

## Concerning the ring-opening polymerization of lactide and cyclic esters by coordination metal catalysts\*

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**Abstract:** A summary of the reactions involved in the ring-opening polymerization (ROP) of lactide (LA) to give polylactides (PLAs) is presented along with competing reactions. Particular attention is given to the stereoselective polymerization of *rac*-LA to give heterotactic PLA and *meso*-LA to give syndiotactic PLA by aluminum Schiff-based catalysts and to the development of highly active group 2 metal single-site catalysts. Melt or solvent-free polymerization is also described along with reactions that lead exclusively to cyclic-poly-lactides.

**Keywords:** biodegradability; cyclic esters; metal–alkoxides; polyesters; ring-opening polymerization.

### INTRODUCTION

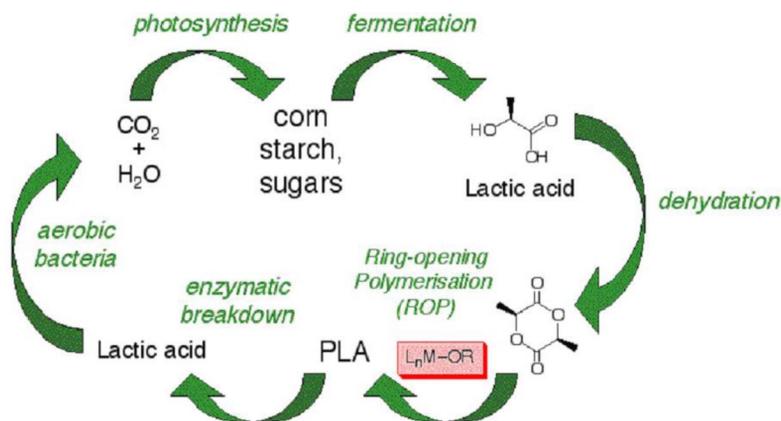
From construction and packaging materials to fibers and even the money we spend, plastics (synthetic polymers) are ubiquitous in our modern world. The development of polyolefins with “dialed-in” microstructure and molecular weight is a major triumph in the field of organometallic chemistry [1–3]. Modern plastics (polyolefins, polyesters, polycarbonates, polyurethanes, and polyamides) are all derived from petroleum, a non-renewable resource. As society becomes increasingly aware of the importance of “sustainability”, there is a move toward developing a chemical industry that is less dependent on petrochemicals. Within this *raison d’être*, polymers from renewable resources represent an emerging market. Polyesters can be derived from the ring-opening polymerization (ROP) of cyclic esters. Polylactide (PLA) is currently one commercially important polyester. It is a clear, colorless polymer that can be readily formed as thin films or fibers. It is biodegradable and derived from a renewable resource—starch. Its life cycle is shown in Scheme 1.

One of PLA’s major applications is as a bulk packaging material where it is considered environmentally friendly in contrast to say polyethylene, which, in the form of plastic bags, is gaining increasingly negative public opinion. Indeed, polyethylene plastic bags are already banned in certain countries and cities.

As a copolymer with polyglycolide (derived from the ROP of glycolide), polylactideglycolide (PLGA) has U.S. Food and Drug Administration (FDA) approval for numerous medical applications being biocompatible. PLA and PLGA find applications as stents, screws, tissue matrices, and time-release drug delivery agents. The ROP of cyclic esters can be brought about by organic [4–9], enzymatic

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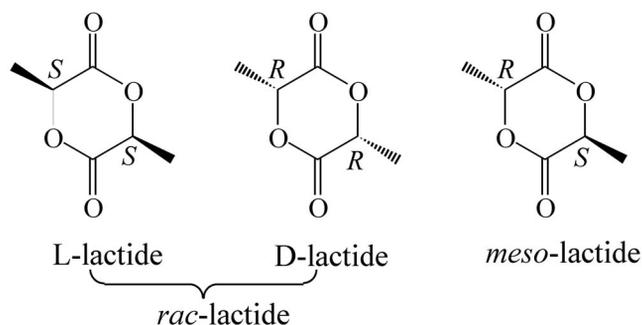
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Scheme 1

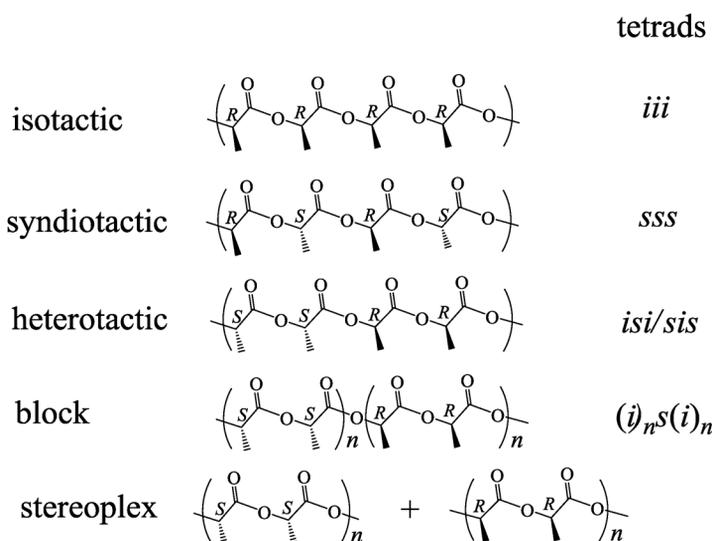
[10–12], or coordination catalysis [13–16]. This article focuses on ROP by coordination catalysis, which can be achieved by complexes involving main group, transition, or lanthanide elements. A particular emphasis among academic chemists in the last decade has been the control of microstructure as well as molecular weight distribution [17].

Lactide (LA) comes in three forms due to the presence of two stereocenters within the six-membered ring as shown below. A 50:50 mixture of D- and L-LA is called *rac*-LA.



ROP of either L-LA or D-LA yields an isotactic PLA, and a 1:1 mixture of poly-(L)-LA and poly-(D)-LA forms a stereoplex polymer having a significantly higher melting point,  $\sim 224^\circ\text{C}$ . It is, of course, a necessity that the catalyst involved does not also affect epimerization of the methine carbon stereocenters or otherwise an atactic or stereo-random polymer will be obtained. When *meso*-LA is polymerized, it is possible to obtain a syndiotactic polymer in which the stereocenters alternate in a regular fashion  $-(RS)_n$  or a heterotactic polymer  $-(RRSS)_n$ . The latter, the heterotactic polymer, can also be obtained from the polymerization of *rac*-LA. A block copolymer involving alternating sequences of poly-L-LA and poly-D-LA can be obtained from the alternate polymerization of L-LA and D-LA or by a catalyst that has a marked stereopreference in the polymerization of *rac*-LA so that initially either L or D is preferentially polymerized followed by the other.

$^1\text{H}$  NMR spectroscopy is usually employed in the determination of stereosequences of the PLA. The methine proton resonance is examined under irradiation of the methyl protons, and following the work of Kricheldorf [18], the sensitivity at the tetrad level is typically employed, though at high fields the sensitivity can be extended toward the pentad level [19]. The stereosequences described above are shown in Scheme 2.



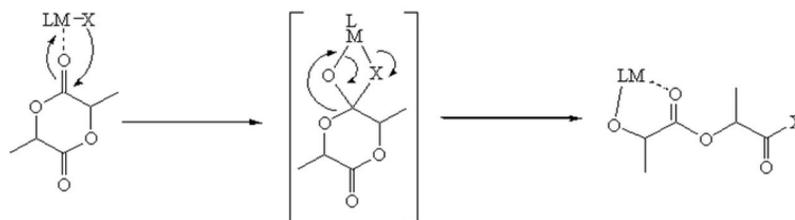
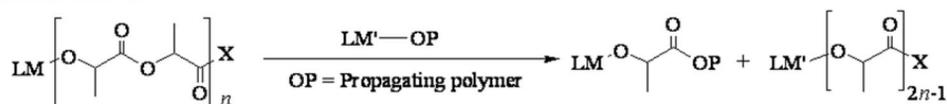
Scheme 2

An inspection of the stereosequences shown in Scheme 2 reveals that, unlike regioregular polypropylene, PLA is an asymmetric polymer. The methine carbon is sandwiched between a ketonic carbon and an ester oxygen. Rather interestingly, the  $^1\text{H}$  and  $^{13}\text{C}$  sensitivity of the methine are in the opposite direction [19].

## MECHANISMS INVOLVED IN RING-OPENING POLYMERIZATION OF LACTIDE

The key reactions involved in ROP of LA are shown in Scheme 3 where LM represents a single metal center and its set of attendant ligands. The initiation of the reaction involves coordination of the LA molecule by its ketonic oxygen. This serves to activate the ketonic carbon toward nucleophilic attack by the nucleophilic ligand X. This is, in essence, a 2 + 2 process that leads to ring-opening and generation of a metal-alkoxide bond. The initiation reaction is typically brought about by X = OH, OR, where R = alkyl, or an amide. The propagation involves the repeat enchainment of the LA monomer and the regeneration of the metal-alkoxide bond.

Unlike the polymerization of an olefin to give a polyolefin, which is really not an olefin but an alkane, the growing polymer chain is a polyester which is unsaturated. Consequently competing with ROP is *trans*-esterification. Typically, this occurs less rapidly than monomer enchainment, but as the monomer LA concentration decreases *trans*-esterification is likely to become significant. *Trans*-esterification leads to a broadening of the molecular weight distribution and in a living polymerization in which  $k_{\text{initiation}} \geq k_{\text{propagation}}$ , with time the polydispersity index (PDI) will increase from 1.0 toward 2. In addition to the inter-chain *trans*-esterification shown in Scheme 3, intra-chain *trans*-esterification can occur and this produces cyclic-oligomers. At  $t_{\infty}$ , cycles and chains will be in equilibrium and at elevated temperatures an equilibrium concentration of monomer LA will be present because the enthalpic drive for ring-opening is compensated by entropy, which favors the small molecule. Additionally, it should be noted that in a stereoselective polymerization involving either *rac*- or *meso*-LA, *trans*-esterification will lead to a scrambling of stereocenters along the growing chain and hence a loss of stereoselectivity.

**Ring opening****Propagation****Transesterification****Chain transfer**

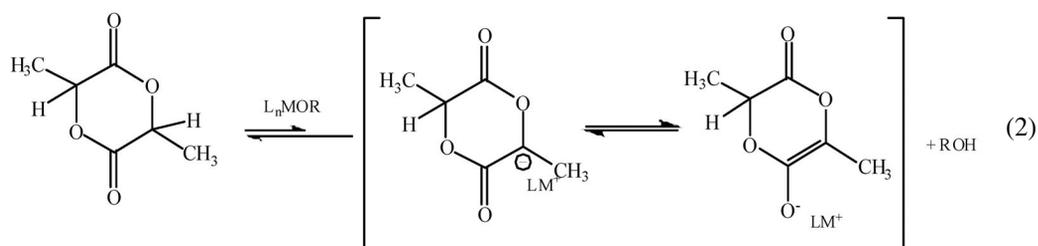
Scheme 3

Two other reactions should be mentioned. The first is chain transfer, which can be brought about as a bimolecular reaction in which the two metal centers are bridged by alkoxide ligands. It can also be brought about by the addition of an alcohol as shown in eq. 1 where OP represents a growing chain.

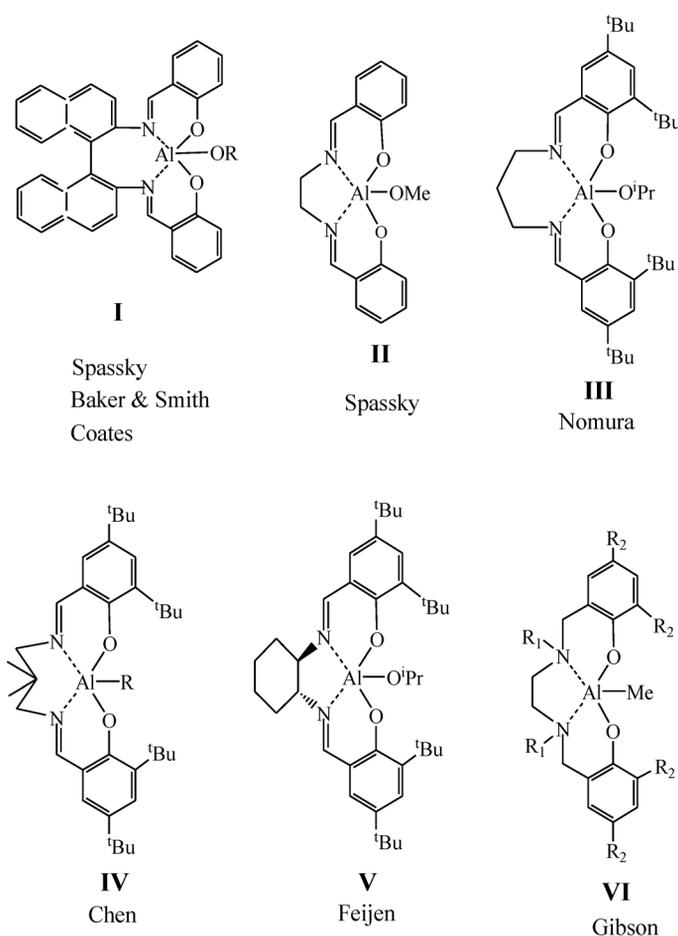


Since  $\text{L}_n\text{MOR}$  represents an initiating molecule, the addition of an alcohol simply increases the number of growing chains and can thus be used to control the molecular weight of the polymer produced.

The second reaction, which is not shown in Scheme 3, is epimerization. This is shown in eq. 2 and is brought about by electropositive metals. This leads to a loss of stereocontrol and atactic polymers.

**ALUMINUM CATALYSTS**

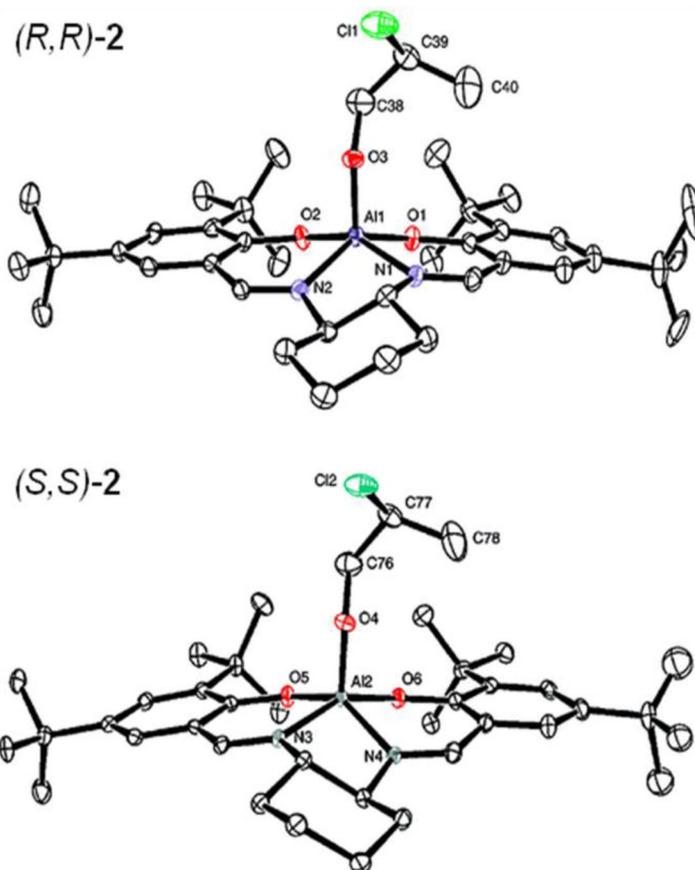
Amongst the largest group of metal catalyst initiators studied to date are Schiff-based aluminum complexes, several of which are shown in Fig. 1. Spassky [20] was the first to show that the use of a chiral metal aluminum complex could achieve stereoselective ROP of *rac*-LA. However, achiral complexes were later shown to effect stereoselective polymerization, e.g., complexes of the types **II**, **III**, **IV**, and **VI** in Fig. 1. Although these aluminum complexes have attracted considerable interest, it is hardly fair



**Fig. 1** Aluminum catalysts in selective ROP of LAs.

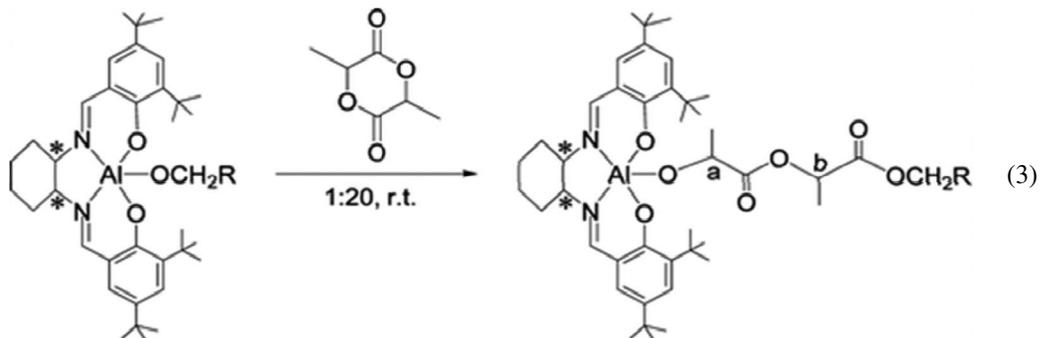
to call them ROP catalysts because typically 100 equiv of LA are enchaind in 1–3 days at 60–80 °C in solvents such as benzene. Turnover frequencies (TOFs) of 1 to 2 per hour can be compared to olefin polymerization catalysts that have TOFs that are limited by diffusion.

The molecular structures of the optically active (salen)Al(OCH<sub>2</sub>CHMeCl)(*S*) complexes are shown in Fig. 2 and are quite revealing [21]. First, it is evident that the stereochemistry of the chiral ligand *S,S*- vs. *R,R*-salen has a negligible effect on the orientation of the chiral *S*-OCH<sub>2</sub>CHMeCl group. Second, the square-pyramidal structure of the Al(3+) center has the alkoxide ligand in the apical position. The vacant sixth coordination site is trans to the alkoxide, and this is clearly not the site that is favorable for the ring-opening of a LA molecule. Thus, while caution has to be applied in relating ground-state structure and reactivity, it is surely not surprising that this complex is not highly active in the ROP of LA. Studies of these compounds' reactivity are, however, illuminating in terms of the competing reactions shown in Scheme 1.



**Fig. 2** Molecular structures of (*R,R*)- and (*S,S*)-(salen)Al(*S*-OCH<sub>2</sub>CHMeCl), deduced from single-crystal X-ray studies (taken from ref. [21]).

For the salen complex **V** in Fig. 2, the rate of ring-opening of LA is dependent on the steric demand of the alkoxide:  $1^\circ > 2^\circ > 3^\circ$ . Indeed, at room temperature for a primary alkoxide the ring-opening of a single LA molecule can be studied in isolation because the rate of ring-opening of LA by the AlOCHMeC(O)OCHMeC(O)OCH<sub>2</sub>R group is negligible. Because of this, it is possible to study the diastereoselectivity of the initial ring-opening event, namely, eq. 3 shown below.



The results of this study are shown in Table 1 for reactions involving the (*R,R*)- and (*S,S*)-salen aluminum alkoxides where the alkoxide is the achiral ethoxide, **1**, and the chiral-*S*-OCH<sub>2</sub>CHMe(Cl), **2**. These results are really quite fascinating and show that the chirality of the salen ligand has a very modest influence in the preference of L vs. D-LA in the ring-opening event for the achiral ethoxide and, furthermore, that the solvent can play a significant role in this stereoselectivity. Note that in chloroform the diastereoselectivity is reversed though of the same magnitude.

**Table 1** Stereoselectivity in the single ring-opening reactions of (salen)AlOR complexes and *rac*-LA taken from ref. [21]).

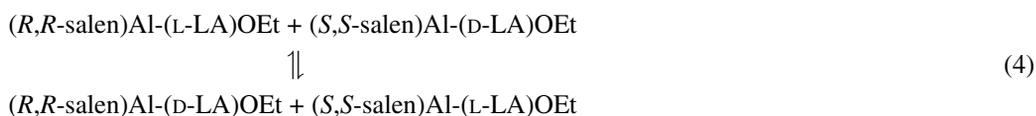
L-D (de%) <sup>a</sup>				
Solvents	( <i>R,R</i> )- <b>1</b> <sup>b</sup>	( <i>S,S</i> )- <b>1</b> <sup>b</sup>	( <i>R,R</i> )- <b>2</b> <sup>b</sup>	( <i>S,S</i> )- <b>2</b> <sup>b</sup>
Toluene	12	-17	-33	-37
C <sub>6</sub> H <sub>6</sub>	20	-18	-31	-40
CHCl <sub>3</sub>	-16	14	-30	-3
THF	22	-20	-33	-13
Pyridine	20	-17	-39	-4

<sup>a</sup>The de% is estimated from <sup>1</sup>H NMR spectra and is proposed to be ~ ±5 %.

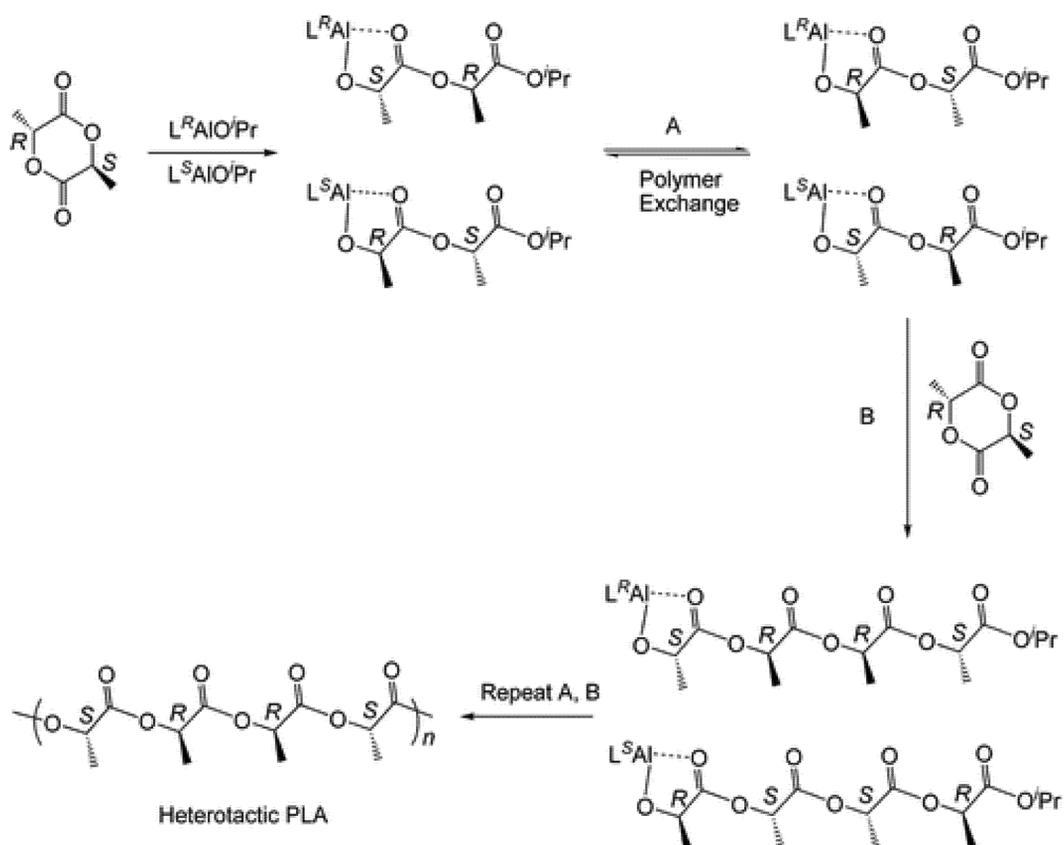
<sup>b</sup>**1**, RO = OCH<sub>2</sub>CH<sub>3</sub>; **2**, RO = *S*-OCH<sub>2</sub>CH(Me)Cl.

In comparing the diastereoselectivity of the ethoxide **1** and the chiral *S*-OCH<sub>2</sub>CH(Me)Cl, **2**, in the solvents benzene and toluene we find that the chirality of the alkoxide is more important than the chirality of the salen. This is also seen in comparing the initial diastereoselectivity of the ring-opening of LA with that of the propagation. For example, (*R,R*-salen)AlOEt shows an initial preference for L-LA but this is reversed in the propagation steps where k(D-LA):k(L-LA) is on the order of 12:1 as noted by Feijen [22]. It is probably fair to state that the design of a stereoselective catalyst system is not yet predictable because of the complex interplay of the chiral end-group of the growing chain, the ligands present at the metal center, which may have an induced chirality by the growing chain, and the solvent.

Because reaction 3 leads to a chemically persistent product at 25 °C in solvents such as chloroform or benzene it was possible to study the reaction shown in eq. 4.



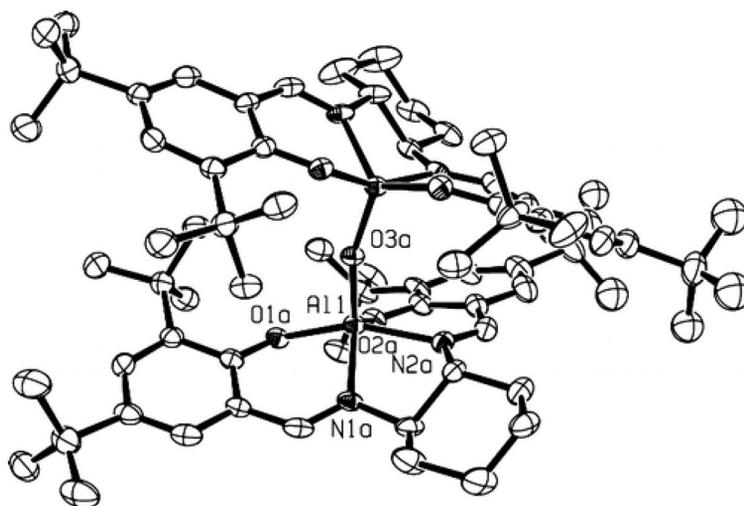
The chemical exchange reaction 4 can be monitored by <sup>1</sup>H NMR spectroscopy and followed to equilibrium. The reaction was found to be notably more rapid than the ring-opening of LA and proceeded to favor (*R,R*-salen)Al-(D-LA)OEt and (*S,S*-salen)Al-(L-LA)OEt by 2:1. The facility of this chain-end exchange reaction provides unequivocal evidence for the Coates' proposal [23] for the formation of heterotactic PLA from the ROP of *meso*-LA with a racemic binaph Al catalyst, **I** in Fig. 1. This chain-end exchange mechanism is shown in Scheme 4. If polymer chain-end exchange were not faster than ring-opening of LA, monomer enchainment, the polymer formed would have been syndiotactic-PLA.



Scheme 4

In studies of the polymerization of LA by Schiff-based aluminum complexes *trans*-esterification is notably slower than chain growth and consequently the PDI is close to 1. Epimerization is not observed. Consequently, these can be viewed as well-behaved systems for oligomerization. They are, however, sensitive to water and this has sometimes led to irreproducible kinetics. Oxo-bridged complexes are formed upon hydrolysis, and these are inactive in ROP. The structure of the oxo-bridged (*R,R*-salen)aluminum complex is shown in Fig. 3.

Although the (salen)AlOR complexes are kinetically slow as ROP catalysts, they are chemically labile toward alcohol for alkoxide exchange and the reversible coordination of LA. Both of these reactions can be monitored by variable-temperature  $^1H$  NMR and seen as dynamic exchange processes [21].

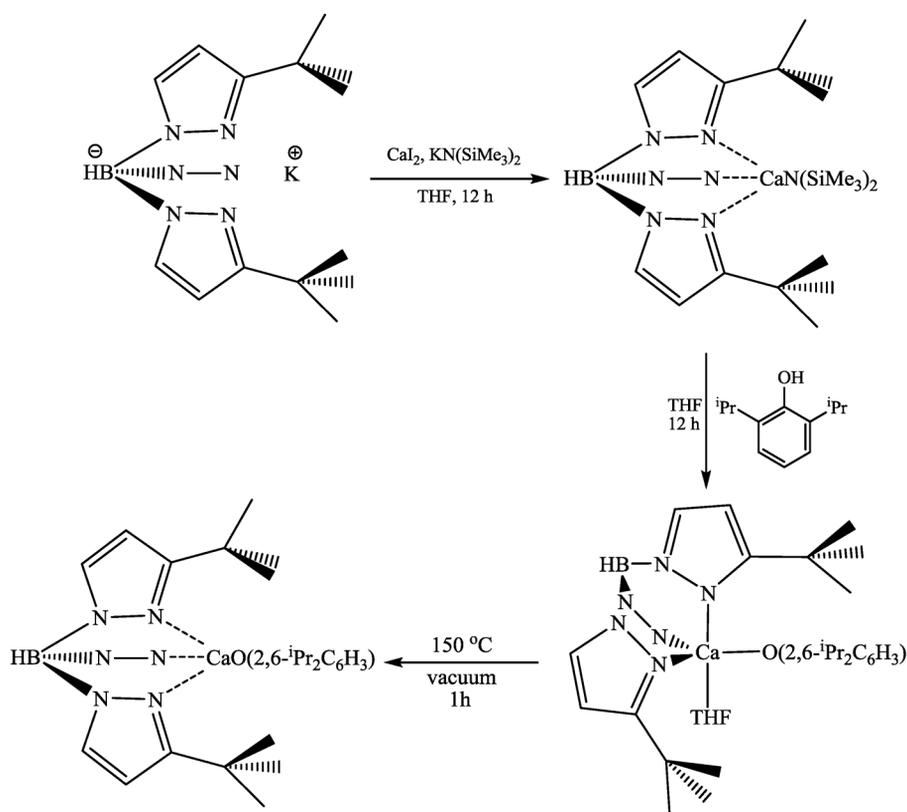


**Fig. 3** Molecular structure of oxo-bridged compound  $(R,R\text{-salen-Al})_2(\mu\text{-O})$ , deduced from single-crystal X-ray studies (taken from ref. [21]). Hydrogen atoms have been omitted for clarity, and 30 % anisotropic displacement ellipsoids are drawn. A 2-fold rotation axis passes through O(3a).

## GROUP 2 METAL COMPLEXES

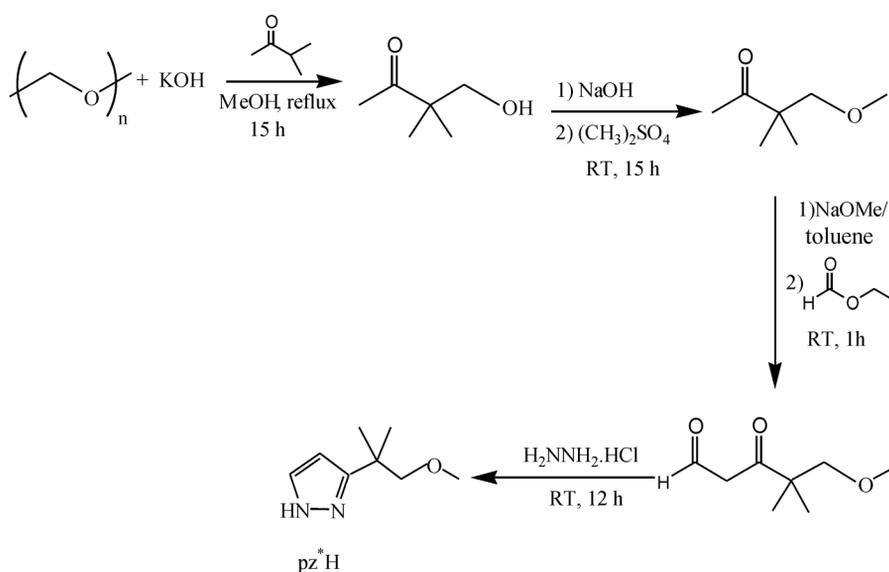
In general, it can be stated that the reactivity of a metal–alkoxide bond toward ROP of LA is dependent on the polarity of the  $M^{\delta+}-\delta^-OR$  bond and steric factors controlling access to the metal center. Bridging alkoxides are notably less nucleophilic than terminal ones, so there is a great advantage in having a single-site catalyst of the form  $L_nMOR$ . The reactivity order of the group 2 metals is  $Ca > Mg > Zn$ , which is a group 2b metal, and notably softer [24–26]. Coates and co-workers [27] showed that the  $\beta$ -diketonate ligand  $CH(CMeNC_6H_3-2,6-Pr_2^i)_2$  with zinc formed active complexes of the form  $LZnOR$ . However, while the related LMOR complexes of Mg and Ca could be formed as THF solvates and were highly active in the initiation of polymerization they did not yield a living system. They were too kinetically labile, and ligand scrambling led to  $L_2M$  complexes and catalyst death [25,28].

The bulky trispyrazolylborate ligand  $HB(pz-3-Bu^t)_3$  led to the isolation of discrete complexes of Ca as shown in Scheme 5 [24,25]. While these were characterizable by single-crystal X-ray studies and were initially highly active in ROP, these too were not kinetically persistent.



Scheme 5

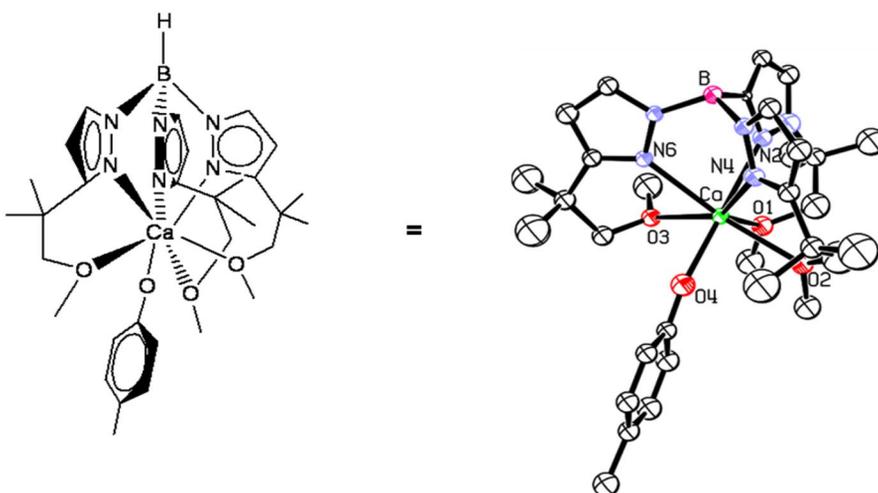
In an attempt to enhance the kinetic persistence of a single-site Ca-alkoxide catalyst, we prepared a sterically demanding trispyrazolylhydroborate with ether arms, namely tris[3(2-methoxy-1,1-dimethylpyrazolyl)]hydroborate, according to the reactions shown in Scheme 6 [29,30]. The complexes  $\text{MTp}^*$ , where  $\text{M} = \text{Li}, \text{Na},$  or  $\text{K}$ , contain a central  $\text{M}^+$  cation encapsulated by the hexadentate  $\text{Tp}^*$  ligand,  $\eta^3\text{-N}, \eta^3\text{-O}$ . Because of the sequestering of the  $\text{M}^+$  ion, these complexes are not as useful as the thallium complex  $\text{TlTp}^*$ , which is formed in near quantitative yield from the reaction between  $\text{NaTp}^*$  and  $\text{TIOAc}$  in methylenechloride over a 24 h period at room temperature. The soft  $\text{Tl}^+$  cation is ligated by three N atoms of the  $\text{Tp}^*$  ligand,  $\text{Tl-N} = 2.60\text{ \AA}$  (ave) and two of the ether arms where  $\text{Tl}\cdots\text{O} = 3.1\text{ \AA}$  (ave). These  $\text{Tl}\cdots\text{O}$  distances are roughly  $0.5\text{ \AA}$  longer than the  $\text{K-O}$  distances in  $\text{KTp}^*$ . Since the ions  $\text{K}^+$  and  $\text{Tl}^+$  are of a similar size, the longer  $\text{Tl}\cdots\text{O}$  distances are a clear indication of softer and less electrophilic nature of the  $\text{Tl}^+$  ion.



**Scheme 6** (M = Li, Na, K).

By reactions similar to those shown in Scheme 5, we have prepared Tp\*Ca-amides and alkoxides [30]. The molecular structure of the derivative from *para*-cresol is shown in Fig. 4 [30]. The Tp\* ligand is hexadentate and, with the phenoxide ligand, the  $\text{Ca}^{2+}$  is seven coordinate. The complex, like the MTP\* complexes described before, is a colorless/white crystalline solid. It is chemically persistent in air and moist hydrocarbon solvents in which it is appreciably soluble. It is active in the polymerization of LA and other cyclic esters and carbonates and is a promising candidate for Ca-based ROP. These matters are currently under investigation.

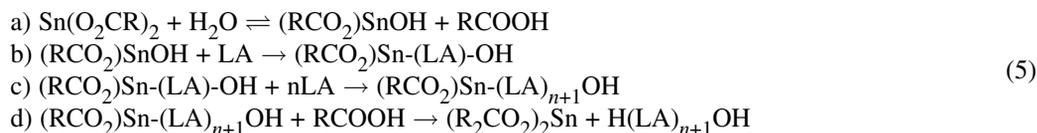
$(\eta^6\text{-Tp}^*)\text{Ca-OC}_6\text{H}_4\text{-p-CH}_3$



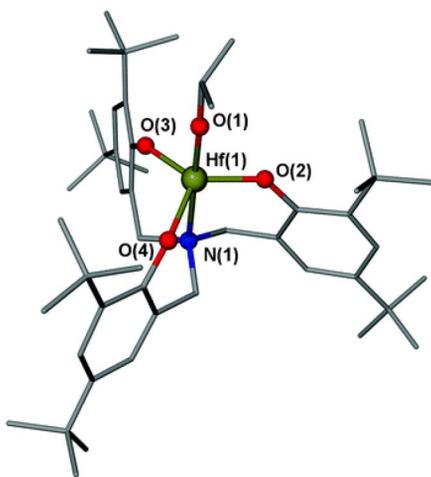
**Fig. 4**

## SN(OCT)<sub>2</sub> AND MELT POLYMERIZATIONS

The problems associated with single-site metal–alkoxide catalysts involving ligand scrambling and hydrolysis are not encountered with the use of Sn(oct)<sub>2</sub>, where oct = 2-ethylhexanoate in the ROP of L-LA to give poly L-LA [31]. This commercially available catalyst precursor is “stable” to water and, indeed, is sold with ~5 equiv of H<sub>2</sub>O, which is important for initiating the reaction by the reversible equilibrium 5a. It is the Sn–OH bond that initiates the ring-opening of the LA monomer to form the Sn–alkoxide group SnOCHMeC(O)OCHMeC(O)OH. In the presence of the carboxylic acid, this reacts reversibly to liberate the alcohol but the Sn–alkoxide is labile to the enchainment of LA, 5b and 5c. In this way, each H<sub>2</sub>O molecule generates a growing chain of polylactic acid H(LA)<sub>n</sub>OH, 5d.



Although Sn(oct)<sub>2</sub> provides a kinetically persistent and immortal or living polymerization system, it is not stereoselective. Also, it is not very active in as much as it reacts in solvents at ~70 to 80 °C, and kinetically is rather similar to the Schiff-based aluminum catalysts described earlier. It can, however, be used in melt polymerizations of LA. The solvent-free polymerization of LA is clearly very attractive from a commercial standpoint and in the production of commercial samples of poly L-LA residual Sn can be found. For any medical application, it is important that any residual metal is benign! Also, it would be commercially advantageous to carry out melt polymerizations that are stereoselective. Recent work toward this end suggests that this may indeed be possible. For example, Davidson and co-workers [32–34] have found that group 4 and 14 derivatives of the form LM(OR), where L is the 3-anionic ligand derived from deprotonation of aminetrisphenols, are effective in stereoselective melt polymerizations. The molecular structure of the hafnium isopropoxide complex is shown in Fig. 5. The bulky aminetrisphenolate ligand adopts a C<sub>3</sub> chiral skew in the solid state, and this is evidently important in the melt-polymerization of *rac*-LA, which is both rapid and stereoselective. At 130 °C in the melt, 100 equiv of *rac*-LA are polymerized to give >90 % heterotactic PLA in 95 % yield in less than 30 min. In



**Fig. 5** Molecular structure of the aminetrisphenolatezirconiumisopropoxide catalyst precursor employed in melt stereoselective polymerizations of *rac*-LA: hydrogen atoms, lattice solvent, and ligand disorder have been omitted for clarity (taken from ref. [32]). Selected bond lengths [Å] and angles [°]: Hf(1)–O(1) 1.920(2), Hf(1)–O(2) 1.949(3), Hf(1)–O(3) 1.944(3), Hf(1)–O(4) 1.999(3), Hf(1)–N(1) 2.406(2), O(1)–Hf(1)–N(1) 179.33(9), O(4)–Hf(1)–O(3) 116.31(13).

a solution study of this polymerization, these authors showed that the polymerization of *rac*-LA was nearly 10 times more rapid than the polymerization of *L*-LA. This work clearly shows the intricate interplay between end-group and enantiomorphic site control in stereoselective polymerization of *rac*-LA.

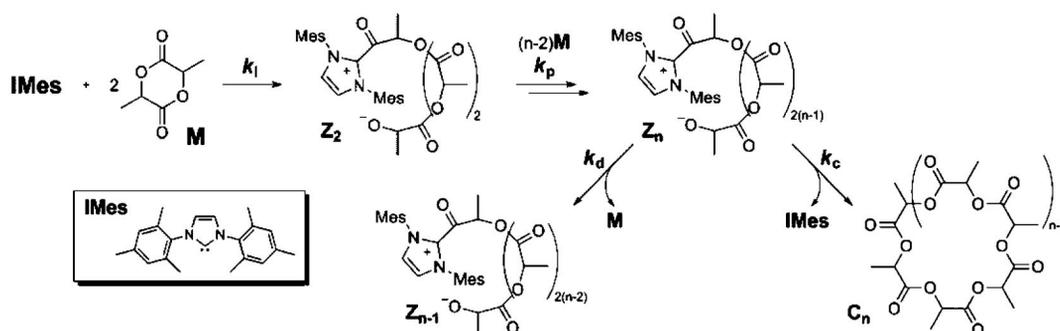
## CYCLIC POLYLACTIDES

As indicated in the earlier discussion of the mechanisms involved in the ROP of LA, at  $t_{\infty}$  *trans*-esterification will lead to an equilibrium mixture of chains and rings with the rings being formed by intra-chain *trans*-esterification [31,35]. Recently, work has been performed that leads to the exclusive formation of rings.

Hedrick and Waymouth and their co-workers [37,38] have developed a Zwitterionic polymerization involving the use of *N*-heterocyclic carbenes. The reaction sequence is shown in Scheme 7. High molecular weights,  $M_n = 5000$  to 30000 g/mol, have been achieved with relatively narrow PDI  $\sim 1.3$ . This reaction sequence is related to the organic nucleophilic polymerization initiated by strong organic nucleophiles such as 4-dimethylaminopyridine (DMAP) in the presence of a primary alcohol as depicted by eq. 6 [4–9].



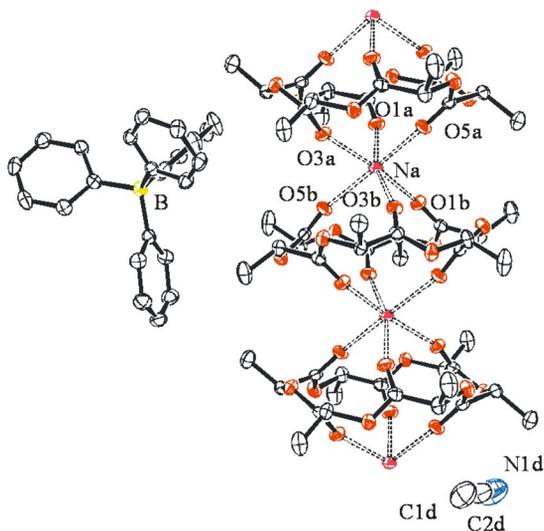
In the absence of the alcohol, the ring-opening can only lead to cycles (Scheme 7).



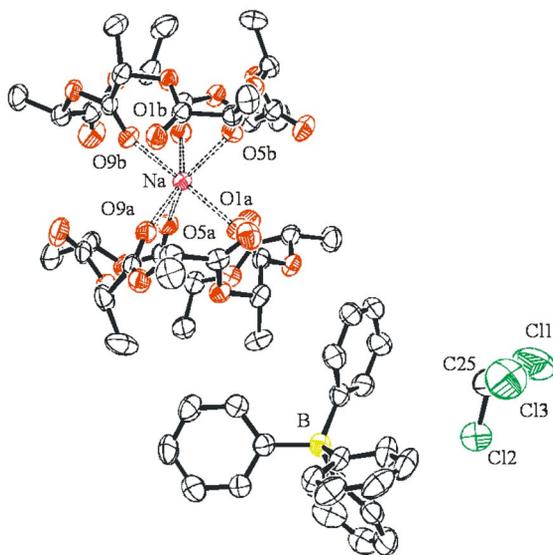
Scheme 7

Another reaction pathway developed in my lab employs the attachment of an ROP catalyst to a support [38,39]. In this way, chains grow on the support, which is suspended in a solvent. Intra-chain *trans*-esterification then releases cycles to the solvent. With time this process generates an equilibrium mixture of rings since the rings, being cyclic esters, are themselves subject to *trans*-esterification. The introduction of NaBPh<sub>4</sub> to this dynamic combinatorial library of rings selectively binds the 18-membered rings. In this way, LA can be converted to the 18-membered ring by chemical amplification in greater than 80 % yield [38,39]. The supported Li-based catalyst is highly active and, in addition to ROP and intra-chain *trans*-esterification, affects epimerization. Consequently, starting with *L*-LA the 18-membered rings, (CHMeC(O)O)<sub>6</sub>, form a mixture of isomers, specifically six enantiomeric pairs and two *meso*-isomers. However, the rate of epimerization is notably less than that of *trans*-esterification so, with some loss in % of conversion of LA to the 18-membered ring, the 6*S*-[CHMeC(O)O]<sub>6</sub> isomer can be isolated in near 50 % yield along with the 5*S*,*R* isomer and the 4*S*,2*R* isomers starting with *L*-LA. Starting with *rac*-LA, the 3*S*,3*R* and 4*S*,2*R*/2*S*,4*R* isomers are enriched. By chromatography, an example of one of each of the six enantiomers and the two *meso*-isomers (*SRSRSR* and *SSSRRR*) have been isolated and characterized. The *meso*-isomer *R,S,R,S,R,S*-[CHMeC(O)O]<sub>6</sub> has crystallographically imposed *S*<sub>6</sub> symmetry with three ketonic oxygens above and three below the plane of the 18-membered

ring. In this geometry, the ring is perfectly suited to bind to  $\text{Na}^+$  ions to form an infinite chain in the structure  $\text{Na}[\text{CHMeC}(\text{O})\text{O}]_6\text{BPh}_4 \cdot \text{CH}_3\text{CN}$ . See Fig. 6. In contrast, the  $6S$ - $[\text{CHMeC}(\text{O})\text{O}]_6$  isomer has three ketonic oxygen atoms exo and three endo to the plane of the ring. This forms a 2:1 complex with the  $\text{Na}^+$  ion as seen in the structure of the salt,  $\text{Na}[\text{CHMeC}(\text{O})\text{O}]_2\text{BPh}_4 \cdot \text{CHCl}_3$  shown in Fig. 7.



**Fig. 6** Depiction of the solid-state structure of  $\text{Na}(\text{SRSRSR-A}_6)\text{BPh}_4 \cdot \text{CH}_3\text{CN}$ , where  $\text{A} = \text{CHMeC}(\text{O})\text{O}$ .



**Fig. 7** Depiction of the solid-state structure of  $\text{Na}(6S\text{-A}_6)\text{BPh}_4 \cdot \text{CHCl}_3$ , where  $\text{A} = \text{CHMeC}(\text{O})\text{O}$ .

## CONCLUDING REMARKS

While the details of the reactions described in this article pertain to lactide, the principles apply well to other cyclic esters within the confines of thermodynamics. Only a limited number of catalyst systems have been mentioned, and notably absent in the discussion has been those of the lanthanides. Thus far, the lanthanides have proved themselves highly active, like those of the active and heavier group 2 metals. The larger size of the lanthanides and their ionic character pose a challenge for the development of single-site catalysts, though stereoselective polymerizations have been achieved [40,41]. It is, however, fair to state that the production of polyesters from renewable resources by single-site metal alkoxide catalysts represents an important new field of catalysis with a significant commercial market as our world learns to embrace sustainability.

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