

# Water-Soluble Esters of Biosynthetic Poly( $\gamma$ -glutamic acid)

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**ABSTRACT:** Water-soluble poly( $\gamma$ -glutamic acid) (PGGA) esters were prepared by transesterification of poly( $\alpha$ -methyl- $\gamma$ -glutamate) with mono-, di-, and triethylene glycols with one hydroxyl end group blocked as methyl ether. Only the monoglycol appeared to be crystalline with melting at 160°C, and glass-transition temperatures were found to increase from 10 to 60°C with the length of the oxyethylene side chain. All these poly( $\gamma$ -glutamate)s are stable up to temperatures near 250°C. Moisture sorption, surface wettability, and hydrodegradability were evaluated as a function of time. It was found that in overall sensitivity to water increased with the glycol chain length but the behavior at short contact times was critically affected by conformational factors. © 2001 John Wiley & Sons, Inc. *J Appl Polym Sci* 82: 2027–2036, 2001

**Key words:** PGGA ester; sorption; wettability; hydrodegradability; transesterification; hydrogels

## INTRODUCTION

Poly( $\gamma$ -glutamic acid) (PGGA) is a bacterially produced water-soluble polyamide that is the object of current interest because of its natural origin and biodegradability.<sup>1</sup> The polymer is different from proteins in that peptide linkages are formed between the  $\alpha$ -amino and the  $\gamma$ -carboxylic acid groups. This poly( $\gamma$ -peptide), however, is able to adopt regular folded conformations similar to the  $\alpha$ -helix characteristic of poly( $\alpha$ -amino acid)s.<sup>2,3</sup> PGGA and its derivatives are considered promising biocompatible materials that could display

functional properties of biomedical interest. In particular, the conformational sensitivity of PGGA to changes in pH and ionic strength makes this biopolymer a potential candidate to produce “smart” hydrogels able to respond intelligently to controlled environmental changes.<sup>4</sup>

Esterification of PGGA is the approach mostly used to render derivatives with improved physical properties and solubility.<sup>5</sup> All PGGA esters investigated to date are alkyl or benzyl esters, in which the ionizable highly hydrophilic carboxylic group is converted into a stable hydrophobic alkoxy-carbonyl or benzyloxy-carbonyl group. Although these PGGA esters display an enhanced solubility in organic solvents and may be handled more easily than PGGA, they interact poorly with water and, as a consequence, they are generally non-water-soluble polymers. To preserve the affinity of PGGA for water, PGGA hydrogels have been prepared by partial crosslinking, using both physical

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**Table I** Characteristics of Poly( $\alpha$ -methyl- $\gamma$ -glutamate)s Used for the Synthesis of PAME<sub>n</sub>G

	$[\eta]$ (dL g <sup>-1</sup> ) <sup>a</sup>	$M_v$ <sup>b</sup>	$M_w$ <sup>c</sup>	PD <sup>c</sup>	D-Enantiomer (%)	Obtained PAME <sub>n</sub> G
PAAG-1 (I)	0.67	35,000	50,200	3.9	~ 90%	PAME <sub>1</sub> G
PAAG-1 (II)	0.87	50,000	82,300	2.5	~ 90%	PAME <sub>2</sub> G, PAME <sub>3</sub> G

<sup>a</sup> Intrinsic viscosity measured in DCA at 25 ± 0.1°C.

<sup>b</sup> Viscosity-average molecular weight estimated by using the equation reported for poly( $\gamma$ -methyl- $\alpha$ -L-glutamate).<sup>13</sup>

<sup>c</sup> Weight-average molecular weight and polydispersity measured by SEC.

and chemical methods such as  $\gamma$ -irradiation<sup>6</sup> and reaction with dibromoalkanes,<sup>7</sup> diamines,<sup>8</sup> or diisocyanates.<sup>9</sup> Biomedical applications intended for these hydrogels include soft tissue augmentation, controlled drug release, selective separation membranes, and biosensors.

In this study we report on a family of water-soluble PGGA esters prepared from mono-, di-, and triethylene glycols with one hydroxyl end group blocked as methyl ether. This is referred to throughout as PAME<sub>n</sub>G, where *n* indicates the number of oxyethylene units contained in the side chain. Oligo(ethylene glycol) chains are biodegradable and biocompatible building blocks widely used in the design of biomedical materials.<sup>10</sup> The synthesis, basic properties, water affinity, and hydrolytic degradability of these new PGGA esters are described.

## EXPERIMENTAL

### Materials and Synthesis

Poly( $\gamma$ -glutamic acid) used in this work was obtained by fermentation of *B. licheniformis* in medium E according to the classical method developed by Thorne et al.<sup>11</sup> and using the specific conditions reported in detail elsewhere.<sup>12</sup> The enantiomeric composition of this PGGA was D : L ≈ 9 : 1 and its molecular weight was estimated by SEC to be about 10<sup>6</sup>. A water solution of this product was irradiated with microwaves to render a PGGA sample with a molecular weight of about 10<sup>5</sup>. Poly( $\alpha$ -methyl- $\gamma$ -glutamate) (PAAG-1) was prepared by reaction of sonicated PGGA with diazomethane. The characteristics of the two PAAG-1 samples used for the preparation of PAME<sub>n</sub>G concerned in this work are shown in Table I. The synthesis of PAME<sub>n</sub>G was performed by transesterification of PGGA-1 according to the recipes described below.

### Poly[ $\alpha$ -(2-methoxy-ethyl)- $\gamma$ -glutamate] (PAME<sub>1</sub>G)

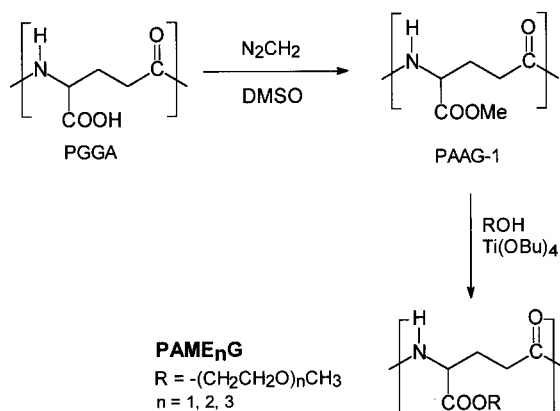
A mixture of 1.7 g (12 mmol) of PAAG-1, 28 mL (360 mmol) of 2-methoxyethanol, and 0.2 mL (0.6 mmol) of Ti(BuO)<sub>4</sub> was placed in a 100-mL round-bottom flask and heated at 125°C under a nitrogen flow for a period of 10 h. The reaction was finished when the area ratio of the OCH<sub>3</sub> signal to the main chain CH signal was 3 in the <sup>1</sup>H-NMR spectrum. The polymer was separated from the reaction mixture by precipitation with diethyl ether and repeatedly washed with this solvent. A slightly yellowish powder was obtained after drying at 50°C under vacuum.

Yield: 90%. FTIR (film from TFE) (cm<sup>-1</sup>): 3297 (amide A), 3065 (amide B), 1652 (amide I), 1560 (amide II); <sup>1</sup>H-NMR (CDCl<sub>3</sub>-TFA),  $\delta$  (ppm): 7.78 (s, br, 1H, NH), 4.69 (m, br, 1H, NCH), 4.51 (d, 2H, COOCH<sub>2</sub>), 3.93 (s, 2H, CH<sub>2</sub>OCH<sub>3</sub>), 3.60 (s, 3H, OCH<sub>3</sub>), 2.63 (m, br, 2H, CH<sub>2</sub>CO), 2.4–2.2 (m, 2H, CHCH<sub>2</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>-TFA),  $\delta$  (ppm): 176.81 (CON), 173.11 (COO), 70.40 (CH<sub>2</sub>OCH<sub>3</sub>), 65.22 (COOCH<sub>2</sub>), 58.59 (OCH<sub>3</sub>), 53.56 (NCH), 31.98 (CH<sub>2</sub>CO), 27.66 (CHCH<sub>2</sub>).

### Poly[ $\alpha$ -2(2-methoxyethoxy)-ethyl- $\gamma$ -glutamate] (PAME<sub>2</sub>G)

A mixture of 0.29 g (2 mmol) of PAAG-1, 7.1 mL (60 mmol) of 2(2-methoxyethoxy)-ethanol, and 0.068 mL (0.2 mmol) of Ti(BuO)<sub>4</sub> was placed in a 25-mL round-bottom flask and heated at 150°C under a nitrogen flow for a period of 24 h. The reaction was finished when the area ratio of the OCH<sub>3</sub> signal to the main chain CH signal was 3 in the <sup>1</sup>H-NMR spectrum. The polymer was separated from the reaction mixture by precipitation with diethyl ether and repeatedly washed with this solvent. A slightly yellowish powder was obtained after drying at 50°C under vacuum.

Yield: 90%. FTIR (film from TFE) (cm<sup>-1</sup>): 3296 (amide A), 3068 (amide B), 1650 (amide I), 1545 (amide II); <sup>1</sup>H-NMR (CDCl<sub>3</sub>-TFA),  $\delta$  (ppm): 7.74 (s, br, 1H, NH), 4.65 (m, br, 1H, NCH), 4.50–4.40 (d, 2H, COOCH<sub>2</sub>), 3.91–3.85 (m, 6H, CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>), 3.55 (s, 3H, OCH<sub>3</sub>),



**Figure 1** Scheme of synthesis leading to PAME<sub>n</sub>G.

2.60 (m, br, 2H, CH<sub>2</sub>CO), 2.37–2.16 (m, 2H, CHCH<sub>2</sub>).  
<sup>13</sup>C-NMR (CDCl<sub>3</sub>-TFA), δ (ppm): 176.42 (CON), 172.91 (COO), 71.24 (CH<sub>2</sub>OCH<sub>3</sub>), 69.68 (OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>), 68.91 (COOCH<sub>2</sub>CH<sub>2</sub>), 65.40 (COOCH<sub>2</sub>), 58.43 (OCH<sub>3</sub>), 53.25 (NCH), 31.77 (CH<sub>2</sub>CO), 27.42 (CHCH<sub>2</sub>).

### Poly[α-2(2-(2-methoxyethoxy)-ethoxy)-ethyl-γ-glutamate] (PAME<sub>3</sub>G)

A mixture of 0.29 g (2 mmol) of PAAG-1, 9.8 mL (60 mmol) of 2(2-(2-methoxyethoxy)-ethoxy)-ethanol, and 0.10 mL (0.3 mmol) of Ti(BuO)<sub>4</sub> was placed in a 25-mL round-bottom flask and heated at 125°C under a nitrogen flow for a period of 30 h. The reaction was finished when the area ratio of the OCH<sub>3</sub> signal to the main chain CH signal was 3 in the <sup>1</sup>H-NMR spectrum. The polymer was separated from the reaction mixture by precipitation with diethyl ether and repeatedly washed with this solvent. A slightly yellowish powder was obtained after drying at 50°C under vacuum.

Yield: 82%. FTIR (film from TFE) (cm<sup>-1</sup>): 3304 (amide A), 3067 (amide B), 1649 (amide I), 1546 (amide II); <sup>1</sup>H-NMR (CDCl<sub>3</sub>-TFA), δ (ppm): 7.72 (s, br, 1H, NH), 4.63 (m, br, 1H, NCH), 4.50–4.40 (d, 2H, COOCH<sub>2</sub>), 3.9–3.88 (m, br, 10H, CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>), 3.56 (s, 3H, OCH<sub>3</sub>), 2.60 (m, br, 2H, CH<sub>2</sub>CO), 2.37–2.16 (m, 2H, CHCH<sub>2</sub>). <sup>13</sup>C-NMR (CDCl<sub>3</sub>-TFA), δ (ppm): 176.51 (CON), 173.04 (COO), 71.37 (CH<sub>2</sub>OCH<sub>3</sub>), 670.14 (OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>), 70.01 (CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>O), 68.97 (COOCH<sub>2</sub>CH<sub>2</sub>), 65.46 (COOCH<sub>2</sub>), 58.36 (OCH<sub>3</sub>), 53.36 (NCH), 31.77 (CH<sub>2</sub>CO), 27.42 (CHCH<sub>2</sub>).

### Methods and Measurements

Elemental analyses were carried out in the Servicio de Microanálisis de CID (CSIC, Barcelona).

**Table II** Synthesis Results

PAME <sub>n</sub> G	t (h) <sup>a</sup>	T (°C) <sup>a</sup>	X (%) <sup>b</sup>	Yield (%)	[η] (dL g <sup>-1</sup> ) <sup>c</sup>	M <sub>v</sub> <sup>d</sup>	M <sub>w</sub> <sup>e</sup>	PD <sup>e</sup>	[D] (%)	Elemental Analysis <sup>f</sup>		
										C (%)	H (%)	N (%)
PAME <sub>1</sub> G	10	125	>95	90	0.48	22,400	28,400	1.8	>80	43.91 (44.86)	6.32 (7.48)	6.29 (6.54)
PAME <sub>2</sub> G	24	150	>95	90	0.58	29,000	43,900	1.8	>80	45.45 (46.50)	6.53 (7.75)	5.80 (5.43)
PAME <sub>3</sub> G	30	125	>95	80	0.67	35,000	63,800	1.9	>80	46.49 (47.68)	7.01 (7.94)	5.04 (4.63)

<sup>a</sup> Conditions used for the transesterification reaction.

<sup>b</sup> Conversion determined by NMR.

<sup>c</sup> Intrinsic viscosity measured in DCA at 25 ± 0.1°C.

<sup>d</sup> Viscosity-average molecular weight estimated by using the equation reported for poly(γ-methyl-α-L-glutamate).<sup>13</sup>

<sup>e</sup> Weight-average molecular weight and polydispersity measured by SEC.

<sup>f</sup> In parentheses, elemental analysis calculated for the respective PAME<sub>n</sub>G containing 1.5 mol of absorbed water per repeating unit.

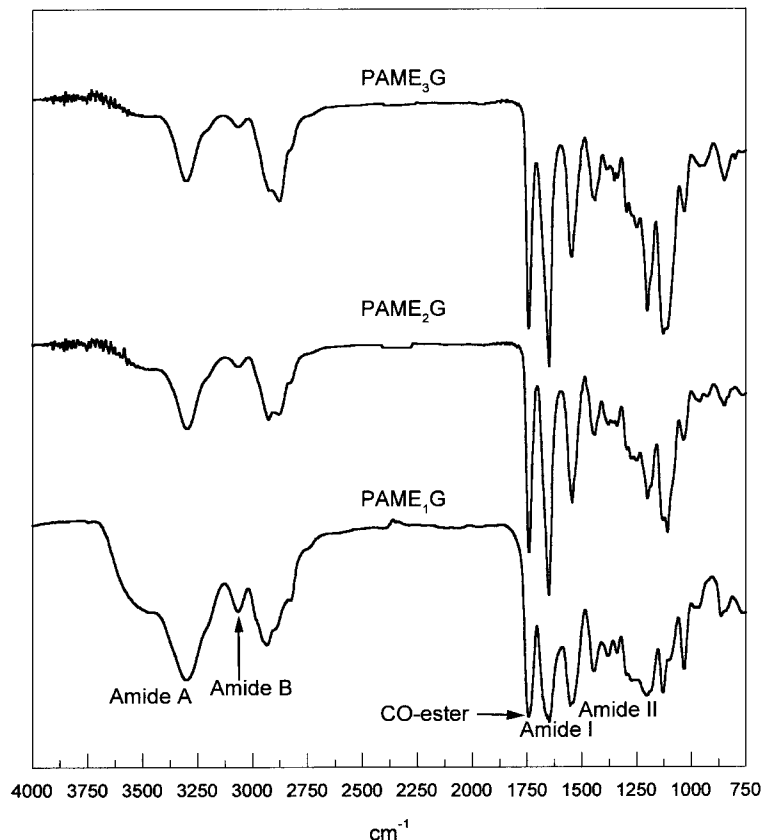


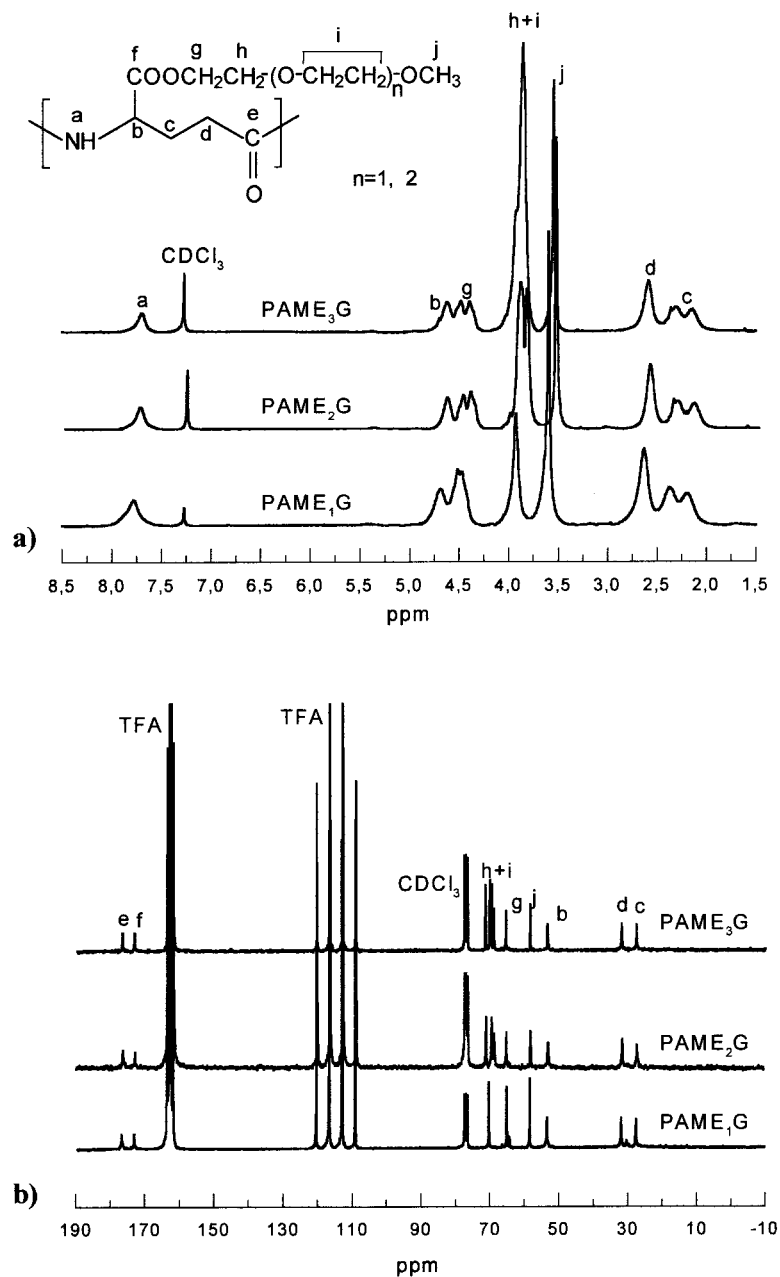
Figure 2 Compared infrared spectra of PAME<sub>n</sub>G.

The enantiomeric composition was determined by HPLC of the polymer hydrolyzates after reaction with the Marphey's reagent, according to a previously described method.<sup>12</sup> Viscosity measurements were performed in dichloroacetic acid (DCA) with a microviscometer (Cannon-Ubbelohde) at a temperature of  $25 \pm 0.1^\circ\text{C}$  and polymer concentrations ranging from 1 to 0.3 g dL<sup>-1</sup>. The Mark-Houwink equation reported for poly( $\alpha$ -methyl- $\gamma$ -L-glutamate)<sup>13</sup> was used for approximate estimations of the viscosity-average molecular weights. Infrared spectra were recorded with a Perkin-Elmer 2000 spectrophotometer from films prepared by casting from TFE solutions on KBr plates. NMR spectra were recorded on an AMX-300 Bruker spectrometer operating at 300.1 and 70.48 MHz for <sup>1</sup>H and <sup>13</sup>C, respectively. Samples were dissolved in a TFA-CDCl<sub>3</sub> mixture and added with tetramethyl silane for calibration.

DSC analysis was made on a Pyris 1 Perkin-Elmer calorimeter calibrated with indium. Samples weighing 3–5 mg were used at heating rates of  $20^\circ\text{C min}^{-1}$  under a nitrogen atmosphere. TGA

measurements were performed on a TGA-6 Perkin-Elmer thermobalance at a heating rate of  $10^\circ\text{C min}^{-1}$ . Onset decomposition temperatures were taken as those given by the intersection of the tangents to the TGA trace at the inflection point and at  $100^\circ\text{C}$ . Isothermal decompositions were measured as the weight remaining after heating at  $200^\circ\text{C}$  for 30 min. X-ray diffraction analysis was performed in a modified Statton camera using monochromatic CuK $\alpha$  radiation of  $\lambda = 0.15418$  nm, and diffraction patterns were recorded on photographic flat films.

Hygroscopicity essays were performed with disks of PAME<sub>n</sub>G prepared by hot-pressing. The disks were exposed to a 100% humid atmosphere at  $20^\circ\text{C}$  and absorbed water was determined by weighing. Contact angles between liquid and solid surfaces were measured by means of a G10 contact angle measuring system. Angle values were registered after 2 min of dropping the corresponding liquid onto the polymer surface and at least 10 measurements were made. Hydrolytic degradation essays were carried out using aque-



**Figure 3**  $^1\text{H}$ -NMR (a) and  $^{13}\text{C}$ -NMR (b) spectra of  $\text{PAME}_n\text{G}$ .

ous solutions of  $\text{PAME}_n\text{G}$  (30 mg in 5 mL) incubated at  $37 \pm 0.1^\circ\text{C}$  for increasing periods of time. For the analysis of the degraded products, the incubated solutions were evaporated to dryness and the residues were dissolved in butanol and evaporated again. This process was repeated as many times as necessary for total removal of the glycol generated in the hydrolysis. Final residues were subjected to SEC and viscosity determinations.

## RESULTS AND DISCUSSION

### Synthesis and Characterization

The route of synthesis followed for preparation of  $\text{PAME}_n\text{G}$  is depicted in Figure 1. Methylation of bacterial PGGA with diazomethane and transesterification of the methyl ester with  $\text{MeO}(\text{CH}_2\text{CH}_2)_n\text{OH}$  catalyzed by  $\text{Ti}(\text{BuO})_4$  led to the oxyalkylated esters in high yields and show-

**Table III Thermal, Wettability, and X-ray Diffraction Data of PAME<sub>n</sub>G**

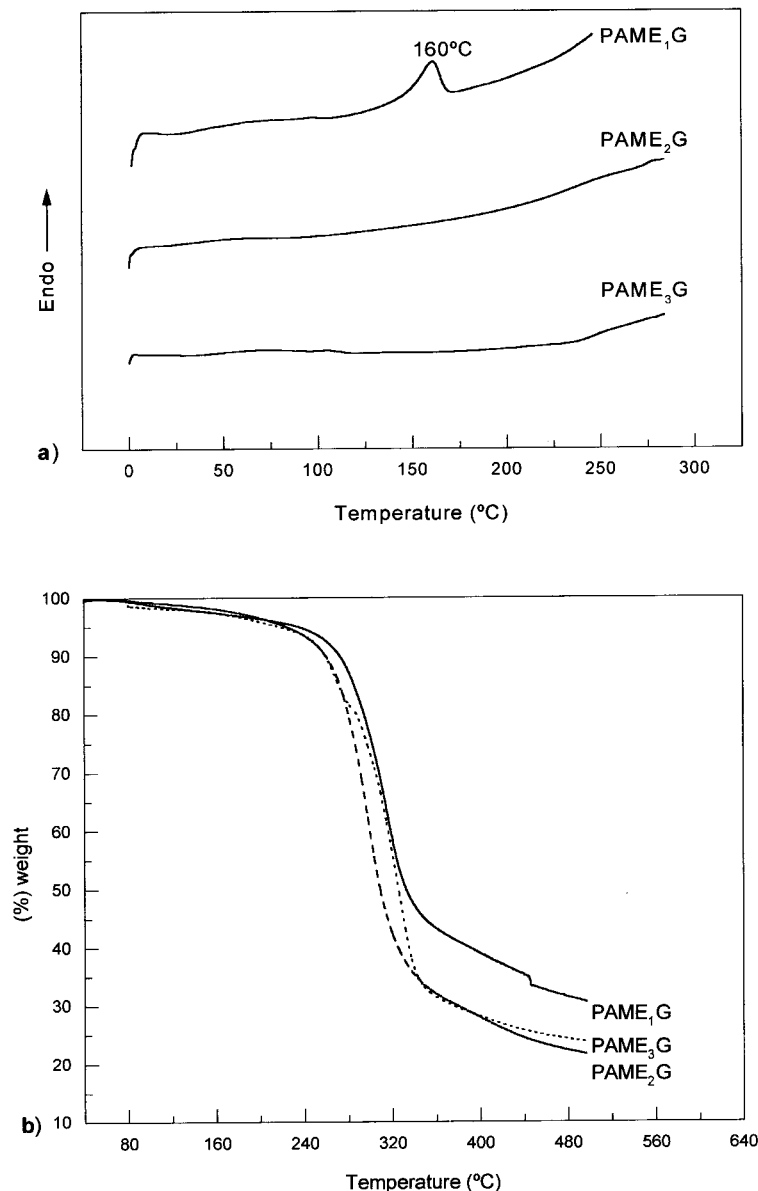
PAME <sub>n</sub> G	Contact Angle Measurements												X-ray Diffraction <i>d</i> <sub>hkl</sub> <sup>j</sup> (nm)
	DSC		TGA				H <sub>2</sub> O <sup>e</sup>		DMSO <sup>f</sup>				
	<i>T</i> <sup>a</sup> (°C)	<i>T</i> <sup>a</sup> (°C)	<sup>o</sup> <i>T</i> <sub>d</sub> <sup>b</sup> (°C)	<sup>d</sup> <i>T</i> <sub>d</sub> <sup>b</sup> (°C)	Δ <i>W</i> <sup>c</sup> (%)	Δ <i>W</i> <sup>d</sup> (%)	θ <sub>w</sub> <sup>g</sup> (deg)	θ <sub>i</sub> <sup>h</sup> (deg)	SES <sup>i</sup> (mM m <sup>-1</sup> )	θ <sub>w</sub> <sup>g</sup> (deg)	θ <sub>i</sub> <sup>h</sup> (deg)	SES <sup>i</sup> (mM m <sup>-1</sup> )	
PAME <sub>1</sub> G	36	160	285	315	31	91	49.5	42.7	57.2	82.3	50.3	38.0	1.46, 1.07, 0.55, 0.45, 0.39, 0.36
PAME <sub>2</sub> G	42	—	270	297	21	87	55.7	40.0	54.4	78.7	50.6	39.1	—
PAME <sub>3</sub> G	49	—	249	267	23	90	70.4	43.0	46.2	78.0	51.8	38.9	—

<sup>a</sup> Glass-transition and melting temperatures.<sup>b</sup> Onset and derivative decomposition temperatures.<sup>c</sup> Remaining weight after heating up to 500°C at a rate of 20°C min<sup>-1</sup>.<sup>d</sup> Remaining weight after heating at 200°C for 30 min.<sup>e</sup> Measurements on films made by casting from water.<sup>f</sup> Measurements on films made by casting from DMSO.<sup>g</sup> Contact angle with water.<sup>h</sup> Contact angle with iodomethane.<sup>i</sup> Solid surface energy estimated according to the Owens equation.<sup>j</sup> Uncalibrated interplanar spacings measured by powder X-ray diffraction.

ing no trace of side chain heterogeneity. Synthesis conditions, results, and characteristics of the obtained polymers are given in Table II. We previously used this method for the preparation of a wide variety of alkyl esters of PGGA.<sup>14</sup> The procedure is known to entail occasional scission of the main chain with the consequent slight reduction in molecular weight, whereas the enantiomeric content of the original PGGA remains unaffected.

The chemical structure of PAME<sub>n</sub>G was assessed by both FTIR and NMR spectroscopy. IR spectra are shown in Figure 2, illustrating how characteristic absorption bands appear at the expected places with the expected intensities. It is worth noting that the relative breadth of bands associated with the amide group in PAME<sub>1</sub>G indicate that a particular interaction of such a group, probably with the 2-methoxy-ethoxycarbonyl side group, is taking place in this polymer. Moreover, the broad absorption appearing at 3500 cm<sup>-1</sup>, indicative of the presence of absorbed water, is corroborated by elemental analysis results. <sup>1</sup>H- and <sup>13</sup>C-NMR spectra for the three PAME<sub>n</sub>G are shown in Figure 3. All signals appearing in both types of spectra are consistent with the expected chemical formulas. Specific mention should be made of the main chain CH and the side chain CH<sub>3</sub> signals appearing in the <sup>1</sup>H spectra at about 4.6 and about 3.5 ppm, respectively, because they are the signals used to follow the advancement of the transesterification reaction and to determine the conversion that is finally achieved.

Thermal properties and X-ray diffraction data of PAME<sub>n</sub>G are compared in Table III. Glass-transition temperatures of these polymers were found to increase with the length of the oligoethylene glycol side group. PAME<sub>1</sub>G was the only member of the series able to show crystallinity. DSC traces of the three polymers are compared in Figure 4(a), which illustrates the endothermic peak at 160°C, characteristic of a fusion process, in contrast to the flatness exhibited by the other two traces. In agreement with DSC results, PAME<sub>1</sub>G was again the only member giving an X-ray diffraction pattern characteristic of a well-ordered structure. Comparison of the observed interplanar spacings for PAME<sub>1</sub>G with those reported for poly(α-butyl-γ-glutamate) (PAAG-4)<sup>15</sup> revealed a close similarity between them, indicating that a common crystal structure is likely adopted in both cases. The structure proposed for PAAG-4 consists of a tetragonal array of intramolecularly hydrogen bonded 5/2 helices of the type described for poly(α-benzyl-γ-L-glutamate) of chemical origin.<sup>16</sup> On the other hand, the thermal stability of PAME<sub>n</sub>G was found to slightly decrease with the size of the side chain. TGA traces are compared in Figure 4(b), showing that the three compounds suddenly decompose when the temperature rises above 250°C. Both onset temperatures (<sup>o</sup>*T*<sub>d</sub>) and those at which degradation occurs at the maximum rate (<sup>d</sup>*T*<sub>d</sub>) were found to decrease with the increase of *n*. Conversely, the thermal resistance below the onset decomposition temperature proved to be essentially independent of the side chain constitution. In fact, isothermal



**Figure 4** DSC (a) and TGA (b) traces of PAME<sub>n</sub>G.

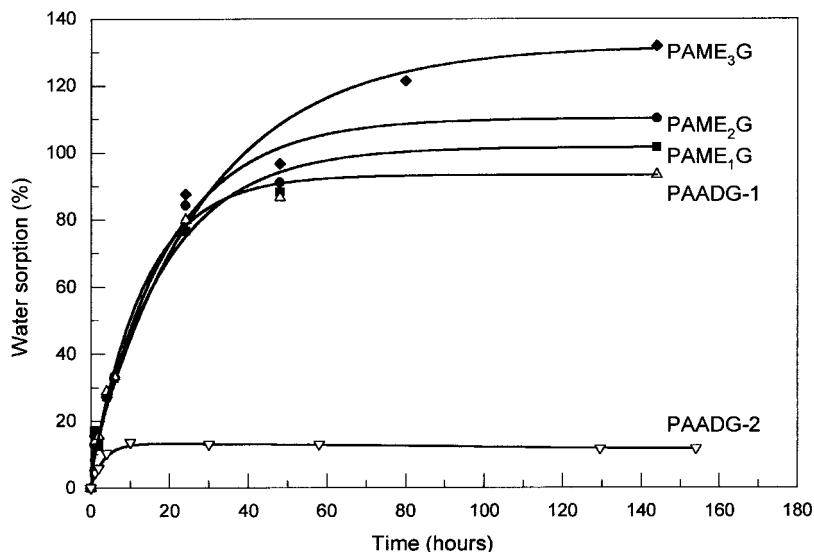
treatment at 200°C showed a weight loss of about 10% after 30 min of heating for the three studied PAME<sub>n</sub>G.

#### Water Interaction and Hydrolytic Degradability

PAME<sub>n</sub>G are water-soluble polymers. When exposed to a humid atmosphere they all take up water very quickly to finally form a viscous solution. The uptake of water against exposure time is plotted in Figure 5 for the three PAME<sub>n</sub>G and for the alkyl esters PAAG-1 and PAAG-2. The

amount of absorbed water increased with the size of the side chain from 100% for PAME<sub>1</sub>G up to 130% for PAME<sub>3</sub>G. The plot reveals that introduction of the oxy group into the side chain enhanced the affinity for water and that small differences in the size of the side chain of the alkyl esters have profound effects on such property.

Contact angle measurements were performed to evaluate the wettability of the surface of these polymers at short times of contact. With this aim, thin films of PAME<sub>n</sub>G were prepared by casting



**Figure 5** Water sorption of PAME<sub>n</sub>G as a function of the exposure time to 100% RH atmosphere.

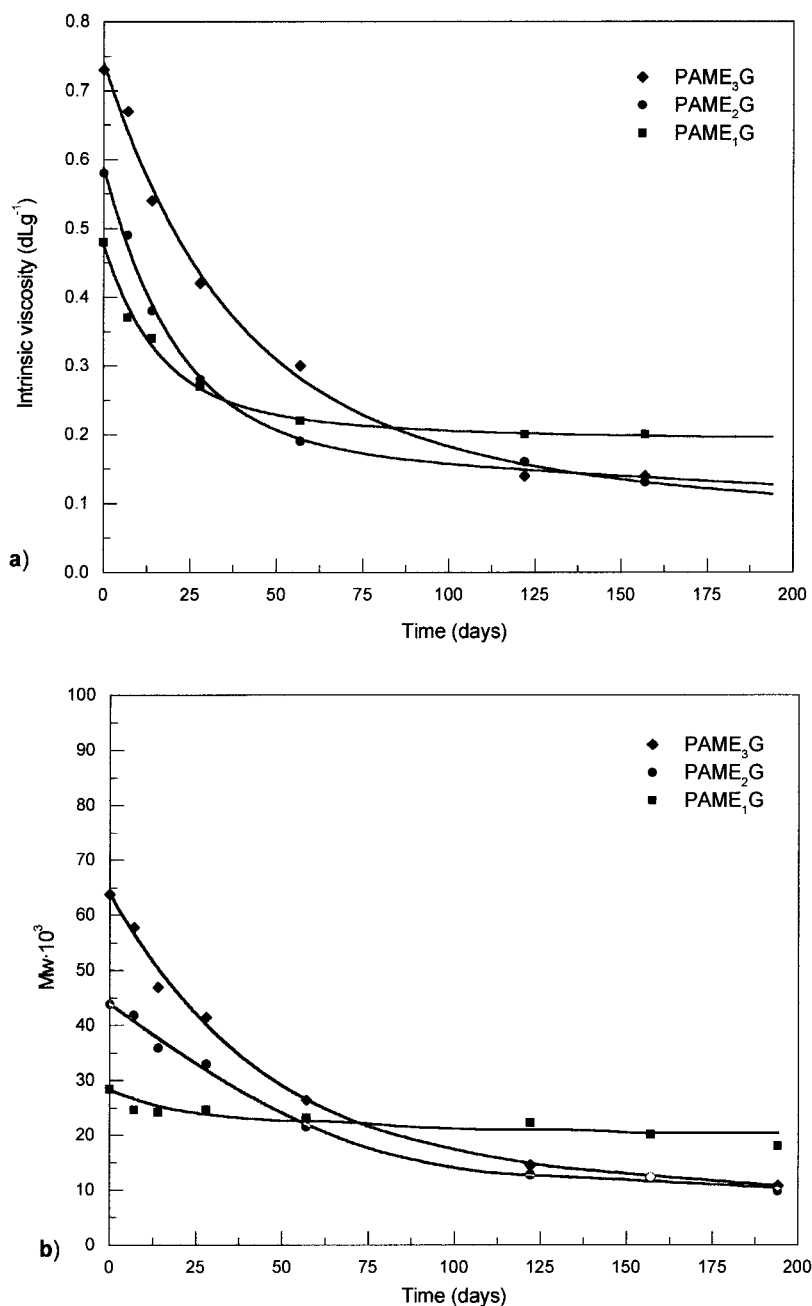
from either distilled water and dimethyl sulfoxide (DMSO), and liquid-to-solid interphase angles with water and iodomethylene were measured. Films prepared from water solution displayed higher wettability, thus affording lower  $\theta_w$  values, differences of which were greater for lower values of  $n$ . It is certainly striking that the observed  $\theta_w$  values were comparable to those reported in the literature for nylon 6,<sup>17</sup> a non-water-soluble polymer that is known to absorb water in limited quantities. On the other hand, contact angles with iodomethylene  $\theta_I$  were smaller than those for water and differences related with the method of preparation of the films appeared to be insignificant in this case. Surface energy of solids (SES), measured according to the Owens equation,<sup>18</sup> were found to be smaller for films prepared from DMSO, mainly the result of the relatively low contribution afforded by the polar component in this case. The conclusion from these results is that films of PAME<sub>n</sub>G show initial moderate wettability and that this property is dependent on the method of preparation. It seems that oxyethylene units on the film surface are more or less accessible to water, depending on the solvent used for casting. Hydrogen-bonding interactions between the oxy groups on the side chains with the main chain amide groups may be invoked to explain such an unexpected behavior.

PAME<sub>n</sub>G dissolved in water were found to degrade at a rate that is dependent on the length of the alkyloxy side chain. The decay of intrinsic

viscosity and weight-average molecular weight of the dissolved polymer with time upon incubation at 37°C is shown in Figure 6. Although the three polymers become degraded by water, the degradation rate increased with the length of the side chain. The evolution of the degradation was also followed by <sup>1</sup>H-NMR. Whereas no changes were perceived in the spectra of PAME<sub>1</sub>G after having been incubated for more than 6 months, the spectra of PAME<sub>2</sub>G and PAME<sub>3</sub>G showed significant changes that could be interpreted as resulting from the occurrence of hydrolytic reactions implicating both the ester side chain group and the amide main chain group. An accelerated degradation experiment carried out with PAME<sub>1</sub>G at 90°C for 1 month showed a sudden decay of the molecular weight down to values near that expected for glutamic acid. It is known that the hydrolytic degradation of PGGA happens very fast mainly because of the autocatalytic effect exerted by the carboxylic side groups.<sup>19</sup> Such an effect must also operate in PAME<sub>n</sub>G as soon as the ester side chain is hydrolyzed, a reaction that is favored by the water solubility displayed by these polymers. An investigative study specifically dealing with the mechanism of degradation, both thermal and hydrolytic, of PGGA as well as of its esters is forthcoming.<sup>14</sup>

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**Figure 6** Viscosity and molecular weight decay of PAME<sub>n</sub>G as a function of the incubation time in water at 37°C.

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