

# Synthesis, Characterization, and Degradation of Block Polyesteramides Containing Poly(L-Lactide) Segments

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## SYNOPSIS

Random multiblock polyesteramides (PEAs) having polyester (PE) content of 20–50 wt % have been prepared by low-temperature polycondensation using sebacyl chloride, 1,6-diaminohexane, and telechelic oligomers of L-lactide with  $M_n = 600$ –1500. The PEAs were characterized by IR and <sup>1</sup>H-NMR spectroscopy, wide-angle X-ray diffraction, and thermal analysis. Only the polyamide segments are able to crystallize, and the crystallinity depends on the composition and architecture of the PEAs. From viscosity and IR measurements it was established that the chain degradation of PEA powders or films suspended in buffer solutions occurs by hydrolysis of the ester linkages. The degradation rate is influenced by pH, PE content, and, to a lesser extent, by crystallinity. © 1992 John Wiley & Sons, Inc.

## INTRODUCTION

In recent years considerable attention has been devoted to biodegradable synthetic polymers for use in medicine as sutures, temporary implants, and drug delivery devices.<sup>1–3</sup> The most extensively investigated biodegradable polymers are derived from lactic, glycolic, and hydroxybutyric acids and  $\alpha$  amino acids. Copolymers of glycolide and lactide with different compositions also have been extensively investigated.<sup>4–6</sup> The biodegradability of synthetic absorbable sutures based on poly( $\alpha$ -hydroxyacids) and related copolymers has been tested *in vitro* under simulated biological conditions and in the human body.<sup>7–9</sup>

Block copolymers, designed for specific use in medicine to fulfill special requirements of durability in the human body, can be prepared by inserting degradable segments into the chain of widely used biocompatible polymers. Of these, polyamides are somewhat resistant to hydrolysis at the pH values

present in the human body. Their degradability may, however, be improved by inserting polyester segments into the chain, giving rise to random multiblock polyesteramides that will also have chemical and physical properties different from those of the polyamide homopolymer. The introduction of the ester segments may, in fact, reduce the crystallinity of the polyamide according to their size and concentration. The presence of hydrolytically cleavable ester bonds and the potential lowering of the crystallinity degree make the polyesteramides promising materials for use in medicine. Aliphatic block polyesteramides, obtained by melt mixing of the corresponding homopolymers have been previously investigated by Tokiwa et al.<sup>10</sup>

In the present study we report on the preparation and chemical and thermal characterization of random multiblock polyesteramides with poly(L-lactide) (PLA) blocks as hydrolytically degradable segments. Also a preliminary investigation of the *in vitro* degradation process has been carried out in buffer solutions, and the results will be related to the structure of the copolymers. The preparation and characterization of the PLA oligomers has been reported elsewhere.<sup>11</sup>

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## EXPERIMENTAL

### Materials

The solvents were purified by standard methods. 1,6-Diaminohexane was crystallized from anhydrous toluene. Sebacyl chloride was distilled *in vacuo* before use.

Three buffer solutions (0.5 M) were prepared for the degradation studies: (1) NaH<sub>2</sub>PO<sub>4</sub>/Na<sub>2</sub>HPO<sub>4</sub>, pH = 6.0; (2) NaH<sub>2</sub>PO<sub>4</sub>/Na<sub>2</sub>HPO<sub>4</sub>, pH = 7.0; (3) Tris/Tris HCl, pH = 8.0 (TRIS = 2-amino-2-hydroxymethyl-1,3-propanediol).

The L-lactide oligomers having —OH end groups (PLAOH) were prepared and characterized as reported.<sup>11</sup> Their  $\bar{M}_n$  were 540 or 620 (PLAOH-600), 1020 (PLAOH-1000), and 1550 (PLAOH-1500).

### Techniques

The IR spectra were recorded on thin films, obtained by slow evaporation of chloroform–formic acid solutions of the polymers, using a Perkin-Elmer 680 or a Bruker IFS-66 FTIR instrument. The <sup>1</sup>H-NMR spectra were obtained at room temperature using a Bruker AC-270 spectrometer, operating at 270 MHz, with solutions of the polymers in CDCl<sub>3</sub> containing a few drops of DCOOD. TMS was the internal standard.

The X-ray powder patterns were obtained in the reflection mode using an automatic Philips diffractometer with Ni-filtered CuK<sub>α</sub> radiation. The thermal analysis was performed on 6–10 mg of sample

using a Mettler TA-300 differential scanning calorimeter with a heating rate of 10°C/min. The inherent viscosities were obtained at 25.0 ± 0.05°C in *m*-cresol (*c* = 0.5 g/dL) using a Canon-Ubbelohde viscosimeter.

### Typical Synthesis of a Polyesteramide

A solution of PLAOH-540, 3.35 g (6.2 mmol) in 8 mL of anhydrous chloroform was added dropwise under nitrogen to a stirred solution of sebacyl chloride, 4.78 g (20.0 mmol) in 10 mL of CHCl<sub>3</sub>. The reaction mixture was heated at 60°C for ≈ 1 h until the HCl evolution ceased. After cooling to room temperature, the solution was flushed with nitrogen, diluted with 20 mL of CHCl<sub>3</sub>, and added to an ice-cooled solution of 1,6-diaminohexane, 1.60 g (13.8 mmol), and NaOH, 1.16 g (29.0 mmol), in 250 mL of water, under high-speed stirring in a blender. After 5 min the precipitate was collected on a glass filter, repeatedly washed with water in the blender, and dried in a vacuum oven at 50°C for 48 h. The product was extracted with boiling benzene for 8 h and dried to give 7.33 g of copolymer C-600 (see Table I), 89% yield.

### Determination of the Average Length of Polyamide Blocks

About 0.5 g of copolymer were fully hydrolyzed according to the method of Ref. 10. The absence of ester groups in the recovered polyamidic blocks was

**Table I** Synthesis and Characterization of Multiblock Polyesteramides and Polyamide 6,10

Code	$\bar{M}_n$ of PLAOH <sup>a</sup>	Yield (%)	$\eta_{in}^b$ (dL/g)	Elemental Analysis			Composition <sup>c</sup>		$\bar{M}_n$ of PA <sup>d</sup>	
				C	H	N	Calcd.	Found	Calcd.	Found
A-600	620	85	1.07	63.94	9.58	6.92	23	28	1600	2300
B-600	620	85	1.40	62.07	9.12	5.80	34	39	1000	1300
C-600	540	89	1.41	60.62	8.40	4.25	47	52	500	—
A-1000	1020	84	1.94	63.44	9.09	6.85	22	28	2600	3700
B-1000	1020	93	1.19	61.95	9.19	5.63	38	38	1700	1800
C-1000	1020	86	1.18	59.08	8.30	4.72	47	53	900	1300
A-1500	1550	83	0.98	64.35	8.89	6.91	21	25	4600	4000
B-1500	1550	84	2.07	62.25	8.75	6.07	37	36	2800	3400
C-1500	1550	84	1.39	59.87	8.21	4.78	47	49	1600	2100
PA-6,10	—	86	1.50	—	—	—	—	—	—	—

<sup>a</sup> Number-average molecular weight of the PLAOH oligomers used.

<sup>b</sup> Inherent viscosity in *m*-cresol at 25°C, *c* = 0.5 g/dL.

<sup>c</sup> wt % of PLA as calculated from the reactant molar ratio and as found from elemental analysis.

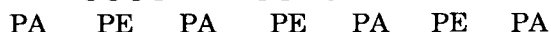
<sup>d</sup> Number-average molecular weight of PA blocks calculated from composition and found by —COOH end-group titration after complete hydrolysis.

checked by IR spectroscopy. The  $\bar{M}_n$  after hydrolysis was determined by potentiometric titration of the carboxyl end groups according to the method of Waltz and Taylor.<sup>12</sup>

## RESULTS AND DISCUSSION

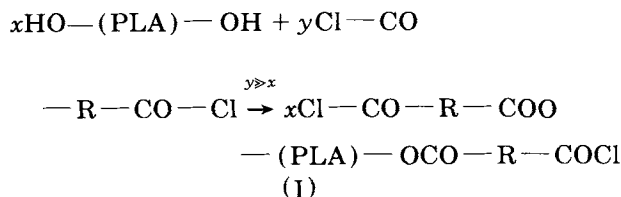
### Synthesis

The investigated multiblock polyestaramides (PEA) can be schematically represented as follows:

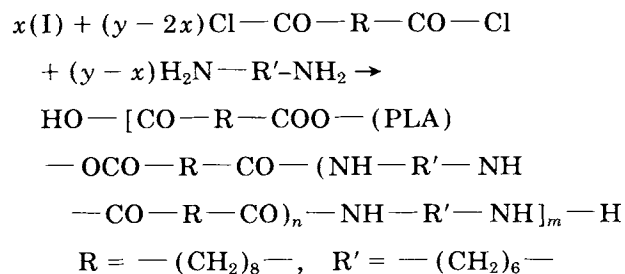


where PA and PE indicate polyamide and polyester segments, respectively. The preformed polyester segments used in the synthesis of multiblock PEA derive from telechelic oligomers of PLA having hydroxyl chain ends and  $\bar{M}_n$  in the range 600–1500 (PLAOH).<sup>11</sup> Their use was suggested by the well-known biodegradability of PLA, which is widely used in medicine as absorbable material. The copolymers were obtained according to the two-step procedure described in the following reaction scheme:

Step 1:



Step 2:



First, the PLAOH oligomers were refunctionalized by reaction with an excess of sebacyl chloride. The reaction mixture, as obtained in step 1, was subsequently reacted in step 2 with the stoichiometric amount of 1,6-diaminohexane according to low-temperature interfacial polycondensation. The expected copolymer architecture is the random multiblock type, if the acid chloride and the inter-

mediate (I) have similar reactivity toward the diamine. The composition depends on the molar ratio of the reactants in step 1 and on the  $\bar{M}_n$  of the used PLA—OH. Polyestaramides containing 23–53 wt % of PE have been prepared using three PLAOH oligomers having  $\bar{M}_n$  of about 600, 1000, and 1500. The preparation of the copolymers is summarized in Table I together with some chemical characterization data. The A, B, and C capital letters in the polymer code indicate an increasing content of PE in the copolymer: A = 25%, B = 35%, C = 50%. The effective compositions were determined by elemental analysis and are close to the target values.

Changes in composition and chemical structure represent a valuable method of tailoring properties such as degradability and biocompatibility, which are relevant in biomedical applications. The average length of the PA blocks built up in step 2 is determined by the copolymer composition and by the  $\bar{M}_n$  of PLA segments and was determined by titration of the —COOH end groups of the PA segments after the complete cleavage of the ester bonds of the PEAs by means of exhaustive hydrolysis in concentrated alcoholic potassium hydroxide. The found values are in good agreement with those calculated on the basis of composition and size of PLA segments.

The prepared polymers are soluble in the typical solvents for polyamides such as *m*-cresol, formic acid, and mixtures of these solvents with chloroform. The inherent viscosity values, which are in the range 1.0–2.0 dL/g, indicate a rather high polymerization degree, close to that found for a polyamide 6,10 comparison sample prepared under the same reaction conditions. The IR spectra of copolymer films show the absorptions expected for the hydrogen-bonded secondary amide group (3306, 1637, and 1541  $\text{cm}^{-1}$ ) and for the ester group (1756, 1190, and 1097  $\text{cm}^{-1}$ ). The relative intensities of the two groups of bands are related to the composition of the investigated PEAs.

The composition and sequence length have also been determined by <sup>1</sup>H-NMR analysis. The 270-MHz spectrum of C-600 is shown in Figure 1 as an example. The resonance assignment was made on the basis of literature data for PLAOH oligomers<sup>11</sup> and for aliphatic polyamides,<sup>13</sup> and by comparing the relative intensities of the resonances of copolymers with different composition and structure. The blocklike structure of the copolymers was confirmed by the presence of two distinct resonances,  $\alpha_1$  and  $\alpha_2$ , for the —CH<sub>2</sub>—CO— protons of the sebacyl acid units. The higher field  $\alpha_2$  resonance was attributed to methylene groups adjacent to amide bonds

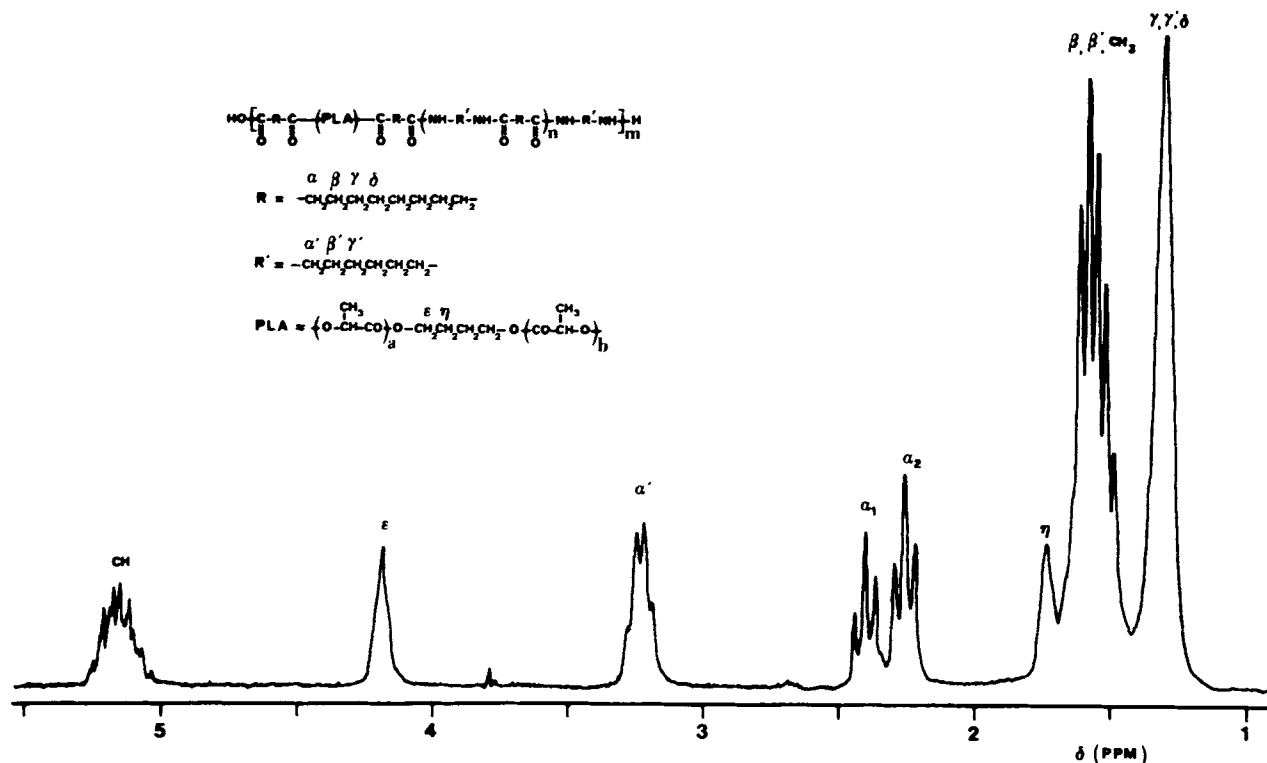


Figure 1  $^1\text{H-NMR}$  spectrum at 270 MHz of C-600 copolymer ( $\text{CDCl}_3/\text{DCOOD}$ ,  $25^\circ\text{C}$ ).

and therefore inserted in PA blocks, while the lower field  $\alpha_1$  resonance was attributed to  $\text{---CH}_2\text{---}$  groups adjacent to ester bonds and therefore belonging to acid units linking two heterotype blocks. The ratio of the integrated  $\alpha_2$ ,  $\alpha_1$  peaks represents the average number of repeat units,  $n$ , of the PA

blocks. In the case of copolymers having short PA and PE segments, the average sequence lengths as obtained by NMR analysis are fairly accurate and are in good agreement with those found by end-group titration after alkaline hydrolysis. The compositions obtained by comparing the integration of PLA  $\text{CH}$

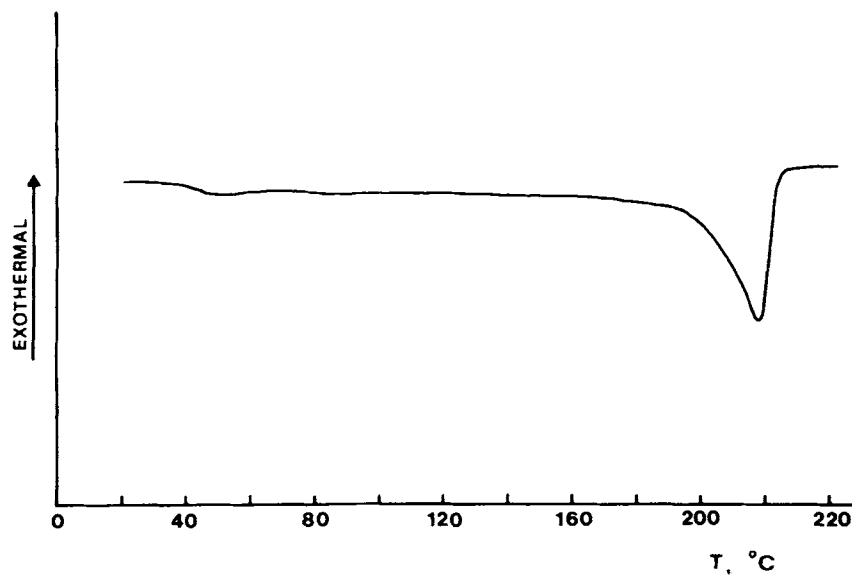


Figure 2 DSC thermogram of A-1000 copolymer.

**Table II Thermal Data for Multiblock Polyesteramides and Polyamide 6,10**

Code	PLA (wt %)	$\bar{M}_n$ of PA <sup>a</sup>	$T_m$ (°C)	$\Delta H_m$ <sup>b</sup> (J/g)
A-600	28	2300	213	36 (50)
B-600	39	1300	219	20 (33)
C-600	52	—	210–216	5 (10)
A-1000	28	3700	218	39 (54)
B-1000	38	1800	219	22 (35)
C-1000	53	1300	217	18 (38)
A-1500	25	4000	218	42 (56)
B-1500	36	3400	218	32 (50)
C-1500	49	2100	215	23 (45)
PA-6,10	—	—	220	58

<sup>a</sup> Number-average molecular weight of PA blocks as determined by —COOH end-group titration after complete hydrolysis.

<sup>b</sup> Apparent melting enthalpy; the values in the brackets are corrected for the PA content.

resonance with those of the  $\alpha_1$ ,  $\alpha_2$  and  $\alpha'$  resonances confirmed the results of elemental analysis.

### Thermal Analysis

Thermodynamic parameters such as melting temperature,  $T_m$ , glass transition temperature,  $T_g$ , and apparent heat of fusion,  $\Delta H_m$ , were determined by thermal analysis for all the prepared polyesteramides. Figure 2 shows a typical differential scanning calorimetry (DSC) thermogram obtained on the A-1000 sample. The temperature of the first-order transition, 218°C, is very close to the  $T_m$  of PA-6,10 (220°C), and this transition was therefore attributed to the melting of the polyamide segments. The broad second-order transition, which falls in the range 30–60°C, is likely due to the overlapping of the glass transitions of PLA (57°C) and PA-6,10 (40°C). The DSC thermograms, therefore, could not show the expected biphasic nature of the amorphous component. Similar thermograms were obtained for all the PEAs. A small and very broad first-order transition due to the PE segments was observed only in the thermogram of C-1500. The thermal data are collected in Table II. The  $\Delta H_m$  values were also calculated taking into account the effective polyamide content in the copolymer. The corrected enthalpies,  $\Delta H_m$ , may be taken as a measure of crystallinity of the PA component. The results show that the melting temperatures are lower than that of PA-6,10 and that clear relations between  $T_m$  and copolymer architecture cannot be found, whereas the  $\Delta H_m$  values depend on the composition and show a similar trend within the three series A, B, and C. The heat of

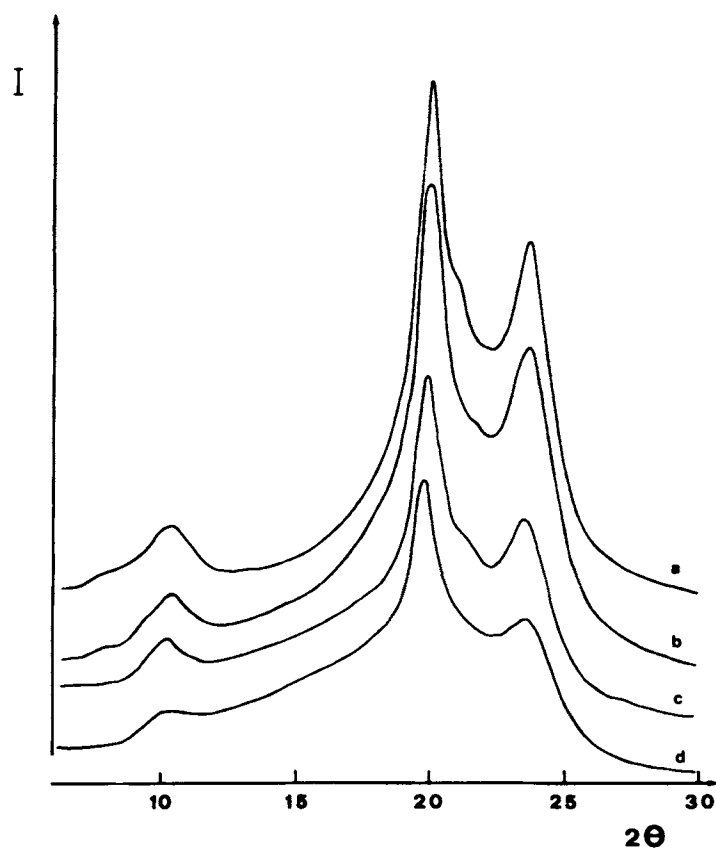
fusion decreases as the PA content decreases and, at the same composition, is lower in the presence of short PLA segments. This result can be reasonably interpreted considering that only the PA component is responsible for the crystallinity and that the critical parameter for ordering in the PA phase will be the average length of PA blocks, which depends on composition and PLA segment length (see Table I).

Further support to this view is provided by comparing the wide angle X-ray diffraction spectra of the copolymers with that of PA-6,10. Representative diffraction patterns for the 600 series are shown in Figure 3. The two strongest reflections of the  $\alpha$  form of PA-6,10 at 24.0 and 20.2 of  $2\theta$  are also found in the spectra of the copolymers. A small shift toward lower values of  $2\theta$  and a strong enhancement of the amorphous halo are easily observed for the PEA samples. Overall crystallinity decreases with an increase in the polyester content, in agreement with the DSC results.

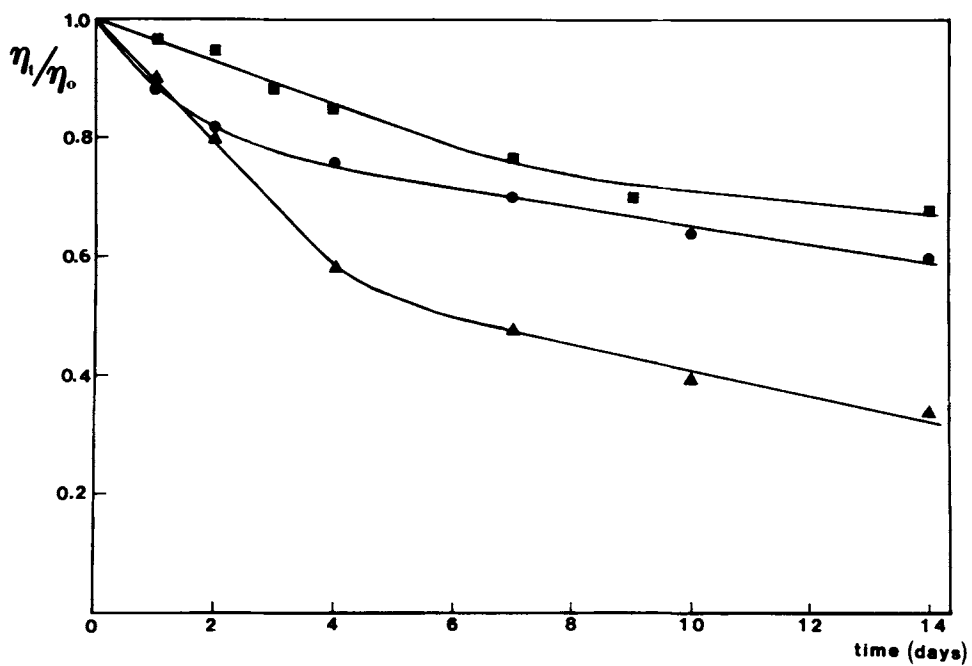
### Degradation of Polyesteramides

Finely powdered samples of A, B, and C series were suspended under stirring at 37°C in a buffer solution for several days, and the amount of degradation was evaluated by determining their inherent viscosity after fixed reaction times. A preliminary investigation on the influence of pH on the degradation rate was performed on the powdered C-1500 copolymer. The results are shown in Figure 4 where the lowering of viscosity as a function of time is reported for three pH values, 6.0, 7.0, and 8.0. The accelerated degradation observed at pH = 8, and to a lesser extent at pH = 6, should be related to a chain scission due to hydrolysis of ester bonds, catalyzed by both base and acid as for monomeric esters. This result is in agreement with those reported by Chu on the degradation of poly(glycolide-lactide) copolymers.<sup>14</sup>

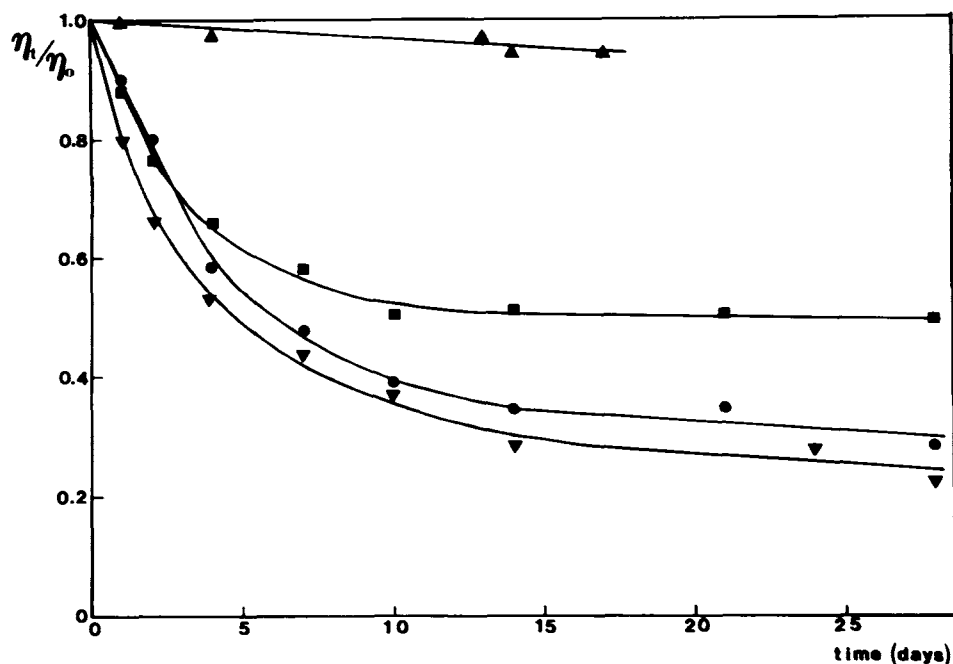
The degradation studies were thereafter performed at pH = 8.0 in order to reduce the time required for significant degradation. The time dependence of the viscosity is shown in Figure 5 for A-600, C-600, and C-1500 copolymers and for a PA-6,10 sample. A very small lowering of the viscosity is observed for the polyamide while a noticeable degradation occurs for the PEAs. The viscosity drop of the copolymers is more relevant during the first week (see also Fig. 4). This feature is not necessarily related to different degradation rates as the cleavage of one ester bond according to (a) or (b) has a different effect on the molecular weight, and consequently on the viscosity:



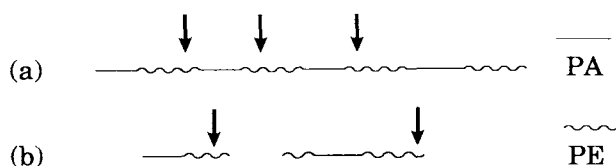
**Figure 3** Wide angle X-ray diffraction patterns of (a) PA-6,10, (b) A-600, (c) B-600, and (d) C-600 copolymers.



**Figure 4** Influence of pH on the degradation rate of C-1500 copolymer: (■) pH = 7.0, (●) pH = 6.0, (▲) pH = 8.0;  $\eta_t$  and  $\eta_0$  are the inherent viscosity values after and before hydrolysis.



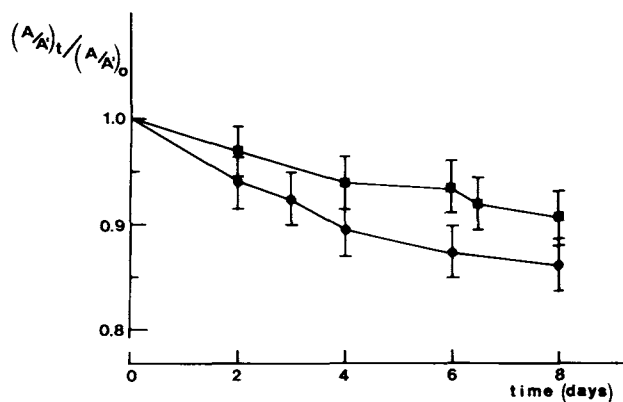
**Figure 5** Effect of the degradation time on the inherent viscosity for ( $\blacktriangle$ ) PA-6,10 and ( $\blacksquare$ ) A-600, ( $\bullet$ ) C-1500 and ( $\blacktriangledown$ ) C-600 copolymers;  $\eta_t$  and  $\eta_0$  are the inherent viscosity values after and before hydrolysis.



At the early stages of the chain degradation the hydrolytic attack will likely occur according to (a) while, increasing the extent of degradation, the bond cleavage will also occur on smaller fragments as in (b) giving rise to soluble small oligomers or lactic acid monomer. In the latter case the effect on molecular weight is much less important than in case (a). Analysis of the  $^1\text{H-NMR}$  spectra of powdered C-600 samples recovered after hydrolysis showed that the composition is unaffected after a few days, whereas for longer degradation times a gradual lowering of the PE content occurs. After 50 days, in fact, the polyester content was reduced to 43% against the 52% of the starting copolymer. This finding is in agreement with the proposed degradation pathways (a) and (b) and is also an additional indication that chain ruptures occur only through the cleavage of ester bonds. Figure 5 also shows that the A-600 copolymer is more resistant to hydrolysis than C-600 and C-1500, suggesting that the degradation rate mainly depends on the ester-

amide molar ratio. Crystallinity of the PA component and length of PE and PA blocks appear to have little influence on the degradation as the C-600 and C-1500 show a similar behavior.

Degradation was also followed by analysis of the IR spectra of thin films of C-600 and C-1500 hydrolyzed at pH 8 for 0–8 days. Upon hydrolysis, a de-



**Figure 6** Dependence of the  $(A/A')_t / (A/A')_0$  ratio on the degradation time for ( $\bullet$ ) C-600 and ( $\blacksquare$ ) C-1500 copolymers;  $A$  and  $A'$  are the integrated intensities of the  $1756\text{ cm}^{-1}$  and  $1637\text{ cm}^{-1}$  absorptions, respectively, in the FTIR spectra of the copolymers after ( $t$ ) and before (0) hydrolysis.

crease in the relative intensities of the bands attributed to the ester group was observed. The degree of hydrolysis was determined according to the ratio of the integrated intensity of the C=O stretching of the ester bond at  $1756\text{ cm}^{-1}$  to that of the C=O stretching of the amide bond at  $1637\text{ cm}^{-1}$ , using the spectra of the films before degradation as a reference. The IR results, reported in Figure 6, show that for both copolymers the degree of hydrolysis regularly decreases with an increase in the degradation time. Moreover, the above phenomenon is more marked in the case of C-600. The latter observation, together with the results reported in Figure 5, confirms that the hydrolysis of PEAs having the same composition is influenced, although to a small extent, by the size of the blocks. This finding can be reasonably ascribed to the lower overall crystallinities found for PEAs having smaller PA blocks.

## CONCLUSIONS

Multiblock polyesteramides with a wide range of compositions and segment sizes may be prepared using hydroxyl-terminated oligomers of L-lactide. Only the PA segments are able to crystallize, and the overall crystallinity depends on the COO/CONH molar ratio and on the average length of the PA blocks.

Degradation occurs by hydrolysis of the ester groups and is clearly influenced by the pH of the solution and by the PE content. A less significant effect of the copolymer architecture, and consequently of crystallinity, on the degradation rate is suggested by IR and viscosity techniques.

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