Stereoselective Ring-Opening Polymerization of *rac*-Lactide with a Single-Site, Racemic Aluminum Alkoxide Catalyst: Synthesis of Stereoblock Poly(lactic acid)

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ABSTRACT: The polymerization of racemic lactide with a racemic aluminum alkoxide catalyst is reported. Microstructural analysis of the polymer produced with ^{1}H NMR spectroscopy revealed that an isotactic stereoblock poly(lactic acid) formed, where each enantiomerically pure block contained an average of 11 lactide monomer units. The melting point of this polymer, 179 °C, was higher than that of the enantiomerically pure polymer, consistent with the cocrystallization of the enantiomeric blocks of the polymer. The mechanism of the polymer formation is currently unknown, although a polymer exchange pathway, where living chain ends switch between metal centers to produce diastereomeric active species, is proposed. © 2000 John Wiley & Sons, Inc. J Polym Sci A: Polym Chem 38: 4686–4692, 2000

Keywords: isotactic; stereoblock; ring-opening polymerization; poly(lactic acid); lactide

INTRODUCTION

Stereochemistry is one of the most critical factors determining the physical and mechanical properties of a polymeric material. Polymers that have stereocenters in the repeat unit can exhibit two structures of maximum order, isotactic and syndiotactic. Sequential stereocenters of isotactic polymers are of the same relative stereochemistry, whereas those of syndiotactic polymers are of the opposite relative configuration. Because of their stereoregularity, isotactic and syndiotactic polymers are typically crystalline, an important feature for many applications. One of the most promising methodologies for the synthesis of stereoregular polymers is the design and implementation of single-site catalysis.[1] Single-site catalysts are homogeneous, molecular compounds that have the general formula L_nMR, where L_n is a ligand set that remains attached to and thus modifies the reactivity of the active metal center (M) during the entire chemical reaction and R is a group that can initiate polymerization. Through ligand design, homogeneous catalysts are now available that can control polymer molecular weights, molecular weight distributions (MWDs), comonomer incorporation, and stereochemistry in ways that are impossible with conventional heterogeneous catalysts. Although remarkable advances have been reported concerning the development of molecular catalysts for olefin polymerization, comparatively few single-site metal catalysts are available for the ring-opening polymerization of heterocycles such as epoxides and lactones.[2–15]

Poly(lactic acid)s (PLAs) have many potential medical, agricultural, and packaging applications because of their biocompatibility and biodegradability.[16] A convenient synthetic route to these polymers is the ring-opening polymerization of lactide, the cyclic diester of lactic acid. The stereochemistry of the polymers determines their me-

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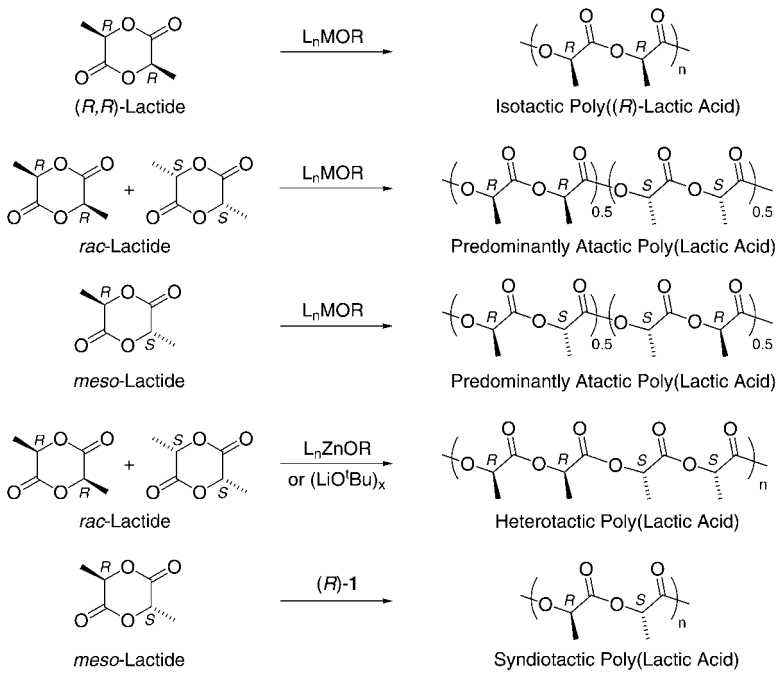


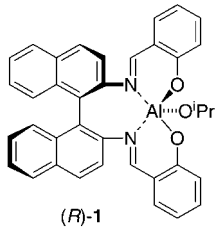
Scheme 1

chanical and physical properties as well as their rates of degradation; therefore, the synthesis of new PLA microstructures is a significant scientific goal. A range of metal alkoxide initiators has been reported to polymerize lactide with retention of configuration (Scheme 1). For example, the polymerization of optically active (*R,R*)-lactide or (*S,S*)-lactide with typical aluminum tris(alkoxide)[17,18] or tin bis(carboxylate)[19] catalysts yields isotactic PLA. The polymerization of *rac*-lactide or *meso*-lactide with these catalysts produces polymers that are effectively atactic (i.e., *rac*-lactide yields polymers with the random placement of -*RR*- and -*SS*- configured units, whereas *meso*-lactide yields polymers with the random placement of -*RS*- and -*SR*- configured units). We recently reported the synthesis of heterotactic PLA from *rac*-lactide with a single-site β-diiminate zinc alkoxide catalyst that controls stereochemistry by a chain-end control mechanism;[4] Kasperczyk et al.[20,21] reported a similar result by employing lithium *t*-butoxide aggregates. We also reported the synthesis of syndiotactic PLA from *meso*-lactide with an enantiomerically pure aluminum-based catalyst [(*R*)-**1**] that controls stereochemistry by an enantiomorphic site-control mechanism (Fig. 1).[3] A remaining synthetic target is the synthesis of isotactic PLA directly from *rac*-lactide, where both enantiomers of the monomer are simultaneously incorporated into poly(*R*)-segments and poly(*S*)-segments. Such a polymer would be of interest for several reasons. First, *rac*-lactide is an inexpensive monomer, and second, the polymer is expected to have an unusually high melting point (T_m) because of the cocrystallization of the enantiomeric polymer sequences. Herein, we report the synthesis of an isotactic stereoblock PLA that contains both poly(*S*)-segments and poly(*R*)-segments in the main chain.

RESULTS AND DISCUSSION

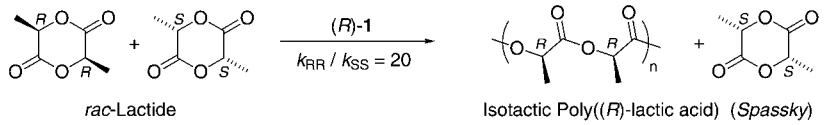
Polymerization of *rac*-Lactide with an Enantiomerically Pure Catalyst

In 1996, Spassky et al.[6] reported the kinetic resolution of *rac*-lactide with the methoxide variant



(*R*)-**1**

Figure 1. (*R*)-**1**.

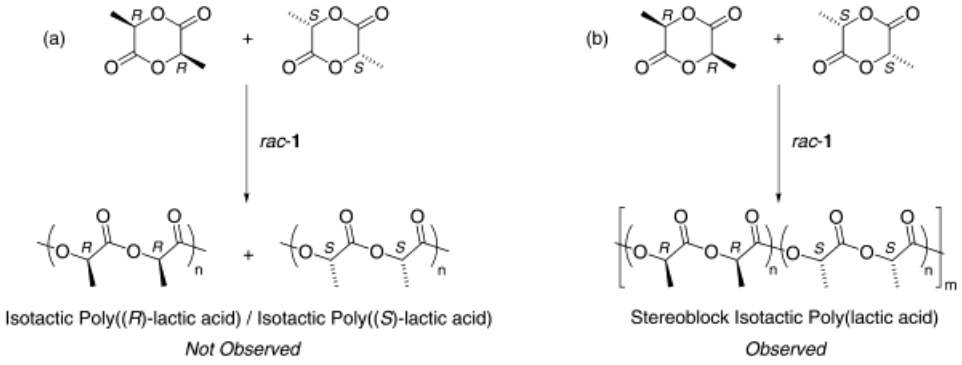


Scheme 2

of (*R*)-**1** (Scheme 2). At 70 °C, the catalyst was highly selective and preferentially polymerized (*R,R*)-lactide over the (*S,S*)-enantiomer with a relative rate ratio of 20. Furthermore, the molecular weight of the resultant polymer was controlled by the monomer/catalyst ratio, and the MWD was narrow, consistent with a living polymerization. When the polymerization of *rac*-lactide was carried out to less than a 50% conversion, the resultant polymer was predominantly isotactic poly[(*R*)-lactic acid]. After approximately 60% conversion, only (*S,S*)-lactide remained, and the reaction only slowly approached 100% conversion because of the kinetic preference for the *R,R*-enantiomer. The high-melting material (T_m = 187 °C) that formed presumably had a tapered stereoblock microstructure, where the monomer composition varied from *R*-units to *S*-units over the length of the polymer chain. Enantiomeric isotactic polylactic acids (T_m = 175 °C)[22] form a stereocomplex (T_m = 230 °C)[23–26] when mixed in a 1/1 ratio. Thus, this tapered stereoblock polymer could presumably adopt a similar morphology in the crystalline state, resulting in the high T_m.

Polymerization of *rac*-Lactide with a Racemic Catalyst

Although the polymerization of *rac*-lactide with (*R*)-**1** yielded a tapered stereoblock PLA, a drawback of that strategy was that the polymer produced had a T_m much lower than the theoretical maximum (230 °C). This was presumably due to a gradient of stereogenic centers in the main chain. To sharpen the stereochemical transition between enantiomeric blocks, it is necessary to either (1) carry out the sequential polymerization of (*R,R*)-lactide/(*S,S*)-lactide with an achiral, living catalyst[22] or (2) use a more selective catalyst for the kinetic resolution of *rac*-lactide. The former approach has the drawback that (*R,R*)-lactide is very expensive relative to the *S,S*-enantiomer. In the latter strategy, an increase in the magnitude of the propagation rate constant of the preferred enantiomer relative to that of the disfavored enantiomer will dramatically lengthen the reaction time if the rate constant of the preferred enantiomer is held constant. An alternate approach to a high melting stereocomplex PLA is the polymerization of *rac*-lactide to form enantiomerically pure isotactic chains [Scheme 3(a)]. Following our research concerning syndiotactic PLA, we reasoned that the polymerization of *rac*-lactide with the racemic form of **1** (*rac*-**1**) might yield enantiomerically pure isotactic chains, where (*R*)-**1** would form poly((*R*)-lactic acid), (*S*)-**1** would form poly((*S*)-lactic acid), and together the chains would form a stereocomplex. Preliminary experiments with *rac*-**1** to polymerize *rac*-lactide produced a highly crystalline, predominantly isotactic material, apparently consistent with Scheme 3(a). However, a recent article by Radano et al.[27] prompted us to reevaluate these experiments.



Scheme 3

Radano et al. reported that *rac*-**1** polymerized *rac*-lactide to give enantiomerically pure chains, as pictured in Scheme 3(a). We propose here that enantiomerically pure chains are not formed. Instead, a novel stereoblock PLA is the product [Scheme 3(b)]. In the following section, the synthesis, microstructural analysis, and possible mechanisms of the formation of this polymer architecture are described.

rac-Lactide was polymerized at 70 °C with *rac*-(**1**) ([monomer]/[Al] = 100) at 70 °C. The resultant polymer, **2**, exhibited a peak T_m at 179 °C, which was higher than the reported T_m of enantiomerically pure PLA. The polymer was analyzed by gel permeation chromatography (GPC), revealing a number-average molecular weight of 22,600 and an MWD of 1.09. The correlation between the predicted and observed molecular weights and the narrow MWD is consistent with a living polymerization. The formation of enantiomerically pure PLA chains [Scheme 3(a)] can only occur if there is no transesterification between enantiomeric chains during the polymerization. The narrow MWD of the polymer in fact suggests there was no significant transesterification. However, Scheme 3(a) precludes the possibility of polymer exchange between catalyst centers of opposite configurations. Such an exchange would not manifest a broadening of the polymer molecular weight, as the chains would not be lengthened or shortened. Because the stereochemical impurities of the polymer serve as a structural recording of the mechanism of the polymerization reaction, we decided to look in detail at the microstructure of polymer **2**.

Figure 2 shows the methine resonances of the homonuclear decoupled ^{1}H NMR spectrum of **2** formed from *rac*-lactide with *rac*-**1** at 70 °C. The peaks were assigned to the appropriate tetrads in accordance with the shifts reported by Munson and Thakur.[28–30] The intensities of the rmm, mmr, and mrm tetrads are approximately equal, with a small rmr peak near 5.22 ppm. The mmm tetrad is the predominant peak in the spectrum. Scheme 4 shows two mechanistic pathways that account for the stereoerrors present in the spectrum. The stereoerror pathway, where the disfavored enantiomer is only occasionally incorporated into the enantiomerically pure chains, yields mmr, mrm, rmr, and rmm impurities in the polymer with a predicted 1/2/1/1 ratio. In contrast, the polymer exchange model introduces only the mmr, mrm, and rmm impurities in a 1/1/1 ratio. An inspection of Figure 2 reveals the

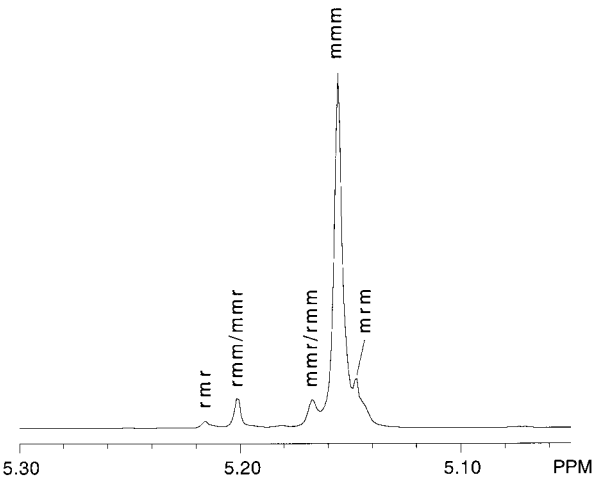
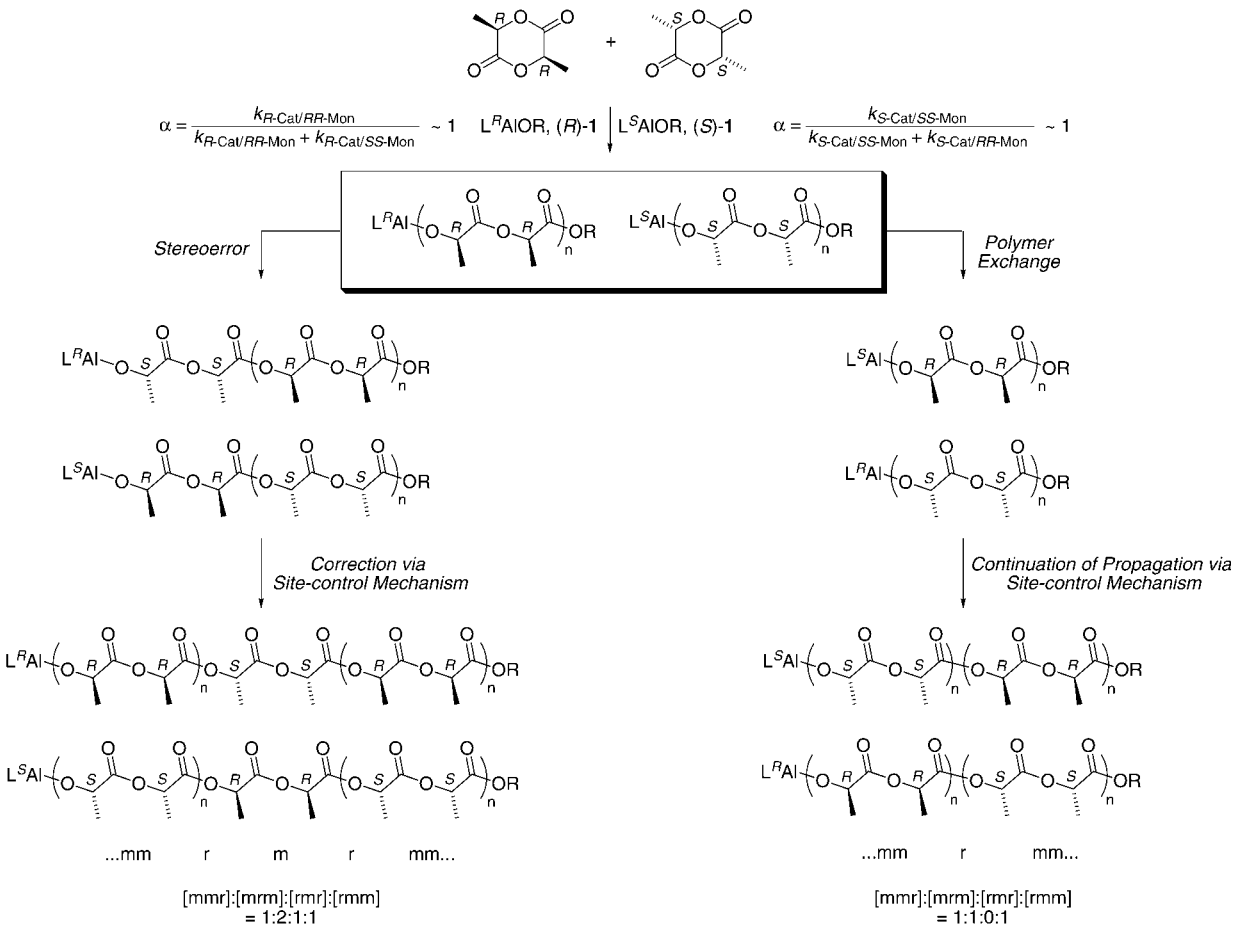


Figure 2. Homonuclear decoupled ^{1}H NMR spectrum of the methine region of PLA prepared with *rac*-**1**/*rac*-lactide at 70 °C (500 MHz, $CDCl_3$).

virtual absence of the rmr tetrad, consistent with the polymer exchange pathway as the major source of stereochemical impurities in the polymer. The rmr peak is clearly present though, suggesting that a relatively small amount of polymerization of the disfavored monomer stereoisomer occurred. The spectrum of **2** was simulated with a statistical model that included both stereoerror and polymer exchange mechanisms to introduce stereochemical defects into the polymer. The difference between the simulated and experimental spectra was minimized when the catalyst exhibited a site-control selectivity[31] (α) of 0.98 and the stereoblocks contained an average of 11 units (n) of enantiomerically pure lactide. Thus, the best depiction of polymer **2** is a stereoblock polymer, where consecutive sequences of *R* and *S* centers are present in the polymer backbone. Because of the high stereoselectivity of the catalyst, the stereoblocks of **2** were essentially free of defects. An alternate explanation is that polymer exchange occurs following stereoerror formation. The mechanism of the formation of this stereoblock polymer is not certain at the current time; however, the polymer exchange model clearly fits the observed spectrum. Therefore, we favor the polymer structure where average block lengths of the enantiomeric segments are equivalent (Scheme 3b); however, other structures (e.g., … *SSSSSRRRRSSSSS* …) are possible. Subsequent work in our laboratory will investigate whether alcoholysis by trace amounts of protic impurities or exchange through μ-alkoxide or ionic species are responsible for the formation of this polymer microstructure.[10]



Scheme 4

In conclusion, we report the polymerization of *rac*-lactide with a racemic aluminum alkoxide catalyst to yield an isotactic stereoblock PLA. The T_m of this polymer was higher than that of the enantiomerically pure polymer, which was likely due to the cocrystallization of the enantiomeric blocks of the polymer. A preliminary microstructural analysis suggested that the blocks of the polymer contained on average 11 lactide units and that the kinetic selectivity of the catalyst was 0.98. The mechanism of the formation of the polymer is currently unknown, although a polymer exchange pathway is proposed where living chain ends switch between metal centers to produce diastereomeric active species. This strategy holds significant promise as a new strategy for not only the synthesis of stereoblock polymers but also block polymers in general where polymer chains can undergo exchange between active species with differing propagation characteristics.

EXPERIMENTAL

General Considerations

All reactions with air-sensitive compounds, water-sensitive compounds, or air-sensitive and water-sensitive compounds were carried out under dry nitrogen with a Braun Labmaster drybox or standard Schlenk line techniques. NMR spectra were recorded on Bruker AF300 (^{1}H, 300 MHz) and Varian UNITY (^{1}H, 500 MHz) spectrometers and were referenced versus residual nondeuterated solvent shifts. GPC analyses were carried out with a Waters instrument (M510 pump, U6K injector) equipped with Waters UV486 and Milton Roy differential refractive index detectors and four 5-μL PL gel columns (Polymer Laboratories; 100 Å, 500 Å, 1000 Å, and mixed C porosities) in series. The GPC columns were eluted with tetrahydrofuran at 45 °C at 1 mL/min and were calibrated with

23 monodisperse polystyrene standards. Differential scanning calorimetry (DSC) analyses were performed on a Seiko DSC 220C instrument with EXSTAR 6000 processing software. The measurements were made in aluminum crimped pans under nitrogen with a heating rate of 10 °C/min. The reported values originated from the second heating scan. Elemental analysis was performed by Galbraith Laboratories.

Materials

Toluene was distilled from sodium benzophenone ketyl; residual gases were removed with a freeze–pump–thaw technique. *rac*-Lactide was purchased from Purac and used without further purification. Aluminum isopropoxide (Strem) was distilled under vacuum immediately before use. The ligands (*R*)-SalBinapH_2 and (*S*)-SalBinapH_2 were synthesized according to a published procedure.[32] All other chemicals were commercially available and used as received.

Complex Synthesis

[(*R*)-(SalBinap)AlO^{i}Pr] [(*R*)-1]

In a glove box, a dry Schlenk tube was loaded with freshly distilled aluminum isopropoxide (0.137 g, 0.671 mmol), (*R*)-SalBinapH_2 (0.329 g, 0.668 mmol), and toluene (10 mL). The mixture was heated to 70 °C and stirred for 2 days. The solvent was removed *in vacuo*, yielding a yellow solid. Despite repeated attempts, we were unable to crystallize the complex, and NMR clearly revealed that impurities or multiple aggregation states were present.

^{1}H NMR (tol-d_8, 300 MHz, δ): 7.92 (1H, s), 7.76 (2H, d, J = 4.3), 7.68 (2H, t), 7.43 (4H, d, J = 8.6), 7.31 (4H, t), 7.18 (2H, t), 6.90–7.14 (18H, m), 6.53 (1H, d, J = 8.6), 6.42 (1H, d, J = 7.5), 6.28–6.36 (2H, m), 6.23 (2H, t), 4.08 (1H, m), 1.34 (3H, d, J = 6.4), 0.71 (3H, d, J = 5.9). ELEM. ANAL. Calcd. for $C_{37}H_{29}AlN_2O_3$: C, 77.07%; H, 5.07%; N, 4.86%. Found: C, 76.37%; H, 5.34%; N, 4.50%.

[(*S*)-(SalBinap)AlO^{i}Pr] [(*S*)-1]

The method described for (*R*)-**1** was used for the synthesis of (*S*)-**1**.

Polymer Synthesis

The following is a representative procedure using *rac*-(SalBinap)AlO^{i}Pr (*rac*-**1**) and *rac*-lactide: In the drybox, a dry Schlenk tube was loaded with (*R*)-**1** as a 0.0106 M solution in toluene (0.657 mL, 0.0069 mmol), (*S*)-**1** as a 0.0117 M solution in toluene (0.592 mL, 0.0069 mmol), *rac*-lactide (0.199 g, 1.38 mmol), and toluene (6 mL). The flask was heated to 70 °C and stirred for 40 h. The reaction was quenched via rapid cooling with liquid N_2. The solvent was removed *in vacuo*, and the polymer was dissolved in CH_2Cl_2 and precipitated from cold MeOH. The white crystalline solid was isolated and dried *in vacuo* to a constant weight, with an isolated yield of 0.1985 g.

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