Solventless Enantioelective Ring-Opening Polymerization of Substituted ϵ-Caprolactones by Enzymatic Catalysis

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ABSTRACT: Highly (*S*)-enriched substituted poly(ϵ-caprolactone)s were synthesized from 4-methyl-ϵ-caprolactone (4-MeCL) and 4-ethyl-ϵ-caprolactone (4-EtCL) by lipase Novozym-435 (from *Candida antarctica*) catalyzed ring-opening polymerizations. The polymerizations were performed in bulk, thus eliminating the need for solvents in the polymerization process. Poly(4-EtCL) and poly(4-MeCL) having >95% enantiomeric purity (ee_p) have been prepared. Number-average molecular weights of the poly(4-EtCL) and poly(4-MeCL) were 4400 and 5400, respectively. The effect of reaction temperature on enzyme enantioselectivity, polymer molecular weight, and monomer conversion was also investigated at 45 and 60 °C. Contrary to many literature reports and conventional wisdom, the enantioselectivity of the lipase was greater at 60 °C, the higher reaction temperature. The solventless polymerization process appeared to be diffusion-controlled in which the monomer conversion and polymer molecular weight increased at higher reaction temperature.

Introduction

Naturally occurring polymers are chiral and show molecular recognition ability and catalytic activity, presumably because of their specific chiral structure. We have now begun to understand the effects of chirality on the physical and chemical properties of macromolecules. The physical and mechanical properties of a polymer are critically dependent on many factors, one of which is stereochemistry. Optically active polymers often play important roles as the key fundamental materials for synthesizing well-defined polymers with specific secondary and tertiary structures. In synthetic polymer chemistry, synthesis of optically active polymers has been one of the most challenging tasks. It is no coincidence then that the synthesis and applications of optically active polymers is attracting much attention lately.[1−3] However, reports that describe synthesis of optically active polymers with chirality in the main chain are exceedingly rare.[2a] Most synthetic chiral polymers are prepared from optically pure starting materials which are, except when isolated from Nature, in limited supply and difficult to prepare.[2] It is therefore far more desirable to design a synthetic strategy for asymmetric polymerization of racemic starting materials. Stereoselective chemical polymerizations of *racemic*- and *meso*- lactide, catalyzed by chiral Schiff's base complexes of aluminum, have recently been reported.[2d−f]

Optically active polyesters such as poly(hydroxy alkanoate)s (PHAs), naturally occurring microbial polyesters, are important materials owing to their biodegradability.[3] Lactide polymers are other optically active polyesters that have many potential medical, agricultural, and packaging applications.[2d−f] Poly(ϵ-caprolactone), a nonchiral polyester, has been extensively studied for its biodegradability and has been used in the manufacture of thin-walled tree seeding containers[4a] and implantable drug delivery devices (Capronol).[4b] It is, therefore, interesting to consider that introduction of stereochemistry in polycaprolactone may provide a handle in modulating its properties and which may possess possibly superior properties relative to nonchiral polycaprolactones. The stereospecific polymerization of substituted caprolactones, to the best of our knowledge, has not been reported.

In recent years, enzymatic polymerizations have received much attention as a new methodology for metal-free polymer synthesis.[1,5−7] Enzymes are an attractive alternative to conventional chemical catalysts because of their selectivity, ability to operate under mild conditions, recyclability, and biocompatibility. Chemical polymerizations, on the other hand, require extremely pure monomers, inert atmosphere, anhydrous conditions, and organometallic initiators, which must be completely removed for any biomedical applications. The utility of lipases in the synthesis of optically active polyesters in nonaqueous solvents has been reported from a few laboratories.[1] Enantioselective polycondensation of a racemic diester with a diol[1a] and enantioelective ring-opening of (*R,S*)-α-methyl-*β*-propiolactone has been reported.[1b] The enantioselective copolymerization of (*R,S*)-*β*-butyrolactone and *δ*-caprolactone with other lactones has also been investigated.[1c] However, the enantiomeric excess (<0.77) in enzymatic stereoselective polymerizations conducted in nonaqueous organic solvents has only been modest.[1]

In this paper, we describe the lipase-catalyzed enantioelective polymerization of substituted ϵ-caprolactone in bulk. The polymerization reactions were investigated at 45 and 60 °C. Relationships between reaction time, polymer yield, enantiomeric excess, and molecular weight were established. Microstructure analyses of the polymers were accomplished from ^{1}H and ^{13}C NMR data. Although resolution of enantiomers is often achieved using enzymes, this polymerization was unusual for two reasons. First, the polymerization was highly enantioselective despite the large distance between the stereocenter and the lactone carbonyl (four bonds); efficient resolution of molecules containing stereocenters as remote are rare. Second, the polymer-

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izations were done in bulk, thus avoiding use of solvents in the polymerization process. To the best of our knowledge, there has been no report on the stereoselective polymerization of these monomers by either chemical or enzymatic catalysts.

Experimental Section

Lipase Novozym-435 was kindly provided by Novo Nordisk Bioindustrial Inc. 4-Methylcyclohexanone, 4-ethylcyclohexanone, and *m*-chloroperoxybenzoic acid (*m*-CPBA) were purchased from Acros Chemical Co. and used as received.

Instrumental Methods. *NMR Spectroscopy.* ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-360 spectrometer at 360 and 90 MHz and a Bruker DPX-250 spectrometer at 250 and 62.9 MHz, respectively. ^{1}H NMR chemical shifts (ppm) are reported downfield from 0.00 ppm using tetramethylsilane (TMS) as an internal standard. The concentrations used were ∼4% w/v in chloroform-*d* ($CDCl_3$).^{13}C NMR spectral chemical shifts in (ppm) are referenced relative to the internal standard chloroform-*d* at 77.00 ppm. 4-Methyl-ϵ-caprolactone monomer conversions were determined from the relative peak areas of ^{1}H NMR signals corresponding to methyl ($-CH_3$) protons in the polymer and the monomer at 0.93 and 0.99 ppm, respectively. 4-Ethyl-ϵ-caprolactone monomer conversions were determined from the relative peak areas of ^{1}H NMR signals corresponding to methylene ($-(CO)-CH_2-$) protons in the polymer and the monomer at 2.27 and 2.68 ppm, respectively.

Gas Chromatography (GC). Gas chromatographic analyses were conducted on a Shimadzu GC-17A chromatograph equipped with a flame ionization detector (FID) and a cyclodex-β chiral capillary column (J&W Scientific, Film: 0.25 μm × 30 m × i.d. of 0.25 mm). Helium was used as a carrier gas. Chiral separations used the following conditions: 64 °C (2 min) to 130 °C (5 min) at 1 °C/min followed by a 10 °C/min gradient to 180 °C (15 min). Carrier gas flow was 1.8 mL/min for analysis of 4-ethyl-ϵ-caprolactone and 2.0 mL/min for 4-methyl-ϵ-caprolactone. The injector and detector temperatures were maintained at 250 and 300 °C, respectively. Optical rotations were measured on an Autopol IV (Rudolph Instruments) automatic polarimeter at 23 °C in $CHCl_3$ at a concentration of 0.5.

Molecular Weight Measurements. Molecular weights were measured by gel permeation chromatography (GPC) using a Shimadzu HPLC system equipped with a model LC-10AD*vp* pump, model SIL-10A autoinjector, model RID-10A refractive index detector (RI), model SPD-10AV UV−vis detector, and Waters HR 4E styragel column. THF (HPLC grade) was used as an eluent at a flow rate of 1.0 mL/min. The sample concentration and injection volumes were 0.5% (w/v) and 100 μL, respectively. EzChrome Elite (Scientific Software Inc.) was used to calculate molecular weights on the basis of a calibration curve generated by narrow molecular weight distribution polystyrene standards (5.00×10^2, 8.00×10^2, 2.10×10^3, 4.00×10^3, 9.00×10^3, 1.90×10^4, 5.00×10^4, 9.26×10^4, 2.33×10^5, and 3.00×10^5 g/mol, Perkin-Elmer). The degree of polymerization (DP) calculated from the ^{1}H NMR spectral analysis was in good agreement with the molecular weight obtained using GPC.

Monomer Synthesis. Following a reported procedure in the literature,[8] the lactones were prepared by Baeyer−Villiger oxidation of substituted cyclohexanones.

4-Ethyl-ϵ-caprolactone. A colorless liquid (74% yield). ^{1}H NMR ($CDCl_3$): δ 4.15−4.35 (m, 2H), 2.6−2.7 (m, 2H), 1.90−2.05 (m, 2H), 1.50−1.60 (m, 2H), 1.25−1.40 (m, 3 H) and 0.95 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 175.26 (C═O), 67.13 (CH_2−O), 40.64 (*C*H), 34.05 (CH_2), 32.09 (CH_2), 27.62 (CH_2), 27.32 (CH_2), and 10.30 (CH_3).

4-Methyl-ϵ-caprolactone. A colorless liquid (76% yield). ^{1}H NMR ($CDCl_3$): δ 4.25 (m, 2H), 2.50−2.75 (m, 2H), 1.75−2.0 (m, 3H), 1.50 (m, 1H), 1.30 (q, J = 1.6 Hz), 1.00 (d, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 175.21 (*C*═O), 67.22 (CH_2−O), 36.48 (*C*H), 34.24 (CH_2), 32.35 (CH_2), 30.03 (CH_2), and 21.35 (CH_3).

General Procedure for the Enzymatic Polymerization. All reactions were carried out in bulk. The lipase was dried[6a] (in a drying pistol over P_2O_5, at 50 °C/0.1 mmHg; 15 h; water content ∼ 0.09 wt %) in 6 mL sample vials. In a glovebag, maintained under nitrogen atmosphere, the monomer was transferred to a 6 mL reaction vial, and the preweighed enzyme (62 mg/mmol of lactone) was added. The reaction vial was capped with a rubber septum and placed in a constant temperature oil bath maintained at 45 and 60 °C for predetermined times. Progress of the polymerization was monitored using GC analysis. Reactions were terminated by dissolution of the contents of the reaction vial in chloroform and removal of the enzyme (insoluble) by filtration (glass fritted filter, medium pore porosity). The filtrates were combined, solvents were removed in vacuo, and the crude products were analyzed by proton (^{1}H) NMR and gel permeation chromatography (GPC). The polymer was purified by precipitation in methanol, and the recovered monomer was analyzed by gas chromatography (GC).

Results and Discussion

The racemic 4-methyl-ϵ-caprolactone and 4-ethyl-ϵ-caprolactone polymerized in this study were synthesized from corresponding cyclohexanones by Baeyer−Villiger oxidation in 76% and 74% yield, respectively, and purified by vacuum distillation over calcium hydride. The high-purity monomers were subjected to chiral GC analyses to achieve enantiomeric analytical resolution (see Experimental Section). (*R*)- and (*S*)-enantiomers were assigned from a co-injection of the corresponding authentic pure (*S*)-enantiomers[9] with the racemic lactones (Figure 1). The enantiomeric excess of the polymer (ee_p) was calculated from the ee of the unreacted monomer and monomer conversion according to the following equations.[1b]

$$ee_p = \frac{S_p - R_p}{S_p + R_p} \tag{1}$$

$$S_p = 0.5 - \left[(1-c)\left\{\frac{S}{S+R}\right\}_m\right]$$

$$R_p = 0.5 - \left[(1-c)\left\{\frac{R}{S+R}\right\}_m\right]$$

where c is monomer conversion determined from ^{1}H NMR. ($S/R + S$) and ($R/R + S$) are the fractions of (*S*)- and (*R*)-enantiomers, respectively, in unreacted monomer and determined from chiral GC analyses.

The enantioselectivity of the lipase Novozym-435 in this study was determined from monomer conversion and the stereochemical purity of recovered monomers. For quantitative determination of the enzyme enantioselectiviy, E was used:[10]

$$E = \frac{\ln[(1-c)(1-ee(R))]}{\ln[(1-c)(1+ee(R))]} \tag{2}$$

where c is monomer conversion determined from ^{1}H NMR and $ee(R)$ is the enantiomeric excess of the unreacted isomer determined from GC.

Enzymatic Synthesis of (*S*)-Poly(4-ethyl-ϵ-caprolactone). Optically active poly(4-ethyl-ϵ-caprolactone), ee > 97%, was synthesized by lipase Novozym-435 catalyzed ring-opening polymerization of (*R*,*S*)-4-ethyl-ϵ-caprolactone at 60 °C in bulk (see Scheme 1). Table 1 lists the results of the polymerization reactions. The molecular weights were determined by GPC on the basis of polystyrene standards and were in good agreement with those determined from the ^{1}H NMR spectral

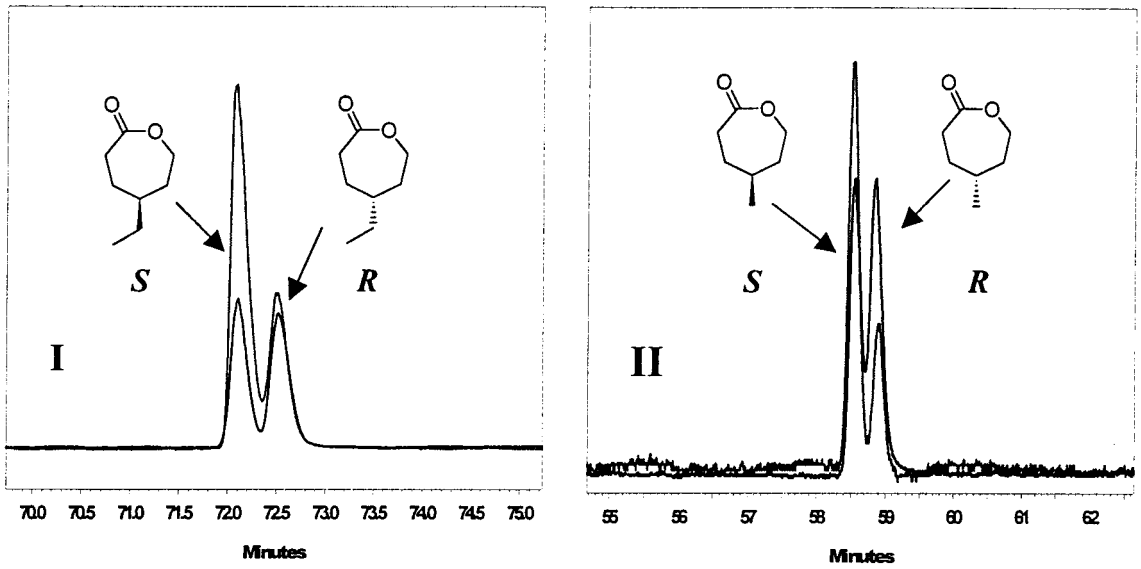


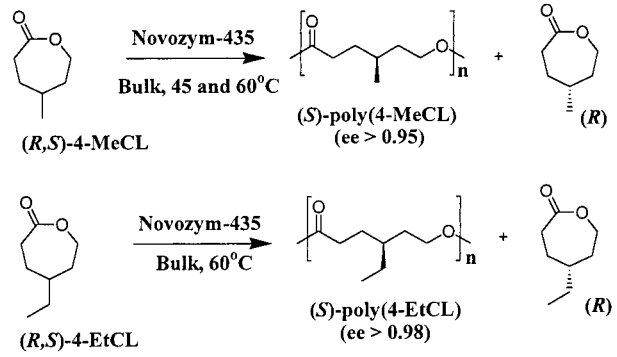
Figure 1. GC chromatograms of *racemic*-4-ethyl- (**I**) and 4-methyl-ϵ-caprolactone (**II**) and their co-injections with the pure (*S*)-enantiomers.

Table 1. Lipase Novozym-435-Catalyzed Enantioelective Ring-Opening Polymerization of 4-Ethyl-ϵ-caprolactone at 60 °C[a]

				(*S*)-poly(4-EtCL)				
no.	time (h)	conv (%)[b]	(*R*)-4-EtCL ee$_m$[c]	ee$_p$[d]	($S_p/R_p + S_p$)[e]	$[\alpha]_D^{23}$	M_n[f] (g/mol)	PDI[f]
1	1.5	19	0.20	0.85	0.93		900	1.62
2	2	29	0.41	0.98	0.99		1200	1.57
3	4	38	0.58	0.95	0.98	−3.80	4400	1.84
4	5	52	0.85	0.79	0.90	−1.80	5000	2.09
5	6	63	0.77	0.45	0.73	−0.73	6200	2.13
6	7	67	0.73	0.36	0.68	−0.55	6600	1.80
7	8	69	0.78	0.35	0.67	−0.49	7500	1.69
8	9	74	0.67	0.23	0.62	−0.20	8500	1.65

[a] Reactions were carried out in bulk; monomer/enzyme (w/w) = 2. [b] Monomer conversion was determined from ^{1}H NMR data. [c] Enantiomeric excess of recovered monomer was calculated from chiral GC. [d] Calculated from eq 1. [e] The fraction of (*S*) enantiomer in the poly(4-EtCL). [f] Determined by GPC (PDI = M_w/M_n).

Scheme 1



analysis but are not absolute. In Figure 2, a plot of percent monomer conversion as a function of time is presented. The monomer conversion increased steadily with time. For example, after 1.5 h the conversion was 19% and reached 74% after 9 h. The monomer conversion kept increasing beyond 50% because the enzyme polymerized both enantiomers in the racemic monomer mixture although the (*S*)-enantiomer was polymerized in preference to the (*R*)-enantiomer.

Number-average molecular weight (M_n) increased with increasing percent monomer conversion (Figure 3). Up to 2.5 h, when the monomer conversion was ∼29%, the molecular weight (M_n 500) did not increase noticeably. However, beyond 29% conversion the molecular weight rose sharply and was 4400 g/mol at 38% monomer conversion and reached 8500 at 74% (9 h) conversion. The molecular weight profile was in accordance with the chain polymerization mechanism proposed for the lipase-catalyzed ring-opening polymerizations.[11] The initial stagnation in molecular weight may very well be indicative of the initiation stage of the polymerization when mostly new chains were being formed. However, as soon as the initiator, i.e., water was consumed (at about 29% conversion), the chain propagation dominates and was reflected in sharp molecular weight increase.

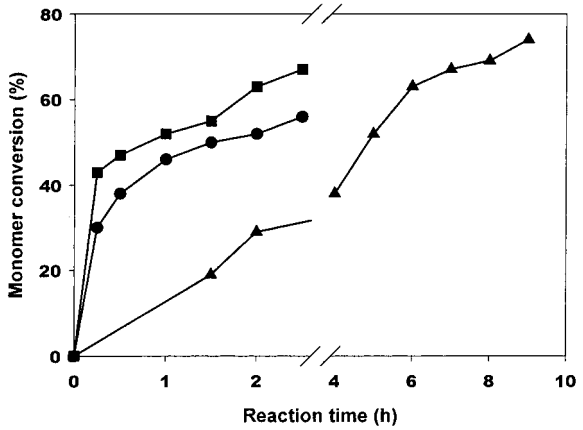


Figure 2. Percent monomer conversion as a function of time for Novozym-435-catalyzed ring-opening bulk polymerization of 4-ethyl-ϵ-caprolactone at 60 °C (▲), 4-methyl-ϵ-caprolactone at 60 °C (■), and 4-methyl-ϵ-caprolactone at 45 °C (●).

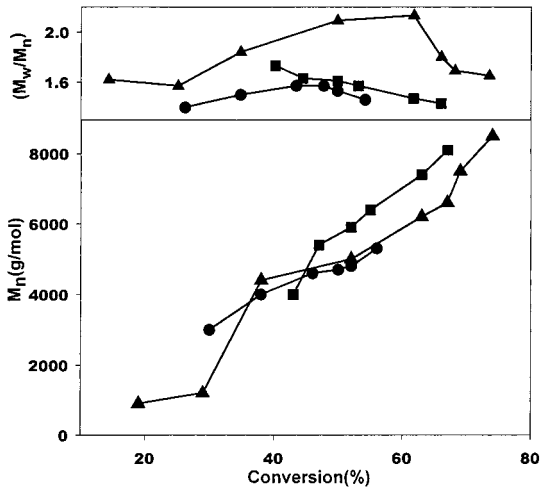


Figure 3. Number-average molecular weight (M_n) as a function of percent monomer conversion during Novozym-435-catalyzed ring-opening bulk polymerization of 4-ethyl-ϵ-caprolactone at 60 °C (▲), 4-methyl-ϵ-caprolactone at 60 °C (■), and 4-methyl-ϵ-caprolactone at 45 °C (●).

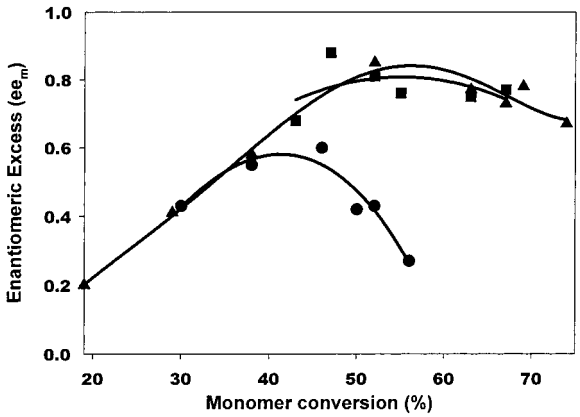


Figure 4. Plots of enantiomeric excess of the recovered monomer (ee_m) as a function of percent monomer conversion during lipase Novozym-435-catalyzed ring-opening polymerization of of 4-ethyl-ϵ-caprolactone at 60 °C (▲), 4-methyl-ϵ-caprolactone at 60 °C (■), and 4-methyl-ϵ-caprolactone at 45 °C (●).

The polydispersity index (M_w/M_n) registered only a slight increase when monomer conversion increased from 19 to 63% and then decreased with further increase in the monomer conversion to 74% (Figure 3). Importantly, the variation in the polydispersity index coincided with the molecular weight profile. In agreement with the previous reports,[7] we found that water in these reactions does have a significant effect on the polymer molecular weight.

Figure 4 shows a plot of enantiomeric excess of the monomer (ee_m) against monomer conversion. The ee_m increased with increasing percent monomer conversion and reached a maximum ~50% conversion. As can be seen from the plot, before 50% conversion, the enzyme can choose freely the "(*S*)"-enantiomer from the racemic mixture and the ee_m of the recovered "(*R*)"-enantiomer increases. During the course of the reaction, the "(*S*)"-enantiomer is gradually depleted, leaving behind the "(*R*)"-enantiomer. Close to 50% conversion, the enhanced relative concentration of the "(*R*)"-enantiomer leads to its increased transformation by the lipase. As a consequence, beyond 50% the ee_m rapidly decreases. The polymerization, however, was highly enantioelective (E = 65, 38% conversion); i.e., the lipase Novozym-435 polymerized selectively the (*S*)-enantiomer of 4-ethyl-ϵ-caprolactone to yield a >97% enriched (*S*)-poly(Et-CL) (Figure 5).

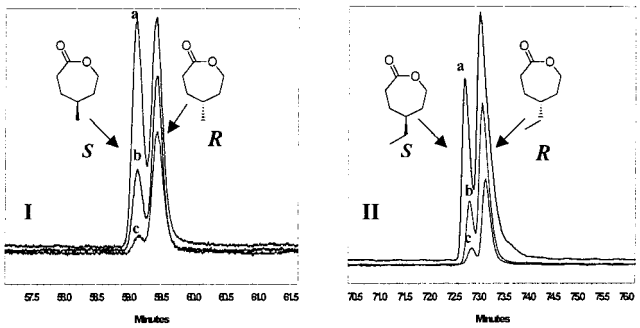


Figure 5. Gas chromatograms of (*R*)-enriched 4-methyl-ϵ-caprolactone (**I**) and 4-ethyl-ϵ-caprolactone (**II**) isolated from Novozym-435-catalyzed bulk polymerizations: (**Ia**) 50:50 (*S*)- and (*R*)-isomer; (b) 22:78 (*S*)- and (*R*)-isomer after 0.25 h (Table 3, entry 1); (c) 6:94 (*S*)- and (*R*)-isomer after 0.5 h (Table 2, entry 2); (**IIa**) 40:60 (*S*)- and (*R*)-isomer after 1.5 h (Table 1, entry 1); (**IIb**) 21:79 (*S*)- and (*R*)-isomer after 4 h (Table 1, entry 3); (**IIc**) 8:92 (*S*)- and (*R*)-isomer after 5 h (Table 1, entry 4).

Enzymatic Synthesis of (*S*)-Poly(4-methyl-ϵ-caprolactone). (*S*)-Enriched poly(4-methyl-ϵ-caprolactone) was synthesized by lipase Novozym-435 catalyzed ring-opening polymerization of 4-methyl-ϵ-caprolactone at 45 and 60 °C, in bulk (Scheme 1). Tables 2 and 3 list the results of the polymerizations at 60 and 45 °C, respectively. The 4-methyl-ϵ-caprolactone was a very good substrate for the lipase Novozym-435 (Figure 2). The polymerization reactions were very fast, and in only 15 min, 43% monomer conversion had resulted at 60 °C (Figure 2). The monomer conversion was affected by change in the reaction temperature and the rate of monomer conversion increased at higher reaction temperature. For example, the conversions were 30% and 43% at 45 and 60 °C, respectively, after 15 min. The rate of 4-MeCL conversions was considerably reduced once the conversions reached 56 and 67% at 45 and 60 °C, respectively. The decrease in the rate of the monomer conversion could be attributed to the high enantioelectivity of the lipase, i.e., as the faster reacting (*S*)-enantiomer is depleted the rate of polymerization decreases. It is also possible that it was an artifact of the increasing diffusion constraints in the reaction mixture, resulting from higher viscosity of the polymer, which limited availability of the monomer to the active site of the lipase. However, increased monomer conversion despite higher enzyme selectivity in these polymerizations at the higher reaction temperature suggests the latter being a more dominant factor that influences the rate of the monomer conversion.

The molecular weight (M_n) of the poly(4-MeCL) was also affected by changing the reaction temperature from 45 to 60 °C. Figure 3 shows variation in polymer number-average molecular weight (M_n) as a function of percent monomer conversion during the polymerization of 4-methyl-ϵ-caprolactone at 45 and 60 °C. Although polymerization of MeCL catalyzed by Novozym-435 was highly efficient at both reaction temperatures, higher reaction temperature (60 °C) generally led to higher molecular weight polymers. The polydispersity index (M_w/M_n) registered a decrease with increasing molecular weight of the polymer chains. The polydispersity index decreased from 1.73 (M_n = 4000) to 1.43 (M_n = 8100) and from 1.57 (M_n = 4600) to 1.46 (M_n = 5300) when

Table 2. Lipase Novozym-435-Catalyzed Enantioelective Ring-Opening Polymerization of 4-Methyl-ϵ-caprolactone at 60 °C[a]

				(*S*)-poly(4-MeCL)				
no.	time (h)	conv (%)[a]	(*R*)-4-MeCL ee_m[b]	ee_p[c]	$(S_p/R_p + S_p)$[d]	$[\alpha]_D^{23}$	M_n[e] (g/mol)	PDI[e]
1	0.25	43	0.68	0.90	0.95	−7.21	4000	1.73
2	0.5	47	0.88	0.95	0.98	−7.90	5400	1.63
3	1.0	52	0.81	0.75	0.87	−5.20	5900	1.61
4	1.5	55	0.76	0.62	0.81	−4.19	6400	1.57
5	2.0	63	0.75	0.44	0.72	−3.70	7400	1.47
6	2.5	67	0.77	0.38	0.69	−2.00	8100	1.43

[a] Reactions were carried out in bulk; monomer/enzyme (w/w) = 2. [b] Monomer conversion was determined from ^{1}H NMR data. [c] Enantiomeric excess of recovered monomer was calculated from chiral GC. [d] Calculated from eq 1. [e] The fraction of (*S*)-enantiomer in the poly(4-EtCL). [f] Determined by GPC (PDI = M_w/M_n).

Table 3. Lipase Novozym-435-Catalyzed Enantioelective Ring-Opening Polymerization of 4-Methyl-ϵ-caprolactone at 45 °C[a]

				(*S*)-poly(4-MeCL)				
no.	time (h)	conv (%)[b]	(*R*)-4-MeCL ee_m[c]	ee_p[d]	$(S_p/R_p + S_p)$[e]	$[\alpha]_D^{23}$	M_n[f] (g/mol)	PDI[f]
1	0.25	30	0.43	0.98	0.99	−8.10	3000	1.40
2	0.5	38	0.55	0.85	0.92	−6.22	4000	1.50
3	1.0	46	0.60	0.70	0.85	−4.82	4600	1.57
4	1.5	50	0.42	0.42	0.71	−3.20	4700	1.57
5	2.0	52	0.43	0.40	0.70	−2.96	4800	1.53
6	2.5	56	0.27	0.13	0.57	−0.53	5300	1.46

[a] Reactions were carried out in bulk; monomer/enzyme (w/w) = 2. [b] Monomer conversion was determined from ^{1}H NMR data. [c] Enantiomeric excess of recovered monomer was calculated from chiral GC. [d] Calculated from eq 1. [e] The fraction of (*S*) enantiomer in the poly(4-EtCL). [f] Determined by GPC (PDI = M_w/M_n).

the polymerizations were conducted at 60 and 45 °C, respectively.

In polymerization conducted at 45 and 60 °C, the enantioselectivity of the enzyme was also affected considerably by the change in reaction temperature. Interestingly, the lipase enantioselctivity, *E*, increased with increase in temperature from 45 to 60 °C. This finding is in contrast to several papers reporting an inverse correlation between the temperature and the lipase enantioselectivity.[12] Unfortunately, the effect of temperature on lipase selectivity is not very well understood,[13] partly because enzymes are temperature labile and variation in temperature is a rather less obvious choice to improve lipase enantioselectivity. In Figure 4, a plot of enantiomeric excess of the recovered lactone as a function of percent conversion of 4-MeCL at 45 and 60 °C is shown. At 45 °C, the enantiomeric excess of the recovered (*R*)-lactone increased with conversion and peaked at about 47% to 0.58. The polymer ee_p, as expected, was high in the initial stages of the polymerization at 45 °C with enantiomeric excess of the polymer, ee_p being 0.98 at 30% monomer conversion. The polymer ee_p subsequently decreased rapidly beyond the 50% monomer conversion. The ring-opening polymerization of 4-MeCL at 60 °C was highly efficient; not only the monomer conversion was 43% but also the enantiomeric excess of the recovered monomer (ee_m) was 0.68 after 15 min, which increased to 0.88 at 47% monomer conversion. The enantiomeric excess of the polymer (ee_p) also reached a maximum of 0.95 ($E = 122$) at 47% monomer conversion when the reaction temperature was 60 °C. Considering the fact that the polymerizations were conducted without added solvents, the enantioselectivity in these reactions was remarkable. The lower reaction rate and the lower ee values in reactions conducted at 45 °C compared to the polymerizations at 60 °C suggested that the increasing viscosity of the reaction mixture, due to the formation of high molecular weight polymers, was a limiting factor in these bulk polymerizations. The higher viscosity in the reaction mixture may limit the accessibility of the unreacted monomer to the lipase active site. The higher reaction temperature, on the other hand, translates into higher fluidity in the reaction mixture and hence explains higher monomer conversion at 60 °C. Interestingly, lipase enantioselectivity in these bulk polymerizations was higher than reported in any lipase-catalyzed polymerizations conducted in organic solvents. Additionally, the high enantioselectivity demonstrated in the polymerization of 4-methyl- and 4-ethyl-ϵ-caprolactone, monomers that contain a stereocenter as remote as four bonds from the reaction site (lactone carbonyl), are extremely rare.

NMR Characterization. The structures of the polymers were confirmed by ^{1}H and ^{13}C NMR spectroscopies. Stereospecific dyads in the NMR data were not observed because of a four-bond separation between the stereocenter and the carbonyl group. ^{1}H and ^{13}C NMR spectra for both polymers along with the peak assignments are shown in Figures 6 and 7. The peak assignments were based on two-dimensional ^{1}H−^{1}H COSY and ^{1}H−^{13}C HETCOR NMR experiments (Supporting Information). In 4-Me-CL, the diastereotopic protons (H_a and H_b) in the two methylenes on either side of the stereocenter were split into two signals. The ^{1}H−^{1}H COSY experiment showed connectivities between the protons *a* and *b* in each set of methylene protons. The ^{1}H−^{13}C HETCOR experiments also had correlations between the methylene carbon signals and the protons *a* and *b* signals in each set. Interestingly, the *a* and *b* protons appeared as two signals ($\Delta\delta \sim 0.19$ ppm) in poly(4-MeCL), but in the poly(4-EtCL) a broad multiplet instead of two separate signals was observed (Figure 6). Besides prominent resonances due to the repeating units of the polymer, small but characteristic resonances ascribed to the α-methylene of the terminal hydroxy and the carboxylic acid groups were also observed in the NMR spectra. The polymers were thus identified to have a hydroxyl and a carboxylic acid group at each chain terminus.

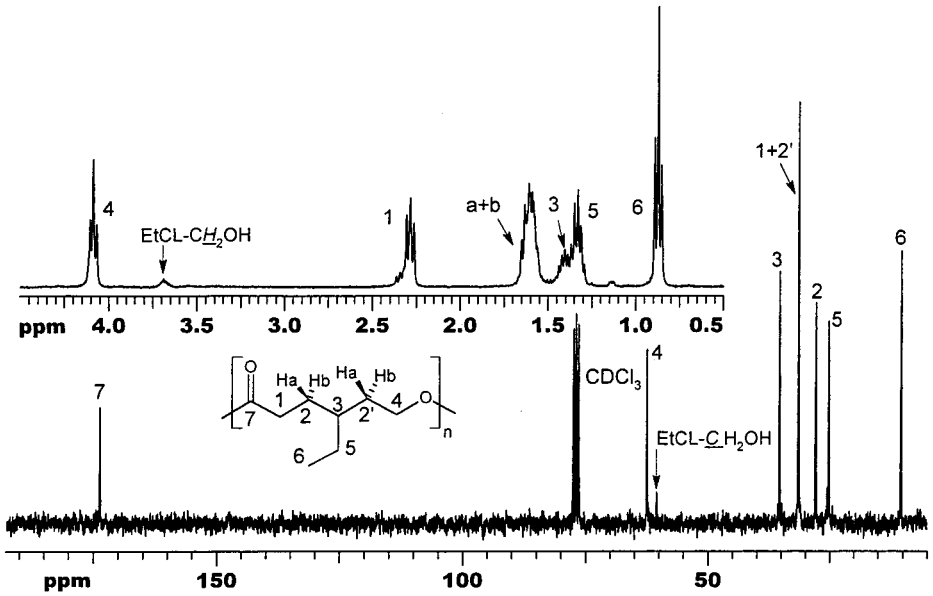


Figure 6. ^{1}H NMR (250 MHz, $CDCl_3$) and ^{1}H NMR (250 MHz, $CDCl_3$, inset) spectra of poly(4-ethyl-ϵ-caprolactone) (entry 4, Table 1) obtained by lipase Novozym-435-catalyzed ring-opening polymerization in bulk at 60 °C.

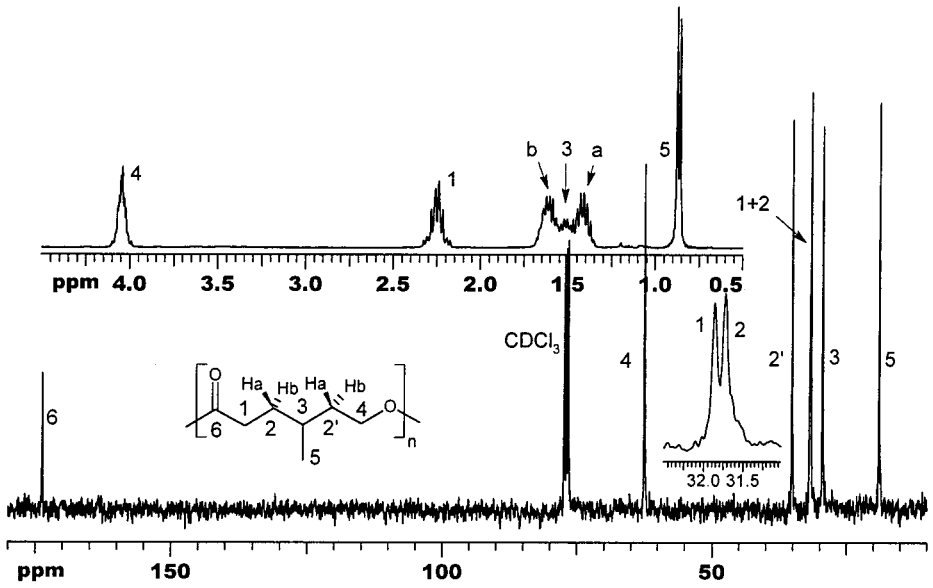


Figure 7. ^{13}C NMR (62.9 MHz, $CDCl_3$) and ^{1}H NMR (250 MHz, $CDCl_3$, inset) spectra of poly(4-methyl-ϵ-caprolactone) (entry6, Table 2) obtained by lipase Novozym-435-catalyzed ring-opening polymerization in bulk at 60 °C.

Conclusion

Chiral substituted poly(ϵ-caprolactone)s were synthesized by enzymatic ring-opening polymerization in bulk from 4-methyl-ϵ-caprolactone and 4-ethyl-ϵ-caprolactone. To the best of our knowledge, there has been no report on the stereoselective polymerization of these monomers by either chemical or enzymatic catalysis. The polymerizations were catalyzed by lipase Novozym-435 (from *Candida antarctica*) at 60 and 45 °C. Highly (*S*)-enriched poly(4-EtCL) (ee_p >0.98, M_n = 4000) and poly(4-MeCL) (ee_p >0.95, M_n = 5400) were prepared. The reaction was also investigated at two different temperatures, viz. 45 and 60 °C. The higher reaction temperature led to higher monomer conversion, polymer molecular weight, and enzyme enantioselectivity. Unfortunately, the effect of reaction temperature on enzyme stereoselectivity is not very well understood, but in future communications this issue will be addressed to a much greater extent.

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Supporting Information Available: 2D COSY and HETCOR NMR spectra of the (*S*)-poly(4-methyl-ϵ-caprolactone) and (*S*)-poly(4-ethyl-ϵ-caprolactone). This material is available free of charge via the Internet at http://pubs.acs.org.

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