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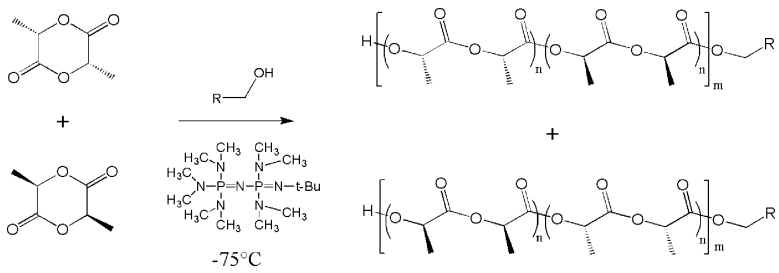

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Organocatalytic Stereoselective Ring-Opening Polymerization of Lactide with Dimeric Phosphazene Bases

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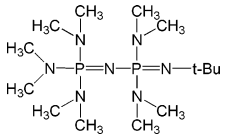
Polylactide (PLA), conventionally synthesized through the ring-opening polymerization (ROP) of lactide (LA), is one of the most important synthetic biocompatible and biodegradable polymers with a wide range of biomedical, pharmaceutical, agricultural, and packing applications.[1] The mechanical, physical, and degradation properties are closely related to the stereochemistry of PLA, so stereocontrol of PLA homopolymers or copolymers is of utmost importance to achieve the desired features for applications. While isotactic poly(L-LA) (PLLA) and poly(D-LA) (PDLA) are typically crystalline with a melting temperature (T_m) around 180 °C, a 1:1 mixture of enantiomerically pure PLLA and PDLA can form a stereocomplex with a T_m of 230 °C,[2] which will have a much higher working temperature. The synthesis of high melting stereocomplex PLA directly from inexpensive feedstock *rac*-LA (a 1:1 mixture of L-LA and D-LA) has been an important synthetic target with two different strategies being exploited: enantiomorphic site-control (the chirality of the catalyst defines the stereochemistry of the monomer insertion)[3] and chain-end control (the stereochemistry of the last inserted monomer defines the stereochemistry of the subsequent ring-opening step).[4,5] Most of the reported stereoselective catalysts to date are single site catalysts with a metal center, which may be bound in the polymer chains and limit their application in biomedical and pharmaceutical fields.[3,4] Recently, we reported potent non-ionic monomeric phosphazene bases[6] as active catalysts for ROP of cyclic esters.[7] Herein, we present the organocatalytic stereoselective ring-opening polymerization of *rac*-LA at low temperature using the dimeric phosphazene base 1-*tert*-butyl-2,2,4,4,4-pentakis(dimethylamino)-2Λ,5,4Λ5-catenadi(phosphazene) (P_2-*t*-Bu, $^{MeCN}pK_{BH^+}$ 33.5, Scheme 1) as catalyst to produce highly isotactic PLA stereocomplex.

The catalytic activity of P_2-*t*-Bu for the ROP of LA was first studied with enantiomerically pure L-LA in toluene at room temperature using 1-pyrenebutanol as the initiator. With a monomer to initiator to catalyst molar ratio of 100:1:1 (initial monomer concentration $[M]_0 = 0.32$ mol/L, targeted degree of polymerization (DP) = 100, Table 1, entry 1), L-LA was quantitatively polymerized in 10 s. This remarkably high catalytic activity is comparable with those of the most active metal[8] or nonmetal catalysts.[9] The resulting PLLA had a molecular weight (M_n) of 25 800 g/mol with a polydispersity (PDI = M_w/M_n) of 1.23 and showed high end-group fidelity (Figure S1). PLLAs with narrower PDI of 1.08 can be synthesized by reducing the starting concentration of monomer (0.08 mol/L), initiator, and catalyst (Table 1, entry 2). M_n increases linearly with the conversion of monomer, which is a characteristic of living polymerization (Figure S2). However, since the equilibrium monomer concentration[10] does not differ enough from the starting concentration, the conversion is incomplete.

Scheme 1. Dimeric Phosphazene Base P_2-*t*-Bu



The ROP of *rac*-LA with the same dilute reaction conditions using P_2-*t*-Bu catalyst at room temperature produced poly(*rac*-LA) (PRLA) with M_n of 13 300 g/mol and PDI of 1.06 at 85% conversion (Table 1, entry 3). The high catalytic activity of P_2-*t*-Bu enables the ROP of *rac*-LA even at −75 °C. The final conversion of monomer is higher since the ROP is exothermic. PRLA with M_n of 27 200 and PDI of 1.11 was obtained at over 99% conversion after 3 h (Table 1, entry 4).

The microstructures of the prepared PRLAs at different temperatures were determined by the analysis of the methine region of the homonuclear decoupled ^{1}H NMR spectra (Figure 1). The resonance peaks of the methine proton were assigned to the appropriate tetrads in accordance with the reported literature.[11] At low temperature, the formation of isotactic sequences is favored as indicated by the predominant *iii* tetrad, characteristic of isotacticity (*i* denotes isotactic and *s* denotes syndiotactic). Three smaller resonance peaks assignable to *isi*, *sii*, and *iis* tetrads have nearly identical intensities, and the *sis* peak is negligible, which suggests the PRLA prepared at −75 °C has stereoblock architectures with long isotactic poly(S) segments and poly(R) segments in the main chain.[3] Parameter P_i, which is the probability of forming a new *i* dyad, determines the relative proportions of the tetrad sequences and therefore provides a measure of the degree of stereoselectivity of a catalyst.[3,10] According to the Markovian statistics, P_i increases from 0.72 for PRLA prepared at room temperature to 0.95 for PRLA prepared at −75 °C. The high level of isotacticity was further confirmed with the ^{13}C NMR spectra at the methine region (Figure S3).

Thermal analysis revealed that PRLA prepared at −75 °C is crystalline due to the high degree of stereoregularity. The resultant polymer exhibited a glass transition temperature (T_g) of 62 °C and a peak T_m of 201 °C (fusion enthalpy $\Delta H_{fus} = 47$ J/g) for the second scan, which is considerably higher than that of PLLA with similar degree of polymerization (DP) (T_m = 163 °C) (Figure S4). The high melting temperature suggests the formation of stereocomplex morphology due to the cocrystallization of the long isotactic PLLA and PDLA blocks. For PRLA prepared at room temperature, no melting peak was observed in the second heating, commensurate with an amorphous polymer. The highest T_m values of PRLA stereocomplexes (with DP around 100) obtained by the stereoselective polymerization of *rac*-PLA using organocatalysts[5] and metal complex catalysts[3,4] were 153.3 and 201 °C. P_2-*t*-Bu shows a better stereocontrol on ROP of *rac*-lactide than all the other organocata-

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Table 1. ROP of *rac*-LA in Toluene Using 1 mol % of P_2-*t*-Bu (to Monomer) as Catalyst

entry	monomer	$[M]_0$ (mol/L)	initiator	$[M]_0/[I]_0$	temp (°C)	time (min)	conversion[a] (%)	DP[a]	M_n[b,c] (g mol^{-1})	PDI[b,c]	P_i[a]
1	L-LA	0.32	PB	100	20	0.17	>99	98	25800[b]	1.23[b]	N/A
2	L-LA	0.08	PB	100	20	25	84	76	13000[b]	1.08[b]	N/A
3	*rac*-LA	0.08	PB	100	20	3	85	76	13300[b]	1.06[b]	0.72
4	*rac*-LA	0.08	PB	100	−75	180	>99	97	27200[c]	1.11[c]	0.95
5	*rac*-LA	0.08	PS_{100}−OH	100	−75	220	99	96	30700[b]	1.10[b]	0.92

[a] Determined by ^{1}H NMR. [b] Determined by GPC in THF using a RI detector. [c] Determined by GPC in $CHCl_3$ using a RI detector.

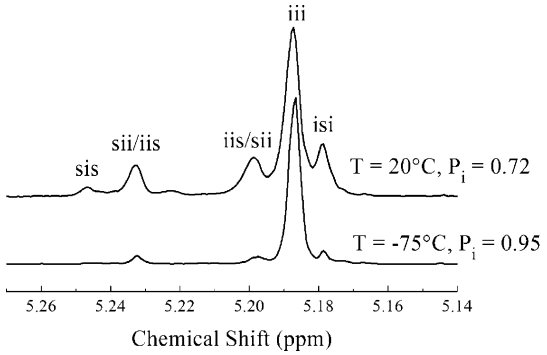

Figure 1. Homonuclear decoupled ^{1}H NMR spectra (400 MHz, $CDCl_3$) of the methine region of poly(*rac*-LA)s prepared using P_2-*t*-Bu catalyst at 20 °C (Table 1, entry 3) and −75 °C (Table 1, entry 4).

lysts, and its stereoselectivity also matches that of the best metal complex catalysts reported to date.

The efficiency and stereoselectivity of the P_2-*t*-Bu catalyst was further demonstrated by a chain extension block copolymerization with hydroxyl-terminated polystyrene macroinitiator (PS_{100}−OH, M_n = 10 000 g/mol, PDI = 1.08)[12] for the ROP of *rac*-LA (Scheme S1). GPC analysis (Figure S5) demonstrated clean chain-extended block copolymers free from unreacted macroinitiator contamination and indicated excellent control of M_n (30 700 g/mol) with correspondingly low PDI (1.10) (Table 1, entry 5). A P_i value of 0.92 for the PLA block and a T_m at 178 °C confirmed the formation of stereocomplex morphology (Figure S6).

The ROP of LA with P_2-*t*-Bu is believed to occur through an activated alcohol mechanism.[7] The chemical shift of −OH in benzyl alcohol shifts downfield from 1.17 to 7.66 ppm upon the addition of P_2-*t*-Bu in toluene-d_8, indicative of an intermolecular hydrogen bond between P_2-*t*-Bu and the alcohol initiator (Figure S7). A chain-end control with stereoerror mechanism is postulated to explain the formation of the microstructure (Scheme S2). At the beginning of the reaction, since P_2-*t*-Bu is a nonchiral catalyst, both D-LA and L-LA should be equally activated for the first single turnover reaction. After that, stereoselective attack by the terminal alkoxide of the last inserted monomer in the polymer chain leads to isotactic enchainment. The bulky P_2-*t*-Bu catalyst presumably influences the steric hindrance around the catalytic site, enhancing the stereoselectivity, especially when the temperature is low and the mobility of the molecule is limited. The preferential propagation of the L-LA enantiomer parallels the preferential propagation of D-LA. Meanwhile, error ROP, whereby an individual polymer chain may effectively open the enantiomeric opposite monomer, may happen at a level consistent with the selectivity of the catalyst.[3d] The following growth of the polymer chain is controlled by the last inserted monomer accounting for the formation of this special microstructure containing consecutive sequence of R and S blocks. Side reactions such as transesterification generally hamper control over the polymerization process. From the NMR spectra, the diminution of a peak at 5.222 ppm attributable to *iiiss*/*ssiii* hexads indicated that the transesterification reaction was completely depressed at −75 °C (Figure S8).[13] MALDITOF mass spectra (Figure S9) presenting peaks only corresponding to lactide repeat units (144 Da) further confirmed this statement.[3]

In conclusion, because of its high basicity, steric hindrance, and high activity at low temperature, dimeric phosphazene base P_2-*t*-Bu exhibits excellent stereocontrol for the ROP of *rac*-lactide. Highly isotactic polymers with high melting point and high crystallinity were obtained due to the effective cocrystallization between PLLA blocks and PDLA blocks. A chain-end control with stereoerror mechanism is postulated to explain the formation of the microstructure. Further mechanistic study with molecular modeling is still under investigation.

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Supporting Information Available: Full experimental details, schemes, and figures of polymerization. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Zhong, Z.; Dijkstra, P. J.; Feijen, J. *J. Biomater. Sci. Polym. Ed.* **2004**, *15*, 929−946. (b) Ueda, H.; Tabata, Y. *Adv. Drug Delivery Rev.* **2003**, *55*, 501−518.
(2) Ikada, Y.; Jamshidi, K.; Tsuji, H.; Hyon, S. H. *Macromolecules* **1987**, *20*, 904−906.
(3) (a) Spassky, N.; Wisniewski, M.; Pluta, C.; Borgne, A. L. *Macromol. Chem. Phys.* **1996**, *197*, 2627−2637. (b) Radano, C. P.; Baker, G. L.; Milton, R.; Smith, I. *J. Am. Chem. Soc.* **2000**, *122*, 1552−1553. (c) Ovitt, T. M.; Coates, G. W. *J. Polym. Sci. Part A: Polym. Chem.* **2000**, *38*, 4686−4692. (d) Ovitt, T. M.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 1316−1326. (e) Zhong, Z.; Dijkstra, P. J.; Feijen, J. *Angew. Chem.* **2002**, *114*, 4692−4695. (f) Zhong, Z.; Dijkstra, P. J.; Feijen, J. *J. Am. Chem. Soc.* **2003**, *125*, 11291−11298. (g) Majerska, K.; Duda, A. *J. Am. Chem. Soc.* **2004**, *126*, 1026−1027. (h) Chisholm, M. H.; Patmore, N. J.; Zhou, Z. *Chem. Commun.* **2005**, 127−129.
(4) (a) Chamberlain, B. M.; Cheng, M.; Moore, D. R.; Ovitt, T. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2001**, *123*, 3229−3238. (b) Nomura, N.; Ishii, R.; Akakura, M.; Aoi, K. *J. Am. Chem. Soc.* **2002**, *124*, 5938−5939. (c) Tang, Z.; Chen, X.; Pang, X.; Yang, Y.; Zhang, X.; Jing, X. *Biomacromolecules* **2004**, *5*, 965−970.
(5) Dove, A. P.; Li, H.; Pratt, R. C.; Lohmeijer, B. G. G.; Culkin, D. A.; Waymouth, R. M.; Hedrick, J. L. *Chem. Commun.* **2006**, 2881−2883.
(6) (a) Schwesinger, R. *Chimia* **1985**, *39*, 269−272. (b) Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1167−1169.
(7) Zhang, L.; Nederberg, F.; Pratt, R. C.; Waymouth, R. M.; Hedrick, J. L.; Wade, C. G. *Macromolecules* **2007**, *40*, 4154−4158.
(8) (a) Chisholm, M. H.; Gallucci, J.; Phomphrai, K. *Inorg. Chem.* **2002**, *41*, 2785−2794. (b) Hodgson, L. M.; White, A. J. P.; Williams, C. K. *J. Polym. Sci. Part A: Polym. Chem.* **2006**, *44*, 6646−6651.
(9) (a) Nyce, G. W.; Glauser, T.; Connor, E. F.; Mock, A.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 3046−3056. (b) Pratt, R. C.; Lohmeijer, B. G. G.; Long, D. A.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 4556−4557.
(10) Penczek, S.; Biela, T.; Duda, A. *Macromol. Rapid Commun.* **2000**, *21*, 941−950.
(11) (a) Kricheldorf, H. R.; Boettcher, C.; Tonnes, K.-U. *Polymer* **1992**, *33*, 2817−2824. (b) Kasperczyk, J. E. *Macromolecules* **1995**, *28*, 3937−3939.
(12) Bosman, A. W.; Vestberg, R.; Heumann, A.; Frechet, J. M. J.; Hawker, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 715−728.
(13) Thakur, K. A. M.; Kean, R. T.; Hall, E. S.; Doscotch, M. A.; Munson, E. J. *Anal. Chem.* **1997**, *69*, 4303−4309.

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