Stereoselective Ring-Opening Polymerization of *meso*-Lactide: Synthesis of Syndiotactic Poly(lactic acid)

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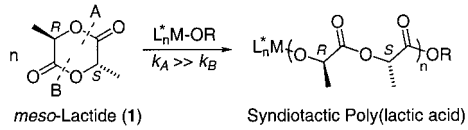
The physical and mechanical properties of a polymeric material are critically dependent on many factors, one of which is stereochemistry. Polymers that have stereocenters in the repeat unit can exhibit two structures of maximum order, isotactic and syndiotactic.[1] Sequential stereocenters of isotactic polymers are of the same relative stereochemistry, whereas those of syndiotactic polymers are of the opposite relative configuration. Due to their stereoregularity, isotactic and syndiotactic polymers are typically crystalline, an important feature for many applications. Isotactic polymers are fairly common; notable examples include isotactic polyolefins as well as virtually all natural polymers. In contrast, syndiotactic polymers are less common due to their inherently more complex alternating stereochemistry. Since syndiotactic polymers often have properties that are similar to, or in some cases better than, their isotactic counterparts,[2] we have initiated a study aimed at the development of new strategies for syndiospecific polymerization. Herein we report the synthesis of syndiotactic poly(lactic acid).

There are currently three main strategies for the synthesis of syndiotactic polymers. The first is the condensation or solid-phase polymerization of an A−B type monomer of the appropriate stereochemistry; this approach is used to produce syndiotactic polypeptides.[3] A second route to syndiotactic polymers is via a chain-end control mechanism, where the last stereocenter of the growing polymer controls the stereochemical outcome of the monomer addition process.[4] Despite many examples of this type, the strategy often suffers from a lack of generality as well as inferior stereocontrol.[5] A third and more recent strategy involves the application of C_s-symmetric catalysts, where regularly alternating monomer insertion at enantiotopic coordination sites forms syndiotactic polymers via a site-control mechanism.[6] Although only applied successfully to polyolefins, this route can yield syndiotactic polymers with an impressive degree of stereochemical integrity.

The subject of this report is a new method for constructing syndiotactic polymers, which consists of the stereoselective ring-opening polymerization of a cyclic monomer that contains two stereocenters.[7] To investigate this strategy we studied the polymerization of lactide, which is the cyclic dimer of lactic acid.

Scheme 1



meso-Lactide (**1**) Syndiotactic Poly(lactic acid)

Lactide polymers are biodegradable and have many potential medical, agricultural and packaging applications.[8−10] A range of metal alkoxide initiators has been reported to polymerize the monomer with retention of configuration.[11] For example, the polymerization of optically active (*R,R*)-lactide yields isotactic poly(lactic acid) (PLA), whereas polymerization of the racemate yields atactic PLA. Notably absent from the range of available microstructures is syndiotactic PLA. Therefore, we began to search for initiators capable of the syndiospecific ring-opening polymerization of *meso*-lactide[12] (**1**) (Scheme 1).[13]

In theory, **1** can be polymerized to syndiotactic PLA by both chain-end and enantiomorphic site-control mechanisms. Since the chain-end control of stereochemistry in metal alkoxide initiated lactide polymerizations is typically poor,[14−16] we chose to study initiators capable of a site-control mechanism. The accepted mechanism of lactide ring-opening is cleavage of a oxygen-acyl bond by the metal alkoxide. Since **1** contains two enantiotopic O-acyl bonds (A, B), a chiral metal alkoxide will exhibit a kinetic preference for reaction at one of the sites; a large preference will produce the syndiotactic polymer. Spassky and co-workers have reported a chiral aluminum methoxide complex that exhibits an unprecedented selectivity in the kinetic resolution polymerization of racemic lactide.[17] This work prompted us to study the synthesis and application of structurally related aluminum (**3**) and yttrium (**4**) metal alkoxides for the polymerization of **1** (Scheme 2).

Reaction of (−)-**2** and the appropriate metal trialkoxide in toluene and subsequent evaporation of solvent in vacuo yields **3** and **4** as solids.[18] To date, we have been unsuccessful at obtaining an X-ray structure of **3**. However **4** was determined to be an alkoxy-bridged dimer in the solid state, with the ligand adopting

(1) Farina, M. *Top. Stereochem.* **1987**, *17*, 1−111.
(2) Tomotsu, N.; Ishihara, N.; Newman, T. H.; Malanga, M. T. *J. Mol. Catal. A* **1998**, *128*, 167−190.
(3) For leading references, see: (a) Hartgerink, J. D.; Clark, T. D.; Ghadiri, M. R. *Chem.—Eur. J.* **1998**, *4*, 1367−1372. (b) Diederichsen, U. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 445−448. (c) Di Blasio, B.; Delduca, V.; Lombardi, A.; Pedone, C.; Lorenzi, G. P.; Benedetti, E. *Int. J. Pept. Protein Res.* **1995**, *45*, 100−105.
(4) Brintzinger, H. H.; Fischer, D.; Mulhaupt, R.; Rieger, B.; Waymouth, R. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1143−1170.
(5) For some exceptions and recent examples, see: (a) Yasuda, H.; Ihara, E. *Adv. Polym. Sci.* **1997**, *133*, 53−101. (b) Brookhart, M.; Wagner, M. I. *J. Am. Chem. Soc.* **1996**, *118*, 7219−7220. (c) Kemnitzer, J. E.; McCarthy, S. P.; Gross, R. A. *Macromolecules* **1993**, *26*, 1221−1229. (d) Resconi, L.; Abis, L.; Francisconi, G. *Macromolecules* **1992**, *25*, 6814−6817. (e) Reference 2.
(6) For examples of syndiospecific catalysts that exhibit site control, see: (a) Alt, H. G.; Samuel, E. *Chem. Soc. Rev.* **1998**, *27*, 323−329 and references therein. (b) Herzog, T. A.; Zubris, D. L.; Bercaw, J. E. *J. Am. Chem. Soc.* **1996**, *118*, 11988−11989. (c) O'Dell, R.; McConville, D. H.; Hofmeister, G. E.; Schrock, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 3414−3423.
(7) Two possible scenarios are (1) the cyclic monomer has two stereocenters of the same configuration (enantiopure), and the polymerization process inverts one of the centers during the ring-opening process and (2) the cyclic monomer has two stereocenters of opposite configuration (meso), and the initiator stereoselectively opens it with retention of stereochemistry. Both form syndiotactic polymer.
(8) Swift, G. *Acc. Chem. Res.* **1993**, *26*, 105−110.
(9) Kricheldorf, H. R.; Kreiser-Saunders: I.; Juergens, C.; Wolter, D. *Macromol. Symp.* **1996**, *103*, 85−102.
(10) Chiellini, E.; Solaro, R. *Adv. Mater.* **1996**, *8*, 305−313.
(11) 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) Chisholm, M. H.; Eilerts, N. W. *Chem. Commun.* **1996**, 853−854. (c) Kricheldorf, H. R.; Lee, S. R.; Bush, S. *Macromolecules* **1996**, *29*, 1375−1381. (d) Stevels, W. M.; Ankoné, M. J. K.; Dijkstra, P. J.; Feijen, J. *Macromolecules* **1996**, *29*, 3332−3333.
(12) *meso*-Lactide can be synthesized with purity greater than 99%, see: Entenmann, G.; Bendix, D. (Boehringer Ingelheim), German Patent DE 3,-820,299, 1988; *Chem. Abstr.* **1989**, *110*, 213592w.
(13) There are several reports of the polymerization of **1**; however, none demonstrate efficient stereochemical control to produce syndiotactic PLA: (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) Kricheldorf, H. R.; Lee, S. R. *Polymer* **1995**, *36*, 2995−3003. (c) Kricheldorf, H. R.; Boettcher, C. *Makromol. Chem.* **1993**, *194*, 1653−1664. (d) Kricheldorf, H. R.; Boettcher, C. *J. Macromol. Sci., Pure Appl. Chem.* **1993**, *A30*, 441−448. (e) Chabot, F.; Vert, M.; Chapelle, S.; Granger, P. *Polymer* **1983**, *24*, 53−59.
(14) Wisniewski, M.; Le Borgne, A.; Spassky, N. *Macromol. Chem. Phys.* **1997**, *198*, 1227−1238.
(15) 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.
(16) Thakur, K. A. M.; Kean, R. T.; Hall, E. S.; Kolstad, J. J.; Munson, E. J. *Macromolecules* **1998**, *31*, 1487−1494.
(17) Spassky, N.; Wisniewski, M.; Pluta, C.; Le Borgne, A. *Macromol. Chem. Phys.* **1996**, *197*, 2627−2637.

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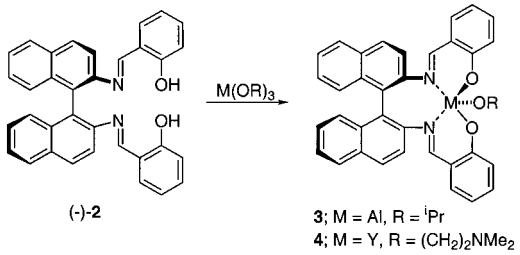
Scheme 2



a cis-β geometry and Δ chirality. Therefore, the illustrated structure of **3** must be considered putative until further studies have been completed.

Compound **4** was initially examined for the polymerization of **1**; in 14 h at 70 °C, the reaction proceeded to 97% conversion ([**1**] = 0.2 M in toluene, [**1**]/[**4**] = 100). Inspection of the polymer microstructure by ^{1}H NMR revealed that **4** affords no stereocontrol in the polymerization of **1**, as atactic PLA is formed. We next investigated the activity of complex **3**; under the same reaction conditions, a 94% conversion was reached in 40 h. Gel-permeation chromatography (THF, versus polystyrene standards) revealed a M_n of 12 030 (theoretical M_n = 13 540) and a molecular weight distribution of 1.05. This narrow polydispersity and the linear correlation between M_n and percent conversion (see Supporting Information) are indicative of a living polymerization as well as a single type of reaction site.

The most notable feature of the reaction using **3** is that the polymer formed is highly syndiotactic. Figure 1 shows the methine resonances of the homonuclear decoupled ^{1}H NMR spectrum of poly(**1**) formed using **3**. The peaks were assigned to the appropriate tetrads in accordance with the shifts reported by Munson and Thakur.[19] The large *rrr* tetrad peak is evidence for a highly syndiotactic polymer. The presence of the small *rmr* tetrad peak impurity necessitates the presence of *rrm*, *mrm*, and *mrr* tetrads as well, assuming an enantiomorphic site-control mechanism.[20] These peaks exhibit near chemical shift equivalence with the *rrr* tetrad[19] and due to their small size cannot be seen. Further evidence for a high level of syndiotacticity are the solitary shifts in the ^{13}C NMR at δ 169.2, 69.3, and 16.3 ppm ($CDCl_3$, 75 MHz). At the current time, we cannot explain the high stereoselectivity of **3** relative to that of **4** in this polymerization.

This reaction is unusual, since an achiral monomer is converted to an achiral polymer and a chiral catalyst is required for syndiotacticity. Due to the achirality of the polymer, it is not possible at the current time to establish whether ring-opening occurs at site A or B. However an enantiotopic selectivity of 96% can be calculated from the intensity of the *rmr* peak, assuming an enantiomorphic site-control mechanism.[21] Due to the high degree of stereoregularity, syndiotactic PLA is crystalline; following annealing at 95 °C for 60 min, the polymer formed at 50 °C exhibits a T_g at 34.1 °C, and a T_m at 152 °C.

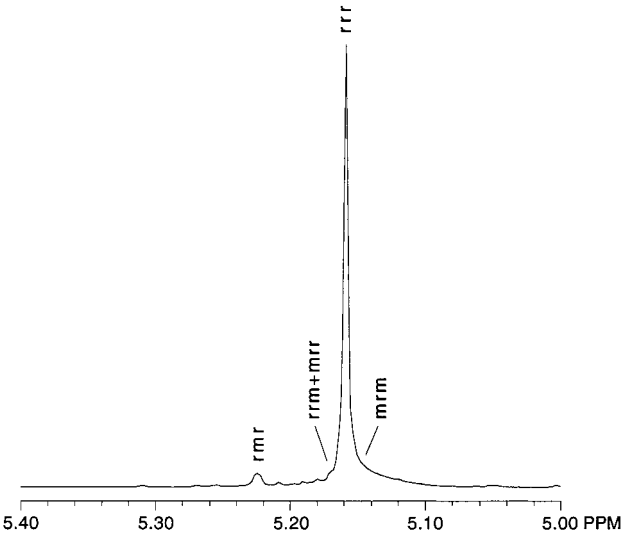


Figure 1. Homonuclear decoupled ^{1}H spectrum of the methine region of poly(**1**) prepared with **3** (500 MHz, $CDCl_3$).

In summary, we report the first synthesis of highly syndiotactic poly(lactic acid), synthesized by the stereoselective ring-opening polymerization of *meso*-lactide. This strategy of selectively opening a cyclic monomer that contains two or more stereocenters holds promise as a new method for preparing polymers of precise tacticity. Further studies are underway to synthesize poly(lactic acid)s, as well as other polymers, with novel microstructures.

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Supporting Information Available: Syntheses of **3** and **4**, polymerization procedure and data, polymer thermal analysis, and crystal structure data for **4** (tables of crystal data, structure solution and refinement, atomic coordinates, bond lengths and angles, and anisotropic thermal parameters) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Spassky's complex is formed by reacting (−)-(**2**) with $AlEt_3$, followed by reaction with methanol. We discovered that a catalytically inactive bimetallic byproduct is formed in approximately 30% yield using this preparation, prompting our modified route. The structure of this unusual compound will be reported separately.

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

(20) It is documented that aluminum-based initiators typically exhibit a *low degree of isospecific* chain-end control in lactide polymerization.[14] Therefore we attribute the *high degree of syndiospecificity* in this reaction to an enantiomorphic site-control mechanism.

(21) The expressions for the tetrad concentrations in terms of the enantiotopic selectivity (α) are: $[rrr] = 0.5(\alpha^2 + (1-\alpha)^2 + \alpha^3 + (1-\alpha)^3)$; $[rmr] = \alpha(1-\alpha)$; $[mrm] = [rrm] = [mrr] = 0.5(\alpha^2(1-\alpha) + \alpha(1-\alpha)^2)$. For Figure 1, $[rmr] = 3.9\%$, $[rrr] + [mrm] + [rrm] + [mrr] = 96.1\%$.