Synthesis and Characterization of Poly(L-lactide-*co*-ε-caprolactone)-*b*-Poly(L-lactide) Biodegradable Diblock Copolyesters: Effect of the Block Lengths on Their Thermal Properties

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ABSTRACT: Poly(L-lactide-*co*-ε-caprolactone)-*b*-poly(L-lactide) [P(LL-*co*-CL)-*b*-PLL] diblock copolyesters were synthesized in a two-step process with 1-dodecanol (DDC) and stannous octoate as the initiating system. In the first-step reaction, a 50:50 mol % amorphous poly(L-lactide-*co*-ε-caprolactone) [P(LL-*co*-CL)] copolyester was synthesized via the bulk copolymerization of L-lactide and ε-caprolactone, which was followed by the polymerization of the PLL crystalline block at the end chain in the second-step reaction. The yielded copolyesters were characterized with dilute-solution viscometry, gel permeation chromatography, ^{1}H- and ^{13}C-NMR, and differential scanning calorimetry methods. The molecular weights of the P(LL-*co*-CL) copolyesters from the first-step reaction were controlled by the DDC concentrations, whereas in the second-step reaction, the molecular weights of the P(LL-*co*-CL)-*b*-PLL diblock copolyesters depended on the starting P(LL-*co*-CL) copolyester molecular weights and L-lactide/prepolymer molar ratios. The starting P(LL-*co*-CL) copolyester molecular weights and PLL block lengths seemed to be the main factors affecting specific thermal properties, including the melting temperature (T_m), heat of melting (ΔH_m), crystallizing temperature (T_c), and heat of crystallizing (ΔH_c), of the final P(LL-*co*-CL)-*b*-PLL diblock copolyester products. T_m, ΔH_m, T_c, and ΔH_c increased when the PLL block lengths increased. However, these thermal properties of the diblock copolyesters also decreased when the P(LL-*co*-CL) block lengths increased. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 106: 3315–3320, 2007

Key words: biodegradable; biomaterials; block copolymers; diblock copolymers; thermal properties

INTRODUCTION

Copolymers of L-lactide (LL) and ε-caprolactone (CL), with both random and block structures, have been shown to have both biocompatible and biodegradable properties.[1] They can be degraded within the human body via a simple, nonenzymatic hydrolysis mechanism. The main biomedical applications of the random copolymer poly(L-lactide-*co*-ε-caprolactone) [P(LL-*co*-CL)] include drug delivery systems,[1,2] surgical sutures,[3] nerve guides,[4] and bone fixation devices.[5] Although a wide range of investigations have been conducted,[2,4,6,7] it is very difficult to tailor P(LL-*co*-CL) copolymers that give a satisfactory balance of the mechanical strength and biodegradative patterns necessary for biomedical applications because their thermal properties, especially their melting temperature (T_m) and heat of melting (ΔH_m; which corresponds to the crystallinity percentage), largely affect their mechanical and biodegradative properties. Consequently, interest in block copolymers, both AB diblocks and ABA triblocks, has increased because of the greater scope, and so products with various microstructures and properties have been created.

Recently, Peter et al.[8] synthesized and characterized poly(L-lactide)-*b*-poly(ε-caprolactone) AB diblock copolymers, whereas Kim et al.[9] described their crystallization behavior. Qian et al.[10] and Cai et al.[11] synthesized poly(L-lactide)-*b*-poly(ε-caprolactone)-*b*-poly(L-lactide) and poly(L-lactide-*co*-glycolide)-*b*-poly(ε-caprolactone)-*b*-poly(L-lactide-*co*-glycolide) ABA triblock copolymers, respectively, each using ethylene glycol and stannous octoate [Sn(Oct)₂] for the initiating system. They reported that the properties of the block copolymers were quite different from those of random copolymers of the same compositions. Moreover, the properties of the block copolymers could be more readily adjusted through the variation of their compositions and microstructure.

Most of these previous works have concentrated on block copolymers in which PCL is synthesized as the

first block. The synthesis and characterization of poly(L-lactide)-*b*-poly(L-lactide-*co*-ε-caprolactone)-*b*-poly(L-lactide) triblock copolyesters for potential use as bioabsorbable sutures have been reported by us previously.[12,13] However, the effect of the block lengths of triblock copolymers on the thermal properties is not clear as in the case of the diblock copolymers. For controlled-release drug delivery applications, the amorphous phase provides good drug distribution, whereas the crystalline phase provides good stability to drug delivery systems. Then, the controlled thermal properties of polymers for use as drug delivery systems are more important. The purpose of this study is to describe the synthesis of poly(L-lactide-*co*-ε-caprolactone)-*b*-poly(L-lactide) [P(LL-*co*-CL)-*b*-PLL] diblock copolyesters and the effect of each block length on the thermal properties of the diblock copolyesters. The copolyester was achieved via a two-step ring-opening polymerization in bulk of the corresponding monomers with Sn(Oct)$_2$ (initiator) and 1-dodecanol (DDC; coinitiator) as the initiating system.

EXPERIMENTAL

Materials

LL was synthesized from L-lactic acid aqueous solution (85–90%, Fluka, Switzerland) according to the procedure described by Hyon et al.[14] and was purified by repeated recrystallization from distilled ethyl acetate. The CL monomer (99%, Acros Organics, NJ, USA) was purified via drying with CaH$_2$ followed by distillation under reduced pressure before being stored over molecular sieves in a refrigerator. The Sn(Oct)$_2$ initiator (95%, Sigma, USA) or tin(II) bis(2-ethylhexanoate) was used without further purification, whereas the coinitiator DDC (90%, Acros Organics, NJ, USA) was purified by fractional distillation under reduced pressure and stored over molecular sieves at room temperature. Ethyl acetate, chloroform (CHCl$_3$), and *n*-hexane were purified by fractional distillation at a normal pressure and stored over molecular sieves.

Synthesis

The P(LL-*co*-CL)-*b*-PLL AB diblock copolyesters are hereafter called diblock copolyesters. They were prepared as follows: first, a 50 : 50 mol % P(LL-*co*-CL) copolyester, hereafter called a prepolymer, was synthesized for use as the A block, and second, this was polymerized with more LL to form the B block, as shown in Scheme 1.

Synthesis of the prepolymers

In the first-step reaction, the synthesis of a 50 : 50 mol % P(LL-*co*-CL) prepolymer was performed in a
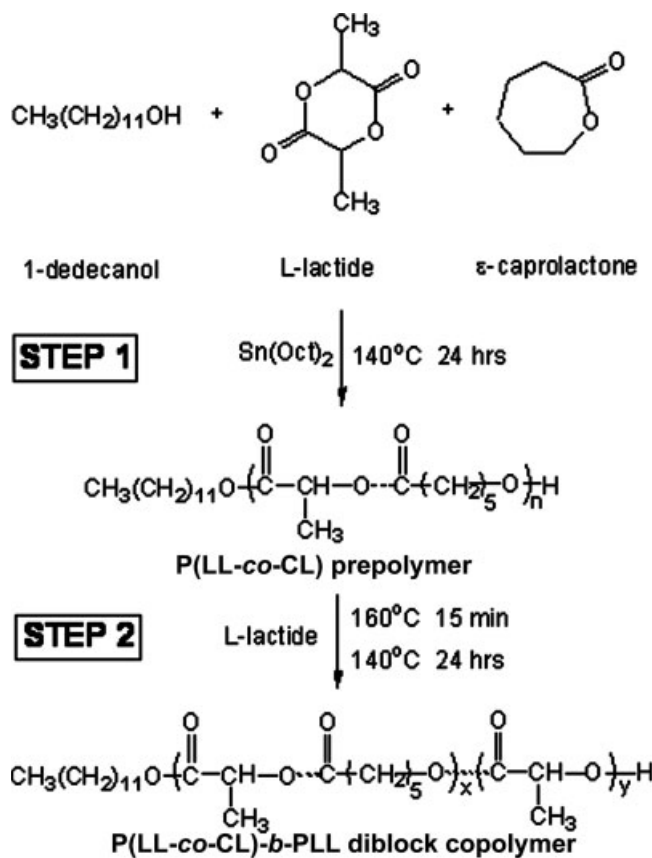
Scheme 1 Two-step preparation for the P(LL-*co*-CL)-*b*-PLL diblock copolyesters.

round-bottom flask under a dry nitrogen atmosphere with a magnetic stirrer. LL and CL, in a 50 : 50 mol % LL/CL ratio, were copolymerized in bulk with DDC (1.76 or 0.88 mol % DDC) and Sn(Oct)$_2$ (0.02 mol %). The flask was closed with a glass stopper under a nitrogen atmosphere and immersed in an oil bath at 140°C for 24 h. At the end of the reaction, the prepolymer was allowed to cool, cut up into small pieces (1–2 mm), and dried to a constant weight in a vacuum oven at 40°C before characterization and copolymerization.

Synthesis of the diblock copolyesters

In the second-step reaction, the prepolymer was mixed with more LL (LL/prepolymer molar ratios of 1.0 and 2.0, which produced overall LL/CL ratios of 75 : 25 and 83 : 17 mol %, respectively) in a round-bottom flask under a dry nitrogen atmosphere with a magnetic stirrer without the further addition of DCC and Sn(Oct)$_2$. The mixture was heated initially at 160°C for 15 min to homogeneous mixing before the temperature was reduced to 140°C for 24 h to minimize degradative side reactions. At the end of the reaction, the diblock copolyester was purified through dissolution in CHCl$_3$ before being precipitated in cool

TABLE I
Molecular Weight Characteristics of the Prepolymers and Diblock Copolyesters

Copolyester	DDC (mol %)	$[\eta]$ (dL/g)[a]	M_n (g/mol)[b]	MWD[b]
Prepolymer 1	1.76	0.2569	7,900	2.49
Prepolymer 2	0.88	0.3660	14,100	2.19
Diblock copolyester 1[c]	—	0.3358	11,400	1.89
Diblock copolyester 2[c]	—	0.4567	17,300	1.99
Diblock copolyester 3[d]	—	0.7452	31,700	2.00
Diblock copolyester 4[d]	—	0.8246	42,400	1.98

[a] Measured at 30°C with $CHCl_3$ as a solvent.
[b] Determined with GPC.
[c] Synthesized from prepolymer 1 with LL/prepolymer molar ratios of 1.0 and 2.0 for diblock copolyesters 1 and 2, respectively.
[d] Synthesized from prepolymer 2 with LL/prepolymer molar ratios of 1.0 and 2.0 for diblock copolyesters 3 and 4, respectively.

n-hexane and dried to a constant weight in a vacuum oven at 50°C before characterization.

Characterization

The intrinsic viscosity $[\eta]$ values of the prepolymers and diblock copolyesters were determined from flow-time measurements of a dilution series of solutions in $CHCl_3$ as a solvent at 30°C with an Ubbelohde viscometer (Mainz, Germany). The number-average molecular weight (M_n) and molecular weight distribution (MWD) were determined by gel permeation chromatography (GPC, MA, USA) with a Waters 717 Plus autosampler and a Waters model 510 apparatus equipped with two Styragel HR mixed bed columns (pore size = 5 μm; 300 × 7.8 mm); it was operated at 30°C and employed a differential refractometry detector. Narrow-MWD polystyrene standards were used for calibration. Tetrahydrofuran was used as the solvent at a flow rate of 1.0 mL/min.

The copolymer compositions and monomer sequencing were characterized with a combination of high-resolution 300-MHz ^{1}H-NMR and 75-MHz ^{13}C-NMR spectrometers. Spectra were obtained from copolymer solutions in deuterated chloroform ($CDCl_3$) with tetramethylsilane as an internal reference.

A thermal analysis was carried out by means of differential scanning calorimetry (DSC, MA, USA) with a Pyris diamond differential scanning calorimeter. For DSC, 5–10-mg copolymer samples were heated at 10°C/min under a nitrogen atmosphere over a temperature range of 30–200°C to observe their T_m and ΔH_m values from the first heating scans and their crystallizing temperature (T_c) and heat of crystallizing (ΔH_c) values from the second heating scans. Between the first and second heating scans of the diblock copolyester, sample cooling was fast (quenching) according to the default cooling mode of the equipment. Before the DSC analysis, the copolymer samples were stored in a vacuum desiccator at room temperature for 1 month to allow crystalli-

zation, as previously reported for 50 : 50 mol % P(LL-co-CL) copolymers.[15]

RESULTS AND DISCUSSION

Prepolymer characterization

The influence of the DDC concentrations on the molecular weight characteristics of the prepolymers is presented in Table I. The molecular weight characterization was carried out by means of a combination of dilute-solution viscometry and GPC methods. It was found that prepolymers with different molecular weights could be obtained through the variation of the DDC concentration. The $[\eta]$ (from viscometry) and M_n (from GPC) values of the prepolymers increased when the DDC concentration decreased. All GPC curves of the prepolymers exhibited similar unimodal MWDs, an example of which is shown in Figure 1(a) for prepolymer 1.

The copolymer compositions of the prepolymers were determined from the ^{1}H-NMR spectra [Fig. 2(a)
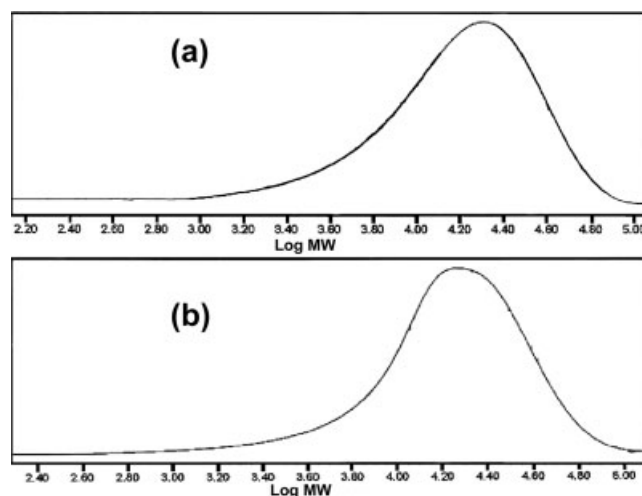
Figure 1 GPC curves for (a) prepolymer 1 and (b) diblock copolyester 1.
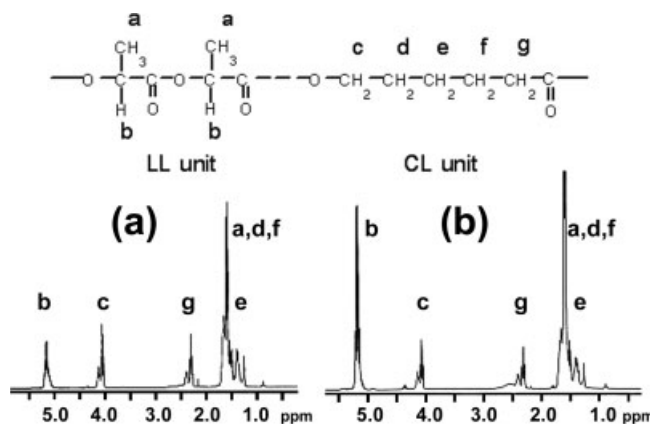
Figure 2 ^{1}H-NMR spectra for (a) prepolymer 1 and (b) diblock copolyester 1.

is a typical spectrum of prepolymer 1] through the ratioing of the integral peak areas corresponding to the LL methine protons at $\delta = 5.0$–5.3 ppm and the CL ε-methylene protons at $\delta = 3.9$–4.2 ppm. The calculated compositions [LL/CL (mol %)] of the prepolymers are presented in Table II and are all the same as the initial LL/CL = 50 : 50 mol % comonomer feeds, as expected, because the copolymerizations were taken to fully quantitative conversions.

The copolymer microstructure and monomer sequencing were characterized with the ^{13}C-NMR spectra and specifically with the expanded carbonyl carbon (C=O) region of $\delta = 169$–174 ppm, as shown in Figure 3(a) for prepolymer 1. The various peaks can be assigned to the C=O carbons of the middle units of various triad sequences, as shown in Figure 3(a). The peaks at $\delta = 169.5$ ppm and $\delta = 173.5$ ppm can be assigned to the LLL and CCC triads, respectively [L = L-lactate (half-LL) unit and C = CL unit]. The appearance of the additional peaks between the LLL and CCC triad peaks indicates that various mixed triad sequences are also present, as would be expected in some random structure of the prepolymer. The average monomer sequence lengths of the LL unit (l_{LL}) and CL unit (l_{CL}) can be estimated from

eqs. (1) and (2), respectively, on the basis of the relationship between the average monomer sequence length and the integral triad peak areas:[16]

$$l_{LL} = \frac{1}{2}\left[\frac{I_{LLL} + (I_{LLC} + I_{CLL})/2}{(I_{LLC} + I_{CLL})/2 + I_{CLC}} + 1\right] \qquad (1)$$

$$l_{CL} = \frac{I_{CCC} + I_{LCC}}{I_{CCL} + I_{LCL}} + 1 \qquad (2)$$

The average monomer sequence length results are reported in Table II. The l_{LL} and l_{CL} values of prepolymer 1 were 3.3 and 2.3, whereas these of prepolymer 2 were 3.0 and 2.3, respectively. The results indicate that the arrangement of monomers created tapered forms of the copolymers. In addition, the appearance of the CLC triad peak for prepolymer 1 in Figure 3(a) provides some qualitative indication of the extent to which transesterification of the lactide units takes place.

The as-polymerized prepolymers were completely amorphous materials; they were stored *in vacuo* at room temperature for 1 month so that they could display some crystallinity before DSC analysis. The first heating scan DSC curves of the prepolymers are shown in Figure 4, and the DSC results are summarized in Table III. The heating scan DSC curves of the prepolymers show melting behaviors in the range of 40–120°C. Prepolymers 1 and 2 showed T_m peaks at 65 and 98°C, respectively, which may have been due to the combination of CL and LL crystalline parts.

Diblock copolyester characterization

P(LL-co-CL)-b-PLL AB diblock copolyesters were synthesized with prepolymer 1 or 2. The yields of the diblock copolyester products were greater than 95%.

The [η] (from viscometry) and M_n (from GPC) values of the diblock copolyesters were higher than those of their prepolymers (Table I). The molecular weights of the diblock copolyesters also increased when the molecular weights of the starting prepoly-

TABLE II
Chemical Compositions and Average Monomer Sequence Lengths of the Prepolymers and Diblock Copolyesters

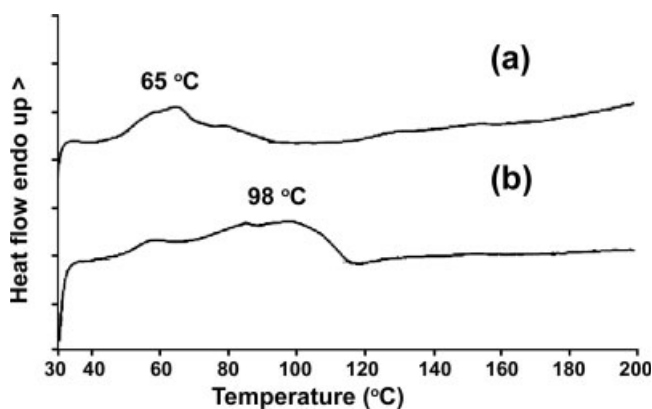| Copolyester	Comonomer composition (LL:CL; mol %)[a]	Copolymer composition (LL:CL; mol %)[b]	l_{LL}[c]	l_{CL}[c]
Prepolymer 1	50 : 50	50 : 50	3.3	2.3
Prepolymer 2	50 : 50	50 : 50	3.0	2.3
Diblock copolyester 1	75 : 25	75 : 25	—	2.1
Diblock copolyester 2	83 : 17	80 : 20	—	2.3
Diblock copolyester 3	75 : 25	73 : 27	—	2.0
Diblock copolyester 4	83 : 17	79 : 21	—	1.9

[a] From the feed ratio of LL to CL.
[b] Determined by ^{1}H-NMR.
[c] Determined by ^{13}C-NMR.
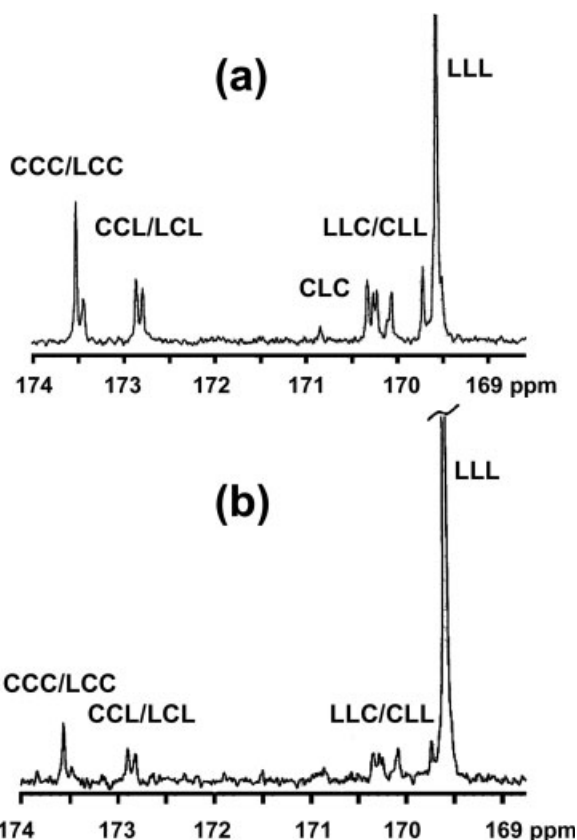
Figure 3 Expanded carbonyl region of the ^{13}C-NMR spectra for (a) prepolymer 1 and (b) diblock copolyester 1 (the peak triad assignment is as shown).

mer and LL/prepolymer molar ratios increased. All GPC curves of the diblock copolyesters exhibited similar unimodal MWDs, and this suggested that no PLL homopolymer fractions were formed in the second-step reaction; an example is shown in Figure 1(b) for diblock copolyester 1. The results indicated that the prepolymer could act as a macroinitiator, polymerizing LL at the end chain in the second-step reaction to form the diblock copolyester.

| Copolyester	T_m (°C)[a]	ΔH_m (J/g)[a]	T_c (°C)[b]	ΔH_c (J/g)[b]
Prepolymer 1	65	5.5	—	—
Prepolymer 2	98	11.3	—	—
Diblock copolyester 1	153	35.1	70	10.2
Diblock copolyester 2	165	40.6	79	17.8
Diblock copolyester 3	162	41.2	78	18.2
Diblock copolyester 4	170	62.2	88	22.0

[a] Measured from the first heating scan of DSC curves.
[b] Measured from the second heating scan of DSC curves.

The copolymer compositions of the diblock copolyesters were determined from ^{1}H-NMR spectra. The calculated compositions are given in Table II and are similar to the comonomer feed ratios. A ^{1}H-NMR spectrum typical for diblock copolyester 1 is shown in Figure 2(b). Only the peaks that corresponded to the LL protons increased; those of the CL protons did not.

The patterns of the expanded carbonyl regions of the ^{13}C-NMR spectra of the diblock copolyesters and the starting prepolymers are the same [Fig. 3(b)], but they are different for the integral peak areas of LLL triads, which increased with respect to the LL/prepolymer ratios. However, it was possible to calculated l_{CL} of the diblock copolyesters, which was present only in the prepolymer (A) block. The calculated l_{CL} values (Table II) slightly decreased from those of their starting prepolymers, and this may have been due to the degradation side reactions, especially transesterification reactions that occurred during the polymerization in the second-step reaction.[16]

When we observed the first and second heating scans of the DSC curves of the diblock copolyesters (Figs. 5 and 6, respectively) and the thermal properties (Table III), we found that the T_m, ΔH_m, T_c, and

Figure 4 DSC thermograms from the first heating scans for prepolymers (a) 1 and (b) 2.
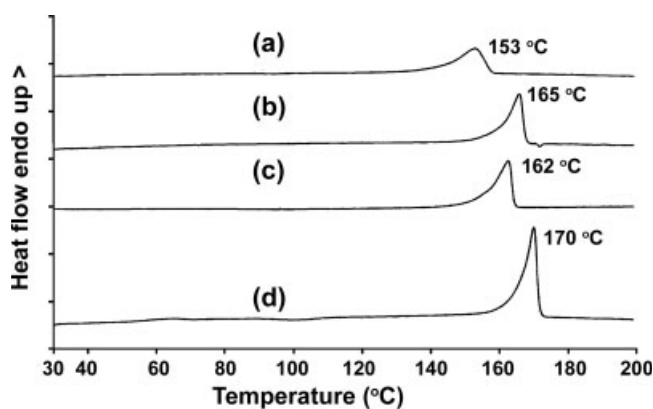
Figure 5 DSC thermograms from the first heating scans for diblock copolyesters (a) 1, (b) 2, (c) 3, and (d) 4.
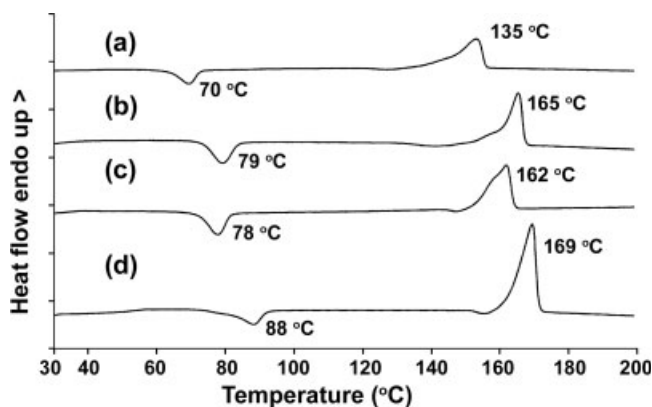
Figure 6 DSC thermograms from the second heating scans for diblock copolyesters (a) 1, (b) 2, (c) 3, and (d) 4.

ΔH_c values of the diblock copolyesters seemed to depend on the crystallizable PLL end block length when a constant P(LL-co-CL) block length was used. The T_m, ΔH_m, T_c, and ΔH_c values of the diblock copolyesters increased when the PLL block length increased. However, diblock copolyesters 2 and 3, with different molecular weights (17,300 and 31,700 g/mol, respectively), showed similar T_m (165 and 162°C), ΔH_m (40.6 and 41.2 J/g), T_c (79 and 78°C), and ΔH_c (17.8 and 18.2 J/g) values; this could be expected because the long P(LL-co-CL) soft block could have inhibited the crystallization of the PLL crystalline block in diblock copolymer 3. On the basis of these finding, it is likely that the thermal properties of the diblock copolyesters were also controlled by the amorphous block length of P(LL-co-CL).

CONCLUSIONS

AB diblock copolyesters, consisting of 50 : 50 mol % P(LL-co-CL) (A) blocks and PLL (B) blocks, were successfully synthesized with DDC and Sn(Oct)$_2$ as the initiating system. In the first-step reaction, P(LL-co-CL) was prepared for use as a macroinitiator to polymerize LL at its chain end in the second-step reaction, thus forming AB diblock copolyesters. The molecular weights of the 50 : 50 mol % P(LL-co-CL) prepolymer

could be controlled through the variation of the DDC concentrations at a fixed Sn(Oct)$_2$ concentration. During the second-step reaction, the randomization of the monomer sequencing of the prepolymers was slightly increased (l_{CL} slightly decreased) because of the transesterification reaction. The T_m, ΔH_m, T_c, and ΔH_c values of the diblock copolyesters depended on the P(LL-co-CL) and PLL block lengths.

The results suggest that the molecular weights and thermal properties of the diblock copolyesters could be manipulated through the variation of the block lengths of P(LL-co-CL) and PLL. These controlled thermal properties and molecular weight diblock copolyesters could give appropriate products for drug delivery applications because these properties influence the drug distribution and biodegradation behavior.

References

1. Schindler, A.; Jeffcoat, R.; Kimmel, G. L. In Contemporary Topics in Polymer Science; Pearce, J. R.; Schaefger, E. M., Eds.; Plenum: New York, 1977; Vol. 2, p 251.
2. Ge, H.; Hu, Y.; Yang, S.; Jiang, X.; Yang, C. J Appl Polym Sci 2000, 75, 874.
3. Tomihata, K.; Suzuki, M.; Oka, T.; Ikada, Y. Polym Degrad Stab 1998, 59, 13.
4. Den Dunnen, W. F. A.; van der Lei, B.; Robinson, P. H.; Holwerda, A.; Pennings, A. J.; Schakenraad, J. M. J Biomed Mater Res 1995, 29, 757.
5. Middleton, J. C.; Tipton, A. J. Biomaterials 2000, 21, 2335.
6. Grijpma, D. W.; Zondervan, G. J.; Pennings, A. J. Polym Bull 1991, 25, 327.
7. Grijpma, D. W.; Pennings, A. J. Polym Bull 1991, 25, 335.
8. Peter, J. A.; Weld, I. N. T.; Velner, E. M.; et al. J Polym Sci Part A: Polym Chem 1997, 35, 219.
9. Kim, J. K.; Park, D. J.; Lee, M. S.; Ihn, K. J. Polymer 2001, 42, 7429.
10. Qian, H.; Bei, J.; Wang, S. Polym Degrad Stab 2000, 68, 423.
11. Cai, Q.; Bei, J.; Wang, S. Polym Adv Technol 2000, 11, 159.
12. Baimark, Y.; Molloy, R. Polym Adv Technol 2005, 16, 332.
13. Baimark, Y.; Molloy, R.; Molloy, N.; Siripitayananon, J.; Punyodom, W.; Sriyai, M. J Mater Sci: Mater Med 2005, 16, 669.
14. Hyon, S. H.; Jamshidi, K.; Ikada, Y. Biomaterials 1997, 18, 1503.
15. Tsuji, H.; Mizuno, A.; Ikada, Y. J Appl Polym Sci 2000, 76, 947.
16. Vanhoorne, P.; Dubois, P.; Jerome, R.; Teyssie, P. Macromolecules 1992, 25, 37.