Comparative Study of the Hydrolytic Degradation of Glycolide/L-Lactide/ε-Caprolactone Terpolymers Initiated by Zirconium(IV) Acetylacetonate or Stannous Octoate

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ABSTRACT: A series of copolymers have been synthesized by the ring-opening polymerization of glycolide, L-lactide, and ε-caprolactone with zirconium(IV) acetylacetonate [Zr(Acac)$_4$] or stannous octoate [Sn(Oct)$_2$] as the catalyst. The resulting terpolymers have been characterized by analytical techniques such as proton nuclear magnetic resonance, size exclusion chromatography, and differential scanning calorimetry. Data have confirmed that Sn(Oct)$_2$ leads to less transesterification of polymer chains than Zr(Acac)$_4$ under similar conditions. The various copolymers have been compression-molded and allowed to degrade in a pH 7.4 phosphate buffer at 37°C. The results show that the degradation rate depends not only on the copolymer composition but also on the chain microstructure, the Sn(Oct)$_2$-initiated copolymers degrading less rapidly than Zr(Acac)$_4$-initiated ones with more random chain structures. The caproyl component appears the most resistant to degradation as its content increases in almost all cases. Moreover, caproyl units exhibit a protecting effect on neighboring lactyl or glycolyl units. The glycolyl content exhibits different features: it decreases because of faster degradation of glycolyl units, which are more hydrophilic than caproyl and lactyl ones, remains stable in the case of abundant C—G—C sequences, which are very resistant to degradation, or even increases because of the formation of polyglycolide crystallites. Terpolymers can crystallize during degradation if the block length of one of the components is sufficiently long, even though they are amorphous initially. © 2007 Wiley Periodicals, Inc. J Appl Polym Sci 107: 3258–3266, 2008

Key words: biodegradable; biomaterials; crystallization; polyesters

INTRODUCTION

Bioresorbable aliphatic polyesters, particularly Food and Drug Administration approved polyglycolide (PGA), polylactide (PLA), and poly(ε-caprolactone) (PCL), constitute a class of biomaterials of growing interest in the fields of temporary therapeutic applications in surgery, sustained drug delivery, and tissue engineering.[1–3] PGA is the first synthetic polymer used as a bioresorbable suture material because of its high crystallinity. However, the absence of practical solvents has limited its applications in the biomedical field. PLA is particularly interesting because its properties can be adjusted within a large scale by the variation of the feed ratio of L-lactide/

D-lactide enantiomers. On the other hand, PCL also appears quite attractive because of its excellent thermal properties and permeability to drugs. In fact, the high decomposition temperature (ca. 350°C) and low melting temperature (T_m; ca. 65°C) provide a large processing range.

PGA, PLA, and PCL polymers are synthesized through the ring-opening polymerization of corresponding cyclic lactones, that is, glycolide, lactide, and ε-caprolactone, by the use of an initiator such as stannous octoate [Sn(Oct)$_2$], zinc lactate [Zn(Lac)$_2$], zirconium(IV) acetylacetonate [Zr(Acac)$_4$], or tetraphenyl tin.[4–9] Sn(Oct)$_2$ is the most widely used catalyst because of its high efficacy, although it is slightly cytotoxic,[10] whereas Zn(Lac)$_2$ and Zr(Acac)$_4$ are known as low-toxicity catalysts.[4,11] The hydrolytic degradation of these polyesters has been extensively investigated during the past 2 decades.[3–9,12–14] It is now well known that degradation proceeds faster inside than at the surface of large-size devices because of the internal autocatalysis of carboxyl end groups formed by chain cleavage.[3,14] In the case of semicrystalline polymers, amorphous regions are preferentially degraded because they are more acces-

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sible to water molecules than crystalline ones. Degradation-induced compositional and morphological changes have also been reported. PLA and PCL homopolymers exhibit very low hydrolytic degradability because of the high hydrophobicity and crystallinity.[1,3,14] In contrast, the degradation behaviors of various copolymers can be tailored by changes in the composition, molecular weight (MW), and chain microstructure or distribution of comonomer units.[3–8] Star-shaped PLA was synthesized by the reaction of L-lactide with glycerol (GL) in the presence of Sn(Oct)$_2$ or tetraphenyl tin.[9] The susceptibility of these PLAs to biodegradation was tested by means of enzymatic hydrolysis (total organic carbon measurements). It was concluded that a high GL content and low crystallinity substantially promoted PLA degradation.[9]

Recently, we reported the synthesis, characterization, and degradation of various copolymers obtained by the ring-opening polymerization of glycolide and ε-caprolactone with Sn(Oct)$_2$ or Zr(Acac)$_4$ as the initiator.[7,8] It was found that copolymers with higher degree of randomness exhibited higher degradation rates. Sequences with odd numbers of glycolyl units such as —CGC— and —CGGGC—, resulting from second-mode transesterification, appeared more resistant to hydrolysis. The hydrolytic degradation of poly(glycolide-co-L-lactide-co-ε-caprolactone) (PGLC) terpolymers initiated by Zr(Acac)$_4$ was also considered.[15] Morphological and compositional changes were detected during degradation.

In this work, we report a comparative study on the hydrolytic degradation of PGLC terpolymers initialed by Sn(Oct)$_2$ or Zr(Acac)$_4$ to elucidate the effect of the chain microstructure. Degradation was carried out on compression-molded samples in a pH = 7.4 phosphate buffer taken as a model of biological fluids and monitored with various analytical techniques. The results are reported herein in comparison with literature data.

EXPERIMENTAL

Materials

PGLC terpolymers with different compositions and chain microstructures were synthesized by the ring-opening polymerization of glycolide, L-lactide, and ε-caprolactone with Zr(Acac)$_4$ or Sn(Oct)$_2$ as the catalyst. Polymerization was carried out in bulk at 110°C, the molar ratio of the comonomers to the initiator being 800 : 1.

Measurements

Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with a Varian Unity Inova spectrometer (Palo Alto, CA) operating at 300 MHz with dried dimethyl sulfoxide-d_6 (DMSO-d_6) as the solvent. Chemical shifts (δ) were given in parts per million with tetramethylsilane as an internal reference. The spectra were obtained at 80°C with 32 scans, a 7-μs pulse width, and a 3.74-s acquisition time.

Differential scanning calorimetry (DSC) was performed from −70 to 230°C with a PerkinElmer DSC 6 instrument (Norwalk, CT), the heating rate being 10°C/min.

Size exclusion chromatography (SEC) measurements were performed for the copolymers soluble in chloroform with a Physics SP 8800 chromatograph apparatus (Santa Clara, CA) equipped with a Shodex SE 61 detector (Tokyo, Japan). Chloroform was used as the mobile phase at a flow rate of 1.0 mL/min. A 20-μL 0.5% (w/v) solution was injected for each analysis. The columns were calibrated with polystyrene standards (Polysciences, Warrington, PA).

The inherent viscosity of the initial copolymers was measured with 1,1,1,3,3,3-hexafluoro-2-propanol as the solvent. Measurements were conducted at 25°C with an Ubbelohde viscometer (Cannon Instrument Co., State College, PA). The concentration of the solutions was 2 g/dm^3.

Degradation

Films of the various terpolymers were prepared by compression molding. Square specimens with dimensions of 10 mm × 10 mm × 1 mm were then cut from the films.

Specimens were placed into vials with 5 mL of a 0.13M phosphate buffer solution (pH = 7.4) containing 0.02% sodium azide to prevent bacterial growth. Degradation was allowed to proceed in an oven thermostated at 37°C.

At each preset degradation time, three samples were withdrawn from the vials and washed with distilled water. They were then vacuum-dried at room temperature until a constant weight before being subjected to analysis. Weight-loss values were calculated with the following equation:

$$\text{Weight loss } (\%) = [(W_0 - W_{\text{dry}})/W_0] \times 100 \quad (1)$$

where W_0 represents the initial weight of the specimens and W_{dry} represents the dry weight (after vacuum drying).

RESULTS AND DISCUSSION

Characterization of the PGLC terpolymers

The molecular characteristics of the PGLC terpolymers were determined by ^{1}H-NMR and inherent viscosity measurements, as shown in Table I. It appears that the composition of the copolymers is very close to that of the feeds, indicating high conversion of the

TABLE I
Molecular Characteristics of PGLC Terpolymers Obtained by the Ring-Opening Polymerization of Glycolide, L-Lactide, and ε-Caprolactone with $Zr(Acac)_4$ or $Sn(Oct)_2$ as a Catalyst

| Sample | Initiator | GG/LL/C[a] | | L_{GG} | L_{LL} | L_C | Inherent viscosity (dL/g) |
		In the feed	In the polymer				
Cop1	$Zr(Acac)_4$	36/34/30	39.5/35.3/25.2	1.8	5.6	1.1	1.2
Cop2	$Zr(Acac)_4$	15/44/41	15.6/44.5/39.9	0.9	3.7	1.5	1.0
Cop3	$Zr(Acac)_4$	66/18/16	62.4/21.2/16.4	3.4	3.0	1.3	1.1
Cop4	$Zr(Acac)_4$	15/60/25	15.0/60.4/24.6	0.9	6.3	1.3	1.0
Cop5	$Sn(Oct)_2$	35/33/32	35.1/33.4/31.5	2.4	5.0	1.4	0.9
Cop6	$Sn(Oct)_2$	16/43/41	15.6/43.4/41.0	1.4	4.1	1.7	0.9
Cop7	$Sn(Oct)_2$	17/23/60	12.9/22.2/64.9	0.9	1.8	1.3	0.8

[a] Molar ratio determined by ^{1}H-NMR.

monomers. The inherent viscosity of the copolymers ranges between 0.8 and 1.2. The average lengths of caproyl blocks (L_C), lactidyl blocks (L_{LL}), and glycolidyl blocks (L_{GG}) mainly depend on the composition of the copolymers. However, it is of interest to compare the block length data of Cop1 and Cop5 and of Cop2 and Cop6, both groups having similar gross compositions. It appears that L_{GG} and L_C of $Sn(Oct)_2$-initiated Cop5 are higher than those of $Zr(Acac)_4$-initiated Cop1, whereas L_{LL} of Cop5 is slightly lower than that of Cop1. On the other hand, L_{GG}, L_{LL}, and L_C of $Sn(Oct)_2$-initiated Cop6 are all higher than those of $Zr(Acac)_4$-initiated Cop2. These findings indicate that $Sn(Oct)_2$ provokes less transesterification along PGLC chains than $Zr(Acac)_4$ under the selected reaction conditions.

Degradation of the PGLC terpolymers

Weight loss

The weight loss of a polymer during degradation reflects the release of soluble oligomers from the bulk sample. Figure 1 presents the weight-loss profiles of the various copolymers. Cop1 and Cop5 show the fastest weight loss. After 3 weeks of lag time, the weight loss of Cop1 initiated by $Zr(Acac)_4$ increases rapidly and almost linearly to reach 64% after 9 weeks, whereas the weight loss of Cop5 initiated by $Sn(Oct)_2$ reaches 44% at 9 weeks. After 13 weeks of degradation, Cop1 and Cop5 lose 74 and 62% of their initial weights, respectively. The fast weight loss of Cop1 and Cop5 can be assigned to the highly random chain structures due to the equivalent contents of the three components. With higher caproyl contents (ca. 40%), $Zr(Acac)_4$-initiated Cop2 loses more material than $Sn(Oct)_2$-initiated Cop6 (32 versus 28%), thus confirming that $Zr(Acac)_4$-initiated copolymers degrade faster than $Sn(Oct)_2$-initiated ones because of the more random structures for the former. In the case of Cop3, Cop4, and Cop7 with the highest GG, LL, and C contents (ca. 60%), respec-

tively, Cop3 exhibits the highest weight loss (54%), Cop4 exhibits the intermediate weight loss (32%), and Cop7 exhibits the lowest one (24%) after 13 weeks of degradation. This indicates that glycolyl units are the most degradable and caproyl units are the most resistant to hydrolysis.
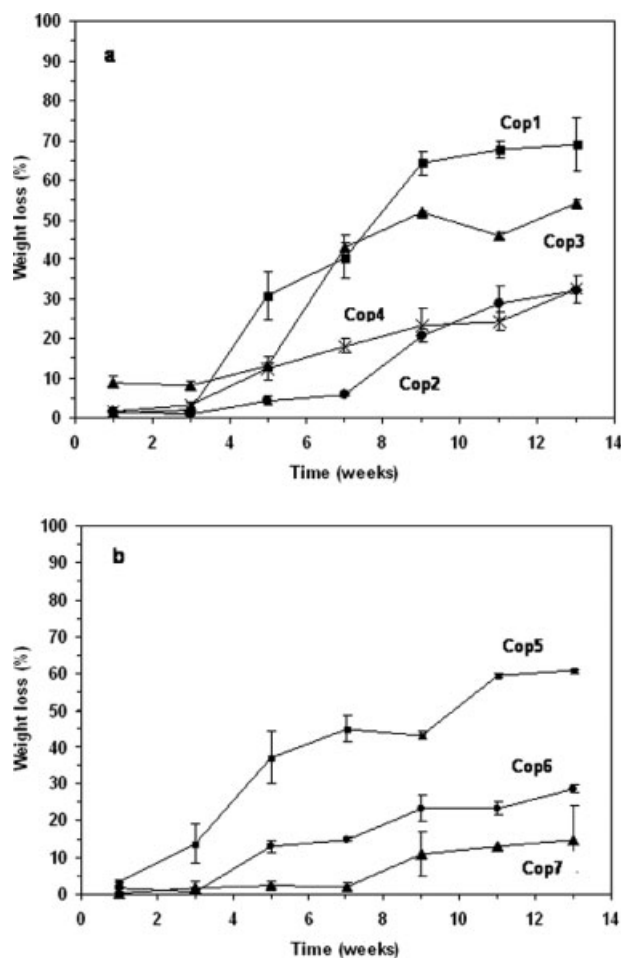

Figure 1 Weight-loss profiles of PGLC terpolymers initiated by (a) $Zr(Acac)_4$ and (b) $Sn(Oct)_2$.
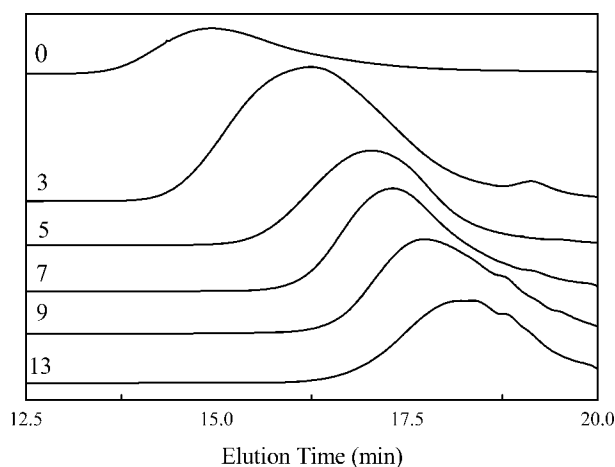
Figure 2 SEC chromatograms of Cop5 during degradation at 37°C in a pH 7.4 phosphate buffer.

MW

MW is a key parameter influencing polymer degradation. A decrease in MW during degradation reflects chain cleavage due to hydrolysis. Figure 2 presents the SEC chromatograms of Cop5 during degradation. MW decreases continuously, as shown by the constant shift of the chromatogram to a longer elution time. After 7 weeks of degradation, the weight-average molecular weight of Cop 5 decreases from the initial value of 26,100 to 1900. In the meantime, the polydispersity index (weight-average molecular weight/number-average molecular weight) slightly increases from 2.8 to 3.1.

Figure 3 presents the MW changes during degradation as determined by SEC. No MW data are available for Cop3 with 62.4% GG content, which makes it insoluble in common solvents. All the terpolymers exhibit similar MW changes. MW rapidly decreases in the first 3 weeks, and this is followed by a slower decrease up to 13 weeks. Nevertheless, different degradation rates are obtained. Cop1 and Cop5 with equivalent GG, LL, and C contents appear the most degradable with a very fast initial MW decrease. On the other hand, MW of Cop7 with the highest C content (ca. 60%) decreases less rapidly than those of the other terpolymers, thus confirming that caproyl units are the most resistant to hydrolysis. Cop2, Cop4, and Cop6 exhibit intermediate degradation rates.

Chemical composition changes during degradation

Monomer reactivity ratios of glycolide and lactide initiated by Zr(Acac)$_4$ at 100–150°C have been reported to be 3.3 and 0.5, respectively.[16] Park et al.[17] found r_G = 6.84 and r_C = 1.03 for bulk copolymerization in the temperature range of 150–

200°C with Sn(Oct)$_2$ as the catalyst.[17] Therefore, glycolide is first incorporated into the growing chains. When the content of glycolide becomes very low, lactide and caprolactone units are incorporated into the chains, and transesterification occurs by the attack of active lactyl or caproyl chain ends.

Chemical composition and chain microstructure changes of the terpolymers during degradation were monitored by ^{1}H-NMR spectroscopy. Figures 4 and 5 show the chain microstructure changes of Cop1 and Cop5 after 0, 1, 3, and 5 weeks of degradation, respectively. The chemical shifts of the various terpolymer sequences are shown in Table II.[18] In the caproyl range before degradation, for example, Cop1 exhibits a G*C* + L*C* signal (16) that is much higher than the C*C* signal (17; Fig. 4), whereas the intensity difference between the two signals is lower in the case of Cop5 (Fig. 5). In the glycolyl range, the C*G*C signal resulting from transesterification is stronger for Cop1 than for Cop5. Similarly, signals (12, 13, and 14) are stronger for Cop1 than for Cop5, whereas the signal of long glycolyl blocks (G*G*GG, 6) is less intense for Cop1 than for Cop5. In contrast, the lactyl range shows no major difference between the two copolymers. Therefore, NMR confirms the more random structure of Zr(Acac)$_4$-initiated copolymers in comparison with Sn(Oct)$_2$-initiated ones.

Distinct changes in chemical structures are observed at the early stage of degradation. For Cop1 after 1 week of degradation, the intensity of G*G*GG (6) and C*G*C (15) sequences increases (Fig. 4). On the contrary, for Cop5 (Fig. 5), a strong decrease in the G*G*GG sequence concentration is observed together with a decrease in the concentration of C*G*GGG, G*G*GGC, L*L*GGL, L*G*GLL, G*G*GGL, L*G*GGG, C*G*GGC, L*L*GGG, G*G*GLL, and X*L*GLX sequences (signals 7, 8, 9, and 10). The intensity of other sequences (1, 2, 12, 13, 14, 15, 16, and 17) increases
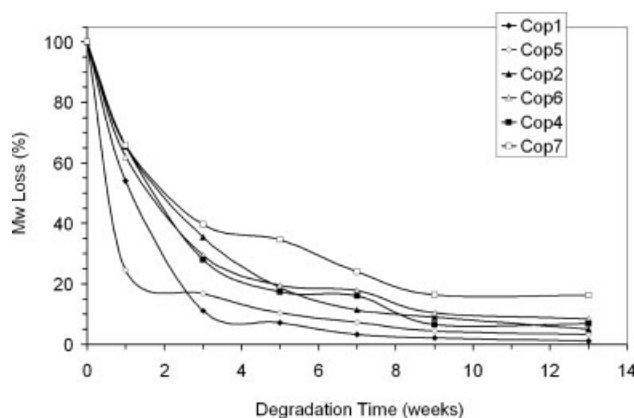

Figure 3 Weight-average molecular weight (M_w) changes in PGLC terpolymers during degradation at 37°C in a pH 7.4 phosphate buffer.
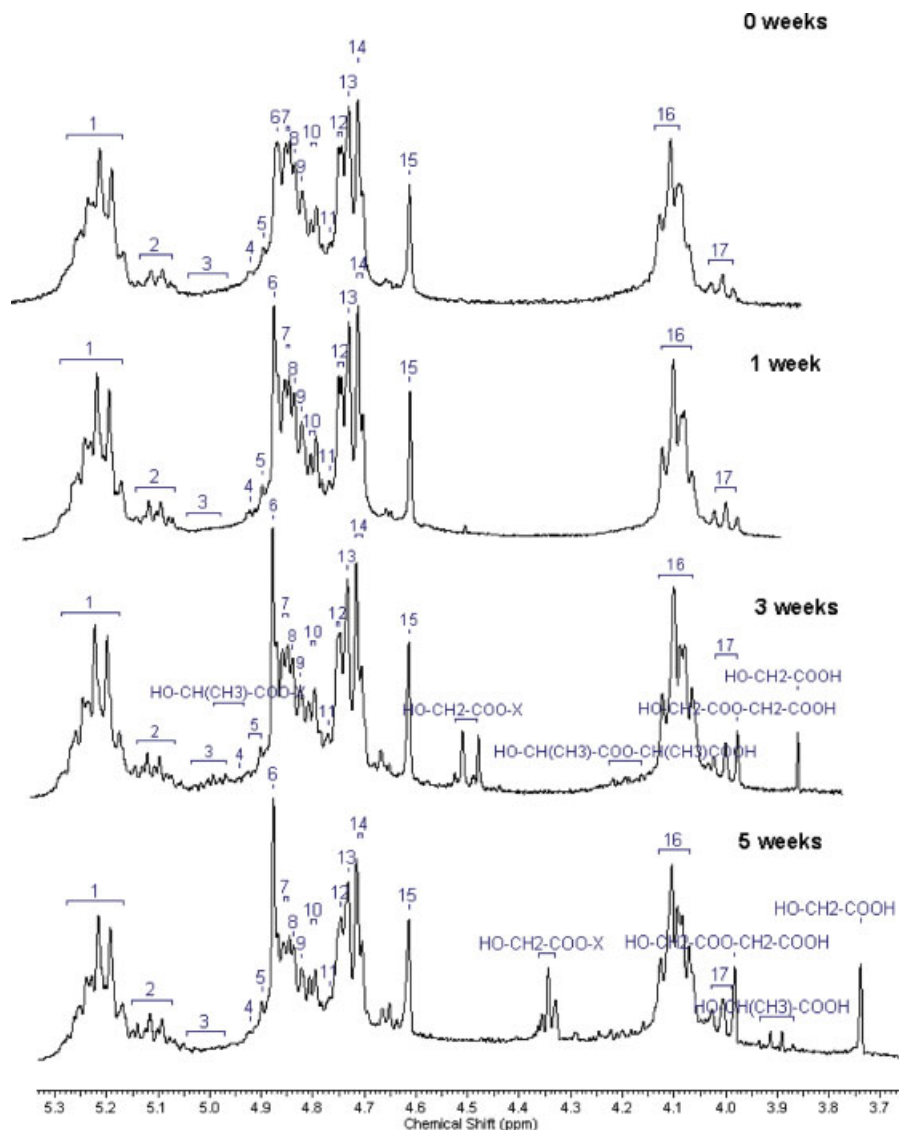
Figure 4 ^{1}H-NMR spectra of Cop1 after 0, 1, 3, and 5 weeks of degradation. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

instead. Small new signals are detected and assigned to —CH$_2$— of glycolyl units linked to the terminal hydroxyl groups, such as HO—CH$_2$—COO—G, HO—CH$_2$—COO—C, or HO—CH$_2$—COO—L sequences, in the range of 4.4–4.6 ppm. After 3 weeks of degradation, the most intense signal is GGGG (signal 6) for Cop1, in contrast to Cop5, for which signal 16 is the most intense. The signal intensities of glycolyl units linked to the terminal hydroxyl groups increase together with the signals at about 3.84 ppm from glycolic acid and 4.05 ppm from hydroxyacid dimer, which overlap with the CC (17) sequence. After 5 weeks of degradation, a distinct intensity increase from signals 12, 13, and 14 is observed for Cop5, in contrast to Cop1, which exhibits an intensity decrease in these signals. An increase in the sig-

nal intensity from the hydroxyacid signals previously described is observed for both copolymers. A new signal (methine quartet at 3.98 ppm) from lactyl units linked to the terminal hydroxyl group is detected.

Therefore, in the glycolyl range, the CGC sequence becomes stronger or remains unchanged after degradation, and this indicates that this sequence is resistant to hydrolytic attack, in agreement with previous work.[8] On the other hand, signals 7, 8, 9, and 10 become weaker after 5 weeks and almost totally disappear after 13 weeks (data not shown). These results show that glycolyl units mainly exist in the CGC sequence (15) or in close junction to caproyl units (12, 13, and 14) because of the protecting effect of the latter. It is of interest to note that the LGL sig-
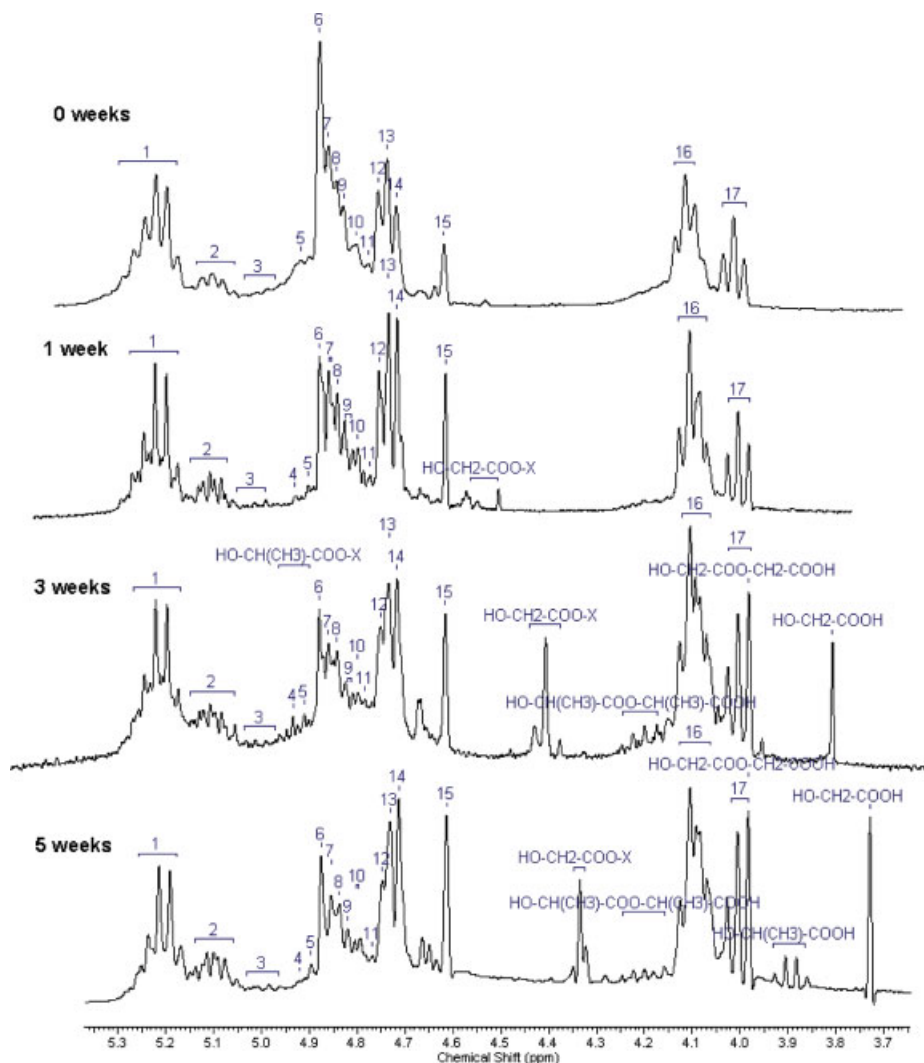
Figure 5 ^{1}HNMR spectra of Cop5 after 0, 1, 3, and 5 weeks of degradation. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

nal (10) decreases or even disappears during degradation, and this suggests that lactyl units present no protecting effect.

The compositional changes of the terpolymers were also followed with NMR. For Cop1 and Cop5 terpolymers initially containing equivalent GG, LL, and C units, a decrease in the lactidyl and glycolidyl contents and an increase in the caproyl contents are observed during degradation, the glycolidyl content decreasing more than the lactidyl content (Fig. 6). This confirms the fact that in the case of amorphous copolymers, the caproyl component is the most resistant to degradation and the glycolyl component is the least resistant. The content of glycolidyl units is low (0.16 mol %) for Cop2 and Cop6 before degradation. No decrease in the glycolidyl content is observed during degradation because glycolyl units are present mainly in XGX segments, which are resistant to degradation (Fig. 7). A slow decrease in

the lactidyl content is observed with a slow increase in the caproyl content.

In the case of Cop3 with a high glycolidyl content (>60 mol %), an increase in the glycolidyl content is observed during degradation (Fig. 8), and this can be assigned to crystallization of glycolyl units as shown in the following. Lactyl and caproyl units are present in mixed sequences that are easily degraded. The content of lactyl units constantly decreases, and after 13 weeks of degradation, lactyl units are almost completely removed from the degrading material. The content of caproyl units increases in the first 5 weeks because of a strong decrease in the lactidyl content followed by a decrease. Cop4 initially contains high lactidyl units in terpolymer chains (ca. 60 mol %). The GG, LL, and C contents remain almost unchanged during degradation (data not shown). This finding can be assigned to the fact that G—L, G—C, and L—C mixed segments degrade faster

TABLE II
Chemical Shifts of the Terpolymer Sequences in the ¹H-NMR
Spectra (with DMSO as a Solvent)

No.	Sequence[a]	δ (ppm)
1	LLLLL + LLLLC + LLLLG + CLLLL + GLLLL	5.20
2	CLLLL + GLLLL + LLLLC + LLLLG + CLLC + GLLG	5.10
3	CLC + XGLGX	5.00
4	GLGGG	4.94
5	GLGGL	4.92
6	GGGGG	4.88
7	CGGGG + GGGGC + LLGGL + LGGLL	4.86
8	GGGGL + LGGGG	4.85
9	CGGGC + LLGGG + GGGLL	4.84
10	XLGLX	4.81
11	GGGLG	4.78
12	GGGGC + LGGGL + LGGLG	4.76
13	CGGGG + CGGGC	4.74
14	CGGC	4.72
15	XCGCX	4.62
16	GC + LC	4.13
17	CC	4.03

[a] X is any unit (G, L, or C).

than alternating CGC segments and that longer lactyl sequences in ordered domains are resistant to degradation. As a result, the contents of all monomeric units remain stable. Such stable compositions are also detected in the case of a high content of caproyl units (>60 mol %) in terpolymer chains (data not shown), and this can be assigned to the protecting effect of caproyl units on the neighboring glycolyl and lactyl units.

Thermal properties

The thermal properties of the various terpolymers were monitored by DSC. Two runs were realized for each sample: after the first heating at 10°C/min, the molten sample was quenched in liquid nitrogen, and a second run was immediately performed. The first run allowed us to evaluate T_m and melting enthalpy (ΔH_m) values of the polymers, whereas the second run was used to detect the glass-transition temperature (T_g) and cold crystallization.

Figure 9 shows the DSC curves of Cop3 after 0, 7, and 13 weeks of degradation. Containing 62.4% GG units, Cop3 initially appears semicrystalline, with T_m = 200.6°C and ΔH_m = 25.2 J/g. After quenching, T_g is detected at 12°C, followed by cold crystallization and melting. After 7 weeks, T_m decreases to 190.0°C, but ΔH_m increases to 55.1 J/g. The second heating exhibits T_g at 21.1°C and very weak cold crystallization and melting. T_m remains at 190.9°C after 13 weeks, but ΔH_m continues to increase and reaches 85.4 J/g. At the second heating, T_g further increases to 25.9°C, with strong cold crystallization and melting. The T_m decrease during degradation can be assigned to an MW decrease, and the ΔH_m increase can be attributed to the preferential degradation of
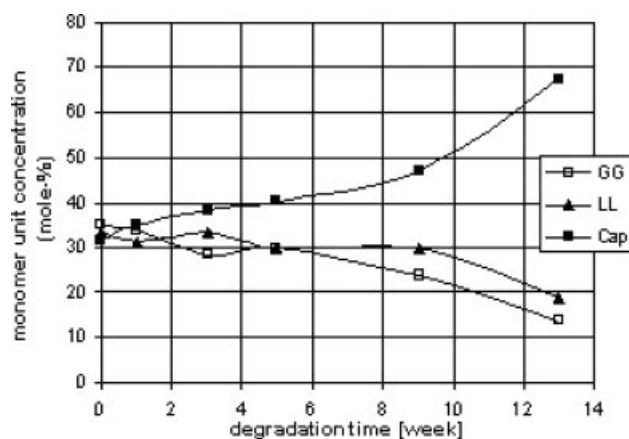

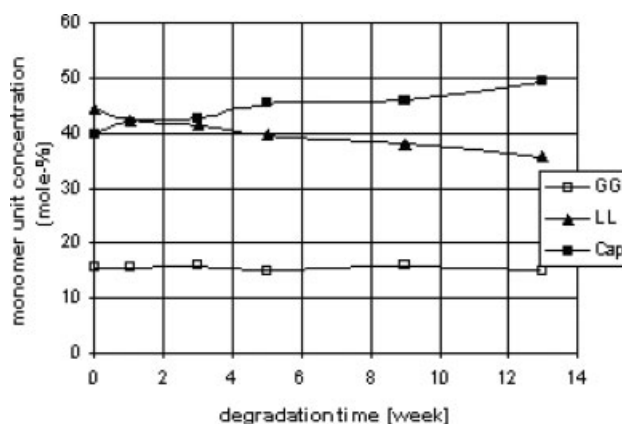**Figure 6** Changes in the monomer unit contents of the Cop5 terpolymer during degradation.

Figure 7 Changes in the monomer unit contents of the Cop2 terpolymer during degradation.
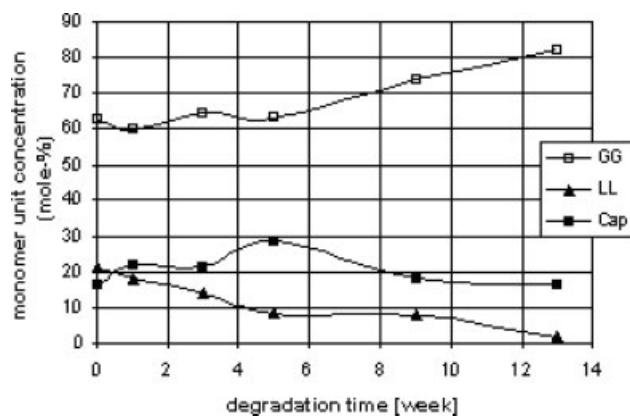
Figure 8 Changes in the monomer unit contents of the Cop3 terpolymer during degradation.

amorphous regions and degradation-induced crystallization. The T_g increase despite the MW decrease may be related to the changes of the chain microstructure, that is, enrichment in GG units (from 62.4 to 82.0%) and increase in L_{GG} (from 3.40 to 6.15).

Cop1 exhibits initially only a T_g at 12.6°C because of its highly random chain structure with equivalent contents of GG, LL, and C components (Table III). T_g decreases to 5.0 and -10.0°C after 7 and 13 weeks because of the MW decrease and enrichment in C units (from 25.2 to 49.7%). No crystallinity is detected despite the increase in the C content. A similar T_g decrease is obtained for Cop5. However, a T_m is detected at 39.9°C after 13 weeks, which can be assigned to the degradation-induced crystallization of C units, whose content largely increases from 31.5 to 67.4%.

A T_g decrease is also observed for Cop2 and Cop6. Degradation-induced crystallization occurs at 13 weeks for Cop2 and at 7 weeks for Cop6, in agreement with the fact that the Zr(Acac)$_4$-initiated terpolymer (Cop2) presents more random chain structure because of more transesterification.

Cop4 with 60.4% LL content is initially intrinsically amorphous, with $T_g = 16$°C. No major changes in T_g are detected during degradation. In contrast, the appearance of crystallinity is observed beyond 7 weeks because of the degradation-induced crystallization of LL units. Similarly, T_g of initially amorphous Cop7 remains almost unchanged. T_m is detected at 7 weeks at 35.9°C, which increases to 42.7°C at 13 weeks because of crystallization of C units, whose content increases from 64.9 to 68.8% during degradation.

In the literature, the degradation of aliphatic polyesters has been extensively investigated. Degradation involves many diffusion-reaction phenomena, including water absorption, ester hydrolysis, diffusion, and solubilization of soluble species.[1,3] In the case of large-size devices, ester cleavage is autocatalyzed by carboxylic acid end groups initially present or generated by hydrolytic degradation. Pitt[14] showed that the mechanism of *in vivo* degradation of PCL, PLA, and their random copolymers was qualitatively the same. The degradation rates of random copolymers was much higher than those of the homopolymers under the same conditions. However, attention has rarely been paid to the hydrolytic degradation of PGLC terpolymers. Sawhney and Hubbell[19] studied a series of terpolymers of glycolide, DL-lactide, and ε-caprolactone. They found that 60/30/10 PGLC remained amorphous and exhibited a half-life time of 17 days, whereas 62.4/21.2/16.4 PGLC (Cop3) in this work crystallized and lost 54% of its weight after 13 weeks. The difference might be due to the presence of DL-lactide, which decreased the chain regularity of terpolymers in Sawhney and Hubbell's work. Cai et al.[20] also reported the synthesis and degradation of PGLC terpolymers synthesized with Sn(Oct)$_2$ as the catalyst. No compositional or morphological changes were reported. Therefore, this work allowed us to elucidate the different degradation behaviors of terpolymers initiated by Zr(Acac)$_4$ or Sn(Oct)$_2$.

CONCLUSIONS

Various poly(glycolide-*co*-L-lactide-*co*-caprolactone)s have been obtained through the ring-opening polymerization of glycolide, L-lactide, and ε-caprolactone with Zr(Acac)$_4$ or Sn(Oct)$_2$ as the catalyst. Different chain microstructures have been obtained, Sn(Oct)$_2$ leading to less transesterification of polymer chains than Zr(Acac)$_4$ under similar conditions. The degradation rate depends on both the copolymer composi-
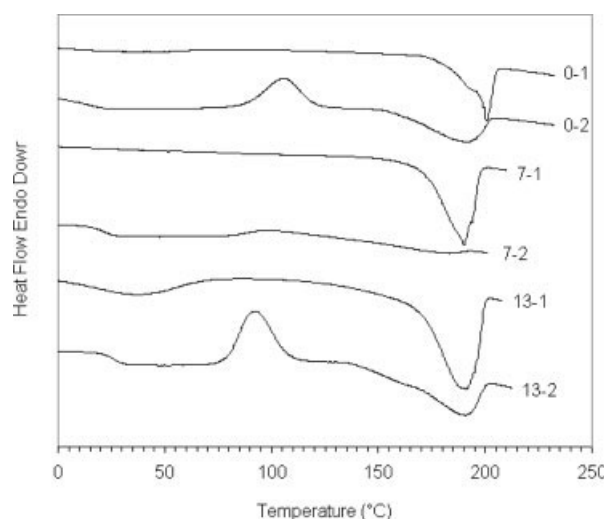

Figure 9 DSC thermograms of Cop3 after 0, 7, and 13 weeks of degradation: (1) first heating and (2) second heating.

TABLE III
Chemical Shifts of Monomeric and Dimeric Hydroxyacids in the ^{1}H-NMR Spectra (with DMSO-d_6 as a Solvent)

Time (weeks)	T_g (°C)[a]						
	Cop1	Cop2	Cop3	Cop4	Cop5	Cop6	Cop7
0	12.6	6.9	12.0	16	−2.4	7.0	−29.6
7	5.0	−1.0	21.1	18	−8.0	−6	−26.4
13	−10	−15	25.8	13.8	−17.9	−11	−30.7

Time (weeks)	T_m (°C)/ΔH_m (J/g)[b]						
	Cop1	Cop2	Cop3	Cop4	Cop5	Cop6	Cop7
0	—	—	200.6/25.2	—	—	—	—
7	—	—	190.0/55.2	79.3/10.7	—	32.8/3.2	35.9/4.2
13	—	35.9/11.3	190.9/85.4	89.3/15.3	39.9/28.2	40.1/8.3	42.7/10.0

[a] Determined from the second run at a heating rate of 10°C/min.
[b] Determined from the first run after quenching in liquid nitrogen.

tion and the chain microstructure. Sn(Oct)$_2$-initiated copolymers degrade less rapidly than Zr(Acac)$_4$-initiated ones with more random chain structures. Caproyl units appear the most resistant to degradation and exhibit a protecting effect on neighboring lactyl or glycolyl units. The glycolyl content exhibits different features: it decreases because of faster degradation of glycolyl units, which are more hydrophilic than caproyl and lactyl ones, remains stable in the case of abundant C—G—C sequences, which are very resistant to degradation, or even increases because of the formation of PGA crystallites. Crystallization can be detected during degradation if the block length of one of the components is sufficiently long, even though the terpolymers are amorphous initially. The terpolymers exhibit T_g's below 37°C, that is, in the range of −30 to 21°C, depending on the composition. It is concluded that these low-T_g terpolymers are of great interest for biomedical applications, especially in the field of controlled drug delivery.

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