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Poly(lactic Acid) and Chain-Extended Poly(lactic acid)−Polyurethane Functionalized with Pendent Carboxylic Acid Groups

Tim R. Cooper and Robson F. Storey*

School of Polymers and High Performance Materials, The University of Southern Mississippi, Hattiesburg, Mississippi 39406

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ABSTRACT: We have synthesized linear poly(lactic acid) (BHMBA−PLA) possessing a pendent carboxylic acid group via ring-opening polymerization (ROP) of L- or D,L-lactide using bis(hydroxymethyl) butyric acid (BHMBA) as initiator and stannous octoate as catalyst. Polymerizations were typically conducted in the bulk for ∼3 h at 130 °C, using a catalyst concentration of 3×10^{-2} wt % Sn. The polymers were characterized by gel permeation chromatography, equipped with a multiangle laser light scattering detector (GPC−MALLS), ^{1}H NMR, ^{13}C NMR, homonuclear correlation spectroscopy (COSY), and heteronuclear single quantum coherence spectroscopy (HSQC). Branching, via possible condensation reaction between the pendent carboxylic acid group of the initiator fragment and the hydroxyl chain ends, was investigated and determined to be negligible under our synthesis conditions. Number-average molecular weights by GPC−MALLS ($M_{n,GPC}$) and ^{1}H NMR ($M_{n,NMR}$) were in good agreement with theoretical values ($M_{n,theo}$) calculated assuming a strictly linear structure. The average number of branches per molecule, $\bar{N}_{br}$, was calculated from NMR data and found to be nearly identical to that of a strictly nonbranched poly(lactide) synthesized using 1,4-butandiol as the initiator. We have chain extended BHMBA−PLA using a diisocyanate, proving its utility in the synthesis of hydrolytically degradable poly(ester−urethane)s containing regularly spaced pendent carboxylic acid groups.

Introduction

Poly(lactic acid) (PLA) plays a significant role in the field of degradable polymers. PLA is currently used in biomedical and packaging applications, including orthopedic implants and beverage containers.[1] A number of factors contribute to the success of PLA in these applications, including its physical properties, favorable degradation characteristics, and benign degradation products.[2] PLA is synthesized via two different polymerization mechanisms, direct polycondensation of lactic acid and ring-opening polymerization[3] (ROP) of the cyclic dimer, lactide. In either case, the lactoyl units may possess a single stereo-configuration, usually L, leading to semicrystalline poly(L-lactic acid) (PLLA), or they may be the racemic mixture, leading to amorphous poly(D,L-lactic acid) (PDLLA). ROP provides more precisely targeted and potentially higher molecular weight.[4] Additionally, one can copolymerize a variety of lactones or carbonates with lactide using ROP.

Extensive research has been devoted to the modification of PLA, through copolymerization, in order to change degradation characteristics and/or enhance physical properties.[5−8] One such modification involves the incorporation of carboxylic acid groups into the PLA backbone. In previous work,[9] we copolymerized D,L-lactide (DLLA) with 5-methyl-5-benzyloxycarbonyl-1,3-dioxan-2-one, a cyclic carbonate containing a latent carboxylic acid group (benzyl ester). After deprotection to the carboxylic acid form, the resulting copolymers showed improved thermal characteristics, i.e., higher T_g; however, deprotection was incomplete and the degree of incorporation and sequencing of the acid pendant groups were subject to the comonomer reactivity ratios of the ring-opening copolymerization (ROP). Other methods have been investigated, in which telechelic carboxylic acid-terminated PLA is created through arduous multistep syntheses.[10,11]

To provide greater synthetic control and ease of synthesis, we recently reported an alternative method of creating PLA with regularly occurring pendent acid groups along the backbone.[12] We utilized a two-step procedure involving the ROP of lactide initiated by 2,2-bis(hydroxymethyl)butyric acid (BHMBA) to form hydroxyl-terminated prepolymers containing a single, pendent carboxylic acid group (BHMBA−PLA), followed by chain extension of the prepolymers with a diisocyanate such as L-lysine diisocyanate methyl ester (LDI) or dicyclohexylmethane 4,4′-diisocyanate (H_{12}MDI) (Scheme 1). Reaction of degradable polyester polyols with polyisocyanates for the purpose of molecular weight advancement[13,14] and cross-linked network formation[15,16] has been reported; however, we have adapted the method to a more specific use, namely, the placement of functional groups regularly along the backbone. The carboxylic acid equivalent weight of the final chain-extended polymer is fixed by the molecular weight of the PLA prepolymer, which can be controlled with great precision. Since the molecular weight distribution of the PLA prepolymer is narrow, the spacing of the acid groups along the backbone is nearly constant. The method allows independent specification of molecular weight and carboxylic acid content and creation of PLA with tailored degradation characteristics and physical properties. Lee and coworkers have demonstrated that systematically adjusting the acid content of modified PLA will provide direct control of hydrolytic degradation.[17] The chain-extended, acid-modified PLA may have utility in and of itself or as a prepolymer component in other polymer systems, such as segmented polyurethanes.

Hedrick and co-workers have made extensive use of 2,2′-bis(hydroxymethyl)propionic acid (bis-MPA), a structural homologue of BHMBA, to create dendrimer-like star polymers and hyperbranched polymers from lactone and lactide monomers.[18−21] In one instance, they polymerized D,L-lactide from this initiator to produce a two-arm star polymer analogous to our prepolymers;[18] however, in this and all cases these authors first blocked the carboxylic acid of bis-MPA to prevent its

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* Corresponding author. E-mail: robson.storey@usm.edu.

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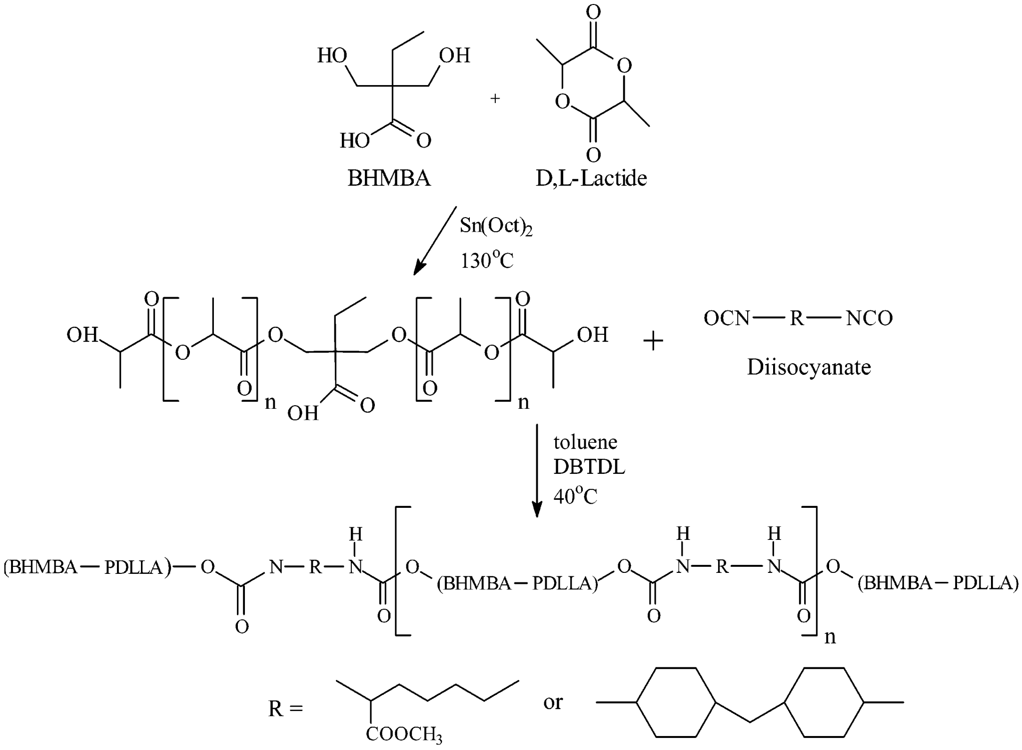
Scheme 1. Ring-Opening Polymerization of D,L-lactide Using BHMBA as an Initiator and Chain Extension of BHMBA−PDLLA with a Diisocyanate



involvement in side reactions during ring-opening polymerization. We were interested in a more practical approach that did not involve the extra steps of blocking and deblocking; however, the presence of the carboxylic acid group within the BHMBA initiator does create the possibility for condensation side reactions during ROP. This would lead to branching and a decrease in acid functionality. In fact, for our system of interest, i.e., lactide/BHMBA/stannous octoate, it was recently claimed that ROP and polycondensation will proceed simultaneously to create hyperbranched polymers.[22] Since we were interested primarily in linear prepolymers with full retention of carboxylic acid functionality, we have carefully examined this issue and, as reported herein, have established a method for characterization of the prepolymers with respect to the average number of branches per molecule using the integrated areas of select proton resonances within the NMR spectrum. We show that predominantly linear polymers result. And finally, we demonstrate that the prepolymers can be smoothly chain extended according to Scheme 1, to create high molecular weight PLA with regularly spaced carboxylic acid functionality.

Experimental Section

Materials. 2,2-Bis(hydroxymethyl)butyric acid (BHMBA, Aldrich Chemical Co.), 2,2-bis(hydroxymethyl)propionic acid (bis-MPA, Aldrich Chemical Co.), 1,4-butanediol (Aldrich Chemical Co.), 1,2-propanediol (Aldrich Chemical Co.), ϵ-caprolactone (CL, Aldrich Chemical Co.), L- and D,L-lactide (Ortec, Inc., Easley, South Carolina), L-lysine diisocyanate (LDI, Kyowa Hakko Chemical Inc., Ltd.), dicyclohexylmethane 4,4′-diisocyanate (H_{12}MDI, Bayer Desmodur W), dibutyltin dilaurate (DBTDL, Aldrich Chemical Co.), and tin(II) 2-ethylhexanoate ($Sn(Oct)_2$, Alfa Aesar) were used as received. Toluene was refluxed over sodium for 24 h and distilled under nitrogen before use.

Instrumentation. Number-average molecular weights ($M_{n,GPC}$) and molecular weight distributions (MWD) of polymers were determined using a GPC system consisting of a Waters Alliance 2695 Separations Module, an on-line multiangle laser light scattering (MALLS) detector (MiniDAWN, Wyatt Technology Inc.), an interferometric refractometer (Optilab DSP, Wyatt Technology Inc.), and either two mixed D (pore size range 50−10^4 Å, 5 μm bead size) or two mixed E (pore size range 50−10^3 Å, 3 μm bead size) PL gel (Polymer Laboratories Inc.) GPC columns connected in series. Freshly distilled THF served as the mobile phase and was delivered at a flow rate of 1.0 mL/min. Sample concentrations were 10−12 mg/mL in freshly distilled THF, and the injection volume was 100 μL. The detector signals were simultaneously recorded using ASTRA software (Wyatt Technology Inc.) and molecular weights were determined using a dn/dc calculated from the refractive index detector response and assuming 100% mass recovery from the columns. Fractional monomer conversion (p) was calculated from the integrated areas of the polymer and monomer peaks in the refractive index trace, assuming equal response factors for polymer and monomer.

Solution ^{1}H NMR spectra were obtained on a Varian Unity 500 MHz spectrometer using 5 mm o.d. tubes with sample concentrations of 20−30% (w/w) in deuterated acetone (C_3D_6O) (Aldrich Chemical Co.) containing (0.03% v/v) tetramethylsilane as an internal reference. ^{1}H spin−lattice relaxation times (T_1) were determined using an inversion−recovery pulse sequence ($180°-\tau-90°$) with a delay of 20 s between scans. As a result of this analysis, all ^{1}H NMR spectra were obtained using a delay time of 5 s, which was in excess of 5 times the T_1 of the slowest proton to return to equilibrium (0.76 s). A homonuclear correlation spectroscopy (COSY) NMR experiment was performed using a delay time of $5T_1$, obtaining 128 increments and 8 scans per increment, within a spectral width of 3988 Hz operating at 499.77 MHz. A heteronuclear single quantum coherence spectroscopy (HSQC) experiment was performed using a delay time of $5T_1$, obtaining 200 increments and 16 scans per increment, within spectral widths of 7530 and 3988 Hz and operating at 125.7 and 499.7 MHz in the ^{13}C and ^{1}H domains, respectively.

Procedure. ROP To Form BHMBA—PLA. Reaction mixtures were formulated within a Vacuum Atmospheres Company Dri-Lab glovebox under an inert N_2 atmosphere. In a representative experiment (experiment 1, Table 1) D,L-lactide was initiated by BHMBA to form BHMBA−PDLLA as follows: 40.00 g (0.28 mol)

Table 1. Experimental Conditions, Molecular Weights, and Average Number of Branches Per Molecule for Polymerizations of L- and D,L-Lactide and ϵ-Caprolactone with BHMBA and Control Initiators

experiment no.	initiator	monomer	catalyst level (ppm Sn)	reacn time (min)	monomer convn (%) (GPC)	$M_{n,theo}$ (g/mol)	$M_{n,NMR}$ (g/mol)	$M_{n,GPC}$ (g/mol)	MWD (M_w/M_n)	$\bar{N}_{br}$(NMR)
1	BHMBA	DLLA	300	190	96.8	2880	2800	3250	1.02	0.020
2	BHMBA	DLLA	800	185	95.9	2849	2750	3440	1.03	0.041
3	BHMBA	DLLA	300	195	96.4	976	950	1120	1.05	0.047
4	BHMBA	LLA	300	180	97.1	2883	2760	3360	1.02	0.043
5	BHMBA	LLA	800	183	97.5	2900	2780	3530	1.03	0.080
6	BHMBA	LLA	800	2076	95.9	2854	2720	3440	1.17	0.089
7	1,4-butanediol	DLLA	300	186	96.9	2883	2700	3420	1.08	0.032
8	1,4-butanediol	DLLA	300	338	96.2	2863	2850	3430	1.10	0.039
9	bis-MPA	DLLA	300	342	97.3	4909	4810	5360	1.02	0.054
10	BHMBA	ϵ-caprolactone	300	240	97.6	2931	2890	2960	1.12	0.068
11	BHMBA	ϵ-caprolactone	300	2000	96.1	2888	4900	5250	1.18	2.73
12	1,2-propanediol	DLLA	300	198	97.5	2894	2690	3370	1.07	0.035

Table 2. Prepolymers and Chain Extenders Used in the Synthesis of CE−PDLLAs

experiment no.	prepolymer[a]	prepolymer monomer convn (%)	prepolymer $M_{n,theo}$ (g/mol)	prepolymer $M_{n,GPC}$ (g/mol)	chain extender	M_n[b] (g/mol)	MWD[b]
13	BHMBA−PDLLA	97.1	980	1170	LDI	8670	1.29
14	BHMBA−PDLLA	96.3	6271	6740	LDI	51 100	1.35
15	BHMBA−PDLLA	95.9	13 439	14 200	LDI	206 000	1.38
16	BHMBA−PDLLA	96.3	6271	6740	H_{12}MDI	47 200	1.38
17	1,2-propanediol−PDLLA	96.8	5036	5550	LDI	49 500	1.39
18	BHMBA−PDLLA	96.8	2874	3340	H_{12}MDI	Table 3	Table 3
19	1,4-butanediol−PDLLA	97.6	3106	3530	H_{12}MDI	Table 3	Table 3

[a] Prepolymers used in the synthesis of CE−PDLLAs (experiments 13−19) are not listed in Table 1, but were synthesized according to the procedure described in the experimental with a catalyst level of 300 ppm Sn and a reaction time of ~180 min. [b] Molecular weight analysis of chain extended polyurethane accomplished by GPC.

of D,L-lactide, 2.10 g (0.0142 mol) of BHMBA, and 0.043 g (0.106 mmol, 300 ppm Sn) of $Sn(Oct)_2$ were added to a 250 mL, 1-neck round-bottom flask. The flask was then equipped with an overhead stirrer, and the polymerization was carried out by the immersion of the flask in a 130 °C thermostated oil bath contained within a dry N_2 glovebox, for 190 min, after which the molten reactor contents were poured into a Teflon dish to cool. Hydroxyl equivalent weight of the prepolymer was calculated as $M_{n,GPC}/(2p)$, where p = fractional conversion of lactide monomer determined by GPC.

Chain Extension of BHMBA—PDLLA Prepolymers Using LDI. A representative procedure (experiment 14, Table 2) was as follows: Into a 1-neck round-bottom flask were charged 20.05 g of BHMBA−PDLLA prepolymer (5.73 mequiv of OH), 0.685 g of LDI (6.06 mequiv of NCO), 0.187 g (0.297 mmol) of DBTDL, and 60 mL of toluene. The flask was then equipped with an overhead stirrer and the polymerization was carried out by the immersion of the flask in a 40.0 °C thermostated oil bath contained within a dry N_2 glovebox, for 25 h, after which the contents were poured into a Teflon dish to cool. The dish and its contents were then put into a vacuum oven, to remove the toluene, for 72 h or until a constant weight was obtained.

Chain Extension of BHMBA—PDLLA Prepolymers Using H_{12}MDI. A representative procedure (experiment 18e, Table 3) was as follows: Into a 1-neck round-bottom flask equipped with an overhead stirrer were charged 10.00 g of BHMBA−PDLLA prepolymer (5.80 mequiv of OH), 0.689 g of H_{12}MDI (6.10 mequiv of NCO), 0.189 g (0.291 mmol) of DBTDL, and 40 mL of toluene. The flask was then equipped with an overhead stirrer and the polymerization was carried out by the immersion of the flask in a 40.0 °C thermostated oil bath contained within a dry N_2 glovebox, for 25 h, after which the contents were poured into a Teflon dish to cool. The dish and its contents were then put into a vacuum oven, to remove the toluene, for 72 h or until a constant weight was obtained.

Results and Discussion

Unblocked BHMBA (free carboxylic acid) was used as an initiator for ring-opening polymerization of lactide in the presence of stannous octoate, as shown in Scheme 1. Experimental conditions, monomer conversions, molecular weights, and MWD values for the resulting polymers and several comparative polymers are listed in Table 1. Theoretical number-average molecular weights ($M_{n,theo}$) were calculated according to eq 1

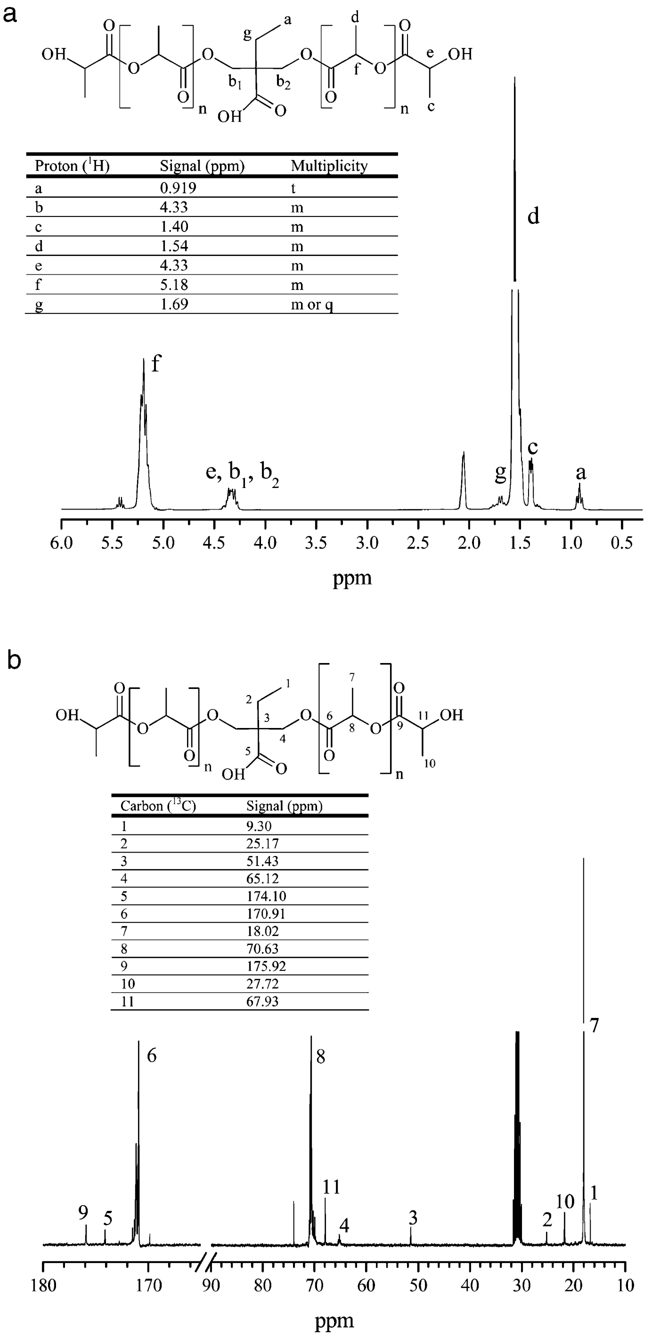
$$M_{n,theo} = \frac{m_I + p \times m_M}{n_I} \qquad (1)$$

where m_I and n_I are the mass and moles of initiator, and m_M and p are the mass and fractional conversion of the monomer, respectively. Monomer conversions in Table 1 (used in eq 1) were calculated from GPC, and these values were in excellent agreement with conversions calculated by ^{1}H NMR. Equation 1 assumes full conversion of the initiator and a strictly linear prepolymer structure (Scheme 1). We note that for BHMBA, the latter assumption is contradictory to a recent report by Gottschalk and Frey,[22] who claimed that the lactide/BHMBA/

Table 3. NCO/OH Ratio and M_n Values of a Series of CE−PDLLA Polymers Based on Experiments 18 and 19 as Defined in Table 2

experiment	NCO/OH (mol/mol)	M_n[a] (g/mol)	experiment	NCO/OH (mol/mol)	M_n[a] (g/mol)
18a	0.96	22 900	19a	0.95	20 800
18b	0.99	23 900	19b	0.99	19 100
18c	1.02	29 200	19c	1.01	23 900
18d	1.04	36 100	19d	1.02	26 800
18e	1.05	30 000	19e	1.04	28 900
18f	1.09	31 300	19f	1.08	32 100
18g	1.12	54 100	19g	1.11	40 000
18h	1.18	96 300	19h	1.17	67 300
18i	1.22	62 000	19i	1.21	45 600
18j	1.29	54 800	19j	1.25	36 300
18k	1.34	47 800	19k	1.33	33 600
18m	1.44	38 100	19m	1.43	20 900

[a] Molecular weight analysis accomplished by GPC−MALLS.



Proton (^{1}H)	Signal (ppm)	Multiplicity
a	0.919	t
b	4.33	m
c	1.40	m
d	1.54	m
e	4.33	m
f	5.18	m
g	1.69	m or q

Carbon (^{13}C)	Signal (ppm)
1	9.30
2	25.17
3	51.43
4	65.12
5	174.10
6	170.91
7	18.02
8	70.63
9	175.92
10	27.72
11	67.93

Figure 1. (a) ^{1}H NMR spectrum of BHMBA−PDLLA. (b) ^{13}C NMR spectrum of BHMBA−PDLLA.

$Sn(Oct)_2$ system, under similar conditions, results in hyperbranched polylactides due to condensation between the carboxylic acid groups of BHMBA and the growing polylactide hydroxyl end groups.

Number-average molecular weights by NMR ($M_{n,NMR}$) of BHMBA−PLA were determined by integrating appropriate signals in the ^{1}H NMR spectrum (Figure 1a) due to main-chain lactoyl units and BHMBA initiator residues. Calculations were performed according to eq 2, which accounts for the possibility of branching through condensation reaction of the carboxylic acid groups of BHMBA.

$$\bar{M}_n = \frac{(A_d + A_c)M_{LA} + A_a M_{BHMBA} - (2A_a - A_c)M_{H_2O}}{A_c - A_a} \qquad (2)$$

In eq 2, A_d, A_c, and A_a are the integrated areas of the H_d-, H_c-, and H_a- proton signals, respectively, of Figure 1a, and M_{LA} = 72.06 g/mol, M_{BHMBA} = 148.15 g/mol, and M_{H2O} = 18.01 g/mol. Analogous equations were used for the comparative polymers in Table 1 that utilized different initiators or ϵ-caprolactone monomer.

A shown in Table 1, $M_{n,NMR}$ and $M_{n,GPC}$ for BHMBA−PDLLA (experiments 1−3) and BHMBA−PLLA (experiments 4−6) were in good agreement with $M_{n,theo}$, particularly the NMR values. This showed that unblocked BHMBA can be used to initiate $Sn(Oct)_2$-catalyzed lactide polymerization at 130 °C with little or no branching due to condensation reactions. As a control we synthesized PDLLA using 1,4-butanediol (experiment 7) under the same conditions. On the basis of the similar molecular weights obtained (e.g., experiments 1 and 2 compared to experiment 7), it appears that the two initiators, BHMBA and 1,4-butanediol, produce similar PDLLA. Experiments 5 and 6 employed high catalyst levels and a long reaction time (experiment 6) in an attempt to force branching. However, $M_{n,NMR}$ and $M_{n,theo}$ differed by less than 5% for either experimental condition, and therefore we concluded that an insignificant amount of branching occurred and that generating a branched polylactide using BHMBA/$Sn(Oct)_2$ is difficult.

In experiment 10, poly(ϵ-caprolactone) was synthesized using BHMBA as the initiator, and based upon the close agreement between $M_{n,theo}$ and the experimental molecular weights, little to no branching occurred. However, in experiment 11 $M_{n,NMR}$ and $M_{n,GPC}$ differ significantly from $M_{n,theo}$, demonstrating that branching can be induced in the poly(ϵ-caprolactone) system through the use of long reaction times. Apparently, the primary hydroxyl group of poly(ϵ-caprolactone) is more prone to condensation and branching compared to the secondary hydroxyl group of poly(D,L-lactide); however, branching is still controllable with the poly(ϵ-caprolactone) system by careful management of reaction time, temperature and catalyst concentration.

We also used 2,2-bis(hydroxymethyl)propionic acid (bis-MPA) in the synthesis of PDLLA (experiment 9) and observed that the theoretical and experimental molecular weights were comparable, indicating insignificant branching. Therefore, either BHMBA or bis-MPA can be used unblocked to produce pendant-acid-functionalized PDLLA with a nearly linear structure.

NMR Structural Analysis of BHMBA—PDLLA. ^{1}H and ^{13}C NMR data of BHMBA−PDLLA are presented in Figure 1, parts a and b. The assignments of the carbon and proton resonances with the structures shown in Figure 1, parts a and b, were confirmed by 2-D NMR. The COSY spectrum (Figure 2), which provides ^{1}H−^{1}H connectivity of neighboring protons, shows correlations between H_g and H_a, H_c and H_e, and H_d and H_f. These correlations are in good agreement with the labeled structure in Figure 1a.

Referring back to Figure 1a, the peaks (∼4.4 ppm) associated with H_e (methine proton of terminal lactoyl residue) and H_b (methylene protons of BHMBA) overlap; the identification of these peaks was achieved using HSQC, which provides information regarding ^{1}H−^{13}C pairs. Figure 3 is the HSQC spectrum showing the ^{1}H−^{13}C pairs of BHMBA−PDLLA (experiment 1). The connectivity of H_b and C_4 and H_e and C_{11} provide the evidence necessary to accurately assign H_b and H_e to the multiplet centered at 4.4 ppm as revealed in Figure 1a. Additionally, one can observe other ^{1}H−^{13}C pairs, i.e., H_g and C_2, and H_a and C_1, and especially the pairing of H_c and C_{10}, which confirms the identity of the methyl group associated with the terminal lactoyl residue.

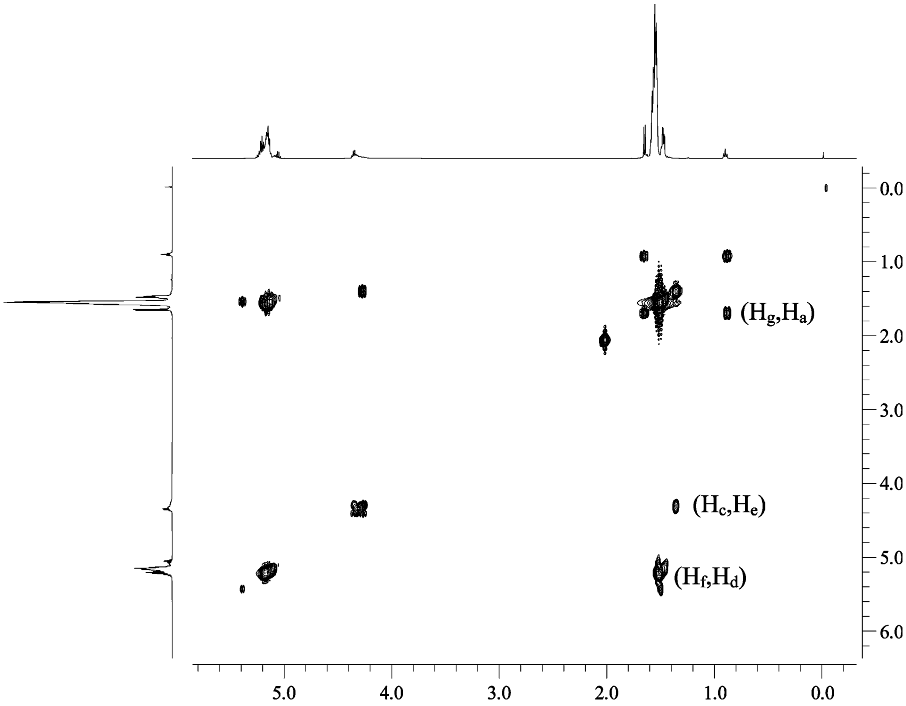


Figure 2. 2D-COSY spectrum of BHMBA−PDLLA.

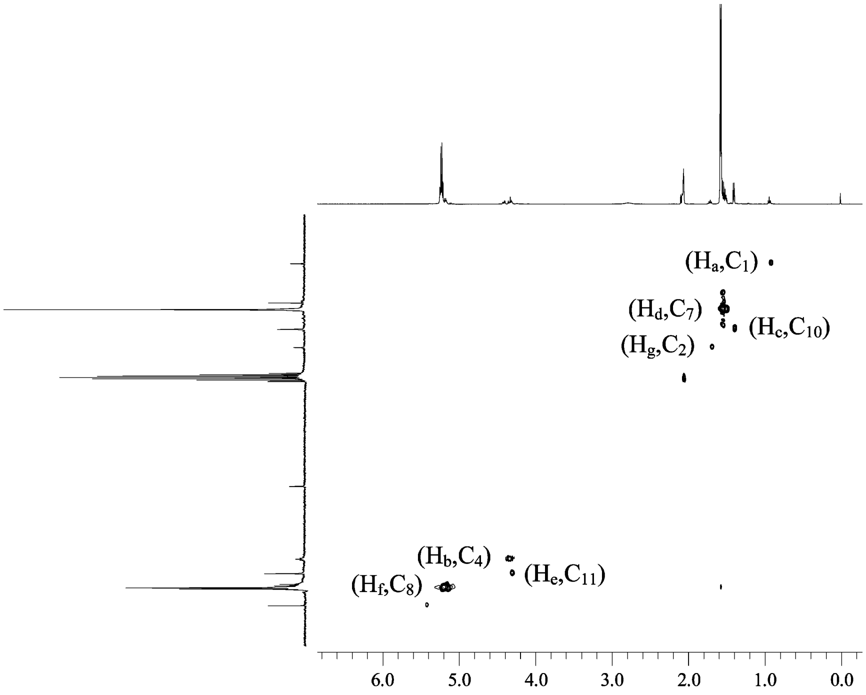


Figure 3. 2D-HSQC spectrum of BHMBA−PDLLA.

If branching were taking place through the carboxylic acid group of BHMBA, as claimed by Gottschalk and Frey,[22] one would expect to see a change in the intensity of the methine peak associated with the terminal lactoyl residue and the formation of a new methine peak (H_{branch}, Figure 4) arising from the condensation reaction. Figure 5 displays the region in which the methine resonances are located. As the reaction progresses beyond a reaction time of 183 to 2076 min, as revealed in Figure 5, no appreciable change in intensity occurs and the formation of a new peak cannot be confirmed.

A comparison of the ^{13}C NMR spectra of BHMBA−PDLLA (experiment 1) and 1,4-butanediol−PDLLA (experiment 7) in Figure 6 shows that a peak at 174.1 ppm is present in the former but not the latter; this provides support that the peak at 174.1 ppm is due to the carbonyl carbon of the BHMBA acid group.

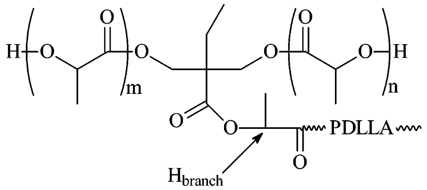


Figure 4. Hypothetical structure of hyperbranched BHMBA−PDLLA defining the methine proton (H_{branch}).

Quantitative Measurement of Extent of Branching. Extent of branching in our polymers was quantified from ^{1}H NMR

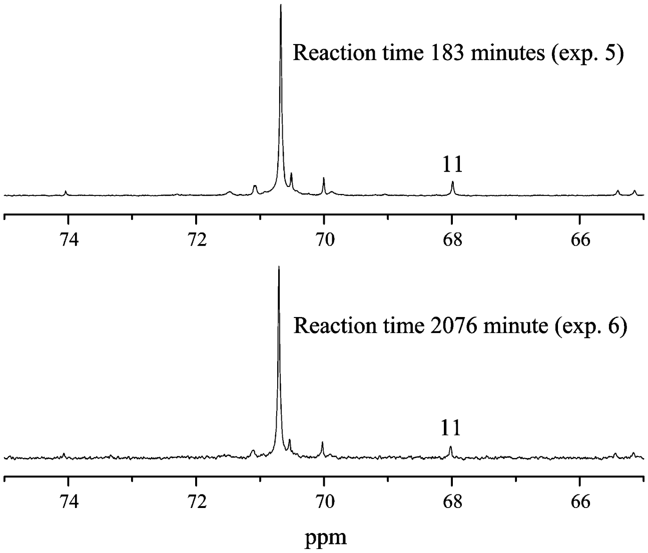


Figure 5. Expansion of methine region of ^{13}C NMR spectrum of BHMBA−PDLLA, experiments 5 and 6.

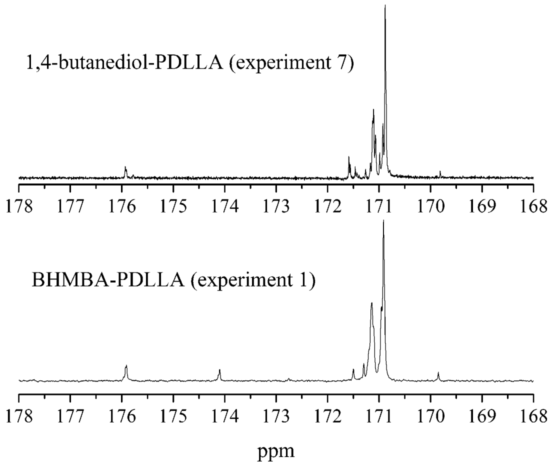


Figure 6. Comparison of the carbonyl regions of BHMBA−PDLLA (experiment 1) and 1,4-butanediol−PDLLA (experiment 7).

data using a method similar to that of Trollsås and Hedrick.[18] We chose to express this measurement in terms of the average number of branches per polymer molecule, $\bar{N}_{br}$, which assumes a value of zero for our targeted structure (Scheme 1), but would increase with polycondensation reactions involving the carboxylic acid groups of BHMBA:

$$\bar{N}_{br} = \frac{N_{BHMBA}}{N} - 1 \tag{3}$$

In eq 3, N_{BHMBA} is the number of BHMBA structural units and N is the number of polymer molecules in the sample. N_{BHMBA} remains constant throughout the reaction and is proportional to the area of the H_a-proton signal, A_a (Figure 1a):

$$N_{BHMBA} = k\frac{A_a}{3} \tag{4}$$

The number of lactoyl hydroxyl end groups, N_{OH}, is proportional to the area of the H_c-proton signal, A_c.

$$N_{OH} = k\frac{A_c}{3} \tag{5}$$

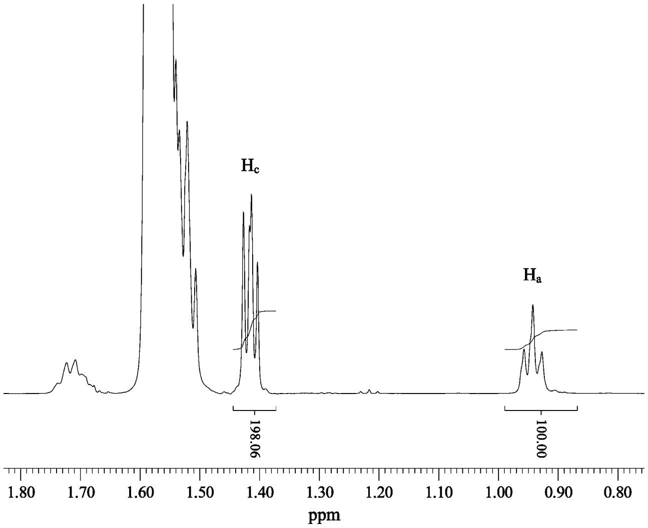


Figure 7. Expanded ^1H NMR spectrum of BHMBA−PDLLA (experiment 1) showing integrated peak areas of protons H_c and H_a.

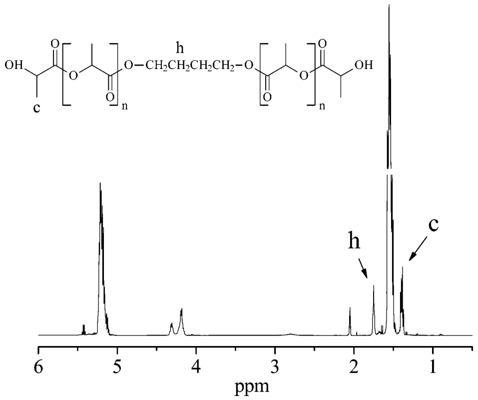


Figure 8. ^1H NMR spectrum of 1,4-butanediol−PDLLA (experiment 7) with methylene protons of initiator (H_h 1.75 ppm) and methyl protons (H_c 1.40 ppm) of terminal lactide residue labeled.

Since the process of condensation reduces N and N_{OH} by equivalent amounts, we may deduce the following relationship:

$$N = k\left(\frac{A_c + A_a}{3}\right) \tag{6}$$

Combining eqs 3, 4, and 6 yields an expression for $\bar{N}_{br}$ in terms of signal areas in the ^1H NMR spectrum that are readily integrated:

$$\bar{N}_{br} = \frac{2A_a - A_c}{A_c - A_a} \tag{7}$$

Figure 7 shows the expanded ^1H NMR spectrum of a representative BHMBA−PDLLA (experiment 1); the relevant end group resonances are entirely resolved and so the foregoing analysis can be successfully completed. Likewise, for polylactides synthesized using 1,4-butanediol, we determined the peak area, A_h, of the inner methylene protons (H_h) of the initiator residue vs A_c (Figure 8) and used the following equation:

$$\bar{N}_{br} = \frac{6A_h - 4A_c}{4A_c - 3A_h} \tag{8}$$

For 1,2-propanediol−PDLLA, we determined the area of the methyl protons of the initiator residue and used eq 7. For poly(ϵ-caprolactone) polymers (experiments 10−11) we compared the area of the methyl protons of the BHMBA resides to the methylene protons, H_i, of the ultimate caprolactoyl units (about 3.6 ppm) and used the following equation:

$$\bar{N}_{br} = \frac{4A_a - 3A_i}{3A_i - 2A_a} \tag{9}$$

Values of $\bar{N}_{br}$ for the various polymers are listed in Table 1. These data suggest that minute amounts of branching occurred since the $\bar{N}_{br}$ values are nonzero. Comparison of experiment 1 to experiment 2 or experiment 4 to experiment 5 shows that an increase in catalyst concentration increases $\bar{N}_{br}$ as expected. However, control polymers created from 1,4-butanediol and 1,2-propanediol (experiments 7 and 12, respectively, Table 1), which do not contain a carboxylic acid group and therefore cannot undergo branching via condensation, also yielded nonzero $\bar{N}_{br}$ in approximately the same range as the BHMBA-based polymers (0.032−0.035). This suggests a minor, systematic error in the measurement that is biased toward higher $\bar{N}_{br}$. Most likely this is caused by slight underestimation of H_c; it is possible that the ultimate methyl groups of very short chains (1−3 lactoyl residues) have chemical shifts that are slightly away from the resonance at 1.4 ppm (Figure 7). In any case, the fact that the control polymers, which cannot be branched, yield similar $\bar{N}_{br}$ to BHMBA−PLA, strongly supports our proposition that the latter polymers are predominantly linear.

At higher BHMBA/lactide feed ratios, the likelihood of branching via condensation should increase, and consequently higher $\bar{N}_{br}$ values might be observed. Therefore, we synthesized BHMBA−PDLLA (experiment 3) having a 15/85 molar ratio of BHMBA/lactide. This is one of the intermediate feed ratios used by Gottschalk and Frey[22] and in the absence of condensation reactions, will produce PDLLA with a M_n of ~1000 g/mol, which is the lowest M_n of PDLLA prepolymers that we anticipate using in the formulation of hydrolytically degradable polyurethanes. The $\bar{N}_{br}$ value of this polyester was 0.047 (Table 1), which falls in the same range as the BHMBA−PDLLA polymers produced at lower BHMBA/lactide ratio.

Chain Extension of BHMBA—PDLLA with Diisocyanates. Chain-extended PDLLAs (CE−PDLLA) containing pendent acid groups were synthesized via step growth polymerization by reacting BHMBA−PDLLA prepolymers of various $M_{n,GPC}$ with either LDI or H_{12}MDI (Scheme 1), as outlined in Table 2. For experiments 13−17, the NCO/OH ratio was 1.05 ± 0.02 depending on conversion (refer to Table 2), with the OH equivalent weight of the prepolymer calculated as $M_{n,GPC}/(2p)$. The CE−PDLLA synthesized in experiment 13 was used for characterization purposes, in order to identify formation of urethane linkages and confirm the preservation of acid functionality (Figure 9). The disappearance of the isocyanate peaks and formation of the peaks characteristic of urethane linkages is consistent with the data reported by Wiggins and co-workers.[23] CE−PDLLA polymers (experiments 14 and 15) were synthesized using prepolymers having $M_{n,GPC}$ of 6740 and 14 200 g/mol, resulting in chain-extended molecular weights of 51 100 (MWD = 1.35) and 206 000 (MWD = 1.38), respectively. These chain-extended polymers contain an average of 9 and 17 pendent acid groups along the polymer backbone, respectively. Their synthesis demonstrates the ability to create linear PDLLA polymers of high molecular weight whose potential degradation can be tuned by the presence of a controlled number of pendent carboxylic acid groups. Experiments 14, 15, 16, and 17 will be the focus of future studies and will provide information concerning the effect of the acid functionality, introduced by BHMBA, and the choice of diisocyanate on hydrolytic degradation.

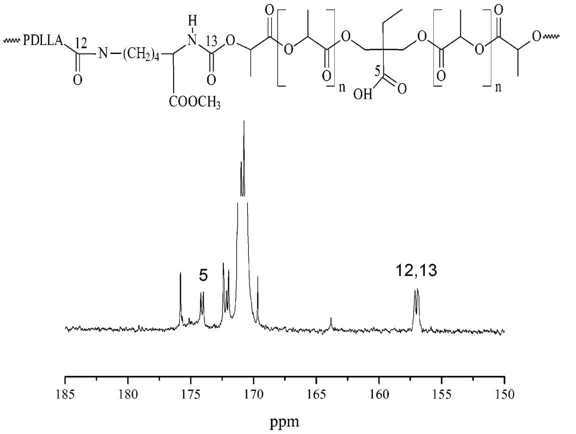


Figure 9. ^{13}C NMR spectrum of CE−BHMBA−PDLLA (experiment 13) showing urethane linkage and acid functionality.

Two series of CE−PDLLA polyesters were synthesized, based on experiments 18 and 19, in which the NCO/OH ratio was varied. Again, OH equivalent weight of the prepolymers was calculated as $M_{n,GPC}/(2p)$. As shown in Table 3, as the NCO/OH ratio increased, the M_n value increased to a maximum and then decreased. The maximum M_n occurred at an NCO/OH ratio of 1.18 for CE-BHMBA−PDLLA (experiment 18) and 1.17 for CE-1,4-butanediol−PDLLA (experiment 19). $M_{n,NMR}$ was 2756 and 2852 g/mol for the prepolymers used in experiments 18 and 19, respectively, and these values were close to $M_{n,theo}$ (2874 and 3106 g/mol) based on the ratio of consumed monomer to initiator. If OH equivalent weight were instead calculated as $M_{n,theo}/(2p)$, the maximum chain extended molecular weight for either series occurred at NCO/OH ≅ 1.02. This is consistent with the well-known tendency for side reactions to reduce the available NCO. Furthermore, this suggests that hydroxyl groups from the initial feed are conserved throughout the polymerization, which is consistent with the other evidence showing that little to no branching occurs during polymerization of DLLA using BHMBA as the initiator. This is further corroborated by the $\bar{N}_{br}$ values for prepolymers of experiments 18 and 19, which were determined to be 0.043 and 0.037, respectively. These experiments also show that optimum chain extension stoichiometry can be simply targeted by setting NCO/OH = 1.02, using $M_{n,theo}/(2p)$ as the OH equivalent weight of the PDLLA. Higher chain extended molecular weights for series 18 are possibly caused by reaction between the pendent acid group and isocyanate during the CE reaction (amide linkage formation)[14] leading to branching and higher molecular weight.

Conclusion

Contrary to a recent literature report,[22] the lactide/BHMBA/stannous octoate polymerization system yields polymers exhibiting a predominantly linear architecture. End group residues and backbone units were defined with great certainty using ^{1}H and ^{13}C NMR spectroscopy. Molecular weight data, in combination with a measure of branching density obtained by ^{1}H NMR end group analysis, provided convincing evidence that branching due to condensation reactions between hydroxyl end groups and the carboxylic acid of BHMBA residues is insignificant under our conditions. An insignificant degree of branching was further confirmed by the absence of resonances in the ^{13}C NMR spectrum representing likely branching structures. Chain-extended BHMBA−PDLLA of high molecular weight (51 100 and 206 000 g/mol) and moderately narrow molecular weight distribution (1.35 and 1.38) containing a controlled number (∼9 and 17) of acid pendant groups per polymer chain were synthesized, providing PDLLA with enhanced and tunable rate of degradation. Additionally, maximum M_n for chain extended PDLLA was obtained at an NCO/OH ratio of 1.02, when the OH equivalent weight of the prepolymer was calculated as $M_{n,theo}/(2p)$. Hydrolytic degradation studies of BHMBA−PLA and chain-extended derivatives will follow in future publications.

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