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Articles

Synthesis of Chiral Polyhydroxy Polyamides Having Chains of Defined Regio and Stereoregularity

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ABSTRACT: 1,6-Diaminohexane and a 2-(*S*)-hydroxypentanedioic acid 5,2-lactone derivative (**3**) were polycondensed to afford an aregic polyamide **4**. A chiral monomer (**5**) having a 2-fold axis of symmetry was chemoselectively constructed from **3**, and upon polymerization with the diamine led to an AABB-type polyamide having a syndioregic orientation of the hydroxyl substituents. The analogous isoregic polyamide **11** was also prepared. The three polymers had the same basic structure, but they differ in their regio and stereoregularity. These polyamides, which displayed optical activity, were characterized by IR and ^{1}H and ^{13}C NMR, and their molecular weights were estimated by GPC, viscosimetry, and matrix-assited ultraviolet laser desorption/ionization time-of-flight mass spectrometry (UV−MALDI−TOF MS). This technique was particularly convenient to confirm the repeat units and to detect the functional groups at both ends of the chains. In accordance with their growth processes polyamides **11** and **12** showed the typical UV−MALDI−TOF spectrum for homopolymerization, and polyamides **4** and **6** showed those corresponding to growing by copolymerization. Besides, in agreement with their stereoregularity, polyamides **6** and **11** showed better crystalline properties than those of **4**.

Introduction

Synthetic nonpolipeptidic stereoregular polyamides containing stereogenic centers are considered high performance materials, which showed improved biocompatibility, biodegradability, and other desired properties.[1] To establish the relation existing between constitution and properties, a number of optically active polyamides have been prepared and their optical properties were studied.[2] It has been reported that the presence of the stereocenter in the polyamide chain may promote important conformational changes. Thus, chiral stereoregular analogues of nylon 3 and nylon 4 adopt helical arrangements similar to those known as typical of polypeptides and proteins.[3,4] These helical nylons displayed particular properties such as liquid crystals formation and piezoelectricity.[5,6] Also, the introduction of asymmetric carbons into the polyamide chain allows the control of the tacticity, and hence the adjustment of the physical and biological properties.[7] As a consequence of all these findings, the interest in the synthesis of new stereoregular polyamides has been renewed during the past decade.

Carbohydrate-based monomers have been employed for the preparation of polyamides containing several asymmetric centers in the backbone of the repeating unit.[8,9] However, severe limitations have been found in the polycondensation of such highly functionalized carbohydrate monomers, specially when the preparation of stereoregular polyamides is intended. A particular difficulty, related with the symmetry of the chiral building blocks appears in the synthesis of the AABB-type of polyamides by condensation of a diacid with a diamine. In this case, the construction of a stereoregular polyamide relies upon the existence of a 2-fold axis of symmetry in the monomers from which it is generated. Otherwise, regioisomerism in the formation of the amide bonds may likely occur affording aregic polyamides. Stereoregular polyamides can be readily prepared from L-tartaric[8,10,11] and other aldaric acids[12−15] which contain a 2-fold axis of symmetry, whereas the synthesis of optically active regioregular polyamides of the AABB type from nonsymmetric monomers is much more laborious.[16]

In our laboratory we have employed the (2*S*)-2-hydroxypentanedioic acid, derived from L-glutamic acid as a precursor of AB-type[17,18] and AABB-type stereoregular polyamides.[19] In the present work, we wish to report the synthesis of a nonstereoregular aregic polyamide and the highly stereocontrolled synthesis of a syndioregic polyamide using **2** as a chiral template. The properties of the resulting polymers and also those corresponding to the isoregic polyamide (**11**) were compared. Particularly, molecular weight distributions were studied by means of the matrix-assisted ultraviolet laser desorption/ionization time-of-flight (UV−MALDI−TOF) mass spectrometry (MS) technique. As the polymers obtained were not soluble in water or common

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organic solvents used in this technique, we described here the use of a polar, non volatile solvent such as dimethyl sulfoxide (DMSO) for the preparation of the samples.

Experimental Section

General Methods. Solvents were dried and purified when necessary, by appropriate standard procedures. TLC was performed on silica gel 60 F_{254} (Merck) with detection by UV light or by heating after immersion in a solution of anisaldehyde (5% v/v) in 95% ethanol containing 5% H_2SO_4. Column chromatography was performed with silica gel 60 (200−400 mesh, Merck). Optical rotations were measured with a Perkin-Elmer 343 polarimeter. Fourier transform infrared (FTIR) spectra (KBr disks) were recorded with a Nicolet 510P instrument. Nuclear magnetic resonance (NMR) spectra were recorded in a Bruker AC 200 spectrometer. Chemical shifts δ are reported as part per million downfield from tetramethylsilane. Elemental analyses were performed by UMYMFOR (CONICET-University of Buenos Aires). Differential scanning calorimetry (DSC) was carried out on a Mettler DSC 20 instrument. Samples (5−10 mg) were heated at a rate of 15 °C/min and cooled to room temperature. Peaks were taken as melting temperatures. Size exclusion chromatography (SEC) analyses were performed with polymers modified as trifluoroacetyl derivatives, in a Shimadzu L6A apparatus with a column shim-pack series GPC 80-801 and 802, calibrated with polystyrene samples of narrow molecular weight distribution, with THF as solvent (flow rate 1 mL/min). Intrinsic viscosities were measured in dichloroacetic acid at 25.0 ± 0.1 °C with a Cannon-Ubbelohde 100/L30 semimicroviscosimeter. X-ray diffraction patterns were recorded in a Siemens D2000 using a nickel-filtered Cu Kα radiation of wavelength of 0.1542 nm.

Pentachlorophenyl (2*S*)-5-Oxo-2-tetrahydrofurancarboxylate (3). **3** was synthesized following the procedure reported from our laboratory,[19] starting from (2*S*)-2-hydroxypentandioic acid 5,2-lactone.[20] Compound **3** gave mp 157−159 °C and $|\alpha|_D$ +27 (*c* 1.0, $CHCl_3$).

Synthesis of Aregic Polyamide 4 (Poly(1,6-[*N*,*N*′-(*S*)-2- or 4-hydroxypentandicarboxy]hexamethylendiamine)). To a suspension of **3** (0.57 g, 1.51 mmol) in dry DMF (0.9 mL) were added *N*,*N*-diisopropylethylamine (0.6 mL) and 1,6-diaminohexane (0.17 g, 1.51 mmol). The resulting solution was stirred at room temperature for 5 days. The polymer precipitated upon addition of MeOH (10 mL) followed by addition of ethyl ether (30 mL). The solid was separated by centrifugation and purified by dissolution in DMSO followed by precipitation with MeOH-ethyl ether (1:3). This purification procedure was repeated three times. The solid was washed with ethyl ether and dried in a vacuum, affording **4** (0.26 g, 77%), $|\alpha|_D$ −24 (*c* 0.5, HCOOH). FTIR: ν_{max} 3408 (s, OH), 3315, 3276 (vs, NH), 3092 (w, amide B), 2940 (s, CH_2), 2860 (m, CH_2), 1650, 1631 (vs, amide I), 1552 (vs, broad, amide II), 642 (w, amide V), 620 cm^{-1} (w, amide VI). NMR data: ^1H (200 MHz, DMSO-d_6) δ 7.77, 7.66 (t, 2 H, NH), 3.82 (m, 1 H, H-2), 3.02 (m, 4 H, CH_2−1′,6′), 2.13 (m, 2 H, H-$4_{a,b}$), 1.85, 1.65 (m, 2 H, H-$3_{a,b}$), 1.39−1.23 (m, 8 H, CH_2−2′-5′); ^{13}C (50 MHz, DMSO-d_6) δ 173.6 (C-5), 171.8 (C-1), 70.6 (C-2), 38.8, 38.5 (C-1′,6′), 31.2, 30.4, 29.0 (×2), 25.9 (×2) (C-3,4,2′-5′). Anal. Calcd for $(C_{11}H_{20}N_2O_3\cdot 0.3H_2O)_n$: C, 56.53; H, 8.88; N, 11.98. Found: C, 56.64; H, 9.18; N, 12.20.

1,6-(*N*,*N*′-Bis[(*S*)-5-oxo-2-tetrahydrofurancarboxy]hexamethylendiamine) (5). To a solution of **3** (1.00 g, 2.64 mmol) in dry DMF (20 mL) and *N*,*N*- diisopropylethylamine (0.4 mL) cooled at 0 °C was added a solution of 1,6-diaminohexane (0.15 g, 1.32 mmol) in DMF (20 mL) dropwise. The mixture was stirred at room temperature for 16 h and then concentrated. The residue was dissolved in dichloromethane and washed with 5% aqueous HCl, water, and finally with a saturated aqueous solution of $NaHCO_3$. The organic extract was dried ($MgSO_4$), filtered, and concentrated. The resulting syrup crystallized upon addition of EtOAc−hexane, to give **5** (0.37 g, 83%): mp 105−107 °C; $|\alpha|_D$ − 32 (*c* 1.0, HCOOH). NMR data: ^1H (200 MHz, $CDCl_3$) δ 6.54 (t, 2 H, NH), 4.82 (m, 2 H, H-2), 3.31−3.22 (m, 4 H, CH_2−1′,6′), 2.65−2.27 (m, 8 H, H-$3_{a,b}$, $4_{a,b}$), 1.53−1.28 (m, 8 H, CH_2−2′-5′); ^{13}C (50 MHz, DMSO-d_6) δ 175.8, 169.3 (C-1, 5), 77.4 (C-2), 38.9 (C-1′,6′), 29.1, 27.5, 26.1, 25.7 (C-3,4,2′-5′). Anal. Calcd for $C_{16}H_{24}N_2O_6$: C, 56.46; H, 7.11; N, 8.23. Found: C, 56.35; H, 7.31; N, 8.15.

Synthesis of Syndioregic Polyamide 6 (Poly(1,6-[*N*, *N*′-(*S*)-2-hydroxypentandicarboxy]hexamethylendiamine)). To a suspension of **5** (0.51 g, 1.51 mmol) in dry DMF (0.9 mL) were added *N*.*N*-diisopropylethylamine (0.6 mL) and 1,6-hexanediamine (0.17 g, 1.51 mmol). The resulting solution was stirred at room temperature for 5 days and then processed and purified as described for the preparation of polyamide **4**. The solid was dried in a vacuum, affording **6** (0.27 g, 80%), $|\alpha|_D$ −56 (*c* 0.5, HCOOC). FTIR ν_{max}: 3410 (s, OH), 3315, 3263 (vs, NH), 3092 (w, amide B), 2945 (s, CH_2), 2870 (m, CH_2), 1655, 1618 (vs, amide I), 1565, 1539 (vs, amide II), 650 cm^{-1} (w, amide V). NMR data: ^1H (200 MHz, DMSO-d_6) and ^{13}C (50 MHz, DMSO-d_6) identical to those of **4**. Anal. Calcd for $(C_{11}H_{20}N_2O_3\cdot 0.2H_2O)_n$: C, 56.97; H, 8.86; N, 12.08. Found: C, 56.89; H, 9.04; N, 12.31.

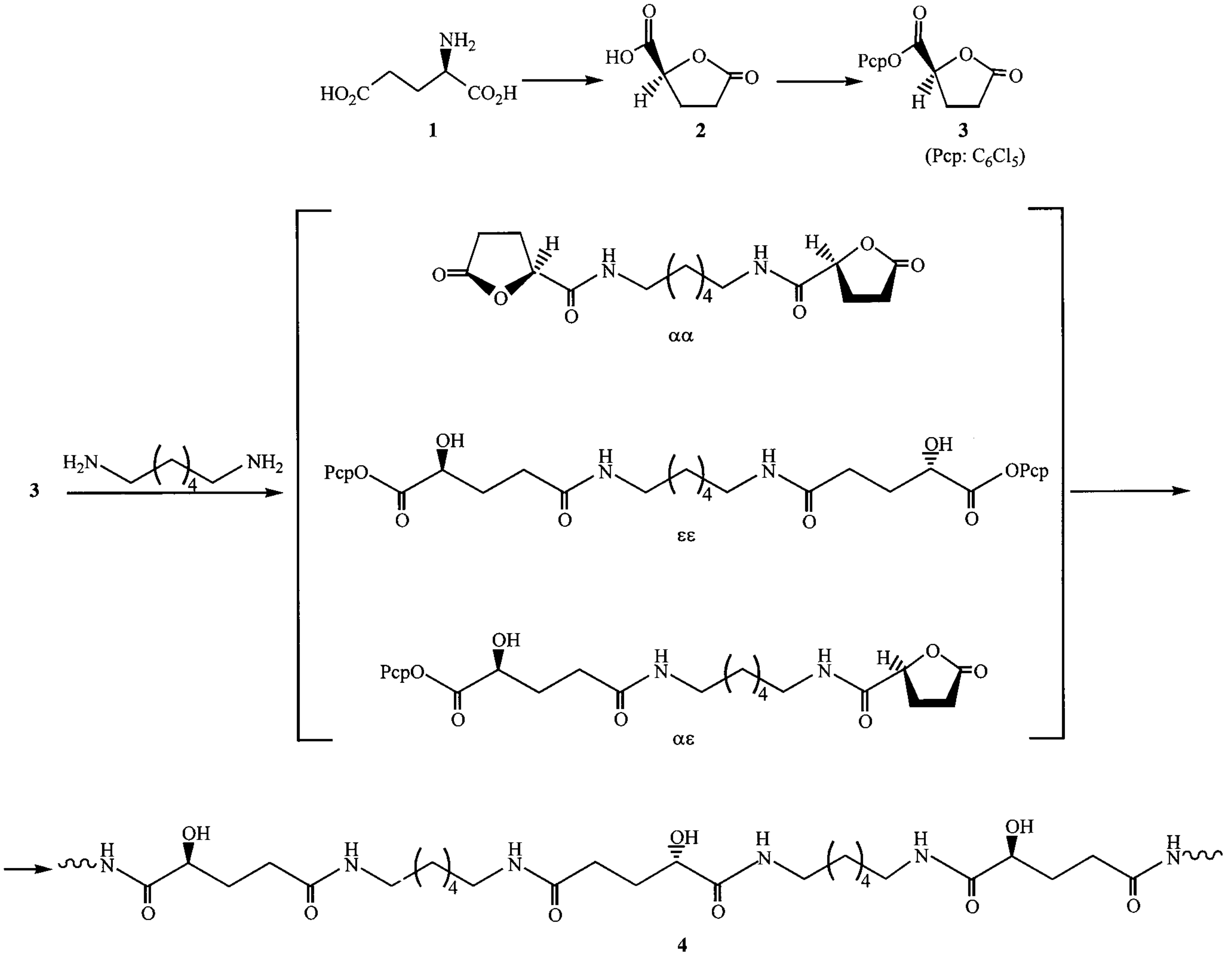
Synthesis of Isoregic Polyamide 11 (Poly(1-[*N*-(*S*)-4-hydroxypentandicarboxy]-6-[*N*′-(*S*)-2-hydroxypentandicarboxy]hexamethylendiamine)). **11** was synthesized from monomer **10** as previously reported.[19] The isolation and purification was the same as that applied to **4** and **6**. Polyamide **11** gave $|\alpha|_D$ −62 (*c* 0.5, HCOOH). FTIR ν_{max}: 3315, 3256 (vs, NH), 3092 (w, amide B), 2920 (vs, CH_2), 2880 (m, CH_2), 1654, 1622 (vs, amide I), 1564, 1535 (vs, amide II), 630, 605 cm^{-1} (amide V, VI); NMR data: ^1H and ^{13}C (DMSO-d_6, 200 and 50 MHz, respectively) identical to those reported for **4** and **6**. Anal. Calcd for $(C_{11}H_{20}N_2O_3\cdot 0.4H_2O)_n$: C, 56.10; H, 9.04; N, 11.89. Found: C, 56.51; H, 9.57; N, 11.59.

Trifluoroacetylation of 4, 6, and 11. To facilitate the SEC analysis of polyamides **4**, **6** and **11** they were trifluoroacetylated with trifluoroacetic anhydride in dry chloroform, according to the procedure reported by Schulz et al.[21] Upon evaporation of the solvent, the TFA polyamides were obtained as transparent films, which were soluble in dry THF.

Matrix-Assisted Ultraviolet Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (UV−MALDI−TOF MS). Several chemicals were attempted as matrices. The best results were obtained by using 9H-pyrido[3,4-*b*]indole (*nor*-harmane), 2,5-dihydroxybenzoic acid (DHB; gentisic acid, GA), *trans*-3-indoleacrylic acid (IAA) and 2-(4-hydroxyphenylazo)benzoic acid (HABA). Several proteins dissolved in (i) aqueous 0.1% trifluoroacetic acid (TFA) and in (ii) DMSO, and cyclodextrins in (i) water (Milli Q grade) and in (ii) DMSO solution, were used for calibration purposes. Solutions of the matrix and the polyamides (analyte), were performed in DMSO. To study the effect of Ag and Na ions on the MALDI spectra, 4.5×10^{-3} M solutions of silver trifluoroacetate and silver acetylacetonate in THF and NaCl in water were used. Matrix stock solutions (5−20 mg/mL) and analyte solutions (1 mg/mL) were prepared in DMSO and in DMSO/H_2O TFA 0.1% 9/1 (v/v).[22,23] Two methods of sample preparation were used. In method A, the probe was coated with 0.5 μL of the matrix solution, removing the solvent by blowing air at room temperature. This was followed by coating with the analyte solution (0.5 μL) and by an additional coating with the matrix solution. In method B, matrix and analyte solutions were mixed in different volumetric ratios (3:1 to 12:1), and two coatings (0.5 μL each) were performed. Spectra of higher quality were obtained by using method B. When doping with Ag^+ or Na^+ in method B, coating of the probe tip with the corresponding salt solution was the first step, followed by the usual procedure.

Measurements were performed using (i) Shimadzu Kratos, Kompact MALDI III UV−laser desorption time-of-flight mass spectrometer and (ii) Shimadzu Kratos, Kompact MALDI 4 (pulsed extraction). Both spectrometers were equipped with a pulsed nitrogen laser (λ = 337 nm; pulse width = 3 ns) but only the latter with tuneable time delay capability. TOF analyzers were used at 20 kV, and ions were obtained by irradiation just above the threshold laser power. Samples were measured in the linear mode, in both positive and negative

Scheme 1



ion modes. Usually, 50 spectra were accumulated. Spectra were calibrated by use of Na^+ and standard chemicals. The Kratos Kompact III and 4 calibration programs were used.

Inspection of the solids ready to be used as samples (stereoscopic microscope NIKON Optiphot, Tokyo, Japan; magnification ×400; digital computarized microscope KEYENCE VH-6300, Keyence Kyoto, Japan; magnification ×800) showed that, from DMSO, IAA produced an homogeneous distribution of needles kept together in circles on the surface; HABA yielded small yellow-orange microcrystals; and *nor*-harmane produced big needles in bunches. The same aspect and distribution of the crystals were observed when these matrices were loaded on the solid polymer previously deposited on the slide.

The molecular weight distribution is defined by the number-average molecular weight (M_n), weight-average molecular weight (M_w), and polydispersity:

$$M_n = \sum M_i N_i / \sum N_i \quad M_w = \sum (M_i)^2 N_i / \sum M_i N_i$$

$$\text{polydispersity} = \text{PD} = M_w / M_n$$

M_i is the mass of the oligomer in the distribution and N_i is its intensity.

Results and Discussion

Polyhydroxy chiral polyamides were obtained by polymerization of 1,6-diaminohexane with conveniently activated (2*S*)-hydroxypentanedioic acid 5,2-lactone (**2**). The latter was obtained[20] (Scheme 1) by nitrous acid deamination of commercially available and inexpensive L-glutamic acid (**1**). The pentachlorophenyl ester **3**, which was prepared from **2**, possesses a reactive ester and a lactone function, both activated for the polycondensation, as lactones also readily react with amines.[24] Since monomer **3** is an asymmetric molecule, its polycondensation with 1,6-diaminohexane will lead to an aregic polyamide due to nonregioselective additions of the diamine to the nonequivalent carboxyl groups. Similarly, the polymerization of tartaric acid derivatives with asymmetric L-lysine produces an aregic polymer.[25] Three structures are possible for a sesquiad consisting of one diamine and two diacid residues, which may be denoted as α,α, α,ϵ and ϵ,ϵ (Scheme 1) in reference to which of the carboxyls of **3** is implied in each amide group. The first arrangement (α,α) would result from the attack of each amine group of the diamine to the ester carboxyl (C-1) of two molecules of **3**. In this sesquiad the hydroxyl groups are located in the chain at 12 atoms of distance. The addition of the diamine to the lactone group (C-5) of each molecule of the diacid leads to the ϵ,ϵ arrangement, with a chain of 16 atoms between of the two hydroxyl groups. Finally, the condensation of the diamine to C-1 and C-5 of two molecules of **3** will produce the α,ϵ structure, in which the hydroxyl groups are separated by 14 atoms. On a statistical basis, the fraction contents of the three possible structures α,α:

Table 1. Molecular Weights of 4, 6, and 11 Determined by Vicosimetry and GPC and UV−MALDI−TOF MS

polyamide	yield (%)	$[\eta]^a$(dL/g)^a	$M_v{}^b$	$M_w{}^c$	$M_n{}^c$	$M_w/M_n{}^c$	$M_w{}^d$	$M_n{}^d$	$M_w/M_n{}^d$
4	77	0.18	2784	1991	1450	1.37	1770	1717	1.03
6	80	0.20	3183	2015	1562	1.35	2789	2542	1.09
11^e	85	0.28	4884	2149	1641	1.31	2530^f	2315^f	1.11^f

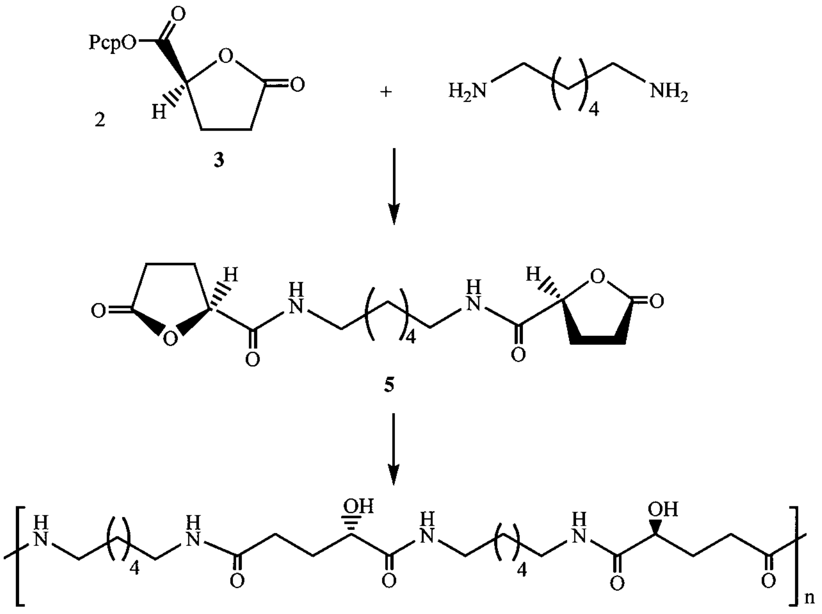
[a] Intrinsic viscosities measured in dichloroacetic acid at 25 °C. [b] Calculated by applying the viscosimetric equation $100[\eta] = 0.5 + 0.352M_v{}^{0.551}$ reported for nylon 6,6. [c] Determined by GPC of the trifluoroacetylated samples. [d] Data obtained from UV−MALDI−TOF MS in positive ion mode. [e] For polyamide **11** in negative ion mode the values are 2711, 2609, and 1.03, respectively. [f] For polyamide **12** (Scheme 3) data obtained are 2159, 1938, and 1.11, respectively.

Table 2. Thermal, Optical, and X-ray Diffraction Data of Polyamides 4, 6, and 11

polyamide	$[\alpha]_D{}^a$	thermal transitions (°C)^b	T_m (°C)^c	ΔH (J·g^{-1})^c	Bragg spacings (Å)
4	−24	57.2, 155.8, 178.2, 190.2	188	53	16.22, 13.07, 4.61, 4.23, 4.07
6	−56	55.0, 166.5, 203.9	202	64	16.81, 12.94, 7.43, 4.69, 4.23, 4.06, 3.90, 3.17
11	−62	50.0, 173.8, 197.0, 205.1	183, 200	65	15.36, 4.69, 4.28, 4.07, 3.16
nylon 6,5[27]			239	73.2	13.60, 6.80, 4.32, 3.96, 3.71

[a] Measured in formic acid (*c* 0.5). [b] Determined by DSC during the first heating cycle. [c] Determined by DSC during the second heating cycle.

Scheme 2



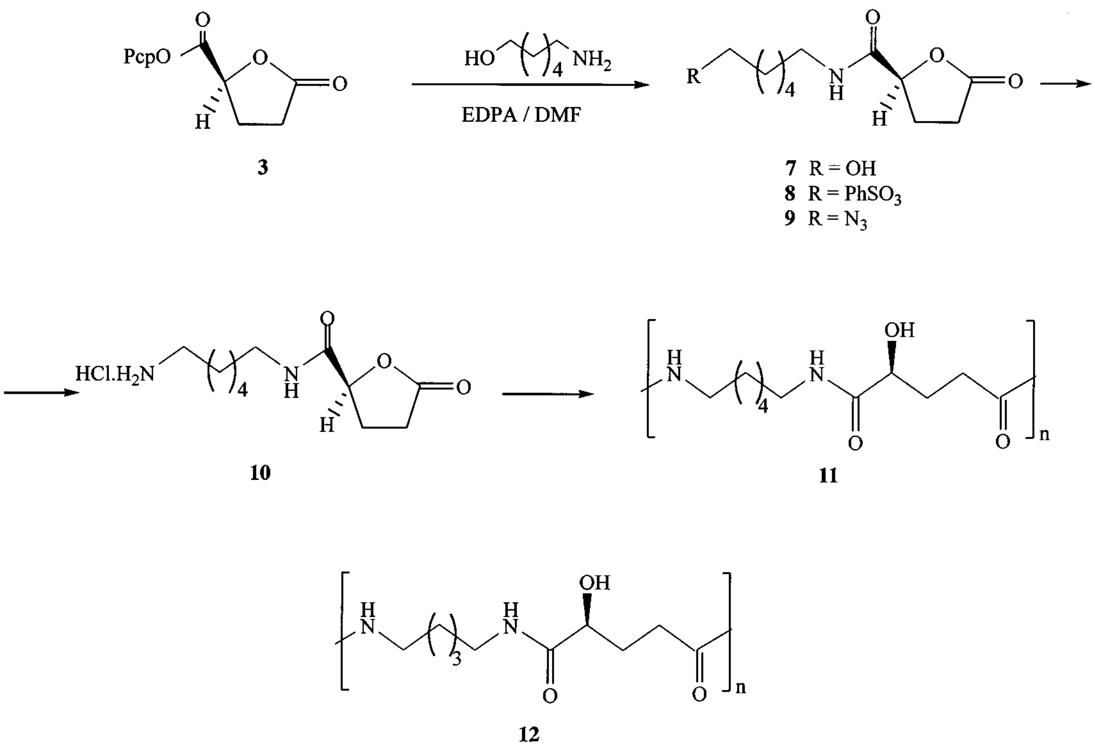
6

ε,ε: α,ε should be 1:1:2, for a perfectly aregic polymer chain.

The polycondensation of **3** with 1,6-diminohexane was performed in DMF using *N*,*N*-diisopropylethylamine as catalyst, conditions which have shown to be adequate for the polymerization of similar precursors by the active ester method.[17,26] After 5 days a gellike mass had been formed, and polyamide **4** was isolated by precipitation with methanol−ethyl ether (1:3). However, the pentachlorophenol, generated in the course of the polymerization, was persistently retained by the polyamide. To remove it completely, the crude polymer was subjected to repeated dissolution in DMSO and precipitation with methanol−ether (1:3). The FTIR spectrum of **4** showed the absorptions for the amide groups at values similar to those reported for nylon 6,5.[27] Furthermore, between 500 and 700 cm^{-1} it showed two weak but well-defined absorptions (642 and 620 cm^{-1}, amide V and VI) which are related to the crystalline structure of the polyamide.[28] In the ^{1}H NMR spectrum of **4** the H-2 signal was shifted upfield respect to the same signal in **3**, which indicates the opening of the lactone ring.

The molecular weight distribution was studied by size exclusion chromatography (SEC) employing Shim-pack columns and tetrahydrofuran (THF) as mobile phase. To make polyamide **4** soluble in this solvent, it was trifluoroacetylated by the method of Schulz et al.[21] The values of M_n, M_w, and polydispersity are shown in Table 1. Also the intrinsic viscosity of **4** was measured, and the viscosimetric molecular weight M_v was calculated employing the Mark−Houwink equation with the parameters reported for nylon 6,6.[29] The occurrence of thermal transitions in **4** was investigated by differential scanning calorimetry (DSC). The thermogram showed four well-defined endotherms for the first heating cycle (Table 2); the first (57.2 °C) was produced by water loss, which was quantified (approximately 5%) by the difference of weight before and after the heating. The other three melting peaks were attributed to the fusion of populations of crystallites differing in size, a phenomenon which is rather common among nylons which crystallize from solution.[30] After a slow cooling of the melted sample a second heating cycle was recorded, and in this case a single melting peak was observed (188 °C, ΔH 53 J·g^{-1}). Regular nylon 6,5[27] shows a higher melting temperature with a higher ΔH (Table 2), which suggests better crystalline properties for this compound, compared with those of **4**. Also, a powder X-ray diffrac-

Scheme 3



tion study of this polyamide revealed that the product was slightly crystalline, as the diffraction diagram showed four weak reflections relative to a strong one, which corresponded to a Bragg spacing of 4.23 Å. In contrast, regular nylon 6,5 showed five intense reflections, corresponding to the spacings reported in Table 2.[27] Polyamide **4** was insoluble in polar and nonpolar organic solvents, but it could be dissolved by aprotic polar solvents as DMSO and DMF at temperatures higher than 40 °C. It was also soluble at room temperature in strong organic acids, such as dichloroacetic and formic acids. Slow evaporation of formic acid from a solution of **4** afforded films which did not show the formation of supramolecular structures, as observed for similar stereoregular polyamides.[17]

For the preparation of a stereoregular polyamide of the AABB type analogue of **4**, the chiral monomer should possess a 2-fold axis of symmetry. In this case, the random attack of the diamine to any of the carboxyl groups of the chiral diacid leads to an ordered (regioregular) repeating unit, in which all the stereocenters have the same configuration. The chiral monomer **5**, having a C_2 axis of symmetry, was prepared by chemoselective condensation of **3** with 1,6-diaminohexane (Scheme 2). A higher reactivity of the pentachlorophenyl ester with respect to the lactone could be expected as the pentachlorophenolate is a better leaving group than the alkoxide and also because the ester group possesses a hydroxyl substituent on the α-carbon, which increases the reaction rate of aminolysis.[31] Slowly addition of a solution of 1,6-diaminohexane (1 molar equivalent) to a diluted solution of **3** (2 molar equiv) in the presence of *N*,*N*-diisopropylethylamine produced the chemoselective formation of **5**, which was isolated as a crystalline product in 83% yield. In the ^{1}H NMR spectrum of **5** the signal for H-2 appeared at low field (4.82 ppm) indicating that the hydroxyl group at C-2 was lactonized.

The polycondensation of **5** with 1,6-diaminohexane would lead to a stereoregular polyamide **6** which will be formed by alternate α,α and ϵ,ϵ arrangements in a 1:1 ratio. In the extended chain conformation of this polyamide, each hydroxyl group will be arranged successively in front and behind of the plane of the chain, defining a syndioregic structure. The polymerization was conducted under conditions identical to those employed for the preparation of **4**. The purification of the resulting polyamide **6** was easier as no pentachlorophenol was liberated as byproduct. However, as physical properties (T_m, $[\alpha]_D$, etc.) of polymers depend to some extent on the story of the specimen, to compare **4** and **6**, the latter was subjected to the same purification process as that applied to **4**. The FTIR spectrum of **6**, similar to that of **4**, showed the characteristic absorptions for the amides, and in the region of 500–700 cm^{-1} (absorptions related with the crystallinity of the polyamide), a single and stronger peak was observed for **6**, in contrast with the two peaks shown by **4**. The ^{1}H and ^{13}C NMR spectra of **6** were identical to those of **4**; therefore, no structural differences could be attained from these spectral data. The molecular weight distribution for **6** was determined by SEC of the TFA derivative (Table 1), and from the intrinsic viscosity of **6**, the M_v was calculated on the basis of the Mark–Houwink equation. The thermal behavior of polyamide **6** was similar to that of **4**. The first heating cycle showed three endotherms, the first was due to water loss, which represented about 5% of weight. After cooling, the second heating cycle showed a single endotherm peak having T_m and ΔH values higher than those showed by aregic **4** and closer to those of nylon 6,5,[27] indicating better thermal properties for **6**. These results seems to be confirmed by the narrower melting range of **6** (180–210 °C) compared to that of **4** (156–198 °C), which suggest reduction in the degree of microstructural heterogeneity.[32] The powder X-ray diffraction diagram

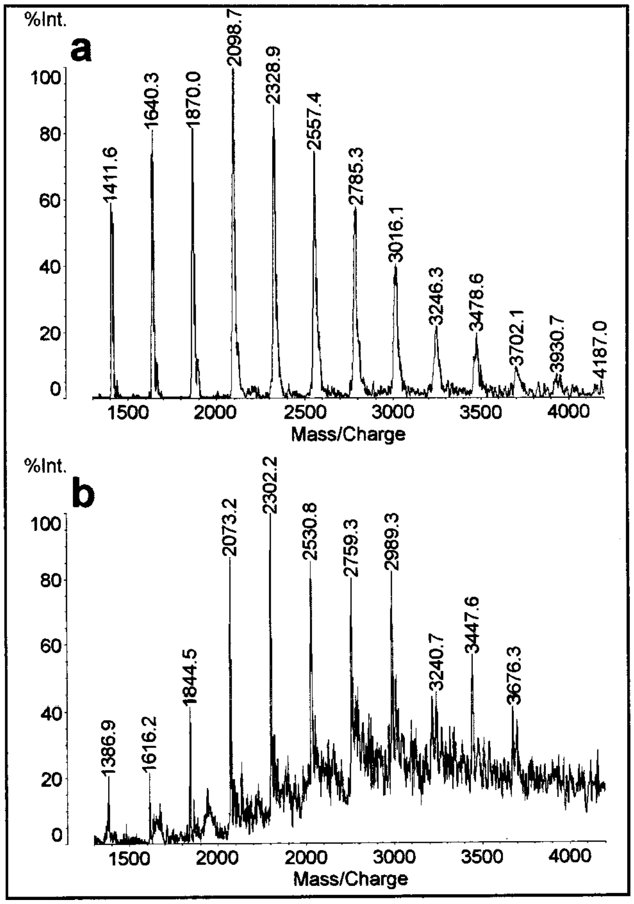


Figure 1. UV−MALDI−TOF mass spectrum of polyamide **11** (a, positive mode, *m*/*z* range 1400−4200; b, negative mode, *m*/*z* range 1400−4200; matrix, HABA; solvent, DMSO/H_2O TFA; sample preparation, method B; see more details in Experimental Section).

of **6** showed five strong reflections at Bragg spacings similar to those of **4**. However, in the diffractogram of **6** a relative increment in the intensity was observed for all the signals respect to the one at 4.28 Å, and three additional weaker diffractions were detected. The better resolution in the diffractogram of **6** and the additional diffractions agree with a better quality of the crystals of **6** with respect to those of **4**.

Taking into account the three arrangements feasible for the sesquiads depicted in Scheme 1, a third polyamide (isoregic) different from **4** (aregic) and **6** (syndioregic) can still be constructed. Such a isoregic polyamide (**11**), which consists only of α,ε units, was synthesized[19] according to the route shown in Scheme 3. The key step in this sequence was the regio and chemoselective condensation of the amino alcohol to **3**, which afforded **7**. Functional group transformations from **7** led to the chiral monomer **10**, which was polymerized to **11** under the same conditions employed for **4** and **6**.

The NMR spectrum of **11** was identical as those of **4** and **6**, whereas the FTIR were similar. Determination of the molecular weight of **11** was conducted by GPC of the TFA derivative, as described for **4** and **6**. The M_w and M_n values obtained for stereoregular polyamides **6** and **11** were higher than that determined by the same technique for **4** (Table 1). Although these molecular weights are rather low, probably due to the precipitation of the forming polymer from the reaction medium, their values are of a magnitude similar to those found for related polymers prepared by the active ester method of polycondensation.[8,26,27] The DSC thermogram for the first heating of **11** showed, besides the broad range transition due to water loss (50 °C), three additional endotherms. The melted sample was cooled and heated again, and this second trace showed the glass transition temperature (T_g 47 °C) and also two endotherms, preceded by a crystallization exotherm at 102 °C. It was found that the enthalpy of crystallization (ΔH 45 $J\cdot g^{-1}$) was identical to the ΔH of fusion of the endotherm at 183 °C. This phenomenon suggests that the crystallite having T_m 183 °C crystallizes during the heating at 102 °C. The T_m and total fusion ΔH of **6** and **11** are higher than those of **4**, indicating a higher crystallinity as expected for stereoregular polymers. Furthermore, **6** and **11** exhibited a similar enthalpy of fusion, which agrees with the fact that both are stereoregular polymers having a similar distribution of molecular weights. The radial scan powder X-ray diagram of **11** showed a single reflection at low angles (15.36 Å), whereas **4** and **6** exhibited two reflections in that region. This different behavior may be attributed to a repetition of interplanar planes in **11** and interplanar planes with an alternate distance in **4** and **6**. Such planes would result from the alignment of hydroxyl groups, whose distance between them is unique (14 atoms) in **11**, whereas alternates between 12 and 16 atoms in **6**. According to Kinoshita[33] the γ-form should be expected for this type of even−odd nylons. However, further structural studies performed for nylon 6,5 revealed a structure different from the conventional α- and γ-forms of nylons, in which each molecule is linked to its four neighbors by a network of hydrogen bonding between amide groups in two different directions.[27] Although no structural studies have been undertaken so far the diffraction spacings reported for regular nylon 6,5 with those determined for its analogues **4**, **6**, and **11** (Table 2) led us to conclude that different structures should be adopted in the present cases. Structural changes could arise from hydrogen bonding formation by the hydroxyl groups substituents located in the chains of **4**, **6**, and **11**, which can alterate the networks associated with hydrogen bonds.

As previously mentioned, chains of syndioregic **6** will consist of an alternating sequence of α,α and ε,ε structures (Scheme 1) whereas isoregic **11** possesses only polyamide α,ε units. Regarding **4**, we have anticipated, on statistical bases, that the α,α:ε,ε:α,ε ratio should be 1:1:2. However, a certain deviation from the random statistical distribution seems reasonable due to the difference in reactivity of the ester and lactone groups in the diacid derivative **3.** The fact that the pentachlorophenyl ester is more reactive than the lactone, suggests that **4** should be formed mainly by repeating units as those formed in **6**. Anyway, other structural arrangements should be present in **4**, which would account for its different physical properties respect to those of **6**.

UV−MALDI−TOF MS Analysis of Polyamides 4, 6, 11, and 12. The interest in the analysis of synthetic polymers by means of MALDI−TOF MS has steadily increased, becoming nowadays an essential tool for their characterization.[34,35] However, not all the synthetic polymers are readily analyzed by UV−MALDI−TOF MS since the solubility of the polymer is an essential factor. Thus, it is difficult to analyze polymers which are nonsoluble, soluble only in solvents that are not compatible with known matrix materials, or soluble in

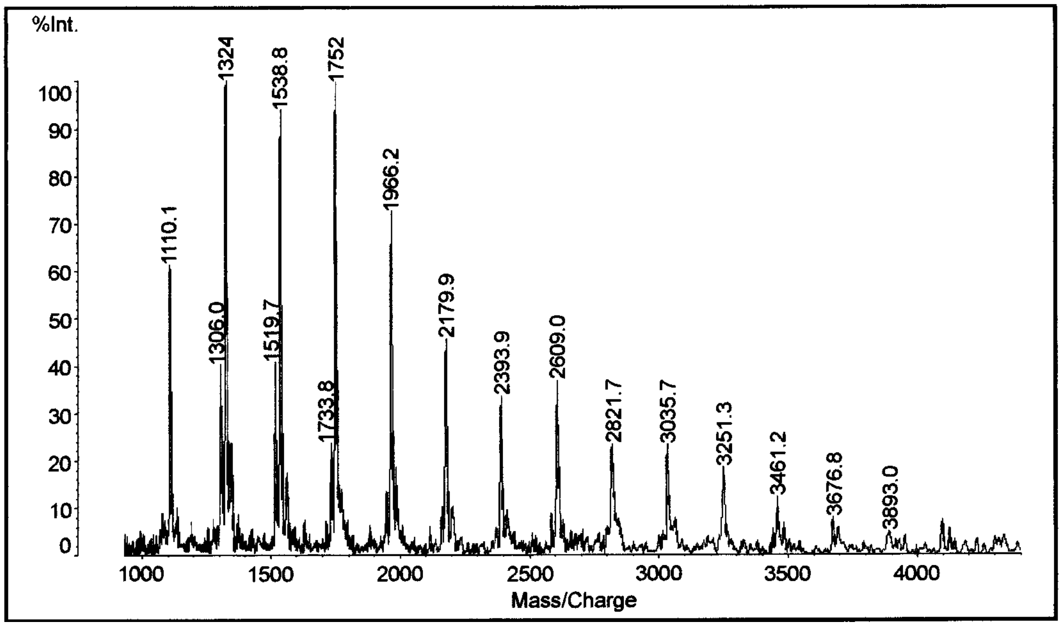


Figure 2. UV−MALDI−TOF mass spectrum of polyamide **12** (positive mode; matrix, HABA; solvent, DMSO; sample doped with NaCl; sample preparation, method B; see more details in Experimental Section; *m*/*z* range 900−4500).

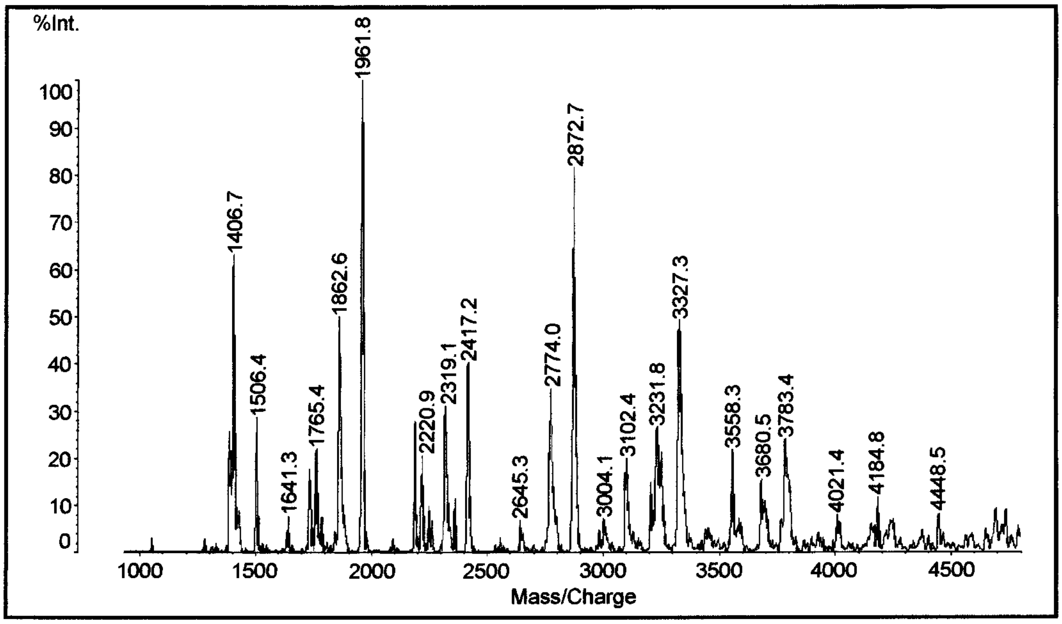


Figure 3. UV−MALDI−TOF mass spectrum of polyamide **6** (positive mode; matrix, HABA; solvent, DMSO/H_2O TFA; sample doped with NaCl; sample preparation, method B; see more details in Experimental Section; *m*/*z* range 900−4800).

solvents difficult to eliminate during the sample preparation. Even nowadays, those polymers classified as nonsoluble polymers[34,36] are generally not analyzable by UV−MALDI MS. In the particular case of polyamides **4**, **6**, **11**, and **12**, which are soluble in DMSO, we attempted their UV−MALDI−TOF MS analysis relaying in our previous experience in the usage of DMSO as solvent when carbazoles were evaluated as UV−MALDI matrices.[22]

For the UV−MALDI experiments, DMSO solutions of different matrices proposed for polymer analysis (HABA, GA, and IAA among others[34,35]) and β-carbolines[22,23] (*nor*-harmane, harmane, harmine, and harmaline) were tested. HABA, GA, IAA, and *nor*-harmane showed the better behavior as they yielded a reproducible distribution of molecular weights. Although Ag^+ was added as cationizing agent, in any case peaks corresponding to Ag-cationized species were observed; on the contrary Ag^+ clusters were clearly detected in the 3000−4600 *m*/*z* region. However, cationization was clearly enhanced when samples were doped with NaCl and also when analyte and matrix solutions were prepared in DMSO−TFA. In these cases spectra of higher quality, in the positive ion mode, were obtained. The UV−MALDI−TOF spectra of polyamides **4**, **6**, **11**, and **12** are respectively shown in Figures 1−4. The width at half-height is typically 6−8 uma and the actual peak positions are accurate within 1−3 uma. The spectra of the polyamides, obtained with and without NaCl, evidenced the presence of $(M + Na)^+$ species. The pattern of the peaks corresponding to the molecular masses of these species allowed the characterization of each of the polyamides studied. Such pattern indicated not only the groups at both ends of the chain, but also

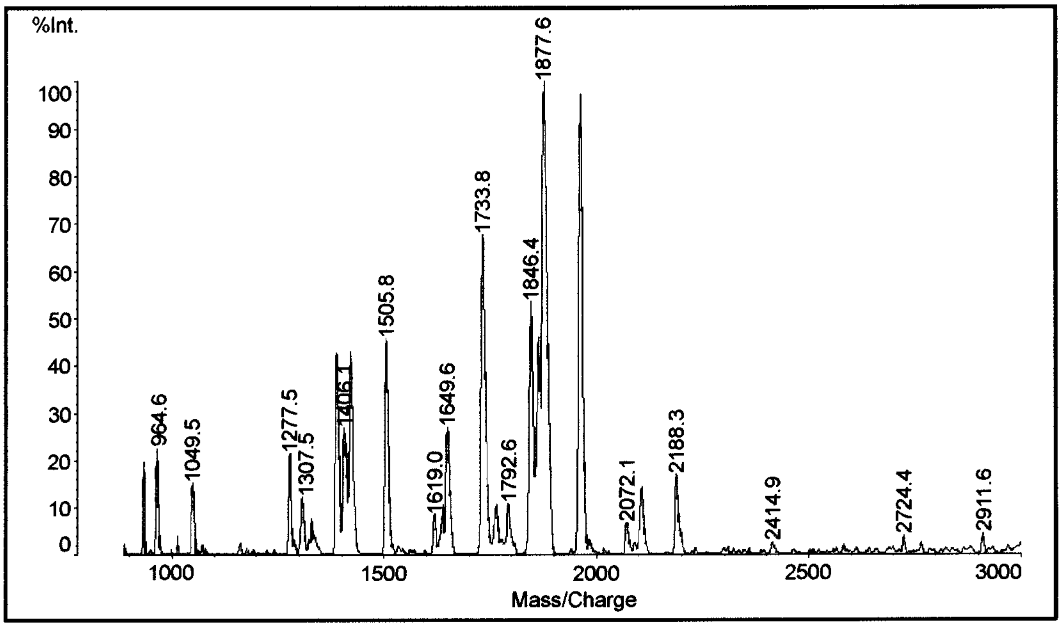


Figure 4. UV–MALDI–TOF mass spectrum of polyamide **4** (positive mode; matrix, HABA; solvent, DMSO/H_2O TFA; sample doped with NaCl; sample preparation, method B; see more details in Experimental Section; *m*/*z* range 800–3200).

how the polymer incorporated the constitutive monomers, during the polycondensation. Therefore, polyamides **4** and **6** showed a rather complex spectra, whereas that of **11** was much simpler. The mass spectrum of **12**, an analogue of **11** which possesses one less methylene group in the hydrocarbon segment of the diamine was also recorded. For both **11** and **12**, the peaks were coincident with the expected molecular weights of intact polyamide chains. The repeat unit, formed by 2-hydroxypentandioic acid and the diamine linked as amide, was confirmed from the spacing between consecutive peaks with the same end groups. In the case of **11** (Figure 1a), as the chain grows from **10** as an homopolymer, the amine and lactone should remain as the terminal groups of the chain. However, the lactone can incorporate a molecule of water to give the corresponding γ-hydroxy acid. Therefore **11** gave a series of peaks having $m/z = (228)_n + 18 + 23$, where n is the number of the repeat units, and 18 and 23 are respectively due to the hydration of the lactone terminal group and the sodium cation. In the same way, the molecular weights for **12** (Figure 2) followed the series at $m/z = (214)_n + 18 + 23$. From the mass and intensity of the peaks of **11** and **12**, the number and weight-average molecular weights (M_n and M_w) and the polydispersity index (PD) were calculated as indicated in the Experimental Section and their values are shown in Table 1. For comparative purposes, the UV–MALDI–TOF mass spectrum of **11** was also recorded in the negative ion mode (Figure 1b). The spectrum was similar to the one obtained in the positive mode. Again, the separation between the peaks corresponded to the molecular weight of the repeat unit (228). The molecular ions followed the series $(228)_n + 18$, confirming a free acid end.

Taking into account the ordered growing of polyamide **6**, in which monomer **5** alternates with 1,6-diaminohexane, we should expect the following sequence of molecular masses: $113 + (228)_n + 116 + 23$ for the chains with a lactone and an amino as terminal groups. As before, 113 corresponds to terminal lactone, 116 to the diamine, 23 to the sodium cation, and 228 to the repeat unit. As in this case, each monomer **5** incorporates two lactone moieties into the chain, so n turns out to be an odd number ($n = 7, 9, 11, ...$). However, instead of such an expected sequence, the mass spectrum of **6** (Figure 3) showed a series of peaks that appeared shifted in 18 units to higher masses (1409–1865–2321–2777–3233...). This fact indicated that the lactone-end group underwent addition of water to give the corresponding γ-hydroxy acid. Overlapped with this series, but somewhat shifted to higher *m*/*z* values (1963–2419–2875–3331–3787...), the more intense peaks of the spectrum were observed. This sequence was originated by condensation of 1,6-diaminohexane (116 mass units) with the lactone terminal group of the polyamide. Such a series can be expressed as $(228)_{n+1} + 116 + 23$ and corresponded to the chains which had two amino terminal groups.

The sequence of molecular ions of higher intensity in the mass spectrum of **4** (Figure 4) belongs to the series $(228)_n + 116 + 23$, which corresponded to chains having two terminal amine groups, similar to the main series found for **6**. Peaks of moderate intensity were also detected for masses of $(228)_n + 114 + 113 + 23$, due to chains having a lactonic terminal group, but the sequence due to the hydrated form of the lactone gave more intense peaks, although with some dispersion from the expected average values, probably due to contributions of peaks of somewhat higher masses. Some fluctuations in the intensity of the peaks in the MS of **4** and **6**, which were not observed for **11** and **12**, could be attributed to the fact that tacticity and monomer orientation in the chain can affect the desorption/ionization UV–MALDI processes.

Comparison of number- and weight-average (M_n and M_w, respectively) molecular weights, and also polydispersity values determined by the UV–MALDI–TOF technique with those measured by GPC, showed a quite good agreement between both procedures. We trust that the MS technique is more accurate, as important deviations occur in GPC analysis when the hydrodynamic volume do not correlate well with the polymer molecular weight. Furthermore, the UV–MALDI–TOF technique gives information not only about the molecular mass average of the polymer, but also on structure and relative concentration of each individual species in the bulk polymer, such as both end groups, and gives also unique mechanistic information about the growth process of the polymer chain.

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