Controlled Ring-Opening Polymerization of Lactide and Glycolide

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1. Introduction

Synthetic petrochemical-based polymers have had a tremendous industrial impact since the 1940s. Despite the numerous advantages of these materials, two major drawbacks remain to be solved, namely, the use of nonrenewable resources in their production and the ultimate fate of these large-scale commodity polymers. Due to their unique properties, biodegradable[1] polymers have long been considered as alternative environmentally friendly polymers, and the spectacular advances achieved over the last 30 years in the synthesis, manufacture, and processing of these materials have given rise to a broad range of practical applications from packaging to more sophisticated biomedical devices.[2−8] Of the variety of biodegradable polymers known, linear aliphatic polyesters are particularly attractive and most used, especially those derived from lactic acid (PLA), glycolic acid (PGA), and their copolymers (PLGA) (Figure 1).[9−14]

Notably these polymers are not only biodegradable (the aliphatic polyester backbone is intrinsically sensitive to water and heat) but also bioassimilable,[15] since their hydrolysis in physiological media gives lactic and glycolic acids, nontoxic components that are eliminated via the Krebs cycle as water and carbon dioxide. Moreover, lactic acid can be obtained by fermentation of renewable resources such as corn and sugar beets. Taking advantage of this attractive feature, Cargill Dow LLC (a 50/50 joint venture between Cargill Inc. and The Dow Chemical Co.) has recently developed a solvent-free, low-cost continuous process for the production of PLA from corn-derived dextrose. The resulting PLA, commercialized under the trade name Nature Works, is the first synthetic polymer to be produced from annually renewable resources.[16−19] Furthermore, the influence of the rheological and physical characteristics of these polymers should not be underestimated. In this regard, the properties of PLGA are inherently rather well suited for their processing and practical applications. Moreover, these properties can be easily tuned and significantly improved by varying the ratio (lactic acid/glycolic acid) and stereochemistry (D- and/or L-lactic acids) of the monomers, i.e., by varying the composition and tacticity of the polymers. Spectacular variations in physical properties can also be achieved during the polymer processing itself, through orientation, blending, branching, cross-linking, or plasticization, for example.[3,20−23]

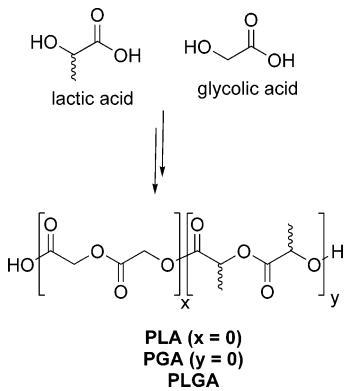

Figure 1. Lactic and glycolic acids and their derived homo- and copolymers.

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Odile Dechy-Cabaret was born near Lille, France, in 1975. She studied at the Ecole Normale Supérieure in Cachan from 1994 to 1998 and obtained her Ph.D. degree in 2001 working on the synthesis of trioxaquines derivatives under the supervision of B. Meunier in Toulouse. She then joined the Laboratoire d'Hétérochimie Fondamentale et Appliquée at the Université Paul Sabatier for a postdoctoral stay, working on PLGA formulations for the sustained release of drugs. Since 2002 she has been an Associate Professor in the Laboratoire de Catalyse Chimie Fine et Polymères headed by P. Kalck in the Ecole Nationale Supérieure des Ingénieurs en Arts Chimiques et Technologiques (ENSIACET) in Toulouse. Her current research is focused on the synthesis of biologically active new terpenoids using metal-catalyzed tandem reactions.

Blanca M. Martin Vaca was born in Valladolid, Spain, in 1968. She studied chemistry at the University of Oviedo, Spain, and obtained her Ph.D. degree in 1995 under the supervision of Professor J. Gimeno. She then joined Dr. Rudler's group at the University Pierre et Marie Curie (Paris) as a postdoctoral fellow supported by the Spanish M. E. C. (1996–1998) and studied cyclopropanation and other cyclization reactions with alkoxycarbenes and ylide complexes of tungsten. Since 1998 she has been an Assistant Professor at the University Paul Sabatier (Toulouse). Her current research interests include the synthesis of oxygen-containing heterocycles, development of catalytic systems for the controlled ROP, and applications of the resulting biodegradable polymers for drug delivery systems.

The combination of well-suited physical properties and biodegradable character makes PLA and PLGA promising substitutes for petrochemical-based plastics in a wide range of single-use packaging and commodity applications.[3,11,17] Indeed, these biodegradable polymers may well offer a practical solution to the ecological problems associated with bioresistant wastes. Flexible films, rigid containers, drink cups, and bottles are representative products already available in the marketplace.

Numerous medical applications have also been considered, taking advantage of the bioassimilable character of PLGA, for both surgical and pharmacological use (Figure 2). Historically, the use of synthetic biodegradable polymers as sutures started in the 1970s,[24] the most widely used bioassimilable sutures being Dexon (a multifilament PGA material) and Vicryl (a PLGA copolymer containing 8% of lactic acid and 92% of glycolic acid).[25] Besides tissue repairing and engineering, biodegradable implants have also been used for fixation of fractured bones and joints. Accordingly, several orthopedic devices are commercially available,[5,7,26,27] such as the ligating clips and bone pins produced from Lactomer (a PLGA copolymer containing 70% lactic acid and 30% glycolic acid). With these biodegradable and bioassimilable devices, there are no particular precautions necessary for their use and no need for a removal operation, which is highly advantageous compared with metal implants.

Didier Bourissou, born in Nice (1972), studied chemistry at the Ecole Normale Superieure in Paris from 1992 to 1994 and obtained his Ph.D. degree in 1998 under the supervision of G. Bertrand in Toulouse (Dina Surdin Award in 2000). He then joined F. Mathey's team at the Ecole Polytechnique in Palaiseau as a Research Associate. Since 1998 he has been Chargé de Recherche at the Laboratoire Hétérochimie Fondamentale et Appliquée (UMR CNRS 5069) in Toulouse and obtained his Habilitation à Diriger les Recherches in 2003. His research is mainly focused on heteroatom chemistry with contributions in highly reactive species (carbenes, diradicals), ligands for transition-metal centers, and biodegradable polymers (design and synthesis of monomers, catalytic systems for controlled ROP, and formulation of active ingredients).

Besides these developments in surgery-related applications, numerous efforts have been devoted to

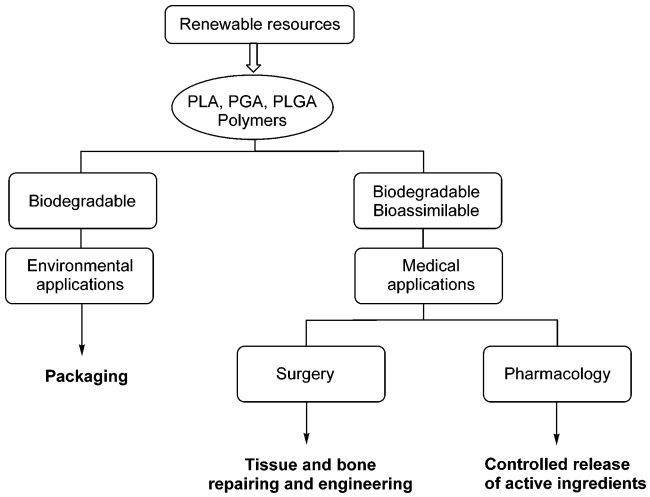


Figure 2. Practical applications of the biodegradable polymers based on lactic and glycolic acids.

pharmacological applications over the last two decades, i.e., on the controlled delivery by drug-loaded biodegradable devices.[28−30] The controlled release of active ingredients aims at improving the therapeutic efficiency and increasing patient compliance. The encapsulation of a drug in a polymeric matrix allows the drug level to be maintained within a desired range, increase its therapeutic activity, decrease side effects, and reduce the number of administrations necessary (Figure 3). Moreover, such formulations can be used both to target the drug to the appropriate active site and to protect the active component from environmental and/or enzymatic degradation.

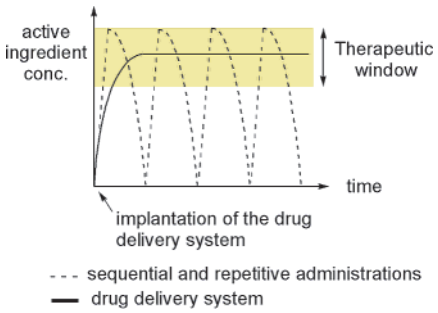


Figure 3. Schematic representation of the basic principle of drug delivery systems.

A wide variety of biologically active agents, from low-molecular-weight steroids to high-molecular-weight polypeptides, have been formulated in this way. The best results have generally been obtained for PLGA with 20−50% of glycolic acid and molecular weights of about 25 000 Da. Drug loadings of 50% in weight and upward have already been achieved, with drug release rates ranging from about 200 mg to 20 μg per day. Of the FDA-approved formulations involving PLGA polymers, the most important are probably Lupron Depot (a PLGA/leuprolide acetate formulation, commercialized by TAP Pharmaceutical Products Inc.) and De-capeptyl, (a PLA/triptorelin pamoate formulation, commercialized by Ipsen Biotech), both being used in the treatment of prostate cancer and endometriosis. Other well-known examples are Nutropin Depot and Sandostatine (two PLGA/human growth hormone formulations, commercialized by Genentech and Novartis Pharma, respectively). Although all of these devices are subcutaneous implants, due to the properties of the polymeric matrix they do not need to be removed. Moreover, recent advances in the preparation of drug-loaded PLGA devices, especially microparticles[13] and nanoparticles,[31,32] increase the likelihood of the forthcoming development of oral[33−35] as well as nasal[36,37] formulations.

All of the practical uses of PLGA involve, at one time or another, their biodegradable character, and thus their decomposition profile has to be precisely matched to the needs of the application. The degradation rate of the polymer depends not only upon external conditions such as pH, temperature, and ionic force, but also on several intrinsic structural parameters such as the polymer composition, its molecular weight and polydispersity index, its tacticity, the polymer chain ends, the sequence of the monomers, etc.[7,13,38]

As a consequence, there is increasing interest in methods that allow for the preparation of PLGA polymers in a reproducible and controlled fashion. These polyesters can be obtained either by condensation from lactic acid, glycolic acid, and light condensates or by ring-opening polymerization (ROP) of the related cyclic dimers, namely, lactide and glycolide (Figure 4). The polycondensation route is known to

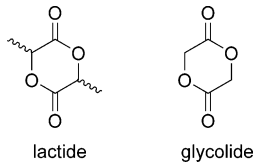


Figure 4. Structure of lactide and glycolide.

be an equilibrium, the liberated water being difficult to remove, which generally limits the molecular weight of the polymer. This limitation can be circumvented, as in the case of the azeotrotopic distillation process patented by Mitsui Toatsu Chemicals Inc.[39] However, the ROP of lactide and glycolide, which allows for a much higher control of the polymerization, remains by far the most widely used method for the synthesis of well-defined materials. From a thermodynamic viewpoint, lactide and glycolide are among the rare examples of polymerizable six-membered rings, and accordingly, the standard state polymerization enthalpy for lactide was estimated to be negative and relatively high in absolute terms (ca. −23 kJ/mol).[40,41] On the basis of X-ray crystallographic data, this peculiar feature has been attributed to an increased ring strain resulting from the presence of two ester moieties with a planar conformation.[40,42] However, this ring strain, which provides the driving force for the ROP, remains modest so that the back reaction becomes nonnegligible at high temperature, leading to increasing monomer concentration at equilibrium (0.011 mol L^{-1} at 20 °C, 0.045 mol L^{-1} at 70 °C, and 0.129 mol L^{-1} at 120 °C for lactide).[41] In practice, appropriate polymerization conditions allow for the controlled ROP of lactide and glycolide, and the mean degree of polymerization (DP) of the resulting polymers is usually equal, or at least proportional, to the monomer conversion times the monomer to initiator molar ratio. In some cases, the termination and transfer reactions can even be limited to such an extent that the polymerization can be considered as living. Compared with the polycondensation route, ROP is also much more suited for control of the monomer sequence (during block copolymer synthesis, for example) as well as of the polymer chain ends.

In practice, the ROP of lactide and glycolide requires an appropriate catalyst to proceed in reasonable conditions and to afford polymers with controlled properties. Since the pioneering work of Kleine et al. in the 1950s,[43] metal-based catalytic systems have been the focus of considerable attention for the polymerization of cyclic esters,[44] and numerous studies have been carried out to elucidate the mechanism of such coordination polymerizations. Through variation in the nature of the metal center and of the surrounding ligands, a broad range of

initiators have been prepared and evaluated.[45] These well-defined complexes have contributed significantly to a better understanding of the factors that govern the polymerization, and spectacular improvements have thereby been achieved in terms of catalytic activity as well as polymerization control. Alternative strategies based on anionic, nucleophilic, or cationic promoters have also been recently (re)evaluated, the preliminary results reported in these fields being rather promising. In particular, organocatalysts might be considered as valuable alternatives to metal catalysts, especially when the resulting polymers are intended for biomedical applications.

This review will focus on the different approaches reported in the literature for the controlled ring-opening polymerization of lactide and glycolide until 2003. The catalytic systems for coordination polymerization will be presented first, following the nature of their ancillary ligands. Then the anionic, nucleophilic and cationic strategies will be discussed successively. Special attention has been devoted to the mechanistic and stereochemical aspects of the various processes, and whenever possible comparisons between the different systems have been attempted.

2. Coordination–Insertion Polymerization

The most widely used complex for the industrial preparation of PLA and PLGA is undoubtedly tin(II) bis(2-ethylhexanoate) (Figure 5). This derivative,

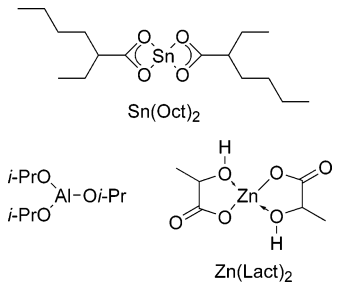


Figure 5. Structure of tin(II) octanoate [$Sn(Oct)_2$], aluminum(III) isopropoxide [$Al(O\textit{i}\text{-}Pr)_3$], and zinc(II) lactate [$Zn(Lact)_2$].

usually referred to as tin(II) octanoate, $Sn(Oct)_2$, is commercially available, easy to handle, and soluble in common organic solvents and in melt monomers. It is highly active (typical reaction times in bulk at 140−180 °C range from minutes to a few hours) and allows for the preparation of high-molecular-weight polymers (up to 10^5 or even 10^6 Da in the presence of an alcohol).[46] Although $Sn(Oct)_2$ has been accepted as a food additive by the U.S. FDA, the toxicity associated with most tin compounds is a considerable drawback in the case of biomedical applications.

Aluminum alkoxides have also proved to be efficient catalysts for the ROP of cyclic esters. The archetypal example, namely, $Al(O\textit{i}\text{-}Pr)_3$, has been largely used for mechanistic studies. However, it has been revealed to be significantly less active than $Sn(Oct)_2$ (in bulk at 125−180 °C, reaction times of several days are usually required and molecular weights are generally lower than 10^5 Da).[46] Moreover, an induction period of a few minutes is systematically observed with $Al(O\textit{i}\text{-}Pr)_3$. This feature has been attributed to aggregation phenomenon.[47] For all these reasons, $Al(O\textit{i}\text{-}Pr)_3$ is much less used for the preparation of biodegradable polyesters, and especially since aluminum ions do not belong to the human metabolism and are suspected of supporting Alzheimer's disease.

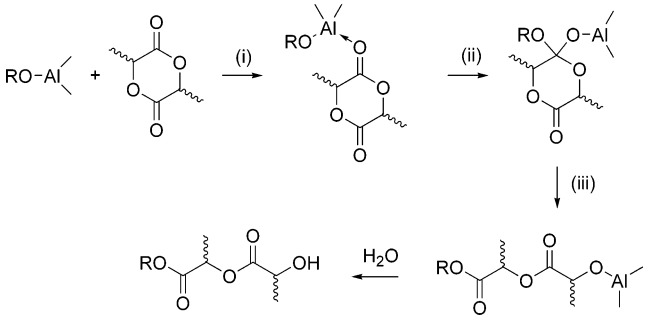
Much interest has thus been devoted to zinc derivatives as potential nontoxic catalysts. Zinc powder itself is a relatively good polymerization catalyst that is used industrially.[48] With reaction times of several days at 140 °C in bulk, it is roughly as active as $Al(O\textit{i}\text{-}Pr)_3$. Numerous zinc salts have also been investigated.[49] So far, the best results regarding lactide conversion and degree of polymerization were observed with zinc(II) lactate, $Zn(Lact)_2$, which is commercially available and can be readily obtained from ZnO and ethyl lactate or lactide. Notably, $Zn(Lact)_2$ allows for a better control of the molecular weight of the resulting polymers compared with zinc powder.

2.1. Mechanistic Considerations

The three-step coordination−insertion mechanism for the ROP of cyclic esters was first formulated in 1971 by Dittrich and Schulz.[50] The first experimental proof for such a mechanism in the $Al(O\textit{i}\text{-}Pr)_3$-initiated polymerization of lactide was independently reported in the late 1980s by Kricheldorf[51] and Teyssié.[52] Recently, further support for such a mechanism has been provided by experimental[46,53] as well as theoretical[54,55] studies. The living character of the polymerization in toluene at 70 °C has also been deduced from the linear dependence of the mean DP on the monomer to initiator molar ratio calculated for the actual monomer conversion.[52]

The first step of the coordination−insertion mechanism (i) consists of the coordination of the monomer to the Lewis-acidic metal center (Scheme 1). The

Scheme 1. Coordination−Insertion Mechanism for the $Al(O\textit{i}\text{-}Pr)_3$-Catalyzed ROP of Lactide[a]



[a] RO refers either to the initiating isopropoxy group or to the growing polymer chain.

monomer subsequently inserts into one of the aluminum−alkoxide bonds via nucleophilic addition of the alkoxy group on the carbonyl carbon (ii) followed by ring opening via acyl−oxygen cleavage (iii). Hydrolysis of the active metal−alkoxide bond leads to the formation of a hydroxyl end group, while the second chain end is capped with an isopropyl ester, as indicated by ^1H NMR characterization of the resulting polymers.

Calculations have revealed the critical influence of the aluminum substituents. Significantly lower activation barriers were predicted for trialkoxides relative to the corresponding monoalkoxides.[54] The sensitivity of aluminum initiators toward steric bulk has also been noted and was attributed to the shortness of the aluminum−oxygen bonds.[55] Accordingly, the activation barrier for the insertion step was found to be about 40% higher for lactide than for glycolide for the model complex $AlMe_2(OMe)$. These data nicely parallel the higher polymerizability of glycolide compared to lactide, an activity ratio r_G/r_L of about 10 being typically observed experimentally.[24]

$Sn(Oct)_2$ is inherently more active than $Al(O\textit{i}\text{-}Pr)_3$, but the polymerization was found to be even faster and better controlled when $Sn(Oct)_2$ was combined with a protic reagent such as an alcohol. The mechanism for the $Sn(Oct)_2$-catalyzed ROP has been the subject of much more controversy. Recent investigations[56,57] have allowed for the characterization of several intermediate tin complexes and strongly support a coordination−insertion mechanism rather than a cationic or activated-monomer mechanism.[58] However, the most debatable question concerns the very nature of the initiating complex. Although it is generally accepted that protic reagents such as alcohols react with $Sn(Oct)_2$ to form covalent tin(II) alkoxides,[59] this coordination step can occur with retention of the octanoate ligands (eq 1)[60] or with liberation of octanoic acid (eq 2),[56,61] and the reaction conditions (in terms of temperature, alcohol-to-tin ratio, solvent, etc.) are believed to strongly influence these processes. It is also widely accepted that impurities present in the monomer (alcohols, lactic acid, water, etc.) may act as co-initiators, especially when $Sn(Oct)_2$ is used without protic additives. Last, it should not be underestimated that besides their involvement in polymerization initiation, protic agents may also be involved in reversible chain transfer with the growing chain (eq 3), making it essential that the ROH to $Sn(Oct)_2$ ratio is carefully optimized.[57]

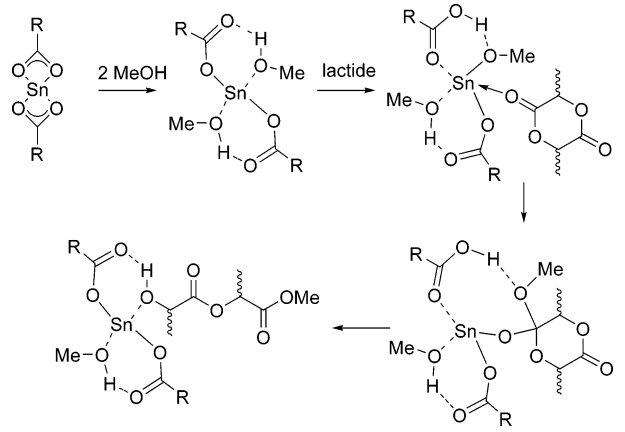
$$Sn(Oct)_2 + ROH \rightleftharpoons (ROH)Sn(Oct)_2 \quad (1)$$

$$Sn(Oct)_2 + ROH \rightleftharpoons (RO)Sn(Oct) + OctH \quad (2)$$

$$RO-(lactide)_n-Sn(Oct) + ROH \rightleftharpoons (RO)Sn(Oct) + RO-(lactide)_n-H \quad (3)$$

Support for the coordination−insertion mechanism has recently been obtained theoretically (Scheme 2).[62] Two molecules of methanol were found to coordinate to $Sn(OAc)_2$ as a model for $Sn(Oct)_2$. Both coordinations are favored by about 59−63 kJ/mol and occur in an associative fashion, i.e., with retention of the two octanoate moieties (hydrogen bonds are formed between the alcohol and octanoate ligands). A weak complexation of lactide was then predicted (coordination enthalpy of 16 kJ/mol). Notably, the latter coordination step induces a proton migration from methanol to the nearby octanoate ligand, so that the alcohol ligand is converted into an alkoxide. Subsequently, the insertion occurs in two steps, namely, nucleophilic attack of this alkoxide on the coordinated

Scheme 2. Predicted Mechanism for the $Sn(Oct)_2$-Catalyzed ROP of Lactide in the Presence of Methanol[a]



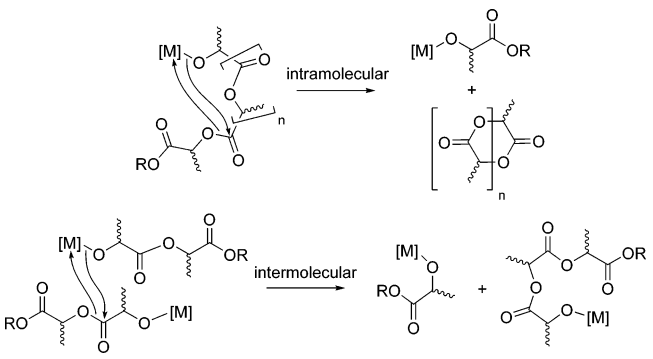
[a] Calculations carried out with R = Me.

lactide followed by ring opening, resulting formally in the insertion of a lactide moiety into the O−H bond of a coordinated methanol. These calculations suggest that the octanoic acid remains coordinated to tin during propagation, but taking into consideration both the entropic term and the reaction temperature, the authors concluded that it might also be possible that the octanoic acid dissociates from the tin−alkoxide complex during ROP.

Comparatively, the mechanism of $Zn(Lact)_2$-catalyzed ROP has been much less studied. However, the combination of $Zn(Lact)_2$ with a primary alcohol was demonstrated to increase its activity and allow for a better control of the polymerization, as in the case of $Sn(Oct)_2$.[63] Thus, it seems rather likely that the polymerization proceeds with $Zn(Lact)_2$ in a similar way to that discussed above for $Sn(Oct)_2$.

In such coordination−insertion polymerizations the efficiency of the molecular-weight control depends from the ratio $k_{propagation}/k_{initiation}$ but also from the extent of transesterification side reactions. These transesterification reactions can occur both intramolecularly (backbiting leading to macrocyclic structures and shorter chains) and intermolecularly (chain redistributions) (Scheme 3).[64] The polymerization/depolymerization equilibrium discussed in the Introduction (section 1) should also be taken into account as a particular case of intramolecular transesterification reaction. All of these side reactions result in

Scheme 3. Schematic Representations for the Intramolecular and Intermolecular Transesterification Side Reactions



broader molecular-weight distributions, sometimes making the molecular weights of the resulting polymers irreproducible. The extent of these undesirable transesterification reactions was found to strongly depend on the metallic initiator.[51,64] Side reactions occur from the very beginning of the polymerization with $Sn(Oct)_2$, leading to rather broad molecular-weight distributions (PDI indexes around 2) but only at high or even complete conversion with $Al(Oi\text{-}Pr)_3$, yielding lower PDI indexes (less than 1.5).[46,53a]

The promising results obtained with $Sn(Oct)_2$, $Al(Oi\text{-}Pr)_3$, and $Zn(Lact)_2$ have given rise to a growing interest in metal-based initiators that would display higher catalytic activity and better control the extent of the undesirable transesterification reactions.

2.2. Catalysts

2.2.1. Metal–Alkoxides and Related Complexes

The relatively low activity of aluminum alkoxides in lactide ROP has stimulated the investigation of alkoxides featuring other metals,[65,66] especially yttrium and lanthanum.[67] Trivalent yttrium and lanthanum alkoxides $Ln(OR)_3$ (Ln = La, Y and R = *i*-Pr, *n*-Bu), prepared by ligand exchange from readily available bulky phenoxides, do polymerize lactide in dichloromethane solution at room temperature within only a few minutes for [monomer]/[$Ln(OR)_3$] $\approx$ 150 and [monomer] $\approx$ 0.2 M.[67] These initiators proved to be much more active than aluminum alkoxides [with $Y(Oi\text{-}Pr)_3$, a propagation rate constant of 1.92×10^3 L mol^{-1} min^{-1} was established in dichloromethane at room temperature[67] compared to 0.60 L mol^{-1} min^{-1} in toluene at 70 °C with $Al(Oi\text{-}Pr)_3$[52]]. In contrast to $Al(Oi\text{-}Pr)_3$, the polymerization proceeds without any induction period, as indicated by in situ UV spectroscopy. Three active chains grow per metallic center, and the resulting polymers feature ester end groups corresponding to the initiating alkoxide ligands. All the data support a coordination−insertion mechanism, identical with that proposed for aluminum alkoxides. However, this situation might be complicated by aggregation phenomenon, as recently pointed out by Soum and coworkers.[68]

Oxoalkoxide clusters of general formula $Ln_5(\mu_5\text{-}O)(Oi\text{-}Pr)_{13}$ (Ln = Y, La, Sm, and Yb), which are intimately related to the corresponding tris(isopropoxides), have also been evaluated for lactide ROP (Figure 6).[69,70] The lanthanum derivative is by far the most active, but it leads to substantially broader molecular-weight distributions than the yttrium and samarium clusters. The presence of isopropyl ester end groups was deduced from ^1H NMR analysis, but all of the isopropoxide groups were found to be active initiators only for Y and La, with an average number of growing chains per metallic center of 2.6 (13/5). Comparatively, the dimeric yttrium complex $[Y(OCH_2CH_2Oi\text{-}Pr)_3]_2$ appeared to be a more convenient initiator, combining high activity and narrow molecular-weight distributions until high conversions.[70b−d,71,72] However, mass spectra of polymer samples obtained with low conversion revealed in all cases the presence of both odd and even numbers of lactate units, demonstrating that ester-exchange reactions occur from the beginning of the polymerization.

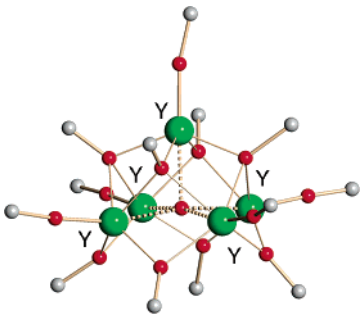


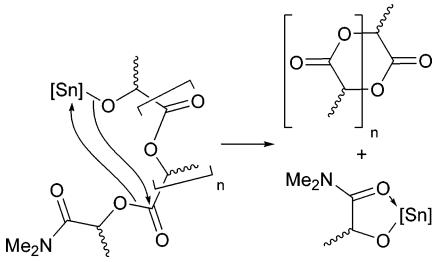
Figure 6. Simplified structure of the yttrium cluster $Y_5(\mu_5\text{-}O)(Oi\text{-}Pr)_{13}$.

As mentioned above, tin(II) alkoxides are most probably the true active species in the $Sn(Oct)_2$-catalyzed ROP of lactide. The behavior of pure tin(II) butoxide, prepared in a two-step synthesis from $SnCl_2$, was compared with that of tin(II) alkoxides generated in situ from $Sn(Oct)_2$ and alcohols.[57,73] As expected, two active chains grow per metallic center, the resulting polymers featuring butyl ester end groups, with the molecular weights of the PLA chains agreeing nicely with those predicted from the monomer-to-alkoxide ratio. The polymerization kinetics for various initiating systems were compared in THF at 50 °C for [monomer] = 1 mol L^{-1} and [monomer]/[initiator] = 20.[57] The $Sn(OBu)_2$-initiated polymerizations proceed about 10 times faster than those performed with $Sn(Oct)_2$/BuOH or $Sn(OBu)_2$/OctH and around 10^2 times faster than with $Sn(Oct)_2$ alone. Moreover, the lactide polymerization remains highly controlled for a wide range of molecular weights, from 10^3 to 10^6 Da. However, the molecular-weight distributions are relatively broad (PDI from 1.2 to 1.8), especially at high conversions, with MALDI-TOF spectra again revealing the occurrence of PLA chains with odd and even numbers of lactate units. Together these data indicate the occurrence of transesterification reactions whose precise nature (intramolecular backbiting and/or intermolecular chain transfer) remains to be determined.

Aiming at reducing the extent of these deleterious transesterification reactions, Chisholm and co-workers recently investigated bis- and trisaryl tin(IV) alkoxides, $Ar_2Sn(OR)_2$ and $Ar_3Sn(OR)$, for lactide ROP.[74a] The tin(IV) derivatives are very resistant upon hydrolysis, but the polymerizations were quite slow, requiring several days to achieve 90% conversion even at 80 °C (benzene solution, [monomer] = 0.084 mol L^{-1} and [monomer]/[initiator] = 50). The much higher activities of the tin(II) alkoxides [with $Sn(OBu)_2$, 90% of lactide conversion is typically reached after only 5 min at 80 °C in THF for [monomer] = 1 mol L^{-1} and [monomer]/[initiator] $\approx$ 50][59b] in comparison with their tin(IV) counterparts most probably result from the more pronounced ability of the metallic center for monomer coordination thanks to electronic[75] and steric factors. Notably, the related bisaryl tin(IV) amides $Ar_2Sn(NMe_2)_2$ appeared to be twice less active initiators than the

corresponding alkoxides, as deduced from the values of the propagation rate constants measured in benzene for [monomer] = 0.084 mol L^{-1} and [monomer]/[initiator] = 25.[74b] Moreover, GPC indicated a bimodal weight distribution which could be attributed to the formation of both PLA chains and macrocycles thanks to electrospray mass spectra. The occurrence of such a large amount of intramolecular backbiting was related to the higher stability of the cyclic [Sn]−OCHMeC(=O)NMe_2 moiety (Scheme 4).

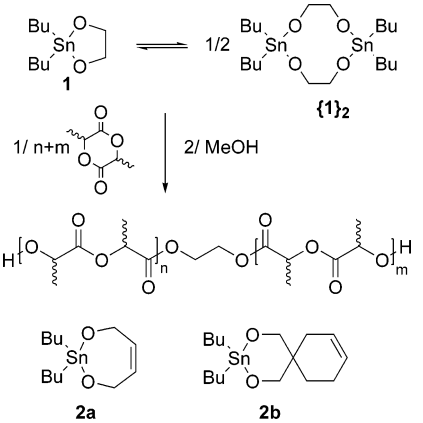
Scheme 4. Intramolecular Backbiting for the $Ar_2Sn(NMe)_2$-Initiated ROP of Lactide Leading to PLA Macrocycles and [Sn]-OCHMeC(=O)NMe_2



Cyclic tin(IV) bisalkoxides have also been evaluated for the lactide ROP (Scheme 5).[76] The archetypical example $Bu_2Sn(-OCH_2CH_2O-)$, **1**, prepared from dibutyltin oxide and ethylene glycol, is much less active than tin(II) alkoxides (typical reaction times range from 12 h to several days in solution at 60 °C for 50−500 equiv of lactide and [monomer] = 0.5 M).[76a] However, the molecular-weight distributions remain narrow (PDI 1.05−1.22) even at high conversions and molecular weights (up to 10^5 Da). Although the actual initiating structure (monomer and/or dimer) has not been clarified, both tin−oxygen bonds were demonstrated to participate in the propagation and hydroxyl telechelic PLA were obtained after alcoholysis. Similar behavior was reported for related tin(IV) derivatives **2a,b** featuring a CC double bond within the bisalkoxide framework, which opens the way to brushlike polymers by postpolymerization[76b] and A−B−A triblock copolymers by one-pot sequential ROP of different monomers.[76c]

Preliminary results have recently been reported for spirocyclic germanium(IV) tetraalkoxides **3** (Figure 7).[77] The reaction rate for the polymerization in solution was however extremely slow. With an initial monomer concentration of 1 mol L^{-1} and a monomer-to-initiator ratio of 50, the conversion reached 90% after only about 1 week even at 120 °C in chlorobenzene.

Scheme 5. Structure of the Cyclic Tin(IV) Bisalkoxide $Bu_2Sn(-OCH_2CH_2O-)$ 1 and Related Derivatives 2a,b Featuring a CC Double Bond within the Bisalkoxide Framework



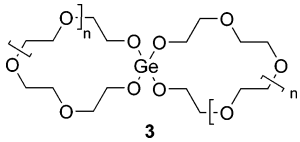
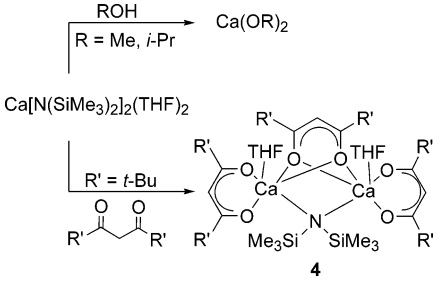


Figure 7. Structure of the spirocyclic germanium(IV) tetraalkoxides **3** (n = 4, 11, 43).

In practice, the catalyst residues are only partly removed from the polymer upon workup, and therefore, there is growing interest in biocompatible catalysts. In this regard, calcium and iron complexes are good candidates since these metals participate in human metabolism.

To minimize aggregation equilibrium and avoid precipitation, calcium dialkoxides $Ca(OR)_2$ (R = *i*-Pr, Me) were prepared in situ by alcoholysis of $Ca[N(SiMe_3)_2]_2(THF)_2$ (Scheme 6).[78] These derivatives

Scheme 6. Synthesis and Structure of the Mononuclear Calcium Dialkoxides and Dinuclear Calcium Complex 4 Featuring an Acetylacetonate Ligand



were found to be highly active for lactide ROP in solution. In marked contrast with that observed for $Al(Oi\text{-}Pr)_3$ and lanthanide clusters, no induction time is observed and complete conversions are achieved in about 30 min at room temperature for a lactide to $Ca(OR)_2$ ratio of 100 and an initial monomer concentration of 1 M. Moreover, extremely narrow molecular-weight distributions were obtained, the polydispersity indexes ranging from 1.03 to 1.07. Treatment of the same calcium precursor with a β-diketone[79] afforded the dinuclear complex **4**.[80] Preliminary investigations suggest that this derivative efficiently polymerizes lactide, provided the reaction is performed in the presence of an alcohol, which probably replaces the bridging amido ligand.

Starting from commercially available ferric ethoxide $Fe(OEt)_3$, Hillmyer and Tolman prepared the iron cluster $Fe_5(\mu_5\text{-}O)(OEt)_{13}$ (Figure 8).[81,82] X-ray analysis revealed a structure similar to that of the lanthanide derivatives $Ln_5(\mu_5\text{-}O)(Oi\text{-}Pr)_{13}$ mentioned above. Although a higher temperature (about 70 °C) is required to achieve reproducible lactide ROP with the iron cluster, polymers with lower polydispersity indexes (about 1.1−1.2) were obtained even at high conversions. The presence of terminal ethoxy ester end groups supports a coordination−insertion mech-

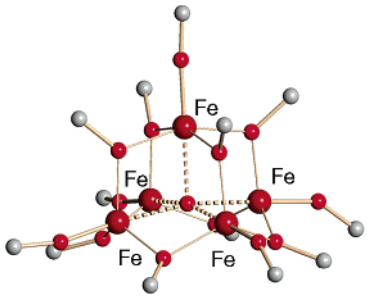
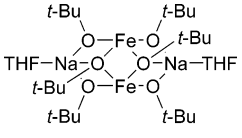


Figure 8. Structures of the neutral iron alkoxides [cluster $Fe_5(\mu_5\text{-}O)(OEt)_{13}$ and dimer **5**].

anism. Notably, a related iron complex has been prepared with a more sterically encumbered alkoxide. X-ray analysis revealed the dimeric structure **5** of $Fe(OCMe_2Ph)_3$, the first homoleptic ferric alkoxide to be structurally characterized (Figure 8).[81] Preliminary experiments show similar activities for the dimer and the cluster, but significantly broader distributions were obtained with the bulkier alkoxide.

Recently, Gibson and co-workers evaluated the related heterobimetallic iron(II) complexes **6** and **7** (Figure 9).[83] Compared with neutral complexes,



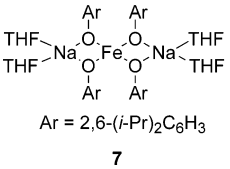


Figure 9. Structure of the heterobimetallic, formally anionic, iron alkoxides **6** and **7**.

higher activities may be anticipated for these formally anionic species since the initiating alkoxide should exhibit enhanced nucleophilicity. Moreover, the monomer may be activated by coordination of the exocyclic oxygen atom to the alkaline metals present in **6** and **7**. Preliminary results demonstrated that both complexes were indeed active for lactide ROP at room temperature, but rather broad molecular-weight distributions were obtained (PDI ranging from 1.4 to 2.3 at high monomer conversions), especially with **7**.

2.2.2. Well-Defined Complexes Featuring Ancillary Ligands

All the studies mentioned above have clearly contributed to a better understanding of the factors that govern the coordination−insertion mechanism with most of these metal alkoxides proving to be convenient initiators for lactide ROP. However, control of the polymerization is often complicated by the complex aggregated or even cluster structures of these derivatives and by the presence of several alkoxide ligands resulting in more than one growing-chain per metallic center. For all these reasons, well-defined single-site catalysts have received increasing interest over the last 20 years, and numerous studies have been devoted to enhance their catalytic activity and limit the deleterious transesterification reactions. Such single-site catalysts can be represented by the general formula L_nMR, where M is the active metal center, R is an initiating group, generally an alkoxide, and L_n are ancillary ligands that are not directly involved in the polymerization but do tune the properties of the metallic center and minimize the aggregation processes and side reactions. A close analogy can be drawn with the design of transition-metal complexes for organometallic catalysis.

2.2.2.1. O-Donor Ligands. Biphenolates and methylenebiphenolates have been evaluated as ancillary ligands for aluminum (Figure 10). Starting from the

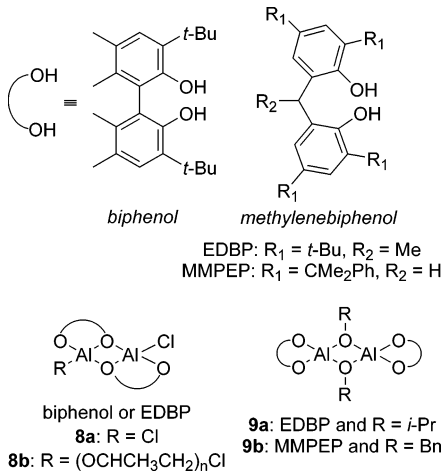
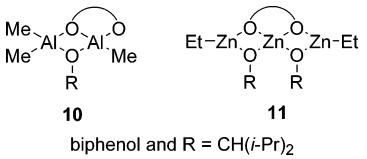


Figure 10. Structure of the dimeric aluminum complexes featuring biphenolate and methylenebiphenolate ligands.

free ligands, the chloride complexes **8a** were directly obtained with $AlEt_2Cl$ while the alkoxides **9a,b** were obtained by successive reaction with $AlMe_3$ and the appropriate alcohol.[84] Despite the presence of bulky groups in the ortho positions, complexes **8a** and **9** adopt a dimeric structure in the solid state. Aluminum chlorides **8a** were found to be inactive in lactide ROP.[84b] Somewhat better results were observed for **8b**, resulting from prepolymerization of propylene oxide with **8a**, demonstrating that initiation was more favored with Al−O rather than Al−Cl bonds. However, only relatively poor polymer yields were obtained at room temperature. In a similar way, lactide polymerization occurs very slowly with the related aluminum dimer **9a**, even at 80 °C, suggesting that the bridging alkoxides are poorly active initiators.[84b] Notably, the more sterically encumbered derivative **9b** proved to be significantly more active.[84c] Polymerization of 20−50 equiv of lactide in refluxing toluene was complete after a few days for an initial monomer concentration of 1 M, and very narrow molecular-weight distributions were obtained (PDI ranging from 1.06 to 1.11). The latter result highlights the critical steric influence of the ancillary

ligands on the catalytic activity of the aluminum complexes.

Treatment of biphenol with 2 and 3 equiv of $AlMe_3$ and $ZnEt_2$ followed by addition of 2,4-dimethylpentan-3-ol afforded the dinuclear aluminum and trinuclear zinc complexes **10** and **11**, respectively (Figure 11).[85] The aluminum compound **10** was found



10 **11**

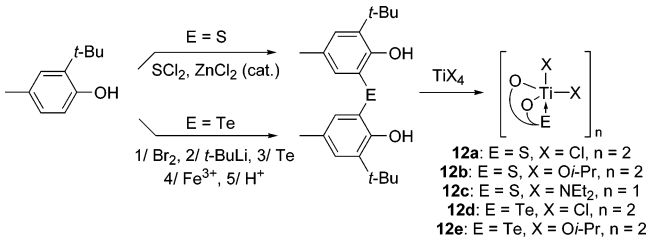
biphenol and R = CH(*i*-Pr)$_2$

Figure 11. Structure of the dinuclear aluminum and trinuclear zinc complexes featuring biphenolate ligands.

to be significantly less active than the zinc derivative **11** in lactide ROP (for [monomer] = 1.2 mol L^{-1} and [monomer]/[initiator] = 200, after 40 h, 96% conversion was obtained with **11** at room temperature but only 40% with **10** at 80 °C). In all cases, however, rather broad molecular-weight distributions were observed (PDI ranging from 1.4 to 2.2).

Starting from 2-*tert*-butyl-4-methylphenol, Nakamura, Harada, and co-workers recently prepared and investigated monomeric and dimeric titanium complexes **12** featuring chalcogen-bridged biphenolate ligands (Scheme 7).[86] Surprisingly, complexes **12b**

Scheme 7. Synthesis and Structure of the Monomeric and Dimeric Titanium Complexes 12 Featuring Chalcogen-Bridged Biphenolate Ligands

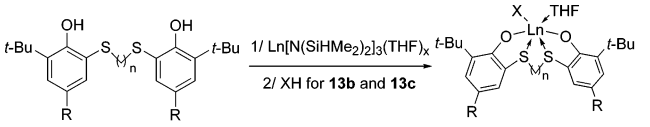


12a: E = S, X = Cl, n = 2
12b: E = S, X = O*i*-Pr, n = 2
12c: E = S, X = NEt$_2$, n = 1
12d: E = Te, X = Cl, n = 2
12e: E = Te, X = O*i*-Pr, n = 2

and **12e** featuring potentially initiating isopropoxide groups were completely inactive, while the solvent was found to have a strong influence on the course of the polymerization with complexes **12a** and **12d**.[86c] The best results were obtained using the dimeric tellurium-containing complex **12d** in anisole or dioxane at 100 °C.[86c] Under these conditions, with an initial monomer concentration of 1 mol L^{-1} and a monomer-to-initiator ratio of 200, high conversions were only achieved after about 40 h, but the molecular-weight distributions remained extremely narrow (PDI lower than 1.13), indicating a minimization in the unwanted transesterification reactions.

Several rare-earth-metal complexes **13** featuring dichalcogen-bridged biphenolate ligands have also been prepared by simple ligand exchange from Ln[N(SiHMe$_2$)$_2$]$_3$(THF)$_x$, the remaining ligand X being eventually introduced by treatment of the amido complex with trityl alcohol or 2,2,6,6-tetramethylheptan-3,5-dione (Scheme 8).[87] The ancillary ligand was demonstrated to have a strong beneficial effect, the corresponding precursors Ln[N(SiHMe$_2$)$_2$]$_3$(THF)$_x$ being less active and showing less control over the

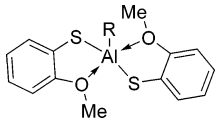
Scheme 8. Synthesis of the Rare-Earth-Metal Complexes 13 Featuring Dichalcogen-Bridged Biphenolate Ligands.



13a: X = N(SiHMe$_2$)$_2$
13b: X = OCPh$_3$
13c: X= OC(*t*-Bu)CHC(*t*-Bu)O
Ln = Sc, Y, Lu
R = Me or *t*-Bu
n = 2 or 3

polymerization. In general, the less hindered the metal center, the higher the activity for ROP of lactide. To date, the best results have been obtained with the amido lutetium complexes **13a** featuring an ethane C_2-backbone. Complete conversion of 300 equiv of monomer was reached after only a few minutes for an initial monomer concentration of 0.87 mol L^{-1} at room temperature in THF, the resulting polymers having relatively narrow molecular-weight distributions (PDI of ca.1.2). However, no amide end groups could be observed. These promising systems clearly deserve further investigation in order to determine the true initiators and some structure/activity relationship.

Thiophenolate ligands have also been used for the preparation of aluminum complexes **14**, which were found to adopt monomeric structures in the solid state due to the chelating ortho methoxy group (Figure 12).[88] Quite surprisingly, only complex **14a**



14a: R = Me
14b: R = Cl

Figure 12. Structure of the aluminum complexes **14** featuring (*o*-methoxy)thiophenolate ligands.

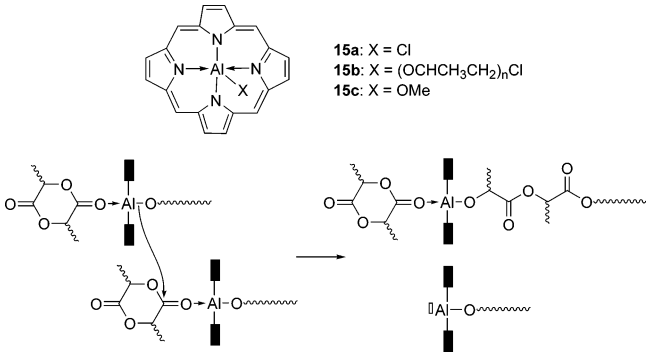
initiates lactide ROP, and for a monomer-to-initiator ratio of 20, high conversions were achieved after about 1 day only in refluxing xylene for an initial monomer concentration of 0.5 M. Interestingly, thiophenolate does not behave simply as an ancillary ligand in that case but is believed to also initiate the polymerization, as deduced from ^{1}H NMR end-group analysis.

2.2.2.2. N-Donor Ligands. With a view to achieving better control of the aggregation phenomenon commonly observed with oxygen-containing frameworks, nitrogen-based ligands have been widely studied. The additional substituent at the nitrogen compared with oxygen was expected to bring about more steric hindrance, and the ensuing N−metal bonds were supposed to be inert toward monomer insertion, at least in the presence of a highly active initiating group such as an alkoxy moiety.

Well-defined catalysts featuring N-donor ligands were first investigated for lactide ROP by Inoue and co-workers about 15 years ago. Among the various metalloporphyrins evaluated,[89] the aluminum complexes were found to be the best initiators.[90] As was the case with biphenolate complexes, initiation was

much more favored with Al−O than Al−Cl bonds. Accordingly, chloride **15a** did not bring about the polymerization of 100 equiv of lactide for an initial monomer concentration of 1.17 mol L^{-1} in dichloromethane at 100 °C, whereas with the alkoxide **15b**, resulting from prepolymerization with propylene oxide, polylactide was obtained in 94% yield after 96 h under the same conditions (Scheme 9). Although

Scheme 9. Structure of the Aluminum Complexes 15a−c Featuring the Tetraphenylporphyrin Ligand, and Schematic Representation of the Propagation Step



the temperature could not be decreased satisfactorily, the polymerization was rather well controlled with one growing chain per initiator and narrow molecular-weight distributions (PDI around 1.1). Notably, the first insertion product could be characterized by ^{1}H NMR with the aluminum methoxide **15c**, thereby demonstrating that the lactide ROP proceeds at the acyl−oxygen bond. Moreover, studies of kinetics on related systems revealed that the polymerization is second order with respect to the (porphirinato)-aluminum alkoxide, suggesting that the propagation involves two molecules of initiator, one as a nucleophilic species involved in chain growth and the other as a Lewis-acidic monomer activator.

2.2.2.2.a. Tridentate Ligands. To increase the Lewis acidity and thus the catalytic activity of the aluminum complexes, replacement of the tetradentate porphyrin framework by tridentate diamidoamino ligands was studied in our group (Figure 13).[91]

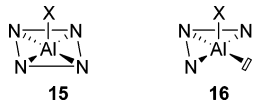
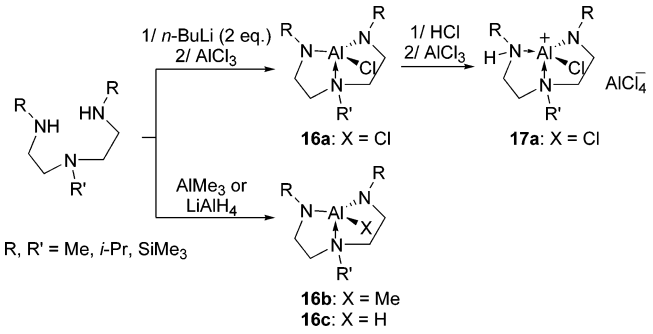


Figure 13. Schematic representation of the aluminum complexes **15** and **16** featuring the tetradentate porphyrin and tridentate diamidoamino ligands, respectively.

Provided the steric hindrance of these ligands prevents aggregation, the related complexes **16** were expected to remain monomeric, and the geometry of these tetracoordinated derivatives should favor a classical monomolecular chain propagation rather than the bimolecular pathway adopted by porphyrin complexes **15**.

Reaction of the dilithium salt of the triamines $(RNHCH_2CH_2)_2NR'$ with $AlCl_3$ afforded the neutral complexes **16a**,[91a] while derivatives **16b** and **16c**[91b] were obtained by treatment of the triamines $(RNHCH_2CH_2)_2NR'$ themselves with $AlMe_3$ and

Scheme 10. Structure and Synthesis of the Neutral and Cationic Aluminum Complexes 16a−c and 17a Featuring Tridentate Diamidoamino Ligands



$LiAlH_4$, respectively (Scheme 10). X-ray analyses revealed that all of complexes **16a−c** adopt monomeric structures, and due to the formation of a rather rigid bicyclic core, the tridentate ligand enforces an approximately trigonal-monopyramidal coordination geometry around the metal. The accessibility of the ensuing empty axial coordination site for substrate binding has been established, but all of the chlorides **16a** remained inert toward lactide ROP in benzene at 80 °C, whatever the substituents at the nitrogen donors. Even the related cationic chlorides **17a**,[91a] obtained by successive treatment of **16a** with HCl and $AlCl_3$, were inactive in these conditions unless they were converted in situ into alkoxides by prepolymerization of propylene oxide. In marked contrast, the neutral complexes **16b** and **16c** initiated lactide ROP in benzene solution at 80 °C. In these conditions, with an initial monomer concentration of 0.28 mol L^{-1} and a monomer-to-initiator ratio of 50, the hydride **16c** proved to be about twice as active as the methyl aluminum complex **16b** in terms of monomer conversion, but rather broad molecular-weight distributions were obtained with both complexes (PDI around 1.7).

The influence of the metallic center was also investigated. The tin derivative **18**,[92a] which might be regarded as an intramolecularly stabilized stannylene, exists in a monomeric form, whereas the related zinc complex **19**[92b] adopts a dimeric structure featuring a central $(Zn-N)_2$ four-membered ring (Figure 14). This striking difference has been at-

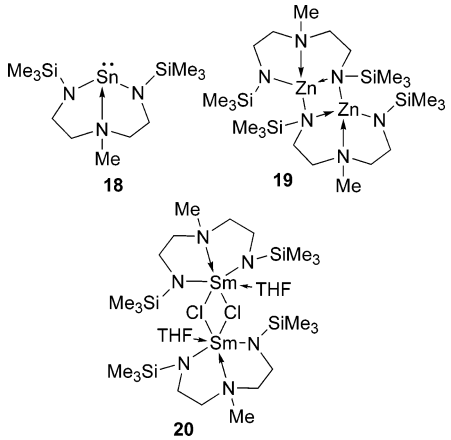


Figure 14. Structure of the tin, zinc, and samarium complexes **18−20** featuring tridentate diamidoamino ligands.

tributed to the geometry enforced by the diamido-amino ligand, which is probably more adapted for a bent arrangement (as observed in **18**) than for a linear, allenic-type geometry (as would be expected for the hypothetical monomeric form of the zinc derivative). The samarium complex **20**[92b] also adopts a dimeric structure but is bridged via the two chlorine atoms, retaining one coordinated THF molecule per metallic center. All of the complexes **18**−**20** were active for the bulk copolymerization of lactide and glycolide with a reactivity order Zn < Sm < Sn. The more active tin complex **18** allows for conversions higher than 95% of both monomers (300 and 842 equiv of glycolide and lactide, respectively) after 2 h at 140 °C and even after only 30 min at 180 °C but at the expense of the molecular-weight distribution (PDI around 3 at 180 °C and around 2 at 140 °C).

Trispyrazolyl- and trisindazolyl-hydroborate ligands are tripodal monoanionic tridentate ligands that can confer the required steric hindrance around the metallic center to prevent aggregation. Starting from the corresponding potassium or thallium(I) salts, Chisholm and co-workers recently reported the synthesis of the monomeric magnesium, zinc, and calcium complexes **21**, some of which retain a coordinated THF molecule (form **21′**) (Figure 15).[93] Most

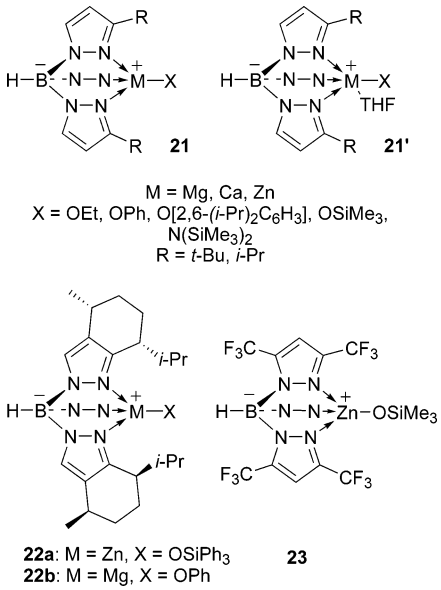
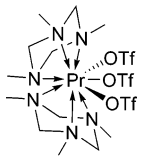


Figure 15. Structure of the magnesium, calcium, and zinc complexes **21**−**23** featuring the trispyrazolyl- and trisindazolyl-hydroborate ligands.

of these complexes were highly active for lactide ROP, with the observed reactivity order Ca > Mg > Zn having been attributed to the difference in polarity of the initiating M−X bonds.[94] The calcium derivatives, which are capable of polymerizing 100 equiv of lactide in only 1 min at room temperature in THF, are among the most active complexes discovered to date.[93c] However, the inverse trend is observed for the molecular-weight distributions of the resulting polymers, calcium derivatives leading to higher polydispersity indexes (about 1.6−1.7) than magnesium and zinc initiators (about 1.1−1.25). Here again, ROP of lactide proceeds by acyl cleavage, as deduced from the presence of ethyl ester end groups (characterized by ^{1}H and ^{13}C NMR spectroscopy) when polylactides were prepared with the magnesium ethoxide initiator. Moreover, the polymerization was shown to be first order with respect to the metal alkoxide,[93b] corroborating the starting hypothesis that tridentate ligands should favor a classical monomolecular chain propagation. Preliminary investigations have also been reported regarding structural modification of such complexes.[93b] Accordingly, complexes **22a,b**, featuring the bulkier trisindazolyl-hydroborate ligand derived from menthone showed significantly higher activity than the related initiators **21**, whereas the introduction of electron-withdrawing CF_3 groups on the pyrazole rings decreased the rate of lactide polymerization to the extent that complex **23** was nearly inactive at room temperature.

The easily accessible 1,3,5-triazacyclohexane ligands have also been recently used as tridentate N-donor ligands in the design of well-defined catalysts (Figure 16). Indeed, the monomeric praseodymium(III)



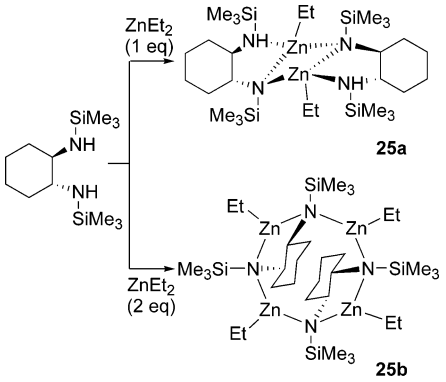
24

Figure 16. Structure of the monomeric praseodymium complex **24** featuring the 1,3,5-triazacyclohexane ligand (Tf = CF_3SO_2).

complex **24** was found to be considerably more active in bulk polymerization of lactide at 170 °C than $Pr(OTf)_3$, leading to a higher yield [for a monomer-to-initiator ratio of 1000, after 18 h, 95% with **24** compared to 74% with $Pr(OTf)_3$] and molecular-weight (18 000 compared with 5700 Da) polymer.[95] However, rather broad molecular-weight distributions were obtained (PDI ranging from 1.8 to 2.7). The true initiator of the polymerization was suspected to be a metal hydroxide, which would result from deprotonation of residual water by the 1,3,5-triazacyclohexane, but further studies are probably necessary to determine the precise role of the ancillary ligand on improvement of the catalyst performance.

2.2.2.2.b. Bidentate Ligands. Numerous complexes based on bidentate N-donor ligands have been evaluated for lactide ROP. Diamido zinc derivatives **25**[96] were prepared by aminolysis of $ZnEt_2$ with (±) *trans*-1,2-$(NHSiMe_3)_2$-cyclohexane (Scheme 11). Depending on the initial ligand to $ZnEt_2$ ratio, the dinuclear and tetranuclear complexes, **25a** and **25b**, respectively, were obtained. Notably, the four-coordinate complex **25a** was considerably less active than the three-coordinate one **25b** for the polymerization of ϵ-caprolactone, whereas both complexes have similar activities toward lactide, leading to about 90% conversion within 2 h in toluene at 70 °C for a monomer-to-initiator ratio of 200 and an initial monomer concentration of 0.3 M. On the basis of GPC analysis, the authors suggested that the two amido groups per metallic center participate in the polymerization, but the precise nature of the initiating groups clearly

Scheme 11. Structure of the Dinuclear and Tetranuclear Zinc Complexes 25a,b Featuring Diamido Ligands



deserves further investigation, such as end-group analysis.

In an alternative approach to well-defined complexes, Tolman and co-workers used amidinates as monoanionic bidentate ligands that can formally be considered as a delocalized combination of an imino and amido moieties (Figure 17). The monomeric

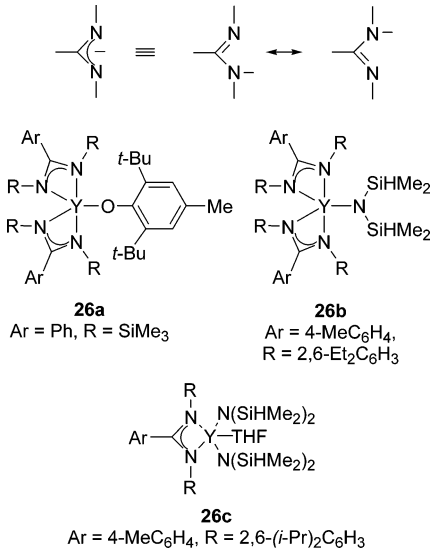


Figure 17. Schematic representation of the amidinate ligands and structure of the related yttrium complexes **26a**−**c**.

yttrium(III) complexes **26a**−**c**[97] were prepared by reaction of the lithium salt of the amidinate with YCl_3, the remaining chlorine atom(s) being subsequently exchanged for phenoxide or bissilylamido co-ligand(s). The number of amidinate ligands, one or two, was found to be controlled by the steric bulk of the nitrogen substituents, as illustrated by comparing **26b** and **26c**. Polymerizations were typically achieved in THF at room temperature. The addition of an exogenous alcohol, such as benzyl alcohol, was shown to significantly improve the catalytic behavior of the bulky phenoxide **26a** in terms of reproducibility, molecular weight, and polydispersity. Moreover, benzyl ester end groups were observed in the ^{1}H NMR spectra of the resulting polylactides, demonstrating that the phenoxide ligand should be initially substituted by benzyl alcohol, as in the case of yttrium and lanthanum trisphenoxides. However, mass spectrometry data indicated the concomitant presence of polymeric species without benzyl ester end group, suggesting that multiple possibly equilibrating species might be involved. The relative amido complexes are also active, the polymerizations promoted by **26c** (97% conversion after 15 min in THF at room temperature for a monomer-to-initiator ratio of 450 and an initial monomer concentration of 1 M) being significantly faster than those catalyzed by **26b** (only 74% conversion after 3 h in the same conditions). In both cases, however, the nature of the initiating groups remains unclear since the expected amide end groups could not be observed by ^{1}H NMR or by MALDI mass spectrometry.

Following the same strategy, several other metal complexes featuring amidinate ligands were prepared such as the tin and iron complexes **27a,b**[98] and **28**,[99] which were demonstrated to adopt monomeric structures both in the solid state and in solution (Figure 18). Variation of the steric demand of the silyl

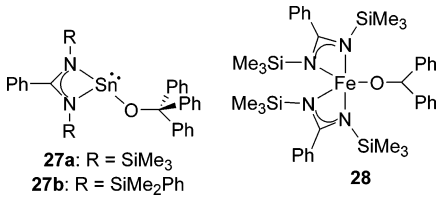


Figure 18. Structure of the tin and iron complexes **27a,b** and **28** featuring bidentate amidinate ligands.

substituents at the nitrogen atoms did not noticeably affect the structure of complexes **27**, as deduced from X-ray analyses, but did significantly influence the catalytic behavior in terms of initiation efficiency and polymerization control. Indeed, 93% conversion of lactide was obtained after 35 min with **27a** in toluene solution at 80 °C, resulting in polymer with M_n = 63 500 Da and PDI = 1.48, whereas under the same conditions, 92% conversion was achieved with **27b** only after 165 min, leading to polylactide with M_n = 28 900 Da and PDI = 1.18. By analogy with the observations made for the yttrium complexes, the addition of benzyl alcohol as an exogenous initiator had a beneficial effect in the lactide ROP promoted by the tin complex **27b**.

Although the iron complex **28** was also active for lactide ROP in toluene at 70 °C, introduction of the ancillary amidinate ligand was found to have a detrimental effect, since the polymerization was both faster and more controlled with the related complex **5** featuring only alkoxide ligands.[99] Moreover, complicated kinetics were determined (one-third and one-half order with respect to the metallic complex **27b** and **28**, respectively), highlighting the dramatic importance of aggregation phenomena for the active species that feature the growing polymer chains in place of the bulky alkoxide co-ligands present on the initiator.

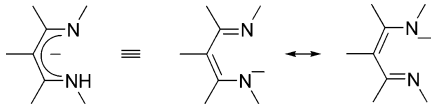
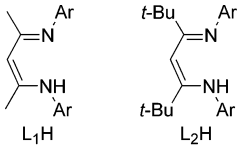


Figure 19. Schematic representation of the β-diiminate ligands.

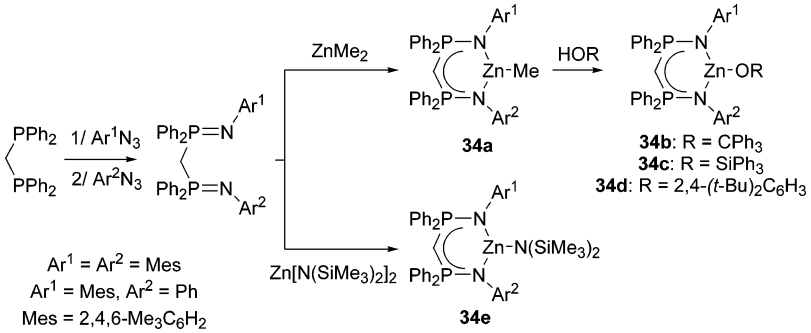
Table 1. Metal Complexes 29−33: Their Synthesis from the Corresponding β-Diiminates and Representative Examples of Lactide ROP in Dichloromethane at Room Temperature



complex	synthesis	[M]/[I]	t (min)	conv. (%)	PDI	ref
$L_1ZnN(SiMe_3)_2$ (**29a**)	$Zn[N(SiMe_3)_2]_2$	200:1	600	97	2.9	101−103
$L_1ZnN(i\text{-}Pr)_2$ (**29b**)	1/LiN(*i*-Pr)$_2$ 2/$ZnCl_2$	100:1	40	94	1.4	104,105
$(L_1ZnOi\text{-}Pr)_2$ (**29c**)	1/$Zn[N(SiMe_3)_2]_2$ 2/HO*i*-Pr	200:1	20	95	1.1	101−103
$L_1Zn(OSiPh_3)(THF)$ (**29d**)	1/$Zn[N(SiMe_3)_2]_2$ 2/$HOCPh_3$	100:1	4200	91	1.4	104,106
$L_1ZnOt\text{-}Bu$ (**29e**)	1/LiN(*i*-Pr)$_2$ 2/$ZnCl_2$ 3/HO*t*-Bu	200:1	10	95	1.1	104
$L_1ZnOCHMeCO_2Me$ (**29f**)	1/$Zn[N(SiMe_3)_2]_2$ 2/$HOCHMeCO_2Me$	200:1	20	97	1.1	103
$(L_1ZnOAc)_2$ (**29g**)	1/*n*-BuLi 2/$Zn(OAc)_2$	200:1	4200	92	2.1	103
L_1ZnEt (**29h**)	$ZnEt_2$	200:1	1200	97	1.8	103
$L_1SnOi\text{-}Pr$ (**30**)	1/*n*-BuLi 2/$SnCl_2$ 3/LiO*i*-Pr	100:1	96	>99	1.1	107
$L_1Mg[N(i\text{-}Pr)_2](THF)$ (**31a**)	$Mg[N(i\text{-}Pr)_2]_2$	100:1[a]	5	94	1.6	104,105
$(L_1MgOi\text{-}Pr)_2$ (**31b**)	1/$Mg[N(SiMe_3)_2]_2$ 2/HO*i*-Pr	200:1	2	>99	1.6	103
		200:1[c]	2	97	1.3	
$L_1Mg(Ot\text{-}Bu)(THF)$ (**31c**)	1/*n*-BuLi 2/MeMgCl 3/HO*t*-Bu	100:1	2	97	1.5	104,106
$L_1Ca[N(SiMe_3)_2](THF)$ (**32**)	1/KN$(SiMe_3)_2$ 2/CaI_2	200:1[a]	120	90		93c
$L_2FeOt\text{-}Bu$ (**33**)	1/*n*-BuLi 2/$FeCl_2$ 3/NaO*t*-Bu	100:1[b]	20	94	1.1	108,109

[a] In THF. [b] In toluene. [c] In the presence of 2-propanol.

Scheme 12. Synthesis and Structure of the Zinc Complexes 34a−e Featuring Methylene−Bis(phosphinimino) Ligands



Numerous studies have also been performed on metal complexes featuring β-diiminate ligands (Figure 19).[100] These readily available bidentate ligands have been widely used for the stabilization of low-valent species. They are vinylogs of amidinates but offer the advantage that the nitrogen substituents point in the direction of the bonded center, and therefore, their steric hindrance might be expected to have a stronger influence.

As far as ROP of lactide is concerned, complexes of divalent metals, mainly zinc and magnesium but also tin, calcium, and iron(II), have been prepared (Table 1),[93c,101−111] either via an exchange reaction from the protonated ligands L_1H and L_2H or via a substitution reaction from the lithium or potassium salt of the β-diiminate. The nature of the metal co-ligand has been varied, e.g., amido, alkoxy, silyloxy, methyl lactate, acetate, and ethyl groups. Depending on the steric bulk of the β-diiminate ligand and of the co-ligand, complexes **29**−**33** adopt monomeric or dimeric structures, with a labile THF molecule being found to be coordinated to the metal center in compounds **29d**, **31a**,**c,** and **32**.[93c,104−106]

All of the complexes **29**−**33** were shown to catalyze lactide ROP efficiently in dichloromethane at room temperature (Table 1). Comparative studies have suggested the reactivity order Mg > Zn ≈ Fe ≈ Ca > Sn,[93c,109] which roughly parallels the electropositive character of the metallic center, taking into consideration that the calcium complex **32** features a poorly active amido initiating group. Indeed, the nature of the initiating group was found to have a dramatic influence on the catalytic behavior, as clearly evidenced for the zinc complexes **29**.[103,104] The methyl lactate complex **29f**, prepared as a model of the first insertion product, depicted the same activity as the isopropoxide derivative **29c**.[103] In marked contrast, the polymerization proceeded much more slowly with silylamido, silylalkoxy, acetate, and ethyl groups than with alkoxy co-ligands. The most active complexes, namely, the magnesium alkoxides **31b**,**c,** led to relatively broad molecular-weight distributions (PDI around 1.5−1.6 compared to 1.1 with the related zinc complexes), but polymerization control could be significantly improved by addition of 2-propanol.[103]

The impressive results obtained with complexes featuring β-diiminate ligands will certainly stimulate the investigation of numerous structural variations. In this regard, preliminary results have already been reported concerning the phosphorus-containing analogues of β-diiminates, namely, methylene-bis(phosphinimino) ligands.[112] The protonated form of these bidentate ligands is readily available from the corresponding methylene-bis(phosphine), and consecutive Staudinger reactions with two different aryl azides allow for the preparation of unsymmetrically substituted frameworks (Scheme 12). Subsequently, several monomeric zinc complexes **34a**−**e** featuring a methyl, alkoxy, aryloxy, silyloxy, or amido co-ligand were prepared.[113] Among these complexes, only the alkoxy and aryloxy derivatives **34b** and **34d** proved to be active for lactide ROP. However, these complexes were considerably less active than those featuring β-diiminate ligands, since it was found that polymerization could only be achieved efficiently in toluene solution at 60 °C with **34b,d**. Moreover, the authors point out that the strong carbanionic character of the bridgehead carbon atom might be a drawback for these methylene−bis(phosphinimino) ligands in terms of achieving polymerization control.

2.2.2.2.c. Monodentate Ligands. Recently, simple amido ligands such as $N(SiMe_3)_2$ and $N(SiHMe_2)_2$ have been evaluated for the metal-promoted ROP of lactide (Figure 20). The divalent tin and zinc com-

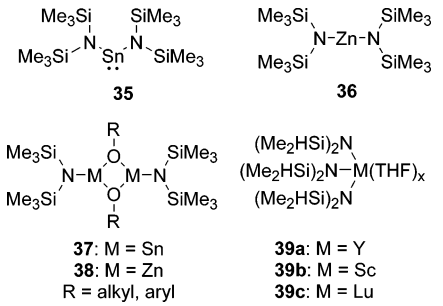
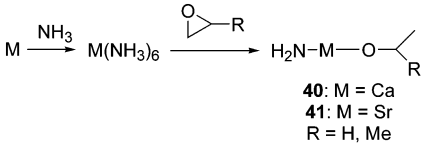


Figure 20. Structure of the amido-containing complexes **35**−**39**.

plexes **35**[114] and **36**[115] were found to be active for the controlled copolymerization of lactide and glycolide with practically complete conversion of both monomers being achieved after 2 h in mesitylene at 140−180 °C for initial monomer concentrations around 4 mol L^{-1} and monomer-to-initiator ratios up to 1000. These conditions allowed for the preparation of copolymers with lactide-to-glycolide ratios ranging from 75:25 to 50:50, molecular weights from 7500 to 100 000 Da, but rather high PDI (from 1.5 to 2). ^{1}H NMR and electrospray mass spectrometric analyses carried out on oligomeric polylactides revealed that without any co-initiator, insertion of the monomer occurred in the M−N bond of **35** and **36**, whereas addition of an exogenous alcohol resulted in selective insertion into the M−O bond of the dimeric complexes **37** and **38** generated in situ. Rather promising results were independently reported for the tris(amido) complexes **39**,[87,97] which proved to be very active even at room temperature (with 450 equiv of lactide, 87% conversion was obtained with **39a** after only 5 min for an initial monomer concentration of 1 M).

Last, it should be mentioned that the calcium and strontium catalysts, **40**[116] and **41**,[117] have been postulated. These complexes, whose precise structures remain unknown, were prepared by treatment of the corresponding metals with liquid ammonia followed by oxidative addition with ethylene or propylene oxide (Scheme 13). Both **40** and **41** are active for

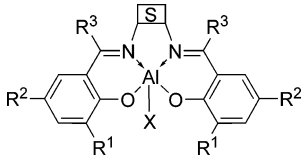
Scheme 13. Postulated Structures for the Calcium and Strontium Complexes 40 and 41



lactide ROP, high conversions typically being achieved in a few hours in toluene solution at 70−80 °C for initial monomer concentrations around 3.5 mol L^{-1} and monomer-to-initiator ratios of 100−600. Although rather broad molecular-weight distributions were observed (PDI from 1.6 to 2.3), ^{1}H NMR end-group analysis revealed that the monomer insertion occurred selectively into the M−O bond.

2.2.2.3. N- and O-Donor Ligands. Chelating ligands combining N- and O-donors have also been involved in the design of well-defined complexes for lactide ROP. Inspired by the work of Inoue and coworkers, several groups have investigated aluminum complexes **42**−**47** featuring SALEN ligands as structural analogues of porphyrins (Table 2).[118−133] The free ligands are readily available from the corre-

Table 2. Aluminum Complexes 42−47 Featuring SALEN Ligands



complex	spacer S	X	R^1	R^2	R^3	ref
42a	$-CH_2CH_2-$	OMe	H	H	H	118−120
42b	$-CH_2CH_2-$	OMe	H	Cl	H	121
42c	$-CH_2CH_2-$	OMe	H	H	Me	122,123
42d	$-CH_2CH_2-$	O*i*-Pr	H	H	Me	123
42e	$-CH_2CH_2-$	O*i*-Pr	H	Cl	H	123
43a	$-CH_2CH_2-$	Et	H	H	H	124
43b	$-CH_2CH_2-$	Et	Me	Me	H	124
43c	$-CH_2CH_2-$	Et	*i*-Pr	H	H	124
43d	$-CH_2CH_2-$	Et	Ph	H	H	124
43e	$-CH_2CH_2-$	Et	*t*-Bu	*t*-Bu	H	124
44	1,2-C_6H_4	O*i*-Pr	H	Cl	H	123
45a	$-CH_2CH_2CH_2-$	Et	H	H	H	124
45b	$-CH_2CH_2CH_2-$	Et	Me	Me	H	124
45c	$-CH_2CH_2CH_2-$	Et	*i*-Pr	H	H	124
45d	$-CH_2CH_2CH_2-$	Et	Ph	H	H	124
45e	$-CH_2CH_2CH_2-$	Et	*t*-Bu	*t*-Bu	H	124
45f	$-CH_2CMe_2CH_2-$	Et	*t*-Bu	*t*-Bu	H	125
46a	(*R*,*R*)-1,2-(*c*-H ex)	O*i*-Pr	*t*-Bu	*t*-Bu	H	126,127
46b	*rac*-1,2-(*c*-Hex)	O*i*-Pr	*t*-Bu	*t*-Bu	H	126,127
47a	(*R*,*R*)-binap	Et	H	H	H	128
47b	(*R*,*R*)-binap	OMe	H	H	H	128
47c	(*R*,*R*)-binap	O*i*-Pr	H	H	H	129−132
47d	(*S*,*S*)-binap	O*i*-Pr	H	H	H	132
47e	*rac*-binap	O*i*-Pr	H	H	H	133

sponding diamines and salicyl carbonyl derivatives, and structural variants can easily be obtained. Coordination can be achieved either by alcoholysis of trialkyl aluminum or by ligand exchange with trialkoxy aluminum precursors. According to X-ray analyses, the geometry at aluminum in these complexes is either square pyramidal (sqb) or trigonal bipyramidal (tbp). However, these geometries are generally not ideal for either sqb or tbp.[134] All of the complexes **42**−**47** were found to be active for the polymerization of lactide, without any induction period, high conversions typically being obtained after a few days at 70 °C in toluene for monomer-to-initiator ratios around 100. Notably, the ethyl derivatives **43a**−**e**, **45a**−**f,** and **47a** required the addition of an exogenous alcohol to generate in situ the corresponding alkoxide initiators. In most cases, the polymerization was well-controlled, as indicated by the narrow molecular-weight distribution and the linear correlation between M_n and conversion. The resulting polylactides featured ester end groups corresponding to the alkoxide co-ligand, as indicated by ^{1}H NMR spectroscopy and MALDI-TOF mass spectrometry. All these data support a typical coordination−insertion mechanism via cleavage of one acyl−oxygen bond of the lactide. In marked contrast to that observed with porphyrin-based catalysts, studies of kinetics revealed a first-order dependence with respect to the aluminum complex **46b**[127] and **47c**.[130] This striking feature of SALEN-based complexes can most probably be attributed to single-site propagating species, the geometry of these complexes, and the relative flexibility of the Schiff base ligands, compared to porphyrins, allowing for a monomolecular propagation. However, the occurrence of alkoxide-bridged bimetallic structures cannot be ruled out.

Several aspects have already been investigated regarding the structure/activity relationship of these SALEN-based aluminum complexes.

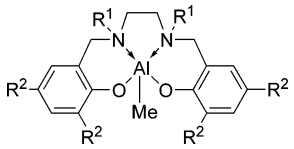
(i) Compared with the parent methoxide **42a**, higher polymerization rates and less transesterification reactions were observed for complex **42b**[121] featuring chlorine atoms in the para position of the phenol ring and even to a greater extent for complex **42c**[122,123] featuring the HAPEN ligand, derived from 2-hydroxyacetophenone. These variations have been tentatively correlated to an enhancement of the aluminum electrophilicity and/or an increase of the polarization of the initiating/propagating Al-X bond.

(ii) Both inter- and intramolecular transesterification reactions were observed for **42a**,[135] but the occurrence of these deleterious side reactions was found to be significantly decreased when bulky groups were introduced at the ortho position of the phenol ring (complexes **43c**−**e**, **45c**−**e,** and **46a,b**).[124,126,127]

(iii) Replacement of the initiating methoxide by an isopropoxide group results in higher activity but at the expense of the transesterification reactions that occur significantly above 35% conversion.[123]

(iv) The polymerization was slowed when the flexible ethane C_2-backbone was substituted by the more rigid benzene (complex **44**),[123] whereas significantly higher activities (typical reaction times of a few hours instead of a few days at 70 °C) were observed for the flexible propane C_3-backbone (complexes **45a**−**f**).[124,125]

Table 3. Aluminum Complexes 48 Featuring SALAN Ligands



complex	R^1	R^2
48a	Me	H
48b	Me	Me
48c	Me	*t*-Bu
48d	Me	Cl
48e	CH_2Ph	H
48f	CH_2Ph	Me
48g	CH_2Ph	*t*-Bu
48h	CH_2Ph	Cl

The stereocontrol of lactide ROP with these SALEN-based aluminum complexes has also stimulated numerous studies, including the preparation and evaluation of chiral complexes **46** and **47**. These results will be discussed in section 2.3.

Gibson and co-workers recently prepared related SALAN ligands and investigated the corresponding aluminum complexes **48** in lactide ROP (Table 3).[136] The free ligands were obtained by reductive amination and subsequently treated with trimethylaluminum to give the desired complexes **48**. A single-crystal X-ray analysis performed on **48b** revealed a trigonal bipyramidal coordination geometry at the metallic center. Notably, the methyl group and expectedly the growing chain as well occupy one of the equatorial positions. The corresponding alkoxide initiators were generated by in situ alcoholysis of **48a**−**f** using benzyl alcohol. High monomer conversions were generally reached after about 1 day at 70 °C in toluene solution for an initial monomer concentration of 0.83 mol L^{-1} and a monomer-to-initiator ratio of 100. The rate of polymerization was found to be significantly influenced by the size of the substituents at the ortho/para positions of the ligands. Accordingly, the highest activities were observed for the SALAN ligands derived from salicylaldehyde itself (R^2 = H), and considerably lower activities were observed with R^2 = *t*-Bu (with **48g**, 77% conversion was obtained after 120 h, and with **48c**, the conversion only reached 66% after 1464 h). In all cases, the polymerization proceeded in a well-controlled fashion, as indicated by the narrow molecular-weight distributions (PDI < 1.1) and the linear correlations between M_n and conversion.

Although most of the SALEN-based complexes studied for lactide ROP feature aluminum as the metallic center, the related yttrium and tin complexes **49**−**51** have also been reported (Figure 21). Despite its dimeric structure, the yttrium derivative **49**[130] was found to be more active than the corresponding aluminum complex **47c** (for an initial monomer concentration of 0.2 mol L^{-1} and a lactide-to-catalyst ratio of 100, at 70 °C in toluene, 97% conversion was obtained after only 14 h with **49** but 40 h with **47c**).

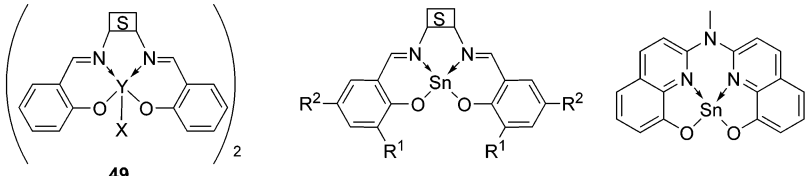


Figure 21. Yttrium and tin complexes **49**−**51** featuring SALEN ligands.

Although the related tin complexes **50** and **51**[137] have been demonstrated to adopt monomeric structures in solution (by ^{119}Sn NMR spectroscopy and cryoscopic molecular-weight determinations), their activity in lactide ROP has not been examined yet.

Chisholm and co-workers recently used a bulky Schiff base to prepare the corresponding zinc complexes **52a,b**,[138] which were shown to adopt monomeric structures by X-ray diffraction studies (Figure 22). Both complexes were active for the lactide ROP

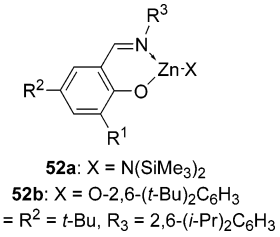


Figure 22. Zinc complexes **52a,b** featuring half-SALEN ligands.

in benzene at room temperature, the polymerization rate being much slower for **52b** featuring the bulky phenoxide initiating group. Complexes **52** can be formally related to those derived from β-diiminate ligands **29**, but preliminary investigations suggested that the metal center was significantly less sterically hindered by the half-SALEN ligands.

Trialkoxyamines, typically represented by triethoxyamine, have been widely used for the coordination of main-group elements as well as metallic centers. Recently, Verkade and co-workers hypothesized that five-coordinate titanatranes **53**[139] might be well suited for the ROP of lactide, since the transannular Ti−N bond could potentially labilize the trans axial OR group (Figure 23).[140] Preliminary investigations gave promising results, all of the titanium(IV) complexes being active in bulk polymerization and in solution at 70−130 °C. The nature

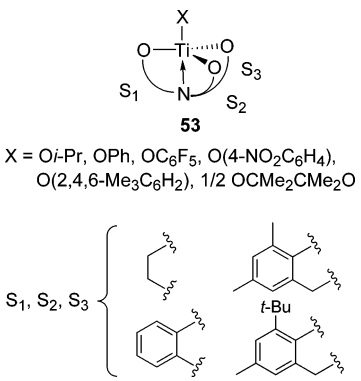


Figure 23. Titanium complexes **53** featuring atrane-type ligands.

of the initiating group X, alkoxide or aryloxide, more or less hindered and electron rich, did not seem to have a great influence, but the size and rigidity of the ancillary ligand proved to have a major effect. So far, the best results in terms of polymer yields and molecular weights were obtained with rigid five-membered ring systems. However, high conversions are usually associated with significant amounts of transesterification, as indicated by the rather broad or even bimodal molecular-weight distributions, and the beneficial effect of the ancillary tetradentate ligand remains to be demonstrated compared with the parent complexes Ti(O*i*-Pr)$_{4-n}$Cl$_n$.

Notably, the corresponding tantalum(V) complexes **54**[141] did not show any observable catalytic activity for lactide ROP, even in the melt at 130 °C (Figure 24). Here, the tetradentate ligand has a detrimental

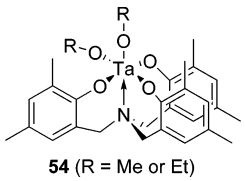


Figure 24. Tantalum complexes **54** featuring atrane-type ligands.

effect, since the related complex Ta(OEt)$_5$ proved to function as a catalyst, producing high polymer yields but relatively low molecular weights and with rather high polydispersity indexes. Although it should be sterically possible for six-coordinate complexes **54** to accommodate the seven-coordinate geometry required for a coordination−insertion mechanism, it is likely that the electrophilicity of the metal is not sufficient to be ligated effectively by the monomer.

Carpentier et al. recently prepared group 3 metal complexes **55a**−**c** by alkane or amine elimination from the corresponding alkoxy-amino-biphenol and MX$_3$(THF)$_2$ [X = CH$_2$SiMe$_3$ or N(SiHMe$_2$)$_2$] precursors (Figure 25).[142] With all of these complexes lactide ROP proceeds rapidly at room temperature in toluene or THF, complete conversion being typically achieved in 1 h for an initial monomer concentration of 0.5 mol L^{-1} and a monomer-to-initiator ratio of 500. The

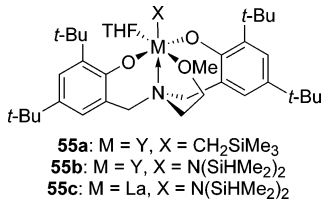
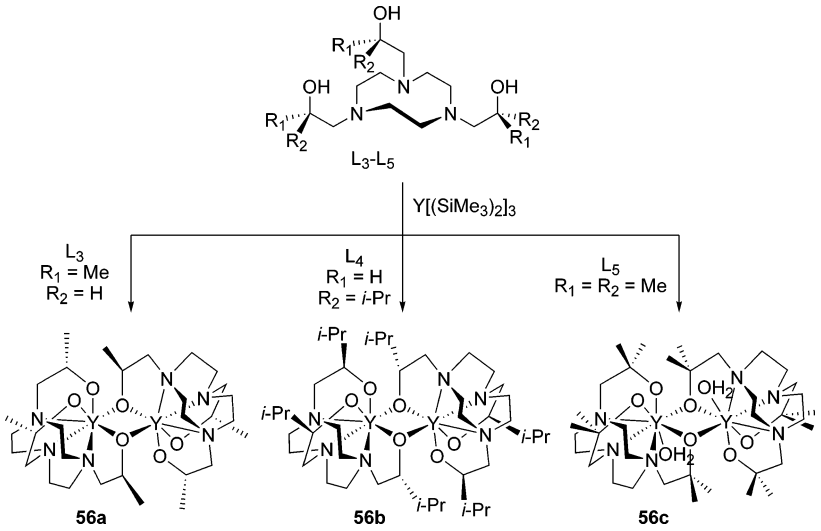


Figure 25. Group 3 metal complexes **55a**−**c** featuring alkoxy-amino-biphenolate ligands.

Scheme 14. Dinuclear Yttrium Complexes 56a–c Featuring Multidentate Ligands Based upon a 1,4,7-Triazacyclononane Framework

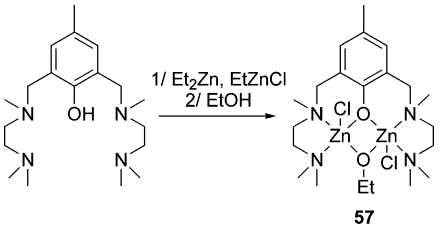


relatively low polydispersity indexes of the resulting polymers (about 1.3) and the linear relationship between the monomer-to-initiator ratio and number-average molecular weight indicate a good control of the polymerization.

Trialkoxy-triamines L_3–L_5 based upon a 1,4,7-triazacyclononane framework have also been used as multidentate N- and O-donor ligands toward yttrium(III).[143] The dinuclear complexes **56a,b**, obtained by treating the appropriate chiral ligand with $Y[N(SiMe_3)_2]_3$, were evaluated for the ROP of lactide at room temperature in dichloromethane solution (Scheme 14). Accordingly, complex **56b** resulted in a significantly faster and somewhat better controlled polymerization than **56a** (for an initial monomer concentration of 1 mol L^{-1} and a monomer-to-initiator ratio of 450, the conversion after 24 h reached 98% with **56b** but only 62% with **56a**; for a monomer-to-initiator ratio of 1000, a roughly linear increase was observed with **56b** between molecular weight and monomer conversion).[143a] However, the molecular-weight distributions of the resulting polymers were rather broad (PDI from 1.55 to 2.20). Interestingly, better results were obtained using the related achiral ligand L_5 featuring two methyl substituents on each C_2-arm. The increased activity of the corresponding complex **56c** (for an initial monomer concentration of 1 mol L^{-1} and a monomer-to-initiator ratio of 1000, conversion of 66% required 96 h with **56b** but only 0.5 h with **56c**) was suspected to result from the presence of coordinated water. This observation has subsequently led to further improvements, with the previous complexes having been treated with benzyl alcohol to afford di- and trinuclear alkoxide initiators.[143b]

Inspired by the cooperative action of metal ions frequently involved in enzyme-catalyzed hydrolysis reactions, Hillmyer and Tolman recently investigated the dinuclear zinc complex **57**,[144] derived from a phenolate-based ligand featuring two ethylenediamine arms (Scheme 15). Complex **57** rapidly polymerized lactide in dichloromethane solution. For an initial monomer concentration of 1 mol L^{-1} and a lactide-to-initiator ratio of 300, 90% conversion was

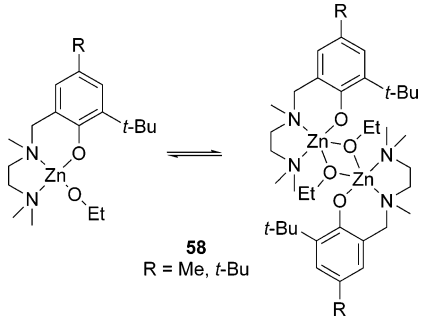
Scheme 15. Synthesis and Structure of the Dinuclear Zinc Complex 57



obtained after only 30 min at room temperature, with all of the characteristic features of a controlled polymerization being observed. Moreover, ^1H NMR analysis revealed the presence of ethoxide polymer end groups, with preliminary studies of kinetics indicating a first-order dependency on both the monomer and initiator, in agreement with a bimetallic coordination–insertion mechanism.

Following these very promising results, a related phenolate-based ligand featuring a single ethylenediamine arm was studied. The zinc ethoxide complexes **58**[145] were found to be dimeric in the solid state, but NMR and mass spectrometric analyses revealed that the monomeric form predominates in solution (Scheme 16). Using these complexes lactide polymerized at a rate faster than any other Zn-containing system reported so far (in dichloromethane at room temperature, the rate constant for lactide ROP with **58** is 5.1 times higher than with the

Scheme 16. Structure and Dimerization Equilibrium of the Zinc Complexes 58



β-diiminate derivative **29c**, 8.2 times higher than with the dinuclear zinc complex **57**, and 1220 times higher than with the trispyrazolyl-hydroborate derivative **21**).[145] Polylactides with molecular weights as large as 130 000 Da and relatively narrow molecular-weight distributions (PDI of ca. 1.4) were obtained. Despite the linear dependence of M_n with lactide conversion, the molecular weights of the resulting polylactides were lower than expected from the initial monomer-to-initiator ratio. The divergence has been attributed to the presence of impurities that may act as a catalyst deactivator and/or as an exchange promoter. These two phenomena have been supported by ^{1}H NMR end-group analyses and studies of kinetics.

2.3. Stereocontrol of Lactide ROP

Since lactide is prepared from lactic acid, it can be found in two diastereomeric forms: *meso*-lactide and D,L-lactide, also called *rac*-lactide (Figure 26). The

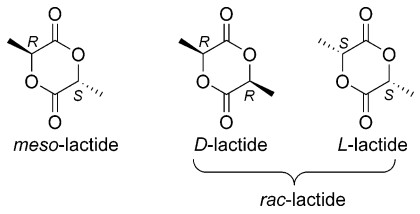


Figure 26. Stereoisomers of lactide.

enantiomerically pure monomers are also available, D-lactide being much more expensive than L-lactide.

Polylactides can exhibit different microstructures depending both on the monomer involved and on the course of the polymerization reaction (Figure 27).[146]

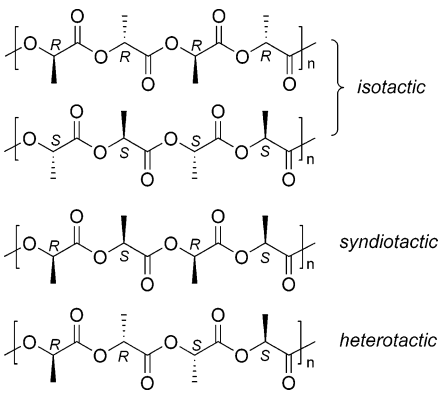


Figure 27. Different types of polylactides.

Isotactic polylactides, either poly(L-lactide) or poly(D-lactide), contain sequential stereocenters of the same relative configuration, while syndiotactic polylactides, namely, poly(*meso*-lactide), contain sequential stereocenters of opposite relative configuration. Regular alternation of L- and D-lactide units leads to another ordered structure, namely, heterotactic polylactides, also described as disyndiotactic polylactides. Last, atactic polylactides are obtained when the polymerization occurs without any stereoregularity.

The stereosequence distribution in polylactide samples is usually determined by NMR spectroscopy through inspection of the methine and/or carbonyl regions (^{13}C NMR and homonuclear decoupled ^{1}H NMR).[147−149] More recently, application of heteronuclear chemical shift correlation (HETCOR) NMR has been proposed by different groups, but the precise assignment of the different signals remains in debate.[150] The physical properties of polylactides are strongly dependent on their stereochemical composition; thus, melting and glass-transition temperatures have been used to characterize the stereoregularity of polylactides. For instance, when pure isotactic poly-(L-lactide), a highly crystalline material with a T_m around 180 °C, is contaminated with *meso*-lactide, the melting point and the crystallinity decrease, consistent with an amorphous polymer with a T_m around 130 °C, when the stereochemical defects reach 15%.[17]

Stereoregular crystalline polylactides retain their mechanical properties near their melting points and thus have higher use temperatures than atactic amorphous polymers. High-melting polylactides are thus attractive targets for a wide variety of new applications, provided their preparation is achievable through efficient and inexpensive processes.

2.3.1. Isotactic Polylactides

The more straightforward route to isotactic polylactides, poly(L-lactide) or poly(D-lactide), undoubtedly involves the enantiomerically pure monomers, provided no epimerization occurs during their polymerization. So far, most of the catalytic systems tested for such a stereocontrolled polymerization proceed with retention of configuration. Nevertheless, this strategy is considerably limited by the requirement for enantiopure monomers, and kinetic resolution of *rac*-lactide has been suggested as an alternative route to isotactic polylactides. This approach was first investigated with aluminum complexes featuring the chiral SALEN ligand derived from (*R,R*)-binaphthyldiamine.[128,131] The enantiomerically pure complexes **47b,c** (Figure 28) were demonstrated to pref-

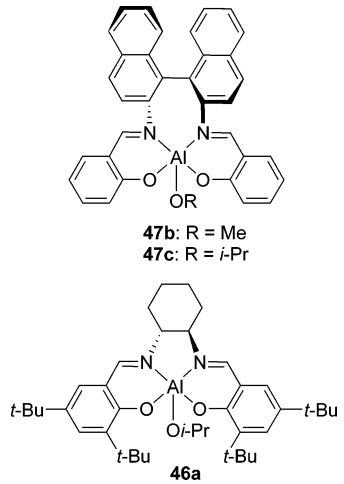


Figure 28. Chiral catalysts **47b,c** and **46a** used for kinetic resolution of *rac*-lactide.

erentially polymerize D-lactide, leading to a predominantly isotactic poly-(D-lactide) from *rac*-lactide. Notably, efficient and *reverse* stereocontrol was reported for the related complex **46a** based on (*R,R*)-

cyclohexanediamine, which preferentially polymerized L-lactide.[126,127] For both complexes the stereocontrolled polymerization proceeds via a site-control mechanism. The preferential polymerization of the "correct isomer" affords enantiomerically enriched isotactic polymers at low monomer conversions. For higher conversions, enrichment of the monomer pool of the "wrong isomer" results in polylactides with gradient L-lactide/D-lactide ratios within the polymer chains.[151]

Interestingly, high melting temperatures are not restricted to enantiomerically pure poly(L-lactide) or poly(D-lactide) (T_m 170−180 °C) and are even surpassed (T_m up to 230 °C) by PLA stereocomplexes[152] and PLA stereoblocks (Figure 29).

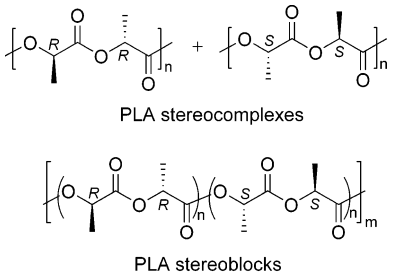


Figure 29. PLA stereocomplexes and stereoblocks.

Conceptually, the simplest approach to the generation of such high-melting PLA samples relies on the chain-end stereocontrolled polymerization of *rac*-lactide with an achiral catalyst. This strategy has only been validated experimentally very recently with SALEN-based aluminum complexes **43a**−**e** and **45a**−**f** (Figure 30).[124,125,153] The formation of PLA stereo-

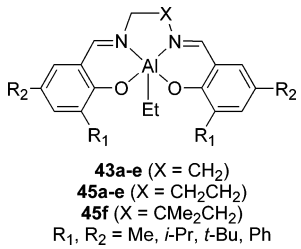


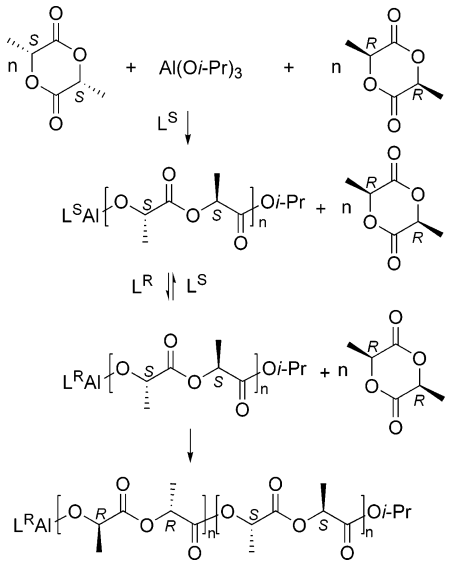
Figure 30. Achiral catalysts **43a**−**e** and **45a**−**f** for chain-end stereocontrolled polymerization of *rac*-lactide.

complexes was supported by powder X-ray diffraction studies. The highest selectivities were obtained for *t*-Bu substituents at the aromatic rings and with a $(CH_2)_3$ carbon linkage, although the polymerization rate was slow. Notably, the contribution of site stereocontrol due to conformational chirality has been ruled out since the activation barrier between the two conformational enantiomers was estimated to be only 13.7 kJ/mol.[124]

Alternatively, racemic aluminum catalysts based on the binaphthyl- and cyclohexyldiamines, **47e** and **46b**, respectively, have been successfully used for the parallel site stereocontrolled synthesis of isotactic poly(D-lactide) and poly(L-lactide) from *rac*-lactide (each enantiomer of the catalyst preferentially polymerizes one lactide enantiomer). In contrast to kinetic resolution of *rac*-lactide with homochiral catalysts, high enantioselectivities are achieved whatever the monomer conversion since the D/L ratio in the monomer pool remains constant during the polymerization. The very nature of the resulting stereoregular polylactides has been the subject of some controversy. Baker and Smith[133] initially claimed the formation of stereocomplexes based on a powder X-ray diffraction analysis, but thanks to detailed NMR studies, Coates[130,131] and Feijen[126,127] demonstrated later on that PLA stereoblocks were formed instead of PLA stereocomplexes.

Last, Duda et al. recently demonstrated the feasibility of another elegant approach, namely, the two-step polymerization of *rac*-lactide combining stereoselection and chiral ligand exchange.[132] A homochiral complex was first generated in situ from aluminum isopropoxide and the SALEN ligand L^S derived from salicylaldehyde and (*S*,*S*)-binaphthyldiamine (Scheme 17). ROP of 70 equiv of lactide (2.3 mol L^{-1} in THF)

Scheme 17. Two-Step Polymerization of *rac*-Lactide Combining Stereoselection and Chiral Ligand Exchange[a]



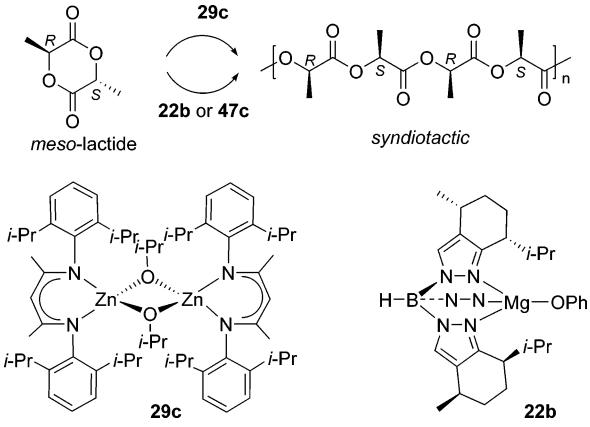
[a] L^S and L^R denote the SALEN ligands derived from salicylaldehyde and (*S*,*S*)- and (*R*,*R*)-binaphthyldiamine, respectively.

was performed at 80 °C, with changes in optical rotation leveling off after about 4 h, which is when monomer conversion approximately reached 50% according to GPC measurements. At that time, addition of the enantiomeric SALEN ligand L^R allowed the polymerization to proceed further. A gradual decrease in the optical rotation and completion of the monomer conversion were observed during the following 4 h. The resulting polylactides are almost monodisperse (PDI ranging from 1.08 to 1.12), high melting (T_m reached 210 °C for molecular weight of about 10^4 Da), and highly crystalline (about 70% according to the melting enthalpies). All these data support the consecutive site-controlled polymerization of both enantiomers of *rac*-lactide, the homochiral ancillary ligand rapidly exchanging with its enantiomer after half conversion. According to kinetic measurements, a given homochiral catalyst exhibits a 28:1 preference for the polymerization of one enantiomer of the monomer over the other. Therefore, the resulting polymers are gradient stereocopolymers rather than pure block stereocopolymers.

2.3.2. Syndiotactic Polylactides

The alternating stereochemistry of syndiotactic polylactides clearly requires the stereocontrolled polymerization of *meso*-lactide. Chain-end stereocontrol was recently investigated by Coates et al. with the bulky β-diiminate complex **29c** (Scheme 18).[103]

Scheme 18. Catalysts for the Preparation of Syndiotactic Polylactides from *meso*-Lactide



NMR analyses revealed the formation of syndiotactic polylactides with 76% racemic linkages between monomer units. Preliminary results were reported concerning the influence of the metal center and the β-diiminate substituents. Replacement of zinc by magnesium or introduction of ethyl rather than isopropyl substituents was shown to dramatically decrease the efficiency of the stereocontrol. The kinetic preference of chiral catalysts to open *meso*-lactide at one of the two enantiotopic O−acyl bonds (site-control strategy) has also been successfully developed. Only partially syndiotactic polylactides were obtained with the chiral tris(pyrazolyl)hydroborate magnesium complex **22b**.[93b] Better results were reported for the chiral SALEN-based aluminum complex **47c**.[129,130] This enantiomerically pure complex leads to more syndiotactic polylactides (up to 96% racemic linkages) than those obtained by chain-end control with the achiral β-diiminate complex. However, once again, stereocontrol is completely lost upon replacement of aluminum by another metallic center such as yttrium.

2.3.3. Heterotactic Polylactides

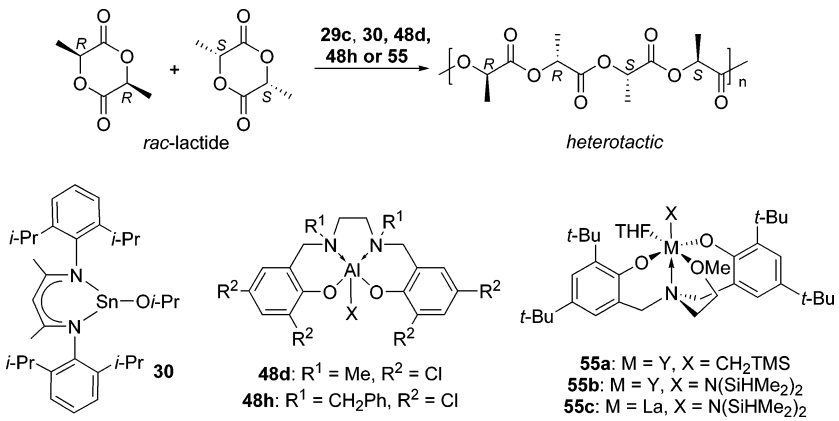
Preparation of heterotactic polylactides from *rac*-lactide results from alternative incorporation of L- and D-lactide and thus requires chain-end control (Scheme 19). Coates et al. demonstrated that β-diiminate dinuclear complex **29c** catalyzed the stereoselective ROP of *rac*-lactide yielding highly heterotactic microstructures, with stereoselectivities of 90% at room temperature and 94% at 0 °C.[102,103] The isopropyl groups at the aryl substituents were found to play a key role on the chain-end control, as indicated by the decreased heterotacticities observed with ethyl (79% at room temperature) and *n*-propyl (76% at room temperature) groups. Comparatively, only modest stereocontrol has been reported for the analogous mononuclear tin initiator **30**.[107] This methodology has been successfully extrapolated to complexes **48** featuring SALAN ligands, and the highest selectivities in heterotactic enchainments were obtained for the chlorinated ligands (88% with **48d** and even 96% with **48h** in toluene at 70 °C).[136] Last, the yttrium complexes **55a,b** lead to stereoselectivities of 80% in tetrahydrofuran but only of 60% in toluene at room temperature.[142] The chain-end control was of similar magnitude for alkyl and amido co-ligands (complexes **55a,b**) but significantly lower for the lanthanum derivative **55c** (64% in tetrahydrofuran).

Coates et al. recently demonstrated that regular alternation of L- and D-lactide units can also be achieved from *meso*-lactide and the racemic aluminum catalyst **47e** (Scheme 20).[130] According to NMR analyses, 80% of the linkages formed during the polymerization occurred between lactic acid units of identical stereochemistry. Although the exact nature of the stereochemical control remains unclear so far, an exchange mechanism was proposed to explain this striking feature.

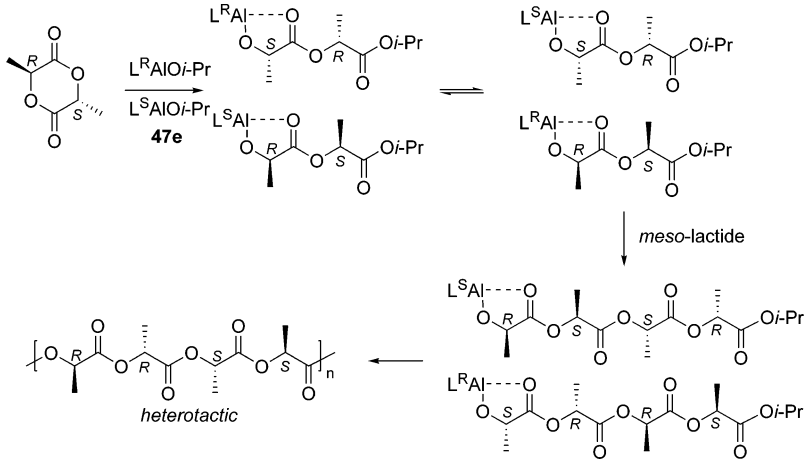
3. Anionic Polymerization

Anionic polymerization of lactide and glycolide has been much less investigated than the coordination−insertion approach. Although higher activities might be anticipated for anionic promoters that typically display strong nucleophilic and/or basic character, the deleterious contribution of transesterification and racemization reactions might be expected to be significantly more important when naked or loosely

Scheme 19. Catalyst for the Preparation of Heterotactic Polylactides from *rac*-Lactide

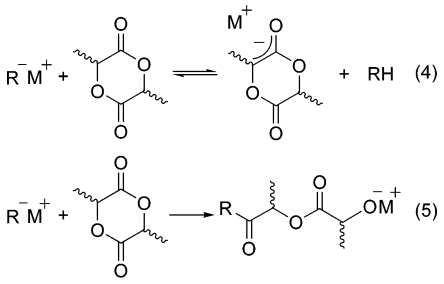


Scheme 20. Proposed Mechanism for the Formation of Heterotactic Polylactides from *meso*-Lactide and Racemic Catalyst 47e[a]



[a] L^S and L^R denote the SALEN ligands derived from salicylaldehyde and (*S*,*S*)- and (*R*,*R*)-binaphthyldiamine, respectively.

bonded anionic species are involved. From a mechanistic point of view, anionic ROP of lactide has been demonstrated to occur via acyl cleavage, the initiation step being either the deprotonation of the monomer (eq 4) or its ring opening by nucleophilic attack (eq 5).[154] Notably, the two initiation pathways are easily differentiated by end-group analysis, since the deprotonation route is associated with the absence of initiator fragments whereas the nucleophilic attack route typically results in ester end groups derived from the alkoxide promoters.



Following the pioneering work of Kleine et al.,[43] the feasibility of anionic ROP of L-lactide in solution at room temperature was fully demonstrated by Kricheldorf et al. with potassium *tert*-butoxide and butyllithium.[155] However, the monomer conversion did not exceed 80%, and the anionic initiator and alkoxide growing chain were both found to induce racemization regardless of solvent and temperature. Significantly higher yields could however be obtained by in situ generation of secondary and primary lithium and potassium alkoxides.[156,157] According to ^{1}H NMR end-group analysis, a considerable fraction of the alkoxide initiator was incorporated into the polylactide chain. The initiation step thus principally occurs via the nucleophilic route, despite the molecular weight of the resulting polymer not paralleling the monomer-to-initiator ratio. Although these promoters required temperatures of 50 °C to achieve the polymerization, the extent of racemization was found to be rather low, especially for the lithium alkoxides, and isotactic poly(L-lactide) with optical purity up to 95% could be prepared. When potassium methoxide was used as a promoter,[158] the ROP of L-lactide could be conveniently achieved in THF, with almost quantitative yields being obtained after 10−135 min at room temperature for initial monomer concentrations of 1.3−2.0 mol L^{-1} and monomer-to-initiator ratios of 50−300. Under these conditions, polymers with molecular weights in agreement with the monomer-to-initiator ratios and relatively narrow molecular-weight distribution (PDI ranging from 1.3 to 1.4) were obtained. Moreover, microstructural analysis by optical rotation measurements and ^{13}C NMR spectroscopy indicated a high degree of isotacticity for the resulting PLA. All these data suggest that potassium methoxide allows for minimization of both transesterification and racemization reactions.

Sipos and Zsuga compared lithium and potassium *tert*-butoxide as anionic promoters for lactide ROP and studied the effect of the addition of crown ethers.[159] Such complexing agents are usually believed to afford rate enhancements due to the conversion of contact- into separated-ion pairs. Surprisingly, a diminution in the rate was observed on addition of 18-crown-6 to potassium *tert*-butoxide and to a lesser extent of 12-crown-6 to lithium *tert*-butoxide. This striking feature was attributed to the formation of 1:1 complexes between the alkaline ion and lactide. According to force field calculations, lithium was predicted to form a stronger complex than potassium, and the 1:1 molar ratio of such activated monomer complexes could be confirmed experimentally for lithium by ^{1}H NMR analyses.

Kasperczyk et al. demonstrated that the use of lithium *tert*-butoxide as a promoter is also interesting for the stereocontrolled polymerization of *rac*-lactide,[148,160] leading, via chain-end control, to highly heterotactic microstructures with stereoselectivities of 90% at room temperature and 94% at −20 °C. However, these results were obtained at only 35% monomer conversion, and due to transesterification reactions, the regular microstructure of the chain tended to be significantly reduced when the monomer conversion was increased.

Superbases such as alkyllithium−lithium alkoxide complexes RLi−LiOR have been shown to be extremely useful in organic synthesis.[161] Using bulky substituents, a few of these oligomeric complexes have been structurally characterized. Indeed, aggregates **59**[85] and **60a,b**[162] featuring the biphenolate and methylenebiphenolate ligands (see section 2.2.2.1) have recently been isolated, analyzed by X-ray, and evaluated in lactide ROP (Figure 31). These lithium

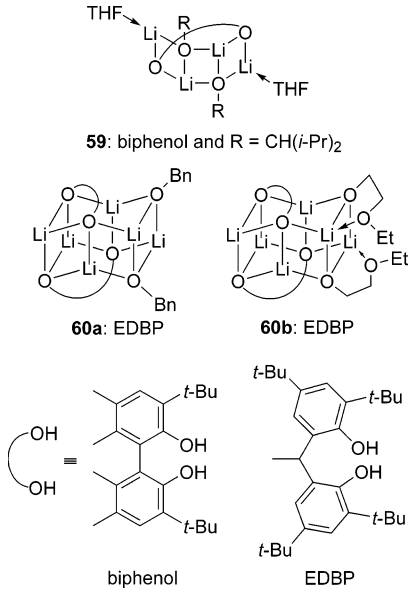


Figure 31. Structure of the lithium aggregates featuring biphenolate and methylenebiphenolate ligands.

aggregates were found to be extremely active initiators, complete conversions of L-lactide (200 equiv, 0.5 M) typically being obtained after only a few hours in dichloromethane even at 0 °C. Notably, the polydispersity indexes of the resulting polymers were significantly lower with promoters **60** (ranging from 1.06 to 1.12) than with **59** (about 1.7). The controlled character of the polymerization promoted by **60a** was also indicated by a linear relationship between the molecular weight and the monomer-to-initiator ratio. Moreover, ^{1}H NMR analyses carried out on the polymers prepared with this promoter revealed that initiation involved the benzyloxy group (as deduced from the presence of benzyl ester end chain) and that epimerization did not occur to any significant extent (as deduced from the presence of only one resonance in the methine region). All these data suggest that the ROP of lactide does not proceed via a true anionic mechanism but rather via a coordination−insertion mechanism. Thus, lactide might coordinate to the less sterically hindered lithium atoms of the aggregates, as supported by the coordination of the two ethoxy groups observed in **60b**.

Last, dibutylmagnesium has also been reported as an efficient promoter for ROP of L-lactide in toluene/THF solution at 0 °C.[163] The polymerizations were typically completed within a few days for an initial monomer concentration of 4 mol L^{-1} and monomer-to-initiator ratios up to 400. Polymers with almost complete optical purity but rather high polydispersity indexes (about 2) were obtained, indicating that these polymerization conditions minimize epimerization but not transesterification reactions. From a mechanistic point of view, *n*-butyl end groups were not detectable by ^{1}H NMR spectroscopy, suggesting that the initiation proceeds by deprotonation of the monomer or of any more acidic impurities. As in the case of lithium aggregates, several observations support a coordination−insertion mechanism, but the anionic mechanism cannot be definitely ruled out. The stereocontrolled polymerization of *rac*-lactide was also investigated with dibutylmagnesium and butyllithium.[164] Although significant extents of heterotactic microstructures could be observed by ^{13}C NMR (about 60−70%), transesterification reactions were found to have a strongly deleterious effect, as was the case with lithium *tert*-butoxide.

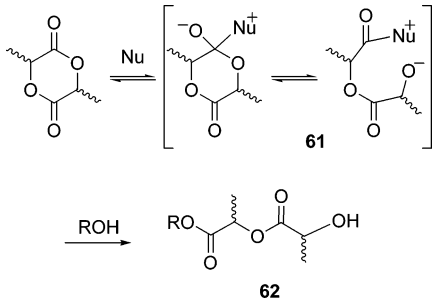
4. Nucleophilic Polymerization

Metal-free catalysts are attracting growing interest as more economical and environmentally friendly alternatives for classical organic transformations. To this end, enzymes (such as lipases) as well as organocatalysts (such as amines, phosphines, and N-heterocyclic carbenes) have recently been investigated for transesterification reactions,[165−168] including lactide ROP.[169−172] These metal-free nucleophilic catalysts are particularly attractive for biomedical applications of the resulting polymers, since there is no concern of contamination, waste, and removal of metals.

4.1. Mechanistic Considerations

In this metal-free approach to lactide ROP, the enzymes, amines, phosphines, and carbenes all act as nucleophilic transesterification catalysts, requiring the presence of a protic agent (typically water for lipases and alcohols for organocatalysts) as an initiator. Although the precise mode of action of these nucleophilic catalysts remains obscure, it would seem likely that the polymerization occurs through a monomer-activated mechanism[170,173] involving a transient lactide−catalyst complex **61** (Scheme 21). The

Scheme 21. Plausible Pathway for the Nucleophilic Lactide ROP[a]



[a] Nu denotes the catalyst (enzyme, amine, phosphine, or N-heterocyclic carbene). ROH refers either to the initiating protic agent or to the secondary alcohol function of the growing polymer chain.

protic initiator ROH would react with this lactide−nucleophile (Nu) complex to form the ring-opened adduct **62** with simultaneous liberation of the nucleophilic catalyst. Chain propagation would proceed analogously by reaction of the ω-hydroxyl group of **62** with an activated-monomer **61**. This mechanism

is in agreement with the nature of the α-chain end of the resulting polylactide, namely, an acid or ester functionality depending on the initiating protic agent. For lipases, a serine moiety has been suggested as the active nucleophilic site, and thus, the enzyme-activated monomer **61** would be an acyl−enzyme complex.

This polymerization pathway differs fundamentally from that involved with metal complexes. Indeed, the nucleophilic catalyst only activates the monomer toward ring opening, whereas the metal complex activates the monomer, initiates the polymerization, and remains bound to the growing chain.

4.2. Catalysts

4.2.1. Enzymes

All the commercially available lipases tested for the lactide ROP proved to be active, except Novozyme 435.[169] *Pseudomonas cepacia* lipase PS showed the highest catalytic activities. High monomer conversions were achieved after several days at 80−130 °C in the bulk. Molecular weights of up to 270 000 Da were obtained with rather narrow distributions (PDI 1.1−1.3). Although the enzyme and oligomers were easily removed from the resulting PLA upon workup, the isolated yields are fairly small (<16%). The formation of these oligomer fractions along with the observed induction periods are characteristic features for lipase-induced polymerizations. Celite-immobilized lipase PS was also found to be active but led to broad dispersities (>4). These results demonstrate the feasibility of enzyme-catalyzed lactide polymerization, but the versatility of this approach clearly deserves to be studied.[174]

4.2.2. Organocatalysts

For all organocatalysts (amines, phosphines, N-heterocyclic carbenes) the living character of the nucleophilic polymerization has been established by the linear correlation between the molecular weight and conversion. As a consequence, the degree of polymerization closely tracks the initial monomer-to-initiator ratio and polylactides of controlled molecular weights and narrow distributions are obtained. Primary and secondary alcohols were found to be efficient initiators, leading to the corresponding ester functionality at the PLA α-chain end.

Organocatalytic polymerization was first reported with pyridines as nucleophilic catalysts. 4-Aminopyridines such as DMAP and PPY (Figure 32) were

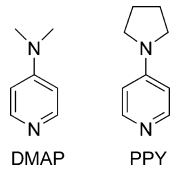


Figure 32. Structure of 4-(dimethylamino)pyridine DMAP and 4-pyrrolidinopyridine PPY.

found to be highly active for the lactide ROP.[170] Provided catalyst concentration is at least equal to that of the initiator, high monomer conversions were obtained both in dichloromethane solution (∼1.4 M) at 35 °C in a few days and in bulk at 135 °C in a few minutes for monomer-to-initiator ratios up to 140. Compared with metal complexes, prolonged reaction times do not induce detectable changes in molecular weight with pyridines, indicating that the undesirable transesterification side reactions and polymerization/depolymerization equilibrium are less effective. Interestingly, polystyrene-immobilized DMAP gives very similar results in terms of molecular weight, polydispersity, as well as polymerization kinetics. Moreover, this supported nucleophilic catalyst was easily removed by filtration after polymerization.

Phosphines also proved to be active in lactide ROP but significantly less so than amines.[171] As expected, the substitution pattern of phosphines has a strong influence on their activity, aryl and bulky alkyl groups resulting in slower polymerizations. High monomer conversions required rather high temperatures (94 °C in toluene solution, 135 °C in bulk), even for the most active phosphine catalyst, namely, P(*n*-Bu)$_3$. Phosphine concentrations above that of the initiator lead to broader molecular-weight distributions (PDI 1.3−1.5). Analogous polydispersity broadening was observed when heating was prolonged after monomer consumption. This observation indicates the higher contribution of adverse transesterification reactions for phosphines compared with amines, something that would be expected because of the higher polymerization temperatures necessary with the former.

Over the last 10 years, N-heterocyclic carbenes have allowed for spectacular achievements in both organometallic catalysis and organic synthesis.[175] Their recent investigation for lactide ROP has clearly been stimulated by the promising results obtained with pyridines and phosphines. The representative imidazol-2-ylidene IMes (Figure 33) proved to be far

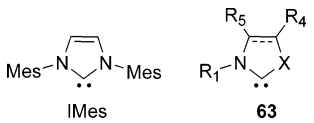


Figure 33. General formula for N-heterocyclic carbenes **63** (X = N−R$_3$ or S), and structure of the representative example IMes (Mes = 2,4,6-Me$_3$C$_6$H$_2$).

more active than phosphines and even amines.[172] For initial monomer concentrations around 1 mol L^{-1} and monomer-to-initiator ratios ranging from 50 to 200, quantitative conversions were achieved in less than 1 h at room temperature in THF. The catalyst-to-initiator ratio has a strong influence on the polymerization control. Ratios from 0.25 to 1.5 allow for the preparation of polylactides with high molecular weights (DP > 100) and low PDI, whereas much lower ratios on the order of 0.0125 are necessary to obtain oligomers (DP ≈ 15) with low PDI. The scope and generality of these nucleophilic polymerizations was then investigated by varying the structure and substituents of the carbene catalyst **63**.[172b] Imidazol-2-ylidenes as well as thiazol-2-ylidenes and imidazolin-2-ylidenes featuring various substituents both at the nitrogen atoms and the carbon framework have been tested. The diaminocarbenes proved to be

the most active catalysts, sterically demanding and electron-withdrawing substituents being as expected less favorable.

Interestingly, the extreme air and moisture sensitivity of N-heterocyclic carbenes can be easily circumvented by their in situ generation from their protonated form. The feasibility of solid-supported catalysis has also been established with thiazolium and imidazolium precatalysts, although some restrictions (limited molecular weights, broader PDI), probably associated with solubility problems, were observed.[172b] Better results were obtained for THF/ionic liquid biphasic catalysis. Indeed, in situ deprotonation of an imidazolium-based ionic liquid generates the corresponding imidazol-2-ylidene, which then migrates to the THF phase and initiates lactide ROP. Rapid and repetitive polymerizations were achieved, the imidazolium precatalyst being easily regenerated by addition of a tertiary ammonium salt. These results as a whole clearly suggest that N-heterocyclic carbenes are most promising nucleophilic catalysts for lactide ROP.[176]

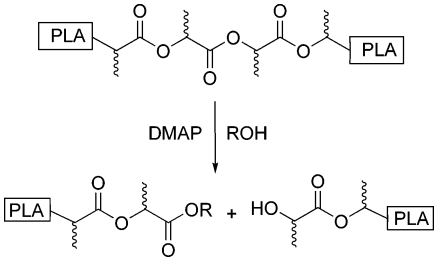
4.3. Stereocontrol of Lactide ROP

So far, only a few preliminary results have been reported for the stereochemically controlled polymerization with nucleophilic catalysts: (i) no racemization occurred in the enzyme-[169] and DMAP-catalyzed[170] polymerization of the enantiomerically pure L-lactide and (ii) no stereosequence enrichment was detected when D,L-lactide was polymerized with lipase PS[169a] or chiral phosphines.[170] The latter result has been attributed to the rather drastic conditions required with phosphines as ROP catalysts (bulk, 135 or 180 °C). However, higher stereocontrol might be anticipated for the much more active N-heterocyclic carbenes since these catalysts efficiently achieve lactide ROP in solution even at room temperature.

4.4. Depolymerization

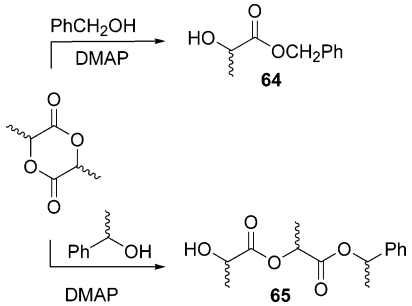
Pyridine catalysts such as DMAP and PPY have also been used for the chain scission of polylactides.[177] Low- as well as high-molecular-weight polymer samples were depolymerized with primary alcohols either in solution at 38 °C or in bulk at 185 °C. The resulting polylactides have DPs consistent with the alcohol-to-polymer ratio and polydispersity indexes in the same range as the initial polymer (Scheme 22). Thus, this transesterification approach allows for the preparation of controlled molecular weight and end-group-functionalized polylactides. Promising results were also reported for more complex macromolecular architectures. Indeed, star-shaped polymers and block copolymers were obtained, respectively, when Pentaerythritol and monohydroxy-functionalized poly(ethylene oxide) oligomers were used as PLA depolymerization initiators.

Scheme 22. Schematic Representation of the DMAP-Catalyzed PLA Depolymerization



These new applications of nucleophilic amine catalysts are based on the influence of the initiating alcohol on the transesterification selectivity. Indeed, primary alcohols react not only with lactide but also with ring-opened esters, whereas secondary alcohols only react with lactide and are inert toward ring-opened products. This marked difference has been clearly demonstrated by the formation of mono- and diadducts **64** and **65** in the DMAP-catalyzed lactide ring opening with excess benzyl alcohol and α-methylbenzyl alcohol, respectively (Scheme 23).[177]

Scheme 23. DMAP-Catalyzed Lactide Ring Opening with Model Primary and Secondary Alcohols



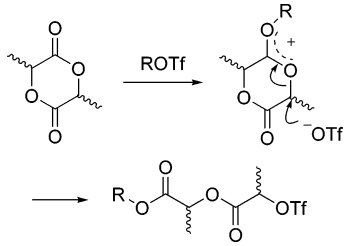
Overall, it would seem that the secondary alcohol functionality is the best compromise for propagating lactide ROP without inducing undesirable transesterification of ring-opened products. This selectivity is responsible for the living character of nucleophilically catalyzed lactide polymerization. However, this inherent feature can be expected to strongly interfere in the lactide/glycolide copolymerization. Indeed, incorporation of glycolide leads to primary alcohol ω-chain ends, for which transesterification side reactions are likely to occur.

5. Cationic Polymerization

The coordination and nucleophilic polymerizations discussed above are undoubtedly the most efficient and general methods reported so far for the ring-opening polymerization of lactones, with cationic polymerization having found comparatively little success. After unsuccessful attempts reported in 1971 by Dittrich and Schulz,[50] the feasibility of such a cationic ROP of lactide was demonstrated by Kricheldorf et al. in the late 1980s.[178] Among the numerous acidic compounds investigated, only trifluoromethanesulfonic acid (HOTf) and methyl trifluoromethanesulfonate (MeOTf) proved to be efficient initiators. The polymerization rates were significantly higher in nitrobenzene than in chlorinated solvents, with 50 °C being found to be the optimum reaction temperature (lower temperatures result in modest yields, and higher temperatures lead to dark-colored samples). According to ^{1}H NMR, polymers with methyl ester end groups were obtained with MeOTf as initiator, suggesting that the polym-

erization occurs via cleavage of the alkyl−oxygen rather than the acyl−oxygen bond. Moreover, the authors proposed that the chain growth proceeds in two steps and involves intermediately ring-opened trifluoromethane sulfonates, since optical rotation measurements revealed that samples of 100% optically active poly(L-lactide) were obtained from L-lactide with both HOTf and MeOTf (Scheme 24).

Scheme 24. Proposed Pathway for the Cationic Lactide ROP[a]



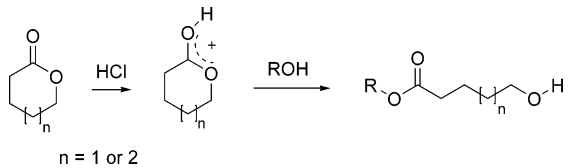
[a] R = H, Me, or growing polymer chain, Tf = CF_3SO_2.

Despite a span of monomer-to-initiator ratios varying from 50 to 400, the resulting polymer samples were shown to be very similar in viscosities (0.15−0.27 dl/g), although precise data concerning the molecular weights of the polymers are not available.[178b] These results clearly indicate that the cationic copolymerization of lactide and glycolide was far from living under these conditions.

Much more promising results were recently obtained by combining an acid (such as HCl·Et_2O) and a protic agent (such as water or an alcohol). Indeed, this combination proved to efficiently polymerize ϵ-caprolactone and δ-valerolactone smoothly in dichloromethane solution at 0 °C.[179] When an alcohol was used as initiator, the resulting polymers feature the corresponding α-chain ester end group, as demonstrated by ^{1}H NMR. Moreover, the polymer molecular weights (from 3000 to 14 300 Da) were found to increase linearly with the monomer to protic agent ratio with narrow polydispersities (PDI < 1.25), in agreement with a living polymerization. All these data strongly support an "activated monomer cationic polymerization", as developed by Penczek[180] and already discussed for nucleophilic polymerization. Accordingly, HCl would only act as a transesterification catalyst, the alcohol being the actual initiator of the polymerization (Scheme 25).

If the aforementioned conditions are applicable to the ROP of lactide and glycolide, cationic polymerization would clearly deserve to be considered as an alternative to the coordination and nucleophilic polymerizations.

Scheme 25. Plausible Activated Monomer Pathway for the Cationic Polymerization of Lactones[a]

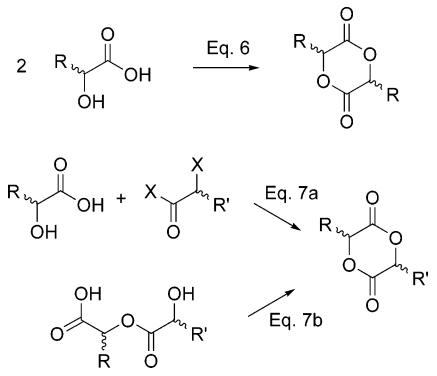


[a] ROH refers either to the initiating protic agent or to the alcohol function of the growing polymer chain.

6. Conclusion and Perspectives

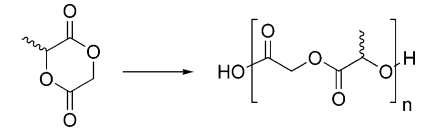
From this review it is clear that enormous progress has been made in the ROP of lactide and glycolide over the last 30 years. Higher activities and better control can be expected in due course by further optimizing the initiator structure and polymerization procedure.[181] In particular, further improvements may be anticipated for the stereocontrolled ROP of lactide using well-defined complexes, with nonmetallic systems being likely to attract increasing interest. It can be reasonably anticipated that the synthesis and practical applications of environmentally friendly PLA, PGA, and PLGA will keep increasing at the industrial scale as well. In this respect, the role of macromolecular engineering should not be underestimated. To tune and further broaden the properties of these biodegradable and bioassimilable polymers, various approaches are currently under investigation, and the two most widely used strategies will be presented hereafter.

The first strategy is the copolymerization of lactide and glycolide with related monomers, especially those featuring functional groups.[182] From a synthetic point of view, the 1,4-dioxane-2,5-dione skeleton can be easily accessed by condensation of α-hydroxyacids (eq 6). This route, which mirrors the standard preparation of lactide, is by far the most simple and general. However, it usually gives only modest isolated yields while also being restricted to symmetrically 3,6-disubstituted monomers. The synthesis of unsymmetrical monomers is usually achieved by step-by-step condensation starting from an α-hydroxyacid and an α-haloacyl halide (eq 7a). Alternatively, Hennink and co-workers recently demonstrated that cyclization of linear α-hydroxy acid dimers can be efficiently carried out with cyanuric chloride (eq 7b),[183] but synthesis of the required precursors necessitated five steps and orthogonal protecting groups.



The ROP of methylglycolide **66**,[184] a crossed dimer, gives PLGA copolymers with equal amounts of lactic and glycolic units (Scheme 26). However, the most interesting aspect of this monomer undoubtedly resides in its unsymmetric structure. Indeed, given the different reactivity of lactide and glycolide ($r_G/r_L \approx 10$), it might be anticipated that the polymerization proceeds preferentially by cleavage of the least sterically hindered acyl moiety. This unique opportunity to prepare alternating PLGA copolymers has been recently validated with tin octanoate as a catalyst,

Scheme 26. Structure of Methylglycolide 66 and of the Derived Alternating PLGA

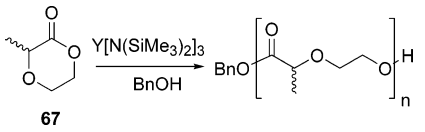


66
methylglycolide

but further developments in this direction are so far limited by the poor availability of methylglycolide.

In a similar way,[185] Hillmyer and Tolman reported the ROP of 3-methyl-1,4-dioxan-2-one **67** by the yttrium complex $Y[N(SiMe_3)_2]_3$ in the presence of benzyl alcohol (Scheme 27). Due to the presence of a

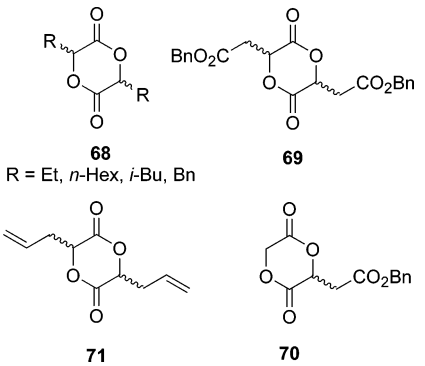
Scheme 27. Structure and Polymerization of 3-Methyl-1,4-dioxan-2-one 67



67

single ester moiety within the six-membered ring, **67** was found to be significantly less reactive than lactide (standard state polymerization enthalpy ca. −12 kJ/mol compared to −23 kJ/mol for lactide). Nevertheless, polymers featuring alternating lactate and ethylene glycol moieties could be obtained. Due to their rather low T_g values (ca. −24 °C), these polymers are good plasticizing agents for PLA, but their use is so far limited by the poor accessibility of **67**.

2,6-Dialkyl and 2,6-dibenzyl-glycolides **68**[186] (Figure 34) are much more readily available than unsymmetrical monomers and have therefore been used to probe the influence of the pendant groups. As expected, the longer the alkyl group, the lower the glass-transition temperature, T_g (the flexible side chain acting as an internal plasticizer), whereas branched alkyl groups result in higher T_g due to hindered rotation of the polymer backbone. The pendant groups on the glycolide ring also give the opportunity to prepare polyesters featuring functional side chains. The more straightforward method is obviously the ROP of protected functionalized monomers, such as the malic-acid-derived rings **69**[187] and **70**.[188] Alternatively, the functional groups may be introduced after the ROP of well-designed mono-



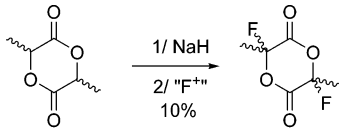
68
R = Et, *n*-Hex, *i*-Bu, Bn
69
71
70

Figure 34. Mono- and disubstituted monomers **68**−**71** derived from glycolide and lactide.

mers such as **71**,[189] whose allyl side groups can be subsequently transformed via olefin metathesis.

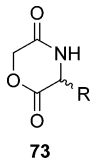
Recently, the introduction of fluorine atoms has also been investigated in order to modify the properties of the polyester backbone (improved chemical resistance, lower water absorption, lower surface energies, higher solubility in supercritical CO_2 can be expected). Successive treatment of a preformed PLA with sodium hydride and *N*-fluorobenzenesulfonimide allowed about 80% of the methine groups to be fluorinated; however, the GPC data of the resulting material indicated significant degradation of the polymer chain. Alternatively, fluorination of lactide itself following the same procedure afforded the desired 2,6-difluorolactide **72** (Scheme 28),[190] albeit in only 10% yield.

Scheme 28. Synthesis of the 2,6-Difluorolactide 72



72

Last, the crossed dimers of α-hydroxy and α-amino acids, namely, morpholine-2,5-diones **73**,[191] clearly deserve to be mentioned (Figure 35). Indeed, these unsymmetrical monomers are usually obtained in better yields than the related 1,4-dioxane-2,5-diones, and introduction of pendant functional groups is straightforward from aspartic acid, glutamic acid, lysine, serine, or cysteine. Although the steric bulk of the protected side chains significantly lowers the reactivity of the six-membered ring, copolymerization with lactide could be conveniently achieved to give polyesteramides with pendant functional groups.



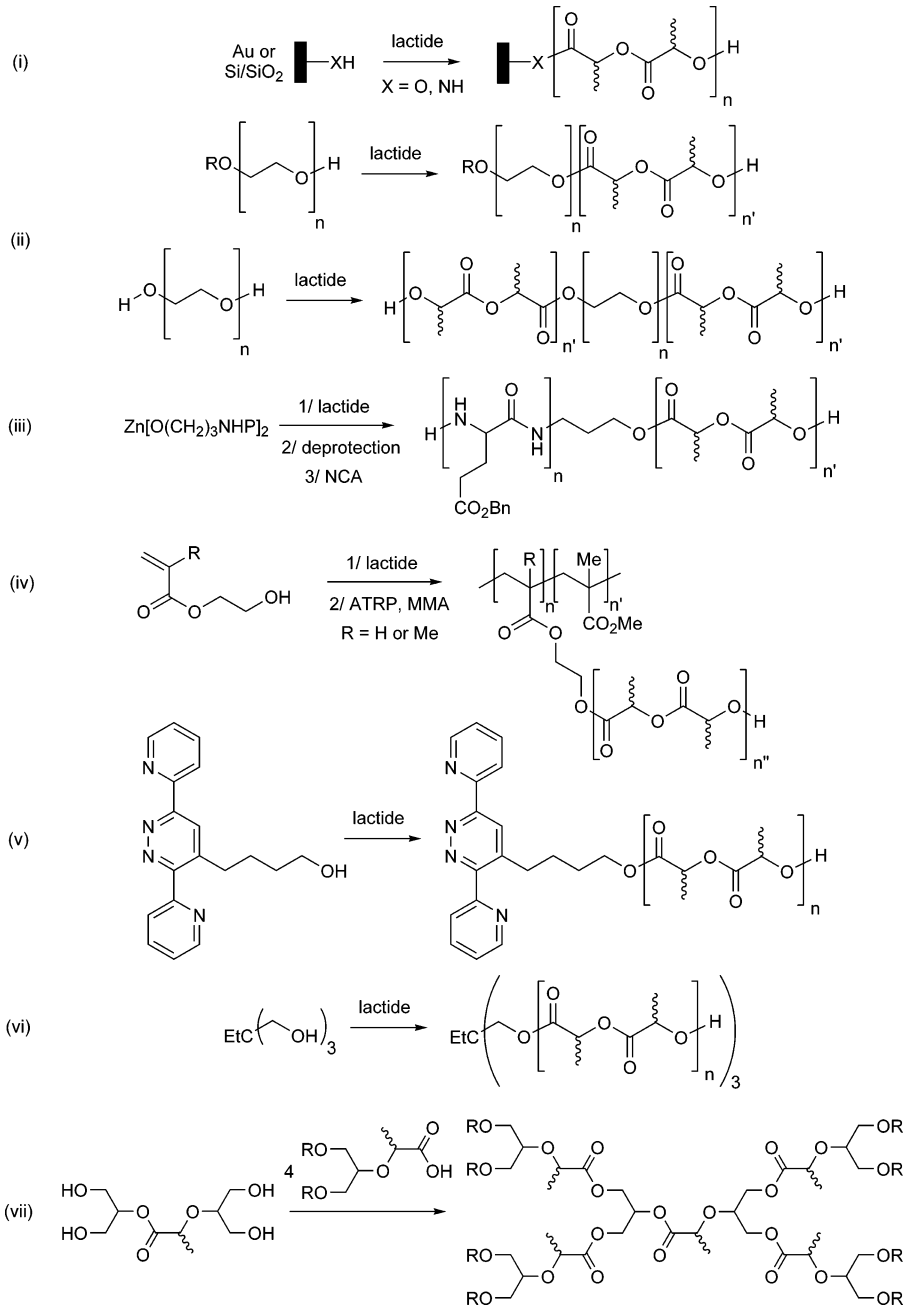
73

Figure 35. Structure of morpholine-2,5-diones **73**.

The second area under investigation for the development of these biodegradable polymers is the preparation of tailored macromolecular architectures,[192] again taking advantage of the recent progress achieved in controlled ROP of lactide and glycolide. A few representative examples of the various polymer topologies already reported are listed hereafter (Scheme 29):

(i) solid coatings prepared by surface-initiated ROP of lactide,[193] (ii) polylactide/poly(ethylene glycol) di- or triblock copolymers prepared by metal-assisted ROP of lactide with PEG as initiators,[194] (iii) polylactide/poly(benzyl glutamate) diblock copolymers prepared by zinc-assisted lactide ROP using an appropriate difunctional initiator and followed by ROP of the *N*-carboxyanhydride of benzyl glutamate (NCA),[195] (iv) polylactide/poly(methyl methacrylate) graft copolymers prepared by atom-transfer radical copolymerization (ATRP) of methyl methacrylate

Scheme 29. Representative Examples of Macromolecular Architectures Derived from PLA, Emphasizing the Involvement of the Lactide Unit



(MMA) and PLA macromonomers resulting from ROP,[196] (v) metallo-supramolecular grid-like polymers prepared by complexation of PLA macroligands featuring a terminal bis(2-pyridyl)pyridazine moiety with copper(I) ions,[197] (vi) star-shaped PLA and related copolymers prepared by ROP with multifunctional initiators,[198] and (vii) lactic acid/glycerol dendritic architectures prepared from a protected trivalent unit via a divergent procedure.[199]

7. Acknowledgments

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8. References and Notes

(1) The term "biodegradable" is used here in the broadest sense, meaning that the polymer will eventually disappear following introduction in the body, without reference to the mechanism of degradation, which may or may not be enzymatically assisted.
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