Macromolecules **2009**, *42*, 2401−2410

One-Shot Block Copolymerization of a Functional Seven-Membered Cyclic Carbonate Derived from L-Tartaric Acid with ε-Caprolactone

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Received November 14, 2008; Revised Manuscript Received January 20, 2009

ABSTRACT: Block copolymerization of a seven-membered cyclic carbonate (5*S*,6*S*)-dimethyl-5,6-isopropylidene-1,3-dioxepin-2-one (ITC) with ε-caprolactone in "one-shot feeding" is reported. The cyclic carbonate monomer ITC was synthesized from naturally occurring L-tartaric acid in three steps. Three catalysts—stannous octanoate, $Sn(Oct)_2$, triisopropoxide aluminum, $Al(O^iPr)_3$, and diethylzinc monohydrate, $ZnEt_2-H_2O$—were tested for the homopolymerization of ITC monomer at 120 °C for 12 h in bulk. The results show that $Sn(Oct)_2$ was the most effective catalyst to carry out the polymerization (M_n = 24 000 g/mol; PDI = 1.6; $[\alpha]_D^{20} = +77.8$). The copolymerization of ITC with ε-caprolactone (CL) in various feed ratios was also investigated. The detailed spectral and thermal analysis of the copolymers catalyzed by $Sn(Oct)_2$ revealed formation of the block copolymer (poly[44%ITC-*block*-56%CL], M_n = 24 000 g/mol; PDI = 1.6; $[\alpha]_D^{20} = +33.8$). Two glass transition temperatures (T_g) were observed for poly(44%ITC)-*block*-poly(56% ε-CL) at −59.1 and −37.2 °C for the poly(CL) and the poly(ITC) block, respectively, confirming the diblock nature of the copolymer. It is the first report of "one-shot" block copolymerization of ε-caprolactone with a cyclic carbonate monomer. The deprotection of the ketal groups resulted in copolymers containing free hydroxy groups in the polymer backbone.

Introduction

Biodegradable polymers have gained increasing interest in the past two decades. Many research groups around the world have devoted their efforts to the development of new biodegradable materials and to explore their potential applications especially in biomedical field. The diversity of the application of biodegradable polymer requires the development of a wide range of biomaterials. Copolymerization of two different monomers or more is an effective method of altering the properties of polymers. Another method is introduction of functional groups in the polymer backbone which is expected to enhance the biodegradability and hydrophilicity and facilitate a variety of applications such as a controlled drug release in polymeric drug delivery systems or in tissue engineering.

Polyesters such as poly(ε-caprolactone) and polylactide find many applications as homopolymers and copolymers in biomedical and pharmaceutical fields.[1] Copolymers of ε-caprolactone with carbonates provide opportunities for development of interesting biomaterial for their biocompatibility and bioresorbability. Because the ester bonds are more sensitive to hydrolysis than carbonates, the copolymerization of ε-caprolactone with carbonates enables tuning of the physical properties of the copolymers and thereby facilitates access to the tailor-made biopolymers. However, when a mixture of two monomers is subjected to polymerization, usually a random polymer and sometimes an alternating copolymer or mixture of two homopolymer are formed. While copolymerization of two monomers results mostly in random copolymers, formation of block polymer has also been reported. The most common method for preparing block polymers is through the sequential addition of the monomers that polymerize via living or controlled polymerization mechanism.[2] Also, an interesting approach to block copolymer synthesis known as "one-shot feeding", in which the two monomers are fed together, has also been described.[3,4] The one-shot feeding methodology is advantageous as the process is much simpler compared to the sequential monomer feeding. However, only a few examples of one-shot block polymerization are available primarily because the polymerization rates of the two monomers must be significantly different. Dissimilar monomers that have very different reactivities or are polymerized by fundamentally different chemistries (e.g., ATRP, cationic or anionic ROP, and free radical polymerization) have only been reported. For example, there have been no reports of one-shot block copolymerization of cyclic carbonates or lactones, which polymerize following similar chemistries.

Biodegradable polymers from renewable resources are attractive materials from the prospective of green chemistry. Many polymeric materials based on naturally occurring compounds have been developed such as carbohydrates and amino acids.[4] L-Tartaric acid, which is mainly obtained from a large variety of fruits, has been employed in polymer synthesis. Different classes of polymers have made based on L-tartaric acid, for example, polyamide,[6] poly(ester−amide),[7] polyesters,[8] and polycarbonate.[9,10] However, the incorporation of tartaric acid or its derivative in degradable polymers has been through condensation polymerization, which is limited by the removal of the condensate, i.e., water or alcohol; efficient removal of the condensate is required to shift the equilibrium to the polymerization. The ring-opening polymerization (ROP) of cyclic monomers is more efficient as no leaving group is involved and, unlike condensation polymerization, can be performed at much lower temperature and is hence energy-efficient. Six-membered cyclic carbonates have been widely used in polycarbonate synthesis via ROP because their polymerization proceeds with minimal decarboxylation, which leads to ether linkages along the polymer chain; the five-membered cyclic carbonate ROP results in extensive decarboxylation.[11] Seven-membered cyclic carbonates exhibit higher polymerizability, but there are only a few examples reported in the literature.[12] The seven-membered cyclic carbonate monomer 1,3-dioxepan-2-one (7CC) has been polymerized by both anionic and cationic catalysts, and its copolymerization with trioxane, δ-valerolactone, and ε-caprolactone has also been reported.[13] We have recently reported the synthesis and enzymatic polymerization

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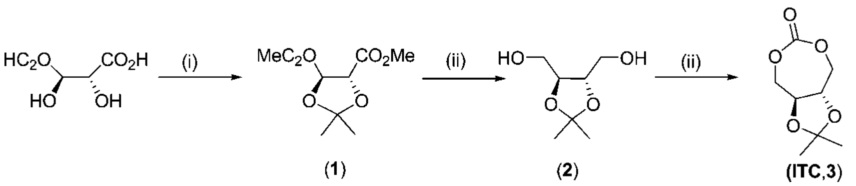
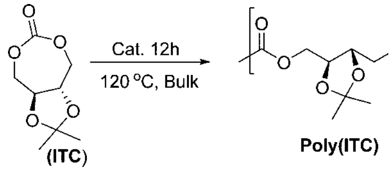
10.1021/ma802546v CCC: $40.75

Scheme 1. Synthesis of Seven-Membered Cyclic Carbonate Monomer from L-Tartaric Acid[a]



[a] (i) DMP, cat. PTS, MeOH, and cyclohexane, azeotrope; (ii) LAH, ether, 0 °C; (iii) triphosgene, pyridine, THF, 0 °C.

Table 1. Ring-Opening Polymerization of ITC Monomer in Bulk at 120 °C



entry	catalyst	M/C[a]	conversion (%)[b]	M_n[c] (g/mol)	M_n[d] (g/mol)	PDI[d]
1	$Sn(Oct)_2$	50	100	9 400	9 000	1.4
2		100	100	18 800	15 500	1.4
3		200	100	37 600	26 000	1.5
4	$ZnEt_2-H_2O$	50	100	9 400	7 500	1.4
5		100	100	18 800	13 500	1.4
6		200	100	37 600	20 500	1.4
7	$Al(O^iPr)_3$	50	74	6 960	5 500	1.5
8		100	75	14 100	11 200	1.5
9		200	72	27 100	16 500	1.6

[a] Monomer/catalyst ratio (mol/mol) = 200. [b] Calculated from ^{1}H NMR. [c] Theoretical M_n calculated using the monomer conversion. [d] Determined from GPC.

of a new seven-membered functional carbonate monomer, (5*S*,6*S*)-dimethyl 5,6-isopropylidene-1,3-dioxepin-2-one (ITC), from naturally occurring L-tartaric acid.[14]

In this report the ROP of ITC, derived from naturally occurring L-tartaric acid, by stannous octanoate, $Sn(Oct)_2$, triisopropoxide aluminum, $Al(O^iPr)_3$, and diethylzinc monohydrate, $ZnEt_2$-H_2O, is reported. The polymerization of the monomer ITC was studied through the relationship between reaction time, monomer conversion, molecular weight, and molecular weight distribution. Copolymerization of ITC with ε-caprolactone was also investigated, and diblock copolymers with different feed ratios were synthesized, importantly in one-shot feeding. This, to best of our knowledge, is the first report of one-shot block polymerization of a lactone and a cyclic carbonate monomer. The homo- and copolymers were characterized by detailed spectral and thermal analyses.

Experimental Section

Materials. All reagents were used without further purification unless specified otherwise. L-Tartaric acid (99%), *p*-toluenesulfonic acid (98.5%), stannous 2-ethylhexanoate (stannous octanoate, 95%), triisopropoxide aluminum, $Al(O^iPr)_3$, diethylzinc monohydrate, $ZnEt_2-H_2O$, and triphosgene were purchased from the Aldrich Chemical Co. 2,2-Dimethoxypropane, triethylamine (99%), and lithium aluminum hydride (95%) were purchased from Acros Chemical Co. Diethyl ether and tetrahydrofuran (THF) were dried over pressed Na metal before use.

Measurements. Molecular weights were measured by gel permeation chromatography (GPC) using a Shimadzu HPLC system equipped with a model LC-10ADvp pump, model SIL-10A autoinjector, model RID-10A refractive index detector (RI), model SPD-10AV UV−vis detector, and Waters HR 4E styragel column. $CHCl_3$ (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 based on 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). ^{1}H and ^{13}C NMR spectra were recorded using a Bruker DPX-250 as well as Varian Inova-400 and -500 spectrometers. Sample concentrations were about 10% (w/v) in $CDCl_3$ containing 1% TMS as an internal reference. Monomer conversions were calculated from ^{1}H NMR spectra upon integration of area of peaks for -2CH_3 of the monomer at 1.38 ppm and for the polymer at 1.43 ppm. The degree of polymerization (DP) calculated from the ^{1}HNMR spectrum by determining the area under the repeat unit resonances and the end group CH_2OH resonance were in good agreement with the molecular weight obtained using GPC.

Optical rotations were measured on an Autopol IV (Rudolph Instruments) automated polarimeter at 20 °C in $CHCl_3$ or MeOH at a concentration of 1.0. Thermal analyses were preformed on a Dupont DSC 2920 TA Instruments attached to a Thermal Analyst 2000 TA Instruments computer. Indium was used as the standard for the temperature calibration, and the analyses were made under constant stream of nitrogen with a heating rate 10 °C/min and cooling rate of 40 °C/min.

Synthesis of Dimethyl 2,3-*O*-Isopropylidene-L-tartrate (1).[10,14] Following a literature procedure, a mixture of L-tartaric acid (0.034 mol, 5 g), *p*-toluenesulfonic acid monohydrate (0.21 mmol, 0.04 g), and 2,2-dimethoxypropane (0.116 mol, 14.3 mL) (2 mL) was refluxed in methanol. The product was collected from chromatography on silica gel eluted with 30% ethyl acetate/hexanes; a pale yellow oil, bp 120−122 °C (8 mmHg) (0.030 mol, 6.52 g, 89%); $[\alpha]_D^{20} = -49.2$ ($c = 1.0$, MeOH). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 4.73$ (s, 2H, 2OCHCO), 3.74(s, 6H, $2OCH_3$), 1.41 (s, 6H, $2CH_3$). ^{13}C NMR (62.5 MHz, $CDCl_3$) $\delta = 25.9$, 52.4, 76.6, 113.5, 169.7.

Synthesis of 2,3-Di-*O*-isopropylidene-L-threitol (2).[10,14] **1** (6 g, 0.028 mol) was reduced using lithium aluminum hydride (0.048 mol, 1.8 g) in diethyl ether (50 mL). The crude product was purified by chromatography on silica gel using 80% ethyl acetate/hexanes as eluent to afford the product; a pale yellow oil, bp 96−98 °C (8 mmHg), (0.02 mol. 3.22 g, 71%); $[\alpha]_D^{20} = +11.0°$ (MeOH, $c = 0.5$). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.42 (s, 6 H, $2CH_3$), 3.73 (m,

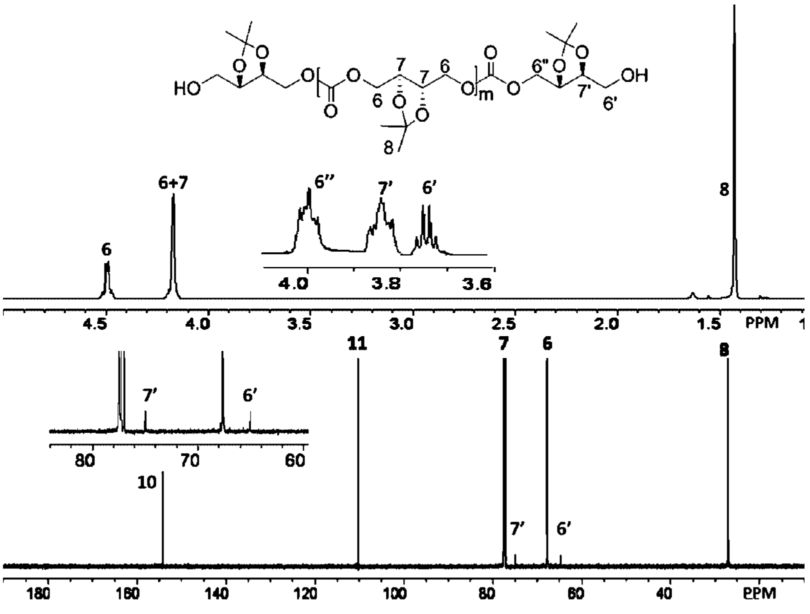


Figure 1. ^{1}H and ^{13}C NMR spectra of poly(ITC) obtained by $Sn(Oct)_2$-catalyzed ROP in bulk at 120 °C for 12 h [Table 1, entry 3].

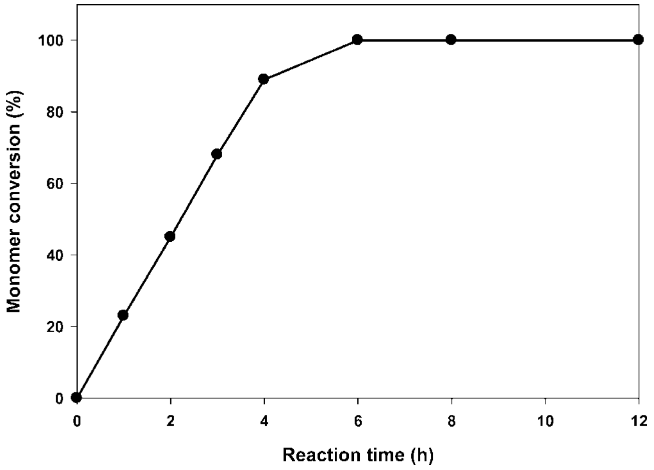


Figure 2. Percent monomer conversion of **3** as a function of time (h) for $Sn(Oct)_2$-catalyzed ring-opening polymerization at 120 °C in bulk for 12 h.

6 H, $2CH_2$ + 2OH), 3.94(m, 2 H, 2CH). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 26.7, 62.1, 78.3, 109.1.

Synthesis of (5*S*,6*S*)-Dimethyl 5,6-*O*-isopropylidene-1,3-dioxepin-2-one (ITC, 3).[14] Triphosgene (0.01 mol, 2.97 g) was dissolved in dry THF (100 mL), and the solution was added dropwise to a mixture of 2,3-di-*O*-isopropylidene-L-threitol (0.02 mol, 3.24 g) and pyridine (0.0633 mol, 4.99 g) dissolved in 200 mL of tetrahydrofuran (THF) at 0 °C over a period of 30 min. The reaction mixture was stirred at room temperature for 6 h. Precipitated pyridine hydrochloride was filtered off, and the filtrate was concentrated under reduced pressure. The product was purified by chromatography on silica gel using 20% ethyl acetate/hexanes as a solvent mixture; white solid, mp 75 °C (0.0114 mol, 2.14 g, 57%); $[\alpha]_D^{20} = +84.8°$ (CH_2Cl_2, $c = 1$). HRMS m/z $[M + H]^+$ Calcd for $C_8H_{13}O_5$: 189.07630. Found: 189.07593. ^{1}H NMR ($CDCl_3$) δ: 1.38 (s, 6 H, $2CH_3$), 4.04 (m, 2H, −CH−O), 4.29 (dd, 5 and 12.5 Hz, 4H, $-CH_2-O$). ^{13}C NMR ($CDCl_3$) δ: 26.9, 67.7, 75.7, 110.7, 154.4.

General Procedure for the Homopolymerization. In a nitrogen atmosphere, ITC (11.6 mmol, 2 g) was charged into dry freshly silanized 15 mL glass Schlenk tubes, and 5×10^{-3} mol of stannous octanoate (2% dry toluene solution) per mole of total monomer was added as a solution in sodium-dried toluene. Subsequently, the toluene was removed by evacuation. The Schlenk tubes were purged three times with dry nitrogen and placed in an oil bath preheated to the polymerization temperature (120 °C). After a predetermined time the Schlenk tubes were removed from the oil bath and rapidly cooled in ice-cold water to quench the polymer-

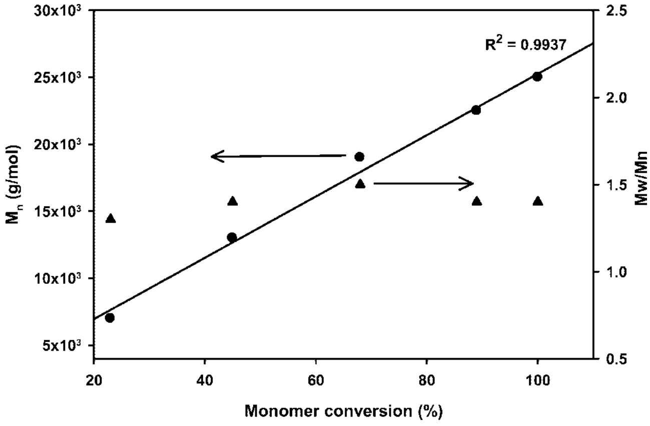


Figure 3. Number-average molecular weight and weight distribution as a function of monomer conversion for $Sn(Oct)_2$-catalyzed ring-opening polymerization at 120 °C in bulk for 12 h.

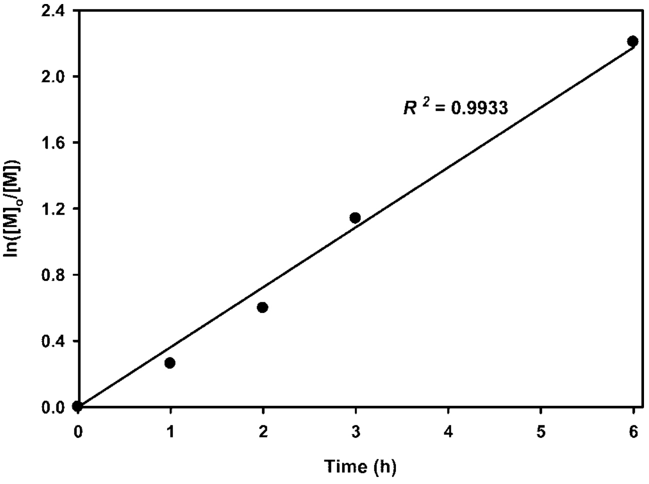


Figure 4. Plot of $\ln([M]_0/[M])$ as a function of polymerization time (h) for $Sn(Oct)_2$-catalyzed ROP of ITC monomer in bulk at 120 °C.

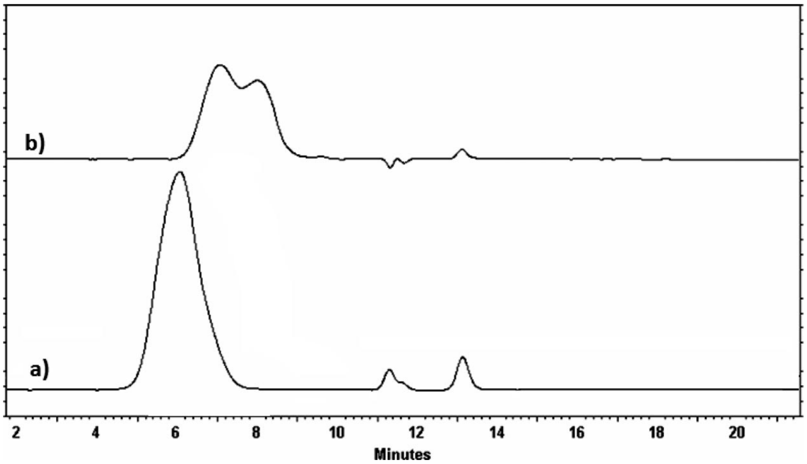
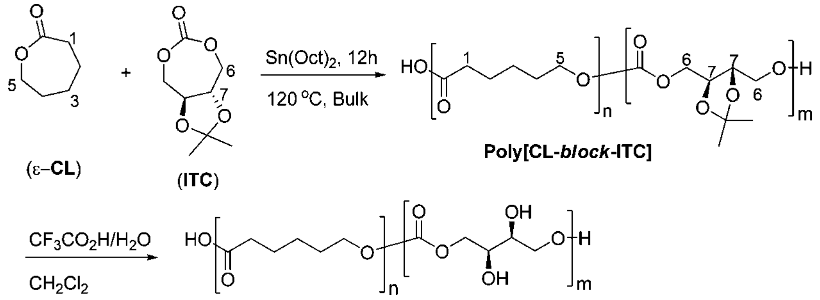


Figure 5. GPC Chromatograms−ROP of ITC with ε-CL in bulk at 120 °C for 12 h (M/C = 200): (a) catalyzed by $Sn(Oct)_2$ (M_n = 24 000 g/mol, PDI = 1.6). (b) Catalyzed by $ZnEt_2-H_2O$.

Scheme 2. Ring-Opening Copolymerization of ITC with ε-CL Catalyzed by $Sn(Oct)_2$ at 120 °C for 12 h in Bulk



ization, and the polymer was dissolved in dichloromethane. Samples were taken for determination of the monomer conversion by ^1H NMR spectroscopy. For purification, the obtained polymers were dissolved in chloroform, filtered through a sintered glass filter, and precipitated into an excess of ice-cold methanol. The precipitated polymers were collected, washed with fresh methanol, and dried at room temperature under reduced pressure.

General Procedure for Copolymerization. In a nitrogen atmosphere, a mixture of ITC and CL (10 g scale) was charged into dried, freshly silanized 15 mL glass Schlenk tubes. The monomer mixture was gently warmed and vigorously shaken in order to obtain a homogeneous mixture of the monomers. To the monomer mixture 5×10^{-3} mol of stannous octanoate (2% dry toluene solution, 1:200 catalyst:monomer ratio) per mole of total monomer was added as a solution in sodium-dried toluene. Subsequently, the toluene was removed by evacuation. The Schlenk tubes were purged three times with dry nitrogen and placed in an oil bath preheated to the polymerization temperature (120 °C). After a predetermined time the Schlenk tubes were quenched to room temperature, and the copolymer was dissolved in dichloromethane. Samples were taken for determination of the monomer conversion by ^1H NMR spectroscopy. For purification, the obtained copolymers were dissolved in chloroform, filtered through a sintered glass filter, and precipitated into an excess of ice-cold methanol. The precipitated polymers were collected, washed with fresh methanol, and dried at room temperature under reduced pressure.

General Procedure for the Removal of Isopropylidene Protective Groups.[15] Copolymer (100 mg) was dissolved in 1 mL of CH_2Cl_2. Then 1 mL of CF_3COOH (80%) was added into the CH_2Cl_2. After the reaction mixture was stirred at room temperature for a predetermined time, the resulting solution was poured into 10 mL of ice-cold methanol. The precipitated polymer was collected by vacuum filtration and dried at room temperature under reduced pressure.

Results and Discussion

Monomer Synthesis. Enantiomerically pure functional seven-membered cyclic carbonate ITC was synthesized from L-tartaric acid in three steps (Scheme 1).[14] We have recently reported the synthesis and enzymatic polymerization of the ITC monomer [mp 75 °C; $[\alpha]_D^{20} = +84.79°$ (CH_2Cl_2, c = 1). HRMS *m/z* [M + H]$^+$ 189.07593]. The bulk polymerization catalyzed by the lipase Novozym 435 at 80 °C led to the formation of optically active poly(ITC) of M_n = 15 000 g/mol (PDI = 1.7; $[\alpha]_D^{20}$ = +77.8). The removal of the ketal protecting group in poly(ITC) resulted in formation of optically pure hydroxy bearing polycarbonate (M_n = 10 000 g/mol, PDI = 2.0; $[\alpha]_D^{20}$ = +56) with minimal chain degradation. In this report the chemical homopolymerization of ITC and its copolymerization with ε-caprolactone catalyzed by stannous octanoate, $[Sn(Oct)_2]$, triisopropoxide aluminum, $Al(O^iPr)_3$, and diethylzinc monohydrate, $ZnEt_2-H_2O$, is being reported.

Bulk Homopolymerization of ITC. Three catalysts—stannous octanoate, $[Sn(Oct)_2]$, triisopropoxide aluminum, $Al(O^iPr)_3$, and diethyl zinc monohydrate, $ZnEt_2-H_2O$, were tested as catalysts for the ring-opening polymerization of the monomer (ITC, **3**). The screening polymerizations were investigated in bulk at 120 °C for 12 h. The monomer-to-catalyst ratio (M/C) was varied to test the efficiency of the catalysts.

Stannous octanoate ($Sn(Oct)_2$) is the most often used catalyst/initiator system for the polymerization of lactones and cyclic carbonates.[16−19] It is the catalyst of choice for ROP for its low cost, low toxicity, and high efficiency and yields almost complete monomer conversions even at high monomer to catalyst ratios. $Sn(Oct)_2$ itself, however, does not contain a reactive alkoxide group, but it has been shown that alcohols (ROH) or residual water in the polymerization system can act as co-initiators, in which at least one octanoate group is substituted in a rapid equilibrium to form a Sn−alkoxide group.[16−19] The Sn−alkoxide is the true initiator of the ring-opening polymerization process. We have previously reported on the synthesis and physical properties of optically enriched polyesters, based on (*R*+*S*)-4-ethyl-*ε*-caprolactone and (*R*+*S*)-4-methyl-*ε*-caprolactone prepared using $SnOct_2$ as a catalyst/initiator system.[20]

Table 1 shows the results obtained of the screening experiment. Both $Sn(Oct)_2$, and $ZnEt_2-H_2O$ catalysts show 100% monomer conversion in 24 h—calculated from the area of the ketal methyl resonances in the ^1H NMR spectra of monomer and the polymer appearing at 1.38 and 1.43 ppm, respectively. The monomer conversions for the polymerizations catalyzed by $Al(O^iPr)_3$ were lower than those with $Sn(Oct)_2$ and $ZnEt_2-H_2O$. The number-average molecular weight (M_n) was dependent upon the catalytic system used; generally higher molecular weight polymers were obtained with $Sn(Oct)_2$. As expected, at higher M/C ratios (entries 3, 6, and 9) the higher M_n poly(ITC) was synthesized. The polydispersity index (PDI), for all M/C ratios, ranged between 1.4 and 1.6. In general, $Sn(Oct)_2$-catalyzed polymerizations had the highest M_n and monomer conversion at all M/C ratio used; therefore, it was chosen for further investigation of the homopolymerization of ITC.

The structure of the poly(ITC) synthesized by $Sn(Oct)_2$-catalyzed ROP was analyzed from its ^1H and ^{13}C NMR (Figure 1) spectral data. The optical rotation measurement for the polymer was $[\alpha]_D^{20} = +77.8$. The absence of any diastereotopic resonances in its ^{13}C NMR spectrum suggested complete retention of its absolute stereochemistry. The covalent character of $Sn(Oct)_2$ catalyst, which catalyzed the polymerization through an insertion-type mechanism, is responsible for preservation of the stereochemistry which has previously been demonstrated in the preparation of optically pure poly(L-lactide).[18] However, the mechanism is still controversial, and several pathways of $Sn(Oct)_2$ initiated ROP have been proposed in the literature.[16−19] The most common include co-initiation with hydroxy groups (e.g., H_2O, alcohol) through monomer insertion-type mechanisms; in bulk polymerization adventitious hydroxy impurity (H_2O) is believed to be the co-initiator.

The assignments in Figure 1 were based on comparison with NMR spectra of the monomer, DEPT-135, two-dimensional $^1H-^1H$ COSY, and $^1H-^{13}C$ HSQC experiments for the polymer (Supporting Information). The acetonide dimethyl hydrogens (H-8) were observed at 1.43 ppm; the repeat unit methylenes (H-6), owing to their diastereotopic relationship, were observed as 4.51 and 4.20 ppm; the methine (H-7) was at 4.20 ppm. End groups H-6′, H-6″, and H-7′ were observed at 3.72, 4.0, and 3.82 ppm, respectively. The end-group assignments were confirmed from the respective $^1H-^{13}C$ correlations observed in the HSQC experiment (Supporting Information). Interestingly, in the HSQC experiment, the resonance at 3.82 (2H) correlated to two carbons, confirming that both H7′ resonances were overlapping. No proton resonances were found around 3.5 ppm for the ether linkages, which indicated that no decarboxylation in the main chain occurred during the polymerization.[11] In the ^{13}C NMR spectrum, the acetonide carbon (C-8) was at 28.7 ppm, the C-6 was at 67.5 ppm, and the C-7 was at 77.2 ppm. The end-group carbons C-6′ and C-7′ were at 64.8 and 75.4 ppm, respectively.

Figure 2 shows monomer conversion as a function of the reaction time for $Sn(Oct)_2$-catalyzed polymerization of ITC at 120 °C in bulk (M/C = 200). The conversion increased linearly with time and reached 89% by 4 h; after 6 h all of the ITC monomer was consumed. The relationship among number-average molecular weight (M_n), molecular weight distribution (PDI), and monomer conversion is plotted in Figure 3. The molecular weight increased linearly with monomer conversion. The correlation coefficient (R^2) of 0.99 from the regression analysis of the number-average molecular weight versus percent monomer conversion suggests that no transfer reaction occurred during the course of polymerization. Poly(ITC) of M_n 26 000 g/mol was isolated after 12 h. The $[\alpha]_D^{20} = +77.8$ suggested formation of an optically pure polymer and that the no racemization of the monomer occurred during the polymerization. The polydispersity index (PDI) ranged from 1.3 to 1.5, which was within experimental error. The narrow molecular weight distribution advocates absence of chain initiation and transfer reactions occurring after 23% monomer conversion and that the main event is chain propagation.

In Figure 4 the $\ln([M]_0/[M])$ is plotted as a function of polymerization time (h), where $[M]_0$ is the initial concentration of the monomer and [M] is the monomer concentration at a given polymerization time (*t*). Analysis of the graph by regression analysis ($R^2 = 0.9933$) suggested a first-order rate law for $Sn(Oct)_2$-catalyzed polymerization of ITC in bulk at 120 °C. These results are in agreement with general ROP mechanism of nonterminating chain polymerization. The apparent rate constant of propagation step (K_{app}) of 1.05×10^{-3} s^{-1} was calculated from the slope of the regression line using the equation $K_{app} = d(-\ln[M]/[M]_0)/dt$.[21]

Copolymerization. The complexity and the broad array of potential applications of biodegradable materials require polymers with varieties of properties. Degradable polyesters based on lactone monomers, such as L-lactide and *ε*-caprolactone are increasingly being considered as environmentally friendly materials. Copolymerization of two or more monomers is one of the most versatile methods for tailoring material properties by changing the composition of the copolymer. Our continuous efforts to develop new biodegradable polymers[22] led us to explore the copolymerization of ITC monomer with *ε*-caprolactone, which is efficient and easy method to tune up the properties of a polymer.

$Sn(Oct)_2$, $ZnEt_2-H_2O$, and $Al(O^iPr)_3$ were screened for the copolymerization of ITC with CL in 50:50 feed ratio in bulk at 120 °C for 12 h. The M/C mole ratios of 1/200 were used for the copolymerization. The copolymers were analyzed by NMR and GPC. The ^1H NMR spectra of the crude products from copolymerization conducted using $Sn(Oct)_2$ and $ZnEt_2-H_2O$ were similar; however, GPC chromatograms of $ZnEt_2-H_2O$-catalyzed copolymerization showed a bimodal distribution indicating the formation of two homopolymers (Figure 5b). In contrast, $Sn(Oct)_2$-catalyzed copolymerization showed a unimodal distribution indicating the formation of a copolymer (Figure 5a). The ^1H NMR spectrum of the copolymerization catalyzed by $Al(O^iPr)_3$ showed only the formation of poly(*ε*-CL), leaving the ITC monomer unreacted. This result is supported by the low reactivity of $Al(O^iPr)_3$ catalyst toward ITC monomer as observed in ITC homopolymerization screening, which showed percent monomer conversion lower seventies after 24 h (Table 1, entries 7−9). A detailed investigation of the copolymerization of ITC with *ε*-CL was, therefore, undertaken catalyzed by $Sn(Oct)_2$.

Copolymerization of ITC and *ε*-CL was first carried out by $Sn(Oct)_2$ in bulk at 120 °C for 12 h as shown in Scheme 2, and the results are summarized in Table 2. It can be seen from Table 2 that $Sn(Oct)_2$ can efficiently initiate the copolymerization of ITC and *ε*-CL as single-component catalyst at 120 °C. The copolymer was obtained in 92% isolated yield after 12 h, when the feeding molar ratio of the monomers is 50:50 under the conditions reported in Table 2 (entry 4). All the copolymers obtained in Table 2 had a unimodal molecular weight distribution with polydispersity index ranging from 1.4 to 1.6, indicating the polymers obtained were pure copolymers without ho-

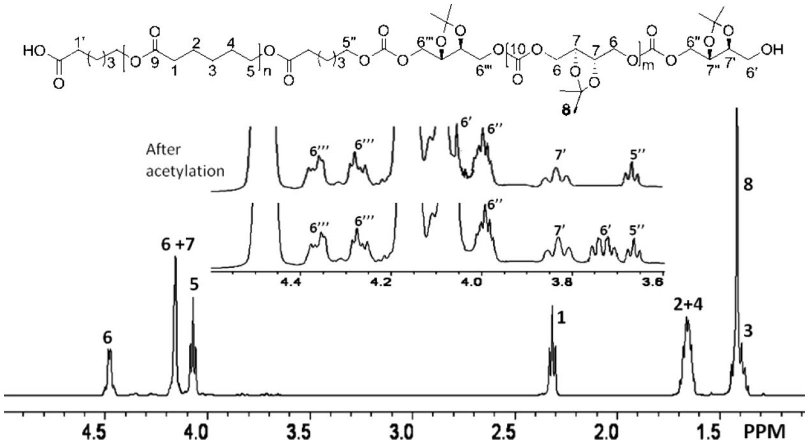


Figure 6. ^{1}H NMR spectra (500 MHz, $CDCl_3$) of poly(ITC-*block*-CL) [Table 2, entry 4], obtained by $Sn(Oct)_2$-catalyzed ROP in bulk at 120 °C for 12 h. The inset in the figure shows a comparison of the data before and after acetylation.

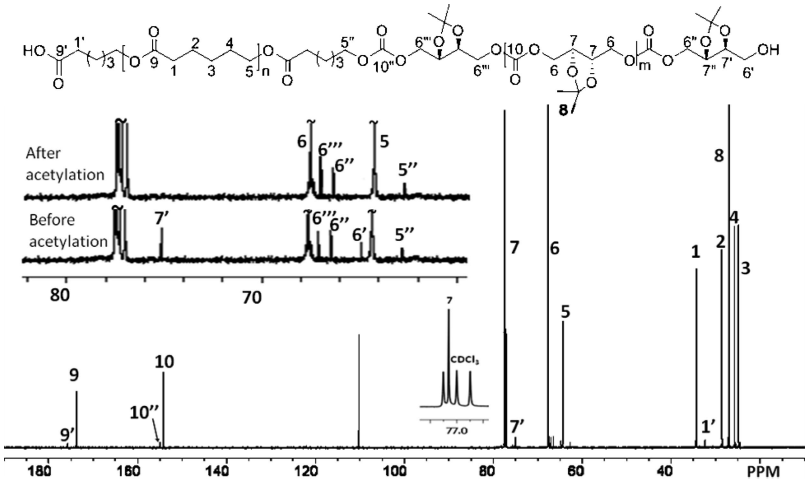


Figure 7. ^{13}C NMR (125 MHz, $CDCl_3$) of poly(ITC-*block*-CL) for $Sn(Oct)_2$-catalyzed copolymerization in bulk at 120 °C for 12 h [Table 2, entry 4]. The inset in the figure shows the expanded region before and after acetylation.

mopolymers of ε-caprolactone and ITC. A GPC curve for the copolymer obtained at the molar monomer feed ratio of 50:50 is shown in Figure 5a as an example. In general, high yields (>87%) were obtained upon precipitation of the copolymer from methanol. The number-average molecular weights (M_n) were in the range of 23 000−26 000 g/mol. Copolymer molar composition revealed that incorporation of ITC monomer was less than that in the monomer feed after 12 h of polymerization reaction. Analyses of the crude polymerization mixture suggested that lost ITC monomer may be in the lower molecular weight fraction. The copolymerization of the optically pure ITC monomer with ε-caprolactone, a nonchiral monomer, was evident as the specific rotation decreased with decreasing ITC content in the copolymers.

NMR Characterization of Copolymers. The copolymers were characterized by detailed analyses of the ^{1}H NMR, ^{13}C NMR, ^{1}H−^{1}H COSY, and ^{1}H−^{13}C HSQC and by comparison with the respective homopolymers spectra. For example, the structure of the poly(ITC-*co*-CL) synthesized by ROP of an equimolar amount of ITC and ε-CL and catalyzed by $Sn(Oct)_2$ was analyzed by ^{1}H and ^{13}C NMR spectra shown in Figures 6 and 7, respectively. The copolymer molar compositions were calculated from relative peak area of the H1 ($-COCH_2-$ at 2.32 ppm) and H6 resonances ($-OCH_2-$ at 4.17 and 4.50 ppm) in the ^{1}H NMR spectrum for ε-CL and ITC repeat units, respectively (Figure 6). The diastereotopic protons ($H6_{a,b}$) were observed at 4.17 and 4.50 ppm; the assignments were based on ^{1}H−^{13}C correlation HSQC experiment (see Supporting Information). The proton resonances belonging to the acetonide methyl (H8) in ITC and H3 of ε-CL repeat unit ($-CH_2-$) overlapped at 1.43 ppm. Upon comparison to the ^{1}H NMR spectrum of the poly(ITC), the low-intensity resonances in the ^{1}H NMR spectrum of the copolymer at 3.72, 3.82, and 4.0 ppm were assigned to H6′ ($-CH_2OH$), H7′ ($-CHO-$), and H6′′ ($-CH_2OCOO$), respectively, of the ITC block (insert in Figure 6). The presence of the free hydroxy end groups is in agreement with previous reports that −O−Sn−R end groups undergo exchange reaction with octanoic acid released from $Sn(Oct)_2$, resulting in hydroxy end groups.[19] Alternatively, the hydroxy end groups can also be generated upon precipitation in methanol; a similar observation was made during precipitation of poly(L-lactide) in cold methanol (+4 °C).[16] The resonances of the methyleneoxy hydrogens (pCL−CH_2−OCOO−pITC) belonging to the CL−ITC link were observed at 3.66 ppm (H-5′′, *CL*-ITC) and at 4.28 and 4.36 ppm (H6′′′, pCL−OCOO−CH_2−pITC). The ^{1}H−^{1}H COSY experiment (Supporting Information) was used to confirm the CL−ITC link assignments in the copolymer (Table 2, entry 4), which showed coupling of H-5′′ to H-4′′ and the H-6′′′ to the H-7′′′. Importantly, no proton resonances were found around 3.5 ppm (ether linkage) in either the homopolymer (polyITC) or the copolymers, which indicated that no decarboxylation in the main chain occurred during the copolymerization.[11] In order to confirm the end-group assignment, the copolymer was subjected to acetylation of the hydroxy end group, and the ^{1}H NMR spectra before and after acetylation are shown in Figure 6 (inset). The new acetate group resonance

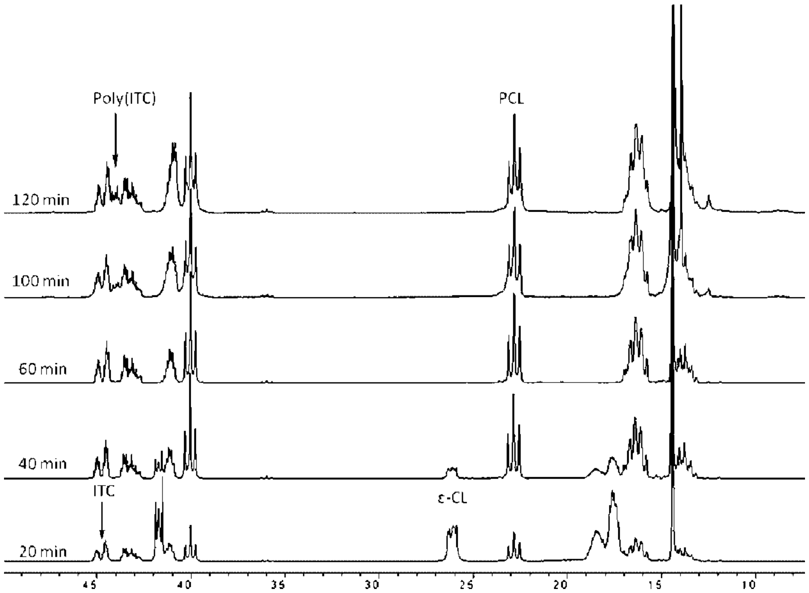


Figure 8. ^{1}H NMR (250 MHz, $CDCl_3$) spectra for various reaction time of $Sn(Oct)_2$-catalyzed copolymerization of ITC monomer with ε-caprolactone (ε-CL) at 120 °C in bulk [1:1 feed ratio].

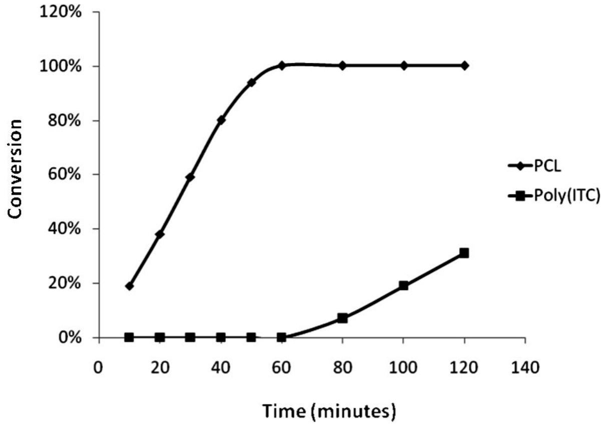


Figure 9. Plot of monomer conversion (%) as a function of reaction time (min) for $Sn(Oct)_2$-catalyzed copolymerization of ITC monomer (■) with ε-caprolactone (◆) at 120 °C in bulk [1:1 feed ratio].

was observed at 1.98 ppm (s, CH_3CO), and its integral suggested that only one acetate group was attached, confirming only one hydroxy end group in the copolymer (HOOC−pCL−pITC−OH). A careful comparison of the data before and after acetylation was used to confirm the assignments in the ^{1}H NMR. Importantly, only the H-1′ was deshielded to 4.1 ppm, suggesting an acetate formation at C-1′. As expected, the resonances arising from the CL−ITC link were unaffected by the end-group acetylation.

The ^{13}C NMR spectrum of the copolymer [Table 2, entry 4] along with peak assignments is shown in Figure 7, and it did not contain resonances expected of the diad and triad sequences originating from a random copolymer, which suggests formation of AB block copolymers. The high-intensity peaks were assigned to the poly(ε-CL) and poly(ITC) resonances. The low-intensity peaks were assigned to the end groups and the PCL−PITC link carbons. The PCL end groups C-1′ ($-CH_2COOH$) and C-9′ ($-COOH$) were observed at 32.8 and 177.0 ppm, respectively. The resonance at 62.8 ppm was assigned to the C-5″ ($-CH_2O$) of the *PCL*−PITC link. The poly(ITC) end group hydroxymethylene (C-6′) was observed at 64.8 ppm, and the C-7′ was at 75.2 ppm. The carbonate carbonyl (C-10′) linking the CL and ITC block was observed at 155.0 ppm. Interestingly, the C-6″ and C-6‴ carbons were observed at 66.3 and 67.2 ppm, owing to their proximity to the end group or the PCL−PITC link. The ^{13}C NMR spectrum of the acetylated copolymer [Table 2, entry 4] was also acquired, and a comparison of the data before and after acetylation is included in Figure 7 (inset). The ^{13}C NMR spectrum after acetylation showed a new peak at 17.0 ppm for the acetate methyl, and the C-6′ ($-CH_2OCOCH_3$) resonance was shifted downfield to 67.4 ppm. The downfield shift only in the resonance position of C-6′ confirmed the structure of the block copolymer and that only one hydroxy end group was present. The AB block copolymer structure was thus established and was in line with observation of only unimodal peaks in the GPC analyses.

Formation of the block copolymers is traditionally accomplished through sequential addition of monomers such that the prepolymer from the first monomer initiates polymerization of the second monomer, and inter- and intrachain transfer reaction are kept to a minimum. For example, polymerization of ε-caprolactone with DXO[23] and lactide[24] has been reported employing the sequential monomer addition strategy. In an interesting approach Saegusa et al.[4] were first to report a unique one-shot block copolymerization, which involves successive polymerizations of each of two monomers that are fed simultaneously.

To understand the mechanism, copolymerization of ITC and ε-CL by $Sn(Oct)_2$ was further investigated. The progress of the copolymerization of equimolar amount of ITC and ε-CL was carefully monitored using ^{1}H NMR spectra collected at predetermined time intervals, and it could be observed that the rate of polymerization of ε-CL was much higher than that of ITC. A stacked plot of ^{1}H NMR spectra acquired during the copolymerization process is shown in Figure 8. The diastereomeric H-6 resonances in ITC monomer are observed as a multiplet centered at 4.3 ppm, and the H-1 in ε-CL monomer were observed at 2.6 ppm. The formation of the poly(ε-CL) prepolymer can be seen with emergence of a new H-1 resonance (a triplet) at 2.2 ppm, while the poly(ITC) formation results in a new H-6 resonance at 4.4 ppm. In the first 60 min, ε-CL conversion reached >98%, but none of ITC monomers had been consumed; in 80 min, ε-CL was completely consumed and ITC conversion was <10% (Figure 9). Clearly, ε-CL was polymerized first, and the polymerization of ITC was initiated only after all of the ε-CL monomer had been consumed (Figure 9). This proposed copolymerization mechanism in Figure 10 is supported

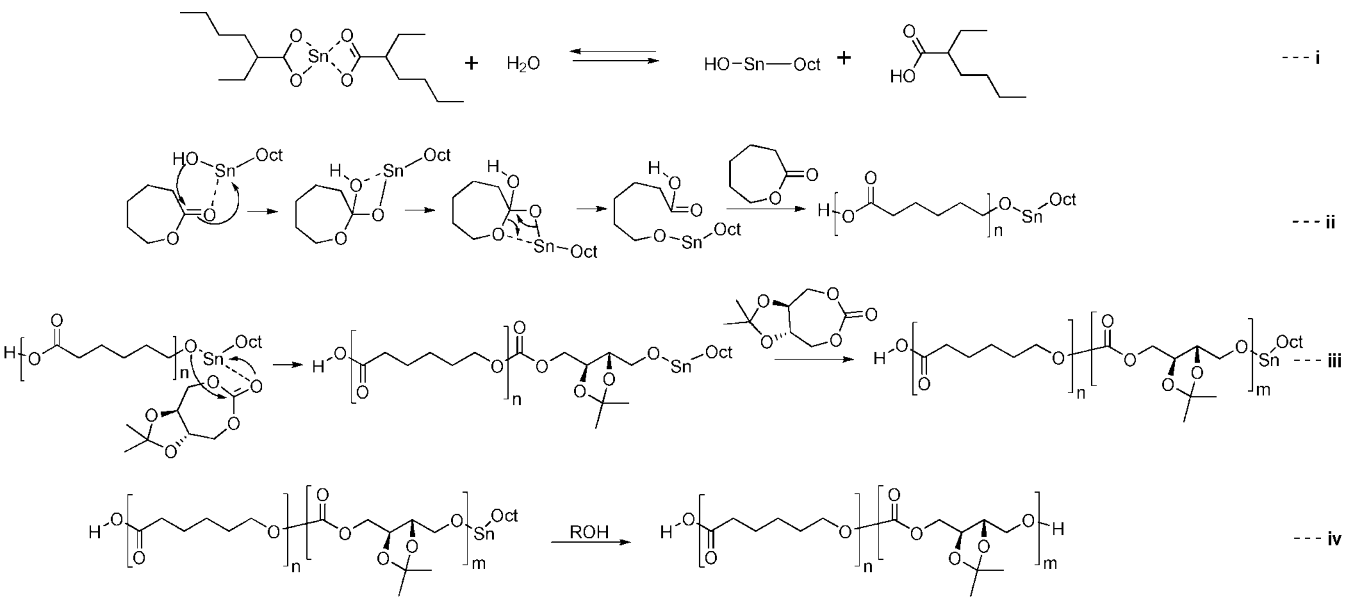


Figure 10. Mechanism of stannous octanoate-catalyzed block polymerization of ε-CL and ITC: (i) formation of stannous octanoate initiator, (ii) coordination/insertion/polymerization of ε-CL, (iii) coordination/insertion/polymerization of ITC to result in AB block copolymer, (iv) formation of the hydroxy end group.

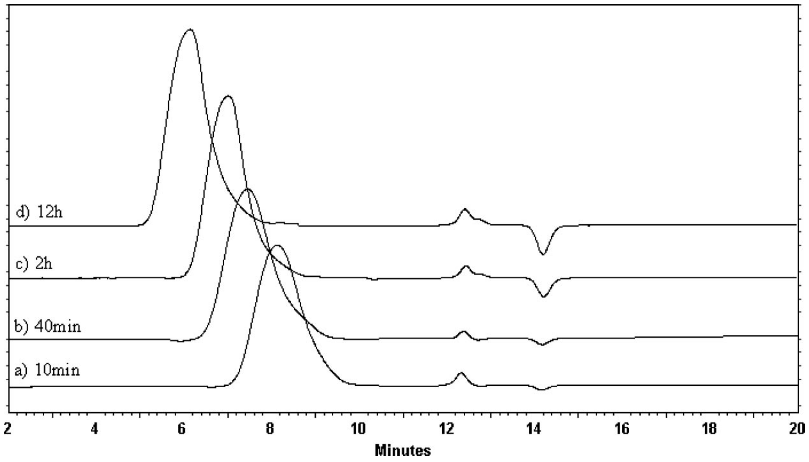


Figure 11. GPC chromatograms of poly[ITC-*block*-CL] at different reaction times catalyzed by $Sn(Oct)_2$ at 120 °C in bulk (M/C = 200): (a) M_n = 1700 g/mol, PDI = 1.5. (b) M_n = 6400 g/mol, PDI = 1.6. (c) M_n = 13 000 g/mol, PDI = 1.6.

Table 2. $Sn(Oct)_2$-Catalyzed Ring-Opening Copolymerizations of ITC and ε-CL[a]

entry	monomer feed ratio[b] [ITC:CL]	copolymer molar composition[c] [ITC:CL]	yield[d] (%)	M_n[e] (g/mol)	PDI[e]	T_m[f] (°C)	ΔH_m[f] (J/g)	$[\alpha]_D^{20}$[g]
1	100:0		87	24 000	1.6	58.8	62.85	+77.8
2	90:10	81:19	88	23 000	1.6	57.0	68.11	+62.5
3	70:30	62:38	91	24 000	1.6	56.5	64.96	+47.9
4	50:50	44:56	92	24 000	1.6	54.6	60.23	+33.8
5	30:70	25:75	92	25 000	1.5	54.1	59.27	+19.3
6	10:90	5:95	95	26 000	1.4	52.7	56.27	+3.3
7	0:100		95	26 000	1.4	52.7	57.1	

[a] Reactions were carried out in bulk for 12 h at 120 °C using monomer/catalyst mole ratio (M/C) = 200. [b] Monomer feed ratio in mol/mol. [c] Calculated from ^1H NMR spectrum. [d] Insoluble portion in methanol. [e] Determined from GPC. [f] Measured from DSC. [g] Specific rotation measured in CH_2Cl_2 (c = 1.0).

Table 3. Removal of the Acetonide Groups[a]

entry	time (min)	conversion (%)[b]	yield (%)[c]	M_n (g/mol)[d]	PDI[d]
1	0			24 000	1.6
2	5	51	89	22 500	1.7
3	10	79	87	22 000	1.8
4	15	99	83	21 000	1.9
5	20	100	75	18 000	2.2

[a] $CH_2Cl_2/CF_3COOH/H_2O$ at room temperature (see Experimental Section). [b] Calculated from ^1H NMR. [c] Insoluble portion in methanol. [d] Determined from GPC.

by the NMR analyses of the reaction mixture and the structure of the AB block copolymer formed.

Figure 11 shows GPC curves during the copolymerization of ITC and ε-CL at predetermined time intervals. The GPC curves were unimodal, and the polymer molecular weight increased with monomer conversion. Importantly, the GPC curves continue to be unimodal and molecular weight increases even after the consumption of ε-CL was complete (Figure 9). For the synthesis of block copolymers it is required that chain transfer reactions do not occur during the polymerization. The polydispersity index of the copolymerization remained unchanged, within experimental error, throughout the course of the copolymerization, suggesting no chain transfer reactions took place. At the polymerization temperature of 120 °C it has been reported that no transesterification reactions occurred during stannous octanoate-catalyzed ring-opening polymerization of DL-lactide.[25]

The copolymerization of ITC with ε-CL catalyzed by $Sn(Oct)_2$ at 120 °C, therefore, resulted in formation of AB block

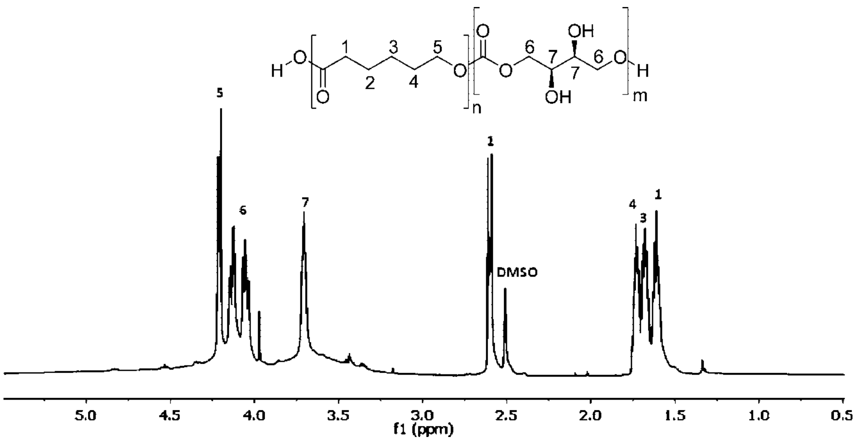


Figure 12. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of poly[ITC-*block*-CL] after deprotection [Table 3, entry 4].

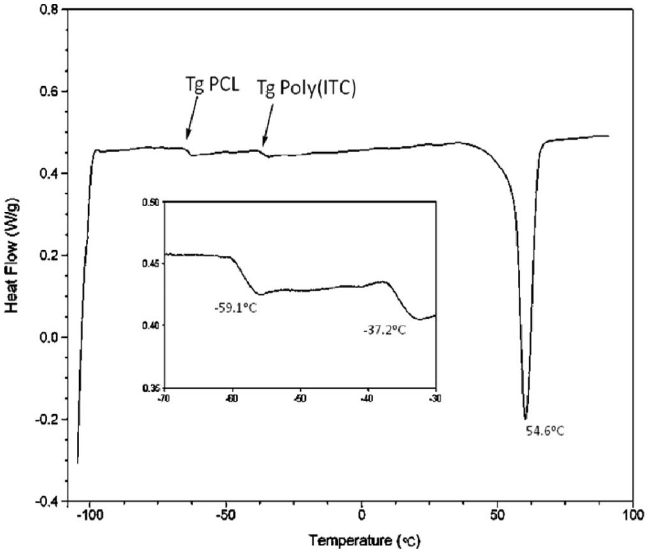


Figure 13. DSC thermogram of poly(44%ITC)-*block*-poly(56% ε-CL) (Table 2, entry 4).

copolymer, poly(ε-CL)-*block*-poly(ITC), in which the poly(ε-CL) prepolymer from the fast reacting monomer, ε-CL, initiated the ROP of the slow reacting ITC monomer. This is the first example, to the best of our knowledge, of the one-shot block polymerization of ε-CL with a carbonate monomer.

Deprotection of Ketal Groups. PCL is important biodegradable synthetic polymer; however, the slow biodegradation rate of PCL due to its hydrophobic nature limits its applications. Introducing hydroxy functional groups in the polymer backbone is expected to enhance PCL hydrophilicity, physical properties, and biodegradability.

Trifluoroacetic acid has been utilized as an efficient deprotecting reagent for the acetonide group of polymers containing carbonate and ester groups in the main chain with minimal degradation.[15] The copolymer in Table 2, entry 4 was chosen as a model to perform the deprotection. Table 3 summarizes the results obtained for the deprotection in various reaction times. The M_n of the copolymer before deprotection was 24 000 g/mol and PDI of 1.6. After 5 min reaction time 51% of the ispropylidene protective were removed, the M_n dropped to 22 500, which was mainly due to the loss of acetonide groups. The conversion was calculated from the new resonance at 3.7 ppm of the methine hydrogens ($-CH-OH$) in the ^{1}H NMR spectrum (Figure 12). After 15 min reaction 99% deprotection was achieved ($M_n = 21\,000$ g/mol) with slight increase in PDI to 1.9, which indicated minimal degradation of the polymer chain. At 20 min reaction time, complete removal of the ketal group was achieved with increase in PDI to 2.2. The specific rotation ($[\alpha]_D^{20}$) of poly(44%ITC)-*block*-poly(56% ε-CL) before and after deprotection is +33.8 [CH_2Cl_2, $c = 1$] and +10.9 [EtOH, $c = 1$], respectively.

Thermal Analysis. The thermal analyses of synthesized polymers were carried out using DSC. The samples were scanned from −100 to +300 °C at a rate of 10 °C/min under a nitrogen atmosphere. Two glass transition temperatures (T_g) were observed for poly(44%ITC)-*block*-poly(56% ε-CL) (Table 2, entry 4) at −59.1 and −37.2 °C for the polyCL and the polyITC block, respectively, confirming the diblock nature of the copolymers (Figure 13). PCL is reported to have a T_g of −60 °C and T_m of 60 °C.[26] The DSC thermogram also showed a sharp exothermic peak (T_m) for the poly[44%ITC-*block*-56%CL] at 54.6 °C with meting enthalpy (ΔH_m) of 60.23 J/g. The melting temperature (T_m) of PCL (M_n 24 000 g/mol; PDI = 1.4; Table 2, entry 7) is found to be 52.7 °C, which is lower than the reported T_m value of 60 °C for a similar M_n PCL.[26] In general, T_m and melting enthalpy (ΔH_m) values in Table 2 decrease with decreasing ITC monomer content in the feed ratio. Interestingly, only one melting temperature was observed for the AB block copolymers, which was because of the overlapping melting transitions of poly(ITC), T_m = 58.8 °C, and poly(CL), T_m = 52.7−60 °C.

After deprotection, the T_m and ΔH_m of poly[44%ITC-*block*-56%CL] increased to 59.4 °C from 54.6 °C and 78.84 from 60.23 J/g, respectively. The ΔH_m increased by 30% after the deprotection, which indicates higher crystallinity of the free hydroxy copolymer.

Conclusion

Enantiomerically pure seven-membered cyclic carbonate (ITC) synthesized from naturally occurring L-tartaric acid in three steps was investigated for its polymerization and copolymerization with ε-CL. From three catalysts, namely stannous octanoate [$Sn(Oct)_2$], triisopropoxide aluminum ($Al(O^iPr)_3$), and diethylzinc monohydrate ($ZnEt_2-H_2O$) screened for the polymerization of the monomer ITC, $Sn(Oct)_2$ was found to be the most efficient catalyst. The homopolymerization of ITC catalyzed by $Sn(Oct)_2$ followed a first-order rate law. The results are in agreement with the general mechanism of the ROP of a nonterminating chain polymerization. Optically active copolymers with various feed ratios were synthesized by the ring-opening copolymerization of ITC with ε-CL catalyzed by $Sn(Oct)_2$ at 120 °C for 12 h, in bulk. Detailed investigation of the copolymers revealed them to be AB block copolymers. It is the first report of “one-shot feeding” block copolymer synthesis of ε-caprolactone by ring-opening polymerization with a cyclic carbonate monomer. The deprotection of the ketal groups using trifluoroacetic acid offered poly[ITC-*block*-CL] with pendant hydroxy groups with minimal degradation in the polymer chain. Physical, chemical, and biodegradation evaluations are currently underway in our laboratories.

Acknowledgment. Financial support from the American Lung Association, American Cancer Society, and the Herman Frasch Foundation (510-HF02) is greatly appreciated.

Supporting Information Available: ^{1}H and ^{13}C NMR, ^{1}H−^{1}H COSY, and ^{1}H−^{13}C HSQC spectra of monomer, poly(ITC), and ITC−CL block polymers. This material is available free of charge via the Internet at http://pubs.acs.org.

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MA802546V