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Gradient Isotactic Multiblock Polylactides from Aluminum Complexes of Chiral Salalen Ligands

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Supporting Information

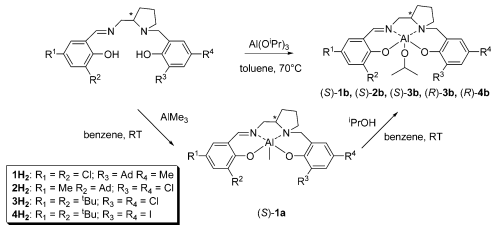
ABSTRACT: Aluminum complexes of enantiomerically pure aminomethylpyrrolidine-based salalen ligands and their application in the stereoselective polymerization of lactide are described. Poly(lactic acid) featuring the new gradient isotactic multiblock microstructure was synthesized by isoselective catalysts, which operate by a combination of enantiomorphic-site and chain-end control mechanisms.

The synthesis of polyesters by the catalytic ring-opening polymerization (ROP) of cyclic esters is attracting a considerable current interest. Poly(lactic acid) (PLA) prepared by the ROP of lactide (LA)[1,2] combines several attractive properties: (1) It is an environmentally friendly material derived from annually renewable resources which can be decomposed postconsumption to nontoxic materials.[3] (2) The presence of two stereogenic centers in the LA monomer may give rise to different polymer stereoregularities which affect properties such as crystallinity and rate of hydrolysis.[4] Polymerizations of the homochiral L- or D-LA yield the respective isotactic polymers PLLA and PDLA, whereas polymerizations of the racemic monomer *rac*-LA may give rise to different stereoregularities ranging from isotactic via atactic to heterotactic PLA depending on the preference of the employed catalyst to elect a certain monomer. Stereoselection may be achieved by either enantiomorphic-site control mechanism (SCM; homochiral preference by the catalyst chirality) or chain-end control mechanism (CEM; homo- or heterochiral preference by the last inserted repeat unit). The possible exchange of polymeryl chains between active catalyst molecules may further diversify the microstructure. Aluminum complexes[4,5] led to the highest stereocontrol in *rac*-LA polymerization with important examples including Spassky's complexes[6] of chiral salen ligands that gave highly isotactic diblock PLA by an SCM controlled kinetic resolution, Nomura's complexes[7] of achiral salen ligands that gave highly isotactic multiblock PLA by the CEM control, and Gibson's salan complexes[8] that gave PLAs of different tacticities as a consequence of the phenolate substituents. Notably, all these aluminum complexes included tetradentate-dianionic sequential {ONNO}-type ligands. Here we describe the polymerization of homochiral-LAs and *rac*-LA by aluminum complexes of chiral salalen ligands. We demonstrate that SCM and CEM stereocontrol mechanisms act simultaneously, and lead to a proposed hitherto unknown polymeric microstructure, viz., the gradient isotactic multiblock PLA.[9,10]

Salalens[11] are {ONNO}-type ligands including an imine- and an amine neutral donors and two phenolate arms, whose complexes have found use as catalysts for isospecific polymerization of α-olefins[12] and as asymmetric oxidation catalysts.[13] They can be readily synthesized from the corresponding diamines by a two-step condensation-substitution sequence. Aluminum complexes of salalen ligands, recently described by Jones, were found to polymerize *rac*-LA giving PLAs whose microstructures ranged from medium-heterotactic to medium-isotactic as a function of the salalen structure.[14,15] We recently found that aminomethylpyrrolidine based salalen ligands which may be easily prepared in their enantiomerically pure form wrap around group 4 metals in a highly diastereoselective manner giving rise to enantiomerically pure stereogenic-at-metal complexes.[12a] Accordingly, the four chiral salalen ligand precursors described here were synthesized as single enantiomers from aminomethylpyrrolidine. To address structure–activity relationships, different combinations of bulky and electron-withdrawing phenolate substituents were chosen. The salalen aluminum complexes of the type [{ONNO}Al(O^{i}Pr)] were prepared either by treatment of these ligand precursors with equimolar amounts of $AlMe_3$ and subsequent reaction with 2-propanol or by direct reaction with $Al(O^iPr)_3$ (Scheme 1). For characterization of the complexes, see the Supporting Information (SI).

^{1}H NMR spectra of the salalen complexes indicated that they were all obtained as single diastereomers despite the presence of several sources of stereoisomerism, including the stereogeneity at the amine-donor and the Al-center and the helicity of the ligand wrapping. Thus, the ability of the aminomethylpyrrolidine

Scheme 1



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backbone to induce chirality-at-metal is demonstrated around this pentacoordinate aluminum center. In contrast, aluminum complexes of salalen ligands having the *trans*-1,2-diaminocyclohexane chiral backbone were obtained as mixtures of diastereomers in solution.[14c] Single crystals of an ethylaluminum complex of proligand (*R*)-**3H$_2$** were crystallized from pentane at −35 °C and the molecular structure as determined by X-ray diffraction is shown in Figure 1. The

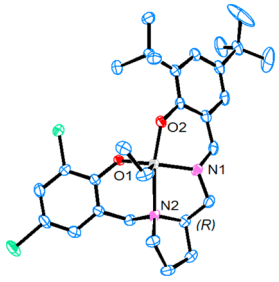

Figure 1. ORTEP representation of the structure of (*R*)-3-Al-Et. Selected bond lengths (Å) and angles (°): O1-Al 1.794, O2-Al 1.816, N1-Al 1.984, N2-Al 2.326, C25-Al 1.974, O2-Al-N2 160.1.

aluminum adopts a geometry intermediate between trigonal-bipyramidal (with the imine-side phenolate O-donor and the pyrrolidine N-donor occupying the apical positions) and square pyramidal (with the ethyl group at the axial vertex). The (*R*)-configuration of the stereogenic center was established, and the bond lengths and angles are close to those found for the aluminum complexes of nonchiral salalen ligands.[14a] We propose that this geometry is retained in solution.

Preliminary experiments revealed that all the aluminum complexes of these chiral salalen ligands polymerized *rac*-LA with activities typical of aluminum catalysts. Representative polymerization results are summarized in Table 1. The molecular

Table 1. Ring−Opening Polymerization of *rac*-LA Promoted by Salalen Aluminum Complexes[a]

run	*I*	conv. (%)	M_n^{calc} (kg/mol)[b]	M_n (kg/mol)[c]	PDI	P_m[d]
1[e]	(*S*)-**1a**	73	10.5	9.1	1.09	0.23
2	(*S*)-**1b**	75	10.8	8.5	1.07	0.24
3	(*S*)-**2b**	42	6.1	6.8	1.05	0.82
4	(*S*)-**3b**	78	11.2	9.0	1.07	0.82
5	(*R*)-**4b**	91	13.1	9.7	1.07	0.59
6	*rac*-**3b**	85	12.3	9.2	1.05	0.70

[a]General conditions: initiator, 20 μmol; toluene, 2 mL; [*rac*-LA]$_0$/[Al], 100; temperature, 80 °C; time, 24 h. [b]Calculated M_n of PLA (g/mol) = 144.14 × ([LA]$_0$/[Al]) × conversion (LA). [c]Experimental M_n values determined by GPC analysis in THF. [d]Determined from the methine region of the homonuclear decoupled ^{1}H NMR spectrum. Calculated from Bernoullian statistics. [e]20 μmol of iPrOH was added to the initiator.

weights of the obtained PLAs were in good agreement with the calculated values, and the molecular weight distributions were narrow (PDI < 1.1), supporting a well-controlled polymerization. Addition of 2-propanol to the corresponding methyl complex (*S*)-**1a** in the presence of *rac*-LA gave a catalyst whose activity was practically identical to that of the isolated isopropoxo complex (*S*)-**1b** (runs 1 and 2). The ^{1}H NMR homodecoupled spectra of the obtained PLAs revealed a clear relationship between the ligand substitution pattern and the PLA stereoregularity. The isolated or *in situ* formed complex (*S*)-**1b** which features halo substituents on the imine-side phenol and bulky alkyl groups on the amine-side phenol gave PLAs of a heterotactic nature (runs 1 and 2). In contrast, all complexes with the opposite phenolate substitution pattern, viz., bulky alkyl substituents on the imine-side phenol and halo groups on the amine-side phenol gave isotactic PLAs (runs 3−6). A similar inclination was reported for other salalen aluminum complexes. However, in those cases the stereocontrol was lower and the presence of chiral ligands on the aluminum center was detrimental for activity.[14c] Complexes (*S*)-**2b** and (*S*)-**3b**, which include either adamantyl or *tert*-butyl groups on the imine-side phenol and chloro substituents on the amine-side phenol, gave the highest isotacticities with identical values of P_m = 82% (runs 3 and 4). Increasing the size of the halo group to iodo resulted in substantial decrease of isotacticity (runs 4 and 5). Employing the racemic version of catalyst **3b**, prepared by mixing equimolar quantities of the homochiral complexes, also resulted in decrease of isotacticity (runs 4 and 6), invoking the involvement of polymeryl exchange events.[16,17]

The availability of these pyrrolidine-based salalen ligands in their enantiomerically pure form, their very highly diastereoselective wrapping around aluminum, and their tendency to give relatively high degrees of isotacticity in *rac*-LA polymerization prompted us to conduct further studies to elucidate the stereocontrol mechanism. To avoid complications due to polymeryl exchange, we employed only enatiomerically pure complexes. First, we followed the kinetics of polymerization of *rac*-, D-, and L-LA by complex (*S*)-**3b** in toluene-d_8 at 70 °C by monitoring the monomer consumption over time by ^{1}H NMR spectroscopy.[18] The semilogarithmic plots are shown in Figure 2.

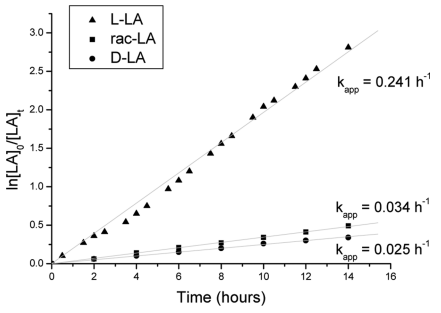

Figure 2. Pseudofirst-order kinetic plots for ROP of lactides (L-LA; D-LA; *rac*-LA) promoted by (*S*)-**3b**. [Al] = 1.0 × 10^{-2} M; [LA]/[Al] = 100; *T* = 70 °C; toluene-d_8 as solvent. $k_{L\text{-}LA}/k_{D\text{-}LA}$ = 10.

Two trends immediately emerge. (1) A first-order kinetics is found for all monomers, viz., all the polymerizations obey the following kinetic law: $-d[LA]/dt = k_{app}[LA]$ and (2) a clear preference for the polymerization of L-LA over that of D-LA with a substantial rate ratio of $\sigma = k_{app(L\text{-}LA)}/k_{app(D\text{-}LA)} = 10$ is found.[6] The close values of $k_{app(rac\text{-}LA)}$ and $k_{app(D\text{-}LA)}$ suggest that the polymerization of D-LA is the rate determining step in the polymerization of *rac*-LA by (*S*)-**3b** (and mirrored for (*R*)-**3b**). We followed the consumption of *rac*-LA by (*S*)-**3b** with time and found that the first order kinetics persisted at least until 90% conversion (Figure S1). Moreover, the opposite enantiomeric complex (*R*)-**3b** was found to exhibit the opposite rates in the polymerization of L- and D-LA and the same rate toward *rac*-LA (Figure S2), ruling out any technical sources for the rate difference. These two trends are inconsistent with either a pure

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chain-end control mechanism for which the consumption of L- and D-LA should be of identical rates, or with a pure enantiomorphic site control (kinetic resolution) mechanism for which the polymerization rate of *rac*-LA should decrease as the faster of the two enantiomers is being consumed.[19] Consistently, the obtained isotactic PLA cannot possess any of the known microstructures of either multialternating D/L-blocks of identical average lengths (CEM), or of a tapered diblock copolymer (SCM). We hypothesize that the CEM and the SCM mechanisms act simultaneously and the polymer obtained exhibits the proposed novel microstructure of gradient isotactic multiblock PLA, viz., consisting of D- and L-blocks of gradually exchanging lengths.

To obtain further insight on the formation of the hypothesized gradient multiblock PLA chains, polymerization runs of *rac*-LA for different times and consequent different conversions were carried out with complex (*S*)-**3b** (Table 2). The ^{1}H NMR spectrum of the sample at low conversion after hydrolytic workup (run 7) showed the existence of HOCH(CH_3)CO- and -OCH(CH_3)$_2$ as exclusive chain end groups. In addition, linear increase of M_n with conversion, and narrow M_w/M_n ratios at all conversions were found. These findings point to the aluminum-isopropoxide group as the sole initiating anchor, supporting the integrity of the salalen-aluminum framework during the polymerization. Chain growth proceeds by consecutive insertions of the lactide acyl-oxygen bond to the aluminum-alkoxo bond of the growing polymeryl chain in a highly living manner. The obtained polymers were analyzed by optical rotation measurements in chloroform. All samples had negative $[\alpha]_D^{25}$ values confirming that the L-LA is preferentially polymerized by (*S*)-**3b**.[20,21] However, the low enantiomeric excess of L-LA units in the obtained polymers (maximum value: 21% for the sample of run 7), determined by comparison of the optical rotation of the polymeric samples with the optical rotation of PLLA samples having the same molecular weights, indicated that both lactide enantiomers are consumed even at low conversions. The selectivity factor (*s*), defined as the ratio of the polymerization rates of the faster reacting monomer over that of the slower reacting monomer, can be determined from the % ee and conversion according to Kagan's equation,[22−24] and was calculated to be 1.6 in favor of L-LA in the polymerization of *rac*-LA by (*S*)-**3b**. This value represents a low preference for the faster enantiomer,[23b] and is in line with the hypothesis of a multiblock copolymerization of the two enantiomers in which at low conversion L-LA is preferentially consumed by (*S*)-**3b**, giving L-LA blocks longer than D-LA blocks. This trend is gradually inverted as the concentration ratio of the two enantiomers changes.

Table 2. Polymerization of *rac*-Lactide at Different Conversions by Complex (*S*)-3b[a]

run	time (h)	conv. (%)	M_n (kg/mol)[b]	PDI[b]	P_m[c]	$[\alpha]_D^{25}$
7[d]	5	26	4.0[e]	n.d.[f]	0.79	−30
8	10	48	5.1	1.12	0.80	−25
9	15	60	7.1	1.08	0.82	−20
4	24	78	9.0	1.07	0.82	−16
10	30	86	9.5	1.08	0.82	−9

[a]General conditions: initiator, 20 μmol; toluene, 2 mL; [*rac*-LA]$_0$/[Al], 100; temperature, 80 °C. [b]Experimental M_n values were determined by GPC analysis in THF. [c]Determined from the methine region of the homonuclear decoupled ^{1}H NMR spectrum. [d]Initiator, 30 μmol. [e]Determined from ^{1}H NMR. [f]n.d. = not determined.

Finally, we conducted tetrad analysis of the homonuclear decoupled ^{1}H NMR spectra, to elucidate the relative roles of the CEM and SCM mechanisms (Figure 3). Second in intensity to the isotactic *mmm* tetrad are the tetrads corresponding to the stereoblock −SSSSRRRR-type sequences, viz., the *mmr*, *mrm*, and *rmm* tetrads. However, the occurrence of the −SSSSRRSSSS-sequence corresponding to a single misinsertion of the opposite enantiomer is also evident by the presence of the *rmr* tetrad. We found that the relative ratio of the *rmr* tetrad diminishes in respect to both the *mmm* and the *rmm* tetrads as a function of conversion. Namely, the CEM control becomes more dominant as a function of conversion. For the polymeric samples obtained in runs 7 (26% conversion) and 4 (78% conversion), we calculated the tetrad probabilities based on both Bernoullian (CEM) and SCM statistics, and these values were compared with the experimental values obtained by the NMR analysis (Tables S1, S2). At 26% conversion, the experimental values deviated significantly from the theoretical values calculated by both statistical treatments, but for the 78% conversion, a good agreement was observed with the tetrad probabilities based on the Bernoullian statistics.

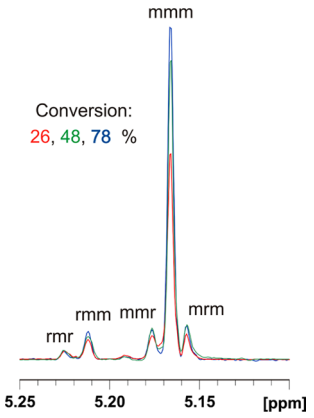

Figure 3. Methine region of the homonuclear-decoupled ^{1}H NMR spectra of isotactic PLAs at different conversions produced using initiator (*S*)-**3b** (runs 7, 8, and 4 in Table 2).

These results indicate that CEM is the prevailing mechanism of sterocontrol operating in the polymerization experiments carried out with this class of isospecific chiral catalysts, although at low conversions the contribution of the SCM is apparent.[25] Consequently, the polymeric chains are not symmetrical, including longer blocks of the faster reacting enantiomer having occasional misinsertions close to the isopropoxo terminus, and longer blocks of the slower reacting enantiomer free of misinsertions close to the hydroxo terminus.

In conclusion, we introduced well-defined single-diastereomeric aluminum complexes of enantiomerically pure amino-methylpyrrolidine-based salalen ligands that acted as active catalysts in lactide polymerization, with stereoselection derived from their specific substitution pattern. Enantiomerically pure isoselective catalysts were found to act by a combination of enantiomorphic-site and chain-end control mechanisms, and led to PLA of a proposed new microstructure, viz., the gradient isotactic multiblock PLA. We are currently investigating the properties of this architecture,[26,27] and extending the polymerization studies of these catalysts to other polymerizations.

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■ ASSOCIATED CONTENT

Supporting Information

Detailed experiments protocols, kinetics data and tetrad distribution analysis; CCDC 950722 with crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) Polymerization of *meso*-LA with (*R*)-**3b** and with *rac*-**3b** led to syndiotactically and heterotactically inclined PLA's, respectively (SI). The formation of syndiotactic-PLA is governed by homochiral preference of an SCM control mechanism, and is consistent with the prevalence of this mechanism at the early stages of *rac*-LA polymerization. Polymeryl exhange between propagating species is degenerate for an enantiomerically pure catalyst. This degeneracy is lifted for the racemic catalyst. The observed reversal of tacticity to heterotactic is an unequivocal support for polymeryl exchange between enantiomorphous metal centers.[16]

(18) Homodecoupled ^{1}H NMR spectra of the PLA samples obtained from enantiopure monomers (D- and L-LA) were perfectly isotactic testifying that no epimerization reactions occur.

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(20) As expected, the PLA obtained with *rac*-**3b** (run 6, Table 1) was not optically active, whereas a polymeric sample obtained by (*R*)-**3b** in the same conditions of run 10 (conversion 90%) showed an $[\alpha]_D^{25}$ of +8 indicating that this catalyst preferentially polymerizes the D-LA enantiomer.

(21) Reactivity ratios may also be established by chiral GC analysis of unreacted monomer. To further validate the data in Table 2, *rac*-LA was polymerized with (*S*)-**3b** until 75% conversion, the polymerization was quenched by precipitation, the remaining lactide was isolated by sublimation, and the PLA formed was analyzed by polarimetry. The enantiomeric excess of the unreacted lactide was 34% according to chiral GC analysis, and 33% according to a calculation based on the optical activity of the polymer (SI).

(22) Kagan's equation: $s = \ln[1 - c(1 + ee)]/\ln[1 - c(1 - ee)]$ where c is the fraction conversion and ee is the enantiomeric excess.

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(25) SCM and CEM mechanisms may play varying roles in any stereoregular polymerization. For a mechanistic study of their interplay in lactide polymerization see refs 7b and 24b.

(26) Preliminary characterization of a gradient isotactic multiblock PLA sample revealed that it was crystalline. X-ray spectral analysis of a raw polymer sample and a polymer sample obtained by casting from DMF solution corresponded to stereocomplex PLA. The T_m of these two samples was 161 °C (ΔH = 25 J/g) and 165 °C (ΔH = 31 J/g). These values are lower than those obtained for stereocomplex-PLA obtained by mixing enantiomerically pure PLLA and PDLA, due to the higher degree of stereoerrors/block lengths in the sample (SI).

(27) Polymerizations of 75:25 and 25:75 L-/D-LA mixtures carried out to 43% conversion yielded polymers with different optical activities, different distribution of stereoerrors, and different degrees of crystallinity, consistent with the CEM and SCM mechanisms preferring either the same or the opposite enantiomer (SI).