308 *Macromolecules* **1999,** *32,* 308−314

Versatile Copolymers from [L]-Lactide and [D]-Xylofuranose

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Received June 8, 1998; Revised Manuscript Received October 28, 1998

ABSTRACT: The new monomer 1,2-*o*-isopropylidene-[D]-xylofuranose-3,5-cyclic carbonate (IPXTC) was prepared. The organometallic catalysts AlR_3-H_2O (R = ethyl, isobutyl), $ZnEt_2-H_2O$, and $Sn(Oct)_2$ were evaluated for the copolymerization of [L]-lactide ([L]-LA) with IPXTC. This work showed that $Sn(Oct)_2$ was preferred for the formation of high molecular weight copolymers. For example, a copolymerization ([L]-LA/IPXTC = 83:17 mol/mol) at 120 °C for 6 h gave poly([L]-LA-*co*-7 mol % IPXTC) with an M_n and polydispersity (M_w/M_n) of 78 400 and 1.9, respectively. The comonomer reactivity ratios were 4.15 and 0.255, respectively, for [L]-LA and IPXTC copolymerizations conducted at 120 °C, $M/C = 200$, and $Sn(Oct)_2$ as catalyst. Structural investigations by NMR revealed that [L]-LA/IPXTC copolymers had short average IPXTC repeat unit segment lengths. Increased copolymer IPXTC content resulted in products with lower melting transition temperatures but higher glass transition temperatures. To obtain hydroxyl functionalized P([L]-LA) copolymers, the pendant IPXTC ketal protecting group was removed. The deprotection was performed in CH_2Cl_2 using CF_3COOH/H_2O without substantial molecular weight decrease. Hence, an efficient route has been developed to synthesize high molecular weight PLA-based copolymers that consist of [L]-lactic acid and [D]-xylofuranose repeat units. The [D]-xylofuranose repeat units have vicinal diol groups that will facilitate further functionalization and modification of these copolymers. The “tailorability” of the new copolymers is expected to be of great value for the development of important new bioresorbable medical materials.

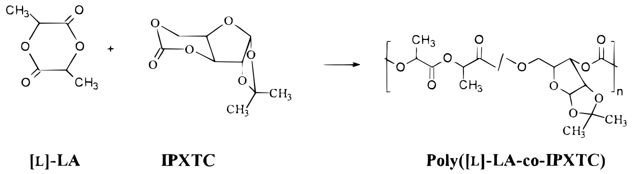
Introduction

Biodegradable materials as implants can gradually transfer load to the healing area and do not require surgical removal. [L]-Polylactide ([L]-PLA), a bioerodable polymer, has been used in surgical applications for many years and has proved to be sterilizable and of low toxicity.[1−3] Although there has been considerable progress toward the development of a family of bioresorbable PLA-based materials, additional work is needed to address current needs for biocompatible/bioresorbable materials that have the ability to provide specific biointeractions with cell types for tissue engineering applications. An important route to such biomaterials will likely involve the preparation of copolymers with various functional groups that permit decoration of polymer chains with bioactive substances.

Bioerodible polymers having reactive pendant groups are of particular interest because they can facilitate covalent prodrug attachment as well as other functionalizations. On derivatization of the pendant functional groups, variations in hydrophilicity, physical properties, and biodegradability can be achieved.[4] Polyesters with pendant carboxyl and amino functional groups such as poly(malic acid)[5−8] and poly([L]-serine ester),[9,10] respectively, are already known. Recently, polydepsipeptides with carboxyl, amino, or thiol groups were reported.[11] Langer and co-workers described the synthesis of an [L]-PLA-based amine functionalized copolymer.[12] Specifically, they prepared poly([L]-lactic acid-*co*-lysine) by copolymerizing [L]-lactide with 3-[N^{ϵ}-(carbonyl-benzoxy)-L-lysyl]-6-L-methyl-2,5-morpholinedione. The latter monomer is a cyclic dimer of [L]-lactic acid and protected [L]-lysine.

Polymers with repeat units containing vicinal diols may impart unique properties to the prepared materials that facilitate a variety of potential applications. For example, linear and cross-linked hydroxyl-containing polyesters can permit the formation of strong hydrogen bonding and nonbonding interactions with organic and inorganic species.[13] Also, hydroxyl-containing aliphatic polycarbonates have been reported to be bioerodible and of importance in medical and pharmaceutical applications.[4] In this paper, we report the preparation of the new monomer 1,2-*o*-isopropylidene-[D]-xylofuranose-3,5-cyclic carbonate (IPXTC). Copolymerizations of [L]-lactide with IPXTC were conducted (Scheme 1). These copolymers, after deprotection of the ketal side groups, gave chains that contain [L]-lactic acid and [D]-xylofuranose repeat units. Such chains are expected to bioerode forming nontoxic natural metabolites. Furthermore, the [D]-xylofuranose comonomers provide a route to decorate PLA-based copolymers with vicinal diol pendant groups. Hence, [L]-LA/IPXTC copolymerizations were investigated using a variety of catalytic systems. Relationships between the catalyst, reaction time, reaction temperature, monomer conversion, copolymer yield, and molecular weight were established Table 1). ^{13}C NMR gave information on the microstructure of the [L]-LA/IPXTC copolymers. Also, the thermal properties of [L]-LA/IPXTC copolymers as well as the products after deprotection were studied.

Scheme 1. Copolymerization of [L]-LA and IPXTC



Experimental Section

Materials. [L]-Lactide from Aldrich was purified by twice recrystallization from anhydrous ethyl acetate under a dry

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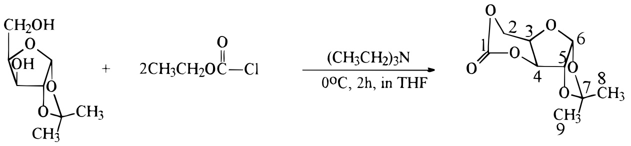
10.1021/ma980895o CCC: $18.00

Table 1. Effect of Catalyst, Reaction Temperature on the IPXTC-[L]-LA Copolymer Yield, Molecular Weight and Composition[a]

entry	catalyst	f_{LA}/f_{IPXTC}[b]	temp (°C)	yield (%)[c]	M_n[d]	M_w/M_n[d]	F_{LA}/F_{IPXTC}[e]
1	$AlEt_3-0.5H_2O$	70/30	120	65	20 900	1.5	87/13
2	$Al^iBu_3-0.5H_2O$	72/28	120	46	20 400	1.2	92/8
3	$Al(O^iPr)_3$	69/31	120	68	20 900	1.5	86/14
4	$Sn(Oct)_2$	82/18	100	75	62 000	2.1	95/5
5	$Sn(Oct)_2$	72/28	100	68	52 400	1.6	93/7
6	$Sn(Oct)_2$	66/34	120	70	44 500	2.0	85/15
7	$Sn(Oct)_2$	71/29	120	71	64 500	1.7	91/9
8	$Sn(Oct)_2$	83/17	120	82	78 400	1.9	93/7
9	$Sn(Oct)_2$	72/28	140	83	32 400	2.0	81/19
10	$Sn(Oct)_2$	82/18	140	83	70 200	2.3	92/8
11	$ZnEt_2-0.5H_2O$	73/27	100	22	29 900	1.8	92/8
12	$ZnEt_2-0.5H_2O$	72/27	120	68	31 900	2.0	88/12
13	$ZnEt_2-0.5H_2O$	71/29	140	68	28 800	1.8	89/11

[a] $M/I = 200$, 6 h. [b] Monomer feed ratio in mol/mol. [c] Methanol-insoluble copolymer (g)/monomer feed (g) × 100%. [d] Number average molecular weight and molecular weight distribution determined by GPC (see Experimental Section). [e] Copolymer molar composition measured by ^1H NMR.

Scheme 2. Synthesis of IPXTC



nitrogen atmosphere (mp 92−94 °C, $[\alpha]^{20}$ °C ($\lambda = 589$ nm) = −285° (c = 1, in toluene)). 1,2-*o*-Isopropylidene-D-xylofuranose was purchased from Aldrich and used as received. Stannous octanoate, $Sn(Oct)_2$, and $Al(O^iPr)_3$ were purchased from Aldrich as a neat liquid and solid, respectively, and were used as received. The organometallic compounds ($AlEt_3$, $Al(^iBu)_3$, $ZnEt_2$) were purchased from Aldrich in toluene solution and were used without further purification. Toluene was dried by distillation from melted sodium. All liquid reagents were transferred by syringe under a dry argon or nitrogen atmosphere.

Monomer Synthesis. IPXTC was prepared by the identical procedure as was used to synthesize 2,2-[2- pentene-1,5-diyl]-trimethylene carbonate (^{c}HTC).[14] Characterization of IPXTC was as follows: mp 143−144 °C; ^1H NMR (see Scheme 2 for labeling): 6.02 ppm (H-6, 1H); 4.90 ppm (H-4, 1H), 4.77 ppm (H-5, 1H), 4.63 ppm (H-3, 1H), 4.56 ppm (H-2, 2H), 1.53/1.37 ppm (H-8,9, 6H); ^{13}C NMR (see Scheme 2 for labeling): 146.61 ppm (C-6), 113.43 ppm (C-7), 105.63 ppm (C-2), 84.11 ppm (C-3), 82.78 ppm (C-4), 69.62 ppm (C-1), 67.14 ppm (C-5), 27.06/26.59 ppm (C-8/9); FTIR (KBr pellet): 1759 cm^{-1}($\nu_{C=O}$).

Preparation of Catalysts. The catalysts AlR_3-H_2O (1:0.5) and $ZnEt_2-H_2O$ (1:0.5) were prepared as described elsewhere.[14−16] Solutions (1 mol/L) of Al $(O^iPr)_3$ and $Sn(Oct)_2$ were prepared in dry toluene.

General Procedure for the Copolymerization. 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 and the catalyst solution were transferred into the ampule using a glovebox to maintain an 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 argon 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 chloroform (8 mL). The chloroform solution was added to methanol (80 mL) to precipitate the polymer, the precipitate was washed with several portions of methanol, and then the volatiles were removed in a vacuum oven (<3 mmHg, 40 °C, 24 h).

Instrumental Methods. FTIR Spectroscopy. A P−E 1720 FTIR spectrometer was used to obtain the spectra after 16 scans (2 cm^{-1} resolution) over the range from 4000 to 400 cm^{-1}. Samples were analyzed as powders by preparing KBr plates.

NMR Spectroscopy. Proton ^1H NMR spectra were recorded on a Bruker ARX-250 spectrometer at 250 MHz or a Bruker DRX-500 spectrometer at 500 MHz. ^1H NMR chemical shifts in parts per million (ppm) are reported downfield from 0.00 ppm using tetramethylsilane (TMS) as an internal reference. The concentration used was 4% w/v in chloroform-*d*. The instrumental parameters were exactly as described elsewhere.[15] Carbon-13 (^{13}C) spectra were recorded at 62.5 MHz on a Bruker ARX-250 spectrometer in 20% w/v chloroform-*d* solutions. The chemical shifts in ppm were referenced relative to the internal standard chloroform-*d* at 77.00 ppm. The acquisition parameters used were described in detail elsewhere.[14]

Molecular Weight Measurements. Number and weight average molecular weights (M_n and M_w, respectively) were determined by gel permeation chromatography (GPC). The experimental details of the method are published elsewhere.[14,15] Polystyrene standards with a low dispersity (Polysciences) were used to generate a calibration curve. Data were recorded and manipulated using the Windows-based Millenium 2.0 software package.

Thermal Analysis. Differential scanning calorimetry (DSC) studies were conducted on a DuPont DSC 912 equipped with a TA 2000 data station. Results of the peak melting temperature (T_m) and the associated enthalpy of fusion (ΔH_f) were reported from data recorded: (i) during the first heating scan using methanol-precipitated samples; (ii) after samples were cooled from the melt to room temperature and annealed at 90 °C for 16 h. Glass transition temperature (T_g) measurements were recorded after the samples were first heated at 10 °C/min to 200 °C, rapidly quenched with liquid nitrogen to −60 °C and then heated once again at 10 °C/min from room temperature to 200 °C. The T_g results from the second of these two scans were taken from the midpoint of the transition.

Ketal Deprotection. Copolymer (0.1 g) was dissolved in 0.8 mL of CH_2Cl_2. To this solution was added either 0.8 mL CF_3COOH/0.16 mL distilled H_2O or 0.3 mL BCl_3 (1 M in CH_2Cl_2). After the solution was stirred at room temperature for a predetermined time, the resulting polymeric product was precipitated from solution by the addition of methanol (~80 mL). The polymer was separated by filtration and dried in a vacuum to constant weight (70−80 mg).

Results and Discussion

The monomer IPXTC was synthesized in 41% yield by a one-pot reaction in tetrahydrofuran (THF) at 0 °C starting from 1,2-*o*-isopropylidene-[D]-xylofuranose (see Scheme 2). Compared to the yields (>80%) of ^{c}HTC[14] and 2,4,8,10-tetraoxaspiro[5,5]undecane-3-one (DOXTC)[17] which were both synthesized from their corresponding diols, the yield of IPXTC was relatively lower. This may be explained by the following: (i) the equilibrium of five- and six-membered ring monosaccharides where the latter does not form the desired cyclic carbonate monomer, and (ii) although ^{c}HTC and DOX-TC are formed by the reaction of two primary hydroxy groups, IPXTC synthesis involves the reaction of a relatively lower reactivity secondary 1,2-*o*-isopropylidene-[D]-xylofuranose hydroxyl functionality (see Scheme 2). The structure and purity of IPXTC were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR, and melting point analysis (see Experimental Section and Supporting Information).

[L]-LA/IPXTC Copolymerization. The preferred route for preparation of high molecular weight [L]-PLA is the bulk polymerization of [L]-LA in the presence of a suitable catalyst. Organometallic compounds of zinc and tin such as $ZnEt_2$,[18] stannous oxide,[19] stannous octoate ($Sn(Oct)_2$),[2a] and tetraphenyl tin[20] are all known to be useful for in-bulk [L]-LA polymerization. Al-based catalysts were found to be effective for cyclic carbonate homo- and copolymerizations.[14,17] Therefore, $Sn(Oct)_2$, $AlR_3{-}H_2O$ (R = ethyl and isobutyl), $Al(O^iPr)_3$, and $ZnEt_2{-}H_2O$ were evaluated as catalysts for [L]-LA/IPXTC copolymerizations. GPC traces showed that the copolymers prepared by these catalysts had unimodal distributions and the polydispersities (M_w/M_n) were in the range of 1.2−2.3. Also, regardless of the catalyst used, the incorporation of IPXTC in the copolymer was less than that used in the monomer feed. This result suggests that the reactivity of [L]-LA is substantially greater than that of IPXTC. Monomer composition was routinely determined by ^{1}H NMR analyses. Comparison of entries 1−3 all conducted at 120 °C showed that the polymerizations with the Al-based catalysts resulted in products of moderate molecular weight (~21 000) and a maximum yield of 68% (entry 3). Polymerizations using $ZnEt_2{-}0.5H_2O$ (entries 11−13) resulted in slightly increased molecular weight (up to 31 900) and yields up to 68% (entries 12 and 13). In contrast, polymerizations catalyzed by $Sn(Oct)_2$ at 120 °C resulted in substantially improved percent-yields and product molecular weights (entries 6−8). Indeed, entry 8 conducted using a monomer feed molar ratio (f_{LA}/f_{IPXTC}) of 83:17 gave a copolymer of M_n 78 400 that had a molar composition (F_{LA}/F_{IPXTC}) of 93:7. Increase in the polymerization temperature from 120 to 140 °C for $Sn(Oct)_2$-catalyzed copolymerizations resulted in decreased M_n but increased IPXTC incorporation in the copolymer (see entries 7 and 9). Hence, on the basis of copolymer yield and molecular weight, the $Sn(Oct)_2$ catalyst at 120 °C was chosen for further investigations of [L]-LA/IPXTC copolymerizations. Note that for ^{c}HTC/[L]-LA copolymerizations, the same conclusion was reached after evaluation of a similar series of organometallic catalysts.[16] This was generally anticipated on the basis of [L]-LA homopolymerization results and considering the low levels of IPXTC and ^{c}HTC that were generally used for the copolymerizations.

Table 2 lists the results of $Sn(Oct)_2$-catalyzed [L]-LA/IPXTC copolymerizations where f_{LA}/f_{IPXTC} was varied. Increasing the IPXTC content in the monomer feed resulted in decreased copolymer percent-yield and M_n values. However, by decreasing f_{LA}/f_{IPXTC} from 83/17 to 36/84, the IPXTC molar content in the copolymers increased from 7 to 39 mol % (see entries 8 and 16). Further increase in the IPXTC monomer feed content from 64 to 84 mol % resulted in only a 6% copolymer yield (entry 17). All of the polymers obtained are white solids including entry 16 even though its molecular weight is relatively low. The homopolymer of IPXTC was not obtained by using $Sn(Oct)_2$ as the catalyst at 120 °C. As was mentioned above, the lower reactivity of IPXTC resulted in consistently lower values of IPXTC in the copolymer relative to that provided in the monomer feed. The monomer reactivity ratios determined by the method of Fineman and Ross[21] were 4.15 and 0.255 for [L]-LA and IPXTC, respectively, using $Sn(Oct)_2$ as the catalyst at 120 °C and $M/C = 200$.

Table 2. Synthesis of IPXTC-[L]-LA Copolymer with Variable Compositions[a]

entry	f_{LA}/f_{IPXTC}[d]	yield (%)[d]	M_n[d]	M_w/M_n[d]	F_{LA}/F_{IPXTC}[d]
14	100/0	99	86 000	2.1	100/0
8	83/17	82	78 400	1.9	93/7
7	71/29	71	64 500	1.7	91/9
6	66/34	70	44 500	2.0	85/15
15	52/48	54	27 900	1.6	79/21
16[b]	36/64	48	13 900	1.7	61/39
17[b,c]	16/84	6	n/d[e]	n/d[e]	n/d[e]

[a] 120 °C, $Sn(Oct)_2$ as catalyst, $M/I = 200$, reaction time: 6 h or [b]24 h. [c] 0.5 1,4-dioxane mL/g IPXTC added as solvent. [d] See Table 1 footnotes. [e] Not determined.

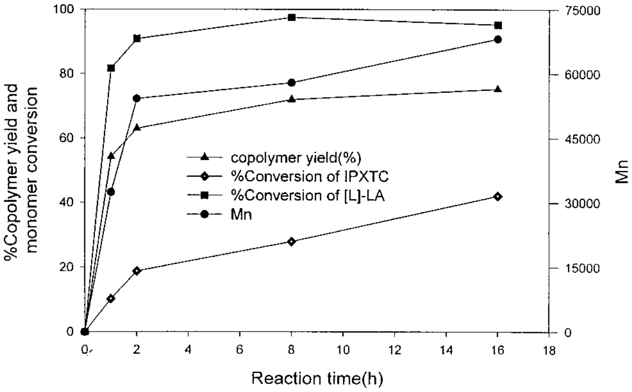


Figure 1. Copolymer yield, M_n, monomer conversion vs reaction time. Reaction conditions: $Sn(Oct)_2$ as catalyst, 120 °C, $M/C = 200$, monomer feed ratio $f_{LA}/f_{IPXTC} = 71/29$ mol/mol.

Plots of copolymer yield, M_n, and monomer conversion versus reaction time are displayed in Figure 1. The $Sn(Oct)_2$-catalyzed polymerization under study was carried out at 120 °C, $M/C = 200$ and f_{LA}/f_{IPXTC} 71/29. The copolymer yield and M_n increased rapidly to 63% and 54 200, respectively, by 2 h. Further increases in copolymer yield and M_n with increased reaction time (2−16 h) occurred gradually. Hence, by 16 h, the copolymer yield and M_n were 75% and 68 200, respectively. The conversion of [L]-LA by 8 h was almost quantitative. In contrast, IPXTC percent-conversion increased slowly to 42% by 16 h. If intermolecular exchange reactions and insertion of the IPXTC monomer into the polymer chains does not occur, a blocklike copolymer would be expected on the basis of the monomer consumption data and the monomer reactivity ratios. Investigations of the copolymer microstructure are described below.

Structural Characterization. ^{1}H and ^{13}C NMR were used to characterize the [L]-LA/IPXTC copolymers. Figure 2 displays the ^{1}H NMR spectrum of poly([L]-LA-*co*-15 mol % IPXTC) synthesized by $Sn(Oct)_2$ at 120 °C (entry 6, Table 1). Comparisons to previously published spectra of [L]-PLA homopolymer[22] showed that the signals at 5.21 and 1.62 ppm are due to [L]-LA repeat unit CH and CH_3 protons, respectively. Signals at 1.33

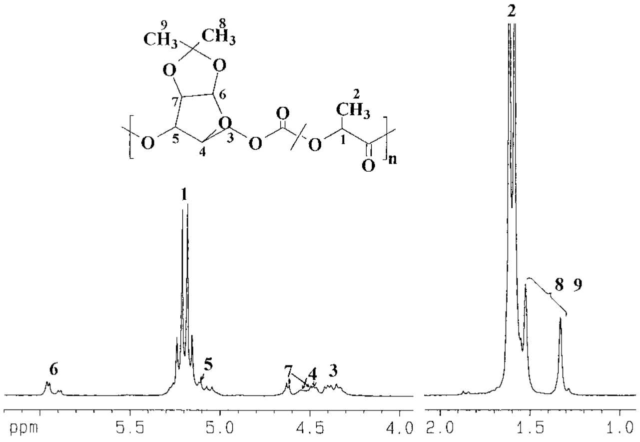


Figure 2. ^{1}H NMR of poly([L]-LA-*co*-15 mol % IPXTC) prepared by Sn(Oct)$_2$ at 120 °C (entry 6, Table 1).

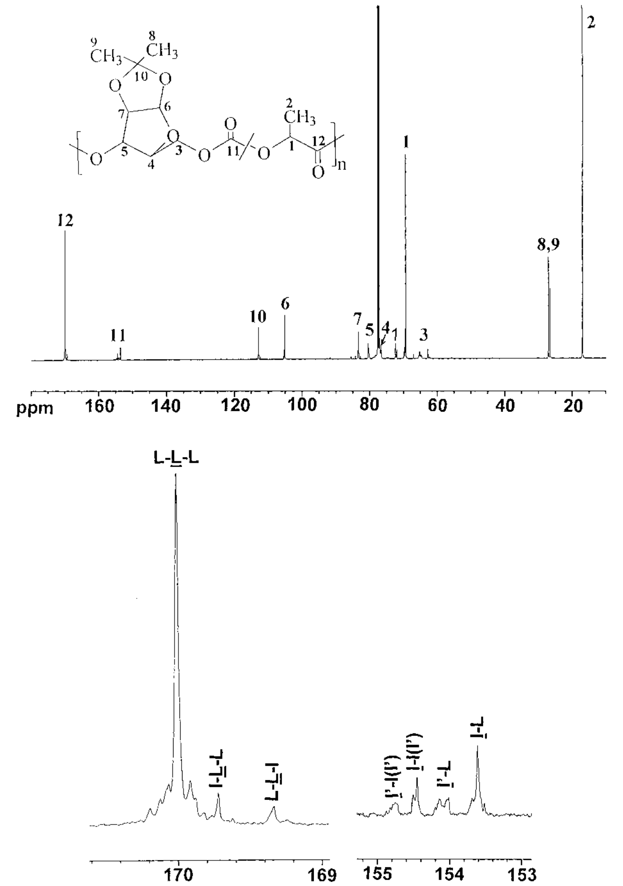


Figure 3. ^{13}C NMR of poly([L]-LA-*co*-39 mol % IPXTC) prepared by Sn(Oct)$_2$ at 120 °C (entry 16, Table 2); (a) full spectrum, (b) expansions of carbonyl region.

and 1.53 ppm were assigned to H8/H9 on the basis of the ^{1}H NMR spectra of copolymers with different compositions and a ^{1}H−^{13}C correlated 2D spectrum (Supporting Information; cross-peaks: ^{1}H-1.53/^{13}C-26.72 ppm, ^{1}H-1.33/^{13}C-26.30 ppm). Other assignments were based on observed correlations in the corresponding ^{1}H−^{1}H correlation spectroscopy (COSY) NMR spectrum (Supporting Information). Correlations of 5.96 with 4.63, 5.12 with 4.48, and 4.48 with 4.37 ppm were used to assign signals resulting from protons 3, 4, 5, 6, and 7. Because a cross-peak was observed between 5.06 and 1.60 ppm, the former was assigned to CH of [L]-LA units in IPXTC-[L]-LA sequences. Additional correlations of 5.89 with 4.48 and 4.55 with 4.37 showed that signals at both 4.63 and 4.48 are due to H7 protons and signals at both 4.48 and 4.55 are due to H4 protons. Hence, signals were not resolved for the protons of H7/H4 as well as H1/H5. Structural complexity in the ^{1}H NMR spectrum of Figure 2 may be due to diad sequence effects as well as to the directionality of IPXTC repeat units. The conclusion of the analyses above was that, at the current level of signal resolution and peak assignments, we cannot obtain quantitative data for repeat unit sequence distribution from ^{1}H NMR spectra.

The ^{13}C NMR full spectrum of poly([L]-LA-*co*-15 mol-% IPXTC) (entry 6, Table 1) is displayed in Figure 3a. Assignments of the major resonances (see Figure 3a) were based on (i) the spectrum of the homopolymer [L]-PLA[22] and (ii) a ^{1}H−^{13}C correlated 2D NMR (HETCOR) spectrum (Supporting Information). The HETCOR spectrum gave cross-peaks between 5.96-^{1}H/104.94-^{13}C, 5.21-^{1}H/69.29-^{13}C, 5.12-^{1}H/80.18-^{13}C, 4.63-^{1}H/83.17-^{13}C, 4.48-^{1}H/77.06 and 76.75-^{13}C, 4.37-^{1}H/65.24 and 62.83-^{13}C, 1.62-^{1}H/16.67-^{13}C, 1.53-^{1}H/26.72-^{13}C, and 1.33 ppm-^{1}H/26.30 ppm-^{13}C. Hence, the ^{13}C NMR signals at 104.94, 83.17, 80.18, 77.06/76.75, 69.29, 65.24/62.83, 26.72/26.30, and 16.67 ppm were assigned to C6, C7, C5, C4, C1, C3, C8,9, and C2, respectively. The ^{13}C NMR signals at 72.42/72.04 have cross-peaks with the ^{1}H NMR signals at 5.06 ppm so that the former were assigned to C-1 in [L]-LA-IPXTC linkages. Expansion of signals in the carbonyl regions of the spectrum shows considerable complexity (Figure 3b). On the basis of comparison to the homopolymer [L]-PLA,[22] the intense signal at 170.00 ppm was assigned to L*L*L sequences (L = lactyl unit with directionality −O−CH(CH$_3$)−CO−). The neighboring signals which appear as shoulders of the 170.00 ppm resonance are likely due to sequence effects beyond triads. For example, these peaks may arise because of IL*L*L and L*L*LI sequences (I=IPXTC units). Interestingly, because IPXTC may ring-open such that the product formed has a primary or secondary hydroxyl terminal group, differences in IPXTC directionality along the chain may result in additional resolved signals and spectrum complexity. For the purposes of this paper, we will define the directionality of I and I′ as −O−CX′CX″CH$_2$−O−CO− and −O−CH$_2$-CX″CX′−O−CO−, respectively. The signals at 168.15 and 169.80 ppm were tentatively assigned to L*L*I(I′) and I(I′)*L*L, respectively. The carbonyl carbons of IPXTC units showed four sets of complex multiplets centered at 153.62, 154.12, 154.46, and 154.74 ppm. Increases in the IPXTC content of copolymers resulted in signals of increased intensity at 154.46 and 154.74. In addition, calculation of peak positions using ACD/CNMR software (Version 1.0 for Microsoft Windows, Bruker Inc.) for *I*-I or *I*′-I′ showed that they were downfield relative to *I*-L or *I*′-L. For the low IPXTC content copolymers, only two peaks at 153.62 and 154.46 ppm were observed. On the basis of relative intensity, the signals at 153.62 and 154.46 ppm were assigned as *I*-L and *I*-I(I′), respectively. This assignment is in agreement with the relative chemical shift position of diads *H*-H and *H*-L in [L]-LA-^{c}HTC copolymer.[16] The remaining two peaks at 154.12 and 154.74 ppm, which were observed in ^{13}C NMR spectra of high IPXTC copolymers, were assigned as *I*′-L and *I*′-I(I′), respectively, on the basis of (i) the relative intensity of peak 154.12−154.74 ppm is equal to that of 153.62−154.46; and (ii) the calculated position of *I*′-X{X = L or I(I′)} was downfield relative to *I*-X. Therefore, the average length of IPXTC chain segments

Table 3. Average Length of IPXTC Repeat Units of Selected Copolymers

entry	catalyst, t (h), f_{LA}/f_{IPXTC}[a]	F_{LA}/F_{IPXTC}	L_{IPXTC} (exptl)[b]	L_{IPXTC} (calcd)[c]	R[d]
2	$Al^{i}Bu_3$−$0.5H_2O$, 6 h, 72/28	92/8	1.30	1.04	0.80
3	$Al(O^{i}Pr)_3$, 6 h, 69/31	86/14	1.35	1.08	0.80
6	$Sn(Oct)_2$, 6 h, 66/34	85/15	1.62	1.09	0.67
15	$Sn(Oct)_2$, 6 h, 52/48	79/21	1.47	1.13	0.77
18	$Sn(Oct)_2$, 16 h, 71/29	85/15	1.31	1.09	0.83

[a] Other reaction conditions: $M/C = 200$, 120 °C. [b] Average IPXTC repeat unit length determined by eq 1 (see text). [c] $L_{IPXTC} = 1/(1-q)$, where q represents the molar percentage of IPXTC based on lactyl and IPXTC units in the copolymer.[23,25] [d] Calculated by L_{IPXTC} (calcd)/L_{IPXTC} (exptl).

(L_{IPXTC}) was calculated by eq 1:

$$L_{IPXTC} = (I_{154.46\ ppm} + I_{154.74\ ppm})/(I_{153.62\ ppm} + I_{154.12\ ppm}) + 1 \quad (1)$$

The calculated IPXTC repeat unit lengths (1.30−1.62) are given in Table 3. Such short IPXTC segment lengths were not expected on the basis of the plot of comonomer consumption versus reaction time (Figure 1) and the monomer reactivity ratios. Furthermore, these results are not explained by propagation that takes place exclusively from the chain end without subsequent inter- or intramolecular exchange reactions. It may be that (i) IPXTC polymerization occurs by intrachain insertion reactions or intermolecular exchange reactions, and (ii) transfer reactions occur primarily at higher conversion. However, there exist in the reaction mixture many functional groups including hydroxyl, carboxyl, esters, carbonates, and alkoxides. In addition, crystallization during polymerization may effect the polymerization.[23,24] Hence, all of these factors present a complicated situation that may not be explained or described simply.

The copolymer randomness was further evaluated by determination of theoretical L_{IPXTC} and the coefficient R (see footnotes, Table 3), where R is 0 for a diblock copolymer and 1 for a statistically random distribution of IPXTC and lactyl units.[25] Comparison of entry 6 and 18 showed that for $Sn(Oct)_2$-catalyzed copolymerizations, increasing of reaction time resulted in greater R values approaching 1. Furthermore, the Al-based catalysts used for entries 2 and 3 gave relatively high (0.80) R values. Therefore, the comonomer sequence distribution was varied more or less toward random by variation in the catalyst and reaction time.

Thermal Properties. Figure 4a shows the first heating DSC scans of [L]-LA/IPXTC copolymers (methanol precipitated) with variable compositions (0, 7, 15, 21, and 39 mol % IPXTC) prepared by $Sn(Oct)_2$ at 120 °C. Two melting transitions at 101 °C ($\Delta H_f = 13.3$ J/g) and 137 °C ($\Delta H_f = 15.8$ J/g) were observed for P([L]-LA-*co*-15 mol % IPXTC) (entry 6, Table 2) which can be explained by the presence of different populations of [L]-LA chain segments having shorter and longer block lengths that phase separate to form lower and higher melting PLA crystalline phases. Decrease of the IPXTC content to 7 mol % (Table 1, entry 8) gave a copolymer with T_m and ΔH_f values of 154 °C and 37 J/g respectively (see Figure 4a). Recently, we reported similar melting behavior for polymers that were prepared by the copolymerization of [L]-LA with the cyclic carbonate 2,2-[2-pentene-1,5-diyl]trimethylene carbonate.[16] The transition peaks observed in curves 4 and 5 likely correspond to physical aging because these transitions are close in temperature to the glass transition (T_g).

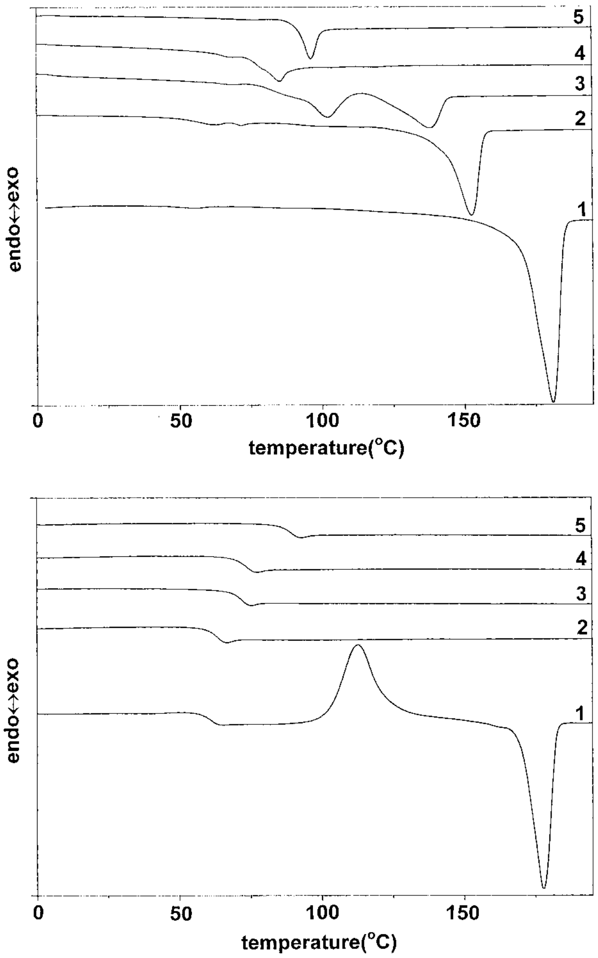


Figure 4. First heating (a) and second heating (b) DSC thermograms of copolymers with variable comonomer composition. Molar percentage of IPXTC (F_{IPXTC}): (1) 0; (2) 7; (3) 15; (4) 21; (5) 39.

Changes in T_g as a function of the copolymer composition are shown in DSC second heating scans which were recorded after the samples were heated above the melt temperature and rapidly quenched in liquid nitrogen (see Figure 4b). In all cases, only one T_g was observed which increased with the copolymer IPXTC content. Specifically, the T_g values for copolymers with 0, 7, 15, 21, and 39 mol % IPXTC were 60, 63, 71, 73, and 89 °C, respectively. A graph of $1/T_g$ (K) vs the weight composition of the copolymers (Supporting Information) showed an almost linear relationship, which was consistent with a copolymer that tends toward a random distribution as opposed to a diblock or multiblock copolymer. The latter would have two separate T_g values for immiscible poly(IPXTC) and [L]-PLA chain segments. Note that thermograms 2−5 in Figure 4b did not show melting transitions. Hence, crystallization of the copolymers from the melt was not rapid. However, when these same

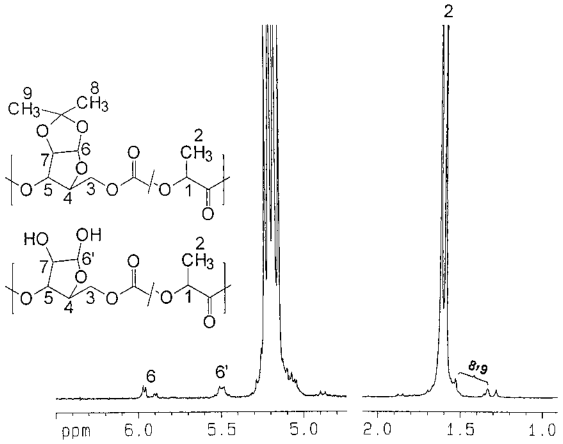


Figure 5. ^{1}H NMR spectrum of deprotected copolymer (entry 2, Table 4). See Figure 2 for the assignments of other signals.

Table 4. Deprotection of Poly([L]-LA-*co*-8% IPXTC)[a]

entry	catalyst	reaction time (min)	$M_n(M_w/M_n)^b$	mol % remaining ketal
DP-1	CF_3COOH/H_2O	5	47 400(2.4)	58
DP-2	CF_3COOH/H_2O	10	64 700(2.2)	38
DP-3	CF_3COOH/H_2O	15	33 200(3.0)	14
DP-4	CF_3COOH/H_2O	20	n/a[c]	0
DP-5	BCl_3	4	9740(1.9)	30

[a] Starting copolymer with $M_n = 70\ 200$, $M_w/M_n = 2.3$. [b] GPC results. [c] Poor solubility in $CHCl_3$ did not permit GPC determination.

samples were annealed at 90 °C for 19 h, the heating scans recorded after annealing (not shown) were similar to those shown in Figure 4a for the methanol-precipitated samples. Hence, the introduction of controlled quantities of IPXTC repeat units along [L]-PLA chains was useful as a method to regulate T_g, T_m, and the crystallinity of [L]-PLA-based materials.

Deprotection. Work was undertaken to remove the ketal protecting groups of poly([L]-LA-*co*-8 mol % IPXTC) ($M_n = 70200$, $M_w/M_n = 2.3$) so that the corresponding vicinal-diols could be formed. Reactions were conducted using either CF_3COOH/H_2O or BCl_3 in CH_2Cl_2 at room temperature. ^{1}H NMR was used to determine the mol % of ketal groups that were converted to vicinal-doils (see Figure 5). Particularly noteworthy was the decrease in intensity of the CH_3 protons corresponding to the ketal groups relative to [L]-LA signals with increased deprotection. Also, the signal at 5.96 ppm because of H6 protons of IPXTC repeat units was shifted upfield to 5.50 ppm by deprotection. The relative integration values of 5.96–5.50 ppm were calculated, the mol % of ketal groups deprotected was determined, and the results obtained are summarized in Table 4. For the series of reactions catalyzed by CF_3COOH/H_2O, the mol % of ketal groups removed increased from 42 to 100 mol % by increasing the reaction time from 5 to 20 min. However, increasing the reaction time from 10 to 15 min resulted in a large decrease in the apparent molecular weight of the product. Entry DP-4 (Table 4) showed poor solubility in chloroform after the deprotection reaction was conducted for 20 min, which may be due to altered product solubility characteristics and/or cross-linking reactions. Cross-linking reactions of ketal-protected vicinal-diols have been reported under acidic conditions. Indeed, the apparent increase in molecular weight of DP-2 relative to DP-1 may be due to cross-linking reactions that occur at low levels or to hydrogen bonding that occurs between chains. Hence, the use of CF_3COOH/H_2O as the catalyst for deprotection was effective to obtain a partially deprotected product of high molecular weight by using reaction times ≤10 min. The use of BCl_3 as the catalyst for only 4 min resulted in extensive chain cleavage but 70 mol % deprotection.

The vicinal-diol groups in the copolymer provide a variety of opportunities for their use in the development of functional biomedical materials. For example, the hydroxyl groups can be used to attach bioactive molecules for biomedical applications. Alternatively, a wide array of important chain segments may be grafted to the main chain by techniques such as ring-opening reactions. Also, the existence of the hydroxyl groups is expected to enhance the hydrolytic degradability of the polymer via the nucleophilic attack at ester or carbonate functions.[4]

Conclusion

In this paper, we first synthesized and used the ketal-protected saccharide containing six-member cyclic carbonate as comonomer to copolymerize with [L]-lactide. High copolymer yield and high molecular weight copolymers were prepared by using $Sn(Oct)_2$ as catalyst. Even though the monomer reactivity ratio of [L]-LA- (4.15) is much greater than that of IPXTC (0.255), very short IPXTC segment lengths were formed. This may be explained by intramolecular exchange reactions or IPXTC insertion reaction during propagation, or by other more complex phenomena.[24,25] The thermal property can be regulated by varying the copolymer compositions. Subsequent deprotection of the ketal structure in the copolymer was successfully carried out in CH_2Cl_2 at room temperature by using CF_3COOH as catalyst. Therefore, this paper provided an important and new route to synthesize high molecular weight polyesters with pendant di-hydroxyl groups which will provide a functional handle to attach bioactive molecules and to prepare graft copolymers.

Acknowledgment. We are grateful for the financial support of this work by the National Science Foundation Biodegradable Polymer Research Center (NSF-BPRC).

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of IPXTC monomer; ^{1}H-^{13}C correlated 2D NMR spectrum (HETCOR) of poly([L]-LA-*co*-39 mol % IPXTC) prepared by $Sn(Oct)_2$ at 120 °C (entry 16, Table 2); ^{1}H-^{1}H correlated 2D NMR spectrum (COSY45) of poly([L]-LA-*co*-15 mol % IPXTC) prepared by $Sn(Oct)_2$ at 120 °C (entry 6, Table 1); $1/T_g$(K) vs the weight composition of the copolymers (4 pages). See any current masthead page for ordering information and Web access instructions.

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MA980895O