Stereoselective Controlled Polymerization of DL-Lactide with [Ti(trisphenolate)O-*i*-Pr]$_2$ Initiators

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Biodegradable polymers, particularly poly(lactic acid) (PLA), have become important industrial commodities[1,2] as well as a focus of research efforts aimed at developing more selective polymerization catalysts.[3] One approach that has been successful in controlling the chain length and stereochemistry of PLA is the metal alkoxide-initiated ROP of the cyclic condensed dimer of lactic acid (LA). Controlled polymerization reactions have been discovered for a number of well-defined metal alkoxide complexes,[4] including those of aluminum,[5,6] calcium,[7] magnesium,[8−10] lanthanides,[11] titanium,[12,13] and zinc,[9,10,14,15] so that isotactic PLA can be prepared starting from L-LA (Figure 1a). Enantiomerically pure or racemic chiral aluminum(III) alkoxide initiators have enabled the preparation of isotactic stereoblock PLA from *rac*-LA[16,17] (Figure 1b) and syndiotactic PLA from *meso*-LA,[17] presumably via enantiomorphic site control (ESC). The ROP of *rac*-LA using achiral metal alkoxide complexes generally favors heterotactic PLA (Figure 1c) via chain-end control (CEC),[10,18−20] the exception being achiral aluminum salen[21] or salan[20] complexes, which yield isotactic stereoblock PLA via CEC. These recent advances and the commercial utility of PLA indicate that further research in this area is valuable, both for improving synthetic methods and for better understanding the mechanisms and constraints of ROP catalytic systems.

Our group has been characterizing titanium(IV) and aluminum(III) trisphenoxide compounds, with the goal of preparing well-defined single site Lewis acid catalysts that can be used in asymmetric synthesis or stereoselective polymerization reactions. We have reported the solution- and solid-state structures of dimeric titanium(IV) alkoxide complexes of trisphenols **1a**,**b** (**2a**,**b**, **3a**, eq 1 of Scheme 1),[22] which possess structural features that encouraged us to explore their reactivity in ROP reactions. The four-coordinate titanium centers in these compounds retain one terminal alkoxide ligand, which is ideal for ROP via the coordination−insertion mechanism established for known metal alkoxide initiators (eq 2 of Scheme 1).[5,23] In addition, the trisphenolate adopts a chiral conformation when coordinated to titanium, resulting in chiral (although racemic) titanium centers. We decided to evaluate the reactivity of these complexes by investigating the ROP of LA. We

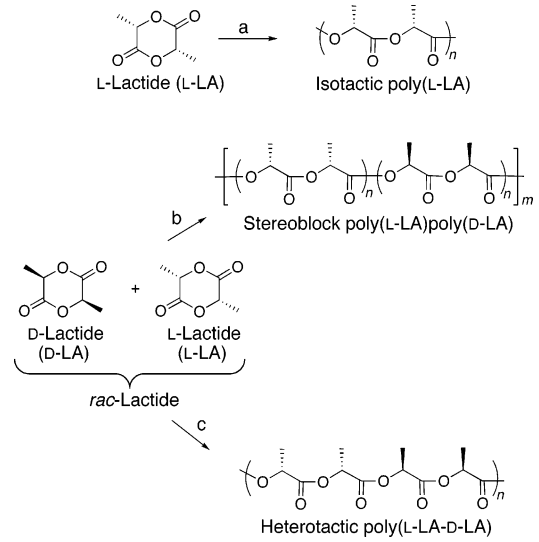
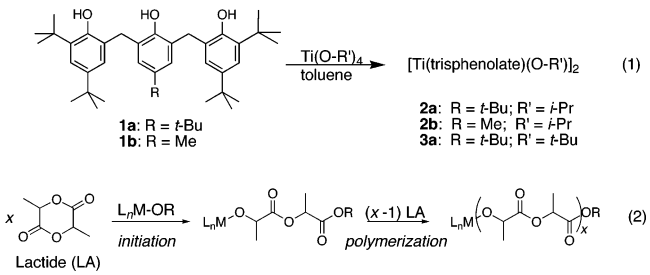


Figure 1. Stereoregular poly(lactic acid) microstructures from (a) L-lactide and (b, c) *rac*-lactide (D-lactide + L-lactide).

Scheme 1



envisioned that if the chirality at titanium were preserved under the ROP reaction conditions, *rac*-LA could polymerize with isotactic stereoselectivity via ESC.

Titanium alkoxides are attractive targets to investigate in ROP reactions because the low toxicity of titanium minimizes concerns regarding its presence in commercial PLA products. At the time that we began this work, there were no published accounts of titanium initiators for the controlled ROP of LA, although Aida, Endo, and co-workers had described similar titanium bis(phenolate)s in the controlled polymerization of ϵ-caprolactone and cyclic carbonates.[24] Subsequently, Verkade and co-workers[12] and Harada and co-workers[13] described the controlled ROP of LA using different titanium tris- and bis(phenolate)s, respectively. In this report, we describe the ROP of LA by **2a** and **2b**, which result in well-behaved catalytic systems, comparable to these recently described titanium initiators.[12,13] In addition, **2a** and **2b** show a greater degree of stereocontrol in the ROP of *rac*-LA than has been observed for previous titanium initiators.[25]

Results and Discussion

Our initial studies examined the potential of complex **2a** as a ROP initiator for LA under different reaction conditions and indicated that **2a** produces a well-controlled catalyst in solution, yielding PLA that retains the stereochemical integrity of the starting monomer. The reaction of L-LA with **2a** at 80 °C results in close to monodisperse, stereochemically pure isotactic poly-

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Table 1. Polymerization of Lactide (LA) Using 2a, 2b, or 3a as Initiator[a]

entry	initiator	monomer	solvent	concn (M)	temp (°C)	time (h)	conv[b] (%)	$M_n \times 10^{-3}$ [c]	$M_n \times 10^{-3}$ [d]	M_w/M_n[d]	P_s[e]
1	**2a**	L-LA	toluene[f]	0.63	80	312	75	10.9	24.3	1.19	
2	**2a**	*rac*-LA	CH_2Cl_2	1.00	60	72	95	13.8	20.1	1.06	0.82
3	**2a**	*rac*-LA	CH_2Cl_2	1.00	80	12	91	13.2	19.7	1.06	0.79
4	**2a**	*rac*-LA	CH_2Cl_2	1.00	100	24	92	13.3	19.9	1.07	0.81
5	**2a**	*rac*-LA	toluene[f]	1.00	60	72	96	13.9	24.1	1.10	0.80
6	**2a**	*rac*-LA	toluene[f]	1.00	80	46	96	13.9	18.5	1.10	
7	**2a**	*rac*-LA	toluene[f]	1.00	100	24	97	14.0	18.4	1.21	
8	**2b**	*rac*-LA	CH_2Cl_2	1.00	80	6	89	12.9	20.6	1.05	0.80
9	**3a**	*rac*-LA	CH_2Cl_2	1.26	80	72	87	12.6	22.6	1.69	

[a] [LA]/[Ti-O-*i*-Pr] = 100. [b] Determined by integration of the methine region in the ^{1}H NMR spectrum of the crude product. [c] Calculated using percent conversion, assuming that each isopropoxide is an initiator and that each polymer chain is terminated by a proton: (% conv) × (144.13) + (60.1) g/mol. [d] Size exclusion chromatography relative to polystyrene standards. [e] P_s is the probability of syndiotactic addition of monomers and is determined from the methine region of the homonuclear decoupled ^{1}H NMR spectrum. [f] 7:1 toluene:CH_2Cl_2.

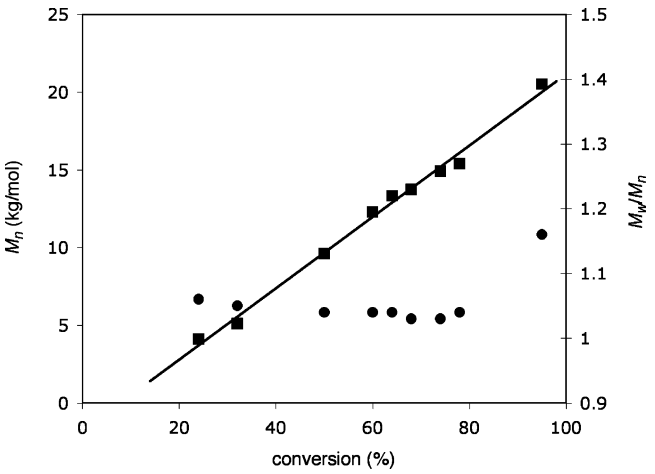

Figure 2. Plot of poly(*rac*-lactide) M_n (squares, size exclusion chromatography relative to polystyrene standards) and polydispersity (circles) as a function of conversion, with *rac*-lactide (LA) and **2a** (CH_2Cl_2, 80 °C, [LA]/[Ti-O-*i*-Pr] = 100).

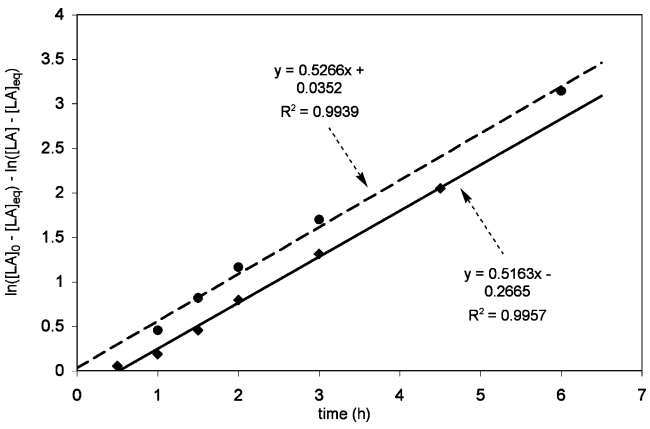

Figure 3. Semilogarithmic plot of *rac*-lactide (LA) conversion with time for initiators **2a** (diamonds) and **2b** (circles); $[LA]_0$ = 1.00 M, [LA]/[Ti-O-*i*-Pr] = 100, CH_2Cl_2, 80 °C; $[LA]_{eq}$ measured as 0.07 M. A linear least-squares fit of each data set resulted in the lines and equations shown.

mer[26] (Table 1, entry 1). Under similar conditions, *rac*-LA also yields nearly monodisperse polymer and shows a high probability for syndiotactic addition (P_s = 0.79, Table 1, entry 3),[27,28] rather than the anticipated isotactic selectivity (vide infra). Consistent with this observed stereoselectivity, *rac*-LA polymerizes in far less time than L-LA (cf. Table 1, entries 1 and 6).

After exploring several different reaction conditions for this polymerization, we concluded that changes in temperature or solvent affect the ROP rate but have very little effect on the stereoregularity or polydispersity of the resultant polymer (cf. Table 1, entries 2−4 and 5−7). At 40 °C, the rate of polymerization is very slow (i.e., trace polymerization within 24 h), while temperatures of 60−100 °C result in reasonable rates of polymerization. We routinely observe excellent polydispersities and very good stereoselectivities under the conditions described in Table 1. It appears that the molecular weight control is better in dichloromethane than in toluene, as is evidenced by the consistent M_n values and smaller PDIs in entries 2−4, as compared with entries 5−7 (Table 1). Therefore, we elected to perform further kinetic and mechanistic studies at 80 °C in dichloromethane.

The ROP of *rac*-LA using **2a** as an initiator was monitored by ^{1}H NMR spectroscopy and size exclusion chromatography (SEC) periodically over the course of the reaction, and plots of molecular weight (M_n) and PDI vs percent conversion were constructed (Figure 2).[29] The linear correlation between the polymer molecular weight and monomer conversion, coupled with very low PDIs throughout the polymerization (Figure 2), are indicative of a well-controlled polymerization. At longer reaction times (e.g., 72 h), SEC reveals a bimodal molecular weight distribution accompanied by an increase in the PDI (i.e., final data point in Figure 2), which we attribute to intermolecular chain transfer (via transesterification) reaction rates becoming significant when the polymerization rate is diminished at high conversion.[30] A semilogarithmic plot of conversion vs time for initiator **2a** shows a first-order dependence of monomer conversion on [LA], which is consistent with a coordination−insertion mechanism (Figure 3, k_{app} = 0.52 h^{-1}).[31] The plot also reveals that there is an induction period before **2a** initiates the ROP reaction (vide infra).

Evidence that the isopropoxide ligand is transferred to the end of the growing polymer chain during initiation was obtained by preparing oligomers of LA and determining their mass distribution by electrospray mass spectrometry (ESI-MS).[32] The masses of the observed ions correspond to sodium-cationized oligomers of LA, which have been initiated by the addition of O-*i*-Pr and terminated by protonation (m/z = [H(OC(H)MeC(=O))$_{2n}$O-*i*-Pr + Na]$^+$, where n = 3−13).[33] MS-MS data obtained by collisional dissociation of m/z = 803 (n = 5) reveal the loss of isopropene (m/z = 761), in addition to losses of (C(H)MeC(=O)O)$_n$ (n = 1−3, m/z = 689, 617, 545).[32]

To determine whether both of the Ti-O-*i*-Pr ligands in **2a** are initiating, we integrated the isopropoxide methyl resonances relative to the PLA methine resonances in the ^{1}H NMR spectrum of these oligomers. These measurements reveal a 12:1 ratio of LA:O-*i*-Pr

in the NMR sample, which agrees reasonably well with the 10:1 LA:Ti-O-*i*-Pr reaction stoichiometry and the results of the ESI-MS experiment. Thus, it appears that the majority of the titanium isopropoxide ligands are initiating this reaction by transfer to the carboxyl group of the first inserted LA.

The mass spectra also reveal that there is little intermolecular chain transfer occurring in the early stages of polymerization because the observed masses correspond to whole number multiples of LA. However, long reaction times (e.g., 72 h) produce lower intensity ions for masses that represent multiples of 0.5 × LA (m/z = 587, 731, 875, 1019, etc.),[32] a phenomenon that has been observed in the ROP of LA using aluminum isopropoxide initiators and attributed to intermolecular chain transfer.[34] Consistent with this observation, the stereoselectivity is unchanged through the early stages of ROP ($P_s = 0.79$ up to 12 h), but at long reaction times the polymer stereoregularity begins to erode (e.g., P_s = 0.75 at 72 h). Altogether, the evidence indicates that chain transfer reactions become important at late stages in this ROP reaction.

In addition to **2a**, we have evaluated complexes **2b** and **3a** as initiators for the ROP of *rac*-LA. We predicted that complex **3a** would be relatively slow to initiate because the transfer of the O-*t*-Bu substituent to the first inserted LA monomer would be hindered by the sterically larger alkoxide. In fact, complex **3a** yields polymer with much broader PDIs (Table 1, entry 9) and a distribution skewed toward lower molecular weight, indicating slow initiation. The overall rates of conversion are also much slower using **3a**. Together, these data confirm that initiation is more difficult with large alkoxides, which has also been observed in other metal alkoxide ROP reactions.[3]

We anticipated that initiators **2a** and **2b** would give comparable polymerization rates because the steric difference between these complexes is at a site distal to the presumed active site of catalysis. In fact, the apparent rate constant for initiator **2b** ($k_{app} = 0.53\ h^{-1}$, Figure 3) is identical (within the error of our measurements) to that of **2a**, although **2b** does not appear to require an induction period before initiating ROP (Figure 3). The ROP using initiator **2b** is also well controlled, as is evidenced by a linear correlation between molecular weight and conversion[32] and narrow PDIs at high conversion (Table 1, entry 8). The structures of **2a** and **2b** are almost identical by ^{1}H NMR spectroscopy,[22,32] so the lack of an induction period for **2b** appears to be related solely to the steric size of the *para* substituent on the central ring. However, we believe that both initiators must undergo the same kind of isomerization or reorganization process before initiating ROP because the active catalysts arising from **2a** and **2b** appear to be virtually identical; not only are the apparent rate constants for the two essentially the same, but also they show identical stereoselectivities in the ROP of *rac*-LA (Table 1, entries 3 and 8). Therefore, the induction process must simply be more facile for the smaller *para*-methyl derivative because the period of induction was not observed for initiator **2b** in our kinetic studies.

In our view, two possibilities emerge to explain these interesting results. One is that the trisphenolate ligand undergoes a conformational change during induction, such as the apparent inversion of a bridging methylene carbon, which necessitates rotations around methylene carbon−phenol carbon bonds and should be easier to achieve with a smaller *para* substituent on phenol. We have evidence that isomerization of this type occurs in these systems over a period of hours at room temperature.[22] A second possibility is that the dimeric complexes **2a** and **2b** are either dissociating to monomers or associating to form tetramers or other higher-order species. Associative processes should be faster for the less-hindered complex **2b**, and both associative and dissociative processes would require some reorganization of the ligand, which again should be faster for the less hindered trisphenolate. Although the reason for these kinetic differences is still unclear, it is remarkable that steric differences in ligands, which apparently have little effect on the metal coordination environment, significantly impact the kinetics of polymerization.

Despite these differences in induction, complexes **2a** and **2b** show the same degree of selectivity for syndiotactic addition, rather than the isotactic addition that would be more consistent with ESC. Syndiotactic preference has been commonly observed in the ROP of *rac*-LA with sterically hindered achiral initiators, arising from a CEC mechanism.[3,18,19] The degree of syndiotactic selectivity has also been shown to correlate with the increased size of the ligands at the metal center.[10,19,20] The heterotactic bias that we observe in our systems suggests that our titanium trisphenolate complexes, even though the titanium centers are formally chiral, are influencing the ROP reaction as if they were simply sterically hindered achiral catalysts. Furthermore, our kinetic studies suggest that the trisphenolate ligand may be conformationally isomerizing under the ROP reaction conditions; this makes it difficult to envision stereocontrol via ESC. Therefore, we attribute our observed stereoselectivity to CEC.

In conclusion, complexes **2a** and **2b** are initiators for the controlled polymerization of *rac*-LA, providing monodisperse PLA with a higher degree of syndiotactic addition than has been observed for other titanium initiators. The reaction shows a first-order dependence on [LA], consistent with a coordination−insertion mechanism, and the titanium isopropoxide ligand is transferred to the end of the growing polymer chain during initiation. Both complexes **2a** and **2b** have the same apparent rate constant for polymerization and show the same degree of stereoselectivity; however, reactions with **2a** have a significant (ca. 0.5 h) induction period, whereas those with **2b** do not. This difference in induction is attributed to the steric size of the *para* substituent on the central phenol ring, suggesting that a conformational isomerization of the trisphenolate ligand is necessary to produce the active catalyst. The stereoselectivity that we observe is high, although the bias toward syndiotactic addition suggests that the chirality at titanium, if it is retained under the reaction conditions, does not provide good ESC. Instead, it appears that the titanium trisphenolate complexes are enhancing the stereoselectivity analogous to sterically hindered achiral initiators, via a CEC mechanism.

Experimental Section

General. All reagents and solvents were purchased from commercial suppliers and used as received, unless noted otherwise. Anhydrous solvents were purchased in Sure/Seal bottles from Aldrich Chemical Co., transferred into an M. Braun glovebox without exposure to air, and used as received, except as specifically noted. Ethyl acetate was distilled from calcium hydride under a nitrogen atmosphere and transferred

into the glovebox without exposure to air. Lactide (L and DL) was sublimed at reduced pressure (0.1 mmHg) and recrystallized from ethyl acetate in the glovebox. Titanium complexes **2a** and **3a** were prepared as described in the literature.[22] Complex **2b** was prepared in an analogous fashion.[32]

NMR spectra were recorded on a Varian Unity Plus spectrometer operating at 400 MHz (^{1}H) in either $CDCl_3$ or C_6D_6. SEC was performed either using a Waters Breeze HPLC system equipped with a Waters 2414 refractive index detector or a Hewlett-Packard 1100 series chromatograph equipped with a Hewlett-Packard 1047A refractive index detector. Both systems were equipped with three Jordi Gel DVB columns of 10^4, 10^3, and 500 Å pore sizes, and THF was used as the mobile phase (either 35 °C (Waters) or 40 °C (H−P) at 1.0 mL/min). Column calibration was performed with polystyrene standards (Waters or Polymer Laboratories).

Polymerization Reactions. The following is a typical polymerization procedure. The anhydrous solvents used in polymerization were passed through a plug of alumina immediately prior to use. In the glovebox, a solution of DL-LA (0.721 g, 5.00 mmol) and **2a** (0.500 mL of a [Ti-O-*i*-Pr] = 0.100 M solution in CH_2Cl_2) was prepared in CH_2Cl_2 at room temperature in a 5 mL volumetric flask. This solution was divided between two pressure reaction tubes (Ace no. 8648, 15 mL), which were then introduced into an oil bath, the temperature of which was regulated to 80 ± 1 °C. After 12 h, a pressure tube was removed from the heat and cooled in an ice bath for 15 min to stop polymerization, and the reaction solution was concentrated by rotary evaporation at room temperature to an orange residue. The extent of conversion (91%) was determined by obtaining a ^{1}H NMR spectrum of the residue and integrating the methine resonances of the polymer (δ 5.10 ppm, C_6D_6) relative to the methine resonance of the monomer (δ 3.65 ppm, C_6D_6). A sample for SEC analysis was prepared by dissolving a portion of the residue in THF (3 mg/mL) and adding 2 drops of methanol (M_n = 19.708 kDa, M_w/M_n = 1.06). Stereochemical analysis was performed by analyzing the methine region of a homonuclear decoupled ^{1}H NMR spectrum of the polymer ($CDCl_3$, P_s = 0.79).[28,35] The polymer was precipitated in methanol at 0 °C (83% yield). ^{1}H NMR (C_6D_6) δ: 5.11 (m, 1 H), 1.40 (m, 2 H), 1.29 (m, 1 H).

Kinetic Studies. The following is a typical procedure for determining the conversion, M_n, and PDI during the course of the polymerization reaction. The general conditions for setting up polymerization reactions were identical to those described above. A CH_2Cl_2 solution of DL-lactide (1.00 M) and initiator **2a** ([Ti-O-*i*-Pr] = 0.0100 M) was prepared in a 10 mL volumetric flask and divided approximately equally among 10 pressure reaction tubes. The reaction tubes were removed from the glovebox and arrayed in a temperature-controlled (80 ± 1 °C) oil bath. At specified time intervals, tubes were removed from the oil bath and cooled to 0 °C for 10 min, after which the solutions were concentrated to orange residues. The residues were analyzed by ^{1}H NMR spectroscopy to determine conversion, as described above. Samples for SEC were prepared as described above. Plots of M_n and PDI vs conversion and semilogarithmic plots of conversion vs time for initiators **2a**, **2b**, and **3a** were obtained. Since this ROP reaction is reversible, the logarithmic expression, $(\ln([LA]_0 - [LA]_{eq}) - \ln([LA] - [LA]_{eq}))$, was used for the kinetic plots. The equilibrium concentration, $[LA]_{eq}$, was determined to be 0.07 M at 80 °C and $[LA]_0$ = 1.0 M.[36]

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Supporting Information Available: Figures S1−S4 and additional experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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