Enzymatic Ring-Opening Polymerization and Copolymerization of 8-Octanolide by Lipase Catalyst

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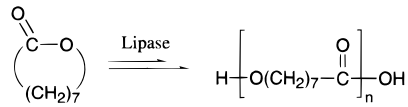
ABSTRACT: Enzymatic ring-opening polymerization and copolymerization of a nine-membered lactone, 8-octanolide (8-OL), was performed in isooctane by using various lipases of different origin as catalyst. The polymerization behavior greatly depended on the lipase origin. *Candida antarctica* and *Pseudomonas cepacia* lipases (lipases CA and PC, respectively) showed high catalytic activity toward the present polymerization. *Pseudomonas fluorescens* lipase (lipase PF) also catalyzed the polymerization of 8-OL. The polymerization catalyzed by lipase CA proceeded much faster than that using other lipases. In the polymerization using lipase PC at 75 °C for 240 h, the polymer with number-average molecular weight of 1.6×10^4 was obtained. 8-OL monomer was recovered unchanged in the polymerization without the enzyme. The initial rate of the polymerization of lactones in different ring size was determined in the presence of 1-octanol. In case of lipase PC or PF, the rate increased with increasing ring size, whereas there was a minimum point for the rate in using 8-OL in the polymerization catalyzed by lipase CA. The enzymatic copolymerization of 8-OL with ϵ-caprolactone or 12-dodecanolide was performed to give the corresponding copolymers having molecular weights of several thousands. According to ^{13}C NMR analysis, the copolymer showed a random structure.

Introduction

Enzyme-catalyzed reactions in organic solvents have become increasingly important in organic synthesis.[1−3] Recently, an enzyme-catalyzed polymerization ("enzymatic polymerization") has been found to provide new polymeric materials.[4−7] Characteristic properties of enzyme catalysis afforded novel polymerization reactions to produce polymers which are often difficult to synthesize by conventional polymerizations. Chemical synthesis of cellulose was first achieved by the polymerization of β-cellobiosyl fluoride in an aqueous acetonitrile catalyzed by cellulase,[8] which is a hydrolysis enzyme of cellulose in nature. This methodology has been applied to synthesis of natural and nonnatural polysaccharides.[9,10] In vitro enzymatic syntheses of polyesters[11−13] and polyaromatics[14−16] have been also extensively investigated for these several years.

Small- (four-membered) and medium-size (six- and seven-membered) lactones are polymerized by various chemical catalysts and initiators.[17] Lipase catalysis has been reported to induce the ring-opening polymerization of these lactones as well as macrolides (12-, 13-, and 16-membered lactones).[18−25] Using traditional catalysts, the macrolides showed much lower reactivity and polymerizability than ϵ-caprolactone (seven-membered lactone, ϵ-CL) due to their lower ring strain.[26,27] However, they were enzymatically polymerized much faster than ϵ-CL, probably due to the strong recognition of the macrolide by lipase.[22−24] The polymerization involves the acyl−lipase intermediate, which is given from the lactone and the serine residue of lipase.[22] The rate-determining step is supposed to be the formation of the intermediate by kinetics;[28] therefore, the polymerization proceeds via a "monomer-activated mechanism".

Scheme 1



8-OL

Polymerization of a nine-membered lactone, 8-octanolide (8-OL), has been performed by neither chemical nor enzymatic catalysts in detail. The alkaline hydrolysis rate of 8-OL is intermediate between those of ϵ-CL and the macrolides.[26] In a series of polyester synthesis via lipase-catalyzed ring-opening polymerization of lactones with different ring sizes, we have first used 8-OL as a new monomer of the enzymatic polymerization and investigated the effect of the ring sizes on the polymerizability (Scheme 1).

Results and Discussion

Enzymatic Polymerization of 8-OL. Our previous studies on the lipase-catalyzed ring-opening polymerization of lactones showed that the lipase origin greatly affected the polymerization. In this study, five lipases with different origin were used as catalyst: lipases derived from *Candida antarctica* (lipase CA), *Candida cylindracea* (lipase CC), *Pseudomonas aeruginosa* (lipase PA), *Pseudomonas cepacia* (lipase PC), and *Pseudomonas fluorescens* (lipase PF). Lipase CA is an immobilized enzyme on polymer beads and the others are powdery enzymes. Polymerization was carried out in isooctane at 60 °C for 240 h (Table 1). The molecular weight was determined by size exclusion chromatography (SEC).

The highest monomer conversion was achieved in using lipase CA (entry 1). The polymerization catalyzed by lipase PC afforded the polymer of the highest molecular weight in good yields (entry 4). Lipase PF

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Table 1. Enzyme Screen for Ring-Opening Polymerization of 8-OL[a]

	lipase					
entry	origin	code	convn[b] (%)	M_n[b] ($\times10^{-3}$)	M_w[b] ($\times10^{-3}$)	M_w/M_n[b]
1	*Candica antarctica*	lipase CA	95	3.6	7.2	2.0
2	*Candida cylindracea*	lipase CC	15	0.5	0.6	1.2
3	*Pseudomonas aeruginosa*	lipase PA	6	<0.5		
4	*Pseudomonas cepacia*	lipase PC	81	9.7	16	1.6
5	*Pseudomonas fluorescens*	lipase PF	38	8.5	14	1.7
6	*c*		0			

[a] Polymerization of 8-OL (1.0 mmol) using lipase catalyst (0.10 g) in isooctane (5 mL) at 60 °C for 240 h. [b] Determined by SEC. [c] Without enzyme.

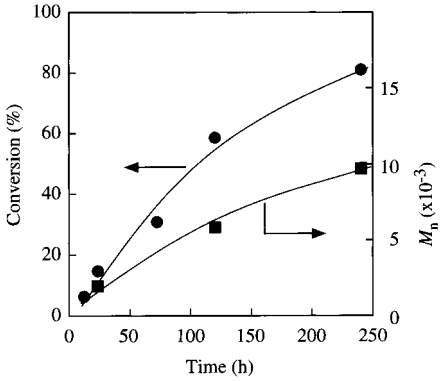


Figure 1. Polymerization time vs monomer conversion and number-average molecular weight of the polymer in the polymerization of 8-OL catalyzed by lipase PC at 60 °C.

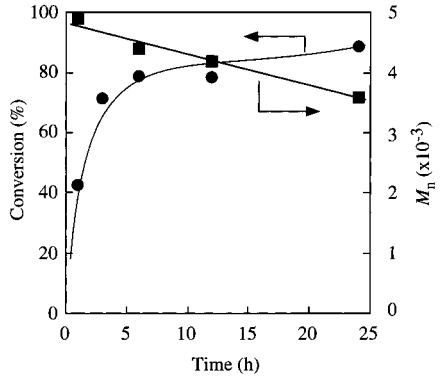


Figure 2. Polymerization time vs monomer conversion and number-average molecular weight of the polymer in the polymerization of 8-OL catalyzed by lipase CA at 60 °C.

provided the polymer of relatively high molecular weight, however, the conversion was not high (entry 5). Lipases CC and PA showed less catalytic activity toward the present polymerization (entries 2 and 3). 8-OL monomer was recovered unchanged in the polymerization without enzyme (entry 6), indicating that the polymerization of 8-OL proceeded through enzyme catalysis. The polymer structure was confirmed by ^{1}H and ^{13}C NMR spectroscopies.

Lipases CA and PC showing the high catalytic activity are mainly used for subsequent experiments throughout the present study. Figure 1 shows time vs the monomer conversion and the number-average molecular weight in the polymerization catalyzed by lipase PC at 60 °C. The molecular weight gradually increased with increased conversion. In case of lipase CA, on the other hand, the molecular weight slightly decreased during the polymerization (Figure 2). Similar behaviors were observed in the lipase-catalyzed polymerization of 7- and 16-membered lactones.[20,25] This may be because of the enzymatic hydrolysis of the polymer chain and/or the

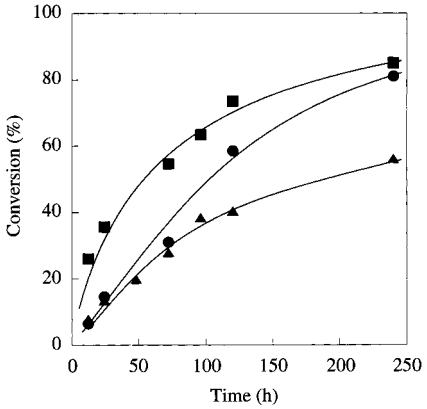


Figure 3. Time−conversion curves in the polymerization of 8-OL catalyzed by lipase PC at (▲) 45, (●) 60, (■) 75 °C.

Table 2. Lipase-Catalyzed Ring-Opening Polymerization of 8-OL Using Lipases CA and PC[a]

entry	lipase	temp (°C)	time (h)	convn[b] (%)	M_n[b] ($\times10^{-3}$)	M_w[b] ($\times10^{-3}$)	M_w/M_n[b]
1	lipase CA	45	12	67	4.4	6.2	1.4
2	lipase CA	45	120	83	5.4	8.1	1.5
3	lipase CA	60	12	78	3.7	7.0	1.9
4	lipase CA	60	120	91	3.9	7.4	1.9
5	lipase CA	75	12	72	5.2	7.7	1.5
6	lipase CA	75	120	87	5.0	9.0	1.8
7	lipase PC	45	120	40	5.0	6.0	1.2
8	lipase PC	45	240	59	5.1	6.1	1.2
9	lipase PC	60	120	59	5.8	10	1.8
10	lipase PC	60	240	81	9.7	16	1.6
11	lipase PC	75	120	74	14	20	1.4
12	lipase PC	75	240	85	16	22	1.4

[a] Polymerization of 8-OL (1.0 mmol) using lipase catalyst (0.10 g) in isooctane (5 mL). [b] Determined by SEC.

increase in the initiation of the polymerization, resulting in the higher total chains and lower molecular weight.[25] The polymerization rate was also very much dependent on the enzyme type. The polymerization catalyzed by lipase CA proceeded much faster than that by lipase PC: the monomer conversion reached 70% only after 3 h in using lipase CA catalyst. The difference of the polymerization behaviors between lipases CA and PC may be based on the enzyme origin. As to the lipase-catalyzed polymerization of lactones with other ring sizes, it was observed that the polymerization rate and the molecular weight of the polymer strongly depended on the lipase origin.[18,22−24,29]

Next, the effect of the polymerization temperature was examined. Figure 3 shows time−conversion curves in the lipase PC-catalyzed polymerization at 45, 60, and 75 °C. The higher the temperature, the larger the polymerization rate is. The molecular weight also increased as a function of the temperature (Table 2). Similar polymerization results were given in using *Pseudomonas* family lipases as catalysts for the poly-

Table 3. Dipole Moment, Rate Constants of Alkaline Hydrolysis and Anionic Polymerization, and Initial Rates of Lipase-Catalyzed Polymerization of Lactones

lactone		dipole	rate constant		initial rate[d] ($\times 10^5$, mol·L^{-1}·h^{-1}·mg^{-1})		
code	ring size	moment[a] (μ)	alkaline hydrolysis[a,b] ($\times 10^4$, L·mol^{-1}·min^{-1})	anionic polymn[c] ($\times 10^4$, min^{-1})	lipase CA	lipase PC	lipase PF
ϵ-CL	7	4.45	2550	12	2300	0.42	1.3
8-OL	9	2.25	116		48	2.2	1.8
DDL	13	1.86	6.0	1.5	1600	4.8	2.5
PDL	16	1.86	6.5		4700	11	8.5
butyl caproate		1.75	8.4				

[a] Data from ref 26. [b] Alkaline: NaOH. Measured in 1,4-dioxane/water (60/40 vol %) at 0 °C. [c] Data from ref 27. Measured using NaOMe initiator (6 mol %) in THF at 0 °C. [d] Polymerization of lactone (0.30 mol·L^{-1}) was carried out using lipase catalyst in the presence of 1-octanol (0.03 mol·L^{-1}) in isopropyl ether at 60 °C.

merization of seven-membered and macrocyclic lactones.[22−24,29] The polymerization at 75 °C produced a polymer with a molecular weight higher than 1×10^4 (entries 11 and 12). In case of lipase CA, the reaction rate and the molecular weight of the polymer scarcely changed in the range from 45 to 75 °C (entries 1−6). In the polymerization of an α-methyl-substituted medium-size lactone catalyzed by lipase CA, a relatively low temperature (35 or 45 °C) provided a higher polymerization rate than 60 °C.[30] These data suggest that the monomer structure as well as the lipase origin affected the polymerization behaviors.

Comparison of Enzymatic Polymerizability between 8-OL and Other Lactones. Reactivities of cyclic compounds generally depend on their ring size. In this study, the enzymatic reactivity of 8-OL was quantitatively compared with those of lactones in different ring size. It is well-known that the ring strain of seven-membered lactone (ϵ-CL) is large, so ϵ-CL possesses a high reactivity in alkaline hydrolysis and anionic polymerizability.[26,27] On the other hand, the macrolides (12−16 membered) having almost no strain in the ring show reactivities similar to those of fatty acid alkyl esters in the hydrolysis.

Table 3 gives dipole moment values, rate constants of alkaline hydrolysis and anionic polymerization, and initial rates of lipase-catalyzed polymerization of lactones. Dipole moment can be taken as an indication of ring strain. The dipole moment value of 8-OL is smaller than that of ϵ-CL, but a little larger than those of the macrolides, 12-dodecanolide (13-membered lactone, DDL), and 15-pentadecanolide (16-membered lactone, PDL). The rate constants of alkaline hydrolysis in these lactones show a similar tendency. From these results, it is supposed that ring strain and chemical reactivities of 8-OL are intermediate between ϵ-CL and the macrolides.

In the present study, the enzymatic polymerizability was evaluated by the initial polymerization rate. Very recently, we have performed the kinetics on the enzymatic polymerization of lactones in the presence of 1-octanol and found that the rate of the monomer consumption was regarded as the polymerization rate in the initial stage of the polymerization.[28] Here, the polymerization was carried out in the presence of 1-octanol in isopropyl ether. The initial rate of four lactone monomers was determined by using gas chromatography (GC). For all the monomers examined in this study, the initial rate of lipase CA was much larger than that of lipase PC or PF (Table 3). In case of the 8-OL polymerization, the rate using lipase CA was more than 20 times larger than that using lipase PC. For other lactones, a much larger difference was observed.[31]

Table 4. Ratio of Initial Reaction Rate in Lipase-Catalyzed Ring-Opening Copolymerization of 8-OL and ϵ-CL[a]

	ratio of initial reaction rate[b]	
feed 8-OL:ϵ-CL	lipase CA[c] 8-OL:ϵ-CL	lipase PC[d] 8-OL:ϵ-CL
20:80	5:95	35:65
50:50	38:62	57:43
80:20	54:46	93:7

[a] Copolymerization of lactones (1.5 mmol) in the presence of 1-octanol (0.15 mmol) at 60 °C in isopropyl ether (5 mL). [b] Determined by GC. [c] Enzyme amount of 2.5 mg. [d] Enzyme amount of 100 mg.

In the polymerization catalyzed by lipase PC or PF, the initial rate increased as a function of the ring size, whereas the rate of 8-OL was the smallest among four lactones by lipase CA catalysis. This specific behavior of 8-OL toward lipase CA will be our future problem to be solved. The monomer conformation and the heterogenity of the reaction mixture also might have an influence on the polymerization behaviors.

Enzymatic Copolymerization of 8-OL with Other Lactones. We have already reported that the ring-opening copolymerization of lactones proceeded though enzyme catalysis. In the combination of δ-valerolactone (six-membered lactone) and ϵ-CL, the copolymer having both units randomly was obtained by using lipase PF catalyst.[32] The copolymerization of ϵ-CL and PDL in the presence of lipase PF afforded the corresponding copolymer, which was not statistically random.[25]

In the copolymerization of 8-OL with ϵ-CL, the ratio of the initial reaction rates of both monomers was determined (Table 4). The copolymerization was performed using lipase CA or PC catalyst in the presence of 1-octanol in isopropyl ether at 60 °C. In case of lipase CA catalyst, a small amount of the enzyme was used owing to the high reactivity toward the lactones. In the lipase CA catalyzed copolymerization, 8-OL showed less reactivity than ϵ-CL, whereas the opposite tendency was observed in using lipase PC. This is consistent with the enzymatic reactivity of both monomers in the homopolymerization shown in Table 3.

Next, the enzymatic copolymerization of 8-OL with other lactones was performed by using lipase CA as catalyst for 48 h. The comonomers used were ϵ-CL and DDL. Copolymerization results are summarized in Table 5. The lower the feed ratio of 8-OL, the higher the yield of the copolymer in both combinations, which tendency well agreed with that of their enzymatic polymerizability. In all cases, the content of 8-OL unit in the copolymer, determined by ^{1}H NMR, was very close to the feed ratio. This may be because most of

Table 5. Lipase-Catalyzed Ring-Opening Copolymerization of 8-OL with Other Lactones

	copolymerization[a]		copolymer				
entry	co-monomer	feed of 8-OL (mol %)	convn[b] (%)	content of 8-OL[c] (mol %)	M_n[b] ($\times 10^{-3}$)	M_w[b] ($\times 10^{-3}$)	M_w/M_n[b]
1	ϵ-CL	25	95	22	5.4	11	2.0
2	ϵ-CL	50	87	47	5.4	10	1.9
3	ϵ-CL	75	82	68	4.9	8.3	1.7
4	DDL	25	97	29	8.9	17	1.9
5	DDL	50	93	47	8.6	16	1.9
6	DDL	75	84	75	5.7	11	1.9

[a] Copolymerization of lactones (1.0 mmol) using lipase CA catalyst (0.10 g) at 60 °C for 48 h in isooctane (5 mL). [b] Determined by SEC. [c] Data of isolated copolymer, determined by ^{1}H NMR.

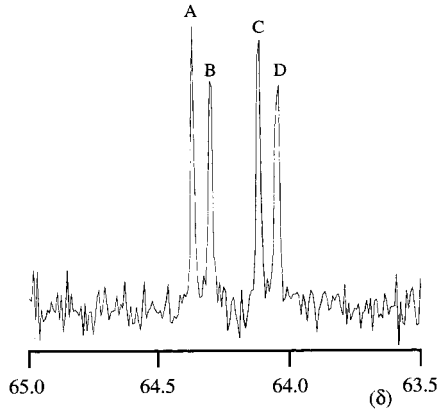


Figure 4. Expanded ^{13}C NMR spectrum (100 MHz) of copolymer (entry 2) in $CDCl_3$.

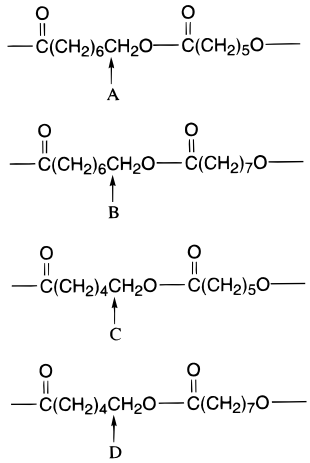
both monomers were consumed for the long reaction time despite the large difference of the enzymatic reactivity of both monomers. In the copolymerization of 8-OL with ϵ-CL, the number-average molecular weight of the copolymer was ca. 5×10^3 and hardly changed for the feed ratios examined (entries 1−3). The molecular weight of the copolymer obtained from 8-OL and DDL depended on the feed ratio: the molecular weight increased with a decrease in the feed of 8-OL (entries 4−6).

The microstructure of the copolymer was analyzed by ^{13}C NMR spectroscopy. Figure 4 shows an enlarged NMR spectrum of the copolymer from 8-OL and ϵ-CL (entry 2) in the region of δ 63.5−65.0. A statistically binary copolymer has four different diads, to which the four peaks due to C(=O)OCH_2C are corresponding. The assignment is shown in Scheme 2. The peak area of the four peaks was almost the same, implying the formation of the random copolymer. The ^{13}C NMR analysis showed that the copolymer from 8-OL and DDL was also of random structure (data not shown). In the homopolymerization of these lactones catalyzed by lipase CA, the polymerizabilities were different with each other, as shown in Table 3. The formation of the random copolymer suggested the occurrence of transesterification between the polymers via the lipase catalysis during the copolymerization.

Conclusion

A nine-membered lactone, 8-OL, was polymerized through lipase catalysis to produce the corresponding polyester. The polymerization behavior depended on the enzyme origin and polymerization conditions. Lipase CA showed a very high activity, and lipases PC and PF were also active as catalysts for the polymerization of 8-OL. The enzymatic reactivity of 8-OL was quantitatively evaluated by using the initial polymerization rate and compared with those of other lactones of different ring sizes. The lipase-catalyzed copolymerization of 8-OL with ϵ-CL and DDL produced the random copolymers. Further investigations on chemical polymerizability of lactones including 8-OL and enzymatic polymerization of lactones of other ring sizes are now underway in our laboratory.

Scheme 2



Experimental Section

Materials. 8-OL was synthesized according by the reaction of cyclooctanone with *m*-chloroperbenzoic acid in dichloromethane.[33] ϵ-CL, DDL, PDL, and polymerization solvents (isooctane and isopropyl ether) were stored over freshly activated type 4 molecular sieves. Lipases CA and PA were gifts from Novo Nordisk Bioindustry, Ltd. and Nagase Seikagaku Co., respectively. Lipases PC and PF were donated by Amano Pharmaceutical Co. Lipase CC was purchased from Biocatalysts, Ltd. Lipases were used without further purification.

Enzymatic Ring-Opening Polymerization of 8-OL. A typical run was as follows (entry 1 in Table 1). A 0.14 g (1.0 mmol) sample of 8-OL, 0.10 g of lipase CA, and isooctane (5 mL) were placed in a dried tube and sealed. The tube was kept under gentle stirring at 60 °C for 240 h. After the evaporation of the solvent under reduced pressure, the residue was extracted with chloroform, and part of the organic solution was separated by filtration. The filtrate was analyzed by GPC for the determination of the monomer conversion and of the polymer molecular weight. The polymer was isolated by the reprecipitation procedure (chloroform as good solvent; methanol as poor solvent). ^{1}H NMR ($CDCl_3$): δ 1.4 (m, $CCH_2C\mathit{H}_2$-CH_2C), 1.6 (m, $CC\mathit{H}_2CH_2C$(=O)O and C(=O)O$CH_2C\mathit{H}_2$C), 2.3 (t, CCH_2C(=O)OC), 2.4 (t, CCH_2C(=O)OH), 3.7 (t, HO$C\mathit{H}_2$C), 4.1 (t, C(=O)OCH_2C). ^{13}C NMR ($CDCl_3$): δ 25, 26, 29 (C$C\mathit{H}_2$C), 34 (C$C\mathit{H}_2$C(=O)O), 65 (C(=O)O$C\mathit{H}_2$C), 174 (C=0).

Enzymatic copolymerization of 8-OL with other lactones was performed by the same procedure of the 8-OL homopolymerization.

Measurements. SEC analysis was carried out using a TOSOH SC8010 apparatus with a refractive index (RI) detector at 40 °C under the following conditions: TSKgel G3000H_{HR} or G4000H_{HR} column and chloroform eluent at a flow rate of 1.0 mL/min. The calibration curves for SEC analysis were obtained using polystyrene standards. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker DPX-400 spectrometer. GC analysis was carried out using a Shimadzu GC-14B apparatus equipped with an FID detector and a TC-5 column (GL Sciences).

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