Carbohydrate-Based Copolymers. Hydrolysis of Copoly(ester amide)s Containing L-Arabinose Units

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ABSTRACT: The in vitro hydrolysis of a series of copoly(ester amide)s abbreviated as PVGA*n*, prepared previously by random copolymerization of 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-5-*O*-[(pentachlorophenoxy)-succinyl]-L-arabinitol hydrochloride and 5-amino-1-*O*-[(pentachlorophenoxy)glutaryl]pentanol hydrochloride, has been performed in phosphate buffer at 37 °C and evaluated by weight loss and intrinsic viscosity. The copoly(ester amide) PVGA46, containing about 50% of the sugar-based monomer, was water-soluble. Its solubility in water displayed a temperature dependence that was studied and related with the hydrolysis process. The degradation of the aliphatic copoly(ester amide) was greatly enhanced with increasing amount of arabinose−succinyl monomer incorporated in the polymer chain. The presence of small amounts of this monomer was enough to produce a noticeable increase in polymer degradability. Spectroscopic investigations of the hydrolysis products provided evidence for succinimide ring formation, supporting the general mechanism proposed for the hydrolysis of poly(ester amide)s containing four-carbon diacid units in their structure.

Introduction

Aliphatic polyamides are a well-known class of synthetic polymers, widely used because of their excellent technical properties.[1] However, their rates of hydrolytic degradation, especially under mild conditions,[2] e.g., pH 7 and 37 °C, are too low for them to be considered useful as biodegradable synthetic materials. The high number of hydrogen bonds, the high crystallinity of the polyamide structure, and the great natural resistance of the amide functions to hydrolysis explain the inertness of these nylons to degradation. Today, however, there is considerable interest in the development of polymers that not only have good technical properties but also are degradable. This interest has arisen because of the potential applications in the medical and pharmaceutical fields[3−5] and as part of the growing concern about environmental problems.[6] Aliphatic polyesters are the best-known examples of biodegradable and biocompatible polymers, as extensively reported and discussed in the scientific literature.[7]

We are interested in poly(ester amide)s, which comprise a class of synthetic polymers between aliphatic polyamides and aliphatic polyesters. Thus, on one hand, the presence of vulnerable ester linkages in the main chain and the potential lowering of the crystallinity degree[8] enhance the degradability of these polymers in comparison with aliphatic polyamides. On the other hand, the presence of amide functions in the polymer chain might lead to better physical properties than aliphatic polyesters usually have. The combination of good physical properties and controlled degradability makes poly(ester amide)s worthy of attention regarding potential applications.[3,5,9]

Some years ago, we reported on poly(ester amide)s derived from naturally occurring sugars.[10] The presence of these carbohydrate units bearing methoxyl groups along the polymer backbone increases the hydrophilicity and enhances the hydrolytic degradability as compared with conventional nylons. These sugar-based polymers can be water-soluble, depending on the nature and/or the amount of the carbohydrate monomer in the polymer chain.[10,11] Recently,[12] we have studied the hydrolytic degradation of poly(ester amide)s derived from conveniently modified L-arabinose and D-xylose sugar monomers and four- or five-carbon diacid units. Higher rates of hydrolytic degradation were observed in those polymers containing four-carbon diacid units. The same result was achieved in the case of aliphatic non-sugar poly(ester amide)s. More recently,[13] the influence of the chemical constitution and microstructure on degradability of poly(ester amide)s derived from amino alcohols, diamines, and diacids has been evaluated. That paper proposed a mechanism involving cyclization to imides, probably by an intramolecular amidolysis reaction, requiring the presence of four-carbon diacid units in the poly(ester amide) chain. Aliphatic poly(ester amide) PVG,[10b] containing five-carbon diacid units along the backbone, showed, as expected, a low degradation rate.[13] Taking this poly(ester amide) as an example, and with the aim of modulating its rate of hydrolysis, we prepared[14] a series of copoly(ester amide)s, referred to as PVGA*n*, by copolymerization of 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-5-*O*-[(pentachlorophenoxy)succinyl]-L-arabinitol hydrochloride (**1**) and 5-amino-1-*O*-[(pentachlorophenoxy)glutaryl]pentanol hydrochloride (**2**) via the active ester polycondensation method (Scheme 1). The structure of these copolymers combines the presence of a carbohydrate monomer, which might favor high degradability, with a microstructure designed so that the mechanism of degradation by cyclization to imides could operate. In the present paper, we report on the in vitro hydrolysis of a series of aliphatic copoly(ester amide)s containing increasing amounts of a sugar-based monomer.

Experimental Section

Measurements. IR spectra (films or KBr disks) were recorded with a Jasco FT/IR-410 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded from samples dissolved in chloroform, using a Bruker AMX-500 spectrometer at 30 °C operating at 500.13 and 125.76 MHz, respectively. Two-

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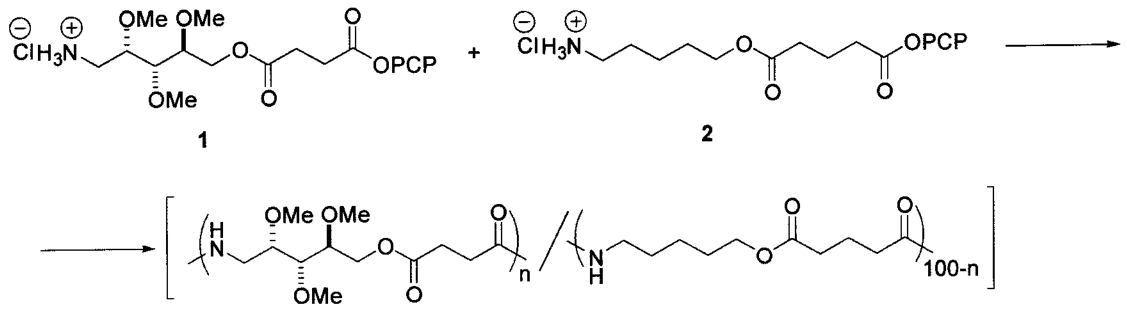
Scheme 1



dimensional $^1H-^1H$ homonuclear and $^{13}C-^1H$ heteronuclear shift correlation spectra were recorded with the *cosy* and *hetcor* pulse sequences. Chemical shifts are reported as parts per million downfield from tetramethylsilane. Elemental analyses were determined in the Microanalysis Laboratories at the Universidad Complutense (Madrid). Intrinsic viscosity measurements were determined in dichloroacetic acid (DCA) with a Cannon-Ubbelohde semi-microviscometer placed in a water bath with the temperature maintained at 25.0 ± 0.1 °C. The thermal properties of the degraded copoly(ester amide)s were determined by differential scanning calorimetry (DSC). DSC was carried out under a nitrogen atmosphere on a Perkin-Elmer DSC-7 instrument calibrated with indium. Samples of about 2−3 mg were heated at a rate of 10 °C/min and rapidly cooled to room temperature. The peak temperatures were taken as melting points. 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. The turbidity of the polymer solution was monitored using a Perkin-Elmer Lambda 5 spectrophotometer. The absorption at 550 nm was recorded.

Copolymerizations. Copoly(ester amide)s were synthesized by the active ester polycondensation method.[14]

Hydrolysis of the Polymers. Hydrolysis experiments were carried out on disks of 13 mm in diameter, ranging from 200 to 350 μm in thickness and 39 to 43 mg in weight, prepared by hot pressing. Disks were incubated at 37 °C in 0.1 M Na_2HPO_4/NaH_2PO_4 buffer solution with 0.03% (w/w) of sodium azide (pH 7.4). Each disk was immersed in the incubating solution and left there for a selected period of time, after which the remaining solid was recovered by filtration, rinsed with distilled water, and dried to constant weight under reduced pressure. The filtered solutions were lyophilized and extracted with dichloromethane in order to separate inorganic salts. In the case of the water-soluble PVGA46 copolymer, the hydrolytic studies were performed in solution using the purified powder directly. The hydrolysis of this copoly(ester amide) was evaluated by turbidity measurements as follows: a polymer sample was dissolved in distilled water or phosphate buffer (0.8 mg/mL; pH 7.4) at 2−5 °C and filtered through a 0.22 μm filter at this temperature. The solutions were kept at 20 °C, and after the selected period of time, the turbidity of an aliquot of the solution was measured.

Methyl 3-[*N*-(5-Hydroxypentyl)carbamoyl]propanoate (3). To a stirred solution of 5-aminopentanol (0.156 g, 1.514 mmol) and monomethyl succinate (0.2 g, 1.514 mmol) in dry dichloromethane (1.5 mL) cooled at 0 °C was added EDC·HCl (0.29 g, 1.544 mmol). After 3 h, the solution was allowed to warm to room temperature, and the stirring was continued overnight. Ethyl acetate (2 mL) was added to the reaction mixture; the resulting solid was filtered out and washed several times with more ethyl acetate. The filtrate and washings were combined, concentrated, and chromatographed (eluent: 10:1 dichloromethane/methanol) to give **3** as an oil (0.2 g, 56%). NMR data ($CDCl_3$): ^1H, δ 6.34 (bt, 1H, NH), 3.60 (s, 3H, OMe), 3.53 (t, 2H, H-10), 3.15 (q, 2H, H-6), 2.58 (t, 2H, H-2), 2.39 (t, 2H, H-3), 1.41 (m, 6H, H-7,8,9). ^{13}C, δ 173.52 (C-1), 171.57 (C-4), 62.04 (C-10), 51.68 (OMe), 39.27, 31.91, 30.69, 29.21, 28.99, 22.82 (C-2, 3, 6, 7, 8, 9). Mass spectrum: *m*/*z* 217.1312 (calcd for $C_{10}H_{19}NO_4$: 217.1314).

***N*-(5-Hydroxypentyl)succinimide (4).** A solution of **3** (0.1 g, 0.47 mmol) in phosphate buffer (pH 7.4, 3 mL) was heated at 70 °C for 24 h. The reaction mixture was concentrated to 0.5 mL and extracted with dichloromethane (4 × 1 mL). The organic phase was concentrated under reduced pressure to give an oil (0.07 g, 84%). NMR data ($CDCl_3$): ^1H, δ 3.48 (t, 2H, H-5), 3.38 (t, 2H, H-1), 2.66 (s, 4H, succinimide), 1.54 (m, 4H, H-2,4), 1.32 (m, 2H, H-3). ^{13}C, δ 177.40 (CO, succinimide), 61.95 (C-5), 38.44 (C-1), 31.79 (C-2), 27.91 (2 CH_2, succinimide), 27.16 (C-4), 22.77 (C-3). Mass spectrum: *m*/*z* 185.1051 (calcd for $C_9H_{15}NO_3$: 185.1052).

Results and Discussion

Copoly(ester amide)s, referred to as PVGA*n*, where *n* indicates the percentage of carbohydrate monomer incorporated in the copoly(ester amide) chain, VG indicates the 5-aminopentyl glutarate unit, and A indicates the 5-aminoarabinitol succinate unit, were obtained by copolymerization of 1-amino-1-deoxy-2,3,4-tri-*O*-methyl-5-*O*-[(pentachlorophenoxy)succinyl]-L-arabinitol hydrochloride (AS monomer **1**) and 5-amino-1-*O*-[(pentachlorophenoxy)glutaryl] pentanol hydrochloride (VG monomer, **2**) via the active ester polycondensation method.

The sensitivity of poly(ester amide)s to hydrolysis has been related to different factors such as the ester/amide ratio in the polymer chain[15] or the chain regicity.[13] However, in the series of copoly(ester amide)s PVGA*n* studied in this paper, the ester/amide ratio remained constant, and the polycondensation method applied was not restricted by the occurrence of directional isomerism yielding, in all cases, regioregular polymers. Therefore, differences observed in the hydrolytic behavior of these copoly(ester amide)s might be explained mainly in terms of length[13] of the diacid unit in the polymer chain. It was expected that the hydrolysis would increase as the AS/VG ratio in the copoly(ester amide)s increases, that is, as the ratio of four- to five-carbon diacid units increases. That was exactly what it was found. The hydrolysis of PVGA*n* was studied by monitoring the change in remaining weight and the intrinsic viscosity of the degraded samples with immersion time. The data from these measurements are represented graphically in Figures 1 and 2. As observed in Figure 1, the hydrolysis of copoly(ester amide)s PVGA*n* increases markedly with the AS/VG ratio in the copolymer composition. This enhanced degradability started to be observable in copoly(ester amide) PVGA5, containing 5% of AS units in its molecular composition, but it became significant as the concentration approached 20%. Thus, PVGA21 lost about 50% of its weight after 8 months of

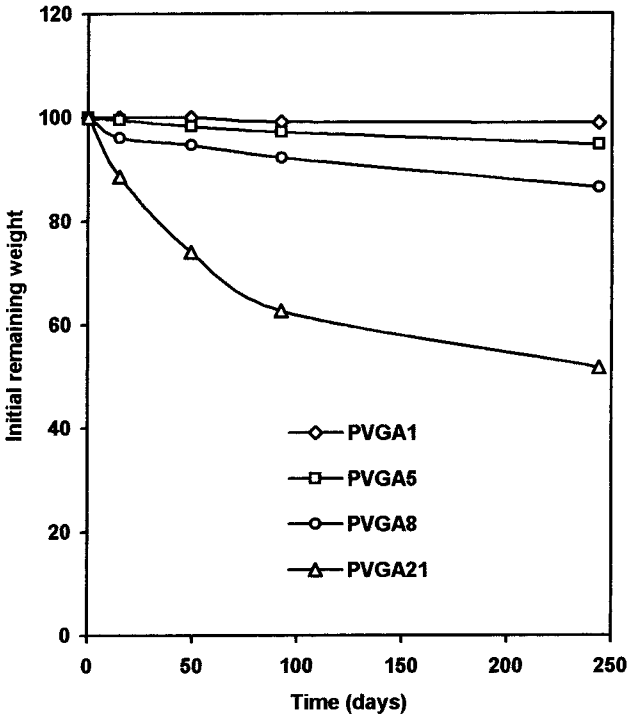


Figure 1. Change in initial weight remaining vs time. Hydrolysis of copoly(ester amide)s PVGA*n* at 37 °C in buffer solution at pH 7.4.

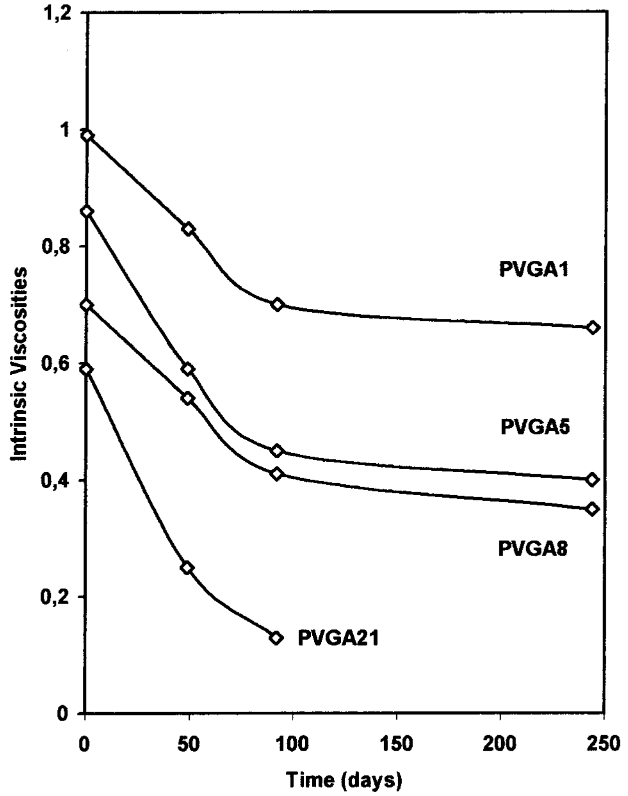


Figure 2. Change in intrinsic viscosity vs time. Hydrolysis of copoly(ester amide)s PVGA*n* at 37 °C in buffer solution at pH 7.4.

immersion in the buffer solution, whereas the reference homopolymer PVG was found essentially unaltered after a similar period of time. In Figure 2, the intrinsic viscosities for the four copoly(ester amide)s are plotted against time of immersion at 37 °C in buffer at pH 7.4. This figure reveals information related with the hydrolytic behavior of the copolymer samples. Thus, the viscosity of the copoly(ester amide)s falls rapidly during the first 3 months of immersion and then continues much more slowly. This result might be explained by the fact that, at the beginning of the hydrolytic experiment, the water molecules will attack randomly the ester linkages of the initially large copoly(ester amide) molecule. This is likely to affect the viscosity much more intensely than in the final steps of the degradation, when the water molecules attack smaller fragments. Figure 1 shows that practically no weight losses occur during the hydrolysis of PVGA1 in phosphate buffer at pH 7.4. However, it is important to note that this copoly(ester amide) degrades despite the lower number of ester linkages (AS monomers) introduced in the copolymer chain (Figure 2). In this case, the aliphatic fragments produced by the hydrolytic process are not soluble in the medium and therefore are not able to exit from the disk samples. As the amount of carbohydrate (AS monomer) increases in the copoly(ester amide), more fragments more soluble in the medium will be produced by the process, and these will easily leave the disk samples. Copoly(ester amide) PVGA46 was obtained as an amorphous foam that was slightly soluble in water. Its hydrolytic study, in contrast to those of the other copoly(ester amide)s, was performed using the purified precipitated copolymer directly. When a sample of PVGA46 was subjected to the hydrolytic conditions, the initial suspension was transformed in the course of some hours into an initially milky solution and a precipitated solid. The weight of PVGA46 remaining after 1 month of hydrolysis was about 8%. Thus, copoly(ester amide) PVGA46 was the fastest hydrolyzed copolymer in the series PVGA*n*, as could be anticipated taking into account that it has the highest AS/VG ratio and an amorphous character. The hydrolysis evolution of copoly(ester amide)s PVGA21 and PVGA46 was also monitored by analysis of their degradation products.

The mechanism proposed recently by some of us[13] for the hydrolysis of poly(ester amide)s derived from succinic and tartaric acids involves cyclization to imides by an intramolecular amidolysis reaction, although an alternative mechanism in two steps—hydrolysis of the ester group and rapid cyclization into imide—cannot be completely ruled out (Figure 3). The presence of succinimide units in the products of the hydrolysis was confirmed by different spectroscopic techniques. Figure 4A shows the infrared spectrum of copoly(ester amide) PVGA46, displaying the characteristic absorption bands anticipated from the constitution of this copolymer: 3300 (amide A), 3080 (amide B), 1731 (CO, ester), 1650 (amide I), and 1550 cm^{-1} (amide II). After 1 month of degradation in phosphate buffer, apart from the bands attributed to the ester and amide functions, two new absorption bands could be observed: one at 1700 cm^{-1} and the other (less intense) at about 1772 cm^{-1} (Figure 4C). These two new absorption bands are characteristic of the succinimide ring.

The ^{1}H and ^{13}C NMR spectra of hydrolyzed PVGA46 corroborated the scission of the ester linkages and the formation of succinimide rings. Thus, the spectra of the solid recovered by filtration of a PVGA46 sample hydrolyzed for 1 month, P2PVGA46 (Figure 5c), showed signals characteristic of chains composed mainly of succinyl-ended VG units of type **5** or **6** (Chart 1). The ^{1}H NMR spectrum showed a singlet signal at 2.68 ppm that was assigned to the resonance of the two methylene

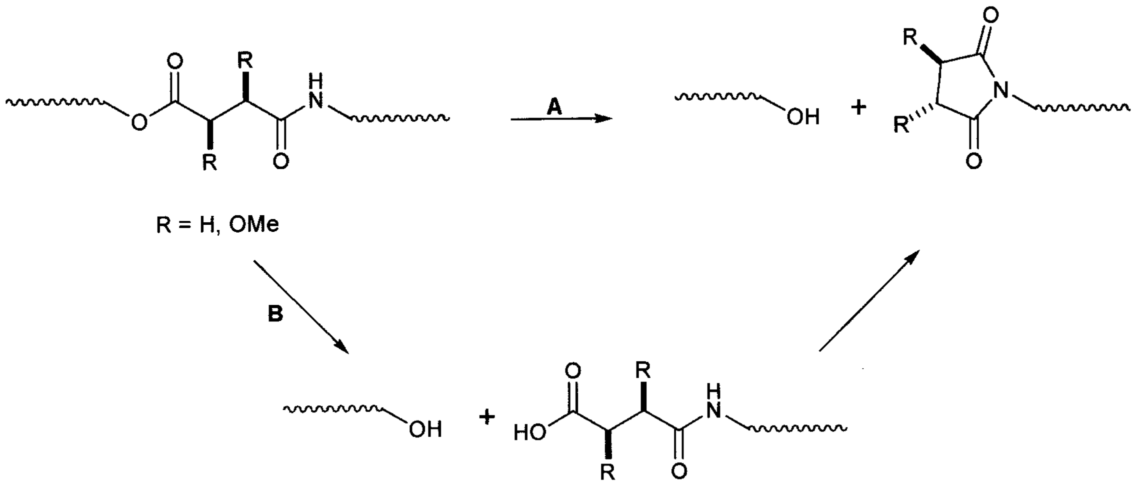
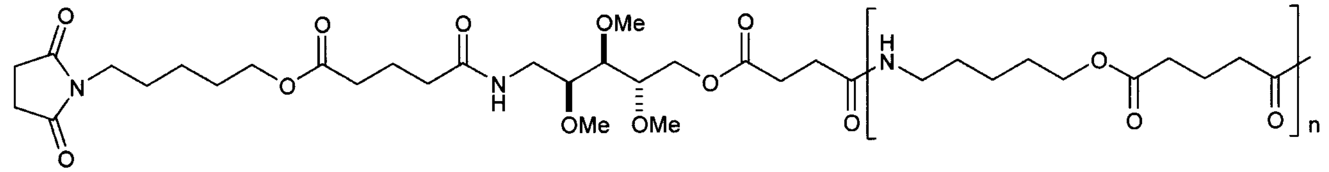


Figure 3. Scheme of the hydrolysis mechanism in poly(ester amide)s.

Chart 1



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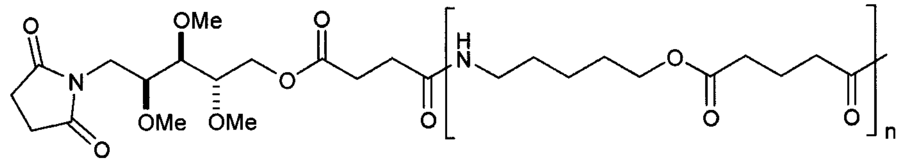

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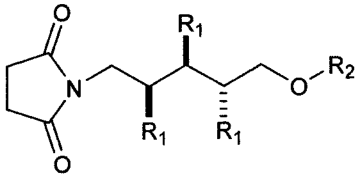
groups of the succinimide ring. By comparison with one of the expected[16] end-hydrolyzed products **7**, compound **5** was found to be predominant in the residue. (**6** would show an intense signal about 3.55 ppm (Figure 5e) in its ^{1}H NMR spectrum.)



4 $R_1 = H, R_2 = H$

7 $R_1 = OMe, R_2 = H$

8 $R_1 = OMe, R_2 = COR$

9 $R_1 = H, R_2 = COR$

The ^{13}C NMR spectrum confirmed the presence of a succinimide ring. Thus, the signals appearing at 28.17 and 177.30 ppm were assigned to the resonances of the two methylene carbons and to the two carbonyl groups of the succinimide ring, respectively (Figure 6c). The low ratio of AS/VG units in **5** could also be easily observed in its ^{13}C NMR spectrum by comparing the intensity of the signals appearing at about 64 and 62 ppm. It was found that the signal at about 64 ppm, due to the oxymethylene carbon of VG units, was much more intense than that at about 62 ppm, due to the oxymethylene carbon of the AS units. The low content in arabinose–succinyl units of these oligomers would explain their insolubility in the medium. The filtrate corresponding to the PVGA46 sample hydrolyzed for 1 month, F2PVGA46, was also analyzed by NMR spectroscopy. Comparison with the spectra of the residue P2PVGA46 clearly showed that most of the carbohydrate-based residues had been extracted by the medium, producing intense signals between 3 and 4 ppm (Figure 5b). The ^{1}H NMR spectrum showed four singlet signals at 2.70, 2.67, 2.669, and 2.66 ppm, which were correlated (*hetcor* spectrum, not shown) with a signal appearing at 28.09 ppm in its ^{13}C NMR spectrum. These four signals were assigned to succinimide rings having slightly different chemical environments, as in compounds **4** and **7**–**9**. The resonances found in model compounds **4** and **7** (Figure 5, d and e, respectively) agree with the assignations made above. In accord with the presence of different succinimide-ended compounds in the filtrate, the ^{13}C NMR spectrum displayed several signals between 177.5 and 176.5 ppm that could be assigned to the carbonyl groups of the succinimide rings (Figure 6b). Furthermore, the presence of this ring in the hydrolyzed products will cause a downfield chemical shift of the methylene groups close to the succinimide ring, mainly H-5 and H-4. Thus, H-5 and H-4 of PVGA46 appeared at 3.19 and 1.48 ppm, respectively, whereas the same methylene groups in model compound

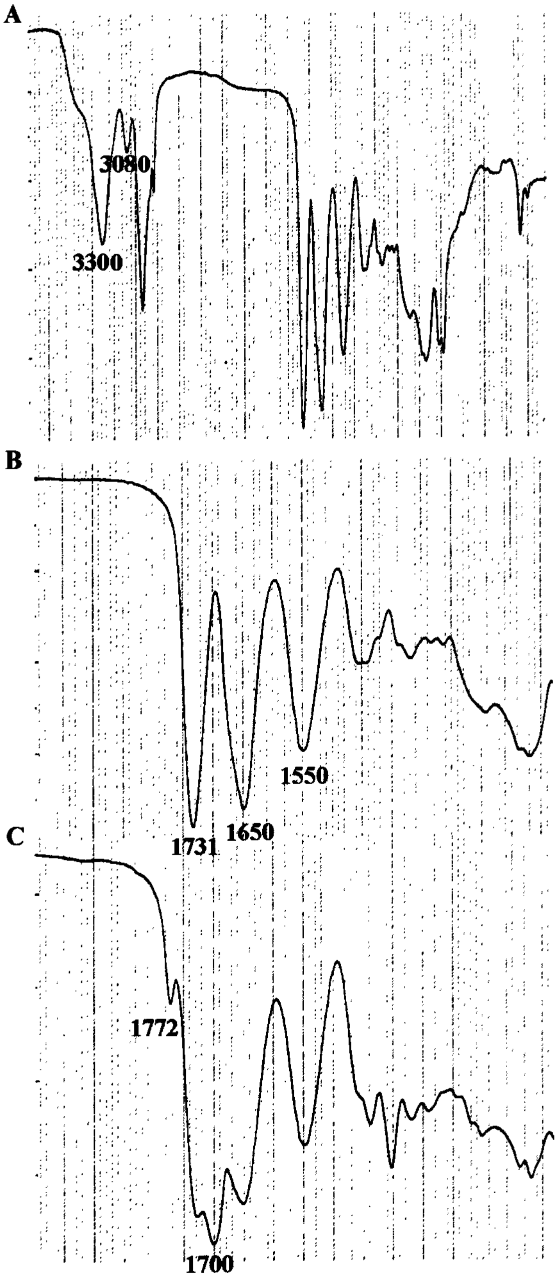


Figure 4. FTIR spectra of copoly(ester amide) PVGA46: (A) initial sample, (B) expanded region of the initial sample, (C) after 1 month of hydrolysis.

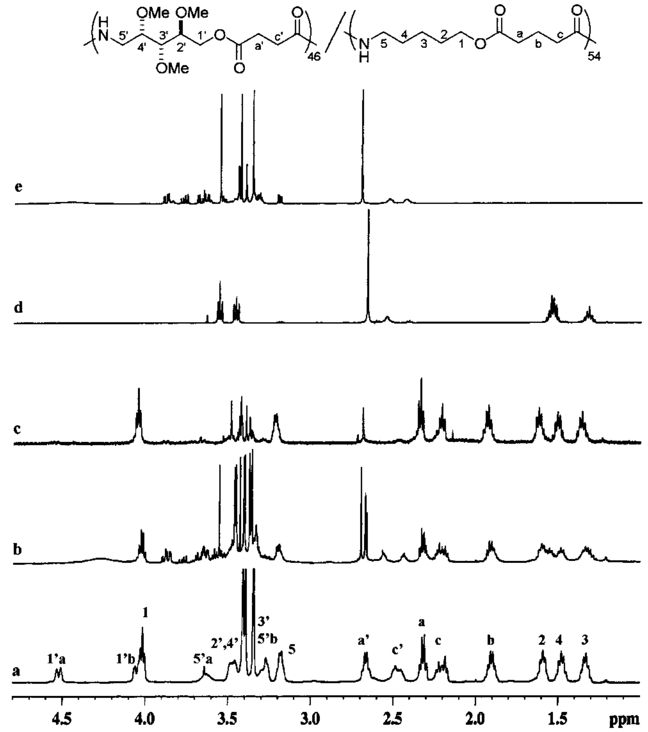


Figure 5. ^{1}H NMR (500.13 MHz) spectra recorded in $CDCl_3$ at 30 °C: (a) PVGA46 before degradation, (b) F2PVGA46 after 1 month of hydrolysis, (c) P2PVGA46 after 1 month of hydrolysis, (d) model compound **4**, and (e) model compound **7**.

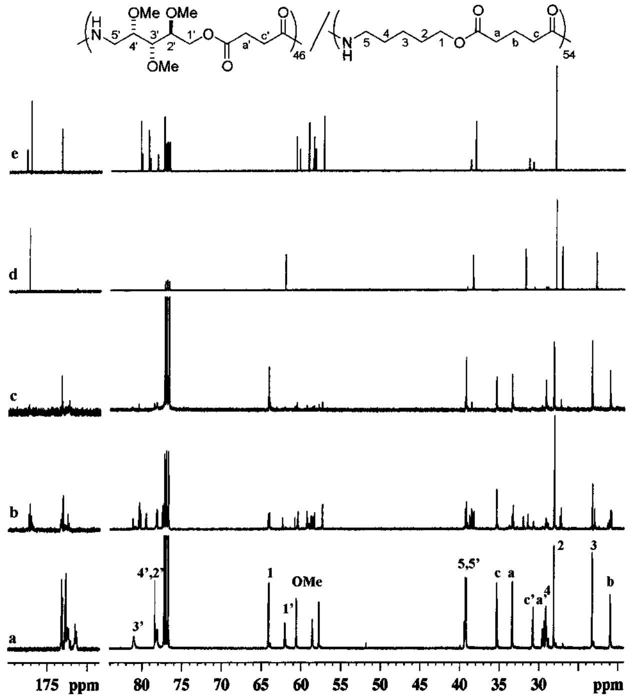


Figure 6. ^{13}C NMR (125.76 MHz) spectra recorded in $CDCl_3$ at 30 °C: (a) PVGA46 before hydrolysis, (b) F2PVGA46 after 1 month of hydrolysis, (c) P2PVGA46 after 1 month of hydrolysis, (d) model compound **4**, and (e) model compound **7**.

4 resonate at 3.44 and 1.52 ppm (Figure 5, a and d, respectively). The ^{1}H NMR spectrum of F2PVGA46 showed an increase in the number of signals appearing in the range 1.2–1.7 ppm. In this narrow zone appeared the resonances of H-2, H-3, and H-4 of the aminopentanol part. This spectrum displayed a new signal at 1.55 ppm that was assigned to H-4 of succinimide-ended products—the downfield shift of H-4 (methylene β to the ring) was small, about 0.07 ppm. This signal was correlated in its *cosy* spectrum (Figure 7A) with another signal appearing at 3.45 ppm, assigned to H-5 of the hydrolyzed products. The downfield shift observed in this case was bigger than the former because this methylene group is now α to the succinimide ring.

Hydrolysis of the ester function of the carbohydrate units (AS) in the copoly(ester amide) was detected not only by the formation of the succinimide ring or because practically no ester signal was observable at 62 ppm but also by the appearance of a new signal at 59.28 ppm (Figure 6b). If the ester function were hydrolyzed, a primary alcohol function on C-1′ would be formed, and a higher field[17] chemical shift would be expected for that carbon atom. That is precisely what it was observed. Furthermore, the chemical shift of this signal agrees with that observed for the hydroxymethylene carbon atom of model compound **7** (Figure 6e).

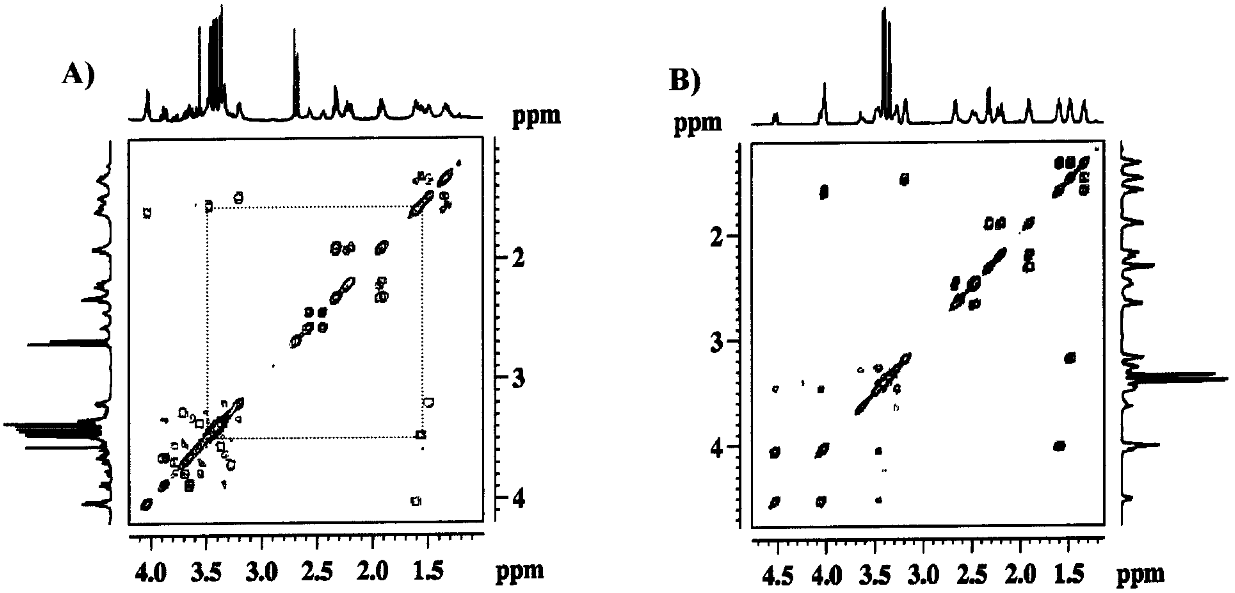
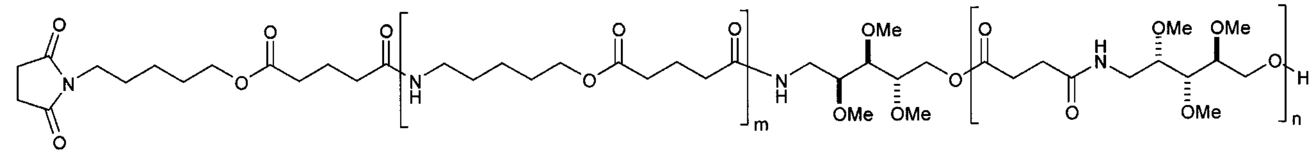


Figure 7. *Cosy* spectrum: (A) F2PVGA46 after 1 month of hydrolysis and (B) PVGA46 before hydrolysis

Chart 2



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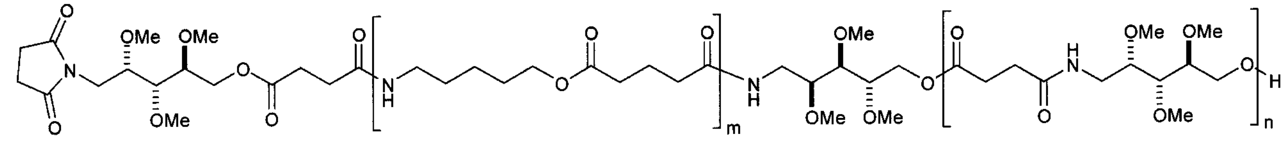

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Fast-atom bombardment mass spectra (FAB-MS) of the filtrates from hydrolyzed samples of PVGA21 and PVGA46 showed similar spectra. Apart from the signal at *m/z* 276, which corresponded to the M + H of **7** (base peak), there were two main series of signals. The first was detected at *m/z* 475, 674, 873, 1072, and 1271, which can be assigned to the protonated molecular ions (M + H) of an oligomeric mixture **10** from $n = 0$, $m = 0$ to $n = 0$, $m = 4$. The second group of signals gave peaks at *m/z* 750, 949, 1148, 1348, 1546, and 1745, possibly produced by **10** from $n = 1$, $m = 0$ to $n = 1$, $m = 5$ or/and by **11** from $n = 0$, $m = 1$ to $n = 0$, $m = 6$ (Chart 2). The elemental composition of some of these peaks belonging to both series was determined by high-resolution FAB-MS; the results are shown in Table 1.

As observed in the MS spectrum (Figure 8), the most intense signals belong to the first series. The explanation might be that the oligomeric mixture **10** is obtained from **11** by nucleophilic attack of the amidic nitrogen on the neighboring carbonyl ester carbon, which would also produce **7**, the base peak of the spectra. The signals found in the two series confirmed the preferential scission of the succinic rather than glutaric ester linkages.

Table 1. Elemental Composition of Some Relevant Signals Appearing in the PVGA46 Mass Spectra Determined by High-Resolution Fast-Atom Bombardment Mass Spectra

m/z [M + 1]	elemental composition	mass calcd	mass found
276	$C_{12}H_{21}NO_6$	276.1447	276.1459
475	$C_{22}H_{39}N_2O_9$	475.2655	475.2690
674	$C_{32}H_{56}N_3O_{12}$	674.3864	674.3870
750	$C_{34}H_{60}N_3O_{15}$	750.4024	750.4011
873	$C_{42}H_{73}N_4O_{15}$	873.5072	873.5105
949	$C_{44}H_{77}N_4O_{18}$	949.5233	949.5265
1072	$C_{52}H_{90}N_5O_{18}$	1072.6281	1072.6309
1148	$C_{54}H_{94}N_5O_{21}$	1148.6441	1148.6407

The thermal properties of hydrolyzed samples PVGA5, PVGA8, and PVGA21 were also studied by DSC as a function of hydrolysis time. Figure 9 shows the traces for the different samples. An initial difference is clearly observed by comparing second heating traces of undegraded samples. It is noticeable that as the amount of AS units increases, the crystallinity of the samples decreases. A second observation is that PVGA5 showed from the beginning of the experiments three endotherms, one of them much more intense than the others. PVGA8 and PVGA21 showed a single endotherm at the beginning of the experiment, although the thermograms of samples hydrolyzed for a longer time showed a pattern similar to that of PVGA5 but after different hydrolysis time. PVGA8 showed three endotherms after 92 days of hydrolysis, whereas PVGA21 displayed that behavior at the end of the hydrolysis study (244 days). The explanation might be that, with hydrolysis, most of the carbohydrate-based residues will pass to the

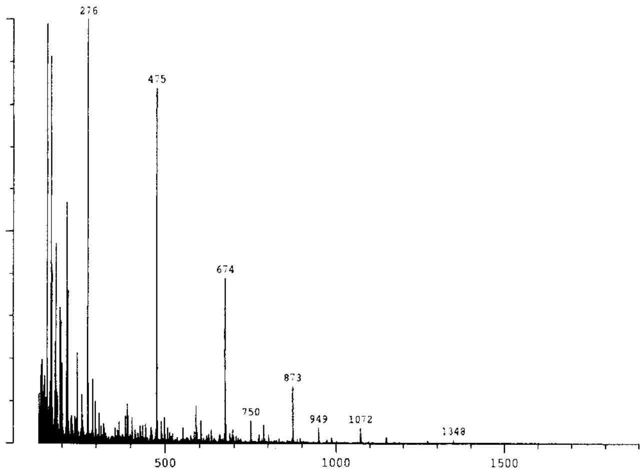

Figure 8. Fast-atom bombardment mass spectrum of F2PVGA46 after 1 month of hydrolysis.

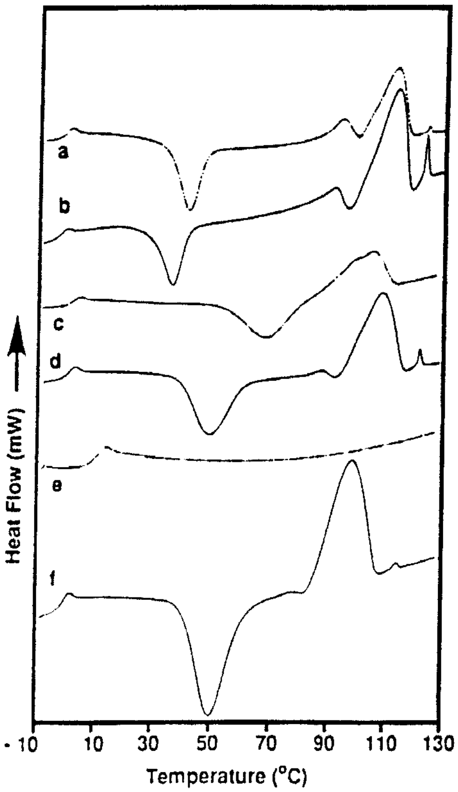

Figure 9. Second heating thermograms of the hydrolyzed copoly(ester amide)s conducted at a heating rate of 10 °C/min: (a) PVGA5 before hydrolysis, (b) PVGA5 after 244 days of hydrolysis, (c) PVGA8 before hydrolysis, (d) PVGA8 after 92 days of hydrolysis, (e) PVGA21 before hydrolysis, and (f) PVGA21 after 244 days of hydrolysis.

Table 2. Results of Thermal Analysis of Copoly(ester amide)s PVGA*n* Hydrolyzed in Phosphate Buffer (pH 7.4) at 37 °C

time	PVGA5			PVGA8			PVGA21		
(days)	T_g	T_m	ΔH	T_g	T_m	ΔH	T_g	T_m	ΔH
0	−4.4	91.5 110.2 122.2	37.2	−3.6	102.3	27.5	6.3		
15	−6.0	90.6 110.8 122.2	32.3	−2.2	103.8	32.1	2.3	91.0	0.9
49	−6.7	88.8 110.5 121.5	40.3	−3.2	103.6	34.1	−2.6	89.1	12.5
92	−6.6	89.3 111.1 121.8	42.4	−4.2	85.0 104.6 118.2	37.7	−4.5	93.1	32.6
244	−6.8	88.4 110.9 121.4	45.1	−6.1	83.2 105.5 118.4	39.3	−6.2	95.1 111.5	40.2

[a] Measured by DSC, second heating.

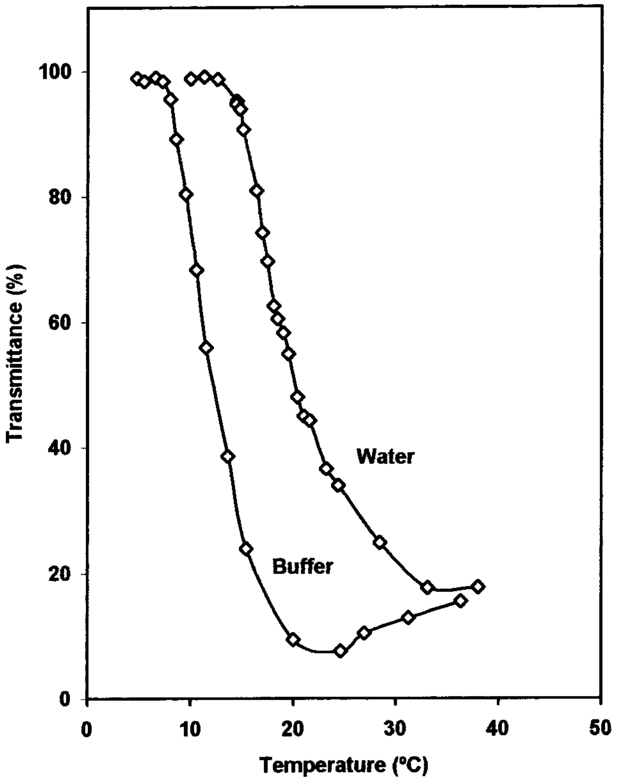

Figure 10. Change in transmittance vs temperature of copoly(ester amide) PVGA46.

solution, and the insoluble polymeric residue becomes more similar to PVGA5 or to the homopolymer PVG (which showed a similar thermal pattern). A last conclusion is that, with increasing hydrolysis, the crystallinity of the hydrolyzed samples increases (judging by the Δ*H* values (Table 2)). Moreover, in PVGA8 and PVGA21 there is clearly a gradual shift of T_g values toward lower temperatures, whereas T_m values are shifted to higher temperatures.

The preparation of copoly(ester amide)s PVGA*n* allowed us to observe the change in some of their physical characteristics as a function of the AS/VG ratio in the polymer chain. For instance, the solubility of the copolymer increases as the AS/VG ratio increases. Copoly(ester amide) PVGA46 was the only water-soluble copolymer in the series. Moreover, it was found that the solubility of this copolymer in aqueous media was temperature-dependent. The lower critical solution temperature (LCST) is a result of the change in the hydrophilic and hydrophobic balance between the polymer and the hydrogen-bonding solvent as the temperature is raised,[18] whereas the polymer is soluble at low temperature because the hydrogen bonding between the hydrophilic part of the polymer and the solvent outweighs the unfavorable exposure of the hydrophobic parts to water; the polymer precipitated when its solution was heated above the LCST temperature. As the temperature increases, hydrogen bonding weakens and hydrophobic interactions become dominant. For instance, when a transparent solution, prepared by

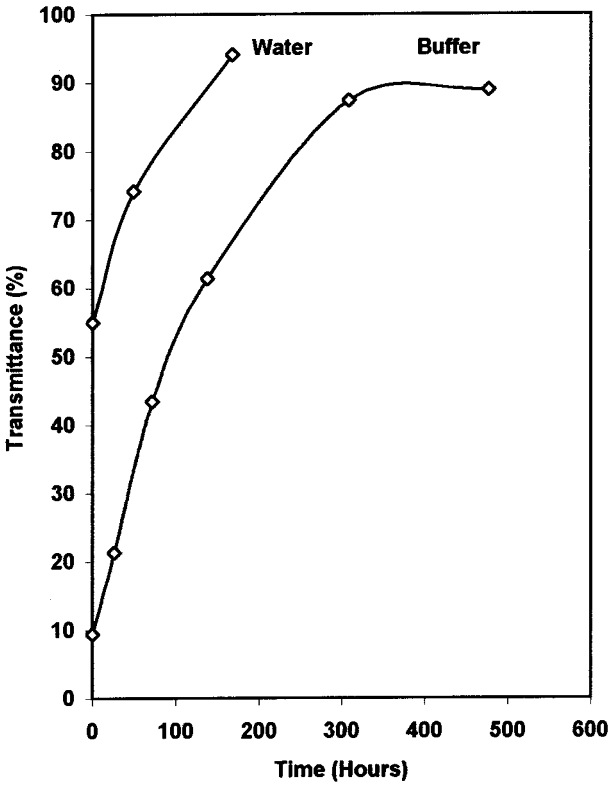

Figure 11. Time evolution of the transmittance of PVGA46 solutions.

dissolving the copoly(ester amide) PVGA46 at low temperature (3−5 °C), was heated above 14 °C, it became turbid. The phase separation behavior of aqueous solutions of PVGA46 is shown in Figure 10. This figure displays the change in transmittance of solutions of PVGA46 (0.8 mg/mL) in distilled water and in buffer solution (pH 7.4). As can be observed, with increasing solution temperature, the solution became turbid at 14.2 °C in the case of PVGA46 in water solution. The LCST changed remarkably when PVGA46 was dissolved in buffer solution (pH 7.4). In this case, the LCST was lower (8.3 °C) under the same experimental conditions. The shift of LCST is usually related with the presence of inorganic salts in the polymer solution. Although the effect is both salt- and polymer-dependent, with possible variations from system to system,[19] in general, most of the inorganic salts cause a “salting out” effect.[20−22] These inorganic salts disrupt the hydrophilic and hydrophobic balance between the polymer and water molecules, resulting in a decrease of LCST.[23]

As can be observed in Figure 10, the phase separation range is broader in water than in the buffer solution. A possible explanation of this broad phase separation could be that the copoly(ester amide) PVGA46 was hydrolyzed under the experimental conditions. As a matter of fact, we can observe in the buffer solution curve of Figure 10 that the percentage of transmittance started to increase from about 20 °C. This increase in transmittance was ascribed to hydrolysis of the copolymer. In the case of PVGA46 in buffer solution, we could observe both processes—phase separation and hydrolysis of the copolymer chain—independently one from the other, but in the case of PVGA46 in water solution, hydrolysis of the chain started before the phase separation became complete. Because hydrolysis of the copolymer affects the turbidity of its aqueous solutions, we planned to monitor the hydrolytic stability of PVGA46 by its phase separation capacity. A sample of PVGA46 was dissolved in the appropriate solvent; the solution was filtered (0.22 μm) and poured into several vials that were kept at 20 °C. From time to time, a vial of the solution was cooled to low temperature under stirring, and finally its turbidity at 20 °C was measured. Figure 11 shows the change in transmittance vs time of incubation. As expected, the transmittance of the solution increased progressively, reaching values close to 100% after several days of degradation. It should be noted that completely transparent solutions of the hydrolyzed copoly(ester amide) PVGA46 cannot be obtained because as the copolymer hydrolyzed, insoluble oligomers of the hydrophobic monomer (VG) precipitated.

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