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par

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Catalyse organique pour la polymerisation par ouverture de cycle d'esters cycliques amorcée par des derives saccharidiques

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Content

Abstract

Biomaterials and environmentally friendly nontoxic plastics received a lot of attention during the past decades. Many of these materials are made from aliphatic polyesters, in particular polylatide (PLA) and poly(ε-caprolactone) (PCL), due to their good biodegradability and biocompatibility. Our work focus on the functionalization of these polyesters with saccharide derivatives by ring-opening polymerization using organocatalysis. The current methods of functionalization of PLA and PCL with saccharide derivatives by ROP and examples of catalysts for stereocontrolled polymerization of lactide are discussed in **Chapter 1**. In **Chapter 2**, the organic base 4-dimethylaminopyridine (DMAP) was proved to be an efficient catalyst for the access to sugar and cyclodextrin-functionalized polylactides. In certain cases, the initiation efficiency is partial, leading to hydrophilic end-capped polyesters in a one-step procedure. In **Chapter 3**, 1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate (BNPH) has been assessed as a catalyst for the ring-opening polymerization of ε-caprolactone and δ-valerolactone. In the presence of benzyl alcohol, the polymerization is quantitative and controlled. When using unprotected sugar bearing 4 free hydroxyl groups, the initiation efficiency is partial, leading to hydrophilic end-capped polyesters in a one-step procedure. In **Chapter 4**, new organocatalytic systems have been assessed for the ring-opening polymerization of *rac*-lactide.

Résumé

Les polymères biodégradables ont suscité un grand intérêt ces dernières années. Il s'agit notamment de polyesters de type polylactide (PLA) et poly(ε-caprolactone) (PCL). Notre objectif au cours de ce travail est d'appliquer la catalyse organique à la fonctionnalisation de ces polyesters par des dérivéss saccharidiques par polymérisation par ouverture de cycle. Dans le **chapitre 1**, les méthodes actuelless de fonctionnalisation de PLA et de PCL par des dérivés de saccharides sont présentées, ainsi que des exemples de catalyseurs pour la polymérisation stérérocontrôlée de lactide. Dans le **chapitre 2**, la base organique 4-dimethylaminopyridine (DMAP) a été utilisée comme catalyseur pour la polymérisation par ouverture de cycle du lactide initiée par des sucres et des cyclodextrines, conduisant à des PLA 100% fonctionnalisés. Dans certains cas, l'amorçage par les groupements hydroxyles n'est pas quantitatif, conduisant à des polyesters fonctionnalisés par des dérivés hydrophiles sucrés en une étape. Dans le **chapitre 3**, l'acide 1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate (BNPH) a été utilisé comme catalyseur pour la polymérisation par ouverture de cycle de l'ε-caprolactone et de la δ-valérolactone. La polymérisation est contrôlée en présence de l'alcool benzylique comme amorceur. L'amorçage n'est pas quantitatif en utilisant le glucose comme amorceur, conduisant ainsi à des polyesters fonctionnalisés par des dérivés hydrophiles en une étape. Dans le **chapitre 4**, de nouveaux systèmes catalytiques organiques ont été appliquées à la polymérisation par ouverture de cycle du *rac*-lactide.

General Introduction

Nowadays, with the development of society and economy, the demand for safer methods to improve our quality of life is becoming larger and larger. Biomaterials and biodegradable plastics are thus manufactured to meet our needs. Biomaterials are designed for the applications in biomedicine such as bone cement, skin repair device, contact lenses and so on (Fig. 1). They must be biocompatible. Biodegradable plastics are mainly employed in packaging industry in order to resolve the environment pollution. These ecologically safer products are usually made from polyesters, due to their good biocompatibility and good biodegradability.

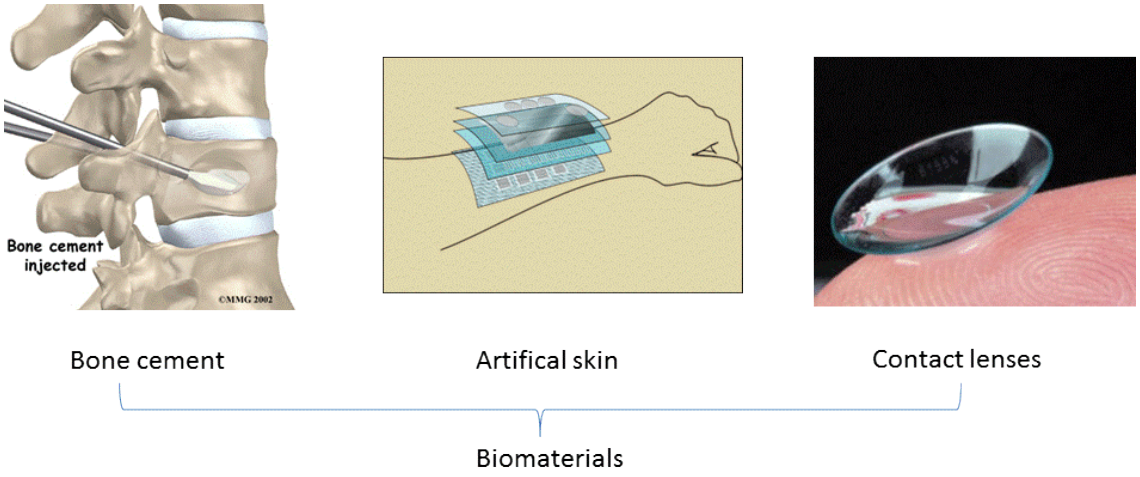
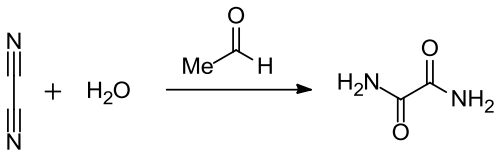


Fig. 1 Biomaterials

Catalysts play an important role in the production of polyesters. They can catalyze the polymerization, but the presence of residues can hamper their use for specific applications. In view of the use of biomaterials and biodegradable plastics, environmentally friendly nontoxic catalysts are strongly desired.

The use of small organic molecules as catalysts has been known for more than a century. In 1860, Justus von Liebig reported the synthesis of oxamide from dicyan and water, with acetaldehyde further identified as the first discovered “organocatalyst” [1] (Scheme 1). This reaction represents the first example of an organocatalytic reaction. The first organocatalyzed polymerization was reported by P.J. Flory in 1940. He discovered that *p*-toluenesulfonic acid is able to catalyze the synthesis of polyesters[2]. The term organocatalysis (a concatenation of the terms “organic” and “catalyst”) was employed for the first time in 2000. Since then, the focus on organocatalysis has increased continuously over the years.



Scheme 1 Liebig's synthesis of oxamide

Organocatalysis offers a number of opportunities in polymer synthesis. J.L. Hedrick's discovery in 2001 about organocatalytic living ring opening polymerization of cyclic esters[3] opened a door for polymeric biomaterial synthesis. The use of organic catalyst can provide advantages for the use of synthetic polyesters for biomedical applications where the presence of metal residues in the final materials can be deleterious to their use.

Aims of the study

The aims of the research in this thesis are to study ring-opening polymerization (ROP) of cyclic esters using organocatalysts and carbohydrates as initiators and to design organocatalysts potentially able to catalyze the stereoselective ring-opening polymerization of cyclic esters.

Outline of the thesis

Different organocatalysts including organic bases to Brönsted and base/acid complexes made thereof were tested as catalysts. These catalysts were chosen by the specificity of the targeted reaction: carbohydrate compounds are not stable in acid condition at high temperature; organic bases are less reactive for ring-opening polymerization of ε-caprolactone *vs* lactide, however organic acids shows a good reactivity instead; using chiral molecules and base/acid complexes made thereof may introduce a stereoselectivity in the ring-opening polymerization.

In **Chapter 1**, a literature overview is presented on the synthetic strategies for biomedical polyesters using different types of catalysts and on how stereoselectivity of the ring-opening polymerization is controlled. In **Chapter 2**, we will present the controlled ring-opening polymerization of *rac*-lacide and L-lactide using carbohydrate compounds as initiators and nitrogen bases as cataysts. **Chapter 3** concerns the synthesis of chiral phosphor acids and their use as organocatalysts for the ROP cyclic esters. In **Chapter 4**, we will present the use of acid/base complexes containing a chiral acid for the potential stereoselective ROP of cyclic esters.

1 Bibliography

1.1 Introduction

Aliphatic polyesters are biocompatible and biodegradable polymers exhibiting good mechanical properties and hydrolyzability. They are among the best characterized and most studied biodegradable systems for temporary biomedical applications such as drug delivery systems, resorbable implants or tissue engineering scaffolds. Properties such as hydrophilicity and biodegradation can be tailored by the introduction of biologically relevant functional groups in the polymer. This chapter focuses on the previous works that have already been reported for the synthesis of polyesters functionalized by carbohydrate derivatives. Different types of catalysts will be presented with different mechanisms. Methods reported for the synthesis of cyclodextrin functionalized polyesters will be discussed more extensively, in view of the interest of cyclodextrins for pharmaceutical and catalytic applications. In the last part of this chapter, an overview will be given on the catalysts that are able to stereocontrol the polymerization of *rac*-lactide resulting in stereoregular microstructure.

1.2 Synthetic Strategies for the carbohydrate functionalization of polyester

1.2.1 Introduction

Polyesters can be synthesized by polycondensation (step growth polymerization) or by ring-opening polymerization (chain growth polymerization). A specific functionality can be introduced in the polymer via these polymerizations using functionalized monomers or functionalized initiators. The presence of functional groups such as hydroxyls for instance can be detrimental for both polymerization methods, leading to deactivation and/or undesirable crosslinking reactions. Protection/deprotection steps are thus usually applied prior and after polymerization. These strategies will be presented and illustrated by relevant examples. Such multistep approaches provide interesting and sophisticated materials but require long production times and high production costs. For practical applications, however, biomedical materials must also be cost-effective, introducing a balance between sophistication and ease

of production. Recent advances enabling a one-pot approach for each strategy are of particular interest [4] and are further presented and discussed in this frame.

The polyesters classically used for biomedical applications are poly(ε-caprolactone), poly(lactic acid), their copolymers (see Fig. 2) and in a lesser extent, poly(3-hydroxybutyrate) and polyorthoesters. This section focuses essentially on the polyesters. These polyesters can be synthesized by the ring-opening polymerization of the corresponding cyclic ester (ε-caprolactone and lactide, the latter being a dimer) and by polycondensation of the corresponding ω-hydroxyacid (6-hydroxyhexanoic and lactic acid respectively). 6-hydroxyhexanoic acid is scarcely isolable, and the polycondensation route for the formation of poly(ε-caprolactone) is rarely used. Lactic acid has a stereocenter, and can be found as L-lactic acid, D-lactic acid or a racemic mixture of both forms. The dimer lactide exhibits thus two diastereomeric forms. The most widely used forms of the polymer are poly(L-lactic acid) or poly(L-lactide) and poly(D,L-lactic acid) or poly(D,L-lactide).

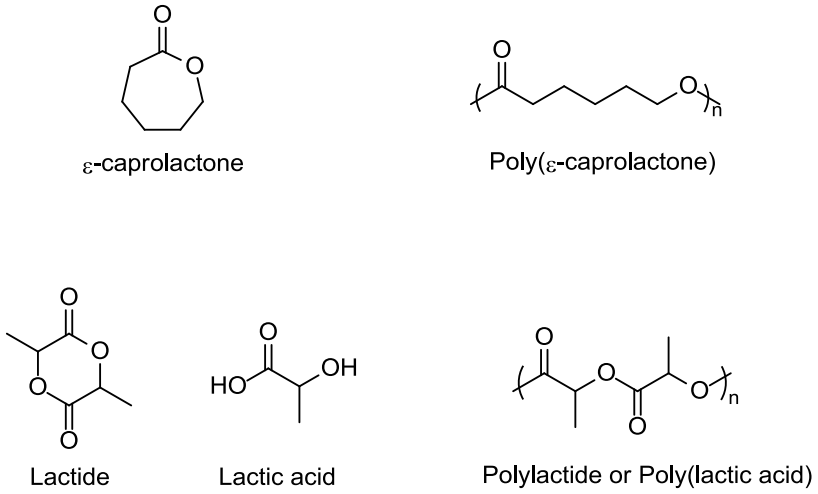


Fig. 2 Polyesters used for biomedical applications and their monomers

1.2.2 Ring-opening polymerization

1.2.2.1 Ring-opening polymerization mechanisms

Ring-opening polymerization of cyclic esters can occur via different mechanisms [5]. The ring-opening polymerization pathways reported here are anionic, coordination-insertion, nucleophile and cationic mechanisms (see Fig. 3). Organocatalytic ring-opening polymerization can be considered when using organic molecules as catalysts or initiators for

the polymerization. It can be found here as nuleophilic or cationic monomer active polymerization.

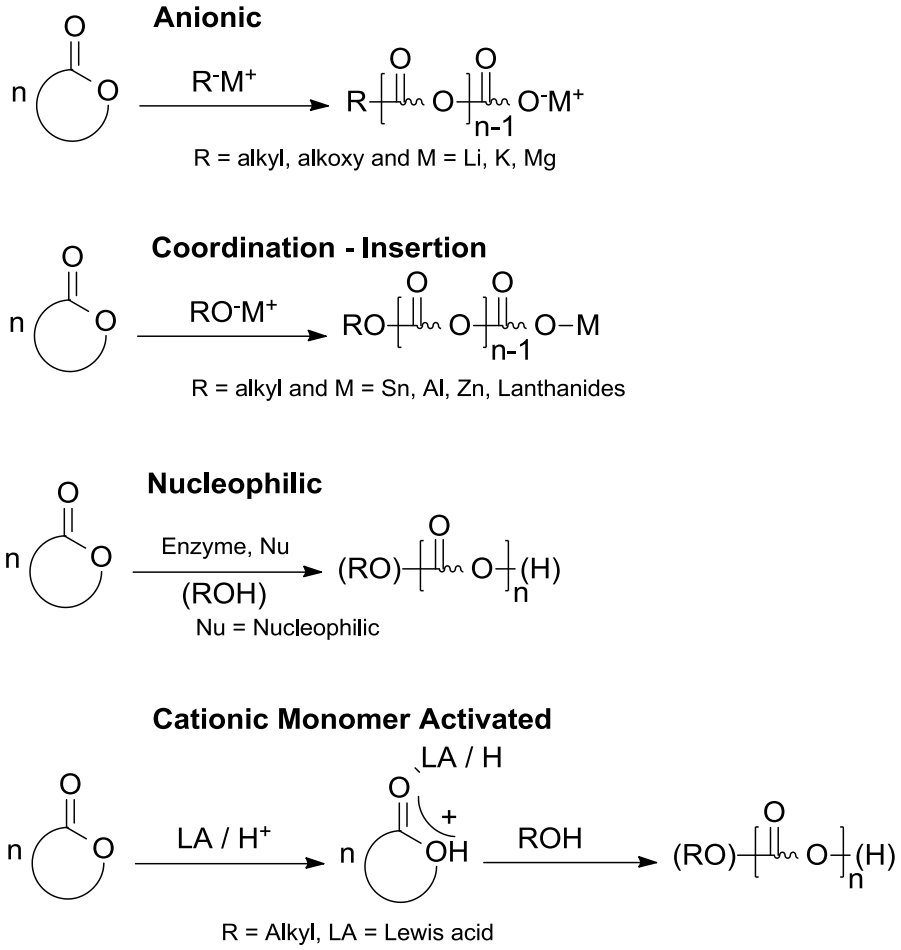
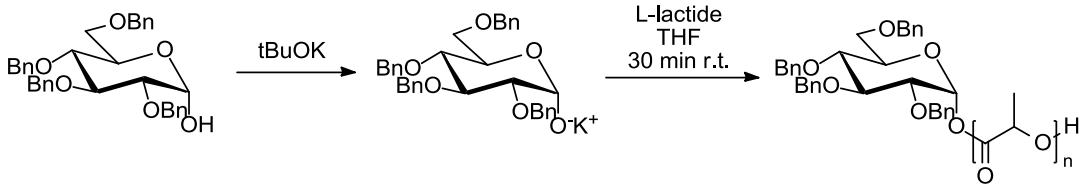


Fig. 3 Ring-opening polymerization mechanisms

1.2.2.2 Anionic ring-opening polymerization

The strategy here consists of using the carbohydrate compound as the counter-ion of the metal catalyst (Scheme 2) [6]. Protected D-glucose bearing a hydroxyl group on the C1 position is allowed to react with the ^{t}BuOK anionic initiator to form the corresponding glucosate. This latter compound is used to polymerize L-lactide in tetrahydrofuran at room temperature. Subsequently, the removal of O-protecting benzyl groups in the terminal carbohydrate can be carried out by hydrogenolysis with Pd/C to obtain D-glucose-end-capped poly(L-lactide). A number-average molecular weight of 5700 g/mol was reported with polydispersity index of 1.35. Due to the living character of anionic polymerization, this strategy can also be used to synthesize monosaccharide end-capped poly(D,L-lactide)-*block*-

polyethylene glycol copolymers [7].



Scheme 2 Poly(L-lactide) end functionalization via anionic ring-opening polymerization

1.2.2.3 Coordination-insertion

The strategy is similar to that reported for anionic polymerization, *i.e.* the carbohydrate compound serves as the counter-ion of the catalyst metal. The main difference resides in the possibility of rapid and reversible chain transfer for coordination-insertion ring-opening polymerization. The reaction can operate in the presence of excess alcohol *vs.* catalyst metal, leading to the growth of several macromolecular chains per metal atom (Fig. 4).

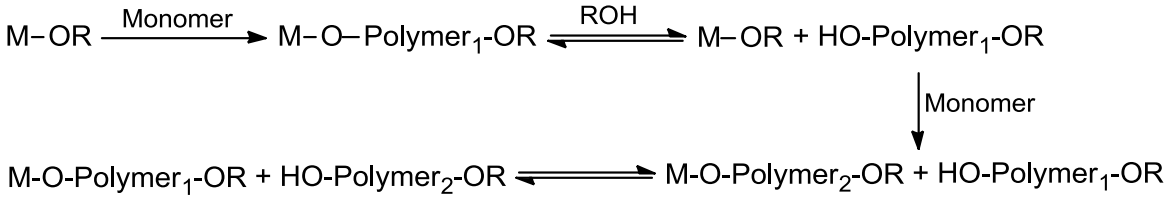
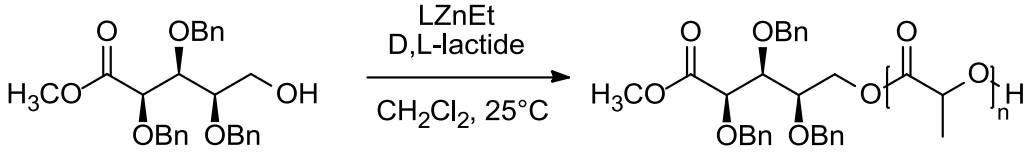


Fig. 4 Transfer reactions in coordination/insertion ring opening polymerization conducted in the presence of excess alcohol *vs.* catalyst

One may distinguish here between end functionalization and grafting from strategy. The former polymerization starts from a single compound such as monosaccharide, while the grafting from method starts from a polymer such as a polysaccharide. Poly(ε-caprolactone) [8] and poly(L-lactide) [9] were polymerized starting from protected monosaccharides, yielding monosaccharides end-capped polymers and eventually nanoparticles [8]. The number-average molecular weight and dispersity were up to 4000 g/mol *vs.* polystyrene standards and 1.2 for poly(L-lactide)[9] and up to 10000 g/mol and 1.1 for poly(ε-caprolactone) [8]. Linear protected carbohydrates end-capped poly(D,L-lactide) [10] (Scheme 3) and macrocyclic polycaprolatone were also synthesized this way [11] as well as poly(ethyleneglycol)-*block*-poly(ε-caprolactone) copolymers [12]. In the latter case, the polymerization is initiated by hydroxyl end-capped poly(ethylene glycol).



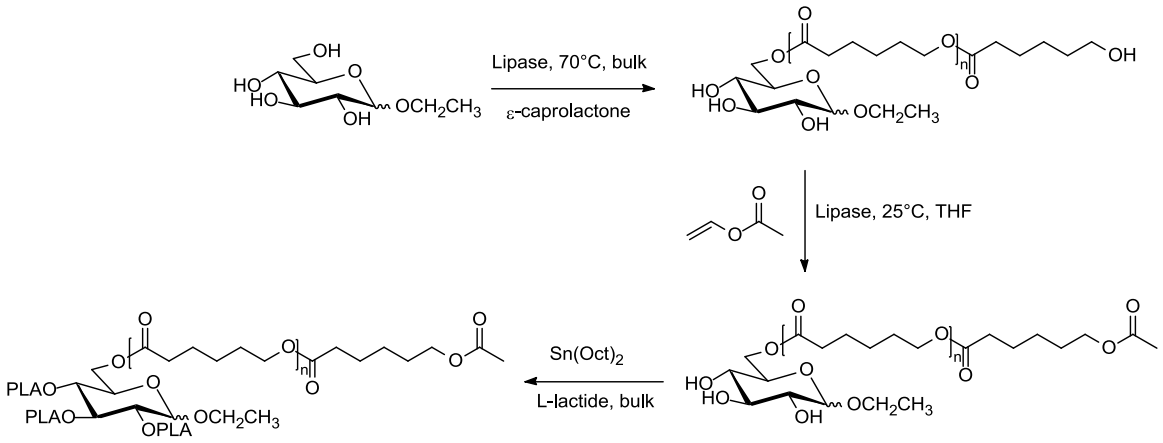
L : Ligand

Scheme 3 Poly(D,L-lactide) end functionalization via coordination/insertion ring-opening polymerization using linear derivatives

Coordination/insertion ring-opening polymerization was also used for grafting from approaches. Dextran was used as an initiator for the grafting from approach, leading to poly(ε-caprolactone)-*graft*-dextran [13] and poly(D,L-lactide)-*graft*-dextran copolymers [14]. The polysaccharide was protected in a first step and could be easily deprotected after the polymerization. Aluminium, tin and zinc alkyls or alkoxy complexes are the most widely used catalysts for the strategies presented in this section.

1.2.2.4 Enzymatic ring-opening polymerization

Poly(ε-caprolatone) was functionalized using *candida antartica* lipase B (Novozym 425) [15] and porcine pancreatic lipase [16]. The reactions were conducted at 60-70°C in bulk, using alkyl galacto- and gluco-pyranoside as carbohydrate initiators (Scheme 4). The reactions conducted without protection-deprotection steps were found to be highly regioselective, the oligo(ε-caprolactone) chains formed being attached by an ester link to the primary hydroxyl moiety of the carbohydrate initiator. Weight-average molecular weights around 4000 g/mol were reported with polydispersity indexes around 1.3 using *Candida antartica* lipase B [15], while weight-average molecular weight of 2200 g/mol (*vs*. polystyrene standards) were reported for porcine pancreatic lipase [16]. The resulting carbohydrate end-capped oligo(ε-caprolactone) can be further used for the synthesis of multi-arm poly((lactide)-*co*-(ε-caprolactone)) via coordination-insertion ring-opening polymerization [17]. The oligo(ε-caprolactone) hydroxyl end group is first protected by lipase catalyzed acetylation and the remaining carbohydrate free hydroxyl groups can then initiate the polymerization of L-lactide mediated by tin octanoate (Scheme 4).



Scheme 4 Regioselective one-step poly(ε-caprolactone) end functionalization via enzymatic ring-opening polymerization and subsequent multi-arm formation via coordination/insertion ring-opening polymerization of L-lactide [17]

1.2.2.5 Organocatalysis

Organocatalysts can provide new opportunities for enhancing the rate of polymerization and influencing the selectivity to generate polymer architectures that are difficult to access by metal-mediated or enzymatic processes. A large scale of organic catalysts has been reported for the ring opening polymerization of cyclic esters, some of them being presented in Fig. 5.

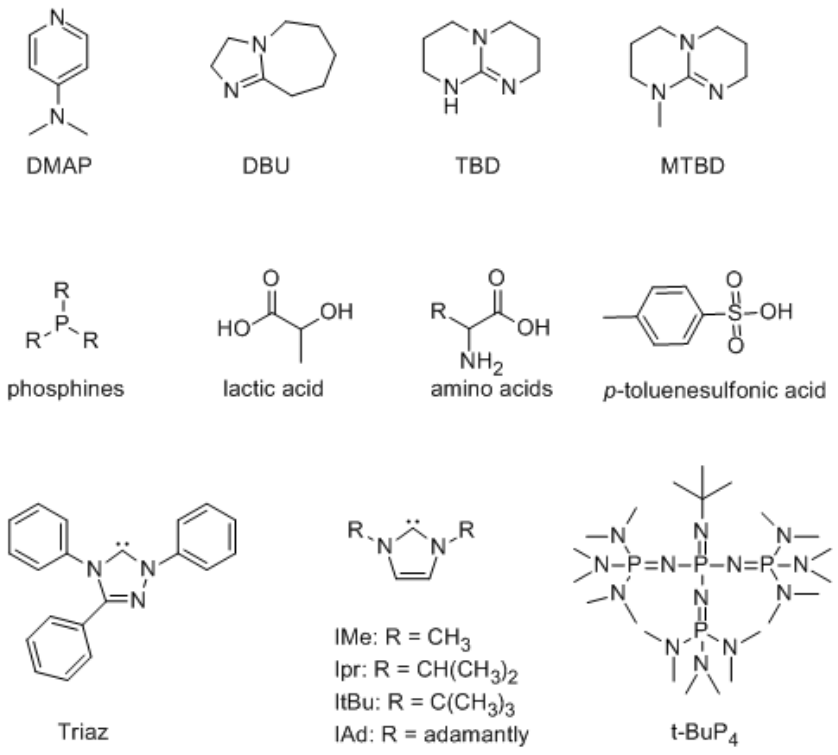
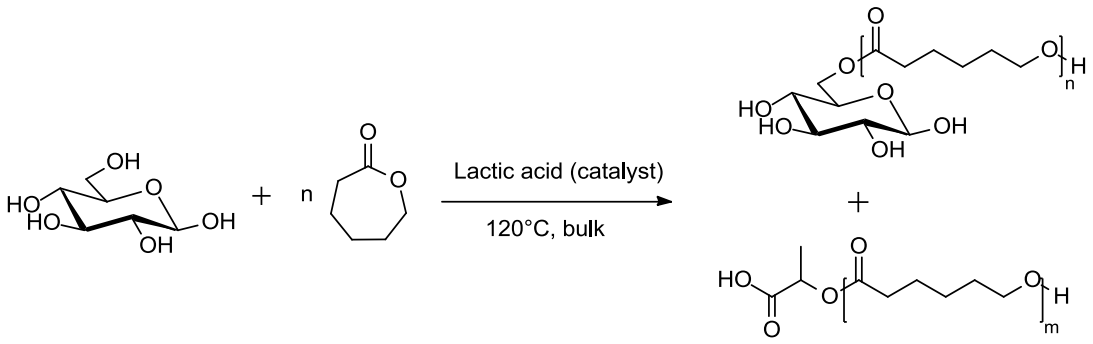


Fig. 5 Representative organic catalysts and initiators for the ROP of lactones

Personn reported the use of lactic acid as a catalyst for the ring-opening polymerization of ε-caprolactone initiated by unprotected mono, di and tri-saccharides [18]. The reaction was conducted at 120 °C in bulk. The main products were regioselectively acylated on the primary hydroxyl groups of the carbohydrate end groups. Weight-average molecular weight of 2000 g/mol (*vs.* polystyrene standards) were reported with polydispersity indexes of 1.5. However, this one-step approach conducted without protection-deprotection steps lead to both carbohydrate (major product) and lactic acid end-capped poly(ε-caprolactone), as lactic acid also initiates the polymerization of ε-caprolactone under the experimental conditions reported (Scheme 5).



Scheme 5 One-pot poly(e-caprolactone) end functionalization via organocatalytic ring-opening polymerization [18]

1.2.2.6 Cyclodextrin functinalized polyesters

Cyclodextrins are particularly interesting in the frame of drug delivery applications. These cyclic oligosaccharides composed of 6(α), 7(β) or 8(γ) glucopyranose units (Fig. 6) are able to host molecules of pharmaceutical interest. This ability to host molecules can also lead to specific effects when conducting ring-opening polymerization of cyclic esters in the presence of cyclodextrins. They can indeed form inclusion complexes with lactones [19] but native cyclodextrins can also initiate the ring-opening polymerization due to bearing hydroxyl groups.

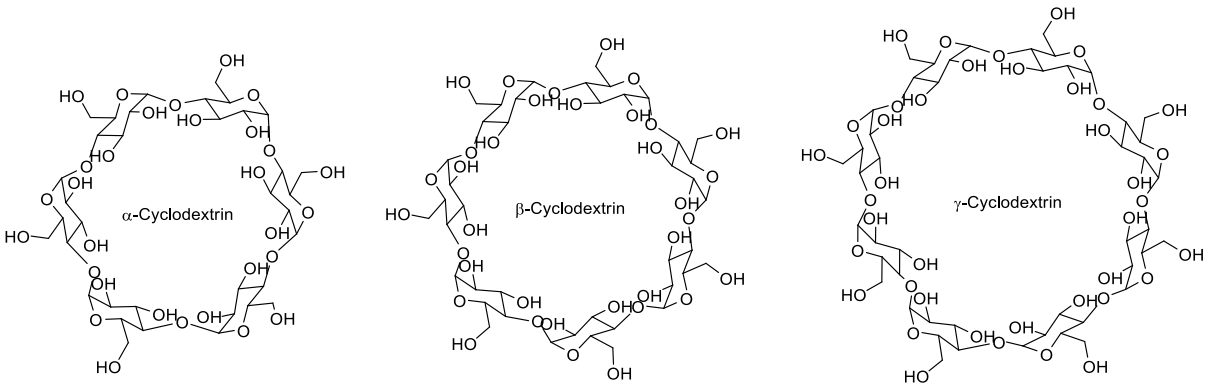
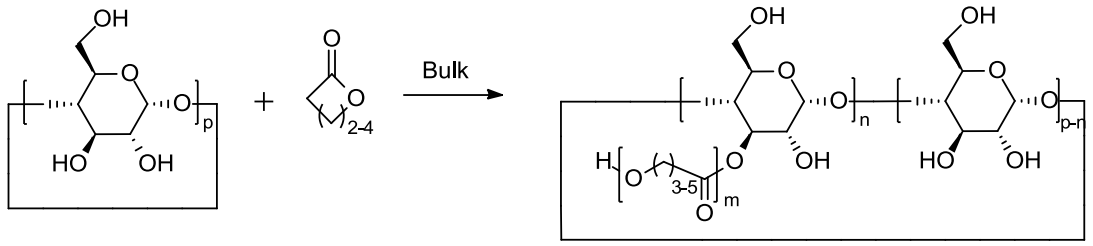


Fig. 6 α-, β- and γ-Cyclodextrins

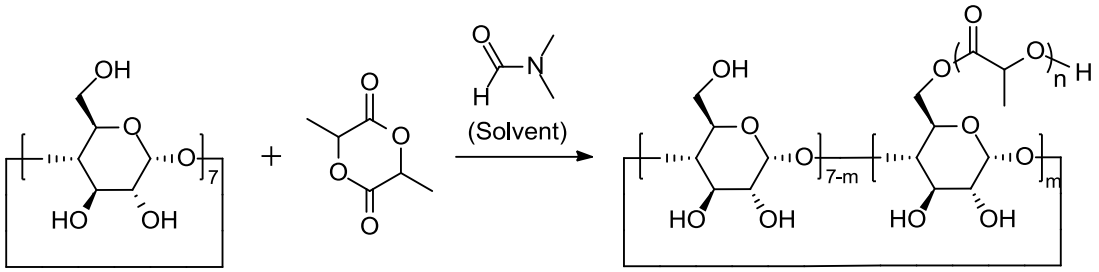
1.2.2.7 Cyclodextrins as initiators for the ring-opening polymerization of cyclic esters conducted without additional co-catalyst

Harada and co-workers reported the use of cyclodextrins as initiators for the ring-opening polymerization of various lactones (Scheme 6) [20-23]. The polymerization yield was found to be dependent on the lactone structure and the cavity of the cyclodextrin, indicating that the reaction takes place via inclusion of the lactone. A smaller lactone (β-butyrolactone) led to higher yields with the smaller α-cyclodextrin while the larger δ-valerolactone and ε-caprolactone led to higher yields with the larger γ-cyclodextrin. Quantitative yields were reported after 48 h to 96 h at 100 °C for the polymerization of δ-valerolactone in the presence of β-cyclodextrin, with dispersities around 1.8 to 1.9. The importance of formation of inclusion complexes between the lactone and the cyclodextrin was further highlighted by the following finding: the polymerization activity of δ-valerolactone can be suppressed by using a β-cyclodextrin-adamantane inclusion complex instead of native β-cyclodextrin as initiator under the same conditions. The polyesters was found to be covalently linked to the C2-hydroxyl group of a single glucopyranose unit as the cyclodextrin, with a partial degree of substitution. If the polymerization mechanism is not fully elucidated, the formation of hydrogen bonds between the hydroxyl group of the cyclodextrins and the carbonyl oxygen of the lactones has been advanced in the initiation step on the basis of FT-IR spectroscopy. The lactones are activated by other remaining secondary hydroxyl groups to give the propagation step via insertion of monomers between the cyclodextrin and the polymer chain.



Scheme 6 Ring-opening polymerization of β-butyrolactone, δ-valerolactone and ε-caprolactone at 100°C in bulk in the presence of α,β and γ-cyclodextrins after Harada and co-workers. *p*= 6 to 8.

β-cyclodextrin was also found to initiate the ring-opening oligomerization of lactide in dimethylformamide at 80-85°C (Scheme 7) [24]. Relatively low amounts of lactide were introduced in order to optimize the solubility of the resulting compound in view of the drug-release applications targeted by the authors. In a typical example, the polymerization yielded oligolactides on the C6 carbon with a number-average degree of polymerization of 4.5 lactic acid units (*n* in Scheme 7) and an average degree of substitution of 1.5 (*m* in Scheme 7) for a yield of 56% after 6 hours at 80°C.



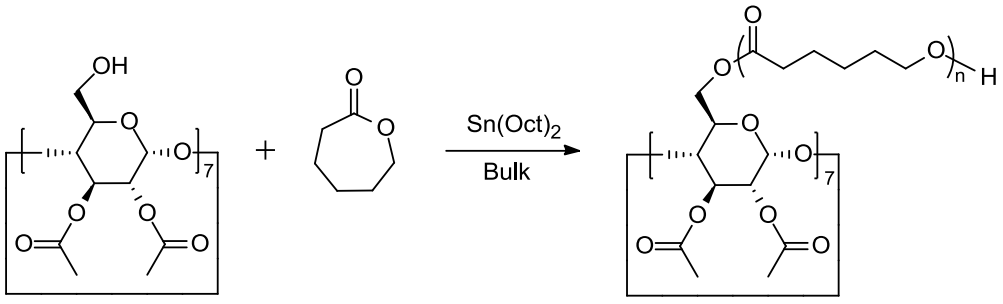
Scheme 7 Ring-opening oligomerization of lactide at 80-85 °C in dimethylformamide in the presence of β-cyclodextrin after[24]

The regioselectivity of the initiation differs between the ring-opening polymerization of lactone conducted in the bulk and the ring-opening polymerization of lactide conducted in dimethylformamide. The ring-opening polymerization of lactone in the bulk is initiated by a primary alcohol, which is more reactive than secondary alcohols. The selectively toward the C2 *vs*. C3 secondary alcohols remains unexplained so far, and it should be noted that the polymerization mechanism has not been fully studied. The ring-opening polymerization of lactide in dimethylformamide is in turn initiated by the primary alcohol on C6. This may be attributed to steric effect, as proposed by the authors. It should also be noted that (i) lactide is a dilactone which structure differs from a monolactone, and (ii) dimethylformamide which is the solvent can play the role of a catalyst in this chemistry. The regioselectivity observed

enables the synthesis of hydrophilic materials in a straightforward one-step procedure, *i.e.* without protection/deprotection steps. Additionally, the functionalized polyester does not contain any residual catalyst even though the use of a toxic solvent is required. The substitution is in turn not quantitative, and the overall initiation efficiency remains weak. This can be circumvented by the use of appropriate catalysts.

1.2.2.8 Cyclodextrins as co-initiators for the ring-opening polymerization of cyclic esters

Cyclodextrins have been used as co-initiators for coordinative, organocatalyzed and anionic ring-opening polymerization of cyclic esters. Several studies report the use of tin octanoate as a catalyst for the cyclodextrin initiated ring-opening polymerization of cyclic esters [25-30]. The selectively protected per-2,3-acetyl-β-cyclodextrin with seven unprotected primary hydroxyl groups has been used as an initiator for the polymerization of ε-caprolactone (Scheme 8) [25]. The reaction is quantitative in 3 h at 120 °C in bulk. The molecular weight can be controlled by adjusting the ε-caprolactone/cyclodextrin ratio, and the distribution is rather narrow ($Đ_M$ < 1.15). Cyclodextrin core poly(ε-caprolactone)-*block*-poly(ethylene glycol) 7 arms star copolymers were further synthesized by coupling reaction of the poly(ε-caprolactone) – OH end groups with carboxylic acid end-capped poly(ethylene glycol). The authors also reported the per-2,3-acetyl-β-cyclodextrin initiated ring-opening copolymerization of ε-caprolactone with 5,5-dibromo-methyl-trimethylene carbonate, enabling further grafting of a drug onto the polyester by click chemistry reactions.[26]

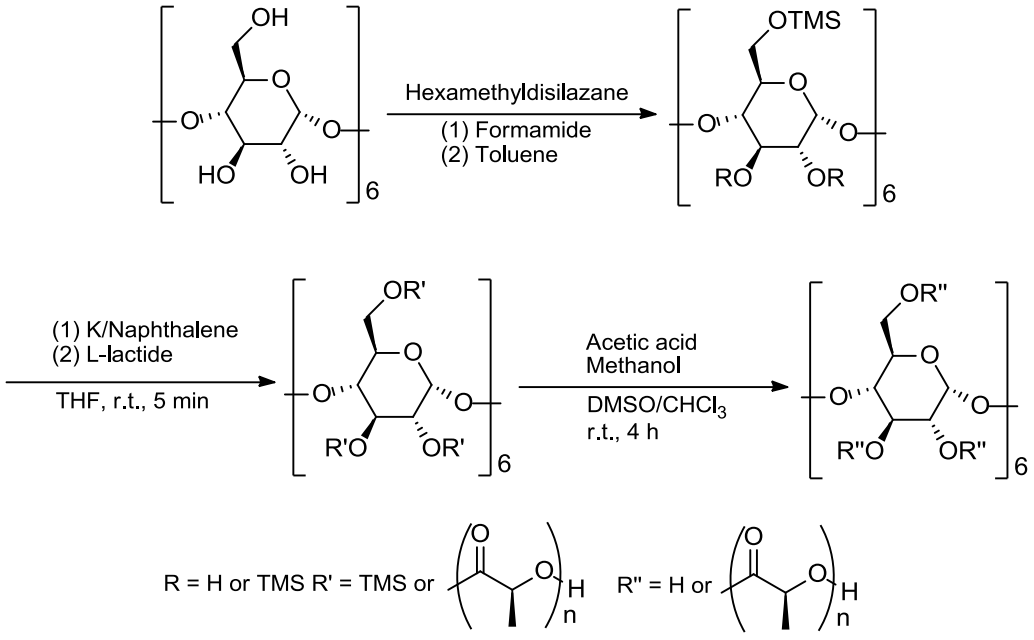


Scheme 8 $Sn(Oct)_2$ catalyzed ring-opening polymerization of ε-caprolactone at 120°C in bulk in the presence of per-2,3-acetyl-β-cyclodextrin [25]

The lactide/glycolide ring-opening copolymerization initiated by β-cyclodextrin was also

reported in the presence of $Sn(Oct)_2$ [27, 28]. High yields and acceptable dispersities ($Đ_M$ < 1.4-1.8) were obtained after 10 h at 140 °C in the bulk. The NMR characterization conducted by the authors did not allow them to fully elucidate the initiation mechanism. The synthesis of polylactide-$(tosyl)_7$-β-cyclodextrin (tosyl = $CH_3C_6H_4SO_2$) was reported by the $Sn(Oct)_2$ catalyzed ring-opening polymerization of lactide starting from C6-tosylated β-cyclodextrin [29]. The secondary C2 and C3 alcohols initiated the reaction. The tosyl groups were further used as initiator for ring-opening polymerization of 2-ethyl-2-oxazoline leading to amphiphilic copolymers containing a cyclodextrin core and polylactide and poly(2-ethyl-2-oxa-zoline) arms.

Ohya *et al.* reported the synthesis of partially protected α-cyclodextrin functionalized PLLA using K/naphthalene as the catalyst [31] (Scheme 9). High yields and relative acceptable dispersities ($Đ_M$ = 1.67) were obtained. This is the only example of the synthesis of cyclodextrin functionalized PLLA via anionic mechanism. After our own publication on functionalizing protected β-CD with polylactide using ring-opening polymerization via organocatalyst, Carpentier *et al.* reported the synthesis of the same β-CD functionalized polylactide by using zinc based organometallic catalyst (for readers interested, see ref [32]) and Shen *et al.* also reported the direct cyclodextrin-mediated ring-opening polymerization of ε-caprolactone in the presence of yttrium trisphenolate catalyst [33].



Scheme 9 Synthesis of α-CD-*graft*-PLLA polymer

Finally, organocatalysists have also been used in combination with cyclodextrins for the ring-opening polymerization of cyclic esters. Sparteine was reported to catalyze the β-cyclodextrin initiatied ring-opening polymerization of β-butyrolactone, leading to the side formation of unfunctionalized poly(β-butyrolactone) [34].

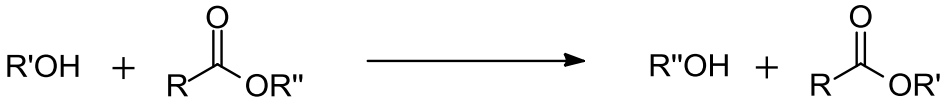
1.2.2.9 Properties of cyclodextrin core star polyester *vs.* properties of single components

Most of the cyclodextrin based macromolecular objects reported are amphiphilic compounds that have been synthesized for use as drug carriers. The polyester represents the hydrophobic part, while the hydrophilic character comes from the water-soluble polymer (*e.g.* polyethylene glycol or poly oxazoline). Such compounds self-assemble into supramolecular structures such as spherical micelles, with the size of the particles in the nanometer range. These are used as nanocarriers for drug delivery after encapsulation of the drug. Nanoparticles have been formed from β-cyclodextrin core star poly(D,L-lactide-*co*-glycolide) polyethylene glycol copolymers based nanoparticles led to higher loading efficiencies, lower particle sizes (120-160 *vs*. 270-350 nm) and slower drug release profiles. Based on these findings, it was proposed that these nanoparticles can be used as a carrier with improved capacity and prolonged delivery for peptide/protein based drugs, such as insulin. In particular when they are used for oral delivery and targeting.

Highly hydrophilic β-cyclodextrin core star oligolactides have also been used for drug delivery purposes, and their potentialities have been compared to that of native β-cyclodextrin. The hydrophilic β-cyclodextrin core star oligolactide is 70 times more soluble in water than native β-cyclodextrin, and is capable of enhancing the solubility and stability of a common drug such as amoxicillin (an antibiotic). The complexation of amoxicillin with the β-cyclodextrin core star oligolactides was found to be much stronger than that with the native β-cyclodextrin at first. After some time, the macromolecular object was shown to decompose moderately into β-cyclodextrin and lactic acid in the presence of water. These β-cyclodextin core star oligolactides are thought to be valuable in a controlled release system for amoxicillin.

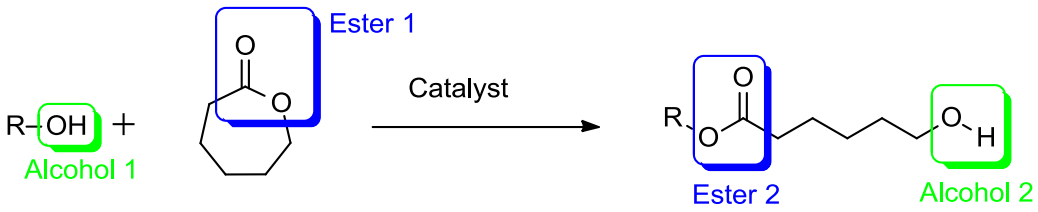
1.3 Transesterification

Transesterification is a process in which the combination of an alcohol with an ester produces a different alcohol and ester (Scheme 10). These reactions are often catalyzed by an acid/electrophile or base/nucleophile.



Scheme 10 Transesterification between an alcohol and an ester

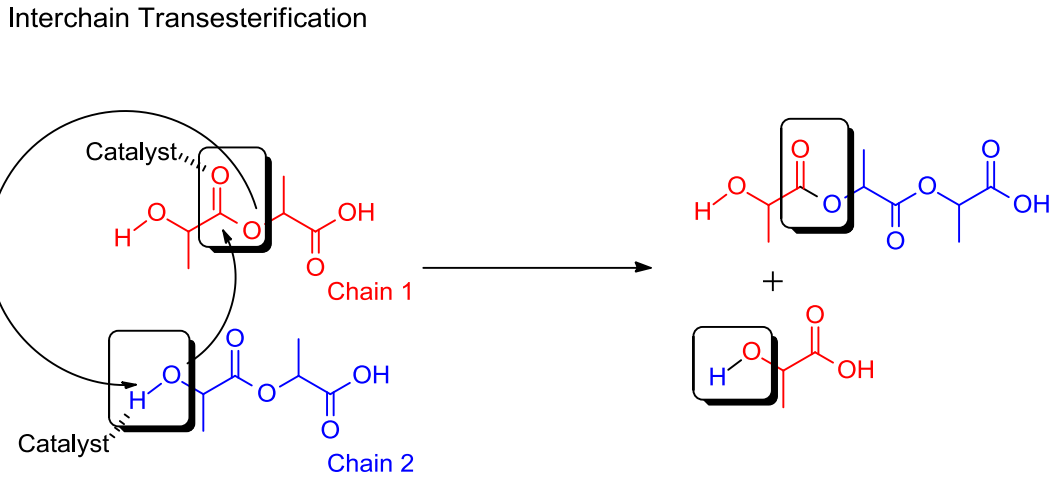
Transesterification is used for many different purposes, the largest scale application of transesterification being in the synthesis of polyesters [35]. The ring-opening polymerization of aliphatic esters is a kind of transesterification. Scheme 11 represents the initiation step of ring-opening polymerization of ε-caprolactone, transesterification performs in presence of catalyst. Alcohol 1 (in green) reacts with ε-caprolactone (considered as an ester in blue) to form another ester (ester 2 in blue) and another alcohol (alcohol 2 in green). The formed alcohol 2 (in green) can furthermore react with another ε-caprolactone monomer to produce a longer polymer chain that is also called the propagation step.



Scheme 11 Transesterification: ring-opening polymerization of ε-caprolactone

In polymer chemistry, transesterification can also be produced between different chains of polymer, which is called interchain transesterification [36]. Scheme 12 shows an example of interchain transesterification between two PLA chains in presence of catalyst. The hydroxyl group of chain 2 (in blue) attacks the ester group of chain 1 (in red) and two new polymer chains are formed. In the case of the polymerization of lactide, the interchain-transesterification can be observed by MALDI-ToF (Matrix-assisted laser desorption ionization time of flight) analysis. Dove *et al.* reported the ROP of lactide using thiourea/tertiary amine as catalyst and astaxanthin as initiator (see Fig. 7) [37]. The polymerization was run over a period of 36 days, sample was taken after 6 hours, 1 day, 2 days, 6 days, 14 days, 21 days, 27 days and 36 days and analyzed by MALDI-ToF.

Comparison of the MALDI-ToF spectra taken shows that after 1 day the dominant distribution is attributable to a 144 Da spacing corresponding to the molecular weight of the lactide dimer which indicates that there is no transesterification observed. But after 21 days, noticeable broadening of the distribution is observed with peaks spaced by 72 Da corresponding to the molecular weight of a single lactic acid at half intensity to the main 144 Da spaced distribution, which indicates that transesterification occurs.



Scheme 12 Interchain transesterification pathway that leads to the formation of chains

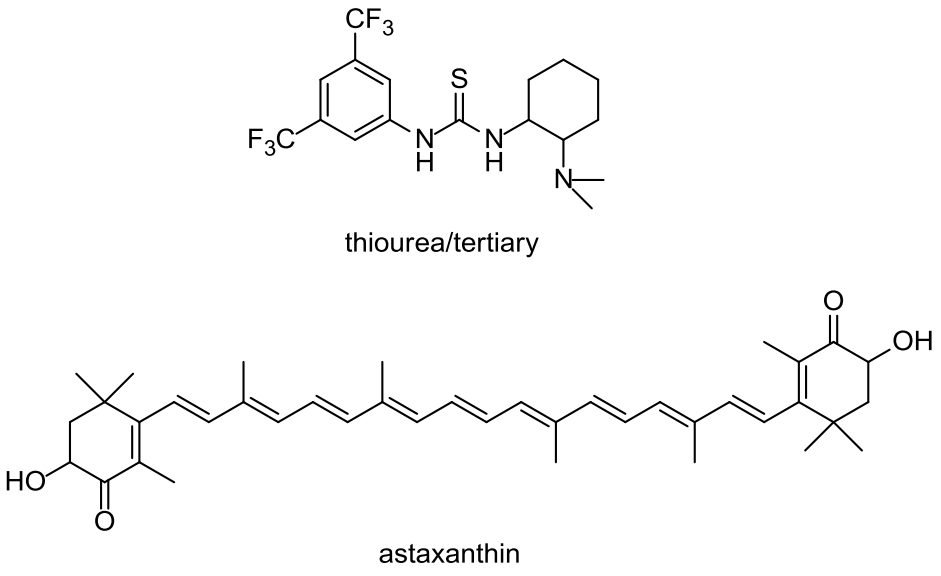


Fig. 7 Chemical structures of thiourea/tertiary amine catalyst and astaxanthin for ROP of lactide

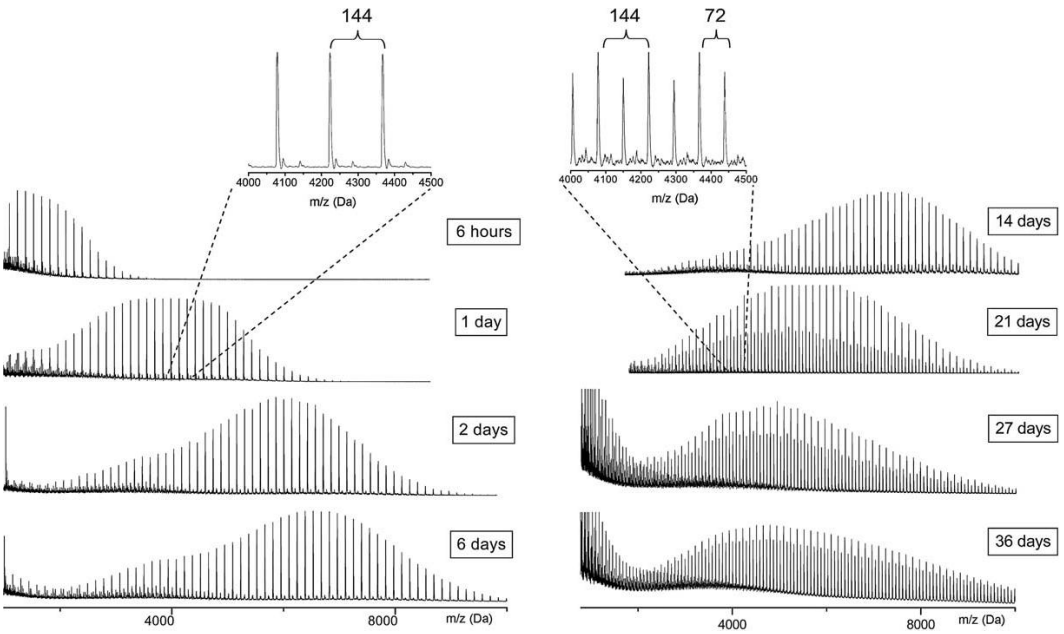
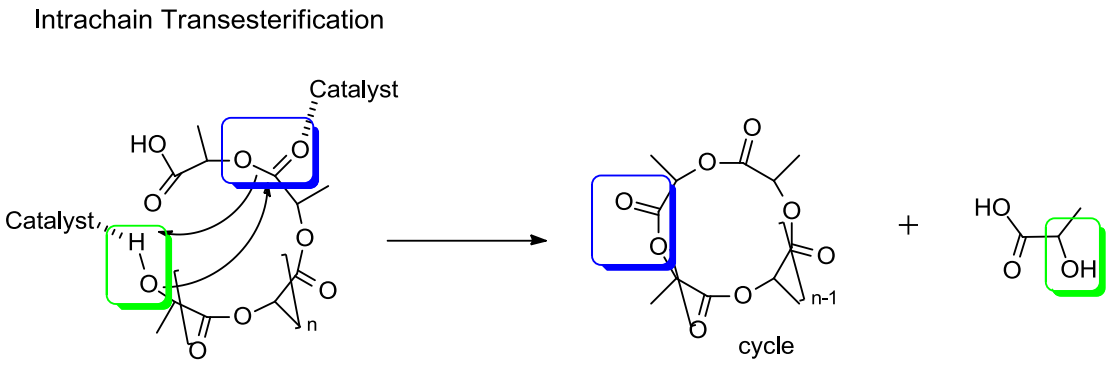


Fig. 8 Comparison of MALDI-ToF mass spectra between 6 hours and 36 days in the ROP of lactide initiated from astaxanthin catalyzed by thiourea/tertiary amine

If the transesterification occurs between the alcohol end group (in green) and an ester (in blue) of the same polymer chain, a cyclic ester and another polymer chain (or oligomer) are produced. This is thus called intrachain transesterification (see Scheme 13).

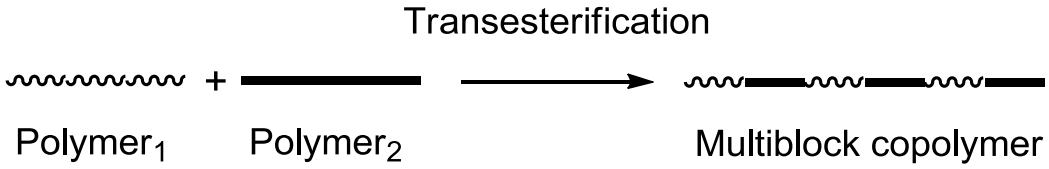
Too much transesterification in the polymerization can lead to a large distribution and thus high dispersity.



Scheme 13 Intrachain transesterification pathway that leads to the formation of cyclic macromolecules

Even if transesterification is considered as a side reaction in controlled ROP, it can be employed for the synthesis of copolymers (Scheme 14). Transesterification of poly(D,L-lactide) and polyethlylene glycol was reported in acetone, without catalysts, leading to copolymers with number-average molecular weights up to 6000 g/mol [38]. The polymer

precursors exhibit number average molecular weight between 2000 and 4000 g/mol. Additional purification steps are necessary in order to remove the remaining homopolymer. The resulting copolymer was shown to form micelles, poly(D,L-lactide) being the hydrophobic segment and polyethylene glycol being the hydrophilic segment, and were later used as drug carriers. The composition of the copolymer can be simply changed by varying the ratio of the polymer precursors. The molecular weights of the resulting copolymers can be significantly increased starting from precursors of higher molecular weight. Using succinic acid as a chain extender in the course of the transesterification between PEG and PLA with titanium isopropoxyde as the transesterification catalyst, molecular weights of up to 40000 g/mol *vs.* polystyrene standard could be achieved [39].



Scheme 14 The application of transesterification in the synthesis of copolymer

1.4 Stereocontrolled ring-opening polymerization of *rac*-lactide

1.4.1 Introduction

Lactide is the cyclic dimer of lactic acid and it has two possible configurations, *R* and *S*, depending on the arrangement of substituents around the chiral carbon. Therefore, there are three possible configuration of lactide: *RR*, *SS* and *RS*. *RR* configuration is referred to as D-lactide, *SS* is referred to as L-lactide and *RS* is reffered to as *meso*-lactide. A mixture of equal amount of D- and L-lactide is referred to as *rac*- or D,L-lactide (Fig. 9).

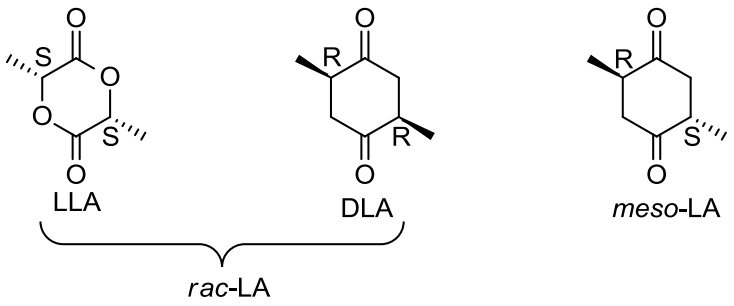


Fig. 9 L-,D- and *meso*-lactide

The stereocontrolled ROP of *rac*-lactide can lead to different types of isotactic polymers and heterotactic PLA (Fig. 10). Different microstructures of PLA can result different physical properties. Heterotactic PLA displays a polymer melting temperature (T_m) of 130 °C and no observable glass temperature (T_g); enantiopure PLLA owns a T_g of 50 °C and a T_m of 180 °C; An equal quantity mixture of PLLA and PDLA displays a similar T_g as PLLA, but has a significant increased T_m which is equal to 230 °C [40]. This increased T_m is attributed to the formation of a stereocomplex between PLLA and PDLA. *Meso*-lactide can lead to both heterotactic and syndiotactic PLA. The latter has a T_g of 34.1°C and a T_m of 152°C [41].

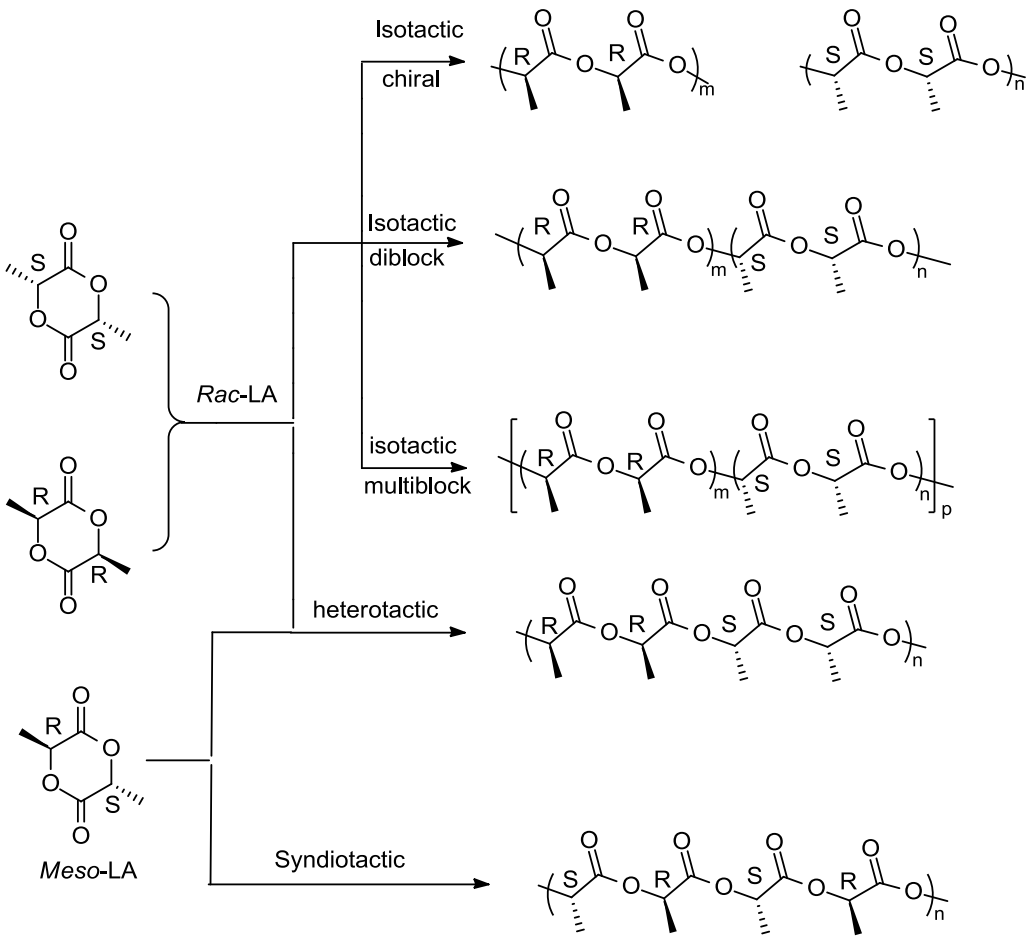


Fig. 10 Various PLA microstructures from the stereocontrolled ROP of lactide

In stereoselective polymerization, the chirality of each newly inserted monomer may be identical or opposite to that of the previously inserted monomer, resulting in isotactic or syndiotactic sequences respectively. This is often referred to as *meso* (*m*) or *racemic* (*r*) enchainment respectively (Fig. 11). Thus, the degree of stereoregularity is expressed as the

probability of *meso* (P_m) or *racemic* (P_r) enchainment. For the ROP of *rac*-lactide, P_m or P_r = 0.50 represents a completely atactic polymer and P_m = 1.00 (P_r = 0.00) or P_r = 1.00 (P_m = 0.00) describes a perfect isotactic or heterotactic polymer respectively. At the tetrad level, the tacticity of the polymer can be determined from homonuclear decoupled ^{1}H NMR analysis. In order to decouple the effect of splitting between the methine and the methyl protons, homomolecular decoupling of methyl signal is performed which results in singlet resonances in the methine region (δ = 5.15-5.25 ppm in $CDCl_3$, See Fig. 12). The parameters can be calculated from the deconvoluted homonulear decoupled ^{1}H NMR spectrum and the theoretical calculations according to Bernoullian statistics reported in Table 1. Fig. 12 shows the microstructures of heterotactic and isotactic PLA and their corresponding homonuclear decoupled ^{1}H NMR spectra. A pure isotactic PLA will have a repeating tetrad of LLLL or DDDD which can be presented by *mmm* whereas a pure heterotactic PLA would contain tetrads of both LLDD and LDDL, or *mrm* and *rmr*, respectively (see Fig. 12).

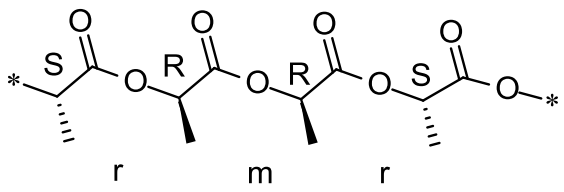


Fig. 11 *meso* and *racemic* enchainements

Table 1 Tetrad probabilities based on bernoullian statistics [42]

tetrad	probability *rac*-lactide
[*mmm*]	$P_m^2+P_rP_m/2$
[*mmr*]	$P_rP_m/2$
[*rmm*]	$P_rP_m/2$
[*rmr*]	$P_r^2/2$
[*rrr*]	0
[*rrm*]	0
[*mrr*]	0
[*mrm*]	$(P_r^2+P_rP_m)/2$

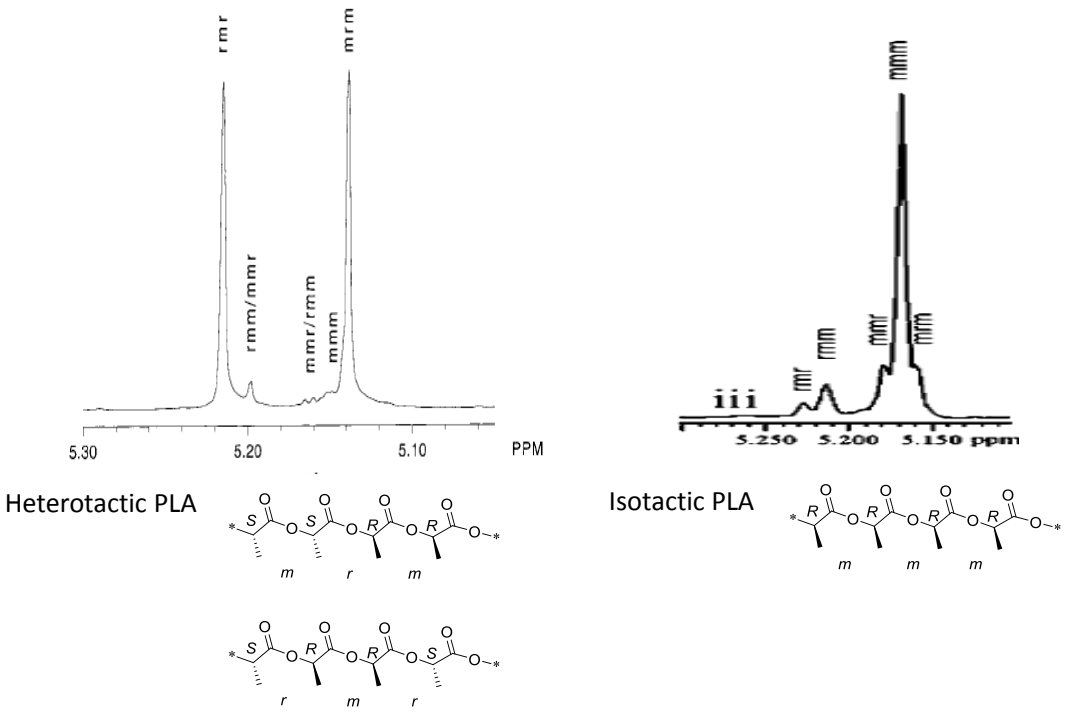


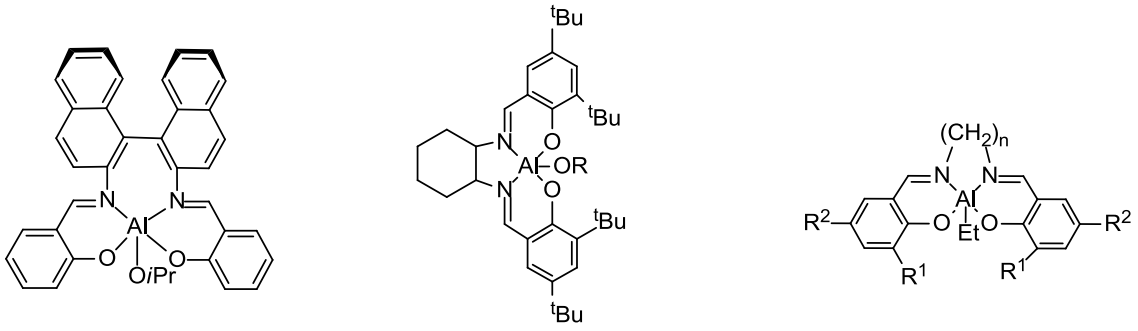
Fig. 12 Heterotactic-enriched PLA [42] and isotactic-enriched PLA [43] and their corresponding decoupled ^{1}H NMR spectrum

However, the catalysts that have been known today are never 100% selective, a pure isotactic or heterotactic polymer has never be formed as far as we know. A number of catalysts have already been studied for the ROP of lactide: metal based catalysts, organocatalysts and enzymes. For metal based catalysts, the stereoselectivity is influenced by factors associated with the type of metal species, the nature of the ligand, the polymerization temperature and the solvent as well. For organocatalysts, the stereoselectivity is usually influenced by the polymerization temperature and the chirality of the organocatalysts. Enzymes are not able to stereocontrol the ROP of D,L-lactide in previous studies and the polymerization is usually not controlled. In the following sections, different examples of catalysts which are stereoselective will be reviewed with an emphasize on organocatalysts, Metal based catalysts for the stereocontrolled ROP of lactide have been reviewed by Thomas *et al.* for readers interested in the field [44].

1.4.2 Metal based catalysts for stereocontrolled ring-opening polymerization of *rac*-lactide

1.4.2.1 Aluminium based complexes

During last decades, a number of metal based catalysts have been reported for the stereoselective for ROP of D,L-lactide. Among these metal species, aluminium complexes have been mostly studied. Spassky *et al.* initiated the study of Al complexes for stereoselective lactide ROP. They demonstrated that a chiral BINAP-based salen aluminium complex (**1** in Fig. 13) is a high selective initiator for ROP of *rac*-lactide (P_m = 0.88) [45, 46]. Later, a relative simple salen Al complex (**2** in Fig. 13) was applied by Feijen *et al*. to catalyze the ROP of *rac*-lactide[47]. Isotactic enriched PLA was obtained (P_m = 0.93). It is remarkable that even in bulk condition (T = 130°C), high stereoselectivity was obtained (P_m = 0.88). Furthermore, Nomura *et al.* [48] have shown that the use of sterically hindered, but achiral aluminium salen type complexes were also prone to produce isotactic enriched PLA from *rac*-lactide (P_m =0.9). This example is particularly relevant from a mechanistic point of view, as it prouves that chiral centers on the catalysts are not a prerequisite to provide the stereocontrol of the polymer enchainment – A chain end controlled mechanism is operating is this case.



1

P_m = 0.88

2

P_m = 0.93
P_m = 0.88, T = 130°C

3

P_m = 0.90

Fig. 13 Aluminium complexes for stereoselective lactide ROP

1.4.2.2 Zinc based complexes

Recently, zinc complexes have attracted much attention as catalysts for ROP of *rac*-lactide. Early examples of organozinc compounds ((β-diketiminato) metal complexes) for stereoselective ROP of lactide have been reported by Coates *et al.* [49] They demonstrated that a (β-diketiminato)zinc isopropoxide species **3** (Fig. 14) was able to initiate ROP of *rac*-lactide with a P_r of 0.94 at room temperature, whereas Tolman *et al.* found a slight stereoselectivity (P_r = 0.6) using zinc complexes of N-heterocyclic carbenes (**4** in Fig. 14)

[43].

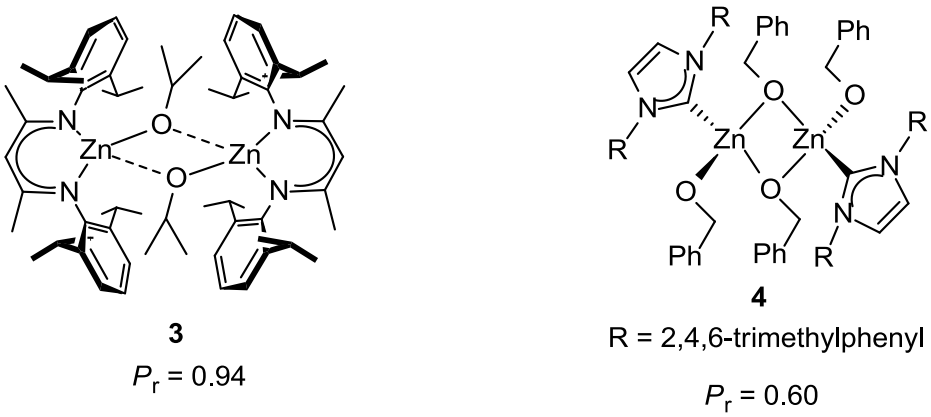


Fig. 14 Zinc complexes for ROP of *rac*-lactide

1.4.2.3 Other metal species based complexes

Besides aluminium complexes and zinc complexes, other metal species such as lithium salt [50, 51], magnesium salt [51] and rare earth based compounds [52, 53] among others were employed in ROP of *rac*-lactide. J. Kasperczyk and M. Bero found that butyllithium was able to catalyze the polymerization of *rac*-lactide, resulting in a P_r of 0.72 and polymerization using magnesium *tert*-butoxide in identical conditions produced a less heterotactic-enriched PLA (P_r = 0.63). Carpentier and co-workers have reported several different rare earth catalysts (lanthanum, yttrium and neodymium complexes) for the polymerization of *rac*-lactide, among which yttrium based catalysts (Fig. 15**)** produced a best heterotacticity in THF at 0 °C (P_r = 0.80) [53] .

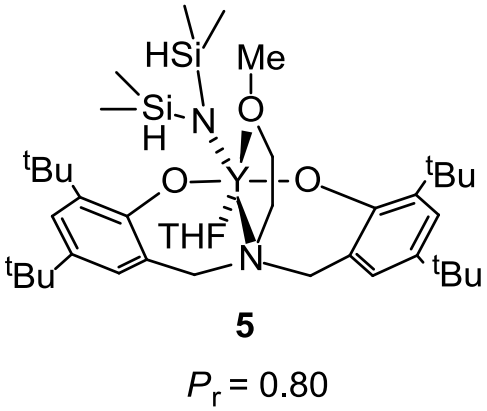


Fig. 15 Yttrium based complex reported by Carpentier *et al.*

1.4.3 Organocatalysts for stereocontrolled ring-opening polymerization of rac-lactide

A lot of success has been achieved for stereocontrolled polymerization of lactide using organometallic catalysts in the last few decades, while using organocatalysts to control the stereoselectivity of ROP of lactide is still an emerging field. Only a few organocatalysts have been reported be able to control the stereoselectivity including carbenes [43, 54] and a phosphazene base as well [55].

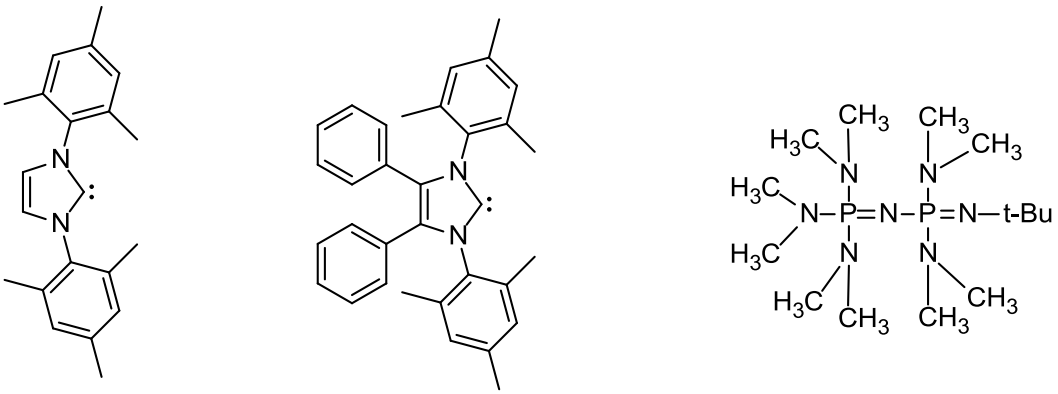
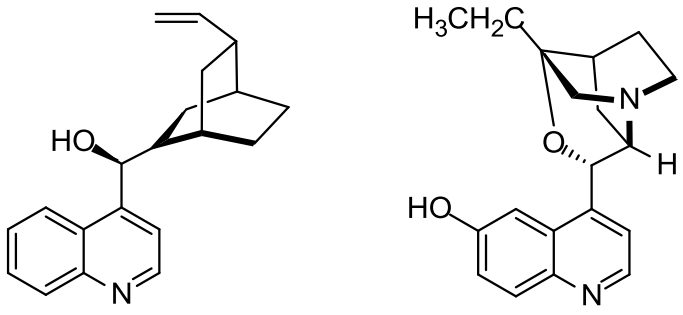


Fig. 16 Organocatalysts for stereocontrolled ROP of lactide

Carbenes are well known for their strong nucleophilicity. As mentioned earlier, Tolman *et al.* found that the polymerization of *rac*-lactide using N-heterocyclic carbene based zinc (NHC) (see compound **4** in Fig. 14) resulted in heterotactic enriched PLA (P_r = 0.6). The reaction was performed at 25 °C in dichloromethane and within 20 minutes, a conversion of 96% was obtained for a targeted degree of polymerization of 130. Interestingly, they discovered a striking difference in the tacticity of the polylactide when using carbene **6**. In contrast to the heterotactic polylactide produced when using carbene based zinc complex **4**, an isotactic enriched PLA (P_m = 0.59) was obtained by using the identical reaction conditions. They improved the stereoselectivity by performing the reaction at low temperature (-20 °C), which leads to a P_m of 0.75. Waymouth and co-workers continued to work on the carbene catalysts for stereocontrolled ROP of *rac*-lactide and *meso*-lactide [54]. A more sterically encumbered NHC (**7**, Fig. 16) was employed to catalyze the polymerization of *rac*-lactide at -70°C producing a highly isotactic PLA (P_m = 0.90) [54]. Catalysts can control the stereochemistry of the resultant PLA by two mechanisms: chain end control, in which the stereochemistry of

the last inserted monomer defines the stereochemistry of the subsequent ring-opening step; and site control polymerization: in which the chirality of the catalyst defines the stereochemistry of the monomer insertions [56]. The fact that similar results were obtained with chiral and racemic mixture of the catalyst suggests a chain end control mechanism. The polymerization of *meso*-lactide was further performed using carbene catalyst **7**. The stereocontrol of *meso*-lactide polymerization would lead to different results depending on the mechanism of stereocontrol. (*e.g.* syndiotactic PLA is most likely obtained by a site controlled mechanism [57], and heterotactic PLA is most likely obtained by a chain end controlled mechanism). A high heterotactic PLA (P_m = 0.83) was obtained by using *meso*-lactide as the monomer and carbene **7** as the catalyst which confirms that the end chain controlled mechanism occurs in the case of carbene catalyzed polymerization of lactide. Another strong organic base, diametric phosphazene base P_2-*t*Bu (**8**, Fig. 16), has also been studied by Wade *et al.* [55] They showed that the P_m increases from 0.72 for the PLA prepared at room temperature using **8** as the catalyst to 0.95 for PLA prepared at -75 °C. Because of the high basicity, steric hindrance, and high activity at low temperature, P_2-*t*Bu (**8**) shows excellent stereocontrol for the ROP of *rac*-lactide. The chain end control mechanism is postulated to explain the formation of the microstructure as the catalyst is not chiral.



9 **10**

Inactive P_m = 0.75

Fig. 17 Cinchona alkaloids catalysts for stereocontrolled ROP of *rac*-lactide

Miyake and Chen explored cinchona alkaloids such as cinchonidine (CCND) (**9**, Fig. 17) and β-isocupreidine (ICPD) (**10**, Fig. 17) which bear both a chiral nucleophilic amine catalyst site and an electrophilic hydroxyl moiety, as bifunctional, stereoselective organocatalysts for the ring opening polymerization of *rac*-lactide and L-lactide [58]. CCND was found inactive in dichloromethane at ambient temperature up to 24 h, reasoning that CCND may be too

sterically bulky to be an effective initiator. However, they demonstrated that ICPD combined with BnOH is able to catalyze the ROP of *rac*-lactide showing a distinct preference for isotactic enchainment (P_m = 0.75). This is so far the only example of stereocontrolled ROP of lactide introduced by the chirality of the catalyst, which operates in mild conditions compared with the other organocatalysts reported previously [43, 54, 55].

1.5 Conclusion

Obviously, metal based catalysts have a big success in the ring-opening polymerization of cyclic esters. Different carbohydrate functionalized polyesters were obtained using metal based catalysts. According to the catalysts, the mechanism can be performed via anionic or coordination-insertion. In all cases, the polymerizations are well controlled leading to carbohydrate end-capped polyesters. Enzyme catalysts are effective to catalyze the ROP of ε-caprolactone, but in the case of the ROP of lactide, enzymes do not show good reactivity. Organocatalysts are complementary to metal based catalysts and enzymes. They have a big advantage in the synthesis of biomaterials and environmentally friendly nontoxic plastics. In stereocontrolled ROP of *rac*-lactide, metal based complexes are the most used strategy to control the degree of stereoregularity of polymer. By using different ligands, the metal based complexes lead to different degrees of stereoregularity and using different metal species can result in different polymer microstructure: isotactic or heterotactic polymer. However, it seems that using organocatalysis to synthesize functionalized and stereocontrolled polyesters is still an emerging field, especially in stereocontrolled ROP. Only few works have been reported about the stereoselectivity of ROP of lactide using organocatalysis compared with using organometallic catalysts. There is still a lot of space to be explored in organocatalysis.

1.6 References

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2 Carbohydrate functionalized PLAs via Organocatalytic Ring-Opening Polymerization

2.1 Introduction

Polylactide is an aliphatic polyester derived from renewable resources. PLA has been used in a number of biomedical applications such as sutures, stents, dialysis media and drug delivery devices. It has also been widely used in tissue engineering. PLA is mainly produced by ring-opening polymerization of the corresponding cyclic ester, lactide, however it can also be obtained by polycondensation of lactic acid. The hydrophobic nature of this polyester can however hamper its use for some specific applications, which can be circumvented by introducing hydrophilic functional groups into the polymer. The use of carbohydrates derivatives seems pertinent toward this issue, since carbohydrate compounds are biocompatible. The introduction of cyclodextrins into polylactide is also of interest in the frame of drug delivery applications, as cyclodextrins are able to host drug molecules[1]. The use of carbohydrate compounds as initiators for ring-opening polymerization has also some further interest for macromolecular engineering for the synthesis of the star or link functionalized polymers (Fig. 18).

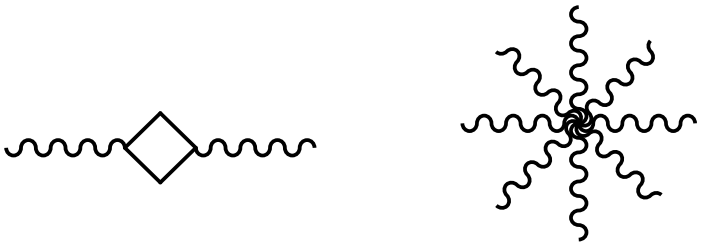


Fig. 18 Link functionalized (left) and star (right) polymers

Different strategies have been reported for introducing carbohydrates into aliphatic polyesters [2, 3]. Most of these strategies are based on metal catalysts and/or initiators [4-11]. Residual metal contaminants can hamper the use of the polymer for biomedical and pharmaceutical applications [12]. The use of organic or enzymatic catalysts is thus considered an interesting alternative in this context.

Enzymatic catalysis was reported as a straightforward way for the synthesis of carbohydrate end-functionalized poly(ε-caprolactone) [13, 14]. Even though enzymes are very good catalysts for the ring-opening polymerization of ε-caprolactone, their performances for the ring-opening polymerization of lactides remain modest, giving rather low yields and high polydipersities in harsh experimental conditions [15-20]. The synthesis of carbohydrate end-capped poly(ε-caprolactone) was also reported using lactic acid as catalyst, but this leads to the simultaneous formation of lactic acid end-capped poly(ε-caprolactone) [21]. Cyclodextrins were also used as initiators for the ring-opening polymerization of various lactones [22, 23] and the ring-opening oligomerization of lactide [24] without additional co-catalyst. The latter polymerization yielded oligolactides on the C6 carbon with a number-average degree of polymerization of 3.5. Sparteine was also reported to catalyze the β-cyclodextrin functionalized ring-opening polymerization of β-butyrolactone, leading to the side formation of unfunctionalized poly(β-butyrolactone) [25]. In contrast, the functionalization of polylactide with various carbohydrates using an organic catalyst has never been systematically studied so far. It is thus of interest to assess an organic catalyst for this purpose.

In that context, a large number of catalysts such as organic acids, amines, phosphines, carbenes and phosphazenes have been used to catalyze the ring-opening polymerization of cyclic esters [26, 27]. We choose 4-dimethylaminopyridine (DMAP, pka = 9.5) as catalyst (see Fig. 19). Mild polymerization conditions produce polylactides with predictable molecular weights and narrow dispersity using this catalyst combined with an alcohol as co-initiator [28]. In this chapter, we present the synthesis of various carbohydrate-functionalized polylactides using 4-dimethylaminopyridine (DMAP) as catalyst for the ring-opening polymerization of lactide as well as a trial using 1,8-Diazabicycloundec-7-ene (DBU) (see Fig. 19) as catalyst.

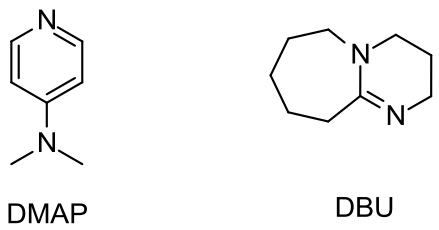


Fig. 19 DMAP and DBU

First of all, the synthesis of the carbohydrate based initiators will be presented. Then, the results of polymerization in solvent will be discussed. The polymerization in bulk will also be discussed after. The NMR study of inclusion complex β-cyclodextrin and DMAP will be presented with the synthesis of the DMAP/**β-CD** inclusion complex. Finally, DBU, another strong organic base, was also tested as the catalyst of the ROP of lactide.

2.2 Synthesis of carbohydrate based initiators

The different carbohydrate initiators used for this study are presented in Fig. 20 and Fig. 21. Since carbohydrate compounds are polyols, the hydroxyl groups can be used to initiate the ROP directly. However, the reactivity of each hydroxyl may be different from one another. Primary alcohols are usually more reactive than secondary alcohols because of steric effects, and primary alcohols are more nucleophilic than secondary alcohols. Even different secondary alcohols may have different reactivity. Thus, it was of interest to use carbohydrate compounds bearing different type of alcohol in order to compare their reactivity. We thus synthesize carbohydrate based initiators with different hydroxyl groups by using selective protection and deprotection methodology. Four sugar initiators are presented in Fig. 20 and three cyclodextrin initiators are presented in Fig. 21. This includes methyl-α-**D**-glucopyranoside (**Glc-Me**) bearing a primary alcohol and three secondary alcohols, native β-cyclodextrin (**β-CD**) and native α-cyclodextrin (**α-CD**) containing twenty-one and eighteen alcohols respectively are commercial and were used directly as initiators. Methyl 2,3,4-tri-*O*-benzyl-α-**D**-glucopyranoside (**Glc-1r**) bearing a free primary alcohol on position 6, methyl 2,3-di-*O*-methyl-α-**D**-glucopyranoside bearing a free secondary alcohol (**Glc-2r**) on position 2, methyl 2,3-di-*O*-methyl-α-**D**-glucopyranoside (**Glc-diol**) bearing a primary alcohol on position 6 and a secondary alcohol on position 4, **CD-diol** bearing two primary alcohols on position 6 are obtained by selective protection and deprotection.

The outline for the synthesis of **Glc-1r**, **Glc-2r**, **Glc-diol** and **CD-diol** will be given hereafter, more details about the synthesis will be presented in the experimental part.

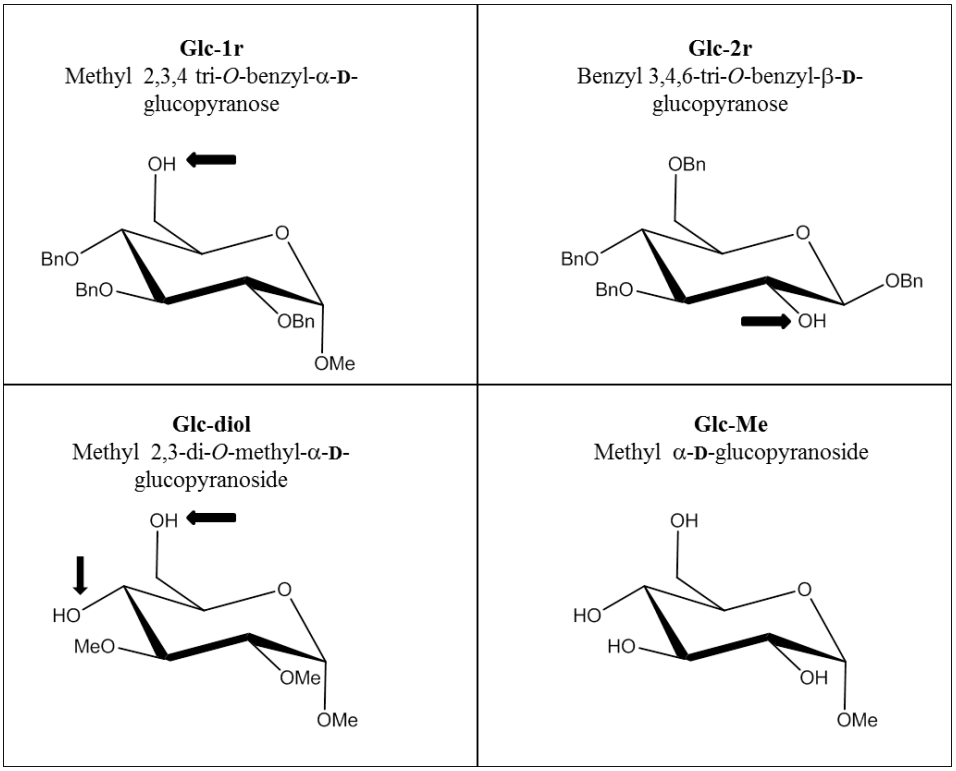


Fig. 20 Sugar initiators used for the ring-opening polymerization of lactide

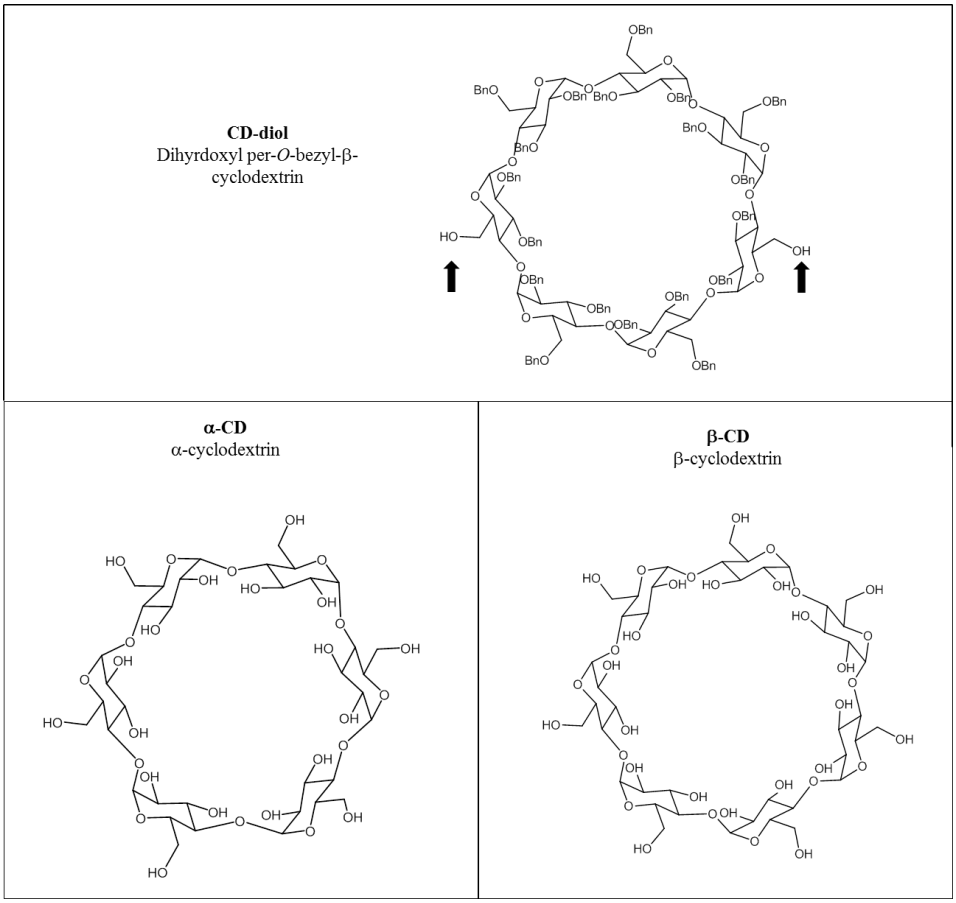
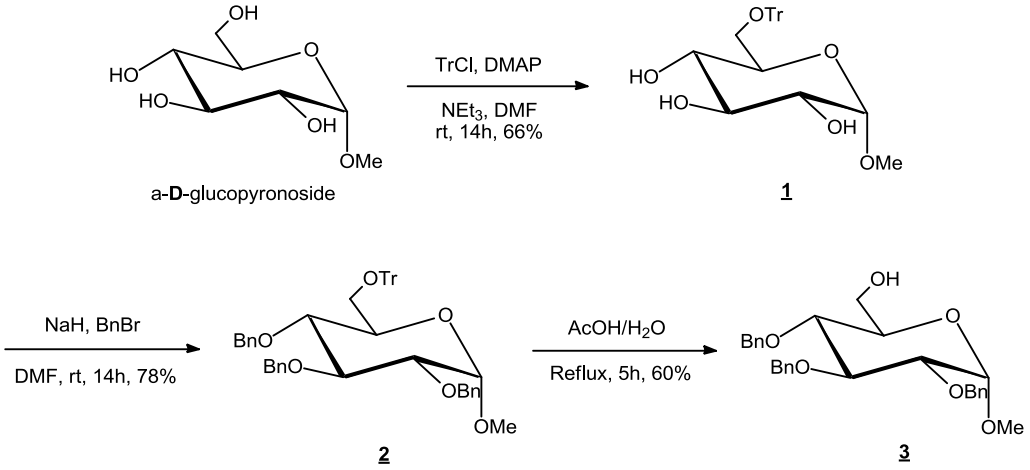


Fig. 21 Cyclodextrin initiators used for the ring-opening polymerization of lactide

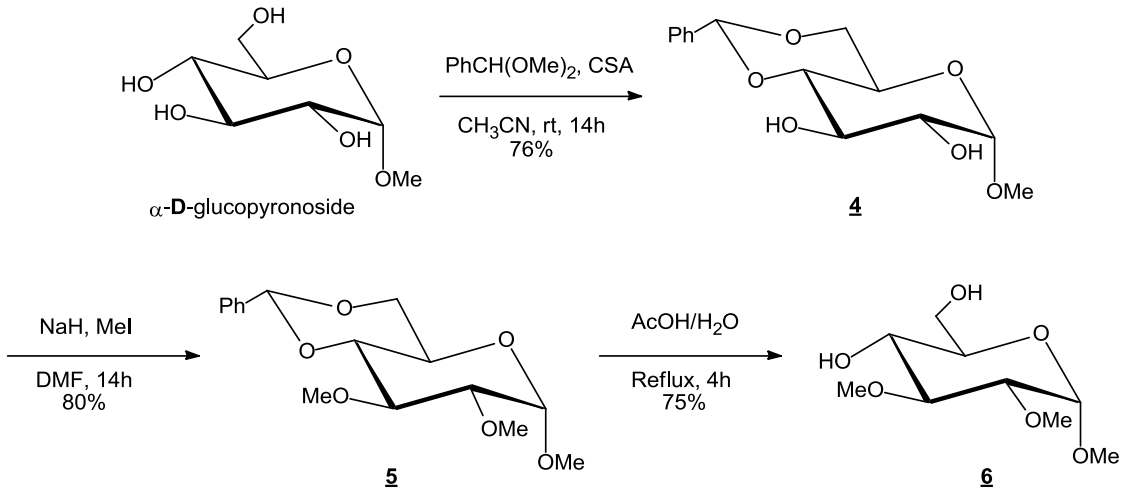
2.2.1 Synthesis of Methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (3 or Glc-1r)



Scheme 15 Glc-1r synthesis

Compound **3** (referred to as **Glc-1r** hereafter) was obtained in a three step procedure (See Scheme 15). At first, selective tritylation of *O*-6 position, then followed by benzylation of *O*-2, *O*-3 and *O*-4 positions and finally the trityl group is removed by refluxing in a mixture of acetic acid and water. The final product was confirmed by ^{1}H NMR analysis which is in agreement with the literature.

2.2.2 Synthesis of Methyl 2,3-di-O-methyl-α-D-glucopyranoside (6 or Glc-diol)

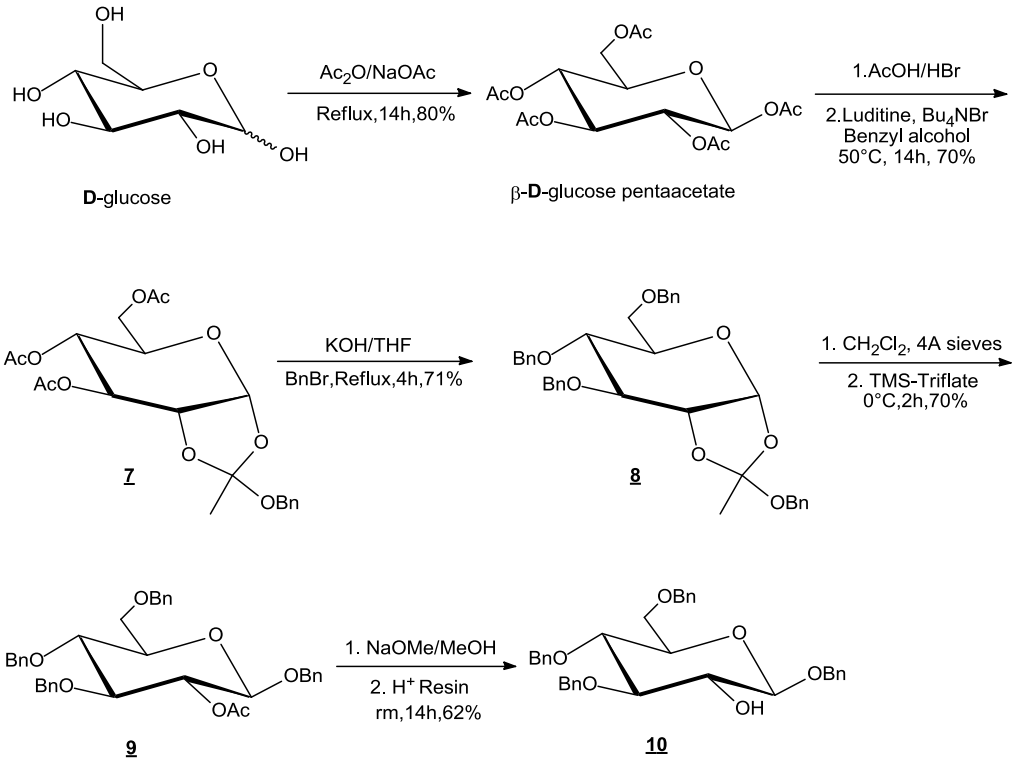


Scheme 16 Glc-diol synthesis

The diol **6** (referred to as **Glc-diol** hereafter) was obtained from α-**D**-glucopyranoside in

three steps (See Scheme 16). Positions *O*-4 and *O*-6 are initially protected under the form of benzylidene by the reaction with benzaldehyde dimethyl acetal. Then, the other hydroxyl groups were protected by methylation. Finally, the benzylidene group was removed in aqueous acidic conditions to access to the Glc-diol **6**.

2.2.3 Synthesis of Benzyl 3,4,6-tri-O-benzyl-β-D-glucopyranoside (10 or Glc-2r)



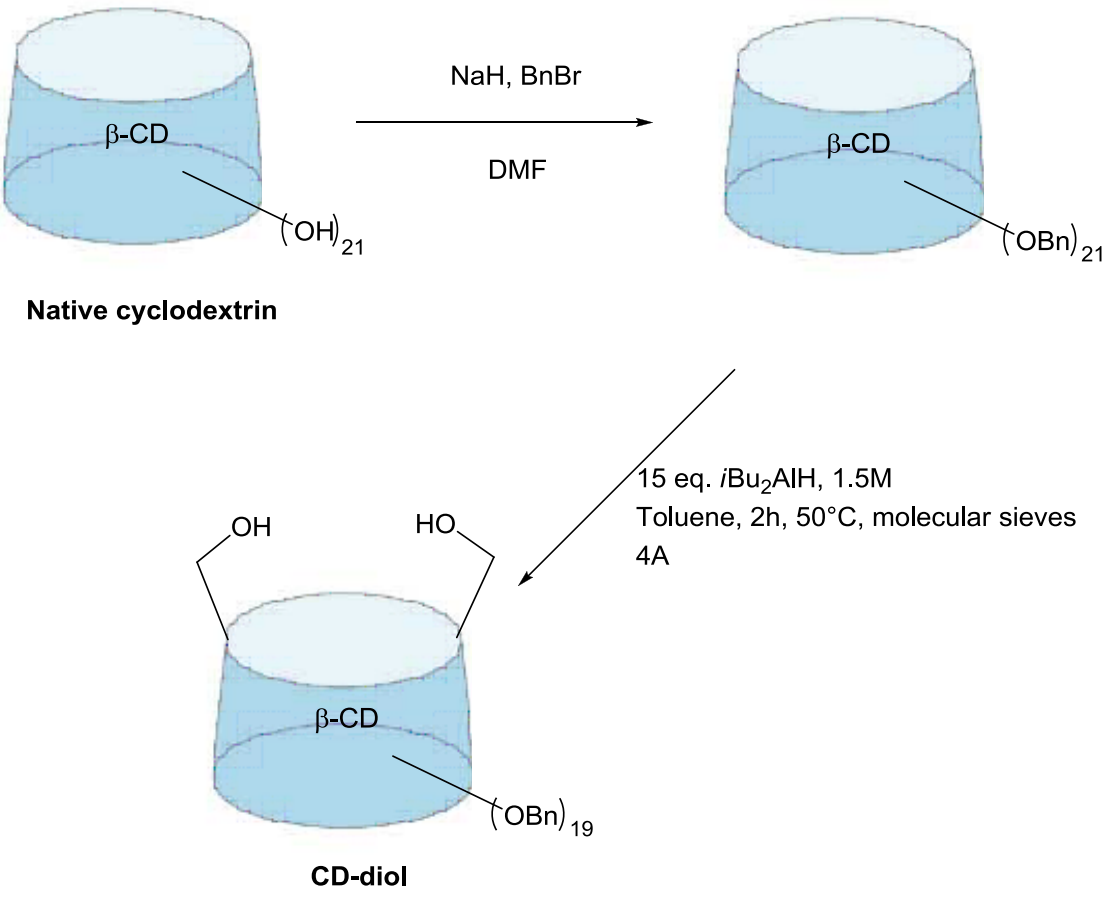
Scheme 17 Glc-2r synthesis

Compound **10** (referred to as **Glc-2r** hereafter) was synthesized in 5 steps (See Scheme 17). Commercial glucose was acetylated to give β-**D**-glucose pentaacetate. This was followed by a transesterification to produce orthoester at *O*-1 and *O*-2 positions and the other acetates were removed by reaction with potassium hydroxide. A further benzylation at the *O*-3, *O*-4 and *O*-6 allows obtaining **10**.

2.2.4 Synthesis of dihydroxyl per-O-benzyl-β-cyclodextrin (CD-diol)

The CD-diol was synthesized in 2 steps according to ref [29] (Scheme 18). Native β-

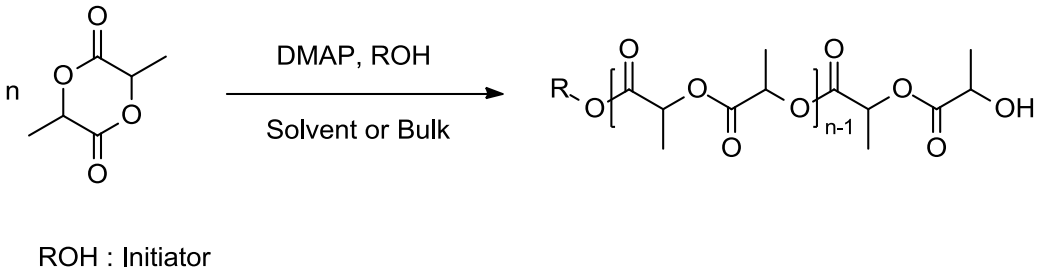
cyclodextin was totally benzyled firstly. Then, the benzyled cyclodextrin was selectively deprotected using DIBAL at 50°C for 2 hours resulting in the expected CD diol bearing two primary alcohol groups. The seven initiators were purified by co-evaporation with toluene, dried under high vacuum and then stored in the glovebox before being used for the polymerization.



Scheme 18 Synthesis of CD-diol

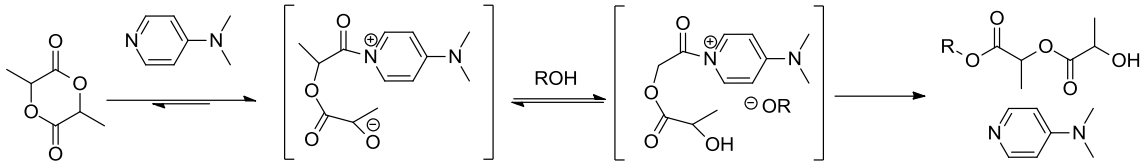
2.2.5 Synthesis of carbohydrate functionalized PLA and mechanism of DMAP catalyzed ROP of lactide

The polymerization was performed in solvent or in bulk according to Scheme 19. The mixture of lactide, DMAP and initiator were stirred magnetically for a certain time to form the functionalized polylactide.



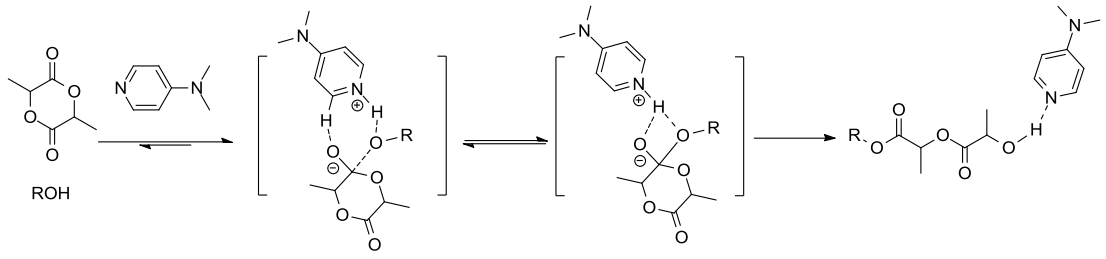
Scheme 19 Polymerization of lactide

DMAP was originally proposed to react via nucleophilic monomer activation mechanism (Scheme 20) [28, 30]. Initiation occurs when a nucleophile such as an alcohol reacts with a lactide-DMAP complex to form the mono adduct, and the α-chain end of the poly(lactide) bears an ester functionality derived from the alcohol, as in related acylation reactions. Polymerization proceeds when the terminal ω-hydroxyl group acts as a nucleophile to facilitate further chain growth.



Scheme 20 Nucleophilic mechanism

However computational studies strongly suggest that an alcohol activation mechanism (either concerted or stepwise) may be operative in the DMAP-catalyzed ROP of lactide (Scheme 21) [31].



Scheme 21 General base mechanism

Recently, Dubois *et al.* showed that both mechanisms can occur simultaneously in the course of the polymerization. are applicable to the polymerization. When DMAP/ROH ≤ 2, a

general base mechanism displays with up to 2 DMAP molecules involved. When DMAP/ROH > 2, the DMAP molecules that are not involved in the general mechanism can co-initiate the polymerization of lactide via nucleophilic mechanism [32].

2.3 DMAP catalyzed ROP of D,L-lactide and L-lactide in solvent media

The carbohydrates used as initiators for the DMAP catalyzed ring-opening polymerization of lactide have already been presented in Fig. 20 and Fig. 21. Protected glucose derivatives bearing a primary and a secondary alcohol (**Glc-1r** and **Glc-2r**) and two di-functional initiators (**Glc-diol** and **CD-diol**) were used in order to achieve link-functionalized polymers. The glucose di-functional initiator is referred to as Glc-diol, while the cyclodextrin di-functional initiator is referred to as **CD-diol**. Methyl-α-**D**-glucopyranoside, a tetra-functional commercial initiator referred to as **Glc-Me**, native β-cyclodextrin containing 21 initiating hydroxyl groups referred to as **β-CD** and native α-cyclodextrin containing 18 initiating hydroxyl groups referred to as **α-CD** were also selected for the synthesis of star PLA.

Representative results of the ring-opening polymerization of lactide initiated by **Glc-1r**, **Glc-2r**, **Glc-diol** and **CD-diol** in chlorinated solvents are presented in Table 2. **Glc-Me**, **α-CD** and **β-CD** are not soluble in these solvents, and were used as initiators in bulk polymerization as discussed in **section II.5**.

2.3.1 Determination of the conversion and molecular weight by ^{1}H NMR analysis

NMR has been used to analyze the crude product and the polymer recovered after precipitation as well. At the end of the reaction, a sample was taken and analyzed directly without any purification, which allows us to determine the conversion. Before purification, there are polymer, unreacted monomer and catalyst in the crude product. DMSO was chosen as the solvent of analysis instead of $CDCl_3$. The only reason is that when the crude product is analyzed by ^{1}H NMR in $CDCl_3$, the peaks of D,L-lactide (unreacted monomer, a) and poly(D,L-lactide) (polymer, b) are overlapped (see the ^{1}H NMR spectra in Fig. 22), from which we could not determine the conversion by integrating the peaks of unreacted monomer and polymer. However, the two peaks mentioned above are well separated in DMSO (see ^{1}H

NMR spectra in Fig. 22). Vert *et al.* also reported that the analysis which is done in DMSO results in a better resolution than that is done in $CDCl_3$ when analyzing the low molecular weight polylatide[33]. The conversion was calculated by the integration of the protons of CH groups of D,L-lactide or L-lactide (a) and the protons of CH groups of polylactide (PLA) (b) which are at δ (ppm) = 5.46 and 5.21, respectively. The conversion was calculated from the ratio CH-PLA(b)/(CH-PLA(b) + CH-lactide(a)). The degree of polymerization was calculated by the integration of the protons of CH groups of PLA(b) and the proton of CH-OH end group(b') which are at δ (ppm) = 5.21 and 4.22 ppm, respectively. The equation for the degree of polymerization is DPn = (Integration of b + integration of b')/2 (lactide is a dimer). And the number average molecular weight Mn = DPn×$M_{monomer}$(molecular weight of the lactide) + M_{ROH}(molecular weight of the initiator). For **Glc-2r**, **CD-diol** and **Glc-Me** functionalized PLA, the end group (4.22 ppm) of PLA is overlapped with the signals of the sugar and deconvolution is required in the ^{1}H NMR analysis for **Glc-2r** and **CD-diol** functionalized PLA.

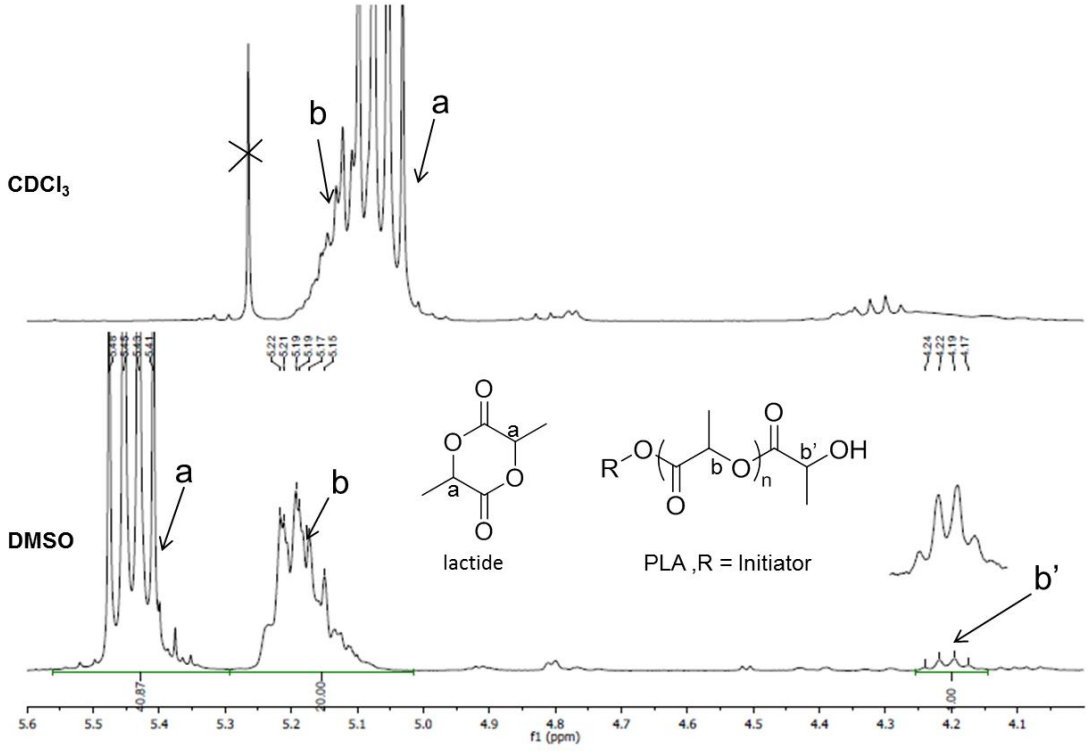


Fig. 22 ^{1}H NMR of crude product of entry 10 in $CDCl_3$ (top) and DMSO (bottom)

2.3.2 Results and discussion

We performed two blank experiments in the beginning: one without DMAP and another one without carbohydrate initiators. They both showed that the lactide ring could not be opened either by DMAP or carbohydrate initiators alone. From the results showed in Table 2, we can summarize that whatever the nature of initiators and the monomer to initiator ratio, narrow distributions are obtained, and the number-average molecular weight (Mn) measured by NMR corresponds perfectly with that calculated considering the growth of one polymeric chain per initiating hydroxyl group, as expected from the literature [28].

The reaction is quantitative using **Glc-1r** under the experimental conditions of ref. [28] for small values of monomer/ROH ratio (entries 1 and 2), but the conversion drops for higher values (entry 3). Usually for a higher targeted molecular weight, longer reaction times, higher catalyst loadings or larger monomer concentrations are needed in order to reach higher yields. In our experiment, we firstly increased the amount of catalyst (see entry 4, DMAP/ROH = 4 *vs.* 2) and the monomer concentration (see entry 5, 400 mg/ml *vs.* 200 mg/ml for a DMAP/ROH ratio of 4), which result in a better yield compared to entry 3. Similar trends are observed using **Glc-2r** as initiator (entry 8 *vs.* 7). It is noticeable that primary alcohols are more reactive toward the initiation step than secondary alcohols (entries 3 *vs.* 7), which may be attributed to steric considerations.

Logically, using a diol bearing a primary alcohol and a secondary alcohol as the initiator should result in a yield value between that obtained using an initiator bearing a primary alcohol and that obtained using an initiator bearing a secondary alcohol. In our experiment, we found that the di-functional **Glc-diol** containing both a primary and a secondary alcohol leads to intermediate yield between **Glc-1r** and **Glc-2r** (entry 10 *vs.* 3 and 7).

We also observed that the ring-opening-polymerization of L-lactide occurs faster than that of D,L-lactide under similar experimental conditions (entries 6 *vs.* 3 for **Glc-1r** and 9 *vs.* 7 for **Glc-2r**). This may be linked to the solubility of L-lactide and D,L-lactide in dichloromethane. L-lactide dissolves readily in this solvent, whereas D,L-lactide needs longer times to be dissolved.

Table 2 DMAP catalyzed ring-opening polymerization of lactide initiated by carbohydrates at 35°C in dichloromethane

Entry	Initiator	Cata./ROH	Lact/ROH	Conc.[a] mg/ml	Time (h)	Conv. (%)	DP/OH[b] calc.	DP /OH[c] NMR	DP/OH tol.[d] NMR	$Đ_M$[e]
1	**Glc-1r**	2	2	200	39	98	2	2	2	nd
2	**Glc-1r**	2	5	200	24	97	5	5	5	nd
3	**Glc-1r**	2	30	200	39	46	14	14	14	1.14
4	**Glc-1r**	4	30	200	39	68	21	21	21	1.16
5	**Glc-1r**	4	30	400	39	91	27	25	25	1.16
6[f]	**Glc-1r**	2	30	200	39	65	20	18	18	1.07
7	**Glc-2r**	2	30	200	39	19	6	6	6	nd
8	**Glc-2r**	4	30	400	39	37	11	10	10	1.20
9[f]	**Glc-2r**	2	30	200	39	32	9	9	9	1.20
10	**Glc-diol**	2	30	200	39	34	10	10	20	1.17
11	**CD-diol**	2	30	200	39	82	25	25	50	1.10
12[g]	**Glc-1r**	4	30	200	39	89	27	27	27	1.32
13[g,h]	**Glc-1r**	4	30	400	24	95	29	29	29	1.19
14[g,h]	**Glc-diol**	4	30	400	24	97	29	28	56	1.32

[a] Lactide concentration in mg/mL; [b] Number-average degree of polymerization per initiating hydroxyl group calculated considering the growth of one macromolecular chain per hydroxyl group and the yield; [c] Number-average degree of polymerization per initiating hydroxyl group measured by ^{1}H NMR; [d] Total number-average degree of polymerization measured by ^{1}H NMR; [e] dispersity measured by size exclusion chromatography ($Đ_M$ = Mw/Mn); [f] L-lactide as monomer; [g] $CHCl_3$ as solvent; [h] Temperature 50°C.

Among the different initiators used in dichloromethane, **CD-diol** leads to the highest yield (entry 11 *vs.* 3, 7 and 10). This accelerating effect on the initiating step may be attributed to supramolecular interactions between the cyclodextrin and the lactide or the catalyst molecule. Harada *et al.* [22, 23] showed in the case of lactones that the reaction takes place via inclusion of the monomer in the cavity of the cyclodextrin. The included lactone is activated by the formation of hydrogen bonds between the hydroxyl group of the cyclodextrin and its carbonyl oxygen in the initiation step. Note that the reaction was conducted without additional catalyst in this case. The formation of inclusion complex between α-aminopyridine or bipyridine and **β-CD** was also reported in the literature [34, 35]. The formation of an inclusion complex between the cyclodextrin and the lactide monomer or the DMAP may accelerate the reaction initiated by **CD-diol** *vs.* other carbohydrates by increasing the probability of meeting between the initiating primary alcohol and the lactide molecule or the catalyst. This point will be more deeply discussed for native β-cyclodextrin in the **section II.6**, when the formation of inclusion complexes between native **β-CD** and lactide/DMAP will be presented. Finally, the use of chloroform as solvent instead of dichloromethane leads to higher yields, at the detriment of the dispersity however (entry 12 *vs.* 4). The reaction can further be performed at 50 °C in this solvent, affording nearly quantitative reactions in 24 h.

2.3.3 MALDI-ToF analyses

MALDI-ToF analyses of the so-formed polylactides were further conducted. A typical example using **Glc-1r** as the initiator is presented in Fig. 23. The major distribution (▲) corresponds to n times 72 g/mol plus the molecular weight of the initiator and a silver ion ($M_{lactide}$ = 144 g/mol). The minor distribution (◆) can be assigned to n times 72 g/mol plus the molecular weight of the initiator and two silver ions. All macromolecular chains are thus **Glc-1r** end-capped. The presence of both odd and even multiple of 72 indicates that transesterification is occurring. The absence of cyclic species shows furthermore that only interchain transesterification is concerned. The MALDI-ToF analyses of the polylactides obtained using **Glc-2r**, **Glc-diol** and **CD-diol** as initiators show similarly that all polymer chains are end-capped with the carbohydrate initiator. Odd and even multiples of 72 were found on the spectra of the PLA obtained using **Glc-diol** and **CD-diol**, while only odd multiple of 144 g/mol are observed using **Glc-2r**. This indicates that transesterification does not occur starting from this latter secondary alcohol. According to Peruch and coworkers [36],

this can be related to DMAP catalyzed-depolymerization experiments of polylactide [37] where it was shown that secondary alcohols are not able to depolymerize polylactide while primary alcohol was able to depolymerize the polymer. From these findings, it was advanced that for primary alcohols, transesterification occurs during the initiation of the polymerization since the growing hydroxylterminated polylactides is a secondary alcohol that may not be able to lead to transesterification. Secondary alcohols are thus less reactive than primary alcohols for both transesterification and initiation, as the polymerization activity is higher using primary alcohols as initiators.

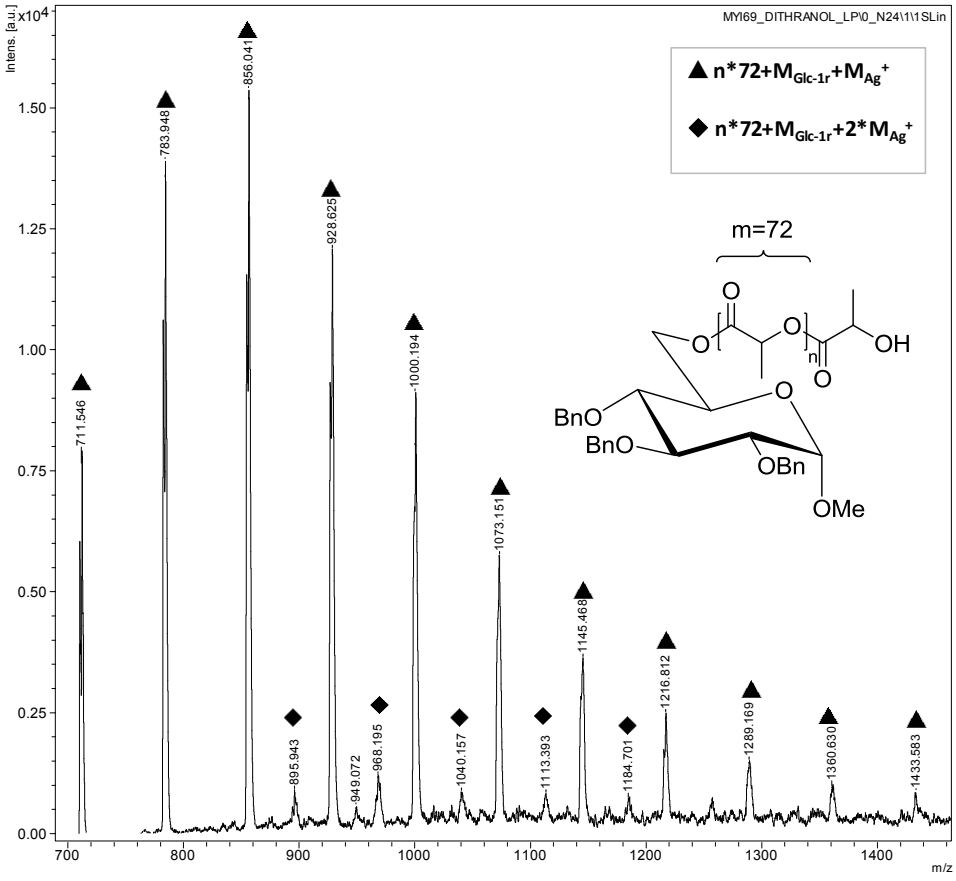


Fig. 23 MALDI-ToF spectra of entry 2

2.3.4 Confirmation of the linkage between PLA and sugar

The ^{1}H NMR of purified sugar functionalized PLA in DMSO-d_6 was furthermore studied in order to confirm that PLA is end-capped by the carbohydrate initiator. A typical example is given in Fig. 24. The spectra of the **Glc-1r** initiator and the corresponding functionalized PLA show the shift of the resonance peaks after the polymerization. Particularly, the resonance

peaks at δ = 3.42 ppm which are assigned to the protons 6 of the methylene group of **Glc-1r** disappeared and new resonance peaks in the 4.26-4.36 ppm range are found which are assigned to the protons 6 of the **Glc-1r** end-capped PLA. Unambiguous assignments of the signal were done by ^{1}H-^{1}H COSY analysis (Fig. 25). Similar analyses were performed for **Glc-2r** and **Glc-diol** and the corresponding end-capped polylactides, leading to similar findings. The spectra of **CD-diol** and the corresponding end-capped polymer did not enable to perform this kind of analysis due to the signal overlapping. The formation of **CD-diol** link functionalized PLA was thus assumed from the MALDI-ToF analysis and the good agreement between calculated and measured number average degree of polymerization. More ^{1}H NMR spectra are presented in annex.

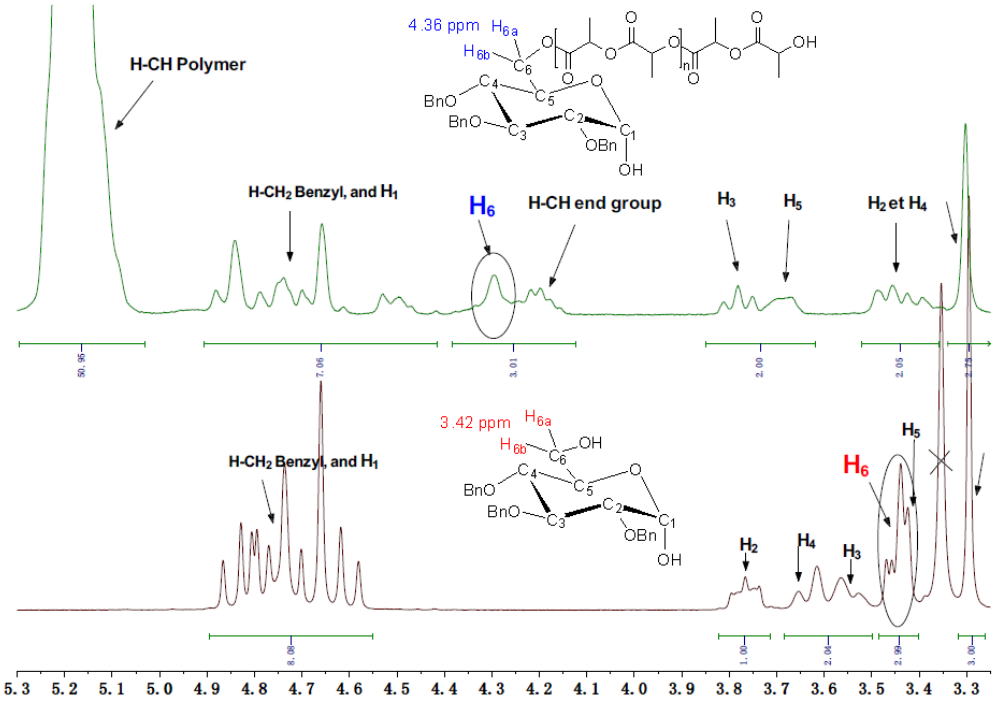


Fig. 24 ^{1}H NMR spectrum in DMSO-d_6 of Glc-1r (bottom) Glc-1r end-capped polylactide (top), entry 3

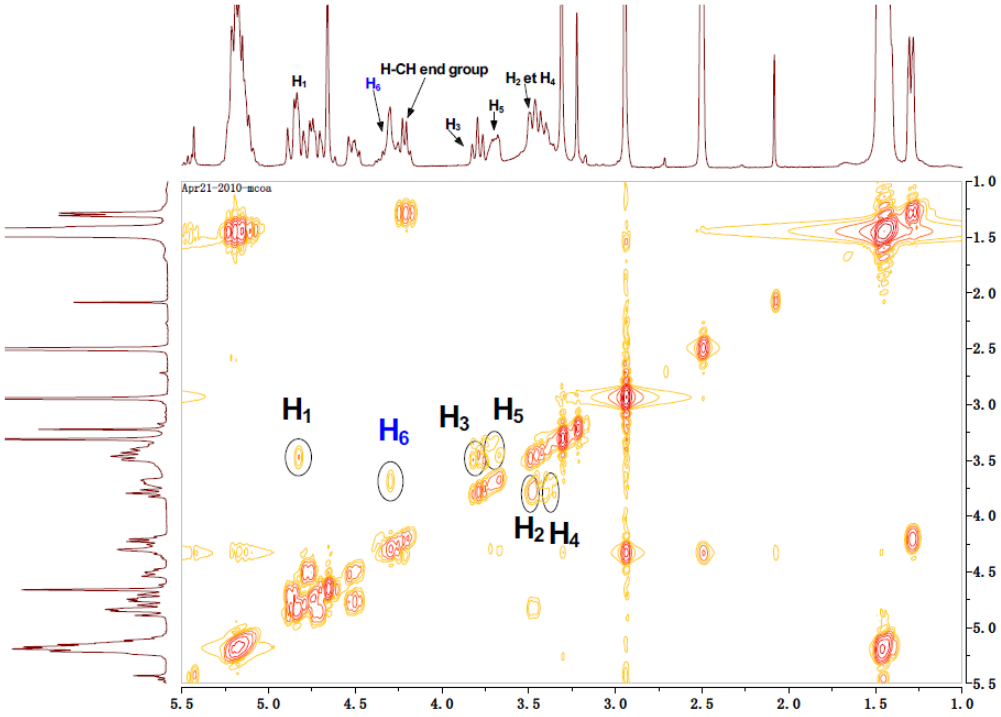


Fig. 25 ^{1}H-^{1}H COSY spectrum of a Glc-1r end-capped PLA, entry 3

2.4 Polymerization in bulk

The polymerization was further assessed in bulk at a temperature of 120°C. The results are presented in Table 3. The reactions are almost quantitative, with measured degrees of polymerization corresponding to calculated ones considering one growing chain per hydroxyl group for **Glc-1r**, **Glc-2r**, **Glc-diol**, **CD-diol** and **Glc-Me**. The dispersity is slightly higher than that obtained in chlorinated solvents. Higher degrees of polymerization per OH group can be obtained in bulk in 1 h at 120 °C (entry 16). The MALDI-ToF analyses show that in the bulk, transesterification occurs in the presence of all initiators, including secondary alcohol. This may be attributed to the higher reaction temperature (120°C *vs.* 35°C in chlorinated solvents). All PLA chains formed are end-capped by a carbohydrate derivative, highlighting a 100% functionalization efficiency in the bulk. The structure was confirmed by NMR analysis using the same procedure as discussed before for **Glc-1r**, **Glc-2r** and **Glc-diol**. The analysis could not be performed for **CD-diol and Glc-Me**, due to overlapping signals. The formation of **CD-diol** link-functionalized PLA and **Glc-Me** core star PLA with a full initiation efficiency were thus assumed from the MALDI-ToF analyses and the good agreement between calculated and measured number-average degree of polymerization.

When M/ROH ≥ 10, the initiation efficiency is 100% and CD-star PLAs were obtained.

When M/ROH<10, the initiation is not complete and some hydroxyl groups still left on cyclodextrins leading to hydrophilic PLA in one step. A comparison of ^{1}H NMR of the PLA obtained from entry 25 and **β-CD** is shown in Fig. 26, we observed that proton of OH-6 at 4.5 ppm disappeared, which indicates that this alcohol was reacted. We can also observe some **β-CD** residues. Similar results were observed when performing the polymerization with **α-CD.** The bulk polymerization enables thus the carbohydrate functionalization of PLA in shorter reaction times. It is notable that when M/ROH ≤ 10, the initiation efficiency is only partial, we obtained the **CD** functionalized PLA with unreacted hydroxyl groups in one step. Usually, these hydrophilic polymers are obtained by protection/deprotection strategies. The obtained hydrophilic **CD** functionalized PLA is not stable in water but soluble in methanol The arms initiated by primary alcohols are certainly longer than those are initiated by secondary alcohols, due to the higher reactivity of the primary alcohols. When M/ROH ≥ 50, the measured degree of polymerization does not correspond well to the calculated degree of polymerization, which may be caused by some degradation. One extra polymerization was carried out using benzyl alcohol as the initiator, lactide as the monomer and β-cyclodextrin as the catalyst instead of DMAP. The aim of this experiment is to verify if benzyl alcohol is able to initiate the ROP of lactide in presence of β-cyclodextrin which was supposed to play the role of the catalyst by forming inclusion complex with benzyl alcohol or lactide. But after 8 hours of reaction, no polymerization observed by ^{1}H NMR analysis. β-cyclodextrin is not able to catalyze of ROP of lactide by itself.

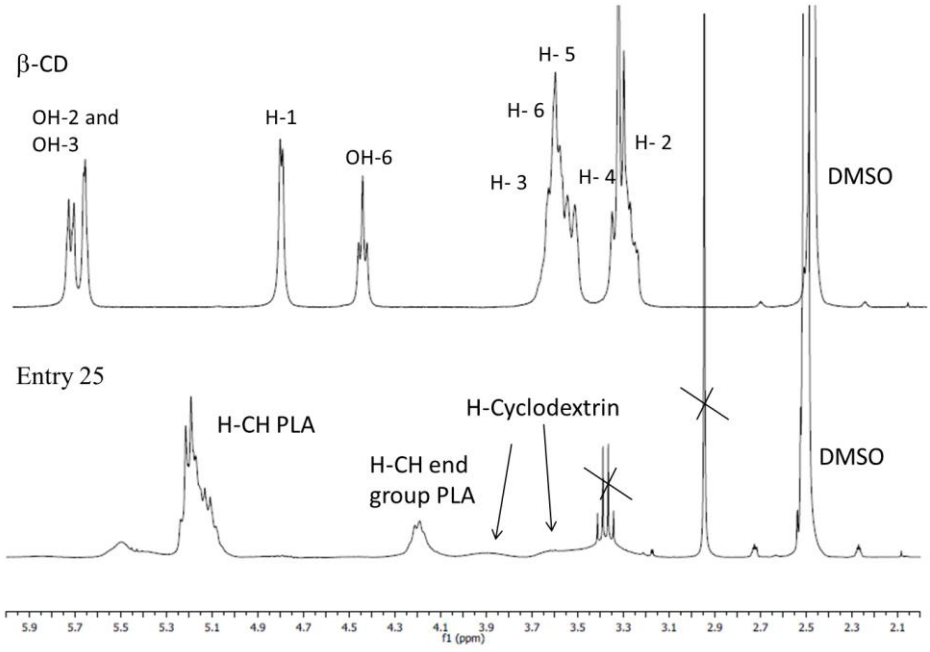


Fig. 26 ^{1}H NMR of β-CD (top) and β-CD functionalized PLA (bottom)

Table 3 DMAP catalyzed ring-opening polymerization of D,L-lactide at 120°C in bulk using carbohydrate initiators (DMAP/ROH = 2)

Entry	Init.	M/ROH	Time (min)	Conv. (%)	DP /OH[a] Cacl.	DP/OH[b] NMR	DP tot.[c] NMR	$Đ_M$[d]
15	**Glc-1r**	30	25	95	29	27	27	1.43
16	**Glc-1r**	100	60	95	95	92	92	1.48
17	**Glc-2r**	30	30	93	28	28	28	1.43
18	**Glc-diol**	30	30	61	18	16	32	1.25
19	**Glc-Me**	5	30	100	5	5	20	1.25
20	**Glc-Me**	30	120	96	29	27	92	1.40
21	**CD-diol**	30	60	92	28	26	52	1.30
22	**α-CD**	2	10	99	2	3	54	nd
23	**α-CD**	10	30	94	10	12	216	nd
24	**α-CD**	30	60	89	27	29	522	1.08
25	**β-CD**	2	10	96	2	3	63	1.10
26	**β-CD**	10	30	97	10	10	210	1.09
27	**β-CD**	20	60	96	19	19	399	1.14
28	**β-CD**	30	60	96	29	30	930	1.10
29	**β-CD**	50	90	91	45	41	860	1.05

[a] Number-average degree of polymerization per initiating hydroxyl group calculated considering the growth of one macromolecular chain per hydroxyl group
[b] Number-average degree of polymerization per initiating hydroxyl group measured by ^{1}H NMR
[c] Total number-aberage degree of polymerization measured by ^{1}H NMR
[d] Dispersity measureed by size exclusion chromatography

2.5 Formation of inclusion complexes

In order to get a better insight into the mechanism involved in the ROP initialed by **β-CD** (a clear β-cyclodextrin model is presented in Fig. 27) and catalyzed DMAP, in particular to know whether the DMAP/**β-CD** or lactide/**β-CD** inclusion complex was formed, a model study experiment using NMR analysis in D_2O (DMSO can enter into the cavity of **β-CD**) was performed using same molar equivalent of DMAP, lactide and β-cyclodextrin in collaboration with prof. Nathalie AZAROUAL, University of Lille II. The mix (1:1) DMAP/**β-CD, β-CD** by itself and the mix (1:1) lactide/ **β-CD** were analyzed by ^{1}H NMR. The three spectra are

and shown in Fig. 28. We observed that the signals of H-3 and H-5 of **β-CD** in DMAP/ **β-CD** mix shifted compared with the **β-CD** itself (see spectrum at bottom and spectrum in the middle in Fig. 28), however we did not observe any important shift of the signals of **β-CD** in lactide/ **β-CD** (top in Fig. 28). A one-dimensional selective ROESY was also used to confirm the interaction between guest molecules (DMAP and lactide) and host molecule (**β-CD**). This model experiment was performed in D_2O (DMSO can enter into the cavity of **β-CD**) using the same molar equivalent of DMAP, lactide and **β-CD**. The lactide cycle is opened in the presence of DMAP, D_2O and **β-CD**. From the spectrum of selective 1D Roesy presented in Fig. 29, we observed NOE effect on DMAP (a and c) and not with the lactide. H-3 is guided toward the cavity of the **β-CD** which indicates the formation of inclusion complex and this allows us to propose the structure represented in Fig. 30 for the inclusion. Based on these results, we conclude that the CD/DMAP complex may be preferably formed during the polymerization of lactide when using DMAP as the catalyst.

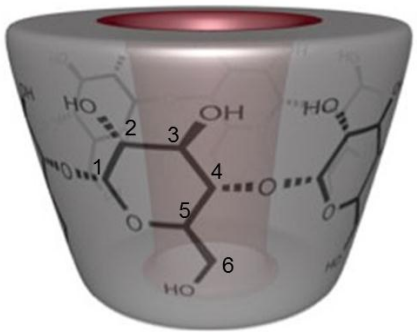


Fig. 27 β-cyclodextrin

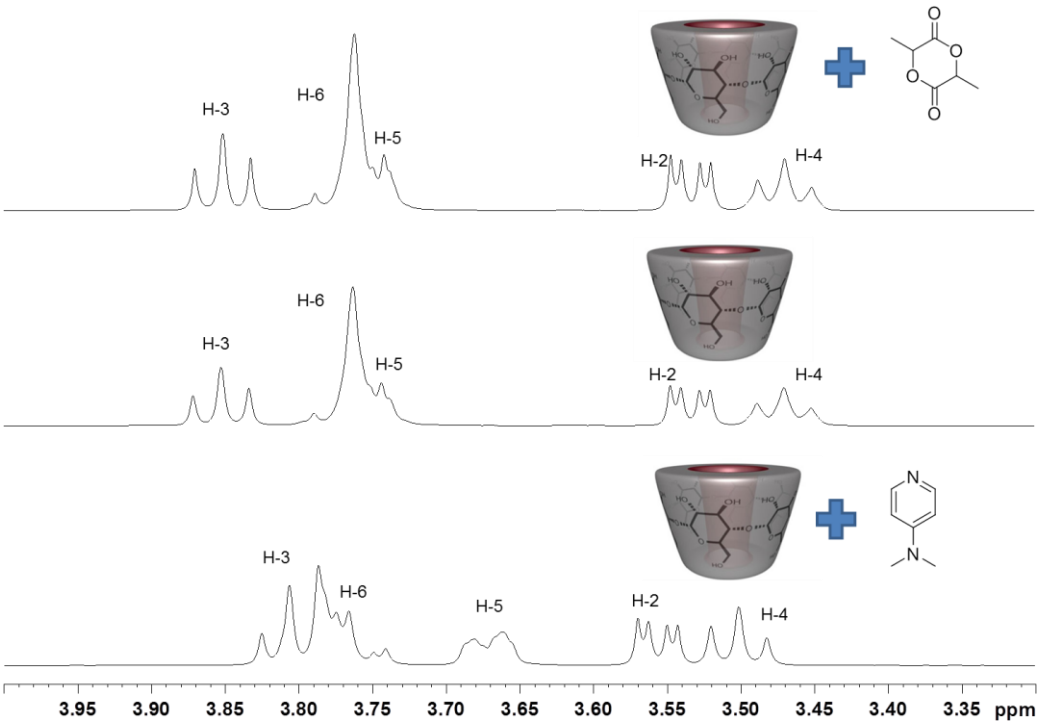


Fig. 28 ^{1}H NMR model study of mix(1:1) DMAP/**β-CD** (bottom), **β-CD** and mix (1:1) lactide/**β-CD** in D_2O

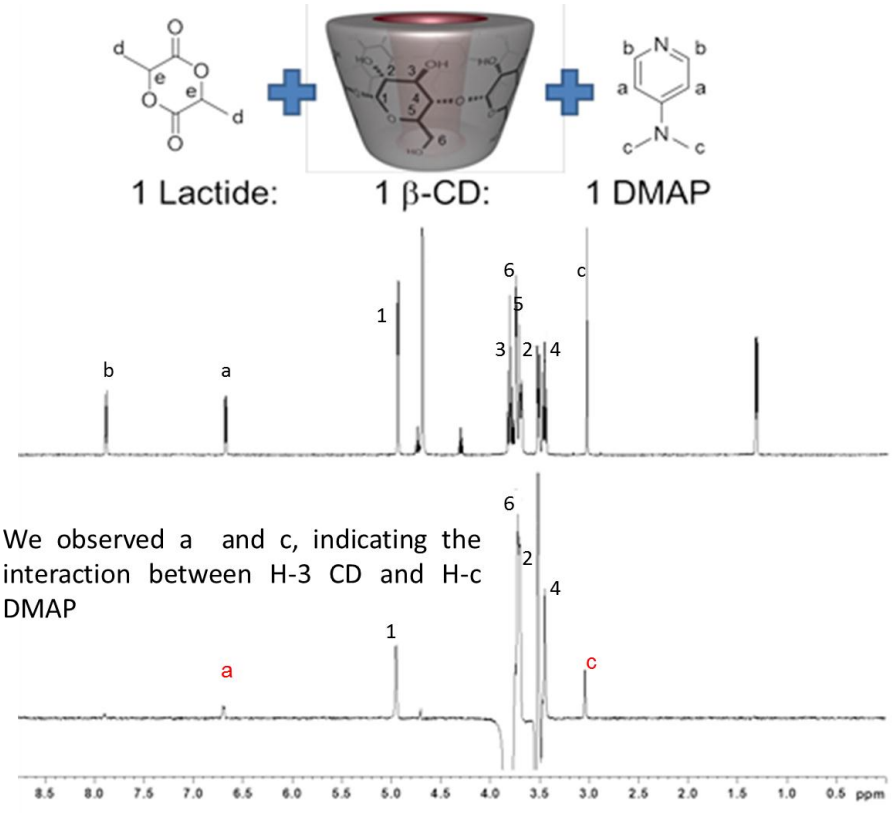


Fig. 29 ^{1}H NMR (in D_2O) of the mixture of **β-CD**, DMAP and lactide (up) vs. Selective 1D Roesy with H-3 (CD) irradiation of the mixture of **β-CD**, DMAP and lactide (bottom)

Based on the model study, we decide to synthesize the inclusion complex DMAP/**β-CD** by applying the synthetic method ever reported for other similar inclusion complexes [34, 35, 38] (Fig. 30). More synthetic details are presented in the experimental part. The ^{1}H NMR of the formed inclusion complex is presented in Fig. 31. We observed the DMAP/**β-CD** ratio is equal to 1. This inclusion complex was furthermore used as the catalyst for the ROP of lactide. The reaction was performed in bulk at 120°C using 1 eq. of inclusion complex and 630 eq. of lactide (30 eq. of lactide for each OH group of β-CD which contains 21 OH group). A conversion of 4% was observed by ^{1}H NMR analysis after 1 hour. More experiments are needed.

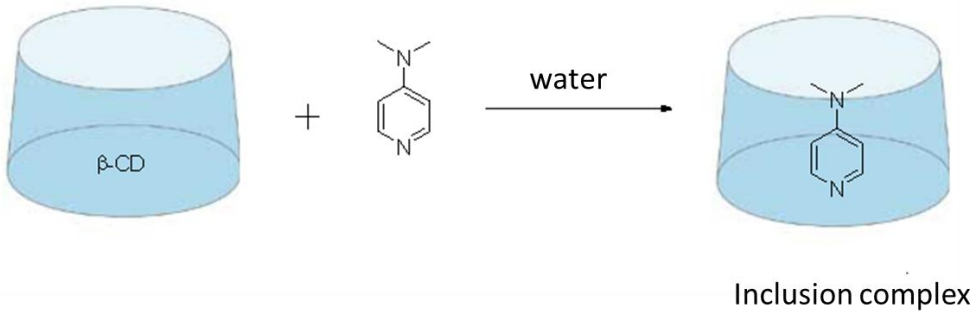


Fig. 30 Synthesis of inclusion complex β-CD/DMAP

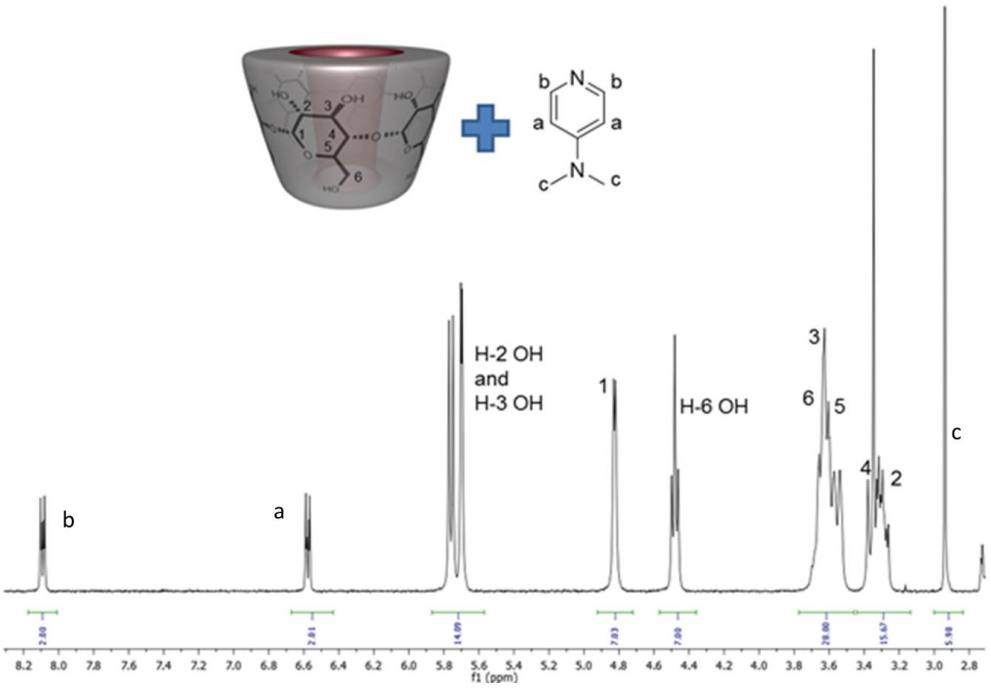


Fig. 31 1HMR of inclusion complex DMAP/**β-CD** in DMSO

2.6 DBU catalyzed ROP of D,L-lactide

DBU as a strong base (pka = 12 *vs.* DMAP : pka = 9.5) has also been tested in the ROP of D,L-lactide. The polymerization is extremely fast. The reaction was performed in the same conditions as entry 3. After 10 minutes, the conversion is nearly 100%. But MALDI-ToF analysis shows that the PLA is not 100% functionalized by the carbohydrate initiator, **Glc-1r**. A slight distribution of water initiated PLA was found. Dubois *et al* reported that DBU can also cause epimerization in the polymerization of lactide and a lot of transesterification [39]. Since using DBU as catalyst does not lead to 100% functionalization efficiency in this polymerization, we did not continue to do more experiments for the purpose of the synthesis of carbohydrate functionalized PLA.

2.7 Conclusion

DMAP is a powerful catalyst for the carbohydrate functionalization of PLA via ring-opening polymerization. The reaction can be either performed in mild conditions in chlorinated solvents or at 120 °C in the melt condition. In all cases, no side initiation occurs, leading to a 100% functionalization efficiency. Carbohydrate end-capped PLA, carbohydrate link-functionalized PLA and carbohydrate core star PLA were synthesized by an organocatalyzed reaction (Fig. 32 and Fig. 33) and should reveal some interesting potentialities for various applications. DBU as a strong base can also catalyze the ROP of lactide, the ROP is extremely fast but results in undesirable non functionalized PLA. In bulk polymerization, When M/ROH $\geq$ 10, the initiation efficiency is 100% and CD-star PLAs were obtained. When M/ROH<10, the initiation is not complete and some hydroxyl groups still left on cyclodextrins leading to hydrophilic PLA in one step. This is particularly interesting as protection/deprotection step are usually recurred for this. It should be noted Shen *et al*. obtained similar results with $y(OPh_3)_3$ and ε-caprolactone [40]. According to the model study, the interaction between the host molecule (**β-CD**) and guest molecule (DMAP or lactide) is clear and the interaction is stronger between **β-CD** and DMAP than between **β-CD** and lactide. The inclusion complex **β-CD**/DMAP was probably formed during the polymerization. We furthermore succeeded to synthesize the inclusion **β-CD**/DMAP complex by using equivalent molar ratio of **β-CD** and DMAP. This complex will be applied in catalysis in the

near future. Applications of the carbohydrate functionalized PLA will be done in collaboration with Prof. Suwabun Chirachanchai (University of Chulalongkorn, Thailand) for the test of crystallization of PLA. Dr. Andreia Valente (University of Lisbon) for tests in biomedicine, Prof. Eric Monflier (University of Lens) and Dr. Jean-Marie Raquez (University of Mons) for the application of cyclodextrin functionalized PLA in catalysis.

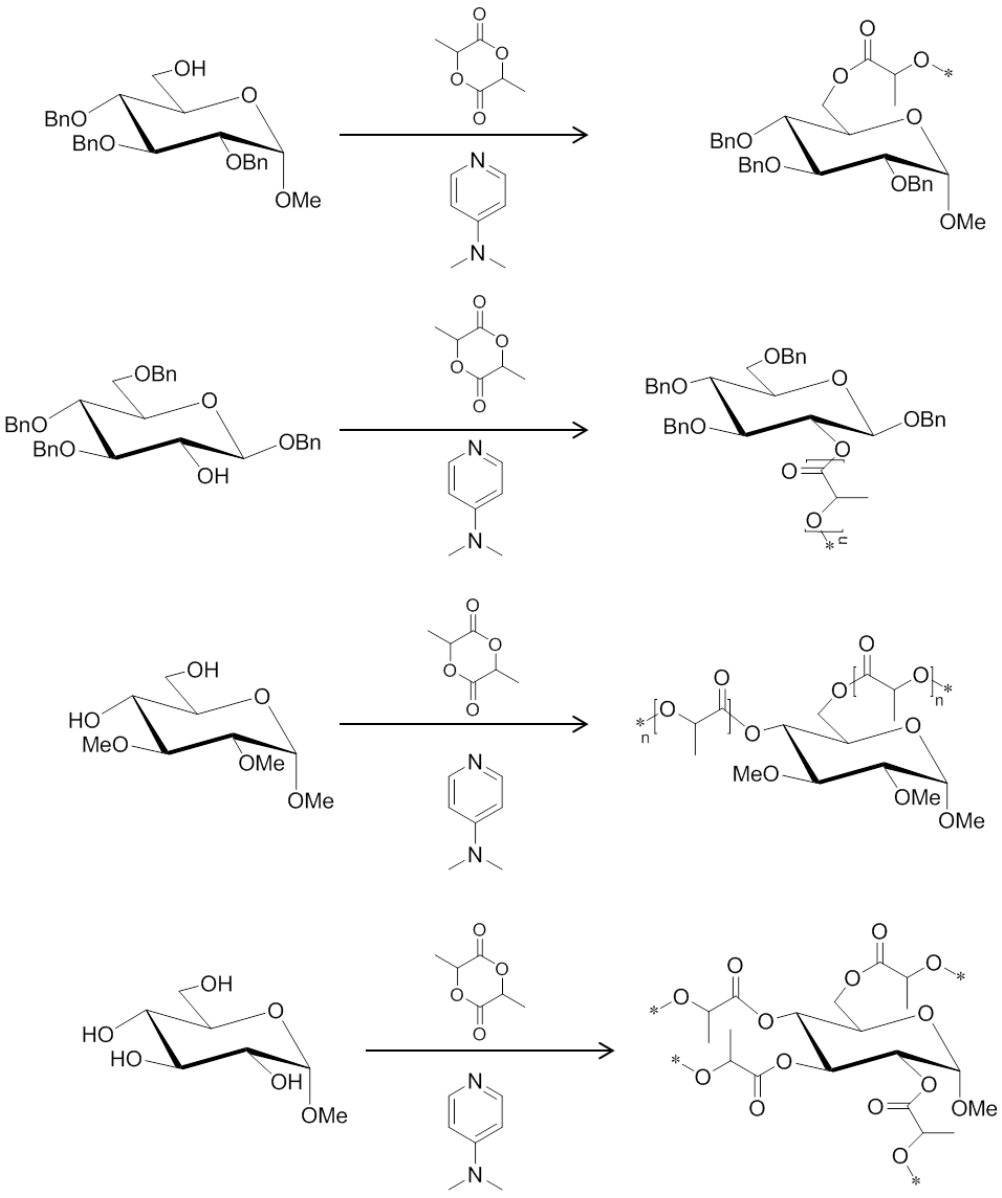


Fig. 32 Sugar functionalized PLA via organocatalytic ROP

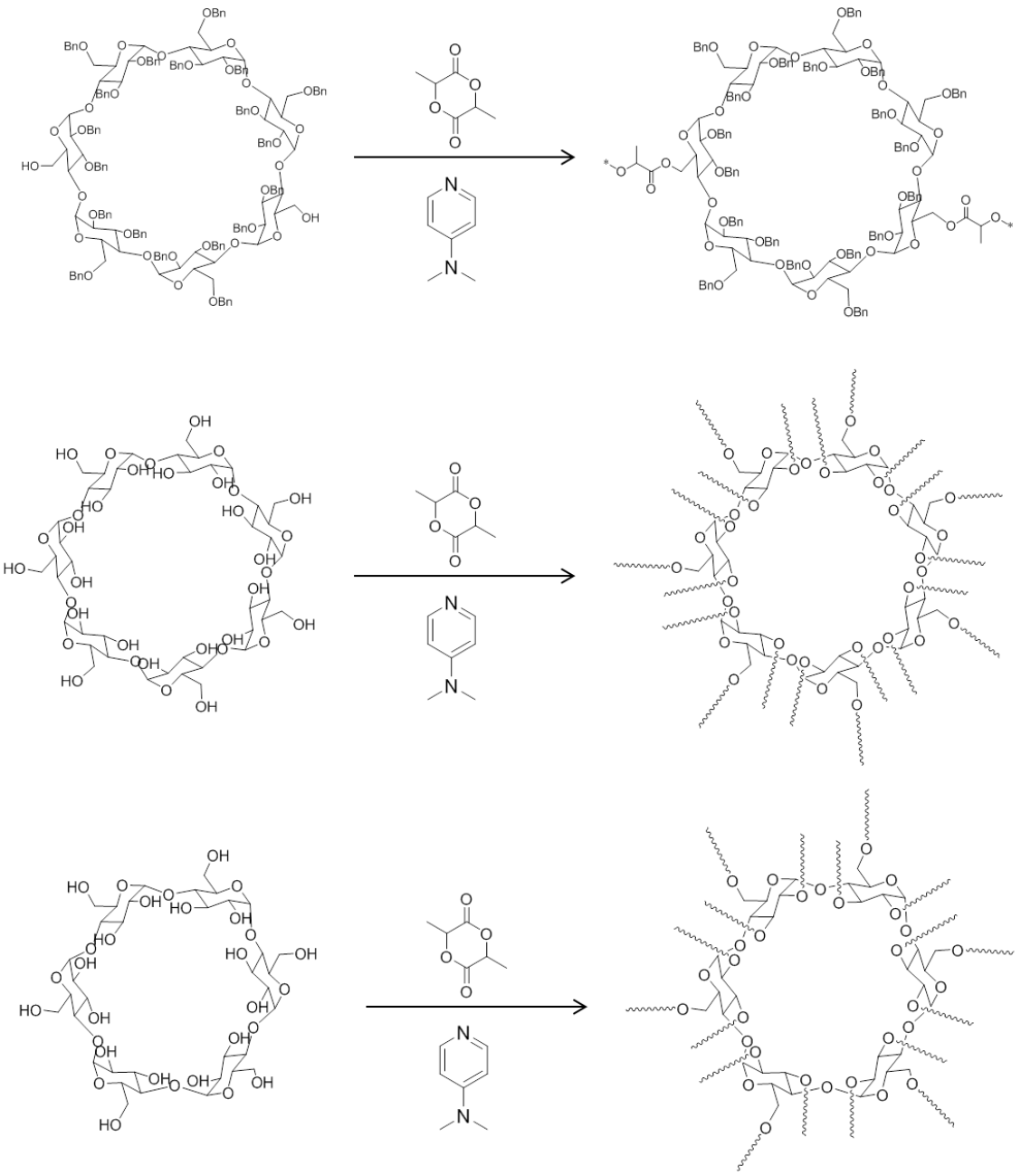


Fig. 33 Cyclodextrins functionalized PLA

2.8 Experiment part

2.8.1 Solvents and reagents

All the experiments were prepared in the glovebox. L-lactide, *rac*-lactide and DMAP were purchased from Aldrich and co-evaporated three times with toluene followed by sublimation under vacuum at 85°C before use. Chloroform was washed with water, dried with $CaCl_2$, put

under reflux with P_2O_5 and distilled. Dicholoromethane was taken from a solvent purification system (MBrau MB SPS 800). DMSO-d_6 was distilled from CaH_2 and stored in the gloves box. DBU was distilled from CaH_2 in high vacuum and stored in the glovebox. All reagents and anhydrous solvents used for the synthesis of the carbohydrate based initiators were purchased from Sigma-Aldrich and used directly without any further purification. α- and β-cyclodextrin were co-evaporated with toluene three times and then dried in high vacuum.

2.8.2 Measurements

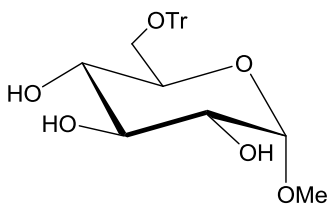
NMR spectra were recorded on a AC 300 Bruker spectrometer at room temperature in DMSO-d_6. Approximately 5 and 40 mg of sample were directly dissolved into the NMR tube in 0.6 mL of solvent for ^1H and ^{13}C NMR, respectively. The chemical shifts were calibrated using the residual resonances of the solvent.

Size exclusion chromatography was performed in THF as eluent at 40 °C using a Waters SIS HPLC-pump, a Water 2414 refractometer and Water styragel column HR3 and HR4. The calibration was done using polystyrene stardards.

MALDI-ToF-MS was performed on an Ultraflex II spectrometer (Bruker). The instrument was operated in either the reflector or linear mode. The spectra were recorded in the positive-ion mode. The samples were prepared by taking 2 μL of a THF solution of the polymer (10 mg/ml) and adding this to 16 μL of 1,8-dihydroxy-9(10H)-anthracenone (dithranol, 10 mg/mL in THF) to which 2 μL of CF_3SO_3Ag (2 mg/mL in THF) had been added. A 1 μL portion of this mixture was applied to the target and 50-100 single shot spectra were accumulated. The given masses represent the average masses of the Ag^+ adducts. The spectrometer was calibrated with an external mixture of angiotensin I, ACTH 18-39 and bovine insulin or PEG 1500.

2.8.3 Procedures

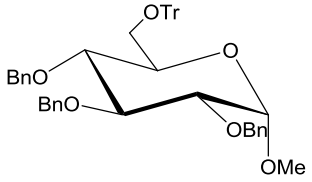
Methyl-6-*O*-trityl-α-D-glucopyranoside 1



A solution of methyl-α-**D**-glucopyranoside (6.0 g, 0.03 mol), tritylchloride (11 g, 1.2 eq.), triethylamine (8 mL), and DMAP (290 mg, 0.5 eq.) in DMF (50 ml) was stirred overnight at room temperature under nitrogen. After 12 h stirring, the reaction mixture was poured into ice-water and extracted with dichloromethane. The organic extracts were washed with water, and dried with magnesium sulfate. After removal of the solvents, the solid was recrystallized from ethanol to give 8.9 g, (66%) of compound **1** as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.32 (m, 15H, H-Aromatic), 4.76 (d, *J* = 3.8 Hz 1H, H-1), 3.98 (m, 1H, H-2), 3.37-3.58 (m, 3H, H-3, H-4 and H-5), 3.42 (s, 3H, H-OMe), 3.32 (m, 2H, H-6a and H-6b)

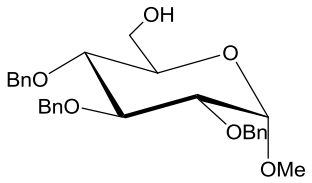
Methyl 2,3,4 tri-*O*-benzyl-6-*O*-trityl-α-D-glucopyranoside 2



A solution of **1** (8.9 g, 0.03 mol) in DMF was added at 0°C to NaH (60% in mineral oil, 3.6 g, 4.5 eq.). After 30 minutes, BnBr (10.5 mL, 4.5 eq.) was added and the reaction mixture was stirred overnight at room temperature. The reaction was then quenched with water (50 mL) and the aqueous layer was washed with ethyl acetate (4×50 mL). The organic extracts were dried with magnesium sulfate. After removal of the solvents, this residue was purified by chromatography (eluent gradient: EtOAc/Petroleum ether 1/5 to 1/3), to afford the compound **2** as a white solid (11 g, 78%).

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.77 – 6.55 (m, 30H, H-Aromatic), 5.13 – 4.58 (m, 6H, H-CH_2-Bn), 4.30 (d, *J* = 4.8 Hz, 1H, H-1), 3.99 (t, *J* = 9.3 Hz, 1H, H-2), 3.88 – 3.75 (m, 1H, H-5), 3.71 – 3.57 (m, 2H, H-6a and H-6b), 3.52 (dd, *J* = 10.0, 1.7 Hz, 1H, H-4), 3.46 (s, 3H, H-OMe), 3.21 (dd, *J* = 10.0, 4.7 Hz, 1H, H-3).

Methyl 2,3,4 tri-*O*-benzyl-α-D-glucopyranoside 3 or **Glc-1r**

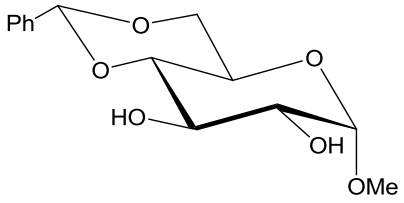


A solution of **2** (11 g, 0.015 mol), in a mixture acetic acid/water (9/1) was stirred at reflux during 5 hours. The solvent was co-evaporated with toluene and the residue was purified by chromatography (Eluent gradient: EtOAc/Petroleum ether 1/3 to 1/1), to afford the compound **3** as a white solide (4.2 g, 60%).

1H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.18-7.28 (m, 15H, CH-Aromatic), 4.48-4.94 (m, 7H, H-1 and 3×CH_2-Bn), 3.93 (t, $J_{2,3} = J_{3,4}$ 9.2 Hz, 1H, H-3), 3.56-3.71 (m, 3H, H-2, H-4 and H-5), 3.45 (m, 2H), 3.29 (s, 3H, CH_3-OMe)

$[\alpha]_D$= +5.42 (c 10, $CHCl_3$)

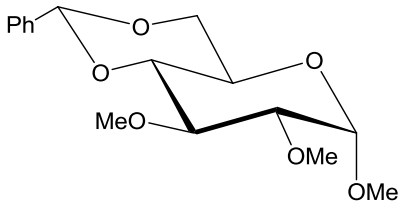
Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside 4



To a solution of methy α-**D**-glucopyranoside (2.11 g, 10.87 mmol) in dry acetonitrile (60mL) was added benzaldehyde dimethyl acetal (2.80 g, 18.40 mmol) and the solution was acidified with camphorsulfonic acid (catalytic amount). After stirring at room temperature overnight, the mixture was neutralized with triethylamine and concentrated in vacuo to dryness using toluene as a cosolvent. The resulting residue was recrystallized from ethyl acetate-hexane to afford compound **4** as a white crystalline solid.

1H NMR (300 MHz $CDCl_3$) δ (ppm) 7.33-7.48 (m, 5H, H-Aromatic), 5.49 ppm (s,1H, H-7), 4.70 ppm (d, 1H, H-1), 3.70-4.25 (m, 4H, H-3, H-5, H-6a and H-6b), 3.57 (m, 1H, H-2), 3.43 (m, 1H, H-4), 3.40 (s, 3H, H-OMe)

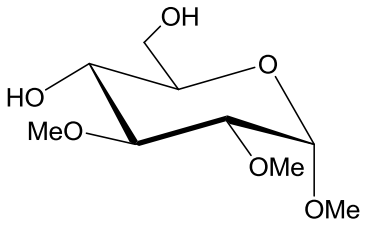
Methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-D-glucopyranoside 5



Methyl 4,6-*O*-benzylidene-α-**D**-glucopyranoside (500 mg, 1.77 mmol) was dissolved in dry DMF (20 mL) under a nitrogen atmosphere. To this was added 60% NaH suspended in oil

(260 mg, 6.6 mmol) followed by the dropwise addition of methyl iodide (340 μL, 5.46 mmol) and the reaction was left to stir for 16 h under a nitrogen atmosphere at room temperature. After this time, the reaction was quenched with water (40 mL) and the aqueous layer was washed with ethyl acetate (3 × 50mL). The combined organic layers were then washed with saturated $NaHCO_3$ and water. The combined organic layers were dried, filtred and the solvent removed in vacuo and the residue recrystallized from ethanol to furnish **5** as a white solid. (270 mg, 49%)

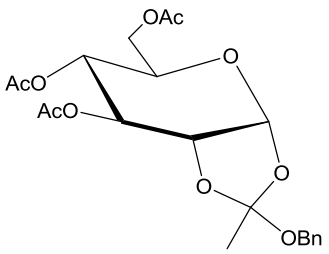
Methyl 2,3-di-*O*-methyl-α-D-glucopyranoside 6 or **Glc-diol**



To methyl 4,6-*O*-benzylidene-2,3-di-*O*-methyl-α-**D**-glucopyranoside (250 mg, 0.81 mmol) was added a solution of 80% acetic acid in water (15 mL) and the mixture was heated to 50 °C. After 4 h, the reaction mixture was cooled, concentrated in vacuum, and then co-evaporated with toluene (3 × 20 mL). The residue was recrystallized from ethyl acetate-petroleum ether to give the desired compound **6** as a white solid. (73 mg, 41%)

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.82 (d, J = 3.3 Hz, 1H, H-1), 3.82 (m, 2H, H_{6a} and H_{6b}), 3.67 – 3.36 (m, 12H, 3×H-OMe, H-2, H-3 and H-4), 3.26 – 3.15 (m, 1H, H-5).

3,4,6-Tri-*O*-acetyl-α-D-glucopyranose-1,2-(benzyl orthoacetate) 7

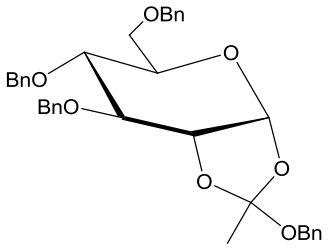


Glucose pentaacetage (5.0 g, 0.013 mol) was dissoved in a solution of HBr (33%) in acetic

acid (15 mL), after 3 h at room temperature, CH_2Cl_2 (100 mL) was added. The organic layer was washed with cold water (3 × 50 mL), and a saturated solution of $NaHCO_3$ (3 × 50 mL), then the dried with magnesium sulfate. After removal of the solvents, the residue was dissolved in lutidine (15 mL) and tetrabutylammonium bromide (1.5 g, 0.3 eq.) and benzyl alcohol (4 mL, 3 eq.) were added. After 1 night at 50 °C, CH_2Cl_2 (100 mL) was added and the organic layer was washed with a 0.5 M solution of HCl and with a saturated solution of $NaHCO_3$ (3 × 50 mL) the dried with $MgSO_4$ and concentrated in vacuum. The residue was purified by chromatography (eluent gradient: EtOAc/pentane 1/4 to 1/2), to afford the orthoester **7** (3.4 g, 70%).

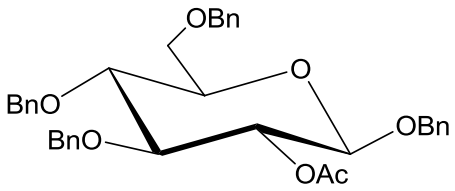
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.45 – 7.20 (m, 5H, H-Aroma), 5.24 (s, 1H, H-1), 5.08 – 4.97 (m, 2H, H-CH_2-Bn), 4.74 (d, J = 11.7 Hz, 1H, H-2), 4.61 (m, 1H, H-3), 4.50 (s, 3H, H-Me), 4.32 – 4.20 (m, 1H, H-4), 4.04 – 3.90 (m, 2H, H_{6a} and H_{6b}), 3.67 (m, 1H, H-5), 2.12 – 1.98 (m, 9H, H-3×OAc).

3,4,6-Tri-O-benzyl-α-D-glucopyranose-1,2-(benzyl orthoacetate) 8



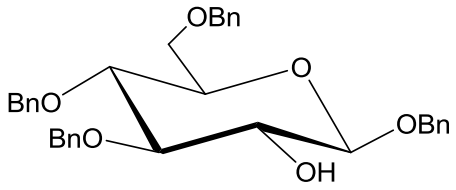
To a solution of **7** (3.4 g, 8 mmol) in THF (50 mL) was added BnCl (5.3 mL, 5eq.) and KOH (4.9 g, 10 eq.). After 3 h refluxing, the reaction was diluted with CH_2Cl_2 (50 mL) and the organic layer was washed with water (3 × 50 mL) and with a saturated solution of $NaHCO_3$ (3 × 50 mL) then dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (eluent gradient: EtOAc/Pentane 1/5 to 1/3) to afford the orthoester **8**. (3.35 g, 71%)

Benzyl 3,4,6-tri-*O*-benzyl-2-*O*-acetyl-β-D-glucopyranoside 9



To a solution of compound **8** (2.0 g, 3.4 mmol) in CH_2Cl_2 (30 mL) in presence of molecular sieves was added at 0 °C TMSOTf (80 μL, 0.8 mmol catalytic). After 2 h, the reaction mixture was washed with a saturated solution of $NaHCO_3$ (3×50 ml) and with water residue was purified by chromatography (eluent gradient: EtOAc/Pentane 1/5 to 1/3), to afford the compound **9** (1.4 g, 70%).

Benzyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside 10 or Glc-2r

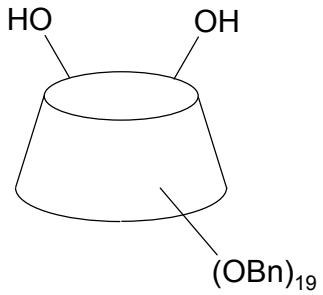


To a solution of compound **9** (1.4 g, 2.4 mmol) in MeOH (5 mL) was added MeONa. After 1 night, the reaction mixture was neutralized with H^+-resin (Amberlire IR-120). After filtration, the organic layer was concentrated in vacuum. The residue was purified by chromatography (eluent gradient: EtOAc/Pentane 1/5 to 1/3), to afford the compound **10** (0.78 g, 62%).

^{1}H NMR (300 MHz, DMSO) δ (ppm) 7.73 – 6.80 (m, 20H, H-aroma), 5.61 (d, *J* = 5.5 Hz, 1H, H-OH), 4.98 – 4.44 (m, 8H, H-CH_2-Bn), 4.38 (d, *J* = 7.7 Hz, 1H, H-1), 3.66 (dd, *J* = 10.9, 7.2 Hz, H-6a and H-6b), 3.46 (m, 3H, H-3, H-4 and H-5), 3.38 – 3.27 (m, 1H, H-2).

$[\alpha]_D$= -1.86 (c 10, $CHCl_3$)

De-O-benzylation of perbenzylated cyclodextrins



Molecular sieves (4 Å, 1 g) were added at room temperature under nitrogen to a solution of per-*O*-benzyl-b-cyclodextrin in anhydrous toluene, and the system was stirred for 1 h. After that, DIBAL was dropwise added. The reaction mixture was stirred with molecular sieves for 6 h at room temperature. The mixture was diluted with EtOAc (50 mL) and filtered, and then

washed with EtOAc (3×100 mL). The organic layer was washed with brine (2×75 mL), dried over $MgSO_4$ and filtered. Organic solvent was removed *in vacuo*. The residue was purified by chromatography (eluent gradient, EtOAc/Pentane: 1/5 to 1/2), to afford the expected diol (3.79 g, 81%) as a white foam. The NMR assignements are in agreement with those reported in ref. [29].

Inclusion complex β-cyclodextrin/DMAP

A mixture of β-CD (1 mmol) and DMAP (1 mmol) was allowed to react in aqueous solution (30 ml) with stirring at 30 °C for 5 h. The solution was slowly cooled to 0 °C, the precipitate formed was filtrated to give white powder. The crude product was recrystallized and purified from water and dried in vacuum to obtain a pure sample. Yield: 60%
^{1}H NMR (300 MHz, DMSO) δ (ppm) 8.09 (d, *J* = 5.0 Hz, 2H), 6.57 (d, *J* = 5.0 Hz, 2H), 5.76 (d, *J* = 6.8 Hz, 6H), 5.70 (d, *J* = 1.9 Hz, 6H), 4.83 (d, *J* = 3.1 Hz, 7H), 4.48 (t, *J* = 5.5 Hz, 7H, H-OH6), 3.78 – 3.45 (m, 28H), 3.43 – 3.20 (m, 21H), 2.94 (s, 6H, 2×H-Me-DMAP).

Polymerization

Polymerization in solvent

In a glovebox, lactide, initiator, DMAP and solvent (dichloromethane or chloroform) were introduced in a tube, the tube was sealed and then took out from glovebox. The reaction mixture was placed in a sand bath at 35°C for a certain time. Then, the mixture was dried in vacuum and a sample was taken for ^{1}H NMR analysis to determine the conversion. After, the dried crude product was dissolved again in a little amount of dichloromethane and then precipitated in cold diethyl ether or cold methanol. The diethyl ether or methanol solution was filtered. The solid part was then dried under vacuum to give a pure product (PLA). Diethyl ether or methanol was evaporated and dried under vacuum (unreacted monomer and catalyst). Both products were analyzed by ^{1}H NMR to determine the yield.

Polymerization in bulk

In a glovebox, lactide, initiator and DMAP were introduced in a tube, the tube was sealed and then took out from glovebox. The reaction mixture was placed in an oil bath at 120°C, all the tube body was sinked into the oil with only the lid outside. The solid was heated until melt before starting stirring. The reaction mixture was stirred for a given time (Usually, until the stirring bar stops stirring). Then a small quantity of dichloromethane was added to dissolve

the solid product, the dichloromethane solution was precipitated in cold diethyl ether, filtered or decanted to give a white power. The diethyl ether or methanol solution was filtered. The solid part was then dried under vacuum to give a pure product (PLA). Diethyl ether or methanol was evaporated and dried under vacuum (unreacted monomer and catalyst). Both products were analyzed by ^{1}H NMR to determine the yield.

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3 Polymerization of ε-caprolactone and δ-valerolactone using binaphathyl-diyl hydrogen phosphate as catalyst

3.1 Introduction

Poly(ε-caprolactone) and poly(δ-valerolactone) like other members of aliphatic ester family are biodegradable and hydrolysable synthetic polymers [1-3]. They play an important role in biomedical applications. In last chapter, we presented that DMAP as an organic base is able to catalyze the ring-opening polymerization of lactide. With the view to perform the stereoselective polymerization of *rac*-lactide, we synthesized a chiral phosphoric acid, which was unfortunately not able to catalyze the ROP of lactide (see chapter IV). In this chapter, we present the polymerization of lactone using this catalyst.

Acid is well known for their capacity to catalyze the polymerization of lactones. The polymerization of lactones can be catalyzed by a variety of acids, including carboxylic acids [4, 5], naturally occurring acids [5, 6] such as citric, lactic and tartaric acids and amino acids [5]. High catalyst loading and high temperatures are required in these latter cases, and hydroxyl acids do furthermore initiate the polymerization via the hydroxyl group in addition to their catalytic activities. This leads to poor functionalization efficiencies in the presence of a protic co-initiator. The $H_2O/HCl/Et_2O$ and the n-BuOH/HCl/Et_2O systems afford the controlled and living cationic ring-opening polymerization of ε-caprolactone and δ-valerolactone in dichloromethane in mild conditions, with substantial catalyst loadings [7, 8]. Sulfonic acids including trifluorometane sulfonic acid present also good potentialities for the controlled cationic polymerization of lactones and lactides in combination with protic co-initiators [9-16].

Phosphoric acid is an important compound which has been widely used in food and pharmaceutical industries. Recently, phosphoric acid combined with alcohol was reported as organocatalytic systems for the ring-opening polymerization of lactone. The controlled polymerization of lactones was reported using diphenyphosphate in combination with an alcochol in mild conditions in toluene [17-19]. We present in this chapter the polymerization of ε-caprolactone and δ-valerolactone using 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (BNPH) as organocatalyst. In the first part of this chapter, we will present the synthesis of the binol-based phosphoric acid as mentioned above and the general procedure of the

polymerization. Then we will study the polymerization of ε-caprolactone and δ-valerolactone using *rac*-BNPH as catalyst and benzyl alcohol as co-initiator. After, carbohydrate initiators will be used together with *rac*-BNPH, *(R)*-BNPH and *(S)*-BNPH to initiate the ring-opening polymerization of ε-caprolactone and δ-valerolactone. In the last part, we will report the BNPH catalyzed polymerization of ε-caprolactone without using any co-initiator.

3.2 Synthesis of 1,1'-binapthyl-2,2'-diyl hydrogen phosphate (BNPH)

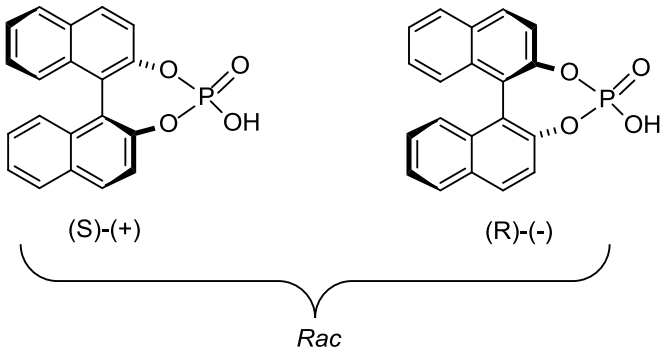
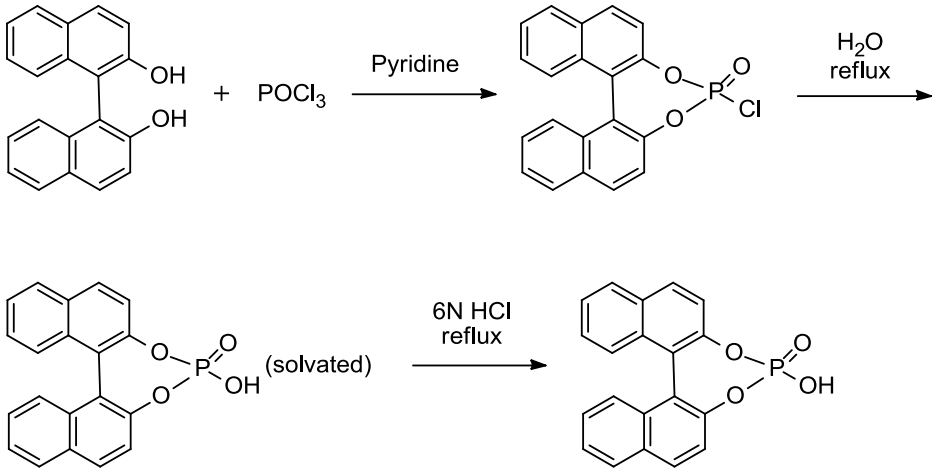


Fig. 34 *Rac*, *(S)*- and *(R)*- BNPH

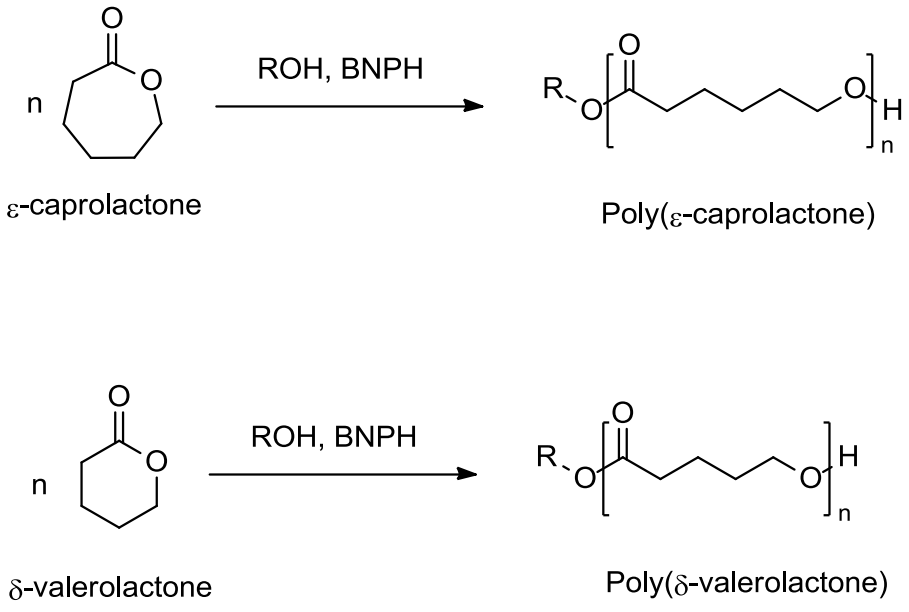
Rac-, *(R)*- and *(S)*- 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (See Fig. 34) were synthesized from the corresponding 1,1'-bi-2-naphthols (binols) in 3 steps (Scheme 22) [20]. Binol was allowed to react with phosphorus oxychloride in pyridine to give the corresponding 1,1'-binaphthyl-2,2'-diyl phosphoryl chloride. And this intermediate was hydrolyzed with water to form the pyridine-solvated binapthylphosphoric acid. The hydrolyzed crude product was acidified with hydrochloric acid to give the final product BNPH. The pure product was confirmed by ^{1}H NMR, which is in agreement with the literature [20].



Scheme 22 Synthesis of *rac*-, *(R)*- and *(S)*- BNPH

3.3 Polymerization

In a typical polymerization procedure, the protic co-initiator, when used, BNPH and the lactone were added in a flask in the glove-box. The mixture was allowed to react at a given temperature for a given time and then was quenched with triethylamine and dissolved in a small amount of dichloromethane and precipitated in methanol. The suspension was filtered. The solide was dried under vacuum at room temperature until constant weight (Scheme 23).



Scheme 23 Polymerization of ε-caprolactone and δ-valerolactone using BNPH

3.4 Polymerization of ε-caprolactone and δ-valerolactone using *rac*-BNPH and benzyl alcohol as co-initiator

Representative results of the polymerization of ε-caprolactone and δ-valerolactone using *rac*-BNPH in combination with benzyl alcohol are presented in Table 4.

Table 4 Polymerization of lactones in bulk at 60°C using 1% *rac*-BNPH in combination with benzyl alcohol

Entry	M[a]	M/OH	Time (h)	Yield (%)	Mn[b] Calc.	Mn[c] NMR	Mn[d] SEC	$Đ_M$[d]	BnO/ CH_2OH[e]
30	VL	50	10 min	85	4300	4400	4500	1.08	1.01
31	VL	50	1	96	4900	5300	4600	1.17	1.01
32	CL	50	1	99	5600	5600	6100	1.11	0.99
33	CL	100	1	80	9100	nd	10300	1.13	nd[h]
34	CL	100	4	99	11300	nd	12600	1.15	nd[h]
35[f]	CL	100	7	100	11400	nd	12200	1.14	nd[h]
36	CL	-	4	-	-	-	-	-	-
37	CL	100	4	-	-	-	-	-	-
38[g]	CL	100	4	21	2100	2800	2900	1.06	0.98
39	CL	200	4	42	9700	7000	7900	1.05	0.86
40	CL	1000	4	11	13000	7800	7400	1.05	0.51

[a] Monomer. CL = ε-caprolactone and VL = δ-valerolactone
[b] Number-average molecular weight calculated considering the growth of one macromolecular chain per OH group
[c] Number-average molecular weight determined by ^{1}H NMR
[d] Number-average molecular weight and dispersity measured by SEC calibrated with poly(styrene) standard in THF and corrected by Mark–Houwink parameters $M_{n,EXP} = M_{n,SEC} \times 0.56$ for PCL and $M_{n,EXP} = Mn_{,SEC} \times 0.57$ [21]
[e] Ratio between the signals of Ar-CH_2O-polymer (5.1 ppm) and polymer-CH_2OH (3.36 ppm) end-groups
[f] Reaction conducted at 40°C
[g] Monomer/*rac*-BNPH = 1000
[h] nd not determined by NMR due to the level of Mn

3.4.1 NMR analyses

^{1}H NMR in $CDCl_3$ is applied to calculate the molecular weight of PCL. An example is shown in Fig. 35. **a**, **b**, **c**, **d**, **e** and **f** are attributed to the different protons of the polymer chain as shown in Fig. 35. The protons of end group **g** is integrated and normalized to 1.00 and the other peaks are integrated after. The molecular weight is calculated by equation Mn = (Integ.$_{\mathbf{g}}$+Integ.$_{\mathbf{f}}$) × $M_{caprolactone}$ + $M_{BnOH.}$ (Integ.$_{\mathbf{g}}$: value of integration of the protons of the end

group **g**; Integ.$_f$: value of integration of the corresponding protons of PCL; $M_{caprolactone}$: molecular weight of ε-caprolactone; M_{BnOH} : molecular weight of benzyl alcohol) The ratio between the signal of the two protons H-CH_2 of the benzyl group (**a**) around 5.1 ppm and the signal of the two protons of the end group of the polymer chain (**g**) at 3.64 ppm is closed to 1 (see Table 4), which indicates that each polymer chain is end capped by a benzyl alcohol. The same analysis was done for polymerization of δ-valerolactone and the similar results were found.

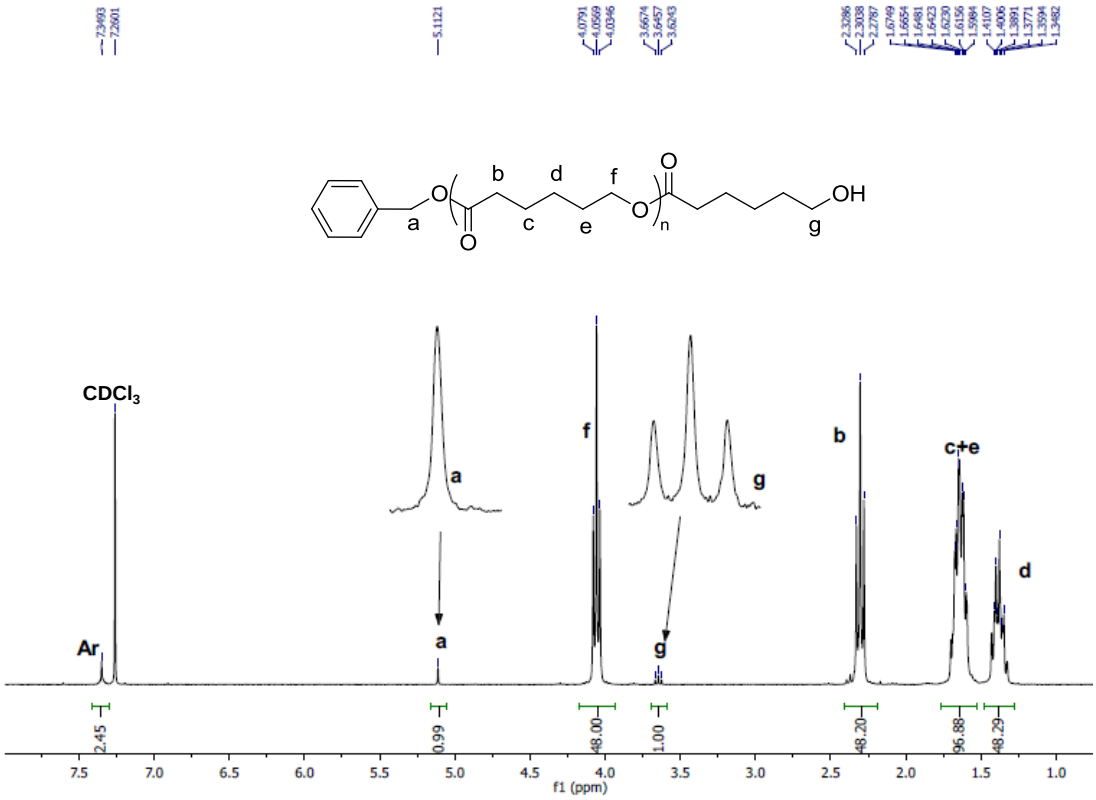


Fig. 35 ^{1}H NMR analysis of entry 32

3.4.2 MALDI-ToF analyses

As discussed in last Chapter, MALDI-ToF analyses allow us to verify the initiation of the polymerization via the presence of end groups. We used this technique to further confirm that all the polymer chains are end capped with benzyl alcohol, which has been proved by comparing the integration of protons of H-CH_2 of benzyl group (a) and the H-CH_2 of the end group (g) above. At the same time, this analysis can indicate if the intra-transesterification occurs during the polymerization. An example (entry 25) of MALDI-ToF is shown In Fig. 36.

We observed that all the peaks shown on the spectrum correspond the equation M = n×114+108+108 (n: repeating unite; 144: molecular weight of ε-caprolactone; 108: molecular weight of benzyl alcohol; 108: molecular weight of Ag^+ (107+109)/2), which reveals that all polymer chains are initiated by a benzyl alcohol and no side reactions occurred in the initiating step. The same analysis was done for the polymerization of δ-valerolactone and the similar results were found.

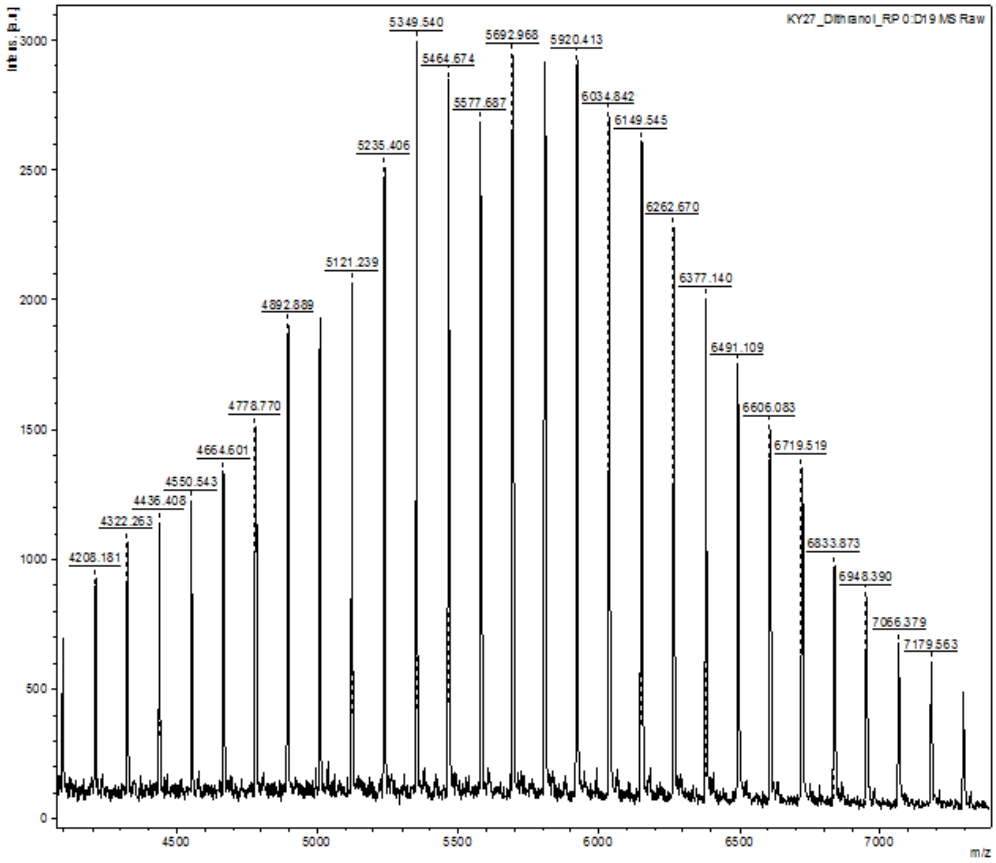


Fig. 36 MALDI-ToF analysis of entry 25

3.4.3 Results and discussion

The reaction is quantitative in several hours using 1 mol% catalyst (BNPH) and 1 to 2 mol% initiator (BnOH) at 40 and 60 °C (entries 30-35). We obtained a yield of 85 % within 10 minutes using δ-valerolactone and 2% initiator (entry 30). The polymerization activity is higher using δ-valerolatone as the monomer than using ε-caprolactone as the monomer, which is in good agreement with the literature for cationic polymerizations [22]. The calculated number-average molecular weight considering the growth of one macromolecular chain per OH group and the yield (**Mn Calc.** in Table 4) is in good agreement with the number-average

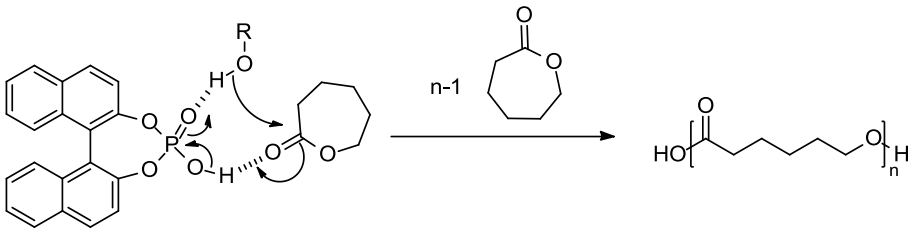
molecular weight determined by ^{1}H NMR end group analysis (Fig. 35) and by SEC. The dispersities are extremely narrow as well ($Đ_M \leq 1.17$). MALDI-ToF analyses (see Fig. 36 for a representative exemple) were performed to verify the initiation of benzyl alcohol. It is noteworthy that using *rac*-BNPH in bulk affords a controlled polymerization with 1% catalyst load, while 2 to 2.5 mol% catalyst load are required using diphenylphosphate in tolene [18, 19]. Blank reactions are performed in the presence of either the catalyst or the initiator using ε-caprolactone as the monomer, but none leads to poly(ε-caprolactone) within 4 hours under similar experimental conditions (entries 36-37).

We further studied the influence of the loading of catalyst to the polymerization. An additional experiment was performed by reducing the loading of BNPH (entry 38). The reaction was run for up to 4 hours at 60 °C. Compared with the reference experiment entry 34, entry 38 has a lower loading of catalyst and this leads to a decrease of the activity together with lower initiation efficiency. The latter was found to be around 75% from the ratio between calculated and measured number-average molecular weights for a BnOH/rac-BNPH ratio of 10.

We also tried to decrease the quantities of benzyl alcohol, which results in lower activities (entries 39-40). From the ratio between the signal of the Ar-CH_2O-polymer signal around 5.1 ppm and the polymer-CH_2-OH end-group around 3.6 ppm, a substantial fraction of the polymeric chains are not terminated by the BnO- group for a CL/BnOH ratio of 1000. The molecular weight becomes furthermore lower than the calculated one considering the growth of one polymer chain per initiating alcohol, highlighting the occurrence of side reactions. Similar trends were reported in the literature using diphenylphosphate as organocatalyst [18, 19]. The ability of the phosphoric acid to initiate the polymerization of lactone without protic co-initiator discussed later may explain the occurrence of side-initiations observed when the polymerization is conducted with high excess of *rac*-BNPH *vs.* benzyl alcohol.

3.4.4 Mechanism

Previous study of the literature on the polymerization of lactones using diphenylphosphate/alcohol combination [18, 19] concluded on an activate monomer mechanism[23]. However computational studies suggest a bi-functional mechanism with participation of both acidic proton and basic P=O moiety, analogous to that observed for sulfonic acids[19]. A similar mechanism can be proposed for BNPH, as represented in Scheme 24.



Scheme 24 Proposed activated monomer mechanism for the cationic polymerization of ε-caprolactone using 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate and benzyl alcohol

3.5 Polymerization of ε-caprolactone and δ-valerolactone using BNPH and carbohydrates as co-initiators

3.5.1 Introduction

The polymerization in bulk enables to use unprotected carbohydrates as initiators, since these compounds are not soluble in most organic solvents that are used for the ring-opening polymerization. We presented in last chapter that the use of an organic catalyst (DMAP) for the quantitative functionalization of polylactide using methy-α-**D**-glucopyranoside (**Glc-Me**) and β-cyclodextrin (**β-CD**) as ring-opening polymerization initiators [24, 25]. We reported above that the poly(ε-caprolactone) and poly(δ-valerolactone) are totally end-capped with benzyl alcohol using BNPH as catalyst. So in this section, we thought of using carbohydrates including **Glc-Me**, **Glc-1r** and **β-CD** instead of benzyl alcohol (see Fig. 37) to initiate the polymerization of ε-caprolactone and δ-valerolactone.

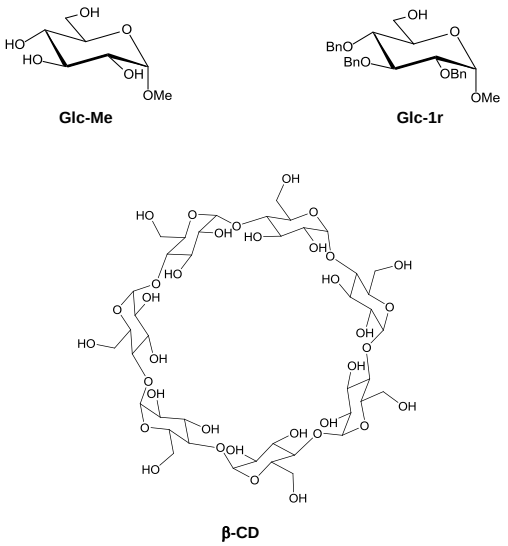


Fig. 37 Carbohydrate initiators

3.5.2 Glc-Me and Glc-1r initiated polymerization of ε-caprolactone and δ-valerolactone

Besides the *rac*-BNPH catalyst that we have used earlier for benzyl alcohol initiated polymerization of ε-caprolactone and δ-valerolactone, in this section we added the two enantiomers of *rac*-BNPH: *(R)*-BNPH and *(S)*-BNPH. The objective is to compare the reactivity of the two enantiomers. Indeed the sugars have several hydroxyl groups of different stereoconfiguration and using chiral catalysts may lead to interesting results in terms of selective initiation. The polymerization of δ-valerolactone and ε-caprolactone using *rac*-BNPH, *(R)*-BNPH and *(S)*-BNPH combined to **Glc-Me** and **Glc-1r** at 60 °C is presented in Table 5.

Table 5 Polymerization of lactones in bulk at 60°C using 1 mol% BNPH in combination with 2% carbohydrate co-initiator

Entry	Catalyst	M[a]	I.[b]	Time (min)	Yield (%)	Mn[c] per OH Calc.	Mn[d] per OH NMR	Initiation efficiency (%)	Mn[e] SEC	$Đ_M$[e]
41	*rac*-BNPH	VL	**Glc-Me**	5	27	1400	3500	40.0	4300	1.13
42	*rac*-BNPH	VL	**Glc-Me**	20	86	4300	8100	53.1	13400[f]	1.18
43	*rac*-BNPH	VL	**Glc-Me**	60	95	4800	9000	53.3	13600[f]	1.27
44	*rac*-BNPH	CL	**Glc-Me**	60	33	2100	6800	30.9	8100[f]	1.14
45	*rac*-BNPH	CL	**Glc-Me**	150	93	5300	9400	56.4	21100[f]	1.18
46	*rac*-BNPH	VL	**Glc-1r**	10	92	4600	4600	100.0	4500	1.08
47	*rac*-BNPH	CL	**Glc-1r**	60	94	5400	5600	96.4	6200	1.10
48	*(R)*-BNPH	VL	**Glc-Me**	20	85	4300	8800	48.9	11900[f]	1.19
49	*(S)*-BNPH	VL	**Glc-Me**	20	76	3800	7200	52.8	10800[f]	1.17

[a] Monomer. CL = ε-caprolactone and VL = δ-valerolactone

[b] Initiator

[c] Number-average molecular weight per OH group calculated considering the growth of one macromolecular chain per OH group (the molecular weight of the carbohydrate initiator is not considered)

[d] Number-average molecular weight per OH group determined by ^{1}H NMR (the molecular weight of the carbohydrate initiator is not considered)

[e] Number-average molecular weight and dispersity determined SEC calibrated with poly(styrene) standard in THF and corrected by Mark–Houwink parameters $M_{n,EXP} = M_{n,SEC} \times 0.56$ for PCL and $M_{n,EXP} = Mn_{,SEC} \times 0.57$ [21]

[f] Multimodal distribution or shoulder

The polymerization is quantitative after 1 h and 2.5 h for δ-valerolactone and ε-caprolactone respectively. From the value of the number-average molecular weight, the initiation efficiency (efficiency = $Mn_{cal.}/Mn_{NRM} \times 100\%$) increases with the reaction time, reaching a maximum of *ca.* 56.4 %. This leads to multimodal molecular weight distribution which can be observed by SEC analysis. For all the polymerizations of ε-caprolactone and δ-valerolactone after 20 minutes involved in using **Glc-Me** as co-initiator, a bimodal molecular weight distribution is observed by SEC analysis (entries 42, 43, 44, 45, 48 and 49), however we observed that the polymerization of δ-valerolactone after 5 minutes still keeps a monomodal molecular weight distribution (entry 41). Using **Glc-1r** bearing one primary alcohol as co-initator instead of using **Glc-Me** in this polymerization always leads to a monomodal molecular weight distribution (entries 46 and 47). Three representative SEC spectra (entries 41, 43 and 46) for the mentioned observation are presented in Fig. 38. This phenomenon may be caused by steric effect. The less hindered primary alcohol initiates the polymerization faster than secondary alcohol, as discussed in the literature for cationic polymerization[26] and highlighted by the polymerization activities in the presence of the selectively **Glc-1r** bearing only a primary alcohol. The functionalization efficiency is quantitative in case of using **Glc-1r**, and the polymerization is quantitative and well controlled ($Đ_M \leq 1.10$) in short reaction times.

The partial initiation efficiency observed using **Glc-Me** as initiator leads to hydrophilic sugar functionalized poly(δ-valerolactone) and poly(ε-caprolactone) *via* organocatalysis in one pot, as around one half of the hydroxyl groups of the sugar do not initiate the polymerization. Protection/deprotection strategies are usually applied to obtain hydrophilic carbohydrates functionalized polyesters [24, 27-31], one-step procedures are less reported. Enzymes [32, 33] and lactic acid [6] were reported as catalyst for the regioselective ring-opening polymerization of ε-caprolactone using alkyl glucopyranoside initiators. The functionalization was found to be partial in this latter case, as the hydroxyl group of lactic acid can also initiate the ring-opening polymerization. The NMR analysis of the sugar functionalized polyesters synthesized in this study reveal a mixture of different products resulting from different initiating sites and show that the initiation step is not regiospecific. The higher reactivity of primary alcohols may however suggest that a substantial part of these moieties initiates the polymerization, while secondary alcohols may initiate in a lesser extent. Polymerizations using the chiral *(R)*-BNPH and *(S)*-BNPH catalysts did not introduce a significant regioselectivity for **Glc-Me** initiated reactions, as the polymerization features and

NMR spectra were found to be similar to those observed with the racemic mixture of the two enantiomers (entries 48 and 49 *vs.* entry 42).

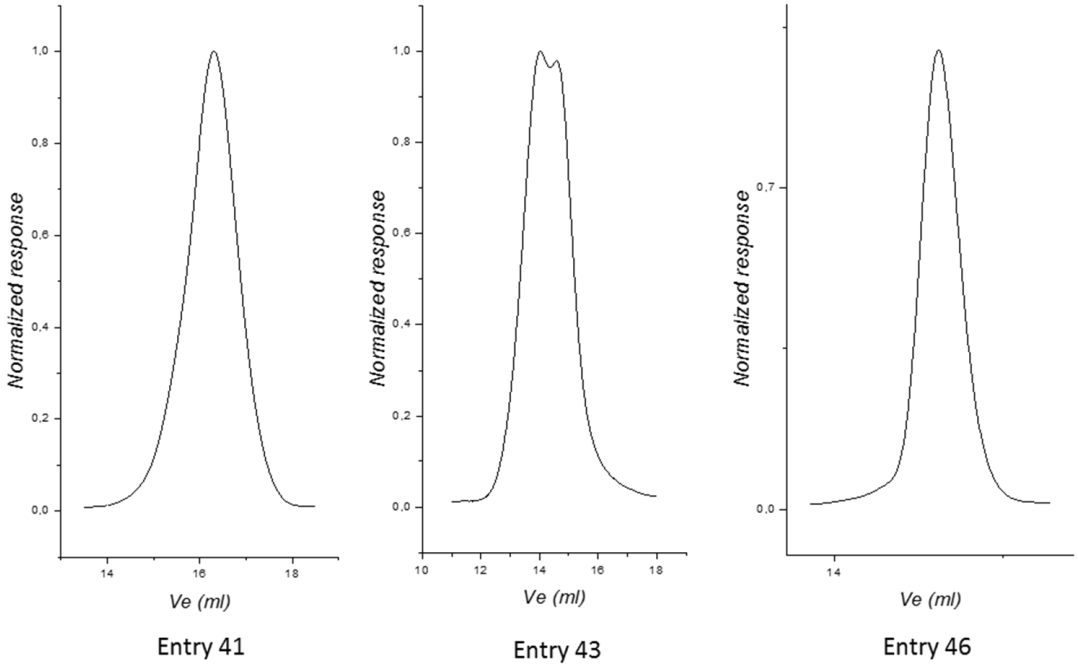


Fig. 38 SEC spectra of entries 41, 43 and 46

3.5.3 Cyclodextrin initiated polymerization of δ-valerolactone

We obtained interesting results in **chapter 2** when polymerizing lactide using cyclodextrin as the initiator and DMAP as the catalyst. Inclusion complex forms between **β-CD** and guest molecule (DMAP or lactide). According to Harada *et al.* [34, 35], **β-CD** can initiate the polymerization of ε-caprolactone and δ-valerolactone without any additional catalyst and the polymerization of δ-valerolactone leads to higher yield than the polymerization of ε-caprolactone. In this context, we decided to study the polymerization of δ-valerolactone using BNPH and **β-CD** as co-initiators. *rac*-BNPH, *(S)*-BNPH and *(R)*-BNPH were used as catalysts in order to study if the chirality of the catalyst can influence the results of the polymerization. The reactions were performed at 60°C as shown in Table 6. All the polymerizations are quantitative within 60 minutes (yield ≥ 80%). In identical conditions, the reactivity is higher using *rac*-BNPH to *(S)*-BNPH and *(R)*-BNPH catalyzed polymerization (entry 50 *vs.* entries 52 and 53). The obtained polymers were analyzed by SEC and the spectra are presented in Fig. 39. The bimodal molecular weights distributions obtained with *(R)*-

BNPH and *(S)*-BNPH are similar, but higher than those obtained using *rac*-BNPH. The high molecular weight distribution becomes less important using the pure enantiomers. As expected, an increase in catalyst and monomer loading using rac-BNPH leads to an increase of the M_n of each distribution (entry 51 *vs.* 50). More experiments are needed in order to evaluate the trends observed.

Table 6 Polymerization of δ-valerolactone in bulk at 60°C using BNPH and **β-CD** as co-initiators

Entry	Catalyst	Cata./OH[a]	M/OH[b]	Time (min)	Yield
50	*rac*-BNPH	0.5	50	30	97%
51	*rac*-BNPH	1	100	60	87%
52	*(S)*-BNPH	0.5	50	60	80%
53	*(R)*-BNPH	0.5	50	60	83%

[a] Ratio of catalyst to per OH group
[b] Ratio of monomer per OH group
[c] Number-average molecular weight per OH group calculated considering the growth of one macromolecular chain per OH group (the molecular weight of the carbohydrate initiator is not considered)
[d] Number-average molecular weight per OH group determined by ^{1}H NMR (the molecular weight of the carbohydrate initiator is not considered)
[e] Number-average molecular weight and dispersity determined by SEC

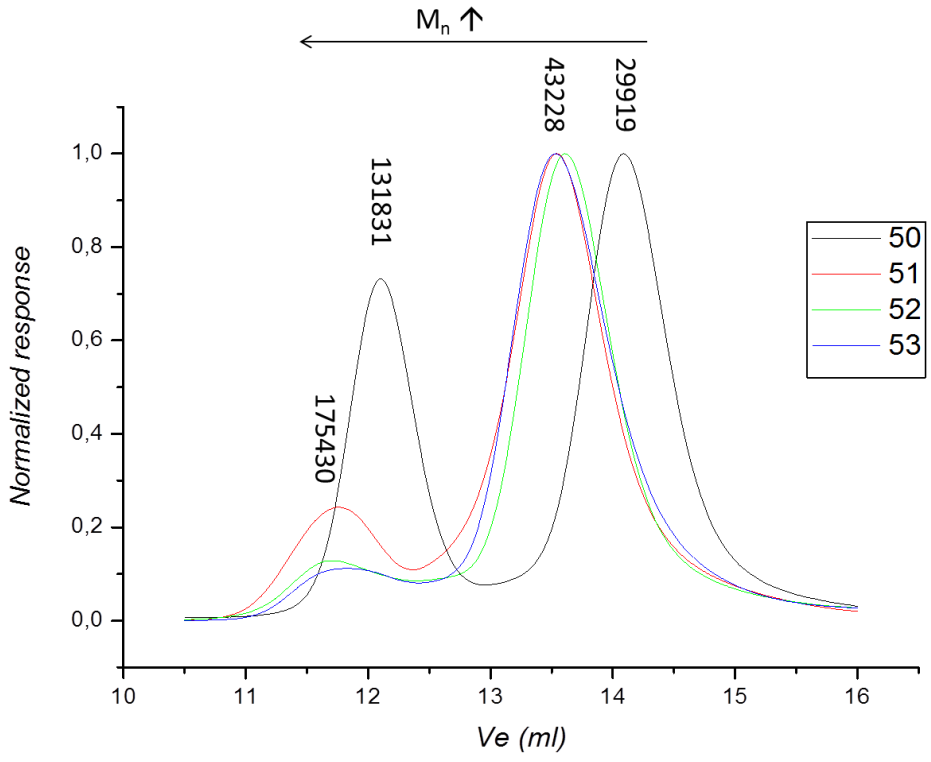


Fig. 39 Overlapped SEC spectra of entries 50, 51, 52 and 53

3.6 Polymerization of ε-caprolactone using rac-BNPH as single catalyst

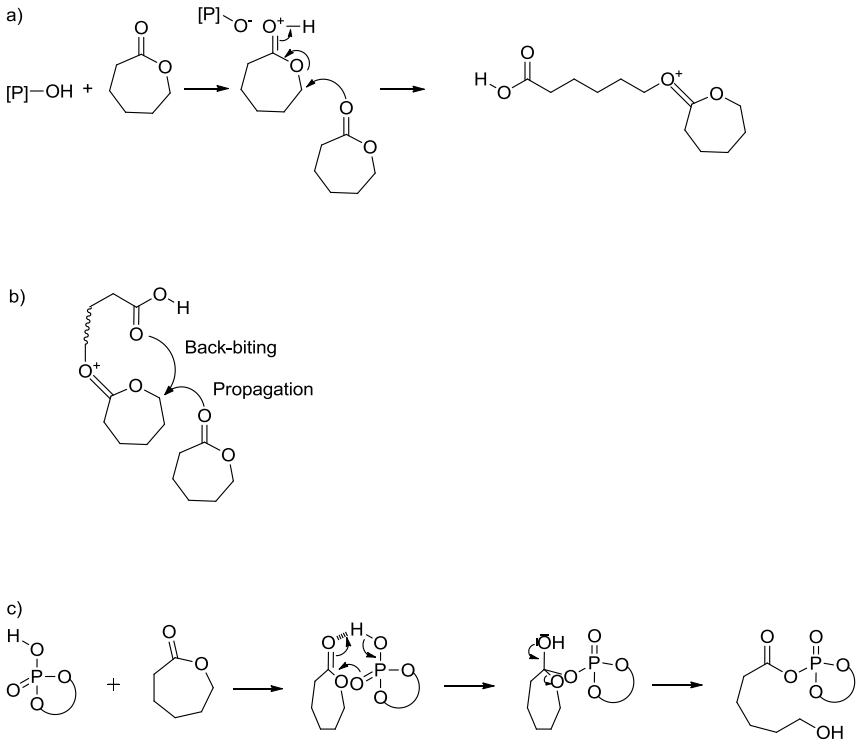
We further performed the polymerization of ε-caprolactone in the presence of *rac*-BNPH as a single catalyst at a temperature of 100°C. Representative results are given in Table 7 Quantitative yields are obtained in one to four hours for the ratio monomer to *rac*-BNPH up to 100 (entries 54,55 and 56), while the activity drops down for higher ratio (entry 57). The dispersity is relative large (around 1.7 to 1.8) using BNPH as single catalyst compared with polymerization using BnOH or carbohydrate compounds as co-initiators ($Đ_M \leq 1.27$). The PCL obtained has a larger number-average molecular weights than the PCL obtain in the presence of an alcohol as initiator. The MALDI-ToF analysis of a typical sample shows the presence of linear polymer and cyclic species as well, the latter being less important than the former. The presence of cyclic oligomers may result in the frame of a cationic polymerization form an active chain end mechanism [23, 36-40] (see a in Scheme 25). The cyclic oligomers are formend by back-biting or end-to-end biting reactions (see b in Scheme 25).

We detected furthermore weak signals around 3.65 ppm that may correspond to the protons of $–CH_2OH$ moieties when performing ^1H NMR analysis of the reactive medium before quench, when in fact these groups should not be observed in the frame of a pure active chain end mechanism. An activated monomer mechanism may thus operate simultaneously starting from the species represented in (c in Scheme 25). This would also explain the relatively high molecular weight obtained at 100°C in the presence of *rac*-BNPH as single catalyst, since polymerization operating via an active chain end mechanism is well known to lead to low number-average molecular weight[36]. The ability of the phosphoric acid to initiate the polymerization without protic co-initiator may explain why the polymerization was not controlled when using BNPH in excess *vs.* BnOH (entries 39 and 40).

Table 7 Polymerization of ε-caprolactone at 100°C in bulk using *rac*-BNPH as catalyst

Entry	CL/BNPH	Time (h)	Yield (%)	Mn[a] SEC	$Đ_M$
54	20	1	97	9300	1.83
55	50	1	78	14700	1.84
56	100	4	94	19000	1.71
57	200	8	31	17800	1.77

[a] Number-average molecular weight and dispersity determined by SEC



Scheme 25 Proposed initiation steps for the polymerization of ε-caprolactone in the presence of a phosphoric acid as a single catalyst considering a) an activated chain end mechanism and c) an activated monomer mechanism. b) shows the competition between propagation and back-biting in the course of the active chain end mechanism. The back-biting reaction leads to cyclic macromolecules. ∿∿ represents poly(ε-caprolactone).

3.7 Conclusion

The BNPH phosphoric acid is an efficient catalyst for the ring-opening polymerization of lactones in bulk. In combination with benzyl alcohol, the polymerization is quantitative and controlled in mild conditions, with dispersities around 1.05-1.17. Using carbohydrates mono- and poly-ols as the initiators leads to different results: when using carbohydrate mono-ol as the initiator, the polymerization is quantitative and well controlled with narrow dispersities (≤1.10); when using poly-ols as initiators, only partial initiation efficiency was observed leading to hydrophilic carbohydrate functionalized poly(ε-caprolactone) and poly(δ-valerolactone) by one-pot reaction. Multimodal distributions were obtained for the **β-CD** initiated polymerization of δ-valerolactone using BNPH as the catalyst. Using BNPH as a single catalyst for catalyze the polymerization of ε-caprolactone at higher temperature affords also the formation polycaprolactone in high yield, with dispersities around 1.7-1.8. The results reported in this work extend the range of applications of phosphoric acids as catalysts for the

ring-opening polymerization of lactones and their functionalization using carbohydrate derivatives.

3.8 Experimental part

3.8.1 Solvents and reagents

All the polymerizations were prepared in the glovebox. ε-caprolactone, δ-valerolactone, DMSO-d_6, pyridine and benzyl alcohol were distilled from CaH_2. β-cyclodextrin (**β-CD**) and methyl-α-**D**-glucopyranoside (**Glc-Me**) were co-evaporated with toluene three times and then dried in high vacuum. Methyl 2,3,4 tri-*O*-benzyl-α-**D**-glucopyranoside (**Glc-1r**) was synthesized from **Chapter II**. Other reagents and solvents were purchased from Sigma-Aldrich and used directly without any further purification.

3.8.2 Measurements

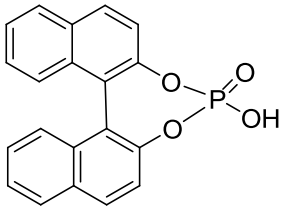
NMR spectra were recorded on a AC 300 Bruker spectrometer at room temperature in $CDCl_3$. Approximately 5 mg of polymer was dissolved into the NMR tube in 0.6 mL of solvent for ^1H NMR analysis. The chemical shifts were calibrated using the residual resonances of the solvent.

Size exclusion chromatography was performed in THF as eluent at 40 °C using a Waters SIS HPLC-pump, a Water 2414 refractometer and Water styragel column HR3 and HR4. The calibration was done using polystyrene stardards.

MALDI-ToF-MS was performed on an Ultraflex II spectrometer (Bruker). The instrument was operated in either the reflector or linear mode. The spectra were recorded in the positive-ion mode. The samples were prepared by taking 2 μL of a THF solution of the polymer (10 mg/ml) and adding this to 16 μL of 1,8-dihydroxy-9(10H)-anthracenone (dithranol, 10 mg/mL in THF) to which 2 μL of CF_3SO_3Ag (2 mg/mL in THF) had been added. A 1 μL portion of this mixture was applied to the target and 50-100 single shot spectra were accumulated. The given masses represent the average masses of the Ag^+ adducts. The spectrometer was calibrated with an external mixture of angiotensin I, ACTH 18-39 and bovine insulin or PEG 1500.

3.8.3 Procedures

(±)-1,1'-binaphthyl-2,2'-dily hydrogen phosphate (*rac*-BNPH)



A 50 mL schlenk is charged with 9 ml of pyridine and, while stirring, with 2 g (7 mmol) of (±)-1,1'-bi-2-naphthol (*rac*-binol). To this stirred suspension, 1.47 g (9.6 mmol) of phosphorus oxychloride is added dropwise, whereupon the temperature rises to about 80°C, most of the binaphthol dissolves, and pyridine hydrochloride crystals form. Complete dissolution is achieved by heating to 90°C. The stirred solution is allowed to cool to 50-60°C (crystallization occurs at about 85°C). To the stirred suspension, 8 mL of water is added dropwise (*Caution! Exothermic reaction!*), which raises the temperature to the boiling point. The resulting solution, cooled to about 60°C, is transferred to a 20 mL syringe and the schlenk is rinsed with 2 mL of pyridine. The solution and rinse are combined and added dropwise (with the syringe) with vigorous stirring to 20 ml of 6 M hydrochloric acid, which gives a precipitate of pyridine-solvated binaphthylphosphoric (BNP) acid. This crude product is collected by suction filtration. The wet cake is transferred to a 100 mL beaker and stirred with 6 mL of 6 M hydrochloric acid. The suspension is heated to boiling and immediately cooled. The solid is thoroughly filtered by suction, washed twice with 1 mL of water. The white product is air-dried and then dried in the oven over night to form a white powder.

Yield = 85%

1H NMR (300 MHz, DMSO-d_6) δ (ppm) : 8.17 (d, 2H), 8.07 (d, 2H), 7.52 (m, 4H), 7.36 (m, 2H), 7.24 (d, 2H)

The same procedure was applied to synthesize (R)-BNPH and (S)-BNPH (yields: 80% and 79%, respectively)

Polymerization procedures

In a glovebox, initiator (BnOH or carbohydrate based initiators) if used, BNPH (*rac*-BNPH, *(S)*-BNPH or *(R)*-BNPH), monomer (ε-caprolactone or δ-valerolactone) were introduced in a

tube, the tube was sealed and then took out from glovebox. The reaction mixture was placed in a sand bath at a set temperature (40, 60 or 100 °C) for a certain time (when the reaction mixture solidified). And then a small amount of triethylamine with 1 to 2 ml dichloromethane was added to quench the reaction. This solution was dried under vacuum, a crude sample was taken and analyzed by ^{1}H NMR to determine the conversion. Then crude product was dissolved in a small amount of dichloromethane and then precipitated in cold methanol. The suspension was then filtrated and the white solid product was dried under vacuum until the weight is stable. The pure product was weighted to calculate the yield. The purified polymer was analyzed by ^{1}H NMR analysis to determine the molecular weight.

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4 Organocatalyzed Polymerization of *rac*-lactide using and study of the microstructure of polylactide

4.1 Introduction

During the 20th century, stereoselective catalysis in organic synthesis and polymerization was dominated by two classes of compounds: organometallic catalysts and enzymes. In organometallic catalysis, a chiral organic ligand forms a complex with a metal center, this kind of complex can be used to catalyze a wide range of asymmetric organic reactions such as hydrogenation, aldol reactions and Diels-Alder reactions [1, 2] and also stereoselective polymerizations [3, 4]. Despite the extreme efficiency of organometallic catalysis in organic and polymeric synthesis, the high cost and toxicity made metal free alternatives an attractive goal. Enzymatic catalysis was one solution to this point. Due to the high degree of stereospecificity of enzyme catalysis, it is able to catalyze reactions with a high enantioselectivity or regioselectivity [5]. Though enzymes avoid the problem of toxicity, the high cost comparative with organometallic catalysis makes them prohibitive for common use. In this context, we became aware of the interest of organic catalysts.

We have already mentioned in **Chapter 1** that only a few organocatalysis including carbenes [6], phosphazene base [7] and cinchona alkaloids [8] have been reported as catalysts for the ring-opening polymerization of *rac*-lactide resulting in isotactic enriched PLA. More organocatalysts leading to a sterroselective polymerization are required to meet our needs for biomaterials and biodegradable plastics. In this chapter, we report the use of chiral acids and their combination with various bases as catalysts for the role of *rac*-lactide.

In the first part, we will present polymerization of *rac*-lactide using DMAP and DBU as catalysts, the calculation of the probability of *meso* enchainment will be

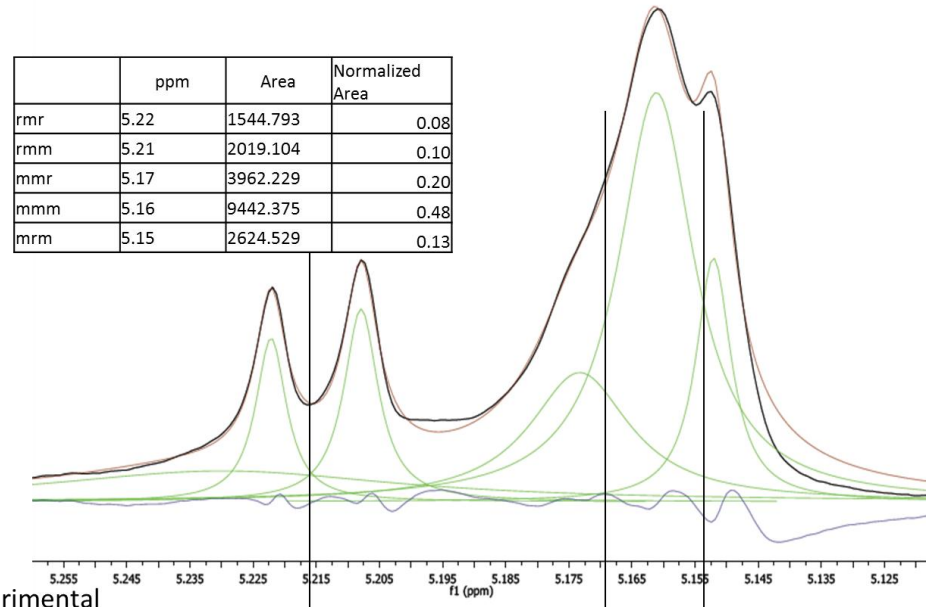
detailed. And then two chiral acids, (+)-camphor-10-sulfonic acid and (*R)*-(-)-1,1'-binaphthyl-2,2'-dily hydrogen phosphate will be employed to catalyzed the polymerization of *rac*-lactide. Finally, the acid/base complexes and the combination of the complexes with DMAP and DBU will also be assessed for in the polymerization of *rac*-lactide.

4.2 Polymerization of *rac*-lactide using DBU and DMAP as the catalysts and the study of the microstructure of the formed PLA

4.2.1 Determination of the probability of *meso* enchainment (P_m)

As discussed in the first chapter, the P_m is determined from the methine region of the homonuclear decoupled ^{1}H NMR (HOMODEC) spectrum. A representative example using DMAP as catalyst is presented in Fig. 40. Usually 5 peaks appear in this region: 5.22, 5.21, 5.17, 5.16 and 5.15 ppm which represents *rmr*, *rmm*, *mmr*, *mmm* and *mrm* enchainment respectively. Usually, the mentioned 5 peaks are integrated and the sum of the values of the integration are normalized to 1. Then these normalized integration percentages are compared with the predicted Bernoullian integration percentages for a given $P_{m[9]}$ to finally determine the P_m of the PLA. Unfortunately the five peaks are usually very closed each other (especially the peaks at 5.17, 5.16 and 5.15 ppm), a deconvolution is involved in obtaining the values of the integration of these peaks. The deconvolution is performed using MestreNova as software. A representative example for entry 63 is presented in Fig. 40. A table of the convolution results for the analysis of entry 63 is shown in Fig. 40, the area values of the five peaks are summed and then normalized to 1. The obtained area percentages are thus the values of the integration percentages of these five peaks. For entry 63, *rmr* (5.22 ppm) = 0.08, *rmm* (5.21 ppm) = 0.10, *mmr* (5.17 ppm) = 0.20, *mmm* (5.16 ppm) = 0.48 and *mrm* (5.15 ppm) = 0.13. Then these values are compared with

predicted Bernoulian integration percentages for a given P_m. The P_m of which the predicted integration percentages are closest to the deconvoluted integration percentages is chosen to be the P_m of the resulted PLA. For entry 63, P_m is closed to 0.60 (see Fig. 40).



	ppm	Area	Normalized Area
rmr	5.22	1544.793	0.08
rmm	5.21	2019.104	0.10
mmr	5.17	3962.229	0.20
mmm	5.16	9442.375	0.48
mrm	5.15	2624.529	0.13

Experimental Chemical shift	→	5.22	5.21	5.17	5.16	5.15
Integral	→	0.08	0.10	0.20	0.48	0.13
Predicted Bernoullian integration percentages for a given P_m	P_m	*rmr*	*rmm*	*mmr*	*mmm*	*mrm*
	0.59	0.08	0.12	0.12	0.47	0.21
	0.60	0.08	0.12	0.12	0.48	0.20
	0.61	0.08	0.12	0.12	0.48	0.20

Fig. 40 Methine region of homonuclear decoupled ^{1}H NMR spectrum of resulted PLA of entry 63 (up) (DMAP catalyzed polymerization) with deconvolution results and the created spectrum from the deconvolution results (bottom) and calculation details

4.2.2 Results and discussion

DMAP and DBU have already been reported in **Chapter 2** for catalyzing the

carbohydrates initiated ring-opening polymerization of *rac*-lactide and L-lactide. DBU is more reactive than DMAP but leading to undesirable non-sugar functionalized PLA. Here we continue to use DBU and DMAP to catalyze the polymerization of *rac*-lactide with high targeted degree of polymerization and the microstructure of the resulted PLA is further studied. The polymerization was performed in dichloromethane at 35 °C using benzyl alcohol as the initiator, *rac*-lactide as the monomer and DBU or DMAP as the catalyst. The ratio of monomer to initiator (targeted DP) is equal to 100:1. The concentration of *rac*-lactide is 300 mg/mL. The representative results are presented in Table 8. DBU catalyzed polymerization is quantitative in 30 minutes (conversion ≥ 97%). The resulted PLAs have relative narrow dispersities ($Đ_M \leq 1.3$). The dispersity can be improved by performing the reaction at a lower temperature (entry 59 at -20 °C, $Đ_M = 1.05$ *vs.* entry 58 at 35 °C, $Đ_M = 1.3$). The dipersity can also be improved by reducing the Cata./In. ratio (entry 60, Cata./In. ratio = 0.2, $Đ_M = 1.1$ *vs.* entry 58, Cata./In. ratio = 1.0, $Đ_M = 1.3$). More than 5 peaks appear in the methine region of the homonuclear decoupled ^{1}H NMR spectrum (see Fig. 41). From the original spectrum, we can observe that there are more than 3 peaks which should be the signals of enchainment *mmr*, *mmm* and *mrm* between 5.14 and 5.19 ppm. The tetrad probabilities based on Bernoullian statistics not applicable for these spectra. P_m can thus not be determined for the polymer obtained from DBU catalyzed polymerization (entries 58, 59 and 60). The appearance of these unknown peaks may be caused by the epimerization of lactide when using DBU as catalyst [10]. Epimerization can occur on the polymer or on the monomer. In this latter case, it results in the formation of *meso*-lactide of which polymerization can yield syndiodactic and heterotactic enchainments. The polymerization of *rac*-lactide leads to isotactic and heterotactic enchainment, of which the sequences appear at 5.22, 5.21, 5.17, 5.16 and 5.15 ppm for *rmr*, *rmm*, *mmr*, *mmm* and *mrm*, respectively. Syndiotactic enchainments lead to *rrr*, *rrm* and *mrr* tetrads that may explain the presence of additional signals observed. More analysis will be done in the future to confirm the occurrence of epimerization. Epimerization occurring directly on the polymer can also be advanced to explain the presence of additional

peaks/tetrads. DMAP is less reactive than DBU (entry 61 *vs.* entry 58). We only obtained a conversion of 7% after 24 hours. For an increased Cata./In. ratio, the conversion is improved (entry 62 *vs.* entry 61), but it is still very low and we could not recover the polymer from the polymerization. We then increased the reaction time from 24 hours to 7 days (entry 61 *vs.* entry 63) using 1:1 Cata./In. ratio. Finally we obtained a conversion of 32% and we were able to obtain a purified PLA to analyze by HOMODEC. A probability of *meso* enchainment closed to 0.6 was found (Fig. 40).

Table 8 Polymerization of *rac*-lactide using BnOH as initiator and DBU and DMAP as catalyst for a targeted DP_n of 100 at 35°C ([*rac*-LA] = 300 mg/mL)

Entry	Cata.	Cata./In.[a]	Time (min)	Conv.[b] (%)	DP_n[c] Cal.	DP[b] NMR	Mn[b] NMR	Mn[d] SEC	$Đ_M$[d]	P_m[e]
58	DBU	1	30	99	99	99	14400	12700	1.3	nd
59[f]	DBU	1	30	97	97	90	13100	10300	1.05	nd
60	DBU	0.2	30	97	97	88	12800	11000	1.1	nd
61	DMAP	1	24h	7	7	nd	nd	nd	nd	nd
62	DMAP	2	24h	12	12	nd	nd	nd	nd	nd
63	DMAP	1	7 d	32	32	50	7300	7800	1.06	0.6

[a] Catalyst/initiator(BnOH) ratio;

[b] Measured by ^{1}H NMR;

[c] Calculated degree of polymerization obtained from targeted DP_n × Conversion;

[d] Number-average molecular weight and dispersity measured by SEC calibrated with poly(styrene) standard in THF and corrected by Mark–Houwink parameters $M_{n,EXP} = M_{n,SEC} \times 0.58$ for Poly(D,L-lactide) [11]

[e] P_m is the probability of *meso* enchainment and is determined from the methine region of the homonuclear decoupled ^{1}H NMR spectrum; [f] Temperature = -20°C

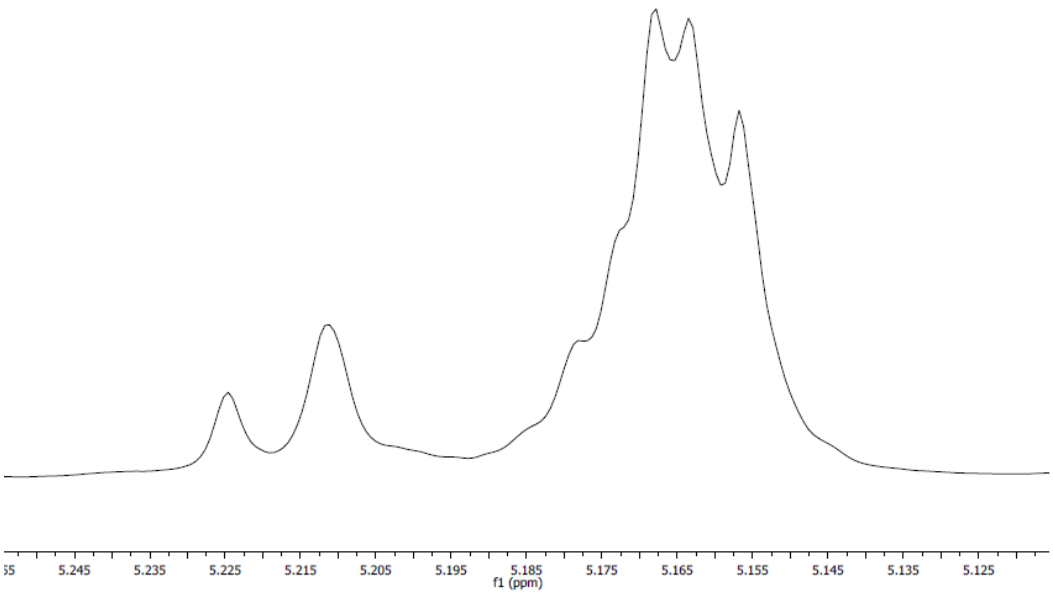
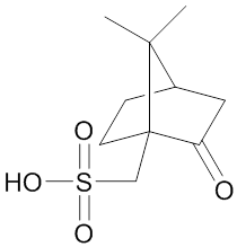


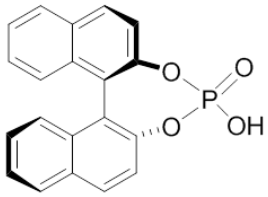
Fig. 41 methine region of the homonuclear decoupled ^{1}H NMR spectrum of entry 60 (DBU catalyzed polymerization)

4.3 Polymerization of *rac*-lactide using (+)-camphor-10-sulfonic acid ((+)-CSA) and *(R)*-(-)- 1,1'-binaphthyl-2,2'-dily hydrogen phosphate as catalysts (*(R)*-BNPH)

A number of acids have been reported for the polymerization of lactide. Miyake and Chen reported that a good stereoselectivity can be introduced by using a chiral base and this is the first example of stereocontrolled polymerization of lactide controlled by the chirality of the organocatalyst[8]. Chiral acids have not been reported in stereocontrolled polymerization of lactide so far. In this context, we tought of using chiral acids as catalysts to polymerize the *rac*-lactide. (+)-camphor-10-sulfonic acid ((+)-CSA) and *(R)*-(-)-1,1'-binaphthyl-2,2'-dily hydrogen phosphate (*(R)*-BNPH) (see Fig. 42) have been tested. The results are presented in Table 9.



(+)-CSA



(R)-BNPH

Fig. 42 (+)-CSA and *(R)*-BNPH

Table 9 Polymerization of *rac*-lactide using BnOH as initiator using *(R)*-BNPH and (+)-CSA as catalyst for a targeted DP_n of 100 at 35°C ([*rac*-LA] = 300 mg/mL)

Entry	Cata.	Cata./In.	Time (h)	Conversion (%)[a]
64	*(R)*-BNPH	1	24	0
65	*(R)*-BNPH	1	48	0
66	*(R)*-BNPH	5	48	0
67[b]	*(R)*-BNPH	1	4	0
68	(+)-CSA	1	24	0
69[b]	(+)-CSA	1	4	0

[a] Measured by ^{1}H NMR; [b] Polymerization in bulk at 120°C

The polymerization was performed in the same conditions as we reported ealier for the DBU and DMAP catalyzed polymerization. We did not observe any polylactide signals on the ^{1}H NMR spectrum when using *(R)*-BNPH as catalyst after 24 hours (entry 64). We decided to run the reaction for a longer time (48 hours, entry 65), but the same result was found. And then we increased the *(R)*-BNPH loadings from Cata./In. = 1 to Cata./In. = 5 (entry 66*vs.* entry 65), always the same result was found. Meanwhile, we observed that the catalyst *(R)*-BNPH is not soluble in dichloromethane. This may be linked to the poor reactivity of *(R)*-BNPH. Bulk conditions enable us to perform the reaction without solvent. We decided to perform this reaction in bulk. We also noticed that *(R)*-BNPH is not soluble in the melt lactide which is considered to be the solvent and the monomer at the same time. There is no polylactide formed according to ^{1}H NMR analysis. We will try to use toluene as solvent in the future for the polymerization using BNPH as catalyst. (+)-CSA is a

chiral acid that has also been used as catalyst, but we did not observe any polymerization when performing the reaction in dichloromethane after 24 hours and in bulk at 120°C after 4 hours. It seems that these two acids are not reactive for the ring-opening polymerization of *rac*-lactide.

4.4 Polymerization of *rac*-lactide by combining acidic and basic sites as the catalysts

Chiral acids (CSA and BNPH) are not reactive for the ring-opening polymerization of *rac*-lactide. Deffieux *et al.* reported that the reactivity of the DMAP can be improved by combing DMAP and the acid/base salt formed between DMAP and HCl [12], proposed mechanism is shown in Fig. 43. Recently, Hedrick *et al.* also reported the use of acid/base complexes for the ring-opening polymerization of L-lactide. They discovered that the salt formed from an equimolar reaction of benzoic acid and DBU produced a catalyst capable of controlling polymerization allowing for targeted molecular weight and narrow dispersities [13]. These acid/base complexes have already been reported in organic synthesis to control the stereoselectivity [14, 15] Inspired by these works, we performed the polymerization of *rac*-lactide using chiral acid/base salts and the combination with their bases with the aim to introduce some stereoselectivities. Firstly the synthesis of the acid/base salts will be presented and then the polymerization of *rac*-lactide using these complexes will be discussed.

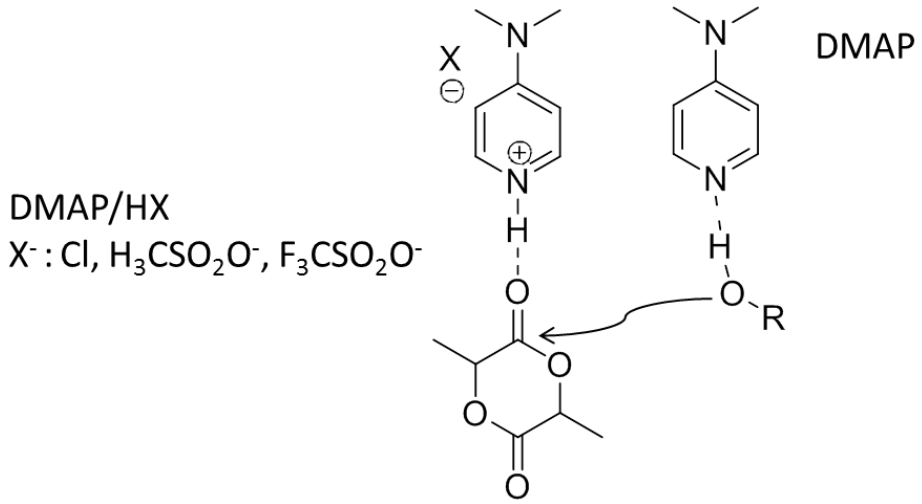
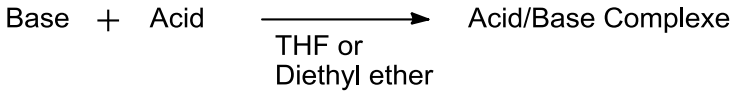


Fig. 43 Proposed mechanism[12]

4.4.1 Synthesis of the acid/base complexes

The acid/base complexes catalysts were synthesized by using equivalent amounts of acid and base (Scheme 26). Benzoic acid (BA), *(R)*-(+)-binaphathyl-diyl hydrogen phosphate (*R*-BNPH), (+)-camphor-10-sulfonic acid (CSA), 4-dimethylaminopyridine (DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5,7-triazabicyclo[4.4.0]dec-5ene (TBD) have been selected and are presented in Fig. 44. Binol base phosphoric acid, *(R)*-(-)-BNPH was synthesized from *(R)*-Binol and phosphoryl chloride, synthetic details were presented in the experimental part of **Chapter 3**. The other acids and bases are commercially available. Finally six salts were obtained: DBU/BA, DBU/BNPH, DBU/CSA, DMAP/CSA, DMAP/BNPH and TBD/BNPH (see Fig. 45).



Scheme 26 General synthesis of acid/base complexes pathway

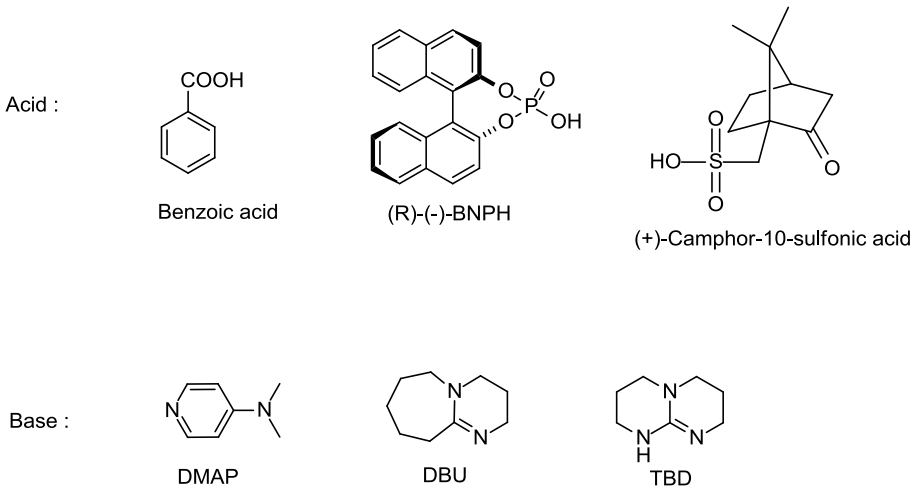


Fig. 44 Acids and bases used for the synthesis of the acid/base complexes

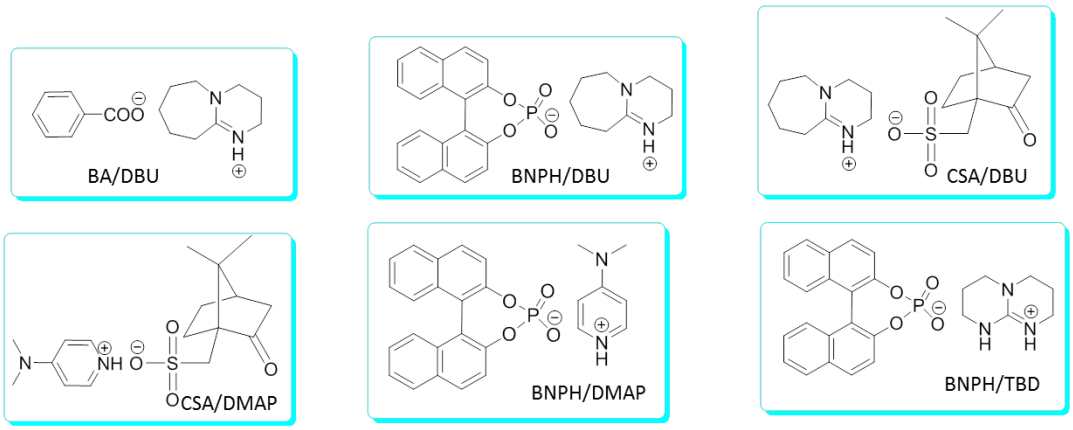


Fig. 45 The formed acid/base complexes

4.4.2 Polymerization of *rac*-lactide using acid/base without additional base

The 6 synthesized acid/base complexes are used as catalysts in the polymerization of *rac*-lactide. The results are presented in Table 10. BNPH/DBU is not able to catalyze the polymerization in the conditions that we tried. We did not obtain any polymer after 24 hours. We increased the Cata./In. ratio, but the same results were found. The salts BNPH/DMAP, CSA/DMAP, CSA/DBU and BNPH/TBD did not show any reactivity for the ROP of *rac*-lactide. CSA/DBU and BNPH/TBD were chosen to catalyze the polymerization in bulk at 120°C, but we could not observe any polymerization after 4 hours. We then use a salt reported as an active catalyst in the

literature to check our experimental conditions. BA/DBU was found to be reactive for the ROP of *rac*-lactide. We obtained a conversion of 14% after 24 hours. We thus conclude that our salts are not able to catalyze the ROP of lactide. Defreux and coworkers reported similar results using DMAP/HCl, DMAP/HOTf etc. It would be very interesting if an acid/base complex can be found for the polymerization of *rac*-lactide which may potentially introduce a stereoselectivity.

Table 10 Polymerization of *rac*-lactide using acid/base complexes as catalyst and BnOH as initiator for a targeted DP_n of 100 at 35°C ([*rac*-LA] = 300 mg/mL)

Entry	Cata.	Cata./In.	Time (h)	Conversion[a] (%)
70	BNPH/DBU	1	24	0
71	BNPH/DBU	2	24	0
72	BNPH/DMAP	1	24	0
73	BNPH/DMAP	5	24	0
74	CSA/DMAP	1	24	0
75	CSA/DMAP	2	24	0
76	CSA/DBU	1	24	0
77[b]	CSA/DBU	1	4	0
78	BNPH/TBD	1	24	0
79[b]	BNPH/TBD	1	4	0
80	BA/DBU	1	24	14

[a] Measured by ^{1}H NMR;
[b] Polymerization in bulk at 120 °C

However, as shown in the literature [12], the acid/base complexes combined with the base can be used as the catalyst with increased reactivity than using the base alone. We decided to use this strategy in our polymerization. We focus on CSA/DMAP and BNPH/DBU combined with DMAP or DBU as catalysts.

4.4.3 Polymerization of rac-lactide using CSA/DMAP combined with DBU or DMAP as catalysts

The results of the polymerization of *rac*-lactide using CSA/DMAP combined with DBU or DMAP as catalysts are presented in Table 11. The polymerization was performed using dichloromethane as solvent for a targeted degree of polymerization of 100. When using 1 equivalent of CSA/DMAP in additional 0.1 to 0.5 equivalent of DBU (entries 81, 82 and 83), the reactivity is very low. We obtained a conversion around 6 % after 24 hours. It's notable that DBU by itself showed a much higher reactivity in (entry 60, Table 8 *vs.* entry 82, Table 11). It seems that it exists an interaction between the CSA/DMAP salt and the DBU, even though this is a negative effect for the polymerization of *rac*-lactide. However, when we increased the Base/(CSA/DMAP) ratio to 1, the polymerization was quantitative in 30 minutes. The number-average molecular calculated from ^{1}H NMR corresponds well with that is measured by SEC. The narrow dispersity obtained ($Đ_M$ = 1.08, entry 84) is small than that obtained using DBU alone in similar conditions, highlighting a positive effect of the salt. Similar trends were reported by Hedrek and coworkers. [13].The purified polymer was then analyzed by HOMODEC. We obtained a spectrum similar to that obtained with using DBU as single catalyst (entries 58-60, Table 8). In the methine region, we observed more than 5 sequences which may be linked to the epimerization of *rac*-lactide in the presence of DBU [10]. For the same reason as explained above, the tetrad probabilities of Bernoullian statistics cannot be applied and The polymerizations using the same conditions as entry 84 were performed using lower temperature (entry 85), shorter reaction times (entries 86-87). At -20°C, the polymerization is much slower (entry 85 *vs.* entry 84). We only observed a conversion of 3 %. It's well known that the temperature plays a very important role in the reactivity of the catalytic system. The reaction is usually slower using low temperature but resulting in a more significant selectivity [6, 16]. The reactions were run for 5, 10 and 10 min (entries 86 and 87) in order to stop the reaction at lower yield when 4% is observed after 5 min. We observed a full conversion after 10 min than 7 min. This results may be linked to the solubility of *rac*-lactide in dichloromethane. In the beginning 5 minutes, the *rac*-lactide was not totally soluble and solution was not homogenous.

DMAP has also been assessed with the CSA/DMAP salt tested. The polymerizations were performed for 24 hours (entries 88 and 90) and 7 days (entry 89) using salt/initiator ratio from 1 to 2 (entry 88 *vs.* entry 90). Longer reaction times and using more equivalent DMAP lead to a higher conversion. It seems that the reactivity of DMAP was slightly improved by combining with DMAP/CSA salt (entry 98, Table 11 *vs.* entry 61, Table 8). This needs however to be confirmed by more experiments. Since the conversion is relative low, we had difficulties to recover the polymer from the purification. We thus could not study the microstructure of the polymer by HOMODEC. Reactions higher base loadings will be performed, which allows us to recover the polymer and analyze the polymer by HOMODEC to assess to stereoselectivity.

Table 11 Polymerization of *rac*-lactide using complex CSA/DMAP combined with DBU and DMAP as catalyst and BnOH as initiator for a targeted DP_n of 100 (ratio acid/base to initiator = 1; [*rac*-LA] = 300 mg/mL)

Entry	Base	Base/salt [a]	T(°C)	Time	Conv.[b] (%)	DP_n[c] Cal.	DP_n[b] NMR	Mn[b] NMR	Mn[c] SEC	$Đ_M$[c]
58	DBU	-	35	30	99	99	99	14400	12700	1.3
81	DBU	0.1	35	24 h	6	6	7	1100	nd	nd
82	DBU	0.2	35	24 h	8	8	nd	nd	nd	nd
83	DBU	0.5	35	24 h	6	6	nd	nd	nd	nd
84	DBU	1	35	30 min	96	96	89	12950	12500	1.08
85	DBU	1	-20	30 min	3	3	nd	nd	nd	nd
86	DBU	1	35	5 min	5	5	nd	nd	nd	nd
87	DBU	1	35	10 min	93	93	89	12950	nd	nd
61	DMAP	-	35	24 h	7	7	nd	nd	nd	nd
88	DMAP	1	35	24 h	11	11	18	2700	nd	nd
89	DMAP	1	35	7 days	34	34	13	5600	nd	nd
90	DMAP	2	35	24h	37	37	30	4450	nd	nd

[a.] Ratio base to acid/base salt;

[b.] Measured by ^{1}H NMR;

[c.] Number-average molecular weight and dispersity measured by SEC calibrated with poly(styrene) standard in THF and corrected by Mark–Houwink parameters $M_{n,EXP} = M_{n,SEC} \times 0.58$ for Poly(D,L-lactide) [11]

4.4.4 Polymerization of *rac*-lactide using BNPH/DBU combined with DBU or DMAP as catalysts

Another salt, BNPH/DBU has also been chosen to combine with DBU or DMAP to catalyze the ring-opening polymerization of *rac*-lactide. The results are shown in Table 12. The targeted degree of polymerization is 100 and the salt/initiator ratio is fixed to 1. We varied base/salt ratio, temperature and the time of the reaction. The reactions are quantitative using only 0.1 and 0.2 base/salt ratio (entries 91 and 92 93). It's noticeable than BHPH/DBU by itself could not catalyze the polymerization of *rac*-lactie (entries 70 and 71, Table 10), but using low additional DBU loadings can lead to quantitative polymerization (entry 60, Table 8). The presence of the BUPH/DBU salt needs to a lower disperisity, than that obtained using DBU alone, as observed for the CSA/DMAP salt. Polymerizations at -20 °C were also performed (entries 93 and 94), low DBU loading (entry 93) leads to only a conversion of 2% after 16 hours. However the same reaction at 35 °C results a conversion of 88% (entry 91). Using DBU/salt ratio up to 1 at -20°C leads to quantitative polymerization. Reactions performed at 35°C using DBU/salt ratio of 1 for shorter times (entries 95, 96 and 97) leads to different results. When the time is less than 5 minutes, the conversion is 0, but when the reaction time is up to 7 minutes, we obtained a conversion of 80%. The polymerization is quantitative after 10 minutes (entry 96). The purified PLA was further analyzed by HOMODEC, a representative example (entry 94) is presented in Fig. 46. There are more than 5 sequence peaks in the decoupled methine region. Since DBU was involved in the polymerization, we thought that epimerization of *rac*-lactide could happen during the reaction as we discussed earlier. Fig. 46 shows a comparison between methine region of the homonuclear decoupled ^{1}H NMR spectrum of PLA obtained from DBU catalyzed polymerization (entry 60) and PLA obtained from DBU/salt catalyzed polymerization. The spectra of entry 60 and entry 94 are quite similar: more than five sequences are observed and tetrad possibilities of Bernoullian statistics are not applicable for calculating the P_m.

The BNPH/DBU salt combined with DMAP is less reactive than BNPH /DBU salt combined with DBU for the polymerization of *rac*-lactide. Among these experiments, the highest conversion (70%) was obtained after 2 weeks using base/salt = 1 (entry 100). A conversion of 29% was observed after 7 days (entry 98). The conversion can be further improved by using more DMAP loadings (entries 99 and 101). The resulted PLA from entry 101 was analyzed by HOMODEC. A second shoulder is observed around 5.17 ppm, highlighting the possible presence of additional tetrads (see Fig. 46). This may be due to the presence of DBU in the reaction medium, and the resulting possible epimerization.

Table 12 Polymerization of *rac*-lactide using complex BNPH/DBU combined with DBU and DMAP as catalyst and BnOH as initiator for a targeted DP_n of 100 (ratio acid/base to Initiator = 1; [*rac*-LA] = 300 mg/mL)

Entry	Base	Base/salt[a]	T(°C)	Time	Conv.[b] (%)	DP_n[c] Cal.	DP_n[b] NMR	Mn[b] NMR	Mn[c] SEC	$Đ_M$[c]
58	DBU	-	35	30	99	99	99	14400	12700	1.3
91	DBU	0.1	35	1 h	88	88	82	11900	10550	1.05
92	DBU	0.2	35	1 h	94	94	87	12700	11600	1.05
93	DBU	0.1	-20	16 h	2	2	nd	nd	nd	nd
94	DBU	1	-20	30 m	93	93	88	12800	10250	1.06
95	DBU	1	35	5 m	0	0	0	0	nd	nd
96	DBU	1	35	10 m	98	98	95	13800	nd	nd
97	DBU	1	35	7 m	80	80	60	8750	nd	nd
98	DMAP	1	35	7 days	29	29	11	1700	nd	nd
61	DMAP	-	35	24 h	7	7	nd	nd	nd	nd
99	DMAP	2	35	72 h	34	34	30	4450	nd	nd
100	DMAP	1	35	2 weeks	70	70	75	10900	nd	nd
101	DMAP	5	35	5 days	54	54	50	7300	8850	1.11

[a.] Ratio base to acid/base salt;

[b.] Measured by ^{1}H NMR;

[c.] Number-average molecular weight and dispersity measured by SEC calibrated with poly(styrene) standard in THF and corrected by Mark–Houwink parameters $M_{n,EXP} = M_{n,SEC} \times 0.58$ for Poly(D,L-lactide) [11]

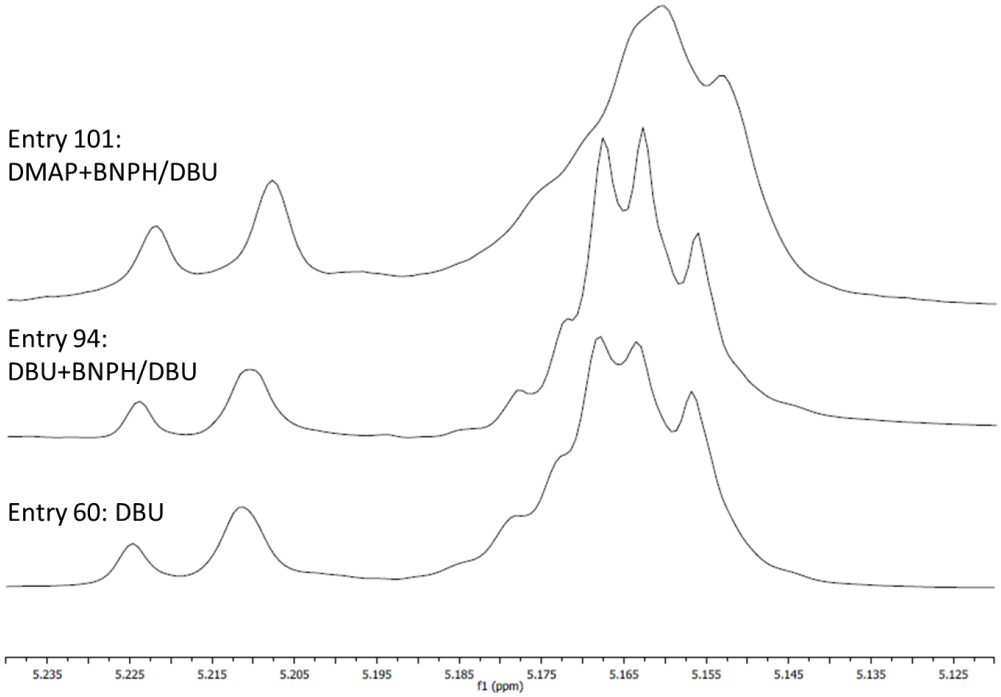


Fig. 46 Methine region of the homonuclear decoupled ^{1}H NMR spectrum of entries 60, 94 and 101

4.5 Conclusion

Different types of catalysts were tested at the catalysts for the ring-opening polymerization of *rac*-lactide. DMAP shows a mild reactivity when performing the reaction in solvent conditions, a P_m of 0.60 was found according the tetrad probabilities of Bernoullian statistics. DBU shows a high reactivity, the polymerizations using DBU as catalyst are quantitative in a short time, but the P_m could not be calculated by the tetrad possibilities of Bernaullain statistics, due to unknown sequences in the decoupled methine region. The 2 chiral acids did not show any reactivity for the polymerization of *rac*-lactide in the conditions that we used. The salts BNPH/DBU, BNPH/DMAP, CSA/DMAP, CSA/DBU and BNPH/TBD by themselves were not able to catalyzed the ROP of *rac*-lactide in our experimental conditions. Two salts, CSA/DMAP and BNPH/DBU, were used in combination with DBU or DMAP to catalyze the polymerization of *rac*-lactide. The combination of both salts with DBU can lead to a decrease of the reactivity accompanied with DBU alone, and interestingly to narrower molecular weight distributions when using a 1/1 mixture of both compounds. Concerning the stereoselectivity, the presence of DBU either as base or in an acid/base salt leads to the presence of tetrads predicted by Bernoullian statistics considering *rac*-lactide: this may be due to some epimerization. The HOMODEC spectra obtained in the presence of a chiral acid/base salt were found to be similar to that obtained using DBU alone. Using DMAP combined to acid/DMAP salts lead to reactivities too low to recover a polymer in high yield. Future works may be oriented towards those of bases more active than DMAP, and loss prone than DBU to induce epimerization, if this latter point is confirmed.

4.6 Experimental part

4.6.1 Solvents and reagents

Reagents were available commercially from Aldrich and used as received unless otherwise noted. Benzyl alcohol and DMSO-d_6 was distilled from CaH_2, 1,8-Diazabicylco[5.4.0]undec-7-ene (DBU) was stirred over CaH_2, vacuum distilled and then stored in the glovebox. Benzoic acid (BA) and DMAP were co-evaporated with

toluene and sublimated in vacuum. *Rac*-lactide was co-evaporated 3 times with toluene and sublimated in vacuum. TBD was dried in high vacuum. (+)-camphor-10-sulfonic acid was dried in the oven over night, (*R)*-(-)-1,1'-binaphthyl-2,2'- hydrogen phosphate was synthesized in last chapter. Dichloromethane was taken from a solvent purification system (MBraun MB SPS 800).

4.6.2 Measurements

NMR spectra were recorded on a AC 300 Bruker spectrometer at room temperature in $CDCl_3$. Approximately 5 mg of polymer was dissolved into the NMR tube in 0.6 mL of solvent for ^1H NMR analysis. The chemical shifts were calibrated using the residual resonances of the solvent. For the homonuclear decoupling spectra, approximately 2 mg of polymer was dissolved in to the NMR tube in 0.6 mL solvent. Methyl protons decoupled from the methine protons during 1.8 s acquisition time, 9 μs pulse width, 3 s pulse delay, digital resolution 64 K, spectre width 4000 Hz and 64 scans were used.

Size exclusion chromatography was performed in THF as eluent at 40 °C using a Waters SIS HPLC-pump, a Water 2414 refractometer and Water styragel column HR3 and HR4. The calibration was done using polystyrene stardards.

4.6.3 Procedures:

DBU/BA Salt (1:1)

A flame dried schlenk was charged with benzoic acid (1.0 g, 8.18 mmol), diethyl ether (20 ml) and a stirring bar under argon atmosphere. To the stirred solution, DBU (1.2 g, 8.18 mmol) was added. Instantly a white precipitate formed and stirring was continued for 1 h. The precipitate, white salt was then washed with excess ether and isolated by decantation. The salt was then dried under high vacuum. Yield = 80%

^1H NMR ($CDCl_3$) δ (ppm) : 8.06-8.12 (bm, 2H), 7.31-7.37 (bm, 3H), 5.34 (t, 2H), 3.36-3.46 (bm, 4H), 2.92-3.02 (bm, 2H), 2.01 (p, 2H), 1.61-1.82 (b, 6H)

DBU/BNPH Salt (1:1)

A flame dried schlenk was charged with (R)-(+)-binaphathyl-diyl hydrogen

phosphate (0.2 g, 0.57 mmol), diethyl ether (8 ml) and a stirring bar under argon atmosphere. To the stirred solution, DBU (86 μL, 0.57 mmol) was added. Instantly a white solid precipitate formed and stirring was continued for 1h. The salt was then dried under high vacuum. Yield = 82 %

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) : 7.86-7.93 (m, 4H), 7.56-7.59 (dd, 2H), 7.36-7.41 (m, 4H), 7.19-7.24 (m, 2H), 3.20-3.29 (m, 4H), 3.12 (t, 2H), 2.57 (t, 2H), 1.73 (p, 2H), 1.52 (m, 6H)

DBU/CSA Salt (1:1)

A flame dried schlenk was charged with (+)-camphor-10-sulfonic acid (0.5 g, 2.15 mmol), THF (10 ml) and a stirring bar under argon atmosphere. To the stirred solution, DBU (322 μL, 2.15 mmol) was added. The stirring was continued for 1h and then dried under vacuum, the residue was precipitated in diethyl ether to form a white precipitate. The formed salt was then dried under high vacuum. Yield = 60 %

^{1}H NMR ($CDCl_3$) δ (ppm, 300 MHz) : 3.45-3.52 (m, 6H), 3.30 (d, 1H), 2.72-2.89 (m, 4H), 2.26-2.33 (dt, 1H), 1.99-2.07 (m, 4H), 1.66-1.89 (m, 8H), 1.30-1.39 (m, 1H), 1.12 (s, 3H), 0.83 (s, 3H)

DMAP/CSA Salt (1:1)

A flame dried schlenk was charged with (+)-camphor-10-sulfonic acid (1.0 g, 4.3 mmol), THF (10 ml) and a stirring bar under argon atmosphere. To the stirred solution, DMAP (0.53 g, 4.3 mmol) was added. Instantly a white solid precipitate formed and stirring was continued for 1h. The salt was then dried under high vacuum.

^{1}H NMR ($CDCl_3$, 300 MHz)

δ (ppm) : 9.08 (2H), 7.76 (2H), 3.73 (2H), 2.68 (6H), 2.15 (2H), 1.99 (1H), 1.84 (2H), 1.60 (2H), 0.99 (6H)

DMAP/BNPH Salt (1:1)

A flame dried schlenk was charged with (R)-(+)-binaphathyl-diyl hydrogen phosphate (0.2 g, 0.57 mmol), diethyl ether (8 ml) and a stirring bar under argon atmosphere. To the stirred solution, DMAP (70.2 mg, 0.57 mmol) was added. Instantly a white solid precipitate formed and stirring was continued for 1h. The salt was then dried under high vacuum.

^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) : 7.84-7.92 (m, 6H), 7.58 (d, 2H), 7.37 (t, 4H), 7.19-7.25 (m, 2H), 6.37 (d, 2H), 3.07 (s, 6H)

TBD/BNPH Salt (1:1)

A flame dried schlenk was charged with *(R)*-(+)-binaphathyl-diyl hydrogen phosphate (1.0 g, mmol), diethyl ether (20 ml) and a stirring bar under argon atmosphere. To the stirred solution, TBD (g, mmol) was added. Instantly a white solid precipitate formed and stirring was continued for 1h. The salt was then dried under high vacuum.

^{1}H NMR ($CDCl_3$, 300 MHz)

δ(ppm): 7.84 – 7.92 (m, 6H), 7.58 (d, 2H), 7.37 (t, 4H) 4.19 (m, 2H), 2.65 -2.55 (m, 6H), 1.6 (m, 4H)

General polymerization procedure

In a glovebox, a schlenck was charged with benzyl alcohol, *rac*-lactide, catalyst and a stirbar. The polymerization was the initiated upon the addition of dichloromethane. Then the schlenck is set to a given temperature for a given reaction time. And the reaction was dried in vacuum (when using DBU and TBD, the reaction was quenched with benzoic acid), a sample of the crude product was taken and analyzed by ^{1}H NMR (DMSO-d_6) to determine the conversion. The crude was then dissolved in a small amount of dichloromethane and the solution is precipitated in cold methanol to give the pure polylactide.

4.7 References

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General conclusion

The main objective of this work is to synthesize biodegradable carbohydrates functionalized polyesters using metal free catalysts which are applicable to biomaterials and environmentally friendly products and to try to develop organocatalysts for the stereoselective polymerization of *rac*-lactide.

In the first chapter, we reviewed the existing strategies in the literature for the synthesis of carbohydrates functionalized poly(lactide) and poly(ε-caprolactone). Metal based catalysts have been widely used as catalysts in the synthesis of these functionalized aliphatic polyesters via ROP. Enzymes are effective to catalyze the ROP of ε-caprolactone and the regioselective carbohydrate functionalization of poly(ε-caprolactone), but have poor reactivity for the synthesis of polylactide. Organocatalyts have not been largely used for this purpose when we began our work. Metal based catalysts have furthermore been widely used for the stereoselective polymerization of lactide, but only few organic catalysts have been reported.

In **Chapter 2**, we found that DMAP is a power catalyst for the carbohydrate functionalization of polylactide via ROP. Using different carbohydrates as initiators can result in different sugar functionalized PLA. The DMAP catalyzed polymerization is applicable in solvent medium and as well as in bulk. Different polymer structures were obtained: end- and link- functionalized PLA and star PLA. The initiation efficiency was found to be quantitative using selectively protected and polyol monosaccharides as initiators. The polymerization leads to a 100% functionalized efficiency without side initiation. The synthesis of cyclodextrin functionalized polylactide using DMAP as the catalysts was also studied. The polymerizations were performed in bulk conditions starting from native cyclodextrins. When Monomer/ROH > 10, the initiation efficiency is quantitative and CD core star PLAs were obtained. When M/ROH < 10, the initiation is not quantitative, yielding hydrophilic cyclodextrin core star polylactide in a one step procedure. According to a model study, we found that DMAP as well as lactide can form inclusion complexes with **β-CD**. The competitive inclusion leads preferentially to the CD/DMAP inclusion complex. Based on this study, we have succeeded to synthesize a **β-CD**/DMAP inclusion complex. Future prospects will aim at applying this complex in polymerization catalysis.

In **Chapter 3**, we focused on the synthesis of poly(ε-caprolactone) and poly(δ-valerolactone) using binol based phosphoric acids. Firstly, the phosphoric acid was synthesized according to the method in the literature. And then it was used as catalyst for the

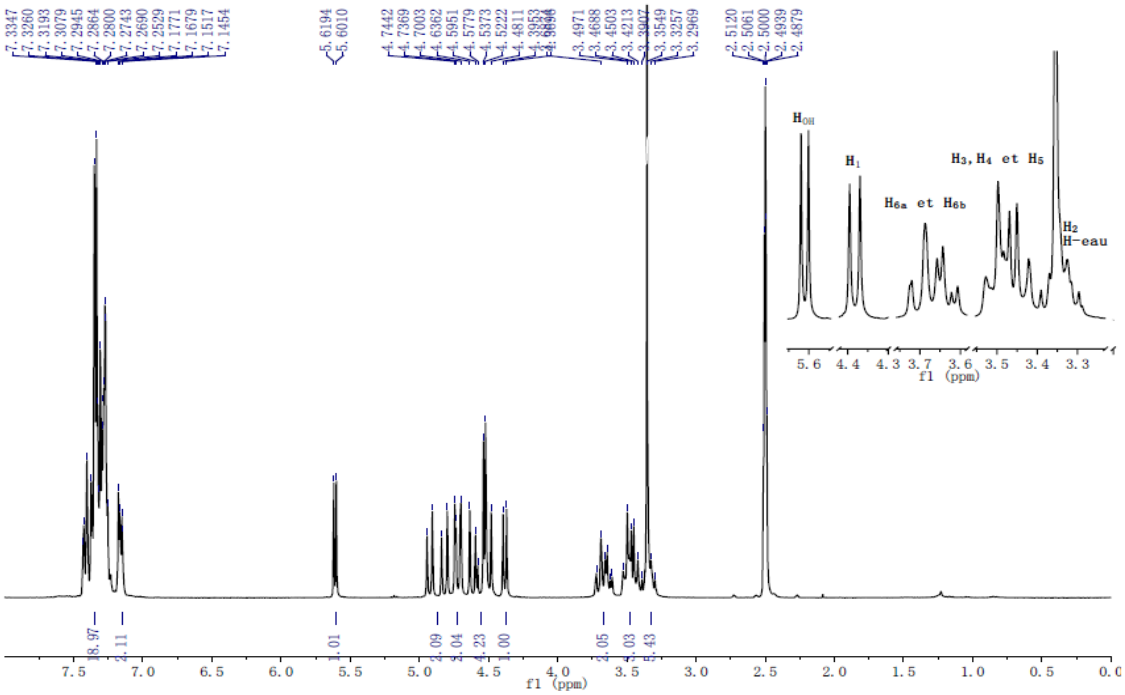
ROP of ε-caprolactone in bulk. In combination with benzyl alcohol, the polymerization is quantitative and controlled in mild conditions resulting in polymers with narrow dispersities. Using carbohydrate mono-ol as initiator leads to quantitative and well controlled polymerization, but only partial initiation efficiency was observed for carbohydrate poly-ols initiated polymerization. This leads interestingly to hydrophilic carbohydrate functionalized poly(ε-caprolactone) and poly(δ-valerolactone) in a one-step reaction. Multimodal molecular weight distributions were obtained using β-CD as the initiator for the polymerization of δ-valerolactone. Finally, we found that BNPH can catalyze the ring-opening polymerization of ε-valerolactone without co- initiator, resulting in high molecular weight polymer.

In the last chapter, we concentrate our efforts on the polymerization of *rac*-lactide using different metal free catalysts and the study of the microstructure of the resulted polymer. We firstly studied the reactivities of organic bases that we used in **Chapter 2**. DMAP shows a mild reactivity and resulted in PLA with a P_m closed to 0.6 as measured by HOMODEC analysis. DBU is much more reactive as found in **chapter 1**. The resulting PLA was also analyzed by HOMODEC, but unknown sequences were shown in the methine region of the of the spectrum, which may be attributed to epimerization. BNPH which has shown a good reactivity for the polymerization of ε-caprolactone and δ-valerolactone earlier and CSA could not catalyze the polymerization of *rac*-lactide in the conditions that we used. The salts BNPH/DBU, BNPH/DMAP, CSA/DMAP, CSA/DBU and BNPH/TBD by themselves were not able to catalyze the ROP of *rac*-lactide in our experimental conditions. CSA/DMAP and BNPH/DBU were used in combination with DBU or DMAP to catalyze the polymerization of *rac*-lactide. The combination of both salts with DBU can lead to a decrease of reactivity compared with DBU alone. Using DBU/salt (1:1) as catalytic system resulted in a narrower dipersities. HOMODEC analysis shows that the polymers formed using DBU or the combination of DBU and another salt have more than five sequences in the methine region.

Our main mission for this thesis has been completed. Different carbohydrates functionalized polyesters have been obtained. The applications of resulted carbohydrates functionalized polyesters will be studied in the future. Hopefully, these polymers can be applied in biomaterials or environmentally friendly products as we expected. Furthermore, there are still a lot more organocatalysts that may be used for the stereoselective ROP of *rac*-lactide. We expect that in the future more organocatalysts can be explored.

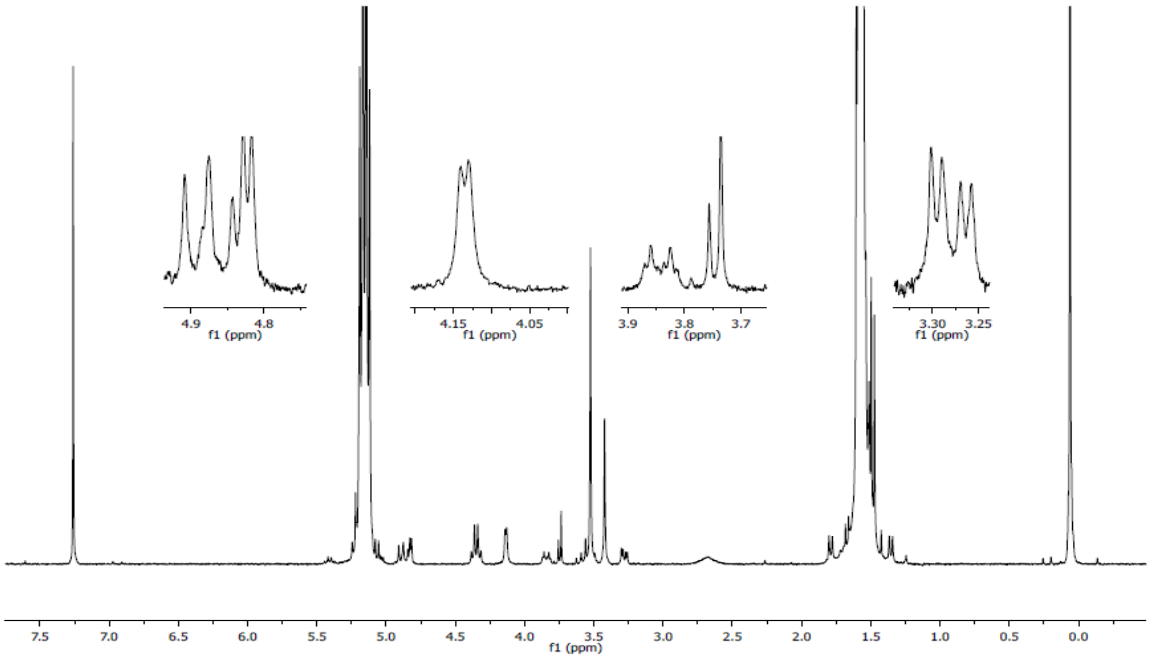
Annex

Annex 1 Glc-2r (DMSO)

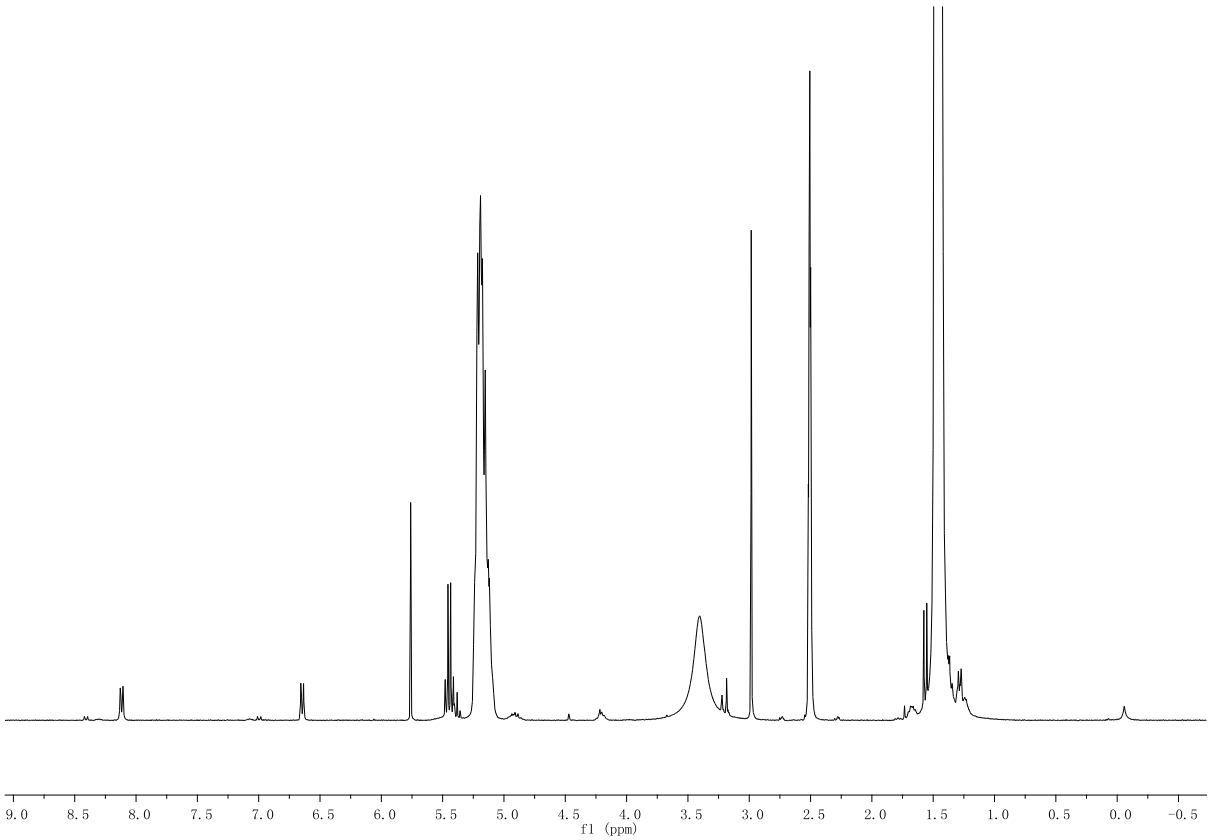


Annex 2

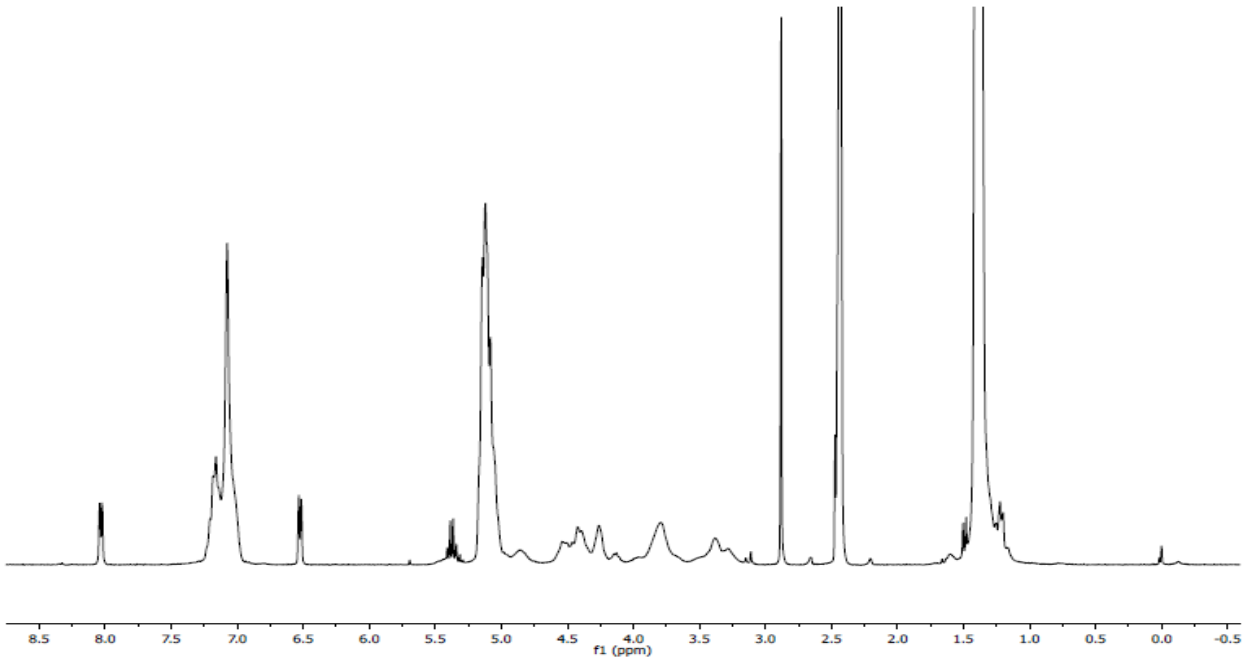
Glc-diol functionalized PLA ($CDCl_3$)



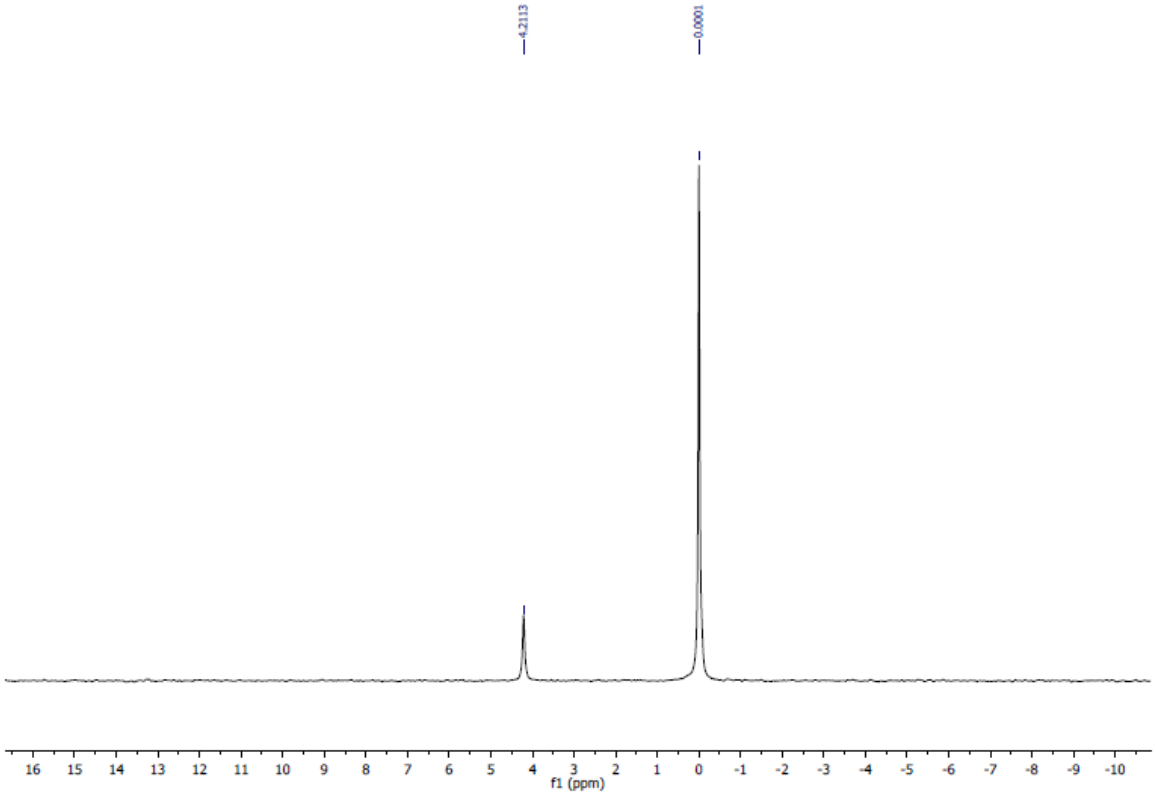
Annex 3 Glc-Me functionalized PLA (DMSO)



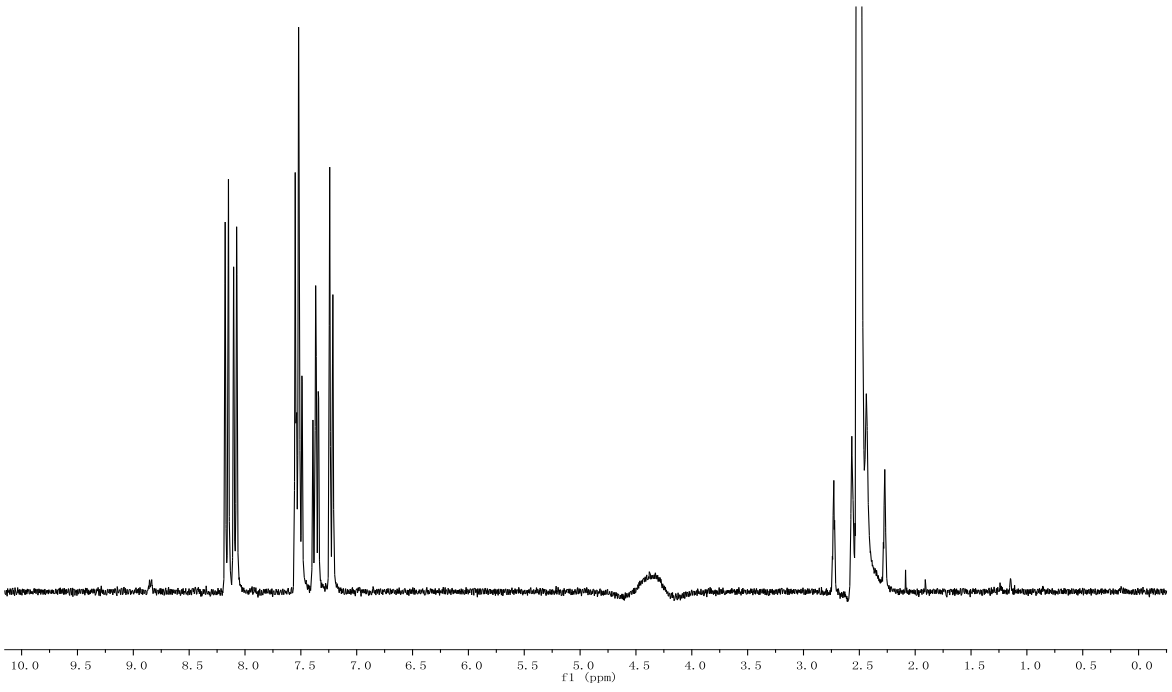
Annex 4 CD-diol functionalized PLA (DMSO)



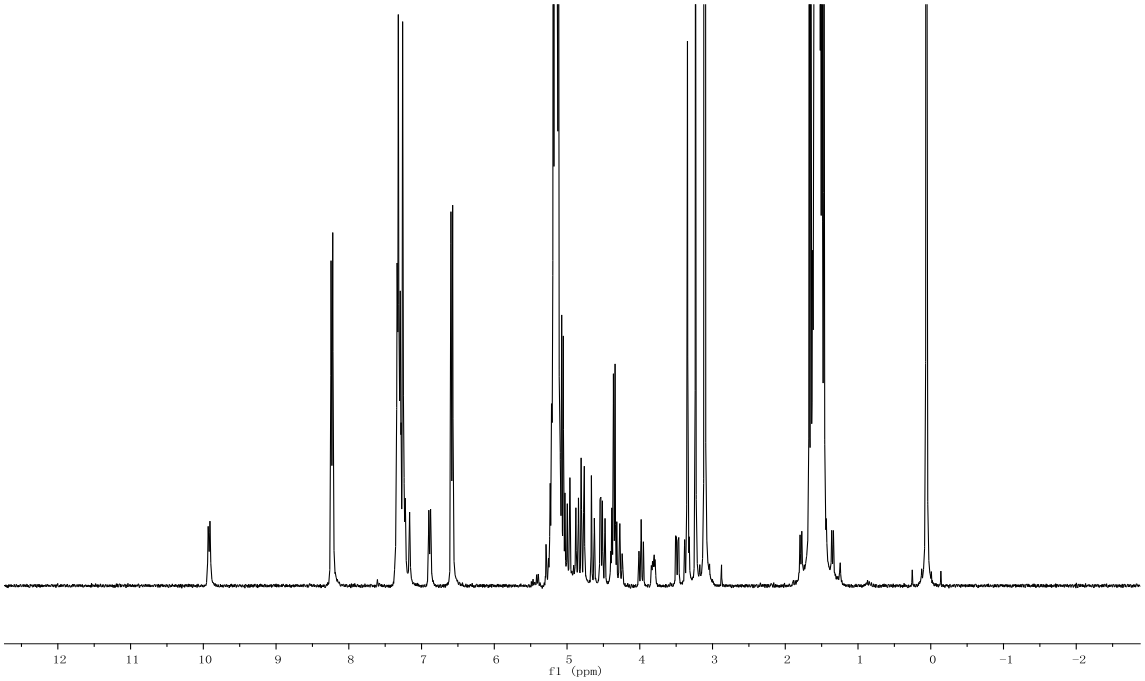
Annex 5 ^{31}P NMR of *rac*-BNPH



Annex 6 BNPH/DBU (DMSO)



Annex 7 BNPH/TBD (CDCl3)



Annex 8 SEC of CD-diol functionalized PLA (entry 11)