

Sequential Poly(ester amide)s Based on Glycine, Diols, and Dicarboxylic Acids: Thermal Polyesterification versus Interfacial Polyamidation. Characterization of Polymers Containing Stiff Units

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ABSTRACT: Sequential poly(ester amide)s derived from glycine were synthesized by a two-step method, involving a final thermal polyesterification. Molecular weights were in general higher than those obtained with the previously reported synthesis on the basis of interfacial polyamidation. Polymers with stiff units like oxaloyl or terephthaloyl residues were thermally characterized and their degradability studied by using different types of enzymes. Polymers containing short diols are degradable in papain solutions, the degradation rate being higher for oxalic derivatives. © 2001 John Wiley & Sons, Inc. *J Polym Sci Part A: Polym Chem* 39: 4283–4293, 2001

Keywords: poly(ester amide)s; biodegradable polymers; terephthalic; oxalic; glycine derivatives; thermal properties; polymerization

INTRODUCTION

New regulations for preservation of the environment have led to recycling waste materials in a more effective way as well as enhanced research and development projects on biodegradable materials. Moreover, specific applications such as sutures, surgical implants, and controlled-release formulations of drugs have encouraged the study of new biodegradable polymers. Among them, poly(ester amide)s constitute a promising family because of their expected properties. Thus, their ester linkages should be hydrolytically degradable, whereas their amide groups should improve both thermal and mechanical characteristics because of their hydrogen-bonding interactions. In this sense, Bayer has recently commercialized a

new poly(ester amide) on the basis of 1,4-butanediol, adipic acid, and caprolactam (BAK 1095®) that appears to be completely biodegradable and shows both good performance and good processing behavior.¹

Among poly(ester amide)s, those derived from α -amino acids constitute an interesting group because their susceptibility to degradation by proteolytic enzymes is also expected. Different studies have been carried out^{2–11} for polymers containing the $-\text{[NHCH(R)CO—O(CH}_2\text{)}_n\text{O—COCH(R)NH—CO(CH}_2\text{)}_m\text{CO]}-$ repeat units. Some of these studies have demonstrated their high degradability with proteolytic enzymes like papain or proteinase K as well as other properties that depended on the composition. Hence, the crystallinity and melting point of polymers decrease when amino acids with bulky side groups are used. In this sense, alanine and glycine derivatives appear to be polymers with a greater applicability because their respective melting temperatures can be

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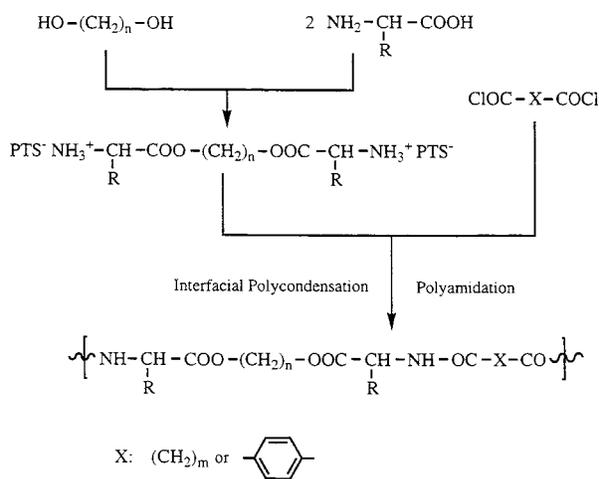
higher than 100 °C. In general, these polymers can be easily prepared by solution or interfacial polymerization (Scheme 1) from a diacid chloride and a monomer derived from the condensation of the appropriate diol with two amino acid residues. However, it is well known that interfacial polycondensation is difficult to control and optimize because of the large number of factors that needs to be considered.¹² Among aliphatic compounds, only those derived from hydrolytically stable diacid chlorides, such as sebacoyl or dodecanoyl chloride, can be obtained with high molecular weights. However, we found that polymers with glycine units still have a rather low molecular weight. To overcome this limitation we used a two-step thermal polyamidation (Scheme 2).

The aliphatic poly(ester amide)s investigated until now have a glass-transition temperature near 0 °C. Consequently, mechanical properties such as Young's modulus are expected to be low. This problem may be avoided with the insertion of stiff units in the main polymer chain. In this sense, a second proposal of this work is the preparation and characterization of new poly(ester amide)s that, in addition to glycine, contain the rigid units provided by terephthaloyl or oxaloyl residues.

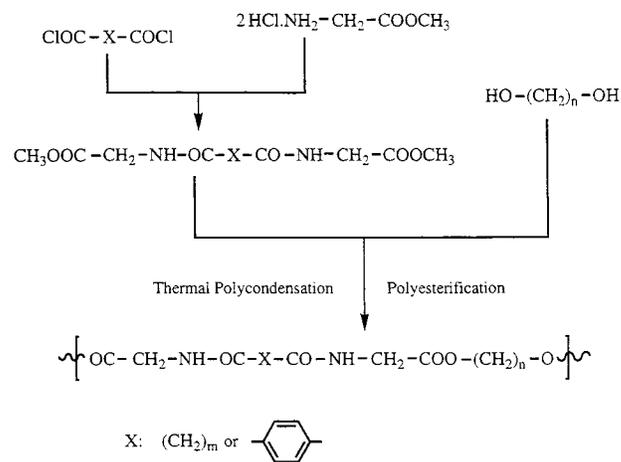
EXPERIMENTAL

Synthesis

All chemicals were American Chemical Society grade and used without further purification. Polymers were synthesized according to the interfa-



Scheme 1



Scheme 2

cial polyamidation previously established for aliphatic compounds⁵ and are outlined in Scheme 1, following the new method on the basis of a thermal polyesterification outlined in Scheme 2. We recall the following notation used in both previous⁵ articles and in this one: each polymer is described by the sequence glycine-diol (E, B, H, and D for 1,2-ethanediol, 1,4-butanediol, 1,6-hexanediol, and 1,12-dodecanediol, respectively)-glycine-diacid (described by the number of its methylene groups in the case of an aliphatic unit or by T in the case of terephthalic acid). Thus, PGBG8 and PGBGT correspond to the polymers derived from glycine, butanediol, and sebacid or terephthalic acid, respectively.

Characterization

Intrinsic viscosities were determined with a Cannon-Ubbelohde microviscometer in dichloroacetic solutions at 25 ± 0.1 °C.

Infrared absorption spectra were recorded with a PerkinElmer 1600 Fourier transform infrared spectrometer in the 4000–500 cm⁻¹ range from powder samples. NMR spectra of poly(ester amide)s were registered from deuterated chloroform/trifluoroacetic acid solutions. Chemical displacements were calibrated using tetramethylsilane (TMS) as an internal standard. A Bruker AMX-300 spectrometer operating at 300.1 and 75.5 MHz was used for the ¹H and ¹³C NMR investigations, respectively.

Thermal analysis was performed by differential scanning calorimetry with a PerkinElmer DSC-PYRIS 1, using indium metal for calibration.

The thermogravimetric analysis was carried out with a PerkinElmer TGA-6 thermobalance.

Powder X-ray diffraction patterns were recorded under vacuum at room temperature. Calcite ($d_B = 3.035 \text{ \AA}$) was used for calibration. A modified Statton camera (W. R. Warhus, Wilmington, DE) with a nickel-filtered radiation of 1.542 \AA was used for these experiments.

Disks of 14 mm diameter and 100–150 μm thickness were cut off from films prepared by slow evaporation of polymer solutions (0.075 g/mL) in chloroform/hexafluoro-2-propanol mixtures (1/3 v/v). Enzymatic degradation studies were performed at 37 °C by using a lipase from *Candida cylindracea* (943 units/mg) as well as proteolytic enzymes such as papain (30,000 units/mg, No. 7144) and proteinase K (*tritirachium album*, 13 units/mg). The media consisted of a sodium phosphate buffer (pH 6.0 for papain and 7.2 for the other enzymes) containing sodium azide (0.03%) to prevent microbial growth as well as the appropriate enzyme. In the case of papain the solution also contained L-cysteine (34 mM) and ethylenediaminetetracetic disodium salt (30 mM) for activation. Solutions were renewed every 72 h because of enzymatic activity loss. In all cases, the disks were placed in glass vials containing 10 mL of the degradation media and removed after the prescribed times. Mass loss and changes in NMR spectra were evaluated in all of these degradation experiments. Scanning electron microscopy (SEM) was used to examine the surface/cross-sectional morphology of samples before and after degradation. Gold coating was accomplished by using a Balzers SCD-004 Sputter Coater. The SEM microphotographs were taken with a JEOL JSM-6400 instrument.

RESULTS AND DISCUSSION

Synthesis and Characterization

Polymers Prepared by Interfacial Polyamidation

Esterification Reaction between a Diol and Two Glycine Amino Acids. A three-necked, round-bottom flask equipped with a CaSO_4 drying tube, a Dean–Stark apparatus, and a magnetic stirrer was charged with the appropriate diol (0.1 mol), glycine (0.22 mol), *p*-toluenesulfonic acid monohydrate (0.22 mol), and toluene (350 mL). The reaction mixture was refluxed for 10 h until no more water was distilled. Then it was cooled to room temperature, and the toluene evaporated under

reduced pressure to obtain a hard solid that was recrystallized.

Synthesis of the 1,6-hexanediol and 1,12-dodecanediol derivatives has previously been reported.^{5,13} All attempts to obtain the 1,4-butanediol derivative following the described procedure were unsuccessful because only the *p*-toluenesulfonic acid salt of glycine was recovered from the reaction medium.

For *p*-toluenesulfonic acid salt of O,O'-bis(glycyl)-ethanediol, recrystallization was from isopropanol/ethyl acetate (2/2.5, v/v). Yield: 54%; mp: 172 °C.

^1H NMR (CDCl_3/TFA , TMS, internal ref.): δ 7.7–7.2 (m, 8H, Ar–H), 4.55 (s, 4H, COOCH_2), 4.12 (q, 4H, $\text{NH}_3^+\text{CH}_2\text{CO}$), 2.43 (s, 6H, CH_3).

ELEM. ANAL. Calcd. for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_{10}\text{S}_2$: C, 46.15%; H, 5.38%; N, 5.38%. Found: C, 46.36%; H, 5.48%; N, 5.33%.

Interfacial Polyamidation. An aqueous solution of the diol derivative (7 mmol) and sodium carbonate (14 mmol) was added dropwise to a stirred solution of dichloride (7 mmol) in the organic solvent. After addition was complete, stirring was continued for 30 min. The polymer, which precipitated during polymerization, was isolated by filtration and successively washed with ethanol, water, ethanol, the polymerization solvent for the organic phase, and ethyl ether before drying in a vacuum desiccator at 60 °C. Polymerizations with oxaloyl dichloride were discarded as a result of the rapid hydrolysis of the diacid chloride.¹⁴ Table I summarizes the used solvents and yields of polymerization, whereas intrinsic viscosities are reported in Table II.

Polymers Prepared by Thermal Polyesterification

Bis-(methylglycyl)-amide of Dicarboxylic Acids. A round-bottom flask equipped with a dropping funnel and a magnetic stirrer was purged with N_2 and charged with glycine methyl ester hydrochloride (0.2 mol), triethylamine (0.4 mol), and 250 mL of chloroform. Then 0.1 mol of the appropriate diacyl chloride dissolved in 150 mL of chloroform were slowly added for 90 min, whereas the reaction was kept at 0 °C by means of an ice–water bath. The reaction was prolonged for an additional period of 90 min at room temperature. The chloroform solution was extracted with $3 \times 30 \text{ mL}$ of water, dried with anhydrous sodium sulphate, filtered, and evaporated under reduced pressure.

Table I. Solvents Used in the Interfacial Polycondensation and Yields Obtained in the Polymerization

Polymer	Organic Phase	Aqueous Phase	Yield (%)
PGEET	CCl ₄ (140 mL)	H ₂ O (70 mL)	20
PGHGT	CCl ₄ (140 mL)	H ₂ O (70 mL)	60
PGDGT	CHCl ₃ (70 mL)	CH ₃ CH ₂ OH (25 mL) + H ₂ O (70 mL)	65
PGHG2 ^a	CH ₂ Cl ₂ (20 mL)	H ₂ O (20 mL)	30
PGDG2	CH ₂ Cl ₂ (60 mL)	CH ₃ COCH ₃ (3 mL) + H ₂ O (70 mL)	50
PGEET	CCl ₄ (120 mL)	H ₂ O (60 mL)	57
PGHG8 ^a	CH ₂ Cl ₂ (20 mL)	H ₂ O (20 mL)	70
PGDG8	CCl ₄ (140 mL)	CH ₃ CH ₂ OH (8 mL) + H ₂ O (70 mL)	80

^a Data from ref. 5.

The resulting hard solid was finally washed with ethyl ether and recrystallized.

For bis-(methylglycyl)-sebacamide, recrystallization from methanol/water was 1/3.3 v/v. Yield: 83%; mp: 119 °C.

¹H NMR (CDCl₃, TMS, internal ref.): δ 6.22 (m, 2H, NH), 4.06 (d, 4H, NHCH₂CO), 3.76 (s, 6H, CH₃), 2.12 (t, 4H, CH₂CONH), 1.63 (m, 4H, CH₂CH₂CO), 1.31 (m, 8H, CH₂CH₂CH₂CO).

ELEM. ANAL. Calcd. for C₁₆H₂₈N₂O₆: C, 55.81%;

H, 8.14%; N, 8.14%. Found: C, 55.95%; H, 8.19%; N, 8.10%.

For bis-(methylglycyl)-succinamide, recrystallization was from isopropanol. Yield: 65%; mp: 136 °C.

¹H NMR (CDCl₃, TMS, internal ref.): δ 8.31 (m, 2H, NH), 4.23 (d, 4H, NHCH₂CO), 3.87 (s, 6H, CH₃), 2.97 (s, 4H, CH₂CONH).

ELEM. ANAL. Calcd. for C₁₀H₁₆N₂O₆: C, 46.15%; H, 6.15%; N, 10.77%. Found: C, 46.94%; H, 6.22%; N, 10.84%.

For bis-(methylglycyl)-oxalamide, recrystallization was from isopropanol. Yield: 47%; mp: 161 °C.

¹H NMR (CDCl₃, TMS, internal ref.): δ 7.85 (m, 2H, NH), 4.08 (d, 4H, NHCH₂CO), 3.77 (s, 6H, CH₃).

ELEM. ANAL. Calcd. for C₈H₁₂N₂O₆: C, 41.38%; H, 5.17%; N, 12.07%. Found: C, 41.22%; H, 5.31%; N, 12.17%.

For bis-(methylglycyl)-terephthalamide, recrystallization was from water. Yield: 75%; mp: 162 °C.

¹H NMR (CDCl₃, TMS, internal ref.): δ 7.04 (t, 2H, NH), 4.24 (d, 4H, NHCH₂CO), 3.82 (s, 6H, CH₃), 8.82 (t, 4H, Ar—H).

ELEM. ANAL. Calcd. for C₁₄H₁₆N₂O₆: C, 54.55%; H, 5.19%; N, 9.06%. Found: C, 54.60%; H, 5.22%; N, 9.10%.

Table II. Comparison between the Intrinsic Viscosities of the Polymers According to the Polymerization Method

Polymer	[η] ^a (dL/g)	
	Interfacial Polyamidation	Thermal Polyesterification
PGEET	0.33	— ^b
PGBGT	— ^c	0.60
PGHGT	0.68	0.74
PGDGT	0.60	0.68
PGBG0	— ^c	0.48
PGHG0	—	0.60
PGDG0	—	0.73
PGBG2	— ^c	0.35
PGHG2	0.23 ^d	0.38
PGDG2	0.20	0.40
PGEET	0.52	— ^b
PGBG8	— ^c	0.73
PGHG8	0.37 ^d	0.51
PGDG8	0.41	0.48

^a Measured in dichloroacetic acid at 25 °C.

^b A high degree of decomposition was observed during the thermal treatment.

^c The monomer derived from 1, 4-butanediol could not be synthesized.

^d Data from ref. 5.

Thermal Polyesterification. A two-necked, round-bottom flask equipped with a magnetic stirrer and a condenser was charged with the appropriate diol (0.02 mol) and the corresponding bis-(methylglycyl)-amide derivative (0.008 mol). Titanium butoxyde (0.3 mol %) was also added as a catalyst for the condensation reaction. The flask was heated in an oil bath at 160–190 °C to melt the mixture. Meanwhile, a slow stream of nitrogen was passed to help eliminate the methanol

Table III(a). Main Spectroscopic Data of the Polymers Studied in This Work: Infrared Spectroscopy^a

Polymer	Amide A	Amide B	C=O (Ester)	Amide I	Amide II
PGEGT	3312	3072	1744	1651	1547
PGBGT	3302	3073	1739	1646	1547
PGHGT	3292	3073	1744	1635	1547
PGDGT	3299	3075	1743	1638	1549
PGBG0	3324	3076	1748	1674	1520
PGHG0	3296	3076	1760	1668	1538
PGDG0	3289	3073	1748	1660	1534
PGBG2	3304	3065	1740	1659	1540
PGHG2	3320	3076	1740	1652	1550
PGDG2	3314	3076	1740	1646	1552
PGEG8	3315	3076	1745	1643	1551
PGBG8	3312	3070	1736	1645	1546
PGHG8	3314	3076	1738	1646	1550
PGDG8	3328	3082	1740	1642	1550

^a Absorption bands in cm^{-1} .

and excess of diol. After 1 h, the second neck was connected to a vacuum pump (0.3 mm Hg) while the temperature of the bath was raised to 200–220 °C. To improve the elimination of the diol, the reaction was periodically stopped (every hour) by cooling it at room temperature, and then the diol that had condensed in the flask wall was removed. The reaction was prolonged until no more diol was distilled off (4–5 h). After cooling down, the polymer was dissolved in formic acid, precipitated by a dropwise addition of acetone, filtered, and repeatedly washed with acetone and ethyl ether. Polymerization yields were in the range of 80–90% except for ethyleneglycol derivatives that showed a high degree of decomposition. Table II summarizes the measured intrinsic viscosities of the polymers prepared by this method.

In general, the obtained results point out the advantages of the thermal polycondensation method versus the previously reported synthesis on the basis of interfacial polymerization. Such advantages include the following: (1) butanediol derivatives can be prepared with high yield avoiding the limitation of the previous method concerning the monomer preparation; (2) oxalic derivatives can be obtained with high viscosity, a fact that is not possible by interfacial polymerization because of the high hydrolysis rate of the oxaloyl dichloride; and (3) the intrinsic viscosities of polymers synthesized by thermal condensation are usually higher, especially when interfacial polymerization implies unstable diacid chlorides such as succinic or the indicated oxalic dichloride. However, the thermal polyesterifications with

ethylene glycol were unsuccessful because a high degree of decomposition was always reached during the prolonged treatment at high temperature. In addition, some polymers such as those containing oxaloyl or terephthaloyl residues showed some coloration, although no decomposition could be observed spectroscopically (thus the changes are below the detection limits of these methods).

In general, film- (from the melt state or from the solution) and fiber-forming properties were found for polymers with an intrinsic viscosity higher than 0.5 dL/g. In this sense, terephthalic and the majority of oxalic derivatives are highly promising.

The main spectroscopic data (IR and NMR) of the synthesized polymers are summarized in Table III. The data agree with previous observations on these kinds of polymers^{5,13} that indicated the establishment of strong hydrogen-bond interactions between amide groups. Amide II deviates toward 1538–1520 cm^{-1} , and the ¹³C NMR carbonyl shift decreases toward 160 ppm for polymers with oxalamide groups as found in polyoxalamides.¹⁵ The NMR spectra of the polymers are independent of the preparation method with the exception of some small signals that could be attributed to terminal groups and that are only detected when the intrinsic viscosity of the polymer is about 0.4 dL/g. In this sense, hydroxyl terminal groups are found in the spectra of low-weight polymers obtained by thermal polyesterification [Fig. 1(a)], whereas only the carboxylic terminal groups can be observed in the polymers prepared by interfa-

Table III(b). Main Spectroscopic Data of the Polymers Studied in This Work: ^1H and ^{13}C NMR Spectroscopies^b

Polymer	CONH	COO	NH	C_6H_4		OCH ₂		NHCH ₂ CO		NHCOCH ₂	
	^{13}C	^{13}C	^1H	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
PGEGT	175.6	172.2	7.77	7.89	136.0,128.3	4.58	63.9	4.40	42.5	—	—
PGBGT	172.7	171.2	7.72	7.90	136.1,128.4	4.35	67.2	4.39	42.7	—	—
PGHGT	172.8	171.0	7.73	7.89	136.0,128.4	4.30	68.0	4.38	42.7	—	—
PGDGT	172.3	170.5	7.67	7.91	136.1,128.4	4.30	68.2	4.39	42.6	—	—
PGBG0	160.5	171.4	8.80	—	—	4.31	67.2	4.31	42.0	—	—
PGHG0	160.3	172.0	8.80	—	—	4.27	67.8	4.27	41.9	—	—
PGDG0	160.2	171.1	8.70	—	—	4.26	68.1	4.26	41.9	—	—
PGBG2	178.6	171.1	8.50	—	—	4.34	67.5	4.34	43.0	3.07	29.5
PGHG2	179.1	171.8	8.60	—	—	4.33	68.7	4.24	43.7	3.05	30.1
PGDG2	178.4	171.1	8.50	—	—	4.32	68.8	4.32	43.1	3.06	29.7
PGEg8	180.5	171.4	7.75	—	—	4.56	64.4	4.27	42.5	2.54	35.3
PGBG8	180.5	171.8	7.89	—	—	4.37	67.3	4.28	42.6	2.56	35.2
PGHG8	180.4	172.5	7.73	—	—	4.28	68.5	4.24	43.0	2.50	35.9
PGDG8	179.1	171.8	7.61	—	—	4.31	68.2	4.26	42.4	2.51	35.6

^b Chemical displacements in parts per million and referred to TMS.

cial polymerization [Fig. 1(b)], as has also been indicated in previous articles.^{5,13}

Thermal Behavior of Poly(ester amide)s Containing Oxaloyl and Terephthaloyl Residues

The calorimetric analysis of each polymer consisted of four DSC scans for PGBGT as shown in Figure 2. In the first run, the samples coming directly from polymerization were heated through fusion and left in the melt state for 2 min. Subsequent cooling was performed to observe crystallization from the melt. A second heating was carried out to check the reproducibility of the transitions and to obtain data for melt-crystallized samples. To determine the glass-transition temperatures, a third heating run was performed with samples quenched from the melt state. Heats of fusion (calculated as the difference between the heats of the observed melting peaks and the corresponding ones related to the cool crystallization peaks when these were detected) were used to evaluate the crystallinity of polymers (solution- and melt-crystallized samples) considering the heats of fusion for 100% crystalline materials. These values were estimated from the reported¹⁶ group contributions of ester (−2.5 kJ/mol), amide (2.0 kJ/mol), methylene (4.0 kJ/mol), and *p*-phenylene (5.0 kJ/mol). Temperatures indicative of the beginning of the decomposition process ($T_{d,0}$) and the 50% weight loss ($T_{d,1/2}$) were determined by thermogravimetry. Table IV

summarizes the main calorimetric parameters of the studied polymers. The following includes some considerations.

First, the polymers show a complex melting behavior. Thus, in general, a double melting peak (with a temperature interval close to 20 °C) is observed. This is a well known characteristic of polyamides^{17,18} that is attributed to a melt and recrystallization process that renders more perfect and thicker crystals. However, polymorphism is also detected in some samples containing oxalic residues. PGBG0 has two fusion peaks (132 and 173 °C) with a large difference in temperature (Fig. 3). X-ray powder patterns (also shown in Fig. 3) clearly demonstrated that two different structures are implied. Therefore, the polymer precipitated with acetone from a formic acid solution shows a diffraction pattern with spacings close to 4.6 Å (weak) and 3.9 Å (strong). This structure can only be associated with the low melting temperature because the high-temperature structure is the consequence of the cold crystallization (exotherm at 137 °C) that takes place after the first fusion. When the polymer is annealed at 150 °C for 1 h, the DSC trace shows only the high melting-temperature peak, and a distinct diffraction pattern is then obtained (main strong reflections at 4.1, 3.8, and 3.2 Å).

Second, the melting temperature decreases in both the oxalic and terephthalic series as the number of methylene groups in the diol unit in-

creases. In the same way, oxalic derivatives have a lower melting point than the related poly(ester amide)s containing terephthaloyl units. The lowest melting temperature (145 °C) is attained for PGDG0, this value being noticeably lower than that of PGDGT (174 °C).

Third, melt-crystallized samples always show a lower degree of crystallinity than those coming from solution precipitation. Furthermore, crystallinity tends to decrease as the methylene content increases for both the oxalic and terephthalic series.

Fourth, a low degree of crystallinity is found for poly(ester amide)s of the terephthalic series when they are quenched from the melt state; a similar result is obtained with the oxalic deriva-

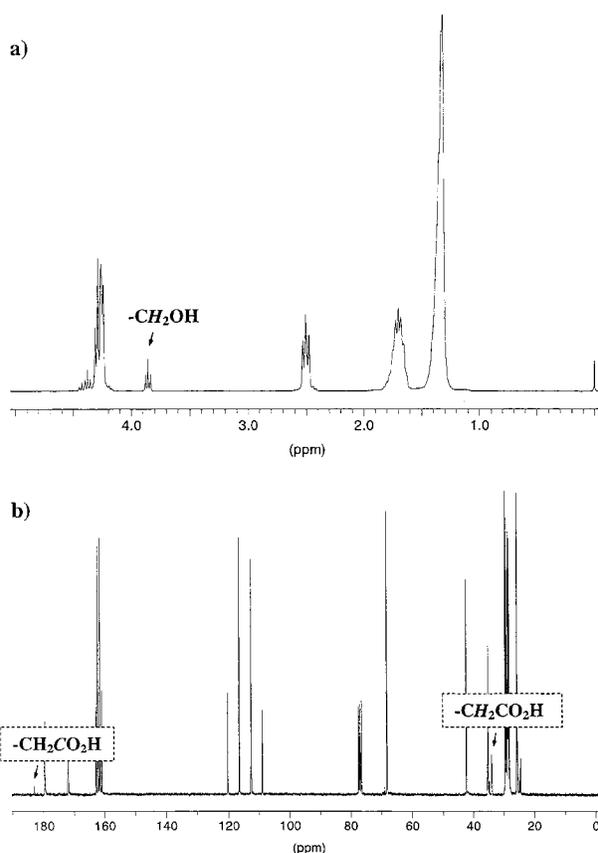


Figure 1. NMR spectra of the poly(ester amide) PGDG8. Signals attributed to terminal groups may be detected in this case because of the moderate molecular weight of the sample. a) ^1H NMR spectra of the polymer obtained by thermal polyesterification. Note the presence of $-\text{CH}_2\text{OH}$ terminal groups. b) ^{13}C NMR spectra of the polymer obtained by interfacial polymerization. In this case, only signals corresponding to terminal carboxylic groups could be observed ($-\text{CH}_2\text{CH}_2\text{COOH}$).

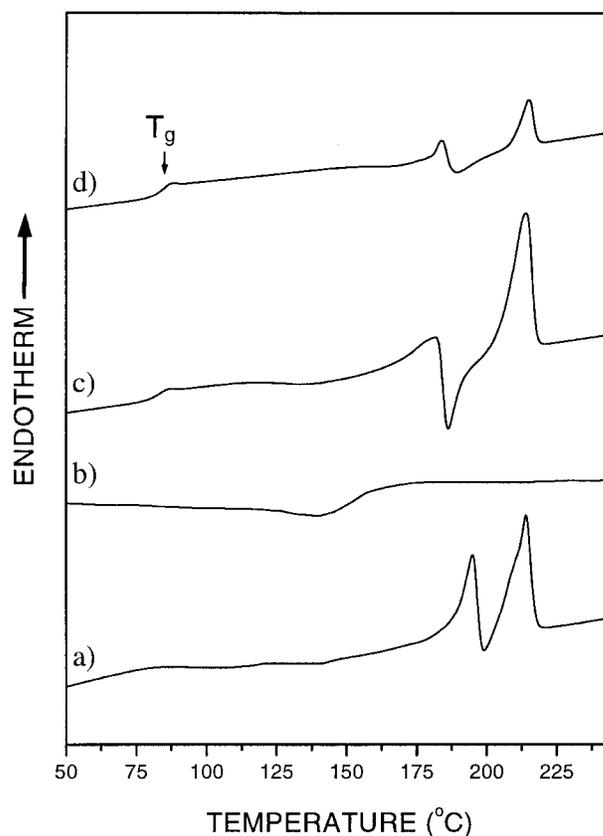


Figure 2. Sequence of four DSC scans carried out with the PGDGT sample: a) heating run at 20 °C/min, b) cooling run at 10 °C/min after keeping the sample in the melt state for 2 min, c) reheating run at 20 °C/min, and d) reheating run at 20 °C/min after quenching the sample from the melt state.

tive PGDGT. Probably the rigid main chain of these polymers hinders their crystallization at low temperatures.

Fifth, the glass-transition temperature decreases as the number of methylene groups of the diol unit (for a given series) increases. In the same way, the transition temperatures of terephthalic derivatives are higher than those of the related polymers constituted by oxaloyl residues, also in agreement with the expected decrease in chain mobility. Only PGDG0 has a glass-transition temperature (17 °C) lower than room temperature, a fact that was usual for the previously studied^{5,13} poly(ester amide)s that were derived from aliphatic dicarboxylic acids.

Sixth, polymers start to decompose at temperatures close to 300 °C, that is, 100 °C over their melting temperatures except for PGEGT. Thus, the majority of these polymers can be well processed from the melt state. Thermogravimetries

Table IV. Main Calorimetric Data for the Poly(ester amide)s Derived from Terephthalic or Oxalic Acid^a

Polymer	First DSC Run			Second DSC Run			Third DSC Run			Fourth DSC Run				
	T_f (°C)	ΔH_f (kJ/mol)	χ (%)	T_c (°C)	ΔH_c (kJ/mol)	T_f (°C)	ΔH_f (kJ/mol)	χ (%)	T_g (°C)	T_f (°C)	ΔH_f (kJ/mol)	χ (%)	$T_{d,0}$ (°C)	$T_{d,1/2}$ (°C)
PGEGT	280, 297	26.6	— ^b	—	—	—	—	—	—	—	—	—	285	408
PGBGT	195, 214 ^c	18.0	62	141	5.3	182, 214 ^c	16.1	39	87	184 ^c , 215 ^c	3.5	3.0	310	396
PGHGT	214	12.3	34	174	11.4	202, 214	11.4	35	82	214	12.7	3.5	315	395
PGDGT	152, 174	30.1	50	105	13.6	151	14.8	25	53	151 ^c	5.3	2.0	260	409
PGBG0	132, 173 ^c	18.3	49	109	5.7	132 ^c , 173 ^c	11.9	33	52	132 ^c , 172 ^c	8.0	7.7	290	375
PGHG0	142, 167	12.5	40	130	9.7	153, 166	10.9	35	40	146, 164 ^c	8.9	28	290	388
PGDG0	106, 138, 145	18.9	34	118	14.7	139	16.1	29	17	137, 145	16.0	29	290	401

^a Temperature of the peak with lower heat of fusion is indicated by italics when a double melting peak is observed.

^b Polymer decomposes, and consequently the value could not be estimated.

^c Cool crystallization peak is observed before the melting peak.

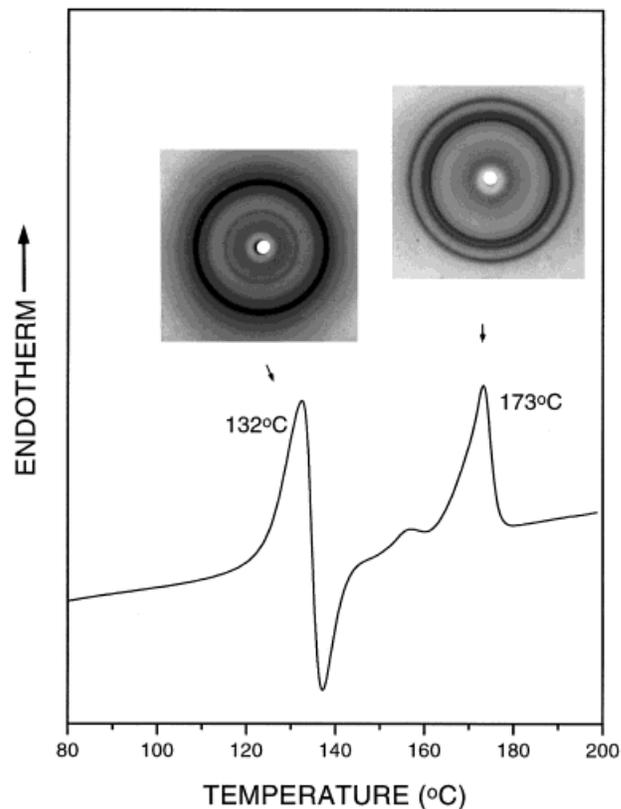


Figure 3. DSC heating run of PGBGO prepared by precipitation with acetone of a formic acid solution. Insets correspond to the X-ray powder patterns of samples with predominant melting points at 132 and 173 °C.

(Fig. 4) show different decomposition steps. The weight loss associated with the first step increases as the length of the diol also increases. The maximum degradation rate in this first step

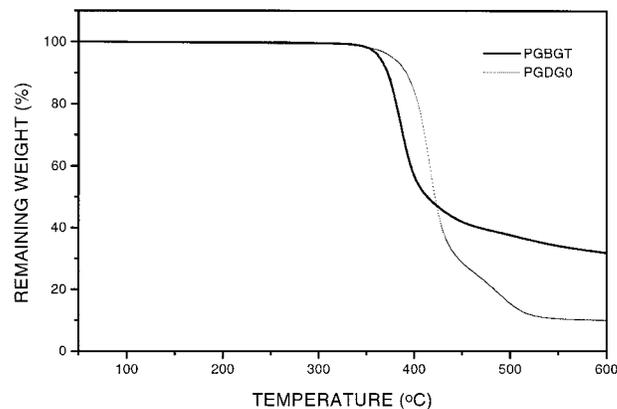
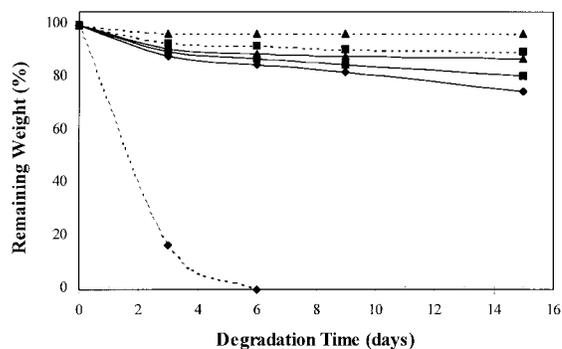


Figure 4. Thermogravimetric analyses of (—) PGBGT and (---) PGDG0 taken as representative polymers of each series.

Table V. Remaining Weight (%) of Poly(ester amide)s Derived from Oxalic or Terephthalic Acid after the Indicated Days of Degradation in Different Enzymatic Media

Time (days)	PGBG0			PGHG0			PGDG0			PGBGT			PGHGT			PGDGT		
	Lipase	Prot.		Lipase	Prot.		Lipase	Prot.		Lipase	Prot.		Lipase	Prot.		Lipase	Prot.	
		Papain	K															
0	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
3	97	93	17	93	63	100	100	100	100	91	90	88	91	91	89	98	96	97
6	97	92	0	93	48	100	100	100	100	89	87	85	90	89	88	97	96	96
9	97	91	0	92	36	100	100	100	100	88	85	82	89	89	88	96	95	95
15	97	90	0	91	13	100	100	100	100	87	81	75	89	89	86	95	95	92


Figure 5. Plot of the remaining weight (%) versus degradation time (days) in enzymatic media containing proteinase K (■), papain (◆), or lipase from *Candida cylindracea* (▲) for PGBG0 (---) and PGBGT (—).

is attained in the 360–400 °C range. A considerable residue (10–35%) remains at temperatures as high as 550 °C.

Enzymatic Degradation of Poly(ester amide)s Containing Oxaloyl and Terephthaloyl Residues

Degradation was only monitored by measurements of the remaining weight after exposure to the degradation media because it is well known that the enzymatic process takes place at the film surface in the initial stages. Thus, the changes in the intrinsic viscosity of the remaining samples were expected to be minimal. The study was carried out with three of the following different enzymes: two proteases (proteinase K and papain) and an esterase (lipase from *Candida cylindracea*) that were found to be the most effective ones for the degradation of related aliphatic poly(ester amide)s containing glycine.¹⁹

Table V lists the remaining weight of all samples after different days of exposure to the indicated media. Figure 5 shows the plot of the remaining weight versus degradation time for PGBG0 and PGBGT that were taken as representative of each series because they were the most degradable compounds. In agreement with our previous results,¹⁹ all polymers are more susceptible to enzymatic attack with papain. On the contrary, they are more resistant to the lipase enzymatic medium.

The degradability of the studied polymers in the papain enzymatic medium is compared in Figure 6. Great differences are found. The highly hydrophilic PGBG0 poly(ester amide) has the highest degradation rate. A valuable degradation rate is also found for the oxalic derivative PGGH0. On the contrary,

polymers with a high number of hydrophobic methylene groups, as those derived from dodecanediol, show little or no weight loss (PGDGT or PGDG0, respectively). Finally, the terephthalic derivative PGBGT degrades slowly but steadily with a 25% weight loss after a 15-day degradation period. In this sense, its behavior is comparable to the related aliphatic derivative PGBG8 that showed¹⁹ a similar weight loss after the same period of exposure to the papain media. However, the higher intrinsic viscosity of this aliphatic derivative (0.73 versus 0.60 dL/g) should also be pointed out.

NMR spectra of the PGBG0 sample after a 3-day degradation period in the papain media were practically identical to those obtained with the initial sample, indicating that polymer fragments produced during degradation were totally solubilized. On the contrary, a great number of additional peaks were detected in the spectra of the terephthalic PGBGT derivative (Fig. 7). They correspond to different kinds of terminal groups that arise from both ester and amide cleavages, as reported for related poly(ester amide)s.¹⁹ Furthermore, the detection of these end groups indicates that solubilization is only possible when small fragments are produced. Consequently, degradation of terephthalic derivatives appears to be underestimated when only weight loss is evaluated.

The superficial texture of the samples changes clearly during degradation. The initial samples have some crevices and pores [Fig. 8(a)] as a result of the preparation method on the basis of the solvent evaporation. After incubation, these pores and

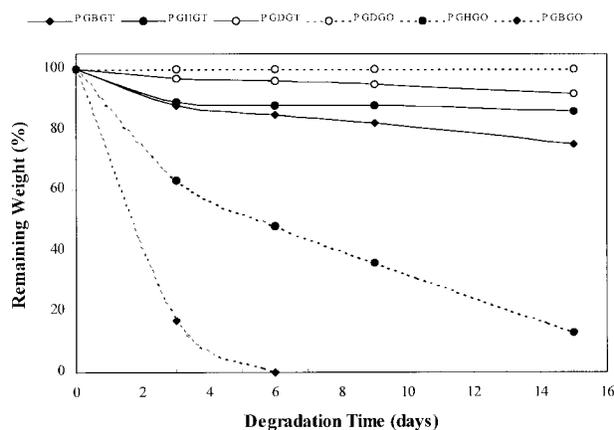


Figure 6. Plot of the remaining weight (%) versus degradation time (days) in a papain enzymatic medium for oxalic (---) and terephthalic (—) derivatives: PGBG0 and PGBGT (◆), PGHG0 and PGHG0 (●), and PGDGT and PGDGT (○).

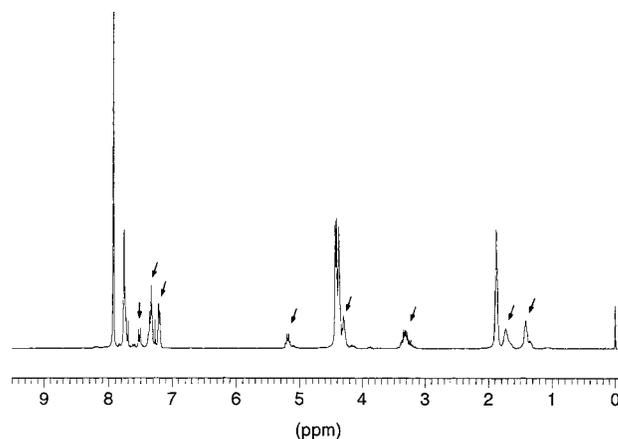


Figure 7. ¹H NMR spectra of a PGBGT sample after exposure up to 15 days in a papain enzymatic medium at 37 °C. Signals corresponding to terminal groups produced by ester (associated with the different kind of methylene groups) or amide (associated with the multiple aromatic and NH peaks) cleavages are indicated.

crevices become deeper and bigger. The changes are dramatic in the last stages of degradation, as shown in Figures 8(b–c) where the PGBG0 sample appears practically desintegrated.

CONCLUSIONS

Poly(ester amide)s defined by the sequence —NHCH₂CO—O(CH₂)_nO—COCH₂NH—COXCO— can be easily synthesized following a two-step procedure that implies a final thermal polyesterification. This new method has been compared in detail with the previously reported synthesis on the basis of interfacial polymerization. The thermal synthesis of the indicated glycine derivatives occurs with high yield and generally provides polymers with the right molecular weight to render fiber- and film-forming properties. Thermal synthesis seems to be useful for preparing polymers derived from diacid chlorides such as oxaloyl or succinoyl chlorides and diols such as 1,4-butanediol because the interfacial synthesis of these polymers is highly deficient. Furthermore, the intrinsic viscosities of the other studied polymers with aliphatic or aromatic components are generally higher when thermal synthesis is used.

Poly(ester amide)s with high glass-transition temperatures may be obtained by using rigid units such those provided by oxaloyl or terephthaloyl moieties. Values of 87 °C (PGBGT) and 52 °C (PGBG0) contrast with those previously reported

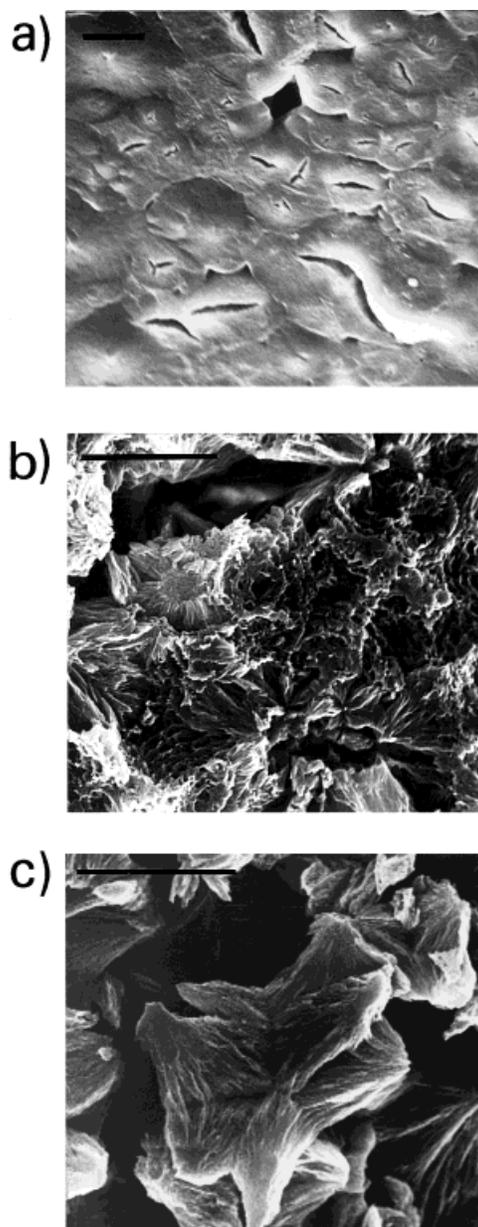


Figure 8. Scanning electron micrographs of PGBG0 samples at different stages of incubation with a papain solution: (a) initial surface, (b) sample after a 1.5-day degradation period, and (c) sample after a 3-day degradation period. Scale bars: 10 μm .

for aliphatic derivatives that were close to 0 $^{\circ}\text{C}$. Furthermore, these new polymers constituted by stiff units appear to be stable through fusion up to 285 $^{\circ}\text{C}$ and consequently can be easily processed. The only exception is the polymer derived from ethyleneglycol and terephthalic acid because of its high melting point (297 $^{\circ}\text{C}$).

The new poly(ester amide)s appear to be susceptible to the proteolytic enzymatic attack with

papain as a result of the presence of glycine units. Degradable polymers may still be obtained when oxaloyl or terephthaloyl units are incorporated. The maximum degradation rate is observed in the two studied series for the polymers derived from 1,4-butanediol. This observation agrees with the high degradability observed for commercial polyesters and poly(ester amide)s derived from this diol (BIONOLLE²⁰ and BAK,¹ respectively).

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