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SYNTHESIS OF NOVEL HYDROPHILIC POLY(ESTER-CARBONATES) CONTAINING PENDENT CARBOXYLIC ACID GROUPS

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SYNTHESIS OF NOVEL HYDROPHILIC POLY(ESTER-CARBONATES) CONTAINING PENDENT CARBOXYLIC ACID GROUPS

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ABSTRACT

A functional cyclic carbonate, 5-methyl-5-benzyloxycarbonyl-1,3-dioxan-2-one (MBC), was utilized in the synthesis of novel poly(ester-carbonates) containing pendent carboxylic acid groups. Copolymers with ϵ -caprolactone (CL) and L-lactide (LLA) were synthesized by ring-opening polymerization (ROP) using either an Al-alkoxide (solution) or Sn(Oct)₂-alcohol (bulk) initiating system. Analysis of the copolymers revealed a random distribution of the comonomer units along the polymer chain. The copolymers exhibited amorphous character at low MBC incorporations despite the crystalline nature of homo-poly(ϵ -caprolactone) (PCL) and homo-poly(L-lactide) (PLLA). Removal of the benzyl protecting group by hydrogenolysis yielded carboxylic acid-functional copolymers. It was observed that the benzyl ester group of MBC became susceptible to transesterification reactions at ROP temperatures $\geq 135^\circ\text{C}$, and the corresponding copolymers were insoluble in both organic and aqueous solvents. It is proposed that carboxylic acid functionality will allow an improvement in the biodegradability and physical properties of PCL and PLLA and possibly improve their utility for biomedical applications such as time-released drug delivery. Moreover, polymerization of comonomers at high temperature may present a pathway toward the synthesis of new biodegradable hydrogels.

Key Words: Ring opening polymerization; Polycarbonate; Biodegradable polymer; Hydrogenolysis; Stannous octoate; Polyester.

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INTRODUCTION

Biodegradable polymers designed for biomedical applications have been known since the 1960's [1]. Polyesters such as poly(lactic acid) (PLA, also known as polylactide) and poly(ϵ -caprolactone) (PCL), and poly(ester-carbonates) derived from lactone and trimethylene carbonate (TMC) comonomers, have been shown to degrade through hydrolysis of ester linkages along the polymer backbone and to produce degradation products that the human body can easily metabolize and eliminate. PLA can be synthesized by the condensation polymerization of D- or L-lactic acid or the ring-opening polymerization (ROP) of the corresponding lactide. ROP is the preferred process to obtain high molecular weight. The rates of biodegradation vary widely depending on the degree of crystallinity and the hydrophilicity of the polymer chain and end groups. For example, stereoregular poly(L-lactide) (PLLA) and PCL are semi-crystalline polymers with degradation times of approximately two years [2]. Poly(D,L-lactide) (PDLLA), synthesized by ROP of the racemic mixture of L-lactide and D-lactide, is a totally amorphous polymer that displays a comparatively higher rate of biodegradation. Co- and terpolymers of ϵ -caprolactone (CL), L-lactide (LLA), D-lactide, and TMC are generally also amorphous, and thus display higher rates of biodegradation, depending on the average hydrophilicity of the comonomers units.

Ring-opening polymerization of lactones has been most frequently carried out using catalysts based on tin (II), such as stannous 2-ethylhexanoate ($\text{Sn}(\text{Oct})_2$) [2-25], tin (IV), or aluminum [3, 26-35]. These catalyst systems are of particular interest because the initiating species can be designed to yield various polymeric architectures such as blocky [19, 21, 34-35], graft and hyperbranched [14-15, 18, 28], and carboxylic acid-functionalized [2-3, 16]. $\text{Sn}(\text{Oct})_2$ -based catalysts are used commercially to supply PLA, PCL, and various copolymers on an industrial scale [1, 25].

Carboxylic acid-functionalized derivatives of CL, TMC, LLA, and other monomers have been used to create biodegradable polymers with enhanced hydrophilicity and degradation rates. Hedrick [2] and Jerome [3] have developed a CL-derived monomer with pendent carboxyl groups. Bisht and coworkers developed water-soluble aliphatic polycarbonates containing pendent carboxyl groups on every repeating unit [36], as well as copolymers of 5-methyl-5-benzoyloxycarbonyl-1,3-dioxan-2-one (MBC) and TMC utilizing enzyme-catalyzed ROP [37].

Several research groups have synthesized simple, aliphatic polyesters containing pendent carboxylic acid groups through the use of malic acid derivatives. Ouchi and coworkers reported the synthesis of poly(α -malic acid) [38], while Vert [39] and Lenz [40] reported poly(β -malic acid). Poly(α -malic acid) was produced by ROP of the 6-membered cyclic dimer; whereas poly(β -malic acid) was produced from the 4-membered monomeric lactone. In either case, the *exo*-cyclic carboxylic acid group was protected during polymerization through formation of the benzyl ester. In all cases, low monomer conversions were observed, and the resulting homopolymers and copolymers with lactide or glycolide were of low molecu-

lar weight. According to the authors, these results were likely due to steric hindrance caused by the bulky benzyl protecting groups. However, the benzyl groups were not cleaved during polymerization, and their elimination after polymerization yielded free carboxylic acid pendent groups without degradation of the polymer backbone.

Our research focus has been the synthesis of novel copolymers of 5-methyl-5-benzoyloxycarbonyl-1,3-dioxan-2-one (MBC) and CL or LLA. Figure 1 displays the synthetic scheme used to prepare the copolymers. Hydrogenolysis of copolymers **1** and **2** afforded poly(ester-carbonates) with pendent carboxylic acid groups. These carboxylic acid functionalized copolymers were analyzed for their structural and physical properties.

EXPERIMENTAL

Materials

2,2-Bis(hydroxymethyl)propionic acid (Aldrich) was recrystallized from tetrahydrofuran (THF). THF, methylene chloride (MeCl_2), chloroform (CHCl_3), and methanol were dried over CaH_2 and distilled just before use. CL (Union Carbide), propylene glycol, and benzyl alcohol were dried over CaH_2 and distilled under reduced pressure just before use. Benzene and toluene were dried over BaO and distilled. Triethylamine (Aldrich), ethyl chloroformate (Aldrich), palladium (10%) on activated carbon (Pd/C, Aldrich), anhydrous MgSO_4 , diethyl ether,

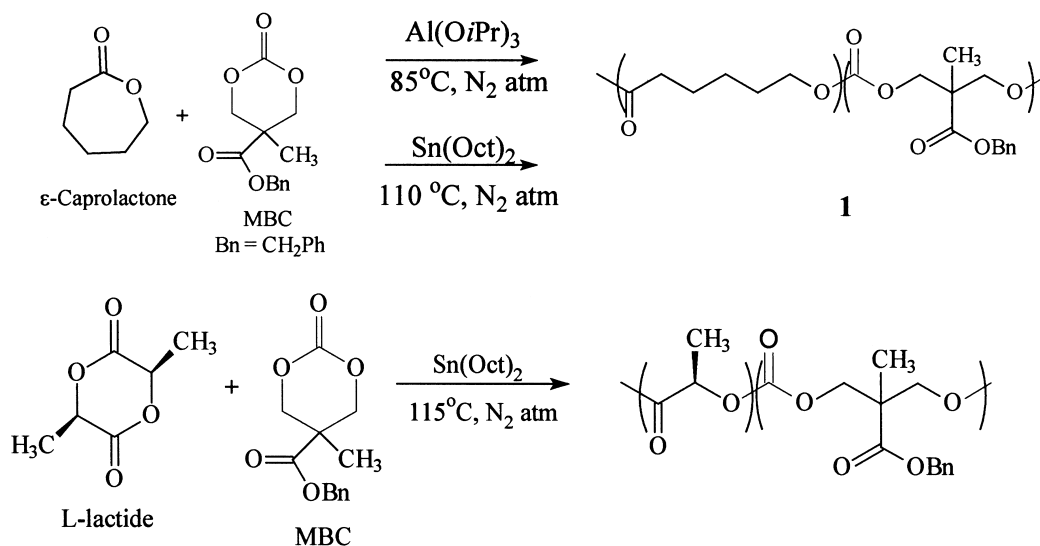


Figure 1. Reaction scheme for metal-catalyzed ROP of CL and MBC to yield poly(CL-co-MBC) (**1**), and LLA and MBC to yield poly(LLA-co-MBC) (**2**).

NaHCO_3 , aluminum isopropoxide ($\text{Al}(\text{O}i\text{Pr})_3$, Aldrich), and activated charcoal were used as received. L-lactide (Boehringer Ingelheim) was recrystallized under N_2 atmosphere from anhydrous ethyl acetate (Aldrich). $\text{Sn}(\text{Oct})_2$ (Aldrich) was fractionally distilled under reduced pressure and stored in dry hexane (0.03 g/mL) over 4 Å molecular sieves. Thin layer chromatography (TLC) was performed on sheets of silica gel 60 F₂₅₄ fixed to an aluminum backing (EM Industries Inc.).

Preparation of Benzyl 2,2-bis(Hydroxymethyl)propionate (Figure 2)

To a 1L round bottom flask equipped with reflux condenser and a calibrated Dean Stark apparatus, were charged 20 g (0.15 mol) of 2,2-bis(hydroxymethyl)propionic acid, 146 mL (1.50 mol) of benzyl alcohol, 100 mL of dry benzene, and 0.1 mL of concentrated H_2SO_4 . The reactor contents were heated to reflux, and water was removed by azeotropic distillation. After essentially complete conversion (determined by TLC), the solution was poured into a 1 L beaker, and 100 mL of saturated aqueous NaHCO_3 was added and stirred for 2 hours. The organic layer was washed once with a 5% solution of aqueous NaHCO_3 and once with 100 mL of saturated brine solution, and was then left overnight to dry over anhydrous MgSO_4 . The solution was filtered, and the product was concentrated by removal of benzyl alcohol under reduced pressure. White crystals spontaneously formed upon cooling and were recrystallized from diethyl ether. Yield = 82%. A side product formed at long reaction times and was isolated by silica gel column chromatography (hexane:ethyl acetate 3:1). NMR analysis was performed, and it was determined that self-condensation of 2,2-bis(hydroxymethyl) propionic acid was competing with the desired esterification.

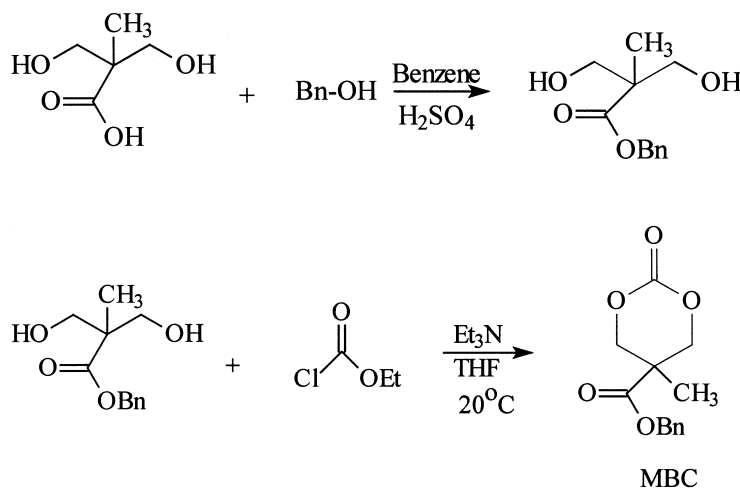


Figure 2. Synthesis of MBC.

Synthesis of MBC (Figure 2)

Benzyl 2,2-bis(hydroxymethyl)propionate, 20.0 g (0.0892 mol), and 50.0 mL (0.525 mol) of ethyl chloroformate were dissolved in 800 mL of THF in a 2 L round bottom flask. Triethylamine, 80.0 mL (0.549 mol), was added dropwise to the mixture over a period of 30 minutes at 0°C, and the reaction mixture was stirred at room temperature for 2 hours. The precipitated triethylamine hydrochloride was removed by filtration, and the filtrate was concentrated under reduced pressure. The product was recrystallized twice from THF/ether (1/2, v/v) by preparing a saturated solution of the solid product at reflux temperature and then cooling to room temperature. A third recrystallization was performed similarly except that the hot solution was first treated with activated charcoal, filtered and then cooled. This procedure yielded white crystals in 92% yield (mp = 74-75°C). ¹H-NMR (CDCl₃): δ 7.4 (5 H, m), δ 5.2 (2 H, s), δ 4.2-4.7 (4 H, 2 d), and δ 1.3 (3 H, s).

Sn(Oct)₂-Catalyzed Copolymerization of CL and MBC

In a dry-N₂ glove box, a single-necked round bottom flask was charged with 4.0 g (35 mmol) CL and 1.0 g (4.0 mmol) MBC. Next, 1.0 mL of a 0.03 g/mL solution of Sn(Oct)₂ in dry hexane was added, and the hexane was evaporated by passing a stream of dry N₂ over the solution. Propylene glycol 0.12 g (1.7 mmol) was added, and the flask was fitted with an overhead mechanical stirrer, immersed in a silicone oil bath, thermostated to 115°C, and stirred for 16 hours. The polymerization was quenched by equilibrating the flask in an ice bath. The soluble copolymer product was dissolved in MeCl₂ and precipitated into cold MeOH. Insoluble copolymers resulted when the ROP temperature was ≥ 135°C. The insoluble copolymers were washed repeatedly with MeCl₂ to remove any soluble material. All of the copolymers were dried *in vacuo* for at least 24 hours before characterization.

Sn(Oct)₂-Catalyzed Copolymerization of LLA and MBC

Copolymerization of LLA and MBC was carried out identically to the copolymerization of CL and MBC (previous section) except that the highest MBC mole fraction in the feed was 0.80 and the time of the reaction was 8 hours.

Aluminum Alkoxide-Catalyzed Copolymerization of CL and MBC

To a 2-necked round bottom flask contained within a dry N₂ glove box and equipped with an overhead stirrer were added 10 mL (0.088 mol) of CL, 2.0 g (8.0 mmol) of MBC, 100 mL of toluene, and 0.083 g (0.40 mmol) Al(*i*PrO)₃. The poly-

merization was carried out at 85°C for 8 hours, after which time the product was precipitated into cold hexane, recovered by filtration, and dried under vacuum at 25°C prior to characterization.

Hydrogenolysis of MBC-Containing Copolymers (Figure 3)

A representative procedure, used for both copolymers, was as follows: A stainless steel reaction vessel was charged with 1.0 g of poly(LLA-*co*-MBC) (8 mmol benzyl groups), 0.050 g of 10% Pd/C, 10 mL of ethyl acetate, and 15 mL of CHCl₃. The vessel was pressurized with H₂ (30 psi) and vented. This procedure was repeated, and then the vessel was pressurized and held under 30 psi H₂ at 25°C with constant stirring for 48 hours. The reaction mixture was then precipitated into excess ether/hexanes (2/1, v/v), and the polymer was collected and dried under reduced pressure for 24 hours prior to characterization.

CHARACTERIZATION

NMR Spectroscopy

Structural characterization of materials was performed using ¹³C and ¹H NMR spectroscopy. Spectra were acquired on a Bruker AC-300 (300 MHz) spectrometer using 5 mm O.D. tubes and deuterated chloroform as solvent with internal standard tetramethylsilane (TMS). Sample concentrations were ~20% (w/v) for ¹³C NMR and ~5% (w/v) for ¹H NMR spectra. MBC conversions were determined from the relative peak areas of the signals corresponding to benzyl (PhCH₂-) protons of the monomer (d 5.22 ppm) and polymer (d 5.17 ppm). CL conversions were calculated from the relative peak areas of the α-methylene (-CO-CH₂-) protons at 2.64 (monomer) and 2.32 ppm (polymer). The comonomer compositions of copolymer **1** were determined from the relative peak areas of the benzyl (PhCH₂-) protons of MBC repeat units (d 5.17 ppm) and the α-methylene (-CO-CH₂-) protons of CL repeat units (d 2.32 ppm). Compositions of copolymer

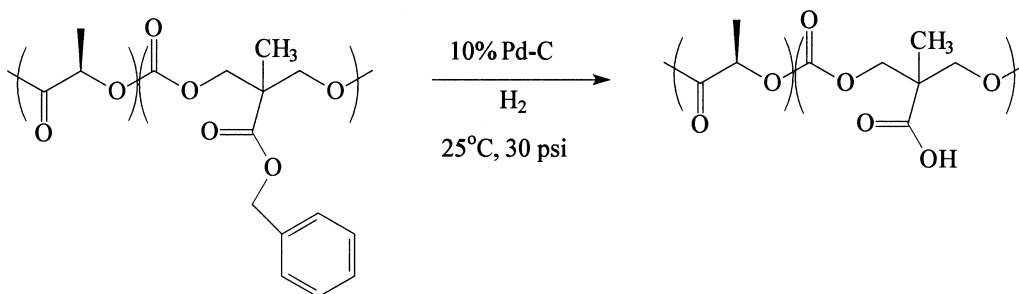


Figure 3. Hydrogenolysis of MBC-based copolymers.

2 were calculated by the relative peak areas of the four backbone methylene protons of MBC repeat units (δ 4.35 ppm) and the methyl (-O-CH(CH₃)-) protons of LLA repeat units (δ 1.61 ppm). Solid State ¹³C-NMR spectroscopy (Bruker MSL-400) was used to analyze the structure of the deprotected copolymer **1** before a suitable solvent system was found.

Heteronuclear correlation (HETCOR) ¹H-¹³C experiments were performed using the standard pulse sequence. The ¹³C 90° and 180° pulse lengths were 7.2 and 14.5 μ s, the ¹H 90° length was 34 μ s, the fixed polarization delay was 4.2 ms, and the refocusing delay 2.1 ms. The incremental delay was set to 204 μ s, and the dwell time in the F2 dimension was 98 μ s, making the sweep widths in F1 and F2 8.1 ppm and 67.6 ppm, respectively. A total of 128 scans with 256 increments were accumulated with a recycle delay of 1.8 s. The number of data points acquired in the F2 dimension was 2048, and 4 pre-equilibrium scans were used for each acquisition. The total experimental time was approximately 17 hours. The data was processed with Gaussian and shifted sine-bell apodization applied to the F2 and F1 domains and the F1 domain zero-filled to 512 points prior to Fourier transformation. Data processing also included magnitude calculation of the F1 data, yielding a 2-D data set with only positive values.

Molecular Weight Measurements

Molecular weights and polydispersities (PDI) of the polymeric materials were determined using a size exclusion chromatography (SEC) system equipped with a Waters Alliance 2690 Separations Module, an on-line multiangle laser light scattering (MALLS) detector (MiniDAWNTM, Wyatt Technology Inc.), an interferometric refractometer (Optilab DSPTM, Wyatt Technology Inc.), and one of two sets of PLgelTM (Polymer Laboratories, Inc.) SEC columns. Each of the sets, consisting of two 3 μ m or two 5 μ m PLgelTM columns connected in series, was attached in separate closed loops with only one of the two column sets active during data acquisition. The 3 μ m pore-size columns were useful for samples that did not contain molecules above ca. 30,000 g/mol. The 5 μ m pore-size columns were useful in separating molecules between ca. 30,000-500,000 g/mol. Freshly distilled THF served as the mobile phase and was delivered at a flow rate of 1.0 mL/min. Sample concentrations were ca. 6-7 mg/mL in freshly distilled THF, and the injection volume was 100 μ L. The detector signals were simultaneously recorded using ASTRATM software (Wyatt Technology, Inc.). Absolute molecular weights were calculated from the MALLS detector signal and the dn/dc value, which in turn was calculated from the signal response from the Optilab DSP, assuming 100% mass recovery from the columns. Copolymer **2** became decreasingly soluble in THF at LLA incorporations > 90%; in those cases, molecular weights were determined using a different SEC system equipped with a Waters 515 HPLC pump, an Alcott 728 Autosampler (Alcott, Inc.), a 2410 Refractive Index Detector (Waters Corp.), and one of two sets of PLgelTM (Polymer

Laboratories Inc.) SEC columns identical to those described above. Freshly distilled CHCl_3 served as the mobile phase and was delivered at a flow rate of 1.0 mL/min. Sample concentrations were ca. 5–10 mg/mL in freshly distilled CHCl_3 , and the injection volume was 100 μL . The SEC columns were calibrated using a series of narrow polystyrene standards with molecular weights ranging from 580–377,000 g/mol (flow marker = toluene). PL Caliber[®] GPC software (Polymer Laboratories Inc.) was used to calculate molecular weights and polydispersities by converting the refractive index detector response of the sample into a molecular weight distribution based on the log M vs. elution time calibration curve.

Thermal Analysis

Differential scanning calorimetry (DSC) was used to analyze the thermal characteristics of the polymers. The glass transition temperature (T_g) and melting temperature (T_m) were measured using either a Mettler DSC 30 or Perkin Elmer DSC-7. The PCL-containing samples were heated from -100°C to 100°C at a heating rate of $10^\circ\text{C}/\text{min}$, quenched, and heated again from -100°C to 100°C at the same rate. The PLLA-containing samples were treated similarly within the range -50°C to 180°C .

RESULTS AND DISCUSSION

CL/MBC Copolymerizations

The copolymerization of CL and MBC was accomplished utilizing a variety of different initiators, reaction temperatures, and comonomer feed ratios; Table 1 summarizes the results. Monomer conversion was calculated using ^1H NMR. Figure 4 shows percent CL conversion as a function of time for the $\text{Sn}(\text{Oct})_2$ -catalyzed ROP (115°C) of CAP-MBC (89.3% CAP: 10.7% BMC in feed) (Sample 1, Table 1). The calculated conversion of CL was approximately 90% after 16 hours. DSC thermal analysis revealed a single glass transition temperature, which indicates a random or non-blocky distribution of comonomer repeat units.

NMR was utilized for compositional (see Experimental section) and microstructural analyses of copolymer **1**. In general, MBC incorporation in the copolymer was nearly equivalent to that in the feed, as expected for high conversion polymerizations. Comonomer incorporation into the copolymers appeared to be random, in agreement with thermal analysis results. The ^1H - ^{13}C HETCOR NMR spectrum shown in Figure 5 revealed that the ϵ carbon of CL repeat units (attached protons at 4.05–4.1 ppm) showed high sensitivity to repeat unit sequence. When this carbon was next to a CL repeat unit (ester linkage) it displayed a chemical shift of 63.8 ppm (CL-CL dyad), but when next to a MBC repeat unit (carbonate linkage), its chemical shift was 67.7 ppm (CL-MBC dyad). Likewise, it was found that when a backbone methylene carbon of MBC was adja-

Table 1. Metal-Catalyzed Ring Opening Copolymerization of CL and MBC

Sample	Temp. (°C)	MBC % in feed	MBC % in copolymer ^a	Target M_n (g/mol $\times 10^{-3}$)	Exp. M_n^b (g/mol $\times 10^{-3}$)	PDI	T_g (°C)	T_m (°C)	$[M]_0/[I]_0 \times 10^{-3}$	Rxn. Time (h)
Sn(Oct) ₂ /Propylene Glycol Initiating System										
1	115	10.7	7.6	30.0	30.5	1.6	-62	40	0.23	16
2	110	27.4	28.4	5.0	4.93	1.7	-47	—	0.033	16
3	130	29.5	25.5	10.0	7.6	8.7	-41	—	0.065	16
4	140	25.3	—	60.0	—	—	-33	—	0.40	16
5	140	25.2	—	100.0	—	—	-36	—	0.68	16
6	140	88.0	—	50.0	—	—	-7	—	0.22	16
Al(OiPr) ₃ Initiating System										
7	85	8.4	6.1	30.0	23.0	3.5	-61	41	0.24	20
8	85	10.6	13.7	40.0	35.7	1.3	-55	31	0.31	8

^aCopolymer composition determined by ¹H NMR.^bMolecular weights determined by SEC.

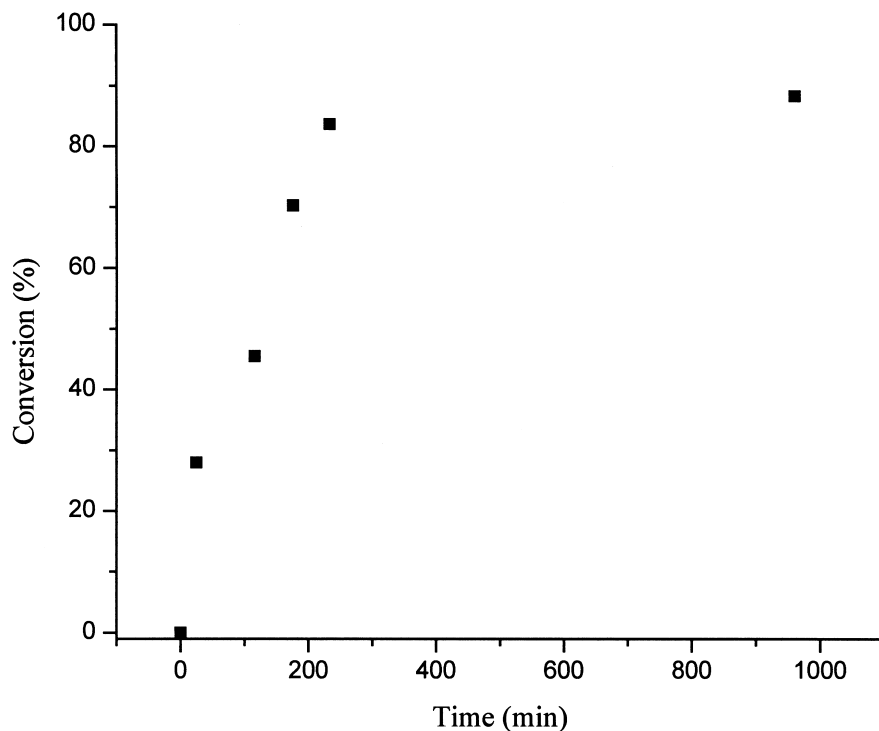


Figure 4. CL conversion as a function of time in $\text{Sn}(\text{Oct})_2$ catalyzed ROP of copolymer **1** (Sample 1, Table 1).

cent to a carbonate linkage ($-\text{CL}-\text{CO}-\text{O}-\text{CH}_2-$ or $-\text{MBC}-\text{CO}-\text{O}-\text{CH}_2-$) it displayed a chemical shift of 68.4 ppm (CL-MBC or MBC-MBC dyad), consistent with the assignment made by Bisht *et al.* [37], but when it was next to an ester linkage ($-\text{CH}_2-\text{O}-\text{CO}-\text{CH}_2-$) it appeared at 65.0 ppm (MBC-CL dyad). Further analysis of the ^{13}C NMR data yielded additional evidence for a random comonomer sequence; for example, additional heterodyad resonances were observed in the carbonate carbonyl ($-\text{O}-\text{CO}-\text{O}-$) and ester carbonyl ($-\text{O}-\text{CO}-$) regions.

Molecular weights were targeted by varying the initial monomer/initiator ratio ($[\text{M}]_0/[\text{I}]_0$). Experimental molecular weights were measured using SEC/MALLS and were found to be equivalent to or slightly less than the theoretical values predicted from Equation 1, assuming 100% conversion of both monomers,

$$M_n(\text{theoretical}) = \frac{w_{\text{CL}} + w_{\text{MBC}}}{M_1} \quad (1)$$

where w_{CL} = weight of CL monomer charged to the reactor, w_{MBC} = weight of MBC monomer charged to the reactor, and M_1 = moles of initiator (propylene glycol or $-\text{OiPr}$).

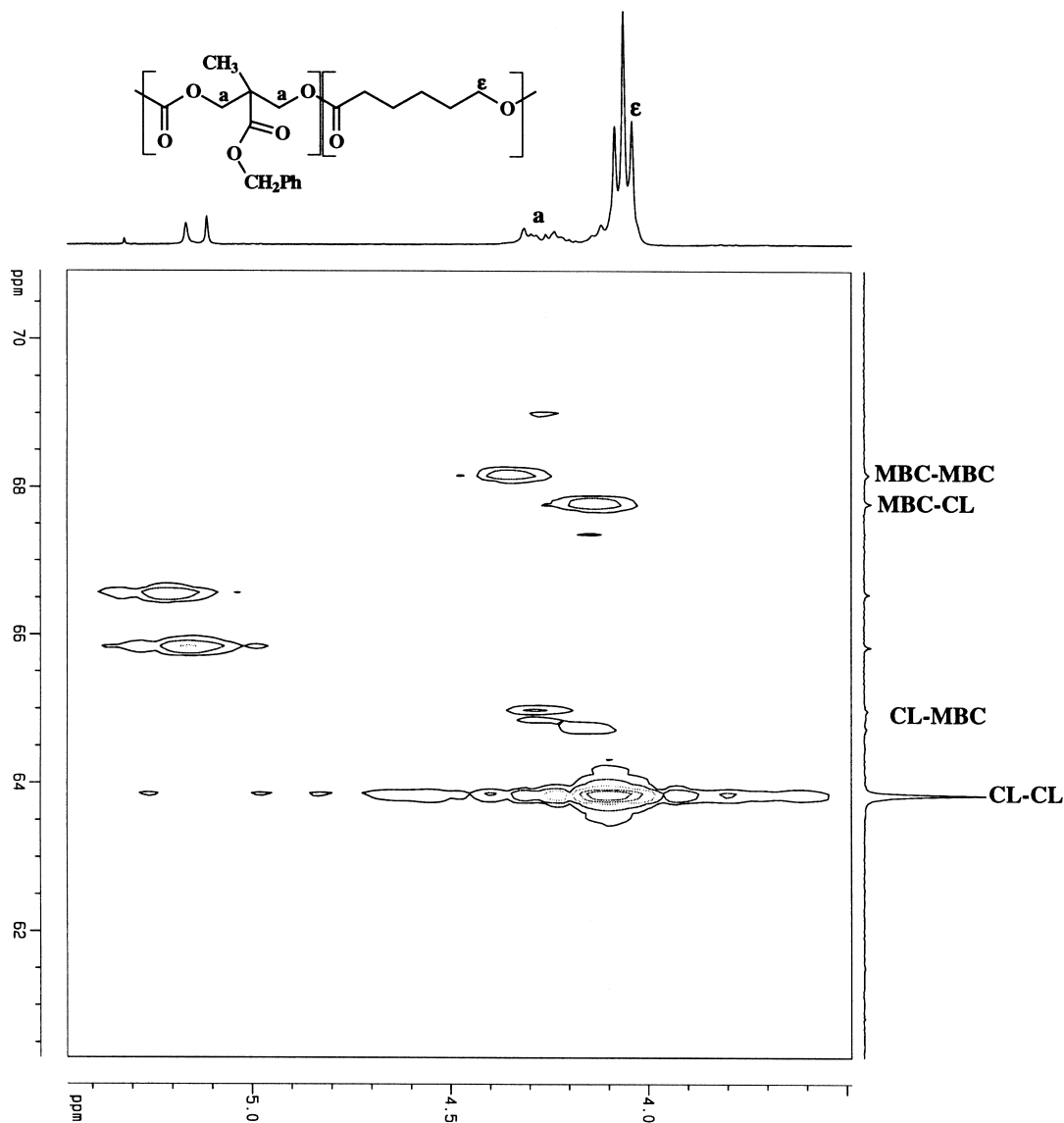


Figure 5. ^1H - ^{13}C HETCOR NMR spectrum of poly(CL-co-MBC) (Sample 7, Table 1).

The molecular weights in Table 1 are much higher than the molecular weights of MBC-containing polymers previously reported in the literature [36-37]. The SEC chromatograms displayed unimodal curves, which indicated the absence of cyclic oligomers.

Gel formation was noted for MBC homopolymerizations and CL-MBC copolymerizations (Samples 4-6, Table 1) carried out at temperature $\geq 135^\circ\text{C}$. At 130°C , even though gel was not observed, the polydispersity was quite broad (Sample 3, Table 1). This tendency toward branching and crosslinking at higher

temperatures is a result of the known tendency for $\text{Sn}(\text{Oct})_2$ to promote inter- and intramolecular transesterification reactions [41]. Figure 6 shows a proposed intermolecular transesterification reaction, involving the benzylic ester protecting groups of MBC repeat units, which causes gelation at higher reaction temperatures. It can be shown that with a difunctional initiator, such as used in this work, such reactions lead directly to crosslinking.

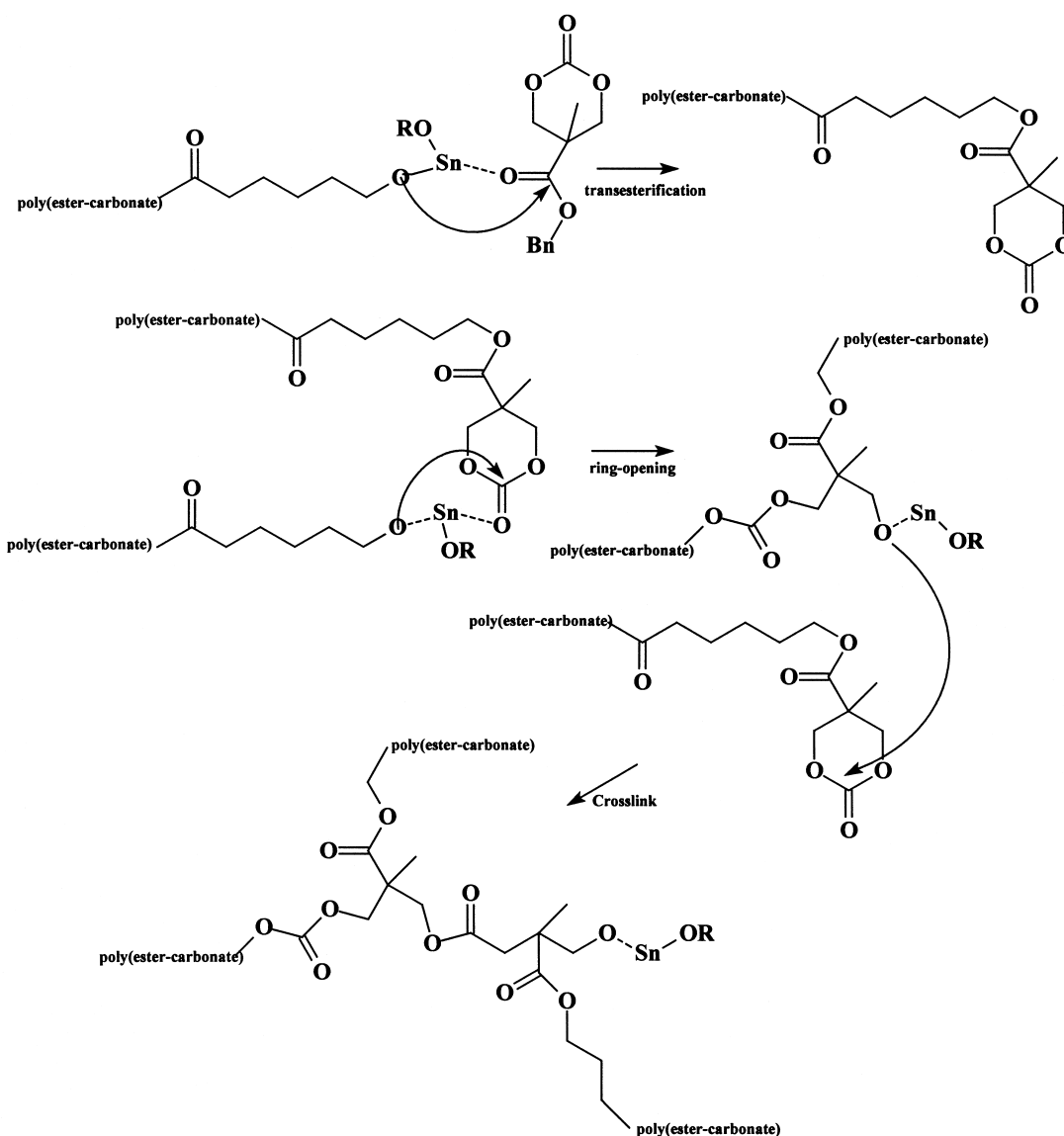


Figure 6. Proposed mechanism for cross-linking reaction of MBC-based copolymers at polymerization temperatures $\geq 135^\circ\text{C}$.

Evidence in support of this benzyl group displacement mechanism was provided by analysis of the transesterification reaction between a model benzyl-blocked carboxylic acid, benzyl 2,2-dimethyl propionate, and primary or secondary alcohols (*n*-pentanol or 2-methyl-1-pentanol) at 138°C in the presence of Sn(Oct)₂. Both alcohols were able to displace benzyl alcohol under these conditions to provide the corresponding aliphatic esters.

The amount of crosslinked material (ca. 50-70%) was measured by dissolving the crude copolymer in MeCl₂ and collecting the gel fractions by filtration prior to precipitation of the soluble copolymer into MeOH. DSC thermal analysis indicated higher glass transition temperatures for the gel compared to the sol fraction as expected. The crosslinked copolymer fractions were insoluble in water and organic solvents, but were swelled by certain organic solvents such as DMSO, CHCl₃, and THF.

LLA/MBC Copolymerizations

The copolymerization of MBC and LLA was achieved with a Sn(Oct)₂-alcohol initiating system for various monomer feed ratios; Table 2 summarizes the results. NMR was used to measure the copolymer compositions by comparing the relative areas of the peaks corresponding to the protons of the LLA and MBC monomer repeat units (see Experimental section). ¹³C NMR spectroscopy results were consistent with a random comonomer sequence; for example, the -CH₂O- region of the spectra generally contained a relatively strong resonance at 69.2 ppm due to lactide methine carbons adjacent to an MBC repeating unit (LLA-MBC dyad). Also in the carbonyl region of the spectra were observed a carbonate resonance at 154.2 ppm due to the LLA-MBC dyad and a lactide carbonyl resonance at 169.8 ppm due to the MBC-LLA dyad. SEC/MALLS (THF eluent) and SEC (CHCl₃ eluent) revealed copolymers with moderate to high molecular weights (10,000-100,000 g/mol) and unimodal molecular weight distributions.

The LLA-MBC copolymers were analyzed by DSC and found to display a single glass transition temperature, indicative of a random copolymer. Figure 7 shows the experimental glass transition data (closed squares) and theoretical Flory-Fox line [42] (open squares) of poly(LLA-*co*-MBC) plotted as a function of wt% MBC; the experimental T_g data are nearly equivalent to the theoretical values. The copolymers were found to be completely amorphous at MBC incorporation > 20 mol% due to the presence of the bulky MBC monomer unit which decreases the crystallinity of PLLA (T_m = 170-180°C).

As with the CL-MBC copolymers, the LLA-MBC copolymers displayed a gel fraction when the ROP was carried out at temperatures ≥135°C; at lower temperatures, however, the products were totally soluble. The insoluble fractions were swellable in chlorinated solvents and toluene. These materials may be suitable for the development of new biodegradable networks.

Table 2. Metal-Catalyzed Ring Opening Copolymerization^a of LLA and MBC

Sample	Temp. (°C)	MBC % in feed	MBC % in copolymer ^b	Target M_n (g/mol $\times 10^{-3}$)	Exp. M_n^c (g/mol $\times 10^{-3}$)	PDI	T_g (°C)	T_m (°C)	$[M]_0/[I]_0 \times 10^{-3}$	Exp. M_n / Target M_n
L-1	115	4.6	0.87	220.0	179	1.4	54.0	176	1.70	0.81
L-2	115	15.9	8.7	120.0	91.5	2.2	50.0	—	0.98	0.76
L-3	115	22.0	22.0	50.0	43.5	2.3	45.2	—	0.43	0.87
L-4	115	22.0	17.6	20.0	18.4	1.3	42.6	136	0.17	0.92
L-5	115	50.4	40.7	60.0	47.4	1.7	31.5	—	0.33	0.79
L-6	115	72.9	77.6	60.0	51.9	1.8	20.0	—	0.28	0.86
L-7	140	17.0	—	60.0	—	—	42.5	—	0.56	—

^aReaction time, 8 h.^bCopolymer composition determined by ¹H NMR.^cMolecular weights determined from size exclusion chromatography.

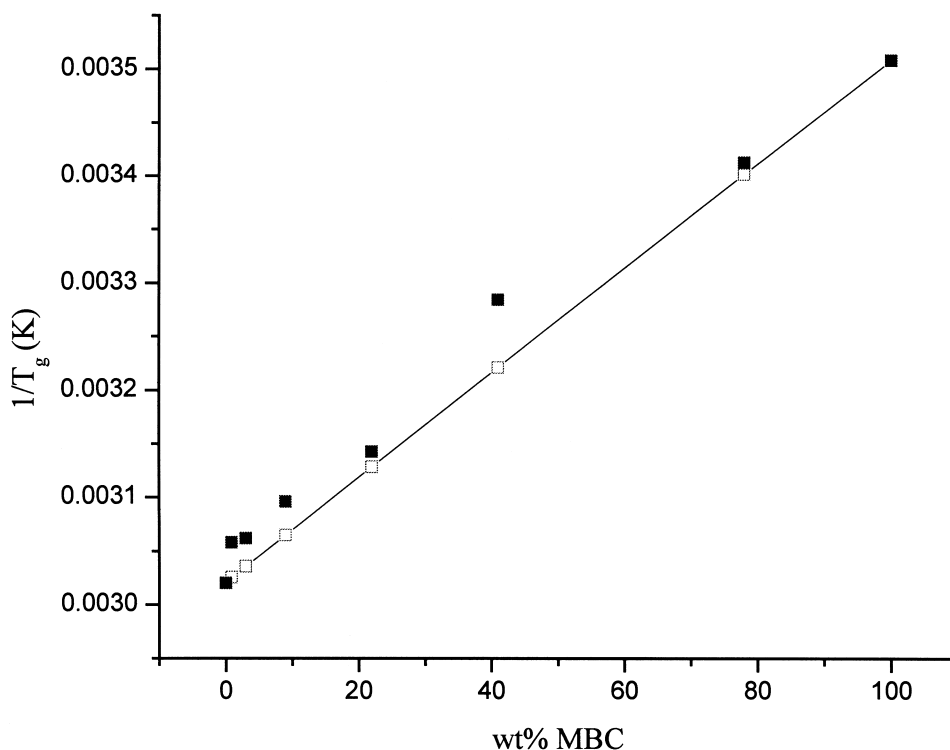


Figure 7. Plot of wt% MBC vs. $1/T_g$ (K), (■) = experimental data; (□) = theoretical data.

Hydrogenolysis

Copolymers **1** and **2** were subjected to hydrogenolysis to eliminate the benzyl protecting groups. Bisht and co-workers reported a successful method for deprotection of the benzyl group from MBC homopolymer [36]; however, they reported some difficulty in the removal of the benzyl group from poly(MBC-co-TMC) [37]. In the case of the CL-MBC copolymer, the de-protection with H_2 in the presence of 10% Pd/C catalyst produced a copolymer that was no longer soluble in chlorinated organic solvents. Solid-state ^{13}C -NMR was used for the initial characterization of the insoluble product; however, it was quickly determined that a mixed solvent system, $DMSO-d_6/CDCl_3$ (2/1, v/v) could be used to provide solution NMR characterization. Figure 8 illustrates the proton NMR spectrum of poly(CL-co-MBC) before and after hydrogenolysis. The fraction of benzyl groups deprotected was calculated according to the following equation:

$$fraction\ deprotected = 1 - \left(\frac{\varepsilon + c}{b} \right)_{before} \left(\frac{b}{\varepsilon + c} \right)_{after}$$

where, b is the integrated area of the benzyl protons (5.1-5.2 ppm) of MBC repeat units and $(\varepsilon + c)$ is the combined integrated area of the ε and backbone methylene

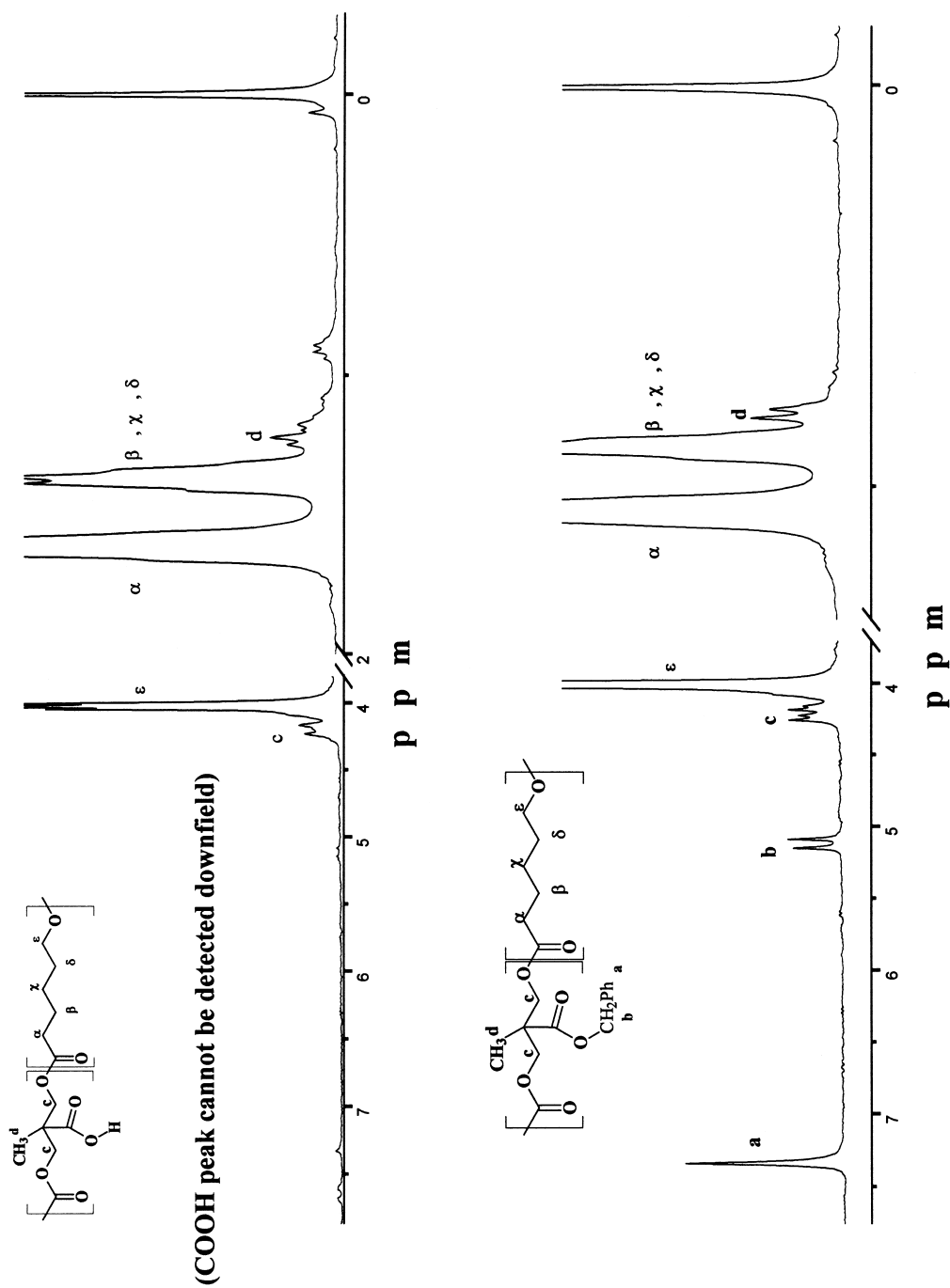


Figure 8. ^1H NMR (300 MHz, $\text{DMSO}-d_6$; CDCl_3 (2/1, v/v)) spectrum of poly(CL-co-MBC) (Sample 7, Table 1) before deprotection (bottom) and after deprotection (top).

protons of CL (4.0–4.1 ppm) and MBC (3.8–4.3 ppm), respectively, measured before and after hydrogenolysis. The spectrum clearly shows the near complete disappearance of the phenyl and benzyl protons corresponding to the benzyl ester moiety. In this case, it was calculated that the CL-MBC copolymer was 90.2% deprotected. The ^{13}C solid-state NMR spectrum showed the presence of a new COOH carbonyl carbon at 176.2 ppm and the disappearance of the COOBn carbonyl at 173 ppm.

The benzyl groups of poly(LLA-*co*-MBC) were also removed with H_2 and 10% Pd/C catalyst at room temperature. These copolymers, after hydrogenolysis, were also no longer soluble in chloroform, and NMR data was acquired in the solvent mixture, $\text{DMSO}_{d-6}:\text{CDCl}_3$ (2:1). Figure 9 shows the ^1H NMR spectrum of poly(LLA-*co*-MBC) and its deprotected derivative, poly(L-lactide-*co*-5-methyl-5-carboxy-1,3-dioxan-2-one) (poly(LLA-*co*-MCC)). The disappearance of the phenyl ($a = 7.3$ ppm) and benzyl protons ($b = 5.37$ ppm) of the protecting group was observed. The degree of debenylation was calculated to be 98% using the following equation:

$$\text{fraction deprotected} = 1 - \left(\frac{c}{b}\right)_{\text{before}} \left(\frac{b}{c}\right)_{\text{after}}$$

where b and c are the integrated areas of the benzyl (5.1–5.2 ppm) and backbone methylene (3.8–4.3 ppm) protons of MBC repeat units, respectively, measured before and after hydrogenolysis. ^{13}C NMR indicated the presence of a new carbonyl carbon at 175.3 ppm corresponding to the carboxylic acid. The T_g of the LLA-MBC copolymer rose from 45.2 to 54.3°C after de-protection as shown in Figure 10. This increase in glass transition temperature is due to the restricted mobility of the polymer chains, which now experience stronger bonding interactions due to the presence of free carboxylic acid groups.

CONCLUSION

The synthesis of novel poly(ester-carbonates) with pendent carboxylic acid groups has been reported for the first time. Copolymers of 5-methyl-5-benzyloxy-carbonyl-1,3-dioxan-2-one (MBC) with LLA or CAP were synthesized in solution or in the bulk by metal-catalyzed ROP. Monomer feed ratios, reaction temperatures, and initiating systems were varied. Copolymer compositions were tailored according to the comonomer feed ratio so that a specific concentration of carboxylic acid moieties could be placed along the polymer backbone. The crystallinity of the copolymers was reduced or eliminated entirely depending on the level of incorporation of MBC.

The reaction temperature of the polymerizations was critical to the production of soluble polymers. It was found that at bulk polymerization temperatures

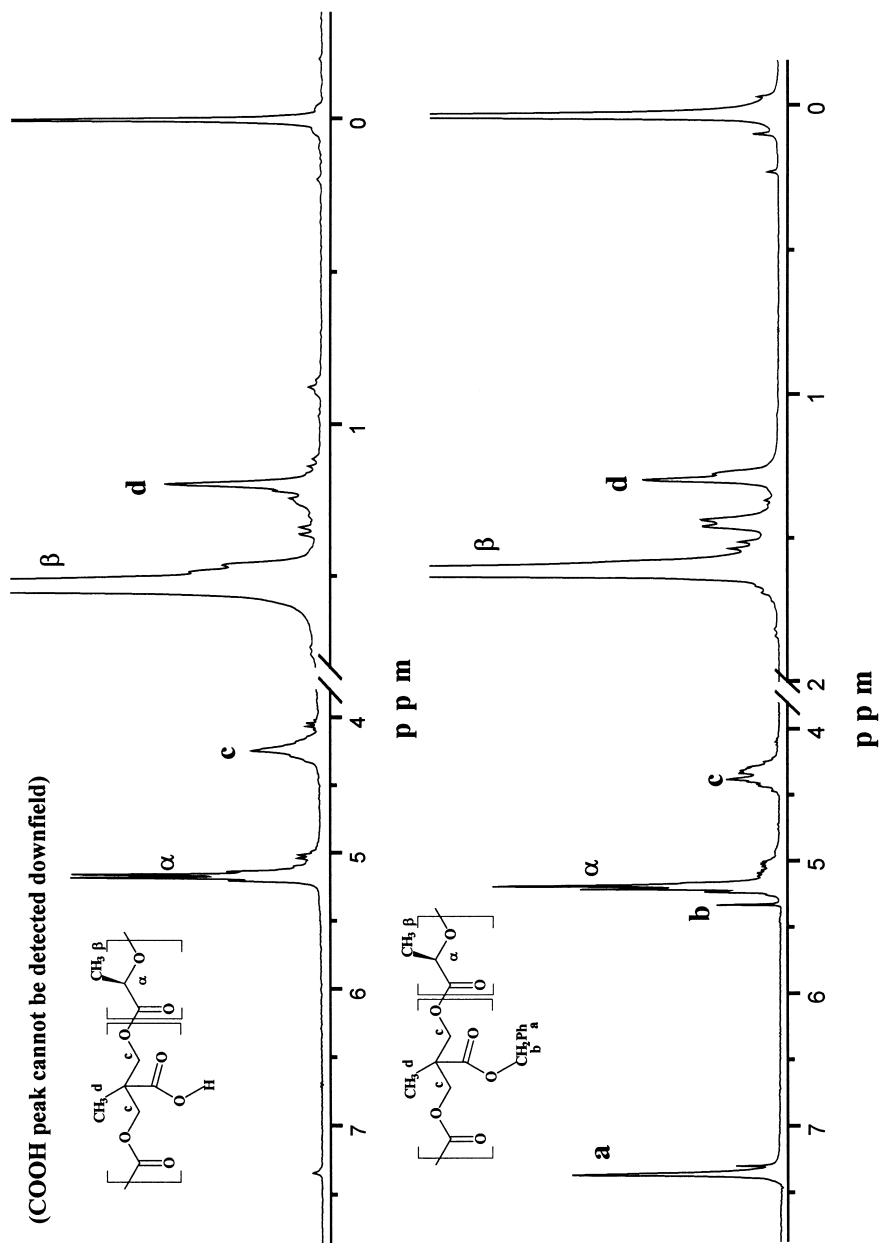


Figure 9. ^1H NMR (300 MHz, $\text{DMSO}-d_6$; CDCl_3 (2/1, v/v)) spectrum of poly(LLA-co-MBC) (Sample L-3, Table 2) before deprotection (bottom) and after deprotection (top).

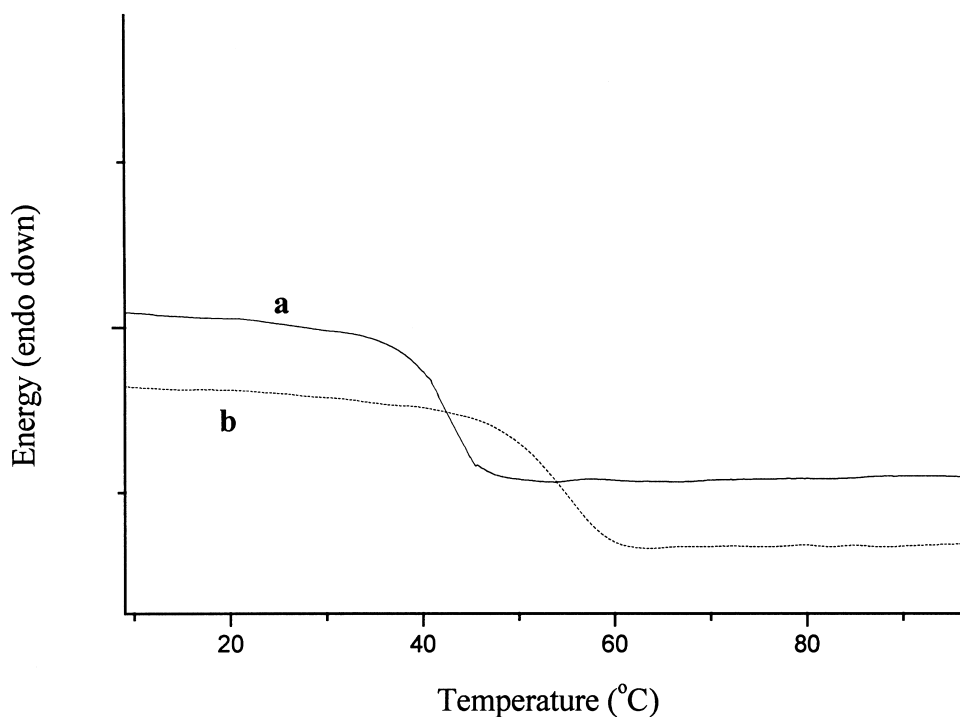


Figure 10. DSC thermograms of poly(LLA-co-MBC), **a** = sample before hydrogenolysis, **b** = sample after hydrogenolysis.

greater than or equal to approximately 135°C, the benzyl protecting group becomes susceptible to transesterification, and the resulting cyclic carbonate end-group presents a site for crosslinking. At bulk ROP temperatures below 135°C, the polymers were completely soluble in a number of organic solvents. In the solution polymerization of copolymer **1** at 85°C, a minute amount of insoluble gel product was noted (> 2%); however, the majority of the product synthesized at this temperature was soluble. Copolymers of moderate to high molecular weight (SEC) were produced by adjusting the monomer to initiator ratio. The copolymers were characterized in great detail by nuclear magnetic resonance and differential scanning calorimetry. These methods confirmed the random distribution of the comonomers and the thermal characteristics of the copolymers before and after the inclusion of carboxylic acid groups. The mechanical and degradation properties of copolymers **1** and **2**, as well as the carboxylic acid-functionalized poly(ester-carbonates) are currently being investigated in our laboratory.

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