Synthesis and Characterization of [L]-Lactide−Ethylene Oxide Multiblock Copolymers

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Received March 18, 1997; Revised Manuscript Received May 19, 1997⊗

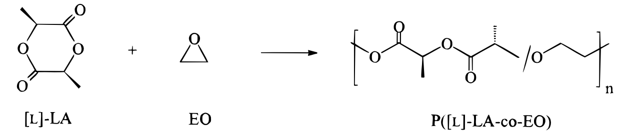
ABSTRACT: [L]-Lactide ([L]-LA)/ethylene oxide (EO) ring-opening copolymerizations were successfully carried out by using various catalysts including isobutylaluminoxane (IBAO), *in situ* $AlR_3{\cdot}0.5H_2O$ systems (R = ethyl, isobutyl) and Sn−Al bimetallic catalysts. Analysis of products by ^1H NMR showed that methanol insoluble copolymer fractions had multiblock structures. The multiblock segment length and molecular weight of the copolymers were regulated by a variation in the reaction temperature, reaction time, reaction medium, and the catalyst structure. An increase in the reaction temperature was used to obtain shorter segment block lengths. Bulk reactions at elevated temperatures gave shorter block lengths than those of corresponding polymerizations conducted in solution (xylene). Differential scanning calorimetry (DSC) results showed two melting transitions corresponding to poly(ethylene oxide) (PEO) and [L]-polylactide ([L]-PLA) crystalline phases. The melting temperature and enthalpy of fusion for the phase-separated [L]-PLA crystalline phase was "tailored" by modulating the copolymer composition and the [L]-PLA block length. Blends with PLA were prepared by substituting poly(ethylene glycol) (PEG) with a high EO content [L]-PLA/EO multiblock copolymer. The idea explored was that the multiblock copolymers would be expected to leach into aqueous environments at a slower rate than PEGs. Substitution of the [L]-PLA/EO copolymer in place of PEG resulted in important increases in the film modulus and yield strength without loss in elongation at yield, break stress, and elongation at break. Thus, we demonstrated a versatile route to important new multiblock [L]-PLA/EO copolymers which have excellent potential to be useful for a wide range of biomedical applications including bioresorbable implant materials and tissue engineering. Furthermore, the synthetic methods developed herein provide routes which will be useful in "fine-tuning" product physicomechanical properties and degradation rates.

Introduction

Polylactides, PLAs, and their random or block copolyesters have been used for applications as drug delivery systems and medical sutures.[1−4] Early studies using poly([L]-lactide), [L]-PLA, showed that it was readily resorbed by living tissues.[5−7] However, the high crystallinity and low hydrophilicity of [L]-PLA decreased its degradation rate and resulted in poorer soft tissue compatibility.[5] An important strategy to fine-tune PLA physical and biological properties is by copolymerization of lactide with other monomers such as other lactones and epoxides.

Poly(ethylene glycol), PEG, and poly(ethylene oxide), PEO, are both water soluble and show favorable biocompatibility.[8] Considerable effort has focused on the preparation of polyester−PEG di- and triblock copolymers.[9] Cohn and Younes[10] synthesized block copolymers of PLA−PEG by polytransesterification reactions of lactide in the presence of PEG (M_n = 600−6000 g/mol) using antimony trioxide (Sb_2O_3) as the catalyst. Kimura *et al.*[11] reported A−B−A triblock copoly(ester−ether)s comprised of PLA and poly(oxypropylene) (PPG) where the latter was the B segment. The copolymers were prepared by the polymerization of [L]-lactide by using the reaction mixture of poly(propylene glycol) (PPG) with $AlMe_3-H_2O$ (1:0.5) as a macroinitiator. Degradation studies carried out both *in vitro* and *in vivo* of fibers formed from these triblock copolymers showed that the hydrolysis rate increased with increasing PPG copolymer content.[11] Stevels *et al.*[12] prepared PLA−PEG−PLA triblock copolymers in toluene at 70 °C by lactide ring opening using PEG and $Sn(Oct)_2$ as the diol prepolymer and catalyst, respectively. The $Al(^iBu)_3-H_3PO_4-H_2O$ catalyst system was also used to prepare triblock PLA−PEG−PLA copolymers.[13]

Scheme 1. [L]-LA−EO Copolymerization



An alternative route to ester−ether block copolymers is living anionic ring-opening polymerization by the sequential addition of cyclic ether and lactone monomers.[14] Indeed, a number of catalysts have been used to prepare polyester−polyether di- and triblock copolymers by living polymerizations.[15] Aluminum tetraphenylporphyrin {(TPP)Al-X} is a representative initiator, which effectively brings about living polymerization of various epoxides such as ethylene oxide, propylene oxide, 1,2-epoxybutane, and epichlorohydrin, affording the corresponding polyethers with a narrow molecular weight distribution (M_w/M_n = 1.05−1.20).[16, 17] Sequential polymerizations of living polyethers with lactones[18−20] or lactides[21] give the corresponding AB and ABC type block copolymers with controlled block length. Interestingly, to our knowledge, there have been no reports describing the direct copolymerization of epoxides and lactides. Recently, our laboratory has focused on the development of suitable catalysts and polymerization conditions to copolymerize ethylene oxide (EO) with various lactones to obtain desired polymer structures.[22]

In this paper, we report on copolymerizations of [L]-LA and EO monomers using a wide range of organometallic catalysts (Scheme 1). Relationships between the comonomer feed, catalyst system and the resulting poly([L]-LA-*co*-EO) microstructure, molecular weight, and thermal properties were reported. The outcome of this work was

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⊗ Abstract published in *Advance ACS Abstracts,* July 1, 1997.

S0024-9297(97)00385-9 CCC: $14.00

Table 1. [L]-Lactide–Ethylene Oxide Ring-Opening Copolymerization in Toluene at 60 °C with Different Catalysts[a]

entry	catalyst	$f_{[L]\text{-LA}}/f_{EO}$[c]	total yield[d] (%)	MeOH-i[e] (%)	$F_{[L]\text{-LA}}/F_{EO}$[f]	$L_{[L]\text{-LA}}/L_{EO}$[g]	M_n[h]	M_w/M_n[h]
1	$AlEt_3 \cdot 0.5H_2O$	1/2	66	78	27/73	13/46	24 800	5.3
2	$Sn(Oct)_2 \cdot 4AlEt_3$	1/2	N/D					
3	$Sn(Oct)_2 \cdot 4AlEt_3 \cdot 2H_2O$	1/2	38	81	30/70	19/85	26 800	3.8
4	$Al((^iBu))_3 \cdot 0.5H_2O$	2/1	39	77	47/53	11/25	12 300	3.6
5	$Al(^iBu)_3 \cdot 0.5H_2O$	1/1	46	84	30/70	25/42	21 100	5.6
6	$Al(^iBu)_3 \cdot 0.5H_2O$	1/2	55	64	22/78	9/44	26 100	6.2
7	$Sn(Oct)_2 \cdot 4Al(^iBu)_3$	1/2	29	14	5/95	N/D		
8	$Sn(Oct)_2 \cdot 4Al(^iBu)_3 \cdot 2H_2O$	1/2	68	79	20/80	12/66	17 600	3.2
9	IBAO[b]	1/2	41	81	35/65	12/53	21 300	3.8
10	$Al(^iBu)_3 \cdot 0.5H_2O$	1/4	40	72	17/83	9/40	23 700	5.1

[a] Polymerization conditions: [L]-LA = 1 M; [[L]-LA]/[Al] = 25; 22 h reaction time; in toluene. [b] IBAO = isobutylaluminoxane. [c] Molar monomer feeding ratio. [d] 100 × petroleum ether and ether insoluble product (g)/total monomer (g). [e] Based on total yield. [f] Molar composition of methanol insoluble fraction, calculated by ^1H NMR analysis (see Experimental Section), [L]-LA = [L]-lactide unit. [g] Average block lengths of [L]-LA and EO repeat units for the methanol insoluble fraction. [h] Molecular weight and molecular weight distribution of the methanol insoluble fraction determined by GPC (see Experimental Section).

the development of methods and new lactide/EO copolymers that provide critical control of copolymer structural variables. Such control has created new opportunities to develop "tailored" copolymers for a wide variety of critical application areas such as tissue engineering, controlled release of bioactive molecules, and controlled rates of copolymer bioresorption.

Experimental Section

Materials. Ethylene oxide (EO, Aldrich, purity > 99.7%) was used as received without further purification. Toluene and xylene (Aldrich) were dried by being distilled over melted sodium and stored under dry argon. [L]-Lactide from Aldrich was recrystallized from dry toluene[23] {mp 92–94 °C; $[\alpha]^{20}$ (λ = 589 nm) = −285° (c = 1, toluene)}. Trialkylaluminum compounds ($AlEt_3$ and $Al(^iBu)_3$) were purchased from Aldrich in toluene solution (1.9 and 1.0 M, respectively) and were used as received. Isobutylaluminoxane (IBAO) was from Akzo Chemicals Inc. in heptane solution (0.95 M). All air-sensitive liquid reagents and dry solvents were stored and subsequently transferred via syringe under an argon atmosphere.

Preparation of *in situ* AlR_3–H_2O Catalysts. The *in situ* catalysts $AlR_3 \cdot 0.5H_2O$ were prepared by modification of a literature procedure.[24] To a previously silanized, flame-dried, and dry argon purged 10 mL Schlenk tube, 1 mL of AlR_3 (in dry toluene) was transferred via syringe. The solution was cooled in an external dry ice–acetone bath followed by slowly adding a solution of distilled water in 1,4-dioxane (1/9 v/v) with vigorous stirring. After 15 min, the dry ice bath was removed and the temperature was increased to ambient temperature. A clear solution was formed and stored in the refrigerator (about 4 °C) for up to 1 month prior to use without loss of catalytic activity.[11]

Preparation of Bimetallic Catalysts. Sn(2-ethylhexanoate)$_2$, $Sn(Oct)_2$, was transferred into a pretreated Schlenk tube in a glovebox which was purged with dry nitrogen atmosphere. The aluminum alkyl solution was transferred via syringe into the Schlenk tube, and the resulting bimetallic solution was then maintained at 60 °C for 1 h after which it was stored at ~4 °C for up to 15 days. The relative molar quantities of these metals are given in Tables 1–4. A deep yellow solution for Sn–Al systems was observed. The Sn–Al–H_2O systems were prepared from Sn–Al solutions by adding H_2O as described above for AlR_3–H_2O preparations.

Copolymerization Procedure (General). The following describes the general procedure used for EO/[L]-LA copolymerizations. Additional information on polymerization conditions is given in Tables 1–4. [L]-Lactide was transferred into a previously silanized, flame-dried, and argon-purged ampule using a dry nitrogen purged glovebox. Subsequently, dry toluene, ethylene oxide, and the catalyst solution were transferred by syringe. The ampule was then flame sealed under dry argon and placed in a thermostated oil bath for a preset time. Subsequently, the reaction product was dissolved in chloroform (~10 mL/g of starting monomers) and precipitated into petroleum ether (~100 mL). The precipitated material was washed several times with petroleum ether and Soxhlet extracted with ether overnight to remove unreacted [L]-LA,[25] and then remaining volatiles were removed *in vacuo* (<3 mmHg, 40 °C, 24 h).

Fractionation Method. The method was similar to that reported for PLA–PEG block copolymers.[10] The petroleum ether insoluble copolymer (~1 g) was added to methanol (100 mL) and subsequently stirred under ambient conditions for 24 h. This procedure was repeated once again by adding 80 mL of fresh methanol to the insoluble material. The methanol insoluble fraction (MeOH-i) was isolated by filtration, the methanol solutions were combined, and methanol was removed by rotoevaporation to give the soluble fraction (MeOH-s). The remaining volatiles were removed from both fractions *in vacuo* (<3 mmHg, 25 °C, 24 h).

Instrumental Methods. (1) Nuclear Magnetic Resonance (NMR). 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 as follows (unless otherwise specified, values in parentheses are specifically for the Bruker DRX-500): temperature 300 K, pulse width 7.80 μs (13.20 μs) (30° for both instruments), 32 K data points, acquisition time 3.18 s (1.59 s), 1 s relaxation delay, and 32 transients.

(2) Molecular Weight Measurements. All molecular weights were determined by gel permeation chromatography (GPC) utilizing a Waters Model 510 pump, Model 410 differential refractometer, Waters 486 tunable absorbance detector, and a Model 717 Plus autosampler with 500, 10^3, 10^4, and 10^5 Å ultrastyragel columns placed in a series. Chloroform was used as the eluent at a flow rate of 1.0 mL/min. The injection volume was 100 μL, and sample concentrations were normally ~0.5% w/v. 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.

(3) Thermal Analysis. Differential scanning calorimetry (DSC) studies were conducted on a DuPont DSC 912 equipped with a TA 2000 data station. Experiments were carried out with 5–8 mg of sample, a heating rate of 10 °C/min, a nitrogen purge, and a heating of samples from room temperature to 200 °C. Data reported for the melting temperature (T_m) and enthalpy of fusion (ΔH_f) were taken from the first heating scan. The reported T_m was the peak melting temperature of the largest endotherm transition. ΔH_f values were taken as the cumulative value over the entire melting transition range. T_g was defined as the midpoint of the transition from the second heating scan (10 °C/min) of the rapidly quenched samples from melt.

Tensile Property. Films (thickness 0.08–0.10 mm) were prepared by solution mixing and casting from 10 wt % chloroform solutions the following polymer blends: (i) [L]-PLA

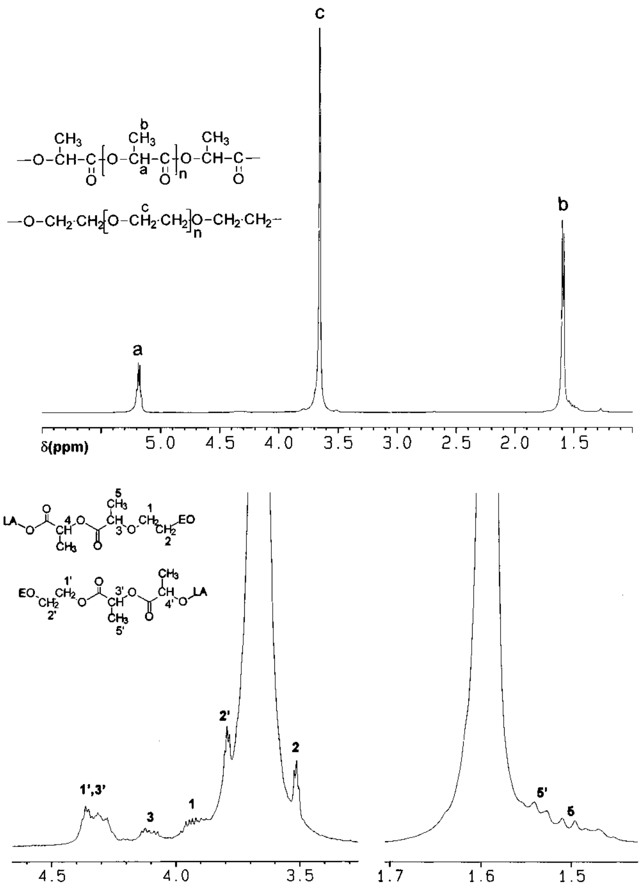

Figure 1. (a) 500 MHz ^{1}H-NMR spectrum of a methanol insoluble [L]-LA–EO copolymer ($F_{[L]\text{-LA}}/F_{EO}$ = 30/70) prepared using Al(^{i}Bu)$_3$·0.5H$_2$O at 80 °C in toluene; (b) expansion of selected spectral regions from the spectrum in 1a.

(Cargill, Inc., M_w/M_n = 168 000/85 400, % [L] = 96)/PEG (Polysciences, Inc., M_n = 18500) and (ii) [L]-PLA (same polymer as in (i)/poly([L]-LA-*co*-EO) (MeOH-i fraction of entry 8, Table 1). After slow evaporation of chloroform (3 days, ambient conditions), the remaining solvent in the films was removed in a vacuum dessicator (<3 mmHg, 25 °C, 24 h). The resulting films were cut to size (1 × 4 cm^2) and aged while storing over Drierite at ambient temperature for 1 week. Film tensile properties were measured on an Instron (Model 1137) at room temperature with a crosshead rate of 1.0 in./min, and the data reported were the mean and standard deviation from five determinations.

Results and Discussion

Structure of [L]-LA–EO Copolymers. The copolymers obtained were characterized by ^{1}H NMR and peak assignments were confirmed by ^{1}H–^{1}H NMR correlated spectroscopy (COSY-45, not shown). Figure 1a displays the full ^{1}H NMR spectrum of an [L]-LA–EO copolymer with a molar composition ($F_{[L]\text{-LA}}/F_{EO}$) of 30/70. This copolymer was prepared by using Al(^{i}Bu)$_3$·0.5H$_2$O as the catalyst (entry 12, MeOH-i fraction, Table 2). The most intense ^{1}H NMR signals at 5.21, 3.66, and 1.62 ppm were assigned (see Figure 1a) on the basis of previous work.[10] In addition to these resonances, expansions of the relatively weak signals at 4.32, 4.10, 3.92, 3.80, 3.53, and 1.57–1.48 ppm were shown in Figure 1b. Since this product was of high molecular weight (M_n = 50 300, M_w/M_n = 3.0), it is unlikely that these signals are due to chain end groups.[26] Assignments of protons 1(1′), 2(2′), 3(3′), and 5(5′) shown in Figure 1b were made on the basis of careful inspection of the ^{1}H–^{1}H COSY 2-D NMR (not shown). Specifically, cross peaks were found as follows: (i) 3.92 and 3.53 ppm, (ii) 4.10 and 1.51 ppm, (iii) 4.32 and 3.80 ppm, and (iv) 1.54 and 4.32 ppm. In addition, 1′ and 3′ will be further downfield relative to 1 and 3, respectively, since an α-ester group is more electron-withdrawing than an α-ether group. The average block lengths of dimeric [L]-LA and EO chain segments ($L_{[L]\text{-LA}}$ and L_{EO}) were determined to be 11 and 24, respectively, by the following equations:

$$L_{[L]\text{-LA}} = (SI_{5.21ppm} + 2SI_{4.10ppm})/2SI_{4.10ppm}$$

$$L_{EO} = \{SI_{3.66ppm} + SI_{3.92ppm} + SI_{3.80ppm} + SI_{3.53ppm} + (SI_{4.32ppm} - SI_{4.10ppm})\}/2(SI_{4.32ppm} - SI_{4.10ppm})$$

where SI is the signal intensity for the corresponding spectral region.

Product Fractionation: Isolation of MeOH-i Multiblock Copolymers. Since EO homopolymers have high solubility in methanol at room temperature,[27] extraction of the polymerization products by methanol was carried out to give MeOH-i and MeOH-s fractions (see Experimental Section). The MeOH-s fractions might contain both PEO homopolymers and high EO copolymers since LA units were observed in ^{1}H NMR spectra. When selected MeOH-i fractions were extracted a second time with methanol, the additional solubilized product was negligible. Therefore, we concluded that one extraction procedure was sufficient to remove the EO homopolymer from MeOH-i fractions. Thus, the determination by ^{1}H NMR that MeOH-i product fractions contain both [L]-LA and EO repeat units (see Tables 1–4) was evidence that copolymers were formed. Furthermore, inspection of Tables 1–4 (see discussions below) shows that the MeOH-i fractions show highly variable chain segment lengths depending on the catalyst and polymerization conditions. However, since product block lengths were generally much shorter than chain lengths, it was concluded that these products are best described as multiblock copolymers.

[L]-LA–EO Copolymerization at 60 °C. The homopolymerizations of lactones and ethylene oxide (EO) were extensively investigated by using Al-, Zn-, Sn-, and Y-organometallic and μ-O-bridged bimetallic catalysts.[28–31] Among the various catalysts reported, the AlR$_3$–H$_2$O system was found to be very effective for the preparation of high molecular weight polymers from both lactones and epoxides.[14] In addition, Sn(Oct)$_2$ is a preferred catalyst for synthesizing high molecular weight PLAs.[5,32] When aluminum compounds were combined with Sn(Oct)$_2$, it was hoped that enhanced catalyst activity for the copolymerization of [L]-LA with EO might result. Therefore, a variety of catalysts including AlR$_3$·0.5H$_2$O (R = ethyl, isobutyl), isobutylaluminoxane (IBAO), and various Sn–Al bimetallic catalysts were evaluated for [L]-LA/EO copolymerizations conducted in toluene at 60 °C (see Table 1). In many cases, the MeOH-i fraction was the major component, and its composition was similar to the monomer feed ratio. Notable exceptions include entries 4, 5, and 7 (see Table 1). When the monomer feed ratio for copolymerizations catalyzed by Al(^{i}Bu)$_3$·0.5H$_2$O were varied, copolymers with compositions ($F_{[L]\text{-LA}}/F_{EO}$) which ranged from 47/53 to 17/83 were prepared. On the basis of the results of entries 4–6 and 10 which showed the highest total yield and MeOH-i fraction, M_n, for the monomer feed ratio ($f_{[L]\text{-LA}}/f_{EO}$) 1/2, this feed ratio was chosen for other subsequent polymerization reactions described in Table 2. Comparison of entries 6 and 8 in Table 1 shows that

Table 2. Effect of Reaction Temperature on [L]-Lactide–Ethylene Oxide Copolymerizations Catalyzed by $AlR_3\cdot0.5H_2O^{a,b}$

entry	catalyst	react time (day)	react temp (°C)	total yield (%)	MeOH-i (%)	$F_{[L]-LA}/F_{EO}$	$L_{[L]-LA}/L_{EO}$	M_n	M_w/M_n
11	$Al(^iBu)_3\cdot0.5H_2O$	3	60	90	96	35/65	15/32	30 700	3.9
12	$Al(^iBu)_3\cdot0.5H_2O$	3	80	90	97	30/70	11/24	50 300	3.0
13	$Al(^iBu)_3\cdot0.5H_2O$	3	100	85	75	24/76	4.4/33	40 500	2.6
14	$Al(^iBu)_3\cdot0.5H_2O$	1	130	84	10	23/77	4.7/18	1460	20
15	$AlEt_3\cdot0.5H_2O$	3	60	91	98	33/67	18/39	30 600	3.6
16	$AlEt_3\cdot0.5H_2O$	3	80	92	98	28/72	10/39	53 200	2.9
17	$AlEt_3\cdot0.5H_2O$	3	100	90	94	31/69	13/39	37 000	2.3
18	$AlEt_3\cdot0.5H_2O$	1	130	82	38	31/69	10/32	17 500	2.7

[a] $f_{[L]-LA}/f_{EO} = 1/2$. [b] Reactions at 130 °C were conducted in xylene; other reaction conditions and abbreviations were described in Table 1 footnotes.

the addition of $Sn(Oct)_2$ increased the total yield and the MeOH-i fraction yield but resulted in a smaller MeOH-i M_n. However, catalysis by $Sn(Oct)_2\cdot4AlEt_3\cdot2H_2O$ resulted in a lower total yield than $AlEt_3\cdot H_2O$ (entries 3 and 1). This may be explained by stronger coordination of the Sn–O–Al structure which contains the smaller ethyl as opposed to isobutyl ligands. This strong coordination may decelerate monomer propagation. Sn–Al binary systems without water only gave low product yields (entries 2 and 7). This highlights the importance of water for the formation of catalytically active Sn–O–Al molecular structures. Comparison of entries 1 and 6 catalyzed by $AlEt_3\cdot0.5H_2O$ and $Al(^iBu)_3\cdot0.5H_2O$, respectively, showed that the former catalyst gave a higher MeOH-i fraction yield but that the M_n values were similar. Also, comparison of entries 9 and 6 showed no advantages to the use of the oligomeric IBAO catalyst instead of the $Al(^iBu)_3\cdot0.5H_2O$ system. Study of $L_{[L]-LA}$ and L_{EO} values in Table 1 shows that all of the catalysts lead to multiblock copolymers. However, substantial differences in block lengths resulted by using different catalysts and monomer feed ratios.

A plot of monomer conversion versus reaction time for a copolymerization carried out at 60 °C, in toluene, catalyzed by $AlEt_3\cdot0.5H_2O$ and with $f_{[L]-LA}/f_{EO} = 1/2$ is shown in Figure 2a. Monomer conversion was determined by ^1H NMR spectral integration and gravimetric analysis of the petroleum ether insoluble product. The total yield increased gradually within 3 days to 91% and reached 100% by 6 days. Furthermore, comparison of EO and [L]-LA conversion showed that EO was more rapidly polymerized. For example, at 5 h, EO and [L]-LA conversion was 39% and 7%, respectively. Consistent with the more rapid conversion of EO, $L_{[L]-LA}/L_{EO}$ was 9.1/122 at 5 h. However, by 72 h, there was a substantial decrease in L_{EO} to 39 and a corresponding increase in $L_{[L]-LA}$ to 18. Evaluation of product molecular weight as a function of reaction time showed no substantial change (see Figure 2a). An identical experiment as above was carried out except that the catalyst used was $Al(^iBu)_3\cdot0.5H_2O$. The results of total yield and monomer conversion versus reaction time were shown in Figure 2b. The profile of total yield versus time was similar for both catalysts. Also, at low total yield (13% at 5 h), EO and [L]-LA conversion was 30 and 3%, respectively. However, by 26 h, EO and [L]-LA conversion was similar (54% and 60%). The rapid conversion of EO at short reaction times (5 h) resulted in $L_{[L]-LA}$ and L_{EO} values of 2.4 and 79, respectively. However, by 26 h, there was a substantial decrease in L_{EO} to 35 and a corresponding increase in $L_{[L]-LA}$ to 21. As from catalysis by $AlEt_3\cdot0.5H_2O$, $Al(^iBu)_3\cdot0.5H_2O$ catalysis resulted in products with similar molecular weight values as a function of reaction time or conversion.

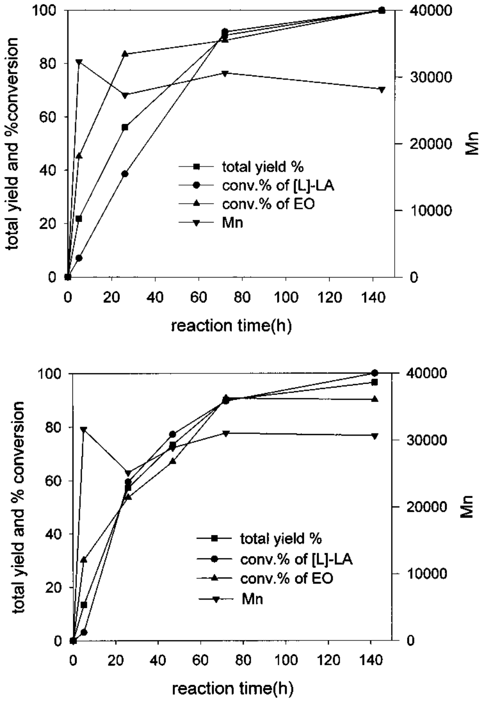

Figure 2. Effects of reaction time on the copolymerizations ([[L]-LA]/[Al] = 25, [EO]/[[L]-LA] = 2, [L]-LA = 1 M in toluene) conducted at 60 °C catalyzed by (a) $AlEt_3\cdot0.5H_2O$ and (b) $Al(^iBu)_3\cdot0.5H_2O$.

These results for both $AlEt_3\cdot0.5H_2O$ and $Al(^iBu)_3\cdot0.5H_2O$ catalysis are consistent with propagation being much faster than initiation and the participation of chain transfer and/or termination reactions. Furthermore, large differences in EO and [L]-LA reactivity for these polymerizations must have resulted in a heterogeneous distribution of chain compositions with different average block lengths.

Effect of Reaction Temperature. Since the reaction temperature can have a significant effect on catalyst structure and reactivity,[33] copolymerizations catalyzed by $AlEt_3\cdot0.5H_2O$ and $Al(^iBu)_3\cdot0.5H_2O$ were carried out at temperatures between 60 and 130 °C. The results in Table 2 show that by increasing the temperature of $Al(^iBu)_3\cdot0.5H_2O$ catalyzed polymerizations from 60 to 100 °C, $L_{[L]-LA}$ decreased from 15 to 4.4. While similar effects were observed between 60 and 80 °C for $AlEt_3\cdot0.5H_2O$ catalyzed polymerizations, further increase in temperature did not decrease $L_{[L]-LA}$. Values of L_{EO} showed no substantial change until the reaction temperature of $Al(^iBu)_3\cdot0.5H_2O$ catalyzed polymerizations was increased from 100 to 130 °C. Variations in polymerization temperature did not change L_{EO} for $AlEt_3\cdot0.5H_2O$ catalyzed polymerizations. Thus, regulation of the reaction temperature was useful to modulate copolymer $L_{[L]-LA}$ but was less effective in changing L_{EO}.

Table 3. [L]-Lactide–Ethylene Oxide Copolymerizations using Different Catalysts in Xylene at 130 °C[a,b]

entry	catalyst	time (h)	total yield (%)	MeOH-i (%)	$F_{[L]\text{-LA}}/F_{EO}$	$L_{[L]\text{-LA}}/L_{EO}$	M_n	M_w/M_n
19	$AlEt_3\cdot 0.5H_2O$	24	82	38	31/69	10/32	17 500	2.7
20	$AlEt_3\cdot 0.5H_2O$	1	74	88	56/44	15/27	33 600	3.9
21	$Sn(Oct)_2\cdot 4AlEt_3\cdot 2H_2O$	1	63	86	59/41	12/15	41 100	4.3
22	$Al(^iBu)_3\cdot 0.5H_2O$	24	84	10	23/77	4.7/18	1460	20
23	$Al(^iBu)_3\cdot 0.5H_2O$	1	70	88	62/38	22/24	39 900	9.6
24	IBAO	1	72	88	57/43	21/31	60 600	5.1
25	$Sn(Oct)_2\cdot 4Al(^iBu)_3\cdot 2H_2O$	1	71	85	59/41	15/18	52 800	7.2

[a] $f_{[L]\text{-LA}}/f_{EO} = 1/2$. [b] Reaction conditions and abbreviations were described in Table 1 footnotes.

Table 4. [L]-Lactide–Ethylene Oxide Bulk Copolymerization by Different Catalysts at 130 °C[a]

entry	catalyst	$f_{[L]\text{-LA}}/f_{EO}$	time (h)	total yield (%)	MeOH-i (%)	$F_{[L]\text{-LA}}/F_{EO}$	$L_{[L]\text{-LA}}/L_{EO}$	M_n	M_w/M_n
26	$Al(^iBu)_3\cdot 0.5H_2O$	2/1	24	93	N/D	N/D	N/D	N/D	N/D
27	$Al(^iBu)_3\cdot 0.5H_2O$	1/1	24	97	N/D	N/D	N/D	N/D	N/D
28	$Al(^iBu)_3\cdot 0.5H_2O$	1/1	1	82	89	76/24	5.1/5.0	39 600	16
29	$Sn(Oct)_2\cdot 4Al(^iBu)_3\cdot 2H_2O$	1/1	1	78	88	79/21	9.8/4.2	45 900	63
30	$AlEt_3\cdot 0.5H_2O$	2/1	1	89	94	81/19	10/4.0	30 500	17
31	$AlEt_3\cdot 0.5H_2O$	1/1	1	85	94	71/29	9.6/6.8	58 700	28
32	$AlEt_3\cdot 0.5H_2O$	1/2	1	67	88	63/37	6.2/8.0	40 700	8.5
33	$Sn(Oct)_2\cdot 4AlEt_3\cdot 2H_2O$	1/1	1	62	88	75/25	11/4.9	52 200	94

[a] [L]-LA]/[Al] = 50; other reaction conditions and abbreviations were described in Table 1 footnotes.

Furthermore, increasing the temperature to 130 °C for both $AlEt_3\cdot 0.5H_2O$ and $Al(^iBu)_3\cdot 0.5H_2O$ catalyzed polymerizations resulted in substantial decreases in the MeOH-i fraction yield and M_n. This may be due to thermal depolymerization reactions as well as catalyst instability at elevated temperatures during the 1 day reactions in xylene. Therefore, additional work was carried out to determine whether shorter reaction times and higher monomer concentrations might lead to useful polymerizations at 130 °C.

[L]-Lactide–Ethylene Oxide Copolymerization at 130 °C. Copolymerizations at 130 °C were carried out in xylene (Table 3) and in bulk (Table 4). Comparison of polymerizations conducted in xylene for 1 and 24 h showed that the former had relatively higher MeOH-i fraction yields and M_n values (see entries 19, 20, 22, and 23). Further comparison of these reactions showed that 1 h polymerizations gave MeOH-i copolymers with higher contents of [L]-LA repeat units. Also, the % conversions of [L]-LA to MeOH-i copolymers for the 1 h polymerizations in Table 3 were >80%. It appears that for longer reaction times at 130 °C, chains and/or chain segments enriched in [L]-LA repeat units degrade while EO conversion continues so that the resulting MeOH-i product has increased EO content and, for $Al(^iBu)_3\cdot 0.5H_2O$ catalysis, decreased $L_{[L]\text{-LA}}$. The apparent decrease in the reactivity of EO relative to [L]-LA for polymerizations conducted at 130 °C relative to 60 °C likely results from a decreased solubility of EO at 130 °C in the reaction medium. In other words, at higher reaction temperatures, the concentration of EO in the gas phase in sealed reaction tubes increases. Polymerizations conducted for 1 h catalyzed by the $Sn(Oct)_2$–AlR_3–H_2O systems and IBAO showed similar results to those catalyzed by the $AlR_3\cdot 0.5H_2O$ systems. However, entries 24 and 25 resulted in MeOH-i products of relatively higher molecular weight.

Comparison of solution and bulk copolymerizations at 130 °C showed similarly high MeOH-i yields, M_n values, and conversions of [L]-lactide to a copolymer. However, $L_{[L]\text{-LA}}$ and L_{EO} values were considerably less and polydispersities greater for the copolymers prepared in bulk reactions (see Tables 3 and 4).

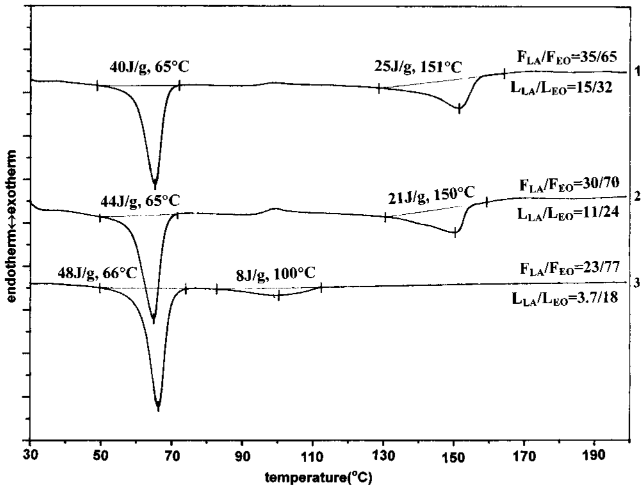

Figure 3. DSC thermograms recorded during the first heating scan of the following copolymer MeOH-i fractions: (1) entry 5, (2) entry 6, and (3) entry 10 (see Table 1 for details).

Thermal Properties of the Methanol Insoluble Copolymers. It was found that all of the copolymers (MeOH-i) have two melting transitions with T_m values that correspond to [L]-PLA and PEO crystalline phases (see Figure 3). The melting transitions for these crystalline phases were influenced by the copolymer composition and the average block lengths. Table 5 provides a summary of T_m and ΔH_f values for selected copolymers. The T_m values of PEO crystalline phases did not change substantially for the copolymers listed in Table 5. In contrast, T_m values of [L]-PLA crystalline phases varied from 100 to 151 °C. The lowest T_m values in Table 5 were observed for entries 10 and 18 which had the smallest $F_{[L]\text{-LA}}$ and $L_{[L]\text{-LA}}$ values, respectively. Calculated ΔH_f values were determined by assuming that [L]-PLA and PEO blocks were infinitely long and that these two components are phase separated both in the crystalline and amorphous phases (see Table 5, footnote 3). Comparison of experimental and calculated values showed that, in all cases, the former were lower. Furthermore, comparison of PLA melting transitions for entries 15, 17, and 18 show that, for products of similar repeat unit composition and L_{EO}, by decreasing $L_{[L]\text{-LA}}$ from 18 or 13 to 10 resulted in a large decrease in T_m (by ~50 °C). Such melting behavior may be explained by reaching block length segment lengths which restrict

Table 5. DSC Analysis of Methanol Insoluble [L]-LA−EO Copolymers

entry	M_w/M_n	$L_{[L]\text{-LA}}/L_{EO}$	$F_{[L]\text{-LA}}/F_{EO}$	$T_m{}^a$ (°C)	$\Delta H_f{}^a$ obsrvd (calcd^c) (J/g)	$T_m{}^b$ (°C)	$\Delta H_f{}^b$ obsrvd (cacld^c) (J/g)
4	44 100/12 300	11/25	47/53	60	25 (36)	136	35 (47)
5	118 000/21 100	25/42	30/70	60	25 (59)	147	23 (37)
6	162 000/26 100	9/44	22/78	64	64 (73)	142	18 (30)
10	121 000/23 700	17/83	17/83	63	63 (84)	127	14 (25)
15	110 000/30 600	18/39	33/67	65	40 (53)	151	25 (39)
17	86 400/37 000	13/39	31/69	65	42 (56)	150	22 (38)
18	46 400/17 500	10/32	31/69	66	47 (56)	100	8 (38)

[a] Melting transition of PEO blocks. [b] Melting transition of PLA blocks. [c] Calculated assuming that the PEO and PLA chain segments are long and do not interact in amorphous or crystalline domains; using ΔH_f values for PEO ($M_v = 4 \times 10^6$) and [L]-PLA ($M_n = 12\ 900$) of 140 and 63 J/g, respectively; using the equations ΔH_f (calcd) $= w_{PEO} \times \Delta H_{f(PEO)}$ or $w_{[L]\text{-PLA}} \times \Delta H_{f([L]\text{-PLA})}$ where w_{PEO} and $w_{[L]\text{-PLA}}$ are the weight fractions of PEO and [L]-PLA segments, respectively.

Table 6. Tensile Properties of [L]-PLA/PEG and [L]-PLA/[L]-LA-*co*-EO Blends[a]

blend	modulus (MPa)	yield stress (MPa)	elongation at yield (%)	break stress (MPa)	elongation at break (%)
[L]-PLA/PEG MW (PEG) = 18 500 (89/11 w/w)	423 ± 20	14.5 ± 2.8	6.0 ± 0.1	25.5 ± 2.8	240 ± 21
[L]-PLA/[L]-LA-*co*-EO[b] (80/20 w/w) $w_{[L]\text{-LA}}/w_{EO} = 89/11$	710 ± 21	24.1 ± 3.1	6.0 ± 0.1	26.2 ± 2.6	204 ± 18

[a] Films were solution cast from chloroform. [b] MeOH-i fraction of entry 8; see Table 1.

crystallization and, therefore, result in poorly ordered crystalline phases and lower crystalline content. However, it is understood that miscibility in the amorphous phase of EO and [L]-LA chain segments may also contribute to the observed melting depression. Indeed, the DSC-determined T_g of the copolymer $F_{[L]\text{-LA}}/F_{EO}$ = 47/53 (entry 4, Table 5) was 26 °C, which was quite close to the calculated value (20 °C) by using the Fox equation. This confirms that miscibility in the amorphous phase may also play a role in the observed T_g depressions of PLA crystalline phases.

Application as Blend Component. PLA blended with PEO or plasticized with poly(ethylene glycol)s have significant improved flexibility and ductility compared to the PLA homopolymer. However, in an aqueous environment, the PEO or poly(ethylene glycol) component of these materials was readily leached which lead to changes in the physicomechanical properties of residual films as well as the introduction of water soluble polymers into environments where they may not be desired.[34] One possible solution is the design of EO/[L]-LA copolymers that, when blended with PLA, show lower leachability and provide equivalent or improved film properties. In this paper, we only considered film properties where, in another paper, the hydrolytic degradability and water solubility of these copolymers and corresponding blends were studied in detail.[35]

Blends of PLA (96% [L]-LA, 8% meso-LA, see Experimental Section) with either an [L]-LA/EO copolymer (MeOH-i) (entry 8, $F_{[L]\text{-LA}}/F_{EO}$ = 20/80, M_n =17 600, $w_{[L]\text{-LA}}/w_{EO}$ 45/55) or PEG (M_n = 18 500) were prepared by solution mixing and casting (see Experimental Section). Each blend had weight fractions of [L]-LA to EO of 89/11. Comparison of the two blends showed that the blend containing the copolymer had substantially higher modulus and yield strength while retaining similar elongation at yield, elongation at break, and break stress (see Table 6). Therefore we concluded that [L]-LA/EO copolymers with high EO content may be useful as a replacement for PEG in blends where there is a need to (i) decrease the water leachability of PEG, (ii) achieve improved blend physicomechanical properties, and (iii) retain biodegradability.

Additional studies are planned which will focus on elucidating relationships between the average block lengths and composition of [L]-LA/EO copolymers and their corresponding crystallization characteristics, physicomechanical properties, and biodegradability.

Conclusions

For the first time, [L]-LA and EO were directly copolymerized to give novel multiblock copolymers. The multiblock structure of the copolymers was confirmed by 1-D and 2-D ^{1}H NMR experiments. AlR_3-H_2O and Sn−Al bimetallic catalysts were found to be efficient for [L]-LA/EO copolymerization. The relationship between copolymer structure, molecular weight, catalyst structure, and reaction conditions (reaction time, temperature, and medium) were established. Copolymers were prepared that had $L_{[L]\text{-LA}}$ values ranging from ~4 to 50 and L_{EO} values ranging from ~4 to 83. Molecular weights (M_n) of the copolymers were up to 60 000. The multiblock copolymers had segment lengths that were sufficiently long so that distinct crystalline phases corresponding to [L]-PLA and PEO were observed. In other words, the crystalline phases of [L]-PLA and PEO were phase separated which resulted in two distinct melting transitions. Variations in chain microstructure and comonomer composition lead to T_m values of the [L]-PLA phase which ranged from 100 to 151 °C. Furthermore, an [L]-LA/EO copolymer was blended with PLA. The use of the [L]-LA/EO copolymer in place of PEG resulted in improved physicomechanical properties. The [L]-LA/EO copolymers are expected to have lower water solubility than PEGs and, thus, should provide improved permanence when these blends are exposed to aqueous environments.

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MA970385E