Single-Site Catalysts for Ring-Opening Polymerization: Synthesis of Heterotactic Poly(lactic acid) from *rac*-Lactide

Ming Cheng, Athula B. Attygalle, Emil B. Lobkovsky, and
Geoffrey W. Coates*

*Department of Chemistry and Chemical Biology
Baker Laboratory, Cornell University
Ithaca, New York 14853-1301*

Received July 29, 1999

Single-site catalysts are revolutionizing polymer synthesis. These homogeneous, molecular compounds 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, comonomer incorporation, and stereochemistry in ways that are impossible using conventional hetereogeneous catalysts. Although remarkable advances have been reported concerning the development of molecular catalysts for olefin polymerization,[1,2] comparatively few single-site metal catalysts are available for the ring-opening polymerization of heterocycles such as epoxides and lactones.[3] Herein we report the synthesis of a zinc alkoxide complex that acts as a single-site catalyst for the synthesis of heterotactic poly-(lactic acid).

Poly(lactic acid)s (PLAs) have many potential medical, agricultural, and packaging applications due to their biocompatibility and biodegradability.[4] A convenient synthetic route to these polymers is the ring-opening polymerization of lactide, the cyclic diester of lactic acid.[5] A range of metal alkoxide initiators has been reported to polymerize lactide with retention of configuration.[6] For example, the polymerization of optically active (*R,R*)-lactide yields isotactic PLA, while polymerization of *meso*-lactide using an optically active initiator can produce syndiotactic PLA.[3a] Polymerization of *rac*-lactide (**1**) typically produces amorphous, atactic polymers. We have recently reported the synthesis of single-site *β*-diiminate zinc complexes that are highly active for the copolymerization of epoxides and carbon dioxide,[3b] as well as the polymerization of optically active lactides.[7] Due to the significant steric bulk of the ligands, we anticipated that these initiators might be capable of stereochemical control in the

Scheme 1
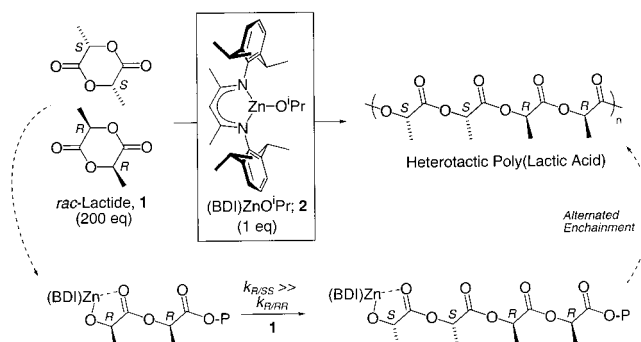
polymerization of *rac*-lactide via a chain-end control mechanism.[8] In such a reaction, the bulky ligands increase the influence of the stereogenic center of the last inserted monomer, which in turn determines whether (*R,R*)- or (*S,S*)-lactide is enchained. Therefore two scenarios are possible: if a chain end of *R* stereochemistry selects (*R,R*)-lactide (meso enchainment; $k_{R/RR} \gg k_{R/SS}$), then isotactic PLA forms; if this chain end selects (*S,S*)-lactide (racemic enchainment; $k_{R/SS} \gg k_{R/RR}$), then heterotactic[9] PLA forms (Scheme 1). Although stereocontrol of this type is conceptually very simple, only a modest degree of chain-end control during lactide polymerization has previously been reported.[10,11]

Reaction of $Zn(N(TMS)_2)_2$ with the 2,6-diisopropylphenyl-substituted *β*-diimine ligand ((BDI)H) produces the zinc complex $[(BDI)ZnN(TMS)_2]$ in quantitative yield. Although this complex slowly initiates the polymerization of lactide, we decided to transform the sterically bulky amido group of this complex into an isopropoxide group that would be a more suitable mimic of the putative propagating alkoxide species (Scheme 1). Reaction of $[(BDI)ZnN(TMS)_2]$ with 2-propanol produces the desired complex $[(BDI)ZnO^iPr]$ (**2**) in 54% isolated yield following crystallization. The molecular structure of **2**, determined by X-ray diffraction, reveals a dimeric species in the solid state where isopropoxide ligands bridge distorted tetrahedral zinc centers (Figure 1).[12]

Compound **2** is highly active for the polymerization of *rac*-lactide (**1**); in 20 min at 20 °C, **2** polymerized **1** to 95% conversion ($[\mathbf{2}] = 2.1 \times 10^{-3}$ M, $[\mathbf{1}]/[\mathbf{2}] = 200$). Gel-permeation chromatography (GPC, versus polystyrene standards) revealed a M_n of 37900 g/mol and a molecular weight distribution (MWD) of 1.10. This narrow polydispersity and the experimentally determined linear correlation between M_n and percent conversion are indica-

(1) Brintzinger, H. H.; Fischer, D.; Mulhaupt, R.; Rieger, B.; Waymouth, R. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1143−1170.

(2) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, 1997.

(3) For some notable exceptions, see: (a) Ovitt, T. M.; Coates, G. W. *J. Am. Chem. Soc.* **1999**, *121*, 4072−4073. (b) Cheng, M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **1998**, *120*, 11018−11019. (c) Chamberlain, B. M.; Sun, Y. P.; Hagadorn, J. R.; Hemmesch, E. W.; Young, V. G.; Pink, R.; Hillmyer, M. A.; Tolman, W. B. *Macromolecules* **1999**, *32*, 2400−2402. (d) Spassky, N.; Wisniewski, M.; Pluta, C.; Le Borgne, A. *Macromol. Chem. Phys.* **1996**, *197*, 2627−2637. (e) Chisholm, M. H.; Eilerts, N. W. *Chem. Commun.* **1996**, 853−854. (f) Kruper, W. J.; Dellar, D. V. *J. Org. Chem.* **1995**, *60*, 725−727. (g) Aida, T.; Inoue, S. *Acc. Chem. Res.* **1996**, *29*, 39−48.

(4) Chiellini, E.; Solaro, R. *Adv. Mater.* **1996**, *8*, 305−313.

(5) These polymers are therefore formally poly(lactide)s, but to simplify the stereochemical nomenclature they will be referred to poly(lactic acid)s in this paper.

(6) For examples of Al, Mg, Sn, and Y-based alkoxide initiators, see: (a) Dubois, P.; Jacobs, C.; Jérôme, R.; Tessié, P. *Macromolecules* **1991**, *24*, 2266−2270. (b) Reference 3e. (c) Kricheldorf, H. R.; Lee, S. R.; Bush, S. *Macromolecules* **1996**, *29*, 1375−1381. (d) Stevels, W. M.; Dijkstra, P. J.; Feijen, J. *Trends Polym. Sci.* **1997**, *5*, 300−305.

(7) Cheng, M.; Ovitt, T. M.; Hustad, P. D.; Coates, G. W. *Polym. Prepr.* **1999**, *40* (1), 542−543.

(8) For some recent examples of polymerization catalysts with bulky ligands that control stereochemistry by a chain-end control mechanism, see: (a) Small, B. L.; Brookhart, M. *Macromolecules* **1999**, *32*, 2120−2130. (b) Resconi, L.; Abis, L.; Franciscono, G. *Macromolecules* **1992**, *25*, 6814−6817.

(9) Heterotactic macromolecules are a rare type of polymer that have alternating pairs of stereogenic centers in the main chain (i.e. only *mr/rm* dyads are present). For some recent examples, see: (a) Hirano, T.; Yamaguchi, H.; Kitayama, T.; Hatada, K. *Polym. J.* **1998**, *30*, 767−769. (b) Yamada, K.; Nakano, T.; Okamoto, Y. *Macromolecules* **1998**, *31*, 7598−7605. (c) Kitayama, T.; Hirano, T.; Hatada, K. *Tetrahedron* **1997**, *53*, 15263−15279. (d) Nakahama, S.; Kobayashi, M.; Ishizone, T.; Hirao, A. *J. Macromol. Sci., Pure Appl. Chem.* **1997**, *A34*, 1845−1855. (e) Fossum, E.; Matyjaszewski, K. *Macromolecules* **1995**, *28*, 1618−1625.

(10) Kasperczyk has reported that LiO^{t}Bu polymerizes *rac*-lactide to PLA that is enriched in heterotactic sequences: Kasperczyk, J. E. *Macromolecules* **1995**, *28*, 3937−3939.

(11) (a) Thakur, K. A. M.; Kean, R. T.; Hall, E. S.; Kolstad, J. J.; Lindgren, T. A.; Doscotch, M. A.; Siepmann, J. I.; Munson, E. J. *Macromolecules* **1997**, *30*, 2422−2428. (b) Thakur, K. A. M.; Kean, R. T.; Hall, E. S.; Kolstad, J. J.; Munson, E. J. *Macromolecules* **1998**, *31*, 1487−1494. (c) Wisniewski, M.; Le Borgne, A.; Spassky, N. *Macromol. Chem. Phys.* **1997**, *198*, 1227−1238. (d) Coudane, J.; Ustariz-Peyret, C.; Schwach, G.; Vert, M. *J. Polym. Sci., Polym. Chem. Ed.* **1997**, *35*, 1651−1658.

(12) Crystal data of **2**: orthorhombic, *Pbca*, colorless; $a = 21.4727(4)$ Å, $b = 19.5105(3)$ Å, $c = 33.3509(3)$ Å; $V = 13972.1(4)$; $Z = 8$; $R = 0.0540$; GOF = 1.033.
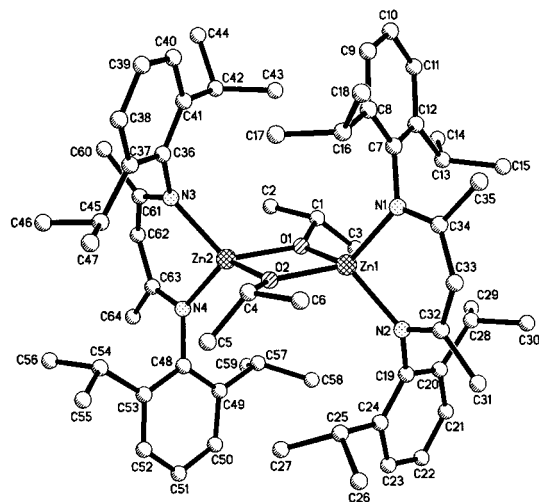
Figure 1. Molecular structure of [**2**]$_2$. Selected bond distances (Å) and angles (deg): Zn(1)−N(1), 2.074(4); Zn(1)−N(2), 2.054(4); Zn(1)−O(1), 1.983(3); N(1)−Zn(1)−N(2), 94.8(2); N(1)−Zn(1)−O(1), 122.95(15); N(2)−Zn(1)−O(1), 126.08(14); O(1)−Zn(1)−O(2), 78.50(12); Zn(1)−O(1)−Zn(2), 101.72(13).

tive of a living polymerization, as well as a single type of reaction site. Microstructural analysis of the polymer by ^{1}H NMR revealed that **2** exerts a significant influence on the tacticity of the polymer formed, as the microstructure is highly heterotactic. On the basis of the spectrum, the probability of a racemic enchainment in the polymer (P_r)[13] is 0.90; in other words, 90% of the linkages formed are between lactide units of opposite stereochemistry. To further increase the stereoregularity of the heterotactic PLA, we performed the polymerization using **2** at 0 °C. The reaction reached 95% conversion after 2 h. GPC revealed a M_n of 38800 g/mol and a MWD of 1.09. Shown in Figure 2 is the homonuclear decoupled ^{1}H NMR spectrum of the methine region of the PLA. The shifts at 5.22 and 5.14 ppm are the heterotactic *rmr* and *mrm* tetrads, respectively. From the intensities of these peaks and those attributed to the *mmm*, *mmr*, and *rmm* impurities,[14] a P_r of 0.94 can be calculated.[13] Despite the stereoregularity of the polymer, it is an amorphous material with a T_g of 49 °C.

To determine that the isopropoxide group of **2** initiates polymerization of lactide while the β-diiminate ligand remains bound to the zinc center, we performed the following experiment.

(13) P_r is the probability of a racemic placement between monomer units (i.e. (R,R)-**1** followed by (S,S)-**1**, or vice versa). P_r can also be expressed in terms of the enchainment rate constants: $P_r = k_{R/SS}/(k_{R/SS} + k_{R/RR}) = k_{S/RR}/(k_{S/RR} + k_{S/SS})$. The expressions for the tetrad concentrations in terms of P_r, assuming Bernoullian statistics and the absence of transesterification, are as follows:[10,11d] [*mmm*] = $(2(1 − P_r)^2 + P_r(1 − P_r))/2$; [*mrm*] = $(P_r^2 + P_r(1 − P_r))/2$; [*mmr*] = [*rmm*] = $(P_r(1 − P_r))/2$; [*rmr*] = $P_r^2/2$.

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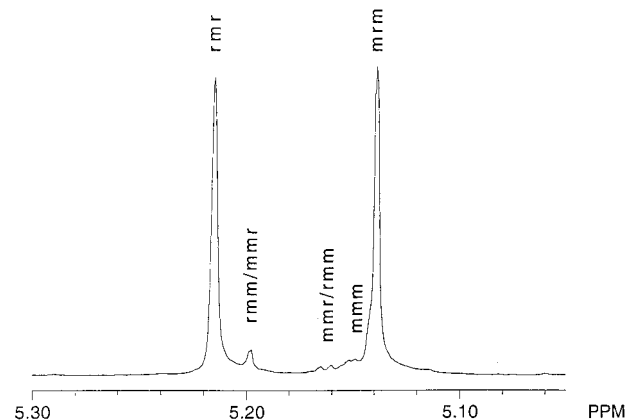

Figure 2. Homonuclear decoupled ^{1}H NMR spectrum of the methine region of heterotactic PLA prepared with **2** at 0 °C (500 MHz, CDCl$_3$).

The reaction of **1** with **2** (9:1) was monitored by ^{1}H NMR; in 5 min, **1** was completely consumed. The reaction was quenched by adding methanol, then the crude material was analyzed by electrospray-ionization mass spectrometry. Molecular ions corresponding to (BDI)H$_2^+$ (m/z 419) and oligomers of the formula H(OCHMeCO)$_{2n}$O^{i}Pr·NH$_4^+$ (n = 3 to 12) were found. This strongly supports our hypothesis that the β-diiminate ligand does not react with lactide, but instead it remains bound to the zinc center while the isopropoxide group initiates polymerization. We propose that the bulky ligand serves to increase the stereochemical influence of the polymer chain-end on stereocontrol, thus forming the highly heterotactic microstructure.

In conclusion, we report a zinc alkoxide complex that acts as a single-site, living initiator for the polymerization of *rac*-lactide to heterotactic PLA. Mass spectrometry experiments revealed that the isopropoxide group initiates polymerization, while the β-diiminate ligand remains chelated to the zinc center. Current work is directed at determining the factors which favor racemic over meso enchainment, as well as employing **2** for the synthesis of new polyester architectures.

Supporting Information Available: Synthesis of **2**, polymerization procedure, mass spectrometry data, and crystal structure data for **2** (PDF). This material is free of charge via the Internet at http://pubs.acs.org.

JA992678O