J|A|C|S
COMMUNICATIONS

Carbonylative Polymerization of Propylene Oxide: A Multicatalytic Approach to the Synthesis of Poly(3-Hydroxybutyrate)

Erin W. Dunn and Geoffrey W. Coates*

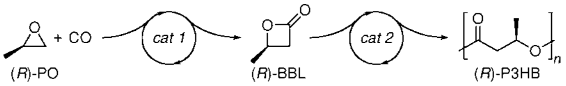
Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University,
Ithaca, New York 14853-1301

Received June 8, 2010; E-mail: gc39@cornell.edu

Abstract: We report a highly efficient method for the synthesis of poly(3-hydroxybutyrate) by the carbonylative polymerization of propylene oxide. The use of compatible epoxide carbonylation and lactone polymerization catalysts allows for a one-pot reaction that eliminates the need to isolate and purify the toxic β-butyrolactone intermediate.

Poly(3-hydroxybutyrate) (P3HB) is a naturally occurring biodegradable and biocompatible polyester that exhibits properties similar to isotactic polypropylene.[1] Current methods to synthesize P3HB include bacterial fermentation, direct copolymerization of propylene oxide (PO) and carbon monoxide (CO), and ring-opening polymerization of β-butyrolactone (BBL). Fermentation produces high molecular weight P3HB with the potential to incorporate various pendant functionality into the polyester; however, the process is energy-intensive and necessitates polymer separation from the bacterial culture.[2] In contrast, the direct copolymerization of CO and PO is atom-economical, yet it suffers from low monomer conversion and polymers of low molecular weight are generally produced.[3−5] Finally, the living ring-opening polymerization of BBL yields a high molecular weight polyester, although it requires the rigorous purification of a toxic lactone.[6] We have initiated a research effort to synthesize P3HB via a one-pot tandem catalytic transformation, where BBL is synthesized from PO and CO and subsequently polymerized *in situ* (Scheme 1). A multicatalytic approach would eliminate the need to isolate and purify the toxic lactone monomer, while still maintaining the atom economy of the CO and PO copolymerization and providing the high-molecular weight polymer achieved by BBL polymerization. Tandem catalysis[7] is a valuable method for synthesizing small molecules[8] but has rarely been utilized for polymer synthesis.[9]

Scheme 1. One-Pot Carbonylative Polymerization of (*R*)-Propylene Oxide to (*R*)-Poly(3-hydroxybutyrate)



Developing a one-pot catalytic system is challenging, as the two catalysts must be compatible not only with each other but also with the solvent, substrate, and reaction side products in order to achieve high activity and selectivity.[10] We have previously reported several catalysts of the form [Lewis acid]$^+$[Co(CO)$_4$]$^-$ to be highly active for the carbonylation of epoxides.[11] Furthermore, (BDI)ZnO^{i}Pr (BDI = β-diiminate) has been shown to be an active catalyst for β-lactone polymerization.[12] We anticipated that the catalysts had orthogonal reactivity and could be combined to create an efficient system for the one-pot carbonylative polymerization of PO.

Scheme 2. Screening Tandem Catalysts for P3HB Synthesis

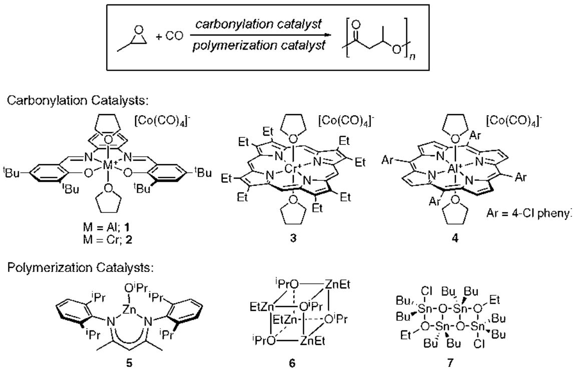


Table 1. Optimization of One-Pot P3HB Synthesis[a]

entry	carbonylation catalyst	polymerization catalyst	product dist. (%) PO	BBL	P3HB
1	**1**	**5**	66	5	29
2	**2**	**5**	7	9	84
3	**3**	**5**	−	10	90
4	**4**	**5**	−	1	99
5	**4**	**6**	10	64	26
6	**4**	**7**	>99	<1	<1

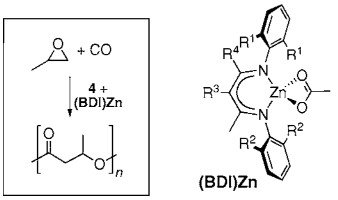
[a] Reaction conditions: 0.1 mol % carbonylation catalyst, 0.1 mol % polymerization catalyst, [PO] = 2.0 M in THF, 850 psi CO, 10 h, 50 °C. Product distribution determined by ^{1}H NMR spectroscopy of the crude reaction.

We initially investigated four catalysts (complexes **1**−**4**) (Scheme 2) for the carbonylation step of the one-pot reaction while using (BDI)ZnO^{i}Pr (**5**) for the polymerization (Table 1). Both complex **1** and complex **2** used with (BDI)ZnO^{i}Pr resulted in incomplete conversions for the carbonylation and polymerization reactions (entries 1 and 2). Catalyst **3** used with **5** completely transformed PO to BBL but resulted in incomplete conversion of BBL to P3HB (entry 3). Finally, complex **4** [(ClTPP)Al(THF)$_2$]$^+$[Co(CO)$_4$]$^-$ (ClTPP = *meso*-tetra(4-chlorophenyl)porphyrinato) used with **5** showed high activities for both the carbonylation and polymerization stages of the reaction, respectively (entry 4).

Equipped with a highly efficient and selective carbonylation catalyst for the one-pot synthesis of P3HB, we screened two additional polymerization catalysts. Complexes **6** and **7** were selected based on literature reports of high activities and their ability to produce a high molecular weight polymer. Ethylzinc isopropoxide[13] (**6**) was a poor catalyst for this system, as it resulted in incomplete conversions for both reactions (entry 5). Distannoxane **7**, reported by Hori and co-workers,[14] impeded the carbonylation catalyst such that no BBL was formed (entry 4). Thus, the original polymerization catalyst (**5**) was the most efficient and selective of the three catalysts studied.

10.1021/ja1049862

Table 2. Screening of β-Diiminate Zinc Polymerization Catalysts[a]



complex	R^1	R^2	R^3	R^4
8	^{i}Pr	Et	H	CF_3
9	Me	Et	CN	CF_3
10	Et	Et	H	CH_3
11	^{i}Pr	^{i}Pr	H	CH_3

entry	(BDI)Zn (mol %)	[PO] (M)	time (h)	BBL (%)	P3HB (%)	M_n (kDa)[b]	PDI[b]
1	**5** (1.0)	3	10	1	99	7	1.5
2	**8** (1.0)	3	15	29	55	4	1.1
3	**9** (1.0)	3	15	2	41	2	1.2
4	**10** (1.0)	2	6	<1	>99	38	1.3
5	**10** (1.0)	2[c]	6	<1	>99	43[d]	1.1[d]
6	**11** (1.0)	2	10	<1	>99	25	1.3
7[e]	**11** (0.5)	2[c]	10	<1	>99	52[d]	1.1[d]

[a] General conditions: 0.1 mol % **4**, THF solvent, 850 psi CO, T_{rxn} = 50 °C. Product distribution determined by ^{1}H NMR of crude reaction. [b] M_n and PDI values determined by GPC in THF with polystyrene standards. [c] (*R*)-PO. [d] M_n and PDI values determined by GPC in $CHCl_3$ with polystyrene standards. [e] 0.05 mol % **4**.

Minor changes in the sterics and electronics of the BDI zinc catalysts have significant effects on their activity;[15] therefore we explored alternative BDI zinc complexes and reaction conditions to optimize the one-pot carbonylative polymerization of PO (Table 2). Although complex **5**, in combination with **4**, proceeded to high conversion of P3HB, the molecular weight of the isolated polyester was low (entry 1). Complexes **8** and **9** with catalyst **4** resulted in incomplete formation of P3HB (entries 2 and 3). Complexes **10** and **11** used with **4** displayed both high activities and produced high molecular weight polymers (entries 4−7).

Under the reaction conditions of entry 4, the number-average molecular weight (M_n) of the polymer grew linearly with conversion and the polydispersity remained narrow throughout the reaction, suggesting living behavior (see Supporting Information). Naturally occurring P3HB is isotactic with all stereocenters in the (*R*) configuration, resulting in semicrystalline morphology.[1] To produce isotactic P3HB, we carbonylatively polymerized (*R*)-PO to (*R*)-P3HB with a molecular weight of 43 kDa (entry 5). Complex **11** with **4** made a polymer with a lower M_n (entry 6) than complex **10** with **4** under the same conditions, and we attribute this to decomposition of the polyester under prolonged exposure to the reaction environment.[12] Finally, we decreased the moles of **4** and **11** to roughly double M_n and synthesized (*R*)-P3HB with a molecular weight of 52 kDa in 10 h using 0.05 mol % catalyst **4** and 0.5 mol % catalyst **11** at 50 °C (entry 7).

To confirm that the reaction proceeded by a two-step mechanism, we monitored the reaction by *in situ* IR spectroscopy.[11d] A plot of absorbance as a function of time confirmed formation of the BBL intermediate that subsequently was consumed to produce P3HB (Figure 1).

We planned to eliminate exposure to the toxic BBL molecule by using tandem catalysis. In order to ensure the lactone was completely transformed over the course of the reaction, we used ^{1}H NMR spectroscopy and gas chromatography to verify the absence of BBL in the crude product (see Supporting Information).

We have reported a new atom-economical and highly efficient method for the synthesis of P3HB from the carbonylative polymerization of propylene oxide. The use of compatible catalysts allows for a one-pot reaction that eliminates the need to isolate and purify the toxic BBL intermediate. Future studies will focus on expanding this methodology to include the incorporation of new monomers.

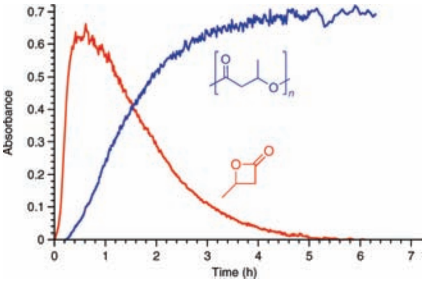


Figure 1. In situ IR spectroscopy of carbonylative polymerization showing formation and subsequent conversion of β-butyrolactone intermediate to poly(3-hydroxybutyrate) (Table 2, entry 4).

Acknowledgment. We thank Dr. J. M. Rowley for initial experiments and Dr. R. C. Jeske for helpful discussions and synthesis of complex **9**. G.W.C. thanks the NSF (CHE-0809778) and DOE (DE-FG02-05ER15687) for financial support.

Supporting Information Available: Experimental procedures, NMR spectra and gas chromatograms, and molecular weight versus conversion data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Doi, Y. *Microbial Polyesters*; VCH Publishers, Inc.: New York, 1990. (b) Müller, H.-M.; Seebach, D. *Angew. Chem., Int. Ed.* **1993**, *32*, 477–502. (c) Mecking, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1078–1085.
(2) (a) Sudesh, K.; Abe, H.; Doi, Y. *Prog. Polym. Sci.* **2000**, *25*, 1503–1555. (b) Lenz, R. W.; Marchessault, R. H. *Biomacromolecules* **2005**, *6*, 1–8.
(3) (a) Allmendinger, M.; Eberhardt, R.; Luinstra, G.; Rieger, B. *J. Am. Chem. Soc.* **2002**, *124*, 5646–5647. (b) Allmendinger, M.; Eberhardt, R.; Luinstra, G. A.; Rieger, B. *Macromol. Chem. Phys.* **2003**, *204*, 564–569.
(4) Lee, J. T.; Alper, H. *Macromolecules* **2004**, *37*, 2417–2421.
(5) In contrast, the living copolymerization of aziridines and CO has been reported: (a) Jia, L.; Sun, H.; Shay, J. T.; Allgeier, A. M.; Hanton, S. D. *J. Am. Chem. Soc.* **2002**, *124*, 7282–7283.
(6) (a) Coulembier, O.; Degée, P.; Hedrick, J. L.; Dubois, P. *Prog. Polym. Sci.* **2006**, *31*, 723–747. (b) O'Keefe, B. J.; Hillmyer, M. A.; Tolman, W. B. *Dalton Trans.* **2001**, 2215–2224. (c) Okada, M. *Prog. Polym. Sci.* **2002**, *27*, 87–133.
(7) For reviews, see: (a) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302–312. (b) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001–1020.
(8) (a) Scroggins, S. T.; Chi, Y.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2009**, *49*, 2393–2396. (b) Ajamian, A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754–3760. (c) Broadwater, S. J.; Roth, S. L.; Price, K. E.; Kobašlija, M.; McQuade, D. T. *Org. Biomol. Chem.* **2005**, *3*, 2899–2906. (d) Goldman, A. S.; Roy, A. H.; Huang, Z.; Ahuja, R.; Schinski, W.; Brookhart, M. *Science* **2006**, *312*, 257–261.
(9) See ref 7b and Komon, Z. J. A.; Bazan, G. C. *Macromol. Rapid Commun.* **2001**, *22*, 467–478.
(10) (a) Poe, S. L.; Kobašlija, M.; McQuade, D. T. *J. Am. Chem. Soc.* **2007**, *129*, 9216–9221. (b) Zhou, J. *Chem. Asian J.* **2010**, *5*, 422–434.
(11) (a) Getzler, Y. D. Y. L.; Mahadevan, V.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 1174–1175. (b) Kramer, J. W.; Lobkovky, E. B.; Coates, G. W. *Org. Lett.* **2006**, *8*, 3709–3712. (c) Schmidt, J. A. R.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2005**, *127*, 11426–11435. (d) Church, T. L.; Getzler, Y. D. Y. L.; Coates, G. W. *J. Am. Chem. Soc.* **2006**, *128*, 10125–10133. (e) Rowley, J. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2007**, *129*, 4948–4960.
(12) Rieth, L. R.; Moore, D. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 15239–15248.
(13) Schechtman, L. A.; Kemper, J. J. *Polym. Preprints* **1999**, *40*, 508–509.
(14) Kobayashi, T.; Yamaguchi, A.; Hagiwara, T.; Hori, Y. *Polymer* **1995**, *36*, 4707–4710.
(15) Moore, D. R.; Cheng, M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2003**, *125*, 11911–11924.

JA1049862