Hydrolytic Degradation of Poly(ester amide)s Made from Tartaric and Succinic Acids: Influence of the Chemical Structure and Microstructure on Degradation Rate

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ABSTRACT: The hydrolytic degradation under physiological conditions of a series of poly(ester amide)s prepared from 1,*n*-amino alcohols and aliphatic dicarboxylic acids including succinic, glutaric, and tartaric acids was examined. Degradability was observed to increase with the content in ester groups. Poly(ester amide)s containing tartaric acid were found to be highly sensitive to hydrolysis while those not containing four-carbon diacid units appeared to be fairly stable. It was also found that degradation of both poly(succinester amide)s and poly(tartarester amide)s critically depended on the regicity of the polymer chain. Whereas isoregic poly(ester amide)s were easily degraded, the syndioregic polymers displayed a great resistance to the action of water. Aregic poly(tartarester amide)s degraded even faster than isoregic polymers. The products resulting from hydrolysis were investigated by both FTIR and NMR spectroscopy. A set of model compounds including ester and amides of L-tartaric acid was synthesized and subjected to hydrolysis to help in the interpretation of the degradation mechanism taking place in poly(tartarester amide)s. It was concluded that chain scission in both isoregic and aregic poly(ester amide)s must take place by intramolecular amidolysis with formation of either succinimide or tartarimide units. This mechanism requires the presence of four-carbon diacid units in the poly(ester amide), and it is unable to operate if the polymer chain has an entirely syndioregic microstructure. The results are relevant to the design of sequential poly(ester amide)s with controlled hydrodegradability.

Introduction

Aliphatic polyamides (nylons) are widely recognized polymers for their excellent technical properties.[1] These polymers are highly stable in aqueous media because the great resistance of the amide groups to hydrolysis. In these past years, sustained efforts have been extensively devoted to render polyamides more hydrophilic and degradable. The purpose is to expand their applications to new fields demanding materials either with lower environmental impact or displaying biodegradable and biocompatible properties.[2] A primary requirement asked of the novel compounds is that the genuine properties of polyamides are not seriously deteriorated upon modification.

The use of building blocks derived from carbohydrates in the design of polyamides with enhanced hydrophilicity and biodegradability constitutes an interesting strategy that is being intensively explored.[3−5] Recently we have reported on poly(tartaramide)s, i.e., polyamides of (*n*,4)-type derived from natural occurring L-tartaric acid.[4,6] These polyamides bear one alkoxy side group attached to every α carbon of the diacid unit which makes them more hydrophilic and susceptible to water attack than conventional nylons. However, the response given by these polyamides to water degradation under mild conditions, i.e., pH ∼7 and ∼37 °C, is still too weak for many potential applications.[7] Insertion of ester linkages in the main chain of a polyamide is known to be an efficient means to increase the hydrodegradability of the polymer. This procedure has been extensively used with a wide variety of nylons[8] and continues to be object of current research.[9] To take advantage from combination of side-group effects and ester linkage vulnerability, several types of carbohydrate-based poly(ester amide)s have been synthesized, and their capability to undergo hydrolysis has been evaluated in certain cases.[10,11] However, no systematic study on the degradability of these poly(ester amide)s in relation to their molecular constitution has been published so far.

In this work we wish to report on the influence that the molecular structure of a poly(ester amide) exerts on its susceptibility toward hydrolysis. First, the effects of a number of chemical factors such as the insertion of ester groups in the main chain, the presence of hydrophilic side groups, or the length of the building blocks are evaluated. Second, the influence of certain subtle structural differences such as the relative orientation of the monomeric units along the polymer chain is determined. To carry out this research, a variety of poly(ester amide)s with the appropriate molecular design have been examined. Their chemical structures are depicted in Figure 1, and their features of major relevance to the objectives pursued in this work are compared in Table 1. All these polymers had been prepared by our group, and duly accounts on their synthesis, structure, and properties have been recently reported.[12−14] On the other hand, a set of model compounds has been also synthesized to help the study of the polymers with degradation data of more simple interpretation and not affected by physical effects. The spectroscopic analysis of the products resulting in the

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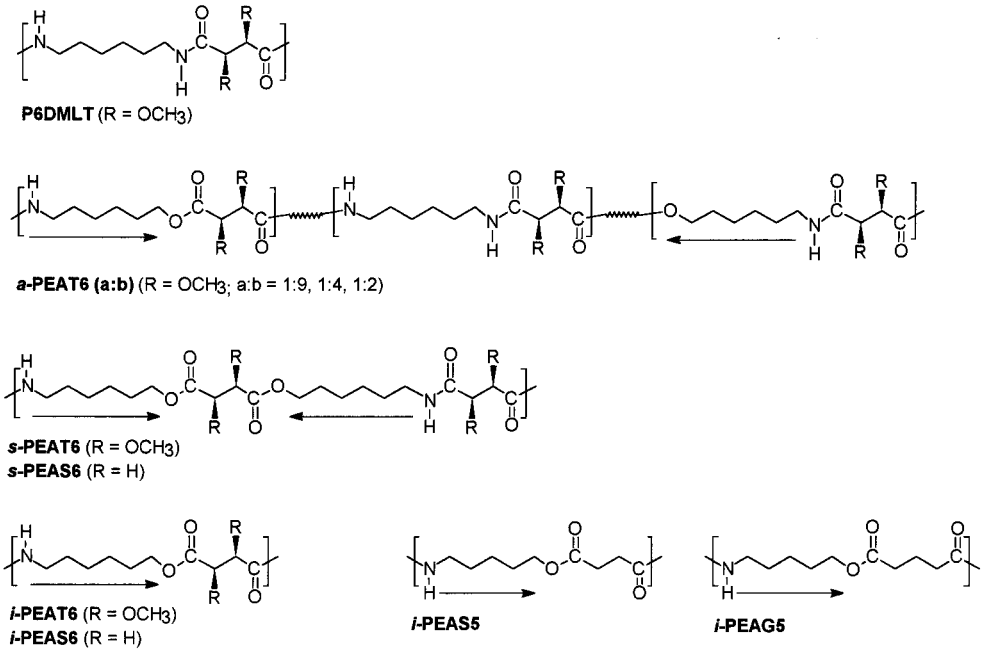

Figure 1. Chemical structures of poly(ester amide)s examined in this work. Poly(hexamethylene 2,3-di-*O*-methyl-L-tartaramide), abbreviated P6DMLT, is included for comparison.

Table 1. Data of Poly(ester amide)s[a]

	i-PEAS5	*i*-PEAG5	i-PEAS6	*s*-PEAS6	*i*-PEAT6	*s*-PEAT6	*a*-PEAT6 (a:b)[e]
$[\eta]$ (dL g^{-1})[b]	0.45	0.63	1.12	0.45	0.74	0.88	1.1−1.8
M_w[c]	4700	9100	32000	3000	44500	64000	121000−86100
M_n[c]	2800	3900			22900	19500	44100−28000
T_g (°C)[d]			32	48	26	24	85−49
T_m (°C)[d]	123	115	166	157	151	134	228−115
ΔH_m[d] (kcal mol^{-1})	3.6	3.8	2.7	3.4	3.4	2.4	1.5−1.0

[a] Data taken from refs 12−14. [b] Intrinsic viscosity measured in dichloroacetic acid at 25 °C. [c] Determined by GPC calibrated against polystyrene standards. [d] Measured by DSC on film samples used for degradation essays. [e] Aregic poly(tartarester amide)s with ester: amide ratios (*a*:*b*) varying from 1:9 to 1:2.

water degradation of both polymers and model compounds has allowed us to formulate a degradation mechanism that can be of value in the designing of novel poly(ester amide)s with adjusted hydrodegradability.

It should be said that crystallinity and crystalline morphology of a polymer sample affect the hydrolysis rate so that a clear separation between physical and chemical effects is difficult.[15] Crystalline structure factors therefore must be taken into account for a correct interpretation of degradation results concerning semicrystalline polymers. All the poly(tartarester amide)s (PEAT's) examined in this work can be considered to originate from the polyamide poly(hexamethylene di-*O*-methyl-L-tartaramide) (PDMLT) by pertinent replacement of amide groups by ester groups. The crystal morphology and structure of P6DMLT have been precisely determined,[16] and we have shown recently that the structure of this polyamide is essentially retained in all the poly(ester amide)s PEAT's derived thereof.[13,14] A similar situation is found for the unsubstituted poly(ester amide)s derived from aliphatic dicarboxylic acids and diamines; preliminary X-ray diffraction studies carried out on succinic acid-derived poly(ester amide)s (PEAS's)[17] have indicated that they adopt a common crystal structure apparently close to the familiar layered α-form of conventional nylons. Although a rigorous comparison of the crystallinity for the whole set of poly(ester amide)s included in this study is not accessible, an approximate estimation may be inferred from the melting enthalpies given in Table 1. On such a basis, a qualitative correlation between crystalline features and degradation results will be made when appropriate.

Experimental Section

Methods and Measurements. Hydrolysis experiments were carried out on 13 mm diameter disks of a thickness ranging from 200 to 350 μm which were prepared by casting in chloroform or by hot-pressing. DSC and powder X-ray diffraction analyses showed that all samples display crystallinity regardless of the method of preparation. Disks were incubated at 37 °C in either distilled water or 0.1 M Na_2HPO_4−NaH_2PO_4 buffer solution at pH 7.4. Each disk was immersed in the incubating solution and left there for the selected period of time. After incubation the remaining solid was recovered by filtration, rinsed with water, and dried to constant weight under reduced pressure. The filtered solution was either evaporated to dryness or subjected to extraction with dichloromethane (DCM) in order to separate inorganic salts. Hydrolysis experiments on model compounds were all made using distilled water at 37 °C as incubating medium. The oily samples were dispersed in water and the two-phase mixtures kept under stirring for selected periods of time. After treatment the two phases were separated and evaporated to dryness and the respective residues subjected to IR and NMR analyses.

Gel permeation chromatography was performed on a Water apparatus equipped with three PL columns and fitted with a refraction index detector and a computerized data station. The mixture chloroform:*o*-chlorophenol (95:5) was used as mobile phase, and molecular weights were estimated against polystyrene standards. IR spectra were recorded on either a Perkin-Elmer FT2000 or a Michelson 100 spectrophotometer with samples melted in KBr disks. Nuclear magnetic reso-

nance spectra were recorded on Bruker 200 ACP or Bruker 300 AMX instruments from samples dissolved in dimethyl sulfoxide (DMSO), chloroform, or chloroform−formic acid mixtures. Chemical shifts are reported in parts per million downfield from tetramethylsilane.

Polymers and Model Compounds. The polyamides and poly(ester amide)s investigated in this work were obtained by polycondensation in solution using the active ester methodology. Detailed accounts of their respective syntheses including intermediate compounds, monomers, and polymerization reaction conditions can be found elsewhere.[6b,12−14] Model compounds **I**−**IV** were prepared by reaction of hexanol or hexylamine with the di-*O*-methyl-L-tartaric acid anhydride or bis(pentachlorophenyl ester) derivatives. The synthesis of these two precursors has been described in full detail elsewhere.[6b,14]

***N*-Hexyl-di-*O*-methyl-L-tartaramic Acid (I).** To a solution of di-*O*-methyl-L-tartaric anhydride (3.43 g, 21.5 mmol) in chloroform (20 mL) was slowly added hexylamine (2.86 mL, 21.5 mmol), and the mixture left to react under stirring for 4 days at room temperature. After evaporation of the solvent, the monoamide **I** was recovered as an oil (5.6 g, 100%). IR (ν_{max}): 3347, 2916, 2558, 2365, 1761, 1698, 1637, 1542, 1458, 1195, 1101, 873 cm^{-1}. ^{1}H NMR (δ, ppm): 0.89 (t, 3H, $CH_2C\mathbf{H}_3$), 1.33 (br, 6H, $(C\mathbf{H}_2)_3CH_3$), 1.53 (m, 2H, $C\mathbf{H}_2CH_2N$), 3.25 (m, 1H, **H**CHN), 3.38 (m, 1H, HC**H**N), 3.46 (s, 3H, NOCCHOC$\mathbf{H}_3$), 3.48 (s, 3H, OOCCHOC$\mathbf{H}_3$), 4.17 (d, 1H, CHCON), 4.30 (d, 1H, CHCOO), 6.75 (t, 1H, NH). ^{13}C NMR (δ, ppm): 13.97 ($CH_2\mathbf{C}H_3$), 22.51 ($\mathbf{C}H_2CH_3$), 26.37 ($\mathbf{C}H_2CH_2CH_2CH_3$), 29.34 ($\mathbf{C}H_2CH_2N$), 31.41 ($\mathbf{C}H_2CH_2CH_3$), 39.31 ($CH_2N$), 59.91 (OOCCHO$\mathbf{C}H_3$), 60.20 (NOCCHO$\mathbf{C}H_3$), 80.35 (**C**HCOO), 82.69 (**C**HCON), 169.20 (CON), 172.97 (COO).

Hexyl *N*-Hexyl-di-*O*-methyl-L-tartaramate (II). To a solution of **I** (2 g, 7.66 mmol) and 1-hexanol (0.79 g, 7.66 mmol) in chloroform (5 mL) was added in drops 10 mL of a solution of *N*-ethyl-*N*-(3,3-(dimethylamino)propyl) carbodiimide hydrochloride (EDC) (1.62 g, 8.43 mmol) in the same solvent. The mixture was left to react overnight at room temperature and then extracted with 3 volumes of water. Evaporation to dryness of the organic solution yielded compound **II** as a colorless oil (1.8 g, 68%). IR (ν_{max}): 3311, 2932, 2860, 1757, 1719, 1655, 1541, 1458, 1377, 1260, 1196, 1104, 1055 cm^{-1}. ^{1}H NMR (δ, ppm): 0.89 (t, 6H, $CH_2C\mathbf{H}_3$), 1.28 (br, 12H, $2(CH_2)_3$), 1.55 (m, 2H, $C\mathbf{H}_2CH_2N$), 1.68 (m, 2H, $C\mathbf{H}_2CH_2O$), 3.24 (m, 1H, **H**CHN), 3.36 (m, 1H, HC**H**N), 3.40 (s, 3H, NOCCHOC$\mathbf{H}_3$), 3.44 (s, 3H, OOCCHOC$\mathbf{H}_3$), 4.11 (d, 1H, CHCON), 4.23 (d, 1H, CHCOO), 6.73 (t, 1H, NH). ^{13}C NMR (δ, ppm): 13.99 ($CH_2\mathbf{C}H_3$), 25.38−26.45 $2(CH_2)_3$, 28.56 ($\mathbf{C}H_2CH_2O$), 29.46 ($\mathbf{C}H_2CH_2N$), 39.12 (CH_2N), 59.78 (OOCCHO$\mathbf{C}H_3$), 60.02 (NOCCHO$\mathbf{C}H_3$), 65.47 (CH_2O), 80.42 (**C**HCOO), 83.17 (**C**HCON), 168.65 (COO), 169.99 (CONH).

Dihexyl-di-*O*-methyl-L-tartrate (III). A mixture of di-*O*-methyl-L-tartaric acid (1 g, 5.62 mmol), 1-hexanol (1.16 g, 11.4 mmol), and *p*-toluenesulfonic acid (0.02 g, 0.1 mmol) in toluene (125 mL) was refluxed for 36 h and the forming toluene−water azeotrope continually separated by means of a Dean-Stark. The reaction mixture was then evaporated to dryness, the residue dissolved in chloroform, and the solution washed with 5% sodium hydrogen carbonate solution. The evaporation of the chloroform solution resulted in an oil that was distilled under vacuum to yield 1.26 g (65%) of compound **III**. IR (ν_{max}): 2932, 2820, 1760, 1733, 1467, 1272, 1187, 1114, 1026 cm^{-1}. ^{1}H NMR (δ, ppm): 0.89 (t, 6H, $CH_2C\mathbf{H}_3$), 1.37 (br, 12H, $2(CH_2)_3$, 1.67 (m, 4H, $C\mathbf{H}_2CH_2O$), 3.46 (s, 6H, OOCCHOC$\mathbf{H}_3$), 4.20 (m, 4H, CH_2O), 4.23 (s, 2H, CH). ^{13}C NMR (δ, ppm): 13.93 ($CH_2\mathbf{C}H_3$), 22.47, 25.47, 28.53, 31.32 $2(CH_2)_4$, 59.54 (OCH_3), 65.39 (CH_2O), 81.13 (CH), 169.25 (COO).

***N,N′*-Dihexyl-di-*O*-methyl-L-tartaramide (IV)**. To a solution of hexylamine (0.9 g, 8.94 mmol) in chloroform (8 mL) was added bis(pentachlorophenyl) di-*O*-methyl-L-tartrate (3 g, 4.44 mmol), and the mixture was left under stirring until total disappearance of the starting products in the thin-layer chromatograms. The mixture is then washed with water and evaporated to dryness to yield **IV** as yellowish oil (1.07 g, 70%). IR (ν_{max}): 3414, 3279, 2931, 2859, 1659, 1534, 1424, 1375, 1277, 1192, 1137, 1097, 989, 716 cm^{-1}. ^{1}H NMR (δ, ppm): 0.88 (t, 6H, $CH_2C\mathbf{H}_3$), 1.31 (br, 12H, $2(CH_2)_3$, 1.51 (m, 4H, $C\mathbf{H}_2CH_2NH$), 3.27 (m, 2H, **H**CHN), 3.37 (m, 2H, HC**H**N), 3.43 (s, 6H, OCH_3), 4.23 (s, 2H, CH). ^{13}C NMR (δ, ppm): 13.97 ($CH_2\mathbf{C}H_3$), 22.52 ($\mathbf{C}H_2CH_3$), 26.45 ($NCH_2CH_2\mathbf{C}H_2$), 29.49 ($NCH_2\mathbf{C}H_2$), 31.42 ($\mathbf{C}H_2CH_2CH_3$), 39.25 (CH_2N), 60.59 (OCH_3), 82.26 (CH), 169.37 (CON).

***N*-Hexyl-di-*O*-methyl-L-tartarimide (V)**. Heating of compound **I** at 100 °C for 3 days under a nitrogen atmosphere afforded compound **V** in quantitative yield. IR (ν_{max}): 2934, 2861, 1716, 1442, 1403, 1355, 1175, 1109, 1073, 988, 815 cm^{-1}. ^{1}H NMR (δ, ppm): 0.89 (t, 3H, $CH_2C\mathbf{H}_3$), 1.29 (br, 6H, $(CH_2)_3$), 1.56 (m, 2H, $C\mathbf{H}_2CH_2NH$), 3.48 (m, 2H, CH_2N), 3.71 (s, 6H, OCH_3), 4.12 (s, 2H, 2 CH). ^{13}C NMR (δ, ppm): 13.95 ($CH_2\mathbf{C}H_3$), 22.41 ($\mathbf{C}H_2CH_3$), 26.37 ($NCH_2CH_2\mathbf{C}H_2$), 27.47 ($NCH_2\mathbf{C}H_2$), 31.22 ($\mathbf{C}H_2CH_2CH_3$), 38.70 (CH_2N), 59.61 (OCH_3), 81.22 (CH), 172.42 (CON).

Results and Discussion

Degradation of Polymers: Influence of the Chemical Structure. (a) Main-Chain Ester Groups. It is well-known that insertion of ester linkages in a polyamide chain enhances the sensitivity of the polymer toward hydrolysis. This is exactly what it is found to happen in poly(tartarester amide)s as it is well illustrated by comparing the hydrolytic degradation of a series of *a*-PEAT6's with ester:amide ratios ranging from 1:9 up to 1:2. These poly(ester amide)s arise from polyamide P6DMLT upon replacement of amide groups by ester groups with a random orientation. They appear to be less crystalline than the regic polymers, and crystallinity tends to decrease overall with the content in ester groups. The degradation results are presented in Figure 2 where the decay in both remaining weight and molecular weight of the degraded samples is plotted against incubation time. The observed response is as it could be anticipated from the composition of the polymers. Degradability markedly increased when ester groups were incorporated in the polyamide chain. Although effects started to be noticeable for ester contents as low as 10%, the vulnerability of the polymer became clearly apparent when their concentration reached 20%. It is worth noting that poly(tartarester amide)s containing 33% of ester groups (*a*-PEAT6 (1:2)) appeared to be degraded very rapidly with half of the initial weight being lost in approximately 1 week. It is commonly observed that hydrolytic degradation of semicrystalline polymers is confined to the amorphous regions,[18] and this has proven to be indeed the case of poly(tartaramide)s.[19] The degradation curves displayed by *a*-PEAT6's suggest that a similar degradation mechanism is operating in these poly(ester amide)s with the final amount of remaining sample weight being associated with the initial content in crystalline phase.

(b) Methoxy Side Groups. It has been shown in earlier works that both hydrophilicity and hydrolytic degradability of poly(tartaramide)s varying in the length of the diamine unit decrease with the distance separating the tartaric units along the polymer chain.[6,7] Comparison of the progress of the hydrolysis reaction in poly(succinester amide)s and poly(tartarester amide)s derived from the same amino alcohol with the same regicity may be used to illustrate the effect exerted by the methoxy side group attached to the α-carbon atom of the diacid unit. The variation in both sample weight and molecular weight with degradation time for the two pairs of poly(ester amide)s *i*-PEAS6/*i*-PEAT6 and *s*-PEAS6/*s*-PEAT6 is shown in Figure 3. Results obtained for the former pair appear to be particularly meaningful. The decreasing of molecular weight with

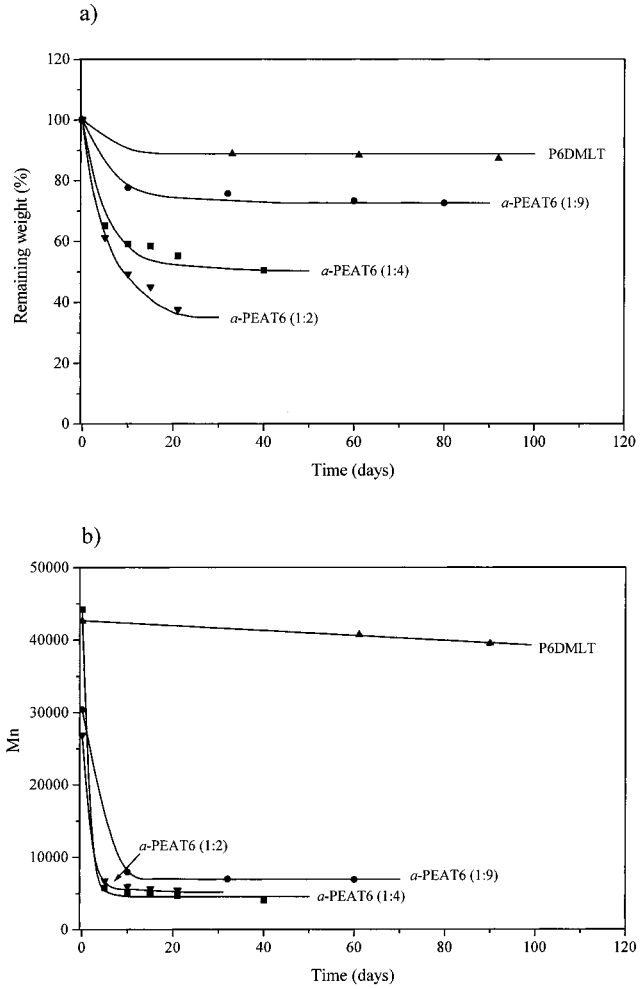

Figure 2. Hydrolytic degradation of aregic poly(tartarester amide)s: (a) remaining weight vs incubation time; (b) number-average molecular weight vs incubation time.

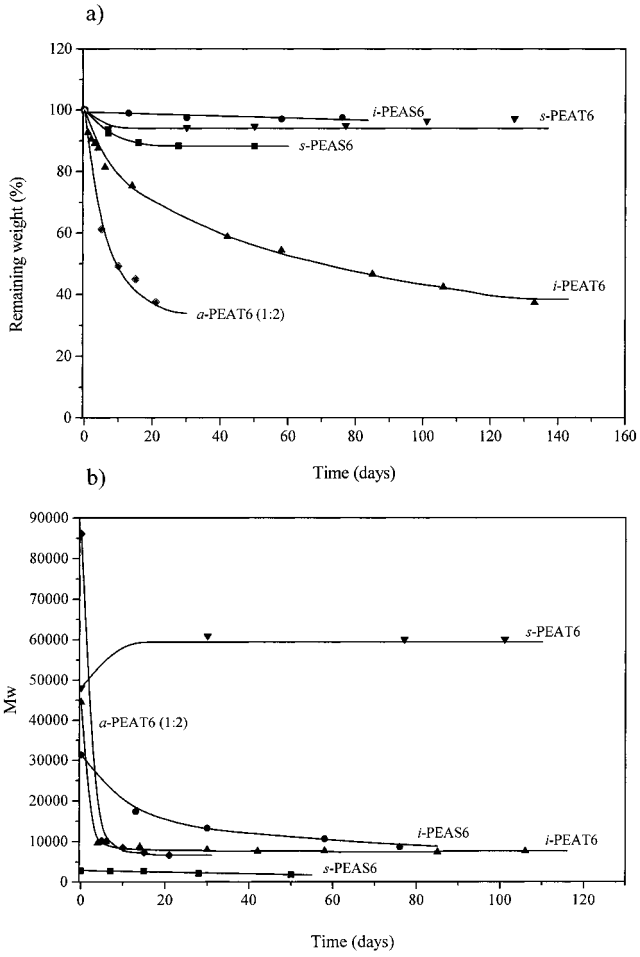

Figure 3. Hydrolytic degradation of poly(tartarester amide)s and poly(succinester amide)s: (a) remaining weight vs incubation time; (b) weight-average molecular weight vs incubation time.

incubation time was found to be noticeable for the two components, but it took place much faster for the substituted polymer. The fact that no weight loss was observed in the degradation of *i*-PEAS6 is inconsistent with the decay observed in molecular weight, and it could be explained as a consequence of the presumed insolubility of the degraded products. On the other hand, the higher degradation rate found for tartaric acid-derived poly(ester amide)s is consistent with the presence of electron-withdrawing methoxy groups which favor the nucleophilic attack necessarily implied in the breaking of the ester/amide bonds. It should be added, however, that water diffusion will be facilitated in the substituted poly(ester amide)s because a more loose chain packing in the amorphous phase is expected to occur. It can be concluded therefore that the remarkable degradability displayed by poly(tartarester amide)s when compared with conventional unsubstituted polyamides is the consequence of the combining action of the two chemical factors considered above, namely the weakness of main-chain ester groups and the activating effect (both electronic and structural) of methoxy side groups. However, the microstructure of the polymer chain is an additional factor that must be taken into account for a complete explanation of results shown in Figure 3; in fact, the very weak response displayed by the pair *s*-PEAS6/*s*-PEAT6 should be related with the syndioregic nature of these poly(ester amide)s as it will be discussed in detail in the next paragraph.

(c) Chain Regicity. Very striking results were obtained in the compared degradation of isomeric poly(ester amide)s differing only in the relative orientation adopted by amide and ester groups along the polymer chain. These results are shown in Figure 3 for the isomeric pairs *i*-PEAS6/*s*-PEAS6 and *i*-PEAT6/*s*-PEAT6. It should be stressed that crystallinity and chain packing are similar for the two components of each pair. Surprisingly, both sample weight and molecular weight of the syndioregic poly(ester amide) *s*-PEAT6 were found essentially unaltered after 8 months of treatment. (The slight increase in molecular weight and the small weight loss observed in the early stages of the incubation period are very likely due to leaching of low molecular weight oligomers, a fact that is not relevant to this analysis.) On the contrary, the molecular weight of the isoregic polymer *i*-PEAT6 decreased down to less than one-third of its initial value after 2 months of treatment. The behavior exhibited by poly(succinester amide)s is largely similar to that found for poly(tartarester amide)s. In fact, the syndioregic polymer *s*-PEAS6 appears to be reluctant to degradation, in contrast with the weak resistance displayed by the isoregic *i*-PEAS6 isomer. These results reveal that polymer regicity, i.e., the relative orientation of the monomeric units along the main chain, is a factor of major importance in determining the hydrolytic degradability of poly(ester amide)s, at least of those concerned in this work. Degradation curves obtained for the aregic poly(tartarester amide)

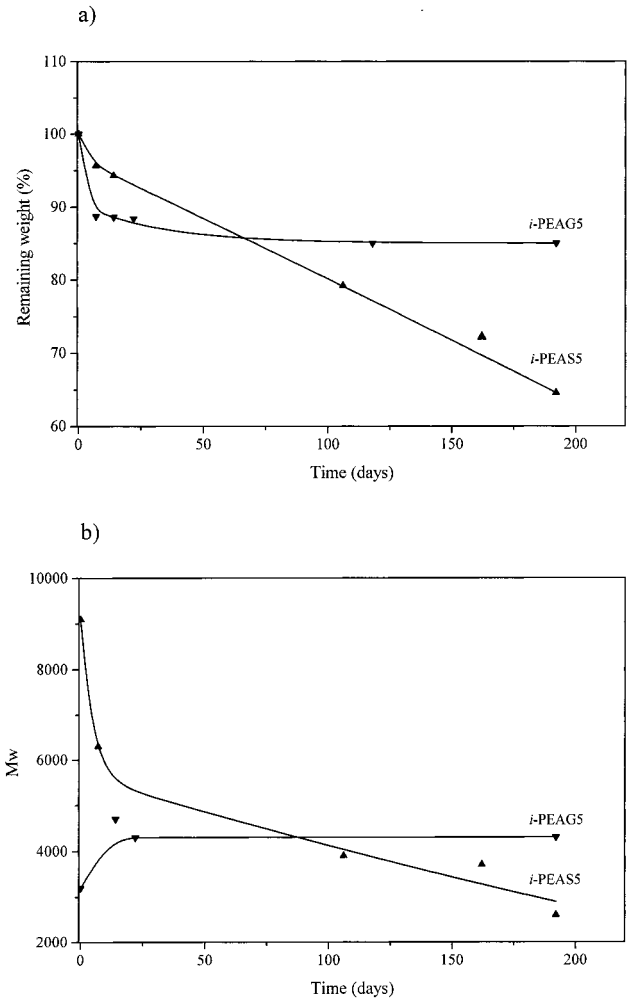

Figure 4. Hydrolytic degradation of poly(ester amide)s *i*-PEAG5 and *i*-PEAS5: (a) remaining weight vs incubation time; (b) weight-average molecular weight vs incubation time.

a-PEAT6 (1:2) have been also included in Figure 3 for a close comparison between regic and aregic polymers. Since the aregic polymer is composed of both isoregic and syndioregic structures, the positive response of *a*-PEAT6 (1:2) to the action of water is according to expectations. What is striking, however, is that it degrades faster and in more extension than *i*-PEAT6 despite containing a lower concentration of ester linkages. Such a particularly pronounced sensitivity of aregic poly(tartarester amide)s toward hydrolysis should be associated with physical factors, more probably to differences concerning the amorphous phase. The lack of regularity characteristic of *a*-PEAT6 chain results in a greater amount of amorphous phase (as reflected in the lower fusion heats measured for these poly(ester amide)s) with a less tied packing of the chains.

(d) Length of the Diacid Unit. Poly(ester amide)s *i*-PEAG5 and *i*-PEAS5 differ from each other in the number of methylenes comprised in the diacid unit. The two poly(ester amide)s are very comparable in terms of crystalline structure since they adopt the same model of crystal packing and have similar melting enthalpies. However, when these two compounds were incubated in an aqueous medium under similar conditions, they displayed a completely different behavior. It was found that *i*-PEAS5 degraded much faster than *i*-PEAG5, the latter remaining essentially unchanged after 6 months of incubation. These results are shown in Figure 4

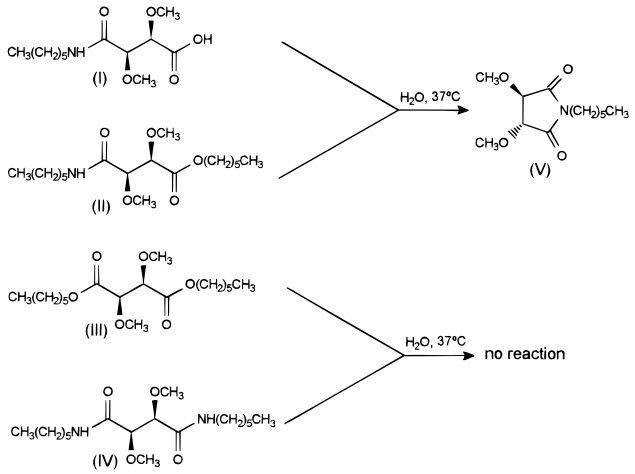

Figure 5. Model compounds and their degradation behavior.

where changes in both remaining weight and molecular weight are represented as a function of time for the two compared poly(ester amide)s immersed in water at pH 7.4 and 37 °C. As it happens with *s*-PEAT6, the slight variations observed along the first few days of incubation of *i*-PEAG5 are probably due to leaching of water-soluble oligomers present in the initial sample. It should be stressed that *i*-PEAS5 appears to be a readily hydrodegradable compound undergoing a weight loss of about 40% of the initial sample accompanied by a noticeable decay in the molecular weight. As shown in Figure 3b, a similar response was observed for *i*-PEAS6 with regard to variation in molecular weight with incubation time. All these results indicate that the length of the diacid unit is decisive to determine the propensity of poly(ester amide)s to water degradation whereas the size of the amino alcohol seems to be a factor not critical for the process

Degradation of Model Compounds. To support the interpretation of the results obtained in the degradation of the poly(ester amide)s, a set of model compounds comprising the monoamide (**I**), the ester amide (**II**), the diester (**III**), and the diamide (**IV**) of di-*O*-methyl-L-tartaric acid was synthesized and subjected to degradation under the same conditions used in the degradation of polymers. The chemical formulas of the compounds investigated and their responses to the treatment are depicted in Figure 5. The evolution of degradation for each compound was followed by IR and NMR spectroscopy. Whereas both the diester (**III**) and the diamide (**IV**) remained essentially unaltered, the ester amide **II** was partially converted into *N*-hexyl-di-*O*-methyl-L-tartarimide (**V**). The onset of compound **V** was detected in the IR spectra by the presence of a broad peak at about 1720 cm^{-1} intermediate between the ester and amide peaks and in the ^1H NMR spectra by a singlet at 3.7 ppm arising from the methoxy protons. These characteristic peaks and signals will be later used as references in the spectroscopic analysis of the degradation products of poly(tartarester amide)s. On the other hand, the *N*-hexyl monoamide (**I**) behaved like (**II**), yielding the tartarimide **V** in a 17% yield after 30 days of incubation.

Infrared and NMR Spectroscopy Analysis of Degradation Products. (a) Poly(ester amide)s i-PEAS5 and i-PEAS6. The IR and NMR spectra of poly(glutarester amide) *i*-PEAG5 taken before and after incubation for 6 months did not show appreciable differences, indicating that this polymer had not un-

Table 2. ^{13}C NMR Chemical Shifts (ppm) of Poly(ester amide)s *i*-PEAS5 and *i*-PEAS6 before and after Hydrolytic Degradation[a]

	succinester amide unit[b]				amino alcohol unit[b]					
	CH_2COO	**C**H_2CON	COO	CON	$^1CH_2$	$^2CH_2$	$^3CH_2$	$^4CH_2$	$^5CH_2$	$^6CH_2$
i-PEAS5										
undegraded	29.0	29.8	170.2	172.0	38.1	28.4	22.5	27.6	63.4	
degraded	29.0	29.8, **27.7**	170.2	172.0, **177.2**	38.1, **37.6**	28.4, **26.7**	22.5	27.6, **31.7**	63.4, **60.2**	
i-PEAS6										
undegraded	29.0	29.8	170.2	172.0	38.2	28.7	25.7	24.8	27.8	63.5
degraded	29.0	29.8, **27.8**	170.2	172.0, **177.2**	38.2, **37.5**	28.7, **28.0**	25.8, **26.7**	24.8, **26.1**	27.8, **32.2**	63.5, **60.5**
compound **VI**		**27.7**		**177.2**	**37.6**	**26.7**	**22.5**	**31.7**	**60.2**	

[a] Chemical shifts in DMSO. [b] Values in bold assigned to the succinimide unit or hydroxyl-ended pentamethylene or hexamethylene chain; numbering from nitrogen to oxygen end.

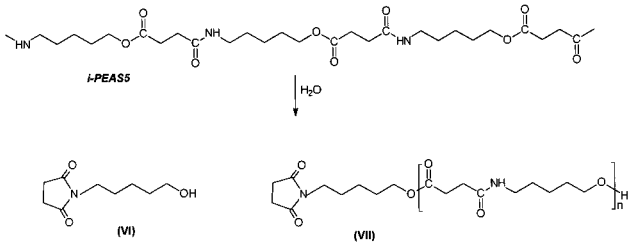

Figure 6. Degradation reaction in water of an isoregic poly(succinester amide) chain

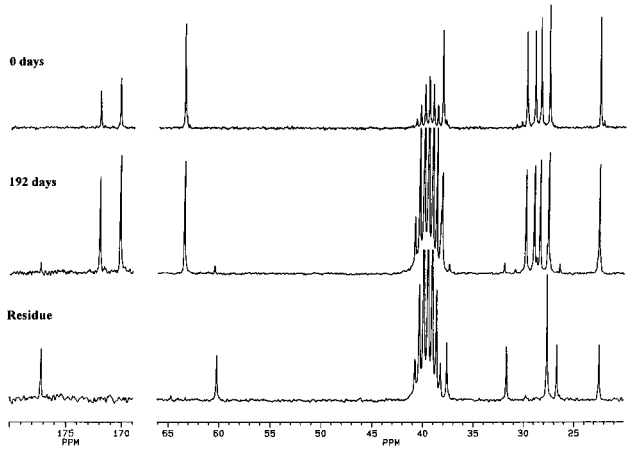

Figure 7. ^{13}C NMR spectra of *i*-PEAS5: initial sample (top); remaining disk after incubation for the indicated time (middle); residue from the DCM extract (botton).

dergone significant decomposition by the treatment. These observations are in full agreement with GPC and weight loss results described above. On the contrary, the same analysis carried out on poly(succinester amide) *i*-PEAS5 revealed notable chemical alterations in the polymer together with the occurrence of low molecular weight products in the incubating medium consistent with the degradation reaction depicted in Figure 6. The ^{13}C NMR spectra recorded from the initial polymer, the polymer remaining after 192 days of treatment and the residue left in the evaporation of the DCM extract resulting from the extraction of the incubating medium, are shown in Figure 7. All the peaks contained in the spectrum recorded from the residue may be assigned to *N*-5-hydroxypentyl succinimide (**VI**), which is considered to be the end product of degradation of *i*-PEAS5. The 1800−1600 cm^{-1} region of the IR spectrum (not shown) of this residue did not contain ester or amide carbonyl absorption bands but a strong absorption peak at 1720 cm^{-1} along with a less intense one about 1800 cm^{-1}, both of them being characteristic of the succinimide ring. On the other hand, the ^{13}C NMR spectrum recorded from the remaining polymer sample contains the signals characteristic of undegraded *i*-PEAS5 along with a few weak but significant peaks indicative of the presence of the succinimide derivative **VI** and hydroxyl-ended oligomers of type **VII**. Such compounds (**VI** and **VII**) were found to be predominant in the residue recovered after evaporation of the incubating solution to dryness, and their existence was assessed by mass spectroscopy (data not included). Similar results were obtained in the analysis of the degradation products of *i*-PEAS6, indicating the occurrence of a common degradation mechanism. ^{13}C NMR chemical shifts observed for the undegraded and degraded poly(ester amide)s *i*-PEAS5 and *i*-PEAS6 and for compound **VI** are compared in Table 2.

(b) Poly(ester amide)s s-PEAT6 and i-PEAT6. The IR and NMR spectra of the syndioregic poly(tartarester amide) *s*-PEAT6 before and after incubation for 8 months did not show appreciable differences, indicating that this polymer is not sensitive to hydrolysis under the applied conditions. This result is consistent with both GPC and weight loss data described above. On the contrary, the same spectroscopic analysis carried out on the isoregic poly(tartarester amide) *i*-PEAT6 revealed notable alterations in the polymer after the treatment together with the occurrence of low molecular weight products in the incubating medium. The 2000−1300 cm^{-1} regions of IR spectra of this poly(ester amide) before and after 30 days of treatment, the residue resulting from the incubating medium upon evaporation to dryness, and the tartarimide model **V** are shown in Figure 8. The presence of tartarimide units is revealed by the peak at 1717 cm^{-1} (spectrum d) which appears as a small shoulder in the spectrum of the degraded polymer (spectrum b) but as a main band in the spectrum of the residue left by the incubating solution (spectrum c). The ^{1}H and ^{13}C NMR spectra of the four same samples contain the peaks expected for the occurrence of tartarimide units. Chemical shits of the signals contained in the ^{1}H NMR spectra of *i*-PEAT6 before and after degradation and of model compound **V** are compared in Table 3. All the changes detected in both IR and NMR spectra upon incubation are in agreement with the occurrence of a degradation reaction similar to that taking place in the degradation of *i*-PEAS5 and *i*-PEAS6 (Figure 6).

(c) Poly(ester amide)s a-PEAT6. Although the analysis of the products yielded in the degradation of *a*-PEAT6's gave results consistent with a degradation mechanism similar to that described for isoregic poly(ester amide)s, specific data indicative of the random microstructure present in these polymers were obtained. The ^{1}H NMR spectra of *a*-PEAT6 (1:2) before and after degradation for a period of 40 days, and of the residue recovered from the incubating medium, are compared

Table 3. ^{1}H NMR Chemical Shifts (ppm) of Poly(ester amide)s *i*-PEAT6 and *a*-PEAT6 before and after Hydrolytic Degradation[a]

	tartaradiamide unit			tartarester amide unit[b]					amino alcohol unit[b]				
				amide			ester						
	NH	CH	OCH_3	HN	CH	OCH_3	CH	OCH_3	$^1CH_2$	$^2CH_2$	$^{3,4}CH_2$,	$^5CH_2$	$^6CH_2$
i-PEAT6													
undegraded				6.67	4.23	3.41	4.10	3.37	3.33	1.53	1.39	1.69	4.21
degraded				6.66	4.24, **4.13**	3.41, **3.71**	4.11	3.37	3.33, **3.40**	1.53	1.39	1.69	4.22, **3.63**
a-PEAT6													
undegraded	6.66	4.21	3.42	6.65	4.21	3.43	4.10	3.40	3.30	1.54	1.38	1.70	4.21
degraded	6.76	4.21	3.41	6.65	4.22, **4.13**	3.42, **3.70**	4.10	3.38	3.30, **3.40**	1.54	1.37	1.69	4.22, **3.64**
compound **V**[c]					**4.12**	**3.70**			**3.45**	1.56	1.29	1.29	(0.89)

[a] Chemical shifts in $CDCl_3$. [b] Values in bold assigned to the tartarimide unit and to hydroxymethyl ended hexamethylene chain; numbering from nitrogen to oxygen end. [c] *N*-Hexyl di-*O*-methyl-L-tartarimide; in parentheses, methyl protons signal.

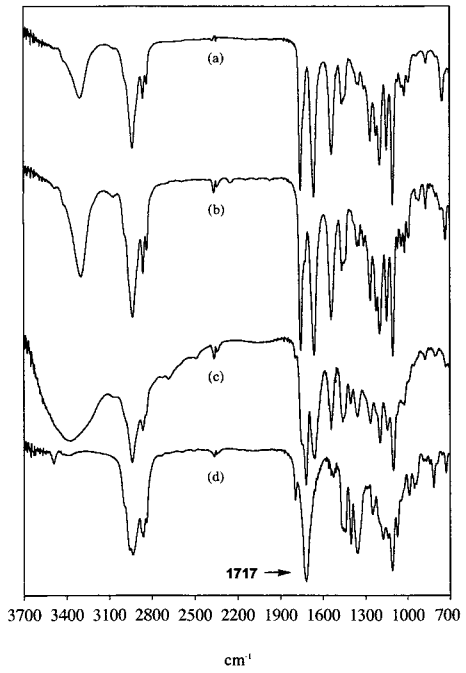

Figure 8. FTIR spectra of *i*-PEAT6: (a) initial sample, (b) disk after 14 days of incubation; (c) residue from the mother solution after 30 days of incubation; (d) spectrum of *N*-hexyl tartarimide model compound.

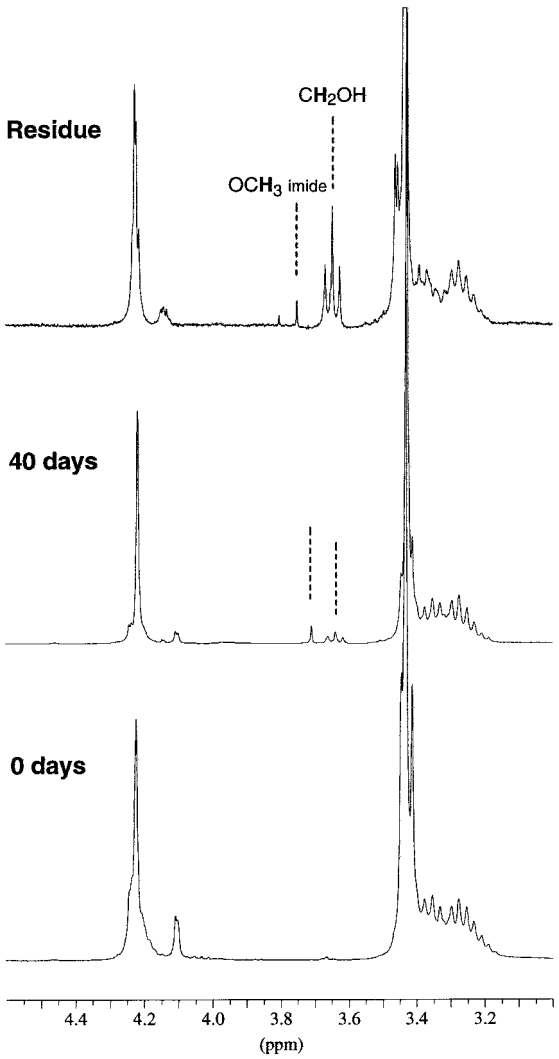

Figure 9. ^{1}H NMR spectra of *a*-PEAT6: (a) initial sample (botton); (b) remaining disk after 40 days of incubation (middle); (c) residue from the mother solution (top).

in Figure 9. Chemical shifts of the signals displayed by spectra of the initial and degraded polymer are included in Table 3. The ^{1}H NMR spectrum of the 40 days degraded polymer shows in addition to the signals of the initial polymer other weak signals at 3.70 and 4.13 ppm arising from the methoxy and methine protons of the tartarimide structure. Conversely, the spectrum given by the degradation products that have passed into the aqueous medium (spectrum labeled as "residue" in Figure 9) displays a strong triplet at 3.60 ppm attributable to hydroxyl protons as well as other weak signals characteristic of tartarimide units. The ^{13}C NMR spectrum of the residue (not shown) was rather complex and could be interpreted as arising from a mixture of hydroxymethyl ended oligotartaramides consisting of 2−3 tartaric units. It is worth noting that neither carboxylic nor amine end group signals were detected in such spectrum. All these results indicate that degradation of *a*-PEAT6 (1:2) must take place by hydrolysis of the ester groups with generation of water-soluble hydroxyl ended oligomers and nonsoluble tartarimide ended polymers of low molecular weights; this is in full agreement with the microstructure of poly(ester amide)s *a*-PEAT6 where, at difference with *i*-PEAT6, fragments capped at both ends with the same functional group are feasible to form.

General Mechanism of Degradation of Poly(succinester amide)s and Poly(tartarester amide)s. The survey of results presented in the previous sections allows us to put forward a general mechanism of hydrolysis of succinic and tartaric derived poly(ester amide)s as that depicted in Figure 10. The mechanism is described as taking place by scission of the weak ester linkages promoted by the nucleophilic attack on the CO ester carbon by the neighboring amidic nitrogen. The

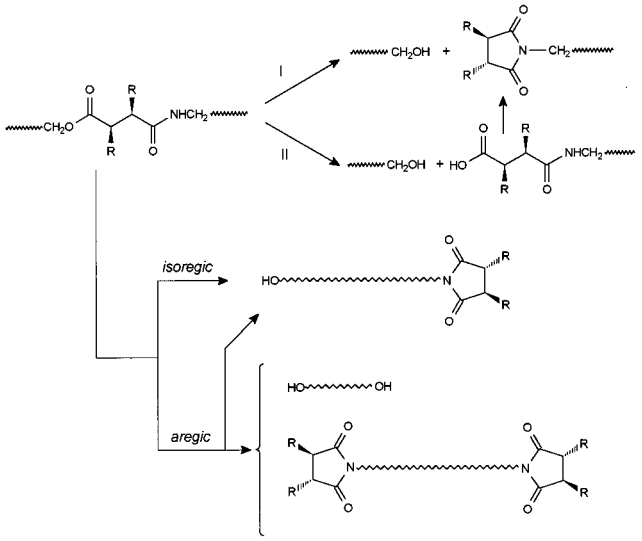

Figure 10. Scheme of the degradation mechanism in poly(ester amide)s: (I) one-step mechanism consisting of imide cyclization by intramolecular amidolysis; (II) two-step mechanism consisting of ester hydrolysis followed by cyclization. Low molecular fragments resulting from degradation of isoregic and aregic poly(tartarester amide)s are also indicated.

main facts supporting this mechanism are the following:

(i) The presence of end CH_2OH groups but not CH_2NH_2 groups in the degraded products indicates that splitting of the chain must occur mainly through the relatively weak ester bonds.

(ii) The fast conversion of ester amide **II** into imide **V** contrasts with the nonoccurrence of reaction in the diester **III** and proves that ester breaking is highly favored by intramolecular amidolysis.

(iii) The insistent presence of succinimide or tartarimide units but the absence of end carboxylic groups in the degradation products indicates that intrachain cyclization to imide must be the main reaction implied in the degradation of poly(succinester amide)s and poly(tartarester amide)s in an aqueous medium.

On the other hand, it should be recalled that results obtained in the hydrolysis of model compound **I** revealed that formation of cyclic imides from carboxylic ended polyamide chains is also feasible. Accordingly an alternative mechanism in two steps, the first entailing the hydrolysis of the ester group and the second consisting of rapid cyclization into imide could be also considered. Although eventual hydrolysis of ester groups cannot be completely discarded, the concerted mechanism based on intramolecular amidolysis is looked to be the preferred mechanism since it is the only one able to explain the differences in degradability observed between syndioregic, isoregic, and aregic polymers.

Concluding Remarks

The influence of the chemical constitution and microstructure on degradability of poly(ester amide)s derived from amino alcohols, diamines, and diacids has been evaluated. It has been concluded that the insertion of ester groups combined with the attachment of electron-withdrawing side groups largely enhances the hydrodegradability of polyamides. It has been further demonstrated that the design of the main chain in terms of sequence and directionality is critical in determining the response of the poly(ester amide) to the water attack. Both aregic and isoregic poly(ester amide)s containing four carbon atom diacid units are easily degraded in water whereas those others not fitting such constitution pattern display a behavior not very different from that shown by their respective parent polyamides.

The spectroscopic analysis of the degradation products has revealed that poly(ester amide)s containing four-carbon diacid units tend to degrade through a mechanism implying cyclization to imides, probably by an intramolecular amidolysis reaction. Such a mechanism is able to account for the striking differences that are observed in the degradation of polymers with different regicity and may constitute one guideline for the design of novel poly(ester amide)s with adjusted hydrodegradability.

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