

# Novel Preparation Method for Poly(L-lactide)-Based Block Copolymers: Extended Chain Crystallites as a Solid-State Macro-Coinitiator

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A novel synthetic method for poly(L-lactide) (PLLA)-based diblock copolymers was developed by the use of PLLA extended chain crystallites (or crystalline residues) as a solid-state macro-coinitiator. In this study, we showed one example, i.e., a synthesis of diblock copolymer composed of a crystalline PLLA chain and an amorphous poly(DL-lactide) chain by ring-opening polymerization of DL-lactide initiated with stannous octoate (i.e., tin(II) 2-ethylhexanoate) in the presence of PLLA extended chain crystallites. The PLLA extended chain crystallites were prepared by hydrolytic degradation of crystallized PLLA films at 97 °C for 70 h. The chains inside the extended chain crystallites are expected to be protected from transesterification reaction. Gel permeation chromatography, polarimetry, <sup>1</sup>H NMR spectroscopy, wide-angle X-ray scattering, and differential scanning calorimetry revealed that the diblock copolymer poly(L-lactide-*block*-DL-lactide) was successfully prepared without significant transesterification.

## Introduction

Biodegradable polyesters such as poly(lactide)s, poly( $\epsilon$ -caprolactone) (PCL), and poly(hydroxybutyrate)s are a matter of concern, because these polymers and copolymers have a variety of biomedical and pharmaceutical applications as well as environmental applications.<sup>1–11</sup> Copolymerization is a general method for preparing biodegradable polyesters having a wide range of physical properties and biodegradation behavior. In marked contrast to random or relatively random copolymers, most block copolymers are crystallizable even when they contain an equal amount of comonomers. Therefore, altering the monomer ratio and block length will give biodegradable polymers with novel biodegradable behavior and physical properties.

The block copolymers of biodegradable polyesters can be synthesized by two-step ring-opening polymerization or by polymerization initiated by a polymeric coinitiator.<sup>12–18</sup> However, in these methods, transesterification<sup>14,16</sup> will take place to randomize the monomer unit sequences, because the chains synthesized in the first step, or the polymeric coinitiator chains, are adjacent to those newly synthesized. To avoid such transesterification, we developed a novel method to synthesize well-defined block copolymers of biodegradable polyesters (Figure 1). In this method, the extended chain crystallites (crystalline residues) of a biodegradable homopolyester are prepared by selective hydrolytic degradation and removal of amorphous chains in the crystallized biodegradable homopolyester, and ring-opening polymerization of another lactone (or lactide) is carried out in the presence of an initiator [e.g., stannous octoate, i.e., tin(II) 2-ethylhexanoate, denoted hereafter as Sn(Oct)<sub>2</sub>] and extended chain crystallites as a solid-state

macro-coinitiator. The extended chain crystallites are anticipated to act as a co-initiator because they have many hydroxyl groups on their surface (Figure 1). In spite of the activity as a coinitiator, the chains inside the extended chain crystallites are inert and expected to be protected from transesterification, due to the rigidity of the crystalline lattice.

In this study, to elucidate this assumption, we carried out ring-opening polymerization of DL-lactide in the presence of poly(L-lactide) (PLLA) extended chain crystallites to synthesize A–B-type block copolymers of a biodegradable polyester, poly(L-lactide-*block*-DL-lactide) [P(LLA-*b*-DLA)], as an example. Polymerization was carried out just above the melting temperature (*T*<sub>m</sub>) for DL-lactide, which is lower than that of PLLA extended chain crystallites.

## Experimental Section

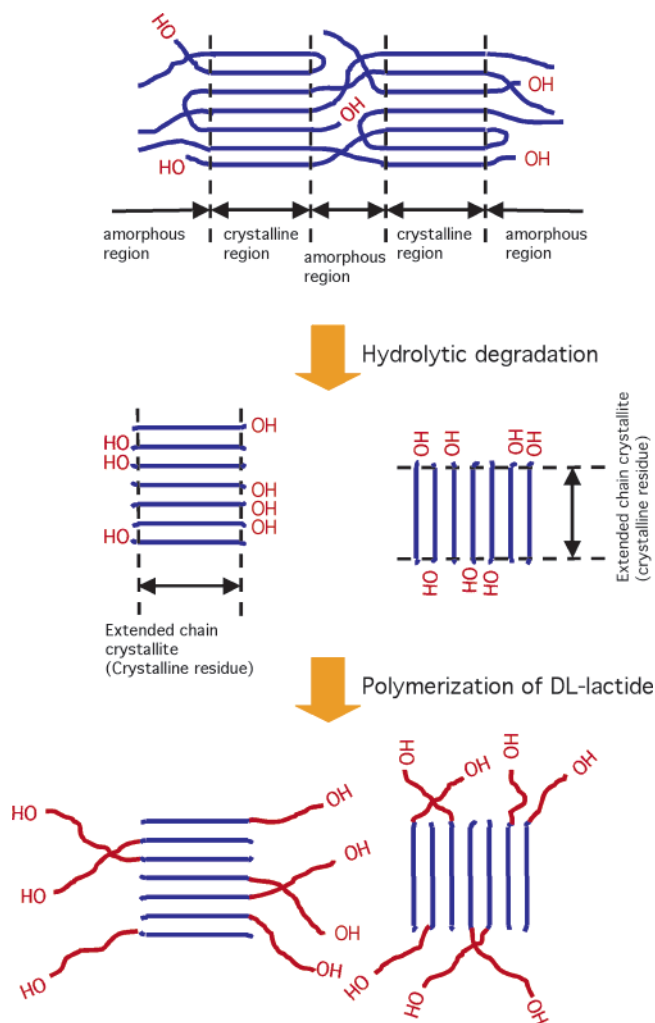
**Materials.** PLLA (intrinsic viscosity 5.7–8.2) was purchased from Polysciences Inc. (Warrington, PA) and was purified by precipitation using dichloromethane and methanol as the solvent and nonsolvent, respectively. DL-Lactide (DLA) was purchased from Aldrich Co. (St. Louis, MO) and was purified by repeated recrystallization using ethyl acetate as the solvent. Sn(Oct)<sub>2</sub> was purchased from Nacalai Tesque Inc. (Kyoto, Japan) and purified by distillation under a reduced pressure.

**Preparation of Extended Chain Crystallites (Crystalline Residues).** PLLA films with a thickness of 200  $\mu$ m were prepared by the solution-casting method using dichloromethane as the solvent. The obtained films were dried in vacuo for at least 7 days. The crystallized PLLA films were prepared from the dried film by the following procedure. Each of the PLLA films (15 mm  $\times$  30 mm  $\times$  200  $\mu$ m) was placed between two Teflon sheets and then sealed in a glass tube under reduced pressure. The sealed films were melted at 200 °C for 5 min and then crystallized at 120 or 160 °C for 10 h, followed by quenching at 0 °C to stop further crystallization. The crystallized films were hydrolytically degraded in a phosphate-buffered solution (pH 7.4) at 97 °C for 70 h to completely remove the amorphous chains, as reported

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**Figure 1.** Schematic representation of formation of PLLA extended chain crystallites (crystalline residues) and synthesis of block copolymers P(LLA-*b*-DLLA).

in our previous study,<sup>19–21</sup> and thereby to obtain PLLA extended chain crystallites or crystalline residues (Figure 1). The obtained PLLA extended chain crystallites were rinsed thoroughly with distilled water and then dried under reduced pressure for at least 2 weeks. The yields of PLLA extended chain crystallites from the crystallized PLLA films were in the range of 30–60%.

**Synthesis of Block Copolymers.** Block copolymers P(LLA-*b*-DLLA) were synthesized by ring-opening polymerization of DLLA (2 g) initiated with Sn(Oct)<sub>2</sub> (6 mg) in the presence of PLLA extended chain crystallites (200 mg) as a solid-state macro-coinitiator (Figure 1) at 120 °C. The polymerization temperature was set at just above the *T<sub>m</sub>* of DLLA (116–119 °C) and lower than that of the PLLA extended chain crystallites (173 and 182 °C). The *T<sub>m</sub>* value of DLLA released by Aldrich Co. (116–119 °C) is slightly lower than shown in ref 22 (124 °C). During polymerization, a small part of DLLA melted and most DLLA gradually sublimated to form a liquid phase. That is, once DLLA sublimated, it did not crystallize at 120 °C. It took more than 5 h for complete sublimation of DLLA. After polymerization, free poly-(DL-lactide) (PDLLA) synthesized with a coinitiator of a trace amount of water was removed by the following procedures. The obtained polymer was suspended in 10 mL of acetone for 24 h, and the suspended polymer solution was centrifuged at 10000 rpm for 20 min using a Hitachi (Tokyo, Japan) SCR20B centrifuge, followed by removal of the supernatant. The series of procedures was repeated three times. Free PDLLA chains are soluble in acetone at room temperature and can be removed as a supernatant acetone solution. Although the obtained block copolymers P(LLA-*b*-DLLA) and PLLA extended chain crystallites become swollen in acetone, they are insoluble, due to the incorporation

of insoluble PLLA chains. For reference, we performed the ring-opening polymerization of DLLA after melting the PLLA extended chain crystallites at 200 °C for 2 min, and polymerization was carried out at 120 °C for 96 h. The polymerized specimen was purified using acetone and methanol as the solvent and nonsolvent, respectively, because insoluble fractions could not be collected even by centrifugation under the same conditions as stated above. The purified polymers were dried in vacuo for at least 7 days and used for the following measurements. In the present study, the copolymers synthesized with the extended chain crystallites, which were prepared by crystallization of PLLA films at 120 and 160 °C and by subsequent hydrolytic degradation, are abbreviated as C120 and C160, respectively; an additional value following a hyphen denotes the polymerization time in hours, and the last “M” (only for “C160-96M”) means that the polymer was synthesized after the PLLA extended chain crystallites were melted at 200 °C (see Table 1).

**Measurements and Observation.** The respective weight- and number-average molecular weights [*M<sub>w</sub>*(GPC) and *M<sub>n</sub>*(GPC)] of extended chain crystallites and synthesized polymers were evaluated in chloroform at 40 °C using a Tosoh (Tokyo, Japan) GPC system with two TSK gel columns (GMH<sub>XL</sub>) and polystyrene standards. The theoretical *M<sub>n</sub>*(GPC) [*M<sub>n</sub>*(GPC-Th)] of copolymers based on the assumption that all DLLA molecules are used in PDLLA chain growth from the extended chain crystallites was calculated by multiplying *M<sub>n</sub>*(GPC) of the extended chain crystallites by 11 [(weight of extended chain crystallites and DLLA)/(weight of extended chain crystallites)]. The specific optical rotation of extended chain crystallites and synthesized polymers ([α]<sub>589</sub><sup>25</sup>) was measured in chloroform at a concentration of 1 g dL<sup>−1</sup> and 25 °C using a JASCO (Tokyo, Japan) DIP-140 polarimeter at a wavelength of 589 nm. The contents of PLLA chains in the extended chain crystallites and synthesized polymers were evaluated using the following equation:<sup>23</sup> where [α]<sub>589</sub><sup>25</sup>(extended chain

$$X_{\text{PLLA}}(\%) = 100W_{\text{PLLA}}/(W_{\text{PLLA}} + W_{\text{PDLLA}}) \\ = 100[\alpha]_{589}^{25}/[\alpha]_{589}^{25}(\text{extended chain crystallites}) \quad (1)$$

crystallites) values are those for the PLLA extended chain crystallites, −128.4 and −137.7 deg dm<sup>−1</sup> g<sup>−1</sup> cm<sup>3</sup>, prepared by crystallization at 120 and 160 °C and by subsequent hydrolytic degradation (i.e., C120-0 and C160-0, respectively), and *W<sub>PLLA</sub>* and *W<sub>PDLLA</sub>* are the weights of the PLLA and PDLLA chains, respectively. The yield values of copolymers synthesized without melting of the extended chain crystallites were estimated according to the following equation using *X<sub>PLLA</sub>* values:

$$\text{yield}(\%) = 100[(0.2(100 - X_{\text{PLLA}})/X_{\text{PLLA}})/2] \quad (2)$$

The molecular structures of the extended chain crystallites and the synthesized polymers were determined from the 300 MHz <sup>1</sup>H NMR spectra obtained in deuterated chloroform (50 mg mL<sup>−1</sup>) by a Varian Mercury 300 spectrometer using tetramethylsilane as the internal standard. The *M<sub>n</sub>* values of the extended chain crystallites and synthesized polymers were also estimated by <sup>1</sup>H NMR spectra [*M<sub>n</sub>*(NMR)] according to the following equation using the peak intensity for methine groups at chain terminals (*I*<sub>1</sub>) and inside the chains (*I*<sub>2</sub>) observed at around 4.4 and 5.2 ppm, respectively:<sup>24–26</sup>

$$M_n(\text{NMR}) = 72.1(I_1 + I_2)/I_1 \quad (3)$$

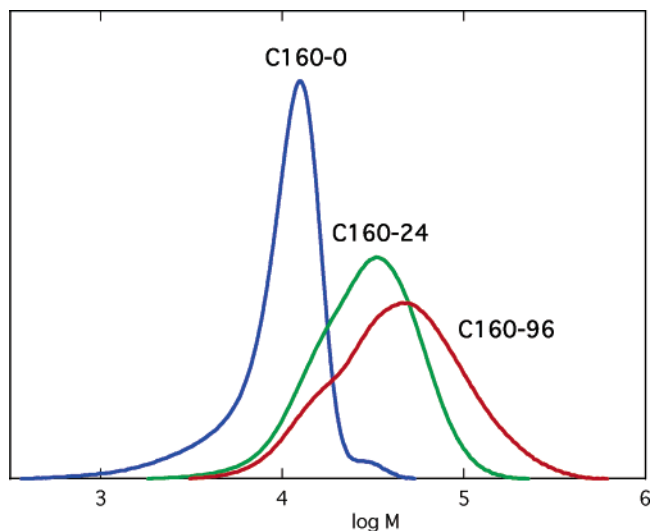
The glass transition, cold crystallization, and melting temperatures (*T<sub>g</sub>*, *T<sub>cc</sub>*, and *T<sub>m</sub>*, respectively) and the enthalpies of cold crystallization and melting (Δ*H<sub>cc</sub>* and Δ*H<sub>m</sub>*, respectively) of the extended chain crystallites and synthesized polymers were determined with a Shimadzu (Kyoto, Japan) DSC-50 differential scanning calorimeter under a nitrogen gas flow at a rate of 50 mL min<sup>−1</sup>. The specimens (sample weight ca. 3 mg) were heated from room temperature to 200 °C at a rate of 10 °C min<sup>−1</sup> (first heating) and then quenched at 25 °C. The

**Table 1.** Characteristics and Crystallinity of Extended Chain Crystallites as a Solid-State Macro-Coinitiator (C120-0 and C160-0) and PLLA-*b*-PDLLA (C120-24, C120-96, C160-24, and C160-96), Together with Those of a Polymer Synthesized by a Conventional Procedure after Melting of Extended Chain Crystallites (C160-96M)

code	crystallization temp (°C)	polymerization time (h)	yield <sup>a</sup> (%)	$M_n$ (NMR) (g mol <sup>-1</sup> )	$M_n$ (GPC-Th) (g mol <sup>-1</sup> )	$M_n$ (GPC) (g mol <sup>-1</sup> )	$M_w$ (GPC)/ $M_n$ (GPC)	$[\alpha]_{589}^{25}$ <sup>b</sup> (deg dm <sup>-1</sup> g <sup>-1</sup> cm <sup>3</sup> )	$X_{\text{PLLA}}^c$ (%)	$X_c^d$ (%)
C120-0	120	0				$6.24 \times 10^3$	1.39	-128.4	100.0	≈100
C120-24		24	2.4		$6.86 \times 10^4$	$1.28 \times 10^4$	1.32	-103.2	80.4	78.4
C120-96		96	5.7		$6.86 \times 10^4$	$1.92 \times 10^4$	1.33	-79.2	63.7	66.1
C160-0	160	0		$4.91 \times 10^3$		$7.74 \times 10^3$	1.45	-137.7	100.0	≈100
C160-24		24	11.0	$6.81 \times 10^3$	$7.74 \times 10^4$	$2.27 \times 10^4$	1.54	-65.7	47.7	48.6
C160-96		96	13.9	$1.64 \times 10^4$	$7.74 \times 10^4$	$3.12 \times 10^4$	1.93	-57.6	41.8	37.1
C160-96M <sup>e</sup>		96	72.1	$2.01 \times 10^4$		$4.01 \times 10^4$	1.43	-17.0	<i>f</i>	12.0

<sup>a</sup> Estimated from  $X_{\text{PLLA}}$  values using eq 2, except for C160-96M, wherein the yield was evaluated from the recovered polymer weight. <sup>b</sup> Specific optical rotation at 589 nm and 25 °C in chloroform. <sup>c</sup> Percentage values of PLLA chains in polymers. <sup>d</sup> Crystallinity of polymers estimated by WAXS measurements.

<sup>e</sup> Polymerization was carried out after melting of the extended chain crystallites at 200 °C for 2 min, and the polymerized specimen was purified using acetone and methanol as the solvent and nonsolvent, respectively. <sup>f</sup> Not estimated because L-lactide sequences were expected to be randomized to some extent during polymerization.

**Figure 2.** Molecular weight distribution of extended chain crystallites (C160-0) (polymerization time 0 h) and of synthesized copolymers C160-24 and C160-96 (polymerization time 24 and 96 h, respectively) without melting of extended chain crystallites.

melt-quenched specimens were again heated from room temperature to 200 °C at a rate of 10 °C min<sup>-1</sup> (second heating). The  $T_g$ ,  $T_{cc}$ ,  $T_m$ ,  $\Delta H_{cc}$ , and  $\Delta H_m$  values were calibrated using tin, indium, and benzophenone as standards. Wide-angle X-ray scattering (WAXS) measurements were carried out at 25 °C using a RINT-2500 (Rigaku Co., Tokyo, Japan) equipped with a Cu K $\alpha$  source ( $\lambda = 0.154$  nm). The crystallinity ( $X_c$ ) values were determined by WAXS measurements.

## Results and Discussion

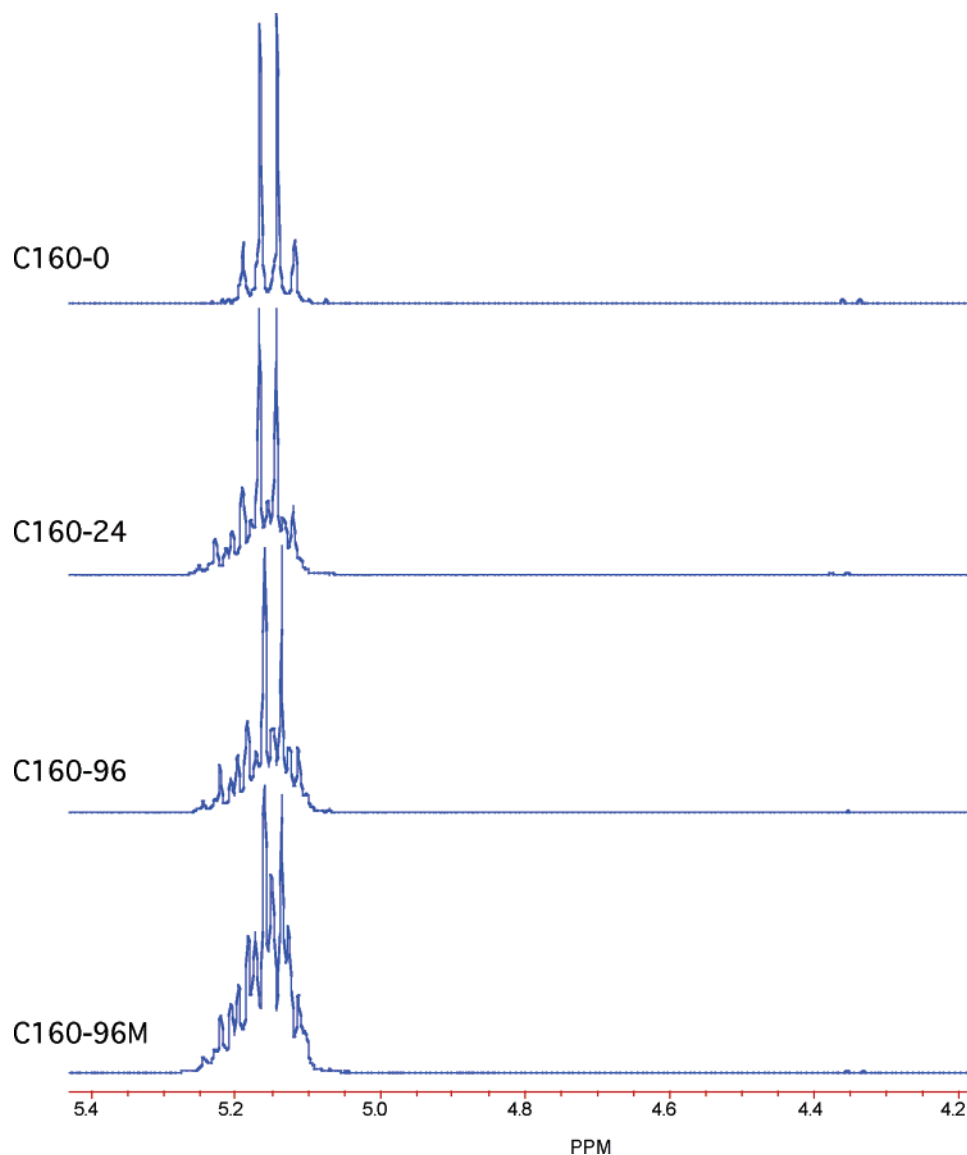
**Gel Permeation Chromatography and Polarimetry.** Figure 2 shows the change in molecular weight distribution during polymerization without melting of the PLLA extended chain crystallites. The peak of the PLLA extended chain crystallites, C160-0 (crystalline residues, polymerization time 0 h) used as the macro-coinitiator, appeared at around  $1 \times 10^4$  g mol<sup>-1</sup>. The rather broad molecular distribution of the extended chain crystallites should be attributed to the broad distribution of the thickness of crystalline regions in the PLLA crystallized films before hydrolytic degradation. The molecular weight distribution curve gradually shifted to a higher molecular weight as a whole with increased polymerization time (C160-24 and C160-96, polymerization time 24 and 96 h, respectively). A similar change in molecular weight distribution with polymerization time was observed for C120-0, C120-24, and C120-96 (data not shown). Such a molecular weight shift was reported for block copo-

lymerization in the presence of a polymeric coinitiator.<sup>27,28</sup> The  $M_n$  and  $M_w/M_n$  of the polymers were estimated from the molecular weight distribution curves and are tabulated in Table 1. As seen, the  $M_n$  values increased with polymerization time. These findings are indicative of the fact that almost all the hydroxyl groups on the surface of the PLLA extended chain crystallites effectively coinitiated the polymerization and that the PDLLA chains were formed from the hydroxyl groups of the extended chain crystallites (Figure 1). However, we cannot exclude the possibility of the presence of unreacted chains in the extended chain crystallites because of the overlapping of molecular weight distribution curves of the extended chain crystallites and synthesized copolymers. The hydroxyl groups trapped inside the extended chain crystallites may have remained unreacted.

The evaluated  $M_n$ (GPC) values of copolymers synthesized without melting of the extended chain crystallites were much lower than the expected  $M_n$ (GPC-Th) values (Table 1). This should be due to the fact that a part of DLLA was consumed for the polymerization of free PDLLA chains, which should have caused a reduction in the amount of DLLA available for PDLLA chain growth from the PLLA extended chain crystallites. Without melting of the extended chain crystallites, the yield was higher for the copolymers synthesized with C160-0 than for those synthesized with C120-0, despite the fact that C120-0 had a higher number of terminal hydroxyl groups per unit mass. It is anticipated that the content of water molecules entrapped by the terminal hydroxyl groups increases with the number of terminal hydroxyl groups. The higher water content of C120-0 compared with that of C160-0 will cause the formation of a larger amount of free PDLLA homopolymers with the higher consumption of DLLA, resulting in the formation of a smaller amount of PDLLA block chains.

As shown in Table 1, the  $[\alpha]_{589}^{25}$  of synthesized polymers decreased with polymerization time. This supports the fact that the length of optically inactive PDLLA chains connected with optically active PLLA chains increased with polymerization time. Besides, the  $M_n$  and  $[\alpha]_{589}^{25}$  data shown in Table 1 show that block copolymers with different PLLA and PDLLA contents and molecular weights can be synthesized by altering the molecular weight of extended chain crystallites and polymerization time. For example, C120-96 and C160-24 have similar molecular weights but completely different  $[\alpha]_{589}^{25}$  values (i.e., different PLLA fractions). The PLLA and PDLLA contents are expected to change by varying the ratio of PLLA extended chain crystallites to DLLA in the feed.

When the polymerization of DLLA was carried out for 96 h after the extended chain crystallites were melted (conventional procedure), the insoluble fraction could not be collected from



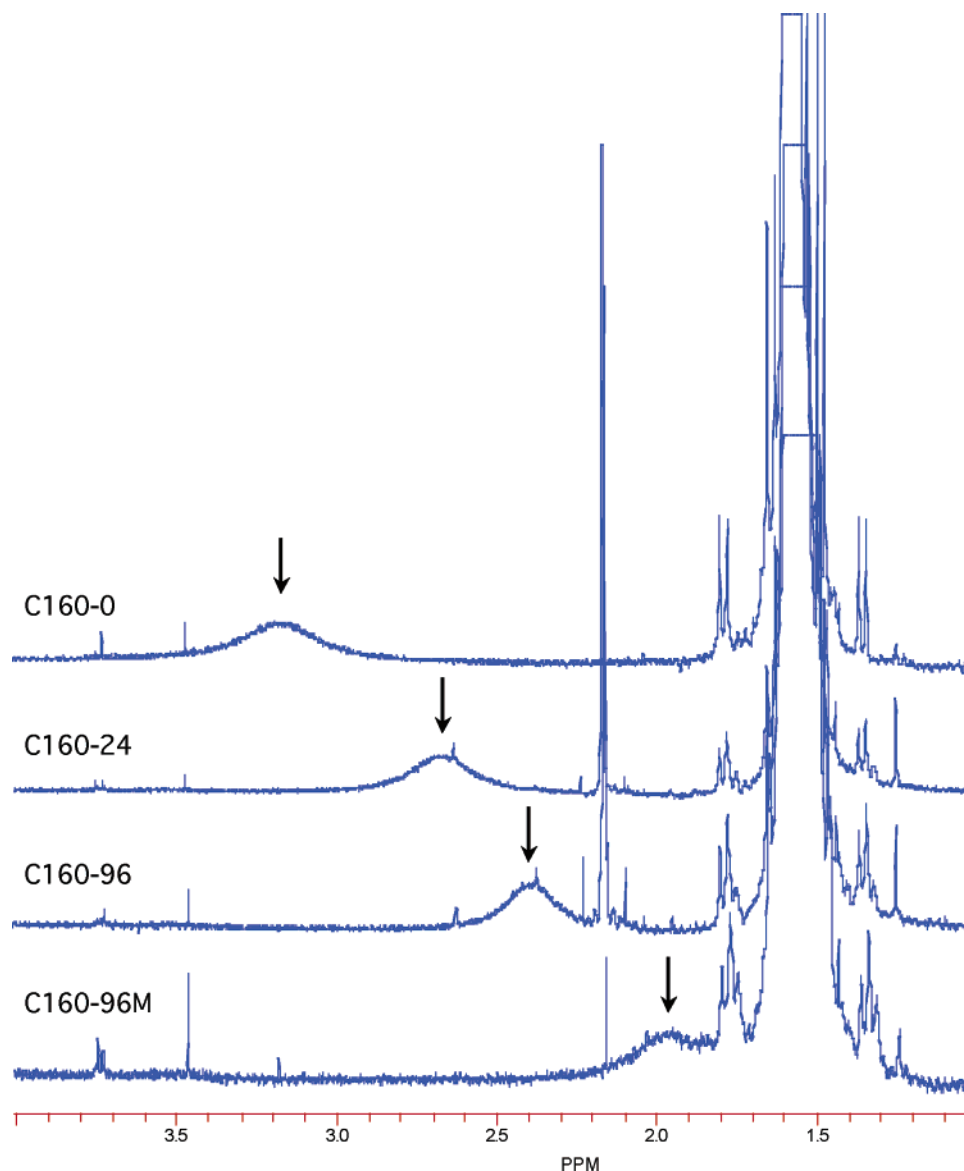
**Figure 3.**  $^1\text{H}$  NMR spectra for the methine proton of extended chain crystallites (C160-0), of copolymers synthesized without melting of extended chain crystallites (C160-24 and C160-96), and of a polymer synthesized after melting of extended chain crystallites (C160-96M).

the resulting polymer suspended in acetone, even by centrifugation. This is in marked contrast with the copolymers synthesized without melting of the extended chain crystallites and is indicative of the difficulty involved in the separation of copolymers composed of PLLA and PDLLA chains from a resulting polymer mixture containing free PDLLA. The polymer suspended in acetone was recovered by precipitation with methanol, which was composed of the copolymer of PLLA and PDLLA chains and the free PDLLA homopolymer. As shown in Table 1, the recovered polymer C160-96M had a much lower  $[\alpha]_{589}^{25}$  value ( $-17.0 \text{ deg dm}^{-1} \text{ g}^{-1} \text{ cm}^3$ ) compared with  $-57.6 \text{ deg dm}^{-1} \text{ g}^{-1} \text{ cm}^3$  for the copolymer synthesized without melting of the extended chain crystallites (C160-96). This reveals that a larger amount of free PDLLA chains was incorporated in C160-96M. On the basis of this fact, the conventional method is not suitable for preparing the block copolymers of PLLA and PDLLA.

**$^1\text{H}$  NMR Spectroscopy.** To investigate PDLLA chain growth during polymerization and the structure of the extended chain crystallites and synthesized polymers, we carried out  $^1\text{H}$  NMR spectroscopy. Figure 3 shows the  $^1\text{H}$  NMR spectra for the methine proton of the extended chain crystallites (C160-0) of the copolymers synthesized without melting of the extended

chain crystallites (C160-24 and C160-96) and of the polymer synthesized after melting of the extended chain crystallites (C160-96M). The well-defined quartet resonance peaks of the methine proton were observed for C160-0, which is typical of pure PLLA.<sup>26</sup> In contrast, 10 and more peaks were seen for the synthesized polymers. Thakur et al. observed quintet methine peaks in a homonuclear decoupled  $^1\text{H}$  NMR spectrum of PDLLA synthesized by polymerization of DLLA with  $\text{Sn}(\text{Oct})_2$ .<sup>29</sup> Here, the chemical shift values of the peaks depend on the monomer sequences such as *isisi*, *iiisi*, *isiii*, *iii*, and *isi*. Therefore, such complicated multiple peaks observed for C160-24, C160-96, and C160-96M are ascribed to the incorporation of PDLLA chains. The splitting position of the spectrum or the area of the broad peak was higher for the polymer synthesized after melting of the extended chain crystallites (C160-96M) than for the copolymers synthesized without melting of the extended chain crystallites (C160-24 and C160-96). This confirms the incorporation of a higher amount of PDLLA chains for the copolymer synthesized after the extended chain crystallites were melted. However, because of the difference in the overall ratio of the L-lactyl unit to the D-lactyl unit between C160-96 and C160-96M, the frequency of the transesterification reaction in





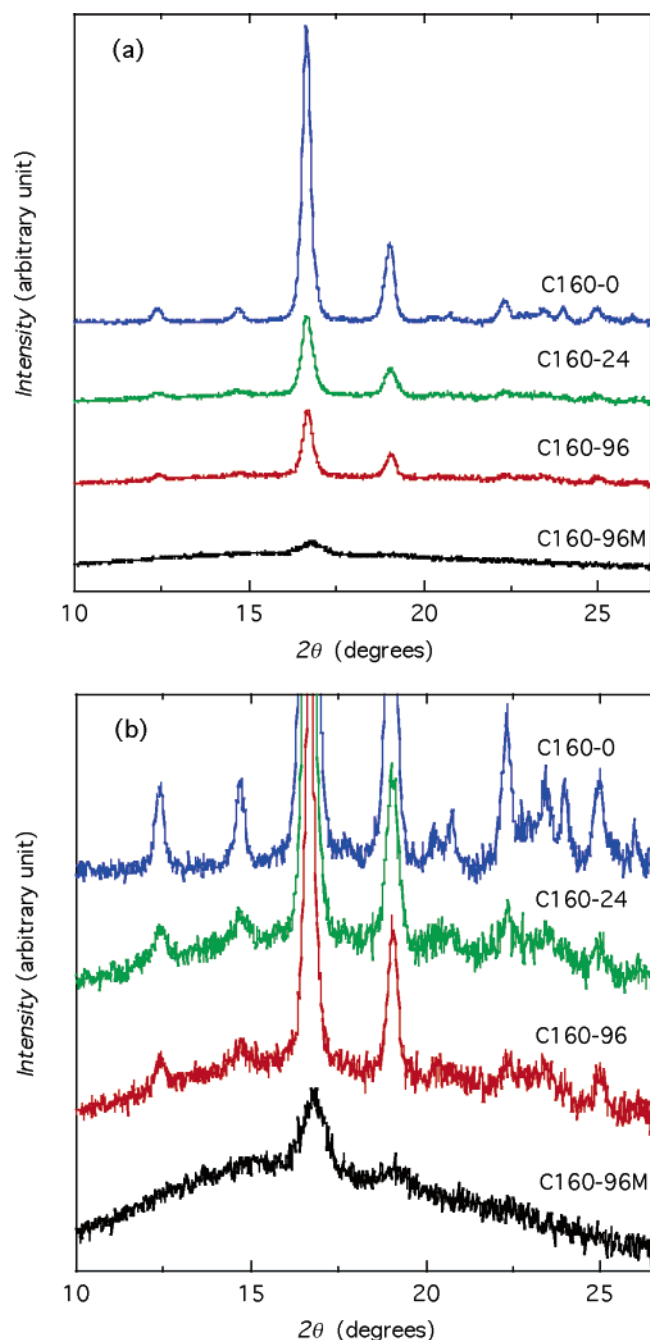
**Figure 4.**  $^1\text{H}$  NMR spectra for the hydroxyl proton of extended chain crystallites (C160-0), of copolymers synthesized without melting of extended chain crystallites (C160-24 and C160-96), and of a polymer synthesized after melting of extended chain crystallites (C160-96M).

solid-state PLLA during polymerization could not be compared with that in an amorphous state.

Figure 4 shows the  $^1\text{H}$  NMR spectra for the hydroxyl proton of the same specimens given in Figure 3. Broad resonance peaks were observed at 1.9–3.2 ppm for all specimens, and the chemical shift value was higher for specimens having a lower molecular weight. The respective chemical shift values of the hydroxyl proton of ethyl D,L-lactate<sup>25</sup> and low molecular weight of PLLA ( $M_n = 2000 \text{ g mol}^{-1}$ )<sup>24</sup> were 3.7 and 3.6 ppm. Furthermore, it is well-known that hydrogen bonding at a lower molecular weight reduces the electron density of the proton, resulting in a higher chemical shift value.<sup>30</sup> Moreover, the peak area at 1.9–3.2 ppm was comparable to that of the terminal methine proton at around 4.4 ppm. These findings strongly suggest that the broad resonances at 1.9–3.2 ppm are due to the hydroxyl proton and that one of the terminals of a chain in the PLLA extended chain crystallites and synthesized polymers was a hydroxyl group.

**Wide-Angle X-ray Scattering.** The WAXS profiles of the extended chain crystallites (C160-0) and copolymers synthesized without melting of the extended chain crystallites (C160-24 and C160-96) are shown in Figure 5, together with that of the

polymer synthesized after melting of the extended chain crystallites (C160-96M). For C160-0, C160-24, and C160-96, intense and sharp diffraction peaks were observed at  $2\theta$  values of  $15^\circ$ ,  $17^\circ$ , and  $19^\circ$ , although C160-96M gave a diffuse diffraction only at a  $2\theta$  value of  $17^\circ$ . These diffraction peaks are typical for the  $\alpha$ -form of PLLA crystallized in a pseudo-orthorhombic unit cell of dimensions  $a = 1.07 \text{ nm}$ ,  $b = 0.595 \text{ nm}$ , and  $c = 2.78 \text{ nm}$ , which contains two  $10_3$  helices.<sup>31</sup> Therefore, all specimens contained  $\alpha$ -form crystallites. The sharp diffraction peaks of the copolymers synthesized without melting of the extended crystallites (C160-24 and C160-96) reflect the stability of the extended chain crystallites during polymerization. For the copolymers synthesized without melting of the extended chain crystallites, by increasing the polymerization time, the diffraction peak heights of the  $\alpha$ -form decreased (Figure 5a) and the broad diffraction which originated from amorphous chains became higher (Figure 5b). The findings here reflect that the content of amorphous PDLLA chains increased with polymerization time. A similar change in the WAXS profiles with polymerization time was observed for C120-0, C120-24, and C120-96 (data not shown). The diffraction peak heights of the  $\alpha$ -form and the broad diffraction which originated from



**Figure 5.** X-ray diffraction profiles of extended chain crystallites (C160-0), of copolymers synthesized without melting of extended chain crystallites (C160-24 and C160-96), and of a polymer synthesized after melting of extended chain crystallites (C160-96M). Parts a and b show whole profiles and magnified base lines, respectively.

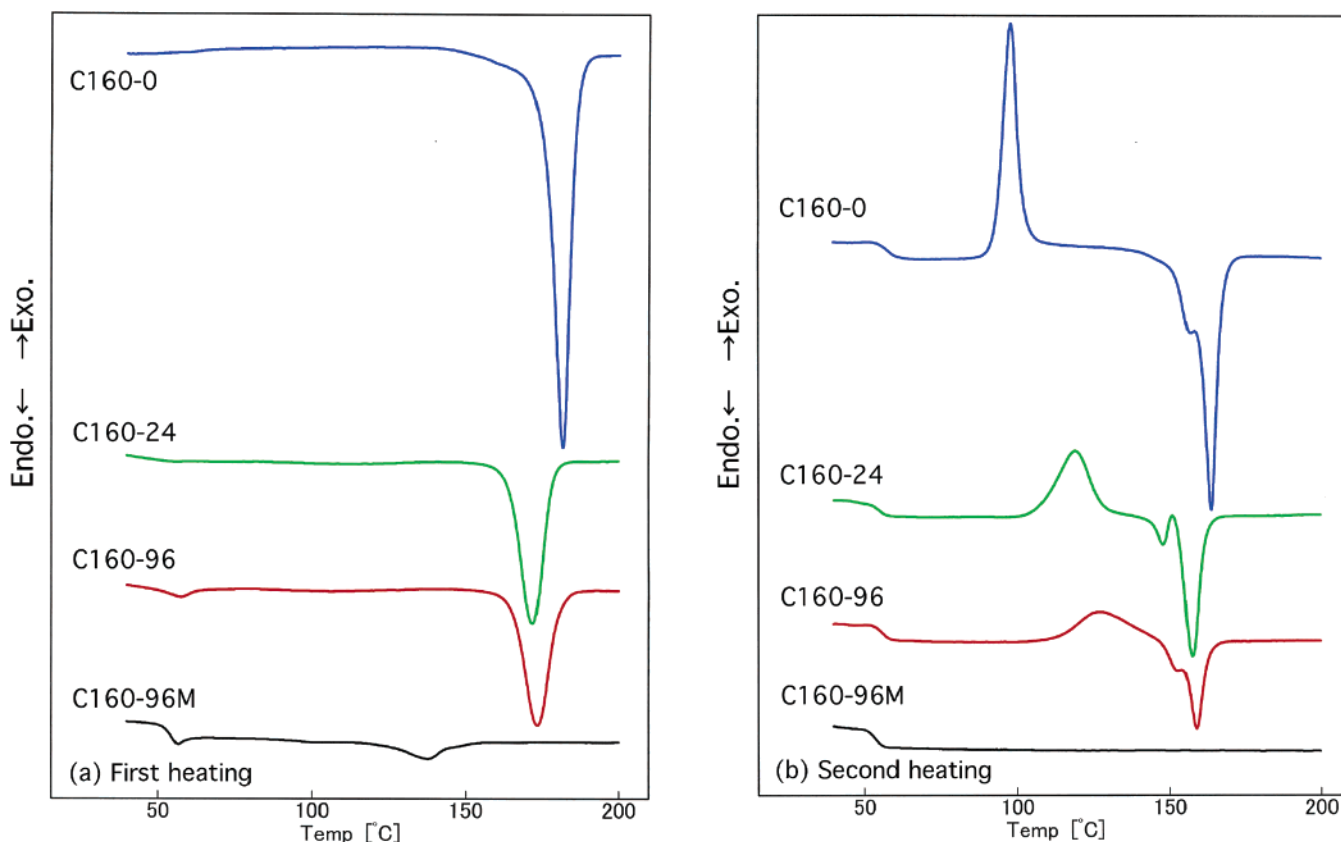
amorphous chains for C160-96M were respectively lower and higher than those of C160-96. This indicates that a larger amount of PDLLA chains was incorporated in C160-96M than in C160-96, due to the remaining free PDLLA chain in the former specimen. The  $X_c$  values estimated from WAXS measurements are given in Table 1. The dependence of  $X_c$  on  $X_{\text{PLLA}}$  is discussed below.

**Differential Scanning Calorimetry.** For further confirmation of the polymerization of DLLA from the extended chain crystallites, for verification of the protection of PLLA chains in the extended chain crystallites during polymerization, and for investigation of crystallizability after melt quenching, we performed DSC measurements. Parts a and b of Figure 6 show the DSC thermograms of the extended chain crystallites

(C160-0) and synthesized polymers C160-24, C160-96, and C160-96M on the first heating and of their melt-quenched specimens on the second heating, respectively. The  $T_g$ ,  $T_{cc}$ ,  $T_m$ ,  $-\Delta H_{cc}$ , and  $\Delta H_m$  values were evaluated from DSC thermograms and are summarized in Table 2. On the first heating (Figure 6a), a melting peak was observed for all specimens in the temperature range of 130–190 °C. The melting peaks of copolymers synthesized without melting of the extended chain crystallites (C160-24 and C160-96) appeared at a slightly lower temperature than that of the extended chain crystallites (C160-0). However, the melting temperature of the polymer synthesized after melting of the extended chain crystallites (C160-96M) was much lower than those of C160-24 and C160-96. Furthermore, a glass transition peak was clearly observed for the synthesized polymers C160-96 and C160-96M in Figure 6a, indicating that a sufficiently large amount of amorphous PDLLA chains was incorporated in these polymers.

On the second heating (Figure 6b), the glass transition, cold crystallization, and melting peaks were noticed for all melt-quenched specimens, except for C160-96M (wherein only the glass transition peak was observed). The  $-\Delta H_{cc}$  value was the same as the  $\Delta H_m$  value for all specimens (see Table 2). This means that the melt-quenched specimens were amorphous before the second heating. On the second heating, the  $T_m$  value of 164 °C for the PLLA extended chain crystallites, C160-0 ( $M_n = 7.7 \times 10^3 \text{ g mol}^{-1}$ ), was comparable to the  $T_m$  values of 158–165 °C reported for as-cast PLLA ( $M_n = 7.1 \times 10^3$  to  $1.5 \times 10^4 \text{ g mol}^{-1}$ ).<sup>32</sup> However, the  $T_m$  values of 157–158 °C for the synthesized copolymers C160-24 and C160-96 ( $M_n = (2.3\text{--}3.1) \times 10^4 \text{ g mol}^{-1}$ ) were much lower than the  $T_m$  values of 172–173 °C reported for as-cast PLLA films ( $M_n = (2.8\text{--}3.1) \times 10^4 \text{ g mol}^{-1}$ ).<sup>32</sup> Also, on the second heating, the respective  $T_{cc}$  values of 119 and 127 °C for C160-24 and C160-96 were higher than the  $T_{cc}$  value of 98 °C for the extended chain crystallites (C160-0), and the respective  $T_m$  values of 157 and 159 °C for C160-24 and C160-96 were lower than the  $T_m$  value of 164 °C for C160-0. These findings indicate that PDLLA chains connected with PLLA chains disturb the formation and growth of PLLA crystallites, resulting in higher  $T_{cc}$  and lower  $T_m$  values of melt-quenched copolymer specimens compared with those of melt-quenched extended chain crystallites. In contrast, the crystallizability of C160-96M during the second heating was completely lost, because of the incorporation of the large amount of amorphous PDLLA chains both as free chains and as chains connected to PLLA chains. Accordingly, facile crystallizability after the melting process is a crucial feature for block copolymers synthesized without melting of the extended chain crystallites (C160-24 and C160-96). Due to facile crystallizability, synthesized block copolymers are expected to have high controllability of highly ordered structures and, therefore, of biodegradability and drug release properties.

Free PDLLA chains polymerized with the coinitiator of a trace amount of water in the polymerization system should have been removed by extraction with acetone, except for C160-96M. Therefore, the gradual decrease of the  $\Delta H_m$ ,  $-\Delta H_{cc}$ , and  $X_c$  values of copolymers C120 and C160 (except for C160-96M) with polymerization time supports the growth of PDLLA chains which were connected to the PLLA chains of the extended chain crystallites. The  $\Delta H_m$  values of the extended chain crystallites and synthesized copolymers on the first heating, the  $-\Delta H_{cc}$  values of their melt-quenched specimens on the second heating, and the  $X_c$  values of extended chain crystallites and synthesized copolymers estimated by WAXS measurements are plotted in Figure 7 as a function of  $X_{\text{PLLA}}$ . Figure 7 does not include data



**Figure 6.** DSC thermograms of extended chain crystallites (C160-0), of copolymers synthesized without melting of extended chain crystallites (C160-24 and C160-96), and of a polymer synthesized after melting of extended chain crystallites (C160-96M) on the first heating (a) and of their melt-quenched specimens on the second heating (b).

**Table 2.** Thermal Properties of Extended Chain Crystallites as a Solid-State Macro-Coinitiator (C120-0 and C160-0) and PLLA-*b*-PDLLA (C120-24, C120-96, C160-24, and C160-96), Together with Those of a Polymer Synthesized by a Conventional Procedure after Melting of Extended Chain Crystallites (C160-96M)

code	crystallization temp (°C)	polymerization time (h)	first heating			second heating				
			$T_g^a$ (°C)	$T_m^b$ (°C)	$\Delta H_m^c$ (J g <sup>-1</sup> )	$T_g^a$ (°C)	$T_{cc}^d$ (°C)	$T_m^b$ (°C)	$\Delta H_{cc}^e$ (J g <sup>-1</sup> )	$\Delta H_m^c$ (J g <sup>-1</sup> )
C120-0	120	0		172.6	83.7	50.8	92.4	157.1	-52.5	52.3
C120-24		24		154.5, 173.9	65.3	50.8	101.6, 122.1	155.6	-42.1	41.9
C120-96		96		152.3, 174.5	59.0	52.4	109.2	146.6, 157.1	-35.8	35.9
C160-0	160	0		181.5	88.0	54.3	97.9	156.9, 163.7	-51.1	51.7
C160-24		24		171.8	42.4	52.8	119.0	147.7, 157.3	-25.6	25.5
C160-96		96	50.2	173.3	37.7	53.1	127.0	152.6, 158.7	-17.0	17.2
C160-96M <sup>d</sup>		96 <sup>f</sup>	51.4	137.6	9.4	50.4			0.0	0.0

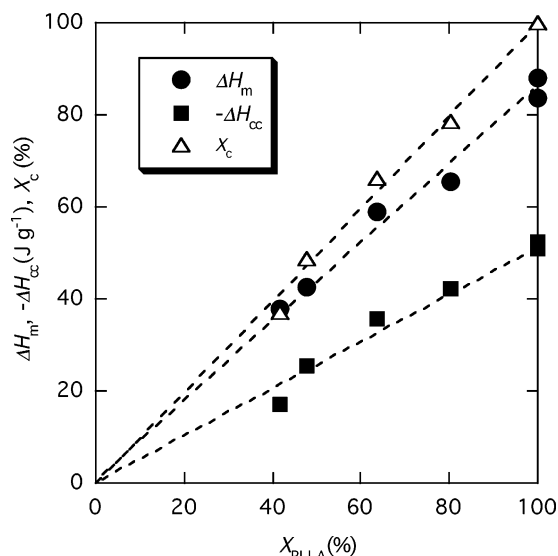
<sup>a</sup> Glass transition temperature. <sup>b</sup> Melting temperature. <sup>c</sup> Enthalpy of melting. <sup>d</sup> Cold crystallization temperature. <sup>e</sup> Enthalpy of cold crystallization. <sup>f</sup> Polymerization was carried out after melting of the extended chain crystallites at 200 °C for 2 min, and the polymerized specimen was purified using acetone and methanol as the solvent and nonsolvent, respectively.

for C160-96M. It is interesting to note that  $\Delta H_m$  on the first heating,  $-\Delta H_{cc}$  on the second heating, and  $X_c$  were proportional to  $X_{PLLA}$ . That is, the experimental  $\Delta H_m$ ,  $-\Delta H_{cc}$ , and  $X_c$  values of the copolymers are in complete agreement with those expected from the experimental  $X_c$  values of the extended chain crystallites (broken line). This indicates that well-defined block copolymers P(LLA-*b*-DLLA) were successfully synthesized without significant transesterification, when the polymerization of DLLA was carried out without melting of the extended chain crystallites. If transesterification had taken place, the experimental values of the copolymers would have been lower than the calculated values because of lattice disorder caused by transesterification.

**Reaction Mechanisms.** Two reaction pathways have been suggested for the polymerization of lactones and lactides with

Sn(Oct)<sub>2</sub>.<sup>14,16</sup> In a mechanism proposed by Kricheldorf et al., a cointiating alcohol and a monomer are both coordinated to Sn(Oct)<sub>2</sub> during propagation.<sup>14,16,25,33</sup> In a mechanism presented by Kowalski et al., Sn(Oct)<sub>2</sub> is converted to tin alkoxide before complexing and ring-opening polymerization.<sup>14,16,34</sup> Here, the tin(II)-alkoxide bond is formed by the reaction of Sn(Oct)<sub>2</sub> with alcohol. In the present study, both mechanisms can explain the formation of PDLLA chains from the many hydroxyl groups on the surface of extended chain crystallites. Also, the polymerization mechanism with the hydroxyl groups of extended chain crystallites should be very similar to the polymerization of lactone or lactide in the presence of a polyol.<sup>13,15,22,35</sup>

On the other hand, the transesterification reaction of polylactones and polylactides proceeds via two mechanisms, intramolecular and intermolecular transesterification. In the



**Figure 7.**  $\Delta H_m$  of extended chain crystallites and copolymers synthesized without melting of extended chain crystallites (on the first heating),  $-\Delta H_{cc}$  values of their melt-quenched specimens (on the second heating), and  $X_c$  values of extended chain crystallites and synthesized copolymers as a function of  $X_{\text{PLLA}}$ .

polymerization of lactide, intramolecular transesterification seems less important,<sup>16</sup> and therefore, the selectivity parameters [ $\gamma$  = the rate constant of propagation ( $k_p$ )/the rate constant of intermolecular transfer ( $k_{tr(2)}$ )] were obtained for various metal alkoxides.<sup>36</sup> Baran et al. indicated that, among the metal alkoxides, one with Sn, tributyltin alkoxide, has a relatively low  $\gamma$  value, i.e., a relatively high reactivity of growing chains toward the chains already formed.<sup>36</sup> Furthermore, Bero et al. reported that  $\text{Sn}(\text{Oct})_2$  is a strong transesterification agent and that the resulting polymers normally have a randomized microstructure.<sup>14,37</sup> In the present study, despite the use of  $\text{Sn}(\text{Oct})_2$  with a strong transesterification property, we could not observe significant transesterification between the growing chains (PDLLA chains) and the chains already formed (PLLA chains) because the latter were protected in the rigid lattice structure.

Finally, the present study should be compared with the solid-state polymerization of polymers such as poly(ethylene terephthalate) (PET) and poly(hexamethylene adipamide) (nylon 6,6).<sup>38</sup> This method was also applied for the synthesis of high-molecular-weight PLLA.<sup>39,40</sup> In solid-state polymerization, the reaction occurs mainly at the chain terminals in the amorphous regions in crystallized polymer pellets. During the reaction, the chains in the rigid crystalline regions are protected from the attack of a monomer, similar to that in the present study. However, the products of solid-state polymerization are homopolymers, not block copolymers. Moreover, in solid-state polymerization, if a different kind of monomer is reacted, well-defined block copolymers will not be formed because the comonomer can react with the tie chains and folding chains in the amorphous regions during the process. This is in marked contrast to the present study.

## Conclusions

From the aforementioned results the following conclusions can be derived.

(1) The polymerization of lactide (or lactone) in the presence of PLLA extended chain crystallites as a solid-state macrocointiator is a useful and promising method for yielding the

poly(L-lactide)-based block copolymers without significant transesterification.

(2) PLLA-*b*-PDLLA with different PLLA contents and overall molecular weights can be synthesized by varying the molecular weight of PLLA extended chain crystallites and the reaction time.

(3) Conventional polymerization after melting of the PLLA extended chain crystallites gave a polymer mixture of free homopolymer PDLLA and the copolymers of PLLA and PDLLA due to the difficulty involved in the separation of the copolymers of PLLA and PDLLA from the polymer mixture.

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