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Synthesis, Modification, and Characterization of L-Lactide/2,2-[2-Pentene-1,5-diyl]trimethylene Carbonate Copolymers

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ABSTRACT: This paper explores the copolymerization of L-lactide (L-LA) with 2,2-[2-pentene-1,5-diyl]-trimethylene carbonate (^{c}HTC). Since ^{c}HTC has a cyclohexene group, this provided a route for preparing poly(lactic acid), (PLA), based chains decorated with controlled quantities of C═C substituents. Ring-opening copolymerizations of L-LA with ^{c}HTC were successfully conducted in bulk by using AlR_3-H_2O (R = ethyl, isobutyl), $Al(O^{i}Pr)_3$, $ZnEt_2-H_2O$ and $Sn(Oct)_2$ as catalysts. Comparison of these copolymerizations showed that the $Sn(Oct)_2$ catalyst system gave copolymers of relatively higher molecular weight. Increasing the reaction time of $Sn(Oct)_2$ catalyzed copolymerizations from 6 to 24 h resulted in higher copolymer ^{c}HTC content and yield but lower copolymer molecular weight. Variation of the comonomer feed ratio was useful in regulating the content of cyclohexene pendant groups in the copolymer. However, regardless of the catalyst used, the mole percent of ^{c}HTC incorporated into the copolymer was lower than that used in the monomer feed. Determination of the comonomer reactivity ratios for $Sn(Oct)_2$ catalyzed copolymerizations gave values of 8.8 and 0.52 for L-LA and ^{c}HTC, respectively. All gel permeation chromatography (GPC) traces showed unimodal molecular weight distributions. Determination by ^{13}C-NMR of the copolymer sequence fractions H*L*L, L*L*L, L*L*H, H*L*H, *H*L, and L*H* (H = ^{c}HTC units, L = L-lactyl units) showed that they were close to those calculated by assuming a Bernoulli statistical propagation. On the basis of these results and the effects of reaction conditions on the copolymer sequence distribution, a mechanism which involves insertion of ^{c}HTC into the polymer chain was proposed. Studies by differential scanning calorimetry (DSC) showed that ^{c}HTC units in the copolymers disrupted ordering of the L-PLA crystalline phase. Furthermore, the glass transition temperatures (T_g) ranged from 60 (L-PLA) to 33 °C (P(^{c}HTC)). Conversion of C═C to epoxy side groups was successfully carried out by using 3-(chloroperoxy)benzoic acid at room temperature with only small decreases in copolymer molecular weight.

Introduction

A variety of degradable polymers have been used as implantable biomaterials and drug delivery systems.[1,2] The main advantage of these polymers is that no retrieval of the device is needed subsequent to their use. L-Poly(lactic acid) (L-PLA) based materials have shown favorable biocompatibility and have gained wide acceptability for applications that require bioresorption *in vivo*.[1−3] 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-lactide with D-lactide,[4] glycolide,[5] ethylene oxide,[6−9] ϵ-caprolactone,[10] and monomers that, upon ring-opening, provide amino acid repeat units.[11,12] Alternatively, many workers have attempted to "tailor" PLA physicomechanical properties and hydrolytic degradability by blending with other polymers.[13]

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 biomaterials with various functional groups that permit decoration of polymer chains with bioactive substances. For example, Langer and coworkers have synthesized poly(L-lactic acid-*co*-lysine) by copolymerizing L-lactide with 3-[N^{ϵ}-(carbonylbenzoxy)-L-lysyl]-6-L-methyl-2,5-morpholinedione, a cyclic dimer of L-lactic acid and protected L-lysine.[12] These copolymers have amine side groups to which bioactive factors, such as the peptide arginine−glycine−aspartic acid (RGD)[12a] or the peptide sequence GRGDY[12b] can be grafted to promote cell adhesion. However, the molecular weight of these copolymers decreased significantly relative to L-LA homopolymerizations even with low 3-[N^{ϵ}-(carbonylbenzoxy)-L-lysyl]-6-L-methyl-2,5-morpholinedione co-monomer feed ratios. For example, the number average molecular weight (M_n) of the copolymer decreased by ∼9 times after adding 5.3 mol % of the lysine protected monomer in the feed.

A number of aliphatic polycarbonates or their copolymers were reported to be degradable. Examples cited in the literature include poly(ethylene carbonate)[14,15] and poly(trimethylene carbonate).[16,17] Other degradable carbonate containing copolymers include trimethylene carbonate/lactide,[18−20] trimethylene carbonate/ϵ-caprolactone,[16] and trimethylene carbonate or 2,2-dimethyltrimethylene carbonate/β-butyrolactone.[21] Recently, we prepared the six-membered cyclic carbonate monomer 2,2-[2-pentene-1,5-diyl]trimethylene carbonate (^{c}HTC) which bears cyclohexene side groups. Polymerizations of ^{c}HTC using organometallic catalysts including aluminoxanes, $ZnEt_2$ and $ZnEt_2-H_2O$ (1:0.5) resulted in the corresponding functional homopolymer in high molecular weight (M_n from 80 000 to 260 000). The pendant C═C groups of P(^{c}HTC) offer a wide range of opportunities for further modification/functionalization. For example, P(^{c}HTC) C═C groups were converted to epoxides with little molecular weight decrease.[22]

The copolymerizations of cyclic carbonates with lactide have been explored.[18,19,23,24] Specifically, 2,2-dim-

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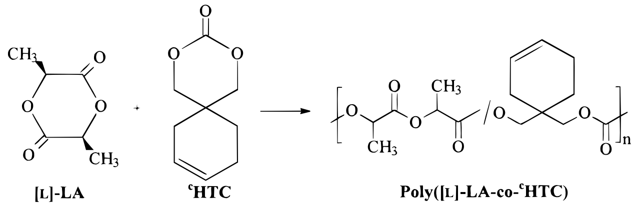
Scheme 1. Ring-Opening Copolymerization of L-LA–^{c}HTC



ethyltrimethylene carbonate L-LA (DTC/L-LA) copolymerizations were conducted using various catalysts including Al(O–*sec*-Bu)$_3$ and ZnEt$_2$ at reaction temperatures from 100 to 130 °C. Copolymer yields and M_n values ranged from 5 to 78% and from 8500 to 36 500, respectively, for 1:1 mol/mol copolymerizations of DTC and L-LA.[23] Investigations of the copolymer microstructure by ^{13}C-NMR revealed that DTC was randomly inserted into L-LA linkages for ZnEt$_2$ catalyzed copolymerizations.[23] Also, copolymerizations of L-LA and TMC were carried out using Sn(Oct)$_2$ as the catalyst.[18,19,24]

In this paper, work was undertaken to prepare high L-LA content copolymers that are decorated with C═C functionalities. C═C substituents would provide a number of opportunities for further polymer modification/functionalization. To this end, different organometallic catalysts were evaluated for the copolymerization of L-LA and ^{c}HTC (Scheme 1). High molecular weight L-LA–^{c}HTC copolymers were prepared having controlled ^{c}HTC contents. The copolymers obtained were characterized by ^{1}H-NMR, ^{13}C-NMR, and differential scanning calorimetry (DSC). Relationships between the copolymerization conditions used and the copolymer repeat unit composition, repeat unit sequence distribution, and molecular weight were investigated. The effects of ^{c}HTC incorporation on the melting characteristics of PLA crystalline phases as well as the glass transition temperature were studied. Also, the transformation of copolymer C═C substituents to epoxides was investigated.

Experimental Part

Materials. L-Lactide from Aldrich was purified by recrystallization from anhydrous ethyl acetate for two times, while all manipulations were carried out under dry nitrogen atmosphere {mp 92–94 °C, $[\alpha]^{20°C}$(at 589 nm) = −285° (*c* = 1, in toluene)}. The method used for 2,2-[2-pentene-1,5-diyl]trimethylene carbonate (^{c}HTC) preparation and purification was described elsewhere.[22] The catalysts Sn(Oct)$_2$ (approximately 95%) and Al(O^{i}Pr)$_3$ (>99.99%) were purchased from Aldrich as neat liquids or solids which were used as received. The organometallic compounds AlEt$_3$, Al(^{i}Bu)$_3$, and ZnEt$_2$ were purchased from Aldrich in toluene solution and used without further purification. Toluene was dried by distillation from sodium metal. All liquid reagents were transferred by syringe under a dry argon atmosphere.

Preparation of Catalysts. The catalysts AlR$_3$–H$_2$O (1:0.5) and ZnEt$_2$–H$_2$O (1:0.5) were prepared by modification of a literature procedure.[25] The following describes the preparation of ZnEt$_2$–H$_2$O catalyst solution, and the identical procedure was used to prepare the AlR$_3$–H$_2$O systems. To a previously silanized and flame-dried 10 mL Schlenk tube, 1 mL of ZnEt$_2$ (1.1 M in toluene) was injected via syringe. The solution was cooled in an external dry ice-acetone bath followed by slow addition of a 1,4-dioxane solution (99 μL) containing 9.9 μL distilled water with vigorous stirring. After 15 min, the dry ice bath was removed and the temperature was increased to 25 °C. The resulting clear solution was stored in the refrigerator (about 4 °C) for up to 2 weeks prior to use without loss of catalytic activity. Solutions (1 mol/L) of Al(O^i-Pr)$_3$ 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 which 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 content of the ampule was 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. The detailed procedures and experimental parameters of ^{1}H-NMR, ^{13}C-NMR, gel permeation chromatography (GPC), DSC, and thermogravimetric analysis (TGA) measurements have been described in our previously publication.[22] The relative intensity of signals from 5.0 to 5.2 ppm (C*H* in lactide units) and from 4.0 to 4.2 ppm (main chain CH_2 in ^{c}HTC units) in ^{1}H-NMR spectra were used for the determination of the copolymer composition (see below).

Epoxidation of Poly(L-LA-*co*-cHTC). The procedure was the same as that described previously[22] except the reaction time (16 h) was decreased to 0.5, 1, and 4 h.

Results and Discussion

Copolymerization of L-LA–^{c}HTC. It was reported that Sn(Oct)$_2$ and Zn based organometallic compounds are preferred catalysts for the synthesis of high molecular weight PLA by ring-opening polymerization.[26] Often, the polymerization reactions are carried out in bulk at temperatures from 110 to 140 °C. For ^{c}HTC homopolymerization, Al and Zn catalysts gave rapid polymerizations and high molecular weight polymer.[22] Therefore, Al, Zn, and Sn(Oct)$_2$ catalysts were evaluated for the copolymerization of L-LA with ^{c}HTC (Table 1). Since our objective in this work was to prepare copolymers that contained primarily L-LA repeat units and controlled low levels (1–30 mol %) of C═C bearing ^{c}-HTC units, the mole percent of L-LA in the monomer feed was normally ≥65. Comparison of copolymerizations conducted by the different catalysts at 120 °C showed that Sn(Oct)$_2$ gave the highest molecular weight copolymers. This was similarly found for investigations of L-LA homopolymerization.[27] For all of the catalysts, the copolymer yield and molecular weight were inversely proportional to the quantity of ^{c}HTC used in the monomer feed. Furthermore, the ^{c}HTC content of the copolymers was always lower than was used in the monomer feed. Thus, ^{c}HTC had lower reactivity than L-LA in these copolymerizations.

Study of the GPC results showed that all of the copolymers prepared in this study had a unimodal molecular weight distribution. The aluminum catalysts resulted in copolymers with relatively smaller polydispersity values (M_w/M_n = 1.4–1.7) than copolymers prepared using Sn(Oct)$_2$ (M_w/M_n = 1.9–2.2) or ZnEt$_2$–H$_2$O (M_w/M_n = 2.2–2.3) as catalysts at 120 °C. Variation of the copolymerization temperature from 100 to 140 °C for Sn(Oct)$_2$ catalyzed copolymerizations (entries 7–9) gave similar product yields. However, polymerizations conducted at 120 °C gave the highest copolymer molecular weight. These effects of reaction temperature were similarly observed for L-LA homopolymerizations

Table 1. Effects of Catalyst and Reaction Temperature on the ^{c}HTC–L-LA Copolymer Yield, Molecular Weight, and Composition^{a}

entry	catalyst	f_{LA}/f_{HTC}^{b}	temp (°C)	yield^{c} (%)	M_n^{d}	M_w/M_n^{d}	F_{LA}/F_{HTC}^{e}
1	1:0.5 AlEt$_3$–H$_2$O	83/17	120	77	34 000	1.5	96/4
2	1:0.5 AlEt$_3$–H$_2$O	67/33	120	67	26 100	1.7	90/10
3	1:0.5 Al^{i}Bu$_3$–H$_2$O	82/18	120	67	47 800	1.7	97/3
4	1:0.5 Al^{i}Bu$_3$–H$_2$O	66/34	120	54	21 700	1.4	94/6
5	Al(O^{i}Pr)$_3$	81/19	120	78	34 900	1.7	95/5
6	Al(O^{i}Pr)$_3$	65/35	120	70	24 700	1.7	88/12
7	Sn(Oct)$_2$	82/18	100	81	72 300	2.1	95/5
8	Sn(Oct)$_2$	82/18	120	84	109 000	1.9	92/8
9	Sn(Oct)$_2$	82/18	140	88	54 200	2.7	88/12
10	Sn(Oct)$_2$	67/33	120	68	82 200	2.1	86/14
11	1:0.5 ZnEt$_2$–H$_2$O	83/17	120	82	49 400	2.3	95/5
12	1:0.5 ZnEt$_2$–H$_2$O	67/33	120	68	45 700	2.2	88/12

[a] $M/I = 200$, 6 h, in bulk. [b] Monomer feed ratio in mole per mole. [c] Methanol insoluble copolymer. [d] Determined by GPC in CHCl$_3$ at room temperature, polystyrene as standard, RI detector. [e] Copolymer composition in mole per mole measured by ^{1}H-NMR.

Table 2. Effect of Monomer Feed Ratio on the ^{c}HTC–L-LA Copolymerization^{a}

entry	f_{LA}/f_{HTC}^{b}	yield^{b} (%)	M_n^{b}	M_w/M_n^{b}	F_{LA}/F_{HTC}^{b}
13	0/100	91	55 700	2.0	0/100
14	30/70	43	35 300	1.9	48/52
15	49/51	47	49 800	2.2	72/28
10	67/33	68	82 200	2.1	86/14
16	82/18	82	99 700	2.0	93/ 7
17	100/0	99	86 000	2.1	100/0

[a] Sn(Oct)$_2$ as catalyst, $M/I = 200$, 120 °C, 6 h. [b] See Table 1 footnotes.

(data not shown). Also, an increase in the reaction temperature resulted in copolymers with increased ^{c}HTC content. Interestingly, the same trend in carbonate copolymer content versus reaction temperature was reported for DTC–L-LA copolymerizations catalyzed by ZnEt$_2$ in bulk.[23]

Copolymers with variable compositions were prepared by changing the monomer feed ratio for Sn(Oct)$_2$ catalyzed polymerizations at 120 °C (Table 2). The homopolymerizations for both monomers resulted in high polymer yields (91 and 99% for ^{c}HTC and L-LA, respectively). The copolymer yield and molecular weight was inversely proportional to the content of ^{c}HTC in the monomer feed. By using 70 mol % ^{c}HTC in the monomer feed, a copolymer was obtained that had 52 mol % ^{c}HTC and an M_n of 35 300 (entry 14, Table 2). Irrespective of the monomer feed ratio, GPC traces of the products were unimodal, and the ^{c}HTC content in the copolymers was less than that in the monomer feed. This latter point can be explained by the lower monomer reactivity ratio of ^{c}HTC. Specifically, using the method of Fineman and Ross,[28] the reactivity ratios using Sn(Oct)$_2$ at 120 °C for L-LA and ^{c}HTC were 8.8 and 0.52, respectively. On the basis of the monomer reactivities, blocklike copolymers would be expected in the absence of transesterification reactions. The repeat unit sequence distribution of selected copolymers and its implications on the propagation mechanism is discussed later.

Further work was conducted on Sn(Oct)$_2$ catalyzed L-LA–^{c}HTC copolymerizations at 120 °C to better define comonomer reactivity and molecular weight behavior. In Figure 1, changes in copolymer yield, molecular weight, molecular weight distribution, and monomer conversion are shown as a function of time for the monomer molar feed ratio (f_{LA}/f_{HTC}) 82/18. The copolymer yield increased rapidly to 79% by 1 h and, thereafter, increased slowly. L-LA conversion was almost quantitative by 1 h. In contrast, ^{c}HTC conversion was much slower, reaching only 14, 35, and 66% by 1, 2, and 16 h, respectively. The molecular weight increased for reaction times up to 6 h and then decreased by 36% from 6 to 16 h. The molecular weight distribution increased slightly with reaction time ($M_w/M_n = 1.9$ and 2.1 for 1 and 16 h, respectively). Such decreases in molecular weight and increase in molecular weight distribution at extended reaction times are consistent with thermal depolymerization reactions, as was described elsewhere for Sn(Oct)$_2$ catalyzed L-LA homopolymerization[27] and copolymerization.[12a] The monomer consumption data suggest that if chain growth occurs only by ring-opening propagation from growing chain ends, then the repeat unit sequence distribution should deviate significantly from random chain propagation statistics.

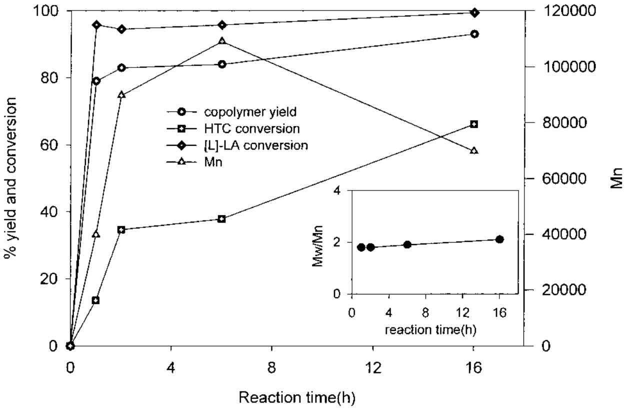


Figure 1. Effect of reaction time on the copolymer yield, monomer conversions, and molecular weight. Polymerization conditions: Sn(Oct)$_2$ as catalyst, $M/I = 200$, $f_{LA}/f_{HTC} = 82/18$, 120 °C, in bulk.

Structural Characterization. The copolymers obtained have been characterized by ^{1}H- and ^{13}C-NMR. The ^{1}H-NMR spectrum of L-LA–^{c}HTC copolymer with F_{LA}/F_{HTC} 72/28 mol/mol (entry 15 in Table 2) is displayed in Figure 2. With the exception of repeat unit sequence effects discussed below, assignments of protons were based on those previously made for the homopolymers PLA[29] and P(^{c}HTC).[22]

It was found that the chemical shift of L-lactyl (–OCH(CH$_3$)C=O–) unit (designated as L) methine protons 1 were sensitive to the repeat unit sequence distribution. Thus, two sets of quartets at 5.21 and 5.06 ppm resulted. Possible diad structures which could give rise to these signals are *LL*, *LH* (H designates ^{c}HTC),

Table 3. Estimated Repeat Unit Length of L-LA−^{c}HTC Copolymers

entry	catalyst	reacn conditions						
		T (h)	T (°C)	f_{LA}/f_{HTC}	F_{LA}/F_{HTC}	L_H[a]	L_L[b]	R[c]
5	Al(O^{i}Pr)$_3$	6h	120	81/19	95/5	1.0	36	1.07
6	Al(O^{i}Pr)$_3$	6h	120	65/35	88/12	1.2	17	0.92
12	ZnEt$_2$-0.5H$_2$O	6h	120	67/33	88/12	1.3	27	0.58
16	Sn(Oct)$_2$	6h	120	82/18	93/7	1.0	39	0.71
18	Sn(Oct)$_2$	16h	120	83/17	88/12	1.2	18	0.87
10	Sn(Oct)$_2$	6h	120	67/33	86/14	1.4	19	0.70
15	Sn(Oct)$_2$	6h	120	49/51	72/28	1.7	9.5	0.65

[a] Average length of ^{c}HTC repeat units determined by eq 2. [b] Average length of lactyl (−OCH(CH$_3$)C=O−) repeat units determined by eq 1. [c] Calculated by $L_{LA}{}^r/L_{LA}{}^e$, $L_{LA}{}^r = {}^1/_2(1 - F_L)$; the superscript r is the value corresponding to a statistically random distribution and superscript e indicates the experimentally determined value (see ref 31).

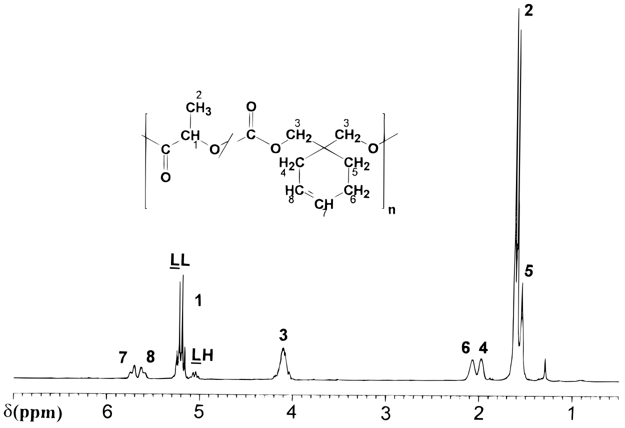


Figure 2. 1H-NMR spectrum of L-LA−^{c}HTC copolymer with F_{LA}/F_{HTC} = 72/28 mol/mol prepared by Sn(Oct)$_2$ catalysis (entry 15 in Table 2). H = ^{c}HTC unit; L = lactyl unit.

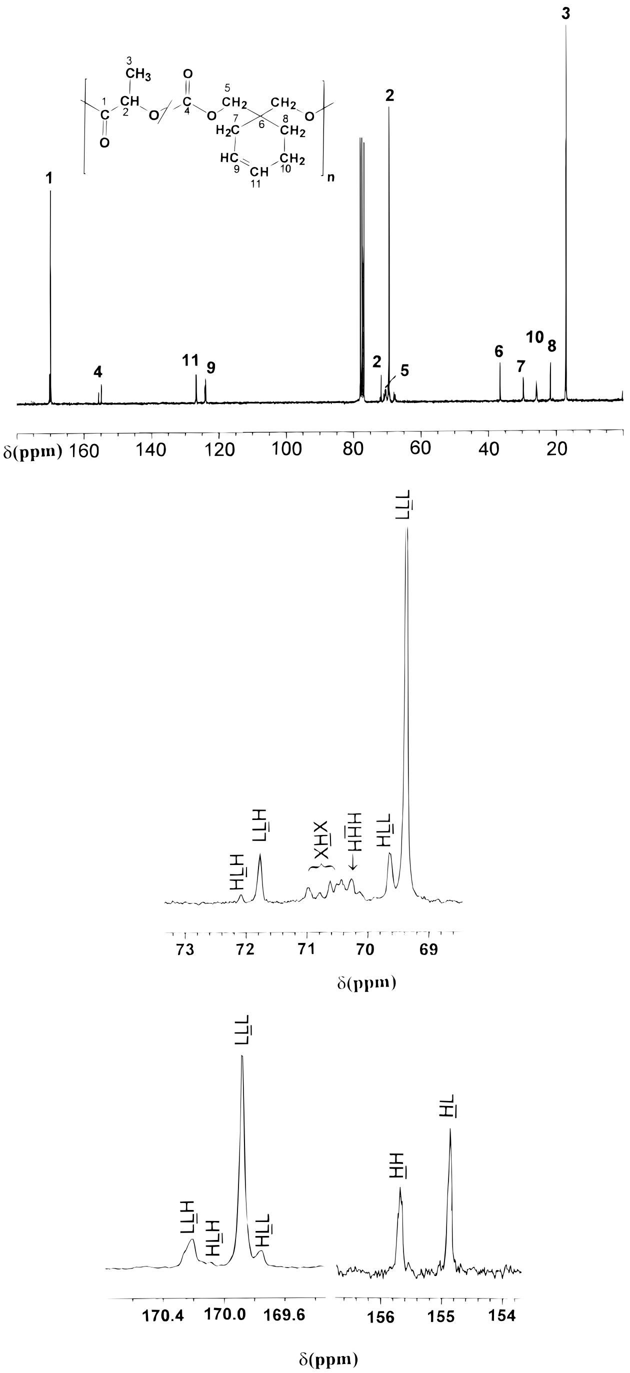


Figure 3. 13C-NMR spectrum of L-LA−^{c}HTC copolymer with F_{LA}/F_{HTC} = 72/28 mol/mol prepared by Sn(Oct)$_2$ catalysis (entry 15 in Table 2): (a, top) full spectrum, (b, middle) main chain *C*H and *C*H$_2$ region expansion, X = H or L, and (c, bottom) carbonyl region expansions.

and H*L*, where we observe the C*H* proton of the underlined repeat unit. Calculations of signal positions were carried out by simulations using appropriate model compounds and ACD/HNMR software (Version 1.0 for Microsoft Windows, Bruker Inc.). The model compounds and results of the calculations are included in the Supporting Information. This work indicated that *L*H is upfield from *L*L and that H*L* and *L*L are not resolved. These assignments were consistent with those made previously for LA/TMC copolymers.[18,19,23] ^{1}H-NMR integration intensities (I) at 5.21 and 5.06 ppm and eq 1 were then used to calculate L-lactyl sequence lengths (L_L). The values of L_L for selected products are listed in Table 3. The chemical shift at 4.0−4.2 ppm

$$L_L = I_{5.21\mathrm{ppm}}/I_{5.06\mathrm{ppm}} + 1 \qquad (1)$$

was due to main chain protons 3 of the ^{c}HTC units (Figure 2).[22] For the ^{c}HTC homopolymer, protons 3 appear as a doublet of doublets due to coupling of diasterotopic protons which have slightly differing chemical shift.[22] In comparison, protons 3 of the copolymer appear as a broad signal which is virtually devoid of coupling features with a peak at 4.10 ppm. In addition, weak signals corresponding to protons 3 were seen as shoulders at 4.05 and 4.20 ppm (see Figure 2). This additional complexity of protons 3 signals for the copolymer is attributed to effects of copolymer sequence distribution.

Figure 3a shows the full ^{13}C-NMR spectrum of the copolymer with F_{LA}/F_{HTC} = 72/28 prepared by Sn(Oct)$_2$ catalysis at 120 °C (entry 15 in Table 2). Except for carbons 2 and 5, the assignments in Figure 3a were made on the basis of the ^{13}C-NMR spectra of the respective homopolymers.[22,30] The complexity of the signals

Table 4. Comonomer Sequence Fractions of L-LA−^{c}HTC Copolymer Determined by the ^{13}C-NMR Carbonyl Region

	reacn conditions[a]			exptl[b] (calcd[c])					
entry	t (h)	f_{LA}/f_{HTC}	F_{LA}/F_{HTC}	L*L*H	L*L*L	H*L*L	H*L*H	*H*H	*H*L
16	6	82/18	93/7	0.05 (0.03)	0.89 (0.90)	0.03 (0.03)	0.01 (0.00)	0.00 (0.00)	0.02 (0.04)
18	16	83/17	88/12	0.09 (0.06)	0.78 (0.82)	0.06 (0.06)	0.01 (0.00)	0.01 (0.00)	0.05 (0.06)
15	6	49/51	72/28	0.15 (0.11)	0.61 (0.59)	0.07 (0.11)	0.02 (0.02)	0.06 (0.03)	0.08 (0.14)

[a] Sn(Oct)$_2$ as catalyst, $M/I = 200$, 120 °C. [b] L = lactyl unit, H = ^{c}HTC unit, determined by ^{13}C-NMR carbonyl relative intensities. [c] Calculated using equations which describe a Bernoullian or random statistical copolymerization[31] by $[L\mathit{L}L] = p^3$, $[L\mathit{L}H] = [H\mathit{L}L] = p^2q$, $[\mathit{H}H] = q^2$, $[\mathit{H}L] = pq$, where p and q represent molar percent of lactyl and ^{c}HTC, respectively, in the copolymer.

between 69 and 73 ppm due to carbons 2 and 5 gives information on polymer microstructure (Figure 3b). A ^{1}H−^{13}C correlated NMR spectrum (Supporting Information) showed the following: (i) cross-peaks of the ^{1}H-NMR signal at 5.21 ppm with ^{13}C-NMR signals at 69.39 and 69.66 ppm; (ii) a cross-peak between the ^{1}H-NMR signal at 5.06 ppm and the ^{13}C-NMR signal 71.78 ppm. On the basis of this information and comparison of other spectra for copolymers of different composition, the C2 signals at 69.39, 69.66, and 71.78 ppm were assigned to the triad sequences L*L*L, H*L*L, L*L*H, respectively. The signal at 72.08 ppm was assigned to the triad sequence H*L*H since it is close in position to L*L*H triads and of weak intensity, which is consistent with a low probability of formation.

Observation of the corresponding ^{1}H−^{13}C correlated NMR spectrum (Supporting Information) showed a cross-peak between the ^{1}H-NMR signal at 4.21 ppm and the complex pattern of ^{13}C-NMR signals between 70.00 and 70.98 ppm. Furthermore, poly(^{c}HTC) hompolymer showed a signal due to C5 at about 70.27 ppm. Thus, the signal at 70.27 ppm was assigned to H*H*H triads, while other signals between 70.00 and 70.98 ppm were designated as X*H*X where X could either be L or H. The complexity of the signals due to C5 is likely due to long-range sequence effects and is inconsistent with a blocky copolymer structure. It should be noted that assignment of signals at 67.5−68.0 ppm was not possible since cross-peaks for this signal region in the ^{1}H−^{13}C correlated NMR spectrum were not observed.

The carbonyl signals were also found to be sensitive to the copolymer repeat unit sequence distribution. Expansions of the carbonyl region are displayed in Figure 3c. The signals at 155.7 and 154.9 ppm were assigned to *H*H/L*H* and *H*L diads, respectively, where the orientations of H and L units are $-OCH_2CXCH_2$-OCO (X = 2-pentene-1,5-diyl) and $-OCH(CH_3)CO-$, respectively. These assignments were based on the relative signal intensities of the copolymers with different compositions and with knowledge that the carbonyl for P(^{c}HTC) homopolymer was at 155.7 ppm. In addition, these assignments agree with those made by Draney *et al.* for TMC−L-LA copolymers.[19,24] The number average sequence length of ^{c}HTC units (L_H) was calculated using the relative integration intensities of the signals at 155.7 and 154.9 ppm and eq 2. Values of L_H are given in Table 3. For all of the copolymers, the

$$L_H = (I_{H-H}/I_{H-L}) + 1 \qquad (2)$$

carbonyl region of L-lactyl units showed three major and additional low-intensity peaks (see Figure 3c). Comparison to homopolymeric L-PLA shows that the peak at 169.9 is due to L*L*L triads. The chemical shifts of L*L*H and H*L*L determined by computer simulation using ACD/CNMR software (Version 1.0 for Microsoft Windows, Bruker Inc.) were 171.58 and 169.80 ppm, respectively. Thus, H*L*L and L*L*H were assigned as the high-intensity signals that were shifted upfield and downfield, respectively, relative to L*L*L triads. The weakest signal at 170.1 ppm was assigned to H*L*H sequences due to its close proximity to L*L*H triads as well as its low probability of occurrence. The comonomer sequence fractions determined by ^{13}C-NMR observation of the carbonyl region are summarized in Table 4. The experimental results for 6 and 16 h polymerizations are in generally good agreement with those calculated by assuming a Bernoullian or random statistical copolymerization (see Table 4).[31]

The copolymer randomness was further evaluated by determination of the coefficient R (see Table 3, footnotes) where R is 0 for a diblock copolymer and 1 for a statistically random distribution of L and H units.[31] The catalysts Al(O^{i}Pr)$_3$ and ZnEt$_2$−H$_2$O (1:0.5) resulted in copolymers with R values approaching 1 and 0.58, respectively. Comparison of entry 16 to entry 18 showed that, for Sn(Oct)$_2$ catalyzed polymerizations, increases in reaction time resulted in larger R values approaching 1. Therefore, the repeat unit sequence distribution of the products was varied more or less toward a random sequence distribution by variation in the catalyst and reaction time.

Mechanistic Considerations. Sn(Oct)$_2$ catalyzed TMC−L-LA copolymerizations at 110 °C reported by Grijpma and Pennings[18] showed that L-LA was the more reactive comonomer. Furthermore, the decrease in L_L as a function of reaction time was unexpectedly large. Transesterification was proposed to explain this phenomenon.[18,32] For the ^{c}HTC−L-LA copolymerizations, we observed that the values of L_H listed in Table 3 for selected ^{c}HTC−L-LA copolymers ranged from 1.0 to 1.7. Such short block lengths for ^{c}HTC would not be expected for a chain-end propagation mechanism based on the results in Figure 1 and/or the monomer reactivity ratio. In other words, since L-LA conversion is almost complete within a 1 h reaction time but ^{c}HTC conversion increased from 14 to 66% between 1 and 16 h, chain-end propagation should have resulted in ^{c}HTC segments that have long block lengths. However, even the 16 h polymerization (entry 18, Table 3) had an L_H of only 1.2 which is inconsistent with ^{c}HTC propagation exclusively at active chain ends without intramolecular exchange reactions. Furthermore, L_L decreased from 39 to 18 by increasing the reaction time from 6 to 16 h (see entries 16 and 18, Table 3). One explanation for the above is that the cyclic carbonate monomer is incorporated between repeat units in chains by an insertion mechanism. In other words, the insertion of ^{c}HTC may occur randomly along the chain which would reduce L_L with increased cyclic carbonate percent conversion. Such a mechanism could lead to H*L*H sequences, as was observed in ^{13}C-NMR spectra. This mechanism is reminiscent of that proposed for alternating DTC−ϵ-caprolactam copolymers which were said to

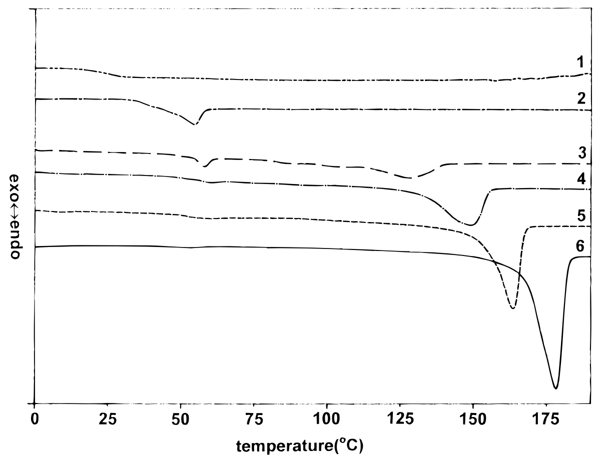


Figure 4. First heating DSC thermograms of L-LA−ᶜHTC copolymers with variable compositions prepared by $Sn(Oct)_2$ catalysis: 10 °C/min, N_2 purge. F_{LA}/F_{HTC} = 0/100 (1), 48/52 (2), 72/28 (3), 86/14 (4), 93/7 (5), and 100/0 (6).

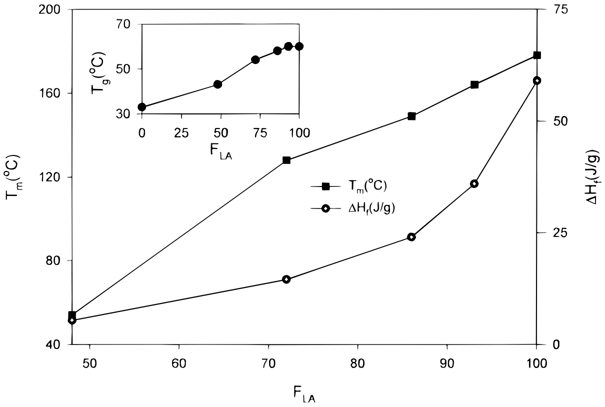


Figure 5. Plot of glass transition temperature (T_g), melting transition temperature (T_m), and enthalpy of fusion (ΔH_f) vs copolymer composition.

be formed by the insertion of ϵ-caprolactam into poly(DTC).[33] An alternative explanation is that ᶜHTC may be polymerized by propagation at chain ends which are subsequently redistributed by intramolecular exchange reactions.

Thermal Properties. Figure 4 shows the first heating DSC scans of L-LA−ᶜHTC copolymers with variable compositions (0, 7, 14, 28, 52, and 100 mol % ᶜHTC) prepared by $Sn(Oct)_2$ at 120 °C for 6 h. Peak melting temperatures (T_m) and enthalpy of fusion (ΔH_f) values as a function of the copolymer composition are shown in Figure 5. The ᶜHTC homopolymer (thermogram 1, Figure 4) did not show a melting transition. Further study of this homopolymer by X-ray diffraction[22] confirmed that it was amorphous. For P(L-LA-*co*-52 mol % ᶜHTC), a low enthalpy melting transition with a T_m at 54 °C was observed, suggesting that short L-LA block lengths (L_L = 4.2 by ^{1}H-NMR) along the chain formed poorly ordered L-PLA crystalline phases. Two melting transitions at 58 °C (ΔH_f = 1.5 J/g) and 128 °C (ΔH_f = 13 J/g) were observed for P(L-LA-*co*-28 mol % ᶜHTC) (entry 15, Table 2), which suggested that different populations of L-LA chain segments having shorter and longer block lengths phase separated to form lower and higher melting L-PLA crystalline phases. Further decrease in ᶜHTC content in copolymers resulted in higher T_m and ΔH_f values (see Figures 4 and 5). Thus, one outcome of introducing ᶜHTC along L-PLA chains is a method to regulate the melting temperature and crystallinity of L-PLA based materials. Changes in the glass transition temperature (T_g) as a function of the copolymer composition are shown as an insert in Figure 5. In all cases, only one T_g was observed which increased with decreased copolymer ᶜHTC content. The T_g values of copolymers with $F_{LA} \geq 72$ mol % slowly approached that of L-LA homopolymer (from 54 to 60 °C). In general, variation in T_g as a function of copolymer composition is consistent with the formation of chains having a substantial fraction of LH and HL diad linkages as opposed to the formation of ᶜHTC−L-PLA multiblock copolymers. The latter would have two separate T_g values (33 and 60 °C) for immiscible P(ᶜHTC) and L-PLA chain segments. P(L-LA-*co*-52 mol % ᶜHTC) had a T_g at 38 °C which is close to body temperature (37 °C). By increasing the copolymer ᶜHTC content to >52 mol %, copolymers may be prepared with T_g values that are below normal body temperature. Since mechanical properties, rate of polymer erosion, and other material characteristics will be a function of whether the copolymer has a T_g below or above that *in vivo*, the ability to manipulate the material T_g around body temperature is important.

Table 5. Epoxidation of L-LA−ᶜHTC Copolymer by 3-(chloroperoxy)benzoic Acid (3-CPBA)[a]

entry	reacn time (h)	M_n[b]	M_w/M_n[b]	% conversion[c]
epoxy-1	0.5	67 800	2.0	33
epoxy-2	1	61 900	1.8	36
epoxy-3	4	58 800	1.9	71

[a] Starting copolymer: entry 10 in Table 1, M_n = 82 200, in $CHCl_3$, room temperature, 3-CPBA/C=C group = 1/1 mol/mol. [b] Molecular weight data of resulting product. [c] mole percent conversion of C=C structure into epoxide determined by ^{1}H-NMR; see ref 22 for details.

Epoxidation of the Copolymer. The copolymer with 14 mol % ᶜHTC repeat units (entry 10, Table 1) was selected for conversion of vinyl substituents to epoxy functionalities. The epoxidations were performed by using a 1:1 molar ratio of the C=C group to 3-(chloroperoxy)benzoic acid (3-CPBA) at room temperature (see Table 5). ^{1}H-NMR spectra of epoxidized products showed new signals at 3.15 ppm (doublet) which were assigned to protons of the epoxy structure (*spectrum deposited in Supporting Information*). Epoxidation reaction efficiency was determined from the relative intensity of signals at 3.15 and 5.5−5.8 ppm (C=C protons 7 and 8: see Figure 2). The percent conversion of C=C to epoxy groups was about 35% for reactions conducted for 0.5 and 1 h. However, by increasing the reaction time from 1 to 4 h, the percent conversion increased from 36 to 71%. The apparent molecular weight decreased only slightly during the epoxidation reaction (Table 4). Interestingly, an increase in the reaction time from 1 to 4 h which doubled the epoxidation efficiency resulted in nearly identical copolymer molecular weights. In other words, increased epoxidation efficiency was achieved without substantial detrimental effects on chain length. It is anticipated that epoxy functional substituents will permit further diversification of chain functionality by subsequent modifications.[34] For example, epoxy groups may be converted to diols,[35] −CH(OH)CH(NHR)−[36] and −CH(OH)CH(OR)−[37] under mild reaction conditions. Furthermore, the epoxy substituents may be used to initiate ring-opening polymerizations of epoxides[38] and lactones[39] in the presence of $FeCl_3$ and $(RE)Cl_3$(RE = rare earth metal), respectively, under mild reaction temperatures (20−100 °C).

Conclusions

^{c}HTC, a cyclohexene containing cyclic carbonate monomer, has been copolymerized with L-LA to introduce C=C functional groups in L-PLA. A variety of organometallic catalysts, including Al, Zn, and Sn(II) based catalysts, have been utilized for the copolymerization. Sn(Oct)$_2$ was found to be the preferred catalyst for the synthesis of high molecular weight copolymer (M_n up to 109 000). On the basis of ^{13}C-NMR analyses of copolymers prepared by Sn(Oct)$_2$ catalysis, it was concluded that the copolymer repeat unit sequence distribution and average block lengths generally were close to that expected for a statistically random distribution of lactyl and ^{c}HTH repeat units. This copolymerization behavior may result from one or both of the following: (*i*) the insertion of ^{c}HTC occurring randomly along the chain and (*ii*) ^{c}HTC polymerization by propagation at chain ends which are subsequently redistributed by intramolecular exchange reactions.

The introduction of increasing ^{c}HTC units into copolymers was useful for decreasing the glass transition, melting transition temperature, and enthalpy of fusion. Modulation of polymer thermal properties by such copolymerizations may, in principle, be exploited to improve copolymer processability relative to L-PLA homopolymer and to increase polymer hydrolytic degradability relative to high-crystallinity L-PLA materials. Furthermore, copolymers with ^{c}HTC content of >52 mol % would be expected to have T_g values that are below normal body temperature. Modulation of L-PLA based copolymer T_g above and below that of normal physiological temperature certainly is of interest as a method for regulating physical properties and bioresorption rates.

The C=C group in the copolymer provides a number of valuable opportunities for further modifications to introduce other functionalities. For example, in this work, the epoxidation of C=C groups was successfully performed by using 3-CPBA as the oxidizing reagent. In one case 71% of C=C groups were converted to epoxides with only a small apparent decrease in copolymer molecular weight. Alternatively, the cyclohexene side groups can be used as sites for free radical crosslinking, which will be important in modulating the rheology of polymer melts during thermal processing.

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Supporting Information Available: Figures showing ^{1}H-NMR simulation results for the calculation of chemical shift positions of lactyl methine protons as a function of neighboring repeat unit composition, the ^{1}H−^{13}C correlated 2D NMR spectrum for the copolymer with F_{LA}/F_{HTC} = 72/28, and the ^{1}H-NMR spectrum for an F_{LA}/F_{HTC} = 86/14 copolymer where 71 mol % of the C=C functionalities were epoxidized (3 pages). Ordering information is given on any current masthead page.

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