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Controlled synthesis of biodegradable lactide polymers and copolymers using novel *in situ* generated or single-site stereoselective polymerization initiators

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Abstract—Polylactides and their copolymers are key biodegradable polymers used widely in biomedical, pharmaceutical and ecological applications. The development of synthetic pathways and catalyst/initiator systems to produce pre-designed polylactides, as well as the fundamental understanding of the polymerization reactions, has continuously been an important topic. Here, we will address the recent advances in the ring-opening polymerization of lactides, with an emphasis on the highly versatile *in situ* generated initiator systems and single-site stereoselective initiators. The *in situ* generated initiators including *in situ* formed yttrium, calcium and zinc alkoxides all have been shown to bring about a rapid and living polymerization of lactides under mild conditions, which facilitated the preparation of a variety of advanced lactide-based biomaterials. For example, well-defined di- and tri-block copolymers consisting of hydrophilic poly(ethylene glycol) blocks and hydrophobic polyester blocks, which form novel biodegradable polymersomes or biodegradable thermosensitive hydrogels, have been prepared. In the past few years, significant progress has also been made in the area of stereoselective polymerization of lactides. This new generation of initiators has enabled the production of polylactide materials with novel microstructures and/or properties, such as heterotactic (−*RRSSRRSSRRSS*−) polylactide, crystalline syndiotactic (−*RSRSRSRSRSRS*−) polylactide and isotactic stereoblock ($-R_nS_nR_nS_n-$) polylactide, exhibiting a high melting temperature. The recently developed polymerizations using *in situ* generated initiators and stereoselective polymerizations have no doubt opened a brand-new avenue for the design and exploration of polylactides and their copolymers.

Key words: Polylactide; ring-opening polymerization; *in situ* polymerization; stereoselective polymerization; living polymerization; biodegradable polymers.

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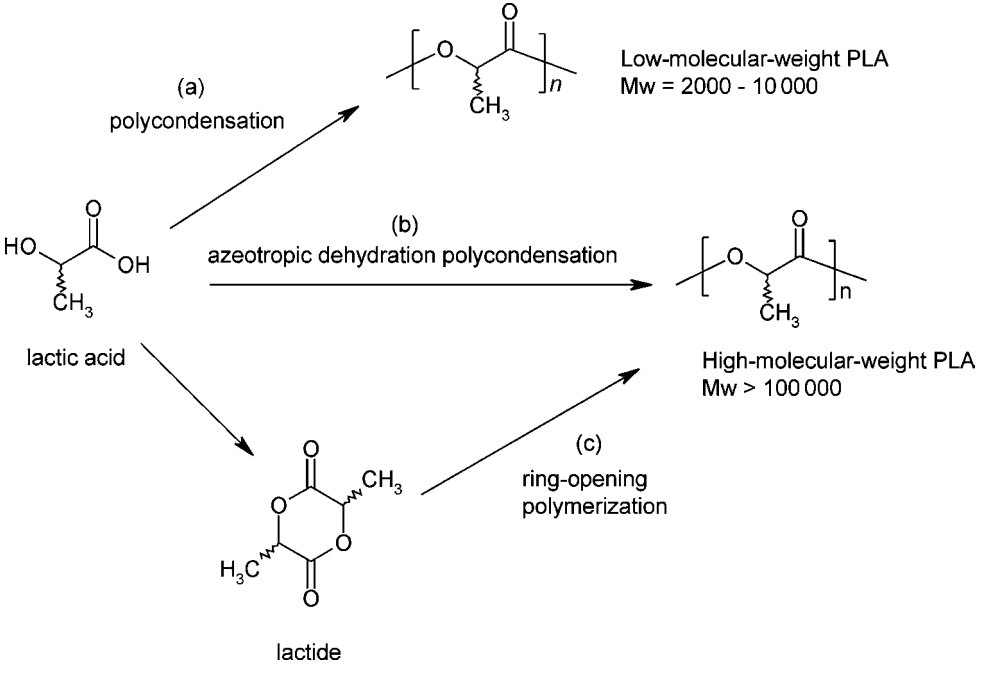
INTRODUCTION

Polylactides (PLAs), featuring biodegradability, biocompatibility and non-toxicity, are particularly useful for temporary medical devices, e.g. drug-delivery systems, resorbable sutures, medical implants and scaffolds for tissue engineering [1–3]. For example, in tissue engineering polylactides and copolymers of lactide and glycolide have appeared as one of the few ideal matrices [4]. These (co)polyesters can readily be processed into open, porous, three-dimensional scaffolds using different processing techniques, have sufficient mechanical strength to maintain the shape of the scaffold, thereby guiding tissue growth, are completely resorbable leaving only the newly formed natural tissue and do not induce a tissue response in the host. The surface of these polymeric scaffolds could be modified to provide optimal cell–scaffold interactions. Furthermore, these polymers could also be manufactured to provide controlled release of hormones and/or growth factors.

PLAs are a first family of polymers made entirely from annually renewable resources such as corn and sugar beets, are fully compostable and have performances comparable to conventional petro-chemical based polyolefins [5]. They have, therefore, also attracted much attention as sustainable environmentally friendly plastics used, e.g. as packaging materials, agricultural films and fibers [3, 5].

The PLA polymers can be prepared by direct polycondensation of lactic acid (Scheme 1a). However, the equilibrium nature of condensation reactions combined with the difficulties in removing trace amount of water during the late stage of

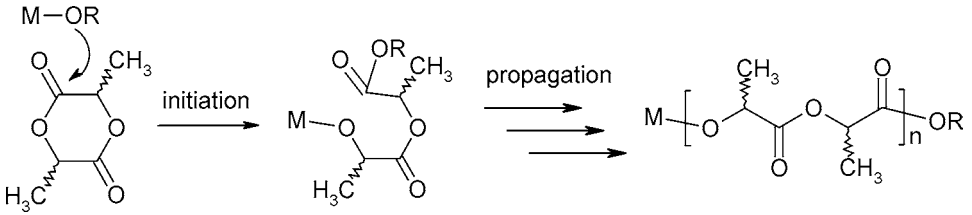


Scheme 1. Synthetic pathways to lactide polymers.

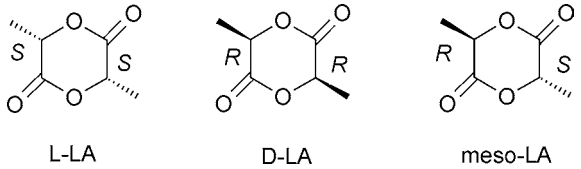
polymerization in general results in PLAs with a low molecular mass and thereby an insufficient strength for practical use. Recently, Mitsui Toatsu Chemicals invented an azeotropic distillation process for efficient dehydration, which enables the production of PLAs with molecular masses ranging from 100 up to 300 kDa employing direct polycondensation (Scheme 1b) [6, 7]. Nevertheless, this polymerization process suffers several drawbacks, among which are a need for a considerable amount of catalyst to achieve an acceptable polymerization rate, a need for a relatively large reactor as a result of low volume efficiency and a need for evaporation and recovery of the high boiling organic solvent.

In contrast, the ring-opening polymerization (ROP) of lactide (LA) in the presence of a catalyst and/or initiator has proven more versatile and efficient in producing PLA polymers (Scheme 1c) [8]. Stannous octoate has been the most often used catalyst because of its good solubility in the melt of LA monomers, high catalytic activity, low levels of racemization, as well as US FDA approval as a food additive. For example, the major PLA supplier Cargill-Dow LLC produces PLA high polymer using a stannous-octoate-catalyzed LA polymerization in the melt. The most probable polymerization mechanism involves tin(II) alkoxide growing species, presumably formed from stannous octoate and hydroxyl-containing impurities such as trace amounts of alcohol and water in the polymerization mixture [9, 10]. Frequently, hydroxyl-containing molecules, such as l-hexanol and l-octanol, are introduced on purpose to control the molecular weight as well as to accelerate the polymerization reaction. More recently, zinc lactate, which showed catalytic characteristics similar to stannous octoate, has been proposed as a less toxic catalyst substitute for PLA production [11, 12]. It should be noted, however, that for both stannous octoate and zinc lactate, high temperatures and long polymerization times are needed and significant transesterification reactions will take place. This has rendered these catalysts ideal for the preparation of random-type (usually amorphous) lactide copolymers such as poly(lactide-co-glycolide) and poly(ε-caprolactone-co-lactide), but made them less suitable for building advanced materials for instance functional polylactides and block copolymers of low polydispersities (M_w/M_n).

In the past two decades, a range of metal alkoxides, including alkali metal alkoxides [13], aluminum alkoxides [14], yttrium and lanthanide alkoxides [15], has been studied for the polymerization of lactides, motivated by a need for an efficient catalyst/initiator system to produce lactide-based materials with controlled parameters. The polymerization in general proceeds via nucleophilic attack of the alkoxide ligand to the carbonyl carbon followed by acyl-oxygen cleavage of the monomer, where the newly formed metal alkoxides continue to grow polymer chains (Scheme 2). The metal alkoxides, however, have a ubiquitous propensity to form aggregates. For example, yttrium isopropoxide and aluminum isopropoxide, both widely investigated for lactide polymerizations, exist as a pentanuclear complex with a formula of $Y_5(\mu\text{-O})(O\textit{i}Pr)_{13}$ [16] and a mixture of trimer ($(Al(O\textit{i}Pr)_3)_3$) and tetramer ($(Al(O\textit{i}Pr)_3)_4$) [17, 18], respectively. This aggregation behavior has



Scheme 2. General scheme for metal alkoxide (M-OR) initiated lactide polymerization.



Scheme 3. LA stereoisomers. *rac*-LA is a 1 : 1 mixture of L-LA and D-LA.

resulted in a slow polymerization, a low initiating efficiency and/or complex polymerization kinetics.

A very unique property of PLA polymers is their main-chain chirality. The physical, mechanical as well as degradation properties of PLAs are intimately dependent on the chain stereochemistry [19, 20]. Isotactic poly(L-LA) and poly(D-LA), highly crystalline materials with a melting temperature (T_m) of 170°C, exhibit excellent mechanical properties and degrade rather slowly. By contrast, atactic PLAs are amorphous and subject to a comparatively fast degradation. Another interesting aspect of PLAs is that poly(L-LA) and poly(D-LA) enantiomeric chains readily co-crystallize in solution and in the melt to form a stereocomplex with a high melting temperature of 230°C [21] and enhanced tensile properties [22]. It was shown that even the stereo-diblock copolymer of L-LA and D-LA has a rather high melting point of 205°C [23]. It is, therefore, essential to control the stereochemical structure of PLA homopolymers and copolymers.

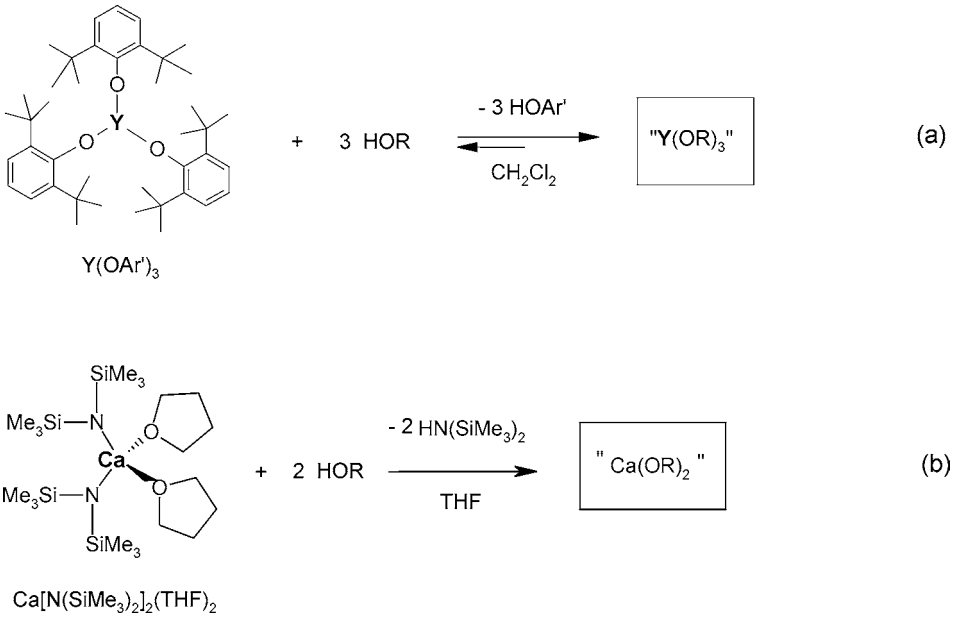
LA monomer, having two stereocenters, exists as three different stereoisomers: L-, D- and *meso*-LA (Scheme 3). It should be noted that using a non-selective catalyst, as often was the case, the polymerization of both *rac*-LA and *meso*-LA gives an atactic PLA. The stereochemistry of PLA chains can in principle be controlled by the feeding ratio of stereoisomers and/or stereoselection during PLA chain propagation. PLA is one of the few polymers in which the microstructure can easily be modified by polymerizing a controlled mixture of stereoisomers to afford high molecular weight amorphous or crystalline materials to meet specific applications. For example, PLA 70/30 (L-LA/*rac*-LA = 70 : 30), which is amorphous but with mechanical properties close to isotactic poly(L-LA), has currently been produced for several orthopedic implants [24–26]. On the other hand, stereoselection requires the use of specific catalysts and represents a challenging approach to control the stereochemical structure of PLAs [27].

Over the past few years, we have explored a range of *in situ* generated metal alkoxides based on soluble yttrium, calcium and zinc precursors. These *in situ* formed initiators, as a contrast to isolated metal alkoxides, induced an extremely fast living polymerization of lactides at room temperature. The resulting polylactides and copolymers have controlled molecular weight, low polydispersity and tailored end-groups and macromolecular architectures. Single-site metal alkoxide initiators with a general formula of L_n-M-OR where L_n is a bulky inert ligand stand for the other current strategy to gain good control over polymerization of lactides [28]. Of particular interest is that some of these single-site initiators were capable of effecting a stereoselective polymerization of lactides, in which polylactides of novel microstructures and properties have been prepared. These highly versatile *in situ* generated initiators and single-site stereoselective polymerization initiators represent the most exciting developments and have not been reviewed before. In this paper, we will describe state-of-the-art *in situ* polymerization and stereoselective polymerization of lactides. The preparative significance of these novel polymerizations will also be discussed.

HIGHLY EFFICIENT *IN SITU* GENERATED INITIATOR SYSTEMS

Yttrium alkoxides, formed *in situ* from sterically crowded tri(2,6-di-*tert*-butylphenoxy) yttrium and a less bulky alcohol (Scheme 4a), are the first reported *in situ* generated initiators that exhibit unprecedentedly high reactivity in initiating living ring-opening polymerization of LAs [29, 30]. The polymerization of L-LA in CH_2Cl_2 at room temperature was complete within a few minutes and furnished polymers of a low polydispersity ($M_w/M_n < 1.25$) and an expected M_n. This reaction was significantly faster than that of commercial yttrium isopropoxide cluster initiated L-LA polymerization where a period of 5 days was required in order to reach high monomer conversion under similar conditions. It should be noted that tri(2,6-di-*t*-butylphenoxy) yttrium, itself, was sluggish towards LA polymerization. The added alcohol molecule will determine the end-group functionalities, chain structure and molecular weight. The polymerization proceeded after instantaneous initiation and kinetic studies revealed a first-order polymerization in both monomer and initiator. In this study, *in situ* UV spectroscopy was established as a useful technique to follow the fast propagation of L-LA [30]. A comparative NMR study revealed that the species formed from $Y(OAr')_3$ and HO*i*Pr is different from $Y_5(\mu\text{-O})(O\textit{i}Pr)_{13}$. Lately, yttrium and neodymium alkoxides were also *in situ* generated by alcoholysis of yttrium and neodymium tris[bis(trimethylsilyl)amide], respectively. Both were reported highly active in the ring-opening polymerization of ε-caprolactone to give poly(ε-caprolactone)s with well-controlled molecular weight and low polydispersity [31, 32].

More recently, a calcium-based initiating system, generated *in situ* from bis(tetrahydrofuran)calcium bis[bis(trimethylsilyl)amide] ($Ca[N(SiMe_3)_2]_2(THF)_2$) and an adequate alcohol (Scheme 4b), was developed for the efficient polymerization of



Scheme 4. *In situ* generation of yttrium alkoxides and calcium alkoxides.

lactides [33–35]. $Ca[N(SiMe_3)_2]_2(THF)_2$ was one of the few structurally well-characterized and easily prepared organocalcium compounds that can readily be dissolved in many common organic solvents such as THF and toluene. The solution polymerization of L-LA in THF using mild conditions was living, yielding PLAs of tailored macromolecular architectures and controlled molecular weights (Fig. 1). Both NMR and DSC analyses revealed the absence of racemization during L-LA polymerizations. The absence of an induction period suggested that both the alcoholysis of $Ca[N(SiMe_3)_2]_2(THF)_2$ and the subsequent initiation of L-LA polymerization are extremely fast. Polymerizations conducted at high 2-propanol/$Ca[N(SiMe_3)_2]_2(THF)_2$ ratios (e.g. 16 : 1) showed that all 2-propanol has initiated a chain polymerization of L-LA, indicating that the active species (coordinated alkoxides and/or growing polymer ends) transfer rapidly and reversibly with the dormant species (free alcohol molecules and/or hydroxyl-capped polymers). In addition, $Ca[N(SiMe_3)_2]_2(THF)_2$ was also useful for surface-initiated ROP of lactides or lactones from patterned hydroxyl group functionalized self-assembled monolayers (SAMs) or hydroxyl group functionalized monolayer-protected gold nanoparticles [36].

The ring-opening polymerization of D,L-3-methyl-glycolide (MG) in the presence of poly(ethylene glycol) (PEG) and $Ca[N(SiMe_3)_2]_2(THF)_2$ provided PMG-PEG-PMG triblock copolymers with alternating lactyl/glycolyl sequences of controlled molecular weight, low polydispersity index and uniform chain structure (Scheme 5) [37]. The site-specific cleavage of MG monomers is most probably due to the other site being more sterically hindered. A solubility test showed that

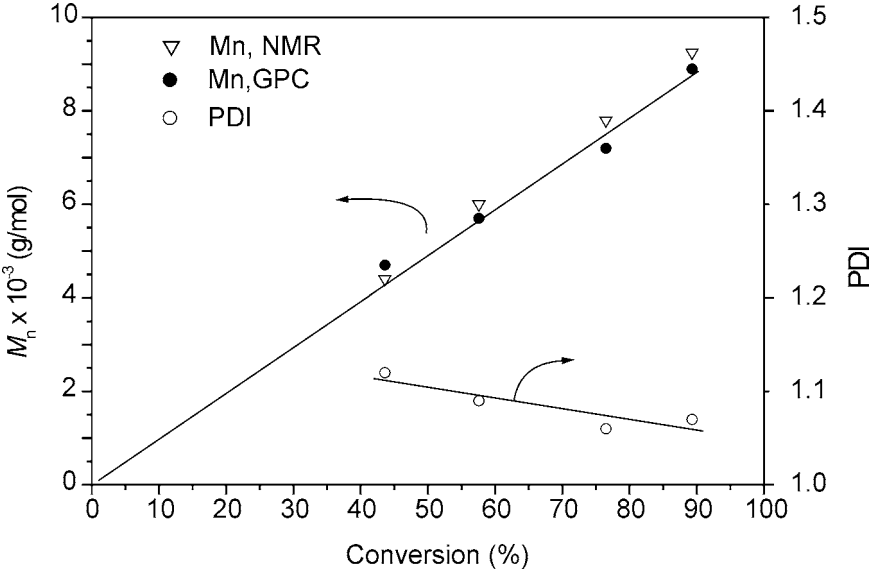
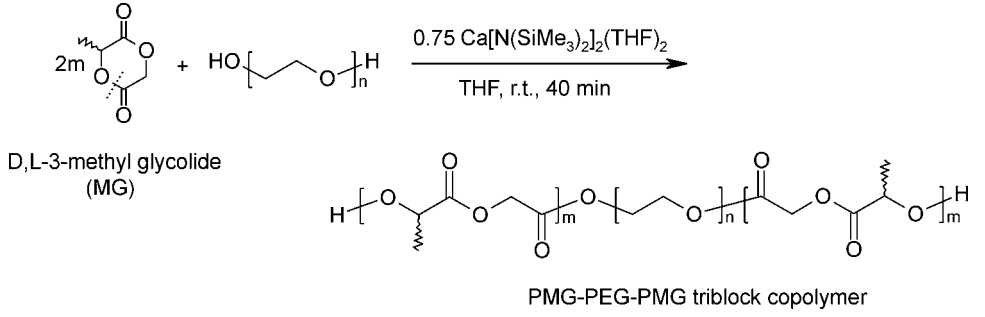


Figure 1. Poly(L-LA) molecular weight and polydispersity index (PDI) *versus* monomer conversion. $[M]_0/[2\text{-PrOH}]_0/[Ca]_0 = 150:2:1$, room temperature, THF, $[M]_0 = 0.8$ mol/l.



Scheme 5. Synthesis of PMG-PEG-PMG triblock copolymers by ROP of D,L-3-methyl glycolide (MG) using poly(ethylene glycol)/Ca[N(SiMe$_3$)$_2$]$_2$(THF)$_2$.

at relatively low temperatures (approx. 10°C) these low-molecular-weight copolymers form clear solutions in water up to high concentrations (50 wt%). Depending on molecular mass ratios of PMG and PEG blocks, a sol–gel transition (Fig. 2) or an increase in viscosity without gel formation was observed upon increasing the temperature of the aqueous solutions. These biodegradable thermosensitive hydrogels are interesting for many biomedical applications, e.g. as drug and cell carriers and as tissue-engineering matrices [38, 39].

In a further development, a single-site calcium catalyst containing chelating tmhd (H-tmhd = 2,2,6,6-tetramethylheptane-3,5-dione) ligands, [(THF)Ca(tmhd)]$_2$[μ-N(SiMe$_3$)$_2$](μ-tmhd), was synthesized (Scheme 6) [40, 41]. The polymerizations promoted by single-site catalysts are expected to have the advantage of

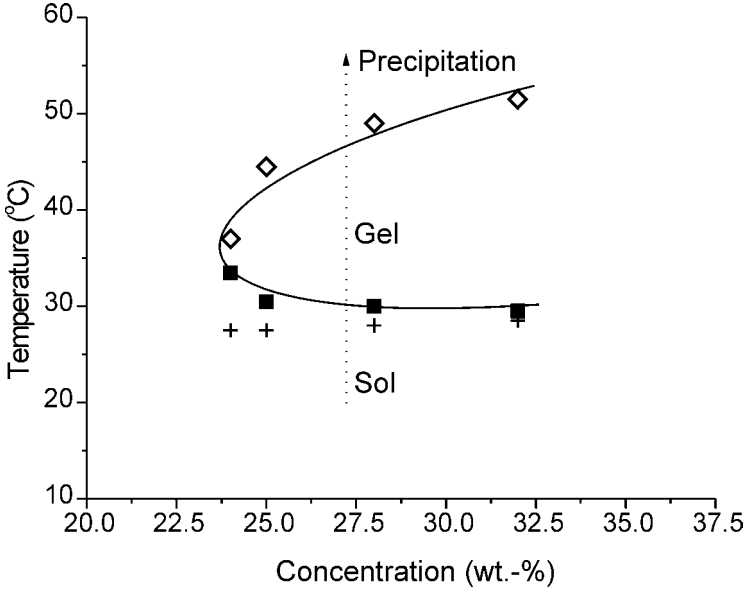
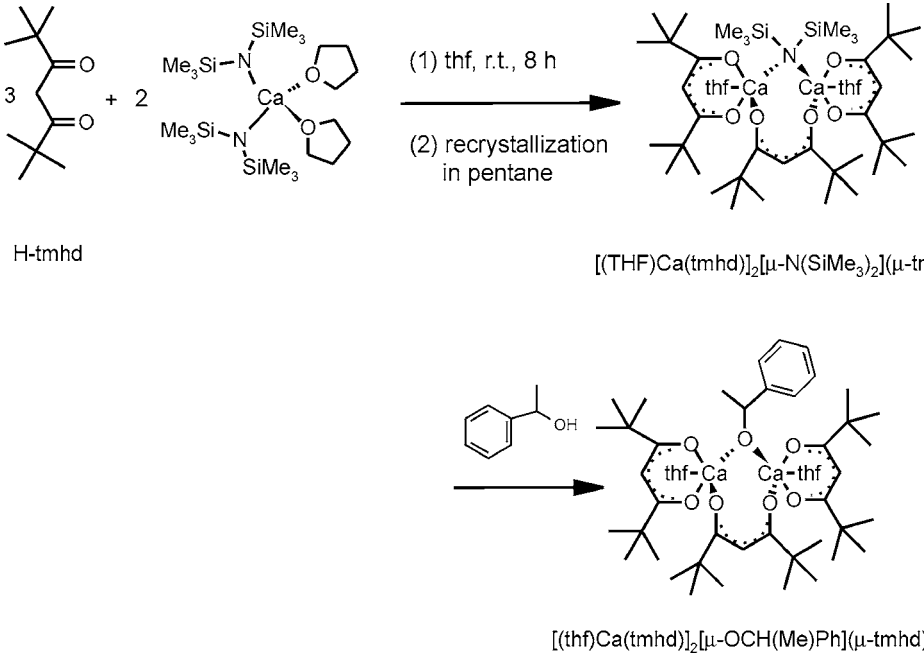
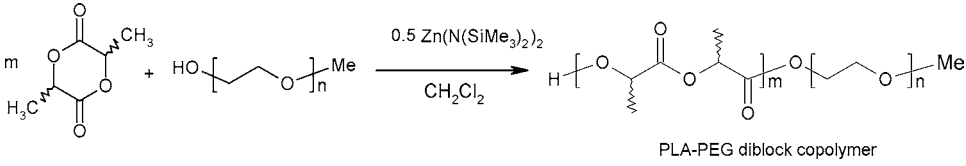


Figure 2. Phase diagram of PMG-PEG-PMG 1400-1450-1400 triblock copolymer in aqueous solution. (+) Cloud point, (■) sol–gel transition temperature, (◇) macrophase separation.

controlled kinetics and no gelation when using di- or multi-hydroxyl molecules. $[(THF)Ca(tmhd)]_2[\mu\text{-}N(SiMe_3)_2](\mu\text{-tmhd})$ exhibited a high catalytic activity and induced fast polymerization of L-LA in THF at room temperature, yielding PLAs with a high polydispersity and a higher molecular weight than calculated assuming that every catalyst molecule produces one polymer chain. On the contrary, in the presence of one equivalent of 2-propanol with respect to $[(THF)Ca(tmhd)]_2[\mu\text{-}N(SiMe_3)_2](\mu\text{-tmhd})$, L-LA was polymerized more rapidly up to high monomer conversions and the obtained PLAs had a low polydispersity, molecular weights as expected and evident end-groups, in accordance with the living nature of the active species [41]. In this way, also structurally defined poly(ε-caprolactone-b-L-lactide) block copolymers can be obtained by sequential polymerization. In order to compare the polymerization activity between *in situ* generated alkoxide compound and the isolated analogue, $[(THF)Ca(tmhd)]_2[\mu\text{-}N(SiMe_3)_2](\mu\text{-tmhd})$ was reacted in THF with isopropanol [40]. The recrystallization from toluene, however, gave the homoleptic dimutation product $[Ca(tmhd)_2]_3$ and a mixture of alkoxide-rich complexes of yet unknown composition. On the other hand, the structure of $[(THF)Ca(tmhd)]_2[\mu\text{-}N(SiMe_3)_2](\mu\text{-tmhd})$ was maintained upon alcoholysis with a sterically more demanding alcohol such as 1-phenylethanol and a compound with a formula $[(THF)Ca(tmhd)]_2[\mu\text{-}OCH(Me)Ph](\mu\text{-tmhd})$ was isolated (Scheme 6). Comparative kinetic experiments revealed that the polymerization of lactide in the presence of either initiating system, $[(THF)Ca(tmhd)]_2[\mu\text{-}N(SiMe_3)_2](\mu\text{-tmhd})$/2-propanol or $[(THF)Ca(tmhd)]_2[\mu\text{-}OCH(Me)Ph](\mu\text{-tmhd})$, was first-order in monomer up to high conversions. $[(THF)Ca(tmhd)]_2[\mu\text{-}OCH$



Scheme 6. Synthesis of [(THF)Ca(tmhd)]$_2$[μ-N(SiMe$_3$)$_2$](μ-tmhd) and [(THF)Ca(tmhd)]$_2$[μ-OCH(Me)Ph](μ-tmhd).



Scheme 7. Controlled synthesis of PLA-PEG diblock copolymers using monomethoxy PEG/Zn(N(SiMe$_3$)$_2$)$_2$ in CH_2Cl_2 at room temperature.

(Me)Ph](μ-tmhd) displayed a pronounced induction period before the polymerization was taking place, whereas the *in situ* initiating system [(THF)Ca(tmhd)]$_2$[μ-N(SiMe$_3$)$_2$](μ-tmhd)/2-propanol initiated an immediate polymerization of lactide with a much higher polymerization rate as compared to isolated compound [(THF)Ca(tmhd)]$_2$[μ-OCH(Me)Ph](μ-tmhd) [41]. It is evident therefore that the *in situ* initiating systems have superior polymerization kinetics.

Very recently, zinc bis[bis(trimethylsilyl)amide], similar to Ca[N(SiMe$_3$)$_2$]$_2$(THF)$_2$, was also found to promote a fast controlled polymerization of lactides at room temperature in the presence of monomethoxy poly(ethylene glycol) (Scheme 7) [42, 43]. The resulting poly(*rac*-lactide)-b-poly(ethylene glycol) diblock copolymers had prescribed molecular weights with low polydispersities. Most interestingly, these diblock copolymers gave rise to polymeric vesicles, also referred to as polymersomes, by introducing an organic solution of the copoly-

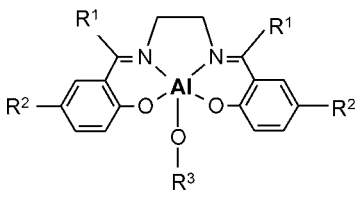
mer into an aqueous medium. By using different combinations of organic solvent and aqueous phase, the size of the polymersomes could be varied in a broad range from 50 nm up to 80 μm with narrow size distributions [42, 43]. These polymersomes are expected to be biodegradable and biocompatible. These novel biodegradable polymersomes have many potential applications for example in drug delivery systems, bioreactors and artificial cells. The catalyst used in this study, zinc bis[bis(trimethylsilyl)amide], is interesting due to its high activity, commercial availability and low toxicity of zinc residues.

These *in situ* initiating systems are remarkably active and versatile. PLA homopolymers and block copolymers with advanced architectures and functionalities can readily be prepared by taking advantage of the living polymerization character and the structure of the starting alcohol molecules.

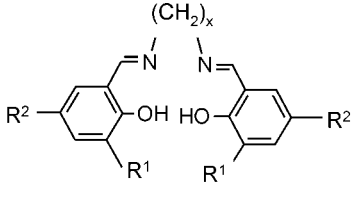
SINGLE-SITE STEREOSELECTIVE POLYMERIZATION INITIATORS

Stereoselective polymerization of lactides via a chain-end control mechanism

A series of aluminum alkoxides based on achiral Schiff's base ligands has been explored for *rac*-LA polymerization (Scheme 8) [44–50]. The polymerization of *rac*-LA using **1** in toluene at 70°C showed a living character up to 60% conversion (M_w/M_n = 1.10–1.20), above which significant transesterification reactions took



1: $R^1 = R^2 = H$, $R^3 = Me$
2: $R^1 = H$, $R^2 = Cl$, $R^3 = Me$
3: $R^1 = Me$, $R^2 = H$, $R^3 = Me$
4: $R^1 = Me$, $R^2 = H$, $R^3 = i$Pr
5: $R^1 = H$, $R^2 = Cl$, $R^3 = i$Pr



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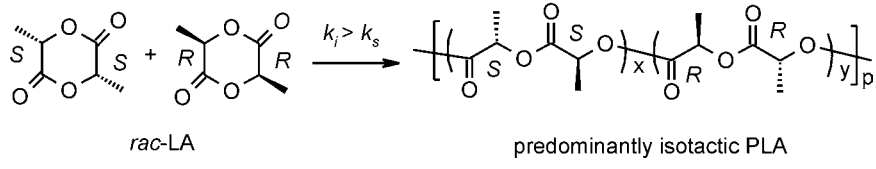
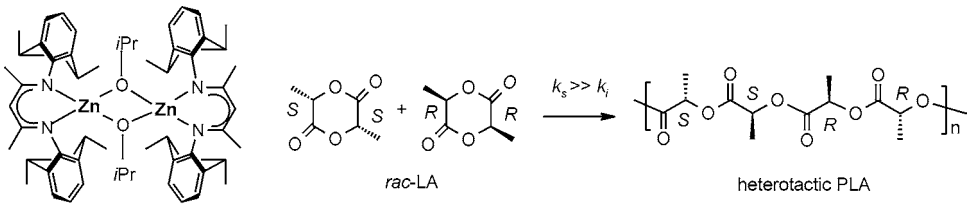
x = 2 or 3
R^1 = H, Me, *i*Pr, Ph or *t*Bu
R^2 = H, Me or *t*Bu



rac-LA predominantly isotactic PLA

Scheme 8. Aluminum alkoxides based on achiral Schiff's base ligands for the stereoselective polymerization of *rac*-LA. k_i and k_s represent rates of isotactic and syndiotactic enchainment, respectively.



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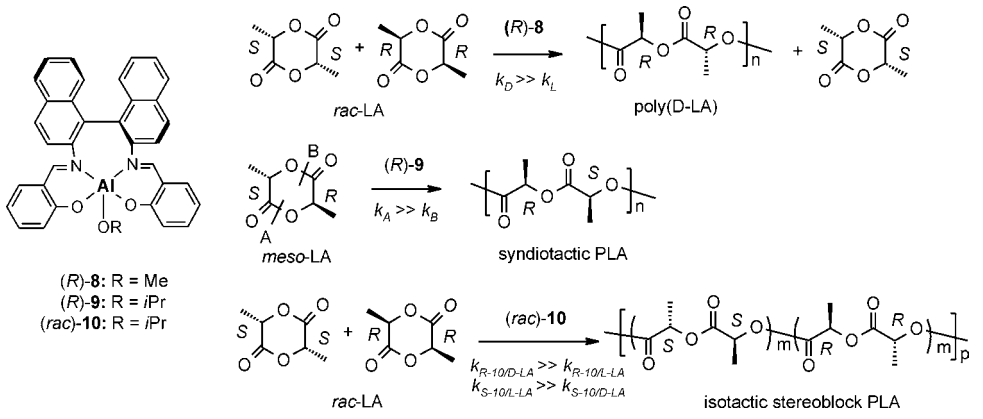
Scheme 9. Diiminate zinc alkoxide for heterotactic polymerization of *rac*-LA.

place [45, 46]. Most interestingly, the isolated polymers were crystalline. A ^{13}C-NMR spectroscopic analysis revealed long isotactic sequences of the obtained PLAs and a reactivity ratio (rates of homo/cross propagation, k_i/k_s) of 2.8. The preference for the isotactic enchainment was explained by a chain-end propagation mechanism. The modified versions, initiator **2** [48] and **3** [49], were capable of polymerizing *rac*-LA in CH_2Cl_2 at ambient temperature, yielding PLAs of low polydispersity ($M_w/M_n \leqslant 1.10$ and 1.20 for **2** and **3**, respectively) and controlled M_n up to high conversions. An improved electrophilicity of the aluminum center in **2** due to the presence of electron withdrawing groups and an increased polarisability of the Al-OMe bond in **3** were proposed to account for the higher reactivity. The substitution of the methoxide by an isopropoxide group (initiator **4** and **5**) also led to an enhanced polymerization rate, although the polymerization was not controlled because of early occurring transesterifications [50]. More recently, achiral Schiff's base aluminum alkoxides *in situ* formed from ligand **6**, Et_3Al and benzyl alcohol were reported to display a preference for the formation of isotactic sequences for *rac*-LA polymerization in toluene at 70°C (Scheme 8) [51]. It is interesting to note that the catalytic reactivity of catalyst with a trimethylene backbone ($x = 3$) was much higher than that with an ethylene backbone ($x = 2$) and larger R^1 in the aromatic rings in general effected a higher isotacticity. The introduction of Ph-substituents into the aromatic rings enhanced both the polymerization rate as well as the selectivity. In contrast, the *t*-butyl substituents slowed the polymerization rate but gave the best selectivity.

Coates and co-workers have discovered that a diiminate ligated zinc complex, **7**, brought about the solution polymerization of *rac*-LA in a fast and living manner at a temperature ranging from 0 to 25°C, to yield a highly heterotactic (−*RRSSRRSSRRSS*−) PLA (Scheme 9) [52, 53]. Despite the chain stereoregularity, the polymer was amorphous with a T_g of 49°C. On the contrary, the magnesium analogue displayed no stereoselectivity under similar polymerization conditions.

Stereoselective polymerization of lactides via an enantiomorphic site control mechanism

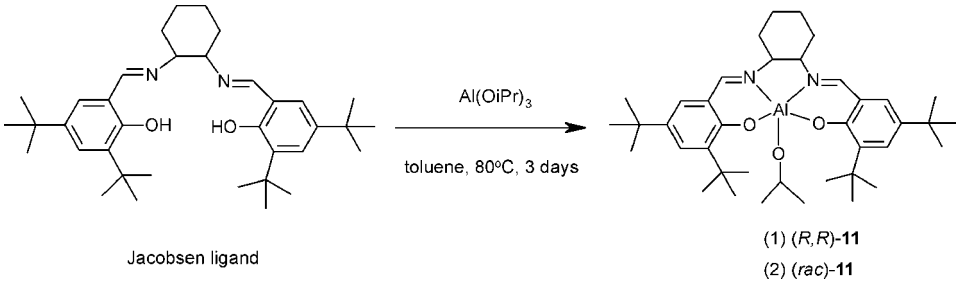
The enantiopure (*R*)-binaphthyl Schiff base aluminum complex, (*R*)-**8**, was reported to initiate a faster and better-controlled polymerization of *rac*-LA than the



Scheme 10. Chiral binaphthyl Schiff's base aluminum alkoxides for the stereoselective polymerization of LAs.

parent achiral initiator **1** in toluene at 70°C and crystalline PLAs of controlled M_n and low polydispersity (M_w/M_n = 1.05–1.30) were obtained up to high conversions (Scheme 10) [54]. The optical rotation measurement of the PLAs at different conversions revealed that (*R*)-**8** has a preference for D-LA over L-LA. The optical purity of the polymer decreased with conversion because of the incorporation of L-LA, which was enriched in the monomer pool. The stereoselectivity originates from the stereogenic environment at the reactive center. Employing a site-control catalyst, (*R*)-**9**, syndiotactic (−*RSRSRSRS*−) PLA, which was crystalline with a T_g = 34.1°C and a T_m = 152°C, has been prepared for the first time by polymerizing *meso*-LA (Scheme 10) [55]. The polymerization of *rac*-LA using a racemic initiator, (*rac*)-**10**, gave PLAs of high melting temperatures (T_m = 179–191°C) as a result of stereocomplex formation between D-LA and L-LA enantiomeric segments produced by (*R*)-**10** and (*S*)-**10**, respectively [56–58]. Homonuclear decoupled ^{1}H-NMR spectroscopy revealed that the resulting PLA was not a mixture of enantiomerically enriched poly(L-LA) and poly(D-LA), but was an isotactic stereoblock copolymer of L-LA and D-LA for which a polymer exchange mechanism has been proposed [58].

Very recently, we discovered that cyclohexylsalen aluminum isopropoxide derived from Jacobsen ligand initiates a controlled and stereoselective polymerization of lactides. Jacobsen ligand is a commercial reagent used for many asymmetric reactions, e.g. asymmetric olefin epoxidation, asymmetric epoxide ring-opening reactions [59] and hydrolytic kinetic resolution of terminal epoxides [60]. The cyclohexylsalen aluminum isopropoxides were readily prepared with high yield by stoichiometric reaction of (*R,R*)- or (*rac*)-Jacobsen ligand with aluminum isopropoxide in toluene at 80°C (Scheme 11) [61–63]. The polymerizations of lactides in toluene at 70°C are living, affording in all cases PLAs with defined end-groups, prescribed molecular weight and low polydispersity (M_w/M_n = 1.04–1.09). The comparative polymerization kinetics (Fig. 3) showed that enantiopure



Scheme 11. Synthesis of cyclohexylsalen aluminum isopropoxides.

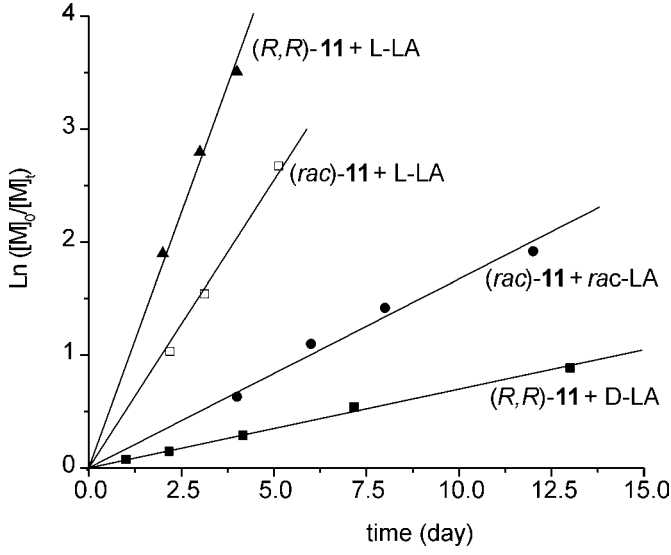


Figure 3. First-order kinetic plots for LA polymerizations in toluene at 70°C with $[M]_0/[Al]_0 = 62$ and $[M]_0 = 0.8$ M.

(*R,R*)-**11** polymerizes L-LA significantly faster than D-LA with a rate ratio k_L/k_D of about 14, indicating that (*R,R*)-**11** has a marked preference for L-LA over D-LA. This has been confirmed by the fact that PLAs obtained by polymerizing *rac*-LA using (*R,R*)-**11** at incomplete conversions have a pronounced levoratory optical rotation (Fig. 4) [63]. This is in contrast with binaphthyl Schiff's base aluminum alkoxides, in which the enantiopure (*R*)-initiator has a preference for D-LA. The equations useful for the determination of the stereoselectivity factor ($s = k_{fast}/k_{slow}$) for an asymmetric enantiomer-differentiating polymerization have recently been re-derived [64]. For example, the stereoselectivity can be calculated based on the specific rotation of the resulting polymer:

$$s = k_{rel} = \ln[1 - c(1 + ee)]/\ln[1 - c(1 - ee)],$$

where ee represents the enantiomeric excess of the monomer units in the polymer and c the monomer conversion. A selectivity factor ($s = k_L/k_D$) of 5.5 has thus been

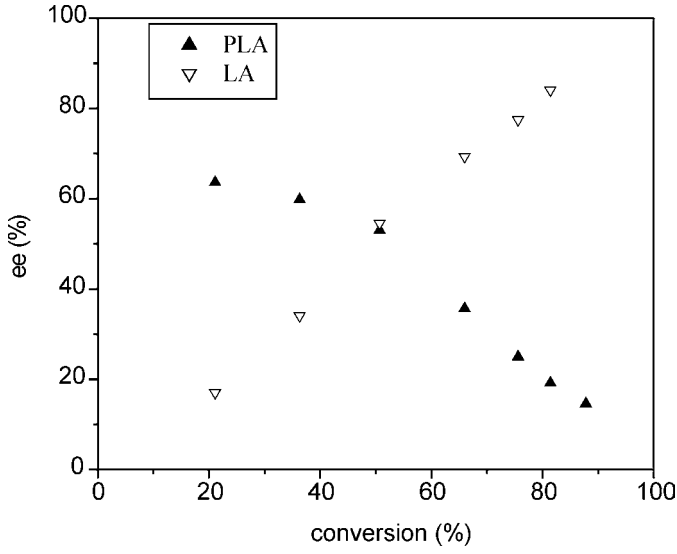


Figure 4. Plots for the enantiomeric excess (ee) of the monomers calculated from the optical purity of the polymer and monomer conversion (**7**) as well as the LA units in the recovered polymer (**4**) as a function of conversion for *rac*-LA polymerization initiated with (*R,R*)-**11** ($[LA]_0/[Al]_0 = 62:1$, $[LA]_0 = 0.8$ M, toluene, 70°C).

determined in (*R,R*)-**11** for *rac*-LA polymerization [63]. ^{13}C-NMR microstructural analysis (Fig. 5) revealed that PLAs resulting from *rac*-LA polymerization using (*R,R*)-**11** have comparably high isotacticity.

The polymerization of L-LA using (*rac*)-**11** has a rate constant slightly higher than half that of (*R,R*)-**11** for L-LA polymerization (Fig. 3). This is in line with our expectation, since only half of the (*rac*)-**11** has the (*R,R*)-configuration and the other half (*S,S*)-**11** can only slowly polymerize L-LA. (*R,R*)-**11** was also employed to polymerize a mixture of *meso*-LA and *rac*-LA (*meso*-LA/rac-LA: 83/17). The *meso*-LA, *rac*-LA and PLA display distinctive methyl resonances at δ1.70(d), 1.66 (d) and 1.55 (m), respectively, in the ^{1}H-NMR spectrum. The results showed that (*R,R*)-**11** also exhibited a preference for *meso*-LA polymerization over *rac*-LA with a relative rate k_{meso}/k_{rac} of 2.8 (diastereoselectivity). During the ring-opening of *meso*-LA, a syndiotactic selectivity was observed, which coupled with diastereoselectivity afforded a crystalline highly syndiotactic PLA at low conversion [36].

The polymerizaiton was first order in initiator where a k_p value of 9.02×10^{-3} $l\,mol^{-1}\,min^{-1}$ has been determined for (*rac*)-**11** initiated *rac*-LA polymerization in toluene at 70°C. This value is lower than that of *rac*-LA polymerization with $Al(O^iPr)_3$ ($k_p = 0.60\ l\,mol^{-1}\,min^{-1}$) [65] or achiral Schiff's base aluminum methoxide ($0.061\ l\,mol^{-1}\,min^{-1}$) [50] under similar conditions. This is most probably due to the rather rigid and bulky nature of the cyclohexylsalen ligand in cyclohexylsalen aluminum isopropoxide. It is worth mentioning herein that (*rac*)-

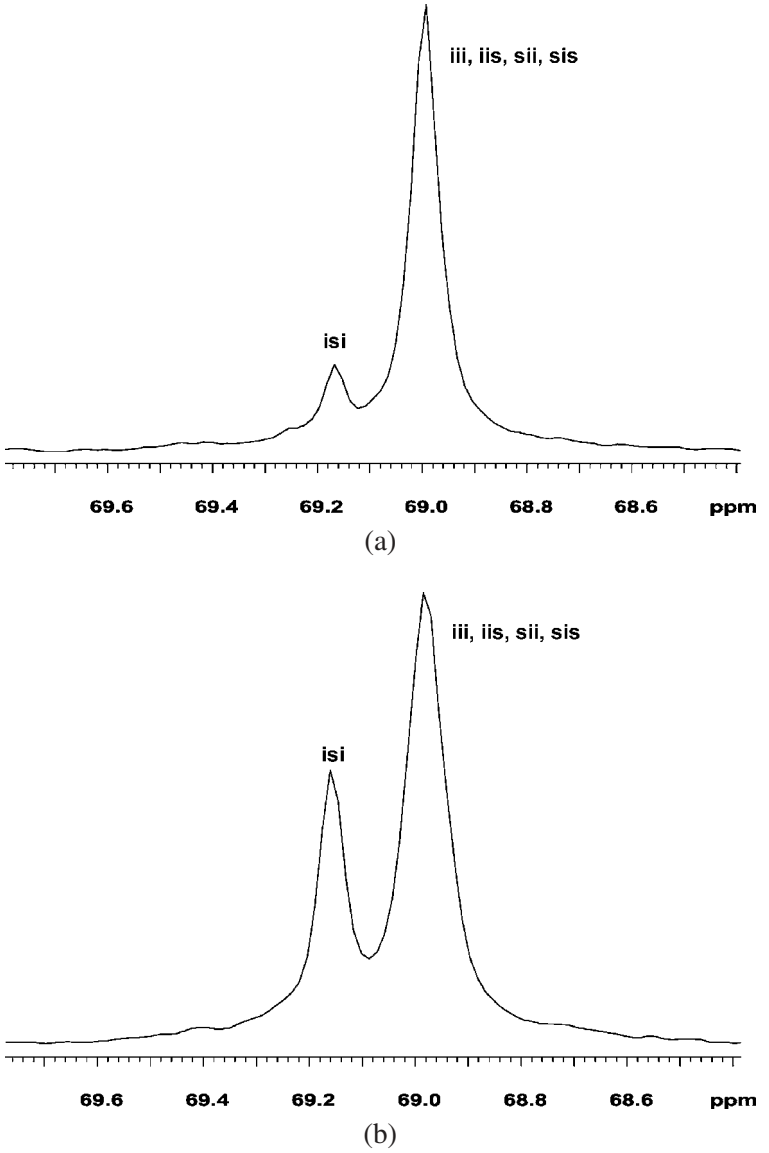


Figure 5. The PLA methine carbon resonances in the ^{13}C-NMR spectra (75 MHz, $CDCl_3$). (a) PLA sample obtained from *rac*-LA polymerization by (*R,R*)-**11** in toluene at 70°C with [LA]/[Al] = 62 : 1 and conversion = 87.8%. (b) PLA prepared by polymerizing *rac*-LA with the non-selective catalyst $Zn(OCH(Me)COO\textit{i}Pr)_2$.

10 brought about a much faster polymerization of *rac*-LA (1.05 l mol^{-1} min^{-1}) [58] than (*rac*)-**11**. The higher activity of (*rac*)-**10** as compared to (*rac*)-**11** might be due to the ability of binaphthyl moiety to delocalize electrons, the absence of bulky substituents in the aromatic rings in the ortho position, and a long diamino bridge (four carbons for (*rac*)-**10** *vs.* two carbons for (*rac*)-**11**). It has been shown that the

replacement of ethylene diamino with trimethylene diamino in achiral Schiff's base aluminum alkoxide significantly increases the polymerization rate [51].

The polymerization of a L-lactide/D-lactide (molar ratio 80 : 20) mixture by enantiopure (*R,R*)-**11** in one pot furnishes an isotactic-atactic block copolylactide, which was highly crystalline with a T_m of about 155°C. Polymerization of *rac*-lactide applying (*rac*)-**11** yields isotactic stereoblock polylactides with a high T_m (approx. 185°C) and a high degree of crystallinity. Tapered stereoblock PLA with configurations varying from long L-sequences to long D-sequences throughout the polymer chain, could be prepared by the polymerization of *rac*-LA employing (*R,R*)-**11**. This stereoselective polymerization might also allow that optically pure D-LA, an expensive enantiomer, is kinetically separated from commodity *rac*-LA by selective polymerization of L-LA with (*R,R*)-**11**.

Most interestingly, excellent molar mass control as well as stereochemical control was implemented even when *rac*-LA was polymerized in the melt at 130°C [61, 62]. At a monomer-to-initiator molar ratio of 200, high conversions were obtained within 2 days, providing PLAs of rather low PDI ($M_w/M_n = 1.18$ for (*R,R*)-**11**, 1.37 for (*rac*)-**11**). The microstructural analysis showed that both polymers contain long isotactic sequences. (*R,R*)-**11** furnished an amorphous PLA, whereas (*rac*)-**11** afforded a hard crystalline material. These results are extraordinary, since no other catalyst reported thus far is able to impose such a high stereoselection in LA polymerization in the absence of solvents.

SUMMARY AND PERSPECTIVES

The past decade has witnessed several innovative PLA technologies, which have largely increased the scope of design and macromolecular engineering of biodegradable polymers. Particularly, the *in situ* generated initiating systems based on structurally characterized yttrium, calcium and zinc precursors have been shown to bring about an efficient ring-opening polymerization of lactides under mild conditions, allowing versatile synthesis of (functional) polylactides and copolymers of predetermined molecular weights and many advanced structures. The calcium and zinc systems are potentially non-toxic, which offer an additional advantage over current catalysts/initiators that are used for the preparation of polymers for biomedical and pharmaceutical applications. The stereoselective initiators, on the other hand, have shown promise in producing polylactides with novel microstructures and properties. It goes without saying that both polymerizations using *in situ* generated initiators and stereoselective polymerizations, as well as their synthetic potentials, warrant further investigation. Rational catalyst/initiator design especially assisted by, e.g. molecular modeling and combinatorial methods, may still afford more efficient initiator systems with improved stereoselectivity.

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