DALTON
PERSPECTIVE

Polymerization of lactide and related cyclic esters by discrete metal complexes

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This perspective highlights recent research on the preparation of polyesters by the ring-opening polymerization of cyclic esters employing well-characterized metal complexes. Particular focus is placed on the preparation of polylactide because of environmental advantages: it is biodegradable and its feedstock, lactide, is a renewable resource. A recurring theme is the correlation of precatalyst structure, often by X-ray crystallography, with polymerization activity and selectivity. Through this systematic approach to the deconvolution of catalyst structure/reactivity relationships, improved mechanistic understanding has been attained and key design criteria required for the development of new catalysts that exert control over the molecular parameters of polyesters and related copolymers have been revealed.

Introduction

Polyester fibers, coatings, and films are ubiquitous engineering materials. A particularly convenient method for the synthesis of polyesters is the ring-opening polymerization of cyclic esters, where the relief of ring-strain is the driving force for polymerization (Fig. 1). Synthetic advantages of this method include molecular weight control, a tendency to yield product polymers with narrow molecular weight distributions, and applicability toward the synthesis of well-defined copolymers.[1] Of the variety of polyesters made this way, poly-D,L-lactide (PLA) is a particularly important material due to its biodegradable characteristics and the renewable nature of its feedstock.

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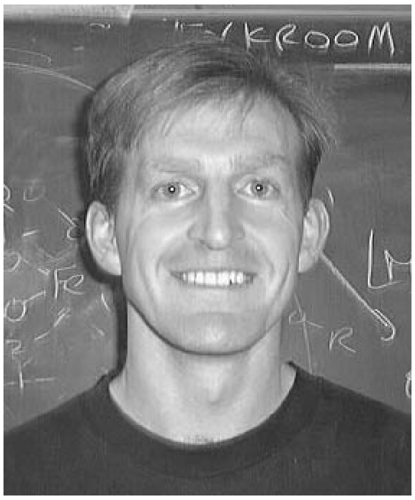

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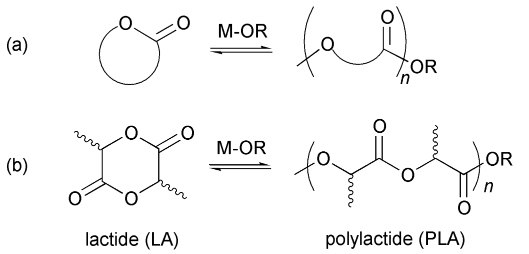


Fig. 1 (a) Generalized scheme for the ring-opening polymerization of cyclic esters by metal alkoxides. (b) Ring-opening polymerization of lactide.

The ring-opening polymerization of lactide (LA) has been investigated for over a century,[2] and in the past three decades focus has been on biomedical applications such as drug delivery excipients and adsorbable sutures. More recently, PLA has garnered interest as a new environmentally-friendly thermoplastic with wide applicability. The starting materials for PLA are derived from corn, beets, and other annually renewable resources. As the depletion of petrochemical feedstocks draws near, the production of new, useful and environmentally friendly polymers is increasingly important for a sustainable future.[3] Because of these attractive features and the announcement of large-scale PLA commercialization,[4] research on PLA chemistry and materials science has been extremely fertile.

With the overall goal of preparing PLA and related copolymers with prescribed molecular characteristics, significant effort has been placed on the design and synthesis of new catalysts that exhibit good activity and selectivity for the polymerization of LA and other cyclic esters. Although several examples of catalytically active species for the polymerization of LA are known, there is a general lack of fundamental understanding of catalyst structural influences on polymerization reactivity and mechanism that are so important for rational design purposes. To address this deficiency, there has been particular emphasis over the past decade on the synthesis of discrete, well-characterized complexes that are active polymerization initiators and are amenable to detailed mechanistic study. New insights into how catalyst structure impacts catalytic reactivity have resulted from these efforts. In this Perspective we review this research, with a particular focus on studies using catalyst precursors that are structurally well-defined, in most cases by X-ray crystallography. As background, we describe some general features of LA (and related cyclic ester) polymerizations followed by specific catalyst systems, organized by the metal ion used.

By far the most common metal-containing species active for the ring-opening polymerization of cyclic esters are metal alkoxides (Fig. 1). While simple sodium, lithium, and potassium alkoxides are effective,[5] the high basicity of these ionic species results in detrimental side reactions such as epimerization of chiral centers in the PLA backbone. Covalent metal alkoxides, on the other hand, are far more selective and widely used as a result.

As with any catalytic process, both activity and selectivity are primary concerns, which in the case at hand may be framed in terms of polymerization control. Because the physical properties of a polymeric material are tied directly to its molecular weight, control of polymer molecular weight is of utmost importance in a synthetic procedure. The control of molecular weight is straightforward in polymerizations with fast initiation and no termination or chain transfer. In these so called living polymerizations, the molecular weight of the polymeric product is a linear function of the monomer-to-initiator ratio.[6] While the polymerization of cyclic esters can exhibit these features, the reversible nature of the LA polymerization can affect molecular weight control. Since the ring strain in LA that provides the driving force for polymerization is modest,[7,8] the back reaction can become important (especially at high temperature) leading to significant monomer (and cyclic oligomer) concentration at equilibrium. Therefore, incomplete conversion of monomer must be taken into account when targeting a specific molecular weight. Still, although the word "living" is misused in many cases, there are many examples of the controlled polymerization of LA and other cyclic esters where the molecular weight of the product polymers is prescribed by the monomer-to-initiator ratio.

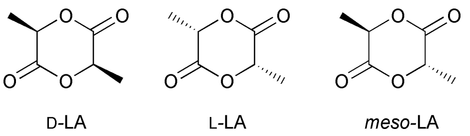


Fig. 2 Stereoisomers of lactide (LA).

Because of fast initiation and limited termination and transfer in controlled and living polymerizations, the molecular weight distribution of the polymers produced is often narrow, as parameterized by the polydispersity index (PDI).[9] A common side reaction in polyester synthesis is transesterification, in which cleavage and reformation of polymer chains leads to a broadening of the molecular weight distribution that has been described theoretically as a function of the monomer conversion.[10] The degree of transesterification is an important selectivity criterion for any LA polymerization system. Minimal transesterification is especially desired in the preparation of discrete A–B block copolyesters where transesterification would compromise the architectural integrity of the copolymer. The occurrence of transesterification may become particularly problematic for more active, and thus less selective, polymerization catalysts.

Stereoselectivity in the polymerization of LA, which exists as three stereoisomers (Fig. 2), also is important to control since the material properties depend strongly on the polymer tacticity.[3] As long as the polymerization catalyst does not effect epimerization of chiral centers in the monomer or polymer, isotactic PLA (PDLA or PLLA) can be accessed by using pure D- or L-LA, respectively. Selectivity issues are more important for the polymerization of D/L-LA mixtures, where a propagating metal alkoxide center may show a preference for enchaining a particular stereoisomer. For example, in a process analogous to a kinetic resolution in small molecule synthesis, in the polymerization of racemic LA, the propagating site may polymerize one enantiomer faster than the other. Isotactic polymer segments result from such a stereoelective reaction.[11] Likewise, in a completely stereoselective polymerization of *meso*-LA, one of the enantiotopic acyl bonds is preferentially opened to yield a syndiotactic polymer, whereas in the absence of stereocontrol, an atactic polymer is produced.

Given some of the general experimental criteria for a well-behaved LA polymerization, attributes of an ideal catalyst include high activity, fast initiation relative to propagation, minimal transesterification, and the ability to control the stereochemical purity of the PLA prepared from an arbitrary mixture of LA stereoisomers. Systematic deconvolution of structure/activity relationships in well-defined catalytic systems is important for the design of polymerization catalysts with these beneficial features. In the following, we describe selected, recently published efforts to achieve these research goals using discrete, structurally well-characterized metal complexes with particular ligand frameworks. We focus primarily on polymerization studies of LA, but also include some discussion of work with related cyclic esters such as caprolactone (ε-CL) and valerolactone (δ-VL) because of structural relationships with LA.

Complexes of aluminium

One of the earliest reports of LA polymerization by discrete metal complexes used tetraphenylporphyrin aluminium alkoxides, **1** and **2**, to polymerize D,L-LA.[12,13] These systems exhibited

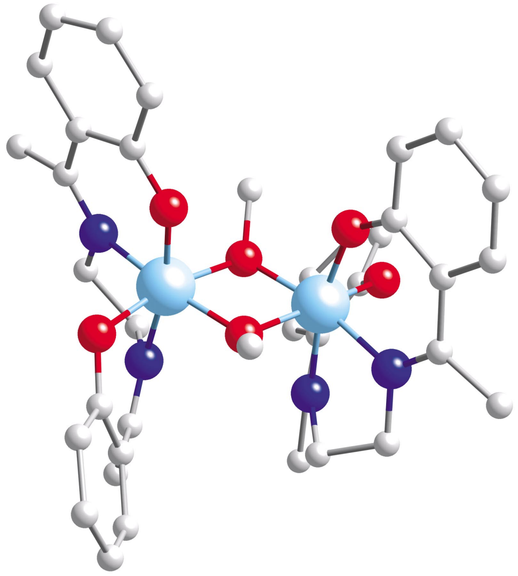
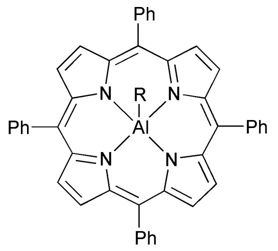


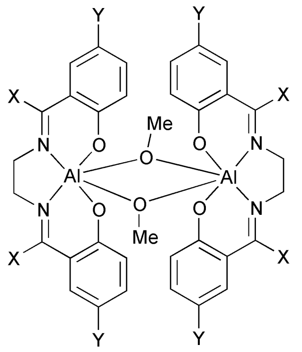
Fig. 3 X-Ray structure of **5** (ref. 15). Key: light blue, Al; dark blue, N; red, O; white, C.

control of molecular weight and a narrow molecular weight distribution (PDI < 1.25), as shown by a linear plot of M_n *vs.* conversion for PLA prepared at 100 °C. Interestingly, the initial intermediate from the ring-opening of LA was observed by ^1H NMR spectroscopy. The quantitative insertion of one equivalent of LA into the Al–OMe bond of **1** was observed at room temperature, with subsequent heating to 100 °C resulting in polymerization. The ring-opening of LA was shown to take place at the acyl-oxygen bond by the observation of a methoxy ester end group in the final polymer.

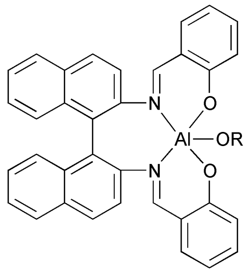
More recently, Schiff's base ligands related to porphyrins were used to prepare a range of aluminium alkoxide complexes that polymerize LA. Of these, **3–5** use an achiral salen-based ligand framework, while incorporation of chiral ligands in **6–8** enabled control of polymer stereochemistry. Complexes **3** and **5** were characterized by X-ray diffraction and both exist as dimers with bridging methoxide ligands in the solid state (Fig. 3).[14,15] Equilibria between the dimers and mononuclear fragments are probably operative in solution, although the catalysts often are treated as being monomeric. Polymerization by the complex of the parent salen ligand, **3**, has received the most attention.[16] Kinetic investigations at 70 °C revealed that the polymerization is first order in LA and in catalyst, with the rate being twice as fast in toluene as in CH_2Cl_2.[17] The polymerization is controlled up to moderate conversions, as shown by a linear increase of M_n with conversion and good agreement between calculated and experimental molecular weights. Reaction of **3** with LA at 70 °C gave polymer samples with narrow molecular weight distributions (PDI 1.05–1.30) up to 70% conversion in CH_2Cl_2 and up to 60% conversion in toluene. Increases in the PDI at higher conversions were attributed to transesterification reactions. Matrix assisted laser desorption ionization mass spectra (Maldi MS) of the polymers revealed linear oligomers with non-integral LA repeat units, consistent with some intermolecular transesterification occurring in parallel to polymerization, even at low conversion.[18] Complexes **4** and **5** display polymerization properties similar to those of **3**, although they exhibit slightly faster rates under milder conditions (*e.g.*, 25 °C in CH_2Cl_2).[19,20] In an improvement on **3**, complex **5** provides polymers with narrow molecular weight distributions up to full conversion in CH_2Cl_2 and toluene.



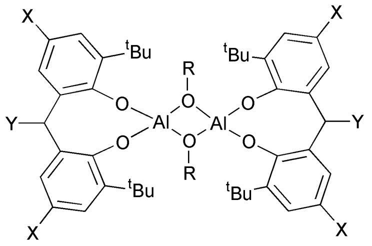
1 R = OMe
2 R = $(OCH_2CH_2)_nCl$



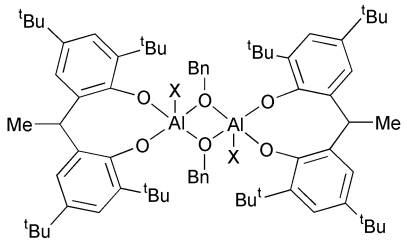
3 X = Y = H
4 X = H, Y = Cl
5 X = Me, Y = H



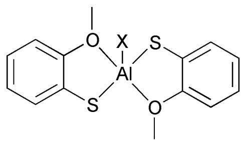
6 R = Me, *R*-
7 R = ^{i}Pr, *R*-
8 R = ^{i}Pr, *R,S*-



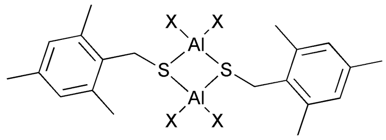
9 R = Bn, X = ^{t}Bu, Y = Me
10 R= ^{i}Pr, X = Me, Y = H



11 X = PhCHO



12 X = Me
13 X = Cl



14 X = Et
15 X = ^{i}Bu

The achiral catalyst **3** showed some amount of stereocontrol. Polymerizations using LA of varying optical purity gave polymers with higher optical rotatory powers than expected from the ratio of D- and L-enantiomers in the monomer feedstock. The results were interpreted to indicate a preference for the formation of isotactic sequences (*i.e.*, short blocks of PLLA and PDLA). These blocks form crystalline stereocomplexes, so the samples exhibited crystallinity regardless of their optical purity. A "chain-end control" mechanism was postulated, whereby the last unit in the growing polymer chain influences which enantiomeric form of the monomer is incorporated next. The degree of chain-end control was modest, however; the

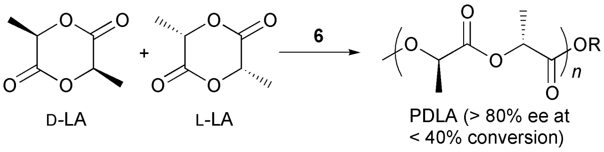


Fig. 4 Stereoelective polymerization of D,L-LA by **6**.

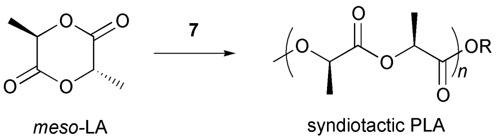


Fig. 5 Stereoselective polymerization of *meso*-LA by **7**.

calculated reactivity ratio, defined as the relative rate constants of homo/cross propagation, was 2.8.

Greater stereoselectivity in a series of experiments by several laboratories was demonstrated by catalysts with chiral supporting ligands, **6–8**.[21–24] In several examples of LA polymerization at 70 °C in toluene, these complexes gave polymers with narrow molecular weight distributions (PDI = 1.05–1.30) up to high conversions, with linear increases in molecular weight with conversion. In addition to exhibiting greater molecular weight control than parent **3**, polymerization rates with **6–8** were generally faster than observed for **3**.

The initial investigation used the enantiopure complex **6** to polymerize D,L-LA.[21] A preference for incorporation of D-LA units into the polymer chain was observed, yielding optically active polymer chains (Fig. 4). At low conversion (<40%) the optical purity of the polymer was very high (>80% ee). At high conversion the optical purity of the polymer was reduced as more L-LA, now in excess in the monomer feed, was incorporated into the polymer. The resulting polymers had melting points indicative of the formation of stereocomplexes between stereosequences of PLLA and PDLA. A plot of the optical purity of unreacted monomer as a function of conversion to polymer was fit by assuming a reactivity ratio (the ratio of rate constants for consumption of the two enantiomers, k_D/k_L) of 20. This strong preference for polymerization of D-LA apparently is due to the stereogenic environment at the reactive metal site; *i.e.*, polymerization by a site-control mechanism.

In a different approach, the enantiopure complex **7** was used to polymerize *meso*-LA to prepare highly syndiotactic, crystalline PLA (Fig. 5).[22] The optically pure catalyst showed a kinetic preference for opening *meso*-LA at one of the acyl-oxygen bonds, but which one was not determined. Analysis of the methine region of the homonuclear decoupled ^{1}H NMR spectrum of the polymer gave an enantiotopic selectivity of 96%, a result rationalized by invoking a site-control mechanism. Unusually, "an achiral monomer is converted to an achiral polymer, but [an enantiopure] chiral catalyst is required for syndiotacticity".[22]

Finally, the racemic catalyst **8** was used to polymerize D,L-LA by two groups with seemingly similar results, but conflicting interpretations.[23,24] One investigation reported stereocomplex formation between a racemic mixture of the isotactic polymers PLLA and PDLA (Fig. 6, top).[23] This result was rationalized by proposing that each enantiomer of **8** preferentially polymerizes one enantiomer of the racemic LA. The high enantioselectivity observed at low conversion in the polymerization of D,L-LA by **6** was maintained at high conversion in this system, indicating that both LA enantiomers were depleted at the same rate. The assignment of the polymer structure as a stereocomplex was based on the scattering profile obtained from powder X-ray diffraction. In separate work a polymer containing isotactic stereoblocks was the proposed product from catalysis by **8** (Fig. 6, bottom).[24] This assignment was based on a compelling analysis of the methine region of the homonuclear decoupled ^{1}H NMR spectrum of the polymer. The proposed mechanism for the formation of this polymer is one of active polymer chain exchange. According to this hypothesis, each enantiomer of **8** preferentially polymerizes one enantiomer of the racemic LA, but the growing polymer chains undergo exchange at the aluminium center. Thus, if a chain of PLLA exchanges so that it is now on an aluminium center of opposite chirality, the growing chain will now produce PDLA. The average length of the stereoblocks was calculated to be 11 LA units according to a statistical analysis of the NMR data, giving a kinetic selectivity for the catalyst of 98%. While there are differing interpretations of the D,L-LA polymerization results using **8**, both invoke a high degree of stereocontrol to give PLA with interesting physical properties. More precise structural information (*e.g.*, X-ray diffraction data) on the chiral cataysts **6–8** will enhance efforts to understand the molecular details of their asymmetric induction.

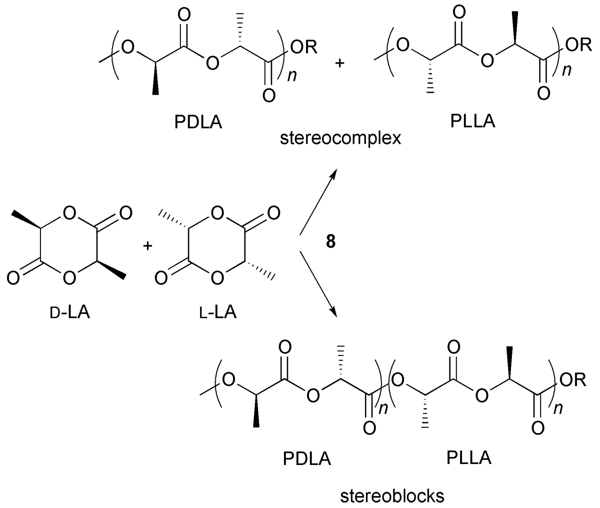


Fig. 6 Polymerization of D,L-LA by **8** to yield PLA as either a stereocomplex (ref. 23) or stereoblocks (ref. 24).

A range of aluminium alkoxides containing ligands other than Schiff's bases also have been used to polymerize cyclic esters. Complexes with bis(phenoxides) as the supporting scaffold along with another alkoxide ligand were shown to polymerize lactones. X-Ray crystal structures of **9–11** revealed them to be dimeric, with terminal chelating phenoxides and bridging alkoxides.[25,26] Complex **9** was active for the controlled polymerization of ε-CL and δ-VL in toluene at 25 °C.[25] The ring-opening of the lactone was shown to occur *via* insertion into the aluminium–benzyl alkoxide bond, rather than the aluminium–phenoxide bond. Interestingly, reaction of **9** with benzaldehyde gave **11**, which was proposed to be a model for an intermediate in the polymerization of lactones, insofar as coordination of the benzaldehyde mimics the coordination of lactone in the polymerization reaction prior to attack of the alkoxide at the lactone carbonyl. Complex **11** was also active for the polymerization of ε-CL, but was slower than **9**, presumably due to inhibition of lactone binding by the coordinated benzaldehyde. While complex **10** is a dimer in the solid state, a molecular weight determination in THF indicated a mononuclear structure, and in non-polar solvents a monomer–dimer equilibrium was proposed to exist.[26] The complex polymerized ε-CL in toluene at 50 °C to give polymer samples with molecular weight distributions less than 1.50.

The polymerization activity of a series of aluminium thiolates **12–15** was investigated with the aim of producing polyesters with thiolate end groups rather than the more common alkoxide end group.[27] X-Ray crystallographic studies showed that **12** and **13** are monomeric while **14** and (by extension) **15** are dimeric. The complexes all polymerized ε-CL at 25 °C in toluene with varying degrees of control. Observation of a thioester end group in the ^{1}H NMR spectrum of a low molecular weight sample of the polymer indicated that the thiolate acts as initiator. Complex **12** was also active for the polymerization of LA, but more vigorous conditions were required (refluxing toluene or xylene).

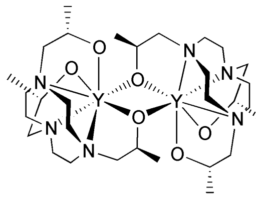
Complexes of yttrium, titanium and lanthanides

While aluminium complexes are effective catalysts for the polymerization of cyclic esters, they are slow relative to complexes of yttrium and lanthanides. In an important early report, a complex formulated as $Y(OCH_2CH_2NMe)_3$ was shown to polymerize LA in a rapid and controlled fashion.[28] Similarly, lanthanide oxo isopropoxides ($Ln_5(O)(O^iPr)_{13}$, Ln = La, Sm, Y, Yb)[29,30] and yttrium isopropoxide species generated *in situ* (from $Y(OAr)_3/^iPrOH$[31,32] and $Y[N(SiMe_3)_2]_3/^iPrOH$[33]) polymerized cyclic esters rapidly. In all of these systems, however, the structure of the precatalyst or catalyst is uncertain and/or mechanistic understanding is hindered by complicated equilibria involving ligand exchange and species of varying nuclearity. Efforts to obviate these problems have generally focused on the use of supporting ligands designed to control the structure of the complexes and their polymerization reactivity.

Multidentate amine–alkoxide ligands intended to encapsulate lanthanide ions and thus control complex geometry were used to prepare yttrium complexes **16–18**.[34] X-Ray crystal structures revealed similar dinuclear structures for the series, the only major difference being coordinated water in **18**. The complexes were active LA polymerization catalysts at 25 °C in CH_2Cl_2 but exhibited differences in rate (**18** > **17** > **16**), molecular weight control, and molecular weight distributions (PDI = 1.25–2.13). These results showed that subtle changes in ligand structure (substituents) can result in significant changes in polymerization activity. The nature of the initiating species is uncertain for these complexes, however, as identification of an end group on the polymers was not possible by ^1H NMR spectroscopy.

Improved catalytic behavior was observed upon incorporation of an exogenous alcohol or alkoxide into the dinuclear complexes.[35] Addition of benzyl alcohol (BnOH) to **16** did not disrupt its dimeric structure; instead, BnOH associated with the dimer *via* hydrogen bonds in the solid state to yield **19**. Polymerization of LA by **19** resulted in products with narrower molecular weight distributions and lower molecular weights than those prepared from **16**. A linear increase of M_n with conversion was observed, indicating some control. Unlike polymerizations by **16**, a benzyl ester end group was observed by ^1H NMR spectroscopy, confirming initiation by BnOH. Kinetic analysis (CD_2Cl_2, 22 °C, $[LA]_0/[Y]_0 \approx 150$) revealed that the polymerization is first order in LA.

In contrast to the reaction with **16**, addition of BnOH to **18** caused extensive rearrangement and yielded a novel trinuclear complex, **20**, that contains two macrocyclic ligands and four BnO^- groups, two on the unique low-coordinate Y(III) center (Fig. 7). ^1H NMR spectroscopy indicated that the trinuclear structure is maintained in solution. Complex **20** reacted with LA to give polymers that had narrower molecular weight distributions and lower molecular weights than that observed for the polymer prepared by **19**. Benzyl end groups were observed and M_n increased linearly with conversion. Interestingly, kinetic studies suggested that not all of the alkoxides were active initiators, with only 2.5 (of 4) initiating sites per complex. At $[LA]_0/[Y]_0 \approx 50$ the polymerization displayed a first order dependency on LA (CD_2Cl_2, 22 °C), but at higher $[LA]_0/[Y]_0$ ratios the kinetics were more complicated. Complex **20** also was shown to polymerize ε-CL, but *via* a different mechanism, since for ε-CL polymerization only 1.5 initiation sites per complex were found, and the kinetics were zero order with respect to [ε-CL] and half order with respect to [**20**] (CD_2Cl_2, 22 °C, $[CL]_0/[Y]_0 \approx 50$–150). Thus, despite successful characterization of the precatalytic species **16–20** responsible for generally controlled cyclic ester polymerization behavior, signific kinetic complexity in these systems belied the presence of multiple and/or structurally intricate catalysts.



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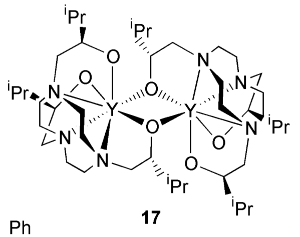

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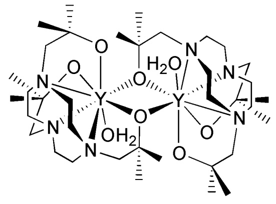

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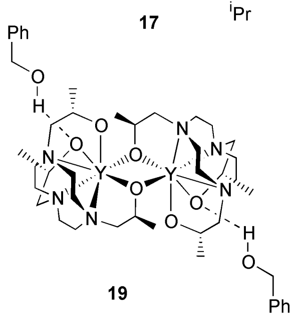

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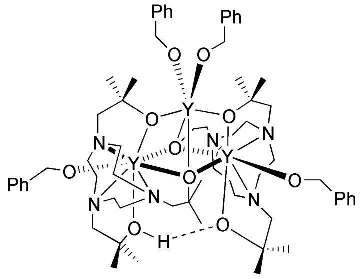

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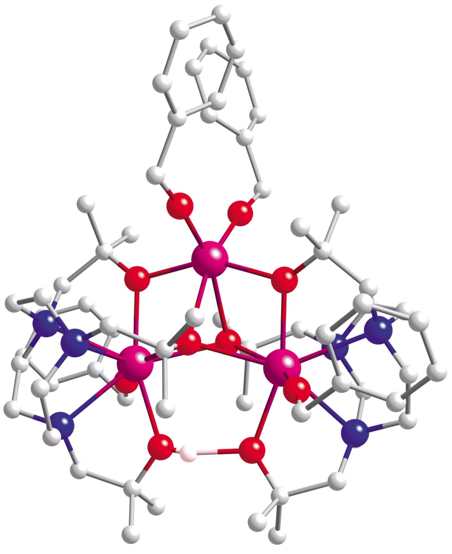


Fig. 7 X-Ray structure of complex **20** (ref. 35). Key: purple, Y; red, O; blue, N; white, C.

Using the same chiral ligand system that enabled Al complexes to exert stereoselectivity in LA polymerizations (*cf.* **6–8**), a yttrium alkoxide **21** was prepared.[22] This complex, which was shown by X-ray diffraction to be dimeric (Fig. 8), polymerized 97 equivalents of *meso*-LA in toluene at 70 °C in 14 h. Unlike the analogous Al complex **7**, which polymerized *meso*-LA to yield syndiotactic PLA, **21** showed no stereoselectivity and produced atactic polymer.

Several studies targeted mononuclear lanthanide complexes as less complicated, potentially more controllable single-site catalysts. For instance, a series of mononuclear yttrium complexes (**22–24**) of arylamidinate ligands were synthesized, structurally characterized by X-ray diffraction, and used for the polymerization of LA.[36] The phenoxide complex **22** polymerized LA, but addition of one equivalent of BnOH was required

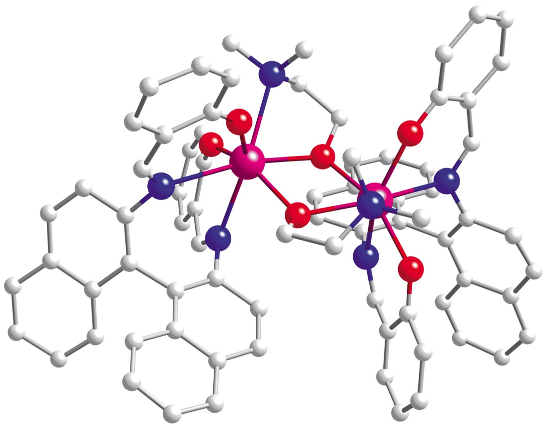
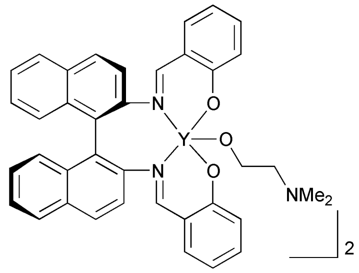


Fig. 8 X-Ray structure of **21** (ref. 22). Key: purple, Y; red, O; blue, N; white, C.



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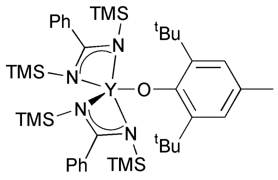

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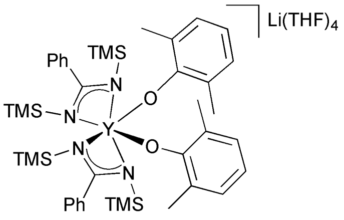

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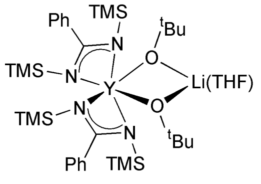

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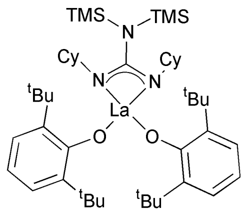
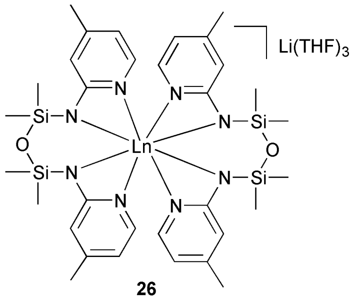


25

for reproducible reaction rates and lower molecular weight distributions (PDI < 1.5). The rate of polymerization with **22**/benzyl alcohol was fast; in THF at 25 °C 1000 equivalents of LA were polymerized inside 1 h. Benzyl ester end groups were observed in the ^{1}H NMR spectrum of the prepared polymer, but MALDI MS analysis suggested that polymeric species without benzyl end groups were also present. The anionic complexes **23** and **24** were inferior catalysts relative to **22**. Conversions were low with complex **23** and polymerization with added benzyl alcohol only gave low molecular weight polymer. Complex **24** gave higher yields of polymer, but M_n decreased and the molecular weight distribution increased with conversion. *tert*-Butoxide end groups were observed by ^{1}H NMR spectroscopy.

Two related studies using N-donor ligands were recently reported. A guanidinate ligand similar to the arylamidinates in **22–24** was used to prepare a monomeric four coordinate lanthanum complex **25**.[37] This structurally defined compound polymerized LA at 25 °C in CH_2Cl_2 with moderate control of molecular weight up to a monomer-to-catalyst ratio of 500, but at higher ratios only low molecular weight polymer was obtained. A wide range of molecular weight distributions were observed (PDI = 1.19–2.25), suggesting significant transesterification. In another example, a lanthanum complex of an amido–pyridine ligand (**26**) was found to polymerize ε-CL and δ-VL.[38] This anionic complex was proposed to be monomeric. The molecular weight distributions of the polymers obtained in THF at 20 °C were broad (PDI = 1.7–2.1).



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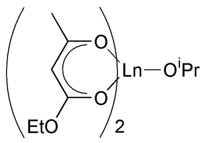
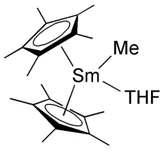


27 Ln = Nd
28 Ln = Y



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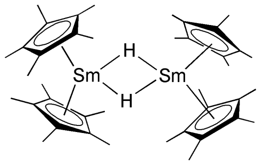

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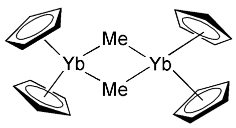

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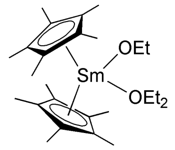

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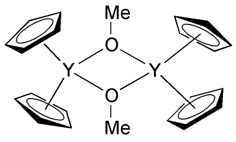

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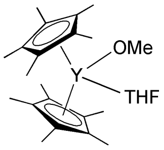
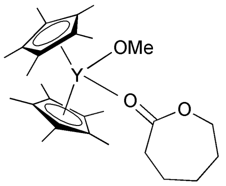


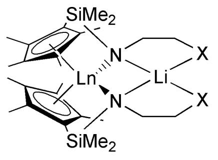
34



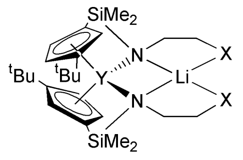
35

Perhaps the most promising lanthanide coordination complexes are the neodymium (**27**) and yttrium (**28**) isopropoxides of diethyl acetoacetate that were used to effect the polymerization of ε-CL.[39] Although no structural characterization data were reported, the complexes were represented as being monomeric, and they displayed polymerization behavior consistent with this assignment. Thus, kinetic studies showed first order dependencies on both monomer and catalyst. Polymerizations were rapid, with the conversion of 600 equivalents of ε-CL being complete in approximately 2 h at 25 °C in THF. Linear increases of M_n with both conversion and monomer-to-catalyst ratio and narrow molecular weight distributions (PDI < 1.10) illustrated the controlled nature of the polymerizations. Further, block copolymers of ε-CL with trimethylene carbonate (TMC) and LA were prepared by the sequential polymerization of the respective monomers. Good control of the block lengths and narrow molecular weight distributions were obtained.

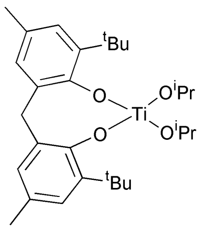
Organometallic lanthanocene ("sandwich") complexes also have been shown to be effective lactone polymerization catalysts. In several studies, samarium(II) compounds were used to polymerize ε-CL, ethylene carbonate and δ-VL, but because the first step in these polymerizations was the oxidation of the metal to Sm(III), the nature of the catalytic species remains ill-defined.[40–42] In separate work, detailed studies of the polymerization behavior of lanthanocene hydride, alkyl and alkoxide complexes (**29–34**) were performed.[43] The alkyl complexes **29** and **31** and the hydride complex **30** polymerized ε-CL. In addition, **29** was shown to also polymerize δ-VL. The obtained polymers had high molecular weights ($M_n > 75\,000$) and narrow molecular weight distributions (PDI < 1.20). For polymerization of ε-CL by **29** a linear increase of M_n with conversion was observed. Initiation by the alkyl complexes was proposed to occur *via* insertion of the monomer into the metal–alkyl bond with ring-opening occurring at the acyl-oxygen bond to give a ketone end group and a metal-coordinated alkoxide. The alkoxide complexes **32–34** polymerized ε-CL, δ-VL, and β-propiolactone (β-PL) in controlled processes (linear relationship between M_n and conversion) to yield products with low molecular weight distributions (PDI = 1.06–1.12). Of particular note was the observation of an intermediate in the initiation step. Addition of a slight excess of lactone, *e.g.*, ε-CL, to **34** resulted in the formation of the lactone coordination complex **35**, identified as such by ^{1}H NMR spectroscopy. This polymerization precursor is stable at 0 °C for 2 h, but gradually decomposed to ring-opened product at room temperature.



36 Ln = Y, X = OMe
37 Ln = Y, X = NMe$_2$
38 Ln = Lu, X = OMe



39 X = OMe
40 X = NMe$_2$



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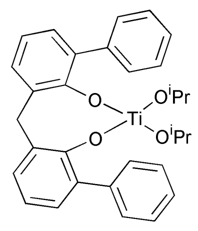


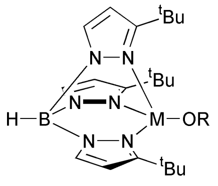
42

A series of lithium complexes of lanthanocenes (**36–40**) was used to polymerize ε-CL.[44] Of these complexes, the structures of **36**, **39** and **40** were confirmed by single crystal X-ray diffraction. Polymerizations of ε-CL at room temperature in toluene or CH_2Cl_2 gave polymer with broad molecular weight distributions (PDI < 2.0) and variable molecular weights. The lutetium complex was the least active catalyst. Interestingly, no end group on the polymer was observed by ^{1}H NMR spectroscopy. The initiation step of polymerization was proposed to be the attack of an amido-nitrogen at the lactone carbonyl to give an alkoxide, which then is the active polymerizing species. Termination was proposed to occur by attack of the alkoxide at the amide bond to reform the starting complex and to produce a cyclic polymer.

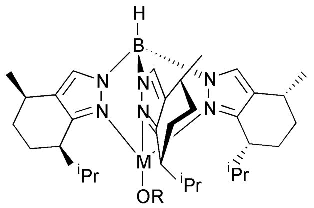
Finally, in related early transition metal studies, two titanium complexes were shown to effectively polymerize ε-CL.[45] The dialkoxide complexes (**41** and **42**) of bulky bis(phenoxide) ligands were thought to be monomeric by analogy to the corresponding dichloride complexes that were characterized by X-ray crystallography. Complex **41** polymerized 100 equivalents of ε-CL to completion in CH_2Cl_2 at 25 °C in 5 h yielding narrow molecular weight distribution products (PDI = 1.15). Complex **42** was a slower catalyst with the same reaction taking 75 h (PDI = 1.10). A linear relationship between M_n and both conversion and the monomer-to-catalyst ratio was observed. The M_n of the obtained polymer was consistent with the presence of two growing polymer chains per titanium center. An isopropoxy ester end group was observed in the ^{1}H NMR spectrum, and there was no evidence for incorporation of a phenoxide into the polymer consistent with initiation by the isopropoxides.

Complexes of magnesium and zinc

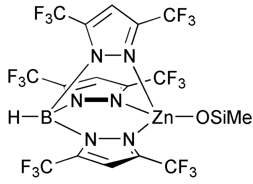
Recent interest in Zn(II) and Mg(II) alkoxide complexes for cyclic ester polymerization has been motivated largely by advantageous features of these ions that include lack of color, low cost, and low toxicity (important in biomedical applications of the polymer). To address problems associated with the kinetic lability of these ions that is so critical to their natural biological function, a key strategy has been to inhibit ligand exchange equilibria and control complex nuclearity through encapsulation by sterically hindered multidentate N-donor ligands. Implementation of this approach has been notably successful, leading to the development of several catalyst systems that effectively polymerize LA and are sufficiently well-behaved to allow effects of the initiating group, polymerization kinetics and polymerization selectivity to be investigated.



43 M = Mg, R = Et
44 M = Zn, R = SiMe$_3$



45 M = Zn, R = SiMe$_3$
46 M = Mg, R = Ph



47

Tris(pyrazolyl- and indazolyl-)hydroborate ligands were used to prepare complexes **43–47**, which were screened for their ability to polymerize LA.[46,47] All of these complexes were proposed to be monomers on the basis of the monomeric structures of related alkyl complexes, a molecular weight determination of **45** in benzene, and the crystal structures of **44** and **47** (Fig. 9). In an initial study using **43**, the ring-opening of LA was shown to occur at the acyl-oxygen bond by the observation of an ethoxy ester end group in the ^{1}H NMR spectra of isolated PLA. The polymerizations of L-LA by **43** and **44** were controlled as indicated by a linear relationship between M_n and conversion and low molecular weight distributions (PDI = 1.1–1.25) up to 90% conversion.

Kinetic analyses allowed meaningful comparisons of catalysts **43–47** to be made. The polymerizations showed first order kinetic dependencies on both LA and metal complex, with the Mg(II) complexes being about 100 times faster than the Zn(II) analogs. The greater activity of the Mg(II) complexes was attributed to the higher polarity of the Mg–OR bond relative to that of the Zn(II) compounds. The more electropositive metal center in the Mg complexes was proposed to be more effective at activating the C=O carbon in LA. Structural and electronic differences in the ligands also resulted in different catalytic activities with the more bulky indazolyl ligand in **45** resulting in a k_{app} an order of magnitude larger than observed for **44**. Electron-withdrawing groups on the pyrazoles resulted in complex **47** being nearly inactive for LA polymerization at room temperature.

The catalysts exhibited some diastereoselectivity with the achiral complexes **43** and **44** showing a significant preference

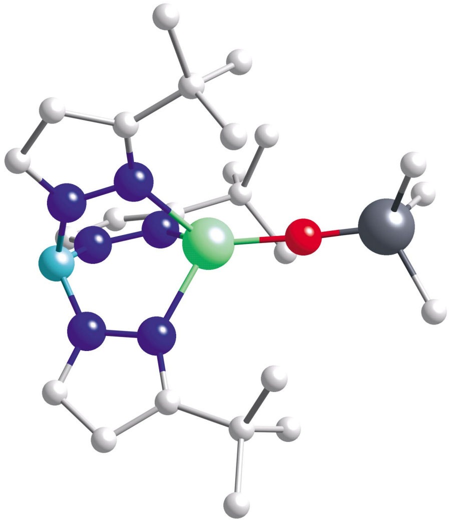


Fig. 9 X-Ray structure of **44** (ref. 47). Key: green, Zn; light blue, B; dark blue, N; red, O; gray, Si; white, C.

for the polymerization of *meso*-LA over D-LA and L-LA in CH_2Cl_2 at 22 °C. The chiral magnesium complex **46** also showed a marked preference for the polymerization of *meso*-LA over D,L-LA. In CD_2Cl_2 at −40 °C *meso*-LA was polymerized exclusively, with D,L-LA remaining unreacted. Analysis of the NMR spectra of the obtained polymer showed only a slight enhancement of syndiotactic sequences, however, indicating only modest stereoselectivity in the enchainment of *meso*-LA. In contrast, the analogous chiral Zn(II) complex **45** showed no preference for *meso*-LA or D,L-LA up to 30% conversion, but then *meso*-LA was polymerized more rapidly.

In an alternate, yet related approach, bidentate β-diketiminate ligands were used to access a number of Zn(II) and Mg(II) complexes, several of which demonstrated excellent LA polymerization behavior.[48–50] Particular attention focused on **48**, which was shown by X-ray crystallography to be a dimer in the solid state with two isopropoxides bridging the two Zn(II) centers. This structure was thought to persist in solution (^1H NMR). For the polymerization of D,L-LA this complex exhibited fast rates (190 equivalents of D,L-LA polymerized in 20 min in CH_2Cl_2 at 20 °C) and good control (PDI = 1.10 and a linear relationship between M_n and conversion). The isopropoxide intiator was seen as an end group by electrospray mass spectroscopy (ES-MS). Despite the narrow molecular weight distribution, ES-MS showed evidence for a small amount of transesterification (peaks corresponding to half-integral LA repeat units).

Comparative studies showed that the nature of both the β-diketiminate subtituents and the initiating group influenced the polymerization behavior. The effect of the initiating group on the polymerization behavior was investigated by using **49–52**, which are based on the same ligand manifold as **48**. Of these complexes only the methyl lactate complex (**51**, Fig. 10), a model of the initial insertion product and polymerizing species, showed similarly good behavior for the polymerization of LA. The alkyl, amido and carboxylate complexes (**49**, **50** and **52**, respectively) displayed inferior polymerization activity with reaction times being significantly longer and the obtained polymers having broad molecular weight distributions.

The importance of the substituent pattern on the β-diketiminate aryl groups was revealed in studies of polymerization stereoselectivity and kinetics. Polymerization of D,L-LA by **48** produced highly heterotactic PLA, *i.e.*, the catalyst showed a preference for polymerizing D- and L-monomers in alternate fashion. At 20 °C 90% of linkages were between monomers of opposite chirality ($P_r = 0.90$), and this preference increased at lower temperature ($P_r = 0.94$ at 0 °C). The analogous complexes

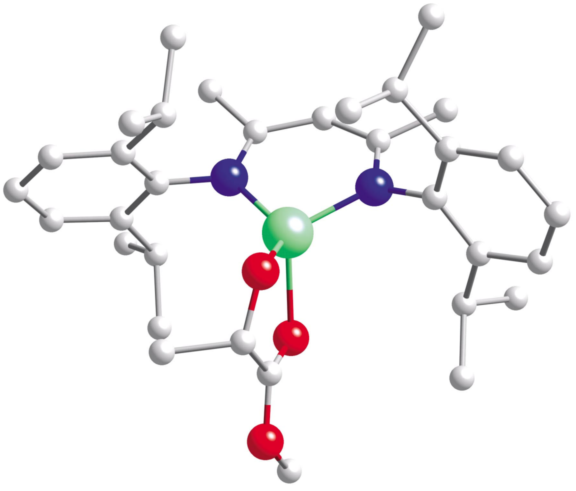
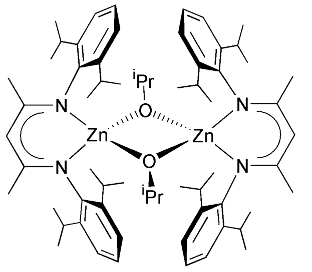
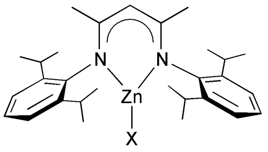


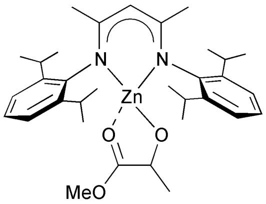
Fig. 10 X-Ray structure of **51** (ref. 50). Key; green, Zn; red, O; blue, N; white, C.



48



49 X = Et
50 X = N(TMS)$_2$



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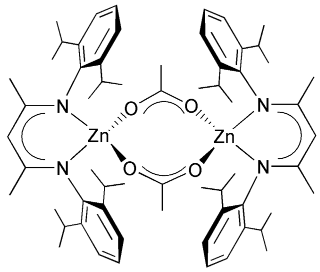
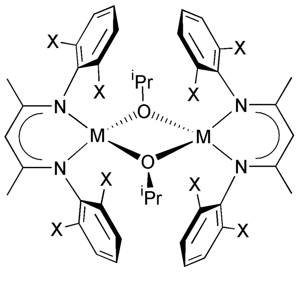
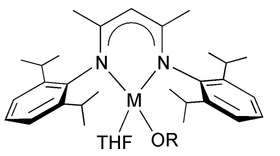


52



53 M = Zn, X = Et
54 M = Zn, X = ^{n}Pr
55 M = Mg, X = ^{i}Pr



56 M = Mg, R = ^{t}Bu
57 M = Zn, R = SiPh$_3$

of less sterically demanding ligands (**53** and **54**) showed lower degrees of heterotacticity ($P_r = 0.79$ and 0.76, respectively at 20 °C). Thus, stereoselectivity was argued to be derived from a chain-end control mechanism and influenced by the steric bulk of the β-diketiminate ligand. Interestingly, polymerization of *meso*-LA by **48** resulted in the formation of syndiotactic PLA ($P_r = 0.76$), but polymerization of *meso*-LA by **53** produced moderately heterotactic PLA. Although reasons for the different stereoselectivities of these two complexes are unknown, the results demonstrate that subtle changes in catalyst structure can result in markedly different polymerization behavior.

Kinetic investigations also revealed interesting catalyst structural effects. For reactions with **48** at 25 °C in CH_2Cl_2, the polymerization of D,L-LA was first order in LA but with an intriguing dependency on Zn(II) of 1.56. This non-integer dependency was attributed to the presence of multiple active species (aggregates) with variable polymerization reactivity. Under identical conditions the polymerization of D,L-LA was 50% faster than the polymerization of *meso*-LA. Also, the polymerization of D,L-LA was about 7 times faster than the polymerization of L-LA, consistent with the observed preference for formation of heterotactic PLA during the polymerization of D,L-LA. The Mg(II) complex **55** was faster for the polymerization of D,L-LA than its Zn(II) analog, consistent with the differences observed in complexes **43** and **44**. However, the molecular weight distribution for polymer produced by **55** was broader (PDI = 1.59), a finding tentatively attributed to slow initiation relative to propagation, as well as transesterification. Addition of one equivalent of isopropanol per Mg(II) to the polymerization reaction resulted in narrower molecular weight distributions (PDI = 1.20–1.35). Unlike its Zn(II) analog, **55** displayed no stereoselectivity.

Finally, in separate work β-diketiminate–Zn(II) and –Mg(II) complexes with sterically hindered alkoxide coligands were studied (**56** and **57**).[51] The Mg(II) complex was determined to be monomeric by X-ray crystallography, and a similar structure for the Zn(II) complex was presumed by analogy. Complex **56** polymerized 100 equivalents of D,L-LA to completion in less than 10 min at room temperature. By contrast, **57** was much less active, with 30 h required to reach 90% conversion under the same conditions. The slow polymerization behavior of **57** was attributed to a slow initiation step involving insertion of LA into the Zn–$OSiPh_3$ bond. The slower activity relative to the aforementioned alkoxide-bridged dimers may be due to the different alkoxide initiating groups or due to the differences in the catalyst nuclearity. Similar to previous observations, **57** showed some preference for the formation of heterotactic PLA in the polymerization of D,L-LA, while **56** showed no such preference.

Complexes of tin and iron

Simple tin complexes have been routinely used for the polymerization of LA and related cyclic esters, with Sn(II)–carboxylates leading the way. In a recent series of papers, the active species in these polymerizations was identified as a Sn(II)–alkoxide, presumably formed by adventitious water or hydroxy containing impurities in the monomer.[52] With this information as a basis, efforts geared toward a single-site Sn(II) complex for the polymerization of LA resulted in the preparation of complex **58**, a Sn(II)–alkoxide containing the β-diketiminate ligand used in complexes **48–52**.[53] The structurally characterized complex slowly polymerized D,L-LA in CH_2Cl_2 at room temperature with complete conversion of 100 equivalents of LA requiring 96 h. In toluene at 60 °C, 85 equivalents of LA were converted in 4 h. Under both conditions the polymerizations yielded polymers with narrow molecular weight distributions (PDI = 1.04–1.11), and a linear increase of M_n with conversion was observed. The slower rate relative to the zinc analog, **48**, was attributed to the lower electrophilicity of the tin center and to the lone pair of electrons on the Sn(II) center that presumably disfavors monomer coordination. The polymerization of D,L-LA using **58** showed a slight preference for the formation of heterotactic PLA.

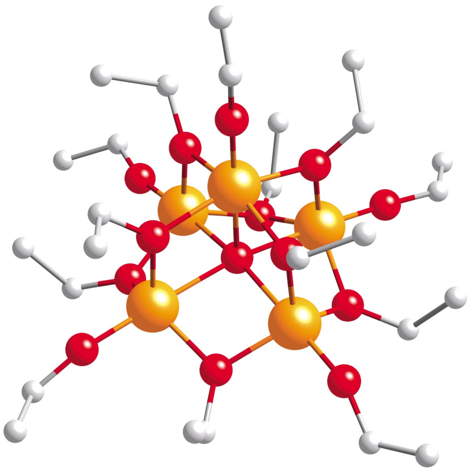
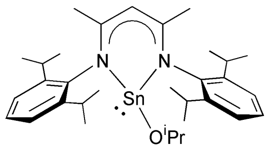


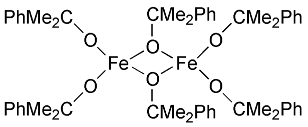
Fig. 11 X-Ray structure of **59** (ref. 55). Key; orange, Fe; red, O; white, C.



58

$Fe_5(O)(OEt)_{13}$

59



60

While tin complexes are widely utilized, the potential toxicity of tin is a drawback. In contrast, complexes of iron are particularly interesting due to the abundant non-toxic metal-containing precursors. Among the iron complexes reported for the polymerization of LA, ferric alkoxides such as iron ethoxide [$Fe(OEt)_3$] hold much promise.[54] However, the lack of structural information on the “$Fe(OEt)_3$” used in previous reports prompted an investigation of structurally discrete Fe(III)–alkoxide complexes. In a recent account, an oxo-bridged pentanuclear cluster (**59**) and a dinuclear complex (**60**) were isolated and characterized crystallographically (*cf.* **59** in Fig. 11).[55] Both complexes were active for the polymerization of LA in toluene at 70 °C. Furthermore, complex **59** was effective for the controlled polymerization of D,L-LA. For example, at $[LA]_0/[Fe]_0 = 450$ conversion of 97% was observed in 21 min, with a narrow molecular weight distribution (PDI = 1.17). Molecular weight distributions increased slightly during the course of reaction and at higher monomer loadings, but still remained relatively narrow (PDI < 1.30). Linear increases of M_n were observed with both conversion at fixed $[LA]_0/[Fe]_0$ and with $([LA]_0 - [LA]_t)/[Fe]_0$. In a reaction with L-LA no epimerization was observed using **59**, and the opening of LA at the acyl-oxygen bond was confirmed by the observation of an ethoxy ester end group in the ^1H NMR spectrum of a low molecular weight polymer sample. Complex **60** displayed similar LA polymerization activity, but the molecular weight distributions were slightly higher in the product polymers. These complexes exhibited superior polymerization behavior with respect to rate, molecular weight distribution control and epimerization relative to other previously reported iron catalysts.

Summary and outlook

As described in this Perspective, efforts over the past decade to augment the pool of catalysts that are active and selective for the ring-opening polymerization of LA and related cyclic esters have been widely successful. Through interdisciplinary research that melds preparative inorganic chemistry, detailed structural characterization, and polymerization catalysis studies, a greater understanding of the relationships between catalyst structure and cyclic ester polymerization activity and selectivity has been achieved. In many respects, this research has parallels in the advancement of the polyolefin industry, which has benefited tremendously from progress in single-site catalyst development for the preparation of hydrocarbon-based polymers with a diverse range of architectures, stereochemistries, and physical properties.[56] Polymers such as PLA that are derived from annually renewable resources and that degrade to non-toxic byproducts are attractive surrogates for the versatile polyolefins. Still, greater control of polyester structure through rational catalyst design is needed. Taking the lead from the olefin polymerization field, precision synthesis combined with comprehensive structural characterization and mechanistic study holds great promise for the development of new catalysts that enable the preparation of a variety of polyesters *via* environmentally sustainable technologies.

Acknowledgements

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