1552 *J. Am. Chem. Soc.* **2000,** *122,* 1552−1553

Stereoselective Polymerization of a Racemic Monomer with a Racemic Catalyst: Direct Preparation of the Polylactic Acid Stereocomplex from Racemic Lactide

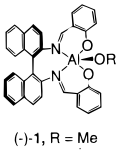
Christopher P. Radano, Gregory L. Baker,* and
Milton R. Smith, III*

Department of Chemistry, Michigan State University
East Lansing, Michigan 48824

Received August 23, 1999

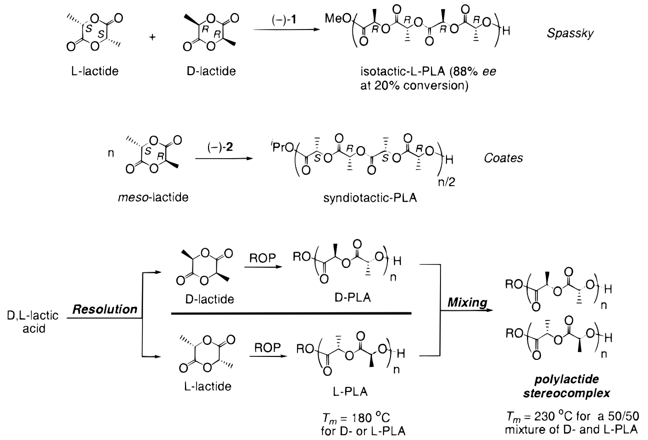
Polylactic acid (PLA) is an attractive polymer because it can be derived from renewable resources and provides a biodegradable alternative to polymers obtained from petrochemical sources.[1] PLA is prepared by the ring opening polymerization (ROP) of lactide, the cyclic dimer of lactic acid. Commercial polylactides usually are synthesized from lactide monomers prepared from a single lactic acid enantiomer, and because the resulting polymers are stereoregular, they have high degrees of crystallinity.[2] The mechanical properties of crystalline polymers are stable to near the polymer melting point, and thus they have higher use temperatures than their amorphous analogues. For example, polymerization of L-lactide gives a semicrystalline polymer with a melting transition near 180 °C and $T_g \sim 67$ °C,[3] properties that make it useful for applications ranging from degradable packaging to surgical implants and matrices for drug delivery.[4] In contrast, the polymer derived from *rac*-lactide, a 1:1 mixture of D- and L-lactide, yields amorphous polymers with glass transitions near room temperature. Although L-lactide can be prepared with relatively high enantiopurity from corn fermentation, the requirement for an enantiopure monomer places restrictions on the polymer synthesis.

As shown in Scheme 1, chiral catalysts have been employed to effect kinetic resolution of racemic lactide. Spassky et al. have reported kinetic resolutions of *rac*-lactide by employing a chiral Schiff's base complex of aluminum, (−)**1**.[5] At low conversions high enantiomeric enrichment in the polymer is observed.[6] This finding is significant because the catalyst overrides the tendency for syndiotactic placements that are typically favored by chain-end control.[7] At higher conversions the enantiomeric enrichment in the polymer decreases. The drop in selectivity can be attributed to the fact that the relative concentration of the "wrong" isomer increases in the monomer pool as the desired enantiomer is incorporated in the polylactide. In a recent report, Coates et al. effected the syndiotactic polymerization of *meso*-lactide by using the isopropoxide catalyst (−)-**2**.[8] Since *meso*-lactide possesses two stereocenters of opposite configuration, the concentration of D and L stereocenters remains constant and the intrinsic selectivity of the catalyst is not diminished by statistical depletion of the preferred stereocenter.



(-)-**1**, R = Me
(-)-**2**, R = ^{i}Pr

Scheme 1



An interesting effect of stereoregularity on lactide properties was first reported by Tsuji and co-workers.[9−11] As shown in Scheme 1, L-PLA and D-PLA form a stereocomplex that has a T_m 50 °C higher than the T_m for the homochiral polymers. Preparation of this stereocomplex presently requires parallel ROP of D- and L-lactide with subsequent combination of the chiral polylactide chains. Despite its improved mechanical properties, practical applications of the stereocomplex are prohibited by the requirement that separate pools of enantiopure lactide monomers must be polymerized to enantiopure polymers. If the same material could be prepared from the *rac*-lactide, it is conceivable that applications of the stereocomplex could be realized.

Spassky's and Coates' results in stereoselective ROP of lactides suggests a strategy for the direct preparation of the polylactide stereocomplex from *rac*-lactide. Specifically, the racemic catalyst, *rac*-**2**, should lead to parallel syntheses of isotactic D-PLA and L-PLA chains since (−)-**2** preferentially polymerizes D-lactide and (+)-**2** preferentially polymerizes L-lactide. In contrast to kinetic resolution of *rac*-lactide with (−)-**1**, the D:L ratio in the monomer pool should remain constant at high conversion since polymerization by the racemic catalyst will remove D and L isomers at equal rates. Thus, the high enantioselectivity that is realized at low conversion in kinetic resolutions using chiral **1** should be maintained at high conversion with *rac*-**1** to give a 1:1 mixture of isotactic chains (Scheme 2).

Polymerization of *rac*-lactide with *rac*-**2** yields nearly monodisperse chains ($M_w/M_n = 1.05$) consistent with a "living" polymerization and the absence of transesterification. This is supported by the linear relationship between the monomer conversion to polymer and M_n.[12−14] More importantly, the ^{1}H NMR spectrum (Figure 1a) is consistent with formation of chains

---

* Corresponding authors. Email: bakerg@pilot.msu.edu and smithmil@msu.edu.

[1] Sinclair, R. G. *J. Macromol. Sci. Pure Appl. Chem.* **1996**, *A33*, 585−597.

[2] Huang, J.; Lisowski, M. S.; Runt, J.; Hall, E. S.; Kean, R. T.; Buehler, N.; Lin, J. S. *Macromolecules* **1998**, *31*, 2593−2599.

[3] Zhang, X. C.; Goosen, M. F. A.; Wyss, U. P.; Pichora, D. *J. Macromol. Sci. Rev. Macromol. Chem. Phys.* **1993**, *C33*, 81−102.

[4] Hollinger, J. O. *Biochemical Applications of Synthetic Degradable Polymers*; CRC Press: Boca Raton, FL, 1995.

[5] Spassky, N.; Wisniewski, M.; Pluta, C.; LeBorgne, A. *Macromol. Chem. Phys.* **1996**, *197*, 2627−2637.

[6] In the kinetic resolution of *rac*-lactide by (−)-**1**, the enantiomeric excess at 20% conversion is 88%.[5] By integration of the NMR spectrum in Figure 1a, we observe similar selectivity (∼ 90%) for isotactic placement of D- and L-lactide units.

[7] Thakur, K. A. M.; Kean, R. T.; Hall, E. S.; Kolstad, J. J.; Munson, E. J. *Macromolecules* **1998**, *31*, 1487−1494.

[8] Ovitt, R. M.; Coates, G. W. *J. Am. Chem. Soc.* **1999**, *121*, 4072−4073.

[9] Ikada, Y.; Jamshidi, K.; Tsuji, H.; Hyon, S. H. *Macromolecules* **1987**, *20*, 904−906.

[10] Tsuji, H.; Horii, F.; Hyon, S. H.; Ikada, Y. *Macromolecules* **1991**, *24*, 2719−2724.

[11] Brizzolara, D.; Cantow, H. J.; Diederichs, K.; Keller, E.; Domb, A. J. *Macromolecules* **1996**, *29*, 191−197.

[12] Penczek, S.; Kubisa, P.; Szymanski, R. *Makromol. Chem. Rapid. Commun.* **1991**, *12*, 77−80.

[13] Matyjaszewski, K. *Macromolecules* **1993**, *26*, 1787−1788.

[14] Matyjaszewski, K.; Grimaud, T. *Polym. Prepr. (Div. Polym. Chem. Am. Chem. Soc.)* **1997**, *38* (1), 456−457.

10.1021/ja9930519 CCC: $19.00

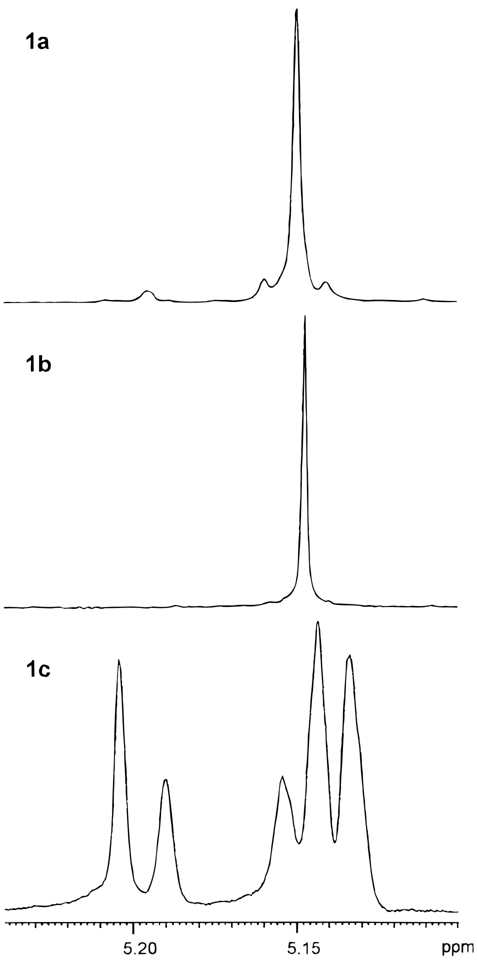
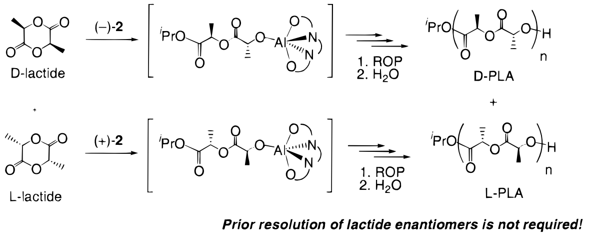


Figure 1. ^{1}H NMR spectra (500 MHz in $CDCl_3$) of PLA methine resonances with selective decoupling of PLA methyl resonances: (a) *rac*-PLA prepared by ROP of *rac*-lactide by *rac*-**2**, (b) L-PLA prepared by ROP of L-lactide by *rac*-**2**, and (c) *rac*-PLA prepared by ROP of *rac*-lactide with Sn(octanoate)$_2$.

Scheme 2



Prior resolution of lactide enantiomers is not required!

that are predominantly isotactic. Two separate control experiments were performed to confirm the tacticity. In the first control experiment, L-lactide was polymerized with the same catalyst batch used to generate the *rac*-PLA. The NMR spectrum of this sample (Figure 1b) demonstrates that epimerization of the lactide monomer does not occur under the experimental conditions. In the second control experiment, *rac*-lactide was polymerized with an achiral catalyst. The homonuclear decoupled spectrum of the methine region, shown in Figure 1c, is similar to that recently reported by Thakur et al. where assignments for various tetrad and hexad stereochemistries have been made.[15] Comparable spectra of and L-PLA are shown in Figures 1a and 1b, respectively. Clearly, the spectrum of *rac*-PLA derived from *rac*-**2** closely resembles the spectrum of L-PLA. This is significant since it confirms the formation of predominantly isotactic chains in the polymerization of *rac*-lactide by *rac*-**2**. The chemical shift for the methine resonance in spectrum b, Figure 1, is consistent with the chemical shift for the **iii** tetrad in c, Figure 1. It is clear from the NMR data that the sample in Figure 1a has a small percentage of **iiisi** hexads that are absent in the sample in Figure 1b.[16] Thus, the stereoselectivity in the ROP of *rac*-lactide by *rac*-**2** yields polymers that have enantiopurities slightly less than that of L-PLA.

The polymers that correspond to the spectra in Figure 1 were characterized by differential scanning calorimetry (DSC). For L-PLA prepared by ROP of L-lactide by *rac*-**2**, the glass, melting, and crystallization temperatures ($T_g = 55$ °C, $T_m = 170$ °C, $T_c = 91$ °C) were comparable to those for samples described in the literature. In addition, the ΔH_{fus} (65 J/g) indicates the sample has a degree of crystallinity of ≈65%.[2] *rac*-PLA prepared using *rac*-**2** has a similar glass transition ($T_g = 55$ °C), but has significantly higher melting and crystallization temperatures ($T_m = 191$ °C, $T_c = 101$ °C). For *rac*-PLA the ΔH_{fus} (42 J/g) indicates a significant degree of crystallinity (≈42%).[17] These results are remarkable. Normally amorphous materials result when *rac*-lactide is polymerized due to random placement of the D and L-lactide units in the individual PLA chains. Small amounts of a minor enantiomer can have deleterious effects on polymer properties when enantioenriched monomers are polymerized with achiral catalysts.[18]

The surprisingly high crystallinity in the *rac*-PLA sample can be explained by two models for the crystalline phase of *rac*-PLA: the formation of the stereocomplex, or a 1:1 mixture of crystalline domains of L-PLA and D-PLA. These two models can be easily distinguished by powder X-ray diffraction because of the large difference in the scattering profiles for the stereocomplex and for L-PLA.[11,19] The diffraction pattern of *rac*-PLA corresponding to the NMR spectrum in Figure 1a matches that of the stereocomplex, confirming that we directly obtained the stereocomplex from the polymerization.[20] The difference between the T_m for the stereocomplex prepared from *rac*-lactide and *rac*-**2** and the T_m for the stereocomplex prepared from enantiopure D- and L-PLA[9] reflects a lower degree of isotacticity in the individual chains in our *rac*-PLA sample.[18,21] Improvements in the polymerization scheme for *rac*-PLA should lead to higher enantiopurities and melting points that approach those of stereocomplexes prepared by mixing enantiopure samples of D-PLA and L-PLA.

Acknowledgment. We appreciate support from the Center for Fundamental Materials Research and the Crop and Food Bioprocessing Center at Michigan State University.

Supporting Information Available: Experimental details for catalyst synthesis, polymerization conditions, and polymer characterization (PDF). This material is available, free of charge, via the Internet at http://pubs.acs.org.

JA9930519

---

(15) Thakur, K. A. M.; Kean, R. T.; Zell, M. T.; Padden, B. E.; Munson, E. J. *Chem. Commun.* **1998**, 1913−1914.

(16) The slight deviations in chemical shifts for the resonance for the **iii** tetrad between our work and that reported by Thakur (δ 5.14 vs δ 5.17) likely arise from deviations in field strength between spectrometers.

(17) In polymerizations of lactide with an achiral Schiff's base aluminum alkoxide, $\Delta H_{fus} = 10$ J/g for samples that are 40% enriched in a particular enantiomer. When *rac*-lactide was polymerized using the same catalyst, there was no evidence for crystalline domains and the melting point of the PLA ($T_m \approx 150$ °C) is considerably lower than we find for the stereocomplex: Wisniewski, M.; LeBorgne, A.; Spassky, N. *Macromol. Chem. Phys.* **1997**, *198*, 1227−1238.

(18) Polymerization of L-lactide with 70% optical purity gives PLA with no crystallinity: Sarasua, J. R.; Prud'homme, R. E.; Wisniewski, M.; Le Borgne, A.; Spassky, N. *Macromolecules* **1998**, *31*, 3895−3905.

(19) X-ray powder diffraction is diagnostic for the formation of the lactide stereocomplex, as well as crystalline domains of D- or L-lactide.[11, 18] Peaks for the latter case are absent in Figure 2.

(20) The powder pattern is available in the Supporting Information.

(21) When *rac*-lactide is polymerized by *rac*-**2** at higher temperatures, the NMR spectra reflect a degree isotacticity that is intermediate between that in Figures 1a and 1c. However, T_m and T_c were not observed for the resulting polymer. This highlights the sensitivity of T_m and T_c with respect to changes in tacticity.