Synthesis, Characterization, and Hydrolytic Degradation of PLA/PEO/PLA Triblock Copolymers with Short Poly(L-lactic acid) Chains

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Received April 19, 1995; Revised Manuscript Received September 15, 1995[⊗]

ABSTRACT: PLA/PEO/PLA triblock copolymers bearing short poly(L-lactic acid) blocks, with the number average degree of polymerization of each PLA block $\overline{DP}_{PLA}$ = 2, 4, 8, and 12, were synthesized by ring opening polymerization of L-lactide initiated by poly(ethylene glycol) in the presence of CaH_2. The length of PEO blocks was varied by using parent PEG of different number average degrees of polymerization $\overline{DP}_{PEG}$ = 14, 26, and 49, respectively, according to SEC and NMR. SEC and ^1H and ^{13}C NMR showed the resulting triblock copolymers did not contain any detectable PLA homopolymer as side product. The use of DMSO-d_6 as solvent for NMR analyses, instead of $CDCl_3$, greatly enhanced the resolution and permitted the distinction of the signals due to the last two constitutive units located at both ends of each PLA block. Data obtained by FTIR spectroscopy and X-ray diffractometry suggested that PEO and PLA blocks were phase separated even for copolymers with very short PLA blocks. Optical microscopy and DSC showed that an increase in the length of PLA blocks led to a decrease in the crystallinity of PEO blocks up to disappearance. Hydrolysis was carried out in DMSO/D_2O in the presence of trifluoroacetic acid and monitored by NMR. Data suggested that intrachain and PEO/PLA connecting ester bonds were cleaved at comparable rates in the selected homogeneous medium.

Introduction

Poly(ethylene glycol) (PEG) presents outstanding physico-chemical and biological properties, including hydrophilicity, solubility in water and in organic solvents, lack of toxicity,[1] and absence of antigenicity and immunogenicity,[2] which allowed PEG to be used for many biomedical and biotechnological applications. The terminal hydroxyl groups of PEG can readily react with a variety of compounds. In particular, small drug molecules have been covalently attached to PEG chains.[3−5] Over the last two decades, another group of polymers has been widely studied to develop systems for sustained drug delivery—the aliphatic polyesters—in particular bioresorbable poly(lactic acid) (PLA) and poly(ϵ-caprolactone) (PCL).[6−8] Recently, block copolymers have been prepared from PEG and lactides (cyclic diesters of lactic acid enantiomers) or from PEG and lactic acid.[9−16] Copolymerization offered the possibility of varying hydrophilic/hydrophobic and soft/hard segment ratios and, thus, constitutes a very attractive means to modulate the basic properties of each homopolymer. PLA/PEG copolymers are of great interest in view of applications in drug delivery systems[17] or as macromonomers for preparation of new macromolecular materials.[18]

So far, different compounds have been reported as co-initiators or catalysts for the polymerization of lactides in the presence of PEG, such as metal oxides (SnO, SnO_2, Sb_2O_3, PbO, GeO_2) and salts ($SnCl_2$ or KtBuO, etc.)[10−12] or hydride (NaH),[13] to yield high molecular weight diblock and triblock copolymers. High molecular weight compounds are also obtained when stannous octoate is used.[10] Nevertheless, stannous octoate, as many other co-initiators, is more or less cytotoxic.[19] In order to avoid any nonbiocompatible impurities in the final product, triblock copolymers were prepared from PEG and L-lactide in the absence of catalyst.[16,20] However, this noncatalyzed synthesis proceeded too slowly.[20]

In the present paper, we report the synthesis, characterization, and hydrolysis of poly(oxyethylene)s (PEOs) bearing short PLA sequences at both ends using CaH_2 as co-initiator. This compound was selected because it was not known as a PLA initiator or co-initiator and because it was not supposed to lead to toxic impurities in the final product. According to literature, such copolymers should be of interest for the preparation of biomedical or pharmacological devices.[17,18] It was also very important to well identify their properties and physico-chemical behaviors because they are good models of the degradation products which are to appear during degradation of high molecular weight triblock PLA/PEO/PLA copolymers. With this regard, the use of DMSO as solvent for NMR analyses was helpful, as it permitted us to go deeper in the characterization of constitutive units close to block connections and to PLA chain ends.

Experimental Section

Materials. L-lactide was purchased from Purac and purified by recrystallization from acetone. PEG600, PEG1000, and PEG2000 were purchased from Fluka. Prior to use, these PEG polymers were purified by dissolution in chloroform and precipitation in diethyl ether at −10 °C, followed by drying through azeotropic distillation in toluene. After evaporation of toluene, PEGs were allowed to stand under reduced pressure (10^{-3} mmHg) at 50 °C for 3 h. Their number average degree of polymerization was then $\overline{DP}_{PEG}$ = 14, 26, and 49, respectively, according to SEC and in good agreement with NMR. CaH_2 powder of 40 mesh size (Aldrich) was used as received. L-Lactic acid (85−90%) was purchased from Janssen.

Methods. PEG (0.02 mol) was introduced into a round-bottomed, three-necked flask equipped with magnetic stirring. The flask was connected to a vacuum system and immersed in an oil bath. The number average molecular weight ($\bar{M}_n$), as determined by SEC, was used for the calculation of the

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⊗ Abstract published in *Advance ACS Abstracts,* November 15, 1995.

0024-9297/96/2229-0050$12.00/0

Table 1. Molecular Weight Data of $PLA_x/PEO_y/PLA_x$ Triblock Copolymers and of Parent PEG Polymers As Deduced from ^1H NMR and SEC Analyses

	^1H NMR				SEC[a]	
polymer	$\overline{DP}_{PLA}$[b]	$\bar{M}_{nPLA}$[c]	$\bar{M}_{nPEO}$[d]	$\bar{M}_n$[e] $PLA_x/PEO_y/PLA_x$	$\bar{M}_n$ $PLA_x/PEO_y/PLA_x$	$\bar{M}_w/\bar{M}_n$ $PLA_x/PEO_y/PLA_x$
PEG600			612		640	1.03
$PLA_2/PEO_{14}/PLA_2$	2.3 (2)[f]	166	610	959	950	1.06
PEG1000			1009		1170	1.02
$PLA_2/PEO_{26}/PLA_2$	1.9 (2)	137	1007	1299	1400	1.05
$PLA_4/PEO_{26}/PLA_4$	3.5 (4)	252	1007	1529	1630	1.06
$PLA_8/PEO_{26}/PLA_8$	6.6 (8)	475	1007	1975	2220	1.08
PEG2000			2168		2170	1.04
$PLA_2/PEO_{49}/PLA_2$	2.4 (2)	173	2166	2530	2470	1.05
$PLA_4/PEO_{49}/PLA_4$	3.8 (4)	274	2166	2731	2750	1.06
$PLA_8/PEO_{49}/PLA_8$	6.2 (8)	446	2166	3077	2980	1.06
$PLA_{12}/PEO_{49}/PLA_{12}$	12.2 (12)	878	2166	3941		

[a] Based on PEO standards. [b] $\overline{DP}_{PLA}$ determined from the integration ratio of the CH_3 groups within PLA blocks *vs* those of the hydroxylated lactyl end units. [c] $\bar{M}_{nPLA} = \overline{DP}_{PLA} \times 72$. [d] $\bar{M}_{nPEO}$ determined from the integration ratio of the OH protons *vs* those of methylene ones. [e] $\bar{M}_{nPLA_x/PEO_y/PLA_x} = \bar{M}_{nPEO} + 2\bar{M}_{nPLA} + 18$. [f] Data in parentheses correspond to feed composition.

reagent quantities. The flask was heated to 50−55 °C and degassed. The pressure in the flask was then equilibrated by introducing argon. A predetermined amount of L-lactide (PEG/lactide mole ratio in the range 1/2 to 1/12) was added, and the mixture was degassed under stirring. CaH_2 was added in a 1/1 mole ratio with respect to the hydroxyl end groups of PEG. The temperature of the reaction mixture was raised to 140−145 °C and maintained constant for 14 h. After cooling, the product was recovered with 50−80 mL of chloroform and precipitated in a 1 L diethyl ether/chloroform mixture (9:1 v/v) at −10 °C. The precipitate was filtered out and dried over P_2O_5 under reduced pressure.

Low molecular weight poly(L-lactic acid) was prepared by polycondensation of L-lactic acid as usual, i.e. by distilling water from an L-lactic acid solution under reduced pressure and up to 130 °C.

Hydrolysis experiments were performed at 25 °C in DMSO-d_6/D_2O in the presence of small amounts of CF_3COOH.

Measurements. Nuclear magnetic resonance (NMR) spectra were recorded at 30 °C with a Bruker AMX-360 spectrometer operating at 360 MHz (^1H) and 90.5 MHz (^{13}C); 6% (^1H) and 14% (^{13}C) w/v solutions in DMSO-d_6 were used. Chemical shifts (δ) were given in ppm using the DMSO signals at 2.49 ppm (^1H) or 39.5 ppm (^{13}C), as references. Spectra were normally registered with a pulse width of 5.5 μs, a relaxation delay of 2 s, and a scan number of 96 (^1H) or 10 000 (^{13}C). FTIR spectra were recorded on a Perkin-Elmer 1760 spectrometer. Thin films were cast from chloroform solutions onto a NaCl plate. SEC measurements were performed on a Spectra Physics apparatus equipped with a differential refractometer as detector and a set of three columns thermostated at 30 °C and connected in series, namely, Waters Styragel HR2, PL gel 100 Å, and PL gel 50 Å. Tetrahydrofuran (THF) was used as the mobile phase at a flow rate of 0.6 mL/min. Calibration was accomplished with PEG standards (Polysciences) for calculation of absolute weight average and number average molecular weights ($\bar{M}_w$ and $\bar{M}_n$). Differential scanning calorimetry (DSC) thermograms were registered with a DuPont instrument DSC series 99 equipped with a DSC 910 accessory, the heating rate being 10 °C/min. Values of glass transition temperatures (T_g) were taken from the midpoint of the transition zone. X-ray diffractometric analyses were carried out using a diffractometer equipped with a Cu Kα ($\lambda = 0.154$ nm) source, an INEL monochromator, and a goniometric plate. For optical microscopy measurements, an optical polarizing microscope Leitz SMPOL equipped with a heating device was used. The sample was placed on a glass lamella, heated to the melting temperature (T_m), and then cooled at 10 °C/min to 25 °C.

Results and Discussion

It was formerly reported that lactide can lead to PLA/PEO/PLA triblock copolymers when polymerized in the presence of PEG and NaH.[13] The reaction proceeded quite rapidly since it was completed within 5 min at 20 °C. However, slight racemization and formation of PLA homopolymers were observed. Furthermore, no triblock copolymer with a PLA block length shorter than 100 units was considered. In the present work, we found that the reaction between PEG and L-lactide in the presence of CaH_2 proceeded smoothly with a reaction time of 14 h at 140−145 °C. At the end of the process, the reaction mixture was colorless or slightly yellowish. The conversion was nearly quantitative with a yield of 80−85% after purification. The products were soluble in DMSO, chlorinated hydrocarbons, THF, and ethanol. The obtained copolymers composed of a PEO central block bearing two short PLA sequences can be presented by the following formula:

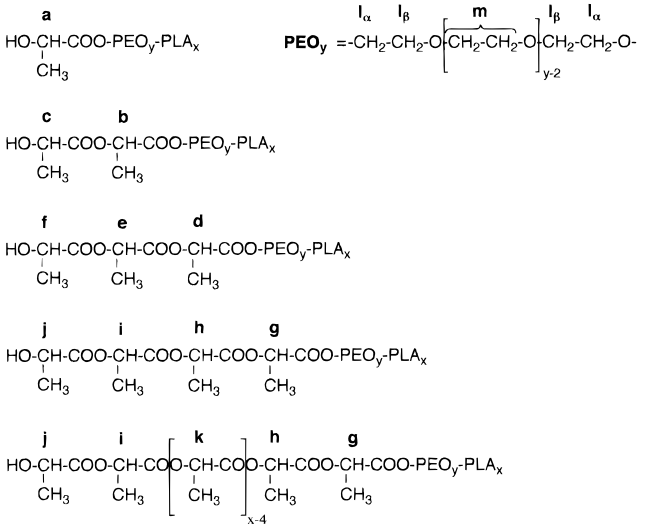
$$HO-[-CH(CH_3)COO-]_x-[-CH_2CH_2O-]_y-[-COCH(CH_3)O-]_x-H$$

Hereafter, these compounds will be denoted $PLA_x/PEO_y/PLA_x$, where x represents the mean number average degree of polymerization of each PLA block ($\overline{DP}_{PLA}$) and y that of PEO sequences ($\overline{DP}_{PEO}$). One must keep in mind that each molecule of lactide led to two lactyl units according to the well-known pair-addition mechanism of ring opening polymerization. The various compounds which were prepared are presented in Table 1.

NMR Spectra. In a previous paper,[21] we have shown for the first time that the resolution of NMR spectra of PLA oligomers can be considerably improved by using DMSO-d_6 as solvent instead of $CDCl_3$, the latter being the solvent generally selected for NMR investigations of PLA polymers and copolymers reported in the literature.[10,11,13] Under these conditions, the last two lactic repeating units at both chain ends led to distinct multiresonance patterns because of neighboring effects. Chemical shifts between these patterns appeared characteristic of the position of units starting from chain ends. Additivity was observed which allowed the assignment of all signals in ^1H and ^{13}C NMR spectra of PLA oligomers up to the pentamer and octamer, respectively. It was also shown that esterification of the COOH end groups resulted in a downfield shift of resonances of the corresponding methyl and methine protons.[21]

In the present study, ^1H and ^{13}C NMR spectra of the various $PLA_x/PEO_y/PLA_x$ were also recorded from solutions in DMSO-d_6 at 30 °C. Under these conditions, the

Chart 1. Constitutive Units of $PLA_x/PEO_y/PLA_x$ Triblock Copolymers



different constitutive units of PLA blocks identified in Chart 1 led to well-separated sets of resonances, which were characteristic of repeating units close to PLA block ends or of units well inside the block. A typical ^{1}H NMR spectrum of $PLA_x/PEO_y/PLA_x$ is shown in Figure 1. Several signals can be distinguished. Resonances in the 5.2−5.0 ppm range (C*H*) and in the 1.5−1.4 ppm range (CH_3) belong to PLA blocks, including both PEO-connecting and main chain units. Signals in the 3.7−3.3 ppm range are characteristic of main chain methylene units within PEO blocks. The α-methylene protons of PLA-connecting EO units (PLA−COO−CH_2−) appear in the 4.3−4.1 ppm range, together with the C*H* protons of the hydroxylated lactyl end units. Methyl protons of these end units appear in the 1.3−1.2 ppm range and are well separated from the other methyl groups. Chemical shifts of protons belonging to the different constitutive units identified in Chart 1 are presented in Table 2.

It is worth noting the absence of carboxylated lactyl end units and of free lactic acid whose methine protons should appear in the 5.0−4.9 ppm range and at 4.03 ppm, respectively.[21] This indicated that homopolymerization of L-lactide did not occur under the selected polymerization conditions.

The resonances of methyl protons in lactyl units arising from connecting and main chain units (1.5−1.4 ppm) on the one hand, and of hydroxylated lactyl end units (1.3−1.2 ppm) on the other hand, were well resolved. This resolution allowed the calculation of $\overline{DP}_{PLA}$ in $PLA_x/PEO_y/PLA_x$ copolymers (Table 1). $\bar{M}_{nPLA}$ was deduced from $\overline{DP}_{PLA}$ by using the following relationship:

$$\bar{M}_{nPLA} = \overline{DP}_{PLA} \times 72 \qquad (1)$$

$\bar{M}_{nPEO}$ was estimated for starting PEG polymers and for the copolymers from their ^{1}H NMR spectra. $\bar{M}_{nPLA_x/PEO_y/PLA_x}$ was then obtained by using the relationship:

$$\bar{M}_{nPLA_x/PEO_y/PLA_x} = \bar{M}_{nPEO} + 2\bar{M}_{nPLA} + 18 \qquad (2)$$

The calculated $\overline{DP}_{PLA}$ values were found to be in good agreement with theoretical values deduced from the EO/LA ratio in the feed in spite of the fact that

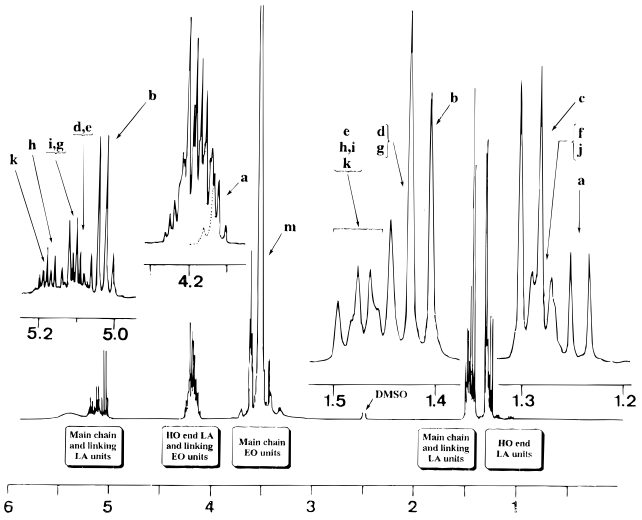


Figure 1. ^{1}H NMR spectrum of $PLA_2/PEO_{14}/PLA_2$ in DMSO-d_6.

Table 2. ^{1}H NMR Chemical Shifts (ppm) of Protons from a−m Units of $PLA_x/PEO_y/PLA_x$ Triblock Copolymers (DMSO-d_6, 360 MHz, 30 °C)

	chemical shift δ (ppm)		
unit	CH	CH_3	CH_2
a	4.13	1.24	
b	5.03	1.41	
c	4.20	1.29	
d	5.10	1.43	
e	5.10	1.44	
f	4.21	1.28	
g	5.11	1.43	
h	5.17	1.45	
i	5.11	1.44	
j	4.21	1.28	
k	5.19	1.46	
$\mathbf{l}_\alpha$			4.21
$\mathbf{l}_\beta$			3.60
m			3.50

copolymers were purified by dissolution−precipitation. A similar feature was observed when stannous octoate was used to prepare PLA/PEO/PLA triblock copolymers.[18]

The presence of signals belonging to forbidden sequences with an odd number of lactyl units (Figure 1), i.e. $x = 1$ (unit **a**) and 3 (units **d**, **e**, and **f**), indicated that transesterification side reactions occurred, a feature already identified in the case of PLA stereocopolymers.[22]

A typical ^{13}C NMR spectrum of $PLA_x/PEO_y/PLA_x$ shown in Figure 2 revealed the presence of the different carbon atoms belonging to the various **a**−**m**-type units (Chart 1). In Table 3, full assignment of the observed signals is reported, which was based on our previous results on PLA oligomers.[21] These assignments were confirmed by the technique of insensitive nuclei enhanced by polarization transfer (INEPT). In this table, comparison is made with the δ values corresponding to the low molecular weight PLA obtained by step-growth polymerization and to PEG homopolymers. For the PLA sequences, there was no major difference between δ values of the homo- and copolymers, except for the *C*O resonances of the carboxylated lactyl end units (**a**, **b**, **d**, and **g**) for which an upfield shift of about 1.4 ppm was observed upon esterification. Therefore, the absence of any signal in the 171.5−172 ppm range (Figure 2), which was assignable to carbonyl carbon atoms of unesterified lactyl end units, agreed with the absence

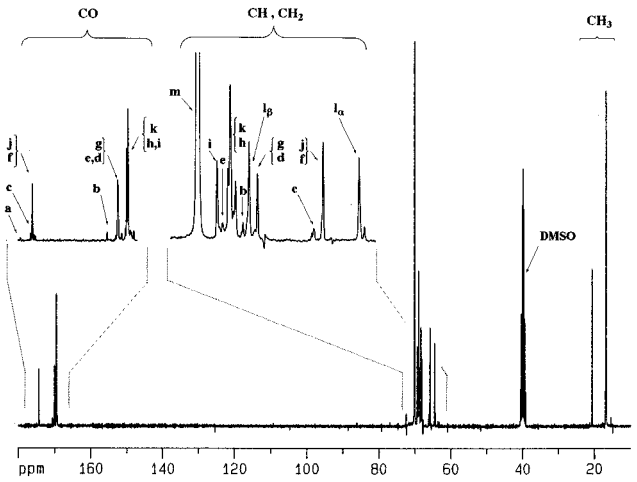


Figure 2. ^{13}C NMR spectrum of $PLA_4/PEO_{26}/PLA_4$ in DMSO-d_6.

of L-lactide homopolymerization, in agreement with ^1H NMR results mentioned above. On the other hand, Table 3 shows that the important difference between the δ values of **l**-type methylene carbons within hydroxylated and esterified forms of PEO chain ends will be useful for the identification of the hydroxyl end groups which are to appear during hydrolytic degradation.

SEC Analysis. Figure 3 presents SEC chromatograms of the copolymers $PLA_4/PEO_{49}/PLA_4$ and $PLA_2/PEO_{14}/PLA_2$, in comparison with that of the low molecular weight poly(L-lactic acid). The molecular weight dispersion of the two copolymers was monomodal and rather narrow, while the sample of low molecular weight poly(L-lactic acid) was composed of various lactic acid oligomers, e.g. monomer, dimer, trimer, tetramer, etc. These oligomers were not detected in copolymers, a finding which discarded the possibility of homopolymerization of L-lactide. As $\overline{DP}_{PLA}$ increased, an increase in MW of $PLA_x/PEO_y/PLA_x$ was detected, as shown in Table 1. It is also noteworthy that, in all cases, polydispersity remained very narrow ($\bar{M}_w/\bar{M}_n \leq 1.08$). The constancy of polydispersity index values obtained for the copolymers as compared to corresponding PEG precursors (Table 1) suggested the formation of PLA blocks with comparable average lengths. A good correlation was found between $\bar{M}_n$ values obtained from ^1H NMR and those from SEC. Both were close to theoretical values corresponding to feed compositions in spite of the purification process.

IR Spectra. IR spectra of the products showed absorption bands related to both PEO and PLA blocks (Figure 4). The position and the relative intensity of the carbonyl stretching vibration depended on $\overline{DP}_{PLA}$. The higher the $\overline{DP}_{PLA}$, the higher the relative intensity as referred to the C−H strecthing band of the PEO block centered at 2883−2878 cm^{-1}, and the larger the wavenumber which shifted from 1751 cm^{-1} in the case of $PLA_2/PEO_{49}/PLA_2$ to 1757 cm^{-1} for $PLA_8/PEO_{49}/PLA_8$. For $PLA_{12}/PEO_{49}/PLA_{12}$, the carbonyl band remained at 1757 cm^{-1}, which is also the value characteristic of the low molecular weight PLA compound. The bands at 947 and 843 cm^{-1} are known to be characteristic of the crystalline phase of PEO,[23] while the band at 756−751 cm^{-1} was assigned to the amorphous phase of PLA.[24] In the IR spectra of the three copolymers shown in Figure 4, absorption maxima characteristic of the crystalline phase of PEO were observed, suggesting the crystallization of PEO blocks within the copolymers under the form of films cast from chloroform solutions.

Optical Microscopy. After melting on glass lamella and cooling to room temperature at 10 °C/min, optical micrographs of crystallized PEG2000, $PLA_2/PEO_{49}/PLA_2$, $PLA_4/PEO_{49}/PLA_4$, and $PLA_8/PEO_{49}/PLA_8$ were taken. Spherulites were always greater for the $PLA_x/PEO_{49}/PLA_x$ than for PEG2000. There was no spherulite detected in the case of copolymer $PLA_{12}/PEO_{49}/PLA_{12}$ which had higher $\overline{DP}_{PLA}$. This copolymer appeared unable to crystallize under the selected conditions. The composition dependence of crystalline phase formation has already been observed for PLA/PEO/PLA triblock copolymers with much longer PLA and PEO sequences by polarized light microscopy.[25]

X-ray Diffraction. The crystallizability of $PLA_x/PEO_{49}/PLA_x$ could be discussed from the X-ray diffraction patterns shown in Figure 5. The PEG2000 diffraction pattern exhibited the well-known two intense diffraction peaks located at $\theta = 9.7$ and 11.8°, which are characteristic of crystallized PEG.[23] These diffraction peaks were also observed for the copolymers. However, their intensities, as referred to the diffusing background, decreased as $\overline{DP}_{PLA}$ increased, thus showing a decrease in crystallinity, in agreement with conclusions deduced from visual examination by optical microscopy. Moreover, the position of the diffraction peaks did not change. Therefore, $PLA_x/PEO_{49}/PLA_x$ had the same crystalline structure as the starting PEG2000. In other words, the PLA blocks were excluded from the PEO crystalline domains, thus suggesting phase separation.

Thermal Properties. Thermal characteristics of $PLA_x/PEO_y/PLA_x$ and of the parent PEG polymers were investigated by DSC. Thermograms are shown in Figure 6. As expected, the T_m of PEG polymers increased with their degree of polymerization: 21 °C for PEG600, 42 °C for PEG1000, and 50 °C for PEG2000. The presence of short PLA sequences attached to PEO blocks decreased the melting temperature of the corresponding PEG. For $PLA_x/PEO_{49}/PLA_x$ with $x = 2$, 4, and 8, T_m values were 43, 38, and 35 °C, respectively (Figure 6a). T_m decreases were also observed for $PLA_4/PEO_{26}/PLA_4$ and $PLA_2/PEO_{14}/PLA_2$ (Figure 6b). In the cases of $PLA_{12}/PEO_{49}/PLA_{12}$ and $PLA_8/PEO_{26}/PLA_8$, which had higher $\overline{DP}_{PLA}$, T_m was not detected. This finding bore out the lower crystallizabilities of these compounds. At the end of the first run, the molten sample was cooled rapidly by immersion in liquid nitrogen in order to obtain an amorphous sample which was used in a second run to observe the glass and the crystallization transitions. As expected, for $PLA_x/PEO_{49}/PLA_x$ with $x = 4$ and 8, a glass transition was detected at −47 °C, followed by a very sharp crystallization peak (T_c) at −41 and −33 °C. In contrast, no T_g nor T_c was detected for PEG2000 and $PLA_2/PEO_{49}/PLA_2$ which crystallized too fast to be made amorphous even by extremely rapid cooling. For $PLA_4/PEO_{26}/PLA_4$ and $PLA_2/PEO_{14}/PLA_2$, which were in the liquid state at room temperature, the second run gave the same pattern as the first one, showing similar T_g, T_c, and T_m. These features suggested that the crystallizability of PEO blocks can be very much decreased by attachment of rather short PLA sequences, the phenomenon depending on the length of PEO blocks.

It is known that blends of two immiscible polymers exhibit the two T_g of each segregated component re-

Table 3. ^{13}C NMR Chemical Shifts (ppm) of Carbon from a−m Units[a] in $PLA_x/PEO_y/PLA_x$ Triblock Copolymers (DMSO-d_6, 90 MHz, 30 °C)

	PLA sequence												PEO sequence		
	a	b	c	d	e	f	g	h	i	j	k		l_α	l_β	m
δ(CO)	174.88	170.52	174.38	170.08	169.99	174.30	170.05	169.54	169.94	174.30	169.46				
	(176.31)[b]	(171.97)	(174.36)	(171.52)	(170.00)	(174.28)	(171.43)	(169.52)	(169.94)	(174.28)	(169.44)				
δ(CH)	66.20	68.50	65.86	68.12	69.22	65.80	68.05	68.80	69.40	65.80	68.95	δ(CH_2)	64.39	68.40	70.10
	(66.04)	(68.53)	(65.89)	(68.15)	(69.24)	(65.83)	(68.07)	(68.88)	(69.40)	(65.80)	(68.95)		(60.12)	(72.10)	(70.10)
δ(CH_3)	20.63	16.90	20.57	16.77	16.81	20.57	16.77	16.68	16.80	20.57	16.70				
	(20.67)	(16.94)	(20.57)	(16.82)	(16.70)	(20.57)	(16.82)	(16.70)	(16.70)	(20.57)	(16.70)				

[a] See Chart 1. [b] Data in parentheses correspond to PLA and PEG homopolymers.

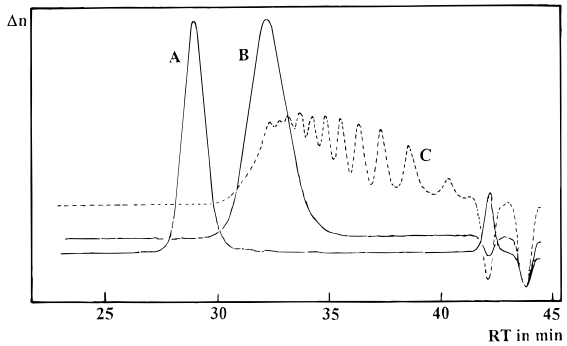


Figure 3. SEC chromatograms of $PLA_4/PEO_{49}/PLA_4$ (A), $PLA_2/PEO_{14}/PLA_2$ (B), and low molecular weight poly(L-lactic acid) (C).

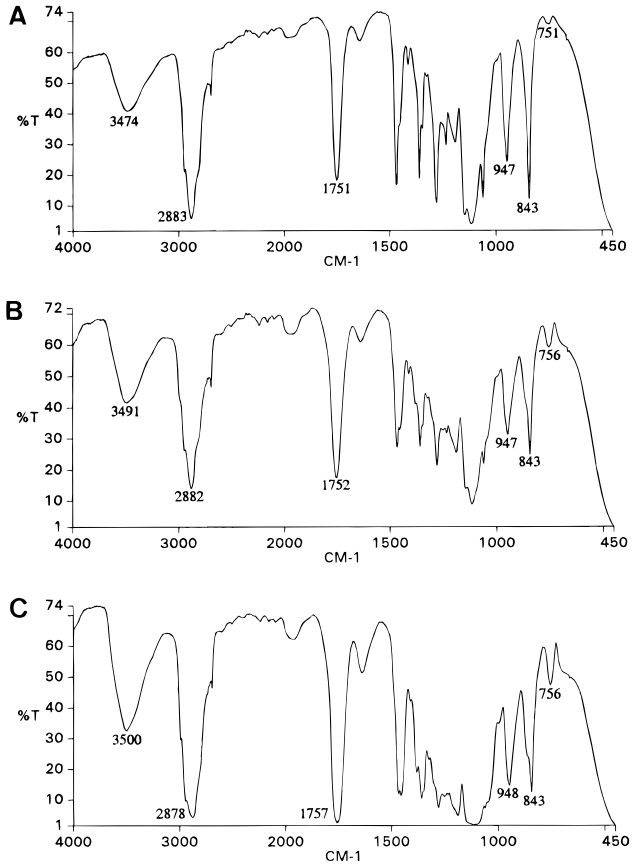


Figure 4. IR spetra of $PLA_2/PEO_{49}/PLA_2$ (A), $PLA_4/PEO_{49}/PLA_4$ (B), and $PLA_8/PEO_{49}/PLA_8$ (C).

gardless of blend composition. In contrast, only one glass transition is observed in the case of blends of two miscible polymers, which varies with composition between the values characteristic of each polymer.[26] As pointed out in the literature,[25,27] it is difficult to evaluate the miscibility of PLA and PEG or of the sequences within PLA/PEO block copolymers from T_g measurements because T_g of PLA and T_m of PEG are very close. In the present work dealing with short PLA sequences, attempts were made to observe T_g changes of the PEO blocks with the length of PLA sequences attached to them, assuming that the miscibility could be increased if the crystallinity of PEO sequences is decreased by the presence of PLA blocks. An increase in T_g of $PLA_x/PEO_y/PLA_x$ was effectively detected, as compared to parent PEG polymers. Located at −60 °C for PEG2000 and PEG1000, T_g increased to −47 °C for $PLA_8/PEO_{49}/PLA_8$ and to −37 °C for $PLA_8/PEO_{26}/PLA_8$. This increase of glass transition temperature appeared much too large to be artifactual. It was considered as reflecting some miscibility. However, this miscibility was still rather low as compared to the full miscibility of polyether and polyester.[25,26]

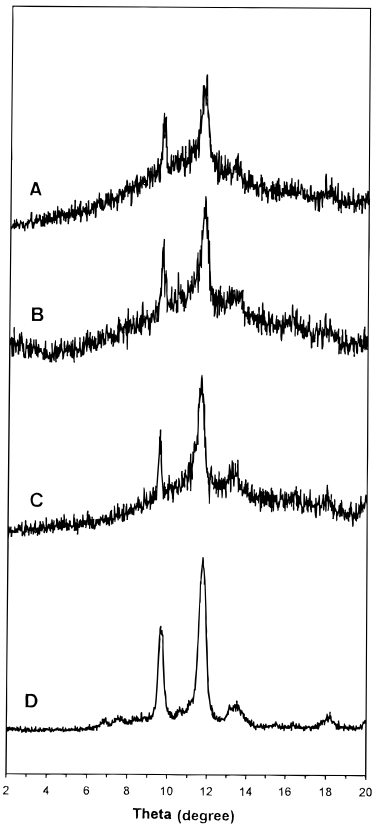


Figure 5. X-ray diffractograms of $PLA_8/PEO_{49}/PLA_8$ (A), $PLA_4/PEO_{49}/PLA_4$ (B), $PLA_2/PEO_{49}/PLA_2$ (C), and PEG2000 (D).

Water Solubility. $PLA_2/PEO_{26}/PLA_2$, $PLA_2/PEO_{49}/PLA_2$, and $PLA_4/PEO_{49}/PLA_4$ were soluble in water at neutral pH values (pH = 7.2), the solutions being stable for at least 48 h. In contrast, $PLA_2/PEO_{14}/PLA_2$, $PLA_4/PEO_{26}/PLA_4$, $PLA_8/PEO_{26}/PLA_8$, $PLA_8/PEO_{49}/PLA_8$, and $PLA_{12}/PEO_{49}/PLA_{12}$ led to turbid mixtures in the presence of water. This turbidity reflected micelle formation, as expected from amphilic triblock copolymers with

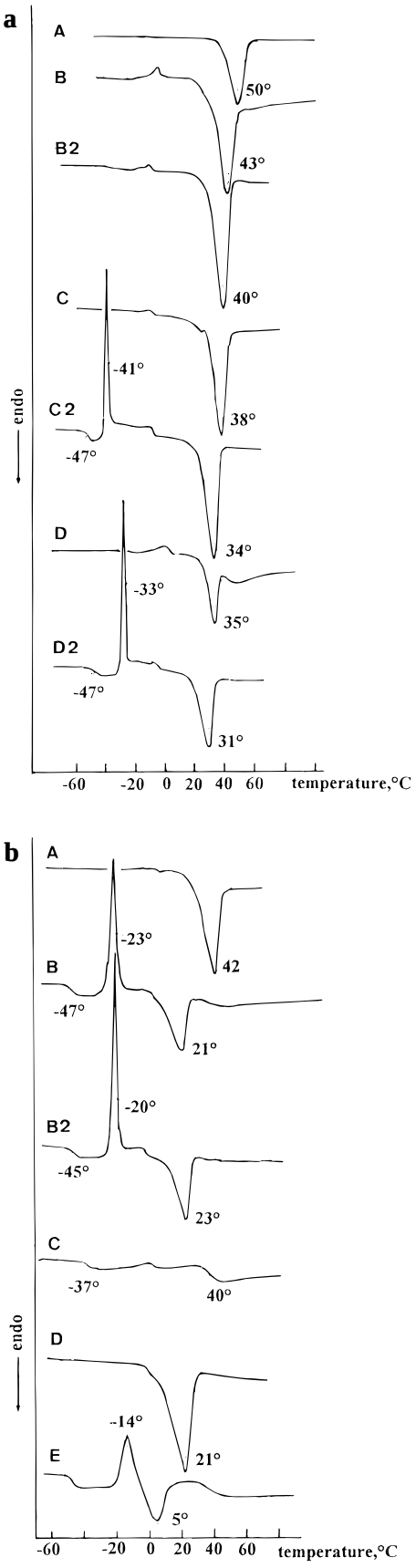


Figure 6. (a) DSC thermograms of PEG2000 (A), $PLA_2/PEO_{49}/PLA_2$ (B), $PLA_4/PEO_{49}/PLA_4$ (C), and $PLA_8/PEO_{49}/PLA_8$ (D). (b) DSC thermograms of PEG1000 (A), $PLA_4/PEO_{26}/PLA_4$ (B), $PLA_8/PEO_{26}/PLA_8$ (C), PEG600 (D), and $PLA_2/PEO_{14}/PLA_2$ (E). (2: second run after 10 °C/min cooling from the melt.)

convenient block lengths.[28] It is noteworthy that within the considered series of $PLA_x/PEO_y/PLA_x$, copolymers

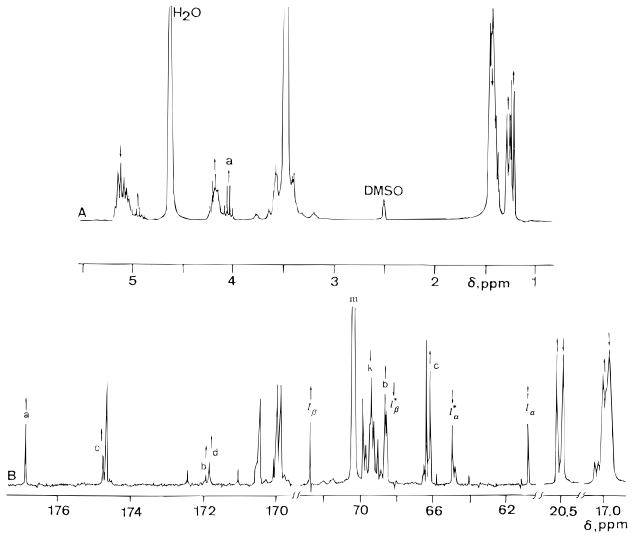


Figure 7. ^1H NMR (A) and ^{13}C NMR (B) spectra of $PLA_8/PEO_{26}/PLA_8$ after 13 days of hydrolysis in the DMSO-d_6/D_2O in the presence of CF_3COOH. (Arrows represent respectively the increase and decrease of the signal intensity during hydrolysis.)

with $\overline{DP}_{PEO}/\overline{DP}_{PLA} > 4$ appeared soluble in water whereas those with $\overline{DP}_{PEO}/\overline{DP}_{PLA} < 4$ were only dispersed and led to turbid mixtures. $PLA_8/PEO_{14}/PLA_8$, with $\overline{DP}_{PEO}/\overline{DP}_{PLA} < 1$, remained apparently unchanged. In the case of soluble compounds, no change in composition or in molecular weights was detected during the first 48 h. In the case of turbid mixtures, a precipitate was formed after 50−60 h, due to micelle aggregation. According to ^1H and ^{13}C NMR spectra, the precipitation did not result from composition changes since precipitates and corresponding original compounds exhibited similar spectra.

Hydrolysis Studies. $PLA_8/PEO_{26}/PLA_8$ was selected for hydrolysis studies. The experiments were carried out in DMSO/D_2O containing small amounts of CF_3-COOH, i.e. under homogeneous conditions, in order to take advantage of both homogeneity of the aging medium and high resolution of ^1H and ^{13}C NMR in DMSO.

Under these conditions, the hydrolysis proceeded relatively slowly at 25 °C. During the first 48 h, no significant change in the spectra was observed. Beyond 2 days, the integration ratio of CH_3 proton signals from PLA blocks (1.5−1.4 ppm) to those from hydroxylated lactyl end units (1.3−1.2 ppm) was found to decrease (Figure 7A). $\overline{DP}_{PLA}$ decreased from a starting average value of 6.6 to 2.5 after 2 weeks. In addition, signals appeared at 4.03 ppm and in the 5.0−4.9 ppm range which were due to methine protons in carboxylated lactyl end units of the **a**, **b**, **d**, and **g** types within lactic acid, dimer, and higher oligomers, respectively.[21]

The appearance of these degradation products was confirmed by ^{13}C NMR (Figure 7B). In the carbonyl region, emergence of signals for the carbonyl carbon in carboxylated lactyl end units (**a**-, **b**-, **d**-, and **g**-type units) was observed. Concurrently, the intensity of methylene carbon signals from connecting EO units (PLA−$COOCH_2CH_2$−, $\mathbf{l}_\alpha$* and $\mathbf{l}_\beta$*) decreased whereas the intensity of methylene signals at 60.1 and 72.1 ppm due to carbons of the hydroxylated EO end units ($HOCH_2CH_2$−, $\mathbf{l}_\alpha$ and $\mathbf{l}_\beta$) increased.

$PLA_x/PEO_y/PLA_x$ copolymers contained two types of sites where hydrolysis could occur, namely ester bonds

within the PLA blocks (A) and ester bonds linking PEO to PLA blocks (B):

From NMR data presented above, it can be concluded that hydrolysis at sites A and B proceeded with comparable rates, in agreement with results reported by Hu *et al*. on hydrolysis of $PLA_x/PEO_y/PLA_x$ copolymer films carried out under heterogeneous conditions.[29]

In conclusion, it has been shown that $PLA_x/PEO_y/PLA_x$ triblock copolymers with short PLA blocks can be synthesized in the bulk at 140 °C from OH-terminated PEG using CaH_2 as co-initiator. Under these conditions, no formation of PLA homopolymer was detectable. Average block lengths and structures were discussed from SEC, NMR, and other analytical techniques. The use of DMSO as solvent for NMR investigations led to better resolution of resonances of repeating units close to PLA/PEO junctions and to PLA chain ends. Distinction of contributions from five different *n*-mer types was possible under these conditions. Optical microscopy and DSC brought in new qualitative information on the dependence of crystallite formation on the length of each block and showed that dramatic differences can be observed for rather small changes of block characteristics. Last but not least, it was shown that PLA−PLA and PLA−PEO ester bonds were cleaved at similar rates during acid-catalyzed degradation in $DMSO/D_2O$ solutions. Data and conclusions reported in this paper should be of great interest to investigate the structure of the intermediate degradation products which are formed during the hydrolytic degradation of high molecular weight PLA/PEO block copolymers under compact or swollen gel states depending on relative block lengths.

Acknowledgment. J.L.E. is indebted to the European Community for a postdoctoral fellowship from the human capital and mobility program (ERBCHBGCT 920137).

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MA950530T