Hydrolytic Degradation of Poly(ester amides) Derived from Carbohydrates

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ABSTRACT: This paper describes the hydrolytic degradation of three stereoregular poly(ester amides) which were obtained by polycondensation reaction of 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-5-*O*-[(pentachlorophenoxy)succinyl]-L-arabinitol, 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-5-*O*-[(pentachlorophenoxy)glutaryl]-L-arabinitol, and 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-5-*O*-[(pentachlorophenoxy)succinyl]-D-xylitol hydrochlorides. The degradation study was carried out at 37 °C in bidistilled water and/or in buffered salt solution at pH 7.4, and was monitored by mass loss, GPC, SEM, and FAB-MS, IR, and NMR spectroscopies. The hydrolytic degradation of these poly(ester amides) occurs by hydrolysis of the ester linkages and is characterized by rapid rates of hydrolysis. The differences in degradation rates are ascribed to differences in crystallinity and hydrophilicity of the polymers. Our results show that the poly(ester amides) derived from succinic anhydride degrade to a final monomeric product in which a succinimide ring has been formed.

Introduction

Biodegradable polymers have been widely investigated both for the development of medical and pharmaceutical applications[1−3] and as part of the growing concern about environmental problems.[4]

Polyesters are one of the most important classes of biodegradable and hydrolyzable synthetic polymers. A series of α-hydroxy polyesters, such as poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and their copolymers with different compositions have been extensively investigated.[5−7] Other types of polyester, such as poly(caprolactone), poly(malic acid), poly(*β*-propiolactone), and poly(butyrolactone), can also be used as biodegradable polymers. Poly(hydroxyalkanoic acids) are produced by microorganisms, and certain bacteria can promote the polymers' environmental biodegradation. Polyanhydrides and polyorthoesters[8] are new families of biodegradable polymers.

Aliphatic polyamides have better mechanical properties than polyesters, but their rates of hydrolytic degradation at the pH values present in the human body are too slow to be considered as biodegradable synthetic polymers. The high number of hydrogen bonds and the high crystallinity of the polyamide structure are possible reasons for the inertness of these nylons to biodegradation. Their degradability may, however, be improved by inserting hydrolytically cleavable ester bonds into the chain, giving rise to poly(ester amides). The introduction of the ester linkages may reduce the crystallinity of the polyamide depending on their size and concentration. The presence of hydrolytically cleavable ester bonds and the potential lowering of the crystallinity degree make the poly(ester amides) promising materials for their use in medicine.

Very few studies on the degradation of poly(ester amides) have been reported so far. Feijen et al. have published the synthesis[9,10] and the *in vitro* degradation studies[11] of copolymers of morpholine-2,5-dione derivatives with D,L-lactic acid or *ϵ*-caprolactone, providing a series of biodegradable poly(ester amides) with a wide range of chemical and physical properties.

The biodegradation of aliphatic block poly(ester amides), obtained by melt mixing of the corresponding homopolymers, has been investigated by Tokiwa et al.[12,13] The synthesis and *in vivo* degradation of a series of alternating poly(ester amides) have been investigated by Barrows et al.[7,14]

Recently, Gonsalves et al.[15] have studied the hydrolytic degradation in buffer solution and the biodegradation by fungi of nonalternating poly(ester amides). Maglio et al.[16] have reported on the preparation, characterization, and *in vitro* degradation in buffer solutions of random multiblock poly(ester amides).

In the present study we report on the *in vitro* degradation of poly(ester amides) **PAS**, **PAG**, and **PXS** which have been prepared[17,18] by polycondensation reactions of 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-5-*O*-[(pentachlorophenoxy)succinyl]-L-arabinitol hydrochloride (**1**), 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-5-*O*-[(pentachlorophenoxy)glutaryl]-L-arabinitol hydrochloride (**2**), and 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-5-*O*-[(pentachlorophenoxy)succinyl]-D-xylitol hydrochloride (**3**), respectively.

Experimental Section

Measurements. Optical rotations were measured at 20 ± 5 °C with a Bellingham & Standley Inc., P20 polarimeter (5-cm cell). TLC was performed on silica gel 60 F254 (Merck) with detection by UV light, charring with sulfuric acid, and ninhydrin. Flash column chromatography was performed using Merck silica gel 60 (230−400 mesh). IR spectra (films or KBr disks) were recorded with a Michelson 100 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded with a Bruker 200 AC-P spectrometer. Chemical shifts are reported as parts per million downfield from tetramethylsilane. The following abbreviations are used to present the ^{1}H NMR spectra results: s = singlet, d = doublet, t = triplet, m = multiplet, and b = broad. Elemental analyses were determined in the Microanalysis Laboratories at the Universidad de Sevilla and the Universidad Complutense de Madrid. Gel permeation chromatography (GPC) analyses were carried out in a Waters apparatus fitted with a Waters Model 410 RI detector and a Millenium 2010 computerized data station. Two GPC columns were placed in series, and the analysis was performed in chloroform at a flow rate of 1 mL/min. Molecular weight studies were determined relative to polystyrene; calibration was done using 12 polystyrene samples of narrow molecular weight distribution. Water sorptions were mea-

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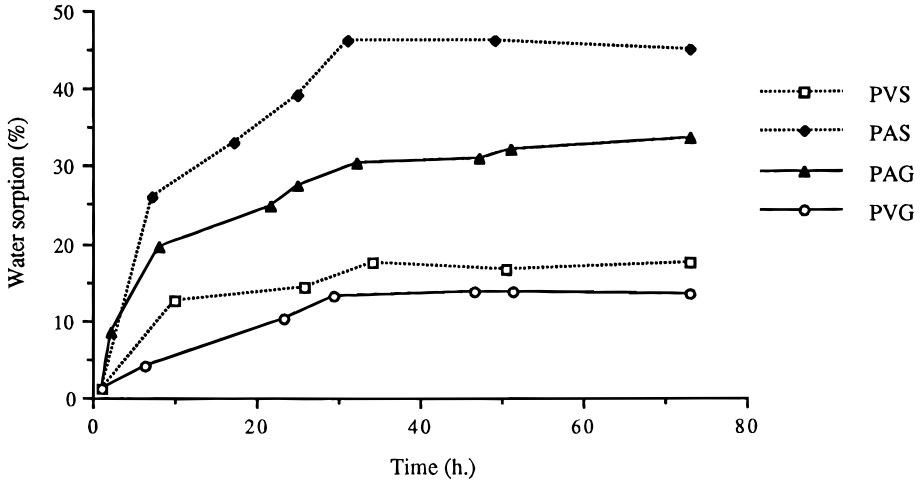


Figure 1. Moisture sorption of poly(ester amides) **PAS**, **PAG**, **PVS**,[18] and **PVG**[18] as a fuction of time at room temperature and under 100% relative humidity.

sured at 100% relative humidity by the method described by Mori.[16] A Philips XL-20 scanning electron microscope was used to examine the surface and the cross section of the films used in the degradation studies. The samples' surfaces were coated with a thin layer of gold for examination under the microscope. FAB-MS analyses were performed on a double-focusing Kratos MS 80RFA mass spectrometer equipped with the standard FAB source. Argon was used as the bombarding gas. Spectra were obtained using nitrobenzene−NaI as a matrix.

Polymerizations. Poly(ester amides) were synthesized by the active ester polycondensation method.[18]

Hydrolytic Degradation. Films of the different polymers were prepared by casting from a 3.6% solution of polymer in chloroform onto aluminum dishes. The solvent was allowed to evaporate slowly in air at room temperature and finally dried under reduced pressure. Subsequently, the films were cut into disks with a diameter of 12 mm, thickness of 150−190 μm, and weight of 16−25 mg. For the hydrolysis experiments, each disk was kept in a bottle filled to 3.0 mL with one of the following solutions: (a) bidistilled water; (b) 0.1 M Na_2HPO_4/NaH_2PO_4 buffer solution pH 7.4. The temperature selected for these experiments was 37 °C. After the immersion time, the specimens were recovered by filtration, rinsed with water, and dried to constant weight under reduced pressure. In the case of **PXS**, the degradation studies were performed in solution because this poly(ester amide) is water soluble.

1-Amino-1-deoxy-2,3,4-tri-*O*-methyl-L-arabinitol Hydrochloride (4). A solution of 1-(*tert*-butoxycarbonylamino)-1-deoxy-2,3,4-tri-*O*-methyl-L-arabinitol[17] (**5**) (0.21 g, 0.73 mmol) in dry ethyl acetate (3.0 mL) was added to a cooled 14% HCl solution in ethyl acetate (5.0 mL). After 30 min of stirring, a stream of nitrogen was bubbled into the solution. The resulting solid was filtered out and washed thoroughly with ethyl ether to give **4** (0.17 g, 100%): mp 129−130 °C; $[\alpha]_D$ - 69° (*c* 0.55, chloroform). IR: ν_{max} 3690−2611 (broad, NH_3^+, OH) cm^{-1}. NMR data (DMSO-d_6): ^1H δ 2.70−3.55 (m, 7H, H-1/5), 3.30, 3.34, 3.37 (3 s, 9H, 3 OCH_3), 4.53 (bs, 1H, OH), 8.15 (bs, 3H, NH); ^{13}C δ 39.75 (C-1), 56.90, 58.94, 59.49 (3 OCH_3), 58.50 (C-5), 77.60, 79.48, 80.85 (C-2/4). Anal. Calcd for $C_8H_{20}ClNO_4$: C, 40.55; H, 8.64; N, 5.91. Found: C, 40.44; H, 8.40; N, 5.73.

5-*O*-Acetyl-1-amino-1-deoxy-2,3,4-tri-*O*-methyl-L-arabinitol Hydrochloride (6). A solution of **5**[17] (0.23 g, 0.79 mmol) in dry ethyl acetate (3.0 mL) was added to a cooled 14% HCl solution in ethyl acetate (5.0 mL). After 48 h of stirring, a stream of nitrogen was bubbled into the solution. The resulting solid was filtered out and washed thoroughly with ethyl ether to give **6** (0.21 g, 100%): mp 131−132 °C; $[\alpha]_D$ - 69° (*c* 0.55, chloroform). NMR data ($CDCl_3$): ^1H δ 2.05 (s, 3H, CH_3CO), 3.35, 3.44, 3.51 (3 s, 9H, 3 OCH_3), 3.00−3.90 (m, 5H, H-1/4), 3.99 (dd, 1H, $J_{4,5a}$ = 3.5 Hz, $J_{5a,5b}$ = 11.8 Hz, H-5a), 4.50 (m, 1H, H-5b), 8.27 (bs, 3H, NH); ^{13}C δ 20.88 (CH_3CO), 40.07 (C-1), 57.80, 59.73, 60.51 (3OCH_3), 61.54 (C-5), 77.00, 78.39, 80.51 (C-2/4), 170.76 (CO). Anal. Calcd for $C_{10}H_{22}ClNO_5$: C, 44.20; H, 8.10; N, 5.15. Found: C, 44.02; H, 7.82; N, 5.25.

Methyl Pentachlorophenyl Succinate (7). To a solution of *mono*methyl succinate (1.0 g, 7.57 mmol) in dry ethyl acetate (4.0 mL) were added pentachlorophenol (2.0 g, 7.57 mmol) and dicyclohexylcarbodiimide (1.57 g, 7.57 mmol) . After 24 h of stirring, the solid formed was filtered out and washed with ethyl acetate. The filtrate and washings were combined, concentrated, and chromatographed (eluent 3:1 to 1:1 hexane/ether) to give **7** as a solid (2.7 g, 94%): mp 110−111 °C. IR: ν_{max} 1774, 1734 cm^{-1} (CO). NMR data (DMSO-d_6): ^1H δ 2.73 (m, 2H, CH_2), 3.03 (m, 2H, CH_2), 3.61 (s, 3H, OCH_3); ^{13}C δ 28.15, 28.25 (2 CH_2), 51.71 (OCH_3), 127.16, 130.73, 131.23, 143.73 (phenyl), 168.70, 171.72 (CO). Anal. Calcd for $C_{11}H_7Cl_5O_4$: C, 34.73; H, 1.85. Found: C, 34.68; H, 2.00.

Methyl 10-*O*-Acetyl-7,8,9-tri-*O*-methyl-4-oxo-5-azadecanoate (8). To a stirred suspension of **6** (0.32 g, 1.40 mmol) in dry dichloromethane (5.8 mL) was added ethyldiisopropylamine (EDPA, 0.25 mL). Once the hydrochloride dissolved, the solution was treated with methyl pentachlorophenyl succinate (**7**, 0.53 g, 1.40 mmol) in dry dichloromethane (3.0 mL). After 24 h of stirring, the solvents were evaporated and the residue chromatographed on a silica gel column (eluent: 30:1 to 10:1 dichloromethane/methanol) to give **8** as a solid (0.49 g, 100%): mp 67−68 °C; $[\alpha]_D$ −15° (*c* 2.4, chloroform). IR: ν_{max} 3332 (Amide A), 3077 (Amide B), 1740 (CO), 1657 (Amide I), 1544 cm^{-1} (Amide II) . NMR data ($CDCl_3$): ^1H δ 2.05 (s, 3H, CH_3CO), 2.45 (m, 2H, CH_2), 2.63 (m, 2H, CH_2), 3.15−3.35 (m, 2H, H-6a,8), 3.40−3.55 (m, 2H, H-7,9), 3.35, 3.40, 3.41, 3.63 (4s, 12H, 4 OCH_3), 3.71 (dt, 1H, $J_{6a,7} = J_{6b,7}$ = 6.0 Hz, $J_{6a,6b}$ = 14.0 Hz, H-6b), 4.00 (dd, 1H, $J_{9,10a}$ = 4.2 Hz, $J_{10a,10b}$ = 12.2 Hz, H-10a), 4.53 (dd, 1H, $J_{9,10b}$ = 2.6 Hz, H-10b), 6.14 (bt, 1H, NH); ^{13}C δ 20.88 (CH_3CO), 29.16, 30.84 (C-2,3), 39.45 (C-6), 51.73, 57.71, 58.56, 60.62 (4 OCH_3), 61.69 (C-10), 77.91, 78.31, 81.27 (C-7/9), 170.80, 171.50, 173.20 (CO). Anal. Calcd for $C_{15}H_{27}NO_8$: C, 51.56; H, 7.78; N, 4.00. Found: C, 51.57; H, 7.78; N, 3.87.

Results and Discussion

The following parameters were evaluated: (1) water absorption, (2) mass loss, (3) molecular weight loss and change in molecular weight distribution, (4) microscopic changes on the surface and cross section of the samples by scanning electron microscopy, and (5) spectroscopic analysis of the degradation products.

Water Sorption. The presence of three methoxy groups along the polymer backbone of these stereoregular poly(ester amides) will increase their hydrophilicities in comparison with their deoxylated analogs **PVS**

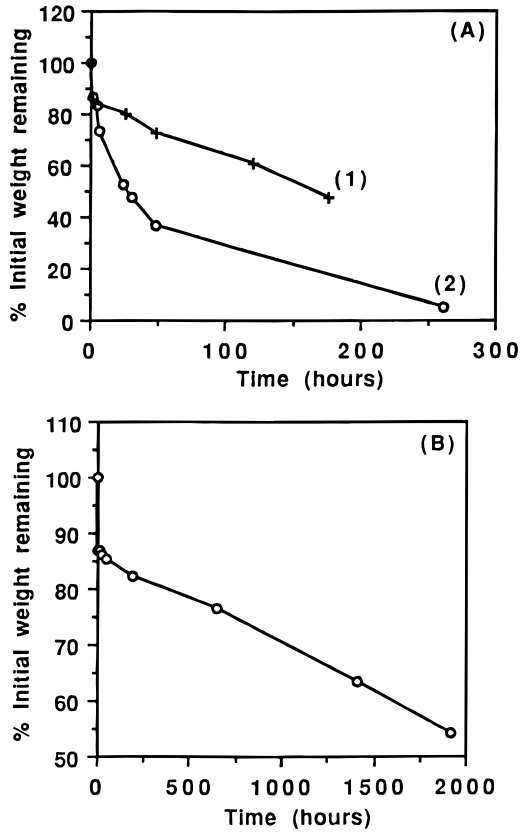


Figure 2. Initial weight remaining change vs time. (A) Degradation of poly(ester amide) **PAS** at 37 °C: in bidistilled water (1) and in buffer solution at pH 7.4 (2). (B) degradation of poly(ester amide) **PAG** at 37 °C in buffer solution at pH 7.4.

and **PVG**. In Figure 1, the moisture sorption determined at room temperature and under a relative humidity of 100% is shown for every sample. As anticipated, the water uptake increases with the density of hydrophilic methoxy groups in the polymer chain. Thus, **PAS** is more hydrophilic than poly(ester amide) **PAG**. The poly(ester amide) **PXS** is highly hydrophilic—being water soluble. This is assumed to be due to the low crystallinity of the sample.[18]

Hydrolytic Degradation. The hydrolytic degradation was followed by determination of the weight loss of the samples. Figure 2 shows the amount of degradation of **PAS** and **PAG** films as a function of immersion time at 37 °C in bidistilled water and/or buffer solution at pH 7.4. From this figure important differences in the hydrolytic behavior can be deduced. In all cases, the weight of the sample decreases continuously with time after the onset of the experiment. The data show that a fast mass loss took place immediately at the beginning of the experiment, and after this initial loss, the decrease in residual weight continued but at a slower rate. This initial mass loss was attibuted to the presence of residual solvent in the films (measured by TGA and estimated as 6−8%) and also to the exit into the medium of small molecules formed by polycondensation during the polymer preparation.

The data displayed in Figure 2 suggest that in buffer solution poly(ester amide) **PAS** degrades faster than **PAG** . Thus, poly(ester amide) **PAS** lost about 50% of its weight after 48 h of immersion, while poly(ester amide) **PAG** took about 80 days for the same decrease in residual weight. It could be concluded that the degradation rate is dependent on the number of methylenes between the two carbonyl groups of the anhydride residue; i.e., as the number of methylenes increases the degradation rate decreases. A similar effect has been observed in other polymers such as polyanhydrides[19] and polytartaramides.[20]

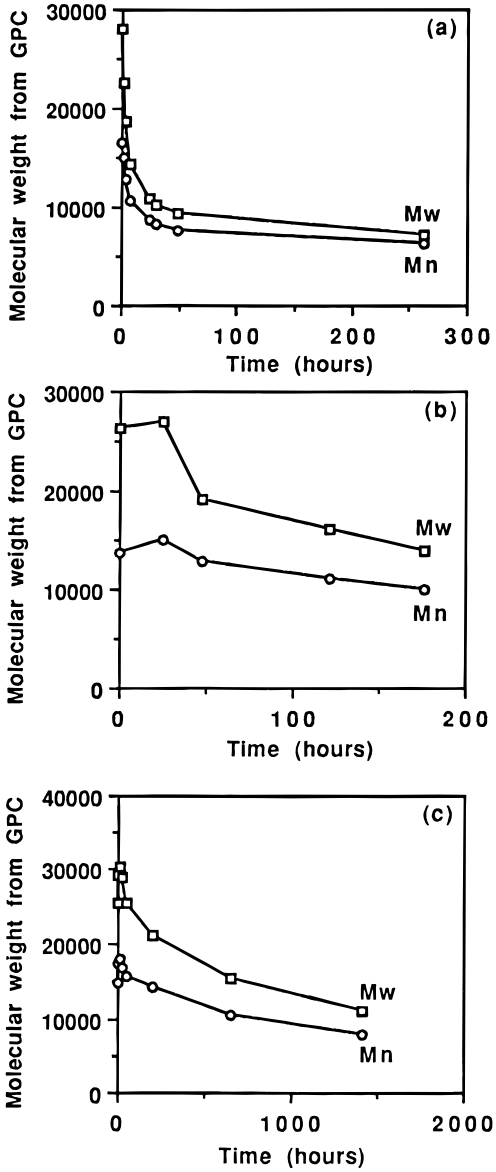


Figure 3. Molecular weight decrease vs time at 37 °C. Degradation of poly(ester amide) **PAS:** in buffer solution at pH 7.4 (a) and in bidistilled water (b). Degradation of poly(ester amide) **PAG** in buffer solution at pH 7.4 (c).

These differences in degradation must be related to structural properties of the poly(ester amides) in particular, crystallinity, and the different degrees of hydrophilicity.

GPC Analysis. Degradation of these poly(ester amides) was also monitored by gel permeation chromatography (GPC) analysis, to determine the changes in molecular weight and molecular weight distribution. The apparent molecular weights of the **PAS** and **PAG** samples as a function of immersion time are shown in Figure 3. Figure 3a shows the M_n and M_w curves during the hydrolysis of **PAS** at 37 °C in buffer solution at pH 7.4. The decrease in molecular weight starts concurrently with the penetration of water into the polymer film. Since an induction period for molecular weight loss usually reflects the time required for water to permeate the polymer film, the absence of induction period found for this poly(ester amide) confirms that

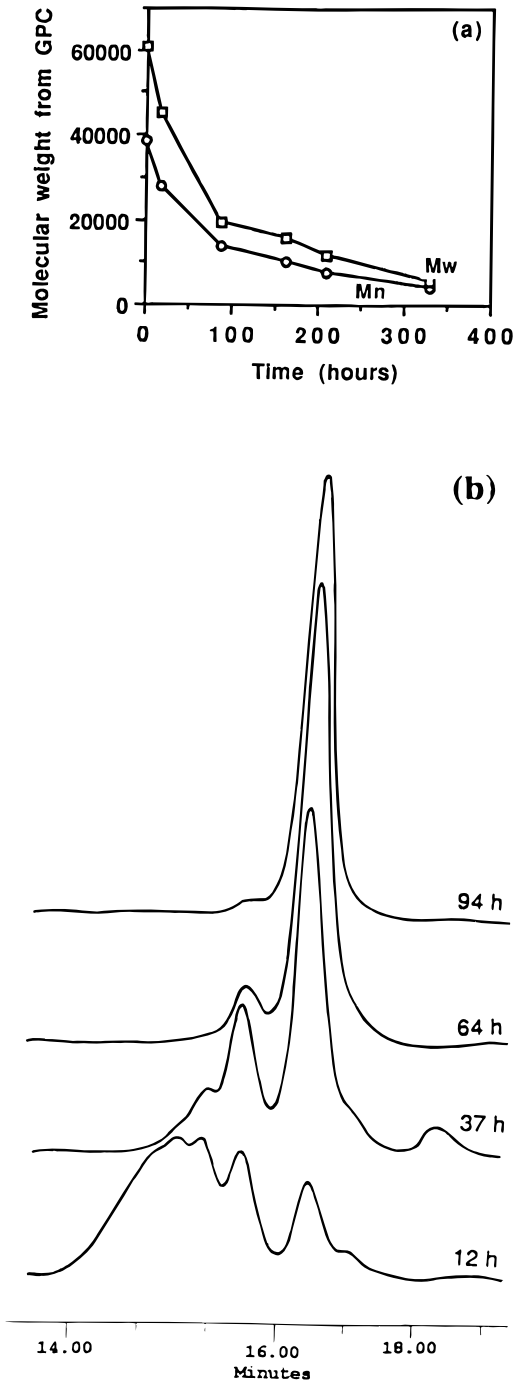


Figure 4. (a) Molecular weight decrease vs degradation time at 37 °C of poly(ester amide) **PXS** in bidistilled water. (b) GPC chromatograms evolution of **PXS** as a function of immersion time in buffer solution at pH 7.4.

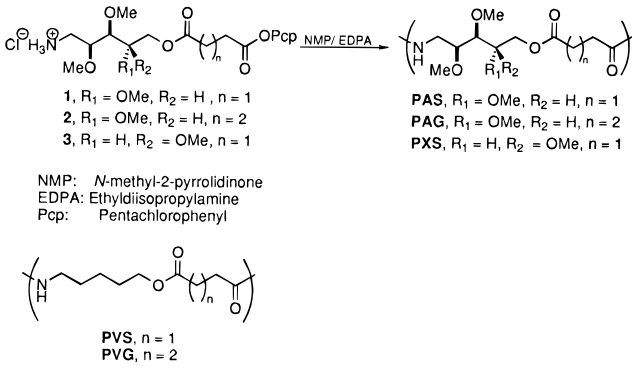
water can penetrate rapidly into the polymer structure. The hydrolysis of this sample is characterized by a continuous and rapid decrease in molecular weight during the first period of degradation and a slower decrease giving low molecular weight fragments in the final stages. The ratio M_w/M_n obtained was not constant but decreased steadily throughout the experiment.

When the degradation of poly(ester amide) **PAS** was carried out in bidistilled water (Figure 3b), the decrease in molecular weight was much slower than when the experiment was performed in buffer solution (Figure 3a). Also, it can be observed that the molecular weight increased at the beginning of the experiment. This could be explained by the fact that a slower degradation rate will let us observe the effect that the presence of residual solvent and/or small molecules in the film would produce on the molecular weight evolution. The same effect was observed during the degradation of poly(ester amide) **PAG** at 37 °C in buffer solution at pH 7.4 (Figure 3c). These data confirm that in buffer solution poly(ester amide) **PAS** degrades faster than poly(ester amide) **PAG**.

The hydrolytic degradation of poly(ester amide) **PXS** was carried out in aqueous solution because this polymer is water soluble. A faster decrease in molecular weight was found for **PXS** (Figure 4a) compared to **PAS** during hydrolysis in bidistilled water. The fastest molecular weight decrease was observed for the degradation of poly(ester amide) **PXS** in buffer solution. The GPC chromatograms of **PXS** as a function of immersion time are presented in Figure 4b. In this figure, it can be observed that the molecular weight distribution became multimodal upon exposure to aqueous buffer solution and that the high molecular weight fractions in the GPC chromatogram disappeared concurrently with the increase in the areas of the low molecular weight fractions. After almost 4 days of degradation, the chromatogram showed only one narrow peak.

Microscopic Analysis. Scanning electron micrographs (SEM) of surfaces and cross sections of disks of poly(ester amides) **PAS** and **PAG**, after 24 h of immersion, are shown in Figure 5. Initially both polymers had smooth surfaces and a dense inner structure. However, the faster rate of degradation of poly(ester amide) **PAS** compared to **PAG** is clearly shown in the scanning electron micrographs. Thus, after 24 h of immersion at 37 °C in buffer solution at pH 7.4, the surface and cross section of **PAS** films showed many holes and cavities (Figure 5a), while the surface and cross section of **PAG** (Figure 5b) remained fundamentally unchanged after 24 h of the degradation experiment.

Analysis of the Degradation Products. Degradation of poly(ester amides) **PAS**, **PXS**, and **PAG** was also monitored by analysis of the MS-FAB, IR, and NMR spectra of their degradation products. In the case of poly(ester amide) **PAG**, the IR and NMR spectra of the degradation products were very similar to those of the original polymer. This seems to support the hypothesis that the decrease in molecular weight was mainly a depolymerization process, so that chain cleavage by a simple hydrolytic mechanism seems to be the only change taking place in this poly(ester amide) during the process of degradation studied. However, the behavior of poly(ester amides) **PAS** and **PXS** was slightly different from that previously commented on in the case of **PAG**.



The fast-atom bombardment mass spectra (FAB-MS) obtained in two different moments during the degrada-

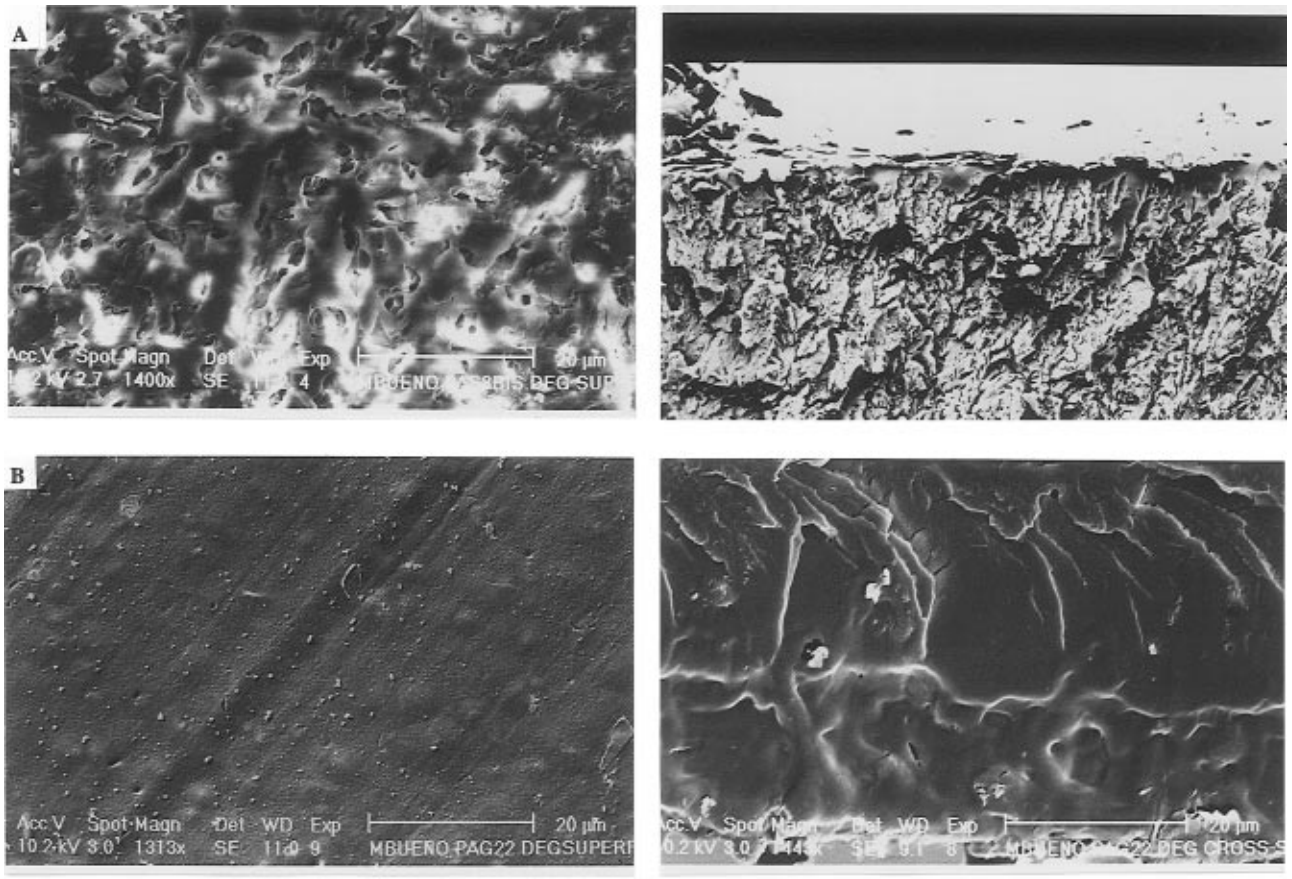


Figure 5. Scanning electron micrographs of surfaces and cross sections after 24 h of immersion in buffers solution at pH 7.4: (A) poly(ester amide) **PAS**; (B) poly(ester amide) **PAG**.

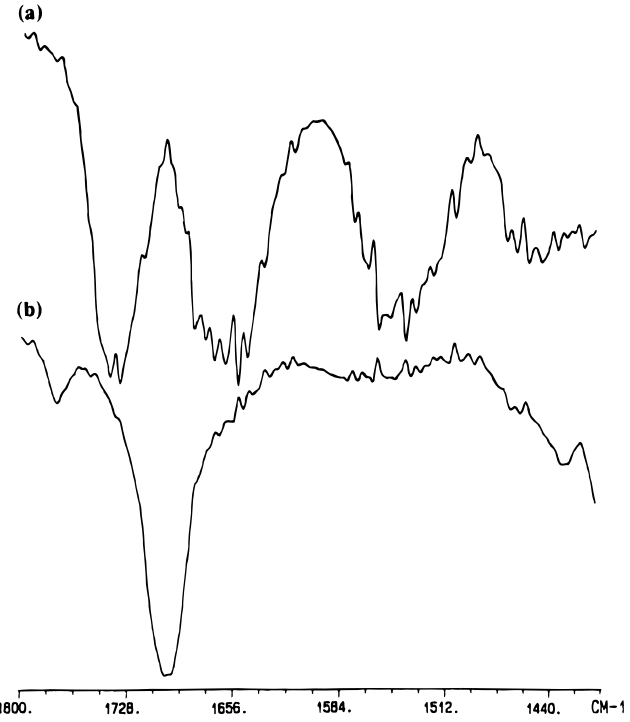
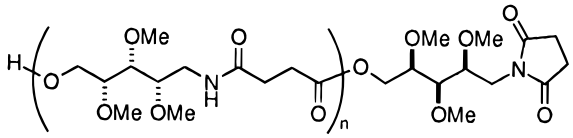


Figure 6. Infrared changes observed in the 1800−1400 cm^{-1} region during degradation of poly(ester amide) **PXS** in buffers solution: (a) before degradation; (b) After 117 h of degradation.

tion of **PXS** in buffer solution at pH 7.4 showed that in the early stages of the chain degradation, five signals could be detected at *m*/*z* 298, 573, 848, 1124, and 1399, assigned to the molecular ion as (M + Na) of an oligomeric mixture **9** from $n = 0$ to 4. However, after 117 h of degradation, the FAB-MS spectrum became much more simple. The signal at *m*/*z* 298, corresponding to the monomer **9** ($n = 0$), was the most intense (100%). The signal at *m*/*z* 338 (34%) was assigned to the molecular ion as (M + Na) of **10**.



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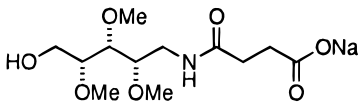

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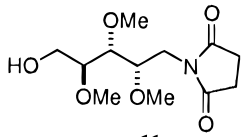

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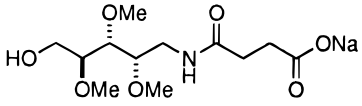

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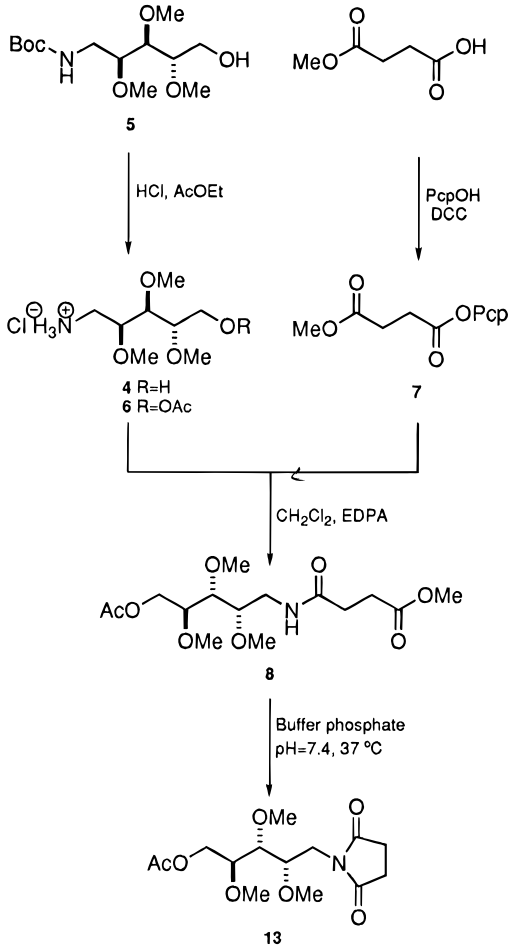
The presence of a succinimido end group in the degradation product **9** was based not only on the results of FAB-MS spectra, but also on the infrared and nuclear

magnetic resonance spectroscopies. Thus, by analysis of the IR spectra (Figure 6) obtained during the degradation experiment of a **PXS** sample hydrolyzed at pH 7.4, we could observe a decrease in the intensities of the bands attributed to the ester and amide functions, while a new band appeared (about 1700 cm^{-1}) whose intensity increased with the time of degradation. After 117 h of degradation, the absorption bands of the functions initially present in the poly(ester amide) had disappeared, and two new absorption bands centered at 1775 and 1700 cm^{-1}, and assigned to the imide function, were observed.

The ^1H and ^{13}C NMR spectra of a sample of **PXS** hydrolyzed for 117 h corroborated the above results. The NMR study showed that the hydrolyzed sample was a mixture of two compounds: **9** ($n = 0$), the main product, and a minor compound that was assigned to **10**, in agreement with the FAB-MS study. In the ^1H NMR spectrum, the most characteristic signal appeared at 2.70 ppm, as a singlet, and was assigned to the resonance of the two methylene groups of the succinimide ring of compound **9** ($n = 0$). Figure 7 shows the corresponding proton-decoupled ^{13}C NMR and DEPT-135 spectra of the same hydrolyzed sample. The signal at higher field (28.07 ppm) was due to the two methylene carbons of the succinimide ring that, as expected, appeared with inverse phase in the DEPT-135 spectrum; the two methylenes of the sugar moiety appeared, also with inverse phase in the DEPT spectrum, at 38.27 and 61.07 ppm, the higher field corresponding to that bonding to the nitrogen. No signals from dimer or oligomers were present in the spectrum because, in that case, the primary alcohol function on C-5 would be esterified and the signal corresponding to that carbon atom would be expected at lower field.[21] The three methoxyl carbons gave three signals at 58.24, 58.29, and 59.92 ppm, and the methine carbons C-2,3,4 appeared at 76.82, 80.15, and 80.72 ppm. The signal at 177.19 ppm, which disappeared in the DEPT-135 spectrum, was due to the two carbonyl groups present in the succinimide ring. These ^{13}C NMR data confirmed the structure assigned to compound **9** ($n = 0$). The spectra also included some other small-intensity signals that were tentatively assigned to compound **10**. The most characteristic signals were due to the two methylene groups of the succinyl moiety that appeared at 31.66 and 31.99 ppm and to the carbonyl groups of the carboxylate and amide functions present in **10** at 178.35 and 173.53 ppm, respectively.

In the case of poly(ester amide) **PAS**, the recovered film and the filtrate were both analyzed after predetermined immersion times. The infrared study of the recovered films after the degradation experiment did not show significant changes compared with the spectrum of the original poly(ester amide). Their GPC chromatograms were unimodal and revealed no major changes, except the continuous shift toward lower molecular weights. However, their filtrates were, as in the case of **PXS**, multimodal at the beginning of the experiment but became single-peaked at the end of the hydrolysis. The FAB-MS, IR, and NMR studies of these filtrates permit us to conclude that the final degradation products of this poly(ester amide) were **11**(main product) and **12**.

The model compound **8** has been prepared in order to confirm the interpretation of NMR data. Removal of the *N*-protecting group of 1-(*tert*-butoxycarbonylamino)-1-deoxy-2,3,4-tri-*O*-methyl-L-arabinitol[17] (**5**) with HCl in dry ethyl acetate led to the hydrochloride **6**. Methyl pentachlorophenyl succinate (**7**) was obtained from commercial monomethyl succinate by treatment with dicyclohexylcarbodiimide and pentachlorophenol. The condensation reaction of **6** and **7** afforded **8** as a solid and in almost quantitative yield. When a finely powdered sample of **8** was treated under the same conditions used for **PAS** or **PAG** (37 °C in a buffer solution, pH 7.4) for two days, it could be observed that **8** had almost disappeared and a new compound **13** with a slightly higher R_f (20:1 dichloromethane/methanol) was formed. After evaporation of the solvent at room



temperature, the crude residue was analyzed by NMR spectroscopy, revealing that a succinimide ring had been formed. Its ^1H NMR spectrum showed a new signal at 2.69 ppm, as a singlet, assignable to the resonance of the two methylene groups of the succinimide ring. At the same time, the signals due to the amido proton, methoxyl group, and the two methylene groups of the succinyl moiety of **8** practically disappeared. The ^{13}C NMR spectrum corroborates the structure assigned to **13**. Thus, the signal appearing at 20.9 ppm was due to the methyl carbon of the acyloxy group on C-5. The two methylene carbons of the new succinimide ring that, as expected, appeared with inverse phase in the DEPT-135 spectrum gave a signal at 28.07 ppm; the two methylenes of the sugar moiety appeared, also with inverse phase in the DEPT spectrum, at 37.99 and 61.56 ppm, the higher field corresponding to that bonding to the nitrogen. In contrast to **9** and **11**, compound **13** had the primary alcohol function esterified as acetate and, as expected,[21] the presence of an acyloxy group caused a downfield (1.5−4 ppm) shift of the resonance of the

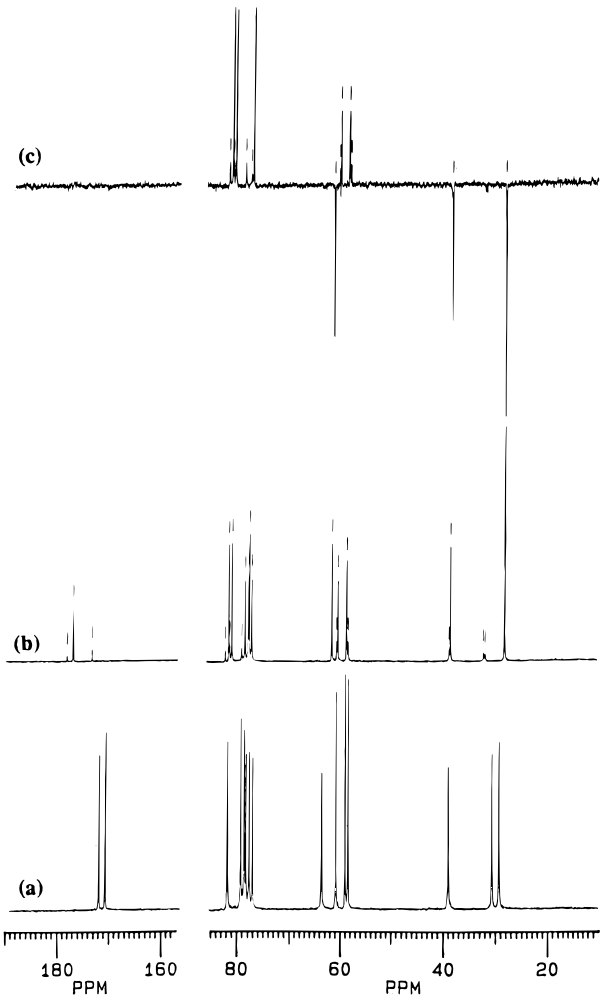


Figure 7. 50.3 MHz ^{13}C NMR spectra of poly(ester amide), **PXS**, before degradation (a), after 94 h of degradation at 37 °C in buffer solution at pH 7.4 (b), and in the DEPT-135 experiment corresponding to b (c).

α-carbon. Thus, the signal of C-5 in **13** was found at 61.56 ppm whereas the same carbon in **11** appeared at 59.26 ppm. The three methoxyl carbons gave three signals at 57.73, 58.62, and 60.88 ppm, and the methine carbons C-2,3,4 appeared at 77.28, 77.87, and 79.62 ppm. The signals appearing at 170.85 and 177.15 ppm, which disappeared in the DEPT-135 spectrum, were due to the carbonyl of the acetoxy group and to the two carbonyl groups of the succinimide ring, respectively. The synthesis of **13**, which presents a succinimide ring at one end and an ester group at the other, suggests that the imidation reaction makes the rupture of ester functions in the chain easier.

Conclusion

The hydrolytic degradation of these poly(ester amides) can be described by a simple hydrolysis of ester bonds and is characterized by rapid rates of hydrolysis. The differences in degradation rate are ascribed to differences in crystallinity and hydrophilicity of the polymers. Our data show that the rate of degradation increases with the increase of hydrophilicity of the poly(ester amides), in agreement with data published by other authors. We have found that the poly(ester amides) derived from succinic anhydride degrade to a final monomeric product which contains a succinimide ring in the molecule.

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