Lipase-Catalyzed Enantioselective Copolymerization of Substituted Lactones to Optically Active Polyesters

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ABSTRACT: Enantioselective copolymerization of racemic substituted lactones with achiral lactones has been examined by using *Candida antarctica* lipase as catalyst. In the copolymerization of racemic *β*-butyrolactone with 12-dodecanolide, the (*S*)-isomer was preferentially reacted to give the (*S*)-enriched optically active copolymer with enantiomeric excess of *β*-butyrolactone unit = 69%, which is much larger than that of the homopolymerization under similar reaction conditions. The absolute configuration of *β*-butyrolactone unit in the copolymer was confirmed by the acid-catalyzed methanolysis to methyl 3-hydroxybutyrate. *δ*-Caprolactone was also enantioselectively copolymerized by the lipase catalyst to give the optically active polyester. The highest ee value (76%) was achieved by the copolymerization of *δ*-caprolactone and 12-dodecanolide in diisopropyl ether.

Introduction

Synthesis of optically active polymers is an important topic in macromolecular science, since they have received much attention as functional materials such as chiral catalysts for asymmetric synthesis, packing materials of chromatographic columns for enantiomer separation, and chiral materials for the preparation of liquid crystal polymers.[1] Therefore, asymmetric polymerizations have been extensively examined for introduction of chirality to the polymer structure. Asymmetric polymerizations are classified into several categories, one of which is an enantioselective polymerization.

In the enantioselective polymerization, one isomer of a racemic monomer is preferentially polymerized to give an optically active polymer. So far, there have been a number of reports on enantioselective polymerizations of α-olefins, methacrylates, and small-sized cyclic compounds (propylene oxide, propylene sulfide, four-membered lactones, and α-amino acid *N*-carboxylic anhydrides (five-membered)).[1b] In most cases, combinations of metal catalysts and chiral cocatalysts have been used. As for the lactones, *β*-butyrolactone (**1a**) was reported to be enantioselectively polymerized by the $ZnEt_2$/(*R*)-(−)-3,3-dimethyl-1,2-butanediol system; however, the selectivity was low, and the propagation rate constant of the (*R*)-isomer was only 1.7 times larger than that of the antipode.[2] An enantioselective polymerization of racemic lactide (a mixture of D- and L-lactides) by a chiral Schiff's base complex of aluminum was reported.[3] At a low conversion, high enantiomeric enrichment in the polymer was observed. Its derivative complex also induced the syndiotactic polymerization of *meso*-lactide.[4]

Lipase is widely used as catalyst of enantio- and regioselective reactions in organic synthetic chemistry.[5] Recently, these characteristic catalyses have been utilized for synthesis of functional polymeric materials.[6] An optically active polyester was prepared by the enantioselective polycondensation of a racemic epoxide-containing activated diester with a diol monomer using porcine pancreas lipase (PPL).[7] As for the enzymatic ring-opening enantioselective polymerization to optically active polyesters, α-methyl-*β*-propiolactone was polymerized in the presence of *Pseudomonas fluorescens* lipase (lipase PF) to give the (*S*)-enriched polyester with enantiomeric excess (ee) value of 50%.[8] The enantioselective polymerization of **1a** took place in the presence of thermophilic lipases to give the polyester enriched in the (*R*)-isomer,[9,10] whose ee value was less than 40%. PPL, lipases derived from *Candida cylindracea* (lipase CC), and *Pseudomonas cepacia* also catalyzed the ring-opening polymerization of **1a**; however, the enantioselection did not occur.[11]

Scheme 1

1a: m=1
1b: m=3

2a: n=5
2b: n=10
2c: n=11
2d: n=14

Candida antarctica lipase (lipase CA) was reported to efficiently catalyze the ring-opening polymerization of achiral lactones and cyclic carbonates.[12] We examined the polymerization of **1a** catalyzed by lipase CA, resulting in the low polymerizability and enantioselectivity.[13] The present paper deals with lipase CA-catalyzed enantioselective copolymerization of racemic **1** with achiral lactones **2** (Scheme 1). The copolymerization increased the consumption rate of **1a**, leading to the improvement of the molecular weight and optical purity of the polymer. A six-membered substituted lactone, *δ*-caprolactone (**1b**), has also been enantioselectively copolymerized with the achiral lactones. To our knowledge, this is the first example of the synthesis of optically active polyesters from a racemic six-membered lactone.

Results and Discussion

Lipase-Catalyzed Enantioselective Copolymerization of *β*-Butyrolactone with Nonsubstituted Lactones. In this study, *ϵ*-caprolactone (**2a**), 11-undecanolide (**2b**), 12-dodecanolide (**2c**), and 15-pentadecanolide (**2d**) (7-, 12-, 13-, and 16-membered lactones, respectively) were used as achiral comonomer. At first, the lipase CA-catalyzed copolymerization of **1a** with **2c**

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Table 1. Ring-Opening Copolymerization of 1a with 2 Using Lipase CA as Catalyst[a]

entry	comonomer	solvent	time (h)	conv[b] (%)		ee$_m$[c] (%)	ee$_p$[d] (%)	$[\alpha]_{365}$[e]	M_n[f]	M_w/M_n[f]
				1a	**2**					
1	**2a**	diisopropyl ether	4	55	100	71 (R)	58	+5.7 (c = 3.1)	700	2.0
2	**2a**	heptane	2	61	96	83 (R)	53	+12 (c = 2.4)	800	2.0
3	**2a**	heptane	9	71	100	100 (R)	41	+8.2 (c = 2.6)	2300	1.5
4	**2c**	diisopropyl ether	4	59	100	100 (R)	69	+4.9 (c = 6.1)	1200	2.3
5	**2c**	heptane	6	67	100	100 (R)	49	+4.6 (c = 5.1)	1400	3.6
6	**2c**	heptane	9	76	100	100 (R)	32	+3.3 (c = 5.3)	1700	3.2
7	**2c**	isooctane	6	67	100	100 (R)	49	+4.3 (c = 5.0)	1500	3.8

[a] Copolymerization of **1a** with **2** (1.0 mmol each) using lipase CA (50 mg) as catalyst at 60 °C in an organic solvent (5 mL). [b] Determined by GC. [c] Enantiomeric excess of unreacted **1a**, determined by using chiral GC on a Chiraldex G-TA column. In parentheses, configuration of the major unreacted monomer. [d] Enantiomeric excess of **1a** unit in the copolymer, calculated on the basis of conversion and optical purity of unreacted **1a**. [e] Measured in chloroform at room temperature. [f] Determined by SEC.

(equimolar feed ratio) was carried out in diisopropyl ether at 60 °C for 4 h (entry 4 in Table 1). After workup procedures, the gas chromatographic (GC) analysis confirmed the conversion of **1a** to be 59% and the quantitative consumption of **2c**. The optical purity of the unreacted monomer was analyzed by using a chiral GC system. Only one peak was detected, and the comparison with the authentic samples ((*R*)- and (*S*)-**1a**) showed the (*R*)-configuration of the residual monomer. On the basis of these data, the (*S*)-content of the **1a** unit in the copolymer was estimated as 85% (ee = 69%). When other lipases such as PPL, lipase CC, and PF were used as the copolymerization catalyst, **1a** was not reacted even for longer reaction time in the bulk.

The copolymer was isolated by removal of the solvent and residual **1a** from the reaction mixture under reduced pressure. The number-average molecular weight and polydispersity were determined by size exclusion chromatography (SEC) to be 1200 and 2.3, respectively. The specific rotation ($[\alpha]_{365}$) of the copolymer was +4.9° (c = 6.1, chloroform).

Lipase-catalyzed reactions are well-known to proceed via an acyl-enzyme intermediate. In the postulated mechanism of the lipase-catalyzed polymerization of lactones,[14] the key step is the reaction of the lactone with the serine residue of lipase involving the ring opening of the lactone to produce the acyl-enzyme intermediate. If the reaction of **1a** proceeds in a similar manner, the bond cleavage between the carbonyl carbon and oxygen atom of the lactone takes place, in which the configuration is retained (see Supporting Information).[15] On the other hand, opening of the monomer at the alkyl−oxygen bond results in inversion or racemization of configuration.

To examine the absolute configuration of **1a** unit in the copolymer, the acid-catalyzed methanolysis was carried out, in which the **1a** unit was converted into methyl 3-hydroxybutyrate.[9] From the data of the derivative obtained by the reaction with (*R*)-(+)-phenylethylisocyanate, the configuration of methyl 3-hydroxybutyrate was of (*S*)-form with optical purity of 92% (ee = 85%), which was fairly close to the calculated value on the basis of the conversion and optical purity of the unreacted monomer. These data support that the present copolymerization proceeds via the acyl cleavage, and (*S*)-**1a** is preferentially copolymerized to give the (*S*)-enriched polyester.[10]

As a model reaction, **1a** has been reacted with methanol using lipase CA catalyst in bulk. The reaction proceeded even at room temperature. After 3 h, the conversion reached 50% to give methyl 3-hydroxybutyrate, and the ee value of unreacted **1** was 73% in (*R*)-enriched form, supporting the larger reactivity of

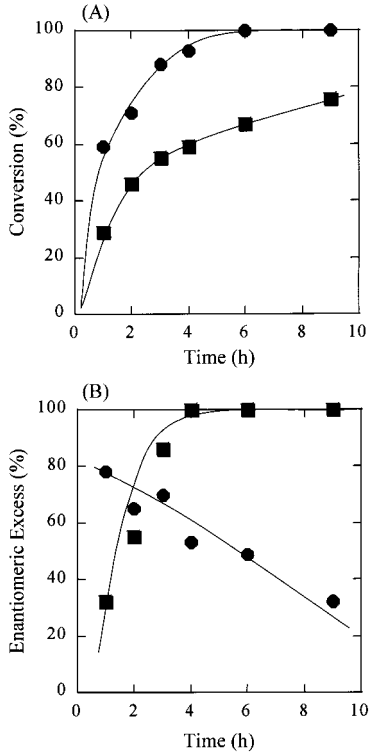

Figure 1. Relationships between reaction time and (A) conversion of **1a** (■) and **2c** (●) and (B) enantiomeric excess of (*R*)-enriched unreacted **1a** (■) and (*S*)-enriched **1a** unit in the copolymer (●). The copolymerization of **1a** and **2c** was performed using lipase CA as catalyst in heptane at 60 °C.

(*S*)-isomer of **1a** toward lipase CA catalyst than that of the antipode. In the case of the PPL-catalyzed reaction of **1a** and benzyl alcohol, it is to be noted that the (*S*)-isomer of **1a** was preferentially reacted to give benzyl (*S*)-3-hydroxybutyrate, and unreacted **1a** was mainly of the (*R*)-form.[16]

Table 1 summarizes the copolymerization results. In the combination of **1a** and **2c**, the enantioselective copolymerization took place in other solvents, heptane and isooctane (entries 5−7), although the ee and specific rotation values were slightly lower than those in diisopropyl ether (entry 4). Lipase CA also induced the enantioselective copolymerization of **1a** with **2a** to give the optically active polyester (entries 1−3). The highest specific rotation was achieved in the short reaction period (entry 2). The molecular weight increased as a function of time; however, the optical purity decreased.

The copolymerization of **1a** and **2c** in heptane was monitored by GC. The consumption rate of **1a** was smaller than that of **2c** (Figure 1A). In the initial stage

Table 2. Ring-Opening Copolymerization of 1b with 2 Using Lipase CA as Catalyst[a]

entry	comonomer	solvent	temp (°C)	time (h)	conv[b] (%) 1b	conv[b] (%) 2	yield[c] (%)	ee_m[d] (%)	ee_p[e] (%)	$[\alpha]_{365}$[f]	M_n[g]	M_w/M_n[g]
1	**2a**	diisopropyl ether	60	4	26	100	48[h]	11 (S)	32	−2.1 (c = 0.9)	3100	2.9
2	**2a**	heptane	60	4	48	100	48[h]	21 (S)	21	−3.3 (c = 2.9)	2000	2.3
3	**2b**	heptane	60	4	48	78	20	32 (S)	35	−3.7 (c = 2.5)	5900	2.2
4	**2c**	heptane	45	8	46	100	35	52 (S)	61	−3.3 (c = 2.9)	9300	2.3
5	**2c**	diisopropyl ether	60	4	35	100	33	21 (S)	76	−1.6 (c = 1.1)	6000	1.9
6	**2c**	heptane	60	4	44	100	38	42 (S)	53	−2.4 (c = 4.0)	7000	2.5
7	**2c**	heptane	75	2	64	100	41	47 (S)	26	−2.1 (c = 5.2)	9200	3.4
8	**2d**	heptane	60	4	46	100	44	30 (S)	35	−8.8 (c = 2.6)	6100	3.1

[a] Copolymerization of **1b** with **2** (1.0 mmol each) using lipase CA (50 mg) as catalyst in an organic solvent (5 mL). [b] Determined by GC. [c] Methanol-insoluble part. [d] Enantiomeric excess of unreacted **1b**, determined by using chiral GC on a Chiraldex G-TA column. In parentheses, configuration of the major unreacted monomer. [e] Enantiomeric excess of **1b** unit in the copolymer, calculated on the basis of conversion and optical purity of unreacted **1b**. [f] Measured in chloroform at room temperature. [g] Determined by **SEC**. [h] Hexane-insoluble part.

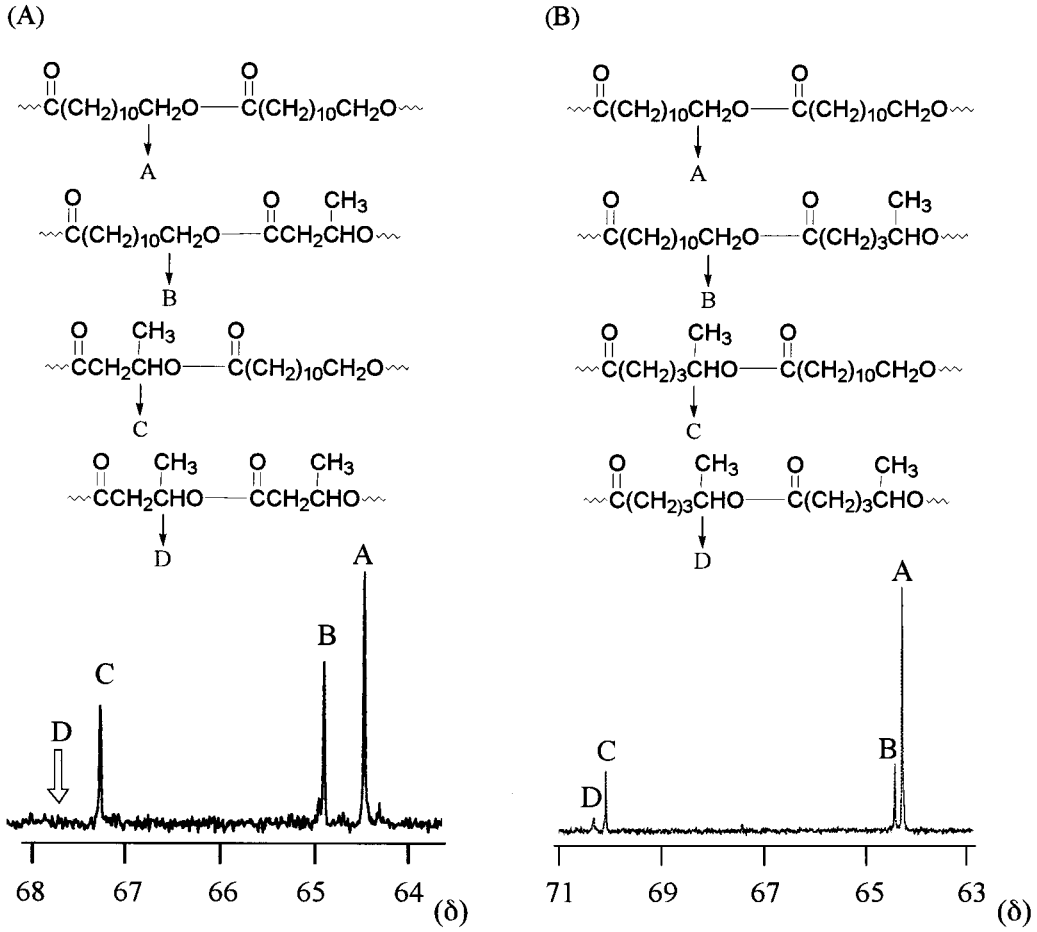

Figure 2. Expanded ^{13}C NMR spectra of (A) the copolymer from **1a** and **2c** (entry 4 in Table 1) and (B) the copolymer from **1b** and **2c** (entry 6 in Table 2).

(after 1 h), the monomer conversion of (*S*)-**1a** was about 8.7-fold larger than that of the (*R*)-isomer, whose value was much larger than the reported one by chemical catalyst.[2] At the higher conversions, the ee value of the polymer decreased (Figure 1B). This drop in selectivity is probably because the relative concentration of the less reactive isomer ((*R*)-isomer) increased in the monomer pool as the preferable enantiomer was incorporated in the copolymer.

Lipase-Catalyzed Enantioselective Copolymerization of *δ*-Caprolactone with Nonsubstituted Lactones. *δ*-Caprolactone (**1b**) having three methylene units is more flexible in ring structure than **1a**, and hence, the optical resolution of **1b** will be difficult by conventional chemical catalysts. It was reported that resolution of racemic **1b** took place only by hog or pig liver esterase catalysis in water, in which the (*R*)-isomer was preferentially hydrolyzed to give the corresponding (*R*)-oxyacid with moderate ee.[17]

In the lipase CA-catalyzed polymerization of **1b** in bulk at 60 °C for 24 h, 54% of the monomer was consumed to produce the (*R*)-enriched polymer of ee = 14% with molecular weight of 920. The polymerization did not take place in organic solvents. The stereochemistry of the product oligomer was similar to that by the esterase resolution;[17] however, the optical purity and molecular weight were relatively low. Thus, the copolymerization with achiral lactones (**2**) has been examined (Table 2). After the copolymerization, the reaction mixture was poured into a large amount

of methanol or hexane to give the white powdery polymer.

In all cases examined, the enantioselection of **1b** occurred to give the optically active polyester. In the combination of **1b** and **2a**, the ee value was not high (entries 1 and 2). The effect of temperature was examined in the polymerization of **1b** and **2c** in heptane (entries 4, 6, and 7). The optical purity of the polymer decreased as a function of temperature. In the reaction of **1b** and **2c** in diisopropyl ether, the highest ee value (76%) was achieved (entry 5).

Microstructure of Copolymer. Copolymer structure was confirmed by ^{1}H and ^{13}C NMR spectroscopies. Microstructural analysis of the copolymer was examined. A statistically binary copolymer has four different diads. In the case of the enzymatic copolymerization of achiral lactones, random copolymers were often formed.[18] In the expanded ^{13}C NMR spectrum of the copolymer from **1a** and **2c** (entry 4 in Table 1) in the region of δ 64−68 (Figure 2A), observed were three peaks due to C(=O)O*C*H$_2$C or C(=O)O*C*H(CH$_3$)C. No peak due to the **1a**−**1a** homolinkage unit was observed, suggesting the lower reactivity of the secondary alcohol derived from **1a**; i.e., the conditions for the homopolymerization of **1a** without solvent brought about the low enantioselectivity.[13] On the other hand, the terminal secondary alcohol of the polymer is preferentially reacted with a nonsubstituted lactone under milder reaction conditions to give polymers with higher optical purity. In the case of the copolymer from **1b** and **2c,** there was a small peak ascribed to **1b**−**1b** homolinkage (Figure 2B). This may be because of the larger enzymatic reactivity of the resulting alcohol from **1b** than that from **1a**.

Conclusion

The enantioselective copolymerization of racemic substituted lactones (**1**) with achiral nonsubstituted lactones (**2**) took place through lipase CA catalysis. In the case of β-butyrolactone (**1a**), the (*S*)-isomer possessed a larger polymerizability than the antipode to give the polymer with relatively high optical purity in the (*S*)-enriched form. The enantioselective conversion of six-membered lactone (**1b**) to the optically active polyester is the first case achieved by using lipase catalyst, in which the (*R*)-isomer was preferentially copolymerized.

Experimental Section

Materials. Lactone monomers and polymerization solvents were commercially available and stored over freshly activated type 4 molecular sieves. Lipases CA and PF were kindly donated by Novo Nordisk Bioindustry Ltd. and Amano Pharmaceutical Co., respectively. Lipase CC and PPL were purchased from Biocatalysts, Ltd., and Sigma Chemical Co., respectively. Lipases were used without further purification.

Enzymatic Copolymerization. A typical run was as follows (entry 4 in Table 1). A mixture of **1a** (1.0 mmol, 0.086 g), **2c** (1.0 mmol, 0.20 g), lipase CA (50 mg), and diisopropyl ether (5.0 mL) was placed in a dried test tube, and the tube was sealed. The tube was kept under gentle stirring at 60 °C for 4 h and then opened. After the evaporation of the solvent under reduced pressure, the residue was extracted with tetrahydrofuran, and part of the organic solution was separated by filtration. The filtrate was used for SEC and GC analyses.

Measurements. SEC analysis was carried out by using a Tosoh SC8010 apparatus equipped with refractive index (RI) detector at 40 °C under the following conditions: TSKgel G3000H$_{HR}$ column and tetrahydrofuran eluent at a flow rate of 1.0 mL/min. The calibration curves were obtained using polystyrene standards. NMR spectra were recorded on a Bruker DPX400 spectrometer. GC analysis was carried out using a Shimadzu GC-14B apparatus equipped with an FID detector and a TC-5 column for monomer conversion (GL Sciences) or a Chiraldex G-TA column for chiral resolution (Tokyo Kasei). The specific rotation measurement was performed by a JASCO P-1010 polarimeter.

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Supporting Information Available: Scheme for mode of ring opening of (*S*)-**1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) In the bulk homopolymerization at 60 °C for 24 h, 59% of **1a** was consumed to give oligomers with M_n = 400. The calculated ee value of the resulting oligomer based on the optical purity of the unreacted monomer was only 4% in (*S*)-enriched form. Furthermore, **1a** was not enzymatically polymerized in organic solvents under the similar reaction conditions as the present copolymerization. Under the similar reaction conditions, nonsubstituted lactones (**2a**−**2d**) were quantitatively polymerized to give the polymers with much higher molecular weight.[12a,j]

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