	6.37
Sum of geometries	Optimal	0.45 / 0.91	0.08 / 0.19	5.161	-	-

Table S183: The comparison list of optimized atomic charges and their initial guess for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
C1	0.233	0.164	24.002
N2	-0.679	-0.703	41.104
N3	-0.031	-0.499	22.994
C2	0.407	0.613	23.378
O2	-0.489	-0.482	6.517
CA2	0.466	0.512	42.773
CB2	-0.593	-0.444	13.655
HB21	0.230	0.230	0.950
HB22	0.230	0.230	0.950
CA3	-0.154	0.043	13.461
HA31	0.090	0.090	0.177
HA32	0.090	0.090	0.177
C	0.510	0.499	10.097
O	-0.510	-0.517	3.479
NR	-0.470	-0.442	6.773
HR	0.310	0.299	0.000
CR	-0.110	-0.108	0.239
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S184: Interaction energies and geometries between probe water and selected N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
Geometry 1				
1	O-C	0.0	-5.45/-5.47/-6.22	1.84/1.77/1.76
2	O-C	90.0	-6.01/-6.48/-6.53	1.83/1.75/1.76
3	O-C	180.0	-5.96/-6.64/-6.64	1.83/1.75/1.75
4	O-C	270.0	-5.67/-5.94/-6.62	1.84/1.76/1.75
5	NR-C	0.0	-1.32/-1.50/-1.08	2.24/2.20/2.22
6	HR2-CR	0.0	-1.10/-1.26/-1.09	2.71/2.66/2.67
7	HR3-CR	0.0	-1.39/-1.22/-1.32	2.66/2.67/2.67
8	N2-C1	0.0	-5.74/-6.45/-6.04	1.95/1.92/1.92
9	N2-C1	90.0	-6.51/-6.37/-7.24	1.90/1.92/1.90
10	N2-C1	180.0	-5.60/-5.66/-7.65	1.96/1.93/1.90
11	N2-C1	270.0	-6.64/-6.59/-7.43	1.90/1.91/1.89
12	O2-C2	0.0	-3.88/-3.93/-3.54	1.88/1.80/1.81
13	O2-C2	90.0	-4.94/-5.15/-4.46	1.84/1.77/1.79
14	O2-C2	180.0	-4.95/-5.20/-4.05	1.84/1.77/1.79
15	O2-C2	270.0	-3.93/-4.12/-3.39	1.87/1.79/1.81
16	HB21-CB2	0.0	-1.84/-1.64/-3.47	2.32/2.48/2.42
17	HB22-CB2	0.0	-1.82/-1.01/-2.42	2.42/2.54/2.46
18	HA31-CA3	0.0	-2.08/-2.47/-1.68	2.70/2.69/2.70
19	HA-CA	0.0	-2.47/-2.76/-1.19	2.49/2.56/2.66
Geometry 2				
20	O-C	0.0	-6.06/-6.90/-7.24	1.86/1.76/1.75
21	O-C	90.0	-5.25/-6.15/-7.32	1.87/1.77/1.75
22	O-C	180.0	-4.71/-5.63/-6.52	1.88/1.77/1.76
23	O-C	270.0	-5.56/-6.46/-6.85	1.86/1.76/1.76
24	HR-NR	0.0	-7.09/-7.67/-7.53	1.93/1.90/1.90
25	HR-NR	45.0	-7.71/-7.90/-7.71	1.91/1.89/1.89
26	HR-NR	90.0	-7.79/-7.84/-7.79	1.90/1.89/1.89
27	HR-NR	135.0	-7.18/-7.62/-7.61	1.92/1.90/1.89
28	HR1-CR	0.0	-0.71/-0.04/0.30	2.50/2.69/2.67
29	HR2-CR	0.0	-1.54/-1.44/-1.38	2.68/2.66/2.66
30	HR3-CR	0.0	-1.84/-1.82/-1.70	2.68/2.67/2.66
31	N2-C1	0.0	-6.46/-6.98/-6.58	1.93/1.91/1.91
32	N2-C1	90.0	-6.88/-6.47/-7.35	1.89/1.91/1.89
33	N2-C1	180.0	-5.73/-5.60/-7.60	1.95/1.93/1.90
34	N2-C1	270.0	-7.31/-7.09/-7.94	1.88/1.91/1.89
35	N3-C1	0.0	-0.22/0.03/-2.15	2.60/2.67/2.17
36	O2-C2	0.0	-4.96/-5.34/-4.95	1.88/1.79/1.80
37	O2-C2	90.0	-5.32/-5.37/-4.66	1.87/1.78/1.80
38	O2-C2	180.0	-5.74/-5.89/-4.71	1.87/1.78/1.81
39	O2-C2	270.0	-5.94/-6.25/-5.51	1.85/1.77/1.79
40	HB21-CB2	0.0	-1.43/-1.20/-3.03	2.33/2.48/2.41
41	HB22-CB2	0.0	-1.29/-0.66/-2.05	2.47/2.56/2.47
42	HA31-CA3	0.0	-3.71/-4.08/-3.49	2.50/2.57/2.57
43	HA-CA	0.0	-2.67/-3.45/-1.93	2.59/2.58/2.69

1.60 Small molecule A of
 2-[(1R,2R)-1-amino-2-hydroxypropyl]-4-(4-hydroxybenzylidene)-5-oxo-4-acetic-5-dihydro-1H-imidazol-1-ylacetic acid(CRO)

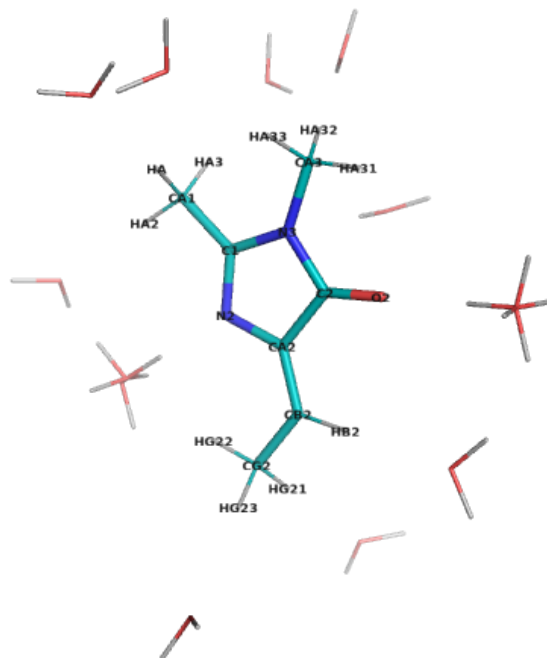


Figure S59: The molecule used for water complex calculations corresponding to (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S185: Statistics of calculated water interaction and dipole moment for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.92/1.64	0.10/0.25	6.526	3.17/0.45	27.81
Optimal	0.49/1.31	0.09/0.22	3.053	3.17/3.55	14.34

Table S186: The comparison list of optimized atomic charges and their initial guess for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA1	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
HA2	0.090	0.090	0.000
HA3	0.090	0.090	0.000
C1	0.233	0.074	23.781
N2	-0.679	-0.703	41.871
N3	-0.080	-0.079	15.706
C2	0.407	0.509	24.002
O2	-0.489	-0.482	6.710
CA2	0.288	0.516	47.153
CB2	-0.105	-0.135	25.469
HB2	0.150	0.150	3.270
CG2	-0.270	-0.274	15.277
HG21	0.090	0.090	1.175
HG22	0.090	0.090	1.175
HG23	0.090	0.090	1.175
CA3	-0.195	-0.271	3.821
HA31	0.090	0.090	0.000
HA32	0.090	0.090	0.000
HA33	0.090	0.090	0.000

Table S187: Interaction energies and geometries between probe water and selected (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA-CA1	0.0	-2.17/-2.61/-1.51		2.59/2.58/2.65	
2	HA2-CA1	0.0	-0.97/-0.86/0.05		2.58/2.64/2.77	
3	HA3-CA1	0.0	-2.55/-2.73/-1.57		2.52/2.57/2.64	
4	N2-C1	0.0	-4.99/-6.30/-5.60		2.09/2.01/2.02	
5	N2-C1	90.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
6	N2-C1	180.0	-5.35/-5.42/-6.38		1.95/2.01/1.99	
7	N2-C1	270.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
8	N3-C1	0.0	-0.26/-0.82/-0.78		2.74/2.52/2.49	
9	O2-C2	0.0	-5.51/-5.57/-5.00		1.85/1.78/1.80	
10	O2-C2	90.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
11	O2-C2	180.0	-5.92/-5.61/-4.27		1.84/1.78/1.81	
12	O2-C2	270.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
13	HB2-CB2	0.0	-1.40/-1.60/-2.82		2.32/2.47/2.44	
14	HG21-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
15	HG23-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
16	HA32-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	
17	HA33-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	

1.61 Small molecule B of
2-[(1R,2R)-1-amino-2-hydroxypropyl]-4-(4-hydroxybenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-ylacetic acid(CRO)

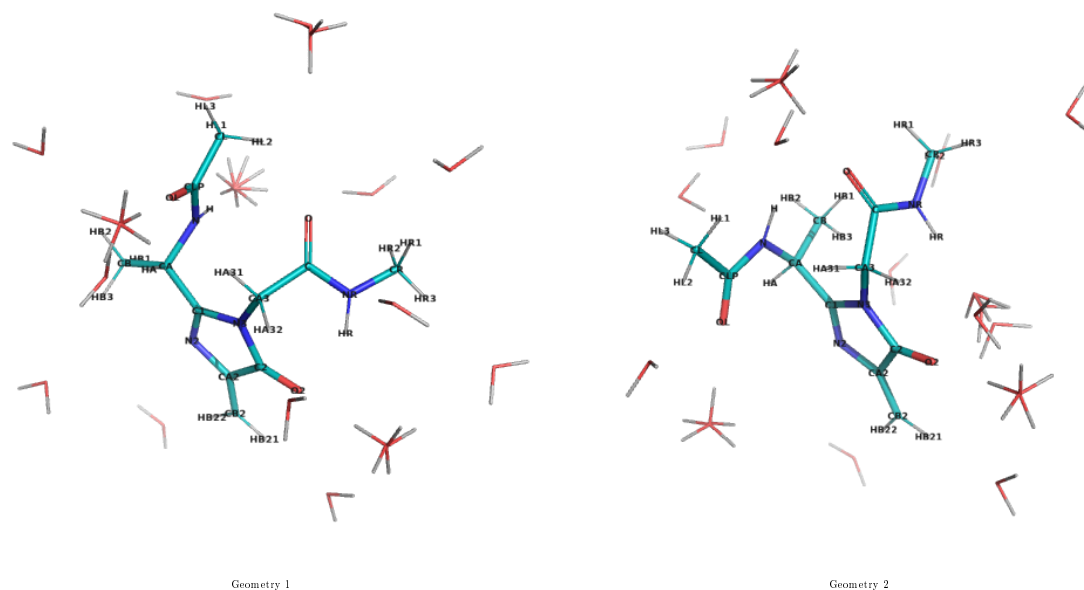


Table S188: The molecule used for water complex calculations corresponding to N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S189: Statistics of calculated water interaction and dipole moment for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide.

		RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
		Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Geometry 1	Initial	0.86 / 2.05	0.07 / 0.17	6.601	1.19 / 4.07	1.19
Geometry 2	Initial	1.02 / 2.07	0.09 / 0.23	6.126	6.37 / 4.43	6.37
Sum of geometries	Initial	0.95 / 2.07	0.08 / 0.23	12.727	-	-
Geometry 1	Optimal	0.36 / 0.81	0.07 / 0.16	2.460	1.19 / 1.37	1.19
Geometry 2	Optimal	0.51 / 0.91	0.08 / 0.19	2.701	6.37 / 7.25	6.37
Sum of geometries	Optimal	0.45 / 0.91	0.08 / 0.19	5.161	-	-

Table S190: The comparison list of optimized atomic charges and their initial guess for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
C1	0.233	0.164	24.002
N2	-0.679	-0.703	41.104
N3	-0.031	-0.499	22.994
C2	0.407	0.613	23.378
O2	-0.489	-0.482	6.517
CA2	0.466	0.512	42.773
CB2	-0.593	-0.444	13.655
HB21	0.230	0.230	0.950
HB22	0.230	0.230	0.950
CA3	-0.154	0.043	13.461
HA31	0.090	0.090	0.177
HA32	0.090	0.090	0.177
C	0.510	0.499	10.097
O	-0.510	-0.517	3.479
NR	-0.470	-0.442	6.773
HR	0.310	0.299	0.000
CR	-0.110	-0.108	0.239
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S191: Interaction energies and geometries between probe water and selected N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
Geometry 1				
1	O-C	0.0	-5.45/-5.47/-6.22	1.84/1.77/1.76
2	O-C	90.0	-6.01/-6.48/-6.53	1.83/1.75/1.76
3	O-C	180.0	-5.96/-6.64/-6.64	1.83/1.75/1.75
4	O-C	270.0	-5.67/-5.94/-6.62	1.84/1.76/1.75
5	NR-C	0.0	-1.32/-1.50/-1.08	2.24/2.20/2.22
6	HR2-CR	0.0	-1.10/-1.26/-1.09	2.71/2.66/2.67
7	HR3-CR	0.0	-1.39/-1.22/-1.32	2.66/2.67/2.67
8	N2-C1	0.0	-5.74/-6.45/-6.04	1.95/1.92/1.92
9	N2-C1	90.0	-6.51/-6.37/-7.24	1.90/1.92/1.90
10	N2-C1	180.0	-5.60/-5.66/-7.65	1.96/1.93/1.90
11	N2-C1	270.0	-6.64/-6.59/-7.43	1.90/1.91/1.89
12	O2-C2	0.0	-3.88/-3.93/-3.54	1.88/1.80/1.81
13	O2-C2	90.0	-4.94/-5.15/-4.46	1.84/1.77/1.79
14	O2-C2	180.0	-4.95/-5.20/-4.05	1.84/1.77/1.79
15	O2-C2	270.0	-3.93/-4.12/-3.39	1.87/1.79/1.81
16	HB21-CB2	0.0	-1.84/-1.64/-3.47	2.32/2.48/2.42
17	HB22-CB2	0.0	-1.82/-1.01/-2.42	2.42/2.54/2.46
18	HA31-CA3	0.0	-2.08/-2.47/-1.68	2.70/2.69/2.70
19	HA-CA	0.0	-2.47/-2.76/-1.19	2.49/2.56/2.66
Geometry 2				
20	O-C	0.0	-6.06/-6.90/-7.24	1.86/1.76/1.75
21	O-C	90.0	-5.25/-6.15/-7.32	1.87/1.77/1.75
22	O-C	180.0	-4.71/-5.63/-6.52	1.88/1.77/1.76
23	O-C	270.0	-5.56/-6.46/-6.85	1.86/1.76/1.76
24	HR-NR	0.0	-7.09/-7.67/-7.53	1.93/1.90/1.90
25	HR-NR	45.0	-7.71/-7.90/-7.71	1.91/1.89/1.89
26	HR-NR	90.0	-7.79/-7.84/-7.79	1.90/1.89/1.89
27	HR-NR	135.0	-7.18/-7.62/-7.61	1.92/1.90/1.89
28	HR1-CR	0.0	-0.71/-0.04/0.30	2.50/2.69/2.67
29	HR2-CR	0.0	-1.54/-1.44/-1.38	2.68/2.66/2.66
30	HR3-CR	0.0	-1.84/-1.82/-1.70	2.68/2.67/2.66
31	N2-C1	0.0	-6.46/-6.98/-6.58	1.93/1.91/1.91
32	N2-C1	90.0	-6.88/-6.47/-7.35	1.89/1.91/1.89
33	N2-C1	180.0	-5.73/-5.60/-7.60	1.95/1.93/1.90
34	N2-C1	270.0	-7.31/-7.09/-7.94	1.88/1.91/1.89
35	N3-C1	0.0	-0.22/0.03/-2.15	2.60/2.67/2.17
36	O2-C2	0.0	-4.96/-5.34/-4.95	1.88/1.79/1.80
37	O2-C2	90.0	-5.32/-5.37/-4.66	1.87/1.78/1.80
38	O2-C2	180.0	-5.74/-5.89/-4.71	1.87/1.78/1.81
39	O2-C2	270.0	-5.94/-6.25/-5.51	1.85/1.77/1.79
40	HB21-CB2	0.0	-1.43/-1.20/-3.03	2.33/2.48/2.41
41	HB22-CB2	0.0	-1.29/-0.66/-2.05	2.47/2.56/2.47
42	HA31-CA3	0.0	-3.71/-4.08/-3.49	2.50/2.57/2.57
43	HA-CA	0.0	-2.67/-3.45/-1.93	2.59/2.58/2.69

1.62 Small molecule A of [2-(3-carbamoyl-1-imino-propyl)-4-(4-hydroxy-benzylidene)-5-oxo-4,5-dihydro-imidazol-1-yl]-aceticacid(CRQ)

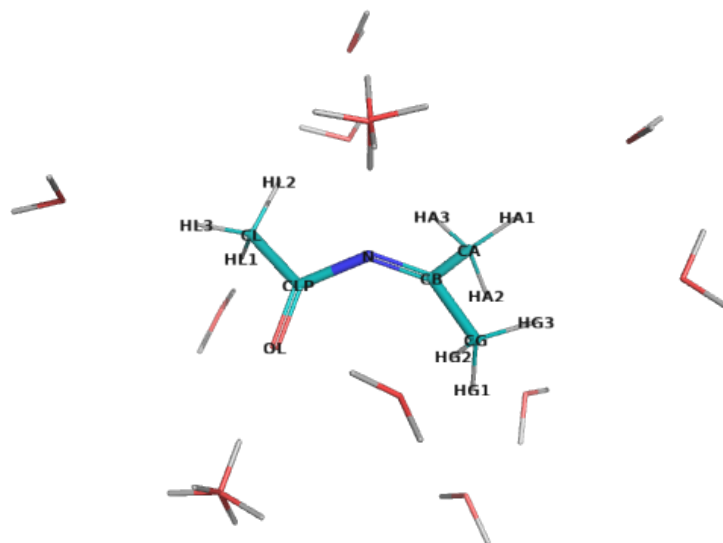


Figure S60: The molecule used for water complex calculations corresponding to N-(propan-2-ylidene)acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S192: Statistics of calculated water interaction and dipole moment for N-(propan-2-ylidene)acetamide.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	3.41/7.36	0.12/0.26	9.096	4.63/6.88	17.09
Optimal	0.43/0.73	0.08/0.13	2.495	4.63/5.33	4.69

Table S193: The comparison list of optimized atomic charges and their initial guess for N-(propan-2-ylidene)acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.270	0.000
HL1	0.090	0.090	0.000
HL2	0.090	0.090	0.000
HL3	0.090	0.090	0.000
CLP	0.510	0.510	0.000
OL	-0.510	-0.510	0.000
N	-0.410	-0.844	113.808
CB	0.166	-0.261	53.301
CG	-0.148	-0.040	36.206
HG1	0.090	0.090	0.250
HG2	0.090	0.090	0.250
HG3	0.090	0.090	0.250
CA	-0.148	-0.040	36.206
HA1	0.090	0.090	0.250
HA2	0.090	0.090	0.250
HA3	0.090	0.090	0.250

Table S194: Interaction energies and geometries between probe water and selected N-(propan-2-ylidene)acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HG1-CG	0.0	-1.84/-1.60/-2.23	2.51/2.61/2.55
2	HG2-CG	0.0	-0.66/-0.55/-0.14	2.49/2.61/2.57
3	HG3-CG	0.0	-1.81/-2.15/-2.97	2.66/2.62/2.55
4	HA1-CA	0.0	-2.42/-2.18/-2.80	2.49/2.60/2.54
5	HA2-CA	0.0	-2.47/-2.48/-3.52	2.53/2.59/2.53
6	HA3-CA	0.0	-1.75/-2.07/-1.91	2.71/2.66/2.68
7	HL1-CL	0.0	-1.27/-0.69/-1.35	2.61/2.71/2.61
8	HL2-CL	0.0	-0.80/-0.95/-0.30	2.79/2.73/2.74
9	HL3-CL	0.0	-0.74/-0.16/-0.82	2.63/2.73/2.61
10	OL-CLP	0.0	-6.39/-7.08/-6.92	1.84/1.76/1.77
11	OL-CLP	90.0	-5.91/-6.59/-6.51	1.85/1.76/1.77
12	OL-CLP	180.0	-6.06/-6.64/-6.97	1.84/1.76/1.76
13	OL-CLP	270.0	-6.51/-7.24/-7.59	1.84/1.75/1.76
14	N-CLP	0.0	-2.98/-2.93/-10.35	2.10/2.06/1.84
15	N-CLP	90.0	-3.47/-3.01/-9.79	2.05/2.06/1.85
16	N-CLP	180.0	-4.10/-4.16/-10.84	2.06/2.04/1.85
17	N-CLP	270.0	-4.41/-4.22/-11.64	2.02/2.03/1.83

1.63 Small molecule B of [2-(3-carbamoyl-1-imino-propyl)-4-(4-hydroxy-benzylidene)-5-oxo-4,5-dihydro-imidazol-1-yl]-aceticacid(CRQ)

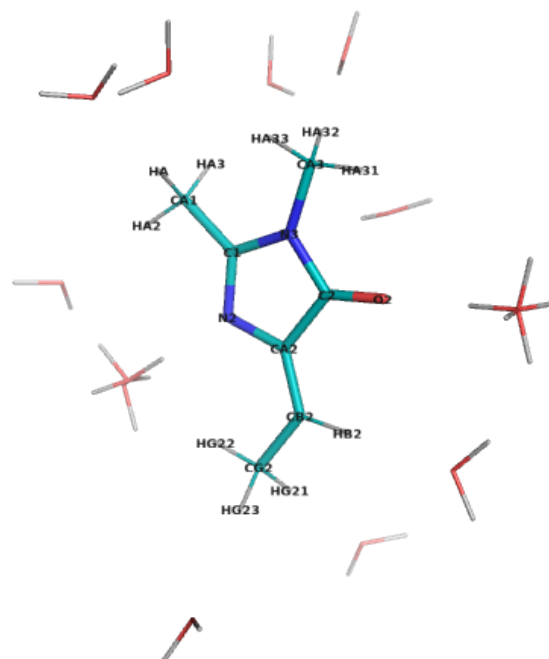


Figure S61: The molecule used for water complex calculations corresponding to (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S195: Statistics of calculated water interaction and dipole moment for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.92/1.64	0.10/0.25	6.526	3.17/0.45	27.81
Optimal	0.49/1.31	0.09/0.22	3.053	3.17/3.55	14.34

Table S196: The comparison list of optimized atomic charges and their initial guess for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA1	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
HA2	0.090	0.090	0.000
HA3	0.090	0.090	0.000
C1	0.233	0.074	23.781
N2	-0.679	-0.703	41.871
N3	-0.080	-0.079	15.706
C2	0.407	0.509	24.002
O2	-0.489	-0.482	6.710
CA2	0.288	0.516	47.153
CB2	-0.105	-0.135	25.469
HB2	0.150	0.150	3.270
CG2	-0.270	-0.274	15.277
HG21	0.090	0.090	1.175
HG22	0.090	0.090	1.175
HG23	0.090	0.090	1.175
CA3	-0.195	-0.271	3.821
HA31	0.090	0.090	0.000
HA32	0.090	0.090	0.000
HA33	0.090	0.090	0.000

Table S197: Interaction energies and geometries between probe water and selected (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA-CA1	0.0	-2.17/-2.61/-1.51		2.59/2.58/2.65	
2	HA2-CA1	0.0	-0.97/-0.86/0.05		2.58/2.64/2.77	
3	HA3-CA1	0.0	-2.55/-2.73/-1.57		2.52/2.57/2.64	
4	N2-C1	0.0	-4.99/-6.30/-5.60		2.09/2.01/2.02	
5	N2-C1	90.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
6	N2-C1	180.0	-5.35/-5.42/-6.38		1.95/2.01/1.99	
7	N2-C1	270.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
8	N3-C1	0.0	-0.26/-0.82/-0.78		2.74/2.52/2.49	
9	O2-C2	0.0	-5.51/-5.57/-5.00		1.85/1.78/1.80	
10	O2-C2	90.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
11	O2-C2	180.0	-5.92/-5.61/-4.27		1.84/1.78/1.81	
12	O2-C2	270.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
13	HB2-CB2	0.0	-1.40/-1.60/-2.82		2.32/2.47/2.44	
14	HG21-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
15	HG23-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
16	HA32-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	
17	HA33-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	

1.64 Small molecule C of [2-(3-carbamoyl-1-imino-propyl)-4-(4-hydroxy-benzylidene)-5-oxo-4,5-dihydro-imidazol-1-yl]-aceticacid(CRQ)

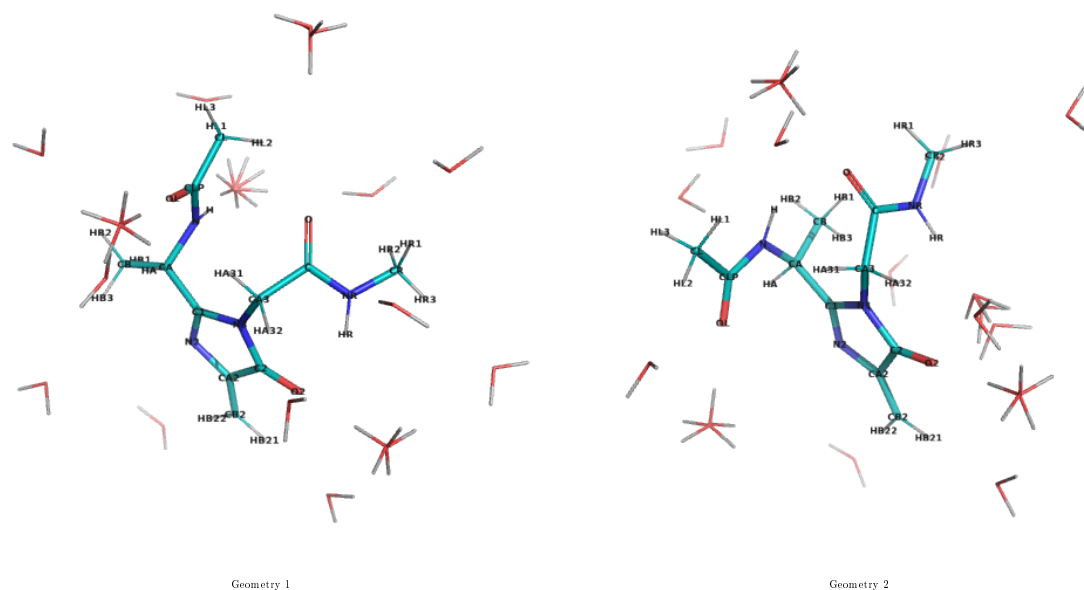


Table S198: The molecule used for water complex calculations corresponding to N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S199: Statistics of calculated water interaction and dipole moment for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide.

		RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
		Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Geometry 1	Initial	0.86 / 2.05	0.07 / 0.17	6.601	1.19 / 4.07	1.19
Geometry 2	Initial	1.02 / 2.07	0.09 / 0.23	6.126	6.37 / 4.43	6.37
Sum of geometries	Initial	0.95 / 2.07	0.08 / 0.23	12.727	-	-
Geometry 1	Optimal	0.36 / 0.81	0.07 / 0.16	2.460	1.19 / 1.37	1.19
Geometry 2	Optimal	0.51 / 0.91	0.08 / 0.19	2.701	6.37 / 7.25	6.37
Sum of geometries	Optimal	0.45 / 0.91	0.08 / 0.19	5.161	-	-

Table S200: The comparison list of optimized atomic charges and their initial guess for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
C1	0.233	0.164	24.002
N2	-0.679	-0.703	41.104
N3	-0.031	-0.499	22.994
C2	0.407	0.613	23.378
O2	-0.489	-0.482	6.517
CA2	0.466	0.512	42.773
CB2	-0.593	-0.444	13.655
HB21	0.230	0.230	0.950
HB22	0.230	0.230	0.950
CA3	-0.154	0.043	13.461
HA31	0.090	0.090	0.177
HA32	0.090	0.090	0.177
C	0.510	0.499	10.097
O	-0.510	-0.517	3.479
NR	-0.470	-0.442	6.773
HR	0.310	0.299	0.000
CR	-0.110	-0.108	0.239
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S201: Interaction energies and geometries between probe water and selected N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
Geometry 1				
1	O-C	0.0	-5.45/-5.47/-6.22	1.84/1.77/1.76
2	O-C	90.0	-6.01/-6.48/-6.53	1.83/1.75/1.76
3	O-C	180.0	-5.96/-6.64/-6.64	1.83/1.75/1.75
4	O-C	270.0	-5.67/-5.94/-6.62	1.84/1.76/1.75
5	NR-C	0.0	-1.32/-1.50/-1.08	2.24/2.20/2.22
6	HR2-CR	0.0	-1.10/-1.26/-1.09	2.71/2.66/2.67
7	HR3-CR	0.0	-1.39/-1.22/-1.32	2.66/2.67/2.67
8	N2-C1	0.0	-5.74/-6.45/-6.04	1.95/1.92/1.92
9	N2-C1	90.0	-6.51/-6.37/-7.24	1.90/1.92/1.90
10	N2-C1	180.0	-5.60/-5.66/-7.65	1.96/1.93/1.90
11	N2-C1	270.0	-6.64/-6.59/-7.43	1.90/1.91/1.89
12	O2-C2	0.0	-3.88/-3.93/-3.54	1.88/1.80/1.81
13	O2-C2	90.0	-4.94/-5.15/-4.46	1.84/1.77/1.79
14	O2-C2	180.0	-4.95/-5.20/-4.05	1.84/1.77/1.79
15	O2-C2	270.0	-3.93/-4.12/-3.39	1.87/1.79/1.81
16	HB21-CB2	0.0	-1.84/-1.64/-3.47	2.32/2.48/2.42
17	HB22-CB2	0.0	-1.82/-1.01/-2.42	2.42/2.54/2.46
18	HA31-CA3	0.0	-2.08/-2.47/-1.68	2.70/2.69/2.70
19	HA-CA	0.0	-2.47/-2.76/-1.19	2.49/2.56/2.66
Geometry 2				
20	O-C	0.0	-6.06/-6.90/-7.24	1.86/1.76/1.75
21	O-C	90.0	-5.25/-6.15/-7.32	1.87/1.77/1.75
22	O-C	180.0	-4.71/-5.63/-6.52	1.88/1.77/1.76
23	O-C	270.0	-5.56/-6.46/-6.85	1.86/1.76/1.76
24	HR-NR	0.0	-7.09/-7.67/-7.53	1.93/1.90/1.90
25	HR-NR	45.0	-7.71/-7.90/-7.71	1.91/1.89/1.89
26	HR-NR	90.0	-7.79/-7.84/-7.79	1.90/1.89/1.89
27	HR-NR	135.0	-7.18/-7.62/-7.61	1.92/1.90/1.89
28	HR1-CR	0.0	-0.71/-0.04/0.30	2.50/2.69/2.67
29	HR2-CR	0.0	-1.54/-1.44/-1.38	2.68/2.66/2.66
30	HR3-CR	0.0	-1.84/-1.82/-1.70	2.68/2.67/2.66
31	N2-C1	0.0	-6.46/-6.98/-6.58	1.93/1.91/1.91
32	N2-C1	90.0	-6.88/-6.47/-7.35	1.89/1.91/1.89
33	N2-C1	180.0	-5.73/-5.60/-7.60	1.95/1.93/1.90
34	N2-C1	270.0	-7.31/-7.09/-7.94	1.88/1.91/1.89
35	N3-C1	0.0	-0.22/0.03/-2.15	2.60/2.67/2.17
36	O2-C2	0.0	-4.96/-5.34/-4.95	1.88/1.79/1.80
37	O2-C2	90.0	-5.32/-5.37/-4.66	1.87/1.78/1.80
38	O2-C2	180.0	-5.74/-5.89/-4.71	1.87/1.78/1.81
39	O2-C2	270.0	-5.94/-6.25/-5.51	1.85/1.77/1.79
40	HB21-CB2	0.0	-1.43/-1.20/-3.03	2.33/2.48/2.41
41	HB22-CB2	0.0	-1.29/-0.66/-2.05	2.47/2.56/2.47
42	HA31-CA3	0.0	-3.71/-4.08/-3.49	2.50/2.57/2.57
43	HA-CA	0.0	-2.67/-3.45/-1.93	2.59/2.58/2.69

Table S203: The comparison list of optimized atomic charges and their initial guess for N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.268	11.341
HL1	0.090	0.090	0.800
HL2	0.090	0.090	0.800
HL3	0.090	0.090	0.800
CLP	0.510	1.166	104.329
OL	-0.510	-0.523	7.580
N1	-0.410	-0.867	109.915
CA1	0.442	-0.250	80.747
CB1	-0.148	-0.039	37.119
HB11	0.090	0.090	1.152
HB12	0.090	0.090	1.152
HB13	0.090	0.090	1.152
C1	0.208	0.430	75.868
N2	-0.541	-0.578	44.740
N3	-0.080	-0.049	29.029
C2	0.407	0.514	21.806
O2	-0.489	-0.482	6.710
CA2	0.221	0.396	48.462
CB2	-0.105	-0.135	25.469
HB2	0.150	0.150	3.270
CG2	-0.270	-0.274	15.277
H01	0.090	0.090	1.175
H02	0.090	0.090	1.175
H03	0.090	0.090	1.175
CA3	-0.195	-0.271	3.821
H1	0.090	0.090	0.000
H2	0.090	0.090	0.000
H3	0.090	0.090	0.000

Table S204: Interaction energies and geometries between probe water and selected N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HL1-CL	0.0	-2.10/-1.55/-1.57		2.54/2.67/2.61	
2	HL2-CL	0.0	-2.25/-2.36/-1.62		2.54/2.64/2.61	
3	HL3-CL	0.0	-1.15/-0.60/-2.15		2.59/2.70/2.58	
4	OL-CLP	0.0	-4.98/-6.25/-4.00		1.89/1.76/1.82	
5	OL-CLP	90.0	-5.11/-6.50/-4.99		1.89/1.76/1.80	
6	OL-CLP	180.0	-4.85/-5.78/-5.34		1.89/1.77/1.79	
7	OL-CLP	270.0	-4.63/-5.54/-4.21		1.90/1.77/1.82	
8	N1-CLP	0.0	-0.23/-0.37/-1.31		5.78/5.00/4.59	
9	HB11-CB1	0.0	-1.38/-2.00/-0.49		2.55/2.57/2.69	
10	HB12-CB1	0.0	-0.72/-1.46/-1.85		2.81/2.73/2.91	
11	HB13-CB1	0.0	-1.01/-1.73/-0.25		2.74/2.62/2.82	
12	N2-C1	0.0	-2.51/-3.29/-3.20		2.28/2.38/2.41	
13	N3-C1	0.0	-0.77/-1.40/-1.19		2.73/2.46/2.76	
14	O2-C2	0.0	-5.45/-5.66/-5.15		1.86/1.78/1.80	
15	O2-C2	90.0	-5.58/-5.60/-4.69		1.85/1.78/1.80	
16	O2-C2	180.0	-5.46/-5.40/-4.13		1.85/1.78/1.81	
17	O2-C2	270.0	-5.62/-5.67/-4.75		1.85/1.78/1.80	
18	HB2-CB2	0.0	-2.03/-1.80/-2.78		2.28/2.47/2.44	
19	HB2-CB2	0.0	-2.03/-1.80/-2.78		2.28/2.47/2.44	
20	H01-CG2	0.0	-1.49/-0.84/-1.05		2.64/2.74/2.72	
21	H02-CG2	0.0	-0.52/-0.97/-0.31		5.47/5.00/5.00	
22	H03-CG2	0.0	-1.46/-0.82/-1.02		2.65/2.74/2.72	

1.66 Small molecule used for s-acetylcysteine(CSA)

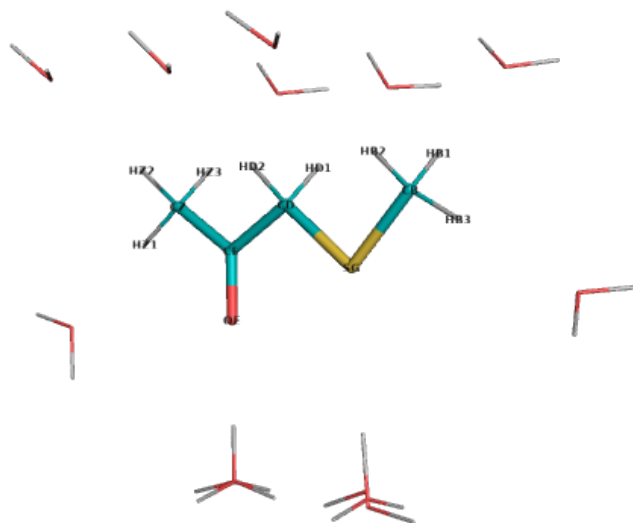


Figure S63: The molecule used for water complex calculations corresponding to 1-(methylsulfonyl)propan-2-one, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S205: Statistics of calculated water interaction and dipole moment for 1-(methylsulfonyl)propan-2-one.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.06/2.15	0.22/0.43	2.483	4.71/4.63	7.40
Optimal	0.71/1.54	0.30/0.62	2.368	4.71/5.29	0.33

Table S206: The comparison list of optimized atomic charges and their initial guess for 1-(methylsulfanyl)propan-2-one, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.185	-0.220	2.500
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
SG	-0.209	-0.045	9.916
CD	0.051	-0.137	9.916
HD2	0.090	0.090	0.000
HD1	0.090	0.090	0.000
CE	0.154	0.392	3.789
OE	-0.362	-0.481	1.080
CZ	-0.169	-0.229	2.500
HZ1	0.090	0.090	0.000
HZ2	0.090	0.090	0.000
HZ3	0.090	0.090	0.000

Table S207: Interaction energies and geometries between probe water and selected 1-(methylsulfanyl)propan-2-one site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.45/-0.71/-0.93	2.57/2.71/2.70
2	HB1-CB	0.0	-1.31/-1.44/-1.35	2.72/2.69/2.70
3	HB2-CB	0.0	-1.31/-1.44/-1.35	2.72/2.69/2.70
4	SG-CB	0.0	-2.89/-4.43/-3.52	2.83/2.31/2.40
5	SG-CB	90.0	-1.76/-2.70/-1.58	2.96/2.41/2.61
6	SG-CB	180.0	-1.08/-1.74/-0.56	3.10/2.48/2.84
7	SG-CB	270.0	-1.76/-2.70/-1.58	2.96/2.41/2.61
8	HD2-CD	0.0	-2.41/-2.55/-2.13	2.51/2.60/2.64
9	HD1-CD	0.0	-2.41/-2.55/-2.13	2.51/2.60/2.64
10	OE-CE	0.0	-5.40/-6.29/-7.15	1.90/1.71/1.67
11	OE-CE	90.0	-4.83/-5.67/-6.90	1.92/1.72/1.67
12	OE-CE	180.0	-4.53/-5.21/-6.69	1.92/1.73/1.68
13	OE-CE	270.0	-4.83/-5.67/-6.90	1.92/1.72/1.67
14	HZ1-CZ	0.0	-1.35/-0.79/-0.63	2.52/2.66/2.67
15	HZ2-CZ	0.0	-2.12/-2.13/-1.90	2.58/2.62/2.63
16	HZ3-CZ	0.0	-2.12/-2.13/-1.90	2.58/2.62/2.63

1.67 Small molecule used for S-hydroxycysteine(CSO)

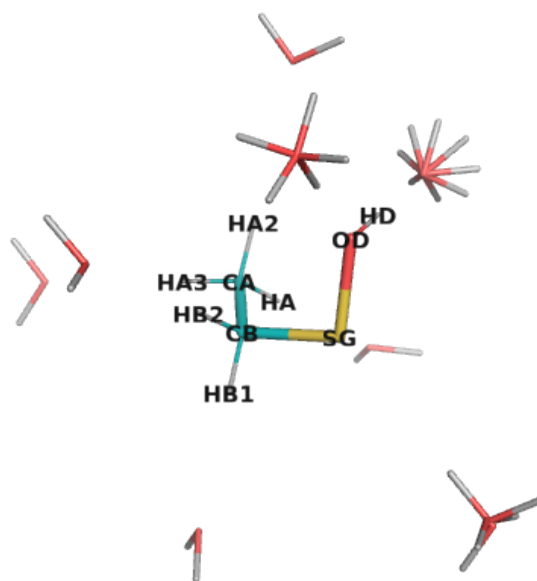


Figure S64: The molecule used for water complex calculations corresponding to ethane-SO-thioperoxol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S208: Statistics of calculated water interaction and dipole moment for ethane-SO-thioperoxol.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	2.39/4.13	5.02/15.11	6.943	2.36/3.47	44.63
Optimal	0.34/0.82	0.27/0.60	1.922	2.36/2.77	2.83

Table S209: The comparison list of optimized atomic charges and their initial guess for ethane-S-O-thioperoxol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	2.500
HA	0.090	0.090	0.000
CB	-0.005	-0.100	5.706
HB1	0.090	0.090	2.500
HB2	0.090	0.090	2.500
SG	-0.053	0.308	235.194!
OD	-0.563	-0.739	235.697
HD	0.441	0.351	17.884

Table S210: Interaction energies and geometries between probe water and selected ethane-SO-thioperoxol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-1.16/-1.20/-1.00	2.76/2.70/2.72
2	HA2-CA	0.0	-1.06/-1.29/-0.30	2.92/2.78/2.76
3	HA-CA	0.0	-1.08/-1.21/-1.37	2.74/2.70/2.70
4	HB1-CB	0.0	-1.76/-1.49/-1.94	2.56/2.66/2.64
5	HB2-CB	0.0	-0.93/-0.71/-0.53	2.63/2.69/2.71
6	SG-CB	0.0	-1.03/-1.84/-2.83	2.98/2.40/3.30
7	SG-CB	90.0	-1.11/-1.74/1.85	2.93/2.41/5.00
8	SG-CB	180.0	-0.52/-0.98/-2.83	3.08/2.49/3.30
9	SG-CB	270.0	-0.74/-1.08/-1.03	2.98/2.47/3.44
10	OD-SG	0.0	-4.73/-4.70/-7.68	1.88/1.91/1.82
11	OD-SG	90.0	-4.72/-4.89/-7.40	1.87/1.89/1.82
12	OD-SG	180.0	-5.25/-5.80/-7.34	1.87/1.87/1.82
13	OD-SG	270.0	-5.51/-5.69/-7.84	1.85/1.88/1.81
14	HD-OD	0.0	-7.49/-7.34/-3.36	1.73/1.79/1.93
15	HD-OD	45.0	-7.24/-7.24/-3.37	1.74/1.79/1.92
16	HD-OD	90.0	-7.11/-7.24/-3.42	1.74/1.79/1.92
17	HD-OD	135.0	-7.36/-7.34/-3.41	1.74/1.79/1.92

1.68 Small molecule used for S-mercaptocysteine(CSS)

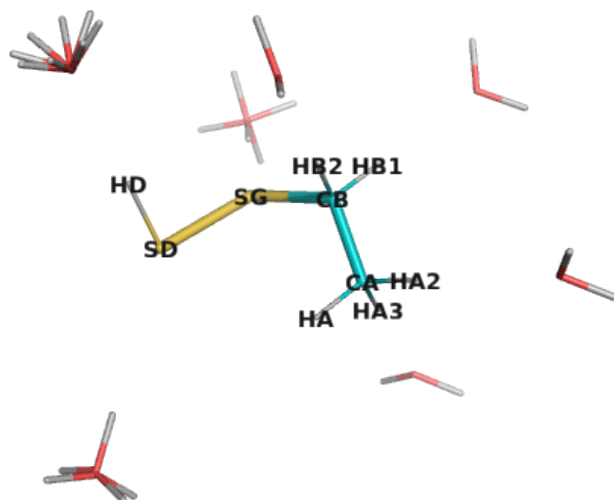


Figure S65: The molecule used for water complex calculations corresponding to ethanedithioperoxol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S211: Statistics of calculated water interaction and dipole moment for ethanedithioperoxol.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.81/1.39	0.41/0.61	2.766	2.16/1.59	27.43
Optimal	0.60/1.08	0.43/0.63	1.866	2.16/2.38	4.80

Table S212: The comparison list of optimized atomic charges and their initial guess for ethane dithioperoxol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.100
HA	0.090	0.090	0.000
CB	0.015	-0.099	2.585
HB1	0.090	0.090	0.100
HB2	0.090	0.090	0.100
SG	-0.173	-0.125	67.191
SD	-0.154	-0.116	67.188
HD	0.132	0.160	6.178

Table S213: Interaction energies and geometries between probe water and selected ethanedithioperoxol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.95/-0.74/-0.42	2.69/2.70/2.75
2	HA2-CA	0.0	-1.12/-1.20/-0.76	2.77/2.70/2.75
3	HB1-CB	0.0	-1.76/-1.44/-0.79	2.55/2.66/2.73
4	HB2-CB	0.0	-1.65/-1.74/-1.25	2.62/2.65/2.72
5	SG-CB	0.0	-1.31/-2.39/-1.83	2.95/2.33/2.38
6	SG-CB	90.0	-1.13/-1.85/-1.52	2.92/2.36/2.40
7	SG-CB	180.0	-0.81/-1.61/-1.58	3.02/2.38/2.40
8	SG-CB	270.0	-1.27/-2.19/-1.91	2.91/2.34/2.38
9	SD-SG	0.0	-0.81/-1.53/-0.95	3.03/2.45/2.53
10	SD-SG	90.0	-1.18/-1.99/-1.37	2.94/2.42/2.48
11	SD-SG	180.0	-0.95/-1.93/-1.53	3.01/2.41/2.46
12	SD-SG	270.0	-0.79/-1.43/-1.07	2.99/2.45/2.51
13	HD-SD	0.0	-2.42/-2.49/-3.78	2.27/2.01/1.95
14	HD-SD	45.0	-2.52/-2.53/-3.79	2.25/2.01/1.95
15	HD-SD	90.0	-2.42/-2.44/-3.73	2.25/2.01/1.95
16	HD-SD	135.0	-2.33/-2.40/-3.72	2.27/2.01/1.95

1.69 Small molecule used for cysteine-S-sulfonicacid(CSU)

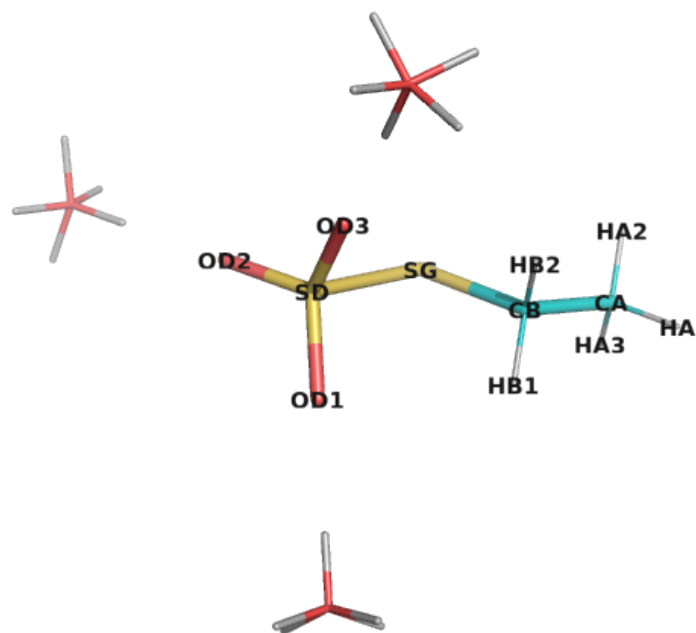


Figure S66: The molecule used for water complex calculations corresponding to (ethylsulfanyl)sulfonic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S214: Statistics of calculated water interaction and dipole moment for (ethylsulfanyl)sulfonic acid.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	1.44/1.83	0.13/0.14	3.948	7.12/8.70	6.69
Optimal	0.09/0.18	0.10/0.11	2.213	7.12/6.78	1.46

Table S215: The comparison list of optimized atomic charges and their initial guess for (ethylsulfanyl)sulfonicacid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	1.150
HA	0.090	0.090	0.000
CB	-0.125	-0.099	8.696
HB1	0.090	0.090	1.150
HB2	0.090	0.090	1.150
SG	-0.222	-0.099	83.884
SD	0.532	0.668	99.367
OD1	-0.455	-0.550	60.312
OD2	-0.455	-0.550	60.312
OD3	-0.455	-0.550	60.312

Table S216: Interaction energies and geometries between probe water and selected (ethylsulfanyl)sulfonicacid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	OD1-SD	0.0	-9.70/-9.73/-10.75	1.84/1.75/1.72
2	OD1-SD	90.0	-9.80/-9.77/-11.14	1.84/1.75/1.71
3	OD1-SD	180.0	-10.14/-10.11/-11.84	1.84/1.74/1.71
4	OD1-SD	270.0	-10.20/-10.11/-11.56	1.84/1.74/1.71
5	OD2-SD	0.0	-9.80/-9.97/-11.03	1.85/1.75/1.72
6	OD2-SD	90.0	-9.86/-9.97/-11.39	1.85/1.75/1.71
7	OD2-SD	180.0	-9.83/-9.95/-11.66	1.85/1.75/1.71
8	OD2-SD	270.0	-9.86/-9.97/-11.39	1.85/1.75/1.71
9	OD3-SD	0.0	-9.70/-9.73/-10.75	1.85/1.75/1.72
10	OD3-SD	90.0	-10.20/-10.11/-11.56	1.83/1.74/1.71
11	OD3-SD	180.0	-10.14/-10.11/-11.84	1.83/1.74/1.71
12	OD3-SD	270.0	-9.80/-9.77/-11.14	1.84/1.75/1.71

1.70 Small molecule used for S-oxycysteine(CSX)

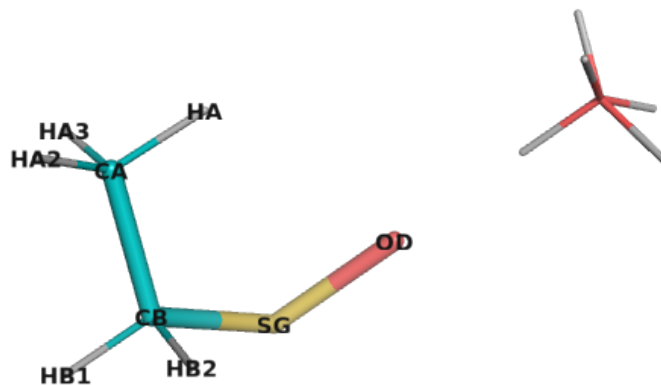


Figure S67: The molecule used for water complex calculations corresponding to ethane-SO-thioperoxol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S217: Statistics of calculated water interaction and dipole moment for ethane-SO-thioperoxol.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	11.09/11.21	0.10/0.10	16.851	5.86/11.29	20.86
Optimal	0.04/0.07	0.01/0.01	4.219	5.86/7.03	4.83

Table S218: The comparison list of optimized atomic charges and their initial guess for ethane-S-O-thioperoxol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	2.500
HA	0.090	0.090	0.000
CB	-0.173	-0.100	5.414
HB1	0.090	0.090	2.500
HB2	0.090	0.090	2.500
SG	-0.232	0.309	363.158!
OD	-0.775	-1.389	363.158!

Table S219: Interaction energies and geometries between probe water and selected ethane-SO-thioperoxol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	OD-SG	0.0	-17.14/-17.21/-28.17	1.66/1.66/1.56
2	OD-SG	90.0	-17.33/-17.30/-28.39	1.65/1.66/1.56
3	OD-SG	180.0	-17.34/-17.35/-28.55	1.65/1.66/1.56
4	OD-SG	270.0	-17.32/-17.27/-28.37	1.65/1.66/1.56

1.71 Small molecule A of N-carboxymethionine(CXM)

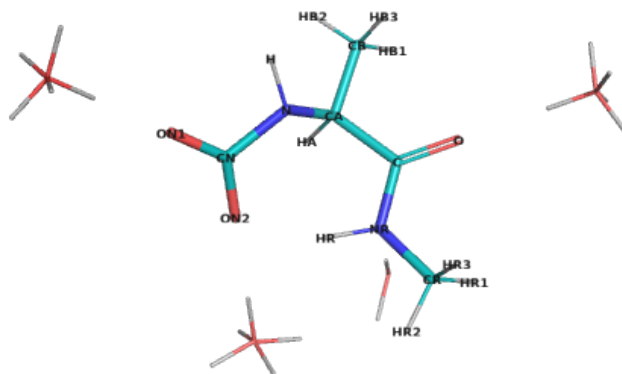


Figure S68: The molecule used for water complex calculations corresponding to N-[(1S)-1-(methylcarbamoyl)ethyl]carbamate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S220: Statistics of calculated water interaction and dipole moment for N-[(1S)-1-(methylcarbamoyl)ethyl]carbamate.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	2.44/4.21	0.11/0.14	7.462	6.22/10.01	6.35
Optimal	0.52/0.84	0.08/0.09	4.373	6.22/6.67	10.98

Table S221: The comparison list of optimized atomic charges and their initial guess for N-[(1S)-1-(methylcarbamoyl)ethyl]carbamate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
N	-0.521	-0.462	43.746
H	0.256	0.307	3.555
CN	0.562	0.518	44.474!
ON1	-0.628	-0.760	17.521
ON2	-0.628	-0.760	17.521
CA	-0.131	0.070	4.473
HA	0.090	0.090	0.375
CB	-0.270	-0.269	2.372
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
HB3	0.090	0.090	0.000
C	0.510	0.509	0.375
O	-0.510	-0.513	0.000
NR	-0.470	-0.474	0.000
HR	0.310	0.312	0.000
CR	-0.110	-0.108	0.000
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S222: Interaction energies and geometries between probe water and selected N-[(1S)-1-(methylcarbamoyl)ethyl]carbamate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	ON1-CN	0.0	-12.22/-11.75/-14.21	1.76/1.69/1.65
2	ON1-CN	90.0	-12.41/-12.01/-14.92	1.76/1.69/1.64
3	ON1-CN	180.0	-12.99/-12.51/-15.98	1.74/1.69/1.64
4	ON1-CN	270.0	-12.70/-12.23/-15.31	1.75/1.69/1.64
5	ON2-CN	0.0	-10.75/-11.07/-12.98	1.80/1.71/1.66
6	ON2-CN	90.0	-10.07/-10.57/-13.49	1.80/1.71/1.65
7	ON2-CN	180.0	-10.98/-11.65/-15.19	1.78/1.69/1.64
8	ON2-CN	270.0	-10.70/-11.54/-14.20	1.78/1.70/1.65
9	O-C	0.0	-9.66/-9.30/-8.42	1.82/1.74/1.75
10	O-C	90.0	-9.77/-9.38/-8.81	1.82/1.74/1.74
11	O-C	180.0	-9.53/-8.77/-8.45	1.82/1.74/1.74
12	O-C	270.0	-9.40/-8.83/-8.23	1.82/1.74/1.75
13	NR-C	0.0	-4.86/-4.59/-4.91	2.20/2.15/2.14

1.72 Small molecule A of
2-amino-6-(cystein-S-yl)-5-oxo-hexanoicacid(CYD)

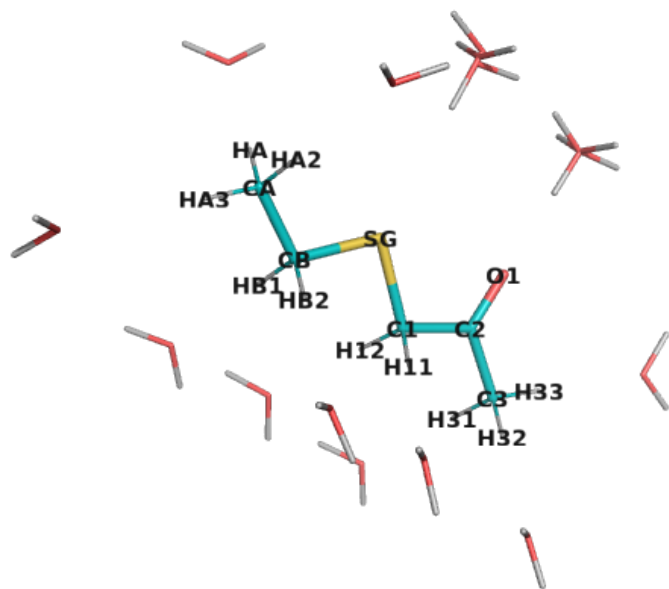


Figure S69: The molecule used for water complex calculations corresponding to 1-(ethylsulfanyl)propan-2-one, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S223: Statistics of calculated water interaction and dipole moment for 1-(ethylsulfanyl)propan-2-one.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	1.10/2.10	0.27/0.54	2.161	4.70/5.38	3.99
Optimal	0.80/1.80	0.29/0.62	2.713	4.70/5.59	0.00

Table S224: The comparison list of optimized atomic charges and their initial guess for 1-(ethylsulfanyl)propan-2-one, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.045
HA	0.090	0.090	0.000
CB	-0.076	-0.065	2.500
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
SG	-0.227	-0.175	9.916
C1	0.088	-0.072	9.916
H11	0.090	0.090	0.000
H12	0.090	0.090	0.000
C2	0.099	0.392	3.789
O1	-0.360	-0.481	1.080
C3	-0.154	-0.229	2.500
H31	0.090	0.090	0.000
H32	0.090	0.090	0.000
H33	0.090	0.090	0.000

Table S225: Interaction energies and geometries between probe water and selected 1-(ethylsulfanyl)propan-2-one site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-1.01/-0.89/-0.97	2.79/2.75/2.74
2	HA2-CA	0.0	-0.87/-0.46/-0.61	2.67/2.73/2.72
3	HA-CA	0.0	-0.87/-0.46/-0.61	2.67/2.73/2.72
4	HB1-CB	0.0	-1.24/-1.63/-1.62	2.77/2.69/2.69
5	HB2-CB	0.0	-1.24/-1.63/-1.62	2.77/2.69/2.69
6	SG-CB	0.0	-3.03/-4.83/-4.68	2.81/2.29/2.31
7	SG-CB	90.0	-1.85/-2.98/-2.60	2.94/2.39/2.44
8	SG-CB	180.0	-1.15/-1.96/-1.47	3.07/2.45/2.52
9	SG-CB	270.0	-1.85/-2.98/-2.60	2.94/2.39/2.44
10	H11-C1	0.0	-2.35/-2.75/-2.49	2.52/2.59/2.61
11	H12-C1	0.0	-2.35/-2.75/-2.49	2.52/2.59/2.61
12	O1-C2	0.0	-5.46/-6.51/-7.53	1.90/1.71/1.67
13	O1-C2	90.0	-4.88/-5.87/-6.98	1.92/1.72/1.68
14	O1-C2	180.0	-4.58/-5.40/-6.57	1.92/1.73/1.68
15	O1-C2	270.0	-4.88/-5.87/-6.98	1.92/1.72/1.68
16	H31-C3	0.0	-2.09/-2.14/-2.05	2.58/2.62/2.62
17	H32-C3	0.0	-2.09/-2.14/-2.05	2.58/2.62/2.62
18	H33-C3	0.0	-1.32/-0.72/-0.68	2.52/2.66/2.66

1.73 Small molecule A of
 5-[2-(2-amino-2-carbamoyl-ethylsulfanyl)-acetylamino]-2-(3,6-dihydroxy-9,9a-dihydro-3h-xanthen-9-yl)-benzoicacid(CYF)

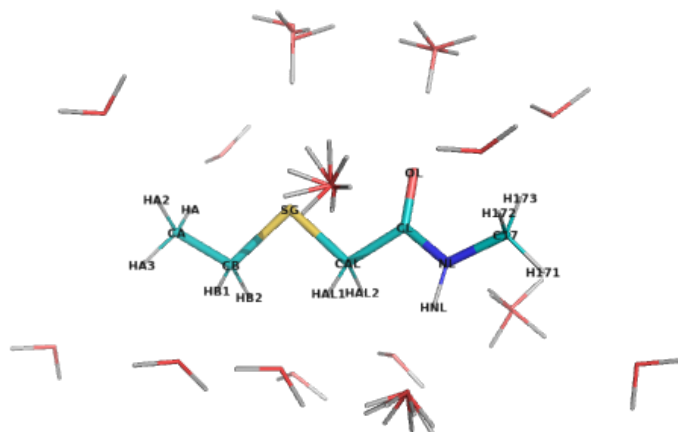


Figure S70: The molecule used for water complex calculations corresponding to 2-(ethylsulfanyl)-N-methylacetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S226: Statistics of calculated water interaction and dipole moment for 2-(ethylsulfanyl)-N-methylacetamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.68/1.73	0.27/0.59	1.736	5.38/5.85	2.19
Optimal	0.84/1.94	0.24/0.62	2.833	5.38/6.59	1.06

Table S227: The comparison list of optimized atomic charges and their initial guess for 2-(ethylsulfanyl)-N-methylacetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.045
HA	0.090	0.090	0.000
CB	-0.055	-0.065	2.500
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
SG	-0.266	-0.175	10.789
CAL	0.038	-0.109	10.789
HAL1	0.090	0.090	0.000
HAL2	0.090	0.090	0.000
CL	0.360	0.482	4.079
OL	-0.500	-0.516	1.805
NL	-0.381	-0.438	2.500
HNL	0.282	0.299	0.000
C17	-0.108	-0.108	0.239
H171	0.090	0.090	0.000
H172	0.090	0.090	0.000
H173	0.090	0.090	0.000

Table S228: Interaction energies and geometries between probe water and selected 2-(ethylsulfanyl)-N-methylacetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.97/-0.90/-0.92		2.80/2.74/2.74	
2	HA2-CA	0.0	-0.84/-0.38/-0.53		2.68/2.73/2.72	
3	HA-CA	0.0	-0.87/-0.40/-0.55		2.66/2.72/2.71	
4	HB1-CB	0.0	-1.11/-1.58/-1.46		2.80/2.71/2.71	
5	HB2-CB	0.0	-1.21/-1.60/-1.46		2.76/2.69/2.69	
6	SG-CB	0.0	-3.83/-5.77/-5.04		2.60/2.26/2.30	
7	SG-CB	90.0	-2.37/-3.61/-2.96		2.74/2.36/2.43	
8	SG-CB	180.0	-1.34/-2.21/-1.58		2.90/2.43/2.52	
9	SG-CB	270.0	-2.11/-3.30/-2.63		2.77/2.38/2.44	
10	HAL1-CAL	0.0	-2.43/-3.29/-2.77		2.58/2.58/2.61	
11	HAL2-CAL	0.0	-1.94/-2.32/-1.82		2.50/2.59/2.64	
12	CL-CAL	90.0	-0.54/-0.02/-0.12		2.98/3.60/3.57	
13	CL-CAL	135.0	-0.55/-0.01/-0.09		3.00/3.60/3.57	
14	OL-CL	0.0	-6.73/-8.10/-7.84		1.84/1.74/1.75	
15	OL-CL	90.0	-6.19/-7.48/-7.32		1.85/1.75/1.75	
16	OL-CL	180.0	-5.51/-6.63/-6.64		1.87/1.76/1.76	
17	OL-CL	270.0	-5.97/-7.18/-7.13		1.86/1.76/1.75	
18	NL-CL	0.0	-0.87/-0.34/-0.54		2.23/2.28/2.26	
19	NL-CL	180.0	-2.16/-2.29/-2.41		2.19/2.18/2.18	
20	NL-CL	270.0	-2.35/-2.66/-2.66		2.15/2.16/2.15	
21	HNL-NL	0.0	-5.87/-6.70/-6.56		1.95/1.91/1.90	
22	HNL-NL	45.0	-6.27/-6.87/-6.70		1.93/1.91/1.90	
23	HNL-NL	90.0	-6.61/-7.15/-6.91		1.91/1.90/1.89	
24	HNL-NL	135.0	-6.21/-6.99/-6.77		1.93/1.90/1.90	
25	H171-C17	0.0	-1.47/-1.58/-1.48		2.71/2.67/2.67	
26	H172-C17	0.0	-0.96/-0.99/-0.95		2.74/2.67/2.68	

1.74 Small molecule B of
 5-[2-(2-amino-2-carbamoyl-ethylsulfanyl)-acetylamino]-2-(3,6-dihydroxy-9,9a-dihydro-3h-xanthen-9-yl)-benzoicacid(CYF)

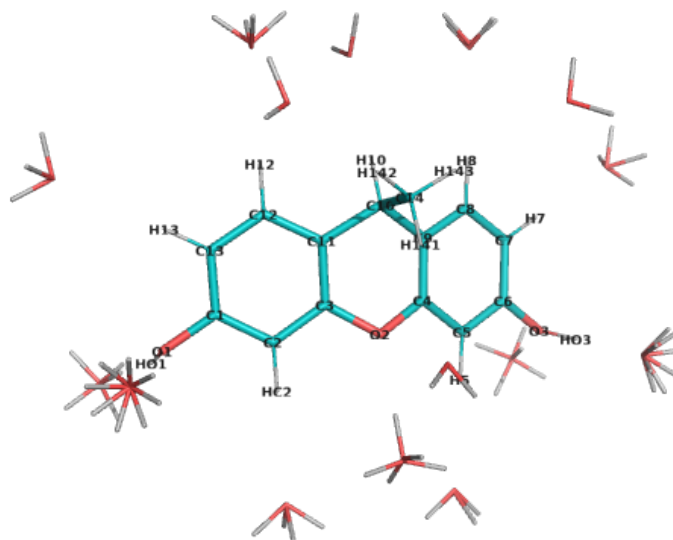


Figure S71: The molecule used for water complex calculations corresponding to 9-methyl-9H-xanthene-3,6-bis(olate), with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S229: Statistics of calculated water interaction and dipole moment for 9-methyl-9H-xanthene-3,6-bis(olate).

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.35/0.70	0.10/0.20	1.587	3.74/3.77	0.32
Optimal	0.36/0.69	0.10/0.21	1.810	3.74/4.42	1.12

Table S230: The comparison list of optimized atomic charges and their initial guess for 9-methyl-9H-xanthene-3,6-bis(olate), referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
H141	0.090	0.090	0.000
H142	0.090	0.090	0.000
H143	0.090	0.090	0.000
C14	-0.270	-0.271	0.000
C10	0.062	-0.095	6.735
H10	0.090	0.090	0.000
C9	-0.027	-0.001	6.311
C8	-0.151	-0.109	1.897
H8	0.115	0.115	0.000
C7	-0.115	-0.116	0.000
H7	0.115	0.115	0.000
C6	0.110	0.109	0.000
O3	-0.530	-0.530	0.000
HO3	0.420	0.420	0.000
C5	-0.115	-0.115	0.000
H5	0.115	0.115	0.000
C4	0.109	0.131	5.109
O2	-0.244	-0.262	6.708
C3	0.109	0.131	5.109
C11	-0.027	-0.001	6.311
C12	-0.151	-0.109	1.897
H12	0.115	0.115	0.000
C13	-0.115	-0.116	0.000
H13	0.115	0.115	0.000
C1	0.110	0.109	0.000
O1	-0.530	-0.530	0.000
HO1	0.420	0.420	0.000
C2	-0.115	-0.115	0.000
HC2	0.115	0.115	0.000

Table S231: Interaction energies and geometries between probe water and selected 9-methyl-9H-xanthene-3,6-bis(olate) site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	H141-C14	0.0	-0.14/-0.32/-0.00	2.71/2.70/2.75
2	H142-C14	0.0	-0.81/-1.17/-0.83	2.83/2.71/2.77
3	H143-C14	0.0	-0.81/-1.17/-0.83	2.83/2.71/2.77
4	H10-C10	0.0	-2.08/-2.25/-1.61	2.57/2.63/2.69
5	H8-C8	0.0	-1.70/-1.54/-1.49	2.60/2.68/2.67
6	H8-C8	90.0	-2.01/-1.67/-1.58	2.52/2.67/2.66
7	H7-C7	0.0	-1.28/-0.89/-1.02	2.60/2.72/2.70
8	H7-C7	90.0	-1.29/-0.90/-1.03	2.60/2.72/2.70
9	O3-C6	0.0	-4.28/-3.60/-3.58	1.91/1.94/1.94
10	O3-C6	90.0	-4.82/-4.46/-4.40	1.88/1.92/1.92
11	O3-C6	180.0	-5.03/-5.10/-5.00	1.89/1.90/1.91
12	O3-C6	270.0	-4.67/-4.20/-4.14	1.88/1.92/1.92
13	HO3-O3	0.0	-7.52/-7.51/-7.62	1.74/1.79/1.79
14	HO3-O3	45.0	-7.51/-7.49/-7.60	1.74/1.79/1.79
15	HO3-O3	90.0	-7.45/-7.43/-7.54	1.74/1.79/1.79
16	HO3-O3	135.0	-7.47/-7.45/-7.56	1.74/1.79/1.79
17	H5-C5	0.0	-1.09/-0.40/-0.46	2.51/2.72/2.72
18	H5-C5	90.0	-0.95/-0.36/-0.42	2.56/2.74/2.73
19	O2-C4	0.0	-3.62/-3.71/-3.80	1.94/1.83/1.82
20	O2-C4	90.0	-4.21/-4.05/-4.09	1.90/1.82/1.81
21	O2-C4	180.0	-3.63/-3.71/-3.80	1.94/1.83/1.82
22	O2-C4	270.0	-4.40/-3.96/-4.18	1.88/1.81/1.80
23	H12-C12	0.0	-1.70/-1.54/-1.49	2.60/2.68/2.67
24	H12-C12	90.0	-2.01/-1.67/-1.57	2.52/2.67/2.66
25	H13-C13	0.0	-1.28/-0.89/-1.02	2.60/2.72/2.70
26	H13-C13	90.0	-1.29/-0.90/-1.03	2.60/2.72/2.70
27	O1-C1	0.0	-4.28/-3.60/-3.58	1.91/1.94/1.94
28	O1-C1	90.0	-4.67/-4.20/-4.14	1.88/1.92/1.92
29	O1-C1	180.0	-5.03/-5.10/-5.00	1.89/1.90/1.91
30	O1-C1	270.0	-4.82/-4.46/-4.40	1.88/1.92/1.92
31	HO1-O1	0.0	-7.53/-7.51/-7.62	1.74/1.79/1.79
32	HO1-O1	45.0	-7.47/-7.45/-7.56	1.74/1.79/1.79
33	HO1-O1	90.0	-7.46/-7.43/-7.54	1.74/1.79/1.79
34	HO1-O1	135.0	-7.51/-7.49/-7.60	1.74/1.79/1.79
35	HC2-C2	0.0	-1.09/-0.40/-0.46	2.51/2.72/2.72
36	HC2-C2	90.0	-0.95/-0.36/-0.42	2.56/2.74/2.73

1.75 Small molecule A of
2-amino-4-(amino-3-oxo-propylsulfanylcarbonyl)-butyric acid(CYG)

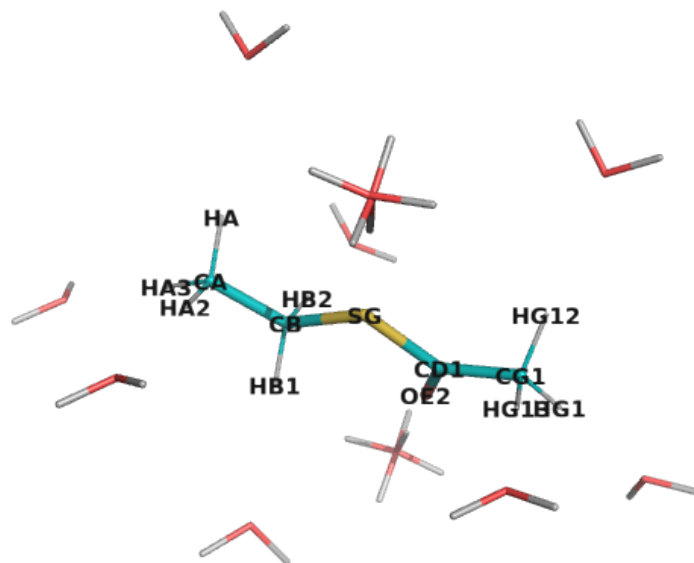


Figure S72: The molecule used for water complex calculations corresponding to 1-(ethylsulfanyl)ethan-1-one, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S232: Statistics of calculated water interaction and dipole moment for 1-(ethylsulfanyl)ethan-1-one.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.32/2.81	0.27/0.53	2.763	1.48/2.50	13.44
Optimal	0.31/0.64	0.25/0.50	1.827	1.48/1.80	0.39

Table S233: The comparison list of optimized atomic charges and their initial guess for 1-(ethylsulfanyl)ethan-1-one, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.620
HA	0.090	0.090	0.000
CB	-0.075	0.002	9.073
HB1	0.090	0.090	0.575
HB2	0.090	0.090	0.575
SG	-0.126	-0.194	68.838
CD1	0.480	0.693	62.403
OE2	-0.453	-0.639	57.902
CG1	-0.276	-0.312	53.675
HG13	0.090	0.090	2.500
HG12	0.090	0.090	2.500
HG1	0.090	0.090	2.500

Table S234: Interaction energies and geometries between probe water and selected 1-(ethylsulfanyl)ethan-1-one site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-1.17/-0.86/-1.15		2.72/2.73/2.69	
2	HA2-CA	0.0	-0.96/-0.70/-0.93		2.70/2.74/2.71	
3	HA-CA	0.0	-0.96/-0.70/-0.93		2.70/2.74/2.71	
4	HB1-CB	0.0	-0.97/-0.65/-0.88		2.52/2.67/2.63	
5	HB2-CB	0.0	-0.97/-0.65/-0.88		2.52/2.67/2.63	
6	SG-CB	0.0	-0.78/-0.76/-0.88		2.98/2.52/2.48	
7	SG-CB	90.0	-1.11/-1.08/-1.19		2.89/2.47/2.44	
8	SG-CB	180.0	-1.01/-1.29/-1.35		2.96/2.45/2.42	
9	SG-CB	270.0	-1.11/-1.08/-1.19		2.89/2.47/2.44	
10	OE2-CD1	0.0	-4.53/-4.76/-6.82		1.90/1.80/1.73	
11	OE2-CD1	90.0	-4.85/-5.12/-7.46		1.89/1.80/1.72	
12	OE2-CD1	180.0	-5.06/-5.33/-7.86		1.89/1.79/1.72	
13	OE2-CD1	270.0	-4.85/-5.12/-7.46		1.89/1.80/1.72	
14	HG13-CG1	0.0	-1.81/-1.40/-1.47		2.50/2.65/2.64	
15	HG12-CG1	0.0	-1.81/-1.40/-1.47		2.50/2.65/2.64	
16	HG1-CG1	0.0	-1.33/-0.69/-0.51		2.52/2.68/2.68	

1.76 Small molecule B of
2-amino-4-(amino-3-oxo-propylsulfanylcarbonyl)-butyric acid(CYG)

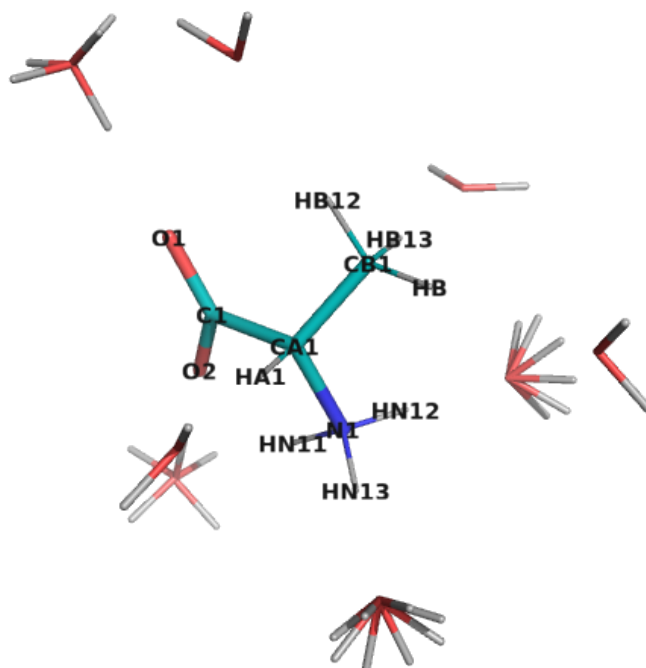


Figure S73: The molecule used for water complex calculations corresponding to (2S)-2-azaniumylpropanoate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S235: Statistics of calculated water interaction and dipole moment for (2S)-2-azaniumylpropanoate.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	2.56/4.03	0.09/0.25	9.229	10.93/14.80	1.11
Optimal	0.76/1.42	0.09/0.26	6.266	10.93/13.35	1.00

Table S236: The comparison list of optimized atomic charges and their initial guess for (2S)-2-azaniumylpropanoate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB	0.090	0.090	2.536
CB1	-0.224	-0.280	30.643
HB12	0.090	0.090	2.536
HB13	0.090	0.090	2.536
CA1	0.278	0.348	102.188
HA1	0.090	0.090	4.013
N1	-0.162	-0.346	37.381
HN11	0.259	0.330	2.536
HN12	0.259	0.330	2.536
HN13	0.259	0.330	2.536
C1	0.095	0.448	99.500
O1	-0.562	-0.760	8.256
O2	-0.562	-0.760	8.256

Table S237: Interaction energies and geometries between probe water and selected (2S)-2-azaniumylpropanoate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial		
1	HB-CB1	0.0	-2.37/-3.69/-3.74	2.73/2.59/2.60		
2	HB12-CB1	0.0	-1.31/-0.27/-0.08	2.31/2.57/2.56		
3	HB13-CB1	0.0	-2.97/-2.75/-3.01	2.45/2.54/2.54		
4	HA1-CA1	0.0	-3.23/-3.44/-4.18	2.39/2.56/2.53		
5	HN12-N1	0.0	-11.22/-11.62/-13.65	1.75/1.80/1.76		
6	HN12-N1	45.0	-11.51/-11.64/-13.69	1.74/1.80/1.76		
7	HN12-N1	90.0	-11.61/-11.92/-13.93	1.75/1.80/1.76		
8	HN12-N1	135.0	-11.34/-11.90/-13.90	1.75/1.80/1.76		
9	HN13-N1	0.0	-11.67/-12.25/-14.35	1.74/1.79/1.75		
10	HN13-N1	45.0	-11.73/-12.35/-14.45	1.74/1.78/1.75		
11	HN13-N1	90.0	-11.88/-12.40/-14.53	1.73/1.78/1.75		
12	HN13-N1	135.0	-11.83/-12.29/-14.43	1.73/1.78/1.75		
13	O1-C1	0.0	-7.69/-8.28/-10.51	1.77/1.72/1.67		
14	O1-C1	90.0	-8.62/-9.66/-12.10	1.76/1.71/1.66		
15	O1-C1	180.0	-9.77/-11.19/-13.76	1.74/1.69/1.65		
16	O1-C1	270.0	-8.84/-9.89/-12.24	1.75/1.70/1.66		
17	O2-C1	0.0	-4.83/-4.13/-5.62	1.80/1.76/1.71		
18	O2-C1	90.0	-8.19/-8.41/-10.58	1.73/1.70/1.65		
19	O2-C1	180.0	-9.96/-11.32/-13.99	1.72/1.68/1.63		
20	O2-C1	270.0	-7.76/-7.89/-10.04	1.73/1.71/1.66		

1.77 Small molecule used for
2-amino-3-phosphonomethylsulfanyl-propionicacid(CYQ)

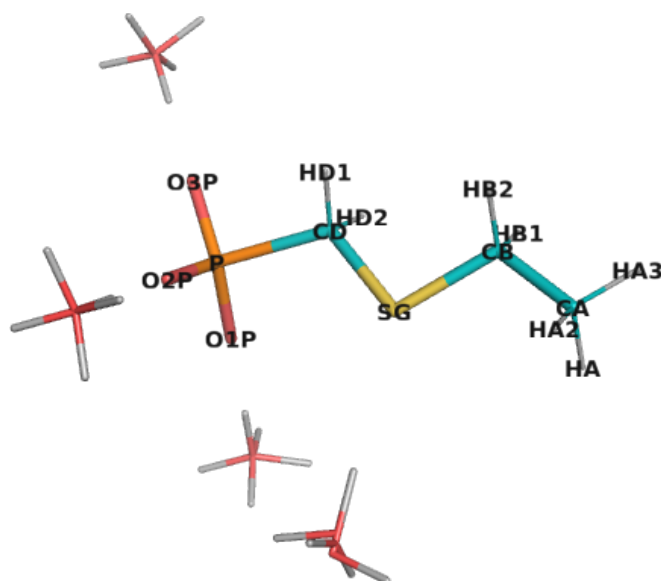


Figure S74: The molecule used for water complex calculations corresponding to [(ethylsulfanyl)methyl]phosphonicacid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S238: Statistics of calculated water interaction and dipole moment for [(ethylsulfanyl)methyl]phosphonicacid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.78/2.45	0.19/0.40	5.132	16.73/18.77	2.78
Optimal	0.61/1.58	0.18/0.37	2.469	16.73/17.03	1.89

Table S239: The comparison list of optimized atomic charges and their initial guess for [(ethylsulfanyl)methyl]phosphonicacid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.045
HA	0.090	0.090	0.000
CB	-0.255	-0.064	8.855
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
SG	-0.171	-0.206	10.841
CD	-0.429	-0.651	10.841
HD1	0.090	0.090	0.000
HD2	0.090	0.090	0.000
P	1.885	1.951	9.856
O1P	-1.130	-1.130	2.500
O2P	-1.130	-1.130	2.500
O3P	-1.130	-1.130	2.500

Table S240: Interaction energies and geometries between probe water and selected [(ethylsulfanyl)methyl]phosphonicacid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	SG-CB	0.0	-12.45/-14.02/-14.90		2.57/2.21/2.18	
2	SG-CB	90.0	-7.53/-7.45/-7.86		2.73/2.37/2.33	
3	SG-CB	180.0	-4.48/-2.91/-2.88		2.89/2.62/2.60	
4	SG-CB	270.0	-7.54/-7.46/-7.87		2.73/2.36/2.33	
5	O1P-P	0.0	-23.38/-23.36/-23.73		1.62/1.57/1.57	
6	O1P-P	90.0	-23.54/-23.60/-23.84		1.62/1.57/1.57	
7	O1P-P	180.0	-23.15/-23.19/-23.36		1.62/1.57/1.57	
8	O1P-P	270.0	-23.05/-23.02/-23.33		1.62/1.57/1.57	
9	O2P-P	0.0	-23.38/-23.35/-23.72		1.62/1.57/1.57	
10	O2P-P	90.0	-23.05/-23.02/-23.33		1.62/1.57/1.57	
11	O2P-P	180.0	-23.16/-23.19/-23.36		1.62/1.57/1.57	
12	O2P-P	270.0	-23.54/-23.60/-23.84		1.62/1.57/1.57	
13	O3P-P	0.0	-23.21/-22.65/-23.17		1.62/1.57/1.57	
14	O3P-P	90.0	-23.64/-23.11/-23.40		1.61/1.57/1.57	
15	O3P-P	180.0	-23.79/-23.36/-23.48		1.61/1.57/1.57	
16	O3P-P	270.0	-23.64/-23.10/-23.40		1.61/1.57/1.57	

1.78 Small molecule used for
2-amino-3-phosphonomethylsulfanyl-propionicacid(CYQP)

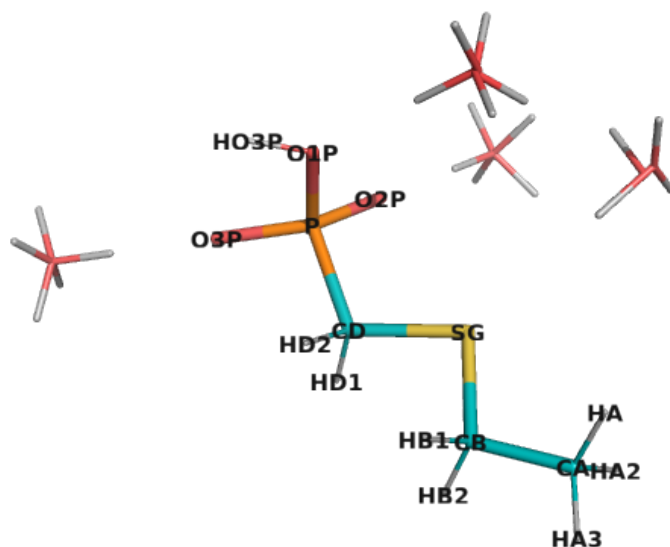


Figure S75: The molecule used for water complex calculations corresponding to [(ethylsulfanyl)methyl]phosphonicacid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S241: Statistics of calculated water interaction and dipole moment for [(ethylsulfanyl)methyl]phosphonicacid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.25/2.58	0.24/0.51	3.359	10.12/9.47	1.81
Optimal	0.45/0.74	0.18/0.37	5.446	10.12/7.65	5.46

Table S242: The comparison list of optimized atomic charges and their initial guess for [(ethylsulfanyl)methyl]phosphonicacid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.045
HA	0.090	0.090	0.000
CB	-0.258	-0.064	8.855
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
SG	-0.022	-0.206	10.841
CD	-0.506	-0.525	10.841
HD1	0.090	0.090	0.000
HD2	0.090	0.090	0.000
P	1.425	1.538	9.856
O1P	-0.741	-0.741	2.500
O2P	-0.809	-0.861	2.500
O3P	-0.809	-0.861	2.500
HO3P	0.360	0.360	0.000

Table S243: Interaction energies and geometries between probe water and selected [(ethylsulfanyl)methyl]phosphonicacid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	SG-CB	0.0	-7.63/-8.37/-10.21	2.67/2.31/2.22
2	SG-CB	90.0	-4.21/-4.20/-5.38	2.87/2.51/2.36
3	SG-CB	270.0	-4.33/-4.35/-5.68	2.86/2.50/2.35
4	O1P-P	0.0	-6.85/-7.13/-6.74	1.95/1.87/1.89
5	O1P-P	90.0	-9.10/-9.39/-9.38	1.90/1.85/1.85
6	O1P-P	180.0	-11.39/-11.97/-12.60	1.88/1.82/1.82
7	O1P-P	270.0	-8.95/-9.39/-9.32	1.90/1.84/1.86
8	O2P-P	0.0	-13.44/-14.13/-15.31	1.76/1.65/1.64
9	O2P-P	90.0	-13.14/-13.69/-14.61	1.76/1.66/1.64
10	O2P-P	180.0	-13.25/-13.70/-14.56	1.76/1.66/1.64
11	O2P-P	270.0	-13.45/-14.13/-15.20	1.76/1.65/1.64
12	O3P-P	0.0	-13.08/-13.10/-13.86	1.75/1.66/1.64
13	O3P-P	90.0	-12.82/-12.53/-13.30	1.75/1.66/1.65
14	O3P-P	180.0	-13.62/-13.16/-14.06	1.74/1.66/1.64
15	O3P-P	270.0	-13.77/-13.60/-14.49	1.74/1.65/1.64

1.79 Small molecule used for 3-(benzoylamino)-L-alanine(DBZ)

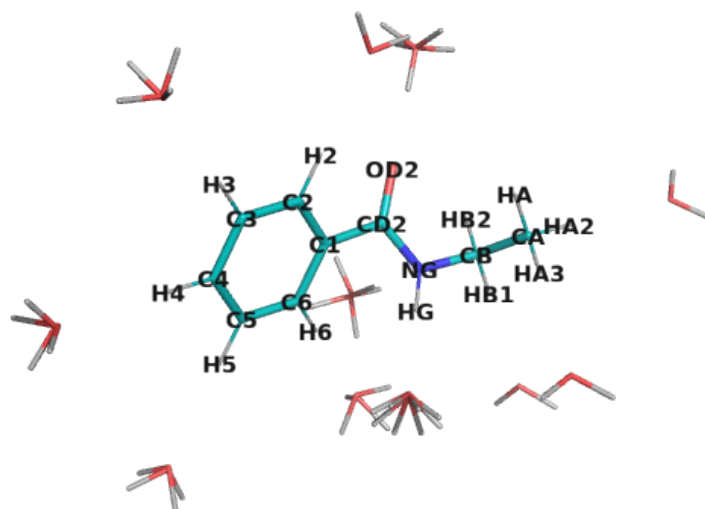


Figure S76: The molecule used for water complex calculations corresponding to N-ethylbenzamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S244: Statistics of calculated water interaction and dipole moment for N-ethylbenzamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.46/1.08	0.08/0.14	1.712	3.87/3.66	5.44
Optimal	0.37/0.79	0.07/0.14	2.124	3.87/4.43	3.66

Table S245: The comparison list of optimized atomic charges and their initial guess for N-ethylbenzamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.359
HA	0.090	0.090	0.000
CB	-0.004	0.045	5.332
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
NG	-0.409	-0.549	5.332
HG	0.288	0.305	0.000
CD2	0.330	0.433	3.532
OD2	-0.460	-0.428	0.000
C1	-0.143	-0.117	3.514
C2	-0.006	-0.067	0.000
H2	0.115	0.115	0.000
C6	-0.006	-0.067	0.000
H6	0.115	0.115	0.000
C3	-0.115	-0.100	0.000
H3	0.115	0.115	0.000
C5	-0.115	-0.100	0.000
H5	0.115	0.115	0.000
C4	-0.115	-0.115	0.000
H4	0.115	0.115	0.000

Table S246: Interaction energies and geometries between probe water and selected N-ethylbenzamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-1.01/-0.95/-0.98	2.86/2.76/2.74
2	HA2-CA	0.0	-0.82/-0.73/-0.89	2.80/2.74/2.72
3	HB1-CB	0.0	-1.36/-1.46/-1.49	2.72/2.68/2.68
4	NG-CB	0.0	-1.72/-1.53/-2.42	2.21/2.20/2.12
5	NG-CB	90.0	-3.51/-4.30/-4.59	2.09/2.07/2.04
6	NG-CB	180.0	-2.09/-2.50/-2.87	2.15/2.14/2.09
7	NG-CB	270.0	-1.17/-0.67/-1.49	2.18/2.23/2.14
8	HG-NG	0.0	-5.38/-5.23/-4.75	1.97/2.00/2.00
9	HG-NG	45.0	-4.58/-4.96/-4.45	2.01/2.01/2.02
10	HG-NG	90.0	-4.75/-5.29/-4.71	2.01/2.00/2.01
11	HG-NG	135.0	-5.48/-5.54/-4.98	1.98/1.99/2.00
12	OD2-CD2	0.0	-6.17/-6.69/-5.71	1.83/1.76/1.79
13	OD2-CD2	90.0	-6.61/-6.99/-6.10	1.82/1.76/1.78
14	OD2-CD2	180.0	-6.40/-6.69/-5.91	1.82/1.76/1.79
15	OD2-CD2	270.0	-6.13/-6.57/-5.69	1.83/1.76/1.79
16	H6-C6	0.0	-2.23/-2.53/-1.97	2.49/2.60/2.63
17	H6-C6	90.0	-1.92/-2.50/-1.92	2.61/2.61/2.65
18	H3-C3	0.0	-1.54/-1.30/-1.21	2.60/2.68/2.68
19	H3-C3	90.0	-1.69/-1.33/-1.24	2.55/2.67/2.68
20	H5-C5	0.0	-1.63/-1.62/-1.46	2.62/2.67/2.68
21	H5-C5	90.0	-1.84/-1.70/-1.54	2.56/2.66/2.67
22	H4-C4	0.0	-1.66/-1.33/-1.28	2.59/2.69/2.69
23	H4-C4	90.0	-1.84/-1.40/-1.35	2.54/2.68/2.68

1.80 Small molecule A of 3-[4-(2-amino-2-carboxy-ethyl)-1H-imidazol-2-yl]-1-carbamoyl-propyl-trimethyl-ammonium(DDE)

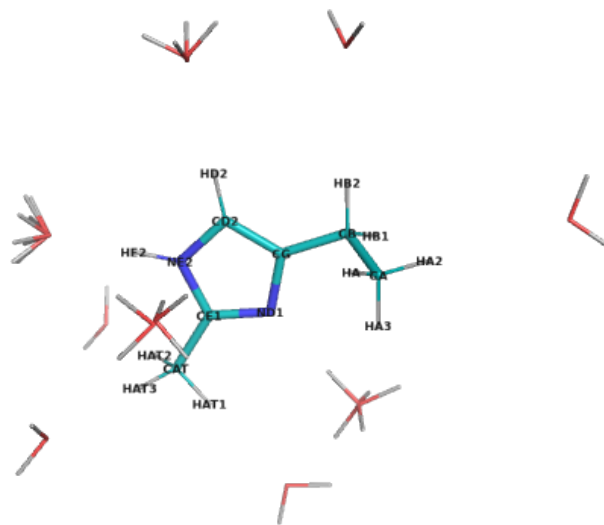


Figure S77: The molecule used for water complex calculations corresponding to 4-ethyl-2-methyl-1H-imidazole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S247: Statistics of calculated water interaction and dipole moment for 4-ethyl-2-methyl-1H-imidazole.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.78/2.22	0.10/0.19	3.455	3.57/3.48	9.15
Optimal	0.29/0.60	0.08/0.20	2.467	3.57/4.32	1.14

Table S248: The comparison list of optimized atomic charges and their initial guess for 4-ethyl-2-methyl-1H-imidazole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.276	0.474
HA	0.090	0.090	0.000
CB	-0.180	-0.080	0.570
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.198	0.221	13.641
ND1	-0.715	-0.699	13.836
CD2	-0.067	-0.028	13.494
HD2	0.109	0.089	0.000
NE2	-0.402	-0.442	16.020
HE2	0.310	0.338	0.000
CE1	0.567	0.270	18.260
CAT	-0.270	-0.113	14.550
HAT1	0.090	0.090	0.000
HAT2	0.090	0.090	0.000
HAT3	0.090	0.090	0.000

Table S249: Interaction energies and geometries between probe water and selected 4-ethyl-2-methyl-1H-imidazole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial		
1	HA2-CA	0.0	-0.25/-0.10/-0.46	2.95/2.84/2.78		
2	HB2-CB	0.0	-0.66/-0.69/-1.32	2.87/2.78/2.69		
3	ND1-CG	0.0	-7.28/-7.05/-8.05	1.90/1.92/1.89		
4	ND1-CG	90.0	-8.49/-8.07/-8.82	1.85/1.90/1.88		
5	ND1-CG	180.0	-7.95/-8.55/-8.77	1.90/1.89/1.88		
6	ND1-CG	270.0	-8.33/-7.90/-8.68	1.86/1.90/1.88		
7	HD2-CD2	0.0	-1.78/-1.90/-1.57	2.55/2.35/2.39		
8	HD2-CD2	90.0	-2.05/-2.02/-1.73	2.48/2.34/2.37		
9	NE2-CD2	0.0	-0.49/-0.04/-1.48	2.49/2.63/2.32		
10	NE2-CD2	90.0	-2.46/-2.73/-4.68	2.28/2.25/2.12		
11	NE2-CD2	180.0	-2.11/-2.08/-3.35	2.28/2.28/2.18		
12	HE2-NE2	0.0	-6.50/-6.70/-6.12	1.87/1.87/1.87		
13	HE2-NE2	45.0	-6.72/-6.78/-6.23	1.85/1.87/1.87		
14	HE2-NE2	90.0	-6.94/-6.86/-6.35	1.84/1.87/1.87		
15	HE2-NE2	135.0	-6.72/-6.78/-6.24	1.85/1.87/1.87		
16	HAT1-CAT	0.0	-0.72/-0.15/-0.07	2.55/2.68/2.67		
17	HAT2-CAT	0.0	-1.40/-1.58/-1.55	2.68/2.65/2.64		
18	HAT3-CAT	0.0	-1.42/-1.61/-1.57	2.68/2.65/2.63		

1.81 Small molecule B of 3-[4-(2-amino-2-carboxy-ethyl)-1H-imidazol-2-yl]-1-carbamoyl-propyl-trimethyl-ammonium(DDE)

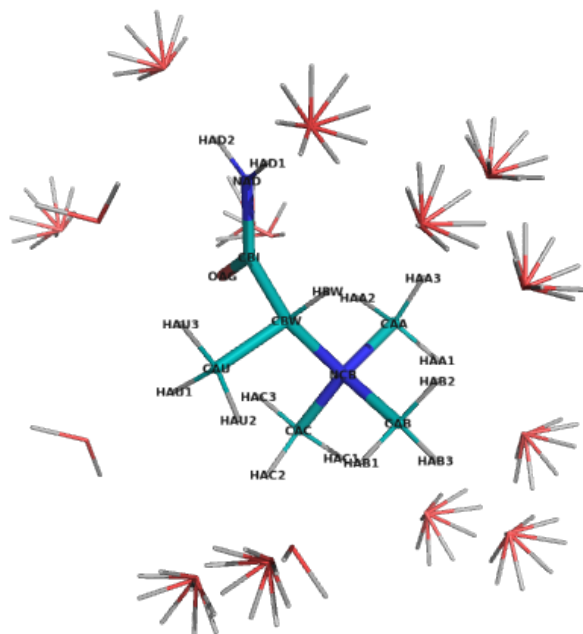


Figure S78: The molecule used for water complex calculations corresponding to (2R)-2-(trimethylamino)propanamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S250: Statistics of calculated water interaction and dipole moment for (2R)-2-(trimethylamino)propanamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.71/4.67	0.31/0.99	4.921	4.97/7.21	9.76
Optimal	0.71/1.73	0.36/1.26	2.711	4.97/4.92	13.32

Table S251: The comparison list of optimized atomic charges and their initial guess for (2R)-2-(trimethylamino)propanamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HAU3	0.090	0.090	2.536
CAU	-0.270	-0.280	28.858
HAU1	0.090	0.090	2.536
HAU2	0.090	0.090	2.536
CBW	0.246	0.246	62.835
HBW	0.090	0.250	6.349
CBI	0.581	0.473	57.630
OAG	-0.462	-0.510	5.225
NAD	-0.570	-0.618	6.995
HAD1	0.313	0.310	2.712
HAD2	0.313	0.310	2.712
NCB	-0.543	-0.576	44.914
CAA	-0.406	-0.375	24.333
HAA1	0.250	0.250	0.030
HAA2	0.250	0.250	0.030
HAA3	0.250	0.250	0.030
CAB	-0.406	-0.375	24.333
HAB1	0.250	0.250	0.030
HAB2	0.250	0.250	0.030
HAB3	0.250	0.250	0.030
CAC	-0.406	-0.375	24.333
HAC1	0.250	0.250	0.030
HAC2	0.250	0.250	0.030
HAC3	0.250	0.250	0.030

Table S252: Interaction energies and geometries between probe water and selected (2R)-2-(trimethylamino)propanamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HAU3-CAU	0.0	-6.67/-5.84/-5.71	2.37/2.56/2.56		
2	HAU1-CAU	0.0	-5.65/-4.95/-4.53	2.43/2.61/2.62		
3	HAU2-CAU	0.0	-7.52/-6.55/-7.03	2.52/2.59/2.59		
4	HBW-CBW	0.0	-11.01/-11.00/-15.01	2.26/2.10/1.98		
5	HBW-CBW	45.0	-10.47/-10.67/-14.70	2.28/2.11/1.99		
6	HBW-CBW	90.0	-9.40/-10.14/-14.08	2.35/2.14/2.00		
7	HBW-CBW	135.0	-9.97/-10.50/-14.43	2.32/2.12/2.00		
8	HAD1-NAD	0.0	-10.70/-11.70/-11.07	1.93/1.85/1.88		
9	HAD1-NAD	45.0	-11.11/-11.83/-11.32	1.91/1.85/1.87		
10	HAD1-NAD	90.0	-12.02/-12.26/-12.05	1.88/1.84/1.86		
11	HAD1-NAD	135.0	-11.62/-12.14/-11.82	1.90/1.84/1.86		
12	HAD2-NAD	0.0	-10.22/-10.17/-8.55	1.83/1.83/1.86		
13	HAD2-NAD	45.0	-10.11/-10.07/-8.43	1.83/1.83/1.86		
14	HAD2-NAD	90.0	-9.96/-9.95/-8.27	1.83/1.84/1.86		
15	HAD2-NAD	135.0	-10.06/-10.04/-8.39	1.83/1.83/1.86		
16	HAA1-CAA	0.0	-8.18/-8.89/-9.40	2.30/2.14/2.13		
17	HAA1-CAA	45.0	-8.57/-9.07/-9.60	2.27/2.13/2.12		
18	HAA1-CAA	90.0	-8.88/-9.18/-9.71	2.25/2.13/2.12		
19	HAA1-CAA	135.0	-8.47/-8.99/-9.50	2.27/2.14/2.13		
20	HAA2-CAA	0.0	-3.59/-3.99/-3.25	2.87/3.02/3.03		
21	HAA2-CAA	45.0	-3.65/-3.81/-3.19	2.77/3.03/3.02		
22	HAA2-CAA	90.0	-2.18/-3.23/-2.48	3.38/3.20/3.24		
23	HAA2-CAA	135.0	-2.31/-3.40/-2.56	3.43/3.18/3.24		
24	HAA3-CAA	0.0	-7.80/-9.53/-10.23	2.37/2.14/2.14		
25	HAA3-CAA	45.0	-8.49/-9.83/-10.78	2.32/2.13/2.12		
26	HAA3-CAA	90.0	-8.36/-9.54/-10.69	2.30/2.14/2.12		
27	HAA3-CAA	135.0	-7.61/-9.21/-10.11	2.35/2.15/2.14		
28	HAB1-CAB	0.0	-8.17/-7.40/-8.15	2.54/2.58/2.55		
29	HAB1-CAB	45.0	-8.75/-7.48/-8.19	2.49/2.57/2.54		
30	HAB1-CAB	90.0	-8.52/-7.45/-8.12	2.51/2.57/2.55		
31	HAB1-CAB	135.0	-7.89/-7.36/-8.07	2.57/2.59/2.55		
32	HAB2-CAB	0.0	-8.21/-9.06/-10.65	2.31/2.14/2.12		
33	HAB2-CAB	45.0	-8.25/-9.16/-10.64	2.31/2.14/2.12		
34	HAB2-CAB	90.0	-8.83/-9.47/-11.06	2.27/2.13/2.10		
35	HAB2-CAB	135.0	-8.77/-9.37/-11.05	2.28/2.13/2.11		
36	HAB3-CAB	0.0	-8.50/-9.04/-9.77	2.28/2.14/2.12		
37	HAB3-CAB	45.0	-8.71/-9.11/-9.85	2.26/2.13/2.12		
38	HAB3-CAB	90.0	-9.05/-9.24/-9.97	2.24/2.13/2.11		
39	HAB3-CAB	135.0	-8.82/-9.15/-9.88	2.25/2.13/2.12		
40	HAC1-CAC	0.0	-7.81/-8.41/-8.80	2.32/2.15/2.15		
41	HAC1-CAC	45.0	-8.17/-8.60/-9.01	2.30/2.15/2.14		
42	HAC1-CAC	90.0	-8.54/-8.75/-9.19	2.27/2.14/2.13		
43	HAC1-CAC	135.0	-8.15/-8.55/-8.97	2.29/2.15/2.14		
44	HAC2-CAC	0.0	-7.44/-8.04/-8.30	2.43/2.21/2.21		
45	HAC2-CAC	45.0	-7.76/-8.23/-8.57	2.38/2.20/2.19		
46	HAC2-CAC	90.0	-8.09/-8.36/-8.72	2.38/2.20/2.19		
47	HAC2-CAC	135.0	-7.79/-8.16/-8.46	2.43/2.21/2.20		
48	HAC3-CAC	0.0	-1.31/-1.68/-1.17	5.99/4.73/5.00		
49	HAC3-CAC	45.0	-1.37/-1.74/-1.18	5.92/4.80/5.00		
50	HAC3-CAC	90.0	-1.38/-1.75/-1.19	5.91/4.81/5.00		
51	HAC3-CAC	135.0	-1.32/-1.70/-1.17	5.99/4.76/5.00		

1.82 Small molecule A of 3-[4-(2-amino-2-carboxy-ethyl)-1H-imidazol-2-yl]-1-carbamoyl-propyl-trimethyl-ammonium(DDEP)

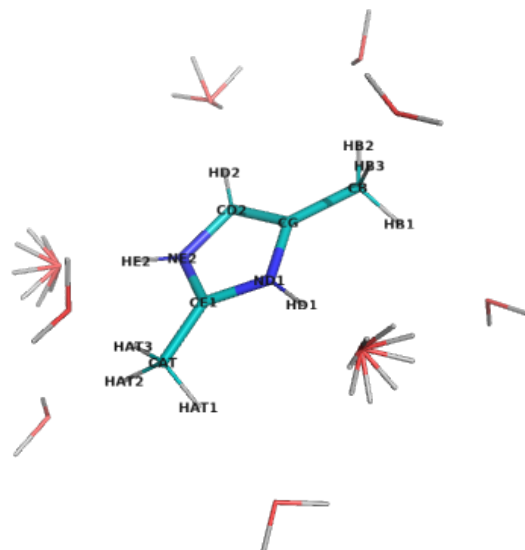


Figure S79: The molecule used for water complex calculations corresponding to 2,4-dimethyl-2,3-dihydro-1H-imidazole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S253: Statistics of calculated water interaction and dipole moment for 2,4-dimethyl-2,3-dihydro-1H-imidazole.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.90/1.42	0.14/0.27	2.824	2.04/1.69	24.92
Optimal	0.43/0.91	0.12/0.25	1.650	2.04/1.90	1.82

Table S254: The comparison list of optimized atomic charges and their initial guess for 2,4-dimethyl-2,3-dihydro-1H-imidazole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.450
CB	-0.074	-0.227	0.891
HB1	0.090	0.090	0.450
HB2	0.090	0.090	0.450
CG	0.074	0.290	12.309
ND1	-0.519	-0.532	19.667
HD1	0.413	0.440	1.296
CD2	0.058	0.188	10.981
HD2	0.181	0.130	0.000
NE2	-0.519	-0.530	18.863
HE2	0.413	0.440	1.295
CE1	0.508	0.352	23.944
CAT	-0.075	-0.091	17.924
HAT1	0.090	0.090	2.263
HAT2	0.090	0.090	2.263
HAT3	0.090	0.090	2.263

Table S255: Interaction energies and geometries between probe water and selected 2,4-dimethyl-2,3-dihydro-1H-imidazole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-6.16/-5.58/-5.38		2.36/2.54/2.56	
2	HB1-CB	0.0	-6.15/-5.57/-5.37		2.36/2.54/2.56	
3	HB2-CB	0.0	-6.31/-5.81/-5.73		2.34/2.53/2.54	
4	HD1-ND1	0.0	-14.50/-14.80/-15.72		1.78/1.77/1.75	
5	HD1-ND1	45.0	-14.91/-15.06/-15.92		1.76/1.77/1.75	
6	HD1-ND1	90.0	-15.46/-15.34/-16.14		1.75/1.76/1.75	
7	HD1-ND1	135.0	-15.04/-15.08/-15.94		1.76/1.77/1.75	
8	HD2-CD2	0.0	-8.43/-8.47/-8.90		2.17/2.17/2.17	
9	HD2-CD2	90.0	-9.10/-8.73/-9.12		2.13/2.16/2.16	
10	HE2-NE2	0.0	-14.63/-14.84/-15.78		1.77/1.77/1.75	
11	HE2-NE2	45.0	-15.20/-15.09/-16.00		1.75/1.76/1.75	
12	HE2-NE2	90.0	-15.64/-15.31/-16.21		1.74/1.76/1.74	
13	HE2-NE2	135.0	-15.07/-15.07/-15.98		1.76/1.76/1.75	
14	HAT1-CAT	0.0	-7.65/-7.01/-6.54		2.29/2.49/2.52	
15	HAT2-CAT	0.0	-7.70/-7.12/-6.63		2.30/2.50/2.52	
16	HAT3-CAT	0.0	-7.58/-6.67/-6.17		2.24/2.49/2.51	

1.83 Small molecule B of 3-[4-(2-amino-2-carboxy-ethyl)-1H-imidazol-2-yl]-1-carbamoyl-propyl-trimethyl-ammonium(DDEP)

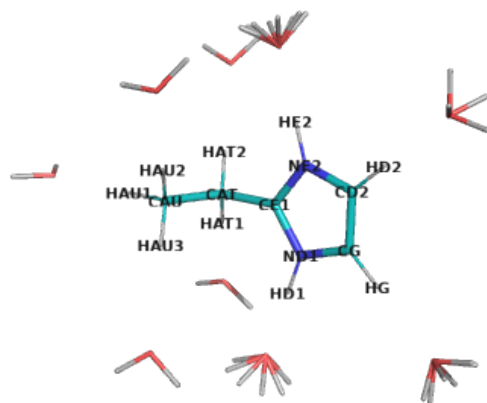


Figure S80: The molecule used for water complex calculations corresponding to 2-ethyl-1H-imidazole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S256: Statistics of calculated water interaction and dipole moment for 2-ethyl-1H-imidazole.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.62/1.19	0.10/0.22	3.978	1.18/2.80	17.18
Optimal	0.49/1.03	0.09/0.20	2.277	1.18/1.78	4.13

Table S257: The comparison list of optimized atomic charges and their initial guess for 2-ethyl-1H-imidazole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CG	0.140	0.195	10.634
HG	0.130	0.130	0.000
ND1	-0.519	-0.524	23.692
HD1	0.413	0.440	1.250
CD2	0.058	0.195	10.634
HD2	0.181	0.130	0.000
NE2	-0.519	-0.524	23.692
HE2	0.413	0.440	1.250
CE1	0.508	0.321	33.613
CAT	0.015	0.005	22.769
HAT1	0.090	0.090	1.768
HAT2	0.090	0.090	1.768
CAU	-0.270	-0.258	14.620
HAU1	0.090	0.090	0.000
HAU2	0.090	0.090	0.000
HAU3	0.090	0.090	0.000

Table S258: Interaction energies and geometries between probe water and selected 2-ethyl-1H-imidazole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HG-CG	0.0	-8.87/-8.10/-8.92	2.14/2.19/2.17
2	HG-CG	60.0	-9.28/-8.25/-9.07	2.11/2.18/2.16
3	HG-CG	120.0	-9.28/-8.25/-9.07	2.11/2.18/2.16
4	HD1-ND1	0.0	-14.91/-15.36/-15.80	1.76/1.76/1.75
5	HD1-ND1	45.0	-15.37/-15.55/-15.98	1.75/1.76/1.75
6	HD1-ND1	90.0	-15.84/-15.77/-16.18	1.74/1.75/1.74
7	HD1-ND1	135.0	-15.38/-15.59/-16.00	1.75/1.76/1.75
8	HD2-CD2	0.0	-8.87/-8.82/-8.92	2.14/2.16/2.17
9	HD2-CD2	90.0	-9.42/-9.01/-9.12	2.10/2.15/2.16
10	HE2-NE2	0.0	-14.90/-15.26/-15.80	1.76/1.76/1.75
11	HE2-NE2	45.0	-15.38/-15.49/-16.01	1.75/1.76/1.75
12	HE2-NE2	90.0	-15.85/-15.69/-16.19	1.74/1.76/1.74
13	HE2-NE2	135.0	-15.37/-15.46/-15.98	1.75/1.76/1.75
14	HAT1-CAT	0.0	-7.52/-7.29/-6.61	2.32/2.51/2.54
15	HAT2-CAT	0.0	-7.52/-7.28/-6.62	2.32/2.51/2.54
16	HAU1-CAU	0.0	-5.51/-4.57/-4.32	2.39/2.58/2.59
17	HAU2-CAU	0.0	-5.17/-5.07/-4.69	2.59/2.64/2.67
18	HAU3-CAU	0.0	-5.18/-5.12/-4.72	2.59/2.64/2.68

1.84 Small molecule used for 3,3-dihydroxy-alanine(DDZ)

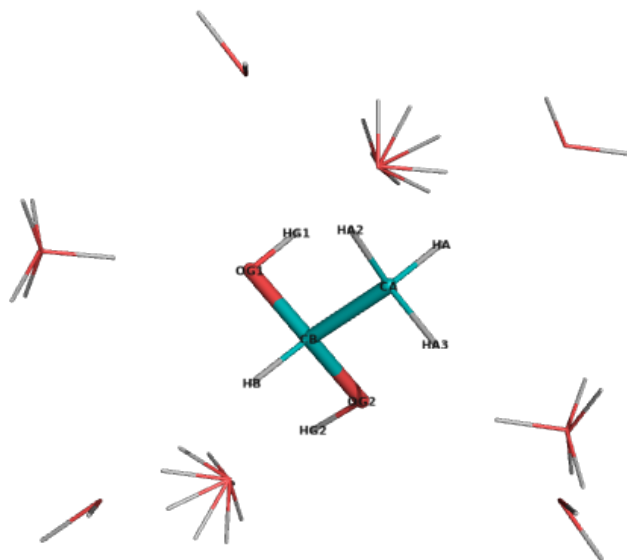


Figure S81: The molecule used for water complex calculations corresponding to ethane-1,1-diol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S259: Statistics of calculated water interaction and dipole moment for ethane-1,1-diol.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.64/1.17	0.05/0.08	1.754	0.18/0.49	89.66
Optimal	0.21/0.34	0.03/0.05	1.015	0.18/0.17	68.86

Table S260: The comparison list of optimized atomic charges and their initial guess for ethane-1,1-diol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.267	0.000
HA	0.090	0.090	0.000
CB	0.360	0.403	10.860
HB	0.090	0.090	0.000
OG1	-0.636	-0.617	8.199
HG1	0.411	0.369	8.913
OG2	-0.636	-0.617	8.199
HG2	0.411	0.369	8.913

Table S261: Interaction energies and geometries between probe water and selected ethane-1,1-diol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.81/-0.52/-0.68	2.71/2.74/2.72
2	HA2-CA	0.0	-0.87/-0.80/-0.94	2.73/2.70/2.69
3	HA-CA	0.0	-0.97/-0.77/-0.80	2.79/2.75/2.73
4	HB-CB	0.0	-1.03/-1.22/-1.42	2.72/2.68/2.66
5	OG1-CB	0.0	-5.15/-4.91/-4.79	1.87/1.88/1.89
6	OG1-CB	90.0	-4.99/-4.65/-4.51	1.86/1.88/1.89
7	OG1-CB	180.0	-4.68/-4.53/-4.20	1.88/1.88/1.90
8	OG1-CB	270.0	-5.34/-4.99/-4.71	1.85/1.87/1.88
9	HG1-OG1	0.0	-6.09/-6.27/-5.28	1.81/1.82/1.85
10	HG1-OG1	45.0	-6.56/-6.36/-5.39	1.79/1.82/1.85
11	HG1-OG1	90.0	-6.09/-6.03/-5.08	1.81/1.83/1.86
12	HG1-OG1	135.0	-5.63/-5.93/-4.97	1.82/1.83/1.86
13	OG2-CB	0.0	-5.27/-5.35/-5.24	1.87/1.88/1.88
14	OG2-CB	90.0	-5.10/-5.17/-5.01	1.85/1.88/1.88
15	OG2-CB	180.0	-4.70/-5.03/-4.68	1.89/1.88/1.89
16	OG2-CB	270.0	-5.44/-5.42/-5.14	1.85/1.87/1.88
17	HG2-OG2	0.0	-6.32/-6.37/-5.36	1.77/1.81/1.84
18	HG2-OG2	45.0	-6.53/-6.39/-5.40	1.76/1.81/1.84
19	HG2-OG2	90.0	-5.93/-6.05/-5.08	1.78/1.82/1.85
20	HG2-OG2	135.0	-5.74/-6.03/-5.04	1.79/1.82/1.85

1.85 The dipeptide of Didehydroaspartate (DYA)

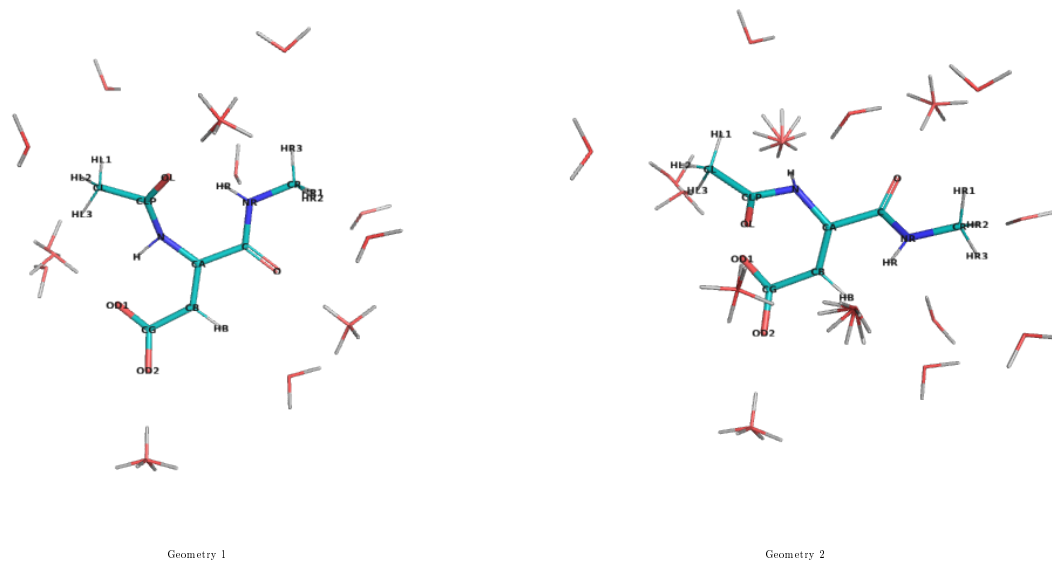


Table S262: The molecule used for water complex calculations corresponding to Didehydroaspartate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S263: Statistics of calculated water interaction and dipole moment for Didehydroaspartate.

		RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
		Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Geometry 1	Initial	1.42 / 3.06	0.10 / 0.13	6.267	10.19 / 13.37	10.19
Geometry 2	Initial	1.36 / 2.46	0.64 / 2.54	5.428	9.45 / 12.66	9.45
Sum of geometries	Initial	1.39 / 3.06	0.46 / 2.54	11.695	-	-
Geometry 1	Optimal	0.64 / 1.39	0.10 / 0.12	3.772	10.19 / 11.31	10.19
Geometry 2	Optimal	0.57 / 1.22	0.23 / 0.60	2.787	9.45 / 9.65	9.45
Sum of geometries	Optimal	0.61 / 1.39	0.18 / 0.60	6.559	-	-

Table S264: The comparison list of optimized atomic charges and their initial guess for Didehydroaspartate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.273	8.367
HL1	0.090	0.090	0.000
HL2	0.090	0.090	0.000
HL3	0.090	0.090	0.000
CLP	0.510	0.525	15.975
OL	-0.510	-0.523	7.454
N	-0.350	-0.526	168.861
H	0.193	0.325	3.688
CA	-0.115	0.158	173.452
CB	-0.128	-0.193	41.581
HB	0.110	0.150	3.536
CG	0.644	0.620	3.713
OD1	-0.677	-0.760	0.175
OD2	-0.677	-0.760	0.175
C	0.510	0.479	57.375
O	-0.510	-0.499	15.568
NR	-0.470	-0.477	4.377
HR	0.310	0.296	1.596
CR	-0.110	-0.082	1.853
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S265: Interaction energies and geometries between probe water and selected Didehydroaspartate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/	Optimal/Initial	QM/	Optimal/Initial
Geometry 1						
1	OL-CLP	0.0	-6.80/-7.00/-7.47		1.87/1.77/1.76	
2	OL-CLP	90.0	-7.55/-8.07/-8.36		1.86/1.76/1.75	
3	OL-CLP	180.0	-7.33/-7.57/-7.44		1.89/1.77/1.77	
4	OL-CLP	270.0	-6.48/-6.38/-6.55		1.89/1.78/1.77	
5	O-C	0.0	-9.20/-9.74/-9.05		1.85/1.74/1.75	
6	O-C	90.0	-8.24/-8.44/-7.69		1.86/1.75/1.76	
7	O-C	180.0	-7.57/-7.29/-6.49		1.86/1.76/1.77	
8	O-C	270.0	-8.32/-8.47/-7.72		1.86/1.75/1.76	
9	NR-C	0.0	-3.16/-2.60/-2.35		2.23/2.17/2.17	
10	OD1-CG	0.0	-5.80/-6.03/-6.10		2.02/2.04/1.98	
11	OD1-CG	90.0	-9.61/-8.21/-9.01		1.75/1.86/1.79	
12	OD1-CG	180.0	-9.95/-8.68/-10.00		1.75/1.84/1.76	
13	OD1-CG	270.0	-6.94/-6.67/-7.34		1.89/1.95/1.85	
14	OD2-CG	0.0	-11.43/-12.02/-13.74		1.78/1.69/1.66	
15	OD2-CG	90.0	-11.42/-12.21/-14.20		1.78/1.68/1.65	
16	OD2-CG	180.0	-11.68/-12.50/-14.74		1.77/1.68/1.65	
17	OD2-CG	270.0	-11.43/-12.20/-14.20		1.78/1.68/1.65	
Geometry 2						
18	OL-CLP	0.0	-8.22/-8.81/-9.20		1.88/1.76/1.75	
19	OL-CLP	90.0	-10.57/-11.70/-12.46		1.85/1.73/1.72	
20	OL-CLP	180.0	-8.29/-9.13/-9.08		1.88/1.75/1.75	
21	OL-CLP	270.0	-7.26/-7.40/-7.25		1.89/1.76/1.76	
22	O-C	0.0	-8.70/-9.41/-8.53		1.85/1.74/1.75	
23	O-C	90.0	-8.21/-8.51/-7.78		1.86/1.75/1.75	
24	O-C	180.0	-7.71/-7.75/-7.10		1.86/1.75/1.76	
25	O-C	270.0	-8.30/-8.73/-8.03		1.86/1.75/1.75	
26	NR-C	0.0	-0.74/-0.65/-0.06		2.46/2.33/5.00	
27	N-CLP	0.0	-7.86/-7.54/-6.82		2.13/2.12/2.11	
28	OD1-CG	0.0	-4.70/-5.61/-5.74		2.29/2.57/2.55	
29	OD1-CG	90.0	-6.01/-6.46/-7.23		1.93/2.53/2.48	
30	OD1-CG	180.0	-6.49/-6.67/-7.95		1.93/2.52/2.47	
31	OD1-CG	270.0	-4.52/-5.74/-6.56		2.62/2.58/2.53	
32	OD2-CG	0.0	-12.08/-11.79/-13.60		1.76/1.69/1.66	
33	OD2-CG	90.0	-12.83/-12.87/-15.01		1.75/1.68/1.65	
34	OD2-CG	180.0	-13.02/-13.10/-15.48		1.75/1.68/1.64	
35	OD2-CG	270.0	-12.30/-12.15/-14.23		1.76/1.68/1.65	

1.86 Small molecule A of Didehydroaspartate(DYA)

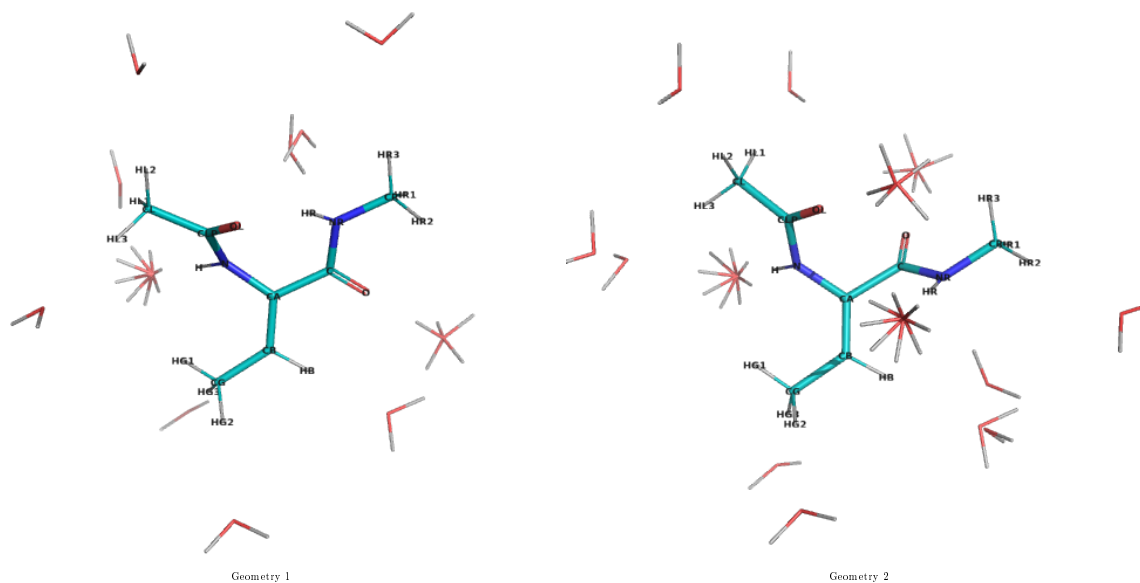


Table S266: The molecule used for water complex calculations corresponding to (2Z)-2-acetamido-N-methylbut-2-enamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S267: Statistics of calculated water interaction and dipole moment for (2Z)-2-acetamido-N-methylbut-2-enamide.

		RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle	
		Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)	
Geometry 1	Initial	0.55 / 0.89	0.08 / 0.18	3.603	5.30 / 3.56	5.30	
Geometry 2	Initial	0.92 / 1.98	0.08 / 0.25	3.138	3.66 / 3.44	3.66	
Sum of geometries		Initial	0.80 / 1.98	0.08 / 0.25	6.742	-	-
Geometry 1	Optimal	0.26 / 0.54	0.07 / 0.15	1.898	5.30 / 5.64	5.30	
Geometry 2	Optimal	0.46 / 0.94	0.12 / 0.56	2.284	3.66 / 4.72	3.66	
Sum of geometries		Optimal	0.40 / 0.94	0.11 / 0.56	4.182	-	-

Table S268: The comparison list of optimized atomic charges and their initial guess for (2Z)-2-acetamido-N-methylbut-2-enamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.273	8.367
HL1	0.090	0.090	0.000
HL2	0.090	0.090	0.000
HL3	0.090	0.090	0.000
CLP	0.510	0.525	15.975
OL	-0.510	-0.523	7.454
N	-0.311	-0.526	168.861
H	0.280	0.325	3.688
CA	-0.064	0.156	174.206
CB	-0.148	-0.044	44.661
HB	0.110	0.150	3.536
CG	-0.137	-0.316	11.520
HG1	0.090	0.090	0.175
HG2	0.090	0.090	0.175
HG3	0.090	0.090	0.175
C	0.510	0.478	58.380
O	-0.510	-0.499	15.568
NR	-0.470	-0.477	4.377
HR	0.310	0.296	1.596
CR	-0.110	-0.082	1.853
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S269: Interaction energies and geometries between probe water and selected (2Z)-2-acetamido-N-methylbut-2-enamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
Geometry 1						
1	HL1-CL	0.0	-2.73/-2.91/-2.49		2.55/2.59/2.62	
2	HL2-CL	0.0	-1.62/-1.08/-0.77		2.51/2.66/2.68	
3	HL3-CL	0.0	-2.45/-1.99/-1.56		2.49/2.63/2.64	
4	O-C	0.0	-6.47/-6.66/-5.66		1.81/1.76/1.77	
5	O-C	90.0	-6.90/-6.93/-6.22		1.80/1.75/1.76	
6	O-C	180.0	-7.01/-7.05/-6.38		1.80/1.75/1.76	
7	O-C	270.0	-6.83/-6.98/-6.10		1.80/1.75/1.77	
8	NR-C	0.0	-3.67/-3.58/-3.47		2.12/2.11/2.12	
9	HR3-CR	0.0	-0.82/-0.76/-1.01		2.73/2.69/2.66	
10	N-CLP	0.0	-2.04/-1.61/-1.58		3.29/3.40/3.35	
11	H-N	0.0	-7.00/-7.43/-7.11		1.89/1.90/1.89	
12	H-N	45.0	-6.91/-7.25/-7.13		1.89/1.90/1.89	
13	H-N	90.0	-7.42/-7.38/-7.27		1.87/1.90/1.89	
14	H-N	135.0	-7.50/-7.56/-7.25		1.87/1.90/1.89	
15	HG2-CG	0.0	-1.57/-1.52/-0.90		2.63/2.64/2.73	
16	HG3-CG	0.0	-1.81/-1.85/-1.21		2.63/2.63/2.71	
Geometry 2						
17	HL1-CL	0.0	-1.72/-1.16/-0.88		2.46/2.61/2.63	
18	HL2-CL	0.0	-0.84/-0.43/-0.20		2.62/2.71/2.73	
19	HL3-CL	0.0	-2.41/-2.36/-1.98		2.55/2.62/2.63	
20	OL-CLP	0.0	-7.53/-8.10/-8.69		1.79/1.74/1.73	
21	OL-CLP	90.0	-7.02/-7.11/-7.60		1.79/1.75/1.74	
22	OL-CLP	180.0	-4.85/-5.57/-5.46		1.85/1.77/1.77	
23	OL-CLP	270.0	-7.02/-7.59/-7.68		1.79/1.74/1.73	
24	O-C	0.0	-6.23/-6.53/-6.26		1.82/1.76/1.76	
25	O-C	90.0	-6.65/-7.16/-6.91		1.81/1.75/1.75	
26	O-C	180.0	-6.93/-7.44/-6.85		1.81/1.75/1.76	
27	O-C	270.0	-6.78/-7.14/-6.52		1.81/1.75/1.76	
28	NR-C	0.0	-3.17/-2.40/-2.07		2.09/2.18/2.13	
29	HR-NR	0.0	-4.18/-4.71/-5.84		1.87/1.88/1.88	
30	HR-NR	45.0	-3.20/-4.15/-5.19		1.91/1.90/1.89	
31	HR-NR	90.0	-3.93/-4.59/-5.64		1.89/1.89/1.88	
32	HR-NR	135.0	-5.00/-5.20/-6.34		1.85/1.87/1.87	
33	HR2-CR	0.0	-1.08/-0.96/-1.37		2.74/2.70/2.67	
34	HB-CB	0.0	-1.60/-1.57/-3.07		2.48/2.56/2.47	
35	HB-CB	90.0	-1.17/-1.39/-2.88		2.62/2.59/2.48	
36	H-N	0.0	-6.03/-6.37/-6.21		1.88/1.89/1.88	
37	H-N	45.0	-6.42/-6.44/-6.39		1.86/1.88/1.87	
38	H-N	90.0	-6.80/-6.66/-6.55		1.84/1.88/1.87	
39	H-N	135.0	-6.41/-6.59/-6.37		1.86/1.88/1.88	
40	HG1-CG	0.0	-1.05/-1.69/-1.10		4.53/3.98/4.29	
41	HG2-CG	0.0	-1.32/-1.64/-0.99		2.71/2.65/2.74	
42	HG3-CG	0.0	-1.53/-1.82/-1.17		2.68/2.63/2.72	

1.87 Small molecule A of (3S)-3-amino-3-[(4Z)-1-(carboxymethyl)-4-[(4-hydroxyphenyl)methylidene]-5-oxo-imidazol-2-yl]propanoic acid(DYG)

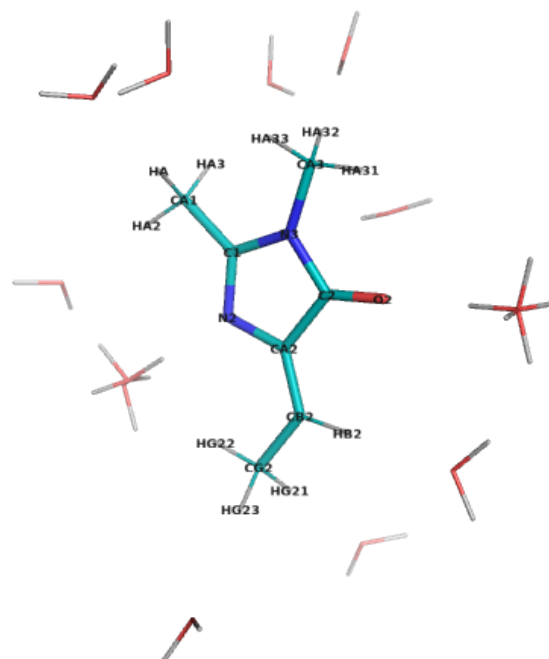


Figure S82: The molecule used for water complex calculations corresponding to (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S270: Statistics of calculated water interaction and dipole moment for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.92/1.64	0.10/0.25	6.526	3.17/0.45	27.81
Optimal	0.49/1.31	0.09/0.22	3.053	3.17/3.55	14.34

Table S271: The comparison list of optimized atomic charges and their initial guess for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA1	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
HA2	0.090	0.090	0.000
HA3	0.090	0.090	0.000
C1	0.233	0.074	23.781
N2	-0.679	-0.703	41.871
N3	-0.080	-0.079	15.706
C2	0.407	0.509	24.002
O2	-0.489	-0.482	6.710
CA2	0.288	0.516	47.153
CB2	-0.105	-0.135	25.469
HB2	0.150	0.150	3.270
CG2	-0.270	-0.274	15.277
HG21	0.090	0.090	1.175
HG22	0.090	0.090	1.175
HG23	0.090	0.090	1.175
CA3	-0.195	-0.271	3.821
HA31	0.090	0.090	0.000
HA32	0.090	0.090	0.000
HA33	0.090	0.090	0.000

Table S272: Interaction energies and geometries between probe water and selected (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA-CA1	0.0	-2.17/-2.61/-1.51		2.59/2.58/2.65	
2	HA2-CA1	0.0	-0.97/-0.86/0.05		2.58/2.64/2.77	
3	HA3-CA1	0.0	-2.55/-2.73/-1.57		2.52/2.57/2.64	
4	N2-C1	0.0	-4.99/-6.30/-5.60		2.09/2.01/2.02	
5	N2-C1	90.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
6	N2-C1	180.0	-5.35/-5.42/-6.38		1.95/2.01/1.99	
7	N2-C1	270.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
8	N3-C1	0.0	-0.26/-0.82/-0.78		2.74/2.52/2.49	
9	O2-C2	0.0	-5.51/-5.57/-5.00		1.85/1.78/1.80	
10	O2-C2	90.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
11	O2-C2	180.0	-5.92/-5.61/-4.27		1.84/1.78/1.81	
12	O2-C2	270.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
13	HB2-CB2	0.0	-1.40/-1.60/-2.82		2.32/2.47/2.44	
14	HG21-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
15	HG23-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
16	HA32-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	
17	HA33-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	

1.88 Small molecule B of (3S)-3-amino-3-[(4Z)-1-(carboxymethyl)-4-[(4-hydroxyphenyl)methylidene]-5-oxo-imidazol-2-yl]propanoic acid(DYG)

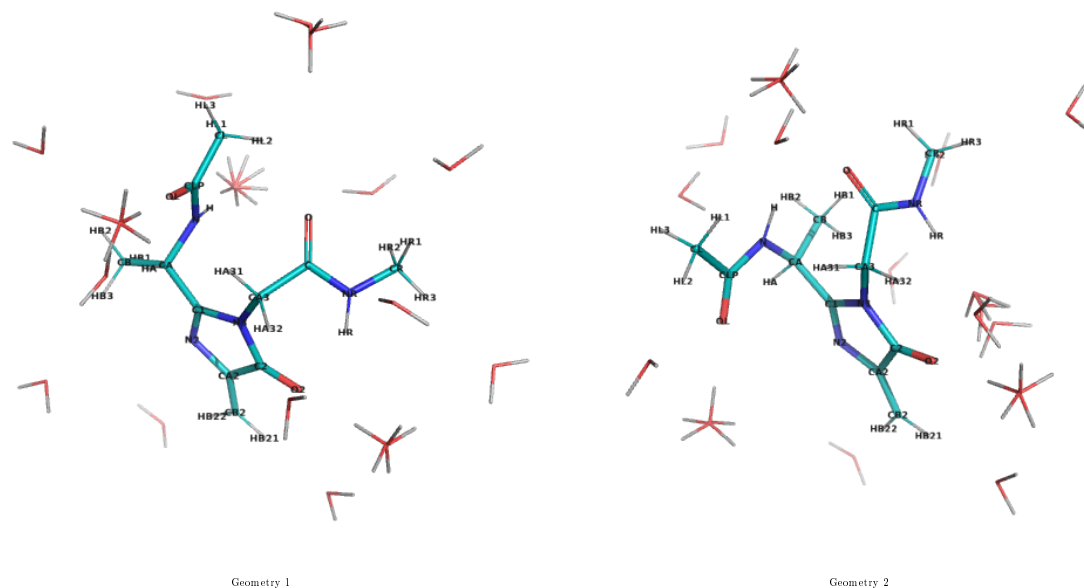


Table S273: The molecule used for water complex calculations corresponding to N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S274: Statistics of calculated water interaction and dipole moment for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide.

		RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
		Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Geometry 1	Initial	0.86 / 2.05	0.07 / 0.17	6.601	1.19 / 4.07	1.19
Geometry 2	Initial	1.02 / 2.07	0.09 / 0.23	6.126	6.37 / 4.43	6.37
Sum of geometries	Initial	0.95 / 2.07	0.08 / 0.23	12.727	-	-
Geometry 1	Optimal	0.36 / 0.81	0.07 / 0.16	2.460	1.19 / 1.37	1.19
Geometry 2	Optimal	0.51 / 0.91	0.08 / 0.19	2.701	6.37 / 7.25	6.37
Sum of geometries	Optimal	0.45 / 0.91	0.08 / 0.19	5.161	-	-

Table S275: The comparison list of optimized atomic charges and their initial guess for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
C1	0.233	0.164	24.002
N2	-0.679	-0.703	41.104
N3	-0.031	-0.499	22.994
C2	0.407	0.613	23.378
O2	-0.489	-0.482	6.517
CA2	0.466	0.512	42.773
CB2	-0.593	-0.444	13.655
HB21	0.230	0.230	0.950
HB22	0.230	0.230	0.950
CA3	-0.154	0.043	13.461
HA31	0.090	0.090	0.177
HA32	0.090	0.090	0.177
C	0.510	0.499	10.097
O	-0.510	-0.517	3.479
NR	-0.470	-0.442	6.773
HR	0.310	0.299	0.000
CR	-0.110	-0.108	0.239
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S276: Interaction energies and geometries between probe water and selected N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
Geometry 1				
1	O-C	0.0	-5.45/-5.47/-6.22	1.84/1.77/1.76
2	O-C	90.0	-6.01/-6.48/-6.53	1.83/1.75/1.76
3	O-C	180.0	-5.96/-6.64/-6.64	1.83/1.75/1.75
4	O-C	270.0	-5.67/-5.94/-6.62	1.84/1.76/1.75
5	NR-C	0.0	-1.32/-1.50/-1.08	2.24/2.20/2.22
6	HR2-CR	0.0	-1.10/-1.26/-1.09	2.71/2.66/2.67
7	HR3-CR	0.0	-1.39/-1.22/-1.32	2.66/2.67/2.67
8	N2-C1	0.0	-5.74/-6.45/-6.04	1.95/1.92/1.92
9	N2-C1	90.0	-6.51/-6.37/-7.24	1.90/1.92/1.90
10	N2-C1	180.0	-5.60/-5.66/-7.65	1.96/1.93/1.90
11	N2-C1	270.0	-6.64/-6.59/-7.43	1.90/1.91/1.89
12	O2-C2	0.0	-3.88/-3.93/-3.54	1.88/1.80/1.81
13	O2-C2	90.0	-4.94/-5.15/-4.46	1.84/1.77/1.79
14	O2-C2	180.0	-4.95/-5.20/-4.05	1.84/1.77/1.79
15	O2-C2	270.0	-3.93/-4.12/-3.39	1.87/1.79/1.81
16	HB21-CB2	0.0	-1.84/-1.64/-3.47	2.32/2.48/2.42
17	HB22-CB2	0.0	-1.82/-1.01/-2.42	2.42/2.54/2.46
18	HA31-CA3	0.0	-2.08/-2.47/-1.68	2.70/2.69/2.70
19	HA-CA	0.0	-2.47/-2.76/-1.19	2.49/2.56/2.66
Geometry 2				
20	O-C	0.0	-6.06/-6.90/-7.24	1.86/1.76/1.75
21	O-C	90.0	-5.25/-6.15/-7.32	1.87/1.77/1.75
22	O-C	180.0	-4.71/-5.63/-6.52	1.88/1.77/1.76
23	O-C	270.0	-5.56/-6.46/-6.85	1.86/1.76/1.76
24	HR-NR	0.0	-7.09/-7.67/-7.53	1.93/1.90/1.90
25	HR-NR	45.0	-7.71/-7.90/-7.71	1.91/1.89/1.89
26	HR-NR	90.0	-7.79/-7.84/-7.79	1.90/1.89/1.89
27	HR-NR	135.0	-7.18/-7.62/-7.61	1.92/1.90/1.89
28	HR1-CR	0.0	-0.71/-0.04/0.30	2.50/2.69/2.67
29	HR2-CR	0.0	-1.54/-1.44/-1.38	2.68/2.66/2.66
30	HR3-CR	0.0	-1.84/-1.82/-1.70	2.68/2.67/2.66
31	N2-C1	0.0	-6.46/-6.98/-6.58	1.93/1.91/1.91
32	N2-C1	90.0	-6.88/-6.47/-7.35	1.89/1.91/1.89
33	N2-C1	180.0	-5.73/-5.60/-7.60	1.95/1.93/1.90
34	N2-C1	270.0	-7.31/-7.09/-7.94	1.88/1.91/1.89
35	N3-C1	0.0	-0.22/0.03/-2.15	2.60/2.67/2.17
36	O2-C2	0.0	-4.96/-5.34/-4.95	1.88/1.79/1.80
37	O2-C2	90.0	-5.32/-5.37/-4.66	1.87/1.78/1.80
38	O2-C2	180.0	-5.74/-5.89/-4.71	1.87/1.78/1.81
39	O2-C2	270.0	-5.94/-6.25/-5.51	1.85/1.77/1.79
40	HB21-CB2	0.0	-1.43/-1.20/-3.03	2.33/2.48/2.41
41	HB22-CB2	0.0	-1.29/-0.66/-2.05	2.47/2.56/2.47
42	HA31-CA3	0.0	-3.71/-4.08/-3.49	2.50/2.57/2.57
43	HA-CA	0.0	-2.67/-3.45/-1.93	2.59/2.58/2.69

1.89 Small molecule used for ethionine(ESC)

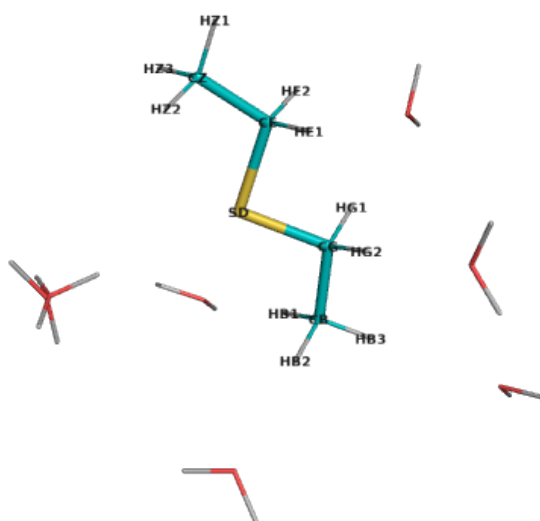


Figure S83: The molecule used for water complex calculations corresponding to (ethylsulfanyl)ethane, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S277: Statistics of calculated water interaction and dipole moment for (ethylsulfanyl)ethane.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.77/1.21	0.35/0.55	1.274	1.75/1.92	0.08
Optimal	0.26/0.40	0.30/0.48	1.743	1.75/1.32	0.10

Table S278: The comparison list of optimized atomic charges and their initial guess for (ethylsulfanyl)ethane, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.270	0.045
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.114	-0.065	0.064
HG1	0.090	0.090	0.000
HG2	0.090	0.090	0.000
SD	-0.131	-0.230	0.064
CE	-0.115	-0.065	0.064
HE2	0.090	0.090	0.000
HE1	0.090	0.090	0.000
CZ	-0.270	-0.270	0.045
HZ1	0.090	0.090	0.000
HZ2	0.090	0.090	0.000
HZ3	0.090	0.090	0.000

Table S279: Interaction energies and geometries between probe water and selected (ethylsulfanyl)ethane site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.92/-0.69/-0.81	2.80/2.76/2.75
2	HB1-CB	0.0	-0.62/-0.36/-0.29	2.73/2.77/2.76
3	HB2-CB	0.0	-0.62/-0.36/-0.29	2.73/2.77/2.76
4	HG1-CG	0.0	-1.04/-0.97/-1.15	2.75/2.73/2.71
5	HG2-CG	0.0	-1.04/-0.97/-1.15	2.75/2.73/2.71
6	SD-CG	0.0	-1.70/-2.10/-2.91	2.88/2.40/2.33
7	SD-CG	90.0	-1.93/-2.13/-2.95	2.82/2.40/2.32
8	SD-CG	180.0	-1.70/-2.10/-2.91	2.88/2.40/2.33
9	SD-CG	270.0	-1.93/-2.13/-2.95	2.82/2.40/2.32

1.90 Small molecule used for 3,4-difluoro-phenylalanine(F2F)

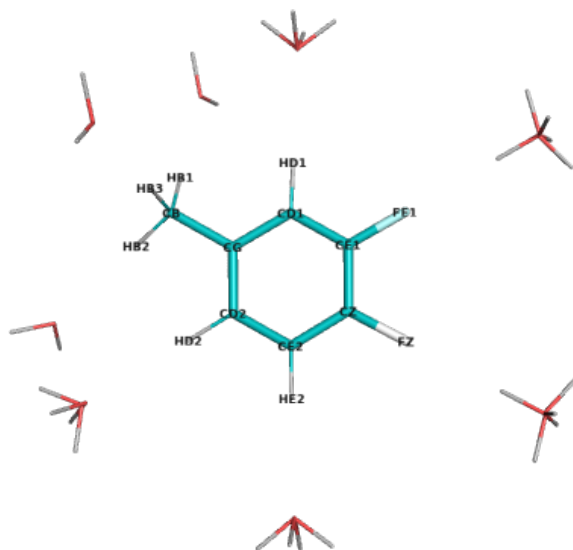


Figure S84: The molecule used for water complex calculations corresponding to 1,2-difluoro-4-methylbenzene, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S280: Statistics of calculated water interaction and dipole moment for 1,2-difluoro-4-methylbenzene.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.54/0.88	0.20/0.27	2.068	3.44/3.07	6.12
Optimal	0.08/0.16	0.15/0.22	2.039	3.44/4.16	0.52

Table S281: The comparison list of optimized atomic charges and their initial guess for 1,2-difluoro-4-methylbenzene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.267	0.474
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.134	-0.033	0.741
CD1	-0.175	-0.128	5.819
HD1	0.150	0.177	0.707
CD2	-0.077	-0.167	0.570
HD2	0.115	0.115	0.000
CE1	0.085	0.189	9.696
FE1	-0.138	-0.207	0.973
CE2	-0.198	-0.101	5.794
HE2	0.171	0.180	0.707
CZ	0.069	0.179	9.696
FZ	-0.136	-0.207	0.973

Table S282: Interaction energies and geometries between probe water and selected 1,2-difluoro-4-methylbenzene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.31/-1.35/-0.86	2.69/2.68/2.74
2	HB1-CB	0.0	-1.68/-1.62/-1.31	2.63/2.66/2.70
3	HB2-CB	0.0	-1.82/-1.80/-1.06	2.63/2.66/2.73
4	HD1-CD1	0.0	-2.04/-2.07/-2.67	2.47/2.43/2.38
5	HD1-CD1	90.0	-2.08/-2.05/-2.61	2.44/2.43/2.39
6	HD2-CD2	0.0	-1.92/-2.02/-1.39	2.58/2.64/2.70
7	HD2-CD2	90.0	-2.24/-2.12/-1.48	2.50/2.63/2.68
8	FE1-CE1	0.0	-1.78/-1.69/-2.00	2.25/2.03/1.98
9	FE1-CE1	90.0	-2.06/-2.10/-2.43	2.23/2.01/1.96
10	FE1-CE1	180.0	-2.36/-2.52/-2.89	2.21/1.99/1.94
11	FE1-CE1	270.0	-2.06/-2.10/-2.43	2.23/2.01/1.96
12	HE2-CE2	0.0	-2.04/-2.04/-2.92	2.45/2.42/2.37
13	HE2-CE2	90.0	-2.05/-2.01/-2.85	2.44/2.42/2.38
14	FZ-CZ	0.0	-2.38/-2.53/-2.90	2.21/1.99/1.94
15	FZ-CZ	90.0	-2.09/-2.14/-2.41	2.23/2.01/1.96
16	FZ-CZ	180.0	-1.83/-1.76/-1.94	2.24/2.03/1.98
17	FZ-CZ	270.0	-2.09/-2.13/-2.41	2.23/2.01/1.96

1.91 Small molecule used for 4-fluoro-glutamicacid(FGA4)

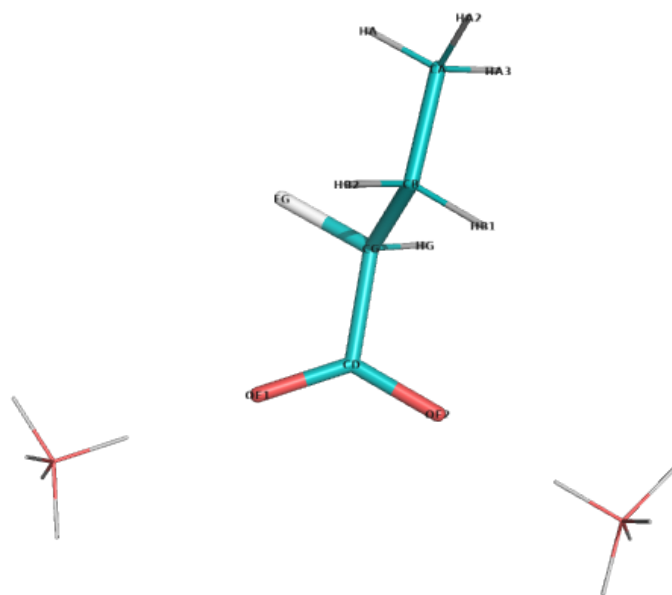


Figure S85: The molecule used for water complex calculations corresponding to 2-fluorobutanoic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S283: Statistics of calculated water interaction and dipole moment for 2-fluorobutanoic acid.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	1.27/1.67	0.09/0.10	3.871	8.32/9.91	0.75
Optimal	0.27/0.37	0.07/0.08	2.812	8.32/8.26	1.88

Table S284: The comparison list of optimized atomic charges and their initial guess for 2-fluorobutanoic acid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.600
HA2	0.090	0.090	0.600
CA	-0.270	-0.270	4.493
HA	0.090	0.090	0.600
CB	-0.201	-0.115	10.678
HB1	0.090	0.090	2.585
HB2	0.090	0.090	2.585
CG	-0.018	-0.012	80.608
HG	0.047	0.110	5.793
CD	0.644	0.591	77.800
FG	-0.220	-0.234	20.695
OE1	-0.716	-0.760	6.586
OE2	-0.716	-0.760	6.586

Table S285: Interaction energies and geometries between probe water and selected 2-fluorobutanoic acid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	OE1-CD	0.0	-13.68/-13.90/-15.02	1.74/1.66/1.65
2	OE1-CD	90.0	-13.51/-13.83/-15.14	1.74/1.67/1.65
3	OE1-CD	180.0	-13.63/-13.87/-15.29	1.74/1.66/1.65
4	OE1-CD	270.0	-13.31/-13.67/-14.89	1.75/1.67/1.65
5	OE2-CD	0.0	-13.28/-12.96/-13.68	1.73/1.67/1.66
6	OE2-CD	90.0	-13.65/-13.42/-14.48	1.73/1.67/1.65
7	OE2-CD	180.0	-14.27/-14.04/-15.48	1.72/1.66/1.64
8	OE2-CD	270.0	-13.73/-13.49/-14.64	1.73/1.67/1.65

1.92 The dipeptide of 2-aminopropanedioic acid (FGL)

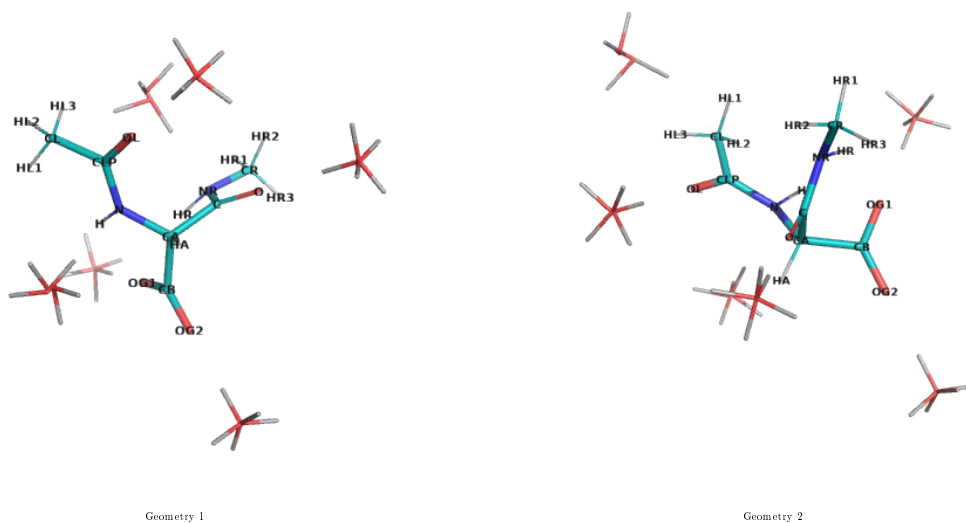


Table S286: The molecule used for water complex calculations corresponding to 2-aminopropanedioic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S287: Statistics of calculated water interaction and dipole moment for 2-aminopropanedioic acid.

		RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
		Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Geometry 1	Initial	1.79 / 3.10	0.12 / 0.17	5.383	8.39 / 10.89	8.39
Geometry 2	Initial	1.53 / 3.07	0.11 / 0.16	5.126	8.53 / 10.95	8.53
Sum of geometries	Initial	1.66 / 3.10	0.11 / 0.17	10.510	-	-
Geometry 1	Optimal	0.58 / 1.67	0.10 / 0.15	3.049	8.39 / 8.37	8.39
Geometry 2	Optimal	0.48 / 1.23	0.11 / 0.23	2.795	8.53 / 8.52	8.53
Sum of geometries	Optimal	0.53 / 1.67	0.10 / 0.23	5.845	-	-

Table S288: The comparison list of optimized atomic charges and their initial guess for 2-aminopropanedioic acid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.270	0.000
HL1	0.090	0.090	0.000
HL2	0.090	0.090	0.000
HL3	0.090	0.090	0.000
CLP	0.510	0.506	0.000
OL	-0.510	-0.510	0.000
N	-0.412	-0.532	0.000
H	0.224	0.477	0.000
CA	-0.038	-0.177	45.246
HA	0.090	0.090	0.000
CB	0.588	0.619	40.284
OG1	-0.642	-0.760	2.150
OG2	-0.642	-0.760	2.150
C	0.273	0.571	47.922
O	-0.441	-0.519	19.435
NR	-0.470	-0.479	18.726
HR	0.310	0.312	0.000
CR	-0.110	-0.108	0.000
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S289: Interaction energies and geometries between probe water and selected 2-aminopropanedioic acid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
Geometry 1						
1	OL-CLP	0.0	-6.98/-6.62/-6.44	1.89/1.78/1.78		
2	OL-CLP	90.0	-7.66/-7.77/-7.90	1.89/1.77/1.77		
3	OL-CLP	180.0	-10.24/-11.03/-11.00	1.85/1.74/1.74		
4	OL-CLP	270.0	-8.73/-9.34/-8.92	1.88/1.75/1.76		
5	O-C	0.0	-9.54/-9.82/-10.22	1.85/1.75/1.74		
6	O-C	90.0	-8.89/-9.07/-9.36	1.86/1.76/1.75		
7	O-C	180.0	-8.17/-8.16/-8.01	1.87/1.77/1.76		
8	O-C	270.0	-9.05/-9.21/-9.16	1.86/1.76/1.75		
9	OG1-CB	0.0	-9.92/-9.82/-10.24	1.78/1.70/1.67		
10	OG1-CB	90.0	-10.79/-10.88/-12.76	1.76/1.69/1.65		
11	OG1-CB	180.0	-11.80/-11.98/-14.67	1.74/1.68/1.63		
12	OG1-CB	270.0	-10.77/-10.83/-12.25	1.76/1.69/1.65		
13	OG2-CB	0.0	-11.44/-11.94/-14.44	1.79/1.70/1.66		
14	OG2-CB	90.0	-10.94/-11.30/-13.99	1.79/1.70/1.66		
15	OG2-CB	180.0	-11.17/-11.51/-14.20	1.79/1.69/1.65		
16	OG2-CB	270.0	-11.35/-12.00/-14.45	1.79/1.69/1.65		
17	N-CLP	0.0	-5.73/-6.73/-7.41	2.24/2.14/2.12		
18	N-CLP	90.0	-4.76/-5.92/-6.60	2.30/2.17/2.13		
19	N-CLP	180.0	-2.40/-2.50/-2.00	2.43/2.28/2.32		
20	N-CLP	270.0	-2.09/-2.24/-1.53	2.49/2.35/2.57		
21	NR-C	180.0	-6.46/-6.26/-4.87	2.06/1.96/1.99		
22	NR-C	270.0	-2.90/-1.23/-0.06	2.06/2.01/2.03		
Geometry 2						
23	OL-CLP	0.0	-6.76/-6.66/-6.37	1.90/1.78/1.78		
24	OL-CLP	90.0	-7.38/-7.74/-7.74	1.90/1.77/1.77		
25	OL-CLP	180.0	-10.38/-11.60/-11.36	1.86/1.73/1.74		
26	OL-CLP	270.0	-8.69/-9.85/-9.22	1.89/1.75/1.76		
27	O-C	0.0	-9.46/-9.78/-10.20	1.85/1.75/1.74		
28	O-C	90.0	-9.01/-9.23/-9.54	1.86/1.76/1.74		
29	O-C	180.0	-8.29/-8.37/-8.23	1.87/1.77/1.76		
30	O-C	270.0	-9.03/-9.27/-9.22	1.86/1.75/1.74		
31	OG1-CB	0.0	-9.92/-9.78/-10.22	1.78/1.70/1.67		
32	OG1-CB	90.0	-10.90/-11.01/-12.86	1.76/1.69/1.65		
33	OG1-CB	180.0	-11.89/-12.10/-14.72	1.74/1.68/1.63		
34	OG1-CB	270.0	-10.85/-10.87/-12.24	1.76/1.69/1.65		
35	OG2-CB	0.0	-11.50/-11.97/-14.44	1.79/1.70/1.66		
36	OG2-CB	90.0	-10.94/-11.25/-13.91	1.79/1.70/1.66		
37	OG2-CB	180.0	-11.21/-11.52/-14.19	1.79/1.69/1.65		
38	OG2-CB	270.0	-11.46/-12.09/-14.53	1.79/1.69/1.65		
39	N-CLP	0.0	-5.99/-6.13/-6.74	2.15/2.10/2.08		
40	N-CLP	90.0	-5.70/-6.13/-6.81	2.17/2.10/2.06		
41	N-CLP	180.0	-3.93/-3.52/-3.22	2.22/2.16/2.16		
42	N-CLP	270.0	-3.41/-2.85/-2.29	2.24/2.21/2.25		
43	NR-C	0.0	-2.12/-1.92/-1.58	4.76/4.70/4.76		
44	NR-C	90.0	-2.54/-2.54/-2.15	4.86/4.63/4.70		
45	NR-C	180.0	-5.20/-5.79/-5.46	4.34/4.20/4.21		
46	NR-C	270.0	-3.20/-3.79/-3.49	4.59/4.44/4.46		

1.93 Small molecule A of N5-formyl-N5-hydroxy-L-ornithine(FHO)

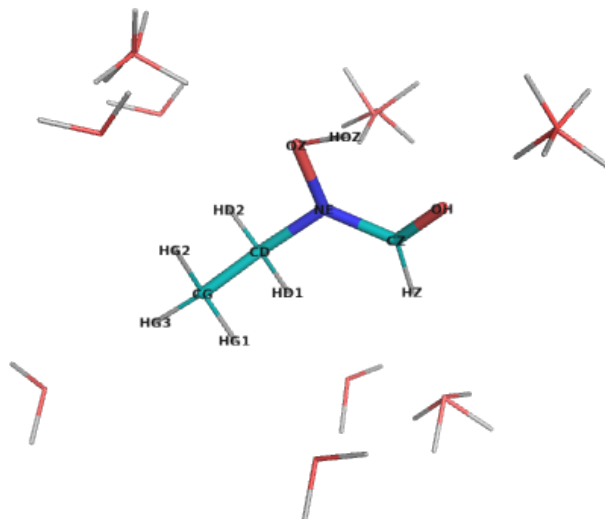


Figure S86: The molecule used for water complex calculations corresponding to N-ethyl-N-hydroxyformamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S290: Statistics of calculated water interaction and dipole moment for N-ethyl-N-hydroxyformamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.87/1.41	0.11/0.19	3.177	3.69/3.02	14.05
Optimal	0.42/0.94	0.08/0.15	3.448	3.69/4.80	0.00

Table S291: The comparison list of optimized atomic charges and their initial guess for N-ethyl-N-hydroxyformamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HG3	0.090	0.090	0.050
CG	-0.223	-0.265	5.022
HG1	0.090	0.090	0.050
HG2	0.090	0.090	0.050
CD	0.069	0.047	10.074
HD1	0.090	0.090	2.541
HD2	0.090	0.090	2.541
NE	-0.230	-0.381	346.670
CZ	0.494	0.415	26.672
HZ	0.013	0.080	2.295
OH	-0.477	-0.519	14.518
OZ	-0.307	-0.247	346.084
HOZ	0.211	0.420	19.754

Table S292: Interaction energies and geometries between probe water and selected N-ethyl-N-hydroxyformamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HG1-CG	0.0	-2.09/-2.29/-1.64	2.62/2.60/2.65
2	HG2-CG	0.0	-0.43/-0.66/-0.48	2.70/2.68/2.82
3	HG3-CG	0.0	-1.47/-1.88/-1.29	2.71/2.64/2.70
4	HD1-CD	0.0	-3.14/-3.16/-2.47	2.48/2.57/2.61
5	HD2-CD	0.0	-1.39/-1.57/-1.06	2.59/2.64/2.69
6	NE-CD	0.0	-2.24/-2.86/-3.62	2.21/2.15/2.07
7	NE-CD	90.0	-0.78/-0.59/-2.15	2.32/2.32/2.13
8	NE-CD	180.0	-0.60/-0.17/-1.79	2.32/2.33/2.14
9	NE-CD	270.0	-2.19/-2.50/-3.26	2.16/2.15/2.07
10	HZ-CZ	0.0	-3.12/-2.64/-2.80	2.39/2.33/2.28
11	HZ-CZ	90.0	-3.40/-2.77/-2.89	2.35/2.32/2.27
12	OH-CZ	0.0	-4.38/-5.32/-4.67	1.90/1.80/1.79
13	OH-CZ	90.0	-4.84/-5.25/-5.50	1.88/1.79/1.77
14	OH-CZ	180.0	-5.23/-5.30/-6.24	1.86/1.79/1.75
15	OH-CZ	270.0	-5.10/-5.44/-5.83	1.86/1.79/1.76
16	OZ-NE	0.0	-3.78/-4.44/-2.37	2.10/1.95/2.06
17	OZ-NE	90.0	-3.82/-4.11/-2.64	2.08/1.95/2.03
18	OZ-NE	180.0	-2.71/-2.65/-2.16	2.14/1.99/2.04
19	OZ-NE	270.0	-3.22/-3.25/-2.11	2.11/1.97/2.05

1.94 Small molecule used for Trifluoroalanine(FLA)

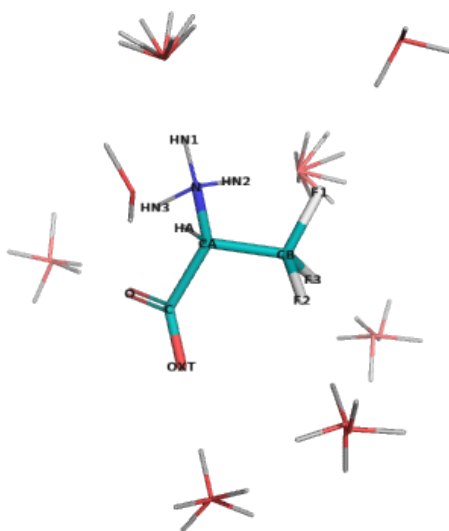


Figure S87: The molecule used for water complex calculations corresponding to 2-amino-3,3,3-trifluoropropanoic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S293: Statistics of calculated water interaction and dipole moment for 2-amino-3,3,3-trifluoropropanoic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	2.30/4.85	0.53/2.42	9.504	10.38/14.48	5.52
Optimal	0.72/1.26	0.27/0.49	4.986	10.38/12.36	0.89

Table S294: The comparison list of optimized atomic charges and their initial guess for 2-aminoo-3,3,3-trifluoropropanoic acid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
N	-0.162	-0.346	38.086
HN3	0.259	0.330	2.674
HN1	0.259	0.330	2.674
HN2	0.259	0.330	2.674
CA	0.386	0.408	127.776
HA	0.090	0.090	5.911
F1	-0.164	-0.140	8.256
F2	-0.164	-0.140	8.256
F3	-0.164	-0.140	8.256
CB	0.374	0.350	82.802
C	0.029	0.448	100.499
O	-0.501	-0.760	8.256
OXT	-0.501	-0.760	8.256

Table S295: Interaction energies and geometries between probe water and selected 2-amino-3,3,3-trifluoropropanoic acid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HN1-N	0.0	-13.94/-13.68/-15.70	1.68/1.77/1.74
2	HN1-N	45.0	-13.69/-13.64/-15.65	1.69/1.77/1.74
3	HN1-N	90.0	-13.35/-13.45/-15.45	1.70/1.77/1.74
4	HN1-N	135.0	-13.59/-13.49/-15.49	1.69/1.77/1.74
5	HN2-N	0.0	-12.99/-12.16/-14.37	1.68/1.79/1.76
6	HN2-N	45.0	-13.56/-12.32/-14.42	1.66/1.79/1.76
7	HN2-N	90.0	-13.69/-12.50/-14.61	1.66/1.79/1.75
8	HN2-N	135.0	-13.08/-12.32/-14.53	1.68/1.79/1.76
9	HA-CA	0.0	-4.92/-4.69/-5.34	2.22/2.51/2.49
10	F1-CB	90.0	-0.86/-0.50/0.05	2.30/1.93/1.98
11	F1-CB	180.0	-1.35/-1.51/-0.95	2.27/1.88/1.92
12	F2-CB	0.0	-1.68/-2.45/-2.33	2.38/1.93/1.98
13	F2-CB	90.0	-2.14/-3.30/-3.22	2.35/1.89/1.92
14	F2-CB	180.0	-0.72/-0.99/-0.36	2.51/2.02/2.19
15	F2-CB	270.0	-0.30/-0.19/0.12	2.58/2.13/5.00
16	F3-CB	0.0	-0.75/-1.30/-0.83	2.46/1.98/2.09
17	F3-CB	180.0	-0.56/-0.85/-0.08	2.44/1.98/2.10
18	F3-CB	270.0	-1.82/-3.07/-2.67	2.33/1.88/1.92
19	O-C	0.0	-3.49/-2.50/-4.89	1.84/1.81/1.71
20	O-C	90.0	-6.65/-6.40/-9.51	1.76/1.74/1.66
21	O-C	180.0	-8.85/-9.79/-13.61	1.74/1.70/1.63
22	O-C	270.0	-6.98/-6.78/-10.07	1.75/1.73/1.66
23	OXT-C	0.0	-7.07/-7.61/-10.50	1.81/1.75/1.67
24	OXT-C	90.0	-7.39/-8.19/-11.59	1.81/1.74/1.66
25	OXT-C	180.0	-8.22/-9.32/-13.07	1.79/1.72/1.65
26	OXT-C	270.0	-7.64/-8.64/-11.88	1.80/1.73/1.66

1.95 Small molecule A of N-formylmethionine(FME)

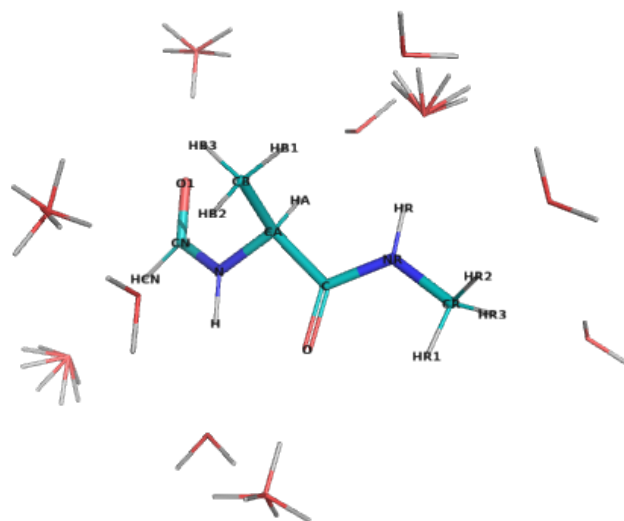


Figure S88: The molecule used for water complex calculations corresponding to (2S)-2-formamido-N-methylpropanamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S296: Statistics of calculated water interaction and dipole moment for (2S)-2-formamido-N-methylpropanamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.37/0.70	0.14/0.28	1.563	3.31/3.35	5.58
Optimal	0.27/0.65	0.13/0.29	1.453	3.31/3.54	0.67

Table S297: The comparison list of optimized atomic charges and their initial guess for (2S)-2-formamido-N-methylpropanamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CN	0.265	0.324	5.356
HCN	0.070	0.080	1.187
O1	-0.469	-0.498	0.000
N	-0.298	-0.395	10.787
H	0.286	0.340	5.664
CA	0.056	0.062	9.615
HA	0.090	0.090	0.000
CB	-0.270	-0.269	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
HB3	0.090	0.090	0.000
C	0.510	0.509	0.000
O	-0.510	-0.513	0.000
NR	-0.470	-0.474	0.000
HR	0.310	0.312	0.000
CR	-0.110	-0.108	0.000
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S298: Interaction energies and geometries between probe water and selected (2S)-2-formamido-N-methylpropanamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HCN-CN	0.0	-2.11/-1.97/-2.40	2.48/2.31/2.29
2	HCN-CN	45.0	-2.09/-1.96/-2.40	2.48/2.31/2.29
3	HCN-CN	90.0	-2.08/-1.95/-2.39	2.47/2.31/2.29
4	HCN-CN	135.0	-2.10/-1.96/-2.40	2.47/2.31/2.29
5	O1-CN	0.0	-6.80/-6.94/-7.23	1.82/1.76/1.75
6	O1-CN	90.0	-6.28/-6.49/-6.84	1.83/1.77/1.75
7	O1-CN	180.0	-5.51/-5.62/-6.04	1.84/1.77/1.76
8	O1-CN	270.0	-6.23/-6.31/-6.66	1.83/1.77/1.76
9	N-CN	0.0	-0.01/-0.11/-0.19	3.59/3.39/3.34
10	N-CN	90.0	-0.22/-0.46/-0.61	3.44/3.26/3.21
11	N-CN	180.0	-0.43/-1.08/-1.13	3.40/3.15/3.13
12	N-CN	270.0	-0.16/-0.47/-0.45	3.43/3.28/3.27
13	H-N	0.0	-1.19/-1.19/-1.72	2.15/2.43/2.37
14	HA-CA	0.0	-1.39/-1.56/-1.37	2.49/2.62/2.63
15	HB1-CB	0.0	-1.40/-1.92/-1.86	2.89/2.70/2.70
16	HB2-CB	0.0	-1.06/-1.06/-0.98	2.62/2.64/2.65
17	O-C	0.0	-4.82/-4.86/-4.75	1.86/1.78/1.78
18	O-C	90.0	-5.38/-5.49/-5.48	1.83/1.77/1.76
19	O-C	180.0	-5.47/-6.01/-6.13	1.83/1.76/1.75
20	O-C	270.0	-5.59/-5.85/-5.92	1.83/1.76/1.76
21	HR-NR	0.0	-7.55/-8.01/-7.98	1.89/1.87/1.87
22	HR-NR	45.0	-7.53/-7.90/-7.85	1.88/1.87/1.87
23	HR-NR	90.0	-7.66/-7.87/-7.82	1.87/1.87/1.87
24	HR-NR	135.0	-7.67/-7.97/-7.93	1.88/1.87/1.87
25	HR2-CR	0.0	-1.64/-1.60/-1.58	2.68/2.66/2.66
26	HR3-CR	0.0	-1.51/-1.51/-1.49	2.69/2.66/2.66

1.96 Small molecule used for 2-fluoro-phenylalanine(FPH2)

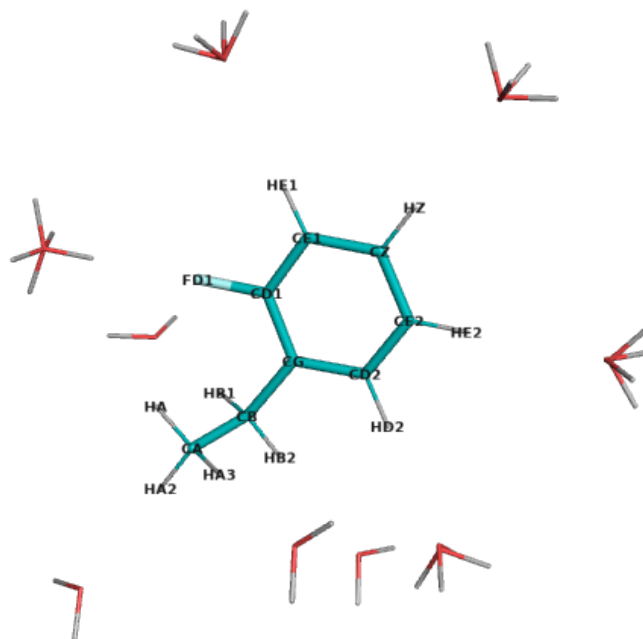


Figure S89: The molecule used for water complex calculations corresponding to 1-ethyl-2-fluorobenzene, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S299: Statistics of calculated water interaction and dipole moment for 1-ethyl-2-fluorobenzene.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.50/0.87	0.16/0.27	1.950	1.55/2.03	6.96
Optimal	0.17/0.40	0.12/0.21	1.572	1.55/1.99	1.66

Table S300: The comparison list of optimized atomic charges and their initial guess for 1-ethyl-2-fluorobenzene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.474
HA	0.090	0.090	0.000
CB	-0.180	-0.194	0.986
HB1	0.090	0.090	0.075
HB2	0.090	0.090	0.075
CG	0.129	0.223	1.211
CD1	-0.031	0.053	1.265
FD1	-0.138	-0.223	0.452
CD2	-0.115	-0.166	0.000
HD2	0.115	0.115	0.000
CE1	-0.109	-0.130	0.499
HE1	0.149	0.180	0.000
CE2	-0.115	-0.095	0.000
HE2	0.115	0.115	0.000
CZ	-0.115	-0.173	0.000
HZ	0.115	0.115	0.000

Table S301: Interaction energies and geometries between probe water and selected 1-ethyl-2-fluorobenzene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.62/-0.59/-0.77		2.81/2.75/2.73	
2	HA2-CA	0.0	-0.69/-0.52/-0.57		2.85/2.78/2.77	
3	HB1-CB	0.0	-0.39/-0.17/-0.20		2.78/2.77/2.76	
4	HB2-CB	0.0	-1.42/-1.30/-1.44		2.70/2.71/2.69	
5	FD1-CD1	0.0	-2.24/-2.35/-3.11		2.18/1.98/1.91	
6	FD1-CD1	90.0	-2.33/-2.37/-3.16		2.18/1.98/1.91	
7	FD1-CD1	180.0	-2.35/-2.36/-3.16		2.18/1.98/1.91	
8	FD1-CD1	270.0	-2.36/-2.40/-3.19		2.17/1.97/1.91	
9	HD2-CD2	0.0	-1.59/-1.59/-1.61		2.62/2.66/2.66	
10	HD2-CD2	90.0	-1.86/-1.66/-1.68		2.54/2.65/2.65	
11	HE1-CE1	0.0	-1.53/-1.52/-1.91		2.52/2.45/2.41	
12	HE1-CE1	90.0	-1.53/-1.48/-1.83		2.51/2.45/2.42	
13	HE2-CE2	0.0	-1.41/-1.29/-1.21		2.64/2.69/2.70	
14	HE2-CE2	90.0	-1.60/-1.35/-1.27		2.58/2.68/2.69	
15	HZ-CZ	0.0	-1.53/-1.24/-1.01		2.61/2.69/2.73	
16	HZ-CZ	90.0	-1.71/-1.30/-1.08		2.55/2.68/2.71	

1.97 Small molecule used for 6-fluoro-l-tryptophan(FT6)

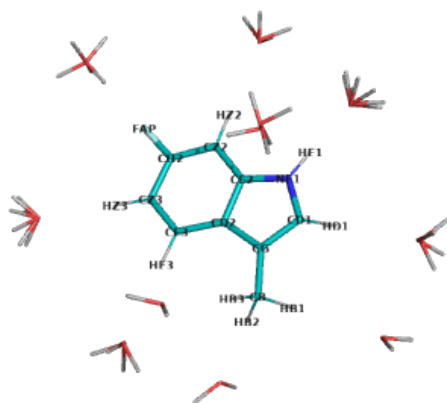


Figure S90: The molecule used for water complex calculations corresponding to 6-fluoro-3-methyl-1H-indole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S302: Statistics of calculated water interaction and dipole moment for 6-fluoro-3-methyl-1H-indole.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.21/2.31	0.16/0.38	3.473	3.16/1.59	17.76
Optimal	0.12/0.26	0.12/0.21	2.158	3.16/3.89	0.92

Table S303: The comparison list of optimized atomic charges and their initial guess for 6-fluoro-3-methyl-o-3-methyl-1H-indole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.278	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.003	-0.038	0.000
CD1	-0.091	-0.163	0.000
HD1	0.135	0.220	0.000
CD2	0.145	0.140	0.825
NE1	-0.360	-0.490	0.696
HE1	0.318	0.363	0.000
CE2	0.163	0.089	1.521
CE3	-0.383	-0.337	0.685
HE3	0.225	0.201	0.000
CZ2	-0.187	-0.196	1.812
HZ2	0.146	0.156	0.000
CZ3	-0.290	-0.195	1.076
HZ3	0.218	0.261	0.658
CH2	0.146	0.207	1.850
FAP	-0.182	-0.210	0.075

Table S304: Interaction energies and geometries between probe water and selected 6-fluoro-3-methyl-1H-indole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.77/-0.86/-0.42		2.80/2.72/2.79	
2	HB1-CB	0.0	-1.17/-1.07/-0.78		2.76/2.74/2.79	
3	HB2-CB	0.0	-0.79/-0.82/-0.47		2.78/2.72/2.78	
4	HD1-CD1	0.0	-2.14/-2.40/-2.86		2.51/2.31/2.25	
5	HD1-CD1	90.0	-2.47/-2.54/-3.00		2.44/2.30/2.24	
6	NE1-CD1	0.0	-1.12/-1.12/-2.93		2.44/2.33/2.16	
7	NE1-CD1	90.0	-2.41/-2.68/-4.73		2.30/2.20/2.08	
8	NE1-CD1	180.0	-1.54/-1.47/-3.85		2.33/2.24/2.09	
9	NE1-CD1	270.0	-0.37/-0.21/-2.15		2.56/2.39/2.19	
10	HE1-NE1	0.0	-6.42/-6.68/-5.86		1.87/1.87/1.87	
11	HE1-NE1	45.0	-6.74/-6.77/-5.98		1.85/1.86/1.87	
12	HE1-NE1	90.0	-7.05/-6.85/-6.10		1.83/1.86/1.86	
13	HE1-NE1	135.0	-6.73/-6.77/-5.98		1.85/1.86/1.87	
14	HE3-CE3	0.0	-1.49/-1.43/-1.62		2.59/2.64/2.64	
15	HE3-CE3	90.0	-1.68/-1.53/-1.72		2.54/2.63/2.63	
16	HZ2-CZ2	0.0	-1.64/-1.74/-1.61		2.55/2.46/2.46	
17	HZ2-CZ2	90.0	-1.91/-1.86/-1.71		2.49/2.45/2.45	
18	HZ3-CZ3	0.0	-1.29/-1.23/-3.28		2.38/2.44/2.34	
19	HZ3-CZ3	45.0	-1.28/-1.22/-3.26		2.38/2.44/2.34	
20	HZ3-CZ3	90.0	-1.28/-1.21/-3.23		2.37/2.44/2.34	
21	HZ3-CZ3	135.0	-1.28/-1.22/-3.26		2.37/2.44/2.34	
22	FAP-CH2	0.0	-2.46/-2.49/-2.56		2.17/1.96/1.94	
23	FAP-CH2	90.0	-2.61/-2.68/-2.52		2.17/1.95/1.95	
24	FAP-CH2	180.0	-2.61/-2.75/-2.32		2.17/1.95/1.96	
25	FAP-CH2	270.0	-2.61/-2.68/-2.52		2.17/1.95/1.95	

1.98 Small molecule used for 5-fluoro-tryptophan(FTR)

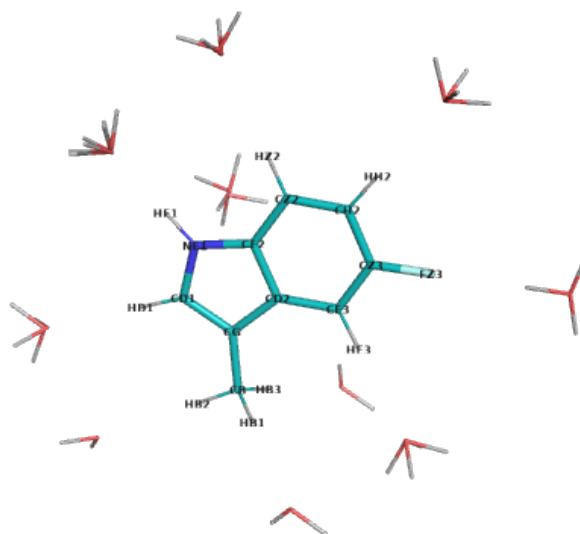


Figure S91: The molecule used for water complex calculations corresponding to 5-fluoro-3-methyl-1H-indole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S305: Statistics of calculated water interaction and dipole moment for 5-fluoro-3-methyl-1H-indole.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	1.11/2.30	0.15/0.34	3.697	3.99/2.89	26.27
Optimal	0.18/0.36	0.11/0.22	2.546	3.99/4.95	0.50

Table S306: The comparison list of optimized atomic charges and their initial guess for 5-fluoro-*o*-3-methyl-1H-indole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.278	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.000	-0.038	0.806
CD1	-0.055	-0.163	0.000
HD1	0.137	0.220	0.000
CD2	-0.004	-0.008	1.556
NE1	-0.424	-0.518	0.000
HE1	0.323	0.363	0.000
CE2	0.320	0.269	0.825
CE3	-0.263	-0.194	1.808
HE3	0.191	0.182	0.478
CZ2	-0.287	-0.363	0.685
HZ2	0.183	0.195	0.000
CZ3	0.063	0.166	1.795
FZ3	-0.183	-0.210	0.075
CH2	-0.192	-0.154	1.076
HH2	0.191	0.261	0.658

Table S307: Interaction energies and geometries between probe water and selected 5-fluoro-3-methyl-1H-indole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.79/-0.74/-0.42		2.76/2.72/2.77	
2	HB1-CB	0.0	-0.79/-0.74/-0.42		2.76/2.72/2.77	
3	HB2-CB	0.0	-1.17/-1.08/-0.68		2.76/2.74/2.80	
4	HD1-CD1	0.0	-2.23/-2.58/-2.77		2.50/2.30/2.25	
5	HD1-CD1	90.0	-2.56/-2.72/-2.91		2.43/2.29/2.25	
6	NE1-CD1	0.0	-1.03/-0.90/-2.55		2.43/2.33/2.17	
7	NE1-CD1	90.0	-2.54/-2.71/-4.61		2.29/2.20/2.09	
8	NE1-CD1	180.0	-1.62/-1.57/-3.92		2.33/2.24/2.10	
9	NE1-CD1	270.0	-0.35/-0.13/-2.00		2.54/2.38/2.20	
10	HE1-NE1	0.0	-6.32/-6.59/-5.78		1.88/1.87/1.87	
11	HE1-NE1	45.0	-6.65/-6.72/-5.93		1.86/1.87/1.87	
12	HE1-NE1	90.0	-6.99/-6.84/-6.08		1.84/1.86/1.87	
13	HE1-NE1	135.0	-6.65/-6.72/-5.93		1.86/1.87/1.87	
14	HE3-CE3	0.0	-1.34/-1.21/-1.70		2.52/2.45/2.42	
15	HE3-CE3	90.0	-1.34/-1.19/-1.64		2.51/2.46/2.43	
16	HZ2-CZ2	0.0	-1.75/-2.05/-1.85		2.63/2.63/2.65	
17	HZ2-CZ2	90.0	-2.22/-2.27/-2.08		2.52/2.61/2.62	
18	FZ3-CZ3	0.0	-2.71/-3.04/-2.73		2.16/1.94/1.94	
19	FZ3-CZ3	180.0	-2.68/-2.91/-2.31		2.16/1.94/1.95	
20	HH2-CH2	0.0	-1.45/-1.44/-3.47		2.35/2.43/2.33	
21	HH2-CH2	90.0	-1.45/-1.40/-3.43		2.35/2.44/2.33	

1.99 Small molecule used for (2-furyl)-alanine(FUA2)

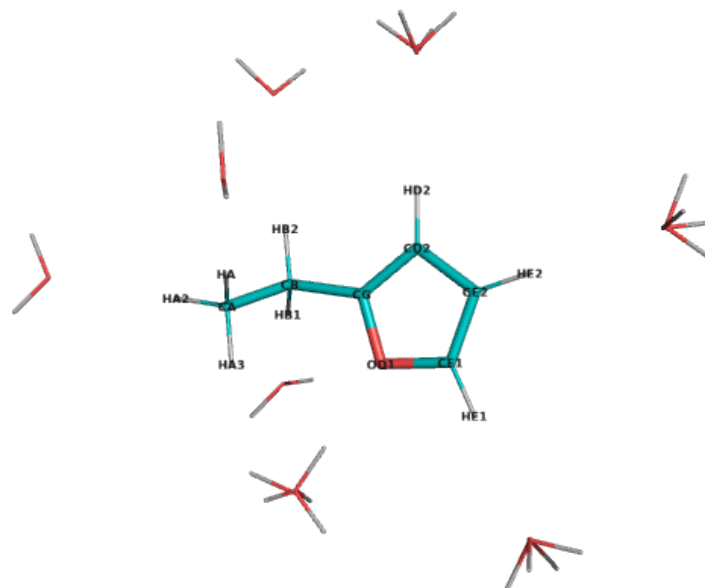


Figure S92: The molecule used for water complex calculations corresponding to 2-ethylfuran, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S308: Statistics of calculated water interaction and dipole moment for 2-ethylfuran.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.51/1.10	0.10/0.17	2.029	0.66/1.14	6.25
Optimal	0.09/0.17	0.08/0.16	1.360	0.66/0.86	4.85

Table S309: The comparison list of optimized atomic charges and their initial guess for 2-ethylfuran, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.269	19.182
HA	0.090	0.090	0.000
CB	-0.115	-0.090	35.599
HB1	0.090	0.090	2.250
HB2	0.090	0.090	2.250
CG	0.186	0.155	34.610
CD2	-0.287	-0.234	0.000
HD2	0.191	0.168	0.000
OD1	-0.269	-0.341	25.596
CE2	-0.292	-0.245	0.000
HE2	0.204	0.175	0.000
CE1	0.063	0.093	2.500
HE1	0.139	0.138	0.000

Table S310: Interaction energies and geometries between probe water and selected 2-ethylfuran site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA2-CA	0.0	-0.77/-0.72/-0.74	2.84/2.75/2.75
2	HA-CA	0.0	-0.39/-0.32/-0.32	2.87/2.77/2.78
3	HB1-CB	0.0	-0.72/-0.60/-0.53	2.75/2.73/2.74
4	HB2-CB	0.0	-1.24/-1.30/-1.37	2.71/2.70/2.69
5	HD2-CD2	0.0	-1.31/-1.32/-1.30	2.64/2.66/2.68
6	HD2-CD2	90.0	-1.51/-1.41/-1.38	2.57/2.65/2.67
7	OD1-CG	0.0	-3.76/-3.82/-4.76	1.95/1.90/1.85
8	OD1-CG	90.0	-3.94/-3.80/-4.75	1.94/1.89/1.84
9	OD1-CG	180.0	-3.51/-3.67/-4.60	1.99/1.89/1.84
10	OD1-CG	270.0	-4.12/-4.01/-4.98	1.92/1.89/1.84
11	HE2-CE2	0.0	-1.34/-1.36/-1.31	2.61/2.65/2.67
12	HE2-CE2	90.0	-1.50/-1.43/-1.37	2.56/2.65/2.66
13	HE1-CE1	0.0	-1.81/-1.84/-1.90	2.46/2.30/2.30
14	HE1-CE1	90.0	-1.89/-1.85/-1.89	2.44/2.30/2.30

1.100 Small molecule used for 3-fluoro-valine(FVAL)

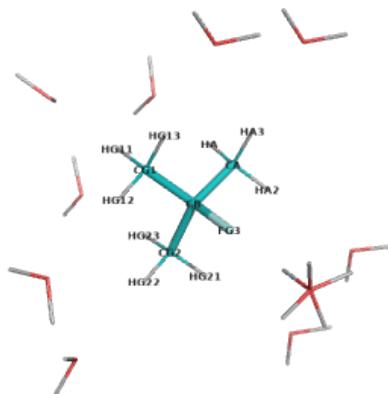


Figure S93: The molecule used for water complex calculations corresponding to 2-fluoro-2-methylpropane, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S311: Statistics of calculated water interaction and dipole moment for 2-fluoro-2-methylpropane.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.16/0.23	0.13/0.23	1.334	2.03/2.27	0.00
Optimal	0.13/0.20	0.14/0.24	0.941	2.03/2.19	0.00

Table S312: The comparison list of optimized atomic charges and their initial guess for 2-fluoro-2-methylpropane, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	3.536
HA2	0.090	0.090	3.536
CA	-0.270	-0.210	8.660
HA	0.090	0.090	3.536
CB	0.265	0.040	10.607
FG3	-0.265	-0.220	0.000
CG1	-0.270	-0.210	8.660
HG11	0.090	0.090	3.536
HG12	0.090	0.090	3.536
HG13	0.090	0.090	3.536
CG2	-0.270	-0.210	8.660
HG21	0.090	0.090	3.536
HG22	0.090	0.090	3.536
HG23	0.090	0.090	3.536

Table S313: Interaction energies and geometries between probe water and selected 2-fluoro-2-methylpropane site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.78/-0.60/-0.56		2.77/2.74/2.74	
2	HA2-CA	0.0	-0.78/-0.60/-0.56		2.77/2.74/2.74	
3	HA-CA	0.0	-1.32/-1.28/-1.24		2.71/2.69/2.70	
4	FG3-CB	0.0	-3.68/-3.72/-3.62		2.07/1.83/1.84	
5	FG3-CB	90.0	-3.68/-3.72/-3.62		2.07/1.83/1.84	
6	FG3-CB	180.0	-3.68/-3.72/-3.62		2.07/1.83/1.84	
7	FG3-CB	270.0	-3.68/-3.72/-3.62		2.07/1.83/1.84	
8	HG11-CG1	0.0	-1.24/-1.25/-1.22		2.75/2.70/2.70	
9	HG12-CG1	0.0	-0.86/-0.66/-0.63		2.75/2.72/2.73	
10	HG13-CG1	0.0	-0.86/-0.66/-0.63		2.75/2.72/2.73	
11	HG21-CG2	0.0	-0.86/-0.66/-0.63		2.75/2.72/2.73	
12	HG22-CG2	0.0	-0.86/-0.66/-0.63		2.75/2.72/2.73	
13	HG23-CG2	0.0	-1.24/-1.25/-1.22		2.75/2.70/2.70	

1.101 Small molecule A of (2S)-2-amino-6-[[[(1Z)-1-[[[(2R,3R,4S,5R)-5-[[[(R)-[[[(R)-[[[(2R,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]methoxy}(hydroxy)phosphoryl]oxy}(hydroxy)phosphoryl]oxy}methyl)-3,4-dihydroxytetrahydrofuran-2-yl]sulfonyl}ethylidene]amino}hexanoic acid(FZN)

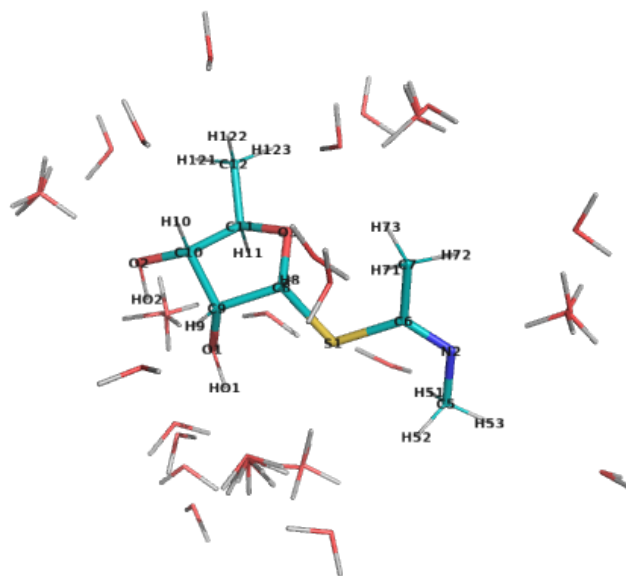


Figure S94: The molecule used for water complex calculations corresponding to (2R,3S,4R,5R)-2-methyl-5-[(1Z)-1-(methylimino)ethyl]sulfanyloxolane-3,4-diol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S314: Statistics of calculated water interaction and dipole moment for (2R,3S,4R,5R)-2-methyl-5-[(1Z)-1-(methylimino)ethyl]sulfanyloxolane-3,4-diol.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.68/1.60	0.40/1.49	3.237	2.20/3.06	24.23
Optimal	0.65/2.07	0.45/1.85	3.079	2.20/2.86	0.07

Table S315: The comparison list of optimized atomic charges and their initial guess for (2R,3S,4R,5R)-2-methyl-5-[(1Z)-1-(methylimino)ethyl]sulfanyloxolane-3,4-diol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
H53	0.090	0.090	0.150
C5	-0.066	-0.052	12.054
H51	0.090	0.090	0.150
H52	0.090	0.090	0.150
N2	-0.668	-0.599	60.280
C6	0.436	0.434	186.398
C7	-0.179	-0.268	63.361
H71	0.090	0.090	2.919
H72	0.090	0.090	2.919
H73	0.090	0.090	2.919
S1	-0.150	-0.115	203.836
C8	0.103	0.171	108.923
H8	0.064	0.090	5.590
O3	-0.348	-0.391	62.418
C9	0.119	0.117	42.299
H9	0.090	0.090	2.500
O1	-0.565	-0.649	2.500
HO1	0.420	0.420	0.000
C10	0.116	0.147	2.500
H10	0.090	0.090	0.000
O2	-0.649	-0.649	0.000
HO2	0.420	0.420	0.000
C11	0.137	0.116	2.500
H11	0.090	0.090	0.000
C12	-0.270	-0.272	0.000
H121	0.090	0.090	0.000
H122	0.090	0.090	0.000
H123	0.090	0.090	0.000

Table S316: Interaction energies and geometries between probe water and selected (2R,3S,4R,5R)-2-methyl-5-[(1Z)-1-(methylimino)ethyl]sulfanyloxolane-3,4-diol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	H51-C5	0.0	-0.54/-0.60/-1.20	2.66/2.72/2.65
2	H52-C5	0.0	-0.05/-0.47/-0.92	3.07/4.92/2.84
3	N2-C5	0.0	-5.83/-5.53/-5.07	1.96/1.95/1.97
4	N2-C5	90.0	-7.35/-6.80/-5.75	1.87/1.92/1.95
5	N2-C5	180.0	-6.84/-7.61/-6.25	1.90/1.91/1.95
6	N2-C5	270.0	-7.52/-7.14/-6.16	1.88/1.92/1.95
7	H71-C7	0.0	-1.97/-2.22/-2.14	2.60/2.62/2.65
8	H72-C7	0.0	-0.35/-0.20/0.04	2.63/2.68/2.74
9	S1-C6	0.0	-0.38/-0.27/-0.60	2.90/2.46/2.46
10	S1-C6	90.0	-1.85/-2.64/-2.23	2.69/2.29/2.33
11	S1-C6	180.0	-1.04/-1.88/-0.86	2.81/2.33/2.40
12	S1-C6	270.0	-0.34/-0.07/0.36	2.83/2.43/2.52
13	H8-C8	0.0	-2.53/-2.96/-3.15	2.93/2.93/2.89
14	O3-C8	0.0	-0.45/-1.29/-1.43	3.04/2.81/2.83
15	O3-C8	90.0	-0.41/-0.55/-0.83	2.97/2.88/2.89
16	O3-C8	180.0	-0.42/-0.23/-0.80	3.29/3.12/2.99
17	O3-C8	270.0	-1.09/-1.46/-1.67	2.91/2.85/2.85
18	H9-C9	0.0	-2.62/-2.93/-2.96	2.50/2.59/2.59
19	O1-C9	180.0	-0.57/-1.12/2.14	2.55/2.06/1.98
20	HO1-O1	0.0	-6.67/-8.40/-7.56	1.78/1.82/1.84
21	HO1-O1	45.0	-6.34/-8.42/-7.59	1.78/1.82/1.84
22	HO1-O1	90.0	-7.51/-8.69/-7.73	1.73/1.81/1.83
23	HO1-O1	135.0	-7.91/-8.69/-7.71	1.72/1.81/1.84
24	H10-C10	0.0	-1.49/-1.29/-1.36	2.64/2.70/2.69
25	O2-C10	0.0	-5.43/-5.82/-5.91	1.85/1.86/1.86
26	O2-C10	90.0	-5.40/-5.74/-5.73	1.84/1.86/1.86
27	O2-C10	180.0	-4.89/-5.64/-5.62	1.87/1.86/1.86
28	O2-C10	270.0	-5.36/-5.87/-5.95	1.84/1.86/1.86
29	HO2-O2	0.0	-0.23/-0.56/-0.14	4.76/4.23/5.00
30	HO2-O2	45.0	-0.15/-0.46/-0.09	5.95/4.54/5.00
31	HO2-O2	90.0	-0.26/-0.61/-0.19	3.84/4.15/5.00
32	HO2-O2	135.0	-0.65/-0.75/-0.23	3.51/3.96/5.00
33	H11-C11	0.0	-0.45/-0.83/-0.33	2.69/2.72/2.76
34	H121-C12	0.0	-0.49/-0.04/0.08	2.63/2.71/2.72
35	H122-C12	0.0	-0.68/-0.60/-0.46	2.84/2.78/2.81
36	H123-C12	0.0	-0.84/-0.71/-0.46	2.74/2.74/2.76

1.102 Small molecule B of (2S)-2-amino-6-{{[(1Z)-1-{{[(2R,3R,4S,5R)-5-{{[(R)-{{[(R)-{{[(2R,3S,4R,5R)-5-(6-amino-9H-purin-9-yl)-3,4-dihydroxytetrahydrofuran-2-yl]methoxy}(hydroxy)phosphoryl]oxy}(hydroxy)phosphoryl]oxy}methyl)-3,4-dihydroxytetrahydrofuran-2-yl]sulfonyl}ethylidene]amino}hexanoicacid(FZN)

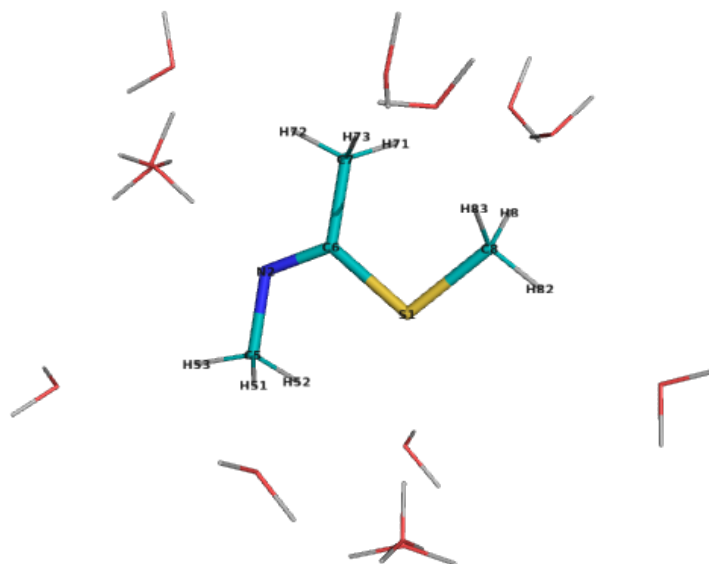


Figure S95: The molecule used for water complex calculations corresponding to (Z)-methyl[1-(methylsulfonyl)ethylidene]amine, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S317: Statistics of calculated water interaction and dipole moment for (Z)-methyl[1-(methylsulfonyl)ethylidene]amine.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.77/1.58	0.24/0.50	2.485	2.61/2.43	16.26
Optimal	0.43/0.71	0.24/0.51	2.935	2.61/3.38	0.00

Table S318: The comparison list of optimized atomic charges and their initial guess for (Z)-methyl[1-(methylsulfanyl)ethylidene]amine, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
C5	-0.066	-0.052	12.054
H51	0.090	0.090	0.150
H52	0.090	0.090	0.150
H53	0.090	0.090	0.150
N2	-0.668	-0.599	60.280
C6	0.436	0.440	186.976
C7	-0.179	-0.268	63.361
H71	0.090	0.090	2.919
H72	0.090	0.090	2.919
H73	0.090	0.090	2.919
S1	-0.150	-0.128	181.376
C8	-0.183	-0.203	20.062
H8	0.090	0.090	1.250
H82	0.090	0.090	1.250
H83	0.090	0.090	1.250

Table S319: Interaction energies and geometries between probe water and selected (Z)-methyl[1-(methylsulfanyl)ethylidene]amine site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	H51-C5	0.0	-0.03/-0.33/-0.76	2.87/2.75/2.69
2	H52-C5	0.0	-0.03/-0.33/-0.76	2.87/2.75/2.69
3	N2-C5	0.0	-5.83/-5.44/-5.09	1.96/1.95/1.97
4	N2-C5	90.0	-7.67/-7.05/-6.08	1.87/1.92/1.95
5	N2-C5	180.0	-7.14/-7.81/-6.45	1.90/1.91/1.94
6	N2-C5	270.0	-7.67/-7.05/-6.08	1.87/1.92/1.95
7	H71-C7	0.0	-2.16/-2.29/-1.70	2.63/2.61/2.66
8	H72-C7	0.0	-0.44/-0.27/0.07	2.60/2.67/2.74
9	H73-C7	0.0	-2.16/-2.29/-1.70	2.63/2.61/2.66
10	S1-C6	0.0	-1.07/-1.71/-1.67	2.91/2.40/2.40
11	S1-C6	90.0	-1.37/-1.75/-1.51	2.83/2.40/2.42
12	S1-C6	180.0	-1.15/-1.53/-1.03	2.92/2.43/2.47
13	S1-C6	270.0	-1.37/-1.75/-1.51	2.83/2.40/2.42
14	H8-C8	0.0	-2.47/-2.33/-1.92	2.54/2.62/2.64
15	H82-C8	0.0	-1.93/-1.22/-1.09	2.52/2.67/2.69
16	H83-C8	0.0	-2.47/-2.33/-1.92	2.54/2.62/2.64

1.103 Small molecule used for Canavanine(GGB)

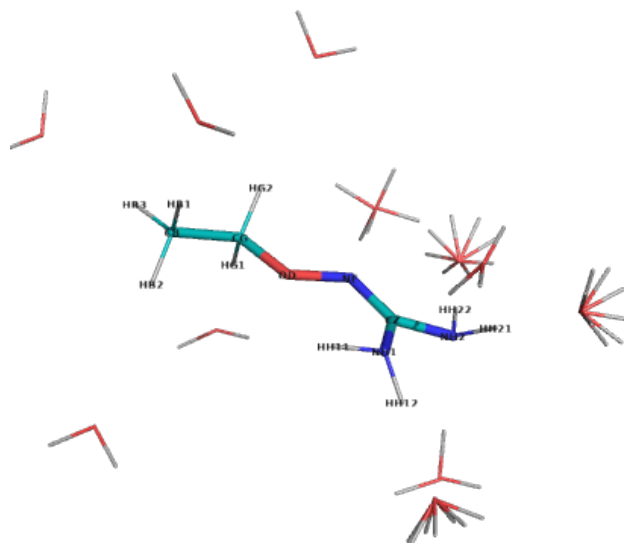


Figure S96: The molecule used for water complex calculations corresponding to N''-ethoxyguanidine, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S320: Statistics of calculated water interaction and dipole moment for N''-ethoxyguanidine.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	1.15/3.27	0.13/0.19	3.917	1.34/2.37	15.19
Optimal	0.36/1.02	0.10/0.15	2.016	1.34/1.71	1.01

Table S321: The comparison list of optimized atomic charges and their initial guess for N''-ethoxyguanidine, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.270	2.250
HB2	0.090	0.090	0.000
HB1	0.090	0.090	0.000
CG	0.040	0.112	29.909
HG1	0.090	0.090	2.250
HG2	0.090	0.090	2.250
OD	-0.218	-0.398	271.857
NE	-0.572	-0.555	269.601
CZ	0.704	0.699	26.922
NH2	-0.841	-0.599	17.431
HH21	0.387	0.290	0.000
HH22	0.387	0.290	0.000
NH1	-0.841	-0.599	17.431
HH12	0.387	0.290	0.000
HH11	0.387	0.290	0.000

Table S322: Interaction energies and geometries between probe water and selected N''-ethoxyguanidine site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial		
1	HB3-CB	0.0	-0.75/-0.71/-0.68	2.82/2.74/2.74		
2	HB2-CB	0.0	-0.27/-0.13/0.24	2.94/2.86/2.96		
3	HB1-CB	0.0	-0.31/-0.07/0.31	2.85/2.80/2.87		
4	NE-OD	0.0	-4.78/-4.50/-4.53	1.98/1.96/1.96		
5	NE-OD	90.0	-7.09/-6.54/-6.43	1.87/1.91/1.91		
6	NE-OD	180.0	-6.54/-7.00/-6.97	1.93/1.90/1.91		
7	NE-OD	270.0	-7.09/-6.60/-6.59	1.87/1.90/1.91		
8	NH2-CZ	0.0	-4.92/-3.90/-1.65	1.96/1.96/2.08		
9	NH2-CZ	180.0	-3.96/-3.38/-1.38	2.00/1.97/2.11		
10	HH21-NH2	0.0	-4.91/-5.05/-4.73	1.92/2.04/2.07		
11	HH21-NH2	45.0	-4.61/-4.86/-4.57	1.94/2.05/2.08		
12	HH21-NH2	90.0	-4.46/-4.80/-4.55	1.94/2.05/2.08		
13	HH21-NH2	135.0	-4.76/-4.98/-4.71	1.93/2.05/2.08		
14	HH22-NH2	0.0	-4.16/-3.98/-3.39	1.89/2.05/2.08		
15	HH22-NH2	45.0	-3.79/-3.80/-3.20	1.91/2.06/2.09		
16	HH22-NH2	90.0	-3.27/-3.55/-2.96	1.95/2.06/2.10		
17	HH22-NH2	135.0	-3.61/-3.73/-3.14	1.93/2.06/2.09		
18	NH1-CZ	0.0	-4.37/-3.82/-2.04	2.00/1.97/2.09		
19	NH1-CZ	180.0	-3.73/-3.65/-1.71	2.03/1.98/2.11		
20	HH12-NH1	0.0	-4.87/-4.66/-4.24	1.91/2.05/2.09		
21	HH12-NH1	45.0	-4.47/-4.45/-4.10	1.93/2.06/2.10		
22	HH12-NH1	90.0	-4.27/-4.40/-4.11	1.94/2.06/2.10		
23	HH12-NH1	135.0	-4.65/-4.60/-4.25	1.92/2.06/2.09		

1.104 Small molecule used for
 (2s,4s)-2,5-diamino-4-hydroxy-5-oxopentanoicacid(GHG)

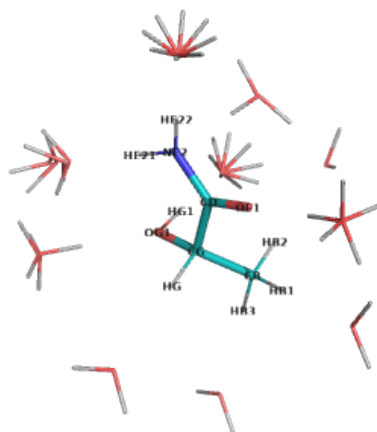


Figure S97: The molecule used for water complex calculations corresponding to (2S)-2-hydroxypropanamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S323: Statistics of calculated water interaction and dipole moment for (2S)-2-hydroxypropanamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.61/1.43	0.13/0.44	1.704	2.84/2.44	7.70
Optimal	0.45/0.85	0.11/0.40	1.670	2.84/3.28	1.36

Table S324: The comparison list of optimized atomic charges and their initial guess for (2S)-2-hydroxypropanamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.268	0.050
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.202	0.165	22.240
HG	0.090	0.090	0.050
OG1	-0.591	-0.623	22.694
HG1	0.396	0.369	1.783
CD	0.385	0.540	12.508
OE1	-0.513	-0.534	1.525
NE2	-0.663	-0.629	18.343
HE21	0.347	0.310	0.262
HE22	0.347	0.310	0.262

Table S325: Interaction energies and geometries between probe water and selected (2S)-2-hydroxypropanamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.11/-1.01/-0.88		2.70/2.69/2.70	
2	HB2-CB	0.0	-1.94/-1.73/-1.75		2.58/2.63/2.63	
3	HG-CG	0.0	-1.35/-1.01/-1.10		2.55/2.67/2.67	
4	OG1-CG	0.0	-4.32/-3.60/-4.46		1.87/1.90/1.88	
5	OG1-CG	90.0	-4.89/-4.43/-5.18		1.85/1.89/1.86	
6	OG1-CG	180.0	-4.28/-4.05/-4.57		1.88/1.90/1.88	
7	OG1-CG	270.0	-3.70/-3.04/-3.72		1.89/1.92/1.90	
8	HG1-OG1	0.0	-7.02/-7.56/-6.28		1.81/1.83/1.87	
9	HG1-OG1	45.0	-7.06/-7.38/-6.17		1.80/1.83/1.87	
10	HG1-OG1	90.0	-7.60/-7.58/-6.35		1.79/1.83/1.86	
11	HG1-OG1	135.0	-7.58/-7.77/-6.46		1.80/1.82/1.86	
12	OE1-CD	0.0	-6.00/-6.55/-6.16		1.84/1.76/1.76	
13	OE1-CD	90.0	-6.12/-6.68/-6.29		1.84/1.75/1.76	
14	OE1-CD	180.0	-6.16/-6.72/-6.33		1.83/1.75/1.76	
15	OE1-CD	270.0	-6.18/-6.74/-6.34		1.83/1.75/1.76	
16	NE2-CD	0.0	-2.62/-1.79/-1.42		2.09/2.10/2.13	
17	NE2-CD	180.0	-2.39/-2.54/-1.60		2.14/2.06/2.12	
18	HE21-NE2	0.0	-3.04/-2.20/-1.61		2.10/2.50/2.54	
19	HE21-NE2	45.0	-1.49/-1.75/-1.11		2.49/2.59/2.65	
20	HE21-NE2	90.0	-0.79/-1.39/-0.80		2.69/2.66/2.73	
21	HE21-NE2	135.0	-1.87/-1.78/-1.23		2.27/2.57/2.61	
22	HE22-NE2	0.0	-5.19/-5.32/-4.95		1.87/1.87/1.89	
23	HE22-NE2	45.0	-4.98/-5.18/-4.82		1.88/1.87/1.89	
24	HE22-NE2	90.0	-4.73/-4.99/-4.64		1.88/1.88/1.90	
25	HE22-NE2	135.0	-4.92/-5.12/-4.76		1.88/1.87/1.90	

1.105 Small molecule A of [(4Z)-2-(1-amino-2-hydroxyethyl)-4-(4-hydroxybenzylidene)-5-oxo-4,5-dihydro-1h-imidazol-1-yl]aceticacid(GYS)

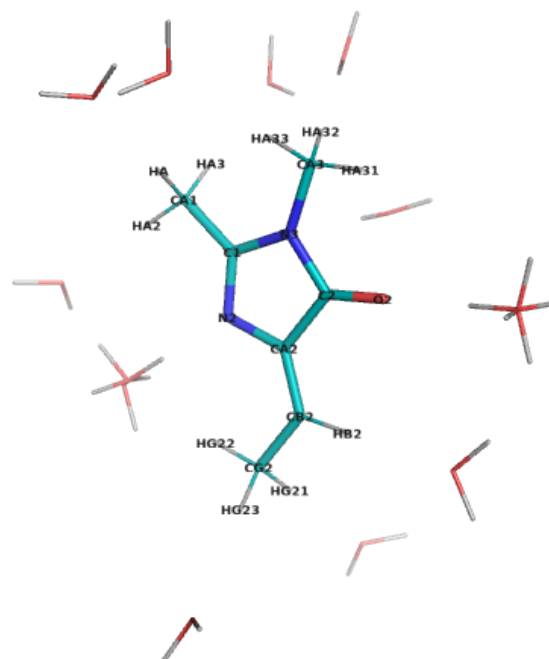


Figure S98: The molecule used for water complex calculations corresponding to (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S326: Statistics of calculated water interaction and dipole moment for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.92/1.64	0.10/0.25	6.526	3.17/0.45	27.81
Optimal	0.49/1.31	0.09/0.22	3.053	3.17/3.55	14.34

Table S327: The comparison list of optimized atomic charges and their initial guess for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA1	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
HA2	0.090	0.090	0.000
HA3	0.090	0.090	0.000
C1	0.233	0.074	23.781
N2	-0.679	-0.703	41.871
N3	-0.080	-0.079	15.706
C2	0.407	0.509	24.002
O2	-0.489	-0.482	6.710
CA2	0.288	0.516	47.153
CB2	-0.105	-0.135	25.469
HB2	0.150	0.150	3.270
CG2	-0.270	-0.274	15.277
HG21	0.090	0.090	1.175
HG22	0.090	0.090	1.175
HG23	0.090	0.090	1.175
CA3	-0.195	-0.271	3.821
HA31	0.090	0.090	0.000
HA32	0.090	0.090	0.000
HA33	0.090	0.090	0.000

Table S328: Interaction energies and geometries between probe water and selected (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA-CA1	0.0	-2.17/-2.61/-1.51		2.59/2.58/2.65	
2	HA2-CA1	0.0	-0.97/-0.86/0.05		2.58/2.64/2.77	
3	HA3-CA1	0.0	-2.55/-2.73/-1.57		2.52/2.57/2.64	
4	N2-C1	0.0	-4.99/-6.30/-5.60		2.09/2.01/2.02	
5	N2-C1	90.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
6	N2-C1	180.0	-5.35/-5.42/-6.38		1.95/2.01/1.99	
7	N2-C1	270.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
8	N3-C1	0.0	-0.26/-0.82/-0.78		2.74/2.52/2.49	
9	O2-C2	0.0	-5.51/-5.57/-5.00		1.85/1.78/1.80	
10	O2-C2	90.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
11	O2-C2	180.0	-5.92/-5.61/-4.27		1.84/1.78/1.81	
12	O2-C2	270.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
13	HB2-CB2	0.0	-1.40/-1.60/-2.82		2.32/2.47/2.44	
14	HG21-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
15	HG23-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
16	HA32-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	
17	HA33-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	

1.106 Small molecule B of [(4Z)-2-(1-amino-2-hydroxyethyl)-4-(4-hydroxybenzylidene)-5-oxo-4,5-dihydro-1h-imidazol-1-yl]acetic acid(GYS)

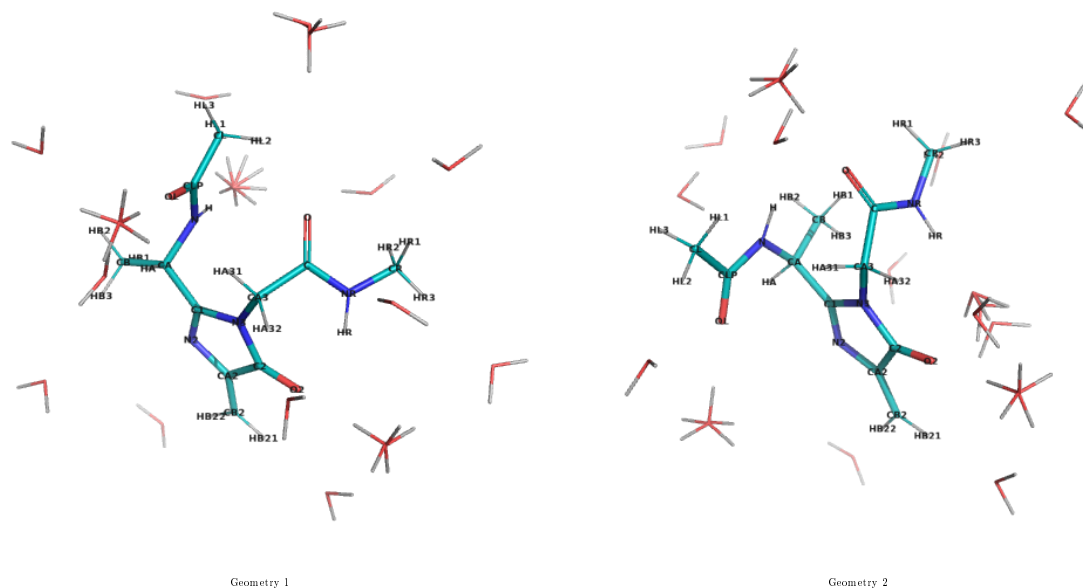


Table S329: The molecule used for water complex calculations corresponding to N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S330: Statistics of calculated water interaction and dipole moment for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide.

		RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
		Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Geometry 1	Initial	0.86 / 2.05	0.07 / 0.17	6.601	1.19 / 4.07	1.19
Geometry 2	Initial	1.02 / 2.07	0.09 / 0.23	6.126	6.37 / 4.43	6.37
Sum of geometries	Initial	0.95 / 2.07	0.08 / 0.23	12.727	-	-
Geometry 1	Optimal	0.36 / 0.81	0.07 / 0.16	2.460	1.19 / 1.37	1.19
Geometry 2	Optimal	0.51 / 0.91	0.08 / 0.19	2.701	6.37 / 7.25	6.37
Sum of geometries	Optimal	0.45 / 0.91	0.08 / 0.19	5.161	-	-

Table S331: The comparison list of optimized atomic charges and their initial guess for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
C1	0.233	0.164	24.002
N2	-0.679	-0.703	41.104
N3	-0.031	-0.499	22.994
C2	0.407	0.613	23.378
O2	-0.489	-0.482	6.517
CA2	0.466	0.512	42.773
CB2	-0.593	-0.444	13.655
HB21	0.230	0.230	0.950
HB22	0.230	0.230	0.950
CA3	-0.154	0.043	13.461
HA31	0.090	0.090	0.177
HA32	0.090	0.090	0.177
C	0.510	0.499	10.097
O	-0.510	-0.517	3.479
NR	-0.470	-0.442	6.773
HR	0.310	0.299	0.000
CR	-0.110	-0.108	0.239
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S332: Interaction energies and geometries between probe water and selected N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
Geometry 1				
1	O-C	0.0	-5.45/-5.47/-6.22	1.84/1.77/1.76
2	O-C	90.0	-6.01/-6.48/-6.53	1.83/1.75/1.76
3	O-C	180.0	-5.96/-6.64/-6.64	1.83/1.75/1.75
4	O-C	270.0	-5.67/-5.94/-6.62	1.84/1.76/1.75
5	NR-C	0.0	-1.32/-1.50/-1.08	2.24/2.20/2.22
6	HR2-CR	0.0	-1.10/-1.26/-1.09	2.71/2.66/2.67
7	HR3-CR	0.0	-1.39/-1.22/-1.32	2.66/2.67/2.67
8	N2-C1	0.0	-5.74/-6.45/-6.04	1.95/1.92/1.92
9	N2-C1	90.0	-6.51/-6.37/-7.24	1.90/1.92/1.90
10	N2-C1	180.0	-5.60/-5.66/-7.65	1.96/1.93/1.90
11	N2-C1	270.0	-6.64/-6.59/-7.43	1.90/1.91/1.89
12	O2-C2	0.0	-3.88/-3.93/-3.54	1.88/1.80/1.81
13	O2-C2	90.0	-4.94/-5.15/-4.46	1.84/1.77/1.79
14	O2-C2	180.0	-4.95/-5.20/-4.05	1.84/1.77/1.79
15	O2-C2	270.0	-3.93/-4.12/-3.39	1.87/1.79/1.81
16	HB21-CB2	0.0	-1.84/-1.64/-3.47	2.32/2.48/2.42
17	HB22-CB2	0.0	-1.82/-1.01/-2.42	2.42/2.54/2.46
18	HA31-CA3	0.0	-2.08/-2.47/-1.68	2.70/2.69/2.70
19	HA-CA	0.0	-2.47/-2.76/-1.19	2.49/2.56/2.66
Geometry 2				
20	O-C	0.0	-6.06/-6.90/-7.24	1.86/1.76/1.75
21	O-C	90.0	-5.25/-6.15/-7.32	1.87/1.77/1.75
22	O-C	180.0	-4.71/-5.63/-6.52	1.88/1.77/1.76
23	O-C	270.0	-5.56/-6.46/-6.85	1.86/1.76/1.76
24	HR-NR	0.0	-7.09/-7.67/-7.53	1.93/1.90/1.90
25	HR-NR	45.0	-7.71/-7.90/-7.71	1.91/1.89/1.89
26	HR-NR	90.0	-7.79/-7.84/-7.79	1.90/1.89/1.89
27	HR-NR	135.0	-7.18/-7.62/-7.61	1.92/1.90/1.89
28	HR1-CR	0.0	-0.71/-0.04/0.30	2.50/2.69/2.67
29	HR2-CR	0.0	-1.54/-1.44/-1.38	2.68/2.66/2.66
30	HR3-CR	0.0	-1.84/-1.82/-1.70	2.68/2.67/2.66
31	N2-C1	0.0	-6.46/-6.98/-6.58	1.93/1.91/1.91
32	N2-C1	90.0	-6.88/-6.47/-7.35	1.89/1.91/1.89
33	N2-C1	180.0	-5.73/-5.60/-7.60	1.95/1.93/1.90
34	N2-C1	270.0	-7.31/-7.09/-7.94	1.88/1.91/1.89
35	N3-C1	0.0	-0.22/0.03/-2.15	2.60/2.67/2.17
36	O2-C2	0.0	-4.96/-5.34/-4.95	1.88/1.79/1.80
37	O2-C2	90.0	-5.32/-5.37/-4.66	1.87/1.78/1.80
38	O2-C2	180.0	-5.74/-5.89/-4.71	1.87/1.78/1.81
39	O2-C2	270.0	-5.94/-6.25/-5.51	1.85/1.77/1.79
40	HB21-CB2	0.0	-1.43/-1.20/-3.03	2.33/2.48/2.41
41	HB22-CB2	0.0	-1.29/-0.66/-2.05	2.47/2.56/2.47
42	HA31-CA3	0.0	-3.71/-4.08/-3.49	2.50/2.57/2.57
43	HA-CA	0.0	-2.67/-3.45/-1.93	2.59/2.58/2.69

1.107 Small molecule used for glutaminehydroxamate(HGA)

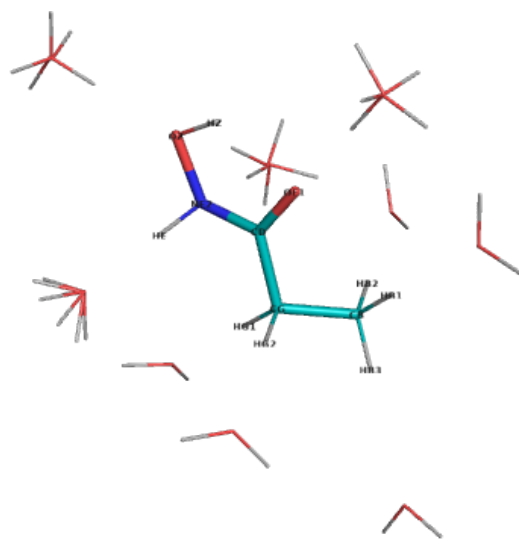


Figure S99: The molecule used for water complex calculations corresponding to N-hydroxypropanamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S333: Statistics of calculated water interaction and dipole moment for N-hydroxypropanamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.10/2.34	0.10/0.21	4.734	3.62/2.64	33.02
Optimal	0.28/0.72	0.05/0.12	2.247	3.62/4.27	5.18

Table S334: The comparison list of optimized atomic charges and their initial guess for N-hydroxypropanamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.262	0.436
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.071	-0.213	25.279
HG2	0.090	0.090	0.000
HG1	0.090	0.090	0.000
CD	0.462	0.489	37.419
OE1	-0.454	-0.508	21.222
NE2	-0.385	-0.426	326.447
HE	0.338	0.343	24.297
OZ	-0.398	-0.293	325.112
HZ	0.328	0.420	19.754

Table S335: Interaction energies and geometries between probe water and selected N-hydroxypropanamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.31/-1.37/-0.70	2.74/2.70/2.77
2	HB1-CB	0.0	-0.48/-0.35/0.45	2.55/2.67/2.76
3	HB2-CB	0.0	-1.28/-1.25/-0.57	2.65/2.65/2.72
4	HG2-CG	0.0	-1.93/-2.13/-1.03	2.55/2.61/2.71
5	HG1-CG	0.0	-2.46/-3.13/-2.06	2.59/2.59/2.67
6	OE1-CD	0.0	-4.83/-4.85/-6.13	1.87/1.80/1.76
7	OE1-CD	90.0	-4.93/-5.11/-5.74	1.87/1.79/1.76
8	OE1-CD	180.0	-4.40/-4.81/-4.48	1.90/1.81/1.80
9	OE1-CD	270.0	-4.70/-4.77/-5.29	1.88/1.80/1.77
10	NE2-CD	0.0	-3.01/-3.00/-2.28	2.13/2.10/2.13
11	NE2-CD	90.0	-3.75/-4.12/-3.18	2.09/2.06/2.09
12	NE2-CD	180.0	-1.93/-1.96/-2.45	2.23/2.16/2.13
13	NE2-CD	270.0	-1.63/-0.91/-1.40	2.20/2.23/2.19
14	HE-NE2	0.0	-6.70/-6.86/-7.03	1.85/1.86/1.85
15	HE-NE2	45.0	-6.92/-6.97/-7.06	1.84/1.85/1.85
16	HE-NE2	90.0	-6.90/-7.01/-7.06	1.84/1.85/1.85
17	HE-NE2	135.0	-6.68/-6.89/-7.02	1.85/1.86/1.85
18	OZ-NE2	0.0	-4.27/-4.17/-1.93	1.93/1.95/2.07
19	OZ-NE2	90.0	-4.57/-4.31/-2.29	1.90/1.93/2.04
20	OZ-NE2	180.0	-3.46/-3.41/-1.72	1.95/1.96/2.06
21	OZ-NE2	270.0	-3.85/-3.53/-1.61	1.92/1.95/2.07

1.108 Small molecule used for 4-methyl-histidine(HICP)

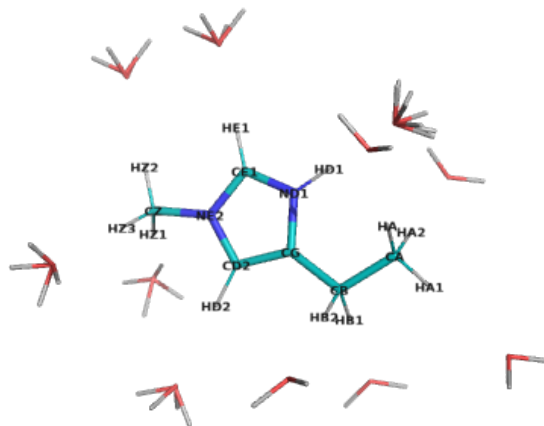


Figure S100: The molecule used for water complex calculations corresponding to 4-ethyl-1-methyl-2,3-dihydro-1H-imidazole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S336: Statistics of calculated water interaction and dipole moment for 4-ethyl-1-methyl-2,3-dihydro-1H-imidazole.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.81/1.55	0.15/0.26	2.506	3.17/3.29	15.71
Optimal	0.41/1.01	0.14/0.24	2.671	3.17/3.95	15.86

Table S337: The comparison list of optimized atomic charges and their initial guess for 4-ethyl-1-methyl-2,3-dihydro-1H-imidazole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.000
HA	0.090	0.090	0.000
CB	0.004	-0.049	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.131	0.191	14.989
ND1	-0.486	-0.511	9.726
HD1	0.407	0.440	0.000
CD2	0.108	0.213	54.233
HD2	0.142	0.116	23.270
CE1	0.337	0.336	48.268
HE1	0.185	0.157	14.504
NE2	-0.486	-0.503	91.228
CZ	0.208	0.160	80.059
HZ1	0.090	0.090	3.537
HZ2	0.090	0.090	3.537
HZ3	0.090	0.090	3.537

Table S338: Interaction energies and geometries between probe water and selected 4-ethyl-1-methyl-2,3-dihydro-1H-imidazole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA1-CA	0.0	-4.88/-3.95/-3.92	2.41/2.60/2.60
2	HA2-CA	0.0	-5.02/-4.78/-5.01	2.56/2.61/2.61
3	HA-CA	0.0	-5.03/-4.78/-5.01	2.56/2.61/2.61
4	HB1-CB	0.0	-5.56/-5.43/-5.54	2.39/2.56/2.56
5	HB2-CB	0.0	-5.56/-5.43/-5.54	2.39/2.56/2.56
6	HD1-ND1	0.0	-12.84/-12.69/-13.80	1.86/1.88/1.84
7	HD1-ND1	45.0	-12.81/-12.85/-13.94	1.87/1.87/1.84
8	HD1-ND1	90.0	-12.82/-13.04/-14.11	1.87/1.87/1.84
9	HD1-ND1	135.0	-12.80/-12.85/-13.94	1.87/1.87/1.84
10	HD2-CD2	0.0	-8.28/-8.17/-8.46	2.18/2.19/2.19
11	HD2-CD2	90.0	-8.90/-8.55/-8.79	2.14/2.18/2.18
12	HE1-CE1	0.0	-11.04/-11.27/-10.43	2.07/1.99/2.01
13	HE1-CE1	90.0	-11.95/-11.70/-10.83	2.03/1.98/2.00
14	HZ1-CZ	0.0	-7.07/-6.62/-6.36	2.27/2.50/2.52
15	HZ1-CZ	90.0	-7.14/-6.66/-6.43	2.27/2.50/2.51
16	HZ2-CZ	0.0	-7.49/-7.43/-6.93	2.35/2.51/2.52
17	HZ2-CZ	90.0	-8.98/-7.98/-7.44	2.24/2.48/2.50
18	HZ3-CZ	0.0	-7.06/-6.61/-6.36	2.27/2.50/2.52
19	HZ3-CZ	90.0	-7.13/-6.65/-6.43	2.27/2.50/2.51

1.109 Small molecule used for ND1-phosphonohistidine(HIP)

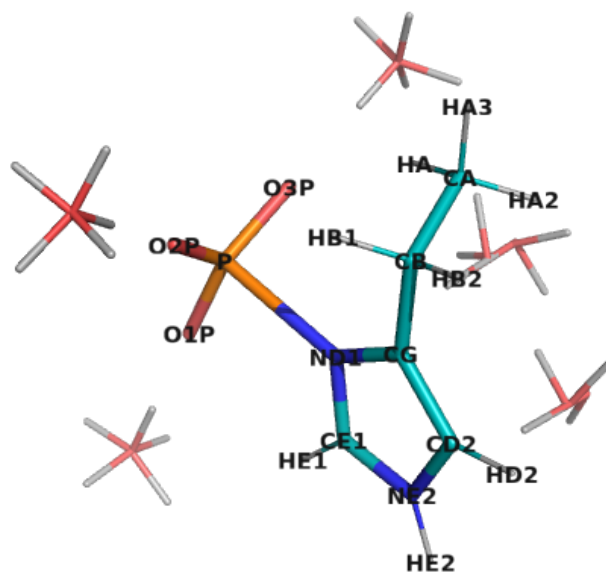


Figure S101: The molecule used for water complex calculations corresponding to (5-ethyl-1H-imidazol-1-yl)phosphonic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S339: Statistics of calculated water interaction and dipole moment for (5-ethyl-1H-imidazol-1-yl)phosphonic acid.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	2.86/5.81	0.16/0.36	9.920	8.02/13.19	7.41
Optimal	0.52/1.37	0.08/0.18	4.666	8.02/8.68	10.59

Table S340: The comparison list of optimized atomic charges and their initial guess for (5-ethyl-1H-imidazol-1-yl)phosphonicacid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.269	0.000
HA	0.090	0.090	0.000
CB	-0.088	-0.088	2.500
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.177	-0.105	71.310
CD2	-0.027	0.217	2.500
HD2	0.130	0.102	0.000
ND1	-0.118	-0.478	97.938
P	1.405	1.323	98.286
O1P	-0.939	-0.949	8.944
O2P	-0.939	-0.949	8.944
O3P	-0.939	-0.949	8.944
CE1	0.253	0.257	52.247
HE1	0.168	0.131	2.500
NE2	-0.909	-0.693	2.500

Table S341: Interaction energies and geometries between probe water and selected (5-ethyl-1H-imidazol-1-yl)phosphonicacid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	ND1-CG	0.0	-11.42/-11.90/-15.43		2.66/2.54/2.30	
2	ND1-CG	90.0	-14.20/-15.56/-20.00		2.46/2.28/2.11	
3	ND1-CG	180.0	-8.51/-8.03/-8.55		2.91/2.75/2.57	
4	ND1-CG	270.0	-8.08/-7.58/-7.93		2.86/2.81/2.64	
5	O1P-P	0.0	-19.77/-19.09/-20.67		1.67/1.61/1.60	
6	O1P-P	90.0	-19.77/-19.20/-20.91		1.66/1.61/1.60	
7	O1P-P	180.0	-19.32/-18.90/-20.75		1.66/1.60/1.60	
8	O1P-P	270.0	-19.69/-19.03/-20.80		1.66/1.61/1.60	
9	O2P-P	0.0	-20.11/-20.20/-21.42		1.66/1.60/1.59	
10	O2P-P	90.0	-19.71/-19.55/-21.09		1.66/1.61/1.60	
11	O2P-P	180.0	-19.45/-19.43/-21.29		1.66/1.61/1.60	
12	O2P-P	270.0	-19.86/-20.01/-21.68		1.66/1.60/1.59	
13	O3P-P	0.0	-19.73/-20.30/-21.59		1.67/1.61/1.60	
14	O3P-P	90.0	-19.20/-19.94/-21.63		1.66/1.61/1.60	
15	O3P-P	180.0	-18.78/-19.37/-21.19		1.66/1.61/1.60	
16	O3P-P	270.0	-19.35/-19.60/-21.12		1.67/1.61/1.60	
17	NE2-CD2	0.0	-16.57/-16.43/-12.93		1.84/1.81/1.87	
18	NE2-CD2	90.0	-16.30/-16.14/-11.78		1.82/1.80/1.88	
19	NE2-CD2	180.0	-15.55/-15.59/-10.44		1.84/1.81/1.89	
20	NE2-CD2	270.0	-16.32/-16.17/-11.82		1.82/1.80/1.88	

1.110 Small molecule used for 3-(1H-1,2,3-triazol-5-yl)-L-alanine(HIX)

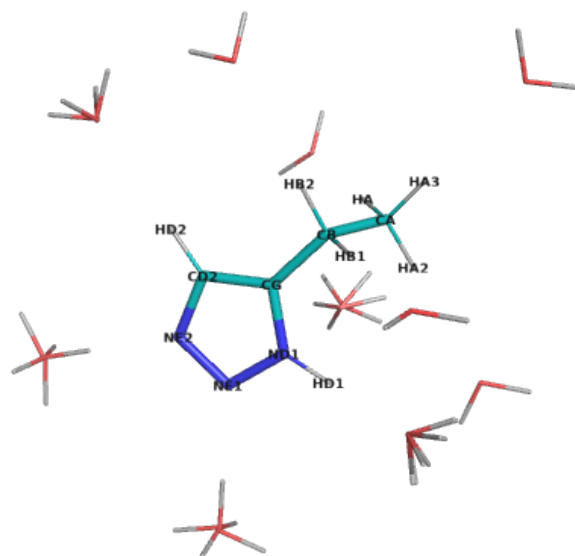


Figure S102: The molecule used for water complex calculations corresponding to 5-ethyl-1H-1,2,3-triazole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S342: Statistics of calculated water interaction and dipole moment for 5-ethyl-1H-1,2,3-triazole.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.17/2.63	0.09/0.23	3.492	5.31/6.25	5.92
Optimal	0.37/0.85	0.06/0.19	3.574	5.31/6.81	1.24

Table S343: The comparison list of optimized atomic charges and their initial guess for 5-ethyl-1H-1,2,3-triazole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.269	0.000
HA	0.090	0.090	0.000
CB	0.011	-0.088	1.500
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.279	-0.257	1.500
ND1	0.237	0.283	13.416
HD1	0.256	0.313	0.000
CD2	0.275	0.245	0.000
HD2	0.077	0.107	0.000
NE1	-0.345	-0.372	13.416
NE2	-0.412	-0.412	0.000

Table S344: Interaction energies and geometries between probe water and selected 5-ethyl-1H-1,2,3-triazole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-1.50/-1.72/-1.38	2.72/2.67/2.70
2	HA2-CA	0.0	-2.79/-3.14/-3.26	2.69/2.64/2.67
3	HA-CA	0.0	-1.65/-1.77/-1.53	2.62/2.63/2.66
4	HB1-CB	0.0	-2.22/-2.82/-2.46	2.59/2.60/2.64
5	HB2-CB	0.0	-2.16/-2.45/-1.90	2.57/2.62/2.66
6	ND1-CG	45.0	-0.16/-0.59/-1.02	3.53/3.55/3.44
7	ND1-CG	90.0	-0.34/-0.70/-1.09	3.53/3.53/3.43
8	ND1-CG	135.0	-0.14/-0.55/-0.90	3.68/3.58/3.48
9	HD1-ND1	0.0	-7.99/-8.13/-10.63	1.79/1.83/1.78
10	HD1-ND1	45.0	-8.18/-8.14/-10.60	1.78/1.83/1.78
11	HD1-ND1	90.0	-8.18/-8.12/-10.54	1.78/1.83/1.78
12	HD1-ND1	135.0	-7.97/-8.10/-10.56	1.79/1.83/1.78
13	HD2-CD2	0.0	-1.66/-1.74/-2.09	2.52/2.33/2.29
14	HD2-CD2	90.0	-1.76/-1.76/-2.07	2.49/2.33/2.29
15	NE1-ND1	0.0	-6.10/-6.59/-6.73	1.99/1.96/1.95
16	NE1-ND1	90.0	-5.19/-4.85/-4.80	2.00/2.00/2.00
17	NE1-ND1	180.0	-3.77/-2.91/-2.60	2.06/2.07/2.07
18	NE1-ND1	270.0	-5.20/-4.84/-4.78	2.00/2.00/2.00
19	NE2-CD2	0.0	-6.67/-6.92/-6.94	1.96/1.95/1.95
20	NE2-CD2	90.0	-6.17/-5.85/-5.88	1.96/1.98/1.98
21	NE2-CD2	180.0	-5.32/-4.72/-4.75	2.00/2.01/2.01
22	NE2-CD2	270.0	-6.15/-5.86/-5.90	1.97/1.98/1.97

1.111 Small molecule used for 4-amino-L-phenylalanine(HOX)

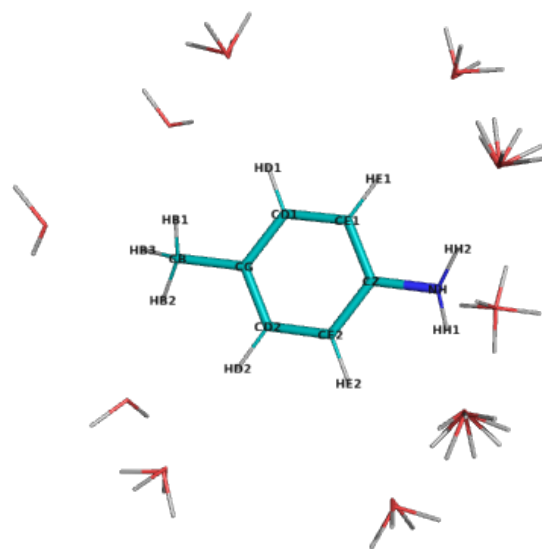


Figure S103: The molecule used for water complex calculations corresponding to 4-methylaniline, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S345: Statistics of calculated water interaction and dipole moment for 4-methylaniline.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.54/0.98	0.08/0.13	1.224	1.50/1.58	6.16
Optimal	0.26/0.48	0.07/0.12	1.258	1.50/1.44	9.99

Table S346: The comparison list of optimized atomic charges and their initial guess for 4-methylaniline, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.270	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.000	0.002	0.000
CD1	-0.115	-0.111	0.000
HD1	0.115	0.115	0.000
CD2	-0.115	-0.111	0.000
HD2	0.115	0.115	0.000
CE1	-0.126	-0.110	0.000
HE1	0.115	0.115	0.000
CE2	-0.125	-0.110	0.000
HE2	0.115	0.115	0.000
CZ	0.125	0.054	0.000
NH	-0.802	-0.838	0.000
HH1	0.349	0.382	0.000
HH2	0.349	0.382	0.000

Table S347: Interaction energies and geometries between probe water and selected 4-methylaniline site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.51/-0.44/-0.44	2.85/2.78/2.78
2	HB1-CB	0.0	-0.95/-0.76/-0.76	2.74/2.74/2.73
3	HB2-CB	0.0	-0.95/-0.76/-0.76	2.74/2.74/2.73
4	HD1-CD1	0.0	-1.09/-0.96/-0.96	2.71/2.71/2.71
5	HD1-CD1	90.0	-1.30/-1.03/-1.04	2.62/2.70/2.70
6	HD2-CD2	0.0	-1.09/-0.96/-0.96	2.71/2.71/2.71
7	HD2-CD2	90.0	-1.30/-1.03/-1.04	2.62/2.70/2.70
8	HE1-CE1	0.0	-1.25/-1.03/-1.00	2.72/2.72/2.73
9	HE1-CE1	90.0	-1.64/-1.18/-1.17	2.58/2.70/2.70
10	HE2-CE2	0.0	-1.25/-1.03/-1.00	2.72/2.72/2.73
11	HE2-CE2	90.0	-1.64/-1.18/-1.17	2.58/2.70/2.70
12	NH-CZ	0.0	-4.98/-4.50/-4.71	1.97/1.97/1.96
13	NH-CZ	90.0	-5.26/-5.20/-5.57	1.97/1.95/1.94
14	NH-CZ	180.0	-6.15/-6.34/-6.93	1.95/1.93/1.91
15	NH-CZ	270.0	-5.26/-5.20/-5.57	1.97/1.95/1.94
16	HH1-NH	0.0	-4.08/-4.33/-4.92	2.02/1.93/1.90
17	HH1-NH	45.0	-3.83/-4.23/-4.81	2.04/1.93/1.90
18	HH1-NH	90.0	-4.28/-4.42/-5.01	2.00/1.92/1.90
19	HH1-NH	135.0	-4.52/-4.51/-5.11	1.99/1.92/1.89
20	HH2-NH	0.0	-4.08/-4.33/-4.92	2.02/1.93/1.90
21	HH2-NH	45.0	-4.52/-4.51/-5.11	1.99/1.92/1.89
22	HH2-NH	90.0	-4.28/-4.42/-5.01	2.00/1.92/1.90
23	HH2-NH	135.0	-3.83/-4.23/-4.81	2.04/1.93/1.90

1.112 Small molecule A of
 (4S)-4-[(2S)-2-amino-3-oxopropyl]sulfanyl-L-homoserine(HTI)

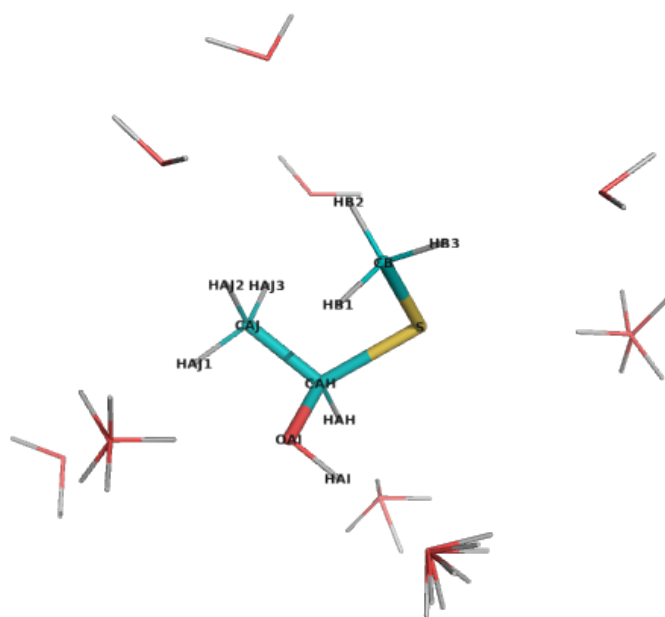


Figure S104: The molecule used for water complex calculations corresponding to (1R)-1-(methylsulfanyl)ethan-1-ol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S348: Statistics of calculated water interaction and dipole moment for (1R)-1-(methylsulfanyl)ethan-1-ol.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.58/1.16	0.19/0.46	3.398	0.21/1.05	160.34
Optimal	0.31/0.58	0.23/0.52	1.952	0.21/0.36	135.11

Table S349: The comparison list of optimized atomic charges and their initial guess for (1R)-1-(methylsulfanyl)ethan-1-ol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CB	-0.162	-0.220	2.563
HB1	0.090	0.090	0.030
HB2	0.090	0.090	0.030
HB3	0.090	0.090	0.030
S	-0.204	-0.125	28.177
CAH	0.196	0.211	27.793
HAH	0.090	0.090	0.424
OAI	-0.565	-0.641	18.445
HAI	0.375	0.413	2.500
CAJ	-0.270	-0.268	0.671
HAI1	0.090	0.090	0.300
HAI2	0.090	0.090	0.300
HAI3	0.090	0.090	0.300

Table S350: Interaction energies and geometries between probe water and selected (1R)-1-(methylsulfanyl)ethan-1-ol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HB2-CB	0.0	-1.29/-1.08/-0.88		2.64/2.68/2.71	
2	HB3-CB	0.0	-1.27/-0.80/-0.65		2.62/2.71/2.74	
3	S-CB	0.0	-1.32/-1.64/-0.95		2.91/2.40/2.49	
4	S-CB	90.0	-1.67/-1.98/-1.34		2.83/2.38/2.45	
5	S-CB	180.0	-1.46/-2.04/-1.47		2.90/2.38/2.44	
6	S-CB	270.0	-1.53/-1.76/-1.12		2.85/2.39/2.47	
7	HAH-CAH	0.0	-1.65/-1.47/-1.68		2.57/2.66/2.65	
8	HAH-CAH	90.0	-1.46/-1.36/-1.57		2.60/2.67/2.66	
9	OAI-CAH	0.0	-5.17/-4.99/-5.76		1.86/1.90/1.87	
10	OAI-CAH	90.0	-5.02/-4.98/-5.88		1.85/1.89/1.86	
11	OAI-CAH	180.0	-4.72/-5.06/-5.88		1.88/1.89/1.86	
12	OAI-CAH	270.0	-5.39/-5.20/-5.94		1.84/1.89/1.86	
13	HAI-OAI	0.0	-6.20/-6.00/-6.60		1.77/1.83/1.82	
14	HAI-OAI	45.0	-6.64/-6.10/-6.72		1.75/1.83/1.81	
15	HAI-OAI	90.0	-5.76/-5.88/-6.58		1.78/1.84/1.82	
16	HAI-OAI	135.0	-5.36/-5.78/-6.46		1.80/1.84/1.82	
17	HAI1-CAJ	0.0	-0.60/-0.19/-0.08		2.77/2.80/2.82	
18	HAI2-CAJ	0.0	-0.96/-0.70/-0.46		2.96/2.97/2.97	
19	HAI3-CAJ	0.0	-0.89/-0.83/-0.94		2.70/2.71/2.70	

1.113 Small molecule used for beta-hydroxy-tryptophane(HTR)

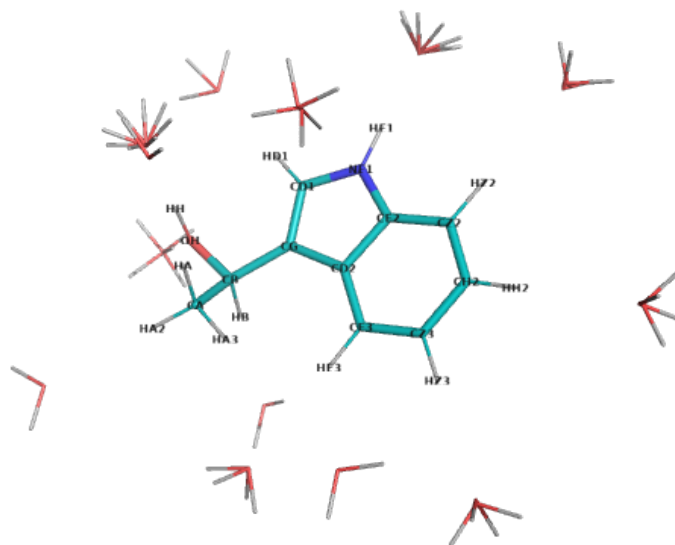


Figure S105: The molecule used for water complex calculations corresponding to (1R)-1-(1H-indol-3-yl)ethan-1-ol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S351: Statistics of calculated water interaction and dipole moment for (1R)-1-(1H-indol-3-yl)ethan-1-ol.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.74/1.88	0.10/0.26	2.071	2.39/2.53	23.04
Optimal	0.18/0.34	0.06/0.16	1.834	2.39/2.98	1.03

Table S352: The comparison list of optimized atomic charges and their initial guess for (1R)-1-(1H-indol-3-yl)ethan-1-ol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.300
HA2	0.090	0.090	0.300
CA	-0.270	-0.275	5.465
HA	0.090	0.090	0.300
CB	0.152	0.135	22.147
HB	0.090	0.090	0.520
OH	-0.632	-0.639	8.063
HH	0.392	0.413	0.725
CG	-0.068	-0.053	30.497
CD1	-0.077	-0.147	19.460
HD1	0.148	0.220	0.030
CD2	0.080	0.095	20.161
NE1	-0.393	-0.517	0.213
HE1	0.319	0.363	0.000
CE2	0.271	0.231	0.331
CE3	-0.284	-0.258	0.274
HE3	0.177	0.201	0.000
CZ2	-0.251	-0.285	0.000
HZ2	0.166	0.195	0.000
CZ3	-0.261	-0.236	0.000
HZ3	0.181	0.196	0.000
CH2	-0.185	-0.195	0.000
HH2	0.175	0.196	0.000

Table S353: Interaction energies and geometries between probe water and selected (1R)-1-(1H-indol-3-yl)ethan-1-ol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.58/-0.41/-0.80	3.96/3.94/3.95
2	HA2-CA	0.0	-0.56/-0.37/-0.32	2.79/2.75/2.76
3	HA-CA	0.0	-0.81/-1.15/-1.03	2.83/2.70/2.70
4	HB-CB	0.0	-0.50/-0.26/-0.18	2.74/2.75/2.77
5	OH-CB	0.0	-5.47/-5.32/-5.29	1.85/1.87/1.87
6	OH-CB	90.0	-5.79/-5.58/-5.69	1.83/1.87/1.86
7	OH-CB	180.0	-5.74/-6.00/-6.14	1.85/1.86/1.86
8	OH-CB	270.0	-5.93/-5.88/-5.90	1.83/1.86/1.86
9	HH-OH	0.0	-5.75/-5.81/-6.40	1.85/1.86/1.84
10	HH-OH	45.0	-6.09/-5.84/-6.49	1.84/1.86/1.84
11	HH-OH	90.0	-5.53/-5.56/-6.10	1.85/1.87/1.85
12	HH-OH	135.0	-5.21/-5.54/-6.02	1.87/1.87/1.85
13	HD1-CD1	0.0	-2.20/-2.41/-3.04	2.41/2.28/2.23
14	HD1-CD1	90.0	-1.87/-2.12/-2.76	2.46/2.30/2.25
15	NE1-CD1	0.0	-1.64/-1.58/-3.22	2.35/2.28/2.15
16	NE1-CD1	90.0	-0.77/-0.64/-2.13	2.44/2.33/2.18
17	NE1-CD1	180.0	-1.37/-1.47/-3.09	2.32/2.23/2.11
18	NE1-CD1	270.0	-2.93/-3.05/-4.81	2.24/2.17/2.07
19	HE1-NE1	0.0	-6.17/-6.44/-5.92	1.88/1.87/1.87
20	HE1-NE1	45.0	-6.44/-6.54/-6.05	1.86/1.87/1.87
21	HE1-NE1	90.0	-6.79/-6.66/-6.21	1.84/1.87/1.86
22	HE1-NE1	135.0	-6.51/-6.57/-6.09	1.86/1.87/1.87
23	HE3-CE3	0.0	-1.63/-1.57/-2.19	2.71/2.72/2.66
24	HE3-CE3	90.0	-1.67/-1.59/-2.19	2.71/2.71/2.65
25	HZ2-CZ2	0.0	-1.45/-1.76/-1.70	2.71/2.66/2.65
26	HZ2-CZ2	90.0	-1.90/-1.98/-1.92	2.57/2.63/2.62
27	HZ3-CZ3	0.0	-0.90/-0.76/-1.38	2.75/2.71/2.65
28	HZ3-CZ3	90.0	-1.08/-0.84/-1.49	2.68/2.70/2.64
29	HH2-CH2	0.0	-1.03/-1.08/-1.46	2.71/2.68/2.64
30	HH2-CH2	90.0	-1.21/-1.17/-1.57	2.64/2.67/2.63

Table S355: The comparison list of optimized atomic charges and their initial guess for N-methyl-N-(2-methylpropyl)acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.186	0.483
HL1	0.090	0.090	0.000
HL2	0.090	0.090	0.000
HL3	0.090	0.090	0.000
CLP	0.510	0.425	5.875
OL	-0.510	-0.531	0.285
N	-0.224	-0.376	10.783
CA	-0.158	-0.088	2.581
HA2	0.090	0.090	0.045
HA3	0.090	0.090	0.045
HA1	0.090	0.090	0.045
CB	-0.068	0.038	9.992
HB2	0.090	0.090	0.638
HB3	0.090	0.090	0.638
CG	-0.090	-0.090	5.579
HG	0.090	0.090	0.350
CD1	-0.270	-0.271	0.350
HD11	0.090	0.090	0.000
HD12	0.090	0.090	0.000
HD13	0.090	0.090	0.000
CD2	-0.270	-0.271	0.350
HD21	0.090	0.090	0.000
HD22	0.090	0.090	0.000
HD23	0.090	0.090	0.000

Table S356: Interaction energies and geometries between probe water and selected N-methyl-N-(2-methylpropyl)acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HL1-CL	0.0	-1.34/-1.27/-1.47		3.55/3.51/3.48	
2	HL2-CL	0.0	-1.83/-1.67/-1.85		2.57/2.64/2.62	
3	HL3-CL	0.0	-0.44/-0.24/-0.26		2.65/2.71/2.69	
4	OL-CLP	0.0	-6.90/-6.63/-7.51		1.81/1.76/1.74	
5	OL-CLP	90.0	-6.75/-6.56/-7.49		1.81/1.76/1.74	
6	OL-CLP	180.0	-6.54/-6.31/-7.23		1.82/1.76/1.74	
7	OL-CLP	270.0	-6.74/-6.51/-7.43		1.81/1.76/1.74	
8	HA2-CA	0.0	-0.39/-0.34/-0.11		2.71/2.70/2.71	
9	HA3-CA	0.0	-1.79/-1.58/-1.76		2.81/2.70/2.69	
10	HB2-CB	0.0	-1.89/-2.20/-2.60		3.03/2.89/2.87	
11	HB3-CB	0.0	-1.94/-1.70/-2.04		2.64/2.67/2.65	
12	HG-CG	0.0	-1.64/-1.68/-1.73		2.97/2.95/2.96	
13	HD11-CD1	0.0	-1.14/-0.91/-1.03		2.78/2.74/2.73	
14	HD12-CD1	0.0	-1.29/-1.39/-1.65		2.81/2.72/2.71	
15	HD13-CD1	0.0	-1.20/-1.13/-1.37		2.81/2.73/2.71	
16	HD21-CD2	0.0	-1.00/-0.76/-0.80		2.81/2.76/2.76	
17	HD22-CD2	0.0	-1.38/-1.16/-1.32		2.76/2.73/2.72	
18	HD23-CD2	0.0	-2.63/-1.57/-1.48		3.15/3.45/3.43	

1.115 Small molecule A of 4-[(isopropylamino)methyl]phenylalanine(IAM)

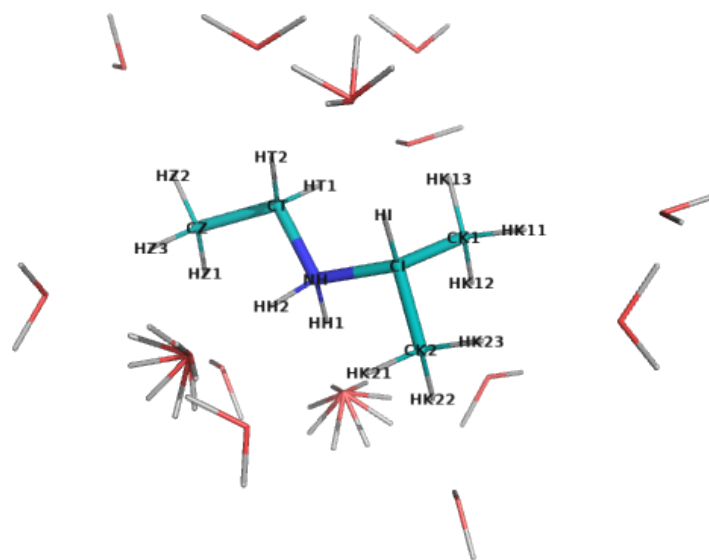


Figure S107: The molecule used for water complex calculations corresponding to ethyl(propan-2-yl)amine, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S357: Statistics of calculated water interaction and dipole moment for ethyl(propan-2-yl)amine.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.76/1.58	0.14/0.25	2.931	1.36/0.84	58.77
Optimal	0.42/0.89	0.14/0.25	1.152	1.36/1.36	7.41

Table S358: The comparison list of optimized atomic charges and their initial guess for ethyl(prop an-2-yl)amine, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CZ	-0.210	-0.344	0.788
HZ1	0.090	0.090	0.045
HZ2	0.090	0.090	0.045
HZ3	0.090	0.090	0.045
CT	0.122	0.202	1.038
HT1	0.090	0.090	0.000
HT2	0.090	0.090	0.000
NH	-0.402	-0.364	1.579
HH1	0.313	0.320	0.078
HH2	0.313	0.320	0.078
CI	0.242	0.244	11.678
HI	0.090	0.090	0.738
CK1	-0.229	-0.229	10.255
HK11	0.090	0.090	0.674
HK12	0.090	0.090	0.674
HK13	0.090	0.090	0.674
CK2	-0.229	-0.229	10.255
HK21	0.090	0.090	0.674
HK22	0.090	0.090	0.674
HK23	0.090	0.090	0.674

Table S359: Interaction energies and geometries between probe water and selected ethyl(prop an-2-yl)amine site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HZ1-CZ	0.0	-6.64/-6.34/-5.75		2.42/2.54/2.58	
2	HZ2-CZ	0.0	-6.30/-5.41/-4.72		2.33/2.54/2.58	
3	HZ3-CZ	0.0	-7.37/-6.69/-6.11		2.35/2.52/2.56	
4	HT1-CT	0.0	-8.03/-7.92/-8.25		2.40/2.56/2.54	
5	HT2-CT	0.0	-8.59/-7.99/-8.34		2.27/2.51/2.49	
6	HH1-NH	0.0	-15.77/-15.72/-16.63		1.79/1.79/1.77	
7	HH1-NH	45.0	-16.15/-15.85/-16.68		1.79/1.79/1.77	
8	HH1-NH	90.0	-15.88/-15.76/-16.64		1.79/1.79/1.77	
9	HH1-NH	135.0	-15.52/-15.64/-16.59		1.79/1.79/1.77	
10	HH2-NH	0.0	-15.34/-15.61/-16.45		1.81/1.80/1.78	
11	HH2-NH	45.0	-15.25/-15.56/-16.43		1.81/1.80/1.79	
12	HH2-NH	90.0	-15.95/-15.84/-16.61		1.81/1.80/1.78	
13	HH2-NH	135.0	-16.02/-15.89/-16.63		1.81/1.80/1.78	
14	HI-CI	0.0	-8.23/-8.10/-8.57		2.30/2.51/2.50	
15	HI-CI	90.0	-8.82/-8.27/-8.72		2.26/2.51/2.50	
16	HK11-CK1	0.0	-6.31/-5.56/-5.77		2.36/2.54/2.54	
17	HK12-CK1	0.0	-6.82/-6.59/-6.92		2.44/2.54/2.53	
18	HK13-CK1	0.0	-7.01/-6.90/-7.37		2.47/2.58/2.56	
19	HK21-CK2	0.0	-6.86/-6.67/-7.01		2.42/2.53/2.52	
20	HK22-CK2	0.0	-6.70/-6.50/-6.80		2.43/2.54/2.53	
21	HK23-CK2	0.0	-6.34/-5.53/-5.72		2.35/2.54/2.54	

1.116 Small molecule used for alpha-amino-2-indanaceticacid(IGL)

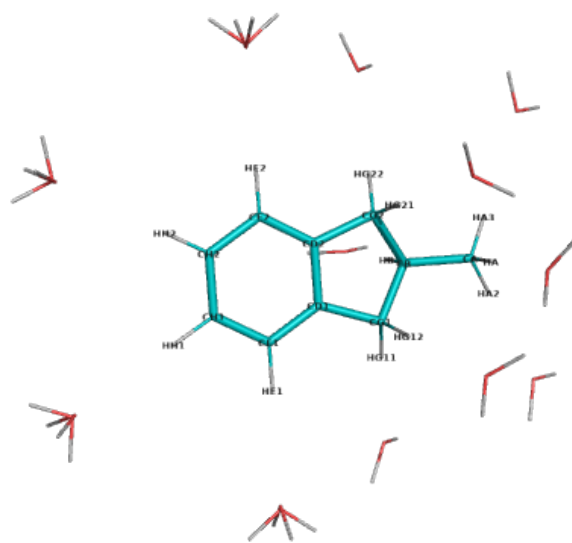


Figure S108: The molecule used for water complex calculations corresponding to 2-methyl-2,3-dihydro-1H-indene, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S360: Statistics of calculated water interaction and dipole moment for 2-methyl-2,3-dihydro-1H-indene.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.18/0.29	0.07/0.13	1.537	0.48/0.78	13.01
Optimal	0.03/0.04	0.06/0.09	1.101	0.48/0.65	8.40

Table S361: The comparison list of optimized atomic charges and their initial guess for 2-methyl-2,3-dihydro-1H-indene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.306	25.816
HA	0.090	0.090	0.000
CB	-0.090	-0.112	29.338
HB	0.090	0.090	0.283
CG1	-0.180	-0.169	18.106
HG11	0.090	0.090	0.000
HG12	0.090	0.090	0.000
CG2	-0.180	-0.169	18.106
HG21	0.090	0.090	0.000
HG22	0.090	0.090	0.000
CD1	0.123	0.208	13.892
CD2	0.125	0.208	13.892
CE1	-0.328	-0.373	0.224
HE1	0.186	0.204	0.000
CE2	-0.328	-0.373	0.224
HE2	0.186	0.204	0.000
CH1	-0.141	-0.217	0.000
HH1	0.159	0.196	0.000
CH2	-0.141	-0.217	0.000
HH2	0.159	0.196	0.000

Table S362: Interaction energies and geometries between probe water and selected 2-methyl-2,3-dihydro-1H-indene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.72/-0.70/-0.55		2.86/2.76/2.81	
2	HA2-CA	0.0	-0.72/-0.70/-0.55		2.86/2.76/2.81	
3	HA-CA	0.0	-0.85/-0.84/-0.79		2.80/2.73/2.76	
4	HB-CB	0.0	-0.69/-0.68/-0.85		2.80/2.74/2.73	
5	HG11-CG1	0.0	-0.81/-0.80/-1.04		2.82/2.75/2.71	
6	HG12-CG1	0.0	-0.68/-0.70/-0.97		2.84/2.75/2.71	
7	HG21-CG2	0.0	-0.68/-0.70/-0.97		2.84/2.75/2.71	
8	HG22-CG2	0.0	-0.81/-0.80/-1.04		2.82/2.75/2.71	
9	HE1-CE1	0.0	-1.07/-1.10/-1.27		2.70/2.68/2.66	
10	HE1-CE1	90.0	-1.22/-1.19/-1.37		2.64/2.66/2.65	
11	HE2-CE2	0.0	-1.07/-1.10/-1.27		2.71/2.68/2.66	
12	HE2-CE2	90.0	-1.22/-1.19/-1.37		2.64/2.66/2.65	
13	HH1-CH1	0.0	-1.00/-1.05/-1.01		2.71/2.68/2.67	
14	HH1-CH1	90.0	-1.16/-1.13/-1.11		2.65/2.67/2.66	
15	HH2-CH2	0.0	-1.00/-1.05/-1.01		2.71/2.68/2.67	
16	HH2-CH2	90.0	-1.16/-1.13/-1.11		2.65/2.67/2.66	

1.117 Small molecule A of (2S)-2-amino-6-[[3-hydroxy-2-methyl-5-(phosphonoxyethyl)pyridin-4-yl]methylideneamino]hexanoic acid (IT1P)

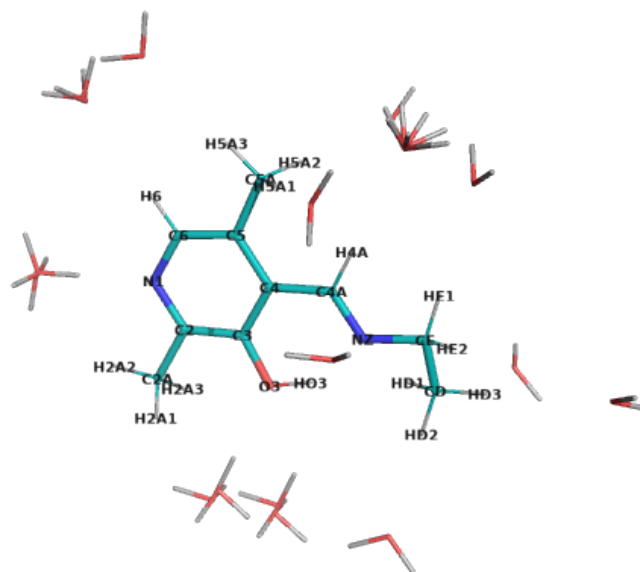


Figure S109: The molecule used for water complex calculations corresponding to 4-[(E)-(ethylimino)methyl]-2,5-dimethylpyridin-3-olate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S363: Statistics of calculated water interaction and dipole moment for 4-[(E)-(ethylimino)methyl]-2,5-dimethylpyridin-3-olate.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.77/1.54	0.12/0.25	4.499	4.76/5.26	26.66
Optimal	0.29/0.65	0.09/0.20	2.640	4.76/6.19	0.00

Table S364: The comparison list of optimized atomic charges and their initial guess for 4-[(E)-(ethylimino)methyl]-2,5-dimethylpyridin-3-olate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HD3	0.090	0.090	0.000
CD	-0.270	-0.263	0.597
HD1	0.090	0.090	0.000
HD2	0.090	0.090	0.000
CE	0.117	0.021	3.263
HE1	0.090	0.090	0.025
HE2	0.090	0.090	0.025
NZ	-0.467	-0.591	3.218
C4A	-0.161	-0.098	15.004
H4A	0.139	0.240	0.250
C4	0.305	0.245	20.733
C3	0.075	0.091	2.104
O3	-0.532	-0.529	2.104
HO3	0.420	0.420	0.000
C2	0.327	0.357	17.715
C2A	-0.323	-0.267	16.637
H2A1	0.112	0.090	2.250
H2A2	0.093	0.090	2.250
H2A3	0.089	0.090	2.250
N1	-0.582	-0.621	14.965
C6	0.077	0.153	2.500
H6	0.121	0.121	0.000
C5	0.010	-0.002	12.965
C5A	-0.270	-0.267	12.965
H5A1	0.090	0.090	0.000
H5A2	0.090	0.090	0.000
H5A3	0.090	0.090	0.000

Table S365: Interaction energies and geometries between probe water and selected 4-[(E)-(ethylimino)methyl]-2,5-dimethylpyridin-3-olate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HD3-CD	0.0	-1.22/-1.46/-0.87		2.76/2.68/2.74	
2	HD1-CD	0.0	-1.31/-1.05/-0.49		2.76/2.74/2.86	
3	HD2-CD	0.0	-1.42/-1.29/-0.41		2.64/2.67/2.74	
4	HE1-CE	0.0	-2.25/-2.58/-2.33		2.68/2.63/2.67	
5	HE2-CE	0.0	-1.33/-1.63/-0.50		2.68/2.65/2.77	
6	NZ-CE	0.0	-3.21/-3.51/-3.41		4.04/3.96/3.95	
7	NZ-CE	90.0	-2.20/-2.06/-2.40		4.19/4.17/4.12	
8	NZ-CE	180.0	-1.61/-1.14/-1.81		4.27/4.33/4.23	
9	NZ-CE	270.0	-2.25/-2.05/-2.47		4.18/4.16/4.11	
10	H4A-C4A	0.0	-2.59/-2.75/-4.00		2.74/2.69/2.56	
11	H4A-C4A	45.0	-2.62/-2.86/-4.10		2.77/2.68/2.55	
12	H4A-C4A	90.0	-2.67/-2.98/-4.22		2.79/2.67/2.55	
13	H4A-C4A	135.0	-2.63/-2.87/-4.11		2.77/2.68/2.55	
14	O3-C3	0.0	-3.06/-2.87/-3.26		2.20/2.33/2.31	
15	O3-C3	90.0	-2.79/-2.86/-2.93		2.38/2.34/2.33	
16	O3-C3	180.0	-2.56/-3.10/-2.50		2.52/2.34/2.38	
17	O3-C3	270.0	-2.81/-3.07/-2.94		2.38/2.33/2.33	
18	N1-C2	0.0	-6.05/-6.07/-5.84		1.95/1.86/1.85	
19	N1-C2	90.0	-6.93/-6.65/-6.42		1.91/1.85/1.84	
20	N1-C2	180.0	-5.94/-6.59/-6.28		1.98/1.86/1.85	
21	N1-C2	270.0	-6.93/-6.60/-6.42		1.91/1.85/1.84	
22	H6-C6	0.0	-1.12/-1.49/-2.15		2.66/2.47/2.43	
23	H6-C6	90.0	-1.34/-1.52/-2.18		2.58/2.47/2.43	
24	H5A1-C5A	0.0	-1.88/-1.94/-2.64		2.62/2.63/2.59	
25	H5A2-C5A	0.0	-1.89/-1.95/-2.66		2.61/2.63/2.59	
26	H5A3-C5A	0.0	-1.74/-1.97/-2.38		2.67/2.63/2.61	

1.118 Small molecule used for S-(pyridin-3-ylcarbonyl)-L-cysteine(JJJ)

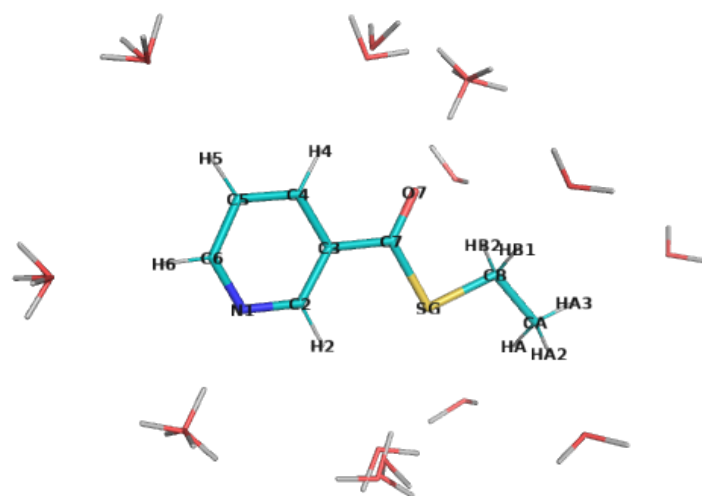


Figure S110: The molecule used for water complex calculations corresponding to (ethylsulfanyl)(pyridin-3-yl)methanone, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S366: Statistics of calculated water interaction and dipole moment for (ethylsulfanyl)(pyridin-3-yl)methanone.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.01/2.24	0.44/1.94	3.907	0.70/1.43	111.87
Optimal	0.26/0.91	0.18/0.48	1.850	0.70/0.91	0.00

Table S367: The comparison list of optimized atomic charges and their initial guess for (ethylsulfanyl)(pyridin-3-yl)methanone, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.620
HA	0.090	0.090	0.000
CB	-0.043	0.002	9.073
HB1	0.090	0.090	0.575
HB2	0.090	0.090	0.575
SG	-0.077	-0.012	99.241
C7	0.234	0.250	99.637
O7	-0.391	-0.505	57.902
C3	0.056	0.084	81.121
C2	0.177	0.192	2.645
H2	0.075	0.105	0.050
C4	-0.060	-0.108	2.500
H4	0.115	0.115	0.000
N1	-0.564	-0.602	0.745
C5	-0.116	-0.117	0.000
H5	0.115	0.115	0.000
C6	0.186	0.177	0.000
H6	0.113	0.124	0.000

Table S368: Interaction energies and geometries between probe water and selected (ethylsulfanyl)(pyridin-3-yl)methanone site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-1.26/-1.02/-1.32	2.71/2.71/2.68
2	HA2-CA	0.0	-1.14/-0.98/-1.42	2.68/2.71/2.68
3	HA-CA	0.0	-1.14/-0.98/-1.42	2.68/2.71/2.68
4	HB1-CB	0.0	-1.02/-0.72/-0.96	2.50/2.67/2.62
5	HB2-CB	0.0	-1.02/-0.72/-0.96	2.50/2.67/2.62
6	SG-CB	0.0	-0.61/-0.87/-0.17	3.06/2.64/5.00
7	SG-CB	180.0	-0.20/-0.30/0.55	2.96/2.49/2.59
8	O7-C7	0.0	-4.59/-4.59/-6.05	1.89/1.81/1.76
9	O7-C7	90.0	-4.79/-4.80/-6.63	1.88/1.81/1.75
10	O7-C7	180.0	-4.50/-4.61/-6.75	1.89/1.81/1.75
11	O7-C7	270.0	-4.79/-4.80/-6.63	1.88/1.81/1.75
12	H2-C2	0.0	-0.57/-0.89/-1.68	2.75/2.76/2.69
13	H2-C2	90.0	-0.54/-0.77/-1.71	3.01/2.81/2.70
14	H4-C4	0.0	-1.58/-0.67/0.24	2.32/2.64/2.68
15	H4-C4	90.0	-0.48/-0.30/0.70	2.58/2.70/2.82
16	N1-C2	0.0	-5.33/-5.27/-5.96	1.97/1.86/1.84
17	N1-C2	90.0	-5.89/-5.72/-6.18	1.93/1.85/1.84
18	N1-C2	180.0	-5.52/-5.66/-5.77	1.97/1.86/1.85
19	N1-C2	270.0	-5.89/-5.71/-6.18	1.93/1.85/1.84
20	H5-C5	0.0	-2.15/-2.03/-1.72	2.52/2.63/2.64
21	H5-C5	90.0	-2.33/-2.07/-1.75	2.47/2.62/2.64
22	H6-C6	0.0	-1.93/-1.87/-1.78	2.48/2.44/2.44
23	H6-C6	90.0	-1.93/-1.85/-1.76	2.47/2.44/2.44

1.119 Small molecule used for N-6-crotonyl-L-lysine(KCR)

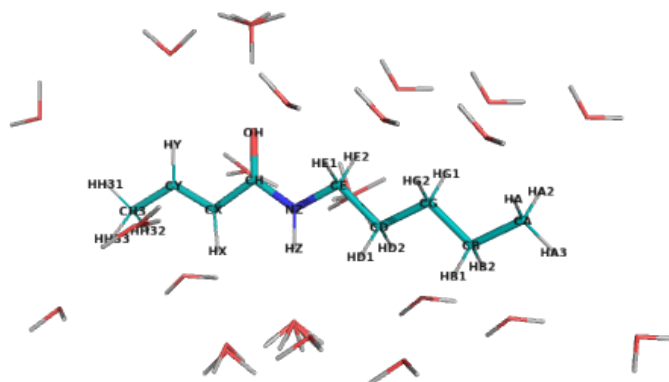


Figure S111: The molecule used for water complex calculations corresponding to (2E)-N-pentylbut-2-enamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S369: Statistics of calculated water interaction and dipole moment for (2E)-N-pentylbut-2-enamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.48/0.86	0.08/0.16	2.530	3.87/3.81	17.91
Optimal	0.66/2.01	0.07/0.22	3.234	3.87/5.04	0.34

Table S370: The comparison list of optimized atomic charges and their initial guess for (2E)-N-pentylbut-2-enamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.000
HA	0.090	0.090	0.000
CB	-0.180	-0.180	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.180	-0.196	3.012
HG1	0.090	0.090	0.000
HG2	0.090	0.090	0.000
CD	-0.180	-0.177	2.481
HD1	0.090	0.090	0.000
HD2	0.090	0.090	0.000
CE	-0.032	0.069	2.667
HE1	0.090	0.090	0.000
HE2	0.090	0.090	0.000
NZ	-0.402	-0.555	2.451
HZ	0.257	0.305	0.000
CH	0.378	0.515	11.796
OH	-0.555	-0.499	0.000
CX	0.050	-0.157	10.830
HX	0.144	0.150	0.000
CY	-0.127	-0.143	10.116
HY	0.107	0.150	1.425
CH3	-0.270	-0.272	0.000
HH31	0.090	0.090	0.000
HH32	0.090	0.090	0.000
HH33	0.090	0.090	0.000

Table S371: Interaction energies and geometries between probe water and selected (2E)-N-pentylbut-2-enamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.66/-0.56/-0.60		2.88/2.79/2.79	
2	HA2-CA	0.0	-0.83/-0.69/-0.72		2.85/2.77/2.78	
3	HA-CA	0.0	-0.83/-0.69/-0.72		2.85/2.77/2.78	
4	HB1-CB	0.0	-0.75/-0.66/-0.77		2.90/2.81/2.80	
5	HB2-CB	0.0	-0.75/-0.66/-0.77		2.90/2.81/2.80	
6	HG1-CG	0.0	-1.13/-0.92/-1.14		2.76/2.72/2.72	
7	HG2-CG	0.0	-1.13/-0.92/-1.14		2.76/2.72/2.72	
8	HD1-CD	0.0	-1.04/-1.16/-1.40		2.84/2.75/2.71	
9	HD2-CD	0.0	-1.04/-1.16/-1.40		2.84/2.75/2.71	
10	HE1-CE	0.0	-0.39/-0.10/-0.78		2.66/2.71/2.65	
11	HE2-CE	0.0	-0.39/-0.10/-0.78		2.66/2.71/2.65	
12	NZ-CE	0.0	-1.22/-0.76/-1.58		2.32/2.34/2.24	
13	NZ-CE	90.0	-2.93/-3.62/-3.43		2.20/2.16/2.14	
14	NZ-CE	180.0	-1.34/-2.31/-1.80		2.33/2.22/2.22	
15	NZ-CE	270.0	-0.48/-0.36/-0.61		2.38/2.35/2.28	
16	HZ-NZ	0.0	-5.13/-5.78/-5.99		1.98/1.97/1.93	
17	HZ-NZ	45.0	-5.56/-6.06/-6.20		1.95/1.95/1.93	
18	HZ-NZ	90.0	-5.97/-6.34/-6.41		1.94/1.94/1.92	
19	HZ-NZ	135.0	-5.56/-6.06/-6.20		1.95/1.95/1.93	
20	OH-CH	0.0	-7.03/-7.81/-6.23		1.80/1.73/1.76	
21	OH-CH	90.0	-7.10/-7.86/-6.50		1.80/1.73/1.76	
22	OH-CH	180.0	-6.84/-7.70/-6.48		1.81/1.73/1.76	
23	OH-CH	270.0	-7.10/-7.86/-6.50		1.80/1.73/1.76	
24	HX-CX	0.0	-1.90/-3.91/-2.68		2.69/2.46/2.53	
25	HX-CX	90.0	-2.57/-4.15/-2.95		2.50/2.45/2.51	
26	HH31-CH3	0.0	-1.30/-0.77/-0.56		2.69/2.73/2.76	
27	HH32-CH3	0.0	-1.23/-1.18/-0.63		2.69/2.73/2.79	
28	HH33-CH3	0.0	-1.23/-1.18/-0.63		2.69/2.73/2.79	

1.120 Small molecule used for lysineNZ-carboxylicacid(KCX)

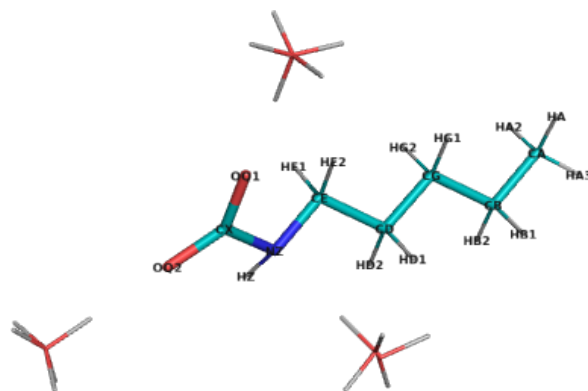


Figure S112: The molecule used for water complex calculations corresponding to pentylcarbamic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S372: Statistics of calculated water interaction and dipole moment for pentylcarbamic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.87/3.51	0.08/0.10	6.278	15.20/18.93	2.02
Optimal	0.38/1.06	0.06/0.11	3.491	15.20/16.45	2.36

Table S373: The comparison list of optimized atomic charges and their initial guess for pentyl carbamic acid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.000
HA	0.090	0.090	0.000
CB	-0.180	-0.180	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.180	-0.196	3.012
HG1	0.090	0.090	0.000
HG2	0.090	0.090	0.000
CD	-0.180	-0.177	3.884
HD1	0.090	0.090	0.000
HD2	0.090	0.090	0.000
CE	-0.046	0.045	7.615
HE1	0.090	0.090	0.375
HE2	0.090	0.090	0.375
NZ	-0.660	-0.539	44.036
HZ	0.191	0.314	3.555
CX	0.777	0.533	44.612
OQ1	-0.721	-0.760	17.521
OQ2	-0.721	-0.760	17.521

Table S374: Interaction energies and geometries between probe water and selected pentyl carbamic acid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	NZ-CE	0.0	-10.85/-11.13/-10.09	1.97/1.97/2.01
2	NZ-CE	90.0	-8.89/-7.83/-5.38	2.03/2.02/2.13
3	NZ-CE	180.0	-8.15/-8.24/-6.14	2.12/2.02/2.11
4	NZ-CE	270.0	-11.67/-12.04/-11.49	1.97/1.95/1.98
5	OQ1-CX	0.0	-13.36/-13.58/-14.85	1.73/1.66/1.64
6	OQ1-CX	90.0	-13.71/-13.74/-15.48	1.72/1.66/1.64
7	OQ1-CX	180.0	-14.24/-14.37/-16.69	1.72/1.66/1.63
8	OQ1-CX	270.0	-13.91/-14.19/-16.12	1.72/1.66/1.64
9	OQ2-CX	0.0	-13.66/-13.53/-14.58	1.73/1.67/1.65
10	OQ2-CX	90.0	-14.18/-13.96/-15.77	1.72/1.66/1.64
11	OQ2-CX	180.0	-14.49/-14.12/-16.40	1.72/1.66/1.64
12	OQ2-CX	270.0	-13.86/-13.62/-15.24	1.73/1.67/1.64

1.121 Small molecule A of (2S)-2-amino-6-[(1-hydroxy-1-oxo-propan-2-ylidene)amino]hexanoicacid(KPI)

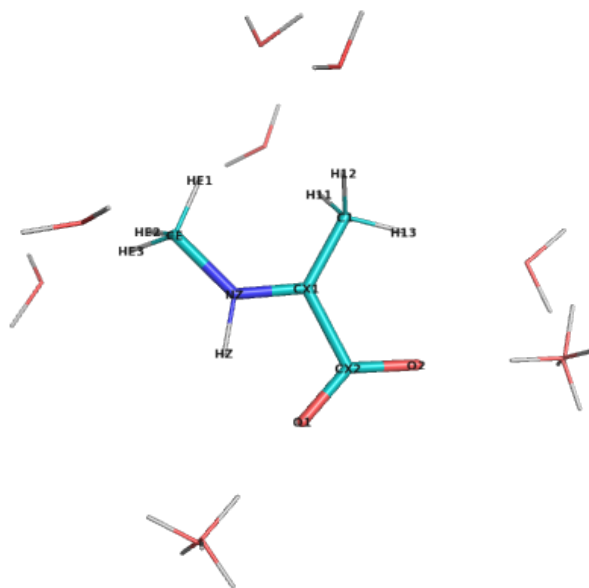


Figure S113: The molecule used for water complex calculations corresponding to (2E)-2-(methyliminium)propanoate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S375: Statistics of calculated water interaction and dipole moment for (2E)-2-(methyliminium)propanoate.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.55/3.86	0.12/0.33	4.010	8.47/10.13	0.79
Optimal	0.78/2.21	0.10/0.18	3.551	8.47/8.16	6.11

Table S376: The comparison list of optimized atomic charges and their initial guess for (2E)-2-(methyliminiumyl)propanoate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HE3	0.090	0.090	0.025
CE	-0.111	-0.078	2.530
HE1	0.090	0.090	0.025
HE2	0.090	0.090	0.025
NZ	-0.706	-0.553	26.076
CX1	0.336	0.237	30.463
C1	-0.356	-0.300	12.408
H11	0.090	0.090	0.862
H12	0.090	0.090	0.862
H13	0.090	0.090	0.862
CX2	0.777	0.674	26.186
O1	-0.740	-0.760	3.186
O2	-0.740	-0.760	3.186

Table S377: Interaction energies and geometries between probe water and selected (2E)-2-(methyliminiumyl)propanoate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	NZ-CE	0.0	-17.41/-18.50/-17.99	2.01/1.89/1.92
2	NZ-CE	90.0	-9.47/-9.14/-7.82	2.29/2.10/2.23
3	NZ-CE	180.0	-7.28/-5.07/-3.42	2.29/2.25/2.61
4	NZ-CE	270.0	-9.46/-9.13/-7.82	2.29/2.10/2.23
5	O1-CX2	0.0	-14.23/-14.69/-15.29	1.73/1.66/1.65
6	O1-CX2	90.0	-13.64/-13.77/-14.86	1.75/1.67/1.65
7	O1-CX2	180.0	-13.72/-13.38/-14.83	1.74/1.67/1.65
8	O1-CX2	270.0	-13.64/-13.77/-14.86	1.75/1.67/1.65
9	O2-CX2	0.0	-12.82/-12.41/-13.36	1.74/1.67/1.66
10	O2-CX2	90.0	-13.48/-13.04/-14.25	1.72/1.67/1.65
11	O2-CX2	180.0	-13.97/-13.68/-15.09	1.72/1.66/1.65
12	O2-CX2	270.0	-13.48/-13.04/-14.25	1.72/1.67/1.65

1.122 Small molecule used for kynurenine(KYN)

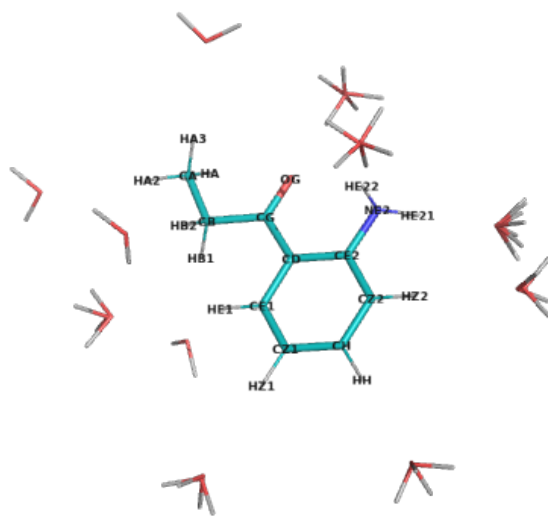


Figure S114: The molecule used for water complex calculations corresponding to 1-(2-aminophenyl)propan-1-one, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S378: Statistics of calculated water interaction and dipole moment for 1-(2-aminophenyl)propan-1-one.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.87/1.69	0.12/0.21	3.192	2.46/3.76	11.50
Optimal	0.27/0.53	0.10/0.18	2.022	2.46/2.93	3.43

Table S379: The comparison list of optimized atomic charges and their initial guess for 1-(2-aminophenyl)propan-1-one, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.269	0.000
HA	0.090	0.090	0.000
CB	-0.190	-0.172	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.310	0.340	2.100
OG	-0.390	-0.470	0.000
CD	0.011	0.118	18.783
CE2	0.156	0.089	22.398
NE2	-0.763	-0.866	20.858
HE21	0.343	0.382	0.000
HE22	0.343	0.382	0.000
CE1	-0.115	-0.111	0.000
HE1	0.115	0.115	0.000
CZ2	-0.115	-0.109	0.000
HZ2	0.115	0.115	0.000
CZ1	-0.115	-0.114	0.000
HZ1	0.115	0.115	0.000
CH	-0.115	-0.110	0.000
HH	0.115	0.115	0.000

Table S380: Interaction energies and geometries between probe water and selected 1-(2-aminophenyl)propan-1-one site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA2-CA	0.0	-0.74/-0.56/-0.68	2.87/2.79/2.77
2	HB1-CB	0.0	-1.69/-1.45/-1.84	2.59/2.67/2.65
3	HB2-CB	0.0	-1.60/-1.36/-1.77	2.58/2.67/2.64
4	OG-CG	0.0	-5.08/-5.60/-6.77	1.85/1.69/1.66
5	OG-CG	90.0	-5.37/-5.35/-6.62	1.82/1.70/1.66
6	OG-CG	180.0	-3.69/-3.79/-5.01	1.90/1.75/1.70
7	OG-CG	270.0	-4.85/-4.76/-5.93	1.83/1.71/1.67
8	NE2-CE2	0.0	-4.41/-4.42/-5.70	2.04/2.00/1.95
9	NE2-CE2	90.0	-4.93/-5.40/-6.58	2.01/1.97/1.93
10	NE2-CE2	180.0	-4.61/-4.91/-5.92	2.03/1.97/1.93
11	NE2-CE2	270.0	-4.00/-3.96/-5.15	2.05/2.00/1.96
12	HE21-NE2	0.0	-4.29/-4.35/-4.31	2.00/1.93/1.92
13	HE21-NE2	45.0	-4.83/-4.56/-4.52	1.97/1.93/1.91
14	HE21-NE2	90.0	-4.75/-4.55/-4.51	1.97/1.93/1.91
15	HE21-NE2	135.0	-4.21/-4.34/-4.30	2.01/1.94/1.92
16	HE1-CE1	0.0	-1.95/-2.35/-2.84	2.87/2.77/2.74
17	HE1-CE1	90.0	-1.99/-2.34/-2.86	2.95/2.77/2.74
18	HZ2-CZ2	0.0	-1.66/-1.55/-1.39	2.67/2.68/2.69
19	HZ2-CZ2	90.0	-2.17/-1.71/-1.56	2.51/2.66/2.67
20	HZ1-CZ1	0.0	-1.28/-1.41/-1.60	2.70/2.69/2.67
21	HZ1-CZ1	90.0	-1.50/-1.48/-1.68	2.62/2.68/2.66
22	HH-CH	0.0	-1.64/-1.31/-1.38	2.58/2.69/2.68
23	HH-CH	90.0	-1.82/-1.38/-1.45	2.53/2.68/2.68

1.123 Small molecule A of N6-[(6R)-6,8-disulfanyloctanoyl]-L-lysine(LA2)

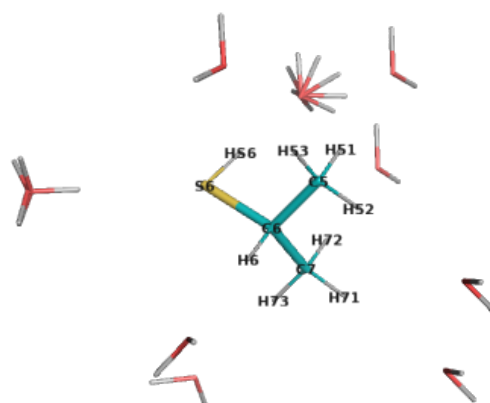


Figure S115: The molecule used for water complex calculations corresponding to propane-2-thiol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S381: Statistics of calculated water interaction and dipole moment for propane-2-thiol.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.64/1.14	0.29/0.45	2.174	1.87/1.60	12.76
Optimal	0.47/0.97	0.27/0.42	1.888	1.87/2.00	3.48

Table S382: The comparison list of optimized atomic charges and their initial guess for propane-2-thiol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
H53	0.090	0.090	0.300
C5	-0.270	-0.269	0.671
H51	0.090	0.090	0.300
H52	0.090	0.090	0.300
C6	0.075	0.006	6.485
H6	0.090	0.090	0.424
S6	-0.289	-0.258	6.485
HS6	0.124	0.160	0.520
C7	-0.270	-0.269	0.671
H71	0.090	0.090	0.300
H72	0.090	0.090	0.300
H73	0.090	0.090	0.300

Table S383: Interaction energies and geometries between probe water and selected propane-2-thiol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	H53-C5	0.0	-0.46/-0.58/-0.49	2.81/2.73/2.75
2	H51-C5	0.0	-1.34/-1.09/-1.12	2.73/2.71/2.72
3	H52-C5	0.0	-1.13/-1.13/-0.90	2.77/2.71/2.74
4	H6-C6	0.0	-1.39/-0.96/-0.63	2.61/2.71/2.76
5	S6-C6	0.0	-1.67/-2.61/-2.19	2.74/2.34/2.37
6	S6-C6	90.0	-1.76/-2.53/-2.24	2.69/2.34/2.37
7	S6-C6	180.0	-1.40/-2.38/-2.23	2.77/2.35/2.37
8	S6-C6	270.0	-1.76/-2.53/-2.24	2.69/2.34/2.37
9	HS6-S6	0.0	-1.70/-1.76/-2.84	2.45/2.08/2.00
10	HS6-S6	45.0	-1.86/-1.80/-2.86	2.42/2.08/2.00
11	HS6-S6	90.0	-2.04/-1.84/-2.90	2.38/2.07/2.00
12	HS6-S6	135.0	-1.86/-1.80/-2.86	2.42/2.08/2.00
13	H71-C7	0.0	-1.11/-1.12/-0.91	2.78/2.71/2.74
14	H72-C7	0.0	-1.17/-1.06/-1.05	2.78/2.72/2.74
15	H73-C7	0.0	-0.68/-0.68/-0.58	2.74/2.71/2.73

1.124 Small molecule used for Penicillamine(LE1)

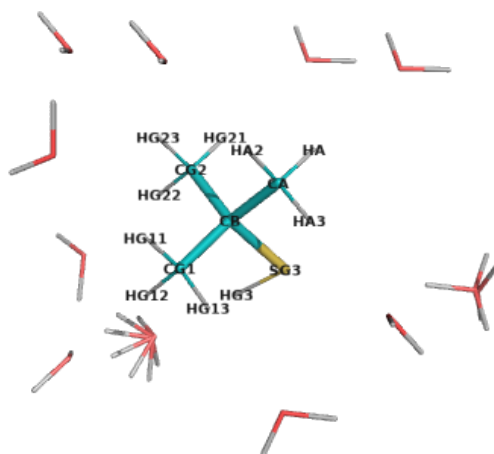


Figure S116: The molecule used for water complex calculations corresponding to 2-methylpropane-2-thiol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S384: Statistics of calculated water interaction and dipole moment for 2-methylpropane-2-thiol.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.93/1.94	0.32/0.54	3.419	1.88/1.08	47.89
Optimal	0.64/1.39	0.32/0.62	1.901	1.88/2.22	0.09

Table S385: The comparison list of optimized atomic charges and their initial guess for 2-methylpropane-2-thiol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.810
HA2	0.090	0.090	0.810
CA	-0.270	-0.329	10.272
HA	0.090	0.090	0.810
CB	0.107	0.218	21.447
SG3	-0.279	-0.201	15.950
HG3	0.114	0.160	1.561
CG2	-0.241	-0.329	10.272
HG23	0.090	0.090	0.810
HG21	0.090	0.090	0.810
HG22	0.090	0.090	0.810
CG1	-0.241	-0.329	10.272
HG11	0.090	0.090	0.810
HG12	0.090	0.090	0.810
HG13	0.090	0.090	0.810

Table S386: Interaction energies and geometries between probe water and selected 2-methylpropane-2-thiol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.97/-0.47/-0.33		2.65/2.74/2.78	
2	HA2-CA	0.0	-1.26/-1.06/-0.56		2.73/2.73/2.78	
3	HA-CA	0.0	-0.64/-0.34/-0.27		2.75/2.77/2.80	
4	SG3-CB	0.0	-1.55/-2.83/-1.61		2.92/2.33/2.43	
5	SG3-CB	90.0	-1.60/-2.78/-1.75		2.87/2.33/2.42	
6	SG3-CB	180.0	-1.28/-2.67/-1.88		2.95/2.33/2.40	
7	SG3-CB	270.0	-1.60/-2.78/-1.75		2.87/2.33/2.42	
8	HG3-SG3	0.0	-1.70/-1.58/-3.65		2.46/2.11/1.97	
9	HG3-SG3	45.0	-1.88/-1.63/-3.67		2.42/2.11/1.97	
10	HG3-SG3	90.0	-2.06/-1.68/-3.70		2.38/2.10/1.97	
11	HG3-SG3	135.0	-1.88/-1.63/-3.67		2.42/2.11/1.97	
12	HG23-CG2	0.0	-1.13/-1.24/-0.66		2.78/2.70/2.77	
13	HG21-CG2	0.0	-0.70/-0.74/-0.54		2.74/2.70/2.75	
14	HG22-CG2	0.0	-1.20/-1.20/-1.09		2.78/2.70/2.74	
15	HG11-CG1	0.0	-1.13/-1.24/-0.66		2.78/2.70/2.77	
16	HG12-CG1	0.0	-1.20/-1.20/-1.09		2.78/2.69/2.74	
17	HG13-CG1	0.0	-0.70/-0.74/-0.54		2.74/2.70/2.75	

1.125 Small molecule used for (4r)-5-oxo-l-leucine(LED)

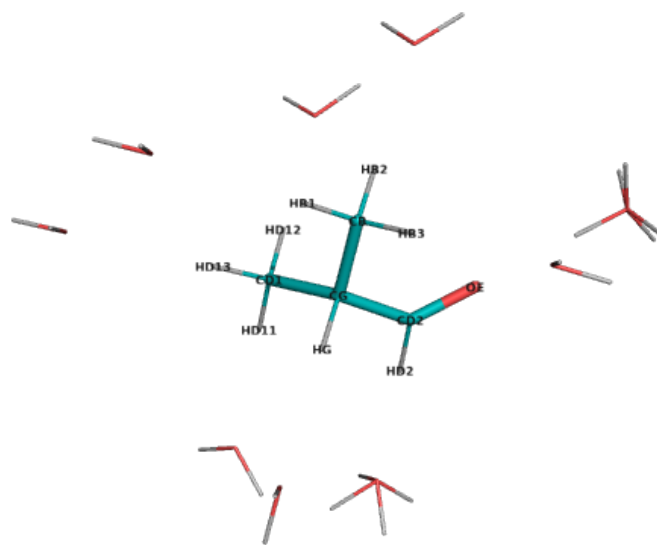


Figure S117: The molecule used for water complex calculations corresponding to 2-methylpropanal, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S387: Statistics of calculated water interaction and dipole moment for 2-methylpropanal.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.36/0.74	0.14/0.33	1.505	3.13/3.32	1.10
Optimal	0.20/0.42	0.13/0.29	2.205	3.13/3.63	5.38

Table S388: The comparison list of optimized atomic charges and their initial guess for 2-methylpropanal, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.150
CB	-0.270	-0.269	2.044
HB1	0.090	0.090	0.150
HB2	0.090	0.090	0.150
CG	0.010	0.002	5.265
HG	0.090	0.090	0.408
CD1	-0.225	-0.269	2.044
HD11	0.090	0.090	0.150
HD12	0.090	0.090	0.150
HD13	0.090	0.090	0.150
CD2	0.158	0.217	5.309
HD2	0.074	0.089	0.587
OE	-0.377	-0.400	0.579

Table S389: Interaction energies and geometries between probe water and selected 2-methylpropanal site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.63/-0.21/-0.26		2.68/2.72/2.72	
2	HB1-CB	0.0	-1.01/-1.11/-1.01		2.81/2.73/2.73	
3	HB2-CB	0.0	-0.42/-0.12/-0.08		2.80/2.78/2.78	
4	HG-CG	0.0	-1.66/-1.75/-1.77		2.65/2.67/2.67	
5	HD11-CD1	0.0	-1.60/-1.83/-1.72		2.72/2.64/2.67	
6	HD12-CD1	0.0	-1.45/-1.26/-1.07		2.64/2.64/2.66	
7	HD13-CD1	0.0	-1.35/-1.54/-1.25		2.72/2.67/2.70	
8	HD2-CD2	0.0	-1.84/-1.92/-2.57		2.58/2.29/2.24	
9	HD2-CD2	90.0	-1.83/-1.93/-2.57		2.57/2.29/2.24	
10	OE-CD2	0.0	-4.80/-4.89/-5.01		1.90/1.82/1.81	
11	OE-CD2	90.0	-4.85/-5.02/-5.07		1.90/1.82/1.81	
12	OE-CD2	180.0	-5.03/-5.11/-5.13		1.90/1.82/1.81	
13	OE-CD2	270.0	-4.83/-5.01/-5.11		1.91/1.82/1.81	

1.126 Small molecule used for (4s)-5-fluoro-1-leucine(LEF)

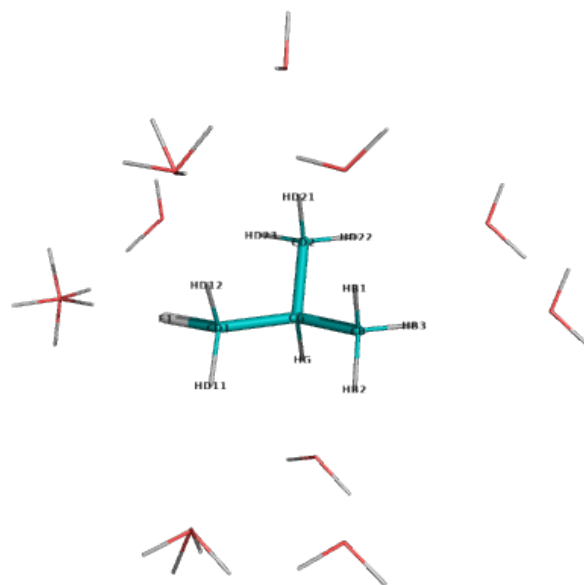


Figure S118: The molecule used for water complex calculations corresponding to 1-fluoro-2-methylpropane, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S390: Statistics of calculated water interaction and dipole moment for 1-fluoro-2-methylpropane.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.08/0.17	0.13/0.24	1.066	2.01/2.19	1.53
Optimal	0.06/0.12	0.14/0.24	1.213	2.01/2.31	2.11

Table S391: The comparison list of optimized atomic charges and their initial guess for 1-fluoro-2-methylpropane, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.600
CB	-0.270	-0.271	6.162
HB2	0.090	0.090	0.600
HB1	0.090	0.090	0.600
CG	0.008	-0.023	15.062
HG	0.090	0.090	1.460
CD1	-0.171	-0.065	16.199
HD11	0.141	0.110	3.626
HD12	0.141	0.110	3.626
F1	-0.209	-0.220	3.626
CD2	-0.270	-0.271	6.162
HD21	0.090	0.090	0.600
HD22	0.090	0.090	0.600
HD23	0.090	0.090	0.600

Table S392: Interaction energies and geometries between probe water and selected 1-fluoro-2-methylpropane site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.06/-1.00/-0.94		2.77/2.72/2.73	
2	HB2-CB	0.0	-1.22/-1.27/-1.25		2.77/2.70/2.70	
3	HB1-CB	0.0	-1.22/-1.21/-1.18		2.76/2.71/2.71	
4	HG-CG	0.0	-0.85/-0.73/-0.72		2.76/2.74/2.74	
5	HD11-CD1	0.0	-1.36/-1.38/-1.29		2.66/2.61/2.63	
6	HD11-CD1	90.0	-1.44/-1.42/-1.33		2.63/2.61/2.63	
7	HD12-CD1	0.0	-1.31/-1.31/-1.22		2.68/2.62/2.64	
8	HD12-CD1	90.0	-1.42/-1.34/-1.25		2.64/2.62/2.63	
9	F1-CD1	0.0	-3.21/-3.29/-3.23		2.10/1.85/1.86	
10	F1-CD1	90.0	-3.33/-3.36/-3.30		2.09/1.85/1.85	
11	F1-CD1	180.0	-3.38/-3.39/-3.33		2.09/1.85/1.85	
12	F1-CD1	270.0	-3.30/-3.34/-3.28		2.09/1.85/1.85	
13	HD21-CD2	0.0	-0.83/-0.77/-0.76		2.86/2.76/2.76	
14	HD22-CD2	0.0	-0.81/-0.78/-0.74		2.84/2.75/2.76	

1.127 Small molecule A of (2S)-2-amino-6-[[3-hydroxy-2-methyl-5-(phosphonoxyethyl)pyridin-4-yl]methylideneamino]hexanoic acid (LLPP)

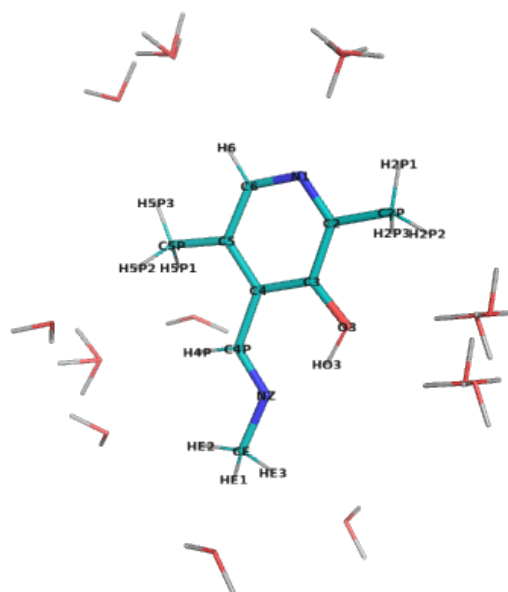


Figure S119: The molecule used for water complex calculations corresponding to 2,5-dimethyl-4-[(E)-(methylimino)methyl]pyridin-3-olate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S393: Statistics of calculated water interaction and dipole moment for 2,5-dimethyl-4-[(E)-(methylimino)methyl]pyridin-3-olate.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.65/1.45	0.11/0.24	4.628	4.78/5.30	25.14
Optimal	0.23/0.53	0.08/0.16	2.847	4.78/6.21	0.00

Table S394: The comparison list of optimized atomic charges and their initial guess for 2,5-dimethyl-4-[(E)-(methylimino)methyl]pyridin-3-olate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HE3	0.090	0.090	0.025
CE	0.030	-0.052	3.180
HE1	0.090	0.090	0.025
HE2	0.090	0.090	0.025
NZ	-0.507	-0.600	3.182
C4P	-0.032	-0.099	14.915
H4P	0.105	0.240	0.250
C4	0.234	0.245	20.733
C3	0.050	0.091	2.104
O3	-0.495	-0.529	2.104
HO3	0.382	0.420	0.000
C2	0.302	0.357	17.715
C2P	-0.270	-0.267	16.637
H2P1	0.090	0.090	2.250
H2P2	0.090	0.090	2.250
H2P3	0.090	0.090	2.250
N1	-0.577	-0.621	14.965
C6	0.074	0.153	2.500
H6	0.099	0.121	0.000
C5	0.065	-0.002	12.965
C5P	-0.270	-0.267	12.965
H5P1	0.090	0.090	0.000
H5P2	0.090	0.090	0.000
H5P3	0.090	0.090	0.000

Table S395: Interaction energies and geometries between probe water and selected 2,5-dimethyl-4-[(E)-(methylimino)methyl]pyridin-3-olate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HE3-CE	0.0	-1.47/-1.59/-0.58		2.64/2.63/2.74	
2	HE1-CE	0.0	-1.47/-1.59/-0.58		2.64/2.63/2.74	
3	HE2-CE	0.0	-2.31/-2.58/-2.31		2.65/2.61/2.65	
4	NZ-CE	0.0	-3.19/-3.45/-3.38		4.04/3.96/3.95	
5	NZ-CE	90.0	-2.23/-2.13/-2.40		4.19/4.15/4.12	
6	NZ-CE	180.0	-1.64/-1.27/-1.77		4.27/4.30/4.24	
7	NZ-CE	270.0	-2.23/-2.13/-2.40		4.19/4.15/4.12	
8	H4P-C4P	0.0	-2.62/-2.76/-3.94		2.74/2.71/2.57	
9	H4P-C4P	90.0	-2.72/-3.00/-4.17		2.79/2.68/2.55	
10	O3-C3	0.0	-3.06/-2.88/-3.23		2.20/2.34/2.31	
11	O3-C3	90.0	-2.77/-2.89/-2.91		2.39/2.35/2.33	
12	O3-C3	180.0	-2.52/-2.84/-2.48		2.52/2.37/2.38	
13	O3-C3	270.0	-2.78/-2.89/-2.91		2.39/2.35/2.33	
14	N1-C2	0.0	-6.04/-6.25/-5.84		1.95/1.86/1.85	
15	N1-C2	90.0	-6.92/-6.66/-6.42		1.91/1.85/1.84	
16	N1-C2	180.0	-5.93/-6.46/-6.28		1.98/1.86/1.85	
17	N1-C2	270.0	-6.92/-6.66/-6.42		1.91/1.85/1.84	
18	H6-C6	0.0	-1.13/-1.18/-2.14		2.66/2.50/2.43	
19	H6-C6	90.0	-1.35/-1.22/-2.18		2.58/2.50/2.43	
20	H5P1-C5P	0.0	-1.91/-2.08/-2.63		2.62/2.62/2.59	
21	H5P2-C5P	0.0	-1.91/-2.08/-2.63		2.62/2.62/2.59	
22	H5P3-C5P	0.0	-1.75/-1.98/-2.38		2.67/2.62/2.61	

1.128 Small molecule used for (3r)-3-methyl-1-glutamicacid(LME)

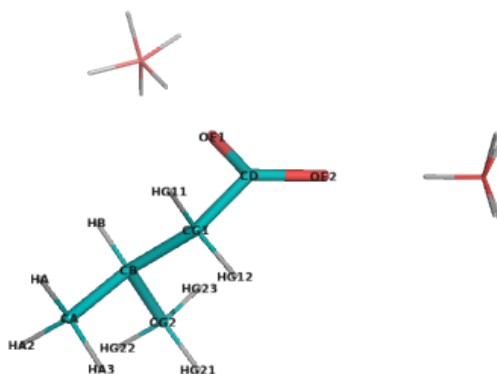


Figure S120: The molecule used for water complex calculations corresponding to 3-methylbutanoic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S396: Statistics of calculated water interaction and dipole moment for 3-methylbutanoic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.56/0.78	0.07/0.07	3.170	9.13/10.07	1.82
Optimal	0.16/0.26	0.06/0.06	3.122	9.13/9.52	2.66

Table S397: The comparison list of optimized atomic charges and their initial guess for 3-methylbutanoic acid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.271	0.345
HA	0.090	0.090	0.000
CB	-0.090	-0.086	3.888
HB	0.090	0.090	0.000
CG2	-0.270	-0.271	0.345
HG21	0.090	0.090	0.000
HG22	0.090	0.090	0.000
HG23	0.090	0.090	0.000
CG1	-0.404	-0.344	5.345
HG12	0.090	0.090	0.000
HG11	0.090	0.090	0.000
CD	0.694	0.682	5.469
OE1	-0.735	-0.760	0.000
OE2	-0.735	-0.760	0.000

Table S398: Interaction energies and geometries between probe water and selected 3-methylbutanoic acid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	OE1-CD	0.0	-13.90/-14.03/-14.42	1.72/1.66/1.65
2	OE1-CD	90.0	-14.23/-14.41/-14.93	1.72/1.66/1.65
3	OE1-CD	180.0	-14.74/-14.89/-15.52	1.71/1.65/1.64
4	OE1-CD	270.0	-14.23/-14.41/-14.92	1.72/1.66/1.65
5	OE2-CD	0.0	-14.05/-13.79/-14.19	1.72/1.66/1.65
6	OE2-CD	90.0	-14.31/-14.20/-14.72	1.72/1.66/1.65
7	OE2-CD	180.0	-14.81/-14.71/-15.33	1.71/1.65/1.65
8	OE2-CD	270.0	-14.31/-14.20/-14.72	1.72/1.66/1.65

1.129 Small molecule used for 4-oxo-l-valine(LVN)

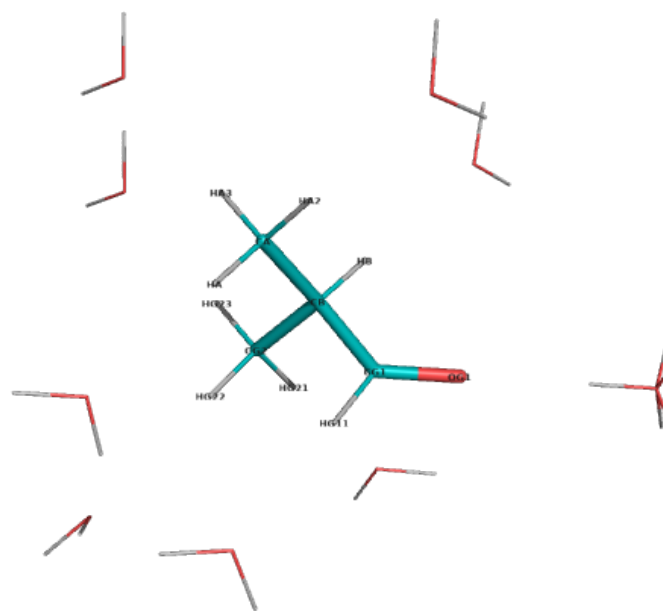


Figure S121: The molecule used for water complex calculations corresponding to 2-methylpropanal, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S399: Statistics of calculated water interaction and dipole moment for 2-methylpropanal.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.26/0.72	0.11/0.34	1.256	3.29/3.32	1.82
Optimal	0.19/0.33	0.11/0.32	1.940	3.29/3.75	4.47

Table S400: The comparison list of optimized atomic charges and their initial guess for 2-methylpropanal, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.150
HA2	0.090	0.090	0.150
CA	-0.270	-0.269	2.044
HA	0.090	0.090	0.150
CB	0.044	0.002	5.265
HB	0.090	0.090	0.408
CG1	0.140	0.217	5.309
HG11	0.088	0.089	0.587
OG1	-0.391	-0.400	0.579
CG2	-0.241	-0.269	2.044
HG21	0.090	0.090	0.150
HG22	0.090	0.090	0.150
HG23	0.090	0.090	0.150

Table S401: Interaction energies and geometries between probe water and selected 2-methylpropanal site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-1.41/-1.40/-1.24		2.72/2.69/2.71	
2	HA2-CA	0.0	-1.31/-0.98/-1.00		2.63/2.66/2.66	
3	HA-CA	0.0	-1.68/-1.67/-1.66		2.69/2.67/2.67	
4	HB-CB	0.0	-0.74/-0.82/-0.69		2.70/2.70/2.71	
5	HG11-CG1	0.0	-1.77/-2.03/-2.48		2.59/2.28/2.25	
6	OG1-CG1	0.0	-4.86/-4.96/-4.85		1.90/1.82/1.82	
7	OG1-CG1	90.0	-4.88/-5.13/-4.93		1.90/1.81/1.82	
8	OG1-CG1	180.0	-5.05/-5.22/-4.98		1.90/1.81/1.82	
9	OG1-CG1	270.0	-4.88/-5.09/-4.93		1.91/1.81/1.82	
10	HG21-CG2	0.0	-1.45/-1.24/-1.08		2.61/2.63/2.65	
11	HG22-CG2	0.0	-1.57/-1.74/-1.61		2.72/2.66/2.68	
12	HG23-CG2	0.0	-1.39/-1.53/-1.24		2.72/2.67/2.71	

1.130 Small molecule A of N''-(2-coenzymeA)-propanoyl-lysine(LYX)

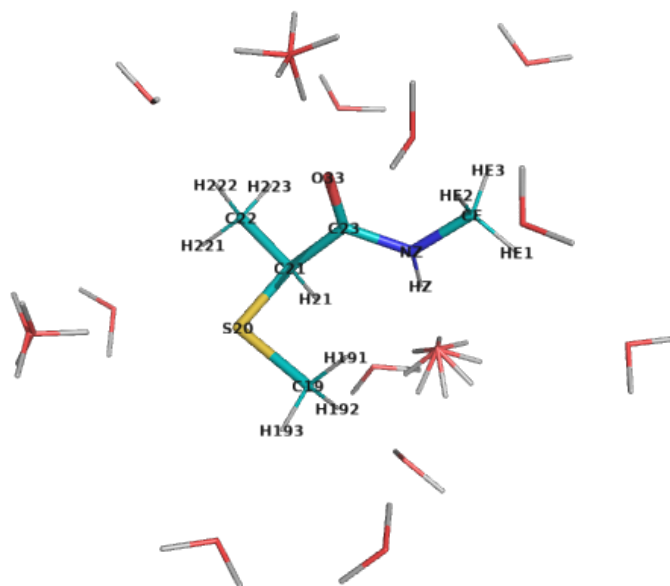


Figure S122: The molecule used for water complex calculations corresponding to (2S)-N-methyl-2-(methylsulfanyl)propanamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S402: Statistics of calculated water interaction and dipole moment for (2S)-N-methyl-2-(methylsulfanyl)propanamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.38/0.67	0.20/0.47	2.243	4.82/4.84	7.50
Optimal	0.40/0.72	0.21/0.49	2.014	4.82/4.89	5.58

Table S403: The comparison list of optimized atomic charges and their initial guess for (2S)-N-methyl-2-(methylsulfanyl)propanamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HE3	0.090	0.090	0.000
CE	-0.110	-0.108	0.000
HE1	0.090	0.090	0.000
HE2	0.090	0.090	0.000
NZ	-0.470	-0.470	2.500
HZ	0.310	0.312	0.000
C23	0.510	0.498	4.288
O33	-0.510	-0.508	2.105
C21	-0.040	-0.063	15.051
H21	0.090	0.090	0.424
C22	-0.270	-0.269	0.671
H221	0.090	0.090	0.300
H222	0.090	0.090	0.300
H223	0.090	0.090	0.300
S20	-0.100	-0.072	15.052
C19	-0.220	-0.220	2.563
H191	0.090	0.090	0.030
H192	0.090	0.090	0.030
H193	0.090	0.090	0.030

Table S404: Interaction energies and geometries between probe water and selected (2S)-N-methyl-2-(methylsulfanyl)propanamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HE3-CE	0.0	-1.19/-1.10/-1.07	2.70/2.67/2.67
2	HE1-CE	0.0	-1.74/-1.64/-1.63	2.66/2.66/2.66
3	HZ-NZ	0.0	-6.41/-7.10/-7.02	1.96/1.91/1.91
4	HZ-NZ	45.0	-6.65/-7.16/-7.09	1.94/1.90/1.90
5	HZ-NZ	90.0	-6.91/-7.26/-7.17	1.93/1.90/1.90
6	HZ-NZ	135.0	-6.67/-7.19/-7.10	1.94/1.90/1.90
7	O33-C23	0.0	-5.85/-6.45/-6.52	1.84/1.76/1.76
8	O33-C23	90.0	-6.09/-6.65/-6.74	1.84/1.76/1.76
9	O33-C23	180.0	-6.53/-7.02/-7.06	1.83/1.76/1.75
10	O33-C23	270.0	-6.45/-6.95/-6.97	1.83/1.76/1.75
11	H21-C21	0.0	-2.66/-2.99/-2.89	2.60/2.63/2.63
12	H221-C22	0.0	-0.78/-0.64/-0.63	2.69/2.74/2.74
13	H223-C22	0.0	-0.82/-0.70/-0.61	2.80/2.74/2.75
14	S20-C21	0.0	-1.22/-1.51/-1.28	2.96/2.46/2.49
15	S20-C21	90.0	-1.86/-2.15/-1.95	2.85/2.42/2.45
16	S20-C21	180.0	-1.39/-1.72/-1.56	2.94/2.45/2.47
17	S20-C21	270.0	-1.28/-1.22/-1.02	2.89/2.48/2.51
18	H191-C19	0.0	-0.68/-0.57/-0.57	4.67/4.50/4.50
19	H192-C19	0.0	-2.17/-2.17/-2.19	2.66/2.67/2.67
20	H193-C19	0.0	-1.50/-0.78/-0.85	2.57/2.71/2.71

1.131 Small molecule used for S-(hydroxymethyl)-L-cysteine(MOH)

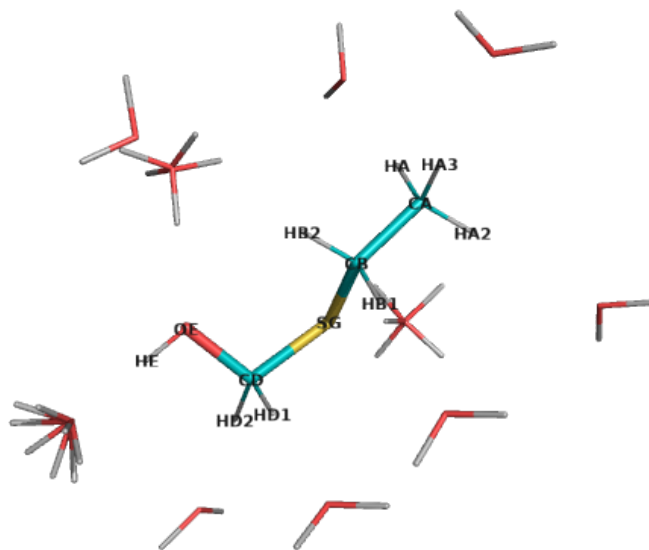


Figure S123: The molecule used for water complex calculations corresponding to (ethylsulfanyl)methanol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S405: Statistics of calculated water interaction and dipole moment for (ethylsulfanyl)methanol.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.70/1.26	0.25/0.57	2.430	2.67/3.26	11.81
Optimal	0.52/1.12	0.25/0.56	1.653	2.67/2.96	4.12

Table S406: The comparison list of optimized atomic charges and their initial guess for (ethylsulfanyl)methanol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.045
HA	0.090	0.090	0.000
CB	-0.048	-0.066	14.230
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
SG	-0.211	-0.226	29.077
CD	0.073	0.162	24.057
HD1	0.090	0.090	0.000
HD2	0.090	0.090	0.000
OE	-0.572	-0.650	21.538
HE	0.398	0.420	2.500

Table S407: Interaction energies and geometries between probe water and selected (ethylsulfanyl)methanol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.89/-0.73/-0.63	2.79/2.75/2.76
2	HA2-CA	0.0	-0.66/-0.33/-0.25	2.74/2.77/2.78
3	HA-CA	0.0	-0.54/-0.09/0.04	2.70/2.75/2.77
4	HB1-CB	0.0	-0.97/-1.15/-1.11	2.80/2.73/2.74
5	SG-CB	0.0	-1.50/-2.46/-2.40	2.91/2.36/2.36
6	SG-CB	90.0	-1.89/-2.94/-3.03	2.83/2.33/2.33
7	SG-CB	180.0	-1.49/-2.61/-2.75	2.91/2.35/2.34
8	SG-CB	270.0	-1.60/-2.28/-2.28	2.85/2.37/2.36
9	HD1-CD	0.0	-1.72/-1.99/-2.34	2.64/2.64/2.61
10	HD2-CD	0.0	-1.44/-1.11/-1.47	2.60/2.68/2.64
11	OE-CD	0.0	-5.06/-4.65/-5.28	1.89/1.93/1.90
12	OE-CD	90.0	-4.46/-4.77/-5.52	1.92/1.92/1.89
13	OE-CD	180.0	-6.28/-6.68/-7.41	1.86/1.87/1.85
14	OE-CD	270.0	-6.03/-5.94/-6.53	1.86/1.90/1.87
15	HE-OE	0.0	-6.61/-6.85/-7.14	1.80/1.82/1.81
16	HE-OE	45.0	-6.72/-6.89/-7.20	1.79/1.82/1.81
17	HE-OE	90.0	-6.84/-6.95/-7.27	1.78/1.82/1.81
18	HE-OE	135.0	-6.73/-6.91/-7.21	1.79/1.82/1.81

1.132 Small molecule used for 3,3-dimethyl-methioninesulfoxide(M2S)

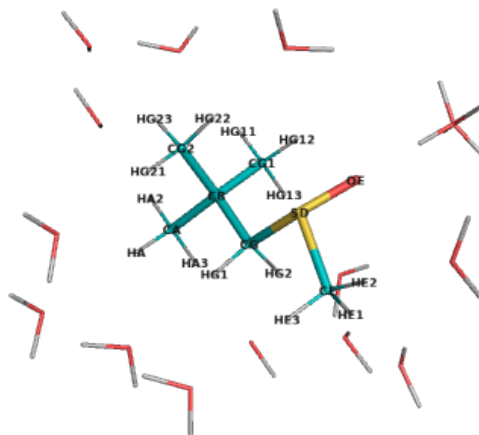


Figure S124: The molecule used for water complex calculations corresponding to (R)-(2,2-dimethylpropyl)(methyl)-lambda3-sulfanol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S408: Statistics of calculated water interaction and dipole moment for (R)-(2,2-dimethylpropyl)(methyl)-lambda3-sulfanol.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.55/1.06	0.08/0.15	2.444	4.35/5.28	3.89
Optimal	0.40/1.18	0.09/0.17	1.984	4.35/5.01	1.02

Table S409: The comparison list of optimized atomic charges and their initial guess for (R)-(2,2-dimethylpropyl)(methyl)-lambda3-sulfanol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	1.300
HA	0.090	0.090	0.000
CB	-0.000	0.003	2.264
CG1	-0.270	-0.270	1.300
HG13	0.090	0.090	0.000
HG11	0.090	0.090	0.000
HG12	0.090	0.090	0.000
CG2	-0.270	-0.270	1.300
HG21	0.090	0.090	0.000
HG22	0.090	0.090	0.000
HG23	0.090	0.090	0.000
CG	-0.041	-0.064	2.264
HG1	0.090	0.090	0.000
HG2	0.090	0.090	0.000
SD	0.261	0.311	2.264
OE	-0.505	-0.550	0.135
CE	-0.165	-0.150	0.135
HE1	0.090	0.090	0.000
HE2	0.090	0.090	0.000
HE3	0.090	0.090	0.000

Table S410: Interaction energies and geometries between probe water and selected (R)-(2,2-dimethylpropyl)(methyl)-lambda3-sulfanol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-1.16/-1.25/-1.20		2.77/2.71/2.71	
2	HA2-CA	0.0	-1.14/-0.88/-0.86		2.74/2.73/2.73	
3	HA-CA	0.0	-1.38/-1.49/-1.46		2.76/2.71/2.71	
4	HG13-CG1	0.0	-0.48/-0.37/-0.28		2.91/2.80/2.82	
5	HG11-CG1	0.0	-0.68/-0.43/-0.39		2.87/2.80/2.80	
6	HG21-CG2	0.0	-1.07/-1.33/-1.36		2.87/2.73/2.74	
7	HG22-CG2	0.0	-2.39/-1.21/-1.33		2.41/2.57/2.56	
8	HG23-CG2	0.0	-1.00/-0.70/-0.70		2.78/2.76/2.76	
9	HG1-CG	0.0	-2.39/-2.75/-2.78		2.59/2.61/2.62	
10	HG2-CG	0.0	-1.65/-1.62/-1.53		2.61/2.64/2.65	
11	OE-SD	0.0	-7.08/-7.30/-7.99		1.79/1.74/1.73	
12	OE-SD	90.0	-7.39/-7.68/-8.35		1.78/1.74/1.72	
13	OE-SD	180.0	-7.53/-7.70/-8.33		1.78/1.74/1.72	
14	OE-SD	270.0	-7.18/-7.32/-7.96		1.78/1.74/1.73	
15	HE1-CE	0.0	-1.92/-1.54/-1.63		2.49/2.61/2.60	
16	HE2-CE	0.0	-1.84/-1.09/-1.25		2.47/2.64/2.62	
17	HE3-CE	0.0	-2.42/-2.45/-2.63		2.52/2.60/2.59	

1.133 The dipeptide of N-methyl-L-alanine (MAA)

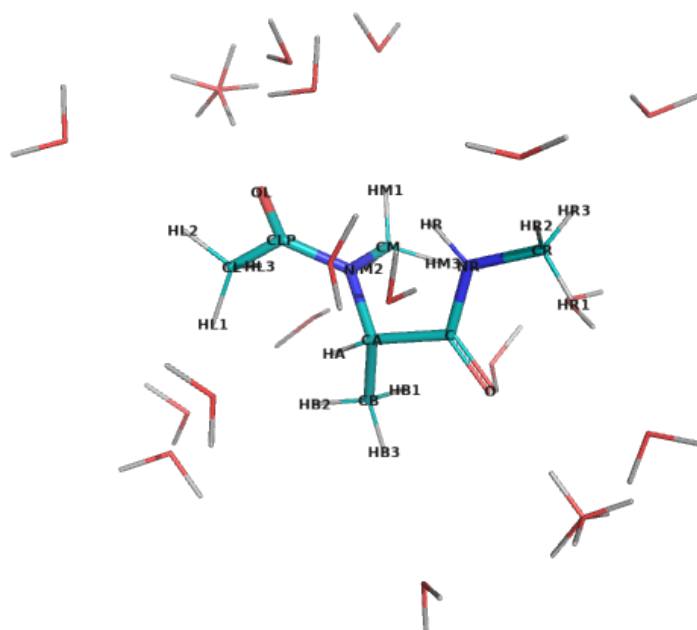


Figure S125: The molecule used for water complex calculations corresponding to (2S)-N-methyl-2-(N-methylacetamido)propanamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S411: Statistics of calculated water interaction and dipole moment for (2S)-N-methyl-2-(N-methylacetamido)propanamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.68/1.96	0.22/0.96	1.508	1.58/1.84	9.41
Optimal	0.44/1.49	0.22/0.94	1.157	1.58/1.77	7.63

Table S412: The comparison list of optimized atomic charges and their initial guess for (2S)-N-methyl-2-(N-methylacetamido)propanamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
N	-0.224	-0.297	11.002
CA	0.022	0.063	8.807
HA	0.090	0.090	0.945
CB	-0.270	-0.270	4.112
HB1	0.090	0.090	0.050
HB2	0.090	0.090	0.050
HB3	0.090	0.090	0.050
CM	-0.158	-0.088	3.627
HM1	0.090	0.090	0.075
HM2	0.090	0.090	0.075
HM3	0.090	0.090	0.075
C	0.510	0.508	2.616
O	-0.510	-0.513	0.414

Table S413: Interaction energies and geometries between probe water and selected (2S)-N-methyl-2-(N-methylacetamido)propanamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	O-C	0.0	-5.95/-6.22/-6.19	1.83/1.76/1.76
2	O-C	90.0	-6.08/-6.39/-6.39	1.83/1.76/1.76
3	O-C	180.0	-5.88/-6.28/-6.31	1.83/1.76/1.76
4	O-C	270.0	-6.00/-6.28/-6.28	1.83/1.76/1.76
5	NR-C	0.0	-1.42/-1.22/-1.45	2.22/2.22/2.21
6	HR-NR	0.0	-1.81/-0.31/0.15	3.29/4.24/4.25
7	HR2-CR	0.0	-1.32/-1.41/-1.40	2.73/2.68/2.68
8	HR3-CR	0.0	-1.39/-1.48/-1.49	2.72/2.67/2.67
9	HA-CA	0.0	-2.16/-2.50/-2.80	3.20/3.15/3.15
10	HL1-CL	0.0	-2.70/-2.42/-2.60	2.53/2.61/2.59
11	HL2-CL	0.0	-0.84/-0.58/-0.63	2.61/2.69/2.67
12	HL3-CL	0.0	-2.48/-3.09/-3.27	2.51/2.56/2.55
13	OL-CLP	0.0	-6.07/-6.27/-7.09	1.84/1.76/1.74
14	OL-CLP	90.0	-5.78/-5.97/-6.79	1.84/1.77/1.75
15	OL-CLP	180.0	-5.63/-5.86/-6.60	1.84/1.77/1.75
16	OL-CLP	270.0	-6.00/-6.26/-7.06	1.84/1.76/1.74
17	HB1-CB	0.0	-1.12/-1.19/-1.35	2.79/2.71/2.71
18	HB2-CB	0.0	-1.79/-1.83/-1.77	2.67/2.64/2.64
19	HM1-CM	0.0	-0.31/-0.29/-0.13	2.67/2.70/2.69
20	HM2-CM	0.0	-0.93/-0.99/-1.02	2.71/2.67/2.65
21	HM3-CM	0.0	-3.46/-2.73/-2.95	2.45/2.57/2.56

1.134 Small molecule A of N-methyl-L-alanine(MAA)

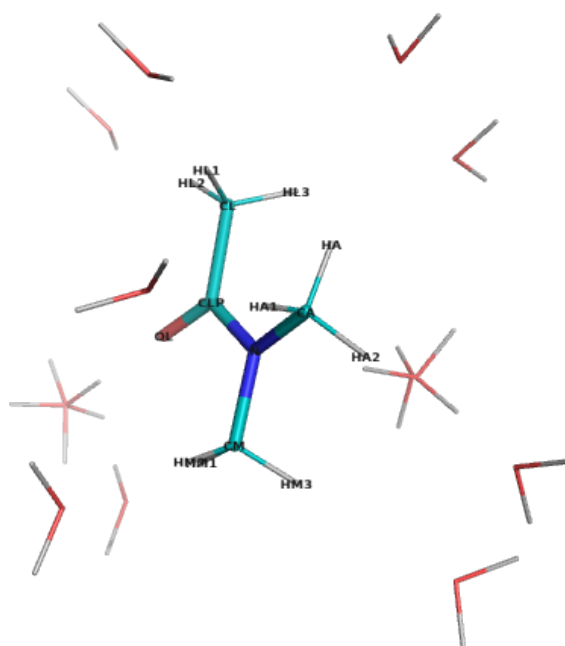


Figure S126: The molecule used for water complex calculations corresponding to N,N-dimethylacetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S414: Statistics of calculated water interaction and dipole moment for N,N-dimethylacetamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.70/1.48	0.06/0.13	2.251	4.09/4.73	1.30
Optimal	0.12/0.24	0.07/0.12	1.005	4.09/3.99	0.76

Table S415: The comparison list of optimized atomic charges and their initial guess for N,N-dimethylacetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.186	0.000
HL1	0.090	0.090	0.000
HL2	0.090	0.090	0.000
HL3	0.090	0.090	0.000
CLP	0.510	0.430	0.000
OL	-0.510	-0.531	0.000
N	-0.224	-0.347	0.000
CA	-0.158	-0.088	0.000
HA	0.090	0.090	0.000
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CM	-0.158	-0.088	0.000
HM1	0.090	0.090	0.000
HM2	0.090	0.090	0.000
HM3	0.090	0.090	0.000

Table S416: Interaction energies and geometries between probe water and selected N,N-dimethylacetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HL1-CL	0.0	-1.68/-1.58/-1.78	2.63/2.66/2.65
2	HL2-CL	0.0	-0.41/-0.18/-0.24	2.67/2.72/2.69
3	HL3-CL	0.0	-1.85/-1.61/-1.79	2.58/2.64/2.62
4	OL-CLP	0.0	-6.65/-6.55/-7.36	1.82/1.76/1.74
5	OL-CLP	90.0	-6.54/-6.48/-7.35	1.82/1.76/1.74
6	OL-CLP	180.0	-6.18/-6.23/-7.06	1.83/1.77/1.75
7	OL-CLP	270.0	-6.51/-6.44/-7.27	1.82/1.76/1.74
8	N-CLP	0.0	-1.05/-1.12/-1.81	2.19/2.26/2.18
9	N-CLP	90.0	-2.60/-2.69/-3.89	2.11/2.19/2.11
10	N-CLP	180.0	-2.34/-2.51/-3.82	2.14/2.21/2.11
11	N-CLP	270.0	-0.84/-0.87/-1.57	2.20/2.28/2.19
12	HA-CA	0.0	-1.93/-2.08/-2.41	3.02/2.96/2.94
13	HA1-CA	0.0	-1.59/-1.67/-1.86	2.69/2.64/2.62
14	HA2-CA	0.0	-1.69/-1.61/-1.81	2.67/2.66/2.64
15	HM2-CM	0.0	-0.89/-0.99/-1.04	2.82/2.70/2.69
16	HM3-CM	0.0	-1.15/-1.15/-1.25	2.76/2.69/2.68

1.135 Small molecule A of NZ-(1-carboxyethyl)-lysine(MCL)

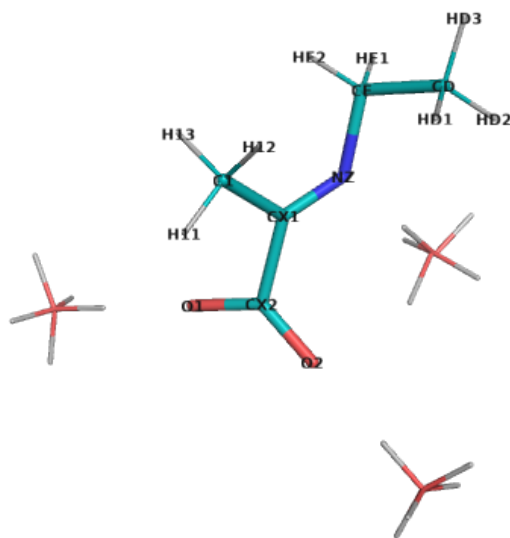


Figure S127: The molecule used for water complex calculations corresponding to (2E)-2-(ethylimino)propionoate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S417: Statistics of calculated water interaction and dipole moment for (2E)-2-(ethylimino)propionoate.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	1.51/3.20	0.07/0.09	4.083	10.56/12.05	5.28
Optimal	0.24/0.48	0.07/0.08	3.028	10.56/10.12	1.79

Table S418: The comparison list of optimized atomic charges and their initial guess for (2E)-2-(ethylimino)propanoate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HD3	0.090	0.090	0.000
CD	-0.270	-0.263	0.597
HD1	0.090	0.090	0.000
HD2	0.090	0.090	0.000
CE	-0.019	0.021	3.263
HE1	0.090	0.090	0.025
HE2	0.090	0.090	0.025
NZ	-0.693	-0.511	24.027
CX1	0.340	0.222	28.145
C1	-0.341	-0.332	8.472
H11	0.090	0.090	0.862
H12	0.090	0.090	0.862
H13	0.090	0.090	0.862
CX2	0.761	0.663	22.110
O1	-0.749	-0.760	3.186
O2	-0.749	-0.760	3.186

Table S419: Interaction energies and geometries between probe water and selected (2E)-2-(ethylimino)propanoate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	NZ-CE	0.0	-14.15/-14.31/-13.28	1.92/1.88/1.93
2	NZ-CE	90.0	-9.47/-9.31/-7.33	1.99/1.93/2.02
3	NZ-CE	180.0	-7.39/-6.91/-4.19	2.03/1.95/2.07
4	NZ-CE	270.0	-10.37/-10.54/-8.47	1.97/1.91/1.99
5	O1-CX2	0.0	-13.29/-13.09/-13.98	1.73/1.67/1.66
6	O1-CX2	90.0	-13.88/-13.86/-14.76	1.73/1.66/1.65
7	O1-CX2	180.0	-14.14/-13.96/-15.13	1.72/1.66/1.65
8	O1-CX2	270.0	-13.41/-13.13/-14.30	1.73/1.67/1.65
9	O2-CX2	0.0	-13.43/-13.69/-14.38	1.74/1.66/1.65
10	O2-CX2	90.0	-13.19/-13.21/-14.34	1.74/1.67/1.65
11	O2-CX2	180.0	-13.79/-13.84/-15.04	1.73/1.66/1.65
12	O2-CX2	270.0	-13.79/-14.16/-14.95	1.74/1.66/1.65

1.136 Small molecule used for malonylcysteine(MCS)

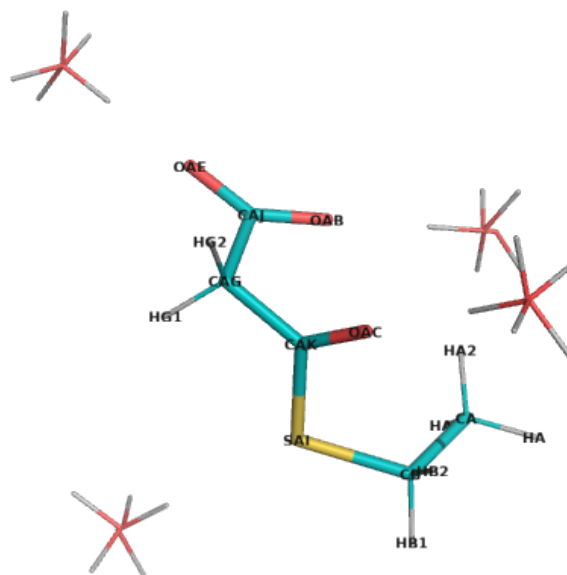


Figure S128: The molecule used for water complex calculations corresponding to 3-(ethylsulfanyl)-3-oxopropanoic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S420: Statistics of calculated water interaction and dipole moment for 3-(ethylsulfanyl)-3-oxopropanoic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	2.09/3.21	0.22/0.40	7.157	9.98/13.65	3.16
Optimal	0.57/1.90	0.23/0.45	3.036	9.98/10.20	1.25

Table S421: The comparison list of optimized atomic charges and their initial guess for 3-(ethylsulfanyl)-3-oxopropanoicacid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.620
HA	0.090	0.090	0.000
CB	-0.172	0.002	9.073
HB1	0.090	0.090	0.575
HB2	0.090	0.090	0.575
SAI	-0.202	-0.194	68.838
CAK	0.712	0.772	87.575
OAC	-0.485	-0.650	57.956
CAG	-0.454	-0.344	69.883
HG1	0.090	0.090	2.500
HG2	0.090	0.090	2.500
CAJ	0.569	0.574	34.780
OAE	-0.664	-0.760	2.450
OAB	-0.664	-0.760	2.450

Table S422: Interaction energies and geometries between probe water and selected 3-(ethylsulfanyl)-3-oxopropanoicacid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	SAI-CB	0.0	-4.22/-4.82/-4.32	2.80/2.37/2.40
2	SAI-CB	90.0	-4.37/-4.99/-4.44	2.75/2.34/2.37
3	SAI-CB	180.0	-2.48/-2.56/-1.50	2.87/2.42/2.50
4	SAI-CB	270.0	-2.74/-2.38/-1.46	2.81/2.44/2.53
5	OAC-CAK	0.0	-7.03/-7.10/-8.68	1.91/1.79/1.72
6	OAC-CAK	90.0	-8.52/-9.10/-11.65	1.88/1.76/1.70
7	OAC-CAK	180.0	-8.20/-8.49/-11.41	1.89/1.77/1.70
8	OAC-CAK	270.0	-7.03/-6.68/-8.88	1.90/1.79/1.72
9	OAE-CAJ	0.0	-12.51/-12.37/-14.19	1.75/1.68/1.65
10	OAE-CAJ	90.0	-12.86/-12.84/-15.03	1.75/1.68/1.65
11	OAE-CAJ	180.0	-13.35/-13.29/-15.62	1.74/1.67/1.64
12	OAE-CAJ	270.0	-12.85/-12.76/-14.73	1.75/1.68/1.65
13	OAB-CAJ	0.0	-9.03/-10.93/-12.21	1.99/1.77/1.72
14	OAB-CAJ	90.0	-11.13/-10.89/-12.48	1.78/1.75/1.70
15	OAB-CAJ	180.0	-11.37/-11.18/-13.93	1.76/1.74/1.69
16	OAB-CAJ	270.0	-11.50/-11.31/-14.02	1.77/1.74/1.69

1.137 Small molecule A of [2-((1S)-1-aminoethyl)-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl]acetic acid(MDO)

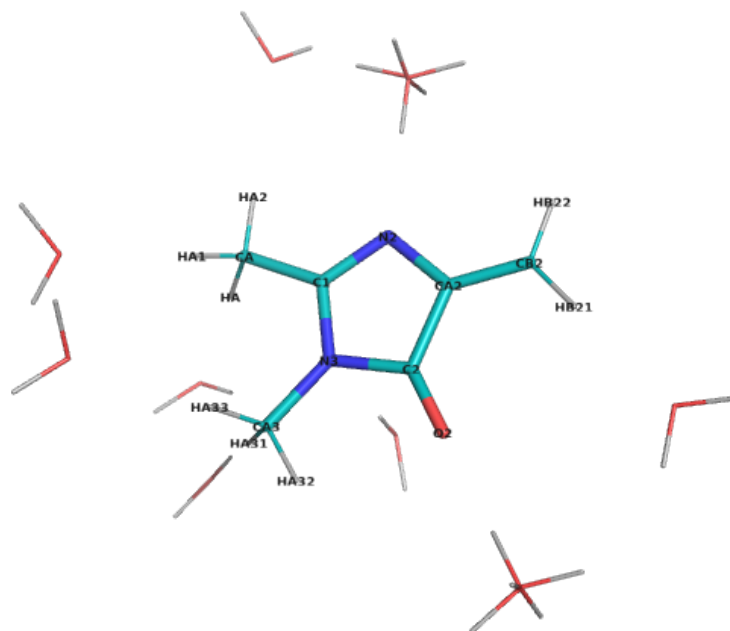


Figure S129: The molecule used for water complex calculations corresponding to 2,3-Dimethyl-5-methylideneimidazol-4-one, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S423: Statistics of calculated water interaction and dipole moment for 2,3-Dimethyl-5-methylideneimidazol-4-one.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.03/1.73	0.13/0.32	7.443	3.52/0.38	91.17
Optimal	0.29/0.55	0.09/0.24	2.372	3.52/4.22	3.15

Table S424: The comparison list of optimized atomic charges and their initial guess for 2,3-Dimethyl-5-methylideneimidazol-4-one, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
C1	0.233	0.074	23.781
N2	-0.679	-0.703	41.101
N3	-0.080	-0.079	15.264
C2	0.407	0.510	20.683
O2	-0.489	-0.482	6.517
CA2	0.466	0.510	42.336
CB2	-0.593	-0.444	13.655
HB21	0.230	0.230	0.950
HB22	0.230	0.230	0.950
CA3	-0.195	-0.271	3.821
HA31	0.090	0.090	0.000
HA32	0.090	0.090	0.000
HA33	0.090	0.090	0.000

Table S425: Interaction energies and geometries between probe water and selected 2,3-Dimethyl-5-methylideneimidazol-4-one site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	N2-C1	0.0	-6.45/-6.93/-6.29		1.93/1.91/1.91	
2	N2-C1	90.0	-7.05/-6.72/-7.36		1.88/1.91/1.89	
3	N2-C1	180.0	-5.75/-5.60/-7.43		1.95/1.93/1.90	
4	N2-C1	270.0	-7.05/-6.72/-7.36		1.88/1.91/1.89	
5	N3-C1	0.0	-0.04/-0.59/-0.97		2.80/2.56/2.49	
6	O2-C2	0.0	-5.18/-5.47/-5.21		1.87/1.78/1.79	
7	O2-C2	90.0	-5.56/-5.72/-4.91		1.86/1.78/1.80	
8	O2-C2	180.0	-5.66/-5.75/-4.38		1.86/1.78/1.81	
9	O2-C2	270.0	-5.56/-5.72/-4.91		1.86/1.78/1.80	
10	HB21-CB2	0.0	-1.50/-1.27/-3.23		2.33/2.48/2.41	
11	HA31-CA3	0.0	-2.30/-2.21/-1.14		2.57/2.63/2.70	
12	HA33-CA3	0.0	-2.30/-2.21/-1.14		2.57/2.63/2.70	
13	HA1-CA	0.0	-2.29/-2.75/-1.43		2.57/2.58/2.65	
14	HA2-CA	0.0	-1.07/-1.00/0.16		2.54/2.63/2.78	
15	HA-CA	0.0	-2.69/-2.87/-1.49		2.50/2.57/2.64	

1.138 Small molecule B of [2-((1S)-1-aminoethyl)-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl]acetic acid(MDO)

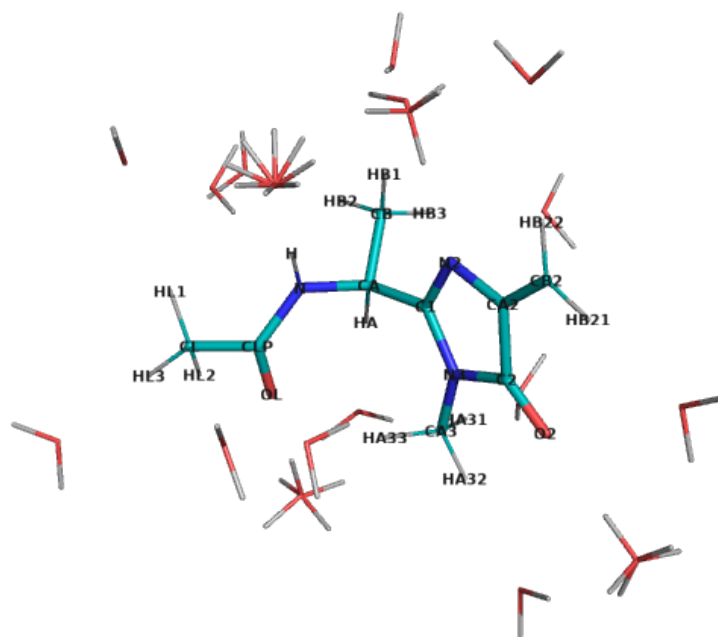


Figure S130: The molecule used for water complex calculations corresponding to N-[(1S)-1-(1-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-2-yl)ethyl]acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S426: Statistics of calculated water interaction and dipole moment for N-[(1S)-1-(1-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-2-yl)ethyl]acetamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.97/1.76	0.44/2.26	6.449	4.14/4.46	51.78
Optimal	0.51/1.11	0.08/0.19	1.846	4.14/4.25	8.20

Table S427: The comparison list of optimized atomic charges and their initial guess for N-[(1S)-1-(1-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-2-yl)ethyl]acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.270	0.000
HL1	0.090	0.090	0.000
HL2	0.090	0.090	0.000
HL3	0.090	0.090	0.000
CLP	0.510	0.513	6.342
OL	-0.510	-0.510	0.000
N	-0.470	-0.452	12.613
H	0.310	0.287	8.293
CA	0.270	0.234	17.154
HA	0.090	0.090	0.520
CB	-0.270	-0.267	2.233
HB1	0.090	0.090	0.300
HB2	0.090	0.090	0.300
HB3	0.090	0.090	0.300
C1	0.233	0.058	27.526
N2	-0.679	-0.703	41.131
N3	-0.080	-0.073	17.082
C2	0.407	0.510	20.808
O2	-0.489	-0.482	6.517
CA2	0.466	0.510	42.290
CB2	-0.593	-0.444	13.655
HB21	0.230	0.230	0.950
HB22	0.230	0.230	0.950
CA3	-0.195	-0.271	3.821
HA31	0.090	0.090	0.000
HA32	0.090	0.090	0.000
HA33	0.090	0.090	0.000

Table S428: Interaction energies and geometries between probe water and selected N-[(1S)-1-(1-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-2-yl)ethyl]acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HL1-CL	0.0	-2.68/-2.54/-2.07		2.50/2.60/2.61	
2	HL2-CL	0.0	-2.37/-1.88/-1.35		2.49/2.62/2.65	
3	HL3-CL	0.0	-1.37/-0.81/-0.56		2.53/2.68/2.69	
4	OL-CLP	0.0	-6.07/-6.66/-6.66		1.81/1.76/1.77	
5	OL-CLP	90.0	-5.68/-6.12/-6.38		1.82/1.76/1.77	
6	OL-CLP	180.0	-4.51/-4.80/-5.83		1.85/1.79/1.78	
7	OL-CLP	270.0	-4.97/-5.68/-6.34		1.85/1.78/1.77	
8	H-N	0.0	-5.97/-6.89/-4.95		1.87/1.86/1.90	
9	H-N	45.0	-5.79/-6.66/-4.68		1.87/1.86/1.91	
10	H-N	90.0	-6.64/-7.14/-5.01		1.83/1.85/1.89	
11	H-N	135.0	-6.88/-7.41/-5.31		1.83/1.84/1.88	
12	HA-CA	0.0	-1.17/-1.68/-0.23		2.81/2.73/2.82	
13	HB1-CB	0.0	-0.31/-0.41/0.11		2.74/2.72/5.00	
14	HB2-CB	0.0	-1.35/-1.76/-1.16		2.69/2.64/2.67	
15	HB3-CB	0.0	-1.43/-1.66/-0.82		2.69/2.65/2.72	
16	N2-C1	0.0	-6.44/-6.58/-6.00		1.90/1.98/1.98	
17	N2-C1	90.0	-7.30/-6.19/-6.79		1.90/1.99/1.97	
18	N2-C1	180.0	-3.96/-3.69/-5.44		2.10/2.05/2.00	
19	N2-C1	270.0	-5.92/-4.96/-5.69		1.91/2.00/1.98	
20	N3-C1	0.0	-2.09/-2.13/-2.47		2.71/2.52/2.48	
21	O2-C2	0.0	-5.35/-5.70/-5.42		1.87/1.78/1.79	
22	O2-C2	90.0	-5.52/-5.68/-4.88		1.86/1.78/1.80	
23	O2-C2	180.0	-5.44/-5.54/-4.18		1.86/1.78/1.81	
24	O2-C2	270.0	-5.48/-5.72/-4.91		1.86/1.78/1.80	
25	HB21-CB2	0.0	-1.64/-1.45/-3.39		2.32/2.47/2.41	
26	HB22-CB2	0.0	-1.38/-0.95/-2.47		2.50/2.56/2.47	
27	HA31-CA3	0.0	-1.49/-1.55/-0.63		2.65/2.64/2.73	

1.139 Small molecule C of [2-((1S)-1-aminoethyl)-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl]acetic acid(MDO)

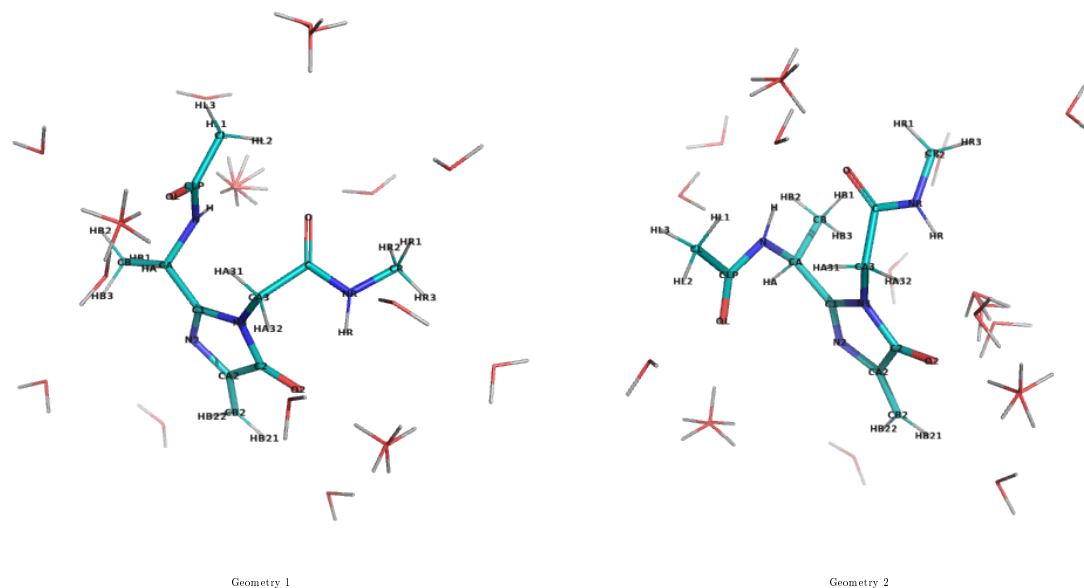


Table S429: The molecule used for water complex calculations corresponding to N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S430: Statistics of calculated water interaction and dipole moment for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide.

		RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
		Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Geometry 1	Initial	0.86 / 2.05	0.07 / 0.17	6.601	1.19 / 4.07	1.19
Geometry 2	Initial	1.02 / 2.07	0.09 / 0.23	6.126	6.37 / 4.43	6.37
Sum of geometries	Initial	0.95 / 2.07	0.08 / 0.23	12.727	-	-
Geometry 1	Optimal	0.36 / 0.81	0.07 / 0.16	2.460	1.19 / 1.37	1.19
Geometry 2	Optimal	0.51 / 0.91	0.08 / 0.19	2.701	6.37 / 7.25	6.37
Sum of geometries	Optimal	0.45 / 0.91	0.08 / 0.19	5.161	-	-

Table S431: The comparison list of optimized atomic charges and their initial guess for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
C1	0.233	0.164	24.002
N2	-0.679	-0.703	41.104
N3	-0.031	-0.499	22.994
C2	0.407	0.613	23.378
O2	-0.489	-0.482	6.517
CA2	0.466	0.512	42.773
CB2	-0.593	-0.444	13.655
HB21	0.230	0.230	0.950
HB22	0.230	0.230	0.950
CA3	-0.154	0.043	13.461
HA31	0.090	0.090	0.177
HA32	0.090	0.090	0.177
C	0.510	0.499	10.097
O	-0.510	-0.517	3.479
NR	-0.470	-0.442	6.773
HR	0.310	0.299	0.000
CR	-0.110	-0.108	0.239
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S432: Interaction energies and geometries between probe water and selected N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
Geometry 1				
1	O-C	0.0	-5.45/-5.47/-6.22	1.84/1.77/1.76
2	O-C	90.0	-6.01/-6.48/-6.53	1.83/1.75/1.76
3	O-C	180.0	-5.96/-6.64/-6.64	1.83/1.75/1.75
4	O-C	270.0	-5.67/-5.94/-6.62	1.84/1.76/1.75
5	NR-C	0.0	-1.32/-1.50/-1.08	2.24/2.20/2.22
6	HR2-CR	0.0	-1.10/-1.26/-1.09	2.71/2.66/2.67
7	HR3-CR	0.0	-1.39/-1.22/-1.32	2.66/2.67/2.67
8	N2-C1	0.0	-5.74/-6.45/-6.04	1.95/1.92/1.92
9	N2-C1	90.0	-6.51/-6.37/-7.24	1.90/1.92/1.90
10	N2-C1	180.0	-5.60/-5.66/-7.65	1.96/1.93/1.90
11	N2-C1	270.0	-6.64/-6.59/-7.43	1.90/1.91/1.89
12	O2-C2	0.0	-3.88/-3.93/-3.54	1.88/1.80/1.81
13	O2-C2	90.0	-4.94/-5.15/-4.46	1.84/1.77/1.79
14	O2-C2	180.0	-4.95/-5.20/-4.05	1.84/1.77/1.79
15	O2-C2	270.0	-3.93/-4.12/-3.39	1.87/1.79/1.81
16	HB21-CB2	0.0	-1.84/-1.64/-3.47	2.32/2.48/2.42
17	HB22-CB2	0.0	-1.82/-1.01/-2.42	2.42/2.54/2.46
18	HA31-CA3	0.0	-2.08/-2.47/-1.68	2.70/2.69/2.70
19	HA-CA	0.0	-2.47/-2.76/-1.19	2.49/2.56/2.66
Geometry 2				
20	O-C	0.0	-6.06/-6.90/-7.24	1.86/1.76/1.75
21	O-C	90.0	-5.25/-6.15/-7.32	1.87/1.77/1.75
22	O-C	180.0	-4.71/-5.63/-6.52	1.88/1.77/1.76
23	O-C	270.0	-5.56/-6.46/-6.85	1.86/1.76/1.76
24	HR-NR	0.0	-7.09/-7.67/-7.53	1.93/1.90/1.90
25	HR-NR	45.0	-7.71/-7.90/-7.71	1.91/1.89/1.89
26	HR-NR	90.0	-7.79/-7.84/-7.79	1.90/1.89/1.89
27	HR-NR	135.0	-7.18/-7.62/-7.61	1.92/1.90/1.89
28	HR1-CR	0.0	-0.71/-0.04/0.30	2.50/2.69/2.67
29	HR2-CR	0.0	-1.54/-1.44/-1.38	2.68/2.66/2.66
30	HR3-CR	0.0	-1.84/-1.82/-1.70	2.68/2.67/2.66
31	N2-C1	0.0	-6.46/-6.98/-6.58	1.93/1.91/1.91
32	N2-C1	90.0	-6.88/-6.47/-7.35	1.89/1.91/1.89
33	N2-C1	180.0	-5.73/-5.60/-7.60	1.95/1.93/1.90
34	N2-C1	270.0	-7.31/-7.09/-7.94	1.88/1.91/1.89
35	N3-C1	0.0	-0.22/0.03/-2.15	2.60/2.67/2.17
36	O2-C2	0.0	-4.96/-5.34/-4.95	1.88/1.79/1.80
37	O2-C2	90.0	-5.32/-5.37/-4.66	1.87/1.78/1.80
38	O2-C2	180.0	-5.74/-5.89/-4.71	1.87/1.78/1.81
39	O2-C2	270.0	-5.94/-6.25/-5.51	1.85/1.77/1.79
40	HB21-CB2	0.0	-1.43/-1.20/-3.03	2.33/2.48/2.41
41	HB22-CB2	0.0	-1.29/-0.66/-2.05	2.47/2.56/2.47
42	HA31-CA3	0.0	-3.71/-4.08/-3.49	2.50/2.57/2.57
43	HA-CA	0.0	-2.67/-3.45/-1.93	2.59/2.58/2.69

1.140 Small molecule used for hydroxy-l-methionine(ME0)

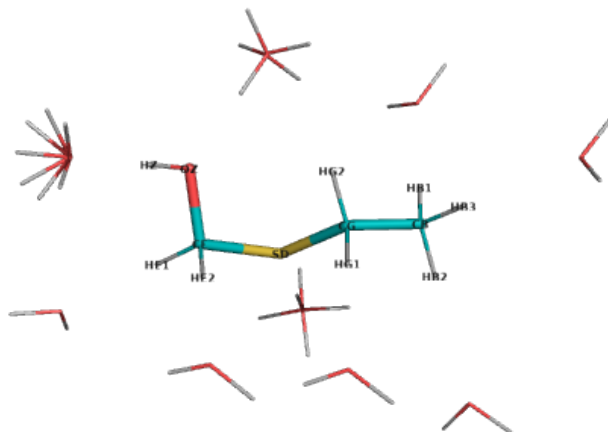


Figure S131: The molecule used for water complex calculations corresponding to (ethylsulfanyl)methanol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S433: Statistics of calculated water interaction and dipole moment for (ethylsulfanyl)methanol.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.70/1.26	0.25/0.57	2.430	2.67/3.27	11.80
Optimal	0.62/1.34	0.26/0.58	1.739	2.67/3.09	2.55

Table S434: The comparison list of optimized atomic charges and their initial guess for (ethylsulfanyl)methanol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.270	0.045
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.035	-0.066	14.230
HG1	0.090	0.090	0.000
HG2	0.090	0.090	0.000
SD	-0.240	-0.226	29.077
CE	0.091	0.162	24.057
HE1	0.090	0.090	0.000
HE2	0.090	0.090	0.000
OZ	-0.574	-0.650	21.538
HZ	0.398	0.420	2.500

Table S435: Interaction energies and geometries between probe water and selected (ethylsulfanyl)methanol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.87/-0.74/-0.61	2.80/2.75/2.76
2	HB1-CB	0.0	-0.54/-0.07/0.04	2.70/2.75/2.77
3	HB2-CB	0.0	-0.66/-0.31/-0.25	2.74/2.77/2.78
4	HG1-CG	0.0	-0.97/-1.20/-1.11	2.80/2.72/2.74
5	SD-CG	0.0	-1.50/-2.67/-2.40	2.91/2.34/2.36
6	SD-CG	90.0	-1.89/-3.17/-3.03	2.83/2.32/2.33
7	SD-CG	180.0	-1.49/-2.83/-2.75	2.91/2.33/2.34
8	SD-CG	270.0	-1.60/-2.50/-2.28	2.85/2.35/2.36
9	HE1-CE	0.0	-1.44/-1.14/-1.47	2.60/2.67/2.64
10	HE2-CE	0.0	-1.72/-2.06/-2.34	2.64/2.64/2.61
11	OZ-CE	0.0	-5.07/-4.61/-5.28	1.89/1.93/1.90
12	OZ-CE	90.0	-4.46/-4.72/-5.52	1.92/1.92/1.89
13	OZ-CE	180.0	-6.28/-6.75/-7.41	1.86/1.87/1.85
14	OZ-CE	270.0	-6.03/-5.97/-6.53	1.86/1.90/1.87
15	HZ-OZ	0.0	-6.61/-6.91/-7.14	1.80/1.82/1.81
16	HZ-OZ	45.0	-6.71/-6.95/-7.20	1.79/1.82/1.81
17	HZ-OZ	90.0	-6.83/-7.01/-7.27	1.78/1.82/1.81
18	HZ-OZ	135.0	-6.72/-6.97/-7.22	1.79/1.82/1.81

1.141 Small molecule used for N1-methylatedhistidine(MHS)

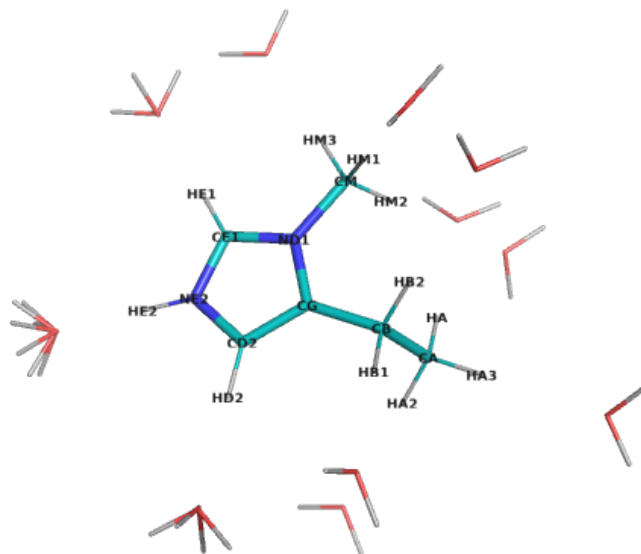


Figure S132: The molecule used for water complex calculations corresponding to 5-ethyl-1-methyl-2,3-dihydro-1H-imidazole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S436: Statistics of calculated water interaction and dipole moment for 5-ethyl-1-methyl-2,3-dihydro-1H-imidazole.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.65/1.25	0.13/0.25	2.462	4.23/3.95	7.33
Optimal	0.34/0.71	0.12/0.24	2.275	4.23/3.91	9.92

Table S437: The comparison list of optimized atomic charges and their initial guess for 5-ethyl-1-methyl-2,3-dihydro-1H-imidazole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.000
HA	0.090	0.090	0.000
CB	-0.020	-0.049	2.500
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.163	0.197	48.680
ND1	-0.446	-0.505	90.023
CM	0.173	0.162	78.311
HM1	0.090	0.090	3.537
HM2	0.090	0.090	3.537
HM3	0.090	0.090	3.537
CD2	0.089	0.191	14.989
HD2	0.169	0.130	0.000
CE1	0.323	0.336	48.268
HE1	0.192	0.157	14.504
NE2	-0.535	-0.509	9.726
HE2	0.442	0.440	0.000

Table S438: Interaction energies and geometries between probe water and selected 5-ethyl-1-methyl-2,3-dihydro-1H-imidazole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-4.52/-3.93/-3.87	2.46/2.61/2.61
2	HA2-CA	0.0	-4.19/-4.22/-4.32	2.60/2.65/2.65
3	HA-CA	0.0	-5.81/-5.10/-4.98	2.81/3.05/3.05
4	HB1-CB	0.0	-6.20/-5.99/-6.07	2.36/2.55/2.55
5	HB2-CB	0.0	-7.24/-6.83/-6.63	2.49/2.59/2.60
6	HM1-CM	0.0	-7.58/-6.91/-6.62	2.26/2.50/2.51
7	HM2-CM	0.0	-5.77/-5.69/-5.48	2.89/3.04/3.06
8	HM3-CM	0.0	-7.63/-7.41/-6.99	2.35/2.51/2.52
9	HD2-CD2	0.0	-8.49/-8.58/-8.74	2.17/2.17/2.17
10	HD2-CD2	90.0	-9.11/-8.82/-8.97	2.13/2.16/2.17
11	HE1-CE1	0.0	-11.19/-11.40/-10.46	2.06/1.99/2.01
12	HE1-CE1	90.0	-12.13/-11.84/-10.88	2.02/1.98/2.00
13	HE2-NE2	0.0	-14.87/-15.08/-15.73	1.75/1.75/1.74
14	HE2-NE2	45.0	-15.26/-15.26/-15.89	1.74/1.75/1.74
15	HE2-NE2	90.0	-15.64/-15.43/-16.04	1.73/1.75/1.74
16	HE2-NE2	135.0	-15.25/-15.26/-15.89	1.74/1.75/1.74

1.142 Small molecule used for N1-methylatedhistidine(MHS)

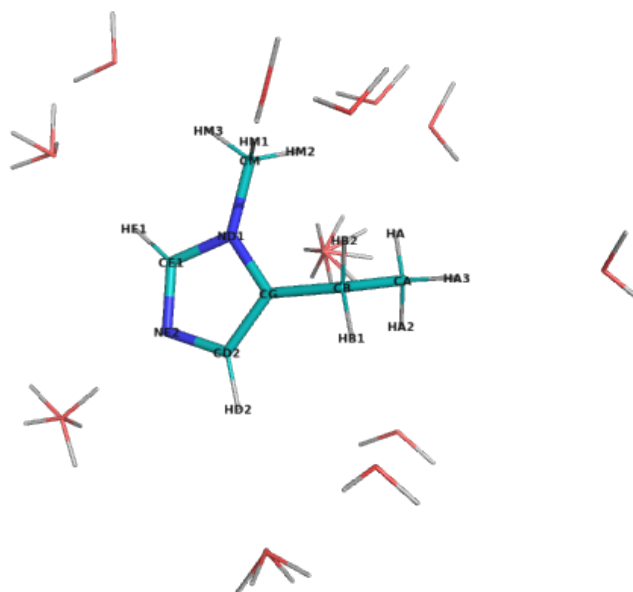


Figure S133: The molecule used for water complex calculations corresponding to 5-ethyl-1-methyl-1H-imidazole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S439: Statistics of calculated water interaction and dipole moment for 5-ethyl-1-methyl-1H-imidazole.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.53/0.89	0.14/0.37	2.487	4.33/4.05	14.46
Optimal	0.22/0.45	0.12/0.33	2.735	4.33/5.58	0.38

Table S440: The comparison list of optimized atomic charges and their initial guess for 5-ethyl-1-methyl-1H-imidazole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.269	0.000
HA	0.090	0.090	0.000
CB	-0.041	-0.088	2.500
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.306	-0.139	2.500
ND1	-0.038	0.028	2.500
CM	-0.044	-0.231	2.500
HM1	0.090	0.090	0.000
HM2	0.090	0.090	0.000
HM3	0.090	0.090	0.000
CD2	0.218	0.218	0.000
HD2	0.102	0.102	0.000
CE1	0.240	0.240	0.000
HE1	0.097	0.097	0.000
NE2	-0.678	-0.678	0.000

Table S441: Interaction energies and geometries between probe water and selected 5-ethyl-1-methyl-1H-imidazole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.96/-1.06/-1.07	2.82/2.73/2.73
2	HA2-CA	0.0	-1.04/-0.89/-1.24	2.69/2.69/2.68
3	HA-CA	0.0	-1.76/-1.78/-1.32	3.16/3.30/3.28
4	HB1-CB	0.0	-1.31/-1.24/-1.63	2.66/2.69/2.67
5	HB2-CB	0.0	-2.10/-2.14/-1.81	2.76/2.71/2.70
6	ND1-CG	0.0	-0.09/-0.23/-0.48	3.73/3.84/3.70
7	ND1-CG	45.0	-0.19/-0.34/-0.64	3.76/3.78/3.65
8	ND1-CG	90.0	-0.16/-0.36/-0.66	3.80/3.79/3.65
9	ND1-CG	135.0	-0.07/-0.24/-0.50	3.77/3.85/3.70
10	HM1-CM	0.0	-2.26/-2.45/-1.57	2.53/2.58/2.66
11	HM2-CM	0.0	-1.86/-2.15/-1.45	2.95/2.93/3.04
12	HM3-CM	0.0	-2.54/-2.99/-1.98	2.56/2.56/2.63
13	HD2-CD2	0.0	-0.71/-0.69/-1.44	2.70/2.37/2.33
14	HD2-CD2	90.0	-0.76/-0.67/-1.41	2.67/2.38/2.33
15	HE1-CE1	0.0	-2.01/-1.94/-1.95	2.48/2.31/2.30
16	HE1-CE1	90.0	-2.27/-2.05/-1.97	2.42/2.31/2.30
17	NE2-CD2	0.0	-7.28/-7.01/-6.73	1.92/1.91/1.92
18	NE2-CD2	90.0	-7.87/-7.46/-7.01	1.89/1.91/1.91
19	NE2-CD2	180.0	-7.67/-7.49/-6.88	1.91/1.91/1.92
20	NE2-CD2	270.0	-7.87/-7.43/-6.99	1.89/1.91/1.91

1.143 Small molecule used for N1-methylatedhistidine(MHSP)

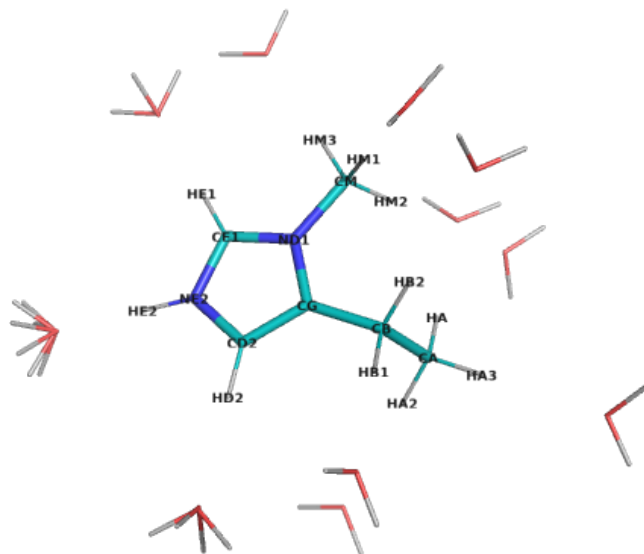


Figure S134: The molecule used for water complex calculations corresponding to 5-ethyl-1-methyl-2,3-dihydro-1H-imidazole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S442: Statistics of calculated water interaction and dipole moment for 5-ethyl-1-methyl-2,3-dihydro-1H-imidazole.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.65/1.25	0.13/0.25	2.462	4.23/3.95	7.33
Optimal	0.34/0.71	0.12/0.24	2.275	4.23/3.91	9.92

Table S443: The comparison list of optimized atomic charges and their initial guess for 5-ethyl-1-methyl-2,3-dihydro-1H-imidazole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.000
HA	0.090	0.090	0.000
CB	-0.020	-0.049	2.500
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.163	0.197	48.680
ND1	-0.446	-0.505	90.023
CM	0.173	0.162	78.311
HM1	0.090	0.090	3.537
HM2	0.090	0.090	3.537
HM3	0.090	0.090	3.537
CD2	0.089	0.191	14.989
HD2	0.169	0.130	0.000
CE1	0.323	0.336	48.268
HE1	0.192	0.157	14.504
NE2	-0.535	-0.509	9.726
HE2	0.442	0.440	0.000

Table S444: Interaction energies and geometries between probe water and selected 5-ethyl-1-methyl-2,3-dihydro-1H-imidazole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-4.52/-3.93/-3.87		2.46/2.61/2.61	
2	HA2-CA	0.0	-4.19/-4.22/-4.32		2.60/2.65/2.65	
3	HA-CA	0.0	-5.81/-5.10/-4.98		2.81/3.05/3.05	
4	HB1-CB	0.0	-6.20/-5.99/-6.07		2.36/2.55/2.55	
5	HB2-CB	0.0	-7.24/-6.83/-6.63		2.49/2.59/2.60	
6	HM1-CM	0.0	-7.58/-6.91/-6.62		2.26/2.50/2.51	
7	HM2-CM	0.0	-5.77/-5.69/-5.48		2.89/3.04/3.06	
8	HM3-CM	0.0	-7.63/-7.41/-6.99		2.35/2.51/2.52	
9	HD2-CD2	0.0	-8.49/-8.58/-8.74		2.17/2.17/2.17	
10	HD2-CD2	90.0	-9.11/-8.82/-8.97		2.13/2.16/2.17	
11	HE1-CE1	0.0	-11.19/-11.40/-10.46		2.06/1.99/2.01	
12	HE1-CE1	90.0	-12.13/-11.84/-10.88		2.02/1.98/2.00	
13	HE2-NE2	0.0	-14.87/-15.08/-15.73		1.75/1.75/1.74	
14	HE2-NE2	45.0	-15.26/-15.26/-15.89		1.74/1.75/1.74	
15	HE2-NE2	90.0	-15.64/-15.43/-16.04		1.73/1.75/1.74	
16	HE2-NE2	135.0	-15.25/-15.26/-15.89		1.74/1.75/1.74	

1.144 Small molecule used for N1-methylatedhistidine(MHSP)

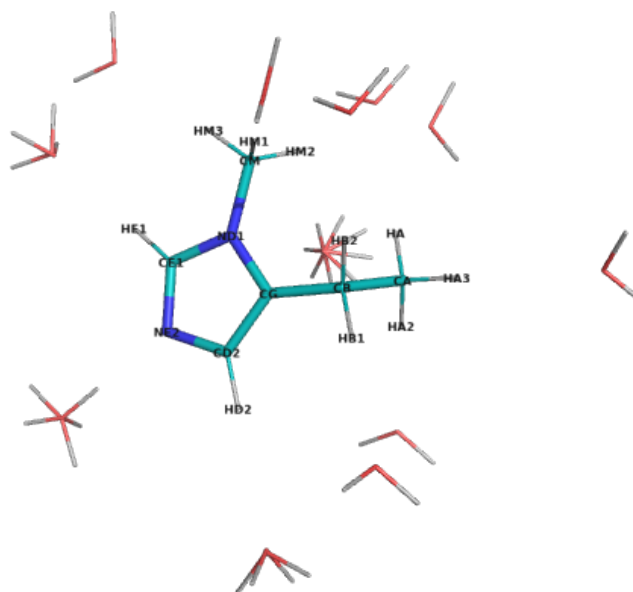


Figure S135: The molecule used for water complex calculations corresponding to 5-ethyl-1-methyl-1H-imidazole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S445: Statistics of calculated water interaction and dipole moment for 5-ethyl-1-methyl-1H-imidazole.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.53/0.89	0.14/0.37	2.487	4.33/4.05	14.46
Optimal	0.22/0.45	0.12/0.33	2.735	4.33/5.58	0.38

Table S446: The comparison list of optimized atomic charges and their initial guess for 5-ethyl-1-methyl-1H-imidazole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.269	0.000
HA	0.090	0.090	0.000
CB	-0.041	-0.088	2.500
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.306	-0.139	2.500
ND1	-0.038	0.028	2.500
CM	-0.044	-0.231	2.500
HM1	0.090	0.090	0.000
HM2	0.090	0.090	0.000
HM3	0.090	0.090	0.000
CD2	0.218	0.218	0.000
HD2	0.102	0.102	0.000
CE1	0.240	0.240	0.000
HE1	0.097	0.097	0.000
NE2	-0.678	-0.678	0.000

Table S447: Interaction energies and geometries between probe water and selected 5-ethyl-1-methyl-1H-imidazole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.96/-1.06/-1.07	2.82/2.73/2.73
2	HA2-CA	0.0	-1.04/-0.89/-1.24	2.69/2.69/2.68
3	HA-CA	0.0	-1.76/-1.78/-1.32	3.16/3.30/3.28
4	HB1-CB	0.0	-1.31/-1.24/-1.63	2.66/2.69/2.67
5	HB2-CB	0.0	-2.10/-2.14/-1.81	2.76/2.71/2.70
6	ND1-CG	0.0	-0.09/-0.23/-0.48	3.73/3.84/3.70
7	ND1-CG	45.0	-0.19/-0.34/-0.64	3.76/3.78/3.65
8	ND1-CG	90.0	-0.16/-0.36/-0.66	3.80/3.79/3.65
9	ND1-CG	135.0	-0.07/-0.24/-0.50	3.77/3.85/3.70
10	HM1-CM	0.0	-2.26/-2.45/-1.57	2.53/2.58/2.66
11	HM2-CM	0.0	-1.86/-2.15/-1.45	2.95/2.93/3.04
12	HM3-CM	0.0	-2.54/-2.99/-1.98	2.56/2.56/2.63
13	HD2-CD2	0.0	-0.71/-0.69/-1.44	2.70/2.37/2.33
14	HD2-CD2	90.0	-0.76/-0.67/-1.41	2.67/2.38/2.33
15	HE1-CE1	0.0	-2.01/-1.94/-1.95	2.48/2.31/2.30
16	HE1-CE1	90.0	-2.27/-2.05/-1.97	2.42/2.31/2.30
17	NE2-CD2	0.0	-7.28/-7.01/-6.73	1.92/1.91/1.92
18	NE2-CD2	90.0	-7.87/-7.46/-7.01	1.89/1.91/1.91
19	NE2-CD2	180.0	-7.67/-7.49/-6.88	1.91/1.91/1.92
20	NE2-CD2	270.0	-7.87/-7.43/-6.99	1.89/1.91/1.91

1.145 Small molecule used for N-methyl-lysine(MLZ)

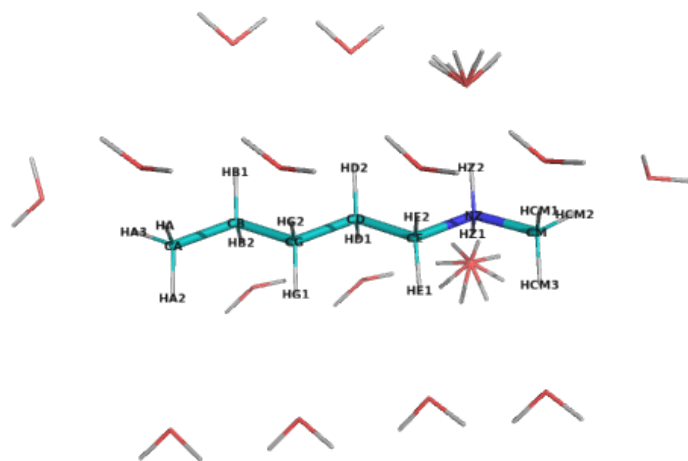


Figure S136: The molecule used for water complex calculations corresponding to methyl(pentyl)amine, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S448: Statistics of calculated water interaction and dipole moment for methyl(pentyl)amine.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.34/0.80	0.12/0.24	4.398	10.00/12.47	4.41
Optimal	0.34/0.84	0.12/0.25	2.705	10.00/11.35	2.76

Table S449: The comparison list of optimized atomic charges and their initial guess for methyl (pentyl)amine, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.000
HA	0.090	0.090	0.000
CB	-0.180	-0.194	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.180	-0.183	0.000
HG1	0.090	0.090	0.000
HG2	0.090	0.090	0.000
CD	-0.123	-0.167	0.844
HD1	0.090	0.090	0.000
HD2	0.090	0.090	0.000
CE	0.178	0.190	1.239
HE1	0.090	0.090	0.085
HE2	0.090	0.090	0.085
NZ	-0.472	-0.455	1.237
HZ1	0.337	0.329	0.000
HZ2	0.337	0.329	0.000
CM	0.113	0.161	1.104
HCM1	0.090	0.090	0.085
HCM3	0.090	0.090	0.085
HCM2	0.090	0.090	0.085

Table S450: Interaction energies and geometries between probe water and selected methyl(pentyl)amine site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-2.82/-2.17/-2.02	2.63/2.71/2.73
2	HA2-CA	0.0	-2.63/-2.18/-1.99	2.75/2.78/2.80
3	HA-CA	0.0	-2.63/-2.18/-1.99	2.75/2.78/2.80
4	HB1-CB	0.0	-3.32/-3.10/-2.78	2.75/2.75/2.78
5	HB2-CB	0.0	-3.32/-3.10/-2.78	2.75/2.75/2.78
6	HG1-CG	0.0	-4.62/-4.60/-4.34	2.61/2.65/2.66
7	HG2-CG	0.0	-4.62/-4.60/-4.34	2.61/2.65/2.66
8	HD1-CD	0.0	-6.60/-6.82/-6.46	2.47/2.55/2.57
9	HD2-CD	0.0	-6.60/-6.82/-6.46	2.47/2.55/2.57
10	HE1-CE	0.0	-8.70/-8.38/-8.48	2.26/2.49/2.49
11	HE2-CE	0.0	-8.70/-8.38/-8.48	2.26/2.49/2.49
12	HZ1-NZ	0.0	-16.42/-16.49/-16.60	1.75/1.77/1.77
13	HZ1-NZ	45.0	-16.41/-16.44/-16.54	1.75/1.78/1.78
14	HZ1-NZ	90.0	-16.70/-16.57/-16.64	1.75/1.77/1.77
15	HZ1-NZ	135.0	-16.70/-16.63/-16.70	1.75/1.77/1.77
16	HZ2-NZ	0.0	-16.42/-16.49/-16.60	1.75/1.77/1.77
17	HZ2-NZ	45.0	-16.70/-16.63/-16.70	1.75/1.77/1.77
18	HZ2-NZ	90.0	-16.71/-16.57/-16.65	1.75/1.77/1.77
19	HZ2-NZ	135.0	-16.42/-16.44/-16.54	1.75/1.78/1.78
20	HCM1-CM	0.0	-8.75/-8.19/-8.70	2.24/2.48/2.46
21	HCM3-CM	0.0	-8.75/-8.19/-8.70	2.24/2.48/2.46
22	HCM2-CM	0.0	-8.77/-7.93/-8.42	2.22/2.48/2.46

1.146 Small molecule used for N1-phosphonohistidine(NEP)

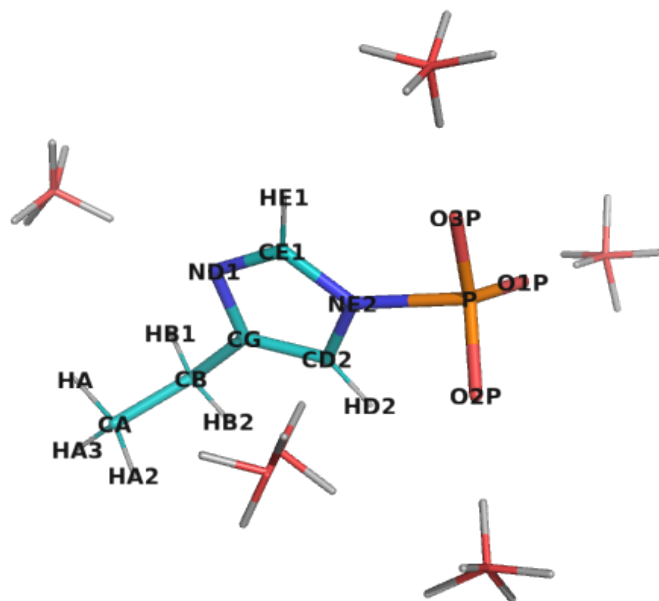


Figure S137: The molecule used for water complex calculations corresponding to (4-ethyl-1H-imidazol-1-yl)phosphonic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S451: Statistics of calculated water interaction and dipole moment for (4-ethyl-1H-imidazol-1-yl)phosphonic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	2.06/4.34	0.13/0.33	9.076	13.10/18.69	1.14
Optimal	0.39/1.18	0.07/0.16	3.488	13.10/13.76	3.29

Table S452: The comparison list of optimized atomic charges and their initial guess for (4-ethyl-1H-imidazol-1-yl)phosphonicacid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.276	0.474
HA	0.090	0.090	0.000
CB	-0.205	-0.080	0.570
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.160	0.229	2.564
ND1	-0.886	-0.691	2.545
CD2	-0.121	-0.144	71.310
HD2	0.159	0.095	2.500
CE1	0.268	0.258	52.247
HE1	0.181	0.131	2.500
NE2	-0.314	-0.448	97.938
P	1.539	1.323	98.286
O1P	-0.987	-0.949	8.944
O2P	-0.987	-0.949	8.944
O3P	-0.987	-0.949	8.944

Table S453: Interaction energies and geometries between probe water and selected (4-ethyl-1H-imidazol-1-yl)phosphonicacid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	ND1-CG	0.0	-16.25/-16.10/-13.55		1.83/1.82/1.86	
2	ND1-CG	90.0	-16.08/-15.88/-12.45		1.82/1.81/1.87	
3	ND1-CG	180.0	-15.30/-15.42/-11.01		1.85/1.81/1.88	
4	ND1-CG	270.0	-16.02/-15.76/-12.34		1.83/1.81/1.87	
5	NE2-CD2	0.0	-11.65/-11.72/-14.37		2.62/2.46/2.29	
6	NE2-CD2	90.0	-8.31/-7.12/-7.44		2.79/2.75/2.61	
7	NE2-CD2	180.0	-8.46/-7.73/-8.47		2.84/2.69/2.53	
8	NE2-CD2	270.0	-15.39/-16.22/-19.73		2.34/2.18/2.08	
9	O1P-P	0.0	-20.86/-20.82/-21.45		1.66/1.60/1.60	
10	O1P-P	90.0	-20.63/-20.61/-21.32		1.66/1.60/1.60	
11	O1P-P	180.0	-20.24/-20.08/-20.94		1.66/1.60/1.60	
12	O1P-P	270.0	-20.44/-20.24/-21.11		1.66/1.60/1.60	
13	O2P-P	0.0	-20.84/-20.85/-21.48		1.66/1.60/1.60	
14	O2P-P	90.0	-20.42/-20.25/-21.11		1.66/1.60/1.60	
15	O2P-P	180.0	-20.23/-20.07/-20.94		1.66/1.60/1.60	
16	O2P-P	270.0	-20.63/-20.62/-21.33		1.66/1.60/1.60	
17	O3P-P	0.0	-20.20/-19.84/-20.60		1.66/1.60/1.60	
18	O3P-P	90.0	-20.27/-20.07/-20.85		1.65/1.60/1.60	
19	O3P-P	180.0	-19.91/-19.94/-20.76		1.66/1.59/1.60	
20	O3P-P	270.0	-20.27/-20.06/-20.84		1.65/1.60/1.60	

1.147 Small molecule used for meta-nitro-tyrosine(NIY)

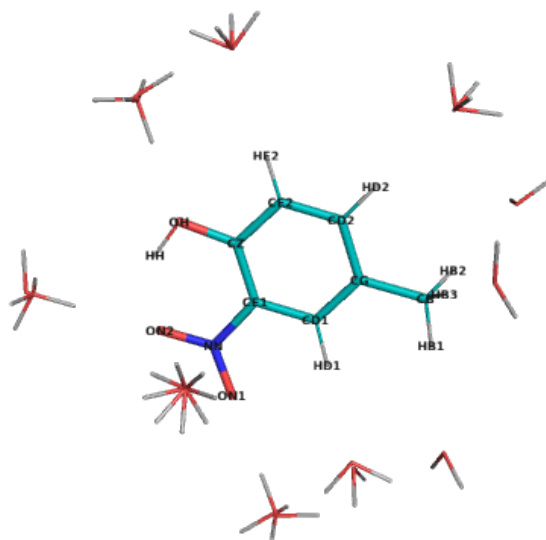


Figure S138: The molecule used for water complex calculations corresponding to 4-methyl-2-nitrobenzen-1-olate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S454: Statistics of calculated water interaction and dipole moment for 4-methyl-2-nitrobenzen-1-olate.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.67/1.15	0.21/0.40	3.411	4.72/3.25	12.17
Optimal	0.72/1.14	0.27/0.61	3.509	4.72/6.14	0.00

Table S455: The comparison list of optimized atomic charges and their initial guess for 4-methyl-2-nitrobenzen-1-olate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.267	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.044	0.001	0.000
CD1	-0.251	-0.181	0.000
HD1	0.168	0.160	0.000
CD2	0.044	-0.114	0.000
HD2	0.115	0.115	0.000
CE1	0.275	0.322	5.679
NN	0.215	0.402	6.076
ON1	-0.288	-0.340	0.000
ON2	-0.288	-0.340	0.000
CE2	-0.110	-0.114	0.000
HE2	0.115	0.115	0.000
CZ	0.126	0.083	5.060
OH	-0.508	-0.532	5.679
HH	0.343	0.420	0.000

Table S456: Interaction energies and geometries between probe water and selected 4-methyl-2-nitrobenzen-1-olate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial		
1	HB3-CB	0.0	-1.52/-1.70/-1.12	2.69/2.68/2.72		
2	HB1-CB	0.0	-2.41/-2.02/-1.89	2.55/2.63/2.65		
3	HB2-CB	0.0	-1.64/-1.79/-1.15	2.67/2.67/2.71		
4	HD1-CD1	0.0	-2.10/-1.57/-2.07	2.37/2.59/2.57		
5	HD1-CD1	90.0	-1.46/-1.17/-1.66	2.52/2.63/2.61		
6	HD2-CD2	0.0	-2.58/-3.01/-1.57	2.47/2.58/2.67		
7	HD2-CD2	90.0	-2.76/-3.05/-1.61	2.43/2.57/2.66		
8	NN-CE1	0.0	-1.31/-0.23/-2.05	2.82/3.43/3.21		
9	NN-CE1	45.0	-1.26/-0.35/-2.14	2.83/3.40/3.20		
10	NN-CE1	90.0	-1.17/-0.36/-2.07	2.83/3.40/3.20		
11	NN-CE1	135.0	-1.23/-0.24/-1.99	2.81/3.42/3.21		
12	ON1-NN	0.0	-1.74/-2.52/-2.27	2.10/1.91/1.90		
13	ON1-NN	90.0	-2.64/-3.59/-3.26	2.04/1.87/1.87		
14	ON1-NN	180.0	-3.30/-4.44/-4.04	2.02/1.86/1.85		
15	ON1-NN	270.0	-2.64/-3.59/-3.26	2.04/1.87/1.87		
16	ON2-NN	0.0	-0.79/-1.74/-0.80	2.23/1.99/2.05		
17	ON2-NN	90.0	-1.54/-2.32/-1.59	2.05/1.92/1.92		
18	ON2-NN	180.0	-1.89/-2.95/-2.37	2.07/1.88/1.87		
19	ON2-NN	270.0	-1.54/-2.32/-1.59	2.05/1.92/1.92		
20	HE2-CE2	0.0	-1.93/-1.50/-0.78	2.45/2.64/2.70		
21	HE2-CE2	90.0	-1.83/-1.41/-0.70	2.46/2.65/2.71		
22	OH-CZ	0.0	-4.20/-5.13/-4.43	1.93/1.91/1.92		
23	OH-CZ	90.0	-4.27/-4.44/-4.28	1.89/1.91/1.91		
24	OH-CZ	180.0	-2.64/-3.07/-3.60	1.99/1.94/1.93		
25	OH-CZ	270.0	-4.27/-4.44/-4.28	1.89/1.91/1.91		

1.148 Small molecule A of
 (4Z)-4-(4-hydroxybenzylidene)-2-[3-(methylthio)propanimidoyl]-5-oxo-4-acetic5-dihydro-1H-imidazol-1-ylaceticacid(NRQ)

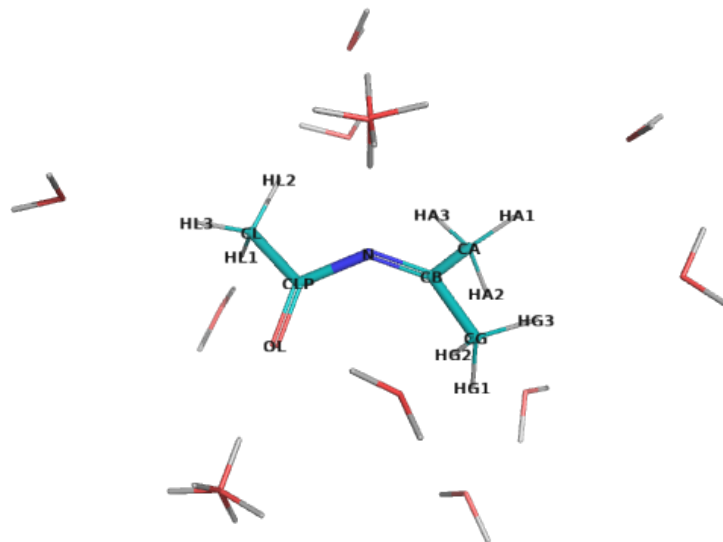


Figure S139: The molecule used for water complex calculations corresponding to N-(propan-2-ylidene)acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S457: Statistics of calculated water interaction and dipole moment for N-(propan-2-ylidene)acetamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	3.41/7.36	0.12/0.26	9.096	4.63/6.88	17.09
Optimal	0.43/0.73	0.08/0.13	2.495	4.63/5.33	4.69

Table S458: The comparison list of optimized atomic charges and their initial guess for N-(propan-2-ylidene)acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.270	0.000
HL1	0.090	0.090	0.000
HL2	0.090	0.090	0.000
HL3	0.090	0.090	0.000
CLP	0.510	0.510	0.000
OL	-0.510	-0.510	0.000
N	-0.410	-0.844	113.808
CB	0.166	-0.261	53.301
CG	-0.148	-0.040	36.206
HG1	0.090	0.090	0.250
HG2	0.090	0.090	0.250
HG3	0.090	0.090	0.250
CA	-0.148	-0.040	36.206
HA1	0.090	0.090	0.250
HA2	0.090	0.090	0.250
HA3	0.090	0.090	0.250

Table S459: Interaction energies and geometries between probe water and selected N-(propan-2-ylidene)acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HG1-CG	0.0	-1.84/-1.60/-2.23	2.51/2.61/2.55
2	HG2-CG	0.0	-0.66/-0.55/-0.14	2.49/2.61/2.57
3	HG3-CG	0.0	-1.81/-2.15/-2.97	2.66/2.62/2.55
4	HA1-CA	0.0	-2.42/-2.18/-2.80	2.49/2.60/2.54
5	HA2-CA	0.0	-2.47/-2.48/-3.52	2.53/2.59/2.53
6	HA3-CA	0.0	-1.75/-2.07/-1.91	2.71/2.66/2.68
7	HL1-CL	0.0	-1.27/-0.69/-1.35	2.61/2.71/2.61
8	HL2-CL	0.0	-0.80/-0.95/-0.30	2.79/2.73/2.74
9	HL3-CL	0.0	-0.74/-0.16/-0.82	2.63/2.73/2.61
10	OL-CLP	0.0	-6.39/-7.08/-6.92	1.84/1.76/1.77
11	OL-CLP	90.0	-5.91/-6.59/-6.51	1.85/1.76/1.77
12	OL-CLP	180.0	-6.06/-6.64/-6.97	1.84/1.76/1.76
13	OL-CLP	270.0	-6.51/-7.24/-7.59	1.84/1.75/1.76
14	N-CLP	0.0	-2.98/-2.93/-10.35	2.10/2.06/1.84
15	N-CLP	90.0	-3.47/-3.01/-9.79	2.05/2.06/1.85
16	N-CLP	180.0	-4.10/-4.16/-10.84	2.06/2.04/1.85
17	N-CLP	270.0	-4.41/-4.22/-11.64	2.02/2.03/1.83

1.149 Small molecule B of
 (4Z)-4-(4-hydroxybenzylidene)-2-[3-(methylthio)propanimidoyl]-5-oxo-4-acetic5-dihydro-1H-imidazol-1-ylaceticacid(NRQ)

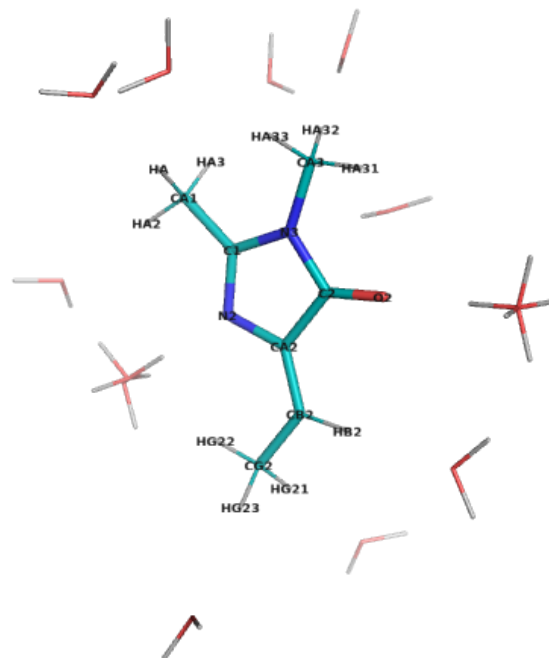


Figure S140: The molecule used for water complex calculations corresponding to (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S460: Statistics of calculated water interaction and dipole moment for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.92/1.64	0.10/0.25	6.526	3.17/0.45	27.81
Optimal	0.49/1.31	0.09/0.22	3.053	3.17/3.55	14.34

Table S461: The comparison list of optimized atomic charges and their initial guess for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA1	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
HA2	0.090	0.090	0.000
HA3	0.090	0.090	0.000
C1	0.233	0.074	23.781
N2	-0.679	-0.703	41.871
N3	-0.080	-0.079	15.706
C2	0.407	0.509	24.002
O2	-0.489	-0.482	6.710
CA2	0.288	0.516	47.153
CB2	-0.105	-0.135	25.469
HB2	0.150	0.150	3.270
CG2	-0.270	-0.274	15.277
HG21	0.090	0.090	1.175
HG22	0.090	0.090	1.175
HG23	0.090	0.090	1.175
CA3	-0.195	-0.271	3.821
HA31	0.090	0.090	0.000
HA32	0.090	0.090	0.000
HA33	0.090	0.090	0.000

Table S462: Interaction energies and geometries between probe water and selected (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA-CA1	0.0	-2.17/-2.61/-1.51		2.59/2.58/2.65	
2	HA2-CA1	0.0	-0.97/-0.86/0.05		2.58/2.64/2.77	
3	HA3-CA1	0.0	-2.55/-2.73/-1.57		2.52/2.57/2.64	
4	N2-C1	0.0	-4.99/-6.30/-5.60		2.09/2.01/2.02	
5	N2-C1	90.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
6	N2-C1	180.0	-5.35/-5.42/-6.38		1.95/2.01/1.99	
7	N2-C1	270.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
8	N3-C1	0.0	-0.26/-0.82/-0.78		2.74/2.52/2.49	
9	O2-C2	0.0	-5.51/-5.57/-5.00		1.85/1.78/1.80	
10	O2-C2	90.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
11	O2-C2	180.0	-5.92/-5.61/-4.27		1.84/1.78/1.81	
12	O2-C2	270.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
13	HB2-CB2	0.0	-1.40/-1.60/-2.82		2.32/2.47/2.44	
14	HG21-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
15	HG23-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
16	HA32-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	
17	HA33-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	

1.150 Small molecule C of
(4Z)-4-(4-hydroxybenzylidene)-2-[3-(methylthio)propanimidoyl]-5-oxo-4-acetic-5-dihydro-1H-imidazol-1-ylaceticacid(NRQ)

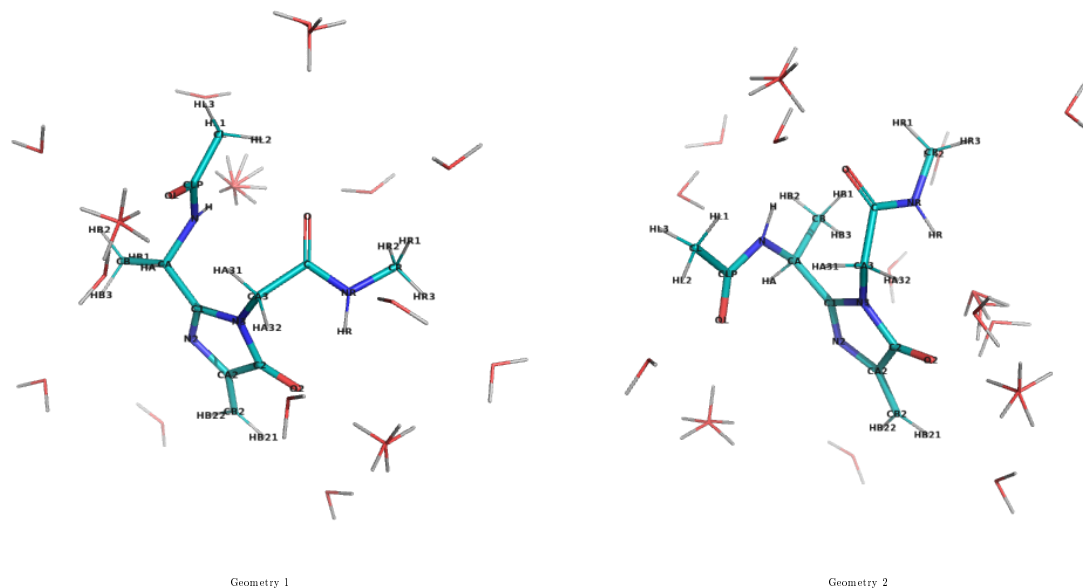


Table S463: The molecule used for water complex calculations corresponding to N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S464: Statistics of calculated water interaction and dipole moment for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide.

		RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
		Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Geometry 1	Initial	0.86 / 2.05	0.07 / 0.17	6.601	1.19 / 4.07	1.19
Geometry 2	Initial	1.02 / 2.07	0.09 / 0.23	6.126	6.37 / 4.43	6.37
Sum of geometries	Initial	0.95 / 2.07	0.08 / 0.23	12.727	-	-
Geometry 1	Optimal	0.36 / 0.81	0.07 / 0.16	2.460	1.19 / 1.37	1.19
Geometry 2	Optimal	0.51 / 0.91	0.08 / 0.19	2.701	6.37 / 7.25	6.37
Sum of geometries	Optimal	0.45 / 0.91	0.08 / 0.19	5.161	-	-

Table S465: The comparison list of optimized atomic charges and their initial guess for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
C1	0.233	0.164	24.002
N2	-0.679	-0.703	41.104
N3	-0.031	-0.499	22.994
C2	0.407	0.613	23.378
O2	-0.489	-0.482	6.517
CA2	0.466	0.512	42.773
CB2	-0.593	-0.444	13.655
HB21	0.230	0.230	0.950
HB22	0.230	0.230	0.950
CA3	-0.154	0.043	13.461
HA31	0.090	0.090	0.177
HA32	0.090	0.090	0.177
C	0.510	0.499	10.097
O	-0.510	-0.517	3.479
NR	-0.470	-0.442	6.773
HR	0.310	0.299	0.000
CR	-0.110	-0.108	0.239
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S466: Interaction energies and geometries between probe water and selected N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
Geometry 1				
1	O-C	0.0	-5.45/-5.47/-6.22	1.84/1.77/1.76
2	O-C	90.0	-6.01/-6.48/-6.53	1.83/1.75/1.76
3	O-C	180.0	-5.96/-6.64/-6.64	1.83/1.75/1.75
4	O-C	270.0	-5.67/-5.94/-6.62	1.84/1.76/1.75
5	NR-C	0.0	-1.32/-1.50/-1.08	2.24/2.20/2.22
6	HR2-CR	0.0	-1.10/-1.26/-1.09	2.71/2.66/2.67
7	HR3-CR	0.0	-1.39/-1.22/-1.32	2.66/2.67/2.67
8	N2-C1	0.0	-5.74/-6.45/-6.04	1.95/1.92/1.92
9	N2-C1	90.0	-6.51/-6.37/-7.24	1.90/1.92/1.90
10	N2-C1	180.0	-5.60/-5.66/-7.65	1.96/1.93/1.90
11	N2-C1	270.0	-6.64/-6.59/-7.43	1.90/1.91/1.89
12	O2-C2	0.0	-3.88/-3.93/-3.54	1.88/1.80/1.81
13	O2-C2	90.0	-4.94/-5.15/-4.46	1.84/1.77/1.79
14	O2-C2	180.0	-4.95/-5.20/-4.05	1.84/1.77/1.79
15	O2-C2	270.0	-3.93/-4.12/-3.39	1.87/1.79/1.81
16	HB21-CB2	0.0	-1.84/-1.64/-3.47	2.32/2.48/2.42
17	HB22-CB2	0.0	-1.82/-1.01/-2.42	2.42/2.54/2.46
18	HA31-CA3	0.0	-2.08/-2.47/-1.68	2.70/2.69/2.70
19	HA-CA	0.0	-2.47/-2.76/-1.19	2.49/2.56/2.66
Geometry 2				
20	O-C	0.0	-6.06/-6.90/-7.24	1.86/1.76/1.75
21	O-C	90.0	-5.25/-6.15/-7.32	1.87/1.77/1.75
22	O-C	180.0	-4.71/-5.63/-6.52	1.88/1.77/1.76
23	O-C	270.0	-5.56/-6.46/-6.85	1.86/1.76/1.76
24	HR-NR	0.0	-7.09/-7.67/-7.53	1.93/1.90/1.90
25	HR-NR	45.0	-7.71/-7.90/-7.71	1.91/1.89/1.89
26	HR-NR	90.0	-7.79/-7.84/-7.79	1.90/1.89/1.89
27	HR-NR	135.0	-7.18/-7.62/-7.61	1.92/1.90/1.89
28	HR1-CR	0.0	-0.71/-0.04/0.30	2.50/2.69/2.67
29	HR2-CR	0.0	-1.54/-1.44/-1.38	2.68/2.66/2.66
30	HR3-CR	0.0	-1.84/-1.82/-1.70	2.68/2.67/2.66
31	N2-C1	0.0	-6.46/-6.98/-6.58	1.93/1.91/1.91
32	N2-C1	90.0	-6.88/-6.47/-7.35	1.89/1.91/1.89
33	N2-C1	180.0	-5.73/-5.60/-7.60	1.95/1.93/1.90
34	N2-C1	270.0	-7.31/-7.09/-7.94	1.88/1.91/1.89
35	N3-C1	0.0	-0.22/0.03/-2.15	2.60/2.67/2.17
36	O2-C2	0.0	-4.96/-5.34/-4.95	1.88/1.79/1.80
37	O2-C2	90.0	-5.32/-5.37/-4.66	1.87/1.78/1.80
38	O2-C2	180.0	-5.74/-5.89/-4.71	1.87/1.78/1.81
39	O2-C2	270.0	-5.94/-6.25/-5.51	1.85/1.77/1.79
40	HB21-CB2	0.0	-1.43/-1.20/-3.03	2.33/2.48/2.41
41	HB22-CB2	0.0	-1.29/-0.66/-2.05	2.47/2.56/2.47
42	HA31-CA3	0.0	-3.71/-4.08/-3.49	2.50/2.57/2.57
43	HA-CA	0.0	-2.67/-3.45/-1.93	2.59/2.58/2.69

1.151 Small molecule D of
(4Z)-4-(4-hydroxybenzylidene)-2-[3-(methylthio)propanimidoyl]-5-oxo-4acetic5-dihydro-1H-imidazol-1-ylaceticacid(NRQ)

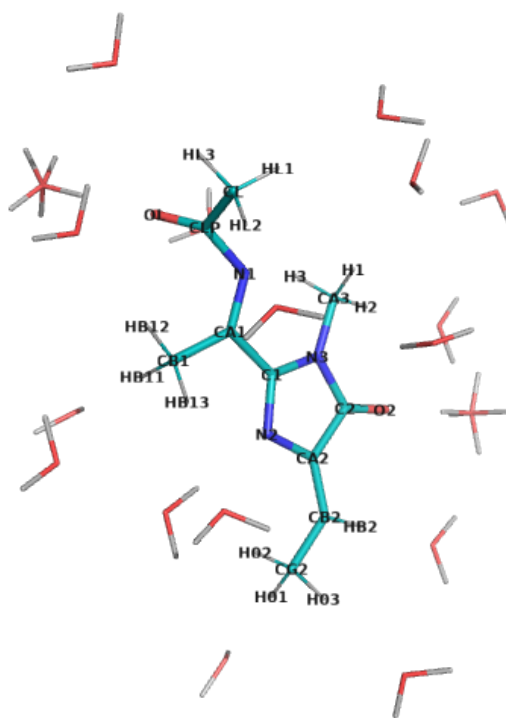


Figure S141: The molecule used for water complex calculations corresponding to N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S467: Statistics of calculated water interaction and dipole moment for N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.75/1.32	0.29/1.19	7.323	3.33/3.51	2.28
Optimal	0.66/1.40	0.23/0.78	2.685	3.33/3.51	4.68

Table S468: The comparison list of optimized atomic charges and their initial guess for N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.268	11.341
HL1	0.090	0.090	0.800
HL2	0.090	0.090	0.800
HL3	0.090	0.090	0.800
CLP	0.510	1.166	104.329
OL	-0.510	-0.523	7.580
N1	-0.410	-0.867	109.915
CA1	0.442	-0.250	80.747
CB1	-0.148	-0.039	37.119
HB11	0.090	0.090	1.152
HB12	0.090	0.090	1.152
HB13	0.090	0.090	1.152
C1	0.208	0.430	75.868
N2	-0.541	-0.578	44.740
N3	-0.080	-0.049	29.029
C2	0.407	0.514	21.806
O2	-0.489	-0.482	6.710
CA2	0.221	0.396	48.462
CB2	-0.105	-0.135	25.469
HB2	0.150	0.150	3.270
CG2	-0.270	-0.274	15.277
H01	0.090	0.090	1.175
H02	0.090	0.090	1.175
H03	0.090	0.090	1.175
CA3	-0.195	-0.271	3.821
H1	0.090	0.090	0.000
H2	0.090	0.090	0.000
H3	0.090	0.090	0.000

Table S469: Interaction energies and geometries between probe water and selected N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HL1-CL	0.0	-2.10/-1.55/-1.57		2.54/2.67/2.61	
2	HL2-CL	0.0	-2.25/-2.36/-1.62		2.54/2.64/2.61	
3	HL3-CL	0.0	-1.15/-0.60/-2.15		2.59/2.70/2.58	
4	OL-CLP	0.0	-4.98/-6.25/-4.00		1.89/1.76/1.82	
5	OL-CLP	90.0	-5.11/-6.50/-4.99		1.89/1.76/1.80	
6	OL-CLP	180.0	-4.85/-5.78/-5.34		1.89/1.77/1.79	
7	OL-CLP	270.0	-4.63/-5.54/-4.21		1.90/1.77/1.82	
8	N1-CLP	0.0	-0.23/-0.37/-1.31		5.78/5.00/4.59	
9	HB11-CB1	0.0	-1.38/-2.00/-0.49		2.55/2.57/2.69	
10	HB12-CB1	0.0	-0.72/-1.46/-1.85		2.81/2.73/2.91	
11	HB13-CB1	0.0	-1.01/-1.73/-0.25		2.74/2.62/2.82	
12	N2-C1	0.0	-2.51/-3.29/-3.20		2.28/2.38/2.41	
13	N3-C1	0.0	-0.77/-1.40/-1.19		2.73/2.46/2.76	
14	O2-C2	0.0	-5.45/-5.66/-5.15		1.86/1.78/1.80	
15	O2-C2	90.0	-5.58/-5.60/-4.69		1.85/1.78/1.80	
16	O2-C2	180.0	-5.46/-5.40/-4.13		1.85/1.78/1.81	
17	O2-C2	270.0	-5.62/-5.67/-4.75		1.85/1.78/1.80	
18	HB2-CB2	0.0	-2.03/-1.80/-2.78		2.28/2.47/2.44	
19	HB2-CB2	0.0	-2.03/-1.80/-2.78		2.28/2.47/2.44	
20	H01-CG2	0.0	-1.49/-0.84/-1.05		2.64/2.74/2.72	
21	H02-CG2	0.0	-0.52/-0.97/-0.31		5.47/5.00/5.00	
22	H03-CG2	0.0	-1.46/-0.82/-1.02		2.65/2.74/2.72	

1.152 Small molecule E of (4Z)-4-(4-hydroxybenzylidene)-2-[3-(methylthio)propanimidoyl]-5-oxo-4acetic 5-dihydro-1H-imidazol-1-ylacetic acid (NRQ)

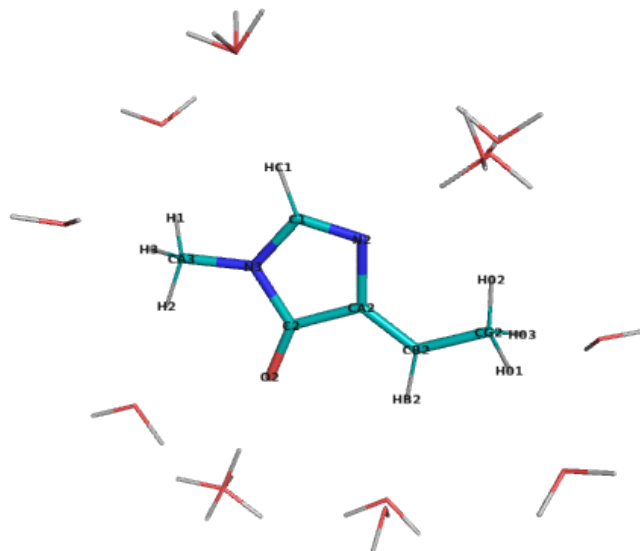


Figure S142: The molecule used for water complex calculations corresponding to N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S470: Statistics of calculated water interaction and dipole moment for N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.19/2.12	0.07/0.13	7.647	2.46/0.89	158.38
Optimal	0.94/2.13	0.10/0.17	2.146	2.46/2.55	8.93

Table S471: The comparison list of optimized atomic charges and their initial guess for N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
C1	0.199	0.106	19.346
HC1	0.163	0.105	1.731
N2	-0.541	-0.710	39.437
N3	-0.080	-0.069	12.754
C2	0.407	0.513	21.676
O2	-0.489	-0.482	6.710
CA2	0.221	0.527	45.069
CB2	-0.105	-0.135	25.469
HB2	0.150	0.150	3.270
CG2	-0.270	-0.274	15.277
H01	0.090	0.090	1.175
H02	0.090	0.090	1.175
H03	0.090	0.090	1.175
CA3	-0.195	-0.271	2.890
H1	0.090	0.090	0.000
H2	0.090	0.090	0.000
H3	0.090	0.090	0.000

Table S472: Interaction energies and geometries between probe water and selected N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HC1-C1	0.0	-3.15/-4.11/-1.43		2.34/2.20/2.33	
2	HC1-C1	90.0	-3.21/-4.10/-1.37		2.33/2.20/2.34	
3	N2-C1	0.0	-4.51/-4.26/-4.86		2.11/2.08/2.03	
4	N2-C1	90.0	-6.59/-4.46/-5.93		1.93/2.06/2.00	
5	N2-C1	180.0	-5.43/-3.99/-6.34		1.95/2.08/1.99	
6	N2-C1	270.0	-6.59/-4.46/-5.93		1.93/2.06/2.00	
7	O2-C2	0.0	-5.42/-5.56/-4.81		1.86/1.78/1.80	
8	O2-C2	90.0	-5.74/-5.68/-4.53		1.85/1.78/1.80	
9	O2-C2	180.0	-5.75/-5.56/-4.05		1.85/1.78/1.82	
10	O2-C2	270.0	-5.74/-5.68/-4.53		1.85/1.78/1.80	
11	HB2-CB2	0.0	-1.63/-1.62/-3.04		2.31/2.47/2.43	
12	HB2-CB2	90.0	-0.37/-1.03/-2.49		2.51/2.52/2.46	
13	H01-CG2	0.0	-1.15/-0.59/-0.97		2.69/2.76/2.73	
14	H03-CG2	0.0	-1.15/-0.59/-0.97		2.69/2.76/2.73	
15	H1-CA3	0.0	-2.00/-1.85/-1.10		2.59/2.64/2.69	
16	H3-CA3	0.0	-2.00/-1.85/-1.10		2.59/2.64/2.69	

1.153 Small molecule used for (2s)-2-amino-4,4-difluorobutanoicacid(OBF)

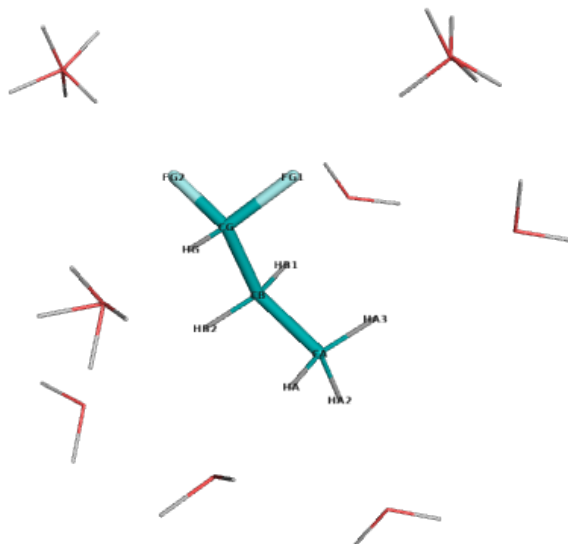


Figure S143: The molecule used for water complex calculations corresponding to 1,1-difluoropropane, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S473: Statistics of calculated water interaction and dipole moment for 1,1-difluoropropane.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.19/0.34	0.22/0.30	1.148	2.42/2.29	3.15
Optimal	0.16/0.30	0.22/0.31	1.168	2.42/2.63	2.71

Table S474: The comparison list of optimized atomic charges and their initial guess for 1,1-difluoropropane, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.600
HA2	0.090	0.090	0.600
CA	-0.270	-0.270	4.493
HA	0.090	0.090	0.600
CB	-0.059	-0.119	8.327
HB1	0.090	0.090	0.786
HB2	0.090	0.090	0.786
CG	0.092	0.219	8.333
HG	0.149	0.100	2.580
FG1	-0.181	-0.190	2.615
FG2	-0.181	-0.190	2.615

Table S475: Interaction energies and geometries between probe water and selected 1,1-difluoropropane site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.82/-0.57/-0.56	2.64/2.70/2.70
2	HA2-CA	0.0	-1.23/-1.17/-1.03	2.74/2.71/2.72
3	HA-CA	0.0	-1.59/-1.56/-1.45	2.69/2.67/2.68
4	HB1-CB	0.0	-1.15/-0.89/-0.83	2.62/2.68/2.70
5	HB2-CB	0.0	-1.62/-1.64/-1.49	2.62/2.65/2.66
6	HG-CG	0.0	-2.19/-2.16/-1.92	2.48/2.54/2.57
7	HG-CG	90.0	-2.30/-2.21/-1.96	2.46/2.54/2.56
8	FG1-CG	0.0	-2.12/-2.29/-2.17	2.19/1.89/1.89
9	FG1-CG	90.0	-2.57/-2.88/-2.68	2.17/1.87/1.87
10	FG1-CG	180.0	-2.54/-2.76/-2.56	2.17/1.87/1.88
11	FG1-CG	270.0	-2.15/-2.22/-2.09	2.19/1.89/1.90
12	FG2-CG	0.0	-2.20/-2.11/-2.00	2.19/1.90/1.91
13	FG2-CG	90.0	-2.18/-2.06/-1.93	2.19/1.90/1.91
14	FG2-CG	180.0	-2.51/-2.61/-2.41	2.18/1.88/1.89
15	FG2-CG	270.0	-2.56/-2.72/-2.52	2.18/1.87/1.88

1.154 Small molecule used for s-(2-hydroxyethyl)-l-cysteine(OCY)

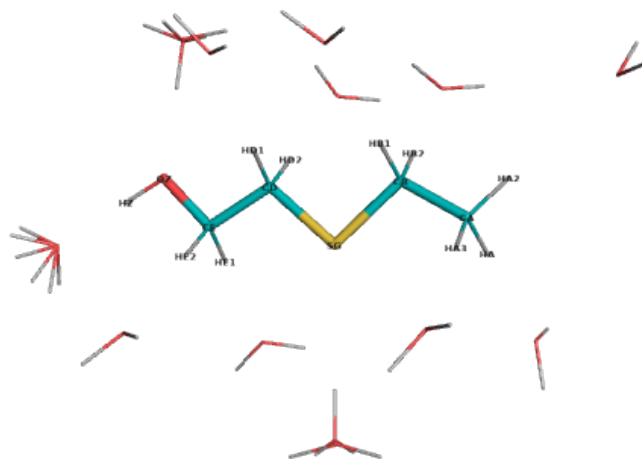


Figure S144: The molecule used for water complex calculations corresponding to 2-(ethylsulfanyl)ethan-1-ol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S476: Statistics of calculated water interaction and dipole moment for 2-(ethylsulfanyl)ethan-1-ol.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.49/1.32	0.23/0.56	1.584	0.16/0.48	52.88
Optimal	0.19/0.50	0.20/0.49	1.952	0.16/0.24	61.17

Table S477: The comparison list of optimized atomic charges and their initial guess for 2-(ethylsulfanyl)ethan-1-ol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.045
HA	0.090	0.090	0.000
CB	-0.125	-0.066	0.045
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
SG	-0.151	-0.236	20.887
CD	0.024	-0.058	21.222
HD1	0.090	0.090	0.000
HD2	0.090	0.090	0.000
CE	-0.113	0.049	14.230
HE2	0.090	0.090	0.000
HE1	0.090	0.090	0.000
OZ	-0.593	-0.649	2.250
HZ	0.418	0.420	0.000

Table S478: Interaction energies and geometries between probe water and selected 2-(ethylsulfanyl)ethan-1-ol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.67/-0.38/-0.30	2.72/2.77/2.77
2	HA2-CA	0.0	-1.00/-0.71/-0.82	2.78/2.76/2.74
3	HA-CA	0.0	-0.48/-0.33/-0.24	2.78/2.79/2.79
4	HB1-CB	0.0	-1.25/-1.22/-1.21	2.69/2.70/2.69
5	HB2-CB	0.0	-1.25/-1.22/-1.21	2.69/2.70/2.69
6	SG-CB	0.0	-1.37/-1.69/-2.12	2.90/2.41/2.35
7	SG-CB	90.0	-1.81/-2.00/-2.69	2.82/2.39/2.32
8	SG-CB	180.0	-1.68/-2.17/-3.00	2.87/2.38/2.31
9	SG-CB	270.0	-1.81/-2.00/-2.69	2.82/2.39/2.32
10	HD1-CD	0.0	-0.89/-0.85/-0.59	2.65/2.68/2.72
11	HD2-CD	0.0	-0.89/-0.85/-0.59	2.65/2.69/2.72
12	HE2-CE	0.0	-0.90/-0.74/-1.16	2.69/2.74/2.67
13	HE1-CE	0.0	-0.90/-0.74/-1.16	2.69/2.74/2.67
14	OZ-CE	0.0	-5.69/-5.77/-6.05	1.85/1.87/1.86
15	OZ-CE	90.0	-5.76/-5.63/-6.00	1.83/1.87/1.86
16	OZ-CE	180.0	-4.89/-4.82/-5.39	1.88/1.88/1.86
17	OZ-CE	270.0	-5.76/-5.63/-6.00	1.83/1.87/1.86
18	HZ-OZ	0.0	-6.26/-6.37/-6.56	1.81/1.82/1.82
19	HZ-OZ	45.0	-6.37/-6.39/-6.60	1.80/1.82/1.82
20	HZ-OZ	90.0	-6.47/-6.41/-6.64	1.79/1.82/1.82
21	HZ-OZ	135.0	-6.37/-6.39/-6.60	1.80/1.82/1.82

1.155 Small molecule used for (betar)-beta-hydroxy-1-tyrosine(OMX)

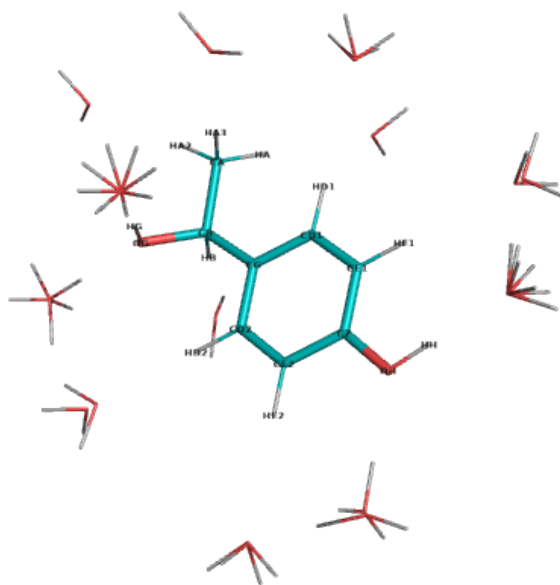


Figure S145: The molecule used for water complex calculations corresponding to 4-[(1S)-1-hydroxyethyl]benzen-1-olate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S479: Statistics of calculated water interaction and dipole moment for 4-[(1S)-1-hydroxyethyl]benzen-1-olate.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.40/0.79	0.08/0.21	2.209	2.79/3.69	2.55
Optimal	0.40/0.75	0.08/0.21	2.179	2.79/3.63	0.05

Table S480: The comparison list of optimized atomic charges and their initial guess for 4-[(1S)-1-hydroxyethyl]benzen-1-olate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.269	0.000
HA	0.090	0.090	0.000
CB	0.091	0.132	3.300
HB	0.090	0.090	0.000
OG	-0.621	-0.643	4.339
HG	0.412	0.413	0.300
CG	0.028	-0.001	4.230
CD1	-0.115	-0.109	2.130
HD1	0.115	0.115	0.000
CD2	-0.115	-0.109	2.130
HD2	0.115	0.115	0.000
CE1	-0.115	-0.116	0.000
HE1	0.115	0.115	0.000
CE2	-0.115	-0.116	0.000
HE2	0.115	0.115	0.000
CZ	0.110	0.108	0.000
OH	-0.530	-0.530	0.000
HH	0.420	0.420	0.000

Table S481: Interaction energies and geometries between probe water and selected 4-[(1S)-1-hydroxyethyl]benzen-1-olate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-1.29/-1.45/-1.50	2.71/2.68/2.67
2	HA2-CA	0.0	-0.41/-0.12/-0.18	2.85/2.81/2.79
3	HA-CA	0.0	-1.14/-1.36/-1.45	2.73/2.68/2.67
4	HB-CB	0.0	-0.63/-0.29/-0.40	2.76/2.78/2.76
5	OG-CB	0.0	-5.66/-5.25/-5.48	1.84/1.88/1.87
6	OG-CB	90.0	-5.84/-5.57/-5.73	1.82/1.87/1.86
7	OG-CB	180.0	-5.41/-5.58/-5.69	1.85/1.87/1.86
8	OG-CB	270.0	-5.68/-5.40/-5.60	1.83/1.87/1.87
9	HG-OG	0.0	-5.54/-5.73/-5.63	1.82/1.86/1.86
10	HG-OG	45.0	-5.19/-5.63/-5.52	1.83/1.86/1.86
11	HG-OG	90.0	-5.73/-5.85/-5.76	1.81/1.86/1.86
12	HG-OG	135.0	-6.08/-5.96/-5.88	1.80/1.85/1.86
13	HD1-CD1	0.0	-1.59/-2.00/-2.04	2.84/2.77/2.76
14	HD1-CD1	90.0	-1.62/-2.06/-2.12	2.89/2.75/2.75
15	HD2-CD2	0.0	-0.84/-0.23/-0.20	2.47/2.68/2.68
16	HE1-CE1	0.0	-2.07/-2.36/-2.34	2.65/2.64/2.64
17	HE1-CE1	90.0	-2.68/-2.60/-2.58	2.49/2.61/2.61
18	HE2-CE2	0.0	-0.92/-0.24/-0.22	2.60/2.75/2.75
19	HE2-CE2	90.0	-0.81/-0.17/-0.14	2.62/2.77/2.77
20	OH-CZ	0.0	-4.11/-3.91/-3.93	1.92/1.93/1.93
21	OH-CZ	90.0	-4.78/-4.32/-4.35	1.87/1.92/1.92
22	OH-CZ	180.0	-3.82/-4.25/-4.29	1.95/1.92/1.92
23	OH-CZ	270.0	-4.82/-4.38/-4.40	1.87/1.92/1.92
24	HH-OH	0.0	-7.18/-6.97/-6.93	1.81/1.87/1.87
25	HH-OH	45.0	-7.69/-7.19/-7.15	1.80/1.87/1.87
26	HH-OH	90.0	-8.15/-7.39/-7.35	1.79/1.86/1.86
27	HH-OH	135.0	-7.72/-7.20/-7.16	1.80/1.87/1.87

1.156 Small molecule used for 4-benzoyl-phenylalanine(PBF)

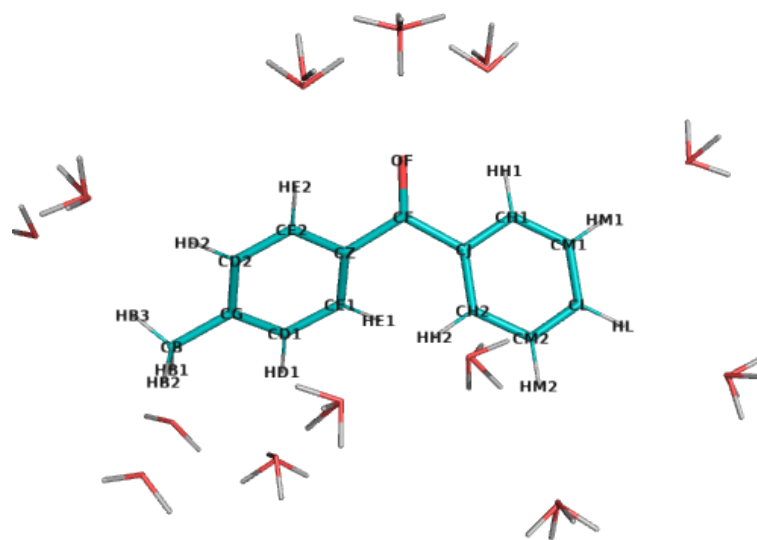


Figure S146: The molecule used for water complex calculations corresponding to (4-methylphenyl)(phenyl)methanone, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S482: Statistics of calculated water interaction and dipole moment for (4-methylphenyl)(phenyl)methanone.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.67/1.50	0.12/0.26	1.977	3.76/3.41	7.55
Optimal	0.78/1.79	0.12/0.25	2.009	3.76/4.01	0.31

Table S483: The comparison list of optimized atomic charges and their initial guess for (4-methylphenyl)(phenyl)methanone, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.267	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.000	-0.001	0.000
CD1	-0.115	-0.115	0.000
HD1	0.115	0.115	0.000
CD2	-0.115	-0.115	0.000
HD2	0.115	0.115	0.000
CE1	-0.115	-0.117	1.700
HE1	0.115	0.115	0.000
CE2	-0.115	-0.117	1.700
HE2	0.115	0.115	0.000
CZ	0.173	0.028	3.400
CF	0.179	0.407	3.400
CJ	0.082	0.028	3.400
OF	-0.434	-0.459	0.000
CH1	-0.115	-0.117	1.700
HH1	0.115	0.115	0.000
CH2	-0.115	-0.117	1.700
HH2	0.115	0.115	0.000
CM1	-0.115	-0.114	0.000
HM1	0.115	0.115	0.000
CM2	-0.115	-0.114	0.000
HM2	0.115	0.115	0.000
CL	-0.115	-0.115	0.000
HL	0.115	0.115	0.000

Table S484: Interaction energies and geometries between probe water and selected (4-methylphenyl)(phenyl)methanone site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.32/-0.99/-0.89	2.70/2.73/2.73
2	HB1-CB	0.0	-1.32/-1.03/-0.94	2.72/2.74/2.74
3	HB2-CB	0.0	-1.12/-0.77/-0.66	2.72/2.75/2.76
4	HD1-CD1	0.0	-1.58/-1.57/-1.40	2.64/2.67/2.68
5	HD1-CD1	90.0	-1.83/-1.63/-1.47	2.56/2.66/2.67
6	HD2-CD2	0.0	-1.53/-1.30/-1.15	2.63/2.68/2.69
7	HD2-CD2	90.0	-1.73/-1.33/-1.19	2.55/2.67/2.68
8	HE1-CE1	0.0	-1.25/-2.34/-2.19	2.60/2.61/2.62
9	HE1-CE1	90.0	-0.40/-1.71/-1.56	2.69/2.65/2.66
10	HE2-CE2	0.0	-0.85/-0.20/-0.23	2.40/2.65/2.66
11	OF-CF	0.0	-5.57/-6.27/-5.98	1.86/1.69/1.69
12	OF-CF	90.0	-5.63/-6.47/-6.05	1.86/1.68/1.69
13	OF-CF	180.0	-5.60/-6.51/-6.00	1.86/1.68/1.69
14	OF-CF	270.0	-5.62/-6.46/-6.04	1.86/1.68/1.69
15	HH2-CH2	0.0	-0.95/-2.54/-2.37	2.58/2.64/2.63
16	HH2-CH2	90.0	-0.35/-2.14/-1.86	2.68/2.66/2.66
17	HM1-CM1	0.0	-1.52/-1.08/-1.14	2.60/2.69/2.69
18	HM1-CM1	90.0	-1.67/-1.11/-1.17	2.55/2.69/2.69
19	HM2-CM2	0.0	-1.57/-1.39/-1.38	2.62/2.69/2.69
20	HM2-CM2	90.0	-1.74/-1.45/-1.43	2.56/2.68/2.68
21	HL-CL	0.0	-1.65/-1.20/-1.22	2.59/2.70/2.70
22	HL-CL	90.0	-1.83/-1.26/-1.28	2.54/2.69/2.69

1.157 Small molecule used for pentafluoro-phenylalanine(PF5)

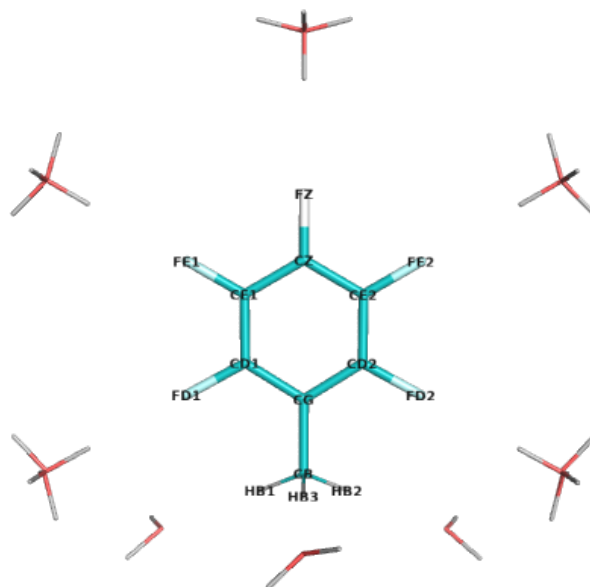


Figure S147: The molecule used for water complex calculations corresponding to 1,2,3,4,5-pentafluoro-6-methylbenzene, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S485: Statistics of calculated water interaction and dipole moment for 1,2,3,4,5-pentafluoro-6-methylbenzene.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.70/1.19	0.30/0.36	4.619	2.41/3.83	0.17
Optimal	0.09/0.19	0.23/0.26	2.055	2.41/2.96	0.36

Table S486: The comparison list of optimized atomic charges and their initial guess for 1,2,3,4,5-pentafluoro-6-methylbenzene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.323	0.845
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.182	0.269	10.912
CD1	0.208	0.268	12.535
FD1	-0.155	-0.194	7.300
CD2	0.208	0.268	12.535
FD2	-0.155	-0.194	7.300
CE1	-0.133	-0.087	16.044
FE1	-0.082	-0.191	7.365
CE2	-0.133	-0.087	16.044
FE2	-0.082	-0.191	7.365
CZ	0.264	0.370	18.462
FZ	-0.122	-0.178	10.324

Table S487: Interaction energies and geometries between probe water and selected 1,2,3,4,5-pentafluoro-6-methylbenzene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.96/-1.96/-2.25	2.56/2.62/2.61
2	HB1-CB	0.0	-1.48/-1.60/-1.77	2.58/2.64/2.64
3	HB2-CB	0.0	-1.48/-1.60/-1.77	2.58/2.64/2.64
4	FD1-CD1	0.0	-0.92/-0.73/-0.73	2.33/2.09/2.06
5	FD1-CD1	90.0	-1.29/-1.26/-1.37	2.30/2.05/2.02
6	FD1-CD1	180.0	-1.62/-1.80/-2.11	2.27/2.01/1.98
7	FD1-CD1	270.0	-1.27/-1.26/-1.38	2.30/2.05/2.02
8	FD2-CD2	0.0	-0.92/-0.73/-0.73	2.33/2.09/2.06
9	FD2-CD2	90.0	-1.27/-1.26/-1.38	2.30/2.05/2.02
10	FD2-CD2	180.0	-1.62/-1.80/-2.11	2.27/2.01/1.98
11	FD2-CD2	270.0	-1.29/-1.26/-1.37	2.30/2.05/2.02
12	FE1-CE1	0.0	-1.33/-1.31/-2.34	2.32/2.09/1.96
13	FE1-CE1	90.0	-1.31/-1.35/-2.40	2.32/2.09/1.97
14	FE1-CE1	180.0	-1.42/-1.49/-2.62	2.32/2.08/1.96
15	FE1-CE1	270.0	-1.31/-1.36/-2.41	2.32/2.09/1.96
16	FE2-CE2	0.0	-1.33/-1.31/-2.34	2.32/2.09/1.96
17	FE2-CE2	90.0	-1.31/-1.36/-2.41	2.32/2.09/1.96
18	FE2-CE2	180.0	-1.42/-1.49/-2.62	2.32/2.08/1.96
19	FE2-CE2	270.0	-1.31/-1.35/-2.40	2.32/2.09/1.97
20	FZ-CZ	0.0	-1.31/-1.38/-1.81	2.33/2.08/2.03
21	FZ-CZ	90.0	-1.23/-1.32/-1.69	2.34/2.09/2.04
22	FZ-CZ	180.0	-1.31/-1.38/-1.81	2.33/2.08/2.03
23	FZ-CZ	270.0	-1.23/-1.33/-1.70	2.35/2.09/2.04

1.158 Small molecule used for aspartylphosphate(PHD)

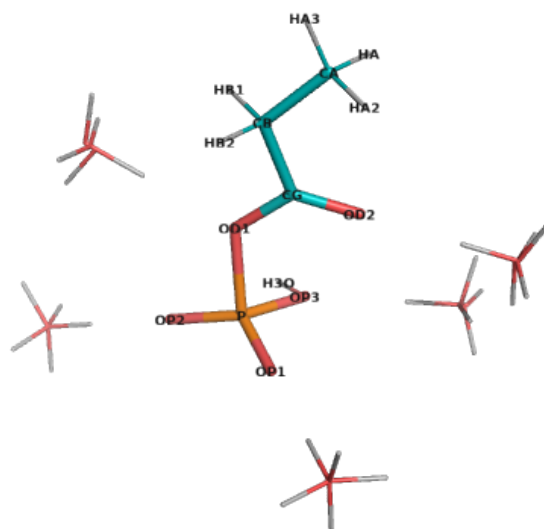


Figure S148: The molecule used for water complex calculations corresponding to (propanoyloxy)phosphonic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S488: Statistics of calculated water interaction and dipole moment for (propanoyloxy)phosphonic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.96/4.11	0.13/0.22	6.150	8.11/7.00	18.52
Optimal	0.35/0.73	0.12/0.22	3.565	8.11/6.93	1.26

Table S489: The comparison list of optimized atomic charges and their initial guess for (propanoyloxy)phosphonicacid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.269	0.125
HA	0.090	0.090	0.000
CB	-0.295	-0.220	2.765
HB1	0.072	0.090	0.125
HB2	0.091	0.090	0.125
CG	0.604	0.541	35.037
OD2	-0.450	-0.649	2.778
OD1	-0.454	-0.366	33.024
P	1.183	1.408	30.526
OP1	-0.719	-0.760	15.770
OP2	-0.719	-0.760	15.770
OP3	-0.651	-0.713	14.910
H3O	0.338	0.338	0.000

Table S490: Interaction energies and geometries between probe water and selected (propanoyloxy)phosphonicacid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	OD2-CG	0.0	-6.68/-6.16/-9.83	1.94/1.82/1.72
2	OD2-CG	90.0	-8.55/-8.73/-12.36	1.91/1.79/1.70
3	OD2-CG	180.0	-10.33/-10.81/-14.44	1.87/1.76/1.68
4	OD2-CG	270.0	-7.64/-7.63/-11.33	1.92/1.80/1.70
5	OD1-CG	0.0	-10.64/-10.78/-8.92	1.90/1.76/1.81
6	OD1-CG	90.0	-7.29/-7.23/-5.48	2.01/1.84/1.91
7	OD1-CG	180.0	-4.99/-4.96/-3.23	2.12/1.90/2.02
8	OD1-CG	270.0	-6.85/-6.83/-5.33	2.02/1.85/1.92
9	OP1-P	0.0	-12.37/-13.09/-13.46	1.79/1.68/1.67
10	OP1-P	90.0	-12.01/-12.34/-11.93	1.79/1.68/1.68
11	OP1-P	180.0	-12.17/-12.52/-12.29	1.79/1.68/1.68
12	OP1-P	270.0	-12.80/-13.41/-13.96	1.78/1.67/1.67
13	OP2-P	0.0	-12.37/-12.26/-11.85	1.77/1.68/1.67
14	OP2-P	90.0	-11.81/-11.63/-11.48	1.78/1.68/1.68
15	OP2-P	180.0	-12.42/-12.17/-12.05	1.77/1.68/1.67
16	OP2-P	270.0	-12.77/-12.66/-12.32	1.77/1.67/1.67
17	OP3-P	0.0	-5.78/-5.41/-5.05	2.05/1.96/1.98
18	OP3-P	90.0	-9.48/-9.74/-11.17	1.94/1.88/1.86
19	OP3-P	180.0	-11.51/-12.20/-13.22	1.90/1.85/1.84
20	OP3-P	270.0	-7.48/-7.45/-6.81	1.99/1.92/1.94

1.159 Small molecule used for aspartylphosphate(PHD)

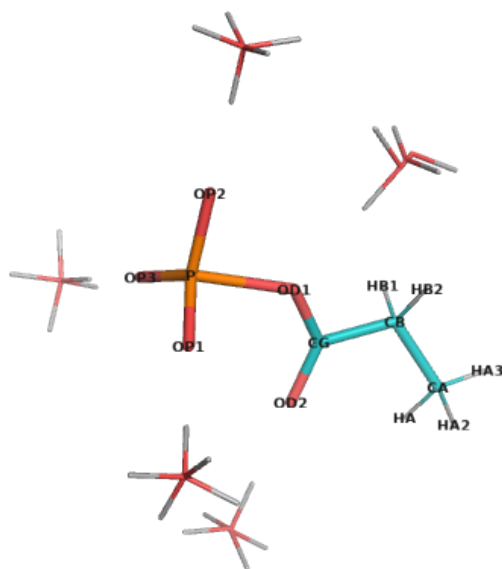


Figure S149: The molecule used for water complex calculations corresponding to (propanoyloxy)phosphonic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S491: Statistics of calculated water interaction and dipole moment for (propanoyloxy)phosphonic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	2.25/6.01	0.09/0.32	6.673	11.79/15.54	2.20
Optimal	0.82/1.83	0.09/0.21	4.019	11.79/13.31	2.71

Table S492: The comparison list of optimized atomic charges and their initial guess for (propanoyloxy)phosphonicacid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.269	0.125
HA	0.090	0.090	0.000
CB	-0.229	-0.220	2.765
HB1	0.128	0.090	0.125
HB2	0.017	0.090	0.125
CG	0.691	0.535	41.288
OD2	-0.644	-0.649	2.778
OD1	-0.632	-0.233	37.616
P	1.402	0.897	39.985
OP1	-0.911	-0.837	22.078
OP2	-0.911	-0.837	22.078
OP3	-0.911	-0.837	22.078

Table S493: Interaction energies and geometries between probe water and selected (propanoyloxy)phosphonicacid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	OD2-CG	0.0	-11.99/-10.44/-10.51	1.78/1.72/1.72
2	OD2-CG	90.0	-13.88/-13.56/-13.74	1.77/1.70/1.69
3	OD2-CG	180.0	-17.18/-17.84/-18.40	1.74/1.67/1.66
4	OD2-CG	270.0	-14.16/-13.93/-14.27	1.77/1.69/1.69
5	OD1-CG	0.0	-18.80/-18.95/-15.33	1.89/1.76/1.88
6	OD1-CG	90.0	-12.82/-12.36/-8.34	2.05/1.88/2.12
7	OD1-CG	180.0	-10.06/-8.23/-4.05	2.19/1.98/2.51
8	OD1-CG	270.0	-13.08/-11.82/-8.37	2.03/1.90/2.12
9	OP1-P	0.0	-20.98/-20.89/-20.50	1.66/1.61/1.62
10	OP1-P	90.0	-19.93/-19.38/-19.28	1.67/1.61/1.62
11	OP1-P	180.0	-19.71/-19.03/-19.45	1.67/1.62/1.62
12	OP1-P	270.0	-20.93/-20.61/-20.80	1.66/1.61/1.61
13	OP2-P	0.0	-21.14/-20.41/-19.51	1.65/1.61/1.62
14	OP2-P	90.0	-20.90/-19.92/-19.80	1.65/1.61/1.61
15	OP2-P	180.0	-20.56/-19.48/-19.92	1.66/1.61/1.61
16	OP2-P	270.0	-20.90/-20.02/-19.83	1.65/1.61/1.61
17	OP3-P	0.0	-20.95/-20.74/-20.43	1.66/1.61/1.62
18	OP3-P	90.0	-20.96/-20.65/-20.81	1.66/1.61/1.61
19	OP3-P	180.0	-19.75/-19.11/-19.47	1.67/1.62/1.62
20	OP3-P	270.0	-19.95/-19.33/-19.25	1.67/1.61/1.62

1.160 Small molecule used for aspartylphosphate(PHDP)

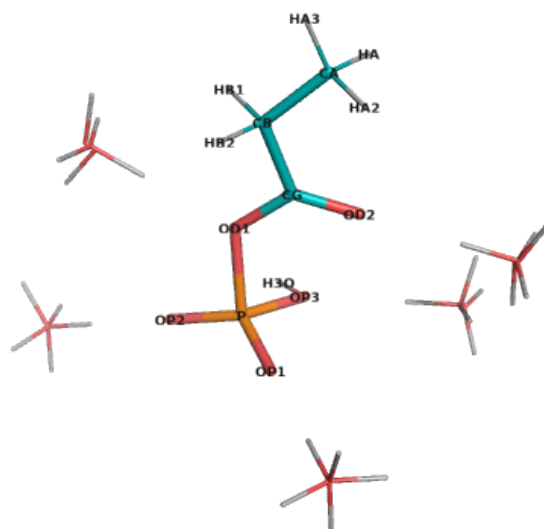


Figure S150: The molecule used for water complex calculations corresponding to (propanoyloxy)phosphonic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S494: Statistics of calculated water interaction and dipole moment for (propanoyloxy)phosphonic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.96/4.11	0.13/0.22	6.150	8.11/7.00	18.52
Optimal	0.35/0.73	0.12/0.22	3.565	8.11/6.93	1.26

Table S495: The comparison list of optimized atomic charges and their initial guess for (propanoyloxy)phosphonicacid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.269	0.125
HA	0.090	0.090	0.000
CB	-0.295	-0.220	2.765
HB1	0.072	0.090	0.125
HB2	0.091	0.090	0.125
CG	0.604	0.541	35.037
OD2	-0.450	-0.649	2.778
OD1	-0.454	-0.366	33.024
P	1.183	1.408	30.526
OP1	-0.719	-0.760	15.770
OP2	-0.719	-0.760	15.770
OP3	-0.651	-0.713	14.910
H3O	0.338	0.338	0.000

Table S496: Interaction energies and geometries between probe water and selected (propanoyloxy)phosphonicacid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	OD2-CG	0.0	-6.68/-6.16/-9.83	1.94/1.82/1.72
2	OD2-CG	90.0	-8.55/-8.73/-12.36	1.91/1.79/1.70
3	OD2-CG	180.0	-10.33/-10.81/-14.44	1.87/1.76/1.68
4	OD2-CG	270.0	-7.64/-7.63/-11.33	1.92/1.80/1.70
5	OD1-CG	0.0	-10.64/-10.78/-8.92	1.90/1.76/1.81
6	OD1-CG	90.0	-7.29/-7.23/-5.48	2.01/1.84/1.91
7	OD1-CG	180.0	-4.99/-4.96/-3.23	2.12/1.90/2.02
8	OD1-CG	270.0	-6.85/-6.83/-5.33	2.02/1.85/1.92
9	OP1-P	0.0	-12.37/-13.09/-13.46	1.79/1.68/1.67
10	OP1-P	90.0	-12.01/-12.34/-11.93	1.79/1.68/1.68
11	OP1-P	180.0	-12.17/-12.52/-12.29	1.79/1.68/1.68
12	OP1-P	270.0	-12.80/-13.41/-13.96	1.78/1.67/1.67
13	OP2-P	0.0	-12.37/-12.26/-11.85	1.77/1.68/1.67
14	OP2-P	90.0	-11.81/-11.63/-11.48	1.78/1.68/1.68
15	OP2-P	180.0	-12.42/-12.17/-12.05	1.77/1.68/1.67
16	OP2-P	270.0	-12.77/-12.66/-12.32	1.77/1.67/1.67
17	OP3-P	0.0	-5.78/-5.41/-5.05	2.05/1.96/1.98
18	OP3-P	90.0	-9.48/-9.74/-11.17	1.94/1.88/1.86
19	OP3-P	180.0	-11.51/-12.20/-13.22	1.90/1.85/1.84
20	OP3-P	270.0	-7.48/-7.45/-6.81	1.99/1.92/1.94

1.161 Small molecule used for aspartylphosphate(PHDP)

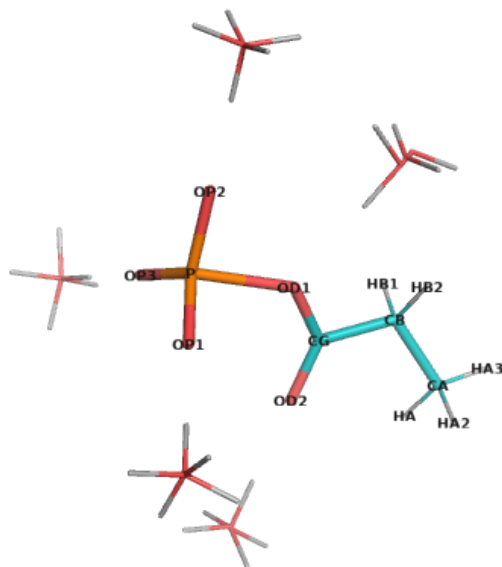


Figure S151: The molecule used for water complex calculations corresponding to (propanoyloxy)phosphonic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S497: Statistics of calculated water interaction and dipole moment for (propanoyloxy)phosphonic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	2.25/6.01	0.09/0.32	6.673	11.79/15.54	2.20
Optimal	0.82/1.83	0.09/0.21	4.019	11.79/13.31	2.71

Table S498: The comparison list of optimized atomic charges and their initial guess for (propanoyloxy)phosphonicacid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.269	0.125
HA	0.090	0.090	0.000
CB	-0.229	-0.220	2.765
HB1	0.128	0.090	0.125
HB2	0.017	0.090	0.125
CG	0.691	0.535	41.288
OD2	-0.644	-0.649	2.778
OD1	-0.632	-0.233	37.616
P	1.402	0.897	39.985
OP1	-0.911	-0.837	22.078
OP2	-0.911	-0.837	22.078
OP3	-0.911	-0.837	22.078

Table S499: Interaction energies and geometries between probe water and selected (propanoyloxy)phosphonicacid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	OD2-CG	0.0	-11.99/-10.44/-10.51	1.78/1.72/1.72
2	OD2-CG	90.0	-13.88/-13.56/-13.74	1.77/1.70/1.69
3	OD2-CG	180.0	-17.18/-17.84/-18.40	1.74/1.67/1.66
4	OD2-CG	270.0	-14.16/-13.93/-14.27	1.77/1.69/1.69
5	OD1-CG	0.0	-18.80/-18.95/-15.33	1.89/1.76/1.88
6	OD1-CG	90.0	-12.82/-12.36/-8.34	2.05/1.88/2.12
7	OD1-CG	180.0	-10.06/-8.23/-4.05	2.19/1.98/2.51
8	OD1-CG	270.0	-13.08/-11.82/-8.37	2.03/1.90/2.12
9	OP1-P	0.0	-20.98/-20.89/-20.50	1.66/1.61/1.62
10	OP1-P	90.0	-19.93/-19.38/-19.28	1.67/1.61/1.62
11	OP1-P	180.0	-19.71/-19.03/-19.45	1.67/1.62/1.62
12	OP1-P	270.0	-20.93/-20.61/-20.80	1.66/1.61/1.61
13	OP2-P	0.0	-21.14/-20.41/-19.51	1.65/1.61/1.62
14	OP2-P	90.0	-20.90/-19.92/-19.80	1.65/1.61/1.61
15	OP2-P	180.0	-20.56/-19.48/-19.92	1.66/1.61/1.61
16	OP2-P	270.0	-20.90/-20.02/-19.83	1.65/1.61/1.61
17	OP3-P	0.0	-20.95/-20.74/-20.43	1.66/1.61/1.62
18	OP3-P	90.0	-20.96/-20.65/-20.81	1.66/1.61/1.61
19	OP3-P	180.0	-19.75/-19.11/-19.47	1.67/1.62/1.62
20	OP3-P	270.0	-19.95/-19.33/-19.25	1.67/1.61/1.62

1.162 Small molecule A of [(4Z)-2-[(1S)-1-aminoethyl]-4-(4-hydroxybenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl]acetic acid(PIA)

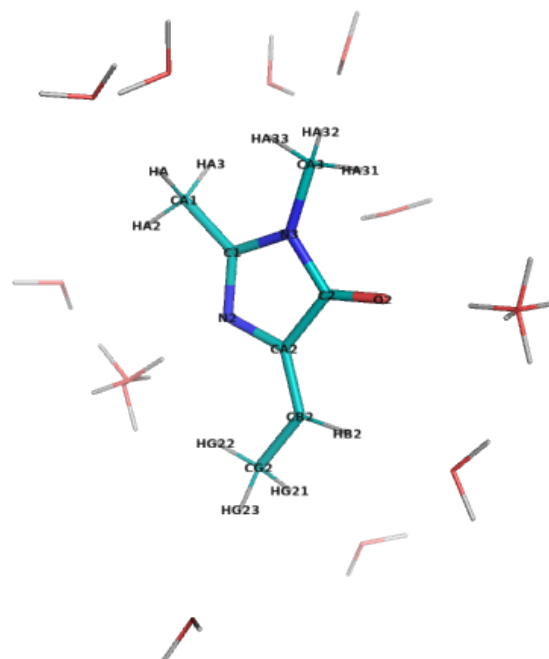


Figure S152: The molecule used for water complex calculations corresponding to (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S500: Statistics of calculated water interaction and dipole moment for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.92/1.64	0.10/0.25	6.526	3.17/0.45	27.81
Optimal	0.49/1.31	0.09/0.22	3.053	3.17/3.55	14.34

Table S501: The comparison list of optimized atomic charges and their initial guess for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA1	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
HA2	0.090	0.090	0.000
HA3	0.090	0.090	0.000
C1	0.233	0.074	23.781
N2	-0.679	-0.703	41.871
N3	-0.080	-0.079	15.706
C2	0.407	0.509	24.002
O2	-0.489	-0.482	6.710
CA2	0.288	0.516	47.153
CB2	-0.105	-0.135	25.469
HB2	0.150	0.150	3.270
CG2	-0.270	-0.274	15.277
HG21	0.090	0.090	1.175
HG22	0.090	0.090	1.175
HG23	0.090	0.090	1.175
CA3	-0.195	-0.271	3.821
HA31	0.090	0.090	0.000
HA32	0.090	0.090	0.000
HA33	0.090	0.090	0.000

Table S502: Interaction energies and geometries between probe water and selected (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA-CA1	0.0	-2.17/-2.61/-1.51		2.59/2.58/2.65	
2	HA2-CA1	0.0	-0.97/-0.86/0.05		2.58/2.64/2.77	
3	HA3-CA1	0.0	-2.55/-2.73/-1.57		2.52/2.57/2.64	
4	N2-C1	0.0	-4.99/-6.30/-5.60		2.09/2.01/2.02	
5	N2-C1	90.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
6	N2-C1	180.0	-5.35/-5.42/-6.38		1.95/2.01/1.99	
7	N2-C1	270.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
8	N3-C1	0.0	-0.26/-0.82/-0.78		2.74/2.52/2.49	
9	O2-C2	0.0	-5.51/-5.57/-5.00		1.85/1.78/1.80	
10	O2-C2	90.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
11	O2-C2	180.0	-5.92/-5.61/-4.27		1.84/1.78/1.81	
12	O2-C2	270.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
13	HB2-CB2	0.0	-1.40/-1.60/-2.82		2.32/2.47/2.44	
14	HG21-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
15	HG23-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
16	HA32-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	
17	HA33-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	

1.163 Small molecule B of [(4Z)-2-[(1S)-1-aminoethyl]-4-(4-hydroxybenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl]acetic acid (PIA)

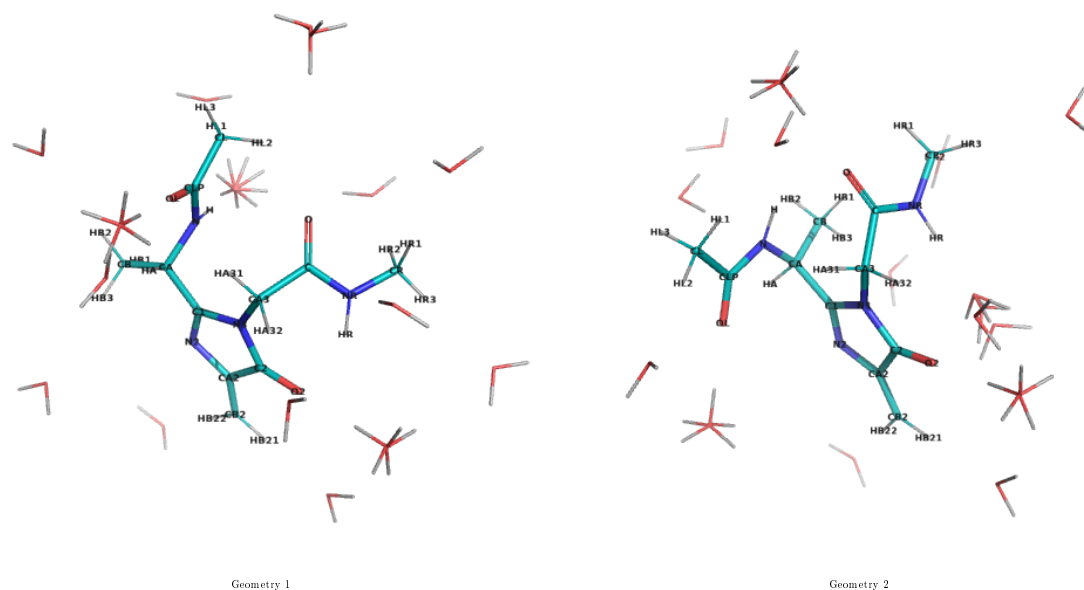


Table S503: The molecule used for water complex calculations corresponding to N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S504: Statistics of calculated water interaction and dipole moment for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide.

		RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
		Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Geometry 1	Initial	0.86 / 2.05	0.07 / 0.17	6.601	1.19 / 4.07	1.19
Geometry 2	Initial	1.02 / 2.07	0.09 / 0.23	6.126	6.37 / 4.43	6.37
Sum of geometries	Initial	0.95 / 2.07	0.08 / 0.23	12.727	-	-
Geometry 1	Optimal	0.36 / 0.81	0.07 / 0.16	2.460	1.19 / 1.37	1.19
Geometry 2	Optimal	0.51 / 0.91	0.08 / 0.19	2.701	6.37 / 7.25	6.37
Sum of geometries	Optimal	0.45 / 0.91	0.08 / 0.19	5.161	-	-

Table S505: The comparison list of optimized atomic charges and their initial guess for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
C1	0.233	0.164	24.002
N2	-0.679	-0.703	41.104
N3	-0.031	-0.499	22.994
C2	0.407	0.613	23.378
O2	-0.489	-0.482	6.517
CA2	0.466	0.512	42.773
CB2	-0.593	-0.444	13.655
HB21	0.230	0.230	0.950
HB22	0.230	0.230	0.950
CA3	-0.154	0.043	13.461
HA31	0.090	0.090	0.177
HA32	0.090	0.090	0.177
C	0.510	0.499	10.097
O	-0.510	-0.517	3.479
NR	-0.470	-0.442	6.773
HR	0.310	0.299	0.000
CR	-0.110	-0.108	0.239
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S506: Interaction energies and geometries between probe water and selected N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
Geometry 1				
1	O-C	0.0	-5.45/-5.47/-6.22	1.84/1.77/1.76
2	O-C	90.0	-6.01/-6.48/-6.53	1.83/1.75/1.76
3	O-C	180.0	-5.96/-6.64/-6.64	1.83/1.75/1.75
4	O-C	270.0	-5.67/-5.94/-6.62	1.84/1.76/1.75
5	NR-C	0.0	-1.32/-1.50/-1.08	2.24/2.20/2.22
6	HR2-CR	0.0	-1.10/-1.26/-1.09	2.71/2.66/2.67
7	HR3-CR	0.0	-1.39/-1.22/-1.32	2.66/2.67/2.67
8	N2-C1	0.0	-5.74/-6.45/-6.04	1.95/1.92/1.92
9	N2-C1	90.0	-6.51/-6.37/-7.24	1.90/1.92/1.90
10	N2-C1	180.0	-5.60/-5.66/-7.65	1.96/1.93/1.90
11	N2-C1	270.0	-6.64/-6.59/-7.43	1.90/1.91/1.89
12	O2-C2	0.0	-3.88/-3.93/-3.54	1.88/1.80/1.81
13	O2-C2	90.0	-4.94/-5.15/-4.46	1.84/1.77/1.79
14	O2-C2	180.0	-4.95/-5.20/-4.05	1.84/1.77/1.79
15	O2-C2	270.0	-3.93/-4.12/-3.39	1.87/1.79/1.81
16	HB21-CB2	0.0	-1.84/-1.64/-3.47	2.32/2.48/2.42
17	HB22-CB2	0.0	-1.82/-1.01/-2.42	2.42/2.54/2.46
18	HA31-CA3	0.0	-2.08/-2.47/-1.68	2.70/2.69/2.70
19	HA-CA	0.0	-2.47/-2.76/-1.19	2.49/2.56/2.66
Geometry 2				
20	O-C	0.0	-6.06/-6.90/-7.24	1.86/1.76/1.75
21	O-C	90.0	-5.25/-6.15/-7.32	1.87/1.77/1.75
22	O-C	180.0	-4.71/-5.63/-6.52	1.88/1.77/1.76
23	O-C	270.0	-5.56/-6.46/-6.85	1.86/1.76/1.76
24	HR-NR	0.0	-7.09/-7.67/-7.53	1.93/1.90/1.90
25	HR-NR	45.0	-7.71/-7.90/-7.71	1.91/1.89/1.89
26	HR-NR	90.0	-7.79/-7.84/-7.79	1.90/1.89/1.89
27	HR-NR	135.0	-7.18/-7.62/-7.61	1.92/1.90/1.89
28	HR1-CR	0.0	-0.71/-0.04/0.30	2.50/2.69/2.67
29	HR2-CR	0.0	-1.54/-1.44/-1.38	2.68/2.66/2.66
30	HR3-CR	0.0	-1.84/-1.82/-1.70	2.68/2.67/2.66
31	N2-C1	0.0	-6.46/-6.98/-6.58	1.93/1.91/1.91
32	N2-C1	90.0	-6.88/-6.47/-7.35	1.89/1.91/1.89
33	N2-C1	180.0	-5.73/-5.60/-7.60	1.95/1.93/1.90
34	N2-C1	270.0	-7.31/-7.09/-7.94	1.88/1.91/1.89
35	N3-C1	0.0	-0.22/0.03/-2.15	2.60/2.67/2.17
36	O2-C2	0.0	-4.96/-5.34/-4.95	1.88/1.79/1.80
37	O2-C2	90.0	-5.32/-5.37/-4.66	1.87/1.78/1.80
38	O2-C2	180.0	-5.74/-5.89/-4.71	1.87/1.78/1.81
39	O2-C2	270.0	-5.94/-6.25/-5.51	1.85/1.77/1.79
40	HB21-CB2	0.0	-1.43/-1.20/-3.03	2.33/2.48/2.41
41	HB22-CB2	0.0	-1.29/-0.66/-2.05	2.47/2.56/2.47
42	HA31-CA3	0.0	-3.71/-4.08/-3.49	2.50/2.57/2.57
43	HA-CA	0.0	-2.67/-3.45/-1.93	2.59/2.58/2.69

1.164 Small molecule A of
1-[(2R)-2-carboxy-2-hydroxyethyl]-L-proline(PR4)

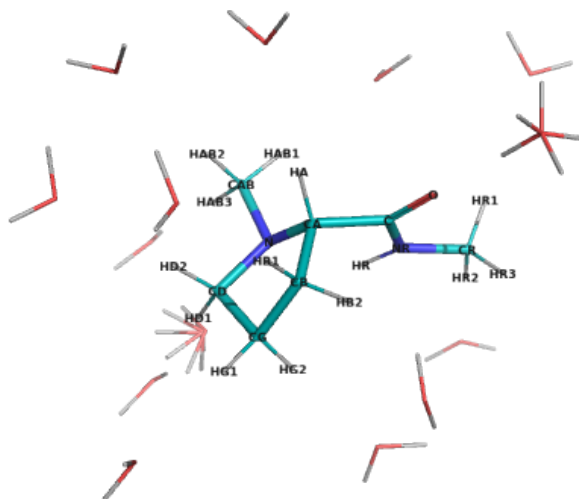


Figure S153: The molecule used for water complex calculations corresponding to (2S)-N,1-dimethylpyrrolidine-2-carboxamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S507: Statistics of calculated water interaction and dipole moment for (2S)-N,1-dimethylpyrrolidine-2-carboxamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.75/1.21	0.34/0.80	4.523	4.33/2.88	21.86
Optimal	0.31/0.66	0.11/0.23	2.800	4.33/5.15	1.72

Table S508: The comparison list of optimized atomic charges and their initial guess for (2S)-N,1-dimethylpyrrolidine-2-carboxamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HAB3	0.090	0.090	3.539
CAB	-0.135	-0.270	!
HAB1	0.090	0.090	3.539
HAB2	0.090	0.090	3.539
N	-0.458	-0.699	52.285
CA	0.022	0.206	38.641
HA	0.090	0.090	1.773
CB	-0.289	-0.228	17.056
HB1	0.090	0.090	0.200
HB2	0.090	0.090	0.200
CG	-0.117	-0.225	14.835
HG1	0.090	0.090	0.000
HG2	0.090	0.090	0.000
CD	0.077	0.124	32.046
HD1	0.090	0.090	1.550
HD2	0.090	0.090	1.550
C	0.510	0.510	27.543
O	-0.510	-0.510	!
NR	-0.470	-0.47	0.000
HR	0.310	0.31	0.000
CR	-0.110	-0.11	0.000
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S509: Interaction energies and geometries between probe water and selected (2S)-N,1-dimethylpyrrolidine-2-carboxamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	O-C	0.0	-7.12/-6.93/-6.10	1.80/1.76/1.77
2	O-C	90.0	-7.03/-6.95/-6.11	1.80/1.76/1.77
3	O-C	180.0	-7.03/-6.78/-6.13	1.80/1.76/1.77
4	O-C	270.0	-7.13/-6.85/-6.28	1.80/1.76/1.77
5	NR-C	0.0	-1.62/-1.94/-1.84	2.33/2.36/2.36
6	HR-NR	0.0	-1.02/-0.95/-0.12	4.32/4.50/5.00
7	HR-NR	45.0	-1.22/-1.08/-0.23	4.26/4.38/5.00
8	HR-NR	90.0	-1.31/-1.10/-0.21	4.20/4.37/5.00
9	HR-NR	135.0	-1.10/-0.96/-0.10	4.27/4.50/5.00
10	HR1-CR	0.0	-0.22/-0.15/-0.62	2.81/2.73/2.67
11	HR2-CR	0.0	-1.24/-1.09/-1.46	2.73/2.70/2.64
12	HA-CA	0.0	-1.02/-0.63/-1.29	2.64/2.72/2.64
13	HAB1-CAB	0.0	-1.78/-1.53/-0.63	2.61/2.62/2.76
14	HAB2-CAB	0.0	-1.28/-1.50/-0.65	2.78/2.66/2.81
15	HAB3-CAB	0.0	-1.28/-1.29/-0.07	2.75/2.71/3.04
16	HG1-CG	0.0	-1.20/-1.42/-1.30	2.75/2.69/2.71
17	HG2-CG	0.0	-1.12/-1.29/-0.94	2.75/2.69/2.74
18	HB1-CB	0.0	-1.06/-0.52/-1.28	2.75/2.81/2.69
19	HD1-CD	0.0	-1.23/-1.85/-1.17	2.77/2.65/2.69
20	HD2-CD	0.0	-1.22/-1.88/-1.58	2.83/2.65/2.66

1.165 Small molecule B of
 1-[(2R)-2-carboxy-2-hydroxyethyl]-L-proline(PR4)

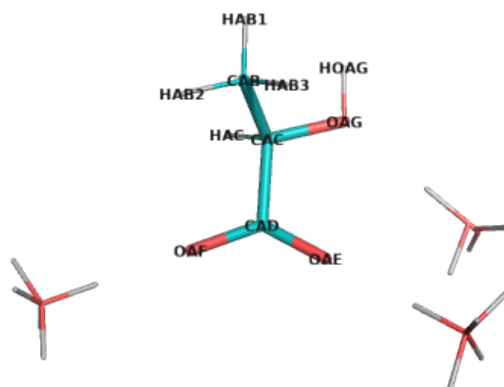


Figure S154: The molecule used for water complex calculations corresponding to (2R)-2-hydroxypropanoate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S510: Statistics of calculated water interaction and dipole moment for (2R)-2-hydroxypropanoate.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.97/1.44	0.07/0.09	3.308	8.05/9.03	2.51
Optimal	0.56/0.97	0.07/0.08	2.417	8.05/7.92	3.23

Table S511: The comparison list of optimized atomic charges and their initial guess for (2R)-2-hydroxypropanoate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
OAE	-0.729	-0.760	0.250
OAF	-0.729	-0.760	0.250
CAD	0.671	0.614	3.551
CAC	-0.071	0.058	3.837
HAC	0.090	0.090	0.000
OAG	-0.579	-0.613	3.613
HOAG	0.347	0.369	3.268
CAB	-0.270	-0.268	0.000
HAB1	0.090	0.090	0.000
HAB2	0.090	0.090	0.000
HAB3	0.090	0.090	0.000

Table S512: Interaction energies and geometries between probe water and selected (2R)-2-hydroxypropanoate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	OAE-CAD	0.0	-14.28/-14.57/-15.56	1.73/1.66/1.65
2	OAE-CAD	90.0	-14.26/-14.83/-15.70	1.73/1.66/1.65
3	OAE-CAD	180.0	-14.42/-14.99/-15.67	1.73/1.65/1.64
4	OAE-CAD	270.0	-13.89/-14.38/-15.19	1.74/1.66/1.65
5	OAF-CAD	0.0	-14.93/-14.61/-15.59	1.71/1.65/1.64
6	OAF-CAD	90.0	-14.25/-13.77/-14.53	1.72/1.66/1.65
7	OAF-CAD	180.0	-13.93/-13.19/-13.73	1.72/1.67/1.66
8	OAF-CAD	270.0	-14.43/-13.98/-14.77	1.72/1.66/1.65
9	OAG-CAC	90.0	-10.10/-9.86/-9.83	2.01/1.94/1.94
10	OAG-CAC	180.0	-15.89/-16.56/-17.02	1.87/1.82/1.81
11	OAG-CAC	270.0	-8.05/-7.08/-6.91	2.09/2.01/2.03

1.166 The dipeptide of Thioproline (PRS)

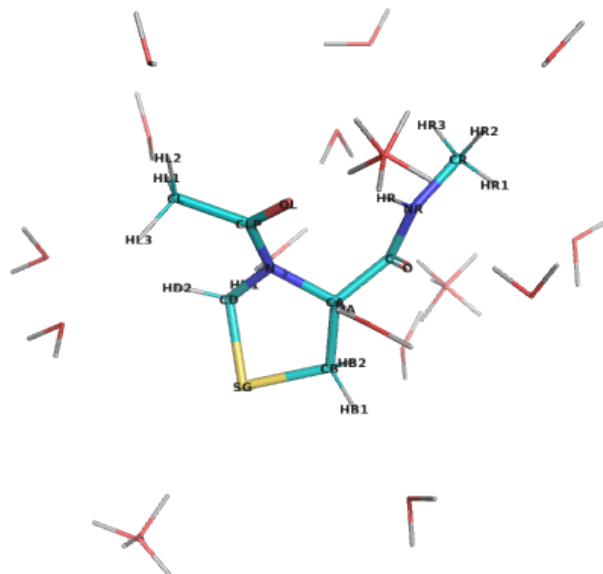


Figure S155: The molecule used for water complex calculations corresponding to (4R)-3-acetyl-N-methyl-1,3-thiazolidine-4-carboxamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S513: Statistics of calculated water interaction and dipole moment for (4R)-3-acetyl-N-methyl-1,3-thiazolidine-4-carboxamide.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.42/0.90	0.25/0.58	1.788	2.89/2.65	6.94
Optimal	0.39/1.00	0.23/0.55	2.313	2.89/3.50	3.37

Table S514: The comparison list of optimized atomic charges and their initial guess for (4R)-3-acetyl-N-methyl-1,3-thiazolidine-4-carboxamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.270	0.000
HL1	0.090	0.090	0.000
HL2	0.090	0.090	0.000
HL3	0.090	0.090	0.000
CLP	0.510	0.510	0.000
OL	-0.510	-0.510	0.000
N	-0.150	-0.286	50.298
CA	-0.036	0.014	43.879
HA	0.090	0.090	2.500
CB	-0.159	-0.090	93.808
HB1	0.090	0.090	5.590
HB2	0.090	0.090	5.590
SG	-0.128	-0.178	131.241
CD	0.023	0.087	98.508
HD1	0.090	0.090	5.590
HD2	0.090	0.090	5.590
C	0.510	0.509	2.500
O	-0.510	-0.501	0.000
NR	-0.470	-0.47	0.000
HR	0.310	0.31	0.000
CR	-0.110	-0.11	0.000
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S515: Interaction energies and geometries between probe water and selected (4R)-3-acetyl-N-methyl-1,3-thiazolidine-4-carboxamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	O-C	0.0	-5.85/-6.36/-5.95	1.83/1.76/1.77
2	O-C	90.0	-6.00/-6.31/-6.11	1.82/1.76/1.76
3	O-C	180.0	-6.22/-6.65/-6.44	1.82/1.76/1.76
4	O-C	270.0	-6.23/-6.80/-6.41	1.82/1.75/1.76
5	NR-C	0.0	-2.13/-1.81/-1.95	2.17/2.17/2.16
6	HR2-CR	0.0	-1.23/-1.10/-1.10	2.68/2.67/2.67
7	HR3-CR	0.0	-0.35/-0.52/-0.51	2.87/2.73/2.72
8	HA-CA	0.0	-1.27/-1.17/-1.26	2.45/2.63/2.62
9	HL1-CL	0.0	-2.60/-2.70/-2.43	2.52/2.59/2.61
10	HL2-CL	0.0	-1.24/-0.93/-0.73	2.56/2.67/2.69
11	HL3-CL	0.0	-2.74/-2.53/-2.27	2.44/2.58/2.59
12	OL-CLP	0.0	-5.00/-5.57/-5.90	1.83/1.75/1.74
13	OL-CLP	90.0	-5.02/-5.44/-5.66	1.83/1.75/1.75
14	OL-CLP	180.0	-3.88/-3.93/-4.03	1.87/1.80/1.80
15	OL-CLP	270.0	-3.88/-4.14/-4.40	1.85/1.78/1.78
16	N-CLP	0.0	-2.51/-2.76/-2.83	3.30/3.22/3.15
17	HB1-CB	0.0	-1.87/-0.88/-1.30	2.52/2.71/2.66
18	SG-CB	0.0	-0.67/-0.89/-1.21	3.02/2.49/2.44
19	SG-CB	90.0	-1.14/-1.41/-1.62	2.92/2.45/2.42
20	SG-CB	180.0	-0.98/-1.61/-1.77	2.99/2.44/2.41
21	SG-CB	270.0	-0.94/-1.17/-1.48	2.94/2.47/2.42
22	HD1-CD	0.0	-2.44/-2.07/-2.17	2.31/2.54/2.54
23	HD2-CD	0.0	-2.70/-2.84/-2.71	2.92/2.90/2.90

1.167 Small molecule used for
(2R)-amino(2-nitrophenyl)ethanoicacid(PRV)

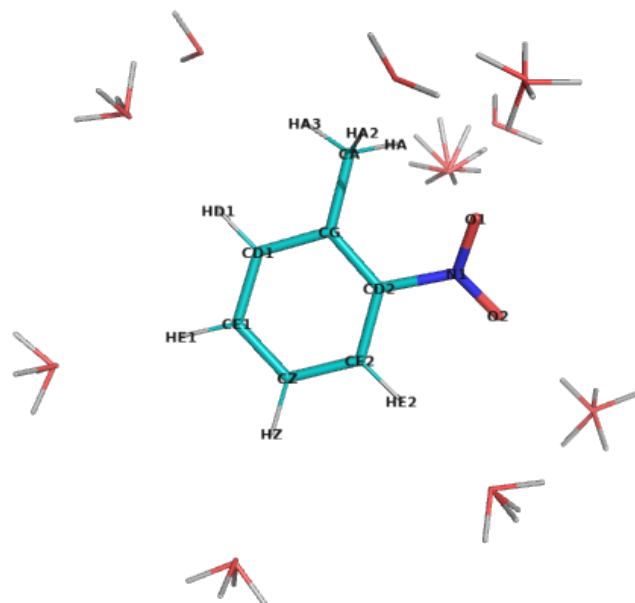


Figure S156: The molecule used for water complex calculations corresponding to 1-methyl-2-nitrobenzene, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S516: Statistics of calculated water interaction and dipole moment for 1-methyl-2-nitrobenzene.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.60/0.92	0.18/0.32	2.529	4.96/4.35	8.41
Optimal	0.67/1.05	0.25/0.58	3.270	4.96/6.18	0.66

Table S517: The comparison list of optimized atomic charges and their initial guess for 1-methyl-2-nitrobenzene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.267	1.500
HA	0.090	0.090	0.000
CG	0.043	-0.033	13.121
CD1	-0.091	-0.114	0.000
HD1	0.115	0.115	0.000
CD2	0.283	0.345	15.880
N1	0.204	0.384	14.898
O1	-0.279	-0.340	0.000
O2	-0.279	-0.340	0.000
CE1	-0.015	-0.115	0.000
HE1	0.115	0.115	0.000
CE2	-0.322	-0.182	0.000
HE2	0.188	0.160	0.000
CZ	-0.077	-0.113	0.000
HZ	0.115	0.115	0.000

Table S518: Interaction energies and geometries between probe water and selected 1-methyl-2-nitrobenzene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-2.05/-1.72/-1.39	2.62/2.68/2.69
2	HA2-CA	0.0	-1.03/-0.53/-0.47	2.53/2.68/2.69
3	HA-CA	0.0	-1.86/-0.86/-1.14	2.45/2.61/2.61
4	HD1-CD1	0.0	-2.26/-2.46/-1.76	2.55/2.61/2.66
5	HD1-CD1	90.0	-2.64/-2.55/-1.83	2.46/2.60/2.65
6	N1-CD2	0.0	-1.11/-0.05/-0.74	3.64/4.22/3.96
7	N1-CD2	45.0	-0.75/-0.02/-0.68	3.75/4.26/3.98
8	N1-CD2	90.0	-0.67/-0.06/-0.68	3.84/4.25/3.99
9	N1-CD2	135.0	-1.02/-0.10/-0.74	3.70/4.21/3.97
10	O1-N1	0.0	-2.31/-3.06/-3.23	2.04/1.89/1.88
11	O1-N1	90.0	-3.42/-4.15/-4.11	1.98/1.86/1.85
12	O1-N1	180.0	-3.80/-4.75/-4.67	1.98/1.85/1.84
13	O1-N1	270.0	-2.99/-3.79/-3.88	1.99/1.87/1.86
14	O2-N1	0.0	-2.52/-3.01/-2.77	2.04/1.90/1.89
15	O2-N1	90.0	-3.24/-3.88/-3.79	2.01/1.87/1.86
16	O2-N1	180.0	-3.68/-4.43/-4.37	1.99/1.86/1.85
17	O2-N1	270.0	-2.90/-3.59/-3.39	2.03/1.88/1.87
18	HE1-CE1	0.0	-2.33/-2.52/-1.62	2.50/2.61/2.67
19	HE1-CE1	90.0	-2.55/-2.59/-1.68	2.46/2.60/2.66
20	HE2-CE2	0.0	-2.23/-1.28/-2.04	2.32/2.59/2.55
21	HE2-CE2	90.0	-1.57/-0.96/-1.69	2.41/2.62/2.58
22	HZ-CZ	0.0	-2.21/-1.89/-1.73	2.52/2.65/2.66
23	HZ-CZ	90.0	-2.41/-1.95/-1.78	2.47/2.64/2.65

1.168 The dipeptide of 2-hydroxy-L-proline (PXU)

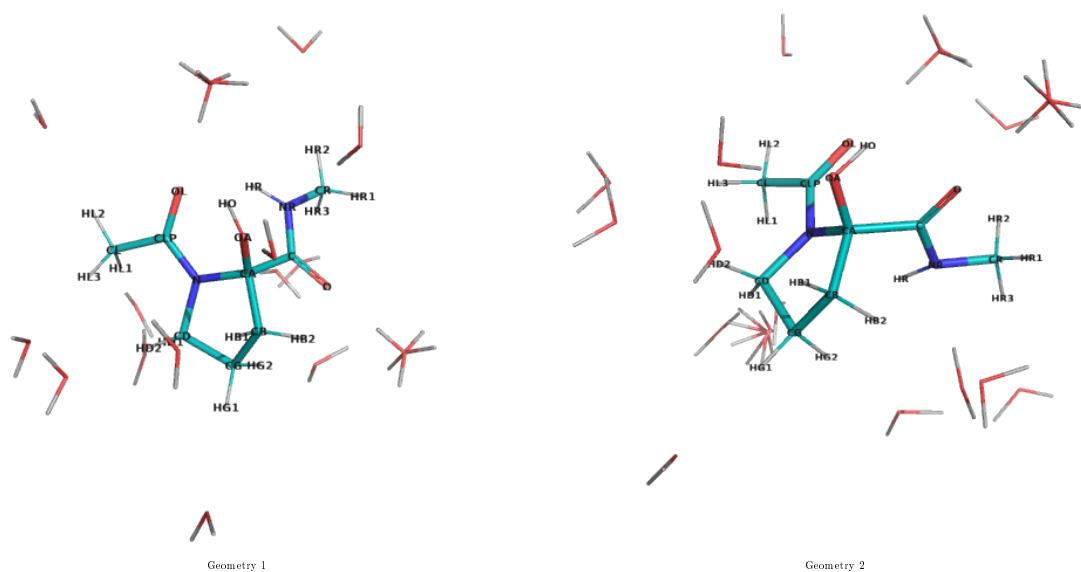


Table S519: The molecule used for water complex calculations corresponding to 2-hydroxy-L-proline, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S520: Statistics of calculated water interaction and dipole moment for 2-hydroxy-L-proline.

		RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle	
		Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)	
Geometry 1	Initial	0.31 / 0.58	0.09 / 0.22	1.875	4.68 / 4.87	4.68	
Geometry 2	Initial	0.50 / 1.07	0.09 / 0.20	2.030	6.91 / 7.45	6.91	
Sum of geometries		Initial	0.42 / 1.07	0.09 / 0.22	3.905	-	-
Geometry 1	Optimal	0.24 / 0.44	0.08 / 0.19	1.788	4.68 / 5.36	4.68	
Geometry 2	Optimal	0.48 / 1.04	0.08 / 0.16	2.127	6.91 / 7.90	6.91	
Sum of geometries		Optimal	0.39 / 1.04	0.08 / 0.19	3.915	-	-

Table S521: The comparison list of optimized atomic charges and their initial guess for 2-hydroxy-L-proline, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.268	0.406
HL1	0.090	0.090	0.000
HL2	0.090	0.090	0.000
HL3	0.090	0.090	0.000
CLP	0.510	0.512	4.992
OL	-0.510	-0.515	0.350
N	-0.193	-0.288	32.038
CA	0.358	0.334	46.920
OA	-0.617	-0.648	40.709
HO	0.379	0.420	3.573
CB	-0.166	-0.184	7.607
HB1	0.090	0.090	0.694
HB2	0.090	0.090	0.694
CG	-0.169	-0.176	2.921
HG1	0.090	0.090	0.040
HG2	0.090	0.090	0.040
CD	-0.036	-0.001	2.628
HD1	0.090	0.090	0.040
HD2	0.090	0.090	0.040
C	0.370	0.502	27.258
O	-0.466	-0.499	4.731
NR	-0.470	-0.473	5.334
HR	0.310	0.315	0.371
CR	-0.110	-0.111	0.350
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S522: Interaction energies and geometries between probe water and selected 2-hydroxy-L-proline site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
Geometry 1						
1	O-C	0.0	-6.02/-6.03/-6.20	1.82/1.77/1.77		
2	O-C	90.0	-6.03/-5.94/-5.99	1.82/1.77/1.77		
3	O-C	180.0	-6.52/-6.62/-6.51	1.81/1.76/1.76		
4	O-C	270.0	-6.68/-6.88/-6.86	1.81/1.76/1.76		
5	NR-C	0.0	-0.98/-1.15/-0.53	2.43/2.30/2.38		
6	HR2-CR	0.0	-1.27/-1.06/-1.25	2.66/2.67/2.66		
7	HR3-CR	0.0	-0.16/-0.20/-0.43	2.91/2.77/2.73		
8	HL1-CL	0.0	-2.58/-2.65/-2.51	2.54/2.60/2.61		
9	HL2-CL	0.0	-1.23/-1.05/-0.95	2.58/2.67/2.68		
10	HL3-CL	0.0	-2.99/-2.93/-2.73	2.54/2.59/2.60		
11	OL-CLP	0.0	-4.05/-4.39/-4.63	1.84/1.76/1.75		
12	OL-CLP	90.0	-4.01/-4.30/-4.39	1.85/1.78/1.77		
13	OL-CLP	180.0	-3.34/-3.35/-3.03	1.89/1.82/1.82		
14	OL-CLP	270.0	-2.94/-3.24/-3.16	1.88/1.80/1.79		
15	N-CLP	0.0	-1.68/-1.98/-1.87	3.87/3.88/3.89		
16	OA-CA	0.0	-5.17/-5.48/-5.65	1.88/1.88/1.87		
17	HB1-CB	0.0	-0.73/-0.57/-0.23	2.71/2.74/2.78		
18	HG1-CG	0.0	-1.48/-1.49/-1.34	2.69/2.69/2.70		
19	HG2-CG	0.0	-0.59/-0.14/-0.08	2.47/2.66/2.68		
20	HD1-CD	0.0	-2.57/-2.98/-2.86	2.63/2.60/2.61		
21	HD2-CD	0.0	-2.48/-2.84/-2.61	2.56/2.59/2.60		
Geometry 2						
22	O-C	0.0	-5.76/-6.09/-5.97	1.86/1.78/1.78		
23	O-C	90.0	-5.63/-5.96/-5.86	1.85/1.78/1.77		
24	O-C	180.0	-5.57/-6.01/-5.87	1.85/1.78/1.77		
25	O-C	270.0	-6.03/-6.40/-6.26	1.85/1.77/1.77		
26	NR-C	0.0	-2.06/-1.57/-1.09	2.17/2.32/2.37		
27	HR-NR	0.0	-2.83/-3.02/-2.89	4.25/4.25/4.26		
28	HR-NR	45.0	-2.91/-3.16/-3.03	4.27/4.21/4.23		
29	HR-NR	90.0	-3.30/-3.33/-3.18	4.14/4.16/4.18		
30	HR-NR	135.0	-3.15/-3.17/-3.03	4.17/4.20/4.22		
31	HR2-CR	0.0	-0.91/-0.59/-0.84	2.53/2.61/2.60		
32	HR3-CR	0.0	-1.33/-1.27/-1.42	2.74/2.70/2.69		
33	HL1-CL	0.0	-2.35/-2.64/-2.47	2.62/2.63/2.64		
34	HL2-CL	0.0	-1.00/-0.71/-0.60	2.58/2.67/2.68		
35	HL3-CL	0.0	-2.52/-2.53/-2.32	2.54/2.60/2.61		
36	OL-CLP	0.0	-4.63/-5.07/-5.37	1.89/1.79/1.77		
37	OL-CLP	90.0	-4.96/-5.91/-6.03	1.90/1.79/1.78		
38	OL-CLP	180.0	-7.24/-8.05/-7.79	1.84/1.76/1.76		
39	OL-CLP	270.0	-4.81/-5.84/-5.83	1.89/1.78/1.77		
40	OA-CA	0.0	-6.78/-7.07/-7.27	1.82/1.85/1.85		
41	HB1-CB	0.0	-0.88/-0.40/-0.12	2.56/2.72/2.76		
42	HB2-CB	0.0	-1.35/-1.33/-1.39	2.54/2.62/2.62		
43	HG1-CG	0.0	-1.79/-1.88/-1.73	2.65/2.67/2.68		
44	HG2-CG	0.0	-2.49/-3.26/-3.14	2.62/2.60/2.61		
45	HD1-CD	0.0	-2.62/-3.48/-3.32	2.74/2.63/2.63		
46	HD2-CD	0.0	-2.10/-2.36/-2.10	2.54/2.58/2.59		

1.169 Small molecule used for 3-(2-Pyridyl)-alanine(PYR2)

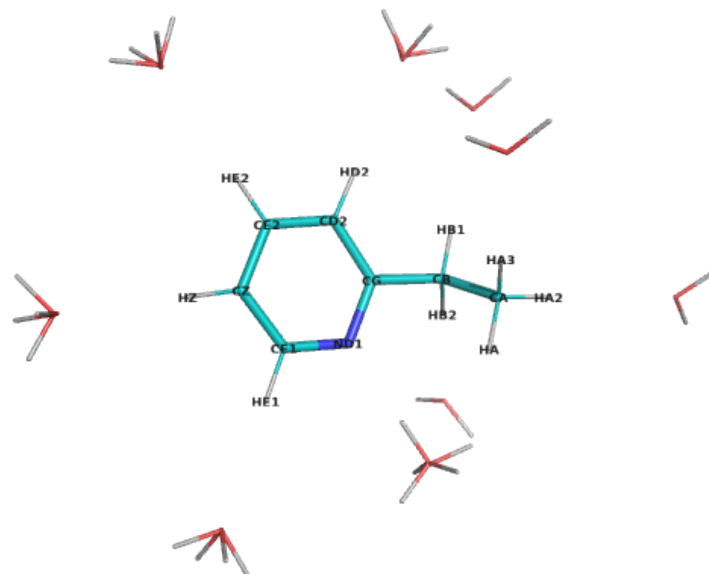


Figure S157: The molecule used for water complex calculations corresponding to 2-ethylpyridine, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S523: Statistics of calculated water interaction and dipole moment for 2-ethylpyridine.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.33/0.89	0.09/0.16	2.479	1.95/2.72	1.03
Optimal	0.15/0.29	0.09/0.14	1.983	1.95/2.54	1.04

Table S524: The comparison list of optimized atomic charges and their initial guess for 2-ethylpyridine, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	14.230
HA	0.090	0.090	0.000
CB	-0.180	-0.182	29.874
HB1	0.090	0.090	2.250
HB2	0.090	0.090	2.250
CG	0.378	0.335	32.587
ND1	-0.582	-0.617	34.071
CE1	0.111	0.149	2.500
HE1	0.127	0.124	0.000
CD2	-0.209	-0.110	0.000
HD2	0.115	0.115	0.000
CE2	-0.032	-0.107	0.000
HE2	0.115	0.115	0.000
CZ	-0.138	-0.117	0.000
HZ	0.115	0.115	0.000

Table S525: Interaction energies and geometries between probe water and selected 2-ethylpyridine site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.47/-0.42/-0.44	2.86/2.77/2.78
2	HA2-CA	0.0	-0.59/-0.45/-0.41	2.87/2.79/2.80
3	HB1-CB	0.0	-1.32/-1.37/-1.47	2.72/2.70/2.69
4	ND1-CG	0.0	-6.63/-6.56/-6.95	1.92/1.86/1.85
5	ND1-CG	90.0	-6.98/-6.78/-7.28	1.90/1.86/1.84
6	ND1-CG	180.0	-6.30/-6.59/-7.19	1.95/1.86/1.84
7	ND1-CG	270.0	-6.72/-6.62/-7.12	1.92/1.86/1.84
8	HE1-CE1	0.0	-1.21/-1.21/-1.31	2.60/2.47/2.46
9	HE1-CE1	90.0	-1.21/-1.19/-1.29	2.58/2.48/2.47
10	HD2-CD2	0.0	-1.60/-1.57/-1.88	2.62/2.67/2.64
11	HD2-CD2	90.0	-1.88/-1.66/-1.96	2.53/2.66/2.63
12	HE2-CE2	0.0	-1.82/-1.64/-1.50	2.56/2.66/2.68
13	HE2-CE2	90.0	-2.00/-1.70/-1.57	2.51/2.65/2.67
14	HZ-CZ	0.0	-1.55/-1.52/-1.59	2.62/2.67/2.66
15	HZ-CZ	90.0	-1.73/-1.59/-1.65	2.56/2.66/2.65

1.170 Small molecule used for 3-(1-pyrazolyl)-alanine(PYZ1)

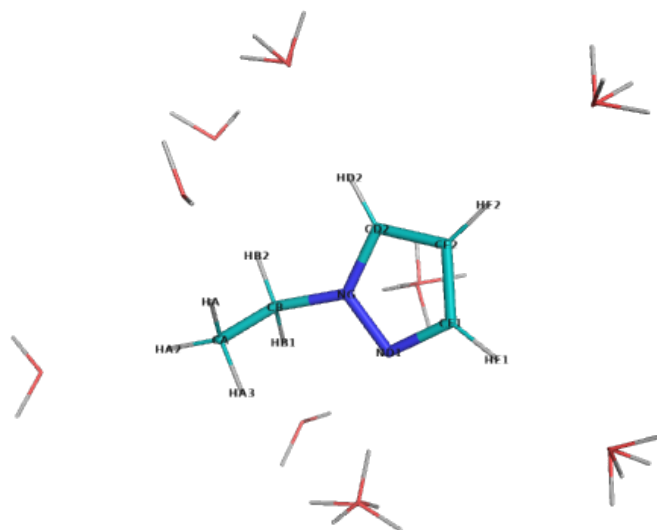


Figure S158: The molecule used for water complex calculations corresponding to 1-ethyl-1H-pyrazole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S526: Statistics of calculated water interaction and dipole moment for 1-ethyl-1H-pyrazole.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.19/3.27	0.22/0.44	2.849	2.41/3.23	4.13
Optimal	0.32/0.87	0.12/0.25	2.040	2.41/2.98	3.82

Table S527: The comparison list of optimized atomic charges and their initial guess for 1-ethyl-1H-pyrazole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.000
HA	0.090	0.090	0.000
CB	-0.040	0.113	0.045
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
NG	0.266	-0.074	0.285
CD2	-0.013	-0.035	0.000
HD2	0.096	0.169	0.000
ND1	-0.572	-0.513	0.285
CE2	-0.319	-0.249	0.000
HE2	0.165	0.157	0.000
CE1	0.105	0.096	0.045
HE1	0.132	0.156	0.000

Table S528: Interaction energies and geometries between probe water and selected 1-ethyl-1H-pyrazole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA2-CA	0.0	-1.08/-1.07/-1.24		2.77/2.71/2.69	
2	HA-CA	0.0	-0.79/-1.00/-0.72		2.79/2.70/2.74	
3	HB1-CB	0.0	-0.81/-0.75/-0.69		2.65/2.68/2.67	
4	HB2-CB	0.0	-2.35/-2.50/-2.69		2.56/2.61/2.60	
5	NG-CB	0.0	-1.98/-2.66/-5.01		2.50/2.31/2.12	
6	NG-CB	90.0	-2.04/-2.91/-5.31		2.48/2.30/2.11	
7	NG-CB	180.0	-0.61/-0.44/-2.05		2.72/2.65/2.28	
8	NG-CB	270.0	-0.81/-0.46/-2.20		2.62/2.59/2.25	
9	HD2-CD2	0.0	-2.40/-2.41/-3.17		2.46/2.32/2.26	
10	HD2-CD2	90.0	-2.74/-2.56/-3.37		2.39/2.31/2.25	
11	ND1-NG	0.0	-6.76/-6.87/-7.13		1.92/1.93/1.93	
12	ND1-NG	90.0	-6.63/-6.45/-6.83		1.91/1.93/1.93	
13	ND1-NG	180.0	-5.77/-5.69/-6.07		1.95/1.94/1.94	
14	ND1-NG	270.0	-6.92/-6.54/-6.96		1.90/1.93/1.92	
15	HE2-CE2	0.0	-1.21/-1.02/-1.16		2.65/2.71/2.69	
16	HE2-CE2	90.0	-1.39/-1.08/-1.24		2.59/2.70/2.68	
17	HE1-CE1	0.0	-1.07/-1.01/-1.40		2.59/2.34/2.30	
18	HE1-CE1	90.0	-1.09/-0.97/-1.37		2.57/2.34/2.30	

1.171 Small molecule used for S-carbamoyl-L-cysteine(QCS)

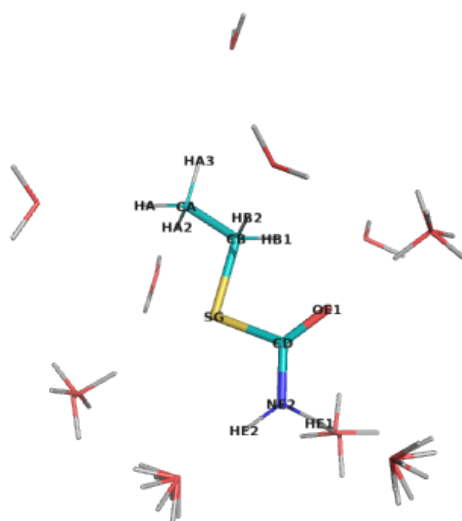


Figure S159: The molecule used for water complex calculations corresponding to (ethylsulfanyl)formamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S529: Statistics of calculated water interaction and dipole moment for (ethylsulfanyl)formamide.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.52/1.46	0.49/2.28	1.552	2.15/2.05	10.39
Optimal	0.32/0.79	0.17/0.33	1.835	2.15/2.64	1.84

Table S530: The comparison list of optimized atomic charges and their initial guess for (ethylsulfanyl)formamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.620
HA	0.090	0.090	0.000
CB	-0.046	0.008	5.711
HB1	0.090	0.090	0.450
HB2	0.090	0.090	0.450
SG	-0.122	-0.254	92.712
CD	0.426	0.517	93.354
NE2	-0.686	-0.646	71.455
OE1	-0.468	-0.485	63.776
HE1	0.358	0.340	2.500
HE2	0.358	0.340	2.500

Table S531: Interaction energies and geometries between probe water and selected (ethylsulfanyl)formamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-1.14/-0.84/-0.95	2.72/2.72/2.71
2	HA2-CA	0.0	-0.89/-0.62/-0.51	2.71/2.74/2.74
3	HA-CA	0.0	-0.89/-0.62/-0.51	2.71/2.74/2.74
4	HB1-CB	0.0	-0.81/-0.31/-0.50	2.49/2.67/2.66
5	HB2-CB	0.0	-0.81/-0.30/-0.49	2.49/2.67/2.66
6	SG-CB	0.0	-0.45/-0.46/-1.31	2.84/2.52/2.39
7	SG-CB	90.0	-1.28/-1.30/-2.26	2.67/2.43/2.33
8	SG-CB	180.0	-1.26/-1.73/-2.72	2.73/2.40/2.31
9	SG-CB	270.0	-1.28/-1.31/-2.26	2.67/2.43/2.33
10	NE2-CD	0.0	-0.14/-0.04/0.15	2.72/2.39/5.00
11	NE2-CD	90.0	-0.77/-0.63/-0.50	2.49/2.29/2.36
12	NE2-CD	180.0	-1.61/-2.40/-1.87	2.41/2.15/2.21
13	NE2-CD	270.0	-1.12/-1.64/-1.02	2.45/2.21/2.30
14	OE1-CD	0.0	-5.45/-5.75/-5.57	1.86/1.78/1.78
15	OE1-CD	90.0	-5.74/-6.06/-5.93	1.85/1.77/1.77
16	OE1-CD	180.0	-5.76/-6.09/-5.98	1.85/1.77/1.77
17	OE1-CD	270.0	-5.74/-6.06/-5.93	1.85/1.77/1.77
18	HE1-NE2	0.0	-5.74/-5.64/-5.70	1.84/1.86/1.86
19	HE1-NE2	45.0	-5.57/-5.51/-5.57	1.84/1.86/1.87
20	HE1-NE2	90.0	-5.41/-5.38/-5.45	1.85/1.87/1.87
21	HE1-NE2	135.0	-5.57/-5.51/-5.57	1.85/1.86/1.87
22	HE2-NE2	0.0	-6.52/-6.48/-6.24	1.85/1.86/1.87
23	HE2-NE2	45.0	-6.64/-6.46/-6.15	1.84/1.86/1.87
24	HE2-NE2	90.0	-6.76/-6.45/-6.07	1.83/1.86/1.87
25	HE2-NE2	135.0	-6.65/-6.46/-6.15	1.84/1.86/1.87

1.172 Small molecule used for
 S-[(1S)-1-carboxy-1-(phosphonoxy)ethyl]-L-cysteine(QPA)

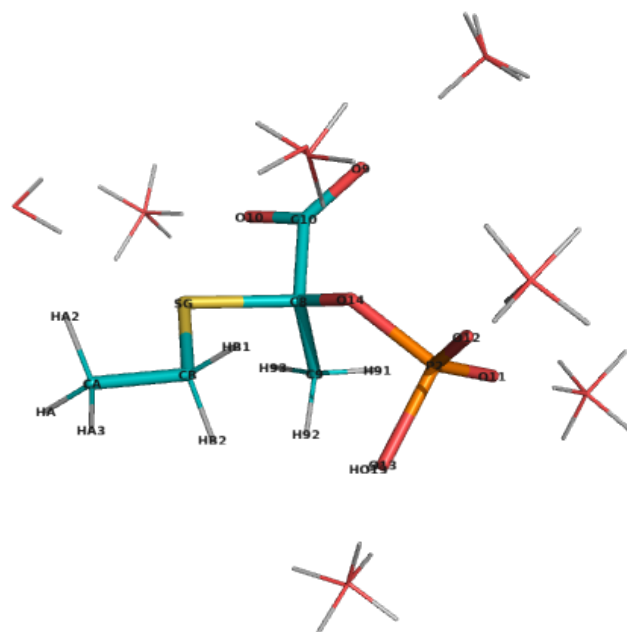


Figure S160: The molecule used for water complex calculations corresponding to 2-(ethylsulfanyl)-2-[(trihydroxy-lambda4-phosphanyl)oxy]propanoicacid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S532: Statistics of calculated water interaction and dipole moment for 2-(ethylsulfanyl)-2-[(trihydroxy-lambda4-phosphanyl)oxy]propanoicacid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.67/5.10	0.14/0.35	6.691	12.15/15.11	4.54
Optimal	0.58/1.59	0.11/0.36	2.797	12.15/12.38	0.33

Table S533: The comparison list of optimized atomic charges and their initial guess for 2-(ethylsulfanyl)-2-[(trihydroxy-lambda4-phosphanyl)oxy]propanoic acid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.271	-0.271	0.854
HA	0.090	0.090	0.000
CB	-0.255	-0.066	6.947
HB1	0.090	0.090	0.090
HB2	0.090	0.090	0.090
SG	-0.232	-0.169	35.536
C8	0.319	0.138	48.526
C9	-0.281	-0.331	11.909
H91	0.090	0.090	0.824
H92	0.090	0.090	0.824
H93	0.090	0.090	0.824
C10	0.533	0.273	5.648
O9	-0.678	-0.600	2.504
O10	-0.746	-0.600	2.504
O14	-0.459	-0.617	39.778
P2	1.330	1.503	3.776
O11	-0.825	-0.825	0.639
O12	-0.825	-0.825	0.639
O13	-0.668	-0.668	0.090
HO13	0.338	0.338	0.000

Table S534: Interaction energies and geometries between probe water and selected 2-(ethylsulfanyl)-2-[(trihydroxy-lambda4-phosphanyl)oxy]propanoic acid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	SG-CB	0.0	-11.35/-12.95/-12.98	2.54/2.19/2.19
2	O9-C10	0.0	-17.73/-17.78/-18.34	1.73/1.66/1.67
3	O9-C10	90.0	-15.32/-15.32/-15.87	1.74/1.67/1.68
4	O9-C10	180.0	-13.67/-12.98/-13.36	1.74/1.68/1.69
5	O9-C10	270.0	-14.75/-14.50/-14.96	1.74/1.68/1.68
6	O10-C10	0.0	-16.90/-16.66/-15.64	1.70/1.65/1.67
7	O10-C10	90.0	-16.61/-16.67/-15.41	1.70/1.64/1.67
8	O10-C10	180.0	-16.12/-16.17/-15.20	1.70/1.65/1.67
9	O10-C10	270.0	-16.05/-16.02/-15.31	1.71/1.65/1.67
10	O14-C8	0.0	-12.33/-11.86/-14.71	1.93/1.81/1.71
11	O14-C8	90.0	-12.76/-13.25/-17.86	1.96/1.81/1.69
12	O14-C8	180.0	-12.29/-11.99/-16.15	1.97/1.84/1.70
13	O14-C8	270.0	-8.92/-8.88/-10.55	2.10/1.92/1.79
14	O11-P2	0.0	-16.66/-18.11/-18.79	1.74/1.64/1.64
15	O11-P2	90.0	-15.55/-16.54/-16.33	1.74/1.64/1.65
16	O11-P2	180.0	-14.12/-14.47/-13.76	1.75/1.65/1.66
17	O11-P2	270.0	-14.82/-15.54/-15.54	1.75/1.65/1.65
18	O12-P2	0.0	-16.64/-16.81/-16.63	1.72/1.64/1.64
19	O12-P2	90.0	-14.99/-14.73/-14.06	1.73/1.65/1.66
20	O12-P2	180.0	-15.28/-14.83/-14.32	1.72/1.65/1.65
21	O12-P2	270.0	-16.54/-16.61/-16.52	1.72/1.64/1.64
22	O13-P2	0.0	-7.45/-6.70/-5.61	1.94/1.95/1.99
23	O13-P2	90.0	-10.47/-10.36/-10.34	1.96/1.93/1.94
24	O13-P2	180.0	-12.75/-12.94/-13.51	1.88/1.87/1.88
25	O13-P2	270.0	-9.01/-8.81/-8.10	1.89/1.91/1.93

1.173 Small molecule used for 3-(2-quinoxalyl)-alanine(QX32)

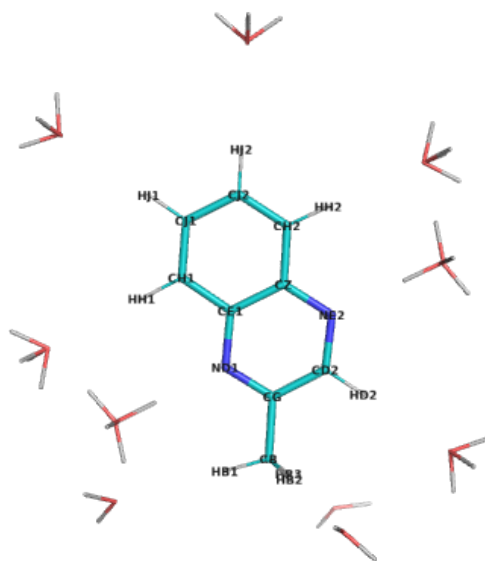


Figure S161: The molecule used for water complex calculations corresponding to 2-methylquinoxaline, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S535: Statistics of calculated water interaction and dipole moment for 2-methylquinoxaline.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.44/1.34	0.11/0.18	3.245	0.40/0.93	143.59
Optimal	0.39/0.65	0.11/0.18	1.748	0.40/0.51	0.02

Table S536: The comparison list of optimized atomic charges and their initial guess for 2-methylquinoxaline, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	2.250
CB	-0.270	-0.269	16.630
HB1	0.090	0.090	2.250
HB2	0.090	0.090	2.250
CG	0.433	0.293	17.706
ND1	-0.595	-0.613	14.965
CE1	0.245	0.316	2.500
CD2	0.080	0.113	0.000
HD2	0.109	0.133	0.000
NE2	-0.541	-0.599	0.000
CZ	0.269	0.344	0.000
CH1	-0.115	-0.109	0.000
HH1	0.115	0.115	0.000
CH2	-0.115	-0.109	0.000
HH2	0.115	0.115	0.000
CJ1	-0.115	-0.115	0.000
HJ1	0.115	0.115	0.000
CJ2	-0.115	-0.115	0.000
HJ2	0.115	0.115	0.000

Table S537: Interaction energies and geometries between probe water and selected 2-methylquinoxaline site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.45/-1.65/-1.18	2.66/2.64/2.68
2	HB1-CB	0.0	-0.42/-0.15/0.36	2.74/2.77/2.92
3	HB2-CB	0.0	-1.52/-1.68/-1.22	2.64/2.63/2.67
4	ND1-CG	0.0	-5.21/-5.62/-5.67	1.98/1.87/1.86
5	ND1-CG	90.0	-6.70/-6.05/-6.63	1.90/1.85/1.84
6	ND1-CG	180.0	-5.07/-5.32/-6.41	2.00/1.87/1.85
7	ND1-CG	270.0	-6.70/-6.05/-6.63	1.90/1.85/1.84
8	HD2-CD2	0.0	-1.91/-2.05/-2.12	2.50/2.44/2.42
9	HD2-CD2	90.0	-1.93/-2.06/-2.11	2.48/2.44/2.42
10	NE2-CD2	0.0	-4.89/-5.10/-5.19	2.00/1.87/1.86
11	NE2-CD2	90.0	-6.08/-5.80/-6.17	1.93/1.86/1.84
12	NE2-CD2	180.0	-5.32/-5.61/-6.15	1.97/1.86/1.84
13	NE2-CD2	270.0	-6.08/-5.80/-6.17	1.93/1.86/1.84
14	HH1-CH1	0.0	-1.00/-0.44/-0.67	2.54/2.72/2.68
15	HH1-CH1	90.0	-0.90/-0.39/-0.58	2.58/2.74/2.71
16	HH2-CH2	0.0	-1.09/-0.49/-0.76	2.52/2.71/2.68
17	HH2-CH2	90.0	-0.94/-0.41/-0.67	2.56/2.73/2.70
18	HJ1-CJ1	0.0	-1.56/-1.30/-1.54	2.60/2.68/2.67
19	HJ1-CJ1	90.0	-1.73/-1.34/-1.59	2.54/2.68/2.66
20	HJ2-CJ2	0.0	-1.54/-1.31/-1.56	2.60/2.68/2.66
21	HJ2-CJ2	90.0	-1.71/-1.35/-1.61	2.55/2.67/2.66

1.174 Small molecule A of 3-[(2,2,5,5-tetramethyl-1-oxo-2,5-dihydro-1H-pyrrolium-3-yl)methyl]disulfanyl-D-alanine(R1A)

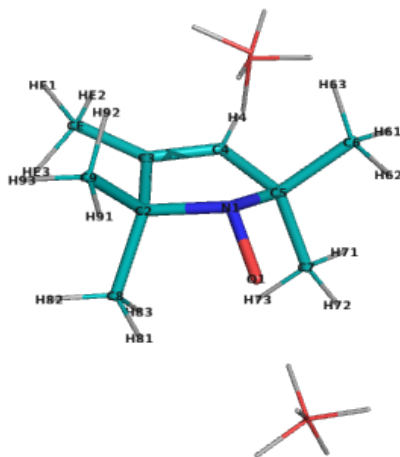


Figure S162: The molecule used for water complex calculations corresponding to 2,2,3,5,5-pentamethyl-2,5-dihydro-1H-pyrrol-1-ol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S538: Statistics of calculated water interaction and dipole moment for 2,2,3,5,5-pentamethyl-2,5-dihydro-1H-pyrrol-1-ol.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	5.61/7.68	0.12/0.21	6.541	7.36/9.54	9.28
Optimal	0.18/0.39	0.03/0.04	2.985	7.36/8.00	2.58

Table S539: The comparison list of optimized atomic charges and their initial guess for 2,2,3,5,5-pentamethyl-2,5-dihydro-1H-pyrrol-1-ol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HE3	0.090	0.090	2.500
CE	-0.242	-0.143	70.198
HE1	0.090	0.090	2.500
HE2	0.090	0.090	2.500
C3	-0.202	-0.169	78.304
C2	0.519	0.341	67.082
C8	-0.362	-0.289	42.916
H81	0.090	0.090	2.409
H82	0.090	0.090	2.409
H83	0.090	0.090	2.409
C9	-0.362	-0.289	42.916
H91	0.090	0.090	2.409
H92	0.090	0.090	2.409
H93	0.090	0.090	2.409
C4	-0.345	-0.218	51.612
H4	0.107	0.143	38.183
N1	-0.587	-1.106	358.514
O1	-0.671	-0.382	351.344
C5	0.519	0.340	66.691
C6	-0.362	-0.289	42.897
H61	0.090	0.090	2.409
H62	0.090	0.090	2.409
H63	0.090	0.090	2.409
C7	-0.362	-0.289	42.897
H71	0.090	0.090	2.409
H72	0.090	0.090	2.409
H73	0.090	0.090	2.409

Table S540: Interaction energies and geometries between probe water and selected 2,2,3,5,5-pentamethyl-2,5-dihydro-1H-pyrrol-1-ol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	N1-C2	0.0	-13.63/-13.79/-21.26	1.93/1.95/1.81
2	N1-C2	90.0	-11.92/-11.53/-18.96	2.01/2.00/1.83
3	N1-C2	180.0	-11.67/-11.69/-19.09	2.04/2.00/1.83
4	N1-C2	270.0	-14.24/-14.44/-21.92	1.91/1.94/1.81
5	O1-N1	0.0	-16.03/-15.96/-13.22	1.66/1.68/1.74
6	O1-N1	90.0	-16.10/-15.95/-13.14	1.66/1.68/1.74
7	O1-N1	180.0	-16.17/-16.17/-13.59	1.66/1.68/1.74
8	O1-N1	270.0	-16.28/-16.24/-13.73	1.65/1.68/1.73

1.175 Small molecule B of 3-[(2,2,5,5-tetramethyl-1-oxo-2,5-dihydro-1H-pyrrolium-3-yl)methyl]disulfanyl-D-alanine(R1A)

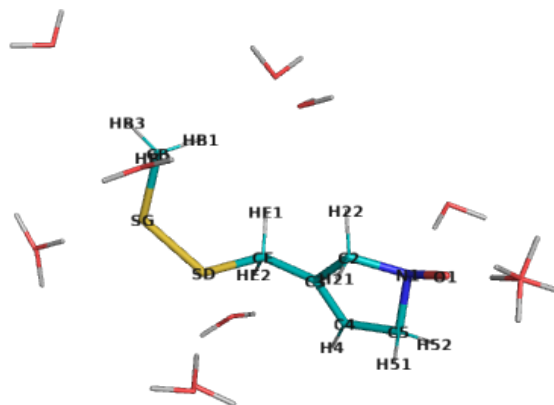


Figure S163: The molecule used for water complex calculations corresponding to 3-[(methyldisulfanyl)methyl]-2,5-dihydro-1H-pyrrol-1-ol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S541: Statistics of calculated water interaction and dipole moment for 3-[(methyldisulfanyl)methyl]-2,5-dihydro-1H-pyrrol-1-ol.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	3.63/7.36	0.28/0.50	9.609	15.42/18.92	7.94
Optimal	1.08/1.53	0.30/0.52	6.895	15.42/18.40	8.93

Table S542: The comparison list of optimized atomic charges and their initial guess for 3-[(methyldisulfanyl)methyl]-2,5-dihydro-1H-pyrrol-1-ol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CB	-0.112	-0.190	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
HB3	0.090	0.090	0.000
SG	-0.080	-0.080	2.500
SD	-0.080	-0.070	17.486
CE	-0.185	0.327	69.910
HE1	0.090	0.090	2.500
HE2	0.090	0.090	2.500
C3	0.007	-0.536	70.011
C2	0.024	0.247	0.169
H21	0.090	0.090	3.500
H22	0.090	0.090	3.500
C4	-0.302	-0.283	3.841
H4	0.096	0.215	0.000
N1	-0.554	-1.154	352.849
O1	-0.648	-0.378	352.611
C5	0.024	0.170	34.907
H51	0.090	0.090	2.450
H52	0.090	0.090	2.450

Table S543: Interaction energies and geometries between probe water and selected 3-[(methyldisulfanyl)methyl]-2,5-dihydro-1H-pyrrol-1-ol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	SG-CB	0.0	-3.21/-3.01/-2.50	2.81/2.39/2.41
2	SG-CB	180.0	-2.30/-1.41/-1.73	2.85/2.48/2.44
3	SD-SG	0.0	-4.47/-5.82/-5.67	2.85/2.33/2.36
4	SD-SG	180.0	-1.23/-0.59/-0.28	3.03/2.54/2.75
5	N1-C2	0.0	-16.11/-15.69/-23.47	1.83/1.85/1.74
6	O1-N1	0.0	-17.12/-15.59/-13.02	1.65/1.69/1.74
7	O1-N1	90.0	-17.10/-15.69/-12.91	1.65/1.69/1.74
8	O1-N1	180.0	-17.17/-16.01/-13.45	1.65/1.68/1.74
9	O1-N1	270.0	-17.22/-15.94/-13.58	1.65/1.68/1.74

1.176 Small molecule used for
O-[(S)-hydroxy(methyl)phosphoryl]-L-serine(SBG)

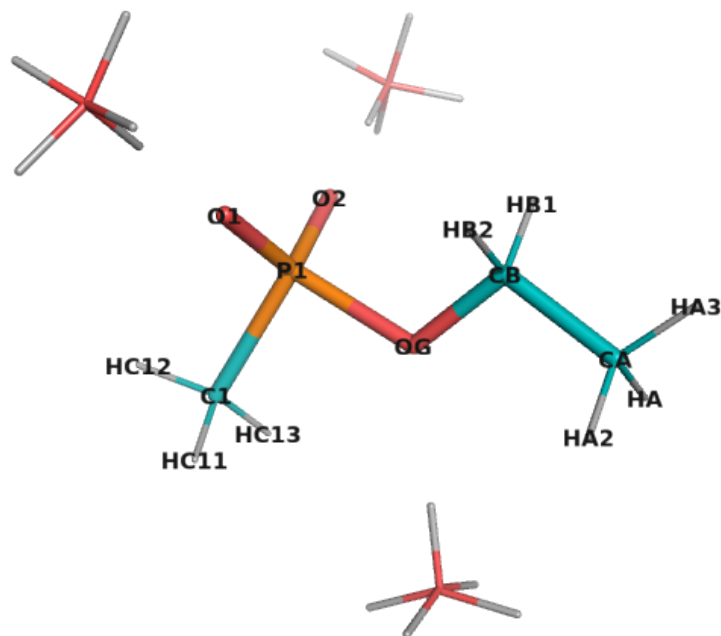


Figure S164: The molecule used for water complex calculations corresponding to ethoxy(methyl)phosphinic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S544: Statistics of calculated water interaction and dipole moment for ethoxy(methyl)phosphinic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	2.27/5.00	0.14/0.24	7.420	5.75/4.10	31.08
Optimal	0.13/0.31	0.10/0.14	2.174	5.75/5.57	1.12

Table S545: The comparison list of optimized atomic charges and their initial guess for ethoxy (methyl)phosphinicacid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.268	0.045
HA	0.090	0.090	0.000
CB	-0.132	-0.079	17.851
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
OG	-0.388	-0.700	29.649
P1	1.037	1.700	31.490
O1	-0.765	-0.818	6.232
O2	-0.765	-0.818	6.232
C1	-0.437	-0.737	27.083
HC11	0.090	0.090	1.431
HC12	0.090	0.090	1.431
HC13	0.090	0.090	1.431

Table S546: Interaction energies and geometries between probe water and selected ethoxy(methyl)phosphinicacid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	OG-CB	0.0	-9.96/-10.26/-14.96	1.88/1.74/1.64
2	OG-CB	90.0	-9.54/-9.45/-12.69	1.86/1.75/1.66
3	OG-CB	180.0	-8.57/-8.53/-11.40	1.89/1.76/1.66
4	OG-CB	270.0	-9.46/-9.33/-12.77	1.86/1.75/1.66
5	O1-P1	0.0	-13.99/-14.11/-13.33	1.74/1.65/1.66
6	O1-P1	90.0	-14.39/-14.52/-13.11	1.73/1.65/1.66
7	O1-P1	180.0	-14.33/-14.30/-13.10	1.73/1.65/1.66
8	O1-P1	270.0	-13.96/-13.87/-13.31	1.74/1.66/1.66
9	O2-P1	0.0	-14.04/-14.14/-13.37	1.74/1.65/1.66
10	O2-P1	90.0	-13.96/-13.86/-13.31	1.74/1.66/1.66
11	O2-P1	180.0	-14.30/-14.27/-13.07	1.74/1.65/1.66
12	O2-P1	270.0	-14.39/-14.52/-13.12	1.74/1.65/1.66

1.177 Small molecule used for O-benzylsulfonyl-serine(SEB)

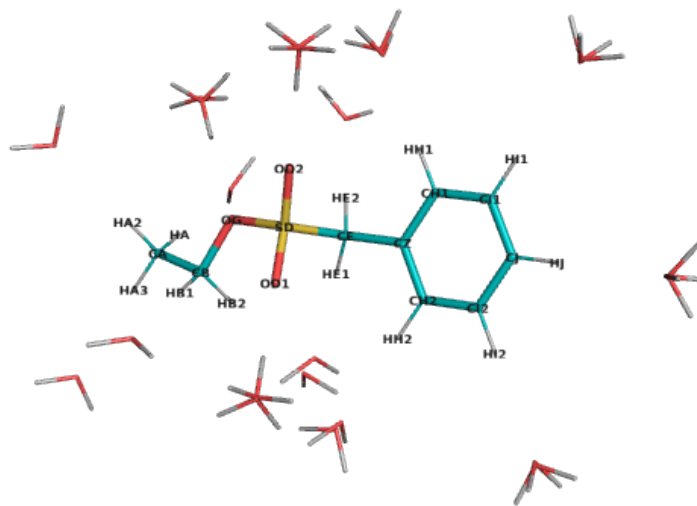


Figure S165: The molecule used for water complex calculations corresponding to ethylphenylmethanesulfonate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S547: Statistics of calculated water interaction and dipole moment for ethylphenylmethanesulfonate.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.07/2.12	0.18/0.34	7.361	4.68/7.04	36.64
Optimal	0.44/0.79	0.15/0.31	3.110	4.68/6.09	0.00

Table S548: The comparison list of optimized atomic charges and their initial guess for ethylphenylmethanesulfonate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.271	2.241
HA	0.090	0.090	0.000
CB	0.080	0.119	2.592
HB1	0.090	0.090	0.250
HB2	0.090	0.090	0.250
OG	-0.177	-0.236	2.959
SD	0.173	0.285	13.130
OD1	-0.315	-0.291	2.500
OD2	-0.315	-0.291	2.500
CE	0.281	0.515	18.833
HE1	0.090	0.090	0.450
HE2	0.090	0.090	0.450
CZ	-0.297	-0.364	19.476
CH1	-0.052	-0.170	9.744
HH1	0.115	0.115	0.000
CH2	0.018	-0.170	9.744
HH2	0.115	0.115	0.000
CI1	-0.108	-0.108	0.000
HI1	0.115	0.115	0.000
CI2	-0.108	-0.108	0.000
HI2	0.115	0.115	0.000
CJ	-0.115	-0.115	0.000
HJ	0.115	0.115	0.000

Table S549: Interaction energies and geometries between probe water and selected ethylphenylmethanesulfonate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-1.61/-1.47/-1.96	2.67/2.68/2.65
2	HA2-CA	0.0	-1.37/-0.93/-1.40	2.59/2.66/2.65
3	HA-CA	0.0	-1.34/-1.40/-2.04	2.72/2.72/2.70
4	HB1-CB	0.0	-1.62/-0.84/-1.92	2.37/2.61/2.57
5	HB2-CB	0.0	-3.06/-3.27/-5.18	2.62/2.65/2.58
6	OG-CB	0.0	-3.70/-4.35/-3.52	2.15/1.86/1.86
7	OG-CB	90.0	-1.91/-1.45/-0.73	2.22/1.97/1.97
8	OG-CB	180.0	-1.89/-1.76/-1.32	2.26/1.95/1.92
9	OG-CB	270.0	-3.56/-4.25/-3.75	2.15/1.87/1.85
10	OD1-SD	0.0	-4.07/-3.98/-2.24	1.93/1.85/1.91
11	OD1-SD	90.0	-3.91/-3.51/-2.76	1.93/1.85/1.89
12	OD1-SD	180.0	-5.28/-5.48/-4.99	1.89/1.81/1.84
13	OD1-SD	270.0	-5.44/-5.91/-4.38	1.89/1.81/1.85
14	OD2-SD	0.0	-5.05/-5.10/-3.51	1.91/1.83/1.88
15	OD2-SD	90.0	-5.50/-5.94/-4.53	1.90/1.82/1.86
16	OD2-SD	180.0	-4.97/-5.32/-4.69	1.91/1.82/1.86
17	OD2-SD	270.0	-4.15/-4.23/-3.35	1.94/1.85/1.89
18	HE1-CE	0.0	-3.14/-3.89/-5.05	2.57/2.60/2.54
19	HE2-CE	0.0	-3.08/-2.86/-4.22	2.31/2.53/2.48
20	HH1-CH1	0.0	-1.30/-1.00/-0.61	2.48/2.63/2.72
21	HH1-CH1	90.0	-2.10/-1.31/-1.01	2.36/2.60/2.66
22	HH2-CH2	0.0	-1.03/-1.64/-0.78	2.65/2.65/2.86
23	HH2-CH2	90.0	-2.25/-2.29/-1.51	2.44/2.61/2.72
24	HI1-CI1	0.0	-1.51/-1.06/-0.29	2.59/2.69/2.77
25	HI1-CI1	90.0	-1.71/-1.13/-0.36	2.54/2.68/2.76
26	HI2-CI2	0.0	-1.49/-1.35/-0.36	2.61/2.68/2.78
27	HI2-CI2	90.0	-1.72/-1.46/-0.45	2.55/2.67/2.76
28	HJ-CJ	0.0	-1.55/-1.11/-0.42	2.60/2.70/2.76
29	HJ-CJ	90.0	-1.75/-1.19/-0.48	2.55/2.69/2.75

1.178 Small molecule used for
O-[N,N-dimethylphosphoramidate]-L-serine(SEN)

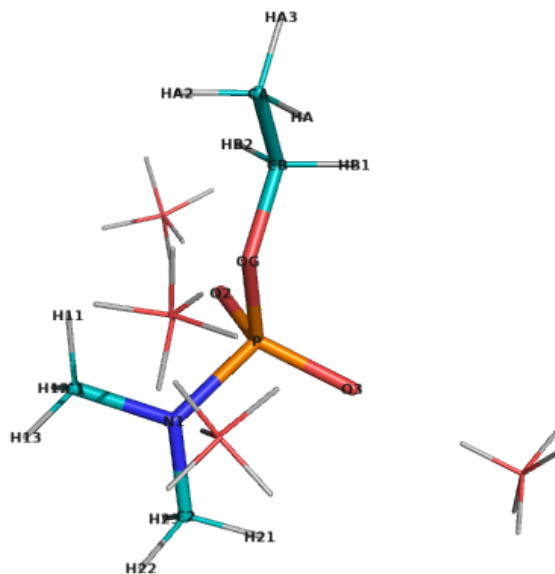


Figure S166: The molecule used for water complex calculations corresponding to (dimethylamino)(ethoxy)phosphinicacid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S550: Statistics of calculated water interaction and dipole moment for (dimethylamino)(ethoxy)phosphinicacid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.15/2.82	0.12/0.21	3.624	5.16/3.96	7.30
Optimal	0.26/0.56	0.09/0.13	3.115	5.16/4.27	4.43

Table S551: The comparison list of optimized atomic charges and their initial guess for (dimethylamino)(ethoxy)phosphinicacid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.268	0.045
HA	0.090	0.090	0.000
CB	-0.193	-0.099	0.538
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
OG	-0.393	-0.568	0.526
P	1.411	1.579	0.288
O2	-0.786	-0.822	0.000
O3	-0.786	-0.822	0.000
N1	-0.591	-0.610	6.132
C1	-0.191	-0.190	6.124
H11	0.090	0.090	2.500
H12	0.090	0.090	2.500
H13	0.090	0.090	2.500
C2	-0.191	-0.190	6.124
H21	0.090	0.090	2.500
H22	0.090	0.090	2.500
H23	0.090	0.090	2.500

Table S552: Interaction energies and geometries between probe water and selected (dimethylamino)(ethoxy)phosphinicacid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	OG-CB	0.0	-11.88/-12.45/-14.71	1.84/1.73/1.67
2	OG-CB	90.0	-9.70/-9.44/-11.55	1.89/1.79/1.71
3	OG-CB	180.0	-8.06/-7.54/-9.50	1.94/1.80/1.72
4	OG-CB	270.0	-8.98/-9.23/-11.34	1.91/1.78/1.71
5	O2-P	0.0	-13.35/-13.65/-13.87	1.75/1.66/1.65
6	O2-P	90.0	-13.92/-13.89/-14.06	1.74/1.65/1.65
7	O2-P	180.0	-13.93/-13.80/-14.07	1.74/1.65/1.65
8	O2-P	270.0	-13.51/-13.55/-13.89	1.74/1.66/1.65
9	O3-P	0.0	-13.60/-13.78/-14.17	1.75/1.66/1.65
10	O3-P	90.0	-13.33/-13.61/-13.98	1.75/1.66/1.65
11	O3-P	180.0	-13.50/-13.56/-13.79	1.75/1.66/1.65
12	O3-P	270.0	-13.72/-13.74/-13.97	1.75/1.66/1.65
13	N1-P	0.0	-7.09/-6.78/-6.65	2.09/2.03/2.05
14	N1-P	90.0	-9.23/-9.19/-9.05	2.05/2.00/2.02
15	N1-P	180.0	-12.58/-12.50/-13.15	1.96/1.95/1.95
16	N1-P	270.0	-9.29/-9.41/-9.87	2.03/1.99/1.99

1.179 Small molecule A of
O-[(S)-methyl(1-methylethoxy)phosphoryl]-L-serine(SGB)

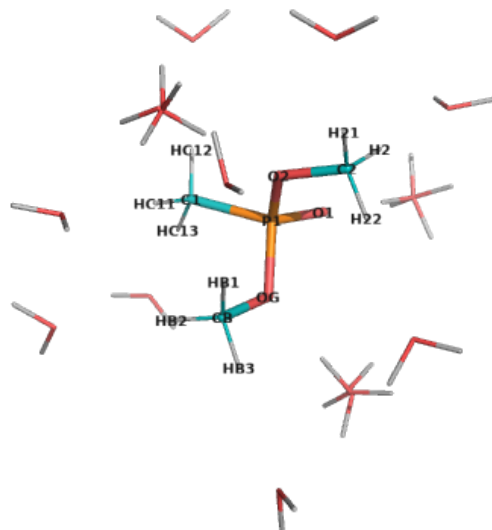


Figure S167: The molecule used for water complex calculations corresponding to dimethylmethylphosphonate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S553: Statistics of calculated water interaction and dipole moment for dimethylmethylphosphonate.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.53/2.64	0.16/0.32	9.464	4.80/0.94	27.40
Optimal	0.91/1.69	0.14/0.26	2.450	4.80/5.00	6.45

Table S554: The comparison list of optimized atomic charges and their initial guess for dimethylmethylphosphonate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB1	0.090	0.090	0.000
CB	0.035	-0.164	19.915
HB3	0.090	0.090	0.000
HB2	0.090	0.090	0.000
OG	-0.613	-0.655	51.582
P1	1.673	2.154	83.881
C1	-0.503	-0.644	71.769
HC11	0.090	0.090	3.476
HC12	0.090	0.090	3.476
HC13	0.090	0.090	3.476
O1	-0.804	-0.682	23.311
O2	-0.474	-0.655	51.582
C2	-0.124	-0.164	19.915
H2	0.090	0.090	0.000
H21	0.090	0.090	0.000
H22	0.090	0.090	0.000

Table S555: Interaction energies and geometries between probe water and selected dimethylmethylphosphonate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB1-CB	0.0	-1.57/-2.13/-0.35	2.79/2.64/2.78
2	HB3-CB	0.0	-1.71/-1.62/-0.30	2.56/2.63/2.81
3	HB2-CB	0.0	-2.37/-2.85/-1.45	2.59/2.56/2.65
4	OG-CB	0.0	-6.11/-7.03/-4.54	1.89/1.72/1.75
5	OG-CB	90.0	-3.69/-4.75/-4.68	1.96/1.75/1.73
6	OG-CB	180.0	-2.41/-3.37/-5.05	2.02/1.76/1.71
7	OG-CB	270.0	-3.71/-4.62/-4.41	1.96/1.75/1.73
8	HC11-C1	0.0	-2.08/-2.18/-1.34	2.62/2.69/2.69
9	HC12-C1	0.0	-1.67/-1.09/-1.38	2.47/2.65/2.65
10	HC13-C1	0.0	-1.99/-1.31/-1.58	2.46/2.63/2.63
11	O1-P1	0.0	-7.83/-9.39/-5.31	1.80/1.68/1.76
12	O1-P1	90.0	-7.63/-9.20/-5.01	1.80/1.69/1.77
13	O1-P1	180.0	-7.30/-8.86/-4.83	1.81/1.69/1.77
14	O1-P1	270.0	-7.19/-8.88/-4.98	1.81/1.69/1.77
15	O2-P1	0.0	-4.09/-4.27/-5.95	1.88/1.77/1.70
16	O2-P1	90.0	-4.71/-4.35/-5.22	1.85/1.77/1.72
17	O2-P1	180.0	-2.66/-2.39/-4.04	1.96/1.83/1.76
18	O2-P1	270.0	-3.45/-2.31/-4.70	1.88/1.81/1.73
19	H2-C2	0.0	-0.61/-0.15/-1.07	2.41/2.59/2.60
20	H21-C2	0.0	-1.54/-0.91/-0.36	2.61/2.72/2.80
21	H22-C2	0.0	-1.10/-1.25/-1.34	2.59/2.63/2.60

1.180 Small molecule used for S-nitroso-cysteine(SNC)

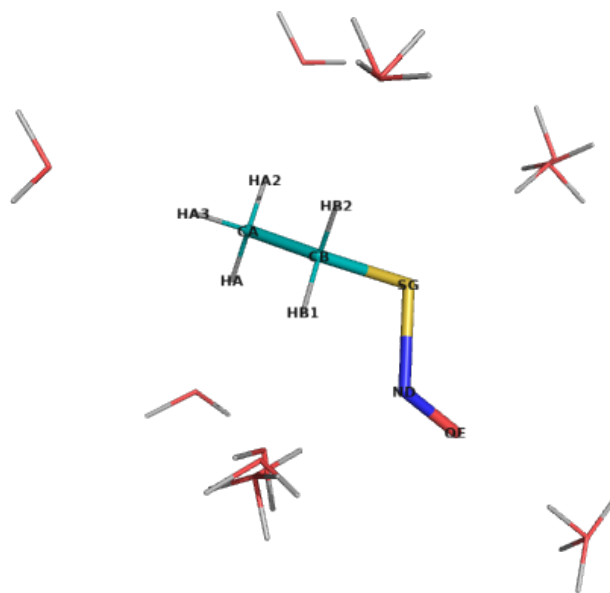


Figure S168: The molecule used for water complex calculations corresponding to (nitrososulfanyl)ethane, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S556: Statistics of calculated water interaction and dipole moment for (nitrososulfanyl)ethane.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.61/1.22	0.35/0.76	2.664	3.09/3.35	10.33
Optimal	0.38/0.81	0.31/0.58	2.565	3.09/3.71	3.09

Table S557: The comparison list of optimized atomic charges and their initial guess for (nitroso sulfanyl)ethane, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	2.500
HA	0.090	0.090	0.000
CB	0.050	-0.099	28.839
HB1	0.090	0.090	2.500
HB2	0.090	0.090	2.500
SG	-0.023	-0.126	238.595
ND	-0.106	-0.048	317.641
OE	-0.101	-0.093	245.109

Table S558: Interaction energies and geometries between probe water and selected (nitroso sulfanyl)ethane site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-1.46/-1.61/-1.79	2.71/2.67/2.64
2	HA2-CA	0.0	-1.56/-1.43/-1.46	2.65/2.66/2.64
3	HA-CA	0.0	-1.45/-1.32/-1.50	2.64/2.64/2.62
4	HB1-CB	0.0	-1.01/-1.60/-1.54	2.73/2.64/2.66
5	HB1-CB	90.0	-1.52/-1.79/-1.66	2.55/2.62/2.65
6	HB2-CB	0.0	-1.97/-2.25/-1.69	2.54/2.61/2.64
7	HB2-CB	90.0	-1.94/-2.23/-1.70	2.55/2.61/2.64
8	SG-CB	0.0	-0.87/-1.48/-2.09	3.07/2.51/2.42
9	SG-CB	90.0	-0.56/-0.86/-1.54	3.09/2.58/2.45
10	SG-CB	180.0	-0.13/-0.25/-1.09	3.25/2.68/2.49
11	SG-CB	270.0	-0.58/-0.81/-1.62	3.08/2.59/2.45
12	ND-SG	0.0	-2.33/-3.14/-2.30	2.39/2.16/2.24
13	ND-SG	90.0	-2.14/-1.79/-1.37	2.38/2.22/2.29
14	ND-SG	270.0	-2.07/-1.95/-1.32	2.38/2.21/2.28
15	OE-ND	0.0	-1.77/-2.17/-1.76	2.34/2.01/2.06
16	OE-ND	180.0	-1.87/-2.21/-1.55	2.33/2.01/2.08
17	OE-ND	270.0	-1.75/-2.19/-1.63	2.35/2.01/2.07

1.181 Small molecule used for Styrylalanine(STYA)

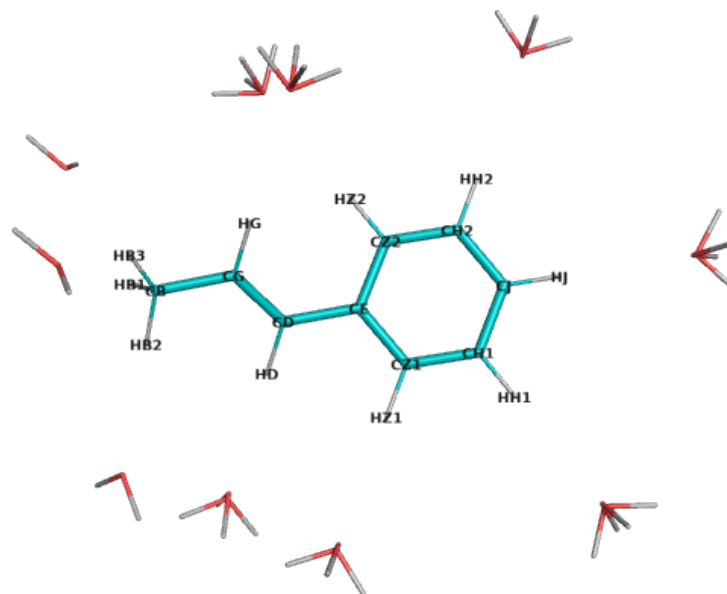


Figure S169: The molecule used for water complex calculations corresponding to [(1E)-prop-1-en-1-yl]benzene, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S559: Statistics of calculated water interaction and dipole moment for [(1E)-prop-1-en-1-yl]benzene.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.24/0.35	0.07/0.13	1.120	0.37/0.02	100.62
Optimal	0.25/0.38	0.07/0.13	0.789	0.37/0.48	0.00

Table S560: The comparison list of optimized atomic charges and their initial guess for [(1E)-prop-1-en-1-yl]benzene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.271	7.986
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.078	-0.142	10.803
HG	0.132	0.150	1.125
CD	-0.164	-0.150	11.540
HD	0.146	0.150	0.000
CE	-0.032	-0.007	9.749
CZ1	-0.119	-0.115	1.107
HZ1	0.115	0.115	0.000
CZ2	-0.115	-0.115	1.107
HZ2	0.115	0.115	0.000
CH1	-0.115	-0.115	0.000
HH1	0.115	0.115	0.000
CH2	-0.115	-0.115	0.000
HH2	0.115	0.115	0.000
CJ	-0.115	-0.115	0.000
HJ	0.115	0.115	0.000

Table S561: Interaction energies and geometries between probe water and selected [(1E)-prop-1-en-1-yl]benzene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.87/-0.71/-0.53	2.78/2.75/2.78
2	HB1-CB	0.0	-0.84/-0.68/-0.50	2.78/2.75/2.78
3	HB2-CB	0.0	-1.11/-0.95/-0.81	2.73/2.73/2.76
4	HG-CG	0.0	-1.41/-1.64/-1.60	2.67/2.59/2.59
5	HG-CG	90.0	-1.30/-1.60/-1.58	2.73/2.60/2.60
6	HD-CD	0.0	-1.21/-1.41/-1.47	2.70/2.59/2.58
7	HD-CD	90.0	-1.51/-1.50/-1.56	2.59/2.58/2.57
8	HZ1-CZ1	0.0	-1.19/-0.98/-1.14	2.68/2.72/2.70
9	HZ1-CZ1	90.0	-1.48/-1.10/-1.25	2.58/2.70/2.68
10	HZ2-CZ2	0.0	-1.26/-1.32/-1.37	2.71/2.70/2.69
11	HZ2-CZ2	90.0	-1.38/-1.38/-1.38	2.72/2.70/2.69
12	HH1-CH1	0.0	-1.16/-0.88/-0.97	2.68/2.72/2.71
13	HH1-CH1	90.0	-1.33/-0.95/-1.03	2.62/2.71/2.70
14	HH2-CH2	0.0	-1.15/-0.91/-0.97	2.68/2.72/2.72
15	HH2-CH2	90.0	-1.32/-0.97/-1.03	2.62/2.71/2.71
16	HJ-CJ	0.0	-1.14/-0.90/-0.96	2.68/2.72/2.72
17	HJ-CJ	90.0	-1.31/-0.96/-1.02	2.62/2.71/2.71

1.182 The dipeptide of (3-amino-2,5-dioxo-1-pyrrolidinyl)acetic acid (SUI)

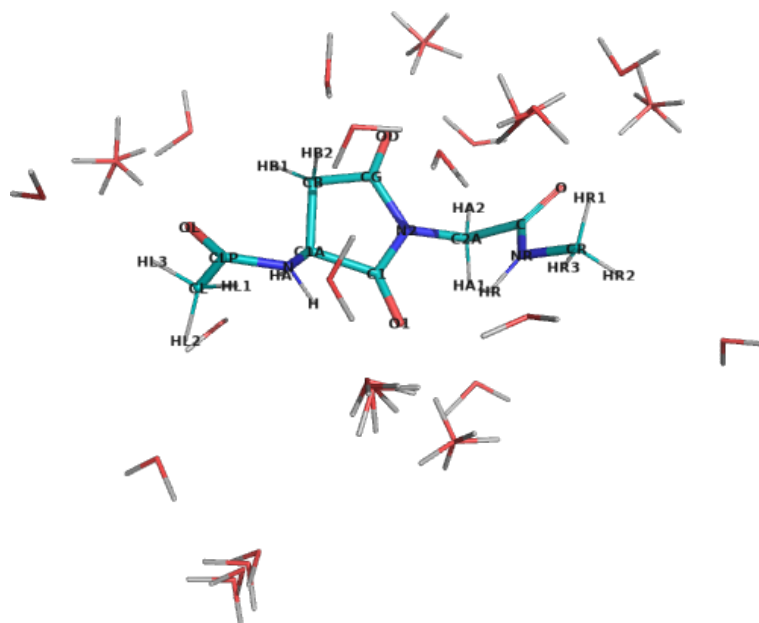


Figure S170: The molecule used for water complex calculations corresponding to 2-[(3S)-3-acetamido-2,5-dioxopyrrolidin-1-yl]-N-methylacetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S562: Statistics of calculated water interaction and dipole moment for 2-[(3S)-3-acetamido-2,5-dioxopyrrolidin-1-yl]-N-methylacetamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.40/3.56	0.13/0.24	3.083	6.43/7.77	3.76
Optimal	0.65/1.65	0.13/0.29	2.321	6.43/7.00	7.58

Table S563: The comparison list of optimized atomic charges and their initial guess for 2-[(3S)-3-acetamido-2,5-dioxopyrrolidin-1-yl]-N-methylacetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.271	3.550
HL1	0.090	0.090	0.000
HL2	0.090	0.090	0.000
HL3	0.090	0.090	0.000
CLP	0.510	0.484	12.328
OL	-0.510	-0.510	4.716
N	-0.284	-0.357	34.427
H	0.229	0.349	6.899
C1A	0.053	0.100	30.298
HA	0.090	0.090	2.724
CB	-0.113	-0.026	5.250
HB1	0.090	0.090	0.224
HB2	0.090	0.090	0.224
CG	0.247	0.312	7.374
OD	-0.411	-0.487	0.134
C1	0.346	0.313	25.834
O1	-0.439	-0.487	2.819
N2	-0.044	-0.139	10.878
C2A	-0.034	-0.002	9.803
HA1	0.090	0.090	0.638
HA2	0.090	0.090	0.638
C	0.510	0.499	4.549
O	-0.510	-0.517	0.316
NR	-0.470	-0.442	2.789
HR	0.310	0.299	0.000
CR	-0.110	-0.108	0.239
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S564: Interaction energies and geometries between probe water and selected 2-[(3S)-3-acetamido-2,5-dioxopyrrolidin-1-yl]-N-methylacetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	O-C	0.0	-6.30/-6.57/-6.87	1.84/1.77/1.76
2	O-C	90.0	-6.18/-6.61/-6.85	1.84/1.76/1.76
3	O-C	180.0	-5.64/-5.94/-6.07	1.85/1.77/1.77
4	O-C	270.0	-5.82/-6.02/-6.22	1.85/1.77/1.77
5	NR-C	0.0	-3.18/-1.53/-1.82	2.12/2.21/2.23
6	HR2-CR	0.0	-0.72/-0.84/-0.83	2.77/2.69/2.68
7	HR3-CR	0.0	-1.12/-1.26/-1.18	2.74/2.69/2.71
8	HA-C1A	0.0	-2.56/-2.40/-2.70	2.40/2.59/2.57
9	HL1-CL	0.0	-2.64/-2.70/-3.10	2.52/2.60/2.59
10	HL2-CL	0.0	-2.52/-2.13/-2.32	2.49/2.61/2.61
11	HL3-CL	0.0	-1.59/-1.06/-1.10	2.51/2.66/2.66
12	OL-CLP	0.0	-5.58/-6.03/-6.09	1.83/1.76/1.75
13	OL-CLP	90.0	-5.42/-5.81/-5.63	1.83/1.76/1.76
14	OL-CLP	180.0	-4.36/-5.03/-4.69	1.88/1.78/1.79
15	OL-CLP	270.0	-5.23/-5.52/-5.49	1.83/1.76/1.76
16	H-N	0.0	-3.78/-4.51/-7.34	2.13/2.03/1.89
17	H-N	45.0	-2.42/-3.89/-6.37	2.32/2.08/1.93
18	H-N	90.0	-3.07/-4.24/-6.73	2.26/2.07/1.92
19	H-N	135.0	-4.56/-4.90/-7.75	2.10/2.02/1.88
20	HB1-CB	0.0	-1.72/-0.70/-1.28	2.34/2.63/2.58
21	HB2-CB	0.0	-2.23/-1.81/-2.31	2.41/2.63/2.59
22	OD-CG	0.0	-3.78/-4.64/-5.51	1.95/1.82/1.78
23	OD-CG	90.0	-4.43/-5.28/-6.31	1.94/1.81/1.77
24	OD-CG	180.0	-4.35/-5.02/-6.20	1.95/1.82/1.78
25	OD-CG	270.0	-3.56/-4.37/-5.39	1.96/1.82/1.78
26	O1-C1	0.0	-3.02/-3.28/-3.78	1.90/1.81/1.78
27	O1-C1	90.0	-3.87/-4.09/-5.11	1.88/1.79/1.76
28	O1-C1	180.0	-3.23/-3.19/-4.29	1.91/1.83/1.79
29	O1-C1	270.0	-2.58/-2.60/-3.27	1.92/1.83/1.80
30	HA1-C2A	0.0	-2.41/-2.50/-2.07	2.38/2.56/2.58

1.183 Small molecule A of
(3-amino-2,5-dioxo-1-pyrrolidinyl)aceticacid(SUI)

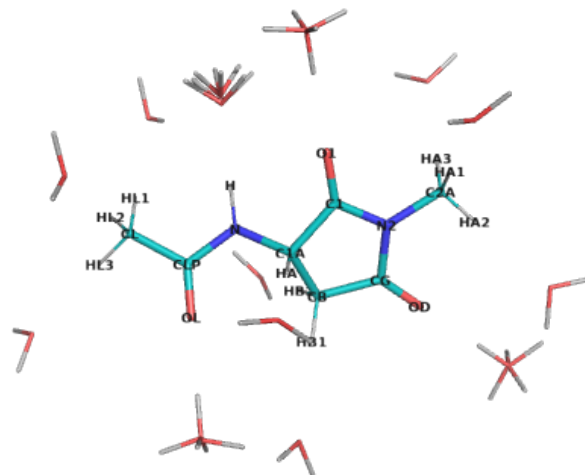


Figure S171: The molecule used for water complex calculations corresponding to N-[(3S)-1-methyl-2,5-dioxopyrrolidin-3-yl]acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S565: Statistics of calculated water interaction and dipole moment for N-[(3S)-1-methyl-2,5-dioxopyrrolidin-3-yl]acetamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.36/3.40	0.12/0.22	3.230	3.06/4.07	16.29
Optimal	0.38/0.84	0.12/0.26	1.945	3.06/3.61	0.81

Table S566: The comparison list of optimized atomic charges and their initial guess for N-[(3S)-1-methyl-2,5-dioxopyrrolidin-3-yl]acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.271	3.550
HL1	0.090	0.090	0.000
HL2	0.090	0.090	0.000
HL3	0.090	0.090	0.000
CLP	0.510	0.484	12.328
OL	-0.510	-0.510	4.716
N	-0.284	-0.357	34.427
H	0.229	0.349	6.899
C1A	0.053	0.100	30.298
HA	0.090	0.090	2.724
CB	-0.113	-0.026	5.250
HB1	0.090	0.090	0.224
HB2	0.090	0.090	0.224
CG	0.247	0.310	5.205
OD	-0.411	-0.487	0.126
C1	0.346	0.311	25.302
O1	-0.439	-0.487	2.819
N2	-0.044	-0.117	2.626
C2A	-0.124	-0.109	0.072
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
HA3	0.090	0.090	0.000

Table S567: Interaction energies and geometries between probe water and selected N-[(3S)-1-methyl-2,5-dioxopyrrolidin-3-yl]acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA-C1A	0.0	-2.04/-2.00/-2.34		2.43/2.60/2.58	
2	HL1-CL	0.0	-2.45/-2.52/-2.96		2.51/2.59/2.58	
3	HL2-CL	0.0	-2.28/-1.94/-2.13		2.50/2.61/2.61	
4	HL3-CL	0.0	-1.38/-0.94/-0.98		2.53/2.66/2.67	
5	OL-CLP	0.0	-5.87/-6.15/-6.21		1.82/1.76/1.75	
6	OL-CLP	90.0	-5.71/-5.88/-5.71		1.82/1.76/1.76	
7	OL-CLP	180.0	-4.77/-5.20/-4.83		1.86/1.78/1.78	
8	OL-CLP	270.0	-5.58/-5.72/-5.68		1.82/1.76/1.76	
9	H-N	0.0	-4.70/-4.35/-7.29		1.89/2.01/1.87	
10	H-N	45.0	-2.60/-3.44/-6.01		2.06/2.06/1.91	
11	H-N	90.0	-2.89/-3.52/-6.08		2.03/2.06/1.91	
12	H-N	135.0	-5.06/-4.44/-7.36		1.87/2.00/1.87	
13	HB1-CB	0.0	-1.34/-0.58/-1.19		2.38/2.64/2.59	
14	HB2-CB	0.0	-1.82/-1.54/-2.07		2.45/2.65/2.60	
15	OD-CG	0.0	-4.98/-5.26/-6.11		1.89/1.80/1.77	
16	OD-CG	90.0	-4.66/-4.93/-5.94		1.90/1.81/1.77	
17	OD-CG	180.0	-4.33/-4.59/-5.74		1.91/1.82/1.78	
18	OD-CG	270.0	-4.73/-5.03/-6.04		1.90/1.81/1.77	
19	O1-C1	0.0	-4.00/-3.95/-4.39		1.91/1.82/1.79	
20	O1-C1	90.0	-4.71/-4.77/-5.74		1.89/1.80/1.77	
21	O1-C1	180.0	-4.72/-4.81/-5.93		1.89/1.80/1.76	
22	O1-C1	270.0	-4.26/-4.25/-4.92		1.90/1.81/1.78	
23	HA1-C2A	0.0	-1.30/-1.22/-0.80		2.55/2.63/2.65	
24	HA2-C2A	0.0	-1.03/-0.33/0.13		2.44/2.64/2.65	
25	HA3-C2A	0.0	-1.31/-1.28/-0.93		2.61/2.64/2.67	

1.184 Small molecule A of
 O-[(R)-(dimethylamino)(ethoxy)phosphoryl]-L-serine(SUN)

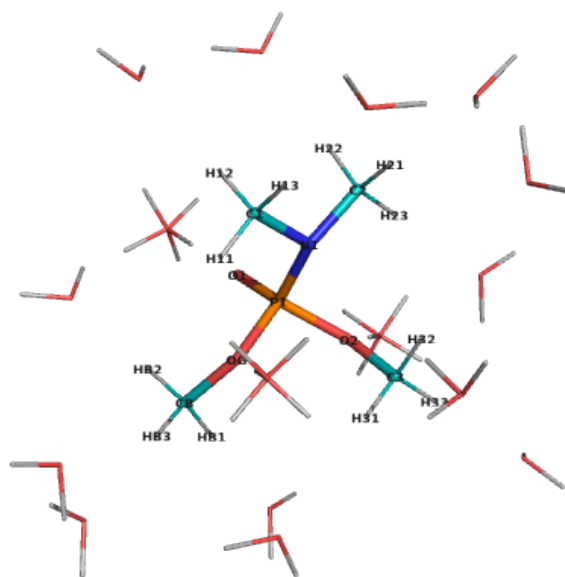


Figure S172: The molecule used for water complex calculations corresponding to (dimethoxyphosphoryl)dimethylamine, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S568: Statistics of calculated water interaction and dipole moment for (dimethoxyphosphoryl)dimethylamine.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.97/2.55	0.16/0.50	7.050	3.97/0.93	14.10
Optimal	0.51/1.05	0.20/0.86	1.408	3.97/4.17	3.45

Table S569: The comparison list of optimized atomic charges and their initial guess for (dimethoxyphosphoryl)dimethylamine, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.047	-0.185	10.207
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
OG	-0.412	-0.513	18.359
P1	1.133	1.990	31.632
O1	-0.671	-0.686	11.045
N1	-0.287	-0.606	25.668
O2	-0.412	-0.513	18.359
C1	-0.169	-0.191	9.045
H11	0.090	0.090	2.502
H12	0.090	0.090	2.502
H13	0.090	0.090	2.502
C2	-0.169	-0.191	9.045
H21	0.090	0.090	2.502
H22	0.090	0.090	2.502
H23	0.090	0.090	2.502
C3	-0.046	-0.185	10.207
H31	0.090	0.090	0.000
H32	0.090	0.090	0.000
H33	0.090	0.090	0.000

Table S570: Interaction energies and geometries between probe water and selected (dimethoxyphosphoryl)dimethylamine site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.45/-1.16/-0.56	2.63/2.68/2.77
2	HB1-CB	0.0	-1.64/-1.44/-1.62	2.48/2.59/2.60
3	HB2-CB	0.0	-0.98/-0.30/-1.14	2.36/2.58/2.58
4	OG-CB	0.0	-4.01/-3.78/-4.09	1.93/1.86/1.87
5	OG-CB	90.0	-3.05/-3.79/-3.22	2.03/1.88/1.92
6	OG-CB	180.0	-3.65/-4.20/-3.58	1.95/1.86/1.89
7	OG-CB	270.0	-3.31/-3.53/-3.36	1.96/1.88/1.91
8	O1-P1	0.0	-7.10/-8.15/-5.58	1.81/1.71/1.75
9	O1-P1	90.0	-7.34/-8.35/-5.68	1.80/1.71/1.75
10	O1-P1	180.0	-7.78/-8.81/-5.94	1.80/1.70/1.75
11	O1-P1	270.0	-7.79/-8.76/-5.93	1.80/1.70/1.75
12	N1-P1	0.0	-0.37/-0.50/-0.94	3.51/3.51/3.52
13	N1-P1	90.0	-0.55/-0.57/-0.96	3.50/3.49/3.52
14	O2-P1	0.0	-2.68/-2.69/-3.36	2.00/1.84/1.78
15	O2-P1	90.0	-4.01/-4.17/-3.26	1.94/1.81/1.80
16	O2-P1	180.0	-6.16/-6.36/-3.61	1.88/1.76/1.81
17	O2-P1	270.0	-3.68/-3.80/-3.07	1.96/1.82/1.81
18	H11-C1	0.0	-0.33/-0.33/-0.10	4.75/4.64/4.62
19	H12-C1	0.0	-1.09/-1.12/-1.37	2.60/2.61/2.63
20	H13-C1	0.0	-1.30/-1.22/-0.48	2.73/2.70/2.79
21	H21-C2	0.0	-1.44/-1.33/-0.58	2.70/2.68/2.77
22	H22-C2	0.0	-0.76/-0.81/-1.18	2.62/2.62/2.64
23	H23-C2	0.0	-0.41/-0.59/-0.99	2.75/2.76/2.67
24	H31-C3	0.0	-0.32/-0.93/-0.55	3.04/2.75/2.72
25	H32-C3	0.0	-0.59/-1.26/-0.30	4.10/3.24/3.60
26	H33-C3	0.0	-1.54/-1.25/-0.48	2.59/2.65/2.77

1.185 Small molecule A of
O-[(R)-ethoxy(methyl)phosphoryl]-L-serine(SVX)

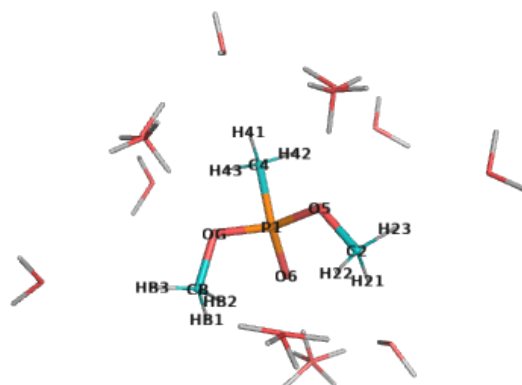


Figure S173: The molecule used for water complex calculations corresponding to dimethylmethylphosphonate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S571: Statistics of calculated water interaction and dipole moment for dimethylmethylphosphonate.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.37/2.62	0.15/0.22	7.595	2.16/1.20	117.46
Optimal	0.45/0.78	0.10/0.16	1.215	2.16/2.44	3.44

Table S572: The comparison list of optimized atomic charges and their initial guess for dimethylmethylphosphonate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.042	-0.164	19.915
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
OG	-0.394	-0.655	51.582
P1	1.014	2.154	83.881
O6	-0.653	-0.682	23.311
O5	-0.394	-0.655	51.582
C4	-0.299	-0.644	71.769
H41	0.090	0.090	3.476
H42	0.090	0.090	3.476
H43	0.090	0.090	3.476
C2	-0.042	-0.164	19.915
H21	0.090	0.090	0.000
H22	0.090	0.090	0.000
H23	0.090	0.090	0.000

Table S573: Interaction energies and geometries between probe water and selected dimethylmethylphosphonate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.43/-1.18/-0.36	2.62/2.67/2.80
2	HB2-CB	0.0	-1.64/-1.80/-1.47	2.89/2.76/2.76
3	OG-CB	0.0	-2.94/-3.03/-4.14	1.99/1.83/1.77
4	OG-CB	90.0	-4.18/-3.76/-4.66	1.88/1.80/1.74
5	OG-CB	180.0	-3.81/-3.99/-5.49	1.91/1.80/1.72
6	OG-CB	270.0	-4.49/-3.97/-5.19	1.87/1.80/1.73
7	O6-P1	0.0	-7.06/-7.79/-4.84	1.80/1.71/1.77
8	O6-P1	90.0	-7.64/-8.42/-5.02	1.79/1.71/1.76
9	O6-P1	180.0	-7.47/-8.25/-4.98	1.79/1.71/1.76
10	O6-P1	270.0	-6.90/-7.61/-4.77	1.80/1.72/1.77
11	O5-P1	0.0	-3.81/-3.99/-5.49	1.91/1.80/1.72
12	O5-P1	90.0	-4.18/-3.76/-4.66	1.88/1.80/1.74
13	O5-P1	180.0	-2.94/-3.03/-4.14	1.99/1.83/1.77
14	O5-P1	270.0	-4.49/-3.97/-5.19	1.87/1.80/1.73
15	H41-C4	0.0	-1.20/-0.91/-0.42	2.52/2.66/2.70
16	H42-C4	0.0	-1.42/-1.00/-1.26	2.52/2.64/2.66
17	H43-C4	0.0	-1.42/-1.00/-1.26	2.52/2.64/2.66
18	H22-C2	0.0	-2.04/-2.00/-1.70	2.79/2.72/2.72
19	H23-C2	0.0	-1.43/-1.18/-0.37	2.61/2.66/2.79

1.186 Small molecule A of
O-[bis(1-methylethoxy)phosphoryl]-L-serine(SVY)

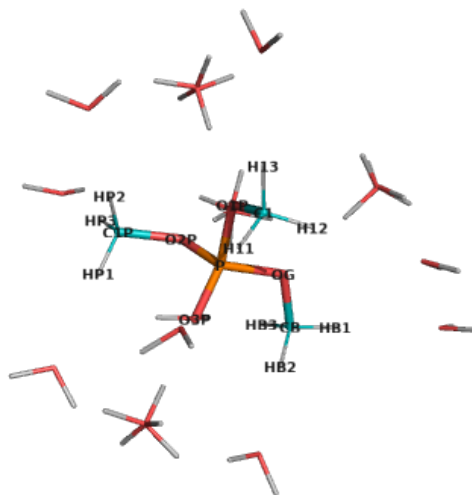


Figure S174: The molecule used for water complex calculations corresponding to trimethylphosphate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S574: Statistics of calculated water interaction and dipole moment for trimethylphosphate.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.63/0.99	0.12/0.23	4.331	0.66/0.32	179.58
Optimal	0.22/0.66	0.11/0.23	1.092	0.66/0.77	0.33

Table S575: The comparison list of optimized atomic charges and their initial guess for trimethylphosphate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.032	-0.164	1.634
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
OG	-0.341	-0.486	3.100
P	0.884	1.818	3.937
O3P	-0.573	-0.678	0.000
O2P	-0.341	-0.486	3.100
O1P	-0.341	-0.486	3.100
C1	-0.033	-0.164	1.634
H11	0.090	0.090	0.000
H12	0.090	0.090	0.000
H13	0.090	0.090	0.000
C1P	-0.033	-0.164	1.634
HP1	0.090	0.090	0.000
HP2	0.090	0.090	0.000
HP3	0.090	0.090	0.000

Table S576: Interaction energies and geometries between probe water and selected trimethylphosphate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.82/-0.97/-1.14	2.60/2.63/2.62
2	HB1-CB	0.0	-1.45/-1.15/-0.58	2.60/2.66/2.75
3	HB2-CB	90.0	-1.38/-0.73/-1.26	2.33/2.56/2.56
4	OG-CB	0.0	-4.43/-4.47/-3.84	1.90/1.80/1.81
5	OG-CB	90.0	-3.28/-3.25/-2.93	1.94/1.84/1.83
6	OG-CB	180.0	-3.74/-3.80/-3.74	1.94/1.83/1.80
7	OG-CB	270.0	-4.91/-4.82/-4.15	1.88/1.80/1.80
8	O3P-P	0.0	-6.91/-7.13/-5.92	1.81/1.74/1.75
9	O3P-P	90.0	-6.90/-7.12/-5.91	1.81/1.74/1.75
10	O3P-P	180.0	-6.91/-7.13/-5.92	1.81/1.74/1.75
11	O3P-P	270.0	-6.92/-7.14/-5.93	1.81/1.74/1.75
12	O2P-P	0.0	-3.74/-3.80/-3.75	1.94/1.83/1.80
13	O2P-P	90.0	-4.92/-4.83/-4.15	1.88/1.80/1.80
14	O2P-P	180.0	-4.44/-4.47/-3.84	1.90/1.80/1.81
15	O2P-P	270.0	-3.28/-3.25/-2.93	1.94/1.84/1.83
16	O1P-P	0.0	-3.73/-3.79/-3.74	1.94/1.83/1.80
17	O1P-P	90.0	-4.91/-4.82/-4.15	1.88/1.80/1.80
18	O1P-P	180.0	-4.44/-4.48/-3.84	1.90/1.80/1.81
19	O1P-P	270.0	-3.28/-3.24/-2.93	1.94/1.84/1.83
20	H11-C1	0.0	-0.78/-0.47/-1.02	2.41/2.59/2.59
21	H12-C1	0.0	-1.08/-1.08/-1.31	2.53/2.62/2.61
22	H13-C1	0.0	-1.52/-1.18/-0.62	2.58/2.66/2.75
23	HP1-C1P	0.0	-0.78/-0.47/-1.02	2.41/2.59/2.59
24	HP2-C1P	0.0	-1.07/-1.08/-1.31	2.53/2.62/2.60
25	HP3-C1P	0.0	-1.52/-1.18/-0.62	2.58/2.66/2.75

1.187 Small molecule A of 2-[(4Z)-2-[(1R)-1-amino-2-hydroxy-ethyl]-4-(1H-indol-3-ylmethylidene)-5-oxo-imidazol-1-yl]ethanoicacid(SWG)

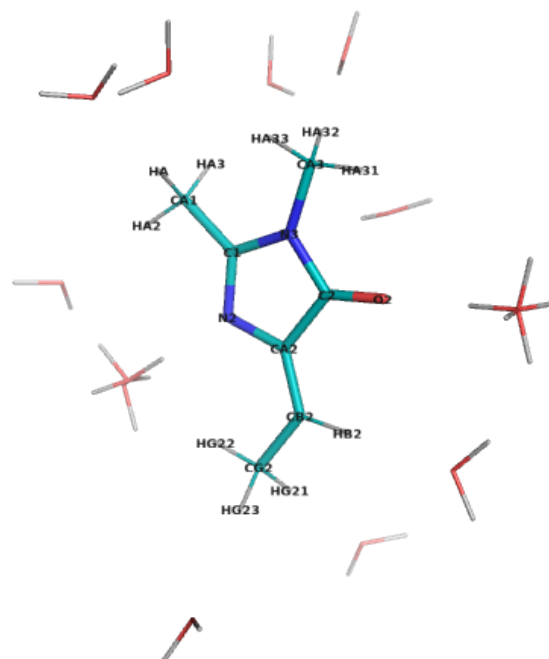


Figure S175: The molecule used for water complex calculations corresponding to (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S577: Statistics of calculated water interaction and dipole moment for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.92/1.64	0.10/0.25	6.526	3.17/0.45	27.81
Optimal	0.49/1.31	0.09/0.22	3.053	3.17/3.55	14.34

Table S578: The comparison list of optimized atomic charges and their initial guess for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA1	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
HA2	0.090	0.090	0.000
HA3	0.090	0.090	0.000
C1	0.233	0.074	23.781
N2	-0.679	-0.703	41.871
N3	-0.080	-0.079	15.706
C2	0.407	0.509	24.002
O2	-0.489	-0.482	6.710
CA2	0.288	0.516	47.153
CB2	-0.105	-0.135	25.469
HB2	0.150	0.150	3.270
CG2	-0.270	-0.274	15.277
HG21	0.090	0.090	1.175
HG22	0.090	0.090	1.175
HG23	0.090	0.090	1.175
CA3	-0.195	-0.271	3.821
HA31	0.090	0.090	0.000
HA32	0.090	0.090	0.000
HA33	0.090	0.090	0.000

Table S579: Interaction energies and geometries between probe water and selected (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA-CA1	0.0	-2.17/-2.61/-1.51		2.59/2.58/2.65	
2	HA2-CA1	0.0	-0.97/-0.86/0.05		2.58/2.64/2.77	
3	HA3-CA1	0.0	-2.55/-2.73/-1.57		2.52/2.57/2.64	
4	N2-C1	0.0	-4.99/-6.30/-5.60		2.09/2.01/2.02	
5	N2-C1	90.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
6	N2-C1	180.0	-5.35/-5.42/-6.38		1.95/2.01/1.99	
7	N2-C1	270.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
8	N3-C1	0.0	-0.26/-0.82/-0.78		2.74/2.52/2.49	
9	O2-C2	0.0	-5.51/-5.57/-5.00		1.85/1.78/1.80	
10	O2-C2	90.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
11	O2-C2	180.0	-5.92/-5.61/-4.27		1.84/1.78/1.81	
12	O2-C2	270.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
13	HB2-CB2	0.0	-1.40/-1.60/-2.82		2.32/2.47/2.44	
14	HG21-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
15	HG23-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
16	HA32-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	
17	HA33-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	

1.188 Small molecule B of 2-[(4Z)-2-[(1R)-1-amino-2-hydroxy-ethyl]-4-(1H-indol-3-ylmethylidene)-5-oxo-imidazol-1-yl]ethanoic acid(SWG)

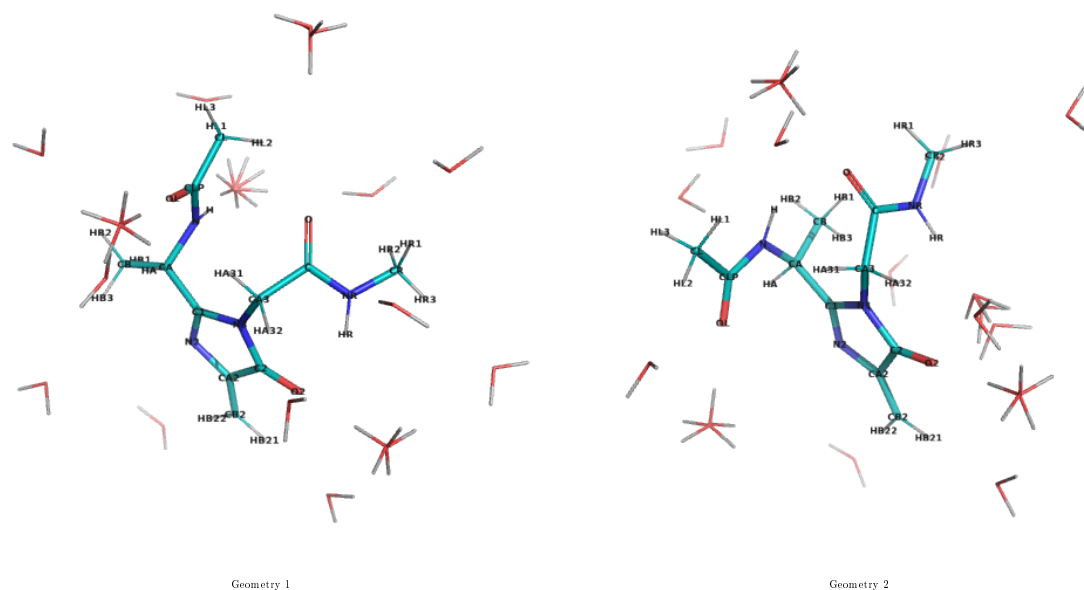


Table S580: The molecule used for water complex calculations corresponding to N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S581: Statistics of calculated water interaction and dipole moment for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide.

		RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
		Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Geometry 1	Initial	0.86 / 2.05	0.07 / 0.17	6.601	1.19 / 4.07	1.19
Geometry 2	Initial	1.02 / 2.07	0.09 / 0.23	6.126	6.37 / 4.43	6.37
Sum of geometries	Initial	0.95 / 2.07	0.08 / 0.23	12.727	-	-
Geometry 1	Optimal	0.36 / 0.81	0.07 / 0.16	2.460	1.19 / 1.37	1.19
Geometry 2	Optimal	0.51 / 0.91	0.08 / 0.19	2.701	6.37 / 7.25	6.37
Sum of geometries	Optimal	0.45 / 0.91	0.08 / 0.19	5.161	-	-

Table S582: The comparison list of optimized atomic charges and their initial guess for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
C1	0.233	0.164	24.002
N2	-0.679	-0.703	41.104
N3	-0.031	-0.499	22.994
C2	0.407	0.613	23.378
O2	-0.489	-0.482	6.517
CA2	0.466	0.512	42.773
CB2	-0.593	-0.444	13.655
HB21	0.230	0.230	0.950
HB22	0.230	0.230	0.950
CA3	-0.154	0.043	13.461
HA31	0.090	0.090	0.177
HA32	0.090	0.090	0.177
C	0.510	0.499	10.097
O	-0.510	-0.517	3.479
NR	-0.470	-0.442	6.773
HR	0.310	0.299	0.000
CR	-0.110	-0.108	0.239
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S583: Interaction energies and geometries between probe water and selected N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
Geometry 1				
1	O-C	0.0	-5.45/-5.47/-6.22	1.84/1.77/1.76
2	O-C	90.0	-6.01/-6.48/-6.53	1.83/1.75/1.76
3	O-C	180.0	-5.96/-6.64/-6.64	1.83/1.75/1.75
4	O-C	270.0	-5.67/-5.94/-6.62	1.84/1.76/1.75
5	NR-C	0.0	-1.32/-1.50/-1.08	2.24/2.20/2.22
6	HR2-CR	0.0	-1.10/-1.26/-1.09	2.71/2.66/2.67
7	HR3-CR	0.0	-1.39/-1.22/-1.32	2.66/2.67/2.67
8	N2-C1	0.0	-5.74/-6.45/-6.04	1.95/1.92/1.92
9	N2-C1	90.0	-6.51/-6.37/-7.24	1.90/1.92/1.90
10	N2-C1	180.0	-5.60/-5.66/-7.65	1.96/1.93/1.90
11	N2-C1	270.0	-6.64/-6.59/-7.43	1.90/1.91/1.89
12	O2-C2	0.0	-3.88/-3.93/-3.54	1.88/1.80/1.81
13	O2-C2	90.0	-4.94/-5.15/-4.46	1.84/1.77/1.79
14	O2-C2	180.0	-4.95/-5.20/-4.05	1.84/1.77/1.79
15	O2-C2	270.0	-3.93/-4.12/-3.39	1.87/1.79/1.81
16	HB21-CB2	0.0	-1.84/-1.64/-3.47	2.32/2.48/2.42
17	HB22-CB2	0.0	-1.82/-1.01/-2.42	2.42/2.54/2.46
18	HA31-CA3	0.0	-2.08/-2.47/-1.68	2.70/2.69/2.70
19	HA-CA	0.0	-2.47/-2.76/-1.19	2.49/2.56/2.66
Geometry 2				
20	O-C	0.0	-6.06/-6.90/-7.24	1.86/1.76/1.75
21	O-C	90.0	-5.25/-6.15/-7.32	1.87/1.77/1.75
22	O-C	180.0	-4.71/-5.63/-6.52	1.88/1.77/1.76
23	O-C	270.0	-5.56/-6.46/-6.85	1.86/1.76/1.76
24	HR-NR	0.0	-7.09/-7.67/-7.53	1.93/1.90/1.90
25	HR-NR	45.0	-7.71/-7.90/-7.71	1.91/1.89/1.89
26	HR-NR	90.0	-7.79/-7.84/-7.79	1.90/1.89/1.89
27	HR-NR	135.0	-7.18/-7.62/-7.61	1.92/1.90/1.89
28	HR1-CR	0.0	-0.71/-0.04/0.30	2.50/2.69/2.67
29	HR2-CR	0.0	-1.54/-1.44/-1.38	2.68/2.66/2.66
30	HR3-CR	0.0	-1.84/-1.82/-1.70	2.68/2.67/2.66
31	N2-C1	0.0	-6.46/-6.98/-6.58	1.93/1.91/1.91
32	N2-C1	90.0	-6.88/-6.47/-7.35	1.89/1.91/1.89
33	N2-C1	180.0	-5.73/-5.60/-7.60	1.95/1.93/1.90
34	N2-C1	270.0	-7.31/-7.09/-7.94	1.88/1.91/1.89
35	N3-C1	0.0	-0.22/0.03/-2.15	2.60/2.67/2.17
36	O2-C2	0.0	-4.96/-5.34/-4.95	1.88/1.79/1.80
37	O2-C2	90.0	-5.32/-5.37/-4.66	1.87/1.78/1.80
38	O2-C2	180.0	-5.74/-5.89/-4.71	1.87/1.78/1.81
39	O2-C2	270.0	-5.94/-6.25/-5.51	1.85/1.77/1.79
40	HB21-CB2	0.0	-1.43/-1.20/-3.03	2.33/2.48/2.41
41	HB22-CB2	0.0	-1.29/-0.66/-2.05	2.47/2.56/2.47
42	HA31-CA3	0.0	-3.71/-4.08/-3.49	2.50/2.57/2.57
43	HA-CA	0.0	-2.67/-3.45/-1.93	2.59/2.58/2.69

1.189 Small molecule used for 3-(2-tetrazolyl)-alanine(TEZA)

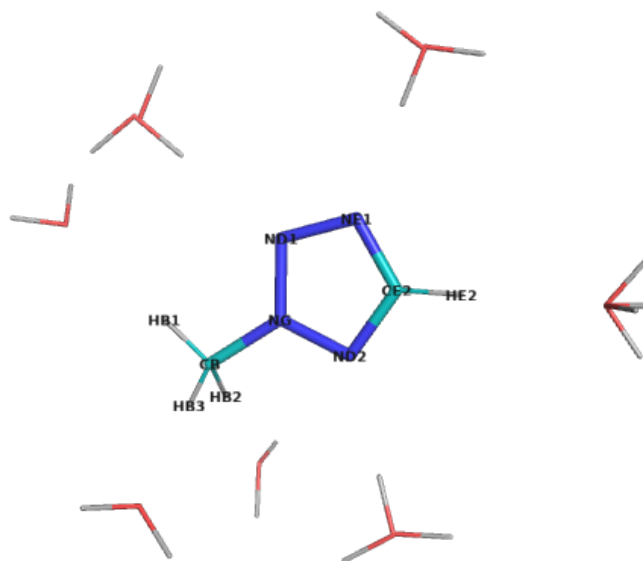


Figure S176: The molecule used for water complex calculations corresponding to 2-methyl-2H-1,2,3,4-tetrazole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S584: Statistics of calculated water interaction and dipole moment for 2-methyl-2H-1,2,3,4-tetrazole.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	1.51/2.95	0.10/0.19	6.754	2.91/5.35	5.61
Optimal	0.40/1.00	0.12/0.21	2.307	2.91/3.52	0.03

Table S585: The comparison list of optimized atomic charges and their initial guess for 2-methyl-2H-1,2,3,4-tetrazole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.180	-0.192	0.289
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
NG	0.721	0.844	27.443
ND1	-0.275	-0.173	23.965
ND2	-0.619	-0.576	28.875
NE1	-0.475	-0.706	10.325
CE2	0.462	0.428	12.354
HE2	0.096	0.105	0.000

Table S586: Interaction energies and geometries between probe water and selected 2-methyl-2H-1,2,3,4-tetrazole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-2.42/-2.34/-2.99	2.43/2.57/2.54
2	HB1-CB	0.0	-2.19/-2.26/-3.02	2.40/2.55/2.52
3	HB2-CB	0.0	-2.30/-2.29/-2.95	2.45/2.57/2.54
4	ND1-NG	0.0	-4.09/-4.70/-4.48	2.24/2.02/2.05
5	ND1-NG	180.0	-1.92/-0.92/0.22	2.34/2.20/2.41
6	ND2-NG	0.0	-4.09/-4.20/-3.70	2.04/1.98/2.00
7	ND2-NG	180.0	-3.27/-2.92/-1.73	2.07/2.01/2.06
8	NE1-ND1	0.0	-4.40/-4.08/-7.05	2.04/2.02/1.91
9	NE1-ND1	180.0	-5.52/-5.87/-8.46	2.00/1.96/1.88
10	HE2-CE2	0.0	-2.63/-2.62/-2.04	2.34/2.25/2.27
11	HE2-CE2	90.0	-2.55/-2.50/-1.90	2.34/2.26/2.28

1.190 Small molecule used for 2-(trifluoromethyl)-phenylglycine(TFG2)

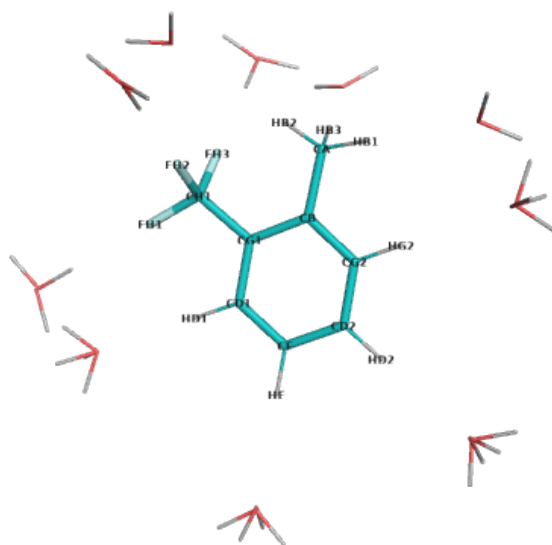


Figure S177: The molecule used for water complex calculations corresponding to 1-methyl-2-(trifluoromethyl)benzene, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S587: Statistics of calculated water interaction and dipole moment for 1-methyl-2-(trifluoromethyl)benzene.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.97/1.25	0.20/0.31	7.054	2.84/1.00	137.65
Optimal	0.47/0.94	0.27/0.43	1.827	2.84/3.51	1.17

Table S588: The comparison list of optimized atomic charges and their initial guess for 1-methyl-2-(trifluoromethyl)benzene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA	-0.270	-0.267	0.645
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
HB3	0.090	0.090	0.000
CB	0.242	0.035	19.145
CG1	-0.354	-0.424	28.706
CH1	0.512	0.813	35.236
FH1	-0.183	-0.159	9.970
FH2	-0.183	-0.159	9.970
FH3	-0.183	-0.159	9.970
CG2	-0.115	-0.115	0.632
HG2	0.115	0.115	0.000
CD1	0.007	-0.201	19.185
HD1	0.142	0.250	1.432
CD2	-0.115	-0.115	0.000
HD2	0.115	0.115	0.000
CE	-0.115	-0.114	0.632
HE	0.115	0.115	0.000

Table S589: Interaction energies and geometries between probe water and selected 1-methyl-2-(trifluoromethyl)benzene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HB1-CA	0.0	-1.53/-1.61/-0.74		2.70/2.67/2.74	
2	HB3-CA	0.0	-1.00/-0.74/-0.38		2.60/2.67/2.75	
3	FH1-CH1	0.0	-0.92/-1.27/0.09		2.35/1.92/2.13	
4	FH1-CH1	180.0	-1.69/-2.63/-0.60		2.28/1.85/2.00	
5	FH2-CH1	0.0	-1.45/-2.01/-1.21		2.29/1.88/1.98	
6	FH2-CH1	180.0	-1.79/-2.57/-0.56		2.27/1.86/2.04	
7	FH3-CH1	0.0	-1.32/-1.92/-1.17		2.28/1.88/1.97	
8	FH3-CH1	180.0	-1.88/-2.75/-0.71		2.24/1.85/2.02	
9	HG2-CG2	0.0	-1.81/-1.97/-0.82		2.61/2.64/2.73	
10	HG2-CG2	90.0	-2.16/-2.06/-0.91		2.51/2.63/2.71	
11	HD1-CD1	0.0	-1.73/-1.55/-2.60		2.45/2.61/2.56	
12	HD1-CD1	90.0	-1.43/-1.35/-2.61		2.54/2.63/2.56	
13	HD2-CD2	0.0	-1.82/-1.52/-0.75		2.57/2.68/2.74	
14	HD2-CD2	90.0	-2.02/-1.59/-0.81		2.52/2.67/2.72	
15	HE-CE	0.0	-1.73/-1.61/-0.92		2.59/2.66/2.73	
16	HE-CE	90.0	-1.92/-1.67/-1.02		2.53/2.66/2.71	

1.191 Small molecule used for 3-(trifluoromethyl)-phenylglycine(TFG3)

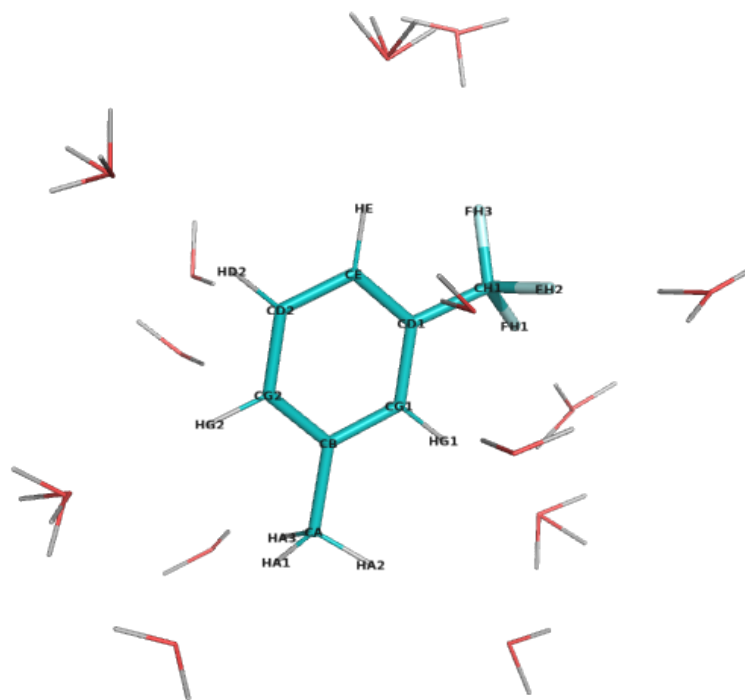


Figure S178: The molecule used for water complex calculations corresponding to 1-methyl-3-(trifluoromethyl)benzene, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S590: Statistics of calculated water interaction and dipole moment for 1-methyl-3-(trifluoromethyl)benzene.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.15/2.09	0.33/0.80	8.039	3.31/1.00	177.37
Optimal	0.50/1.15	0.29/0.48	2.233	3.31/3.99	6.69

Table S591: The comparison list of optimized atomic charges and their initial guess for 1-methyl-3-(trifluoromethyl)benzene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA	-0.270	-0.267	0.000
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
HA3	0.090	0.090	0.000
CB	-0.000	0.000	0.632
CG1	0.093	-0.202	19.185
HG1	0.115	0.250	1.432
CG2	-0.115	-0.116	0.000
HG2	0.115	0.115	0.000
CD1	-0.332	-0.427	28.711
CH1	0.523	0.804	35.242
FH1	-0.202	-0.159	9.970
FH2	-0.202	-0.159	9.970
FH3	-0.202	-0.159	9.970
CD2	-0.115	-0.114	0.632
HD2	0.115	0.115	0.000
CE	0.092	-0.201	19.185
HE	0.115	0.250	1.432

Table S592: Interaction energies and geometries between probe water and selected 1-methyl-3-(trifluoromethyl)benzene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA1-CA	0.0	-1.39/-1.18/-0.45	2.71/2.72/2.78
2	HA2-CA	0.0	-1.64/-1.65/-0.92	2.66/2.66/2.76
3	HA3-CA	0.0	-1.27/-1.08/-0.27	2.69/2.71/2.79
4	HG1-CG1	0.0	-1.91/-1.80/-2.54	2.43/2.59/2.55
5	HG1-CG1	90.0	-1.79/-1.64/-2.62	2.45/2.60/2.54
6	HG2-CG2	0.0	-1.86/-1.63/-0.62	2.59/2.67/2.75
7	HG2-CG2	90.0	-2.12/-1.71/-0.70	2.52/2.66/2.74
8	FH1-CH1	0.0	-1.16/-1.72/-0.48	2.32/1.88/2.04
9	FH1-CH1	180.0	-1.84/-2.93/-0.57	2.27/1.83/2.02
10	FH2-CH1	0.0	-1.63/-2.21/-1.20	2.28/1.86/1.98
11	FH2-CH1	180.0	-1.88/-2.81/-0.47	2.27/1.85/2.06
12	FH3-CH1	0.0	-1.17/-1.64/-0.41	2.32/1.88/2.04
13	FH3-CH1	180.0	-1.79/-2.94/-0.58	2.27/1.83/2.01
14	HD2-CD2	0.0	-1.80/-1.89/-0.79	2.57/2.64/2.74
15	HD2-CD2	90.0	-2.00/-1.95/-0.88	2.52/2.64/2.72
16	HE-CE	0.0	-1.85/-1.81/-2.53	2.42/2.59/2.55
17	HE-CE	90.0	-1.64/-1.64/-2.59	2.46/2.60/2.55
18	CE-CD1	0.0	-0.63/-0.03/-2.72	3.03/2.87/2.23
19	CG1-CB	0.0	-1.65/-2.05/-2.82	2.81/2.43/2.24
20	CG2-CB	0.0	-0.93/-1.01/-2.82	2.82/2.34/2.28
21	CD2-CG2	0.0	-1.18/-0.75/-2.48	2.85/2.45/2.28

1.192 Small molecule used for 4-(trifluoromethyl)-phenylglycine(TFG4)

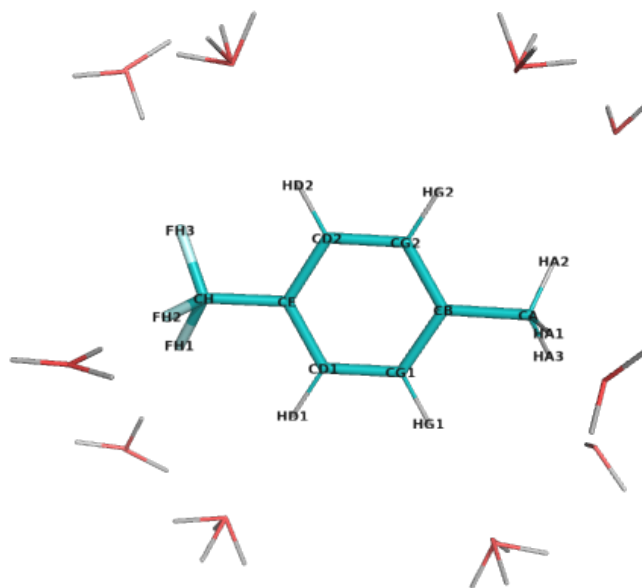


Figure S179: The molecule used for water complex calculations corresponding to 1-methyl-4-(trifluoromethyl)benzene, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S593: Statistics of calculated water interaction and dipole moment for 1-methyl-4-(trifluoromethyl)benzene.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	1.04/1.45	0.20/0.30	8.332	3.52/1.02	179.96
Optimal	0.24/0.47	0.24/0.40	2.390	3.52/4.14	0.57

Table S594: The comparison list of optimized atomic charges and their initial guess for 1-methyl-4-(trifluoromethyl)benzene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA	-0.270	-0.267	0.000
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
HA3	0.090	0.090	0.000
CB	0.162	-0.001	0.000
CG1	-0.068	-0.115	0.632
HG1	0.115	0.115	0.000
CG2	-0.068	-0.115	0.632
HG2	0.115	0.115	0.000
CD1	-0.181	-0.201	19.185
HD1	0.211	0.250	1.432
CD2	-0.181	-0.201	19.185
HD2	0.211	0.250	1.432
CE	-0.374	-0.427	28.711
CH	0.553	0.804	35.242
FH1	-0.165	-0.159	9.970
FH2	-0.165	-0.159	9.970
FH3	-0.165	-0.159	9.970

Table S595: Interaction energies and geometries between probe water and selected 1-methyl-4-(trifluoromethyl)benzene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA1-CA	0.0	-1.31/-1.38/-0.17	2.68/2.67/2.81
2	HA2-CA	0.0	-1.73/-1.77/-0.52	2.63/2.65/2.77
3	HA3-CA	0.0	-1.72/-1.76/-0.51	2.63/2.65/2.77
4	HG1-CG1	0.0	-1.83/-1.91/-0.79	2.60/2.64/2.74
5	HG1-CG1	90.0	-2.10/-2.01/-0.89	2.52/2.63/2.72
6	HG2-CG2	0.0	-1.83/-1.91/-0.79	2.60/2.64/2.74
7	HG2-CG2	90.0	-2.10/-2.02/-0.90	2.52/2.63/2.72
8	HD1-CD1	0.0	-1.90/-1.73/-2.53	2.41/2.58/2.55
9	HD1-CD1	90.0	-1.69/-1.66/-2.59	2.45/2.59/2.55
10	HD2-CD2	0.0	-1.90/-1.73/-2.53	2.41/2.58/2.55
11	HD2-CD2	90.0	-1.69/-1.65/-2.59	2.45/2.59/2.55
12	FH1-CH	0.0	-1.18/-1.47/-0.43	2.32/1.92/2.04
13	FH1-CH	180.0	-1.82/-2.28/-0.57	2.27/1.88/2.01
14	FH2-CH	0.0	-1.65/-2.13/-1.20	2.28/1.89/1.98
15	FH2-CH	180.0	-1.92/-2.16/-0.47	2.27/1.91/2.06
16	FH3-CH	0.0	-1.18/-1.47/-0.42	2.32/1.92/2.04
17	FH3-CH	180.0	-1.83/-2.28/-0.57	2.27/1.88/2.01

1.193 Small molecule used for 5,5,5-trifluoro-leucine(TFLE)

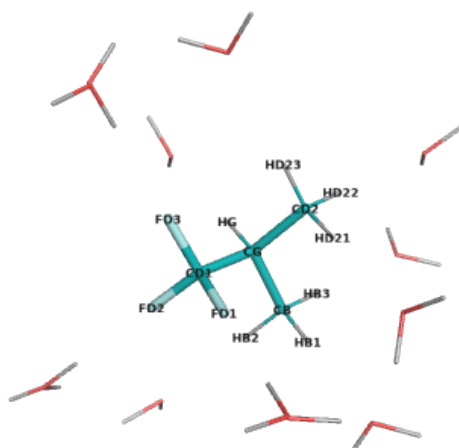


Figure S180: The molecule used for water complex calculations corresponding to 1,1,1-trifluoro-2-methylpropane, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S596: Statistics of calculated water interaction and dipole moment for 1,1,1-trifluoro-2-methylpropane.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.21/0.39	0.24/0.37	1.303	2.52/2.06	2.78
Optimal	0.24/0.52	0.25/0.37	1.439	2.52/3.02	2.23

Table S597: The comparison list of optimized atomic charges and their initial guess for 1,1,1-trifluoro-2-methylpropane, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.600
CB	-0.270	-0.271	6.162
HB1	0.090	0.090	0.600
HB2	0.090	0.090	0.600
CG	0.122	-0.010	12.449
HG	0.090	0.090	0.600
CD1	0.138	0.342	13.805
FD1	-0.121	-0.140	3.557
FD2	-0.121	-0.140	3.557
FD3	-0.121	-0.140	3.557
CD2	-0.257	-0.271	6.162
HD21	0.090	0.090	0.600
HD22	0.090	0.090	0.600
HD23	0.090	0.090	0.600

Table S598: Interaction energies and geometries between probe water and selected 1,1,1-trifluoro-2-methylpropane site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.56/-1.56/-1.17		2.67/2.67/2.71	
2	HB1-CB	0.0	-1.26/-1.03/-0.91		2.60/2.66/2.68	
3	HB2-CB	0.0	-1.08/-0.98/-0.92		2.62/2.67/2.68	
4	HG-CG	0.0	-1.75/-1.84/-1.51		2.55/2.64/2.67	
5	FD1-CD1	0.0	-1.20/-1.38/-1.30		2.31/1.94/1.94	
6	FD1-CD1	180.0	-1.88/-2.40/-1.99		2.26/1.89/1.91	
7	FD2-CD1	0.0	-1.24/-1.25/-1.14		2.31/1.95/1.96	
8	FD2-CD1	180.0	-1.86/-2.27/-1.86		2.26/1.89/1.91	
9	FD3-CD1	0.0	-1.24/-1.22/-1.14		2.31/1.95/1.96	
10	FD3-CD1	180.0	-1.86/-2.27/-1.86		2.26/1.89/1.91	
11	HD21-CD2	0.0	-1.09/-1.03/-0.87		2.65/2.67/2.69	
12	HD22-CD2	0.0	-1.45/-1.57/-1.14		2.72/2.67/2.71	
13	HD23-CD2	0.0	-1.04/-1.03/-0.89		2.63/2.66/2.69	

1.194 Small molecule used for 2-(trifluoromethyl)-phenylalanine(TFP2)

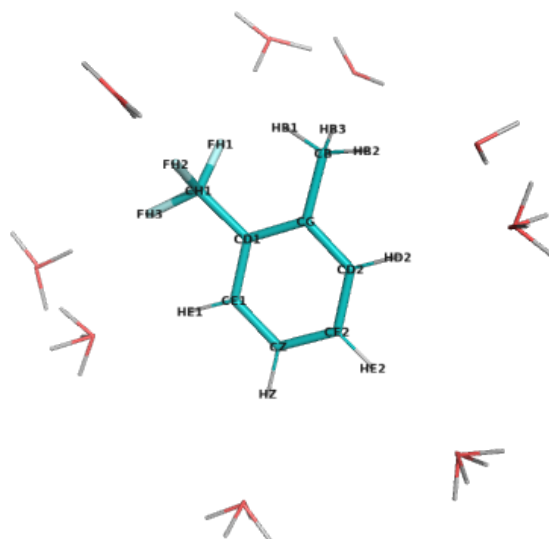


Figure S181: The molecule used for water complex calculations corresponding to 1-methyl-2-(trifluoromethyl)benzene, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S599: Statistics of calculated water interaction and dipole moment for 1-methyl-2-(trifluoromethyl)benzene.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.97/1.25	0.20/0.31	7.053	2.84/1.00	137.58
Optimal	0.47/0.94	0.26/0.43	1.860	2.84/3.53	1.17

Table S600: The comparison list of optimized atomic charges and their initial guess for 1-methyl-2-(trifluoromethyl)benzene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.267	0.645
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.246	0.035	19.145
CD1	-0.360	-0.424	28.706
CH1	0.503	0.813	35.236
FH1	-0.180	-0.159	9.970
FH2	-0.180	-0.159	9.970
FH3	-0.180	-0.159	9.970
CD2	-0.115	-0.115	0.632
HD2	0.115	0.115	0.000
CE1	0.009	-0.201	19.185
HE1	0.142	0.250	1.432
CE2	-0.115	-0.115	0.000
HE2	0.115	0.115	0.000
CZ	-0.115	-0.114	0.632
HZ	0.115	0.115	0.000

Table S601: Interaction energies and geometries between probe water and selected 1-methyl-2-(trifluoromethyl)benzene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.84/-0.62/-0.40	2.66/2.69/2.76
2	HB2-CB	0.0	-1.77/-1.70/-0.81	2.63/2.66/2.73
3	FH1-CH1	0.0	-1.33/-1.91/-1.17	2.28/1.88/1.97
4	FH1-CH1	180.0	-1.88/-2.74/-0.71	2.24/1.85/2.02
5	FH2-CH1	0.0	-1.45/-2.00/-1.21	2.29/1.88/1.98
6	FH2-CH1	180.0	-1.79/-2.56/-0.56	2.27/1.86/2.04
7	FH3-CH1	0.0	-0.91/-1.27/0.09	2.35/1.92/2.13
8	FH3-CH1	180.0	-1.69/-2.63/-0.60	2.28/1.85/2.00
9	HD2-CD2	0.0	-1.81/-1.98/-0.82	2.61/2.64/2.73
10	HD2-CD2	90.0	-2.16/-2.07/-0.91	2.51/2.63/2.71
11	HE1-CE1	0.0	-1.73/-1.54/-2.60	2.45/2.61/2.56
12	HE1-CE1	90.0	-1.43/-1.35/-2.61	2.54/2.63/2.56
13	HE2-CE2	0.0	-1.82/-1.52/-0.75	2.57/2.68/2.74
14	HE2-CE2	90.0	-2.02/-1.60/-0.81	2.52/2.67/2.72
15	HZ-CZ	0.0	-1.73/-1.61/-0.92	2.59/2.66/2.73
16	HZ-CZ	90.0	-1.92/-1.67/-1.02	2.53/2.66/2.71

1.195 Small molecule used for 3-(trifluoromethyl)-phenylalanine(TFP3)

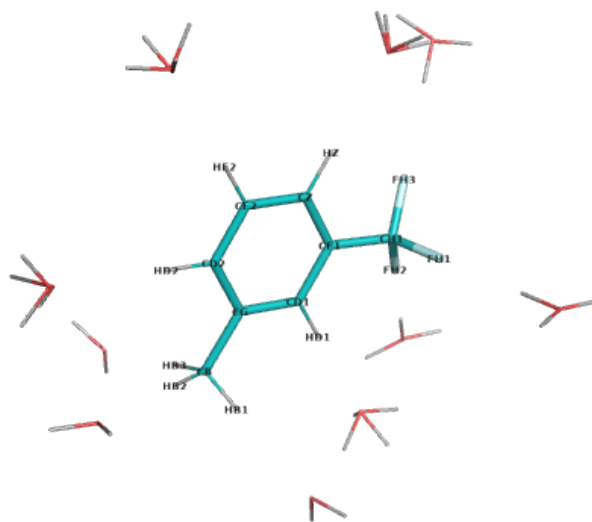


Figure S182: The molecule used for water complex calculations corresponding to 1-methyl-3-(trifluoromethyl)benzene, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S602: Statistics of calculated water interaction and dipole moment for 1-methyl-3-(trifluoromethyl)benzene.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	1.01/1.42	0.20/0.30	8.039	3.31/1.00	177.42
Optimal	0.24/0.47	0.25/0.40	2.181	3.31/3.84	1.85

Table S603: The comparison list of optimized atomic charges and their initial guess for 1-methyl-3-(trifluoromethyl)benzene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.267	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.126	0.000	0.632
CD1	-0.139	-0.202	19.185
HD1	0.190	0.250	1.432
CD2	-0.063	-0.116	0.000
HD2	0.115	0.115	0.000
CE1	-0.374	-0.427	28.711
CH1	0.553	0.804	35.242
FH1	-0.167	-0.159	9.970
FH2	-0.167	-0.159	9.970
FH3	-0.167	-0.159	9.970
CE2	-0.051	-0.114	0.632
HE2	0.115	0.115	0.000
CZ	-0.177	-0.201	19.185
HZ	0.206	0.250	1.432

Table S604: Interaction energies and geometries between probe water and selected 1-methyl-3-(trifluoromethyl)benzene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.23/-1.16/-0.28	2.70/2.69/2.79
2	HB1-CB	0.0	-1.83/-1.70/-1.09	2.60/2.64/2.72
3	HB2-CB	0.0	-1.62/-1.61/-0.53	2.65/2.67/2.76
4	HD1-CD1	0.0	-1.91/-1.84/-2.54	2.43/2.58/2.55
5	HD1-CD1	90.0	-1.79/-1.78/-2.62	2.45/2.59/2.54
6	HD2-CD2	0.0	-1.86/-2.06/-0.62	2.59/2.63/2.75
7	HD2-CD2	90.0	-2.12/-2.16/-0.70	2.52/2.62/2.74
8	FH1-CH1	0.0	-1.63/-2.09/-1.20	2.28/1.89/1.98
9	FH1-CH1	180.0	-1.88/-2.15/-0.47	2.27/1.90/2.06
10	FH2-CH1	0.0	-1.17/-1.44/-0.49	2.32/1.92/2.04
11	FH2-CH1	180.0	-1.84/-2.29/-0.57	2.27/1.88/2.02
12	FH3-CH1	0.0	-1.17/-1.47/-0.41	2.32/1.92/2.05
13	FH3-CH1	180.0	-1.79/-2.26/-0.58	2.27/1.88/2.01
14	HE2-CE2	0.0	-1.80/-1.73/-0.79	2.57/2.65/2.74
15	HE2-CE2	90.0	-2.00/-1.82/-0.88	2.52/2.64/2.72
16	HZ-CZ	0.0	-1.85/-1.68/-2.53	2.42/2.58/2.55
17	HZ-CZ	90.0	-1.64/-1.59/-2.59	2.46/2.59/2.55

1.196 Small molecule used for 4-(Trifluoromethyl)-phenylalanine(TFP4)

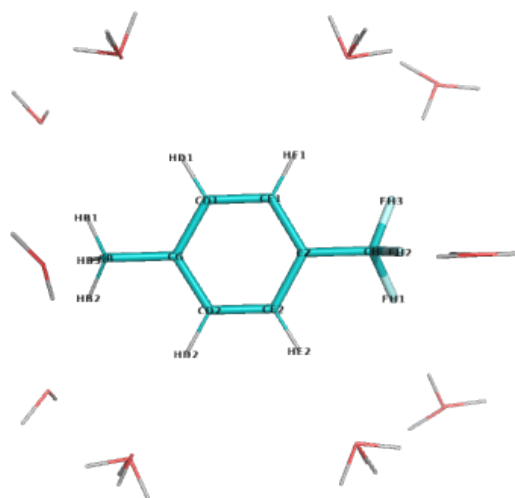


Figure S183: The molecule used for water complex calculations corresponding to 1-methyl-4-(trifluoromethyl)benzene, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S605: Statistics of calculated water interaction and dipole moment for 1-methyl-4-(trifluoromethyl)benzene.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	1.04/1.45	0.20/0.30	8.333	3.53/1.02	179.81
Optimal	0.24/0.48	0.24/0.40	2.396	3.53/4.14	0.52

Table S606: The comparison list of optimized atomic charges and their initial guess for 1-methyl-4-(trifluoromethyl)benzene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.267	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.165	-0.001	0.000
CD1	-0.068	-0.115	0.632
HD1	0.115	0.115	0.000
CD2	-0.068	-0.115	0.632
HD2	0.115	0.115	0.000
CE1	-0.181	-0.201	19.185
HE1	0.211	0.250	1.432
CE2	-0.181	-0.201	19.185
HE2	0.211	0.250	1.432
CZ	-0.374	-0.427	28.711
CH	0.553	0.804	35.242
FH1	-0.166	-0.159	9.970
FH2	-0.166	-0.159	9.970
FH3	-0.166	-0.159	9.970

Table S607: Interaction energies and geometries between probe water and selected 1-methyl-4-(trifluoromethyl)benzene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.31/-1.38/-0.17	2.68/2.67/2.81
2	HB1-CB	0.0	-1.72/-1.77/-0.51	2.63/2.65/2.77
3	HB2-CB	0.0	-1.72/-1.77/-0.51	2.63/2.65/2.77
4	HD1-CD1	0.0	-1.83/-1.91/-0.79	2.59/2.64/2.74
5	HD1-CD1	90.0	-2.10/-2.02/-0.90	2.52/2.63/2.72
6	HD2-CD2	0.0	-1.83/-1.91/-0.79	2.59/2.64/2.74
7	HD2-CD2	90.0	-2.10/-2.02/-0.90	2.52/2.63/2.72
8	HE1-CE1	0.0	-1.90/-1.73/-2.53	2.41/2.58/2.55
9	HE1-CE1	90.0	-1.69/-1.66/-2.59	2.45/2.59/2.55
10	HE2-CE2	0.0	-1.90/-1.73/-2.53	2.41/2.58/2.55
11	HE2-CE2	90.0	-1.69/-1.65/-2.59	2.45/2.59/2.55
12	FH1-CH	0.0	-1.19/-1.47/-0.43	2.32/1.92/2.04
13	FH1-CH	180.0	-1.83/-2.28/-0.57	2.27/1.88/2.01
14	FH2-CH	0.0	-1.65/-2.13/-1.19	2.28/1.89/1.98
15	FH2-CH	180.0	-1.92/-2.16/-0.47	2.27/1.91/2.06
16	FH3-CH	0.0	-1.18/-1.47/-0.43	2.32/1.92/2.04
17	FH3-CH	180.0	-1.83/-2.28/-0.58	2.27/1.88/2.01

1.197 Small molecule used for 2-thienylglycine(THG2)

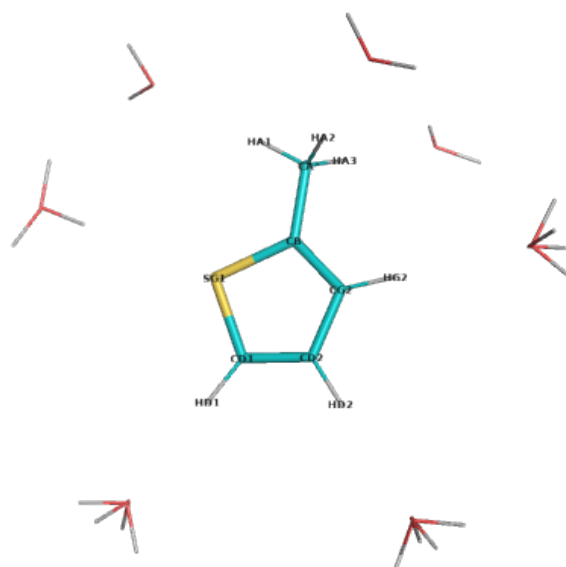


Figure S184: The molecule used for water complex calculations corresponding to 2-methylthiophene, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S608: Statistics of calculated water interaction and dipole moment for 2-methylthiophene.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.63/1.09	0.24/0.50	2.933	0.84/0.55	112.81
Optimal	0.21/0.50	0.22/0.49	1.370	0.84/1.03	1.31

Table S609: The comparison list of optimized atomic charges and their initial guess for 2-methylthiophene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA	-0.270	-0.229	43.092
HA1	0.090	0.090	2.500
HA2	0.090	0.090	2.500
HA3	0.090	0.090	2.500
CB	0.125	0.013	60.735
SG1	-0.003	-0.013	59.406
CG2	-0.174	-0.217	0.483
HG2	0.160	0.137	0.025
CD1	-0.259	-0.085	2.500
HD1	0.196	0.180	0.000
CD2	-0.254	-0.226	0.452
HD2	0.209	0.170	0.000

Table S610: Interaction energies and geometries between probe water and selected 2-methylthiophene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA1-CA	0.0	-1.32/-0.82/-0.68	2.59/2.70/2.72
2	HA2-CA	0.0	-0.99/-0.82/-0.55	2.72/2.73/2.75
3	HA3-CA	0.0	-0.99/-0.82/-0.55	2.72/2.73/2.75
4	SG1-CB	0.0	-0.80/-1.12/-0.80	3.02/2.53/2.57
5	SG1-CB	180.0	-0.65/-0.85/-0.98	3.05/2.57/2.54
6	HG2-CG2	0.0	-1.30/-1.43/-0.57	2.66/2.66/2.77
7	HG2-CG2	90.0	-1.47/-1.50/-0.64	2.60/2.65/2.76
8	HD1-CD1	0.0	-1.73/-1.73/-2.81	2.50/2.30/2.25
9	HD1-CD1	90.0	-1.89/-1.78/-2.85	2.46/2.30/2.25
10	HD2-CD2	0.0	-1.31/-1.40/-1.16	2.63/2.65/2.68
11	HD2-CD2	90.0	-1.48/-1.47/-1.23	2.57/2.64/2.68

1.198 Small molecule used for 3-thienylglycine(THG3)

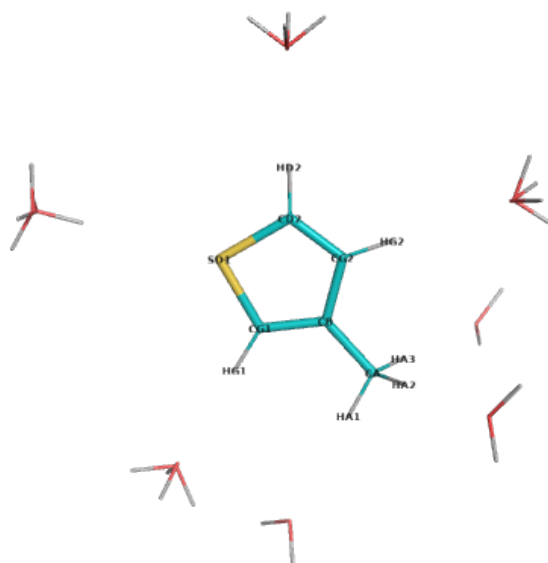


Figure S185: The molecule used for water complex calculations corresponding to 3-methylthiophene, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S611: Statistics of calculated water interaction and dipole moment for 3-methylthiophene.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.74/1.28	0.35/0.61	1.783	1.08/0.99	7.93
Optimal	0.14/0.25	0.27/0.48	1.360	1.08/1.25	1.58

Table S612: The comparison list of optimized atomic charges and their initial guess for 3-methylthiophene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA	-0.270	-0.244	2.531
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
HA3	0.090	0.090	0.000
CB	0.152	-0.045	2.534
CG1	-0.247	-0.088	2.500
HG1	0.167	0.201	0.000
CG2	-0.233	-0.242	0.483
HG2	0.185	0.170	0.025
SD1	0.020	-0.131	2.500
CD2	-0.232	-0.071	0.452
HD2	0.188	0.180	0.000

Table S613: Interaction energies and geometries between probe water and selected 3-methylthiophene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA1-CA	0.0	-1.32/-1.10/-1.25	2.71/2.71/2.72
2	HA2-CA	0.0	-0.86/-0.79/-0.50	2.78/2.74/2.78
3	HA3-CA	0.0	-0.86/-0.79/-0.50	2.78/2.74/2.78
4	HG1-CG1	0.0	-1.76/-1.81/-3.04	2.52/2.31/2.23
5	HG1-CG1	90.0	-2.00/-1.88/-3.08	2.45/2.31/2.23
6	HG2-CG2	0.0	-1.41/-1.52/-1.18	2.63/2.65/2.68
7	HG2-CG2	90.0	-1.57/-1.58/-1.25	2.57/2.64/2.68
8	SD1-CG1	0.0	-0.73/-0.98/-1.69	3.04/2.57/2.43
9	SD1-CG1	90.0	-0.91/-1.03/-1.74	2.96/2.56/2.42
10	SD1-CG1	180.0	-0.74/-0.98/-1.62	3.04/2.56/2.43
11	SD1-CG1	270.0	-0.91/-1.03/-1.74	2.96/2.56/2.42
12	HD2-CD2	0.0	-1.86/-1.89/-2.53	2.48/2.30/2.26
13	HD2-CD2	90.0	-2.02/-1.94/-2.55	2.44/2.29/2.26

1.199 Small molecule used for thio-citrulline(THIC)

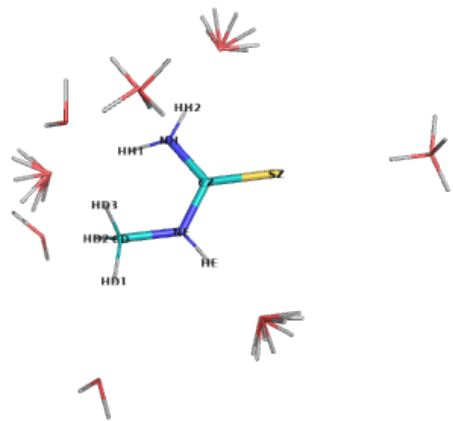


Figure S186: The molecule used for water complex calculations corresponding to methylthiourea, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S614: Statistics of calculated water interaction and dipole moment for methylthiourea.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.10/1.89	0.19/0.39	2.385	5.94/5.75	0.39
Optimal	1.18/2.64	0.19/0.43	3.326	5.94/7.10	1.67

Table S615: The comparison list of optimized atomic charges and their initial guess for methyl thiourea, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HD3	0.090	0.090	0.000
CD	0.033	-0.029	4.704
HD1	0.090	0.090	0.000
HD2	0.090	0.090	0.000
NE	-0.376	-0.354	59.360
HE	0.315	0.263	5.608
CZ	0.039	0.197	77.359
SZ	-0.420	-0.377	90.710
NH	-0.555	-0.650	59.856
HH1	0.347	0.340	2.500
HH2	0.347	0.340	2.500

Table S616: Interaction energies and geometries between probe water and selected methylthiourea site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	SZ-CZ	0.0	-2.03/-4.61/-3.87	2.73/2.31/2.34
2	SZ-CZ	90.0	-2.04/-4.64/-3.88	2.73/2.31/2.34
3	SZ-CZ	180.0	-2.07/-4.67/-3.92	2.73/2.31/2.34
4	SZ-CZ	270.0	-2.10/-4.74/-3.99	2.73/2.30/2.34
5	HH1-NH	0.0	-4.69/-4.67/-4.03	2.30/2.40/2.44
6	HH1-NH	45.0	-4.74/-4.47/-3.87	2.27/2.42/2.45
7	HH1-NH	90.0	-5.48/-4.96/-4.27	2.21/2.36/2.40
8	HH1-NH	135.0	-5.43/-5.17/-4.43	2.23/2.34/2.38
9	HH2-NH	0.0	-5.55/-5.27/-4.82	1.82/1.86/1.88
10	HH2-NH	45.0	-4.84/-4.96/-4.57	1.84/1.87/1.89
11	HH2-NH	90.0	-4.32/-4.74/-4.39	1.87/1.88/1.90
12	HH2-NH	135.0	-5.00/-5.03/-4.63	1.84/1.87/1.89
13	HE-NE	0.0	-5.67/-5.02/-4.13	1.81/1.88/1.93
14	HE-NE	45.0	-5.48/-4.94/-4.07	1.82/1.88/1.93
15	HE-NE	90.0	-4.67/-4.61/-3.81	1.85/1.89/1.94
16	HE-NE	135.0	-4.85/-4.68/-3.86	1.84/1.89/1.94
17	NH-CZ	0.0	-2.33/-1.92/-2.57	2.12/2.12/2.07
18	NH-CZ	90.0	-0.96/-0.84/-1.59	2.25/2.16/2.10
19	NH-CZ	180.0	-3.44/-4.76/-4.73	2.10/2.01/2.00
20	NH-CZ	270.0	-3.82/-4.89/-4.92	2.08/2.03/2.01
21	HD1-CD	0.0	-2.74/-2.92/-2.40	2.48/2.56/2.59
22	HD2-CD	0.0	-2.95/-3.34/-2.86	2.51/2.55/2.57
23	HD3-CD	0.0	-1.88/-2.15/-1.74	2.51/2.58/2.61

1.200 Small molecule used for 3-(2-thienyl)-alanine(TIH)

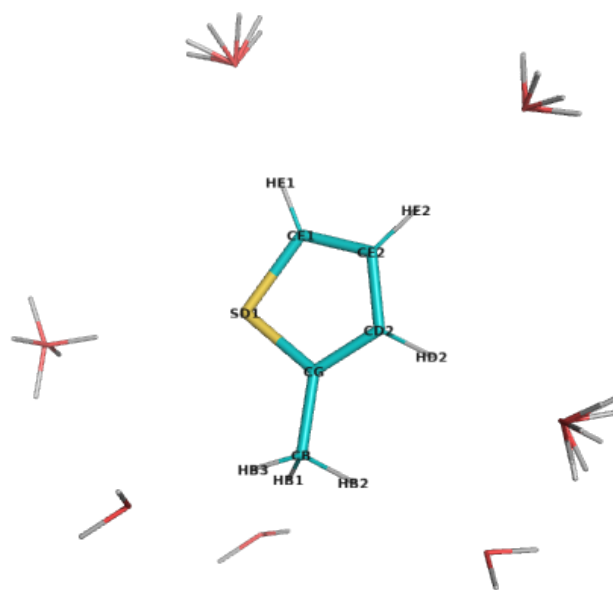


Figure S187: The molecule used for water complex calculations corresponding to 2-methylthiophene, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S617: Statistics of calculated water interaction and dipole moment for 2-methylthiophene.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.64/1.05	0.24/0.49	2.847	0.83/0.55	106.95
Optimal	0.15/0.29	0.22/0.48	1.355	0.83/1.02	0.97

Table S618: The comparison list of optimized atomic charges and their initial guess for 2-methylthiophene, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	2.500
CB	-0.270	-0.229	43.092
HB1	0.090	0.090	2.500
HB2	0.090	0.090	2.500
CG	0.114	0.013	60.735
CD2	-0.172	-0.217	0.483
HD2	0.162	0.137	0.025
SD1	-0.003	-0.013	59.406
CE2	-0.253	-0.226	0.452
HE2	0.207	0.170	0.000
CE1	-0.250	-0.085	2.500
HE1	0.195	0.180	0.000

Table S619: Interaction energies and geometries between probe water and selected 2-methylthiophene site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HE1-CE1	0.0	-1.76/-1.78/-2.81	2.50/2.30/2.25
2	HE1-CE1	45.0	-1.84/-1.81/-2.83	2.48/2.30/2.25
3	HE1-CE1	90.0	-1.92/-1.83/-2.85	2.45/2.30/2.25
4	HE1-CE1	135.0	-1.84/-1.81/-2.83	2.48/2.30/2.25
5	HE2-CE2	0.0	-1.33/-1.41/-1.16	2.62/2.65/2.68
6	HE2-CE2	45.0	-1.42/-1.44/-1.20	2.60/2.64/2.68
7	HE2-CE2	90.0	-1.50/-1.48/-1.23	2.57/2.64/2.68
8	HE2-CE2	135.0	-1.42/-1.44/-1.20	2.60/2.64/2.68
9	HD2-CD2	0.0	-1.36/-1.51/-0.63	2.65/2.66/2.76
10	HD2-CD2	45.0	-1.49/-1.55/-0.67	2.60/2.65/2.76
11	HD2-CD2	90.0	-1.62/-1.59/-0.71	2.56/2.65/2.75
12	HD2-CD2	135.0	-1.49/-1.55/-0.67	2.61/2.65/2.76
13	SD1-CG	0.0	-0.81/-1.09/-0.79	3.02/2.54/2.57
14	SD1-CG	90.0	-0.95/-1.06/-0.97	2.95/2.54/2.54
15	SD1-CG	180.0	-0.72/-0.92/-1.03	3.03/2.56/2.54
16	SD1-CG	270.0	-0.95/-1.06/-0.97	2.95/2.54/2.54
17	HB1-CB	0.0	-1.01/-0.73/-0.60	2.68/2.72/2.73
18	HB2-CB	0.0	-1.43/-1.20/-0.80	2.68/2.71/2.73
19	HB3-CB	0.0	-1.01/-0.73/-0.60	2.68/2.72/2.73

1.201 Small molecule used for 1-hydroperoxy-L-tryptophan(TOX)

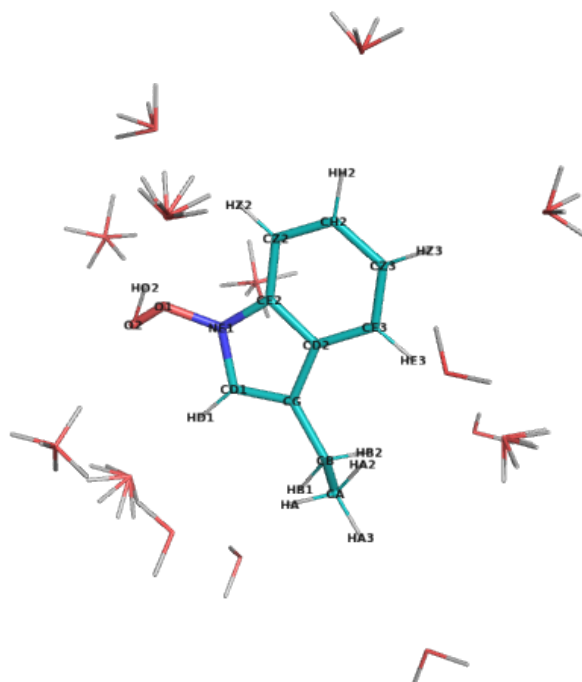


Figure S188: The molecule used for water complex calculations corresponding to 3-ethyl-1H-indole-1-peroxol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S620: Statistics of calculated water interaction and dipole moment for 3-ethyl-1H-indole-1-peroxol.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	3.05/6.66	0.52/2.80	7.625	1.72/4.71	39.54
Optimal	0.25/0.62	0.13/0.23	1.500	1.72/2.04	2.40

Table S621: The comparison list of optimized atomic charges and their initial guess for 3-ethyl-1H-indole-1-peroxol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.277	0.000
HA	0.090	0.090	0.000
CB	-0.133	-0.187	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.072	-0.037	17.090
CD1	-0.227	-0.233	41.493
HD1	0.211	0.230	17.929
CD2	0.092	0.119	22.534
NE1	-0.023	-0.169	286.320
O1	-0.142	-0.486	440.722
O2	-0.332	-0.088	337.960
HO2	0.373	0.500	27.169
CE2	0.337	0.364	40.160
CE3	-0.258	-0.258	0.000
HE3	0.201	0.201	0.000
CZ2	-0.363	-0.285	2.500
HZ2	0.195	0.195	0.000
CZ3	-0.236	-0.236	0.000
HZ3	0.196	0.196	0.000
CH2	-0.195	-0.195	0.000
HH2	0.196	0.196	0.000

Table S622: Interaction energies and geometries between probe water and selected 3-ethyl-1H-indole-1-peroxol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.78/-0.75/-0.48	2.85/2.76/2.80
2	HA2-CA	0.0	-0.85/-0.88/-0.71	3.18/3.07/3.16
3	HA-CA	0.0	-0.93/-0.72/-0.09	2.72/2.71/2.83
4	HB1-CB	0.0	-1.38/-1.09/-0.58	2.70/2.73/2.77
5	HB2-CB	0.0	-1.07/-1.14/-0.73	2.73/2.71/2.75
6	HD1-CD1	0.0	-2.08/-2.09/-1.29	2.38/2.25/2.27
7	HD1-CD1	45.0	-2.03/-2.02/-1.22	2.38/2.26/2.27
8	HD1-CD1	90.0	-2.13/-2.04/-1.09	2.36/2.26/2.28
9	HD1-CD1	135.0	-2.18/-2.11/-1.15	2.36/2.25/2.27
10	NE1-CD1	0.0	-1.65/-1.89/-4.75	2.50/2.30/2.09
11	NE1-CD1	90.0	-1.92/-2.02/-4.06	2.47/2.29/2.13
12	NE1-CD1	180.0	-1.54/-1.79/-4.63	2.50/2.29/2.09
13	NE1-CD1	270.0	-1.63/-1.98/-5.75	2.50/2.27/2.05
14	O1-NE1	0.0	-2.49/-2.82/-7.12	2.07/1.87/1.68
15	O1-NE1	90.0	-2.02/-2.18/-6.95	2.10/1.91/1.68
16	O1-NE1	180.0	-2.56/-2.91/-9.22	2.07/1.88/1.65
17	O1-NE1	270.0	-2.72/-3.27/-9.09	2.05/1.86/1.66
18	O2-O1	0.0	-2.81/-2.62/0.16	2.20/2.04/5.00
19	O2-O1	90.0	-3.32/-3.15/-0.72	2.15/2.01/2.32
20	O2-O1	180.0	-2.89/-3.31/-1.73	2.19/1.99/2.18
21	O2-O1	270.0	-2.94/-3.01/-0.73	2.16/2.00/2.30
22	HO2-O2	0.0	-4.18/-4.78/-10.39	1.87/1.86/1.72
23	HO2-O2	45.0	-5.09/-5.22/-11.08	1.79/1.85/1.71
24	HO2-O2	90.0	-6.88/-6.25/-11.88	1.75/1.83/1.71
25	HO2-O2	135.0	-6.17/-6.06/-11.45	1.80/1.83/1.71
26	HE3-CE3	0.0	-1.74/-1.99/-1.99	2.58/2.61/2.60
27	HE3-CE3	45.0	-1.81/-2.00/-1.97	2.58/2.62/2.61
28	HE3-CE3	90.0	-1.98/-2.04/-1.97	2.54/2.61/2.61
29	HE3-CE3	135.0	-1.92/-2.03/-1.99	2.54/2.61/2.60
30	HZ2-CZ2	0.0	-2.41/-2.15/-2.47	2.45/2.59/2.57
31	HZ2-CZ2	90.0	-1.91/-1.90/-1.88	2.51/2.61/2.61
32	HZ3-CZ3	0.0	-1.24/-1.48/-1.67	2.68/2.64/2.63
33	HZ3-CZ3	90.0	-1.43/-1.59/-1.77	2.62/2.63/2.62
34	HH2-CH2	0.0	-1.42/-1.53/-1.92	2.64/2.64/2.62
35	HH2-CH2	90.0	-1.60/-1.62/-2.00	2.59/2.63/2.61

1.202 Small molecule used for
5-(2-carboxy-2-aminoethyl)-2-hydroxy-1,4-benzoquinone(TPQ)

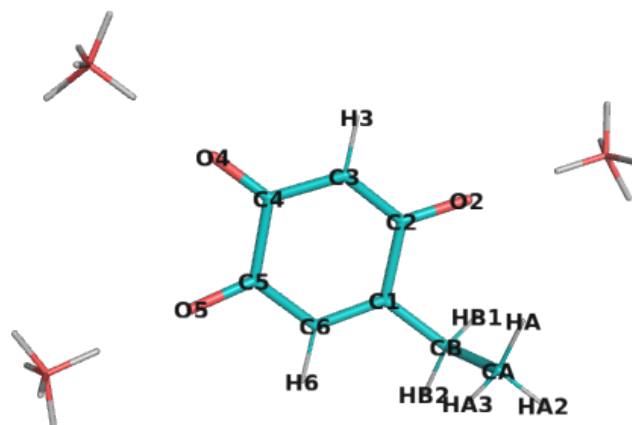


Figure S189: The molecule used for water complex calculations corresponding to 5-ethylcyclohex-5-ene-1,2,4-trione, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S623: Statistics of calculated water interaction and dipole moment for 5-ethylcyclohex-5-ene-1,2,4-trione.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	5.63/9.53	0.17/0.23	14.991	8.18/14.94	16.22
Optimal	0.09/0.23	0.14/0.20	2.736	8.18/7.65	1.87

Table S624: The comparison list of optimized atomic charges and their initial guess for 5-ethylcyclohex-5-ene-1,2,4-trione, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.025
HA2	0.090	0.090	0.025
CA	-0.270	-0.269	2.343
HA	0.090	0.090	0.025
CB	-0.262	-0.236	4.152
HB1	0.090	0.090	0.150
HB2	0.090	0.090	0.150
C1	0.222	0.151	23.696
C2	0.177	0.327	28.959
O2	-0.495	-0.437	12.156
C3	-0.371	-0.250	28.590
H3	0.068	0.230	13.596
C4	0.380	0.121	147.002!
O4	-0.610	-1.009	143.829
C5	0.274	0.350	56.660
O5	-0.394	-0.441	3.633
C6	-0.185	-0.137	31.411
H6	0.016	0.150	2.878

Table S625: Interaction energies and geometries between probe water and selected 5-ethylcyclohex-5-ene-1,2,4-trione site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	O2-C2	0.0	-10.22/-10.23/-7.38	1.79/1.64/1.68
2	O2-C2	90.0	-10.66/-10.65/-7.94	1.78/1.63/1.68
3	O2-C2	180.0	-11.11/-11.14/-8.37	1.78/1.63/1.68
4	O2-C2	270.0	-10.59/-10.61/-7.80	1.78/1.63/1.68
5	O4-C4	0.0	-10.79/-10.78/-19.39	1.80/1.75/1.63
6	O4-C4	90.0	-10.79/-10.85/-19.96	1.80/1.75/1.63
7	O4-C4	180.0	-11.40/-11.32/-20.94	1.79/1.75/1.62
8	O4-C4	270.0	-10.93/-10.99/-20.19	1.80/1.75/1.63
9	O5-C5	0.0	-9.24/-9.42/-12.55	1.87/1.68/1.64
10	O5-C5	90.0	-8.11/-8.19/-9.77	1.89/1.70/1.67
11	O5-C5	180.0	-7.47/-7.24/-7.31	1.90/1.71/1.70
12	O5-C5	270.0	-8.06/-8.09/-9.48	1.90/1.70/1.68

1.203 Small molecule used for
5-(2-carboxy-2-aminoethyl)-2-hydroxy-1,4-benzoquinone(TPQP)

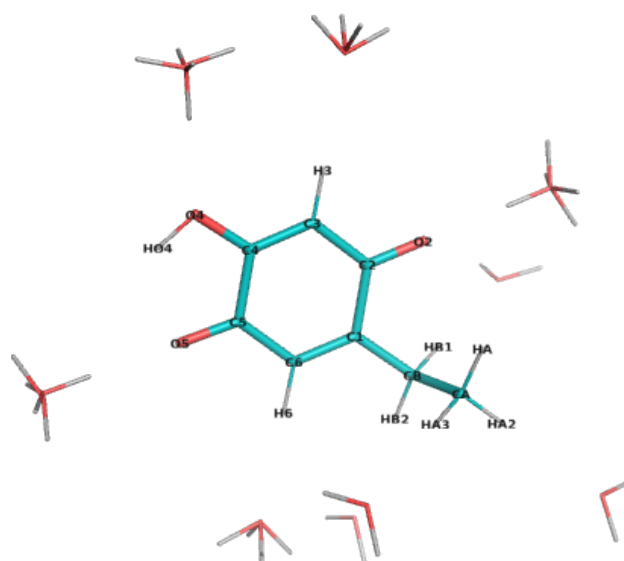


Figure S190: The molecule used for water complex calculations corresponding to 2-ethyl-5-hydroxycyclohexa-2,5-diene-1,4-dione, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S626: Statistics of calculated water interaction and dipole moment for 2-ethyl-5-hydroxycyclohexa-2,5-diene-1,4-dione.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.96/1.85	0.16/0.25	3.314	2.16/1.90	51.22
Optimal	0.10/0.21	0.13/0.21	2.294	2.16/2.66	3.26

Table S627: The comparison list of optimized atomic charges and their initial guess for 2-ethyl-5-hydroxycyclohexa-2,5-diene-1,4-dione, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.025
HA2	0.090	0.090	0.025
CA	-0.270	-0.269	2.343
HA	0.090	0.090	0.025
CB	-0.128	-0.236	4.152
HB1	0.090	0.090	0.150
HB2	0.090	0.090	0.150
C1	0.114	0.151	23.696
C2	0.239	0.322	28.827
O2	-0.335	-0.437	12.156
C3	-0.311	-0.237	23.419
H3	0.231	0.230	4.824
C4	0.123	0.118	69.392
O4	-0.445	-0.434	60.945
HO4	0.357	0.420	9.376
C5	0.376	0.350	53.822
O5	-0.365	-0.441	3.633
C6	-0.178	-0.137	31.411
H6	0.142	0.150	2.878

Table S628: Interaction energies and geometries between probe water and selected 2-ethyl-5-hydroxycyclohexa-2,5-diene-1,4-dione site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-1.35/-1.55/-1.33	2.78/2.70/2.73
2	HA2-CA	0.0	-1.17/-0.96/-0.52	2.74/2.73/2.78
3	HB1-CB	0.0	-0.53/-0.55/0.28	2.68/2.71/2.83
4	HB2-CB	0.0	-2.26/-2.31/-1.80	2.59/2.64/2.68
5	O2-C2	0.0	-4.11/-4.18/-5.96	1.91/1.75/1.69
6	O2-C2	90.0	-4.49/-4.53/-5.93	1.91/1.74/1.69
7	O2-C2	180.0	-4.74/-4.73/-5.83	1.90/1.74/1.70
8	O2-C2	270.0	-4.39/-4.49/-5.91	1.91/1.74/1.69
9	H3-C3	0.0	-1.95/-1.75/-2.49	2.36/2.48/2.45
10	H3-C3	90.0	-1.52/-1.53/-2.24	2.41/2.50/2.47
11	O4-C4	0.0	-3.33/-3.45/-2.65	1.96/1.96/1.98
12	O4-C4	90.0	-3.52/-3.45/-2.60	1.93/1.95/1.98
13	O4-C4	180.0	-2.79/-2.96/-2.00	2.01/1.97/2.01
14	O4-C4	270.0	-3.54/-3.45/-2.59	1.93/1.95/1.98
15	O5-C5	0.0	-2.75/-2.83/-3.41	1.99/1.79/1.74
16	O5-C5	90.0	-3.32/-3.32/-4.36	1.95/1.76/1.71
17	O5-C5	180.0	-3.51/-3.47/-4.82	1.94/1.75/1.70
18	O5-C5	270.0	-3.31/-3.32/-4.37	1.95/1.76/1.71
19	H6-C6	0.0	-2.67/-2.66/-2.77	2.38/2.50/2.48
20	H6-C6	90.0	-2.62/-2.61/-2.63	2.38/2.50/2.49

1.204 Small molecule used for (S)-2-amino-3-(6,7-dihydro-6-imino-7-oxo-1H-indol-3-yl)propanoic acid(TQQ)

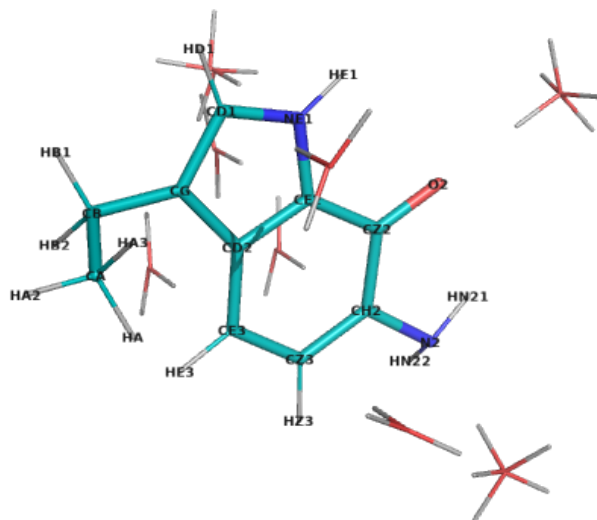


Figure S191: The molecule used for water complex calculations corresponding to 3-ethyl-6-imino-6,7-dihydro-1H-indol-7-one, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S629: Statistics of calculated water interaction and dipole moment for 3-ethyl-6-imino-6,7-dihydro-1H-indol-7-one.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.51/1.03	0.17/0.50	3.474	5.14/5.15	11.95
Optimal	0.29/0.62	0.12/0.25	3.019	5.14/6.67	0.18

Table S630: The comparison list of optimized atomic charges and their initial guess for 3-ethyl-6-imino-6,7-dihydro-1H-indol-7-one, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.276	0.000
HA	0.090	0.090	0.000
CB	-0.057	-0.055	1.450
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.019	-0.034	25.153
CD1	-0.069	-0.067	10.117
HD1	0.129	0.161	0.000
NE1	-0.140	-0.240	13.334
HE1	0.316	0.380	2.500
CD2	-0.096	-0.133	74.256
CE2	-0.295	-0.379	43.482
CE3	-0.238	-0.215	72.008
HE3	0.188	0.150	3.561
CZ2	0.629	0.716	47.404
O2	-0.469	-0.456	17.100
CZ3	-0.096	-0.078	32.341
HZ3	0.155	0.150	3.078
CH2	0.287	0.315	82.825
N2	-0.668	-0.715	72.331
HN21	0.263	0.326	59.000

Table S631: Interaction energies and geometries between probe water and selected 3-ethyl-6-imino-6,7-dihydro-1H-indol-7-one site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.96/-1.06/-0.71	2.82/2.74/2.77
2	HA2-CA	0.0	-1.01/-1.25/-1.01	2.82/2.71/2.73
3	HA-CA	0.0	-0.75/-1.22/-0.69	3.25/3.32/3.75
4	HB1-CB	0.0	-1.70/-2.00/-1.77	2.70/2.66/2.68
5	HB2-CB	0.0	-1.66/-1.89/-1.32	2.67/2.66/2.69
6	HD1-CD1	0.0	-2.96/-2.98/-3.24	2.41/2.29/2.27
7	HD1-CD1	90.0	-3.27/-3.15/-3.42	2.36/2.28/2.26
8	NE1-CD1	0.0	-1.14/-1.76/-2.17	2.64/2.39/2.30
9	HE1-NE1	0.0	-8.02/-7.86/-8.70	1.74/1.81/1.79
10	HE3-CE3	0.0	-2.24/-2.26/-1.43	2.51/2.55/2.62
11	O2-CZ2	0.0	-4.42/-4.22/-3.65	1.88/1.71/1.73
12	O2-CZ2	90.0	-5.10/-5.18/-4.42	1.86/1.70/1.72
13	O2-CZ2	180.0	-5.21/-5.75/-4.68	1.87/1.70/1.72
14	O2-CZ2	270.0	-5.07/-5.16/-4.39	1.86/1.70/1.72
15	HZ3-CZ3	0.0	-1.29/-1.18/-1.16	2.48/2.54/2.54
16	N2-CH2	0.0	-6.53/-6.91/-6.59	1.94/1.92/1.92
17	N2-CH2	180.0	-5.10/-4.77/-4.84	1.99/1.96/1.95

1.205 Small molecule used for 2-hydroxy-tryptophan(TRO)

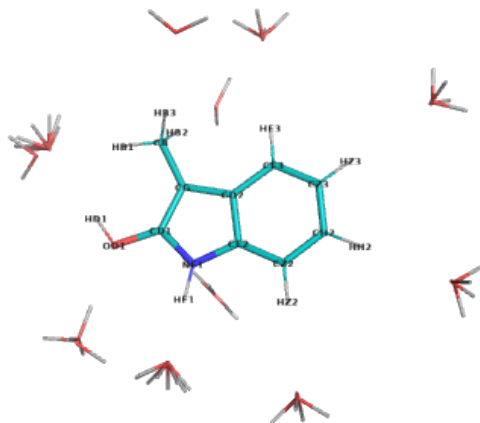


Figure S192: The molecule used for water complex calculations corresponding to 3-methyl-1H-indol-2-ol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S632: Statistics of calculated water interaction and dipole moment for 3-methyl-1H-indol-2-ol.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	1.22/2.23	0.23/0.56	4.298	1.57/1.45	96.87
Optimal	0.31/0.69	0.19/0.49	1.692	1.57/2.04	0.03

Table S633: The comparison list of optimized atomic charges and their initial guess for 3-methyl-1H-indol-2-ol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.277	2.295
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.073	0.036	31.983
CD1	0.156	0.179	76.468
OD1	-0.529	-0.546	70.649
HD1	0.475	0.420	4.985
CD2	0.006	0.062	23.091
NE1	-0.405	-0.574	39.295
HE1	0.346	0.363	2.250
CE2	0.332	0.254	23.966
CE3	-0.291	-0.259	0.000
HE3	0.197	0.201	0.000
CZ2	-0.298	-0.285	0.000
HZ2	0.174	0.195	0.000
CZ3	-0.247	-0.236	0.000
HZ3	0.202	0.196	0.000
CH2	-0.247	-0.195	0.000
HH2	0.202	0.196	0.000

Table S634: Interaction energies and geometries between probe water and selected 3-methyl-1H-indol-2-ol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.77/-0.64/-1.03	2.77/2.73/2.70
2	HB1-CB	0.0	-4.29/-4.15/-3.73	2.52/2.56/2.55
3	HB2-CB	0.0	-0.76/-0.61/-1.06	2.76/2.73/2.69
4	OD1-CD1	0.0	-3.86/-4.12/-4.96	1.91/1.91/1.89
5	OD1-CD1	90.0	-4.15/-4.00/-5.04	1.87/1.90/1.88
6	OD1-CD1	180.0	-2.07/-2.61/-3.99	2.00/1.95/1.91
7	OD1-CD1	270.0	-4.15/-4.00/-5.03	1.87/1.90/1.88
8	HD1-OD1	0.0	-3.76/-3.32/-2.58	2.60/3.01/3.08
9	HD1-OD1	45.0	-3.95/-3.36/-2.65	2.55/3.00/3.07
10	HD1-OD1	90.0	-4.10/-3.41/-2.72	2.50/2.99/3.06
11	HD1-OD1	135.0	-3.96/-3.36/-2.66	2.54/3.00/3.07
12	NE1-CD1	0.0	-1.13/-1.41/-3.11	2.51/2.40/2.18
13	NE1-CD1	180.0	-1.39/-1.96/-3.62	2.40/2.27/2.13
14	HE1-NE1	0.0	-6.07/-6.17/-4.39	1.84/1.85/1.88
15	HE1-NE1	45.0	-6.14/-6.14/-4.37	1.83/1.85/1.88
16	HE1-NE1	90.0	-6.21/-6.11/-4.34	1.82/1.85/1.88
17	HE1-NE1	135.0	-6.14/-6.14/-4.37	1.83/1.85/1.88
18	HE3-CE3	0.0	-0.95/-0.87/-1.70	2.72/2.70/2.63
19	HE3-CE3	90.0	-1.17/-1.00/-1.85	2.65/2.68/2.62
20	HZ2-CZ2	0.0	-1.33/-1.41/-1.56	2.71/2.67/2.64
21	HZ2-CZ2	90.0	-1.73/-1.61/-1.71	2.58/2.65/2.62
22	HZ3-CZ3	0.0	-0.72/-0.84/-1.33	2.78/2.68/2.65
23	HZ3-CZ3	90.0	-0.88/-0.94/-1.44	2.71/2.67/2.64
24	HH2-CH2	0.0	-0.82/-0.96/-1.43	2.75/2.67/2.64
25	HH2-CH2	90.0	-0.99/-1.06/-1.53	2.68/2.66/2.63

1.206 Small molecule used for 2-amino-3-(6,7-dioxo-6,7-dihydro-1H-indol-3-yl)-propionic acid (TRQ)

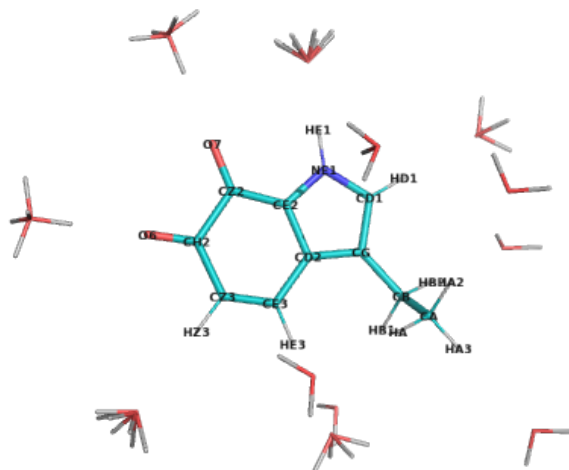


Figure S193: The molecule used for water complex calculations corresponding to 3-ethyl-6,7-dihydro-1H-indole-6,7-dione, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S635: Statistics of calculated water interaction and dipole moment for 3-ethyl-6,7-dihydro-1H-indole-6,7-dione.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.88/2.80	0.27/1.04	3.816	7.14/5.84	3.74
Optimal	0.54/1.30	0.14/0.34	3.983	7.14/8.82	0.68

Table S636: The comparison list of optimized atomic charges and their initial guess for 3-ethyl-6,7-dihydro-1H-indole-6,7-dione, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.276	0.000
HA	0.090	0.090	0.000
CB	-0.036	-0.055	1.450
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.010	-0.034	25.153
CD1	-0.049	-0.067	10.117
HD1	0.104	0.161	0.000
CD2	-0.028	-0.129	74.811
NE1	-0.094	-0.240	13.334
HE1	0.309	0.380	2.500
CE2	-0.272	-0.379	38.858
CE3	-0.189	-0.222	73.213
HE3	0.196	0.150	3.836
CZ2	0.507	0.737	36.138
O7	-0.422	-0.485	17.934
CZ3	-0.186	-0.101	24.820
HZ3	0.182	0.150	2.741
CH2	0.155	0.430	24.389
O6	-0.347	-0.470	6.189

Table S637: Interaction energies and geometries between probe water and selected 3-ethyl-6,7-dihydro-1H-indole-6,7-dione site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-1.17/-1.55/-1.07		2.79/2.69/2.73	
2	HA2-CA	0.0	-1.15/-1.47/-0.82		2.79/2.70/2.77	
3	HA-CA	0.0	-2.32/-2.37/-0.88		2.87/2.83/3.91	
4	HB1-CB	0.0	-2.01/-2.57/-1.42		2.65/2.62/2.69	
5	HB2-CB	0.0	-1.90/-2.44/-1.85		2.67/2.64/2.68	
6	HD1-CD1	0.0	-3.14/-3.06/-3.29		2.40/2.31/2.26	
7	HD1-CD1	90.0	-3.46/-3.23/-3.47		2.35/2.29/2.25	
8	NE1-CD1	0.0	-1.06/-1.85/-2.31		2.67/2.43/2.29	
9	NE1-CD1	90.0	-0.68/-1.99/-3.49		2.67/2.32/2.17	
10	HE1-NE1	0.0	-8.67/-8.23/-8.85		1.73/1.81/1.79	
11	HE1-NE1	45.0	-8.03/-7.88/-8.54		1.74/1.81/1.79	
12	HE1-NE1	90.0	-7.35/-7.52/-8.22		1.75/1.82/1.79	
13	HE1-NE1	135.0	-7.93/-7.85/-8.50		1.74/1.81/1.79	
14	HE3-CE3	0.0	-2.83/-2.86/-1.64		2.45/2.52/2.61	
15	HE3-CE3	90.0	-3.15/-3.07/-1.78		2.42/2.51/2.60	
16	O7-CZ2	0.0	-3.69/-4.03/-4.02		1.93/1.74/1.72	
17	O7-CZ2	90.0	-4.83/-5.54/-5.28		1.91/1.71/1.70	
18	O7-CZ2	180.0	-5.95/-6.88/-6.38		1.88/1.69/1.69	
19	O7-CZ2	270.0	-4.81/-5.52/-5.27		1.91/1.71/1.70	
20	HZ3-CZ3	0.0	-1.75/-1.43/-1.95		2.45/2.53/2.51	
21	HZ3-CZ3	45.0	-1.67/-1.39/-1.88		2.46/2.53/2.51	
22	HZ3-CZ3	90.0	-1.58/-1.34/-1.81		2.47/2.54/2.52	
23	HZ3-CZ3	135.0	-1.66/-1.39/-1.88		2.47/2.53/2.51	
24	O6-CH2	0.0	-5.37/-6.09/-6.23		1.91/1.72/1.69	
25	O6-CH2	90.0	-4.65/-5.43/-5.64		1.94/1.74/1.70	
26	O6-CH2	180.0	-4.30/-4.89/-5.18		1.94/1.74/1.71	
27	O6-CH2	270.0	-4.67/-5.46/-5.66		1.94/1.73/1.70	

Table S639: The comparison list of optimized atomic charges and their initial guess for 3-ethyl-6-(2-phenylhydrazin-1-yl)-1H-indol-7-ol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.277	0.000
HA	0.090	0.090	0.000
CB	-0.180	-0.187	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.016	-0.039	0.000
CD1	-0.172	-0.161	0.000
HD1	0.196	0.220	0.000
CD2	0.061	0.109	2.500
NE1	-0.382	-0.501	2.500
HE1	0.366	0.363	0.000
CE2	0.106	0.240	3.577
CE3	-0.329	-0.258	0.000
HE3	0.205	0.201	0.000
CZ2	0.159	0.010	5.568
O7	-0.569	-0.530	3.603
HO7	0.417	0.420	0.075
CZ3	-0.292	-0.235	0.000
HZ3	0.181	0.196	0.000
CH2	0.373	0.298	6.452
N6	-0.679	-0.792	6.540
HN6	0.399	0.473	0.000
N1	-0.528	-0.716	0.000
HN1	0.324	0.473	0.000
C1	0.180	0.245	0.000
C2	-0.115	-0.116	0.000
HC2	0.115	0.115	0.000
C3	-0.115	-0.115	0.000
HC3	0.115	0.115	0.000
C4	-0.115	-0.115	0.000
HC4	0.115	0.115	0.000
C5	-0.115	-0.115	0.000
HC5	0.115	0.115	0.000
C6	-0.115	-0.116	0.000
HC6	0.115	0.115	0.000

Table S640: Interaction energies and geometries between probe water and selected 3-ethyl-6-(2-phenylhydrazin-1-yl)-1H-indol-7-ol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.57/-0.53/-0.59	2.90/2.79/2.79		
2	HA2-CA	0.0	-0.40/-0.33/-0.48	2.88/2.81/2.78		
3	HA-CA	0.0	-0.41/-0.34/-1.00	3.10/3.07/3.12		
4	HB1-CB	0.0	-0.63/-0.62/-0.98	2.82/2.77/2.76		
5	HB2-CB	0.0	-1.05/-0.87/-0.98	2.79/2.78/2.77		
6	HD1-CD1	0.0	-2.07/-2.69/-2.97	2.50/2.26/2.24		
7	HD1-CD1	90.0	-2.34/-2.80/-3.06	2.44/2.26/2.24		
8	NE1-CD1	0.0	-2.00/-2.91/-4.02	2.34/2.21/2.13		
9	NE1-CD1	90.0	-2.64/-3.66/-3.96	2.29/2.16/2.12		
10	NE1-CD1	180.0	-1.70/-2.83/-3.09	2.34/2.18/2.13		
11	NE1-CD1	270.0	-0.96/-1.77/-2.55	2.49/2.28/2.20		
12	HE1-NE1	0.0	-6.00/-6.25/-5.03	1.80/1.82/1.85		
13	HE1-NE1	45.0	-5.51/-5.92/-4.71	1.81/1.83/1.86		
14	HE1-NE1	90.0	-5.16/-5.67/-4.45	1.82/1.84/1.87		
15	HE1-NE1	135.0	-5.63/-5.98/-4.75	1.81/1.83/1.86		
16	HE3-CE3	0.0	-1.35/-1.51/-2.36	2.63/2.64/2.59		
17	HE3-CE3	90.0	-1.54/-1.51/-2.35	2.59/2.64/2.59		
18	O7-CZ2	0.0	-6.91/-8.45/-8.31	1.76/1.81/1.82		
19	O7-CZ2	90.0	-7.69/-6.70/-6.93	1.75/1.82/1.83		
20	O7-CZ2	180.0	-0.56/-0.43/-1.29	2.29/2.07/2.05		
21	O7-CZ2	270.0	-7.79/-6.71/-6.80	1.75/1.82/1.83		
22	HZ3-CZ3	0.0	-1.78/-1.95/-2.77	2.61/2.61/2.56		
23	HZ3-CZ3	90.0	-1.92/-1.91/-2.67	2.54/2.61/2.56		
24	N6-CH2	90.0	-0.53/-0.73/-1.14	4.28/4.27/4.06		
25	N6-CH2	180.0	-1.17/-1.28/-1.84	4.02/3.95/3.80		
26	N6-CH2	270.0	-0.43/-0.42/-0.78	4.23/4.29/4.07		
27	HN6-N6	0.0	-4.15/-4.52/-4.78	1.97/1.92/1.90		
28	HN6-N6	45.0	-4.54/-4.74/-5.12	1.95/1.91/1.89		
29	HN6-N6	90.0	-4.14/-4.52/-4.87	1.97/1.92/1.89		
30	HN6-N6	135.0	-3.75/-4.29/-4.52	1.99/1.93/1.91		
31	N1-N6	0.0	-5.27/-5.38/-6.85	1.95/2.00/1.95		
32	N1-N6	90.0	-4.30/-4.13/-5.33	1.96/2.03/1.97		
33	N1-N6	180.0	-3.79/-4.24/-5.99	2.00/2.03/1.96		
34	N1-N6	270.0	-5.41/-5.82/-7.87	1.94/1.99/1.93		
35	HN1-N1	0.0	-4.68/-4.42/-6.22	1.98/2.00/1.91		
36	HN1-N1	45.0	-3.06/-3.67/-5.57	2.07/2.03/1.92		
37	HN1-N1	90.0	-3.44/-3.83/-5.99	2.05/2.02/1.91		
38	HN1-N1	135.0	-4.94/-4.50/-6.57	1.98/2.00/1.90		
39	HC2-C2	0.0	-1.58/-1.49/-1.63	2.61/2.66/2.66		
40	HC2-C2	90.0	-2.22/-1.70/-1.97	2.46/2.63/2.63		
41	HC3-C3	0.0	-1.25/-1.05/-1.03	2.65/2.70/2.71		
42	HC3-C3	90.0	-1.43/-1.12/-1.11	2.59/2.69/2.69		
43	HC4-C4	0.0	-1.08/-1.01/-0.95	2.70/2.71/2.71		
44	HC4-C4	90.0	-1.25/-1.07/-1.01	2.63/2.70/2.70		
45	HC5-C5	0.0	-1.25/-0.98/-0.84	2.63/2.70/2.71		
46	HC5-C5	90.0	-1.42/-1.04/-0.89	2.59/2.69/2.70		
47	HC6-C6	0.0	-0.59/-0.02/0.39	2.76/2.96/5.00		
48	HC6-C6	90.0	-1.02/-0.27/0.30	2.71/2.88/5.00		

1.208 Small molecule used for
 (2S,3S,4R)-2-amino-3,4-dihydroxy-3-methylpentanoicacid(TS9)

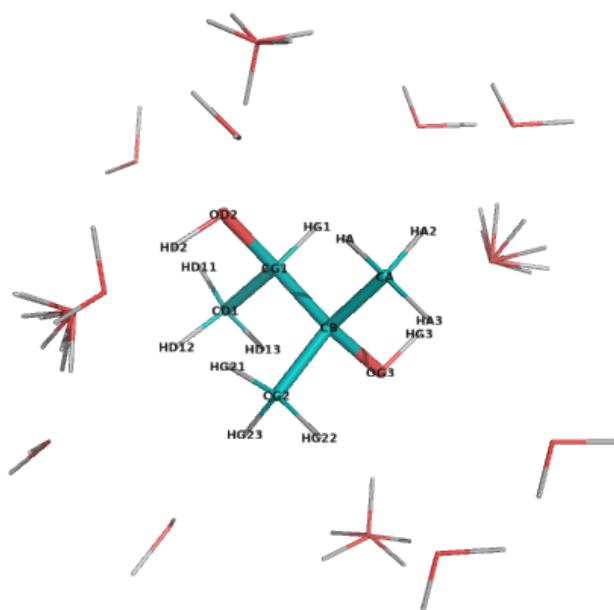


Figure S195: The molecule used for water complex calculations corresponding to 2-methylbutane-2,3-diol, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S641: Statistics of calculated water interaction and dipole moment for 2-methylbutane-2,3-diol.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.52/1.20	0.04/0.12	1.241	0.27/0.34	41.13
Optimal	0.14/0.30	0.04/0.10	1.048	0.27/0.35	0.00

Table S642: The comparison list of optimized atomic charges and their initial guess for 2-methylbutane-2,3-diol, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.273	4.792
HA	0.090	0.090	0.000
CB	0.208	0.222	9.357
OG3	-0.603	-0.640	6.477
HG3	0.377	0.420	0.075
CG2	-0.254	-0.273	4.792
HG21	0.090	0.090	0.000
HG22	0.090	0.090	0.000
HG23	0.090	0.090	0.000
CG1	0.154	0.148	5.143
HG1	0.090	0.090	0.550
OD2	-0.638	-0.655	1.498
HD2	0.396	0.419	0.512
CD1	-0.270	-0.268	3.555
HD11	0.090	0.090	0.060
HD12	0.090	0.090	0.060
HD13	0.090	0.090	0.060

Table S643: Interaction energies and geometries between probe water and selected 2-methylbutane-2,3-diol site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-0.55/-0.47/-0.42	2.84/2.76/2.77
2	HA2-CA	0.0	-1.60/-1.65/-1.77	2.68/2.64/2.64
3	HA-CA	0.0	-0.40/-0.10/-0.05	2.70/2.80/2.81
4	OG3-CB	0.0	-5.76/-5.68/-5.84	1.84/1.88/1.87
5	OG3-CB	90.0	-6.10/-5.97/-6.28	1.82/1.87/1.86
6	OG3-CB	180.0	-5.26/-5.50/-5.93	1.86/1.87/1.86
7	OG3-CB	270.0	-5.68/-5.46/-5.72	1.83/1.88/1.87
8	HG3-OG3	0.0	-6.03/-6.16/-7.23	1.87/1.87/1.83
9	HG3-OG3	45.0	-6.21/-6.16/-7.23	1.85/1.86/1.83
10	HG3-OG3	90.0	-6.32/-6.19/-7.26	1.85/1.86/1.83
11	HG3-OG3	135.0	-6.13/-6.19/-7.25	1.87/1.86/1.83
12	HG21-CG2	0.0	-2.50/-2.33/-2.31	2.58/2.60/2.61
13	HG22-CG2	0.0	-0.55/-0.28/-0.12	2.81/2.79/2.83
14	HG23-CG2	0.0	-0.81/-0.70/-0.56	2.83/2.79/2.82
15	HG1-CG1	0.0	-1.28/-1.42/-1.49	2.77/2.70/2.70
16	OD2-CG1	0.0	-5.67/-5.69/-5.80	1.84/1.86/1.86
17	OD2-CG1	90.0	-5.58/-5.50/-5.65	1.83/1.86/1.86
18	OD2-CG1	180.0	-5.27/-5.46/-5.58	1.85/1.86/1.86
19	OD2-CG1	270.0	-5.89/-5.91/-6.02	1.82/1.86/1.85
20	HD2-OD2	0.0	-5.80/-5.83/-6.33	1.91/1.91/1.88
21	HD2-OD2	45.0	-5.97/-5.83/-6.36	1.91/1.91/1.88
22	HD2-OD2	90.0	-5.80/-5.79/-6.29	1.92/1.91/1.89
23	HD2-OD2	135.0	-5.65/-5.79/-6.27	1.92/1.91/1.89
24	HD11-CD1	0.0	-0.77/-0.70/-0.71	2.77/2.72/2.72
25	HD12-CD1	0.0	-1.57/-1.76/-1.75	2.75/2.68/2.68

1.209 Small molecule used for 6-amino-7-hydroxy-l-tryptophan(TTQ)

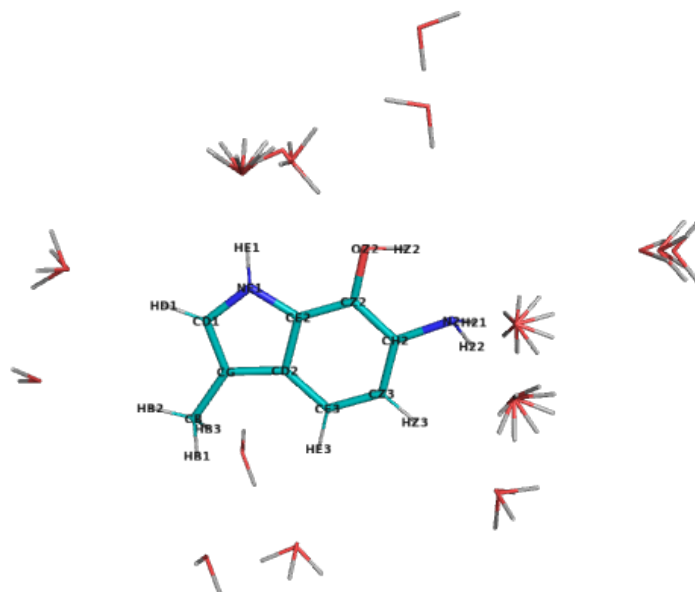


Figure S196: The molecule used for water complex calculations corresponding to 6-amino-3-methyl-1H-indol-7-olate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S644: Statistics of calculated water interaction and dipole moment for 6-amino-3-methyl-1H-indol-7-olate.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.95/1.47	0.37/1.25	3.685	0.79/2.45	29.27
Optimal	0.37/1.13	0.38/1.25	1.700	0.79/1.03	1.28

Table S645: The comparison list of optimized atomic charges and their initial guess for 6-amino-3-methyl-1H-indol-7-olate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.278	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.093	-0.038	0.000
CD1	-0.144	-0.163	0.000
HD1	0.189	0.220	0.000
CD2	0.089	0.107	2.500
NE1	-0.431	-0.502	2.500
HE1	0.361	0.363	0.000
CE2	0.283	0.244	3.630
CE3	-0.292	-0.254	0.000
HE3	0.166	0.201	0.000
CZ2	0.082	0.010	4.614
OZ2	-0.639	-0.532	4.789
HZ2	0.526	0.420	0.075
CZ3	-0.188	-0.229	0.000
HZ3	0.173	0.196	0.000
CH2	0.108	0.049	3.250
N2	-0.869	-0.848	3.474
H21	0.338	0.382	0.000
H22	0.341	0.382	0.000

Table S646: Interaction energies and geometries between probe water and selected 6-amino-3-methyl-1H-indol-7-olate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.44/-0.27/-0.57	2.83/2.80/2.76
2	HB1-CB	0.0	-0.44/-0.26/-0.56	2.83/2.80/2.76
3	HB2-CB	0.0	-0.98/-0.62/-0.83	2.79/2.80/2.77
4	HD1-CD1	0.0	-1.91/-2.41/-2.75	2.52/2.28/2.25
5	HD1-CD1	90.0	-2.19/-2.52/-2.86	2.45/2.27/2.24
6	HE1-NE1	0.0	-5.75/-5.81/-4.69	1.81/1.83/1.85
7	HE1-NE1	45.0	-5.35/-5.50/-4.42	1.82/1.84/1.86
8	HE1-NE1	90.0	-5.00/-5.23/-4.18	1.83/1.85/1.87
9	HE1-NE1	135.0	-5.37/-5.51/-4.43	1.82/1.84/1.86
10	HE3-CE3	0.0	-0.93/-0.98/-1.82	2.72/2.70/2.62
11	HE3-CE3	90.0	-1.11/-1.06/-1.92	2.65/2.69/2.61
12	OZ2-CZ2	0.0	-6.95/-8.09/-7.59	1.77/1.81/1.84
13	OZ2-CZ2	90.0	-7.82/-6.88/-6.65	1.75/1.81/1.84
14	OZ2-CZ2	180.0	-1.64/-1.90/-2.32	2.10/1.96/1.98
15	OZ2-CZ2	270.0	-7.85/-6.92/-6.68	1.75/1.81/1.84
16	HZ2-OZ2	0.0	-0.17/-0.26/-0.31	6.25/5.00/5.00
17	HZ2-OZ2	45.0	-0.20/-0.30/-0.36	5.93/4.94/5.00
18	HZ2-OZ2	90.0	-0.24/-0.34/-0.43	5.48/4.77/4.80
19	HZ2-OZ2	135.0	-0.20/-0.30/-0.37	5.91/4.94/5.00
20	HZ3-CZ3	0.0	-1.21/-1.61/-2.00	2.77/2.66/2.64
21	HZ3-CZ3	90.0	-1.48/-1.73/-2.20	2.67/2.64/2.62
22	N2-CH2	180.0	-0.70/-0.61/-1.21	4.33/4.61/4.20
23	H21-N2	0.0	-4.00/-4.06/-5.37	2.00/1.93/1.87
24	H21-N2	45.0	-3.89/-4.03/-5.36	2.01/1.93/1.87
25	H21-N2	90.0	-3.79/-3.92/-5.22	2.01/1.93/1.88
26	H21-N2	135.0	-3.90/-3.94/-5.22	2.00/1.93/1.88
27	H22-N2	0.0	-4.01/-4.13/-5.36	2.00/1.92/1.87
28	H22-N2	45.0	-3.90/-4.01/-5.21	2.00/1.93/1.88
29	H22-N2	90.0	-3.79/-3.99/-5.21	2.01/1.93/1.88
30	H22-N2	135.0	-3.90/-4.11/-5.36	2.01/1.93/1.87

1.210 Small molecule used for 3-amino-L-tyrosine(TY2)

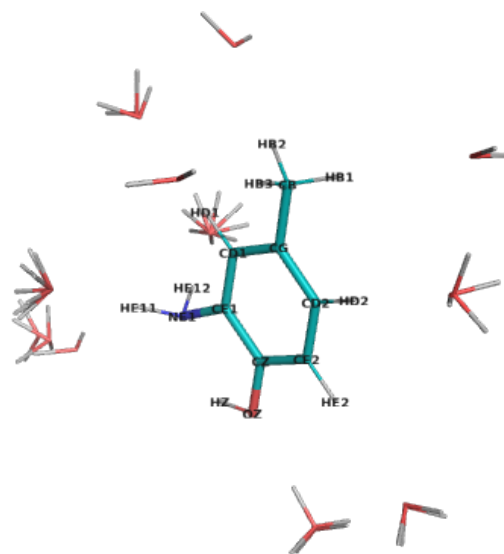


Figure S197: The molecule used for water complex calculations corresponding to 2-amino-4-methylbenzen-1-olate, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S647: Statistics of calculated water interaction and dipole moment for 2-amino-4-methylbenzen-1-olate.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.93/1.58	0.36/1.13	1.916	3.09/3.71	2.36
Optimal	0.25/0.75	0.39/1.22	1.966	3.09/3.65	3.21

Table S648: The comparison list of optimized atomic charges and their initial guess for 2-amino-o-4-methylbenzen-1-olate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.267	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.000	0.004	0.000
CD2	-0.115	-0.114	0.000
HD2	0.115	0.115	0.000
CD1	-0.078	-0.109	0.000
HD1	0.115	0.115	0.000
CE2	-0.115	-0.111	0.000
HE2	0.115	0.115	0.000
CE1	0.110	0.065	3.195
NE1	-0.719	-0.848	3.418
HE11	0.303	0.382	0.000
HE12	0.303	0.382	0.000
CZ	0.085	0.113	2.846
OZ	-0.545	-0.532	3.195
HZ	0.426	0.420	0.000

Table S649: Interaction energies and geometries between probe water and selected 2-amino-4-methylbenzen-1-olate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-0.71/-0.75/-0.66		2.81/2.74/2.75	
2	HB1-CB	0.0	-1.09/-0.99/-0.94		2.72/2.71/2.72	
3	HB2-CB	0.0	-1.22/-1.23/-1.07		2.74/2.72/2.73	
4	HD2-CD2	0.0	-1.22/-1.07/-1.03		2.67/2.70/2.70	
5	HD2-CD2	90.0	-1.40/-1.12/-1.08		2.60/2.69/2.69	
6	HD1-CD1	0.0	-1.68/-1.92/-1.71		2.69/2.66/2.70	
7	HD1-CD1	90.0	-2.02/-2.07/-1.90		2.59/2.64/2.67	
8	HE2-CE2	0.0	-0.78/-0.04/-0.07		2.59/2.76/2.75	
9	HE11-NE1	0.0	-4.35/-4.45/-5.86		1.99/1.93/1.86	
10	HE11-NE1	45.0	-4.26/-4.36/-5.77		1.99/1.93/1.87	
11	HE11-NE1	90.0	-4.20/-4.39/-5.77		1.99/1.93/1.87	
12	HE11-NE1	135.0	-4.28/-4.48/-5.86		1.99/1.93/1.87	
13	HE12-NE1	0.0	-4.35/-4.45/-5.87		1.99/1.93/1.86	
14	HE12-NE1	45.0	-4.28/-4.48/-5.86		2.00/1.93/1.87	
15	HE12-NE1	90.0	-4.19/-4.39/-5.77		2.00/1.93/1.87	
16	HE12-NE1	135.0	-4.26/-4.36/-5.77		1.99/1.93/1.87	
17	OZ-CZ	0.0	-5.25/-5.15/-5.03		1.88/1.90/1.91	
18	OZ-CZ	90.0	-5.61/-5.41/-5.27		1.85/1.89/1.89	
19	OZ-CZ	180.0	-4.70/-5.23/-5.06		1.91/1.89/1.90	
20	OZ-CZ	270.0	-5.61/-5.42/-5.28		1.85/1.89/1.89	
21	HZ-OZ	0.0	-0.24/-0.42/-0.52		6.00/4.77/4.87	
22	HZ-OZ	45.0	-0.28/-0.48/-0.59		5.63/4.63/4.71	
23	HZ-OZ	90.0	-0.34/-0.54/-0.67		4.70/4.50/4.56	
24	HZ-OZ	135.0	-0.28/-0.48/-0.59		5.62/4.63/4.71	

1.211 Small molecule used for 3-amino-6-hydroxy-tyrosine(TYQ)

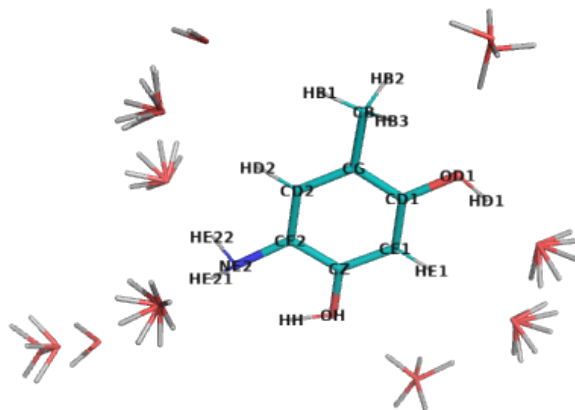


Figure S198: The molecule used for water complex calculations corresponding to 4-amino-6-methylbenzene-1,3-bis(olate), with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S650: Statistics of calculated water interaction and dipole moment for 4-amino-6-methylbenzene-1,3-bis(olate).

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.95/1.82	0.33/1.19	1.894	1.92/2.58	10.40
Optimal	0.33/0.67	0.33/1.19	1.762	1.92/2.35	0.71

Table S651: The comparison list of optimized atomic charges and their initial guess for 4-amin o-6-methylbenzene-1,3-bis(olate), referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.266	0.474
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.030	0.001	0.570
CD1	0.036	0.109	0.474
OD1	-0.521	-0.529	0.474
HD1	0.427	0.420	0.000
CD2	-0.052	-0.107	0.000
HD2	0.115	0.115	0.000
CE1	-0.088	-0.112	0.000
HE1	0.115	0.115	0.000
CE2	0.091	0.065	3.195
NE2	-0.732	-0.848	3.418
HE21	0.302	0.382	0.000
HE22	0.302	0.382	0.000
CZ	0.100	0.115	2.846
OH	-0.560	-0.532	3.195
HH	0.435	0.420	0.000

Table S652: Interaction energies and geometries between probe water and selected 4-amino-6-methyl benzene-1,3-bis(olate) site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HE21-NE2	0.0	-4.28/-4.45/-6.05	2.00/1.93/1.86
2	HE21-NE2	45.0	-4.19/-4.36/-5.96	2.00/1.93/1.86
3	HE21-NE2	90.0	-4.12/-4.38/-5.94	2.00/1.93/1.87
4	HE21-NE2	135.0	-4.21/-4.47/-6.02	2.00/1.93/1.86
5	HE22-NE2	0.0	-4.28/-4.45/-6.05	2.00/1.93/1.86
6	HE22-NE2	45.0	-4.21/-4.47/-6.02	2.00/1.93/1.86
7	HE22-NE2	90.0	-4.12/-4.38/-5.94	2.00/1.93/1.87
8	HE22-NE2	135.0	-4.19/-4.36/-5.96	2.00/1.93/1.86
9	HH-OH	0.0	-0.25/-0.45/-0.63	5.95/4.76/4.76
10	HH-OH	45.0	-0.29/-0.51/-0.71	5.58/4.62/4.61
11	HH-OH	90.0	-0.36/-0.57/-0.79	4.60/4.50/4.49
12	HH-OH	135.0	-0.29/-0.51/-0.71	5.58/4.62/4.61
13	HD1-OD1	0.0	-7.45/-7.61/-7.46	1.80/1.84/1.84
14	HD1-OD1	45.0	-7.91/-7.71/-7.56	1.78/1.83/1.84
15	HD1-OD1	90.0	-8.27/-7.79/-7.64	1.78/1.83/1.83
16	HD1-OD1	135.0	-7.91/-7.71/-7.56	1.78/1.83/1.84
17	OH-CZ	0.0	-5.38/-5.44/-5.18	1.88/1.89/1.90
18	OH-CZ	90.0	-5.61/-5.42/-5.17	1.84/1.88/1.89
19	OH-CZ	180.0	-4.23/-4.69/-4.47	1.91/1.89/1.90
20	OH-CZ	270.0	-5.61/-5.42/-5.17	1.84/1.88/1.89
21	OD1-CD1	0.0	-2.46/-2.84/-2.79	2.36/2.44/2.44
22	OD1-CD1	90.0	-2.28/-2.82/-2.82	2.53/2.43/2.43
23	OD1-CD1	180.0	-2.00/-2.61/-2.68	2.64/2.43/2.43
24	OD1-CD1	270.0	-2.28/-2.82/-2.82	2.53/2.43/2.43
25	HE1-CE1	0.0	-1.65/-1.24/-1.23	2.56/2.67/2.67
26	HE1-CE1	45.0	-1.80/-1.27/-1.26	2.51/2.66/2.66
27	HE1-CE1	90.0	-1.97/-1.31/-1.30	2.46/2.65/2.65
28	HE1-CE1	135.0	-1.80/-1.27/-1.26	2.51/2.66/2.66
29	HD2-CD2	0.0	-1.76/-2.09/-1.73	2.66/2.64/2.69
30	HD2-CD2	45.0	-1.94/-2.16/-1.82	2.60/2.63/2.67
31	HD2-CD2	90.0	-2.13/-2.22/-1.91	2.55/2.63/2.66
32	HD2-CD2	135.0	-1.94/-2.16/-1.82	2.60/2.63/2.67
33	HB1-CB	0.0	-1.12/-1.17/-0.87	2.79/2.73/2.77

1.212 Small molecule used for O-sulfo-L-tyrosine(TYS)

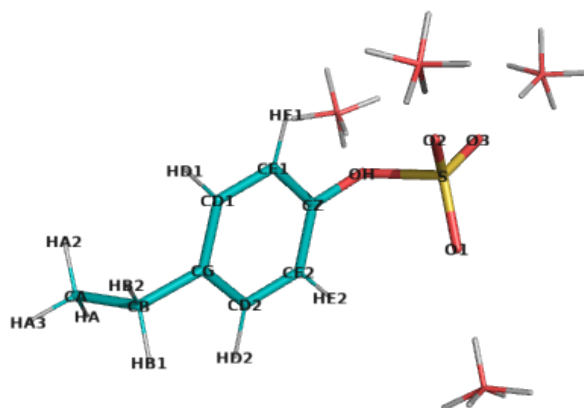


Figure S199: The molecule used for water complex calculations corresponding to (4-ethylphenyl)oxidanesulfonic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S653: Statistics of calculated water interaction and dipole moment for (4-ethylphenyl)oxidanesulfonic acid.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	3.36/6.62	0.21/0.33	5.419	12.20/15.21	4.23
Optimal	0.28/0.63	0.14/0.19	3.826	12.20/10.34	1.25

Table S654: The comparison list of optimized atomic charges and their initial guess for (4-ethylphenyl)oxidanesulfonicacid, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.270	0.000
HA	0.090	0.090	0.000
CB	-0.180	-0.184	0.000
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	-0.000	-0.004	0.000
CD1	-0.224	-0.108	0.000
HD1	0.115	0.115	0.000
CD2	-0.224	-0.108	0.000
HD2	0.115	0.115	0.000
CE1	-0.158	-0.111	2.483
HE1	0.115	0.115	0.000
CE2	-0.158	-0.111	2.483
HE2	0.115	0.115	0.000
CZ	0.309	0.323	39.769
OH	-0.400	-0.721	38.172
S	0.970	1.334	30.940
O1	-0.525	-0.650	2.500
O2	-0.525	-0.650	2.500
O3	-0.525	-0.650	2.500

Table S655: Interaction energies and geometries between probe water and selected (4-ethylphenyl)oxidanesulfonicacid site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	OH-CZ	0.0	-10.02/-10.27/-16.64	1.89/1.72/1.60
2	OH-CZ	90.0	-7.62/-7.78/-13.00	1.96/1.77/1.63
3	OH-CZ	180.0	-6.55/-6.44/-10.70	1.98/1.79/1.65
4	OH-CZ	270.0	-7.62/-7.77/-13.00	1.96/1.77/1.63
5	O1-S	0.0	-9.15/-9.77/-11.26	1.86/1.74/1.70
6	O1-S	90.0	-9.44/-9.37/-11.93	1.85/1.74/1.69
7	O1-S	180.0	-9.56/-9.49/-11.94	1.85/1.74/1.70
8	O1-S	270.0	-9.79/-10.12/-11.64	1.85/1.74/1.70
9	O2-S	0.0	-9.14/-9.77/-11.26	1.86/1.74/1.70
10	O2-S	90.0	-9.78/-10.12/-11.64	1.85/1.74/1.70
11	O2-S	180.0	-9.56/-9.49/-11.94	1.85/1.74/1.70
12	O2-S	270.0	-9.44/-9.37/-11.93	1.85/1.74/1.69
13	O3-S	0.0	-9.57/-9.79/-12.25	1.86/1.74/1.69
14	O3-S	90.0	-9.50/-9.62/-11.80	1.86/1.74/1.70
15	O3-S	180.0	-9.40/-9.45/-11.41	1.86/1.74/1.70
16	O3-S	270.0	-9.50/-9.62/-11.80	1.86/1.74/1.70

1.213 Small molecule used for (4-thiazolyl)-alanine(TZA4)

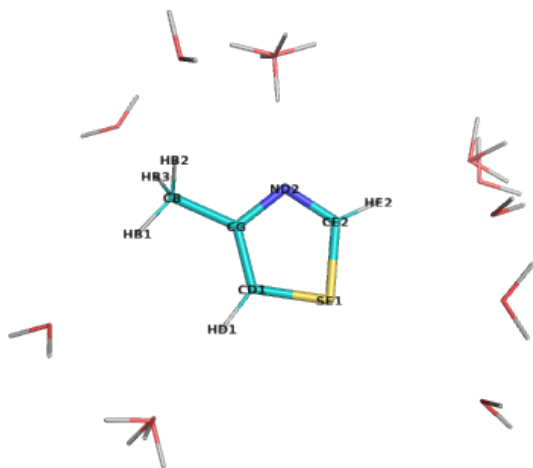


Figure S200: The molecule used for water complex calculations corresponding to 4-methyl-1,3-thiazole, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S656: Statistics of calculated water interaction and dipole moment for 4-methyl-1,3-thiazole.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.46/0.81	0.17/0.40	2.085	1.25/1.54	16.99
Optimal	0.27/0.60	0.15/0.36	1.978	1.25/1.63	0.00

Table S657: The comparison list of optimized atomic charges and their initial guess for 4-methyl-1,3-thiazole, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.450
CB	-0.270	-0.246	6.938
HB1	0.090	0.090	0.450
HB2	0.090	0.090	0.450
CG	0.423	0.338	7.285
CD1	-0.280	-0.314	2.500
HD1	0.163	0.177	0.000
ND2	-0.637	-0.603	5.563
SE1	-0.023	0.012	2.500
CE2	0.227	0.226	0.424
HE2	0.127	0.140	0.000

Table S658: Interaction energies and geometries between probe water and selected 4-methyl-1,3-thiazole site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	ND2-CG	0.0	-5.83/-5.79/-5.48	1.97/1.94/1.95
2	ND2-CG	90.0	-6.21/-6.03/-5.88	1.94/1.94/1.94
3	ND2-CG	180.0	-5.75/-5.82/-5.80	1.97/1.94/1.94
4	ND2-CG	270.0	-6.21/-6.03/-5.88	1.94/1.94/1.94
5	SE1-CD1	0.0	-2.55/-2.82/-3.23	4.44/4.26/4.24
6	SE1-CD1	45.0	-1.59/-2.01/-2.36	3.92/3.73/3.71
7	SE1-CD1	90.0	-0.18/-0.78/-0.99	3.99/3.64/3.59
8	SE1-CD1	135.0	-0.09/-0.46/-0.66	4.02/3.71/3.65
9	HE2-CE2	0.0	-2.52/-2.54/-2.97	2.37/2.25/2.23
10	HE2-CE2	90.0	-2.53/-2.48/-2.92	2.36/2.26/2.24
11	HD1-CD1	0.0	-2.20/-2.36/-2.23	2.46/2.30/2.30
12	HD1-CD1	90.0	-2.44/-2.43/-2.31	2.40/2.29/2.29
13	HB1-CB	0.0	-1.41/-1.51/-1.33	2.70/2.67/2.69
14	HB2-CB	0.0	-0.63/-0.32/-0.22	2.74/2.75/2.76
15	HB3-CB	0.0	-0.76/-0.41/-0.30	2.69/2.72/2.74

1.214 Small molecule used for S-cyano-L-cysteine(XCN)

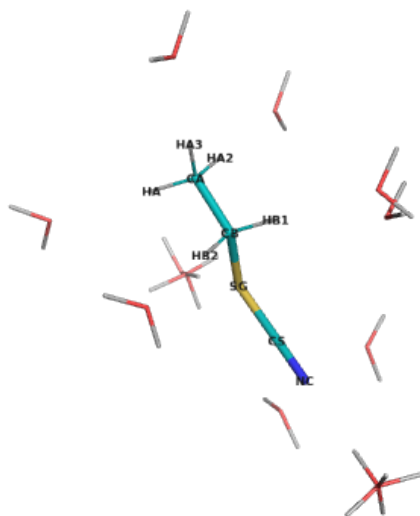


Figure S201: The molecule used for water complex calculations corresponding to (ethylsulfanyl)carbonitrile, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S659: Statistics of calculated water interaction and dipole moment for (ethylsulfanyl)carbonitrile.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.92/1.33	0.40/0.77	5.192	4.60/2.37	9.16
Optimal	0.34/0.64	0.27/0.58	3.019	4.60/5.71	0.52

Table S660: The comparison list of optimized atomic charges and their initial guess for (ethylsulfanyl)carbonitrile, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA3	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.270	-0.271	15.147
HA	0.090	0.090	0.000
CB	0.095	-0.065	4.723
HB1	0.090	0.090	2.350
HB2	0.090	0.090	2.350
SG	-0.002	-0.237	305.871
CS	0.123	0.583	305.774
NC	-0.396	-0.460	40.429

Table S661: Interaction energies and geometries between probe water and selected (ethylsulfanyl)carbonitrile site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HA3-CA	0.0	-2.00/-2.08/-1.15	2.61/2.64/2.71
2	HA2-CA	0.0	-1.93/-2.00/-0.84	2.58/2.63/2.73
3	HA-CA	0.0	-1.93/-2.00/-0.84	2.58/2.63/2.73
4	HB1-CB	0.0	-2.67/-2.87/-2.04	2.40/2.54/2.62
5	HB2-CB	0.0	-2.67/-2.87/-2.04	2.40/2.54/2.62
6	SG-CB	0.0	-0.44/-0.88/-1.48	3.18/2.60/2.43
7	SG-CB	90.0	-0.18/-0.20/-1.51	3.18/2.71/2.42
8	SG-CB	270.0	-0.18/-0.20/-1.51	3.18/2.71/2.42
9	NC-CS	0.0	-4.62/-5.25/-3.98	2.05/1.94/1.96
10	NC-CS	90.0	-4.51/-5.01/-3.86	2.05/1.94/1.96
11	NC-CS	180.0	-4.32/-4.74/-3.72	2.06/1.94/1.97
12	NC-CS	270.0	-4.51/-5.01/-3.86	2.05/1.94/1.96

1.215 Small molecule A of [(4Z)-2-[(1Z)-ethanimidoyl]-4-(4-hydroxybenzylidene)-5-oxo-4,5-dihydro-1h-imidazol-1-yl]acetic acid(XYG)

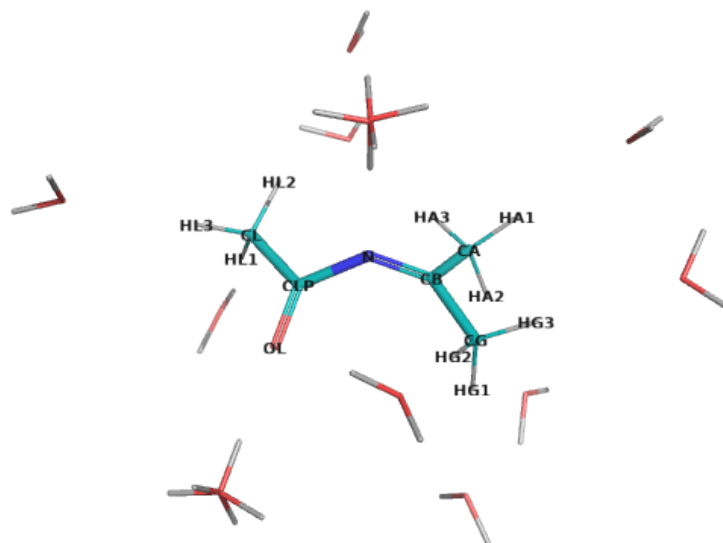


Figure S202: The molecule used for water complex calculations corresponding to N-(propan-2-ylidene)acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S662: Statistics of calculated water interaction and dipole moment for N-(propan-2-ylidene)acetamide.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	3.41/7.36	0.12/0.26	9.096	4.63/6.88	17.09
Optimal	0.43/0.73	0.08/0.13	2.495	4.63/5.33	4.69

Table S663: The comparison list of optimized atomic charges and their initial guess for N-(propan-2-ylidene)acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.270	0.000
HL1	0.090	0.090	0.000
HL2	0.090	0.090	0.000
HL3	0.090	0.090	0.000
CLP	0.510	0.510	0.000
OL	-0.510	-0.510	0.000
N	-0.410	-0.844	113.808
CB	0.166	-0.261	53.301
CG	-0.148	-0.040	36.206
HG1	0.090	0.090	0.250
HG2	0.090	0.090	0.250
HG3	0.090	0.090	0.250
CA	-0.148	-0.040	36.206
HA1	0.090	0.090	0.250
HA2	0.090	0.090	0.250
HA3	0.090	0.090	0.250

Table S664: Interaction energies and geometries between probe water and selected N-(propan-2-ylidene)acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HG1-CG	0.0	-1.84/-1.60/-2.23	2.51/2.61/2.55
2	HG2-CG	0.0	-0.66/-0.55/-0.14	2.49/2.61/2.57
3	HG3-CG	0.0	-1.81/-2.15/-2.97	2.66/2.62/2.55
4	HA1-CA	0.0	-2.42/-2.18/-2.80	2.49/2.60/2.54
5	HA2-CA	0.0	-2.47/-2.48/-3.52	2.53/2.59/2.53
6	HA3-CA	0.0	-1.75/-2.07/-1.91	2.71/2.66/2.68
7	HL1-CL	0.0	-1.27/-0.69/-1.35	2.61/2.71/2.61
8	HL2-CL	0.0	-0.80/-0.95/-0.30	2.79/2.73/2.74
9	HL3-CL	0.0	-0.74/-0.16/-0.82	2.63/2.73/2.61
10	OL-CLP	0.0	-6.39/-7.08/-6.92	1.84/1.76/1.77
11	OL-CLP	90.0	-5.91/-6.59/-6.51	1.85/1.76/1.77
12	OL-CLP	180.0	-6.06/-6.64/-6.97	1.84/1.76/1.76
13	OL-CLP	270.0	-6.51/-7.24/-7.59	1.84/1.75/1.76
14	N-CLP	0.0	-2.98/-2.93/-10.35	2.10/2.06/1.84
15	N-CLP	90.0	-3.47/-3.01/-9.79	2.05/2.06/1.85
16	N-CLP	180.0	-4.10/-4.16/-10.84	2.06/2.04/1.85
17	N-CLP	270.0	-4.41/-4.22/-11.64	2.02/2.03/1.83

1.216 Small molecule B of [(4Z)-2-[(1Z)-ethanimidoyl]-4-(4-hydroxybenzylidene)-5-oxo-4,5-dihydro-1h-imidazol-1-yl]aceticacid(XYG)

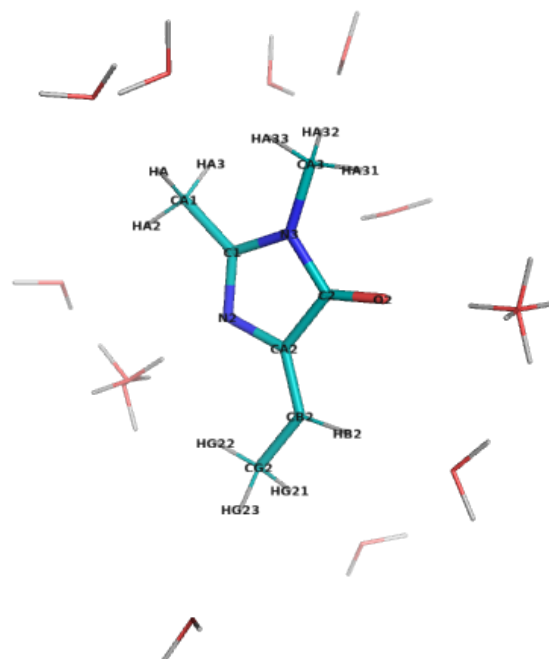


Figure S203: The molecule used for water complex calculations corresponding to (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S665: Statistics of calculated water interaction and dipole moment for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one.

	RMS/Max Deviation from QM		Electrostatic potential RMS (kcal/mol/Å)	Dipole moment QM/MM (Debye)	Dipole angle difference (°)
	Energy (kcal/mol)	Distance (Å)			
Initial	0.92/1.64	0.10/0.25	6.526	3.17/0.45	27.81
Optimal	0.49/1.31	0.09/0.22	3.053	3.17/3.55	14.34

Table S666: The comparison list of optimized atomic charges and their initial guess for (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CA1	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
HA2	0.090	0.090	0.000
HA3	0.090	0.090	0.000
C1	0.233	0.074	23.781
N2	-0.679	-0.703	41.871
N3	-0.080	-0.079	15.706
C2	0.407	0.509	24.002
O2	-0.489	-0.482	6.710
CA2	0.288	0.516	47.153
CB2	-0.105	-0.135	25.469
HB2	0.150	0.150	3.270
CG2	-0.270	-0.274	15.277
HG21	0.090	0.090	1.175
HG22	0.090	0.090	1.175
HG23	0.090	0.090	1.175
CA3	-0.195	-0.271	3.821
HA31	0.090	0.090	0.000
HA32	0.090	0.090	0.000
HA33	0.090	0.090	0.000

Table S667: Interaction energies and geometries between probe water and selected (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HA-CA1	0.0	-2.17/-2.61/-1.51		2.59/2.58/2.65	
2	HA2-CA1	0.0	-0.97/-0.86/0.05		2.58/2.64/2.77	
3	HA3-CA1	0.0	-2.55/-2.73/-1.57		2.52/2.57/2.64	
4	N2-C1	0.0	-4.99/-6.30/-5.60		2.09/2.01/2.02	
5	N2-C1	90.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
6	N2-C1	180.0	-5.35/-5.42/-6.38		1.95/2.01/1.99	
7	N2-C1	270.0	-7.07/-6.37/-6.45		1.90/1.99/1.99	
8	N3-C1	0.0	-0.26/-0.82/-0.78		2.74/2.52/2.49	
9	O2-C2	0.0	-5.51/-5.57/-5.00		1.85/1.78/1.80	
10	O2-C2	90.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
11	O2-C2	180.0	-5.92/-5.61/-4.27		1.84/1.78/1.81	
12	O2-C2	270.0	-5.87/-5.71/-4.73		1.84/1.78/1.80	
13	HB2-CB2	0.0	-1.40/-1.60/-2.82		2.32/2.47/2.44	
14	HG21-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
15	HG23-CG2	0.0	-1.01/-0.46/-0.86		2.72/2.77/2.74	
16	HA32-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	
17	HA33-CA3	0.0	-2.16/-2.10/-1.23		2.59/2.63/2.70	

1.217 Small molecule C of [(4Z)-2-[(1Z)-ethanimidoyl]-4-(4-hydroxybenzylidene)-5-oxo-4,5-dihydro-1h-imidazol-1-yl]aceticacid(XYG)

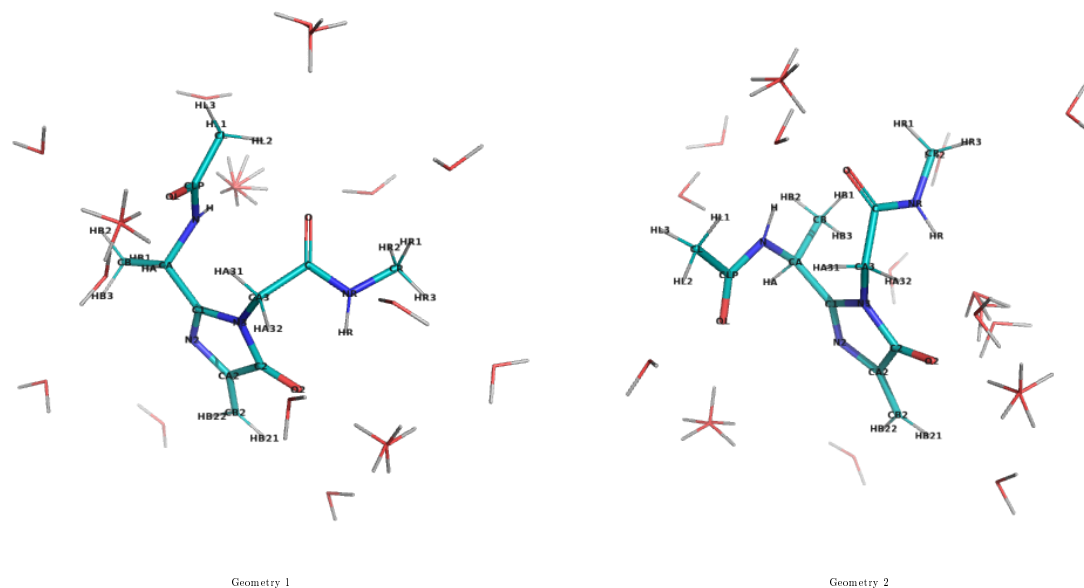


Table S668: The molecule used for water complex calculations corresponding to N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S669: Statistics of calculated water interaction and dipole moment for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide.

		RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
		Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Geometry 1	Initial	0.86 / 2.05	0.07 / 0.17	6.601	1.19 / 4.07	1.19
Geometry 2	Initial	1.02 / 2.07	0.09 / 0.23	6.126	6.37 / 4.43	6.37
Sum of geometries	Initial	0.95 / 2.07	0.08 / 0.23	12.727	-	-
Geometry 1	Optimal	0.36 / 0.81	0.07 / 0.16	2.460	1.19 / 1.37	1.19
Geometry 2	Optimal	0.51 / 0.91	0.08 / 0.19	2.701	6.37 / 7.25	6.37
Sum of geometries	Optimal	0.45 / 0.91	0.08 / 0.19	5.161	-	-

Table S670: The comparison list of optimized atomic charges and their initial guess for N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HA1	0.090	0.090	0.000
HA2	0.090	0.090	0.000
CA	-0.070	-0.115	13.925
HA	0.090	0.090	0.000
C1	0.233	0.164	24.002
N2	-0.679	-0.703	41.104
N3	-0.031	-0.499	22.994
C2	0.407	0.613	23.378
O2	-0.489	-0.482	6.517
CA2	0.466	0.512	42.773
CB2	-0.593	-0.444	13.655
HB21	0.230	0.230	0.950
HB22	0.230	0.230	0.950
CA3	-0.154	0.043	13.461
HA31	0.090	0.090	0.177
HA32	0.090	0.090	0.177
C	0.510	0.499	10.097
O	-0.510	-0.517	3.479
NR	-0.470	-0.442	6.773
HR	0.310	0.299	0.000
CR	-0.110	-0.108	0.239
HR1	0.090	0.090	0.000
HR2	0.090	0.090	0.000
HR3	0.090	0.090	0.000

Table S671: Interaction energies and geometries between probe water and selected N-methyl-2-(2-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
Geometry 1				
1	O-C	0.0	-5.45/-5.47/-6.22	1.84/1.77/1.76
2	O-C	90.0	-6.01/-6.48/-6.53	1.83/1.75/1.76
3	O-C	180.0	-5.96/-6.64/-6.64	1.83/1.75/1.75
4	O-C	270.0	-5.67/-5.94/-6.62	1.84/1.76/1.75
5	NR-C	0.0	-1.32/-1.50/-1.08	2.24/2.20/2.22
6	HR2-CR	0.0	-1.10/-1.26/-1.09	2.71/2.66/2.67
7	HR3-CR	0.0	-1.39/-1.22/-1.32	2.66/2.67/2.67
8	N2-C1	0.0	-5.74/-6.45/-6.04	1.95/1.92/1.92
9	N2-C1	90.0	-6.51/-6.37/-7.24	1.90/1.92/1.90
10	N2-C1	180.0	-5.60/-5.66/-7.65	1.96/1.93/1.90
11	N2-C1	270.0	-6.64/-6.59/-7.43	1.90/1.91/1.89
12	O2-C2	0.0	-3.88/-3.93/-3.54	1.88/1.80/1.81
13	O2-C2	90.0	-4.94/-5.15/-4.46	1.84/1.77/1.79
14	O2-C2	180.0	-4.95/-5.20/-4.05	1.84/1.77/1.79
15	O2-C2	270.0	-3.93/-4.12/-3.39	1.87/1.79/1.81
16	HB21-CB2	0.0	-1.84/-1.64/-3.47	2.32/2.48/2.42
17	HB22-CB2	0.0	-1.82/-1.01/-2.42	2.42/2.54/2.46
18	HA31-CA3	0.0	-2.08/-2.47/-1.68	2.70/2.69/2.70
19	HA-CA	0.0	-2.47/-2.76/-1.19	2.49/2.56/2.66
Geometry 2				
20	O-C	0.0	-6.06/-6.90/-7.24	1.86/1.76/1.75
21	O-C	90.0	-5.25/-6.15/-7.32	1.87/1.77/1.75
22	O-C	180.0	-4.71/-5.63/-6.52	1.88/1.77/1.76
23	O-C	270.0	-5.56/-6.46/-6.85	1.86/1.76/1.76
24	HR-NR	0.0	-7.09/-7.67/-7.53	1.93/1.90/1.90
25	HR-NR	45.0	-7.71/-7.90/-7.71	1.91/1.89/1.89
26	HR-NR	90.0	-7.79/-7.84/-7.79	1.90/1.89/1.89
27	HR-NR	135.0	-7.18/-7.62/-7.61	1.92/1.90/1.89
28	HR1-CR	0.0	-0.71/-0.04/0.30	2.50/2.69/2.67
29	HR2-CR	0.0	-1.54/-1.44/-1.38	2.68/2.66/2.66
30	HR3-CR	0.0	-1.84/-1.82/-1.70	2.68/2.67/2.66
31	N2-C1	0.0	-6.46/-6.98/-6.58	1.93/1.91/1.91
32	N2-C1	90.0	-6.88/-6.47/-7.35	1.89/1.91/1.89
33	N2-C1	180.0	-5.73/-5.60/-7.60	1.95/1.93/1.90
34	N2-C1	270.0	-7.31/-7.09/-7.94	1.88/1.91/1.89
35	N3-C1	0.0	-0.22/0.03/-2.15	2.60/2.67/2.17
36	O2-C2	0.0	-4.96/-5.34/-4.95	1.88/1.79/1.80
37	O2-C2	90.0	-5.32/-5.37/-4.66	1.87/1.78/1.80
38	O2-C2	180.0	-5.74/-5.89/-4.71	1.87/1.78/1.81
39	O2-C2	270.0	-5.94/-6.25/-5.51	1.85/1.77/1.79
40	HB21-CB2	0.0	-1.43/-1.20/-3.03	2.33/2.48/2.41
41	HB22-CB2	0.0	-1.29/-0.66/-2.05	2.47/2.56/2.47
42	HA31-CA3	0.0	-3.71/-4.08/-3.49	2.50/2.57/2.57
43	HA-CA	0.0	-2.67/-3.45/-1.93	2.59/2.58/2.69

1.218 Small molecule D of [(4Z)-2-[(1Z)-ethanimidoyl]-4-(4-hydroxybenzylidene)-5-oxo-4,5-dihydro-1h-imidazol-1-yl]acetic acid(XYG)

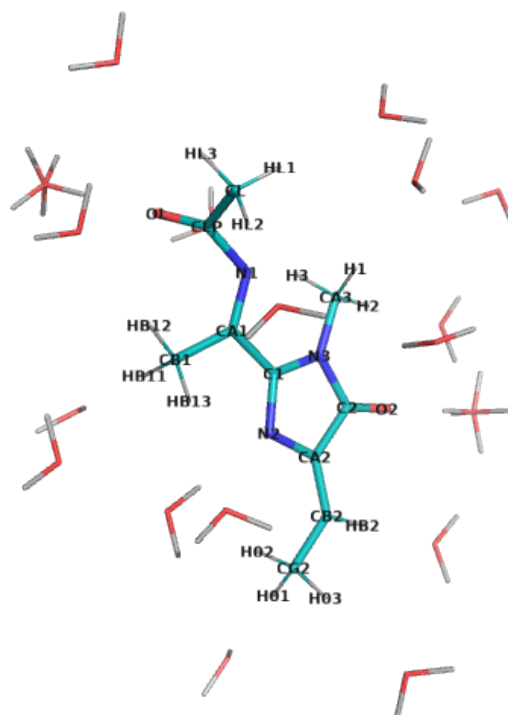


Figure S204: The molecule used for water complex calculations corresponding to N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S672: Statistics of calculated water interaction and dipole moment for N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.75/1.32	0.29/1.19	7.323	3.33/3.51	2.28
Optimal	0.66/1.40	0.23/0.78	2.685	3.33/3.51	4.68

Table S673: The comparison list of optimized atomic charges and their initial guess for N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
CL	-0.270	-0.268	11.341
HL1	0.090	0.090	0.800
HL2	0.090	0.090	0.800
HL3	0.090	0.090	0.800
CLP	0.510	1.166	104.329
OL	-0.510	-0.523	7.580
N1	-0.410	-0.867	109.915
CA1	0.442	-0.250	80.747
CB1	-0.148	-0.039	37.119
HB11	0.090	0.090	1.152
HB12	0.090	0.090	1.152
HB13	0.090	0.090	1.152
C1	0.208	0.430	75.868
N2	-0.541	-0.578	44.740
N3	-0.080	-0.049	29.029
C2	0.407	0.514	21.806
O2	-0.489	-0.482	6.710
CA2	0.221	0.396	48.462
CB2	-0.105	-0.135	25.469
HB2	0.150	0.150	3.270
CG2	-0.270	-0.274	15.277
H01	0.090	0.090	1.175
H02	0.090	0.090	1.175
H03	0.090	0.090	1.175
CA3	-0.195	-0.271	3.821
H1	0.090	0.090	0.000
H2	0.090	0.090	0.000
H3	0.090	0.090	0.000

Table S674: Interaction energies and geometries between probe water and selected N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HL1-CL	0.0	-2.10/-1.55/-1.57		2.54/2.67/2.61	
2	HL2-CL	0.0	-2.25/-2.36/-1.62		2.54/2.64/2.61	
3	HL3-CL	0.0	-1.15/-0.60/-2.15		2.59/2.70/2.58	
4	OL-CLP	0.0	-4.98/-6.25/-4.00		1.89/1.76/1.82	
5	OL-CLP	90.0	-5.11/-6.50/-4.99		1.89/1.76/1.80	
6	OL-CLP	180.0	-4.85/-5.78/-5.34		1.89/1.77/1.79	
7	OL-CLP	270.0	-4.63/-5.54/-4.21		1.90/1.77/1.82	
8	N1-CLP	0.0	-0.23/-0.37/-1.31		5.78/5.00/4.59	
9	HB11-CB1	0.0	-1.38/-2.00/-0.49		2.55/2.57/2.69	
10	HB12-CB1	0.0	-0.72/-1.46/-1.85		2.81/2.73/2.91	
11	HB13-CB1	0.0	-1.01/-1.73/-0.25		2.74/2.62/2.82	
12	N2-C1	0.0	-2.51/-3.29/-3.20		2.28/2.38/2.41	
13	N3-C1	0.0	-0.77/-1.40/-1.19		2.73/2.46/2.76	
14	O2-C2	0.0	-5.45/-5.66/-5.15		1.86/1.78/1.80	
15	O2-C2	90.0	-5.58/-5.60/-4.69		1.85/1.78/1.80	
16	O2-C2	180.0	-5.46/-5.40/-4.13		1.85/1.78/1.81	
17	O2-C2	270.0	-5.62/-5.67/-4.75		1.85/1.78/1.80	
18	HB2-CB2	0.0	-2.03/-1.80/-2.78		2.28/2.47/2.44	
19	HB2-CB2	0.0	-2.03/-1.80/-2.78		2.28/2.47/2.44	
20	H01-CG2	0.0	-1.49/-0.84/-1.05		2.64/2.74/2.72	
21	H02-CG2	0.0	-0.52/-0.97/-0.31		5.47/5.00/5.00	
22	H03-CG2	0.0	-1.46/-0.82/-1.02		2.65/2.74/2.72	

1.219 Small molecule used for cysteine-s-acetamide(YCM)

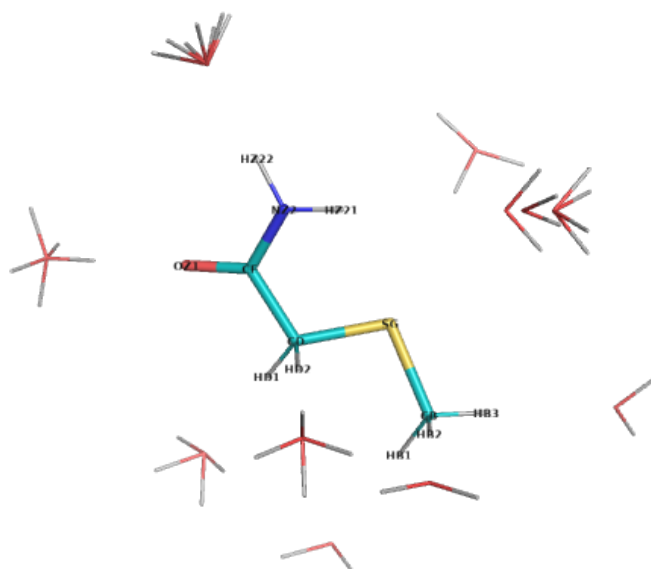


Figure S205: The molecule used for water complex calculations corresponding to 2-(methylsulfanyl)acetamide, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S675: Statistics of calculated water interaction and dipole moment for 2-(methylsulfanyl)acetamide.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	1.30/2.74	0.42/1.15	3.113	3.99/4.28	12.98
Optimal	0.87/1.62	0.41/1.03	2.270	3.99/4.59	3.28

Table S676: The comparison list of optimized atomic charges and their initial guess for 2-(methylsulfanyl)acetamide, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.067	-0.220	2.500
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
SG	-0.229	-0.045	10.789
CD	-0.163	-0.182	10.789
HD2	0.090	0.090	0.000
HD1	0.090	0.090	0.000
CE	0.525	0.542	4.071
OZ1	-0.510	-0.542	1.805
NZ2	-0.624	-0.623	2.500
HZ21	0.309	0.310	0.000
HZ22	0.309	0.310	0.000

Table S677: Interaction energies and geometries between probe water and selected 2-(methylsulfanyl)acetamide site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)	Distance (Å)
			QM/Optimal/Initial	QM/Optimal/Initial
1	HB3-CB	0.0	-1.90/-1.64/-1.15	2.53/2.63/2.70
2	HB1-CB	0.0	-1.95/-2.02/-1.44	2.57/2.60/2.66
3	HB2-CB	0.0	-2.00/-2.22/-1.65	2.61/2.61/2.67
4	HZ21-NZ2	0.0	-0.21/-1.76/-2.95	2.85/2.54/2.50
5	HZ21-NZ2	45.0	-0.29/-1.91/-2.99	3.15/2.56/2.50
6	HZ21-NZ2	90.0	-0.26/-1.64/-2.86	3.67/2.65/2.53
7	HZ21-NZ2	135.0	-0.11/-1.48/-2.81	3.67/2.64/2.53
8	HZ22-NZ2	0.0	-5.22/-4.54/-4.80	1.86/1.89/1.89
9	HZ22-NZ2	45.0	-5.02/-4.41/-4.65	1.87/1.90/1.89
10	HZ22-NZ2	90.0	-4.78/-4.25/-4.47	1.88/1.90/1.90
11	HZ22-NZ2	135.0	-4.97/-4.37/-4.61	1.87/1.90/1.89
12	OZ1-CE	0.0	-6.00/-6.39/-6.84	1.85/1.77/1.75
13	OZ1-CE	90.0	-5.99/-6.36/-6.83	1.85/1.77/1.75
14	OZ1-CE	180.0	-5.92/-6.30/-6.67	1.85/1.77/1.75
15	OZ1-CE	270.0	-6.05/-6.47/-6.80	1.85/1.77/1.75
16	SG-CB	0.0	-0.79/-1.89/-0.38	2.97/2.36/2.56
17	SG-CB	180.0	-0.90/-1.96/-0.73	2.94/2.35/2.50
18	HD1-CD	0.0	-1.26/-0.42/-0.44	2.48/2.72/2.70
19	HD1-CD	90.0	-1.27/-0.43/-0.47	2.48/2.71/2.70
20	HD2-CD	0.0	-2.25/-1.62/-1.61	2.51/2.68/2.66
21	HD2-CD	90.0	-2.40/-1.61/-1.58	2.47/2.67/2.66

1.220 Small molecule used for 3-fluorotyrosine(YOF)

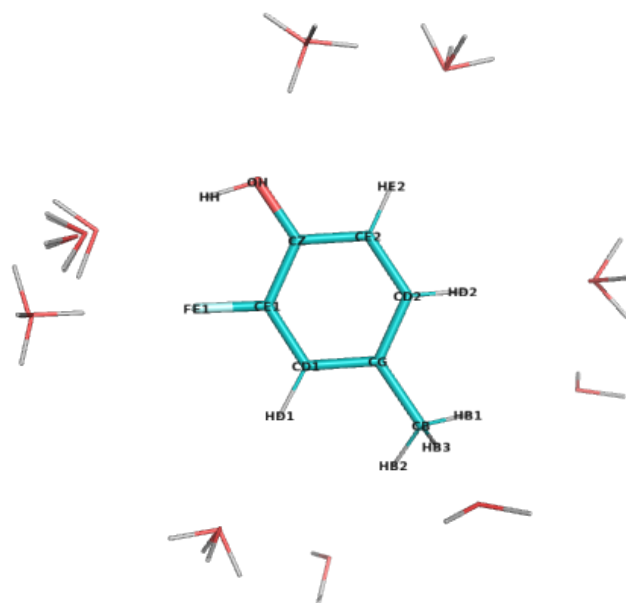


Figure S206: The molecule used for water complex calculations corresponding to 2-fluoro-4-methylbenzoic acid, with possible interacting water positions. NOTE, only one water molecule was included in each calculation.

Table S678: Statistics of calculated water interaction and dipole moment for 2-fluoro-4-methylbenzoic acid.

	RMS/Max Deviation from QM		Electrostatic potential	Dipole moment	Dipole angle
	Energy (kcal/mol)	Distance (Å)	RMS (kcal/mol/Å)	QM/MM (Debye)	difference (°)
Initial	0.64/1.53	0.26/0.66	1.565	1.74/1.42	11.80
Optimal	0.45/1.27	0.24/0.63	1.537	1.74/2.07	0.92

Table S679: The comparison list of optimized atomic charges and their initial guess for 2-fluoro-4-methylbenzen-1-olate, referring to the penalties of initial guess

Atom	Charges		
	Optimal	Initial	Penalty
HB3	0.090	0.090	0.000
CB	-0.270	-0.270	0.474
HB1	0.090	0.090	0.000
HB2	0.090	0.090	0.000
CG	0.073	-0.037	0.474
CD1	-0.163	-0.126	5.351
HD1	0.165	0.177	0.000
CD2	-0.103	-0.101	0.000
HD2	0.115	0.115	0.000
CE1	-0.002	0.104	26.541
FE1	-0.162	-0.223	23.041
CE2	-0.109	-0.164	0.000
HE2	0.115	0.115	0.000
CZ	0.174	0.246	27.391
OH	-0.574	-0.526	18.309
HH	0.471	0.420	0.075

Table S680: Interaction energies and geometries between probe water and selected 2-fluoro-4-methylbenzen-1-olate site calculated using the optimized and initial charges

N	Probe site	Angle (°)	Energy (kcal/mol)		Distance (Å)	
			QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial	QM/Optimal/Initial
1	HH-OH	0.0	-2.71/-1.44/-1.18		2.28/2.91/2.94	
2	HH-OH	45.0	-1.89/-1.28/-1.00		2.51/2.95/2.99	
3	HH-OH	90.0	-1.36/-1.15/-0.85		2.68/2.98/3.04	
4	HH-OH	135.0	-1.91/-1.29/-1.00		2.50/2.95/2.99	
5	OH-CZ	0.0	-4.36/-4.54/-3.79		1.91/1.91/1.94	
6	OH-CZ	90.0	-4.71/-4.72/-3.94		1.87/1.90/1.93	
7	OH-CZ	180.0	-3.60/-4.33/-3.63		1.95/1.91/1.94	
8	OH-CZ	270.0	-4.72/-4.72/-3.94		1.87/1.90/1.93	
9	FE1-CE1	0.0	-1.83/-1.93/-2.27		2.20/1.97/1.93	
10	FE1-CE1	90.0	-1.75/-1.65/-2.00		2.20/1.99/1.94	
11	FE1-CE1	180.0	-1.30/-1.04/-1.42		2.27/2.05/1.99	
12	FE1-CE1	270.0	-1.75/-1.65/-2.01		2.20/1.99/1.94	
13	HE2-CE2	0.0	-1.34/-0.59/-0.58		2.52/2.71/2.72	
14	HE2-CE2	90.0	-1.26/-0.52/-0.53		2.52/2.72/2.73	
15	HD1-CD1	0.0	-1.83/-1.98/-2.42		2.49/2.43/2.40	
16	HD1-CD1	90.0	-1.90/-1.98/-2.38		2.47/2.43/2.40	
17	HD2-CD2	0.0	-1.59/-1.58/-1.21		2.62/2.66/2.69	
18	HD2-CD2	90.0	-1.86/-1.65/-1.26		2.54/2.65/2.68	
19	HB3-CB	0.0	-1.03/-1.01/-0.74		2.74/2.71/2.75	
20	HB1-CB	0.0	-1.53/-1.40/-1.02		2.65/2.68/2.72	
21	HB2-CB	0.0	-1.44/-1.34/-1.20		2.65/2.68/2.71	

2 The Detail of Small Molecules Used in Bonded Terms Optimization

2.1 The small molecule used for bonded terms optimization of phenylglycine (004)

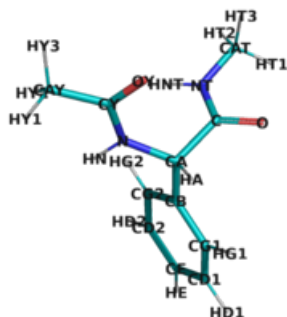


Figure S207: The energy minimized structure corresponding to (2S)-2-acetamido-N-methyl-2-phenylacetamide.

Table S681: The calculated geometric terms of (2S)-2-acetamido-N-methyl-2-phenylacetamide.

Terms	QM	CHARMM	Abs. diff.
N-HN	1.02	0.99	0.02
N-CA	1.46	1.46	0.01
N-CY	1.38	1.34	0.04
CA-HA	1.10	1.08	0.02
CA-CB	1.51	1.52	0.01
CA-C	1.54	1.52	0.01
CB-CG1	1.40	1.41	0.01
CB-CG2	1.40	1.41	0.01
CG1-HG1	1.09	1.08	0.01
CG1-CD1	1.40	1.40	0.01
CG2-HG2	1.09	1.08	0.01
CG2-CD2	1.40	1.40	0.01
CD1-HD1	1.09	1.08	0.01
CD1-CE	1.40	1.40	0.00
CD2-HD2	1.09	1.08	0.01
CD2-CE	1.40	1.40	0.00
CE-HE	1.09	1.08	0.01
C-O	1.23	1.23	0.00
C-NT	1.36	1.35	0.02
NT-HNT	1.01	0.99	0.02
NT-CAT	1.45	1.44	0.01
CAT-HT1	1.09	1.12	0.03
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.10	1.11	0.02
CAY-HY1	1.09	1.11	0.02
CAY-HY2	1.09	1.11	0.02
CAY-HY3	1.09	1.11	0.02
CAY-CY	1.51	1.48	0.03
CY-OY	1.23	1.22	0.01

Terms	QM	CHARMM	Abs. diff.
N-CA-HA	110.15	106.73	3.42
N-CA-CB	110.87	112.43	1.55
N-CA-C	112.18	115.23	3.05
N-CY-CAY	115.11	116.42	1.32
N-CY-OY	121.51	122.75	1.24
HN-N-CA	115.95	115.55	0.40
HN-N-CY	117.60	118.92	1.32
CA-N-CY	119.15	124.89	5.74
CA-CB-CG1	119.03	119.28	0.25
CA-CB-CG2	121.61	121.80	0.18
CA-C-O	120.49	120.66	0.17
CA-C-NT	114.68	117.98	3.30
HA-CA-CB	109.78	109.54	0.23
HA-CA-C	104.06	104.81	0.76
CB-CA-C	109.60	107.74	1.86
CB-CG1-HG1	119.37	119.81	0.44
CB-CG1-CD1	120.35	120.62	0.27
CB-CG2-HG2	120.08	120.41	0.33
CB-CG2-CD2	120.23	120.45	0.21
CG1-CB-CG2	119.31	118.92	0.39
CG1-CD1-HD1	119.72	120.04	0.32
CG1-CD1-CE	120.18	119.95	0.23
HG1-CG1-CD1	120.28	119.56	0.72
CG2-CD2-HD2	119.71	120.16	0.45
CG2-CD2-CE	120.24	120.03	0.22
HG2-CG2-CD2	119.69	119.14	0.55
CD1-CE-CD2	119.68	120.04	0.36
CD1-CE-HE	120.18	119.91	0.28
HD1-CD1-CE	120.10	120.01	0.10
CD2-CE-HE	120.13	120.05	0.08
HD2-CD2-CE	120.05	119.82	0.23
C-NT-HNT	115.66	119.27	3.60
C-NT-CAT	119.26	121.80	2.54
O-C-NT	124.18	121.18	3.00
NT-CAT-HT1	108.22	111.12	2.90
NT-CAT-HT2	108.97	110.54	1.57
NT-CAT-HT3	112.02	110.31	1.71
HNT-NT-CAT	117.87	118.50	0.62
HT1-CAT-HT2	109.49	108.10	1.39
HT1-CAT-HT3	108.52	108.07	0.45
HT2-CAT-HT3	109.59	108.62	0.97
CAY-CY-OY	123.38	120.82	2.56
HY1-CAY-HY2	108.44	109.71	1.27
HY1-CAY-HY3	108.43	108.59	0.16
HY1-CAY-CY	109.55	109.72	0.17
HY2-CAY-HY3	109.81	108.75	1.07
HY2-CAY-CY	111.97	111.02	0.95
HY3-CAY-CY	108.58	109.00	0.43

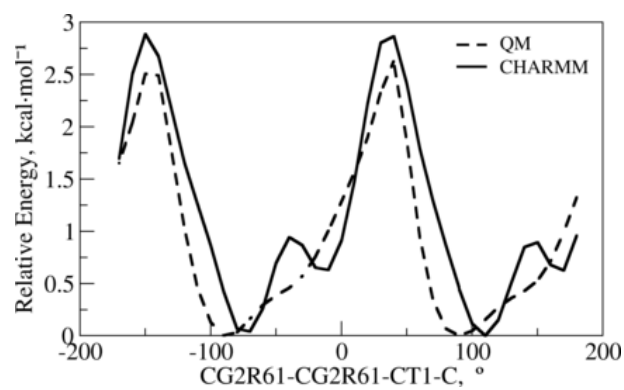


Figure S208: The PES scan for flexible dihedral corresponding to (2S)-2-acetamido-N-methyl-2-phenylacetamide.

2.2 The small molecule used for bonded terms optimization of 7-hydroxy-1-tryptophan (0AF)

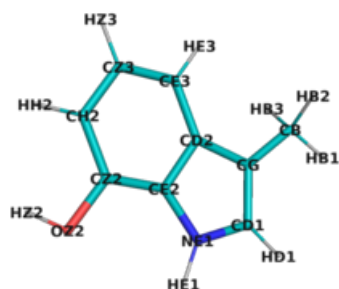


Figure S209: The energy minimized structure corresponding to 3-methyl-1H-indol-7-olate.

Table S682: The calculated geometric terms of 3-methyl-1H-indol-7-olate.

Terms	QM	CHARMM	Abs. diff.
CD1-NE1-HE1	126.55	127.47	0.92
CD1-NE1-CE2	108.77	111.07	2.30
HD1-CD1-NE1	120.59	124.13	3.55
CD2-CE2-NE1	108.07	105.94	2.13
CD2-CE2-CZ2	122.41	120.73	1.68
CD2-CE3-HE3	120.95	119.67	1.28
CD2-CE3-CZ3	118.50	119.79	1.28
NE1-CE2-CZ2	129.51	133.33	3.82
HE1-NE1-CE2	124.69	121.47	3.22
CE2-CD2-CE3	118.94	119.92	0.98
CE2-CZ2-OZ2	116.57	122.20	5.63
CE2-CZ2-CH2	117.78	119.17	1.39
CZ2-OZ2-HZ2	108.07	107.36	0.71
CZ2-CH2-CZ3	120.52	120.27	0.25
CZ2-CH2-HH2	119.75	120.51	0.76
OZ2-CZ2-CH2	125.64	118.63	7.01
CE3-CZ3-HZ3	119.75	119.91	0.16
CE3-CZ3-CH2	121.83	120.12	1.71
HE3-CE3-CZ3	120.55	120.54	0.00
CZ3-CH2-HH2	119.72	119.21	0.51
HZ3-CZ3-CH2	118.42	119.97	1.55

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.10	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.10	1.11	0.01
CB-CG	1.50	1.51	0.01
CG-CD1	1.38	1.37	0.01
CG-CD2	1.43	1.44	0.00
CD1-HD1	1.08	1.08	0.00
CD1-NE1	1.38	1.38	0.00
CD2-CE2	1.42	1.40	0.02
CD2-CE3	1.41	1.39	0.02
NE1-HE1	1.01	1.01	0.00
NE1-CE2	1.37	1.38	0.01
CE2-CZ2	1.40	1.40	0.00
CZ2-OZ2	1.38	1.42	0.04
CZ2-CH2	1.39	1.40	0.01
OZ2-HZ2	0.97	0.96	0.01
CE3-HE3	1.09	1.08	0.01
CE3-CZ3	1.39	1.40	0.01
CZ3-HZ3	1.09	1.08	0.00
CZ3-CH2	1.42	1.40	0.01
CH2-HH2	1.09	1.08	0.01
HB3-CB-HB1	107.81	108.80	0.99
HB3-CB-HB2	107.41	108.86	1.45
HB3-CB-CG	111.42	109.75	1.68
CB-CG-CD1	127.03	128.00	0.96
CB-CG-CD2	126.46	124.62	1.84
HB1-CB-HB2	107.81	108.88	1.07
HB1-CB-CG	110.79	110.72	0.07
HB2-CB-CG	111.42	109.81	1.62
CG-CD1-HD1	129.59	128.15	1.44
CG-CD1-NE1	109.83	107.72	2.11
CG-CD2-CE2	106.83	107.90	1.07
CG-CD2-CE3	134.23	132.18	2.05
CD1-CG-CD2	106.51	107.38	0.87

2.3 The small molecule used for bonded terms optimization of (3S)-3-(methylsulfonyl)-L-aspartic acid (0TD)

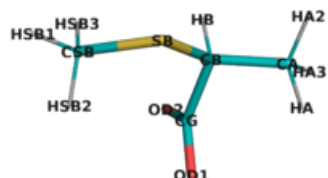


Figure S210: The energy minimized structure corresponding to 2-(methylsulfonyl)propanoic acid.

Table S683: The calculated geometric terms of 2-(methylsulfonyl)propanoic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.10	1.11	0.01
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.56	0.03
CB-HB	1.10	1.11	0.02
CB-SB	1.83	1.84	0.01
CB-CG	1.56	1.55	0.01
SB-CSB	1.81	1.82	0.01
CSB-HSB1	1.10	1.11	0.01
CSB-HSB2	1.09	1.11	0.02
CSB-HSB3	1.09	1.11	0.02
CG-OD1	1.27	1.26	0.01
CG-OD2	1.27	1.26	0.01
HA3-CA-HA2	108.26	109.02	0.77
HA3-CA-HA	108.43	108.51	0.08
HA3-CA-CB	109.27	110.21	0.94
HA2-CA-HA	109.68	108.89	0.78
HA2-CA-CB	111.98	110.42	1.56
CA-CB-HB	110.80	107.28	3.52
CA-CB-SB	107.84	111.87	4.03
CA-CB-CG	111.45	110.68	0.77
HA-CA-CB	109.16	109.73	0.58
CB-SB-CSB	99.98	97.74	2.24
CB-CG-OD1	115.98	117.18	1.20
CB-CG-OD2	114.59	115.53	0.94
HB-CB-SB	107.77	107.92	0.15
HB-CB-CG	107.45	106.36	1.09
SB-CB-CG	111.49	112.40	0.92
SB-CSB-HSB1	107.23	111.14	3.91
SB-CSB-HSB2	109.99	110.67	0.68
SB-CSB-HSB3	111.42	110.78	0.64
HSB1-CSB-HSB2	109.66	107.94	1.71
HSB1-CSB-HSB3	109.44	108.62	0.82

Terms	QM	CHARMM	Abs. diff.
HSB2-CSB-HSB3	109.08	107.56	1.52
OD1-CG-OD2	129.42	127.28	2.15

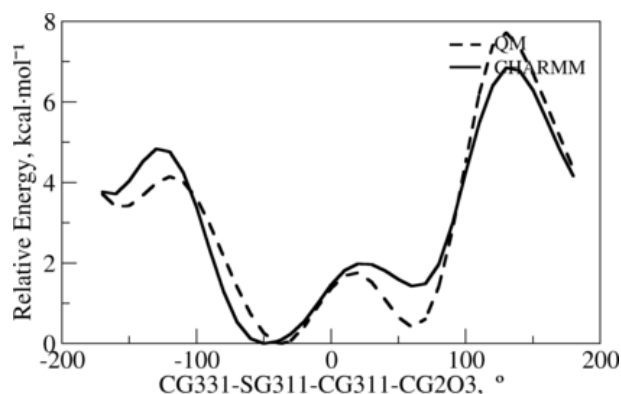


Figure S211: The PES scan for flexible dihedral corresponding to 2-(methylsulfonyl)propanoic acid.

2.4 The small molecule 1 used for bonded terms optimization of S-2,3-dihydro-5-glycin-2-yl-isoxazol-3-yl-cysteine (143)

Terms	QM	CHARMM	Abs. diff.
HI1-CI-HI3	107.74	109.03	1.30
HI2-CI-HI3	108.88	109.24	0.36

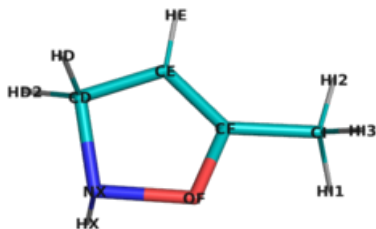


Figure S212: The energy minimized structure corresponding to 5-methyl-2,3-dihydro-1,2-oxazole.

Table S684: The calculated geometric terms of 5-methyl-2,3-dihydro-1,2-oxazole.

Terms	QM	CHARMM	Abs. diff.
HD2-CD	1.10	1.10	0.01
CD-HD	1.10	1.10	0.01
CD-NX	1.48	1.48	0.00
CD-CE	1.51	1.50	0.01
NX-HX	1.03	1.02	0.01
NX-OF	1.47	1.48	0.01
CE-HE	1.08	1.08	0.00
CE-CF	1.34	1.35	0.01
OF-CF	1.39	1.37	0.02
CF-CI	1.49	1.49	0.01
CI-HI1	1.09	1.11	0.02
CI-HI2	1.09	1.11	0.02
CI-HI3	1.09	1.11	0.02
HD2-CD-HD	108.22	106.48	1.74
HD2-CD-NX	108.59	111.69	3.10
HD2-CD-CE	115.32	117.54	2.22
CD-NX-HX	105.84	105.85	0.01
CD-NX-OF	104.12	104.15	0.03
CD-CE-HE	126.48	125.66	0.82
CD-CE-CF	106.80	107.25	0.44
HD-CD-NX	109.09	107.73	1.36
HD-CD-CE	111.98	109.31	2.66
NX-CD-CE	103.40	103.77	0.37
NX-OF-CF	106.12	106.18	0.06
HX-NX-OF	100.55	100.56	0.01
CE-CF-OF	113.13	113.29	0.15
CE-CF-CI	133.07	132.76	0.31
HE-CE-CF	126.20	126.50	0.30
OF-CF-CI	113.77	113.85	0.07
CF-CI-HI1	110.69	109.54	1.14
CF-CI-HI2	110.29	110.30	0.01
CF-CI-HI3	109.98	109.48	0.50
HI1-CI-HI2	109.20	109.21	0.01

2.5 The small molecule 2 used for bonded terms optimization of S-2,3-dihydro-5-glycin-2-yl-isoxazol-3-yl-cysteine (143)

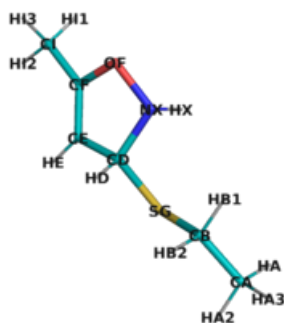


Figure S213: The energy minimized structure corresponding to (3R)-3-(ethylsulfanyl)-5-methyl-2,3-dihydro-1,2-oxazole.

Table S685: The calculated geometric terms of (3R)-3-(ethylsulfanyl)-5-methyl-2,3-dihydro-1,2-oxazole.

Terms	QM	CHARMM	Abs. diff.
CA-HA	1.09	1.11	0.02
CA-HA3	1.09	1.11	0.02
CA-HA2	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.82	1.82	0.00
SG-CD	1.81	1.81	0.00
CD-HD	1.10	1.10	0.00
CD-NX	1.49	1.47	0.01
CD-CE	1.50	1.50	0.00
NX-HX	1.03	1.02	0.01
NX-OF	1.48	1.48	0.00
CE-HE	1.08	1.08	0.01
CE-CF	1.34	1.35	0.01
OF-CF	1.38	1.37	0.01
CF-CI	1.49	1.50	0.02
CI-HI1	1.09	1.11	0.02
CI-HI2	1.09	1.11	0.02
CI-HI3	1.09	1.11	0.02
CA-CB-HB1	110.69	108.68	2.02
CA-CB-HB2	110.42	108.76	1.65
CA-CB-SG	109.58	112.56	2.97
HA-CA-HA3	108.09	108.40	0.31
HA-CA-HA2	108.31	108.29	0.02
HA-CA-CB	111.14	110.53	0.61
HA3-CA-HA2	108.24	108.43	0.18
HA3-CA-CB	109.89	110.61	0.72
HA2-CA-CB	111.07	110.51	0.55
CB-SG-CD	99.35	98.09	1.26
HB1-CB-HB2	108.14	106.94	1.20

Terms	QM	CHARMM	Abs. diff.
HB1-CB-SG	109.40	109.87	0.47
HB2-CB-SG	108.57	109.87	1.30
SG-CD-HD	108.06	107.91	0.15
SG-CD-NX	110.86	110.84	0.02
SG-CD-CE	113.69	112.31	1.39
CD-NX-HX	104.79	105.18	0.39
CD-NX-OF	104.55	105.37	0.82
CD-CE-HE	125.57	124.73	0.84
CD-CE-CF	107.17	107.76	0.59
HD-CD-NX	108.76	111.43	2.67
HD-CD-CE	111.96	111.33	0.63
NX-CD-CE	103.39	103.04	0.36
NX-OF-CF	105.97	105.57	0.40
HX-NX-OF	101.01	105.31	4.29
CE-CF-OF	113.46	113.05	0.41
CE-CF-CI	132.67	133.32	0.66
HE-CE-CF	126.74	127.41	0.67
OF-CF-CI	113.84	113.43	0.41
CF-CI-HI1	110.48	109.95	0.53
CF-CI-HI2	110.30	110.32	0.03
CF-CI-HI3	110.02	109.97	0.05
HI1-CI-HI2	109.22	108.83	0.39
HI1-CI-HI3	107.79	108.94	1.15
HI2-CI-HI3	108.97	108.79	0.19

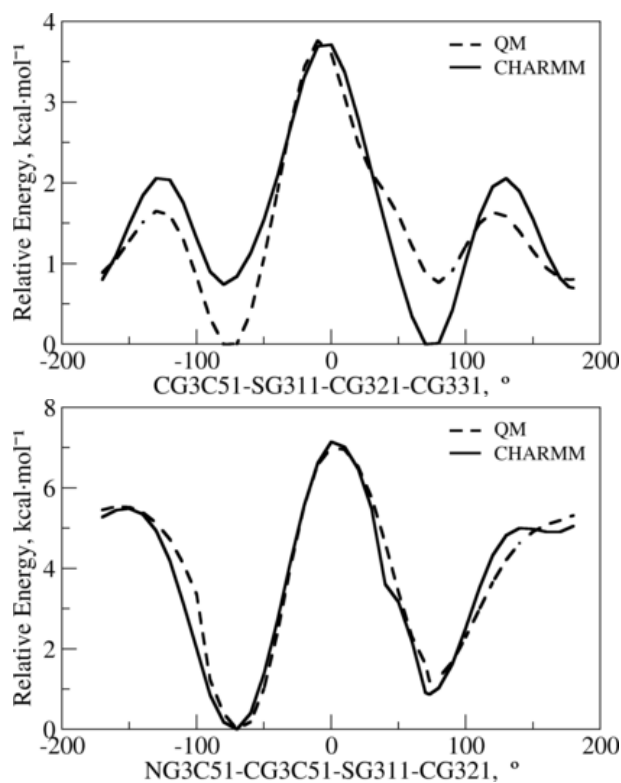


Figure S214: The PES scan for flexible dihedrals corresponding to (3R)-3-(ethylsulfanyl)-5-methyl-2,3-dihydro-1,2-oxazole.

2.6 The small molecule 3 used for bonded terms optimization of S-2,3-dihydro-5-glycin-2-yl-isoxazol-3-yl-cysteine (143)

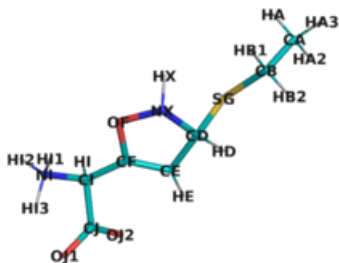


Figure S215: The energy minimized structure corresponding to 2-amino-2-[3-(ethylsulfanyl)-2,3-dihydro-1,2-oxazol-5-yl]acetic acid.

Table S686: The calculated geometric terms of 2-amino-2-[3-(ethylsulfanyl)-2,3-dihydro-1,2-oxazol-5-yl]acetic acid.

Terms	QM	CHARMM	Abs. diff.
CA-HA	1.09	1.11	0.02
CA-HA3	1.09	1.11	0.02
CA-HA2	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.82	1.82	0.00
SG-CD	1.83	1.81	0.02
CD-HD	1.10	1.10	0.01
CD-NX	1.48	1.48	0.01
CD-CE	1.49	1.49	0.00
NX-HX	1.03	1.02	0.01
NX-OF	1.48	1.48	0.01
CE-HE	1.08	1.08	0.00
CE-CF	1.34	1.35	0.02
OF-CF	1.38	1.38	0.01
CF-CI	1.49	1.53	0.04
CI-HI	1.09	1.11	0.01
CI-NI	1.51	1.49	0.02
CI-CJ	1.60	1.54	0.06
NI-HI1	1.03	1.01	0.01
NI-HI2	1.02	1.01	0.01
NI-HI3	1.05	1.03	0.03
CJ-OJ1	1.27	1.26	0.01
CJ-OJ2	1.24	1.26	0.02
CA-CB-HB1	109.89	108.75	1.14
CA-CB-HB2	110.23	108.64	1.59
CA-CB-SG	109.63	111.94	2.31
HA-CA-HA3	108.18	108.44	0.26
HA-CA-HA2	108.29	108.15	0.14
HA-CA-CB	111.10	110.58	0.51

Terms	QM	CHARMM	Abs. diff.
HA3-CA-HA2	108.30	108.28	0.02
HA3-CA-CB	109.99	110.87	0.88
HA2-CA-CB	110.88	110.42	0.46
CB-SG-CD	99.64	100.64	1.00
HB1-CB-HB2	108.04	107.10	0.95
HB1-CB-SG	110.15	110.34	0.20
HB2-CB-SG	108.88	109.94	1.05
SG-CD-HD	107.77	108.55	0.78
SG-CD-NX	116.38	111.52	4.86
SG-CD-CE	109.74	113.03	3.30
CD-NX-HX	109.09	111.88	2.80
CD-NX-OF	104.91	105.27	0.36
CD-CE-HE	126.80	126.64	0.16
CD-CE-CF	107.27	108.54	1.27
HD-CD-NX	107.38	110.40	3.02
HD-CD-CE	114.00	110.29	3.71
NX-CD-CE	101.70	102.97	1.28
NX-OF-CF	103.66	106.06	2.40
HX-NX-OF	100.07	102.27	2.20
CE-CF-OF	113.95	111.84	2.11
CE-CF-CI	132.25	132.81	0.57
HE-CE-CF	125.63	124.46	1.17
OF-CF-CI	113.80	114.43	0.62
CF-CI-HI	111.78	108.89	2.89
CF-CI-NI	109.12	110.33	1.21
CF-CI-CJ	111.97	112.12	0.15
CI-NI-HI1	111.44	110.42	1.02
CI-NI-HI2	113.34	111.01	2.33
CI-NI-HI3	97.89	101.24	3.35
CI-CJ-OJ1	111.42	117.43	6.00
CI-CJ-OJ2	114.93	115.23	0.30
HI-CI-NI	109.26	108.74	0.52
HI-CI-CJ	110.10	108.70	1.40
NI-CI-CJ	104.31	107.98	3.67
HI1-NI-HI2	109.04	112.99	3.95
HI1-NI-HI3	114.15	110.75	3.40
HI2-NI-HI3	110.71	109.81	0.90
OJ1-CJ-OJ2	133.65	127.33	6.31

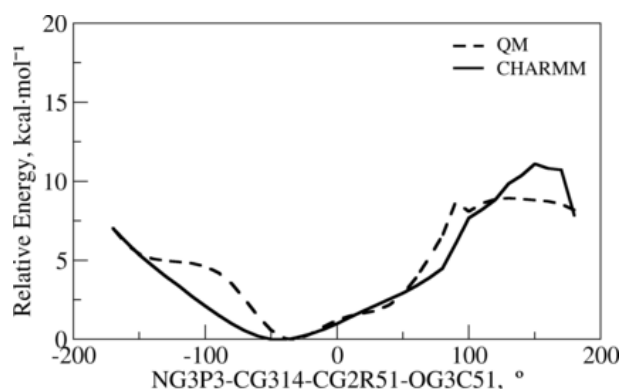


Figure S216: The PES scan for flexible dihedral corresponding to 2-amino-2-[3-(ethylsulfanyl)-2,3-dihydro-1,2-oxazol-5-yl]acetic acid.

2.7 The small molecule used for bonded terms optimization of 2-amino-6-oxopimelic acid (26P)

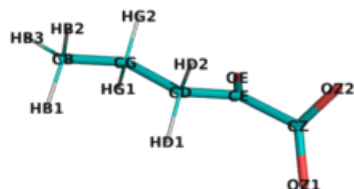


Figure S217: The energy minimized structure corresponding to 2-oxopentanoic acid.

Table S687: The calculated geometric terms of 2-oxopentanoic acid.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.10	1.11	0.01
CB-HB2	1.10	1.11	0.01
CB-HB1	1.10	1.11	0.01
CB-CG	1.53	1.53	0.00
CG-HG2	1.10	1.11	0.02
CG-HG1	1.10	1.11	0.02
CG-CD	1.52	1.54	0.02
CD-HD2	1.10	1.11	0.01
CD-HD1	1.10	1.11	0.01
CD-CE	1.52	1.51	0.01
CE-OE	1.24	1.24	0.00
CE-CZ	1.53	1.57	0.04
CZ-OZ1	1.27	1.27	0.00
CZ-OZ2	1.27	1.27	0.00
HB3-CB-HB2	107.84	108.69	0.85
HB3-CB-HB1	107.86	108.66	0.80
HB3-CB-CG	111.63	110.57	1.06
CB-CG-HG2	110.14	109.44	0.70
CB-CG-HG1	110.16	109.41	0.75
CB-CG-CD	112.22	113.06	0.84
HB2-CB-HB1	107.57	108.46	0.89
HB2-CB-CG	110.90	110.23	0.68
HB1-CB-CG	110.88	110.19	0.70
CG-CD-HD2	111.02	109.00	2.03
CG-CD-HD1	111.35	109.02	2.33
CG-CD-CE	114.38	115.06	0.68
HG2-CG-HG1	105.94	107.29	1.36
HG2-CG-CD	109.13	108.71	0.41
HG1-CG-CD	109.05	108.75	0.30
CD-CE-OE	121.18	120.95	0.24
CD-CE-CZ	114.71	114.87	0.15
HD2-CD-HD1	105.80	107.85	2.06
HD2-CD-CE	107.02	107.85	0.83
HD1-CD-CE	106.78	107.83	1.05

Terms	QM	CHARMM	Abs. diff.
CE-CZ-OZ1	113.27	116.92	3.65
CE-CZ-OZ2	115.41	116.87	1.46
OE-CE-CZ	124.09	124.19	0.09
OZ1-CZ-OZ2	131.27	126.19	5.08

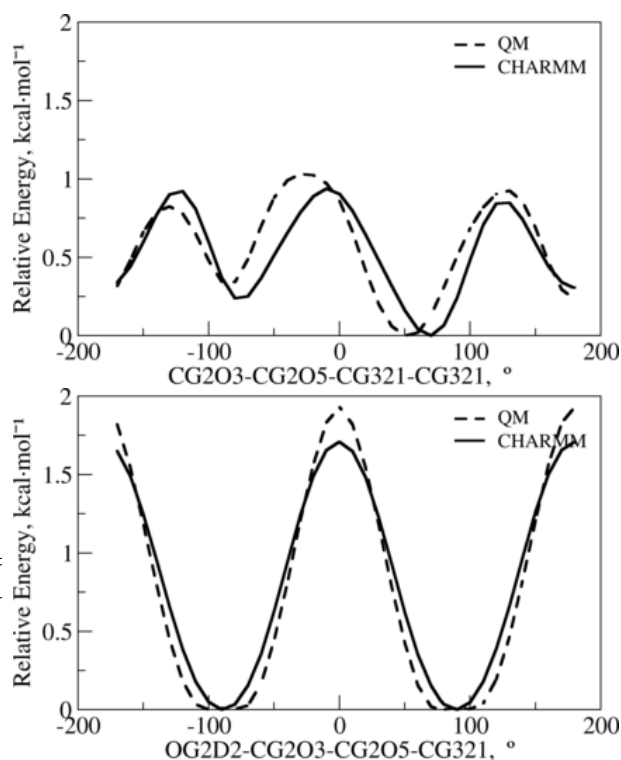


Figure S218: The PES scan for flexible dihedrals corresponding to 2-oxopentanoic acid.

2.8 The small molecule used for bonded terms optimization of 2-allyl-glycine (2AG)

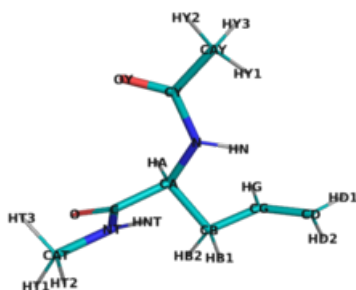


Figure S219: The energy minimized structure corresponding to (2S)-2-acetamido-N-methylpent-4-enamide.

Table S688: The calculated geometric terms of (2S)-2-acetamido-N-methylpent-4-enamide.

Terms	QM	CHARMM	Abs. diff.
N-HN	1.02	0.99	0.02
N-CA	1.46	1.46	0.00
N-CY	1.38	1.34	0.04
CA-HA	1.10	1.08	0.02
CA-CB	1.54	1.56	0.02
CA-C	1.53	1.53	0.00
CB-HB1	1.10	1.11	0.02
CB-HB2	1.10	1.11	0.02
CB-CG	1.50	1.51	0.01
CG-HG	1.09	1.11	0.01
CG-CD	1.34	1.34	0.00
CD-HD1	1.09	1.10	0.02
CD-HD2	1.09	1.10	0.01
C-O	1.23	1.23	0.00
C-NT	1.37	1.35	0.02
NT-HNT	1.01	0.99	0.02
NT-CAT	1.45	1.44	0.01
CAT-HT1	1.09	1.11	0.03
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.10	1.11	0.02
CAY-HY1	1.09	1.11	0.02
CAY-HY2	1.09	1.11	0.02
CAY-HY3	1.09	1.11	0.02
CAY-CY	1.51	1.48	0.03
CY-OY	1.23	1.22	0.01
N-CA-HA	110.47	107.24	3.24
N-CA-CB	109.30	110.33	1.03
N-CA-C	112.29	115.05	2.76
N-CY-CAY	115.12	116.31	1.19
N-CY-OY	121.63	122.96	1.33
HN-N-CA	115.82	114.06	1.76
HN-N-CY	118.00	119.43	1.44
CA-N-CY	119.61	125.53	5.92

Terms	QM	CHARMM	Abs. diff.
CA-CB-HB1	109.00	108.99	0.02
CA-CB-HB2	107.29	108.48	1.19
CA-CB-CG	111.48	112.66	1.18
CA-C-O	120.97	121.15	0.18
CA-C-NT	114.52	117.44	2.92
HA-CA-CB	109.95	108.86	1.09
HA-CA-C	104.86	105.72	0.85
CB-CA-C	109.88	109.38	0.50
CB-CG-HG	116.54	115.66	0.88
CB-CG-CD	124.05	125.89	1.85
HB1-CB-HB2	107.68	106.65	1.03
HB1-CB-CG	110.44	110.69	0.25
HB2-CB-CG	110.82	109.17	1.64
CG-CD-HD1	121.77	121.11	0.67
CG-CD-HD2	121.39	120.87	0.51
HG-CG-CD	119.39	118.45	0.94
HD1-CD-HD2	116.81	118.00	1.19
C-NT-HNT	115.17	118.99	3.82
C-NT-CAT	119.08	121.89	2.81
O-C-NT	123.79	121.38	2.41
NT-CAT-HT1	108.33	111.19	2.86
NT-CAT-HT2	108.97	110.62	1.66
NT-CAT-HT3	111.96	110.19	1.77
HNT-NT-CAT	117.67	118.48	0.81
HT1-CAT-HT2	109.50	108.18	1.32
HT1-CAT-HT3	108.48	108.01	0.47
HT2-CAT-HT3	109.58	108.56	1.01
CAY-CY-OY	123.25	120.72	2.53
HY1-CAY-HY2	109.81	108.92	0.89
HY1-CAY-HY3	108.39	109.61	1.22
HY1-CAY-CY	111.99	110.92	1.07
HY2-CAY-HY3	108.43	108.60	0.17
HY2-CAY-CY	108.65	108.96	0.31
HY3-CAY-CY	109.51	109.78	0.27

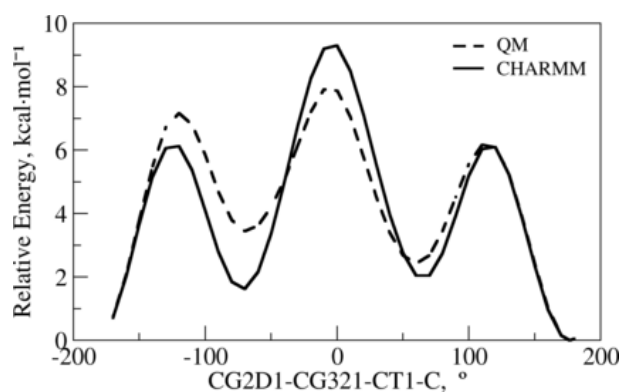


Figure S220: The PES scan for flexible dihedral corresponding to (2S)-2-acetamido-N-methylpent-4-enamide.

2.9 The small molecule used for bonded terms optimization of S-hydroperoxycysteine (2CO)

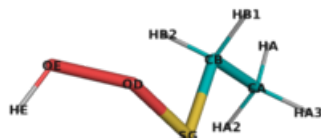


Figure S221: The energy minimized structure corresponding to (ethylsulfanyl)peroxol.

Table S689: The calculated geometric terms of (ethylsulfanyl)peroxol.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.53	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.80	1.82	0.01
SG-OD	1.68	1.68	0.00
OD-OE	1.49	1.50	0.01
OE-HE	0.98	0.96	0.02
HA3-CA-HA2	108.43	108.48	0.06
HA3-CA-HA	107.95	108.49	0.54
HA3-CA-CB	111.39	110.51	0.88
HA2-CA-HA	107.98	108.40	0.42
HA2-CA-CB	111.33	110.47	0.86
CA-CB-HB1	111.13	109.66	1.47
CA-CB-HB2	110.97	109.63	1.34
CA-CB-SG	108.91	112.23	3.32
HA-CA-CB	109.64	110.42	0.78
CB-SG-OD	100.07	100.46	0.39
HB1-CB-HB2	108.84	107.31	1.52
HB1-CB-SG	108.68	108.93	0.26
HB2-CB-SG	108.24	108.94	0.70
SG-OD-OE	109.38	109.50	0.12
OD-OE-HE	98.64	98.42	0.22

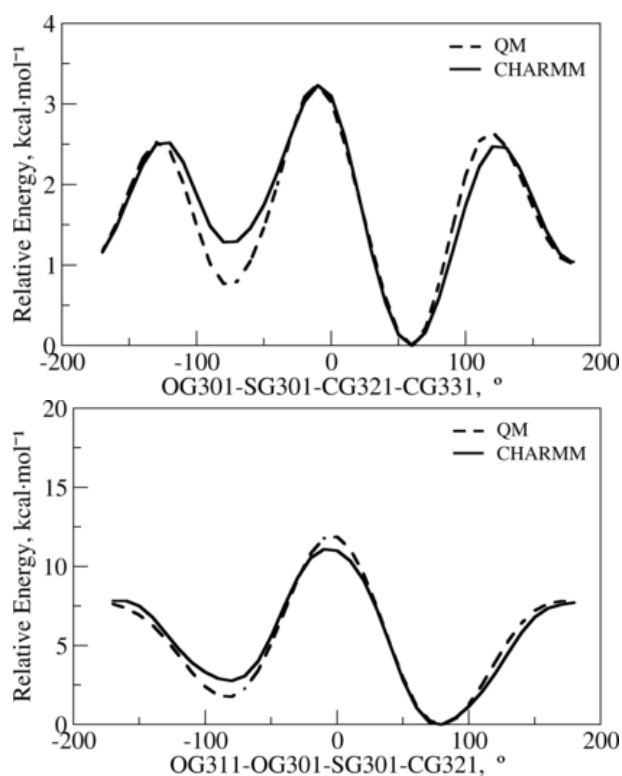


Figure S222: The PES scan for flexible dihedrals corresponding to (ethylsulfanyl)peroxol.

2.10 The small molecule used for bonded terms optimization of s-(difluoromethyl)-homocysteine (2FM)

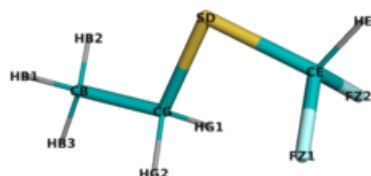


Figure S223: The energy minimized structure corresponding to [(difluoromethyl)sulfanyl]ethane.

Table S690: The calculated geometric terms of [(difluoromethyl)sulfanyl]ethane.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.52	1.53	0.01
CG-HG1	1.09	1.11	0.02
CG-HG2	1.09	1.11	0.02
CG-SD	1.82	1.82	0.00
SD-CE	1.79	1.79	0.01
CE-HE	1.09	1.08	0.01
CE-FZ1	1.37	1.35	0.02
CE-FZ2	1.37	1.35	0.02
HB3-CB-HB1	108.12	108.41	0.29
HB3-CB-HB2	108.11	108.43	0.32
HB3-CB-CG	109.60	110.49	0.89
CB-CG-HG1	110.95	108.59	2.35
CB-CG-HG2	110.94	108.66	2.29
CB-CG-SD	109.40	112.87	3.47
HB1-CB-HB2	108.42	108.48	0.06
HB1-CB-CG	111.24	110.47	0.77
HB2-CB-CG	111.25	110.49	0.76
CG-SD-CE	97.80	97.42	0.39
HG1-CG-HG2	108.66	106.93	1.73
HG1-CG-SD	108.41	109.79	1.37
HG2-CG-SD	108.40	109.82	1.42
SD-CE-HE	109.95	110.11	0.16
SD-CE-FZ1	111.57	111.39	0.18
SD-CE-FZ2	111.57	111.42	0.15
HE-CE-FZ1	108.86	108.33	0.53
HE-CE-FZ2	108.87	108.37	0.50
FZ1-CE-FZ2	105.90	107.11	1.21

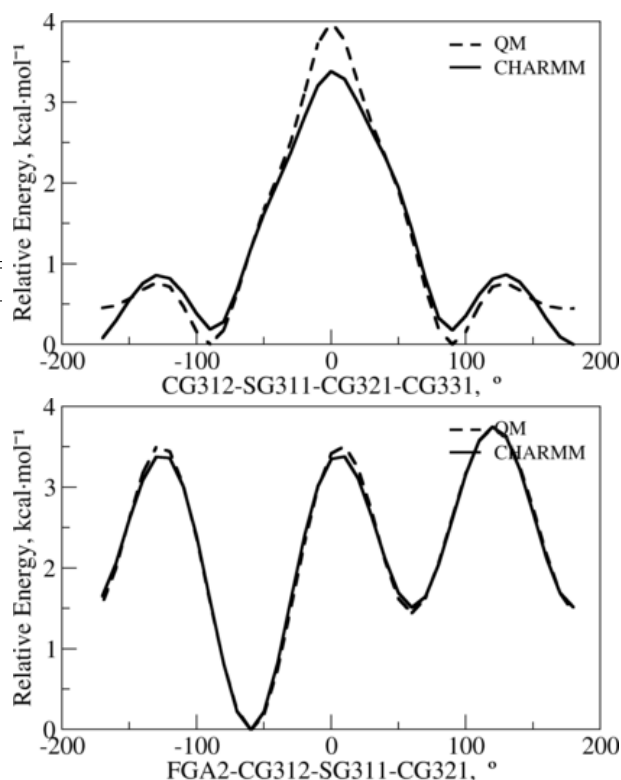


Figure S224: The PES scan for flexible dihedrals corresponding to [(difluoromethyl)sulfanyl]ethane.

2.11 The small molecule used for bonded terms optimization of 2-fluoro-1-histidine (2HF)

Terms	QM	CHARMM	Abs. diff.
NE2-CE1-F1	125.64	125.61	0.03

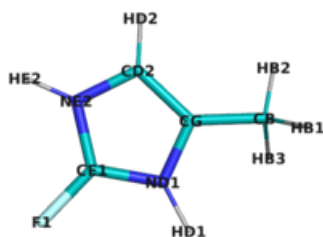


Figure S225: The energy minimized structure corresponding to 2-fluoro-4-methyl-2,3-dihydro-1H-imidazole.

Table S691: The calculated geometric terms of 2-fluoro-4-methyl-2,3-dihydro-1H-imidazole.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.49	1.50	0.01
CG-ND1	1.40	1.37	0.03
CG-CD2	1.37	1.35	0.02
ND1-HD1	1.02	1.00	0.02
ND1-CE1	1.33	1.31	0.02
CD2-HD2	1.08	1.09	0.01
CD2-NE2	1.39	1.38	0.01
CE1-NE2	1.33	1.32	0.01
CE1-F1	1.30	1.34	0.03
NE2-HE2	1.02	1.00	0.02
HB3-CB-HB1	108.86	108.89	0.04
HB3-CB-HB2	108.18	108.44	0.26
HB3-CB-CG	111.16	110.21	0.95
CB-CG-ND1	122.51	122.24	0.27
CB-CG-CD2	131.92	131.09	0.83
HB1-CB-HB2	108.16	108.42	0.26
HB1-CB-CG	111.14	110.19	0.95
HB2-CB-CG	109.25	110.63	1.38
CG-ND1-HD1	126.34	126.96	0.62
CG-ND1-CE1	109.44	109.27	0.17
CG-CD2-HD2	130.72	128.19	2.53
CG-CD2-NE2	107.55	106.55	1.00
ND1-CG-CD2	105.57	106.67	1.10
ND1-CE1-NE2	108.77	108.72	0.05
ND1-CE1-F1	125.59	125.66	0.08
HD1-ND1-CE1	124.21	123.77	0.45
CD2-NE2-CE1	108.66	108.79	0.12
CD2-NE2-HE2	126.89	128.32	1.43
HD2-CD2-NE2	121.72	125.26	3.53
CE1-NE2-HE2	124.45	122.90	1.55

2.12 The small molecule used for bonded terms optimization of 2-fluoro-1-histidine (2HFD)

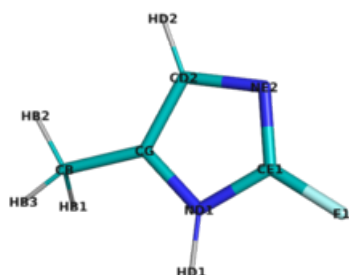


Figure S226: The energy minimized structure corresponding to 2-fluoro-5-methyl-1H-imidazole.

Table S692: The calculated geometric terms of 2-fluoro-5-methyl-1H-imidazole.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.10	1.11	0.02
CB-HB1	1.10	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.49	1.50	0.01
CG-CD2	1.38	1.37	0.01
CG-ND1	1.39	1.38	0.01
CD2-HD2	1.08	1.08	0.00
CD2-NE2	1.39	1.39	0.00
ND1-HD1	1.01	1.00	0.01
ND1-CE1	1.36	1.35	0.01
NE2-CE1	1.30	1.31	0.01
CE1-F1	1.34	1.34	0.00
HB3-CB-HB1	108.09	109.06	0.96
HB3-CB-HB2	107.80	108.65	0.85
HB3-CB-CG	111.95	110.02	1.93
CB-CG-CD2	132.88	130.95	1.93
CB-CG-ND1	122.97	123.35	0.38
HB1-CB-HB2	107.81	108.65	0.84
HB1-CB-CG	111.97	110.02	1.95
HB2-CB-CG	109.05	110.41	1.36
CG-CD2-HD2	127.42	129.44	2.02
CG-CD2-NE2	111.96	110.79	1.18
CG-ND1-HD1	127.62	128.64	1.02
CG-ND1-CE1	106.38	105.95	0.43
CD2-CG-ND1	104.15	105.70	1.55
CD2-NE2-CE1	103.18	103.51	0.33
HD2-CD2-NE2	120.62	119.77	0.85
ND1-CE1-NE2	114.33	114.06	0.27
ND1-CE1-F1	119.40	119.61	0.21
HD1-ND1-CE1	126.00	125.41	0.59
NE2-CE1-F1	126.26	126.33	0.06

2.13 The small molecule used for bonded terms optimization of l-2-amino-6-methylene-pimelic acid (2NP)

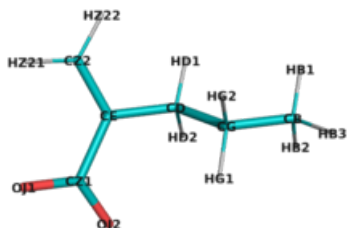


Figure S227: The energy minimized structure corresponding to 2-methylidenepentanoic acid.

Table S693: The calculated geometric terms of 2-methylidenepentanoic acid.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.10	1.11	0.01
CB-HB2	1.10	1.11	0.02
CB-HB1	1.10	1.11	0.01
CB-CG	1.53	1.53	0.00
CG-HG1	1.09	1.12	0.02
CG-HG2	1.10	1.11	0.01
CG-CD	1.53	1.54	0.01
CD-HD2	1.10	1.11	0.02
CD-HD1	1.10	1.11	0.01
CD-CE	1.50	1.52	0.02
CE-CZ1	1.54	1.53	0.02
CE-CZ2	1.35	1.36	0.01
CZ1-OJ1	1.27	1.27	0.00
CZ1-OJ2	1.27	1.27	0.00
CZ2-HZ22	1.09	1.09	0.00
CZ2-HZ21	1.09	1.10	0.01
HB3-CB-HB2	107.87	108.70	0.83
HB3-CB-HB1	107.85	108.95	1.10
HB3-CB-CG	111.70	110.56	1.13
CB-CG-HG1	110.10	109.08	1.02
CB-CG-HG2	109.87	109.42	0.46
CB-CG-CD	112.48	112.76	0.29
HB2-CB-HB1	107.80	108.47	0.67
HB2-CB-CG	110.35	109.82	0.52
HB1-CB-CG	111.12	110.28	0.84
CG-CD-HD2	108.33	107.26	1.08
CG-CD-HD1	109.47	108.58	0.89
CG-CD-CE	111.99	113.67	1.68
HG1-CG-HG2	107.57	107.43	0.14
HG1-CG-CD	107.76	108.74	0.98
HG2-CG-CD	108.92	109.27	0.35
CD-CE-CZ1	117.25	121.83	4.58
CD-CE-CZ2	121.79	114.59	7.20

Terms	QM	CHARMM	Abs. diff.
HD2-CD-HD1	108.42	106.21	2.21
HD2-CD-CE	108.67	108.19	0.47
HD1-CD-CE	109.88	112.54	2.66
CE-CZ1-OJ1	116.76	118.92	2.16
CE-CZ1-OJ2	114.33	116.08	1.75
CE-CZ2-HZ22	121.77	120.63	1.14
CE-CZ2-HZ21	119.80	118.46	1.34
CZ1-CE-CZ2	120.96	123.30	2.34
HZ22-CZ2-HZ21	118.43	120.90	2.47
OJ1-CZ1-OJ2	128.91	124.97	3.94

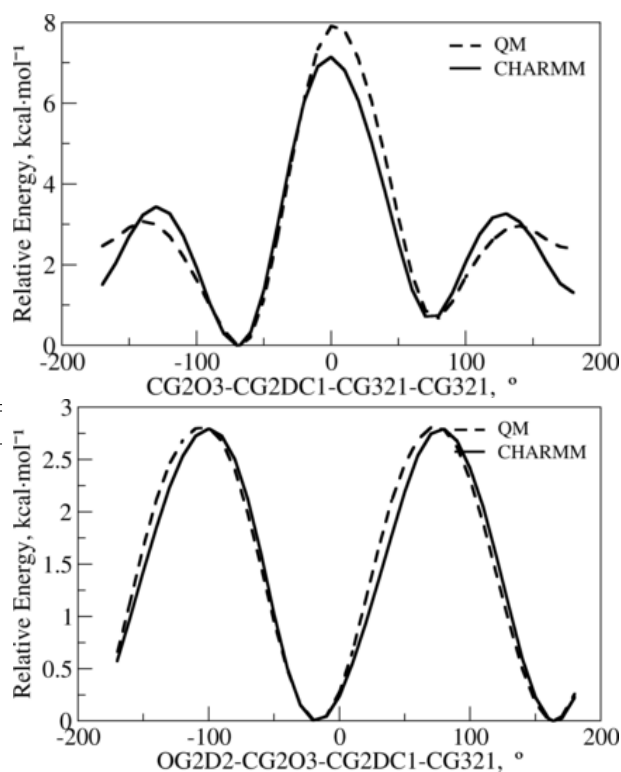
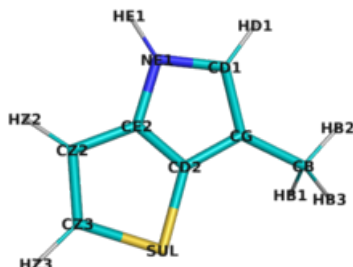


Figure S228: The PES scan for flexible dihedrals corresponding to 2-methylidenepentanoic acid.

2.14 The small molecule used for bonded terms optimization of 3-(4H-thieno[3,2-b]pyrrol-6-yl)-L-alanine (32T)



Terms	QM	CHARMM	Abs. diff.
CD2-CE2-NE1	106.81	111.28	4.46
CD2-CE2-CZ2	114.58	121.00	6.42
CD2-SUL-CZ3	90.99	87.58	3.41
NE1-CE2-CZ2	138.60	127.72	10.88
HE1-NE1-CE2	126.11	128.03	1.93
CE2-CD2-SUL	110.52	113.02	2.50
CE2-CZ2-HZ2	126.44	127.32	0.88
CE2-CZ2-CZ3	110.09	105.70	4.39
SUL-CZ3-CZ2	113.82	112.71	1.12
SUL-CZ3-HZ3	119.04	119.18	0.14
CZ2-CZ3-HZ3	127.14	128.11	0.97
HZ2-CZ2-CZ3	123.47	126.98	3.50

Figure S229: The energy minimized structure corresponding to 6-methyl-4H-thieno[3,2-b]pyrrole.

Table S694: The calculated geometric terms of 6-methyl-4H-thieno[3,2-b]pyrrole.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.10	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.49	1.51	0.01
CG-CD1	1.39	1.41	0.02
CG-CD2	1.42	1.35	0.07
CD1-HD1	1.08	1.08	0.00
CD1-NE1	1.38	1.42	0.03
CD2-CE2	1.40	1.27	0.14
CD2-SUL	1.73	1.69	0.04
NE1-HE1	1.01	1.01	0.00
NE1-CE2	1.37	1.36	0.02
CE2-CZ2	1.42	1.35	0.07
SUL-CZ3	1.74	1.78	0.03
CZ2-HZ2	1.09	1.08	0.01
CZ2-CZ3	1.38	1.40	0.03
CZ3-HZ3	1.08	1.08	0.00
HB3-CB-HB1	107.48	108.76	1.27
HB3-CB-HB2	107.85	108.81	0.96
HB3-CB-CG	111.38	109.87	1.51
CB-CG-CD1	127.07	128.99	1.92
CB-CG-CD2	127.96	128.64	0.68
HB1-CB-HB2	107.84	108.82	0.98
HB1-CB-CG	111.45	109.88	1.57
HB2-CB-CG	110.66	110.66	0.01
CG-CD1-HD1	129.29	127.68	1.61
CG-CD1-NE1	110.02	109.35	0.67
CG-CD2-CE2	109.31	113.85	4.54
CG-CD2-SUL	140.17	133.13	7.04
CD1-CG-CD2	104.98	102.38	2.60
CD1-NE1-HE1	125.01	128.83	3.82
CD1-NE1-CE2	108.88	103.14	5.74
HD1-CD1-NE1	120.69	122.97	2.27

2.15 The small molecule used for bonded terms optimization of 3-chloro-tyrosine (3MY)

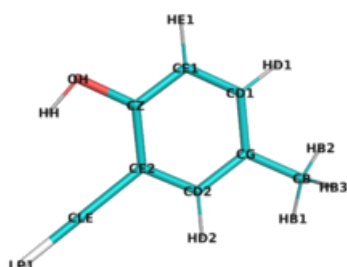


Figure S230: The energy minimized structure corresponding to 2,4-dimethylphenol.

Table S695: The calculated geometric terms of 2,4-dimethylphenol.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.10	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.51	1.50	0.01
CG-CD1	1.40	1.40	0.00
CG-CD2	1.40	1.40	0.01
CD1-HD1	1.09	1.08	0.01
CD1-CE1	1.39	1.40	0.01
CD2-HD2	1.09	1.08	0.01
CD2-CE2	1.39	1.40	0.01
CE1-HE1	1.09	1.08	0.01
CE1-CZ	1.40	1.40	0.00
CE2-CLE	1.75	1.74	0.00
CE2-CZ	1.40	1.41	0.01
CZ-OH	1.37	1.41	0.05
OH-HH	0.98	0.96	0.02
HB3-CB-HB1	107.76	109.75	1.98
HB3-CB-HB2	107.65	109.84	2.19
HB3-CB-CG	111.22	108.66	2.56
CB-CG-CD1	121.09	120.20	0.89
CB-CG-CD2	120.70	120.13	0.57
HB1-CB-HB2	108.02	109.22	1.20
HB1-CB-CG	111.09	109.84	1.25
HB2-CB-CG	110.94	109.52	1.42
CG-CD1-HD1	119.55	119.81	0.26
CG-CD1-CE1	121.32	120.17	1.15
CG-CD2-HD2	120.55	119.89	0.66
CG-CD2-CE2	120.52	120.38	0.15
CD1-CG-CD2	118.18	119.66	1.49
CD1-CE1-HE1	121.53	120.31	1.22
CD1-CE1-CZ	120.47	120.10	0.37
HD1-CD1-CE1	119.13	120.02	0.89
CD2-CE2-CLE	119.93	118.90	1.03
CD2-CE2-CZ	121.20	119.79	1.41

Terms	QM	CHARMM	Abs. diff.
HD2-CD2-CE2	118.93	119.73	0.81
CE1-CZ-CE2	118.31	119.89	1.58
CE1-CZ-OH	117.79	119.09	1.31
HE1-CE1-CZ	118.00	119.59	1.59
CE2-CZ-OH	123.91	121.02	2.89
CLE-CE2-CZ	118.87	121.31	2.44
CZ-OH-HH	108.31	106.37	1.94

2.16 The small molecule 1 used for bonded terms optimization of (4S)-4-fluoro-L-proline (4FB)

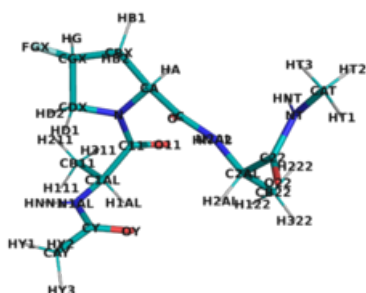


Figure S231: The energy minimized structure corresponding to 2-[1-(2-acetamidoacetyl)-4-fluoropyrrolidin-2-yl]formamido-N-methylacetamide.

Table S696: The calculated geometric terms of 2-[1-(2-acetamidoacetyl)-4-fluoropyrrolidin-2-yl]formamido-N-methylacetamide.

Terms	QM	CHARMM	Abs. diff.
N1AL-HNN1	1.01	0.99	0.02
N1AL-C1AL	1.46	1.46	0.00
N1AL-CY	1.37	1.34	0.03
C1AL-H1AL	1.09	1.08	0.01
C1AL-CB11	1.53	1.54	0.01
C1AL-C11	1.54	1.54	0.01
CB11-H111	1.10	1.11	0.01
CB11-H211	1.10	1.11	0.01
CB11-H311	1.09	1.11	0.02
C11-O11	1.23	1.23	0.00
C11-N	1.36	1.38	0.01
CAY-HY1	1.09	1.11	0.02
CAY-HY2	1.09	1.11	0.02
CAY-HY3	1.09	1.11	0.02
CAY-CY	1.52	1.48	0.04
CY-OY	1.23	1.22	0.00
N-CA	1.50	1.46	0.03
N-CDX	1.46	1.46	0.00
CA-HA	1.10	1.10	0.01
CA-CBX	1.54	1.56	0.02
CA-C	1.56	1.53	0.03
CBX-HB1	1.09	1.10	0.00
CBX-HB2	1.09	1.10	0.01
CBX-CGX	1.53	1.53	0.00
CGX-HG	1.10	1.09	0.01
CGX-FGX	1.39	1.37	0.02
CGX-CDX	1.53	1.51	0.02
CDX-HD1	1.10	1.10	0.01
CDX-HD2	1.09	1.10	0.01
C-O	1.23	1.22	0.00
C-N2AL	1.36	1.35	0.01
N2AL-HNN2	1.02	1.00	0.02

Terms	QM	CHARMM	Abs. diff.
N2AL-C2AL	1.47	1.45	0.01
C2AL-H2AL	1.10	1.08	0.01
C2AL-CB22	1.53	1.55	0.01
C2AL-C22	1.54	1.53	0.01
CB22-H122	1.10	1.11	0.02
CB22-H222	1.10	1.11	0.01
CB22-H322	1.09	1.11	0.02
C22-O22	1.22	1.23	0.01
C22-NT	1.37	1.35	0.02
NT-HNT	1.01	0.99	0.02
NT-CAT	1.45	1.44	0.01
CAT-HT1	1.09	1.12	0.03
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.10	1.11	0.02
N1AL-C1AL-H1AL	108.78	105.59	3.19
N1AL-C1AL-CB11	111.15	111.93	0.78
N1AL-C1AL-C11	113.71	116.25	2.53
N1AL-CY-CAY	116.31	116.75	0.44
N1AL-CY-OY	121.01	122.05	1.04
HNN1-N1AL-C1AL	118.89	116.97	1.92
HNN1-N1AL-CY	119.73	119.16	0.57
C1AL-N1AL-CY	119.99	123.79	3.80
C1AL-CB11-H111	110.33	110.34	0.01
C1AL-CB11-H211	112.53	112.04	0.48
C1AL-CB11-H311	109.45	109.82	0.37
C1AL-C11-O11	117.42	117.28	0.13
C1AL-C11-N	120.92	123.31	2.38
H1AL-C1AL-CB11	108.59	106.60	1.98
H1AL-C1AL-C11	101.88	104.80	2.92
CB11-C1AL-C11	112.18	110.81	1.36
H111-CB11-H211	108.25	108.48	0.23
H111-CB11-H311	108.01	107.65	0.36
H211-CB11-H311	108.15	108.39	0.24
C11-N-CA	121.34	123.53	2.19
C11-N-CDX	127.63	125.53	2.11
O11-C11-N	121.53	119.41	2.11
CAY-CY-OY	122.68	121.20	1.48
HY1-CAY-HY2	109.18	109.01	0.18
HY1-CAY-HY3	108.86	109.12	0.26
HY1-CAY-CY	113.76	111.13	2.62
HY2-CAY-HY3	107.29	108.33	1.05
HY2-CAY-CY	108.71	109.51	0.80
HY3-CAY-CY	108.84	109.68	0.84
N-CA-HA	107.34	110.41	3.07
N-CA-CBX	104.31	104.41	0.10
N-CA-C	112.77	112.79	0.02
N-CDX-CGX	101.86	103.43	1.57
N-CDX-HD1	112.70	107.72	4.98
N-CDX-HD2	111.69	113.41	1.72
CA-N-CDX	109.84	110.21	0.37
CA-CBX-HB1	112.36	112.76	0.40
CA-CBX-HB2	108.56	113.17	4.61
CA-CBX-CGX	105.10	105.08	0.03
CA-C-O	120.96	119.17	1.79
CA-C-N2AL	115.57	118.57	3.00
HA-CA-CBX	112.41	106.95	5.46
HA-CA-C	108.27	108.57	0.30
CBX-CA-C	111.68	113.52	1.84

Terms	QM	CHARMM	Abs. diff.
CBX-CGX-HG	112.23	109.62	2.62
CBX-CGX-FGX	112.34	112.89	0.55
CBX-CGX-CDX	103.31	103.03	0.29
HB1-CBX-HB2	108.56	105.26	3.30
HB1-CBX-CGX	113.24	111.85	1.39
HB2-CBX-CGX	108.87	108.81	0.06
CGX-CDX-HD1	108.64	111.19	2.55
CGX-CDX-HD2	112.99	112.62	0.37
HG-CGX-FGX	107.46	108.53	1.08
HG-CGX-CDX	110.82	110.02	0.80
FGX-CGX-CDX	110.71	112.66	1.94
HD1-CDX-HD2	108.85	108.36	0.50
C-N2AL-HNN2	115.33	116.39	1.06
C-N2AL-C2AL	120.46	124.77	4.32
O-C-N2AL	123.45	122.26	1.19
N2AL-C2AL-H2AL	108.97	107.24	1.72
N2AL-C2AL-CB22	109.55	109.40	0.15
N2AL-C2AL-C22	113.08	114.64	1.55
HNN2-N2AL-C2AL	117.20	115.32	1.88
C2AL-CB22-H122	110.39	109.81	0.58
C2AL-CB22-H222	111.29	111.23	0.06
C2AL-CB22-H322	109.51	110.55	1.04
C2AL-C22-O22	120.94	121.40	0.45
C2AL-C22-NT	114.78	116.85	2.07
H2AL-C2AL-CB22	109.50	108.95	0.54
H2AL-C2AL-C22	104.79	106.33	1.54
CB22-C2AL-C22	110.81	110.08	0.73
H122-CB22-H222	108.81	108.42	0.39
H122-CB22-H322	108.36	108.02	0.34
H222-CB22-H322	108.41	108.72	0.31
C22-NT-HNT	116.13	117.88	1.75
C22-NT-CAT	121.34	123.08	1.74
O22-C22-NT	123.74	121.75	1.98
NT-CAT-HT1	107.74	111.96	4.22
NT-CAT-HT2	110.09	110.31	0.21
NT-CAT-HT3	112.18	109.88	2.30
HNT-NT-CAT	118.12	118.32	0.19
HT1-CAT-HT2	109.42	108.03	1.39
HT1-CAT-HT3	108.38	108.07	0.31
HT2-CAT-HT3	108.98	108.49	0.49

2.17 The small molecule 2 used for bonded terms optimization of (4S)-4-fluoro-L-proline (4FB)

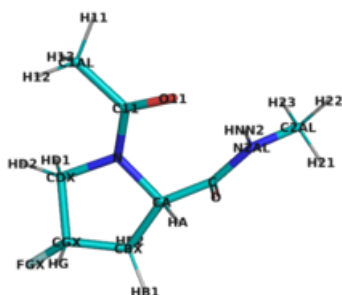


Figure S232: The energy minimized structure corresponding to (2S,4S)-1-acetyl-4-fluoro-N-methylpyrrolidine-2-carboxamide.

Table S697: The calculated geometric terms of (2S,4S)-1-acetyl-4-fluoro-N-methylpyrrolidine-2-carboxamide.

Terms	QM	CHARMM	Abs. diff.
C1AL-H11	1.09	1.11	0.02
C1AL-H12	1.09	1.11	0.02
C1AL-H13	1.09	1.11	0.02
C1AL-C11	1.51	1.49	0.03
C11-O11	1.24	1.23	0.02
C11-N	1.36	1.37	0.00
N-CA	1.48	1.47	0.01
N-CDX	1.46	1.47	0.01
CA-HA	1.10	1.10	0.01
CA-CBX	1.53	1.55	0.02
CA-C	1.54	1.52	0.02
CBX-HB1	1.09	1.10	0.01
CBX-HB2	1.09	1.10	0.01
CBX-CGX	1.52	1.52	0.00
CGX-HG	1.10	1.09	0.01
CGX-FGX	1.39	1.37	0.03
CGX-CDX	1.52	1.52	0.01
CDX-HD1	1.10	1.10	0.00
CDX-HD2	1.09	1.10	0.01
C-O	1.24	1.23	0.01
C-N2AL	1.35	1.34	0.01
N2AL-HNN2	1.02	1.00	0.02
N2AL-C2AL	1.45	1.44	0.01
C2AL-H21	1.09	1.11	0.02
C2AL-H22	1.09	1.11	0.02
C2AL-H23	1.10	1.11	0.02
C1AL-C11-O11	121.44	118.84	2.61
C1AL-C11-N	117.24	118.09	0.85
H11-C1AL-H12	108.87	108.43	0.44
H11-C1AL-H13	109.57	108.55	1.01
H11-C1AL-C11	107.51	108.99	1.48
H12-C1AL-H13	108.14	109.82	1.68

Terms	QM	CHARMM	Abs. diff.
H12-C1AL-C11	111.14	110.39	0.76
H13-C1AL-C11	111.57	110.61	0.97
C11-N-CA	120.39	123.01	2.62
C11-N-CDX	127.74	123.30	4.44
O11-C11-N	121.32	123.07	1.76
N-CA-HA	107.92	110.20	2.28
N-CA-CBX	104.02	103.49	0.53
N-CA-C	109.70	114.92	5.21
N-CDX-CGX	101.36	103.90	2.54
N-CDX-HD1	111.80	108.09	3.71
N-CDX-HD2	111.93	113.90	1.97
CA-N-CDX	110.75	111.34	0.59
CA-CBX-HB1	112.53	113.10	0.57
CA-CBX-HB2	108.88	112.03	3.15
CA-CBX-CGX	104.91	103.73	1.18
CA-C-O	122.27	119.80	2.47
CA-C-N2AL	113.81	118.08	4.27
HA-CA-CBX	113.35	106.96	6.39
HA-CA-C	109.82	108.45	1.37
CBX-CA-C	111.78	112.50	0.73
CBX-CGX-HG	112.51	110.00	2.51
CBX-CGX-FGX	111.97	113.12	1.16
CBX-CGX-CDX	103.44	102.34	1.09
HB1-CBX-HB2	108.77	106.36	2.41
HB1-CBX-CGX	113.26	113.18	0.07
HB2-CBX-CGX	108.33	108.47	0.15
CGX-CDX-HD1	108.93	111.52	2.59
CGX-CDX-HD2	113.44	111.38	2.06
HG-CGX-FGX	107.53	108.50	0.97
HG-CGX-CDX	110.60	110.05	0.55
FGX-CGX-CDX	110.82	112.72	1.89
HD1-CDX-HD2	109.20	108.03	1.17
C-N2AL-HNN2	116.36	117.96	1.61
C-N2AL-C2AL	120.14	122.51	2.36
O-C-N2AL	123.92	122.12	1.81
N2AL-C2AL-H21	108.93	110.76	1.84
N2AL-C2AL-H22	108.71	110.41	1.70
N2AL-C2AL-H23	111.97	110.55	1.43
HNN2-N2AL-C2AL	119.98	118.85	1.14
H21-C2AL-H22	109.57	108.42	1.16
H21-C2AL-H23	108.30	108.19	0.10
H22-C2AL-H23	109.33	108.43	0.91

2.18 The small molecule used for bonded terms optimization of 4-fluoro-tryptophan (4FW)

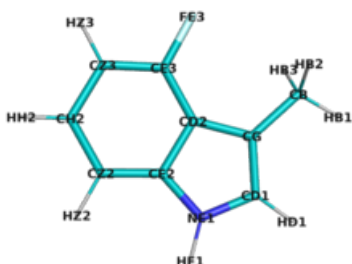


Figure S233: The energy minimized structure corresponding to 4-fluoro-3-methyl-1H-indole.

Table S698: The calculated geometric terms of 4-fluoro-3-methyl-1H-indole.

Terms	QM	CHARMM	Abs. diff.
CD1-NE1-CE2	109.56	111.00	1.44
HD1-CD1-NE1	120.58	123.95	3.37
CD2-CE2-NE1	106.33	106.14	0.19
CD2-CE2-CZ2	122.94	121.08	1.85
CD2-CE3-FE3	118.51	121.16	2.65
CD2-CE3-CZ3	121.60	121.21	0.40
NE1-CE2-CZ2	130.73	132.78	2.05
HE1-NE1-CE2	125.24	123.20	2.04
CE2-CD2-CE3	117.07	118.60	1.53
CE2-CZ2-HZ2	121.69	119.56	2.12
CE2-CZ2-CH2	117.19	120.05	2.86
CE3-CZ3-HZ3	119.34	119.84	0.51
CE3-CZ3-CH2	119.51	119.75	0.24
FE3-CE3-CZ3	119.89	117.63	2.26
CZ2-CH2-CZ3	121.69	119.32	2.38
CZ2-CH2-HH2	119.50	120.62	1.12
HZ2-CZ2-CH2	121.12	120.39	0.74
CZ3-CH2-HH2	118.81	120.06	1.26
HZ3-CZ3-CH2	121.15	120.41	0.74

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.50	1.50	0.01
CG-CD1	1.38	1.37	0.01
CG-CD2	1.43	1.44	0.01
CD1-HD1	1.08	1.08	0.00
CD1-NE1	1.38	1.39	0.00
CD2-CE2	1.42	1.40	0.02
CD2-CE3	1.40	1.39	0.01
NE1-HE1	1.01	1.01	0.00
NE1-CE2	1.38	1.37	0.01
CE2-CZ2	1.40	1.39	0.02
CE3-FE3	1.36	1.36	0.00
CE3-CZ3	1.38	1.39	0.01
CZ2-HZ2	1.09	1.08	0.01
CZ2-CH2	1.39	1.40	0.01
CZ3-HZ3	1.09	1.08	0.00
CZ3-CH2	1.41	1.40	0.01
CH2-HH2	1.09	1.08	0.00
HB3-CB-HB1	108.18	108.91	0.73
HB3-CB-HB2	107.23	108.56	1.33
HB3-CB-CG	111.31	109.74	1.57
CB-CG-CD1	127.44	127.59	0.15
CB-CG-CD2	126.93	125.44	1.49
HB1-CB-HB2	108.18	108.91	0.72
HB1-CB-CG	110.49	110.95	0.47
HB2-CB-CG	111.31	109.74	1.57
CG-CD1-HD1	129.37	128.20	1.17
CG-CD1-NE1	110.05	107.85	2.20
CG-CD2-CE2	108.43	108.04	0.39
CG-CD2-CE3	134.50	133.36	1.14
CD1-CG-CD2	105.63	106.96	1.34
CD1-NE1-HE1	125.19	125.79	0.60

2.19 The small molecule used for bonded terms optimization of O-[(S)-hydroxy[(3R)-3-hydroxy-2,2-dimethyl-4-oxo-4-(3-oxo-3-[(2-sulfanylethyl)amino]propylamino)butyl]oxyphosphoryl]-L-serine (4HH)

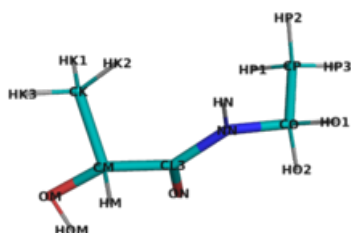


Figure S234: The energy minimized structure corresponding to (2R)-N-ethyl-2-hydroxypropanamide.

Table S699: The calculated geometric terms of (2R)-N-ethyl-2-hydroxypropanamide.

Terms	QM	CHARMM	Abs. diff.
CK-HK1	1.09	1.11	0.02
CK-HK2	1.10	1.11	0.01
CK-HK3	1.09	1.11	0.02
CK-CM	1.53	1.55	0.02
CM-HM	1.10	1.11	0.01
CM-OM	1.41	1.43	0.02
CM-CL3	1.53	1.53	0.00
OM-HOM	0.98	0.96	0.02
CL3-ON	1.24	1.23	0.01
CL3-NN	1.35	1.35	0.00
NN-HN	1.01	0.99	0.02
NN-CO	1.46	1.44	0.02
CO-HO1	1.09	1.12	0.02
CO-HO2	1.09	1.12	0.03
CO-CP	1.52	1.53	0.00
CP-HP1	1.09	1.11	0.02
CP-HP2	1.09	1.11	0.02
CP-HP3	1.09	1.11	0.02
CK-CM-HM	109.84	108.60	1.23
CK-CM-OM	110.36	107.41	2.95
CK-CM-CL3	110.41	112.64	2.23
HK1-CK-HK2	108.92	109.09	0.17
HK1-CK-HK3	108.53	107.72	0.81
HK1-CK-CM	109.29	110.22	0.93
HK2-CK-HK3	108.77	108.12	0.65
HK2-CK-CM	112.14	111.99	0.15
HK3-CK-CM	109.12	109.59	0.46
CM-OM-HOM	104.13	106.30	2.16

Terms	QM	CHARMM	Abs. diff.
CM-CL3-ON	119.92	121.74	1.81
CM-CL3-NN	117.02	117.52	0.50
HM-CM-OM	108.51	107.31	1.19
HM-CM-CL3	109.19	106.83	2.36
OM-CM-CL3	108.50	113.82	5.33
CL3-NN-HN	118.88	120.38	1.50
CL3-NN-CO	121.36	122.91	1.55
ON-CL3-NN	123.05	120.72	2.33
NN-CO-HO1	107.51	108.01	0.50
NN-CO-HO2	107.06	110.72	3.65
NN-CO-CP	112.47	115.88	3.41
HN-NN-CO	119.23	116.47	2.76
CO-CP-HP1	109.64	109.95	0.31
CO-CP-HP2	110.89	110.47	0.41
CO-CP-HP3	110.52	110.72	0.20
HO1-CO-HO2	107.97	105.35	2.62
HO1-CO-CP	111.28	108.02	3.27
HO2-CO-CP	110.33	108.32	2.01
HP1-CP-HP2	108.86	108.40	0.45
HP1-CP-HP3	108.50	108.44	0.06
HP2-CP-HP3	108.38	108.79	0.41

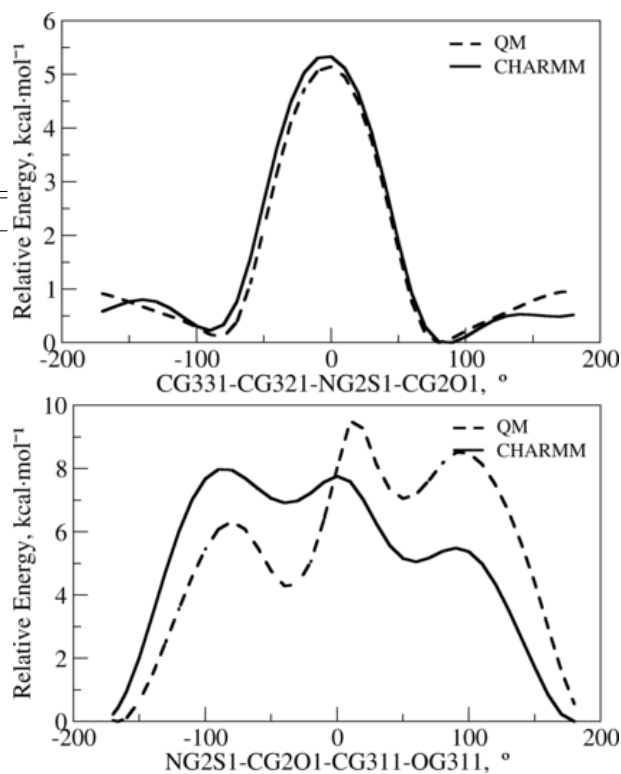


Figure S235: The PES scan for flexible dihedrals corresponding to (2R)-N-ethyl-2-hydroxypropanamide.

2.21 The small molecule used for bonded terms optimization of 4-amino-1-tryptophan (4IN)

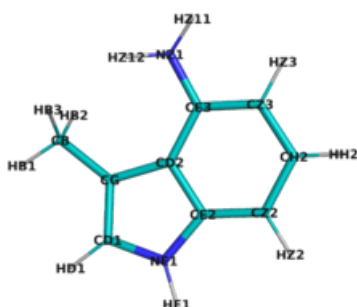


Figure S237: The energy minimized structure corresponding to 3-methyl-1H-indol-4-amine.

Table S701: The calculated geometric terms of 3-methyl-1H-indol-4-amine.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.10	1.11	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.50	1.51	0.01
CG-CD1	1.38	1.37	0.01
CG-CD2	1.44	1.44	0.01
CD1-HD1	1.08	1.08	0.00
CD1-NE1	1.38	1.38	0.01
CD2-CE2	1.42	1.40	0.02
CD2-CE3	1.42	1.41	0.01
NE1-HE1	1.01	1.01	0.00
NE1-CE2	1.38	1.37	0.01
CE2-CZ2	1.40	1.38	0.02
CZ2-HZ2	1.09	1.08	0.01
CZ2-CH2	1.39	1.40	0.01
CZ3-HZ3	1.09	1.08	0.01
CZ3-CE3	1.39	1.40	0.00
CZ3-CH2	1.41	1.40	0.01
CE3-NZ1	1.41	1.39	0.02
NZ1-HZ11	1.02	1.00	0.02
NZ1-HZ12	1.02	1.00	0.02
CH2-HH2	1.09	1.08	0.00
HB3-CB-HB1	106.99	108.67	1.68
HB3-CB-HB2	107.78	109.15	1.37
HB3-CB-CG	112.32	109.88	2.44
CB-CG-CD1	125.43	126.40	0.97
CB-CG-CD2	128.46	126.55	1.92
HB1-CB-HB2	107.97	108.64	0.67
HB1-CB-CG	110.18	110.74	0.57
HB2-CB-CG	111.40	109.72	1.68
CG-CD1-HD1	129.35	128.13	1.21
CG-CD1-NE1	109.88	108.02	1.86
CG-CD2-CE2	107.62	107.51	0.11
CG-CD2-CE3	133.84	133.23	0.61

Terms	QM	CHARMM	Abs. diff.
CD1-CG-CD2	106.09	107.05	0.96
CD1-NE1-HE1	125.31	126.38	1.07
CD1-NE1-CE2	109.53	110.96	1.43
HD1-CD1-NE1	120.78	123.85	3.07
CD2-CE2-NE1	106.88	106.46	0.42
CD2-CE2-CZ2	123.36	121.47	1.89
CD2-CE3-CZ3	118.11	119.13	1.01
CD2-CE3-NZ1	120.11	123.81	3.70
NE1-CE2-CZ2	129.70	132.07	2.37
HE1-NE1-CE2	125.13	122.66	2.46
CE2-CD2-CE3	118.46	119.25	0.79
CE2-CZ2-HZ2	121.86	119.96	1.89
CE2-CZ2-CH2	116.54	119.47	2.93
CZ2-CH2-CZ3	121.53	119.69	1.84
CZ2-CH2-HH2	119.57	120.35	0.78
HZ2-CZ2-CH2	121.57	120.56	1.00
CZ3-CE3-NZ1	121.40	117.06	4.34
CZ3-CH2-HH2	118.87	119.96	1.08
HZ3-CZ3-CE3	118.99	119.83	0.84
HZ3-CZ3-CH2	119.14	119.17	0.03
CE3-CZ3-CH2	121.78	120.99	0.80
CE3-NZ1-HZ11	111.75	111.35	0.40
CE3-NZ1-HZ12	112.60	111.64	0.96
HZ11-NZ1-HZ12	109.14	120.05	10.91

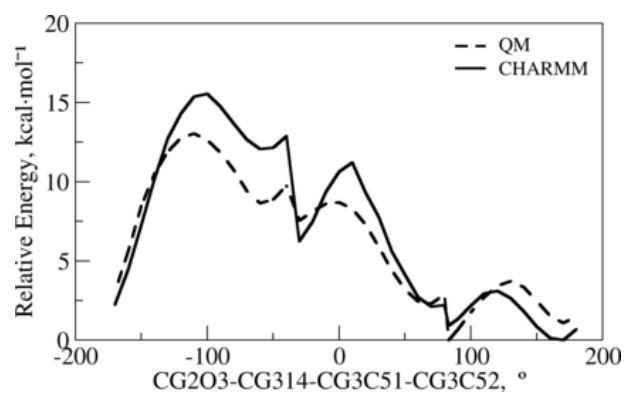


Figure S239: The PES scan for flexible dihedral corresponding to 2-[3-(ethylsulfanyl)-1,2-oxazolidin-5-yl]-2-(trihydridonickelio)aceticacid.

2.23 The small molecule used for bonded terms optimization of (2R)-2-azanyl-3-[(3R)-1-ethyl-2,5-bis(oxidanylidene)pyrrolidin-3-yl]sulfanyl-propanoicacid (6V1)

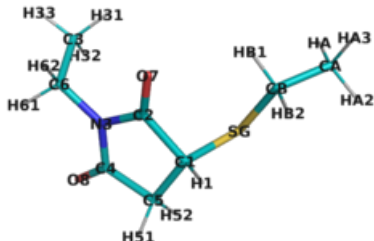


Figure S240: The energy minimized structure corresponding to (3R)-1-ethyl-3-(ethylsulfanyl)pyrrolidine-2,5-dione.

Table S703: The calculated geometric terms of (3R)-1-ethyl-3-(ethylsulfanyl)pyrrolidine-2,5-dione.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.82	1.82	0.00
SG-C1	1.82	1.83	0.01
C1-H1	1.09	1.10	0.00
C1-C2	1.52	1.54	0.01
C1-C5	1.53	1.53	0.01
C2-O7	1.22	1.23	0.01
C2-N3	1.39	1.38	0.01
C5-H51	1.10	1.10	0.01
C5-H52	1.09	1.10	0.00
C5-C4	1.52	1.52	0.00
C4-O8	1.22	1.23	0.01
C4-N3	1.39	1.38	0.01
N3-C6	1.46	1.44	0.01
C6-H61	1.09	1.12	0.02
C6-H62	1.09	1.12	0.02
C6-C3	1.52	1.53	0.01
C3-H31	1.09	1.11	0.02
C3-H32	1.09	1.11	0.02
C3-H33	1.09	1.11	0.02
HA3-CA-HA2	108.19	108.40	0.21
HA3-CA-HA	108.10	108.30	0.20
HA3-CA-CB	109.65	110.49	0.83
HA2-CA-HA	108.37	108.42	0.05

Terms	QM	CHARMM	Abs. diff.
HA2-CA-CB	111.34	110.65	0.69
CA-CB-HB1	111.16	108.33	2.83
CA-CB-HB2	110.49	108.67	1.81
CA-CB-SG	109.00	112.66	3.66
HA-CA-CB	111.08	110.51	0.58
CB-SG-C1	100.62	100.66	0.04
HB1-CB-HB2	108.20	106.98	1.21
HB1-CB-SG	109.27	110.18	0.91
HB2-CB-SG	108.68	109.84	1.16
SG-C1-H1	109.28	111.34	2.06
SG-C1-C2	109.40	107.37	2.03
SG-C1-C5	109.66	109.37	0.29
C1-C2-O7	127.48	127.01	0.48
C1-C2-N3	107.74	105.20	2.54
C1-C5-H51	111.44	110.75	0.70
C1-C5-H52	114.37	114.58	0.20
C1-C5-C4	104.76	105.27	0.50
H1-C1-C2	110.25	111.41	1.17
H1-C1-C5	113.90	112.43	1.48
C2-C1-C5	104.20	104.59	0.40
C2-N3-C4	113.53	116.99	3.45
C2-N3-C6	123.01	121.11	1.90
O7-C2-N3	124.76	127.80	3.04
C5-C4-O8	128.03	126.43	1.59
C5-C4-N3	107.24	105.15	2.08
H51-C5-H52	107.54	105.80	1.74
H51-C5-C4	108.42	108.17	0.25
H52-C5-C4	110.17	112.20	2.03
C4-N3-C6	123.26	121.59	1.67
O8-C4-N3	124.70	128.39	3.69
N3-C6-H61	106.73	109.16	2.43
N3-C6-H62	106.75	108.80	2.05
N3-C6-C3	111.23	117.72	6.49
C6-C3-H31	110.24	110.54	0.29
C6-C3-H32	110.22	110.40	0.18
C6-C3-H33	110.26	110.56	0.30
H61-C6-H62	109.24	104.97	4.27
H61-C6-C3	111.34	107.64	3.69
H62-C6-C3	111.34	107.81	3.53
H31-C3-H32	109.07	108.52	0.55
H31-C3-H33	108.48	108.41	0.08
H32-C3-H33	108.52	108.35	0.17

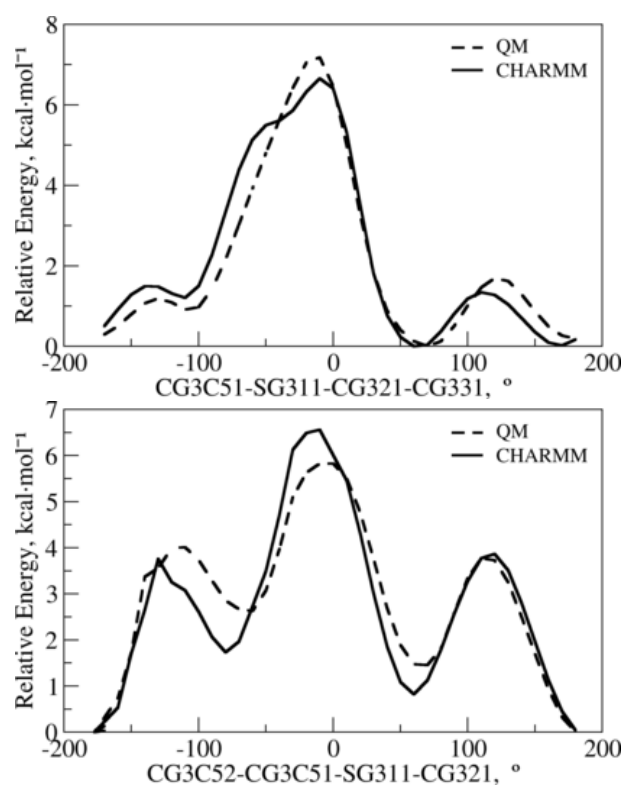


Figure S241: The PES scan for flexible dihedrals corresponding to (3R)-1-ethyl-3-(ethylsulfanyl)pyrrolidine-2,5-dione.

2.24 The small molecule 1 used for bonded terms optimization of (2S)-2,3-dihydro-1H-pyrrole-2-carboxylic acid (8LJ)

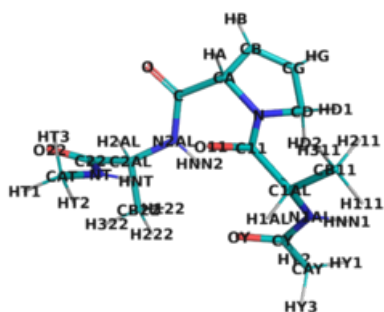


Figure S242: The energy minimized structure corresponding to 2-[1-(2-acetamidoacetyl)-2,5-dihydro-1H-pyrrol-2-yl]formamido-N-methylacetamide.

Table S704: The calculated geometric terms of 2-[1-(2-acetamidoacetyl)-2,5-dihydro-1H-pyrrol-2-yl]formamido-N-methylacetamide.

Terms	QM	CHARMM	Abs. diff.
N1AL-HNN1	1.01	0.99	0.02
N1AL-C1AL	1.46	1.45	0.01
N1AL-CY	1.37	1.34	0.03
C1AL-H1AL	1.10	1.08	0.01
C1AL-CB11	1.53	1.54	0.01
C1AL-C11	1.54	1.54	0.01
CB11-H111	1.10	1.11	0.01
CB11-H211	1.10	1.11	0.01
CB11-H311	1.09	1.11	0.02
C11-O11	1.23	1.23	0.00
C11-N	1.36	1.37	0.01
CAY-HY1	1.09	1.11	0.01
CAY-HY2	1.09	1.11	0.02
CAY-HY3	1.10	1.11	0.02
CAY-CY	1.52	1.48	0.04
CY-OY	1.23	1.22	0.01
N-CA	1.48	1.45	0.03
N-CD	1.48	1.46	0.02
CA-HA	1.10	1.10	0.01
CA-CB	1.51	1.52	0.02
CA-C	1.55	1.52	0.02
CB-HB	1.08	1.09	0.00
CB-CG	1.33	1.37	0.04
CG-HG	1.08	1.08	0.00
CG-CD	1.51	1.51	0.00
CD-HD1	1.10	1.10	0.00
CD-HD2	1.10	1.10	0.00
C-O	1.22	1.23	0.01
C-N2AL	1.36	1.35	0.01
N2AL-HNN2	1.02	1.00	0.02
N2AL-C2AL	1.46	1.45	0.01

Terms	QM	CHARMM	Abs. diff.
C2AL-H2AL	1.09	1.08	0.01
C2AL-CB22	1.53	1.54	0.01
C2AL-C22	1.55	1.53	0.02
CB22-H122	1.10	1.11	0.01
CB22-H222	1.09	1.11	0.02
CB22-H322	1.09	1.11	0.02
C22-O22	1.22	1.23	0.00
C22-NT	1.37	1.35	0.02
NT-HNT	1.02	1.00	0.02
NT-CAT	1.45	1.45	0.01
CAT-HT1	1.09	1.11	0.02
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.10	1.11	0.01
N1AL-C1AL-H1AL	108.80	106.37	2.43
N1AL-C1AL-CB11	110.61	110.30	0.31
N1AL-C1AL-C11	114.25	116.95	2.69
N1AL-CY-CAY	116.49	117.05	0.56
N1AL-CY-OY	121.32	121.96	0.64
HNN1-N1AL-C1AL	117.30	116.13	1.16
HNN1-N1AL-CY	118.32	119.35	1.04
C1AL-N1AL-CY	120.84	123.26	2.42
C1AL-CB11-H111	110.50	110.05	0.45
C1AL-CB11-H211	112.26	111.78	0.48
C1AL-CB11-H311	109.37	110.44	1.06
C1AL-C11-O11	117.82	116.28	1.54
C1AL-C11-N	120.92	124.01	3.09
H1AL-C1AL-CB11	108.86	106.90	1.96
H1AL-C1AL-C11	102.47	104.76	2.29
CB11-C1AL-C11	111.40	110.84	0.56
H111-CB11-H211	108.38	108.44	0.06
H111-CB11-H311	107.92	107.70	0.22
H211-CB11-H311	108.29	108.32	0.03
C11-N-CA	118.55	121.28	2.73
C11-N-CD	129.29	125.40	3.88
O11-C11-N	121.18	119.71	1.47
CAY-CY-OY	122.18	120.98	1.20
HY1-CAY-HY2	109.32	108.91	0.41
HY1-CAY-HY3	108.69	109.09	0.40
HY1-CAY-CY	113.62	111.49	2.13
HY2-CAY-HY3	107.34	108.21	0.88
HY2-CAY-CY	108.91	109.62	0.71
HY3-CAY-CY	108.77	109.45	0.68
N-CA-HA	109.97	111.20	1.23
N-CA-CB	102.23	102.90	0.67
N-CA-C	117.01	115.48	1.53
N-CD-CG	102.23	103.39	1.16
N-CD-HD1	111.55	110.72	0.83
N-CD-HD2	111.77	109.85	1.92
CA-N-CD	111.95	112.98	1.02
CA-CB-HB	120.96	122.35	1.39
CA-CB-CG	111.76	110.53	1.23
CA-C-O	118.00	118.42	0.42
CA-C-N2AL	117.72	120.03	2.31
HA-CA-CB	112.37	109.47	2.90
HA-CA-C	104.23	108.95	4.72
CB-CA-C	111.29	108.56	2.73
CB-CG-HG	126.45	126.15	0.30
CB-CG-CD	111.70	110.08	1.62

Terms	QM	CHARMM	Abs. diff.
HB-CB-CG	127.26	127.11	0.15
CG-CD-HD1	112.35	112.31	0.03
CG-CD-HD2	112.00	112.32	0.32
HG-CG-CD	121.84	123.74	1.90
HD1-CD-HD2	107.03	108.20	1.17
C-N2AL-HNN2	119.46	119.83	0.37
C-N2AL-C2AL	120.73	123.22	2.50
O-C-N2AL	124.26	121.55	2.71
N2AL-C2AL-H2AL	107.88	107.03	0.85
N2AL-C2AL-CB22	110.56	110.29	0.27
N2AL-C2AL-C22	113.30	114.73	1.43
HNN2-N2AL-C2AL	117.18	115.29	1.89
C2AL-CB22-H122	110.47	110.04	0.43
C2AL-CB22-H222	111.40	111.00	0.40
C2AL-CB22-H322	109.20	110.48	1.28
C2AL-C22-O22	120.33	121.31	0.98
C2AL-C22-NT	115.44	117.27	1.83
H2AL-C2AL-CB22	109.82	108.36	1.47
H2AL-C2AL-C22	104.16	105.66	1.49
CB22-C2AL-C22	110.85	110.44	0.41
H122-CB22-H222	108.38	108.42	0.04
H122-CB22-H322	108.55	108.07	0.48
H222-CB22-H322	108.78	108.76	0.02
C22-NT-HNT	117.94	119.58	1.64
C22-NT-CAT	120.08	122.69	2.60
O22-C22-NT	123.60	121.40	2.21
NT-CAT-HT1	108.68	111.19	2.51
NT-CAT-HT2	109.17	110.36	1.19
NT-CAT-HT3	112.34	110.76	1.58
HNT-NT-CAT	116.50	117.44	0.93
HT1-CAT-HT2	109.59	107.96	1.62
HT1-CAT-HT3	108.15	108.12	0.03
HT2-CAT-HT3	108.88	108.33	0.55

2.25 The small molecule 2 used for bonded terms optimization of (2S)-2,3-dihydro-1H-pyrrole-2-carboxylic acid (8LJ)

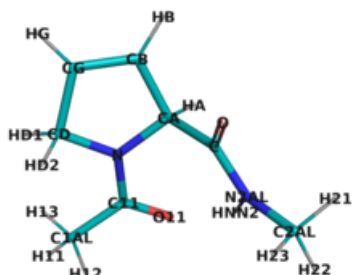


Figure S243: The energy minimized structure corresponding to (2S)-1-acetyl-N-methyl-2,5-dihydro-1H-pyrrole-2-carboxamide.

Table S705: The calculated geometric terms of (2S)-1-acetyl-N-methyl-2,5-dihydro-1H-pyrrole-2-carboxamide.

Terms	QM	CHARMM	Abs. diff.
C1AL-H11	1.09	1.11	0.02
C1AL-H12	1.09	1.11	0.02
C1AL-H13	1.09	1.11	0.01
C1AL-C11	1.51	1.49	0.02
C11-O11	1.24	1.23	0.02
C11-N	1.36	1.36	0.00
N-CA	1.48	1.44	0.03
N-CD	1.47	1.45	0.01
CA-HA	1.10	1.10	0.00
CA-CB	1.50	1.53	0.03
CA-C	1.54	1.54	0.00
CB-HB	1.08	1.08	0.00
CB-CG	1.34	1.37	0.03
CG-HG	1.08	1.08	0.00
CG-CD	1.50	1.51	0.01
CD-HD1	1.10	1.10	0.01
CD-HD2	1.10	1.10	0.00
C-O	1.24	1.23	0.01
C-N2AL	1.35	1.35	0.01
N2AL-HNN2	1.02	1.00	0.02
N2AL-C2AL	1.45	1.44	0.01
C2AL-H21	1.09	1.11	0.02
C2AL-H22	1.09	1.11	0.02
C2AL-H23	1.10	1.11	0.02
C1AL-C11-O11	121.53	118.83	2.70
C1AL-C11-N	116.63	118.34	1.71
H11-C1AL-H12	109.71	108.48	1.24
H11-C1AL-H13	108.00	109.93	1.93
H11-C1AL-C11	111.69	110.47	1.22
H12-C1AL-H13	108.88	108.48	0.41
H12-C1AL-C11	107.81	108.98	1.17

Terms	QM	CHARMM	Abs. diff.
H13-C1AL-C11	110.72	110.46	0.26
C11-N-CA	120.73	122.58	1.85
C11-N-CD	125.50	124.09	1.41
O11-C11-N	121.84	122.83	0.98
N-CA-HA	108.64	112.04	3.40
N-CA-CB	102.00	101.79	0.21
N-CA-C	112.54	114.90	2.37
N-CD-CG	102.10	102.22	0.12
N-CD-HD1	111.02	111.23	0.21
N-CD-HD2	111.64	109.50	2.14
CA-N-CD	112.07	113.32	1.24
CA-CB-HB	122.09	122.75	0.66
CA-CB-CG	111.61	110.44	1.17
CA-C-O	121.58	121.28	0.30
CA-C-N2AL	114.35	117.43	3.08
HA-CA-CB	113.62	107.46	6.16
HA-CA-C	109.26	109.51	0.25
CB-CA-C	110.67	110.70	0.02
CB-CG-HG	126.08	126.07	0.01
CB-CG-CD	111.64	109.98	1.66
HB-CB-CG	126.22	126.55	0.33
CG-CD-HD1	112.36	112.29	0.08
CG-CD-HD2	112.01	113.03	1.02
HG-CG-CD	122.26	123.52	1.25
HD1-CD-HD2	107.71	108.47	0.76
C-N2AL-HNN2	117.15	118.36	1.21
C-N2AL-C2AL	120.33	122.51	2.18
O-C-N2AL	124.05	121.29	2.77
N2AL-C2AL-H21	109.24	110.69	1.45
N2AL-C2AL-H22	108.68	110.47	1.80
N2AL-C2AL-H23	111.88	110.58	1.30
HNN2-N2AL-C2AL	120.96	118.92	2.04
H21-C2AL-H22	109.56	108.36	1.20
H21-C2AL-H23	108.20	108.24	0.04
H22-C2AL-H23	109.26	108.42	0.84

2.26 The small molecule used for bonded terms optimization of cis-amcilenomycin (ACZ)

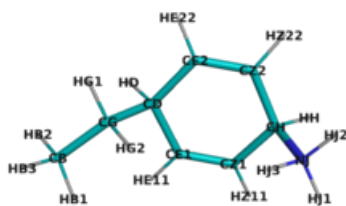


Figure S244: The energy minimized structure corresponding to (1s,4s)-4-ethylcyclohexa-2,5-dien-1-amine.

Table S706: The calculated geometric terms of (1s,4s)-4-ethylcyclohexa-2,5-dien-1-amine.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.53	1.54	0.01
CG-HG1	1.10	1.12	0.02
CG-HG2	1.10	1.11	0.01
CG-CD	1.55	1.56	0.01
CD-HD	1.10	1.11	0.01
CD-CE1	1.50	1.53	0.03
CD-CE2	1.50	1.53	0.03
CE1-HE11	1.09	1.10	0.02
CE1-CZ1	1.34	1.36	0.01
CE2-HE22	1.09	1.10	0.01
CE2-CZ2	1.34	1.36	0.01
CZ1-HZ11	1.09	1.10	0.01
CZ1-CH	1.49	1.52	0.03
CZ2-HZ22	1.09	1.10	0.01
CZ2-CH	1.49	1.52	0.03
CH-HH	1.10	1.12	0.02
CH-NJ	1.56	1.48	0.08
NJ-HJ1	1.03	1.04	0.01
NJ-HJ2	1.03	1.04	0.01
NJ-HJ3	1.03	1.04	0.01
HB3-CB-HB1	107.48	107.57	0.09
HB3-CB-HB2	107.71	107.75	0.03
HB3-CB-CG	110.19	110.27	0.08
CB-CG-HG1	109.59	107.16	2.43
CB-CG-HG2	110.31	109.01	1.30
CB-CG-CD	113.71	114.45	0.73
HB1-CB-HB2	108.31	108.48	0.17
HB1-CB-CG	112.08	111.70	0.38
HB2-CB-CG	110.90	110.92	0.02
CG-CD-HD	106.52	106.78	0.25

Terms	QM	CHARMM	Abs. diff.
CG-CD-CE1	111.87	110.44	1.43
CG-CD-CE2	110.09	109.34	0.75
HG1-CG-HG2	106.60	106.98	0.38
HG1-CG-CD	107.95	108.86	0.91
HG2-CG-CD	108.41	110.09	1.67
CD-CE1-HE11	117.42	116.46	0.96
CD-CE1-CZ1	124.04	122.75	1.29
CD-CE2-HE22	116.85	116.41	0.44
CD-CE2-CZ2	124.29	122.78	1.51
HD-CD-CE1	107.89	107.77	0.12
HD-CD-CE2	108.05	107.61	0.44
CE1-CD-CE2	112.16	114.56	2.41
CE1-CZ1-HZ11	120.63	120.41	0.22
CE1-CZ1-CH	121.74	121.57	0.17
HE11-CE1-CZ1	118.53	120.67	2.14
CE2-CZ2-HZ22	120.73	120.44	0.29
CE2-CZ2-CH	121.52	121.54	0.01
HE22-CE2-CZ2	118.86	120.72	1.86
CZ1-CH-CZ2	114.56	115.76	1.19
CZ1-CH-HH	111.83	109.16	2.67
CZ1-CH-NJ	107.16	107.26	0.10
HZ11-CZ1-CH	117.62	117.84	0.22
CZ2-CH-HH	111.92	109.14	2.77
CZ2-CH-NJ	107.09	107.31	0.22
HZ22-CZ2-CH	117.74	117.83	0.09
CH-NJ-HJ1	111.95	109.90	2.04
CH-NJ-HJ2	111.92	109.94	1.99
CH-NJ-HJ3	108.52	107.29	1.23
HH-CH-NJ	103.42	107.93	4.51
HJ1-NJ-HJ2	108.20	110.53	2.33
HJ1-NJ-HJ3	108.07	109.54	1.47
HJ2-NJ-HJ3	108.05	109.58	1.53

2.27 The small molecule used for bonded terms optimization of S-(S)-amino[(4-aminobutyl)amino]methyl-L-cysteine (AGT)

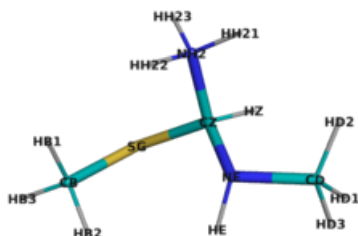


Figure S245: The energy minimized structure corresponding to [(S)-amino(methylsulfanyl)methyl](methyl)amine.

Table S707: The calculated geometric terms of [(S)-amino(methylsulfanyl)methyl](methyl)amine.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.82	1.83	0.01
SG-CZ	1.79	1.81	0.02
CZ-HZ	1.10	1.12	0.02
CZ-NH2	1.55	1.45	0.10
CZ-NE	1.42	1.46	0.04
NH2-HH21	1.03	1.04	0.01
NH2-HH22	1.03	1.04	0.01
NH2-HH23	1.03	1.04	0.01
NE-HE	1.02	1.03	0.01
NE-CD	1.47	1.48	0.01
CD-HD1	1.10	1.11	0.02
CD-HD2	1.09	1.11	0.02
CD-HD3	1.09	1.12	0.03
HB3-CB-HB1	107.66	107.10	0.56
HB3-CB-HB2	108.42	106.97	1.45
HB3-CB-SG	104.79	110.33	5.54
CB-SG-CZ	101.82	100.95	0.87
HB1-CB-HB2	110.25	108.17	2.08
HB1-CB-SG	112.97	112.14	0.83
HB2-CB-SG	112.41	111.88	0.53
SG-CZ-HZ	106.05	107.20	1.15
SG-CZ-NH2	109.52	110.51	1.00
SG-CZ-NE	116.21	116.63	0.41
CZ-NH2-HH21	111.41	109.12	2.30
CZ-NH2-HH22	108.20	106.69	1.51
CZ-NH2-HH23	111.71	110.71	1.00
CZ-NE-HE	110.12	111.86	1.74
CZ-NE-CD	115.06	116.88	1.82
HZ-CZ-NH2	103.72	107.28	3.55

Terms	QM	CHARMM	Abs. diff.
HZ-CZ-NE	115.50	109.38	6.12
NH2-CZ-NE	105.06	105.51	0.45
HH21-NH2-HH22	107.25	108.51	1.27
HH21-NH2-HH23	108.84	111.30	2.46
HH22-NH2-HH23	109.32	110.38	1.07
NE-CD-HD1	112.99	111.48	1.51
NE-CD-HD2	110.42	111.93	1.51
NE-CD-HD3	108.11	110.35	2.25
HE-NE-CD	110.39	105.86	4.53
HD1-CD-HD2	108.96	108.30	0.66
HD1-CD-HD3	109.17	107.43	1.74
HD2-CD-HD3	107.02	107.15	0.13

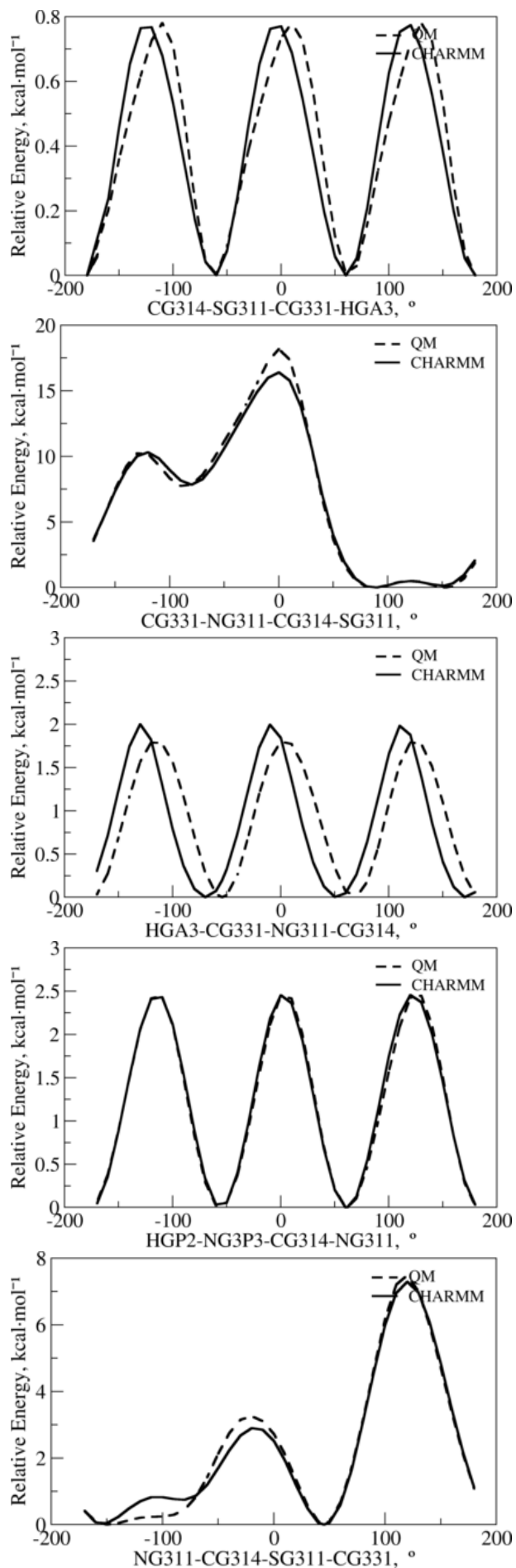


Figure S246: The PES scan for flexible dihedrals corresponding to [(S)-amino(methylsulfanyl)methyl](methyl)amine.

2.28 The small molecule used for bonded terms optimization of (3S)-3-(sulfooxy)-L-serine (ALS)

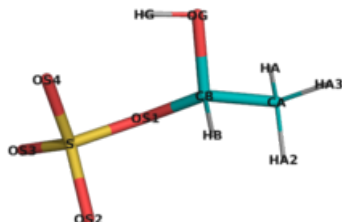


Figure S247: The energy minimized structure corresponding to [(1S)-1-hydroxyethoxy]sulfonic acid.

Table S708: The calculated geometric terms of [(1S)-1-hydroxyethoxy]sulfonic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.51	1.53	0.02
CB-HB	1.10	1.12	0.02
CB-OG	1.42	1.42	0.00
CB-OS1	1.43	1.41	0.01
OG-HG	0.99	0.97	0.02
OS1-S	1.71	1.56	0.15
S-OS2	1.48	1.45	0.03
S-OS3	1.47	1.45	0.02
S-OS4	1.50	1.45	0.04
HA3-CA-HA2	109.77	109.12	0.65
HA3-CA-HA	109.24	108.92	0.32
HA3-CA-CB	109.78	110.52	0.74
HA2-CA-HA	109.45	108.61	0.85
HA2-CA-CB	109.87	109.80	0.07
CA-CB-HB	111.87	106.68	5.19
CA-CB-OG	108.11	106.58	1.53
CA-CB-OS1	107.03	107.58	0.55
HA-CA-CB	108.70	109.84	1.13
CB-OG-HG	103.75	100.27	3.49
CB-OS1-S	113.15	112.76	0.38
HB-CB-OG	109.96	109.54	0.41
HB-CB-OS1	108.30	114.15	5.85
OG-CB-OS1	111.57	111.87	0.31
OS1-S-OS2	104.81	104.33	0.48
OS1-S-OS3	101.61	103.54	1.93
OS1-S-OS4	102.53	105.20	2.66
OS2-S-OS3	116.25	114.04	2.21
OS2-S-OS4	113.50	114.15	0.65
OS3-S-OS4	115.57	114.00	1.57

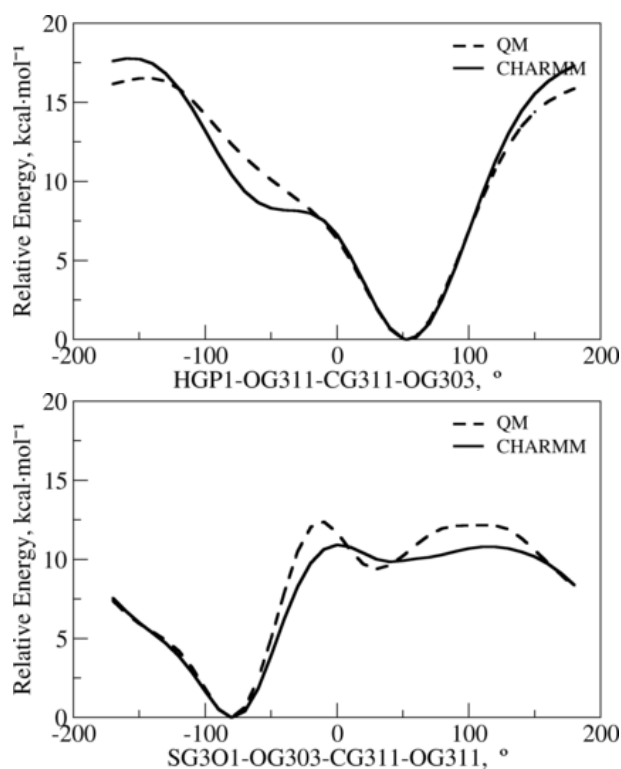


Figure S248: The PES scan for flexible dihedrals corresponding to [(1S)-1-hydroxyethoxy]sulfonic acid.

2.29 The small molecule used for bonded terms optimization of 5'-O-[(S)-[(5S)-5-amino-6-oxohexyl]amino(hydroxy)phosphoryl]adenosine (APK)

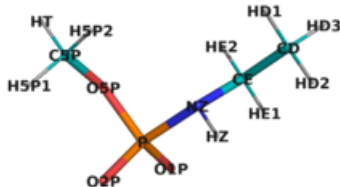


Figure S249: The energy minimized structure corresponding to (ethylamino)(methoxy)phosphinic acid.

Table S709: The calculated geometric terms of (ethylamino)(methoxy)phosphinic acid.

Terms	QM	CHARMM	Abs. diff.
HD3-CD	1.10	1.11	0.01
CD-HD1	1.09	1.11	0.02
CD-HD2	1.10	1.11	0.01
CD-CE	1.53	1.52	0.00
CE-HE1	1.10	1.12	0.02
CE-HE2	1.09	1.12	0.02
CE-NZ	1.46	1.42	0.04
NZ-HZ	1.02	1.02	0.00
NZ-P	1.74	1.71	0.03
P-O1P	1.51	1.50	0.01
P-O2P	1.52	1.50	0.01
P-O5P	1.68	1.63	0.05
O5P-C5P	1.43	1.43	0.00
C5P-H5P1	1.10	1.11	0.02
C5P-H5P2	1.10	1.11	0.02
C5P-HT	1.10	1.11	0.02
HD3-CD-HD1	108.95	108.24	0.70
HD3-CD-HD2	107.83	108.29	0.46
HD3-CD-CE	111.16	109.95	1.21
CD-CE-HE1	110.24	111.39	1.15
CD-CE-HE2	109.94	111.10	1.16
CD-CE-NZ	110.49	104.83	5.65
HD1-CD-HD2	107.94	108.67	0.73
HD1-CD-CE	110.19	110.59	0.40
HD2-CD-CE	110.68	111.03	0.34
CE-NZ-HZ	111.81	109.48	2.34
CE-NZ-P	116.76	116.07	0.69
HE1-CE-HE2	106.48	110.25	3.77
HE1-CE-NZ	112.48	109.90	2.58
HE2-CE-NZ	107.08	109.22	2.14
NZ-P-O1P	110.66	108.76	1.89

Terms	QM	CHARMM	Abs. diff.
NZ-P-O2P	105.36	107.65	2.29
NZ-P-O5P	98.72	102.65	3.93
HZ-NZ-P	108.55	110.28	1.73
P-O5P-C5P	115.83	117.84	2.01
O1P-P-O2P	124.68	119.47	5.21
O1P-P-O5P	104.96	108.63	3.67
O2P-P-O5P	109.48	108.38	1.09
O5P-C5P-H5P1	110.93	111.01	0.08
O5P-C5P-H5P2	110.74	111.01	0.27
O5P-C5P-HT	106.59	109.42	2.83
H5P1-C5P-H5P2	109.00	109.00	0.01
H5P1-C5P-HT	109.90	108.14	1.76
H5P2-C5P-HT	109.65	108.18	1.47

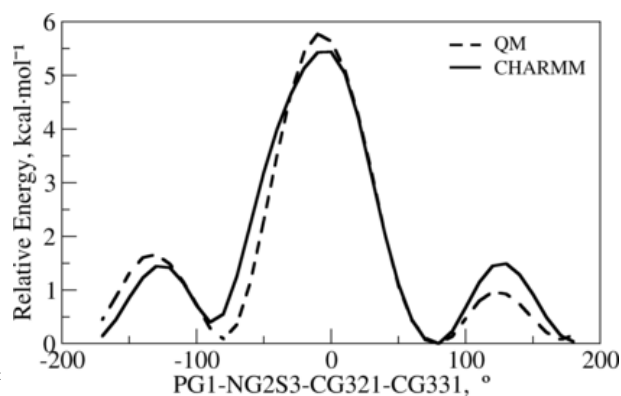


Figure S250: The PES scan for flexible dihedral corresponding to (ethylamino)(methoxy)phosphinic acid.

2.30 The small molecule used for bonded terms optimization of c-gamma-hydroxyarginine (ARO)

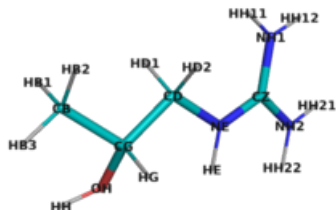


Figure S251: The energy minimized structure corresponding to N-[(2R)-2-hydroxypropyl]guanidine.

Table S710: The calculated geometric terms of N-[(2R)-2-hydroxypropyl]guanidine.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.10	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.52	1.53	0.02
CG-HG	1.09	1.11	0.02
CG-OH	1.43	1.42	0.01
CG-CD	1.53	1.56	0.03
OH-HH	0.97	0.96	0.01
CD-HD1	1.10	1.11	0.01
CD-HD2	1.09	1.10	0.01
CD-NE	1.46	1.49	0.03
NE-HE	1.02	1.00	0.02
NE-CZ	1.33	1.35	0.02
CZ-NH1	1.34	1.34	0.00
CZ-NH2	1.34	1.34	0.00
NH1-HH11	1.01	0.99	0.02
NH1-HH12	1.01	0.99	0.02
NH2-HH21	1.01	0.99	0.02
NH2-HH22	1.01	0.99	0.02
HB3-CB-HB1	108.74	108.29	0.45
HB3-CB-HB2	108.32	107.82	0.50
HB3-CB-CG	109.81	110.59	0.77
CB-CG-HG	110.31	109.63	0.69
CB-CG-OH	112.81	107.82	4.99
CB-CG-CD	112.25	109.09	3.16
HB1-CB-HB2	108.12	108.20	0.09
HB1-CB-CG	110.65	111.00	0.35
HB2-CB-CG	111.13	110.83	0.30
CG-OH-HH	108.61	106.51	2.09
CG-CD-HD1	110.24	107.03	3.21
CG-CD-HD2	110.45	108.38	2.08
CG-CD-NE	106.65	112.73	6.08
HG-CG-OH	104.83	108.63	3.80

Terms	QM	CHARMM	Abs. diff.
HG-CG-CD	108.15	109.08	0.92
OH-CG-CD	108.12	112.56	4.44
CD-NE-HE	112.88	116.84	3.96
CD-NE-CZ	126.78	125.01	1.77
HD1-CD-HD2	109.27	107.81	1.46
HD1-CD-NE	110.28	109.22	1.06
HD2-CD-NE	109.93	111.47	1.54
NE-CZ-NH1	120.93	120.77	0.16
NE-CZ-NH2	120.12	119.52	0.59
HE-NE-CZ	120.17	116.56	3.62
CZ-NH1-HH11	121.31	117.98	3.32
CZ-NH1-HH12	121.09	120.12	0.98
CZ-NH2-HH21	121.15	119.55	1.60
CZ-NH2-HH22	120.76	119.43	1.34
NH1-CZ-NH2	118.94	119.71	0.77
HH11-NH1-HH12	117.58	121.89	4.31
HH21-NH2-HH22	117.33	121.03	3.70

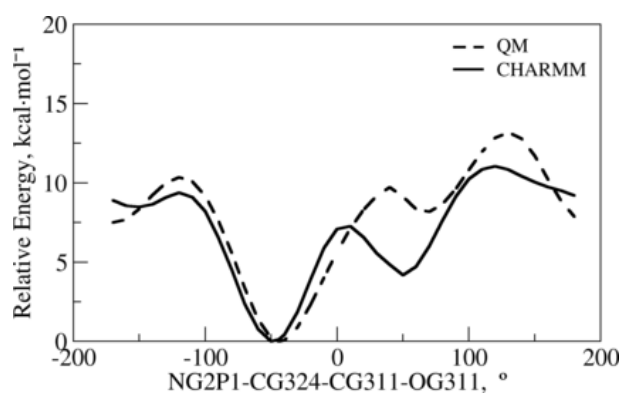


Figure S252: The PES scan for flexible dihedral corresponding to N-[(2R)-2-hydroxypropyl]guanidine.

2.31 The small molecule used for bonded terms optimization of aspartic acid-4-carboxymethyl ester (ASB)

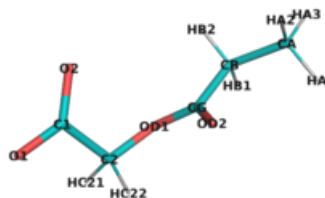


Figure S253: The energy minimized structure corresponding to 2-(propanoyloxy)acetic acid.

Table S711: The calculated geometric terms of 2-(propanoyloxy)acetic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.54	0.02
CB-HB1	1.10	1.11	0.01
CB-HB2	1.10	1.11	0.01
CB-CG	1.51	1.54	0.03
CG-OD2	1.23	1.22	0.01
CG-OD1	1.35	1.33	0.02
OD1-C2	1.45	1.46	0.01
C2-HC21	1.09	1.11	0.02
C2-HC22	1.09	1.11	0.02
C2-C1	1.55	1.54	0.01
C1-O1	1.27	1.26	0.01
C1-O2	1.26	1.26	0.01
HA3-CA-HA2	108.73	108.51	0.21
HA3-CA-HA	108.41	108.76	0.36
HA3-CA-CB	110.56	110.64	0.07
HA2-CA-HA	107.62	108.16	0.54
HA2-CA-CB	110.34	110.12	0.21
CA-CB-HB1	111.92	110.37	1.55
CA-CB-HB2	111.54	110.11	1.44
CA-CB-CG	113.04	112.73	0.31
HA-CA-CB	111.10	110.58	0.52
CB-CG-OD2	124.59	124.69	0.10
CB-CG-OD1	110.43	108.31	2.12
HB1-CB-HB2	106.65	108.67	2.03
HB1-CB-CG	108.44	107.96	0.48
HB2-CB-CG	104.81	106.85	2.05
CG-OD1-C2	114.56	115.25	0.69
OD2-CG-OD1	124.97	126.91	1.94
OD1-C2-HC21	104.74	108.63	3.89
OD1-C2-HC22	110.01	110.91	0.90

Terms	QM	CHARMM	Abs. diff.
OD1-C2-C1	111.53	116.59	5.06
C2-C1-O1	112.51	114.62	2.12
C2-C1-O2	116.61	117.40	0.79
HC21-C2-HC22	109.83	107.35	2.48
HC21-C2-C1	110.35	105.97	4.38
HC22-C2-C1	110.25	106.94	3.31
O1-C1-O2	130.88	127.97	2.91

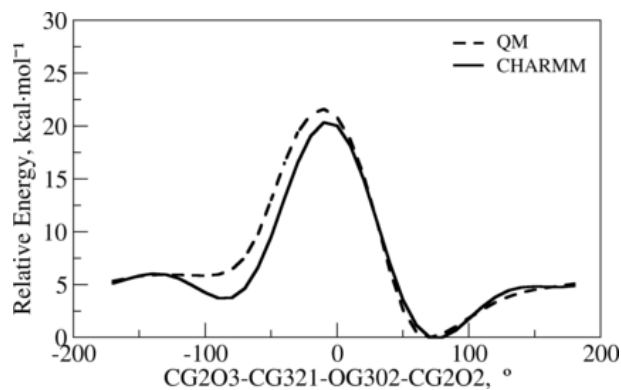


Figure S254: The PES scan for flexible dihedral corresponding to 2-(propanoyloxy)acetic acid.

2.32 The small molecule used for bonded terms optimization of asparticacid-4-carboxyethyl ester (ASL)

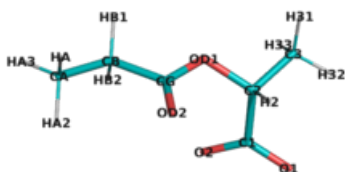


Figure S255: The energy minimized structure corresponding to (2R)-2-(propanoyloxy)propanoic acid.

Table S712: The calculated geometric terms of (2R)-2-(propanoyloxy)propanoic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.55	0.02
CB-HB1	1.10	1.11	0.01
CB-HB2	1.10	1.11	0.01
CB-CG	1.51	1.54	0.03
CG-OD2	1.23	1.22	0.01
CG-OD1	1.35	1.32	0.03
OD1-C2	1.46	1.45	0.01
C2-H2	1.10	1.11	0.02
C2-C1	1.56	1.56	0.00
C2-C3	1.52	1.55	0.03
C1-O1	1.27	1.26	0.01
C1-O2	1.26	1.26	0.00
C3-H31	1.10	1.11	0.01
C3-H32	1.09	1.11	0.02
C3-H33	1.10	1.11	0.02
HA3-CA-HA2	108.72	108.58	0.14
HA3-CA-HA	108.40	108.91	0.52
HA3-CA-CB	110.56	110.65	0.09
HA2-CA-HA	107.63	108.12	0.49
HA2-CA-CB	110.32	110.00	0.32
CA-CB-HB1	111.93	110.55	1.37
CA-CB-HB2	111.59	110.12	1.48
CA-CB-CG	113.06	113.05	0.01
HA-CA-CB	111.11	110.51	0.60
CB-CG-OD2	124.60	124.99	0.39
CB-CG-OD1	110.41	108.28	2.13
HB1-CB-HB2	106.70	108.70	2.00
HB1-CB-CG	108.43	107.95	0.48
HB2-CB-CG	104.68	106.29	1.61

Terms	QM	CHARMM	Abs. diff.
CG-OD1-C2	114.94	113.21	1.73
OD2-CG-OD1	124.98	126.66	1.68
OD1-C2-H2	108.66	110.46	1.80
OD1-C2-C1	110.12	115.77	5.65
OD1-C2-C3	105.69	105.91	0.22
C2-C1-O1	112.80	115.54	2.73
C2-C1-O2	116.70	117.01	0.31
C2-C3-H31	111.12	110.13	0.99
C2-C3-H32	108.65	110.04	1.39
C2-C3-H33	109.77	109.59	0.18
H2-C2-C1	108.83	106.23	2.60
H2-C2-C3	111.18	107.73	3.45
C1-C2-C3	112.28	110.53	1.75
O1-C1-O2	130.50	127.46	3.04
H31-C3-H32	109.78	109.30	0.48
H31-C3-H33	108.81	109.08	0.27
H32-C3-H33	108.68	108.68	0.00

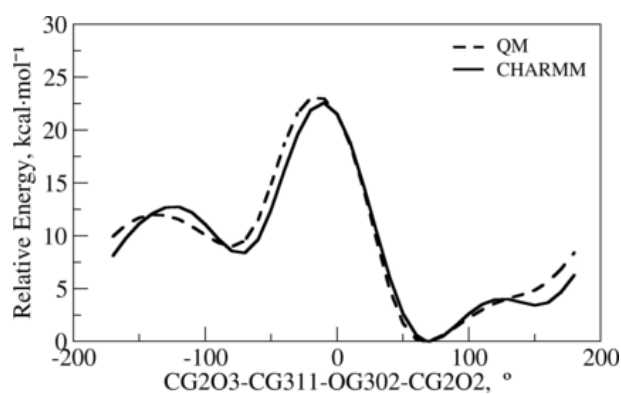


Figure S256: The PES scan for flexible dihedral corresponding to (2R)-2-(propanoyloxy)propanoic acid.

2.33 The small molecule 1 used for bonded terms optimization of azido-alanine (AZDA)

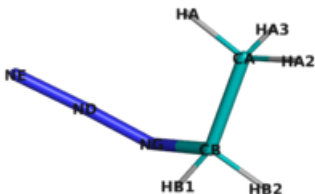


Figure S257: The energy minimized structure corresponding to 1-ethyl-2lambda4-triaza-1,2-diene.

Table S713: The calculated geometric terms of 1-ethyl-2lambda4-triaza-1,2-diene.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB1	1.10	1.12	0.02
CB-HB2	1.09	1.11	0.02
CB-NG	1.48	1.49	0.01
NG-ND	1.24	1.25	0.00
ND-NE	1.16	1.24	0.08
HA3-CA-HA2	108.75	108.48	0.27
HA3-CA-HA	108.52	108.37	0.15
HA3-CA-CB	110.23	110.13	0.10
HA2-CA-HA	108.11	108.45	0.34
HA2-CA-CB	110.23	110.49	0.26
CA-CB-HB1	111.18	109.94	1.24
CA-CB-HB2	111.16	109.06	2.10
CA-CB-NG	112.33	112.69	0.36
HA-CA-CB	110.93	110.85	0.08
CB-NG-ND	115.14	115.55	0.41
HB1-CB-HB2	107.92	107.09	0.83
HB1-CB-NG	109.63	109.87	0.24
HB2-CB-NG	104.32	108.00	3.68
NG-ND-NE	172.76	172.26	0.51

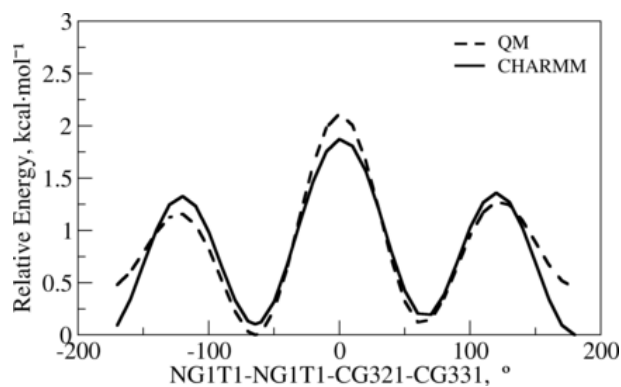


Figure S258: The PES scan for flexible dihedral corresponding to 1-ethyl-2lambda4-triaza-1,2-diene.

2.34 The small molecule 2 used for bonded terms optimization of azido-alanine (AZDA)

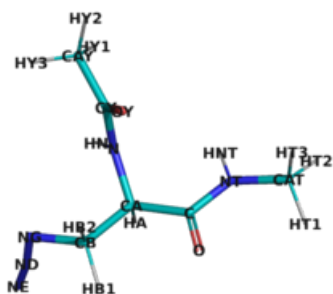


Figure S259: The energy minimized structure corresponding to 2-acetamido-N-methyl-3-(2lambda4-triaza-1,2-dien-1-yl)propanamide.

Table S714: The calculated geometric terms of 2-acetamido-N-methyl-3-(2lambda4-triaza-1,2-dien-1-yl)propanamide.

Terms	QM	CHARMM	Abs. diff.
N-HN	1.02	0.99	0.02
N-CA	1.46	1.46	0.00
N-CY	1.38	1.34	0.04
CA-HA	1.10	1.08	0.02
CA-CB	1.53	1.55	0.03
CA-C	1.53	1.52	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-NG	1.49	1.50	0.02
NG-ND	1.25	1.25	0.00
ND-NE	1.16	1.24	0.08
C-O	1.23	1.23	0.00
C-NT	1.36	1.35	0.01
NT-HNT	1.01	0.99	0.02
NT-CAT	1.45	1.44	0.01
CAT-HT1	1.09	1.11	0.02
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.10	1.11	0.02
CAY-HY1	1.09	1.11	0.02
CAY-HY2	1.09	1.11	0.02
CAY-HY3	1.09	1.11	0.02
CAY-CY	1.51	1.48	0.03
CY-OY	1.23	1.22	0.01
N-CA-HA	106.52	104.31	2.21
N-CA-CB	112.14	113.12	0.98
N-CA-C	111.71	116.18	4.46
N-CY-CAY	114.96	116.55	1.59
N-CY-OY	121.51	122.82	1.31
HN-N-CA	115.19	116.56	1.37
HN-N-CY	115.63	117.31	1.69
CA-N-CY	118.94	123.45	4.51
CA-CB-HB1	110.52	111.10	0.58

Terms	QM	CHARMM	Abs. diff.
CA-CB-HB2	109.74	108.48	1.26
CA-CB-NG	110.20	111.61	1.41
CA-C-O	121.09	121.12	0.03
CA-C-NT	114.37	117.11	2.73
HA-CA-CB	109.27	106.61	2.66
HA-CA-C	107.10	105.83	1.26
CB-CA-C	109.89	109.91	0.03
CB-NG-ND	115.24	115.54	0.30
HB1-CB-HB2	108.54	107.18	1.37
HB1-CB-NG	111.58	110.37	1.21
HB2-CB-NG	106.14	107.93	1.79
NG-ND-NE	172.58	172.45	0.14
C-NT-HNT	115.80	119.33	3.53
C-NT-CAT	119.43	121.63	2.20
O-C-NT	124.09	121.74	2.35
NT-CAT-HT1	108.36	111.59	3.23
NT-CAT-HT2	108.92	110.87	1.95
NT-CAT-HT3	111.78	109.81	1.97
HNT-NT-CAT	118.16	117.55	0.61
HT1-CAT-HT2	109.50	108.05	1.44
HT1-CAT-HT3	108.60	108.03	0.58
HT2-CAT-HT3	109.65	108.38	1.26
CAY-CY-OY	123.52	120.63	2.89
HY1-CAY-HY2	109.88	108.99	0.89
HY1-CAY-HY3	108.34	109.50	1.16
HY1-CAY-CY	111.65	111.14	0.51
HY2-CAY-HY3	108.83	108.58	0.25
HY2-CAY-CY	108.66	108.65	0.02
HY3-CAY-CY	109.44	109.94	0.49

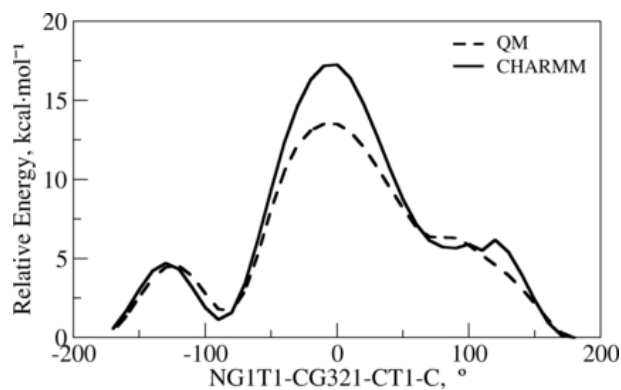


Figure S260: The PES scan for flexible dihedral corresponding to 2-acetamido-N-methyl-3-(2lambda4-triaza-1,2-dien-1-yl)propanamide.

2.35 The small molecule used for bonded terms optimization of azidohomoalanine (AZH)

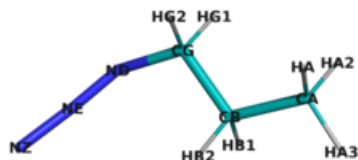


Figure S261: The energy minimized structure corresponding to 1-propyl-2lambda4-triaza-1,2-diene.

Table S715: The calculated geometric terms of 1-propyl-2lambda4-triaza-1,2-diene.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.53	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.10	1.11	0.02
CB-CG	1.52	1.54	0.01
CG-HG1	1.09	1.11	0.02
CG-HG2	1.10	1.11	0.02
CG-ND	1.48	1.50	0.01
ND-NE	1.24	1.25	0.00
NE-NZ	1.16	1.24	0.08
HA3-CA-HA2	107.85	108.17	0.32
HA3-CA-HA	107.85	108.30	0.45
HA3-CA-CB	110.90	110.50	0.40
HA2-CA-HA	107.98	108.46	0.48
HA2-CA-CB	110.98	110.59	0.40
CA-CB-HB1	110.52	109.06	1.46
CA-CB-HB2	109.97	108.71	1.26
CA-CB-CG	111.67	114.08	2.41
HA-CA-CB	111.14	110.74	0.39
CB-CG-HG1	110.77	108.64	2.13
CB-CG-HG2	110.81	109.66	1.15
CB-CG-ND	112.73	112.93	0.20
HB1-CB-HB2	106.94	107.31	0.38
HB1-CB-CG	108.47	108.26	0.21
HB2-CB-CG	109.14	109.20	0.07
CG-ND-NE	115.13	115.96	0.82
HG1-CG-HG2	107.85	107.23	0.62
HG1-CG-ND	104.55	108.25	3.70
HG2-CG-ND	109.86	109.95	0.10
ND-NE-NZ	172.65	172.25	0.41

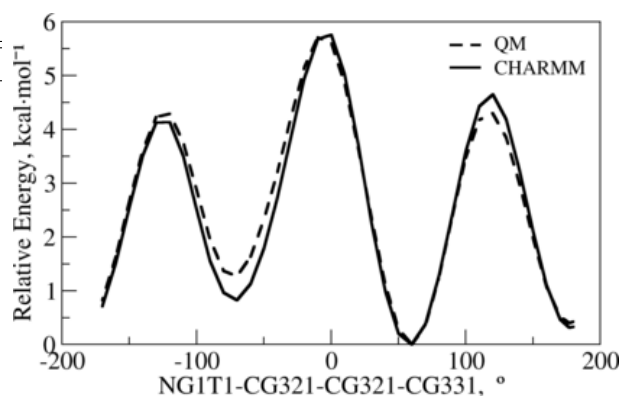


Figure S262: The PES scan for flexible dihedral corresponding to 1-propyl-2lambda4-triaza-1,2-diene.

2.36 The small molecule 1 used for bonded terms optimization of Chromophore(Thr, Trp, Gly) (B2H)

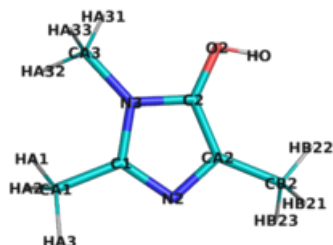


Figure S263: The energy minimized structure corresponding to trimethyl-1H-imidazol-5-ol.

Table S716: The calculated geometric terms of trimethyl-1H-imidazol-5-ol.

Terms	QM	CHARMM	Abs. diff.
CA1-HA1	1.10	1.11	0.01
CA1-HA2	1.10	1.11	0.01
CA1-HA3	1.09	1.11	0.02
CA1-C1	1.49	1.50	0.01
C1-N2	1.33	1.31	0.01
C1-N3	1.38	1.38	0.00
N2-CA2	1.38	1.38	0.00
N3-C2	1.37	1.38	0.01
N3-CA3	1.45	1.47	0.02
CA2-C2	1.38	1.37	0.01
CA2-CB2	1.49	1.50	0.00
C2-O2	1.37	1.38	0.00
O2-HO	0.97	0.96	0.01
CB2-HB21	1.09	1.11	0.02
CB2-HB22	1.10	1.11	0.01
CB2-HB23	1.10	1.11	0.01
CA3-HA31	1.09	1.11	0.02
CA3-HA32	1.09	1.11	0.02
CA3-HA33	1.09	1.11	0.02
CA1-C1-N2	125.81	122.97	2.84
CA1-C1-N3	123.01	123.54	0.54
HA1-CA1-HA2	107.78	109.91	2.13
HA1-CA1-HA3	108.51	108.76	0.25
HA1-CA1-C1	112.22	109.96	2.26
HA2-CA1-HA3	108.37	108.78	0.41
HA2-CA1-C1	112.33	109.73	2.60
HA3-CA1-C1	107.51	109.67	2.16
C1-N2-CA2	106.39	103.94	2.45
C1-N3-C2	106.35	105.44	0.91
C1-N3-CA3	128.00	127.17	0.83
N2-C1-N3	111.19	113.48	2.30
N2-CA2-C2	108.80	111.32	2.52
N2-CA2-CB2	122.20	117.01	5.18

Terms	QM	CHARMM	Abs. diff.
N3-C2-CA2	107.27	105.82	1.45
N3-C2-O2	118.06	120.76	2.71
N3-CA3-HA31	108.28	111.49	3.21
N3-CA3-HA32	109.48	111.07	1.59
N3-CA3-HA33	111.09	110.38	0.71
CA2-C2-O2	134.66	133.41	1.25
CA2-CB2-HB21	110.01	109.43	0.58
CA2-CB2-HB22	111.27	111.00	0.27
CA2-CB2-HB23	112.13	109.39	2.75
C2-N3-CA3	125.57	127.39	1.83
C2-CA2-CB2	128.98	131.67	2.69
C2-O2-HO	107.17	107.34	0.17
HB21-CB2-HB22	107.61	109.19	1.58
HB21-CB2-HB23	107.66	108.49	0.84
HB22-CB2-HB23	107.99	109.30	1.31
HA31-CA3-HA32	109.43	107.47	1.96
HA31-CA3-HA33	109.17	107.80	1.37
HA32-CA3-HA33	109.36	108.50	0.86

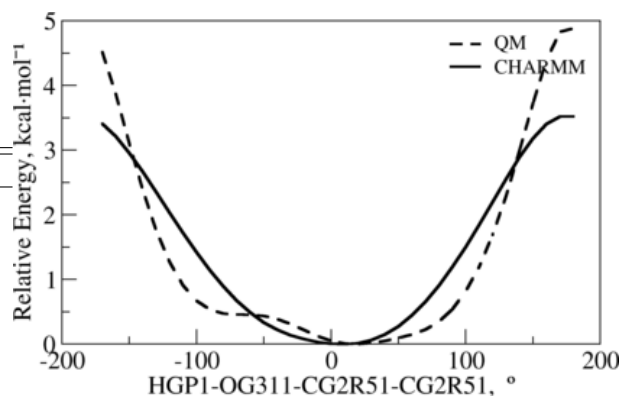


Figure S264: The PES scan for flexible dihedral corresponding to trimethyl-1H-imidazol-5-ol.

2.37 The small molecule 2 used for bonded terms optimization of Chromophore(Thr, Trp, Gly) (B2H)

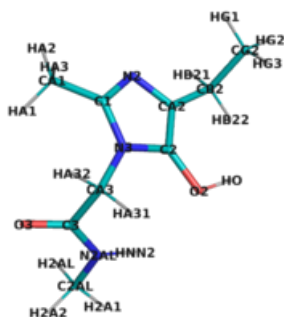


Figure S265: The energy minimized structure corresponding to 2-(4-ethyl-5-hydroxy-2-methyl-1H-imidazol-1-yl)-N-methylacetamide.

Table S717: The calculated geometric terms of 2-(4-ethyl-5-hydroxy-2-methyl-1H-imidazol-1-yl)-N-methylacetamide.

Terms	QM	CHARMM	Abs. diff.
CA1-HA1	1.09	1.11	0.02
CA1-HA3	1.10	1.11	0.01
CA1-HA2	1.09	1.11	0.02
CA1-C1	1.49	1.50	0.01
C1-N2	1.33	1.32	0.01
C1-N3	1.38	1.38	0.00
N2-CA2	1.38	1.38	0.00
N3-C2	1.37	1.38	0.01
N3-CA3	1.45	1.47	0.02
CA2-C2	1.38	1.37	0.01
CA2-CB2	1.49	1.51	0.01
C2-O2	1.38	1.38	0.00
O2-HO	0.97	0.96	0.01
CB2-HB21	1.10	1.11	0.02
CB2-HB22	1.10	1.11	0.01
CB2-CG2	1.53	1.54	0.01
CA3-HA31	1.09	1.11	0.02
CA3-HA32	1.09	1.11	0.02
CA3-C3	1.53	1.50	0.03
CG2-HG1	1.09	1.11	0.02
CG2-HG2	1.09	1.11	0.02
CG2-HG3	1.09	1.11	0.02
C3-O3	1.23	1.22	0.01
C3-N2AL	1.36	1.34	0.02
N2AL-HNN2	1.02	1.00	0.02
N2AL-C2AL	1.45	1.44	0.01
C2AL-H2AL	1.09	1.11	0.02
C2AL-H2A1	1.09	1.11	0.02
C2AL-H2A2	1.09	1.11	0.02
CA1-C1-N2	126.49	122.77	3.72
CA1-C1-N3	122.62	123.75	1.13

Terms	QM	CHARMM	Abs. diff.
HA1-CA1-HA3	107.99	109.83	1.84
HA1-CA1-HA2	109.23	108.67	0.56
HA1-CA1-C1	111.47	110.08	1.39
HA3-CA1-HA2	108.30	108.95	0.65
HA3-CA1-C1	112.08	109.69	2.38
HA2-CA1-C1	107.70	109.60	1.90
C1-N2-CA2	106.69	104.24	2.45
C1-N3-C2	106.42	104.93	1.49
C1-N3-CA3	127.78	128.28	0.50
N2-C1-N3	110.88	113.43	2.54
N2-CA2-C2	108.55	110.58	2.03
N2-CA2-CB2	121.75	118.58	3.17
N3-C2-CA2	107.43	106.81	0.62
N3-C2-O2	117.42	120.73	3.31
N3-CA3-HA31	108.25	110.92	2.66
N3-CA3-HA32	109.23	111.15	1.92
N3-CA3-C3	110.39	110.99	0.61
CA2-C2-O2	135.10	132.46	2.64
CA2-CB2-HB21	108.98	107.99	0.99
CA2-CB2-HB22	109.67	109.12	0.55
CA2-CB2-CG2	112.25	114.41	2.17
C2-N3-CA3	125.43	126.72	1.29
C2-CA2-CB2	129.66	130.82	1.16
C2-O2-HO	107.42	107.07	0.35
CB2-CG2-HG1	109.54	109.97	0.42
CB2-CG2-HG2	111.33	110.54	0.79
CB2-CG2-HG3	110.65	111.08	0.42
HB21-CB2-HB22	106.10	106.89	0.79
HB21-CB2-CG2	109.56	108.85	0.70
HB22-CB2-CG2	110.10	109.30	0.80
CA3-C3-O3	121.48	120.58	0.90
CA3-C3-N2AL	113.91	117.17	3.25
HA31-CA3-HA32	109.33	107.10	2.23
HA31-CA3-C3	111.58	108.50	3.08
HA32-CA3-C3	108.04	108.04	0.00
HG1-CG2-HG2	108.73	108.17	0.57
HG1-CG2-HG3	108.04	108.33	0.30
HG2-CG2-HG3	108.46	108.68	0.22
C3-N2AL-HNN2	118.00	119.12	1.12
C3-N2AL-C2AL	121.36	122.15	0.80
O3-C3-N2AL	124.60	122.25	2.35
N2AL-C2AL-H2AL	111.70	110.50	1.20
N2AL-C2AL-H2A1	109.79	110.57	0.78
N2AL-C2AL-H2A2	107.63	110.83	3.20
HNN2-N2AL-C2AL	119.24	118.37	0.87
H2AL-C2AL-H2A1	109.26	108.24	1.02
H2AL-C2AL-H2A2	108.85	108.20	0.65
H2A1-C2AL-H2A2	109.57	108.41	1.16

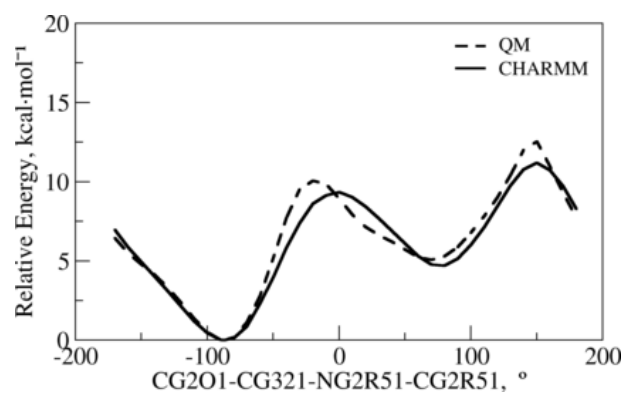


Figure S266: The PES scan for flexible dihedral corresponding to 2-(4-ethyl-5-hydroxy-2-methyl-1H-imidazol-1-yl)-N-methylacetamide.

2.38 The small molecule used for bonded terms optimization of benzylcysteine (BCS)

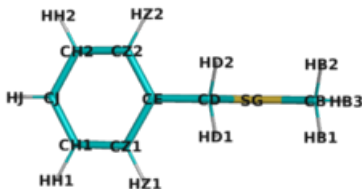


Figure S267: The energy minimized structure corresponding to [(methylsulfanyl)methyl]benzene.

Table S718: The calculated geometric terms of [(methylsulfanyl)methyl]benzene.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.81	1.82	0.01
SG-CD	1.82	1.82	0.00
CD-HD1	1.10	1.11	0.02
CD-HD2	1.10	1.11	0.02
CD-CE	1.50	1.51	0.00
CE-CZ1	1.40	1.41	0.01
CE-CZ2	1.40	1.41	0.01
CZ1-HZ1	1.09	1.08	0.01
CZ1-CH1	1.40	1.40	0.01
CZ2-HZ2	1.09	1.08	0.01
CZ2-CH2	1.40	1.40	0.01
CH1-HH1	1.09	1.08	0.01
CH1-CJ	1.40	1.40	0.00
CH2-HH2	1.09	1.08	0.01
CH2-CJ	1.40	1.40	0.00
CJ-HJ	1.09	1.08	0.01
HB3-CB-HB1	108.55	107.64	0.91
HB3-CB-HB2	108.55	107.60	0.95
HB3-CB-SG	107.52	110.68	3.16
CB-SG-CD	98.69	96.69	2.00
HB1-CB-HB2	109.43	108.19	1.24
HB1-CB-SG	111.34	111.30	0.04
HB2-CB-SG	111.34	111.27	0.07
SG-CD-HD1	109.23	111.04	1.81
SG-CD-HD2	109.22	111.06	1.83
SG-CD-CE	109.39	109.69	0.31
CD-CE-CZ1	120.47	120.43	0.04
CD-CE-CZ2	120.48	120.34	0.14
HD1-CD-HD2	108.25	107.89	0.35
HD1-CD-CE	110.37	108.51	1.85
HD2-CD-CE	110.36	108.57	1.79

Terms	QM	CHARMM	Abs. diff.
CE-CZ1-HZ1	119.46	119.98	0.52
CE-CZ1-CH1	120.54	120.39	0.15
CE-CZ2-HZ2	119.46	120.04	0.58
CE-CZ2-CH2	120.54	120.34	0.21
CZ1-CE-CZ2	119.02	119.23	0.21
CZ1-CH1-HH1	119.85	119.98	0.13
CZ1-CH1-CJ	120.07	120.02	0.05
HZ1-CZ1-CH1	120.00	119.63	0.38
CZ2-CH2-HH2	119.85	120.02	0.17
CZ2-CH2-CJ	120.07	120.05	0.02
HZ2-CZ2-CH2	120.00	119.62	0.38
CH1-CJ-CH2	119.75	119.97	0.22
CH1-CJ-HJ	120.13	119.97	0.16
HH1-CH1-CJ	120.08	120.00	

2.39 The small molecule used for bonded terms optimization of 5-bromo-l-isoleucine (BIU)

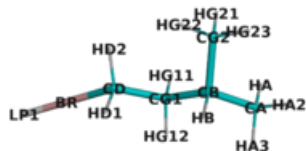


Figure S269: The energy minimized structure corresponding to (3-methylbutyl)borane.

Table S719: The calculated geometric terms of (3-methylbutyl)borane.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.10	1.11	0.01
CA-CB	1.53	1.53	0.00
CB-HB	1.10	1.12	0.02
CB-CG2	1.53	1.53	0.01
CB-CG1	1.53	1.54	0.00
CG2-HG21	1.10	1.11	0.01
CG2-HG22	1.09	1.11	0.01
CG2-HG23	1.09	1.11	0.02
CG1-HG12	1.10	1.11	0.02
CG1-HG11	1.10	1.11	0.02
CG1-CD	1.52	1.54	0.02
CD-HD1	1.09	1.11	0.02
CD-HD2	1.09	1.11	0.02
CD-BR	1.97	1.97	0.00
HA3-CA-HA2	108.11	108.65	0.55
HA3-CA-HA	108.01	108.45	0.43
HA3-CA-CB	111.28	110.35	0.93
HA2-CA-HA	107.93	108.63	0.71
HA2-CA-CB	110.98	110.61	0.38
CA-CB-HB	108.03	107.91	0.12
CA-CB-CG2	110.47	110.29	0.18
CA-CB-CG1	109.65	109.58	0.07
HA-CA-CB	110.40	110.09	0.31
CB-CG2-HG21	110.31	110.01	0.30
CB-CG2-HG22	112.39	111.28	1.12
CB-CG2-HG23	110.61	110.17	0.44
CB-CG1-HG12	109.40	108.33	1.08
CB-CG1-HG11	109.52	109.08	0.44
CB-CG1-CD	113.05	114.30	1.25
HB-CB-CG2	108.33	108.49	0.16
HB-CB-CG1	107.92	108.69	0.77
CG2-CB-CG1	112.29	111.78	0.52

Terms	QM	CHARMM	Abs. diff.
HG21-CG2-HG22	108.06	108.78	0.72
HG21-CG2-HG23	107.83	108.31	0.48
HG22-CG2-HG23	107.47	108.22	0.75
CG1-CD-HD1	112.10	111.23	0.87
CG1-CD-HD2	113.03	111.86	1.17
CG1-CD-BR	110.87	111.31	0.44
HG12-CG1-HG11	106.78	107.28	0.51
HG12-CG1-CD	108.63	108.35	0.27
HG11-CG1-CD	109.26	109.27	0.01
HD1-CD-HD2	109.56	109.50	0.06
HD1-CD-BR	105.67	106.50	0.83
HD2-CD-BR	105.13	106.18	1.05

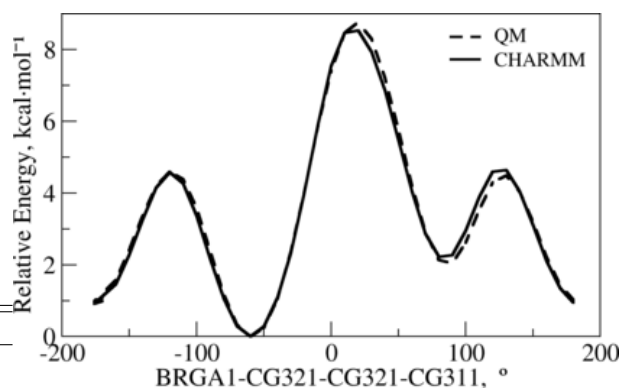


Figure S270: The PES scan for flexible dihedral corresponding to (3-methylbutyl)borane.

2.40 The small molecule used for bonded terms optimization of (2S)-2-azanyl-3-[ethyl(methyl)carbamoyl]oxy-propanoic acid (BXT)

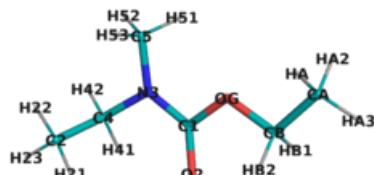


Figure S271: The energy minimized structure corresponding to ethylN-ethyl-N-methylcarbamate.

Table S720: The calculated geometric terms of ethylN-ethyl-N-methylcarbamate.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.51	1.53	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.12	0.02
CB-OG	1.45	1.45	0.00
OG-C1	1.37	1.36	0.01
C1-O2	1.23	1.23	0.00
C1-N3	1.37	1.38	0.01
N3-C5	1.46	1.45	0.00
N3-C4	1.46	1.46	0.00
C5-H51	1.09	1.11	0.02
C5-H52	1.09	1.11	0.02
C5-H53	1.10	1.11	0.01
C4-H41	1.09	1.12	0.03
C4-H42	1.10	1.11	0.02
C4-C2	1.52	1.53	0.01
C2-H21	1.09	1.11	0.02
C2-H22	1.09	1.11	0.02
C2-H23	1.09	1.11	0.02
HA3-CA-HA2	108.55	108.53	0.01
HA3-CA-HA	108.56	108.62	0.06
HA3-CA-CB	109.92	110.56	0.64
HA2-CA-HA	108.61	108.41	0.20
HA2-CA-CB	110.59	110.33	0.26
CA-CB-HB1	112.17	109.73	2.44
CA-CB-HB2	112.22	109.55	2.67
CA-CB-OG	106.40	108.80	2.40
HA-CA-CB	110.56	110.33	0.23
CB-OG-C1	113.73	115.34	1.61
HB1-CB-HB2	107.80	108.41	0.62

Terms	QM	CHARMM	Abs. diff.
HB1-CB-OG	109.12	110.16	1.04
HB2-CB-OG	109.08	110.18	1.10
OG-C1-O2	123.73	122.30	1.43
OG-C1-N3	111.10	112.33	1.23
C1-N3-C5	121.43	122.17	0.74
C1-N3-C4	116.45	117.32	0.87
O2-C1-N3	125.16	125.37	0.21
N3-C5-H51	109.69	110.41	0.72
N3-C5-H52	108.00	107.12	0.88
N3-C5-H53	112.65	107.35	5.30
N3-C4-H41	107.25	109.31	2.06
N3-C4-H42	107.15	107.85	0.70
N3-C4-C2	113.00	117.83	4.83
C5-N3-C4	118.33	117.77	0.56
H51-C5-H52	108.99	109.67	0.69
H51-C5-H53	108.67	111.37	2.70
H52-C5-H53	108.77	110.81	2.04
C4-C2-H21	109.66	109.99	0.33
C4-C2-H22	111.31	110.58	0.73
C4-C2-H23	110.54	110.70	0.16
H41-C4-H42	108.05	105.13	2.92
H41-C4-C2	110.23	107.74	2.48
H42-C4-C2	110.96	108.25	2.71
H21-C2-H22	108.86	108.38	0.49
H21-C2-H23	108.35	108.42	0.07
H22-C2-H23	108.04	108.71	0.66

2.41 The small molecule used for bonded terms optimization of (C12)

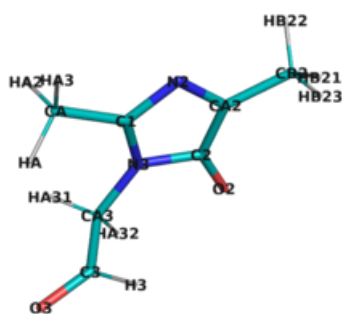


Figure S722: The energy minimized structure corresponding to 2-(2,4-dimethyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetaldehyde.

Table S721: The calculated geometric terms of 2-(2,4-dimethyl-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetaldehyde.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.10	1.11	0.01
CA-HA	1.10	1.11	0.01
CA-C1	1.49	1.50	0.01
C1-N2	1.34	1.31	0.02
C1-N3	1.38	1.38	0.00
N2-CA2	1.38	1.39	0.00
CA2-C2	1.41	1.38	0.03
CA2-CB2	1.49	1.50	0.01
C2-O2	1.28	1.29	0.00
C2-N3	1.43	1.39	0.04
N3-CA3	1.43	1.47	0.04
CA3-HA31	1.10	1.11	0.01
CA3-HA32	1.10	1.11	0.01
CA3-C3	1.51	1.50	0.01
C3-H3	1.11	1.11	0.00
C3-O3	1.23	1.22	0.02
CB2-HB21	1.10	1.11	0.01
CB2-HB22	1.10	1.11	0.01
CB2-HB23	1.10	1.11	0.01
HA3-CA-HA2	107.96	109.05	1.08
HA3-CA-HA	108.34	108.97	0.62
HA3-CA-C1	107.53	109.51	1.98
HA2-CA-HA	107.14	109.74	2.60
HA2-CA-C1	112.71	109.26	3.45
CA-C1-N2	125.48	122.32	3.16
CA-C1-N3	123.36	123.36	0.00
HA-CA-C1	112.98	110.30	2.68
C1-N2-CA2	106.71	103.45	3.26
C1-N3-C2	109.19	105.52	3.67
C1-N3-CA3	128.48	126.79	1.69
N2-C1-N3	110.04	113.89	3.85

Terms	QM	CHARMM	Abs. diff.
N2-CA2-C2	111.77	111.64	0.13
N2-CA2-CB2	122.15	116.79	5.37
CA2-C2-O2	136.03	134.56	1.47
CA2-C2-N3	102.14	105.38	3.24
CA2-CB2-HB21	112.70	109.47	3.22
CA2-CB2-HB22	111.45	109.42	2.03
CA2-CB2-HB23	109.01	109.87	0.86
C2-CA2-CB2	125.90	131.56	5.66
C2-N3-CA3	121.34	126.47	5.12
O2-C2-N3	121.83	119.98	1.85
N3-CA3-HA31	112.94	110.22	2.73
N3-CA3-HA32	105.07	110.69	5.61
N3-CA3-C3	111.05	110.90	0.15
CA3-C3-H3	114.43	115.90	1.48
CA3-C3-O3	124.66	125.42	0.76
HA31-CA3-HA32	109.59	107.46	2.14
HA31-CA3-C3	109.78	108.91	0.87
HA32-CA3-C3	108.20	108.58	0.37
H3-C3-O3	120.91	118.62	2.29
HB21-CB2-HB22	107.24	109.22	1.99
HB21-CB2-HB23	107.72	109.39	1.67
HB22-CB2-HB23	108.59	109.46	0.87

2.42 The small molecule used for bonded terms optimization of 3-chloro-D-alanine (C2N)

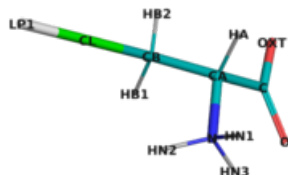


Figure S723: The energy minimized structure corresponding to 3-chloro-D-alanine.

Table S722: The calculated geometric terms of 3-chloro-D-alanine.

Terms	QM	CHARMM	Abs. diff.
N-HN1	1.02	1.01	0.01
N-HN2	1.03	1.01	0.01
N-HN3	1.05	1.03	0.03
N-CA	1.50	1.49	0.01
CA-HA	1.09	1.11	0.02
CA-CB	1.51	1.55	0.04
CA-C	1.59	1.54	0.05
CL-CB	1.80	1.80	0.00
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
C-OXT	1.24	1.26	0.02
C-O	1.27	1.26	0.01
N-CA-HA	109.54	108.95	0.59
N-CA-CB	111.56	110.10	1.46
N-CA-C	104.19	109.08	4.88
HN1-N-HN2	108.22	112.72	4.50
HN1-N-HN3	109.61	109.60	0.01
HN1-N-CA	112.55	110.77	1.77
HN2-N-HN3	114.65	111.23	3.42
HN2-N-CA	113.82	109.67	4.14
HN3-N-CA	97.77	102.37	4.61
CA-CB-CL	112.32	112.14	0.18
CA-CB-HB1	110.95	111.25	0.30
CA-CB-HB2	108.18	109.68	1.50
CA-C-OXT	114.60	114.81	0.22
CA-C-O	111.71	117.62	5.91
HA-CA-CB	111.26	110.20	1.07
HA-CA-C	111.66	108.58	3.08
CL-CB-HB1	107.30	108.33	1.03
CL-CB-HB2	108.97	106.98	1.99
CB-CA-C	108.42	109.90	1.48
HB1-CB-HB2	109.07	108.29	0.77
OXT-C-O	133.63	127.57	6.07

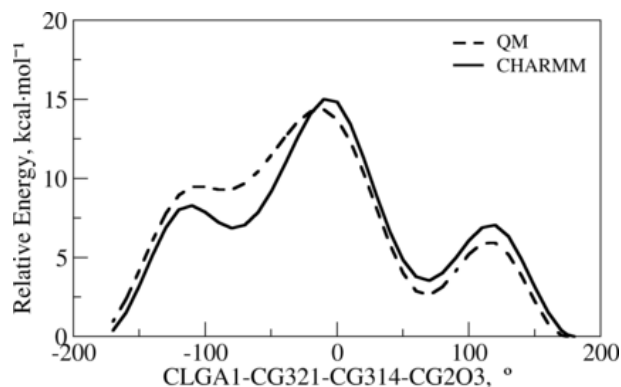


Figure S274: The PES scan for flexible dihedral corresponding to 3-chloro-D-alanine.

2.43 The small molecule used for bonded terms optimization of canaline (CAN)

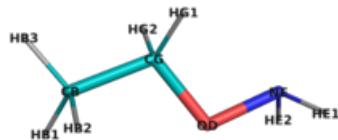


Figure S275: The energy minimized structure corresponding to O-ethylhydroxylamine.

Table S723: The calculated geometric terms of O-ethylhydroxylamine.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.51	1.53	0.02
CG-HG1	1.10	1.11	0.02
CG-HG2	1.10	1.11	0.02
CG-OD	1.43	1.42	0.01
OD-NE	1.45	1.46	0.01
NE-HE1	1.02	1.02	0.00
NE-HE2	1.02	1.02	0.00
HB3-CB-HB1	108.63	108.81	0.18
HB3-CB-HB2	108.62	108.77	0.15
HB3-CB-CG	110.27	110.60	0.33
CB-CG-HG1	111.50	109.61	1.89
CB-CG-HG2	111.51	109.58	1.93
CB-CG-OD	106.30	109.41	3.11
HB1-CB-HB2	108.51	108.35	0.17
HB1-CB-CG	110.37	110.14	0.23
HB2-CB-CG	110.37	110.12	0.26
CG-OD-NE	107.46	107.52	0.07
HG1-CG-HG2	107.77	108.71	0.94
HG1-CG-OD	109.88	109.78	0.09
HG2-CG-OD	109.89	109.74	0.15
OD-NE-HE1	102.65	102.64	0.00
OD-NE-HE2	102.65	102.62	0.03
HE1-NE-HE2	105.27	109.10	3.82

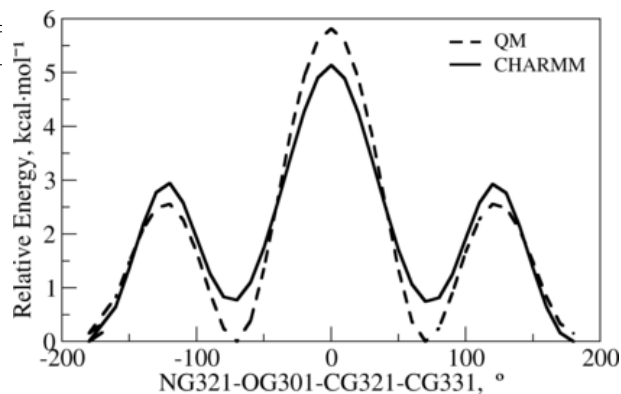


Figure S276: The PES scan for flexible dihedral corresponding to O-ethylhydroxylamine.

2.44 The small molecule used for bonded terms optimization of carboxymethylatedcysteine (CCS)

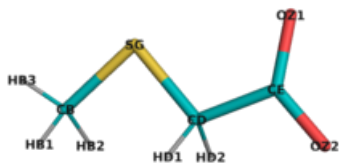


Figure S277: The energy minimized structure corresponding to 2-(methylsulfonyl)acetic acid.

Table S724: The calculated geometric terms of 2-(methylsulfonyl)acetic acid.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.10	1.11	0.02
CB-HB2	1.10	1.11	0.02
CB-HB1	1.10	1.11	0.01
CB-SG	1.81	1.81	0.00
SG-CD	1.82	1.82	0.00
CD-HD2	1.10	1.11	0.01
CD-HD1	1.10	1.11	0.01
CD-CE	1.56	1.52	0.03
CE-OZ1	1.26	1.26	0.01
CE-OZ2	1.27	1.26	0.01
HB3-CB-HB2	108.26	108.16	0.10
HB3-CB-HB1	108.26	108.18	0.08
HB3-CB-SG	108.16	110.84	2.68
CB-SG-CD	97.27	93.40	3.88
HB2-CB-HB1	108.59	108.06	0.53
HB2-CB-SG	111.73	110.74	0.99
HB1-CB-SG	111.73	110.76	0.97
SG-CD-HD2	109.66	110.56	0.90
SG-CD-HD1	109.66	110.56	0.90
SG-CD-CE	113.03	113.06	0.03
CD-CE-OZ1	116.87	120.61	3.74
CD-CE-OZ2	112.90	112.62	0.28
HD2-CD-HD1	107.84	108.29	0.45
HD2-CD-CE	108.25	107.08	1.17
HD1-CD-CE	108.25	107.08	1.17
OZ1-CE-OZ2	130.23	126.77	3.46

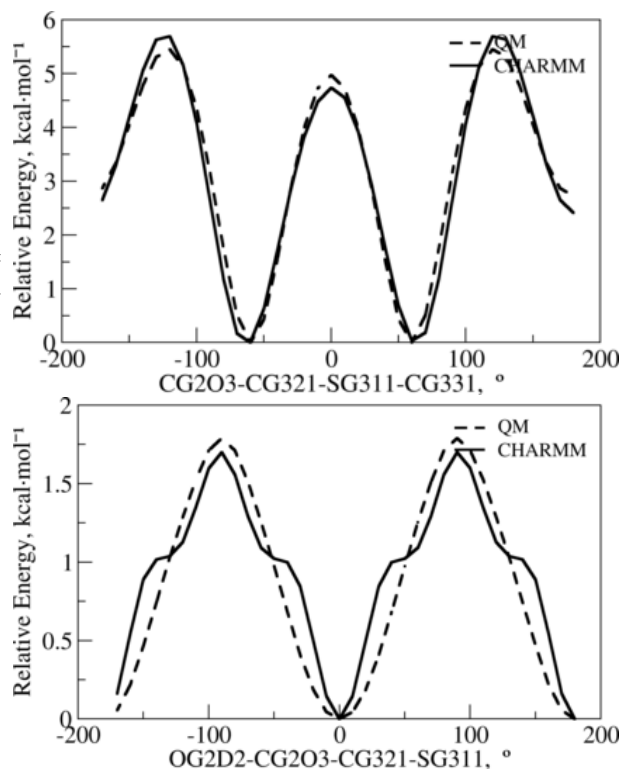


Figure S278: The PES scan for flexible dihedrals corresponding to 2-(methylsulfonyl)acetic acid.

2.45 The small molecule used for bonded terms optimization of gamma-carboxy-glutamic acid (CGU)

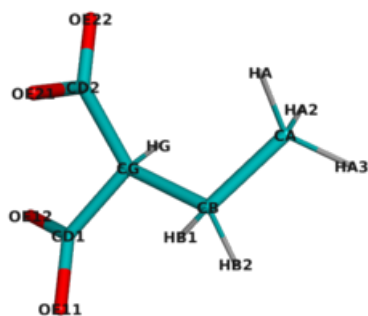


Figure S279: The energy minimized structure corresponding to 2-ethylpropanedioic acid.

Table S725: The calculated geometric terms of 2-ethylpropanedioic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.10	1.11	0.01
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.53	0.00
CB-HB1	1.09	1.11	0.02
CB-HB2	1.10	1.11	0.01
CB-CG	1.53	1.58	0.05
CG-HG	1.10	1.10	0.01
CG-CD1	1.56	1.50	0.07
CG-CD2	1.56	1.49	0.07
CD1-OE12	1.28	1.26	0.02
CD1-OE11	1.27	1.26	0.01
CD2-OE22	1.28	1.27	0.01
CD2-OE21	1.28	1.26	0.01
HA3-CA-HA2	107.73	109.38	1.65
HA3-CA-HA	108.51	108.76	0.26
HA3-CA-CB	111.79	110.88	0.91
HA2-CA-HA	108.57	108.01	0.56
HA2-CA-CB	110.76	109.92	0.84
CA-CB-HB1	110.21	110.13	0.08
CA-CB-HB2	109.47	109.46	0.01
CA-CB-CG	112.93	112.45	0.48
HA-CA-CB	109.40	109.83	0.43
CB-CG-HG	109.64	106.00	3.64
CB-CG-CD1	108.41	112.76	4.34
CB-CG-CD2	111.32	111.61	0.30
HB1-CB-HB2	107.88	107.43	0.46
HB1-CB-CG	107.28	108.62	1.34
HB2-CB-CG	108.93	108.62	0.31
CG-CD1-OE12	116.12	116.70	0.58
CG-CD1-OE11	116.93	117.66	0.73
CG-CD2-OE22	115.80	116.07	0.27
CG-CD2-OE21	117.47	118.30	0.83

Terms	QM	CHARMM	Abs. diff.
HG-CG-CD1	105.66	104.23	1.44
HG-CG-CD2	106.23	106.46	0.23
CD1-CG-CD2	115.32	114.88	0.44
OE12-CD1-OE11	126.83	125.59	1.24
OE22-CD2-OE21	126.68	125.59	1.09

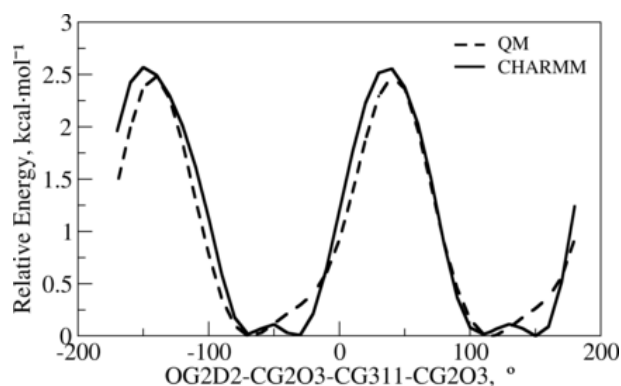


Figure S280: The PES scan for flexible dihedral corresponding to 2-ethylpropanedioic acid.

2.46 The small molecule used for bonded terms optimization of gamma-carboxy-glutamicacid (CGUP)

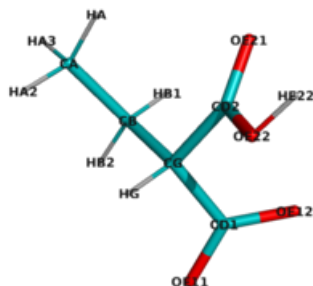


Figure S281: The energy minimized structure corresponding to 2-ethylpropanedioicacid.

Table S726: The calculated geometric terms of 2-ethylpropanedioicacid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.10	1.11	0.01
CA-HA	1.10	1.11	0.02
CA-CB	1.53	1.53	0.00
CB-HB1	1.10	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.53	1.57	0.05
CG-HG	1.10	1.11	0.01
CG-CD1	1.59	1.51	0.08
CG-CD2	1.49	1.51	0.02
CD1-OE12	1.26	1.26	0.00
CD1-OE11	1.26	1.26	0.00
CD2-OE22	1.37	1.40	0.02
CD2-OE21	1.23	1.22	0.01
OE22-HE22	0.98	0.96	0.02
HA3-CA-HA2	107.74	108.64	0.90
HA3-CA-HA	107.77	108.35	0.58
HA3-CA-CB	111.25	110.39	0.86
HA2-CA-HA	108.23	108.58	0.35
HA2-CA-CB	110.63	110.35	0.29
CA-CB-HB1	109.83	109.97	0.14
CA-CB-HB2	110.75	109.27	1.47
CA-CB-CG	113.50	112.46	1.04
HA-CA-CB	111.08	110.48	0.60
CB-CG-HG	109.93	108.00	1.93
CB-CG-CD1	110.96	113.00	2.04
CB-CG-CD2	112.13	112.84	0.71
HB1-CB-HB2	107.45	107.61	0.16
HB1-CB-CG	108.58	108.92	0.34
HB2-CB-CG	106.52	108.49	1.97
CG-CD1-OE12	115.97	117.55	1.58
CG-CD1-OE11	113.40	115.15	1.76
CG-CD2-OE22	112.28	114.02	1.74

Terms	QM	CHARMM	Abs. diff.
CG-CD2-OE21	127.12	127.38	0.27
HG-CG-CD1	106.18	106.89	0.71
HG-CG-CD2	108.35	107.89	0.47
CD1-CG-CD2	109.08	107.94	1.14
OE12-CD1-OE11	130.64	127.30	3.34
CD2-OE22-HE22	104.66	109.33	4.67
OE22-CD2-OE21	120.60	118.59	2.01

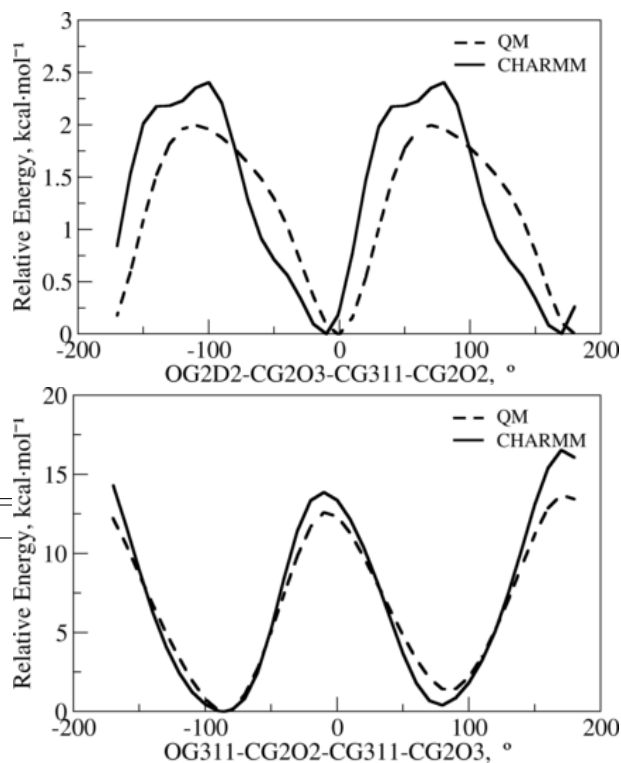


Figure S282: The PES scan for flexible dihedrals corresponding to 2-ethylpropanedioicacid.

2.47 The small molecule used for bonded terms optimization of S-[(R)-carboxy(hydroxy)methyl]-L-cysteine (CGV)

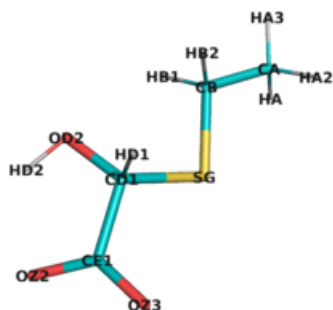


Figure S283: The energy minimized structure corresponding to (2R)-2-(ethylsulfanyl)-2-hydroxyacetic acid.

Table S727: The calculated geometric terms of (2R)-2-(ethylsulfanyl)-2-hydroxyacetic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.10	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.53	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.10	1.11	0.01
CB-SG	1.82	1.82	0.01
SG-CD1	1.84	1.84	0.00
CD1-HD1	1.10	1.11	0.01
CD1-OD2	1.41	1.44	0.03
CD1-CE1	1.57	1.56	0.00
OD2-HD2	1.00	0.97	0.03
CE1-OZ2	1.28	1.27	0.01
CE1-OZ3	1.26	1.26	0.00
HA3-CA-HA2	108.14	108.67	0.53
HA3-CA-HA	108.23	108.69	0.46
HA3-CA-CB	110.48	110.50	0.03
HA2-CA-HA	108.01	108.39	0.38
HA2-CA-CB	111.21	110.26	0.95
CA-CB-HB1	110.71	109.17	1.54
CA-CB-HB2	109.93	109.28	0.65
CA-CB-SG	110.41	113.07	2.66
HA-CA-CB	110.66	110.27	0.39
CB-SG-CD1	97.57	98.86	1.29
HB1-CB-HB2	108.06	106.75	1.31
HB1-CB-SG	108.08	109.17	1.09
HB2-CB-SG	109.59	109.21	0.38
SG-CD1-HD1	107.34	107.00	0.34
SG-CD1-OD2	111.74	115.22	3.48
SG-CD1-CE1	108.25	110.88	2.63
CD1-OD2-HD2	99.57	100.85	1.28
CD1-CE1-OZ2	112.74	116.46	3.72

Terms	QM	CHARMM	Abs. diff.
CD1-CE1-OZ3	116.73	116.87	0.14
HD1-CD1-OD2	109.39	105.61	3.78
HD1-CD1-CE1	110.35	104.60	5.75
OD2-CD1-CE1	109.74	112.64	2.90
OZ2-CE1-OZ3	130.53	126.58	3.94

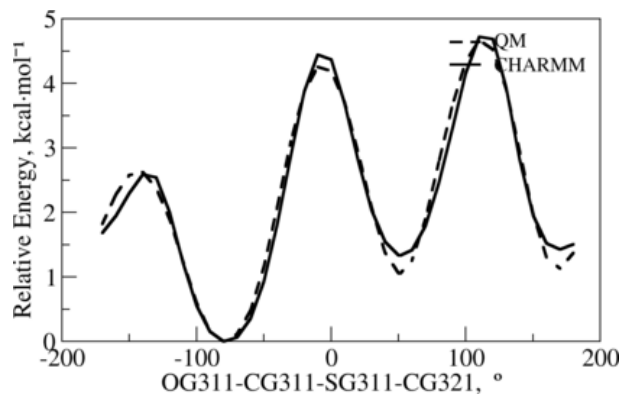


Figure S284: The PES scan for flexible dihedral corresponding to (2R)-2-(ethylsulfanyl)-2-hydroxyacetic acid.

2.48 The small molecule used for bonded terms optimization of 3-chloro-4-hydroxy-phenylglycine (CHP)

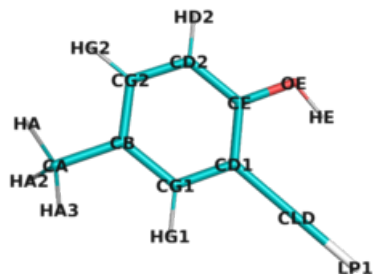


Figure S285: The energy minimized structure corresponding to 2,4-dimethylphenol.

Table S728: The calculated geometric terms of 2,4-dimethylphenol.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.10	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.51	1.50	0.01
CB-CG1	1.40	1.40	0.00
CB-CG2	1.40	1.40	0.00
CG1-HG1	1.09	1.08	0.01
CG1-CD1	1.39	1.40	0.01
CG2-HG2	1.09	1.08	0.01
CG2-CD2	1.39	1.40	0.01
CD2-HD2	1.09	1.08	0.01
CD2-CE	1.40	1.40	0.00
CD1-CLD	1.75	1.74	0.00
CD1-CE	1.40	1.41	0.01
CE-OE	1.37	1.41	0.05
OE-HE	0.98	0.96	0.01
HA3-CA-HA2	107.75	109.81	2.06
HA3-CA-HA	108.02	109.23	1.21
HA3-CA-CB	111.09	109.84	1.25
HA2-CA-HA	107.66	109.85	2.20
HA2-CA-CB	111.22	108.66	2.56
CA-CB-CG1	120.71	120.13	0.58
CA-CB-CG2	121.09	120.19	0.89
HA-CA-CB	110.94	109.43	1.51
CB-CG1-HG1	120.55	119.87	0.68
CB-CG1-CD1	120.53	120.43	0.10
CB-CG2-HG2	119.55	119.79	0.24
CB-CG2-CD2	121.32	120.13	1.19
CG1-CB-CG2	118.16	119.67	1.51
CG1-CD1-CLD	119.93	118.95	0.99
CG1-CD1-CE	121.21	119.73	1.48
HG1-CG1-CD1	118.91	119.70	0.79
CG2-CD2-HD2	121.52	120.23	1.30

Terms	QM	CHARMM	Abs. diff.
CG2-CD2-CE	120.48	120.14	0.35
HG2-CG2-CD2	119.12	120.08	0.96
CD2-CE-CD1	118.29	119.91	1.62
CD2-CE-OE	117.79	119.10	1.31
HD2-CD2-CE	118.00	119.64	1.64
CD1-CE-OE	123.92	120.99	2.93
CLD-CD1-CE	118.86	121.33	2.47
CE-OE-HE	108.34	106.41	1.93

2.49 The small molecule used for bonded terms optimization of S,S-(2-hydroxyethyl)thiocysteine (CME)

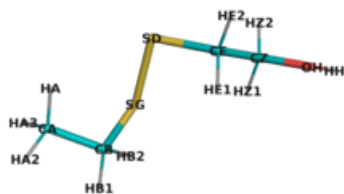


Figure S286: The energy minimized structure corresponding to 2-(ethylsulfanyl)ethan-1-ol.

Table S729: The calculated geometric terms of 2-(ethylsulfanyl)ethan-1-ol.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB1	1.10	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.82	1.82	0.01
SG-SD	2.06	2.03	0.03
SD-CE	1.82	1.82	0.00
CE-HE1	1.09	1.11	0.02
CE-HE2	1.09	1.11	0.02
CE-CZ	1.52	1.54	0.02
CZ-HZ1	1.10	1.11	0.02
CZ-HZ2	1.10	1.11	0.01
CZ-OH	1.43	1.43	0.00
OH-HH	0.97	0.96	0.01
HA3-CA-HA2	108.59	108.50	0.08
HA3-CA-HA	108.44	108.21	0.23
HA3-CA-CB	110.74	110.46	0.28
HA2-CA-HA	108.16	108.40	0.23
HA2-CA-CB	110.09	110.60	0.51
CA-CB-HB1	110.94	109.15	1.79
CA-CB-HB2	111.32	109.48	1.83
CA-CB-SG	113.96	111.94	2.02
HA-CA-CB	110.74	110.60	0.15
CB-SG-SD	102.20	103.85	1.65
HB1-CB-HB2	107.29	107.48	0.19
HB1-CB-SG	104.09	109.09	5.00
HB2-CB-SG	108.81	109.60	0.78
SG-SD-CE	102.18	103.97	1.79
SD-CE-HE1	110.26	109.93	0.33
SD-CE-HE2	105.86	109.46	3.59
SD-CE-CZ	112.94	112.42	0.53

Terms	QM	CHARMM	Abs. diff.
CE-CZ-HZ1	109.77	109.73	0.03
CE-CZ-HZ2	109.65	109.33	0.32
CE-CZ-OH	106.06	109.90	3.83
HE1-CE-HE2	107.91	107.43	0.48
HE1-CE-CZ	110.00	108.88	1.12
HE2-CE-CZ	109.67	108.59	1.08
CZ-OH-HH	107.59	107.89	0.29
HZ1-CZ-HZ2	108.25	108.59	0.35
HZ1-CZ-OH	111.47	109.52	1.95
HZ2-CZ-OH	111.62	109.74	1.89

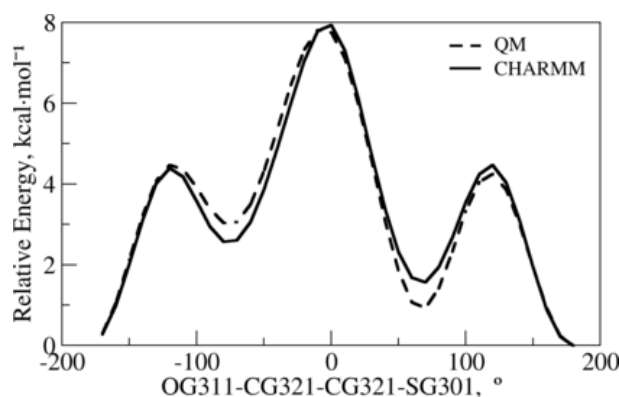


Figure S287: The PES scan for flexible dihedral corresponding to 2-(ethylsulfanyl)ethan-1-ol.

2.50 The small molecule used for bonded terms optimization of (2S)-2-[(2R)-2-amino-2-carboxyethyl]sulfanylbutanedioic acid (CML)

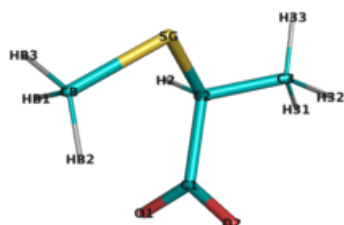


Figure S288: The energy minimized structure corresponding to 2-(methylsulfanyl)propanoic acid.

Table S730: The calculated geometric terms of 2-(methylsulfanyl)propanoic acid.

Terms	QM	CHARMM	Abs. diff.
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-HB3	1.10	1.11	0.01
CB-SG	1.81	1.82	0.01
SG-C2	1.83	1.84	0.01
C2-H2	1.10	1.11	0.02
C2-C1	1.56	1.55	0.01
C2-C3	1.52	1.55	0.03
C1-O1	1.27	1.26	0.01
C1-O2	1.27	1.26	0.00
C3-H31	1.10	1.11	0.01
C3-H32	1.09	1.11	0.02
C3-H33	1.10	1.11	0.01
CB-SG-C2	99.98	100.06	0.09
HB1-CB-HB2	109.08	107.59	1.48
HB1-CB-HB3	109.44	108.54	0.90
HB1-CB-SG	111.42	110.94	0.48
HB2-CB-HB3	109.66	107.68	1.97
HB2-CB-SG	110.00	110.91	0.91
HB3-CB-SG	107.23	111.05	3.82
SG-C2-H2	107.78	108.48	0.71
SG-C2-C1	111.49	109.60	1.89
SG-C2-C3	107.84	112.37	4.53
C2-C1-O1	114.59	115.49	0.90
C2-C1-O2	115.98	117.29	1.31
C2-C3-H31	109.27	110.26	1.00
C2-C3-H32	109.16	109.54	0.38
C2-C3-H33	111.98	110.45	1.53
H2-C2-C1	107.45	106.79	0.66
H2-C2-C3	110.80	107.99	2.82
C1-C2-C3	111.45	111.40	0.05
O1-C1-O2	129.43	127.08	2.35

Terms	QM	CHARMM	Abs. diff.
H31-C3-H32	108.43	108.52	0.09
H31-C3-H33	108.26	109.17	0.91
H32-C3-H33	109.68	108.85	0.83

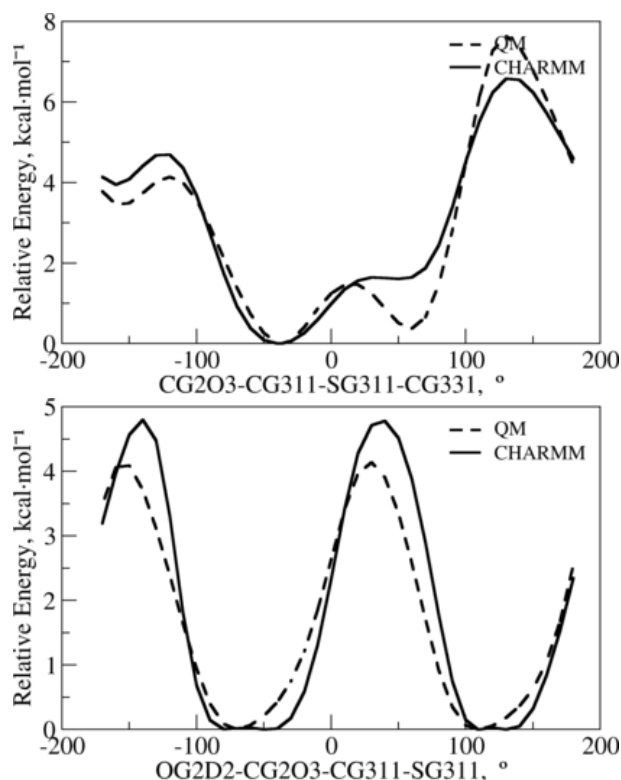
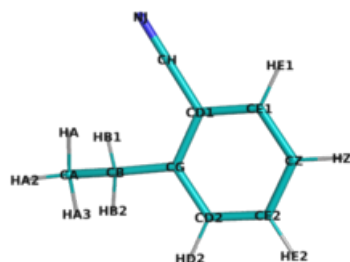


Figure S289: The PES scan for flexible dihedrals corresponding to 2-(methylsulfanyl)propanoic acid.

2.51 The small molecule used for bonded terms optimization of 2-cyano-phenylalanine (CNP2)



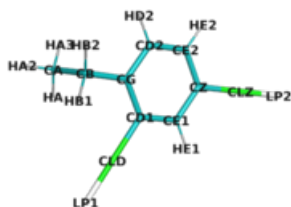
Terms	QM	CHARMM	Abs. diff.
CG-CD1-CE1	121.58	119.88	1.69
CG-CD2-HD2	118.82	119.68	0.86
CG-CD2-CE2	121.57	120.62	0.95
CD1-CG-CD2	117.38	119.21	1.83
CD1-CH-NJ	179.58	179.73	0.15
CD1-CE1-HE1	119.52	120.39	0.87
CD1-CE1-CZ	119.56	120.26	0.70
CH-CD1-CE1	118.91	118.92	0.02
CD2-CE2-HE2	119.84	119.93	0.10
CD2-CE2-CZ	120.10	120.02	0.08
HD2-CD2-CE2	119.61	119.70	0.10
CE1-CZ-CE2	119.80	120.01	0.21
CE1-CZ-HZ	119.85	120.04	0.19
HE1-CE1-CZ	120.91	119.35	1.57
CE2-CZ-HZ	120.35	119.96	0.40
HE2-CE2-CZ	120.06	120.05	0.01

Figure S290: The energy minimized structure corresponding to 2-ethylbenzonitrile.

Table S731: The calculated geometric terms of 2-ethylbenzonitrile.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.53	0.00
CB-HB1	1.10	1.11	0.02
CB-HB2	1.10	1.11	0.02
CB-CG	1.51	1.51	0.01
CG-CD1	1.41	1.41	0.00
CG-CD2	1.40	1.40	0.01
CD1-CH	1.44	1.44	0.00
CD1-CE1	1.40	1.41	0.00
CH-NJ	1.18	1.18	0.00
CD2-HD2	1.09	1.08	0.01
CD2-CE2	1.40	1.40	0.00
CE1-HE1	1.09	1.08	0.00
CE1-CZ	1.39	1.40	0.01
CE2-HE2	1.09	1.08	0.01
CE2-CZ	1.40	1.40	0.00
CZ-HZ	1.09	1.08	0.01
HA3-CA-HA2	108.39	108.08	0.31
HA3-CA-HA	108.34	108.47	0.13
HA3-CA-CB	110.57	111.06	0.49
HA2-CA-HA	108.06	107.81	0.25
HA2-CA-CB	110.70	110.19	0.51
CA-CB-HB1	109.54	110.83	1.29
CA-CB-HB2	109.85	110.21	0.36
CA-CB-CG	111.94	109.69	2.25
HA-CA-CB	110.69	111.11	0.42
CB-CG-CD1	121.32	122.11	0.79
CB-CG-CD2	121.22	118.68	2.54
HB1-CB-HB2	106.89	107.53	0.63
HB1-CB-CG	109.79	109.46	0.33
HB2-CB-CG	108.69	109.08	0.38
CG-CD1-CH	119.51	121.19	1.69

2.52 The small molecule used for bonded terms optimization of 2,4-dichloro-phenylalanine (CP24)



Terms	QM	CHARMM	Abs. diff.
CG-CD1-CE1	122.36	120.09	2.28
CG-CD2-HD2	118.51	119.62	1.11
CG-CD2-CE2	122.50	120.45	2.05
CD1-CG-CD2	116.68	119.17	2.49
CD1-CE1-HE1	120.47	119.90	0.56
CD1-CE1-CZ	118.76	120.28	1.52
CLD-CD1-CE1	117.31	118.46	1.15
CD2-CE2-HE2	121.03	120.60	0.43
CD2-CE2-CZ	118.71	119.99	1.29
HD2-CD2-CE2	118.99	119.93	0.95
CE1-CZ-CE2	120.97	120.02	0.96
CE1-CZ-CLZ	119.17	120.05	0.88
HE1-CE1-CZ	120.77	119.82	0.95
CE2-CZ-CLZ	119.85	119.93	0.08
HE2-CE2-CZ	120.26	119.41	0.85

Figure S291: The energy minimized structure corresponding to 1-ethyl-2,4-dimethylbenzene.

Table S732: The calculated geometric terms of 1-ethyl-2,4-dimethylbenzene.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.53	0.00
CB-HB1	1.09	1.11	0.02
CB-HB2	1.10	1.11	0.02
CB-CG	1.51	1.51	0.00
CG-CD1	1.40	1.41	0.01
CG-CD2	1.40	1.41	0.00
CD1-CLD	1.74	1.74	0.00
CD1-CE1	1.40	1.40	0.00
CD2-HD2	1.09	1.08	0.01
CD2-CE2	1.39	1.40	0.01
CE1-HE1	1.09	1.08	0.01
CE1-CZ	1.39	1.40	0.01
CE2-HE2	1.09	1.08	0.01
CE2-CZ	1.39	1.40	0.00
CZ-CLZ	1.74	1.74	0.00
HA3-CA-HA2	108.32	108.19	0.12
HA3-CA-HA	108.26	108.37	0.11
HA3-CA-CB	110.47	111.13	0.66
HA2-CA-HA	108.23	107.93	0.31
HA2-CA-CB	110.74	110.36	0.39
CA-CB-HB1	109.85	110.74	0.90
CA-CB-HB2	109.67	110.45	0.78
CA-CB-CG	111.99	109.69	2.30
HA-CA-CB	110.73	110.76	0.03
CB-CG-CD1	122.83	121.73	1.10
CB-CG-CD2	120.41	119.09	1.32
HB1-CB-HB2	106.89	107.84	0.95
HB1-CB-CG	109.87	109.02	0.85
HB2-CB-CG	108.43	109.06	0.62
CG-CD1-CLD	120.32	121.45	1.13

2.53 The small molecule used for bonded terms optimization of 2-chloro-phenylglycine (CPG2)

Terms	QM	CHARMM	Abs. diff.
CLG-CG2-CD2	118.22	118.97	0.75
CD1-CE-CD2	119.84	119.90	0.06
CD1-CE-HE	120.53	120.11	0.42
HD1-CD1-CE	120.29	119.95	0.35
CD2-CE-HE	119.63	119.99	0.36
HD2-CD2-CE	120.99	120.42	0.57

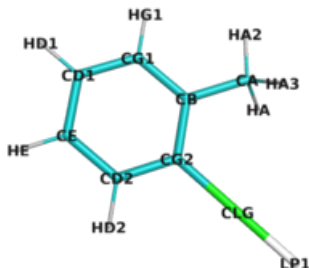


Figure S292: The energy minimized structure corresponding to 1,2-xylylene.

Table S733: The calculated geometric terms of 1,2-xylylene.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.50	1.50	0.00
CB-CG1	1.40	1.40	0.00
CB-CG2	1.40	1.41	0.01
CG1-HG1	1.09	1.08	0.01
CG1-CD1	1.40	1.40	0.01
CG2-CLG	1.75	1.74	0.01
CG2-CD2	1.39	1.40	0.01
CD1-HD1	1.09	1.08	0.01
CD1-CE	1.40	1.40	0.01
CD2-HD2	1.09	1.08	0.01
CD2-CE	1.39	1.40	0.01
CE-HE	1.09	1.08	0.01
HA3-CA-HA2	108.46	109.63	1.17
HA3-CA-HA	107.20	109.79	2.59
HA3-CA-CB	111.18	108.74	2.44
HA2-CA-HA	108.46	109.57	1.12
HA2-CA-CB	110.26	110.42	0.16
CA-CB-CG1	121.19	120.13	1.06
CA-CB-CG2	121.83	120.47	1.36
HA-CA-CB	111.18	108.68	2.50
CB-CG1-HG1	118.57	119.76	1.19
CB-CG1-CD1	121.80	120.39	1.41
CB-CG2-CLG	119.56	120.89	1.33
CB-CG2-CD2	122.22	120.14	2.08
CG1-CB-CG2	116.98	119.40	2.42
CG1-CD1-HD1	119.94	120.06	0.13
CG1-CD1-CE	119.77	119.99	0.22
HG1-CG1-CD1	119.63	119.86	0.23
CG2-CD2-HD2	119.62	119.40	0.23
CG2-CD2-CE	119.38	120.18	0.80

2.54 The small molecule 1 used for bonded terms optimization of 2-[1-amino-2-(1h-imidazol-5-yl)ethyl]-1-(carbOymethyl)-4-[(4-Oocyclohexa-2,5-dien-1-ylidene)methyl]-1h-imidazol-5-olate (CR8D)

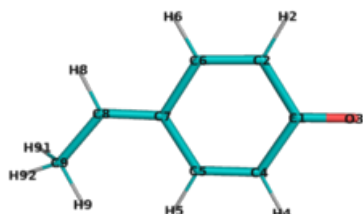


Figure S293: The energy minimized structure corresponding to 4-ethylidenecyclohexa-2,5-dien-1-one.

Table S734: The calculated geometric terms of 4-ethylidenecyclohexa-2,5-dien-1-one.

Terms	QM	CHARMM	Abs. diff.
C9-H9	1.09	1.11	0.02
C9-H91	1.10	1.11	0.02
C9-H92	1.10	1.11	0.02
C9-C8	1.49	1.51	0.02
C8-H8	1.09	1.10	0.01
C8-C7	1.36	1.35	0.01
C7-C5	1.46	1.49	0.03
C7-C6	1.46	1.49	0.03
C5-H5	1.09	1.10	0.01
C5-C4	1.35	1.36	0.01
C6-H6	1.09	1.10	0.01
C6-C2	1.35	1.36	0.01
C2-H2	1.09	1.10	0.01
C2-C1	1.47	1.51	0.04
C4-H4	1.09	1.10	0.01
C4-C1	1.47	1.51	0.04
C1-O3	1.24	1.23	0.01
C9-C8-H8	115.14	114.69	0.45
C9-C8-C7	128.07	128.11	0.04
H9-C9-H91	108.14	107.02	1.12
H9-C9-H92	108.13	106.92	1.21
H9-C9-C8	113.21	113.97	0.76
H91-C9-H92	106.72	107.27	0.54
H91-C9-C8	110.21	110.68	0.48
H92-C9-C8	110.19	110.67	0.47
C8-C7-C5	123.84	123.05	0.79
C8-C7-C6	118.99	119.80	0.81
H8-C8-C7	116.79	117.20	0.41
C7-C5-H5	119.24	119.54	0.30

Terms	QM	CHARMM	Abs. diff.
C7-C5-C4	121.28	122.00	0.72
C7-C6-H6	117.58	119.14	1.55
C7-C6-C2	122.05	122.17	0.12
C5-C7-C6	117.16	117.15	0.01
C5-C4-H4	121.66	118.99	2.66
C5-C4-C1	122.01	121.31	0.70
H5-C5-C4	119.48	118.46	1.02
C6-C2-H2	121.95	119.14	2.81
C6-C2-C1	121.31	121.14	0.17
H6-C6-C2	120.37	118.69	1.67
C2-C1-C4	116.19	116.23	0.05
C2-C1-O3	122.09	121.85	0.24
H2-C2-C1	116.74	119.72	2.98
C4-C1-O3	121.73	121.92	0.20
H4-C4-C1	116.34	119.70	3.36

2.55 The small molecule 2 used for bonded terms optimization of 2-[1-amino-2-(1h-imidazol-5-yl)ethyl]-1-(carbOymethyl)-4-[(4-Oocyclohexa-2,5-dien-1-ylidene)methyl]-1h-imidazol-5-olate (CR8D)

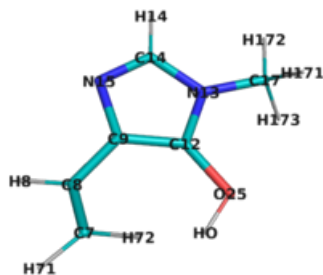


Figure S294: The energy minimized structure corresponding to 4-ethenyl-1-methyl-1H-imidazol-5-ol.

Table S735: The calculated geometric terms of 4-ethenyl-1-methyl-1H-imidazol-5-ol.

Terms	QM	CHARMM	Abs. diff.
C14-H14	1.08	1.09	0.01
C14-N13	1.38	1.36	0.02
C14-N15	1.32	1.32	0.00
N13-C17	1.45	1.47	0.01
N13-C12	1.37	1.37	0.01
C17-H171	1.09	1.11	0.02
C17-H172	1.09	1.11	0.02
C17-H173	1.09	1.11	0.02
C12-O25	1.36	1.38	0.02
C12-C9	1.39	1.38	0.01
O25-HO	0.98	0.96	0.01
N15-C9	1.38	1.40	0.01
C9-C8	1.45	1.44	0.01
C8-H8	1.09	1.10	0.01
C8-C7	1.35	1.36	0.01
C7-H71	1.08	1.10	0.02
C7-H72	1.09	1.10	0.01
C14-N13-C17	128.36	127.63	0.73
C14-N13-C12	106.01	105.22	0.79
C14-N15-C9	105.44	106.55	1.10
H14-C14-N13	121.58	122.53	0.95
H14-C14-N15	126.08	124.89	1.19
N13-C14-N15	112.34	112.59	0.25
N13-C17-H171	110.50	110.11	0.39
N13-C17-H172	108.16	112.05	3.89
N13-C17-H173	109.89	110.20	0.31
N13-C12-O25	118.98	119.22	0.24
N13-C12-C9	107.15	108.91	1.76
C17-N13-C12	125.63	127.15	1.52

Terms	QM	CHARMM	Abs. diff.
H171-C17-H172	109.53	108.24	1.29
H171-C17-H173	109.21	107.96	1.25
H172-C17-H173	109.54	108.16	1.38
C12-O25-HO	106.08	106.34	0.26
C12-C9-N15	109.04	106.73	2.31
C12-C9-C8	127.43	129.65	2.22
O25-C12-C9	133.82	131.75	2.07
N15-C9-C8	123.43	123.59	0.17
C9-C8-H8	115.70	114.85	0.85
C9-C8-C7	124.58	127.74	3.16
C8-C7-H71	121.33	120.55	0.78
C8-C7-H72	122.05	121.67	0.38
H8-C8-C7	119.71	117.36	2.35
H71-C7-H72	116.53	117.58	1.06

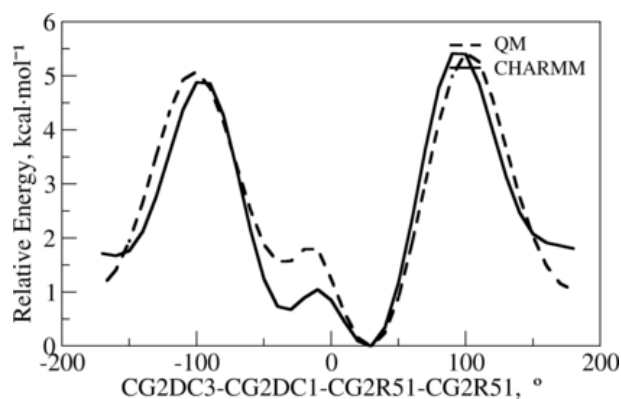


Figure S295: The PES scan for flexible dihedral corresponding to 4-ethenyl-1-methyl-1H-imidazol-5-ol.

2.56 The small molecule used for bonded terms optimization of s-acetylcysteine (CSA)

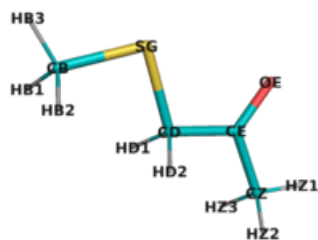


Figure S296: The energy minimized structure corresponding to 1-(methylsulfonyl)propan-2-one.

Table S736: The calculated geometric terms of 1-(methylsulfonyl)propan-2-one.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.81	1.82	0.01
SG-CD	1.81	1.83	0.02
CD-HD2	1.10	1.11	0.01
CD-HD1	1.10	1.11	0.01
CD-CE	1.52	1.51	0.01
CE-OE	1.23	1.23	0.00
CE-CZ	1.51	1.50	0.02
CZ-HZ1	1.09	1.11	0.02
CZ-HZ2	1.09	1.11	0.02
CZ-HZ3	1.09	1.11	0.01
HB3-CB-HB1	108.40	107.62	0.79
HB3-CB-HB2	108.40	107.62	0.79
HB3-CB-SG	107.13	110.61	3.48
CB-SG-CD	97.12	96.78	0.33
HB1-CB-HB2	109.41	108.23	1.18
HB1-CB-SG	111.68	111.31	0.38
HB2-CB-SG	111.69	111.31	0.38
SG-CD-HD2	110.89	110.26	0.63
SG-CD-HD1	110.89	110.26	0.63
SG-CD-CE	110.89	111.08	0.19
CD-CE-OE	121.89	123.81	1.92
CD-CE-CZ	115.86	115.75	0.11
HD2-CD-HD1	106.85	108.35	1.50
HD2-CD-CE	108.60	108.41	0.19
HD1-CD-CE	108.60	108.41	0.19
CE-CZ-HZ1	109.15	109.02	0.13
CE-CZ-HZ2	110.40	110.10	0.30
CE-CZ-HZ3	110.41	110.14	0.27
OE-CE-CZ	122.25	120.44	1.81
HZ1-CZ-HZ2	109.70	108.89	0.81
HZ1-CZ-HZ3	109.70	108.92	0.78

Terms	QM	CHARMM	Abs. diff.
HZ2-CZ-HZ3	107.46	109.74	2.28

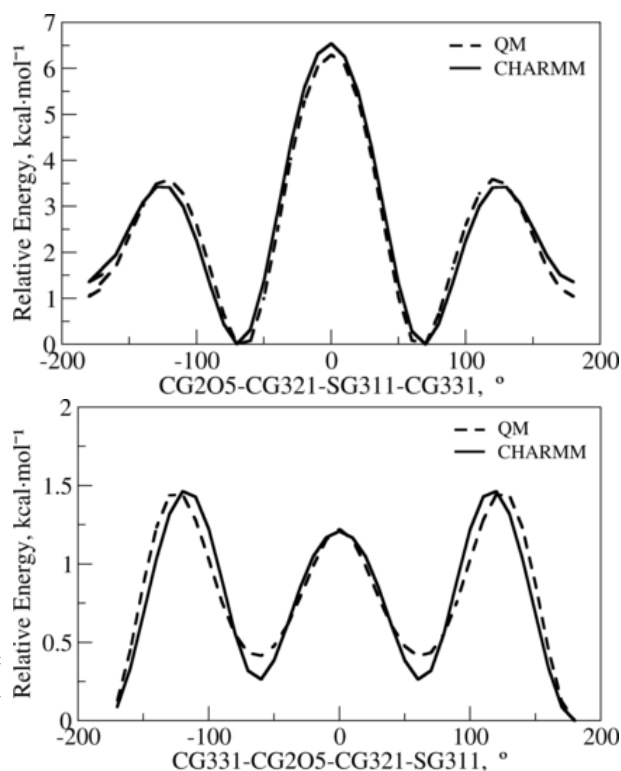


Figure S297: The PES scan for flexible dihedrals corresponding to 1-(methylsulfonyl)propan-2-one.

2.57 The small molecule used for bonded terms optimization of S-hydroxycysteine (CSO)

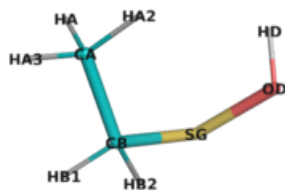


Figure S298: The energy minimized structure corresponding to ethane-SO-thioperoxol.

Table S737: The calculated geometric terms of ethane-SO-thioperoxol.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB1	1.10	1.11	0.01
CB-HB2	1.09	1.11	0.02
CB-SG	1.80	1.82	0.01
SG-OD	1.70	1.70	0.00
OD-HD	0.98	0.96	0.01
HA3-CA-HA2	107.77	108.19	0.42
HA3-CA-HA	108.58	108.45	0.12
HA3-CA-CB	110.54	110.38	0.16
HA2-CA-HA	108.67	108.60	0.07
HA2-CA-CB	110.23	110.54	0.30
CA-CB-HB1	111.12	109.23	1.89
CA-CB-HB2	111.01	109.36	1.65
CA-CB-SG	113.95	112.70	1.25
HA-CA-CB	110.96	110.60	0.36
CB-SG-OD	99.60	99.79	0.19
HB1-CB-HB2	107.48	107.51	0.03
HB1-CB-SG	104.42	108.96	4.53
HB2-CB-SG	108.47	108.95	0.48
SG-OD-HD	106.13	106.20	0.07

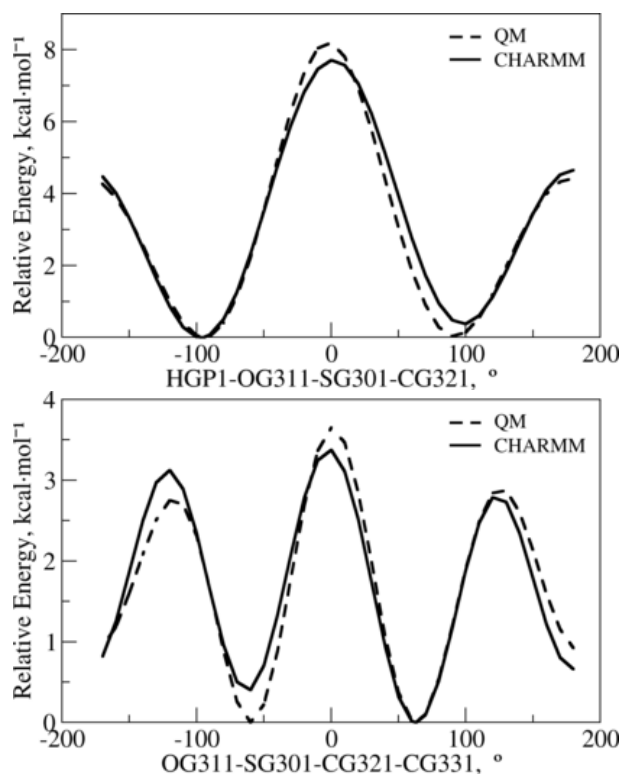


Figure S299: The PES scan for flexible dihedrals corresponding to ethane-SO-thioperoxol.

2.58 The small molecule used for bonded terms optimization of (CSP)

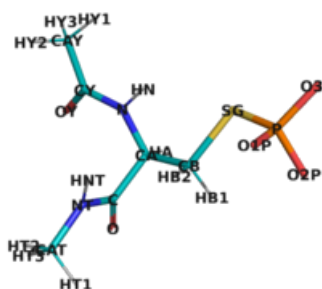


Figure S300: The energy minimized structure corresponding to [(2R)-2-acetamido-2-(methylcarbamoyl)ethyl]sulfanylphosphonic acid.

Table S738: The calculated geometric terms of [(2R)-2-acetamido-2-(methylcarbamoyl)ethyl]sulfanylphosphonic acid.

Terms	QM	CHARMM	Abs. diff.
N-HN	1.03	1.00	0.03
N-CA	1.46	1.45	0.01
N-CY	1.35	1.34	0.01
CA-HA	1.10	1.08	0.02
CA-CB	1.54	1.55	0.01
CA-C	1.52	1.52	0.00
CB-HB1	1.10	1.12	0.02
CB-HB2	1.10	1.12	0.02
CB-SG	1.82	1.86	0.04
SG-P	2.34	1.53	0.81
P-O1P	1.54	1.48	0.06
P-O2P	1.54	1.48	0.06
P-O3P	1.53	1.48	0.06
C-O	1.24	1.23	0.01
C-NT	1.37	1.34	0.02
NT-HNT	1.01	1.00	0.02
NT-CAT	1.45	1.44	0.01
CAT-HT1	1.10	1.11	0.01
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.09	1.11	0.02
CAY-HY1	1.09	1.11	0.01
CAY-HY2	1.10	1.11	0.01
CAY-HY3	1.09	1.11	0.02
CAY-CY	1.52	1.48	0.04
CY-OY	1.25	1.23	0.02
N-CA-HA	110.49	109.21	1.28
N-CA-CB	106.51	108.02	1.51
N-CA-C	111.24	114.54	3.31
N-CY-CAY	114.81	117.56	2.75
N-CY-OY	124.34	123.08	1.25
HN-N-CA	110.78	110.26	0.52
HN-N-CY	120.20	123.08	2.88

Terms	QM	CHARMM	Abs. diff.
CA-N-CY	124.53	125.42	0.89
CA-CB-HB1	109.24	109.35	0.12
CA-CB-HB2	110.88	111.29	0.41
CA-CB-SG	111.82	113.48	1.66
CA-C-O	123.38	123.37	0.01
CA-C-NT	114.65	114.77	0.12
HA-CA-CB	110.65	109.95	0.70
HA-CA-C	107.11	108.87	1.76
CB-CA-C	110.89	106.16	4.74
CB-SG-P	94.11	104.02	9.90
HB1-CB-HB2	107.60	108.75	1.15
HB1-CB-SG	108.99	107.44	1.55
HB2-CB-SG	108.20	106.34	1.86
SG-P-O1P	99.15	110.55	11.41
SG-P-O2P	99.48	111.92	12.44
SG-P-O3P	99.48	111.41	11.93
O1P-P-O2P	116.08	107.42	8.67
O1P-P-O3P	117.88	107.53	10.36
O2P-P-O3P	118.24	107.82	10.42
C-NT-HNT	117.05	115.61	1.44
C-NT-CAT	120.57	122.99	2.42
O-C-NT	121.82	121.86	0.04
NT-CAT-HT1	111.71	109.61	2.10
NT-CAT-HT2	108.58	109.86	1.28
NT-CAT-HT3	109.64	110.56	0.92
HNT-NT-CAT	119.55	119.67	0.12
HT1-CAT-HT2	109.37	108.89	0.48
HT1-CAT-HT3	108.20	108.73	0.53
HT2-CAT-HT3	109.31	109.15	0.15
CAY-CY-OY	120.78	119.36	1.43
HY1-CAY-HY2	108.99	109.39	0.40
HY1-CAY-HY3	109.78	109.19	0.58
HY1-CAY-CY	112.66	111.50	1.17
HY2-CAY-HY3	108.00	108.56	0.56
HY2-CAY-CY	108.85	109.47	0.62
HY3-CAY-CY	108.46	108.68	0.22

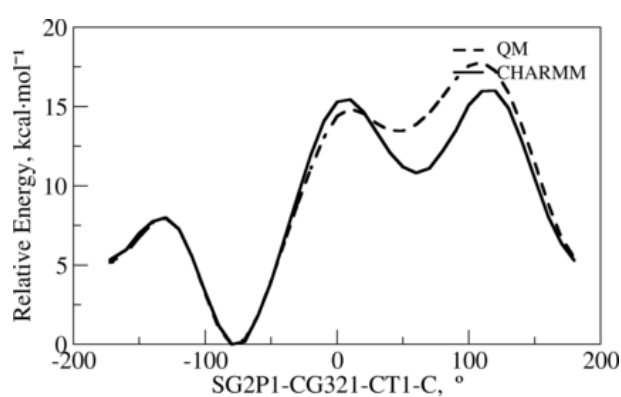


Figure S301: The PES scan for flexible dihedral corresponding to [(2R)-2-acetamido-2-(methylcarbamoyl)ethyl]sulfanylphosphonic acid.

2.59 The small molecule used for bonded terms optimization of (CSPP)

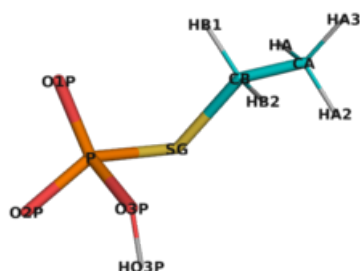


Figure S302: The energy minimized structure corresponding to (ethylsulfanyl)phosphonic acid.

Table S739: The calculated geometric terms of (ethylsulfanyl)phosphonic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.10	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.82	1.83	0.01
SG-P	2.16	2.00	0.15
P-O1P	1.51	1.47	0.03
P-O2P	1.51	1.47	0.04
P-O3P	1.68	1.61	0.08
O3P-HO3P	0.98	0.96	0.01
HA3-CA-HA2	108.18	108.50	0.32
HA3-CA-HA	108.25	108.44	0.19
HA3-CA-CB	110.36	110.14	0.22
HA2-CA-HA	107.99	108.57	0.58
HA2-CA-CB	111.14	110.60	0.54
CA-CB-HB1	111.04	110.64	0.40
CA-CB-HB2	110.42	110.76	0.35
CA-CB-SG	110.56	110.75	0.19
HA-CA-CB	110.82	110.53	0.29
CB-SG-P	98.64	99.39	0.75
HB1-CB-HB2	107.79	109.03	1.25
HB1-CB-SG	107.99	107.71	0.28
HB2-CB-SG	108.96	107.84	1.12
SG-P-O1P	107.77	118.22	10.44
SG-P-O2P	104.83	117.42	12.59
SG-P-O3P	100.89	102.43	1.54
P-O3P-HO3P	105.99	112.70	6.70
O1P-P-O2P	126.89	112.07	14.82
O1P-P-O3P	105.99	103.00	2.99
O2P-P-O3P	107.59	100.00	7.59

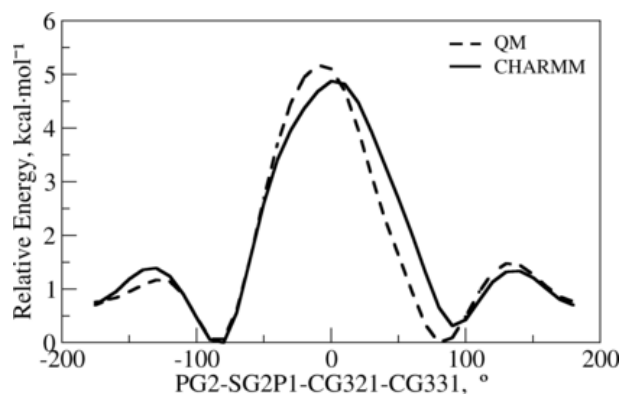


Figure S303: The PES scan for flexible dihedral corresponding to (ethylsulfanyl)phosphonic acid.

2.60 The small molecule used for bonded terms optimization of S-mercaptocysteine (CSS)

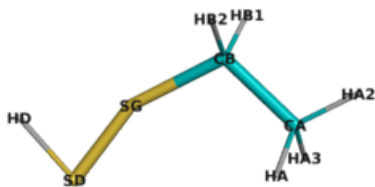


Figure S304: The energy minimized structure corresponding to ethanedithioperoxol.

Table S740: The calculated geometric terms of ethanedithioperoxol.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB1	1.10	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.82	1.82	0.00
SG-SD	2.06	2.07	0.01
SD-HD	1.35	1.33	0.02
HA3-CA-HA2	108.60	108.49	0.11
HA3-CA-HA	108.46	108.29	0.16
HA3-CA-CB	110.73	110.35	0.39
HA2-CA-HA	108.12	108.46	0.34
HA2-CA-CB	110.07	110.55	0.48
CA-CB-HB1	110.82	109.16	1.67
CA-CB-HB2	111.39	109.50	1.89
CA-CB-SG	114.12	111.85	2.27
HA-CA-CB	110.79	110.63	0.16
CB-SG-SD	102.47	104.07	1.60
HB1-CB-HB2	107.42	107.48	0.06
HB1-CB-SG	103.71	109.08	5.37
HB2-CB-SG	108.92	109.68	0.76
SG-SD-HD	99.30	99.30	0.01

2.61 The small molecule used for bonded terms optimization of cysteine-S-sulfonicacid (CSU)

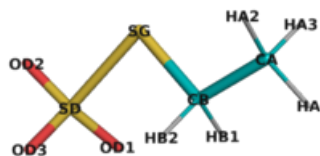


Figure S305: The energy minimized structure corresponding to (ethylsulfanyl)sulfonic acid.

Table S741: The calculated geometric terms of (ethylsulfanyl)sulfonic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.10	1.11	0.02
CA-HA	1.10	1.11	0.01
CA-CB	1.53	1.53	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.82	1.82	0.00
SG-SD	2.18	2.19	0.01
SD-OD1	1.49	1.45	0.04
SD-OD2	1.48	1.45	0.03
SD-OD3	1.49	1.45	0.04
HA3-CA-HA2	108.12	108.44	0.32
HA3-CA-HA	108.20	108.74	0.54
HA3-CA-CB	111.07	110.17	0.90
HA2-CA-HA	108.18	108.79	0.61
HA2-CA-CB	111.05	110.19	0.86
CA-CB-HB1	110.64	109.73	0.92
CA-CB-HB2	110.62	109.71	0.91
CA-CB-SG	110.38	111.30	0.92
HA-CA-CB	110.12	110.46	0.34
CB-SG-SD	96.77	97.00	0.22
HB1-CB-HB2	108.16	107.36	0.80
HB1-CB-SG	108.47	109.33	0.86
HB2-CB-SG	108.48	109.32	0.84
SG-SD-OD1	104.10	104.52	0.42
SG-SD-OD2	101.58	103.20	1.62
SG-SD-OD3	104.08	104.49	0.41
OD1-SD-OD2	115.47	113.76	1.71
OD1-SD-OD3	113.81	115.36	1.55
OD2-SD-OD3	115.46	113.72	1.74

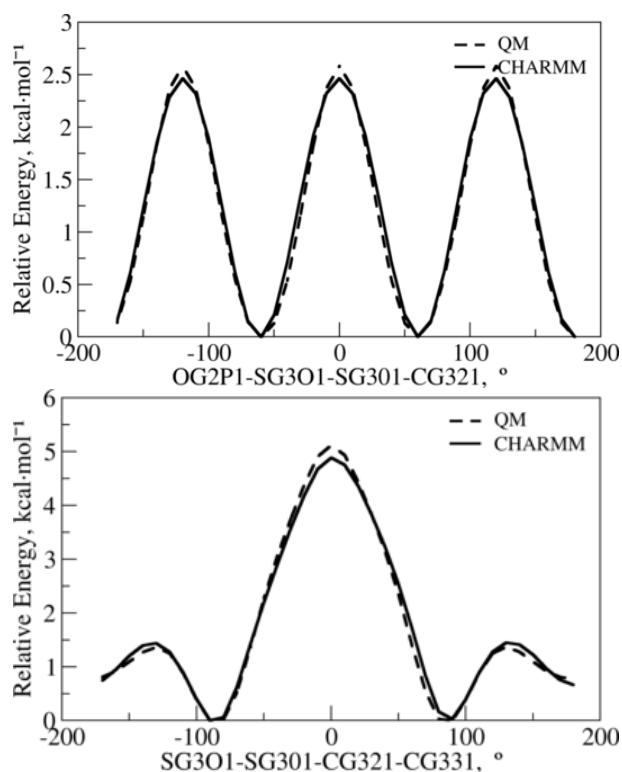


Figure S306: The PES scan for flexible dihedrals corresponding to (ethylsulfanyl)sulfonic acid.

2.62 The small molecule used for bonded terms optimization of S-oxycysteine (CSX)

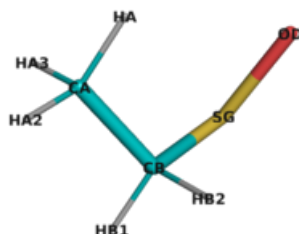


Figure S307: The energy minimized structure corresponding to ethane-SO-thioperoxol.

Table S742: The calculated geometric terms of ethane-SO-thioperoxol.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.10	1.11	0.01
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.53	0.01
CB-HB1	1.10	1.11	0.01
CB-HB2	1.10	1.11	0.01
CB-SG	1.82	1.81	0.01
SG-OD	1.62	1.62	0.00
HA3-CA-HA2	108.81	109.54	0.73
HA3-CA-HA	108.08	107.94	0.13
HA3-CA-CB	110.43	110.17	0.26
HA2-CA-HA	109.13	109.01	0.12
HA2-CA-CB	111.90	111.06	0.83
CA-CB-HB1	111.38	109.98	1.40
CA-CB-HB2	109.26	109.36	0.10
CA-CB-SG	112.24	111.51	0.73
HA-CA-CB	108.41	109.04	0.63
CB-SG-OD	103.13	103.46	0.33
HB1-CB-HB2	108.28	108.34	0.06
HB1-CB-SG	106.99	109.61	2.62
HB2-CB-SG	108.56	107.96	0.60

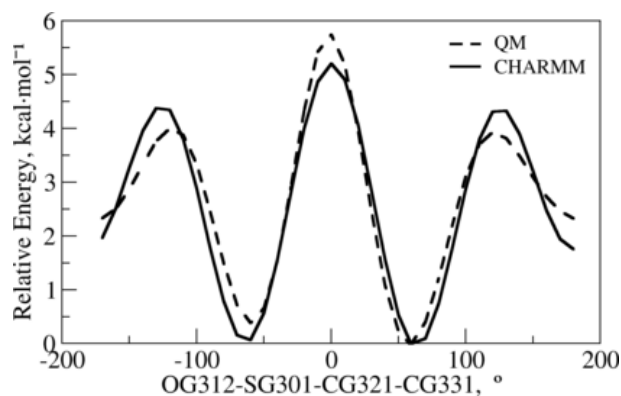


Figure S308: The PES scan for flexible dihedral corresponding to ethane-SO-thioperoxol.

2.63 The small molecule used for bonded terms optimization of 7-chloro-tryptophan (CTE)

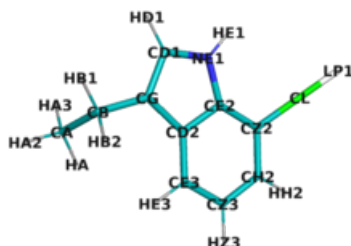


Figure S309: The energy minimized structure corresponding to 3-ethyl-7-methyl-1H-indole.

Table S743: The calculated geometric terms of 3-ethyl-7-methyl-1H-indole.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.54	0.00
CB-HB1	1.10	1.11	0.02
CB-HB2	1.10	1.11	0.02
CB-CG	1.50	1.51	0.01
CG-CD1	1.38	1.37	0.01
CG-CD2	1.43	1.44	0.00
CD1-HD1	1.08	1.08	0.00
CD1-NE1	1.38	1.39	0.01
CD2-CE2	1.42	1.40	0.02
CD2-CE3	1.41	1.39	0.01
NE1-HE1	1.01	1.01	0.00
NE1-CE2	1.37	1.38	0.01
CE2-CZ2	1.40	1.39	0.00
CE3-HE3	1.09	1.08	0.01
CE3-CZ3	1.39	1.40	0.01
CZ2-CL	1.74	1.74	0.00
CZ2-CH2	1.39	1.40	0.01
CZ3-HZ3	1.09	1.08	0.00
CZ3-CH2	1.41	1.40	0.01
CH2-HH2	1.09	1.08	0.01
HA3-CA-HA2	108.42	108.21	0.21
HA3-CA-HA	107.79	108.28	0.49
HA3-CA-CB	110.24	110.58	0.34
HA2-CA-HA	108.31	108.30	0.01
HA2-CA-CB	111.19	110.42	0.77
CA-CB-HB1	109.65	108.80	0.85
CA-CB-HB2	109.62	109.47	0.14
CA-CB-CG	112.52	113.86	1.34
HA-CA-CB	110.79	110.95	0.17
CB-CG-CD1	127.06	127.72	0.66
CB-CG-CD2	126.57	124.92	1.66

Terms	QM	CHARMM	Abs. diff.
HB1-CB-HB2	106.28	106.94	0.66
HB1-CB-CG	109.08	109.07	0.01
HB2-CB-CG	109.50	108.47	1.03
CG-CD1-HD1	129.53	127.60	1.92
CG-CD1-NE1	109.98	107.75	2.23
CG-CD2-CE2	107.04	107.94	0.91
CG-CD2-CE3	134.02	132.13	1.88
CD1-CG-CD2	106.29	107.35	1.06
CD1-NE1-HE1	126.21	127.45	1.23
CD1-NE1-CE2	108.98	111.06	2.08
HD1-CD1-NE1	120.49	124.65	4.16
CD2-CE2-NE1	107.71	105.89	1.81
CD2-CE2-CZ2	121.61	120.68	0.92
CD2-CE3-HE3	120.76	119.47	1.30
CD2-CE3-CZ3	118.85	119.72	0.87
NE1-CE2-CZ2	130.69	133.43	2.74
HE1-NE1-CE2	124.79	121.49	3.30
CE2-CD2-CE3	118.93	119.92	1.00
CE2-CZ2-CL	119.40	122.03	2.63
CE2-CZ2-CH2	118.80	119.20	0.40
CE3-CZ3-HZ3	119.77	120.09	0.32
CE3-CZ3-CH2	121.74	119.97	1.76
HE3-CE3-CZ3	120.38	120.81	0.43
CZ2-CH2-CZ3	120.07	120.50	0.43
CZ2-CH2-HH2	119.46	118.75	0.71
CL-CZ2-CH2	121.80	118.77	3.03
CZ3-CH2-HH2	120.47	120.75	0.28
HZ3-CZ3-CH2	118.49	119.93	1.45

2.64 The small molecule used for bonded terms optimization of 4-chloro-threonine (CTH)

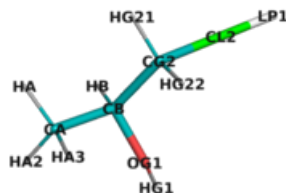


Figure S310: The energy minimized structure corresponding to butan-2-ol.

Table S744: The calculated geometric terms of butan-2-ol.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB	1.09	1.12	0.02
CB-OG1	1.42	1.42	0.00
CB-CG2	1.52	1.55	0.03
OG1-HG1	0.97	0.96	0.01
CG2-HG21	1.09	1.11	0.02
CG2-HG22	1.09	1.11	0.02
CG2-CL2	1.78	1.79	0.01
HA3-CA-HA2	108.30	108.28	0.02
HA3-CA-HA	108.14	108.51	0.38
HA3-CA-CB	110.51	111.18	0.66
HA2-CA-HA	108.78	108.03	0.74
HA2-CA-CB	109.32	110.18	0.86
CA-CB-HB	109.91	108.72	1.19
CA-CB-OG1	111.34	107.03	4.31
CA-CB-CG2	110.25	113.54	3.29
HA-CA-CB	111.72	110.56	1.15
CB-OG1-HG1	107.46	107.67	0.21
CB-CG2-HG21	110.56	109.59	0.97
CB-CG2-HG22	110.13	110.04	0.08
CB-CG2-CL2	112.32	114.32	2.00
HB-CB-OG1	104.43	107.75	3.31
HB-CB-CG2	108.69	108.07	0.61
OG1-CB-CG2	112.04	111.56	0.48
HG21-CG2-HG22	108.53	108.87	0.34
HG21-CG2-CL2	107.62	106.73	0.89
HG22-CG2-CL2	107.55	107.10	0.45

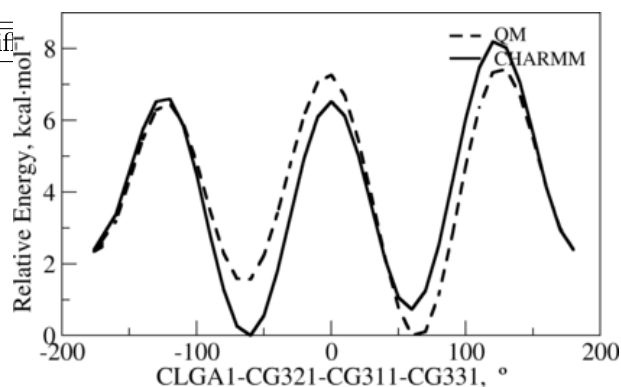


Figure S311: The PES scan for flexible dihedral corresponding to butan-2-ol.

2.65 The small molecule used for bonded terms optimization of N-carboxymethionine (CXM)

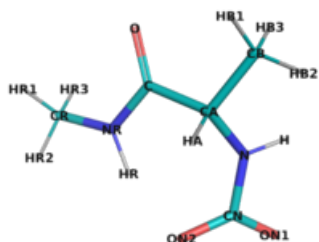


Figure S312: The energy minimized structure corresponding to N-[(1S)-1-(methylcarbamoyl)ethyl]carbamate.

Table S745: The calculated geometric terms of N-[(1S)-1-(methylcarbamoyl)ethyl]carbamate.

Terms	QM	CHARMM	Abs. diff.
N-H	1.02	0.99	0.03
N-CN	1.44	1.34	0.10
N-CA	1.46	1.46	0.01
CN-ON1	1.26	1.25	0.01
CN-ON2	1.28	1.25	0.03
CA-HA	1.10	1.11	0.01
CA-CB	1.52	1.54	0.02
CA-C	1.54	1.53	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.10	1.11	0.01
CB-HB3	1.09	1.11	0.02
C-O	1.25	1.23	0.02
C-NR	1.35	1.34	0.01
NR-HR	1.04	1.01	0.03
NR-CR	1.45	1.44	0.01
CR-HR1	1.09	1.11	0.02
CR-HR2	1.09	1.11	0.02
CR-HR3	1.10	1.11	0.01
N-CN-ON1	115.41	110.59	4.83
N-CN-ON2	115.21	115.39	0.18
N-CA-HA	109.06	107.83	1.23
N-CA-CB	110.24	109.33	0.91
N-CA-C	109.88	113.21	3.34
H-N-CN	109.91	113.01	3.10
H-N-CA	113.96	117.73	3.77
CN-N-CA	120.54	128.79	8.25
ON1-CN-ON2	129.36	134.01	4.65
CA-CB-HB1	110.80	110.91	0.11
CA-CB-HB2	109.66	109.64	0.02
CA-CB-HB3	110.29	110.19	0.10
CA-C-O	123.31	122.75	0.56
CA-C-NR	113.16	115.45	2.29
HA-CA-CB	109.78	108.51	1.27

Terms	QM	CHARMM	Abs. diff.
HA-CA-C	107.13	106.87	0.26
CB-CA-C	110.69	110.92	0.23
HB1-CB-HB2	109.15	108.78	0.36
HB1-CB-HB3	107.57	108.75	1.17
HB2-CB-HB3	109.33	108.53	0.80
C-NR-HR	115.01	113.85	1.16
C-NR-CR	120.85	124.46	3.62
O-C-NR	123.53	121.78	1.74
NR-CR-HR1	110.43	110.51	0.07
NR-CR-HR2	108.33	110.01	1.68
NR-CR-HR3	111.61	110.20	1.41
HR-NR-CR	122.00	121.46	0.53
HR1-CR-HR2	109.37	108.74	0.63
HR1-CR-HR3	107.78	108.65	0.88
HR2-CR-HR3	109.30	108.68	0.61

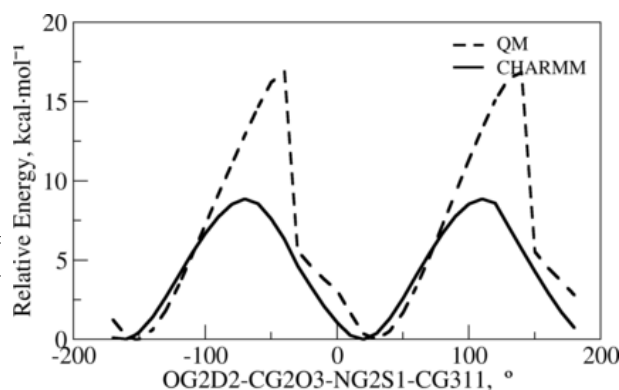


Figure S313: The PES scan for flexible dihedral corresponding to N-[(1S)-1-(methylcarbamoyl)ethyl]carbamate.

2.66 The small molecule used for bonded terms optimization of 2-amino-6-(cystein-S-yl)-5-oxo-hexanoicacid (CYD)

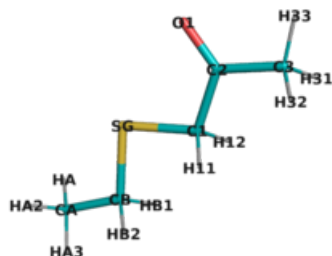


Figure S314: The energy minimized structure corresponding to 1-(ethylsulfanyl)propan-2-one.

Table S746: The calculated geometric terms of 1-(ethylsulfanyl)propan-2-one.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB1	1.10	1.11	0.02
CB-HB2	1.10	1.11	0.02
CB-SG	1.82	1.82	0.00
SG-C1	1.81	1.83	0.02
C1-H11	1.10	1.11	0.01
C1-H12	1.10	1.11	0.01
C1-C2	1.52	1.51	0.01
C2-O1	1.23	1.23	0.00
C2-C3	1.51	1.50	0.02
C3-H31	1.09	1.11	0.02
C3-H32	1.09	1.11	0.02
C3-H33	1.09	1.11	0.02
HA3-CA-HA2	108.22	108.45	0.23
HA3-CA-HA	108.22	108.45	0.23
HA3-CA-CB	110.14	110.70	0.56
HA2-CA-HA	108.26	108.20	0.06
HA2-CA-CB	110.95	110.48	0.47
CA-CB-HB1	110.08	108.70	1.39
CA-CB-HB2	110.08	108.68	1.40
CA-CB-SG	109.51	112.41	2.90
HA-CA-CB	110.95	110.48	0.47
CB-SG-C1	97.43	97.22	0.21
HB1-CB-HB2	107.93	107.25	0.68
HB1-CB-SG	109.61	109.84	0.23
HB2-CB-SG	109.61	109.82	0.21
SG-C1-H11	110.92	110.26	0.66
SG-C1-H12	110.91	110.27	0.64
SG-C1-C2	110.97	111.20	0.23
C1-C2-O1	121.97	123.72	1.75

Terms	QM	CHARMM	Abs. diff.
C1-C2-C3	115.81	115.94	0.13
H11-C1-H12	106.83	108.31	1.47
H11-C1-C2	108.53	108.35	0.18
H12-C1-C2	108.53	108.37	0.17
C2-C3-H31	110.40	110.14	0.27
C2-C3-H32	110.40	110.14	0.26
C2-C3-H33	109.15	109.06	0.09
O1-C2-C3	122.22	120.33	1.89
H31-C3-H32	107.46	109.72	2.26
H31-C3-H33	109.70	108.87	0.83
H32-C3-H33	109.70	108.87	0.83

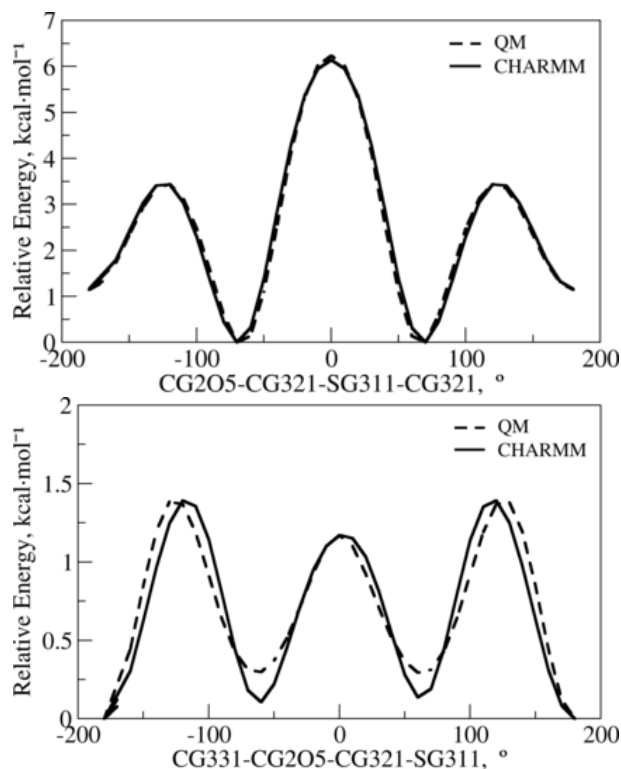


Figure S315: The PES scan for flexible dihedrals corresponding to 1-(ethylsulfanyl)propan-2-one.

2.67 The small molecule used for bonded terms optimization of 5-[2-(2-amino-2-carbamoyl-ethylsulfanyl)-acetyl-amino]-2-(3,6-dihydroxy-9,9a-dihydro-3h-xanthen-9-yl)-benzoic acid (CYF)

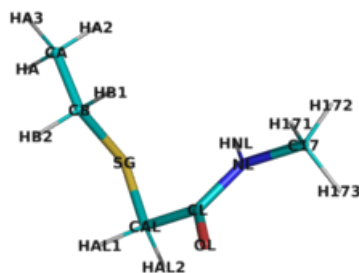


Figure S316: The energy minimized structure corresponding to 2-(ethylsulfanyl)-N-methylacetamide.

Table S747: The calculated geometric terms of 2-(ethylsulfanyl)-N-methylacetamide.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.82	1.82	0.00
SG-CAL	1.81	1.83	0.02
CAL-HAL1	1.09	1.11	0.02
CAL-HAL2	1.10	1.11	0.02
CAL-CL	1.53	1.50	0.03
CL-OL	1.23	1.23	0.01
CL-NL	1.36	1.35	0.01
NL-HNL	1.01	1.00	0.02
NL-C17	1.45	1.44	0.01
C17-H171	1.09	1.11	0.02
C17-H172	1.09	1.11	0.02
C17-H173	1.09	1.11	0.02
HA3-CA-HA2	108.13	108.51	0.38
HA3-CA-HA	108.19	108.44	0.25
HA3-CA-CB	109.90	110.65	0.74
HA2-CA-HA	108.29	108.30	0.01
HA2-CA-CB	111.13	110.47	0.66
CA-CB-HB1	110.56	108.63	1.93
CA-CB-HB2	110.47	108.81	1.66
CA-CB-SG	110.00	112.18	2.18
HA-CA-CB	111.10	110.41	0.69
CB-SG-CAL	98.72	97.61	1.11

Terms	QM	CHARMM	Abs. diff.
HB1-CB-HB2	108.19	106.91	1.27
HB1-CB-SG	108.96	110.22	1.26
HB2-CB-SG	108.62	109.94	1.33
SG-CAL-HAL1	110.53	110.47	0.06
SG-CAL-HAL2	106.52	109.68	3.16
SG-CAL-CL	117.31	115.21	2.10
CAL-CL-OL	119.84	120.62	0.78
CAL-CL-NL	116.11	117.33	1.22
HAL1-CAL-HAL2	107.31	106.61	0.70
HAL1-CAL-CL	106.73	107.57	0.84
HAL2-CAL-CL	108.02	106.89	1.13
CL-NL-HNL	117.85	119.64	1.80
CL-NL-C17	121.75	121.85	0.10
OL-CL-NL	124.01	121.33	2.68
NL-C17-H171	107.47	110.62	3.16
NL-C17-H172	110.14	110.49	0.36
NL-C17-H173	111.59	110.50	1.09
HNL-NL-C17	120.26	118.48	1.78
H171-C17-H172	109.66	108.47	1.19
H171-C17-H173	108.84	108.14	0.70
H172-C17-H173	109.11	108.54	0.57

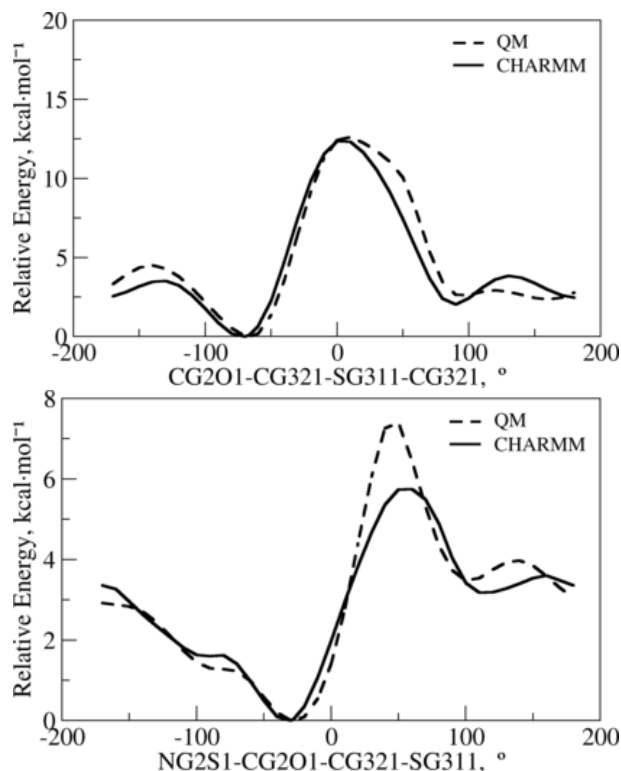


Figure S317: The PES scan for flexible dihedrals corresponding to 2-(ethylsulfanyl)-N-methylacetamide.

2.68 The small molecule 1 used for bonded terms optimization of 2-amino-4-(amino-3-oxo-propylsulfanylcarbonyl)-butyric acid (CYG)

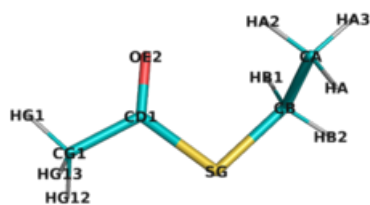


Figure S318: The energy minimized structure corresponding to 1-(ethylsulfanyl)ethan-1-one.

Table S748: The calculated geometric terms of 1-(ethylsulfanyl)ethan-1-one.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.82	1.83	0.01
SG-CD1	1.78	1.78	0.00
CD1-OE2	1.22	1.22	0.00
CD1-CG1	1.51	1.52	0.01
CG1-HG13	1.09	1.11	0.02
CG1-HG12	1.09	1.11	0.02
CG1-HG1	1.09	1.11	0.02
HA3-CA-HA2	108.23	108.18	0.05
HA3-CA-HA	108.42	108.47	0.05
HA3-CA-CB	109.89	110.45	0.56
HA2-CA-HA	108.85	108.56	0.30
HA2-CA-CB	110.24	110.41	0.17
CA-CB-HB1	110.90	108.94	1.96
CA-CB-HB2	111.56	108.53	3.03
CA-CB-SG	113.12	113.09	0.04
HA-CA-CB	111.13	110.69	0.44
CB-SG-CD1	98.91	99.64	0.72
HB1-CB-HB2	108.47	106.29	2.17
HB1-CB-SG	106.95	110.61	3.66
HB2-CB-SG	105.54	109.14	3.60
SG-CD1-OE2	122.89	123.06	0.16
SG-CD1-CG1	114.04	114.28	0.24
CD1-CG1-HG13	108.69	110.00	1.31
CD1-CG1-HG12	112.07	110.01	2.06
CD1-CG1-HG1	108.55	109.07	0.52
OE2-CD1-CG1	123.05	122.67	0.38

Terms	QM	CHARMM	Abs. diff.
HG13-CG1-HG12	108.60	109.46	0.87
HG13-CG1-HG1	108.55	109.18	0.62
HG12-CG1-HG1	110.31	109.10	1.20

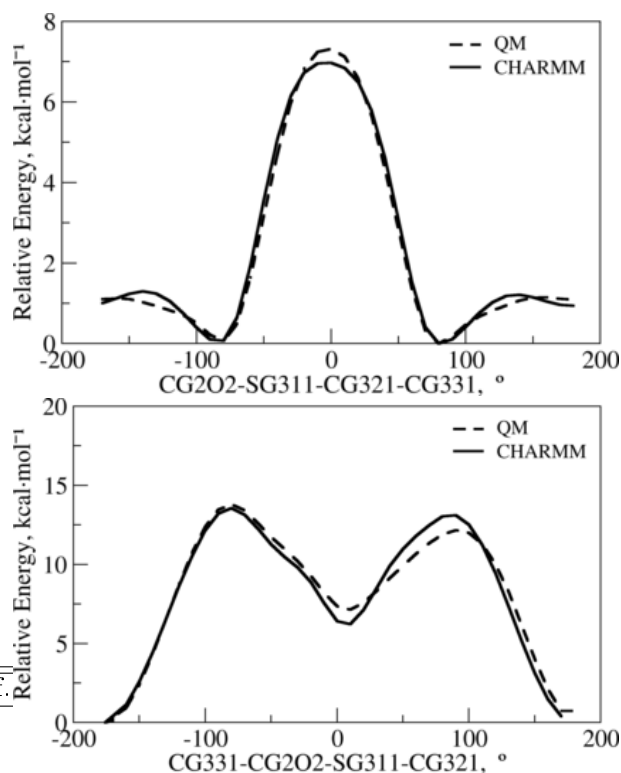


Figure S319: The PES scan for flexible dihedrals corresponding to 1-(ethylsulfanyl)ethan-1-one.

2.69 The small molecule 2 used for bonded terms optimization of 2-amino-4-(amino-3-oxo-propylsulfanylcarbonyl)-butyric acid (CYG)

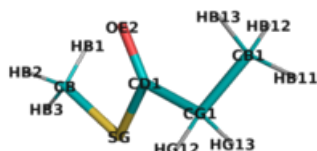


Figure S320: The energy minimized structure corresponding to 1-(methylsulfanyl)propan-1-one.

Table S749: The calculated geometric terms of 1-(methylsulfanyl)propan-1-one.

Terms	QM	CHARMM	Abs. diff.
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-HB3	1.09	1.11	0.02
CB-SG	1.81	1.82	0.01
SG-CD1	1.79	1.79	0.01
CD1-OE2	1.22	1.22	0.00
CD1-CG1	1.52	1.53	0.02
CG1-HG13	1.10	1.11	0.02
CG1-HG12	1.10	1.11	0.01
CG1-CB1	1.52	1.54	0.02
CB1-HB12	1.09	1.11	0.02
CB1-HB13	1.09	1.11	0.02
CB1-HB11	1.09	1.11	0.02
CB-SG-CD1	98.16	98.32	0.16
HB1-CB-HB2	109.23	107.63	1.60
HB1-CB-HB3	109.92	107.97	1.95
HB1-CB-SG	110.36	111.08	0.73
HB2-CB-HB3	109.90	107.96	1.94
HB2-CB-SG	110.45	111.00	0.55
HB3-CB-SG	106.95	111.04	4.09
SG-CD1-OE2	121.98	122.31	0.33
SG-CD1-CG1	114.14	113.37	0.77
CD1-CG1-HG13	108.34	107.93	0.41
CD1-CG1-HG12	107.72	109.91	2.19
CD1-CG1-CB1	111.99	110.97	1.01
OE2-CD1-CG1	123.88	124.31	0.44
CG1-CB1-HB12	110.80	110.71	0.09
CG1-CB1-HB13	110.76	110.41	0.35
CG1-CB1-HB11	110.24	110.68	0.44
HG13-CG1-HG12	106.09	108.51	2.42
HG13-CG1-CB1	111.36	105.91	5.45
HG12-CG1-CB1	111.10	113.37	2.27

Terms	QM	CHARMM	Abs. diff.
HB12-CB1-HB13	107.72	108.11	0.39
HB12-CB1-HB11	108.56	108.53	0.02
HB13-CB1-HB11	108.68	108.31	0.37

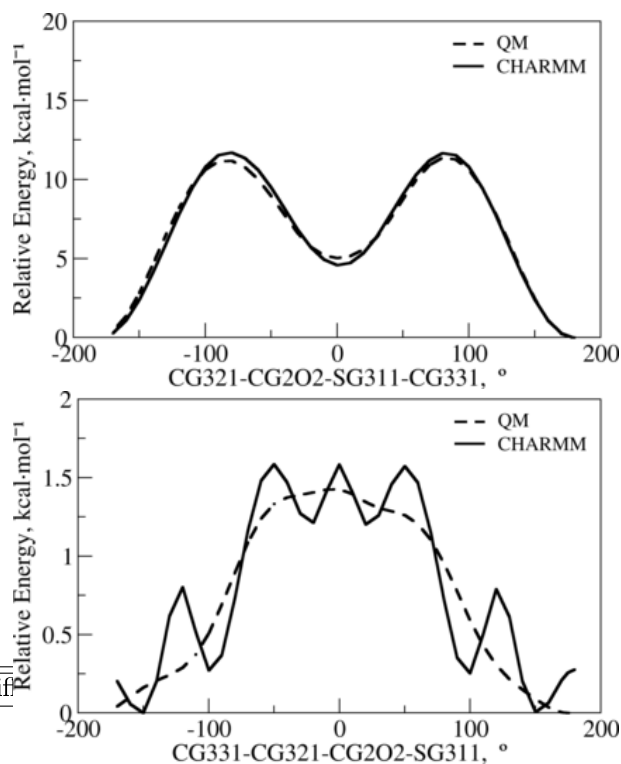


Figure S321: The PES scan for flexible dihedrals corresponding to 1-(methylsulfanyl)propan-1-one.

2.70 The small molecule used for bonded terms optimization of 2-amino-3-phosphonomethylsulfanyl-propionicacid (CYQ)

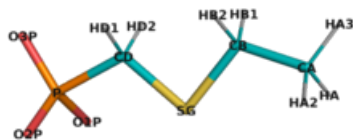


Figure S322: The energy minimized structure corresponding to [(ethylsulfanyl)methyl]phosphonic acid.

Table S750: The calculated geometric terms of [(ethylsulfanyl)methyl]phosphonic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.10	1.11	0.01
CA-HA	1.10	1.11	0.02
CA-CB	1.53	1.53	0.01
CB-HB1	1.10	1.11	0.01
CB-HB2	1.10	1.11	0.01
CB-SG	1.82	1.82	0.00
SG-CD	1.82	1.84	0.03
CD-HD1	1.10	1.10	0.00
CD-HD2	1.10	1.10	0.00
CD-P	1.92	1.86	0.06
P-O1P	1.55	1.52	0.04
P-O2P	1.55	1.52	0.04
P-O3P	1.56	1.52	0.04
HA3-CA-HA2	108.30	108.99	0.69
HA3-CA-HA	108.30	108.98	0.68
HA3-CA-CB	111.37	110.53	0.83
HA2-CA-HA	107.77	108.43	0.66
HA2-CA-CB	110.49	109.96	0.54
CA-CB-HB1	109.57	109.44	0.13
CA-CB-HB2	109.57	109.42	0.15
CA-CB-SG	111.19	113.22	2.04
HA-CA-CB	110.50	109.91	0.59
CB-SG-CD	99.85	92.63	7.22
HB1-CB-HB2	107.20	106.99	0.21
HB1-CB-SG	109.60	108.83	0.77
HB2-CB-SG	109.62	108.74	0.88
SG-CD-HD1	108.52	110.63	2.11
SG-CD-HD2	108.54	110.67	2.13
SG-CD-P	116.46	116.25	0.22
CD-P-O1P	103.90	101.62	2.28
CD-P-O2P	103.90	101.59	2.31

Terms	QM	CHARMM	Abs. diff.
CD-P-O3P	98.72	98.20	0.51
HD1-CD-HD2	109.93	108.43	1.50
HD1-CD-P	106.62	105.24	1.38
HD2-CD-P	106.66	105.19	1.47
O1P-P-O2P	115.92	118.12	2.20
O1P-P-O3P	115.55	116.12	0.57
O2P-P-O3P	115.53	116.04	0.51

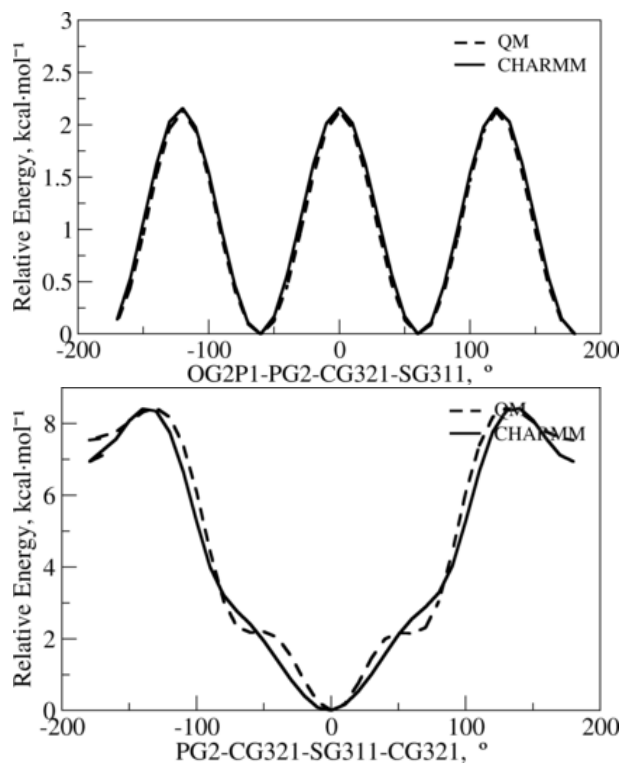


Figure S323: The PES scan for flexible dihedrals corresponding to [(ethylsulfanyl)methyl]phosphonic acid.

2.71 The small molecule used for bonded terms optimization of 2-amino-3-phosphonomethylsulfanyl-propionic acid (CYQP)

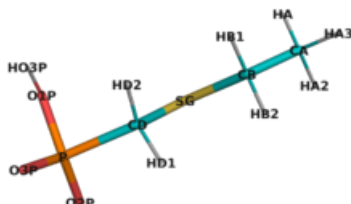


Figure S324: The energy minimized structure corresponding to [(ethylsulfanyl)methyl]phosphonic acid.

Table S751: The calculated geometric terms of [(ethylsulfanyl)methyl]phosphonic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.54	0.01
CB-HB1	1.10	1.11	0.02
CB-HB2	1.10	1.11	0.01
CB-SG	1.82	1.82	0.00
SG-CD	1.81	1.82	0.01
CD-HD1	1.10	1.10	0.00
CD-HD2	1.10	1.10	0.00
CD-P	1.85	1.85	0.00
P-O1P	1.69	1.59	0.10
P-O2P	1.51	1.50	0.01
P-O3P	1.52	1.50	0.02
O1P-HO3P	0.98	0.96	0.01
HA3-CA-HA2	108.27	108.64	0.37
HA3-CA-HA	108.22	108.64	0.42
HA3-CA-CB	110.67	110.54	0.13
HA2-CA-HA	108.02	108.41	0.39
HA2-CA-CB	110.79	110.21	0.57
CA-CB-HB1	109.89	109.06	0.83
CA-CB-HB2	109.83	108.97	0.86
CA-CB-SG	110.39	113.62	3.23
HA-CA-CB	110.78	110.34	0.44
CB-SG-CD	98.17	92.11	6.06
HB1-CB-HB2	107.68	106.92	0.76
HB1-CB-SG	109.55	109.02	0.53
HB2-CB-SG	109.46	109.03	0.42
SG-CD-HD1	109.76	110.18	0.41
SG-CD-HD2	109.59	111.06	1.47
SG-CD-P	114.29	114.36	0.07
CD-P-O1P	100.39	95.16	5.22

Terms	QM	CHARMM	Abs. diff.
CD-P-O2P	108.60	106.03	2.57
CD-P-O3P	105.84	103.21	2.63
HD1-CD-HD2	108.64	108.08	0.56
HD1-CD-P	106.83	106.05	0.78
HD2-CD-P	107.55	106.79	0.75
P-O1P-HO3P	104.65	107.80	3.15
O1P-P-O2P	108.86	114.20	5.34
O1P-P-O3P	105.57	109.30	3.74
O2P-P-O3P	124.88	124.05	0.83

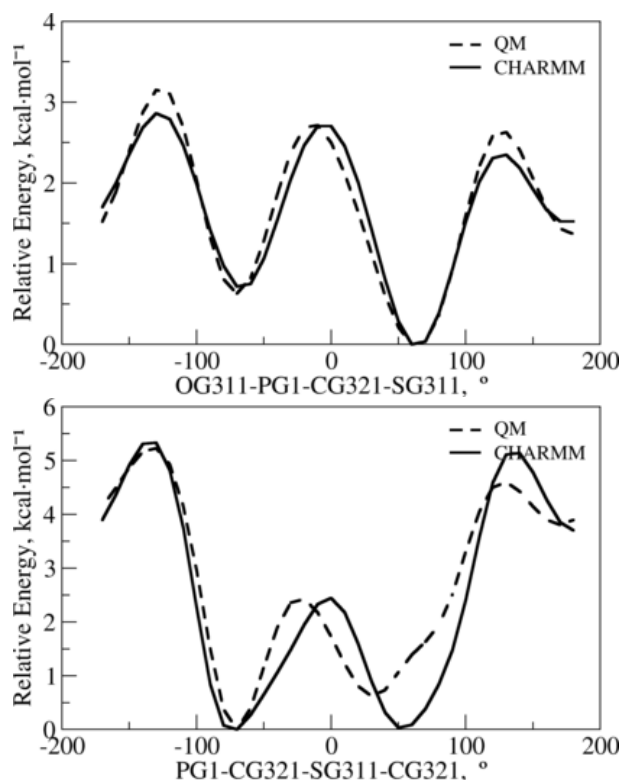


Figure S325: The PES scan for flexible dihedrals corresponding to [(ethylsulfanyl)methyl]phosphonic acid.

2.72 The small molecule used for bonded terms optimization of NG,NG-dimethyl-L-arginine (DA2)

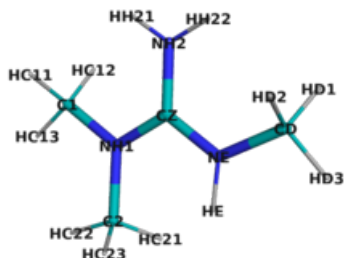


Figure S326: The energy minimized structure corresponding to N,N,N'-trimethylguanidine.

Table S752: The calculated geometric terms of N,N,N'-trimethylguanidine.

Terms	QM	CHARMM	Abs. diff.
HD3-CD	1.09	1.11	0.03
CD-HD1	1.09	1.12	0.02
CD-HD2	1.09	1.11	0.02
CD-NE	1.46	1.47	0.01
NE-HE	1.01	0.99	0.02
NE-CZ	1.34	1.35	0.01
CZ-NH2	1.35	1.33	0.01
CZ-NH1	1.34	1.36	0.03
NH2-HH21	1.01	0.99	0.02
NH2-HH22	1.01	0.99	0.02
NH1-C1	1.47	1.48	0.01
NH1-C2	1.47	1.48	0.01
C1-HC11	1.09	1.11	0.02
C1-HC12	1.09	1.11	0.02
C1-HC13	1.09	1.12	0.02
C2-HC21	1.09	1.11	0.02
C2-HC22	1.09	1.11	0.02
C2-HC23	1.09	1.11	0.02
HD3-CD-HD1	108.61	106.80	1.80
HD3-CD-HD2	108.33	106.94	1.39
HD3-CD-NE	107.75	110.72	2.97
CD-NE-HE	117.41	120.03	2.62
CD-NE-CZ	124.17	125.32	1.15
HD1-CD-HD2	110.33	108.53	1.80
HD1-CD-NE	111.99	111.82	0.17
HD2-CD-NE	109.72	111.77	2.05
NE-CZ-NH2	119.25	119.37	0.12
NE-CZ-NH1	120.58	120.39	0.19
HE-NE-CZ	117.20	114.64	2.57
CZ-NH2-HH21	121.25	118.54	2.70
CZ-NH2-HH22	121.02	118.23	2.79
CZ-NH1-C1	121.46	121.55	0.09
CZ-NH1-C2	121.24	121.33	0.09

Terms	QM	CHARMM	Abs. diff.
NH2-CZ-NH1	120.16	120.24	0.07
HH21-NH2-HH22	117.14	123.19	6.05
NH1-C1-HC11	111.23	111.61	0.38
NH1-C1-HC12	110.00	111.72	1.72
NH1-C1-HC13	108.09	111.50	3.41
NH1-C2-HC21	111.36	111.54	0.19
NH1-C2-HC22	108.07	111.57	3.51
NH1-C2-HC23	109.93	111.77	1.85
C1-NH1-C2	117.30	117.12	0.18
HC11-C1-HC12	110.31	108.63	1.68
HC11-C1-HC13	108.95	106.66	2.29
HC12-C1-HC13	108.18	106.45	1.73
HC21-C2-HC22	108.87	106.60	2.27
HC21-C2-HC23	110.28	108.58	1.71
HC22-C2-HC23	108.24	106.50	1.75

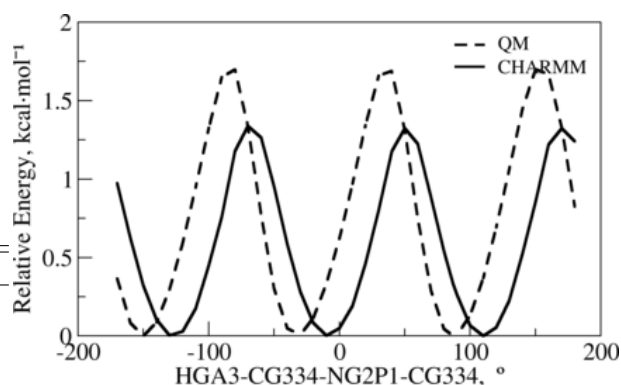


Figure S327: The PES scan for flexible dihedral corresponding to N,N,N'-trimethylguanidine.

2.73 The small molecule used for bonded terms optimization of 3,4-Dihydroxy-phenylalanine (DAH)

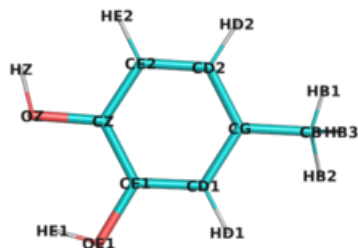


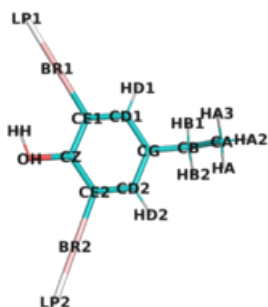
Figure S328: The energy minimized structure corresponding to 4-methylbenzene-1,2-diol.

Table S753: The calculated geometric terms of 4-methylbenzene-1,2-diol.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.10	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-CG	1.51	1.50	0.01
CG-CD2	1.40	1.40	0.00
CG-CD1	1.40	1.40	0.00
CD2-HD2	1.09	1.08	0.01
CD2-CE2	1.40	1.40	0.00
CD1-HD1	1.09	1.08	0.01
CD1-CE1	1.39	1.40	0.01
CE2-HE2	1.09	1.08	0.01
CE2-CZ	1.39	1.40	0.01
CE1-OE1	1.37	1.41	0.04
CE1-CZ	1.40	1.41	0.01
OE1-HE1	0.98	0.96	0.01
CZ-OZ	1.38	1.42	0.03
OZ-HZ	0.97	0.96	0.01
HB3-CB-HB2	107.53	109.84	2.32
HB3-CB-HB1	107.78	109.88	2.10
HB3-CB-CG	111.31	108.69	2.61
CB-CG-CD2	121.13	120.21	0.92
CB-CG-CD1	120.08	120.11	0.03
HB2-CB-HB1	107.99	109.16	1.18
HB2-CB-CG	111.14	109.60	1.54
HB1-CB-CG	110.94	109.65	1.29
CG-CD2-HD2	119.87	119.61	0.26
CG-CD2-CE2	120.88	120.32	0.56
CG-CD1-HD1	121.08	119.95	1.13
CG-CD1-CE1	120.83	120.34	0.49
CD2-CG-CD1	118.77	119.68	0.91
CD2-CE2-HE2	120.38	119.38	1.01
CD2-CE2-CZ	119.62	120.11	0.49
HD2-CD2-CE2	119.25	120.07	0.82

Terms	QM	CHARMM	Abs. diff.
CD1-CE1-OE1	119.89	118.84	1.05
CD1-CE1-CZ	119.67	119.99	0.31
HD1-CD1-CE1	118.09	119.72	1.63
CE2-CZ-CE1	120.22	119.57	0.65
CE2-CZ-OZ	125.12	118.87	6.24
HE2-CE2-CZ	120.00	120.51	0.52
CE1-OE1-HE1	106.77	105.37	1.40
CE1-CZ-OZ	114.66	121.56	6.90
OE1-CE1-CZ	120.44	121.17	0.74
CZ-OZ-HZ	108.88	107.66	1.22

2.74 The small molecule used for bonded terms optimization of 3,5-dibromotyrosine (DBY)



Terms	QM	CHARMM	Abs. diff.
CG-CD1-CE1	119.95	120.55	0.60
CG-CD2-HD2	120.29	119.75	0.54
CG-CD2-CE2	120.79	120.57	0.22
CD1-CG-CD2	118.54	119.46	0.92
CD1-CE1-BR1	119.59	117.92	1.67
CD1-CE1-CZ	122.43	119.98	2.45
HD1-CD1-CE1	119.42	119.81	0.39
CD2-CE2-BR2	119.70	117.50	2.20
CD2-CE2-CZ	121.56	119.92	1.63
HD2-CD2-CE2	118.91	119.68	0.77
CE1-CZ-CE2	116.72	119.51	2.79
CE1-CZ-OH	124.40	119.22	5.17
BR1-CE1-CZ	117.98	122.10	4.12
CE2-CZ-OH	118.88	121.27	2.38
BR2-CE2-CZ	118.74	122.57	3.83
CZ-OH-HH	107.90	106.33	1.57

Figure S329: The energy minimized structure corresponding to 2,6-diboranyl-4-ethylphenol.

Table S754: The calculated geometric terms of 2,6-diboranyl-4-ethylphenol.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.53	0.00
CB-HB1	1.10	1.11	0.02
CB-HB2	1.10	1.11	0.02
CB-CG	1.51	1.50	0.00
CG-CD1	1.40	1.40	0.00
CG-CD2	1.40	1.40	0.00
CD1-HD1	1.09	1.08	0.01
CD1-CE1	1.39	1.40	0.01
CD2-HD2	1.09	1.08	0.01
CD2-CE2	1.39	1.40	0.01
CE1-BR1	1.91	1.91	0.00
CE1-CZ	1.40	1.41	0.01
CE2-BR2	1.90	1.91	0.01
CE2-CZ	1.40	1.41	0.01
CZ-OH	1.36	1.41	0.06
OH-HH	0.98	0.96	0.02
HA3-CA-HA2	108.33	107.99	0.34
HA3-CA-HA	107.93	108.36	0.42
HA3-CA-CB	110.55	111.09	0.54
HA2-CA-HA	108.32	108.00	0.32
HA2-CA-CB	111.03	110.25	0.78
CA-CB-HB1	109.82	110.71	0.89
CA-CB-HB2	109.80	110.67	0.87
CA-CB-CG	111.81	109.53	2.28
HA-CA-CB	110.58	111.04	0.46
CB-CG-CD1	120.73	120.23	0.50
CB-CG-CD2	120.63	120.30	0.33
HB1-CB-HB2	106.71	108.24	1.53
HB1-CB-CG	109.31	108.82	0.48
HB2-CB-CG	109.27	108.82	0.45
CG-CD1-HD1	120.62	119.64	0.98

2.75 The small molecule used for bonded terms optimization of 3-(benzoylamino)-L-alanine (DBZ)

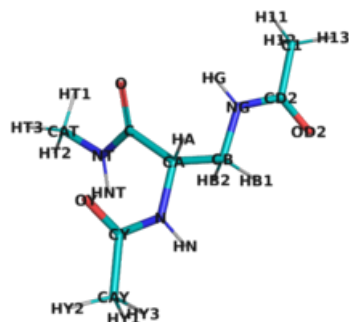


Figure S330: The energy minimized structure corresponding to (2S)-2,3-diacetamido-N-methylpropanamide.

Table S755: The calculated geometric terms of (2S)-2,3-diacetamido-N-methylpropanamide.

Terms	QM	CHARMM	Abs. diff.
N-HN	1.02	0.99	0.02
N-CA	1.46	1.46	0.01
N-CY	1.38	1.34	0.04
CA-HA	1.10	1.08	0.02
CA-CB	1.53	1.55	0.03
CA-C	1.53	1.52	0.00
CB-HB1	1.10	1.12	0.02
CB-HB2	1.10	1.11	0.01
CB-NG	1.45	1.45	0.00
NG-HG	1.02	1.00	0.02
NG-CD2	1.36	1.34	0.03
CD2-OD2	1.23	1.22	0.01
CD2-C1	1.51	1.48	0.03
C1-H11	1.09	1.11	0.02
C1-H12	1.09	1.11	0.02
C1-H13	1.09	1.11	0.02
C-O	1.24	1.23	0.01
C-NT	1.36	1.35	0.01
NT-HNT	1.01	0.99	0.02
NT-CAT	1.45	1.45	0.01
CAT-HT1	1.09	1.11	0.02
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.09	1.11	0.02
CAY-HY1	1.09	1.11	0.02
CAY-HY2	1.09	1.11	0.02
CAY-HY3	1.09	1.11	0.02
CAY-CY	1.51	1.48	0.03
CY-OY	1.23	1.22	0.01
N-CA-HA	110.44	106.78	3.67
N-CA-CB	110.22	112.27	2.05
N-CA-C	112.35	116.23	3.89
N-CY-CAY	115.29	116.37	1.08

Terms	QM	CHARMM	Abs. diff.
N-CY-OY	121.16	122.70	1.54
HN-N-CA	117.17	116.58	0.59
HN-N-CY	117.68	118.38	0.70
CA-N-CY	118.85	124.75	5.90
CA-CB-HB1	110.61	107.43	3.19
CA-CB-HB2	109.85	109.57	0.28
CA-CB-NG	108.90	113.36	4.47
CA-C-O	120.13	120.77	0.64
CA-C-NT	115.09	117.75	2.66
HA-CA-CB	109.38	107.36	2.01
HA-CA-C	104.93	104.98	0.05
CB-CA-C	109.37	108.61	0.76
CB-NG-HG	118.15	117.52	0.63
CB-NG-CD2	120.21	122.12	1.91
HB1-CB-HB2	107.57	107.05	0.52
HB1-CB-NG	108.44	109.63	1.19
HB2-CB-NG	111.46	109.59	1.86
NG-CD2-OD2	121.84	122.08	0.25
NG-CD2-C1	115.37	116.88	1.51
HG-NG-CD2	121.61	120.35	1.26
CD2-C1-H11	112.74	111.04	1.70
CD2-C1-H12	109.11	109.77	0.66
CD2-C1-H13	108.51	109.50	0.99
OD2-CD2-C1	122.78	121.03	1.74
H11-C1-H12	108.72	109.22	0.50
H11-C1-H13	109.66	108.75	0.91
H12-C1-H13	108.00	108.51	0.51
C-NT-HNT	115.81	119.87	4.06
C-NT-CAT	120.04	121.67	1.63
O-C-NT	123.63	121.39	2.23
NT-CAT-HT1	108.19	111.05	2.86
NT-CAT-HT2	108.95	110.68	1.73
NT-CAT-HT3	111.83	110.59	1.24
HNT-NT-CAT	118.23	117.91	0.32
HT1-CAT-HT2	109.60	108.04	1.55
HT1-CAT-HT3	108.64	108.14	0.49
HT2-CAT-HT3	109.61	108.24	1.37
CAY-CY-OY	123.55	120.92	2.63
HY1-CAY-HY2	109.79	108.52	1.27
HY1-CAY-HY3	108.41	109.25	0.84
HY1-CAY-CY	111.96	111.03	0.93
HY2-CAY-HY3	108.46	108.45	0.02
HY2-CAY-CY	108.58	109.37	0.79
HY3-CAY-CY	109.56	110.16	0.60

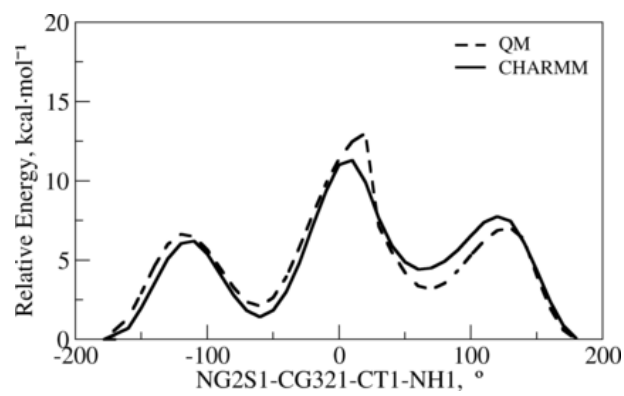


Figure S331: The PES scan for flexible dihedral corresponding to (2S)-2,3-diacetamido-N-methyl propanamide.

2.76 The small molecule used for bonded terms optimization of 3-[4-(2-amino-2-carboxy-ethyl)-1H-imidazol-2-yl]-1-carbamoyl-propyl-trimethyl-ammonium (DDE)

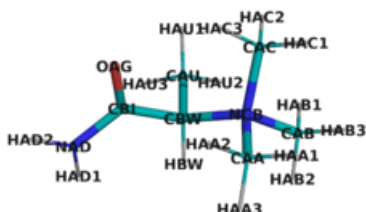


Figure S332: The energy minimized structure corresponding to (2R)-2-(trimethylamino)propanamide.

Table S756: The calculated geometric terms of (2R)-2-(trimethylamino)propanamide.

Terms	QM	CHARMM	Abs. diff.
HAU3-CAU	1.09	1.11	0.02
CAU-HAU1	1.09	1.11	0.02
CAU-HAU2	1.09	1.11	0.02
CAU-CBW	1.52	1.56	0.03
CBW-HBW	1.10	1.11	0.02
CBW-CBI	1.54	1.54	0.00
CBW-NCB	1.53	1.56	0.03
CBI-OAG	1.23	1.24	0.00
CBI-NAD	1.35	1.36	0.01
NAD-HAD1	1.01	1.00	0.02
NAD-HAD2	1.01	1.00	0.02
NCB-CAA	1.51	1.51	0.00
NCB-CAB	1.50	1.50	0.00
NCB-CAC	1.51	1.50	0.01
CAA-HAA1	1.09	1.08	0.01
CAA-HAA2	1.09	1.09	0.00
CAA-HAA3	1.09	1.08	0.01
CAB-HAB1	1.09	1.09	0.00
CAB-HAB2	1.09	1.08	0.01
CAB-HAB3	1.09	1.09	0.00
CAC-HAC1	1.09	1.08	0.01
CAC-HAC2	1.09	1.08	0.01
CAC-HAC3	1.09	1.09	0.00
HAU3-CAU-HAU1	107.49	107.41	0.08
HAU3-CAU-HAU2	107.23	106.81	0.43
HAU3-CAU-CBW	107.57	110.12	2.54
CAU-CBW-HBW	110.39	105.30	5.09
CAU-CBW-CBI	108.49	108.19	0.30
CAU-CBW-NCB	113.47	110.91	2.55
HAU1-CAU-HAU2	109.98	108.60	1.38

Terms	QM	CHARMM	Abs. diff.
HAU1-CAU-CBW	111.05	111.75	0.70
HAU2-CAU-CBW	113.24	111.93	1.31
CBW-CBI-OAG	121.35	122.54	1.18
CBW-CBI-NAD	114.46	117.32	2.86
CBW-NCB-CAA	109.54	111.01	1.47
CBW-NCB-CAB	108.86	112.52	3.66
CBW-NCB-CAC	112.91	112.05	0.86
HBW-CBW-CBI	110.37	110.68	0.32
HBW-CBW-NCB	103.78	104.76	0.98
CBI-CBW-NCB	110.29	116.43	6.13
CBI-NAD-HAD1	123.79	121.87	1.91
CBI-NAD-HAD2	117.81	116.90	0.91
OAG-CBI-NAD	124.14	120.14	4.00
HAD1-NAD-HAD2	117.85	121.03	3.17
NCB-CAA-HAA1	108.13	110.81	2.69
NCB-CAA-HAA2	108.84	110.75	1.91
NCB-CAA-HAA3	108.68	111.93	3.25
NCB-CAB-HAB1	109.57	111.06	1.49
NCB-CAB-HAB2	108.99	111.72	2.74
NCB-CAB-HAB3	108.15	110.83	2.68
NCB-CAC-HAC1	107.35	111.66	4.31
NCB-CAC-HAC2	108.92	111.27	2.35
NCB-CAC-HAC3	108.31	110.36	2.06
CAA-NCB-CAB	107.88	107.36	0.53
CAA-NCB-CAC	108.90	105.80	3.10
HAA1-CAA-HAA2	110.35	107.05	3.31
HAA1-CAA-HAA3	109.92	107.60	2.32
HAA2-CAA-HAA3	110.86	108.51	2.35
CAB-NCB-CAC	108.62	107.75	0.87
HAB1-CAB-HAB2	110.48	108.15	2.33
HAB1-CAB-HAB3	109.64	107.28	2.36
HAB2-CAB-HAB3	109.97	107.62	2.35
HAC1-CAC-HAC2	109.67	108.13	1.54
HAC1-CAC-HAC3	111.23	107.93	3.30
HAC2-CAC-HAC3	111.25	107.32	3.92

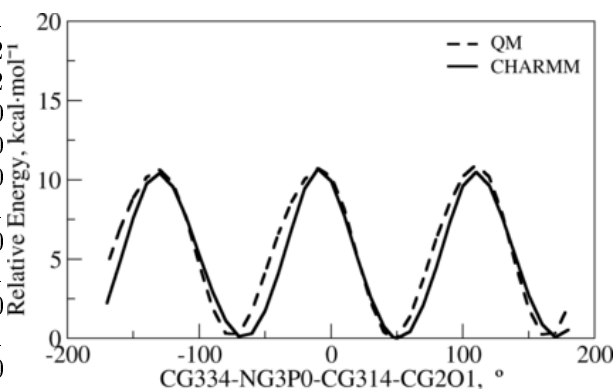


Figure S333: The PES scan for flexible dihedral corresponding to (2R)-2-(trimethylamino)propanamide.

2.77 The small molecule 1 used for bonded terms optimization of 3-[4-(2-amino-2-carboxy-ethyl)-1H-imidazol-2-yl]-1-carbamoyl-propyl-trimethyl-ammonium (DDEP)

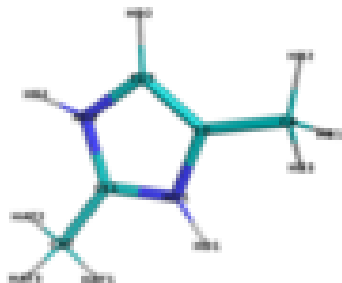


Figure S334: The energy minimized structure corresponding to 2,4-dimethyl-2,3-dihydro-1H-imidazole.

Table S757: The calculated geometric terms of 2,4-dimethyl-2,3-dihydro-1H-imidazole.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.49	1.50	0.02
CG-ND1	1.39	1.37	0.02
CG-CD2	1.37	1.34	0.03
ND1-HD1	1.02	1.00	0.02
ND1-CE1	1.35	1.33	0.02
CD2-HD2	1.08	1.09	0.01
CD2-NE2	1.38	1.37	0.01
NE2-HE2	1.02	1.00	0.02
NE2-CE1	1.34	1.33	0.02
CE1-CAT	1.49	1.50	0.01
CAT-HAT1	1.09	1.11	0.02
CAT-HAT2	1.09	1.11	0.02
CAT-HAT3	1.09	1.11	0.02
HB3-CB-HB1	108.74	108.88	0.14
HB3-CB-HB2	108.12	108.43	0.31
HB3-CB-CG	111.14	110.20	0.94
CB-CG-ND1	123.04	122.30	0.74
CB-CG-CD2	131.88	131.15	0.72
HB1-CB-HB2	108.12	108.42	0.29
HB1-CB-CG	111.15	110.22	0.94
HB2-CB-CG	109.47	110.64	1.17
CG-ND1-HD1	124.61	124.24	0.37
CG-ND1-CE1	111.78	110.89	0.89
CG-CD2-HD2	130.66	128.84	1.82
CG-CD2-NE2	106.98	106.29	0.69
ND1-CG-CD2	105.08	106.54	1.47
ND1-CE1-NE2	105.19	105.56	0.37

Terms	QM	CHARMM	Abs. diff.
ND1-CE1-CAT	127.34	127.13	0.21
HD1-ND1-CE1	123.60	124.87	1.26
CD2-NE2-HE2	125.15	124.66	0.49
CD2-NE2-CE1	110.97	110.71	0.26
HD2-CD2-NE2	122.36	124.86	2.50
NE2-CE1-CAT	127.40	127.15	0.24
HE2-NE2-CE1	123.88	124.63	0.75
CE1-CAT-HAT1	110.32	110.20	0.12
CE1-CAT-HAT2	110.18	110.13	0.05
CE1-CAT-HAT3	110.91	109.69	1.22
HAT1-CAT-HAT2	108.07	108.62	0.56
HAT1-CAT-HAT3	108.67	109.09	0.42
HAT2-CAT-HAT3	108.62	109.07	0.46

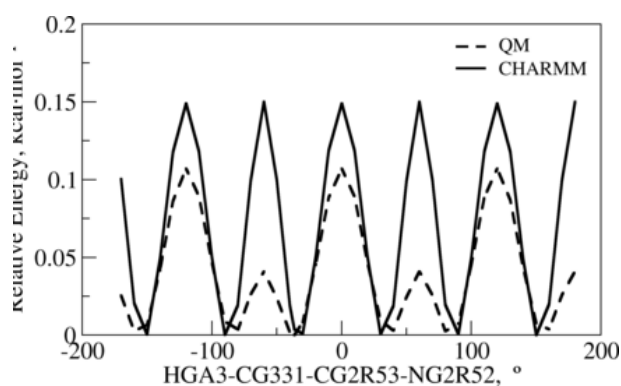


Figure S335: The PES scan for flexible dihedral corresponding to 2,4-dimethyl-2,3-dihydro-1H-imidazole.

2.78 The small molecule 2 used for bonded terms optimization of 3-[4-(2-amino-2-carboxy-ethyl)-1H-imidazol-2-yl]-1-carbamoyl-propyl-trimethyl-ammonium (DDEP)

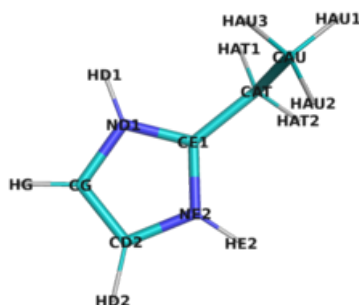


Figure S336: The energy minimized structure corresponding to 2-ethyl-1H-imidazole.

Table S758: The calculated geometric terms of 2-ethyl-1H-imidazole.

Terms	QM	CHARMM	Abs. diff.
CG-HG	1.08	1.09	0.01
CG-ND1	1.38	1.37	0.01
CG-CD2	1.37	1.34	0.03
ND1-HD1	1.02	1.00	0.02
ND1-CE1	1.35	1.33	0.01
CD2-HD2	1.08	1.09	0.01
CD2-NE2	1.38	1.37	0.01
NE2-HE2	1.02	1.00	0.02
NE2-CE1	1.35	1.33	0.01
CE1-CAT	1.49	1.51	0.02
CAT-HAT1	1.09	1.11	0.02
CAT-HAT2	1.09	1.11	0.02
CAT-CAU	1.54	1.54	0.00
CAU-HAU1	1.09	1.11	0.02
CAU-HAU2	1.09	1.11	0.02
CAU-HAU3	1.09	1.11	0.02
CG-ND1-HD1	125.05	124.28	0.76
CG-ND1-CE1	111.18	111.00	0.19
CG-CD2-HD2	131.13	128.77	2.35
CG-CD2-NE2	106.21	106.46	0.25
HG-CG-ND1	122.67	124.24	1.57
HG-CG-CD2	131.11	129.34	1.77
ND1-CG-CD2	106.22	106.42	0.20
ND1-CE1-NE2	105.20	105.30	0.10
ND1-CE1-CAT	127.32	127.30	0.02
HD1-ND1-CE1	123.77	124.72	0.95
CD2-NE2-HE2	125.06	124.80	0.26
CD2-NE2-CE1	111.19	110.82	0.37
HD2-CD2-NE2	122.66	124.76	2.10
NE2-CE1-CAT	127.34	127.29	0.05
HE2-NE2-CE1	123.75	124.37	0.62

Terms	QM	CHARMM	Abs. diff.
CE1-CAT-HAT1	108.24	108.77	0.53
CE1-CAT-HAT2	108.21	108.76	0.56
CE1-CAT-CAU	112.38	113.48	1.10
CAT-CAU-HAU1	109.43	110.23	0.80
CAT-CAU-HAU2	111.19	111.40	0.21
CAT-CAU-HAU3	111.20	111.38	0.19
HAT1-CAT-HAT2	106.38	107.06	0.68
HAT1-CAT-CAU	110.70	109.29	1.42
HAT2-CAT-CAU	110.70	109.28	1.42
HAU1-CAU-HAU2	108.22	107.65	0.57
HAU1-CAU-HAU3	108.20	107.69	0.51
HAU2-CAU-HAU3	108.50	108.33	0.17

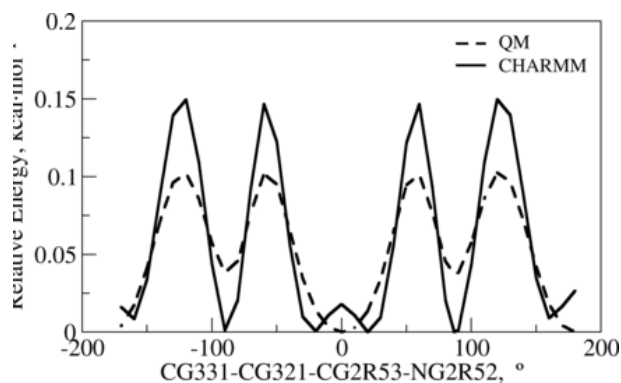


Figure S337: The PES scan for flexible dihedral corresponding to 2-ethyl-1H-imidazole.

2.79 The small molecule used for bonded terms optimization of 3,3-dihydroxy-alanine (DDZ)

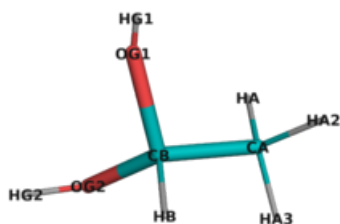


Figure S338: The energy minimized structure corresponding to ethane-1,1-diol.

Table S759: The calculated geometric terms of ethane-1,1-diol.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.51	1.52	0.01
CB-HB	1.10	1.12	0.02
CB-OG1	1.42	1.40	0.02
CB-OG2	1.42	1.40	0.02
OG1-HG1	0.98	0.96	0.02
OG2-HG2	0.97	0.96	0.02
HA3-CA-HA2	109.54	108.46	1.08
HA3-CA-HA	108.30	108.15	0.15
HA3-CA-CB	110.56	109.97	0.59
HA2-CA-HA	109.29	108.88	0.41
HA2-CA-CB	109.94	110.41	0.48
CA-CB-HB	111.38	110.03	1.35
CA-CB-OG1	112.79	108.00	4.79
CA-CB-OG2	106.69	108.52	1.83
HA-CA-CB	109.19	110.90	1.72
CB-OG1-HG1	105.94	101.12	4.83
CB-OG2-HG2	106.19	102.65	3.54
HB-CB-OG1	103.86	109.22	5.36
HB-CB-OG2	111.15	109.82	1.33
OG1-CB-OG2	111.07	111.23	0.16

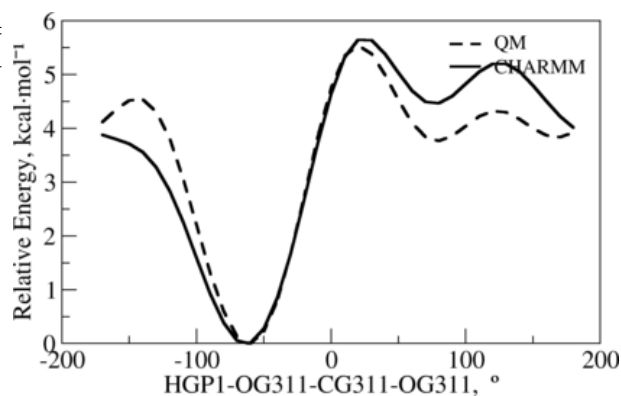


Figure S339: The PES scan for flexible dihedral corresponding to ethane-1,1-diol.

2.80 The small molecule used for bonded terms optimization of (DYAP)

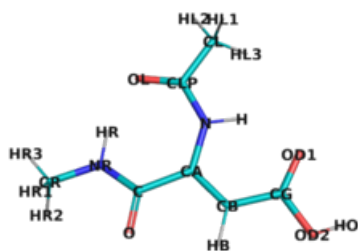


Figure S340: The energy minimized structure corresponding to (2Z)-3-acetamido-3-(methylcarbamoyl)prop-2-enoic acid.

Table S760: The calculated geometric terms of (2Z)-3-acetamido-3-(methylcarbamoyl)prop-2-enoic acid.

Terms	QM	CHARMM	Abs. diff.
CL-HL1	1.10	1.11	0.01
CL-HL2	1.09	1.11	0.02
CL-HL3	1.09	1.11	0.02
CL-CLP	1.52	1.48	0.04
CLP-OL	1.23	1.22	0.00
CLP-N	1.38	1.35	0.03
N-H	1.03	1.00	0.03
N-CA	1.40	1.41	0.01
CA-CB	1.36	1.36	0.00
CA-C	1.54	1.54	0.00
CB-HB	1.08	1.10	0.02
CB-CG	1.46	1.49	0.03
CG-OD1	1.23	1.22	0.01
CG-OD2	1.35	1.38	0.03
OD2-HO	0.98	0.96	0.02
C-O	1.23	1.23	0.00
C-NR	1.34	1.34	0.00
NR-HR	1.02	1.01	0.02
NR-CR	1.45	1.44	0.01
CR-HR1	1.10	1.11	0.02
CR-HR2	1.10	1.11	0.02
CR-HR3	1.09	1.11	0.02
CL-CLP-OL	120.30	119.41	0.90
CL-CLP-N	113.23	115.21	1.98
HL1-CL-HL2	107.75	108.67	0.92
HL1-CL-HL3	108.35	109.25	0.90
HL1-CL-CLP	108.85	109.90	1.05
HL2-CL-HL3	109.81	108.88	0.92
HL2-CL-CLP	108.47	109.41	0.95
HL3-CL-CLP	113.46	110.68	2.78
CLP-N-H	114.01	112.49	1.52
CLP-N-CA	136.54	135.23	1.31

Terms	QM	CHARMM	Abs. diff.
OL-CLP-N	126.45	125.38	1.07
N-CA-CB	118.05	118.99	0.94
N-CA-C	128.16	127.72	0.44
H-N-CA	109.44	112.27	2.83
CA-CB-HB	117.03	121.70	4.68
CA-CB-CG	124.60	121.76	2.84
CA-C-O	118.14	121.51	3.37
CA-C-NR	118.94	120.15	1.21
CB-CA-C	113.79	113.24	0.55
CB-CG-OD1	126.64	128.27	1.63
CB-CG-OD2	112.47	112.24	0.23
HB-CB-CG	118.38	116.53	1.84
CG-OD2-HO	106.19	109.14	2.95
OD1-CG-OD2	120.89	119.50	1.40
C-NR-HR	119.65	118.68	0.97
C-NR-CR	119.73	122.77	3.04
O-C-NR	122.93	118.34	4.59
NR-CR-HR1	110.88	110.95	0.06
NR-CR-HR2	110.96	110.63	0.33
NR-CR-HR3	108.49	110.34	1.85
HR-NR-CR	120.61	118.24	2.37
HR1-CR-HR2	107.68	108.28	0.60
HR1-CR-HR3	109.41	108.25	1.16
HR2-CR-HR3	109.40	108.30	1.09

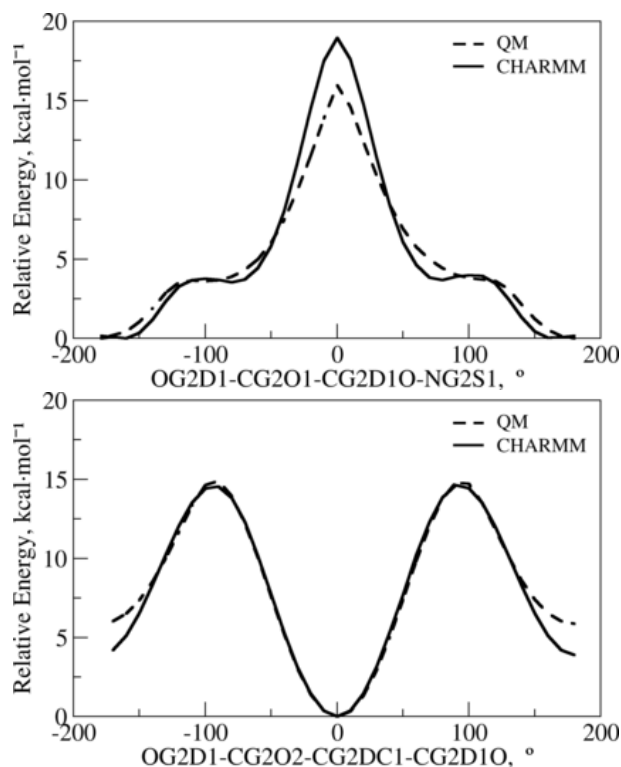


Figure S341: The PES scan for flexible dihedrals corresponding to (2Z)-3-acetamido-3-(methylcarbamoyl)prop-2-enoic acid.

2.81 The small molecule used for bonded terms optimization of (3S)-3-amino-3-[(4Z)-1-(carboxymethyl)-4-[(4-hydroxyphenyl)methylidene]-5-oxo-imidazol-2-yl]propanoic acid (DYG)

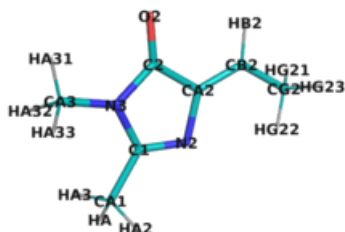


Figure S342: The energy minimized structure corresponding to (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one.

Table S761: The calculated geometric terms of (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one.

Terms	QM	CHARMM	Abs. diff.
CA1-HA	1.09	1.11	0.01
CA1-HA2	1.09	1.11	0.02
CA1-HA3	1.09	1.11	0.01
CA1-C1	1.49	1.50	0.01
C1-N2	1.31	1.33	0.02
C1-N3	1.39	1.39	0.00
N2-CA2	1.41	1.41	0.00
N3-C2	1.40	1.38	0.02
N3-CA3	1.45	1.47	0.02
C2-O2	1.23	1.24	0.01
C2-CA2	1.49	1.48	0.01
CA2-CB2	1.35	1.35	0.00
CB2-HB2	1.09	1.10	0.01
CB2-CG2	1.49	1.51	0.02
CG2-HG21	1.10	1.11	0.02
CG2-HG22	1.09	1.11	0.02
CG2-HG23	1.10	1.11	0.02
CA3-HA31	1.09	1.11	0.02
CA3-HA32	1.09	1.11	0.02
CA3-HA33	1.09	1.11	0.02
CA1-C1-N2	124.60	121.77	2.83
CA1-C1-N3	120.85	121.89	1.04
HA-CA1-HA2	109.22	108.67	0.55
HA-CA1-HA3	107.77	109.67	1.91
HA-CA1-C1	111.12	109.93	1.19
HA2-CA1-HA3	109.22	108.67	0.54
HA2-CA1-C1	108.37	109.93	1.56
HA3-CA1-C1	111.12	109.93	1.19
C1-N2-CA2	104.87	102.65	2.22

Terms	QM	CHARMM	Abs. diff.
C1-N3-C2	108.14	106.52	1.62
C1-N3-CA3	128.47	126.83	1.64
N2-C1-N3	114.55	116.34	1.79
N2-CA2-C2	110.12	110.13	0.01
N2-CA2-CB2	125.91	126.25	0.34
N3-C2-O2	126.32	128.21	1.89
N3-C2-CA2	102.32	104.36	2.04
N3-CA3-HA31	106.27	111.14	4.87
N3-CA3-HA32	111.19	110.98	0.21
N3-CA3-HA33	111.19	110.97	0.23
C2-N3-CA3	123.38	126.65	3.26
C2-CA2-CB2	123.97	123.61	0.36
O2-C2-CA2	131.36	127.44	3.92
CA2-CB2-HB2	116.54	116.84	0.30
CA2-CB2-CG2	124.33	124.76	0.44
CB2-CG2-HG21	110.53	110.96	0.43
CB2-CG2-HG22	110.55	112.64	2.09
CB2-CG2-HG23	110.53	111.00	0.47
HB2-CB2-CG2	119.14	118.40	0.74
HG21-CG2-HG22	109.14	107.22	1.92
HG21-CG2-HG23	106.87	107.62	0.75
HG22-CG2-HG23	109.14	107.17	1.97
HA31-CA3-HA32	109.33	107.57	1.77
HA31-CA3-HA33	109.33	107.55	1.78
HA32-CA3-HA33	109.45	108.49	0.96

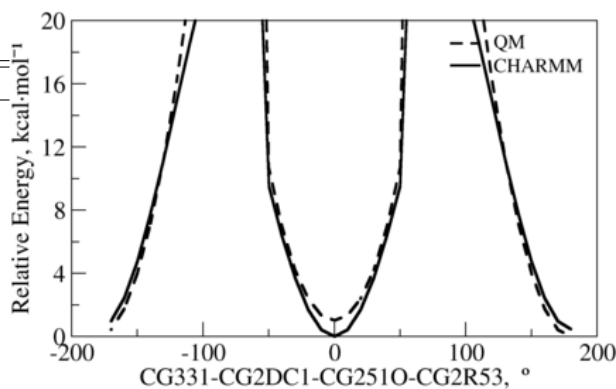


Figure S343: The PES scan for flexible dihedral corresponding to (4Z)-4-ethylidene-1,2-dimethyl-4,5-dihydro-1H-imidazol-5-one.

2.82 The small molecule used for bonded terms optimization of 3,4-difluoro-phenylalanine (F2F)

Terms	QM	CHARMM	Abs. diff.
HD2-CD2-CE2	119.12	119.89	0.77
CE1-CZ-CE2	120.11	120.71	0.60
CE1-CZ-FZ	119.06	121.07	2.02
FE1-CE1-CZ	118.87	121.11	2.24
CE2-CZ-FZ	120.83	118.21	2.62
HE2-CE2-CZ	118.99	120.59	1.60

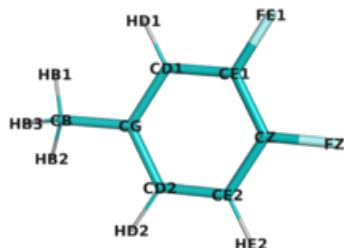


Figure S344: The energy minimized structure corresponding to 1,2-difluoro-4-methylbenzene.

Table S762: The calculated geometric terms of 1,2-difluoro-4-methylbenzene.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.10	1.11	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.51	1.50	0.01
CG-CD1	1.40	1.40	0.00
CG-CD2	1.40	1.40	0.00
CD1-HD1	1.09	1.08	0.01
CD1-CE1	1.39	1.39	0.01
CD2-HD2	1.09	1.08	0.01
CD2-CE2	1.40	1.40	0.00
CE1-FE1	1.35	1.36	0.01
CE1-CZ	1.39	1.40	0.01
CE2-HE2	1.09	1.08	0.01
CE2-CZ	1.39	1.39	0.01
CZ-FZ	1.35	1.36	0.01
HB3-CB-HB1	107.69	109.84	2.15
HB3-CB-HB2	107.80	109.98	2.18
HB3-CB-CG	111.13	108.59	2.53
CB-CG-CD1	120.18	119.61	0.58
CB-CG-CD2	121.16	120.29	0.87
HB1-CB-HB2	108.06	109.19	1.12
HB1-CB-CG	111.11	109.65	1.46
HB2-CB-CG	110.91	109.58	1.32
CG-CD1-HD1	121.42	120.01	1.40
CG-CD1-CE1	120.10	119.04	1.05
CG-CD2-HD2	119.63	119.39	0.24
CG-CD2-CE2	121.25	120.73	0.52
CD1-CG-CD2	118.62	120.09	1.47
CD1-CE1-FE1	120.44	118.16	2.29
CD1-CE1-CZ	120.69	120.73	0.04
HD1-CD1-CE1	118.49	120.95	2.46
CD2-CE2-HE2	121.78	120.72	1.06
CD2-CE2-CZ	119.23	118.69	0.54

2.83 The small molecule used for bonded terms optimization of 4-fluoro-glutamicacid (FGA4)

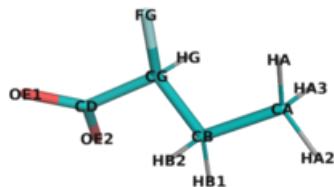


Figure S345: The energy minimized structure corresponding to 2-fluorobutanoicacid.

Table S763: The calculated geometric terms of 2-fluorobutanoicacid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.10	1.11	0.01
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.53	0.01
CB-HB1	1.10	1.11	0.02
CB-HB2	1.10	1.11	0.02
CB-CG	1.52	1.54	0.03
CG-HG	1.10	1.09	0.01
CG-CD	1.55	1.56	0.01
CG-FG	1.43	1.39	0.05
CD-OE1	1.26	1.26	0.00
CD-OE2	1.27	1.27	0.01
HA3-CA-HA2	107.87	108.84	0.97
HA3-CA-HA	107.99	108.45	0.46
HA3-CA-CB	110.65	110.17	0.48
HA2-CA-HA	108.23	108.69	0.46
HA2-CA-CB	111.29	110.48	0.81
CA-CB-HB1	110.94	109.33	1.61
CA-CB-HB2	110.31	109.48	0.83
CA-CB-CG	113.40	113.55	0.15
HA-CA-CB	110.68	110.16	0.52
CB-CG-HG	111.05	107.81	3.25
CB-CG-CD	111.39	111.86	0.46
CB-CG-FG	107.15	108.27	1.12
HB1-CB-HB2	107.57	107.49	0.08
HB1-CB-CG	106.96	108.46	1.50
HB2-CB-CG	107.40	108.34	0.94
CG-CD-OE1	118.21	118.24	0.03
CG-CD-OE2	111.21	113.64	2.43
HG-CG-CD	109.06	109.15	0.09
HG-CG-FG	105.10	106.51	1.41
CD-CG-FG	112.92	112.99	0.07
OE1-CD-OE2	130.53	128.12	2.42

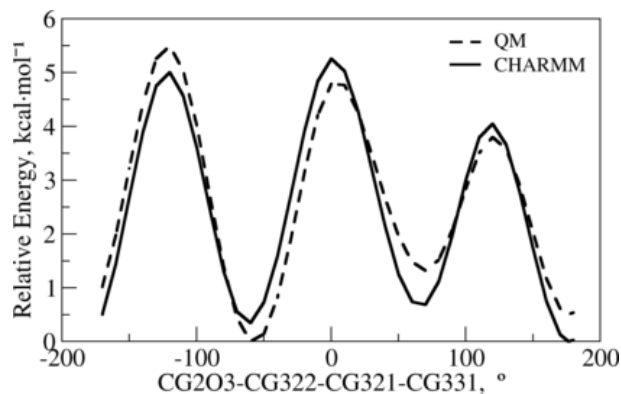


Figure S346: The PES scan for flexible dihedral corresponding to 2-fluorobutanoicacid.

2.84 The small molecule used for bonded terms optimization of 2-aminopropanedioic acid (FGL)

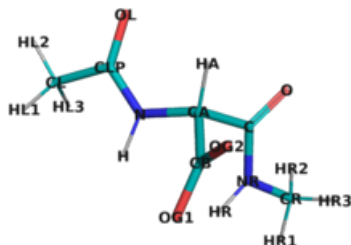


Figure S347: The energy minimized structure corresponding to (2R)-2-acetamido-2-(methylcarbamoyl)acetate.

Table S764: The calculated geometric terms of (2R)-2-acetamido-2-(methylcarbamoyl)acetate.

Terms	QM	CHARMM	Abs. diff.
CL-HL1	1.09	1.11	0.02
CL-HL2	1.09	1.11	0.02
CL-HL3	1.10	1.11	0.01
CL-CLP	1.52	1.48	0.04
CLP-OL	1.24	1.22	0.02
CLP-N	1.35	1.34	0.01
N-H	1.02	0.99	0.03
N-CA	1.46	1.46	0.01
CA-HA	1.09	1.11	0.02
CA-CB	1.57	1.54	0.03
CA-C	1.53	1.50	0.03
CB-OG1	1.28	1.27	0.01
CB-OG2	1.25	1.26	0.01
C-O	1.24	1.23	0.01
C-NR	1.37	1.34	0.03
NR-HR	1.02	1.00	0.02
NR-CR	1.45	1.44	0.01
CR-HR1	1.09	1.11	0.02
CR-HR2	1.09	1.11	0.02
CR-HR3	1.10	1.11	0.01
CL-CLP-OL	120.90	120.12	0.77
CL-CLP-N	115.01	115.49	0.48
HL1-CL-HL2	109.60	109.23	0.37
HL1-CL-HL3	108.89	109.53	0.64
HL1-CL-CLP	112.91	109.88	3.03
HL2-CL-HL3	108.04	109.21	1.17
HL2-CL-CLP	108.64	109.26	0.61
HL3-CL-CLP	108.64	109.71	1.07
CLP-N-H	121.24	120.58	0.65
CLP-N-CA	124.79	125.94	1.15
OL-CLP-N	124.09	124.39	0.29
N-CA-HA	111.23	111.32	0.09

Terms	QM	CHARMM	Abs. diff.
N-CA-CB	106.23	110.57	4.34
N-CA-C	111.75	110.42	1.33
H-N-CA	112.37	113.32	0.95
CA-CB-OG1	112.85	115.68	2.83
CA-CB-OG2	117.07	117.19	0.12
CA-C-O	123.83	121.97	1.87
CA-C-NR	113.06	116.57	3.51
HA-CA-CB	111.43	108.80	2.63
HA-CA-C	108.19	108.46	0.27
CB-CA-C	107.99	107.15	0.83
OG1-CB-OG2	130.07	127.13	2.94
C-NR-HR	113.15	115.97	2.82
C-NR-CR	119.21	122.31	3.10
O-C-NR	123.10	121.44	1.66
NR-CR-HR1	108.67	110.32	1.65
NR-CR-HR2	109.17	110.29	1.12
NR-CR-HR3	112.16	110.05	2.10
HR-NR-CR	118.51	120.09	1.59
HR1-CR-HR2	109.30	108.87	0.43
HR1-CR-HR3	109.42	108.83	0.59
HR2-CR-HR3	108.08	108.42	0.34

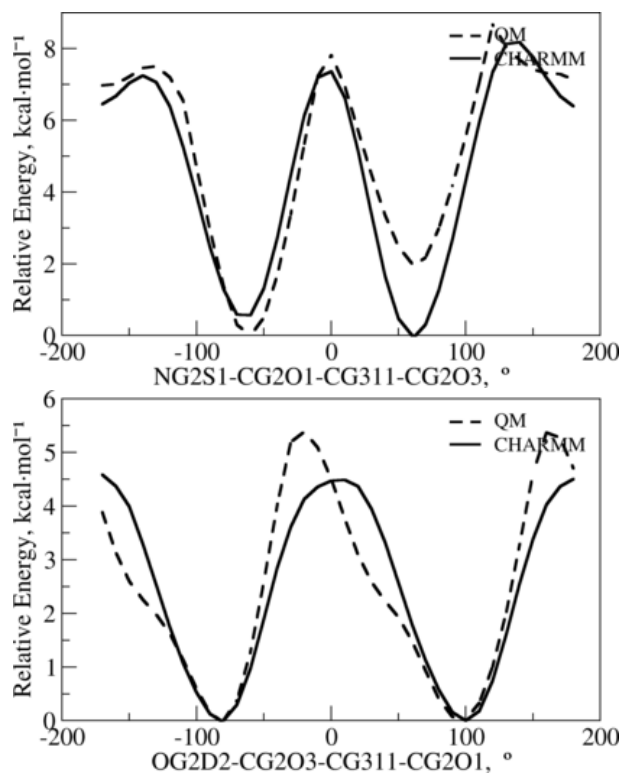


Figure S348: The PES scan for flexible dihedrals corresponding to (2R)-2-acetamido-2-(methylcarbamoyl)acetate.

2.85 The small molecule used for bonded terms optimization of N5-formyl-N5-hydroxy-L-ornithine (FHO)



Figure S349: The energy minimized structure corresponding to N-ethyl-N-hydroxyformamide.

Table S765: The calculated geometric terms of N-ethyl-N-hydroxyformamide.

Terms	QM	CHARMM	Abs. diff.
HG3-CG	1.09	1.11	0.02
CG-HG1	1.09	1.11	0.02
CG-HG2	1.09	1.11	0.02
CG-CD	1.52	1.53	0.01
CD-HD1	1.09	1.11	0.02
CD-HD2	1.09	1.11	0.02
CD-NE	1.45	1.46	0.01
NE-CZ	1.35	1.36	0.01
NE-OZ	1.41	1.42	0.01
CZ-HZ	1.10	1.10	0.00
CZ-OH	1.24	1.23	0.01
OZ-HOZ	0.99	0.96	0.03
HG3-CG-HG1	108.59	108.89	0.31
HG3-CG-HG2	108.77	108.64	0.12
HG3-CG-CD	110.10	110.95	0.84
CG-CD-HD1	111.66	107.58	4.07
CG-CD-HD2	111.14	107.90	3.24
CG-CD-NE	113.00	117.67	4.67
HG1-CG-HG2	108.72	108.06	0.65
HG1-CG-CD	110.49	110.19	0.30
HG2-CG-CD	110.13	110.03	0.10
CD-NE-CZ	126.27	129.51	3.24
CD-NE-OZ	112.41	112.80	0.39
HD1-CD-HD2	107.66	106.56	1.11
HD1-CD-NE	105.89	108.71	2.82
HD2-CD-NE	107.17	107.91	0.74
NE-CZ-HZ	113.38	114.44	1.06
NE-CZ-OH	122.08	124.09	2.01
NE-OZ-HOZ	100.26	101.08	0.83
CZ-NE-OZ	114.52	112.88	1.64
HZ-CZ-OH	124.44	121.36	3.09

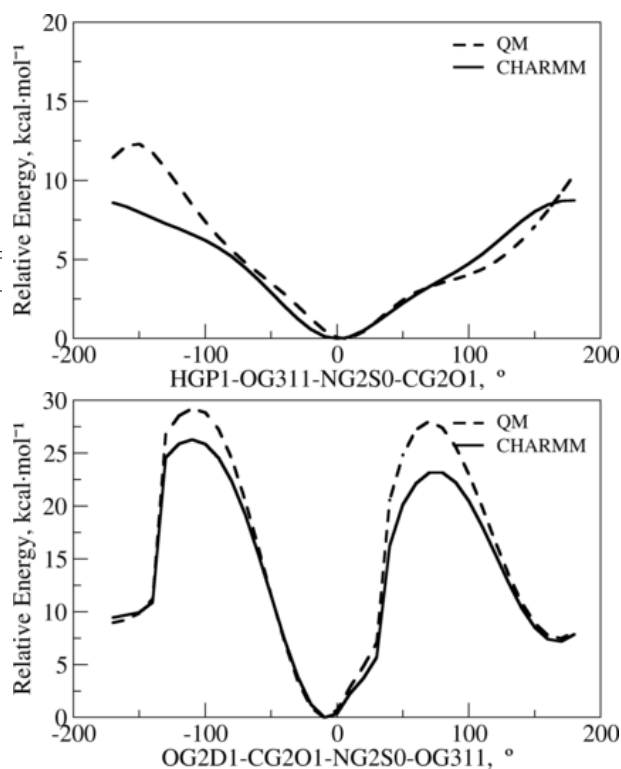


Figure S350: The PES scan for flexible dihedrals corresponding to N-ethyl-N-hydroxyformamide.

2.86 The small molecule used for bonded terms optimization of Trifluoroalanine (FLA)



Figure S351: The energy minimized structure corresponding to 2-amino-3,3,3-trifluoroalanine.

Table S766: The calculated geometric terms of 2-amino-3,3,3-trifluoroalanine.

Terms	QM	CHARMM	Abs. diff.
N-HN3	1.02	1.01	0.01
N-HN1	1.03	1.01	0.01
N-HN2	1.06	1.03	0.03
N-CA	1.50	1.49	0.00
CA-HA	1.09	1.11	0.02
CA-CB	1.50	1.63	0.13
CA-C	1.60	1.53	0.07
F1-CB	1.37	1.37	0.00
F2-CB	1.33	1.37	0.04
F3-CB	1.36	1.37	0.01
C-O	1.27	1.26	0.01
C-OXT	1.23	1.25	0.02
N-CA-HA	109.61	107.48	2.13
N-CA-CB	108.87	110.99	2.12
N-CA-C	103.82	108.70	4.88
HN3-N-HN1	109.13	112.39	3.26
HN3-N-HN2	114.72	110.37	4.36
HN3-N-CA	115.00	111.62	3.39
HN1-N-HN2	108.78	109.38	0.60
HN1-N-CA	111.71	110.96	0.75
HN2-N-CA	96.98	101.59	4.62
CA-CB-F1	110.15	111.07	0.93
CA-CB-F2	112.75	115.15	2.41
CA-CB-F3	110.16	114.71	4.55
CA-C-O	110.08	117.57	7.48
CA-C-OXT	115.59	115.06	0.53
HA-CA-CB	109.36	106.07	3.29
HA-CA-C	110.30	106.84	3.46
F1-CB-F2	108.18	104.75	3.43
F1-CB-F3	105.86	104.52	1.34
F2-CB-F3	109.50	105.63	3.88
CB-CA-C	114.68	116.31	1.64
O-C-OXT	134.32	127.35	6.96

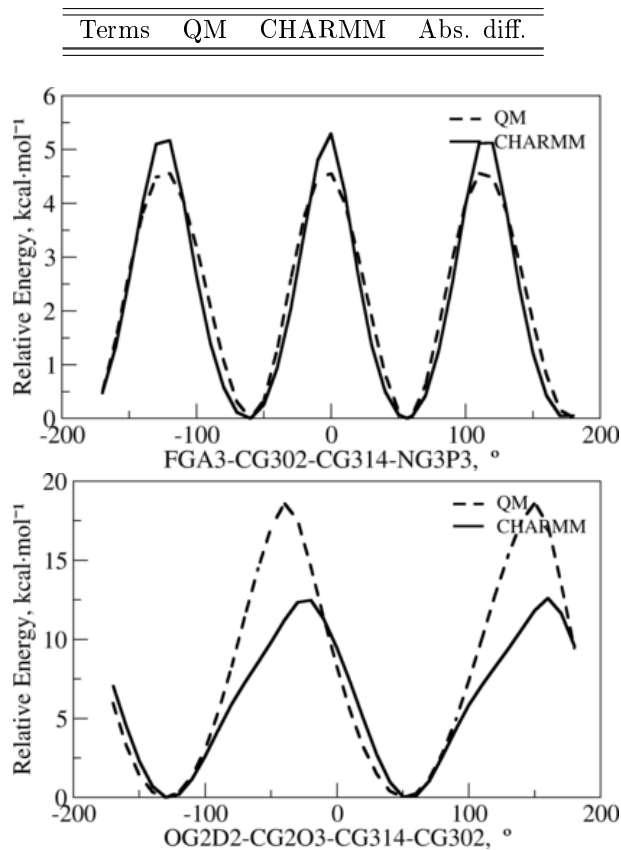


Figure S352: The PES scan for flexible dihedrals corresponding to 2-amino-3,3,3-trifluoroalanine.

2.87 The small molecule used for bonded terms optimization of N-formylmethionine (FME)

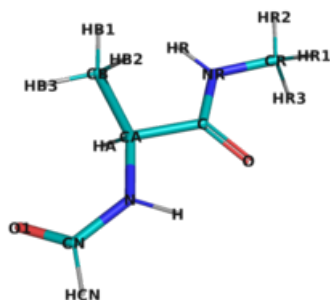


Figure S353: The energy minimized structure corresponding to (2S)-2-formamido-N-methylpropanamide.

Table S767: The calculated geometric terms of (2S)-2-formamido-N-methylpropanamide.

Terms	QM	CHARMM	Abs. diff.
CN-HCN	1.10	1.09	0.01
CN-O1	1.23	1.23	0.00
CN-N	1.35	1.34	0.01
N-H	1.02	1.00	0.02
N-CA	1.45	1.44	0.00
CA-HA	1.10	1.11	0.02
CA-CB	1.53	1.55	0.02
CA-C	1.53	1.51	0.02
CB-HB1	1.09	1.11	0.01
CB-HB2	1.09	1.11	0.02
CB-HB3	1.09	1.11	0.02
C-O	1.24	1.23	0.01
C-NR	1.36	1.35	0.01
NR-HR	1.01	0.99	0.02
NR-CR	1.45	1.45	0.01
CR-HR1	1.09	1.11	0.03
CR-HR2	1.09	1.11	0.02
CR-HR3	1.09	1.11	0.02
CN-N-H	122.24	122.28	0.04
CN-N-CA	121.38	122.75	1.37
HCN-CN-O1	122.80	124.75	1.95
HCN-CN-N	112.91	112.37	0.54
O1-CN-N	124.28	122.88	1.40
N-CA-HA	108.08	109.86	1.78
N-CA-CB	111.65	112.13	0.47
N-CA-C	106.87	105.85	1.02
H-N-CA	116.23	114.32	1.91
CA-CB-HB1	111.24	111.85	0.60
CA-CB-HB2	109.59	110.66	1.07
CA-CB-HB3	108.82	109.22	0.39
CA-C-O	121.37	120.30	1.07
CA-C-NR	114.85	117.93	3.08
HA-CA-CB	109.04	110.02	0.98

Terms	QM	CHARMM	Abs. diff.
HA-CA-C	110.33	107.65	2.69
CB-CA-C	110.82	111.18	0.36
HB1-CB-HB2	108.83	109.07	0.24
HB1-CB-HB3	108.93	107.92	1.01
HB2-CB-HB3	109.40	108.01	1.39
C-NR-HR	118.50	120.25	1.75
C-NR-CR	122.33	121.81	0.52
O-C-NR	123.72	121.77	1.95
NR-CR-HR1	107.20	111.08	3.89
NR-CR-HR2	110.41	110.58	0.17
NR-CR-HR3	111.26	110.54	0.72
HR-NR-CR	118.98	117.94	1.04
HR1-CR-HR2	109.55	108.09	1.46
HR1-CR-HR3	109.08	108.07	1.02
HR2-CR-HR3	109.30	108.38	0.91

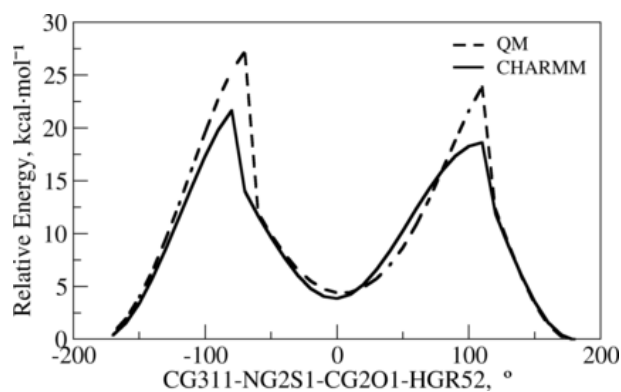


Figure S354: The PES scan for flexible dihedral corresponding to (2S)-2-formamido-N-methylpropanamide.

2.88 The small molecule used for bonded terms optimization of (2-furyl)-alanine (FUA2)

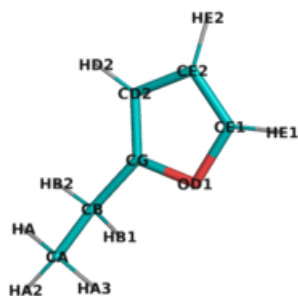


Figure S355: The energy minimized structure corresponding to 2-ethylfuran.

Table S768: The calculated geometric terms of 2-ethylfuran.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.54	0.01
CB-HB1	1.10	1.11	0.01
CB-HB2	1.10	1.11	0.02
CB-CG	1.49	1.51	0.02
CG-CD2	1.37	1.36	0.01
CG-OD1	1.37	1.37	0.01
CD2-HD2	1.08	1.08	0.00
CD2-CE2	1.43	1.36	0.06
OD1-CE1	1.37	1.37	0.00
CE2-HE2	1.08	1.08	0.00
CE2-CE1	1.37	1.36	0.00
CE1-HE1	1.08	1.08	0.00
HA3-CA-HA2	108.39	108.36	0.03
HA3-CA-HA	108.16	108.35	0.18
HA3-CA-CB	110.42	110.49	0.06
HA2-CA-HA	108.43	108.42	0.01
HA2-CA-CB	110.88	110.48	0.40
CA-CB-HB1	109.73	109.15	0.58
CA-CB-HB2	110.37	108.99	1.38
CA-CB-CG	112.66	114.72	2.06
HA-CA-CB	110.47	110.67	0.20
CB-CG-CD2	134.36	132.71	1.64
CB-CG-OD1	116.18	116.31	0.14
HB1-CB-HB2	106.81	107.24	0.43
HB1-CB-CG	109.47	107.94	1.53
HB2-CB-CG	107.61	108.54	0.93
CG-CD2-HD2	125.81	125.82	0.01
CG-CD2-CE2	106.90	106.98	0.07
CG-OD1-CE1	107.13	104.27	2.86
CD2-CG-OD1	109.45	110.97	1.52
CD2-CE2-HE2	127.57	126.92	0.65

Terms	QM	CHARMM	Abs. diff.
CD2-CE2-CE1	106.16	107.01	0.85
HD2-CD2-CE2	127.29	127.21	0.08
OD1-CE1-CE2	110.36	110.77	0.41
OD1-CE1-HE1	115.62	118.36	2.73
CE2-CE1-HE1	134.01	130.87	3.14
HE2-CE2-CE1	126.27	126.07	0.20

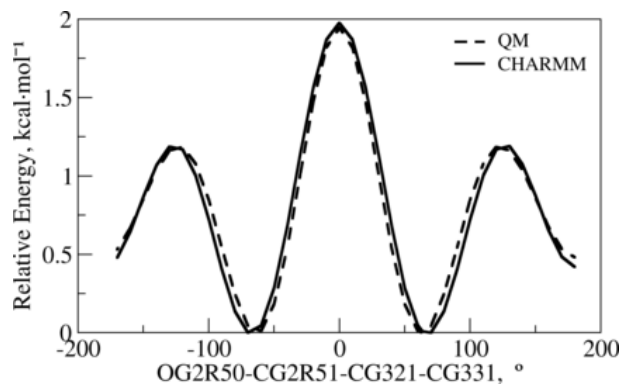


Figure S356: The PES scan for flexible dihedral corresponding to 2-ethylfuran.

2.89 The small molecule 1 used for bonded terms optimization of 3-fluoro-valine (FVAL)

Terms	QM	CHARMM	Abs. diff.
HG21-CG2-HG22	108.54	108.10	0.44
HG21-CG2-HG23	108.76	108.44	0.32
HG22-CG2-HG23	108.76	108.50	0.26



Figure S357: The energy minimized structure corresponding to 2-fluoro-2-methylpropane.

Table S769: The calculated geometric terms of 2-fluoro-2-methylpropane.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.52	0.00
CB-FG3	1.42	1.38	0.04
CB-CG1	1.52	1.52	0.00
CB-CG2	1.52	1.52	0.00
CG1-HG11	1.09	1.11	0.02
CG1-HG12	1.09	1.11	0.02
CG1-HG13	1.09	1.11	0.02
CG2-HG21	1.09	1.11	0.02
CG2-HG22	1.09	1.11	0.02
CG2-HG23	1.09	1.11	0.02
HA3-CA-HA2	108.56	108.21	0.35
HA3-CA-HA	108.75	108.43	0.32
HA3-CA-CB	109.97	110.56	0.59
HA2-CA-HA	108.78	108.40	0.38
HA2-CA-CB	109.98	110.54	0.56
CA-CB-FG3	106.37	106.11	0.26
CA-CB-CG1	112.39	112.60	0.21
CA-CB-CG2	112.39	112.61	0.21
HA-CA-CB	110.76	110.63	0.13
CB-CG1-HG11	110.75	110.63	0.12
CB-CG1-HG12	109.95	110.55	0.59
CB-CG1-HG13	109.96	110.48	0.53
CB-CG2-HG21	109.98	110.53	0.54
CB-CG2-HG22	109.98	110.55	0.57
CB-CG2-HG23	110.77	110.64	0.13
FG3-CB-CG1	106.36	106.15	0.21
FG3-CB-CG2	106.37	106.15	0.22
CG1-CB-CG2	112.39	112.57	0.18
HG11-CG1-HG12	108.79	108.49	0.30
HG11-CG1-HG13	108.77	108.47	0.31
HG12-CG1-HG13	108.57	108.14	0.43

2.90 The small molecule 2 used for bonded terms optimization of 3-fluoro-valine (FVAL)

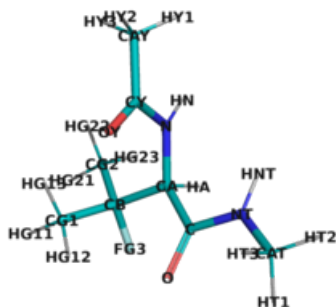


Figure S358: The energy minimized structure corresponding to (2S)-2-acetamido-3-fluoro-N,3-dimethylbutanamide.

Table S770: The calculated geometric terms of (2S)-2-acetamido-3-fluoro-N,3-dimethylbutanamide.

Terms	QM	CHARMM	Abs. diff.
N-HN	1.01	0.99	0.02
N-CA	1.46	1.47	0.01
N-CY	1.38	1.34	0.04
CA-HA	1.10	1.08	0.02
CA-CB	1.54	1.56	0.02
CA-C	1.54	1.52	0.02
CB-FG3	1.41	1.38	0.03
CB-CG1	1.52	1.52	0.00
CB-CG2	1.52	1.53	0.01
CG1-HG11	1.09	1.11	0.02
CG1-HG12	1.09	1.11	0.02
CG1-HG13	1.09	1.11	0.02
CG2-HG21	1.09	1.11	0.02
CG2-HG22	1.09	1.11	0.02
CG2-HG23	1.10	1.11	0.01
C-O	1.23	1.23	0.00
C-NT	1.37	1.35	0.02
NT-HNT	1.01	0.99	0.02
NT-CAT	1.45	1.45	0.01
CAT-HT1	1.09	1.11	0.02
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.10	1.11	0.02
CAY-HY1	1.09	1.11	0.02
CAY-HY2	1.09	1.11	0.02
CAY-HY3	1.09	1.11	0.02
CAY-CY	1.51	1.48	0.03
CY-OY	1.23	1.22	0.01
N-CA-HA	105.72	103.18	2.54
N-CA-CB	114.71	114.52	0.19
N-CA-C	110.63	114.99	4.36
N-CY-CAY	114.77	116.57	1.80
N-CY-OY	121.99	122.93	0.94

Terms	QM	CHARMM	Abs. diff.
HN-N-CA	116.00	116.17	0.17
HN-N-CY	116.31	117.39	1.08
CA-N-CY	121.68	125.44	3.76
CA-CB-FG3	103.72	107.21	3.49
CA-CB-CG1	116.95	117.06	0.11
CA-CB-CG2	110.33	111.22	0.89
CA-C-O	123.47	123.29	0.17
CA-C-NT	113.20	116.53	3.33
HA-CA-CB	104.27	103.22	1.06
HA-CA-C	104.93	102.42	2.52
CB-CA-C	115.37	115.91	0.54
CB-CG1-HG11	108.04	110.24	2.20
CB-CG1-HG12	110.00	111.68	1.67
CB-CG1-HG13	111.11	110.83	0.29
CB-CG2-HG21	108.69	109.90	1.20
CB-CG2-HG22	111.46	110.85	0.60
CB-CG2-HG23	110.73	110.91	0.18
FG3-CB-CG1	107.38	106.89	0.49
FG3-CB-CG2	105.68	103.38	2.29
CG1-CB-CG2	111.80	110.04	1.76
HG11-CG1-HG12	109.54	107.74	1.80
HG11-CG1-HG13	109.05	108.12	0.93
HG12-CG1-HG13	109.07	108.11	0.96
HG21-CG2-HG22	108.37	107.98	0.39
HG21-CG2-HG23	108.13	107.86	0.27
HG22-CG2-HG23	109.37	109.25	0.12
C-NT-HNT	116.21	119.69	3.48
C-NT-CAT	118.90	121.60	2.70
O-C-NT	122.88	120.13	2.76
NT-CAT-HT1	108.62	111.27	2.65
NT-CAT-HT2	108.76	110.85	2.09
NT-CAT-HT3	111.89	110.38	1.51
HNT-NT-CAT	117.98	117.88	0.10
HT1-CAT-HT2	109.45	108.15	1.30
HT1-CAT-HT3	108.48	107.59	0.88
HT2-CAT-HT3	109.61	108.48	1.13
CAY-CY-OY	123.23	120.50	2.72
HY1-CAY-HY2	109.72	108.81	0.91
HY1-CAY-HY3	108.29	109.89	1.60
HY1-CAY-CY	111.88	111.16	0.72
HY2-CAY-HY3	108.64	107.74	0.90
HY2-CAY-CY	108.53	109.27	0.74
HY3-CAY-CY	109.72	109.89	0.17

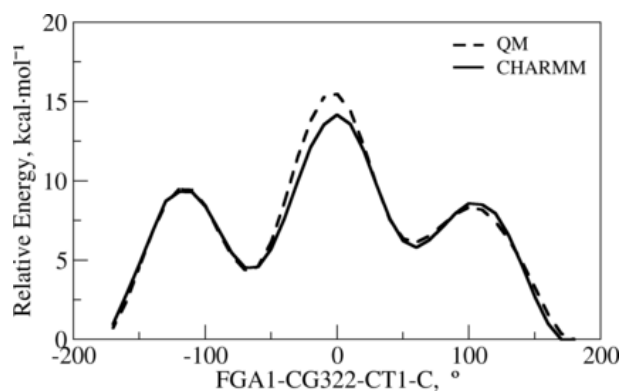


Figure S359: The PES scan for flexible dihedral corresponding to (2S)-2-acetamido-3-fluoro-N,3-dimethylbutanamide.

2.91 The small molecule 1 used for bonded terms optimization of (2S)-2-amino-6-[1-[(2R,3R,4S,5R)-5-[[[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-3,4-dihydroxy-oxolan-2-yl]methoxy-hydroxy-phosphoryl]oxy-hydroxy-phosphoryl]oxymethyl]-3,4-dihydroxy-oxolan-2-yl]sulfanylethylideneamino]hexanoicacid (FZN)

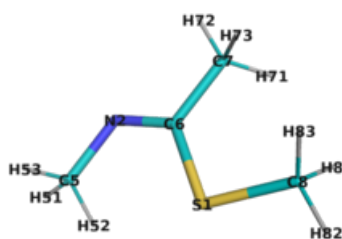


Figure S360: The energy minimized structure corresponding to (Z)-methyl[1-(methylsulfanyl)ethylidene]amine.

Table S771: The calculated geometric terms of (Z)-methyl[1-(methylsulfanyl)ethylidene]amine.

Terms	QM	CHARMM	Abs. diff.
C5-H51	1.10	1.11	0.02
C5-H52	1.10	1.11	0.02
C5-H53	1.09	1.11	0.02
C5-N2	1.46	1.46	0.00
N2-C6	1.28	1.31	0.03
C6-C7	1.50	1.51	0.00
C6-S1	1.79	1.80	0.01
C7-H71	1.09	1.11	0.01
C7-H72	1.09	1.11	0.02
C7-H73	1.09	1.11	0.01
S1-C8	1.81	1.83	0.01
C8-H8	1.09	1.11	0.02
C8-H82	1.09	1.11	0.02
C8-H83	1.09	1.11	0.02
C5-N2-C6	118.27	118.34	0.07
H51-C5-H52	107.91	107.12	0.79
H51-C5-H53	108.70	105.37	3.33
H51-C5-N2	111.39	113.70	2.31
H52-C5-H53	108.70	105.38	3.32
H52-C5-N2	111.39	113.72	2.33
H53-C5-N2	108.68	110.89	2.20
N2-C6-C7	118.84	118.80	0.04
N2-C6-S1	121.92	122.03	0.11
C6-C7-H71	111.68	110.97	0.70

Terms	QM	CHARMM	Abs. diff.
C6-C7-H72	107.13	110.97	3.85
C6-C7-H73	111.68	110.97	0.70
C6-S1-C8	103.69	103.68	0.01
C7-C6-S1	119.25	119.17	0.07
H71-C7-H72	109.15	107.33	1.81
H71-C7-H73	108.03	109.11	1.08
H72-C7-H73	109.15	107.33	1.81
S1-C8-H8	112.05	111.68	0.37
S1-C8-H82	105.65	110.27	4.62
S1-C8-H83	112.05	111.73	0.32
H8-C8-H82	108.39	107.17	1.21
H8-C8-H83	110.09	108.64	1.45
H82-C8-H83	108.39	107.14	1.25

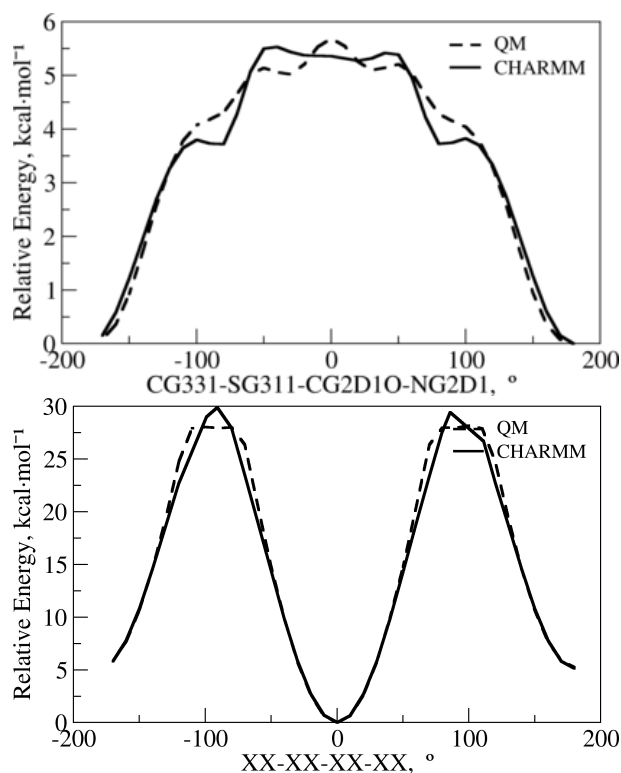


Figure S361: The PES scan for flexible dihedrals corresponding to (Z)-methyl[1-(methylsulfanyl)ethylidene]amine.

2.92 The small molecule 2 used for bonded terms optimization of (2S)-2-amino-6-[1-[(2R,3R,4S,5R)-5-[[[(2R,3S,4R,5R)-5-(6-aminopurin-9-yl)-3,4-dihydroxy-oxolan-2-yl]methoxy-hydroxy-phosphoryl]oxy-hydroxy-phosphoryl]oxymethyl]-3,4-dihydroxy-oxolan-2-yl]sulfanylethylideneamino]hexanoic acid (FZN)

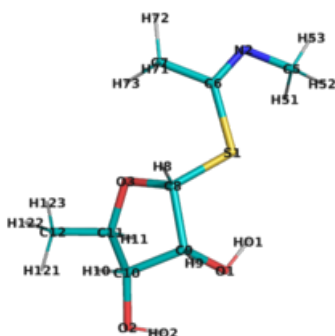


Figure S362: The energy minimized structure corresponding to (2R,3S,4R,5R)-2-methyl-5-[(1Z)-1-(methylimino)ethyl]sulfanyloxolane-3,4-diol.

Table S772: The calculated geometric terms of (2R,3S,4R,5R)-2-methyl-5-[(1Z)-1-(methylimino)ethyl]sulfanyloxolane-3,4-diol.

Terms	QM	CHARMM	Abs. diff.
H53-C5	1.09	1.11	0.02
C5-H51	1.10	1.11	0.02
C5-H52	1.10	1.11	0.02
C5-N2	1.46	1.46	0.00
N2-C6	1.28	1.31	0.03
C6-C7	1.50	1.51	0.00
C6-S1	1.80	1.79	0.01
C7-H71	1.10	1.11	0.01
C7-H72	1.09	1.11	0.02
C7-H73	1.09	1.11	0.02
S1-C8	1.82	1.83	0.01
C8-H8	1.09	1.10	0.01
C8-O3	1.43	1.44	0.01
C8-C9	1.54	1.57	0.03
O3-C11	1.44	1.43	0.01
C9-H9	1.10	1.10	0.00
C9-O1	1.43	1.44	0.01
C9-C10	1.53	1.55	0.02
O1-HO1	0.97	0.96	0.01
C10-H10	1.10	1.10	0.01
C10-O2	1.41	1.43	0.02
C10-C11	1.53	1.53	0.00
O2-HO2	0.98	0.97	0.01

Terms	QM	CHARMM	Abs. diff.
C11-H11	1.10	1.10	0.00
C11-C12	1.51	1.53	0.02
C12-H121	1.09	1.11	0.02
C12-H122	1.09	1.11	0.02
C12-H123	1.09	1.11	0.02
H53-C5-H51	108.65	105.22	3.44
H53-C5-H52	108.66	105.23	3.43
H53-C5-N2	108.61	110.92	2.31
C5-N2-C6	118.87	118.85	0.02
H51-C5-H52	108.05	107.25	0.80
H51-C5-N2	111.27	113.70	2.43
H52-C5-N2	111.52	113.83	2.30
N2-C6-C7	119.25	118.37	0.88
N2-C6-S1	121.36	121.20	0.15
C6-C7-H71	111.24	111.19	0.05
C6-C7-H72	107.10	111.14	4.04
C6-C7-H73	111.44	110.96	0.48
C6-S1-C8	102.65	103.70	1.05
C7-C6-S1	119.38	120.42	1.04
H71-C7-H72	108.47	107.30	1.17
H71-C7-H73	108.37	108.92	0.55
H72-C7-H73	110.18	107.16	3.02
S1-C8-H8	108.37	108.82	0.45
S1-C8-O3	113.49	114.07	0.58
S1-C8-C9	109.86	110.23	0.37
C8-O3-C11	108.07	110.23	2.15
C8-C9-H9	111.73	111.22	0.51
C8-C9-O1	114.11	115.82	1.70
C8-C9-C10	101.90	100.25	1.65
H8-C8-O3	107.53	107.23	0.30
H8-C8-C9	110.45	109.62	0.83
O3-C8-C9	107.11	106.77	0.34
O3-C11-C10	101.87	103.36	1.49
O3-C11-H11	110.08	106.85	3.23
O3-C11-C12	108.98	109.92	0.94
C9-O1-HO1	108.73	108.51	0.22
C9-C10-H10	110.11	109.51	0.60
C9-C10-O2	114.03	114.54	0.52
C9-C10-C11	101.01	102.19	1.18
H9-C9-O1	110.57	109.77	0.80
H9-C9-C10	113.75	108.54	5.21
O1-C9-C10	104.36	110.72	6.37
C10-O2-HO2	105.18	106.83	1.65
C10-C11-H11	109.16	110.19	1.03
C10-C11-C12	115.30	116.04	0.74
H10-C10-O2	107.63	108.24	0.61
H10-C10-C11	108.45	108.64	0.18
O2-C10-C11	115.40	113.48	1.92
C11-C12-H121	109.25	110.14	0.89
C11-C12-H122	109.84	110.41	0.58
C11-C12-H123	110.92	110.25	0.67
H11-C11-C12	111.04	109.93	1.11
H121-C12-H122	109.05	108.63	0.42
H121-C12-H123	109.00	108.90	0.10
H122-C12-H123	108.75	108.46	0.29

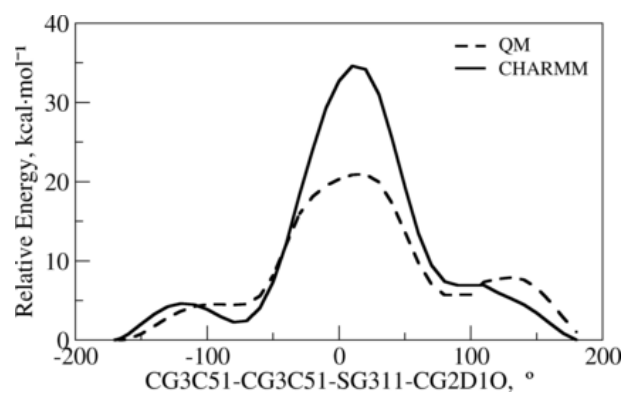


Figure S363: The PES scan for flexible dihedral corresponding to (2R,3S,4R,5R)-2-methyl-5-[(1Z)-1-(methylimino)ethyl]sulfanyloxolane-3,4-diol.

2.93 The small molecule used for bonded terms optimization of 2-amino-3-guanidinopropionic acid (GDPR)

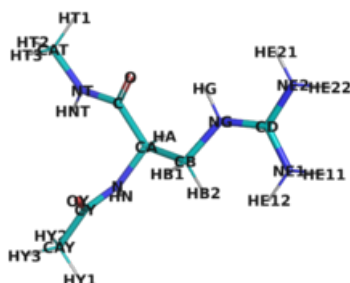


Figure S364: The energy minimized structure corresponding to (2R)-3-carbamimidamido-2-acetamido-N-methylpropanamide.

Table S773: The calculated geometric terms of (2R)-3-carbamimidamido-2-acetamido-N-methylpropanamide.

Terms	QM	CHARMM	Abs. diff.
N-HN	1.01	1.00	0.02
N-CA	1.45	1.47	0.02
N-CY	1.39	1.34	0.04
CA-HA	1.10	1.08	0.02
CA-CB	1.54	1.57	0.03
CA-C	1.54	1.53	0.01
CB-HB1	1.09	1.11	0.01
CB-HB2	1.09	1.11	0.01
CB-NG	1.46	1.48	0.01
NG-HG	1.03	1.00	0.03
NG-CD	1.32	1.34	0.02
CD-NE1	1.34	1.33	0.01
CD-NE2	1.35	1.33	0.01
NE1-HE11	1.01	0.99	0.02
NE1-HE12	1.01	0.99	0.02
NE2-HE22	1.01	0.99	0.02
NE2-HE21	1.01	0.99	0.02
C-O	1.25	1.23	0.02
C-NT	1.34	1.35	0.01
NT-HNT	1.01	0.99	0.02
NT-CAT	1.46	1.45	0.01
CAT-HT1	1.09	1.11	0.03
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.09	1.11	0.02
CAY-HY1	1.09	1.11	0.02
CAY-HY2	1.09	1.11	0.02
CAY-HY3	1.09	1.11	0.02
CAY-CY	1.51	1.48	0.03
CY-OY	1.23	1.22	0.01
N-CA-HA	107.72	106.13	1.58
N-CA-CB	110.15	112.29	2.14

Terms	QM	CHARMM	Abs. diff.
N-CA-C	110.91	114.56	3.66
N-CY-CAY	115.58	116.88	1.29
N-CY-OY	120.09	122.05	1.96
HN-N-CA	118.45	117.81	0.64
HN-N-CY	118.81	117.89	0.92
CA-N-CY	119.48	124.28	4.81
CA-CB-HB1	108.67	108.99	0.32
CA-CB-HB2	108.15	106.64	1.52
CA-CB-NG	110.31	113.04	2.73
CA-C-O	121.51	121.14	0.37
CA-C-NT	114.92	117.60	2.67
HA-CA-CB	109.06	107.04	2.02
HA-CA-C	106.91	105.41	1.50
CB-CA-C	111.94	110.77	1.17
CB-NG-HG	110.95	113.94	2.98
CB-NG-CD	126.25	125.83	0.42
HB1-CB-HB2	109.98	106.97	3.01
HB1-CB-NG	110.24	109.81	0.43
HB2-CB-NG	109.46	111.16	1.70
NG-CD-NE1	121.68	121.97	0.29
NG-CD-NE2	119.80	118.89	0.91
HG-NG-CD	121.39	116.07	5.32
CD-NE1-HE11	120.71	119.86	0.85
CD-NE1-HE12	121.08	117.96	3.12
CD-NE2-HE22	120.28	119.99	0.29
CD-NE2-HE21	119.48	118.89	0.59
NE1-CD-NE2	118.42	119.13	0.72
HE11-NE1-HE12	117.51	121.83	4.32
HE22-NE2-HE21	116.66	121.02	4.36
C-NT-HNT	117.29	121.05	3.75
C-NT-CAT	120.91	121.67	0.76
O-C-NT	122.91	121.13	1.78
NT-CAT-HT1	108.69	111.48	2.79
NT-CAT-HT2	108.47	110.74	2.26
NT-CAT-HT3	111.16	110.57	0.59
HNT-NT-CAT	118.94	116.92	2.02
HT1-CAT-HT2	109.68	107.79	1.90
HT1-CAT-HT3	108.99	107.90	1.09
HT2-CAT-HT3	109.82	108.24	1.58
CAY-CY-OY	124.32	121.07	3.26
HY1-CAY-HY2	108.27	109.29	1.01
HY1-CAY-HY3	108.60	108.20	0.40
HY1-CAY-CY	109.97	110.27	0.30
HY2-CAY-HY3	109.73	108.53	1.20
HY2-CAY-CY	111.76	111.31	0.45
HY3-CAY-CY	108.45	109.17	0.72

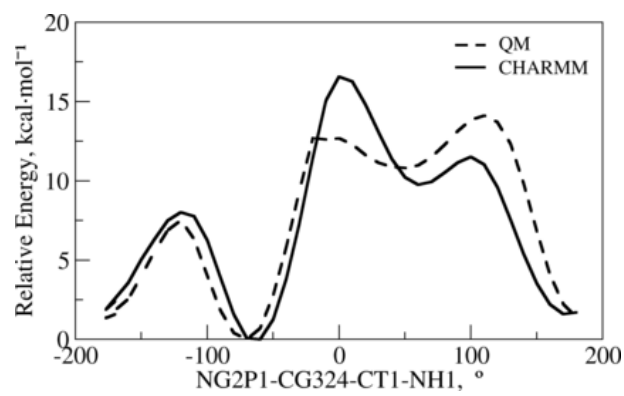


Figure S365: The PES scan for flexible dihedral corresponding to (2R)-3-carbamimidamido-2-acetamido-N-methylpropanamide.

2.94 The small molecule used for bonded terms optimization of Canavanine (GGB)

Terms	QM	CHARMM	Abs. diff.
CZ-NH1-HH11	111.35	98.59	12.76
NH2-CZ-NH1	114.80	106.25	8.55
HH21-NH2-HH22	110.27	107.35	2.93
HH12-NH1-HH11	112.89	103.86	9.02

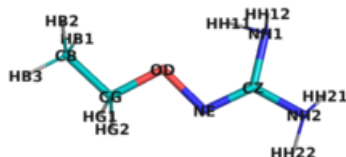


Figure S366: The energy minimized structure corresponding to N'-ethoxyguanidine.

Table S774: The calculated geometric terms of N'-ethoxyguanidine.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-CG	1.51	1.53	0.02
CG-HG1	1.10	1.12	0.02
CG-HG2	1.10	1.11	0.02
CG-OD	1.43	1.42	0.01
OD-NE	1.44	1.44	0.01
NE-CZ	1.30	1.30	0.00
CZ-NH2	1.40	1.38	0.02
CZ-NH1	1.38	1.39	0.01
NH2-HH21	1.02	1.01	0.01
NH2-HH22	1.02	1.01	0.01
NH1-HH12	1.01	1.01	0.01
NH1-HH11	1.02	1.01	0.00
HB3-CB-HB2	108.50	108.64	0.14
HB3-CB-HB1	108.61	108.67	0.06
HB3-CB-CG	110.21	110.50	0.29
CB-CG-HG1	111.60	109.57	2.02
CB-CG-HG2	111.64	109.60	2.04
CB-CG-OD	106.45	109.65	3.20
HB2-CB-HB1	108.61	108.57	0.04
HB2-CB-CG	110.49	110.27	0.22
HB1-CB-CG	110.37	110.14	0.23
CG-OD-NE	107.29	107.26	0.04
HG1-CG-HG2	108.12	108.69	0.57
HG1-CG-OD	109.63	109.66	0.03
HG2-CG-OD	109.38	109.65	0.27
OD-NE-CZ	108.39	109.10	0.71
NE-CZ-NH2	118.92	125.22	6.30
NE-CZ-NH1	126.28	128.48	2.20
CZ-NH2-HH21	111.53	101.28	10.25
CZ-NH2-HH22	109.99	100.74	9.25
CZ-NH1-HH12	112.79	100.64	12.15

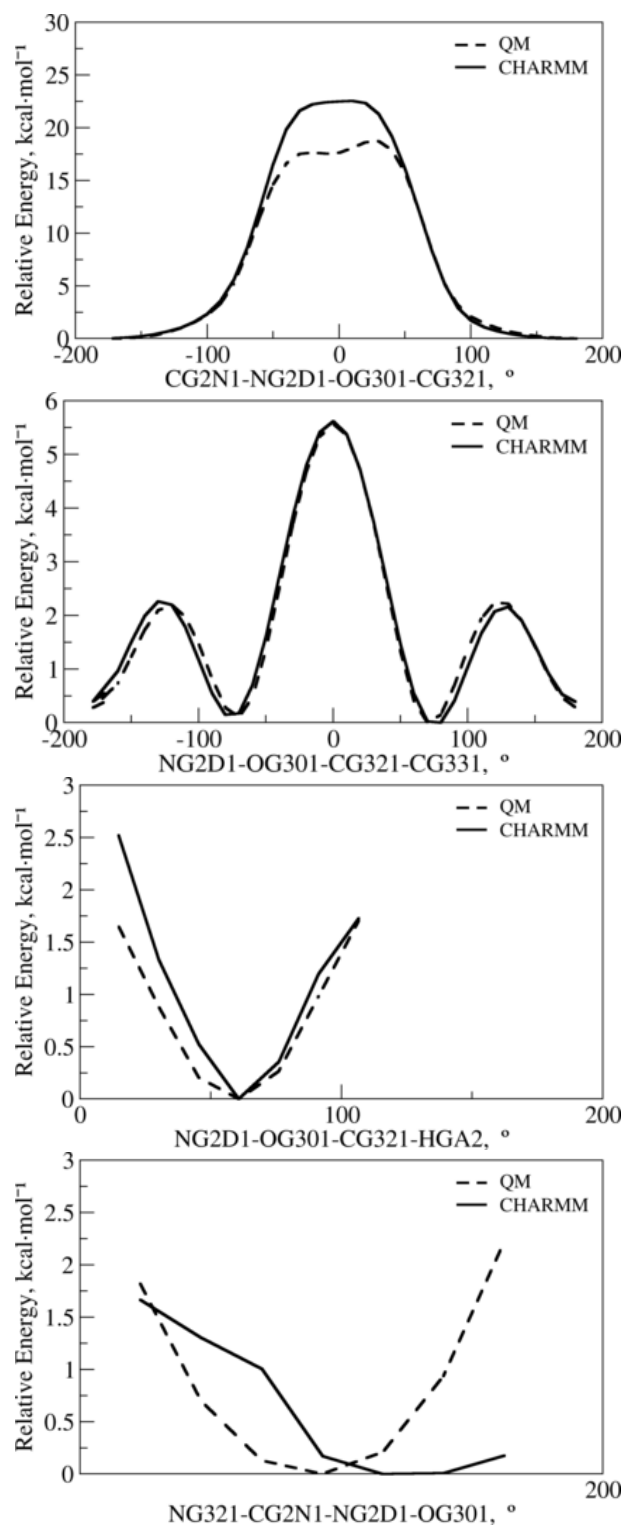


Figure S367: The PES scan for flexible dihedrals corresponding to N''-ethoxyguanidine.

2.95 The small molecule used for bonded terms optimization of (2s,4s)-2,5-diamino-4-hydroxy-5-oxopentanoicacid (GHG)

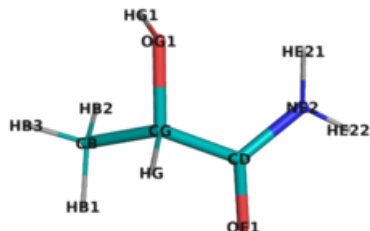


Figure S368: The energy minimized structure corresponding to (2S)-2-hydroxypropanamide.

Table S775: The calculated geometric terms of (2S)-2-hydroxypropanamide.

Terms	QM	CHARMM	Abs. diff
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.10	1.11	0.01
CB-CG	1.52	1.54	0.02
CG-HG	1.10	1.11	0.02
CG-OG1	1.43	1.43	0.00
CG-CD	1.53	1.53	0.00
OG1-HG1	0.97	0.96	0.01
CD-OE1	1.23	1.23	0.00
CD-NE2	1.36	1.36	0.00
NE2-HE21	1.01	1.00	0.01
NE2-HE22	1.01	1.00	0.02
HB3-CB-HB1	109.83	107.98	1.85
HB3-CB-HB2	108.90	108.92	0.02
HB3-CB-CG	110.11	110.45	0.33
CB-CG-HG	109.73	108.80	0.93
CB-CG-OG1	112.43	106.87	5.56
CB-CG-CD	110.67	110.99	0.32
HB1-CB-HB2	107.87	108.15	0.28
HB1-CB-CG	109.95	110.09	0.13
HB2-CB-CG	110.13	111.16	1.03
CG-OG1-HG1	106.66	104.93	1.73
CG-CD-OE1	121.43	120.14	1.30
CG-CD-NE2	114.33	120.44	6.11
HG-CG-OG1	104.76	107.98	3.23
HG-CG-CD	106.59	106.62	0.03
OG1-CG-CD	112.32	115.41	3.10
CD-NE2-HE21	118.47	119.04	0.57
CD-NE2-HE22	117.29	116.69	0.60
OE1-CD-NE2	124.23	119.41	4.82
HE21-NE2-HE22	119.49	123.47	3.99

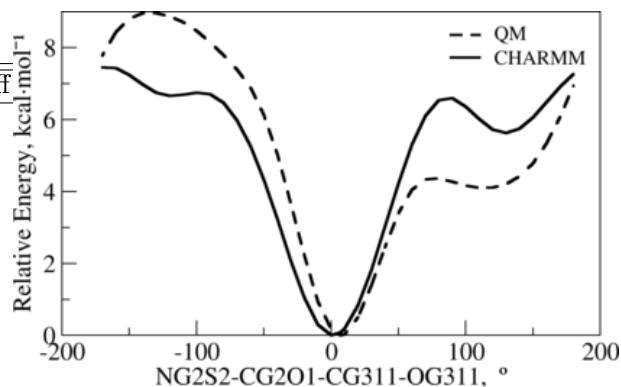


Figure S369: The PES scan for flexible dihedral corresponding to (2S)-2-hydroxypropanamide.

2.96 The small molecule 1 used for bonded terms optimization of Thioglycin (GL3)

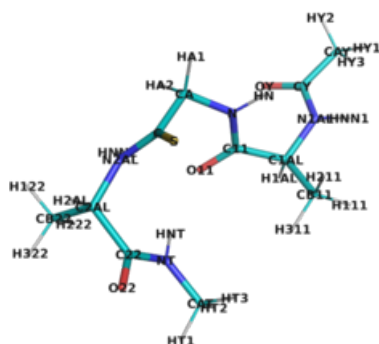


Figure S370: The energy minimized structure corresponding to 2-acetamido-N-((methylcarbamoyl)methyl)carbamothiomethylacetamide.

Table S776: The calculated geometric terms of 2-acetamido-N-((methylcarbamoyl)methyl)carbamothiomethylacetamide.

Terms	QM	CHARMM	Abs. diff.
N1AL-HNN1	1.01	0.99	0.02
N1AL-C1AL	1.46	1.46	0.01
N1AL-CY	1.38	1.34	0.03
C1AL-H1AL	1.10	1.08	0.01
C1AL-CB11	1.53	1.54	0.01
C1AL-C11	1.54	1.53	0.01
CB11-H111	1.10	1.11	0.02
CB11-H211	1.10	1.11	0.02
CB11-H311	1.09	1.11	0.02
C11-O11	1.23	1.23	0.00
C11-N	1.35	1.35	0.00
CAY-HY1	1.09	1.11	0.01
CAY-HY2	1.09	1.11	0.02
CAY-HY3	1.10	1.11	0.01
CAY-CY	1.52	1.48	0.04
CY-OY	1.22	1.22	0.00
N-HN	1.01	0.99	0.02
N-CA	1.46	1.45	0.01
CA-HA1	1.09	1.11	0.02
CA-HA2	1.10	1.11	0.02
CA-C	1.53	1.51	0.03
C-S	1.66	1.63	0.03
C-N2AL	1.35	1.36	0.01
N2AL-HNN2	1.02	1.00	0.02
N2AL-C2AL	1.46	1.45	0.01
C2AL-H2AL	1.09	1.08	0.01
C2AL-CB22	1.53	1.54	0.01
C2AL-C22	1.55	1.53	0.02
CB22-H122	1.10	1.11	0.02
CB22-H222	1.10	1.11	0.01
CB22-H322	1.09	1.11	0.02
C22-O22	1.22	1.23	0.01

Terms	QM	CHARMM	Abs. diff.
C22-NT	1.36	1.35	0.01
NT-HNT	1.02	1.00	0.02
NT-CAT	1.45	1.45	0.01
CAT-HT1	1.09	1.12	0.02
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.10	1.11	0.01
N1AL-C1AL-H1AL	109.76	107.42	2.35
N1AL-C1AL-CB11	110.11	109.44	0.67
N1AL-C1AL-C11	112.32	115.58	3.26
N1AL-CY-CAY	115.65	116.85	1.20
N1AL-CY-OY	121.43	122.45	1.02
HNN1-N1AL-C1AL	117.34	116.22	1.11
HNN1-N1AL-CY	118.46	119.07	0.62
C1AL-N1AL-CY	120.80	124.22	3.42
C1AL-CB11-H111	110.54	110.23	0.31
C1AL-CB11-H211	111.48	111.26	0.22
C1AL-CB11-H311	109.95	110.71	0.75
C1AL-C11-O11	120.81	121.09	0.28
C1AL-C11-N	115.91	116.87	0.96
H1AL-C1AL-CB11	109.80	108.98	0.82
H1AL-C1AL-C11	104.14	105.92	1.78
CB11-C1AL-C11	110.55	109.28	1.27
H111-CB11-H211	108.81	108.41	0.40
H111-CB11-H311	107.92	107.81	0.11
H211-CB11-H311	108.03	108.32	0.29
C11-N-HN	118.49	119.28	0.79
C11-N-CA	121.91	124.34	2.43
O11-C11-N	122.87	122.03	0.84
CAY-CY-OY	122.92	120.71	2.21
HY1-CAY-HY2	109.39	108.94	0.45
HY1-CAY-HY3	108.53	109.21	0.68
HY1-CAY-CY	113.36	111.45	1.91
HY2-CAY-HY3	107.53	108.14	0.60
HY2-CAY-CY	108.77	109.55	0.78
HY3-CAY-CY	109.10	109.49	0.39
N-CA-HA1	107.88	109.27	1.39
N-CA-HA2	108.94	110.30	1.36
N-CA-C	112.29	111.44	0.84
HN-N-CA	118.94	116.26	2.68
CA-C-S	121.37	121.06	0.31
CA-C-N2AL	112.90	113.21	0.31
HA1-CA-HA2	108.50	106.79	1.71
HA1-CA-C	108.42	109.17	0.75
HA2-CA-C	110.70	109.75	0.96
C-N2AL-HNN2	114.80	118.03	3.23
C-N2AL-C2AL	125.78	126.98	1.20
S-C-N2AL	125.73	125.73	0.01
N2AL-C2AL-H2AL	107.61	107.63	0.02
N2AL-C2AL-CB22	109.75	109.25	0.50
N2AL-C2AL-C22	114.13	114.25	0.12
HNN2-N2AL-C2AL	115.41	113.07	2.35
C2AL-CB22-H122	110.77	109.92	0.85
C2AL-CB22-H222	111.37	110.99	0.38
C2AL-CB22-H322	109.27	110.75	1.48
C2AL-C22-O22	120.25	121.19	0.93
C2AL-C22-NT	115.27	117.26	1.99
H2AL-C2AL-CB22	110.10	109.03	1.07
H2AL-C2AL-C22	104.36	106.22	1.86

Terms	QM	CHARMM	Abs. diff.
CB22-C2AL-C22	110.70	110.30	0.40
H122-CB22-H222	108.85	108.44	0.41
H122-CB22-H322	108.53	107.95	0.58
H222-CB22-H322	107.97	108.71	0.74
C22-NT-HNT	119.25	119.34	0.10
C22-NT-CAT	120.55	122.26	1.71
O22-C22-NT	123.85	121.55	2.30
NT-CAT-HT1	108.72	111.27	2.55
NT-CAT-HT2	109.33	110.45	1.11
NT-CAT-HT3	112.29	110.74	1.55
HNT-NT-CAT	117.79	118.30	0.51
HT1-CAT-HT2	109.46	107.81	1.65
HT1-CAT-HT3	107.87	107.97	0.10
HT2-CAT-HT3	109.12	108.49	0.63

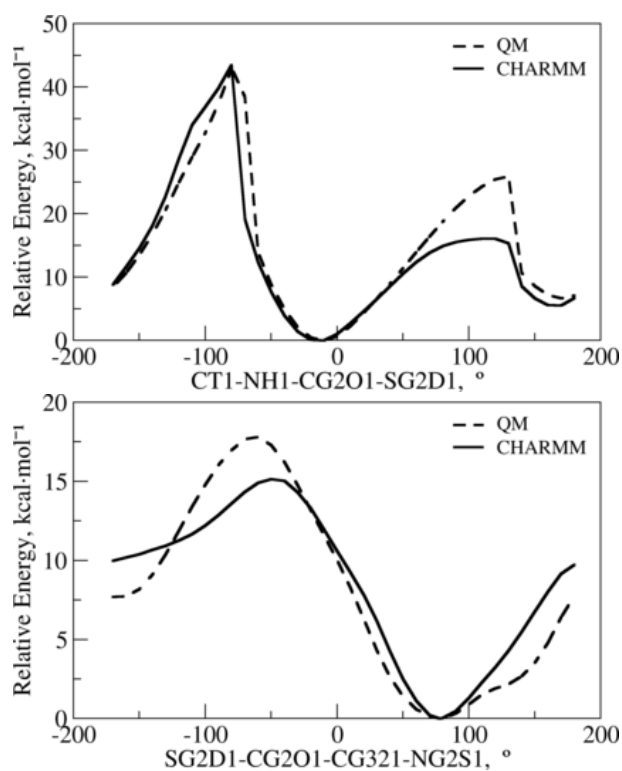


Figure S371: The PES scan for flexible dihedrals corresponding to 2-acetamido-N-((methylcarbamoyl)methyl)carbamothioylmethyl)acetamide.

2.97 The small molecule 2 used for bonded terms optimization of Thioglycin (GL3)

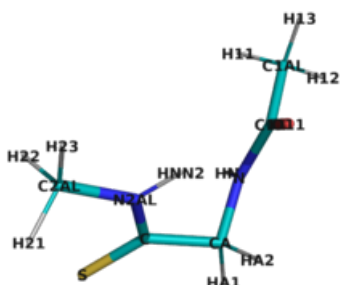


Figure S372: The energy minimized structure corresponding to N-[(methylcarbamothioyl)methyl]acetamide.

Table S777: The calculated geometric terms of N-[(methylcarbamothioyl)methyl]acetamide.

Terms	QM	CHARMM	Abs. diff.
C1AL-H11	1.09	1.11	0.02
C1AL-H12	1.09	1.11	0.02
C1AL-H13	1.09	1.11	0.02
C1AL-C11	1.51	1.48	0.03
C11-O11	1.24	1.23	0.01
C11-N	1.36	1.34	0.02
N-HN	1.01	0.99	0.02
N-CA	1.46	1.45	0.01
CA-HA1	1.09	1.11	0.02
CA-HA2	1.10	1.12	0.02
CA-C	1.52	1.51	0.02
C-S	1.65	1.64	0.02
C-N2AL	1.34	1.35	0.01
N2AL-HNN2	1.02	1.01	0.02
N2AL-C2AL	1.45	1.44	0.01
C2AL-H21	1.09	1.11	0.02
C2AL-H22	1.09	1.11	0.02
C2AL-H23	1.09	1.11	0.02
C1AL-C11-O11	121.83	120.94	0.89
C1AL-C11-N	116.00	116.66	0.65
H11-C1AL-H12	108.67	109.43	0.76
H11-C1AL-H13	109.58	108.70	0.88
H11-C1AL-C11	112.85	110.39	2.46
H12-C1AL-H13	108.08	108.68	0.60
H12-C1AL-C11	108.89	110.28	1.38
H13-C1AL-C11	108.65	109.33	0.68
C11-N-HN	119.59	119.96	0.37
C11-N-CA	121.67	123.52	1.86
O11-C11-N	122.09	122.40	0.31
N-CA-HA1	108.55	109.21	0.66
N-CA-HA2	107.56	111.65	4.09
N-CA-C	112.24	109.56	2.68
HN-N-CA	118.08	116.46	1.62

Terms	QM	CHARMM	Abs. diff.
CA-C-S	122.05	121.66	0.39
CA-C-N2AL	112.92	113.57	0.64
HA1-CA-HA2	109.19	106.94	2.24
HA1-CA-C	108.92	110.51	1.60
HA2-CA-C	110.32	108.93	1.40
C-N2AL-HNN2	116.79	118.78	1.99
C-N2AL-C2AL	122.86	124.04	1.17
S-C-N2AL	125.01	124.78	0.24
N2AL-C2AL-H21	110.05	110.70	0.65
N2AL-C2AL-H22	110.59	110.73	0.15
N2AL-C2AL-H23	108.26	110.30	2.04
HNN2-N2AL-C2AL	119.80	117.06	2.74
H21-C2AL-H22	107.88	108.64	0.76
H21-C2AL-H23	109.97	108.21	1.76
H22-C2AL-H23	110.09	108.18	1.92

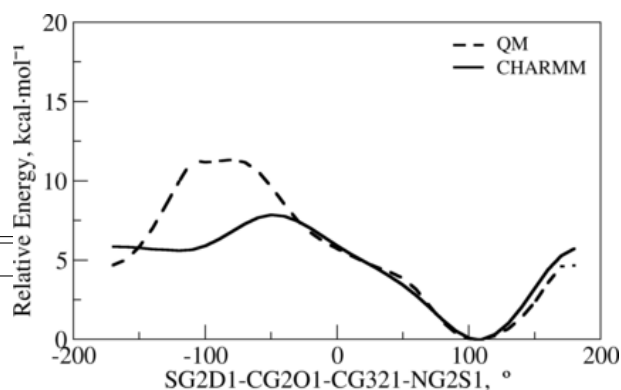


Figure S373: The PES scan for flexible dihedral corresponding to N-[(methylcarbamothioyl)methyl]acetamide.

2.98 The small molecule used for bonded terms optimization of glutaminehydroxamate (HGA)

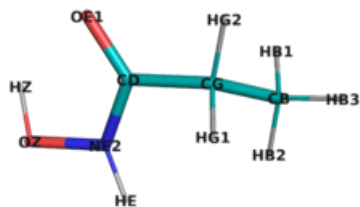


Figure S374: The energy minimized structure corresponding to N-hydroxypropanamide.

Table S778: The calculated geometric terms of N-hydroxypropanamide.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.53	1.54	0.02
CG-HG2	1.10	1.11	0.02
CG-HG1	1.10	1.11	0.02
CG-CD	1.51	1.50	0.01
CD-OE1	1.24	1.23	0.01
CD-NE2	1.37	1.35	0.02
NE2-HE	1.02	1.00	0.02
NE2-OZ	1.41	1.42	0.01
OZ-HZ	0.99	0.97	0.02
HB3-CB-HB1	108.97	108.01	0.97
HB3-CB-HB2	108.40	108.05	0.35
HB3-CB-CG	110.59	110.04	0.54
CB-CG-HG2	109.97	109.52	0.45
CB-CG-HG1	110.96	110.26	0.70
CB-CG-CD	110.79	112.20	1.41
HB1-CB-HB2	108.30	108.42	0.12
HB1-CB-CG	109.89	110.67	0.78
HB2-CB-CG	110.63	111.54	0.91
CG-CD-OE1	124.17	120.71	3.46
CG-CD-NE2	115.78	117.25	1.47
HG2-CG-HG1	107.50	108.10	0.60
HG2-CG-CD	107.23	107.80	0.56
HG1-CG-CD	110.26	108.84	1.42
CD-NE2-HE	118.83	132.97	14.13
CD-NE2-OZ	114.65	115.77	1.12
OE1-CD-NE2	119.91	122.03	2.12
NE2-OZ-HZ	100.30	100.11	0.19
HE-NE2-OZ	109.09	109.69	0.60

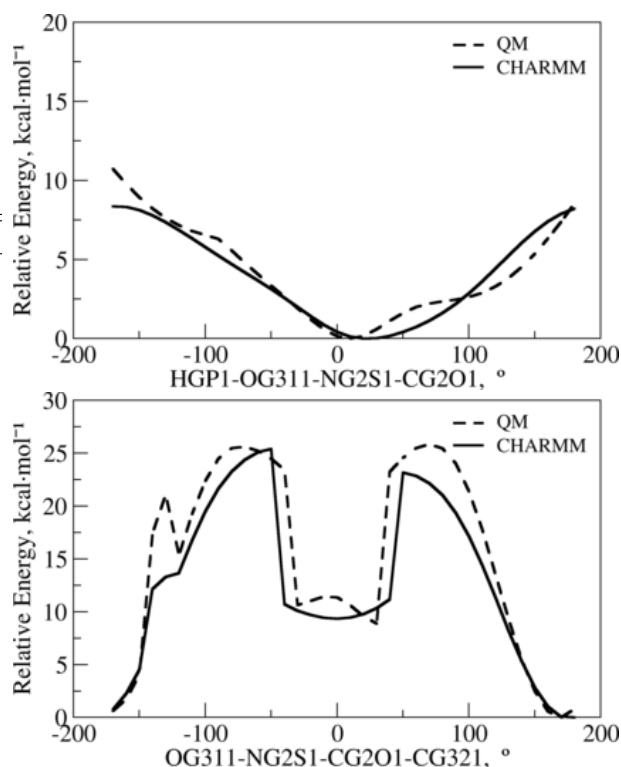


Figure S375: The PES scan for flexible dihedrals corresponding to N-hydroxypropanamide.

2.99 The small molecule used for bonded terms optimization of 4-methyl-histidine (HICP)

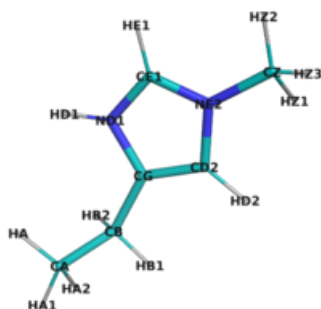


Figure S376: The energy minimized structure corresponding to 4-ethyl-1-methyl-2,3-dihydro-1H-imidazole.

Table S779: The calculated geometric terms of 4-ethyl-1-methyl-2,3-dihydro-1H-imidazole.

Terms	QM	CHARMM	Abs. diff.
HA1-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.54	0.00
CB-HB1	1.09	1.11	0.02
CB-HB2	1.10	1.11	0.02
CB-CG	1.49	1.51	0.02
CG-ND1	1.38	1.37	0.01
CG-CD2	1.38	1.35	0.02
ND1-HD1	1.02	1.00	0.02
ND1-CE1	1.34	1.33	0.02
CD2-HD2	1.08	1.09	0.00
CD2-NE2	1.38	1.37	0.00
CE1-HE1	1.08	1.08	0.00
CE1-NE2	1.34	1.33	0.01
NE2-CZ	1.47	1.48	0.01
CZ-HZ1	1.09	1.11	0.02
CZ-HZ2	1.09	1.11	0.02
CZ-HZ3	1.09	1.11	0.02
HA1-CA-HA2	108.31	107.84	0.47
HA1-CA-HA	107.50	107.80	0.31
HA1-CA-CB	109.84	110.26	0.42
HA2-CA-HA	108.38	108.42	0.05
HA2-CA-CB	110.90	111.02	0.12
CA-CB-HB1	110.25	108.44	1.81
CA-CB-HB2	110.54	109.13	1.41
CA-CB-CG	112.77	114.60	1.83
HA-CA-CB	111.79	111.36	0.43
CB-CG-ND1	123.09	122.55	0.54
CB-CG-CD2	131.92	130.62	1.30
HB1-CB-HB2	106.44	106.73	0.29
HB1-CB-CG	107.42	109.02	1.60
HB2-CB-CG	109.17	108.63	0.54

Terms	QM	CHARMM	Abs. diff.
CG-ND1-HD1	125.11	124.36	0.75
CG-ND1-CE1	110.75	109.00	1.74
CG-CD2-HD2	130.24	129.00	1.24
CG-CD2-NE2	107.99	106.99	1.00
ND1-CG-CD2	104.97	106.81	1.84
ND1-CE1-HE1	126.55	125.86	0.69
ND1-CE1-NE2	107.20	108.51	1.32
HD1-ND1-CE1	124.15	126.63	2.48
CD2-NE2-CE1	109.10	108.69	0.41
CD2-NE2-CZ	125.43	124.03	1.40
HD2-CD2-NE2	121.78	124.02	2.24
CE1-NE2-CZ	125.47	127.28	1.81
HE1-CE1-NE2	126.25	125.63	0.62
NE2-CZ-HZ1	109.00	109.45	0.45
NE2-CZ-HZ2	108.62	110.75	2.13
NE2-CZ-HZ3	108.99	109.41	0.42
HZ1-CZ-HZ2	109.82	108.96	0.86
HZ1-CZ-HZ3	110.54	109.32	1.22
HZ2-CZ-HZ3	109.84	108.94	0.90

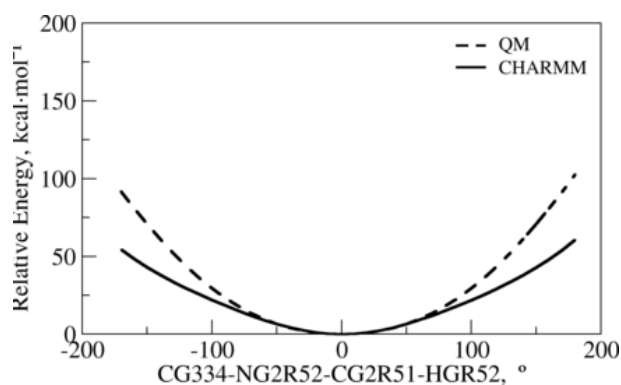


Figure S377: The PES scan for flexible dihedral corresponding to 4-ethyl-1-methyl-2,3-dihydro-1H-imidazole.

2.100 The small molecule used for bonded terms optimization of ND1-phosphonohistidine (HIP)

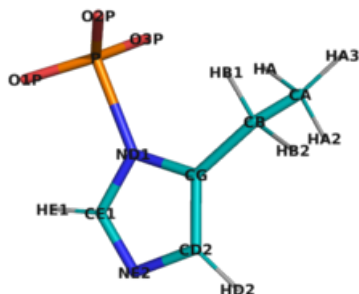


Figure S378: The energy minimized structure corresponding to (5-ethyl-1H-imidazol-1-yl)phosphonic acid.

Table S780: The calculated geometric terms of (5-ethyl-1H-imidazol-1-yl)phosphonic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.10	1.11	0.01
CA-HA	1.10	1.11	0.02
CA-CB	1.54	1.53	0.00
CB-HB1	1.10	1.11	0.02
CB-HB2	1.10	1.11	0.01
CB-CG	1.50	1.51	0.01
CG-CD2	1.39	1.37	0.03
CG-ND1	1.38	1.39	0.01
CD2-HD2	1.09	1.08	0.01
CD2-NE2	1.38	1.39	0.01
ND1-P	1.94	2.02	0.08
ND1-CE1	1.36	1.35	0.01
P-O1P	1.54	1.53	0.01
P-O2P	1.54	1.52	0.02
P-O3P	1.54	1.52	0.02
CE1-HE1	1.08	1.09	0.01
CE1-NE2	1.35	1.33	0.02
HA3-CA-HA2	108.35	109.66	1.31
HA3-CA-HA	109.14	108.26	0.88
HA3-CA-CB	110.82	110.72	0.09
HA2-CA-HA	109.48	108.20	1.27
HA2-CA-CB	110.46	110.62	0.16
CA-CB-HB1	109.18	109.29	0.10
CA-CB-HB2	110.22	109.50	0.71
CA-CB-CG	112.98	113.48	0.50
HA-CA-CB	108.58	109.31	0.73
CB-CG-CD2	130.71	129.92	0.79
CB-CG-ND1	123.10	124.56	1.46
HB1-CB-HB2	108.55	107.39	1.16
HB1-CB-CG	107.86	108.19	0.33
HB2-CB-CG	107.93	108.80	0.88

Terms	QM	CHARMM	Abs. diff.
CG-CD2-HD2	127.75	128.90	1.15
CG-CD2-NE2	110.88	111.09	0.21
CG-ND1-P	128.61	129.73	1.12
CG-ND1-CE1	105.96	106.65	0.69
CD2-CG-ND1	106.18	105.51	0.67
CD2-NE2-CE1	103.10	103.85	0.76
HD2-CD2-NE2	121.36	120.00	1.36
ND1-P-O1P	99.16	98.77	0.39
ND1-P-O2P	99.86	100.91	1.05
ND1-P-O3P	100.46	100.94	0.48
ND1-CE1-HE1	120.54	119.96	0.59
ND1-CE1-NE2	113.88	112.89	0.99
P-ND1-CE1	125.41	123.61	1.80
O1P-P-O2P	117.91	116.77	1.15
O1P-P-O3P	117.45	117.23	0.22
O2P-P-O3P	116.09	116.79	0.70
HE1-CE1-NE2	125.57	127.14	1.57

2.101 The small molecule used for bonded terms optimization of 3-(1H-1,2,3-triazol-5-yl)-L-alanine (HIX)

Terms	QM	CHARMM	Abs. diff.
ND1-NE1-NE2	106.10	104.16	1.94
HD1-ND1-NE1	118.36	118.79	0.43
CD2-NE2-NE1	108.47	110.53	2.06
HD2-CD2-NE2	121.25	120.00	1.25

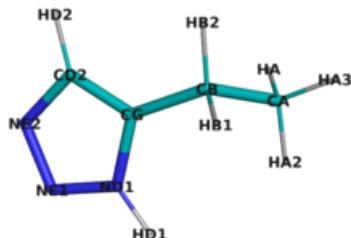


Figure S379: The energy minimized structure corresponding to 5-ethyl-1H-1,2,3-triazole.

Table S781: The calculated geometric terms of 5-ethyl-1H-1,2,3-triazole.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.53	0.00
CB-HB1	1.10	1.11	0.02
CB-HB2	1.09	1.12	0.02
CB-CG	1.49	1.51	0.01
CG-ND1	1.36	1.37	0.01
CG-CD2	1.39	1.35	0.03
ND1-HD1	1.01	1.01	0.01
ND1-NE1	1.35	1.35	0.00
CD2-HD2	1.08	1.08	0.00
CD2-NE2	1.36	1.38	0.02
NE1-NE2	1.33	1.31	0.02
HA3-CA-HA2	107.96	108.14	0.18
HA3-CA-HA	108.51	108.09	0.41
HA3-CA-CB	110.72	110.35	0.36
HA2-CA-HA	107.90	108.37	0.46
HA2-CA-CB	111.22	111.15	0.06
CA-CB-HB1	110.06	109.52	0.54
CA-CB-HB2	109.90	108.86	1.04
CA-CB-CG	112.84	113.02	0.18
HA-CA-CB	110.43	110.63	0.20
CB-CG-ND1	124.11	125.70	1.59
CB-CG-CD2	133.59	131.74	1.85
HB1-CB-HB2	106.31	107.00	0.69
HB1-CB-CG	109.85	109.07	0.78
HB2-CB-CG	107.66	109.19	1.53
CG-ND1-HD1	128.70	127.41	1.29
CG-ND1-NE1	112.94	113.80	0.86
CG-CD2-HD2	128.52	131.06	2.54
CG-CD2-NE2	110.23	108.95	1.28
ND1-CG-CD2	102.25	102.56	0.30

2.102 The small molecule used for bonded terms optimization of (4S)-4-[(2S)-2-amino-3-oxopropyl]sulfanyl-L-homoserine (HTI)



Figure S380: The energy minimized structure corresponding to (1R)-1-(methylsulfanyl)ethan-1-ol.

Table S782: The calculated geometric terms of (1R)-1-(methylsulfanyl)ethan-1-ol.

Terms	QM	CHARMM	Abs. diff.
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-HB3	1.09	1.11	0.02
CB-S	1.81	1.82	0.01
S-CAH	1.83	1.82	0.01
CAH-HAH	1.10	1.12	0.02
CAH-OAI	1.42	1.42	0.01
CAH-CAJ	1.51	1.53	0.02
OAI-HAI	0.97	0.96	0.01
CAJ-HAJ1	1.09	1.11	0.02
CAJ-HAJ2	1.09	1.11	0.02
CAJ-HAJ3	1.09	1.11	0.02
CB-S-CAH	99.45	100.64	1.19
HB1-CB-HB2	110.10	107.82	2.28
HB1-CB-HB3	108.94	107.81	1.14
HB1-CB-S	109.17	111.26	2.09
HB2-CB-HB3	108.87	107.57	1.30
HB2-CB-S	112.13	111.36	0.78
HB3-CB-S	107.55	110.86	3.31
S-CAH-HAH	103.29	108.34	5.06
S-CAH-OAI	112.21	112.62	0.41
S-CAH-CAJ	114.22	113.44	0.78
CAH-OAI-HAI	107.02	104.89	2.12
CAH-CAJ-HAJ1	108.99	110.12	1.12
CAH-CAJ-HAJ2	110.48	110.88	0.40
CAH-CAJ-HAJ3	110.61	110.46	0.15
HAH-CAH-OAI	111.01	107.47	3.54
HAH-CAH-CAJ	109.86	107.43	2.44
OAI-CAH-CAJ	106.31	107.26	0.95
HAI-CAJ-HAJ2	108.13	107.96	0.17
HAI-CAJ-HAJ3	109.32	108.57	0.75
HAI-CAJ-HAJ3	109.25	108.78	0.47

Terms	QM	CHARMM	Abs. diff.
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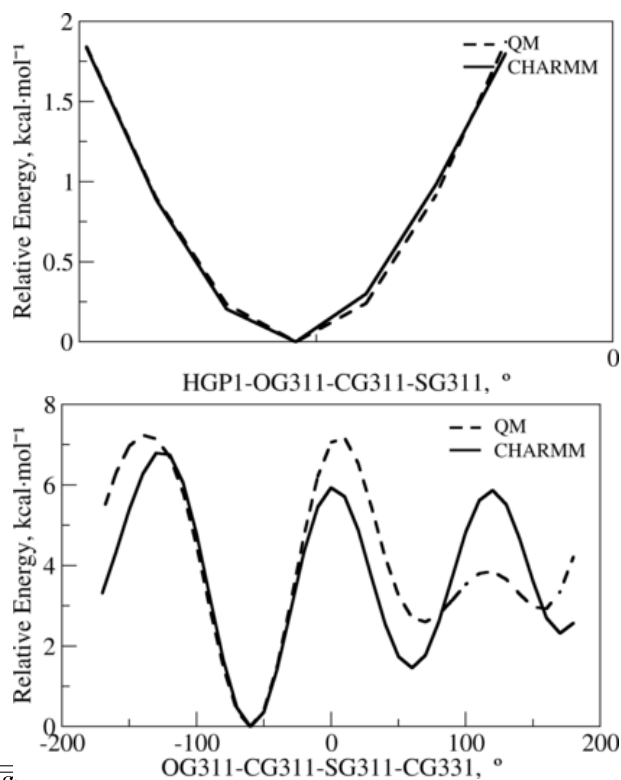


Figure S381: The PES scan for flexible dihedrals corresponding to (1R)-1-(methylsulfanyl)ethan-1-ol.

2.103 The small molecule used for bonded terms optimization of beta-hydroxy-tryptophane (HTR)

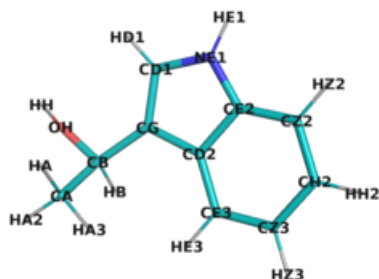


Figure S382: The energy minimized structure corresponding to (1R)-1-(1H-indol-3-yl)ethan-1-ol.

Table S783: The calculated geometric terms of (1R)-1-(1H-indol-3-yl)ethan-1-ol.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.10	1.11	0.01
CA-CB	1.53	1.53	0.01
CB-HB	1.10	1.12	0.02
CB-OH	1.44	1.42	0.02
CB-CG	1.50	1.52	0.02
OH-HH	0.97	0.96	0.01
CG-CD1	1.38	1.37	0.01
CG-CD2	1.44	1.44	0.00
CD1-HD1	1.08	1.08	0.00
CD1-NE1	1.38	1.38	0.01
CD2-CE2	1.42	1.40	0.02
CD2-CE3	1.41	1.39	0.02
NE1-HE1	1.01	1.01	0.00
NE1-CE2	1.38	1.37	0.01
CE2-CZ2	1.40	1.38	0.02
CE3-HE3	1.09	1.08	0.01
CE3-CZ3	1.39	1.40	0.01
CZ2-HZ2	1.09	1.08	0.01
CZ2-CH2	1.39	1.40	0.01
CZ3-HZ3	1.09	1.08	0.00
CZ3-CH2	1.41	1.40	0.01
CH2-HH2	1.09	1.08	0.00
HA3-CA-HA2	109.11	108.07	1.04
HA3-CA-HA	107.62	108.18	0.56
HA3-CA-CB	111.82	110.76	1.06
HA2-CA-HA	108.98	108.49	0.49
HA2-CA-CB	109.82	110.20	0.38
CA-CB-HB	109.22	109.24	0.02
CA-CB-OH	110.03	106.76	3.28
CA-CB-CG	112.56	114.45	1.89
HA-CA-CB	109.43	111.05	1.62

Terms	QM	CHARMM	Abs. diff.
CB-OH-HH	105.85	104.76	1.09
CB-CG-CD1	124.76	130.69	5.92
CB-CG-CD2	128.68	122.57	6.11
HB-CB-OH	103.95	107.73	3.78
HB-CB-CG	109.89	108.27	1.62
OH-CB-CG	110.84	110.20	0.64
CG-CD1-HD1	129.28	127.81	1.47
CG-CD1-NE1	109.67	108.07	1.60
CG-CD2-CE2	107.10	108.09	0.98
CG-CD2-CE3	134.58	132.34	2.24
CD1-CG-CD2	106.55	106.74	0.18
CD1-NE1-HE1	125.14	126.00	0.86
CD1-NE1-CE2	109.50	110.96	1.45
HD1-CD1-NE1	121.03	124.11	3.08
CD2-CE2-NE1	107.16	106.15	1.01
CD2-CE2-CZ2	122.79	121.21	1.59
CD2-CE3-HE3	121.00	120.32	0.68
CD2-CE3-CZ3	119.10	119.59	0.49
NE1-CE2-CZ2	130.04	132.64	2.60
HE1-NE1-CE2	125.29	123.02	2.28
CE2-CD2-CE3	118.28	119.57	1.29
CE2-CZ2-HZ2	121.48	120.12	1.36
CE2-CZ2-CH2	117.31	119.26	1.95
CE3-CZ3-HZ3	119.48	119.92	0.43
CE3-CZ3-CH2	121.39	120.33	1.06
HE3-CE3-CZ3	119.90	120.09	0.19
CZ2-CH2-CZ3	121.10	120.04	1.06
CZ2-CH2-HH2	119.45	120.19	0.74
HZ2-CZ2-CH2	121.21	120.62	0.58
CZ3-CH2-HH2	119.44	119.76	0.32
HZ3-CZ3-CH2	119.13	119.75	0.63

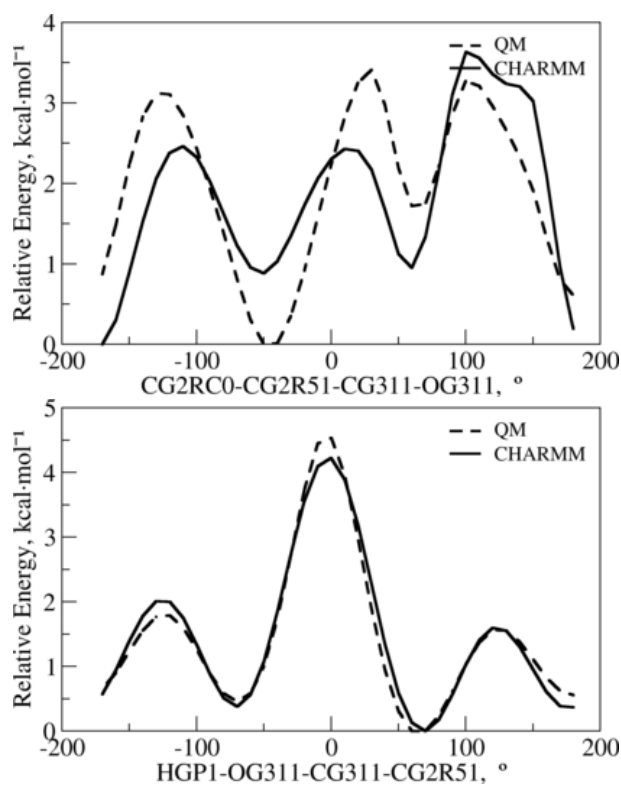


Figure S383: The PES scan for flexible dihedrals corresponding to (1R)-1-(1H-indol-3-yl)ethan-1-ol.

2.104 The small molecule used for bonded terms optimization of N-(2-methylpropyl)glycine (I4G)

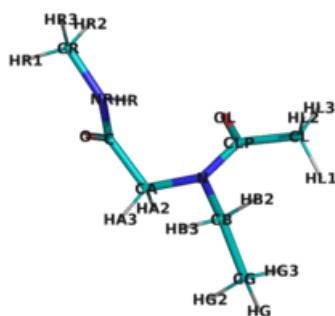


Figure S384: The energy minimized structure corresponding to 2-(N-ethylacetamido)-N-methylacetamide.

Table S784: The calculated geometric terms of 2-(N-ethylacetamido)-N-methylacetamide.

Terms	QM	CHARMM	Abs. diff.
CL-HL1	1.09	1.11	0.02
CL-HL2	1.09	1.11	0.02
CL-HL3	1.09	1.11	0.02
CL-CLP	1.52	1.49	0.03
CLP-OL	1.23	1.22	0.01
CLP-N	1.38	1.37	0.01
N-CA	1.46	1.49	0.02
N-CB	1.46	1.47	0.00
CA-HA2	1.10	1.11	0.02
CA-HA3	1.09	1.11	0.02
CA-C	1.53	1.52	0.01
CB-HB2	1.09	1.11	0.02
CB-HB3	1.10	1.12	0.02
CB-CG	1.53	1.53	0.01
CG-HG	1.09	1.11	0.02
CG-HG2	1.09	1.11	0.02
CG-HG3	1.09	1.11	0.02
C-O	1.23	1.23	0.00
C-NR	1.37	1.35	0.02
NR-HR	1.01	0.99	0.02
NR-CR	1.45	1.44	0.01
CR-HR1	1.09	1.11	0.02
CR-HR2	1.10	1.11	0.02
CR-HR3	1.09	1.11	0.02
CL-CLP-OL	121.76	117.69	4.07
CL-CLP-N	117.75	119.79	2.04
HL1-CL-HL2	108.06	110.15	2.09
HL1-CL-HL3	109.06	108.46	0.60
HL1-CL-CLP	111.89	110.46	1.43
HL2-CL-HL3	109.19	108.41	0.78
HL2-CL-CLP	111.56	110.51	1.05
HL3-CL-CLP	107.03	108.79	1.76

Terms	QM	CHARMM	Abs. diff.
CLP-N-CA	115.32	120.03	4.71
CLP-N-CB	122.85	122.32	0.53
OL-CLP-N	120.44	122.52	2.09
N-CA-HA2	111.79	109.15	2.64
N-CA-HA3	107.97	109.99	2.02
N-CA-C	113.42	117.36	3.94
N-CB-HB2	108.69	111.20	2.51
N-CB-HB3	107.32	107.76	0.45
N-CB-CG	113.28	117.00	3.73
CA-N-CB	117.15	115.88	1.27
CA-C-O	121.58	121.14	0.44
CA-C-NR	114.17	117.02	2.85
HA2-CA-HA3	109.02	106.66	2.36
HA2-CA-C	106.19	106.95	0.77
HA3-CA-C	108.34	106.18	2.15
CB-CG-HG	110.49	110.88	0.39
CB-CG-HG2	110.87	110.19	0.68
CB-CG-HG3	110.76	110.35	0.41
HB2-CB-HB3	106.53	103.87	2.65
HB2-CB-CG	110.59	108.30	2.30
HB3-CB-CG	110.16	107.85	2.31
HG-CG-HG2	108.11	108.68	0.57
HG-CG-HG3	108.40	108.75	0.35
HG2-CG-HG3	108.12	107.92	0.20
C-NR-HR	115.26	118.92	3.66
C-NR-CR	119.05	121.69	2.64
O-C-NR	123.58	121.73	1.86
NR-CR-HR1	108.29	111.04	2.75
NR-CR-HR2	112.13	110.23	1.91
NR-CR-HR3	108.96	110.63	1.67
HR-NR-CR	117.58	118.51	0.93
HR1-CR-HR2	108.41	108.08	0.34
HR1-CR-HR3	109.45	108.39	1.06
HR2-CR-HR3	109.56	108.39	1.16

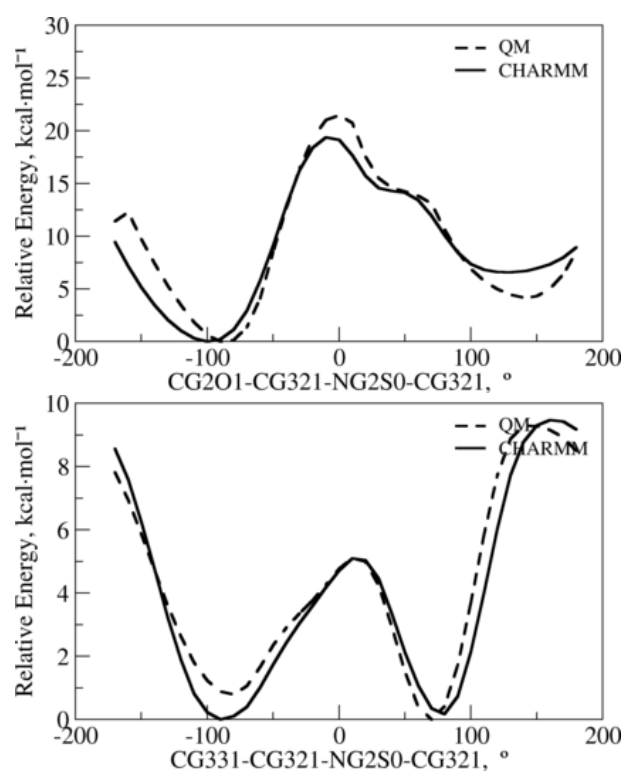


Figure S385: The PES scan for flexible dihedrals corresponding to 2-(N-ethylacetamido)-N-methylacetamide.

2.105 The small molecule 1 used for bonded terms optimization of alpha-amino-2-indanetic acid (IGL)

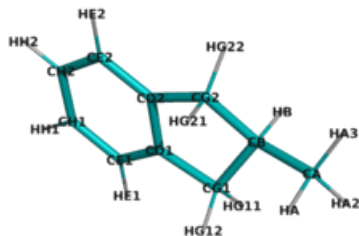


Figure S386: The energy minimized structure corresponding to 2-methyl-2,3-dihydro-1H-indene.

Table S785: The calculated geometric terms of 2-methyl-2,3-dihydro-1H-indene.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.10	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB	1.10	1.11	0.01
CB-CG1	1.54	1.52	0.02
CB-CG2	1.54	1.52	0.02
CG1-HG11	1.10	1.10	0.00
CG1-HG12	1.10	1.10	0.00
CG1-CD1	1.51	1.52	0.01
CG2-HG21	1.10	1.10	0.00
CG2-HG22	1.10	1.10	0.00
CG2-CD2	1.51	1.52	0.01
CD1-CD2	1.40	1.41	0.01
CD1-CE1	1.39	1.39	0.01
CD2-CE2	1.39	1.39	0.01
CE1-HE1	1.09	1.08	0.01
CE1-CH1	1.40	1.40	0.00
CE2-HE2	1.09	1.08	0.01
CE2-CH2	1.40	1.40	0.00
CH1-HH1	1.09	1.08	0.01
CH1-CH2	1.40	1.40	0.00
CH2-HH2	1.09	1.08	0.01
HA3-CA-HA2	107.87	108.60	0.72
HA3-CA-HA	107.99	108.46	0.47
HA3-CA-CB	111.20	110.46	0.74
HA2-CA-HA	107.99	108.46	0.47
HA2-CA-CB	111.21	110.46	0.75
CA-CB-HB	109.12	105.95	3.18
CA-CB-CG1	114.48	115.85	1.37
CA-CB-CG2	114.48	115.85	1.37
HA-CA-CB	110.44	110.33	0.11
CB-CG1-HG11	112.76	113.38	0.61

Terms	QM	CHARMM	Abs. diff.
CB-CG1-HG12	109.95	108.44	1.51
CB-CG1-CD1	102.83	103.61	0.78
CB-CG2-HG21	109.92	108.44	1.48
CB-CG2-HG22	112.76	113.38	0.61
CB-CG2-CD2	102.82	103.61	0.79
HB-CB-CG1	107.27	107.04	0.23
HB-CB-CG2	107.25	107.04	0.20
CG1-CB-CG2	103.75	104.54	0.78
CG1-CD1-CD2	109.82	109.05	0.77
CG1-CD1-CE1	129.63	130.46	0.83
HG11-CG1-HG12	107.14	105.80	1.33
HG11-CG1-CD1	113.69	115.29	1.60
HG12-CG1-CD1	110.47	110.24	0.24
CG2-CD2-CD1	109.83	109.05	0.78
CG2-CD2-CE2	129.62	130.46	0.84
HG21-CG2-HG22	107.14	105.80	1.34
HG21-CG2-CD2	110.48	110.24	0.24
HG22-CG2-CD2	113.71	115.29	1.58
CD1-CD2-CE2	120.54	120.45	0.09
CD1-CE1-HE1	120.78	119.87	0.92
CD1-CE1-CH1	118.95	119.20	0.26
CD2-CD1-CE1	120.54	120.45	0.10
CD2-CE2-HE2	120.78	119.87	0.92
CD2-CE2-CH2	118.95	119.20	0.26
CE1-CH1-HH1	119.83	120.05	0.22
CE1-CH1-CH2	120.51	120.35	0.16
HE1-CE1-CH1	120.27	120.93	0.67
CE2-CH2-CH1	120.51	120.35	0.16
CE2-CH2-HH2	119.82	120.05	0.23
HE2-CE2-CH2	120.27	120.93	0.67
CH1-CH2-HH2	119.66	119.60	0.07
HH1-CH1-CH2	119.66	119.60	0.06

Terms	QM	CHARMM	Abs. diff.
NT-CAT-HT1	108.57	111.03	2.47
NT-CAT-HT2	108.85	110.62	1.77
NT-CAT-HT3	111.82	110.30	1.52
HNT-NT-CAT	117.98	118.12	0.14
HT1-CAT-HT2	109.46	108.19	1.27
HT1-CAT-HT3	108.48	108.08	0.40
HT2-CAT-HT3	109.63	108.53	1.11
CAY-CY-OY	123.16	120.37	2.79
HY1-CAY-HY2	109.77	108.86	0.91
HY1-CAY-HY3	108.39	109.81	1.41
HY1-CAY-CY	111.99	111.07	0.92
HY2-CAY-HY3	108.51	108.43	0.07
HY2-CAY-CY	108.57	108.80	0.23
HY3-CAY-CY	109.55	109.82	0.26

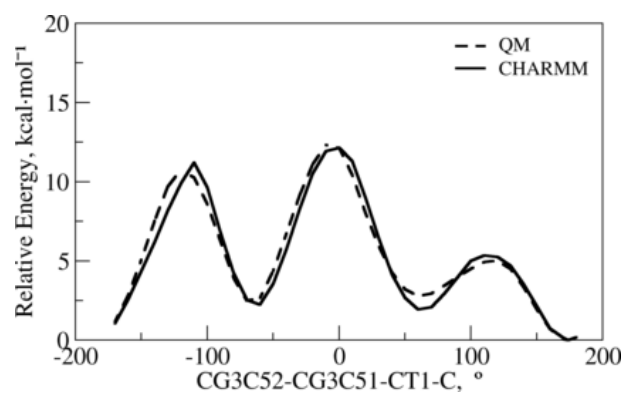


Figure S388: The PES scan for flexible dihedral corresponding to (2R)-2-(2,3-dihydro-1H-inden-2-yl)-2-acetamido-N-methylacetamide.

2.107 The small molecule used for bonded terms optimization of (2S)-2-amino-6-[[3-hydroxy-2-methyl-5-(phosphonooxymethyl)pyridin-4-yl]methylidene amino]hexanoic acid (IT1P)

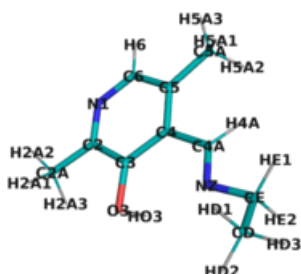


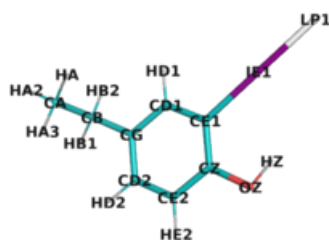
Figure S389: The energy minimized structure corresponding to 4-[(E)-(ethylimino)methyl]-2,5-dimethylpyridin-3-olate.

Table S787: The calculated geometric terms of 4-[(E)-(ethylimino)methyl]-2,5-dimethylpyridin-3-olate.

Terms	QM	CHARMM	Abs. diff.
HD3-CD	1.09	1.11	0.02
CD-HD1	1.09	1.11	0.02
CD-HD2	1.09	1.11	0.02
CD-CE	1.52	1.53	0.01
CE-HE1	1.10	1.12	0.02
CE-HE2	1.10	1.11	0.02
CE-NZ	1.46	1.46	0.00
NZ-C4A	1.29	1.29	0.00
C4A-H4A	1.10	1.10	0.00
C4A-C4	1.46	1.49	0.03
C4-C3	1.41	1.43	0.02
C4-C5	1.42	1.42	0.01
C3-O3	1.35	1.43	0.08
C3-C2	1.41	1.42	0.01
O3-HO3	1.00	0.97	0.03
C2-C2A	1.50	1.49	0.01
C2-N1	1.34	1.32	0.02
C2A-H2A1	1.09	1.11	0.01
C2A-H2A2	1.09	1.11	0.02
C2A-H2A3	1.09	1.11	0.01
N1-C6	1.35	1.32	0.03
C6-H6	1.09	1.08	0.01
C6-C5	1.39	1.40	0.01
C5-C5A	1.51	1.52	0.01
C5A-H5A1	1.10	1.11	0.02
C5A-H5A2	1.09	1.11	0.02
C5A-H5A3	1.09	1.11	0.02
HD3-CD-HD1	108.53	108.54	0.01
HD3-CD-HD2	108.65	108.65	0.00

Terms	QM	CHARMM	Abs. diff.
HD3-CD-CE	110.49	110.63	0.14
CD-CE-HE1	110.65	108.19	2.46
CD-CE-HE2	110.00	109.58	0.42
CD-CE-NZ	109.85	111.50	1.65
HD1-CD-HD2	108.38	108.21	0.16
HD1-CD-CE	110.38	110.27	0.11
HD2-CD-CE	110.35	110.48	0.13
CE-NZ-C4A	118.01	116.19	1.83
HE1-CE-HE2	107.80	108.41	0.61
HE1-CE-NZ	110.98	111.29	0.31
HE2-CE-NZ	107.50	107.82	0.32
NZ-C4A-H4A	120.26	119.97	0.29
NZ-C4A-C4	121.94	122.03	0.09
C4A-C4-C3	120.78	124.19	3.41
C4A-C4-C5	121.18	117.26	3.91
H4A-C4A-C4	117.80	118.00	0.20
C4-C3-O3	123.37	122.85	0.52
C4-C3-C2	119.64	117.55	2.09
C4-C5-C6	117.53	117.88	0.36
C4-C5-C5A	122.59	124.29	1.71
C3-C4-C5	118.05	118.54	0.49
C3-O3-HO3	106.61	106.16	0.45
C3-C2-C2A	119.59	120.66	1.07
C3-C2-N1	121.76	121.97	0.22
O3-C3-C2	116.98	119.59	2.61
C2-C2A-H2A1	110.85	108.60	2.25
C2-C2A-H2A2	108.88	109.47	0.58
C2-C2A-H2A3	110.85	108.55	2.30
C2-N1-C6	118.33	121.38	3.05
C2A-C2-N1	118.65	117.37	1.28
H2A1-C2A-H2A2	109.66	110.03	0.36
H2A1-C2A-H2A3	106.91	110.14	3.23
H2A2-C2A-H2A3	109.66	110.02	0.36
N1-C6-H6	115.44	117.51	2.07
N1-C6-C5	124.70	122.67	2.03
C6-C5-C5A	119.89	117.82	2.07
H6-C6-C5	119.86	119.82	0.03
C5-C5A-H5A1	112.02	109.28	2.73
C5-C5A-H5A2	112.01	109.12	2.89
C5-C5A-H5A3	109.73	110.37	0.64
H5A1-C5A-H5A2	107.77	110.18	2.41
H5A1-C5A-H5A3	107.55	108.80	1.25
H5A2-C5A-H5A3	107.56	109.08	1.52

2.108 The small molecule used for bonded terms optimization of 3-iodo-tyrosine (IYR)



Terms	QM	CHARMM	Abs. diff.
CG-CD1-CE1	121.05	120.69	0.36
CG-CD2-HD2	119.48	119.72	0.24
CG-CD2-CE2	121.01	120.18	0.82
CD1-CG-CD2	118.43	119.47	1.04
CD1-CE1-IE1	119.68	117.64	2.04
CD1-CE1-CZ	119.65	119.49	0.17
HD1-CD1-CE1	119.56	119.96	0.39
CD2-CE2-HE2	121.91	120.18	1.73
CD2-CE2-CZ	120.19	120.27	0.08
HD2-CD2-CE2	119.52	120.10	0.59
CE1-CZ-CE2	119.66	119.90	0.24
CE1-CZ-OZ	124.78	121.55	3.22
IE1-CE1-CZ	120.67	122.87	2.21
CE2-CZ-OZ	115.56	118.55	2.99
HE2-CE2-CZ	117.90	119.55	1.65
CZ-OZ-HZ	112.09	106.35	5.74

Figure S390: The energy minimized structure corresponding to 4-ethyl-2-iodophenol.

Table S788: The calculated geometric terms of 4-ethyl-2-iodophenol.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.11	1.11	0.01
HA2-CA	1.11	1.11	0.01
CA-HA	1.11	1.11	0.01
CA-CB	1.57	1.53	0.03
CB-HB1	1.11	1.11	0.01
CB-HB2	1.11	1.11	0.01
CB-CG	1.53	1.50	0.03
CG-CD1	1.43	1.40	0.02
CG-CD2	1.43	1.40	0.03
CD1-HD1	1.09	1.08	0.02
CD1-CE1	1.43	1.40	0.03
CD2-HD2	1.10	1.08	0.02
CD2-CE2	1.42	1.40	0.01
CE1-IE1	2.16	2.13	0.03
CE1-CZ	1.43	1.41	0.02
CE2-HE2	1.09	1.08	0.01
CE2-CZ	1.42	1.40	0.03
CZ-OZ	1.42	1.41	0.01
OZ-HZ	0.99	0.96	0.03
HA3-CA-HA2	108.57	108.09	0.49
HA3-CA-HA	108.02	108.28	0.27
HA3-CA-CB	110.28	110.91	0.62
HA2-CA-HA	108.61	108.14	0.47
HA2-CA-CB	111.13	110.34	0.79
CA-CB-HB1	109.37	110.68	1.31
CA-CB-HB2	109.41	110.64	1.22
CA-CB-CG	111.65	109.53	2.12
HA-CA-CB	110.15	110.98	0.83
CB-CG-CD1	120.56	120.02	0.54
CB-CG-CD2	120.98	120.50	0.49
HB1-CB-HB2	107.39	108.26	0.86
HB1-CB-CG	109.37	108.87	0.50
HB2-CB-CG	109.54	108.82	0.72
CG-CD1-HD1	119.39	119.35	0.03

2.109 The small molecule used for bonded terms optimization of S-(pyridin-3-ylcarbonyl)-L-cysteine (JJJ)

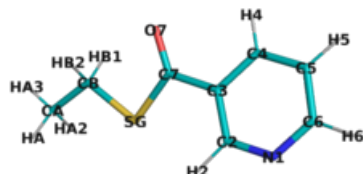


Figure S391: The energy minimized structure corresponding to (ethylsulfanyl)(pyridin-3-yl)methanone.

Table S789: The calculated geometric terms of (ethylsulfanyl)(pyridin-3-yl)methanone.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.82	1.82	0.00
SG-C7	1.78	1.78	0.00
C7-O7	1.23	1.23	0.00
C7-C3	1.49	1.50	0.01
C3-C2	1.40	1.41	0.01
C3-C4	1.40	1.41	0.01
C2-H2	1.09	1.08	0.01
C2-N1	1.34	1.33	0.01
C4-H4	1.09	1.08	0.01
C4-C5	1.39	1.40	0.01
N1-C6	1.34	1.33	0.01
C5-H5	1.09	1.08	0.01
C5-C6	1.40	1.40	0.01
C6-H6	1.09	1.08	0.01
HA3-CA-HA2	108.06	108.41	0.35
HA3-CA-HA	108.12	108.37	0.26
HA3-CA-CB	109.43	110.40	0.97
HA2-CA-HA	108.35	108.38	0.03
HA2-CA-CB	111.40	110.61	0.79
CA-CB-HB1	111.51	108.84	2.68
CA-CB-HB2	111.50	108.66	2.84
CA-CB-SG	109.45	113.14	3.69
HA-CA-CB	111.36	110.58	0.78
CB-SG-C7	98.20	97.29	0.91
HB1-CB-HB2	107.69	106.81	0.89
HB1-CB-SG	108.34	109.55	1.21

Terms	QM	CHARMM	Abs. diff.
HB2-CB-SG	108.23	109.65	1.42
SG-C7-O7	122.16	122.13	0.03
SG-C7-C3	115.97	116.19	0.22
C7-C3-C2	123.27	123.89	0.62
C7-C3-C4	118.02	119.25	1.23
O7-C7-C3	121.85	121.63	0.22
C3-C2-H2	120.92	120.15	0.78
C3-C2-N1	123.41	122.74	0.67
C3-C4-H4	119.46	119.97	0.51
C3-C4-C5	118.34	119.85	1.51
C2-C3-C4	118.70	116.83	1.87
C2-N1-C6	117.09	120.35	3.27
H2-C2-N1	115.66	117.12	1.46
C4-C5-H5	121.04	121.11	0.07
C4-C5-C6	118.78	118.33	0.46
H4-C4-C5	122.20	120.18	2.02
N1-C6-C5	123.66	121.90	1.76
N1-C6-H6	115.72	117.69	1.97
C5-C6-H6	120.61	120.41	0.20
H5-C5-C6	120.17	120.56	0.39

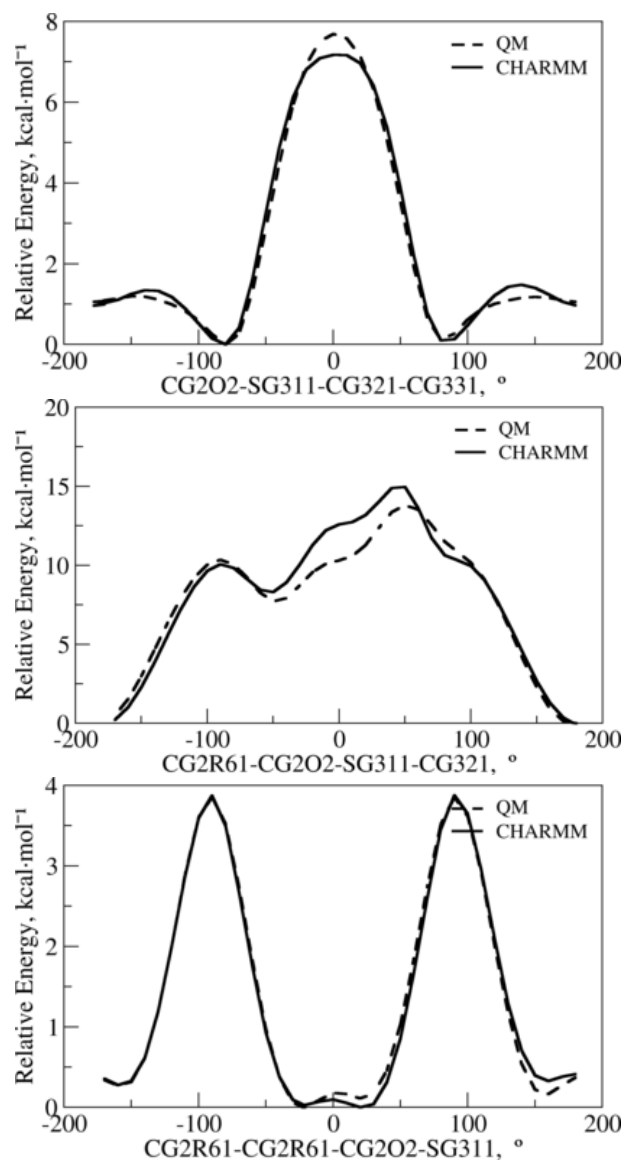


Figure S392: The PES scan for flexible dihedrals corresponding to (ethylsulfanyl)(pyridin-3-yl)methanone.

2.110 The small molecule used for bonded terms optimization of N-6-crotonyl-L-lysine (KCR)

Terms	QM	CHARMM	Abs. diff.
CY-CH3-HH33	111.54	112.96	1.42
HY-CY-CH3	118.04	117.11	0.93
HH31-CH3-HH32	106.85	107.31	0.47
HH31-CH3-HH33	108.36	107.45	0.91
HH32-CH3-HH33	108.38	107.47	0.91

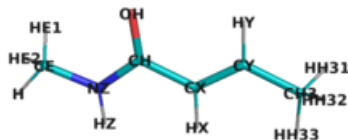


Figure S393: The energy minimized structure corresponding to (2E)-N-methylbut-2-enamide.

Table S790: The calculated geometric terms of (2E)-N-methylbut-2-enamide.

Terms	QM	CHARMM	Abs. diff.
H-CE	1.09	1.11	0.02
CE-HE1	1.09	1.11	0.02
CE-HE2	1.10	1.11	0.02
CE-NZ	1.45	1.44	0.01
NZ-HZ	1.01	0.99	0.02
NZ-CH	1.37	1.35	0.02
CH-OH	1.24	1.23	0.01
CH-CX	1.49	1.49	0.00
CX-HX	1.09	1.10	0.01
CX-CY	1.34	1.35	0.01
CY-HY	1.09	1.10	0.01
CY-CH3	1.49	1.51	0.01
CH3-HH31	1.10	1.11	0.02
CH3-HH32	1.10	1.11	0.02
CH3-HH33	1.09	1.11	0.02
H-CE-HE1	109.62	108.45	1.17
H-CE-HE2	109.27	108.47	0.80
H-CE-NZ	109.32	110.63	1.32
CE-NZ-HZ	118.70	117.17	1.53
CE-NZ-CH	120.89	120.95	0.06
HE1-CE-HE2	108.39	108.03	0.36
HE1-CE-NZ	108.04	110.63	2.59
HE2-CE-NZ	112.17	110.55	1.62
NZ-CH-OH	122.22	120.88	1.34
NZ-CH-CX	114.43	116.55	2.13
HZ-NZ-CH	118.74	121.89	3.15
CH-CX-HX	118.94	117.60	1.35
CH-CX-CY	120.37	124.83	4.46
OH-CH-CX	123.34	122.57	0.77
CX-CY-HY	117.00	118.28	1.28
CX-CY-CH3	124.96	124.61	0.35
HX-CX-CY	120.69	117.57	3.12
CY-CH3-HH31	110.76	110.68	0.07
CY-CH3-HH32	110.80	110.74	0.06

2.111 The small molecule used for bonded terms optimization of lysineNZ-carboxylicacid (KCX)

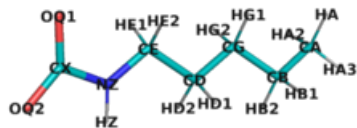


Figure S394: The energy minimized structure corresponding to pentylcarbamic acid.

Table S791: The calculated geometric terms of pentylcarbamic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.10	1.11	0.02
CA-HA	1.10	1.11	0.02
CA-CB	1.53	1.53	0.00
CB-HB1	1.10	1.11	0.02
CB-HB2	1.10	1.11	0.02
CB-CG	1.53	1.54	0.01
CG-HG1	1.10	1.11	0.01
CG-HG2	1.10	1.11	0.01
CG-CD	1.53	1.54	0.01
CD-HD1	1.10	1.11	0.02
CD-HD2	1.10	1.11	0.01
CD-CE	1.53	1.53	0.00
CE-HE1	1.10	1.11	0.01
CE-HE2	1.09	1.12	0.02
CE-NZ	1.45	1.43	0.02
NZ-HZ	1.02	1.00	0.02
NZ-CX	1.46	1.35	0.11
CX-OQ1	1.27	1.25	0.02
CX-OQ2	1.27	1.25	0.02
HA3-CA-HA2	107.91	108.54	0.64
HA3-CA-HA	107.90	108.74	0.84
HA3-CA-CB	111.79	110.74	1.05
HA2-CA-HA	107.66	108.29	0.63
HA2-CA-CB	110.78	110.11	0.67
CA-CB-HB1	109.65	109.41	0.24
CA-CB-HB2	109.59	109.23	0.36
CA-CB-CG	113.03	113.29	0.27
HA-CA-CB	110.65	110.35	0.30
CB-CG-HG1	109.10	109.44	0.34
CB-CG-HG2	108.99	109.12	0.13
CB-CG-CD	113.56	112.71	0.85
HB1-CB-HB2	106.43	107.37	0.93

Terms	QM	CHARMM	Abs. diff.
HB1-CB-CG	108.82	108.70	0.12
HB2-CB-CG	109.11	108.67	0.44
CG-CD-HD1	110.03	110.25	0.21
CG-CD-HD2	109.56	108.83	0.74
CG-CD-CE	112.86	114.04	1.19
HG1-CG-HG2	106.48	107.70	1.22
HG1-CG-CD	108.77	109.34	0.57
HG2-CG-CD	109.70	108.40	1.30
CD-CE-HE1	109.53	110.16	0.63
CD-CE-HE2	108.93	109.20	0.27
CD-CE-NZ	114.80	111.17	3.63
HD1-CD-HD2	107.56	107.73	0.18
HD1-CD-CE	107.46	107.72	0.25
HD2-CD-CE	109.22	108.07	1.14
CE-NZ-HZ	113.94	118.37	4.43
CE-NZ-CX	117.12	124.45	7.33
HE1-CE-HE2	108.02	107.44	0.58
HE1-CE-NZ	108.57	109.30	0.73
HE2-CE-NZ	106.77	109.49	2.72
NZ-CX-OQ1	115.33	114.62	0.70
NZ-CX-OQ2	114.36	110.80	3.56
HZ-NZ-CX	109.17	115.32	6.15
OQ1-CX-OQ2	130.30	134.57	4.27

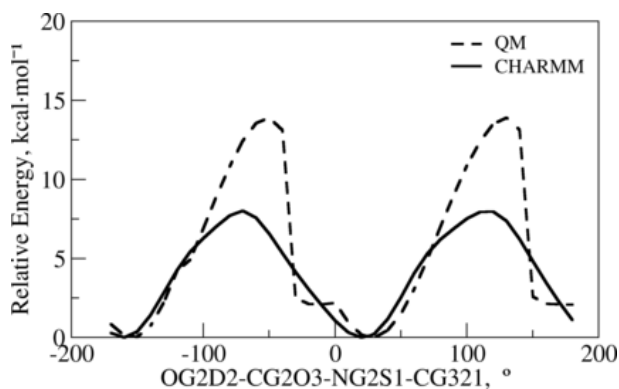


Figure S395: The PES scan for flexible dihedral corresponding to pentylcarbamic acid.

2.112 The small molecule used for bonded terms optimization of (2S)-2-amino-6-[(1-hydroxy-1-oxo-propan-2-ylidene)amino]hexanoicacid (KPI)

Terms	QM	CHARMM	Abs. diff.
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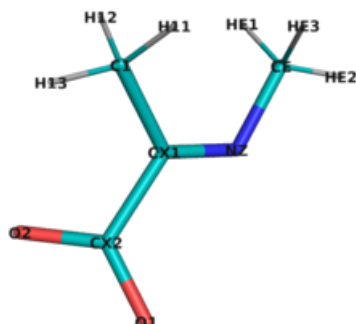


Figure S396: The energy minimized structure corresponding to (2E)-2-(methyliminiumyl)propanoate.

Table S792: The calculated geometric terms of (2E)-2-(methyliminiumyl)propanoate.

Terms	QM	CHARMM	Abs. diff.
HE3-CE	1.10	1.12	0.02
CE-HE1	1.10	1.11	0.01
CE-HE2	1.10	1.11	0.01
CE-NZ	1.46	1.45	0.00
NZ-CX1	1.29	1.31	0.02
CX1-C1	1.52	1.52	0.00
CX1-CX2	1.58	1.54	0.04
C1-H11	1.10	1.11	0.01
C1-H12	1.10	1.11	0.01
C1-H13	1.09	1.11	0.02
CX2-O1	1.24	1.27	0.02
CX2-O2	1.26	1.27	0.01
HE3-CE-HE1	108.18	108.08	0.10
HE3-CE-HE2	106.67	104.63	2.04
HE3-CE-NZ	108.52	115.37	6.85
CE-NZ-CX1	118.77	117.20	1.57
HE1-CE-HE2	108.18	105.11	3.07
HE1-CE-NZ	116.37	112.16	4.20
HE2-CE-NZ	108.52	110.73	2.22
NZ-CX1-C1	125.13	124.54	0.59
NZ-CX1-CX2	118.99	121.18	2.19
CX1-C1-H11	111.69	111.26	0.43
CX1-C1-H12	111.69	109.78	1.90
CX1-C1-H13	106.74	111.95	5.21
CX1-CX2-O1	116.01	119.65	3.64
CX1-CX2-O2	113.51	115.57	2.06
C1-CX1-CX2	115.88	114.21	1.67
H11-C1-H12	107.47	108.91	1.44
H11-C1-H13	109.63	107.26	2.36
H12-C1-H13	109.62	107.53	2.09
O1-CX2-O2	130.48	124.77	5.71

2.113 The small molecule used for bonded terms optimization of kynurenine (KYN)

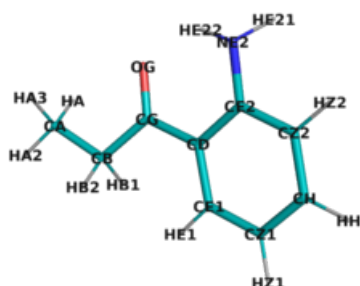


Figure S397: The energy minimized structure corresponding to 1-(2-aminophenyl)propan-1-one.

Table S793: The calculated geometric terms of 1-(2-aminophenyl)propan-1-one.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.54	0.02
CB-HB1	1.10	1.11	0.01
CB-HB2	1.10	1.11	0.01
CB-CG	1.52	1.51	0.01
CG-OG	1.24	1.23	0.01
CG-CD	1.48	1.50	0.02
CD-CE2	1.42	1.43	0.00
CD-CE1	1.41	1.41	0.00
CE2-NE2	1.38	1.39	0.01
CE2-CZ2	1.41	1.40	0.01
NE2-HE21	1.01	1.00	0.01
NE2-HE22	1.01	1.01	0.01
CE1-HE1	1.09	1.08	0.00
CE1-CZ1	1.39	1.40	0.01
CZ2-HZ2	1.09	1.08	0.01
CZ2-CH	1.39	1.40	0.01
CZ1-HZ1	1.09	1.08	0.00
CZ1-CH	1.40	1.40	0.00
CH-HH	1.09	1.08	0.01
HA3-CA-HA2	108.64	108.30	0.33
HA3-CA-HA	107.57	108.10	0.53
HA3-CA-CB	110.90	110.66	0.23
HA2-CA-HA	108.68	108.37	0.31
HA2-CA-CB	110.08	110.60	0.52
CA-CB-HB1	110.38	108.63	1.74
CA-CB-HB2	110.66	108.90	1.76
CA-CB-CG	112.34	113.34	1.00
HA-CA-CB	110.90	110.71	0.18
CB-CG-OG	118.68	119.09	0.41
CB-CG-CD	119.23	120.30	1.07
HB1-CB-HB2	105.96	108.57	2.61

Terms	QM	CHARMM	Abs. diff.
HB1-CB-CG	108.71	108.63	0.08
HB2-CB-CG	108.56	108.68	0.12
CG-CD-CE2	121.25	121.99	0.74
CG-CD-CE1	119.93	119.67	0.26
OG-CG-CD	122.08	120.60	1.48
CD-CE2-NE2	122.47	123.05	0.58
CD-CE2-CZ2	118.41	119.94	1.52
CD-CE1-HE1	119.37	121.42	2.05
CD-CE1-CZ1	121.98	120.99	0.99
CE2-CD-CE1	118.71	118.32	0.39
CE2-NE2-HE21	115.67	111.90	3.77
CE2-NE2-HE22	115.17	109.65	5.53
CE2-CZ2-HZ2	118.44	120.17	1.73
CE2-CZ2-CH	121.58	120.77	0.80
NE2-CE2-CZ2	118.90	117.01	1.89
HE21-NE2-HE22	116.08	119.99	3.91
CE1-CZ1-HZ1	120.32	120.02	0.30
CE1-CZ1-CH	119.06	120.11	1.05
HE1-CE1-CZ1	118.64	117.59	1.05
CZ2-CH-CZ1	120.22	119.87	0.35
CZ2-CH-HH	119.47	120.01	0.54
HZ2-CZ2-CH	119.97	119.05	0.92
CZ1-CH-HH	120.29	120.12	0.17
HZ1-CZ1-CH	120.60	119.87	0.73

2.114 The small molecule 1 used for bonded terms optimization of Penicillamine (LE1)

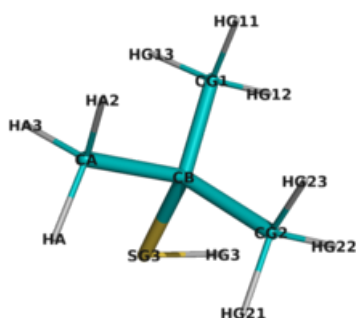


Figure S398: The energy minimized structure corresponding to 2-methylpropane-2-thiol.

Table S794: The calculated geometric terms of 2-methylpropane-2-thiol.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.01
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.54	0.01
CB-SG3	1.84	1.85	0.01
CB-CG2	1.53	1.53	0.00
CB-CG1	1.53	1.53	0.00
SG3-HG3	1.34	1.32	0.02
CG2-HG23	1.10	1.11	0.01
CG2-HG21	1.09	1.11	0.02
CG2-HG22	1.09	1.11	0.02
CG1-HG11	1.10	1.11	0.01
CG1-HG12	1.09	1.11	0.02
CG1-HG13	1.09	1.11	0.02
HA3-CA-HA2	108.35	108.47	0.12
HA3-CA-HA	108.54	108.48	0.06
HA3-CA-CB	111.10	110.66	0.45
HA2-CA-HA	108.28	108.39	0.11
HA2-CA-CB	109.39	110.18	0.79
CA-CB-SG3	105.57	105.74	0.17
CA-CB-CG2	110.24	108.67	1.56
CA-CB-CG1	110.23	108.63	1.59
HA-CA-CB	111.09	110.59	0.50
CB-SG3-HG3	96.23	94.56	1.67
CB-CG2-HG23	109.74	110.17	0.43
CB-CG2-HG21	110.89	110.56	0.34
CB-CG2-HG22	111.12	110.45	0.66
CB-CG1-HG11	109.84	110.10	0.26
CB-CG1-HG12	111.18	110.47	0.70
CB-CG1-HG13	110.92	110.57	0.35
SG3-CB-CG2	110.12	108.90	1.22
SG3-CB-CG1	110.14	108.88	1.26
CG2-CB-CG1	110.44	115.56	5.12
HG23-CG2-HG21	108.71	108.48	0.23

Terms	QM	CHARMM	Abs. diff.
HG23-CG2-HG22	108.02	108.47	0.46
HG21-CG2-HG22	108.27	108.64	0.37
HG11-CG1-HG12	107.98	108.51	0.53
HG11-CG1-HG13	108.60	108.50	0.10
HG12-CG1-HG13	108.24	108.64	0.40

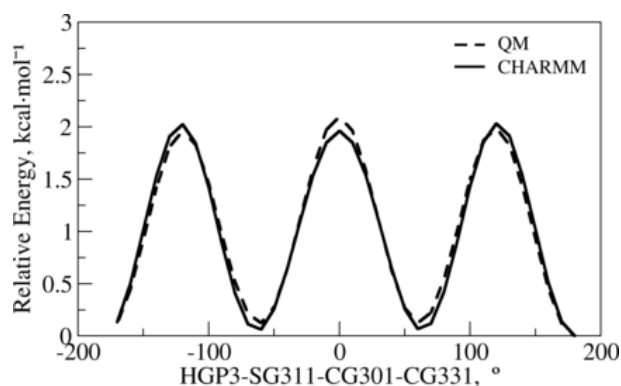


Figure S399: The PES scan for flexible dihedral corresponding to 2-methylpropane-2-thiol.

2.115 The small molecule 2 used for bonded terms optimization of Penicillamine (LE1)

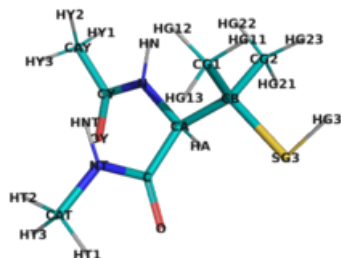


Figure S400: The energy minimized structure corresponding to 2-acetamido-N,3-dimethyl-3-sulfanylbutanamide.

Table S795: The calculated geometric terms of 2-acetamido-N,3-dimethyl-3-sulfanylbutanamide.

Terms	QM	CHARMM	Abs. diff.
N-HN	1.01	0.99	0.02
N-CA	1.46	1.47	0.01
N-CY	1.38	1.34	0.04
CA-HA	1.10	1.08	0.02
CA-CB	1.55	1.55	0.01
CA-C	1.53	1.53	0.00
CB-SG3	1.84	1.86	0.02
CB-CG2	1.53	1.54	0.01
CB-CG1	1.53	1.54	0.01
SG3-HG3	1.34	1.32	0.02
CG2-HG23	1.09	1.11	0.02
CG2-HG21	1.09	1.11	0.02
CG2-HG22	1.10	1.11	0.01
CG1-HG11	1.09	1.11	0.02
CG1-HG12	1.10	1.11	0.01
CG1-HG13	1.09	1.11	0.02
C-O	1.23	1.23	0.00
C-NT	1.37	1.35	0.02
NT-HNT	1.01	0.99	0.02
NT-CAT	1.46	1.44	0.01
CAT-HT1	1.09	1.11	0.02
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.10	1.11	0.02
CAY-HY1	1.09	1.11	0.02
CAY-HY2	1.09	1.11	0.02
CAY-HY3	1.09	1.11	0.02
CAY-CY	1.51	1.48	0.03
CY-OY	1.23	1.22	0.01
N-CA-HA	109.78	105.87	3.91
N-CA-CB	110.34	111.91	1.57
N-CA-C	110.81	113.61	2.80
N-CY-CAY	115.08	116.52	1.45
N-CY-OY	121.60	122.97	1.37

Terms	QM	CHARMM	Abs. diff.
HN-N-CA	117.96	116.08	1.88
HN-N-CY	116.99	118.59	1.60
CA-N-CY	119.18	125.04	5.87
CA-CB-SG3	105.32	110.50	5.18
CA-CB-CG2	109.31	108.30	1.02
CA-CB-CG1	112.96	111.92	1.04
CA-C-O	120.58	121.13	0.55
CA-C-NT	115.58	118.15	2.57
HA-CA-CB	107.95	106.24	1.70
HA-CA-C	103.54	103.83	0.28
CB-CA-C	114.12	114.36	0.24
CB-SG3-HG3	93.44	95.29	1.85
CB-CG2-HG23	110.23	110.52	0.30
CB-CG2-HG21	110.82	110.53	0.28
CB-CG2-HG22	111.78	111.26	0.52
CB-CG1-HG11	109.79	109.75	0.04
CB-CG1-HG12	111.13	111.22	0.09
CB-CG1-HG13	110.91	111.13	0.23
SG3-CB-CG2	108.77	105.90	2.88
SG3-CB-CG1	109.94	106.80	3.14
CG2-CB-CG1	110.35	113.27	2.91
HG23-CG2-HG21	108.38	108.42	0.04
HG23-CG2-HG22	106.74	107.66	0.91
HG21-CG2-HG22	108.75	108.34	0.41
HG11-CG1-HG12	107.51	107.90	0.39
HG11-CG1-HG13	108.64	107.60	1.04
HG12-CG1-HG13	108.77	109.12	0.35
C-NT-HNT	115.41	119.70	4.29
C-NT-CAT	118.53	121.47	2.94
O-C-NT	123.48	120.71	2.77
NT-CAT-HT1	108.48	111.04	2.56
NT-CAT-HT2	108.79	110.76	1.97
NT-CAT-HT3	111.80	110.40	1.40
HNT-NT-CAT	117.67	118.35	0.68
HT1-CAT-HT2	109.52	108.21	1.32
HT1-CAT-HT3	108.51	108.05	0.45
HT2-CAT-HT3	109.71	108.29	1.43
CAY-CY-OY	123.33	120.51	2.82
HY1-CAY-HY2	108.49	109.56	1.07
HY1-CAY-HY3	108.37	108.76	0.39
HY1-CAY-CY	109.55	109.67	0.13
HY2-CAY-HY3	109.71	108.73	0.99
HY2-CAY-CY	112.12	111.01	1.10
HY3-CAY-CY	108.54	109.07	0.53

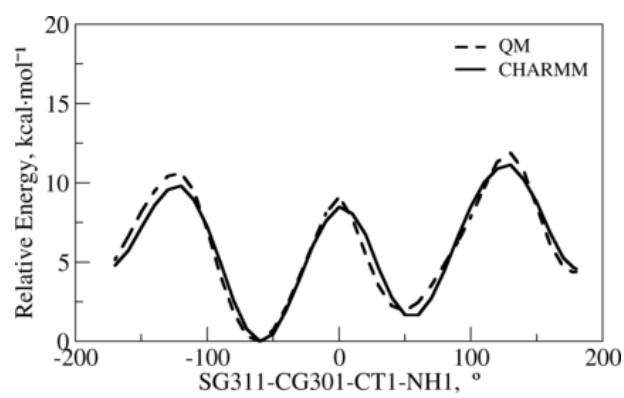


Figure S401: The PES scan for flexible dihedral corresponding to 2-acetamido-N,3-dimethyl-3-sulfanylbutanamide.

2.116 The small molecule 1 used for bonded terms optimization of (4s)-5-fluoro-1-leucine (LEF)



Figure S402: The energy minimized structure corresponding to 1-fluoro-2-methylpropane.

Table S796: The calculated geometric terms of 1-fluoro-2-methylpropane.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-HB1	1.10	1.11	0.02
CB-CG	1.53	1.54	0.01
CG-HG	1.10	1.12	0.02
CG-CD1	1.52	1.52	0.01
CG-CD2	1.53	1.54	0.01
CD1-HD11	1.10	1.08	0.01
CD1-HD12	1.10	1.08	0.01
CD1-F1	1.40	1.37	0.03
CD2-HD21	1.10	1.11	0.01
CD2-HD22	1.09	1.11	0.02
CD2-HD23	1.09	1.11	0.02
HB3-CB-HB2	107.92	108.35	0.42
HB3-CB-HB1	107.74	108.32	0.58
HB3-CB-CG	110.56	110.16	0.41
CB-CG-HG	108.83	108.46	0.37
CB-CG-CD1	109.73	109.93	0.20
CB-CG-CD2	111.81	110.87	0.94
HB2-CB-HB1	108.12	108.67	0.55
HB2-CB-CG	111.67	110.75	0.91
HB1-CB-CG	110.68	110.52	0.16
CG-CD1-HD11	111.51	110.88	0.63
CG-CD1-HD12	110.84	110.78	0.05
CG-CD1-F1	109.96	111.50	1.54
CG-CD2-HD21	110.41	110.52	0.11
CG-CD2-HD22	110.89	110.34	0.55
CG-CD2-HD23	110.71	110.40	0.31
HG-CG-CD1	106.96	108.53	1.57
HG-CG-CD2	108.68	108.40	0.28
CD1-CG-CD2	110.69	110.58	0.11
HD11-CD1-HD12	108.96	107.22	1.74
HD11-CD1-F1	107.69	108.00	0.30
HD12-CD1-F1	107.76	108.31	0.55

Terms	QM	CHARMM	Abs. diff.
HD21-CD2-HD22	107.97	108.60	0.63
HD21-CD2-HD23	108.23	108.52	0.29
HD22-CD2-HD23	108.54	108.41	0.13

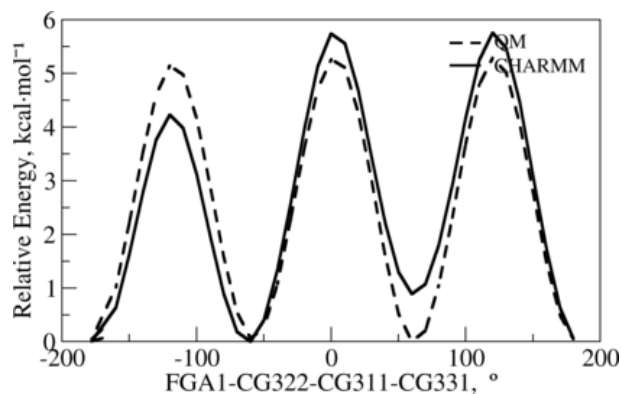


Figure S403: The PES scan for flexible dihedral corresponding to 1-fluoro-2-methylpropane.

2.117 The small molecule 2 used for bonded terms optimization of (4s)-5-fluoro-1-leucine (LEF)

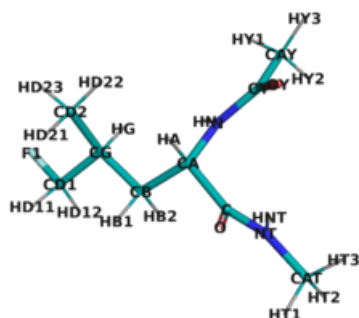


Figure S404: The energy minimized structure corresponding to (2S,4S)-2-acetamido-5-fluoro-N,4-dimethylpentanamide.

Table S797: The calculated geometric terms of (2S,4S)-2-acetamido-5-fluoro-N,4-dimethylpentanamide.

Terms	QM	CHARMM	Abs. diff.
N-HN	1.01	0.99	0.02
N-CA	1.46	1.46	0.00
N-CY	1.38	1.34	0.04
CA-HA	1.10	1.08	0.01
CA-CB	1.53	1.56	0.03
CA-C	1.53	1.53	0.00
CB-HB1	1.10	1.11	0.02
CB-HB2	1.10	1.11	0.01
CB-CG	1.53	1.55	0.01
CG-HG	1.10	1.12	0.02
CG-CD1	1.52	1.53	0.01
CG-CD2	1.53	1.54	0.01
CD1-HD11	1.10	1.08	0.01
CD1-HD12	1.10	1.08	0.01
CD1-F1	1.40	1.37	0.03
CD2-HD21	1.10	1.11	0.02
CD2-HD22	1.09	1.11	0.02
CD2-HD23	1.09	1.11	0.02
C-O	1.23	1.23	0.00
C-NT	1.37	1.35	0.02
NT-HNT	1.01	0.99	0.02
NT-CAT	1.45	1.44	0.01
CAT-HT1	1.09	1.11	0.02
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.10	1.11	0.02
CAY-HY1	1.09	1.11	0.02
CAY-HY2	1.09	1.11	0.02
CAY-HY3	1.09	1.11	0.02
CAY-CY	1.51	1.48	0.03
CY-OY	1.23	1.22	0.01
N-CA-HA	109.95	106.95	3.00
N-CA-CB	110.87	111.30	0.44

Terms	QM	CHARMM	Abs. diff.
N-CA-C	112.03	114.97	2.94
N-CY-CAY	115.44	116.55	1.11
N-CY-OY	121.31	122.65	1.34
HN-N-CA	118.05	116.41	1.64
HN-N-CY	118.16	119.05	0.89
CA-N-CY	119.58	124.46	4.88
CA-CB-HB1	106.44	108.09	1.64
CA-CB-HB2	108.75	109.26	0.52
CA-CB-CG	115.05	115.10	0.05
CA-C-O	120.82	120.92	0.10
CA-C-NT	114.72	117.59	2.87
HA-CA-CB	110.28	108.78	1.50
HA-CA-C	104.14	105.12	0.98
CB-CA-C	109.38	109.35	0.03
CB-CG-HG	109.87	108.99	0.88
CB-CG-CD1	108.64	109.45	0.82
CB-CG-CD2	113.20	112.60	0.61
HB1-CB-HB2	106.90	107.57	0.68
HB1-CB-CG	109.17	107.96	1.21
HB2-CB-CG	110.18	108.61	1.57
CG-CD1-HD11	110.86	111.03	0.18
CG-CD1-HD12	111.53	111.22	0.31
CG-CD1-F1	109.59	111.19	1.60
CG-CD2-HD21	110.45	110.61	0.16
CG-CD2-HD22	111.70	110.88	0.82
CG-CD2-HD23	109.94	110.42	0.49
HG-CG-CD1	105.58	107.73	2.16
HG-CG-CD2	108.71	108.18	0.53
CD1-CG-CD2	110.56	109.76	0.80
HD11-CD1-HD12	109.09	107.13	1.96
HD11-CD1-F1	107.91	108.28	0.37
HD12-CD1-F1	107.74	107.82	0.08
HD21-CD2-HD22	108.04	108.52	0.48
HD21-CD2-HD23	108.39	108.38	0.02
HD22-CD2-HD23	108.22	107.94	0.28
C-NT-HNT	115.37	119.51	4.14
C-NT-CAT	119.21	121.96	2.75
O-C-NT	123.73	121.45	2.28
NT-CAT-HT1	108.27	111.08	2.80
NT-CAT-HT2	108.99	110.76	1.78
NT-CAT-HT3	112.00	110.31	1.69
HNT-NT-CAT	117.72	118.08	0.36
HT1-CAT-HT2	109.51	108.06	1.45
HT1-CAT-HT3	108.46	107.96	0.50
HT2-CAT-HT3	109.57	108.57	1.00
CAY-CY-OY	123.15	120.80	2.35
HY1-CAY-HY2	108.30	109.54	1.24
HY1-CAY-HY3	109.57	108.59	0.98
HY1-CAY-CY	112.39	111.07	1.32
HY2-CAY-HY3	108.44	108.63	0.19
HY2-CAY-CY	109.69	110.01	0.32
HY3-CAY-CY	108.37	108.95	0.58

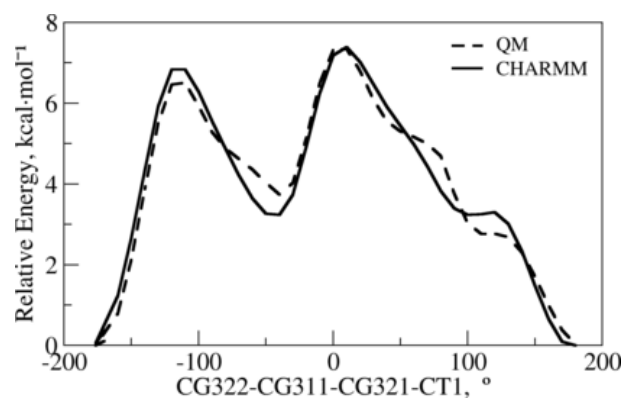


Figure S405: The PES scan for flexible dihedral corresponding to (2*S*,4*S*)-2-acetamido-5-fluoro-N,4-dimethylpentanamide.

2.118 The small molecule used for bonded terms optimization of (2S)-2-amino-6-[[3-hydroxy-2-methyl-5-(phosphonomoxyethyl)pyridin-4-yl]methylidene amino]hexanoic acid (LLPP)

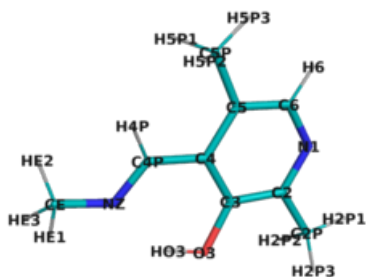


Figure S406: The energy minimized structure corresponding to 2,5-dimethyl-4-[(E)-(methylimino)methyl]pyridin-3-olate.

Table S798: The calculated geometric terms of 2,5-dimethyl-4-[(E)-(methylimino)methyl]pyridin-3-olate.

Terms	QM	CHARMM	Abs. diff.
HE3-CE	1.09	1.11	0.02
CE-HE1	1.09	1.11	0.02
CE-HE2	1.10	1.12	0.02
CE-NZ	1.45	1.46	0.00
NZ-C4P	1.29	1.29	0.00
C4P-H4P	1.10	1.10	0.00
C4P-C4	1.46	1.49	0.03
C4-C3	1.41	1.43	0.02
C4-C5	1.42	1.42	0.01
C3-O3	1.35	1.43	0.08
C3-C2	1.41	1.41	0.00
O3-HO3	1.00	0.97	0.03
C2-C2P	1.50	1.49	0.01
C2-N1	1.34	1.32	0.01
C2P-H2P1	1.09	1.11	0.02
C2P-H2P2	1.09	1.11	0.02
C2P-H2P3	1.09	1.11	0.01
N1-C6	1.35	1.32	0.02
C6-H6	1.09	1.08	0.01
C6-C5	1.39	1.40	0.01
C5-C5P	1.51	1.51	0.01
C5P-H5P1	1.09	1.11	0.02
C5P-H5P2	1.09	1.11	0.02
C5P-H5P3	1.09	1.11	0.02
HE3-CE-HE1	107.85	105.58	2.27
HE3-CE-HE2	109.23	105.61	3.62
HE3-CE-NZ	108.93	110.89	1.96
CE-NZ-C4P	117.84	116.62	1.22
HE1-CE-HE2	109.22	106.82	2.41

Terms	QM	CHARMM	Abs. diff.
HE1-CE-NZ	108.93	111.74	2.81
HE2-CE-NZ	112.58	115.55	2.97
NZ-C4P-H4P	120.35	120.28	0.07
NZ-C4P-C4	121.89	121.41	0.48
C4P-C4-C3	120.81	124.32	3.51
C4P-C4-C5	121.14	117.65	3.49
H4P-C4P-C4	117.76	118.31	0.55
C4-C3-O3	123.39	122.70	0.69
C4-C3-C2	119.65	118.19	1.46
C4-C5-C6	117.53	118.02	0.49
C4-C5-C5P	122.60	124.07	1.46
C3-C4-C5	118.05	118.03	0.02
C3-O3-HO3	106.67	106.22	0.45
C3-C2-C2P	119.59	120.52	0.92
C3-C2-N1	121.76	121.75	0.01
O3-C3-C2	116.96	119.10	2.15
C2-C2P-H2P1	108.89	109.29	0.40
C2-C2P-H2P2	110.85	108.67	2.17
C2-C2P-H2P3	110.85	108.70	2.14
C2-N1-C6	118.32	121.22	2.90
C2P-C2-N1	118.65	117.73	0.92
H2P1-C2P-H2P2	109.66	109.96	0.29
H2P1-C2P-H2P3	109.67	109.94	0.27
H2P2-C2P-H2P3	106.91	110.25	3.34
N1-C6-H6	115.45	117.31	1.86
N1-C6-C5	124.70	122.79	1.91
C6-C5-C5P	119.87	117.90	1.97
H6-C6-C5	119.85	119.90	0.05
C5-C5P-H5P1	112.02	109.06	2.96
C5-C5P-H5P2	112.02	109.25	2.77
C5-C5P-H5P3	109.72	110.38	0.67
H5P1-C5P-H5P2	107.78	110.22	2.44
H5P1-C5P-H5P3	107.55	109.10	1.55
H5P2-C5P-H5P3	107.55	108.82	1.28

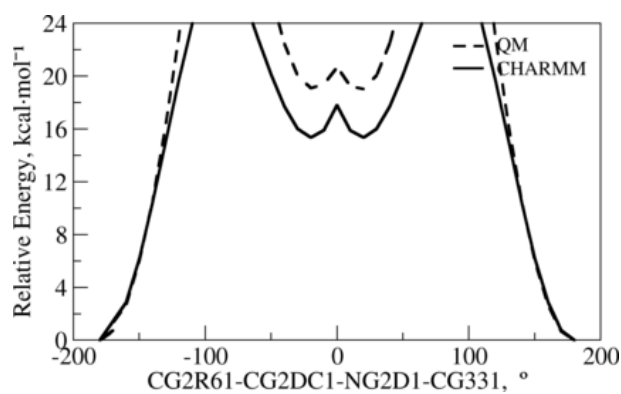


Figure S407: The PES scan for flexible dihedral corresponding to 2,5-dimethyl-4-[(E)-(methylimino)methyl]pyridin-3-olate.

2.119 The small molecule used for bonded terms optimization of vinylglycine (LVG)

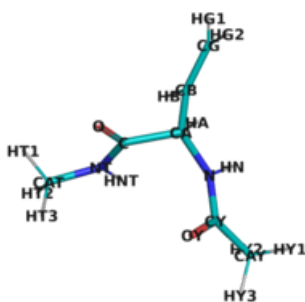


Figure S408: The energy minimized structure corresponding to (2S)-2-acetamido-N-methylbut-3-enamide.

Table S799: The calculated geometric terms of (2S)-2-acetamido-N-methylbut-3-enamide.

Terms	QM	CHARMM	Abs. diff.
N-HN	1.02	0.99	0.02
N-CA	1.46	1.46	0.01
N-CY	1.38	1.34	0.04
CA-HA	1.10	1.08	0.01
CA-CB	1.50	1.51	0.01
CA-C	1.53	1.53	0.01
CB-HB	1.09	1.10	0.01
CB-CG	1.34	1.35	0.01
CG-HG1	1.09	1.10	0.02
CG-HG2	1.09	1.10	0.02
C-O	1.23	1.23	0.00
C-NT	1.37	1.35	0.02
NT-HNT	1.01	0.99	0.02
NT-CAT	1.45	1.44	0.01
CAT-HT1	1.09	1.11	0.02
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.10	1.11	0.02
CAY-HY1	1.09	1.11	0.02
CAY-HY2	1.09	1.11	0.02
CAY-HY3	1.09	1.11	0.02
CAY-CY	1.51	1.48	0.03
CY-OY	1.23	1.22	0.01
N-CA-HA	110.84	107.03	3.81
N-CA-CB	109.11	109.57	0.46
N-CA-C	111.63	115.11	3.47
N-CY-CAY	115.16	116.22	1.06
N-CY-OY	121.49	123.02	1.53
HN-N-CA	116.03	115.02	1.01
HN-N-CY	117.57	117.86	0.29
CA-N-CY	119.34	125.15	5.81
CA-CB-HB	116.33	115.36	0.98
CA-CB-CG	123.03	126.74	3.71
CA-C-O	121.18	120.96	0.22

Terms	QM	CHARMM	Abs. diff.
CA-C-NT	114.26	117.78	3.52
HA-CA-CB	110.50	110.45	0.04
HA-CA-C	105.08	105.61	0.53
CB-CA-C	109.63	108.96	0.67
CB-CG-HG1	121.49	121.29	0.20
CB-CG-HG2	121.48	120.84	0.64
HB-CB-CG	120.62	117.81	2.82
HG1-CG-HG2	117.02	117.85	0.84
C-NT-HNT	115.33	118.73	3.40
C-NT-CAT	118.93	122.27	3.34
O-C-NT	124.00	121.20	2.80
NT-CAT-HT1	108.36	111.27	2.91
NT-CAT-HT2	108.96	110.62	1.66
NT-CAT-HT3	111.94	110.20	1.74
HNT-NT-CAT	117.66	118.26	0.59
HT1-CAT-HT2	109.48	108.23	1.25
HT1-CAT-HT3	108.47	107.97	0.50
HT2-CAT-HT3	109.60	108.46	1.14
CAY-CY-OY	123.35	120.76	2.59
HY1-CAY-HY2	108.42	109.40	0.97
HY1-CAY-HY3	108.45	108.50	0.05
HY1-CAY-CY	109.59	109.97	0.39
HY2-CAY-HY3	109.80	108.89	0.91
HY2-CAY-CY	111.96	110.91	1.06
HY3-CAY-CY	108.56	109.13	0.57

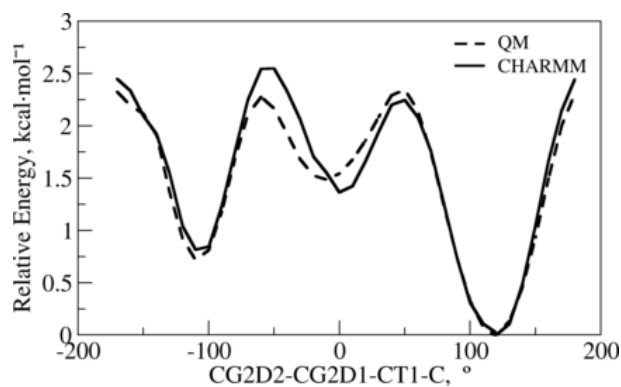


Figure S409: The PES scan for flexible dihedral corresponding to (2S)-2-acetamido-N-methylbut-3-enamide.

2.120 The small molecule used for bonded terms optimization of N''-(2-coenzymeA)-propanoyl-lysine (LYX)

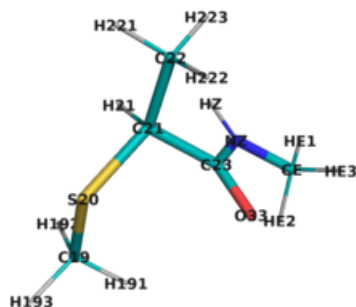


Figure S410: The energy minimized structure corresponding to (2S)-N-methyl-2-(methylsulfonyl)propanamide.

Table S800: The calculated geometric terms of (2S)-N-methyl-2-(methylsulfonyl)propanamide.

Terms	QM	CHARMM	Abs. diff.
HE3-CE	1.10	1.11	0.02
CE-HE1	1.09	1.11	0.02
CE-HE2	1.09	1.11	0.02
CE-NZ	1.45	1.45	0.01
NZ-HZ	1.01	0.99	0.02
NZ-C23	1.37	1.35	0.02
C23-O33	1.23	1.23	0.01
C23-C21	1.52	1.51	0.01
C21-H21	1.10	1.11	0.01
C21-C22	1.53	1.55	0.03
C21-S20	1.82	1.83	0.01
C22-H221	1.09	1.11	0.02
C22-H222	1.09	1.11	0.02
C22-H223	1.09	1.11	0.02
S20-C19	1.81	1.82	0.01
C19-H191	1.09	1.11	0.02
C19-H192	1.09	1.11	0.02
C19-H193	1.09	1.11	0.02
HE3-CE-HE1	109.33	108.27	1.06
HE3-CE-HE2	108.43	108.02	0.41
HE3-CE-NZ	112.00	110.90	1.10
CE-NZ-HZ	118.87	118.06	0.81
CE-NZ-C23	120.84	121.42	0.58
HE1-CE-HE2	109.70	108.40	1.30
HE1-CE-NZ	109.27	110.70	1.43
HE2-CE-NZ	108.09	110.46	2.37
NZ-C23-O33	122.61	120.96	1.65
NZ-C23-C21	114.84	116.86	2.02
HZ-NZ-C23	118.82	120.52	1.70
C23-C21-H21	110.29	107.12	3.17
C23-C21-C22	109.76	110.13	0.37
C23-C21-S20	110.70	111.30	0.60

Terms	QM	CHARMM	Abs. diff.
O33-C23-C21	122.54	122.18	0.35
C21-C22-H221	110.80	110.16	0.64
C21-C22-H222	109.49	110.30	0.81
C21-C22-H223	109.94	111.31	1.37
C21-S20-C19	100.17	99.30	0.87
H21-C21-C22	109.85	107.52	2.33
H21-C21-S20	107.98	107.93	0.05
C22-C21-S20	108.23	112.60	4.37
H221-C22-H222	109.63	108.07	1.56
H221-C22-H223	108.63	108.38	0.25
H222-C22-H223	108.31	108.53	0.22
S20-C19-H191	111.78	111.27	0.50
S20-C19-H192	111.39	111.42	0.03
S20-C19-H193	106.80	110.55	3.76
H191-C19-H192	109.64	108.25	1.39
H191-C19-H193	108.77	107.29	1.48
H192-C19-H193	108.33	107.89	0.44

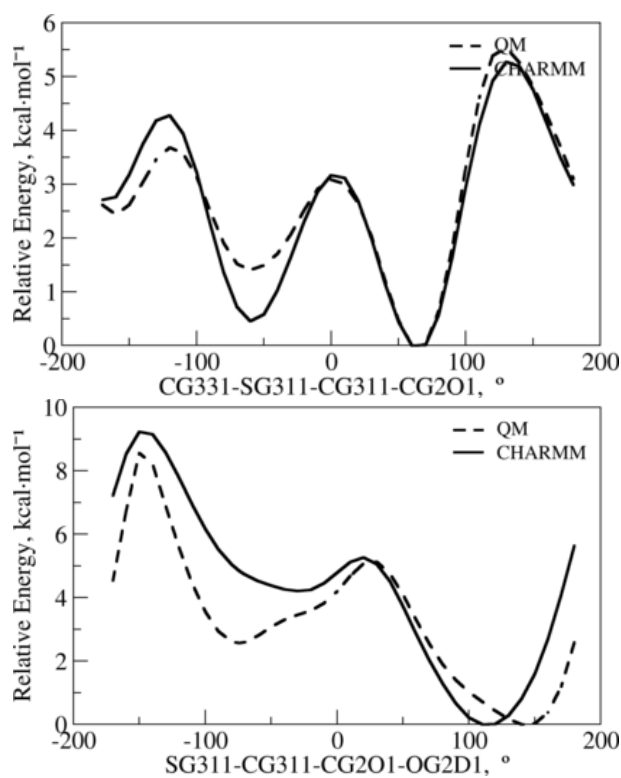


Figure S411: The PES scan for flexible dihedrals corresponding to (2S)-N-methyl-2-(methylsulfonyl)propanamide.

2.121 The small molecule used for bonded terms optimization of S-(hydroxymethyl)-L-cysteine (MOH)

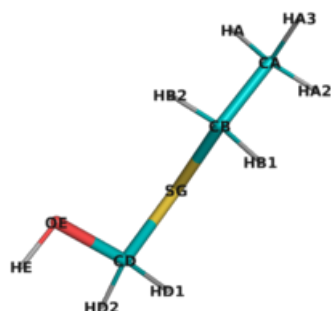


Figure S412: The energy minimized structure corresponding to (ethylsulfanyl)methanol.

Table S801: The calculated geometric terms of (ethylsulfanyl)methanol.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB1	1.10	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.82	1.82	0.00
SG-CD	1.79	1.82	0.02
CD-HD1	1.10	1.11	0.01
CD-HD2	1.10	1.11	0.02
CD-OE	1.43	1.42	0.00
OE-HE	0.97	0.96	0.01
HA3-CA-HA2	108.12	108.53	0.42
HA3-CA-HA	108.20	108.41	0.21
HA3-CA-CB	109.98	110.56	0.58
HA2-CA-HA	108.30	108.37	0.07
HA2-CA-CB	111.22	110.57	0.65
CA-CB-HB1	110.36	108.87	1.49
CA-CB-HB2	110.84	108.79	2.04
CA-CB-SG	109.88	112.63	2.75
HA-CA-CB	110.93	110.34	0.59
CB-SG-CD	98.61	97.42	1.20
HB1-CB-HB2	108.46	107.05	1.41
HB1-CB-SG	109.17	109.86	0.69
HB2-CB-SG	108.08	109.48	1.40
SG-CD-HD1	109.72	110.56	0.84
SG-CD-HD2	106.29	109.60	3.31
SG-CD-OE	109.43	110.42	0.99
CD-OE-HE	107.17	107.47	0.30
HD1-CD-HD2	108.62	107.97	0.64
HD1-CD-OE	110.90	109.43	1.47
HD2-CD-OE	111.76	108.79	2.96

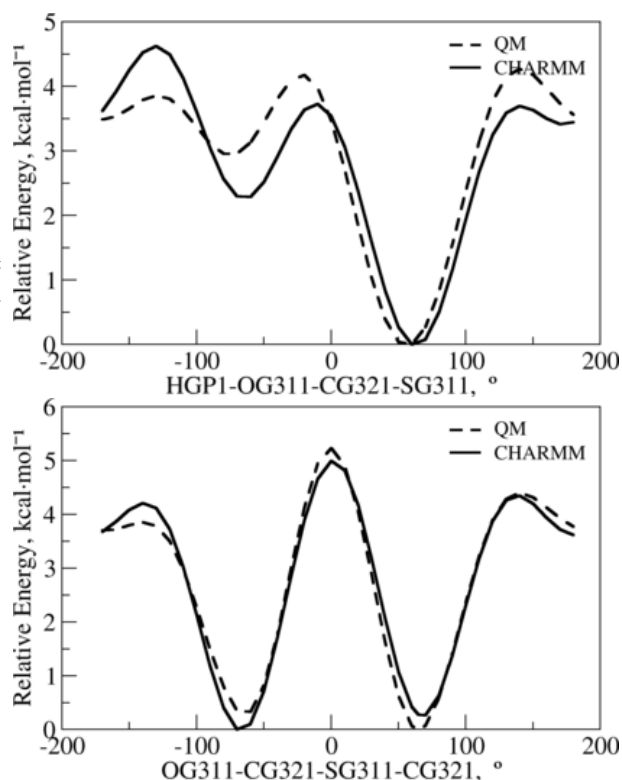


Figure S413: The PES scan for flexible dihedrals corresponding to (ethylsulfanyl)methanol.

2.122 The small molecule used for bonded terms optimization of 3,3-dimethyl-methioninesulfonide (M2S)

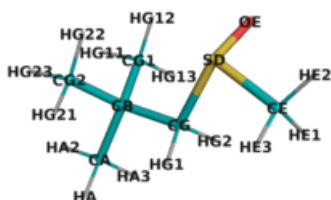


Figure S414: The energy minimized structure corresponding to (R)-(2,2-dimethylpropyl)(methyl)-lambda3-sulfanol.

Table S802: The calculated geometric terms of (R)-(2,2-dimethylpropyl)(methyl)-lambda3-sulfanol.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.02
HA2-CA	1.10	1.11	0.01
CA-HA	1.10	1.11	0.01
CA-CB	1.53	1.54	0.01
CB-CG1	1.53	1.54	0.01
CB-CG2	1.53	1.54	0.01
CB-CG	1.54	1.55	0.02
CG1-HG13	1.10	1.11	0.01
CG1-HG11	1.10	1.11	0.01
CG1-HG12	1.09	1.11	0.02
CG2-HG21	1.10	1.11	0.01
CG2-HG22	1.09	1.11	0.02
CG2-HG23	1.09	1.11	0.02
CG-HG1	1.10	1.11	0.01
CG-HG2	1.10	1.11	0.01
CG-SD	1.82	1.82	0.00
SD-OE	1.52	1.53	0.01
SD-CE	1.81	1.79	0.02
CE-HE1	1.09	1.11	0.02
CE-HE2	1.09	1.11	0.02
CE-HE3	1.09	1.11	0.02
HA3-CA-HA2	107.94	108.34	0.40
HA3-CA-HA	108.28	108.80	0.52
HA3-CA-CB	111.00	110.36	0.64
HA2-CA-HA	108.06	108.44	0.38
HA2-CA-CB	110.17	110.18	0.00
CA-CB-CG1	109.13	108.11	1.02
CA-CB-CG2	109.12	108.21	0.91
CA-CB-CG	106.96	108.43	1.47
HA-CA-CB	111.27	110.67	0.61
CB-CG1-HG13	110.52	110.54	0.02
CB-CG1-HG11	109.79	110.36	0.57

Terms	QM	CHARMM	Abs. diff.
CB-CG1-HG12	111.44	110.88	0.56
CB-CG2-HG21	111.28	110.71	0.57
CB-CG2-HG22	111.77	110.96	0.81
CB-CG2-HG23	109.81	109.94	0.13
CB-CG-HG1	109.84	109.65	0.20
CB-CG-HG2	110.15	110.43	0.29
CB-CG-SD	114.79	112.85	1.94
CG1-CB-CG2	109.92	109.16	0.75
CG1-CB-CG	110.77	111.73	0.96
HG13-CG1-HG11	108.01	108.65	0.65
HG13-CG1-HG12	107.80	108.20	0.40
HG11-CG1-HG12	109.20	108.13	1.07
CG2-CB-CG	110.88	111.09	0.21
HG21-CG2-HG22	108.27	108.95	0.68
HG21-CG2-HG23	107.96	108.44	0.48
HG22-CG2-HG23	107.61	107.76	0.15
CG-SD-OE	108.92	107.30	1.62
CG-SD-CE	95.28	95.58	0.30
HG1-CG-HG2	108.73	109.76	1.03
HG1-CG-SD	105.54	107.06	1.52
HG2-CG-SD	107.55	106.98	0.57
SD-CE-HE1	109.34	110.56	1.22
SD-CE-HE2	107.01	110.08	3.07
SD-CE-HE3	110.40	111.33	0.93
OE-SD-CE	106.84	104.57	2.27
HE1-CE-HE2	109.30	107.69	1.61
HE1-CE-HE3	110.93	108.77	2.16
HE2-CE-HE3	109.78	108.31	1.46

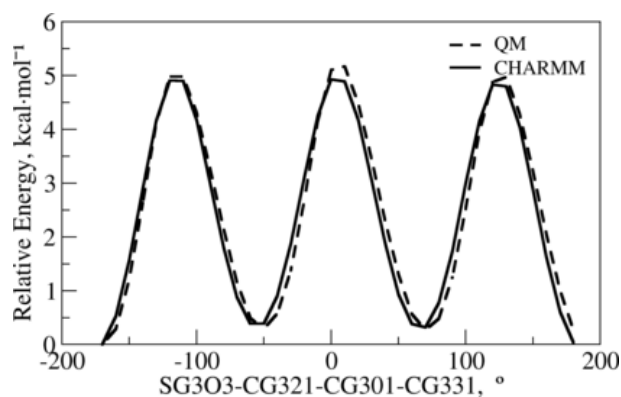


Figure S415: The PES scan for flexible dihedral corresponding to (R)-(2,2-dimethylpropyl)(methyl)-lambda3-sulfanol.

2.123 The small molecule used for bonded terms optimization of N-trimethyllysine (M3L)

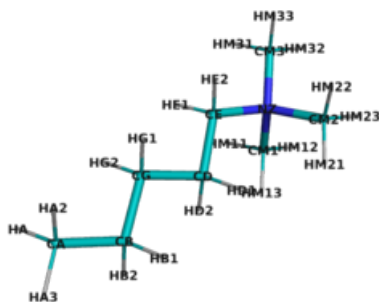


Figure S416: The energy minimized structure corresponding to trimethyl(pentyl)amine.

Table S803: The calculated geometric terms of trimethyl(pentyl)amine.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.53	0.01
CB-HB1	1.10	1.11	0.02
CB-HB2	1.10	1.11	0.02
CB-CG	1.53	1.53	0.01
CG-HG1	1.10	1.11	0.02
CG-HG2	1.10	1.11	0.02
CG-CD	1.53	1.54	0.00
CD-HD1	1.09	1.11	0.02
CD-HD2	1.09	1.11	0.02
CD-CE	1.52	1.54	0.02
CE-HE1	1.09	1.09	0.01
CE-HE2	1.09	1.09	0.01
CE-NZ	1.52	1.52	0.00
NZ-CM1	1.50	1.50	0.00
NZ-CM2	1.50	1.50	0.00
NZ-CM3	1.50	1.50	0.00
CM1-HM11	1.09	1.08	0.01
CM1-HM12	1.09	1.08	0.01
CM1-HM13	1.09	1.09	0.00
CM2-HM21	1.09	1.09	0.00
CM2-HM22	1.09	1.08	0.01
CM2-HM23	1.09	1.08	0.01
CM3-HM31	1.09	1.08	0.01
CM3-HM32	1.09	1.08	0.01
CM3-HM33	1.09	1.08	0.01
HA3-CA-HA2	107.86	108.20	0.34
HA3-CA-HA	107.86	108.20	0.34
HA3-CA-CB	110.93	110.54	0.38
HA2-CA-HA	108.05	108.40	0.35
HA2-CA-CB	111.01	110.71	0.30
CA-CB-HB1	109.71	108.90	0.81

Terms	QM	CHARMM	Abs. diff.
CA-CB-HB2	109.71	108.91	0.80
CA-CB-CG	112.22	113.19	0.97
HA-CA-CB	111.01	110.71	0.30
CB-CG-HG1	109.32	108.39	0.93
CB-CG-HG2	109.32	108.37	0.94
CB-CG-CD	112.16	112.50	0.34
HB1-CB-HB2	106.62	107.31	0.70
HB1-CB-CG	109.21	109.17	0.04
HB2-CB-CG	109.21	109.19	0.02
CG-CD-HD1	108.65	108.07	0.58
CG-CD-HD2	108.65	108.09	0.56
CG-CD-CE	109.46	109.31	0.16
HG1-CG-HG2	106.75	107.75	1.00
HG1-CG-CD	109.57	109.86	0.28
HG2-CG-CD	109.57	109.84	0.27
CD-CE-HE1	110.54	107.66	2.88
CD-CE-HE2	110.54	107.70	2.84
CD-CE-NZ	116.18	116.62	0.44
HD1-CD-HD2	107.76	108.17	0.42
HD1-CD-CE	111.12	111.53	0.40
HD2-CD-CE	111.12	111.55	0.43
CE-NZ-CM1	110.85	110.52	0.32
CE-NZ-CM2	110.85	110.50	0.34
CE-NZ-CM3	108.02	110.08	2.06
HE1-CE-HE2	108.11	105.64	2.47
HE1-CE-NZ	105.52	109.32	3.80
HE2-CE-NZ	105.52	109.34	3.83
NZ-CM1-HM11	108.69	111.47	2.78
NZ-CM1-HM12	108.46	111.52	3.06
NZ-CM1-HM13	109.36	110.52	1.16
NZ-CM2-HM21	109.36	110.49	1.13
NZ-CM2-HM22	108.69	111.49	2.81
NZ-CM2-HM23	108.46	111.50	3.04
NZ-CM3-HM31	108.75	111.43	2.69
NZ-CM3-HM32	108.86	110.97	2.11
NZ-CM3-HM33	108.75	111.48	2.73
CM1-NZ-CM2	109.49	108.68	0.81
CM1-NZ-CM3	108.79	108.52	0.27
HM11-CM1-HM12	110.10	108.00	2.10
HM11-CM1-HM13	110.31	107.35	2.96
HM12-CM1-HM13	109.88	107.80	2.08
CM2-NZ-CM3	108.79	108.48	0.30
HM21-CM2-HM22	110.31	107.36	2.95
HM21-CM2-HM23	109.88	107.80	2.08
HM22-CM2-HM23	110.11	108.02	2.09
HM31-CM3-HM32	110.14	107.37	2.77
HM31-CM3-HM33	110.17	107.99	2.17
HM32-CM3-HM33	110.14	107.40	2.74

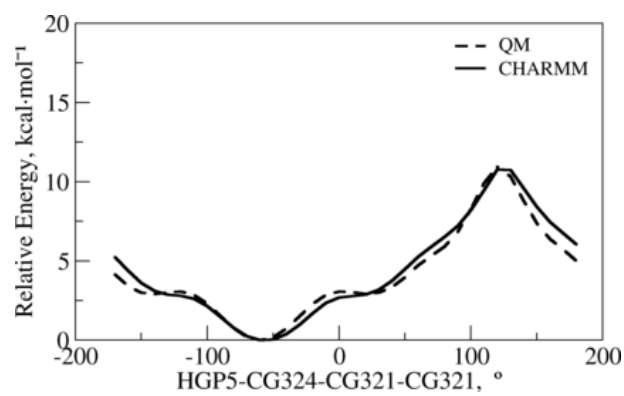


Figure S417: The PES scan for flexible dihedral corresponding to trimethyl(pentyl)amine.

2.124 The small molecule used for bonded terms optimization of N-methyl-L-alanine (MAA)



Figure S418: The energy minimized structure corresponding to N,N-dimethylacetamide.

Table S804: The calculated geometric terms of N,N-dimethylacetamide.

Terms	QM	CHARMM	Abs. diff.
CL-HL1	1.10	1.11	0.01
CL-HL2	1.09	1.11	0.02
CL-HL3	1.09	1.11	0.02
CL-CLP	1.52	1.49	0.03
CLP-OL	1.23	1.23	0.00
CLP-N	1.39	1.38	0.01
N-CA	1.47	1.47	0.00
N-CM	1.46	1.46	0.00
CA-HA	1.09	1.11	0.02
CA-CB	1.54	1.56	0.02
CA-C	1.55	1.52	0.03
CB-HB1	1.09	1.11	0.01
CB-HB2	1.09	1.11	0.02
CB-HB3	1.09	1.11	0.02
CM-HM1	1.09	1.11	0.03
CM-HM2	1.10	1.11	0.02
CM-HM3	1.10	1.11	0.01
C-O	1.23	1.23	0.00
C-NR	1.36	1.35	0.02
NR-HR	1.01	0.99	0.02
NR-CR	1.45	1.45	0.01
CR-HR1	1.09	1.11	0.02
CR-HR2	1.10	1.11	0.02
CR-HR3	1.09	1.11	0.02
CL-CLP-OL	120.73	117.07	3.65
CL-CLP-N	117.50	120.15	2.65
HL1-CL-HL2	108.47	108.26	0.21
HL1-CL-HL3	107.30	109.66	2.36
HL1-CL-CLP	110.62	110.79	0.16
HL2-CL-HL3	109.59	108.29	1.30
HL2-CL-CLP	107.17	108.85	1.69
HL3-CL-CLP	113.60	110.91	2.69
CLP-N-CA	121.94	123.11	1.17
CLP-N-CM	117.44	118.40	0.97

Terms	QM	CHARMM	Abs. diff.
OL-CLP-N	121.76	122.77	1.01
N-CA-HA	108.28	109.35	1.08
N-CA-CB	113.63	114.64	1.02
N-CA-C	113.87	110.93	2.94
N-CM-HM1	107.03	111.45	4.42
N-CM-HM2	111.54	107.75	3.79
N-CM-HM3	112.11	108.30	3.81
CA-N-CM	120.62	118.22	2.40
CA-CB-HB1	112.49	112.04	0.45
CA-CB-HB2	110.90	109.98	0.92
CA-CB-HB3	108.30	110.15	1.85
CA-C-O	120.34	120.74	0.40
CA-C-NR	115.86	117.62	1.76
HA-CA-CB	106.89	105.33	1.56
HA-CA-C	103.72	106.10	2.38
CB-CA-C	109.73	109.99	0.25
HB1-CB-HB2	108.80	108.99	0.19
HB1-CB-HB3	107.97	107.94	0.02
HB2-CB-HB3	108.26	107.61	0.65
HM1-CM-HM2	109.17	109.53	0.37
HM1-CM-HM3	109.01	108.75	0.26
HM2-CM-HM3	107.93	111.06	3.12
C-NR-HR	117.39	119.36	1.97
C-NR-CR	121.84	122.30	0.46
O-C-NR	123.59	121.62	1.97
NR-CR-HR1	107.78	111.45	3.67
NR-CR-HR2	112.07	110.52	1.55
NR-CR-HR3	109.96	110.47	0.51
HR-NR-CR	117.88	118.15	0.26
HR1-CR-HR2	108.59	107.91	0.68
HR1-CR-HR3	109.50	107.97	1.53
HR2-CR-HR3	108.89	108.41	0.49

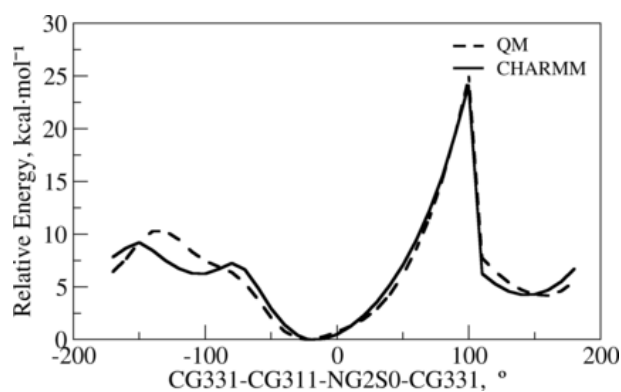


Figure S419: The PES scan for flexible dihedral corresponding to N,N-dimethylacetamide.

2.125 The small molecule used for bonded terms optimization of NZ-(1-carboxyethyl)-lysine (MCL)

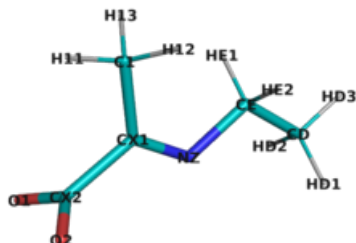


Figure S420: The energy minimized structure corresponding to (2E)-2-(ethylimino)propanoate.

Table S805: The calculated geometric terms of (2E)-2-(ethylimino)propanoate.

Terms	QM	CHARMM	Abs. diff.
HD3-CD	1.10	1.11	0.01
CD-HD1	1.09	1.11	0.02
CD-HD2	1.09	1.11	0.02
CD-CE	1.52	1.53	0.00
CE-HE1	1.10	1.12	0.01
CE-HE2	1.10	1.12	0.01
CE-NZ	1.46	1.45	0.01
NZ-CX1	1.29	1.31	0.01
CX1-C1	1.52	1.52	0.00
CX1-CX2	1.53	1.53	0.00
C1-H11	1.09	1.11	0.02
C1-H12	1.10	1.11	0.01
C1-H13	1.10	1.11	0.01
CX2-O1	1.26	1.27	0.01
CX2-O2	1.27	1.27	0.00
HD3-CD-HD1	108.79	109.01	0.22
HD3-CD-HD2	108.92	108.99	0.08
HD3-CD-CE	111.35	110.84	0.51
CD-CE-HE1	109.43	108.95	0.48
CD-CE-HE2	109.52	108.65	0.87
CD-CE-NZ	109.33	110.51	1.18
HD1-CD-HD2	107.83	108.13	0.31
HD1-CD-CE	109.95	109.91	0.04
HD2-CD-CE	109.93	109.91	0.02
CE-NZ-CX1	117.57	117.28	0.29
HE1-CE-HE2	106.74	109.40	2.66
HE1-CE-NZ	110.37	109.60	0.77
HE2-CE-NZ	111.41	109.71	1.69
NZ-CX1-C1	124.29	125.64	1.35
NZ-CX1-CX2	120.49	120.26	0.23
CX1-C1-H11	109.95	111.73	1.78
CX1-C1-H12	110.61	110.54	0.06
CX1-C1-H13	111.09	110.41	0.68

Terms	QM	CHARMM	Abs. diff.
CX1-CX2-O1	117.53	118.01	0.49
CX1-CX2-O2	111.99	116.74	4.75
C1-CX1-CX2	115.12	114.06	1.06
H11-C1-H12	107.88	107.47	0.41
H11-C1-H13	109.49	107.83	1.65
H12-C1-H13	107.75	108.75	1.00
O1-CX2-O2	130.41	125.24	5.17

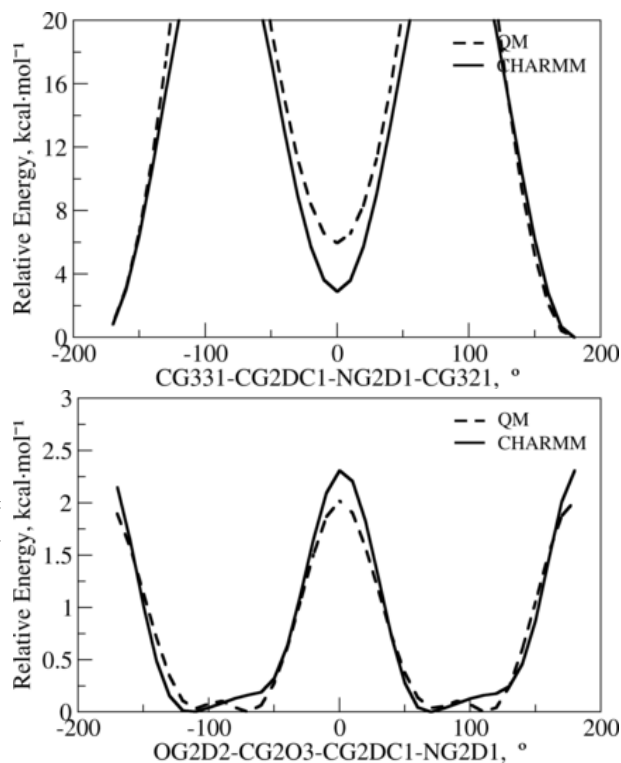
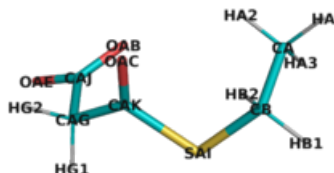


Figure S421: The PES scan for flexible dihedrals corresponding to (2E)-2-(ethylimino)propanoate.

2.126 The small molecule used for bonded terms optimization of malonylcysteine (MCS)



Terms	QM	CHARMM	Abs. diff.
OAC-CAK-CAG	125.26	124.49	0.77
CAG-CAJ-OAE	113.02	114.60	1.58
CAG-CAJ-OAB	115.75	117.07	1.31
HG1-CAG-HG2	109.26	108.75	0.52
HG1-CAG-CAJ	108.15	112.85	4.70
HG2-CAG-CAJ	107.94	104.73	3.22
OAE-CAJ-OAB	131.22	128.33	2.89

Figure S422: The energy minimized structure corresponding to 3-(ethylsulfanyl)-3-oxopropanoic acid.

Table S806: The calculated geometric terms of 3-(ethylsulfanyl)-3-oxopropanoic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.10	1.11	0.01
CA-CB	1.53	1.53	0.01
CB-HB1	1.10	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SAI	1.81	1.83	0.01
SAI-CAK	1.81	1.82	0.01
CAK-OAC	1.23	1.22	0.00
CAK-CAG	1.49	1.50	0.01
CAG-HG1	1.10	1.10	0.01
CAG-HG2	1.09	1.12	0.02
CAG-CAJ	1.59	1.50	0.10
CAJ-OAE	1.26	1.26	0.00
CAJ-OAB	1.26	1.25	0.01
HA3-CA-HA2	107.68	107.77	0.09
HA3-CA-HA	108.61	108.94	0.33
HA3-CA-CB	110.79	110.61	0.18
HA2-CA-HA	109.15	108.43	0.71
HA2-CA-CB	110.44	110.05	0.39
CA-CB-HB1	111.60	108.60	2.99
CA-CB-HB2	110.86	109.26	1.60
CA-CB-SAI	111.96	112.06	0.10
HA-CA-CB	110.11	110.95	0.84
CB-SAI-CAK	98.18	100.49	2.31
HB1-CB-HB2	108.50	106.88	1.62
HB1-CB-SAI	106.48	109.35	2.87
HB2-CB-SAI	107.22	110.53	3.31
SAI-CAK-OAC	121.03	121.50	0.47
SAI-CAK-CAG	113.68	113.99	0.31
CAK-CAG-HG1	111.60	113.14	1.54
CAK-CAG-HG2	109.06	106.56	2.49
CAK-CAG-CAJ	110.75	110.26	0.49

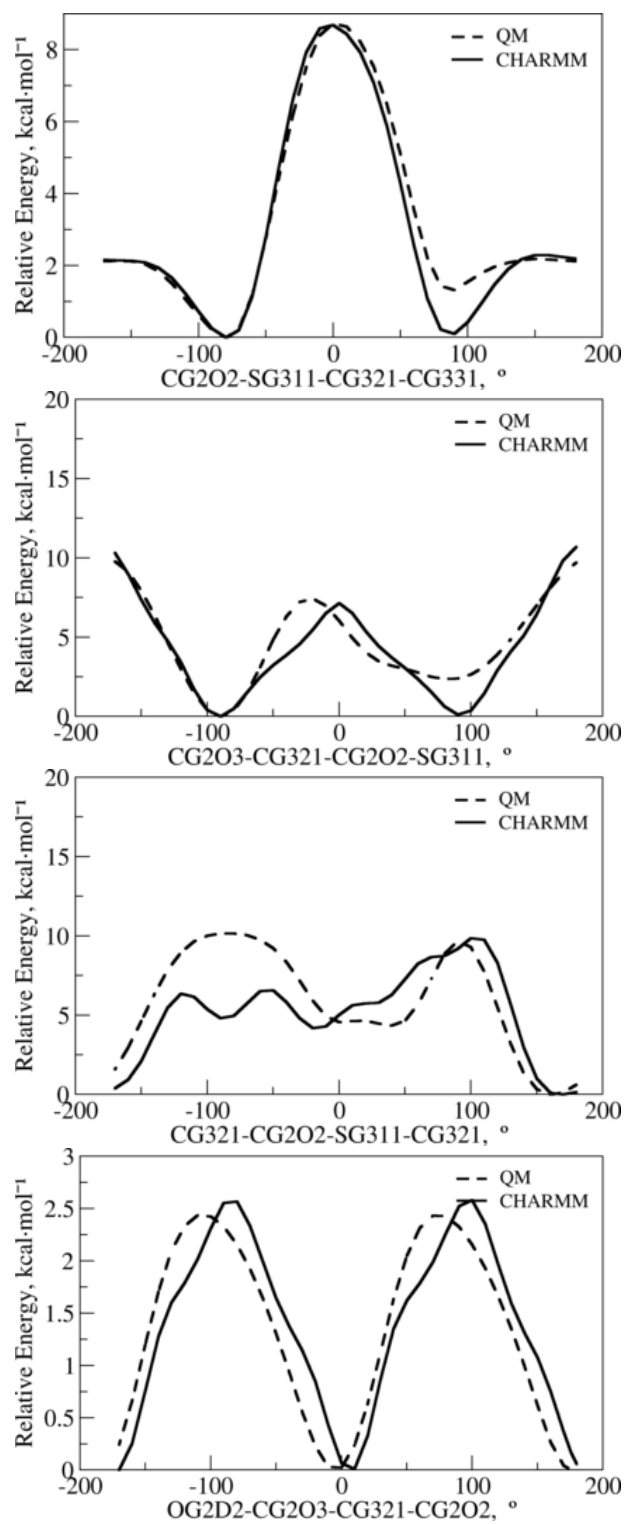


Figure S423: The PES scan for flexible dihedrals corresponding to 3-(ethylsulfanyl)-3-oxopropanoic acid.

2.127 The small molecule 1 used for bonded terms optimization of [2-((1S)-1-aminoethyl)-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl]acetic acid (MDO)

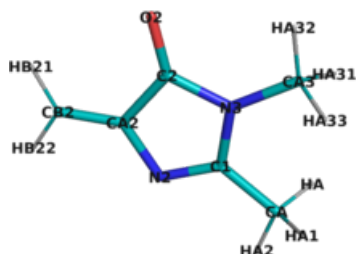


Figure S424: The energy minimized structure corresponding to 2,3-Dimethyl-5-methylideneimidazol-4-one.

Table S807: The calculated geometric terms of 2,3-Dimethyl-5-methylideneimidazol-4-one.

Terms	QM	CHARMM	Abs. diff.
HA1-CA	1.09	1.11	0.01
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.01
CA-C1	1.49	1.50	0.01
C1-N2	1.31	1.33	0.02
C1-N3	1.40	1.39	0.01
N2-CA2	1.41	1.41	0.00
N3-C2	1.40	1.38	0.02
N3-CA3	1.45	1.47	0.02
C2-O2	1.23	1.24	0.02
C2-CA2	1.50	1.50	0.00
CA2-CB2	1.34	1.34	0.00
CB2-HB21	1.09	1.10	0.01
CB2-HB22	1.08	1.10	0.01
CA3-HA31	1.09	1.11	0.02
CA3-HA32	1.09	1.11	0.02
CA3-HA33	1.09	1.11	0.02
HA1-CA-HA2	109.26	108.63	0.62
HA1-CA-HA	107.79	109.65	1.86
HA1-CA-C1	111.06	109.95	1.11
HA2-CA-HA	109.26	108.63	0.62
HA2-CA-C1	108.37	109.99	1.61
CA-C1-N2	124.55	121.64	2.91
CA-C1-N3	120.72	121.72	1.00
HA-CA-C1	111.06	109.95	1.11
C1-N2-CA2	104.86	102.67	2.19
C1-N3-C2	108.11	106.70	1.42
C1-N3-CA3	128.45	126.75	1.70
N2-C1-N3	114.73	116.64	1.91
N2-CA2-C2	109.96	110.00	0.03

Terms	QM	CHARMM	Abs. diff.
N2-CA2-CB2	125.79	125.84	0.05
N3-C2-O2	126.56	127.57	1.01
N3-C2-CA2	102.34	104.00	1.67
N3-CA3-HA31	111.17	110.98	0.19
N3-CA3-HA32	106.31	111.23	4.92
N3-CA3-HA33	111.17	110.98	0.19
C2-N3-CA3	123.44	126.55	3.11
C2-CA2-CB2	124.25	124.16	0.08
O2-C2-CA2	131.10	128.43	2.68
CA2-CB2-HB21	119.62	120.66	1.04
CA2-CB2-HB22	121.01	118.31	2.69
HB21-CB2-HB22	119.37	121.03	1.65
HA31-CA3-HA32	109.33	107.48	1.85
HA31-CA3-HA33	109.48	108.55	0.93
HA32-CA3-HA33	109.33	107.48	1.85

2.128 The small molecule 2 used for bonded terms optimization of [2-((1S)-1-aminoethyl)-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl]acetic acid (MDO)

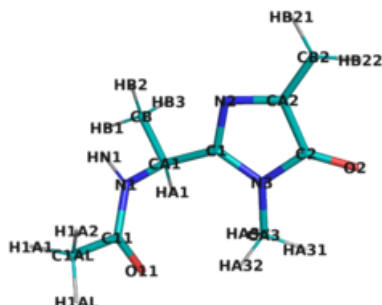


Figure S425: The energy minimized structure corresponding to N-[(1S)-1-(1-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-2-yl)ethyl]acetamide.

Table S808: The calculated geometric terms of N-[(1S)-1-(1-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-2-yl)ethyl]acetamide.

Terms	QM	CHARMM	Abs. diff.
C1AL-H1AL	1.09	1.11	0.02
C1AL-H1A1	1.09	1.11	0.02
C1AL-H1A2	1.09	1.11	0.02
C1AL-C11	1.51	1.48	0.03
C11-O11	1.24	1.22	0.02
C11-N1	1.37	1.33	0.04
N1-HN1	1.01	0.99	0.02
N1-CA1	1.46	1.44	0.02
CA1-HA1	1.09	1.12	0.02
CA1-CB	1.52	1.54	0.02
CA1-C1	1.50	1.53	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-HB3	1.09	1.11	0.02
C1-N2	1.31	1.34	0.03
C1-N3	1.39	1.40	0.01
N2-CA2	1.41	1.41	0.00
N3-C2	1.40	1.38	0.02
N3-CA3	1.45	1.47	0.02
C2-O2	1.23	1.24	0.02
C2-CA2	1.50	1.49	0.00
CA2-CB2	1.34	1.34	0.01
CB2-HB21	1.08	1.10	0.01
CB2-HB22	1.09	1.10	0.01
CA3-HA31	1.09	1.11	0.02
CA3-HA32	1.09	1.11	0.02
CA3-HA33	1.09	1.11	0.02
C1AL-C11-O11	122.15	121.34	0.81

Terms	QM	CHARMM	Abs. diff.
C1AL-C11-N1	115.08	116.31	1.23
H1AL-C1AL-H1A1	108.23	108.65	0.43
H1AL-C1AL-H1A2	109.61	108.73	0.88
H1AL-C1AL-C11	108.45	109.35	0.90
H1A1-C1AL-H1A2	108.57	109.56	0.98
H1A1-C1AL-C11	109.09	110.02	0.93
H1A2-C1AL-C11	112.79	110.49	2.30
C11-N1-HN1	119.22	120.44	1.22
C11-N1-CA1	122.23	124.52	2.30
O11-C11-N1	122.66	122.35	0.31
N1-CA1-HA1	105.68	110.28	4.61
N1-CA1-CB	110.68	108.74	1.94
N1-CA1-C1	108.52	108.66	0.14
HN1-N1-CA1	116.27	115.03	1.24
CA1-CB-HB1	109.66	110.10	0.45
CA1-CB-HB2	110.21	110.59	0.38
CA1-CB-HB3	110.25	110.57	0.32
CA1-C1-N2	121.97	121.03	0.94
CA1-C1-N3	122.62	122.39	0.22
HA1-CA1-CB	110.48	106.73	3.75
HA1-CA1-C1	110.16	109.96	0.19
CB-CA1-C1	111.17	112.45	1.28
HB1-CB-HB2	109.69	108.33	1.36
HB1-CB-HB3	109.08	108.69	0.39
HB2-CB-HB3	107.93	108.50	0.57
C1-N2-CA2	104.65	103.49	1.16
C1-N3-C2	107.70	106.84	0.86
C1-N3-CA3	128.94	127.71	1.23
N2-C1-N3	115.24	115.29	0.05
N2-CA2-C2	109.80	109.98	0.17
N2-CA2-CB2	125.92	125.85	0.07
N3-C2-O2	126.57	127.77	1.21
N3-C2-CA2	102.59	104.39	1.79
N3-CA3-HA31	106.30	111.36	5.06
N3-CA3-HA32	110.21	110.91	0.71
N3-CA3-HA33	110.89	111.58	0.69
C2-N3-CA3	123.28	125.45	2.16
C2-CA2-CB2	124.27	124.17	0.10
O2-C2-CA2	130.84	127.84	3.00
CA2-CB2-HB21	121.10	118.68	2.42
CA2-CB2-HB22	119.55	120.42	0.87
HB21-CB2-HB22	119.35	120.90	1.55
HA31-CA3-HA32	110.51	107.17	3.34
HA31-CA3-HA33	108.90	107.30	1.59
HA32-CA3-HA33	109.97	108.33	1.65

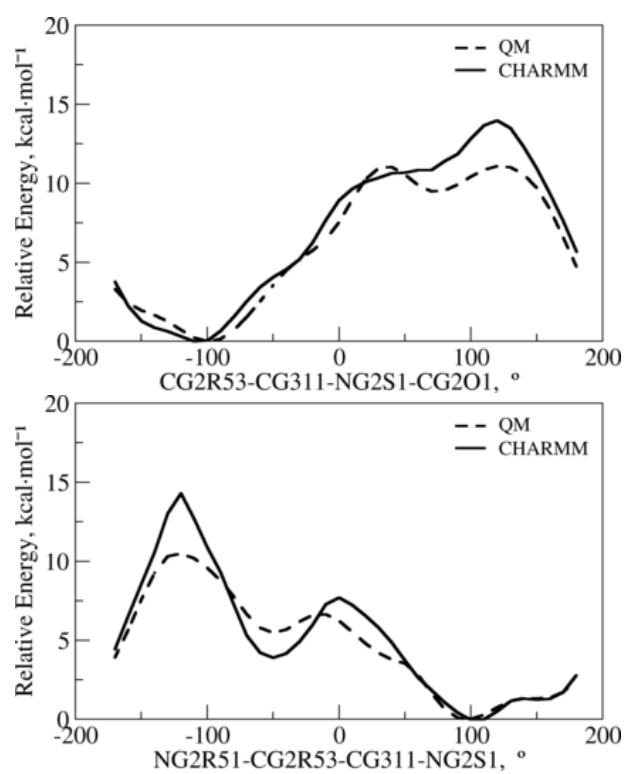


Figure S426: The PES scan for flexible dihedrals corresponding to N-[(1S)-1-(1-methyl-4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-2-yl)ethyl]acetamide.

2.129 The small molecule used for bonded terms optimization of hydroxy-l-methionine (ME0)

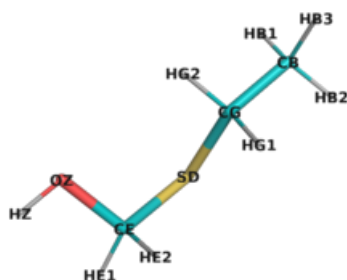


Figure S427: The energy minimized structure corresponding to (ethylsulfanyl)methanol.

Table S809: The calculated geometric terms of (ethylsulfanyl)methanol.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.52	1.53	0.01
CG-HG1	1.10	1.11	0.02
CG-HG2	1.09	1.11	0.02
CG-SD	1.82	1.82	0.00
SD-CE	1.79	1.82	0.02
CE-HE1	1.10	1.11	0.02
CE-HE2	1.10	1.11	0.01
CE-OZ	1.43	1.42	0.00
OZ-HZ	0.97	0.96	0.01
HB3-CB-HB1	108.20	108.48	0.27
HB3-CB-HB2	108.12	108.60	0.48
HB3-CB-CG	109.97	110.63	0.66
CB-CG-HG1	110.36	108.88	1.48
CB-CG-HG2	110.85	108.83	2.02
CB-CG-SD	109.87	112.54	2.67
HB1-CB-HB2	108.29	108.27	0.01
HB1-CB-CG	110.93	110.31	0.62
HB2-CB-CG	111.23	110.48	0.74
CG-SD-CE	98.60	97.36	1.24
HG1-CG-HG2	108.47	107.06	1.41
HG1-CG-SD	109.16	109.84	0.68
HG2-CG-SD	108.07	109.52	1.46
SD-CE-HE1	106.32	109.50	3.18
SD-CE-HE2	109.73	110.55	0.82
SD-CE-OZ	109.43	110.77	1.34
CE-OZ-HZ	107.15	107.46	0.31
HE1-CE-HE2	108.66	107.91	0.75
HE1-CE-OZ	111.73	108.66	3.07
HE2-CE-OZ	110.86	109.39	1.47

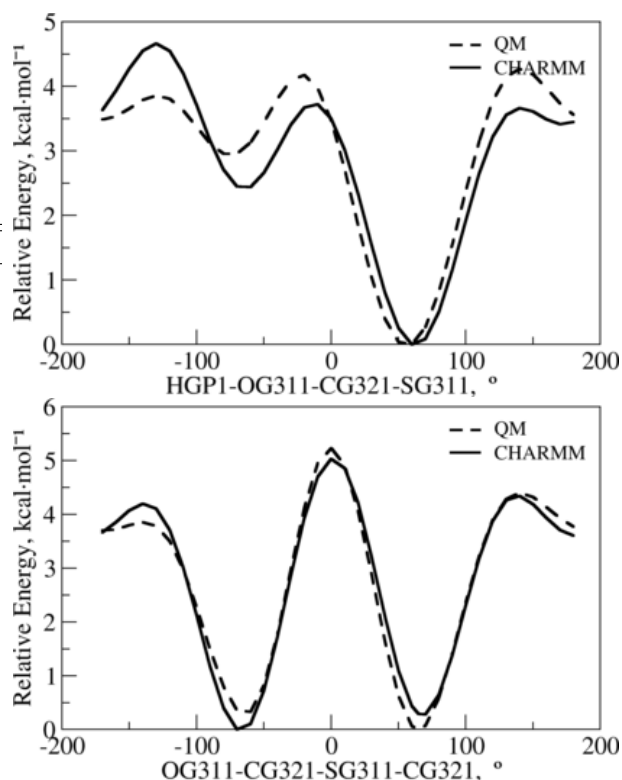
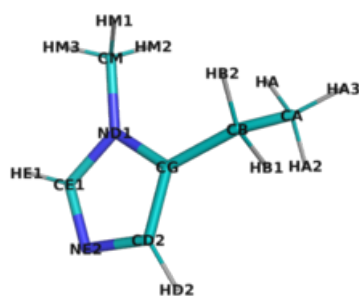


Figure S428: The PES scan for flexible dihedrals corresponding to (ethylsulfanyl)methanol.

2.130 The small molecule used for bonded terms optimization of N1-methylatedhistidine (MHS)



Terms	QM	CHARMM	Abs. diff.
CG-ND1-CE1	107.16	106.04	1.12
CG-CD2-HD2	127.11	129.44	2.33
CG-CD2-NE2	111.67	110.94	0.73
ND1-CG-CD2	104.47	105.90	1.43
ND1-CM-HM1	110.61	110.32	0.29
ND1-CM-HM2	110.90	110.04	0.86
ND1-CM-HM3	108.24	111.64	3.39
ND1-CE1-HE1	121.79	122.49	0.69
ND1-CE1-NE2	112.30	112.63	0.34
CM-ND1-CE1	125.82	126.84	1.02
HM1-CM-HM2	109.29	108.42	0.86
HM1-CM-HM3	108.85	108.09	0.76
HM2-CM-HM3	108.91	108.23	0.67
CD2-NE2-CE1	104.40	104.49	0.09
HD2-CD2-NE2	121.22	119.62	1.60
HE1-CE1-NE2	125.91	124.88	1.03

Figure S429: The energy minimized structure corresponding to 5-ethyl-1-methyl-1H-imidazole.

Table S810: The calculated geometric terms of 5-ethyl-1-methyl-1H-imidazole.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.53	0.00
CB-HB1	1.10	1.12	0.02
CB-HB2	1.10	1.11	0.01
CB-CG	1.49	1.51	0.02
CG-ND1	1.38	1.38	0.00
CG-CD2	1.38	1.37	0.02
ND1-CM	1.45	1.46	0.01
ND1-CE1	1.37	1.37	0.00
CM-HM1	1.09	1.11	0.02
CM-HM2	1.09	1.11	0.02
CM-HM3	1.09	1.11	0.02
CD2-HD2	1.08	1.08	0.00
CD2-NE2	1.37	1.38	0.01
CE1-HE1	1.08	1.09	0.01
CE1-NE2	1.33	1.32	0.01
HA3-CA-HA2	108.51	108.29	0.22
HA3-CA-HA	108.00	108.37	0.36
HA3-CA-CB	110.96	110.39	0.57
HA2-CA-HA	107.79	108.28	0.50
HA2-CA-CB	110.06	110.42	0.36
CA-CB-HB1	109.35	108.54	0.82
CA-CB-HB2	109.96	109.80	0.16
CA-CB-CG	113.37	113.34	0.04
HA-CA-CB	111.40	111.00	0.40
CB-CG-ND1	123.68	125.19	1.51
CB-CG-CD2	131.75	128.80	2.95
HB1-CB-HB2	106.03	106.65	0.63
HB1-CB-CG	107.50	108.89	1.40
HB2-CB-CG	110.33	109.39	0.95
CG-ND1-CM	126.93	127.11	0.18

2.131 The small molecule used for bonded terms optimization of N1-methylatedhistidine (MHSP)

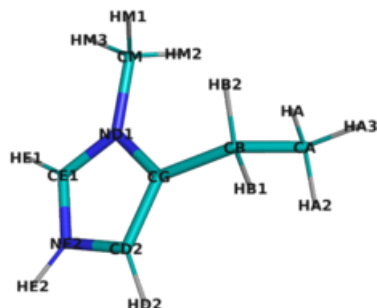


Figure S430: The energy minimized structure corresponding to 5-ethyl-1-methyl-2,3-dihydro-1H-imidazole.

Terms	QM	CHARMM	Abs. diff.
HB2-CB-CG	109.54	109.47	0.07
CG-ND1-CM	125.72	125.70	0.02
CG-ND1-CE1	109.91	108.75	1.16
CG-CD2-HD2	130.49	128.31	2.18
CG-CD2-NE2	107.16	107.19	0.03
ND1-CG-CD2	105.81	106.67	0.86
ND1-CM-HM1	109.29	109.54	0.25
ND1-CM-HM2	109.35	109.46	0.11
ND1-CM-HM3	108.39	110.94	2.55
ND1-CE1-HE1	126.30	125.41	0.88
ND1-CE1-NE2	107.29	108.66	1.37
CM-ND1-CE1	124.33	125.54	1.21
HM1-CM-HM2	110.43	109.35	1.08
HM1-CM-HM3	109.69	108.76	0.93
HM2-CM-HM3	109.66	108.77	0.89
CD2-NE2-CE1	109.84	108.73	1.11
CD2-NE2-HE2	125.72	125.08	0.64
HD2-CD2-NE2	122.36	124.50	2.14
CE1-NE2-HE2	124.44	126.19	1.74
HE1-CE1-NE2	126.41	125.92	0.49

Table S811: The calculated geometric terms of 5-ethyl-1-methyl-2,3-dihydro-1H-imidazole.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.54	0.00
CB-HB1	1.09	1.11	0.02
CB-HB2	1.10	1.11	0.02
CB-CG	1.49	1.52	0.03
CG-ND1	1.39	1.38	0.01
CG-CD2	1.38	1.36	0.02
ND1-CM	1.47	1.48	0.01
ND1-CE1	1.34	1.33	0.01
CM-HM1	1.09	1.11	0.02
CM-HM2	1.09	1.11	0.02
CM-HM3	1.09	1.11	0.02
CD2-HD2	1.08	1.09	0.01
CD2-NE2	1.37	1.37	0.00
CE1-HE1	1.08	1.08	0.00
CE1-NE2	1.34	1.33	0.02
NE2-HE2	1.02	1.00	0.01
HA3-CA-HA2	108.27	107.77	0.50
HA3-CA-HA	107.87	107.89	0.02
HA3-CA-CB	109.85	110.19	0.34
HA2-CA-HA	108.16	108.31	0.15
HA2-CA-CB	110.63	110.95	0.32
CA-CB-HB1	109.85	107.87	1.98
CA-CB-HB2	110.75	109.54	1.21
CA-CB-CG	112.90	115.17	2.27
HA-CA-CB	111.95	111.59	0.35
CB-CG-ND1	123.80	124.73	0.92
CB-CG-CD2	130.31	128.58	1.74
HB1-CB-HB2	106.13	105.90	0.24
HB1-CB-CG	107.39	108.47	1.09

2.132 The small molecule used for bonded terms optimization of N1-phosphohistidine (NEP)

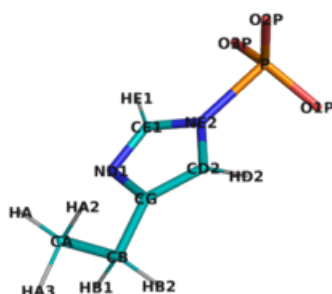


Figure S431: The energy minimized structure corresponding to (4-ethyl-1H-imidazol-1-yl)phosphonic acid.

Table S812: The calculated geometric terms of (4-ethyl-1H-imidazol-1-yl)phosphonic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.10	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.54	0.01
CB-HB1	1.10	1.11	0.01
CB-HB2	1.10	1.11	0.01
CB-CG	1.50	1.51	0.01
CG-ND1	1.38	1.39	0.00
CG-CD2	1.39	1.36	0.03
ND1-CE1	1.35	1.33	0.02
CD2-HD2	1.08	1.08	0.01
CD2-NE2	1.37	1.38	0.01
CE1-HE1	1.08	1.09	0.01
CE1-NE2	1.35	1.35	0.01
NE2-P	1.94	1.96	0.02
P-O1P	1.54	1.52	0.02
P-O2P	1.54	1.52	0.02
P-O3P	1.54	1.52	0.02
HA3-CA-HA2	108.64	109.24	0.61
HA3-CA-HA	108.95	109.06	0.11
HA3-CA-CB	111.96	110.83	1.13
HA2-CA-HA	107.82	108.04	0.22
HA2-CA-CB	109.95	110.13	0.18
CA-CB-HB1	108.72	109.41	0.69
CA-CB-HB2	109.79	109.28	0.52
CA-CB-CG	112.47	114.65	2.18
HA-CA-CB	109.42	109.48	0.06
CB-CG-ND1	121.26	118.89	2.36
CB-CG-CD2	129.08	130.43	1.35
HB1-CB-HB2	106.89	107.57	0.69
HB1-CB-CG	110.11	107.47	2.64
HB2-CB-CG	108.71	108.22	0.49

Terms	QM	CHARMM	Abs. diff.
CG-ND1-CE1	103.60	104.04	0.44
CG-CD2-HD2	132.16	131.81	0.35
CG-CD2-NE2	107.44	105.80	1.64
ND1-CG-CD2	109.64	110.68	1.04
ND1-CE1-HE1	125.27	127.47	2.20
ND1-CE1-NE2	113.79	112.46	1.33
CD2-NE2-CE1	105.53	107.02	1.49
CD2-NE2-P	126.62	126.29	0.33
HD2-CD2-NE2	120.38	122.39	2.01
CE1-NE2-P	127.71	126.67	1.04
HE1-CE1-NE2	120.92	120.06	0.86
NE2-P-O1P	99.22	99.21	0.01
NE2-P-O2P	100.74	99.36	1.38
NE2-P-O3P	99.02	97.91	1.11
O1P-P-O2P	116.77	117.05	0.29
O1P-P-O3P	117.83	117.79	0.04
O2P-P-O3P	117.14	118.23	1.09

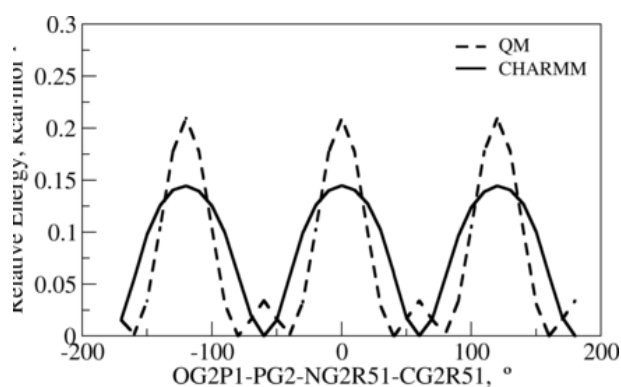
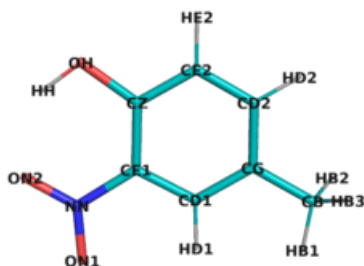


Figure S432: The PES scan for flexible dihedral corresponding to (4-ethyl-1H-imidazol-1-yl)phosphonic acid.

2.133 The small molecule used for bonded terms optimization of meta-nitro-tyrosine (NIY)



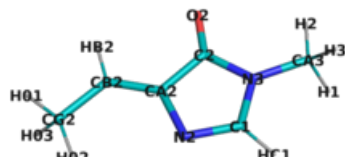
Terms	QM	CHARMM	Abs. diff.
CD2-CE2-HE2	121.53	119.64	1.89
CD2-CE2-CZ	121.19	120.60	0.59
HD2-CD2-CE2	119.08	120.17	1.09
CE1-NN-ON1	118.89	117.63	1.26
CE1-NN-ON2	118.38	117.75	0.63
CE1-CZ-CE2	117.06	120.84	3.78
CE1-CZ-OH	125.90	124.73	1.17
NN-CE1-CZ	120.94	123.38	2.45
ON1-NN-ON2	122.73	124.62	1.89
CE2-CZ-OH	117.04	114.43	2.61
HE2-CE2-CZ	117.28	119.76	2.48
CZ-OH-HH	106.66	107.70	1.04

Figure S433: The energy minimized structure corresponding to 4-methyl-2-nitrobenzen-1-olate.

Table S813: The calculated geometric terms of 4-methyl-2-nitrobenzen-1-olate.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.51	1.50	0.01
CG-CD1	1.39	1.40	0.01
CG-CD2	1.41	1.40	0.01
CD1-HD1	1.09	1.08	0.00
CD1-CE1	1.40	1.42	0.02
CD2-HD2	1.09	1.08	0.01
CD2-CE2	1.39	1.40	0.01
CE1-NN	1.46	1.47	0.02
CE1-CZ	1.41	1.43	0.03
NN-ON1	1.24	1.23	0.01
NN-ON2	1.26	1.23	0.03
CE2-HE2	1.09	1.08	0.00
CE2-CZ	1.40	1.40	0.01
CZ-OH	1.35	1.42	0.07
OH-HH	0.99	0.97	0.02
HB3-CB-HB1	108.05	109.22	1.17
HB3-CB-HB2	107.60	109.91	2.31
HB3-CB-CG	111.01	109.07	1.94
CB-CG-CD1	121.28	120.24	1.04
CB-CG-CD2	120.66	120.01	0.65
HB1-CB-HB2	108.05	109.18	1.14
HB1-CB-CG	110.99	110.37	0.62
HB2-CB-CG	111.01	109.07	1.93
CG-CD1-HD1	121.16	118.56	2.60
CG-CD1-CE1	120.54	122.01	1.47
CG-CD2-HD2	119.46	119.74	0.28
CG-CD2-CE2	121.46	120.10	1.37
CD1-CG-CD2	118.05	119.74	1.69
CD1-CE1-NN	117.37	119.90	2.53
CD1-CE1-CZ	121.69	116.71	4.98
HD1-CD1-CE1	118.30	119.44	1.13

2.134 The small molecule 1 used for bonded terms optimization of (4Z)-4-(4-hydroxybenzylidene)-2-[3-(methylthio)propanimidoyl]-5-oxo-4acetic5-dihydro-1H-imidazol-1-ylaceticacid (NRQ)



Terms	QM	CHARMM	Abs. diff.
N3-C2-CA2	102.30	104.02	1.71
N3-CA3-H1	110.97	110.66	0.31
N3-CA3-H2	106.44	111.64	5.20
N3-CA3-H3	110.97	110.66	0.31
C2-N3-CA3	124.10	127.30	3.20
C2-CA2-CB2	124.04	123.81	0.23
O2-C2-CA2	131.39	127.30	4.09
CA2-CB2-HB2	116.47	116.77	0.30
CA2-CB2-CG2	124.42	124.84	0.42
CB2-CG2-H01	110.45	111.12	0.67
CB2-CG2-H02	110.63	112.88	2.26
CB2-CG2-H03	110.45	111.10	0.65
HB2-CB2-CG2	119.11	118.39	0.72
H01-CG2-H02	109.17	107.05	2.13
H01-CG2-H03	106.88	107.38	0.51
H02-CG2-H03	109.18	107.03	2.14
H1-CA3-H2	109.38	107.76	1.61
H1-CA3-H3	109.63	108.15	1.48
H2-CA3-H3	109.38	107.82	1.55

Figure S434: The energy minimized structure corresponding to N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide.

Table S814: The calculated geometric terms of N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide.

Terms	QM	CHARMM	Abs. diff.
C1-HC1	1.09	1.09	0.01
C1-N2	1.30	1.33	0.03
C1-N3	1.39	1.39	0.00
N2-CA2	1.41	1.42	0.00
N3-C2	1.40	1.38	0.02
N3-CA3	1.45	1.47	0.02
C2-O2	1.23	1.24	0.02
C2-CA2	1.49	1.48	0.01
CA2-CB2	1.35	1.35	0.00
CB2-HB2	1.09	1.10	0.01
CB2-CG2	1.49	1.52	0.03
CG2-H01	1.10	1.11	0.02
CG2-H02	1.09	1.11	0.02
CG2-H03	1.10	1.11	0.02
CA3-H1	1.09	1.11	0.02
CA3-H2	1.09	1.11	0.02
CA3-H3	1.09	1.11	0.02
C1-N2-CA2	104.00	102.76	1.24
C1-N3-C2	107.62	107.07	0.56
C1-N3-CA3	128.27	125.63	2.64
HC1-C1-N2	123.98	123.47	0.51
HC1-C1-N3	120.20	120.67	0.47
N2-C1-N3	115.82	115.86	0.04
N2-CA2-C2	110.25	110.29	0.05
N2-CA2-CB2	125.72	125.90	0.18
N3-C2-O2	126.30	128.68	2.38

2.135 The small molecule 2 used for bonded terms optimization of (4Z)-4-(4-hydroxybenzylidene)-2-[3-(methylthio)propanimidoyl]-5-oxo-4acetic5-dihydro-1H-imidazol-1-ylaceticacid (NRQ)

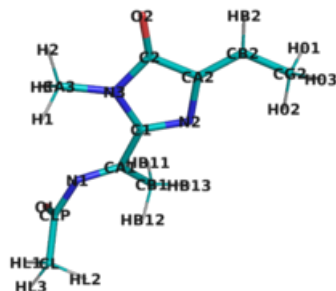


Figure S435: The energy minimized structure corresponding to N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide.

Table S815: The calculated geometric terms of N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide.

Terms	QM	CHARMM	Abs. diff.
CL-HL1	1.09	1.11	0.02
CL-HL2	1.09	1.11	0.02
CL-HL3	1.09	1.11	0.02
CL-CLP	1.51	1.48	0.02
CLP-OL	1.22	1.22	0.00
CLP-N1	1.42	1.42	0.01
N1-CA1	1.29	1.28	0.01
CA1-CB1	1.50	1.52	0.01
CA1-C1	1.47	1.47	0.00
CB1-HB11	1.09	1.11	0.02
CB1-HB12	1.09	1.11	0.02
CB1-HB13	1.09	1.11	0.02
C1-N2	1.32	1.35	0.03
C1-N3	1.39	1.43	0.04
N2-CA2	1.40	1.41	0.01
N3-C2	1.40	1.38	0.02
N3-CA3	1.46	1.47	0.02
C2-O2	1.23	1.24	0.01
C2-CA2	1.49	1.46	0.02
CA2-CB2	1.35	1.35	0.00
CB2-HB2	1.09	1.10	0.01
CB2-CG2	1.49	1.51	0.03
CG2-H01	1.10	1.11	0.02
CG2-H02	1.09	1.11	0.02
CG2-H03	1.10	1.11	0.02
CA3-H1	1.09	1.11	0.02

Terms	QM	CHARMM	Abs. diff.
CA3-H2	1.09	1.11	0.02
CA3-H3	1.09	1.11	0.02
CL-CLP-OL	124.52	123.60	0.92
CL-CLP-N1	113.17	113.51	0.34
HL1-CL-HL2	107.47	109.30	1.83
HL1-CL-HL3	110.06	108.56	1.50
HL1-CL-CLP	109.67	110.33	0.66
HL2-CL-HL3	110.18	108.82	1.35
HL2-CL-CLP	110.13	110.69	0.56
HL3-CL-CLP	109.32	109.10	0.22
CLP-N1-CA1	120.49	120.95	0.46
OL-CLP-N1	122.09	122.54	0.44
N1-CA1-CB1	126.83	129.04	2.21
N1-CA1-C1	117.41	114.77	2.64
CA1-CB1-HB11	109.37	110.04	0.68
CA1-CB1-HB12	111.32	111.89	0.57
CA1-CB1-HB13	109.65	113.34	3.69
CA1-C1-N2	120.81	120.26	0.55
CA1-C1-N3	124.32	127.02	2.70
CB1-CA1-C1	115.76	116.17	0.41
HB11-CB1-HB12	108.49	107.28	1.21
HB11-CB1-HB13	107.16	107.74	0.59
HB12-CB1-HB13	110.75	106.25	4.50
C1-N2-CA2	104.78	105.25	0.47
C1-N3-C2	107.43	107.71	0.28
C1-N3-CA3	130.84	128.87	1.97
N2-C1-N3	114.86	112.08	2.78
N2-CA2-C2	110.07	109.96	0.10
N2-CA2-CB2	125.69	125.79	0.10
N3-C2-O2	126.33	128.22	1.89
N3-C2-CA2	102.86	104.96	2.11
N3-CA3-H1	110.94	110.67	0.26
N3-CA3-H2	105.52	111.72	6.21
N3-CA3-H3	110.70	111.07	0.37
C2-N3-CA3	121.64	123.42	1.78
C2-CA2-CB2	124.25	124.25	0.00
O2-C2-CA2	130.81	126.81	4.00
CA2-CB2-HB2	116.42	117.24	0.81
CA2-CB2-CG2	124.45	124.09	0.35
CB2-CG2-H01	110.40	110.92	0.52
CB2-CG2-H02	110.73	112.86	2.13
CB2-CG2-H03	110.42	110.89	0.47
HB2-CB2-CG2	119.13	118.67	0.46
H01-CG2-H02	109.18	107.11	2.07
H01-CG2-H03	106.82	107.69	0.87
H02-CG2-H03	109.19	107.12	2.07
H1-CA3-H2	110.30	107.50	2.79
H1-CA3-H3	109.08	108.16	0.91
H2-CA3-H3	110.28	107.54	2.74

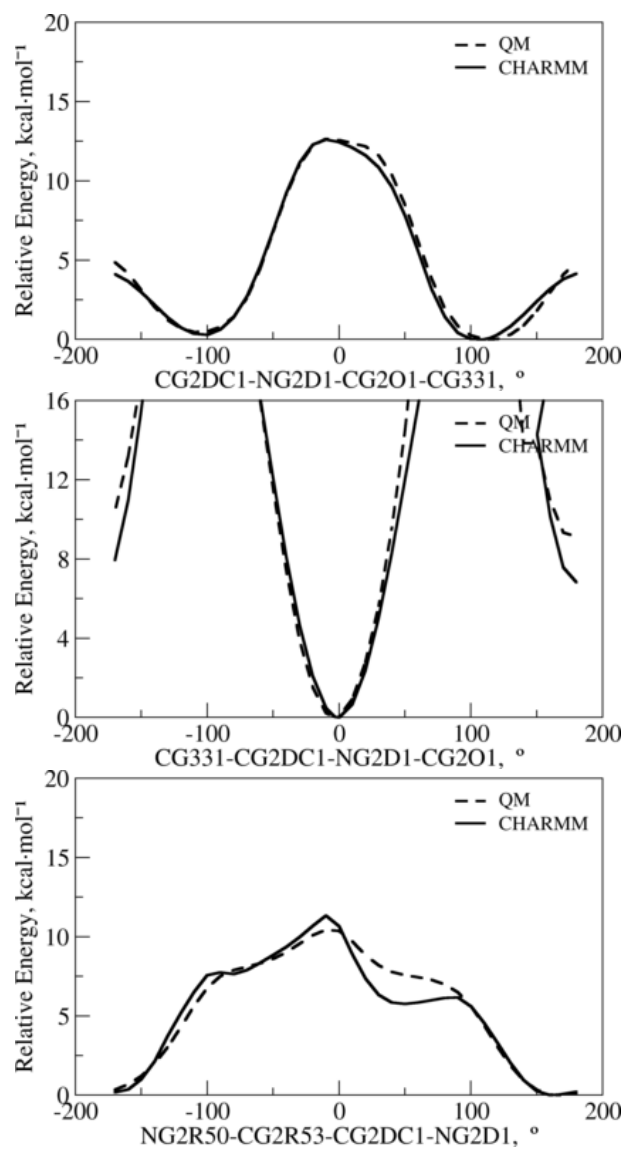


Figure S436: The PES scan for flexible dihedrals corresponding to N-[(1E)-1-[(4Z)-4-ethylidene-1-methyl-5-oxo-4,5-dihydro-1H-imidazol-2-yl]ethylidene]acetamide.

2.136 The small molecule 3 used for bonded terms optimization of (4Z)-4-(4-hydroxybenzylidene)-2-[3-(methylthio)propanimidoyl]-5-oxo-4acetic5-dihydro-1H-imidazol-1-ylaceticacid (NRQ)

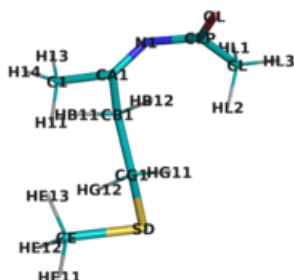


Figure S437: The energy minimized structure corresponding to N-[(2Z)-4-(methylsulfanyl)butan-2-ylidene]acetamide.

Table S816: The calculated geometric terms of N-[(2Z)-4-(methylsulfanyl)butan-2-ylidene]acetamide.

Terms	QM	CHARMM	Abs. diff.
CL-HL1	1.09	1.11	0.02
CL-HL2	1.09	1.11	0.02
CL-HL3	1.09	1.11	0.02
CL-CLP	1.51	1.49	0.02
CLP-OL	1.23	1.22	0.00
CLP-N1	1.41	1.42	0.01
N1-CA1	1.29	1.27	0.01
CA1-CB1	1.51	1.51	0.00
CA1-C1	1.50	1.50	0.00
CB1-HB11	1.09	1.11	0.01
CB1-HB12	1.09	1.11	0.02
CB1-CG1	1.53	1.55	0.02
CG1-HG11	1.09	1.11	0.02
CG1-HG12	1.10	1.11	0.02
CG1-SD	1.81	1.82	0.01
SD-CE	1.81	1.82	0.01
CE-HE11	1.09	1.11	0.02
CE-HE12	1.09	1.11	0.02
CE-HE13	1.09	1.11	0.02
C1-H11	1.10	1.11	0.01
C1-H13	1.09	1.11	0.02
C1-H14	1.10	1.11	0.02
CL-CLP-OL	123.61	123.41	0.20
CL-CLP-N1	113.15	113.38	0.23
HL1-CL-HL2	107.37	109.24	1.87
HL1-CL-HL3	109.61	108.68	0.93
HL1-CL-CLP	109.05	110.28	1.23

Terms	QM	CHARMM	Abs. diff.
HL2-CL-HL3	110.50	108.77	1.73
HL2-CL-CLP	110.97	110.70	0.26
HL3-CL-CLP	109.30	109.12	0.18
CLP-N1-CA1	121.95	121.55	0.40
OL-CLP-N1	122.84	122.91	0.07
N1-CA1-CB1	124.64	129.87	5.22
N1-CA1-C1	118.32	123.99	5.68
CA1-CB1-HB11	108.79	109.28	0.49
CA1-CB1-HB12	110.18	110.12	0.07
CA1-CB1-CG1	110.32	115.04	4.72
CA1-C1-H11	110.78	111.52	0.73
CA1-C1-H13	110.15	110.99	0.84
CA1-C1-H14	109.76	111.31	1.54
CB1-CA1-C1	117.00	106.14	10.85
CB1-CG1-HG11	109.58	108.13	1.45
CB1-CG1-HG12	111.04	109.80	1.24
CB1-CG1-SD	114.17	114.40	0.23
HB11-CB1-HB12	107.73	105.43	2.30
HB11-CB1-CG1	110.06	109.72	0.34
HB12-CB1-CG1	109.71	106.80	2.91
CG1-SD-CE	99.68	97.61	2.07
HG11-CG1-HG12	107.23	106.76	0.47
HG11-CG1-SD	105.41	108.25	2.84
HG12-CG1-SD	109.04	109.21	0.17
SD-CE-HE11	107.02	110.60	3.57
SD-CE-HE12	111.03	111.18	0.15
SD-CE-HE13	112.28	111.53	0.75
HE11-CE-HE12	108.43	107.71	0.71
HE11-CE-HE13	108.23	107.45	0.79
HE12-CE-HE13	109.70	108.22	1.48
H11-C1-H13	109.59	107.26	2.33
H11-C1-H14	107.12	108.34	1.22
H13-C1-H14	109.37	107.22	2.15

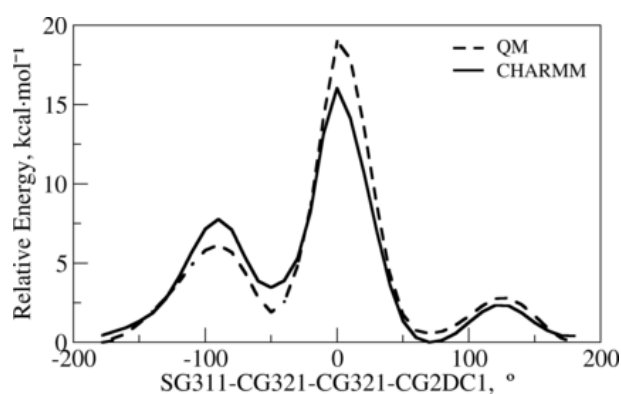


Figure S438: The PES scan for flexible dihedral corresponding to N-[(2Z)-4-(methylsulfanyl)butan-2-ylidene]acetamide.

2.137 The small molecule used for bonded terms optimization of o-acetylserine (OAS)

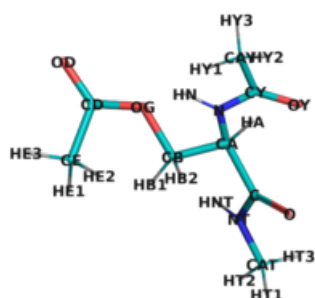


Figure S439: The energy minimized structure corresponding to (2S)-2-acetamido-2-(methylcarbamoyl)ethylacetate.

Table S817: The calculated geometric terms of (2S)-2-acetamido-2-(methylcarbamoyl)ethylacetate.

Terms	QM	CHARMM	Abs. diff.
N-HN	1.02	1.00	0.02
N-CA	1.46	1.46	0.01
N-CY	1.38	1.34	0.04
CA-HA	1.10	1.08	0.01
CA-CB	1.52	1.55	0.04
CA-C	1.53	1.52	0.01
CB-HB1	1.10	1.11	0.02
CB-HB2	1.09	1.12	0.02
CB-OG	1.44	1.44	0.00
OG-CD	1.38	1.34	0.04
CD-OD	1.21	1.22	0.00
CD-CE	1.51	1.51	0.00
CE-HE3	1.09	1.11	0.02
CE-HE1	1.09	1.11	0.01
CE-HE2	1.09	1.11	0.01
C-O	1.23	1.23	0.00
C-NT	1.37	1.35	0.02
NT-HNT	1.01	0.99	0.02
NT-CAT	1.46	1.44	0.01
CAT-HT1	1.09	1.11	0.02
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.10	1.11	0.02
CAY-HY1	1.09	1.11	0.02
CAY-HY2	1.09	1.11	0.02
CAY-HY3	1.09	1.11	0.02
CAY-CY	1.51	1.48	0.03
CY-OY	1.23	1.22	0.01
N-CA-HA	111.15	106.75	4.40
N-CA-CB	109.01	112.06	3.05
N-CA-C	112.80	116.10	3.30
N-CY-CAY	115.00	116.37	1.37
N-CY-OY	121.41	122.59	1.18

Terms	QM	CHARMM	Abs. diff.
HN-N-CA	114.30	114.90	0.59
HN-N-CY	117.10	118.18	1.08
CA-N-CY	118.36	124.77	6.41
CA-CB-HB1	110.15	109.57	0.58
CA-CB-HB2	108.95	107.88	1.07
CA-CB-OG	105.93	108.07	2.15
CA-C-O	120.94	120.78	0.16
CA-C-NT	114.21	117.52	3.31
HA-CA-CB	109.47	107.83	1.64
HA-CA-C	105.72	106.10	0.37
CB-CA-C	108.59	107.56	1.02
CB-OG-CD	120.77	121.99	1.22
HB1-CB-HB2	109.70	109.93	0.24
HB1-CB-OG	110.29	110.06	0.23
HB2-CB-OG	111.75	111.26	0.49
OG-CD-OD	118.13	123.77	5.64
OG-CD-CE	117.42	114.23	3.19
CD-CE-HE3	107.74	107.50	0.24
CD-CE-HE1	111.58	110.98	0.59
CD-CE-HE2	110.70	110.66	0.05
OD-CD-CE	124.44	122.00	2.43
HE3-CE-HE1	109.56	108.16	1.40
HE3-CE-HE2	109.32	108.00	1.32
HE1-CE-HE2	107.93	111.38	3.46
C-NT-HNT	114.87	119.25	4.37
C-NT-CAT	118.81	121.78	2.97
O-C-NT	124.05	121.60	2.45
NT-CAT-HT1	108.40	111.31	2.91
NT-CAT-HT2	108.89	110.65	1.76
NT-CAT-HT3	111.80	110.24	1.57
HNT-NT-CAT	117.36	117.87	0.51
HT1-CAT-HT2	109.52	108.20	1.32
HT1-CAT-HT3	108.54	108.08	0.47
HT2-CAT-HT3	109.65	108.27	1.38
CAY-CY-OY	123.58	121.04	2.55
HY1-CAY-HY2	109.93	108.78	1.15
HY1-CAY-HY3	108.24	109.44	1.20
HY1-CAY-CY	111.65	110.62	1.02
HY2-CAY-HY3	108.68	108.54	0.14
HY2-CAY-CY	108.71	109.35	0.64
HY3-CAY-CY	109.58	110.07	0.49

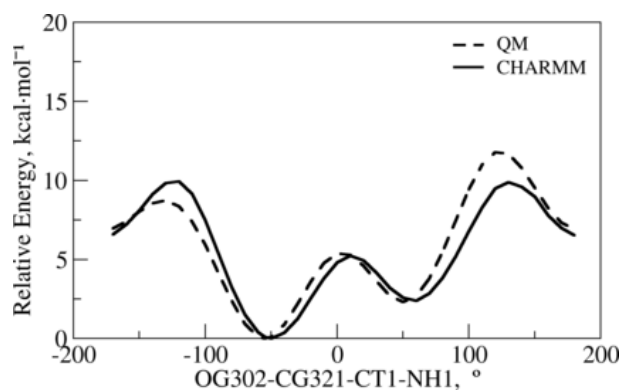


Figure S440: The PES scan for flexible dihedral corresponding to (2S)-2-acetamido-2-(methylcarbamoyl)ethylacetate.

2.138 The small molecule 1 used for bonded terms optimization of (2s)-2-amino-4,4-difluorobutanoic acid (OBF)

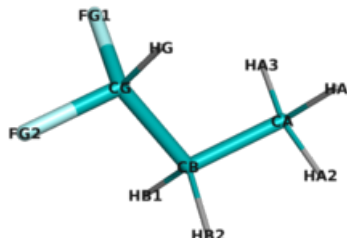


Figure S441: The energy minimized structure corresponding to 1,1-difluoropropane.

Table S818: The calculated geometric terms of 1,1-difluoropropane.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.54	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.50	1.53	0.02
CG-HG	1.09	1.08	0.01
CG-FG1	1.38	1.35	0.03
CG-FG2	1.37	1.35	0.02
HA3-CA-HA2	108.40	108.13	0.27
HA3-CA-HA	108.20	108.38	0.18
HA3-CA-CB	110.52	110.63	0.10
HA2-CA-HA	107.82	108.24	0.43
HA2-CA-CB	110.61	110.42	0.19
CA-CB-HB1	111.14	109.35	1.79
CA-CB-HB2	111.20	109.45	1.74
CA-CB-CG	112.21	112.49	0.28
HA-CA-CB	111.19	110.96	0.23
CB-CG-HG	114.18	111.46	2.72
CB-CG-FG1	109.78	111.23	1.45
CB-CG-FG2	109.90	110.86	0.97
HB1-CB-HB2	107.50	107.52	0.03
HB1-CB-CG	106.77	108.83	2.06
HB2-CB-CG	107.79	109.07	1.29
HG-CG-FG1	107.56	108.11	0.55
HG-CG-FG2	107.87	108.20	0.33
FG1-CG-FG2	107.31	106.79	0.52

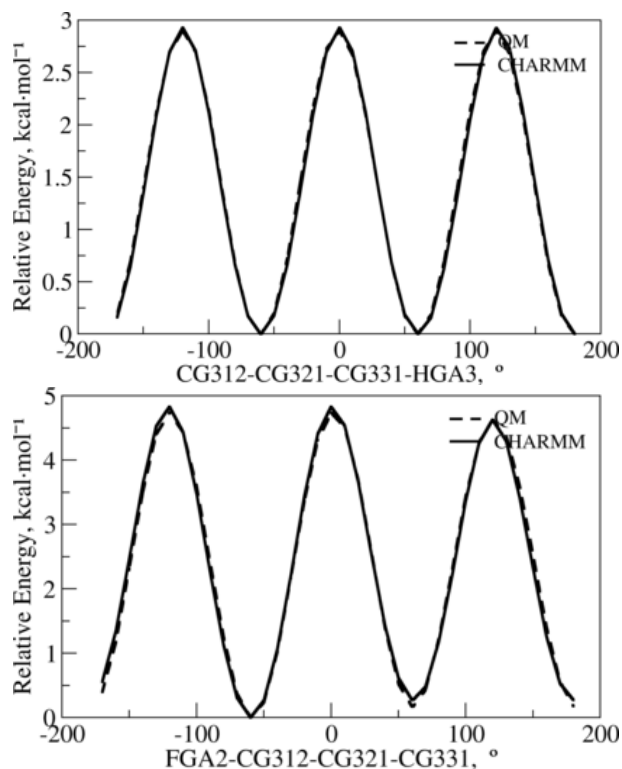


Figure S442: The PES scan for flexible dihedrals corresponding to 1,1-difluoropropane.

2.139 The small molecule 2 used for bonded terms optimization of (2S)-2-amino-4,4-difluorobutanoic acid (OBF)

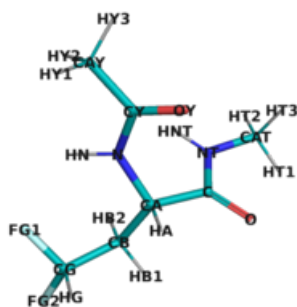


Figure S443: The energy minimized structure corresponding to (2S)-2-acetamido-4,4-difluoro-N-methylbutanamide.

Table S819: The calculated geometric terms of (2S)-2-acetamido-4,4-difluoro-N-methylbutanamide.

Terms	QM	CHARMM	Abs. diff.
N-HN	1.01	1.00	0.02
N-CA	1.46	1.46	0.00
N-CY	1.38	1.34	0.04
CA-HA	1.10	1.08	0.02
CA-CB	1.53	1.56	0.03
CA-C	1.53	1.52	0.01
CB-HB1	1.10	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.50	1.53	0.02
CG-HG	1.09	1.08	0.01
CG-FG1	1.39	1.35	0.04
CG-FG2	1.37	1.35	0.02
C-O	1.23	1.23	0.00
C-NT	1.37	1.35	0.02
NT-HNT	1.01	0.99	0.02
NT-CAT	1.45	1.45	0.01
CAT-HT1	1.09	1.11	0.02
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.10	1.11	0.02
CAY-HY1	1.09	1.11	0.02
CAY-HY2	1.09	1.11	0.02
CAY-HY3	1.09	1.11	0.02
CAY-CY	1.51	1.48	0.03
CY-OY	1.23	1.22	0.01
N-CA-HA	110.47	107.39	3.07
N-CA-CB	111.14	111.94	0.81
N-CA-C	112.08	114.69	2.61
N-CY-CAY	115.10	116.39	1.29
N-CY-OY	121.45	122.87	1.42
HN-N-CA	116.62	115.64	0.98
HN-N-CY	118.08	118.40	0.32

Terms	QM	CHARMM	Abs. diff.
CA-N-CY	118.67	125.00	6.32
CA-CB-HB1	108.25	109.42	1.17
CA-CB-HB2	110.71	109.93	0.78
CA-CB-CG	114.01	113.32	0.70
CA-C-O	120.76	120.80	0.04
CA-C-NT	114.33	117.58	3.25
HA-CA-CB	110.14	109.05	1.09
HA-CA-C	104.25	105.58	1.33
CB-CA-C	108.54	107.89	0.65
CB-CG-HG	114.41	112.14	2.27
CB-CG-FG1	110.11	111.49	1.38
CB-CG-FG2	109.65	110.24	0.59
HB1-CB-HB2	107.91	107.42	0.50
HB1-CB-CG	107.57	107.50	0.07
HB2-CB-CG	108.18	109.07	0.89
HG-CG-FG1	107.18	108.38	1.20
HG-CG-FG2	108.47	107.85	0.62
FG1-CG-FG2	106.72	106.51	0.21
C-NT-HNT	115.38	119.57	4.20
C-NT-CAT	119.26	121.89	2.63
O-C-NT	124.13	121.58	2.54
NT-CAT-HT1	108.30	111.37	3.07
NT-CAT-HT2	108.95	110.57	1.62
NT-CAT-HT3	111.89	110.24	1.65
HNT-NT-CAT	117.82	117.90	0.08
HT1-CAT-HT2	109.52	108.11	1.41
HT1-CAT-HT3	108.53	107.93	0.60
HT2-CAT-HT3	109.60	108.52	1.08
CAY-CY-OY	123.45	120.74	2.71
HY1-CAY-HY2	108.35	109.58	1.23
HY1-CAY-HY3	108.47	108.52	0.04
HY1-CAY-CY	109.53	109.82	0.29
HY2-CAY-HY3	109.85	109.03	0.81
HY2-CAY-CY	111.93	110.99	0.94
HY3-CAY-CY	108.66	108.86	0.20

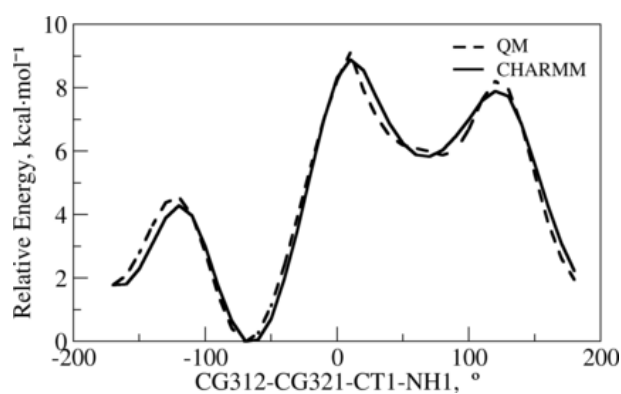


Figure S444: The PES scan for flexible dihedral corresponding to (2S)-2-acetamido-4,4-difluoro-N-methylbutanamide.

2.140 The small molecule used for bonded terms optimization of cysteinesulfonicacid (OCS)



Figure S445: The energy minimized structure corresponding to (2R)-2-acetamido-2-(methylcarbamoyl)ethane-1-sulfonic acid.

Table S820: The calculated geometric terms of (2R)-2-acetamido-2-(methylcarbamoyl)ethane-1-sulfonic acid.

Terms	QM	CHARMM	Abs. diff.
N-HN	1.03	1.01	0.03
N-CA	1.46	1.45	0.01
N-CY	1.36	1.34	0.02
CA-HA	1.10	1.08	0.01
CA-CB	1.53	1.56	0.03
CA-C	1.53	1.53	0.00
CB-HB1	1.09	1.11	0.01
CB-HB2	1.09	1.11	0.01
CB-SG	1.82	1.80	0.02
SG-OD1	1.51	1.45	0.06
SG-OD2	1.49	1.45	0.04
SG-OD3	1.49	1.45	0.04
C-O	1.24	1.23	0.01
C-NT	1.37	1.35	0.02
NT-HNT	1.02	0.99	0.02
NT-CAT	1.45	1.44	0.01
CAT-HT1	1.09	1.11	0.02
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.10	1.11	0.02
CAY-HY1	1.09	1.11	0.02
CAY-HY2	1.09	1.11	0.02
CAY-HY3	1.09	1.11	0.02
CAY-CY	1.52	1.48	0.03
CY-OY	1.24	1.22	0.02
N-CA-HA	109.96	108.18	1.78
N-CA-CB	109.87	109.47	0.40
N-CA-C	111.55	113.48	1.93
N-CY-CAY	115.30	115.50	0.19
N-CY-OY	122.97	123.81	0.84
HN-N-CA	113.95	110.67	3.28
HN-N-CY	119.80	118.43	1.37
CA-N-CY	120.89	127.98	7.09

Terms	QM	CHARMM	Abs. diff.
CA-CB-HB1	109.17	110.07	0.90
CA-CB-HB2	111.34	111.80	0.46
CA-CB-SG	113.26	111.96	1.30
CA-C-O	122.38	122.34	0.05
CA-C-NT	114.36	116.25	1.89
HA-CA-CB	109.42	109.51	0.09
HA-CA-C	106.40	107.39	0.99
CB-CA-C	109.57	108.74	0.83
CB-SG-OD1	103.11	103.95	0.83
CB-SG-OD2	104.61	103.55	1.06
CB-SG-OD3	104.62	104.11	0.50
HB1-CB-HB2	109.29	109.40	0.11
HB1-CB-SG	106.94	106.70	0.24
HB2-CB-SG	106.67	106.72	0.04
OD1-SG-OD2	113.60	114.17	0.57
OD1-SG-OD3	113.18	114.40	1.22
OD2-SG-OD3	115.95	114.76	1.18
C-NT-HNT	114.40	117.19	2.80
C-NT-CAT	119.37	122.81	3.44
O-C-NT	122.72	121.41	1.32
NT-CAT-HT1	108.95	110.81	1.85
NT-CAT-HT2	108.68	110.37	1.69
NT-CAT-HT3	111.78	110.11	1.67
HNT-NT-CAT	117.61	119.51	1.90
HT1-CAT-HT2	109.24	108.57	0.67
HT1-CAT-HT3	108.43	108.25	0.18
HT2-CAT-HT3	109.72	108.66	1.06
CAY-CY-OY	121.72	120.69	1.03
HY1-CAY-HY2	110.10	109.42	0.67
HY1-CAY-HY3	108.69	108.86	0.17
HY1-CAY-CY	112.51	110.35	2.16
HY2-CAY-HY3	108.06	109.09	1.02
HY2-CAY-CY	108.97	109.67	0.70
HY3-CAY-CY	108.39	109.42	1.03

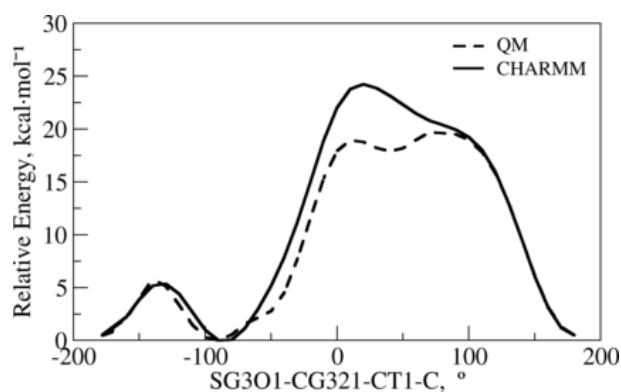


Figure S446: The PES scan for flexible dihedral corresponding to (2R)-2-acetamido-2-(methylcarbamoyl)ethane-1-sulfonic acid.

2.141 The small molecule used for bonded terms optimization of s-(2-hydroxyethyl)-l-cysteine (OCY)

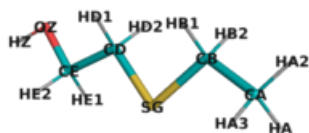


Figure S447: The energy minimized structure corresponding to 2-(ethylsulfanyl)ethan-1-ol.

Table S821: The calculated geometric terms of 2-(ethylsulfanyl)ethan-1-ol.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.82	1.82	0.00
SG-CD	1.81	1.82	0.01
CD-HD1	1.09	1.11	0.02
CD-HD2	1.09	1.11	0.02
CD-CE	1.52	1.54	0.02
CE-HE2	1.10	1.11	0.01
CE-HE1	1.10	1.11	0.02
CE-OZ	1.43	1.43	0.00
OZ-HZ	0.97	0.96	0.01
HA3-CA-HA2	108.23	108.36	0.13
HA3-CA-HA	108.30	108.32	0.03
HA3-CA-CB	111.00	110.54	0.46
HA2-CA-HA	108.19	108.36	0.17
HA2-CA-CB	110.04	110.63	0.59
CA-CB-HB1	110.31	108.68	1.63
CA-CB-HB2	110.31	108.67	1.64
CA-CB-SG	109.96	112.81	2.85
HA-CA-CB	110.99	110.54	0.45
CB-SG-CD	98.58	96.32	2.26
HB1-CB-HB2	108.05	107.06	0.99
HB1-CB-SG	109.08	109.73	0.65
HB2-CB-SG	109.09	109.71	0.63
SG-CD-HD1	110.22	109.77	0.45
SG-CD-HD2	110.23	109.77	0.45
SG-CD-CE	110.03	113.48	3.45
CD-CE-HE2	110.01	109.54	0.47
CD-CE-HE1	109.99	109.56	0.44

Terms	QM	CHARMM	Abs. diff.
CD-CE-OZ	106.09	109.78	3.69
HD1-CD-HD2	108.59	107.08	1.52
HD1-CD-CE	108.86	108.26	0.60
HD2-CD-CE	108.87	108.26	0.61
CE-OZ-HZ	107.57	108.07	0.50
HE2-CE-HE1	108.09	108.71	0.62
HE2-CE-OZ	111.33	109.61	1.73
HE1-CE-OZ	111.33	109.63	1.70

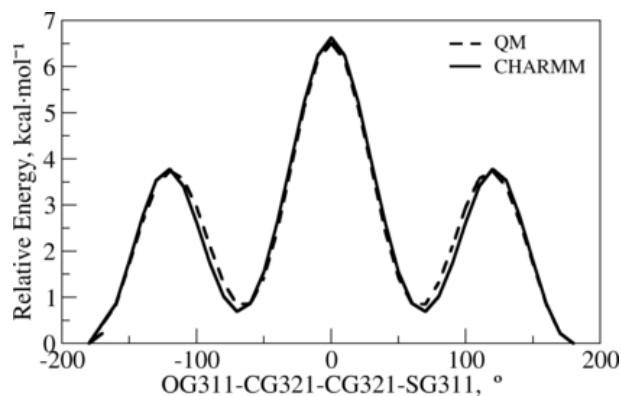


Figure S448: The PES scan for flexible dihedral corresponding to 2-(ethylsulfanyl)ethan-1-ol.

2.142 The small molecule used for bonded terms optimization of (betaR)-3-chloro-beta-hydroxy-L-tyrosine (OMY)

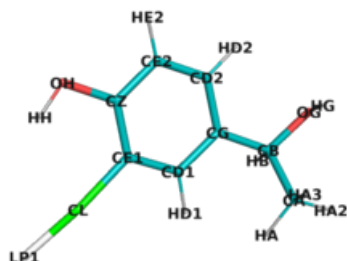


Figure S449: The energy minimized structure corresponding to 4-(1-hydroxyethyl)-2-methylphenol.

Table S822: The calculated geometric terms of 4-(1-hydroxyethyl)-2-methylphenol.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.54	0.02
CB-HB	1.10	1.11	0.02
CB-OG	1.43	1.42	0.01
CB-CG	1.52	1.53	0.01
OG-HG	0.97	0.96	0.02
CG-CD1	1.40	1.41	0.01
CG-CD2	1.40	1.41	0.01
CD1-HD1	1.09	1.08	0.01
CD1-CE1	1.39	1.40	0.01
CD2-HD2	1.09	1.08	0.01
CD2-CE2	1.39	1.40	0.01
CE1-CL	1.75	1.74	0.00
CE1-CZ	1.40	1.40	0.00
CE2-HE2	1.09	1.08	0.01
CE2-CZ	1.40	1.40	0.00
CZ-OH	1.36	1.41	0.05
OH-HH	0.98	0.96	0.01
HA3-CA-HA2	108.69	108.27	0.42
HA3-CA-HA	108.42	108.61	0.19
HA3-CA-CB	110.53	111.32	0.79
HA2-CA-HA	108.28	107.37	0.91
HA2-CA-CB	108.68	110.10	1.42
CA-CB-HB	108.84	108.27	0.57
CA-CB-OG	110.22	106.48	3.75
CA-CB-CG	114.40	110.79	3.61
HA-CA-CB	112.16	111.04	1.11
CB-OG-HG	106.35	105.42	0.93
CB-CG-CD1	122.43	119.18	3.25
CB-CG-CD2	119.10	122.49	3.39
HB-CB-OG	103.42	106.97	3.55

Terms	QM	CHARMM	Abs. diff.
HB-CB-CG	108.77	108.80	0.03
OG-CB-CG	110.59	115.27	4.68
CG-CD1-HD1	121.55	120.26	1.29
CG-CD1-CE1	120.23	121.04	0.82
CG-CD2-HD2	118.96	120.00	1.04
CG-CD2-CE2	121.11	120.79	0.32
CD1-CG-CD2	118.44	118.30	0.14
CD1-CE1-CL	119.80	118.97	0.82
CD1-CE1-CZ	121.38	119.77	1.61
HD1-CD1-CE1	118.22	118.70	0.48
CD2-CE2-HE2	121.44	120.27	1.17
CD2-CE2-CZ	120.59	120.06	0.53
HD2-CD2-CE2	119.93	119.20	0.73
CE1-CZ-CE2	118.25	119.99	1.74
CE1-CZ-OH	123.93	121.10	2.83
CL-CE1-CZ	118.82	121.26	2.44
CE2-CZ-OH	117.83	118.91	1.08
HE2-CE2-CZ	117.97	119.66	1.70
CZ-OH-HH	108.44	106.49	1.95

2.143 The small molecule used for bonded terms optimization of 4-benzoyl-phenylalanine (PBF)

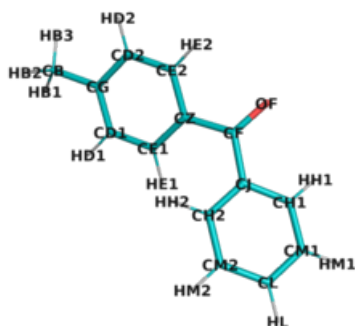


Figure S450: The energy minimized structure corresponding to (4-methylphenyl)(phenyl)methanone.

Table S823: The calculated geometric terms of (4-methylphenyl)(phenyl)methanone.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.10	1.11	0.02
CB-CG	1.51	1.50	0.01
CG-CD1	1.40	1.40	0.00
CG-CD2	1.40	1.40	0.00
CD1-HD1	1.09	1.08	0.01
CD1-CE1	1.39	1.40	0.01
CD2-HD2	1.09	1.08	0.01
CD2-CE2	1.39	1.40	0.01
CE1-HE1	1.09	1.08	0.01
CE1-CZ	1.40	1.41	0.01
CE2-HE2	1.09	1.08	0.01
CE2-CZ	1.40	1.41	0.01
CZ-CF	1.49	1.50	0.00
CF-CJ	1.49	1.50	0.00
CF-OF	1.24	1.23	0.00
CJ-CH1	1.40	1.41	0.01
CJ-CH2	1.40	1.41	0.01
CH1-HH1	1.09	1.08	0.01
CH1-CM1	1.39	1.40	0.01
CH2-HH2	1.09	1.08	0.01
CH2-CM2	1.40	1.40	0.00
CM1-HM1	1.09	1.08	0.01
CM1-CL	1.40	1.40	0.00
CM2-HM2	1.09	1.08	0.01
CM2-CL	1.40	1.40	0.00
CL-HL	1.09	1.08	0.01
HB3-CB-HB1	108.16	109.11	0.95
HB3-CB-HB2	107.60	109.75	2.15
HB3-CB-CG	111.07	109.64	1.43
CB-CG-CD1	120.93	120.18	0.75

Terms	QM	CHARMM	Abs. diff.
CB-CG-CD2	120.77	120.15	0.61
HB1-CB-HB2	107.68	109.89	2.20
HB1-CB-CG	111.10	109.76	1.34
HB2-CB-CG	111.07	108.68	2.39
CG-CD1-HD1	119.38	119.63	0.24
CG-CD1-CE1	121.21	120.18	1.03
CG-CD2-HD2	119.36	119.76	0.40
CG-CD2-CE2	121.07	120.21	0.86
CD1-CG-CD2	118.28	119.66	1.39
CD1-CE1-HE1	119.92	118.72	1.20
CD1-CE1-CZ	119.93	120.79	0.86
HD1-CD1-CE1	119.40	120.19	0.78
CD2-CE2-HE2	121.10	119.24	1.86
CD2-CE2-CZ	120.17	120.89	0.72
HD2-CD2-CE2	119.56	120.03	0.47
CE1-CZ-CE2	119.31	118.23	1.08
CE1-CZ-CF	122.39	123.61	1.22
HE1-CE1-CZ	120.12	120.48	0.36
CE2-CZ-CF	118.18	118.07	0.10
HE2-CE2-CZ	118.72	119.87	1.14
CZ-CF-CJ	119.51	119.74	0.22
CZ-CF-OF	120.35	120.12	0.22
CF-CJ-CH1	117.99	118.05	0.06
CF-CJ-CH2	122.14	123.56	1.41
CJ-CF-OF	120.14	120.14	0.00
CJ-CH1-HH1	118.67	119.91	1.24
CJ-CH1-CM1	120.10	120.90	0.80
CJ-CH2-HH2	120.01	120.58	0.56
CJ-CH2-CM2	119.85	120.71	0.86
CH1-CJ-CH2	119.77	118.30	1.47
CH1-CM1-HM1	119.90	119.89	0.01
CH1-CM1-CL	120.10	119.96	0.14
HH1-CH1-CM1	121.23	119.19	2.05
CH2-CM2-HM2	119.77	120.04	0.28
CH2-CM2-CL	120.24	120.05	0.19
HH2-CH2-CM2	120.11	118.70	1.41
CM1-CL-CM2	119.93	120.05	0.12
CM1-CL-HL	120.06	119.88	0.18
HM1-CM1-CL	120.00	120.14	0.15
CM2-CL-HL	120.01	120.07	0.05
HM2-CM2-CL	119.99	119.91	0.09

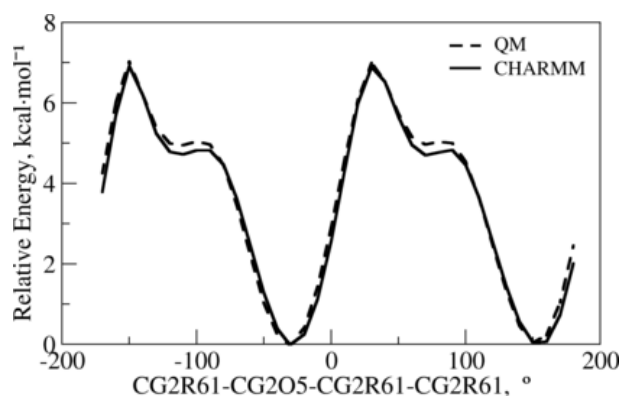


Figure S451: The PES scan for flexible dihedral corresponding to (4-methylphenyl)(phenyl)methanone.

2.144 The small molecule used for bonded terms optimization of aspartylphosphate (PHD)

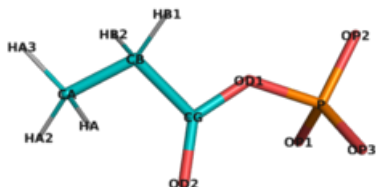


Figure S452: The energy minimized structure corresponding to (propanoyloxy)phosphonic acid.

Table S824: The calculated geometric terms of (propanoyloxy)phosphonic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.10	1.11	0.01
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.54	0.02
CB-HB1	1.10	1.11	0.01
CB-HB2	1.10	1.11	0.01
CB-CG	1.55	1.54	0.01
CG-OD2	1.25	1.22	0.03
CG-OD1	1.29	1.30	0.01
OD1-P	2.01	1.56	0.45
P-OP1	1.53	1.51	0.02
P-OP2	1.54	1.52	0.02
P-OP3	1.53	1.52	0.02
HA3-CA-HA2	108.28	109.18	0.90
HA3-CA-HA	109.17	109.36	0.20
HA3-CA-CB	111.54	110.57	0.97
HA2-CA-HA	107.18	108.14	0.96
HA2-CA-CB	110.49	109.69	0.80
CA-CB-HB1	110.23	110.72	0.49
CA-CB-HB2	111.45	109.97	1.49
CA-CB-CG	113.50	112.67	0.83
HA-CA-CB	110.06	109.86	0.21
CB-CG-OD2	118.14	123.96	5.81
CB-CG-OD1	111.04	106.57	4.47
HB1-CB-HB2	106.54	108.71	2.17
HB1-CB-CG	106.74	106.09	0.65
HB2-CB-CG	108.03	108.53	0.50
CG-OD1-P	131.53	132.43	0.90
OD2-CG-OD1	130.79	129.46	1.34
OD1-P-OP1	100.88	104.63	3.74
OD1-P-OP2	94.85	102.36	7.51
OD1-P-OP3	100.38	104.44	4.06
OP1-P-OP2	117.25	113.79	3.46
OP1-P-OP3	118.69	115.98	2.71

Terms	QM	CHARMM	Abs. diff.
OP2-P-OP3	117.27	113.67	3.61

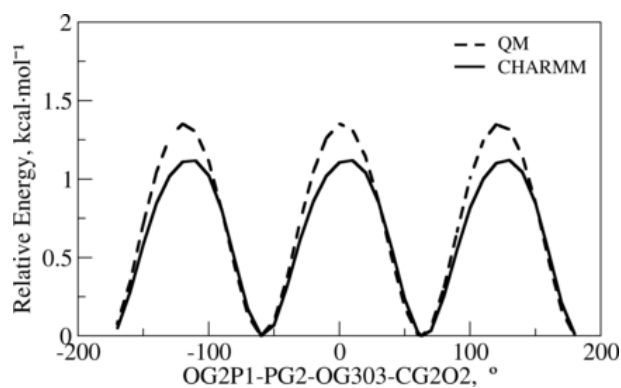


Figure S453: The PES scan for flexible dihedral corresponding to (propanoyloxy)phosphonic acid.

2.145 The small molecule used for bonded terms optimization of aspartylphosphate (PHDP)

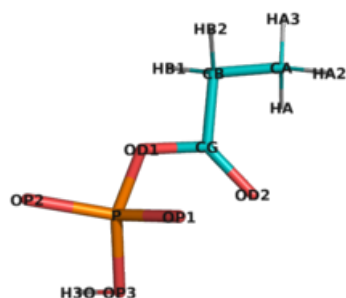


Figure S454: The energy minimized structure corresponding to (propanoyloxy)phosphonic acid.

Table S825: The calculated geometric terms of (propanoyloxy)phosphonic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.54	0.02
CB-HB1	1.10	1.11	0.01
CB-HB2	1.10	1.11	0.01
CB-CG	1.52	1.53	0.01
CG-OD2	1.23	1.22	0.01
CG-OD1	1.34	1.32	0.02
OD1-P	1.75	1.59	0.17
P-OP1	1.50	1.50	0.00
P-OP2	1.51	1.50	0.01
P-OP3	1.66	1.59	0.07
OP3-H3O	0.98	0.96	0.01
HA3-CA-HA2	108.72	108.64	0.08
HA3-CA-HA	108.55	108.74	0.20
HA3-CA-CB	110.59	110.65	0.06
HA2-CA-HA	107.39	108.18	0.79
HA2-CA-CB	110.68	110.20	0.48
CA-CB-HB1	111.61	110.25	1.36
CA-CB-HB2	111.27	110.25	1.02
CA-CB-CG	112.98	111.84	1.14
HA-CA-CB	110.81	110.36	0.45
CB-CG-OD2	123.35	124.60	1.25
CB-CG-OD1	109.81	107.63	2.18
HB1-CB-HB2	105.90	108.62	2.72
HB1-CB-CG	107.74	108.17	0.44
HB2-CB-CG	106.96	107.61	0.65
CG-OD1-P	123.82	123.56	0.26
OD2-CG-OD1	126.84	127.78	0.94
OD1-P-OP1	107.37	107.26	0.11
OD1-P-OP2	102.18	105.29	3.11
OD1-P-OP3	99.76	105.86	6.10
P-OP3-H3O	105.28	110.00	4.72

Terms	QM	CHARMM	Abs. diff.
OP1-P-OP2	126.51	120.04	6.47
OP1-P-OP3	109.98	111.23	1.25
OP2-P-OP3	107.55	106.19	1.35

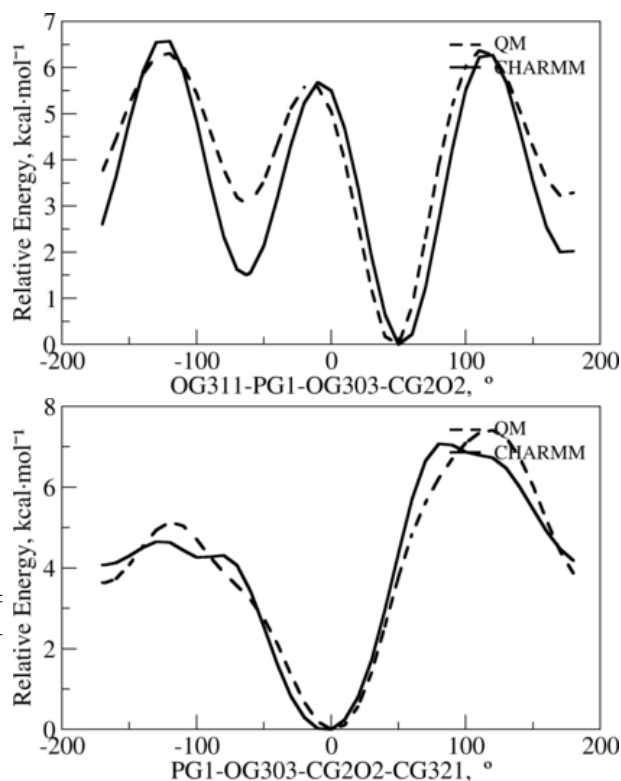


Figure S455: The PES scan for flexible dihedrals corresponding to (propanoyloxy)phosphonic acid.

2.146 The small molecule used for bonded terms optimization of 1-[(2R)-2-carboxy-2-hydroxyethyl]-L-proline (PR4)

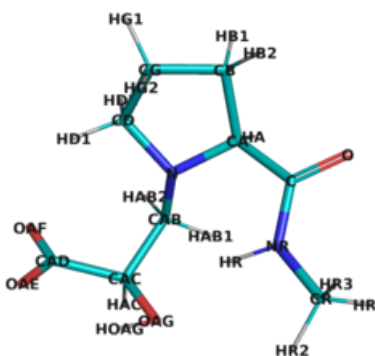


Figure S456: The energy minimized structure corresponding to 2-hydroxy-3-[2-(methylcarbamoyl)pyrrolidin-1-yl]propanoic acid.

Table S826: The calculated geometric terms of 2-hydroxy-3-[2-(methylcarbamoyl)pyrrolidin-1-yl]propanoic acid.

Terms	QM	CHARMM	Abs. diff.
OAE-CAD	1.27	1.26	0.01
OAF-CAD	1.25	1.26	0.01
CAD-CAC	1.57	1.58	0.02
CAC-HAC	1.10	1.11	0.01
CAC-OAG	1.43	1.46	0.03
CAC-CAB	1.54	1.56	0.02
OAG-HOAG	1.00	0.98	0.02
CAB-HAB1	1.10	1.11	0.02
CAB-HAB2	1.10	1.11	0.01
CAB-N	1.46	1.47	0.01
N-CA	1.46	1.50	0.04
N-CD	1.46	1.48	0.02
CA-HA	1.11	1.10	0.01
CA-CB	1.55	1.55	0.00
CA-C	1.54	1.53	0.02
CB-HB1	1.10	1.10	0.00
CB-HB2	1.09	1.10	0.01
CB-CG	1.54	1.53	0.01
CG-HG1	1.10	1.10	0.00
CG-HG2	1.10	1.10	0.01
CG-CD	1.53	1.52	0.01
CD-HD1	1.09	1.10	0.01
CD-HD2	1.11	1.10	0.01
C-O	1.24	1.23	0.01
C-NR	1.35	1.35	0.00
NR-HR	1.03	1.01	0.02
NR-CR	1.45	1.44	0.01
CR-HR1	1.10	1.11	0.01
CR-HR2	1.09	1.11	0.02
CR-HR3	1.10	1.11	0.01
OAE-CAD-OAF	129.68	127.54	2.14

Terms	QM	CHARMM	Abs. diff.
OAE-CAD-CAC	113.50	116.31	2.80
OAF-CAD-CAC	116.82	116.15	0.67
CAD-CAC-HAC	107.30	104.41	2.88
CAD-CAC-OAG	108.65	116.54	7.89
CAD-CAC-CAB	113.77	111.03	2.74
CAC-OAG-HOAG	99.70	100.52	0.82
CAC-CAB-HAB1	108.07	106.43	1.64
CAC-CAB-HAB2	107.98	108.90	0.92
CAC-CAB-N	113.59	114.73	1.14
HAC-CAC-OAG	109.17	107.02	2.16
HAC-CAC-CAB	107.12	107.05	0.07
OAG-CAC-CAB	110.69	110.14	0.55
CAB-N-CA	117.66	117.37	0.29
CAB-N-CD	117.28	117.62	0.34
HAB1-CAB-HAB2	107.66	106.95	0.72
HAB1-CAB-N	107.67	109.43	1.75
HAB2-CAB-N	111.65	110.07	1.58
N-CA-HA	112.11	106.99	5.12
N-CA-CB	105.24	105.08	0.16
N-CA-C	113.72	114.08	0.37
N-CD-CG	102.84	103.31	0.48
N-CD-HD1	110.79	111.13	0.34
N-CD-HD2	111.53	109.56	1.96
CA-N-CD	109.89	106.17	3.72
CA-CB-HB1	109.42	109.30	0.13
CA-CB-HB2	111.73	113.87	2.14
CA-CB-CG	104.08	105.27	1.19
CA-C-O	120.33	119.33	1.00
CA-C-NR	116.25	118.96	2.71
HA-CA-CB	109.20	109.75	0.55
HA-CA-C	104.68	107.32	2.64
CB-CA-C	111.97	113.42	1.45
CB-CG-HG1	112.86	113.45	0.59
CB-CG-HG2	110.77	110.86	0.09
CB-CG-CD	102.47	102.12	0.35
HB1-CB-HB2	107.38	106.03	1.35
HB1-CB-CG	109.81	110.47	0.66
HB2-CB-CG	114.36	111.94	2.42
CG-CD-HD1	113.72	112.69	1.03
CG-CD-HD2	110.69	112.64	1.95
HG1-CG-HG2	108.10	107.11	0.99
HG1-CG-CD	112.83	113.25	0.43
HG2-CG-CD	109.75	110.06	0.31
HD1-CD-HD2	107.33	107.50	0.17
C-NR-HR	119.17	115.31	3.86
C-NR-CR	121.49	129.68	8.19
O-C-NR	123.41	121.70	1.71
NR-CR-HR1	111.09	110.36	0.73
NR-CR-HR2	108.25	109.83	1.59
NR-CR-HR3	111.36	110.29	1.07
HR-NR-CR	118.89	114.96	3.93
HR1-CR-HR2	109.38	108.79	0.59
HR1-CR-HR3	107.51	108.74	1.23
HR2-CR-HR3	109.22	108.78	0.44

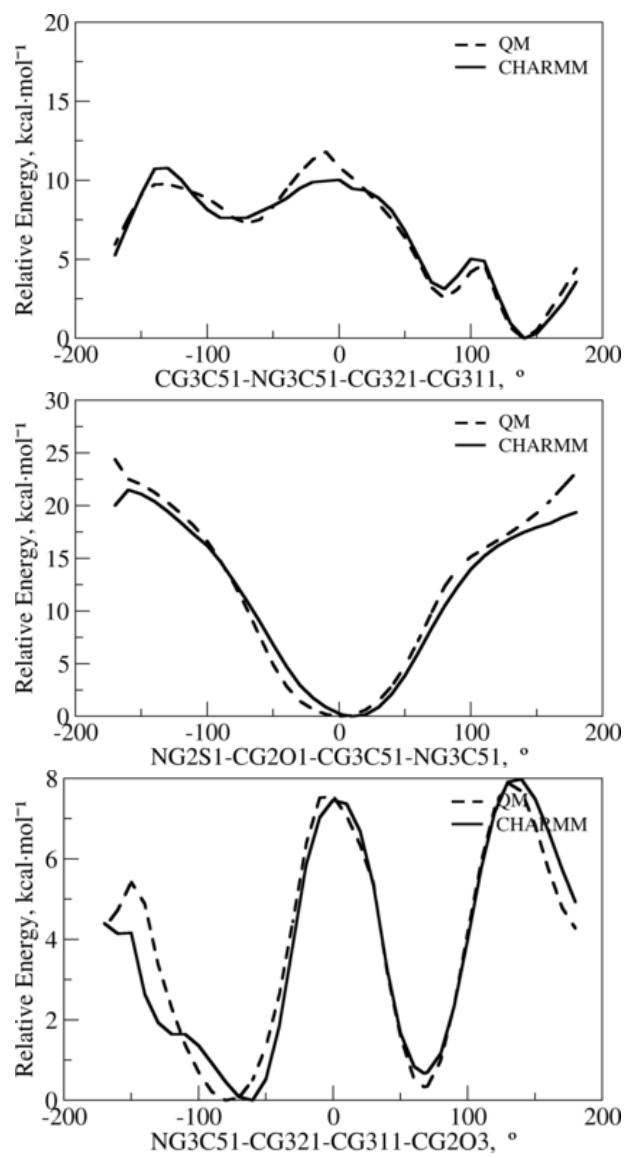


Figure S457: The PES scan for flexible dihedrals corresponding to 2-hydroxy-3-[2-(methylcarbamoyl)pyrrolidin-1-yl]propanoic acid.

Terms	QM	CHARMM	Abs. diff.
HB1-CB-SG	109.93	111.12	1.19
HB2-CB-SG	110.34	113.48	3.14
SG-CD-HD1	110.04	112.40	2.36
SG-CD-HD2	109.20	110.56	1.36
HD1-CD-HD2	109.06	107.63	1.43
C-N2AL-HNN2	120.17	121.12	0.95
C-N2AL-C2AL	120.57	122.43	1.86
O-C-N2AL	123.87	121.66	2.22
N2AL-C2AL-H2AL	108.02	107.32	0.70
N2AL-C2AL-CB22	110.88	110.60	0.28
N2AL-C2AL-C22	112.77	114.18	1.41
HNN2-N2AL-C2AL	117.66	114.93	2.73
C2AL-CB22-H122	110.53	110.14	0.39
C2AL-CB22-H222	111.51	111.00	0.51
C2AL-CB22-H322	109.08	110.47	1.40
C2AL-C22-O22	120.47	121.42	0.95
C2AL-C22-NT	115.25	117.01	1.76
H2AL-C2AL-CB22	109.78	108.55	1.23
H2AL-C2AL-C22	104.23	105.89	1.66
CB22-C2AL-C22	110.88	110.02	0.86
H122-CB22-H222	108.29	108.37	0.08
H122-CB22-H322	108.58	108.13	0.45
H222-CB22-H322	108.79	108.65	0.14
C22-NT-HNT	118.05	119.25	1.21
C22-NT-CAT	120.57	122.66	2.09
O22-C22-NT	123.69	121.56	2.14
NT-CAT-HT1	108.32	111.55	3.23
NT-CAT-HT2	109.49	110.28	0.79
NT-CAT-HT3	112.29	110.40	1.89
HNT-NT-CAT	116.91	117.61	0.71
HT1-CAT-HT2	109.62	107.95	1.67
HT1-CAT-HT3	108.27	108.13	0.14
HT2-CAT-HT3	108.82	108.43	0.39

2.148 The small molecule 2 used for bonded terms optimization of Thioproline (PRS)

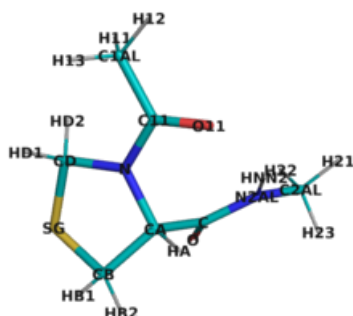


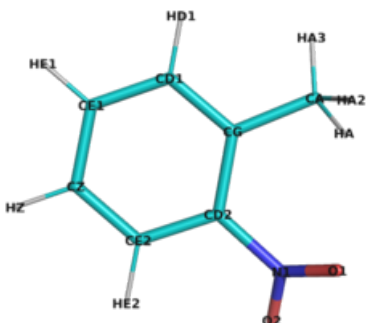
Figure S459: The energy minimized structure corresponding to (4R)-3-acetyl-N-methyl-1,3-thiazolidine-4-carboxamide.

Table S828: The calculated geometric terms of (4R)-3-acetyl-N-methyl-1,3-thiazolidine-4-carboxamide.

Terms	QM	CHARMM	Abs. diff.
C1AL-H11	1.09	1.11	0.02
C1AL-H12	1.09	1.11	0.02
C1AL-H13	1.09	1.11	0.02
C1AL-C11	1.51	1.49	0.02
C11-O11	1.24	1.23	0.02
C11-N	1.36	1.37	0.00
N-CA	1.47	1.46	0.01
N-CD	1.47	1.47	0.01
CA-HA	1.10	1.10	0.01
CA-CB	1.52	1.54	0.02
CA-C	1.54	1.52	0.02
CB-HB1	1.09	1.10	0.01
CB-HB2	1.09	1.10	0.01
CB-SG	1.81	1.82	0.01
SG-CD	1.81	1.82	0.01
CD-HD1	1.10	1.10	0.00
CD-HD2	1.09	1.10	0.01
C-O	1.24	1.23	0.01
C-N2AL	1.35	1.34	0.01
N2AL-HNN2	1.02	1.00	0.02
N2AL-C2AL	1.45	1.44	0.01
C2AL-H21	1.09	1.11	0.02
C2AL-H22	1.09	1.11	0.02
C2AL-H23	1.09	1.11	0.02
C1AL-C11-O11	121.60	118.70	2.90
C1AL-C11-N	116.86	118.49	1.63
H11-C1AL-H12	109.15	108.35	0.80
H11-C1AL-H13	107.91	109.93	2.02
H11-C1AL-C11	110.89	110.43	0.46
H12-C1AL-H13	109.47	108.35	1.12
H12-C1AL-C11	107.62	108.99	1.37
H13-C1AL-C11	111.78	110.72	1.05

Terms	QM	CHARMM	Abs. diff.
C11-N-CA	120.47	121.82	1.35
C11-N-CD	123.19	122.50	0.70
O11-C11-N	121.53	122.81	1.29
N-CA-HA	107.47	112.22	4.75
N-CA-CB	105.82	106.64	0.82
N-CA-C	113.54	111.75	1.79
N-CD-SG	105.65	106.81	1.16
N-CD-HD1	110.64	108.76	1.88
N-CD-HD2	111.14	110.42	0.72
CA-N-CD	115.31	115.60	0.29
CA-CB-HB1	111.20	109.69	1.51
CA-CB-HB2	110.40	112.82	2.42
CA-CB-SG	104.62	104.91	0.29
CA-C-O	121.81	120.36	1.45
CA-C-N2AL	114.54	117.68	3.14
HA-CA-CB	111.39	106.01	5.38
HA-CA-C	107.99	106.77	1.21
CB-CA-C	110.63	113.40	2.77
CB-SG-CD	89.48	91.44	1.97
HB1-CB-HB2	110.64	105.35	5.30
HB1-CB-SG	110.88	110.74	0.14
HB2-CB-SG	108.93	113.41	4.48
SG-CD-HD1	111.24	111.87	0.62
SG-CD-HD2	108.93	111.64	2.71
HD1-CD-HD2	109.19	107.34	1.85
C-N2AL-HNN2	117.66	118.55	0.89
C-N2AL-C2AL	119.97	122.42	2.45
O-C-N2AL	123.63	121.96	1.67
N2AL-C2AL-H21	108.61	110.54	1.93
N2AL-C2AL-H22	109.38	110.98	1.60
N2AL-C2AL-H23	111.74	110.48	1.26
HNN2-N2AL-C2AL	120.69	118.78	1.91
H21-C2AL-H22	109.53	108.20	1.34
H21-C2AL-H23	109.37	108.39	0.98
H22-C2AL-H23	108.18	108.17	0.02

2.149 The small molecule used for bonded terms optimization of (2R)-amino(2-nitrophenyl)ethanoic acid (PRV)



Terms	QM	CHARMM	Abs. diff.
CD2-N1-O1	117.82	116.61	1.21
CD2-N1-O2	117.46	116.61	0.85
CD2-CE2-HE2	119.26	118.93	0.33
CD2-CE2-CZ	118.95	121.20	2.25
N1-CD2-CE2	116.01	119.82	3.81
O1-N1-O2	124.72	126.12	1.41
CE1-CZ-CE2	119.60	119.92	0.32
CE1-CZ-HZ	120.59	119.87	0.72
HE1-CE1-CZ	120.24	119.93	0.30
CE2-CZ-HZ	119.81	120.21	0.40
HE2-CE2-CZ	121.79	119.87	1.92

Figure S460: The energy minimized structure corresponding to 1-methyl-2-nitrobenzene.

Table S829: The calculated geometric terms of 1-methyl-2-nitrobenzene.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CG	1.51	1.51	0.00
CG-CD1	1.40	1.40	0.00
CG-CD2	1.40	1.43	0.02
CD1-HD1	1.09	1.08	0.01
CD1-CE1	1.39	1.40	0.00
CD2-N1	1.47	1.44	0.02
CD2-CE2	1.39	1.42	0.02
N1-O1	1.24	1.23	0.02
N1-O2	1.24	1.23	0.01
CE1-HE1	1.09	1.08	0.01
CE1-CZ	1.40	1.40	0.00
CE2-HE2	1.09	1.08	0.00
CE2-CZ	1.39	1.40	0.01
CZ-HZ	1.09	1.08	0.00
HA3-CA-HA2	108.80	109.60	0.80
HA3-CA-HA	108.48	108.93	0.45
HA3-CA-CG	109.25	110.81	1.57
HA2-CA-HA	107.01	109.41	2.40
HA2-CA-CG	111.22	108.70	2.52
CA-CG-CD1	119.92	117.66	2.26
CA-CG-CD2	124.46	122.50	1.97
HA-CA-CG	111.97	109.36	2.61
CG-CD1-HD1	118.29	119.61	1.32
CG-CD1-CE1	122.35	120.78	1.57
CG-CD2-N1	120.49	121.95	1.46
CG-CD2-CE2	123.50	118.23	5.27
CD1-CG-CD2	115.61	119.84	4.23
CD1-CE1-HE1	119.79	120.05	0.26
CD1-CE1-CZ	119.98	120.02	0.04
HD1-CD1-CE1	119.36	119.61	0.25

2.150 The small molecule 1 used for bonded terms optimization of 2-hydroxy-L-proline (PXU)

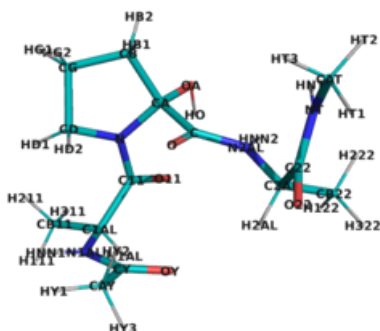


Figure S461: The energy minimized structure corresponding to 2-[1-(2-acetamidoacetyl)-2-hydroxypyrrolidin-2-yl]formamido-N-methylacetamide.

Table S830: The calculated geometric terms of 2-[1-(2-acetamidoacetyl)-2-hydroxypyrrolidin-2-yl]formamido-N-methylacetamide.

Terms	QM	CHARMM	Abs. diff.
N1AL-HNN1	1.01	0.99	0.02
N1AL-C1AL	1.46	1.46	0.00
N1AL-CY	1.38	1.34	0.03
C1AL-H1AL	1.09	1.08	0.01
C1AL-CB11	1.53	1.54	0.01
C1AL-C11	1.54	1.54	0.00
CB11-H111	1.10	1.11	0.02
CB11-H211	1.10	1.11	0.01
CB11-H311	1.09	1.11	0.02
C11-O11	1.24	1.23	0.01
C11-N	1.36	1.37	0.01
CAY-HY1	1.09	1.11	0.01
CAY-HY2	1.10	1.11	0.02
CAY-HY3	1.09	1.11	0.02
CAY-CY	1.51	1.48	0.03
CY-OY	1.23	1.22	0.00
N-CA	1.49	1.45	0.04
N-CD	1.47	1.46	0.00
CA-OA	1.40	1.43	0.03
CA-CB	1.55	1.55	0.01
CA-C	1.56	1.55	0.01
OA-HO	0.99	0.97	0.02
CB-HB1	1.09	1.10	0.01
CB-HB2	1.09	1.10	0.01
CB-CG	1.54	1.55	0.00
CG-HG1	1.09	1.10	0.00
CG-HG2	1.10	1.10	0.01
CG-CD	1.53	1.53	0.01
CD-HD1	1.09	1.10	0.00
CD-HD2	1.10	1.10	0.01
C-O	1.23	1.23	0.00
C-N2AL	1.35	1.35	0.00

Terms	QM	CHARMM	Abs. diff.
N2AL-HNN2	1.01	1.00	0.02
N2AL-C2AL	1.47	1.45	0.01
C2AL-H2AL	1.09	1.08	0.01
C2AL-CB22	1.53	1.54	0.01
C2AL-C22	1.54	1.53	0.01
CB22-H122	1.10	1.11	0.01
CB22-H222	1.10	1.11	0.01
CB22-H322	1.09	1.11	0.02
C22-O22	1.22	1.23	0.01
C22-NT	1.37	1.35	0.02
NT-HNT	1.01	0.99	0.02
NT-CAT	1.45	1.45	0.01
CAT-HT1	1.09	1.11	0.02
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.10	1.11	0.01
N1AL-C1AL-H1AL	107.51	106.13	1.38
N1AL-C1AL-CB11	111.95	111.78	0.17
N1AL-C1AL-C11	112.09	115.03	2.94
N1AL-CY-CAY	116.52	117.55	1.03
N1AL-CY-OY	120.78	121.43	0.64
HNN1-N1AL-C1AL	119.49	117.66	1.83
HNN1-N1AL-CY	119.60	119.74	0.13
C1AL-N1AL-CY	119.75	122.24	2.49
C1AL-CB11-H111	109.87	109.79	0.08
C1AL-CB11-H211	112.96	112.53	0.42
C1AL-CB11-H311	109.67	110.26	0.59
C1AL-C11-O11	118.31	117.51	0.81
C1AL-C11-N	120.29	122.40	2.11
H1AL-C1AL-CB11	108.48	106.67	1.81
H1AL-C1AL-C11	101.97	104.31	2.34
CB11-C1AL-C11	114.09	112.09	2.00
H111-CB11-H211	108.07	107.98	0.09
H111-CB11-H311	108.23	107.66	0.58
H211-CB11-H311	107.91	108.47	0.56
C11-N-CA	120.52	121.93	1.41
C11-N-CD	129.32	125.81	3.52
O11-C11-N	121.38	120.04	1.33
CAY-CY-OY	122.68	121.02	1.66
HY1-CAY-HY2	109.34	109.21	0.13
HY1-CAY-HY3	109.41	109.24	0.17
HY1-CAY-CY	113.75	111.81	1.94
HY2-CAY-HY3	107.62	107.93	0.32
HY2-CAY-CY	107.54	108.82	1.28
HY3-CAY-CY	108.99	109.75	0.75
N-CA-OA	112.53	112.19	0.34
N-CA-CB	103.94	103.39	0.55
N-CA-C	104.19	106.91	2.73
N-CD-CG	101.86	101.57	0.29
N-CD-HD1	111.12	113.39	2.27
N-CD-HD2	110.60	109.29	1.31
CA-N-CD	109.74	110.57	0.83
CA-OA-HO	104.85	105.50	0.65
CA-CB-HB1	109.84	111.73	1.89
CA-CB-HB2	108.65	112.75	4.10
CA-CB-CG	105.69	105.94	0.25
CA-C-O	119.96	118.86	1.10
CA-C-N2AL	116.03	119.52	3.49
OA-CA-CB	111.44	108.18	3.27

Terms	QM	CHARMM	Abs. diff.
OA-CA-C	113.72	114.05	0.33
CB-CA-C	110.37	111.64	1.27
CB-CG-HG1	112.79	113.34	0.55
CB-CG-HG2	110.56	109.99	0.57
CB-CG-CD	103.50	103.09	0.41
HB1-CB-HB2	109.25	105.48	3.77
HB1-CB-CG	110.39	110.08	0.30
HB2-CB-CG	112.94	110.94	2.00
CG-CD-HD1	112.75	112.46	0.30
CG-CD-HD2	110.93	111.36	0.43
HG1-CG-HG2	108.26	107.14	1.12
HG1-CG-CD	112.13	113.52	1.40
HG2-CG-CD	109.54	109.73	0.19
HD1-CD-HD2	109.41	108.64	0.77
C-N2AL-HNN2	116.59	118.88	2.29
C-N2AL-C2AL	121.81	124.71	2.90
O-C-N2AL	123.98	121.61	2.37
N2AL-C2AL-H2AL	108.21	107.34	0.87
N2AL-C2AL-CB22	109.88	108.75	1.13
N2AL-C2AL-C22	112.89	114.94	2.06
HNN2-N2AL-C2AL	119.73	115.47	4.26
C2AL-CB22-H122	110.53	109.62	0.91
C2AL-CB22-H222	111.45	110.81	0.64
C2AL-CB22-H322	109.45	110.77	1.32
C2AL-C22-O22	120.82	121.40	0.58
C2AL-C22-NT	114.95	116.95	2.00
H2AL-C2AL-CB22	109.87	109.10	0.77
H2AL-C2AL-C22	105.03	106.17	1.14
CB22-C2AL-C22	110.80	110.35	0.45
H122-CB22-H222	108.95	108.67	0.28
H122-CB22-H322	108.13	108.02	0.12
H222-CB22-H322	108.24	108.88	0.65
C22-NT-HNT	116.38	117.80	1.42
C22-NT-CAT	121.38	123.01	1.63
O22-C22-NT	123.73	121.64	2.08
NT-CAT-HT1	107.81	111.66	3.85
NT-CAT-HT2	110.00	110.44	0.44
NT-CAT-HT3	112.18	110.31	1.87
HNT-NT-CAT	117.98	118.50	0.52
HT1-CAT-HT2	109.44	107.92	1.53
HT1-CAT-HT3	108.39	108.02	0.38
HT2-CAT-HT3	108.97	108.39	0.58

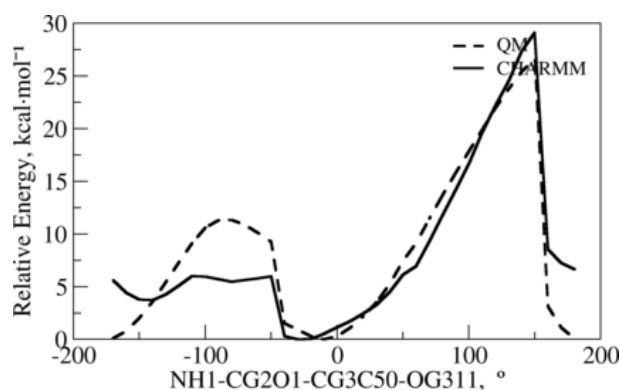


Figure S462: The PES scan for flexible dihedral corresponding to 2-[1-(2-acetamidoacetyl)-2-hydroxypyrrolidin-2-yl]formamido-N-methylacetamide

2.151 The small molecule 2 used for bonded terms optimization of 2-hydroxy-L-proline (PXU)

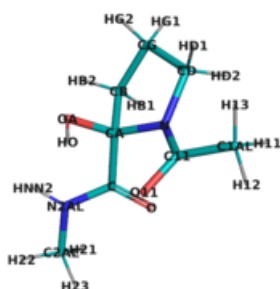


Figure S463: The energy minimized structure corresponding to (2R)-1-acetyl-2-hydroxy-N-methylpyrrolidine-2-carboxamide.

Table S831: The calculated geometric terms of (2R)-1-acetyl-2-hydroxy-N-methylpyrrolidine-2-carboxamide.

Terms	QM	CHARMM	Abs. diff.
C1AL-H11	1.09	1.11	0.02
C1AL-H12	1.09	1.11	0.02
C1AL-H13	1.09	1.11	0.01
C1AL-C11	1.51	1.49	0.02
C11-O11	1.25	1.23	0.02
C11-N	1.36	1.36	0.00
N-CA	1.46	1.45	0.01
N-CD	1.46	1.47	0.01
CA-OA	1.42	1.43	0.01
CA-CB	1.53	1.54	0.01
CA-C	1.54	1.55	0.00
OA-HO	0.98	0.96	0.02
CB-HB1	1.09	1.10	0.01
CB-HB2	1.09	1.10	0.01
CB-CG	1.53	1.54	0.01
CG-HG1	1.09	1.10	0.00
CG-HG2	1.09	1.10	0.01
CG-CD	1.53	1.53	0.00
CD-HD1	1.09	1.10	0.01
CD-HD2	1.10	1.10	0.00
C-O	1.23	1.23	0.00
C-N2AL	1.35	1.35	0.00
N2AL-HNN2	1.01	1.00	0.01
N2AL-C2AL	1.45	1.44	0.01
C2AL-H21	1.09	1.11	0.02
C2AL-H22	1.09	1.11	0.02
C2AL-H23	1.09	1.11	0.02
C1AL-C11-O11	122.45	119.10	3.35
C1AL-C11-N	117.35	118.04	0.69
H11-C1AL-H12	109.77	108.49	1.29
H11-C1AL-H13	108.15	109.94	1.79
H11-C1AL-C11	110.86	110.59	0.27

Terms	QM	CHARMM	Abs. diff.
H12-C1AL-H13	109.13	108.33	0.80
H12-C1AL-C11	108.02	108.82	0.80
H13-C1AL-C11	110.89	110.62	0.27
C11-N-CA	118.34	120.53	2.19
C11-N-CD	128.64	121.35	7.29
O11-C11-N	120.19	122.83	2.64
N-CA-OA	111.72	111.52	0.20
N-CA-CB	103.38	101.89	1.49
N-CA-C	108.58	113.22	4.64
N-CD-CG	101.30	105.26	3.96
N-CD-HD1	111.07	112.50	1.44
N-CD-HD2	110.67	108.01	2.66
CA-N-CD	112.76	112.74	0.02
CA-OA-HO	102.79	105.40	2.62
CA-CB-HB1	109.27	110.90	1.62
CA-CB-HB2	109.73	113.28	3.54
CA-CB-CG	104.36	104.85	0.49
CA-C-O	120.35	119.47	0.88
CA-C-N2AL	113.90	118.73	4.83
OA-CA-CB	109.91	104.96	4.96
OA-CA-C	112.69	114.81	2.12
CB-CA-C	110.16	109.26	0.90
CB-CG-HG1	113.00	113.51	0.51
CB-CG-HG2	110.25	109.51	0.74
CB-CG-CD	102.59	103.17	0.58
HB1-CB-HB2	109.03	106.21	2.82
HB1-CB-CG	110.15	109.26	0.89
HB2-CB-CG	114.14	112.37	1.77
CG-CD-HD1	113.16	111.50	1.66
CG-CD-HD2	111.49	111.22	0.28
HG1-CG-HG2	108.65	106.86	1.79
HG1-CG-CD	112.68	113.72	1.04
HG2-CG-CD	109.55	110.05	0.49
HD1-CD-HD2	108.99	108.31	0.68
C-N2AL-HNN2	116.27	119.50	3.23
C-N2AL-C2AL	122.03	121.73	0.30
O-C-N2AL	125.50	121.78	3.72
N2AL-C2AL-H21	107.32	110.69	3.38
N2AL-C2AL-H22	110.24	110.62	0.38
N2AL-C2AL-H23	111.41	110.41	0.99
HNN2-N2AL-C2AL	120.91	118.73	2.18
H21-C2AL-H22	109.63	108.42	1.21
H21-C2AL-H23	108.97	108.23	0.74
H22-C2AL-H23	109.24	108.37	0.87

2.152 The small molecule used for bonded terms optimization of S-carbamoyl-L-cysteine (QCS)

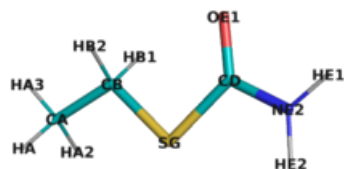


Figure S464: The energy minimized structure corresponding to (ethylsulfanyl)formamide.

Table S832: The calculated geometric terms of (ethylsulfanyl)formamide.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.82	1.83	0.01
SG-CD	1.80	1.75	0.05
CD-NE2	1.36	1.35	0.01
CD-OE1	1.22	1.23	0.01
NE2-HE1	1.01	1.00	0.02
NE2-HE2	1.01	0.99	0.02
HA3-CA-HA2	108.08	108.40	0.32
HA3-CA-HA	108.09	108.39	0.30
HA3-CA-CB	109.47	110.39	0.93
HA2-CA-HA	108.34	108.45	0.12
HA2-CA-CB	111.38	110.57	0.81
CA-CB-HB1	111.39	108.66	2.74
CA-CB-HB2	111.40	108.67	2.73
CA-CB-SG	109.36	112.84	3.49
HA-CA-CB	111.37	110.56	0.81
CB-SG-CD	97.77	97.73	0.05
HB1-CB-HB2	107.83	106.80	1.03
HB1-CB-SG	108.39	109.84	1.45
HB2-CB-SG	108.38	109.84	1.47
SG-CD-NE2	112.95	112.80	0.15
SG-CD-OE1	123.19	124.80	1.61
CD-NE2-HE1	117.65	116.89	0.76
CD-NE2-HE2	122.83	119.38	3.45
NE2-CD-OE1	123.86	122.40	1.46
HE1-NE2-HE2	119.51	123.72	4.21

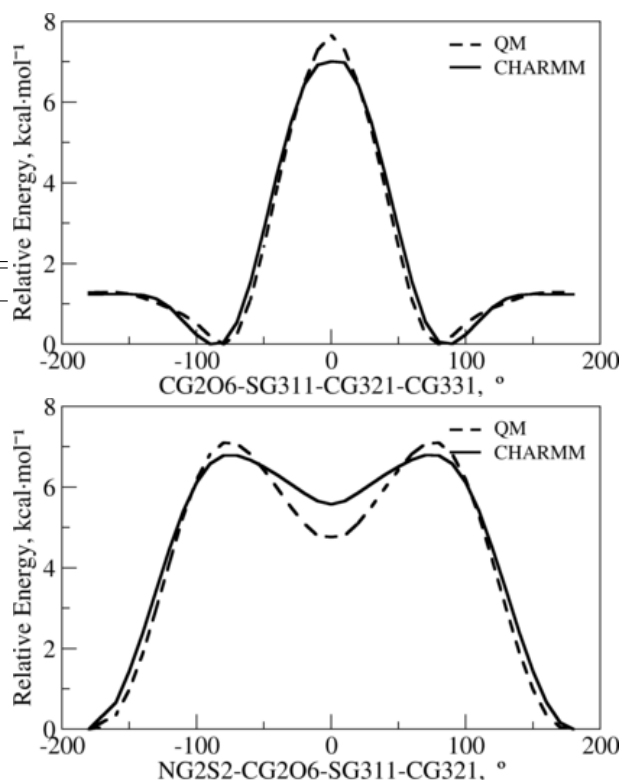


Figure S465: The PES scan for flexible dihedrals corresponding to (ethylsulfanyl)formamide.

2.153 The small molecule used for bonded terms optimization of S-[(1S)-1-carboxy-1-(phosphonoxy)ethyl]-L-cysteine (QPA)

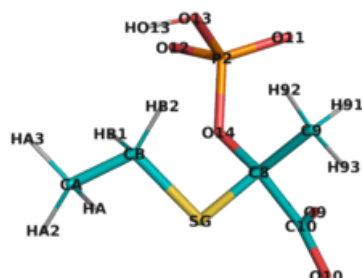


Figure S466: The energy minimized structure corresponding to 2-(ethylsulfanyl)-2-[(trihydroxy-lambda4-phosphanyl)oxy]propanoic acid.

Table S833: The calculated geometric terms of 2-(ethylsulfanyl)-2-[(trihydroxy-lambda4-phosphanyl)oxy]propanoic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.10	1.11	0.02
CA-HA	1.10	1.11	0.02
CA-CB	1.53	1.53	0.00
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.82	1.82	0.01
SG-C8	1.88	1.90	0.02
C8-C9	1.53	1.56	0.03
C8-C10	1.58	1.60	0.02
C8-O14	1.42	1.43	0.01
C9-H91	1.09	1.11	0.01
C9-H92	1.10	1.11	0.01
C9-H93	1.09	1.11	0.02
C10-O9	1.26	1.27	0.01
C10-O10	1.28	1.27	0.01
O14-P2	1.67	1.58	0.08
P2-O11	1.51	1.50	0.00
P2-O12	1.52	1.50	0.01
P2-O13	1.71	1.60	0.11
O13-HO13	0.98	0.96	0.01
HA3-CA-HA2	108.21	108.83	0.62
HA3-CA-HA	108.19	108.90	0.71
HA3-CA-CB	110.49	110.47	0.01
HA2-CA-HA	107.87	108.47	0.61
HA2-CA-CB	110.74	110.03	0.71
CA-CB-HB1	110.66	109.07	1.60
CA-CB-HB2	110.25	109.25	1.00
CA-CB-SG	109.58	112.78	3.20
HA-CA-CB	111.24	110.09	1.15

Terms	QM	CHARMM	Abs. diff.
CB-SG-C8	100.20	104.73	4.53
HB1-CB-HB2	107.81	107.15	0.65
HB1-CB-SG	108.18	108.91	0.73
HB2-CB-SG	110.32	109.52	0.80
SG-C8-C9	109.57	104.45	5.12
SG-C8-C10	102.87	106.74	3.87
SG-C8-O14	106.73	108.17	1.43
C8-C9-H91	108.80	109.79	0.99
C8-C9-H92	111.34	111.35	0.01
C8-C9-H93	107.47	109.71	2.24
C8-C10-O9	118.24	117.66	0.58
C8-C10-O10	112.11	117.94	5.82
C8-O14-P2	129.02	128.84	0.18
C9-C8-C10	109.52	106.22	3.30
C9-C8-O14	114.59	113.90	0.68
H91-C9-H92	108.38	109.35	0.97
H91-C9-H93	110.43	107.96	2.48
H92-C9-H93	110.41	108.62	1.80
C10-C8-O14	112.83	116.49	3.66
O9-C10-O10	129.63	123.39	6.25
O14-P2-O11	112.35	111.79	0.56
O14-P2-O12	104.39	106.52	2.13
O14-P2-O13	101.78	105.86	4.08
P2-O13-HO13	103.53	106.80	3.27
O11-P2-O12	124.84	119.48	5.36
O11-P2-O13	106.09	108.96	2.87
O12-P2-O13	104.87	103.14	1.73

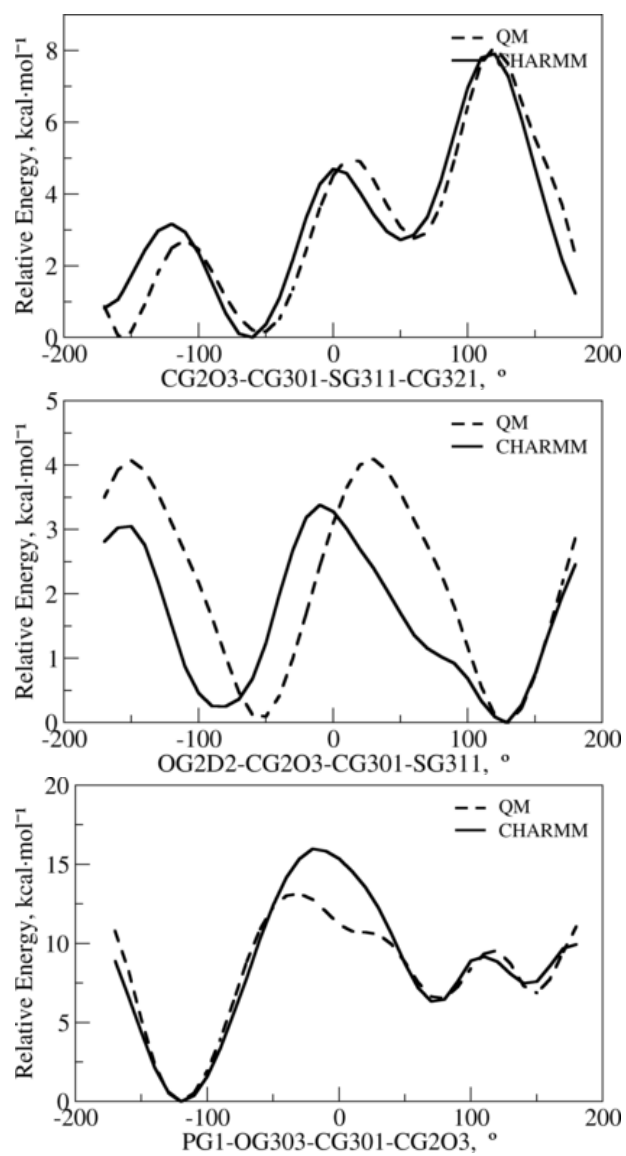


Figure S467: The PES scan for flexible dihedrals corresponding to 2-(ethylsulfanyl)-2-[(trihydroxy-1- λ 4-phosphanyl)oxy]propanoic acid.

2.154 The small molecule 1 used for bonded terms optimization of 3-[(2,2,5,5-tetramethyl-1-oxo-2,5-dihydro-1H-pyrrolium-3-yl)methyl]disulfanyl-D-alanine (R1A)

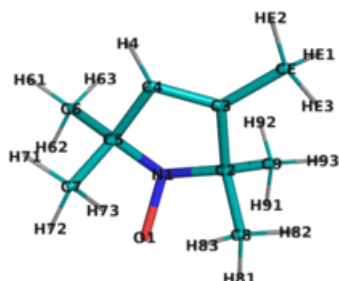


Figure S468: The energy minimized structure corresponding to 2,2,3,5,5-pentamethyl-2,5-dihydro-1H-pyrrol-1-ol.

Table S834: The calculated geometric terms of 2,2,3,5,5-pentamethyl-2,5-dihydro-1H-pyrrol-1-ol.

Terms	QM	CHARMM	Abs. diff.
HE3-CE	1.10	1.11	0.01
CE-HE1	1.10	1.11	0.01
CE-HE2	1.10	1.11	0.01
CE-C3	1.50	1.51	0.01
C3-C2	1.51	1.53	0.02
C3-C4	1.35	1.37	0.02
C2-C8	1.54	1.54	0.00
C2-C9	1.53	1.53	0.00
C2-N1	1.50	1.49	0.01
C8-H81	1.10	1.11	0.01
C8-H82	1.10	1.11	0.01
C8-H83	1.10	1.10	0.00
C9-H91	1.10	1.11	0.02
C9-H92	1.10	1.11	0.01
C9-H93	1.10	1.11	0.01
C4-H4	1.09	1.08	0.02
C4-C5	1.50	1.51	0.01
N1-O1	1.41	1.41	0.00
N1-C5	1.50	1.49	0.00
C5-C6	1.53	1.52	0.01
C5-C7	1.54	1.53	0.00
C6-H61	1.10	1.11	0.01
C6-H62	1.10	1.11	0.02
C6-H63	1.10	1.11	0.01
C7-H71	1.10	1.11	0.01
C7-H72	1.10	1.11	0.01
C7-H73	1.09	1.10	0.01
HE3-CE-HE1	106.99	109.23	2.24
HE3-CE-HE2	108.23	108.97	0.73
HE3-CE-C3	111.07	109.78	1.29

Terms	QM	CHARMM	Abs. diff.
CE-C3-C2	122.82	122.84	0.02
CE-C3-C4	127.39	128.86	1.47
HE1-CE-HE2	108.26	108.85	0.59
HE1-CE-C3	111.19	109.79	1.40
HE2-CE-C3	110.94	110.20	0.74
C3-C2-C8	111.71	109.97	1.74
C3-C2-C9	113.81	114.36	0.55
C3-C2-N1	101.75	106.50	4.75
C3-C4-H4	125.08	126.98	1.90
C3-C4-C5	111.40	108.34	3.06
C2-C3-C4	109.78	108.30	1.48
C2-C8-H81	105.90	109.05	3.15
C2-C8-H82	111.34	109.69	1.64
C2-C8-H83	111.73	112.87	1.13
C2-C9-H91	107.56	109.37	1.80
C2-C9-H92	109.69	110.56	0.86
C2-C9-H93	112.18	110.12	2.06
C2-N1-O1	113.30	113.90	0.61
C2-N1-C5	106.90	102.25	4.65
C8-C2-C9	109.05	111.89	2.84
C8-C2-N1	113.67	112.85	0.83
H81-C8-H82	110.75	108.23	2.52
H81-C8-H83	108.72	108.21	0.51
H82-C8-H83	108.37	108.68	0.30
C9-C2-N1	106.68	100.92	5.77
H91-C9-H92	108.43	108.59	0.15
H91-C9-H93	109.29	108.77	0.52
H92-C9-H93	109.59	109.41	0.18
C4-C5-N1	101.35	107.14	5.78
C4-C5-C6	113.24	113.63	0.39
C4-C5-C7	111.91	107.30	4.61
H4-C4-C5	123.51	124.25	0.73
N1-C5-C6	107.38	102.90	4.48
N1-C5-C7	113.79	113.74	0.05
O1-N1-C5	113.26	113.64	0.38
C5-C6-H61	111.67	110.31	1.36
C5-C6-H62	108.14	109.12	0.97
C5-C6-H63	109.58	110.42	0.84
C5-C7-H71	110.48	109.44	1.04
C5-C7-H72	107.53	109.33	1.79
C5-C7-H73	111.40	113.00	1.60
C6-C5-C7	109.00	112.15	3.15
H61-C6-H62	109.32	109.01	0.30
H61-C6-H63	109.46	109.44	0.02
H62-C6-H63	108.60	108.50	0.10
H71-C7-H72	110.66	108.05	2.62
H71-C7-H73	108.54	108.26	0.28
H72-C7-H73	108.20	108.65	0.45

2.155 The small molecule 2 used for bonded terms optimization of 3-[(2,2,5,5-tetramethyl-1-oxo-2,5-dihydro-1H-pyrrolium-3-yl)methyl]disulfanyl-D-alanine (R1A)

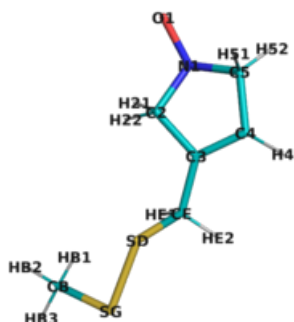


Figure S469: The energy minimized structure corresponding to 3-[(methyldisulfanyl)methyl]-2,5-dihydro-1H-pyrrol-1-ol.

Table S835: The calculated geometric terms of 3-[(methyldisulfanyl)methyl]-2,5-dihydro-1H-pyrrol-1-ol.

Terms	QM	CHARMM	Abs. diff.
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-HB3	1.09	1.11	0.02
CB-SG	1.82	1.81	0.00
SG-SD	2.06	2.03	0.04
SD-CE	1.84	1.82	0.02
CE-HE1	1.10	1.11	0.01
CE-HE2	1.10	1.11	0.01
CE-C3	1.49	1.50	0.01
C3-C2	1.51	1.51	0.00
C3-C4	1.35	1.37	0.01
C2-H21	1.11	1.10	0.01
C2-H22	1.10	1.10	0.00
C2-N1	1.48	1.47	0.00
C4-H4	1.09	1.08	0.01
C4-C5	1.50	1.52	0.01
N1-O1	1.40	1.38	0.02
N1-C5	1.48	1.48	0.00
C5-H51	1.11	1.10	0.01
C5-H52	1.10	1.10	0.00
CB-SG-SD	101.37	102.23	0.85
HB1-CB-HB2	109.40	107.83	1.57
HB1-CB-HB3	108.94	108.39	0.56
HB1-CB-SG	111.05	110.48	0.57
HB2-CB-HB3	109.43	108.46	0.97
HB2-CB-SG	110.84	110.58	0.25
HB3-CB-SG	107.12	111.01	3.89
SG-SD-CE	102.08	103.03	0.95
SD-CE-HE1	107.76	111.83	4.07

Terms	QM	CHARMM	Abs. diff.
SD-CE-HE2	108.83	109.86	1.03
SD-CE-C3	109.25	108.93	0.32
CE-C3-C2	125.18	120.36	4.81
CE-C3-C4	126.70	130.64	3.94
HE1-CE-HE2	109.24	108.39	0.84
HE1-CE-C3	110.44	108.54	1.91
HE2-CE-C3	111.24	109.25	1.99
C3-C2-H21	111.91	105.93	5.98
C3-C2-H22	114.79	119.68	4.89
C3-C2-N1	102.32	104.54	2.22
C3-C4-H4	125.44	126.12	0.68
C3-C4-C5	108.47	108.71	0.24
C2-C3-C4	108.03	108.59	0.56
C2-N1-O1	111.64	112.34	0.70
C2-N1-C5	101.78	104.52	2.74
H21-C2-H22	108.16	106.21	1.96
H21-C2-N1	108.73	105.89	2.84
H22-C2-N1	110.72	113.61	2.89
C4-C5-N1	102.36	104.25	1.89
C4-C5-H51	111.57	107.03	4.55
C4-C5-H52	115.48	119.34	3.87
H4-C4-C5	126.06	124.82	1.24
N1-C5-H51	108.46	107.52	0.94
N1-C5-H52	110.51	111.45	0.94
O1-N1-C5	111.55	112.31	0.76
H51-C5-H52	108.19	106.68	1.51

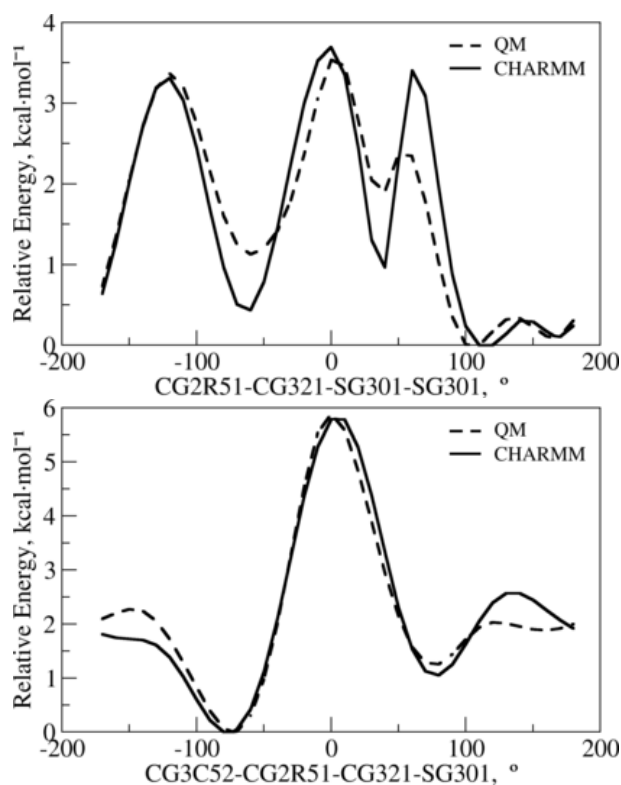


Figure S470: The PES scan for flexible dihedrals corresponding to 3-[(methyldisulfanyl)methyl]-2,5-dihydro-1H-pyrrol-1-ol.

2.156 The small molecule used for bonded terms optimization of O-[(S)-hydroxy(methyl)phosphoryl]-L-serine (SBG)

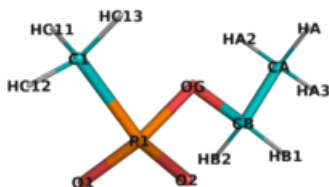


Figure S471: The energy minimized structure corresponding to ethoxy(methyl)phosphinic acid.

Table S836: The calculated geometric terms of ethoxy(methyl)phosphinic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.10	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB1	1.10	1.12	0.02
CB-HB2	1.10	1.12	0.02
CB-OG	1.43	1.43	0.00
OG-P1	1.71	1.63	0.08
P1-O1	1.52	1.51	0.02
P1-O2	1.52	1.51	0.02
P1-C1	1.83	1.83	0.00
C1-HC11	1.09	1.10	0.01
C1-HC12	1.10	1.10	0.00
C1-HC13	1.09	1.10	0.01
HA3-CA-HA2	108.65	108.99	0.34
HA3-CA-HA	108.78	109.04	0.26
HA3-CA-CB	110.69	110.68	0.01
HA2-CA-HA	108.42	108.36	0.06
HA2-CA-CB	110.09	109.88	0.21
CA-CB-HB1	110.59	109.87	0.72
CA-CB-HB2	110.84	109.87	0.96
CA-CB-OG	107.78	106.40	1.38
HA-CA-CB	110.15	109.85	0.30
CB-OG-P1	114.56	116.24	1.67
HB1-CB-HB2	108.20	109.04	0.84
HB1-CB-OG	109.75	110.80	1.05
HB2-CB-OG	109.68	110.84	1.16
OG-P1-O1	107.91	111.56	3.65
OG-P1-O2	108.33	111.60	3.27
OG-P1-C1	95.70	96.45	0.75
P1-C1-HC11	110.23	107.93	2.31
P1-C1-HC12	108.44	107.72	0.72
P1-C1-HC13	110.16	107.86	2.30

Terms	QM	CHARMM	Abs. diff.
O1-P1-O2	121.64	124.27	2.63
O1-P1-C1	110.14	104.18	5.96
O2-P1-C1	109.94	104.22	5.72
HC11-C1-HC12	109.15	110.92	1.77
HC11-C1-HC13	109.84	111.26	1.42
HC12-C1-HC13	108.98	110.98	2.00

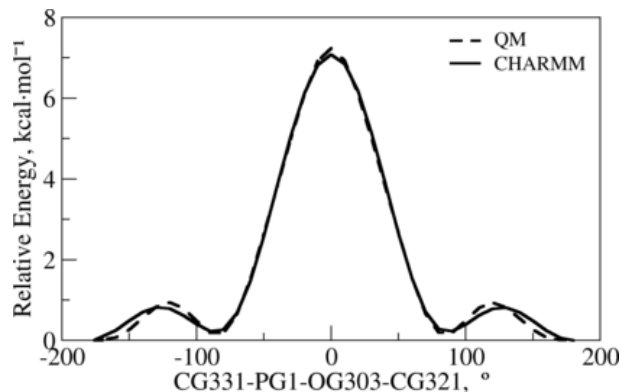


Figure S472: The PES scan for flexible dihedral corresponding to ethoxy(methyl)phosphinic acid.

2.157 The small molecule used for bonded terms optimization of O-benzylsulfonyl-serine (SEB)

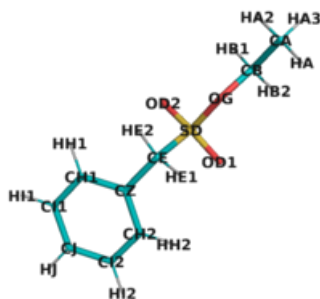


Figure S473: The energy minimized structure corresponding to ethylphenylmethanesulfonate.

Table S837: The calculated geometric terms of ethylphenylmethanesulfonate.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.51	1.53	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-OG	1.46	1.44	0.02
OG-SD	1.64	1.60	0.04
SD-OD1	1.46	1.44	0.02
SD-OD2	1.46	1.44	0.02
SD-CE	1.79	1.80	0.02
CE-HE1	1.09	1.11	0.02
CE-HE2	1.09	1.11	0.02
CE-CZ	1.50	1.52	0.02
CZ-CH1	1.40	1.41	0.01
CZ-CH2	1.40	1.41	0.01
CH1-HH1	1.09	1.08	0.01
CH1-CI1	1.39	1.40	0.01
CH2-HH2	1.09	1.08	0.01
CH2-CI2	1.39	1.40	0.01
CI1-HI1	1.09	1.08	0.01
CI1-CJ	1.40	1.40	0.00
CI2-HI2	1.09	1.08	0.01
CI2-CJ	1.40	1.40	0.00
CJ-HJ	1.09	1.08	0.01
HA3-CA-HA2	108.66	108.59	0.07
HA3-CA-HA	108.66	108.64	0.02
HA3-CA-CB	109.63	110.47	0.84
HA2-CA-HA	108.91	108.52	0.39
HA2-CA-CB	110.47	110.28	0.19
CA-CB-HB1	112.07	110.15	1.92
CA-CB-HB2	112.07	110.11	1.96
CA-CB-OG	106.19	107.55	1.37

Terms	QM	CHARMM	Abs. diff.
HA-CA-CB	110.47	110.29	0.18
CB-OG-SD	113.59	114.48	0.89
HB1-CB-HB2	109.36	108.68	0.68
HB1-CB-OG	108.49	110.11	1.61
HB2-CB-OG	108.49	110.23	1.74
OG-SD-OD1	109.09	108.51	0.58
OG-SD-OD2	109.08	108.54	0.55
OG-SD-CE	96.03	96.61	0.58
SD-CE-HE1	106.33	107.91	1.57
SD-CE-HE2	106.33	107.82	1.49
SD-CE-CZ	109.40	109.83	0.42
OD1-SD-OD2	120.12	121.71	1.58
OD1-SD-CE	109.91	109.26	0.65
OD2-SD-CE	109.91	109.29	0.62
CE-CZ-CH1	120.12	120.42	0.30
CE-CZ-CH2	120.12	120.26	0.14
HE1-CE-HE2	109.32	110.49	1.17
HE1-CE-CZ	112.54	110.25	2.29
HE2-CE-CZ	112.54	110.48	2.06
CZ-CH1-HH1	119.73	120.26	0.53
CZ-CH1-CI1	120.06	120.25	0.19
CZ-CH2-HH2	119.73	120.13	0.40
CZ-CH2-CI2	120.06	120.27	0.21
CH1-CZ-CH2	119.72	119.32	0.40
CH1-CI1-HI1	119.76	119.85	0.09
CH1-CI1-CJ	120.14	120.19	0.05
HH1-CH1-CI1	120.21	119.49	0.73
CH2-CI2-HI2	119.76	119.79	0.02
CH2-CI2-CJ	120.14	120.15	0.01
HH2-CH2-CI2	120.21	119.59	0.62
CI1-CJ-CI2	119.88	119.82	0.06
CI1-CJ-HJ	120.06	120.10	0.04
HI1-CI1-CJ	120.10	119.96	0.14
CI2-CJ-HJ	120.06	120.08	0.01
HI2-CI2-CJ	120.10	120.06	0.04

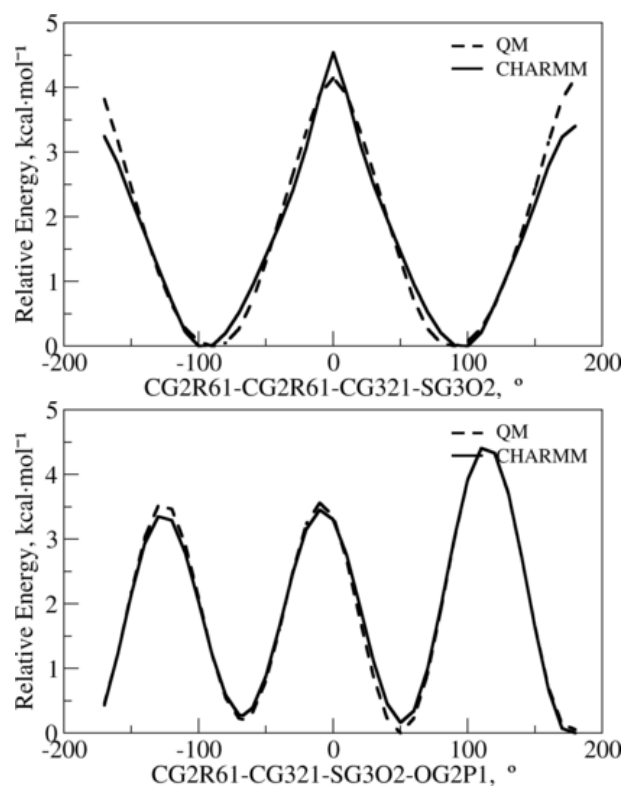


Figure S474: The PES scan for flexible dihedrals corresponding to ethylphenylmethanesulfonate.

2.158 The small molecule used for bonded terms optimization of O-[N,N-dimethylphosphoramidate]-L-serine (SEN)

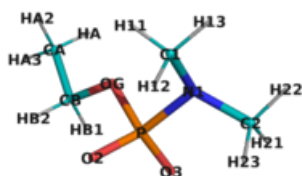


Figure S475: The energy minimized structure corresponding to (dimethylamino)(ethoxy)phosphinic acid.

Table S838: The calculated geometric terms of (dimethylamino)(ethoxy)phosphinic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-HB1	1.10	1.12	0.02
CB-HB2	1.10	1.12	0.02
CB-OG	1.43	1.43	0.00
OG-P	1.69	1.64	0.05
P-O2	1.52	1.51	0.01
P-O3	1.52	1.51	0.00
P-N1	1.73	1.74	0.01
N1-C1	1.46	1.45	0.01
N1-C2	1.46	1.45	0.01
C1-H11	1.09	1.11	0.02
C1-H12	1.10	1.11	0.01
C1-H13	1.10	1.11	0.01
C2-H21	1.09	1.11	0.02
C2-H22	1.10	1.11	0.01
C2-H23	1.11	1.11	0.01
HA3-CA-HA2	108.69	108.96	0.27
HA3-CA-HA	108.84	108.92	0.09
HA3-CA-CB	110.63	110.71	0.07
HA2-CA-HA	108.36	108.29	0.07
HA2-CA-CB	110.06	109.95	0.11
CA-CB-HB1	110.38	110.16	0.22
CA-CB-HB2	111.48	109.98	1.50
CA-CB-OG	107.42	106.27	1.15
HA-CA-CB	110.20	109.96	0.24
CB-OG-P	115.23	118.59	3.35
HB1-CB-HB2	107.96	109.03	1.07
HB1-CB-OG	109.94	110.60	0.66
HB2-CB-OG	109.66	110.78	1.12

Terms	QM	CHARMM	Abs. diff.
OG-P-O2	106.61	107.98	1.37
OG-P-O3	110.53	106.65	3.87
OG-P-N1	95.21	102.03	6.81
P-N1-C1	114.75	115.53	0.78
P-N1-C2	114.54	115.75	1.22
O2-P-O3	122.04	118.92	3.12
O2-P-N1	111.38	109.95	1.43
O3-P-N1	107.78	109.90	2.12
N1-C1-H11	109.32	110.21	0.89
N1-C1-H12	112.61	109.56	3.04
N1-C1-H13	109.03	108.89	0.14
N1-C2-H21	108.97	110.35	1.38
N1-C2-H22	109.08	108.91	0.17
N1-C2-H23	112.75	109.56	3.19
C1-N1-C2	111.83	112.83	1.01
H11-C1-H12	108.40	109.76	1.37
H11-C1-H13	108.71	108.86	0.15
H12-C1-H13	108.69	109.52	0.83
H21-C2-H22	109.38	108.75	0.63
H21-C2-H23	108.77	109.82	1.05
H22-C2-H23	107.85	109.43	1.58

2.159 The small molecule used for bonded terms optimization of O-[(S)-methyl(1-methylethoxy)phosphoryl]-L-serine (SGB)

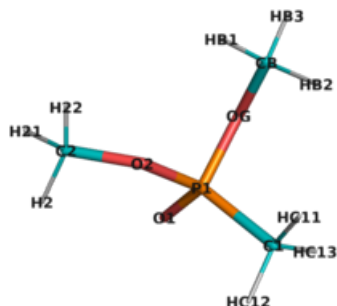


Figure S476: The energy minimized structure corresponding to dimethylmethylphosphonate.

Table S839: The calculated geometric terms of dimethylmethylphosphonate.

Terms	QM	CHARMM	Abs. diff.
HB1-CB	1.09	1.12	0.02
CB-HB3	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-OG	1.44	1.42	0.01
OG-P1	1.63	1.59	0.04
P1-C1	1.80	1.80	0.00
P1-O1	1.48	1.47	0.01
P1-O2	1.63	1.59	0.03
C1-HC11	1.09	1.10	0.01
C1-HC12	1.09	1.10	0.01
C1-HC13	1.09	1.10	0.01
O2-C2	1.45	1.43	0.02
C2-H2	1.09	1.12	0.03
C2-H21	1.09	1.11	0.02
C2-H22	1.09	1.12	0.02
HB1-CB-HB3	109.89	106.92	2.97
HB1-CB-HB2	109.87	109.37	0.50
HB1-CB-OG	111.06	112.09	1.03
CB-OG-P1	120.31	118.71	1.60
HB3-CB-HB2	109.30	107.08	2.22
HB3-CB-OG	106.10	109.05	2.95
HB2-CB-OG	110.54	112.07	1.53
OG-P1-C1	106.37	106.75	0.38
OG-P1-O1	111.21	109.84	1.37
OG-P1-O2	104.69	104.85	0.16
P1-C1-HC11	111.58	108.46	3.12
P1-C1-HC12	108.89	107.85	1.04
P1-C1-HC13	109.10	107.99	1.11
P1-O2-C2	116.19	119.20	3.01
C1-P1-O1	117.11	117.27	0.16
C1-P1-O2	100.07	107.04	6.98
HC11-C1-HC12	108.80	110.70	1.91

Terms	QM	CHARMM	Abs. diff.
HC11-C1-HC13	109.51	111.15	1.64
HC12-C1-HC13	108.93	110.56	1.63
O1-P1-O2	116.03	110.32	5.71
O2-C2-H2	110.16	111.44	1.28
O2-C2-H21	105.87	109.69	3.81
O2-C2-H22	110.36	111.57	1.22
H2-C2-H21	110.65	107.61	3.04
H2-C2-H22	109.73	108.63	1.11
H21-C2-H22	110.01	107.75	2.26

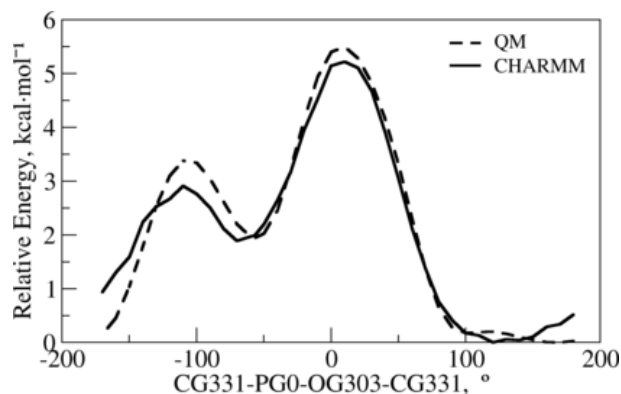


Figure S477: The PES scan for flexible dihedral corresponding to dimethylmethylphosphonate.

2.160 The small molecule used for bonded terms optimization of S-nitroso-cysteine (SNC)

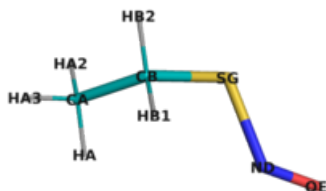


Figure S478: The energy minimized structure corresponding to (nitrososulfanyl)ethane.

Table S840: The calculated geometric terms of (nitrososulfanyl)ethane.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.54	0.01
CB-HB1	1.10	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.81	1.83	0.02
SG-ND	1.81	1.83	0.02
ND-OE	1.21	1.22	0.00
HA3-CA-HA2	108.14	108.57	0.43
HA3-CA-HA	108.48	108.37	0.11
HA3-CA-CB	109.93	110.55	0.63
HA2-CA-HA	108.20	108.39	0.19
HA2-CA-CB	111.36	110.61	0.74
CA-CB-HB1	111.15	108.37	2.78
CA-CB-HB2	111.37	108.87	2.51
CA-CB-SG	113.20	113.18	0.02
HA-CA-CB	110.65	110.27	0.38
CB-SG-ND	94.35	94.54	0.19
HB1-CB-HB2	107.83	106.17	1.66
HB1-CB-SG	104.80	111.06	6.26
HB2-CB-SG	108.14	108.94	0.80
SG-ND-OE	115.33	115.22	0.11

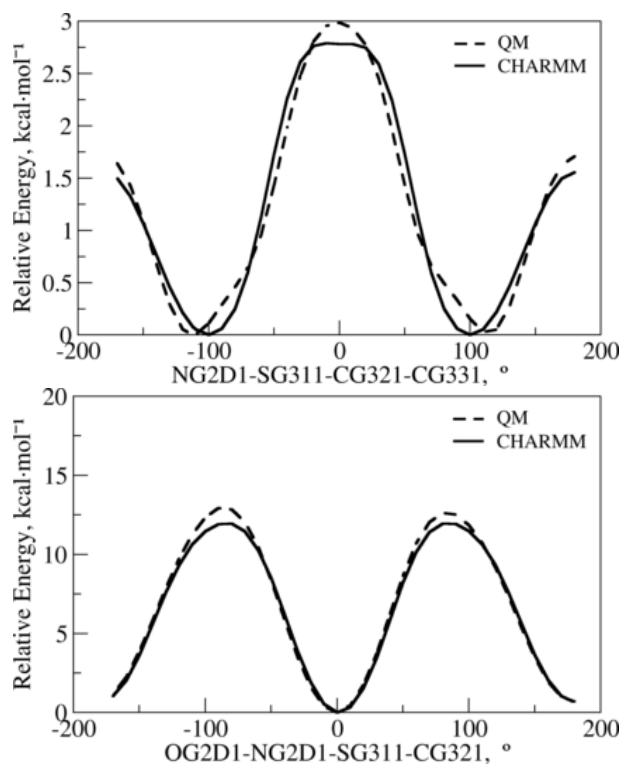
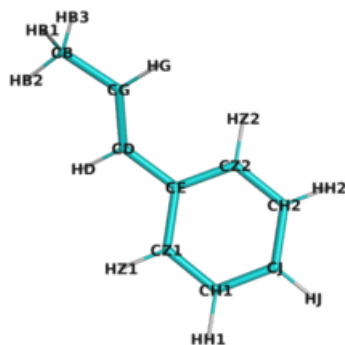


Figure S479: The PES scan for flexible dihedrals corresponding to (nitrososulfanyl)ethane.

2.161 The small molecule used for bonded terms optimization of Styrylalanine (STYA)



Terms	QM	CHARMM	Abs. diff.
CE-CZ1-CH1	120.96	120.59	0.38
CE-CZ2-HZ2	119.53	120.48	0.95
CE-CZ2-CH2	120.72	120.58	0.15
CZ1-CE-CZ2	118.35	118.76	0.41
CZ1-CH1-HH1	119.80	119.95	0.16
CZ1-CH1-CJ	120.09	120.07	0.01
HZ1-CZ1-CH1	119.80	118.82	0.99
CZ2-CH2-HH2	119.67	119.95	0.27
CZ2-CH2-CJ	120.31	120.02	0.29
HZ2-CZ2-CH2	119.73	118.94	0.79
CH1-CJ-CH2	119.55	119.98	0.43
CH1-CJ-HJ	120.25	120.05	0.20
HH1-CH1-CJ	120.11	119.97	0.14
CH2-CJ-HJ	120.20	119.97	0.23
HH2-CH2-CJ	120.01	120.03	0.02

Figure S480: The energy minimized structure corresponding to [(1E)-prop-1-en-1-yl]benzene.

Table S841: The calculated geometric terms of [(1E)-prop-1-en-1-yl]benzene.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.10	1.11	0.02
CB-HB1	1.10	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.50	1.51	0.01
CG-HG	1.09	1.10	0.01
CG-CD	1.35	1.35	0.00
CD-HD	1.09	1.10	0.01
CD-CE	1.47	1.47	0.00
CE-CZ1	1.40	1.41	0.00
CE-CZ2	1.41	1.41	0.01
CZ1-HZ1	1.09	1.08	0.01
CZ1-CH1	1.39	1.40	0.01
CZ2-HZ2	1.09	1.08	0.01
CZ2-CH2	1.39	1.40	0.01
CH1-HH1	1.09	1.08	0.01
CH1-CJ	1.40	1.40	0.00
CH2-HH2	1.09	1.08	0.01
CH2-CJ	1.40	1.40	0.00
CJ-HJ	1.09	1.08	0.01
HB3-CB-HB1	106.97	107.58	0.61
HB3-CB-HB2	108.13	107.37	0.76
HB3-CB-CG	111.14	110.84	0.30
CB-CG-HG	116.61	117.17	0.56
CB-CG-CD	124.22	123.90	0.32
HB1-CB-HB2	108.25	107.44	0.81
HB1-CB-CG	111.18	110.79	0.39
HB2-CB-CG	111.01	112.60	1.59
CG-CD-HD	118.53	116.12	2.41
CG-CD-CE	125.25	126.89	1.64
HG-CG-CD	119.17	118.94	0.24
CD-CE-CZ1	119.51	118.21	1.30
CD-CE-CZ2	122.14	123.03	0.88
HD-CD-CE	116.19	116.94	0.75
CE-CZ1-HZ1	119.23	120.60	1.37

2.162 The small molecule used for bonded terms optimization of (3-amino-2,5-dioxo-1-pyrrolidinyl)aceticacid (SUI)

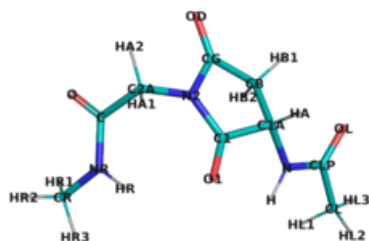


Figure S481: The energy minimized structure corresponding to 2-[(3S)-3-acetamido-2,5-dioxopyrrolidin-1-yl]-N-methylacetamide.

Table S842: The calculated geometric terms of 2-[(3S)-3-acetamido-2,5-dioxopyrrolidin-1-yl]-N-methylacetamide.

Terms	QM	CHARMM	Abs. diff.
CL-HL1	1.09	1.11	0.02
CL-HL2	1.09	1.11	0.02
CL-HL3	1.09	1.11	0.02
CL-CLP	1.51	1.48	0.03
CLP-OL	1.23	1.22	0.01
CLP-N	1.38	1.34	0.03
N-H	1.02	1.00	0.02
N-C1A	1.44	1.45	0.00
C1A-HA	1.10	1.05	0.05
C1A-CB	1.53	1.52	0.01
C1A-C1	1.52	1.53	0.01
CB-HB1	1.09	1.10	0.01
CB-HB2	1.10	1.10	0.00
CB-CG	1.52	1.52	0.01
CG-OD	1.22	1.23	0.01
CG-N2	1.42	1.39	0.03
C1-O1	1.23	1.23	0.00
C1-N2	1.37	1.39	0.01
N2-C2A	1.46	1.46	0.00
C2A-HA1	1.10	1.11	0.02
C2A-HA2	1.09	1.12	0.03
C2A-C	1.53	1.50	0.03
C-O	1.23	1.23	0.01
C-NR	1.36	1.35	0.01
NR-HR	1.02	1.00	0.02
NR-CR	1.45	1.44	0.01
CR-HR1	1.09	1.12	0.03
CR-HR2	1.09	1.12	0.02
CR-HR3	1.09	1.11	0.02
CL-CLP-OL	123.62	120.21	3.41
CL-CLP-N	115.37	116.84	1.47

Terms	QM	CHARMM	Abs. diff.
HL1-CL-HL2	108.47	109.70	1.23
HL1-CL-HL3	109.82	108.65	1.17
HL1-CL-CLP	111.75	110.81	0.94
HL2-CL-HL3	108.52	108.70	0.18
HL2-CL-CLP	109.62	110.02	0.40
HL3-CL-CLP	108.61	108.90	0.30
CLP-N-H	119.39	120.54	1.15
CLP-N-C1A	118.15	122.86	4.71
OL-CLP-N	121.01	122.95	1.94
N-C1A-HA	110.60	110.79	0.19
N-C1A-CB	115.78	112.63	3.15
N-C1A-C1	108.73	109.88	1.14
H-N-C1A	115.66	116.40	0.74
C1A-CB-HB1	113.98	112.10	1.88
C1A-CB-HB2	110.19	112.74	2.55
C1A-CB-CG	104.24	103.74	0.50
C1A-C1-O1	125.91	127.27	1.35
C1A-C1-N2	108.04	104.87	3.17
HA-C1A-CB	109.27	111.93	2.66
HA-C1A-C1	108.13	107.35	0.78
CB-C1A-C1	103.90	103.90	0.01
CB-CG-OD	129.25	126.77	2.47
CB-CG-N2	107.01	104.54	2.46
HB1-CB-HB2	108.05	106.71	1.33
HB1-CB-CG	111.54	111.14	0.40
HB2-CB-CG	108.74	110.49	1.75
CG-N2-C1	112.76	115.80	3.04
CG-N2-C2A	122.56	122.01	0.55
OD-CG-N2	123.74	128.66	4.92
C1-N2-C2A	124.67	121.81	2.86
O1-C1-N2	126.05	127.85	1.80
N2-C2A-HA1	108.14	111.17	3.03
N2-C2A-HA2	107.28	111.17	3.89
N2-C2A-C	113.68	110.57	3.12
C2A-C-O	121.25	120.95	0.30
C2A-C-NR	114.80	117.35	2.55
HA1-C2A-HA2	110.01	107.28	2.73
HA1-C2A-C	110.21	108.86	1.35
HA2-C2A-C	107.46	107.66	0.20
C-NR-HR	118.38	120.12	1.74
C-NR-CR	120.12	122.07	1.94
O-C-NR	123.94	121.70	2.24
NR-CR-HR1	108.94	111.26	2.31
NR-CR-HR2	111.86	110.33	1.52
NR-CR-HR3	108.84	110.33	1.50
HR-NR-CR	120.05	117.78	2.27
HR1-CR-HR2	108.27	108.18	0.09
HR1-CR-HR3	109.57	108.13	1.44
HR2-CR-HR3	109.34	108.51	0.83

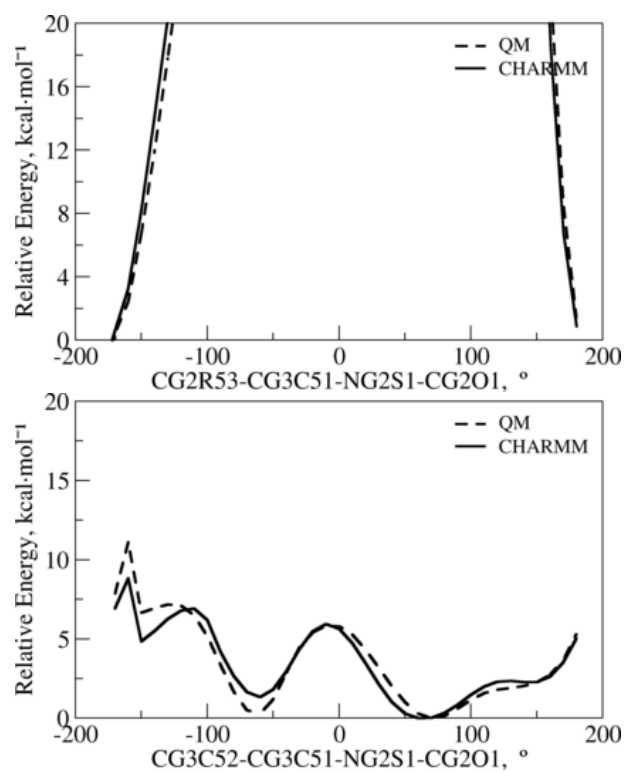


Figure S482: The PES scan for flexible dihedrals corresponding to 2-[(3*S*)-3-acetamido-2,5-dioxopyrrolidin-1-yl]-*N*-methylacetamide.

2.163 The small molecule used for bonded terms optimization of O-[(R)-(dimethylamino)(ethoxy)phosphoryl]-L-serine (SUN)

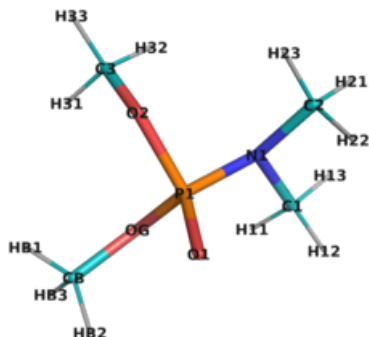


Figure S483: The energy minimized structure corresponding to (dimethoxyphosphoryl)dimethylamine.

Table S843: The calculated geometric terms of (dimethoxyphosphoryl)dimethylamine.

Terms	QM	CHARMM	Abs. diff.
P1-N1-C2	114.00	115.40	1.39
P1-O2-C3	118.98	118.97	0.01
O1-P1-N1	120.64	121.69	1.05
O1-P1-O2	111.11	112.86	1.76
N1-P1-O2	103.07	100.47	2.59
N1-C1-H11	109.46	110.81	1.36
N1-C1-H12	112.25	110.09	2.15
N1-C1-H13	108.19	108.88	0.69
N1-C2-H21	108.48	108.90	0.42
N1-C2-H22	112.19	110.00	2.19
N1-C2-H23	109.66	110.91	1.25
O2-C3-H31	110.44	111.86	1.42
O2-C3-H32	110.49	111.65	1.16
O2-C3-H33	105.74	109.12	3.39
C1-N1-C2	112.27	111.97	0.30
H11-C1-H12	109.49	109.91	0.43
H11-C1-H13	108.81	108.16	0.65
H12-C1-H13	108.58	108.93	0.35
H21-C2-H22	108.93	108.98	0.06
H21-C2-H23	108.77	108.27	0.49
H22-C2-H23	108.76	109.74	0.98
H31-C3-H32	109.53	109.16	0.37
H31-C3-H33	110.17	107.41	2.76
H32-C3-H33	110.43	107.44	2.98

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.12	0.02
CB-HB2	1.09	1.12	0.03
CB-OG	1.45	1.43	0.02
OG-P1	1.62	1.60	0.02
P1-O1	1.49	1.48	0.01
P1-N1	1.68	1.68	0.00
P1-O2	1.62	1.60	0.02
N1-C1	1.47	1.45	0.01
N1-C2	1.47	1.45	0.02
O2-C3	1.44	1.43	0.02
C1-H11	1.09	1.11	0.03
C1-H12	1.10	1.11	0.02
C1-H13	1.09	1.11	0.02
C2-H21	1.09	1.11	0.02
C2-H22	1.10	1.11	0.02
C2-H23	1.09	1.11	0.02
C3-H31	1.09	1.11	0.02
C3-H32	1.09	1.11	0.02
C3-H33	1.09	1.11	0.02
HB3-CB-HB1	109.93	107.65	2.28
HB3-CB-HB2	110.82	107.45	3.37
HB3-CB-OG	105.66	109.35	3.69
CB-OG-P1	116.16	116.05	0.11
HB1-CB-HB2	109.65	108.90	0.75
HB1-CB-OG	110.31	111.83	1.52
HB2-CB-OG	110.40	111.49	1.09
OG-P1-O1	114.96	112.05	2.92
OG-P1-N1	99.33	100.52	1.19
OG-P1-O2	106.02	107.66	1.64
P1-N1-C1	117.05	115.64	1.40

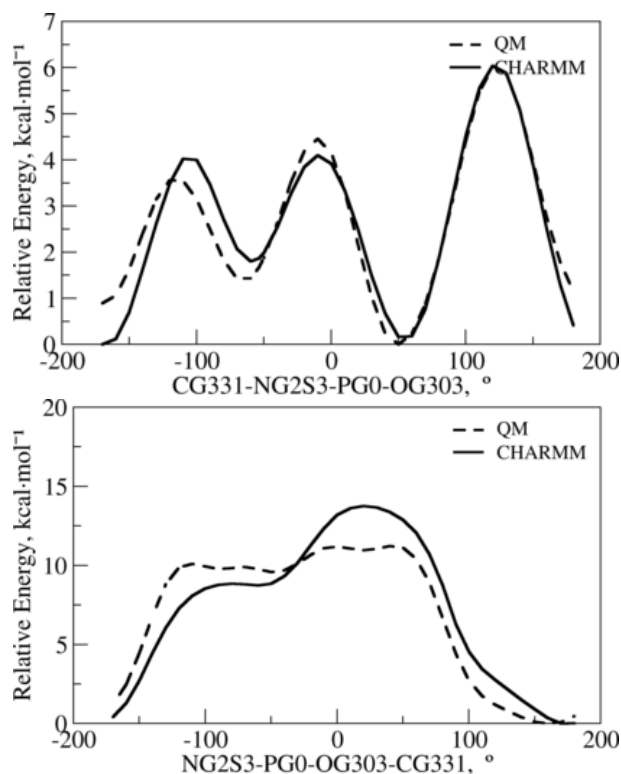


Figure S484: The PES scan for flexible dihedrals corresponding to (dimethoxyphosphoryl)dimethylamine.

2.164 The small molecule used for bonded terms optimization of O-[(R)-ethoxy(methyl)phosphoryl]-L-serine (SVX)



Figure S485: The energy minimized structure corresponding to dimethylmethylphosphonate.

Table S844: The calculated geometric terms of dimethylmethylphosphonate.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.12	0.02
CB-HB2	1.09	1.11	0.02
CB-OG	1.44	1.43	0.02
OG-P1	1.63	1.59	0.04
P1-O6	1.49	1.48	0.02
P1-O5	1.63	1.59	0.04
P1-C4	1.79	1.80	0.00
O5-C2	1.44	1.42	0.02
C4-H41	1.09	1.10	0.01
C4-H42	1.09	1.10	0.01
C4-H43	1.09	1.10	0.01
C2-H21	1.09	1.12	0.02
C2-H22	1.09	1.11	0.02
C2-H23	1.09	1.11	0.02
HB3-CB-HB1	110.53	107.50	3.03
HB3-CB-HB2	109.52	107.72	1.80
HB3-CB-OG	106.03	109.28	3.25
CB-OG-P1	118.49	117.82	0.67
HB1-CB-HB2	109.99	108.97	1.02
HB1-CB-OG	110.52	111.32	0.81
HB2-CB-OG	110.17	111.89	1.71
OG-P1-O6	114.19	110.72	3.47
OG-P1-O5	106.36	108.33	1.97
OG-P1-C4	100.50	103.49	2.99
P1-O5-C2	118.50	118.12	0.37
P1-C4-H41	110.01	108.39	1.62
P1-C4-H42	109.28	108.24	1.04
P1-C4-H43	109.27	108.26	1.01
O6-P1-O5	114.19	110.79	3.40
O6-P1-C4	119.16	119.29	0.13
O5-P1-C4	100.50	103.47	2.96
O5-C2-H21	110.51	111.76	1.24

Terms	QM	CHARMM	Abs. diff.
O5-C2-H22	110.17	111.43	1.27
O5-C2-H23	106.03	109.20	3.17
H41-C4-H42	109.41	110.67	1.26
H41-C4-H43	109.39	110.64	1.25
H42-C4-H43	109.47	110.55	1.08
H21-C2-H22	109.99	109.31	0.68
H21-C2-H23	110.54	107.41	3.14
H22-C2-H23	109.53	107.56	1.96

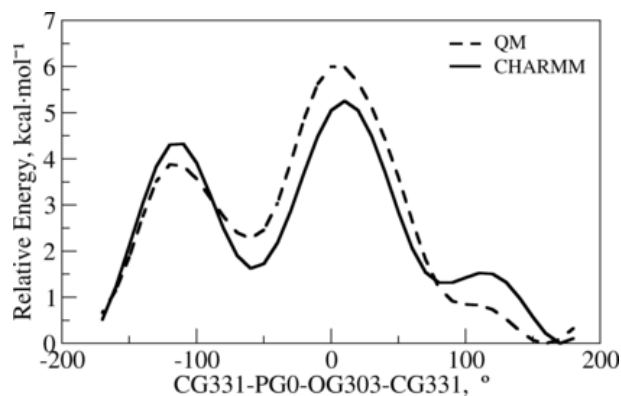


Figure S486: The PES scan for flexible dihedral corresponding to dimethylmethylphosphonate.

2.165 The small molecule used for bonded terms optimization of 2-[(4Z)-2-[(1R)-1-amino-2-hydroxy-ethyl]-4-(1H-indol-3-ylmethylidene)-5-oxo-imidazol-1-yl]ethanoicacid (SWG)

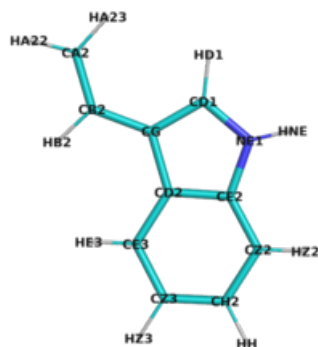


Figure S487: The energy minimized structure corresponding to 3-ethenyl-1H-indole.

Table S845: The calculated geometric terms of 3-ethenyl-1H-indole.

Terms	QM	CHARMM	Abs. diff.
HA22-CA2	1.08	1.10	0.02
HA23-CA2	1.09	1.10	0.01
CA2-CB2	1.34	1.35	0.01
CB2-HB2	1.09	1.10	0.01
CB2-CG	1.46	1.44	0.02
CG-CD1	1.38	1.38	0.00
CG-CD2	1.44	1.45	0.01
CD1-HD1	1.08	1.08	0.00
CD1-NE1	1.38	1.38	0.01
CD2-CE2	1.42	1.40	0.02
CD2-CE3	1.41	1.40	0.01
NE1-HNE	1.01	1.01	0.00
NE1-CE2	1.38	1.36	0.02
CE2-CZ2	1.40	1.38	0.02
CE3-HE3	1.09	1.08	0.01
CE3-CZ3	1.39	1.40	0.01
CZ2-HZ2	1.09	1.08	0.01
CZ2-CH2	1.39	1.40	0.01
CZ3-HZ3	1.09	1.08	0.01
CZ3-CH2	1.41	1.40	0.01
CH2-HH	1.09	1.08	0.01
HA22-CA2-HA23	116.99	117.77	0.78
HA22-CA2-CB2	121.41	120.88	0.53
HA23-CA2-CB2	121.61	121.35	0.26
CA2-CB2-HB2	118.79	116.59	2.20
CA2-CB2-CG	124.79	126.78	1.98
CB2-CG-CD1	127.11	129.71	2.60
CB2-CG-CD2	126.67	126.63	0.04
HB2-CB2-CG	116.41	116.63	0.22
CG-CD1-HD1	129.49	126.00	3.49
CG-CD1-NE1	109.66	110.02	0.36

Terms	QM	CHARMM	Abs. diff.
CG-CD2-CE2	107.50	109.80	2.29
CG-CD2-CE3	133.71	131.60	2.11
CD1-CG-CD2	106.23	103.66	2.56
CD1-NE1-HNE	124.94	126.88	1.93
CD1-NE1-CE2	109.62	110.68	1.06
HD1-CD1-NE1	120.83	123.99	3.16
CD2-CE2-NE1	106.98	105.85	1.13
CD2-CE2-CZ2	122.65	121.79	0.86
CD2-CE3-HE3	120.66	119.89	0.77
CD2-CE3-CZ3	118.84	120.17	1.33
NE1-CE2-CZ2	130.36	132.36	2.00
HNE-NE1-CE2	125.22	122.44	2.78
CE2-CD2-CE3	118.79	118.61	0.18
CE2-CZ2-HZ2	121.64	120.16	1.48
CE2-CZ2-CH2	117.14	119.27	2.13
CE3-CZ3-HZ3	119.60	120.04	0.44
CE3-CZ3-CH2	121.31	120.14	1.17
HE3-CE3-CZ3	120.50	119.94	0.56
CZ2-CH2-CZ3	121.27	120.02	1.25
CZ2-CH2-HH	119.37	120.23	0.87
HZ2-CZ2-CH2	121.22	120.57	0.65
CZ3-CH2-HH	119.36	119.75	0.39
HZ3-CZ3-CH2	119.10	119.82	0.73

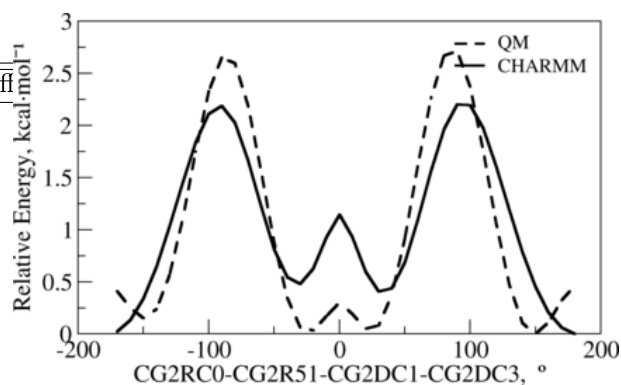


Figure S488: The PES scan for flexible dihedral corresponding to 3-ethenyl-1H-indole.

2.166 The small molecule 1 used for bonded terms optimization of 3-(2-tetrazolyl)-alanine (TEZA)

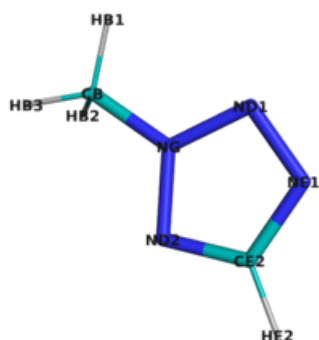


Figure S489: The energy minimized structure corresponding to 2-methyl-2H-1,2,3,4-tetrazole.

Table S846: The calculated geometric terms of 2-methyl-2H-1,2,3,4-tetrazole.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-NG	1.45	1.45	0.00
NG-ND1	1.34	1.34	0.00
NG-ND2	1.33	1.33	0.00
ND1-NE1	1.33	1.30	0.03
ND2-CE2	1.35	1.33	0.02
NE1-CE2	1.35	1.34	0.01
CE2-HE2	1.08	1.09	0.01
HB3-CB-HB1	110.75	108.89	1.86
HB3-CB-HB2	110.11	108.97	1.15
HB3-CB-NG	109.14	109.44	0.30
CB-NG-ND1	122.24	122.48	0.23
CB-NG-ND2	122.93	120.08	2.85
HB1-CB-HB2	110.75	108.85	1.90
HB1-CB-NG	106.85	111.22	4.37
HB2-CB-NG	109.16	109.43	0.27
NG-ND1-NE1	105.16	101.72	3.45
NG-ND2-CE2	100.53	98.54	1.98
ND1-NG-ND2	114.83	117.45	2.62
ND1-NE1-CE2	105.98	109.28	3.30
ND2-CE2-NE1	113.50	113.02	0.49
ND2-CE2-HE2	122.65	123.75	1.10
NE1-CE2-HE2	123.84	123.23	0.61

2.167 The small molecule 2 used for bonded terms optimization of 3-(2-tetrazolyl)-alanine (TEZA)

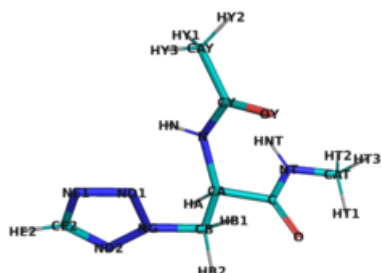


Figure S490: The energy minimized structure corresponding to (2R)-2-acetamido-N-methyl-3-(2H-1,2,3,4-tetrazol-2-yl)propanamide.

Table S847: The calculated geometric terms of (2R)-2-acetamido-N-methyl-3-(2H-1,2,3,4-tetrazol-2-yl)propanamide.

Terms	QM	CHARMM	Abs. diff.
N-HN	1.02	0.99	0.02
N-CA	1.46	1.46	0.01
N-CY	1.39	1.34	0.04
CA-HA	1.10	1.08	0.02
CA-CB	1.53	1.56	0.03
CA-C	1.53	1.53	0.00
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-NG	1.45	1.46	0.00
NG-ND1	1.35	1.34	0.00
NG-ND2	1.33	1.34	0.01
ND1-NE1	1.34	1.30	0.04
ND2-CE2	1.35	1.32	0.02
NE1-CE2	1.35	1.34	0.01
CE2-HE2	1.08	1.09	0.01
C-O	1.23	1.23	0.00
C-NT	1.36	1.35	0.01
NT-HNT	1.01	0.99	0.02
NT-CAT	1.45	1.45	0.01
CAT-HT1	1.09	1.11	0.02
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.09	1.11	0.02
CAY-HY1	1.09	1.11	0.02
CAY-HY2	1.09	1.11	0.02
CAY-HY3	1.09	1.11	0.02
CAY-CY	1.51	1.48	0.03
CY-OY	1.23	1.22	0.01
N-CA-HA	107.16	106.85	0.32
N-CA-CB	111.77	112.11	0.33
N-CA-C	112.29	115.73	3.44
N-CY-CAY	115.13	116.50	1.37

Terms	QM	CHARMM	Abs. diff.
N-CY-OY	120.91	122.65	1.74
HN-N-CA	116.36	116.63	0.27
HN-N-CY	116.33	117.08	0.75
CA-N-CY	118.87	124.73	5.85
CA-CB-HB1	110.40	108.65	1.75
CA-CB-HB2	111.46	109.04	2.42
CA-CB-NG	108.80	117.89	9.09
CA-C-O	120.79	120.64	0.15
CA-C-NT	114.40	118.25	3.85
HA-CA-CB	108.97	106.85	2.12
HA-CA-C	108.03	104.83	3.20
CB-CA-C	108.51	109.80	1.29
CB-NG-ND1	122.02	121.18	0.84
CB-NG-ND2	122.90	119.08	3.82
HB1-CB-HB2	109.92	106.55	3.37
HB1-CB-NG	107.58	107.66	0.07
HB2-CB-NG	108.57	106.51	2.07
NG-ND1-NE1	105.33	101.89	3.44
NG-ND2-CE2	100.70	98.71	1.99
ND1-NG-ND2	114.53	116.97	2.44
ND1-NE1-CE2	105.88	109.39	3.51
ND2-CE2-NE1	113.54	113.02	0.53
ND2-CE2-HE2	122.66	123.82	1.17
NE1-CE2-HE2	123.80	123.14	0.66
C-NT-HNT	115.75	119.90	4.15
C-NT-CAT	119.45	121.63	2.18
O-C-NT	124.37	121.05	3.32
NT-CAT-HT1	108.35	111.37	3.02
NT-CAT-HT2	108.90	110.83	1.93
NT-CAT-HT3	111.74	110.57	1.17
HNT-NT-CAT	118.16	117.97	0.18
HT1-CAT-HT2	109.50	107.86	1.64
HT1-CAT-HT3	108.65	107.80	0.84
HT2-CAT-HT3	109.67	108.28	1.39
CAY-CY-OY	123.96	120.85	3.11
HY1-CAY-HY2	109.90	108.79	1.10
HY1-CAY-HY3	108.65	109.66	1.01
HY1-CAY-CY	111.86	111.08	0.79
HY2-CAY-HY3	109.15	108.26	0.89
HY2-CAY-CY	108.83	109.44	0.61
HY3-CAY-CY	108.40	109.55	1.16

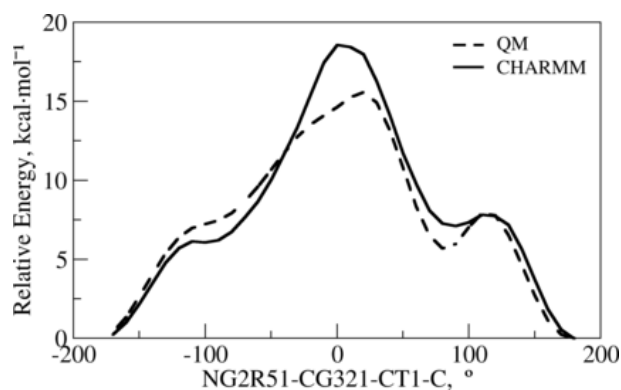
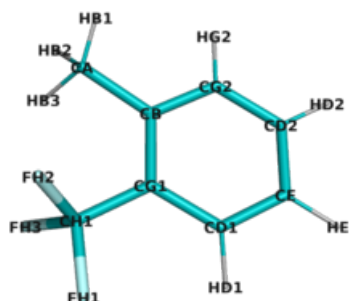


Figure S491: The PES scan for flexible dihedral corresponding to (2R)-2-acetamido-N-methyl-3-(2H-1,2,3,4-tetrazol-2-yl)propanamide.

2.168 The small molecule used for bonded terms optimization of 2-(trifluoromethyl)-phenylglycine (TFG2)



Terms	QM	CHARMM	Abs. diff.
CG1-CH1-FH2	111.81	112.82	1.00
CG1-CH1-FH3	112.00	112.81	0.81
CG1-CD1-HD1	119.70	121.08	1.38
CG1-CD1-CE	120.06	120.79	0.73
CH1-CG1-CD1	118.77	120.41	1.64
FH1-CH1-FH2	106.66	105.12	1.54
FH1-CH1-FH3	106.75	105.09	1.65
FH2-CH1-FH3	106.69	106.26	0.43
CG2-CD2-HD2	119.87	120.28	0.41
CG2-CD2-CE	119.87	119.59	0.28
HG2-CG2-CD2	119.46	119.60	0.13
CD1-CE-CD2	119.61	120.29	0.68
CD1-CE-HE	119.90	119.76	0.14
HD1-CD1-CE	120.24	118.13	2.11
CD2-CE-HE	120.49	119.95	0.54
HD2-CD2-CE	120.27	120.14	0.13

Figure S492: The energy minimized structure corresponding to 1-methyl-2-(trifluoromethyl)benzene.

Table S848: The calculated geometric terms of 1-methyl-2-(trifluoromethyl)benzene.

Terms	QM	CHARMM	Abs. diff.
CA-HB1	1.09	1.11	0.02
CA-HB2	1.09	1.11	0.02
CA-HB3	1.09	1.11	0.02
CA-CB	1.51	1.50	0.01
CB-CG1	1.41	1.42	0.01
CB-CG2	1.40	1.40	0.00
CG1-CH1	1.50	1.49	0.01
CG1-CD1	1.40	1.42	0.02
CH1-FH1	1.35	1.34	0.01
CH1-FH2	1.36	1.34	0.02
CH1-FH3	1.36	1.34	0.01
CG2-HG2	1.09	1.08	0.01
CG2-CD2	1.40	1.40	0.00
CD1-HD1	1.08	1.08	0.00
CD1-CE	1.39	1.40	0.00
CD2-HD2	1.09	1.08	0.01
CD2-CE	1.39	1.40	0.00
CE-HE	1.09	1.08	0.01
CA-CB-CG1	122.88	122.44	0.44
CA-CB-CG2	119.74	117.76	1.98
HB1-CA-HB2	108.29	109.07	0.78
HB1-CA-HB3	108.21	109.04	0.82
HB1-CA-CB	109.81	110.66	0.84
HB2-CA-HB3	107.58	110.12	2.54
HB2-CA-CB	111.71	108.99	2.72
HB3-CA-CB	111.12	108.96	2.15
CB-CG1-CH1	119.88	120.99	1.11
CB-CG1-CD1	121.31	118.59	2.71
CB-CG2-HG2	118.72	119.46	0.74
CB-CG2-CD2	121.81	120.94	0.87
CG1-CB-CG2	117.34	119.80	2.46
CG1-CH1-FH1	112.54	113.99	1.45

2.169 The small molecule used for bonded terms optimization of 5,5,5-trifluoro-leucine (TFLE)

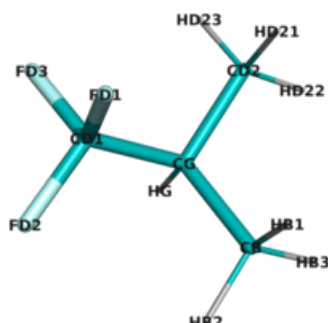


Figure S493: The energy minimized structure corresponding to 1,1,1-trifluoro-2-methylpropane.

Table S849: The calculated geometric terms of 1,1,1-trifluoro-2-methylpropane.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.53	1.55	0.02
CG-HG	1.10	1.11	0.02
CG-CD1	1.51	1.53	0.03
CG-CD2	1.53	1.55	0.02
CD1-FD1	1.36	1.34	0.02
CD1-FD2	1.36	1.34	0.02
CD1-FD3	1.36	1.34	0.02
CD2-HD21	1.09	1.11	0.02
CD2-HD22	1.09	1.11	0.02
CD2-HD23	1.09	1.11	0.02
HB3-CB-HB1	108.29	108.20	0.08
HB3-CB-HB2	108.39	108.17	0.22
HB3-CB-CG	109.76	109.97	0.21
CB-CG-HG	109.39	108.42	0.97
CB-CG-CD1	110.39	110.55	0.16
CB-CG-CD2	112.10	110.98	1.12
HB1-CB-HB2	108.55	108.62	0.07
HB1-CB-CG	110.40	110.75	0.35
HB2-CB-CG	111.38	111.05	0.33
CG-CD1-FD1	111.88	112.23	0.35
CG-CD1-FD2	111.82	111.79	0.03
CG-CD1-FD3	111.84	111.78	0.06
CG-CD2-HD21	110.37	110.71	0.33
CG-CD2-HD22	109.73	109.92	0.18
CG-CD2-HD23	111.36	111.15	0.21
HG-CG-CD1	104.98	107.90	2.92
HG-CG-CD2	109.36	108.42	0.94
CD1-CG-CD2	110.37	110.47	0.11
FD1-CD1-FD2	107.01	106.97	0.04
FD1-CD1-FD3	107.04	106.96	0.07

Terms	QM	CHARMM	Abs. diff.
FD2-CD1-FD3	106.93	106.76	0.17
HD21-CD2-HD22	108.30	108.16	0.14
HD21-CD2-HD23	108.56	108.64	0.08
HD22-CD2-HD23	108.44	108.18	0.25

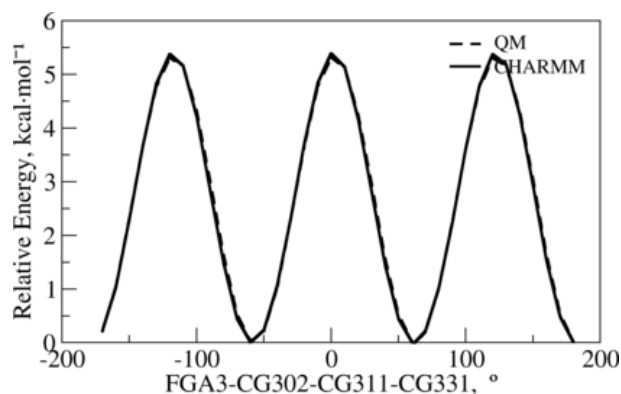


Figure S494: The PES scan for flexible dihedral corresponding to 1,1,1-trifluoro-2-methylpropane.

2.170 The small molecule used for bonded terms optimization of 2-thienylglycine (THG2)

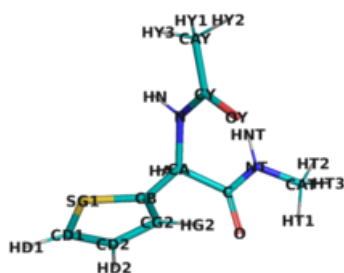


Figure S495: The energy minimized structure corresponding to (2S)-2-acetamido-N-methyl-2-(thiophen-2-yl)acetamide.

Table S850: The calculated geometric terms of (2S)-2-acetamido-N-methyl-2-(thiophen-2-yl)acetamide.

Terms	QM	CHARMM	Abs. diff.
N-HN	1.02	0.99	0.02
N-CA	1.47	1.47	0.00
N-CY	1.38	1.35	0.04
CA-HA	1.10	1.08	0.02
CA-CB	1.50	1.53	0.03
CA-C	1.54	1.53	0.01
CB-SG1	1.73	1.72	0.02
CB-CG2	1.38	1.37	0.01
SG1-CD1	1.72	1.71	0.01
CG2-HG2	1.08	1.08	0.00
CG2-CD2	1.42	1.38	0.04
CD1-HD1	1.08	1.08	0.00
CD1-CD2	1.38	1.37	0.01
CD2-HD2	1.09	1.08	0.00
C-O	1.23	1.23	0.00
C-NT	1.37	1.35	0.02
NT-HNT	1.01	0.99	0.02
NT-CAT	1.45	1.44	0.01
CAT-HT1	1.09	1.11	0.02
CAT-HT2	1.09	1.11	0.02
CAT-HT3	1.10	1.11	0.02
CAY-HY1	1.09	1.11	0.01
CAY-HY2	1.09	1.11	0.02
CAY-HY3	1.09	1.11	0.01
CAY-CY	1.51	1.48	0.03
CY-OY	1.23	1.22	0.01
N-CA-HA	105.57	104.60	0.97
N-CA-CB	112.42	110.59	1.83
N-CA-C	110.38	115.23	4.85
N-CY-CAY	115.02	116.74	1.73
N-CY-OY	121.70	122.80	1.10
HN-N-CA	114.82	116.00	1.17

Terms	QM	CHARMM	Abs. diff.
HN-N-CY	115.79	117.00	1.20
CA-N-CY	118.82	125.04	6.22
CA-CB-SG1	119.55	119.70	0.14
CA-CB-CG2	129.22	130.64	1.42
CA-C-O	122.89	122.58	0.31
CA-C-NT	113.11	116.71	3.60
HA-CA-CB	109.53	106.23	3.30
HA-CA-C	105.59	104.44	1.15
CB-CA-C	112.85	114.60	1.75
CB-SG1-CD1	92.24	92.82	0.58
CB-CG2-HG2	122.18	122.36	0.18
CB-CG2-CD2	112.58	114.18	1.60
SG1-CB-CG2	110.90	109.35	1.56
SG1-CD1-HD1	120.28	120.41	0.13
SG1-CD1-CD2	111.24	110.25	0.98
CG2-CD2-CD1	113.03	113.38	0.35
CG2-CD2-HD2	124.10	122.80	1.30
HG2-CG2-CD2	125.23	123.46	1.77
CD1-CD2-HD2	122.87	123.82	0.94
HD1-CD1-CD2	128.45	129.33	0.88
C-NT-HNT	115.87	119.68	3.81
C-NT-CAT	118.89	121.83	2.95
O-C-NT	123.54	120.61	2.93
NT-CAT-HT1	108.56	111.13	2.57
NT-CAT-HT2	108.83	110.85	2.02
NT-CAT-HT3	111.80	110.49	1.31
HNT-NT-CAT	117.95	117.82	0.12
HT1-CAT-HT2	109.46	107.91	1.55
HT1-CAT-HT3	108.53	107.79	0.74
HT2-CAT-HT3	109.63	108.56	1.06
CAY-CY-OY	123.28	120.46	2.83
HY1-CAY-HY2	109.84	108.88	0.96
HY1-CAY-HY3	108.43	109.67	1.24
HY1-CAY-CY	111.91	111.42	0.50
HY2-CAY-HY3	108.64	108.29	0.35
HY2-CAY-CY	108.68	108.60	0.08
HY3-CAY-CY	109.29	109.92	0.63

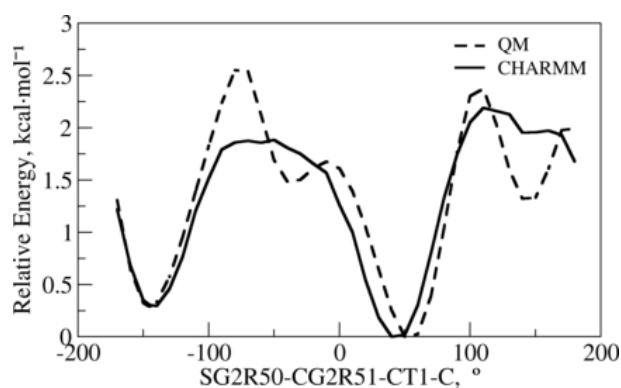


Figure S496: The PES scan for flexible dihedral corresponding to (2S)-2-acetamido-N-methyl-2-(thiophen-2-yl)acetamide.

2.171 The small molecule used for bonded terms optimization of thio-citrulline (THIC)

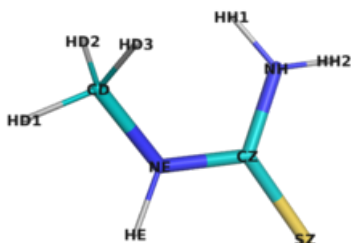


Figure S497: The energy minimized structure corresponding to methylthiourea.

Table S851: The calculated geometric terms of methylthiourea.

Terms	QM	CHARMM	Abs. diff.
HD3-CD	1.09	1.11	0.02
CD-HD1	1.09	1.11	0.02
CD-HD2	1.10	1.11	0.02
CD-NE	1.45	1.44	0.01
NE-HE	1.01	1.00	0.01
NE-CZ	1.36	1.36	0.01
CZ-SZ	1.66	1.60	0.06
CZ-NH	1.37	1.34	0.03
NH-HH1	1.01	0.99	0.02
NH-HH2	1.01	1.00	0.01
HD3-CD-HD1	108.92	108.12	0.79
HD3-CD-HD2	109.03	109.33	0.30
HD3-CD-NE	111.17	110.60	0.56
CD-NE-HE	119.08	118.03	1.05
CD-NE-CZ	124.95	126.00	1.06
HD1-CD-HD2	107.69	108.17	0.48
HD1-CD-NE	108.24	109.98	1.74
HD2-CD-NE	111.69	110.55	1.14
NE-CZ-SZ	122.69	122.90	0.21
NE-CZ-NH	114.48	114.15	0.33
HE-NE-CZ	113.96	115.75	1.80
CZ-NH-HH1	118.92	120.02	1.11
CZ-NH-HH2	113.74	116.39	2.65
SZ-CZ-NH	122.80	122.95	0.15
HH1-NH-HH2	114.90	121.18	6.28

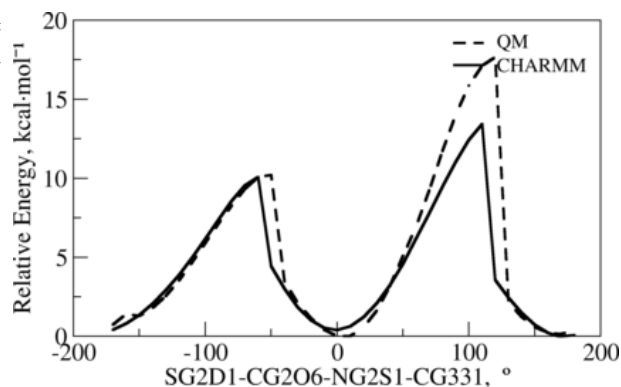


Figure S498: The PES scan for flexible dihedral corresponding to methylthiourea.

2.172 The small molecule 1 used for bonded terms optimization of 3-(2-thienyl)-alanine (TIH)

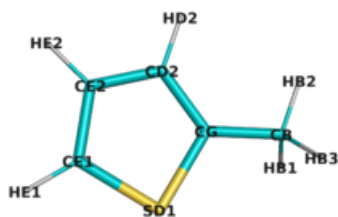


Figure S499: The energy minimized structure corresponding to 2-methylthiophene.

Table S852: The calculated geometric terms of 2-methylthiophene.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.50	1.50	0.01
CG-CD2	1.38	1.37	0.01
CG-SD1	1.73	1.71	0.02
CD2-HD2	1.09	1.08	0.00
CD2-CE2	1.42	1.38	0.04
SD1-CE1	1.72	1.71	0.01
CE2-HE2	1.09	1.08	0.00
CE2-CE1	1.37	1.37	0.01
CE1-HE1	1.08	1.08	0.00
HB3-CB-HB1	107.85	108.96	1.10
HB3-CB-HB2	107.94	108.87	0.93
HB3-CB-CG	111.87	109.78	2.10
CB-CG-CD2	128.06	128.37	0.31
CB-CG-SD1	121.60	121.67	0.07
HB1-CB-HB2	107.93	108.91	0.98
HB1-CB-CG	111.87	109.77	2.10
HB2-CB-CG	109.23	110.54	1.31
CG-CD2-HD2	122.40	122.53	0.13
CG-CD2-CE2	113.42	113.94	0.52
CG-SD1-CE1	92.45	92.41	0.03
CD2-CG-SD1	110.34	109.96	0.38
CD2-CE2-HE2	124.41	123.37	1.04
CD2-CE2-CE1	112.40	113.24	0.84
HD2-CD2-CE2	124.18	123.53	0.65
SD1-CE1-CE2	111.40	110.44	0.95
SD1-CE1-HE1	120.25	119.94	0.31
CE2-CE1-HE1	128.36	129.61	1.26
HE2-CE2-CE1	123.19	123.38	0.20

2.173 The small molecule 2 used for bonded terms optimization of 3-(2-thienyl)-alanine (TIH)

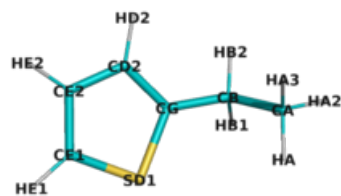


Figure S500: The energy minimized structure corresponding to 2-ethylthiophene.

Table S853: The calculated geometric terms of 2-ethylthiophene.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.54	0.01
CB-HB1	1.10	1.11	0.02
CB-HB2	1.10	1.11	0.02
CB-CG	1.50	1.51	0.01
CG-CD2	1.38	1.37	0.01
CG-SD1	1.73	1.72	0.02
CD2-HD2	1.09	1.08	0.01
CD2-CE2	1.42	1.38	0.04
SD1-CE1	1.72	1.71	0.01
CE2-HE2	1.09	1.08	0.00
CE2-CE1	1.38	1.37	0.01
CE1-HE1	1.08	1.08	0.00
HA3-CA-HA2	108.50	108.30	0.20
HA3-CA-HA	107.98	108.36	0.38
HA3-CA-CB	110.35	110.78	0.43
HA2-CA-HA	108.18	108.13	0.05
HA2-CA-CB	110.89	110.42	0.46
CA-CB-HB1	109.71	109.21	0.50
CA-CB-HB2	109.71	108.85	0.85
CA-CB-CG	113.05	114.34	1.29
HA-CA-CB	110.85	110.76	0.09
CB-CG-CD2	128.09	128.44	0.35
CB-CG-SD1	121.60	121.68	0.08
HB1-CB-HB2	106.41	106.90	0.49
HB1-CB-CG	110.22	108.38	1.83
HB2-CB-CG	107.50	108.90	1.39
CG-CD2-HD2	122.33	122.52	0.19
CG-CD2-CE2	113.45	114.02	0.57
CG-SD1-CE1	92.45	92.44	0.01
CD2-CG-SD1	110.27	109.88	0.39
CD2-CE2-HE2	124.44	123.35	1.09

Terms	QM	CHARMM	Abs. diff.
CD2-CE2-CE1	112.39	113.19	0.80
HD2-CD2-CE2	124.21	123.46	0.75
SD1-CE1-CE2	111.43	110.47	0.96
SD1-CE1-HE1	120.24	119.95	0.29
CE2-CE1-HE1	128.33	129.58	1.25
HE2-CE2-CE1	123.17	123.47	0.29

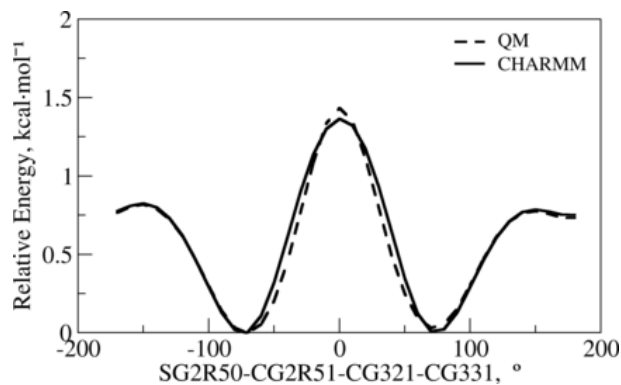


Figure S501: The PES scan for flexible dihedral corresponding to 2-ethylthiophene.

2.174 The small molecule used for bonded terms optimization of 1-hydroperoxy-L-tryptophan (TOX)

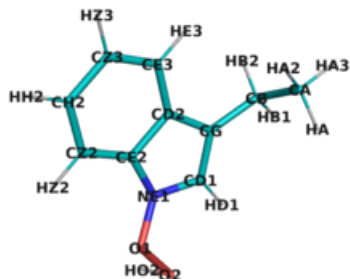


Figure S502: The energy minimized structure corresponding to 3-ethyl-1H-indole-1-peroxol.

Table S854: The calculated geometric terms of 3-ethyl-1H-indole-1-peroxol.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.54	0.00
CB-HB1	1.10	1.11	0.02
CB-HB2	1.10	1.11	0.02
CB-CG	1.50	1.51	0.01
CG-CD1	1.37	1.37	0.00
CG-CD2	1.45	1.44	0.01
CD1-HD1	1.08	1.08	0.00
CD1-NE1	1.39	1.38	0.01
CD2-CE2	1.41	1.40	0.01
CD2-CE3	1.40	1.39	0.01
NE1-O1	1.35	1.36	0.00
NE1-CE2	1.39	1.38	0.01
O1-O2	1.52	1.54	0.02
O2-HO2	0.98	0.96	0.02
CE2-CZ2	1.39	1.39	0.00
CE3-HE3	1.09	1.08	0.01
CE3-CZ3	1.39	1.40	0.01
CZ2-HZ2	1.09	1.08	0.01
CZ2-CH2	1.39	1.40	0.01
CZ3-HZ3	1.09	1.08	0.00
CZ3-CH2	1.41	1.40	0.01
CH2-HH2	1.09	1.08	0.00
HA3-CA-HA2	108.28	108.32	0.03
HA3-CA-HA	108.44	108.23	0.21
HA3-CA-CB	111.01	110.40	0.61
HA2-CA-HA	107.84	108.24	0.40
HA2-CA-CB	110.94	110.94	0.00
CA-CB-HB1	109.75	108.81	0.95
CA-CB-HB2	109.72	109.57	0.15
CA-CB-CG	112.15	113.74	1.59

Terms	QM	CHARMM	Abs. diff.
HA-CA-CB	110.21	110.61	0.40
CB-CG-CD1	127.27	127.84	0.57
CB-CG-CD2	126.00	124.96	1.04
HB1-CB-HB2	106.43	106.93	0.50
HB1-CB-CG	109.11	108.98	0.13
HB2-CB-CG	109.51	108.58	0.92
CG-CD1-HD1	131.54	130.21	1.34
CG-CD1-NE1	109.13	107.75	1.38
CG-CD2-CE2	107.79	108.18	0.38
CG-CD2-CE3	133.72	132.16	1.56
CD1-CG-CD2	106.70	107.17	0.47
CD1-NE1-O1	122.19	122.28	0.10
CD1-NE1-CE2	109.46	111.32	1.87
HD1-CD1-NE1	119.23	122.03	2.80
CD2-CE2-NE1	106.43	105.57	0.85
CD2-CE2-CZ2	123.61	120.98	2.63
CD2-CE3-HE3	120.91	119.73	1.18
CD2-CE3-CZ3	118.67	119.61	0.94
NE1-O1-O2	108.21	108.58	0.38
NE1-CE2-CZ2	129.85	133.44	3.59
O1-NE1-CE2	121.92	121.98	0.06
O1-O2-HO2	98.35	98.74	0.38
CE2-CD2-CE3	118.46	119.66	1.20
CE2-CZ2-HZ2	121.53	119.44	2.09
CE2-CZ2-CH2	116.59	119.31	2.72
CE3-CZ3-HZ3	119.48	119.87	0.39
CE3-CZ3-CH2	121.45	120.56	0.89
HE3-CE3-CZ3	120.42	120.66	0.24
CZ2-CH2-CZ3	121.17	119.88	1.29
CZ2-CH2-HH2	119.43	120.29	0.85
HZ2-CZ2-CH2	121.87	121.24	0.63
CZ3-CH2-HH2	119.39	119.83	0.44
HZ3-CZ3-CH2	119.07	119.57	0.50

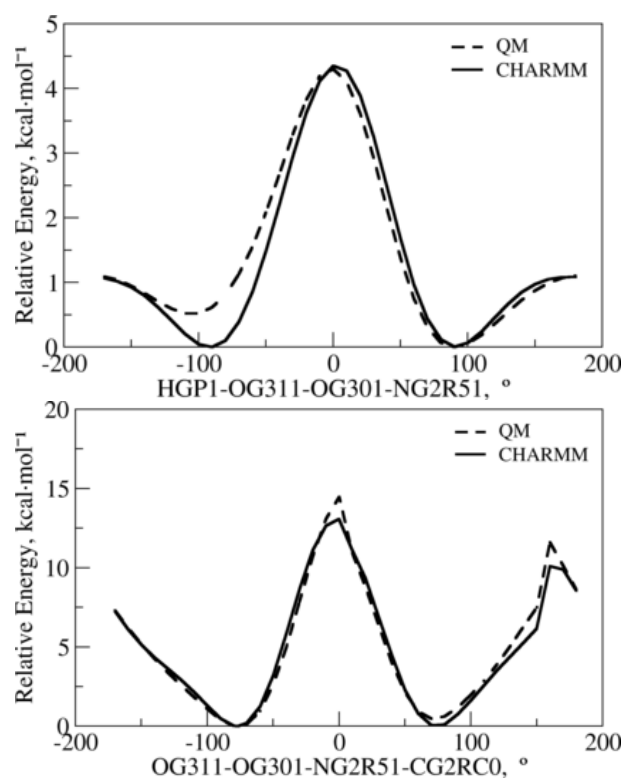


Figure S503: The PES scan for flexible dihedrals corresponding to 3-ethyl-1H-indole-1-peroxol.

2.175 The small molecule 1 used for bonded terms optimization of 5-(2-carboxy-2-aminoethyl)-2-hydroxy-1,4-benzoquinone (TPQ)

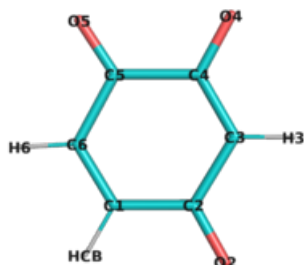


Figure S504: The energy minimized structure corresponding to cyclohex-5-ene-1,2,4-trione.

Table S855: The calculated geometric terms of cyclohex-5-ene-1,2,4-trione.

Terms	QM	CHARMM	Abs. diff.
HCB-C1	1.09	1.10	0.01
C1-C2	1.50	1.50	0.00
C1-C6	1.35	1.36	0.00
C2-O2	1.27	1.23	0.04
C2-C3	1.42	1.50	0.09
C3-H3	1.09	1.10	0.01
C3-C4	1.42	1.36	0.05
C4-O4	1.26	1.27	0.01
C4-C5	1.54	1.60	0.05
C5-O5	1.24	1.24	0.01
C5-C6	1.48	1.50	0.02
C6-H6	1.09	1.10	0.01
HCB-C1-C2	115.41	120.11	4.71
HCB-C1-C6	121.88	118.67	3.21
C1-C2-O2	116.42	118.94	2.51
C1-C2-C3	117.69	121.47	3.77
C1-C6-C5	120.06	120.20	0.14
C1-C6-H6	122.85	118.37	4.48
C2-C1-C6	122.63	121.22	1.42
C2-C3-H3	117.73	120.68	2.95
C2-C3-C4	123.36	118.91	4.44
O2-C2-C3	125.86	119.60	6.26
C3-C4-O4	126.34	121.65	4.70
C3-C4-C5	116.35	119.99	3.64
H3-C3-C4	117.88	120.40	2.53
C4-C5-O5	121.76	123.49	1.73
C4-C5-C6	118.26	118.21	0.05
O4-C4-C5	117.21	118.36	1.15
C5-C6-H6	116.82	121.43	4.61
O5-C5-C6	119.98	118.30	1.68

2.176 The small molecule 2 used for bonded terms optimization of 5-(2-carboxy-2-aminoethyl)-2-hydroxy-1,4-benzoquinone (TPQ)

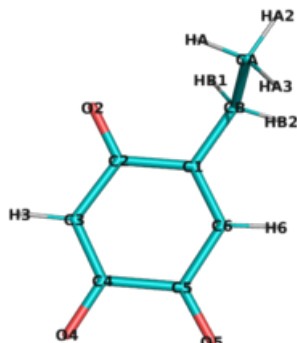


Figure S505: The energy minimized structure corresponding to 5-ethylcyclohex-5-ene-1,2,4-trione.

Table S856: The calculated geometric terms of 5-ethylcyclohex-5-ene-1,2,4-trione.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.02
HA2-CA	1.10	1.11	0.01
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.54	0.01
CB-HB1	1.10	1.11	0.02
CB-HB2	1.10	1.11	0.01
CB-C1	1.50	1.52	0.02
C1-C2	1.51	1.52	0.01
C1-C6	1.35	1.36	0.00
C2-O2	1.27	1.23	0.04
C2-C3	1.41	1.51	0.09
C3-H3	1.09	1.10	0.01
C3-C4	1.42	1.36	0.06
C4-O4	1.26	1.27	0.01
C4-C5	1.54	1.59	0.05
C5-O5	1.24	1.24	0.01
C5-C6	1.47	1.50	0.03
C6-H6	1.09	1.10	0.01
HA3-CA-HA2	108.24	108.56	0.31
HA3-CA-HA	108.85	108.44	0.41
HA3-CA-CB	110.50	110.81	0.31
HA2-CA-HA	108.64	108.22	0.42
HA2-CA-CB	110.88	110.45	0.43
CA-CB-HB1	108.90	107.96	0.94
CA-CB-HB2	110.08	108.95	1.13
CA-CB-C1	111.37	113.14	1.77
HA-CA-CB	109.67	110.28	0.61
CB-C1-C2	117.26	121.10	3.85
CB-C1-C6	122.14	119.26	2.89
HB1-CB-HB2	108.62	106.34	2.28
HB1-CB-C1	108.70	108.62	0.08
HB2-CB-C1	109.11	111.55	2.43

Terms	QM	CHARMM	Abs. diff.
C1-C2-O2	116.74	120.11	3.37
C1-C2-C3	118.15	122.14	3.99
C1-C6-C5	121.62	121.03	0.59
C1-C6-H6	121.89	117.78	4.11
C2-C1-C6	120.60	119.44	1.15
C2-C3-H3	117.29	120.85	3.56
C2-C3-C4	123.75	118.76	4.99
O2-C2-C3	125.09	117.74	7.35
C3-C4-O4	126.30	121.77	4.53
C3-C4-C5	116.10	119.85	3.74
H3-C3-C4	117.77	120.39	2.63
C4-C5-O5	121.63	123.37	1.75
C4-C5-C6	118.30	118.65	0.34
O4-C4-C5	117.53	118.38	0.86
C5-C6-H6	116.22	121.18	4.96
O5-C5-C6	120.07	117.98	2.09

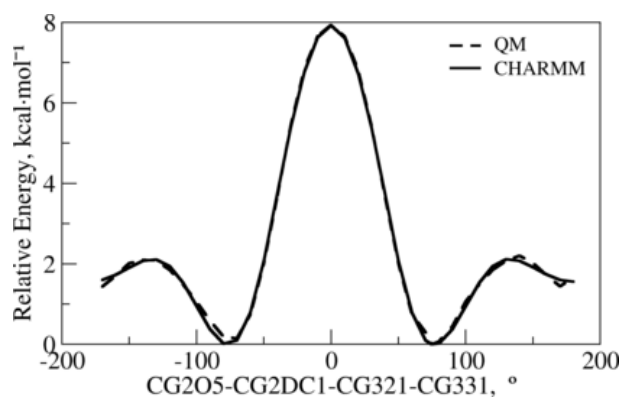


Figure S506: The PES scan for flexible dihedral corresponding to 5-ethylcyclohex-5-ene-1,2,4-trione.

2.177 The small molecule used for bonded terms optimization of 5-(2-carboxy-2-aminoethyl)-2-hydroxy-1,4-benzoquinone (TPQP)

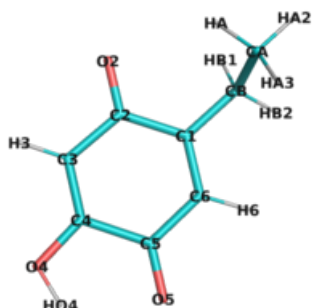


Figure S507: The energy minimized structure corresponding to 2-ethyl-5-hydroxycyclohexa-2,5-diene-1,4-dione.

Table S857: The calculated geometric terms of 2-ethyl-5-hydroxycyclohexa-2,5-diene-1,4-dione.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.54	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.10	1.11	0.02
CB-C1	1.50	1.51	0.02
C1-C2	1.50	1.52	0.01
C1-C6	1.35	1.36	0.01
C2-O2	1.24	1.23	0.01
C2-C3	1.46	1.51	0.04
C3-H3	1.09	1.10	0.01
C3-C4	1.35	1.35	0.00
C4-O4	1.34	1.36	0.02
C4-C5	1.49	1.58	0.09
O4-HO4	0.99	0.96	0.02
C5-O5	1.24	1.23	0.01
C5-C6	1.46	1.50	0.03
C6-H6	1.09	1.10	0.01
HA3-CA-HA2	108.24	108.21	0.04
HA3-CA-HA	108.86	108.50	0.36
HA3-CA-CB	110.68	111.16	0.48
HA2-CA-HA	108.37	107.86	0.51
HA2-CA-CB	110.28	110.26	0.02
CA-CB-HB1	109.25	108.04	1.20
CA-CB-HB2	110.12	108.68	1.44
CA-CB-C1	111.66	112.69	1.03
HA-CA-CB	110.34	110.75	0.41
CB-C1-C2	116.95	120.49	3.54
CB-C1-C6	123.24	119.80	3.44
HB1-CB-HB2	108.02	105.94	2.07

Terms	QM	CHARMM	Abs. diff.
HB1-CB-C1	108.76	109.36	0.60
HB2-CB-C1	108.96	111.84	2.88
C1-C2-O2	119.33	120.02	0.69
C1-C2-C3	119.42	122.04	2.62
C1-C6-C5	121.11	120.96	0.15
C1-C6-H6	122.29	118.56	3.73
C2-C1-C6	119.79	119.50	0.28
C2-C3-H3	118.04	120.94	2.90
C2-C3-C4	119.88	118.07	1.81
O2-C2-C3	121.25	117.94	3.32
C3-C4-O4	124.12	124.03	0.09
C3-C4-C5	121.27	121.10	0.18
H3-C3-C4	122.07	120.98	1.09
C4-O4-HO4	104.95	105.24	0.29
C4-C5-O5	117.82	121.26	3.44
C4-C5-C6	118.53	118.23	0.30
O4-C4-C5	114.61	114.87	0.26
C5-C6-H6	116.60	120.48	3.87
O5-C5-C6	123.66	120.51	3.15

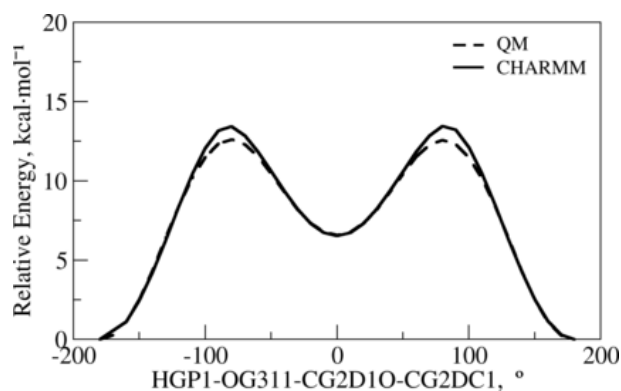


Figure S508: The PES scan for flexible dihedral corresponding to 2-ethyl-5-hydroxycyclohexa-2,5-diene-1,4-dione.

2.178 The small molecule used for bonded terms optimization of (S)-2-amino-3-(6,7-dihydro-6-imino-7-oxo-1H-indol-3-yl)propanoic acid (TQQ)

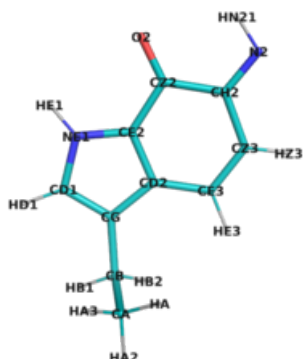


Figure S509: The energy minimized structure corresponding to 3-ethyl-6-imino-6,7-dihydro-1H-indol-7-one.

Table S858: The calculated geometric terms of 3-ethyl-6-imino-6,7-dihydro-1H-indol-7-one.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.10	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.54	0.00
CB-HB1	1.10	1.11	0.02
CB-HB2	1.10	1.11	0.01
CB-CG	1.50	1.51	0.02
CG-CD1	1.40	1.36	0.04
CG-CD2	1.42	1.38	0.04
CD1-HD1	1.08	1.08	0.00
CD1-NE1	1.37	1.37	0.00
NE1-HE1	1.02	1.01	0.00
NE1-CE2	1.37	1.38	0.01
CD2-CE2	1.41	1.38	0.02
CD2-CE3	1.45	1.45	0.00
CE2-CZ2	1.43	1.46	0.02
CE3-HE3	1.09	1.10	0.01
CE3-CZ3	1.36	1.37	0.01
CZ2-O2	1.25	1.24	0.01
CZ2-CH2	1.53	1.54	0.01
CZ3-HZ3	1.09	1.10	0.01
CZ3-CH2	1.47	1.48	0.02
CH2-N2	1.30	1.29	0.01
N2-HN21	1.03	1.00	0.03
HA3-CA-HA2	108.36	108.37	0.01
HA3-CA-HA	107.86	108.25	0.39
HA3-CA-CB	110.43	110.74	0.31
HA2-CA-HA	108.22	108.32	0.10
HA2-CA-CB	110.94	110.51	0.43
CA-CB-HB1	109.75	108.91	0.84
CA-CB-HB2	109.78	109.17	0.61

Terms	QM	CHARMM	Abs. diff.
CA-CB-CG	112.32	113.82	1.50
HA-CA-CB	110.93	110.58	0.35
CB-CG-CD1	126.26	124.49	1.77
CB-CG-CD2	127.35	125.25	2.10
HB1-CB-HB2	106.37	106.62	0.25
HB1-CB-CG	108.97	109.12	0.15
HB2-CB-CG	109.47	108.95	0.52
CG-CD1-HD1	129.92	129.02	0.90
CG-CD1-NE1	109.00	107.08	1.92
CG-CD2-CE2	107.48	105.67	1.81
CG-CD2-CE3	132.56	132.75	0.19
CD1-CG-CD2	106.24	110.26	4.01
CD1-NE1-HE1	126.72	126.48	0.24
CD1-NE1-CE2	109.25	108.21	1.04
HD1-CD1-NE1	121.06	123.90	2.83
NE1-CE2-CD2	107.94	108.79	0.85
NE1-CE2-CZ2	127.14	127.06	0.08
HE1-NE1-CE2	124.02	125.31	1.30
CD2-CE2-CZ2	124.29	124.15	0.14
CD2-CE3-HE3	119.72	120.52	0.80
CD2-CE3-CZ3	120.12	119.71	0.42
CE2-CD2-CE3	119.78	121.58	1.80
CE2-CZ2-O2	125.07	121.17	3.91
CE2-CZ2-CH2	113.70	113.48	0.22
CE3-CZ3-HZ3	121.87	120.97	0.90
CE3-CZ3-CH2	121.64	121.50	0.13
HE3-CE3-CZ3	120.09	119.77	0.32
CZ2-CH2-CZ3	119.69	119.57	0.13
CZ2-CH2-N2	120.35	120.51	0.17
O2-CZ2-CH2	121.19	125.35	4.16
CZ3-CH2-N2	119.95	119.92	0.03
HZ3-CZ3-CH2	116.38	117.53	1.15
CH2-N2-HN21	107.72	107.96	0.24

2.179 The small molecule used for bonded terms optimization of 2-hydroxy-tryptophan (TRO)

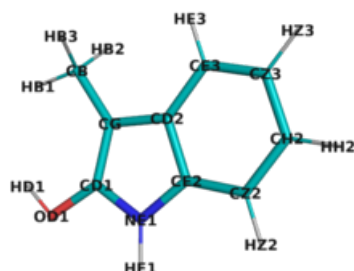


Figure S510: The energy minimized structure corresponding to 3-methyl-1H-indol-2-ol.

Table S859: The calculated geometric terms of 3-methyl-1H-indol-2-ol.

Terms	QM	CHARMM	Abs. diff.
CD1-OD1-HD1	107.51	106.10	1.41
CD1-NE1-HE1	123.94	123.90	0.04
CD1-NE1-CE2	108.77	110.36	1.58
OD1-CD1-NE1	116.03	116.98	0.95
CD2-CE2-NE1	106.82	106.26	0.56
CD2-CE2-CZ2	122.70	120.99	1.72
CD2-CE3-HE3	120.58	120.03	0.55
CD2-CE3-CZ3	118.97	119.40	0.43
NE1-CE2-CZ2	130.48	132.75	2.27
HE1-NE1-CE2	127.29	125.75	1.54
CE2-CD2-CE3	118.65	119.84	1.19
CE2-CZ2-HZ2	121.54	119.91	1.63
CE2-CZ2-CH2	117.25	119.34	2.09
CE3-CZ3-HZ3	119.56	119.79	0.23
CE3-CZ3-CH2	121.26	120.48	0.78
HE3-CE3-CZ3	120.45	120.57	0.13
CZ2-CH2-CZ3	121.17	119.96	1.22
CZ2-CH2-HH2	119.33	120.24	0.90
HZ2-CZ2-CH2	121.22	120.75	0.46
CZ3-CH2-HH2	119.49	119.81	0.31
HZ3-CZ3-CH2	119.18	119.73	0.56

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.10	1.11	0.02
CB-HB1	1.10	1.11	0.01
CB-HB2	1.10	1.11	0.02
CB-CG	1.50	1.51	0.02
CG-CD1	1.38	1.37	0.01
CG-CD2	1.44	1.44	0.00
CD1-OD1	1.37	1.37	0.00
CD1-NE1	1.37	1.37	0.01
OD1-HD1	0.97	0.96	0.01
CD2-CE2	1.42	1.41	0.02
CD2-CE3	1.41	1.39	0.01
NE1-HE1	1.01	1.01	0.01
NE1-CE2	1.38	1.37	0.01
CE2-CZ2	1.40	1.38	0.01
CE3-HE3	1.09	1.08	0.01
CE3-CZ3	1.39	1.40	0.01
CZ2-HZ2	1.09	1.08	0.01
CZ2-CH2	1.39	1.40	0.01
CZ3-HZ3	1.09	1.08	0.00
CZ3-CH2	1.41	1.40	0.01
CH2-HH2	1.09	1.08	0.00
HB3-CB-HB1	107.03	108.80	1.78
HB3-CB-HB2	107.63	108.65	1.02
HB3-CB-CG	111.59	109.70	1.88
CB-CG-CD1	127.97	129.82	1.85
CB-CG-CD2	126.82	124.30	2.52
HB1-CB-HB2	107.01	108.78	1.76
HB1-CB-CG	111.75	111.17	0.59
HB2-CB-CG	111.56	109.69	1.88
CG-CD1-OD1	132.86	133.46	0.61
CG-CD1-NE1	111.11	109.56	1.56
CG-CD2-CE2	108.08	107.94	0.14
CG-CD2-CE3	133.27	132.22	1.05
CD1-CG-CD2	105.21	105.89	0.67

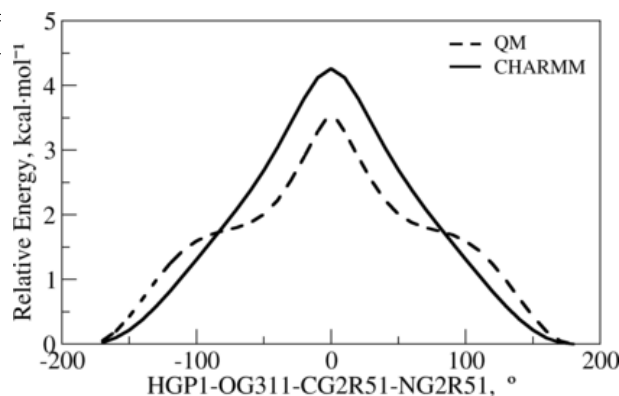


Figure S511: The PES scan for flexible dihedral corresponding to 3-methyl-1H-indol-2-ol.

2.180 The small molecule used for bonded terms optimization of 2-amino-3-(6,7-dioxo-6,7-dihydro-1H-indol-3-yl)-propionica cid (TRQ)

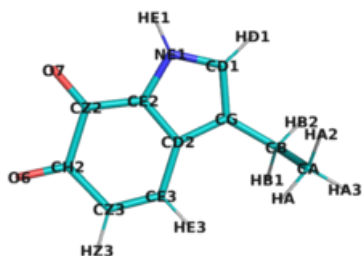


Figure S512: The energy minimized structure corresponding to 3-ethyl-6,7-dihydro-1H-indole-6,7-dione.

Table S860: The calculated geometric terms of 3-ethyl-6,7-dihydro-1H-indole-6,7-dione.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.53	1.54	0.00
CB-HB1	1.10	1.11	0.02
CB-HB2	1.10	1.11	0.02
CB-CG	1.50	1.51	0.02
CG-CD1	1.40	1.36	0.03
CG-CD2	1.42	1.38	0.04
CD1-HD1	1.08	1.08	0.00
CD1-NE1	1.37	1.37	0.00
CD2-CE2	1.40	1.38	0.02
CD2-CE3	1.45	1.45	0.00
NE1-HE1	1.01	1.01	0.00
NE1-CE2	1.37	1.37	0.01
CE2-CZ2	1.44	1.45	0.01
CE3-HE3	1.09	1.10	0.01
CE3-CZ3	1.36	1.37	0.01
CZ2-O7	1.24	1.23	0.00
CZ2-CH2	1.55	1.56	0.01
CZ3-HZ3	1.09	1.10	0.01
CZ3-CH2	1.48	1.51	0.04
CH2-O6	1.23	1.23	0.00
HA3-CA-HA2	108.40	108.30	0.10
HA3-CA-HA	108.30	108.22	0.07
HA3-CA-CB	111.06	110.51	0.55
HA2-CA-HA	107.81	108.25	0.44
HA2-CA-CB	110.37	110.74	0.37
CA-CB-HB1	109.77	109.13	0.64
CA-CB-HB2	109.70	108.92	0.79
CA-CB-CG	112.33	113.82	1.49

Terms	QM	CHARMM	Abs. diff.
HA-CA-CB	110.79	110.72	0.08
CB-CG-CD1	126.30	124.40	1.89
CB-CG-CD2	127.35	125.38	1.98
HB1-CB-HB2	106.24	106.50	0.27
HB1-CB-CG	109.55	109.03	0.51
HB2-CB-CG	109.07	109.18	0.11
CG-CD1-HD1	129.87	129.32	0.55
CG-CD1-NE1	108.87	107.04	1.83
CG-CD2-CE2	107.58	105.48	2.09
CG-CD2-CE3	132.70	132.45	0.25
CD1-CG-CD2	106.23	110.22	3.99
CD1-NE1-HE1	127.11	126.84	0.28
CD1-NE1-CE2	109.43	108.20	1.23
HD1-CD1-NE1	121.25	123.64	2.39
CD2-CE2-NE1	107.87	109.06	1.19
CD2-CE2-CZ2	125.18	123.96	1.22
CD2-CE3-HE3	119.34	119.81	0.46
CD2-CE3-CZ3	120.72	120.90	0.18
NE1-CE2-CZ2	126.88	126.98	0.10
HE1-NE1-CE2	123.45	124.96	1.51
CE2-CD2-CE3	119.67	122.07	2.40
CE2-CZ2-O7	124.84	123.96	0.88
CE2-CZ2-CH2	113.53	113.97	0.44
CE3-CZ3-HZ3	121.91	119.74	2.17
CE3-CZ3-CH2	122.04	119.88	2.16
HE3-CE3-CZ3	119.93	119.29	0.64
CZ2-CH2-CZ3	118.74	119.22	0.49
CZ2-CH2-O6	118.97	119.37	0.39
O7-CZ2-CH2	121.63	122.08	0.45
CZ3-CH2-O6	122.29	121.41	0.88
HZ3-CZ3-CH2	116.02	120.38	4.36

2.181 The small molecule used for bonded terms optimization of TRW3-(2-amino-3-hydroxypropyl)-6-(N'-cyclohexylhydrazino)octahydro-indol-7-ol (TRW)

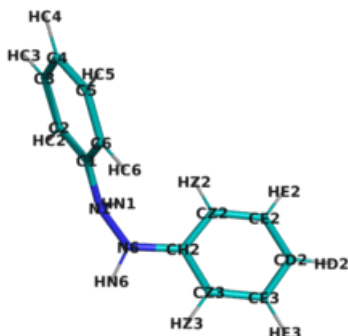


Figure S513: The energy minimized structure corresponding to 1,2-diphenylhydrazine.

Table S861: The calculated geometric terms of 1,2-diphenylhydrazine.

Terms	QM	CHARMM	Abs. diff.
CD2-HD2	1.09	1.08	0.01
CD2-CE2	1.40	1.40	0.00
CD2-CE3	1.40	1.40	0.00
CE2-HE2	1.09	1.08	0.01
CE2-CZ2	1.40	1.40	0.01
CE3-HE3	1.09	1.08	0.01
CE3-CZ3	1.39	1.40	0.01
CZ2-HZ2	1.09	1.08	0.01
CZ2-CH2	1.40	1.41	0.01
CZ3-HZ3	1.09	1.08	0.01
CZ3-CH2	1.40	1.41	0.00
CH2-N6	1.41	1.42	0.01
N6-HN6	1.02	1.02	0.00
N6-N1	1.41	1.45	0.04
N1-HN1	1.02	1.02	0.01
N1-C1	1.42	1.42	0.01
C1-C2	1.40	1.41	0.00
C1-C6	1.40	1.41	0.01
C2-HC2	1.09	1.08	0.01
C2-C3	1.39	1.40	0.01
C3-HC3	1.09	1.08	0.01
C3-C4	1.40	1.40	0.00
C4-HC4	1.09	1.08	0.01
C4-C5	1.40	1.40	0.00
C5-HC5	1.09	1.08	0.01
C5-C6	1.39	1.40	0.01
C6-HC6	1.09	1.08	0.01
CD2-CE2-HE2	119.99	120.09	0.10
CD2-CE2-CZ2	120.92	119.91	1.01
CD2-CE3-HE3	120.19	120.07	0.12
CD2-CE3-CZ3	120.41	119.89	0.52

Terms	QM	CHARMM	Abs. diff.
HD2-CD2-CE2	120.40	119.97	0.43
HD2-CD2-CE3	120.34	120.03	0.31
CE2-CD2-CE3	119.25	120.00	0.74
CE2-CZ2-HZ2	120.03	119.04	0.99
CE2-CZ2-CH2	119.61	120.91	1.29
HE2-CE2-CZ2	119.08	120.00	0.92
CE3-CZ3-HZ3	120.14	119.04	1.10
CE3-CZ3-CH2	120.23	121.08	0.85
HE3-CE3-CZ3	119.41	120.04	0.64
CZ2-CH2-CZ3	119.57	118.22	1.35
CZ2-CH2-N6	121.27	124.73	3.46
HZ2-CZ2-CH2	120.34	120.04	0.29
CZ3-CH2-N6	119.09	117.05	2.03
HZ3-CZ3-CH2	119.63	119.87	0.24
CH2-N6-HN6	112.47	112.64	0.17
CH2-N6-N1	117.32	121.65	4.33
N6-N1-HN1	111.46	106.48	4.97
N6-N1-C1	115.19	120.17	4.99
HN6-N6-N1	109.00	105.86	3.14
N1-C1-C2	118.77	117.02	1.74
N1-C1-C6	121.37	124.80	3.44
HN1-N1-C1	111.33	111.47	0.14
C1-C2-HC2	119.75	119.89	0.14
C1-C2-C3	120.13	121.12	0.99
C1-C6-C5	119.59	121.04	1.45
C1-C6-HC6	119.15	119.51	0.36
C2-C1-C6	119.72	118.17	1.55
C2-C3-HC3	119.38	120.12	0.73
C2-C3-C4	120.39	119.85	0.54
HC2-C2-C3	120.12	118.98	1.13
C3-C4-HC4	120.36	120.07	0.28
C3-C4-C5	119.21	120.00	0.79
HC3-C3-C4	120.23	120.03	0.19
C4-C5-HC5	119.93	120.27	0.34
C4-C5-C6	120.95	119.82	1.13
HC4-C4-C5	120.43	119.93	0.50
C5-C6-HC6	121.25	119.44	1.80
HC5-C5-C6	119.12	119.91	0.80

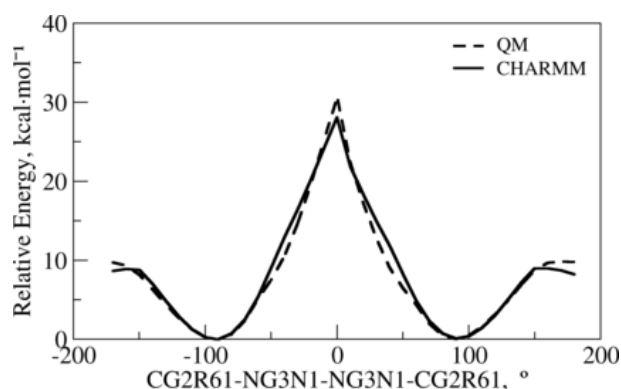


Figure S514: The PES scan for flexible dihedral corresponding to 1,2-diphenylhydrazine.

2.182 The small molecule used for bonded terms optimization of (2S,3S,4R)-2-amino-3,4-dihydroxy-3-methylpentanoicacid (TS9)

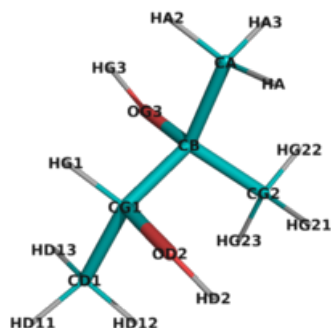


Figure S515: The energy minimized structure corresponding to 2-methylbutane-2,3-diol.

Table S862: The calculated geometric terms of 2-methylbutane-2,3-diol.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.10	1.11	0.01
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.53	0.01
CB-OG3	1.44	1.42	0.02
CB-CG2	1.52	1.54	0.02
CB-CG1	1.54	1.55	0.00
OG3-HG3	0.97	0.96	0.02
CG2-HG21	1.09	1.11	0.02
CG2-HG22	1.09	1.11	0.02
CG2-HG23	1.09	1.11	0.02
CG1-HG1	1.10	1.12	0.02
CG1-OD2	1.43	1.42	0.01
CG1-CD1	1.52	1.54	0.02
OD2-HD2	0.97	0.96	0.01
CD1-HD11	1.09	1.11	0.02
CD1-HD12	1.10	1.11	0.01
CD1-HD13	1.09	1.11	0.02
HA3-CA-HA2	108.47	108.90	0.43
HA3-CA-HA	109.67	108.32	1.36
HA3-CA-CB	109.74	110.59	0.85
HA2-CA-HA	107.68	108.13	0.46
HA2-CA-CB	110.29	111.01	0.72
CA-CB-OG3	109.95	105.77	4.18
CA-CB-CG2	110.87	109.44	1.42
CA-CB-CG1	109.94	112.06	2.12
HA-CA-CB	110.94	109.82	1.13
CB-OG3-HG3	106.87	105.04	1.83
CB-CG2-HG21	110.82	110.54	0.28
CB-CG2-HG22	109.41	109.90	0.49
CB-CG2-HG23	110.87	111.02	0.15
CB-CG1-HG1	106.53	107.33	0.80

Terms	QM	CHARMM	Abs. diff.
CB-CG1-OD2	111.23	112.18	0.94
CB-CG1-CD1	114.13	115.61	1.47
OG3-CB-CG2	104.91	106.05	1.14
OG3-CB-CG1	108.45	110.09	1.64
CG2-CB-CG1	112.57	113.01	0.44
HG21-CG2-HG22	108.28	108.19	0.09
HG21-CG2-HG23	109.41	109.20	0.21
HG22-CG2-HG23	107.97	107.91	0.06
CG1-OD2-HD2	106.72	105.26	1.46
CG1-CD1-HD11	109.68	110.19	0.51
CG1-CD1-HD12	110.82	111.32	0.50
CG1-CD1-HD13	110.69	110.12	0.56
HG1-CG1-OD2	104.22	106.86	2.64
HG1-CG1-CD1	108.80	107.73	1.08
OD2-CG1-CD1	111.29	106.74	4.56
HD11-CD1-HD12	108.01	108.44	0.44
HD11-CD1-HD13	109.49	108.33	1.15
HD12-CD1-HD13	108.10	108.35	0.25

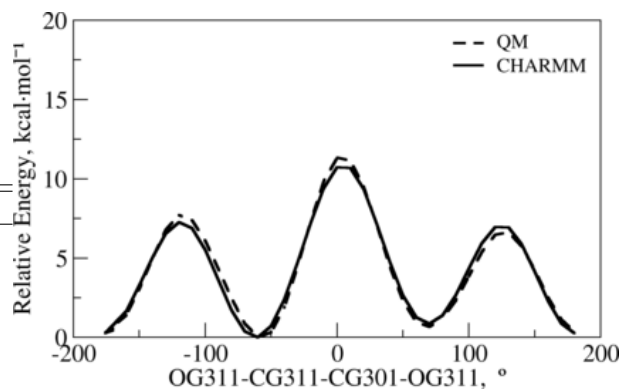


Figure S516: The PES scan for flexible dihedral corresponding to 2-methylbutane-2,3-diol.

2.183 The small molecule used for bonded terms optimization of O-sulfo-L-tyrosine (TYS)

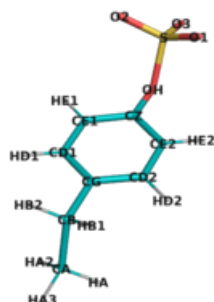


Figure S517: The energy minimized structure corresponding to (4-ethylphenyl)oxidanesulfonic acid.

Table S863: The calculated geometric terms of (4-ethylphenyl)oxidanesulfonic acid.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.10	1.11	0.01
HA2-CA	1.10	1.11	0.02
CA-HA	1.10	1.11	0.02
CA-CB	1.53	1.54	0.00
CB-HB1	1.10	1.11	0.01
CB-HB2	1.10	1.11	0.01
CB-CG	1.51	1.50	0.00
CG-CD1	1.40	1.40	0.00
CG-CD2	1.40	1.40	0.00
CD1-HD1	1.09	1.08	0.01
CD1-CE1	1.40	1.40	0.01
CD2-HD2	1.09	1.08	0.01
CD2-CE2	1.40	1.40	0.01
CE1-HE1	1.09	1.08	0.01
CE1-CZ	1.40	1.41	0.00
CE2-HE2	1.09	1.08	0.01
CE2-CZ	1.40	1.41	0.00
CZ-OH	1.37	1.39	0.01
OH-S	1.76	1.58	0.18
S-O1	1.48	1.45	0.03
S-O2	1.48	1.45	0.03
S-O3	1.47	1.45	0.03
HA3-CA-HA2	108.38	108.49	0.11
HA3-CA-HA	108.39	108.49	0.10
HA3-CA-CB	111.47	110.45	1.02
HA2-CA-HA	107.73	108.27	0.54
HA2-CA-CB	110.37	110.52	0.14
CA-CB-HB1	109.44	110.89	1.45
CA-CB-HB2	109.44	110.91	1.47
CA-CB-CG	112.29	109.58	2.71
HA-CA-CB	110.38	110.55	0.17
CB-CG-CD1	120.93	120.17	0.76
CB-CG-CD2	120.90	120.17	0.73
HB1-CB-HB2	106.73	108.40	1.67

Terms	QM	CHARMM	Abs. diff.
HB1-CB-CG	109.39	108.49	0.91
HB2-CB-CG	109.40	108.50	0.90
CG-CD1-HD1	119.38	119.91	0.53
CG-CD1-CE1	121.30	120.09	1.21
CG-CD2-HD2	119.35	119.93	0.59
CG-CD2-CE2	121.29	120.09	1.20
CD1-CG-CD2	118.11	119.66	1.54
CD1-CE1-HE1	121.77	120.88	0.89
CD1-CE1-CZ	119.71	120.57	0.86
HD1-CD1-CE1	119.32	120.00	0.68
CD2-CE2-HE2	121.78	120.89	0.88
CD2-CE2-CZ	119.73	120.57	0.85
HD2-CD2-CE2	119.36	119.98	0.61
CE1-CZ-CE2	119.86	118.97	0.89
CE1-CZ-OH	120.04	120.24	0.21
HE1-CE1-CZ	118.48	118.54	0.06
CE2-CZ-OH	120.04	120.24	0.20
HE2-CE2-CZ	118.46	118.52	0.06
CZ-OH-S	114.43	116.42	1.99
OH-S-O1	103.11	105.01	1.91
OH-S-O2	103.11	105.04	1.92
OH-S-O3	99.62	102.51	2.89
O1-S-O2	114.89	114.68	0.22
O1-S-O3	116.30	113.94	2.36
O2-S-O3	116.31	113.96	2.35

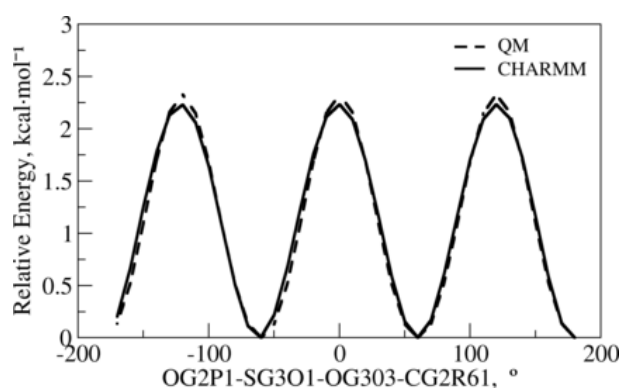


Figure S518: The PES scan for flexible dihedral corresponding to (4-ethylphenyl)oxidanesulfonic acid.

2.184 The small molecule used for bonded terms optimization of (4-thiazolyl)-alanine (TZA4)

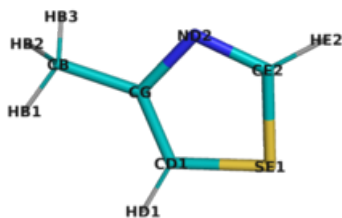


Figure S519: The energy minimized structure corresponding to 4-methyl-1,3-thiazole.

Table S864: The calculated geometric terms of 4-methyl-1,3-thiazole.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-CG	1.50	1.49	0.01
CG-CD1	1.38	1.37	0.01
CG-ND2	1.38	1.40	0.02
CD1-HD1	1.08	1.08	0.00
CD1-SE1	1.71	1.71	0.01
ND2-CE2	1.31	1.33	0.01
SE1-CE2	1.73	1.70	0.03
CE2-HE2	1.08	1.09	0.01
HB3-CB-HB1	108.63	109.24	0.60
HB3-CB-HB2	107.67	108.94	1.27
HB3-CB-CG	110.45	109.42	1.03
CB-CG-CD1	126.23	128.48	2.25
CB-CG-ND2	119.11	116.31	2.80
HB1-CB-HB2	108.63	109.24	0.60
HB1-CB-CG	110.90	110.56	0.34
HB2-CB-CG	110.46	109.42	1.03
CG-CD1-HD1	128.13	128.83	0.70
CG-CD1-SE1	110.61	109.99	0.62
CG-ND2-CE2	110.41	108.81	1.60
CD1-CG-ND2	114.65	115.21	0.56
CD1-SE1-CE2	88.99	90.05	1.06
HD1-CD1-SE1	121.26	121.18	0.08
ND2-CE2-SE1	115.34	115.94	0.61
ND2-CE2-HE2	123.80	125.52	1.72
SE1-CE2-HE2	120.86	118.53	2.33

2.185 The small molecule used for bonded terms optimization of S-cyano-L-cysteine (XCN)

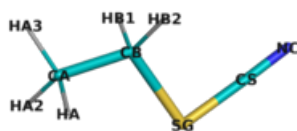


Figure S520: The energy minimized structure corresponding to (ethylsulfanyl)carbonitrile.

Table S865: The calculated geometric terms of (ethylsulfanyl)carbonitrile.

Terms	QM	CHARMM	Abs. diff.
HA3-CA	1.09	1.11	0.02
HA2-CA	1.09	1.11	0.02
CA-HA	1.09	1.11	0.02
CA-CB	1.52	1.54	0.01
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.83	1.82	0.01
SG-CS	1.70	1.70	0.00
CS-NC	1.19	1.18	0.01
HA3-CA-HA2	108.09	108.38	0.29
HA3-CA-HA	108.11	108.33	0.22
HA3-CA-CB	109.30	110.41	1.11
HA2-CA-HA	108.61	108.49	0.12
HA2-CA-CB	111.31	110.58	0.73
CA-CB-HB1	111.16	108.70	2.46
CA-CB-HB2	111.17	108.70	2.47
CA-CB-SG	108.40	113.41	5.01
HA-CA-CB	111.30	110.56	0.74
CB-SG-CS	98.65	98.73	0.08
HB1-CB-HB2	108.97	106.87	2.10
HB1-CB-SG	108.53	109.46	0.93
HB2-CB-SG	108.53	109.49	0.96
SG-CS-NC	179.10	178.61	0.49

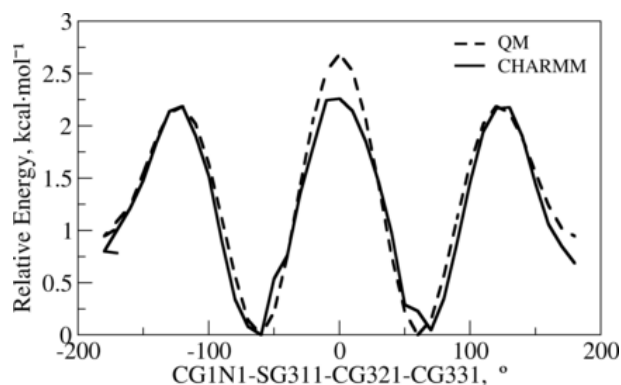


Figure S521: The PES scan for flexible dihedral corresponding to (ethylsulfanyl)carbonitrile.

2.186 The small molecule 1 used for bonded terms optimization of [(4Z)-2-[(1Z)-ethanimidoyl]-4-(4-hydroxybenzylidene)-5-oxo-4,5-dihydro-1H-imidazol-1-yl]acetic acid (XYG)

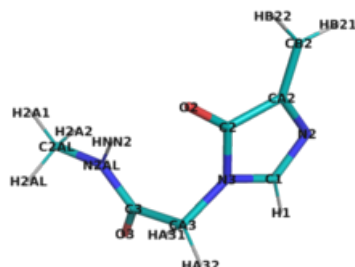


Figure S522: The energy minimized structure corresponding to N-methyl-2-(4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide.

Table S866: The calculated geometric terms of N-methyl-2-(4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide.

Terms	QM	CHARMM	Abs. diff.
C1-H1	1.09	1.09	0.01
C1-N2	1.30	1.33	0.03
C1-N3	1.39	1.39	0.01
N2-CA2	1.41	1.41	0.00
N3-CA3	1.45	1.47	0.02
N3-C2	1.39	1.38	0.01
CA3-HA31	1.10	1.11	0.02
CA3-HA32	1.09	1.11	0.02
CA3-C3	1.53	1.50	0.04
C2-O2	1.23	1.24	0.01
C2-CA2	1.49	1.49	0.01
CA2-CB2	1.34	1.34	0.00
CB2-HB21	1.08	1.10	0.01
CB2-HB22	1.09	1.10	0.01
C3-O3	1.23	1.23	0.01
C3-N2AL	1.36	1.34	0.01
N2AL-HNN2	1.02	1.00	0.02
N2AL-C2AL	1.45	1.44	0.01
C2AL-H2AL	1.09	1.11	0.02
C2AL-H2A1	1.09	1.11	0.02
C2AL-H2A2	1.09	1.11	0.02
C1-N2-CA2	104.17	103.49	0.68
C1-N3-CA3	128.03	126.60	1.43
C1-N3-C2	107.67	106.93	0.75
H1-C1-N2	124.55	123.53	1.02
H1-C1-N3	119.88	120.86	0.98
N2-C1-N3	115.57	115.61	0.04
N2-CA2-C2	109.91	109.49	0.42

Terms	QM	CHARMM	Abs. diff.
N2-CA2-CB2	125.60	128.88	3.28
N3-CA3-HA31	107.71	110.41	2.70
N3-CA3-HA32	109.10	110.42	1.31
N3-CA3-C3	111.83	111.73	0.11
N3-C2-O2	126.06	127.45	1.39
N3-C2-CA2	102.67	104.47	1.80
CA3-N3-C2	124.30	126.47	2.17
CA3-C3-O3	121.20	121.02	0.18
CA3-C3-N2AL	113.61	116.66	3.06
HA31-CA3-HA32	109.44	107.63	1.81
HA31-CA3-C3	110.92	108.66	2.25
HA32-CA3-C3	107.80	107.86	0.06
C2-CA2-CB2	124.49	121.63	2.87
O2-C2-CA2	131.27	128.06	3.21
CA2-CB2-HB21	120.88	119.00	1.88
CA2-CB2-HB22	119.73	121.06	1.33
HB21-CB2-HB22	119.39	119.94	0.56
C3-N2AL-HNN2	117.97	118.59	0.62
C3-N2AL-C2AL	121.78	122.31	0.53
O3-C3-N2AL	125.19	122.31	2.88
N2AL-C2AL-H2AL	107.47	110.78	3.31
N2AL-C2AL-H2A1	110.22	110.58	0.36
N2AL-C2AL-H2A2	111.32	110.51	0.82
HNN2-N2AL-C2AL	119.76	118.84	0.92
H2AL-C2AL-H2A1	109.52	108.36	1.16
H2AL-C2AL-H2A2	109.16	108.15	1.01
H2A1-C2AL-H2A2	109.11	108.38	0.74

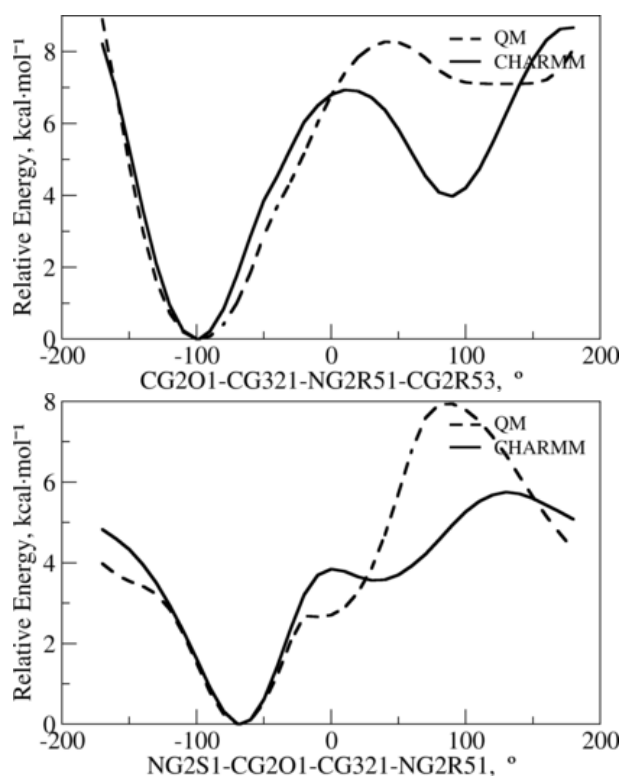


Figure S523: The PES scan for flexible dihedrals corresponding to N-methyl-2-(4-methylidene-5-oxo-4,5-dihydro-1H-imidazol-1-yl)acetamide.

2.188 The small molecule 3 used for bonded terms optimization of [(4Z)-2-[(1Z)-ethanimidoyl]-4-(4-hydroxybenzylidene)-5-oxo-4,5-dihydro-1h-imidazol-1-yl]aceticacid (XYG)

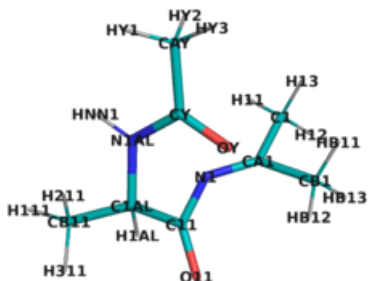


Figure S526: The energy minimized structure corresponding to (2S)-2-acetamido-N-(propan-2-ylidene)propanamide.

Table S868: The calculated geometric terms of (2S)-2-acetamido-N-(propan-2-ylidene)propanamide.

Terms	QM	CHARMM	Abs. diff.
N1AL-HNN1	1.01	1.00	0.02
N1AL-C1AL	1.45	1.45	0.00
N1AL-CY	1.37	1.34	0.03
C1AL-H1AL	1.09	1.12	0.03
C1AL-CB11	1.53	1.54	0.02
C1AL-C11	1.53	1.54	0.01
CB11-H111	1.09	1.11	0.02
CB11-H211	1.09	1.11	0.02
CB11-H311	1.09	1.11	0.02
C11-O11	1.23	1.23	0.01
C11-N1	1.41	1.45	0.04
CAY-HY1	1.09	1.11	0.02
CAY-HY2	1.10	1.11	0.02
CAY-HY3	1.09	1.11	0.02
CAY-CY	1.51	1.48	0.03
CY-OY	1.24	1.22	0.01
N1-CA1	1.29	1.28	0.01
CA1-CB1	1.51	1.51	0.00
CA1-C1	1.50	1.50	0.00
CB1-HB11	1.09	1.11	0.02
CB1-HB12	1.09	1.11	0.02
CB1-HB13	1.10	1.11	0.02
C1-H11	1.09	1.11	0.02
C1-H12	1.10	1.11	0.02
C1-H13	1.10	1.11	0.02
N1AL-C1AL-H1AL	108.28	106.70	1.58
N1AL-C1AL-CB11	110.22	109.59	0.62
N1AL-C1AL-C11	112.61	115.67	3.06
N1AL-CY-CAY	115.49	117.61	2.12

Terms	QM	CHARMM	Abs. diff.
N1AL-CY-OY	121.57	120.17	1.40
HNN1-N1AL-C1AL	117.24	118.46	1.21
HNN1-N1AL-CY	117.81	119.89	2.08
C1AL-N1AL-CY	119.03	121.28	2.25
C1AL-CB11-H111	110.38	109.63	0.75
C1AL-CB11-H211	110.42	111.10	0.68
C1AL-CB11-H311	109.43	112.45	3.02
C1AL-C11-O11	121.32	121.80	0.48
C1AL-C11-N1	114.06	114.58	0.52
H1AL-C1AL-CB11	110.09	107.56	2.53
H1AL-C1AL-C11	106.04	107.50	1.46
CB11-C1AL-C11	109.51	109.48	0.02
H111-CB11-H211	109.10	107.38	1.72
H111-CB11-H311	109.10	107.24	1.87
H211-CB11-H311	108.36	108.85	0.49
C11-N1-CA1	120.20	126.80	6.60
O11-C11-N1	123.98	123.61	0.36
CAY-CY-OY	122.94	122.21	0.73
HY1-CAY-HY2	108.47	109.31	0.84
HY1-CAY-HY3	109.79	108.57	1.22
HY1-CAY-CY	111.97	110.69	1.27
HY2-CAY-HY3	108.63	108.52	0.11
HY2-CAY-CY	109.25	110.26	1.01
HY3-CAY-CY	108.67	109.44	0.77
N1-CA1-CB1	125.26	132.58	7.32
N1-CA1-C1	117.90	127.73	9.83
CA1-CB1-HB11	110.24	110.64	0.40
CA1-CB1-HB12	111.38	112.63	1.25
CA1-CB1-HB13	109.11	111.31	2.21
CA1-C1-H11	110.33	110.94	0.61
CA1-C1-H12	109.97	111.89	1.92
CA1-C1-H13	110.31	111.83	1.53
CB1-CA1-C1	116.83	99.68	17.14
HB11-CB1-HB12	109.27	106.53	2.74
HB11-CB1-HB13	108.24	107.56	0.68
HB12-CB1-HB13	108.54	107.92	0.62
H11-C1-H12	109.56	106.98	2.58
H11-C1-H13	109.65	106.91	2.74
H12-C1-H13	106.96	108.03	1.07

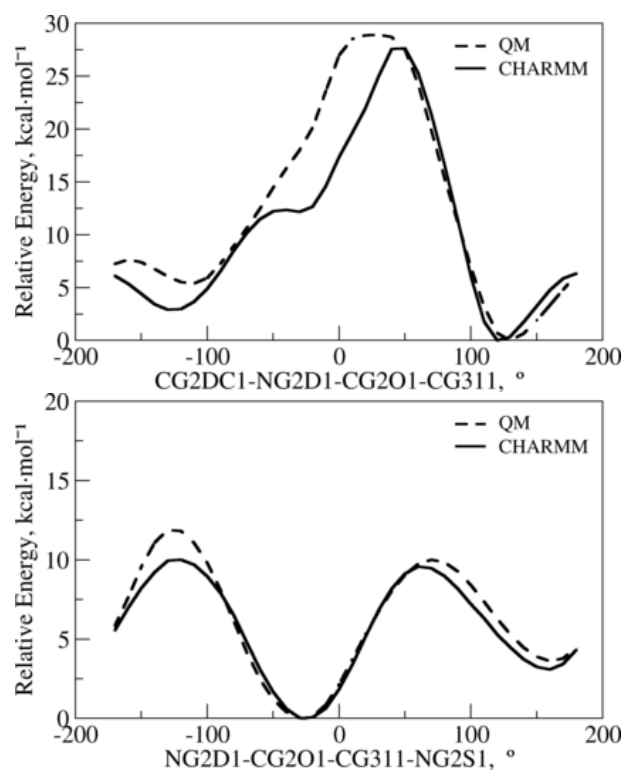


Figure S527: The PES scan for flexible dihedrals corresponding to (2*S*)-2-acetamido-N-(propan-2-ylidene)propanamide.

2.189 The small molecule used for bonded terms optimization of cysteine-s-acetamide (YCM)

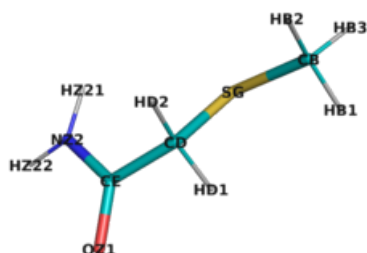


Figure S528: The energy minimized structure corresponding to 2-(methylsulfanyl)acetamide.

Table S869: The calculated geometric terms of 2-(methylsulfanyl)acetamide.

Terms	QM	CHARMM	Abs. diff.
HB3-CB	1.09	1.11	0.02
CB-HB1	1.09	1.11	0.02
CB-HB2	1.09	1.11	0.02
CB-SG	1.81	1.82	0.01
SG-CD	1.82	1.84	0.02
CD-HD2	1.10	1.11	0.01
CD-HD1	1.09	1.11	0.02
CD-CE	1.52	1.50	0.02
CE-OZ1	1.23	1.23	0.00
CE-NZ2	1.37	1.36	0.01
NZ2-HZ21	1.01	0.99	0.02
NZ2-HZ22	1.01	0.99	0.02
HB3-CB-HB1	108.66	107.85	0.81
HB3-CB-HB2	108.80	107.90	0.90
HB3-CB-SG	107.35	110.82	3.48
CB-SG-CD	98.59	95.63	2.96
HB1-CB-HB2	109.67	108.01	1.66
HB1-CB-SG	111.09	111.05	0.03
HB2-CB-SG	111.19	111.07	0.12
SG-CD-HD2	109.04	110.93	1.89
SG-CD-HD1	111.13	110.17	0.96
SG-CD-CE	112.20	113.00	0.80
CD-CE-OZ1	121.64	120.25	1.39
CD-CE-NZ2	115.02	118.43	3.41
HD2-CD-HD1	109.13	107.38	1.75
HD2-CD-CE	108.45	108.29	0.16
HD1-CD-CE	106.79	106.82	0.03
CE-NZ2-HZ21	120.67	118.53	2.14
CE-NZ2-HZ22	116.73	116.69	0.04
OZ1-CE-NZ2	123.20	121.27	1.93
HZ21-NZ2-HZ22	118.22	123.11	4.89

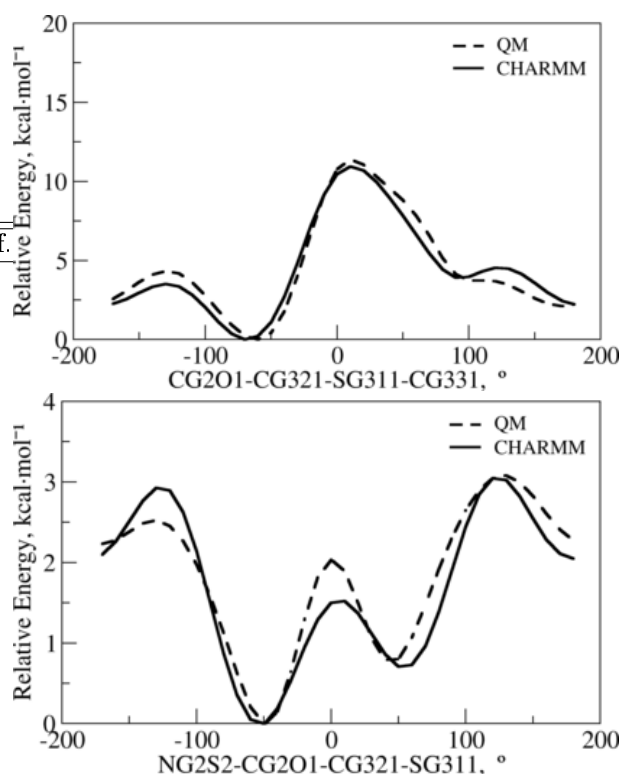


Figure S529: The PES scan for flexible dihedrals corresponding to 2-(methylsulfanyl)acetamide.

3 The details of MD simulations for proteins containing modified amino acids

Table S870: Root Mean Square (RMSD) deviation in molecular dynamics simulations

Amino acid	RMSD (Å)		
	^a Backbone	^b Backbone	^c Residue
2HF	0.53 (0.05)	0.40 (0.06)	0.15 (0.04)
4FB	0.68 (0.10)	0.59 (0.06)	0.59 (0.17)
BCS	1.15 (0.33)	0.81 (0.12)	0.28 (0.09)
CCS	1.14 (0.28)	0.89 (0.21)	0.91 (0.15)
CME	1.31 (0.15)	0.83 (0.17)	0.57 (0.22)
CSS	0.82 (0.07)	0.60 (0.05)	0.11 (0.03)
GGB	0.70 (0.07)	0.81 (0.11)	0.39 (0.07)
HTI	0.45 (0.03)	0.53 (0.05)	0.32 (0.10)
KCX	1.14 (0.16)	0.64 (0.11)	0.76 (0.33)
LE1	1.34 (0.20)	0.68 (0.11)	0.14 (0.04)
LLP	0.59 (0.04)	0.55 (0.05)	0.36 (0.05)
MAA	0.66 (0.13)	0.37 (0.08)	0.14 (0.06)
NRQ	0.50 (0.03)	0.53 (0.05)	0.55 (0.07)
OCS	1.65 (0.23)	0.89 (0.11)	0.29 (0.22)
PBF	1.48 (0.18)	0.99 (0.13)	0.40 (0.09)
SNC	1.06 (0.14)	0.80 (0.18)	0.66 (0.24)
XYG	0.46 (0.03)	0.46 (0.04)	0.31 (0.09)
MDO	0.49 (0.03)	0.49 (0.05)	0.24 (0.07)
4FW	0.70 (0.12)	0.78 (0.16)	0.18 (0.05)
CSO	0.78 (0.12)	0.62 (0.11)	0.68 (0.24)

^aRMSD was computed for unrestrained backbone atoms after superposition on the experimental structure; ^bRMSD was computed based on backbone heavy atoms within 10 Å sphere around the non-standard amino acid; ^cRMSD was computed for the heavy atoms of the non-standard amino acid.

Table S871: Selected average non-bond distances (Å) in MD simulations of proteins with the non-standard amino acids. Values in parenthesis represent the standard deviation.

Residue	^a Atom pair	X-ray str.	MD simulation	Abs. diff
2HF	ND1 _{2HF597} -OE1/OE2 _{Glu704}	2.72	2.70 (0.13)	0.02
4FB	O _{4fb76} -N _{Gly92}	2.73	2.92 (0.19)	0.19
BCS	OB _{cs145} -HN _{Val148}	2.41	2.71 (0.37)	0.30
CCS	N _{Gly75} -OZ2 _{Ccs106}	2.62	3.19 (0.47)	0.57
CME	O _{Phe285} -N _{Cme288}	2.93	3.03 (0.19)	0.10
CSS	N _{Css247} -OG _{Ser274}	2.96	3.19 (0.21)	0.23
CSS	SD _{Css247} -OG1 _{Thr252}	3.65	3.24 (0.18)	0.41
CSS	O _{Css247} -N _{Trp275}	2.86	3.05 (0.19)	0.19
GGB	NE _{Ggb1} -OD1/OD2 _{Asp35}	2.76	2.65 (0.11)	0.11
GGB	NG _{gb1} -OD1/OD2 _{Asp81}	2.64	2.70 (0.15)	0.06
GGB	NH2 _{Ggb1} -OD1/OD2 _{Asp219}	2.75	2.75 (0.14)	0.00
HTI	O _{Hti136} -N _{Leu140}	3.01	2.90 (0.17)	0.11
HTI	NAL _{Hti136} -OE1/OE2 _{Glu243}	2.62	2.76 (0.14)	0.14
KCX	O _{Kcx84} -N _{Ala88}	2.92	2.93 (0.17)	0.01
KCX	OG _{Ser81} -OQ1 _{Kcx84}	2.74	3.38 (0.90)	0.64
LE1	O _{Leu12} -N _{Leu116}	2.94	2.96 (0.17)	0.02
LE1	O _{Leu116} -N _{Glu20}	2.92	3.00 (0.21)	0.08
LLP	OH _{Tyr73} -OP2 _{Llp255}	2.65	2.58 (0.12)	0.07
LLP	N _{Ala110} -OP1 _{Llp255}	2.84	3.24 (0.32)	0.40
LLP	N _{Tyr111} -OP3 _{Llp255}	2.87	3.04 (0.21)	0.17
MAA	O _{Maa8} -N _{Val12}	3.10	3.18 (0.30)	0.08
NRQ	OH _{Nrq63} -OE1 _{Glu145}	3.89	3.81 (0.70)	0.08
NRQ	O2 _{Nrq63} -NH1/NH2 _{Arg92}	2.97	2.90 (0.29)	0.07
OCS	N _{Lys42} -OD1/OD2/OD3 _{Ocs48}	2.36	2.95 (0.27)	0.59

Residue	^a Atom pair	X-ray str.	MD simulation	Abs. diff
OCS	NH1 _{arg123} -OD1/OD2/OD3 _{Ocs48}	1.89	3.36 (1.82)	1.47
OCS	NH2 _{arg123} -OD1/OD2/OD3 _{Ocs48}	2.58	3.48 (1.80)	0.90
PBF	O _{Pbf72} -OG1 _{Thr76}	2.74	2.76 (0.15)	0.02
SNC	O _{Val6} -N _{Snc69}	2.89	2.94 (0.18)	0.05
XYG	O2 _{Xyg66} -NH1/NH2 _{Arg95}	2.89	2.83 (0.16)	0.06

^aprotein atoms (left) are labeled by the amino acid to which they belong; when several atoms are given, the minimum distance with corresponding atoms is provided.

Table S872: Rotatable dihedral angles observed in MD simulations and experimental structures. Standard deviations are given in parenthesis.

Modified AA	Dihedral	Experimental	Average (sd)	Difference
2HF	C-CA-CB-CG	-178.2	-175.1 (9.1)	3.1
2HF	CA-CB-CG-ND1	166.0	166.0 (11.3)	0.0
4FB	CA _{ILE75} -C _{ILE75} -N-CA	-1.9	9.4 (19.8)	11.3
4FB	N-CA-C-N _{THR77}	146.4	154.7 (11.3)	8.3
BCS	C-CA-CB-SG	-61.5	-74.0 (8.3)	12.5
BCS	CA-CB-SG-CD	168.0	156.4 (14.4)	11.6
CCS	C-CA-CB-SG	77.0	72.9 (9.2)	4.1
CCS	CA-CB-SG-CD	-147.6	-125.4 (34.5)	22.2
CME	C-CA-CB-SG	-179.7	-178.8 (9.4)	0.9
CME	CA-CB-SG-SD	-81.7	-80.7 (16.3)	1.0
CSS	C-CA-CB-SG	45.4	44.3 (5.9)	1.0
CSS	CA-CB-SG-SD	112.1	113.4 (7.6)	1.4
GGB	C-CA-CB-CG	50.6	53.0 (9.2)	2.5
GGB	CA-CB-CG-OD	108.8	53.3 (8.8)	55.5
GGB	CB-CG-OD-NE	-174.1	-182.1 (6.4)	8.0
HTI	C-CA-CB-S	-80.8	-70.5 (6.9)	10.3
HTI	CA-CB-S-CAH	-103.2	-107.1 (11.1)	3.9
KCX	C-CA-CB-CG	162.3	157.4 (28.9)	4.9
KCX	CA-CB-CG-CD	-172.6	-171.9 (25.5)	0.7
LE1	C-CA-CB-SG3	-177.1	-183.5 (8.6)	6.4
LE1	CA-CB-SG3-HG3	70.8	63.9 (22.4)	6.9
LLP	C-CA-CB-CG	-161.5	-176.0 (8.2)	14.5
LLP	CA-CB-CG-CD	-86.3	-57.4 (7.0)	28.9
MAA	CCYS423-N-CA-C	53.1	56.3 (11.7)	3.2
MAA	N-CA-C-N _{SER441}	-131.9	-125.7 (11.2)	6.2
NRQ	CG1-CB1-CA1-C1	65.0	83.7 (36.2)	18.7
NRQ	CB1-CA1-C1-N3	-170.0	-176.7 (13.1)	6.7
NRQ	C1-N3-CA3-C	78.1	60.8 (8.8)	17.3
NRQ	N3-CA3-C-N _{SER66}	0.3	32.9 (40.3)	32.6
OCS	C-CA-CB-SG	174.3	171.8 (8.5)	2.5
OCS	CA-CB-SG-OD1	66.8	63.0 (7.6)	3.8
OCS	CA-CB-SG-OD2	-151.6	-175.7 (9.1)	24.1
OCS	CA-CB-SG-OD3	-32.6	-55.8 (7.5)	23.2
PBF	C-CA-CB-CG	46.6	48.2 (8.4)	1.6
PBF	CA-CB-CG-CD1	-114.0	-116.9 (12.7)	2.9
SNC	C-CA-CB-SG	168.3	177.3 (11.1)	9.0
SNC	CA-CB-SG-ND	-75.5	-85.8 (25.4)	10.3
XYG	CB1-CA1-C1-N3	171.5	188.6 (12.8)	17.1
XYG	C1-N3-CA3-C	93.0	84.5 (9.9)	8.5
XYG	N3-CA3-C-N _{ASN69}	-3.8	-9.0 (35.2)	5.2

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