# Poly(ester amide)s Derived from L-Malic Acid

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ABSTRACT: A series of *aregic* poly(ester amide)s (*ar*-PEALM) with ester to amide groups ratios (*a:b*) ranging from 1:50 up to 1:2 were prepared from *O*-methyl-L-malic acid, 1,6-hexanediol, and 1,6-hexanediamine. The ester linkage was incorporated in the poly(ester amide) chain using 6-aminohexyl-pentachlorophenyl *O*-methyl-L-malate as comonomer in the polycondensation of bis(pentachlorophenyl) *O*-methyl-L-malate with 1,6-hexanediamine. The polycondensation of the amino ester alone afforded *isoregic ir*-PEALM (1:1) with both the amino alcohol and the malic units oriented in a unique manner along the polymer chain. The composition of *ar*-PEALM was found to be close to that of the feed used for polycondensation, with the diamine units incorporated in slight excess. The molecular weights of PEALM roughly oscillated between 10 000 and 50 000. All the poly(ester amide)s were semicrystalline with  $T_m$  decreasing with the content in ester groups from 168 to 144 °C and  $T_g$  falling down in parallel from 60 to 10 °C. The thermal decomposition of PEALM initiated around 260 °C and proceeded through a mechanism involving an intramolecular amidolysis reaction with generation of N-substituted cyclic malimides. PEALM poly(ester amide)s were easily degraded in water at pH 7.4, 37 °C, at a rate that increased with the content in ester groups. The hydrolytic process was found to occur preferentially on the ester linkages and to involve also the occurrence of intramolecular amidolysis reactions.

### Introduction

Polymers that are sensitive to moisture have attracted great attention due to the practical advantages that can be taken of their degradability in water. Poly-(ester amide)s are polycondensates combining the amide and ester groups in their backbone. Such hybrid nature is expected to render polymers susceptible to hydrolytic and biological degradation but retaining the good mechanical properties and processing behavior that distinguish their parent polyamides. Since Carothers<sup>1</sup> synthesized for the first time in 1932 poly(ester amide)s from diacids, diols, and diamines, a good number of these polymers covering a wide variety of constitutions have been described.<sup>2</sup> Among them, special interest presently exists for poly(ester amide)s made from naturally occurring compounds for their potential as biomedical materials. Within this group, poly(ester amide)s made from  $\alpha$ -amino acids<sup>3</sup> and from carbohydrate deriving monomers<sup>4,5</sup> constitute the two main families currently under investigation.

In this work we want to present the synthesis, characterization, and properties of a series of poly(ester amide)s obtained from L-malic acid, 6-aminohexanol, and 1,6-hexanediamine, in which the hydroxy side group of malic acid is protected as methyl ether. These poly-(ester amide)s are called PEALM (a:b), a and b being the molar content in ester and amide groups, respectively. Some years ago we reported extensively on poly-(tartaraester amide)s (PEAT), a family of semicrystalline polyamides made from 2,3-di-O-methyltartaric acid.<sup>5</sup> PEAT were proved to undergo hydrolysis under physiological conditions at a rate highly depending on the microstructure of the polymer.<sup>6</sup> Poly(tartaraester amide)s can be envisaged as deriving from poly(succinester amide)s in which two vicinal methoxy side groups have been inserted in the diacidic moiety (Scheme



1). The presence of these two methoxy groups makes PEAT very sensitive to water. The constitution of poly-(malaester amide)s are at halfway between poly(ester amide)s deriving from succinic and tartaric acid, and they are expected to show therefore intermediate properties between them. PEALM are here examined in this regards as well as to evaluate the potential of naturally occurring L-malic acid as an easily accessible monomer for the preparation of poly(ester amide)s. The use of L-malic as a diacidic monomer for the preparation of *aregic* polymalamides has been recently reported.<sup>7</sup>

## **Experimental Section**

**Materials and Methods.** All chemicals were obtained commercially from either Aldrich or Merck. They were analytical grade or higher and used without further purification. Solvents to be used under anhydrous conditions were dried by standard methods. Viscosities were measured in dichloroacetic acid at  $25.0 \pm 0.1$  °C using an Ubbelohde microviscometer. Infrared spectra were recorded on a FT-IR Perkin-Elmer 2000 instrument from films prepared by casting from trifluoroethanol (TFE). <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at room temperature on a Bruker AMX-300 spectrometer. Spectra of intermediate compounds, monomers, and polymers were taken in CDCl<sub>3</sub>, either pure or containing 10% of trifluoroacetic acid (TFA) or in pure TFA- $d_1$ . Sample concentrations about 1 and 5% (w/v) were used for <sup>1</sup>H and <sup>13</sup>C analysis, respectively,

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and tetramethylsilane was used as an internal reference.  $^{13}\mathrm{C}$  NMR measurements were made under proton decoupling conditions at 75.48 MHz. For typical <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra, the numbers of accumulated scans were 64 and 300–1500, respectively.

Hygroscopicity was measured according to Mori et al.8 in a 100% relative humidity atmosphere at 18 °C using disks of 12 mm diameter. These disks were dye-cut from approximately 200  $\mu$ m thick films, which were prepared by casting from TFE. Solubility essays were made following the method reported by Braun.9 Differential scanning calorimetry (DSC) was carried out using a Perkin-Elmer Pyris 1 instrument calibrated with indium. 2-5 mg samples placed under a nitrogen atmosphere were heated at a rate of 10 °C min<sup>-1</sup> and cooled at varying rates in the 30-200 °C temperature range. Thermogravimetric measurements (TGA) were performed under a nitrogen atmosphere with a Perkin-Elmer TGA6 thermobalance at heating rates of 10 or 20 °C min<sup>-1</sup>. Hydrolysis experiments were carried out on 12 mm diameter and 250  $\mu$ m thick disks, which were prepared as before. DSC analysis showed that all samples displayed a similar level of crystallinity. Disks were separately incubated in 0.1 M Na<sub>2</sub>HPO<sub>4</sub>-NaH<sub>2</sub>PO<sub>4</sub> buffer solution at pH 7.4. 37 °C. After the selected incubation period of time, the remaining solid was recovered, rinsed with water, and dried to constant weight under vacuum. Analysis of the residual polymer was made by viscosimetry, FTIR, and  $^1\!\mathrm{H}$  NMR spectroscopy. The residue recovered from the incubating solution upon evaporation was analyzed by spectroscopy.

**Synthesis of Monomers and Polymers.** The route of synthesis leading to PEALM is depicted in Schemes 2 and 3.

Compounds I, II, III, and VI were obtained as previously described elsewhere. The synthesis of polyamide P6MLM was performed as recently reported.<sup>7</sup>

**O-Methyl-L-malic Anhydride (IV).** This compound was obtained by treating O-methyl-L-malic acid (**II**) with Ac<sub>2</sub>O following the method described in the literature for the synthesis of 2,3-di-O-methyl-L-tartaric acid.<sup>10</sup>

IR ( $\nu_{max}$ , cm<sup>-1</sup>): 3006; 2942; 2840; 1872; 1796; 1465; 1410; 1235; 1134; 1078; 1037. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$ , ppm: 2.94 (dd, CH<sub>2</sub>, 1H); 3.30 (dd, CH<sub>2</sub>, 1H); 3.63 (s, OCH<sub>3</sub>, 3H); 4.44 (dd, CH, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$ , ppm: 35.76 (CH<sub>2</sub>); 59.09 (OCH<sub>3</sub>); 75.16 (CH); 167.55 (CH<sub>2</sub>COOCO); 169.57 (CHCOOCO).

*N-tert-Butoxycarbonyl-3-methoxy-4-oxo-5-oxy-11-aminoundecanoic Acid (VII).* Compounds VI (6.5 g, 0.030 mol) and IV (3.9 g, 0.030 mol) were dissolved in dried THF (50 mL), and the mixture was left under stirring at 60 °C for 6 h. The residue left after rotavaporating the reaction mixture was dissolved in AcOEt and washed with water. The organic layer was dried on anhydrous  $Na_2SO_4$  and evaporated to a slightly yellowish oily, which crystallized in the freezer to afford compound **VII** in 70% yield.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ, ppm: 1.36 (m CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O, 4H); 1.44 (s, (CH<sub>3</sub>)<sub>3</sub>C, 9H); 1.48 (m, CH<sub>2</sub>CH<sub>2</sub>NH, 2H); 1.65 (m, CH<sub>2</sub>-CH<sub>2</sub>O, 2H); 2.83 (m, CH<sub>2</sub>COOH, 2H); 3.11 (m, CH<sub>2</sub>NH, 2H); 3.50 (s, OCH<sub>3</sub>, 3H); 4.18 (m, CH<sub>2</sub>OCO, 2H); 4.21 (m, CH, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ, ppm: 26.20, 25.31 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O); 28.43 (C(CH<sub>3</sub>)<sub>3</sub>); 28.14 (CH<sub>2</sub>CH<sub>2</sub>O); 29.80 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH); 37.32 (CH<sub>2</sub>COOH); 39.97 (CH<sub>2</sub>NH); 59.10 (OCH<sub>3</sub>); 65.32 (CH<sub>2</sub>OCO); 75.20 (CH); 79.8 (C(CH<sub>3</sub>)<sub>3</sub>); 157 (OCONH); 167 (OCO); 171 (COOH).

**Pentachlorophenyl N-tert-Butoxycarbonyl-3-methoxy-4-oxo-5-oxy-11-ami-noundecanoate (VIII).** To a solution of compound **VII** (3 g, 0.0086 mol) and pentachlorophenol (2.75 g, 0.0103 mol) in AcOEt (40 mL), a solution (30 mL) of dicyclohexylcarbodiimide (DCCI) (2.12 g, 0.0103 mol) in the same solvent was added dropwise. The mixture was left under stirring at room temperature for 5 days, filtered and concentrated to half volume, and left in the freezer. The precipitated dicylcohexylurea was filtered out, and the operation was repeated several times until complete removal of this compound. The final solution was evaporated to render **VIII** in nearly 100% yield.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ, ppm: 1.38 (m, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O, 4H); 1.45 (s, C(CH<sub>3</sub>)<sub>3</sub>, 9H); 1.50 (m, CH<sub>2</sub>CH<sub>2</sub>NH, 2H); 1.71 (m, CH<sub>2</sub>-CH<sub>2</sub>O, 2H); 3.12 (m, CH<sub>2</sub>NH, 2H); 3.12 (m, CH<sub>2</sub>COOPcp, 2H); 3.51 (s, OCH<sub>3</sub>, 3H); 4.19 (m, CH<sub>2</sub>OCO, 2H); 4.3 (dd, CH, 1H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ, ppm: 26.31, 25.55 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CO); 28 (C(CH<sub>3</sub>)<sub>3</sub>); 28.5 (CH<sub>2</sub>CH<sub>2</sub>O); 29.91 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH); 37.30 (CH<sub>2</sub>COOPcp); 40.38 (CH<sub>2</sub>NH); 59.20 (OCH<sub>3</sub>); 65.40 (CH<sub>2</sub>OCO); 75.60 (CH); 79.09 (C(CH<sub>3</sub>)<sub>3</sub>); 127.58; 131.91; 132.07; 143.58 (aromatics); 156.01 (OCONH); 166.22 (COOPcp); 170.84 (OCO).

**Pentachlorophenyl-3-methoxy-4-oxo-5-oxy-11-aminoundecanoate Hydrobromide (IX).** To a stirred solution of compound **VIII** (7.5 g, 0.013 mol) in AcOH (70 mL) at room temperature was added 33% HBr–AcOH (36 mL). The excess of acid was evaporated to a solid residue that was dispersed in ethyl ether and recovered by filtration. Crystallization in THF/AcOEt rendered compound **IX** in 60% yield.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ, ppm: 1.48 (m, CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O, 4H); 1.80 (m, CH<sub>2</sub>CH<sub>2</sub>NH<sub>3</sub>, 2H); 1.85 (m, CH<sub>2</sub>CH<sub>2</sub>O, 2H); 3.11 (m, CH<sub>2</sub>NH, 2H); 3.12 (m, CH<sub>2</sub>COOPcp, 2H); 3.52 (s, OCH<sub>3</sub>, 3H); 4.19 (m, CH<sub>2</sub>OCO, 2H); 4.3 (t, CH,1H); 7.97 (t, NH<sub>3</sub>, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ, ppm: 25.95, 25.11 (CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O); 27.22 (CH<sub>2</sub>CH<sub>2</sub>O); 28.16 (CH<sub>2</sub>CH<sub>2</sub>NH); 37.27 (CH<sub>2</sub>COOPcp); 39.98 (CH<sub>2</sub>NH<sub>3</sub>); 59.19 (OCH<sub>3</sub>); 65.35 (CH<sub>2</sub>OCO); 75.60 (CH); 127.58; 131.91; 132.07; 143.58 (aromatics); 166.22 (COOPcp); 170.84 (OCO). Elemental analysis (C<sub>17</sub>H<sub>2</sub>I<sub>0</sub>S<sub>c</sub>I<sub>5</sub>Br): Found: C, 35.19%; H, 3.705%; Cl, 30.45%; Br, 14.49%. Calculated: C, 35.41%; H, 3.67%; Cl, 30.74%; Br, 13.86%.

**General Procedure for Polymerization.** To a vigorously stirring solution of compound **X** and  $Et_3N$  in *N*,*N*-dimethyl-formamide (DMF), a mixture of compounds **III** and **IX** in the selected ratio was slowly added. The reaction was left to proceed at 60 °C for 1 week. The polymer was precipitated by adding ethyl ether and recovered by filtration. Purification of



*ar*-PEALM was performed by reprecipitation from TFE with ether. For the preparation of *ir*-PEALM (1:1), compound **IX** was added to a solution of  $Et_3N$  in DMF, and the reaction mixture was worked up as before.

### **Results and Discussion**

Synthesis and Characterization. It is well-known that polycondensation of amino alcohols with diacids usually fails to produce poly(ester amide)s with predetermined ester-to-amide ratios due to the much lower reactivity of the hydroxyl group relative to the amine group. To circumvent such shortcoming, we have designed a synthesis strategy based on the use of the activated amino acidic comonomer IX, in which the ester linkage was previously inserted (Scheme 2). The starting products for the preparation of compound IX were L-malic acid (I) and 6-amine-1-hexanol (V). The synthesis is based on the regiospecific reaction of *N*-tertbutoxycarbonyl-6-aminohexanol (VI) with the O-methyl-L-malic anhydride (IV), the latter compound being obtained straightforwardly by dehydration of the Omethyl-L-malic acid (II). The hydroxy side group of L-malic acid was converted into methoxy in order to prevent any undesirable side esterification reaction leading to cross-linked polycondensates. The methyl group was the preferred one for this purpose since its small size is expected to cause moderate perturbation in chain packing and therefore minimum depression in crystallinity. This blocking method has proven to be highly efficient previously in the preparation of a fair number of polyamides derived from tartaric acid<sup>11</sup> and other higher aldaric acids.<sup>12</sup>

According to Scheme 3, the polycondensation of mixtures of **III**, **IX**, and **X** led to *aregic* poly(ester amide)s *ar*-PEALM, with ester-to-amide ratios (*a:b*) which could be roughly adjusted by the diamine **X** to compound **IX** ratio that is chosen for feeding the reaction. The *aregic* nature of these (polyester amide)s

arises from the two possible orientations that both the amino alcohol, and the diacid units can take up in the polymer chain. Conversely, polycondensation of compound **IX** led to the *isoregic* poly(ester amide) *ir*-PEALM showing an unique orientation for the chemical blocks. On the other hand, polycondensation of 1,6-hexanediamine (**X**) with the pentachlorophenyl-*O*-methyl L-malate (**III**) produced the *aregic* polymalamide P6MLM with the diacid units oriented at random. This polyamide was used in this work for only comparative purposes. The synthesis, characterization, and properties of P6MLM have been previously described in full detail.<sup>7</sup>

The results obtained in the polycondensations leading to poly(ester amide)s are compared in Table 1. The content in monomeric units of the resulting copolymers was accurately determined by <sup>1</sup>H NMR. It can be seen that although the composition of the polymer is close to that present in the feed from which they are formed, some noticeable deviations arise due to a slight deficiency in the incorporation of compound IX in the growing chain. As a consequence, the ester:amide ratios in the resulting poly(ester amide)s are in general lower than expected. On the other hand, the elemental compositions determined by combustion analysis were generally in agreement with the chemical formula of the poly(ester amide) with the composition in comonomers adjusted according to NMR data and considering that a certain amount of water was retained by the polymer. Such absorbed water is difficult to remove by the habitual drying methods, and its presence was assessed by NMR spectroscopy. This situation is usually found in methoxy-substituted polyamides and poly(ester amide)s derived from carbohydrates. The polymerization yields oscillated between 80 and 90%, and intrinsic viscosities of the poly(ester amide)s ranged between 0.9 and 0.3 dL  $g^{-1}$ , with the polymer size decreasing with

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	feed composition		polymer composition <sup>a</sup>		elem	elemental analysis <sup>b</sup>			
poly(ester amide)	<b>[IX]/[X]/[III]</b>	( <i>a</i> : <i>b</i> )	<b>[IX]/[X]/[III]</b>	( <i>a</i> : <i>b</i> )	C (%)	H (%)	N (%)	yield (%) <sup>c</sup>	$[\eta]^d$ (dL g <sup>-1</sup> )
ar-PEALM (1:50)	2.6/48.7/48.7	1:38	2/49/49	1:50	55.21 (55.69)	8.65 (8.60)	11.38	85	0.60
ar-PEALM (1:25)	5.0/47.5/47.5	1:20	4/48/48	1:25	56.10 (55.68)	8.39 (8.58)	(11.17) (11.35)	83	0.93
ar-PEALM (1:17)	8.2/45.9/45.9	1:12	6/47/47	1:17	55.27	8.67 (8.56)	(11.38) (11.14)	90	0.70
ar-PEALM (1:12)	11.0/44.5/44.5	1:9	8/46/46	1:12	55.45 (55.66)	8.45 (8.55)	10.74 (10.94)	85	0.50
ar-PEALM (1:5)	25.0/37.5/37.5	1:4	21/40/39	1:5	56.14 (55.61)	8.63 (8.47)	10.56 (9.76)	80	0.35
ar-PEALM (1:2)	50.0/25.0/25.0	1:2	42/29/29	1:2.4	55.68 (55.50)	8.51 (8.35)	11.80 (8.30)	80	0.30
<i>ir</i> -PEALM (1:1)	100/0/0	1:1	100/0/0	1:1	54.40 (55.46)	7.79 (8.17)	5.77	85	0.30

Table 1. Polycondensation Data of Poly(ester amide)s PEALM (a:b)

<sup>*a*</sup> Determined by <sup>1</sup>H NMR. <sup>*b*</sup> In parentheses, values calculated for the polymer with the experimentally found compositions and with 0.5 mol of added water. <sup>*c*</sup> Polycondensation yields referred to the isolated and purified polymer. <sup>*d*</sup> Intrinsic viscosities measured in dichloroacetic acid at  $25 \pm 0.1$  °C.



**Figure 1.** Compared FTIR spectra of poly(ester amide)s PEALM and polyamide P6MLM.

the content in ester groups. This range of viscosities would roughly correspond to number-average molecular weights between 50 000 and 7000 if comparison with data reported for poly(ester amide)s obtained from 6-aminohexanol and di-O-methyl-L-tartaric acid was made.<sup>5b</sup>

The chemical constitution of PEALM was confirmed by both FTIR and NMR spectroscopy. The FTIR spectra of the poly(ester amide)s are compared in Figure 1 where the spectrum of the *aregic* poly(hexamethylene L-O-methylmalamide) has been included for comparison. As expected, the spectra of PEALM are similar, all showing absorption bands consistent with the chemical formula of the polymer. The presence of the ester linkage is brought out by the peak appearing at 1740  $cm^{-1}$  with an intensity that increases proportional to the *a*:*b* ratio. A detailed inspection of this peak reveals the occurrence of a weak shoulder at 1710 cm<sup>-1</sup> which becomes most apparent for *ar*-PEALM (1:2) but that is almost inappreciable for *ir*-PEALM. A similar observation was reported in the FTIR analysis of poly(ester amide)s derived from tartaric acid<sup>5a</sup> and therein explained as due to the existence of a second minor population of ester groups differing from the major one, either in conformation or in the manner in which the chains are associated with each other in the solid state.

The <sup>1</sup>H and <sup>13</sup>C NMR spectra of the poly(ester amide)s and polyamide P6MLM are shown in parts a and b of Figure 2, respectively. It should be noticed that <sup>1</sup>H NMR spectra of *ar*-PEALM increase in complexity with the content of the polymer in ester groups. Four new signals attributed to CH, COOCH<sub>2</sub>, OCH<sub>3</sub>, and OCH<sub>2</sub>CH<sub>2</sub> protons are seeing with increasing intensity although they do not show splitting due to orientation effects. Apparently, the length of the hexamethylene segment mitigates any possible magnetic influence between neighboring malic moieties. This means that the description of the microstructure of these poly(ester amide)s in terms of dyads defined by the relative orientation of either two consecutive diacid units or two consecutive oxyaminohexamethylene units is not achievable. It can be reasonably assumed, however, that these poly(ester amide)s are essentially *aregic* polymers, since this is the microstructure reported to be present in the polymalamides obtained by condensation of III with X.

The thermal behavior of PEALM has been characterized by DSC. In Figure 3a the heating and cooling DSC traces obtained from PEALM (1:12) are reproduced for illustration. All PEALM show melting and crystallization peaks at heating and cooling, respectively, as well as sharp  $T_{\rm g}$  inflection points at the second heating traces. The thermal data afforded by the DSC analysis are listed in Table 2. In Figure 3b, the  $T_g$  and  $T_m$  values for the whole series are plotted against the percentage of the polymer in ester groups, illustrating the trend followed by the two transition temperatures with composition. Both temperatures were observed to decrease with the content in ester groups. It is worthy to mention that, as represented in Figure 3b, PEALM (1:2) showed two endothermic peaks which could be interpreted to correspond to the melting of two populations of crystals differing in size. Since no similar effects were observed for other compositions, comparison of PEALM (1:2) to



**Figure 2.** <sup>1</sup>H NMR (a) and <sup>13</sup>C NMR (b) spectra of PEALM. Copolymer compositions indicated in (a).

the other PEALMs in this regard is uncertain. The trend curve for  $T_{\rm m}$  shown in Figure 3b was drawn for the higher  $T_{\rm m}$  value found for PEALM (1:2); a minimum would result instead for this polymer if the lower had been chosen. On the other hand, the crystallinity of PEALM, estimated by the melting enthalpy, follows the same trend as the melting temperature.

The solubility of PEALM has been evaluated in a series of solvents of different nature, and the results are compared in Table 2. It appears that all of them are insoluble in water but soluble in hydrogen bond breaking solvents as TFE, TFA, and formic acid. The solubility in nonacidic organic solvents depends on both the polarity of the solvent and the amide:ester ratio of the poly(ester amide). Thus, they are soluble in chloroform and dimethyl sulfoxide for ester contents higher than 20% whereas they remain insoluble in ethanol for the whole range of compositions. These poly(ester amide)s are highly hydrophilic polymers as it is reflected in their sorption of moisture (Figure 4), which arrives to be more than 20% for PEALM (1:2). The water uptake increases with the content in ester groups which could be due in part to the fact that both  $T_{g}$  and crystallinity diminish in that sense. However, the high affinity for water displayed by these polymers should be directly



**Figure 3.** (a) DSC of *ar*-PEALM (1:12). (b) Variation of  $T_g$  and  $T_m$  in PEALM as a function of the content in ester groups.

associated with the presence of the methoxy side group. Such a group not only constitutes an anchoring point for water molecules but also hinders the close packing of the polymer chains, making the material more accessible to water diffusion. This would explain that, for the same ester:amide ratio, PEAT (with two methoxy groups in the diacid unit) are more hygroscopic than PEALM (with only one methoxy group per repeating unit).

**Thermal Degradation.** The thermal stability of both *aregic* and *isoregic* PEALM has been examined by thermogravimetry by means of both dynamical and isothermal experiments. The TGA traces of *ir*-PEALM (1:1) and *ar*-PEALM (1:25) representing the remaining weight as a function of temperature at a heating rate of 10 °C min<sup>-1</sup> and as a function of time under heating at 250 °C are shown in Figure 5. The thermal decomposition parameters evaluated for the whole set of poly-(ester amide)s studied in this work as well as for the polyamide P6MLM are given in Table 2.

The onset of decomposition of *ar*-PEALM was observed in the dynamical traces between 275 and 280 °C, the upper limit being very close to the onset temperature of polymalamide P6MLM, which is 284 °C. In all cases decomposition was found to occur in two stages, the first one taking place above 300 °C and the second one above 460 °C with weight losses of 40–60% in both of them. The isothermal treatment at 250 °C initially produced an abrupt loss of weight in the polymer, which after a few minutes stabilized in a plateau for an approximately constant value of about 70% of the initial mass. The steady state was found to be achieved faster as the content of the polymer in ester

Table 2. Thermal Properties and Solubilities of Poly(ester amide)s PEALM (a:b)

	thermal properties							solubility <sup>c</sup>						
poly(ester amide)	$T_{g}^{a}$	$T_{\rm m}{}^a$	$^{0}T_{\mathrm{d}}{}^{b}$	${}^{\mathrm{I}}T_{\mathrm{d}}{}^{b}$	${}^{\mathrm{II}}T_{\mathrm{d}}{}^{b}$	$\Delta W^c$	$H_2O$	EtOH	$CHCl_3$	DMSO	HCOOH	TFE	TFA	
P6MLM	68	179 (59)	284	316 (69)	466 (19)	92								
ar-PEALM (1:50)	58	166 (32)	280	315 (95)	474 (5)	86	_	-	_	+	+ +	+ +	+ +	
ar-PEALM (1:25)	52	167 (24)	280	311 (65)	466 (13)	86	_	-	±	+	+ +	+ +	+ +	
ar-PEALM (1:17)	51	159 (18)	279	312 (62)	473 (8)	86	_	-	±	+	+ +	+ +	+ +	
ar-PEALM (1:12)	38	158 (19)	272	311 (63)	464 (13)	81	_	-	±	+	+ +	+ +	+ +	
ar-PEALM (1:5)	43	150 (14)	269	303 (65)	462 (15)	81	_	-	+	+ +	+ +	+ +	+ +	
ar-PEALM (1:2) <sup>d</sup>	26	145 (13)	275	301 (40)	475 (0)	81	_	$\pm$	+ +	+ +	+ +	+ +	+ +	
<i>ir</i> -PEALM (1:1)	10	144 (43)	261	286 (25)	458 (8)	47	_	±	+ +	+ +	+ +	++	+ +	

<sup>*a*</sup> Glass ( $T_g$ ) and melting temperatures measured by DSC in °C; In parentheses, the melting enthalpy in J g<sup>-1</sup>. <sup>*b*</sup> Onset ( ${}^{0}T_d$ ) and first ( ${}^{1}T_d$ ) and second ( ${}^{II}T_d$ ) stage decomposition temperatures measured by TGA in °C; in parentheses, the % remaining weight of the initial mass at each decomposition stage. <sup>*c*</sup> (++) soluble at room temperature; (+) soluble on warning; (+-) slightly soluble; (-) insoluble. <sup>*c*</sup> Remaining weight upon heating at 250 °C for 10 min. <sup>*d*</sup> This PEALM showed another melting peak at 112 °C.



**Figure 4.** Absorbed moisture as a function of exposure time for *aregic* poly(ester amide)s *ar*-PEALM, *aregic* poly(taraester amide) PEAT (1:2) (data taken from reference), and *aregic* polymalamide P6MLM.

groups increased. The regioregular poly(ester amide) *ir*-PEALM (1:1) displayed the same pattern of behavior as the *aregic* ones with changes taking place at significantly lower temperatures and entailing larger weight losses, indicative of its lower thermal stability.

Decomposition at higher temperatures (above 450 °C) is known to happen by extensive scission of main chain C-C bonds to produce volatile compounds and carbonaceous residues and ashes. On the other hand, the changes taking place around 300 °C are usually associated with specific reactions between functional groups. To get insight into the molecular mechanism operating in the decomposition of these poly(ester amide)s at the lower temperature decomposition stage, the products resulting upon heating at 250 °C the poly(ester amide)s ar-PEALM and ir-PEALM (1:1) were analyzed by both FTIR and NMR spectroscopy. In Figure 6, the IR spectra of the residual polymer and the released gases resulting in the degradation of *ir*-PEALM (1:1) are compared to that registered from the original polymer. The most apparent changes are those perceived in the carbonyl region, where the ester band initially present at 1740 cm<sup>-1</sup> completely disappeared, and a new intense peak at 1705  $\text{cm}^{-1}$  together with a weak one at 1780  $\text{cm}^{-1}$ , both of them indicative of the presence of cyclic imide structures, are brought out. The intensity of the amide bands also diminished in the spectrum of the residual polymer and became almost vanished in the spectrum of the gases. On the other hand, the absorption above



**Figure 5.** TGA traces of *ir*-PEALM (1:1) (top) and *ar*-PEALM (1:25) (bottom). The isothermal traces were recorded at 250 °C.

3000 cm<sup>-1</sup> broadened and intensified at the same time as it shifted to higher wavenumber values, indicating that hydroxyl groups should have been formed in the thermal decomposition. Similar changes were observed for *ar*-PEALM (1:5) although in this case the disappearance of the ester band was not complete.

The NMR analysis confirmed the results of the IR analysis and provided further information to support unambiguously the interpretation of the decomposition mechanism. The <sup>1</sup>H NMR spectra of the initial *ir*-PEALM (1:1), the residual polymer after heating at 250



**Figure 6.** FTIR of *ir*-PEALM (1:1): (a) pristine sample, (b) residue after heating at 250 °C for 1 h, and (c) released gases.

°C for 60 min, and the gases released at increasing times of heating are compared in Figure 7. The presence of imide units and CH<sub>2</sub>OH end groups in the degraded polymer (Figure 7a) is evidenced by signals appearing at 4.81 ppm (two doublets, CH<sub>imide</sub>), 3.82 ppm (singlet, OCH<sub>3 imide</sub>), 3.10–3.50 ppm (two doublets, CH<sub>2 imide</sub>), and 4.10 ppm (end C**H**<sub>2</sub>OH).

The spectra of the gases (Figure 7b) are all the same regardless of the heating time, and they correspond to almost pure N-(6-hydroxyethyl)-2-methoxy-L-malimide. The decomposition reaction compatible with spectroscopy data is depicted in Scheme 4. The process can be reasonably described as consisting of an intramolecular amidolysis of the ester group which is favored by the formation of stable cyclic N-substituted malimide. It should be noticed that a similar reaction could also be feasible for diamide sequences with formation in this case of N-(6-aminoethyl)-2-methoxy-L-malimide. Such reaction has been reported to occur in the degradation of polytartaramides<sup>5c</sup> and polymalamides.<sup>7</sup> The fact that the stability of PEALM is observed to decrease with the content in ester groups is consistent with the higher reluctance of the amide linkage to the nucleophilic attack.

**Hydrolytic Degradation.** It has been recently reported that polyamides derived from L-malic acid and aliphatic diamines are scarcely degraded by water.<sup>7</sup> Despite the favorable effects exerted by the hydrophilic electron-withdrawing methoxy side group, the polyamide chain continues to be too resistant to water attack. The same occurs for polytartaramides in spite that they have two methoxy groups per repeating unit.<sup>13</sup> On the contrary, poly(tartaraester amide)s are much more susceptible to hydrolysis than their parent polytartara



**Figure 7.** <sup>1</sup>H NMR spectra of *ir*-PEALM (1:1): (a) original and residual disk; (b) released gases at increasing heating times, as indicated.



mides, and it has been also shown that their degradation in water is depending on the regicity of the poly(ester amide) chain.<sup>6</sup> The effect of inserting ester linkages into the backbone of P6MLM is expected to have a similar effect on hydrodegradability of these polyamides. The changes taking place in PEALM and P6MLM with time by effect of water pH 7.4 at 37 °C are shown in Figure 8 for a variety of ester:amide ratios.

The enhancing effect of the ester group on the hydrodegradability of PEALM is made apparent by comparing the plots among them and to those obtained for polyamide P6MLM. Both the viscosity and the



**Figure 8.** Decay of viscosity and remaining weight of poly-(ester amide)s *ar*-PEALM and polymalamide P6MLM with incubation time.

remaining weight of the initial polymer were found to decrease for all PEALM with the time of incubation, a trend that appeared to be more pronounced as the content in ester groups increased. After 20-30 days of incubation both magnitudes became stable, indicating that degradation apparently ceased. The fact that the decay in remaining weight is slightly more pronounced than in viscosity is probably due to leaching of degraded fragments of large size. FTIR and NMR spectroscopies were used to explain these observations and to disclose the degradation mechanism operating in the presence of water. Figure 9 shows the FTIR spectra of the original *ir*-PEALM (1:1), the residual polymer disk, and the residue recovered from the incubating solution. For this study, the temperature was risen to 70 °C in order to enhance the degradation rate and facilitate the analysis of the degradation products without lengthening excessively the incubation time. Whereas almost insignificant changes are detected in the degraded polymer, the degradation products transferred to the solution contain a considerable amount of imide groups. Furthermore, the broad band appearing at 3200–3400 cm<sup>-1</sup> indicates the extensive presence of hydroxyl end groups. The <sup>1</sup>H NMR spectra of the same samples are compared in Figure 10, which corroborated the conclusions drawn from the IR analysis. Similar results were obtained in the degradation study of ar-PEALM (1:5).

It seems therefore that degradation of PEALM in water involves mainly the splitting of the ester groups



**Figure 9.** FT-IR of *ir*-PEALM subjected to hydrolytic degradation at 70 °C for 6 days: (a) pristine sample, (b) residual disk, and (c) residue from the incubating solution.



**Figure 10.** <sup>1</sup>H NMR spectra of *ir*-PEALM after incubation for 6 days at 70 °C: (a) original disk, (b) residual polymer, and (c) residue left by the incubating solution upon evaporation.

with formation of hydroxyl-ended fragments and cyclic imide groups. The generation of such structures may occur by intramolecular cyclic amidolysis, as it happens in the thermal degradation, or it can be the result of the dehydration of carboxylic-ended fragments that were previously generated by hydrolysis. These two possibilities are depicted in Scheme 4.

## **Concluding Remarks**

L-Malic acid has been used for the first time to produce poly(ester amide)s. The method designed for this synthesis has proven to be useful for obtaining both aregic and isoregic polymers. As expected from their intermediate constitution, thermal properties, water affinity, and solubility of these poly(ester amide)s are in between polymalamides and poly(tartarester amide)s. Although PEALM are well stable to heating, they degrade hydrolytically much faster than both tartaric acid and malic acid deriving polyamides. The molecular mechanism operating in the degradation process seems to be the same as for poly(tartaraester amide)s with ester hydrolysis and cyclic imide formation being involved in both cases. The access to these novel poly(ester amide)s fills the gap existing between unsubstituted poly(succinester amide)s and double substituted poly-(tartarester amide)s and contributes to enrich the assortment of methoxy-substituted polyamides and poly(ester amide)s that can be produced from aldaric acids deriving monomers.

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