Functionalized Polylactides: Preparation and Characterization of [L]-Lactide-*co*-Pentofuranose

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ABSTRACT: The new monomer 1,2-*O*-isopropylidene-3-benzyloxy-pentofuranose-4,4′-cyclic carbonate (IPPTC) was prepared. IPPTC has both a ketal-protected diol and a benzyl ether-protected hydroxyl. Thus, these two sets of hydroxyl groups can be independently deprotected to give IPPTC repeat units with one, two, or three free hydroxyl groups. Stannous octanoate at 130 °C was used for the copolymerization of [L]-LA with IPPTC. When f_{LA}/f_{IPPTC} was 91/9, the percent yield, M_n, and percent incorporation of IPPTC units were 78%, 77 800 g/mol, and 4 mol %, respectively. By the method of Fineman and Ross, the [L]-LA and IPPTC comonomer reactivity ratios were 8.6 and 0.51, respectively. Relative to poly([L]-LA), incorporation of IPPTC units into [L]-LA/IPPTC copolymers gave products that are lower melting (112 °C, 14 mol % IPPTC) and have higher thermal stabilities and higher glass transition temperatures (69 °C, 100 mol % IPPTC). The liberation of hydroxyl pendant groups by the selective removal of the benzyl ether, the ketal groups, or both was possible without substantial loss in the product molecular weight. The removal of the protecting groups of poly([L]-LA-*co*-4.0 mol % IPPTC) did not change the T_m value (160 °C) but did alter the copolymer crystallization kinetics and thermal stability.

Introduction

Functional polymers are attractive materials not only for basic research but also for various industrial applications. The availability of strategically placed functional groups facilitates covalent prodrug attachment as well as other functionalizations. By derivatization of the pendant functional groups, variations in hydrophilicity, physical properties, and biodegradability can be achieved.

Materials based on [L]-poly(lactic acid) ([L]-PLA) have gained wide acceptability for applications that require bioresorption in vivo.[1−4] The degradation rate of [L]-PLA-based polymeric materials is a function of the amorphous/crystalline and hydrophilic/hydrophobic properties. Strategies to regulate these factors have involved copolymerizations of [L]-LA with [D]-LA,[5] glycolide,[6] ethylene oxide,[7−10] ϵ-caprolactone (CL),[11] and monomers that, upon ring-opening, provide amino acid repeat units.[12−14] Also, many workers have attempted to "tailor" PLA physicomechanical properties and hydrolytic degradability by blending PLA with other polymers.[15]

Polyesters with pendant carboxylic and amino functional groups, such as poly(malic acid)[16−19] and poly([L]-serine ester),[20,21] respectively, are known. Polydepsipeptides with carboxylic, amino, or thiol groups have also been reported.[22] The functionalization of polymer chains to facilitate the attachment of various bioactive substances is important in tissue engineering applications.[13,20,21,23−25] For example, a copolymer of poly(lactic acid-*co*-lysine) with RGD (arginine-glycine-aspartic acid tripeptide) attached to the lysine residues at a surface concentration of 310 fmol/cm^2 was prepared to promote cell adhesion.[13] A problem encountered was that the molecular weight of poly(lactic acid-*co*-lysine) decreased significantly relative to that obtained by [L]-LA homopolymerization, even when low 3-[*N*-(carbonyl-benzoxy)-L-lysyl]-6-L-methyl-2,5-morpholinedione comonomer feed ratios were used. This has restricted the use of these copolymers to, for example, bioerodible coatings.

A number of aliphatic polycarbonates or their copolymers were reported to be degradable. Examples cited in the literature include poly(ethylene carbonate)[26,27] and poly(trimethylene carbonate) (TMC).[28,29] Other degradable carbonate-containing copolymers include TMC/LA,[30−32] TMC/CL,[28] and TMC or 2,2-dimethyltrimethylene carbonate/β-butyrolactone.[33]

Tian et al.[34] prepared copolymers of 1,4,8-trioxaspiro-[4,6]-9-undecanone (or 5-ethylene ketal-caprolactone) and then removed the ketal protecting groups to give hydroxyl side chains. Vandenberg and Tian[35] prepared a cyclic carbonate monomer from 2,2-dimethyl-5,5-bis-(hydroxymethyl)-1,3-dioxane. These workers used diethylzinc to polymerize this monomer to a high-molecular-weight polymer. Deprotection led to a water-insoluble but water-swollen product.

Our laboratory has explored the introduction of functional entities into homo- and copolymers that are linked by carbonate or ester/carbonate bonds.[10,36−38] High-molecular-weight polycarbonates bearing vinyl pendant groups were prepared by the homopolymerization of 4,4-cyclohexene-1,3-trimethylene carbonate.[36] The vinyl pendant groups were partially or completely converted into epoxides by oxidation with chloroperoxybenzoic acid.[36] Recently, we prepared the cyclic carbonate monomer 1,2-*O*-isopropylidene-D-xylofuranose-3,5-cyclic carbonate (IPXTC) from a natural sugar. This monomer was successfully homopolymerized as well as copolymerized with [L]-LA[38,39] and TMC.[40] The ketal groups were hydrolyzed to give copolymers of lactic acid and xylofuranose that have hydroxyl side groups. The homopolymerization of IPXTC catalyzed by Y(O^{i}Pr)$_3$ gave a carbohydrate-based polymer (M_n 13 200 g/mol) with carbonate main-chain linkages.

This paper describes the preparation of [L]-LA copolymers with extraordinary control of both the quantity and the proximity of hydroxyl groups that can be made

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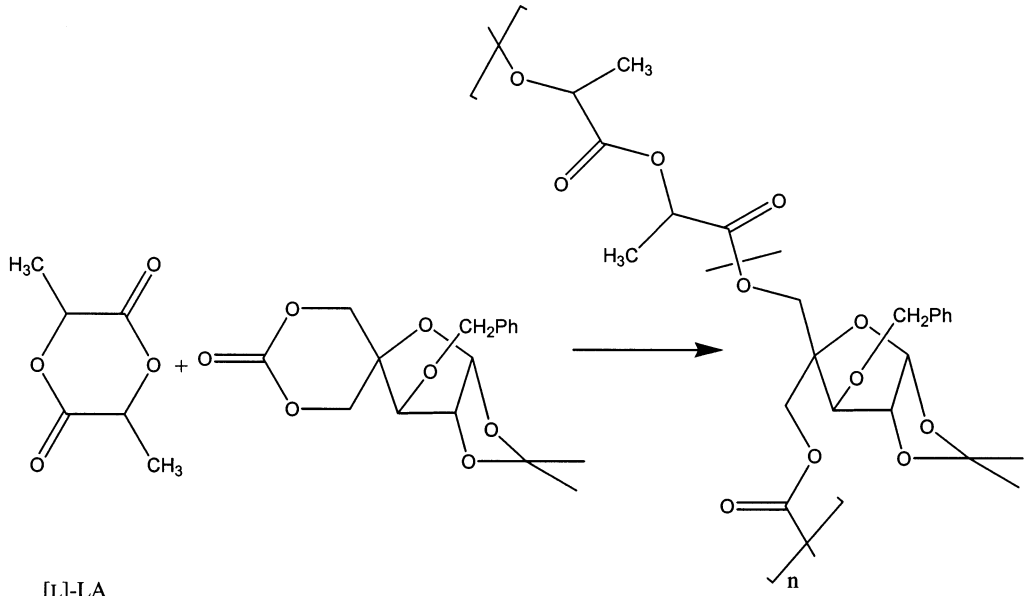
Scheme 1. Copolymerization of [l]-LA and IPPTC



available along chains. To this end, the new monomer 1,2-*O*-isopropylidene-3-benzyloxy-pentofuranose-4-cyclic carbonate (IPPTC) was prepared from glucose. Copolymerization of [L]-lactide with IPPTC was studied using $Sn(Oct)_2$ (Scheme 1). Basic relationships between the reaction time, reaction temperature, monomer conversion, copolymer yield, and molecular weights were established. Deprotection of the ketal and benzyl ether side groups gave chains that contain [L]-lactic acid and pentofuranose repeat units. Such chains are expected to resorb, forming nontoxic natural metabolites. The IPPTC comonomers allow the functionalizations of PLA-based copolymers with monohydroxy, vicinal diol, or both of these pendant groups. Also, the system was designed so that, by the sequential removal of the ketal and then the benzyl ether protecting groups, different bioactive groups can be placed with control of their special proximity within repeat units.

Experimental Section

Materials. [L]-Lactide (LLA), procured from Aldrich Cemical Co., was purified by repeated recrystallization from anhydrous ethyl acetate under a dry nitrogen atmosphere to yield purified LLA (mp 93−95 °C). Stannous octanoate [$Sn(Oct)_2$] was also purchased from Aldrich Chemical Co. as a neat liquid and used as received. Toluene and tetrahydrofuran (THF) were dried by distillation over sodium metal. 4-*C*-Hydroxymethyl-1,2-*O*-(1-methylethylidene)-3-*O*-(phenylmethyl)-α-D-pentofuranose was prepared and purified according to a literature procedure.[41] All other reagents and chemicals were purchased from Aldrich Chemical Co. and used as received. All liquid reagents were transferred by syringe under dry argon or nitrogen atmosphere.

Monomer Synthesis. *Preparation of Cyclic Carbonate of 4-C-Hydroxymethyl-1,2-O−(1-methylethylidene)-3-O-(phenylmethyl)-α-D-pentofuranose.* This compound was prepared by a procedure similar to that published for 1,2-*O*-isopropylidene-[D]-xylofuranose-3,5-cyclic carbonate (IPXTC).[38] In summary, triethylamine (3.42 g, 0.034 mol) was added dropwise to a mixture of 4-*C*-hydroxymethyl-1,2-*O*-(1-methylethylidene)-3-*O*-(phenylmethyl)-α-D-pentofuranose (5.0 g, 0.016 mol) and ethyl chloroformate (3.68 g, 0.034 mol) dissolved in THF (50 mL) at 0 °C over 30 min. The reaction mixture was stirred for 2 h at room temperature and monitored by thin layer chromatorgraphy (TLC; ethyl acetate/petroleum ether, 1:4). After completion, the precipitated triethylamine hydrochloride was removed by filtration, and the filtrate was concentrated under reduced pressure and the residue recrystallized from THF and diethyl ether.

Yield 65.0% (3.5 g); mp145−146 °C; ^{1}H NMR δ 7.20−7.30 (m, 5H, Ph), 6.0 (d, 1H, H-7), 4.71 (d, 1H, OC$\underline{H}_a$Ph), 4.69 (d, 1H, H-6), 4.50 (d, 1H, OC$\underline{H}_b$Ph), 4.46 (d, 1H, $\overline{H}$-2$_a$), 4.43 (dd, 1H, H-4$_a$), 4.37 (d, 1H, H-$\overline{2}_b$), 4.28 (dd, 1H, H-4$_b$), 3.8 (s, 1H, H-5), 1.51 (s, 3H, H-9), and 1.31 (s, 3H, H-10); ^{13}C NMR δ 148.0 (C-1), 136.0 (C-7), 127.0−129.0 (C_6H_5), 113.0 (OCH_2Ph), 105.0 (C-8), 83.0 (C-2), 82.0 (C-4), 80.0 (C-3), 72.0 (C-6), 71.0 (C-5), and 27.0/26.0 (C-9/C-10); FTIR (KBr pellet) 1750 cm^{-1}.

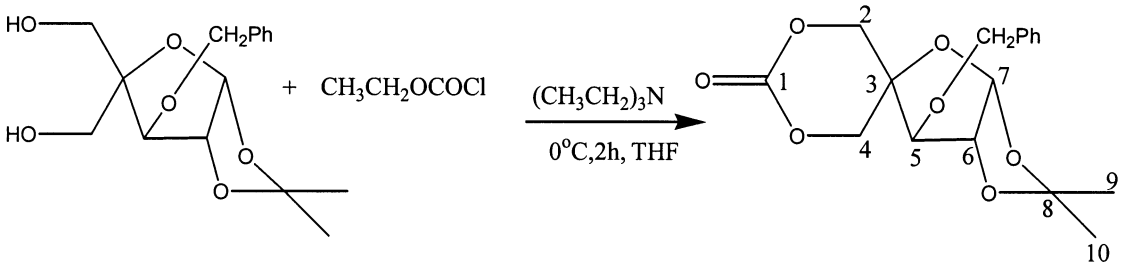
Preparation of Initiator. The initiator solution of $Sn(Oct)_2$ was prepared in dry toluene (0.38 g/2.79 mL).

Polymerization Procedure. 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 [L]-LA (2.01 g, 15.60 mmol) and IPPTC (0.55 g, 1.73 mmol) and the initiator solution (127 μL of a 0.38 g/2.79 mL solution) were transferred into the ampule under an inert argon atmosphere. The ampule was degassed by several vacuum-purge cycles that also removed solvent introduced in the initiator solution. The ampule was then sealed under argon and placed in an oil bath for 6 h at a 130 °C temperature. 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 to precipitate the polymer, the precipitate was washed with several portions of methanol and dried in a vacuum oven (3 mmHg, 40 °C, 24 h) to give 1.97 g (78%) of the product (entry 2, Table 1).

Removal of the Benzyl Ether Group. Pd/C (10%, 50 mg) was added to a solution of 100 mg of copolymer poly([L]-LA-*co*-4.0 mol % IPPTC) (M_n 77 800, M_w/M_n 1.95) in 10 mL of anhydrous THF. The air was displaced with hydrogen gas (H_2), and the contents were stirred for 16 h. The Pd/C was filtered off and washed with tetrahydrofuran (THF). The combined filtrate was evaporated to give the debenzylated copolymer **3** as a white solid (72 mg). The polymer was dissolved in $CDCl_3$ to acquire the NMR spectral data. The resulted product had M_n 74 700, M_w/M_n 2.26, and a degree of benzyl ether removal of 90%.

Ketal Deprotection. To 50 mg of copolymer poly([L]-LA-*co*-4.0 mol % IPPTC) (M_n 77 800, M_w/M_n 1.95) was added 0.5 mL of 80% CF_3COOH in water, and the reaction mixture was

Scheme 2. Synthesis of IPPTC



stirred for a predetermined time at room temperature. Water (10 mL) was added to precipitate the resulting deprotected polymeric product. The polymer was separated by filtration, washed with 5 mL of methanol, and dried in a vacuum to a constant weight (35 mg) (M_n 66 000, entry 1, Table 3).

Characterization. *FTIR Spectroscopy.* A Nicolet FTIR spectrometer (Magna-IR 760) was used to obtain spectra after 32 scans (8 cm^{-1} resolution) over the range 4000−400 cm^{-1}. Samples were analyzed as powders by preparing KBr pellets.

NMR Spectroscopy. Proton (^1H) NMR spectra were recorded on a Bruker spectrometer at 300 MHz. The 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*. Carbon-13 (^{13}C) NMR spectra were recorded at 75.5 MHz on a Bruker spectrometer in 20% w/v chloroform-*d* solutions. The chemical shifts in ppm are referenced relative to the internal standard chloroform-*d* at 77.00 ppm.

Molecular Weight Measurements. Number- and weight-average molecular weights (M_n and M_w, respectively) were determined by gel permeation chromatography (GPC). The GPC analyses were performed at room temperature using a Waters HPLC system that includes a model 510 pump; model 717 autosampler; model 410 refractive index detector (RI); and Styragel HR5, HR4, HR3, and HR1 columns in series. These columns are packed with rigid 5-μm styrene divinylbenzene particles, and they are narrow molecular weight range columns that cover the ranges 50 000−(4×10^6), 5000−600 000, 500−30 000, and 100−5000, respectively. Chloroform (HPLC-grade) was used as the eluent at a flow rate of 1.0 mL/min. The sample concentration and injection volume were 0.2% (wt/wt) and 100 μL, respectively. Molecular weights were determined by using conventional calibration generated with narrow-dispersity polystyrene standards (Polymer Laboratories). Viscotec TriSEC (version 3) software was used for data processing.

Thermal Analysis. Differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) were performed using a DSC 2920 differential scanning calorimeter and a high-resolution TGA 2950 thermogravimetric analyzer, commercially available from TA instruments Inc., equipped with a TA 2000 data station. The amounts of samples used were between 5 and 10.0 mg, the heating rate was10 °C/min, and a nitrogen purge were applied. During the DSC measurements, solution-precipitated samples were first heated from 20 to 200 °C (first heating scan). The samples were then cooled at 10 °C/min from 200 to 20 °C, and the second heating scan was immediately recorded at a heating rate of 10 °C/min.

Results and Discussion

The goal of this work was to develop functional, safe, bioresorbable polymers that satisfy the following criteria: (i) They should be built from a functional monomer of natural origin that will be safely metabolized when the chain is decomposed; (ii) The functional monomer should have multiple sites that allow selective attachment of substances such as bioactive molecules. (iii) The functional monomer should be copolymerizable with already accepted building blocks for medical polymers such as [L]-lactide. (iv) The copolymerizations should be possible with $Sn(Oct)_2$ or other initiators that are accepted for use in preparing polymers for medical applications. (v) The copolymers should be of sufficiently high molecular weight both before and after removal of protecting groups to allow them to have useful physical properties.

Table 1. Effect of the Reaction Temperature on the Copolymer Yield, M_n, M_w/M_n, and product composition for [L]-LA/IPPTC copolymerizations (f_{LA}/f_{IPPTC} 91/9, M/C = 400) Using $Sn(Oct)_2$ for 6 h

entry	temp (°C)	isolated yield (%)[a]	M_n (g/mol)	M_w/M_n	F_{LA}/F_{IPPTC}
1	120	74	33 500	2.06	98/2
2	130	78	77 800	1.95	96/4
3	140	70	40 500	2.04	94/6
4	155	60	24 400	1.99	92/8
5	165	56	15 300	1.79	91/9
6	180	43	9870	1.53	90/10

[a] After methanol precipitation, see Experimental Section.

In accordance with the above considerations, the monomer 1,2-*O*-isopropylidene-3-benzyloxy-pentofuranose-4,4-cyclic carbonate (IPPTC) was designed and synthesized starting from 1,2-*O*-isopropylidene-3-benzyloxy-4-(bishydroxymethyl) pentofuranose in 65.0% yield at 0 °C in THF by a one-pot reaction (Scheme 2). The structure and purity of IPPTC were confirmed from its FTIR, ^1H NMR, and ^{13}C NMR spectra and by melting point analysis.

[L]-LA/IPPTC Copolymerization. Stannous octanoate [$Sn(Oct)_2$] is the initiator that is normally used to prepare medical-grade bioresorbable polymers. Therefore, for copolymerizations of [L]-LA/IPPTC, we focused on the use of $Sn(Oct)_2$ and bulk conditions. The effect of reaction temperature on the $Sn(Oct)_2$-initiated copolymerization of [L]-LA with IPPTC was studied, and the results are shown in Table 1. The yield of copolymer was similar from 120 to 140 °C and decreased from 78 to 43% as the reaction temperature was raised from 130 to 180 °C. Also, the polydispersity was similar from 120 to 155 °C but decreased from 1.99 to 1.53 as the reaction temperature was increased from 155 to 180 °C. Furthermore, the incorporation of IPPTC repeat units into the product increased from 2 to 10 mol % as the reaction temperature was increased from 120 to 180 °C. Thus, for reaction temperatures of 120, 130, and 140 °C for 6 h, the incorporation of IPPTC in the copolymer was less than that used in the monomer feed. However, at 155, 165, and 180 °C, there was a good correlation between the monomer feed composition and the product IPPTC content (Table 1). Earlier, during copolymerizations of [L]-LA with the cyclic carbonate monomers 2,2-[2-pentene-1,5-diyl]-trimethylene carbonate (cHTC)[37] and 1,2-*O*-isopropylidene-[D]-xylofuranose-3,5-cyclic carbonate (IPXTC),[38] an increase in temperature from 120 to 140 °C was found to result in a decrease in the product molecular weight. In contrast, copolymerizations of

Table 2. Effect of the Monomer Feed Ratio (f_{LA}/f_{IPPTC}) on the Copolymer Yield, M_n, M_w/M_n, and Product Composition for [L]-LA/IPPTC Copolymerizations at 130 °C Using $Sn(Oct)_2$ as the Catalyst (M/C = 400) for 6 h

entry	f_{LA}/f_{IPPTC}	isolated[a] yield (%)	M_n (g/mol)	M_w/M_n	F_{LA}/F_{IPPTC}[d]
1	100/0	98	83 400	2.14	100/0
2	91/9	78	77 800	1.95	96/4
3	73/27	74	40 800	2.05	94/7
4	64/36	70	13 000	2.00	86/14
5	50/50	35	nd[b]	nd[b]	79/21
6[c]	0/100	28	7870	1.47	0/100

[a] After methanol precipitation; see Experimental Section. [b] Not determined. [c] Polymerization conducted at 145 °C. [d] Product composition.

IPPTC and [L]-LA, initiated by $Sn(Oct)_2$ at 130 °C, resulted in substantially improved percent yields and product molecular weights. The high thermal stability of IPPTC, which has a decomposition temperature above 200 °C, made it possible to carry out the polymerizations above 140 °C.

Because the preparation of [L]-LA/IPPTC copolymers having high molecular weights is critical to the retention of their useful physical properties, we continued more detailed studies on copolymer synthesis at 130 °C. Thus, with the temperature maintained at 130 °C for 6 h, [L]-LA/IPPTC copolymerizations were conducted with variations in the monomer feed ratio (f_{LA}/f_{IPPTC}). Table 2 shows that, upon increasing IPPTC content in the monomer feed, the percent yield and M_n values decreased, but the content of IPPTC units in the copolymer increased. For example, when f_{LA}/f_{IPPTC} was changed from 91/9 to 64/36, the percent yield and M_n decreased from 78 to 70% and from 77 800 to 13 000, respectively. However, the percent incorporation of IPPTC units in the product increased from 4 to 14 mol %. At the extreme, IPPTC was successfully homopolymerized to give a product with M_n 7870 in 28% yield. The polymerization of [L]-LA is a reversible process with the equilibrium monomer concentration ($[M]_{eq}$) increasing at higher temperatures.[42] IPPTC repeat units are likely more reversible to monomer (higher $[M]_{eq}$) than poly([L]-LA), which might result in lower yields of homopoly(IPPTC) and co-poly(LA/IPPTC) relative to poly([L]-LA). It also might be that low-level impurities of noncyclized diol are present along with IPPTC. If so, diol from such impurities might initiate chains and contribute to reduced M_n values for IPPTC homo- and copolymers.

Further work was conducted on $Sn(Oct)_2$-initiated [L]-LA/IPPTC copolymerizations at 130 °C to better define comonomer reactivity and molecular weight behavior. Figure 1 shows plots of the copolymer yield, M_n, and percent monomer conversion versus reaction time for the [L]-LA/IPPTC copolymerization at 130 °C, M/C = 400, and f_{LA}/f_{IPPTC} 91/9. The copolymer yield and M_n increased rapidly to 66% and 56 300, respectively, in 4 h. Further increases in copolymer yield and M_n with increased reaction time occurred gradually. Hence, by 18 h, the copolymer yield and M_n were 77% and 51 500, respectively. The molecular weight increased for reaction times up to 6 h and then decreased by 32% from 6 to 18 h. Also, by 6 h, [L]-LA conversion was almost quantitative. The molecular weight distribution increased slightly with reaction time (M_w/M_n = 1.9 and 2.3 for 1 and 18 h, respectively). Such decreases in molecular weight and increases in molecular weight distribution at extended reaction times might be associated with thermal depolymerization reactions. Also, the increase in M_w/M_n with conversion might result from intermolecular transesterification reactions between PLA segments, leading to the segmental exchange.[43] However, by extending the reaction time from 6 to 18 h, the percent conversion of IPPTC increased from ~32 to 49%. The relatively lower reactivity of the IPPTC monomer was further shown during kinetic measurements of comonomer reactivity ratios. By the method of Fineman and Ross,[44] the comonomer reactivity ratios were found to be 8.6 and 0.51. In the absence of intermolecular exchange reactions and insertion of the IPPTC monomer into the polymer chain, the above results suggest that the copolymer is blocklike. Our investigation of the copolymer microstructure is described in the following section.

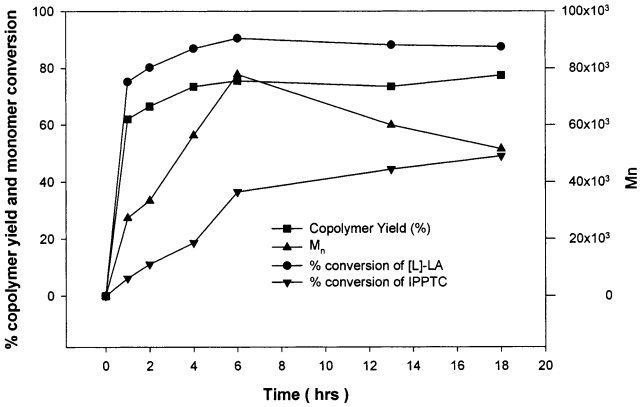


Figure 1. Plots of the copolymer yield, M_n, and percent monomer conversion versus reaction time for [L]-LA/IPPTC copolymerization (f_{LA}/f_{IPPTC} = 91/9, M/C = 400) at 130 °C.

Structural Characterization. ^1H and ^{13}C NMR spectral data were used to characterize the [L]-LA/IPPTC copolymers. Figure 2 displays the ^1H NMR spectrum of poly([L]-LA-*co*-14 mol % IPPTC) synthesized by $Sn(Oct)_2$ at 130 °C (rxn entry 4, Table 2). Comparisons to previously published spectra of [L]-PLA homopolymer[43] showed that the signals at 5.10 and 1.62 ppm are due to the [L]-LA repeat unit C<u>H</u> and C<u>H</u>$_3$ protons, respectively. The chemical shifts of the methine protons of the L-lactyl [−OC<u>H</u>(CH_3)C=O−] unit (designated as L) were sensitive to the repeat unit sequence distribution. Thus, two sets of quartets at 5.10 and 5.02 ppm resulted. Possible dyad structures that could give rise to these signals are <u>L</u>L, <u>L</u>I (I designates IPPTC), and I<u>L</u>, where we observe the C<u>H</u> proton of the underlined repeat unit. A cross-peak was also observed between 5.1 and 1.65 ppm; the former was assigned to C<u>H</u> of [L]-LA units in IPPTC-[L]-LA dyads. In addition, an increase in the IPPTC content of copolymers resulted in signals of increased intensity at δ 5.02, which indicated that <u>L</u>I is upfield from <u>L</u>L and that I<u>L</u> and <u>L</u>L are not resolved. These assignments are consistent with those made previously for L-LA/cHTC.[37] The signals at δ 1.30 and δ 1.45 ppm were assigned to H10/H11 on the basis of the ^1H NMR spectra of copolymers with different compositions and a $^1H-^{13}C$ correlated 2D spectrum. The signal at δ 7.40 ppm was assigned to phenyl ring protons H-2′ to H-6′ present in IPPTC repeat units. Other assignments were based on observed correlations in the corresponding $^1H-^1H$ correlation spectroscopy (COSY) NMR spectrum. Correlations of δ 5.9 with 4.7 and δ 4.7 with 4.5 were used to assign signals resulting from protons H-8, H-7 of sugar moiety,

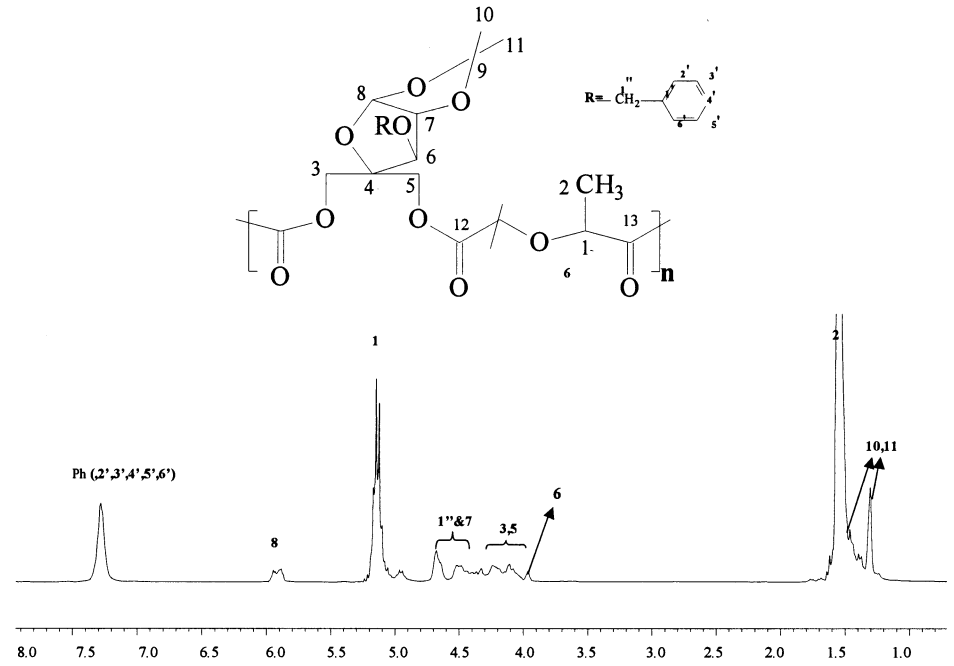


Figure 2. ^{1}H NMR spectrum of poly([L]-LA-*co*-14 mol % IPPTC).

and H-1″ of the benzylic moiety. The benzylic protons were gem-coupled and showed signals at δ 4.7 and 4.5 for one proton each. The H-6 proton showed no correlations and appears as a singlet at δ 3.90. Additional correlations of signals at δ 4.44 with 4.42 and δ 4.36 with 4.30 showed that the δ 4.44 and 4.42 signals are due to H-3 protons that are gem-coupled. Similarly, the signals at δ 4.36 and 4.30 are due to H-5 protons and are also gem-coupled. Hence, the signals were not resolved for the protons of H-5/H-3 or for H-6 and the benzylic protons H-1″. Structural complexity in the ^{1}H NMR spectrum (Figure 2) might be due to dyad sequence effects. Thus, at the current level of the ^{1}H NMR signal resolution, it was not possible to obtain quantitative data for copolymer sequence distribution.

The full ^{13}C NMR spectrum of poly([L]-LA-*co*-14 mol % IPPTC) (rxn entry 4, Table 2) is displayed in Figure 3a. Assignments of the major resonances were based on (i) the spectrum of the homopolymer [L]-PLA[45] and (ii) a ^{1}H−^{13}C correlated 2D NMR (HETCOR) spectrum. The HETCOR spectrum gave cross-peaks between the pairs 4.75-^{1}H/85.2-^{13}C, 4.44-^{1}H/72.5-^{13}C, 4.22-^{1}H/82.5-^{13}C, and 3.91-^{1}H/71.5-^{13}C (with both ^{1}H and ^{13}C values given in ppm). Hence, on the basis of these correlations and comparison with the ^{13}C NMR spectrum of the IPPTC homopolymer, the ^{13}C NMR spectral signals at δ 137.5, 112.5, 104.5, 85.5, 84.0, 72.5, 71.0, 69.0, 27.0, 26.0, and 17.5 were assigned to C1′, C9, C8, C1″, C7, C3, C5, C1, C11, C10, and C2, respectively. Expansions of signals in the carbonyl regions of the spectrum show considerable complexity (Figure 3b). On the basis of a comparison to the homopolymer [L]-PLA,[43] the intense signal at 169.50 ppm was assigned to LLL sequences [L is a lactyl unit with directionality −O−CH−(CH$_3$)−CO−]. The neighboring signals that appear are shoulders of the δ 169.50 ppm resonance that are likely due to sequence effects beyond triads. For example, these peaks might arise as a result of ILL and LLI sequences (I = IPPTC units). Because IPPTC is formed by the reaction of two primary hydroxyl groups, the difference in reactivity between the two diastereotopic faces of the IPPTC monomer should be small. Hence, because of the symmetrical nature of IPPTC, the finding of no effect leads to the assumption that the difference in environments between X′ and X″ on the carbonyl or other carbon signal will be negligible, i.e., CX′CX″CH$_2$ versus CH$_2$−CX″CX′ in the directionality along the chain, as was previously reported for 1,2-*O*-isoproylidene-[D]-xylofuranose-3,5-cyclic carbonate (IPXTC).[38] Therefore, we can define the directionality of IPPTC as −O−CX′CX″CH$_2$−O−CO− and −O−CH$_2$−CX″CX′−O−CO−, respectively. The signals at δ 169.56 and 169.48 ppm were tentatively assigned to IL̲L and LL̲I, respectively. The carbonyl carbons of IPPTC units showed two sets of signals as compared to IPXTC, which showed four sets of signals[38] centered at δ 154.24 and 154.08 ppm. The ring-opening of symmetrical carbonate has less impact on the different potential faces of addition that result in different directionality in the copolymer sequence, but it was not observed at current level of resolution. Increased IPPTC content increases the peak intensity at δ 154.24, indicating the I̲I is at δ 154.24 and IL̲ is at 154.08. In addition, on comparison with the IPPTC homopolymer the signal at δ 154.24 was assigned to I̲I whereas the signal at δ 154.08 was assigned to IL̲.

Deprotection. IPPTC was designed so that the deprotection of functional groups could be performed with control of the site and degree of deprotection. For this purpose, IPPTC has two types of protecting groups, i.e., benzyl ether and ketal moieties. Although a number of different reagents allow the facile removal of benzyl and ketal groups, work was undertaken to remove each these two functional entities selectively in the presence of the other.

Hydrogenation using Pd/C as the catalyst is a useful and mild method for the removal of the benzyl ether group. Work was performed to determine a preferred solvent for this reaction. Because of the low solubility of [L]-LA/IPPTC copolymers in ethyl acetate, acetone and acetonitrile were tried; debenzylation performed in these solvents was slow. Even though the copolymers were highly soluble in chloroform, dichloromethane, and toluene, attempts at debenyzylation in these solvents

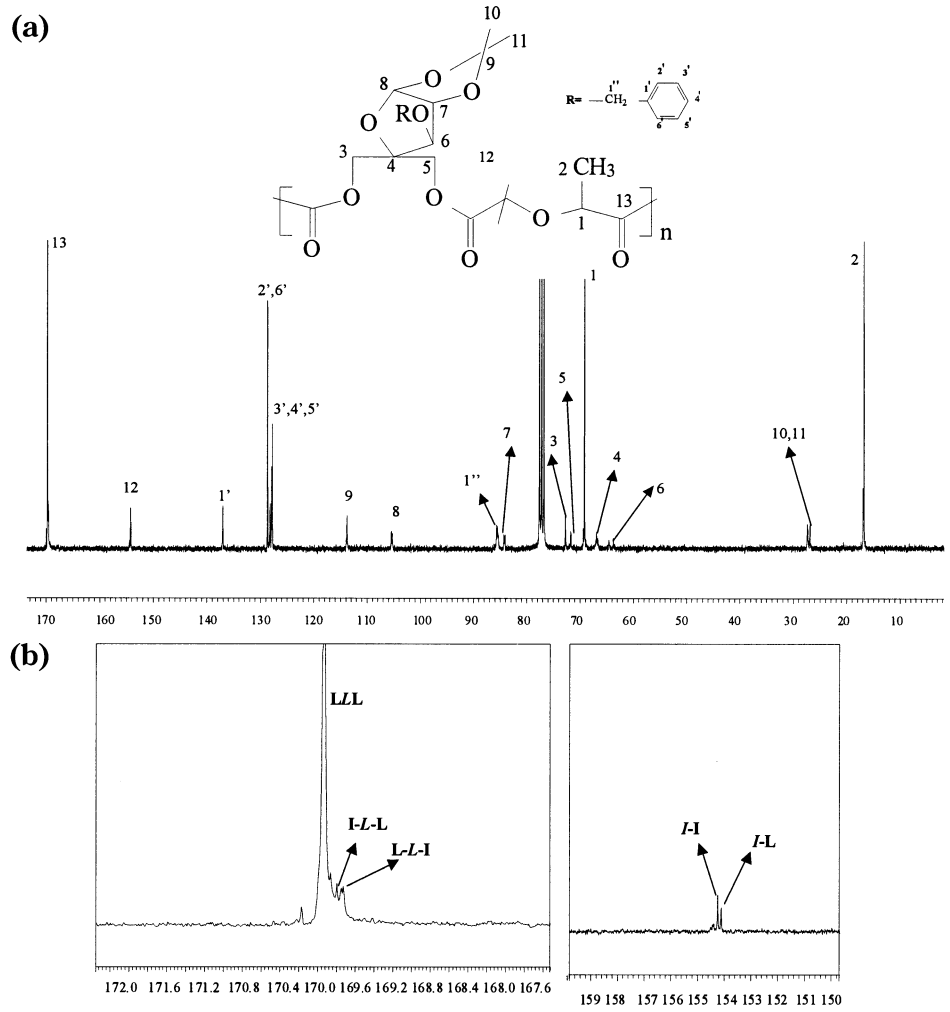
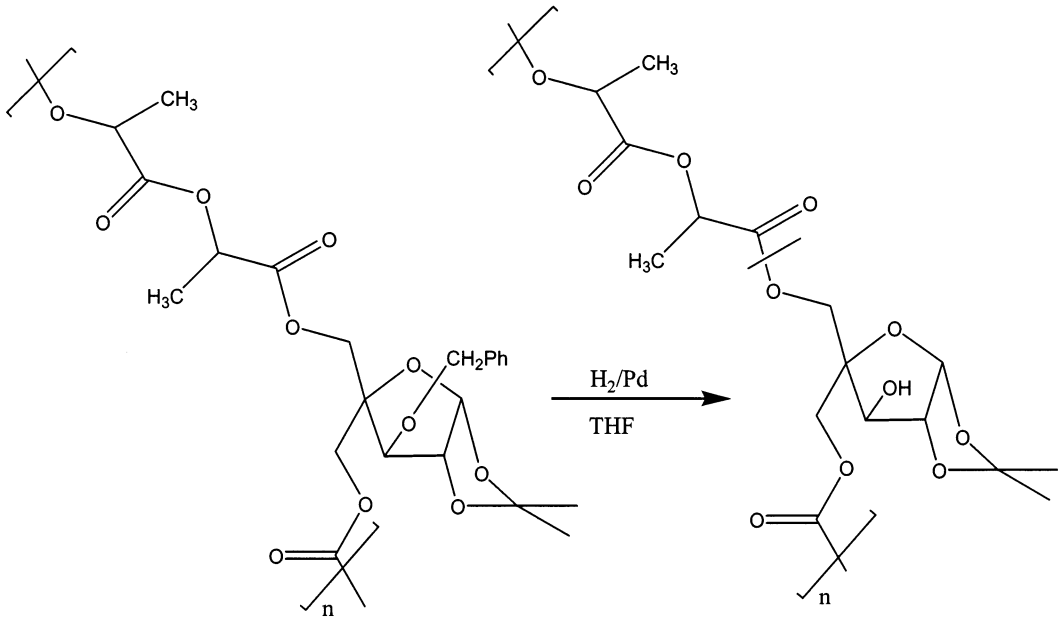


Figure 3. (a) ^{13}C NMR spectrum of poly([L]-LA-*co*-14 mol % IPPTC), (b) expansion of the carbonyl region from the full spectrum.

Scheme 3. Debenzylation of Poly([l]-LA-*co*-IPPTC)



were unsuccessful. Fortunately, tetrahydrofuran was a useful solvent for this system that resulted in a high extent of debenzylation in 16 h (Scheme 3). ^1H NMR spectroscopy was used to determine the degree of debenzylation by monitoring the extent of decrease of the phenyl group protons at δ 7.3 relative to proton H-1 at δ 5.92 (Figure 4). For example, poly([L]-LA-*co*-4.0 mol % IPPTC) (M_n 77 800, M_w/M_n 1.95) was debenzylated in tetrahydrofuran under catalytic hydrogenation conditions with Pd/C at room temperature for 16 h. The

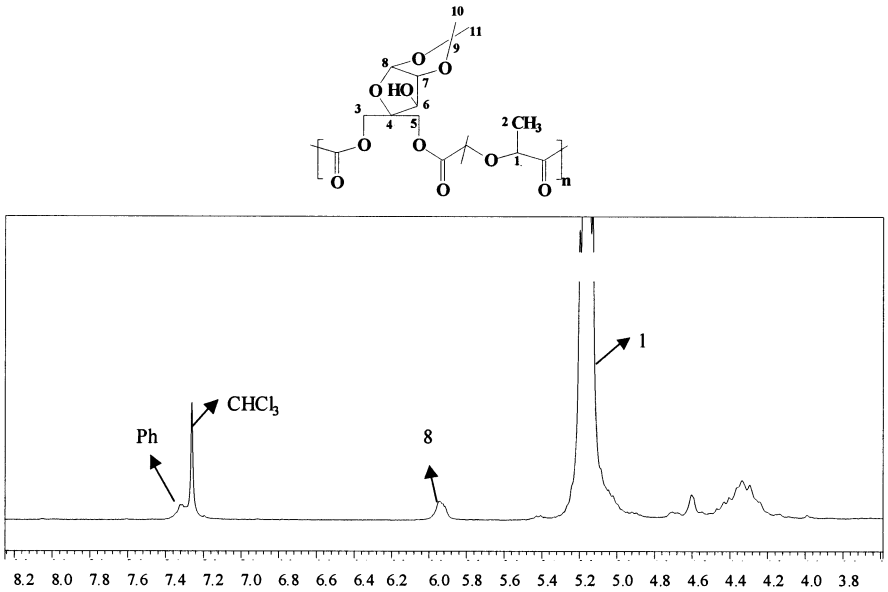


Figure 4. ^{1}H NMR spectrum of debenzylated poly([L]-LA-*co*-4 mol % IPPTC).

Table 3. Removal of the Ketal Protecting Groups as a Function of the Reaction Time[a]

entry	time (min)	M_n	mol % of ketal groups hydrolyzed	M_w/M_n
1	5	66 000	100	1.62
2	10	65 300	100	1.70
3	15	56 700	100	1.55
4	20	40 800	100	2.05

[a] Poly([L]-LA-*co*-4.0 mol % IPPTC) (M_n 77 800, M_w/M_n 1.95) was treated with CF_3COOH/H_2O (80:20) at room temperature.

copolymer after debenzylation was isolated in quantitative yield as a white solid, and the molecular weight was determined by GPC analysis. The resulting product had M_n 74 700, M_w/M_n 2.26, and a degree of benzyl ether removal of 90%.

The ketal groups were also removed selectively to prepare copolymers with vicinal diol pendant groups. Judging from previous work on IPXTC,[38] we chose trifluoroacetic acid in chloroform for the deprotection of the ketal group. The decrease in the molecular weight was very high using trifluroacetic acid as it is a very strong acid and thus hydrolyzed the ester linkages. Therefore, we focused on tuning the conditions for this system to reduce the hydrolysis of the ester linkages. We evaluated different ratios of trifluoroacetic acid to water (from 50 to 90% trifluoroacetic acid in water) and found that 80% of trifluoroacetic acid in water gave the best results, i.e., the highest degree of ketal hydrolysis and a very small extent of ester hydrolysis. For example, removal of the ketal protecting groups of poly([L]-LA-*co*-4.0 mol % IPPTC) (M_n 77 800, M_w/M_n 1.95) was studied using a CF_3COOH/H_2O ratio 80:20 at room temperature for 5, 10, 15, and 20 min. By following the relative peak intensities of the protons H-8 that are shifted upfield from δ 5.92 to 5.50 ppm upon removal of ketal groups, the mole percent of ketal hydrolysis was determined and tabulated (Table 3). Within only 5 min, quantitative deprotection of the vicinal diol moiety occurred with a small apparent decrease in M_n. This reaction can be continued for another 5 min with negligible further decrease in the product molecular weight. However, if the reaction time is extended further, large decreases in the product molecular weight result. For example, after 20 min, the M_n of the product is 40 800 (Table 3).

Thermal Analysis. To better understand the potential to melt process the copolymers prepared herein, their thermal properties were studied. Studies were performed to determine how the thermal stability and thermal transitions (i.e., T_g, T_m) were effected by the following parameters: (i) the content of IPPTC repeat units in the copolymers, (ii) selective deprotection of the ketal groups exposing vicinal diol moieties, and (iii) selective deprotection of the benzyl ether groups exposing only one hydroxyl group on each IPPTC unit. The results from an analysis of the thermal decomposition behavior of copolymers by thermal gravimetric analysis (TGA) are shown in Table 4, and the TGA curves are provided as Supporting Information. Inspection of Table 4 shows that, according to the temperatures at which 5, 20, and 50% weight losses occur as well as the onset decomposition temperature, the thermal stability of poly(IPPTC) is greater than that of poly([L]-LA). Furthermore, differential scanning calorimetric (DSC) analysis shows that the T_g of poly(IPPTC) is greater than that of poly([L]-LA) (69 versus 58 °C, Table 5). The fused five-membered rings of pendant IPPTC units might increase the chain stiffness and, thereby, enhance the thermal stability of the polymer. Moreover, by incorporating up to 14 mol % IPPTC units into copolymers, the copolymer thermal stability was increased relative to that of poly([L]-LA). However, an increase in the mole percent of IPPTC units from 4 to 14% resulted in a small decrease in the onset decomposition temperature (from 290 to 284 °C). This might be due to the lower molar mass of poly([L]-LA-*co*-14 mol % IPPTC) relative to that of poly([L]-LA-*co*-4 mol % IPPTC) (13 k versus 78 k).

Deprotection of the ketal groups along poly([L]-LA-*co*-4.0 mol % IPPTC) resulted in a 47 °C decrease in the 5% weight loss temperature (from 280 to 233 °C) and a 97 °C decrease in the onset decomposition temperature (from 290 to 193 °C, Table 4). In contrast, debenzylation of poly([L]-LA-*co*-4.0 mol % IPPTC) resulted in a 12 °C decrease in the 5% weight loss temperature (from 280 to 268 °C) and a 15 °C decrease in the onset decomposition temperature (from 290 to 275 °C, Table 4). The origin of the difference in thermal stability between the

Table 4. Thermal Decomposition of [L]-LA/IPPTC Copolymers before and after Deprotection

		weight loss temp[a] (°C)			decomposition temp[a] (°C)	
entry	sample	5% wt loss	20% wt loss	50% wt loss	onset[b]	max rate[c]
1	PLA	250	268	277	258	280
2	poly(IPPTC)	288	305	322	293	322
3	poly([L]-LA-*co*-4.0 mol % IPPTC)	280	298	312	290	317
4	debenzylated poly([L]-LA-*co*-4.0 mol % IPPTC)	268	303	331	275	336
5	ketal-deprotected poly([L]-LA-*co*-4.0 mol % IPPTC) (vicinal diol)	233	302	346	193	364
6	poly([L]-LA-*co*-14 mol % IPPTC)	269	295	320	284	320

[a] A heating rate of 10 °C/min was used [b] The onset decomposition temperatures were calculated from the TGA curves. [c] Maximum decomposition rate temperatures were calculated from the peak value of the differential TGA curves.

Table 5. Thermal Transitions of [L]-LA/IPPTC Copolymers with and without Protection of Hydroxyl Functionalities

entry	sample	M_n	T_m[a] (°C)	ΔH_f[a] (J/g)	T_g[b] (°C)
1	[L]-PLA	83 400	175	61	58
2	poly(IPPTC)	7880	76	8	69
3	poly([L]-LA-*co*-1.0 mol % IPPTC)	27 400	166	38	52
4	poly([L]-LA-*co*-4.0 mol % IPPTC)	77 800	160	35	59
5	poly([L]-LA-*co*-14 mol % IPPTC)	13 000	112	20	61
6	debenzylated poly([L]-LA-*co*-4.0 mol % IPPTC)	77 400	160	30	58
7	ketal-deprotected poly([L]-LA-*co*-4.0 mol % IPPTC) (vicinol diol)	66 000	160	38	52

[a] T_m and ΔH_f were determined from the first heating scan. A scanning rate of 10 °C/min was used. [b] T_g was determined from the second heating scan. A scanning rate of 10 °C/min was used.

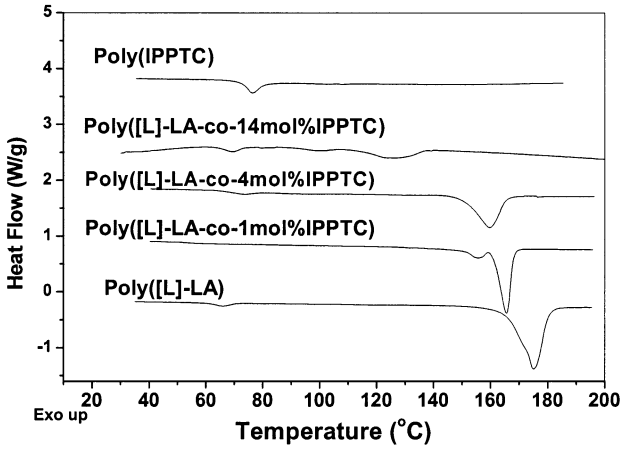


Figure 5. DSC thermograms recorded during the first heating scan of the following polymers: poly(IPPTC), poly([L]-LA-*co*-14 mol % IPPTC), poly([L]-LA-*co*-4 mol % IPPTC), poly([L]-LA-*co*-1 mol % IPPTC), and poly([L]-LA). A heating rate of 10 °C/min was used.

ketal-deprotected and benzyl-deprotected products is currently unclear. Nevertheless, it is clear that deprotection of C-3 rather than C-1/C-2 of the pentofuranose-4,4′-carbonate repeat units leads to more thermally stable [L]-LA/IPPTC copolymers.

Figure 5 shows the first DSC heating scan of [L]-LA/IPPTC copolymers as a function of IPPTC content (for the second heating scans, see the Supporting Information). Figure 6a and 6b shows the first and second heating DSC scans, respectively, of (1) poly([L]-LA), (2) poly([L]-LA-*co*-4.0 mol % IPPTC), (3) the polymer in 2 deprotected by debenzylation to give one free hydroxyl group per IPPTC repeat unit, and (4) the polymer in 2 deprotected by hydrolysis of the ketal groups to give two free vicinal hydroxyl groups per IPPTC repeat unit. The first heating scan was used to determine the peak melting temperature (T_m) and the corresponding enthalpy of fusion (ΔH_f). The second heating scan was used

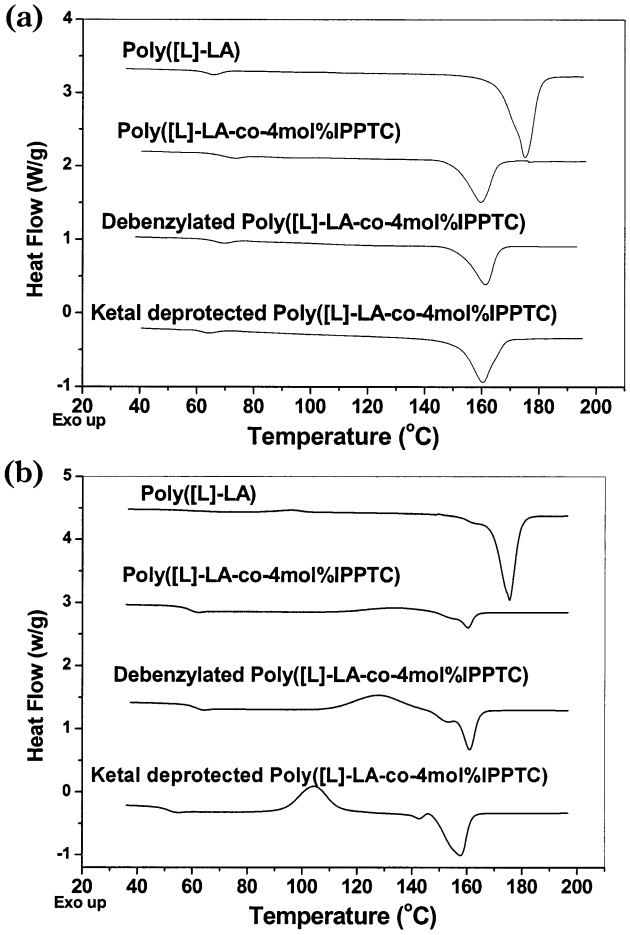


Figure 6. DSC thermograms recorded during the (a) first heating scan and (b) second heating scan for the following polymers: [L]-PLA, poly([L]-LA-*co*-4.0 mol % IPPTC), debenzylated poly([L]-LA-*co*-4.0 mol % IPPTC), and ketal-deprotected poly([L]-LA-*co*-4.0 mol % IPPTC). A scanning rate of 10 °C/min was used.

to determine the glass transition temperature (T_g). The results of this work are summarized in Table 5. A comparison of the DSC scans for the [L]-PLA homopolymer and the corresponding [L]-LA/IPPTC copolymers showed that the incorporation of even low levels of IPPTC units caused substantial reductions in the T_m and ΔH_f values. For example, a comparison of copolymers with 0 and 1 mol % IPPTC units showed that the latter had reductions in T_m by 9 °C (from 175 to 166 °C) and in ΔH_f by 23 J/g (from 61 to 38 J/g). A further increase in the IPPTC content from 1 to 4 mol % did not significantly alter the ΔH_f value but did cause a decrease in T_m from 166 to 160 °C. An increase in the copolymer IPPTC content from 4 to 14 mol % caused further decreases in both the T_m and ΔH_f to 112 °C and 20 J/g, respectively. Further study of Table 5 shows that deprotection of the poly([L]-LA-*co*-4.0 mol % IPPTC) hydroxyl moieties by either debenzylation or hydrolysis of the ketal groups did not substantially change the T_m values of the copolymers. However, deprotection of the poly([L]-LA-*co*-4.0 mol % IPPTC) hydroxyl groups did alter the crystallization behavior. The general trend observed was that, by deprotection of the IPPTC hydroxyl groups, the crystallization of the copolymers upon cooling from the melt and/or during the second heating occurred more rapidly. However, the comparison of these copolymers in Figure 6b shows that the ketal-deprotected copolymer crystallized most rapidly. This might be due to the lower T_g of the ketal-deprotected copolymer relative to those of the debenzylated and nondeprotected copolymers (52 versus 58 and 59 °C, respectively).

The homopolymer of IPPTC was successfully prepared, but its molecular weight was low (M_n 7880). Comparison of [L]-PLA and poly(IPPTC) showed that the latter had a higher T_g (69 versus 58 °C). The T_m and ΔH_f of poly(IPPTC) are 76 °C and 8 J/g, respectively.

Conclusions

The six-membered cyclic carbonate monomer 1,2-*O*-isopropylidene-3-benzyloxy-pentofuranose-4,4′-cyclic carbonate (IPPTC) was prepared. IPPTC consists of pentofuranose with benzyl ether- and ketal-protected hydroxyl groups. The copolymerization of IPPTC with [L]-lactide was performed at 130 °C, in the bulk, initiated by stannous octanoate. Studies were conducted on the post-product modification of [L]-lactide/IPPTC copolymers. The benzyl ether group of the IPPTC repeat units was successfully removed under mild conditions using Pd/C as a catalyst in tetrahydrofuran without affecting the ketal groups. Also, the ketal groups were successfully hydrolyzed by using CF_3COOH/H_2O with stirring at room temperature in the presence of the benzyl ether groups. Thus, the IPPTC units within the copolymers can have one, two, or three hydroxyl groups that can be further modified to fine-tune the biomaterial properties. Also, this system allows control of the position and proximity of bioactive substituents within IPXTC units. The high thermal stability of IPPTC, which has a decomposition temperature above 200 °C, made it possible to carry out the polymerizations above 140 °C. However, polymerizations at 130 °C were found to be most suitable to obtain both high product yields and high molecular weights with acceptable levels of IPPTC incorporation. The more rapid polymerization of [L]-LA relative to IPPTC was shown by their reactivity ratios, which are 8.6 and 0.51, respectively. Studies by thermal analysis gave information on the thermal transitions and stability of [L]-LA/IPPTC copolymers. Increasing the incorporation of IPPTC units in [L]-LA/IPPTC copolymers gives products that have lower melting transitions. The IPPTC units in the copolymers also increased the thermal stability and glass transition temperature relative to poly([L]-LA). According to our assessment of the melting and decomposition temperatures both before and after removal of the benzyl ether or ketal protecting groups, poly([L]-LA-*co*-14 mol % IPPTC) and debenzylated poly([L]-LA-*co*-4.0 mol % IPPTC) should be melt processible without substantial decomposition.

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Supporting Information Available: $^1H-^1H$ correlated (COSY 45) NMR spectra of IPPTC monomer, $^1H-^1H$ correlated (COSY 45) NMR spectra of poly([L]- LA-*co*-14 mol % IPPTC, and TGA and DSC thermograms of LA/IPPTC copolymers. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Chasin, M.; Langer, R. *Biodegradable Polymers as Drug Delivery Systems*; Marcel Dekker: New York, 1990.
(2) Langer, R. *Science* **1990**, *249*, 1527.
(3) Laurencin, C. T.; Ambrosio, A. M.; Attawia M. A.; Ko, F. K.; Borden, M. D. In *Polymers from Renewable Resources, Biopolyesters and Biocatalysis*; ACS Symposium Series 764; Scholz, C., Gross, R., Eds.; American Chemical Society: Washington, DC, 2000; p 294.
(4) Wise, D. L.; Fellman, T. D.; Sanderson, J. E.; Wentworth, R. L. In *Drug Carriers in Biology and Medicine*; Gregoriadis, G., Ed.; Academic Press: London, 1979.
(5) Andriano, K. P.; Pohionen, T.; Toermaelae, P. *J. Appl. Biomater.* **1994**, *5* (2), 133.
(6) Holland, S. J.; Tighe, B. J.; Gould, P. L. *J. Controlled Release* **1986**, *4*, 155.
(7) Cohn, D.; Younes, H. *J. Biomed. Mater. Res.* **1988**, *22*, 993.
(8) Sawhney, A. S.; Hubbell, J. A. *J. Biomed. Mater. Res.* **1990**, *24*, 1397.
(9) Zhu, K. J.; Song, B. H.; Yang, S. L. *J. Polym. Sci. A: Polym. Chem.* **1989**, *27*, 2151.
(10) Chen, X.; McCarthy, S. P.; Gross, R. A. *Macromolecules* **1997**, *30*, 4295.
(11) Pitt, C. G.; Jeffcoat, R. A.; Schindler, A.; Zweidinger, R. A. *J. Biomed. Mater. Res.* **1979**, *13*, 497.
(12) Schankenraad, J. M.; Nieuwenhuis, P.; Molenaar, L.; Helder, J.; Dijksta, P. J.; Feijen, J. *J. Biomed. Mater. Res.* **1989**, *23*, 1271.
(13) Barrera, D. A.; Zylstra, E.; Lansbury, P. T.; Langer, R. *Macromolecules* **1995**, *28*, 425.
(14) Barrera, D. A.; Zylstra, E.; Lansbury, P. T.; Langer, R. *J. Am. Chem. Soc.* **1993**, *115*, 11010.
(15) Park, T. G.; Cohen, S.; Langer, R. *Macromolecule*s **1992**, *25*, 116.
(16) Ouchi, T.; Fujino, A. *Makromol. Chem.* **1989**, *190*, 1523.
(17) Arnold, S. C.; Lenz, R. W. *Makromol. Chem., Macromol. Symp.* **1986**, *6*, 285.
(18) Guerin, P.; Vert, M.; Braud, C.; Lenz, R. W. *Polym. Bull. (Berlin)* **1985**, *14*, 187.
(19) Vert, M.; Fournier, P.; Boustta, M.; Domurado, D.; Guerin, P.; Braud, C.; Holler, H. *Macromol. Rep.* **1994**, *A31*, 723–730.
(20) Fietier, I.; Le Borgne, A.; Spassky, N. *Polym. Bull. (Berlin)* **1990**, *24*, 349.
(21) Zhou, Q. X.; Kohn, J. *Macromolecules* **1990**, *23*, 3399.
(22) In't Veld, P. J. A.; Dijkstra, P. J.; Feijen, J. *Makromol. Chem.* **1992**, *193*, 2713.
(23) Kimura, Y.; Shirotani, K.; Yamane, H.; Kitao, T. *Macromolecules* **1988**, *21*, 3338.
(24) Massia, S. P.; Hubbell, J. A. *J. Cell Biol.* **1991**, *114*. 1089.

(25) Kuhling, S.; Keul, H.; Hocker, H. *Makromol. Chem*. **1992**, *193*, 1207.
(26) Kawaguchi, T.; Nakano, M.; Juni, K.; Inoue, S.; Yoshida, Y. *Chem. Pharm. Bull*. **1983**, *31*, 1400, 4157.
(27) Nishida, H.; Tokiwa, Y. *Chem. Lett*. **1994**, *3*, 421.
(28) Albertsson, A. C.; Eklund, S. J. *Appl. Polym. Sci*. **1995**, *57*, 87.
(29) Zhu, K. J.; Hendren, R. W.; Jensen, K.; Pitt, C. G. *Macromolecules* **1991**, *24*, 1736.
(30) Grijpma, D. W.; Pennings, A. J. *Macromol. Chem. Phys*. **1994**, *195*, 1633.
(31) Buchholz, B. J. *Mater. Sci., Mater. Med*. **1993**, *4*, 381.
(32) Storey, R. F.; Hickey, T. P. *Polymer* **1994**, *35* (4), 830.
(33) Hori, Y.; Gonda, Y.; Takahashi, Y. Hagiwara, T. *Macromolecules* **1996**, *29*, 804.
(34) Tian, D.; Dubois, P.; Grandfils, C.; Jerome, R. *Macromolecules* **1997**, *30*, 406.
(35) Vandenberg, E. J.; Tian, D. *Macromolecules* **1999**, *32*, 3613.
(36) Chen, X.; McCarthy, S. P.; Gross, R. A. *Macromolecules* **1997**, *30*, 3470.
(37) Chen, X.; McCarthy, S. P.; Gross, R. A. *Macromolecules* **1998**, *31*, 662.
(38) Chen, X.; Gross, R. A. *Macromolecules* **1999**, *32*, 308.
(39) Shen, Y.; Chen, X.; Gross, R. A. *Macromolecules* **1999**, *32*, 3891.
(40) Shen, Y.; Chen, X.; Gross, R. A. *Macromolecules* **1999**, 32, 2799.
(41) Sharma, S. K.; Roy, S.; Kumar, R.; Parmar, V. S. *Tetrahedron Lett*. **1999**, *40*, 9145.
(42) Duda, A.; Penczek, S. *Macromolecules* **1990**, *23*, 1636.
(43) Penczek, S.; Duda, A.; Szymanski, R. *Macromol. Symp*. **1998**, *132*, 441.
(44) Odian, G. In *Principles of Polymerization*, 3rd ed.; Wiley-Interscience: New York, 1991; p 469.
(45) Li, S. M.; Espartera, J. L.; Foch, P.; Vert, M. *J. Biomater. Sci., Polym. Ed*. **1996**, *8*, 165.

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