Copolymerizations of ω-Pentadecalactone and Trimethylene Carbonate by Chemical and Lipase Catalysis

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ABSTRACT: Copolymerizations of ω-pentadecalactone (PDL) with trimethylene carbonate (TMC) were studied using chemical and enzyme catalysts. By using stannous octanoate, methylaluminoxane (MAO), or aluminum isopropoxide, copolymerizations of PDL with TMC with 1:1 feed ratio resulted in either homo-polyTMC or PDL/TMC block copolymers. These catalysts polymerize TMC more rapidly than PDL. A copolymerization catalyzed by MAO gave poly(TMC-*co*-16 mol % PDL) with M_n 26.4 × 10^3g/mol and randomness numder (*B*) about 1.1. The sodium ethoxide-catalyzed copolymerization led to products with low M_n (<6.8 × 10^3) but nearly random sequence distribution. The copolymerization of PDL with TMC was also studied by using lipase catalysts. Of the six lipases evaluated for PDL/TMC copolymerizations in toluene at 70 °C, an immobilized form of lipase B from *Candida antarctica* (Novozyme-435) was preferred. Changing the PDL/TMC comonomer feed ratio from 1:10 to 10:1 (mol/mol) provided copolymers that ranged in M_n and PDL mol % from 7.3 × 10^3 to 25.2 × 10^3 and 28 to 88, respectively. In contrast to the chemical catalyst systems, Novozyme-435 catalysis showed that PDL was consumed more rapidly than TMC. Also, in contrast to most of the chemical catalysts, ^{1}H and ^{13}C NMR analyses showed that the copolymers from Novozyme-435 catalysis were able to give a random distribution of the repeat units at extended reaction times. Furthermore, in contrast to TMC polymerization in the presence of preformed polyPDL with MAO, Novozyme-435 catalyzed polymerization led to random copolymers.

Introduction

Recent activities that use in-vitro enzyme catalysis for the preparation of monomers, oligomers, and polymers have shown great promise for providing mild reaction conditions and reactions that can proceed with enantio- and regioselectivity.[1−3] In addition, since enzymes operate by a mechanism that is different from traditional chemical catalysts, the polymers formed using lipases may have unique tacticity or comonomer repeat unit structures. Furthermore, traditional catalysts may currently not be available that provide sufficient catalytic activity for certain polymerization challenges.

Aliphatic polycarbonates and their copolymers with polyesters are of interest for use in bioresorbable suture filament, artificial skin, prostheses, bone fixation plates, ligature clamps, and galenic formulations.[4] Poly(ω-pentadecalactone), poly(PDL), is a semicrystalline polymer with a melting point of about 95 °C,[5] while poly(trimethylene carbonate), poly(TMC), is normally amorphous.[4] An ability to synthesize copolymers of PDL and TMC with control of the copolymer repeat unit sequence distribution would allow a full interrogation of PDL/TMC copolymer properties.

The ability of traditional catalysts to perform homo- and copolymerizations of lactones and cyclic carbonates is directly relevant to this study. The homopolymerization of TMC has been effectively carried out using catalysts such as tin octanoate, aluminum isopropoxide, and MAO at elevated temperatures (80−120 °C) for 24 h. The resulting poly(TMC) had high yields and M_n (>85%, (30−52) × 10^3g/mol).[18,19] Random copolymerization of TMC with ϵ-caprolactone (CL)/lactide has been performed using tin octanate,[15] aluminum isopropoxide,[17] rare-earth chloride−epoxide, and isopropoxide.[14] The polymerization of macrolactones (i.e., undecanolide and dodecanolide) in bulk with metal methoxide as anionic initiators at 90−120 °C resulted in 23−94% isolated yields and M_n from ∼5 × 10^3 to 10 × 10^3 g/mol. It was also observed that methyllithium, butyllithium, and diethylzinc were not efficient initiators for these macrocyclic esters. Under similar conditions, the rate of ϵ-CL polymerization was found to be much faster than these macrolides.[7] Thus far, copolymerizations with TMC where PDL is used in place of ϵ-CL have not been reported. This may be due to the low ring strain of PDL that has proved difficult to overcome using traditional chemical methods.

Kobayashi and co-workers were first to recognize the ability of lipases to catalyze polymerizations of PDL and other macrolactones.[6,7] Studies have been reported on lipase-catalyzed copolymerization of β-propiolactone with ϵ-CL[3] and PDL with dodecanolactone (DDL), undecanolactone (UDL), valerolactone (VL), and CL.[6] These copolymerizations were conducted in bulk and required long reaction times (10 days) at 60−75 °C to reach high monomer conversions (95%). The products formed were of low molecular weight (M_n < 6000 g/mol). Slight improvement in rates (82−95% monomer conversion in 48 h) and product M_n (up to 9 × 10^3 g/mol) were made by Kobayashi and co-workers when octanolide (8-OL) was copolymerized with CL and DDL in isooctane at 60 °C for 48 h using *Candida antarctica* lipase as the catalyst.[8] Matsumura and co-workers reported that, using porcine pancreatic lipase (PPL) as the catalysts, lactide was copolymerized with TMC.[9] The polymerization was conducted at 100 °C for nearly 12 days. The product formed was claimed to be random poly(lactide-*co*-TMC) copolymers with M_w up to 21 × 10^3. Questions remain as to whether the activity of PPL was retained to some extent at 100 °C over days. Furthermore, at 100 °C, TMC polymerization may in part occur by thermal-mediated processes.[20]

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Table 1. Copolymerization of PDL and TMC Using Chemical Catalysts[a]

reaction product[b]	Cat	$[Cat]_0$ (mmol)	time (h)	temp (°C)	solvent	F_{PDL}/F_{TMC}[c]	obs$[PDL]_0/[TMC]_0$	% yield	$M_n \times 10^3$ [d]	M_w/M_n[d]
1	$Sn(Oct)_2$	0.01	24	115	toluene	1:1	04/96	43	10.2	2.07
2	Al Iso	0.01	24	70	toluene	1:1	04/96	24	4.1	1.21
3	Al Iso	0.01	24	70	bulk	1:1	03/97	41	26.1	1.28
4	MAO	0.01	24	90	toluene	1:1	16/84	40	26.4	2.59
5	MAO	0.01	24	90	toluene	0:1	0/100	95	55.0	1.89
6	MAO	0.01	24	90	toluene	1:0	100/0	96	5.7	1.76
7	$NaOC_2H_5$	0.1	24	90	toluene	1:1	44/56	60	6.8	1.68
8	$NaOC_2H_5$	0.2	6	70	THF	1:1	53/47	61	5.8	1.44

[a] Monomer concentration (1 mmol). [b] Designates the reaction conditions/reagents and the product formed. [c] Monomer feed ratio. [d] M_n and M_w/M_n of the samples were determined by GPC in $CHCl_3$.

Recently, our laboratory reported that lipase-catalyzed PDL polymerization can occur rapidly to give high molecular weight polyesters under mild reaction conditions. For example, Novozyme-435-catalyzed PDL polymerization for 2 h, at 70 °C, in toluene (toluene/PDL 1:1 v/w), gave poly(PDL) with M_n 86.4 $\times$ 10^3 g/mol in 90% isolated yield.[10] Also, Novozyme-435 catalyzed transacylation reactions between preformed aliphatic polyester chains. For example, the reaction between poly(caprolactone) ($M_n = 9.2 \times 10^3$, $M_w/M_n = 1.17$) and poly(PDL) ($M_n = 4.3 \times 10^3$, $M_w/M_n = 2.69$) in bulk at 70−75 °C for 1 h gave random copolymers.[12] Novozyme-435 still catalyzed transacylation reactions between preformed PCL and poly(PDL) even when their initial M_n values were >40.0 $\times$ 10^3 g/mol. However, the reaction proceeded more slowly than for the corresponding lower molar mass substrates, so that times of >24 and ≤30 h were required to convert the starting materials to random copolymers. These results and others discussed elsewhere showed conclusively that lipase B from *Candida antartica* is a potent catalyst for the transacylation of aliphatic polymeric substrates.[12] We postulated that reactions between polyesters involve intrachain cleavage by the lipase to form an enzyme-activated-chain segment (EACS).[12] This EACS can then react with the terminal hydroxyl unit of another chain. The rate of these lipase-catalyzed transacylation reactions is a function of the polyester chain length and the availability of chain-end hydroxyl groups. This hypothesis was supported by the finding that acetylation of chain-end hydroxyl units causes a large decrease in the rate of transacylation reactions between PCL and poly(PDL) chains.[12] This paper is concerned with whether lipase provides unique attributes for the catalysis of lactone/carbonate copolymerizations. PDL/TMC copolymerizations were performed in monophasic organic media (toluene) using Novozyme-435 (immobilized form of lipase B from *Candida antarctica*) and other lipase catalysts. For comparison, PDL/TMC copolymerizations were attempted using well-known tin-, sodium-, and aluminum-based chemical catalyst systems. The microstructure and molecular weight of products were studied. In addition, the contribution of lipase-catalyzed transacylation reactions for this system which consists of mixed ester/carbonate linkages is discussed.

Experimental Section

A. Materials and Methods. ω-Pentadecalactone, methyl aluminum oxide, tin octanate, aluminum isopropoxide, sodium ethoxide, and toluene were purchased from Aldrich Chemical Co., Inc. Toluene was dried over calcium hydride and distilled under nitrogen atmosphere. Stock solution of tin octanate was prepared in toluene and used for polymerization. Coulomat A and Coulomat C were purchased from EMscience. Lipases from *Aspergillus niger*, *Candida rugosa*, and *Pseudomonas cepacia* were a gift from Amano International Corp., and porcine pancreas, *Candida antarctica*, and *Candida cylindracea* were purchased from Sigma. Novozyme-435 (specified activity 7000 PLU/g) was a gift from Novo Nordisk Co.

Table 2. Lipase Screening for Copolymerization of PDL and TMC in Toluene for 24 h

enzyme[a]	yield (%)	$[PDL]_0/[TMC]_0$[b]	$M_n \times 10^3$ [c]	M_w/M_n[c]
Novozyme-435	90	50/50	18.8	1.65
PSC	22	63/37	0.6	2.0
lipase AY	25	57/43	1.6	1.79
lipase AK	NA			
PPL	NA			

[a] 10 wt % enzyme with respect to monomers. [b] Observed molar ratio of the monomers in the copolymer calculated by ^{1}H NMR. [c] M_n and M_w/M_n of the samples were determined by GPC in $CHCl_3$.

Synthesis of Trimethylene Carbonate. Trimethylene carbonate (TMC) was synthesized following a procedure described elsewhere.[13] The product was recrystallized twice from diethyl ether. White crystals were obtained in 60% yield: mp 45 °C (lit.[13] mp 45 °C). The ^{1}H NMR spectrum (4H, 4.5 ppm; 2 H, 2.21 ppm) was consistent with the literature.[13]

Copolymerization of PDL and TMC Using Chemical Catalysts. The polymerization ampules (10 mL) were treated with trimethylsilyl chloride, washed with three 5 mL portions of methanol, dried at 100 °C in an oven, and flame-dried while being purged with dried argon. Monomers (1 mmol) and the catalyst (see Table 1) were transferred into the ampule under inert nitrogen atmosphere. The ampule was degassed by several vacuum−purge cycles that also removed solvent introduced in the catalyst solution. The ampule was then sealed under nitrogen and placed in an oil bath for a predetermined reaction time. At the end of the reaction period, the contents of the ampule were dissolved in a minimum amount of chloroform. The chloroform was then added into methanol to precipitate the polymer formed. The precipitate was filtered, washed with methanol several times, and then dried in a vacuum oven (0.1 mmHg, 50 °C, 24 h).

Novozyme-435-Catalyzed Copolymerization of PDL with TMC. Novozyme-435 (1/10 w/w of monomers) dried in a vacuum desiccator (0.1 mmHg, 25 °C, 24 h) was transferred under nitrogen atmosphere into oven-dried 10 mL Pyrex culture tubes containing PDL and TMC (molar ratio mentioned in Table 3). The vials were stoppered with rubber septa and further sealed with Teflon tape. Dry toluene (2:1 v/w of the monomers) was subsequently added via syringe under nitrogen into the reaction vial. The vial was then placed into a constant temperature (70 °C) oil bath with stirring for a predetermined time. The reaction was efficiently terminated by adding excess cold chloroform and removing the enzyme by filtration (glass-fritted filter, medium pore porosity). The insoluble material was washed several times with hot chloroform. The filtrates were combined, chloroform was rotary evaporated, and the product was precipitated in methanol. The product was filtered and dried in a vacuum oven (0.1 mmHg, 50 °C, 24 h). The sample prepared for different enzymatic reaction time periods had different yield, M_n, and polydispersity (M_w/M_n) (see Table 3).

Table 3. Copolymerization of PDL and TMC Using Novozyme-435 at 70 °C

reaction product[a]	F_{PDL}/F_{TMC}	time	% yield	[PDL]/[TMC][b]	P*−P obs (cal)	P*−T obs (cal)	T*−P obs (cal)	T*−T obs (cal)	L_{PDL}/L_{TMC}[c]	M_n[d] (g/mol)	M_w/M_n[d]
9	1:1	5 min	5	92/08	0.85 (0.85)	0.06 (0.07)	0.06 (0.07)	0.03 (0.01)	15/1	5390	2.69
10	1:1	15 min	18	88/12	0.84 (0.77)	0.06 (0.11)	0.06 (0.11)	0.04 (0.02)	15/2	5570	2.44
11	1:1	30 min	44	87/13	0.81 (0.75)	0.07 (0.11)	0.07 (0.11)	0.05 (0.07)	12/2	7100	2.31
12	1:1	1 h	62	80/20	0.84 (0.64)	0.06 (0.16)	0.06 (0.16)	0.04 (0.04)	13/3	7310	2.39
13	1:1	3 h	69	75/25	0.61(0.56)	0.13 (0.19)	0.13 (0.19)	0.13 (0.06)	06/02	13000	2.07
14	1:1	24 h	83	50/50	0.25 (0.25)	0.23 (0.25)	0.23 (0.25)	0.29(0.25)	02/02	18800	1.65
15	1:4	24 h	42	21/79	0.04 (0.04)	0.18 (0.17)	0.19 (0.17)	0.59 (0.62)	01/04	10600	2.37
16	4:1	24 h	85	75/25	0.49 (0.56)	0.22 (0.19)	0.21 (0.19)	0.08 (0.06)	03/01	24200	1.96
17	1:10	24 h	28	28/72	0.15 (0.08)	0.14 (0.20)	0.15 (0.20)	0.56 (0.52)	02/05	7320	1.32
18	10:1	24 h	92	88/12	0.70 (0.77)	0.13 (0.10)	0.13 (0.10)	0.03 (0.01)	07/01	25200	1.85

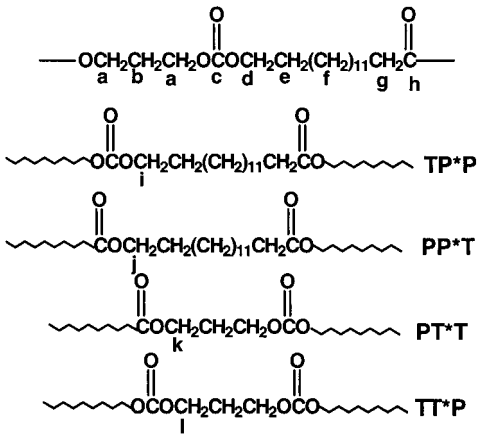
[a] Designates the reaction conditions/reagents and the product formed. [b] Observed PDL/TMC fraction by ^{1}H NMR. [c] $L_{TMC} = f_{TMC*PDL} + f_{TMC*TMC}/f_{TMC*PDL}$, $L_{PDL} = f_{PDL*TMC} + f_{PDL*PDL}/f_{PDL*TMC}$, where L is the average sequence length and f is the integral of the corresponding diad signal in the proton spectrum. [d] M_n and M_w/M_n of the samples were determined by GPC in $CHCl_3$.

B. Instrumentation Methods. Molecular weights were determined by gel permeation chromatography (GPC) using a Waters HPLC system equipped with model 510 pump, Waters model 717 autosampler, model 410 refractive index detector, and model T-50/T-60 detector from Viscotek Corp. with 500, 10^3, 10^4, and 10^5 Å Ultrastyragel columns in series. Trisec GPC software version 3 was used for calculations. Chloroform was used as the eluent at a flow rate of 1.0 mL/min. Sample concentrations of 0.2% w/v and injection volumes of 100 μL were used. Molecular weights were determined on the basis of a conventional calibration curve generated by narrow molecular weight polystyrene standards obtained from Aldrich Chemical Co.

Reaction initial water contents (wt % water) were measured by using an Aqua star C 3000 titrator with Coulomat A and Coulomat C from EMscience. The water wt/wt in reaction mixtures was determined by stirring 53 mg of Novozyme-435, 1.68 g of toluene, and 0.53 g of monomer in coulomat A, in a closed septum container that is part of the instrument, and titrating it against coulomat C by the instrument. The total water content (wt/wt) in the reactions was ~0.8−1.3%.

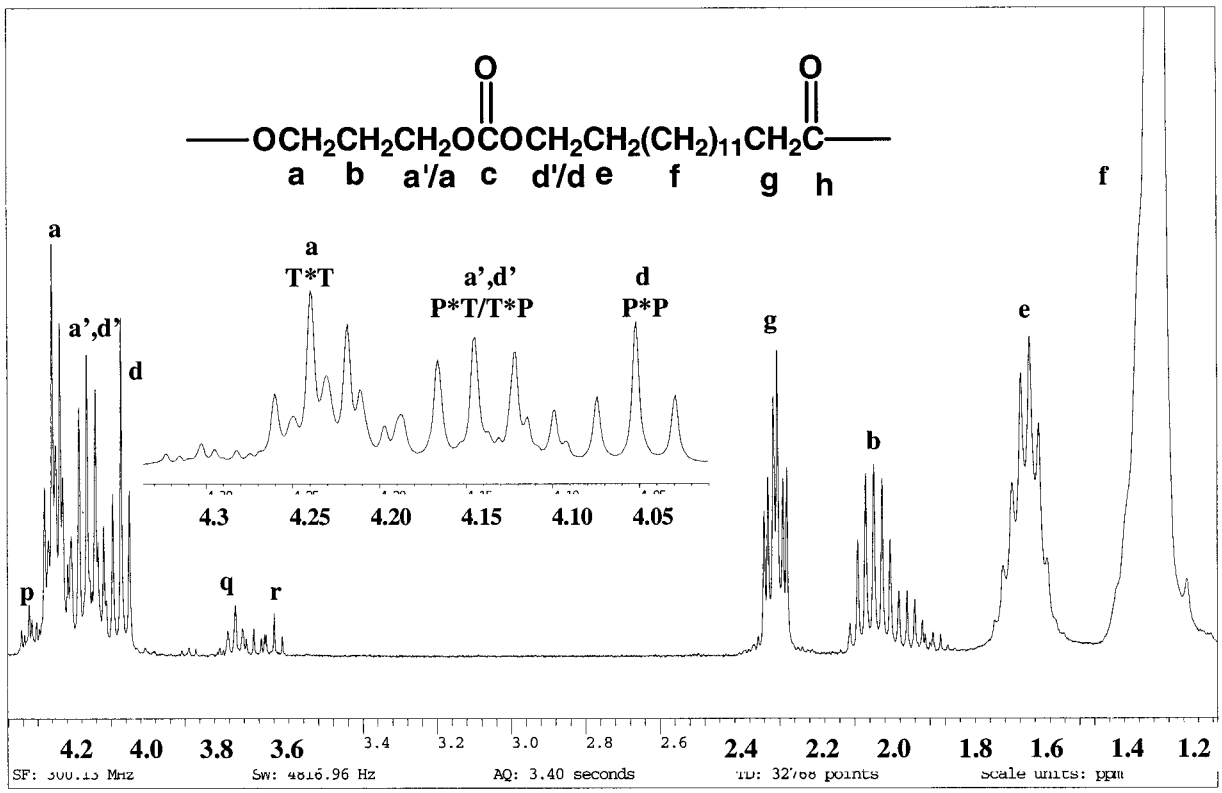
Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Bruker spectrometer model DPX300 at 300 and 75.13 MHz, respectively. The chemical shifts in parts per million (ppm) for ^{1}H and ^{13}C NMR spectra were referenced relative to tetramethylsilane (TMS) and chloroform as an internal reference at 0.00 and 77.00 ppm, respectively. NMR spectra of poly(PDL-*co*-50 mol % TMC) (−O═C−CH_2−CH_2−{−CH_2−CH_2−}$_5$−CH_2−CH_2−O)−(O−CO−CH_2−CH_2−CH_2−O−) with isolated yield of 83% in 24 h (M_n = 18.8 × 10^3 g/mol, PDI = 1.65) was as follows: ^{1}H NMR ($CDCl_3$): δ 4.28 (t, HOCH$_2$CH$_2$CH_2O), 4.26−4.18 (m, OCH_2T*−T), 4.18−4.08 (m, co-diad, OCH_2T*−P/P*−T), 4.08−4.02 (t, OCH_2, P*−P), 3.72 (t, J 6.5 Hz, HOCH_2-CH$_2$CH$_2$O), 3.64 (t, HOCH_2{CH$_2$}$_{12}$), 2.28 (m, COCH_2, P), 2.08−1.88 (m, OCOCH$_2$CH_2, T), 1.88−1.84 (m, OCOCH$_2$CH_2CH$_2$OH), 1.68−1.52, 1.40 and 1.20 (m, remaining CH_2, PDL) ppm, where P = PDL, T = TMC, and * denotes the repeat unit of the sequence whose proton(s) are observed for determination of repeat unit sequence distribution. ^{13}C NMR spectra were recorded to determine the relative fractions of diad repeat unit sequences. The parameters used were as follows: 8.0 % w/w polymer in $CDCl_3$, temperature 28 °C, pulse width 60°, 18 000 data points, relaxation delay 5.0 s, and 14 000−18 000 transients. ^{13}C NMR ($CDCl_3$): δ 174.30 (O*C*OCH$_2$, TP*PT), 174.00 (O*C*OCH$_2$, TP*P), 173.80 (O*C*OCH$_2$, PP*T), 173.70, (O*C*OCH$_2$, TP*T), 155.50 (O*C*OCH$_2$, PT*TP), 155.27 (O*C*OCH$_2$, PT*P), 155.20 (O*C*OCH$_2$, TT*P), 155.04, 155.0 (O*C*OCH$_2$, PT*T), 154.94 (O*C*OCH$_2$, TT*T), 68.22 (O*C*OCH$_2$, PP*T), 68.0 (O*C*-OCH$_2$, TT*P), 64.60, 64.3 (O*C*H$_2$, P*P), 64.1 (O*C*H$_2$, T*T), 60.80 (O*C*H$_2$, PT*T), 60.60, 60.49 (O*C*H$_2$, TP*P), 34.40 (OCO*C*H$_2$, P*P), 34.20 (OCO*C*H$_2$, P*T), 29.50−29.20, 28.60 (*C*H$_2$ PDL), 28.03 (CH$_2$−*C*H$_2$−CH$_2$, TMC) 25.80, 25.60, 24.90 (*C*H$_2$, PDL) ppm (see Supporting Information). Here, T and P are abbreviations for repeat units formed by the ring opening of TMC and PDL, respectively. Also, * denotes the repeat unit of the sequence whose carbon(s) are observed for determination of repeat unit sequence distribution.

Scheme 1



Results and Discussion

Microstructure Analysis of the Copolymer. Proton (^{1}H) NMR and carbon (^{13}C) NMR spectroscopy were used to analyze the microstructure of the copolymers. A schematic of representative copolymer triads and the corresponding linkages between units is shown in Scheme 1. The assignments of the peaks in the ^{1}H NMR spectrum of poly(PDL-*co*-50 mol % TMC) (product 14) are shown in Figure 1 and listed in the Experimental Section. These assignments were based on previous ^{1}H NMR studies of the respective homopolymers.[10,20] Since a triplet at δ 3.45 was not observed in the ^{1}H NMR spectrum, we conclude that decarboxylation during propagation did not occur.[20] The integral ratio of the signals at 2.28 ppm (m, COCH_2, P) and 2.02 ppm (m, COCH$_2$CH_2, T) was used to determine the repeat unit composition of the copolymer. The observed diad sequences (see Table 3) were calculated on the basis of the OCH_2 signals (4.28−4.04 ppm) in the ^{1}H NMR spectra. Specifically, based on our previous work on respective homopolymers,[10,20] the integrals of signals at 4.24 (m, 4H, OCH_2) and 4.04 (t, 2H, OCH_2) were used to calculate the T*−T and P*−P diads, respectively. The integral of the signals between 4.08 and 4.18 (m, 4H, OCH_2) was assigned to the T*−P/P*−T codiads. The diad, triad, and tetrad assignments for the ^{13}C NMR spectrum of poly(PDL-*co*-50% TMC) were made by comparison of the signals to those in spectra recorded of the corresponding homopolymers [poly(PDL), poly(TMC)][10,20] and copolymers of different repeat unit composition (25 and 79 mol % TMC) (see Supporting Information). The carbonyl carbon signals of PDL and TMC repeat units for poly(PDL-*co*-50 mol % TMC) were



p=HOCH$_2$CH$_2$C*H$_2$*O, q= HOC*H$_2$*CH$_2$CH$_2$O, r= HOC*H$_2$*CH$_2$(CH$_2$)$_{11}$,

Figure 1. ^{1}H NMR spectrum at 27 °C in $CDCl_3$ of the poly(PDL-*co*-50 mol % TMC) copolymer formed by Novozyme-435-catalyzed copolymerization of TMC and PDL (1:1 w/w) after 48 h.

observed in the spectral regions of 173.7−174.3 and 154.9−155.5 ppm, respectively. The signals at δ 68.4−68.0 and 60.5−60.9 were assigned to (j, l) and (k, i), respectively (see Figure 2). These signals can only appear when we have PP*T, TT*P and PT*T, TP*P types of triads and the increased intensity of these signals supports random copolymerization. Well resolved diads were observed for PDL CO*C*H$_2$ and other CH$_2$*C*H$_2$ signals at δ 34.4 (g, P*−P), 34.2 (g, P*−T) and 26.0 (f, P*−P), 25.7 (f, P*−T), 25.1 (f, P*−P), and 25.0 (f, P*−T), respectively (see Supporting Information). Theoretical diad fractions assuming a Bernoulli or random statistical copolymerization of PDL and TMC were calculated[21] and compared to the experimental ^{1}H NMR results (see Experimental Section). The values of experimental and calculated diad fractions are given in Table 3.

The potential of using traditional catalysts for the copolymerization of PDL and TMC was evaluated. The catalysts were selected on the basis of their general versatility for many lactone and carbonate polymerizations.[14−17] They included stannous octanoate, methylaluminoxane (MAO), sodium ethoxide, and aluminum isopropoxide. Similarly, the reaction time and temperatures used were based on values that proved useful for achieving high polymer yields for related reactions with these catalysts.[14−17] Table 1 shows the results of a series of PDL/TMC copolymerizations where chemical catalysts were used. Copolymerizations of TMC and PDL (F_{PDL}/F_{TMC} 1:1) with tin octanoate (115 °C) and aluminum isopropoxide (70 °C) resulted in copolymers with high TMC content (≥96%) (products 1−3). MAO catalysis at 90 °C in toluene for 24 h resulted in poly(PDL-*co*-84 mol % TMC) in 40% yield with M_n 26.4 × 10^3 g/mol. ^{1}H and ^{13}C NMR provided information on the copolymer repeat unit sequence distribution. Scheme 1 shows representative triads and key carbons that were used for this analysis. NMR analysis of product 4 showed that the average segment lengths of PDL and TMC (L_{PDL} and L_{TMC}) were 2 and 11, respectively (for calculation see footnote of Table 3). Thus, this product is blocklike. Homopolymerizations of PDL and TMC using MAO gave poly(PDL) and poly(TMC) in quantitative yields (products 5 and 6). However, the molecular weight of the poly(TMC) was much greater than poly(PDL), presumably due to the low ring strain of PDL (products 5 and 6). Decrease in yields for their copolymer under similar polymerization conditions (product 4) can be explained by that PDL/TMC copolymers have lower solubility than homo-PDL. Thus, even though the molecular weight of PDL/TMC copolymers is greater than homo-PDL, copolymer may be lost due to fractionation during product precipitation.

Sodium ethoxide proved useful for the catalysis of PDL/TMC copolymerizations (products 7 and 8). The observed diad fractions for products 7 and 8 were P*P 0.18, T*T 0.40, P*T/T*P 0.21 and P*P 0.17, T*T 0.21, P*T/T*P 0.31, respectively. These values corresponded relatively closely to those calculated for a random statistical distribution of repeat units than for the other chemical catalysts under study. The molecular weights obtained for products 7 and 8 were low (<7 × 10^3 g/mol). Thus, the use of tin- and aluminum-based organometallic catalysts showed higher reactivity for TMC than PDL, resulting in copolymers enriched in TMC with a blocklike microstructure. Copolymerizations initiated by sodium ethoxide in THF provided almost random copolymers but of low molecular weights. Although the potential to improve the results of chemical catalyzed PDL/TMC copolymerizations surely exists, this work

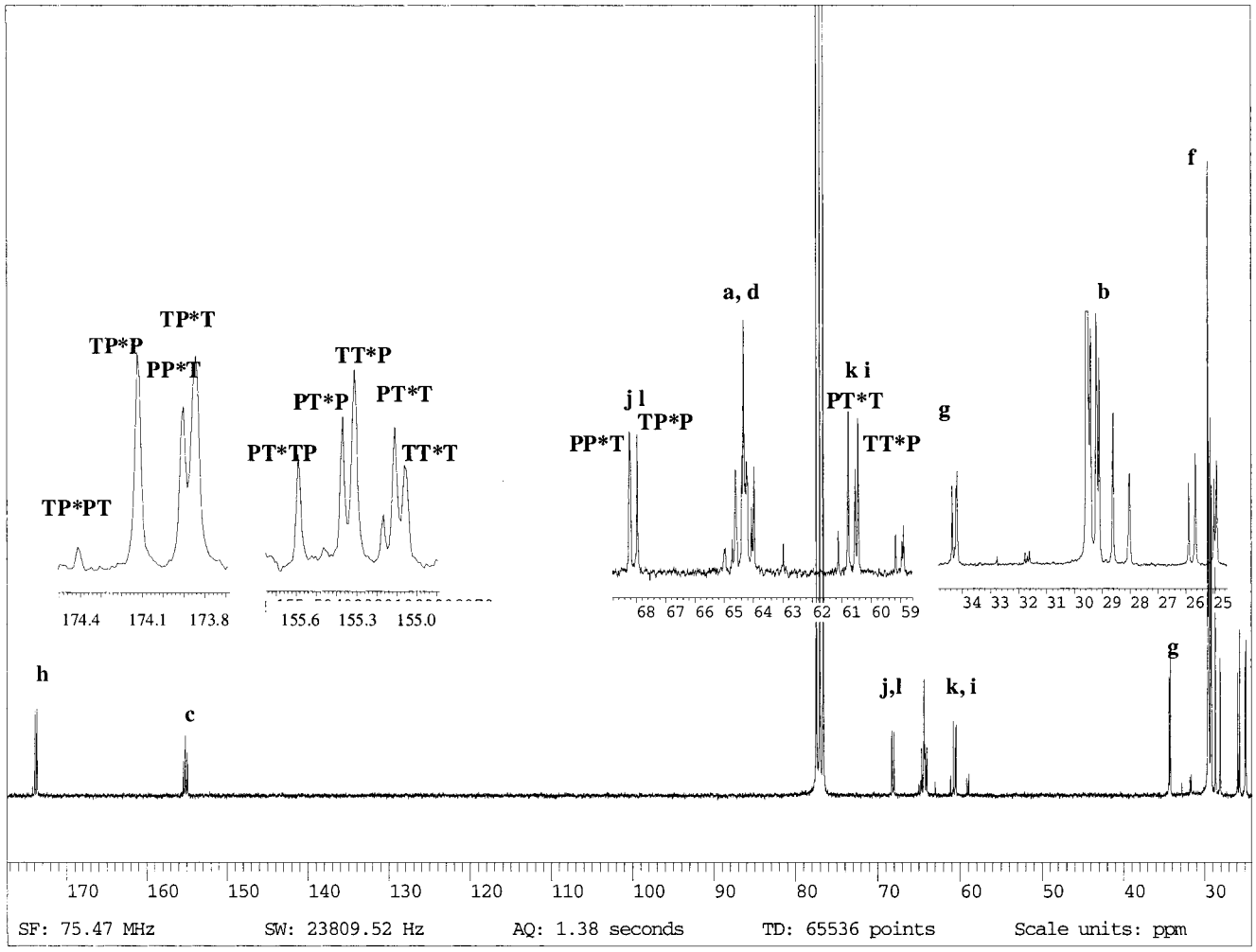


Figure 2. ^{13}C NMR spectrum at 27 °C in $CDCl_3$ of the P(PDL-*co*-50 mol % TMC) copolymer formed by Novozyme-435-catalyzed copolymerization of TMC and PDL (1:1 w/w) after 24 h.

demonstrates that by using these methods, limits exist in our ability to prepare a full range of copolymers with control of both molecular weight and repeat unit sequence distribution.

The ability of the lipases from *Aspergillus niger (AK), Candida antarctica, Candida rugosa* (AY), *Pseudomonas cepacia* (PSC), and porcine pancreas (PPL) to catalyze PDL/TMC copolymerization was assessed. The study was performed at 70 °C, in toluene (2:1, toluene: monomers, v/w), with a F_{PDL}/F_{TMC} of 1:1. The isolated yields, copolymer composition, and the molecular weight of products were determined, and the results are listed in Table 2. From review of Table 2, Novozyme-435 (immobilized *Candida antarctica* lipase B) was found to be the best of those studied for the formation of copolymers with high molar mass.

Further studies of Novozyme-435-catalyzed copolymerization of TMC and PDL at 70 °C in toluene (2:1, toluene: monomers) were carried out with varying reaction times and monomer feed ratios (see Table 3). At F_{PDL}/F_{TMC} 1:1, the isolated yield and M_n of the copolymer increased from 5 to 83% and 5.4×10^3 to 18.8×10^3 from 5 min to 24 h, respectively (reactions 9−14). Figure 3 shows the isolated yield of the copolymer along with the observed $[PDL]_0/[TMC]_0$ composition calculated by NMR. By 1 h, the isolated yield of the copolymer was 62%, and the observed $[PDL]_0/[TMC]_0$ was 80/20. It was observed that that PDL was consumed more rapidly than TMC. Thus, while most of the PDL was consumed within only 1 h, 80 mol % of TMC in the reaction was slowly converted to polymer. By extending the reaction time to 24 h, the copolymer contained 50 mol % of both TMC and PDL. Analysis of the copolymer microstructure showed the product to be random. This may be explained on the basis of the transesterification of TMC with the polymeric chains. Increasing the PDL to TMC feed ratio from 1:1 to 4:1 and 10:1 for 24 h polymerizations resulted in increases in the copolymer PDL mol % from 50 to 75 and 88 (products 14, 16, and

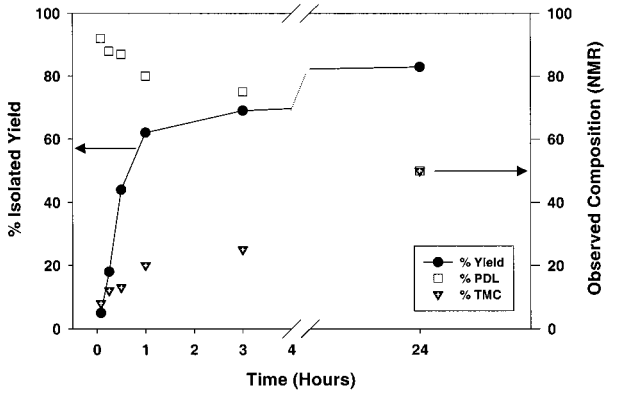


Figure 3. Novozyme-435 (10 wt % of the monomers) catalyzed PDL/TMC copolymerization (1:1 feed) at 70 °C in toluene (2:1 toluene:monomers, v/w).

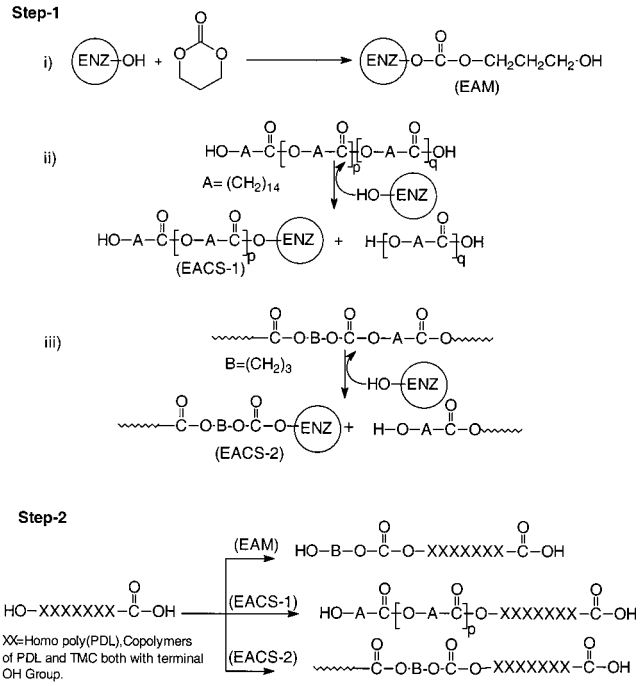
18). Furthermore, these increases in the PDL to TMC feed ratio resulted in an increase of the copolymer M_n from 18.8×10^3 to 24.2×10^3 and 25.2×10^3, respectively. As anticipated, decrease in the PDL to TMC feed ratio from 1:1 to 1:10 for 24 h polymerizations resulted in a decrease in the copolymer PDL content from 50 to 28 mol %. However, this decrease in the PDL to TMC feed ratio also resulted in large decreases in both the isolated yield (83 to 28%) and M_n (18.8×10^3 to 7.3×10^3). These results are consistent with the relatively lower polymerizability of TMC relative to PDL using Novozyme-435 as the catalyst. Nonetheless, Novozyme-435 catalysis provided a route to poly(PDL-*co*-TMC) in a full range of compositions, with M_n values up to $\sim 25 \times 10^3$, and where the consumption of PDL was more rapid than TMC.

For polymerizations carried out with a PDL/TMC feed ratio of 1:1, the average sequence lengths of PDL and TMC units (L_{PDL} and L_{TMC}, respectively) at reaction times of 5 min and 1 h were 15/1 (L_{PDL}/L_{TMC}) and 13/3, respectively (Table 3). Thus, at these relatively short reaction times, copolymers were formed that consist of PDL blocks inturrupted by one or two TMC units. Increase in the reaction time to 3 and 24 h resulted in decreased block sizes (L_{PDL}/L_{TMC} 6/2 and 2/2, respectively). In other words, the copolymer repeat unit sequence distribution changed from block to almost random. This is further illustrated by that the observed and calculated diad fractions were close in value after a 24 h reaction time (reaction 14). These results are explained by the ability of lipase B from *Candida antartica* to catalyze transesterification or transacylation (see discussion below).

The ability of Novozyme-435 to catalyze transacylation reactions for chains of mixed ester−carbonate linkages was further evaluated. TMC was added to preformed poly(PDL) chains (M_n 12 $\times 10^3$, M_w/M_n 2.0) under reaction conditions that were identical to those used for PDL/TMC copolymerizations (see Experimental Section). The molar ratio of TMC to the repeat units of preformed poly(PDL) was 1 to 1. The product formed after 48 h was poly(PDL-*co*-53 mol % TMC), in 90% isolated yield, with M_n 5.2×10^3 g/mol and M_w/M_n 1.57. The observed and calculated (assuming a random distribution) diad fractions were P*−P 0.21, T*−T 0.27, P*−T/T*P 0.54 and P*−P 0.23, T*−T 0.27, P*−T/T*P 0.50, respectively. At present, we do not know whether this result is due to Novozyme-435-catalyzed transacylation reactions between (i) poly(PDL) chains that have terminal TMC units, (ii) poly(PDL) chains with terminal TMC chain segments, (iii) the formation of oligomeric TMC chains that undergo transacylation reactions with poly(PDL), or (iv) a combination of the reactions described in (i)−(iii) (see Scheme 2).

Recently, our laboratory described a mechanism for transacylation reactions between preformed polyester chains of different structure.[12] Mechanism for transacylation in this work is believed to occur similarly. The only potential difference is that lipase B from *Candida antarctica* might also cleave carbonate linkages within chains that can be transferred to the terminal hydroxyl group of another chain (see Scheme 2). The relative frequency at which carbonate and ester linkages are cleaved during Novozyme-435-catalyzed acylation is currently under study and will be the subject of a separate paper.

Scheme 2



Summary of Results

An efficient lipase-catalyzed route to random poly(TMC-*co*-PDL) is reported herein. Evaluation of aluminum and tin-based organometallic systems for the catalysis of PDL/TMC copolymerizations showed that TMC has a much greater reactivity than PDL. In contrast, for Novozyme-435-catalyzed copolymerizations, PDL has a greater reactivity than TMC. The higher reactivity of PDL relative to TMC, and the ability of Novozyme-435 to catalyze the conversion of PDL/TMC from multiblock to random copolymers, led us to conclude that Novozyme-435 actively promotes transesterification or transacylation reactions for chains that consist of mixed ester/carbonate linkages. The ability to manipulate the block lengths in these copolymers is expected to allow fine-tuning of the physical and biological properties of these copolymers. Furthermore, the potential to apply lipase catalysis for a range of low-temperature transesterification reactions opens up a number of new opportunities in macromolecular synthesis. Additional work is underway to extend these findings to other systems, to better understand the factors that promote and disfavor the transesterification pathway, and to better understand the mechanism of these reactions.

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Supporting Information Available: Copies of three different expended regions of ^{13}C NMR spectra of compounds 14, 15, and 16 shown as overlaid plot in S-1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Calculations of diad fractions were used to determine what the relative diad distribution would be assuming Bernoulli random statistics, where P is the probability of finding the same monomer units next to each other. For example, the fraction of diads where PDL units neighbor PDL units is given as PDL* − PDL = P^2_{PDL}, PDL next to TMC or TMC next to PDL is given as PDL* − TMC = TMC* − PDL = $2P_{PDL}(1 - P_{PDL})$; similarly, TMC next to TMC is given as TMC*−TMC = $(1 - P_{PDL})^2$.

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