Chemoselective Ring-Opening Polymerization of a Lactone Having *exo*-Methylene Group with Lipase Catalysis

Hiroshi Uyama and Shiro Kobayashi*

Department of Materials Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 606-8501, Japan

Masatake Morita, Shigeki Habaue, and Yoshio Okamoto

Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8603, Japan

Received May 22, 2001

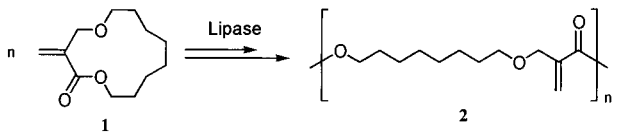
For the past decades, enzyme-catalyzed polymerizations ("enzymatic polymerizations") have been of increasing importance as new trend in macromolecular science.[1] Enzyme catalysis has provided a new synthetic strategy for useful polymers, most of which are difficult to produce by conventional chemical catalysts. In vitro enzymatic syntheses of polymers via nonbiosynthetic pathways, therefore, are recognized as a new area of precision polymer syntheses.

Aliphatic polyesters have received much attention as biodegradable and biomedical materials.[2] There have been many studies on syntheses of aliphatic polyesters by fermentation[3] and chemical[4] processes. Recently, a lipase-catalyzed synthesis of aliphatic polyesters was established as another approach of polyester production.[5] Lipases are enzymes that catalyze the hydrolysis of fatty acid esters, normally in an aqueous environment in living systems. However, lipases are sometimes stable in organic solvents and can be used as catalysts for esterifications and transesterifications. Polyester syntheses have been achieved by various polymerization modes by utilizing such catalytic specificities of lipase under mild reaction conditions. So far, lactones with various ring sizes were subjected to enzymatic ring-opening polymerization. Lipase showed unique catalysis for lactone polymerizations; macrolides (12-, 13-, 16-, and 17-membered lactones) having much lower anionic polymerizability than ϵ-caprolactone (ϵ-CL) were enzymatically polymerized much faster than ϵ-CL.[6] This is probably due to the strongly recognizable nature of the macrolides by lipase.

Chemoselective polymerizations of monomers having more than two polymerizable groups should afford a new class of highly reactive polymers. Monomers having an unsaturated polymerizable group, however, are often difficult to chemoselectively polymerize without reaction of the unsaturated groups because of their high reactivity toward various polymerization catalysts. We have achieved a chemoselective polymerization of a phenol derivative having a methacryloyl group by utilizing specific catalysis of peroxidase.[7] The methacryloyl group was not involved in the polymerization, giving rise to a polymer having it in the side chain. The resulting polymer was readily cured both thermally and photochemically. In addition, a polyphenol having an acetylenic group in the side chain was chemoselectively synthesized from *m*-ethynylphenol using peroxidase catalyst.[8]

α-(Alkyoxymethyl)acrylates are well-known to radically polymerize. Recently, stereocontrol was achieved by polymerization in the presence of a catalytic amount of a Lewis acid; zinc bromide catalytically affected the stereochemistry in the polymerization of α-(alkyoxymethyl)acrylate, yielding an isotactic polymer.[9] In the anionic polymerization of an α-(alkoxymethyl)- or α-(aminomethyl)acrylate, the strong coordination power of the α-substituent produced highly syndiotactic polymers.[10]

Scheme 1



1 **2**

Most lactones are readily polymerized by anionic initiators to give aliphatic polyesters. Very recently, 2-methylene-4-oxa-12-dodecanolide (**1**), a macrocyclic α-(alkyoxymethyl)acrylate, was subjected to vinyl polymerization by anionic initiators such as *n*-butyllithium and cyclohexylmagnesium bromide−tetramethylethylenediamine to produce isotactic polymers having a macrocyclic moiety in the main chain.[11] The present study deals with the lipase-catalyzed chemoselective ring-opening polymerization of **1** (Scheme 1). Relevant to this study, a seven-membered lactone having an acrylic group in the side chain using radical and anionic initiators was reportedly polymerized;[12] the radical initiator polymerized the acryl moiety to give a polymer having a lactone group in the side chain, and the ring-opening polymerization proceeded anionically, yielding a reactive polymer bearing the unsaturated group in the side chain.

The polymerization of **1** was carried out using *Candida antarctica* lipase in toluene at 60 °C. The enzyme showed high catalytic activity toward the ring-opening polymerization of lactones and transesterification between polyesters.[13] Figure 1 shows the ^{1}H NMR spectra of **1** and the resulting product after 24 h. Singlet peaks A and B due to the vinylidene moiety of **1** were observed at δ 5.7 and 6.3. After the polymerization, these peaks completely disappeared, and new peaks P and Q were seen at δ 5.8 and 6.2, respectively. The ratio of the integrated area of peaks P, Q, and S (α-methylene protons of the ether moiety) were 1:1:2, indicating that the monomer was quantitatively consumed and the vinylidene group did not react during the polymerization to give polyester (**2**). The polymer structure was confirmed by ^{13}C NMR spectroscopy (see Supporting Information). The pattern of the peaks of **2**, especially that of the α-(alkyoxymethyl)acrylate moiety, was very similar to that of **1**, although some peaks slightly shifted; in the case of the anionic vinyl polymerization, peaks B and C completely disappeared.[11] These data support that the lipase catalyst exclusively induced the ring-opening polymerization of **1**.

The polymerization results are summarized in Table 1. The monomer conversion was determined by ^{1}H NMR. The molecular weight of the polymer was estimated by size exclusion chromatography (SEC). In all cases, the lipase catalysis induced the polymerization to give **2**. Polymer formation was quantitative at 60 and 75 °C after 24 h (entries 4 and 8). The polymerization rate at 75 °C was somewhat larger than that at 60 °C.

10.1021/ma010893v CCC: $20.00
Published on Web 08/11/2001

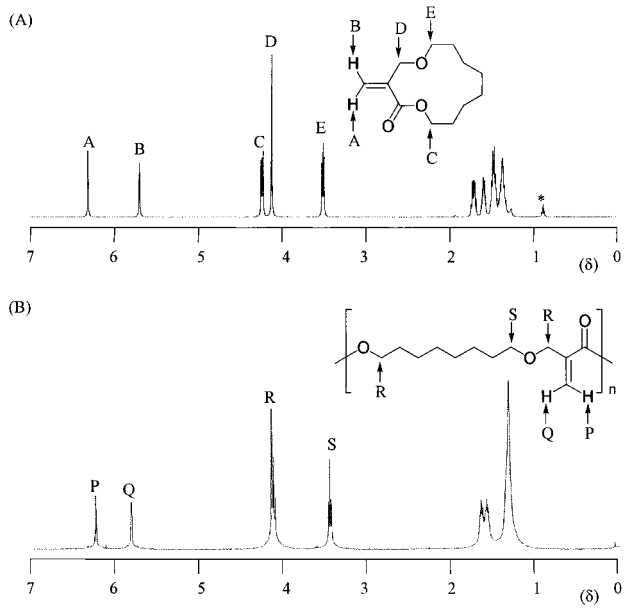


Figure 1. ^{1}H NMR spectra of (A) **1** and (B) **2** (entry 4).

Table 1. Lipase-Catalyzed Ring-Opening Polymerization of 1[a]

entry	temp (°C)	time (h)	conv[b] (%)	M_n[c]	M_w/M_n[c]
1	45	48	83	2600	1.6
2	60	4	55	3900	1.9
3	60	8	89	6100	2.0
4	60	24	100	7600	2.2
5[d]	60	24	0		
6	75	2	46	2900	1.4
7	75	4	77	4100	1.6
8	75	24	100	8100	1.9

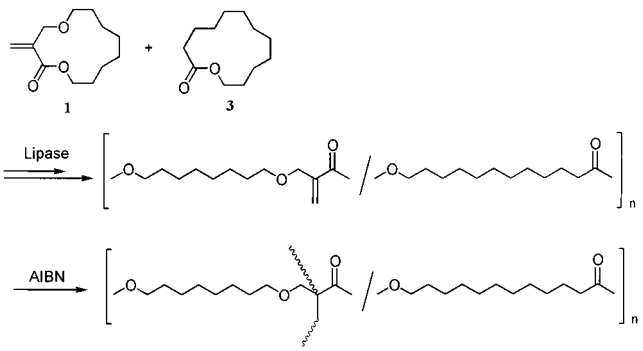
[a] Polymerization of **1** (1.0 mmol) using lipase catalyst (20 mg) in toluene (0.40 mL) under argon. [b] Determined by ^{1}H NMR. [c] Determined by SEC using THF eluent. [d] Without enzyme.

The polymerization also proceeded at 45 °C; however, the reaction rate was much smaller (entry 1). The molecular weight of **2** increased as a function of the polymerization time and temperature. In the polymerization without lipase (control experiment), the monomer was recovered unchanged (entry 5), indicating that the present polymerization took place via the lipase catalysis.

For reference, the polymerization of **1** using tin(II) octanoate, one of the most typical initiators for polymerization of lactones and lactides,[14] was examined. The reaction was carried out in the presence of tin(II) octanoate (5 mol % for **1**) at 100 °C in toluene for 24 h, resulting in recovery of all of the monomer unchanged, whereas ϵ-CL was, of course, quantitatively consumed under similar reaction conditions to give the corresponding polyester. These data imply that lipase is a very efficient catalyst for the ring-opening polymerization of **1** under milder reaction conditions.

A reactive copolyester was synthesized by the lipase-catalyzed ring-opening copolymerization of an equimolar mixture of **1** and 12-dodecanolide (**3**) at 60 °C in toluene for 24 h to give the copolymer with number-average molecular weight of 1×10^4 quantitatively (Scheme 2). The copolymer solution was kept at 60 °C in the presence of AIBN initiator (5 mol % for the lactones). After 1 h, the solution became a gel. The yield of an insoluble gel, determined by gravimetric measurement, was quantitatively achieved by cross-linking for 24 h.

Scheme 2



In conclusion, lipase catalysis chemoselectively induced the ring-opening polymerization of **1**, yielding a polyester having the reactive *exo*-methylene group in the main chain. This is significantly in contrast with the anionic vinyl polymerization of **1**; the present polymer **2** could not be obtained using a conventional chemical initiator under mild reaction conditions. Further studies on the enzymatic synthesis of functional polyesters via the selective catalysis of lipase and anionic polymerization of macrocyclic α-(alkoxymethyl)-acrylates are under way.

Acknowledgment. We acknowledge the gift of lipase from Novozymes Japan Ltd.

Supporting Information Available: Text describing the synthesis and enzymatic polymerization of **1** and ^{13}C NMR spectra of **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Kobayashi, S.; Shoda, S.; Uyama, H. *Adv. Polym. Sci.* **1995**, *121*, 1. (b) Kobayashi, S.; Shoda, S.; Uyama, H. In *The Polymeric Materials Encyclopedia*; Salamone, J. C., Ed.; CRC Press: Boca Raton, FL, 1996; pp 2102−2107. (c) Kobayashi, S.; Shoda, S.; Uyama, H. In *Catalysis in Precision Polymerization*; Kobayashi, S., Ed.; John Wiley & Sons: Chichester, 1997; Chapter 8. (d) Ritter, H. In *Desk Reference of Functional Polymers, Syntheses and Applications*; Arshady, R., Ed.; American Chemical Society: Washington, DC, 1997; pp 103−113. (e) Gross, R. A., Kaplan, D. L., Swift, G., Eds. *ACS Symp. Ser.* **1998**, *684*. (f) Kobayashi, S.; Uyama, H. In *Materials Science and Technology−Synthesis of Polymers*; Schlüter, A.-D., Ed.; Wiley-VCH: Weinheim, 1998; Chapter 16. (g) Joo, H.; Yoo, Y. J.; Dordick, J. S. *Korean J. Chem. Eng.* **1998**, *15*, 362. (h) Kobayashi, S.; Uyama, H.; Ohmae, M. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 613. (i) Kobayashi, S.; Uyama, H. In *Encyclopedia of Polymer Science and Technology*, 3rd ed.; Kroschwitz, J. I., Ed.; John Wiley & Sons: New York, in press. (j) Kobayashi, S.; Uyama, H.; Kimura, S. *Chem. Rev.*, in press.

(2) Ikada, Y.; Tsuji, H. *Macromol. Rapid Commun.* **2000**, *21*, 117.

(3) (a) Doi, Y. *Macromol. Symp.* **1995**, *98*, 585. (b) Lee, S. Y. *Biotechnol. Bioeng.* **1996**, *49*, 1. (c) Steinbüchel, A. *Macromol. Biosci.* **2001**, *1*, 1.

(4) (a) Fujimaki, T. *Polym. Degrad. Stab.* **1998**, *59*, 209. (b) Kricheldorf, H. R.; Kreiser-Saunders; I.; Damrau, D.-O. *Macromol. Symp.* **1999**, *144*, 269. (c) Spassky, N.; Simic, V. *ACS Symp. Ser.* **2000**, *764*, 146. (d) Duda, A.; Penczek, S. *ACS Symp. Ser.* **2000**, *764*, 160.

(5) (a) Kobayashi, S.; Uyama, H. In *Advance in Biopolyesters*; Babel, W., Steinbüchel, A., Eds.; Springer-Verlag: Heidelberg, 2001; pp 241−262. (b) Kobayashi, S.; Uyama, H. *Curr. Org. Chem.*, in press. (c) Kobayashi, S.; Uyama, H. In *Biopolymers*; Steinbüchel, A., Ed.; Wiley-VCH: Weinheim, Vol. 5, in press.

(6) (a) Uyama, H.; Takeya, K.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 56. (b) Uyama, H.; Takeya, K.; Hoshi, N.; Kobayashi, S. *Macromolecules* **1995**, *28*, 7046. (c) Kobayashi,

S.; Uyama, H.; Namekawa, S. *Polym. Degrad. Stab.* **1998**, *59*, 195. (d) Namekawa, S.; Uyama, H.; Kobayashi, S. *Proc. Jpn. Acad.* **1998**, *74B*, 65. (f) Namekawa, S.; Suda, S.; Uyama, H.; Kobayashi, S. *Int. J. Biol. Macromol.* **1999**, *25*, 145. (g) Kobayashi, S.; Uyama, H. *Macromol. Symp.* **1999**, *144*, 237.

(7) Uyama, H.; Lohavisavapanich, C.; Ikeda, R.; Kobayashi, S. *Macromolecules* **1998**, *31*, 554.

(8) Tonami, H.; Uyama, H.; Kobayashi, S.; Fujita, T.; Taguchi, Y.; Osada, K. *Biomacromolecules* **2000**, *1*, 149.

(9) (a) Habaue, S.; Okamoto, Y. *Chem. Rec.* **2001**, *1*, 46. (b) Habaue, S.; Uno, T.; Okamoto, Y. *Polym. J.* **1999**, *31*, 900. (c) Habaue, S.; Uno, T.; Baraki, H.; Okamoto, Y. *Macromolecules* **2000**, *33*, 820.

(10) (a) Habaue, S.; Yamada, H.; Okamoto, Y. *Macromolecules* **1996**, *29*, 3326. (b) Habaue, S.; Uno, T.; Okamoto, Y. *Macromolecules* **1997**, *30*, 3125.

(11) Morita, M.; Habaue, S.; Okamoto, Y. *Polym. Prepr. Jpn.* **2000**, *49*, 170, 1431.

(12) Mecerreyes, D.; Humes, J.; Miller, R. D.; Hedrick, J. L.; Detrembleur, C.; Lecomte, P.; Jérôme, R.; San Roman, J. *Macromol. Rapid Commun.* **2000**, *21*, 779.

(13) (a) Uyama, H.; Suda, S.; Kikuchi, H.; Kobayashi, S. *Chem. Lett.* **1997**, 1109. (b) Bisht, K. S.; Deng, F.; Gross, R. A.; Kaplan, D. L.; Swift, G. *J. Am. Chem. Soc.* **1998**, *120*, 1363. (c) Córdova, A.; Iversen, T.; Hult, K. *Macromolecules* **1998**, *31*, 1040−1045. Córdova, A.; Hult, A.; Hult, K.; Ihre, H.; Iversen, T.; Malmström, E. *J. Am. Chem. Soc.* **1998**, *120*, 13521. (d) Kumar, A.; Gross, R. A. *Biomacromolecules* **2000**, *1*, 133. (e) Kumar, A.; Kalra, B.; Dekhterman, A.; Gross, R. A. *Macromolecules* **2000**, *33*, 6303. (f) Kumar, A.; Gross, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 11767. (g) Takamoto, T.; Kerep, P.; Uyama, H.; Kobayashi, S. *Macromol. Biosci.*, in press.

(14) (a) Zhang, X.; Macdonald, D. A.; Goosen, M. F. A.; Mcauley, K. B. *J. Polym. Sci., Polym. Chem. Ed.* **1994**, *32*, 2970. (b) Albertsson, A.-C.; Gruvegård, M. *Polymer* **1995**, *36*, 1009. (c) Kricheldorf, H. R.; Kreiser-Saunders, I.; Boettcher, C. *Polymer* **1995**, *36*, 1253. (d) Liu, Y.; Schulze, M.; Albertsson, A.-C. *J. Macromol. Sci., Pure Appl. Chem.* **1998**, *A35*, 207. (e) Kowalski, A.; Duda, A.; Penczek, S. *Macromol. Rapid Commun.* **1998**, *19*, 567. (f) Kasperczyk, J. *Macromol. Chem. Phys.* **1999**, *200*, 903. (g) Duda, A.; Penczek, S. *ACS Symp. Ser.* **2000**, *764*, 160.

MA010893V