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Hydrolytic degradation of PLA/PEO/PLA triblock copolymers prepared in the presence of Zn metal or CaH$_2$

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Various PLA/PEO/PLA triblock copolymers were prepared by ring-opening polymerization of L-lactide in the presence of poly(ethylene glycol), using CaH$_2$ or zinc metal as co-initiator. The degradation behavior of these copolymers was investigated in a pH = 7.4 phosphate buffer at 37°C. Various techniques such as weighing, size exclusion chromatography, differential scanning calorimetry, X-ray diffractometry, and infra-red and ^{1}H nuclear magnetic resonance spectrometries were used to monitor the changes in water absorption, weight loss, molar mass distribution, thermal properties, degree of crystallinity and composition. The results showed that introduction of PEO sequences considerably increased the hydrophilicity of the copolymers as compared with PLA homopolymers. However, the degradability of PLA blocks was not enhanced because of the phase separation between PLA and PEO blocks. Bimodal molar mass distributions were detected at the later stages of degradation, which were assigned to the formation of crystalline degradation byproducts within the bulk material. © 1998 Elsevier Science Ltd. All rights reserved.

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INTRODUCTION

Degradable polymers are of growing interest in the field of biomedical applications such as sustained drug delivery systems, surgical sutures, osteosynthesis devices, etc.[1–3]. Beside the attention paid to degradable polyesters, poly-orthoesters and polyanhydrides, copolymers composed of polyester and polyether blocks are increasingly considered as worthwhile degradable materials, especially in the field of parenteral drug delivery. Actually, introduction of hydrophilic polyether blocks into degradable polyester chains is a means to make compounds with variable hydrophilicity and degradability. Poly(ethylene glycol) (PEG) or poly(ethylene oxide) (PEO) has been used as a source of hydrophilicity because of its outstanding physi-cochemical and biological properties including solubility in water and in organic solvents, lack of toxicity, absence of antigenicity and immunogenicity[4,5], as well as filtrability through kidney when the molar mass is below 20 000. The terminal hydroxyl groups of PEG can readily react with a variety of compounds, thus allowing copolymerization with lactones such as chiral lactides, glycolide and ε-caprolac-tone to yield ABA-type copolymers[6–13]. In a series of recent papers, we reported the synthesis, characterization and preliminary data on the degradation of PLA/PEO/PLA triblock copolymers with PLA (polylactic acid) and PEO blocks of various lengths prepared by ring-opening poly-merization of L-lactide in the presence of PEG, using non-toxic Zn metal or CaH$_2$ as co-initiator instead of stannous octoate or other catalytic systems[14,15]. Interestingly, copo-lymers with appropriate PLA and PEO block lengths can

yield hydrogels when water is introduced into their organic solutions, PLA blocks constituting nanometric nods in the gel network[16]. This kind of hydrogel appears very promising for the simultaneous delivery of hydrophilic macromolecules such as proteins and of hydrophobic ones such as steroids. Nevertheless, the hydrolytic degradation behaviour of these polyester/polyether block copolymers had to be investigated in detail before considering potential applications. Little attention has been paid to this important point, so far[10–12].

In this paper, we wish to report on the hydrolytic degradation of PLA/PEO/PLA triblock copolymers which were previously synthesized and characterized[14,15]. Degra-dation was carried out in a 0.13 M pH = 7.4 phosphate buffer at 37°C and monitored by using various complemen-tary techniques. The collected data are discussed with respect to changes in molar mass, morphology and composition during the degradation process. Comparison with literature data was made in order to elucidate the degradation characteristics of various PLA/PEO/PLA tri-block copolymers.

EXPERIMENTAL

Materials

The selected copolymers were synthesized by ring-opening polymerization of L-lactide in the presence of PEG2000, using non-toxic Zn metal or CaH$_2$ as co-initiator[14,15]. L-lactide was purchased from Purac and recrystallized from acetone before use. PEG2000 was used as received from Fluka. Its actual number average molar mass ($\overline{M}_n$) was found to be 1800 as determined by size exclusion chromatography (SEC) using PEG standards. The

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Table 1 $PLA_x/PEO_y/PLA_x$ triblock copolymers obtained from polymerization of L-lactide in the presence of PEG2000 using Zn or CaH_2 as co-initiator

Copolymer	Initial LA/EO	Final LA/EO^a	$\overline{DP}_{PEO}$^{b}	$\overline{DP}_{PLA}$^{b}	$\overline{M}_{PLA}$^{c}	$\overline{M}_n$^{d}
$PLA_{21}/PEO_{41}PLA_{21}$ (CaH_2)	1	1.0	41	21	4 800	4 200
$PLA_{43}/PEO_{41}/PLA_{43}$($CaH_2$)	2	2.1	41	43	7 950	7 800
$PLA_{44}/PEO_{41}/PLA_{44}$ (Zn)	2	2.1	41	44	8 090	7 700
$PLA_{109}/PEO_{41}/PLA_{109}$(Zn)	5	5.3	41	109	15 650	n.d.^{e}

^{a}Determined by using the integration ratio of resonances due to PEO blocks at 3.65 ppm and to PLA blocks at 1.46 ppm in the ^{1}H n.m.r. spectra
^{b}$\overline{DP}_{PEO} = 1800/44$, $\overline{DP}_{PLA} = \overline{DP}_{PEO} \times (LA/EO)/2$
^{c}$\overline{M}_n = 44 \times \overline{DP}_{PEO} + 2 \times 72 \times \overline{DP}_{PLA}$
^{d}Obtained by SEC measurements
^{e}n.d., not determined

lactyl/(ethylene oxide) ratio (LA/EO), in the feed was in the range of 1/1 to 5/1. The LA/EO ratio in the products was calculated from ^{1}H nuclear magnetic resonance (n.m.r.) as previously reported[14,15]. All the data of LA/EO ratio, $\overline{DP}_{PEO}$, $\overline{DP}_{PLA}$ and $\overline{M}_n$ are shown in *Table 1*.

The copolymer $PLA_{21}/PEO_{41}/PLA_{21}$($CaH_2$) was in the form of a translucent wax, whereas $PLA_{43}/PEO_{41}/PLA_{43}$($CaH_2$), $PLA_{44}/PEO_{41}/PLA_{44}$(Zn) and $PLA_{109}/PEO_{41}/PLA_{109}$(Zn) were solid materials and were compression moulded to yield 1 mm thick plates.

Measurements

SEC analysis was performed at room temperature with a Waters apparatus equipped with a Waters 410 differential refractometer and a 60 cm PLgel 5 μm MIXED-C column, using tetrahydrofuran (THF) as solvent. The flow rate was 1 ml min^{-1}. Calibration was based on polystyrene standards. This SEC system permits, in principle, to cover a molar mass range from 200 to 3 000 000 daltons. Differential scanning calorimetry (d.s.c.) measurements were carried out at a heating rate of 10°C min^{-1} with a DuPont Instrument Series 99 Thermal Analyser. For each analysis 10 mg of material was used. X-ray diffractometric analysis was conducted with a Philips apparatus using CuKα source (0.154 nm). Infra-red (i.r.) spectra of the copolymers were recorded on a Perkin Elmer 1760 Fourier transform i.r. (*FT*i.r.) spectrometer, the films being cast from chloroform solutions. ^{1}H n.m.r. spectra were recorded at 60°C with a Bruker AMX-360 spectrometer operating at 360 MHz. DMSO-d_6 (deuterated dimethyl sulfoxide) was used as solvent. The signal at 2.49 ppm of DMSO was taken as reference.

Hydrolytic degradation

For each degradation study, copolymer specimens of about 200 mg were placed into small flasks filled with 25 ml of pH = 7.4 isoosmolar phosphate buffer (0.13 M) containing 0.02% NaN_3 to prevent bacteria growth. The flasks were allowed to stand in a thermostated oven at 37°C for predetermined periods of time. Two specimens were withdrawn from the aging media at each degradation time, and washed with distilled water. After wiping, the specimens were weighed and vacuum dried at room temperature for 2 weeks before being subjected to various analyses.

RESULTS

The four triblock copolymers behaved quite differently in the degradation medium taken as a model of body fluids. Within 1 week, a milky suspension was formed in the flasks containing $PLA_{21}/PEO_{41}/PLA_{21}$($CaH_2$). The residual degradation products had to be recovered by centrifugation which yielded a waxy material. It was not possible to collect

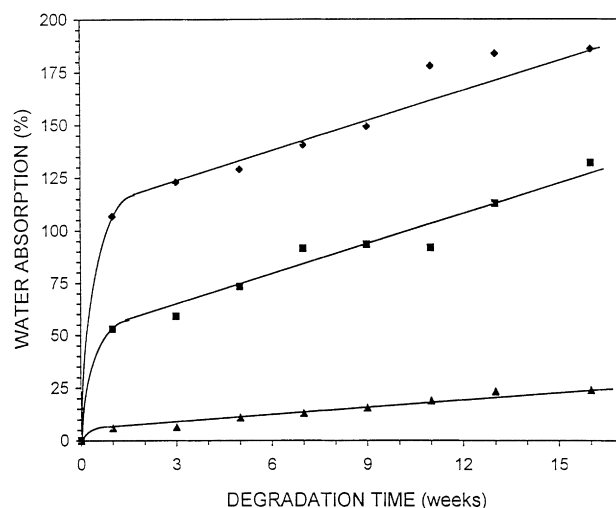**Figure 1** Water absorption of of $PLA_{43}/PEO_{41}/PLA_{43}$($CaH_2$) (♦), $PLA_{44}/PEO_{41}/PLA_{44}$(Zn) (■) and $PLA_{109}/PEO_{41}/PLA_{109}$(Zn) (▲) with degradation

information on water absorption and weight loss for this compound. In parallel, $PLA_{43}/PEO_{41}/PLA_{43}$($CaH_2$) and $PLA_{44}/PEO_{41}/PLA_{44}$(Zn) specimens, which were initially translucent, became whitish in the degradation medium. After 9 weeks, the specimens became very fragile. $PLA_{109}/PEO_{41}/PLA_{109}$(Zn) which was initially opaque turned also whitish upon degradation, but remained rather rigid although cracks were visible at the surface of the plates beyond 1 week.

Figure 1 shows the time-dependence profiles of water absorption which was obtained by the following equation:

$$\text{water absorption (\%)} = (W_w - W_d)/W_d \quad (1)$$

where W_w and W_d represent respectively the wet weight and the dry weight after degradation. $PLA_{109}/PEO_{41}/PLA_{109}$(Zn) showed a slow but constant increase with 24% of absorbed water at the end of 16 weeks. In contrast, the copolymer $PLA_{43}/PEO_{41}/PLA_{43}$($CaH_2$) appeared much more hydrophilic. It absorbed rapidly 107% of water after 1 week. Later on, the water absorption ratio increased continuously to reach 186% after 16 weeks. In the case of $PLA_{44}/PEO_{41}/PLA_{44}$(Zn), an inermediate value of 136% was obtained at 16 weeks. Water absorption data were not available beyond 16 weeks due to the disintegration of the samples.

Weight loss data are obtained by equation (2):

$$\text{weight loss (\%)} = (W_0 - W_d)/W_0 \quad (2)$$

where W_0 is the initial weight of the samples. *Figure 2* shows that $PLA_{109}/PEO_{41}/PLA_{109}$(Zn) did not exhibit any weight loss before 3 weeks. Afterwards, weight loss
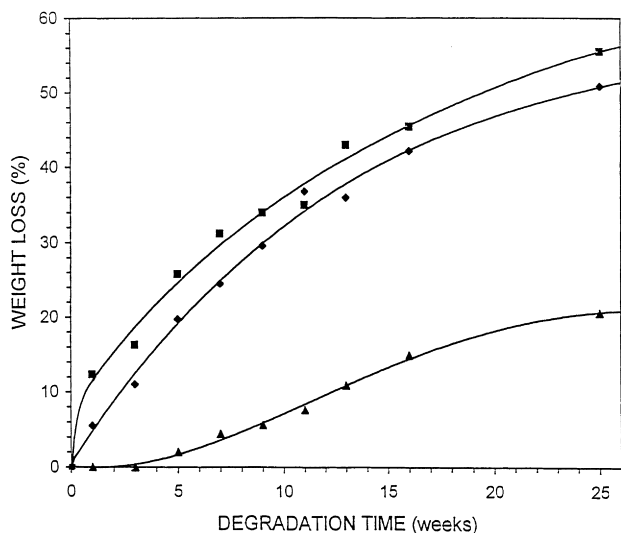
Figure 2 Mass loss of PLA$_{43}$/PEO$_{41}$/PLA$_{43}$(CaH$_2$) (◆), PLA$_{44}$/PEO$_{41}$/PLA$_{44}$(Zn) (■) and PLA$_{109}$/PEO$_{41}$/PLA$_{109}$(Zn) (▲) with degradation
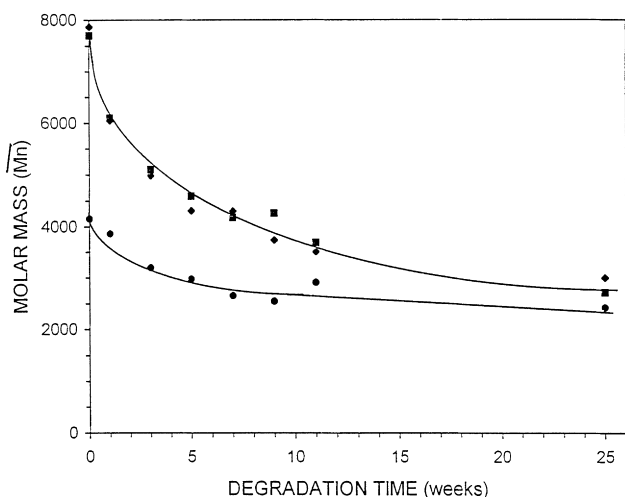
Figure 3 Molar mass changes of PLA$_{21}$/PEO$_{41}$/PLA$_{21}$(CaH$_2$) (•), PLA$_{43}$/PEO$_{41}$/PLA$_{43}$(CaH$_2$) (◆), and PLA$_{44}$/PEO$_{41}$/PLA$_{44}$(Zn) (■) with degradation

increased progressively to reach 21% at the end of 25 weeks. For the two copolymers PLA$_{44}$/PEO$_{41}$/PLA$_{44}$(Zn) and PLA$_{43}$/PEO$_{41}$/PLA$_{43}$(CaH$_2$), the release of degradation products was already detected at 1 week. Beyond, weight loss increased continuously to reach respectively 56% and 51% after 25 weeks. Finally at the end of 93 weeks, very little residual material still remained in the degradation medium.

Figure 3 presents the variations of $\overline{M}_n$ of the degraded samples of PLA$_{21}$/PEO$_{41}$/PLA$_{21}$(CaH$_2$), PLA$_{43}$/PEO$_{41}$/PLA$_{43}$(CaH$_2$) and PLA$_{44}$/PEO$_{41}$/PLA$_{44}$(Zn). The latter two exhibited similar $\overline{M}_n$ decrease patterns: the $\overline{M}_n$ value for PLA$_{43}$/PEO$_{41}$/PLA$_{43}$(CaH$_2$) decreased progressively from an initial 7800 to 3000 after 25 weeks, whereas for PLA$_{44}$/PEO$_{41}$/PLA$_{44}$(Zn), it decreased from 7700 to 2700. The very small amount of degradation residues which remained at the end of 93 weeks had $\overline{M}_n$ values in the range of 1100 to 1200 for both compounds. PLA$_{21}$/PEO$_{41}$/PLA$_{21}$(CaH$_2$) with lower initial $\overline{M}_n$ showed a slower $\overline{M}_n$ decrease: from 4200 to 2400 at the end of 25 weeks. It should be noted that $\overline{M}_n$ values of the undegraded polymers

obtained by SEC measurements are very close to those obtained by ^{1}H n.m.r. (*Table 1*). SEC data of PLA$_{109}$/PEO$_{41}$/PLA$_{109}$(Zn) could not be collected initially due to its insolubility in THF. This insolubility was attributed to the presence of rather long L-lactyl blocks. However, its degradation products became soluble in THF after 25 weeks. The SEC $\overline{M}_n$ value at this time was 3600, as compared to the initial $\overline{M}_n$ of 15 650 obtained by ^{1}H n.m.r.

All the copolymers exhibited initially a monomodal molar mass distribution. After 3 weeks in the degradation medium, the SEC peak of PLA$_{21}$/PEO$_{41}$/PLA$_{21}$(CaH$_2$) became broader with formation of low molar mass species (*Figure 4A*). The proportion of these species increased as degradation proceeded. At week 11, the SEC trace turned bimodal, molar masses of the two peaks being 4200 and 2200, respectively. Finally at 25 weeks, the chromatogram remained bimodal with an increase of the relative intensity of the low molar mass peak. PLA$_{43}$/PEO$_{41}$/PLA$_{43}$(CaH$_2$) behaved similarly with appearance of bimodal distributions at weeks 16 and 25 (*Figure 4B*), the molar masses corresponding to the two peaks being 4800 and 2800 at 25 weeks, respectively. At the end of 93 weeks, the residual material showed a monomodal and very narrow distribution ($\overline{M}_w/\overline{M}_n = 1.3$). Similar features were observed for PLA$_{44}$/PEO$_{41}$/PLA$_{44}$(Zn) with bimodal distributions at 16 and 25 weeks and only one narrow SEC peak at 93 weeks (*Figure 4C*). In so far as PLA$_{109}$/PEO$_{41}$/PLA$_{109}$(Zn) is concerned, the SEC chromatogram exhibited also a bimodal distribution after 25 weeks. Unfortunately, no samples were available beyond 25 weeks.

Thermal property changes were investigated by d.s.c. At the end of the first run, the molten sample was immediately quenched with liquid nitrogen to be made amorphous. A second heating was then performed in order to observe glass transition and crystallization phenomena. PLA$_{44}$/PEO$_{41}$/PLA$_{44}$(Zn) was initially slightly crystalline with a small melting peak $T_m = 98°C$ (*Figure 5A*). The large endothermal peak appearing around 50°C was assigned to chain relaxation phenomena. The second run showed only a small glass transition, at temperature $T_g = 33°C$. At 5 weeks, the melting peak was detected at *ca.* 100–105°C. At week 13, a well defined melting peak was detected at 104°C, T_g being at 30°C as shown by the second run. At 25 weeks, Tm slightly increased to 107°C and T_g decreased to 25°C. Finally after 93 weeks, the recovered residual products appeared more crystalline with an intense melting peak at 68°C, while T_g further decreased to 23°C. PLA$_{43}$/PEO$_{41}$/PLA$_{43}$(CaH$_2$) which had the same molecular characteristics as PLA$_{44}$/PEO$_{41}$/PLA$_{44}$(Zn), exhibited similar thermal property changes.

The thermograms of PLA$_{21}$/PEO$_{41}$/PLA$_{21}$(CaH$_2$) were rather complex because of the waxy nature of this material. It showed initially a glass transition around 20°C. Nevertheless, a melting peak was detected at 95°C at week 25, indicating the presence of crystalline material. The second heating led to a crystallization peak $T_c = 25°C$ and a melting peak $T_m = 65°C$.

PLA$_{109}$/PEO$_{41}$/PLA$_{109}$(Zn) with longer PLA blocks was initially more crystalline than the three other copolymers. Before immersion, the melting temperature at the first run was $T_{m1} = 151°C$ (*Figure 5B*). On the second heating, T_g, T_c and T_{m2} were detected at 37, 80 and 148°C, respectively. During the degradation period up to 25 weeks, T_g slightly decreased to 35°C. T_{m1} and T_{m2} decreased to 148 and 144°C, respectively, in agreement with the decrease of molar mass. The T_c changes appeared more complex. T_c first decreased
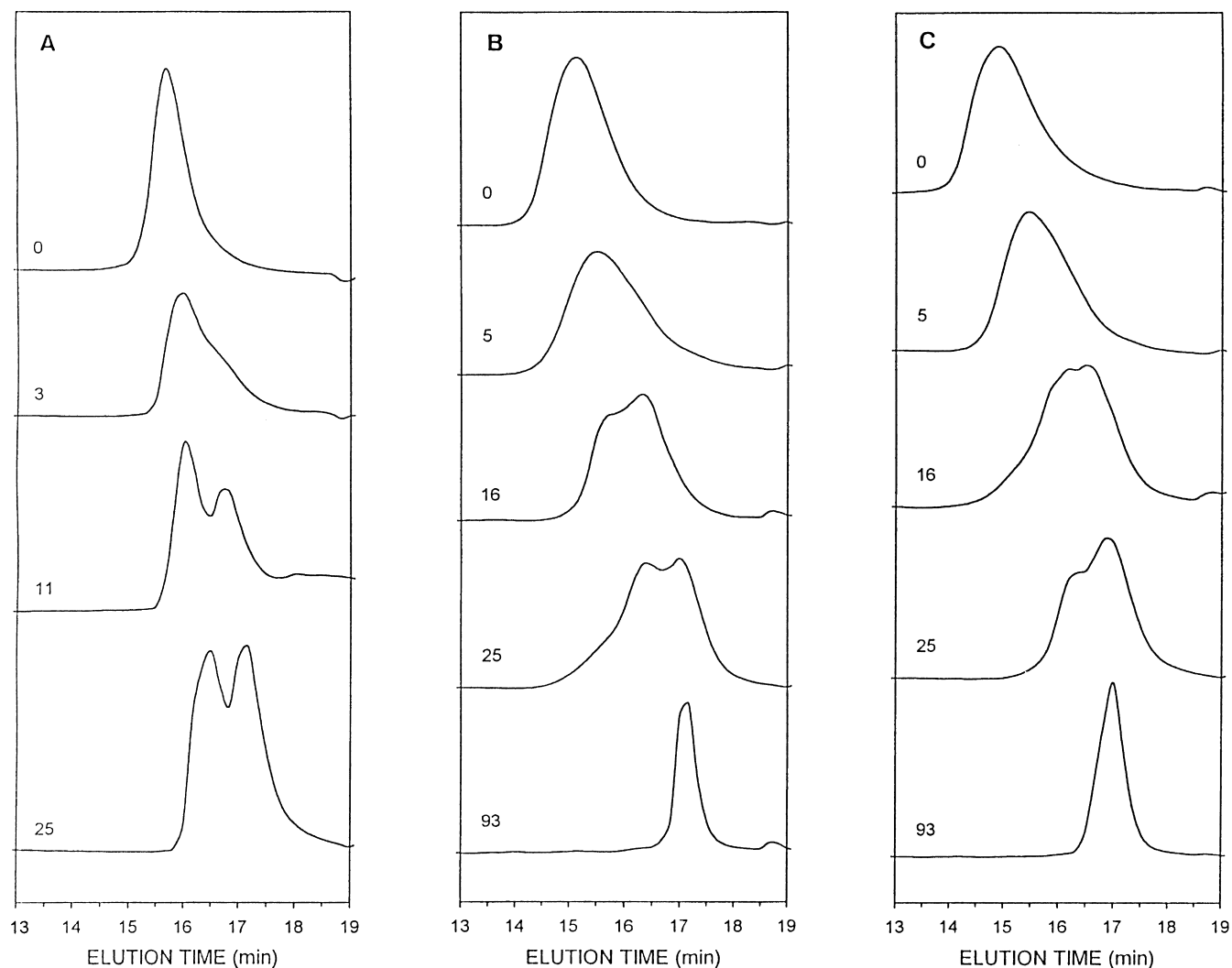
Figure 4 (A) SEC chromatograms of $PLA_{21}/PEO_{41}/PLA_{21}(CaH_2)$ after 0, 3, 11 and 25 weeks degradation. (B) SEC chromatograms of $PLA_{43}/PEO_{41}/PLA_{43}(CaH_2)$) after 0, 5, 16, 25 and 93 weeks degradation. (C) SEC chromatograms of $PLA_{44}/PEO_{41}/PLA_{44}(Zn)$ after 0, 5, 16, 25 and 93 weeks degradation

Table 2 Crystallinity changes of PLA/PEO/PLA triblock copolymers with degradation

Degradation time (weeks)	$PLA_{43}/PEO_{41}/$ $PLA_{43}(CaH_2)$	$PLA_{44}/PEO_{41}/$ $PLA_{44}(Zn)$	$PLA_{109}/PEO_{41}/$ $PLA_{109}(Zn)$
0	2.5	14	38
5	14	21	40
11	20	22	49
25	23	25	52
93	51	54	n.d.[a]

[a] n.d., not determined

to 70°C at 5 weeks and then progressively increased to reach 90°C at 25 weeks. The initial T_c decrease could be explained by chain relaxation and rearrangement made possible by aging at 37°C in an aqueous medium. The T_c increase between 5 and 25 weeks suggested a lower crystallizability as molar mass decreased. Similar phenomena had already been observed for poly(L-lactide) homopolymers[17].

The morphological changes were also investigated by X-ray diffraction (*Figure 6*). The pattern of $PLA_{44}/PEO_{41}/$ $PLA_{44}(Zn)$ exhibited the two small peaks at 8.3° and 9.5° characteristic of the crystalline structures of poly(L-lactide)[17]. Therefore, PEO blocks were not included in PLA crystalline domains. Its initial crystallinity (*Table 2*), as

deduced from the diffraction spectrum, was *ca.* 14%. During degradation, the crystallinity increased continuously to attain 54% at the end of 93 weeks (*Figure 6A* and *Table 2*). $PLA_{43}/PEO_{41}/PLA_{43}(CaH_2)$ was initially almost amorphous (crystallinity = 3%). The difference between the initial crystallinities of $PLA_{43}/PEO_{41}/PLA_{43}(CaH_2)$ and $PLA_{44}/PEO_{41}/PLA_{44}(Zn)$ could be attributed to the partial racemization of PLA blocks in the case of CaH_2-initiated copolymers as previously reported[14,15]. However, $PLA_{43}/$ $PEO_{41}/PLA_{43}(CaH_2)$ showed also a crystallinity increase during degradation, as in the case of $PLA_{44}/PEO_{41}/$ $PLA_{44}(Zn)$. $PLA_{21}/PEO_{41}/PLA_{21}(CaH_2)$ was initially totally amorphous. After 9 weeks, the X-ray diffraction pattern exhibited two small peaks located at 8.3 and 9.5°, thus indicating the appearance of crystallinity. In so far as $PLA_{109}/PEO_{41}/PLA_{109}(Zn)$ was concerned, it was initially much more crystalline than the three other compounds (*Figure 6B*). The crystallinity also increased during degradation, from an initial 39% to 52% at 25 weeks (*Table 2*).

I.r. analysis is a means to examine qualitatively compositional changes of the copolymers. *Figure 7* shows the i.r. spectra of $PLA_{44}/PEO_{41}/PLA_{44}(Zn)$ before and after degradation. The copolymers absorbed in the 2800—3000 cm^{-1} range: the C–H stretching bands of PLA
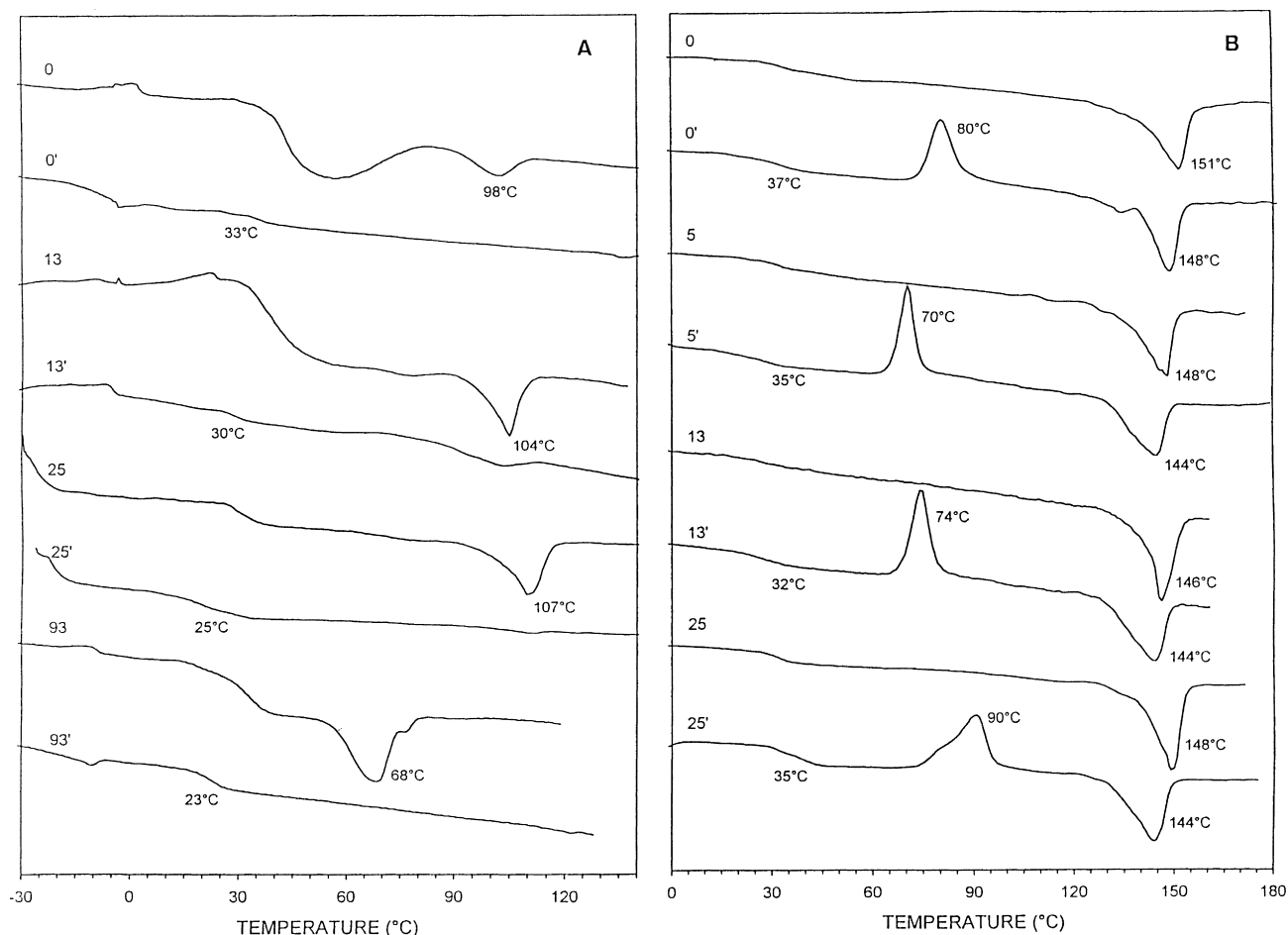
Figure 5 (A) D.s.c. thermograms of $PLA_{44}/PEO_{41}/PLA_{44}(Zn)$ after 0, 13, 25 and 93 weeks degradation (', second heating). (B) D.s.c. thermograms of $PLA_{109}/PEO_{41}/PLA_{109}(Zn)$ after 0, 5, 13 and 25 weeks degradation (', second heating)

blocks at 2995 and 2944 cm^{-1}, and the C–H stretching band of PEO blocks at 2876 cm^{-1}. The bands at 2944 cm^{-1} and at 2876 cm^{-1} were initially at the same level. After 25 and 93 weeks, the relative intensity of the band at 2876 cm^{-1} decreased, suggesting a decrease in PEO content. On the other hand, the band at 3510 cm^{-1} due to the OH endgroups became larger after degradation, in agreement with chain cleavage leading to formation of OH endgroups. Similar features were observed for the three other compounds.

^{1}H n.m.r. spectra of $PLA_{44}/PEO_{41}/PLA_{44}(Zn)$ and band assignments are shown in *Figure 8*. Initially, the copolymer presented the signals characteristic of PLA main chain and terminal units, and of PEO main chain and jonction units[6,8,9]. The resonance of methine protons (a, b, c) in PLA blocks appeared in the 5.3–4.1 ppm range, while the methyl protons (a', b', c') were detected in the 1.7–1.2 ppm range. The signal at 3.5 ppm was assigned to methylene protons (e) of PEO blocks. The methylene protons (d) of LA–EO junctions overlapped with the HO-terminated methine protons of PLA at 4.3–4.1 ppm. The assignments were made possible by the use of DMSO-d_6 which is known as a resolution-enhancing solvent for NMR analysis of PLA polymers[18]. At 11 weeks, some new signals appeared on the ^{1}H n.m.r. spectrum (*Figure 8*):

  4.9–4.8 ppm, **CH** of terminal carboxylate of PLA (–**CH**(CH$_3$)–COO$^-$);
  3.9 ppm, **CH** of lactates (HO–**CH**(CH$_3$)–COO$^-$);
  1.4–1.3 ppm, **CH$_3$** of terminal carboxylate of PLA (–CH(**CH$_3$**)–COO$^-$);
  1.25–1.15 ppm, **CH$_3$** of lactates (HO–CH(**CH$_3$**)–COO$^-$).

Table 3 Evolution of LA/EO ratio of the copolymers with degradation

Degradation time (weeks)	$PLA_{43}/PEO_{41}/$ $PLA_{43}(CaH_2)$	$PLA_{44}/PEO_{41}/$ $PLA_{44}(Zn)$	$PLA_{109}/PEO_{41}/$ $PLA_{109}(Zn)$
0	2.1	2.1	5.3
5	2.5	2.3	6.0
11	3.1	2.5	6.1
25	3.4	2.7	6.3
93	8.2	6.7	n.d.^{a}

^{a}n.d., not determined

The appearance of these signals reflected the formation of PLA oligomers as well as lactates after hydrolytic cleavage of PLA blocks. At 25 weeks, these new bands were still present, the bands of lactates becoming more important. In contrast, at the end of 93 weeks, the bands of lactates disappeared, and the band at 3.5 ppm of PEO remained but very much diminished. Similar changes were detected for the other compounds. The LA/EO ratio was determined by using the integrations of the bands at 1.5 and 3.5 ppm due to LA and EO units, respectively. In all cases, the LA/EO ratio increased with degradation time (*Table 3*). This trend reflected the release of soluble chains composed of PEO blocks attached with short PLA ones, in agreement with mass loss data.

DISCUSSION

Among the copolymers considered in this study, the waxy $PLA_{21}/PEO_{41}/PLA_{21}(CaH_2)$ led rapidly to the formation of a suspension. This can be assigned to the rather short PLA
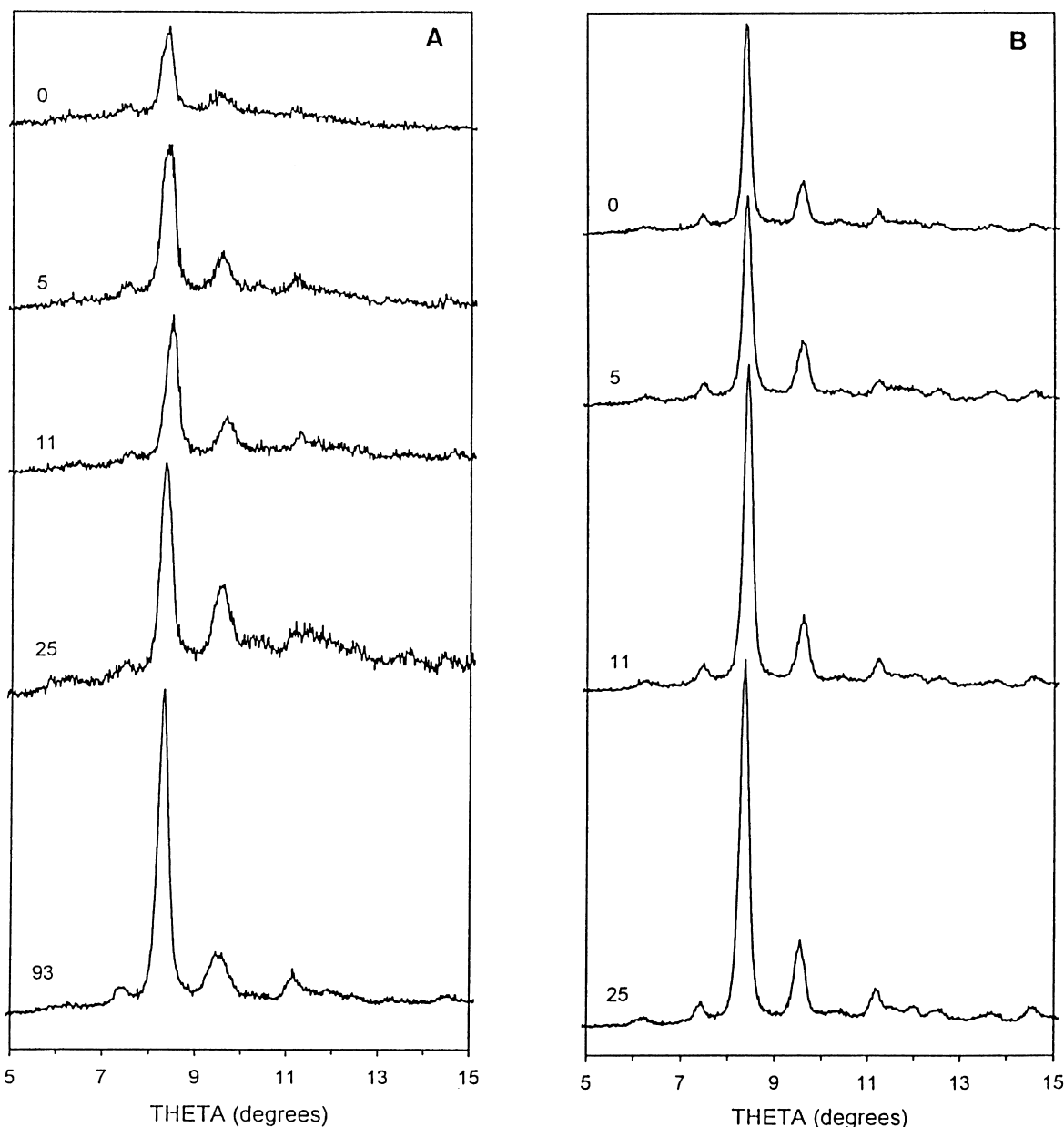
Figure 6 (A) X-ray diffractograms of $PLA_{44}/PEO_{41}/PLA_{44}(Zn)$ after 0, 5, 11, 25 and 93 weeks degradation. (B) X-ray diffractograms of $PLA_{109}/PEO_{41}/PLA_{109}(Zn)$ after 0, 5, 11 and 25 weeks degradation

block length ($\overline{DP}_{PLA} = 21$) which allowed the solubilization or dispersion of triblock copolymer chains in the phosphate buffer solution. In contrast, $PLA_{109}/PEO_{41}/PLA_{109}(Zn)$ with long PLA blocks ($\overline{DP}_{PLA} = 109$) exhibited no weight loss during the first 3 weeks, showing the absence of initially soluble species. Beyond, weight loss was observed due to the release of PLA short chains and PEO segments attached with short PLA blocks. $PLA_{43}/PEO_{41}/PLA_{43}(CaH_2)$ and $PLA_{44}/PEO_{41}/PLA_{44}(Zn)$ with intermediate PLA block lengths ($\overline{DP}_{PLA} = 43$ or 44) presented intermediate behaviours. Weight loss was detected at the very beginning, suggesting the presence of initially soluble species. Interestingly, $PLA_{43}/PEO_{41}/PLA_{43}(CaH_2)$ appeared more hydrophilic than $PLA_{44}/PEO_{41}/PLA_{44}(Zn)$, which could be attributed to the partial racemization of PLA blocks in the case of CaH_2-initiated copolymers as previously reported[14,15]. The partial racemization led to a lower initial crystallinity (*Table 2*). Nevertheless, no major difference was observed between the degradation characteristics of

$PLA_{43}/PEO_{41}/PLA_{43}(CaH_2)$ and $PLA_{44}/PEO_{41}/PLA_{44}(Zn)$, in particular weight loss and $\overline{M}_n$ decrease profiles. Furthermore, $PLA_{109}/PEO_{41}/PLA_{109}(Zn)$ showed also a rather rapid $\overline{M}_n$ decrease although it absorbed less water due to higher initial crystallinity. These behaviours could be related to a microphase separation between PLA and PEO blocks, in agreement with d.s.c. and X-ray diffraction data. In fact, the large amounts of water absorbed by the copolymers were located in the PEO swollen phase, PLA blocks degrading at similar rates as proposed by Shah *et al.*[19]. The enhanced weight loss rate, as compared to PLA homopolymers[17], mainly resulted from the presence of PEO hydrophilic segments.

The literature is rather confusing in so far as the location of hydrolytic attacks is concerned. Cohn and Younes stated that PLA blocks are cleaved at random, the LA–EO and LA–LA linkages having the same reactivity[10]. This conclusion was based on the fact that some LA–EO junction units were still present after degradation as
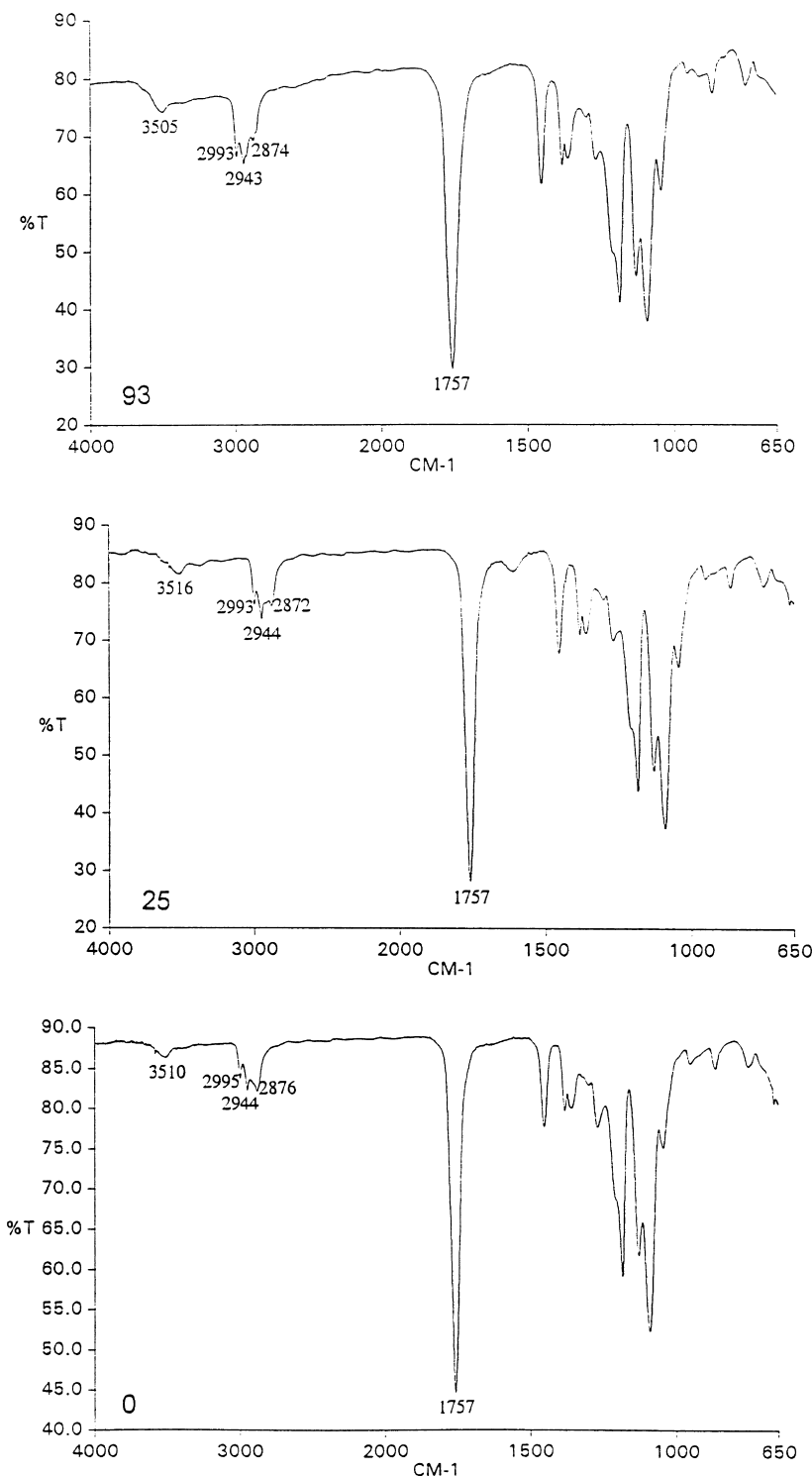
Figure 7 I.r. spectra of $PLA_{44}/PEO_{41}/PLA_{44}(Zn)$ after 0, 25 and 93 weeks degradation

shown by ^1H n.m.r. spectra. Similarly, Hu and Liu observed by n.m.r. the formation of hydroxyl endgroups connected to PEG blocks and carboxyl endgroups connected to PLA blocks after hydrolysis of PLA/PEO/PLA triblock copolymers[11]. Moreover, an increase of PEG content was detected up to 600 h hydrolysis for the copolymers containing initially 2 to 10% of PEG. The authors suggested that the chain scission during the initial period occurs at the ester linkage connecting PEG and PLA blocks, in addition to ester groups within the PLA blocks. However, it was not clear whether hydrolytic cleavage proceeds preferentially at junction ester groups. Kissel *et al.* proposed that in the case of PLA/PEO/PLA triblock copolymers, the cleavage of ester–ether junctions occurs more rapidly. This conclusion was based on a rapid loss of PEO during the first 24 h[12]. $\overline{M}_n$ also decreased rapidly during this period. In contrast, in the case of PLAGA/PEO/PLAGA triblock copolymers, degradation was fast and continuous. The difference between these two kinds of triblock copolymers was attributed to a microphase separation since in the former case, PLA blocks crystallized[12]. However, this interpretation could not explain why the composition of PLA/PEO/
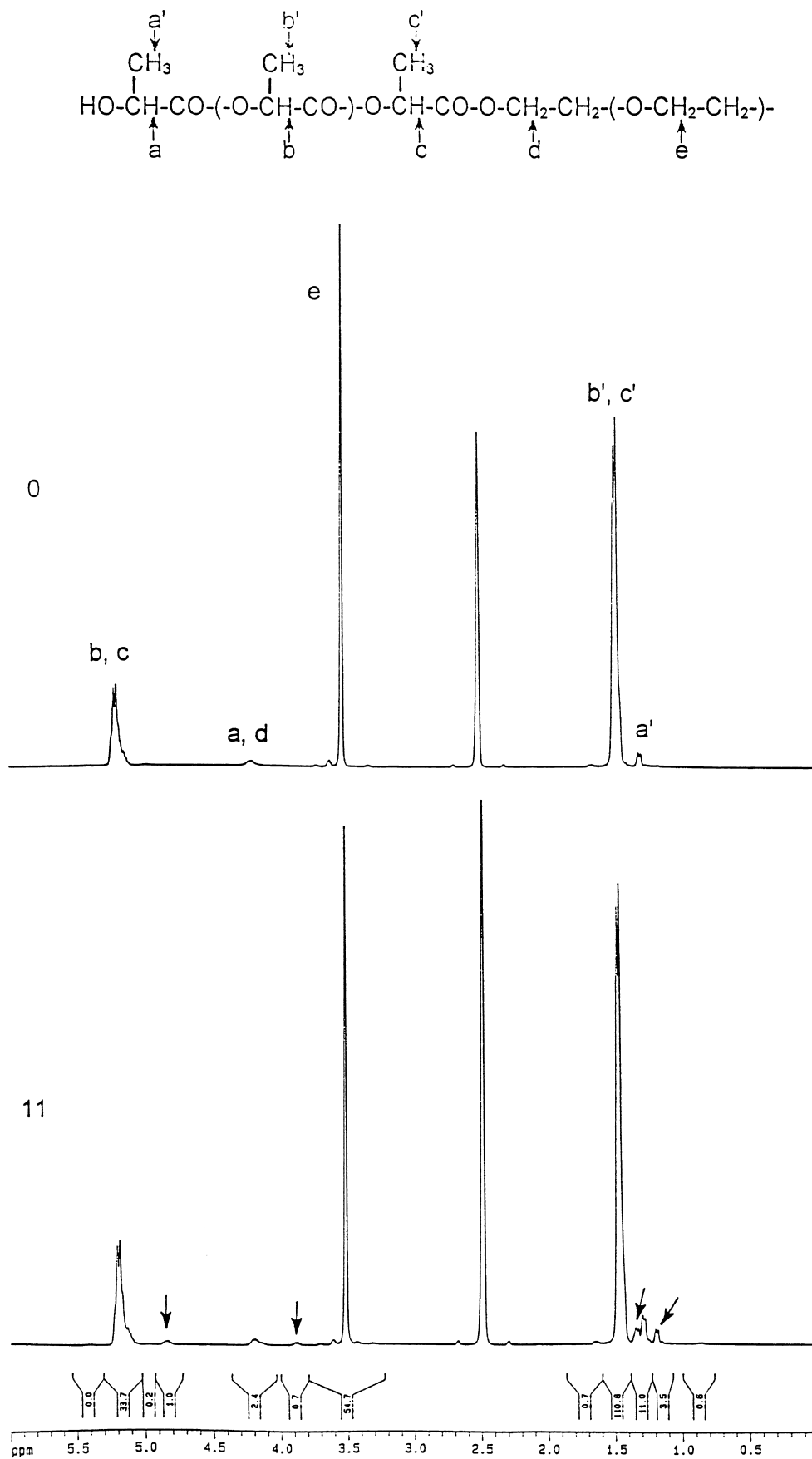
Figure 8 ^{1}H n.m.r. spectra of PLA$_{44}$/PEO$_{41}$/PLA$_{44}$(Zn) after 0 and 11 weeks degradation

PLA copolymers remained almost constant after the dramatic initial changes.

The n.m.r. spectra shown in *Figure 8* confirmed the formation of PLA oligomers and lactates in the degraded copolymers. On the other hand, some LA–EO junctions remained even at the end of 93 weeks. This argues against the preferential cleavage of LA–EO junctions suggested by Kissel and coworkers[12]. In view of literature data and of the results shown above, it is likely that the cleavage of PLA blocks occurred at random, leading to PLA segments together with PEO ones terminated by short PLA blocks. An increase of PEO content should be observed if soluble PLA oligomers are released at the early stages of degradation before the solubilization of PEO segments attached with short PLA ones. This was the case for the PLA/PEO/PLA triblock copolymers with relatively long PLA blocks investigated by Hu and Liu[11]. In contrast, there should be no increase of the PEO content if ester–ether junctions are preferentially cleaved as suggested by Kissel and coworkers[12]. As degradation advances, PEO blocks attached with very short PLA sequences should be released, which will lead to a LA/EO ratio increase in the residual material. This is what was observed in the present study. In Kissel *et al.*'s work, the initial rapid loss of PEO content might be related to the solubilization of initially present PEO-rich chains rather than a preferential cleavage at ester–ether junctions[12]. Actually, the presence of these initially soluble copolymer chains should be possible since the molar mass of PEO blocks was 10 000 and the initial PEO contents were as high as 48 and 52%.

In the literature, Hu and Liu reported bimodal SEC chromatograms for degraded PLA/PEO/PLA triblock copolymers[11]. The authors did not give any explanation. In the case of PLA and PLAGA homo- and copolymers, bimodal molar mass distributions have been reported many times[17,20–23]. At least three origins can be distinguished. First, a degradation faster inside than at surface of amorphous polymers is known to give rise to rather large bimodal chromatograms according to the heterogeneous degradation mechanism[20,21]. Second, degradation of initially amorphous but crystallizable polymers generates a narrow peak with low molar mass beside the main peak. This narrow peak is related to degradation-induced crystalline domains[17,21,22]. Finally, degradation of initially crystalline polymers results in bimodal or multimodal molar mass distributions due to the selective degradation in amorphous zones and at the edges of crystalline zones[17,23]. Similar features were observed for highly crystalline PCL and PHB polymers[24,25].

In the cases of $PLA_{21}/PEO_{41}/PLA_{21}(CaH_2)$, $PLA_{43}/PEO_{41}/PLA_{43}(CaH_2)$ and $PLA_{44}/PEO_{41}/PLA_{44}(Zn)$, the obtained bimodal chromatograms were attributed to the second mechanism mentioned above. This interpretation was strongly supported by d.s.c. and X-ray diffraction data (*Figures 5 and 6*). In fact, both PLA segments and PEO central blocks attached with short PLA blocks were formed during the random hydrolytic cleavage of PLA blocks. PLA segments which were long enough to be insoluble, crystallized under the degradation conditions as reported in literature for PLA-related polymers[17,21,22]. Once crystallized, these segments were more resistant to hydrolytic attack and solubilization. As a consequence, SEC chromatograms became bimodal with a main peak reflecting the PEO blocks attached with PLA blocks and a peak of lower molar mass reflecting the crystallized PLA segments. In fact, melting peak and crystallinity were detected for

initially amorphous $PLA_{21}/PEO_{41}/PLA_{21}(CaH_2)$. In the cases of the initially slightly crystalline $PLA_{43}/PEO_{41}/PLA_{43}(CaH_2)$ and $PLA_{44}/PEO_{41}/PLA_{44}(Zn)$, T_m and melting peak area increased during the first 25 weeks because the released PLA blocks crystallized better than those attached to PEO central blocks. The crystallinity also increased as shown by X-ray diffraction spectra.

In contrast, the bimodal chromatogram observed for $PLA_{109}/PEO_{41}/PLA_{109}(Zn)$ at 25 weeks was assigned to the third mechanism. In this case, PLA blocks were initially long enough to yield well developed crystalline structures. Degradation occurred preferentially in the amorphous zones as well as at the edges of crystalline ones, leading to bimodal molar mass distributions[17,23]. Other consequences of this preferential degradation were that crystallinity increased and T_m decreased.

CONCLUSION

PLA/PEO/PLA triblock copolymers obtained by ring-opening polymerization of L-lactide in the presence of PEG and Zn metal or CaH_2 as co-initiator present interesting degradation characterisitics. The introduction of PEO sequences greatly increased the hydrophilicity and decreased the crystallinity of the copolymers. Both features are of great interest for applications in the field of sustained drug delivery, residual crystalline particles being a potential source of inflammatory responses. Nevertheless, the degradation rate of these copolymers was not enhanced due to the phase separation between PLA and PEO blocks. Hydrolytic attack proceeded randomly along PLA blocks. The released water insoluble PLA fragments were able to crystallize, leading to bimodal molar mass distributions. On the other hand, the solubilization of PEO blocks attached with short PLA ones led to LA/EO ratio increase in the residual material.

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