New polymers synthesis by organocatalyzed step-growth polymerization of aldehydic monomers : polyaldols, linear polybenzoin and hyperbranched polyacetals

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List of Abbreviations

AcOH	Acetic acid
AFM	Atomic Force Microscopy
AROP	Anionic ring-opening polymerization
ATRP	Atom Transfer Radical Polymerisation
$[\alpha_D]$	Rotation angle
n-BuLi	*n*-butyl lithium
t-BuLi	*tert*-butyl lithium
BIP	Benzimidazole-pyrrolidine
CaH_2	Calcium hydride
Cata.	Catalyst
CCP	Condensative chain polymerization
CD	Circular dichroism
CRP	Controlled Radical Polymerisation
CSA	Camphor-10-sulfonic acid
CuAAC	Copper-catalyzed azide-alkyne cycloaddition
D	Dispersity (Mw/Mn)
DABCO	1,4-diazabicyclo[2.2.2]octane
DB	Degree of branching
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene-ortho-
DCM	Dichloromethane
DLS	Dynamic light scattering
DMSO	Dimethyl sulfoxide
DMF	N,N'-dimethylformamide
DP	Degree of polymerization
DP_n, X_n	Number average degree of polymerization
DPMK	Diphenyl methyl potassium
DSC	Differential Scanning Calorimetry
e.e.	Enantiomeric excess
eq.	Molar equivalent
Et_3N	Triethylamine
EtOAc	Ethyl acetate
EO	Ethylene oxide
f	Functionality
g	Gramme
GC	Gaz chromatography
HPLC	High Pressure Liquid Chromatography
IA	Isophthalaldehyde
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium Diisopropylamide
L	Liter
Ln	Ligand
M	Metal
Me	Methyl

MeOH	Methanol
M_n	Number average molecular weight
M_p	Peak molecular weight
M_w	Weight average molecular weight
MW	Molecular weight
MALDI-TOF	Matrix Assisted Laser Desorption Ionisation -Time of Flight
$Ni(acac)_2$	Nickel acetylacetonate
$Ni(dppp)Cl_2$	1,3-bis(diphenylphosphino)propane Nickel(II) chloride
NHCs	*N*-Heterocyclic carbenes
NMR	Nuclear magnetic resonance
o.a.p.	Optically active polymers
o.i.p.	Optically inactive polymers
PAEs	Poly(arylene ethers)
PCS	Pyridinium camphorsulfonate
PEO	Poly(ethylene oxide)
PET	Poly(ethylene terephthalate)
PEG	Poly(ethylene glycol)
PPE	Poly(phenyleneenynylene)
ppm	Parts per million
PPP	Poly(para-phenylene)
PPV	Poly(p-phenylenevinylene)
PS	Polystyrene
PT	Polythiophene
PTC	Phase-transfer catalyst
PU	Polyurethane
Py	Pyrene
RAFT	Reversible Addition-Fragmentation Chain Transfer Polymerization
Rg	Radius of gyration
R_H	Hydrodynamic radius
ROP	Ring-opening polymerization
RT	Room temperature
T	Temperature
Tg	Glass transition temperature
TA	Tterephethalaldehyde
TAS	Ttris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	Tetrabuylamonium bromide
TBAT	Tetrabutylammonium difluorotriphenylsilicate
TEM	Transmission Electron Microscopy
TFA	Trifluoroacetic acid
TGA	Thermo Gravimetric Analysis
THF	Tetrahydrofuran
SEC	Size exclusion chromatography
p-TSA	*p*-toluenesulfonic acid
UV	Ultra Violet
δ	Chemical shift

Introduction Générale

Plus de 80 ans après les travaux pionniers de Carothers[1], les polymères obtenus par polymérisation par étapes sont aujourd'hui intégrés dans de nombreux domaines d'applications de la vie courante, principalement comme matériaux polymères techniques et polymères de hautes performances. Une très grande variété de structures macromoléculaires est accessible par cette méthode, en raison d'un choix extrêmement large de molécules monomères disponibles commercialement. De ce point de vue, leurs propriétés thermo-mécaniques (résistance, dureté, stabilité thermique, …) dépassent souvent celles des polymères de commodité produits par l'autre principale méthode de polymérisation, en l'occurrence, la polymérisation en chaine (par voie radicalaire ou par catalyse Ziegler-Natta).[2] Il semble que la polymérisation par étapes ait connu son apogée vers la fin des années 1970. Toutefois, ce domaine reste en évolution et laisse encore entrevoir de nouvelles innovations technologiques, comme en témoigne le nombre de publications et de brevets qui n'a cessé de croitre au cours de la dernière décennie.

Parmi les matériaux les plus importants, au plan économique, obtenus par polymérisation par étapes, on peut citer les polyesters, les polyamides, les polyimides, les polyuréthanes, les polyépoxydes, ou encore les poly(éther de phénylène)s.[2a] La plupart de ces polymères sont générés par répétition de réactions élémentaires clés de la chimie moléculaire (substitution nucléophile, addition électrophile, etc.). D'autres réactions ont été adaptées plus récemment à la synthèse de « polymères par étapes », contribuant à donner un nouvel essor au domaine. Par exemple, les réactions de Heck et de Suzuki sont appliquées avec succès à la synthèse de polymères π-conjugués,[3] des polytriazoles sont préparés par « chimie click » *via* la cycloaddition dipolaire 1,3 dite de Huisgen entre fonctions alcyne et azoture,[4] des « polymères dynamiques (dynamères) » peuvent être créés par la répétition de réactions réversibles. Il est évident que bien d'autres réactions de chimie moléculaire n'ont pas encore été examinées en polymérisation par étapes et pourraient apporter de nouvelles fonctionnalités, *via* l'obtention de nouveaux polymères.

Dans ce travail de thèse, nous proposons trois développements innovants au domaine de la polymérisation par étapes, chacun faisant l'objet d'un chapitre de ce document. Le trait d'union de ces trois chapitres est l'utilisation de nouveaux monomères porteurs d'une (ou de deux) fonction(s) aldéhyde(s). Un autre point commun à toute cette étude est l'utilisation de catalyseurs non-métalliques (organiques ou minéraux) pour induire les différentes réactions de polymérisation par étapes. Comme illustré par la Figure 1 résumant l'ensemble du travail accompli, différentes familles de polymères ont ainsi été obtenues selon les monomères

aldéhydiques et le catalyseur mis en jeu : polyaldols (= poly(β-cétoalcools)), polybenzoïnes (= poly(α-cétoalcools)), polyesters et polyacétals.

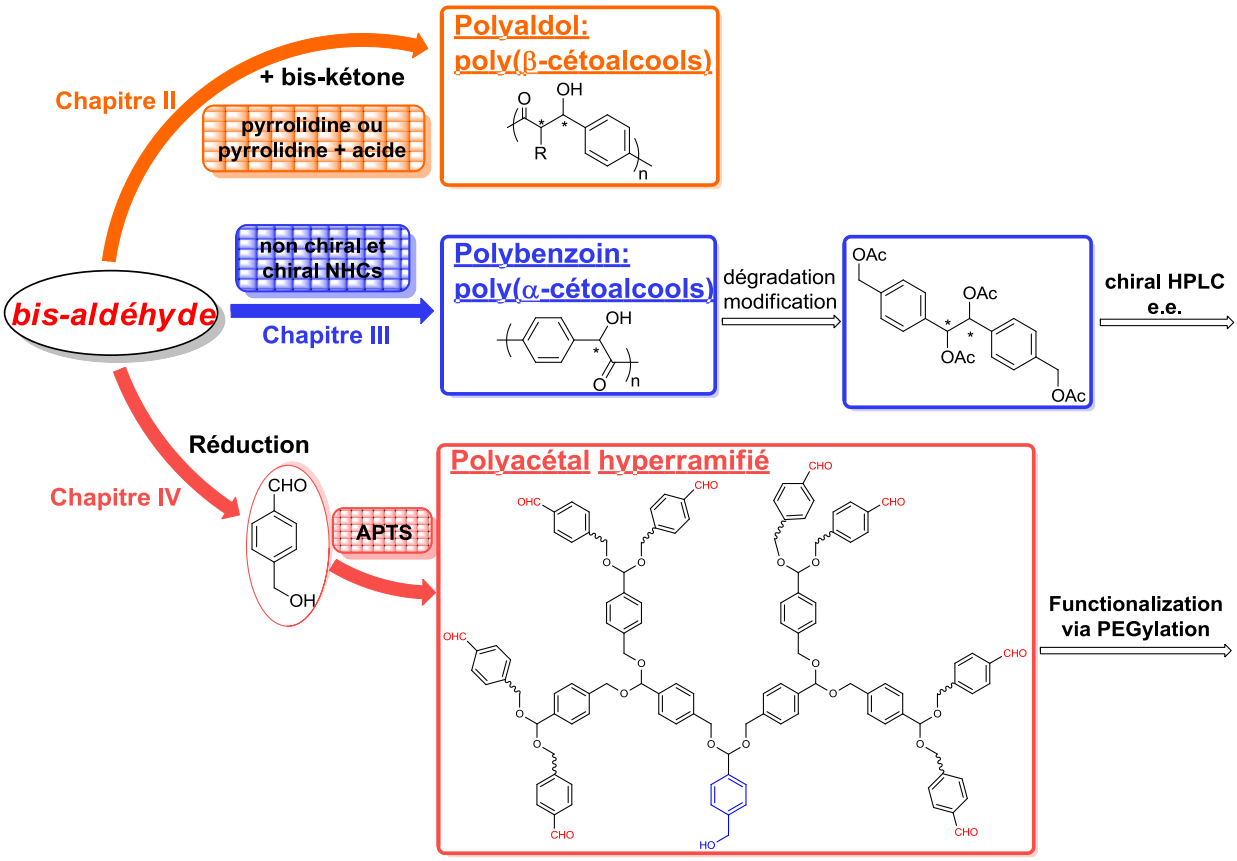

Figure 1. Présentation des voies d'accès aux différents polymères élaborés dans ce travail de thèse par polymérisation par étapes organocatalysée.

Une étude bibliographique - **chapitre I** – fait préalablement le point sur les polymérisations par étapes et sur leur importance en chimie des polymères. Ce chapitre discute en particulier les concepts et les principes généraux de cette méthode de polymérisation. Il donne aussi un aperçu des principaux polymères obtenus par cette voie. Une sélection de quelques développements utilisant des réactions élémentaires mises en œuvre récemment en polymérisation par étapes est également présentée.

Le **chapitre II** décrit la synthèse de polyaldols, c'est à dire des chaines polymères renfermant des unités monomères de type β-cétoalcool. De tels polymères ont pour la première fois été obtenus par polymérisation de monomères bifonctionnels spécialement conçus, en l'occurrence, des bis-cétones énolisables jouant le rôle de monomères nucléophiles donneurs, et des bis-aldéhydes non-énolisables servant de monomères électrophiles accepteurs. A notre connaissance, il n'existe pas d'antécédents dans la littérature où la réaction élémentaire d'aldolisation impliquant un aldéhyde non-énolisable et une cétone énolisable a été appliquée à

la synthèse de polyaldols. Ces réactions de « polyaldolisation » ont été induites par organocatalyse en utilisant une amine secondaire cyclique, la pyrrolidine, en conjonction avec l'acide acétique comme co-catalyseur. L'influence de paramètres expérimentaux, tels que l'effet du solvant, la nature et la concentration du catalyseur sur la réaction de polyaldolisation a été étudiée. L'analyse des polymères ainsi obtenus a montré qu'une certaine proportion des unités aldols –de 20 à 30% selon en fonction de la procédure de la polymérisation– est déshydratée, en formant des unités vinylidènes dans la chaine principale (réaction de crotonisation).

Le **chapitre III** concerne la polymérisation organocatalysée de monomères bis-aldéhydes par des carbènes *N*-hétérocycliques chiraux et achiraux. Une étude antérieure menée au laboratoire (thèse de J. Pinaud – Université de Bordeaux - 2010) avait déjà montré que la polymérisation d'un bis-aldéhyde commercial, le téréphtaldéhyde, par des NHCs achiraux préalablement synthétisés pouvait conduire à poly(α-cétoalcool)s, par réactions répétées de « condensation de benzoïne». Il s'est agi ici d'appliquer cette approche à de nouveaux monomères bis-aléhydes avec des précurseurs de NHCs chiraux, dans l'espoir de pouvoir transmettre la chiralité du catalyseur aux unités de répétition α-cétoalcools. En chimie moléculaire, la réaction asymétrique de condensation de benzoïne peut conduire à des excès énantiomères très élevés (e.e. > 95%) avec certains NHCs chiraux. Pour rendre compte de cet effet, il nous a fallu concevoir des monomères porteurs de liens clivables chimiquement (à base de liaisons C-Si et esters) pour dégrader ultérieurement les chaines polymères et analyser la chiralité des fragments moléculaires résultants, par analyse HPLC chirale. En d'autres termes, nous avons tenté de réaliser des réactions de polymérisation par étapes asymétriques et organocatalysées, ce qui, à notre connaissance, n'a jamais été décrit dans la littérature. Pour ce faire, nous avons employé des sels de triazolium chiraux disponibles commercialement, les catalyseurs NHCs ayant été générés *in situ* par déprotonation à l'aide d'une base forte. Reconnaissons dés maintenant qu'il nous est toutefois difficile de conclure à un transfert effectif de la chiralité des catalyseurs aux unités α-cétoalcools.

Le **Chapitre IV** de ce manuscrit est une nouvelle illustration de la réactivité de la fonction aldéhyde en polymérisation. Cette fois, les monomères impliqués sont constitués non seulement d'une fonction aldéhyde –protégée sous forme acétal ou non-, mais aussi d'une fonction alcool primaire. En milieu acide, les deux groupements fonctionnels réagissent de manière antagoniste pour former des liens covalents –mais clivables- de type acétal, par transacétalisation ou par acétalisation selon que la fonction aldéhyde est protégée ou pas. Des monomères et macromonomères de type AB_2 conduisent, par catalyse acide, à des polyacétals hyperramifiés dotés de multiples fonctions aldéhydes en périphérie. De manière très intéressante, le *p*-hydroxyméthyl benzaldéhyde non protégé conduit, par polyacétalisation, à des polyacétals

hyperramifiés sans défauts structuraux, c'est à dire de degré de ramification égal à l'unité. La présence des fonctions aldéhydes à la périphérie de ces polyacétals hyperramifiés a ensuite permis d'introduire des chaines de PEO par réaction de "PEGylation", à l'aide de PEOs linéaires portant une fonction amino terminale. Une telle modification conduit à des polyacétals hyperramifiés « PEGylés » présentant une architecture cœur-écorce. Enfin, tous ces dérivés hyperramifiés à base de polyacétal sont dégradables par essence, en raison de la sensibilité des unités dendritiques acétal en milieu acide. La dégradation chimique en solution aqueuse à pH = 4 de divers composés a en effet été vérifiée.

Ce travail de thèse a été effectué au LCPO (Université Bordeaux 1 – CNRS – IPB) sous la co-direction des Pr. Henri Cramail et Daniel Taton et du Dr. Joan Vignolle. L'étude a été menée dans le cadre d'un projet ANR –Programme Blancs 2010-2013- ayant pour acronyme CHIRPOL, en collaboration étroite avec l'équipe du Pr. Yannick Landais (ISM – Université Bordeaux 1). Seules l'introduction et la conclusion générales de ce document sont rédigées en Français. Tous les chapitres, incluant la partie bibliographique, sont rédigés en anglais.

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Chapter I

Step-Growth Polymerization: Principles and Recent Developments

Chapter I. Step-Growth Polymerization: Principles and Recent Developments

1. Introduction

Eighty years after Carothers's early works,[1] step-growth polymerization has become a major synthetic approach to tailored polymers for a variety of applications. Step-growth polymers play a key role, mostly as engineering plastics and as high performance polymeric materials, contributing to the quality, safety, and health of our modern life. Applications of step-growth polymers include many areas such as energy, information, transportation, biomedical, etc. It is remarkable that in a little over 50 years, step-growth polymerization has emerged as an interdisciplinary field of study.

Step-growth polymerizations can be achieved from a very wide range of monomer and polymer structures, allowing for a fine-tuning of the thermo-mechanical properties of related materials. In this regard, step-growth polymers often outperform vinylic polymers produced by chain-growth polymerization accounting for 90% of the commodity polymers. For instance, toughness, stiffness, and thermal stability of step-growth polymers are markedly improved compared to early free-radical derived polymers.[2a] For these reasons, many step-growth polymers (e.g. polyetherketones, polysulfones, polyimides, …) are ranked in the top of the pyramid corresponding to added value polymers with high mechanical performances.

This bibliographic chapter will cover concepts and principles pertaining to step-growth polymerization. Not only traditional synthetic methodologies will be presented, but a selection of a few recent synthetic developments in step-growth polymerization will be discussed to highlight that this field is evolving and has still potential for innovative materials. Although the peak in research, development, and innovation was admittedly around 1970, the number of publications and patents in this field is continuously increasing.

It is obvious that this overview cannot cover all categories of synthetic polymers grown by step-growth polymerization and all types of reactions applied. Excellent specialized textbooks, book chapters and review articles already exist.[2,5] In the same line, important aspects of step-growth polymerizations such as kinetic treatments, equilibrium considerations or synthetic processes will not be discussed here, due to space limitations. We acknowledge that our choice to shed light on some aspects –in particular regarding recent synthetic advances- can be perceived as somewhat arbitrary.

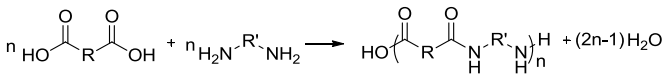
2. Historical perspective and principles

Synthesis of polyesters and polyamides by step-growth polymerization was pioneered at Dupont de Nemours in the 1930's by Wallace Carothers.[1] Polymer synthesis was achieved by repetitive condensation reactions between reactive monomeric functional groups, forming a new

bond through the elimination of a small molecule at each step. In addition, variation of the monomer functionality led to different types of polymer structures and topologies with distinct properties.

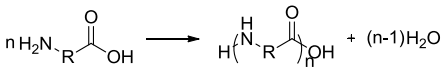
Unlike conventional free-radical polymerization, early polycondensation polymers were easily cleavable and could be subjected to hydrolysis, hampering the production of high molecular weight polymers.[1a] Such polymerizations are referred to as polycondensations, but some step-growth polymers (e.g. polyurethanes) are formed by successive addition reactions. Hence, the general terms «step-growth polymerization » are preferred and include polycondensations and specific polyadditions, and differentiate these reactions from those proceeding by a «chain-growth polymerization » mechanism.[2b] Polycondensation produces polymers through the elimination of a small-molecule by-product such as hydrochloric acid, water, methanol, acetic acid, and others.[2b] This method depends largely on the removal of the condensate in order to drive equilibrium-based reactions toward high molecular weight polymers. In contrast, polyaddition proceeds without the formation of by-products and typically requires highly reactive end groups or catalysts to synthesize polymers. Examples of polyaddition polymers are polyurethanes (PUs) and epoxide curing; however, novel click polymers and ionenes are emerging as new modern classes of polyaddition step-growth polymers.[6]

Another distinction should be made depending on the type of monomer(s) polymerized.[2b] A first category involves two different bifunctional and/or polyfunctional monomers in which each monomer possesses only one type of functional group (a *polyfunctional monomer* is a monomer with more than one functional group per molecule, whereas a *bifunctional monomer* possesses two functional groups per molecule). The second category involves a single monomer containing both types of functional groups. The synthesis of polyamides illustrates both types of polymerizations. Thus polyamides can be obtained from the reaction of diacids with diamines (Scheme 2.1):



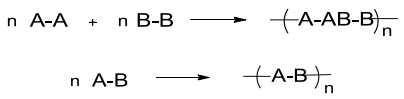
Scheme 2.1 Synthesis of polyamide from a diacid and a diamine.

or from the reaction of amino acids with themselves (Scheme 2.2):



Scheme 2.2 Self-polycondensation of amino acids to synthesize a polyamide.

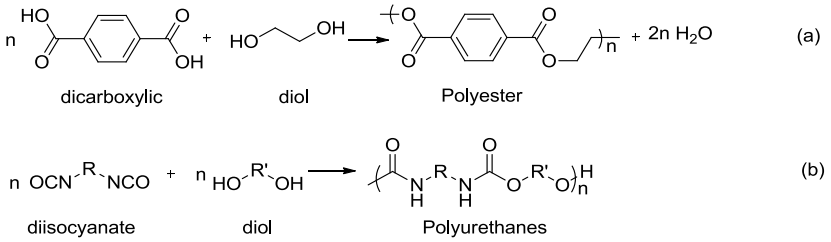
The two groups of reactions can be represented in a general manner by the following equations, where A and B are the two different types of functional groups.



Scheme 2.3 General synthetic polycondensation methods.

A large number of chemical reactions can be used in step-growth polymerization, including esterification, amidation, urethane formation, aromatic substitution, and others.[6] Such reactions usually involve two different functional groups, for example, hydroxyl and carboxyl groups, or isocyanate and hydroxyl groups, forming a new single functional group (examples are given in Scheme 2.4). Variation of monomer functionality, as well as monomer composition, affords polymers with tailored performances.

For example, an addition–elimination reaction between two monomers, a dicarboxylic acid and a diol, creates a dimer of the two monomers chemically linked through a new ester bond and elimination of the condensate, water (Scheme 2.4a). Stepwise reaction of the dimers with subsequent monomers or dimers produces trimers and tetramers, respectively. Because of the sequence of monomer addition, the monomers within the reaction are rapidly consumed during the initial stages.



Scheme 2.4 (a) water as a condensate eliminated from reaction of dicarboxylic and diol forming ester; (b) urethane produced from the addition reaction of diisocyanate and diol.

The species within the polymerization will transition from high monomer and end group concentrations to oligomers and lower concentrations of end groups. This change in reactive species will inherently alter the kinetics of polymerization. Changes in reaction polarity, volume, and viscosity ultimately impact the reaction. As the polymerization reaches high conversions, the viscosity will increase dramatically and limit the mobility of the polymer end groups, and thus their statistical likelihood of reactions.

Some step-growth polymerizations proceed through an equilibrium reaction.[2b] The forward reaction promotes the growth of the polymer chain, and the reverse reaction can be referred to as the depolymerization. The removal of the condensate can drive the reaction forward. In addition, long reaction times are often required because high extent of conversion is necessary for high molecular weight polymers. Thus, many step-growth reactions require the aid of catalysts.

3. Molecular weight "control"

Molecular weight is arguably the most important polymer parameter. As such, an understanding and control of molecular weight is crucial in the synthesis and development of step-growth polymers.[2,5a] Predicting molecular weight evolution, as a function of monomer conversion, for linear step-growth polymerizations is possible, however. In an ideal case, a simple relationship between the conversion and the molecular weight (MW) –or the number average degree of polymerization ($\overline{DP}_n$ or $\overline{X}_n$)- can be established, as first described by W. Carothers in the 1930s,[1a] and expanded by P. Flory,[7] as discussed below.

In the case of a polymerization between two bifunctional monomers AA + BB, the number of A and B functional groups are given by N_a and N_b respectively. N_a and N_b are equal to twice the number of AA and BB molecules. The stoichiometric ratio or imbalance, *r*, has always a value equal to or less than - but never greater than- unit. The total number of monomer molecules is given by $(N_a + N_b)/2$ or $N_a(1 + 1/r)/2$. The extent of reaction *p* is defined as the fraction of the limiting groups (A groups) that have reacted at a particular time. The fraction of B groups that have reacted is given by *rp*. The fractions of unreacted A and B groups are $(1 - p)$ and $(1 – rp)$. The total numbers of unreacted A and B groups are, $N_a(1 - p)$ and $N_b(1 – rp)$, respectively. The total number of polymer chain ends is given by the sum of the total number of unreacted A and B groups. Since each polymer chain has two chain ends, the total number of polymer molecules is one half the total number of chain ends or $[N_a(1 – p) + N_b(1 – rp)]/2$. The number-average degree of polymerization $\overline{X}_n$ is the total number of "AA" and "BB" molecules initially present divided by the total number of polymer molecules:

$$\overline{X}_n = \frac{N_a(1+1/r)/2}{[N_a(1-p)+N_b(1-rp)]/2} = \frac{1+r}{1+r-2rp} \quad \text{(eq. 1.1)}$$

This equation shows the variation of $\overline{X}_n$ with the stoichiometric imbalance *r* and the extent of reaction *p*. There are two limiting forms of this relationship. When the two bifunctional monomers are present in stoichiometric amounts ($r = 1$), this equation is reduced to the Carothers relationship:

$$\overline{X}_n = \frac{1}{1-p} \quad \text{(eq. 1.2)}$$

If the conversion *p* up to 100%, the equation could also be reduced to:

$$\overline{X}_n = \frac{1+r}{1-r} \quad \text{(eq. 1.3)}$$

An important implication of the Carother's equation[1a] (eq. 1.2) is that high MW polymers only form at very high conversions in step-growth polymerization. The following synthetic considerations are also required:[2a]

1. high monomer conversion (> 99.9%);
2. bifunctional monomers (f = 2);
3. monomer stoichiometry of A:B = 1:1;
4. elimination of side reactions such as degradation or cyclization;
5. accessibility of end groups;
6. high monomer purity.
7. often prolonged reaction times

It is worth mentioning that synthetic techniques have been developed to bypass stringent 1:1 monomer stoichiometry requirements, for example, interfacial polymerization.[2b]

In the synthesis of small organic molecules, a reaction conversion of 90% is considered excellent, while a value of p = 0.9 limits the DP of the final product to only 10 in a step-growth polymerization. Such a polymer is unlikely to possess the desirable mechanical properties.

Figure 3.1 shows $\overline{DP}$ as a function of r. From this plot, high DPs are only attained when the stoichiometric ratio reaches approximately 98% or higher. Under stoichiometric conditions for which $N_a = N_b$, the expression for the dispersity index (D) is D = (1+p). When conversion reaches 1, the dispersity equals to 2.

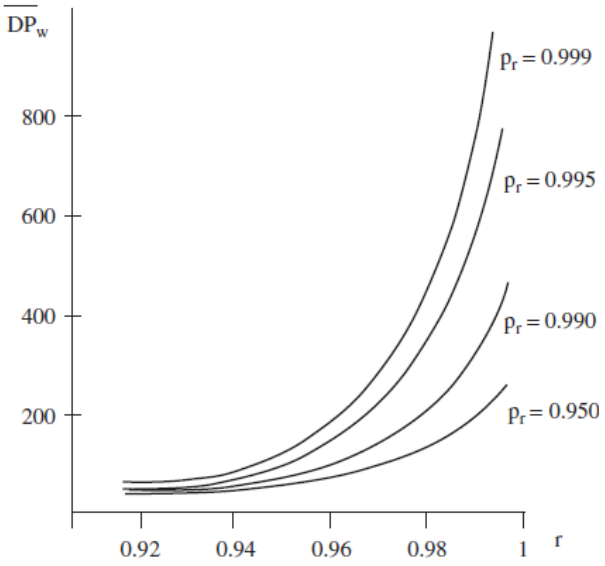


Figure 3.1 Mass average degree of polymerization as a function of the stoichiometric imbalance ratio (r) for a step-growth polymerization of (AA + BB) type and various extents of reaction.[5a]

On the other hand, equation 1.1 highlights ways to purposefully manipulate the MW in a step polymerization, in particular, by unbalancing the stoichiometry (for AA-BB), but also by adding a monofunctional component. In the latter case, the Carothers equation can be written as follows:[5a]

$$\overline{X}_n = (1 + r) / (1 - p + r) \text{ (eq. 1.4)}$$

Kricheldorf and co-workers[8] have shown that, in agreement with the predictions of Stepto[9] and Gordonin,[10] ring closure competes with propagation at any concentration at any stage of the polymerization for $A_2 + B_2$ and AB monomer combinations. As a result, all reaction products are necessarily macrocycles at 100% conversion when side reactions are absent.

There are many reasons why knowing the MW of step-growth polymers is important.

1. Many useful polymer properties level off at moderately high MW, and very high values do not provide any benefit in some cases.
2. Polymer melt and solution viscosity increase monotonically with molecular weight, and very high MW polymers are more difficult to process.
3. Properties can change during processing (due to further reaction between polymeric chains in melt or in solution), unless the MW is deliberately capped.

There are, however, several issues that can perturb the course of a step-growth polymerization. For instance,

1. Impurities can react with monomeric, oligomeric and polymeric species can contaminate the reaction mixture.
2. Impurities can poison and thus deactivate the catalyst (used in most cases).
3. Monomer(s) can decompose during polymerization due to the harsh conditions sometimes implemented (high temperature, high pressure); monomer(s) can thus be chemically or physically lost during reaction
4. Unwanted side reactions involving functional groups can occur (e.g. cyclization, decarboxylation from COOH end groups, etc.)
5. Polymerization can reach an unfavorable equilibrium with no means to eliminate the side product (reversible polycondensation).

4. Main step-growth polymers (commercially available)

Important examples of polymers made by polycondensation or by polyaddition are presented in the following tables, including some of their significant features.[2b,5b]

Table 4.1 Conventional polycondensation in step-growth polymerization (continue)

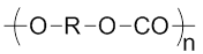
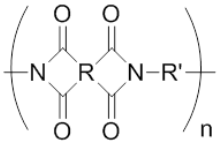
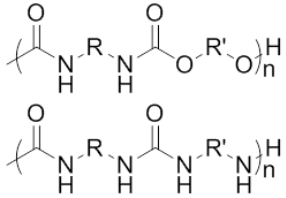
Type	Structure of monomeric units	By-product	Typical polymers	World production in 2012 (million tons)	applications	Trade name	T_g/T_f (°C)
Polyester		H_2O, R''OH or HX	Poly(ethylene terephthalate) **PET**	58	Fibers, engineering thermoplastic resins, bottle and container resins, films.	Rynite, Mylar and Dacron (DuPont); Eastapak (Eastman); Ertalyte(DSM),Impet (Ticona); Tergal (Tergal fibres)	70 / 245
Polyamide		H_2O, HX	Polyamide 6 **PA6 and PA6,6** Poly(para-phenylene terephthalate) **PPPT**	5.5	Textile filament, Staple fibers , Carpet yarns, Industrial yarn, Tire yarn	Nylon (Dupont); Technyl (Rhodia); Rilsan and Rilsamid (Arkema) Kevlar (Dupont)	50 / T_m= 250°C
Polycarbonate		HX, PhOH	**PC** (R=Ph-C(Me)$_2$-Ph)	3.7	solid organic glass, kitchen utensils sterilized, bulletproof windows, break resistant lenses, compact discs	Lexan (Sabic), Tuffak (Arkema), Makrolon and Makroblend (Bayer), **Polygal (polygal)**	145
Polyimide		H_2O	**PI** (R=Ph)	0.8	flexible cables, alignment coating for liquid crystal devices, molecular composites, aerospace, opto-electronic targets, bearing materials, thrust washers, and semi conductor wafer clamps.…	*Vespel, Kapton (Dupont), VTEC(RBI)*	>400
Polyether		NaX	Poly(*p*-phenylene oxide) **PEE**	-	structural parts, electronics, household and automotive items, dimensional stability and accuracy, plastic sterilizable instruments	-	215

Table 4.1 Conventional polycondensation in step-growth polymerization (continue)

Type	Structure of monomeric units	By-product	Typical polymers	World production in 2012 (million tons)	applications	Trade name	T_g/T_f (°C)
Poly(arylene ether)		HX	poly(arylene ether ether ketone) **PEEK**	-	fire-retardant materials , bearings, piston parts, pumps, HPLC columns, compressor plate valves, and cable insulation, ultra-high vacuum applications	Victrex PEEK (ICI); poly(arylene ether ketone)(PEK), Stilan (Raychem),poly(arylene ether ketone ether ketone ketone) (PEKEKK), Ultrapek (BASF)	143
Polysulfide		NaX	Polysulfide	-	Sealant in building,aircraft and civil engineering…	Thioplast (Akzonoble)	-
Polyacetal		H_2O	Poly(oxymethylene) (**POM**)	-	inforcement with fibers, plumbing fittings, pump and valve components, bearings and gears, computer hardware, automobile body parts, and appliance housings…	Celcon (Ticona Hostaform), Delrin (DuPont), Duracon (Ticona), Iupital (Mitsubishi), Ultraform (BASF)	melting point of 175° C

Table 4.2 Conventional polyadditions in step-growth polymerization

Type	Structure of monomeric units	Typical polymers	World production in 2012 (million tons)	applications	Trade name	T_g/T_f (°C)
Polyurethane and Polyurea		PU	18	Oil and solvent resistant, Load bearing capacity, Tear resistant, Weather resistant, Excellent noise abatement properties, Flex-Life, Heat and cold resistant, Flex-Life, foams elastomers coatings, adhesives/sealants/binders, encapsulants elastomeric fibers, films, gels composites, microcellular elastomers, rubbers/millable gums	Ecolan (Porvair), Isoplast (Dow)	low
Epoxy resins	-	-	2.2	metal coatings, electronics / electrical components, high tension electrical insulators, fiber-reinforced plastic materials and structural adhesives, bind gutta percha	Araldite and Razeen (JANA),	-

4.1. Polycondensation polymers

As emphasized above, elimination of a small-molecule by-product takes place when forming polycondensation polymers. Aromatic polyesters, polyamides, poly(arylene ether)s, or polyimides are typical examples of such polymers. One generally resorts to simple organic elementary reactions, such as carbonyl or aromatic addition–elimination reactions, to achieve these polymers. The resulting polymer linkages provide properties such as hydrolyzability (e.g. esters, carbonates), hydrogen-bonding interactions (e.g. amides), and dipolar interactions.

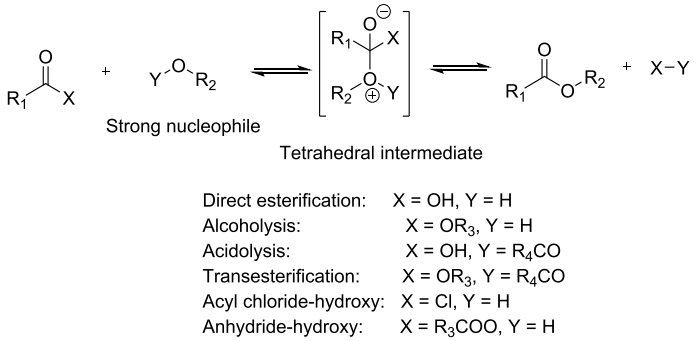
4.1.1. Polyesters

Polyesters represent an economically important commercial commodity and have found utility in a variety of applications including fibers, thermoplastic elastomers, coatings, and high-performance polymers.[2a] Ester linkages are hydrolytically unstable, and this attribute has launched a growing field of biodegradable polyester research from recyclable polymers for packaging with degradable and controllable drug delivery vehicles.[11]

Polyesters have been dominating the total amount of polymer-based synthetic fibers, most notably poly(ethylene terephthalate) (PET), since the last decade, contributing to nearly 60% of all fiber production in 2000.[12] Because of its chain stiffness and crystallinity, fibers based on PET show excellent tensile properties, solvent resistance, toughness, and fatigue resistance. Solid-state resins account for the second largest application of PET. Polyesters also assume an important role in food packaging industry. PET films are often bi-axially stretched in order to induce crystallization. Interestingly, these films are optically clear although the film is nearly 50% crystalline.[2a]

Variation of polyester properties can be achieved by a proper selection of the monomer(s). For example, exchanging ethylene glycol (EG) for longer glycols such as 1,4-butanediol increases crystallization rate and allows faster production; however, the cost of production for PET is much less compared to poly(butylene terephthalate) (PBT).

Scheme 4.1 illustrates the mechanistic pathway of polyester synthesis, which involves a carbonyl addition-elimination mechanism, formation of a tetrahedral intermediate, reaction proceeding through an equilibrium mechanism. Most polyester syntheses are conducted in the melt phase at elevated temperatures, above the boiling point of by-product, the removal of which drives the reaction toward polymerization.[2a]

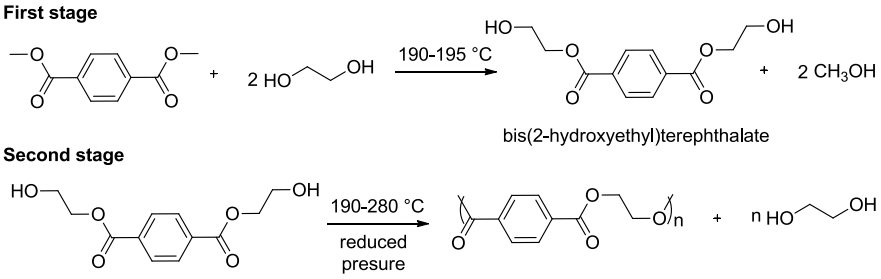


Scheme 4.1 Equilibrium addition–elimination mechanism occurring in polyesterification reactions.

Bulk polymerization is performed at least 10–20 ℃ above the melting point of the polymer (usually in the range 150-350 ℃), under an inert atmosphere, and most often under vigorous stirring so as to promote diffusion of the reactive end groups and to facilitate removal of the condensate.[12] However, care should be taken in order to minimize side reactions (e.g. etherification between alcoholic functions, cyclization…) and/or degradation (e.g. chain scission by thermal or oxidative degradation). A gradual increase in MW results in a large increase in melt viscosity due to progressive formation of chain entanglements. High vacuum is applied to the final stages of bulk polymerizations to attain high MW.

Polyesterification reactions generally require long reaction times and catalysts to increase reaction rates. Typical polyesterification catalysts employed are metal alkyls based on tin, antimony, and titanium. Metal alkyls form metal alcoholate complexes to facilitate ligand exchange. In contrast, Lewis acid catalysts, such as zinc or manganese, coordinate with the carbonyl oxygen of the ester to increase the electrophilicity of carbonyl compound.[2a]

PET is actually obtained by polytransesterification using dimethyl terephthalate (DMT) instead of terephtalic acid as ingredient, ethylene glycol being removed as by-product (Scheme 4.2). Polymerization utilizes metal acetate catalysts such as calcium, manganese, cobalt, and zinc.[2a]



Scheme 4.2 Two stages of industrial method to synthesize PET.

The first stage occurs at 190–195 ℃, below the boiling point of EG, 197 ℃, and above the melting point of DMT, 140–142 ℃. These conditions facilitate methanol distillation driving the reaction forward, forming bis(2-hydroxyethyl)terephthalate and oligomers. In the second

stage, increase in reaction temperature from 190 to 280 ℃ and reduced pressure during the last hour of the reaction continue polymerization through transesterification and removal of EG. Melt heterogeneity can result in large dispersities because polymeric chains within crystals are inaccessible for ester interchange. Metal acetates catalyze the first stage of the reaction, and antimony (III) oxide is often added during the second stage of the reaction to continue condensation.[2a]

Polyesters can also be synthesized by interfacial polycondensation.[13] One advantage of this method is that 1:1 stoichiometry is not required to acquire high MW, because polymerization occurs at the solvent interface. Synthesis of polyesters using this approach occurs through a reaction between an acyl halide and glycol in two immiscible solvents. Each solvent contains one of the reactive monomers and polymers can be isolated as a film or a filament through drawing the polymer from the interface. However, the use of solvent, monomer expense, and acidic by-product are often undesirable in large-scale production of polymers.

Current research interests focus on monomers derived from renewable resources, for instance, to transform plant-based starches to useful diols.[14] Recently, a review from Fenouillot *et al.*[14b] discussed the advantages of utilizing cyclic diols as monomers, and which arise from cereal-based polysaccharides, 1,4: 3,6-dianhydrohexitols. The advantage of these monomers is their increased rigidity within the polymer backbone. Garaleh *et al.* investigated all-aliphatic copolyesters derived from isosorbide, 1,4-cyclohexane dicarboxylic acid (CHDA), and succinic acid to develop biodegradable polyesters from renewable monomers.[15] These copolyesters indicated tunable high T_g's depending on the stereochemistry of the bicyclic diol. However, one limitation arises from monomer purity preventing transition of sugar-based diols into large-scale commercial production. In particular, monomer degradation and deleterious side reaction during monomer synthesis lead to discoloration of the resulting polymers as well as reduced MW.

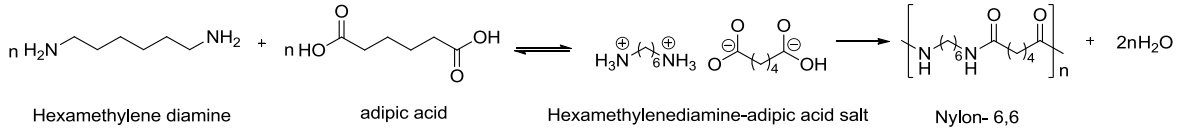
In addition to polymers derived from starch, vegetable oil-derived polymers including triglycerides and fatty acids such as stearic, oleic, and linoleic acid have also been described.[14b,16] Triglycerides are typically hydrolyzed to produce glycerol and a mixture of fatty acids. Due to the presence of unsaturated functionality in the mixture of fatty acid monomer, these monomers are suitable for many post-reactions such as dimerization or epoxidation reactions. Similar to separation and purification difficulties for isomannides, by-product removal presents a challenge for the large-scale production and utilization of these triglyceride-based monomers for industrial applications. Another challenge is the lack of perfect bifunctionality in the monomer structure.[14b] Many common fatty acid monomers only contain a single carboxylic acid with the exception of ricinoleic acid, a naturally occurring bifunctional fatty acid that is suitable for various polyester syntheses.

4.1.2. Polyamides

Aliphatic polyamides, referred to as "nylons", are high melting and thermally stable polymers with excellent mechanical properties. This is due to the amide functional groups within the polymer backbone affording strong intermolecular interactions by hydrogen-bondings.[2a]

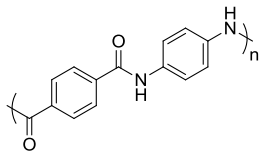
Direct amidation utilizes bifunctional monomers, A–A and B–B, whereas self-amidation uses AB-type monomers often from amino acid derivatives (see Scheme 1.1 and 1.2).

Side reactions such as oligomeric cyclization can occur with diamines containing less than four methylene units. Decarboxylation of diacid monomers with lower MW is also a concern. Many polyamides, for instance, Nylon-6,6 employ the "salt solution method" (Scheme 4.4).[17] In this method, the reaction between hexamethylene diamine and adipic acid firstly forms the salt (from the carboxylate and protonated amine) that precipitates out of the solution. This conveniently provides a 1:1 stoichiometry.[2a] This salt further reacts under pressure to avoid volatilization of hexamethylene diamine, using stepwise increases temperature from 210 to 290 ℃. Further reaction removes the condensate, water, and drives the reaction forward. Prepolymers are reacted within melt extruders where a solid-state polymerization occurs at atmospheric pressure and 290 ℃, rather than melt reaction as used in polyester synthesis. At high reaction temperatures and reduced pressures, indeed, polyamides are subjected to branching side reactions that cause substantial coloring of the polymer.[2a]



Scheme 4.4 Industrial synthesis of nylon-6,6 from hexamethylene diamine and adipic acid.

Aromatic polyamides, referred to as aramids, represent another important class of step-growth polyamides.[18] Poly(para-phenylene terephthalate) (PPPT), whose trade name is Kevlar®, is the most representative example of aramids (Scheme 4.5).[19] Aramids are characterized by high polymer chain stiffness and high directionality from the anisotropic liquid crystalline solution, providing outstanding thermal, mechanical as well as flame-resistant properties. Due to the high degree of crystallinity, polyaramides are difficult to melt-extrude or redissolve for solution casting which limits their versatility in applications. Many aromatic polyamides can be directly spun into fibers from the polymer solution.[2a] Complete information about synthesis and properties of aramids can be found in the review of Garcia *et al.*[20]



Poly(*p*-phenylene terephthaldate)
(PPPT)

Scheme 4.5 Commercially significant aromatic polyamides PPPT (Kevlar®).

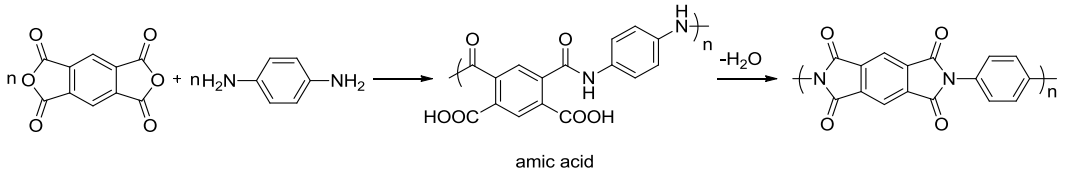
Typical polyaramide synthesis utilizes acyl chloride method due to the reduced basicity of aromatic diamines.[2a] Low-temperature and high-temperature solution polymerizations are two main methods for synthesizing aramids. Later developments in the synthesis of PPPT replaced hexamethylphosphoramide (HMPA) with polar solvents such as N-methyl-2-pyrrolidone (NMP), N,N-dimethylformamide (DMF), and N,N-dimethylacetamide (DMAC) with calcium chloride to aid in disrupting the strong hydrogen bonds. The requirement for high monomer purity remains an obstacle in polyaramide synthesis, rendering difficult the obtainment of high MW.

Current research efforts focus on the possibility to incorporate new monomers, which can increase chain flexibility, disrupts chain regularity, decreases the hydrogen-bonding intermolecular interactions, and increases aramids solubility in solvents such as DMF, NMP, and dimethyl sulfoxide (DMSO).

4.1.3. Polyimides

Polyimides are highly thermally stable polymers possessing both aromatic and heterocyclic building blocks in their monomer units and which can be processed at low temperature.[2a] They find applications in a variety of technologies, including high-performance resins, structural foams, and molecular composites, but also electronics, microelectronic devices, membranes for gas separation and fuel cell applications.[2b]

Polyimide synthesis employs aliphatic or aromatic dianhydrides and diamines (Scheme 4.6) following a nucleophilic addition–elimination mechanism. The anhydride ring-opening reaction results in the so-called amic acid. The reaction is generally performed under dry conditions in polar aprotic solvents such as DMF, DMAC, and NMP at low temperatures.[21] However, melt polymerization from tetracarboxylic acid and aliphatic diamines has also been described.[22] The amic acid intermediate polymer remains soluble. Further reaction between the carboxylic acid and amide eliminates water and create the cyclic imide functional group, forming a polyimide that is no more soluble in the reaction mixture. This thermal imidization step can be catalyzed by tertiary alkyl amines or aromatic pyridines.[2a]

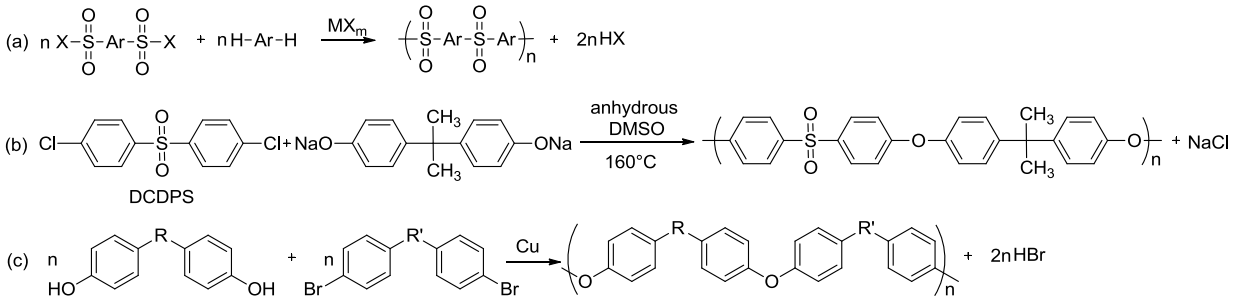


Scheme 4.6 General reaction between dianhydrides and diamines forming a polyimide through an amic acid intermediate that undergoes dehydration and cyclization.

4.1.4. Poly(arylene ether)s

Poly(arylene ether)s (PAEs) are also highly stable high-performance polymers with enhanced mechanical properties, and excellent resistance to hydrolysis and oxidation.[2a,23] These properties are related to the aromatic ether linkage which gives rise to chain flexibility. PAEs have been also widely used as engineering thermoplastics due to their good mechanical properties and thermal stability. Applications of PAEs include proton exchange membranes and fuel cells.

PAEs can be synthesized by a) electrophilic aromatic substitution Friedel–Crafts reactions, or b) nucleophilic aromatic substitution, or c) using metal-catalyzed coupling reactions (Scheme 4.7).[2a] Activated arenesulfonyl halides can react with benzene to form a sulfone linkage; application of this reaction to bifunctional monomers leads to polysulfones. A good example of poly(ether sulfone)s synthesis involves the disodium bisphenolate and 4,4'-dichlorodiphenyl sulfone (DCDPS). Alternatively, the reaction between diphenylether-type monomers and terephthaloyl chloride derivatives produces poly(arylene ether ketone)s.



Scheme 4.7 (a) Friedel–Crafts sulfonylation to synthesize poly(arylene ether sulfone) catalyzed by Lewis acids; (b) typical nucleophilic synthesis of bisphenol polysulfone. (c) Synthesis of PAEs via Ullman coupling of bisphenols and dibromoarylenes using a copper catalyst.

Friedel–Crafts reactions -method a) can be carried out either in bulk at 230–250 ℃ or in methylene chloride solution, in the presence of a metal catalyst such as $FeCl_3$, $AlCl_3$, and $AlBr_3$. However, the final polymer generally precipitates, which somehow limits its MW.[2a] Side reactions and/or crosslinkings observed in bulk conditions, are minimized by lowering the temperature and using limited amounts of catalyst (0.1–4 wt.%). [24]

The nucleophilic aromatic substitution of activated aryl halides –method b) occurs in solution and requires higher temperatures than the previous one.[2a] The addition step of the nucleophile onto electropositive carbon, forming resonance-stabilized Meisenheimer complex intermediate, is the rate-limiting step. This is dictated by the strength of the nucleophile and the electronegativity of the halide substituent (F >> Cl > Br > I), and this step is favored with electron-withdrawing groups such as NO_2, SO_2, and CO. The second step consists in the re-aromatization of the benzene ring and the removal of leaving group.

The Ullman coupling reaction between diphenol and aromatic halide is a common synthetic approach to PAEs -method c).[25] One drawback of this method is the use of a copper- or a nickel-based catalyst that must be removed after the polymer synthesis.

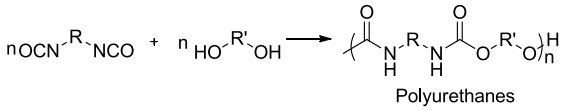
4.2. Polyaddition polymers

Polyaddition polymers do not form small-molecule by-products. Typical examples of this class include polyurethanes (PUs) and epoxy resins (see Table 4.2).

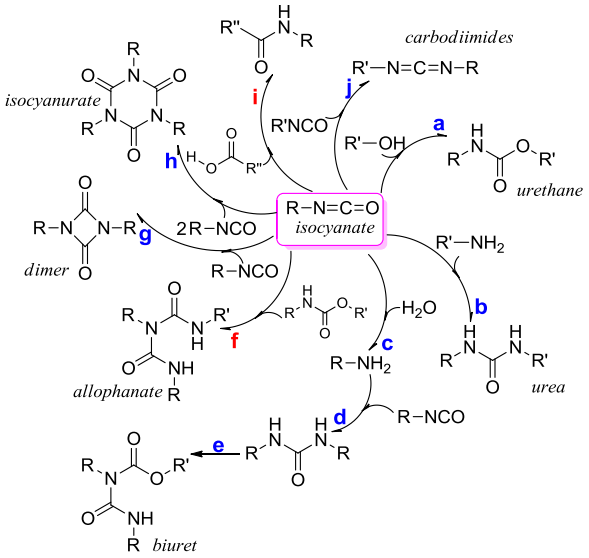
4.2.1. Polyurethanes

PUs incorporate carbamate linkages within the backbone. They were developed in the 1930s by Bayer *et al.* at I. G. Farbenindustrie (Germany), and quickly competed polyamides.[26] Since then, the applications of PUs have expanded to encompass coatings, shoe soles, foams, and thermoplastic elastomers. Within the past decade, PUs have also reached the biomedical industry and now have found applications in implants, soft tissue replacement, angioplasty balloons, drug delivery, and biocompatible tissue scaffolds.[2a,27]

Polymerization involving repeated nucleophilic addition reactions between a diol and diisocyanate is the standard synthetic method to linear PUs (Scheme 4.8). Side reactions can occur through the additional reaction of the urethane (Scheme 4.9, reaction f) or urea nitrogen to unreacted isocyanates. Scheme 4.9 illustrates possible side reactions that occur from the nucleophilic nitrogen of the urethane linkage.[28] In particular, the reaction between an isocyanate and carboxylic acid gives rise to an amide linkage (Scheme 4.9, reaction i) and carbon dioxide. Formation of polymer foams often takes advantage of this by-product to create voids within the polymer. [29]

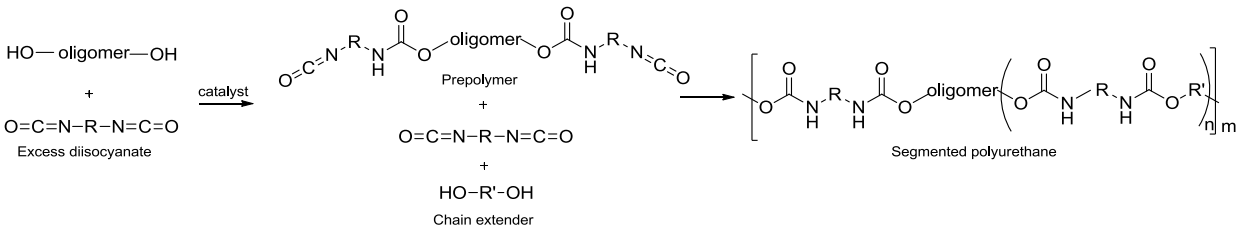


Scheme 4.8 Polyurethane synthesized from polyaddition of a bis-isocyanate with a diol.



Scheme 4.9 Various reactions involving the isocyanate function.

PUs are characterized by intermolecular interactions by hydrogen bonding between the urethane and urea groups, which contributes to their crystallinity. However, this interaction is weaker than in urea and amide groups.[30] The hydrogen-bonding unit within the hard segment block gives rise to the high T_g and the microphase separation behavior typically seen in segmented PUs. Many thermoplastic elastomers based on PUs (so-called TPUs for thermoplastic polyurethanes) that are segmented block copolymers of PUs, take advantage of strong hydrogen-bonding intermolecular interaction to impart exceptional elastomeric properties such as high strain and low mechanical hysteresis. Scheme 4.10 shows an example for synthesizing segmented block PUs. Soft segment blocks include polyether, polyesters, polybutadiene, polycaprolactone, and polycarbonate polyols that are reacted with excess diisocyanate. Subsequent addition of a diol chain extender will react with the prepolymer and excess diisocyanate to produce a hard segment block with a higher density of urethane linkages.[2a]



Secheme 4.10 Synthesis of segmented PUs using a prepolymer.

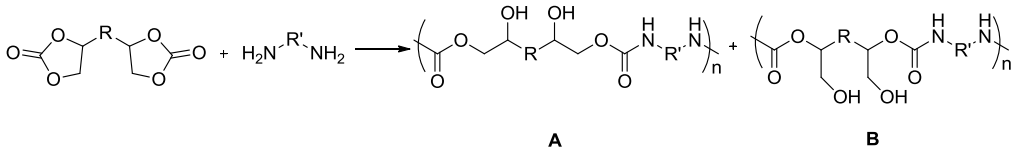
The block structure allows for microphase separation to create physical crosslinks. The careful choice of the hard block and the soft block composition determines the application and processing window.[31] However, they generally do not show a long-range microphase separation. Such segmented block copolymers generally have alternating block lengths with MWs between 1000 and 5000 g/mol. The type of morphology as a function of MW of the blocks has been

studied in details.[32] Overall, the morphological behavior and related thermo-mechanical properties of segmented PUs strongly correlate with the monomer pairing, in particular of the diisocyanate symmetry.[33] MW and dispersities, crystallizability of the hard segment, and thermal history also matter.

Segmented poly(ester-urethane)s have been explored as shape memory materials, finding potential in biomedical applications, due to their shape recovery properties and biodegradability from polyester blocks such as poly(lactic acid) and poly(ε-caprolactone). In these materials, physical network formation occurs through microphase separation and crystallization of the hard segment.[30]

PU synthesis generally employs tertiary amines (e.g. 1,5-diazabicyclo[5.4.0]undec-5-ene = DBU or triethylamine) or organotin catalysts (e.g. dibutyltin dilaurate = DBTDL), which allows minimizing side reactions such as branchings and/or crosslinkings, and increasing reaction rates.[34]

An emerging area in PU synthesis concerns the devlopment of non-isocyanate routes utilizing renewable and naturally occuring resources, mostly deriving from plants.[35] In particular, vegetable oils are being intensively invetigated, due to their large scale availability.[36] They can either serve as a source of polyols or as polycyclocarbonates (Scheme 4.11) obtained from epoxidized oils, leading to «green and biosourced »PUs.

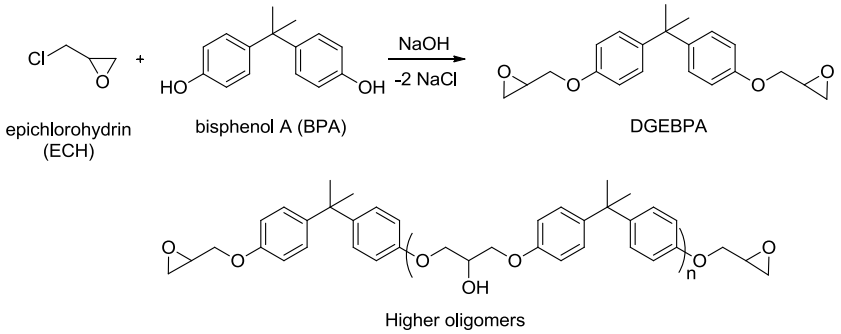


Scheme 4.11 β-hydroxyurethane moieties of nonisocyanate polyurethanes from a cyclocarbonate and adiamine; A: with secondary or B: with primary hydroxyl groups.

4.2.2. Epoxy resins

Epoxy resins represent another important class of step-growth polyaddition polymers. In contrast to PUs that can exist as linear monodimensional thermoplastics or as thermosets, epoxy resins solely serve as thermoset networks.[2a]

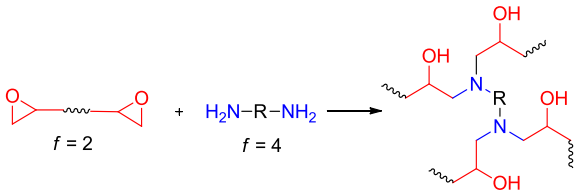
Epoxy thermosets result from the reaction between an epoxy resin oligomer, that is, a small molecule or a pre-polymer featuring epoxide end groups, and a so-called hardener playing the role of the crosslinking agent (functionality > 2). Such polymerizations proceed *via* oligomer formation, branching, and finally crosslinking. Introduction of the epoxide functionality into small molecules and pre-polymers is usually achieved using polyol precursors and epichlorohydrin (Scheme 4.12).[2b]



Scheme 4.12 Synthesis of epoxy diglycidyl ether of bisphenol-A (DGEBA) from epichlorohydrin and bisphenol A, and higher oligomers.

The branching reaction forming and further crosslinking occurring between the epoxy resin and a hardener such as a diamine is depicted in Scheme 4.13.[5b] The less sterically hindered carbon of the epoxide is preferably attacked, forming a secondary alcohol. Besides amines, alcohols and carboxylic acid-containing nucleophiles can be employed as hardeners. However, alkyl halides and isocyanates can be used as electrophiles reacting with epoxides. Interestingly, epoxy curing occurs quickly and does not require the aid of catalysts.[37]

Epoxy resin thermosets serve as coatings and adhesives. The lower MW epoxy resins, when cured with, for example, amines or anhydrides, are used as two-component adhesives and in liquid coatings. Beverage and food packaging cans are coated on inside with such systems for good sterilization performance. Epoxy resins are popular for their properties in many other coating applications also, but predominantly in primers and coatings for indoor use.[5b]



Scheme 4.13 Epoxy resin curing from a diepoxide (f = 2) and a diamine (f = 4).

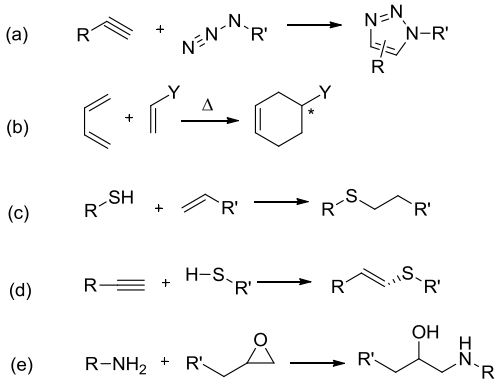
5. Recent synthetic developments in step-growth polymerization

In the following sections, we wish to highlight a few non-traditional routes to step-growth polymers that have emerged in recent years. In this regard, bio-sourced monomers and enzymatic catalysis are receiving a great attention.[38] From a processing viewpoint, development of non-conventional polymerization media (e.g. polymerization in ionic liquids[39]) has also emerged. These new techniques most often revisit and explore high-yielding and highly specific reactions of organic or organometallic molecular chemistries, sometimes in an "orthogonal" manner, that is, by using different chemistries that do not interfere with each other. Due to space limitations, however, it is not possible to review all methodologies that have allowed polymer

chemists to vastly expand the field of step-growth polymerization, and possibilities to achieve unprecedented polymer structures. In this chapter, focus is placed on several non-conventional step-growth polymerization methods, including those utilizing "click chemistry", polymerization under nonstoichiometric conditions, "chain-growth polycondensation", and metal-mediated coupling polymerization reactions forming π-conjugated polymers.

5.1. Use of "click chemistry"

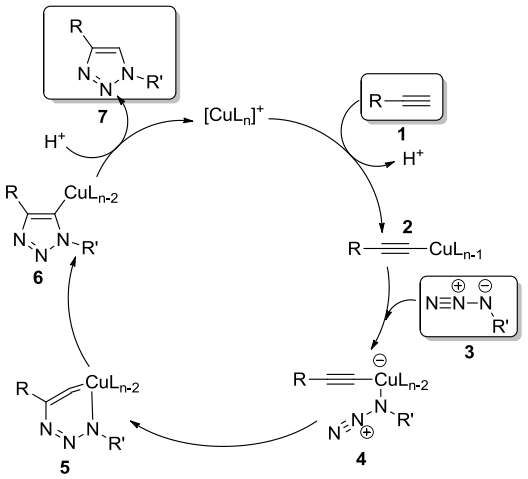
The terms "click chemistry" were coined by Kolb *et al.* who revisited the Huisgen's 1,3-dipolar cycloadditions between azides and alkynes (or nitriles) using copper salts as catalysts.[40] More generally speaking, click chemistry is a versatile method of C-C bond (or C-N) formation, combining mild experimental conditions, tolerance of functional groups and high yields, generally without the elimination of a small-molecule by-product. Hence, not only the reaction between an azide and an alkyne (Scheme 5.1a), but many other reactions are termed 'click'.[41] Typical other examples are the Diels-Alder reaction, thiol-ene and thiol-yne reactions, or reaction of an epoxide with an amine (Scheme 5.1).



Scheme 5.1 Typical "click" reactions: (a) Azide-alkyne cycloaddition, (b) Diels-Alder reaction, (c) thiol-ene and (d) thiol-yne reactions, (e) reaction of an epoxide with an amine.

5.1.1. The Huisgen's 1,3-dipolar "click" cycloaddition of azides and alkynes

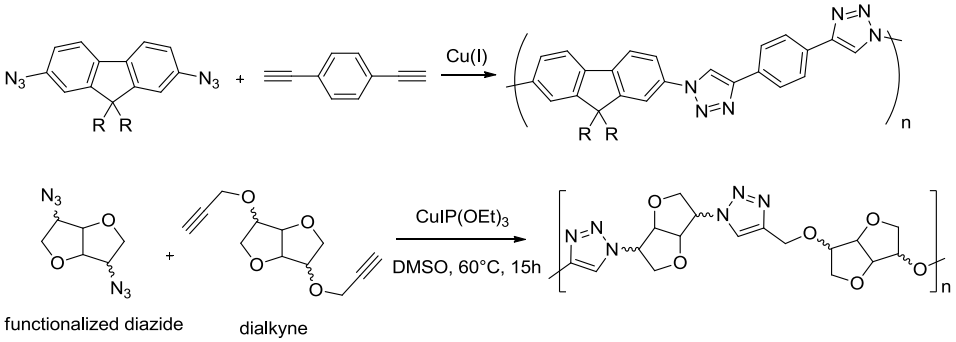
The mechanism involved in this click reaction is shown in Scheme 5.2.[42] The stepwise catalytic cycle starts from the formation of Cu(I)-acetylide (**2**) from the addition of Cu(I) catalyst on the terminal alkyne (**1**), and azide (**3**) generates a copper acetylide-azide complex (**4**). Complexation of the azide favours the nucleophilic attack of the acetylide carbon on the azide. In the as-generated metallocycle (**5**), the azide is properly located for subsequent ring contraction by a transannular association, to form triazole copper derivative (**6**). Protonation of the latter species followed by dissociation of product (**7**) ends the reaction and regenerates the Cu(I) catalyst. Unlike copper, ruthenium catalysts were found to trigger oxidative coupling of the azide and the alkyne to give 1,5-disubstituted triazoles.[43]



Scheme 5.2 Mechanism cycle of the copper-catalyzed azide-alkyne cycloaddition (CuAAC).

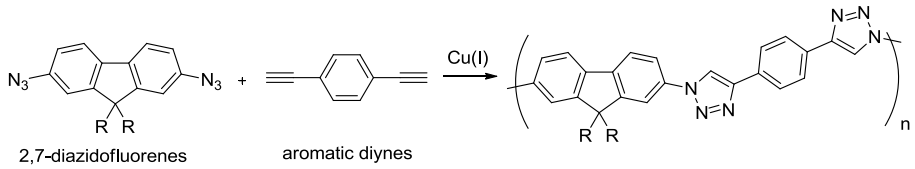
Click chemistry has experienced a rapid expansion in the polymer community, and its application in macromolecular engineering, including the synthesis of polymers, dendrimers, gels, etc. has been reviewed many times.[4,44]

Use of alkyne-containing monomers with azido-containing ones in the copper-catalyzed azide-alkyne cycloaddition (CuAAC) form 1,2,3-triazole repeating units in a polyaddition process; step-growth polymers synthesized in this way are referred to as polytriazoles (PTA's) (Scheme 5.3).[45] Development of this convenient synthetic tool in step-growth polymerization has been reviewed.[46] Efficiency of click reaction allows achieving high conversions at relatively low temperatures in various solvents, including aqueous media. A wide range of polymer structures, including linear, graft, hyperbranched, and dendritic polymers can be obtained in this way. However, step-growth polymerization *via* CuAAC suffers from a few drawbacks, including a poor solubility of the final product and the need for removing copper-based catalysts.



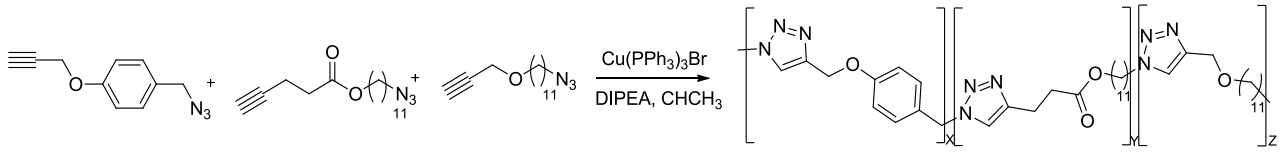
Scheme 5.3 Synthesis of starch-based polytriazoles through CuAAC step growth polymerization.[45b]

Scheme 5.4 illustrates the synthesis of π-conjugated linear PTA's by CuAAC polymerizations of 2,7-diazidofluorenes and aromatic diynes, as reported by Van steenis *et al.*[47]



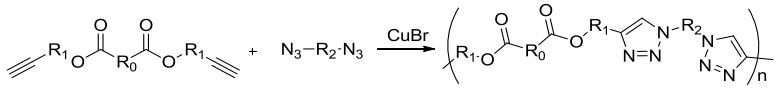
Scheme 5.4 Polymerization of 2,7-diazidofluorenes and aromatic diynes by click chemistry.

Another example is shown in Scheme 5.5 and relates to the synthesis of multiblock copolymers by CuAAC.[48]



Scheme 5.5 Multi-block copolymers synthesized by click chemistry.

Bisalkyne monomers containing ester functional groups were reacted with diazides to form polyesters containing triazole rings under mild conditions. Incorporation of heterocyclic triazole rings allowed increasing the thermal properties of the resulting polmers (Scheme 5.6).[49]

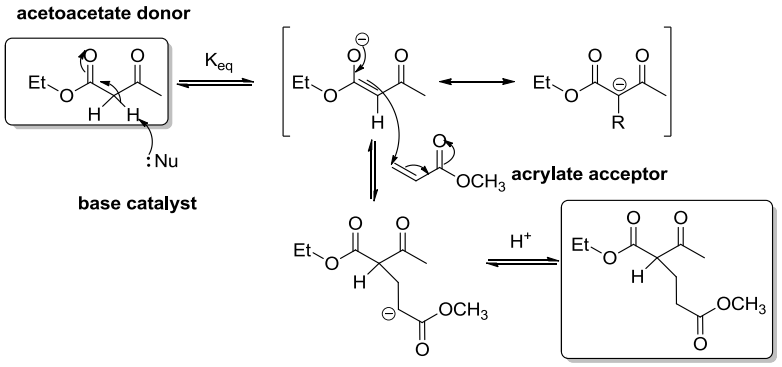


Scheme 5.6 Polyester synthesized *via* "click" reaction.

5.1.2. The Michael addition

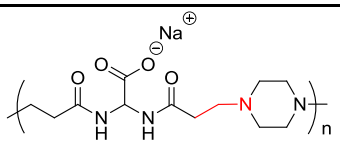
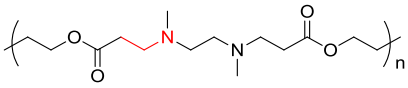
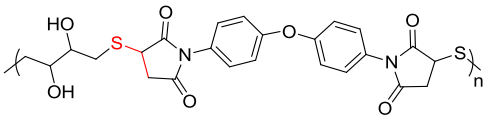
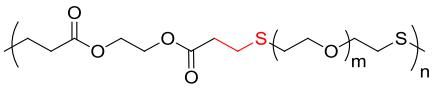
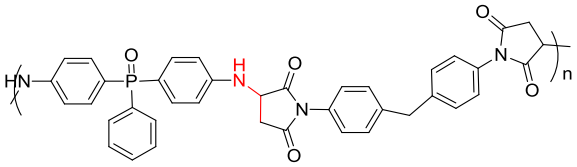
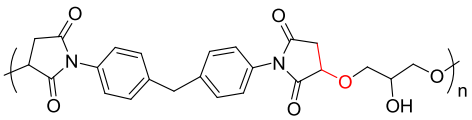
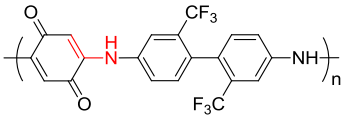
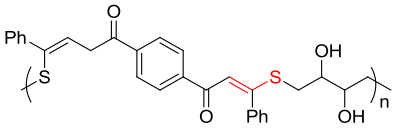
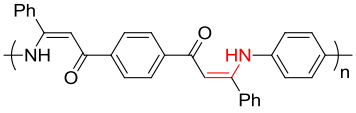
The Michael reaction involves the 1,4-conjugate addition between a nucleophile called the Michael donor with an activated olefin or alkyne referred to as the Michael acceptor.[50] This addition rapidly takes place and is quite tolerant to functional groups. In this regard, it can be regarded as a particular coupling click reaction. Amines can act as both the base catalyst and the Michael donor. Lewis acids (e.g. $TiCl_4$) and phosphines can also catalyze this reaction. There are numerous examples of the application of the Michael reaction to macromolecular engineering, and in particular to synthesize novel step-growth polymers, as reviewed by Mather *et al.*[51]

A typical Michael donor is an enolate, or an amino-containing reagent or a thiol, whereas alkyl acrylates often play the role of the Michael acceptor (Scheme 5.7). Interestingly, nitrogen atoms of primary amines behave as a bifunctional Michael donor reacting twice with two Michael acceptors.



Scheme 5.7 Proposed mechanism for Michael addition.

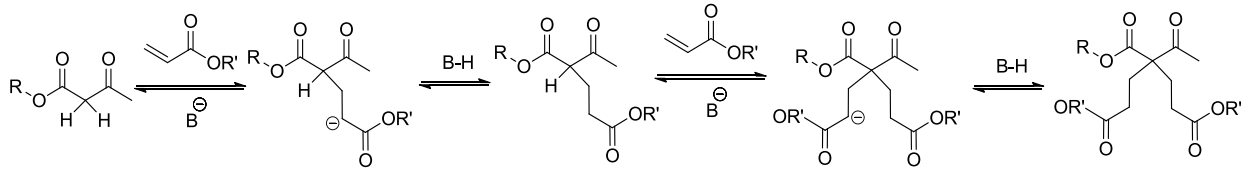
Table 5.1 Polymers synthesized *via* step growth Michael polyaddition.

Polymer	Structure	Reference
Poly(amido amine)		52
Poly(amino ester)		53
Poly(imido sulfide)		54
Poly(ester sulfide)		55
Poly(aspartamide)		56
Poly(imido ether)		57
Poly(amino quinine)		58
Poly(enone sulfide)		54
Poly(enamine ketone)		59

The red part is the structure formed after Michael polyaddition.

The same is true with the acidic protons of some enolates derived from activated methylene proton (CH_2-C=O). Hence, the reaction between acetoacetate-functionalized

oligomers (f = 4) and diacrylates (f = 2) yields crosslinked networks (Scheme 5.8), finding potential in applications such as coatings, adhesives, and laminates.[51] Thiols and amines have both been utilized to produce linear polymers, as well as hyperbranched polymers[60] and dendrimers by step-growth polymerization, while monomers featuring one acrylate group and one acetoacetate functionality have been used to form hyperbranched polymers. Examples of linear polymers grown by step-growth Michael polyaddition are provided in Table 5.1.

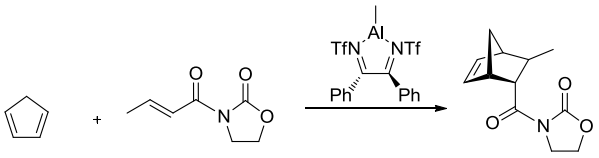


Scheme 5.8 Michael addition as an efficient by-product-free method toward novel networks.

By using acid-labile diacrylates, Long *et al.* have reported Michael polyaddition-derived degradable networks by chemical cleavage.[61] Photo-degradable networks have also been described.[62]

5.1.3. The Diels–Alder "click" coupling reaction

The Diels–Alder reaction is a [4+2]-cycloaddition C-C-bond forming reaction between a conjugated diene and a substituted alkene called dienophile, producing a substituted cyclohexene with no by-products (Scheme 5.9). This reaction was discovered by O. P. H. Diels and K. Alder in 1928.[63]

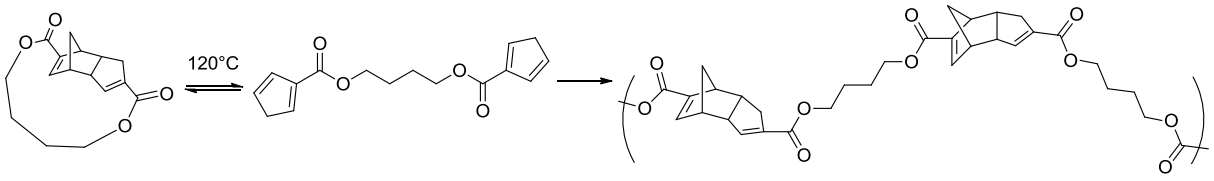


Scheme 5.9 Asymmetric Diels-Alder reaction catalyzed by a chiral Lewis acid based on Al.

The Diels-Alder reaction can be thermally induced without the aid of catalysts. However, the stereochemistry can be controlled using chiral Lewis acid catalysts (deriving from aluminum, titanium, boron, lanthanide, or transition-metals).[64] With the recent development of organocatalysis, asymmetric Diels-Alder reaction could also be efficiently promoted from organic catalysts, as recently reviewed by Pellisier.[65]

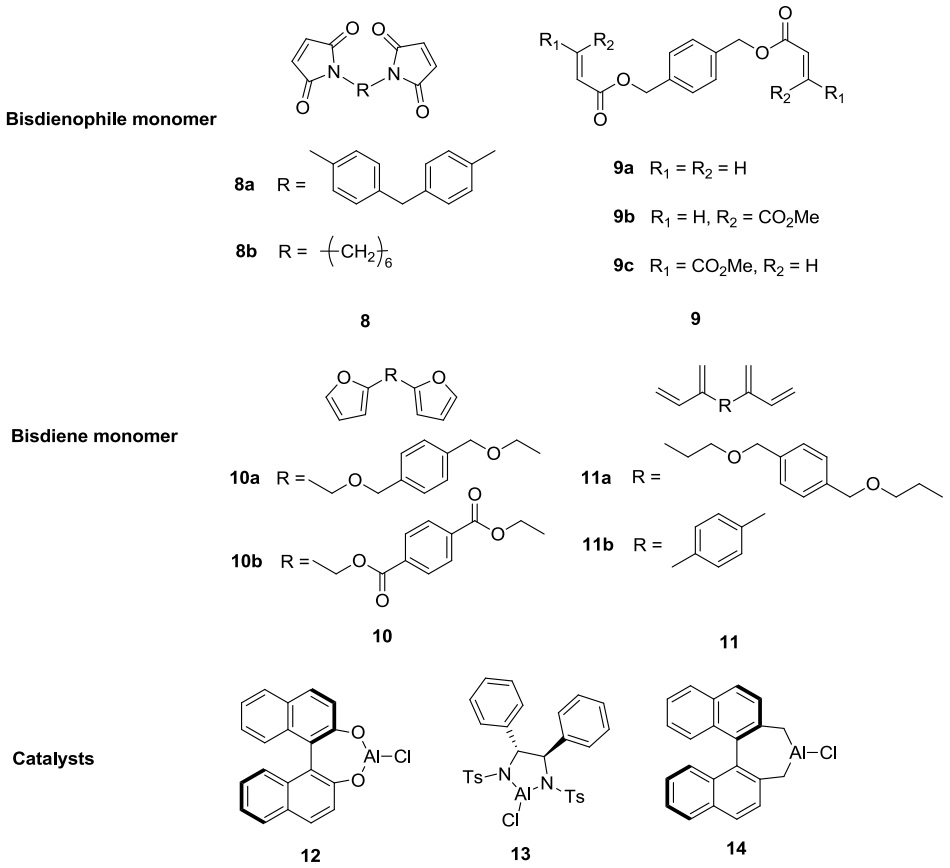
Interestingly, Diels–Alder reaction is reversible, the backward reaction being referred to as retro-Diels–Alder reaction. In the context of macromolecular engineering, this has been exploited to construct various self-healing materials (Scheme 5.10).[66] Although the reaction mechanism was established by Alder and Stein, early works by Staudinger showed that synthesis of poly(cyclopentadiene) could be achieved by a [2 + 4] cycloaddition reaction.[66c,d]

Diels–Alder reaction itself has been extensively investigated these recent years as a synthetic tool for side chain coupling, star formation, brush polymers, and step-growth polymer syntheses as well,[67] including linear polymers, ladder polymers, and remendable polymer networks.[66c]

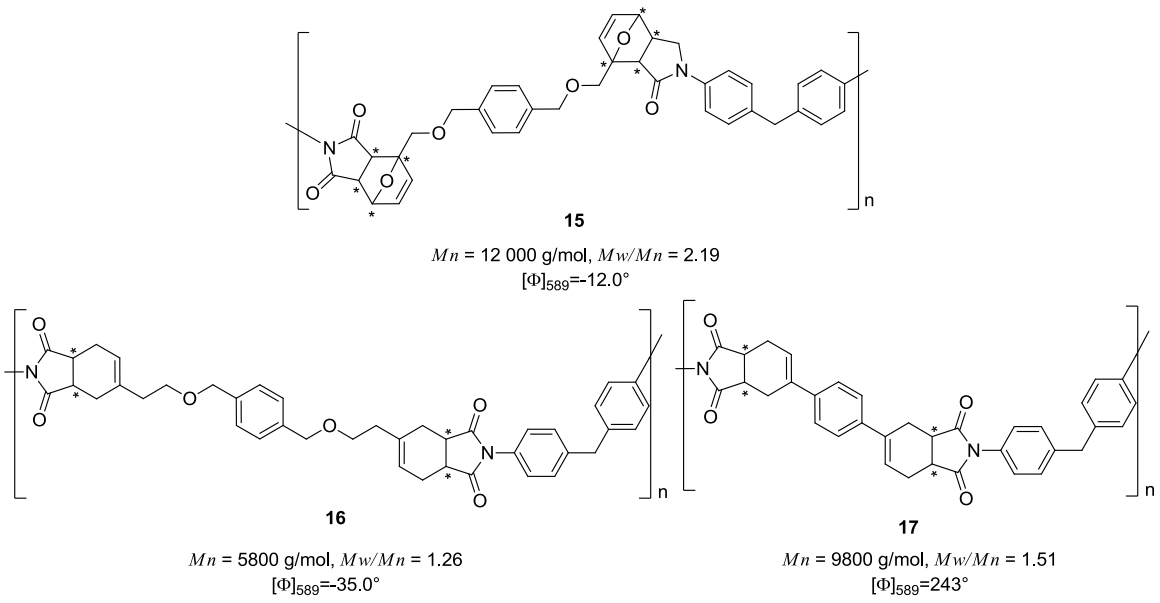


Scheme 5.10 Synthesis of healable materials via Diels-Alder polymerization.

Synthesis of main chain optically active step-growth polymers *via* Diels-Alder polyaddition was also described. The first example was reported in 1998 by Mallakpour *et al.* who polymerized optically active monomers (2-methoxy- 4-(1-propenyl)phenyl 2-(S)-N-phthaloyl-4-methylpentanoate).[68] More recently, Itsuno *et al.* investigated the asymmetric polymerization of prochiral substituted bis-diene and bis-dienophile monomer substrates *via* Diels-Alder reactions (Scheme 5.11).[69] The polymerization employed chiral organometallic catalysts (**12**-**14** in Scheme 5.11) that were found to transfer their chiral information to the polymer backbone (a process known as *asymmetric polymerization*), forming optically active step-growth polymers (Scheme 5.12).



Scheme 5.11 Monomers and catalysts investigated in asymmetric Diels-Alder polymerization.



Scheme 5.12 Polymers synthesized *via* asymmetric Diels-Alder polymerization.

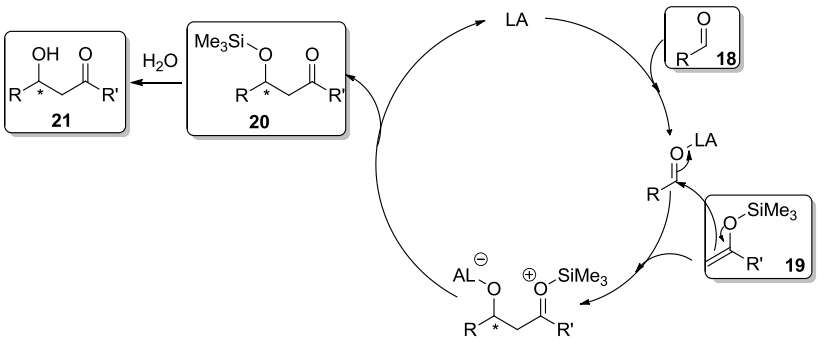
5.2. Asymmetric reactions utilizing the aldehyde functionality for the synthesis of chiral polymers

Aldehydes (R-CHO) are attractive building blocks due to their ability to easily react with many nucleophiles. In polymer chemistry, the polymerization of some bis-aldehyde monomers has been scarcely reported. In this thesis, novel bis-aldehydes monomers were synthesized and their polymerization investigated using original chemical tools.

5.2.1. The Mukaiyama aldol reaction

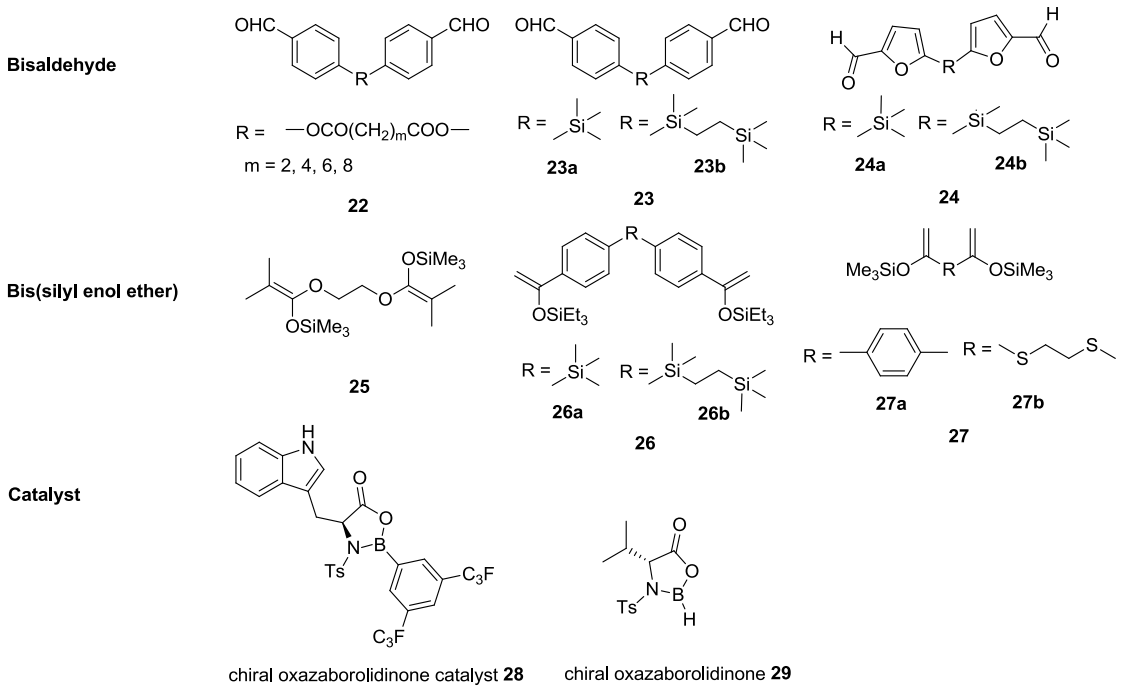
The Mukaiyama aldol addition is a reaction between a silylenol ether (**19**) and the aldehyde (**18**), forming a β-hydroxyketone (**21**). The reaction can be catalyzed either by a Lewis, or a Bronsted acid, or a Lewis or a Bronsted base.[70] The choice of reactants allows avoiding the self-condensation of the aldehyde. This reaction was pioneered by Mukaiyama *et al.* in 1973 who initially studied the $TiCl_4$ mediated cross-aldol reaction.[70a] As the Diels-Alder reaction discussed above, the Mukaiyama aldol reaction creates a stereogenic center and can be optimized for asymmetric control.

The mechanism of the Mukaiyama aldol addition is shown in Scheme 5.13. It involves the coordination of the aldehyde's oxygen to the Lewis acid, which increases the electrophilic character of the carbonyl moiety. The nucleophilic silyl enol ether (**19**) then adds onto such an activated carbonyl.[71]



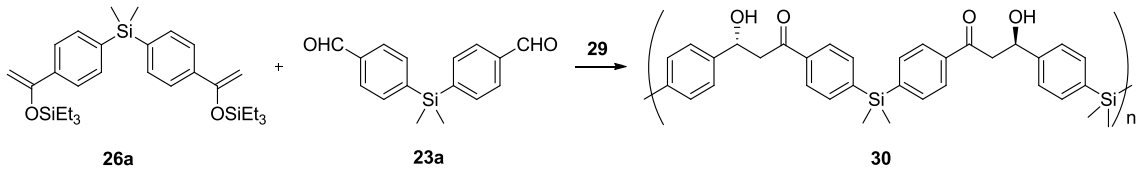
Scheme 5.13 Mechanism of the Mukaiyama aldol reaction.

In the context of a step-growth polymerization *via* Mukaiyama aldolization, commercially available or purposely designed bifunctional prochiral monomers were employed, as reviewed by Itsuno.[72] Chiral oxazaborolidinone catalysts served to synthesize optically active polymers by asymmetric Mukaiyama aldol polyaddition.[72] Representative examples of these monomers are shown in Scheme 5.14 (**22** to **27**).



Scheme 5.14 Monomers and catalysts investigated in asymmetric Mukaiyama aldol polyaddition.

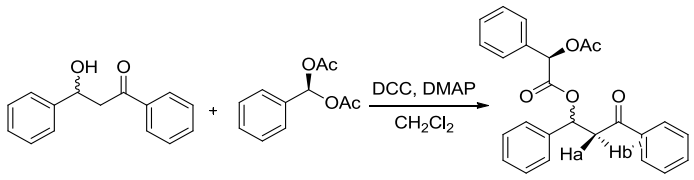
For instance, the polymerization of the silyl-containing bis-aldehyde monomer (**23a**) with the bis(silyl enol ether) (**26a**) led to a polymer of MW of 22 500 g/mol with a dispersity of 4.44 (Scheme 5.15).



26a 23a 30

Scheme 5.15 Polymer (**30**) synthesized from dialdehyde (**23a**) and bis(silyl enol ether) (**26a**) via asymmetric Mukaiyama aldol polyaddition.

The enantiomeric excess (e.e.) of the polymers, which arised from the transfer of chirality from the catalyst to the main chain, was determined by chiral HPLC analysis after selective degradation of the polymer backbone forming optically active aldol monomer units. Alternatively, e.e. could be obtained by NMR analysis after derivatization of the polymers with the enantiopure (R)-O-acetylmandelic acid. A model reaction was first implemented, as depicted in Scheme 5.16, the e.e. being determinded by the measure of the relative intensity of diastereotropic H_a and H_b protons in ^1H NMR. For instance, an e.e. of 94% was obtained for polymer (**30**).[72]



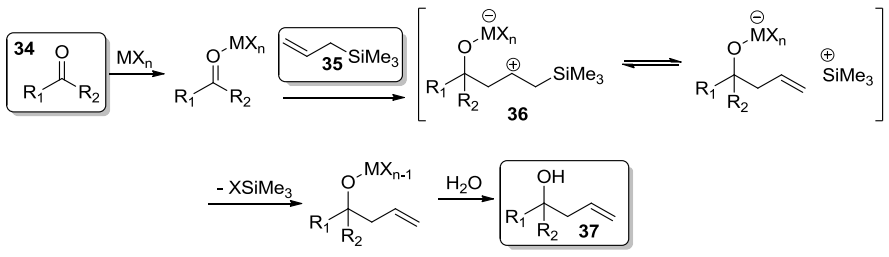
31 32 33

Scheme 5.16 Model reaction in synthesis of optically pure product.

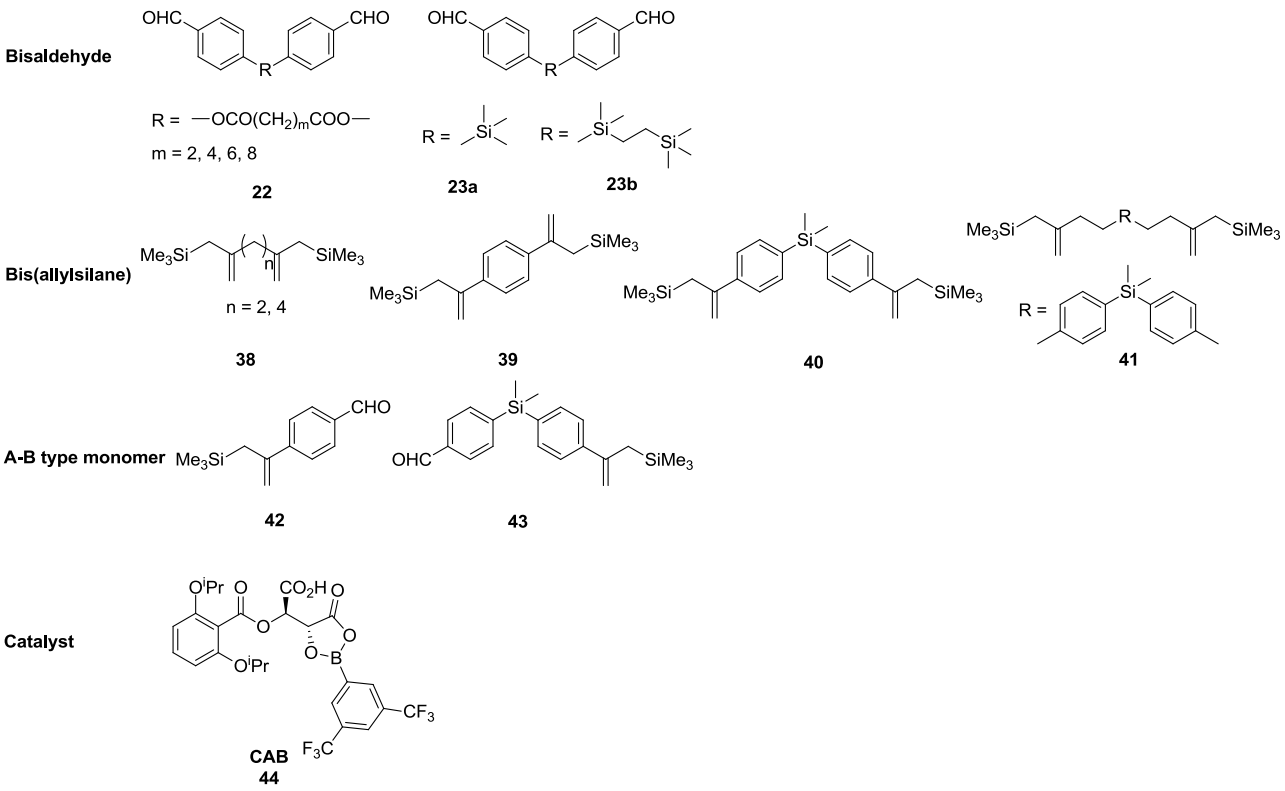
5.2.2. The Hosomi-Sakurai allylation

The Hosomi-Sakurai reaction consists in the Lewis acid-promoted allylation of various electrophiles – mainly ketones and aldehydes- with allyltrimethysilane (Scheme 5.17).[73]

The mechanism involves activation of carbonyl-containing substrates (**34**) by a Lewis acid, forming a β cation (**36**) that is stabilized by hyperconjugation with the Si center, followed by the addition of the allylsilane (**35**). After hydrolysis, allylic alcohol is obtained (**37**, Scheme 5.17). Here also, a stereogenic carbon is generated, hence chiral catalysts can be used for asymmetric Hosomi-Sakurai reactions.[71]



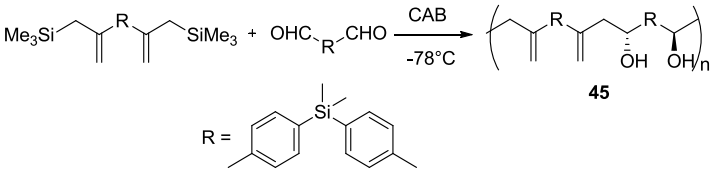
Scheme 5.17 Mechanism proposed for the Hosomi-Sakurai allylation.



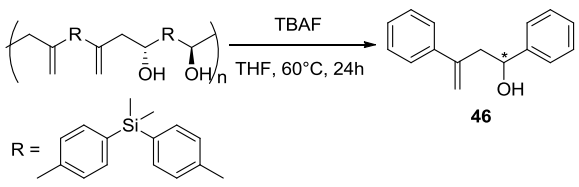
Scheme 5.18 Monomers and catalysts used in asymmetric Hosomi-Sakurai allylation.

Besides the Mukaiyama-aldol reaction mentioned above, Itsuno *et al.* investigated also the asymmetric Hosomi-Sakurai polyaddition of either bis-allylsilane and bis-aldehyde monomers, or AB-type monomers featuring both an allyltrimethylsilyl and an aldehyde functionalities (Scheme 5.18). A chiral acyloxy borane (CAB, **44**) was employed as a catalyst to induce a stereoselective polymerization for producing chiral polymers.[74]

Polymers' optical activity was evidenced from the same indirect methods (NMR and chiral HPLC) as those used for the Mukaiyama-aldol-derived polymers. For instance, a polymer possessing biphenyldimethylsilyl groups in the monomer units could be readily cleaved by tetrabutylammonium bromide (TBAF) into small fragments for further analysis by chiral HPLC.



Scheme 5.19 Polymer **45** synthesized *via* asymmetric Hosomi-Sakurai allylation in presence of catalyst CAB at -78 ℃.



Scheme 5.20 Degradation of polymer **45** by TBAF at 60 ℃.

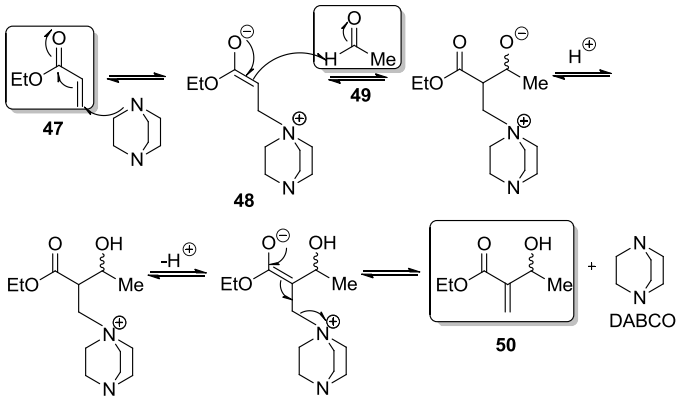
A value of e.e. equal to 72 % (with ratio of R: S = 86.1: 13.9) was found for polymer **45**, confirming that transfer of chirality from the catalyst occurred by repeated Hosomi-Sakurai allylation reactions. Higher e.e. values were observed, as expected, at lower temperature.

5.3. Other reactions utilizing the aldehyde functionality for nonchiral polymer synthesis

5.3.1. Baylis-Hilman reaction

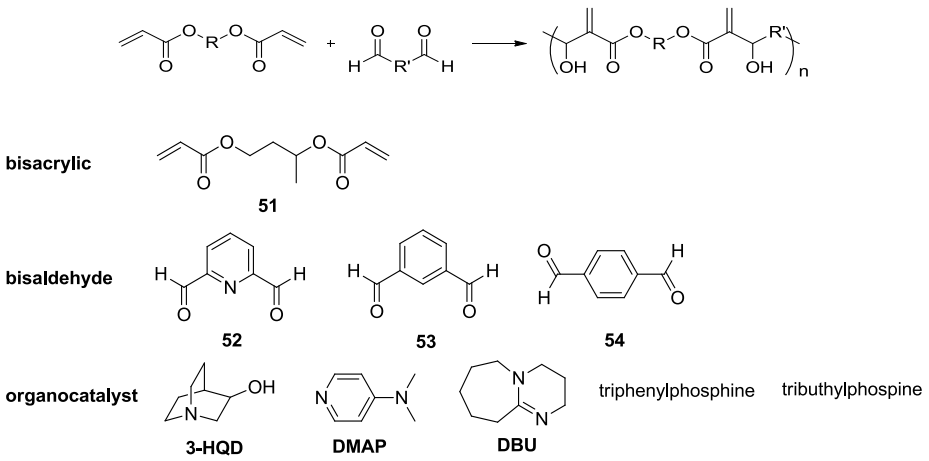
The Baylis-Hilman reaction was discovered 40 years ago.[75] It also employs an aldehyde substrate that is here reacted with an activated alkene (typically an acrylate, as in the case of the Michael reaction mentioned above). This coupling reaction forms an allylic alcohol product and is generally catalyzed by tertiary amines (e.g. DABCO = 1,4-Diazabicyclo[2.2.2]octane[75b,76], DMAP = 4-dimethylaminopyridine[77], 3-HQD = 3-hydroxyquinuclidine[78] or DBU = 1,8-diazabicycloundec-7-ene) or phosphines[79] (Scheme 5.21). Enantioselective reactions may be carried out with chiral catalysts. Complete information can be found in the review by Basavaiah and Veeraraghavaiah.[80]

The mechanism of the Baylis-Hilman reaction involves, first, a Michael addition of the catalyst to acrylate (**47**), forming a zwitterionic enolate intermediate (**48**) that further adds onto an aldehyde (**49**) *via* an aldol condensation (Scheme 5.21). After proton transfer and release of the catalyst, the allylic alcohol (**50**) is obtained.



Scheme 5.21 Proposed mechanism of the Baylis-Hillman reaction here involving ethylacrylate (**47**) and acetaldehyde (**48**) as substrates, and DABCO as catalyst.

Application of the Baylis-Hilman reaction in step-growth polymerization was reported only very recently by the group of Klok. Not only linear polymers were derived, but also hyperbranched polymers.[81] The step-growth polymerization of bis-aldehydes and bis-acrylics led to linear polyesters featuring allylic double bonds in their repeating units (Scheme 5.22).[82]

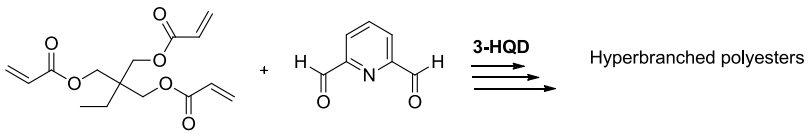


Scheme 5.22 Synthesis reaction of polyesters *via* Baylis-Hilman polymerization and related monomers and catalysts investigated.

Polymers thus obtained were of low MW; for instance, DABCO-catalyzed polymerization of 1,3-butanediol diacrylate (**51**) and 2,6-pyridinedicarboxaldehyde (**52**) gave polymers with DP of 25, after 24h at room temperature in $CHCl_3$.[83]

Interestingly, the α-methylene-β-hydroxycarbonyl groups present along the polymer chain, could be further modified, for example, using methyl-3-mercaptopropionate.[83]

As already mentioned, synthesis of hyperbranched polyesters *via* the Baylis-Hillman reaction involving an "$A_2 + B_3$ approach" was also reported.[81]



Scheme 5.23 Hyperbranched polymers synthesized via Baylis-Hillman polyaddition.

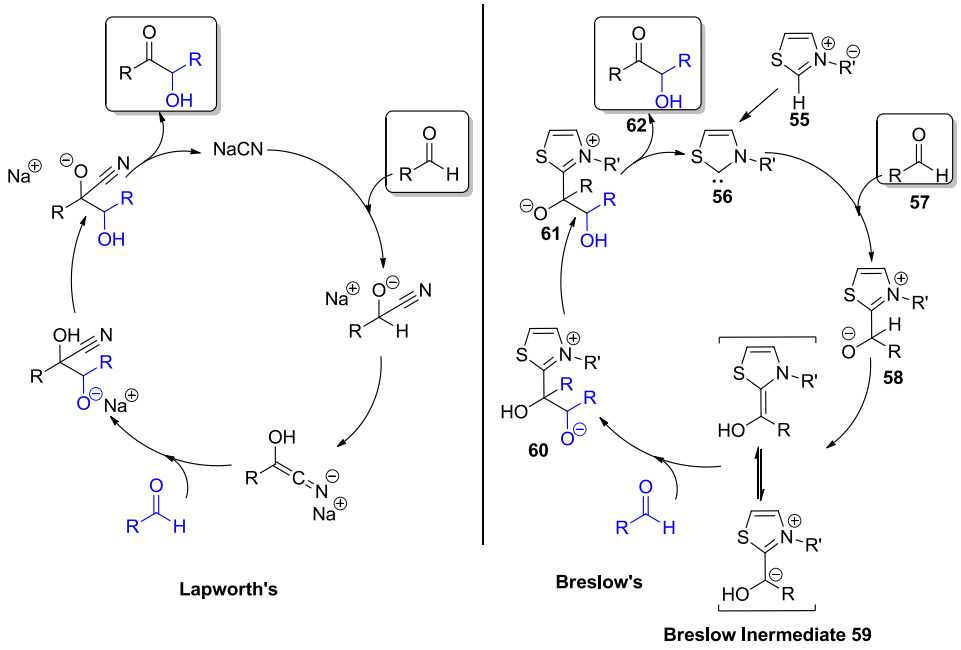
The presence of three distinct functional groups (hydroxyls, allylic and pyridine moieties) in these hyperbranched polymers allowed the authors to implement post-polymerization modification reactions, using phenyl isocyanate, methyl-3-mercaptopropionate, and methyl iodide, respectively, as reactants of the three aforementioned functional groups.[81]

5.3.2. Benzoin condensation

Investigations into the benzoin condensation date back to 1832 with the works by Wöhler and Liebig who employed the cyanide anion as catalyst.[84] The mechanism of the homocoupling reaction of benzaldehyde involves an activated aldehyde of inverted polarity ("Umpolung" in German) resulting from the nucleophilic addition of the catalyst onto one benzaldehyde molecule, and a non-activated electrophilic aldehyde.

In 1903, Lapworth reported a mechanism for the cyanide-catalyzed benzoin condensation.[85] An intermediate aldehyde cyanohydrin is deprotonated to generate an acyl anion

equivalent of inverted reactivity (Scheme 5.24, left).[86] A similar mechanism employing an *N*-heterocyclic carbene (NHC) as a catalyst was proposed by Breslow in 1958[84,86-87] and is depicted in Scheme 5.24 (right).

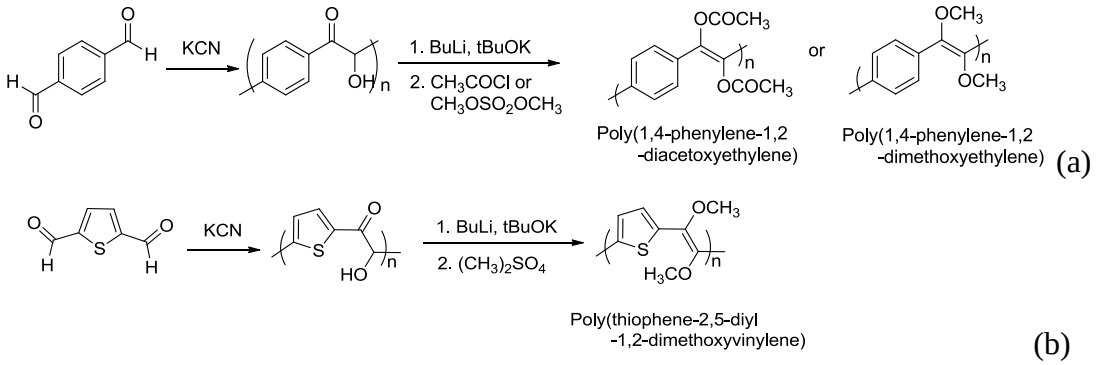


Scheme 5.24 Comparisons for benzoin condensation Lapworth's and Breslow's mechanism.

The initially formed zwitterionic adduct (**58**) undergoes a proton transfer to generate a carbanion, stabilised by negative hyper-conjugation (Scheme 5.24).[88] This so-called Breslow intermediate, **59**, results from a C→O proton transfer in (**58**); it adds to the electrophilic carbon of a second aldehyde molecule, forming (**60**). The latter intermediate undergoes a proton transfer, and the α-hydroxyketone (benzoin), **62**, is released, while the NHC catalyst is regenerated. Recently, the mechanism of benzoin condensation involving aliphatic aldehydes has been studied both experimentally and computationally and several intermediates could be characterized.[89]

Since a stereogenic center is generated in this reaction, a wide variety of asymmetric NHC catalysts have been developed and high enantio-selectivities (e.e.>90%) could be achieved.[84,90]

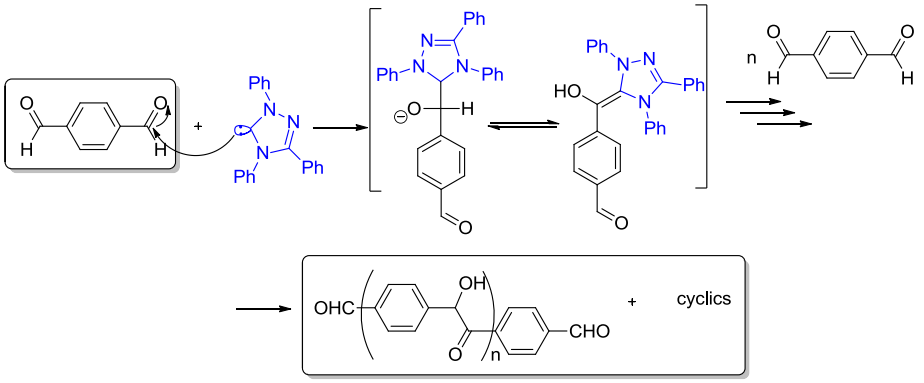
Benzoin condensation has been applied to the step-growth polymerization of bis-aldehydes. The first example was reported in 1990 by Kaul *et al.*[91] who used cyanide to catalyze the step-growth polymerization of terephthalaldehyde and 2,5-thiophenedicarboxaldehyde. The poly(2,5-thienylene-1-oxo-2-hydroxyethylene)[92] and poly(1,4-phenylene-1-oxo-2-hydroxyethylene)[91] thus obtained were subsequently modified by a strong base to produce a polydianion, which furher reacts as a nucleophile with dimethyl sulfate to access π-conjugated poly(1,4-phenylenevinylene) (PPV) homologues (Scheme 5.25 a).



Scheme 5.25 Polybenzoins from terephthalaldehdye **a** and thiophenedicarboxaldehyde **b**.

More recently, Pinaud *et al.* polymerized terephtaldehyde by a NHC catalysis (Scheme 5.26) under relatively mild conditions (THF or DMSO at 40 °C).[93] Out of the four organocatalysts employed in this study, 1,3,4-triphenyl-1,2,4-triazol-5-ylidene was the most active. Formation of cyclic polymers during the polymerization, however, was also noticed, the cyclic content depending on the reaction media used and the monomer conversion.

In this PhD work, new synthetic developments to polybenzoins *via* a NHC catalysis will be proposed (chapter 3). In particular, new bis-aldehyde monomer substrates will be employed and chiral NHC precursors will be tested.



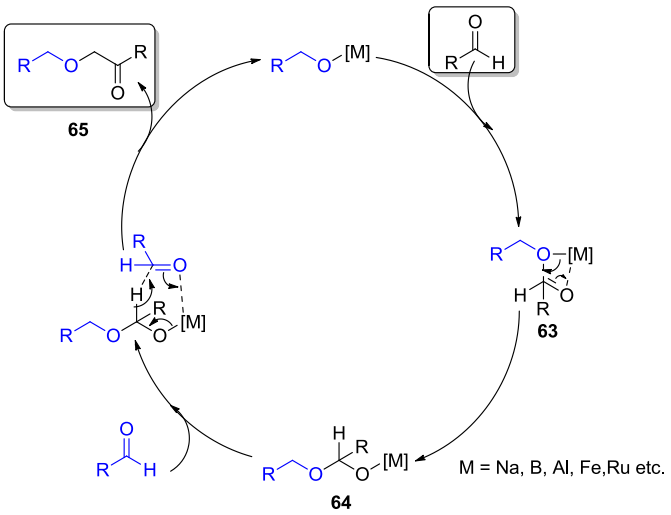
Scheme 5.26 NHC-catalyzed benzoin condensation in step-growth polymerization.

5.3.3. The Tishchenko coupling reaction

The Tishchenko coupling reaction is a disproportionation reaction between two aldehyde molecules, leading to an ester product. This reaction is being known for more than a century and is widely applied in industry for ester synthesis entering in applications such as fragrances or food industry.[94-95] Aluminium or sodium alkoxides were originally employed as catalysts, but further other catalysts, including transition-metal,[96] lanthanide,[97] and actinide derivatives[98] have been developed, as recently reviewed by Seki *et al.*[94]

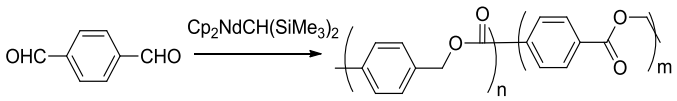
The mechanism of the Tishchenko reaction involves coordination of the metal-alcoholate to one aldehyde molecule, which favors the addition of the alcoholate to the carbonyl group, generating a hemiacetal intermediate **63** (Scheme 5.27). Coordination of another molecule of

aldehyde, followed by an intramolecular hydride shift, yields the ester product **65** and regenerates the catalyst.



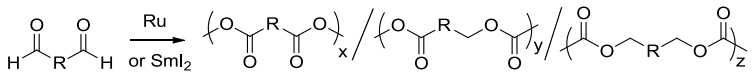
Scheme 5.27 Mechanism cycle of Tishchenko reaction and catalysts used in literature.

The first example of polyester synthesis *via* Tishchenko polyaddition of terephthalaldehyde was reported in the early 1960's.[99] No further related work was published until 1996 when Onozawa *et al.* employed a lanthanoid, $Cp^*_2LnCH(SiMe_3)_2$ (Ln = La, Nd), as a catalyst in Tishchenko reactions of mono- and bis-aldehydes (Scheme 5.28).[97b] For instance, polyaddition of terephthalaldehyde gave polyester with a MW of 7000g/mol with a dispersity of 1.8.



Scheme 5.28 Polyaddtion of terephthalaldehyde via the Tishchenko reaction catalyzed.

Lately, Yamamoto's group polymerized terephthalaldehyde, isophtaldehyde and 1,12-dodecanedial *via* ruthenium complex or SmI_2 as catalysts (Scheme 5.29).[100] Polymers MWs thus obtained were relatively low (< 9 000 g/mol).



Scheme 5.29 Tishchenko polyaddtion of bisaldehydes catalyzed by Ru-catalyst.

Theoretically, the Tishchenko polyadditon reaction of bis-adehydes should lead to three different types of monomer units, which are as follows: [OCH_2--C_6H_4--CH_2O], [OCH_2--C_6H_4--CO], and [CO--C_6H_4--CO], in a ratio of 1: 2: 1. All the three structures could be indeed identified, as verified by NMR analysis after cleavage of the polyester.

Similar works were reported at the same time by Choi *et al.*[101] who used EtMgBr-Sp (Sp = sparteine) as catalyst. MW of their polymers were lower (2000 g/mol) than those obtained

from by Ru- and Sm-based complexes, regardless of the solvent of the reactions (THF, $CHCl_3$ or CH_2Cl_2).

5.4. Synthesis of π-conjugated polymers by transition metal-catalyzed coupling and cross-coupling polyaddition reactions

In the past decade, significant progress has been made in thin-film device technologies employing π-conjugated polymers for organic electronics, including field-effect transistors,[102] bulk heterojunction solar cells[103] or light emitting diodes.[104] This is due to their solution-processability combined with their specific optoelectronic properties such as conjugation length, light absorption, carrier mobility and exciton dynamics that can be varied through changes in their molecular structure.

Most of π-conjugated polymers are based on aryl-aryl or aryl-vinyl repeating units consisting of sp^2-hybridized carbon atoms, mostly through alternation between simple and double carbon-carbon bonds.[105] However, heteroatoms can be introduced in the π-conjugation system: for instance, the –C=N- double bond is isoelectronic with the –C=C- one. The basic structure of most representative π-conjugated donor (D= p-type) polymers is shown in Figure 5.1. Common D monomer units are thiophene, carbazole, fluorene, silicon- or carbon-fused fluorene and many derivatives from these simple building blocks, while acceptors (A = n-type) usually derive from benzothiadiazole, thienopyrazine, substituted-benzo-dithiophene and diketo-pyrrolo-pyrrole. By incorporating various substituents on the aryl or vinyl moieties, hundreds examples of π-conjugated polymers have been reported.[102,106]

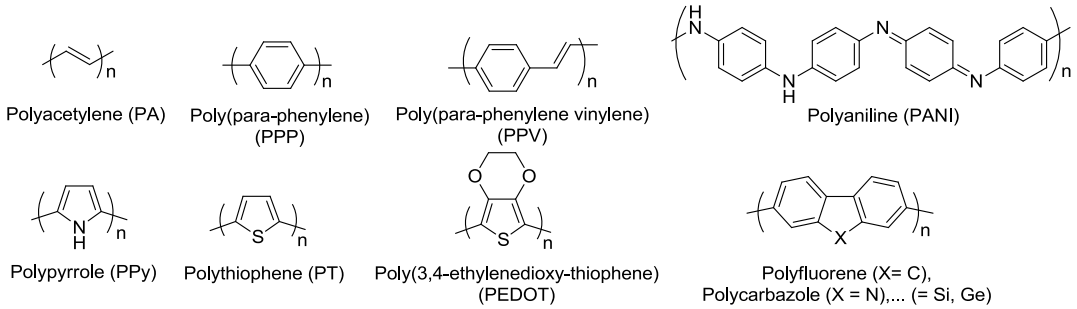
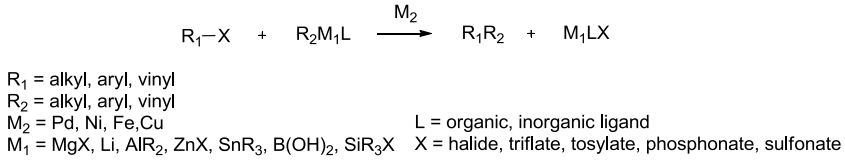


Figure 5.1 Main π-conjugated polymer donors (possibilities for substitutions are not shown).

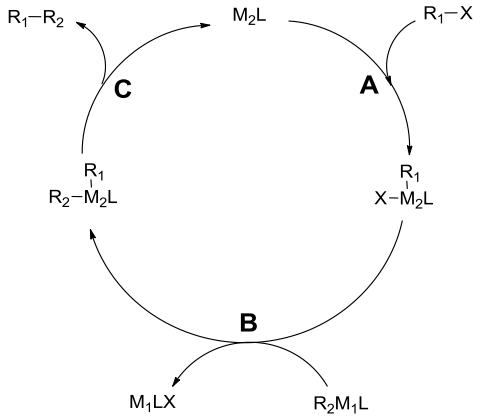
Synthesis of these π-conjugated polymers generally requires transition metal-based catalysts. Typical C-C bond forming elementary coupling or cross-coupling reactions include oxidative coupling, electrochemical reactions, dehalogenative (Yamamoto), Suzuki-Miyaura, Stille, or Heck and Suzuki reactions. Palladium(0)-based catalysts have been extensively used for these reactions, and their importance has been emphasized by the award of the 2010 Nobel Prize in chemistry to R. Heck, A. Suzuki and E. Negishi.

However, many other transition metals are effective promoters and catalysts for cross-coupling and homo-coupling reactions, including copper, nickel and iron (Scheme 5.30).



Scheme 5.30 General reaction scheme of metal-catalyzed coupling reactions.

A common feature of these reactions relates to the mechanism forming the π-conjugated units, which involves these three following elementary steps, occurring sequentially: i) oxidative addition, ii) transmetallation, and reductive elimination (Scheme 5.31).

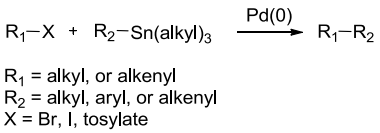


Scheme 5.31 General mechanism cycle of a metal-catalyzed coupling reaction: oxidative addition (A), transmetallation (B), and reductive elimination (C).

Application of transition metal-catalyzed elementary (cross) coupling reactions to π-conjugated polymer synthesis has been largely documented. Some examples are presented below, but the discussion is by no means exhaustive.

5.4.1. The Stille reaction

Stille coupling is a coupling reaction that can take place under neutral conditions and is tolerant to a wide range of functional groups.[107] It was discovered together by J. K. Stille and D. Milstein in 1977.[108] The reaction involves an organostannane and an aryl halide and is catalyzed by Pd(0)-based complexes (Scheme 5.32). One drawback, however, relates to the toxicity of stannane reagents, limiting the application of this reaction to small scale. An excellent review by Espinet *et al.* discussing factors (ligands, solvents and additives) affecting the Stille reaction can be found.[109]

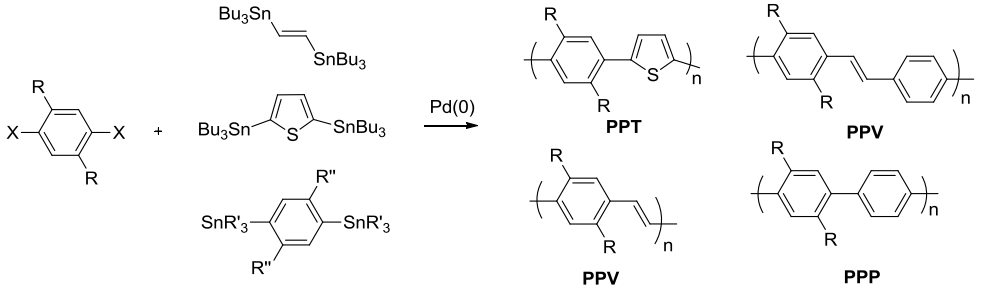


Scheme 5.32 Reaction scheme of Stille reaction.

Stille coupling has been employed as a versatile synthetic tool in polymer chemistry to achieve π-conjugated polymers from thiophene, vinylene, phenylene-based bis-stannanes and bis-aryl halides (e.g. deriving from fluorene, naphthalene, benzimidazol, pyrazine or phenyl moieties) by a Pd(0) catalysis. Representative examples are shown in scheme 5.33. For a comprehensive overview on "Stille step-growth polymerization", the recent review by Carsten *et al.* is available.[110]

Among synthesized functional materials *via* Stille polycondensation, polymer solar cell materials (OPVs) have emerged as a promising low-cost alternative to inorganic solar cell materials. Therefore, they have the potential to fabricate flexible, large, and lightweight devices in a more cost-effective manner using solution processing.[103b]

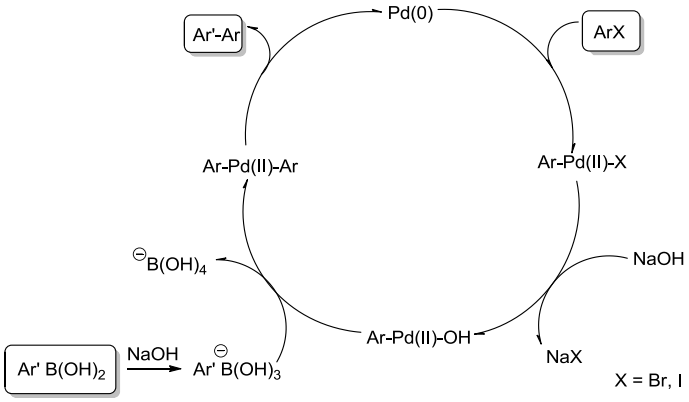
Since aryl or alkenyl halide fragments can be coupled to aryl, alkenyl, or alkynylstannanes, the Stille reaction has great versatility and can be employed in the synthesis of PPT, PPP- and PPV- type polymers which are all the high performance polymers studied in OPVs especially the low band gap thiophene-based materials (Scheme 5.33).[111] Other examples of highly efficient polymer solar cells can be found elsewhere.[112]



Scheme 5.33. PPT, PPP and PPV derivatives synthesized *via* Stille polymerization.

5.4.2. The Miyaura-Suzuki reaction

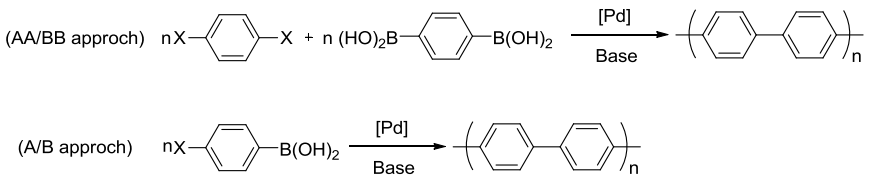
The Suzuki-Miyaura reaction is a cross-coupling reaction between a boronic acid and an aryl or vinyl halide, in the presence of a base and a Pd(0) catalyst.[71] Potassium trifluoroborates and organoboranes or boronate esters can be used instead of boronic acids. In contrast to Stille coupling, Suzuki-Miyaura coupling requires a base to activate the boronic acid, in order to facilitate transmetallation (Scheme 5.34).



Scheme 5.34 The mechanism of Suzuki reaction with the aid of base (here NaOH).

Due to the stability, ease of preparation and low toxicity of boronic acid reagents, Suzuki coupling has gained a considerable attention as a synthetic tool, in particular, in step-growth polymerization to synthesize PPP's of higher MW compared to other methods.[113]

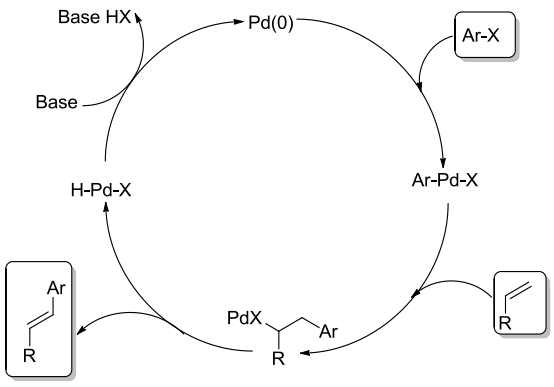
Typical examples of PPP grown *via* Suzuki-Miyaura polyaddition of AA + BB or AB-type bifunctional monomers are shown in Scheme 5.35. This was first reported by Rehahn *et al.* in 1989.[113] The author discussed pros and cons of each method in a review article and a book chapter.[3b,114]



Scheme 5.35 PPP synthesized from Suzuki-Miyaura polymerization.

5.4.3. The Heck reaction

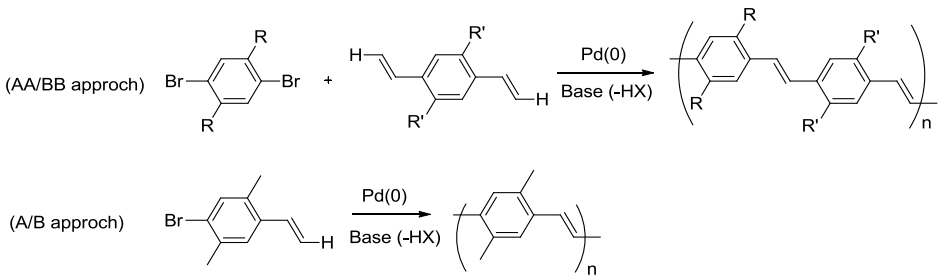
The Heck reaction was independently discovered by T. Mizoroki and R. F. Heck in the early 1970's. It is a Pd(0)-catalyzed C-C coupling reaction between aryl halides or vinyl halides and activated alkenes in the presence of a base (e.g. a sterically hindered amine).[115] A major benefit of this coupling reaction is its high trans-selectivity.



Scheme 5.36 The mechanism of Heck reaction.

The mechanism cycle involves a coordinated olefin inserting into a Pd-Ar bond, followed by a β-Hydrogen elimination to yield an alkene and a hydropalladium halide (Scheme 5.36), the latter reacting with a base to regenerate the Pd(0) catalyst.[71]

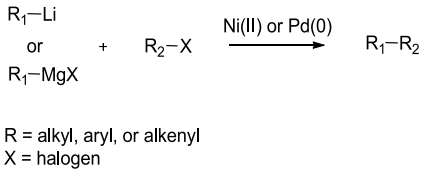
The Heck reaction is an important synthetic route to different forms of PPV by polymerization of AB- or AA+BB-type monomer, as highlighted in the review article by Lee *et al.* in 2006.[3a] Typical PPV synthesis is shown in Scheme 5.37.



Scheme 5.37 Heck polymerization of AA+BB or AB-type monomers catalyzed by Pd(0).

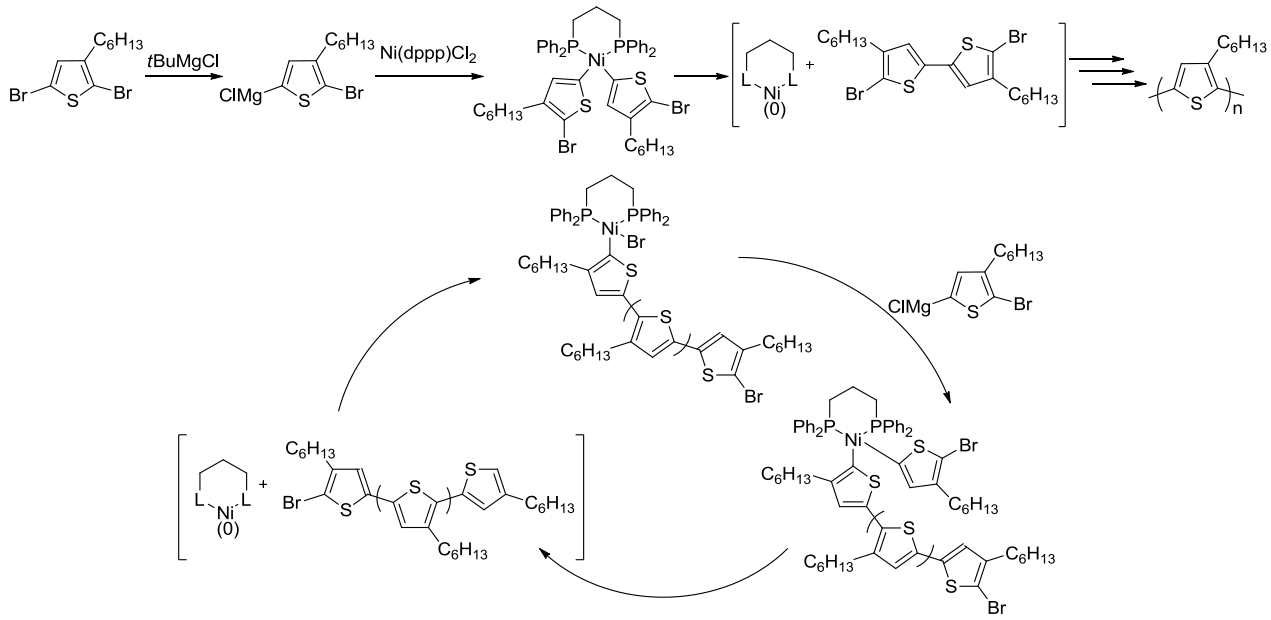
5.4.4. Kumada and Yamamoto couplings

The Kumada coupling reaction can be conducted at room temperature and utilizes Nickel(II) complexes [e.g. 1,3-bis(diphenylphosphino)propane dichloro nickel= Ni(dppp)Cl_2) or palladium(0)] as catalysts. It was developed independently in 1972 by the groups of R. Corriu and of M. Kumada.[116] It involves the direct coupling of Grignard reagents (R_1MgX) with alkyl, vinyl or aryl halides (Scheme 5.38).



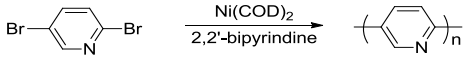
Scheme 5.38 Reaction scheme of Kumada coupling reaction.

Interestingly, Yokozawa *et al.* discovered in 2004[117] that Ni(dppp)Cl_2 could catalyze the polymerization of 2-bromo-5-chloromagnesio-3-hexylthiophene, the reaction mechanism exhibiting the attributes, to some extent, of a "controlled/living" chain-growth mechanism. Conjugated polymers with controlled MW's and relatively low dispersities could be obtained in this way, including PT, PPP, PPy, and polyfluorene (Scheme 5.39).[118]



Scheme 5.39 Proposed mechanism for the nickel-initiated cross-coupling polymerization.

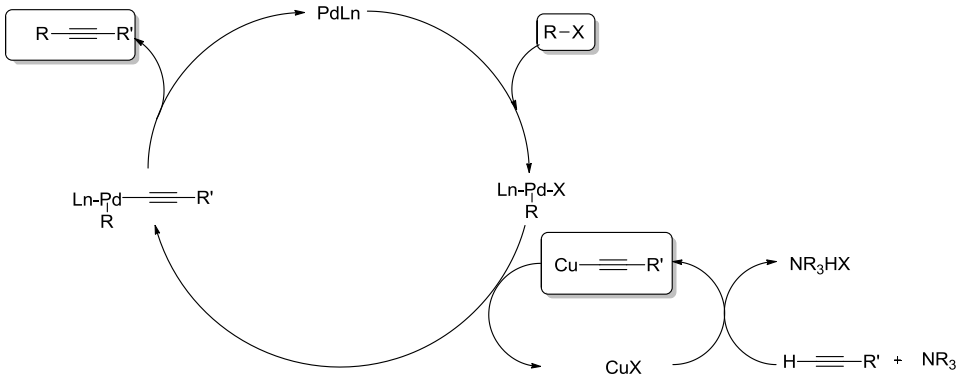
Synthesis of poly(2,5-pyridinediyl)s could also be achieved via Ni(0)-mediated homocoupling, as reported by T. Yamamoto in 1988 (Scheme 5.40).[119] The synthetic application of $Ni(COD)_2$ and $Ni(PPh_3)_4$ were developed extensively by A. Yamamoto, and their use in polycondensation of aryl halides, heteroaryl halides is often dubbed "Yamamoto Coupling."[120] In this case, one halide is removed from the monomer creating a radical species that can further add to a halide, which releases Br_2 as a by-product. This reaction is commonly used to polymerize bis-fluorene- and phenylene-containing monomers.[121] But the major deficiency of the emerging Ni(0) mediated homocoupling reactions is the stoichiometric levels of the Ni(0) or Ni(II) precursor employed, and demonstrated that the homocoupling reaction can be made catalytic in Ni if stoichiometric levels of Zn(0) are used.



Scheme 5.40 Ni(0)-based polymerization of 2,5-dibromopyridine yields.

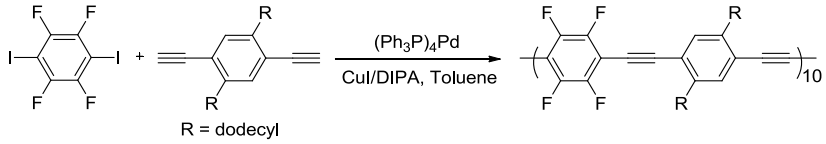
5.4.5. The Sonogashira reaction

The Sonogashira reaction is an efficient coupling reaction between terminal alkynes with aryl or vinyl halides, using a palladium catalyst such as $Pd(PPh_3)_4$ and $(PPh_3)_2PdCl2$, a copper(I) co-catalyst for the transmetallation step, and an amine base.[122] This reaction was disclosed in 1975. Originally, the reaction required anhydrous and anaerobic conditions, but newer procedures have been developed where these restrictions are not important (Scheme 5.41).[123]



Scheme 5.41 General reaction scheme of Sonogashira reaction.

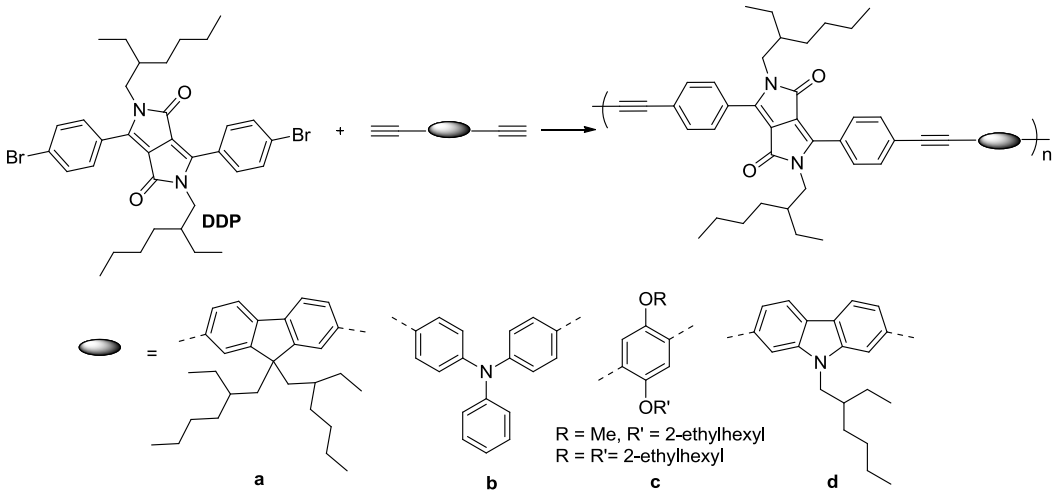
Sonogashira cross-coupling has become a popular method for the synthesis of polymers consisting of aryl acetylene units, such as poly(phenylene enynylene)s (PPE's) (Scheme 5.42),[124] and poly(aryleneethynylene)s (PAE's).[125]



Scheme 5.42 Poly(phenylene enynylene)s synthesized *via* Sonogashira coupling reaction.

A series of donor–acceptor type PAE's have been synthesized through Sonogashira polycondensation[125] (Scheme 5.43). The polymers consist of an electron donating 9,9-bis(2-ethylhexyl)-9H-fluorene (Scheme 5.43, polymer **a**), triphenylamine (Scheme 5.43, polymer **b**), 1,4-dialkoxybenzene or 9-(2-ethylhexyl)- 9H-carbazole unit (Scheme 5.43, polymer **d**) and an electron accepting 2,5-bis(2-ethylhexyl)-3,6-diphenylpyrrolo[3,4-c]pyrrole-1,4(2H,5H)-dione (EH-DPP) unit, alternately connected through ethynyl bridge for various optoelectronic-device applications.

Besides, poly(arylethynyl) nanoparticles have been achieved by repeated Sonogashira coupling reactions under aqueous emulsion conditions.[126]



Scheme 5.43 Synthesis of PAE's catalyzed by $(PPh_3)_2PdCl_2$, CuI and di-isopropylamine.

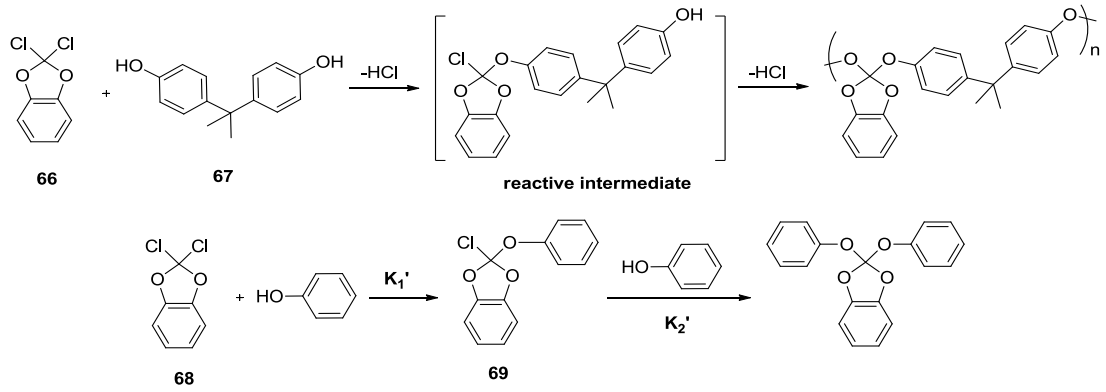
6. New synthetic methodologies in step-growth polymerization

6.1. Nonstoichiometric polycondensation

As already emphasized, high MW step-growth polymers can be preferably obtained upon reacting functional groups each other used at stoichiometry. Due to impurities present in monomers, or competing reactions, or decomposition of functional groups during polymerization, or cyclization, working under perfect stoichiometry all along the polymerization is a challenging task. There are several practical examples of so-called "nonstoichiometric polycondensation" that do allow reaching high MW polymers. This can be due to a drastic change of chemical reactivity, for instance, after reaction between AA and BB monomers, forming a stoichiometric AB-type dimer intermediate with an enhanced reactivity for further reactions ("chemical method"). Another category of nonstoichiometric polycondensation involves a change of polymer structure in the course of the polymerization ("physical method").

6.1.1. Nonstoichiometric polycondensation via chemical methods

A typical example is the polycondensation of α,α'-dihalogenated monomers with diphenols reported by Kihara *et al.*[127] The effect of stoichiometric imbalance and kinetic study has been described in details. The polycondensation of 2,2-dichloro-1,3-benzodioxole (**66**) and 4,4' isopropylidenediphenol (**67**) with a feed ratio 5:3 gave a MW of 120 000 g/mol with a dispersity of 2.52. The first reaction actually yields a reactive intermediate, giving rise to enhancement of the rate of the second reaction (Scheme 6.1). Kinetic investigations into a model reaction revealed that the rate constant of the second nucleophilic substitution on monochloride compound (**69**) formed (k_2') was 27 times higher than that of the first substitution reaction (k_1').

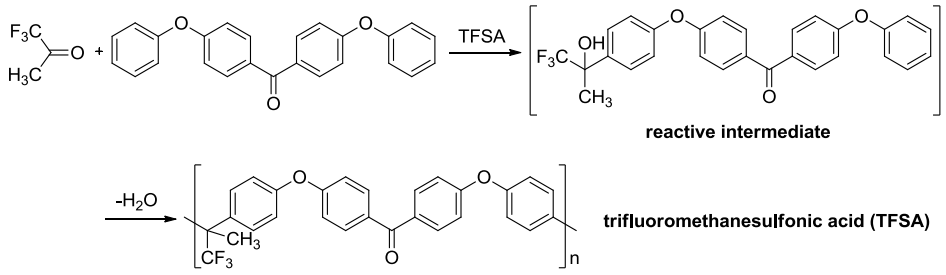


66 67 68 69

Scheme 6.1 Polycondensation of 2,2-dichloro-1,3-benzodioxole and 4,4' isopropylidenediphenol and model reaction of 2,2-dichloro-1,3-benzodioxole (**68**) and phenol.

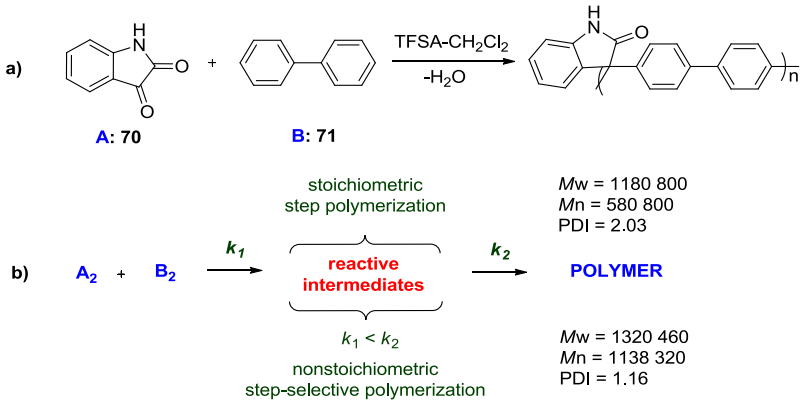
Another example is given by the polyhydroxyalkylation reaction, which is catalyzed by a Bronsted acid, in the presence of a small excess of the carbonyl compound. In the stoichiometric

polycondensation of trifluoracetone and 4,4'-diphenoxybenzophenone, a neat difference in reactivity between the first and the second substitution step is created (Scheme 6.2).[128]



Scheme 6.2 Acid-catalyzed nonstoichiometric polycondensation of trifluoracetone and 4,4'-diphenoxybenzophenone.

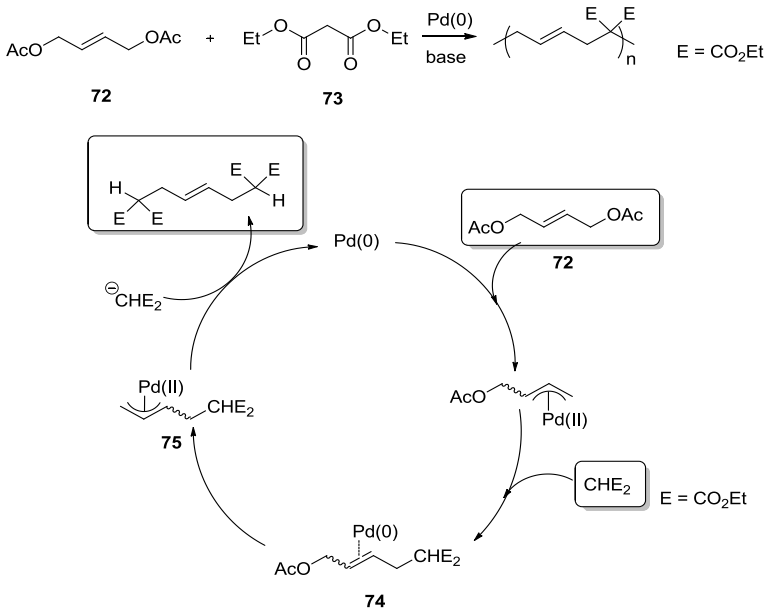
Following a similar acid-catalyzed polyhydroxyalkylation pathway, Cruz *et al.* reported the synthesis of polymers with MW up to 100 000−300 000 g/mol (Scheme 6.3).[129] In the case of stoichiometric step-growth polymerization of isatin and biphenyl, dipersity of 2.03 of the formed polymer was obtained which is typical for a step-growth polymerization. Of particular interest, this nonstoichiometric step-growth polymerization gave a polymer with a dispersity equals to 1.16, the process exhibiting a "living" character. This was explained by a decrease in reactivity (nucleophilicity) of the oligomers formed, because the carbonyl compound of (**70**) selectively reacts with the biphenyl monomer (**71**) forming diaryl dimer, and then gradually with dimers and tetramers etc. As a matter of fact, the larger the molecules are, the lesser is their reactivity with the carbonylated compound.



Scheme 6.3 a) Step-selective polyhydroxyalkylation of isatin and biphenyl; b) stoichiometric step polymerization and nonstoichiometric step-selective polymerization pathways.

Another type of nonstoichiometric polycondensation uses palladium catalyst to control the polycondensation by changing the reactivity of monomers. Nomura *et al.* have thus polymerized an excess of 1,4-diacetoxybut-2-ene with diethyl malonate via the Pd(0)-catalyzed allylic substitution, referred to as the Tsuji–Trost reaction (Scheme 6.4).[130] After first allylation between (**72**) and (**73**), the olefin-Pd(0) complex (**74**) selectively forms an allypalladium(II)

complex (**75**) upon acetate departure. Hence, even with an excess of (**72**), the polymer is always ended by a malonic ester moiety.

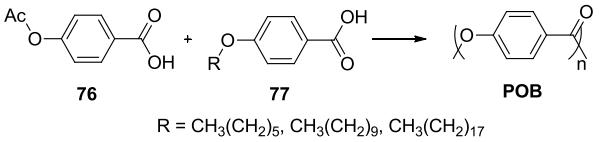


Scheme 6.4 Nonstoichiometric polymerization of 1,4-diacetoxybut-2-ene (**72**) and diethyl malonate (**73**) catalyzed by palladium in presence of base.

6.1.2. Nonstoichiometric polycondensation via physical methods

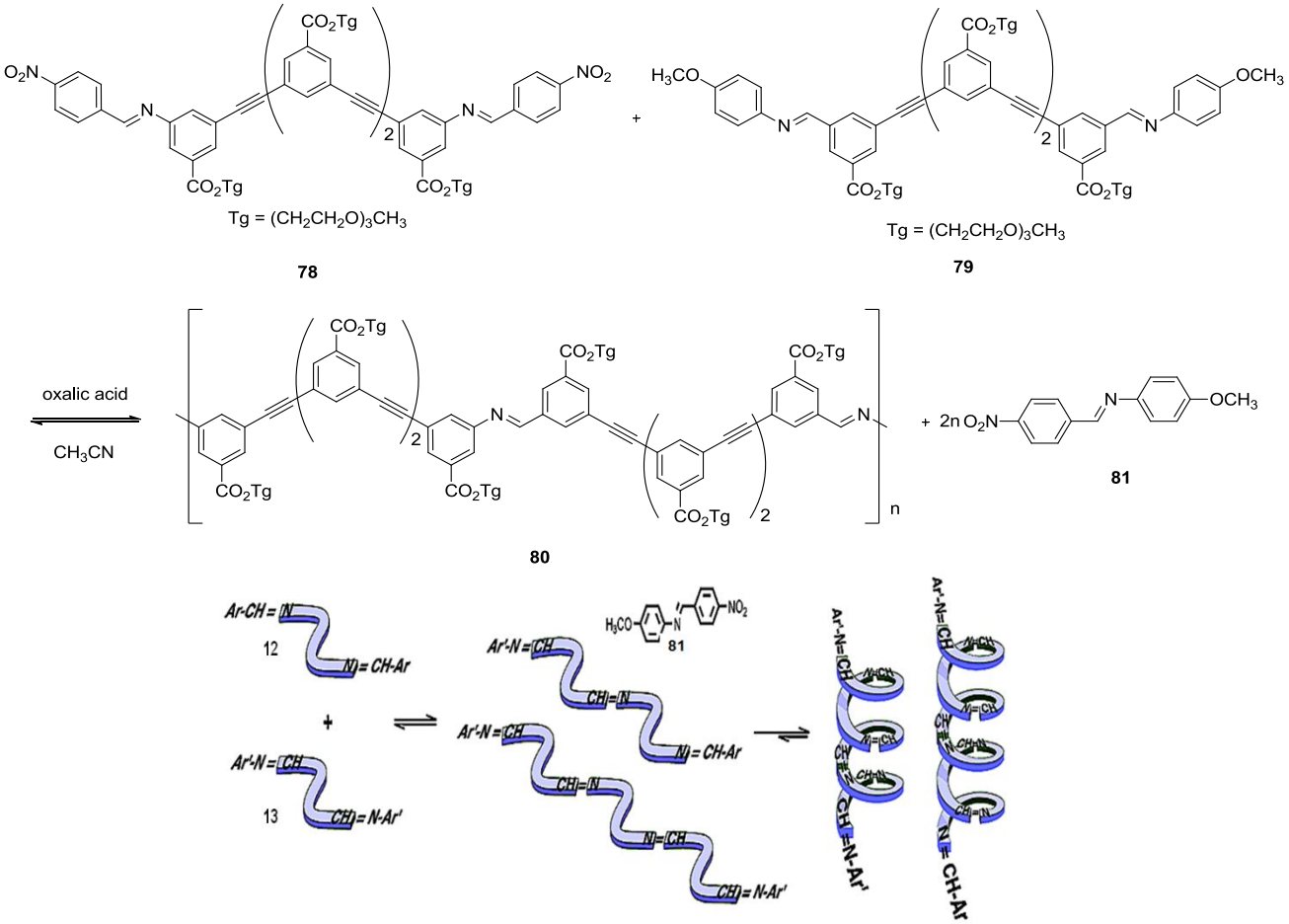
One of the illustrations of the "physical method" pertaining to nonstoichiometric polycondensations is the interfacial polymerization in which monomers diffuse at the interface where they *de facto* react at stoichiometry. Highly reactive monomers, which constitute a large volume of the reaction mixture, are required. Polymers that can be prepared by interfacial polymerization include polyamides, polyureas, polyurethanes, polyesters, polysulfonamides, phenol-formaldehyde polymers and polycarbonates with high MW. In this polymerization, the monomers employed need not to be of the highest degree of purity.[131]

Another example is the polycondensation of *p*-acetoxybenzoic acid (**76**) with an aromatic monofunctional alkyloxybenzoic acid like (**77**, Scheme 6.5).[132] Poly(p-oxybenzoyl) (POB) with a high DP (around 400) can be prepared using alkyloxybenzoic acid containing 18 carbon atoms in the alkyl chain, owing to the crystallization of oligomers. Though end-capped oligomers by mononofunctional alkyloxybenzoic acid are also crystallized, polycondensation proceeds with elimination of the end capping groups of the oligomers by transesterification, when they crystallize. Although some of the end-capped oligomers (-OAc) by monofunctional compound are embedded in the crystals, end capping groups are excluded by solid state polymerization.



Scheme 6.5 Nonstoichiometric synthesis of poly(p-oxybenzoyl) induced by crystallization.

Reversible polymerizations occurring in a closed system is another possibility to achieve high MW polymers *via* nonstoichiometric polycondensation. For instance, polymerization in solution of m-phenyleneethynylene derivatives, **78** and **79**, (Mw up to 350 000g/mol) is driven by the folding energy of helical polymers forming, which results in a novel size distribution under imbalanced stoichiometry by the so-called nucleation-elongation mechanism (Scheme 6.6).[133] Oligomer with a certain length starts folding in solution, and further extending the molecule would result in polymers with increasing folding stability. Excess monomer remains unreacted at equilibrium, because it would not take part in producing the folded polymer.

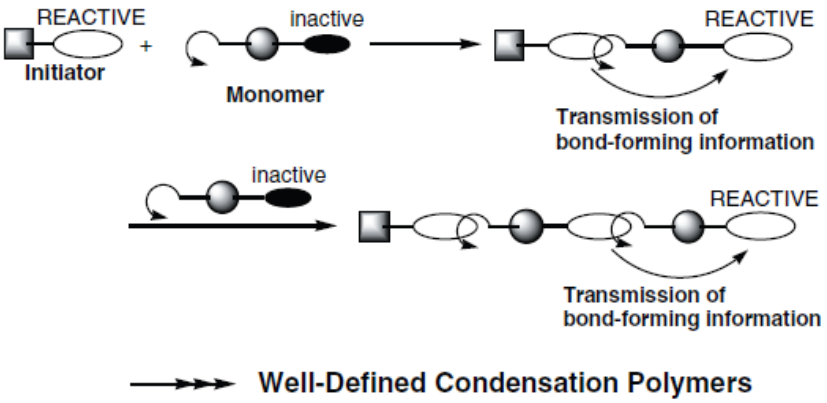


Scheme 6.6 Polymerization of m-phenyleneethynylene (mPE) by a nonstoichiometric route.

6.2. Condensative chain polymerization

As emphasized above, the synthesis of well-defined step-growth polymer structures (ca. dispersity close to unity and access to block copolymers) is ruled out, the "most probable

distribution" approaching 2 at high conversion. A few years ago, however, the group of Yokozawa in Japan established that, by creating a difference in the reactivity of the functional groups of purposely designed monomers, the polymerization can be converted from a step-growth to a chain-growth mechanism. Because a low molar-mass by-product is extruded at each step, this type of polymerization was coined "condensative chain polymerization" (CCP). Based on this concept, several examples of polymers exhibiting a narrow MW distribution (though of moderate MW's) have been designed by CCP. In addition, various architectures, including block copolymers, star polymers, graft copolymers, etc., could be synthesized following a CCP route.[134] A key point is that polymer end groups are more reactive than monomers, so as to avoid monomer's self-reaction (Scheme 6.7).[135] Monomers thus selectively react with the polymer end group, which in turn becomes more reactive after a stimulation of bond-forming between the monomer and the polymer end group (or initiator at the first step).

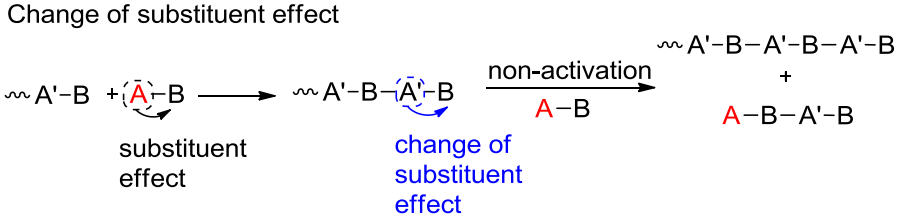


Scheme 6.7 Chain-growth polycondensation concept.

The four following strategies can be implemented to favor the selective reaction between the monomer and the polymer end-group.

6.2.1. Change of substituent effect

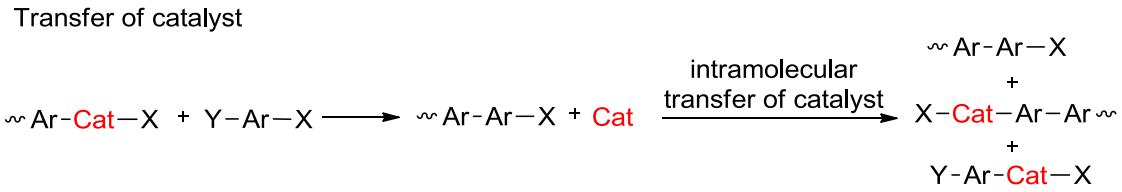
One method consists in the activation of the polymer end groups by playing with substituent effects between monomers and polymers, as in aromatic polyamides, polyesters, polyethers, poly(ether sulfone)s and poly(ether ketone)s (Scheme 6.8). In these cases, formation of a new functional linkage in monomer unit results in a steep change of reactivity of the polymer end groups, that is significantly enhanced compared to that of the monomer. [134b]



Scheme 6.8 Change of substituent effect in CCP.

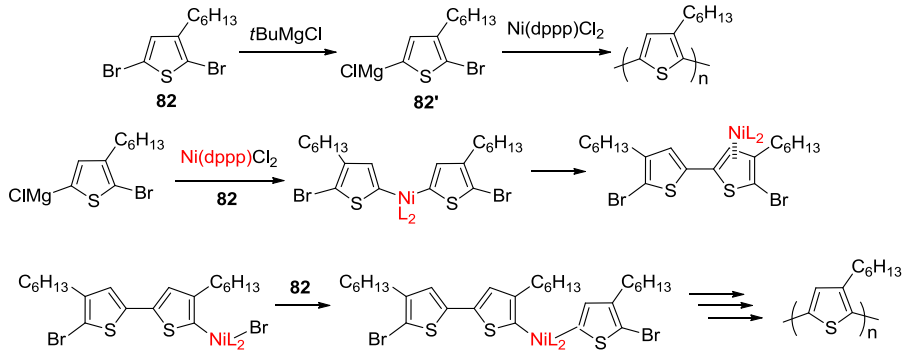
6.2.2. Transfer of catalyst

Another method aims at activating polymer end groups by intramolecularly transferring them to the catalyst, as in polythiophenes, polyphenylenes, polypyrroles and polyfluorenes (Scheme 6.9).[134b]



Scheme 6.9 Chain-growth polymerization by transfering catalyst intramolecularly.

For instance, the polymerization of A-B Grignard thiophene monomer (**82'**) with Ni(dppp)Cl_2 (dppp: 1,3-bis(diphenylphosphino)propane), at room temperature, to form polythiophene *via* chain-growth polymerization should be performed with care; an exact amount of isopropylmagnesium chloride for generation of monomer (**82'**) from (**82**) is required, as discussed in section 5.4.4.[117] After a detailed study of the polymerization of (**82'**), four important points were clarified: (1) the polymer end groups are uniform among molecules (one end group is Br and the other is H); (2) the propagating end group is a polymer-Ni-Br complex; (3) one Ni molecule forms one polymer chain; and (4) the chain initiator is a dimer of (**82'**) formed *in situ*. On the basis of these results, a catalyst transfer condensation polymerization mechanism has been proposed (Scheme 6.10). Thus, Ni(dppp)Cl_2 reacts with 2 eq. of (**82**), and the coupling reaction occurs with concomitant generation of a zero-valent Ni complex. The Ni(0) complex does not diffuse into the reaction mixture but is inserted intramolecularly into C-Br bond, thus moving to the polymer end group.

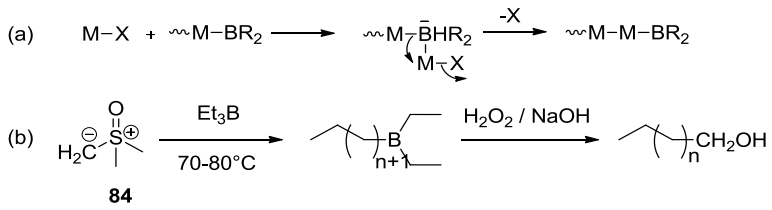


Scheme 6.10. Proposed mechanism for the chain-growth polycondensation.

6.2.3. Transfer of reactive species

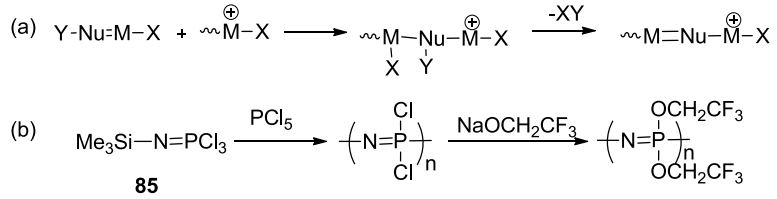
The third method is based on the transfer of the reactive species derived from the initiator to the polymer end groups and eliminate small molecules for certain specific elements.

The first category is that where propagation involves insertion of ylide monomer to the terminal M-BR_2 bond; the propagating end group and the initiator have the same structure and eliminate an X group (Scheme 6.11).[136]



Scheme 6.11. General scheme of chain-growth condensation polymerization of ylide with trialkylborane (a); polymethylene synthesized from the polymerization of (**84**) (b).

The second one is transfer of the cationic species stemmed from the initiator with a departure of XY group.[137] One typical example is the polymerization of trichloro(trimethylsilyl)phosphoranimine (**85**) with PCl_5, at ambient temperature, with elimination of trimethylsilyl chloride. The resulting poly(dichlorophosphazene) was treated with an excess of $NaOCH_2CF_3$ to give polymer depicted in Scheme 6.12.



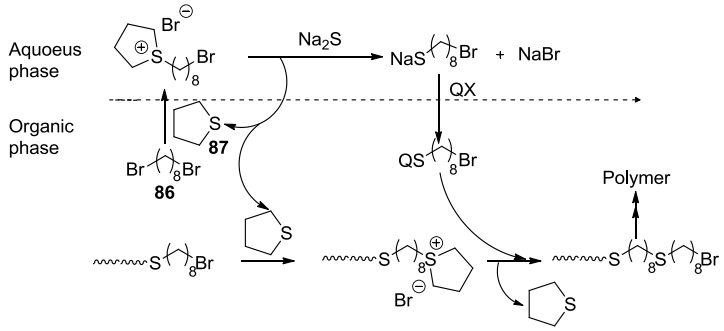
Scheme 6.12. Chain-growth condensation polymerization with transfer of cationic species stemmed from the initiator (a); synthesis of polyphosphazenes (b).

6.2.4. Phase-transfer polymerization

Finally, one can implement a phase-transfer polymerization consisting of a monomer storage phase and a polymerization phase, as in the synthesis of aliphatic polyesters and polysulfides.[2a] Because monomers are in their solid state, they cannot react with each other. With the aid of a phase-transfer catalyst, monomers can however be dispersed in the organic solvent and transferred to the solution phase where chain-growth polymerization starts.

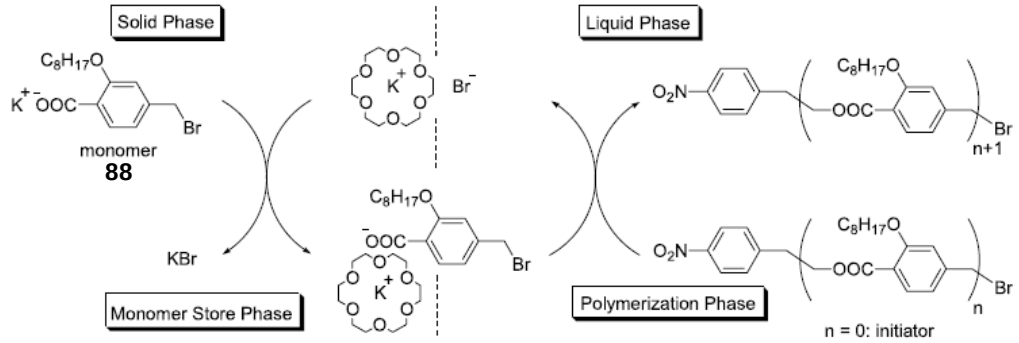
Shaffer and Kramer studied the phase transfer catalyzed-polymerization of sodium sulfide and a variety of α, ω–dibromoalkanes in detail.[138] They found that very high MW polythioethers with low dispersity (M_n = 683000; D = 1.24) were obtained when 1,8-dibromooctane (**86**) was used as a monomer, together with a catalytic amount of tetrahydrothiophene (THT) (**87**).[138] In the proposed polymerization mechanism, THT serves as an inverse phase transfer catalyst (PTC). THT reacted with (**86**) to afford a sulfonium salt, which reacts with sodium sulfide in the water phase. The resulting sulfide is extracted into the

organic phase as a quaternary ammonium salt of 8-bromooctyl sulfide, by virtue of the PTC QX. Last, the transferred ammonium salt adds onto the reactive sulfonium polymer chain end in the organic phase. This chain-end sulfonium is indeed electrophilically more reactive than the monomer (Scheme 6.13).



Scheme 6.13 Phase-transfer-catalyzed polymerization to synthesize polysulfides from sodium sulfide and 1,8-dibromooctane (**86**).

Another example is given by the phase-transfer polymerization of potassium 4-bromomethyl-2-octyloxybenzoate, (**88**), a solid monomer, in the presence of 18-crown-6 as a PTC and 4-nitrobenzyl bromide as the initiator in acetone (Scheme 6.14).[139] In the proposed mechanism, the solid state of (**88**) would prevent the reaction of monomer molecules with each other, and the monomer dissolving in an organic solvent with the aid of a PTC in a certain amount would react with an initiator and the polymer end group in the solution phase.



Scheme 6.14 Phase-transfer catalysis for chain-growth polymerization.

7. Concluding remarks

The first part of this bibliographic survey has focused on basic principles of step-growth polymerization and traditional step-growth polymers, including polyesters, polyamides, polyimides, poly(arylene ether), polyurethanes or polyepoxies. A wide variety of macromolecular structures –mostly used as high performance polymeric materials- can be produced in this way. However, the lack of available monomers for specific reactions can sometimes limit the commercial development of step-growth polymers. Both techniques and synthetic methods in traditional step-growth polymers have developed significantly since

Carother's early works.

Besides process improvements and intensification, the last two decades have witnessed a renaissance of step-growth polymerization, through the development of new synthetic strategies or new process developments and/or utilizing monomers/functionalities. For instance, synthesis of particles at the sub-micron size range of various step-growth polymers (e.g. polyesters, polyamides, polyurethanes, etc) can be achieved by non-aqueous dispersion polymerization.[140] Replacement of metal-based catalysts by enzymatic or organic catalysts in some step-growth polymerization reactions is another emerging field. In order to decrease our dependency on petroleum feed stocks, bio-sourced synthons arising from plants have also been investigated as new monomers for bio-based step-growth polymers.[38]

By no means, this overview could be complete; due to space limitations, important aspects have been omitted. For instance, synthesis of dendrimers and hyperbranched polymers that are two special classes of step-growth polymers has not been covered.[141] Likewise, supramolecular polymerization, another important method of non-conventional step-growth polymerization where monomer units are held together by non-covalent interactions, has not been discussed.[142]

On the other hand, numerous elementary reactions of molecular chemistry, which had been so far overlooked in polymer chemistry, have been adapted in step-growth polymerization of purposely designed monomers. Representative examples of such trends have been discussed in the second part of this chapter. There are probably still a lot of elementary molecular reactions that have not yet been examined in polymer chemistry, thus leaving plenty of room for novel breakthroughs in this field.

In this PhD thesis work, we propose three different innovative developments in the field of step-growth polymerization based on diverse aldehyde-containing monomers. Each of them will be the topic of a particular chapter. Thus, in chapter II, bis-aldehyde monomers are employed as acceptor-type monomers to be reacted with bis-ketones monomers acting as donor-type monomers, forming unprecedented polyaldols *via* repeated elementary aldolization reactions. Chapter III discusses the synthesis of cleavable polybenzoins grown by step-growth polymerization of bis-aldehydes catalyzed by chiral and non-chiral *N*-heterocyclic carbenes. Chapter IV is dedicated to the design of novel acid-sensitive hyperbranched polyacetals with a degree of branching of 100%. Here again, bis-aldehydes serve as synthons to be readily derivatized into hydroxyl-aldehyde–containing monomers undergoing an acid-catalyzed polycondensation forming perfectly branched hyperbranched polyacetals.

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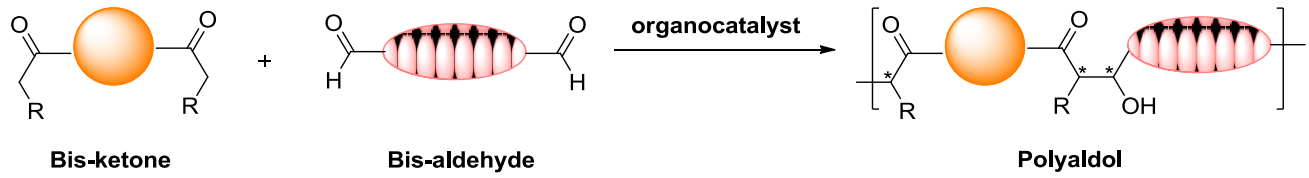
Chapter II

Polyaldol Synthesis by Direct Organocatalyzed Polyaldolization of Bis-ketones and Bis-aldehydes

Chapter II. Polyaldol Synthesis by Direct Organocatalyzed Polyaldolization of Bis-ketones and Bis-aldehydes



Bis-ketone **Bis-aldehyde** **Polyaldol**

Keywords: Bis-ketone, Bis-aldehyde, Polyaldolization, Organocatalysis, Polycondensation

Mots clés : Bis-cétone, Bis-aldéhyde, Polyaldolisation, Catalyseur organique, Polycondensation

Chapter II. Polyaldol Synthesis by Direct Organocatalyzed Polyaldolization of Bis-ketones and Bis-aldehydes

1. Introduction

As highlighted in the first chapter, numerous elementary reactions of molecular chemistry have been applied in step-growth polymerization. Most of these polymerizations employ metallic catalysts. Replacement of such metal-based catalysts by enzymatic or organic catalysts in some key polymerization reactions is another emerging field.[1] Among organic catalysts employed for the purpose of polymer synthesis, *N*-heterocyclic carbenes (NHCs), dialkylaminopyridines, guanidines, strong Bronsted acids, phosphazenes and thiourea derivatives are the most popular.[2]

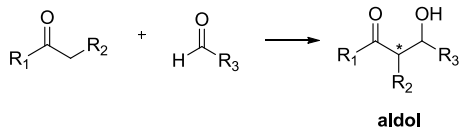
The objective of this PhD thesis was to investigate specific step-growth polymerization reactions involving aldehyde-containing monomers, following an organocatalytic pathway. In this chapter, we report on how properly selected bis-aldehyde monomers can react with bis-ketones *via* organocatalyzed aldolization reactions, to yield novel polyaldols –made of β-ketoalcohol units-. To the best of our knowledge, though the direct intermolecular aldol reaction between an enolizable ketone and a non-enolizable aldehyde has been extensively investigated in the past decades, its direct application in polymer chemistry has not yet been considered.

This part of polyaldolization work has been accomplished in close collaboration with the group of Professor Yannick Landais at ISM (Institut des Sciences Moléculaires, Université Bordeaux 1) in the frame of an ANR Program called CHIRPOL. In particular, the synthesis of bifunctional monomers, i.e. bis-aldehydes and bis-ketones used for polyaldol synthesis, has been performed by Anthony Martin during his PhD thesis (defended in December 2012).

In the following lines, essential features of the aldolization reaction are first introduced, with a special focus on typical reaction partners and types of catalysts. An overview of polymers exhibiting structural features of polyaldols along with related synthetic methods will then be given. The objectives of this part of the work and main results obtained are next presented.

2. The aldol reaction

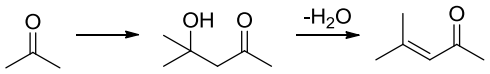
The name aldol actually originates from the contraction between *ald*ehyde and alcoh*ol*, the two chemical functions found in the product of the aldol reaction. This C-C bond forming reaction is extremely popular in molecular organic chemistry, as an atom-economic synthetic method.[3] There are also numerous naturally occurring compounds featuring the aldol moiety.[4] Originally involving only an aldehyde and a ketone as substrates, or two identical molecules, the term aldolization has been generalized to the reaction of any enolizable carbonyl-containing reagent with the carbonyl group of an aldehyde or a ketone (Scheme 1).[5] The enolate thus behaves as a nucleophile, while the second molecule exhibits the reactivity of an electrophile.



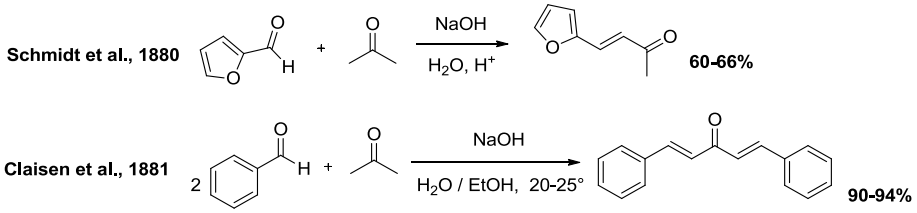
Scheme 1. Direct aldolization of a ketone and an aldehyde.

The aldol reaction results in the formation of a β-hydroxy aldehyde (or ketone). It can take place either intra- or intermolecularly. An asymmetric carbon atom being created during the reaction, control of the stereochemistry of the reaction has been the focus of extensive studies.[6]

The aldol adduct can undergo a dehydration (called crotonization) and be directly converted *in situ* to the α,β-unsaturated carbonyl derivative, the driving force being the formation of a conjugated system (Scheme 2). This elimination reaction can be induced either thermally or under acidic or basic catalysis. This dehydration can also occur spontaneously, preventing the isolation of the aldol product, the whole process being a condensation reaction. The first example of aldolization/crotonization reaction was reported by Kane et al. in 1838,[7] with the self-condensation of acetone giving the 4-methyl-3-penten-2-one (Scheme 2). The first aldolization carried out under basic conditions was independently described by Schmidt et al.,[8] and Claisen et al.[9] (Scheme 3). Wurtz et al. established the presence of both the aldehyde and alcohol functions in the product of the acid-catalyzed self-condensation of acetaldehyde.[10]

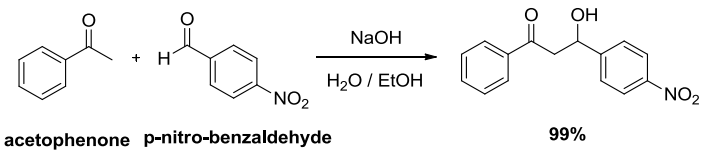


Scheme 2. Synthesis of 4-methyl-3-penten-2-one *via* self- aldol condensation of acetone.



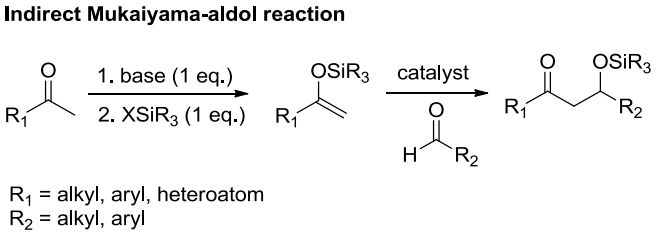
Scheme 3. The first examples of aldol reaction.

To avoid the formation of a complex mixture, it is preferable to employ a non-enolizable electrophilic aldehyde (or ketone) and to react it with an enolizable nucleophilic ketone. A typical example of such an intermolecular cross aldolization reaction involves the reaction between acetophenone and p-nitro-benzaldehyde (Scheme 4).[11]



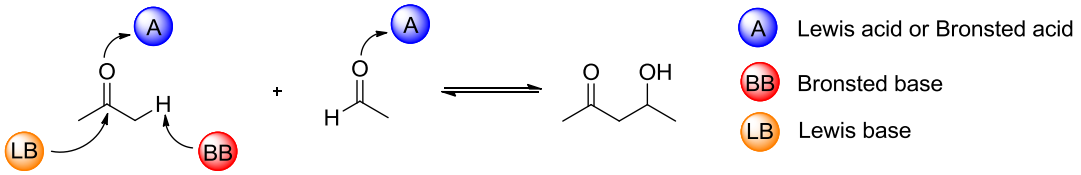
Scheme 4. Aldolization of p-nitro-benzaldehyde with acetophenone.

Formation of a nucleophilic enolate derivative, prior to its reaction with the electrophilic aldehyde, is also common and refers to as the indirect aldolization reaction. Use of silylated precursors such as silyl enol ether has been extensively studied, the reaction being referred to as the Mukaiyama-aldol reaction (Scheme 5).[12]



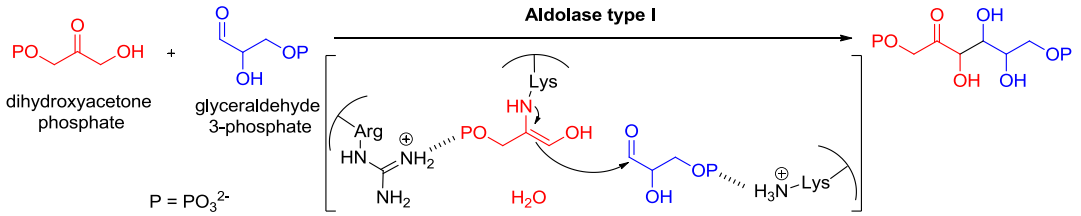
Scheme 5. Indirect Mukaiyama aldolization.

The main advantage of the direct aldolization is to use a catalyst and unmodified ketones. Various catalysts have been investigated, including Bronsted and Lewis acids and bases (Scheme 6).[13]



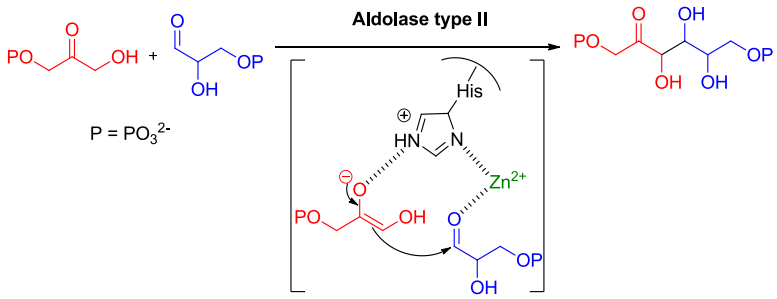
Scheme 6. Strategies for aldolization activation.

Naturally occurring enzymatic catalysts, such as aldolases of type I, that can be found in some plants and mammals, can trigger aldol formation, *via* a cooperative stereo specific mechanism, involving a Lewis base and an acid (Scheme 7).[14] The ketone is here activated by a lysine residue *via* the formation of an enamine.



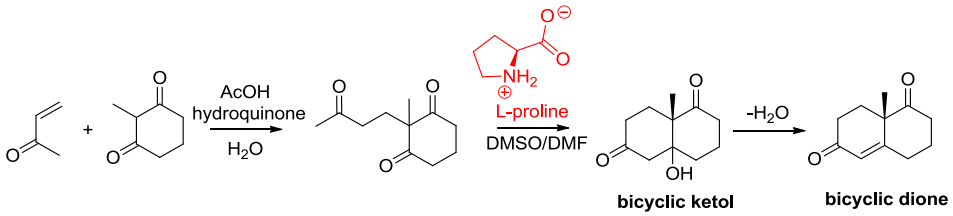
Scheme 7. Addition of dihydroxyacetone phosphate to glyceraldehyde 3-phosphate catalyzed by aldolase of type I.

As for aldolases of type II,[14] they require the use of a zinc(II) cofactor as a Lewis acid to activate the aldehyde substrate, while enolization of the ketone is favored by an histidine residue (Scheme 8).



Scheme 8. Addition of dihydroxyacetone phosphate to glyceraldehyde 3-phosphate catalyzed by aldolase of type II.

Besides enzymes, use of chiral catalysts has allowed spectacular achievements for highly enantioselective aldolization of prochiral substrates; this has led to the asymmetric synthesis of a variety of natural derivatives.[3b,6] Although asymmetric organometallic catalysts have been initially developed, some organic molecules have also proven powerful asymmetric catalysts for the aldolization reaction, mimicking the *modus operandi* of enzymes.[15] A representative example is the synthesis of the Wieland-Miescher ketone, a bicyclic diketone (enedione) developed in 1970 at an industrial scale, *via* an enantioselective organocatalytic aldol process, employing L-proline as chiral organocatalyst (Scheme 9).[16] This reaction was first reported by Hajos and Parrish in 1971,[17] and the reaction is known as the Hajos-Parrish-Eder-Sauer-Wiechert reaction.[18] The optically active intermediate bicyclic ketol could be isolated, when the reaction was performed at room temperature in anhydrous dimethylformamide. In contrast, use of DMSO as solvent does not allow isolation of the bicyclic ketol intermediate, and directly leads to the optically active bicyclic dione.[16]



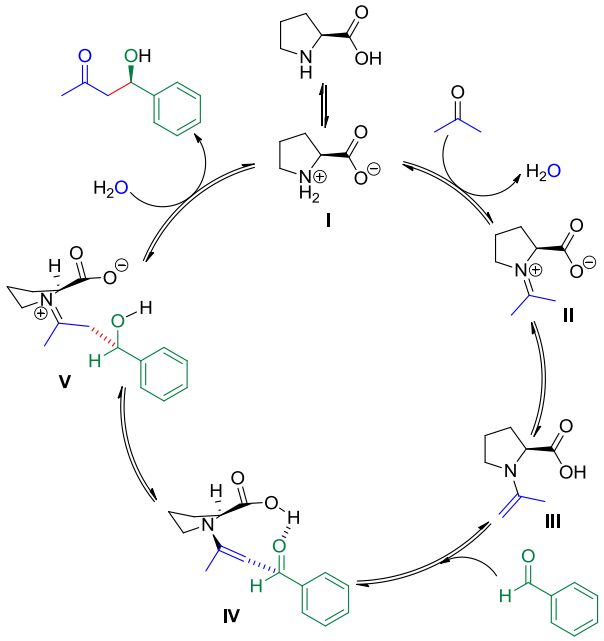
Scheme 9. Synthesis of Wieland-Miescher ketone using L-proline.

The Wieland–Miescher ketone is an important industrial synthon that is employed in the total synthesis of many natural products, such as sesquiterpenoids, diterpenes and steroids. For instance, the optically active enantiomer serves as precursor for ancistrofuran[19] and the Danishefsky total synthesis of Taxol.[20] However, the original Wieland–Miescher ketone prepared by Robinson annulation of 2-methyl-1,3-cyclohexanedione and methyl vinyl ketone, is racemic and the intermediate alcohol is not isolated.[21]

Almost 30 years after the Hajos-Parrish-Eder-Sauer-Wiechert reaction was disclosed, Barbas, List et al. extensively (re)investigated aminoacids, for the purpose of asymmetric organocatalyzed aldol reaction.[22] They have in particular established that the success of the L-

proline-catalyzed aldol reaction, in terms of enantioselectivity and yield, dramatically depends on reaction parameters, such as the ratio of ketone / aldehyde and the nature of the aldehyde partner. Use of large excess of ketone and a relatively high loading of catalyst (30% mol) are generally required.

The catalytic cycle of the aldol reaction involving L-proline as catalyst, generates an iminium **II** and enamine intermediates **III**, as shown in Scheme 10.[23]



Scheme 10. Catalytic cycle of aldolization catalyzed by L-proline.

Representative examples of metal-based and organic catalysts used in the aldol reaction are provided in Figure 1.

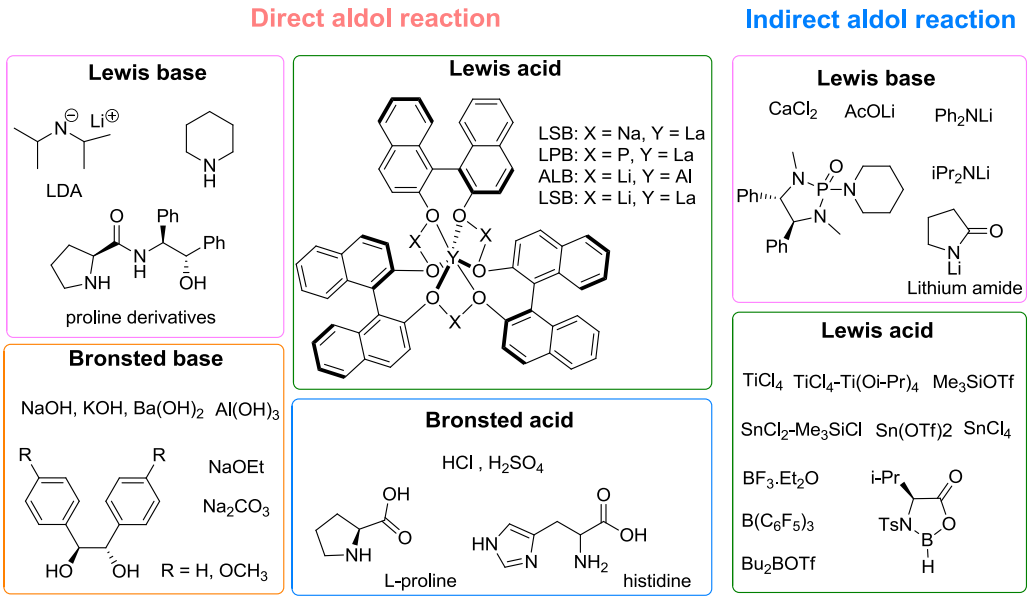
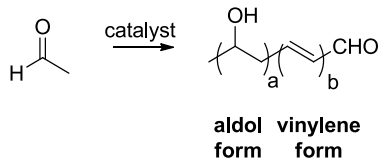


Figure 1. Representative catalysts of the aldol reaction.

In this chapter, we describe the first examples of the direct polyaldolization reaction between bis-aldehydes and bis-ketones, as a means to synthesize novel polyaldols by an organocatalytic pathway. Very surprisingly, indeed, the application of the intermolecular aldol reaction in polymer chemistry has not been investigated.

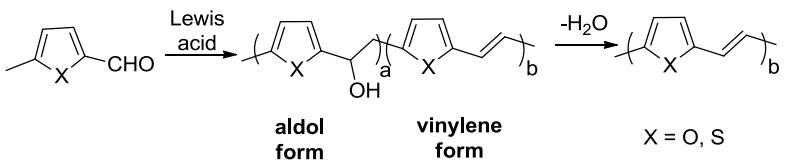
3. Examples of polyaldols previously reported in the literature

A few examples of polyaldol synthesis, by repetition of aldol condensation reactions (= polyaldolization), have however been reported. It is worth pointing out, that most examples deal with the self-polymerization of aldehydes or ketones, with the aid of various types of catalysts, such as Bronsted acids or bases, metal or alkali metal amalgams, or transition metal-based catalysts. Related works were pioneered in the early 1960's. For instance, self polyaldolization of acetaldehyde catalyzed by Na/Hg amalgam or amines or transition metals can lead to poly(vinyl alcohol).[24] As depicted in Scheme 11, the polymer also contains vinylene units, due to partial dehydration (crotonisation) of vinyl alcohol units.



Scheme 11. Self-polyaldolization of acetaldehyde forming poly(vinyl alcohol) and vinylene units.

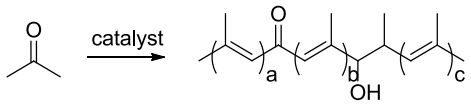
The latter feature was further exploited to derive π-conjugated polymer materials exhibiting an electronic conductivity. For instance, by directly polymerizing 5-methylfuran-2-carbaldehyde *via* a self-polyaldolization pathway, the polyaldol precursor readily yielded a stable poly(2,5-furan-diylvinylene) by dehydration (Scheme 12, X = O).[25] After doping the π-conjugated polymer compound with Lewis acids, the electrical conductivity could be varied from 10^{-8} to $1.5x10^{-2}$ Scm^{-1}. Kreja et al. further applied this approach to synthesize poly(2,5-thienylenevinylene) (Scheme 12, X = S) and related copolymers.[26]



Scheme 12. Synthesis of π-conjugated polymers *via* polyaldolization followed by dehydration.

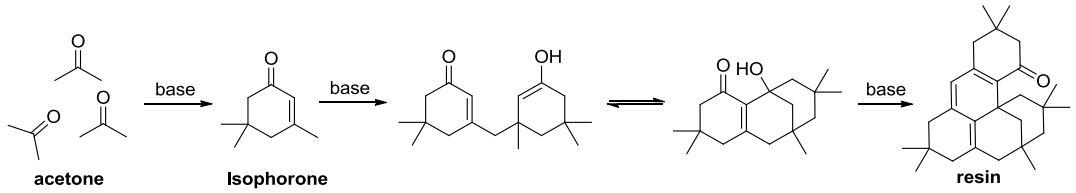
Cataldo reported that acetone yielded a solid resin *via* polyaldolic condensation when polymerized in the presence of strong Bronsted acids, such as H_2SO_4 or CF_3SO_3H, as well as Lewis acids such as $AlCl_3$ (Scheme 13).[27] It was proposed that the polymer structure resembled

that of poly(methylacetylene) possessing functional groups in the main chain, such as carbonyls and hydroxyls.



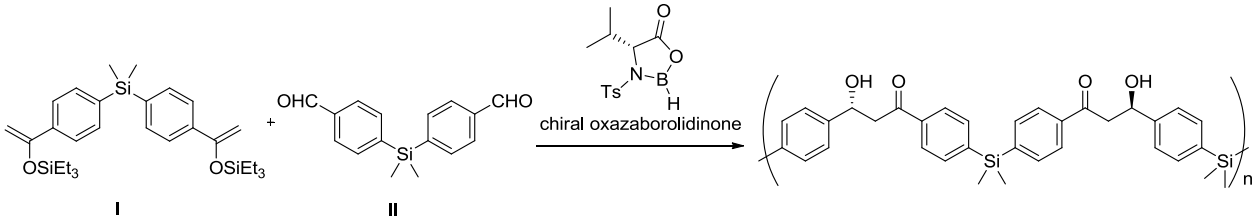
Scheme 13. Poly(methylacetylene) type of polymer synthesized via polyaldolization of acetone.

Upon using bases (e.g. NaOH or NaOEt) instead of acids to trigger the polymerization of acetone, the same author obtained a different liquid resin (Scheme 14).[28] It was shown that isophorone was first obtained while the formation of the resin eventually resulted from the condensation of acetone with isophorone and the self-condensation of isophorone.



Scheme 14. Liquid resin synthesized from self-condensation of acetone and isophorone under basic condition.

An indirect synthetic pathway to polyaldols was also developed by the group of Itsuno, as discussed in chapter I (section 5.2.1).[29] The method is based on repeated Mukaiyama-aldol reactions between bis(silylenolether) and bis-aldehyde monomers (Scheme 15). Interestingly, specific chiral Lewis acids allowed synthesizing optically active polyaldols by asymmetric step-growth polymerization, the chiral information being transferred from the catalyst to each monomer unit.[30]



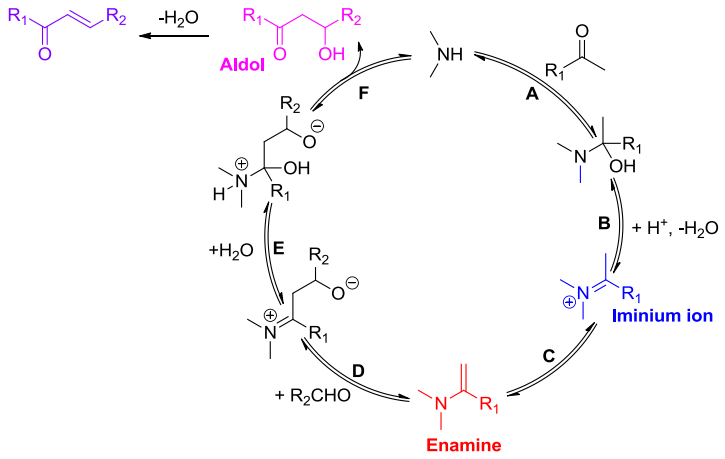
Scheme 15. Asymmetric Mukaiyama aldol polyaddition of dialdehyde **II** and bis(silyl enol ether) **I**.

4. Aim of the present work

In this part of this PhD work, we have developed a novel synthetic strategy to polyaldols by repetition of direct intermolecular aldolization reactions between properly selected bis-aldehyde and bis-ketone monomers. These polyaldolization reactions were triggered *via* an organocatalyzed pathway, utilizing pyrrolidine in conjunction with acetic acid. The influence of different parameters on the polyaldolization reaction, such as solvent effects, the nature and the

amount of the catalyst, the concentration of monomers, was investigated to gain an insight into factors controlling these unprecedented polyaldolizations.

To the best of our knowledge, although the amine-catalyzed direct intermolecular aldol reaction involving an enolizable ketone and an aldehyde is extremely well documented (Scheme **16**), the application of this elementary reaction in polymer synthesis to achieve polyaldols has never been reported. We have shown that this method leads to polymers, consisting of β-ketoalcohol monomer unit that is polyaldols, the structure of which has been investigated by NMR spectroscopy. The propensity of aldol monomer units to dehydrate (crotonization) and form unsaturations in the main chain is also discussed.

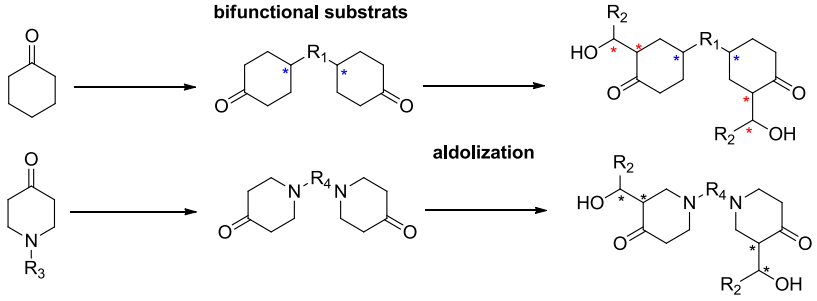


Scheme 16. Amine-catalytic cycle of direct aldolization.

5. Design of bis-aldehydes and bis-ketones as bifunctional monomer substrates

5.1. Preparation of bis-ketone and bis-aldehyde monomers

Direct polyaldol synthesis requires antagonist bifunctional monomers of sufficient reactivity to implement aldol reactions under stoichiometric conditions. Furthermore, the aldol reaction creating a stereogenic centre, it is also preferable to employ substrates free of stereogenic centers before reaction, for sake of simplicity. For instance, *N*-substituted bis-piperidinones were preferred over bis-cyclohexanones as potential monomers (Scheme 17), the latter substrates featuring two additional asymmetric carbon atoms, making NMR analysis of related polyaldols more complex.



Scheme 17. Comparison of the aldol products obtained from cyclohexanone and piperidinone.

In addition, aldehydes should obviously not self-dimerize (or self-polymerize) under the reaction conditions; hence they should be non-enolizable. Monofunctional ketones and aldehyde models have obviously inspired the synthesis of the bifunctional monomer substrates. Aldehydes carrying electron withdrawing groups such as $-NO_2$ **2**, **4** (Figure 2) or ester group **3** (Figure 2) have been favored since their electrophilicity is enhanced. In contrast, ketones are expected to behave as nucleophilic partners and should thus feature an enolizable proton (methylene or methyl group) in α–position of the carbonyl group **1** (Figure 2). Self-condensation of the ketone should also be avoided here while the cross-reaction with the electrophilic aldehyde should be favored.

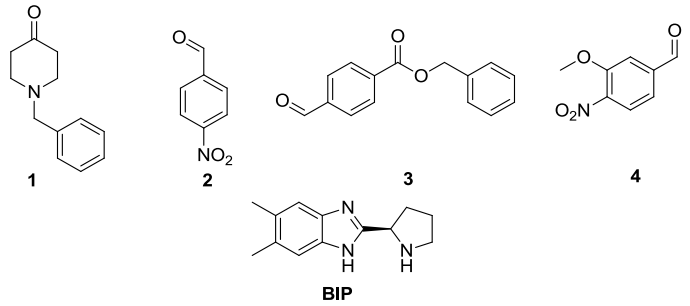
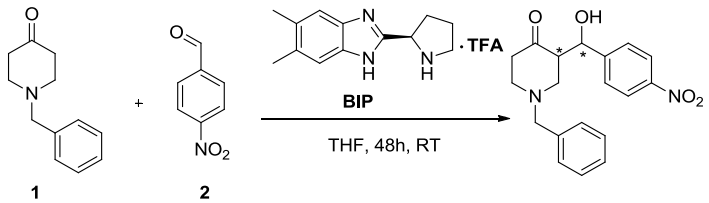


Figure 2. Monofunctional ketone and aldehyde models and BIP catalyst used for asymmetric aldol reaction.

Lastly, further dehydration of the aldol product under the reaction conditions to form C=C double bonds, has also to be taken into account; this can be easily monitored by spectroscopic techniques.

With these pre-requirements in mind, screening of both monofunctional model aldehyde and ketone substrates (Figure 2) that could expectedly mimic the reactivity of bifunctional homologues was achieved at ISM, University of Bordeaux (part of Anthony Martin's PhD thesis under the supervision of Prof. Yannick Landais). Representative bisaldehyde **3** and bisketone **5** reaction partners are shown in Figure 3. It is important to note that use of a particular catalyst, namely, benzimidazole-pyrrolidine (BIP) in combination with trifluoroacetic acid, was selected to trigger asymmetric aldolization reactions. For instance, reaction of piperidinone **1** with the aldehyde **2** at stoichiometry gave rise to a relatively high diastereotioselectivity (anti/syn = 8.7/1), and an aldol yield up to 82%, when catalyzed by BIP/ trifluoroacetic acid (TFA), after 48h in THF (Scheme 18). In the context of polyaldolization reactions further discussed, only nonchiral amine organic catalysts were tested.[31]



Scheme 18. Model asymmetric aldol reaction of ketone **1** and aldehyde **2** catalyzed by BIP/TFA.

5.2. Synthesis of bis-ketones and bis-aldehydes monomers

The bifunctional homologues were also designed at ISM. Selected bis-ketones and bis-aldehydes are shown in Figure 3.

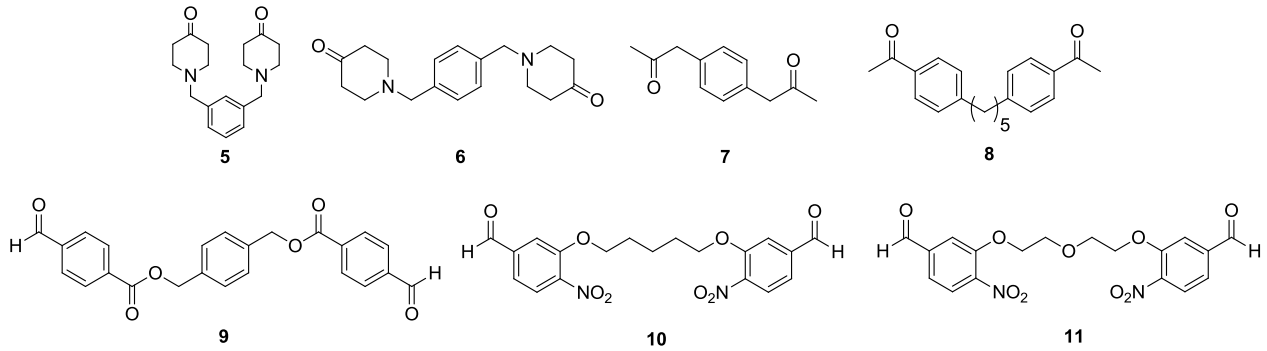
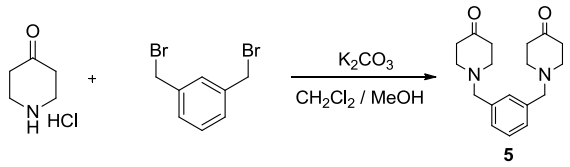


Figure 3. Bis-ketones and bis-aldehydes investigated in this chapter.

A typical synthesis is illustrated below for bis-ketone **5** and bis-aldehyde **9**. For instance, piperidinone hydrochloride was treated with K_2CO_3 in the presence of 1,3-bis(bromomethyl)benzene, giving the bis-ketone **5** with a yield of 89% (Scheme 19). Bis-ketone **6** was obtained with a yield of 71% using the same method. ^{1}H NMR spectrum of bis-ketone **5** is shown in Figure 4. Signals corresponding to the piperidinone (C and D), and those of the 1,3-bis(bromomethyl) benzene (A and B) appearing a 16 / 8 ratio, in agreement with the bis-piperidinone (bromomethyl) benzene structure of **5**. Moreover, proton B shifted from 4.45 ppm in 1,3-bis(bromomethyl) benzene to 3.63 ppm in **5**.



Scheme 19. Synthesis of bis-ketone monomer **5**.

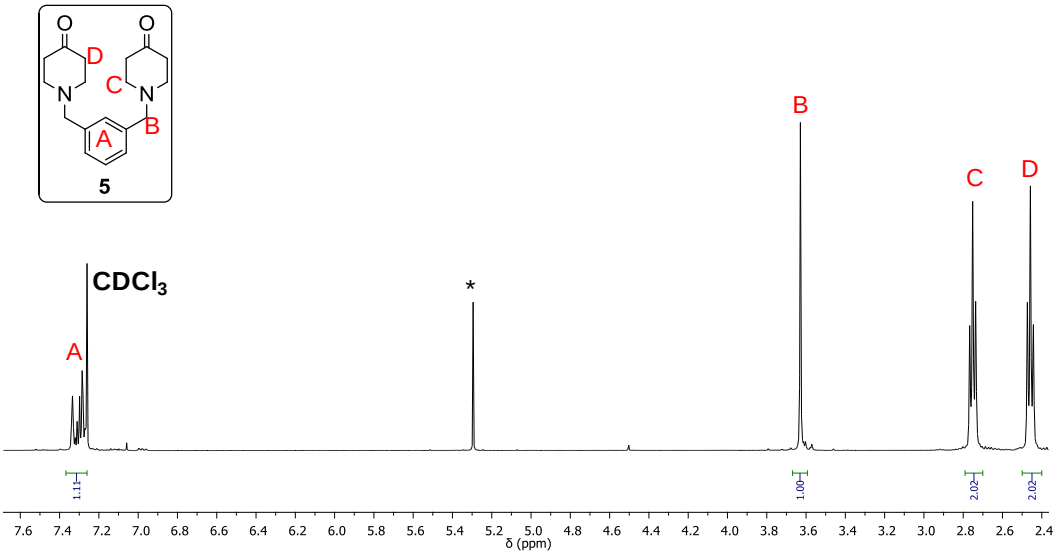
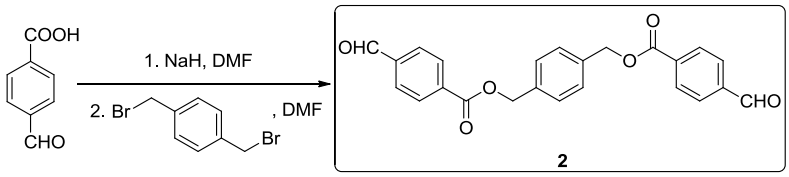


Figure 4. ^{1}H NMR (400 MHz, $CDCl_3$) of bis-ketone monomer **5**; * = residual CH_2Cl_2.

Monomer **9** featuring an ester function was also purposely designed. Its synthesis involved a one step reaction between sodium 4-formylbenzoate and bis(chloromethyl)benzene in DMF (Scheme 20). After purification by flash chromatography, compound **9** was obtained as a white solid in good yield (76%). The aldehyde proton (C*H*O) peak I was found at 10.10 ppm, while the two doublets signals due to para heterodisubstituted aromatic moiety, E and F, appeared at 8.23 and 7.97 ppm (J = 8.2 Hz). Aromatic proton G was observed at 7.50 ppm as a singlet signal. The methylene protons of the ester group (CH_2OC=O) was detected at 5.41 ppm. The integral ratio of these peaks is 2 / 8 / 4 / 4, in accordance with the structure of monomer **2** (Figure 5).



Scheme 20. Synthesis of bis-aldehyde **9** containing an aromatic-ester group.

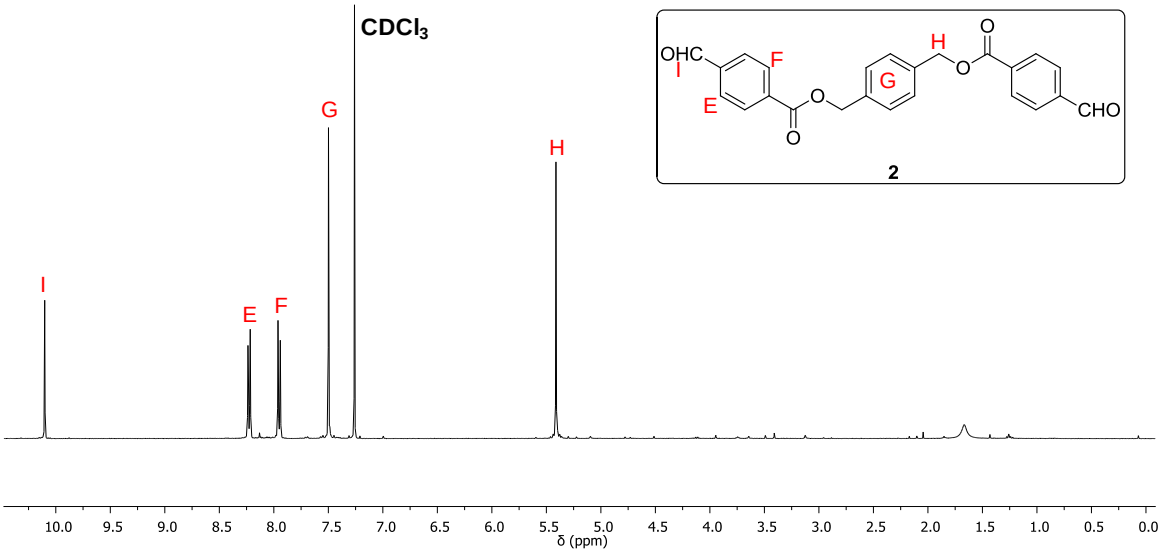


Figure 5. ^{1}H NMR (400 MHz, $CDCl_3$) of monomer **2** aromatic ester-contained bis-aldehyde.

6. Organocatalyzed polymerization of bis-aldehydes and bis-ketones

6.1. Synthesis of polyaldols from the bis-piperidinone 5 and the bis-aldehyde 9

Being soluble in THF, both the bis-piperidinone **5** and the bis-aldehyde **9** were first selected as reaction partners for a screening of reaction conditions of the polyaldolization, at room temperature (RT). Table 1 summarizes these preliminary investigations. Various cyclic and acyclic secondary and tertiary amines (Figure 6) were tested as organic catalysts. However, acyclic secondary amines, such as diisopropyl amine, and tertiary amines such as triethylamine and diisopropyl ethylamine, proved inefficient to promote the polymerization, even after 5 days at RT. Similarly, cyclic secondary amines such as the six-membered rings morpholine and

piperidine, did not show any noticeable catalytic activity, in spite of the ability of such amines to catalyze the aldol reaction *via* enamine or iminium type activation (entries 1-5, Table 1).[3a,b]

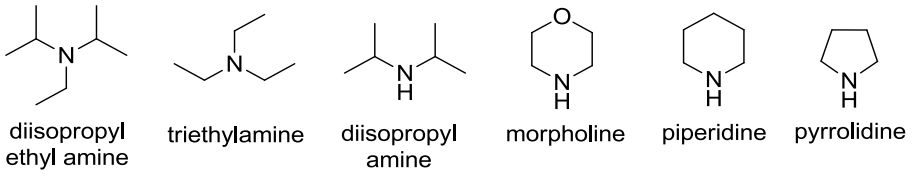
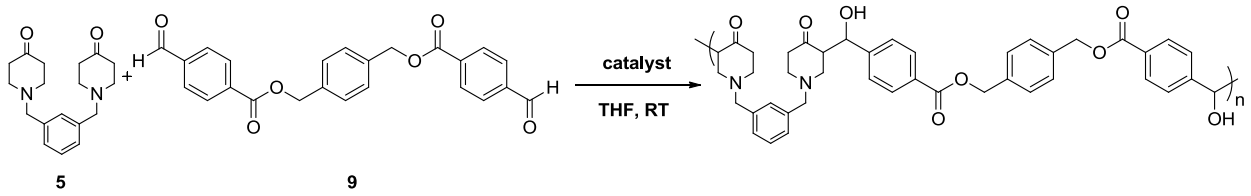


Figure 6. Amine catalysts investigated in this work.

Table 1. Screening of catalysts and reaction conditions for the polyaldolization in THF at 25 °C between the bis-piperidinone **5** and the bis-aldehyde **9**.



entry	[M] (mol/l)[a]	catalyst (0.3 eq)	AcOH (eq)	time (d)	$\overline{M}_n$ (g/mol)[b]	$\overline{M}_w$ (g/mol)[b]	D[b]	$\overline{M}_n$ (g/mol)[d]	$\overline{M}_w$ (g/mol)[d]	D[d]
1	0.5	Diisopropyl amine	none	5	-[c]	-	-	-	-	-
2	0.5	morpholine	none	5	-[c]	-	-	-	-	-
3	0.5	triethylamine	none	5	-[c]	-	-	-	-	-
4	0.5	piperidine	none	5	-[c]	-	-	-	-	-
5	0.5	diisopropyl ethyl amine	none	5	-[c]	-	-	-	-	-
6	0.5	pyrrolidine	none	3	nd 2360	3600 [e] 3570	nd 1.51	6,700	12,900	1.9
7	0.5	pyrrolidine	1.5	3	nd 2570	5400 [e] 4330	nd 1.68	7,800	20,400	2.6
8	1	pyrrolidine	1.5	3	nd 2860	8050 [e] 5460	nd 1.90	11,100	54,700	4.9
9	Only 1mol/L of **5** [f]	pyrrolidine	1.5	10	trimer	-	-	-	-	-

[a] concentration of monomers **5** and **9**. [b] molecular weights and dispersity determined by SEC in THF (calibration using polystyrene as standards). [c] only oligomers are formed. [d] molecular weights and dispersity of precipitated polymers after 5 days of reaction, as determined by SEC in DMF (calibration using polystyrene as standards). [e] peak molecular weights correspond to the first peaks observed by SEC. [f] A blank test with only bis-piperidinone **5** as monomer was investigated, that the monomer concentration is 1 mol/L.

In contrast, a closely related five membered ring cyclic secondary amine, namely, pyrrolidine was found catalytically active, though a rather high loading of 30 mol% relative to

monomers was required. Under such conditions, polymers with M_w = 12,900 g/mol and a dispersity (D) of 1.9 (SEC in DMF, relative to PS standards, entry 6, Table 1) could be obtained after 3 days at RT. SEC traces of polymers synthesized in this way show multimodal distributions that were typical of a step-growth polymerization process. A control experiment under the same reaction conditions as entry 8, using bis-piperidinone **5** as monomer only (entry 9, Table 1), gave only oligomers after 10 days of reaction.

Interestingly, adding acetic acid as co-catalyst (150 mol% relative to monomers) allowed increasing the polymer molecular weight (M_w) up to 20,400 g/mol, after 3 days at RT, as illustrated in Figure 6 (red). The role of acetic acid would be to facilitate the nucleophilic addition of pyrrolidine onto the carbonyl group of the bis-ketone substrate, thus favoring the formation of iminium and ene-amine intermediates (Scheme 16 above).[32] Finally, polymers with M_w up to 54,700 g/mol could be achieved by increasing the catalyst concentration from 0.5 to 1M, in presence of 150 mol% of acetic acid as co-catalyst, as illustrated in Figure 7.

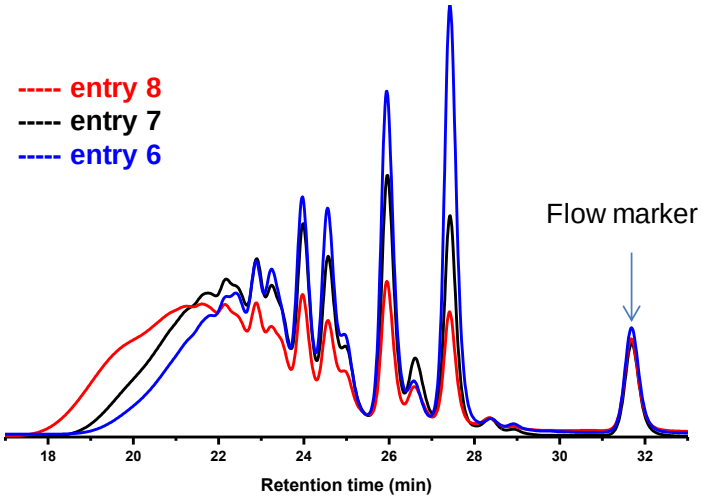


Figure 7. SEC traces in THF of polymers obtained from the polymerization of bis-piperidinone **5** and bis-aldehyde **9** at 25 ℃ in THF, in the presence of 30 mol% pyrrolidine as catalyst (blue curve, entry 6, Table 1) and [Monomers] = 0.5M; 30 mol% pyrrolidine and 150 mol% acetic acid as catalytic system and [Monomers] = 0.5M (black curve); 30mol% pyrrolidine and 150 mol% acetic acid as catalytic system and [Monomers] = 1M (red curve).

Representative ^{1}H and ^{13}C NMR spectra of a polymer derived from the organocatalyzed polymerization of bis-piperidinone **5** and bis-aldehyde **9** are shown in Figure 8.

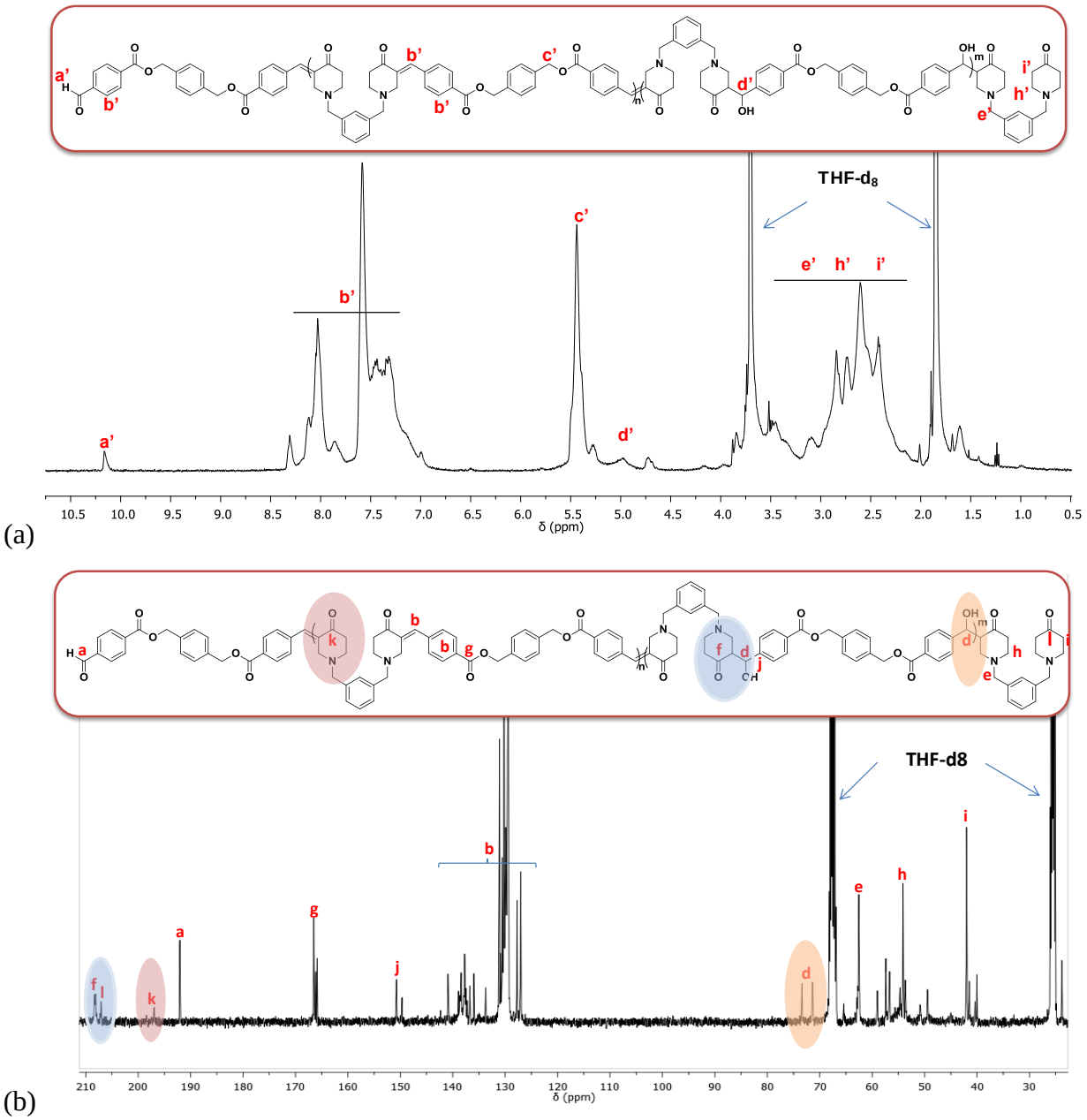
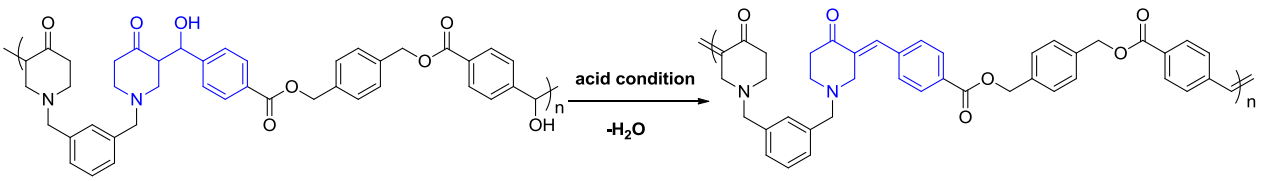


Figure 8. ^{1}H NMR and ^{13}C NMR spectra (THF-d_8) of polymer obtained from the polymerization of bis-piperidinone **5** and bis-aldehyde **9** (entry 6, Table 1).

Formation of aldol monomer units can be evidenced by ^{13}C NMR through the presence of characteristic signals, (f) and (d), at 208.2 and 73.4-71.4 ppm, respectively, corresponding to the ketone group and <u>C</u>HOH groups of the aldol moiety. The signal g at 166.1 ppm can be assigned to the main-chain ester functions, while the sharp peak (a) at 192.0 ppm is due to the presence of aldehyde end-groups. Noteworthy is the presence of a further ketone signal (k) at 196.9 ppm, that is, 11 ppm upshifted compared to the signal of carbon (f), and which corresponds to the carbon atom of an α,β-unsaturated ketone. These conjugated double bonds arise from partial dehydration (crotonization) of aldol monomer units, the enone being the thermodynamic product (Scheme 21).



Scheme 21. Vinylene form of polyaldol-**5**,**9** by dehydration under acid conditions.

The two signals appearing both in the ^{13}C and the ^{1}H NMR spectra correspond to the four diastereoisomers (RS, SR and RR, SS forms) generated by the aldol reactions. Analysis by two-dimensional NMR confirms the presence of these configurations (see Figure 9). It is interesting to note that the two signals appear at a significantly different chemical shift, which could be of practical use in view of further determining the diastereoisomeric excess of chiral polyaldols synthesized from asymmetric polymerization, in the presence of a chiral catalyst.

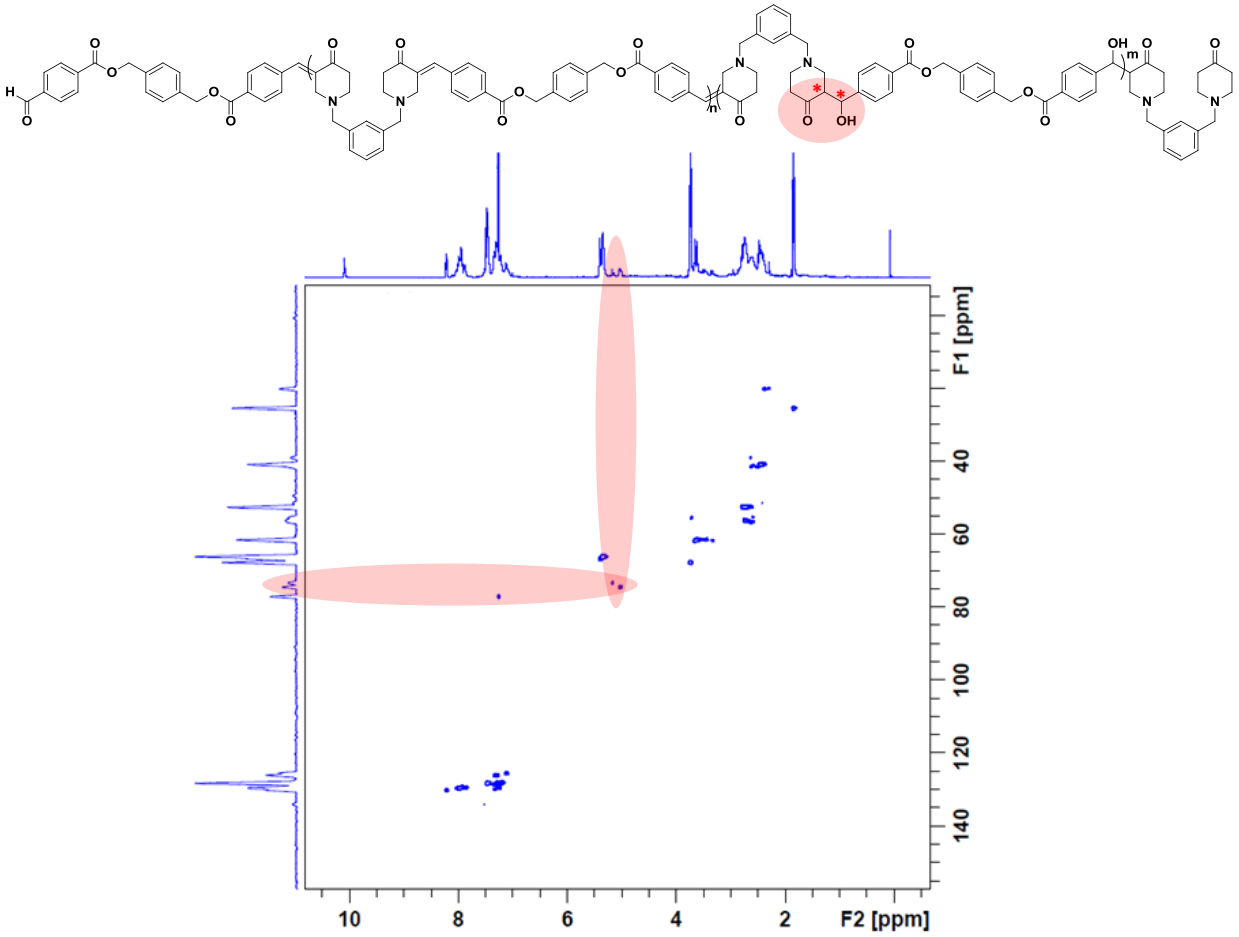


Figure 9. 2D NMR spectrum ($CDCl_3$) of polyaldol obtained from the polymerization of bis-piperidinone **5** and bis-aldehyde **9** (entry 6, Table 1).

6.2. Characterization of polyaldols by quantitative NMR, DSC and TGA

Quantitative analysis by ^{13}C NMR was used to determine the extent of α,β–unsaturated ketone double bonds. This percentage was calculated from the intensity of signals (k) and (f), using the following equation: $I_k = I_k/(I_k + I_f)$, where I is the intensity of corresponding signals measured by integration. For instance, the polyaldol obtained from monomers **5** and **9** (entry 6,

Table 1, Figure 10) was constituted of 20% of conjugated double bonds, as a result of the dehydration of the parent aldol units.

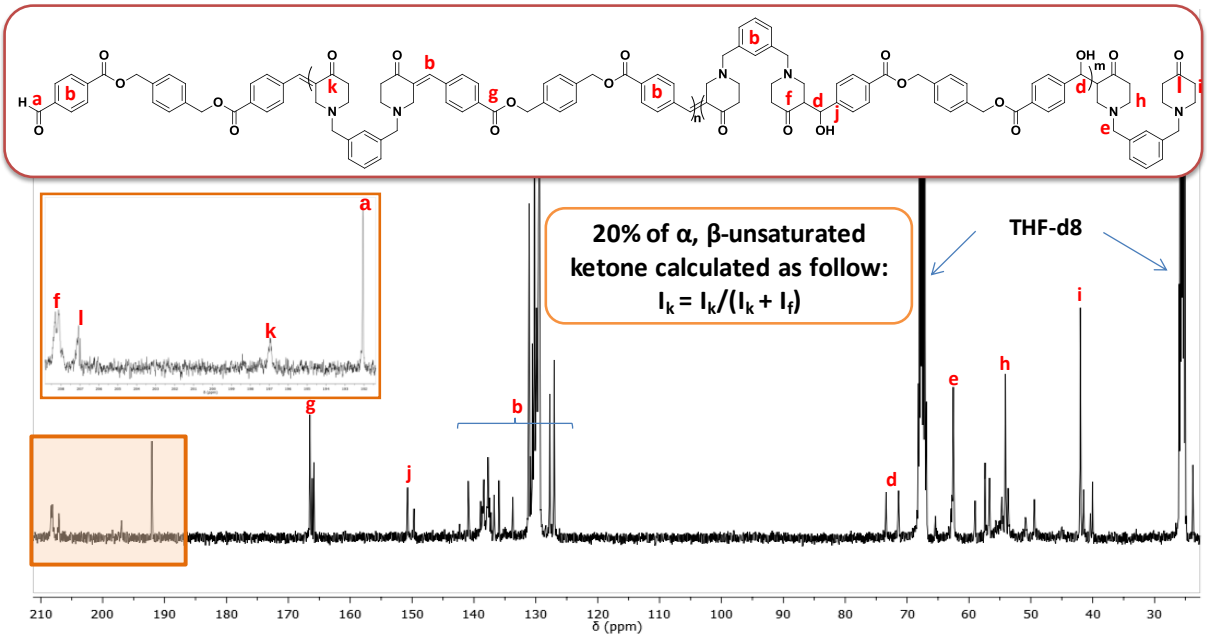


Figure 10. ^{13}C NMR spectra (THF-d_8) of polymer obtained from the polymerization of the bis-piperidinone **5** and the bis-aldehyde **9** (entry 6, Table 1).

Further analysis of the same polyaldol by DSC indicated the formation of an amorphous material, with a glass transition temperature of (T_g) equals to 32.9 ℃ after the second heating cycle (Figure 11). As for TGA, it showed an initial weight loss of the polymer at 100 ℃, presumably due to dehydration of aldol monomer units, while further degradation continued up to 900 ℃ (Figure 12).

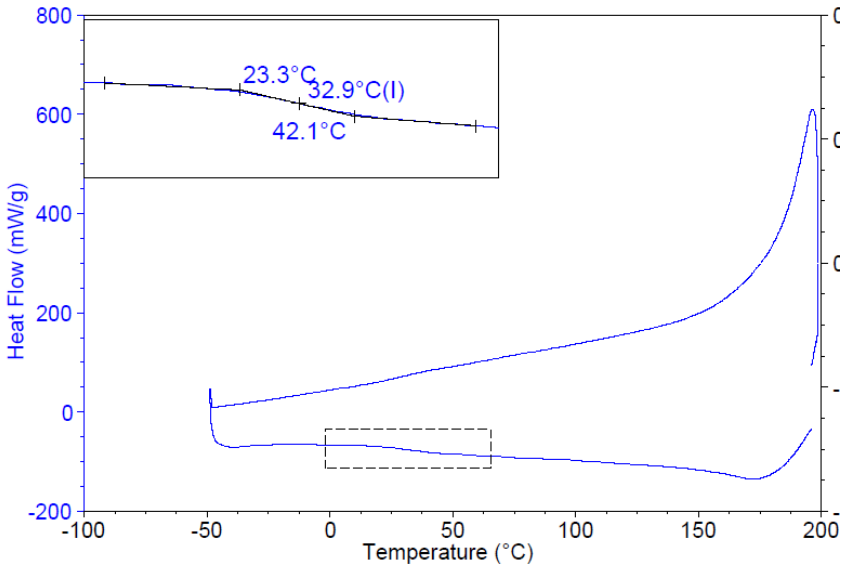


Figure 11. DSC analysis of polyaldol obtained from the polymerization of bis-piperidinone **5** and bis-aldehyde **9** (entry 6, Table 1).

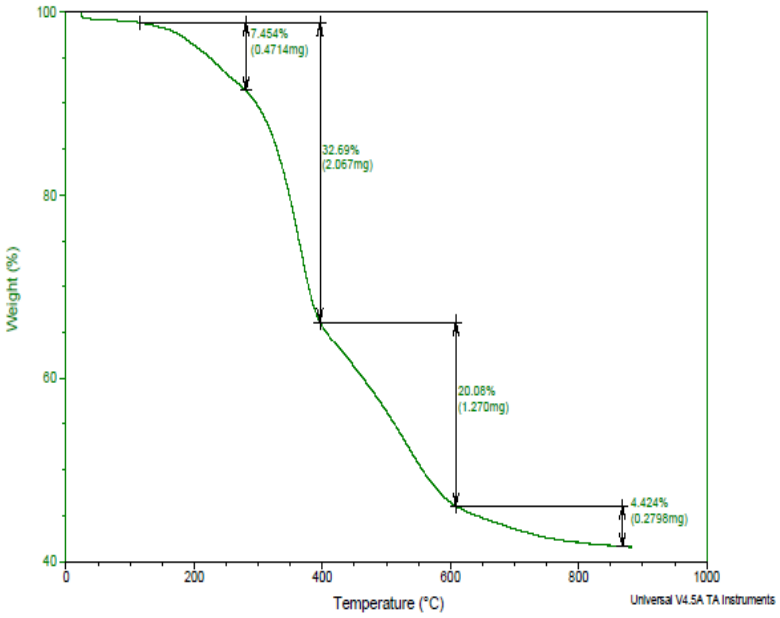


Figure 12. TGA curve of the polyaldol obtained from the polymerization of bis-piperidinone **5** and bis-aldehyde **9** (entry 6, Table 1).

6.3. Solvent effect on the polyaldolization

In view of further optimizing the polymerization reaction conditions, we noticed that distillation of pyrrolidine led to higher polymerization rates, greater conversion (80%) and higher apparent mass-average molecular weights, ranging from 54,700 g/mol to 103,000 g/mol (SEC in DMF relative to PS standards, Figure 13).

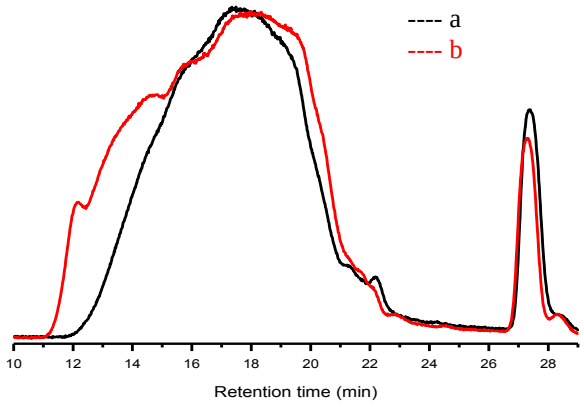


Figure 13. SEC in DMF of (a) polyaldol-**5**,**9** (entry 8, Table 1): M_w (D) = 54,700 g/mol (4.9) and (b) polyaldol-**5**,**8** is obtained from distilled pyrrolidine (0.3 eq) plus acetic acid (1.5eq) as to catalyst, in THF: M_w (D) = 103,000 g/mol (7.2).

Solvent effect on the polymerization of bis-piperidinone **5** and bis-aldehyde **9** was also studied, as summarized in Table 2. DMSO, DMF and DCM were all found suitable as polyaldolization solvents, similar M_w values being observed by SEC (apparent M_w = 117,000-151,000 g/mol) under otherwise identical experimental conditions. In contrast, toluene led to a

lower M_w value (24,900 g/mol), likely due to the poor solvation capability of this solvent towards the resulting polyaldol.

Table 2. Polyaldolization of bis-piperidinone **5** and bis-aldehyde **9** in different solvents.[a]

entry	solvent	$\overline{M}_n$ (g/mol)[b]	$\overline{M}_w$ (g/mol)[b]	D[b]
1	DMSO	15,000	117,000	7.7
2	DMF	15,400	118,600	7.7
3	CH_2Cl_2	11,900	151,000	4.6
4	Toluene[c]	8,800	24,900	2.9

[a] The reaction was catalyzed by pyrrolidine-acetic acid (30 : 150 mol%) at 25 °C, with [Monomers] = 1M. Polymers were precipitated in ether after 2 days. Yields are around 65% for all runs. [b] Molecular weights and *D* determined by SEC in DMF (calibrated with PS standards) [c] Polymer precipitated after 5 min of reaction; the yield was 50%.

6.4. Synthesis of polyaldols from different bis-aldehydes and bis-ketones

To extend the scope of the pyrrolidine/acetic acid-catalyzed polyaldolization, different combinations of bis-aldehydes and bis-ketones were tested (see Figure 14), using the following optimized conditions: 30 mol% distilled pyrrolidine- 150 mol% acetic acid catalysts, 1M monomers concentration, in THF at 25 °C (see Table 3).

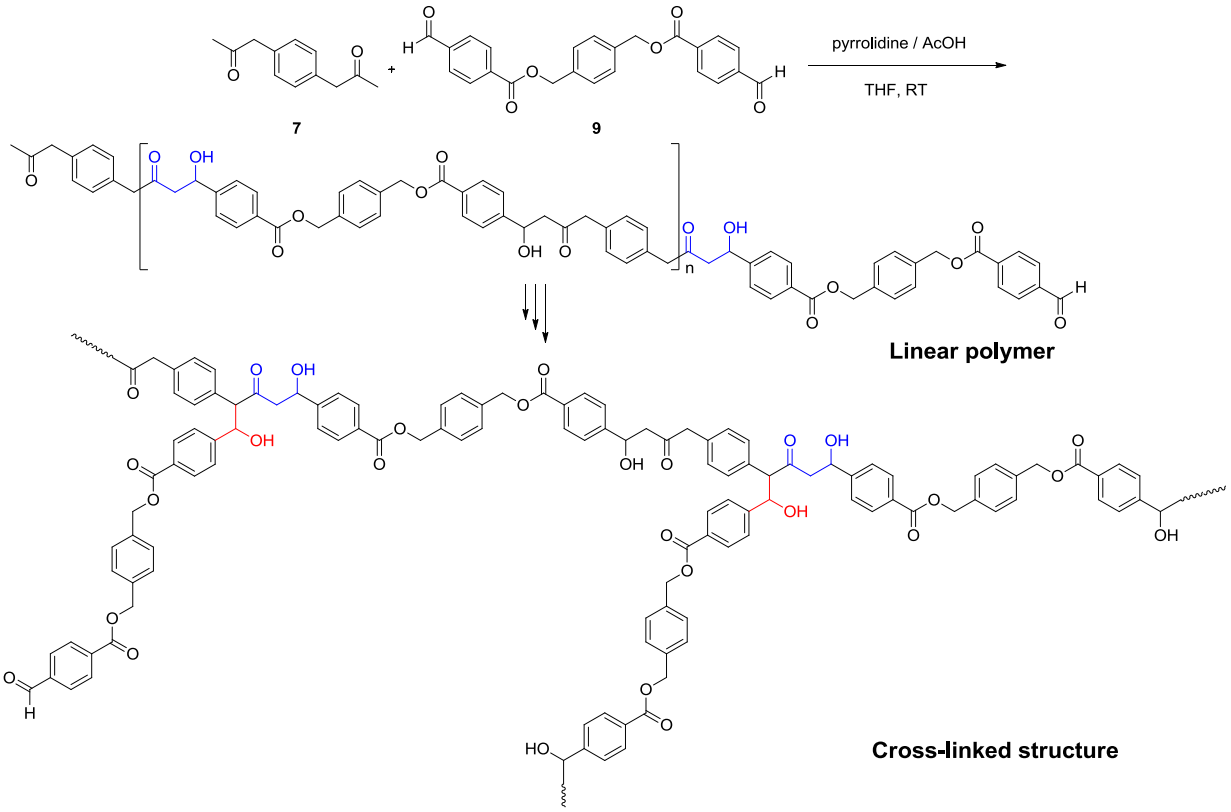
Table 3. Step growth polyaldolization of bis-ketones and bis-aldehydes in THF at 25 °C in the presence of distilled pyrrolidine (0.3 eq.) and acetic acid (1.5 eq.) as catalyst.[a]

entry	Monomer donor	Monomer acceptor	Time	$\overline{M}_n$ (g/mol)[b]	$\overline{M}_w$ (g/mol)[b]	D[b]
1	**5**	**11**	12h	17,000	145,000	8.5
2	**6**	**9**	18h	14,700	105,400	7.19
3	**5**	**9**	18h	14,300	103,000	7.2
4[d]	**7**	**9**	18h	7,600	23,500	3.11
5	**8**	**9**	3d	-[c]	-[c]	-[c]
6	**5**	**10**	3d	-[c]	-[c]	-[c]

[a] [Monomers] = 1M. Polymers were precipitated in diethyl ether to eliminate residual monomers; some small oligomers were also removed by fractionation. [b] Apparent molecular weights and dispersity determined by SEC in DMF (calibrated with polystyrene as standards) [c] Only oligomers were formed. [d] Gelation occurred at the end of the polymerization.

Not surprisingly, the 1,3-bis-piperidinone **5** could be polymerized with the more reactive bis-nitro-aldehyde **11**. Good conversion (82%) and an apparent M_w of 145,000 g/mol (D = 8.5) were obtained within 12h (entry 1, Table 3). Similarly, the isomeric 1,4-bis-piperidinone monomer **6** could smoothly be polymerized with the bis-benzaldehyde monomer **9** (entry 2),

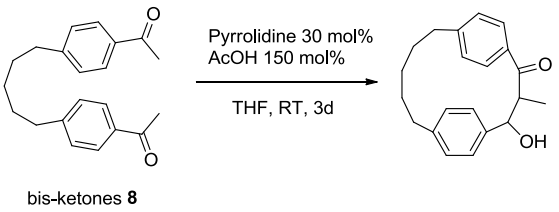
affording the corresponding polyaldol with an average molecular weight of 105,400 g/mol (D = 7.19) within 18 h. The para-substituted bis-ketone **7** was also found suitable to engage in polyaldolization with bis-aldehyde **9**, although lower average molecular weight was obtained in this case (M_w = 23,500 g/mol; D = 3.11). It is worth mentioning that prolonged reaction time led to gel formation. This could be explained by the presence of multiple acidic sites in the structure of **7**, which can be subjected to further aldolization reactions leading, ultimately, to a cross-linked structure (Scheme 22). We hypothesized that this phenomenenet leads to branched polymers, thus increasing the polyaldol dispersity in Table 3.



Scheme 22. Possible cross-linked structure formed from polyaldolization of bis-ketone **7** and bis-aldehyde **9** (entry 4, Table 3).

Reaction between the commercial bis-acetophenone derivative **8** and the bis-aldehyde **9** yielded only oligomers (entry 5, Table 3), even after a reaction time of 3 days. Given that the only difference between bis-ketones **8** and **7** is the flexible structure of the former monomer (entries 4 and 5), intramolecular aldol reaction may have occurred, between an activated nucleophilic ketone and the electrophilic tethered one (scheme 23), instead of the desired intermolecular process.

Polymerization of the bis-piperidinone **5** with the bis-aldehyde **10** (entry 6, Table 3) also resulted in the production of oligomers, even after prolonged reaction time (up to 3 days). In this case, the lower reactivity of the bis-aldehyde **5** might be ascribed to the presence of a deactivating mesomeric donor oxygen atom in para position of the aldehyde function.



Scheme 23. Proposed product structure from intramolecular aldolization of monomer **8**.

Analysis of the polymer synthesized from bis-ketone **5** and bis-aldehyde **9** (entry 3, Table 3) by quantitative ^{13}C NMR revealed the formation of up to 33% of vinylene units generated by dehydration of the parent polyaldol (Figure 14). Therefore, a higher extent of dehydration is noted here than in the case of the polymer arising from the polymerization of monomers **5** and **9** (entry 6, Table 2) employing pyrrolidine in absence of acetic acid (20%). Thus, it can be suspected that the acid catalyst promotes the dehydration of the polyaldol.

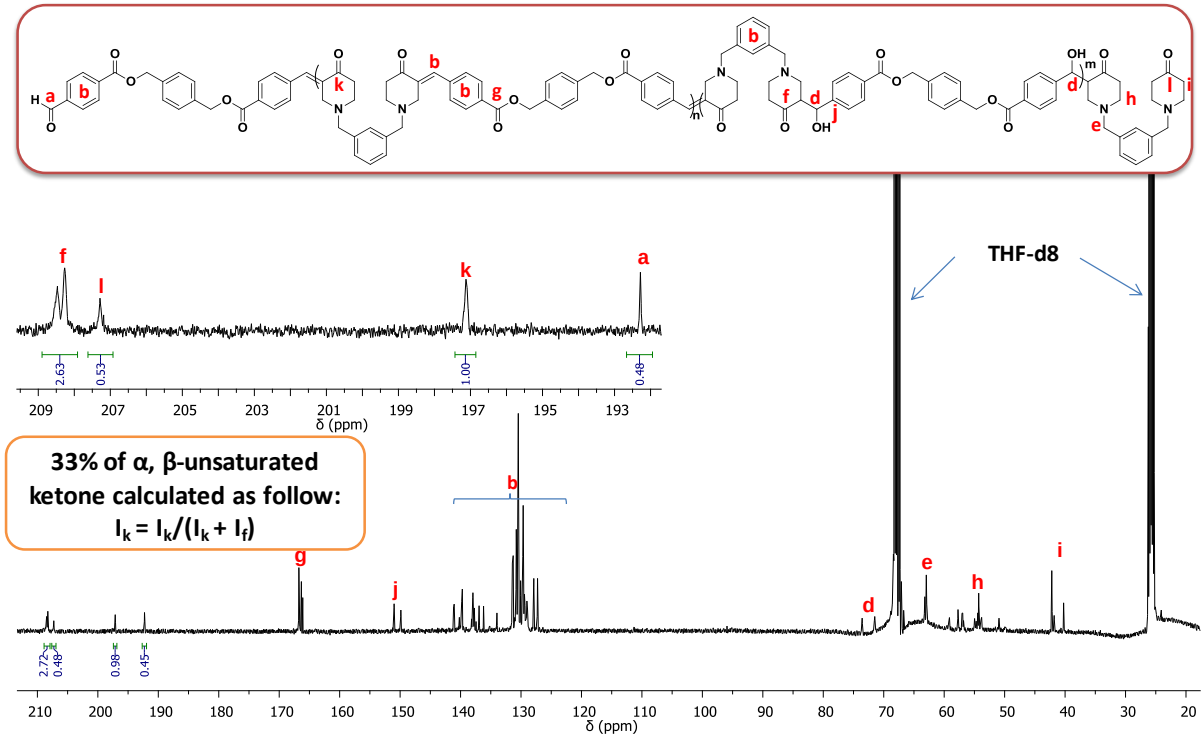


Figure 14. Quantitative ^{13}C NMR spectra (THF-d_8) of polymer obtained from the polymerization of bis-piperidinone **5** and bis-aldehyde **9** (entry 3, Table 3).

Hence, the catalytic system composed of purified pyrrolidine in conjunction with acetic acid provides a higher polyaldolization rate, while dehydration of aldol units is also more favored nder such conditions. Moreover, a similar percentage of vinylene units generated from the parent polyaldol of bis-ketone **6** and bis-aldehyde **9** (entry 2, Table 3) is also found by ^{13}C NMR spectroscopy analysis, that is 25%. (Figure 15)

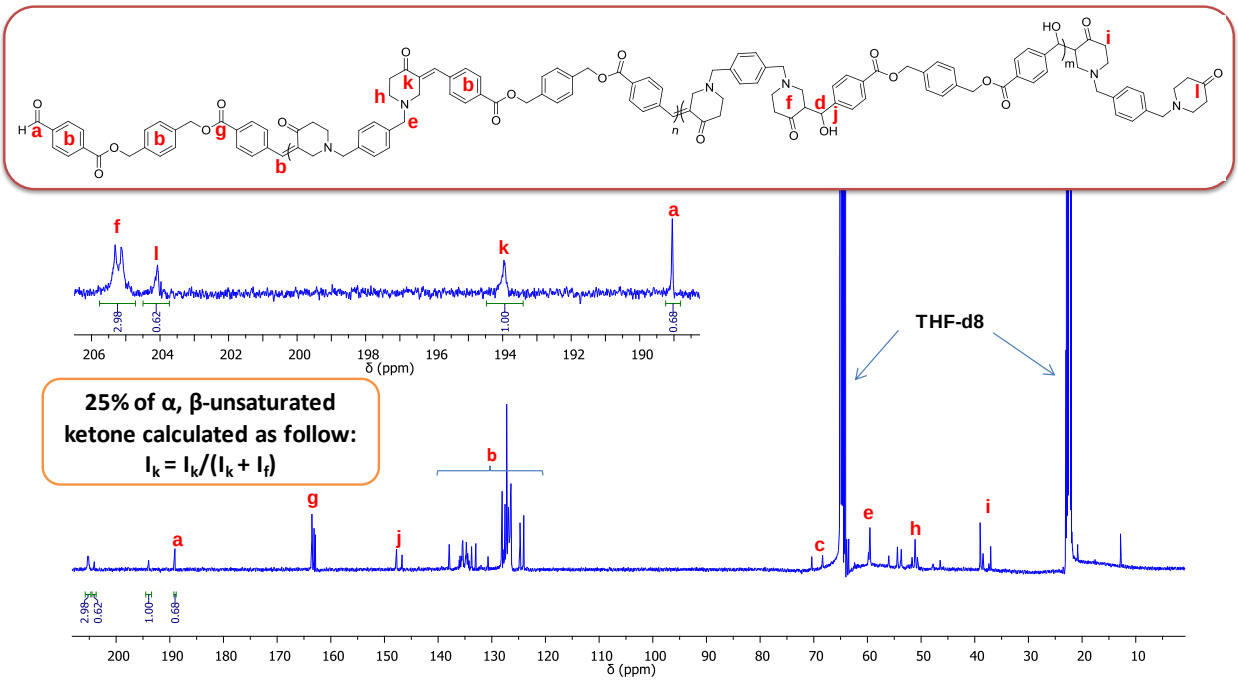


Figure 15. Quantitative ^{13}C NMR spectra (THF-d_8) of polymer obtained from the polymerization of bis-piperidinone **6** and bis-aldehyde **9** (entry 2, Table 3).

6.5. Preliminary attempt of asymmetric polyaldolization

A preliminary experiment of asymmetric polyaldolization was investigated using BIP as a chiral catalyst. Polymerization of bis-piperidinone **5** and bis-aldehyde **9** was thus carried out for 3 days at 25 ℃, at a concentration of 0.5M in THF, in the presence of 30 mol% of BIP in conjunction with 30 mol% of TFA. The corresponding polyaldol-**5**,**9** was characterized by SEC in THF: $M_w(D)$ = 3000 g/mol (1.8) and peak molecular weight was up to 5600 g/mol. Peaks' assignment of polyaldol-**5**,**9** is shown in the ^1H NMR spectrum (Figure 16).

As discussed above, the two small peaks of d' represent the diastereoisomeric protons of aldol function formed (RS, SR form as D1 and RR, SS form as D2). The diastereoisomeric excess (d.e.) is calculated by d.e. = [(D1 – D2) / (D1 + D2)] *100%, thus the diastereoisomeric excess of the polymer obtained could be calculated as:

$$\text{d.e.} = [(0.68 - 0.51) / (0.68 + 0.51)] *100\% = 14\%.$$

This preliminary result is encouraging for it attests that chiral polyaldols could be generated *via* direct asymmetric polyaldolization triggered by a chiral organocatalyst such as BIP. A more systematic investigation is however required, by examining other chiral catalysts and by optimizing experimental conditions to achieve higher d.e. values. One way to assess the chiral character of these polyaldols would be to further degrade them and separate the resulting enantiomers by high-performance liquid chromatography (HPLC).

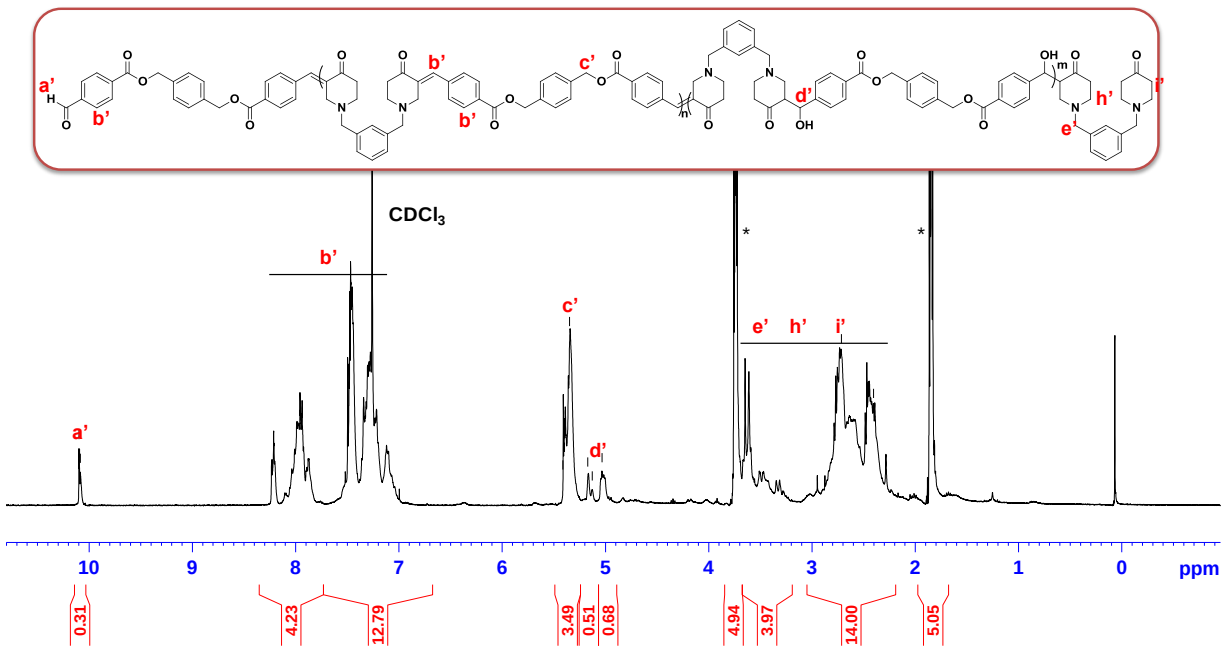


Figure 16. ^{1}H NMR spectra ($CDCl_3$) of polymer obtained from the polymerization of bis-piperidinone **5** and bis-aldehyde **9** (entry 2, Table 3).

7. Conclusion

Bis-ketone and bis-aldehyde monomers can be directly polymerized under stoichiometric conditions by a step-growth polyaldolization process, affording unprecedented poly(β-ketoalcohol)s referred to as polyaldols. *N*-Substituted bis-piperidinones are enolisable monomers and nulceophile of choice, which can efficiently react with non-enolisable bis-aldehydes, the reactivity of which can be enhanced by incorporating electron withdrawing groups, such as nitro or ester groups in para position of the aldehyde. Such a monomer design allows selectively driving the polymerization towards direct aldol-type polymers, preventing the occurrence of the self-polymerization of the bis-aldehyde or the bis-ketone under the experimental conditions examined in this work.

Triggering these polymerizations by an organocatalyic pathway utilizing secondary amines, in particular pyrrolidine in conjunction with acetic acid, produce organosoluble polyaldols exhibiting a multimodal molecular weight distribution, that is characteristics of a step-growth polymerization. A subtle change of the catalyst structure has a dramatic impact on the polymerization reaction. The nature of the solvent has virtually no effect on the polymerization. In contrast, both the monomer concentration and the temperature are crucial parameters, high monomer concentration leading to insoluble cross-linked polymers, likely by intermolecular cross-linking of polyaldol chains.

Polyaldols can undergo partial dehydration forming conjugated vinylene units whose extent depends on the structure of the parent polymer. This feature could be further exploited to

achieve π-conjugated polymers arising from complete dehydration of polyaldols grown by the metal-free synthetic approach developed in the present work.

This also opens avenues to design chiral polyaldols through the use of chiral catalysts *via* asymmetric polymerization, through the transfer of chirality from the catalyst to the stereogenic centers created at each aldol reaction step. Further work is needed, however, to measure the enantiomeric excess of such polyaldols. It might be expected that physicochemical properties of related chiral polyaldols be different from those of their racemic counterparts.

8. Experimental section

Materials.

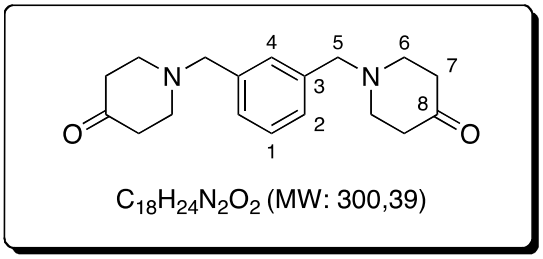
All reagents and solvents were of commercial grade and used as received. All other chemicals and reagents were acquired from Sigma-Aldrich (Buchs, Switzerland). Pyrrolidine was purified by fractional distillation from KOH. Deuterated solvents for NMR spectroscopy were acquired from Armar Chemicals (Dottigen, Switzerland).

Instrumentation.

NMR spectra were recorded on a Bruker AC-400 spectrometer in appropriate deuterated solvents. Molar masses were determined by size exclusion chromatography (SEC) in THF as the eluent (1mL/min) and with trichlorobenzene as a flow marker at 25 ℃, using both refractometric (RI) and UV detectors (Varian). Analyses were performed using a three-column set of TSK gel TOSOH (G4000, G3000, G2000 with pore sizes of 20, 75, and 200 Å respectively, connected in series) calibrated with polystyrene standards. Differential scanning calorimetry (DSC) measurements were performed on a DSC Q100 apparatus from TA Instruments. Data were recorded during the second run for temperatures ranging from 20 to 200 ℃at a heating rate of 10 ℃ min-1. The cooling rate between the first and second runs was also equal to 10 ℃ min-1. The glass transition temperature (Tg) was determined by taking the inflection point of the transition. Thermogravimetric analysis (TGA) analyses were performed on a TA instruments TGA-Q500, under N_2 atmosphere at a heating rate of 5 ℃/min.

Synthetic procedures.

Synthesis of 1,1'-(1,3-phenylenebis(methylene))bis(piperidin-4-one) (**5**)

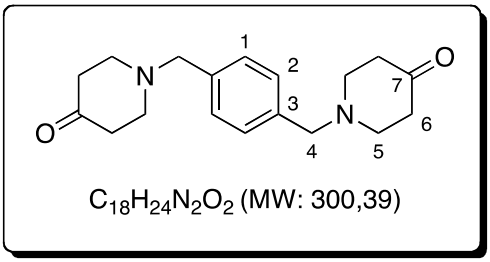


$C_{18}H_{24}N_2O_2$ (MW: 300,39)

To a suspension of 4-piperidinone hydrochloride (4.03 g, 26.04 mmol) in a 30/1 CH_2Cl_2/MeOH mixture (124 mL) in a round-bottom flask equipped with a magnetic stirrer were successively added K_2CO_3 (7,20 mg, 52.08 mmol) and 1,3-bis(bromomethyl)benzene (3.44 g, 13.02 mmol). The resulting mixture was stirred at room temperature for 48h. The reaction was quenched by addition of water (150 mL). After separation, the organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and evaporated to give a residue, which was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 100/0 to 95/5). The desired product was obtained

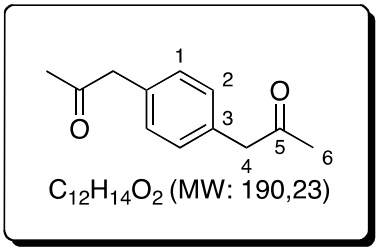
as a white solid. (3.91g, quantitative yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.36 – 7.24 (m, 4H, CH_{ar}), 3.63 (s, 4H, H5), 2.75 (t, *J* = 6.0 Hz, 8H, H6), 2.46 (t, *J* = 6.0 Hz, 8H, H7). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.3 (C8), 138.4 (C3), 129.4 (C4), 128.5 (C1), 128.0 (C2), 62.0 (C5), 53.0 (C6), 41.4 (C7). IR (KBr) ν_{max} = 2959, 2912, 2812, 2769, 1714 cm^{-1}.

Synthesis of 1,1'-(1,4-phenylenebis(methylene))bis(piperidin-4-one) (**6**)



The same protocol was used for the synthesis of 1,1'-(1,3-phenylenebis(methylene))bis(piperidin-4-one) **6**. The residue was chromatographied on silica gel (CH_2Cl_2/MeOH, 97/3) to afford the desired product as a white solid (3.63 g, 71%). Analytical data matched those reported in the literature.[33] R_f = 0.34 (CH_2Cl_2/MeOH, 95/5), ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.32 (s, 4H, CH_{ar}), 3.61 (s, 4H, H4), 2.75 (t, *J* = 6.1 Hz, 8H, H5), 2.46 (t, *J* = 6.1 Hz, 8H, H6).

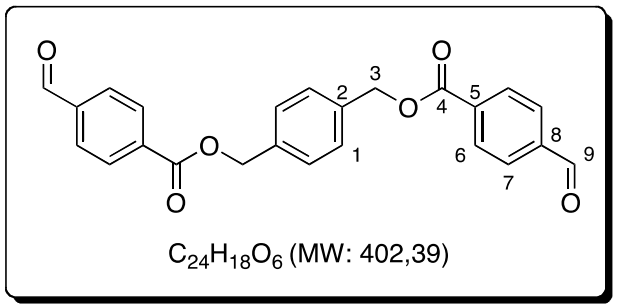
Synthesis of 1,1'-(1,4-phenylene)bis(propan-2-one) (**7**)



A procedure reported in the literature was followed.[34] Analytical data matched those reported in the literature.[32]

4,4'-pentamethylenebis(acetophenone) (**8**) was of commercial grade and used as received.

Synthesis of 1,4-phenylenebis(methylene) bis(4-formylbenzoate) (**9**)



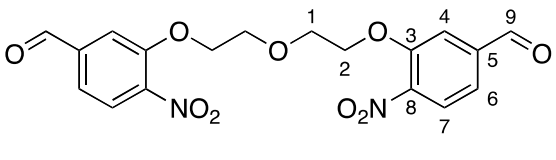
$C_{24}H_{18}O_6$ (MW: 402,39)

To a suspension of NaH (160.0 mg, 6.66 mmol) in anhydrous DMF (15 mL) was slowly added a solution of 4-formylbenzoic acid (1.00 g, 6.66 mmol) in anhydrous DMF (5 mL) at 0 ℃ under argon. The reaction mixture was stirred for 15 min at the same temperature. Then, a solution of 1,4-bis(bromomethyl)benzene (586.00 mg, 2.22 mmol) in anhydrous DMF (5 mL) was slowly added, and the reaction mixture was stirred at 0 ℃ for 10 min. The resulting mixture was then stirred at 60 ℃ for 12h. The mixture was quenched with a 1M HCl solution (30 mL). The aqueous layer was extracted with EtOAc (3 x 90 mL) and the organic layers were washed with a saturated aquaeous KCl solution (2 x 30 mL), and then with a 1M NaOH solution (2 x 30mL), dried over Na_2SO_4, filtered, and the solvents evaporated in vacuo. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 100/0 to 90/10) to afford the desired product as a white solid (681 mg, 76%). R_f = 0.72 (Petroleum ether/EtOAc, 1/1), m.p. = 169-170 ℃, IR (neat): 2947 cm^{-1}, 2847, 2746, 1708, ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.10 (s, 2H, H10), 8.23 (d, *J* = 8.2 Hz, 4H, H7), 7.97-7.92 (m, 4H, H6), 7.50 (s, 4H, H1), 5.41 (s, 4H, H3), ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.7 (C9), 165.4 (C4), 139.4 (C8), 136.0 (C5), 135.1 (C2), 130.4 (C6), 129.6 (C7), 128.8 (C1), 67.0 (C3), HRMS (ESI) $[M+Na]^+$ $C_{24}H_{18}O_6Na$: calcd. 425.1001; found: 425.1002.

*Synthesis of Bis-aldehyde **10***

A procedure reported in the literature was followed.[35]

Synthesis of 3,3'-((oxybis(ethane-2,1-diyl))bis(oxy))bis(4-nitrobenzaldehyde) (**11**)



$C_{18}H_{16}N_2O_9$ (MW: 404,32)

To a solution of 3-hydroxy-4-nitrobenzaldehyde (2.50 g, 15.00 mmol) in DMF (60 mL) was added oxybis(ethane-2,1-diyl) bis(4-methylbenzenesulfonate) (3.10 g, 7.48 mmol) and K_2CO_3 (6.21 g, 44.88 mmol). The reaction mixture was heated to 80 ℃ under N_2 for 15h, and then

quenched with a 1M HCl solution (60 mL). The aqueous layer was extracted with EtOAc (3 x 60 mL) and the organic layers were washed with a saturated aqueous $NaHCO_3$ solution (3 x 60 mL), then with water (2 x 60 mL) and with brine (2 x 60 mL) dried over Na_2SO_4, filtered, and the solvents evaporated in vacuo. The crude product was purified by flash chromatography ($CHCl_3$/EtOAc, 9/1) to afford the desired product as a light yellow solid (2.2 g, 73%). R_f = 0.16 (Petroleum ether/EtOAc, 7/3), m.p. = 97-98 °C, IR (neat): 1705 cm^{-1}, 1607, 1523, 1291, 1277, ^1H NMR (300 MHz, $CDCl_3$) δ = 10.04 (s, 2H, H10), 7.90 (d, *J* = 8.1 Hz, 2H, H8), 7.59 (d, *J* = 1.4 Hz, 2H, H7), 7.52 (dd, *J* = 8.1 Hz, 1.5 Hz, 2H, H5), 4.23 (t, *J* = 6.1 Hz, 4H, H3), 2.02-1.88 (m, 4H, H2), 1.80-1.66 (m, 2H, H1), ^{13}C NMR (75 MHz, $CDCl_3$) δ = 190.5 (C10), 152.6 (C4), 143.6 (C9), 139.7 (C6), 126.0 (C8), 122.4 (C7), 113.7 (C5), 69.8 (C3), 28.4 (C2), 22.5 (C1), HRMS (ESI) $[M+Na]^+$ $C_{19}H_{18}N_2O_8Na$: calcd. 425.0955; found: 425.0937.

General polymerization procedure

To a solution of bis-ketone at 0.25 mol/L in the required solvent, 30 mol% of catalyst with or without 150 mol% of acetic acid was added. After 10 minutes of stirring, a stoichiometric amount of bis-aldehyde (0.25 mol/L) was added. After the time indicated in the tables, polymerization reactions were stopped and resulting polymers were purified by two consecutive precipitations in 100 mL of ether, to eliminate catalysts, unreacted monomers and oligomers. Polymers were then dried under vacuum and obtained white solids.

*Polymerization of bis-piperidinone **5** and bis-aldehyde **9**.*

Polymerization of bis-piperidinone **5** and bis-aldehyde **9** was carried out under air (entry 8 in Table 2), using a bottle of 10 mL which could be closed by a lid. 80.0 mg of bis-piperidinone **5** (0.25 mmol) was dissolved in 0.5 mL of THF and 6 µL (30 mol%) of pyrrolidine and 21 µL (150 mol%) of AcOH were added to the solution. The resulting clear solution was stirred for 10 minutes stirring and 100.5 mg of bis-aldehyde **9** (0.25 mmol) was added. At the beginning, bis-aldehyde **9** was not well soluble in THF but the suspension of monomers and catalysts turns to a clear and yellow solution after the polymerization had begun. The polymerization was controlled. After 3 days of reaction at 25 °C, the crude solution was analyzed by ^{1}HNMR (400MHz, THF-d_8) to determine the conversion (85%). The rest of the solution was precipitated in ether two times and the resulting polymer was obtained as a white solid (100mg, 60%). Mw = 103,000 g/mol, D = 7.2 analyzed in SEC DMF (UV detector).

P*olymerization of bis-ketone **5**(entry 9, Table 1)*

Polymerization of bis-ketone **5** which was carried out under air (entry 8 in Table 2), using a bottle of 10 mL which could be closed by a lid. 80.0 mg of bis-piperidinone **5** (0.25 mmol) was dissolved in 0.5 mL of THF and 6 µL (30 mol%) of pyrrolidine and 21 µL (150 mol%) of AcOH were added to the solution. Oligomers were obtained that was proved by the SEC analysis after 3 days' reaction.

*Polymerization of bis-piperidinone **5** and bis-aldehyde **11**.*

Polymerization of bis-piperidinone **5** and bis-aldehyde **11** was carried out under air, using a bottle of 10 mL which could be closed by a lid. 80.0 mg of bis-piperidinone **5** (0.25 mmol) was dissolved in 0.5 mL of THF and 6 µL (30 mol%) of pyrrolidine and 21 µL (150 mol%) of AcOH were added to the solution. The resulting clear solution was stirred for 10 minutes stirring and 101.1 mg of bis-aldehyde **11** (0.25 mmol) was added. The polymerization was controlled. After 3 days of reaction at 25 ℃, the crude solution was analyzed by ^{1}HNMR (400MHz, THF-d_8) to determine the conversion (82%). The rest of the solution was precipitated in ether two times and the resulting polymer was obtained as a white solid (100mg, 55%). Mw =145,000 g/mol, D = 8.5 analyzed in SEC DMF (UV detector). (entry 1, Table 3)

*Polymerization of bis-piperidinone **6** and bis-aldehyde **9**.*

Polymerization of bis-piperidinone **6** and bis-aldehyde **9** was carried out under an open air condition using a bottle of 10ml which could be closed by a lid. 80.0 mg of bis-piperidinone **6** (0.25 mmol) was dissolved in 0.5 mL of THF and 6 µL (30 mol%) of pyrrolidine and 21 µL (150 mol%) of AcOH were added to the solution. The resulting clear solution was stirred for 10 minutes stirring and 100.5 mg of bis-aldehyde **9** (0.25 mmol) was added. The polymerization was controlled. After 3 days of reaction at 25 ℃, the crude solution was analyzed by ^{1}HNMR (400MHz, THF-d_8) to determine the conversion (80%). The rest of the solution was precipitated in ether two times and the resulting polymer was obtained as a white solid (100mg, 62%). Mw =105,400 g/mol, D = 7.19 analyzed in SEC DMF (UV detector). (entry 2, Table 3)

*Polymerization of bis-ketone **7** and bis-aldehyde **9** with distilled pyrrolidine.*

Polymerization of bis-ketone **7** and bis-aldehyde **9** was carried out under an open air condition using a bottle of 10ml which could be closed by a lid. 47.6 mg of bis-ketone **7** (0.25 mmol) was dissolved in 0.5 mL of THF and 6 µL (30 mol%) of distilled pyrrolidine and 21 µL (150 mol%) of AcOH were added to the solution. The resulting clear solution was stirred for 10 minutes stirring and 100.5 mg of bis-aldehyde **9** (0.25 mmol) was added. The polymerization was

controlled. After 18h of reaction at 25 ℃, gelation occurred at the end. The part which is soluble in DMF was analyzed in SEC DMF (UV detector), observed Mw =23,500 g/mol, D = 3.11. (See Table 3, entry 4)

*Polymerization of bis-piperidinone **5** and bis-aldehyde **9** (entry 3, Table 3), bis-ketone **8** and bis-aldehyde **9** (entry 5, Table 3) and bis-ketone **5** and bis-aldehyde **10** (entry 6, Table 3) with distilled pyrrolidine.*

Polymers from bis-piperidinone **5** and bis-aldehyde **9** (entry 3, Table 3) bis-ketone **8** and bis-aldehyde **9** (entry 5, Table 3) and bis-ketone **5** and bis-aldehyde **10** (entry 6, Table 3) were synthesized in the same fashion with previous ones only changed the corresponding bis-ketones and bis-aldehyde. Oligomers were obtained that was proved by the SEC analysis after 3 days' reaction.

*Asymmetric polyaldolization of bis-piperidinone **5** and bis-aldehyde **9** catalyzed by BIP.*

Polymerization of bis-piperidinone **5** and bis-aldehyde **9** was carried out under air (entry 8 in Table 2), using a bottle of 10 mL which could be closed by a lid. 80.0 mg of bis-piperidinone **5** (0.25 mmol) was dissolved in 0.5 mL of THF and 11.2 mg (20 mol%) of BIP and 4.3 μL (20 mol%) of TFA were added to the solution. The resulting clear solution was stirred for 10 minutes stirring and 100.5 mg of bis-aldehyde **9** (0.25 mmol) was added The polymerization was controlled. After 3 days of reaction at 25 ℃, the crude solution was analyzed by ^{1}HNMR (400MHz, THF-d_8) to determine the conversion (81%). The rest of the solution was precipitated in ether two times and the resulting polymer was obtained as a white solid (105mg, 61%). Mw = 3000 g/mol, D = 1.8 analyzed in SEC DMF (UV detector).

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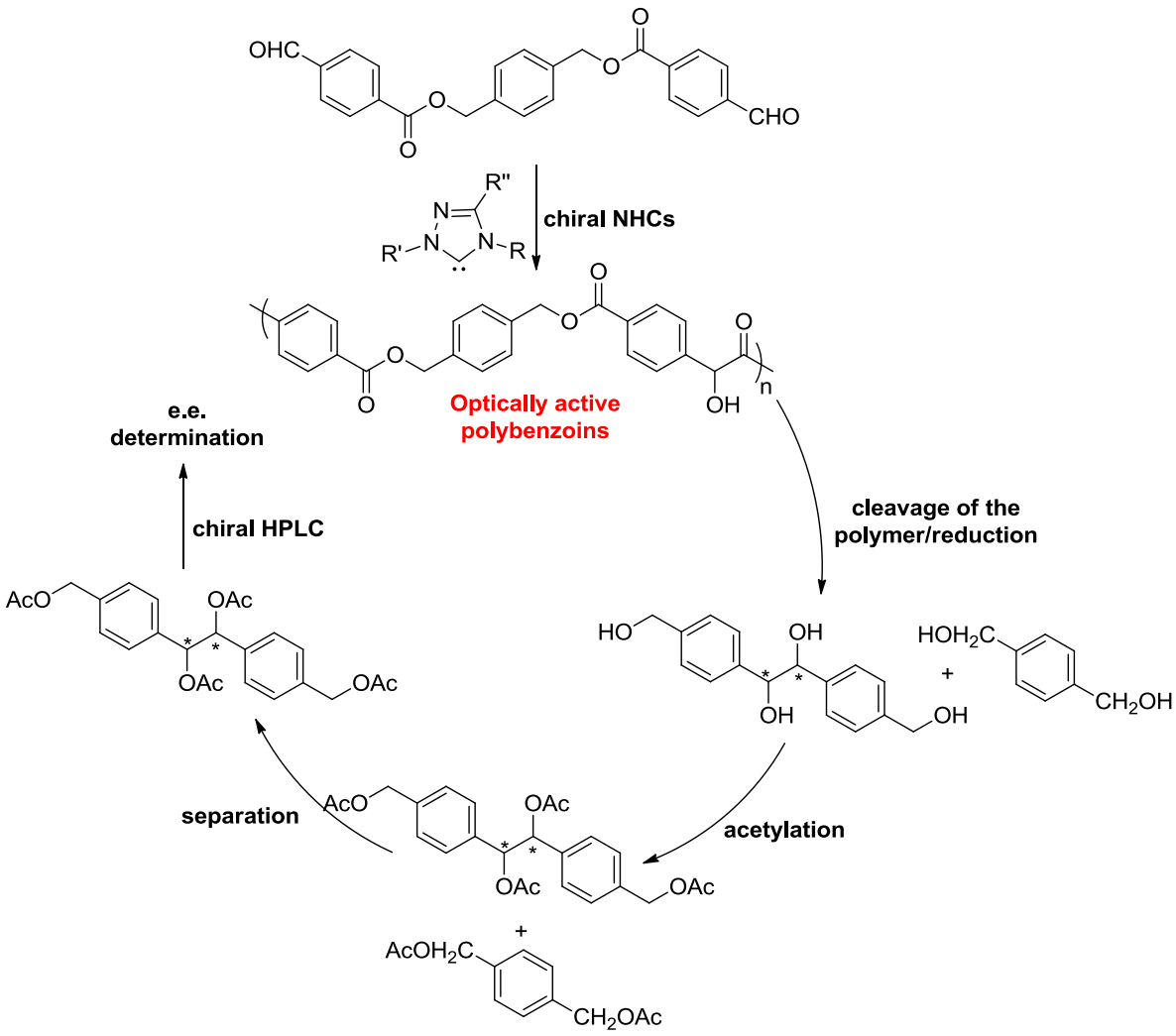
Chapter III

Novel Polybenzoins by Step-growth Polymerization of Bis-aldehydes Catalyzed by Chiral *N*-Heterocyclic Carbenes

Chapter III. Novel Polybenzoins by Step-growth Polymerization of Bis-aldehydes Catalyzed by Chiral *N*-Heterocyclic Carbenes



Keywords: Benzoin condensation, Step-growth polymerization, *N*-heterocylic carbenes (NHCs), Bis-aldehydes, Chirality

Mots clés : condensation de benzoïne, Polycondensation, Carbènes *N*-hétérocycliques (NHCs), Bis-aldéhydes, Chiralité

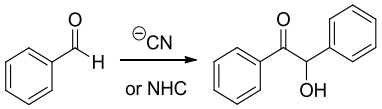
Chapter III. Novel Polybenzoins by Step-growth Polymerization of Bis-aldehydes Catalyzed by Chiral *N*-Heterocyclic Carbenes

1. Introduction

The previous chapter has discussed how properly selected bis-aldehyde monomers can react with bis-ketones via organocatalyzed aldolization reaction, to yield novel polyaldols. The next chapter will illustrate the potential of hydroxyaldehyde monomers to access hyperbranched polyacetals with a perfect degree of branching (100%).

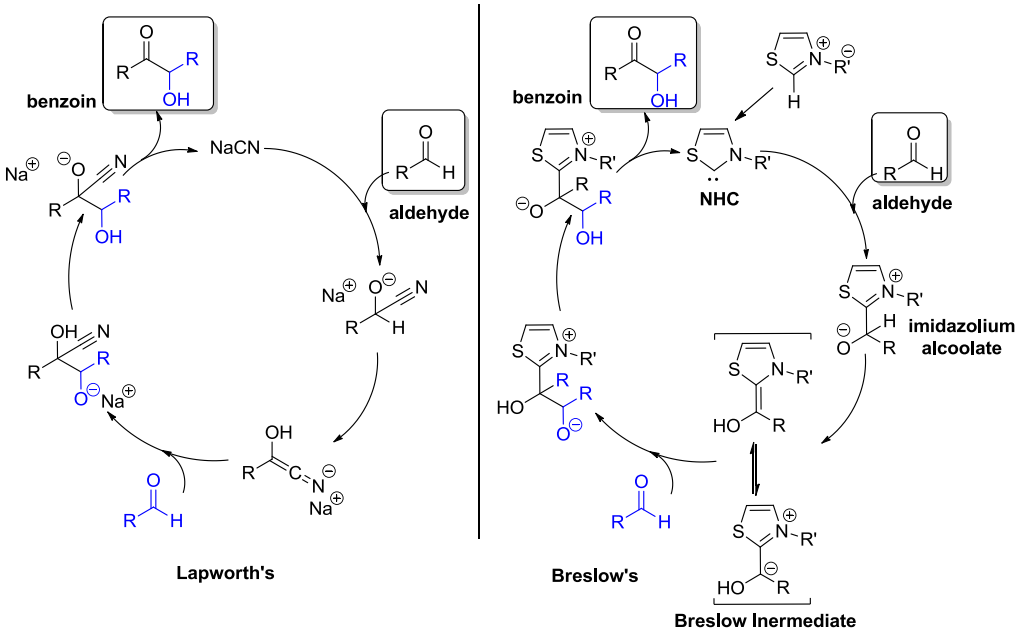
In this chapter, N-heterocyclic carbenes (NHCs) have been used to catalyze the step-growth polymerization of novel bis-aldehydes, on the basis of the so-called benzoin condensation. Corresponding polymers referred to as "polybenzoins" are thus constituted of α-ketoaldochol repeating units.

The benzoin condensation is an organic transformation, discovered in 1832 by Wöhler and Liebig, involving the coupling of two aldehyde molecules to yield a β-ketoalcohol, namely benzoin (see also chapter I for an introduction to this reaction).[1] Surprisingly, only the cyanide anion proved able to catalyze this reaction, as reported by Lapworth since 1903.[2] In particular, addition of the cyanide anion to the electrophilic aldehyde yields an α-cyano-alcoolate, which undergoes a proton transfer from C to O, generating a carbanion stabilized by the cyano group. In other words, the electrophilic aldehyde is transformed into a nucleophilic species upon reaction with the catalyst, which can add onto another molecule of aldehyde (Scheme 1). The change of polarity of the benzaldehyde substrate is called "umpolung", the German translation for "polarity inversion".[3]



Scheme 1. Catalysis of the benzoin condensation by cyanide or NHC (see Figure 1 further regarding the general structure of NHCs).

Besides cyanide, it was shown by Ugai that benzoin condensation could be catalyzed by thiazolium salt under basic conditions.[4] In this reaction, the active catalyst is the corresponding thiazolylidene, formed by deprotonation of the C_2-H, as suggested by Breslow while studying the role of the thiamine cofactor.[5] By analogy with cyanide (Lapworth's mechanism), the mechanism of benzoin condensation involves the addition of the NHC onto the aldehyde, forming an imidazolium alcoolate, which rearranges upon C→O proton transfer to the corresponding eneaminol, that is, the so-called "Breslow intermediate" where the carbanion is stabilized by the imidazolium cation (Scheme 2). Note that recent work by Teles *et al.* have shown that such intermediates could be enough stabilized, so that they can be characterized and even isolated.[6]



Scheme 2. Benzoin condensation: Lapworth's and Breslow's mechanism.

Stable NHCs contains a divalent carbon with six peripheral electrons, four of them being involved in two σ-bonds with two adjacent substituents, while two nonbonded electrons remain at the central carbon (Figure 1). NHCs have emerged as a fruitful research area in synthetic organic chemistry, a field that has been reviewed many times.[7] Advantage of NHC over cyanide catalysis is that chirality can be introduced on the imidazole backbone, and a variety of chiral NHCs have been developed for asymmetric benzoin condensation.[8]

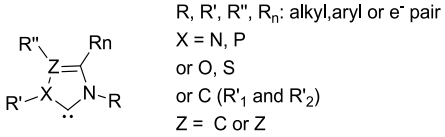
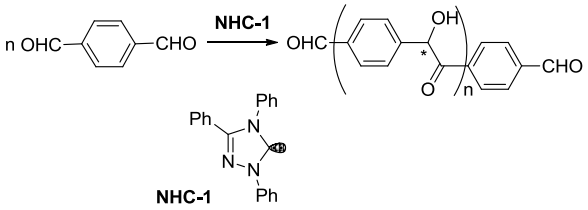


Figure 1. General structure of *N*-heterocyclic carbenes.

Polybenzoin synthesis by step-growth polymerization of terephthalaldehyde was first reported using cyanide as catalyst.[9] Interestingly, these polymers could be derivatized into poly(1,4-phenylenevinylene) (PPV) and high-performance quinoxalines (section 5.3.2, chapter I). In 2009, Pinaud *et al.* described the use of NHCs as catalysts for the step-growth polymerization of terephthalaldehyde, yielding linear and cyclic polybenzoins, albeit with a moderate molecular weight (M_n = 1000-3000 g/mol).[10] Polymerizations were performed at 40 ℃ catalyzed by 1,3,4-triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ylidene (**NHC-1**) in THF (Scheme 3). Under these experimental conditions, however, polybenzoin precipitated out of the solution.

Here we propose to take polybenzoin synthesis one step further. In particular, new monomers were designed and related polymers showed an improved solubility in organic solvents. A stereogenic center being formed at each benzoin condensation step, the control of their stereochemistry, through the use of chiral NHC catalyst, was also investigated with the aim

at synthesizing optically active polybenzoins. In other words, it was expected that the chirality of the NHC catalyst could be transferred to the polymer backbone during the course of the step-growth polymerization.



Scheme 3. Polybenzoin synthesized from terephthalaldehdye catalyzed by organo-catalyst 1,3,4-triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ylidene (NHC-1).[10]

2. Synthesis of monomers

In order to broaden the scope of the NHC-catalyzed step-growth polymerization of bis-aldehydes, new monomers, such as **1**, **2** and **3** (Figure 2), incorporating a dimethylsilyl and a diester functionality, respectively, were considered. One objective was to improve both the flexibility and the solubility of the corresponding polybenzoins. In addition, related polybenzoin polymers could be subsequently cleaved off (at the silyl or ester sites) into elementary building blocks, the chirality of which could be determined by chiral HPLC.

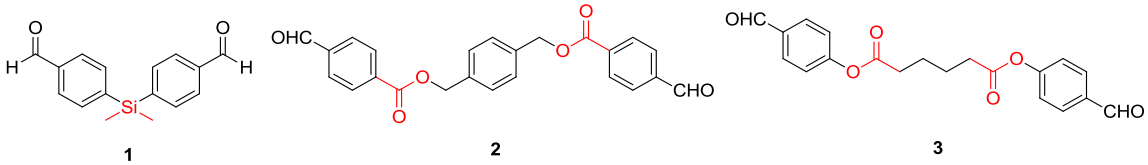
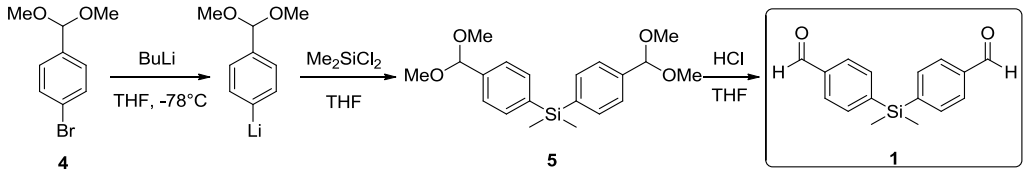


Figure 2. Monomers studied in this chapter: bis-aldehyde with silylated group (**1**) and ester-containing bis-aldehyde (**2** and **3**).

The silyl moiety characterizing monomer **1** was selected as a potential cleavable unit, given the relative fragility of Si-C bonds, as demonstrated by Itsuno with the cleavage by TBAF (tetra-*n*-butylammonium fluoride) of synthesized polymer incorporating silyl moieties.[11]

The synthesis of this monomer involves a two-step sequence starting from a lithium/halogen exchange of precursor **4**, followed by quenching with Me_2SiCl_2. This afforded the bis-acetal **5** whose hydrolysis led to the targeted bis-aldehyde monomer **1** upon acidic workup (Scheme 4).[12] The monomer was characterized by ^1H NMR in THF-d_8. A typical aldehyde proton (C*H*O, a) was found at 10.02 ppm, while the two doublets (J = 8.0 Hz) corresponding to a para heterodisubstituted aromatic moiety were observed at 7.68 and 7.85 ppm. The methyl protons of silyl group were detected at 0.64 ppm. The integral ratio of these peaks was 2 / 8 / 6, in accordance with the expected structure (Figure 3).



Scheme 4. Synthesis of bis-aldehyde **1** containing a silylated group.

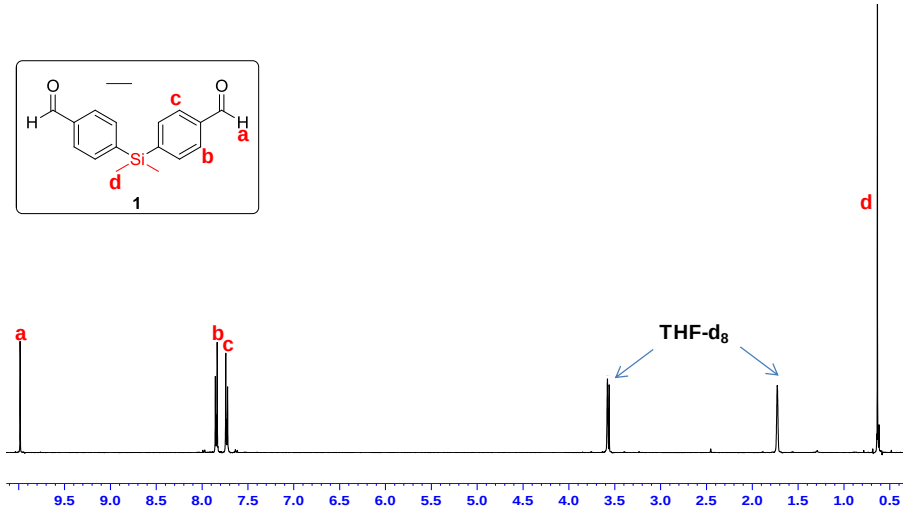
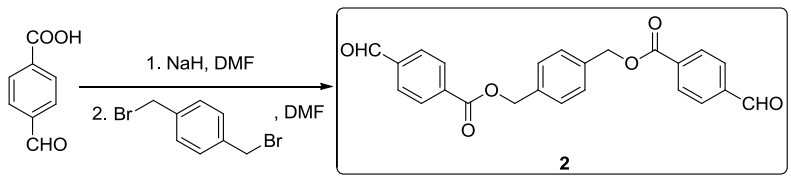


Figure 3. ^{1}H NMR (400 MHz, THF-d_8) of silyl-containing bis-aldehyde **1**.

Monomer **2** possessing a cleavable ester function was also purposely designed. The synthesis involved a one step reaction between sodium 4-formylbenzoate and bis(chloromethyl)benzene in DMF. After purification by flash chromatography, monomer **2** was obtained as a white solid in good yield (76%, Scheme 20). This monomer was also utilized for the synthesis of polyaldolisation described in chapter II. The aldehyde proton (C*H*O) peak a was found at 10.10 ppm, while the two doublets signals due to para heterodisubstituted aromatic moiety, e and f, appeared at 8.23 and 7.97 ppm (J = 8.2 Hz). Aromatic proton g was observed at 7.50 ppm as a singlet signal. The methylene protons of the ester group (C*H*$_2$OC=O) was detected at 5.41 ppm. The integral ratio of these peaks is 2 / 8 / 4 / 4, in accordance with the structure of monomer **2** (Figure 4).



Scheme 5. Synthesis of bis-aldehyde **2** containing an aromatic-ester group.

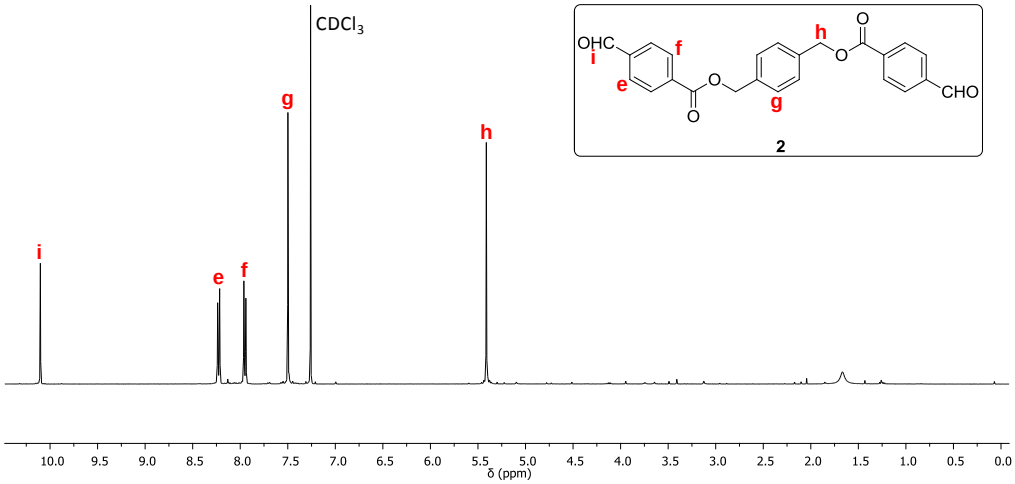
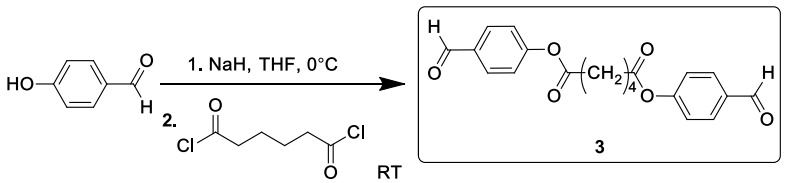


Figure 4. ^{1}H NMR (400 MHz, $CDCl_3$) of monomer **2** aromatic ester-contained bis-aldehyde.

As for monomer **3**, it was synthesized *via* esterification of a bisacyl chloride with the alcohol of hydroxyaldehyde, under basic conditions (Scheme 6).[13] The final compound was obtained by recrystallizaiton of the crude product. Characterization by ^{1}H NMR spectroscopy in $CDCl_3$ showed the presence of the aldehyde proton (C*H*O) at 10.00 ppm, while the two doublets corresponding to the para heterodisubstituted aromatic moiety appeared at 7.30 and 7.93 ppm (J = 8.2 Hz). The aliphatic protons were found at 1.90 and 2.65 ppm. The integral ratio of these peaks is 2 / 8 / 4 / 4, in agreement with the expected structure for monomer **3**. (Figure 5)



Scheme 6. Synthesis of bis-aldehyde **3** containing an ester group.

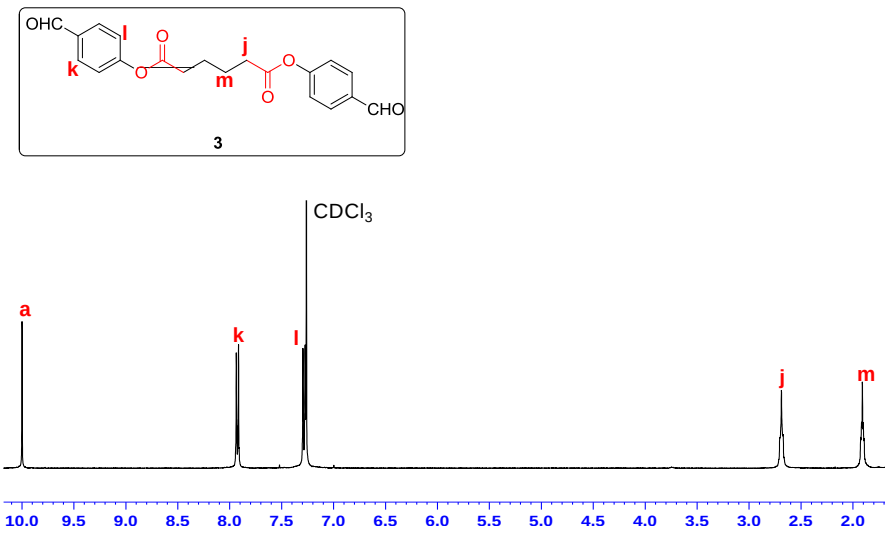


Figure 5. ^{1}H NMR (400 MHz, $CDCl_3$) of aliphatic ester-containing bis-aldehyde **3**.

3. Polymerization of novel bis-aldehydes and characterization of related polybenzoin

3.1. Polymerization

The polymerization of monomers **1**, **2** and **3** was performed in THF at different concentrations of the triazolydene **NHC-1.**[14] As summarized in Table 1, **NHC-1** promoted the polymerization of both monomers **1** and **2** (entry 1-6), monomer conversions between 60 to 82% and peak molecular weights being obtained at room temperature (1700-5600 g/mol). Importantly, and in sharp contrast to the polymerization of terephthalaldehyde by **NHC-1**,[10] polymers resulting from the polymerization of **1** and **2** remained fully soluble in THF during the whole reaction. However, like in the case of terephthalaldehyde, polymerization times were rather high (3-7 days).[10] For the polymerization of monomer **1**, increase of the catalyst concentration, from 1 to 5%, resulted in an increase in molecular weight of the polymer, from 1200 to 3000 g/mol, while decreasing the polymerization time from 7 to 3 days. A further increase of the catalyst concentration, from 5 to 10%, resulted in an increase of the monomer conversion (from 76 to 82%) and a further increase of the peak molecular weight (from 3100 to 5000 g/mol). Figure 6 shows the evolution of molecular weights with time of corresponding polybenzoin (**PBz-1**) obtained from polymerization of monomer **1** (entry 3, Table 1).

Table 1. Step-growth polymerization in THF of bis-aldehyde monomers in the presence of **NHC-1**.[a]

entry	monomer	NHC-1 mol%	time (d)	T (°C)	conv[b] (%)	$\overline{M}_w$ g/mol[c]	M_p g/mol[d]	D^c
1	**1**	1	7	RT	65%	1200	1700	1.8
2	**1**	1	7	50 °C	70%	2800	3000	1.7
3	**1**	5	3	50 °C	76%	2900	3100	1.69
4	**1**	10	3	50 °C	82%	3500	5000	1.9
5	**2**	10	3	RT	60%	3200	4700	1.9
6	**2**	10	3	50 °C	65%	3800	5600	1.8
7	**3**	1	7	50 °C	dimer	-	-	-

[a] polymerization concentration of bis-aldehydes **1** and **3** is 0.4 mol/L and for bis-aldehydes **2** is 0.2 mol/L. [b][conv] = conversions of polymerization which are determined by ^{1}H NMR before purification of polymer by precipitations. [c] mass-average molecular weights M_w and dispersity D are determined by SEC in THF (calibration using polystyrene as standards). [d] peak molecular weights M_p is determined by SEC in THF which corresponds to the highest peak molecular weight of each samples.

^{1}H NMR spectrum of polybenzoin (**PBz-1**) obtained from monomer **1** is shown in Figure 7. The peak (a) at 10.0 ppm in the spectrum is assignable to the aldehyde protons of terminal units. As expected, the methyl protons of silyl group (C*H*$_3$Si-, d) are found around 0.5 ppm as a broad signal. The forming benzoin proton in α-position of the carbonyl group (O=CC*H*, n) is

clearly found at 5.85 ppm, attesting to the formation of α-keto-alcohol units. Polymerization conversions could be calculated from the ratio of proton n and d.

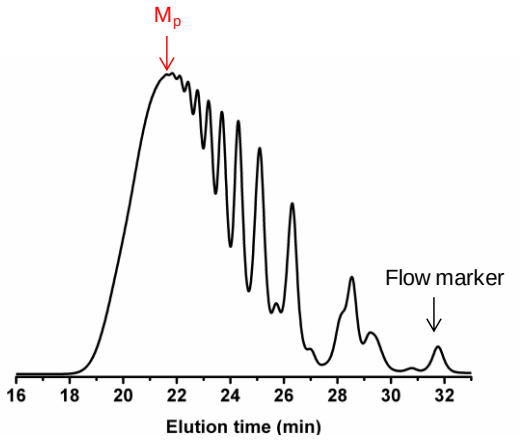


Figure 6. SEC traces (UV detection in THF; relative to PS standards) of polybenzoin (**PBz-1**) obtained from monomer **1** (entry 3, Table 1); M_p corresponds to the apparent molecular weight of the polymer at the maximum.

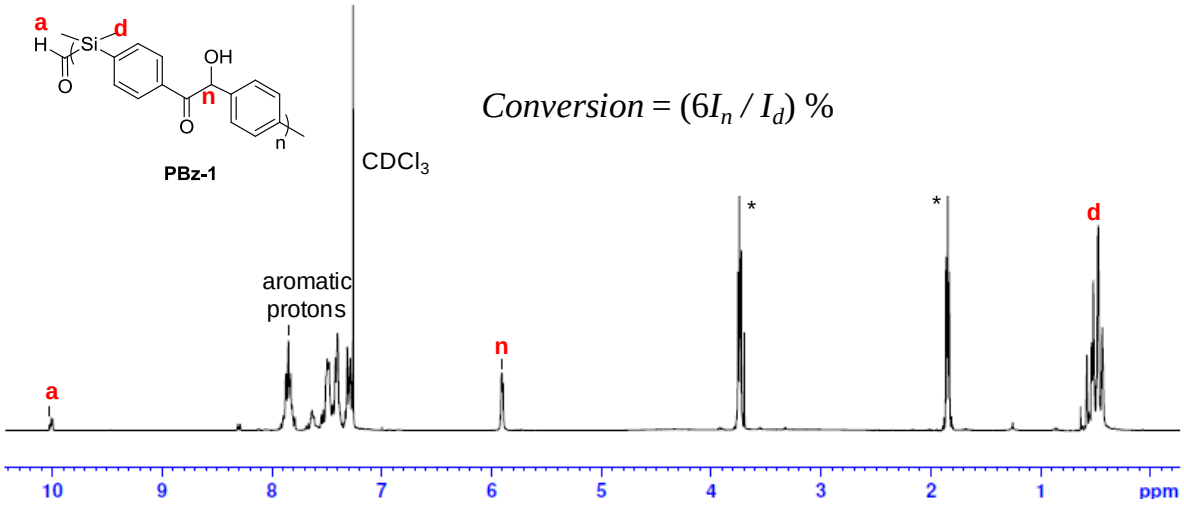


Figure 7. ^{1}H NMR (400 MHz, $CDCl_3$) of polybenzoin (**PBz-1**) obtained from monomer **1** (entry 3, Table 1); * are the peaks of THF residue in the polymer.

In the ^{13}C NMR spectrum (Figure 8), the signal corresponding to the aldehyde chain ends CHO (a') appeared at 193.2-193.5 ppm, whereas the peak attributed to the carbonyl group (o') could be distinguished at 199.9 ppm. The characteristic carbonyl groups of α-ketoalcohol units (O=CCH, n') were observed at 76.9 ppm.

MALDI-ToF MS analysis was run on the polymer **PBz-1** obtained from monomer **1** and the **NHC-1** (entry 4, Figure 9). A distribution of peaks with a mass increment of *m/z* 268.1 corresponding to one monomer unit (monomer **1**) was observed. The observed *m/z* values were in perfect agreement with a molar mass of **PBz-1** containing, at one chain end, the triazolydene moiety deriving from **NHC-1** in the form of a Breslow intermediate, while the other chain end consisted of an aldehyde group (Figure 9). For instance, the peak observed at *m/z* 1370.3

corresponds to the following structure: $C_{20}H_{15}N_3$-$C_{15}H_{15}OSi$-[$C_{16}H_{16}O_2Si$]$_3$-CHO,H^+, *i.e.* a polymer made of three monomer repeating units derived from **1** that was cationized by H^+. Importantly, no macrocycle could be detected in this sample (no population at *m/z* n*268.1). Thus, the sample was constituted of 13 benzoin units and featured a NHC and an aldehyde on each chain-end (4051.5 g/mol).

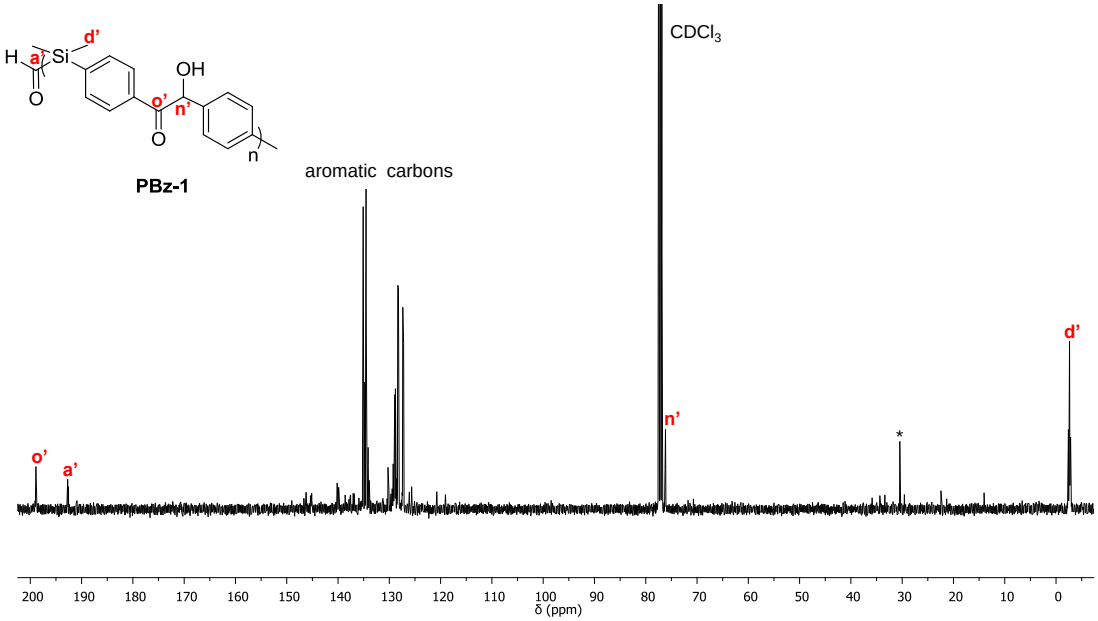


Figure 8. ^{13}C NMR ($CDCl_3$; 100 MHz) of polybenzoin (entry 3, Table 1); * is due to solvent.

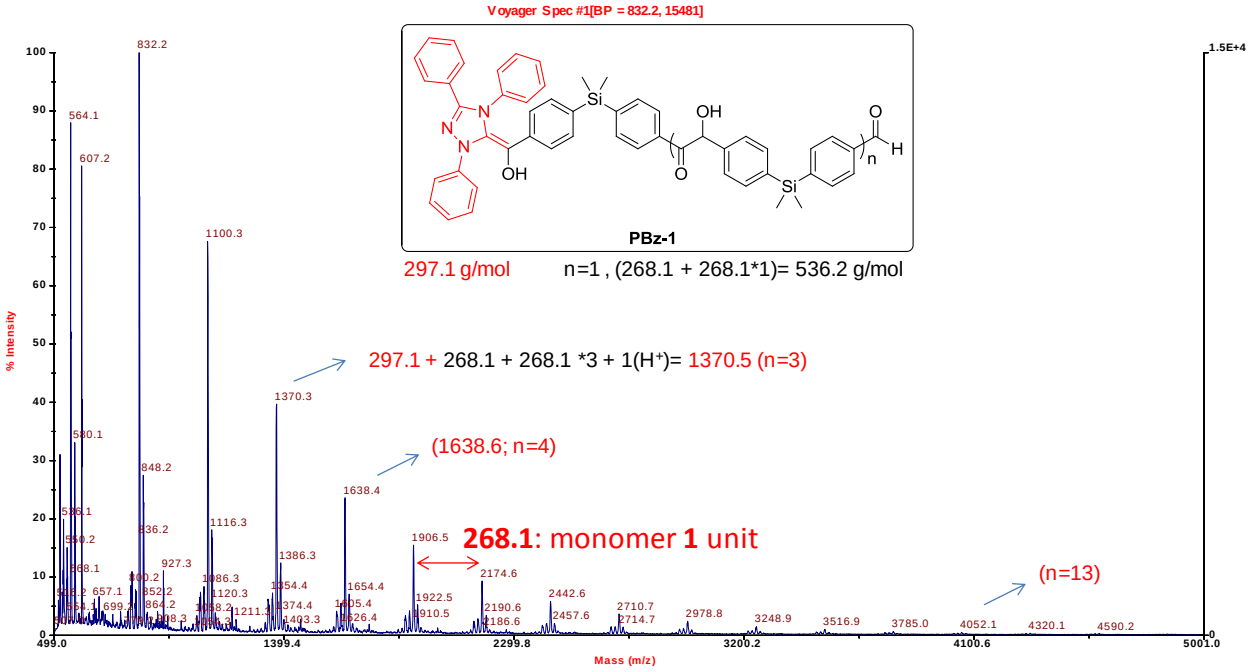


Figure 9. MALDI-ToF MS spectrum reflector mode of polybenzoin **PBz-1** (entry 4, Table 1).

In the case of the NHC-catalyzed step-growth polymerization of bis-aldehyde **2,** the molecular weight increased upon rising the temperature, from RT to 50 ℃ (entry 5 *vs* entry 6). The SEC trace of this polybenzoin, denoted as **PBz-2**, is shown in Figure 10.

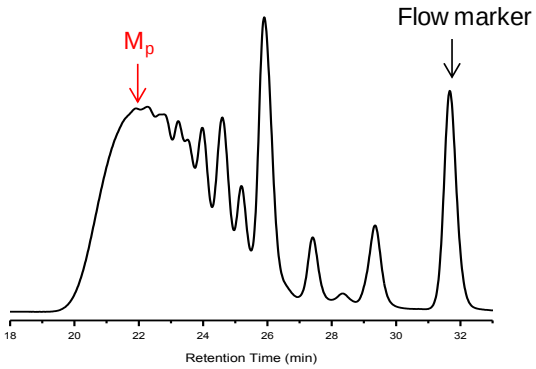


Figure 10. SEC trace (UV detection in THF; relative to PS standards) of polybenzoin **PBz-2** obtained from monomer **2** (entry 6, Table 1); M_p corresponds to the peak molecular weight.

Figure 11 shows the ^{1}H NMR spectrum of this polybenzoin **PBz-2**. The aldehyde proton (i) due to polymer chain end was observed at 10.09 ppm, while the proton in α-position of the carbonyl group (O=CC*H*OH, p) was clearly detected at 5.99 ppm. The methylene protons of the ester groups of the main chain (C*H*$_2$OC=O, peak h) were seen at 5.3 ppm as a broad signal. From these observations, the polymerization conversions could be estimated from the intensity ratio between proton p and h.

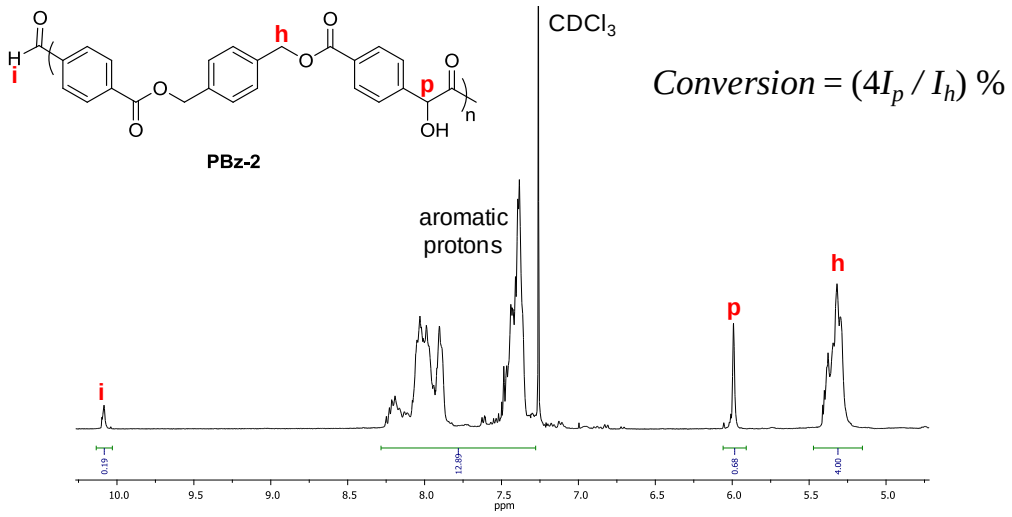


Figure 11. ^{1}H NMR (400 MHz, $CDCl_3$) of polybenzoin **PBz-2** (entry 6, Tableau 1).

In the ^{13}C NMR spectrum (Figure 12), signals corresponding to the aldehyde chain end units (*C*HO, peak i') appeared at 193.2-193.5 ppm, whereas signals attributed to the carbonyl atom of benzoin units (O=*C*CHOH, peak q') could be distinguished at 199.9 ppm. The characteristic carbon of benzoin group (O=C*C*HOH, p') was detected at 76.9 ppm, while peak h' was due to the methylene carbon atom of the ester group (*C*H$_2$OC=O).

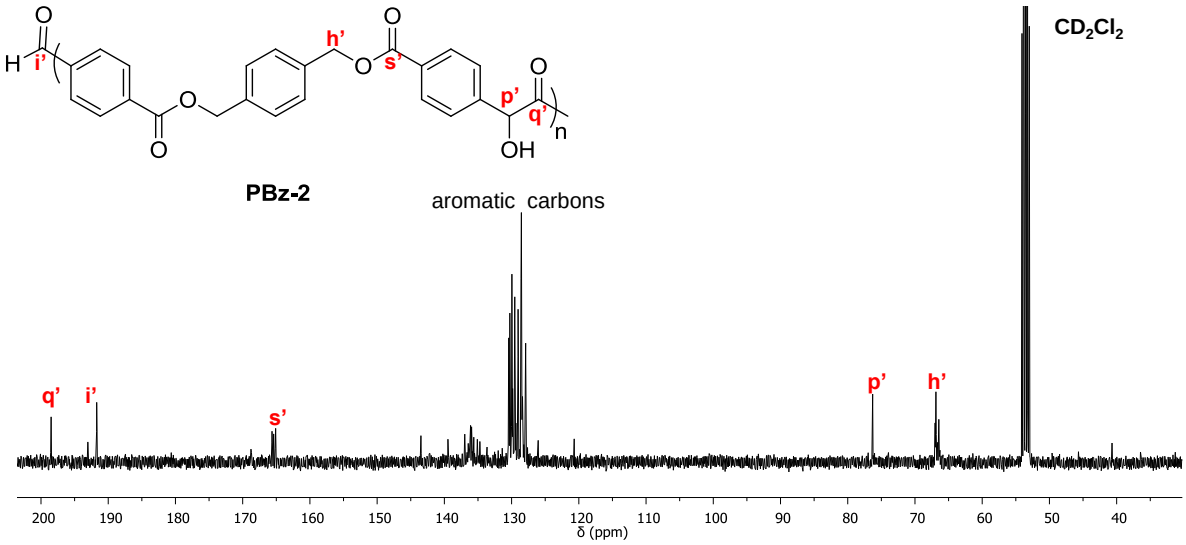


Figure 12. ^{13}C NMR (100 MHz, CD_2Cl_2) of polybenzoin **PBz-2** (entry 6, Tableau 1).

Analysis of this polybenzoin **PBz-2** by MALDI-ToF mass spectrometry is shown in Figure 13. In this case also, a distribution of peaks with a mass increment of *m/z* = 402 (molar mass of monomer **2** is 402.1 g/mol) was noted (Figure 13). However, two main series of peaks could be identified: the higher intensity one could be attributed to the triazolydene moiety deriving from **NHC-1** at one polymer chain end, while the other chain end consisted of the aldehyde group, similarly to **PBz-1** described above. The other population was ascribed to polymer chains terminated at both ends with an aldehyde moiety (Figure 13). The peak at *m/z* of 1502.2, for instance, corresponded to the following formula: $C_{20}H_{15}N_3$-$C_{23}H_{17}O_6$-$[C_{24}H_{18}O_6]_3$-CHO,H^+, *i.e.* a polymer structure involving three monomer **2** repeating units, cationized by H^+. 1 or 2 *m/z* values was found shifted for the same sample when changing the matrix from a mixture of IAA (Indole acrylic acid solution) adding sodium to matrix IAA only. The linear polymer ended only by one aldehyde function was indeed observed in this case, that was, at *m/z* might be n*402.1. For instance, the peak at *m/z* = 1229.1 corresponded to the following population: $C_{23}H_{17}O_6$-$[C_{24}H_{18}O_6]_2$-CHO,Na^+, *i.e.* the polymer with two monomer **2** repeating units, cationized by Na^+. Overall, MALDI-ToF mass spectroscopy confirmed the formation of poly(α-ketoalcohol)s arising from monomer **2**.

In contrast, attempts to polymerize monomer **3** by a **NHC-1** catalysis met with limited success. The SEC trace indeed showed the formation of presumably a dimer and a trimer only. The poor polymerizability of **3** –compared to monomer **2** that did polymerize- might be explained by the presence of ester moieties that decreased the reactivity of the aldehyde functions.

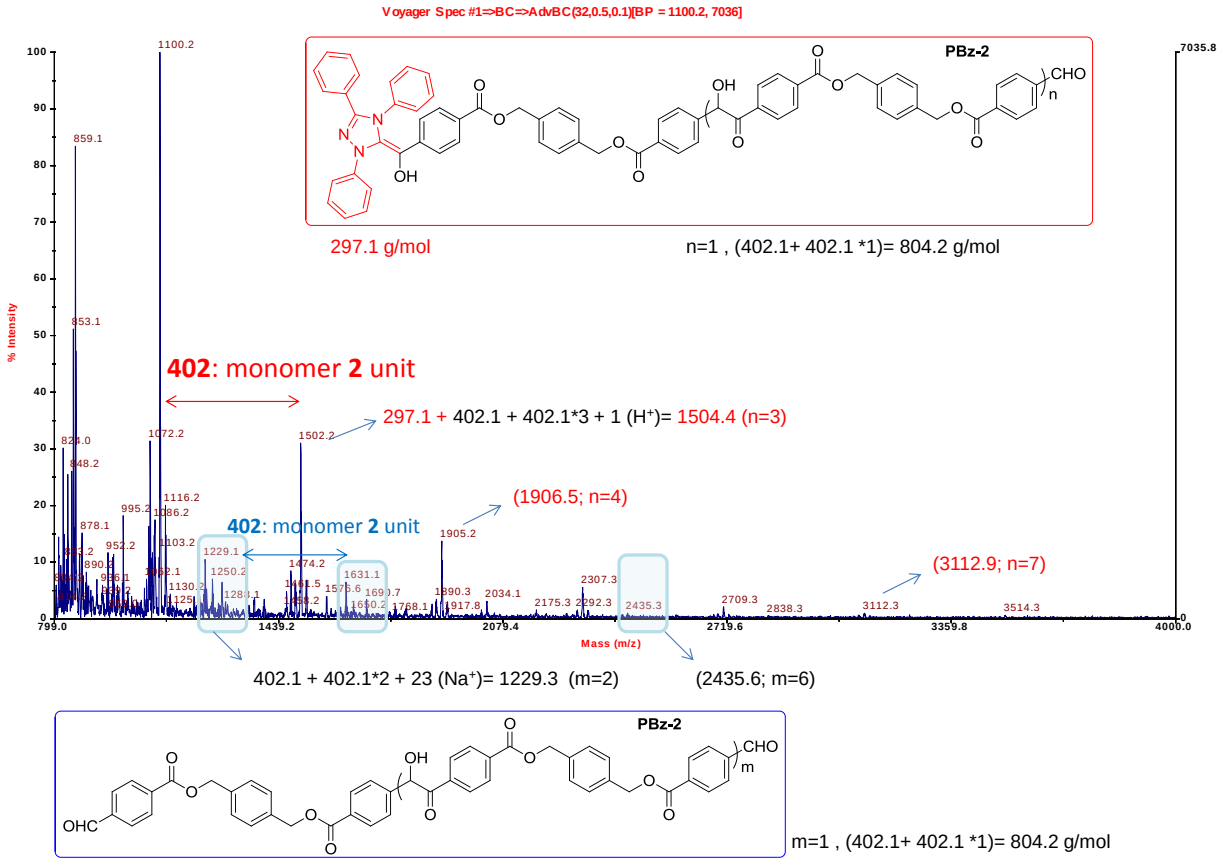


Figure 13. MALDI-ToF MS spectrum reflector mode of polybenzoin **PBz-2** (entry 6, Table 1).

3.2. Characterization of polymers PBz-1 and PBz-2 by DSC

Previously reported polybenzoins obtained from terephthalaldehyde were all amorphous in nature, with a glass transition temperature (T_g) value increasing with the molecular weight of polymers. For instance, the T_g measured for a molecular weight of 1670 g/mol (by ^{1}H NMR) was 149 ℃.[10] In the present work, both polybenzoin **PBz-1** (M_p = 5000 g/mol, entry 4, Table 1) and **PBz-2** (M_p = 5600 g/mol, entry 6, Table 1) are also amorphous, with a lower T_g value: 72.8 ℃ and 81.9 ℃, respectively, as measured by DSC analysis (Figures 14 and 15). This can be explained by the increase in flexibility brought by the silylated or the ester group.

Compared to terephthalaldehyde, more flexible monomers such as the silylated bis-aldehyde **1** or the bis-aldehyde **2** containing ester linkages allowed us to achieve novel polybenzoins under homogenous conditions in THF at 50 ℃. As a result, relatively high monomer conversions and molar masses (M_p) around 3000-5600 g/mol could be obtained, using 1,3,4-triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ylidene (**NHC-1**) as catalyst.

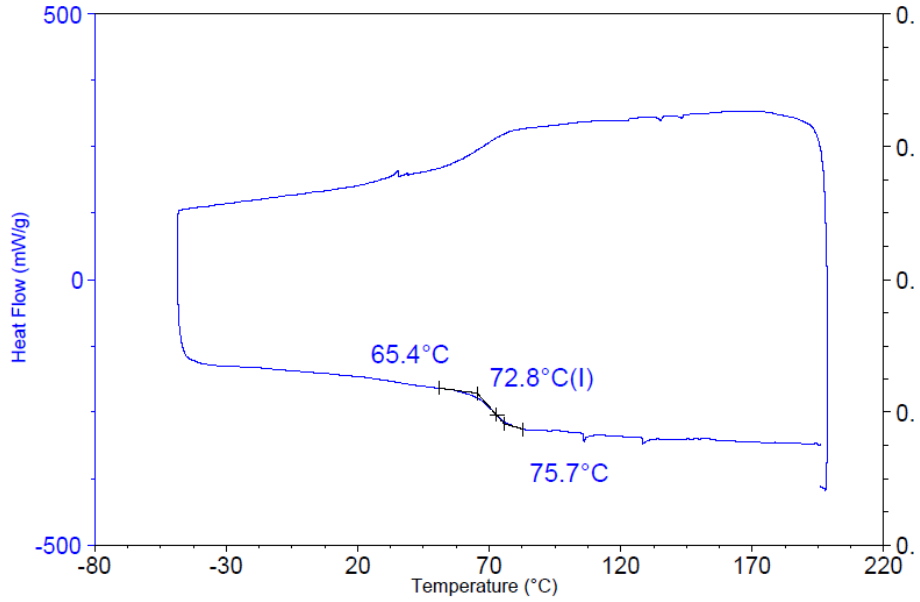


Figure 14. DSC thermograms of polybenzoin **PBz-1** synthesized from bis-aldehyde **1** (entry 4, Table 1).

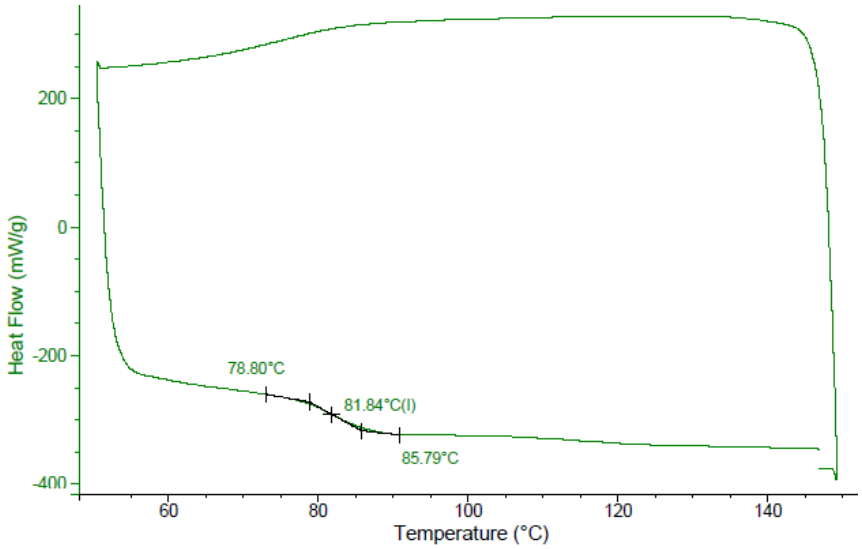


Figure 15. DSC thermograms of polybenzoin **PBz-2** synthesized from bis-aldehyde **2** (entry 6, Table 1).

4. Attempts to cleave off novel polybenzoins

In this part, cleavage of polybenzoins **PBz-1** and **PBz-2** described above was investigated to identify the conditions the best suited to generate molecular benzoin-type motifs. This step is indeed necessary prior to the analysis of the potential chiral character of the obtained polymer, due to the possible transfer of chirality from the catalyst to the growing chain. As discussed above, cleavage of polybenzoin **PBz-1** constituted of dimethylsilyl moieties in the main chain was expected to readily occur, given the sensitivity of Si-C_{aryl} bonds towards fluoride catalysts.[12] We first employed a classical fluorinated agent, namely, tetra-*n*-butylammonium fluoride (TBAF), as Itsuno did to disrupt Si-C_{aryl} bonds of polymer synthesized

from asymmetric Hosomi-Sakurai allylation (see section 5.2.2, chapter I).[15] Thus polybenzoin **PBz-1** was treated with TBAF in THF at room temperature, and the reaction was monitored by NMR and SEC analysis. As shown in Figure 16, other fluorinated agents were also tested.

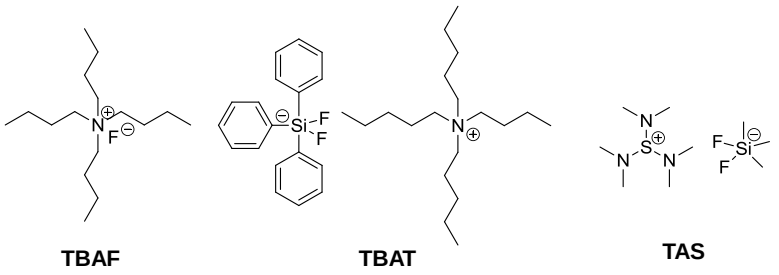
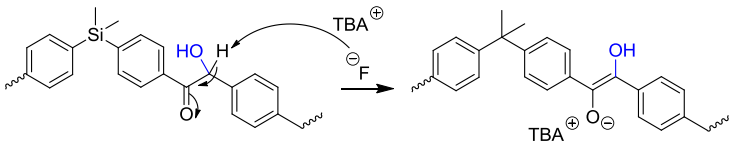


Figure 16. Fluorinated agents tested to cleave polybenzoins PBz1: tetra-*n*-butylammonium fluoride (TBAF), tetrabutylammonium difluorotriphenylsilicate (TBAT) and tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS).

Surprisingly, none of these catalysts allowed for a complete cleavage of polybenzoin **PBz-1**; the reaction did form compounds of lower molecular weight than that of the parent **PBz-1**, but oligomers thus generated were not suitable for a chirality analysis. Although an increase in the quantity of TBAF used coupled with a higher temperature (65 °C) in THF resulted in an increase of "benzoin motifs", the majority of the reaction product consisted in oligomers with 200 $< M_w <$1500 g/mol.

Under these forcing conditions, the C*H*OH proton of polybenzoin **PBz-1** disappeared, suggesting that TBAF was basic enough to deprotonate this proton in α-position of the carbonyl group, thus generating a tetrabutyl ammonium enolate (Scheme 7). Consequently, the chiral information of the stereogenic center was lost due to racemization, preventing further analysis.



Scheme 7. Proposed degradation mechanism of polybenzoin causing racemization.

This result was also confirmed from a model reaction involving the direct degradation by TBAF of molecular benzoin (prepared separately). The disappearance of the C*H*OH proton happened again when analyzing the ^{1}H NMR spectrum of degraded products, corresponding to a complicate mixture where aromatic protons are multiplied (Figure 17).

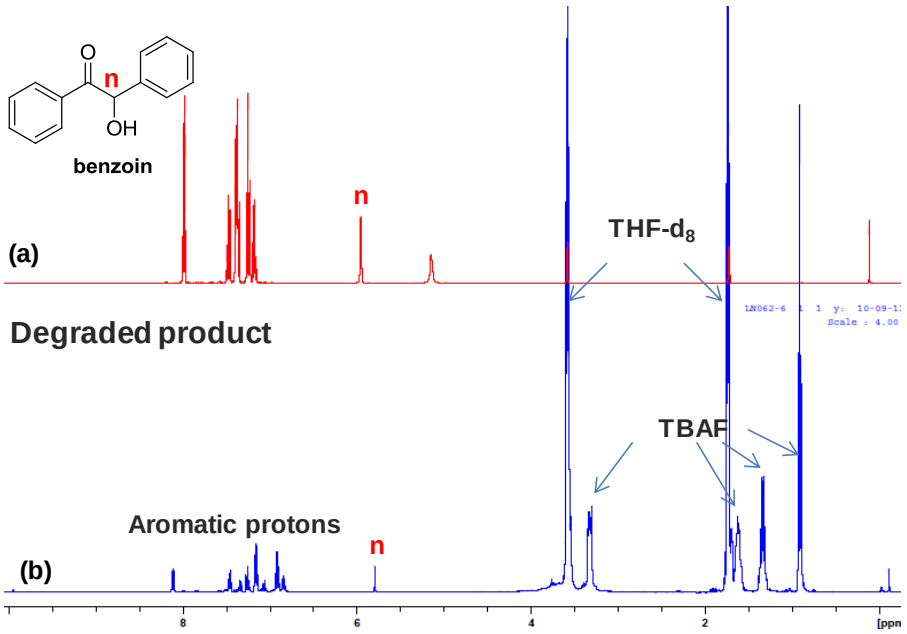


Figure 17. ^{1}H NMR (400 MHz, THF-d_8) of (a) benzoin and (b) benzoin treated by TBAF in THF for 3 days at 60 ℃.

Interestingly, using TAS as fluorinated agent did not cleave Si-C_{aryl} bonds of polybenzoin **PBz-1**; in contrast, molecular weights increased after treatment, as verified by SEC in THF (Figure 18): molecular weight increased from M_w = 5000 g/mol (D is 1.9) to M_w = 25000 g/mol (D is 2.7).

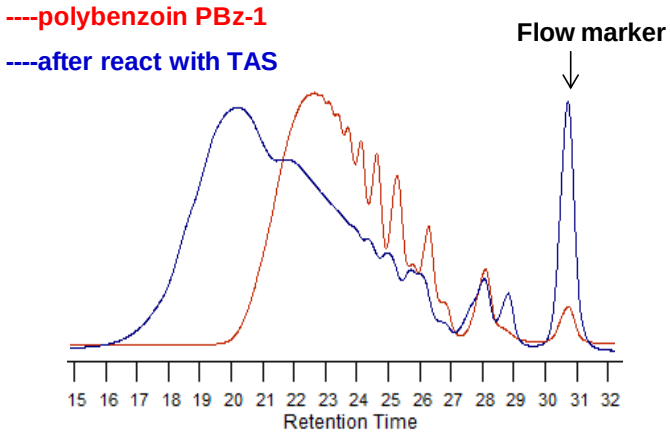
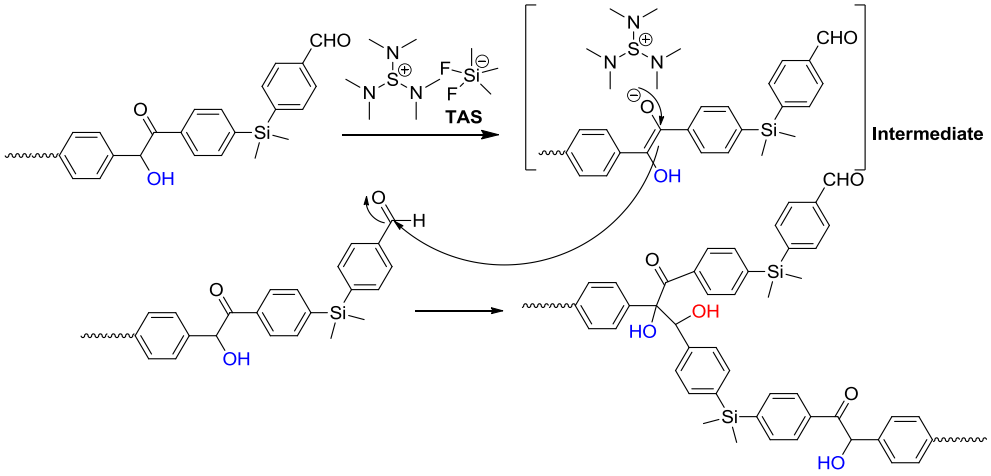


Figure 18. SEC traces (UV detection in THF; relative to PS standards) of polybenzoin **PBz-1** (entry 4, Table 1) and of the reaction compound after treatment by TAS.

To explain this result, we hypothesized that TAS could coordinate the negatively charged enolate oxygen, forming an intermediate that could add onto a terminal group aldehyde. Further reactions of this type could lead a three-dimensional polymeric structure, as depicted in Scheme 8.

We next focused our attention to the cleavage of the ester-containing polybenzoin **PBz-2**. While hydrolysis of ester groups under acidic or basic conditions was expected, we also anticipated that racemization of chiral centers could occur. To circumvent this issue, protection

of carbonyl groups was thus required. Acetalization is likely the common method for carbonyl protection;[16] however, it is generally performed under acidic conditions, which are not compatible with polybenzoin **PBz-2**. We thus turned to the reduction of carbonyl as a way to protect the chiral information of stereogenic centers of the repeating units. The hydrobenzoin formed upon reduction of the benzoin motif is indeed no longer sensitive to acidic or basic conditions. It should be possible then to hydrolyze ester linkages of thus-formed poly(hydrobenzoin) without any loss of the chiral information. Instead of hydrolysis, however, we chose to reduce the carbonyl and the ester groups, one pot, as a mean to access diols containing the chiral information in a straightforward manner.



Scheme 8. Posible reaction mechanism involving polybenzoin **PBz-1** with TAS.

As illustrated in Figure 19, reduction of benzoin leads to diastereomeric diols, the configurations of which are RR, SS, RS and SR. Given the symmetric nature of hydrobenzoin, both enantiomers RS and SR are identical (the two -OH groups are in *anti* position; see Figure 19) and represent a single *meso* diastereomer. As a matter of fact, the information concerning the initial configuration (R or S) of the benzoin precursor is unfortunately lost.

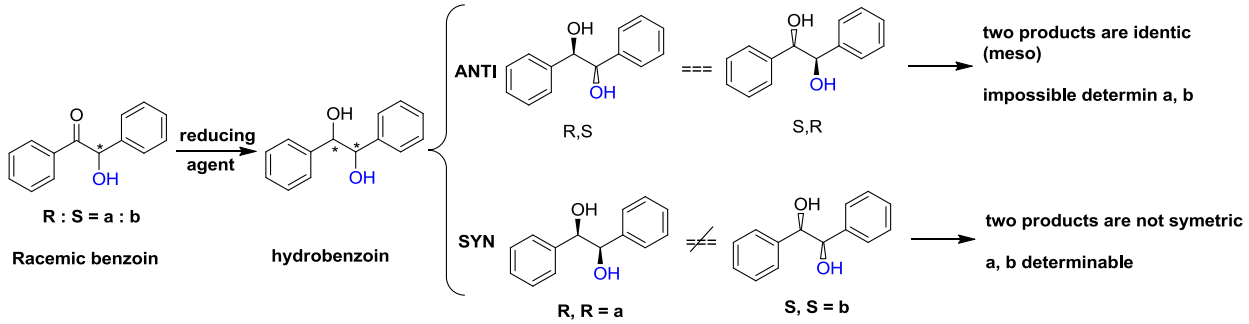


Figure 19. Reduction procedure of benzoin into hydrobenzoin, and different diastereomers of hydrobenzoin after reduction.

In contrast, the *syn* diastereomers are constituted of two enantiomeric pairs, RR and SS, in a a:b ratio. Thus, since the original chiral information of polybenzoin **PBz-2** is contained in the *syn* diastereomers. The diastereoselectivity of the reduction step is thus of prime importance.

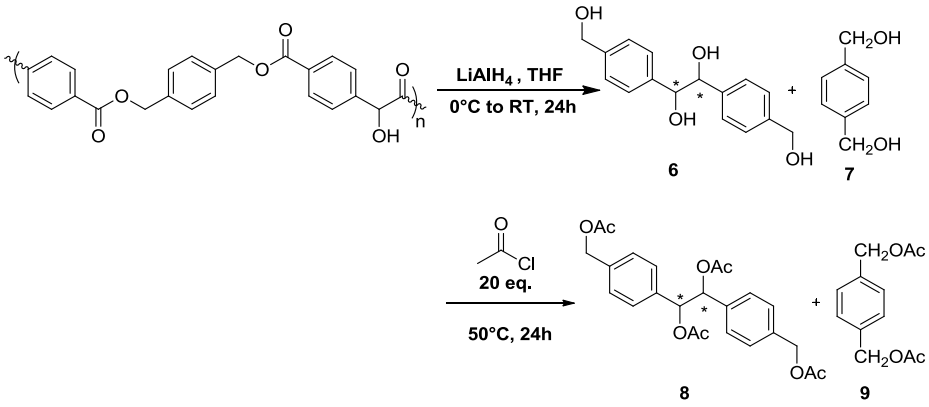
Two reducing agents, namely, $NaBH_4$ and $LiAlH_4$, were selected and model reactions involving molecular benzoin itself were conducted. The diastereoselectivity observed after reduction of the carbonyl groups is in favor of the *anti*-selectivity.[17] Reduction of benzoin with $NaBH_4$ and $LiAlH_4$ provided the hydrobenzoin quantitatively after 24h, but only 8 and 10% of *syn*-selectivity were observed, respectively.

Table 2. Reduction tests for benzoin and polybenzoin.[a]

entry	Reactant	Reducing agent	T (℃)	solvent	*syn*%[b]
1	Benzoin	$NaBH_4$	0 ℃ to RT	THF/Methanol = 1/1	8%
2	Benzoin	$LiAlH_4$	0 ℃ to RT	THF	10%
3	**PBz-2**	$LiAlH_4$	0 ℃ to RT	THF	10%

[a] reduction reactions are realized in 1mol/L concentration of monomer (or polymer) with 100% conversion after one night. [b] percentage of racemic hydrobenzoin containing in the product is determined by ^{1}H NMR.

$LiAlH_4$ was thus selected for the one-pot reduction/cleavage of polybenzoin **PBz-2.** The degradation process and reaction products are shown in Scheme 9.



Scheme 9. Degradation of polybenzoin **PBz-2** reaction products formed.

According to SEC analysis (Figure 20), polybenzoin **PBz-2** could be completely cleaved into elementary molecular motifs of hydrobenzoin, after reaction with 5 eq. of $LiAlH_4$, in THF at 0 ℃ (entry 3, Table 2).

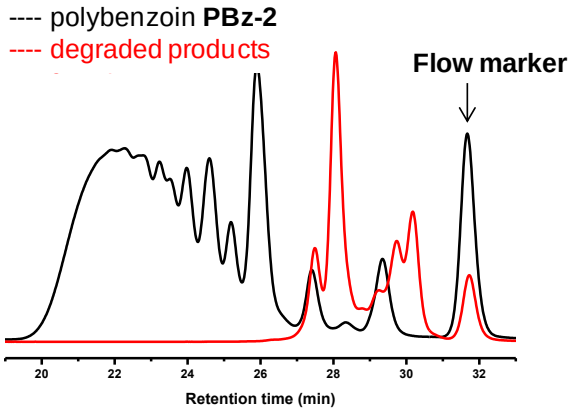


Figure 20. SEC traces (UV detection in THF; relative to PS standards) of polybenzoin **PBz-2** and its degraded products obtained after treatment with $LiAlH_4$.

The structure of these degraded products was verified by ^1H NMR in MeOD (Figure 21), where broad signals of polybenzoin **PBz-2**, as well as the C*H*OH benzoin proton at 5.6-6.0 ppm disappeared. The upfield shift observed for the C*H*OH proton (from 5.6-6.0 ppm to 4.8 ppm) was in agreement with the transformation of the carbonyl groups of **PBz-2** into hydroxyl groups due to hydrobenzoin. The methylene protons of the ester groups of **PBz-2** (CH_2CCO, peak h – though broad- signals at 5.3 ppm) were shifted to 4.55 ppm (peak t) as multiple peaks. The second fragment resulting from the cleavage of the polyhydrobenzoin could be clearly identified at 7.3 ppm (peak w, singlet) as the dibenzylalcohol **7** (see Scheme 9).

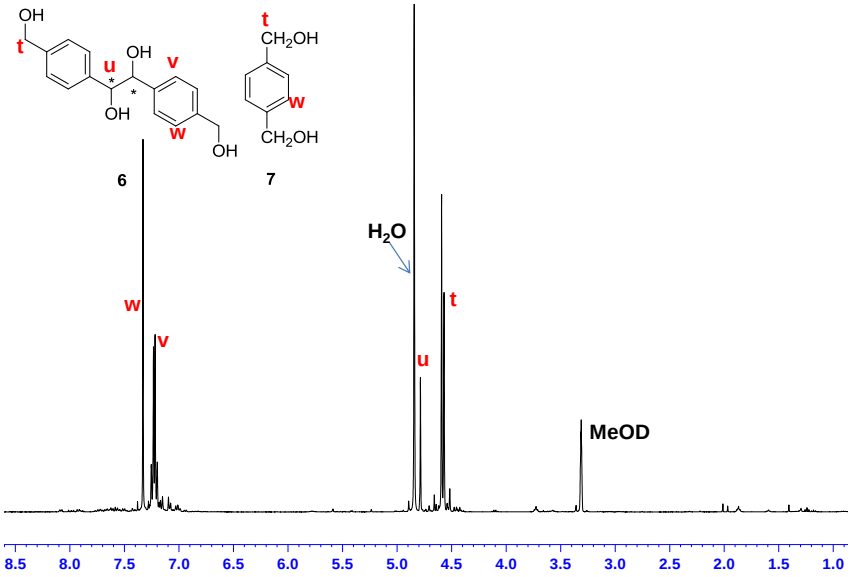


Figure 21. ^1H NMR (400 MHz, MeOD) of polybenzoin **PBz-2** degraded by $LiAlH_4$ in THF.

These products had to be separated before analysis of their chirality. However, they proved too polar to be efficiently separated by column chromatography over silica, using MeOH/H_2O as eluent. Thus an additional acetylating step was performed to lower the polarity of the tetraol **6** and the diol **7** (Scheme 9). This acetylation step was conducted using a large excess of acetyl chloride (20 eq.) that was directly added on the crude mixture of polybenzoin **PBz-2**

reduced by $LiAlH_4$. After 24h of stirring at 50 °C, the reaction mixture was evaporated to dryness and acetylated products were extracted with dichloromethane before the residue was chromatografied over silica. The tetraacylated compound **8** and the diacetylated compound **9** could thus be well separated.

In addition, by running carefully the separation, the *meso* diastereoisomer could be somehow separated from the RR/SS diastereoisomers, as evidenced by the integration of the C*H*OH and CH_2OH signal at 6.06 and 5.08 ppm, respectively, for the meso compound, and signals detected at 6.03 and 5.03 ppm due to the RR+SS enantiomers, respectively (Figure 21). In contrast, the enantiomeric RR/SS pair was contaminated with various amounts of the *meso* compound (30% minimum), as can be seen in the ^{1}H NMR spectrum in Figure 22. Most importantly, however, this relative ratio of syn products was high enough for a chiral HPLC analysis.

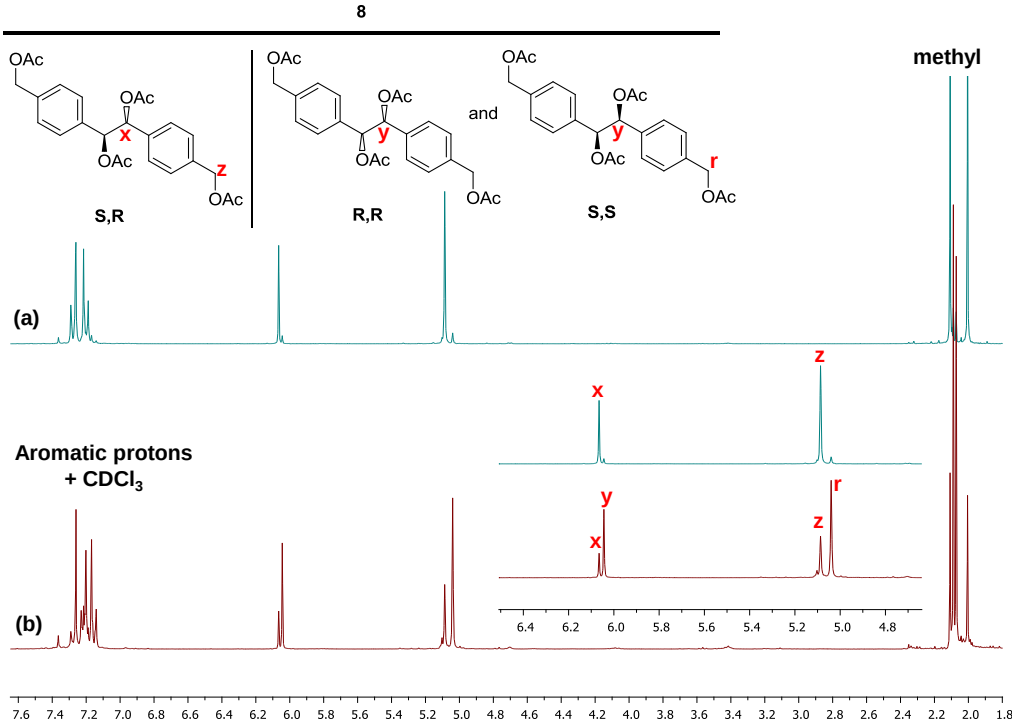


Figure 22. ^{1}H NMR (400 MHz, $CDCl_3$) of **8** resulting from the degradation of **PBz-2** at different fractions of purification by flash chromatography: (a) earlier fraction; (b) later fraction containing more racemic form (peak x and z are bigger).

The next section describes the use of chiral NHCs for the asymmetric step-growth polymerization of the bis-aldehyde **2**. A procedure was developed so as to perform, one pot, the polymerization reaction, the reduction of the resulting polybenzoins with $LiAlH_4$, followed by the acetylation of the as-obtained fragments. Isolation of the tetraacetylated diastereoisomers was then achieved by flash chromatography, before fractions containing high enough content of syn diastereoisomers could be analyzed by chiral HPLC.

5. Step-growth polymerization of bis-aldehyde 2 using chiral NHC organocatalysts

The polymerization of bis-aldehyde **2** with various commercially available NHCs derived from chiral triazolium salts was examined (Figure 23). We first investigated the deprotonation of these triazolium salt precursors (= pre-catalysts) with strong bases, such as potassium bis(trimethylsilyl)amide (KHMDS) and lithium di-isopropylamine (LDA), as well as with a neutral base, namely, 1,8-diazabicycloundec-7-ene (DBU).[18]

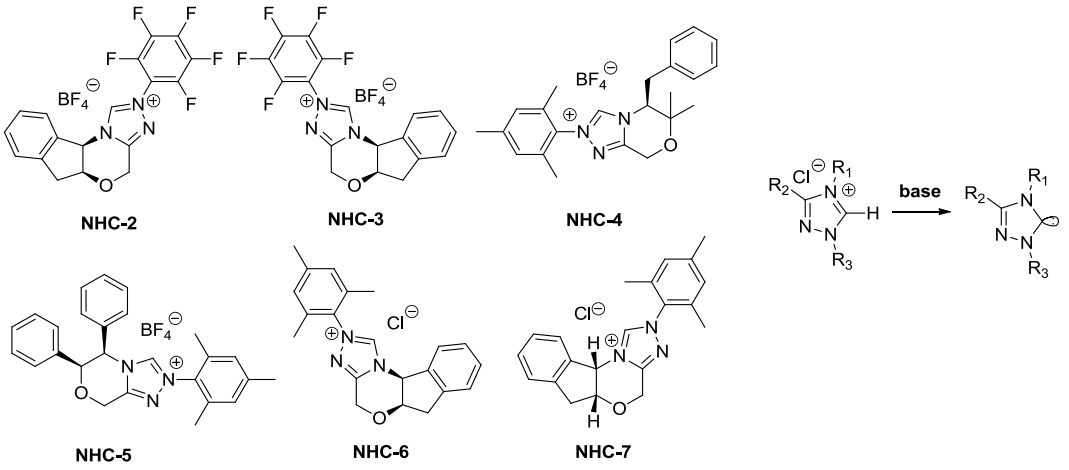
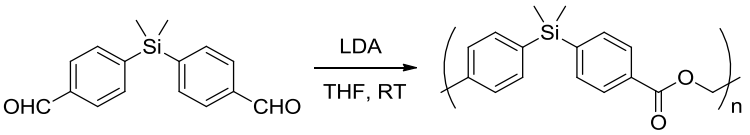


Figure 23. Commercial chiral triazolium salts employed as pre-catalysts to polymerize **2** (left) and activation of these precursors by deprotonation with a base (right).

Blank reactions involving the strong base in absence of the tyriazolium salt were first performed. Surprisingly, both KHMDS and LDA could promote the oligomerization of the bis-aldehyde monomers **1** or **2** at room temperature, in THF (entries 1 and 2, Table 3). However, we established that the ensuing oligomers consisted of ester linkages in the polymer backbone, as deduced from the characteristic signals observed 5.35 ppm (*C<u>H₂</u>*OC=O) and 1686 cm^{-1} (C=O) in their respective ^{1}H NMR and IR spectra. In other words, these oligomers were not made of characteristic α-ketoalcool units of polybenzoin chains.

The repeating units were actually formed *via* repeated disproportionation reactions involving two aldehyde functions, referred to as the Tishchenko reaction (Scheme 10). This elementary reaction has been presented in the bibliographic chapter (see section 5.3.3, chapter I). Aluminium or sodium alkoxides were originally generally employed to catalyze this reaction, but other catalysts have been developed, as recently reviewed by Onaka *et al.*[19] It was already applied in polymer chemistry, in a few cases, to derive aromatic polyesters, in particular from terephthalaldehyde.[20] Here, we discovered here that KHMDS could directly promote the polymerization of bis-aldehydes, *via* the Tishchenko reaction, which was never reported before (Scheme 11).

Scheme 10. The Tishchenko reaction forming an ester.



Scheme 11. Tishchenko polyaddtion of bis-aldehyde **1** catalyzed by LDA (entry 2, Table 3).

Besides KHMDS and LDA, DBU was also examined in absence of the triazolium precursor (entry 3, Table 3). In this case, however, no polymerization was observed, even at 50 ℃. In contrast, DBU was found particularly suitable for the deprotonation of azolium salts in THF (entries 4-9, Table 3), forming NHCs the latter species catalyzing polybenzoin synthesis.

Table 3. Step-growth polymerization of bis-aldehydes (**1** and **2**) triggered by *in situ* prepared NHCs.[a]

entry	NHCs 10mol%	Base (mol%)	conv[b] (%)	$\overline{M}_w$ (g/mol)[c]	M_p (g/mol)[c]	D[c]	$[\alpha_D]_p$[d]	$[\alpha_D]_{NHC}$[e]	T_g[f]
1	-	KHMDS 5	nd	dimer	800	-	nd	nd	nd
2[g]	-	LDA 10	78%	2200	3500	1.9	nd	nd	nd
3	-	DBU 10	-	-	-	-	nd	nd	nd
4	**NHC-2**	DBU 10	62%	5800	14000	2.2	19.26	+136	113.3
5	**NHC-3**	DBU 10	67%	5900	18000	2.7	-9.62	-140	116.4
6	**NHC-4**	DBU 10	73%	2100	3900	1.7	-2.72	-123	88.1
7	**NHC-5**	DBU 10	50%	2300	3200	1.6	3.25	+74	88.2
8	**NHC-6**	DBU 10	67%	2400	3300	1.8	17.23	+158	90.7
9	**NHC-7**	DBU 10	60%	2000	2300	1.8	-18.25	-156	84.7

[a] concentration of bis-aldehyde **2** (entries 1 and from 3 to 9) is 0.2 mol/L in THF at 25 ℃. [b] conversions are determined by NMR before purification of polymer by precipitations. [c] mass-average molecular weights and dispersity *D* are determined by SEC in THF (calibration using polystyrene as standards) after 3 days' reaction. [d] rotation angles [α_D] of obtained polybenzoins are measured by polarimeter. [e] rotation angles [α_D] of corresponding utilized catalysts azolium salts offered from Sigma-Aldrich data. [f] Glass transition temperature T_g of polymers was analyzed by DSC thermogramme. [g] bis-aldehyde **1** was investigated in this polymerization, monomer concentration is 0.4 mol/L in THF, SEC results shown were determined at 7 days' reaction at RT.

Moderate to good conversions of monomer **2** (50-73%) were achieved, regardless of the nature of the catalyst. Molecular weights ranging from 2000 to 5900 g/mol were thus obtained with the six different triazolium salts tested, after 3 days of polymerization at room temperature. Samples in Table 3 (entries 4-9) exhibited similar SEC profiles and NMR spectra were also identical to those obtained from the polymerization of monomer **2** catalyzed by the nonchiral **NHC-1**.

Peaks' assignment in the ^{1}H NMR spectrum of **PBz-3,** obtained from the polymerization of monomer **2** catalyzed by **NHC-3**, is shown in Figure 24. Here also, a characteristic signal is peak h at 5.29 ppm, corresponding to the benzoin group (O=CC*H*OH). Furthermore, the signal (i) confirms the presence of aldehyde groups at the polymer chain ends. The ^{13}C NMR spectrum of **PBz-3** shows the presence of the aldehyde end-group with peak i' (*C*HO) at 192.1 to 193.6 ppm (Figure 25).

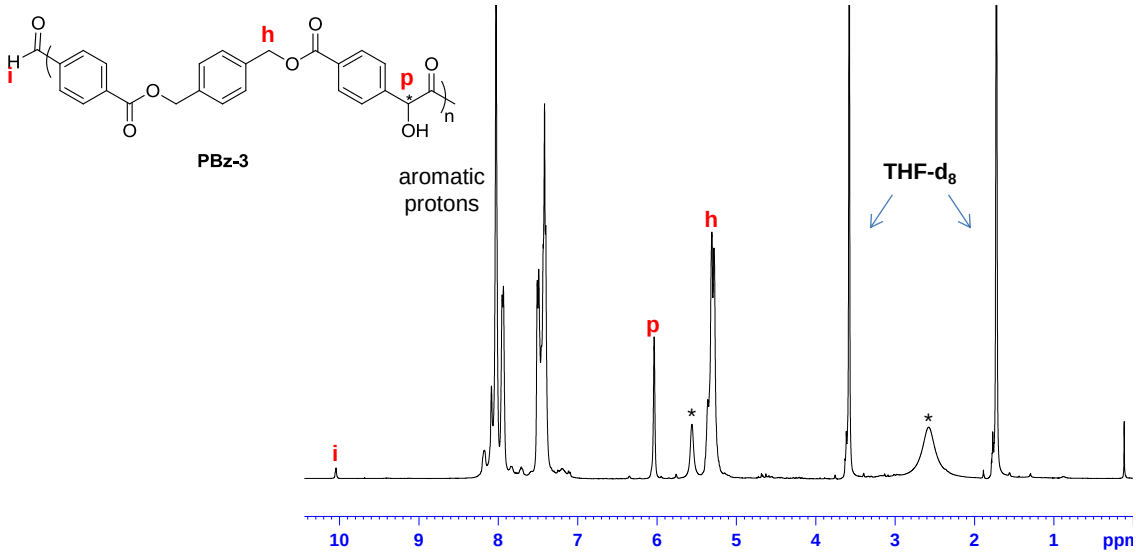


Figure 24. ^{1}H NMR (400 MHz, THF-d$_8$) of polybenzoin **PBz-3**; * are peaks of solvent or impurity.

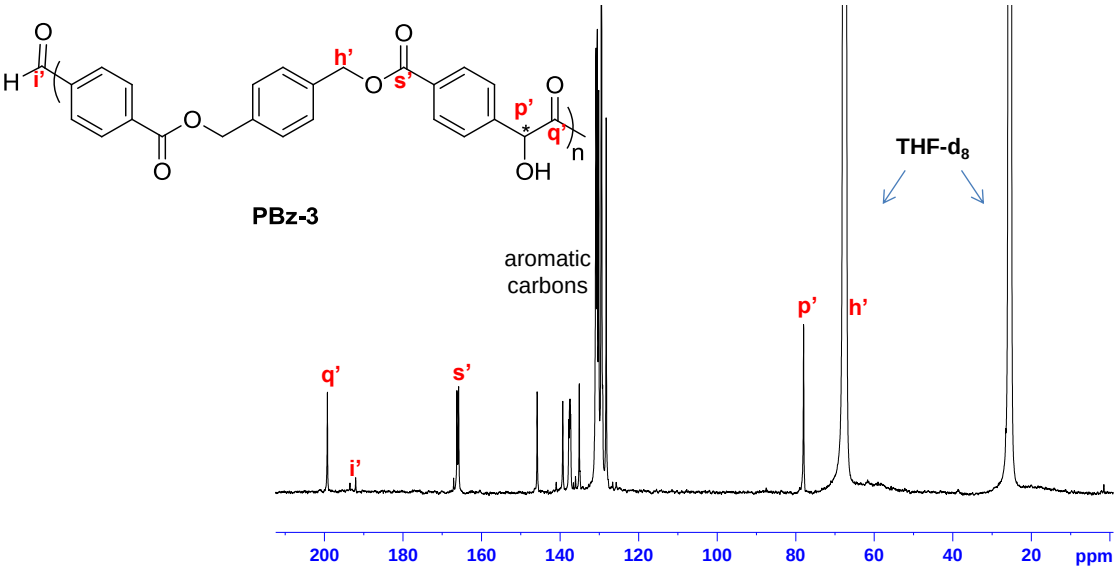


Figure 25. ^{13}C NMR (THF-d$_8$) of polybenzoin **PBz-3**.

These polybenzoins (entries 4-9, Table 3) were next characterized by differential scanning calorimetry (DSC). For instance, the DSC curve of **PBz-3** obtained from **NHC-3** (entry 5) is shown in Figure 26. The glass transition temperature T_g of **PBz-3** was determined by taking the inflection point of the transition at 116.3 °C. Polybenzoins (entries 4-9) were all amorphous, higher glass transition temperature (T_g) values being found for polymers exhibiting the higher molecular weights (113.3 °C, entry 4 and 116.3 °C, entry 5).

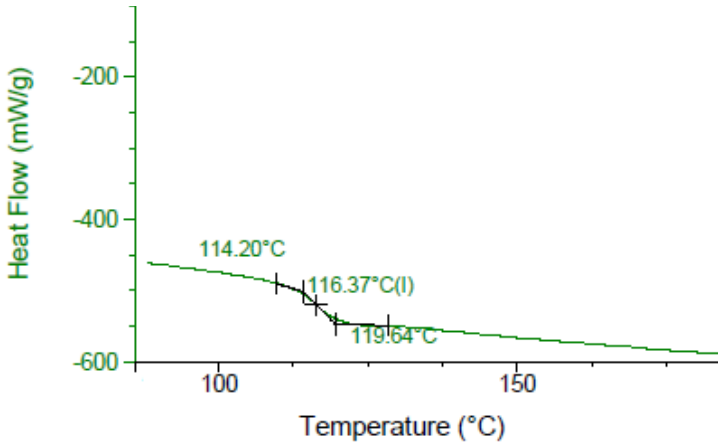


Figure 26. DSC thermograms of polybenzoin **PBz-3** at a heating rate of 10 °C min^{-1}

Interestingly, these polybenzoins proved optically active, as proven by their rotatory power that was determined by optical polarimetry in THF solution (Table 3). Thus, polybenzoins synthesized from polymerization catalyzed by **NHC-2, NHC-6** and **NHC-7**, denoted as **PBz-4**, **PBz-5** and **PBz-6**, respectively, show rotatory power values [α_D] equal to 19.26 °, 17.23 ° and -18.25 °, respectively. It should be noted that polybenzoin **PBz-2** synthesized from the non-chiral catalyst **NHC-1** gave an [α_D] value less than 5 °.

The optical rotation could reflect a preferential configuration of the main chain stereocenters.[21] Indeed, the presence of an optically active NHC at the polymer chain end may induce a preferential conformation, given that the rotation angle of the NHC and that of the polybenzoin is the same. The rotation angle of polybenzoins $[\alpha_D]_p$ and the rotation angle of $[\alpha_D]_{NHC}$ of the NHC are always in the same sense. This could mean that the **NHC** chain end dictates the optical rotation of the polymers in THF solution. However, a more systematic study would be needed to support this statement.

Attempts to determine the enantiomeric excess (e.e.) of related polybenzoins were realized after the polymers were selectively degraded, according to the synthetic procedure described above. The degradation products could indeed be separated by flash chromatography and e.e. values were evaluated by chiral HPLC.

Firstly, the racemic product degraded from polybenzoin **PBz-2** that was achieved from the non-chiral **NHC-1** was separated in a mixture of n-heptane/2-propanol/diethyl amine (70/30/1 in vol.; see Figure 27a). The ratio corresponding to three main peaks is as follows:

22 : 22 : 56, corresponding to the ratio between RR (SS), SS (RR) and SR forms (Figure 20). Figure 28b shows the chiral HPLC analysis of the degraded products in the case of **PBz-6** (entry 9, Table 1). Unfortunately, the same 22 : 22 : 56 ratio was measured, corresponding to 0% of e.e. This result seems to indicate that the chiral catalyst triazolium salt **NHC-7** does not show any significant enantioselectivity for the benzoin polycondensation of monomer **2**. The e.e. of the other polybenzoins could not be measured accurately. However, we hypothesized that this could be ascribed to the racemisation during the step of degradation *via* $LiAlH_4$, thus there are e.e. equals to 0%. Further studies of the choice of reducing agents could confirm this hypothesis.

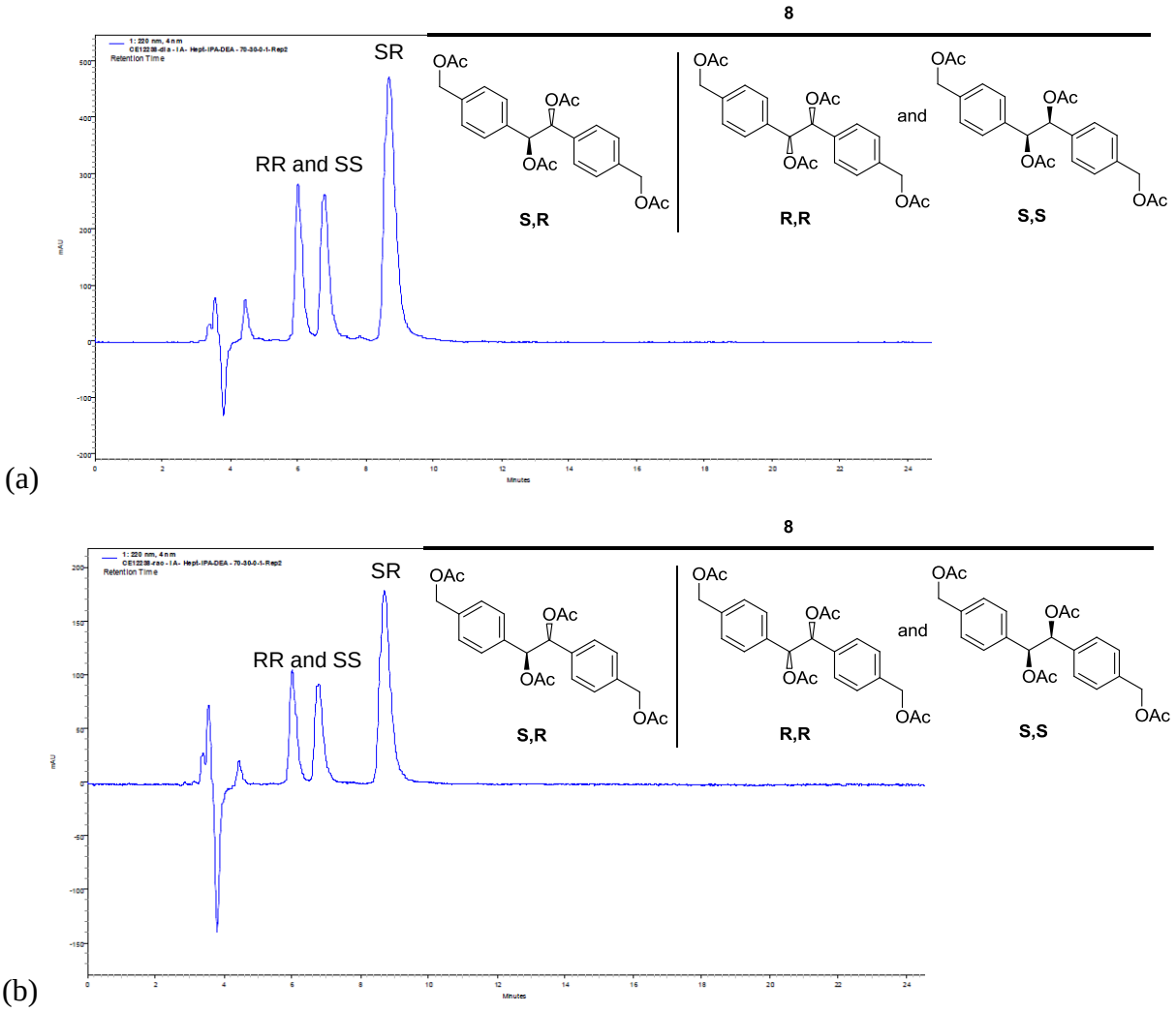


Figure 27. Determination of enantiomeric excess (e.e.) from the separation of enantiomers by HPLC; (a) from degraded achiral polybenzoin **PBz-2** (b) from degraded chiral polybenzoin (entry 9, Table 1)

6. Conclusion

The direct NHC-catalyzed step-growth polymerization of novel bis-aldehyde monomers, namely, di(4-formylphenyl) dimethylsilane, and 1,4-phenylenebis(methylene) bis(4-formylbenzoate), provides a relatively easy synthetic method to unprecedented polybenzoin-type polymers that can be well solubilized in organic solvents. Polymers with molecular weights (M_p) ranging from 5600 g/mol to 14000 g/mol were obtained, using chiral triazolium salt precursors serving as pre-catalysts to be deprotonated into chiral NHCs in the presence of a strong base.

Polymerization experiments utilizing the strong base alone in absence of triazolium lead to repeated Tischenko elementary reactions, forming aromatic polyesters.

While the degradation of silylated-containing polybenzoins met with limited success, ester-containing polybenzoins could be readily cleaved using $LiAlH_4$. Although the diastereoslectivity of the reduction products of the benzoin units is very low (10%), it allows the e.e. to be measured upon acetylation of the hydrobenzoin fragments.

Despite of all these efforts, no e.e. could be finally measured regardless of the nature of the chiral NHC precursor. It can thus be concluded that the transfer of chirality from the catalyst to the monomer units remains a challenging task and further studies are indispensable to access chiral polybenzoin-type polymers. While the design of NHCs with the chirality in closer position to the reactive center may be a way to follow, the optimization of the reaction conditions (e.g. the temperature) has to be taken into account. Besides the chirality aspect, the relatively high molecular weights polybenzoin obtained could be interesting precursors for the synthesis of π-conjugated polymers by an organo-catalytic pathway.

In the following chapter, hydroxyl-aldehyde monomers are polymerized in a step-growth fashion via an acid catalysis for hyperbranched polyacetal synthesis.

7. Experimental section

Materials.

All reagents and solvents were of commercial grade and used as received. All other chemicals and reagents were acquired from Sigma-Aldrich (Buchs, Switzerland) with purity ≥ 99% unless otherwise stated except **NHC-7** is commercially by the company TCI (99%, Tokyo Chemical Industry Co., Ltd. Japan). Heptane, DEA (diethyl amine) (all HPLC grade), 2-propanol (HPLC/MS grade) were purchased from Sigma-Aldrich (Buchs, Switzerland). All the polymerizations were performed under an inert atmosphere using standard Schlenk techniques. Dry, oxygen-free solvents and monomers were employed. For the monomers, they were prepared by dissolving in dry dioxane and dried by a lyophisation for 2 hours. THF was distilled over Na/benzophenone prior to use. DMF was distilled over CaH_2 before use following a minimum of 4 h of reflux. Benzyl alchohol was purified by fractional distillation. Deuterated solvents for NMR spectroscopy were acquired from Armar Chemicals (Dottigen, Switzerland).

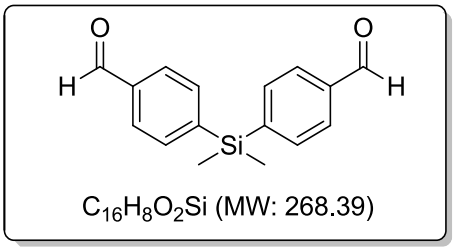
Instrumentation.

NMR spectra were recorded on a Bruker AC-400 spectrometer in appropriate deuterated solvents. Molar masses were determined by size exclusion chromatography (SEC) in THF as the eluent (1mL/min) and with trichlorobenzene as a flow marker at 25 ℃, using both refractometric (RI) and UV detectors (Varian). Analyses were performed using a three-column set of TSK gel TOSOH (G4000, G3000, G2000 with pore sizes of 20, 75, and 200 Å respectively, connected in series) calibrated with polystyrene standards. Differential scanning calorimetry (DSC) measurements were performed on a DSC Q100 apparatus from TA Instruments. Data were recorded during the second run for temperatures ranging from 20 to 200 ℃ at a heating rate of 10 ℃ min-1. The cooling rate between the first and second runs was also equal to 10 ℃ min-1. The glass transition temperature (T_g) was determined by taking the inflection point of the transition. MALDI-ToF spectrometry was performed using a Voyager-DE STR (Applied Biosystems) spectrometer equipped with a nitrogen laser (337 nm), a delay extraction and a reflector. The instrument is equipped with a pulsed nitrogen laser (337 nm) and a time-delayed extracted ion source. Spectra were recorded in the positive-ion mode using the reflectron and with an accelerating voltage of 20 kV. Samples were dissolved in THF at 10 mg/mL, The IAA matrix (Indole acrylic acid) solution was prepared with the prepared sample solution. One to two microliters of the obtained solution mixture was deposited onto the sample target and vacuum-dried at room temperature. Optical rotation was obtained using a Perkin-Elmer 243B polarimeter, polymers are soluble in 1M THF to analyze the rotation angle. HPLC was carried out using the system LC-10AD from Shimadzu Austria. Columns CHIRALPAK®

IA (250 mm length, 4.6 mm in diameter) was Chiral technologies europe, France. The temperature of the columns was 22 ℃. UV (absorbance A) and circular dichroism (differential absorbance Δ A) intensities in arbitrary units are at a fixed wavelength between 220 and 420 nm. 10 mg/mL sample solution was prepared with n-Heptane / 2-Propanol / Diethyl amine as 70 / 30 / 1, the same solvent mixture was used for HPLC separation. UV detector was fixed at 220 nm where the product is sensible. The fate of eluent is 0.5 mL/min.

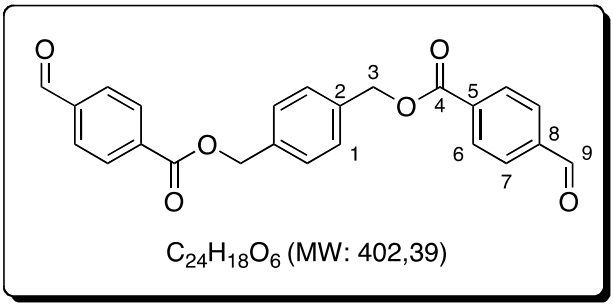
Synthesis of monomers

*Synthesis of di(4-formylphenyl) dimethylsilane (bis-aldehyde **1**)*



Di(4-formylphenyl) dimethylsilane (bis-aldehyde **1**) is prepared following protocol published in literature.[12] 4-Bromobenzaldehyde dimethyl acetal 1 (7.40 g, 32.03 mmol) was dissolved in THF (120 mL) under nitrogen. n-BuLi/hexane solution (1.6 M, 32.0 mmol, 20 mL) was added slowly at −78°C over 30 min. After stirring the mixture for 1 h at −78°C, dichlorodimethylsilane (1.5 mL, 12.52 mmol) was added to the above suspension. The reaction mixture was then stirred for 1 h at −78°C, allowed to warm to room temperature and was stirred for 12 h. The reaction mixture was quenched with 2N HCl and extracted with ether. The organic phase was washed with brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave the crude acetal/aldehyde mixture. To the crude mixture acetic acid (10 mL) and H_2O (3 mL) were added and stirred for 3 h at room temperature. The reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ and extracted with ether. The combined extract was washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude product was purified by column chromatography (pentane: EtOAc, 4:1) to give bis-aldehyde **1** as a white solid (2.18 g, 8.1 mmol, 65%); mp 78–80 ℃, ^{1}H NMR ($CDCl_3$): 10.02 (s, 2H, C*H*O), 7.85 (d, J=8.0 Hz, 4H, Ph-*H*), 7.68 (d, J=8.0 Hz, 4H, Ph-*H*), 0.64 (s, 6H, SiCH_3); ^{13}C NMR ($CDCl_3$): 192.8, 146.0, 137.2, 135.0, 129.1, −2.5.

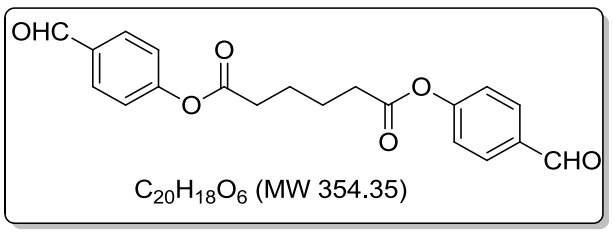
*Synthesis of 1,4-phenylenebis(methylene) bis(4-formylbenzoate) (bis-aldehyde **2**)*



$C_{24}H_{18}O_6$ (MW: 402,39)

To a suspension of NaH (160 mg, 6.66 mmol) in anhydrous DMF (15 mL) was slowly added a solution of 4-formylbenzoic acid (1 g, 6.66 mmol) in anhydrous DMF (5 mL) at 0 ℃ under argon. The reaction mixture was stirred for 15 min at the same temperature. Then, a solution of 1,4-bis(bromomethyl)benzene (586 mg, 2.22 mmol) in anhydrous DMF (5 mL) was slowly added, and the reaction mixture was stirred at 0 ℃ for 10 min. The resulting mixture was then stirred at 60 ℃ for 12h. The mixture was quenched with a 1M HCl solution (30 mL). The aqueous layer was extracted with EtOAc (3 x 90 mL) and the organic layers were washed with a saturated aqueous KCl solution (2 x 30 mL), and then with a 1M NaOH solution (2 x 30mL), dried over Na_2SO_4, filtrated, and the solvents evaporated in vacuum. The crude product was purified by flash chromatography (CH_2Cl_2/MeOH, 100/0 to 90/10) to afford the desired product as a white solid (681 mg, 76%). R_f = 0.72 (Petroleum ether/EtOAc, 1/1), m.p. = 169-170 ℃, IR (neat): 2947 cm^{-1}, 2847, 2746, 1708, ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.10 (s, 2H, C*H*O), 8.23 (d, *J* = 8.2 Hz, 4H, Ph-*H*), 7.97-7.92 (m, 4H, Ph-*H*), 7.50 (s, 4H, Ph-*H*), 5.41 (s, 4H, Ph-*H*), ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.7 (*C*HO), 165.4 (C4, Ph-*C*), 139.4 (C8, Ph-*C*), 136.0 (C5, Ph-*C*), 135.1 (C2, Ph-*C*), 130.4 (C6, Ph-*C*), 129.6 (C7, Ph-*C*), 128.8 (C1, Ph-*C*), 67.0 (C3, *C*H_2OCO), HRMS (ESI) $[M+Na]^+$ $C_{24}H_{18}O_6Na$: calcd. 425.1001; found: 425.1002.

*Synthesis of bis-aldehyde **3**[13]*



$C_{20}H_{18}O_6$ (MW 354.35)

To a stirred suspension of NaH (0.20 g, 8.33 mmol) in anhydrous THF was added 4-hydroxybenzaldehyde (1.02 g, 8.33 mmol) under nitrogen atmosphere, and the mixture was stirred at 0 ℃ for 1 h. Adipoyl chloride (0.77 g, 4.21 mmol) was then added and stirred for 20 h at RT. Then water was slowly added into the resulting mixture. Agter the organic layer was separated, the residual aqueous layer was extracted twice with ethyl acetate (EtOAc). The

combined organic layer was dried over Na_2SO_4, filtrated, and concentrated to give the crude solid product, which was washed with hot water. Recrystallization from pentane/ EtOAc afforded monomer 3 as a white crystal. (1.50 g, 41% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.00 (s, 2H, C*H*O), 7.93 (d, *J* = 8.3 Hz, 4H, Ph-*H*), 7.28 (d, *J* = 8.9 Hz, 4H, Ph-*H*), 2.67 (br s, 4H, C*H*$_2$COO-Ph), 1.90 (s, 4H, C*H*$_2$CH$_2$COO-Ph). ^{13}C NMR (75 MHz, $CDCl_3$): 190.8, 170.9, 155.3, 134.0, 131.2, 122.3, 22.9, 24.1.

Polymerization

All polymerization reactions were carried out under a dry and inert atmosphere using vacuumed flame-dried special Schlenk apparatus equipped with a withdrawal vial on the side of the main flask. Catalysts NHCs and monomers are stocked in glove box.

*Polymerization of di(4-formylphenyl) dimethylsilane (bis-aldehyde **1**).*

In a typical polymerization, to a solution of bis-aldehyde **1** (215 mg, 0.80 mmol) in 2 mL THF, add quantity needed of catalyst **NHC-1** (10 mol%, 24 mg, entry 4 in Table 1) in glove box using Schlenk equipment. Schlenk tube is fixed in an oil bath at 50 ℃ (entry 4, Table 1; or at 25 ℃ for RT) under stirring. At precise time intervals, aliquots were taken under dry argon flux and quenched with a droplet of degassed MeOH. At the end, the reaction was quenched by adding few drops of methanol to the reaction mixture. The polybenzoin was precipitated in pentane to eliminate monomer residue and catalyst and dried under vacuum to obtain **PBz-1** as a white solid (136 mg, yield 63%). The conversions are calculated by ^{1}H NMR spectroscopy before precipitation. Molecular weights and dispersities were obtained by SEC analysis in THF.

*Polymerization of di(4-formylphenyl) dimethylsilane (bis-aldehyde **2**) catalyzed by **NHC-1**.*

To a solution of bis-aldehyde **2** (160 mg, 0.40 mmol) in 2 mL THF, added quantity needed of catalyst **NHC-1** (10 mol%, 12 mg, entry 6 in Table 1) in glove box using Schlenk equipment. Schlenk tube is fixed in an oil bath at 50 ℃ (entry 6, Table 1; or at 25 ℃ for RT, entry 5) under stirring. At precise time intervals, aliquots were taken under dry argon flux and quenched with a droplet of degassed MeOH. At the end, the reaction was quenched by adding few drops of methanol to the reaction mixture. The polybenzoin was precipitated in pentane to eliminate monomer residue and catalyst and dried under vacuum to obtain **PBz-2** as a white solid (107 mg, yield 67%). The conversions are calculated by ^{1}H NMR spectroscopy before precipitation. Molecular weights and dispersities were obtained by SEC analysis in THF (Table 1).

*Polymerization of bis-aldehyde **2** catalyzed by chiral catalysts **NHC-2** to **NHC-7**.*

In a typical polymerization, dissolve monomer 160 mg (0.40 mmol) bis-aldehyde **2** by 1.5 mL of THF in the Schlenk tube in glove box, 18 mg (0.04 mmol) of **NHC-3** (entry 4, Table 3) are added, after the entire solid completely soluble in THF, 0.5 mL solution of DBU in dry-THF with add to the mixture with a concentration of 0.08 mmol/L. Schlenk tube is then fixed in an oil bath at 25 ℃ under stirring. At precise time intervals, aliquots were taken under dry argon flux and quenched with a droplet of degassed MeOH. At the end, the reaction was quenched by adding few drops of methanol to the reaction mixture. The polybenzoin was precipitated in pentane to eliminate monomer residue and catalyst and dried under vacuum to obtain **PBz-2** as a white solid. The conversions are calculated by ^{1}H NMR spectroscopy before precipitation. Molecular weights and dispersities were obtained by SEC analysis in THF (Table 3).

Blank tests

*bis-aldehyde **2** plus KHMDS.*

The same protocol used as previous polymerization procedure, except without adding NHC. To a solution of bis-aldehyde **2** (160 mg, 0.40 mmol) in 2 mL THF, added 8 mg (0.04 mmol) KHMDS in glove box using Schlenk equipment (entry 1 in Table 3). Then the tube is fixed in an oil bath at 25 ℃ under stirring. The reaction is followed by taking aliquots from the reaction under dry argon flux and quenched with a droplet of degassed MeOH. Molecular weight and dispersity were obtained by SEC analysis in THF.

*Bis-aldehyde **2** plus DBU.*

To a solution of bis-aldehyde **2** (160 mg, 0.40 mmol) in 2 mL THF, added 0.5 mL of DBU in dry-THF with a concentration of 0.08 mmol/L in glove box using Schlenk equipment (entry 2 in Table 3). Then the tube is fixed in an oil bath at 50 ℃ under stirring. The reaction is followed by taking aliquots from the reaction under dry argon flux and quenched with a droplet of degassed MeOH. Molecular weight and dispersity were obtained by SEC analysis in THF.

Reduction of benzoin.

The reduction of benzoin to hydrobenzoin utilizing $NaBH_4$ has been described in literature. [22] $NaBH_4$ (680 mg, 17.9 mmol) was added in several portions to a solution of benzoin (0.5 g, 2.43 mmol) in 12 mL of CH_3OH plus 12 mL THF at 0 ℃. Leaving the reaction turned to RT for 24 h. At the end of reaction, excess of $NaBH_4$ was quenched with cold water. (entry 1, Table 2) Organic layer was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and the solvent was evaporated by rotary evaporator. The resulting white solid was identified as 1,2-diphenylethane-

1,2-diol in quantitative yield. m.p: 138 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 (m, 10H), 4.84 (s, 2H), 2.20 (s, 2H); ^{13}C NMR (75MHz, $CDCl_3$): δ = 140.3, 127.3, 126.9, 126.8, 77.3;

Analogy the described reduction procedure by $LiAlH_4$[17], freshly dried benzoin (0.50 g, 2.43 mmol, by lyophisation with dry dioxane for 2 hours) was dissolved in 24 mL dried THF, to the reaction, lithium aluminum hydride $LiAlH_4$ (0.37 mL of THF solution with concentration of 1 mL/mol.) was added at 0 ℃.(entry 2, Table 2) Leaving the reaction turned to RT for 24 h. At the end of reaction, excess of $LiAlH_4$was quenched with cold water. The inorganic precipitate was thoroughly washed with ether, after evaporating the organic solvents, extraction by EtOAc was combined, dried (Na_2SO_4), and the solvent was removed, obtained 1,2-diphenylethane-1,2-diol in quantitative yield.

Degradation and modification of polybenzoins

*Degradation of polybenzoins (**PBz-1**) synthesized from bis-aldehyde **1** by TBAF, TBAT and TAS.*

To the solution of polymerization bis-aldehyde **1** (100 mg, 2.48 mmol) containing 2 mL THF, 10 equivalents TBAF (8 mL) THF solution of 1M/L concentration added under dry argon flux. Then reaction is heating in an oil bath at 50 ℃ under stirring. The reaction is followed by taking aliquots from the reaction and analyzing by SEC and ^{1}H NMR, under dry argon flux and quenched with a droplet of degassed MeOH.

In the case of using TBAT as degradation agent, 10 equivalents TBAT (8 mL) THF solution of 1M/L concentration added under dry argon flux. Similar procedure was investigated in the degradation by TAS. The reaction is followed by taking aliquots from the reaction and analyzing by SEC and ^{1}H NMR, under dry argon flux and quenched with a droplet of degassed MeOH. Molecular weights and dispersities were obtained by SEC analysis in THF.

*One-pot degradation and modification of polybenzoin (**PBz-2**) synthesized from bis-aldehyde **2***

To the solution of polymerization bis-aldehyde **2** (100 mg, 2.48 mmol) containing 2 mL THF, 5 equivalent of $LiAlH_4$ 4 mL THF solution with 1M/L concentration added under dry argon flux at 0 ℃. Waiting for the reaction come back to RT, the Schlenk tube is fixed in an oil bath at 50°C under stirring. After 24 hours' reaction, 1.1 ml 20 equivalent of acetyl chloride is added to the solution at 0 ℃. Waiting for the reaction come back to RT, the Schlenk tube is again fixed in an oil bath at 50 ℃ under stirring. Cold water is slowly added to stop reaction after 24 hours. The acid solution is neutralized by saturated Na_2CO_3 and after evaporating THF; products are extracted by CH_2Cl_2, then washed by saturated NaCl and dried over Na_2SO_4 to get yellow oil.

This oil then is purified by flash chromatography with Pentane/EtOAc of 8/2 to get the derivate hydrobenzoin **4.** (White solid: 70 mg; yield 70%)

General procedure to synthesis of polyesters via Tishchenko polyaddition

In a typical polymerization, 215 mg dried monomer (0.80 mmol) monomer **1** was dissolved in 2 mL of fresh distilled THF in the Schelenk tube. 10 mol% of catalyst (8.56 mg of LDA) was added to the solution in glove box at RT of 25 ℃. At precise time intervals, aliquots were taken under dry argon flux and quenched with a droplet of degassed MeOH. At the end, the reaction was quenched by adding few drops of methanol to the reaction mixture. The polybenzoin was precipitated in pentane to eliminate monomer residue and catalyst and dried under vacuum to obtain polymer as a white solid (yield 63%). The conversions are calculated by ^{1}H NMR spectroscopy before precipitation (80%). Molecular weights and dispersities were obtained by SEC analysis in THF (Mw = 2200 g/mol, D = 1.9). ^{1}H NMR spectroscopy characterize the polyester synthesized from monomer **1** is shown in Figure 28. The signal of the terminal or residue monomer aldehyde proton (C*H*O) appears at 10.01 ppm while the aromatic protons of polymers are detected between 7.3 to 8.2 ppm. The methylene protons of ester formed after the Tishchenko reaction of bis-aldehyde (peak α) is found at 5.35 ppm. Two methyl group of silylated monomer (peak ε) is found as a broad peak at 0.5 ppm.

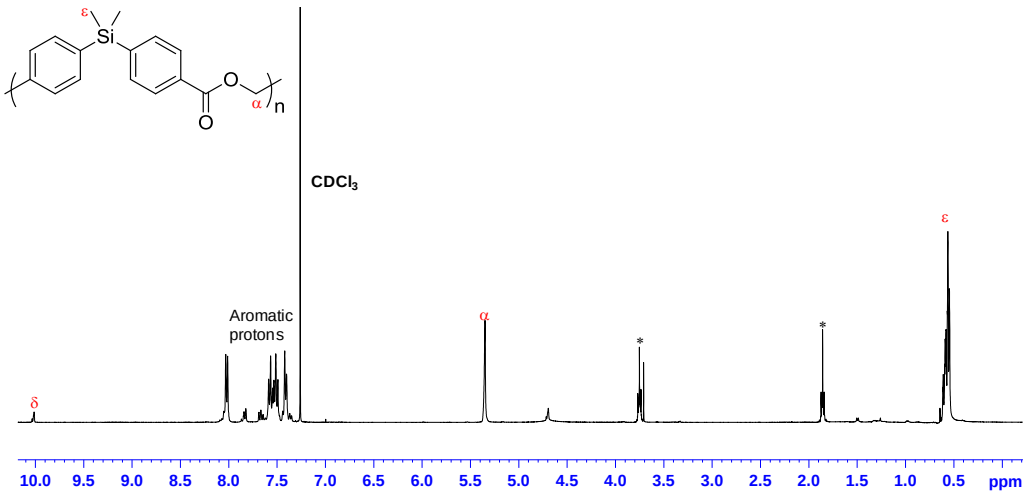


Figure 28. ^{1}H NMR (400 MHz, $CDCl_3$) analysis of polyester synthesized from monomer **1**. * are peaks of solvents.

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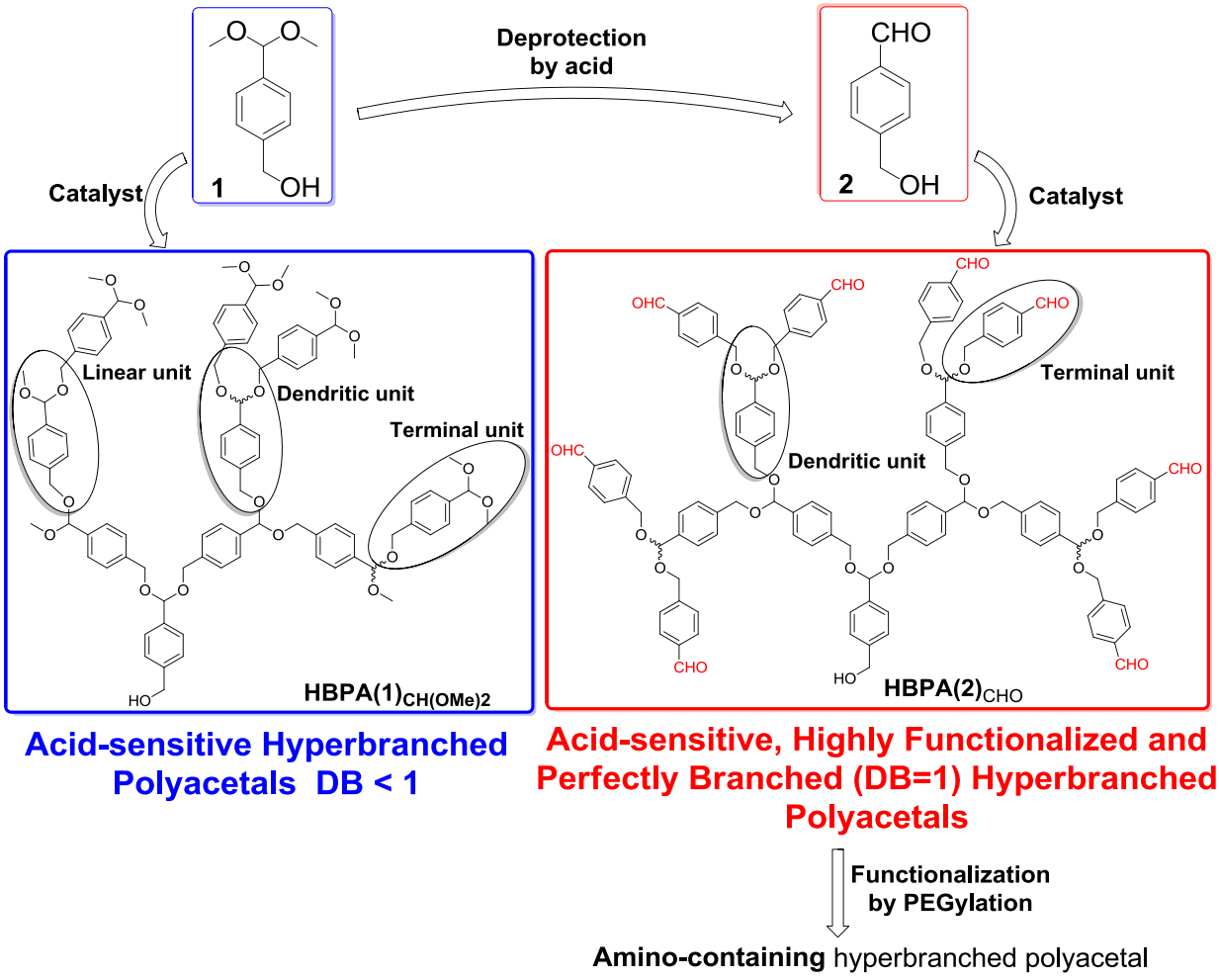
Chapter IV

One-pot Synthesis and PEGylation of Acid-sensitive Hyperbranched Polyacetals with a Degree of Branching of 100%

Chapter IV.One-pot Synthesis and PEGylation of Acid-sensitive Hyperbranched Polyacetals with a Degree of Branching of 100%



Keywords: Hyperbranched, Polyacetal, Degree of branching (DB), DB = 1, AB_2-type monomer, Acid-degradable, Aldehyde, PEGylation

Mots clés : Hyperramifiés, Polyacétals, Degré de ramification, Monomère de type AB_2, Dégradable par voie acide, Aldéhyde, PEGylation

Chapter IV. One-pot Synthesis and PEGylation of Acid-sensitive Hyperbranched Polyacetals with a Degree of Branching of 100%

1. Introduction

The previous chapters have shown that bis-aldehyde monomers can serve to derive novel polyaddition polymers, such as polybenzoins, polyesters and polyaldols.

This chapter now describes the acid-catalyzed polymerization of para-hydroxymethyl benzaldehyde derivatives, containing both an aldehyde and a hydroxy (or an acetal) function, to form hyperbranched polyacetals through simple self-acetalization polycondensation. Very surprisingly, and to the best of our knowledge, the direct polycondensation of hydroxy-aldehyde monomers has never been reported. In the course of this PhD work, however, Ramakrishnan *et al.* described, in 2011, a related synthetic approach to hyperbranched polyacetals.[1] The authors employed AB_2-type monomers, carrying both a hydroxyl (A) group and a B_2-type dialkyl acetal, that were readily polymerized *via* melt poly(transacetalization).

In the following lines, essential features and examples of pH-sensitive polymer materials and polyacetal are first introduced. The important principle of hyperbranched polymers will then be presented. The syntheses of hyperbranched polyacetals, their characterization and their subsequent degradation will be detailed after.

2. Acid-sensitive polymer materials

2.1. pH-sensitive polymer nano-carriers

Polymer materials used in active delivery applications encompass a wide range of shape persistent architectures either at the macroscale, such as gels and hydrogels, or at the nanoscale, which includes polymeric micelles, nanogels, dendrimers, hyperbranched polymers, polymer–drug conjugates, etc.[2] "Controlled/living" polymerization methods are now commonly used as synthetic tools often combined with versatile coupling reactions, such as "click chemistry" (e.g. 1,3-copper-catalyzed Huisgen cycloaddition coupling, Diels-Alder or thiol-ene reactions, etc), for the creative design of nano-carriers with engineered characteristics such as colloidal stability, tunable sizes, and protection of the active during transportation.[3] In addition, polymer nanoscale devices can be designed to respond specifically to external stimuli by a steep change of their physical or chemical properties. For instance, chain conformation or extent of association and/or solubility can be altered or irreversible degradation of the device can occur upon stimulation. Such materials are referred to as stimuli-responsive polymers, and many systems combining two or more stimuli-responsive mechanisms have been reported.[4] External stimuli can be categorized in two families that are i) physical stimuli (e.g. temperature, magnetic fields, or mechanical stress) and ii) chemical or biochemical stimuli such as pH, ionic strength and chemical agent or enzymes. In active delivery applications (detergency, cosmetics, nanomedicine), such vehicles allow for a release of the active compound and/or for a disruption

of the nano-container after release.

In this context, pH-sensitive polymers have been extensively investigated. They include polymers featuring ionizable groups in their backbone (forming polyacidic or polybasic polyelectrolytes) and polymers containing a pH-cleavable linker.[5] Acid-degradable polymers have become more popular in the last decade.[6] Cargos that can be further degraded are of great interest for controlled drug release applications, their cleavage under acidic conditions taking place in tumor tissue, endosomes, or lysosomes. The acid-sensitive linkers most commonly employed include orthoester, acetal, or imine and hydrazine functionalities (Figure 1).[4a,7] These functions have been introduced in the main chain or as pendant groups of a variety of macromolecular architectures, allowing for subsequent degradation. In this chapter, emphasis is placed on acetal-type functions; more information about other acid-sensitive linkers can be found elsewhere.[8,9]

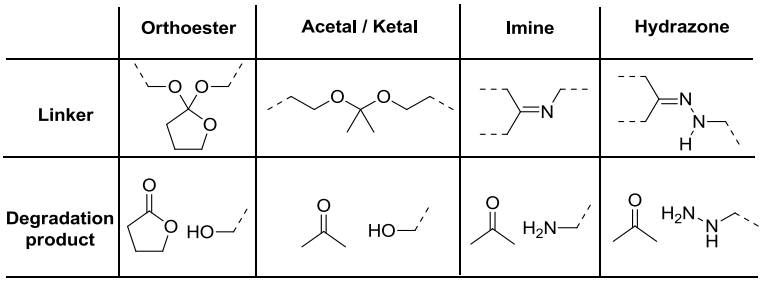


Figure 1. Examples of acid-degradable bonds and their degradation products.

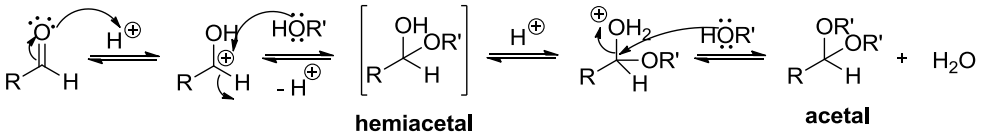
2.2. Synthetic methods to acid-degradable polymers with acetal moieties

Owing to their erodible properties, generating relatively benign degradation products, polymers constituted of acetal moieties have gained an increasing interest in the past decade in research laboratories.[7,10] A wide variety of macromolecular structures and assemblies based on acetal functions have in fact been designed, ranging from "simple" linear polyacetals to micelle-like structures resulting from the self-assembly of block copolymers, to branched polymers including star-like, dendrimer-like, and hyperbranched polymers, or hydrogels and cross-linked particles. Depending on the chemistry implemented, degradable acetal functionalities can either be part of the main chain, or be present as pendant groups[6c,11] or constitute the crosslinking points of the polymer structure. In dendritic scaffolds, acetal functions can be introduced at the branching points or at the periphery of the dendrimer to be further cleaved under acidic conditions.[12]

2.2.1. Polyacetals from direct synthetic polymerization

As illustrated by Figures 2 and 3, acetal moieties can be introduced in polymer chains using different synthetic strategies. A general strategy consists in the formation of acetal

linkages in the course of the polymerization (Figure 2). An obvious method is by repeated acetalization reactions (polyacetalization, Figure 2a) between an aldehyde-containing molecule (whose functionality, f, is equal to 2) and a diol (f = 2 also). Acetalization involves the acid-catalyzed addition of an alcohol to a ketone or an aldehyde with elimination of water (Scheme 1). The hemiacetal intermediate being not stable under acid conditions, the reaction can be driven to acetal formation if water is removed during the reaction.



Scheme 1. Mechanism of acid-catalyzed acetalization of an aldehyde with an alcohol.

A recent example utilizing polyacetalization concerns the design of acid-sensitive polymers with acetal moieties in the main chain, by polycondensation of poly(ethylene glycol) (PEG) with lilial, an aldehyde widely used in fragrance applications.[13]

The most important polyacetal material, however, is polyoxymethylene (POM), resulting from the direct acid-catalyzed polymerization of formaldehyde (Figure 2b). Another synthetic method to polyacetals is by polycondensation of α,ω-diacetals (Figure 2c). An example of this method has been recently described by Mecking's group[14] who polymerized plant oil-derived α,ω-diacetals, yielding polyacetals with molecular weight of ca. M_n = 2 × 10^4 g mol^{-1}. In addition to affording tunable degradation profiles, the long methylene sequences provide melt and crystallization temperatures (T_m = 88 ℃ and T_c = 68 ℃ for y = 23).

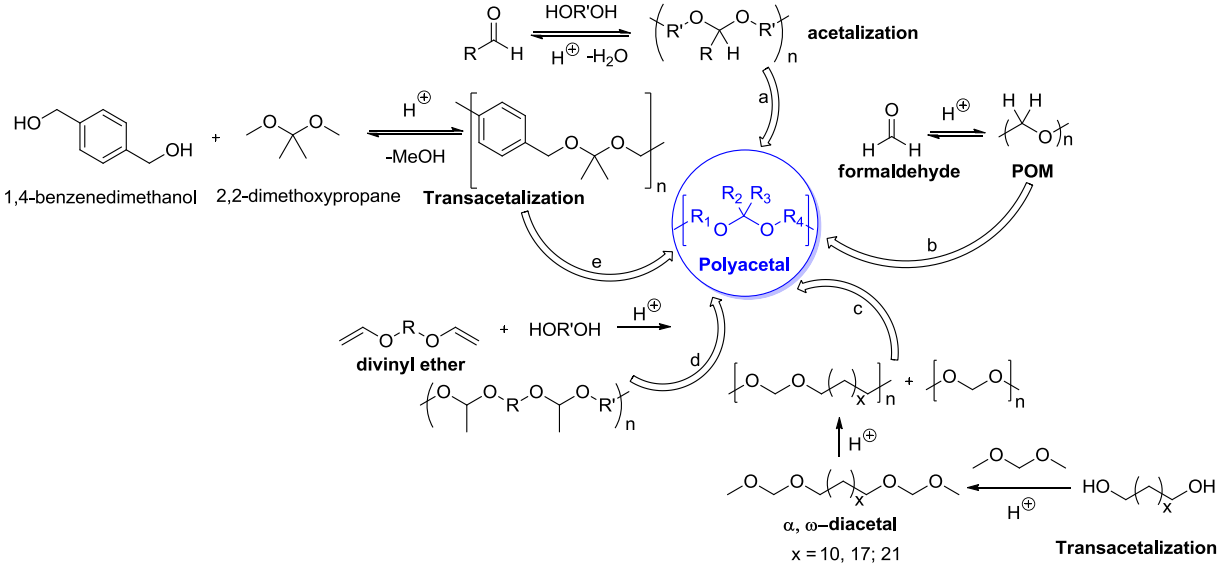


Figure 2. Synthetic polymerization pathways forming acetal linkages.

An alternative synthetic pathway to linear polyacetals is by condensation of polyols with divinyl ethers, as thoroughly investigated by the groups of Heller and Tomlinson (Figure 2d).[7d,7f,g,15] On this basis, acid-sensitive anticancer polyacetal-based polymeric drugs could be

designed through incorporation into the polymer backbone of diethylstilbestrol, a non-steroidal oestrogen drug having a bishydroxyl functionality. Based on the same chemistry, Sui *et al.* have recently reported the synthesis of acetal-based polymer networks from the reaction of the hydroxyl pendant groups of a polymer precursor with 1,4-cyclohexanedimethanol divinyl ether.[16] Cross-linked thermo-responsive multiblock copolymers with polyacetal linkages and Pluronic® blocks could also be derived by coupling a Pluronic® triblock copolymer with diethylene glycol divinyl ether.[7b]

Formation of acetal linkages during polymerization can also be achieved by poly(transacetalization) reaction, between a diol and a ketal-containing monomer (Figure 2e). Murthy *et al.* have thus prepared a linear polyketal by polycondensation of 1,4-benzenedimethanol and 2,2-dimethoxypropane.[10c] Dexamethasone-loaded nanoparticles were subsequently elaborated from this polyketal precursor using an emulsion procedure.[7c]

Chatterjee and Ramakrishnan have recently reported the synthesis of hyperbranched polyacetals *via* melt poly(transacetalization) of AB_2-type monomers, where A is a hydroxyl group and B groups are dialkyl acetals.[17] A dramatic dependence of the degradation rates under mildly acidic pH (pH = 4), as a function of the nature of peripheral alkyl substituents, was noted for such hyperbranched polyacetals.

2.2.2. Polyacetals from acetal-containing monomers

Another general method to incorporate acetal groups into polymers is to resort to monomers already containing the acetal function that are polymerized, either by step-growth or chain-growth polymerization (Figure 3a). The Fréchet's group thus derived miscellaneous polyurethanes and polyureas-polyacetals by step-growth polymerization of bis(p-nitrophenyl carbamate/ carbonate) or diisocyanate monomers possessing a ketal-containing diamine. Kinetic studies showed that hydrolysis dramatically depended on the hydrophobicity of the polymer precursor. Microparticles were processed from some of these precursors and proved more effective in generating an immune response compared to the free protein.[10a]

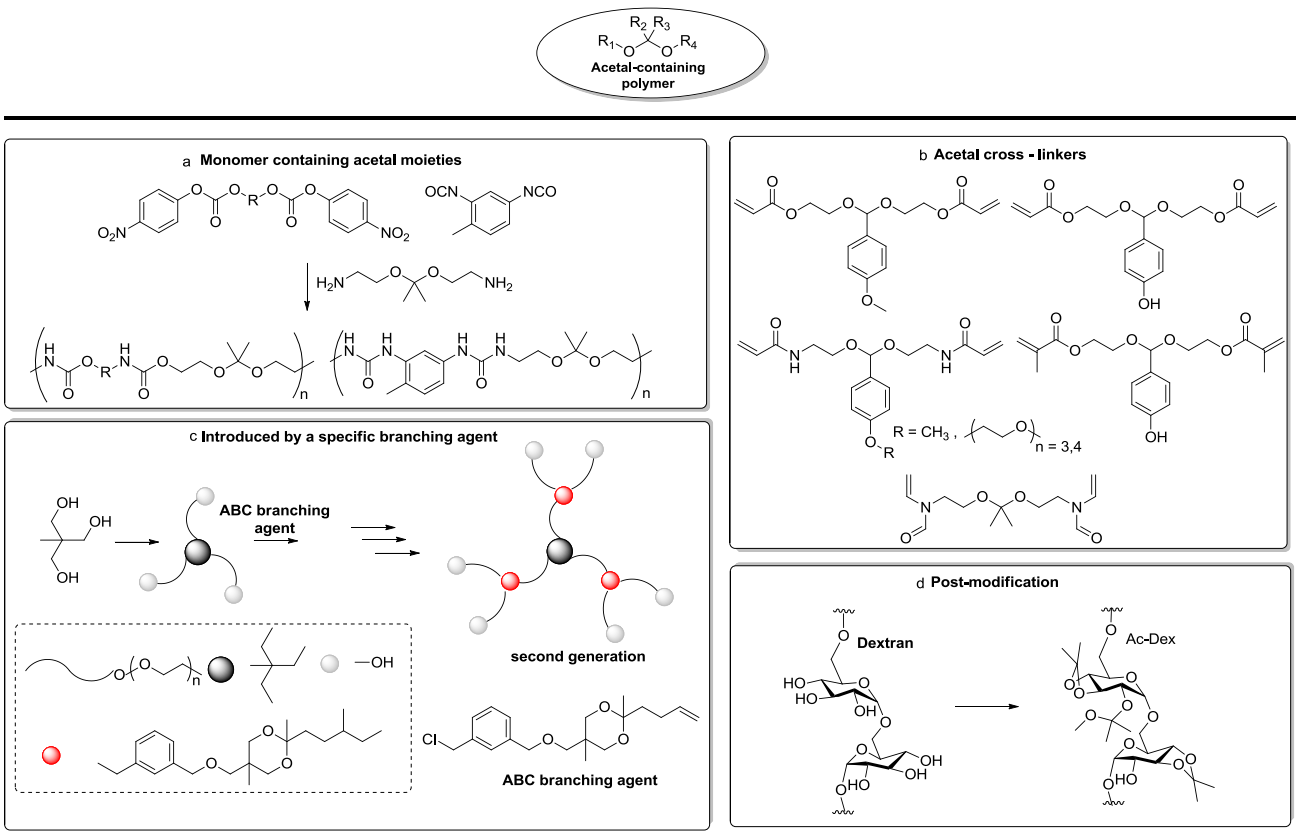


Figure 3. Acetal cross-linkers used for the synthesis of acid-cleavable particles by inverse-emulsion polymerisation.

Polyamide microcapsules possessing acid-degradable moieties were also designed by interfacial polycondensation reaction of acid chlorides with ketal-containing diamine.[18] When loaded with paclitaxel as anti-cancer agent, these microcapsules exhibited a high cytotoxicity.

Step-growth polyaddition *via* Michael reactions of divinylic monomers having acid-sensitive acetal moieties with amino functions could also be implemented (Figure 3b).[7e]

In the context of chain-growth polymerization, cyclic carbonate could serve for ring-opening polymerization (ROP) starting from an alpha-hydroxy polyoxyethylene precursor, leading to block copolymers that self assembled into micelles. Subsequent hydrolysis of the acetals made the polycarbonate more hydrophilic, enhancing the swelling behavior of the micelle.[11a,19]

Besides the aforementioned monomers leading to linear acid-sensitive polymers, acetal-containing crosslinkers were extensively employed to access cross-linked particles, a topic that has been pioneered by the group of Fréchet in 2002.[20] Various cross-linkers (Figure 3b) were purposely designed and various nanostructured polymers such as nano/microgels,[16,21] hydrogels,[22] nanocapsules,[8b,23] and cross-linked micelles with specific degradation profiles were obtained. For instance, acetal-containing divinylic cross-linkers were used for controlled radical crosslinking copolymerization *via* the reversible addition fragmentation chain transfer (RAFT) method. In this way, the crosslinker is copolymerized with a vinylic monomer to form a

crosslinked core of a micelle.[24] Alternatively, a post-crosslinking approach can be applied, where either the core or the shell of a micelle generated by self-assembly of a block copolymer precursor is temporary fixed by a cleavable acetal-containing crosslinker (e.g. of diamino- or diazido-type).[24b,25]

The acetal function can also be introduced by a specific branching agent for the purpose of dendrimer synthesis, as reported by Feng *et al.* (Figure 3c).[12] Thus, acid-sensitive dendrimer-like poly(ethylene oxide)s were synthesized following a divergent approach based on ROP of ethylene oxide and arborization using an ABC-type branching agent featuring an acid sensitive ketal group. The degradation of the seventh generation dendrimer-like PEO, whose initial molar mass reached a value as high as 446 kg/mol, occurred readily under acidic conditions, forming linear PEO chains of low molar mass (~ 2 Kg/mol).[12a]

Lastly, acetal functions can be introduced by post-modification. For instance, Fréchet et al. derivatized dextran, a naturally occurring polysaccharide, with acetal moieties the thus-modified dextran being more hydrophobic and acid-sensitive as well (Figure 3d).[26] Nanoparticles were thus processed using emulsion techniques. The acetal groups could be hydrolyzed under acidic conditions.

3. Synthesis of hyperbranched polymers

3.1. Differences and similarities between dendrimers and hyperbranched polymers

Both regular dendrimers and hyperbranched polymers exhibit very unique properties compared with those of their linear analogues, in particular a much lower viscosity in solution and a high solubility. This is due to the high connectivity of their repeating units that in turn shape them in globular structures.[27] Also, the presence of numerous peripheral reactive groups allows for further derivatization. Dendrimers also share with hyperbranched polymers the inability to entangle owing to their generations generally of monomeric size between their branching points. Because of the latter feature, both dendrimers and hyperbranched polymers are often amorphous polymer materials, branching preventing crystallization. Also due to the absence of physical cross-links by chain entanglements, hyperbranched polymers are generally brittle (for materials with a high T_g value) or behave as oils (when having a low T_g value).[28]

In contrast to regular dendrimers (Figure 4, right) that are perfectly defined (isomolecular) with a degree of branching (DB) equal to unity, hyperbranched polymers are irregular structures that are in fact randomly branched. They indeed contain unreacted B sites characterizing linear units (**L**) that coexist with dendritic units (**D**) and terminal units (**T**) (Figure 4, left). In other words, branching is not achieved for every monomer unit in hyperbranched polymers (DB < 1). However, hyperbranched structures may be preferred over true dendrimers for industrial

applications, due the more reasonable cost of their one-pot synthesis.[29]

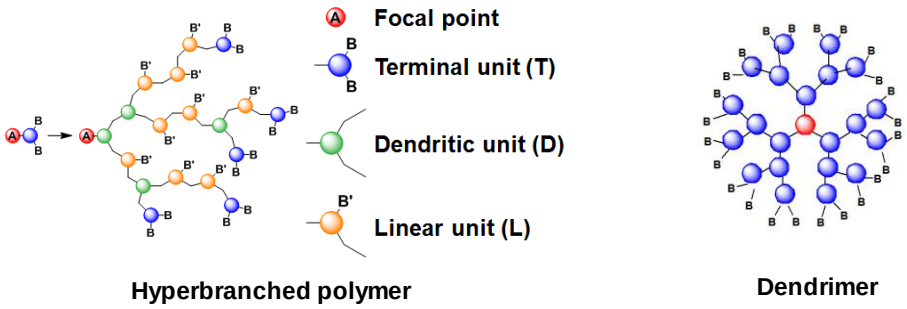


Figure 4. Schematic representation of a hyperbranched polymer and a dendrimère.

Hyperbranched polymers have been extensively investigated as speciality polymers in a wide range of areas including catalysis[30], biological molecular recognition-where dendrimers can engage in host-guest interactions[31], energy and electron transfer[32], surface modification[33], coatings, formulations[34], etc. Thermosets deriving from hyperbranched polymers and utilizing their reactive peripheral groups have been reported.[35] Introduction of polymerizable groups such as acrylates, vinyl ethers, allyl ethers, or epoxides enabled their use in coatings.[34,36] Several commercially available hyperbranched polymers can be found, the most widespread ones being 'Boltorn™' based on polysters from Perstorp, 'Hybrane™' based on poly(esteramide)s from DSM, 'Lupasol™' based on polyethylenimines from BASF AG and others based on poly(urethane)s[37] and on polyesters[38] developed by BASF.

3.2. Synthetic developments of hyperbranched polymers

First attempts to synthesize hyperbranched polymers appeared in the early 1990's, long after Flory suggested that AB_x monomers - where A and B are antagonist functional groups- should be able to experience self-condensation, forming soluble and highly branched materials with a three-dimensional globular shape *via* one pot synthesis. The first example of hyperbranched polymers was in the form of soluble polyphenylenes and was reported by Kim and Webster in 1988.[39]

Besides the most frequently applied method that consists in polycondensing AB_2-type (or AB_n-type) monomers, other synthetic developments to hyperbranched polymers have been reported. An obvious method is to perform the polymerization of an $A_3 + B_2$ monomer mixture (or $A_4 + B_2$ or more generally $A_n + B_m$, wherein $n>m$, $n\geq2$, that is, a mixture of monomers with an average functionality higher than 2). It is well established, indeed, that before polymerization reaches gelation, highly branched and soluble polymers are first generated. Above this critical conversion, highly cross-linked and intractable products are finally obtained.[27]

Other synthetic methods include self-condensing vinyl polymerization (SCVP) of latent AB_2-type monomers and ring opening multi-branching polymerization (ROMBP) also referred

to as self-condensing ring-opening polymerization (SCROP) (Figure 5). Interestingly, the latter methods allow for the incorporation of cyclic ether and vinyl monomers, respectively, for constructing hyperbranched copolymers. One can also mention the catalytic 'chain-walking' polymerization of ethylene leading to hyperbranched polyolefins.[40]

A major drawback of hyperbranched polymers, however, relates to their very high dispersity, which can exceed the range of 5–10, in many cases. From a process viewpoint, the "core-dilution/slow-monomer-addition" technique has allowed both enhancing the degree of branching and minimizing the molar mass distribution of hyperbranched polymers.[41] Use of a polyfunctional core (B_f) is also of particular interest to improve the control over polymerization by the core/monomer ratio. Finally, "non-conventional" media such as ionic liquids can be advantageous over classical solvents to synthesize some hyperbranched polymers (e.g. polyesters), as recently reported by Fradet *et al.*[42]

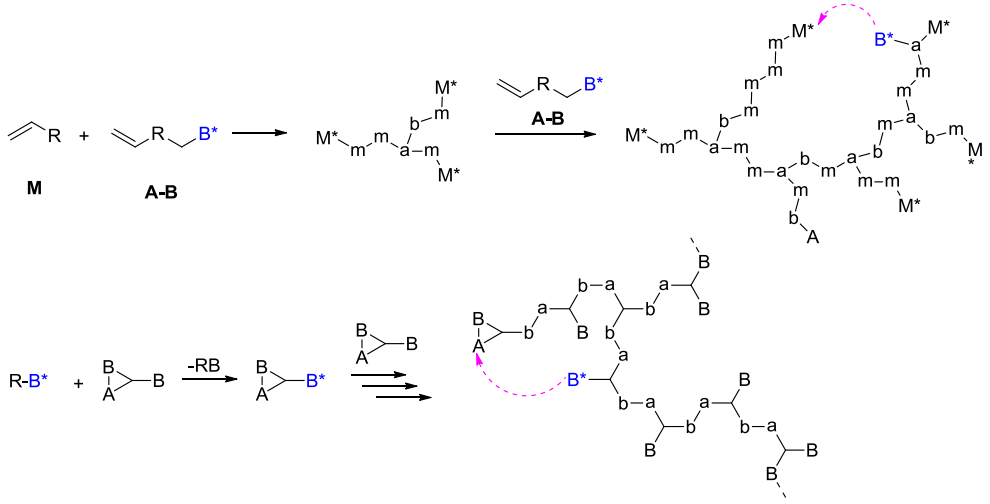


Figure 5. Self-condensing vinyl copolymerization (SCVCP, top) and ROMBP (bottom). Note: The asterisks in the structures indicate an initiating site; small letters stand for reacted groups.

3.3. Typical monomers used for hyperbranched polymer synthesis

It has to be acknowledged that most monomers used for hyperbranched polymer synthesis are not commercially available. Figure 6 shows representative examples of AB_2-type monomers used with related methods of polymerization. A very broad range of hyperbranched polymers with various chemical structures has been described in the past 20 years, including polyphenylenes, aliphatic and aromatic polyesters, polycarbonates, polyethers and polyether-ketones, polyamides and polyamines, polyurethanes and polyureas, polysilanes and polysiloxanes, polyimides and polyetherimides, vinyl polymers, etc…. Excellent review articles and book chapters discussing the essential features and synthetic developments of these polymers can be found elsewhere.[27,31b,43]

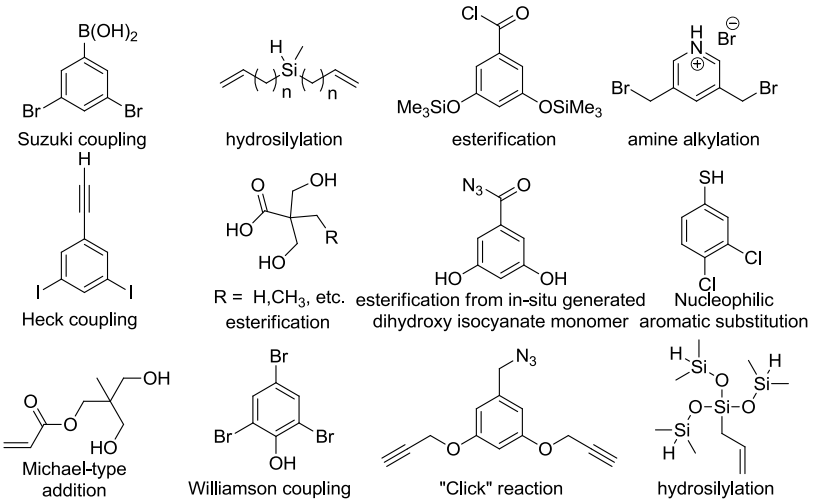


Figure 6. Traditional AB_n-monomers used for hyperbranched polymer synthesis.

3.4. Degree of branching (DB)

As already mentioned, the DB is one of the most important intrinsic parameters of hyperbranched polymers, being related to the compact structure and the number of end groups. In theory, DB is close to 50% for a polymer derived from the polymerization of an AB_2 monomer, on the basis of a hypothetically equal reactivity of the two B functional groups, and absence of side reactions, such as the formation of cycles. In a "regular" dendrimer, the DB is equal to 1, while for linear polymers the DB is 0. A slow monomer addition process can increase the DB from 50% to 66%, in the case of an AB_2 system. In hyperbranched polymers, in general, the DB is expressed as follows, as a function of the ratio of the dendritic (D), terminal (T), and linear (L) units[44]:

$$\mathrm{DB} = \frac{T + D}{T + D + L}$$

Interestingly, DB value can be determined by NMR spectroscopy, which often requires the design of model compounds for chemical assignments. It is important to note that the above expression is only valid for rather high molecular weight hyperbranched polymers with a number of L approaching the number of T. Analysis by NMR of polymers resulting from the polymerization of A_2+B_y is more complicated.[45] In addition, side reactions such as cyclizations can interfere in the determination of the structural units. DB value can also be manipulated by the ratio, and/or the sequence and/or the rate of monomer addition.[43d] Another possibility to vary the DB is by designing AB_3 or AB_4 monomers, and so on, instead of AB_2 monomers. In addition, introduction of an AB-type monomer with an AB_n-type of monomer or an inimer (in SCVP) leads to a decrease of the DB.[43e,46] For a hyperbranched polymer with large MW, the number of terminal units (T) is very close to that of dendritic units (D). The equation can be simplified as

DB $= \frac{1}{1+L/2D} = \frac{2D}{2D+L}$. This equation is quite useful since L/D or L/T could be easily calculated from the corresponding nuclear magnetic resonance (NMR) spectrum, whereas it is always difficult to know the exact numbers of units.

3.5.Hyperbranched polymers with DB = 100%

In recent years, a few groups have reported synthetic strategies to hyperbranched polymers with a DB equal to unity (100% of branching like in dendrimers, but still polydisperse unlike monodisperse dendrimers), as reviewed recently by Ueda *et al.*[47] As pointed out by these authors, a polymer of DB 100% may have many isomers and may exhibit a non-spherical or non-globular structure. (Figure 7)

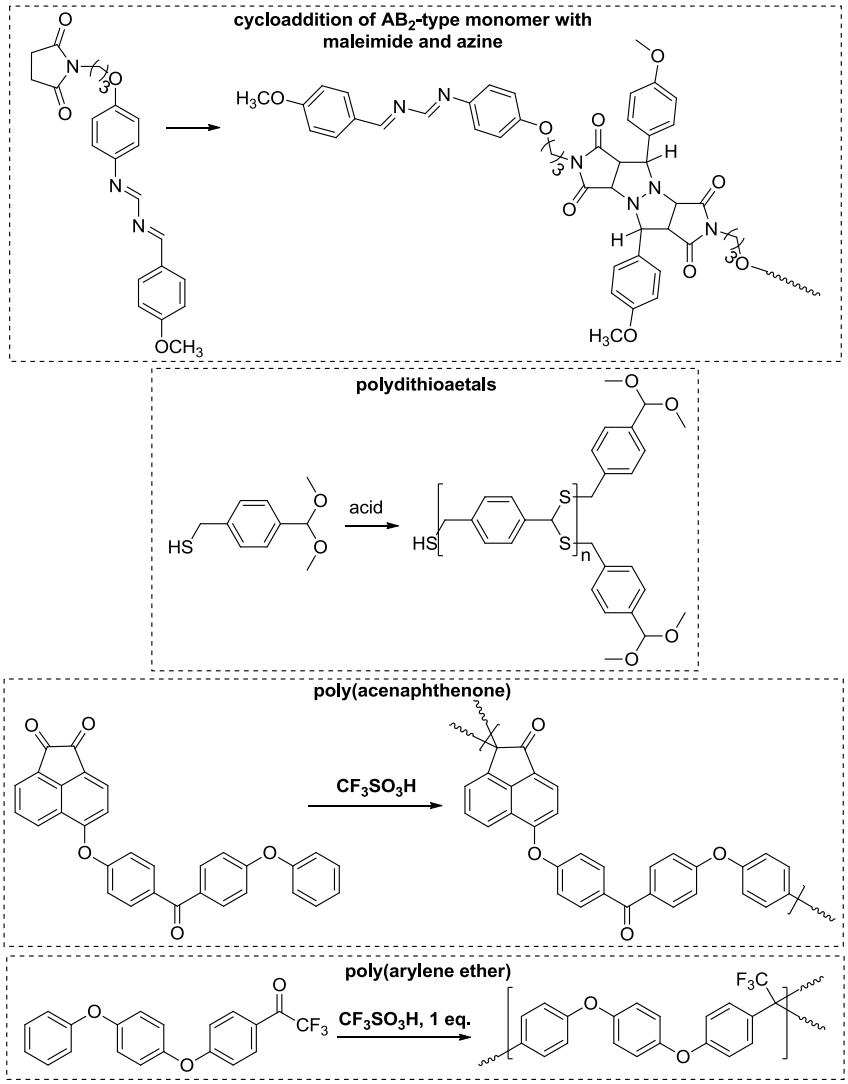


Figure 7. Some examples of syntheses hyperbranched polymers with DB = 100%.

Early works by Hobson and Feast have suggested a way to activate the second B group of AB_2 monomers, after the first one has reacted.[48] However, the most common method is to form an unstable intermediate, which occurs reversibly through the reaction between A and one

B group. Subsequent reaction of the second B group occurs irreversibly to produce a stable dendritic unit. Characteristic examples of such AB_2-type monomer, and related hyperbranched polymers with DB = 1 (e.g. based on monomer containing maleimide and azine monomer[49], polydithioaetals[50], polyacenaphthenones[51], poly(arylene ether) with controlled DB from 0 to 1 by changing the quantity of acid added[1]), are provided in Figure 7. Most of these investigations, however, required rather complex synthesis of monomers and could be hardly generalized.

Finally, a method based on the "catalyst-transfer chain-growth condensation polymerization" can be adapted to achieve defect-free hyperbranched π-conjugated polymers (e.g. polyphenylenes[52], polycarbazoles[53], and polythiophenes[54]) with a DB of 100%, from AB_2-type monomers. The polymerization is typically catalyzed by Pd. (e.g. Heck, Suzuki –Miyaura coupling). This DB of 100% seems to result from an efficient catalyst migration from one aryl site of AB_2 monomer to the other.

4. Aim of the present work

In this chapter, the acid-catalyzed polymerization of para-hydroxymethyl benzaldehyde derivatives, containing both an aldehyde and a hydroxy (or an acetal) function have been described. Under such conditions, the bifunctional aldehyde (B_2) group can readily react with the alcohol (A) function, through simple self-acetalization polycondensation reaction. The water thus formed has to be removed from the reaction to drive the equilibrium toward polyacetal formation. In other words, precursors containing both functions behave (aldehyde-alcohol) as AB_2-type monomers, forming hyperbranched polyacetals for the first time.

Ramakrishnan *et al.* described, however, in 2011, a related synthetic approach to hyperbranched polyacetals. As discussed in section 2.2, the authors employed AB_2-type monomers, carrying both a hydroxyl (A) group and a B_2-type dialkyl acetal, that were readily polymerized *via* melt poly(transacetalization) at 100 °C, releasing alcohol as by-product, under reduced pressure. In this way, hyperbranched polyacetals with DB < 1 were produced. The degradation profiles of these compounds under acidic conditions (pH = 4) were found to dramatically depend on the nature of the alkyl substituents. In a subsequent contribution, the same authors established that AB_2-type monomers featuring a thiol (instead of an alcohol) as the A group,[50] with a dialkyl acetal moiety, yielded polydithioacetals with 100% branching *via* poly(transthioketalization). Previous published works by the group of Ueda had already accounted for the possibility to derive polydithioacetals with DB = 1, from monomers possessing both a keto group and a thiol functionality.[1]

In our work, four monomers were investigated (Figure 8), including hydroxymethyl benzaldehyde dimethylacetal **1,** hydroxymethyl benzaldehyde **2** and AB_2-type macromonomer

analogues, **3** and **4**, possessing a poly(ethylene oxide) (PEO) chain between the two reactive functions.

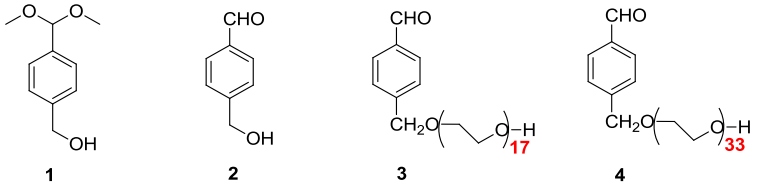


Figure 8. AB_2-type (macro)monomers investigated in this chapter.

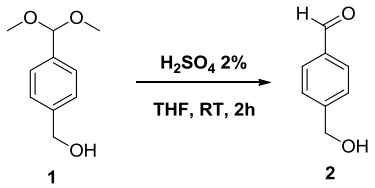
We investigated the conditions best suited to prepare acid-sensitive hyperbranched polyacetals of relatively high molecular weights, *via* polycondensation of hydroxy-aldehyde substituted aromatic monomers, using simple Bronsted acids as catalysts. Characterization of the hyperbranched structures –in particular their DB- was established by combined methods. Further derivatization of the multiple peripheral aldehydes was accomplished through "PEGylation" reaction with mono-amino poly(ethylene oxide) of different molecular weights. Lastly, degradation of the polyacetal nanoparticles under acidic conditions was demonstrated.

5. Synthesis and polymerization of para-hydroxymethylbenzaldehyde monomers

5.1. Monomer syntheses

Synthesis of the AB_2-monomer **2** was readily achieved following an improved and straightforward one step procedure compared with the direct reduction of terephthtalaldehyde (Scheme 2).[55] *p*-Hydroxymethyl benzaldehyde dimethylacetal (monomer **1**) was simply treated with sulfuric acid in THF at room temperature, affording *p*-hydroxymethyl benzaldehyde (monomer **2**) that was dried by lyophilization. Monomer **2** was obtained as a white solid and stored in glove box.

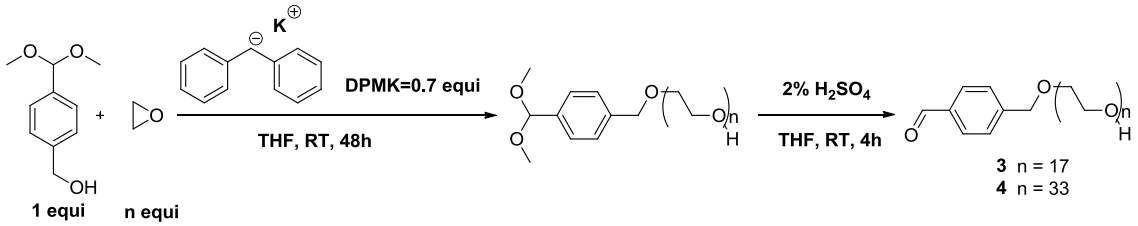
The dimethylacetal homologue of **2**, *p*-hydroxymethyl benzaldehyde dimethylacetal (monomer **1**), which is commercially available (97%, Aldrich), was also considered in this work, eventhough investigations into the polymerization of this monomer, and that of other alkyl homologues, was already reported by Ramakrishnan *et al.*[17]



Scheme 2. Synthesis of 4-(hydroxymethyl) benzaldehyde (monomer **2**).

Two PEGylated AB_2 macromonomer analogues, consisting of a short poly(ethylene oxide) chain between the aldehyde and the hydroxyl functions, and of different molecular weights, were also designed (monomers **3** and **4**). As depicted in Scheme 3, these PEG

precursors were synthesized from 4-hydroxymethyl benzaldehyde dimethylacetal in a two-step procedure, including anionic ring-opening polymerization (AROP) of ethylene oxide in DMSO and partial deprotonation of the hydroxyl group, followed by deprotection.[12a]



Scheme 3. Synthesis of AB_2-type macromonomer **3** and **4** via anionic ring-opening polymerization of ethylene oxide followed by deprotection under acidic condition.

A typical ^{1}H NMR spectrum recorded in $CDCl_3$ of this AB_2-type PEO is shown in Figure 9. The signal of the terminal aldehyde proton (C*H*O) appears as a singlet at 9.99 ppm, while two doublets corresponding to aromatic protons are clearly detected between 7.86 and 7.52 ppm (doublet, J_{HH} = 8.4 Hz). The ethyleneoxy protons of PEG (C*H*$_2$-C*H*$_2$O) are found around at 3.63 ppm while the terminal C*H*$_2$OH is found at 4.64 ppm. The integral ratio of these peaks is 1 / 4 / 68 / 2, in accordance with the theoretical value. The corresponding $M_{n\ NMR}$ value obtained in this way is very close to the targeted one (872 g/mol; yield 65%). Similarly, a macromonomer **4** was synthesized *via* the same protocol and the obtained molecular weight is 1589 g/mol.

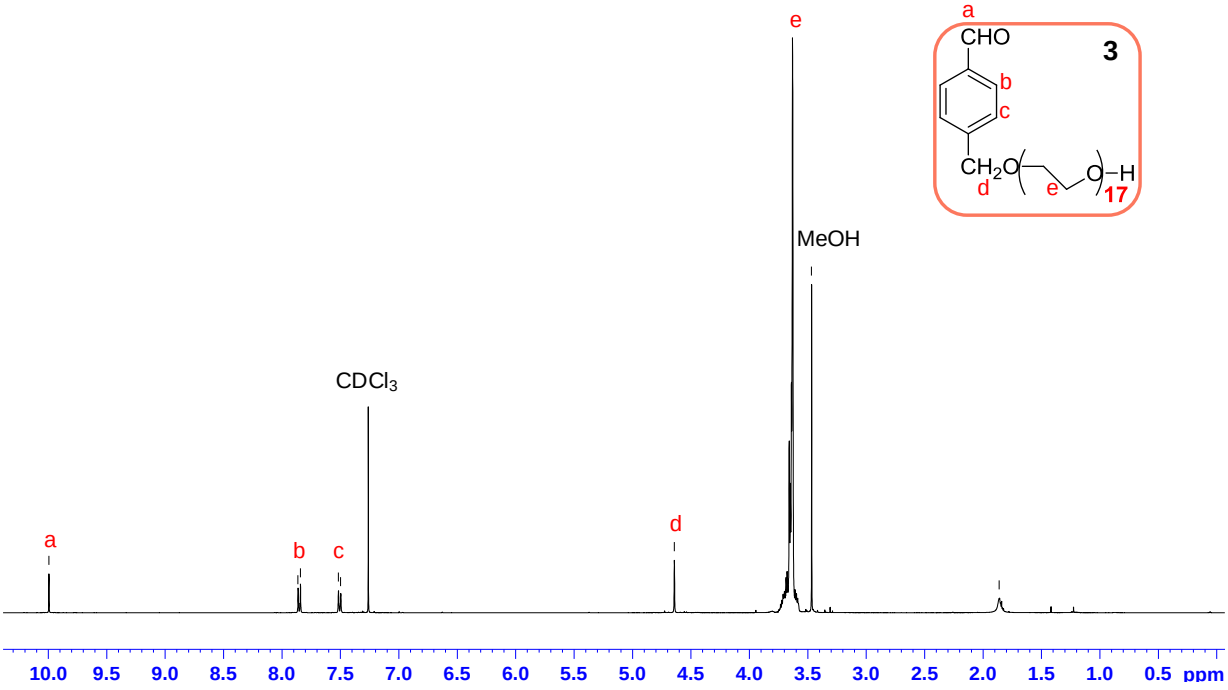


Figure 9. ^{1}H NMR spectrum of the AB_2-type macromonomer **3**.

5.2. Acid-catalyzed polymerization of monomers 1 and 2

Polymerizations either by polyacetalization (monomers **2**, **3** and **4**) or by polytransacetalization (monomer **1**) were conducted under an inert atmosphere in solution in

toluene or in THF, with the aid of 20 mol% of a Bronsted acid catalyst, such as *p*-toluenesulfonic acid (*p*-TSA), or camphor-10-sulfonic acid (CSA) or pyridinium camphorsulfonate (PCS) (Figure 10). The latter catalytic system was investigated in the work of Ramakrishnan *et al.*[17]

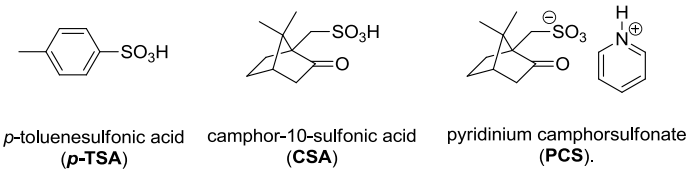


Figure 10. Catalysts investigated for the synthesis of hyperbranched polyacetals.

Table 1 summarizes the implemented experimental polymerization conditions and the molecular characteristics of the as-obtained polymers. Crude reaction products were first analyzed by SEC in THF, after the polymerization was quenched by triethylamine to avoid degradation of the acetal linkages by the acid catalyst. Polymers were recovered as white solids by precipitation twice into MeOH/Et_3N, from a THF or toluene solution. Molecular weights were then determined by SEC and polymers were characterized by NMR spectroscopy.

Polymerizations were initially performed in toluene using a Dean & Stark apparatus to remove water (entries 1-2, Table 1). These conditions led to polymers of low molecular weights (around 1000 g/mol) regardless the nature of the catalyst. Dried molecular sieves 4 Å were thus selected to trap the removed water and THF was used as polymerization solvent instead of toluene. Note that molecular sieves have already proven their efficiency for water scavenging in aliphatic polyester synthesis.[56] By directly adding molecular sieves 4 Å in the reaction vessel, a slight increase in monomer conversion was noted, though the molecular weights were still relatively low (from 900 to 3300 g/mol; entry 3-4, Table 1). A significant amount of unreacted AB_2-type monomer was also noted, as confirmed by ^{1}H NMR and SEC (at 30 min; see a typical SEC trace in Figure 11).

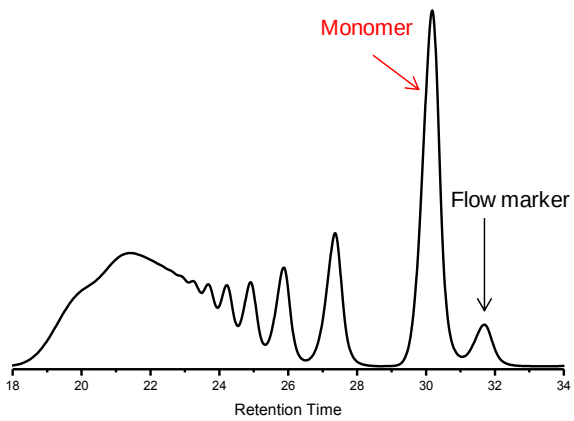


Figure 11. SEC traces of entry 4 in Table 1.

Table 1. Acid-catalyzed polymerization of AB_2-type (macro)monomers.[a]

entry	Monomer	cata. (eq.)	scavenger	Solvant	T (°C)	time	$\overline{M}_n$ (g/mol)	$\overline{M}_w$ (g/mol)	D	Conv[b]
1	**2**	TSA (0.2)	Dean-Stark	Toluene	Reflux 130 °C	4d	590	910	1.5	38%
2	**2**	CSA (0.2)	Dean-Stark	Toluene	Reflux 130 °C	4d	400	800	1.9	51%
3	**2**	CSA (0.2)	Molecular sieves	THF	50 °C	4d	810	1600	2	54%
4	**2**	TSA (0.2)	Molecular sieves	THF	50 °C	4d	1400	3300	2.3	61%
5[C]	**2**	TSA (0.2)	Molecular sieves	THF	50 °C	7d	1600	19 300	12.1	86%
6	**2**	PCS (0.02)	Vacuum [d]	None[d]	150 °C[e]	24h	4800	13 700	2.9	70%
7	**1**	PCS (0.02)	Vacuum	None	100 °C	2h	12 000	20 400	1.7	85%
8	**1**	TSA (0.2)	Molecular sieves	THF	50 °C	6d	8500	17 800	2.1	81%
9	**4**	TSA (0.2)	Molecular sieves	THF	50 °C	6d	2960	4100	1.3	75%
10	**3**	TSA (0.2)	Molecular sieves	THF	50 °C	6d	3900	7400	1.86	81%
11	**3**	TSA (0.2)	Dean-Stark	Toluene	Reflux 130 °C	6d	3750	12000	3.2	40%

[a] Polymerization of *p*-hydroxymethyl benzaldehyde with a concentration in monomer of 0.7 mol.L^{-1}. Molecular weights and dispersities were determined by SEC in THF (calibration using polystyrene as standards). Number-average, mass-average molecular weights and dispersity (D) were determined without taking peaks of both dimer and monomer into account. [cata.] = catalysts investigated in the polymerizations. [b] Conversion was determined by ^{1}H NMR of the crude solution. [c] the molecular sieves were changed every two days. Molecular weights and dispersity D measured by SEC in THF of polymers that were purified by precipitation in MeOH-Et_3N. [d] Polymerization in bulk was carried out under reduced pressure at high temperature. [e] after 2h at 100 °C, only oligomers formed. Thus the temperature was increased to 150 °C.

However, monomer conversion could be significantly improved by changing molecular sieves every 2 days, allowing for the production of polyacetals of much higher molecular weights (M_w up to 19,300 g/mol and M_p up to 106,000 g/mol, Figure 12), as measured by SEC

after purification by precipitation (entry 5, Table 1). Moreover, the monomer conversion was nearly quantitative, as determined by ^{1}H NMR. In the meantime, a dramatic increase of the molecular weight distribution can be observed, which is typical for hyperbranched polymers prepared *via* self-condensation of an AB_2 monomer.[27] Compared to the Dean-Stark apparatus, molecular sieves thus proved much more efficient to drive the equilibrium towards the formation of polyacetals.

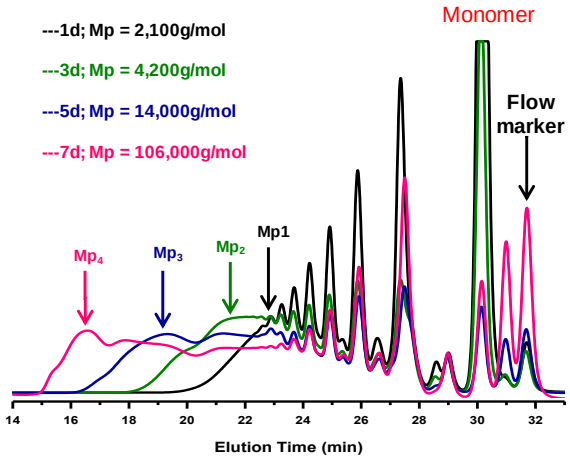


Figure 12. SEC traces (UV detection in THF; relative to PS standards) of hyperbranched polyacetals **HBPA(2)**$_{CHO}$ obtained from monomer **2** at different intervals (entry 5, Table 1). M_p's correspond to peak molecular weights of four samples injected.

Figure 12 shows the evolution of molecular weights with time, as observed by SEC in THF, when polymerizing monomer **2** by introducing fresh molecular sieves at regular intervals. This simple technical trick allowed synthesizing hyperbranched polymers with very high molecular weights, though only apparent values relative to polystyrene standards are measured by SEC. Figure 13 highlights the difference of SEC traces obtained before and after purification by precipitation: one can note that the peaks of monomer and oligomers have disappeared after precipitation due to fractionation.

Monomer **2** was also polymerized *via* polyacetalization at 150 ℃ (entry 6) using the same catalyst, PCS, employed by Ramakrishnan *et al.* for the polytransacetalization of **1**.[17] The sample was taken out after 2h of reaction, but only revealed the formation of oligomers at 100 ℃, as observed by SEC in THF. However, the molecular weight of the polymer obtained at 150 ℃ after 24 h was up to 13,700 g/mol.

Similarly, the acid-catalyzed polymerization of *p*-hydroxymethyl benzaldehyde dimethylacetal (**1**) was attempted with PCS (entry 7, Table 1). Under vacuum, we obtained polyacetals with molecular weight values close to those reported by Ramakrishnan *et al.* (M_w in reference is 21,000 g/mol with dispersity, D, of 3.0 with Kugelrohr apparatus).

Using PCS as catalyst but at a lower temperature (100 ℃ instead of 150 ℃ because MeOH is easier to remove than H_2O), polymer molecular weights obtained from monomer **1** were significantly higher (entry 7) than that of polyacetals obtained from monomer **2** (entry 6).

Most importantly, monomer **2** is expected to form defect-free hyperbranched polyacetals (DB = 100%, see further discussion), in contrast to polymers generated from the self-transacetalization of monomer **1**.

Finally, appropriate conditions to prepare polyacetals of significantly high molecular weights consisted in polymerizing **1** or **2** at 50 ℃, in the presence of 20 mol% *p*-TAS as catalyst and molecular sieves as water scavenger (entry 8).

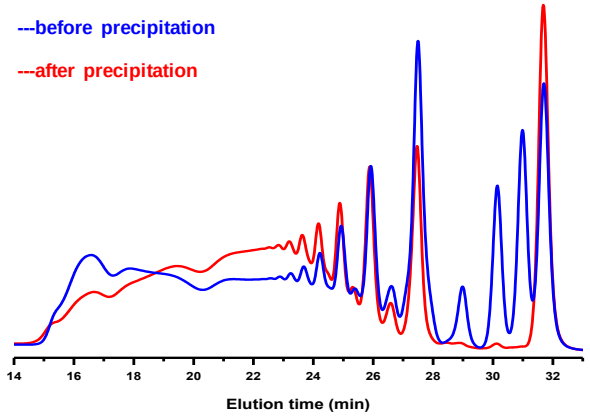


Figure 13. SEC traces (UV detection in THF; calibration with PS standards) of **HBPA(2)**$_{CHO}$ before and after precipitation (entry 5, Table 1).

^{1}H NMR spectra of polymers arising from monomers **1** and **2** are shown in Figure 14. The peak at 10.0 ppm in the ^{1}H NMR spectrum of the polymer obtained from monomer **1**, denoted as **HBPA(1)**$_{CH(OMe)_2}$, is assignable to the aldehyde protons (a) formed by partial hydrolysis of the terminal dimethylacetal units (estimated at 4.2%). (Figure 14B)

As expected, the methylene protons of the benzylic groups of monomer **2** (PhC$\underline{H_2}$OH, peak f at 4.8 ppm, Figure 14D) are converted into benzyloxy protons after polyacetalization. Of particular interest, whereas the methine proton of the acetal unit of monomer **1** (k, at 5.37 ppm, Figure 14A)[17] splits into three distinct peaks in **HBPA(1)**$_{CH(OMe)_2}$ (peaks h, j, k, Figure 14B), only one –though broad- signal can be seen around 5.8 ppm (peak h, Figure 14C) for polymer **HBPA(2)**$_{CHO}$ obtained from monomer **2**.

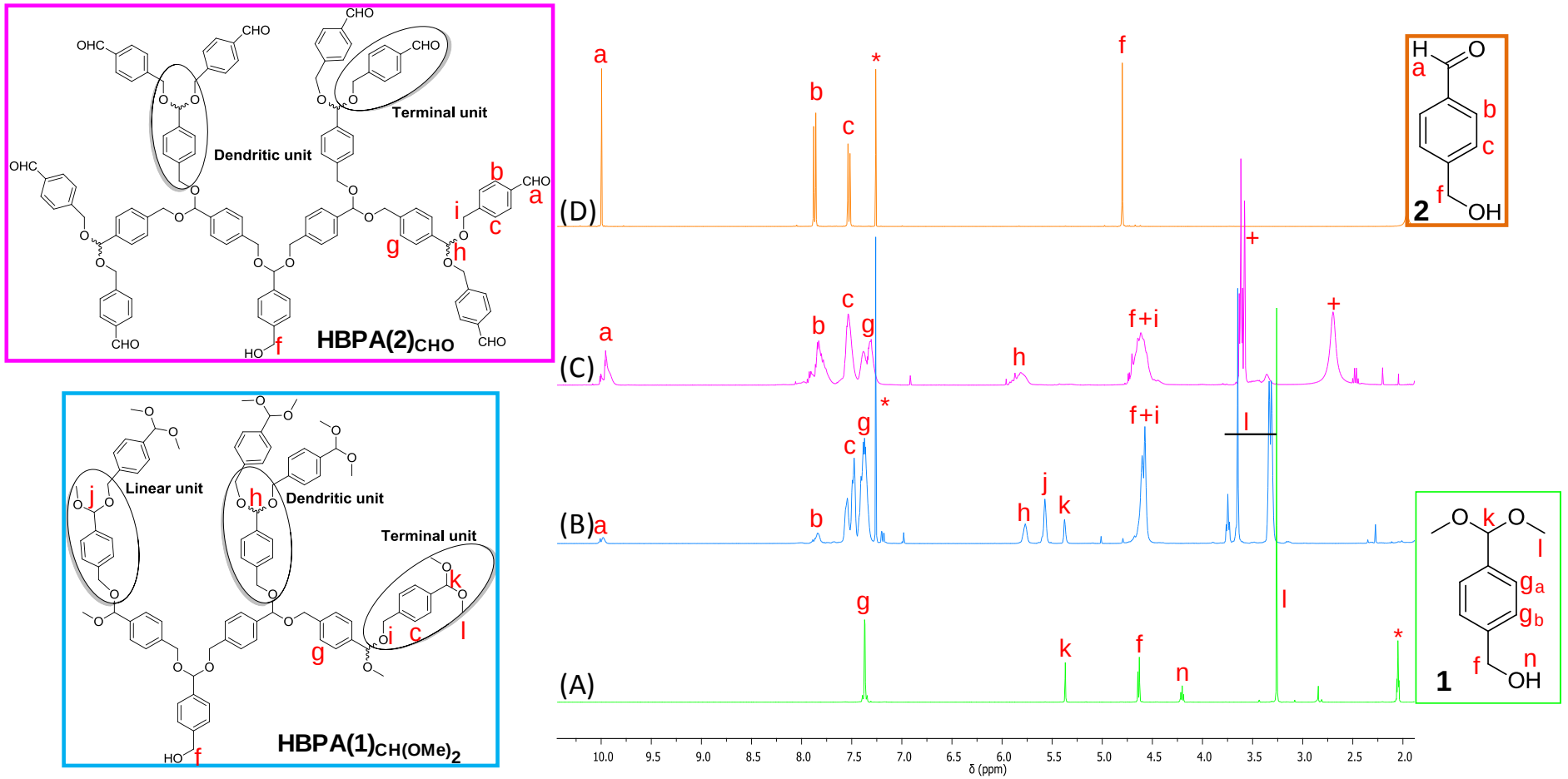
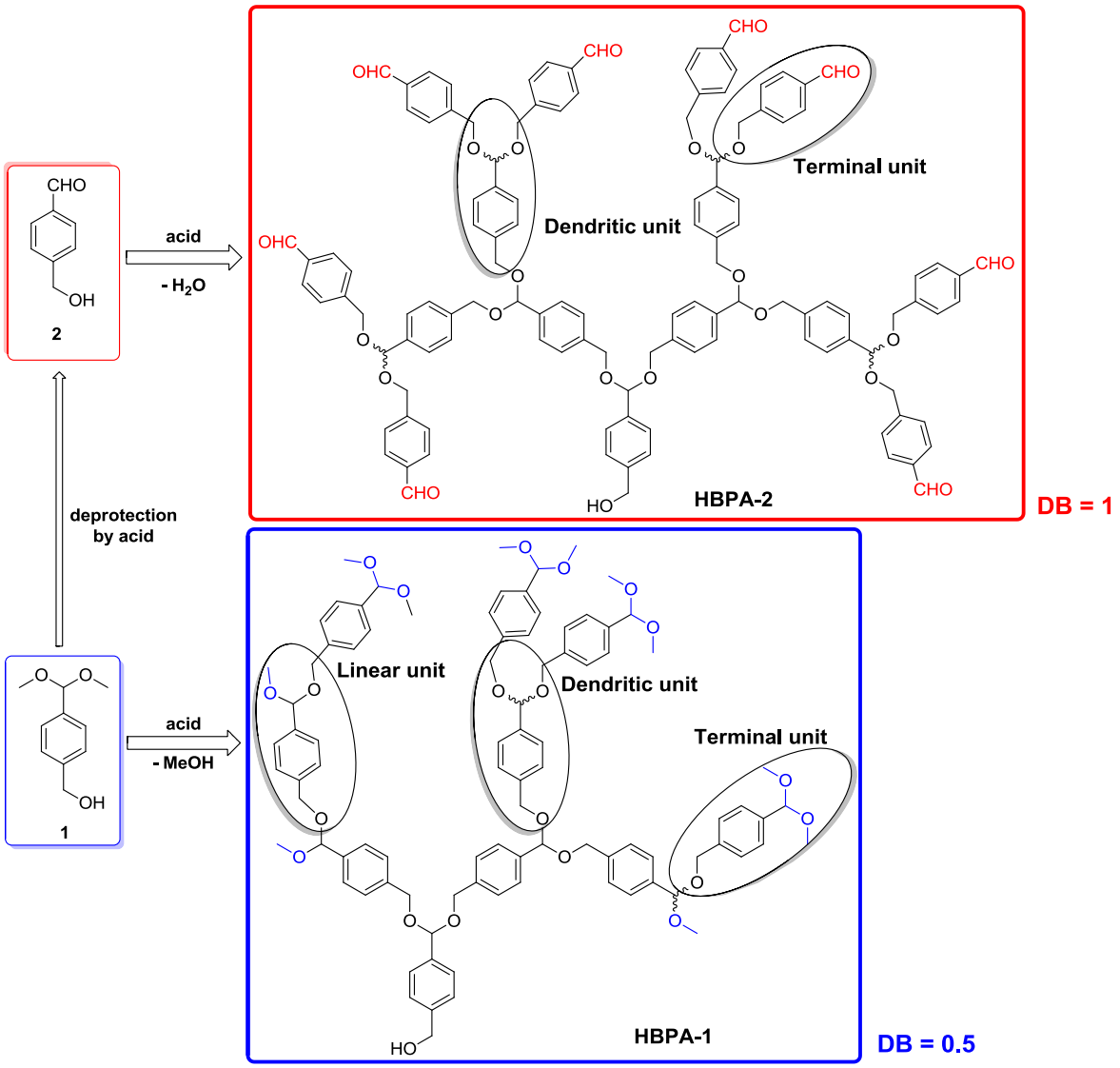


Figure 14. ^{1}H NMR (400 MHz; THF-d_8) spectrum of monomers **1** and **2** and corresponding polyacetals: **HBPA(2)**$_{CHO}$ (entry 5, Table 1) and **HBPA(1)**$_{CH(OMe)_2}$ (entry 8, Table 1). * are peaks of deuterated solvent CDCl3, for spectra (A) was obtained in acetone-d_6. + are peaks of other solvents residues.

In the former case, these three peaks can be assigned to dendritic (D), linear (L), and terminal (T) units, at 5.77, 5.57 and 5.38 ppm, respectively. Peaks' assignment of hyperbranched polyacetal is based both on the comparison with the monomer spectra (Figure 14 A and D) and data reported by Ramakrishnan *et al.*[17] From the relative intensities of these three peaks, a direct estimation of the degree of branching (DB) of the hyperbranched polyacetal **HBPA**(**1**)$_{CH(OMe)_2}$ was possible: the DB was found to be around 0.51, which is an expected value for a statistically random growth process.[57]

In addition to the methine protons of the acetal units, the ^{1}H NMR spectrum of **HBPA**(**2**)$_{CHO}$ (Figure 14C) shows characteristic signals of aldehydic protons around 10 ppm corresponding to terminal units, as well as aromatic protons between 7 and 8 ppm. Interestingly, aromatic protons adjacent to the numerous terminal aldehydes (protons a) can be differentiated from aromatic protons of dendritic acetal units (protons c and g, respectively).

The single peak h observed at 5.8 ppm in the spectrum of **HBPA**(**2**)$_{CHO}$ (Figure 14C) can be assigned to dendritic (D) units solely. This is due to the fact that the intermediate linear hemiacetal is unstable and is rapidly transformed into an acetal linkage (see Scheme 1 above). Monomer **2** thus leads to acetal linkages, that is, each acetalization elementary reaction generates a dendritic unit. In other words, **HBPA**(**2**)$_{CHO}$ obtained by polyacetalization is a defect-free hyperbranched polyacetal, that is, with a DB equal to unity, in sharp contrast to **HBPA**(**1**)$_{CH(OMe)_2}$ synthesized by polytransacetalization (Scheme 4).



Scheme 4. Synthetic routes to hyperbranched polyacetals: DB = 1 *via* polyacetalisation of monomer **2** and DB = 0.5 *via* polytransacetalisation of monomer **1**.

The ^{13}C NMR spectrum of **HBPA(2)**$_{CHO}$ confirmed the presence of one single type of methine carbon atoms due to the dendritic acetal units around 101 ppm (Figure 15). This was also supported by characterization of this polymer by 2D NMR spectroscopy showing only one population for the methine proton, around 101 ppm in ^{13}C NMR and 5.8 ppm in ^{1}HNMR (Figure 16).

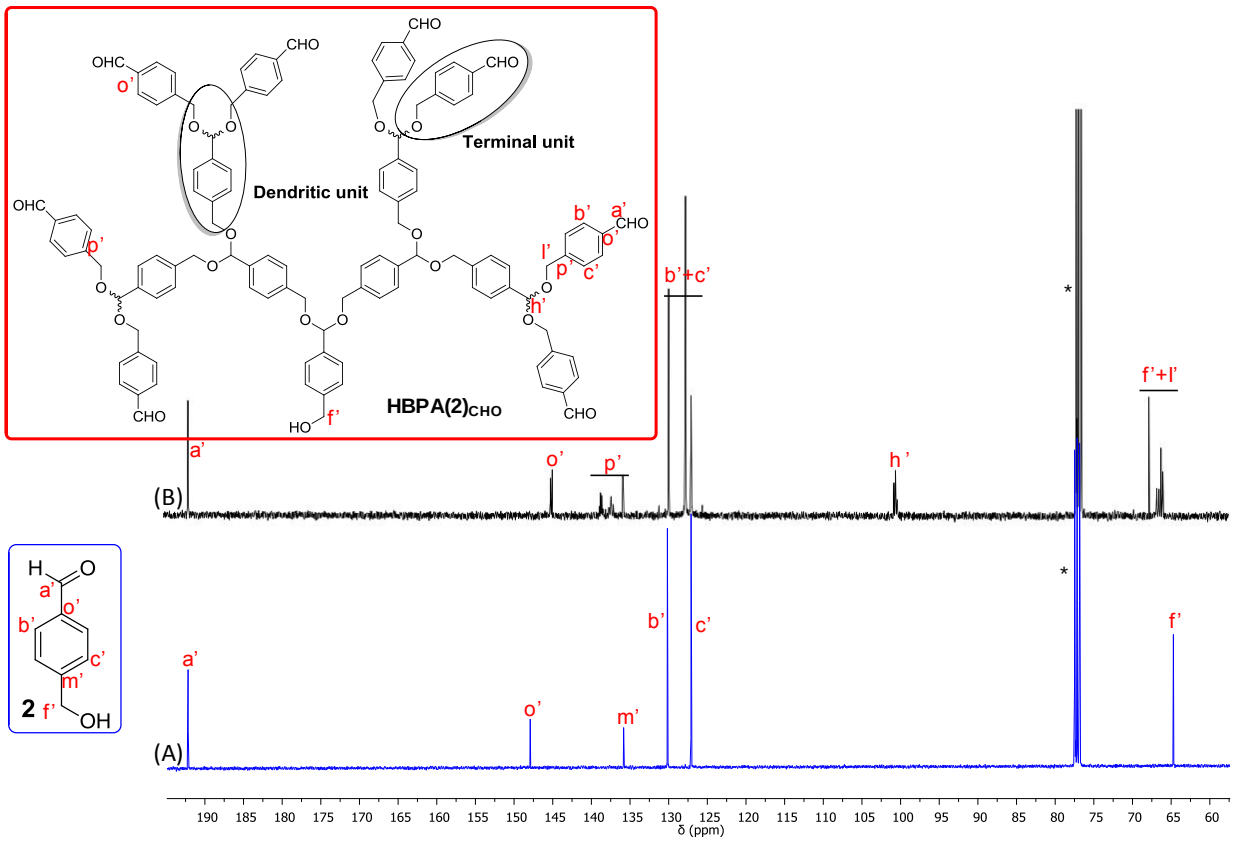


Figure 15. ^{13}C NMR spectrum (100 MHz; $CDCl_3$) of (B) hyperbanched polyacetal **HBPA(2)**$_{CHO}$ (entry 4 in Table 1) and (A) monomer **2** (*).

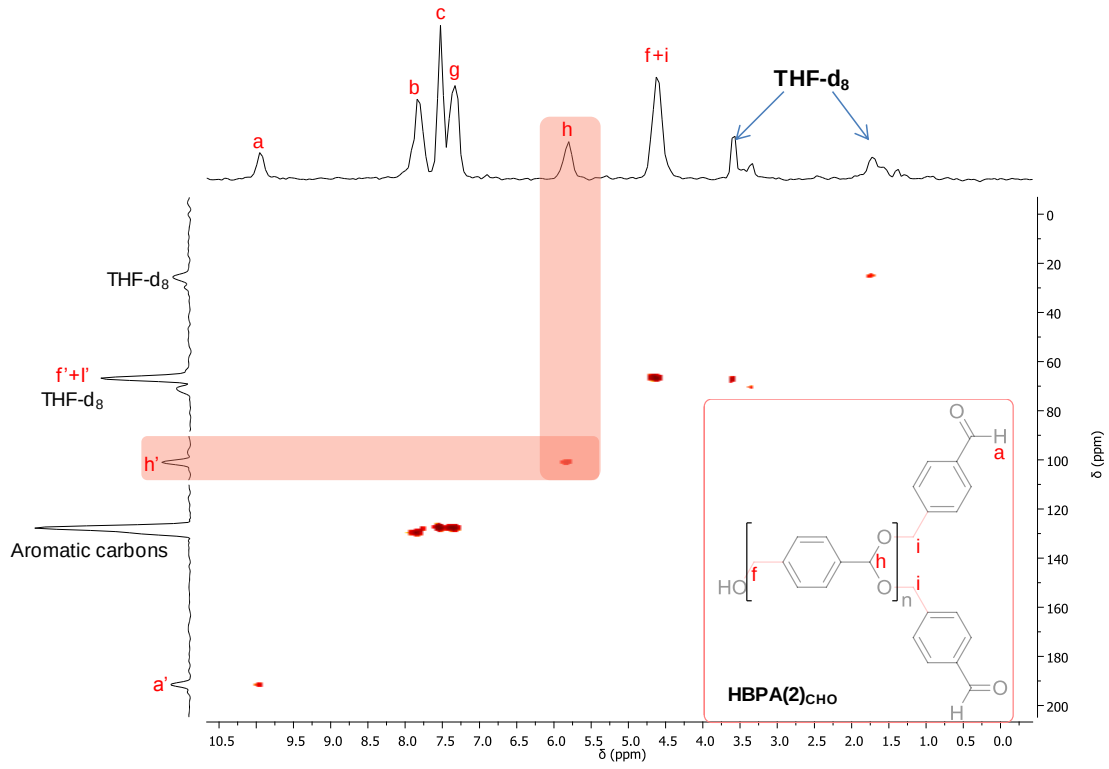


Figure 16. 2D NMR spectrum (400 MHz; THF-d_8) of hyperbanched polyacetal **HBPA(2)**$_{CHO}$.

5.3. Polymerization of AB_2-type PEG macromonomers 3 and 4

Attempts to polymerize PEGylated homologues of monomer **1** were also investigated. These AB_2-type macromonomers**, 3** and **4**, were thus polymerized under the same acidic conditions described above (Table 1). It was expected here to directly access water-soluble defect-free hyperbranched polyacetals constituted of PEG chains between the branching points. For instance, polymerization of **3** and **4** was carried out in THF in the presence of molecular sieves (entries 9 and 10). A polymerization in toluene under reflux for 6 days with the aid of a Dean & Stark apparatus was also performed (entry 11).

However, SEC traces of polymers thus obtained revealed the presence of substantial amounts of the residual macromonomer that was analyzed by SEC separately. Only oligomers could be achieved, irrespectively of the size of the PEG chain and experimental conditions tested. Hence, the aldehyde and hydroxyl functional groups hardly react with each other when separated by PEG chains. Attempts to purify the obtained oligomers from the residual macromonomer by fractionation were unsuccessful.

Surprisingly, the ^{1}H NMR spectrum of polymers prepared in THF using molecular sieves (entries 9 and 10, Table 1) showed the presence of three distinct peaks due to methine proton of the acetal units (h, j and k, Figure 17), attributable to dendritic, linear and terminal units. Thus, these hyperbranched polyacetals synthesized in THF from macromonomers **4** are characterized by a DB < 1 (a rough estimation by NMR indicates a DB value of 53%), in sharp contrast to the defect-free hyperbranched polyacetals arising from the AB_2-type "molecular" homologue (monomer **2**, entries 1 to 6, Table 1). This might be ascribed to the steric hindrance of the PEG chain that would prevent the aldehyde groups from quantitatively converting into acetal linkages, making the intermediate PEG-based hemiacetal better stabilized by intra or inter hydrogen bond PEG chain (Figure 18), in comparison to hyperbranched polyacetals generated from monomer **2**.

Figure 19 shows the presence of the peak of the macromonomer **4** at 23.6 min in the SEC traces of **HBPA(4)**$_{\text{-(PEO)}_{33}\text{-CHO}}$, while the M_p value of the as-obtained oligomers is around 5600 g/mol.

In contrast to the polymer structure synthesized from macromonomer **4** (33 units of PEG chain), the polymer obtained from shorter PEG chain of macromonomer **3** (17 units of PEG chain) in toluene using the Dean-Stark equipment (entry 11), only one type of methine proton (peak h) was noted at 5.6 ppm in its ^{1}H NMR spectrum (Figure 20). This would indicate, in this case, the formation of a defect-free hyperbranched polyacetal. Besides, using Dean-Stark equipment, the possible residue MeOH may be eliminated with toluene during the reaction that could avoid the side reaction between MeOH and the aldehyde of monomer. In these conditions, a molecular weight M_p of **HBPA(3)**$_{\text{-(PEO)}_{17}\text{-CHO}}$ around 12000 g/mol was obtained.

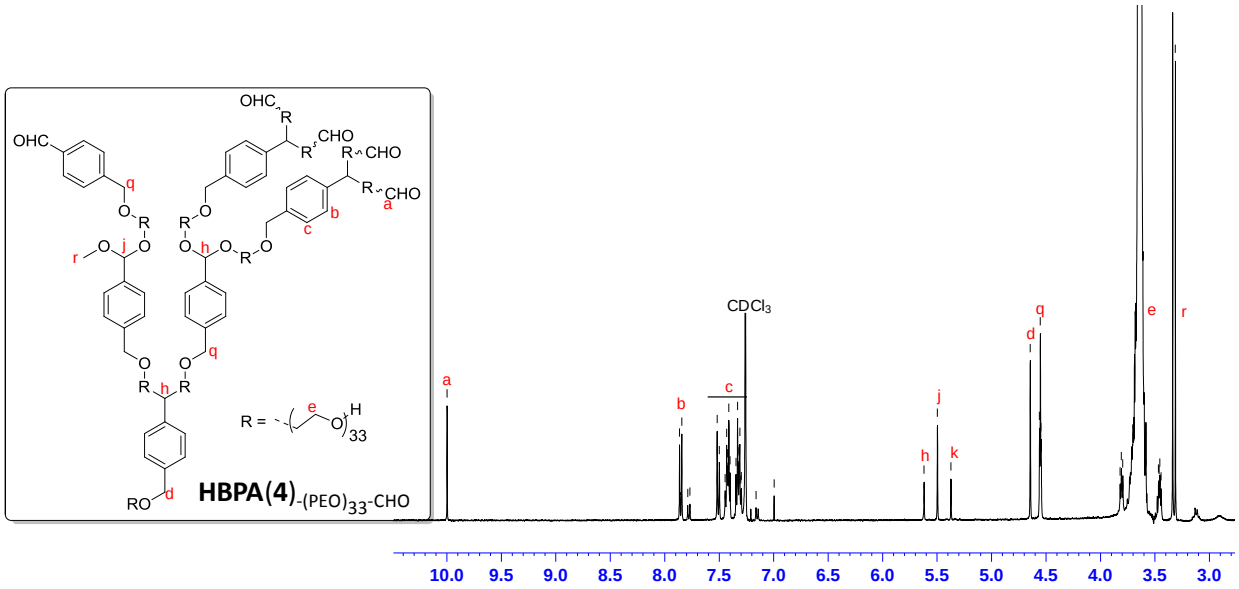


Figure 17. ^{1}H NMR ($CDCl_3$; 400 MHz) of polymer derived from macromonomer **4** (entry 9, Table 1).

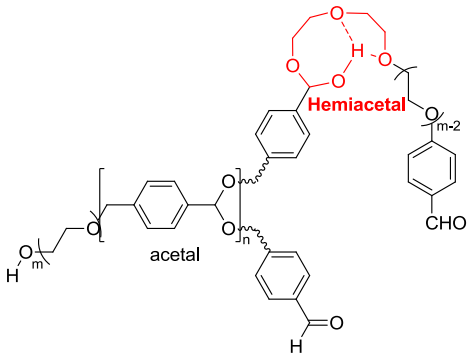


Figure 18. Hemiacetal of polyacetal synthesized from macromomonomer stabilized by intra hydrogen bond PEG chain.

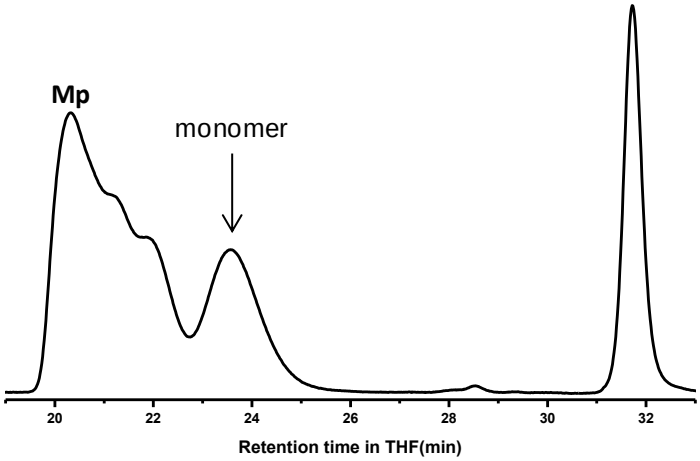


Figure 19. SEC traces of polymer derived from macromonomer **4** (entry 9, Table 1).

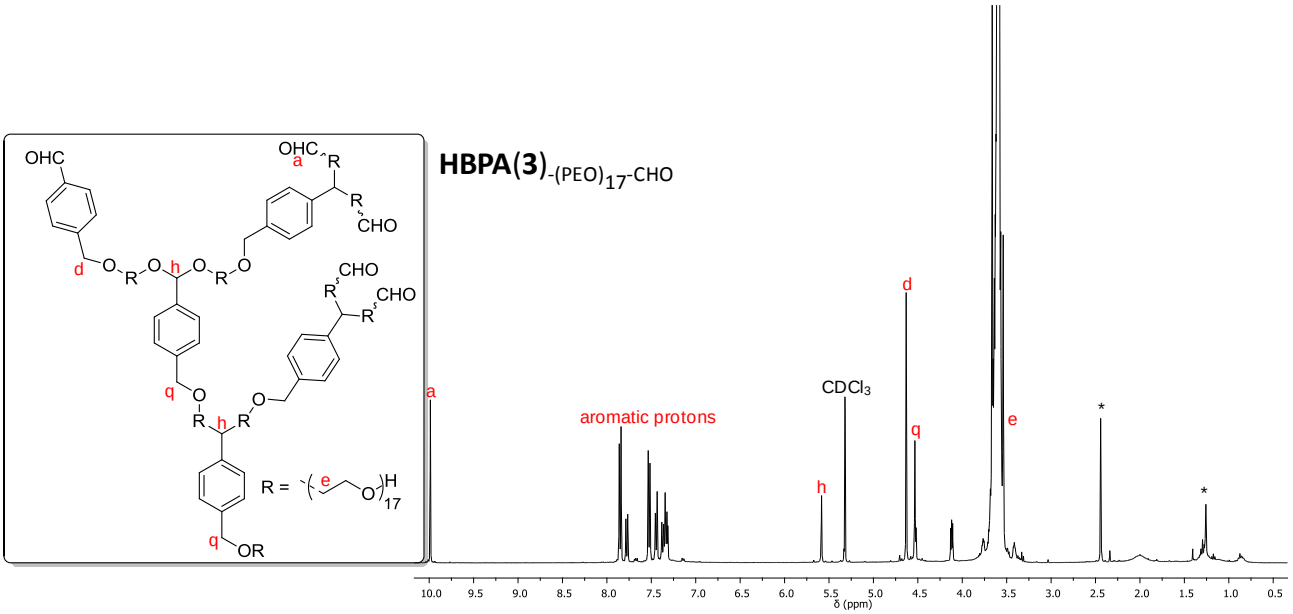


Figure 20. ^{1}H NMR ($CDCl_3$; 400 MHz) of polymer derived from macromonomer **3** (entry 11, Table 1).

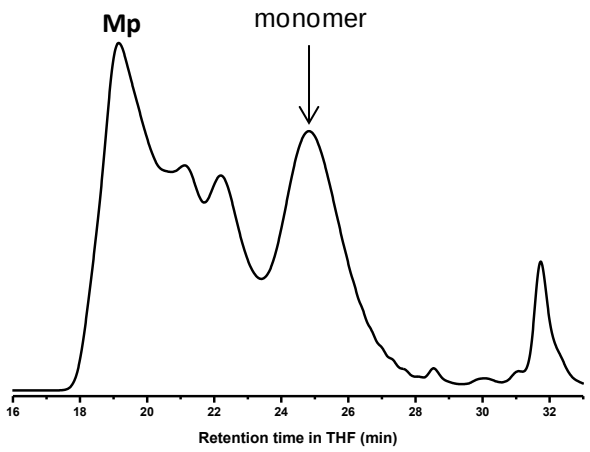


Figure 21. SEC traces of polymer derived from macromonomer **3** (entry 11, Table 1).

A more systematic investigation would be needed, however, to confirm whether the polymerization of these macromonomers **4** could form defect-free polyacetals with Dean-Stark equipment in toluene, and also to optimize the conditions to achieve higher molecular weights from PEGylated AB_2-type macromonomers.

5.4. Calculation of the number of hyperbranched polyacetals' peripheral aldehydes

As discussed above, NMR analysis allowed us to account for the branching density of hyperbranched polyacetals. Interestingly, a calculation of the number of terminal aldehyde units was also possible in the case of defect-free hyperbranched polymers (DB = 1) derived from monomer **2**. Knowing this number with accuracy is particularly important for the purpose of further functionalization of the periphery of hyperbranched polymers (in our case, for instance, by PEGylation, see further). Chemical modification of the periphery of hyperbranched polymers

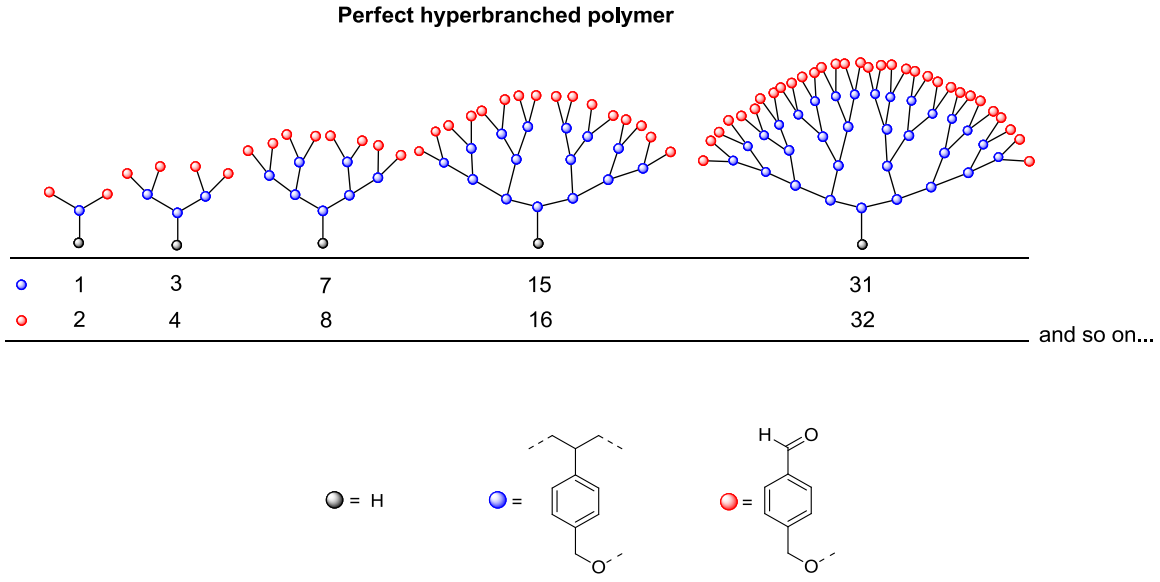
with DB = 1 has already been reported, for instance by Smet *et al.*[58] However, a large excess of functionalizing reagents was required to achieve a complete modification.

Figure 22 shows the schematic representation of individual defect-free hyperbranched architectures of increasing generation number, which can be viewed as individual dendrimers (absence of any linear units in each individual molecule). This scheme illustrates that the number of terminal units can be deduced from that of the dendritic units according to the following relationship: D = T – 1. For hyperbranched polymers of sufficiently high molecular weights (in particular when purified by fractionation), the D number thus nearly equals the T number. For instance, the hyperbranched polyacetal shown in Scheme 4 (DB = 1) contains acetal-type dendritic units (D) and aldehyde-type terminal units (T) whose molecular weights are 119 g/mol and 135 g/mol, respectively, with D ≅ T. Hence, the mol%. number of each type of unit can be easily deduced in the following manner:

$$n_D * 119 + m_T * 135 = X \text{ (g)},$$

where X is a given mass quantity of any hyperbranched polyacetal with DB = 1,

$$\text{thus, } n_D \cong m_T = X / 254.$$



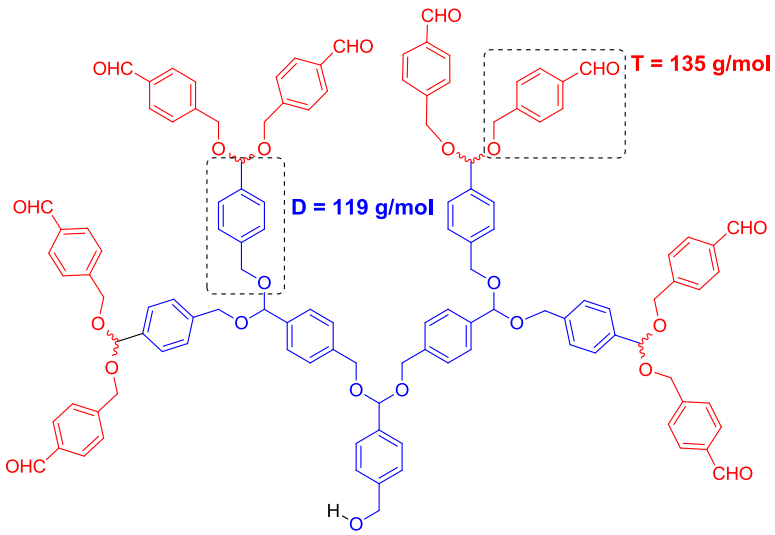


Figure 22. Schematic representation of defect-free hyperbranched polyacetals of increasing generation number: dendritic unit (D) in blue; terminal unit (T) in red; focal point in grey.

6. Derivatization of hyperbranched polyacetals with DB = 1

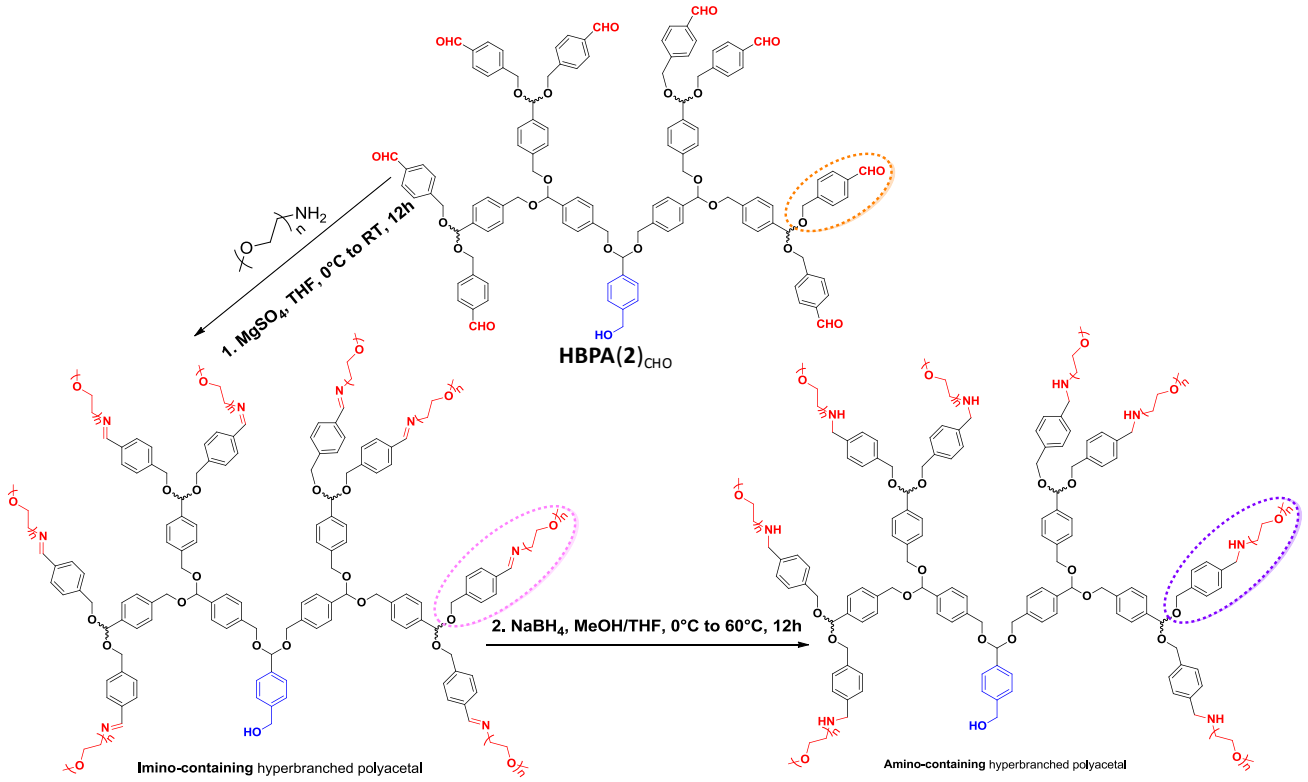
The presence of numerous terminal aldehydes in defect-free hyperbranched polyacetals offers the opportunity to access a wide range of hyperbranched derivatives. As emphasized in section 1.1 of this chapter, the aldehyde functionality can readily react with a variety of chemical functions including hydroxy-, or primary amino- or hydrazine-containing reagents. Here we were interested in elaborating water-soluble, acid-sensitive and biocompatible hyperbranched polyacetals. The terminal aldehydes were thus subjected to the reaction with commercially available α-methoxy,ω-amino-PEO's of different molecular weights (750, 2000, 5000, 12000 g/mol) to prepare hyperbranched polyacetal-PEO's. The motivation here was to provide a straightforward synthetic route to perfectly branched PEO's.

PEO is often referred to as poly(ethylene glycol) (PEG) and covalent attachment of PEG chains is known as the PEGylation reaction,[59] which provides specific properties of PEG such as stealth effect, biocompatibility, non-toxicity, low immunogenicity and antigenicity.

6.1. Chemical modification of defect-free hyperbranched polyacetals

As depicted in Scheme 5, condensation of the primary amino group of the PEO precursor (M_n = 750 g/mol) with the multiple aldehyde terminal units of hyperbranched polyacetal **HBPA(2)**$_{CHO}$ (entry 5, Table 1) gave a hyperbranched core-shell structure with imine linkages between the hyperbranched polyacetal core and the surrounding PEO arms. This condensation reaction was performed in THF, using a slight excess of the PEO precursor (1.2 eq. relative to **HBPA(2)**$_{CHO}$), in the presence of $MgSO_4$ to trap the water molecules released.

It is well-documented that imine functions are sensitive to hydrolysis, hence requiring a further reduction into secondary amines. The imino-containing hyperbranched polyacetal-PEO_{750} **Imino**(HBPA(2)$_{\text{-CH=N-}}PEO_{750}$)**-1** was thus treated with $NaBH_4$, in a mixture of MeOH and THF (1/1 in vol), giving rise to stable amino-containing hyperbranched polyacetal-PEO_{750} (**Amino**(HBPA(2)$_{\text{-CH}_2\text{NH-}}PEO_{750}$)**-1**). The excess of linear PEO precursor could be easily removed from the hyperbranched polyacetal-PEO_{750} derivative **Amino**(HBPA(2)$_{\text{-CH}_2\text{NH-}}PEO_{750}$)**-1** by dialysis against water during 10 days, using a membrane with a cut-off of molecular weight 1000 Da. Polymers were finally recovered as white powders by lyophilization.



Amino(HBPA(2)$_{\text{-CH2NH-}}PEO_{750}$)**-1:** PEO precursor ($M_n$ = 750 g/mol)
Amino(HBPA(2)$_{\text{-CH2NH-}}PEO_{2000}$)**-2:** PEO precursor ($M_n$ = 2000 g/mol)
Amino(HBPA(2)$_{\text{-CH2NH-}}PEO_{5000}$)**-3:** PEO precursor ($M_n$ = 5000 g/mol)
Amino(HBPA(2)$_{\text{-CH2NH-}}PEO_{12000}$)**-4:** PEO precursor ($M_n$ = 12000 g/mol)

Scheme 5. PEGylation of the terminal aldehyde units of hyperbranched polyacetal **HBPA(2)**$_{CHO}$ with amino-PEO precursors of different molecular weights and transformation into amino hyperbranched polyacetals.

6.2. Characterization of the hyperbranched polyacetal-PEO's

Chemical transformations of the periphery of hyperbranched polyacetals could be easily monitored by ^{1}H NMR spectroscopy, as illustrated in Figure 23. After reaction with the α-MeO,ω-NH_2 PEO_{750} precursor of 750 g/mol, the aldehyde protons at 10.2 ppm (peak a) completely disappeared, while characteristic signals of the imine protons appeared concomitantly at 8.4 ppm (peak u). Introduction of external PEO chains was also confirmed by

the presence of a broad signal around 3.5 ppm (peak e), as well as by a distinguished signal due to the protons of the methoxy end groups at 3.4 ppm (peak t).

Subsequent reduction of the imino functions by $NaBH_4$ successfully occurred, as attested by the complete disappearance of the signal at 8.4 ppm. Moreover, the different characteristic protons could be integrated and compared with the expected value for a 100% functionalization reaction. In theory, the ratio between methoxy protons of PEO chain ends (t), aromatic protons (w), methine and methylene protons of the acetal units (h, and f, i) and methylene protons (s) adjacent to the amino function (after reduction of the imino groups) plus e (-CH_2 of PEO chain overlapping with THF-d_8 at 3.58 ppm), is as follows:

$$t : w : h : (f + i) : (e + s) = 3: 8: 1: 4: 79.$$

NMR characterization of **Amino**(HBPA(2)$_{\text{-}CH_2NH\text{-}}PEO_{750}$)**-1** gave the following experimental ratio: 3: 8.1: 0.9: 4.1: 79 (Figure 24), which was very close to the theoretical values. This result allowed us to conclude that functionalization of the hyperbranched polyacetal by the PEO chains quantitatively occurred.

Other hyperbranched polyacetal-PEO's were prepared in a similar manner using α-MeO,ω-NH_2 PEO precursors of 2000, 5000, 12000 g/mol. A slight excess of each precursor was always added to the hyperbranched polyacetal **HBPA(2)**$_{CHO}$ (entry 5, Table 1). In these cases, however, linear PEO chains used in excess could not be totally eliminated by dialysis against water. Quantitative derivatizations could nonetheless be established, through the complete disappearance of aldehyde protons a of the **HBPA(2)**$_{CHO}$ precursor and concomitant appearance of imine moieties with the presence of vinylic protons (u) of the imino-hyperbranched polyacetal-PEO_{2000} derivative. Subsequent reduction of the latter compound by $NaBH_4$ led to the targeted hyperbranched polyacetal-PEO_{2000} with amino linkages (**Amino**(HBPA(2)$_{\text{-}CH_2NH\text{-}}PEO_{2000}$)**-2**). Characterization of the latter compound by ^{1}H NMR gave the following ratio:

$$t : w : h : (f + i) : (e + s) = 3 : 10.21: 1.01 : 6.16: 181$$

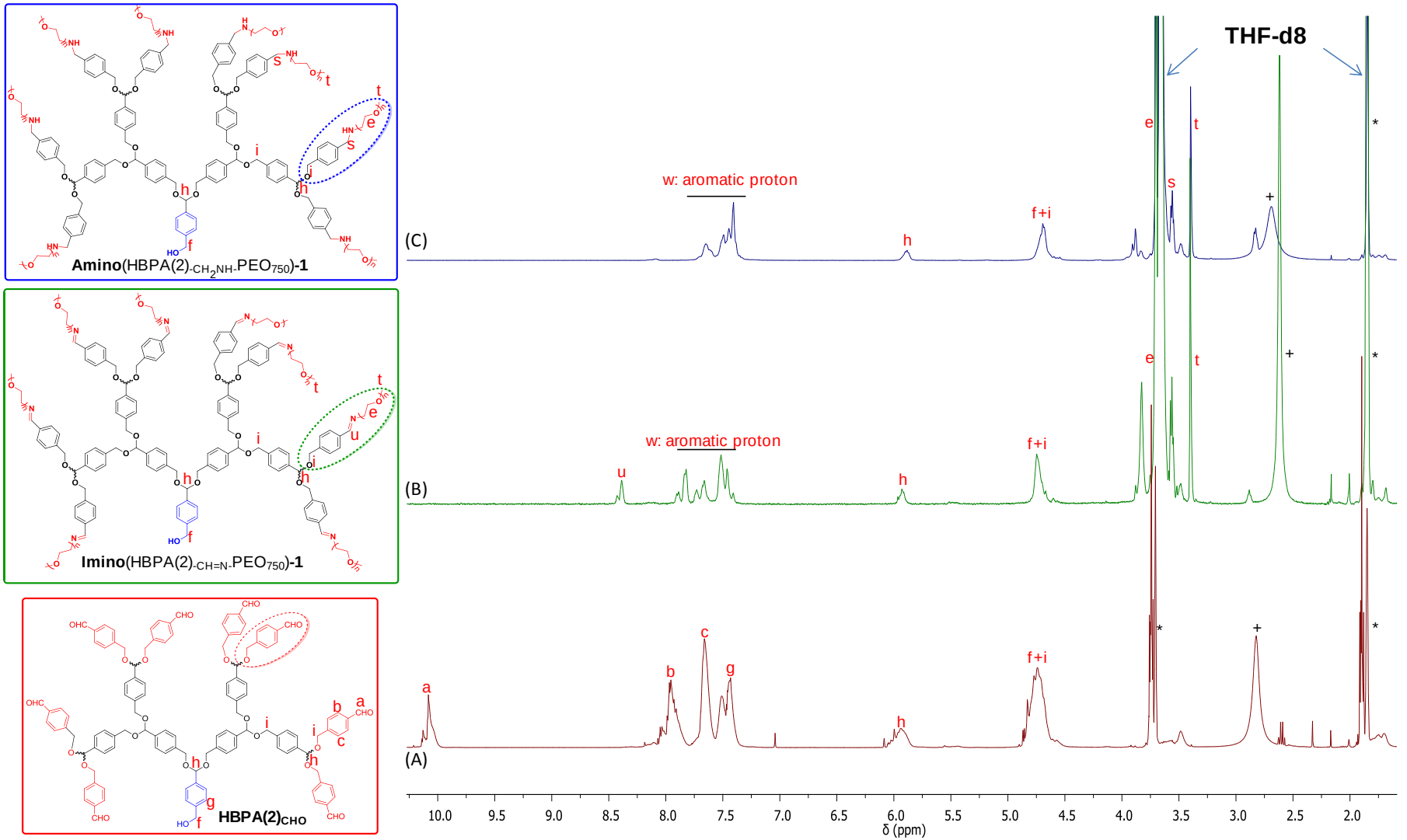


Figure 23. ^{1}H NMR analysis (400 MHz, THF-d_8) of hyperbranched polyacetals with: (A) aldehyde terminal units; (B) imino linkages and PEO_{750} segments; (C) secondary amino linkages and PEO_{750} segments; peaks ***** are THF- d_8 and peaks **+** are water in THF-d_8.

The theoretical ratio for a quantitatively modified and pure polymer should be as follows: 3: 8: 1: 4: 181. Therefore, the integration of PEO chains was higher than expected, which might be explained by the presence of residual linear PEO_{2000} chains that could not be totally removed by dialysis. This was also true for hyperbranched polyacetal-PEO derivatives with PEO segments of higher molecular weight: PEO_{5000} and PEO_{12000}.

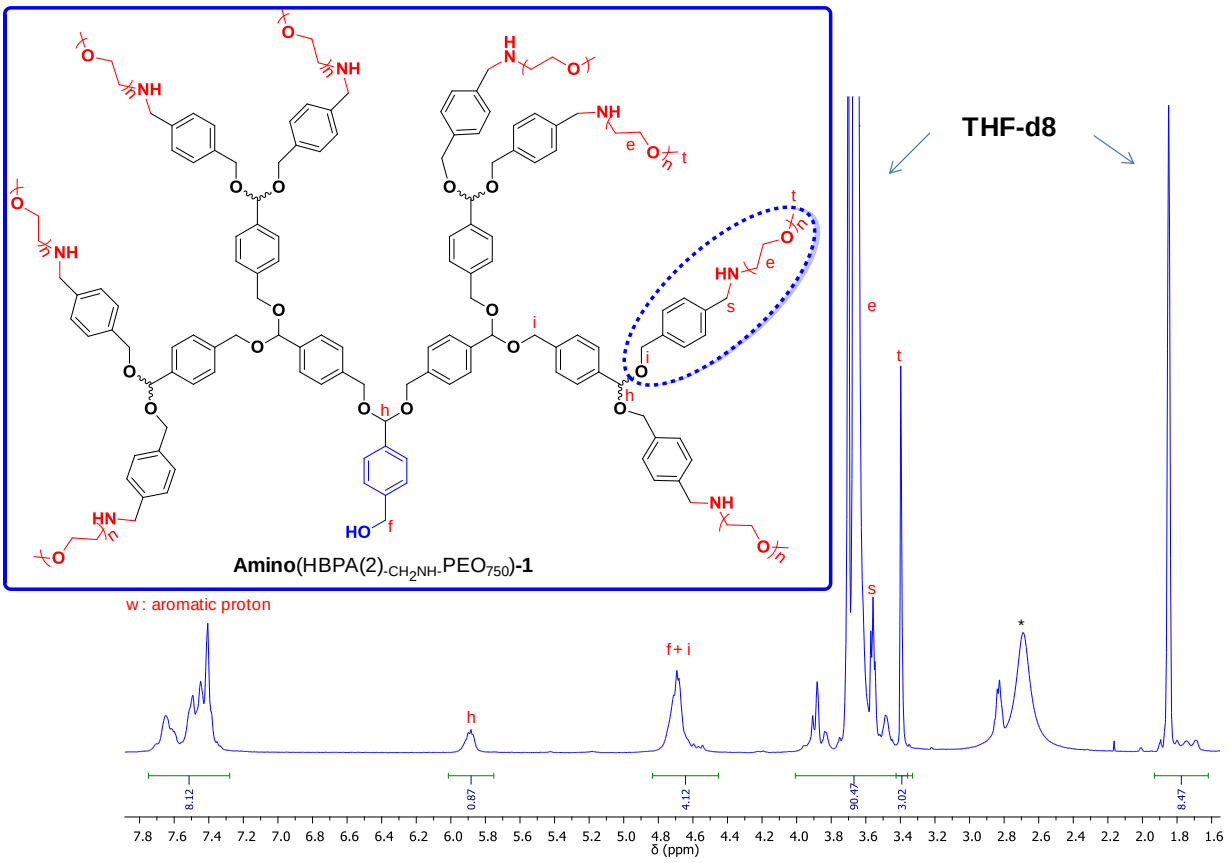


Figure 24. ^{1}H NMR (400 MHz, THF-d_8) characterization of hyperbranched polyacetal-PEO with amino linkages and PEO_{750} segments (**Amino**(HBPA(2)$_{\text{-CH}_2\text{NH-}}PEO_{750}$)**-1**); peaks * are due to water in THF-d_8 and amine proton -N*H*.

These hyperbranched polyacetals were next characterized by SEC in DMF with UV detection. Figure 25 shows an overlay of the three types of hyperbranched polyacetals. The molecular weight of **HBPA(2)**$_{CHO}$ (in black) is 38,000 g/mol with D = 6.2. After the PEGylation with α-MeO,ω-NH_2 PEO of 750 g/mol, molecular weight of **Imino**(HBPA(2)$_{\text{-CH=N-}}$PEO$_{750}$)**-1** (in red) is increased up to 52,600 g/mol with D = 1.9. A similar range of molecular weights was obtained for **Amino**(HBPA(2)$_{\text{-CH}_2\text{NH-}}PEO_{750}$)**-1** (blue curve) with M_n up to 59,300 g/mol and D = 2.03, after reduction of **Imino**(HBPA(2)$_{\text{-CH=N-}}$PEO$_{750}$)**-1**.

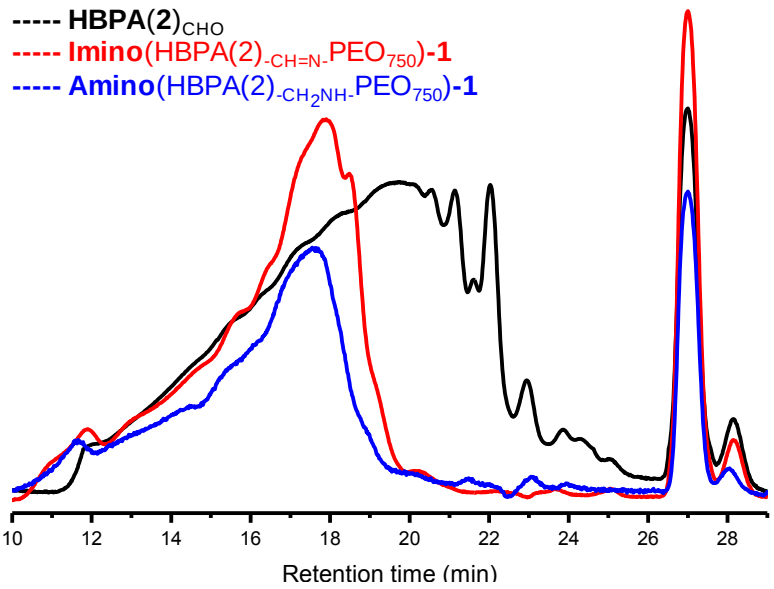


Figure 25. SEC traces (UV detection in DMF, relative to PS standards) of hyperbranched polyacetal **HBPA(2)**$_{CHO}$, **Imino**(HBPA(2)$_{-CH=N-}$PEO$_{750}$)**-1** and **Amino**(HBPA(2)$_{-CH_2NH-}$PEO$_{750}$)-**1**.

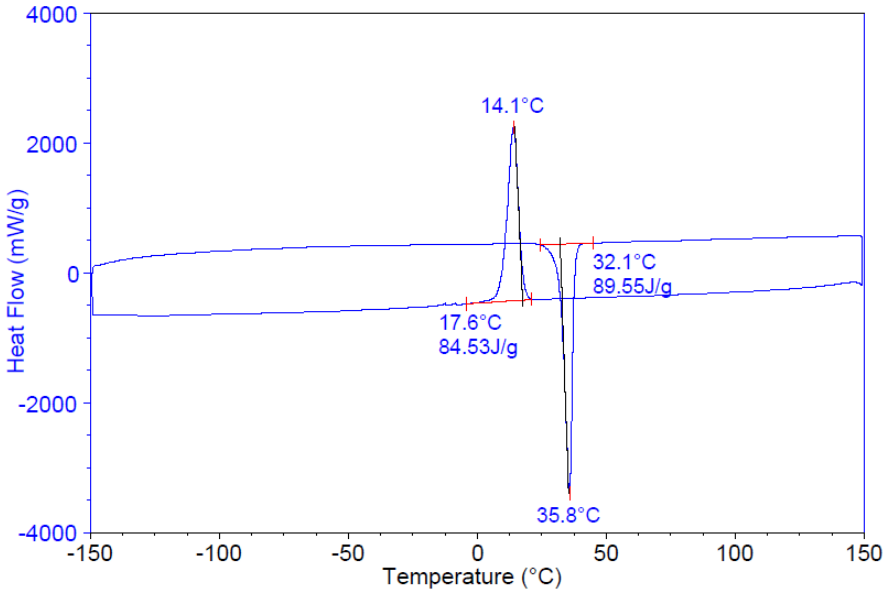


Figure 26. DSC thermograms of polymer **Imino**(HBPA(2)$_{-CH=N-}$PEO$_{750}$)**-1** at a heating rate of 10 ℃ min^{-1}.

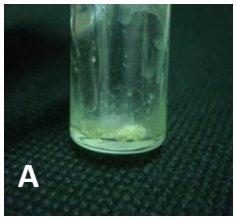
The analysis of DSC thermograms of imino- and amino-containing hyperbranched polyacetals revealed a 2 ℃ difference only (35.8 ℃ vs 34.0 ℃, Figure 16) of the melting temperature of imino hyperbranched polyacetal-PEO$_{750}$ **Imino**(HBPA(2)$_{-CH=N-}$PEO$_{750}$)**-1** and that of amino hyperbranched polyacetal-PEO$_{750}$ **Amino**(HBPA(2)$_{-CH_2NH-}$PEO$_{750}$)**-1**. In contrast, DSC measurement of hyperbranched polyacetal **HBPA(2)**$_{-CHO}$ shows a T_g at -23.6 ℃, and no melting temperature could be detected in agreement with the absence of PEO chains. The same

trend was observed from the comparison of other different imino- and amino-hyperbranched polyacetal-PEO's.

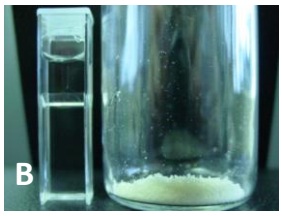
Main characteristics of the different hyperbranched polyacetal-PEO's are compared in Table 2. As expected, the melting temperature increases with the length of the PEO segments, from 35.8 to 61 ℃.

Table 2. Main characteristics of hyperbranched polyacetal-PEO's **Amino**(HBPA(2)$_{\text{-CH}_2\text{NH-}}PEO_{750}$)**-1**, **Amino**(HBPA(2)$_{\text{-CH}_2\text{NH-}}PEO_{2000}$)**-2** and **Amino**(HBPA(2)$_{\text{-CH}_2\text{NH-}}PEO_{12000}$)**-4**.

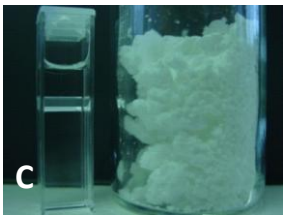
Amino Hyperbranched Polyacetal (AHBP)	AHBP-1	AHBP-2	AHBP-4
MeO-(PEG)n-NH2 (Mw)	750 g/mol	2,000 g/mol	12,000 g/mol
GPC in DMF: Mw-UV (D)	59300 (2.61)	100000 (1.88)	269000 (1.42)
GPC in DMF: Mw-IR (D)	44200 (2.03)	93000 (1.76)	350000 (1.44)
DSC : melting T° (℃)	35.8	53.3	61



Hyperbranched polyacetal **HBPA(2)$_{\text{CHO}}$**



Imino-hperbranched polyacetal-PEG$_{2000}$ **Imino**(HBPA(2)$_{\text{-CH=N-}}$PEO$_{750}$)**-1** and its solubility in water



Amino-hperbranched polyacetal-PEG$_{2000}$ **Amino**(HBPA(2)$_{\text{-CH}_2\text{NH-}}PEO_{750}$)**-1** and its solubility in water

Figure 27. Photographs of (a) hyperbranched polyacetal with aldehyde terminal units **HBPA**(**2**)$_{\text{CHO}}$, (b) hyperbranched polyacetal via imino linkages and PEO$_{750}$ segments **Imino**(HBPA(2)$_{\text{-CH=N-}}$PEO$_{750}$)**-1** (c) hyperbranched polyacetal via amino linkages and PEO$_{750}$ segments **Amino**(HBPA(2)$_{\text{-CH}_2\text{NH-}}PEO_{750}$)**-1.**

Solubility features and visual aspects of some compounds are illustrated in Figure 27. Both compounds made of the PEO$_{750}$ with imino or amino linkages were obtained as white solids that were found soluble in organic solvents (e.g. chloroform, THF, toluene) and in water

as well. As anticipated, however, the imino-hyperbranched polyacetal-PEO_{750} **Imino**(HBPA(2)$_{\text{-CH=N-}}PEO_{750}$)**-1** was not stable in aqueous solution, even at pH = 7; a progressive degradation occurred with time, both the linear PEO chains and the aldehyde-terminated hyperbranched polyacetal precursor being released by hydrolysis. As shown in Figure 28, the aqueous solution (pH = 7) turned turbid after 7 days at room temperature.

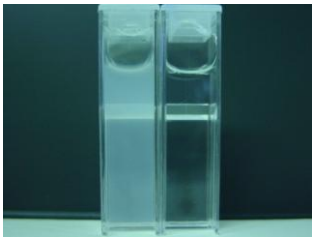


Figure 28. Photographs of hyperbranched polyacetal with imino linkages and PEO_{750} segments **Imino**(HBPA(2)$_{\text{-CH=N-}}PEO_{750}$)**-1** (left) hyperbranched polyacetal via amino linkages and PEO_{750} segments **Amino**(HBPA(2)$_{\text{-CH}_2\text{NH-}}PEO_{750}$)**-1** (right) solubilize in pH = 7 of water after 7days.

Although macroscopically well soluble in aqueous solutions, hyperbranched polyacetal-PEO's are amphiphilic in essence, due to the presence of a hydrophobic inner polyacetal and an outer hydrophilic PEO shell. As illustrated in Figure 29, analysis by ^1H NMR in D_2O of hyperbranched polyacetal **Amino**(HBPA(2)$_{\text{-CH}_2\text{NH-}}PEO_{2000}$)**-2** shows poorly resolved signals for the hydrophobic polyacetal part, while the signal due to protons of PEO (peak e) are clearly detected at 3.5ppm. This suggests that the core of the amphiphilic structure undergoes a contraction phenomenon. By progressively adding THF-d_8 in the NMR tube, the solubilization of the polyacetal core is however improved, and the intensity of characteristic protons (peak h and aromatic peak w) gradually increases, THF being a good solvent of both parts.

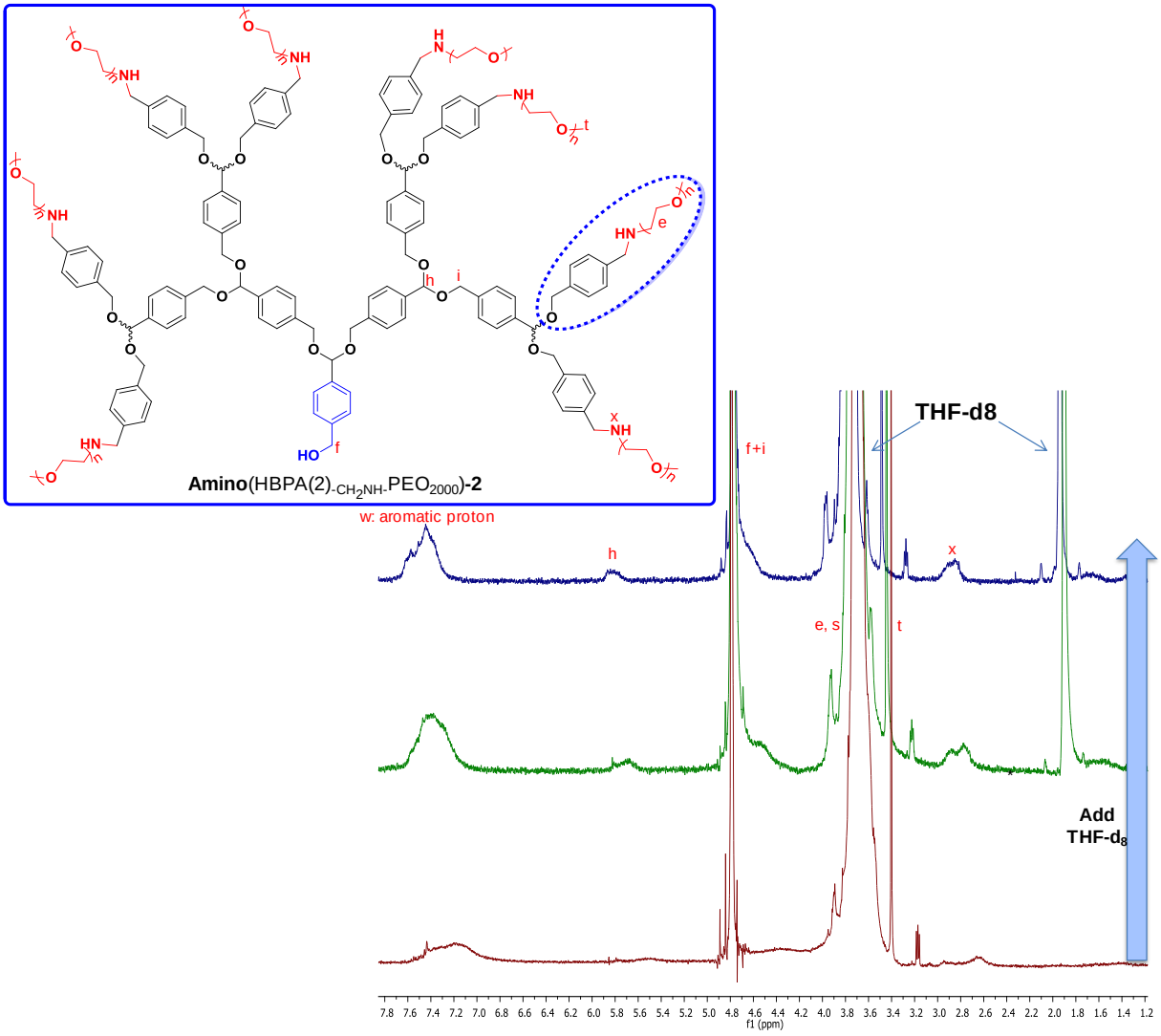


Figure 29. ^{1}H NMR spectra of hyperbranched polyacetal-PEO_{2000} **Amino**(HBPA(2)$_{\text{-}CH_2NH\text{-}}PEO_{2000}$)**-2** (400 MHz) in D_2O with increased amounts of THF-d_8.

6.3. Characterization of hyperbranched polyacetal by DLS and TEM

The hyperbranched polyacetal-PEO derivatives (**Amino**(HBPA(2)$_{\text{-}CH_2NH\text{-}}PEO_{2000}$)**-2**) were next analyzed by dynamic light scattering (DLS) in water. For instance, the hydrodynamic radius of the compound obtained from PEO with 2000 g/mol was found to be $R_H = 22.7 \pm 10$nm (Figure 30, first peak), again suggesting a core shrinkage in water. However, the size distribution is very large (0.42). A much higher size (187 ± 10 nm) was determined for the same compound in THF, which may in this case reflect the propensity of the hyperbranched structure to aggregate in this solvent.

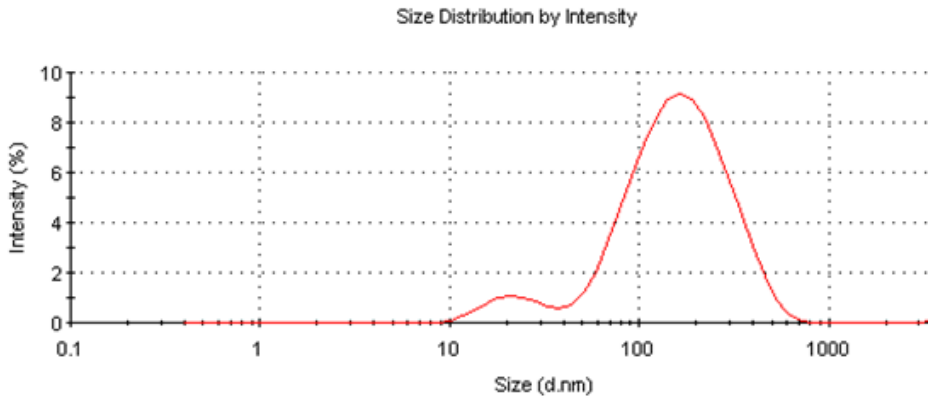


Figure 30. Dynamic light scattering profile of the hyperbranched polyacetal via amino linkages and PEO_{2000} segments **Amino**(HBPA(2)$_{\text{-}CH_2NH\text{-}}PEO_{2000}$)**-2** measured at 90 °.

Analysis by transmission electron microscopy (TEM) of the same sample showed the formation of rather spherical objects with an average diameter around 25 nm (Figure 31).

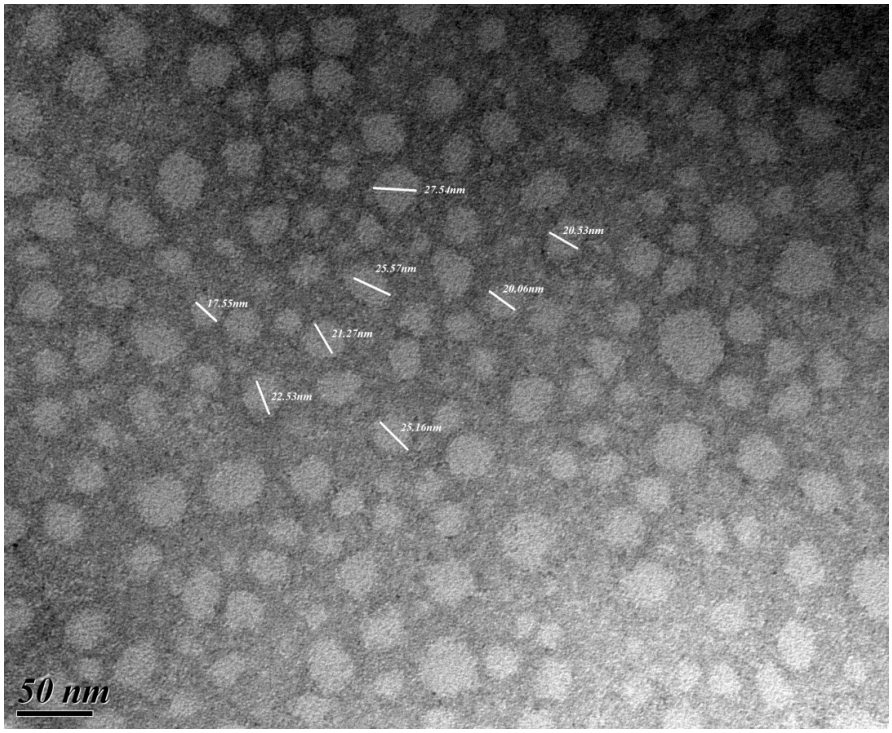


Figure 31. TEM image of hyperbranched polyacetal via amino linkages and PEO_{2000} segments **Amino**(HBPA(2)$_{\text{-}CH_2NH\text{-}}PEO_{2000}$)**-2**.

Different sizes of this **Amino**(HBPA(2)$_{\text{-}CH_2NH\text{-}}PEO_{2000}$)**-2** were measured from DLS (R_H = 22.7 ± 10nm), whereas TEM analysis showed images of spherical objects with an average radius of 13 nm. The difference in size measured by TEM and DLS might due to differences in sample preparation. For TEM analysis, samples were indeed prepared by spraying a 3mg/mL solution of the polymer onto a copper grid (200 mesh coated with carbon) using a homemade

spray tool. In DLS analysis, the preparation required 1 mL of sample ([polymer] =10 mg/mL), that was more concentrated, increasing the probability to form large aggregates.

7. Degradation of hyperbranched polyacetals under acidic conditions

As expected, hyperbranched polyacetal derivatives were all prone to an acid-catalyzed degradation. Ramakrishnan *et al.*[17] reported that hyperbranched polyacetals (DB<1) degraded under mildly acidic pH (pH = 4) with a degradation profile showing a short induction period. Similarly, hyperbranched polyacetals **HBPA(1)**$_{CH(OMe)_2}$ prepared in this work from monomer **1** were incubated in three different pH buffer solutions for 4 days. Reactions products were next analyzed by SEC in THF. Figure 32 shows that **HBPA(1)**$_{CH(OMe)_2}$ were readily cleaved under acidic conditions into the hydroxyaldehyde monomer **2**. As expected, lower pH (pH = 3, green curve) induced a faster degradation.

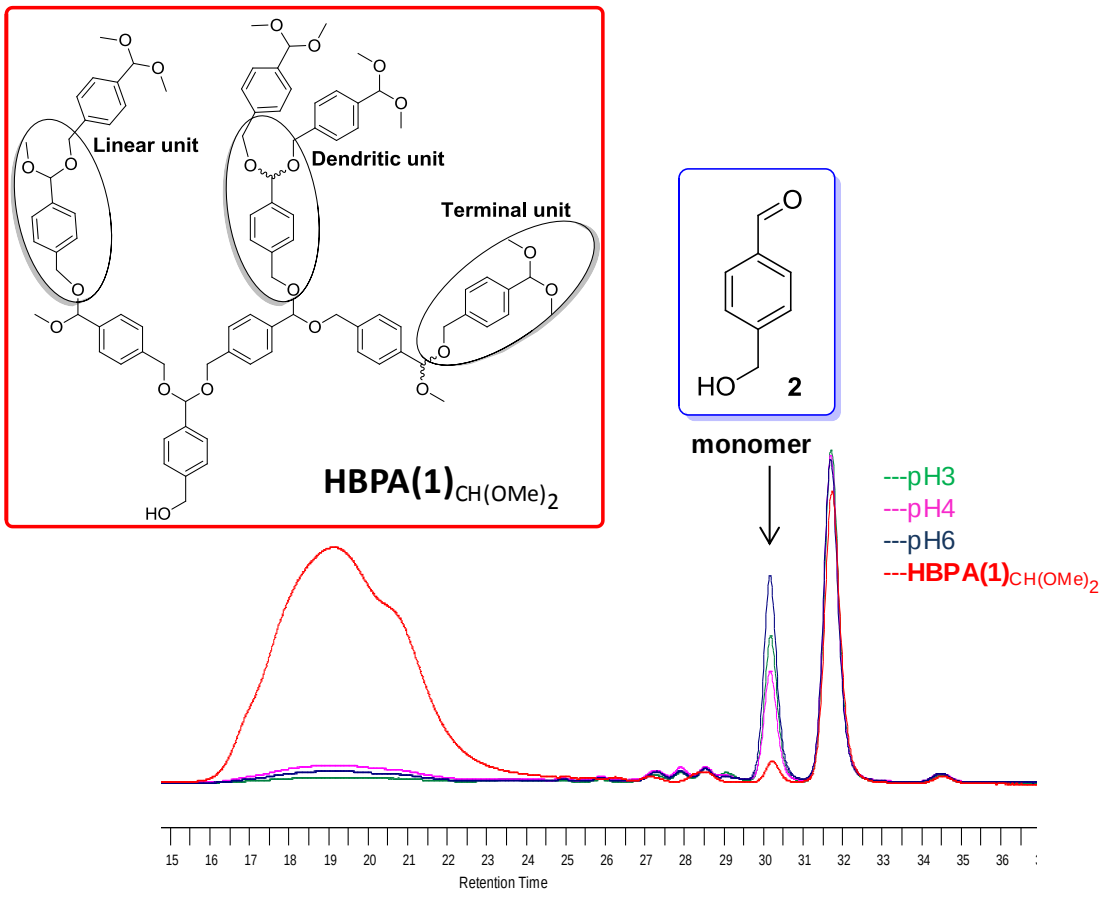


Figure 32. Overlay of SEC traces (UV detection in THF, relative to PS standards) of hyperbranched polyacetal **HBPA(1)**$_{CH(OMe)_2}$ and degradated products via three different pHs.

PEO functionalized hyperbranched polyacetals deriving from monomer **2** were obviously also prone to an acid-catalyzed degradation. For instance, degradation of a parent hyperbranched polyacetal with peripheral aldehydes (**HBPA(2)**$_{CHO}$, entry 5, Table 1) was

complete after 300 min of exposure in $CHCl_3$ solution containing trifluoroacetic acid (5 mol%). This was verified by SEC with the total disappearance of the peak due to polymer along with the formation of two major populations at 22.5 and 30.5 min, corresponding to the hydroxyl amino PEG **5** and the monomer **2**.

The polymer derivative possessing the PEO_{2000} arms linked to the hyperbranched polyacetal core *via* amino linkages (**Amino**(HBPA(2)$_{\text{-CH}_2\text{NH-}}PEO_{2000}$)**-2**) was also readily cleaved in aqueous buffer solution at pH = 4. SEC traces obtained after treatment under such acidic conditions showed the formation of both the parent PEO precursor of 2000 g/mol and *p*-hydroxymethyl benzaldehyde (monomer **2)** whose intensity increases with time, thus confirming that acid-catalyzed degradation occurred (Figure 33). The degradation was found relatively fast at the beginning, the parent **Amino**(HBPA(2)$_{\text{-CH}_2\text{NH-}}PEO_{2000}$)**-2** being degraded to oligomers within 15 min.

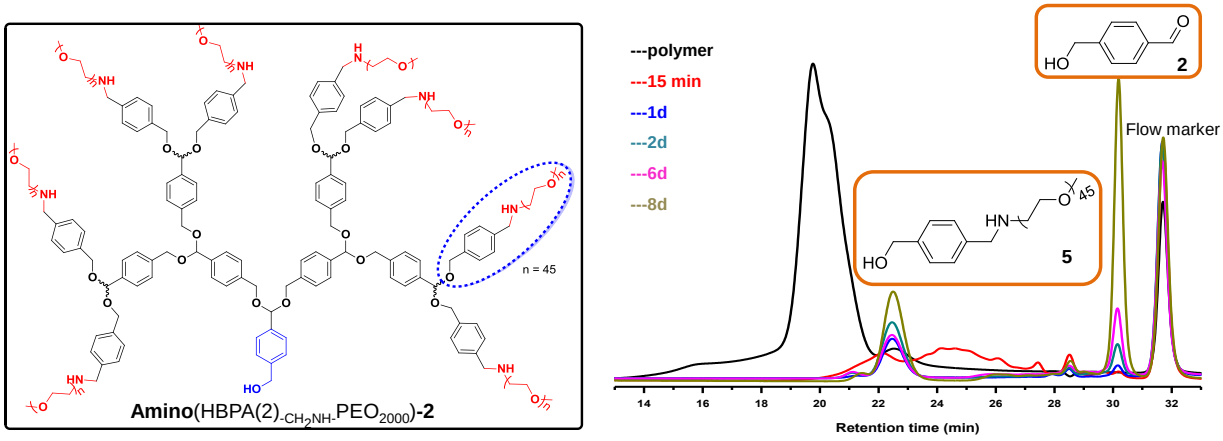


Figure 33. SEC traces (UV detection in THF, relative to PS standards) of hyperbranched polyacetal **Amino**(HBPA(2)$_{\text{-CH}_2\text{NH-}}PEO_{2000}$)**-2** and degraded products at different time intervals.

8. Conclusion

The direct polymerization of AB_2-type monomers, namely, *p*-hydroxymethyl benzaldehyde dimethylacetal (**1**) and *p*-hydroxymethyl benzaldehyde (**2**) provides a facile synthetic approach to hyperbranched polyacetals carrying numerous peripheral aldehyde functions. Polymerization of monomers **1** and **2** proceeds by Bronsted acid-catalyzed repeated transacetalization and acetalization reactions, forming methanol and water as by-product, respectively. Bronsted acids include *p*-toluenesulfonic acid, camphorsulfonic acid, or pyridinium camphorsulfonic acid. Use of regularly renewed molecular sieves in the course of the polymerization allows driving the polymerization towards the formation of polymers of high molecular weights (apparent M_w up to 100,000 g/mol).

While the polytransacetalization of monomer **1** leads to hyperbranched polyacetals with a degree of branching (DB) around 50% (DB = 0.5), polyacetalization of monomer **2** allows for a direct access to defect-free hyperbranched polyacetals (DB = 1), owing to the formation of more reactive hemiacetal intermediate linear units (compared to the aldehyde), favoring the formation acetal dendritic units. This is one rare example of defect-free hyperbranched polymer synthesis utilizing a very simple AB_2-type monomer.

Polyacetalyzation reaction can also be applied to AB_2-type macromonomers of different molecular weights (**3** and **4**) featuring a PEG chain between the reactive functions, leading to hyperbranched polyacetals with PEG chains between the branching points. Substantial amounts of residual macromonomer being observed, further optimization of the experimental conditions is required to achieve higher molecular weights.

The presence of terminal aldehydes at the periphery of hyperbranched polyacetals allows introducing external PEG branches through a PEGylation with amino PEG's of different molecular weight. This post-polymerization approach affords PEGylated hyperbranched polyacetals with a core-shell architecture at the nanoscale, as established by combined techniques.

Last but not least, all hyperbranched polyacetal derivatives are degradable in essence, being readily hydrolyzed under acidic conditions. All together, our strategy combines several advantages, including the straightforward synthesis from commercially available or easily accessible precursors, production of hyperbranched polymers with 100% branching as for regular dendrimers, the presence of multiple functional and reactive aldehyde end groups, for instance towards PEG chains allowing to derive biocompatible materials, and acid-sensitivity of the hyperbranched scaffolds. This synthetic polymerization approach to polyacetals utilizing monomers with aldehyde and hydroxyl functions might be applied to many other monomer precursors.

For instance, very preliminary experiments have shown that the direct polyacetalization of a poly(ethylene glycol) with a bis-aldehyde such as terephtaldehyde leads to chemically polyacetal networks that can yet be chemically disrupted by acidic treatment. This straightforward chemistry, involving commercially available or easily accessible monomer substrates opens new avenues for elaborating on new temporary gels that may find a potential in acid-sensitive active delivery applications. A proper selection of the monomer should allow tuning the overall properties of related hyperbranched or crosslinked polyacetals. In addition, a wide variety of other functional moieties could be employed to react with the peripheral aldehydes of these hyperbranched polyacetals, among which hydrazine-, amino, or hydroxyl-containing compounds.

9. Experimental section

Materials.

Tetrahydrofuran (THF) was distilled over sodium/benzophenone, toluene was distilled over PS-Li and dioxane was distilled over CaH_2 prior to use. Anhydrous toluenesulfonic acid (*p*-TSA, 98%, Aldrich) was obtained by heating at 100 ℃ under dynamic vacuum for 24h and then it was stocked in a Glove box. Ethylene oxide (EO) (Fluka, 99.8%) was distilled over sodium into a buret. Diphenylmethylpotassium (DPMK) was prepared in THF and titrated with acetanilide according to well-known procedures.[60] All PEO precursors were dried by freeze-drying from a dioxane solution. All other reagents were of commercial grade and used as received. Molecular sieve 4 Å, pearl-shaped, 2 - 3 mm was purchased from Scharlau. All other chemicals and reagents were acquired from Sigma-Aldrich (Buchs,Switzerland). Deuterated solvents for NMR spectroscopy were acquired from Armar Chemicals (Dottigen, Switzerland).

Instrumentation.

NMR spectra were recorded on a Bruker AC-400 spectrometer in appropriate deuterated solvents. Molar masses were determined by size exclusion chromatography (SEC) in THF as the eluent (1mL/min) and with trichlorobenzene as a flow marker at 25 ℃, using both refractometric (RI) and UV detectors (Varian). Analyses were performed using a three-column set of TSK gel TOSOH (G4000, G3000, G2000 with pore sizes of 20, 75, and 200 Å respectively, connected in series) calibrated with polystyrene standards. Differential scanning calorimetry (DSC) measurements were performed with aluminium sealed pans on a DSC Q100 apparatus from TA Instrument, USA. Data were recorded during the second run for temperatures ranging from 20 to 200 ℃. A constant heating/cooling rate of 10 ℃/min and gas purging (N_2) at a flow rate of 100ml/min was used for all experiments. The glass transition temperature (Tg) was given by the inflection point of the transition. Dynamic light scattering (DLS) experiments was performed using an ALV Laser goniometer, which consisted of a 35 mW HeNe linear polarized laser with a wavelength of 632.8 nm. Samples were kept at constant temperature (25 ℃) during all the experiments. 1 mL of sample ([polymer] = 10 mg/ml) introduced in a 10 mm diameter cylindrical plastic cell was immersed in a filtered water bath. The data acquisition was done with the ALV correlator control software and the counting time for dynamic was fixed for each sample at 60 s. Mean hydrodynamic diameter and dispersity were determined using cumulant analysis methods. Water was thoroughly filtered with 0.1 μm filters and directly employed for the preparation of the solutions. Transmission electron microscopy (TEM) images were recorded on a Hitachi H7650 microscope working at 80 kV equipped with a GATAN Orius 10.5 Megapixel camera (Bordeaux Imaging Center, BIC).

Samples were prepared by spraying a 3 g/L solution of the polymer onto a copper grid (200 mesh coated with carbon) using a homemade spray tool.

Monomer synthesis

p-hydroxymethylbenzaldehyde dimethylacetal (monomer **1**) is commercially available. (97%, Aldrich)

*Synthesis of monomer p-hydroxymethylbenzaldehyde (monomer **2**).*

Monomer **2** was synthesized according to the procedure published in literature.[55] A solution of 5.68 g of *p*-hydroxymethylbenzaldehyde dimethylacetal (97%, Aldrich) (monomer **1**) in 10 ml of THF was stirred with 10 ml of 2% H_2SO_4 in water. After 3 h, H_2SO_4 was neutralized by the addition of solid Na_2CO_3. The mixture was then taken up into diethyl ether and the aqueous phase was separated. The ether extract was washed with saturated NaCl solution and dried over a mixture of Na_2SO_4 and $MgSO_4$. After filtration, the solvent was removed using a rotary evaporator and *p*-hydroxymethyl benzaldehyde **2** (3.23 g; 76%) is obtained. ^{1}H NMR of *p*-hydroxymethyl benzaldehyde ($CDCl_3$), 10.00 (s, 1H, C*H*O), 7.88 (*J* = 8.4 Hz, 2H, Ph-*H*), 7.53 (*J* = 8.4 Hz, 2H, Ph-*H*), 4.81 (s, 2H, C*H*$_2$OH), 2.02 (br, 1H, CH_2O*H*). ^{13}C NMR ($CDCl_3$), 192.0, 147.8, 135.7, 130.1, 127.0, 64.6. Monomer **1** obtained as a white solid was dried by lyophilization.

*Synthesis of macromonomer **3***

To a two-neck 250-mL flask charged with the lyophilized dry precursor (monomer **1,** 1.02 g, 7.24 mmol) was added dry THF (50 mL) under vacuum. DPMK (5 mmol) was introduced at -20 ℃, and the temperature was slowly raised to room temperature and stirred until the red color of DPMK disappeared and homogeneous solution was formed. The flask was cooled down to -20 ℃, and EO (5.5 mL, 110 mmol) was added. The polymerization was carried out at room temperature for 3 days and the resulting alkoxides were deactivated with methanol. The solvent was distilled off under vacuum, and the macromonomer precursor (5.6 g, 96%) was obtained by double precipitation with diethyl ether from a THF solution. To a solution of 4 g of macromonomer precursor in 8 ml of THF, 1.2 ml of 2% H_2SO_4 in water was added. After 3 h the H_2SO_4 was neutralized by the addition of solid Na_2CO_3. The mixture was then taken up into diethyl ether and the aqueous phase was separated. The ether extract was washed with saturated NaCl solution and dried over a mixture of Na_2SO_4 and $MgSO_4$. After filtration, the solvent was removed using a rotary evaporator. Macromonomer **3** was obtained as a white solid (3.7 g, 65%) ^{1}H NMR (δ ppm, $CDCl_3$): 9.99 (s, 1H, C*H*O), 7.86 (*J* = 8.4 Hz, 2H, Ph-*H*), 7.52 (*J* = 8.4 Hz, 2H,

Ph-*H*), 4.64 (s, 2H, Ph-C*H*$_2$O), 3.63 (br, 68H, OC*H*$_2$C*H*$_2$O). $Mn_{(NMR)}$ = 852 g/mol, $Mw/Mn_{(SEC)}$ = 1.25.

*Synthesis of macromonomer **4***

To a two-neck 250-mL flask charged with the lyophilized dry precursor (monomer **1,** 1.02 g, 7.24 mmol OH) was added dry THF (50 mL) under vacuum. DPMK (5 mmol) was introduced at -20 ℃, and the temperature was slowly raised to room temperature and stirred until the red color of DPMK disappeared and homogeneous solution was formed. The flask was cooled down to -20 ℃, and EO (10mL, 200 mmol) was added. In the similar fashion, macromonomer **4** was obtained as a white solid (6.8 g, 75%) ^{1}H NMR (δ ppm, $CDCl_3$): 9.99 (s, 1H, C*H*O), 7.86 (*J* = 8.4 Hz, 2H, Ph-*H*), 7.52 (*J* = 8.4 Hz, 2H, Ph-*H*), 4.64 (s, 2H, Ph-C*H*$_2$O), 3.63 (br, 132H, OC*H*$_2$C*H*$_2$O). $Mn_{(NMR)}$ = 1589 g/mol, $Mw/Mn_{(SEC)}$ = 1.3.

Activation of molecular sieves

Molecular sieves were normally activated by heating at high temperature around 500 ℃ or by microwave oven.[18] In our work, Schlenk equipment containing molecular sieves was well flamed under dynamic vacuum. Then the equipment was kept dynamic vacuum for 1h and heated again. This process was repeated 3 times, these activated molecular sieves were stocked in a Schlenk tube in a glove box.

Synthesis of catalyst pyridinium camphorsulfonate (PCS).

The synthesis of catalyst was followed protocol published in literature.[61] Camphorsulfonic acid CSA (5.0 g) was added to 10 mL of dry pyridine, and the contents were stirred for 30 min at room temperature. The excess pyridine was removed under reduced pressure, and the residue was recrystallized from dry acetone (yield 81%; melting point 194 ℃).

Polymerization procedure via different by-product remover methods

Synthesis of hyperbranched polyacetals using Dean-Stark system

A 5 mL round-bottom flask equipped with a micro-Dean-Stark (V=10 ml of container side) was charged with 200 mg (1.5 mmol) of *p*-hydroxymethylbenzaldehyde (monomer **2**) and 0.3 mmol (20% mol) of catalyst (polymerization catalyzed by camphorsulfonic acid (CSA) 70 mg, entry 1, Table 1; polymerization catalyzed by *p*-toluenesulfonic acid (*p*-TSA) 52 mg, entry 2, Table 1). The side container of the Dean-Stark was filled by freshly distilled toluene, and 2 ml of toluene was added to the reaction under argon. The mixture was heated to 130 ℃ to get the reflux for 4 days. The reaction was followed by analyzing aliquots of the reaction at different time by SEC to determine molecular weights. After 4 days, a small quantity of Et_3N was added to stop the

reaction. An aliquot of the polymerization mixture was taken to determine the conversion by ^{1}H NMR in THF-d_8 (38% utilizing CSA as catalyst, entry 1 in Table 1; 51% using *p*-TSA as catalyst, entry 2 in Table 1). This polymer solution was then precipitated twice in 20 ml methanol containing a little Et_3N and dried by vacuum pump. Polymer was obtained as a white solid. Molecular characteristics were determined by SEC in THF (Table 1).

*Synthesis of hyperbranched polyacetals from monomer **2** using molecular sieves as desiccant*

Polymerization was carried out under a dry and inert atmosphere using Schlenk equipments (entries 3 to 5). In a typical polymerization, 0.51 g (3.75 mmol) of *p*-hydroxymethylbenzaldehyde (monomer **2**), anhydrous *p*-toluenesulfonic acid (*p*-TSA) 0.13 g (0.75 mmol, 20 mol%) (entry 4 in Table 1; polymerization catalyzed by camphorsulfonic acid (CSA) 0.18 g is entry 3 in Table 1) and 5 g of activated molecular sieves were introduced in a vacuumed flame-dried Schlenk special apparatus equipped with a withdrawal digit on the side of the main flask (ESI) in a glove box. 5 ml of freshly distilled THF was introduced. For entry 5 in Table 1, another Schlenk was prepared and the molecular sieves were changed every two days in glove box. These reactions were heating at 50 ℃ and followed by analyzing aliquots taken under argon from polymerization at different time and measured by SEC to determine molecular weights. Polymerization was stopped by adding a small quantity of Et_3N, then the solution of polymer was diluted by THF, filtered out molecular sieves and the filtrate concentrated. An aliquot of the polymerization mixture was taken to determine the conversion by ^{1}H NMR in THF-d_8. The concentrated solution was precipitated twice in methanol containing a little Et_3N. Molecular characteristics were determined by SEC in THF (Table 1). Yield = 72%, polymer is as white solid.

The polymerization of monomer **1** was carried out in a similar fashion where 0.68 g 3.75 mmol of *p*-hydroxymethyl benzaldehyde dimethylacetal (monomer **1**) and (*p*-TSA) 0.13 g (0.75 mmol, 20 mol%) of *p*-toluenesulfonic acid were introduced in 5 ml of fresh distilled in THF. (entry 8, Table 1) Yield = 72%, polymer is as a white solid.

Synthesis of hyperbranched polyacetals realized by vacuum pump catalyzed by pyridinium camphorsulfonate (PCS).

The synthesis of hyperbranched polyacetal **HBPA(1)**$_{CH(OMe)_2}$ was followed protocol published in literature.[17] *p*-hydroxymethyl benzaldehyde dimethylacetal (97%, Aldrich) (monomer **1**) 0.5 g (2.74 mmol) was taken in a polymerization flask along with 2 mol% of pyridinium camphorsulfonate (PCS). (entry 7, Table 1) The reaction mixture was degassed by purging with N_2 for 15 min and then heated to 80 ℃ under a N_2 atmosphere to ensure homogeneous mixing of the catalyst and monomers. Then the polymerization was carried out at 100 ℃ for 1 h under

N_2 flow. Then the polymerization tube was connected to vacuum, and the polymerization was continued at 100 ℃ for 30 min. The polymer was dissolved in THF, and the solution of the polymer was neutralized by solid $NaHCO_3$ and filtered. An aliquot of the polymerization mixture was taken out to determine the conversion by ^1H NMR in $CDCl_3$. Then the filtrate was concentrated and poured into dry methanol containing a small quantity of Et_3N to precipitate the polymer. This polymer was further purified through by re-precipitation using THF-methanol and was obtained as a white solid (Yield = 75%).

In the case of monomer **2**, polymerization was carried out under vacuum for 1 day at 150 ℃ (entry 6, Table 1) and yielded 51% of polymer as a white solid.

Calculation of polyacetal's concentration

Purified polyacetal (entry 5, Table 1) was soluble in dry dioxane and dried by a lyophilization. Then 20 mL of distilled THF was added to the dry polyacetal 1.01 g to prepare the solution of hyperbranched polyacetal with an exact concentration of polymer. This polyacetal contains a unique structure (Figure 22): dendritic unit **D** (molar mass is 119 g/mol) and aldehyde end chain terminal unit **T** (molar mass is 135 g/mol), respectively, with D ≅ T. Hence, the mol% number of each type of unit can be easily deduced in the following manner:

$$n_D * 119 + m_T * 135 = X \text{ (g)},$$

where X is a given mass quantity of any hyperbranched polyacetal with DB = 1,

$$\text{thus, } n_D \cong m_T = X / 254.$$

The concentration of purified polyacetal was calculated from the number of mole of terminal unit and the volume of solvent added.

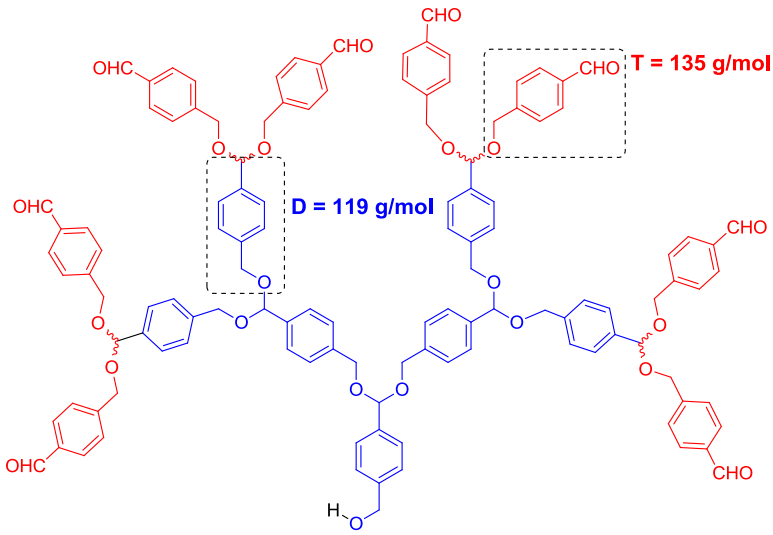


Figure 22. Schematic representation of defect-free hyperbranched polyacetals of increasing generation number: dendritic unit (D) in blue; terminal unit (T) in red, the focal point is shown in grey. Chemically, the point focal of hyperbranched polymers are the function alcohol (CH_2OH).

One-pot functionalization of hyperbranched polyacetal

5 ml polyacetal **HBPA(2)**$_{CHO}$ solution of entry 5 in Table 1 (0.2 mol/l) was introduced in a vacuumed flame-dried Schlenk, then 1 g (1.2 eq) of MeO-PEG_{750}-NH_2 and 81 mg of $MgSO_4$ were added at 0 ℃ to obtain imino-hyperbranched polyacetal (**Imino**(HBPA(2)$_{-CH=N-}PEO_{750}$)**-1**). The reaction was stirred then at RT. An aliquot of the reaction mixture was taken after 12 hours to determine the conversion by ^{1}H NMR in $CDCl_3$ (100%) and analyzed by SEC in DMF to determine the molecular weight. 76 mg of $NaBH_4$ (4 eq., 2 mmol) and 5 ml MeOH was added in the Schlenk at 0 ℃. The reaction was then stirred at RT for 12 hours. The reaction was ended by a drop of water. After evaporating THF, a dialysis of the product in water for 3 days was realized to eliminate excess of PEG precursor. Evaporation of water after dialysis, yielded 940 mg of amino-hyperbranched polyacetal **Amino**(HBPA(2)$_{-CH_2NH-}PEO_{750}$)**-1** as a white solide (74%).

In a similar fashion, **Amino**(HBPA(2)$_{-CH_2NH-}PEO_{2000}$)**-2**, **Amino**(HBPA(2)$_{-CH_2NH-}PEO_{5000}$)**-4** and **Amino**(HBPA(2)$_{-CH_2NH-}PEO_{12000}$)**-3** from **HBPA(2)**$_{CHO}$ from the precursors MeO-PEG_{2000}-NH_2, MeO-PEG_{5000}-NH_2 and MeO-PEG_{12000}-NH_2 were also successfully synthesized, difficulties were occurred during the elimination of excess of PEG precursor but the reaction conversions were still 100%.

Degradation of hyperbranched polyacetal

Degradation of hyperbranched polyacetal ***HBPA(2)****$_{CHO}$*

For degradation studies in chloroform, 56 mg of polymer was dissolved in 400 μL of CDCl3. Proton NMR spectra were taken. Then 40 μL of 0.04M CDCl3 solution of TFA was added into it. Proton NMR spectra of the solution were taken in certain intervals. Percentage hydrolysis was calculated from the relative decreasement of the acetal peak at 4.6 ppm.

Degradation of hyperbranched polyacetal ***HBPA(1)****$_{CH(OMe)_2}$*

For degradation study, 80 mg hyperbranched polyacetal **HBPA(1)**$_{CH(OMe)_2}$ was solubilized into 2 ml of solutions (pH = 3, pH = 4 and pH = 6) under open-air system. After 4 days, degradation reactions were neutralized by $NaHCO_3$ and extracted by EtOAc. The products after remove the volatiles were then injected in SEC in THF (Figure 32).

Degradation of amino-hyperbranched polyacetal ***(Amino****(HBPA(2)*$_{-CH_2NH-}$*PEO*$_{2000}$*)-2)*

A similar process was investigated in the degradation of amino-hyperbranched polyacetal **Amino**(HBPA(2)$_{-CH_2NH-}$PEO$_{2000}$)**-2** in buffer solution pH = 4. Then samples were neutralized by $NaHCO_3$ and extracted by EtOAc by different time and injected in SEC in THF to follow the degradation. (Figure 33)

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Conclusion générale et perspectives

Ce travail de thèse s'inscrivait dans le cadre d'un projet ANR Blanc intitulé CHIRPOL qui visait, comme but ultime, la synthèse de polymères chiraux selon un mécanisme de croissance des chaînes polymères par polymérisation par étapes de manière asymétrique et en utilisant une voie organocatalytique. Un catalyseur organique chiral était en effet censé permettre le transfert de l'information chirale du catalyseur vers la chaîne en croissance, et ce à chaque étape, laissant espérer la synthèse de nouveaux polymères optiquement actifs. Aucun exemple, à notre connaissance, n'a montré une telle possibilité de préparer des polymères chiraux par polymérisation par étapes organocatalysée.

Des monomères incorporant une ou deux fonctions aldéhyde(s) ont été choisis initialement, en raison de leur caractère prochiral mais aussi à cause de leur grande réactivité vis à vis d'un certain nombre de groupements fonctionnels (alcool, cétone, hydrazine, etc). Bien que certains aspects de ce projet ANR aient été notamment abordés dans le deuxième et troisième chapitre, la complexité des systèmes visés, *i.e.* la synthèse de monomères appropriés, portant des fonctions clivables, la mise en œuvre de réactions intermoléculaires dans des conditions stœchiométriques ou encore la difficulté à analyser la chiralité portée par les polymères, nous a conduits à reconsidérer nos objectifs et cibler des versions non chirales des différents polymères envisagés. Nous avons alors voulu exploiter la richesse de la fonction aldéhyde et sa propension à réagir avec divers partenaires pour accéder à toute une variété de polymères, linéaires et ramifiés, selon la structure initiale des monomères impliqués, mais aussi selon la nature du catalyseur organique employé. Ainsi, des réactions moléculaires élémentaires aussi diverses que la 'condensation de benzoïne', la réaction de dismutation dite de Tishchenko, les réactions d'aldolisation et d'acétalisation ont été mises en œuvre dans ce travail, dans un contexte de polymérisation par étapes organocatalysée. Les matériaux polymères ainsi préparés sont, pour la plupart d'entre eux, totalement inédits et présentent probablement des propriétés singulières qu'il s'agira d'exploiter plus avant dans le futur.

Nos premiers travaux ont porté sur la synthèse de polyaldols dont on trouve très peu d'exemples dans la littérature, une thématique que nous avons abordée conjointement avec nos partenaires de l'ISM dans le cadre de l'ANR CHIRPOL. La chimie que nous avons développée met en jeu des réactions répétées d'aldolisation croisée directe entre des bis-aldéhydes non énolisables (monomères électrophiles) et des bis-cétones énolisables (monomères « nucléophiles »). Ces nouveaux monomères bifonctionnels ont été spécifiquement conçus dans l'équipe de notre partenaire. Ces réactions d'aldolisation s'est révélée extrêmement sensible à la nature du catalyseur utilisée : seule la pyrrolidine, une amine secondaire cyclique à 5 chaînons,

s'est montrée catalytiquement active dans les conditions expérimentales testées. La présence d'acide acétique comme co-catalyseur permet une cinétique de polymérisation plus rapide, conduisant à des polymères de masses molaires plus élevées. Comme attendu, la cinétique de polymérisation est également sensible aux effets de concentrations en monomères et en catalyseurs, ainsi qu'au pourcentage d'acide acétique ajouté au milieu. Plusieurs paires de monomères ont alors été polymérisées en solution dans le THF à température ambiante et divers polyaldols ont ainsi été obtenus. Cette approche, à notre connaissance, est totalement nouvelle pour la synthèse de polyaldols. L'analyse de ces polymères par RMN a toutefois révélé une certaine propension des unités aldol (entre 20 et 30%) à se déshydrater pour donner des unités vinylidènes, *via* une réaction bien connue dite de crotonisation (déshydratation des unités aldols). Des essais préliminaires de polyaldolisation asymétrique utlisant un système catalytique chiral (BIP/TFA) ont tout de même été réalisés, dans le but de générer des polyaldols optiquement actifs. Dans ce cas, un excès diastéréoisomérique faible, estimé à de 14%, a pu être déterminé par analyse RMN. Ce résultat est encourageant et démontre la possibilité de transférer la chiralité du catalyseur, de manière répétée, vers les unités monomères. Un certain nombre de travaux doivent cependant être menés, avant de pouvoir affirmer qu'on peut induire des réactions de polyaldolisation asymétrique par organocatalyse chirale. Par exemple, il faudrait pouvoir déterminer un excès énantiomérique (e.e.) en étant capable de dégrader sélectivement les polyaldols en « briques » pouvant être analysées par HPLC chirale. C'est par exemle ce que nous avons réussi à mettre en œuvre dans le chapitre III dédié à la polymérisation asymétrique par condensation de benzoïne, mais dans ce cas des valeurs de e.e. quasi-nulles ont malheureusement été obtenues… Cette partie de la thèse offre néanmoins des perspectives intéressantes pour obtenir nouveaux polyaldols, à partir de divers bis-aldéhydes et bis-cétones, par simple répétition de réactions d'aldolisation directe croisée. A nouveau, il reste à établir clairement que transfert de l'information chirale du catalyseur vers le polymère est effectif. Le cas échéant, il s'agit aussi de comparer les propriétés physico-chimiques des polyaldols optiquement actifs et racémiques pour juger du le potentiel de ces nouveaux matériaux et de l'influence de la chiralité sur ces propriétés.

Dans un deuxième volet, nous avons étudié la polymérisation organo-catalysée de monomères bis-aldéhydes par des précurseurs de carbènes *N*-hétérocycliques chiraux et achiraux. Ce type de polymérisation conduit à des poly(α-cétoalcool)s par la répétition d'une réaction connue sous le nom de réaction de 'condensation de benzoïne'. En présence de catalyseurs organiques chiraux, l'idée était, là encore, de transférer la chiralité du catalyseur NHC à la chaîne polymère en croissance, étape par étape. Comme déjà indiqué, un moyen indirect de mesurer la chiralité du polymère obtenu est de le dégrader en fragments élémentaires

et de mesurer l'excès énantiomérique de ces fragments, par HPLC chirale. Il nous a donc fallu concevoir des monomères bis-aldéhydes contenant des fonctions *a priori* fragiles, en l'occurence contenant des groupements de type Si-C, d'une part, et ester, d'autre part. La polymérisation organocatalysée de ces nouveaux monomères a été préalablement conduite avec succès en présence de NHCs non chiraux. Les poly(α-cétoalcool)s ainsi obtenus présentent des masses molaires moyennes en masse, M_w jusqu'à 5600 g/mol, correspondant à des degrés de polymérisation de l'ordre de 13 Par rapport aux poly(α-cétoalcool)s précédemment décrits dans la littérature (dérivés du téréphtaldéhyde), les nouveaux exemples produits dans ce travail de thèse présentent une plus grande solubilité dans le THF et sont aussi caractérisé par l'absence de de structures cycliques. Nous nous sommes ensuite intéressés à la polymérisation asymétrique du bis-aldéhyde contenant le groupement ester clivable. En présence d'un NHC chiral, formé *in situ* par déprotonation du sel de triazolium commercial à l'aide d'une base forte, la polymérisation de ce bis-aldéhyde a été également réalisée avec succès. Les poly(α-cétoalcool)s ainsi obtenus ont alors pu être dégradés, par traitement avec $LiAlH_4$, convertissant en même temps, les unités α-cétoalcools du polymère en fragments bis-alcools (sous forme d'hydrobenzoïne), *via* des coupures sélectives dans la chaîne principale au niveau des liens ester (réduits en alcool). Les tétraols ainsi obtenus ont dû être acétylés afin d'abaisser la polarité de ces fragments et permettre leur analyse par HPLC chirale pour en déterminer l'excès énantiomérique (e.e.). Malheureusement, sur l'échantillon analysé, un e.e. inférieur à 5% à été déterminé, n'apportant donc aucune preuve claire du transfert de l'information chirale du catalyseur vers la chaîne en croissance. Les perspectives dans ce domaine sont, bien évidemment, de développer cette méthode de synthèse en testant toute une série de bis-aldéhydes portant des fonctions clivables, mais aussi et surtout, d'évaluer d'autres NHCs chiraux pour synthétiser des poly(α-cétoalcool)s optiquement actifs. Dans ce sens, il serait sans doute intéressant de tester des NHCs portant une chiralité axialle ou planaire et non centrale comme celle présente sur les NHCs chiraux que nous avons testés dans ce travail. En parallèle de ces travaux, nous avons mis en évidence que des bases fortes telles que le KHMDS ou le LDA (sans le précurseur triazolium) induisent la réaction connue sous le nom de réaction de Tishchenko qui conduit, dans un contexte de polymérisation de bis-aldéhydes, à la formation de polyesters. Bien que ces catalyseurs n'avaient jamais été évalués pour la synthèse de polyesters à partir de bis-aldéhydes, la régiosélectivité de la réaction reste similaire à celle obtenue avec d'autres systèmes catalytiques décrits dans la littérature. Aussi, avons-nous avons décidé de ne pas approfondir cet aspect du travail. Une régiosélectivité différente ou plus importante serait ici une vraie originalité pour de futurs travaux.

Le dernier chapitre a concerné la synthèse de polyacétals hyper-ramifiés. Dans ce cas, les monomères mis en jeu portent une fonction aldéhyde –protégée sous forme acétal ou non- et aussi une fonction alcool primaire. Différentes conditions de polymérisation ont été mises en œuvre pour obtenir des polymères de masses molaires élevées. L'utilisation d'un acide de Bronsted organique et de tamis moléculaire comme déshydratant a notamment été une solution efficace pour accéder à des polyacétals de masses molaires moyennes en masse (M_w) jusqu'à 100,000 g/mol. Si le monomère *p*-hydroxyméthyl benzaldéhyde diméthylacetal forme, par polytransacétalisation, des polyacétals hyperramifiés avec un degré de ramification de l'ordre de 50% environ (valeur très classique pour un polymère hyperramifié), son homologue non protégé, en l'occurrence le *p*-hydroxyméthyl benzaldéhyde conduit, par polyacétalisation, à des polyacétals hyperramifiés sans défauts structuraux, c'est à dire de degré de ramification égal à l'unité. Cette différence de comportement entre les deux monomères s'explique très probablement par la formation de groupements hémiacétals instables dans le cas de la polymérisation du *p*-hydroxyméthyl benzaldéhyde, favorisant la formation d'unités dendritiques. La présence de nombresues fonctions aldéhydes à la périphérie des polyacétals hyperramifiés a ensuite permis d'introduire des chaines de PEO, par greffage de PEOs linéaires portant une fonction amino terminale (réaction dite de "PEGylation"). Une telle modification conduit à des polyacétals hyperramifiés « PEGylés » présentant une architecture amphiphile de type cœur-écorce. Enfin, tous ces polyacétals hyperramifiés sont dégradables par essence, c'est à dire hydrolysable, en raison de la sensibilité des unités acétal dendritiques en milieu aqueux acide. La dégradation chimique en solution aqueuse à pH = 4 de divers composés a, en effet, pu être vérifiée. Les travaux futurs dans ce domaine seront, par exemple, de diminuer la dispersité de ces polyacétals hyperramifiés si on envisage de les utiliser dans des applications biomédicales. La conception de nouvelles structures de monomère de type AB_2 ou A_2B_3 pour synthétiser de nouveaux polymères hyper-ramifiés pourra également être envisagée pour élargir la gamme de matériaux et donc de propriétés de ces systèmes

En conclusion, même si tous les systèmes que nous avons développés ne conduisent pas nécessairement à l'obtention de polymères chiraux, ce travail de thèse, a permis de poser les bases d'une chimie nouvelle, riche et diverse en réactions de polymérisation par étapes, à partir des mêmes briques élémentaires portant des fonctions aldéhydes et mettant en jeu des catalyseurs différents. Ces travaux, certes encore préliminaires, ouvrent des perspectives intéressantes qu'il faudra exploiter pour développer de nouveaux matériaux polymères à haute valeur ajoutée où l'application requiert des propriétés d'activité optique. L'influence de la chiralité sur les propriétés physico-chimiques de manière générale est aussi un sujet d'étude passionnant, qui mérite qu'on y consacre du temps dans le futur.

NOUVEAUX POLYMERES ISSUS DE LA POLYMERISATION PAR ETAPES ORGANOCATALYSEE DE MONOMERES ALDEHYDIQUES: POLYALDOLS ET POLYBENZOÏNES LINEAIRES ET POLYACETALS HYPERRAMIFIES

Résumé:

A partir des mêmes briques élémentaires portant des fonctions aldéhydes et mettant en jeu des catalyseurs différents, trois types de nouveaux polymères ont été synthétisés par la polymérisation par étape dans ce travail. Dans la première partie, bis-cétone et bis-aldéhyde monomères ont directement polymérisé dans des conditions stoechiométriques par ce processus offrant polyaldols. Divers catalyseurs et des effets de la nature du solvant ont ensuite été étudiés. Dans la deuxième partie, nous avons travaillé sur la polymérisation organo-catalysée de monomères bis-aldéhydes par des précurseurs de carbènes *N*-hétérocycliques chiraux et achiraux pour synthétiser les polymères chiraux. Enfin, la directe polymérisation des monomères de type AB_2 avec une fonction aldéhyde fournit une facile synthétique approche à polyacétals hyperbrramifiés portant nombreux périphéries aldehyiques. Ces polyacétals hyperramifiés sans défauts structuraux ont ensuit été introduirs é par des chaines de PEO par réaction de «PEGylation». L'utilisation de la postpolymymérisation permet d'offre un large varité de la propriété du polymère, à l'aide ces périphéries aldéhydiques. Enplus, les polyacétals hyperramifiés sont dégradables, et facilement hydrolysés en milieu acide.

Mots clés : Polymérisation par étape, Organocatalyse, Monomères aldéhydiques, Polyaldols, Polybenzoïnes linéaires, Carbènes *N*-hétérocycliques, Polyacétals hyperramifiés, Dégradable par voie acide.

NEW POLYMERS SYNTHESIS BY ORGANOCATALYZED STEP-GROWTH POLYMERIZATION OF ALDEHYDIC MONOMERS: POLYALDOLS, LINEAR POLYBENZOIN AND HYPERBRANCHED POLYACETALS

Summary:

Using the same building blocks carrying aldehyde function with different catalysts, three types of new polymers were synthesized by step-growth polymerization in this work. In the fist part, bis-ketone and bis-aldehyde monomers have been directly polymerized under stoichiometric conditions by this process affording polyaldols. The effects of different catalysts and solvent nature have also been studied. In the second part, we have studied the organo-catalyzed polymerization of bis-aldehyde monomers by precursors of chiral and achiral *N*-heterocyclic carbene for synthesis of chiral polymer. Finally, polymerization of AB_2-type monomers with

one function of aldehyde provides a facile synthetic approach to hyperbranched polyacetals carrying numerous peripheral aldehydes. These defect free hyperbranched polyacetals have been introduced PEO chains by "PEGylation" reaction. A wide variety of other functional moieties could be introduced by postpolymerization with peripheral aldehydes. Besides, the hyperbranched polyacetals are degradable in essence, being readily hydrolyzed under acidic condition.

Keywords: Step-growth polymerization, Organocatalysis, Aldehydic monomer, Polyaldol, Linear polybenzoin, *N*-heterocyclic carbenes, Hyperbranched polyacetal, Acid degradable.

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