Helical Nylons 3. Synthesis and Crystal Structure of Poly(β-L-aspartate)s with Branched Alkyl Side Chains

Montserrat García-Alvarez, Salvador León, Carlos Alemán, J. Lourdes Campos, and Sebastián Muñoz-Guerra*

Departament d'Enginyeria Química, Universitat Politècnica de Catalunya, ETSEIB, Diagonal 647, E-08028 Barcelona, Spain

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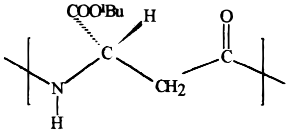
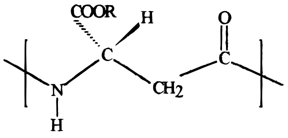
ABSTRACT: A set of poly(β-L-aspartate)s bearing branched alkyl side groups of varying shapes and sizes has been synthesized, and the crystal structures of these polymers have been investigated by X-ray diffraction and computational methods. The anionic ring-opening polymerization of 4-((*S*)-alkoxycarbonyl)-β-lactams (the alkyl groups being isopropyl, isopentyl, and neopentyl) afforded the corresponding poly(α-alkyl β-L-aspartate)s with high molecular weights in good yields. The thermal behavior of these poly(β-L-aspartate)s parallels that described for their linear alkyl side chain homologues with a melting−decomposition process taking place above 250 °C. The analysis of fiber X-ray diffraction diagrams complemented with molecular mechanics modeling and LALS refinement revealed that helical conformations of α-helix type were adopted in the three cases. Whereas the isopentyl derivative crystallized in a quasi-hexagonal form with the chains in the right-handed 13/4 helical conformation characteristic of this family of compounds, a hexagonal array of 16/5 helices was found to be the arrangement preferred by the isopropyl and neopentyl derivatives. These two polymers displayed in addition the second crystal form common in poly(β-L-aspartate)s, which consists of a tetragonal structure of right-handed 4/1 helices. Energy calculations showed negligible energy differences between the two crystal forms in both systems. Conformation and crystal packing of linear and branched poly(β-L-aspartate)s were compared and their features discussed with regards to the architecture of the alkyl side group.

Introduction

Studies carried out in this laboratory during the last decade showed that poly(α-isobutyl β-L-aspartate), usually abbreviated PAIBLA, is able to adopt helical conformations with features similar to the well-known α-helix of polypeptides and proteins.[1−3] This constituted a remarkable finding since it was the first time that such a type of structure was described for a non-polypeptidic polymer. In fact, PAIBLA is a nylon 3 with an isobutoxycarbonyl group stereoregularly attached to the β-carbon atom of the repeating unit. Later, certain properties associated with the helical nature of the chain such as generation of cholesteric liquid crystal phases[4] and piezoelectricity[5] were observed for PAIBLA.



PAIBLA



PAALA's (R = C_nH_{2n+1})

In the last few years the structural study of poly(β-L-aspartate)s has been extended to a number of homologues bearing linear alkyl side chain of different length (PAALA's).[6−9] As a result, the idea that formation of helical structures of α-helix type may be a property common to the whole family of poly(α-alkyl β-L-aspartate)s has gained consistence. A variety of conformations showing significant differences, either in the symmetry of the helix or in the mode of packing of the helices in the crystal phase, were observed according to the size of the side group. The knowledge embodied about the structure of this family of compounds may be summarized as follows.

(i) The right-handed 13/4 helix turns to be the most frequent conformation for PAALA's.

(ii) The right handed 4/1 is the second more frequently found helix. Its occurrence has been demonstrated for compounds with alkyl side chains with $2 \leq n \leq 4$.

(iii) A third helical right-handed conformation with 17/4 symmetry seems to be the arrangement preferred by PAALA's bearing alkyl side groups with $n \leq 2$. These compounds are able to adopt an additional crystal form that is similar to the β-pleated sheet of polypeptides with chains in almost extended conformation.

(iv) Both 13/4 and 17/4 helices tend to crystallize in a pseudohexagonal form, which is actually monoclinic since the true unit cell contains two chains in antiparallel arrangement. Conversely, 4/1 helices crystallize in a primitive tetragonal lattice made up of parallel helices. The transition from the hexagonal to the tetragonal form is known to occur in the solid state by effect of both temperature and solvents.

(v) PAALA's with $n \geq 12$ tend to be organized in a layered structure of 13/4 helices with main chains arranged side-by-side and alkyl lateral groups crystallized in a separated paraffinic phase. These compounds form cholesteric and nematic phases when heated at temperatures above the melting point of the paraffinic phase.

Such a collection of results demonstrates that poly(β-L-aspartate)s not only conform a structural pattern similar to that of poly(α-amino acid)s,[10,11] but that they are able to exhibit a wider conformational versatility. This is thought to be due to the higher chain flexibility that arises from the presence of a second methylene unit in the repeating unit. As it is indicated in Figure 1,

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* To whom all correspondence should be addressed.

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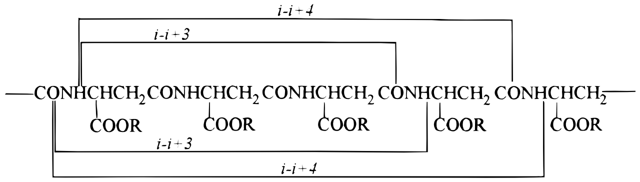


Figure 1. Hydrogen-bonding schemes used for generating α-helix-like conformations in poly(β-L-aspartate)s.

more than one hydrogen-bonding scheme is compatible with each of the helical symmetries that have been observed to date. Furthermore, both right- and left-handed structures are in principle feasible for every scheme. The right-handed arrangements with hydrogen bonds set between the amino group of the *i* residue and the carbonyl group of either the $i + 3$ or $i + 4$ residue have been shown to be the models adopted by the 13/4 helix or both the 4/1 and 17/4 helices, respectively. In the three helices, hydrogen bonds are oriented with polarity in opposed direction to that of the amide groups in the main chain.

Whereas a good amount of data has been gathered for PAALA's bearing linear alkyl side groups, the study of members with branched groups has been restricted so far to the only case of PAIBLA, which paradoxically was the poly(β-L-aspartate) first investigated.[1-3] In this work we wish to report on the synthesis and crystal structure of three PAALA's with alkyl side groups differing either in the degree of branching or in the distance at which the branching point is spaced from the main chain. The selected compounds are the isopropyl, isopentyl (or isoamyl), and neopentyl esters of poly(β-L-aspartic acid), abbreviated PAIPLA, PAIALA, and PANPLA, respectively. The chemical structures of these three compounds together with that of PAIBLA are depicted in Figure 2.

The main objective of the present study is to evaluate the influence of the architecture of the side chain on both conformation and mode of packing of poly(β-L-aspartate)s and to see how branched side chain members compare with their linear side chain isomers. The information that is expected to be drawn from these systems combined with that already available for the isobutyl derivative will provide a comprehensive picture of the conformational behavior of branched side chain PAALA's with $n \leq 5$. Finally to say that a structural study on poly(β-L-aspartate)s bearing cycloaliphatic side groups has been carried out very recently.[12,13] In these cases the 13/4 helical conformation is again preferred although helices were found to crystallize in an arrangement that deviates slightly from the familiar pseudohexagonal model.

Experimental Section

All reagents and solvents were PA grade or higher. L-Aspartic acid ($[\alpha]_D^{25} = +24.7° \pm 0.5$, $c = 5$ in 5N HCl) was supplied by Fluka. Solvents to be used under anhydrous conditions were dried according to standard procedures.[14]

Synthesis. The three poly(β-L-aspartate)s investigated in this work were prepared by non-assisted anionic ring-opening polymerization of the corresponding optically pure (*S*)-4-(alkoxycarbonyl)-2-azetidinones. The scheme of reactions leading from L-aspartic acid to polymers is depicted in Scheme 1 where the following abbreviations have been used: Bn = benzyl; TMS = trimethylsilyl; NaPy = sodium pyrrolidone; DMSO = dimethyl sulfoxide.

(*S*)-(4-(Benzyloxy)carbonyl)-2-azetidinone (**I**) was obtained according to Salzmann by cyclization of dibenzyl L-aspartate.[15]

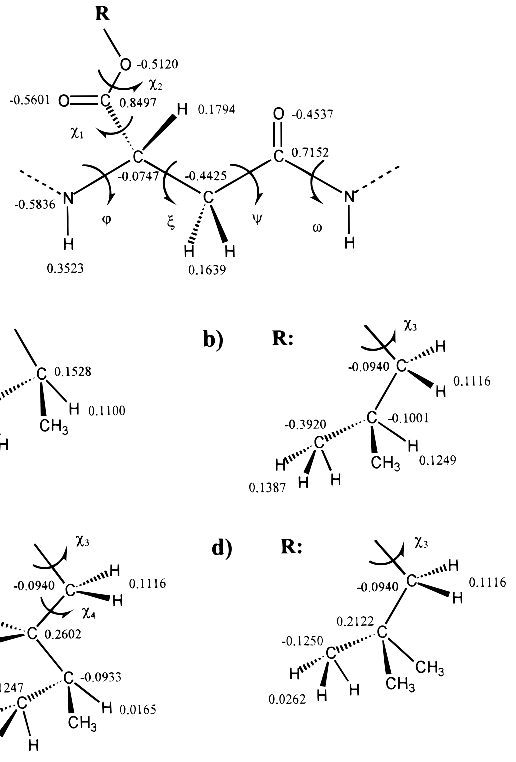
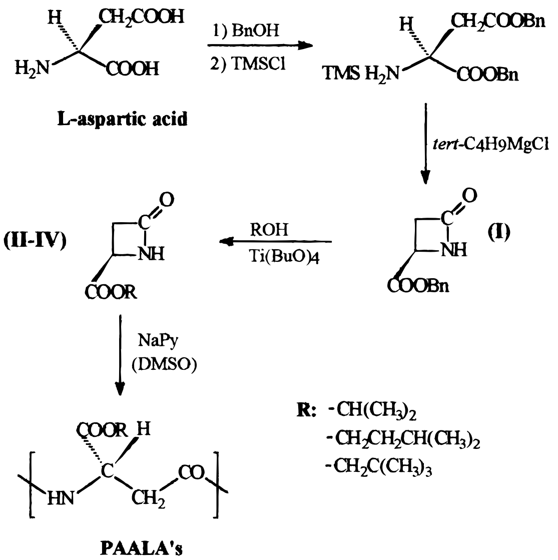


Figure 2. Schematic representation of the monomeric unit of the three PAALA's studied in this work: (a) isopropyl; (b) isobutyl; (c) isopentyl; (d) neopentyl. Notations used for all main chain and side chain torsion angles are labeled. The peptide torsion angle $\omega = 180°$ is omitted for simplicity. Parametrized charges are indicated on the corresponding atoms.

Scheme 1



Compounds **II**–**IV** were prepared from **I** by transesterification with isopropyl, isopentyl, and neopentyl alcohol, respectively. A fully detailed description of the synthesis of monomers and their precursors was reported recently elsewhere.[16]

For the preparation of the polymers, the procedure previously described for the synthesis of linear side chain homologues[17] was here applied. Briefly it is as follows: at room temperature, 3.5 mL of a 0.75% (w/v) solution of sodium pyrrolidone in dimethyl sulfoxide was added onto 1.5 mL of a vigorously stirred solution (66%, w/v) of the corresponding (*S*)-4-(alkoxycarbonyl)-2-azetidinone in the same solvent. The mixture was left under stirring for a further period of 24 h. The resulting polymer was recovered from the gel-like mass

Table 1. Polymerization Data and Thermal Properties of Poly(α-alkyl β-L-aspartate)s[a]

				M_v (10^{-5})[c]			T_d (°C)[e]		weight loss (%)[f]	
polymer	alkyl group	yield (%)	$[\eta]$[b] (dL g^{-1})	**I**	**II**	T_m (°C)[d]	**I**	**II**	**I**	**II**
PAIPLA	$-CH(CH_3)_2$	74	1.82	3.4	1.4	306	308	368	42 (38)	74
PAIBLA	$-CH_2CH(CH_3)_2$	55	1.40	2.5	0.9	260	265	355	45 (43)	75
PAIALA	$-CH_2CH_2CH(CH_3)_2$	57	1.94	3.7	1.5	337	345	379		93
PANPLA	$-CH_2C(CH_3)_3$	51	1.21	2.2	0.8	343	348	377		79

[a] Polymerizations carried out at room temperature under the following conditions: monomer/solvent, 18% (w/w); initiator/monomer, 4% (w/w); reaction time, 24 h; solvent, DMSO. [b] Intrinsic viscosity measured in dichloroacetic acid at 25 °C. [c] Molecular weights estimated by applying the viscometric equation reported for poly(γ-benzyl α-L-aspartate) (**I**) and poly(γ-methyl α-L-glutamate) (**II**) in the same solvent. [d] Melting temperature determined as the peak of the endotherm present in DSC thermograms. [e] Temperatures for the double peak observed in TGA curves. [f] Weight loss corresponding to the first decomposition stage (**I**) and to the overall decomposition proccess (**II**); values calculated for complete imidation are given in brackets.

by adding methanol and purified by repeated precipitation with methanol from chloroform−trifluoroacetic acid solutions.

Poly(α-isopropyl β-L-aspartate) (PAIPLA). From 1 g of (*S*)-4-((1-methyl-ethoxy)carbonyl)-2-azetidinone, 0.74 g of the title polymer was obtained. Yield: 74%. Anal. Calcd for $C_7H_{11}NO_3$: C, 53.59; H, 7.05; N, 8.91. Found: C, 53.01; H, 6.97; N, 8.93. IR (cm^{-1}): 3290 (amide A), 3091 (amide B), 1743 (CO ester), 1660 (amide I), 1549 (amide II). ^{1}H NMR; 8.05 (d, 1H, N**H**), 5.01 (hep, 1H, COOC**H**), 4.87 (m, 1H, HNC**H**), 3.10 (m, 2H, C**H**$_2$CONH), 1.22 (m, 6H, CH$_3$). ^{13}C NMR (ppm): 173.41 (**C**OO), 172.84 (**C**ONH), 73.93 (COO**C**H), 50.60 (HN**C**H), 37.26 (**C**H$_2$CONH), 21.36 (**C**H$_3$).

Poly(α-isopentyl β-L-aspartate) (PAIALA). From 1 g of (*S*)-4-((3-methyl-butoxy)carbonyl)-2-azetidinone, 0.57 g of the title polymer was obtained. Yield: 57%. Anal. Calcd for $C_9H_{15}NO_3$: C, 58.37; H, 8.16; N, 7.56. Found: C, 58.40; H, 8.27; N, 7.54. IR (cm^{-1}): 3286 (amide A), 3089 (amide B), 1748 (CO ester), 1657 (amide I), 1547 (amide II). ^{1}H NMR; 7.98 (d, 1H, N**H**), 4.88 (m, 1H, HNC**H**), 4.22 (d, 2H, COOC**H**$_2$), 3.08 (m, 2H, C**H**$_2$CONH), 1.61 (m, 1H, C**H**(CH$_3$)$_2$), 1.50 (m, 2H, COOCH$_2$C**H**$_2$), 0.87 (d, 6H, CH$_3$). ^{13}C NMR (ppm): 172.85 (**C**OO), 172.65 (**C**ONH), 67.20 (COO**C**H$_2$), 50.05 (HN**C**H), 37.00 (COOCH$_2$CH$_2$**C**H), 36.83 (**C**H$_2$CONH), 25.35 (COOCH$_2$**C**H$_2$), 22.14 (**C**H$_3$).

Poly(α-neopentyl β-L-aspartate) (PANPLA). From 1 g of (*S*)-4-((2,2′-dimethylpropoxy)carbonyl)-2-azetidinone, 0.51 g of the title polymer were obtained. Yield: 51%. Anal. Calcd for $C_9H_{15}NO_3$: C, 58.37; H, 8.16; N, 7.56. Found: C, 57.63; H, 8.04; N, 7.36. IR (cm^{-1}): 3276 (amide A), 3077 (amide B), 1736 (CO ester), 1656 (amide I), 1544 (amide II). ^{1}H NMR; 8.05 (d, 1H, N**H**), 4.95 (m, 1H, HNC**H**), 3.86 (d, 2H, COOC**H**$_2$) 3.10 (m, 2H,C**H**$_2$CONH), 0.89 (m, 9H, CH$_3$). ^{13}C NMR (ppm): 171.96 (**C**OO), 171.39 (**C**ONH), 76.34 (COO**C**H$_2$), 49.34 (HN**C**H), 36.53 (**C**H$_2$CONH), 31.17 (COOCH$_2$ **C**), 5.91 (**C**H$_3$).

Measurements. Densities were measured by the flotation method in aqueous KBr solutions. Viscosities were determined with an Ubbelhode viscometer in dichloroacetic acid at 25 °C. Viscosity average molecular weights were calculated by using the viscometric equations reported for poly(γ-benzyl α-L-glutamate)[18] and poly(γ-methyl α-L-glutamate)[19] which are $[\eta] = 2.78 \times 10^{-5} M_v^{0.87}$ and $[\eta] = 2.9 \times 10^{-4} M_v^{0.74}$, respectively. Infrared spectra of polymers were registered on a Perkin-Elmer 2000 FT-IR instrument from films prepared by casting in trifluoroacetic acid (TFA). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX-300 instrument operating at frequencies of 300.1 and 75.5 MHz respectively, from polymers dissolved in deuterated chloroform−TFA mixtures with tetramethylsilane as internal reference. Calorimetric measurements were performed with a Mettler TA-4000 thermoanalyzer equipped with a thermobalance TG-50. Sample weights between 5 and 10 mg were heated at a rate of 10 °C min^{-1} under a nitrogen atmosphere.

Structural Methods. Films prepared by casting in chloroform or chloroform−TFA mixtures were uniaxially oriented by mechanical stretching at a temperature of 160 °C. For X-ray diffraction, oriented samples were placed normally to the beam and diagrams were recorded on flat films (DEF, Kodak) under vacuum and at room temperature. A modified Statton camera (W. H. Wharhus, Wilmington, DE) mounted on a generator provided with a graphite monochromator producing a nickel-filtered Cu Kα radiation of wavelength 1.542 Å was used for these experiments. Specimen to film distances were calibrated with molybdenum sulfide ($d_{200} = 6.47$ Å). Diffraction intensities were measured with a unidimensional Joyce-Loebl MK III CS microdensitometer. Radial scans were registered and the area under the peaks estimated by weighing. Polarization and Lorentz factors were systematically applied and appropriate corrections were made to take into account orientation effects. No absorption correction was required since the films were very thin and multiplicity corrections were introduced when necessary.

Energy calculations were performed with explicit consideration of all atoms using the AMBER 3.0 Rev A package[20] with all-atom parametrization.[21] A similar electrostatic charge distribution was considered for the main chain atoms of the three polymers. Parametrization of side chain atoms was performed following the methodology used for other poly(α-alkyl β-L-aspartate)s previously studied by us.[22] The charge values resulting for the repeating unit of each polymer are indicated on the chemical formulas depicted in Figure 2. The bonding parameters used for the ester side group were those adopted in the conformational analysis of PAIBLA and PANBLA.[22,23] Energy optimizations were carried out in two steps. First the worst steric conflicts were removed by 300 cycles of steepest descent optimization, and second, conformations were optimized by means of a conjugate gradient algorithm until the difference in energy was less than 10^{-7} kcal mol^{-1}. Approximate molecular models compatible with both the length of the repeating unit and helical symmetry provided by X-rays were built with the GEMOX program.[24] Geometry optimizations were made firstly for the isolated chain and then for the helices packed into the crystal lattice. Models consisting of 12 chains were considered for all cases in order to mimic rigorously the crystal environment. The packing energies were estimated by taking into account all non-bonded interactions between atoms contained in the central monomeric units. One to four interactions were scaled to 0.5 Å, and nonbonding interactions were cutoff at 8 Å.

The averaged coordinates provided by energy optimization were used as the starting conformation for LALS (linked-atom least-squares) refinement.[25] Standard bond lengths and angles were kept fixed and the peptide torsion angle ω was held in *trans* conformation. Hydrogen bonds were assumed to be linear with a starting approximate length of 2.90 Å. First the conformation of the main chain was adjusted to satisfy contour conditions, and then the whole crystal structure was refined against X-ray diffraction intensities. At this stage, both main chain and side chains were taking into account so that intra- and intermolecular interactions could be simultaneously minimized. Calculations were performed on a Silicon Graphics RI-4000 at our laboratory.

Results

(A) Synthesis and Properties of Poly(β-L-aspartate)s. Data concerning polymerization and thermal properties of the three poly(β-L-aspartate)s investigated in this work are collected in Table 1 together with those

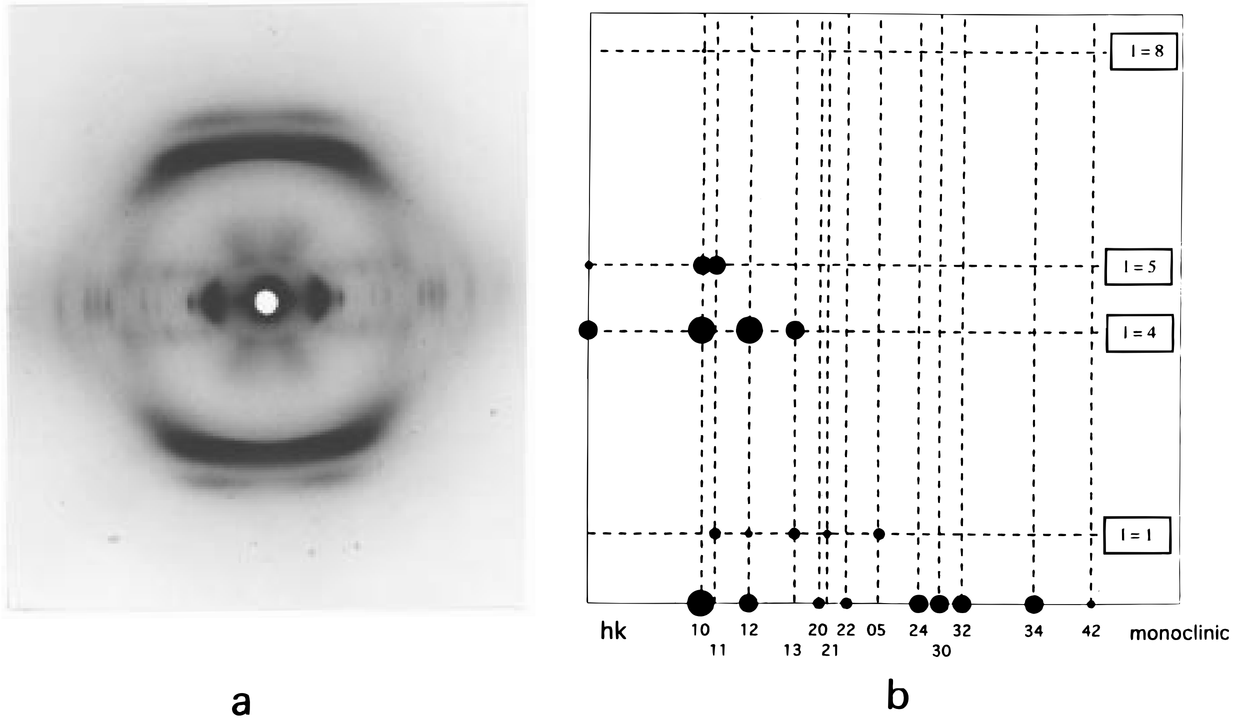


Figure 3. X-ray diffraction pattern of an oriented film of PAIALA (a) and its schematic representation (b) with reflection intensities approximately represented by circle sizes. The stretching direction is vertical.

of PAIBLA used for comparison. The anionic polymerization of β-lactams **II**−**IV** in DMSO initiated by sodium pyrrolidone has been the procedure followed here for the synthesis of PAIPLA, PAIALA, and PANPLA, respectively. This method was developed by us some years ago to prepare PAIBLA from (*S*)-4-(isobutoxycarbonyl)-2-azetidinone[26] and then applied to the synthesis of other poly(β-L-aspartate)s. By this method, polymer yields, which had been reported to be unacceptably low when halogenated solvents were used as reaction media, are largely improved. However, it is known that certain 4-(alkoxycarbonyl)-2-azetidinones are unfeasible to polymerize in DMSO because the occurrence of extensive imidation reactions. In the case of the β-lactams concerned in this work, polymerizations were found to proceed in the absence of secondary elimination reactions so high molecular weight polymers free of imide units could be obtained in good yields. As described in the Experimental Section, both chemical and spectroscopic analyses assessed the correct constitution of the three poly(β-L-aspartate)s, and no traces of racemization were detected in the NMR spectra.

The thermal behavior displayed by these polymers conforms to the general pattern outlined by members bearing linear alkyl groups. It is characterized by the simultaneous occurrence of melting and decomposition, this second process taking place in two stages.[17] Thus the DSC curve registered at heating consists of a prominent endotherm corresponding to a sudden two-step fall in the TGA curve (thermograms not shown). Infrared spectra and weight loss measurements revealed that intramolecular imidation reactions involving the releasing of the corresponding alcohol take place at the first stage. Main chain bond scissions leading to an extensive degradation of the polymer are assumed to occur in the second stage of decomposition.

(B) X-ray Diffraction. (1) The Hexagonal Form. The so-called hexagonal form of poly(β-L-aspartate)s is the crystal structure usually present in samples which come from solution in chloroform. The X-ray diffraction pattern produced by a fiber of PAIALA which was obtained by stretching a film of the polymer prepared by casting in chloroform, is shown in Figure 3a. A schematic representation of the diagram including all the reflections that are observable in the original picture is depicted in Figure 3b. The pattern exhibits the features habitually used to identify the hexagonal form. The layer lines are indicative of a 13/4 helix with an axial

Table 2. Observed and Calculated Spacings (Å) for the Fiber Pattern Obtained from Poly(α-isoamyl β-L-aspartate)

layer line	d_{obsd}	d_{calcd}[a]	*hkl*
ll = 0	12.97	12.97	100, 020
	9.18	9.17	120
	6.46	6.48	200, 040
	5.80	5.80	220, 140
	4.61	4.59	240
	4.36	4.32	300, 060
	4.13	4.10	320, 160
	3.63	3.60	340, 260
	3.19	3.14	420, 180
ll = 1	10.04	10.03	111
	8.29	8.33	121
	6.78	6.77	131
	5.91	6.00	211
	5.06	5.02	051, 231
ll = 4	4.99	4.98, 4.89	004, 014
	4.61	4.65	104, 024
	4.39	4.38, 4.32	124, 034
	4.10	4.10	134
ll = 5	4.02	3.99, 3.94	005, 015
	3.86	3.81	105, 025
	3.74	3.77	115
ll = 8	2.40	2.45	108, 028

[a] Calculated from a monoclinic unit cell containing two molecules: $a_0 = 12.97$ Å, $b_0 = 25.94$ Å, $c_0 = 19.93$ Å, and $\alpha = \beta = \gamma = 90°$.

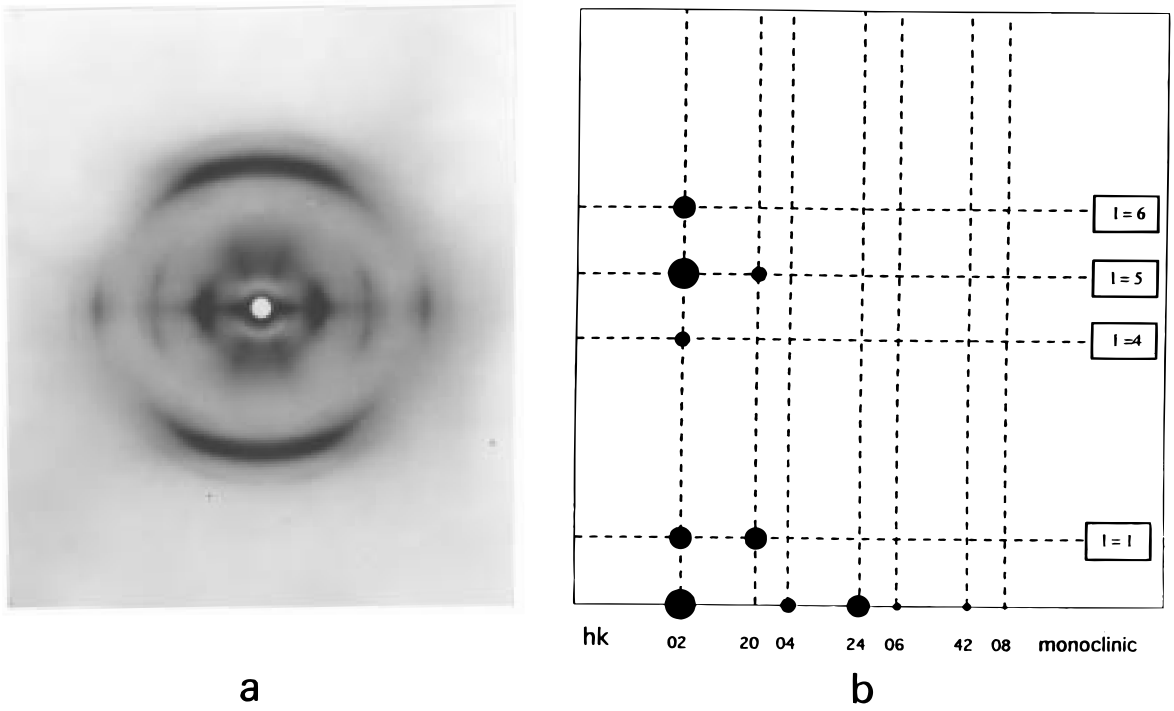


Figure 4. X-ray diffraction pattern of an oriented film of PAIPLA (a) and its schematic representation (b).

repeat of 19.9 Å and the strong equatorial reflection with a spacing of about 13 Å corresponds to the 100 interplanar distance of the structure. Nevertheless the set of reflections appearing on the equator cannot be fully accounted for by means of a hexagonal array of helices but they have to be indexed on the basis of a centered rectangular lattice. The resulting unit cell is monoclinic with parameters $a_0 = 12.97$ Å, $b_0 = 25.94$ Å, $c_0 = 19.93$ Å (chain axis), and $\alpha = \beta = \gamma = 90°$. The calculated density for this structure with two chains in the unit cell is 1.19 g mL^{-1}, in good agreement with the observed density which was estimated to be 1.16 g mL^{-1}. The complete list of observed and calculated interplanar spacings for the hexagonal form of PAIALA is given in Table 2.

Fibers of both PAIPLA and PANPLA obtained in the same manner as indicated above for PAIALA, produced similar diffraction patterns displaying also the overall characteristics of the hexagonal form. The diagram arising from PAIPLA together with its schematic representation is shown in Figure 4. In these two polymers, the distribution of layer lines indicated that the length of the axial repeat of the structure is around 24–25 Å and that five helical turns must be contained in such a period of length. Density considerations led to conclude that 16 residues should be comprised in the axial repeat. With regards to the side-by-side packing of the chains, the scattering along the equator of these diagrams could be satisfactorily indexed on the basis of a hexagonal lattice with $a_0 = 12.79$ or 13.72 Å for PAIPLA or PANPLA respectively. By analogy with all preceding cases studied to date, the unit cell is assumed in both cases to be made of two chains arranged in antiparallel so that the resulting structures are formally monoclinic with parameters, $a_0 = 12.79$ Å, $b_0 = 22.16$ Å, $c_0 = 25.49$ Å, and $\alpha = \beta = \gamma = 90°$ (PAIPLA) and $a_0 = 13.72$ Å, $b_0 = 23.76$ Å, $c_0 = 24.31$ Å, and $\alpha = \beta = \gamma = 90°$ (PANPLA). The calculated densities for these structures are 1.16 and 1.11 g mL^{-1}, in agreement with their respective experimental values of 1.16 and 1.24 g mL^{-1}. In Table 3, the experimentally observed spacings for these two polymers are compared with those calculated for their respective proposed crystal structures.

Table 3. Observed and Calculated Spacings (Å) for the Hexagonal Form of Poly(α-isopropyl β-L-aspartate) and Poly(α-neopentyl β-L-aspartate)

layer line	PAIPLA		PANPLA		*hkl*	
	d_{obsd}	d_{calcd}	d_{obsd}	d_{calcd}	**I**[a]	**II**[b]
ll = 0	11.08	11.08	11.88	11.88	100	110, 020
	5.54	5.54	5.95	5.94	200	220, 040
	4.17	4.19	4.48	4.49	120	310, 240
	3.69	3.69			300	330, 060
	3.21	3.20	3.44	3.43	220	260, 400
	3.04	3.07	3.28	3.29	130	420
			2.98	2.97	400	440, 080
ll = 1	10.20	10.16	10.62	10.67	101	111, 021
			8.42	8.42		121
			7.50	7.53		031
	6.19	6.20	6.61	6.60	111	131, 201
ll = 3			7.68	7.67		013
ll = 4			5.88	5.98		014
	5.48	5.52	5.41	5.41	104	114, 024
ll = 5			4.80	4.86	005	005
			4.80	4.76	005	005
				4.76		015
	4.64	4.63	4.57	4.58		105
				4.50	105	115, 025
			4.30	4.28		125
	4.02	3.99			115	205
ll = 6	3.96	3.97	4.00	4.05	106	116, 026
				3.99		016
ll = 10	2.49	2.48			10, 10	11, 10, 02, 10
	2.36	2.37			11, 10	20,10

[a] Indexed on the basis of a pseudohexagonal unit cell: $a_0 = 12.79$ Å and $c_0 = 25.49$ Å (PAIPLA) and $a_0 = 13.72$ Å and $c_0 = 24.31$ Å (PANPLA). [b] Indexed on the basis of a monoclinic unit cell containing two chains: $a_0 = 12.79$ Å, $b_0 = 22.16$ Å and $c_0 = 25.49$ Å (PAIPLA) and $a_0 = 13.72$ Å, $b_0 = 23.76$ Å and $c_0 = 24.31$ Å (PANPLA), with $\alpha = \beta = \gamma = 90°$ in both cases.

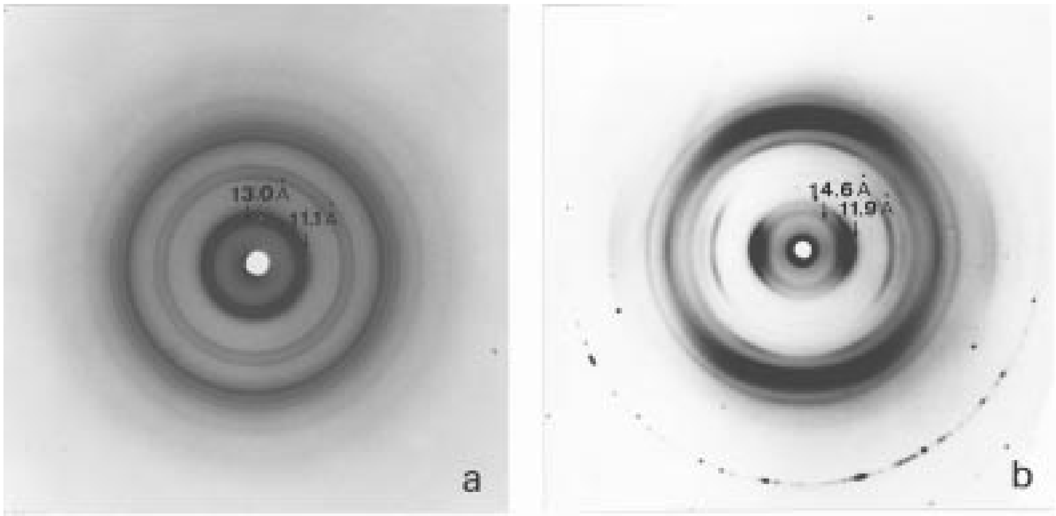


Figure 5. (a) Powder diagram of a sample of PAIPLA containing similar amounts of hexagonal and tetragonal forms. (b) Diagram of a fiber of PANPLA after annealing. The innermost equatorial reflection at 14.6 Å arises from the tetragonal form present in minor amounts.

Table 4. Observed and Calculated Spacings (Å) for the Tetragonal Form of Poly(α-isopropyl *β*-L-aspartate)

d_{obsd}[a]	d_{calcd}[b]	hkl
13.05 (vs)	13.05	100
6.62 (m)	6.52	200
5.85 (m)	5.84	210
4.64 (s)	4.63, 4.62	101, 220
4.39 (m)	4.36, 4.35	111, 300
4.17 (m)	4.13	130
3.65 (m)	3.65, 3.62	211, 230
3.18 (w)	3.17, 3.16	311, 410
3.05 (w)	3.08	330

[a] Visual intensity estimations denoted as vs (very strong), s (strong), m (medium), w (weak). [b] Calculated for a primitive tetragonal unit cell of parameters: $a_0 = 13.05$ Å and $c_0 = 4.95$ Å.

(2) The Tetragonal Form. The existence of the second characteristic crystal form in poly(α-alkyl *β*-L-aspartate)s, *i.e.*, the tetragonal structure made up of 4/1 helices, has been explored too. At this end the usual methods known to promote the appearance of this form, such as soaking in slight alcohols or thermal annealing, were applied to samples which initially were in the hexagonal form. The results attained were found to be highly depending on the polymer of choice. Samples of PAIPLA in the hexagonal form partially converted into tetragonal when they were either annealed at temperatures around 200 °C or immersed in methanol. The diagram shown in Figure 5a was obtained from a powdered sample of this polymer prepared by precipitation from chloroform with methanol and then annealed at 195 °C. The composed pattern contains the characteristic reflection of the hexagonal form at 11.1 Å together with a second inner reflection at 13.0 Å attributable to the tetragonal form. Comparison of this diagram with that arising from the pure hexagonal form allows one to identify up to 9 reflections specifically associated with the tetragonal phase. On the basis of these data, a unit cell of $a_0 = 13.05$ Å and $c_0 = 4.95$ Å can be proposed for the tetragonal form of PAIPLA (Table 4).

The tetragonal form of PANPLA has been detected only in oriented samples. The diagram shown in Figure 5b corresponds to a film prepared by casting from 2-chloroethanol and then mechanically stretched. The reflection at 14.6 Å may be reasonably associated with the 100 spacing of the tetragonal form which has evolved from the initially present hexagonal form. Other reflections in the diagram aside from those arising from the hexagonal phase are not well resolved as to be valuable for help in defining the geometry of the tetragonal structure. Nevertheless a unit cell with $a_0 = 14.6$ Å and $c_0 \approx 4.9$ Å, consistent with the dimensions usually observed for this structure in other poly(*β*-L-aspartate)s, may be tentatively put forward.

On the other hand, no trace of tetragonal form could be detected when similar treatments were applied to PAIALA whichever was the texture of the initial sample. This polymer stands as the only poly(*β*-L-aspartate) bearing branched side chain that is not able to crystallize in a tetragonal structure. This behavior is in line with previous observations made on linear side chain poly(α-alkyl *β*-L-aspartate)s which suggested that the existence of the tetragonal form should be confined to members with alkyl side groups containing no more than four carbon atoms.

C. Modeling and Refinement. (1) Energy Calculations. The hexagonal form has been modeled and subjected to energy minimization for the three polymers under study. Models for a 16/5 compatible with the axial repeating distance determined by X-rays and all hydrogen bonds intramolecularly made were searched by GEMOX. All allowable models were found to correspond to the $i - i + 3$ hydrogen-bonding scheme shown in Figure 1. On the other side right-handed 13/4 and 4/1 helices were built using the atomic coordinates available for the homologue poly(α-isobutyl *β*-L-aspartate).[22] These helices are based on hydrogen-bonding schemes entailing the *i* residue linked to the $i + 3$ and $i + 4$ residue respectively. Molecular mechanics calculations were first performed on the isolated chain, and then crystal environment effects were taken into account. Thus arrays of helices were built according to the lattice parameters provided by X-rays and investigated for both parallel and antiparallel arrangements in the case of 13/4 and 16/5 helices and only for the former in the case of 4/1 helices. Both right-handed and left-handed conformations were examined for each case.

As described for other poly(*β*-L-aspartate)s, a monoclinic unit cell in the space group $P2_1$ comprised of right-handed helices was found to be the most favored

Table 5. Conformational Parameters and Hydrogen Bond Geometry for the Hexagonal and Tetragonal Forms of Poly(α-alkyl β-L-aspartate)s with Branched Side Chains

	PAIPLA			PAIBLA[a]			PAIALA		PANPLA	
	HEX		TET	HEX		TET	HEX		HEX	TET
	MM[b]	LALS[c]	MM	MM	LALS	MM	MM	LALS	MM	MM
				Torsional Angles (deg)						
main chain										
ϕ	145.0	141.2	142.5	151.3	145.7	148.4	148.2	143.9	144.1	143.6
ξ	−55.9	−59.2	−67.3	−59.1	−62.0	−65.8	−61.8	−61.9	−60.9	−72.1
ψ	121.7	133.1	138.6	118.1	130.8	136.0	125.2	131.7	128.2	140.8
ω	175.1	180.0	64.6	180.0	180.0	180.0	−174.0	180.0	−175.7	168.0
side chain										
χ_1	−175.3	−172.0	163.1	−171.2	175.0	−135.3	−171.6	175.0	−172.6	176.5
χ_2	173.4	180.0	−177.9	178.7	180.0	180.0	172.9	180.0	164.0	−176.8
χ_3	110.1	117.0	168.0	−70.7	−101.2	−128.8	173.0	180.0	165.2	174.0
χ_4				107.7	114.1	−145.8	177.8	177.8	178.3	174.9
χ_5							103.1	116.2		
				H-Bond Geometry						
d(H···O) (Å)	2.09	1.87	1.82	2.11	1.91	1.83	2.12	1.89	2.12	2.02
d(N···O) (Å)	3.07	2.86	2.82	3.09	2.90	2.83	3.10	2.89	3.09	3.01
∠NHO (deg)	170.3	164.9	176.4	174.7	171.8	177.9	175.1	165.3	171.1	177.8
R factor (%)		12.5						18.4		
energy (kcal/mol)[d]	0.1		0.0	1.7	0.0				0.0	0.0

[a] Data taken from refs 22 and 23. [b] MM = Molecular mechanics calculations. [c] LALS = Linked-atom least-squares calculations. [d] Relative energies.

Table 6. Observed (F_o) and Calculated (F_c) Structure Factors for the Hexagonal Form of Poly(α-isopropyl β-L-aspartate) (PAIPLA) and Poly(α-isoamyl β-L-aspartate) (PAIALA)

PAIPLA						PAIALA					
spot	d_{hkl}[a]	hkl[b]	F_o	F_c	$F_o - F_c$	spot	d_{hkl}[a]	hkl[b]	F_o	F_c	$F_o - F_c$
1	11.08	110	224.4	204.2	−20.2	1	12.97	100	538.2	591.1	52.9
		020						020			
									31.8	51.1	19.3
2	5.54	220	22.9	12.9	−10.0	2	9.18	120			
		040									
						3	6.46	200	31.6	16.8	−14.8
3	4.17	310	131.8	124.6	−7.2			040			
		240									
						4	5.80	140	33.0	25.2	−7.8
4	3.69	330	45.7	24.8	−20.9			220			
		060									
						5	4.61	240	62.7	42.3	−20.4
5	3.21	260	18.9	8.4	−10.5						
		400				6	4.36	300	17.3	33.9	16.6
		420						060			
6	10.20	111	12.9	4.8	−8.1	7	4.13	320	74.3	55.7	−18.6
		021						160			
7	6.19	201	33.8	43.4	9.6	8	3.63	340	59.5	64.6	5.1
		131						260			
8	3.96	114	30.9	44.6	13.7	9	6.78	131	60.8	68.8	8.0
		024									
						10	5.06	051	56.5	36.2	−20.3
9	4.64	105	518.5	530.9	12.3			231			
		115									
		205				11	4.99	004	694.0	780.3	86.3
								014			
10	3.96	116	85.8	112.4	26.6						
		016				12	4.6−4.4	104	813.4	985.8	172.4
		026						024			
								124			
								034			
						13	4.10	134	154.2	240.7	86.4
						14	3.9−3.7	105	150.2	210.5	50.3
								025			
								115			

[a] Observed spacings. [b] Indexed for the monoclinic unit cell containing two molecules.

arrangement for the called hexagonal form of PAIPLA, PANPLA, and PAIALA. As also expected, a parallel arrangement of right-handed helices with the same orientation around the chain axis corresponding to a space group $P4_1$ was the preferred model for the tetragonal form. The dihedral angles resulting for the energy minimized models for both crystal forms, hexagonal and tetragonal, are given in Table 5 where similar data earlier reported for the isobutyl derivative have also been included for comparison. Energy differences between the two crystal forms are shown to be very small (PAIPLA) or even negligible (PANPLA), as was the case for other poly(β-L-aspartate)s displaying this kind of dimorphism.[9,23]

(2) LALS Refinement. Only samples of PAIPLA and PAIALA in the hexagonal form provided suitable X-ray data to justify the analysis and refinement of their structures by LALS. For this, the minimum energy conformations obtained in the preceding section were used for building the respective 16/5 and 13/4 helical chains. In a first stage, backbone and side chain dihedrals were refined under contour conditions to minimize steric interactions between the side group with the main chain and between atoms within the main chain itself. Then the helical geometry was refined against the X-ray intensities measured on fiber diagrams as those shown in Figures 3a and 4a. Observed and calculated structure factors are compared in Table 6, showing that a satisfactory agreement has been attained. In fact, *R*-factors of 12.5 and 18.3 were obtained for PAIPLA and PAIALA respectively, which turn to be exceedingly good values for such a type of polymer systems. The dihedral angles and hydrogen-bonding geometry parameters resulting for the refined model of each polymer are given in Table 5 where they are compared with data obtained by energy calculations. Changes affecting the main chain dihedrals appear to be smaller than 12° while those concerning the side group show more significant variations. The axial and equatorial projections of the 16/5 and 13/4 helices resulting after refinement are depicted in Figure 6. The projections down the chain axis of $P2_1$ unit cells of PAIPLA and PAIALA are represented in Figure 7.

Discussion

A set of three new poly(α-alkyl β-L-aspartate)s bearing branched side chains with different shapes and sizes has been prepared by applying the general route of synthesis previously developed by us for the preparation of this class of nylon 3 derivatives. High molecular weight polymers without perceivable constitutional or configurational defects could be obtained in good yields. The thermal behavior of these new poly(β-L-aspartate)s is characterized by a melting-decomposition process that takes place in the 300−350 °C range with a loss of weight between 70 and 90% of the initial polymer sample. The pattern is qualitatively similar to that reported for poly(β-L-aspartate)s bearing linear alkyl side chains[17] with no other heat changes taking place along the examined range of temperatures.

The general trend displayed by poly(α-alkyl β-L-aspartate)s toward the formation of helical conformations of α-helix type is not modified by the existence of bulky side chains potentially involving steric interactions between neighboring residues. Furthermore, the results obtained in these cases corroborate previous conclusions drawn from studies carried out on linear side chain derivatives. The structural features of the helices and crystal lattices found for branched side chain poly(β-L-aspartate)s in the hexagonal form are compared in Table 7. Although a new helical conformation has been observed for the case of PAIPLA and PANPLA, the similarity of this helix with the "classical" 13/4 helix is manifested when the main helical parameters, such as number of residues per turn and pitch, are brought into comparison. On the other hand the crystal geometry is also essentially the same for the four compounds and is coincident with the type of geometry habitually observed for the hexagonal form of poly(α-alkyl β-L-aspartate)s with linear alkyl side chains. In all cases the packing of the helices is hexagonal or quasi-hexagonal despite that the unit cell has to be doubled as a consequence of the up-and-down arrangement of the chains. The low symmetry of the helix imposes a monoclinic symmetry for the lattice corresponding to the space group $P2_1$. The slight deviation from the hexagonal geometry (γ = 116.6°) observed for the case of PAIALA may be explained if the influence of the length of the side chain on crystal packing is taken into account. The poly(α-*n*-octyl β-L-aspartate), which was reported[8] to crystallize in a rectangular lattice of lateral parameters a_0 = 18.0 Å and b_0 = 12.3 Å, constitutes an illustrative precedent for the case. In this system, the two very different distances separating the chains in the lattice are due to the preference displayed by the polymer to crystallize with the side chains aligned along the *a*-direction in the crystal.

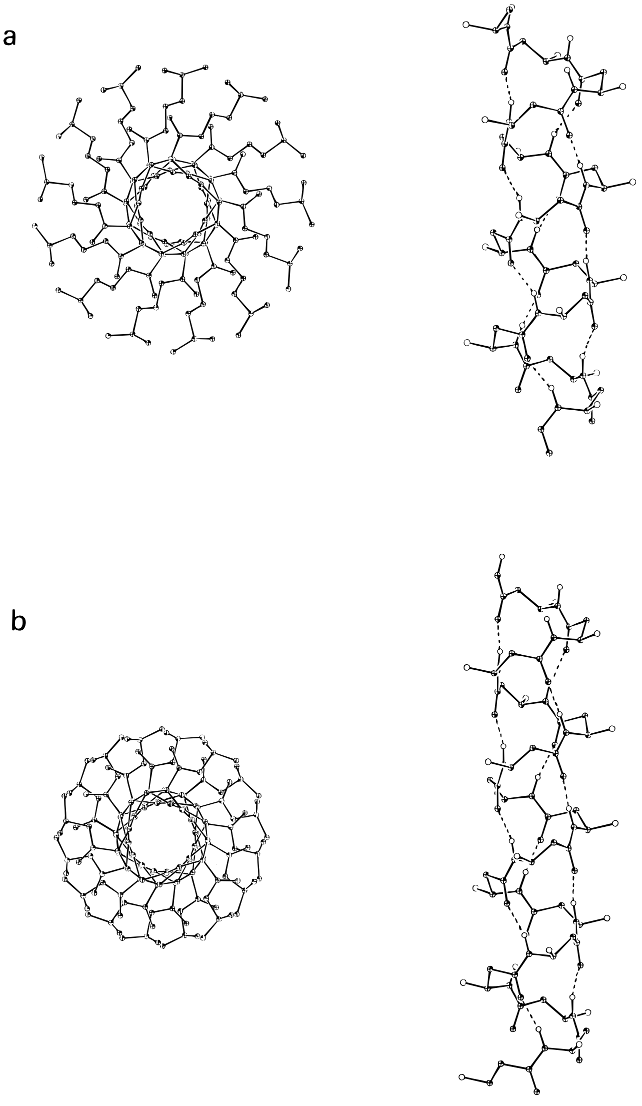


Figure 6. Equatorial (left) and axial (right) projections of models after energy minimization and refining by LALS: (a) right-handed 13/4 helix of PAIALA; (b) right-handed 16/5 helix of PAIPLA. In the axial views dashed lines are hydrogen bonds and side groups are indicated by empty circles in order to make clearer the representation.

At this point it will be worthwhile to examine in a comprehensive manner the packing of the chains in poly(α-alkyl β-L-aspartate)s as a function of the size and shape of the alkyl side group. For this purpose, the a_0

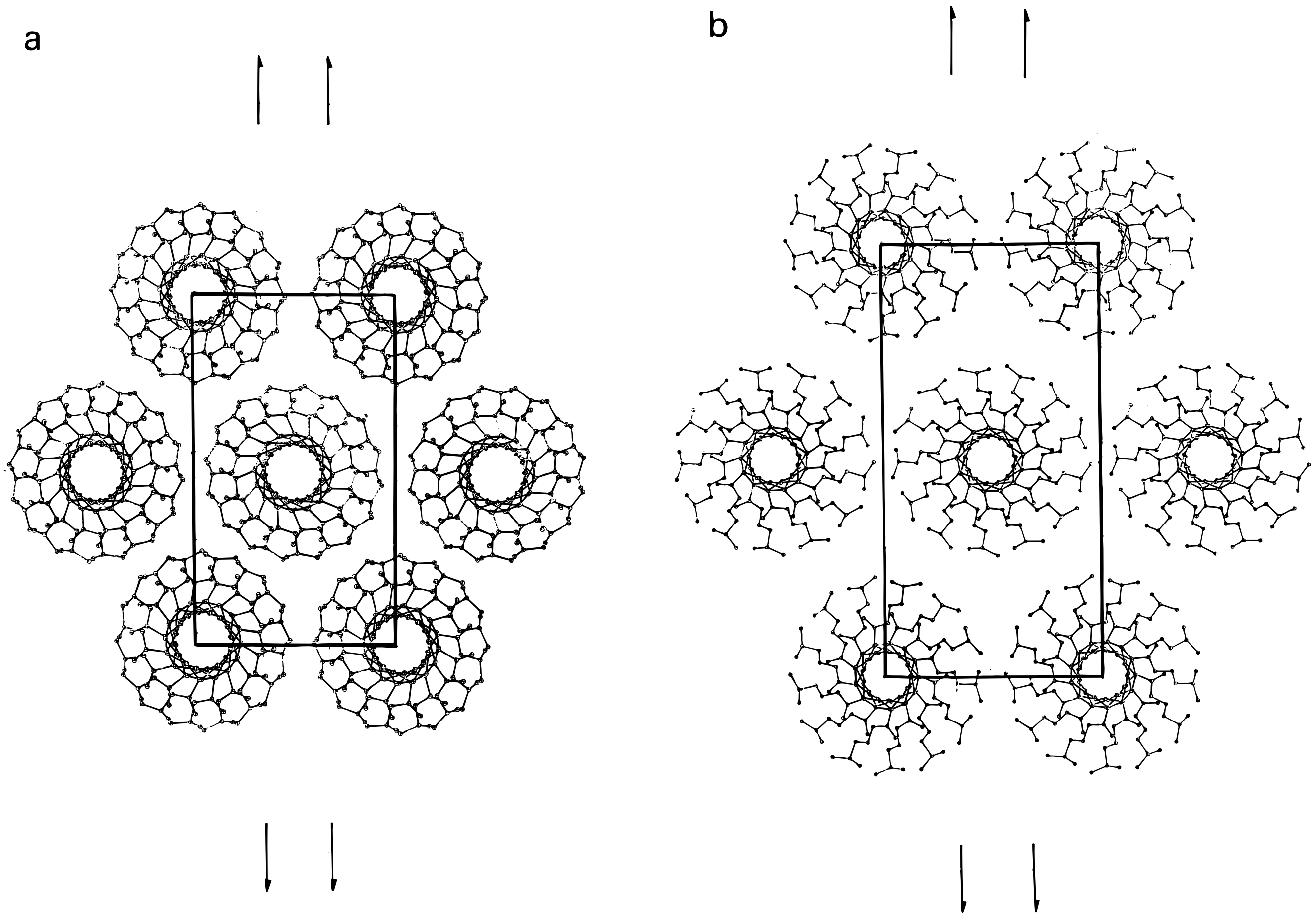


Figure 7. Projections along the *c*-axis of the unit cell of the hexagonal form of PAIPLA (a) and PAIALA (b) obtained by combining energy calculations and LALS refinement.

Table 7. Structural Data of Poly(α-alkyl β-L-aspartate)s with Branched Side Groups

	ρ (g mL^{-1})		unit cell (Å)		space group	helix[a]			
polymer	obsd	calcd	MONOC (two chains)	HEX (one chain)[b]		u/t	N	P (Å)	h (Å)
PAIPLA	1.16	1.16	$a_0 = 12.79$, $b_0 = 22.16$, $c_0 = 25.49$, $\alpha = \beta = \gamma = 90°$	$a_0 = 12.79$, $c_0 = 25.49$, $\alpha = \beta = 90°$, $\gamma = 120°$	$P2_1$	16/5	3.20	5.10	1.59
PAIBLA[c]	1.17	1.18	$a_0 = 13.50$, $b_0 = 23.40$, $c_0 = 19.90$, $\alpha = \beta = \gamma = 90°$	$a_0 = 13.50$, $c_0 = 19.90$, $\alpha = \beta = 90°$, $\gamma = 120°$	$P2_1$	13/4	3.25	4.97	1.53
PAIALA	1.16	1.19	$a_0 = 12.97$, $b_0 = 25.94$, $c_0 = 19.93$, $\alpha = \beta = \gamma = 90°$	$a_0 = 12.97$, $b_0 = 14.50$ $c_0 = 19.93$, $\alpha = \beta = 90°$, $\gamma = 116.6°$	$P2_1$	13/4	3.25	4.98	1.53
PANPLA	1.11	1.24	$a_0 = 13.72$, $b_0 = 23.76$, $c_0 = 24.31$, $\alpha = \beta = \gamma = 90°$	$a_0 = 13.72$, $c_0 = 24.31$, $\alpha = \beta = 90°$, $\gamma = 120°$	$P2_1$	16/5	3.20	4.86	1.52

[a] $u/t = N$ = number of residues per turn; P = pitch; h = residue height. [b] Quasi-hexagonal unit cell. [c] Data taken from ref 2.

parameter of the pseudohexagonal unit cell (quasi-hexagonal for the case of PAIALA), which corresponds to the interchain distance, is taken for comparison. The effective radius of the helix is estimated to be the half of the a_0 distance. The apparent radius R_a, which will be more suitable for comparison, is defined as $(A_{001}/\pi)^{1/2}$ where A_{001} is the area of the 001 plane corresponding to one chain. The length of the side chain was estimated for the alkyl group in a fully extended conformation and taking into account the contour of the chain. Standard values for the van der Waals radii were used.[27] The values resulting for these packing parameters are compared in Table 8 for all linear and branched derivatives for which crystallographic data are presently available.

The plot of a_0 against the number of carbon atoms contained in the alkyl side group is shown in Figure 8a. As logically expected, the interchain distance steadily increases with n as far as linear groups are concerned. The fact that no correlation is apparent for branched derivatives indicates the additional influence of other geometrical factors. A more convenient representation was attained when the apparent radius was plotted against the length of the alkyl side chain, as depicted in Figure 8b. By this means, a linear variation was found for both series with PANPLA remaining as the only member unable to fit. Several conclusions related with the packing properties of poly(β-L-aspartate)s can be drawn from such representation. The slope of the straight lines is similar for both series indicating that

Table 8. Compared Structural Parameters for Poly(β-L-aspartate)s with Linear and Branched Alkyl Side Groups

polymer	side group	a_0 (Å)^a	L^b (Å)	$A_{001}{}^c$ (Å^2)	$R_a{}^d$ (Å)
PAMLA	$-CH_3$	12.03	2.14	125.4	6.32
PAELA	$-CH_2CH_3$	12.67	3.39	139.0	6.65
PAIPLA	$-CH(CH_3)_2$	12.79	3.39	143.7	6.76
PAPLA	$-CH_2CH_2CH_3$	12.82	4.64	142.3	6.73
PAIBLA	$-CH_2CH(CH_3)_2$	13.50	4.64	157.9	7.09
PANPLA	$-CH_2C(CH_3)_3$	13.72	4.64	163.0	7.20
PANBLA	$-CH_2CH_2CH_2CH_3$	13.50	5.89	157.9	7.09
PAIALA	$-CH_2CH_2CH(CH_3)_2$	12.97	5.89	168.2	7.32

[a] Side of the pseudohexagonal unit cell; Data for PAMLA and PAELA are taken from ref 9 and for PAIBLA from ref 2. [b] Length of the alkyl side chain in full extended conformation. [c] Area of 001 plane per chain. [d] Apparent radius of the helix estimated as $(A_{001}/\pi)^{1/2}$.

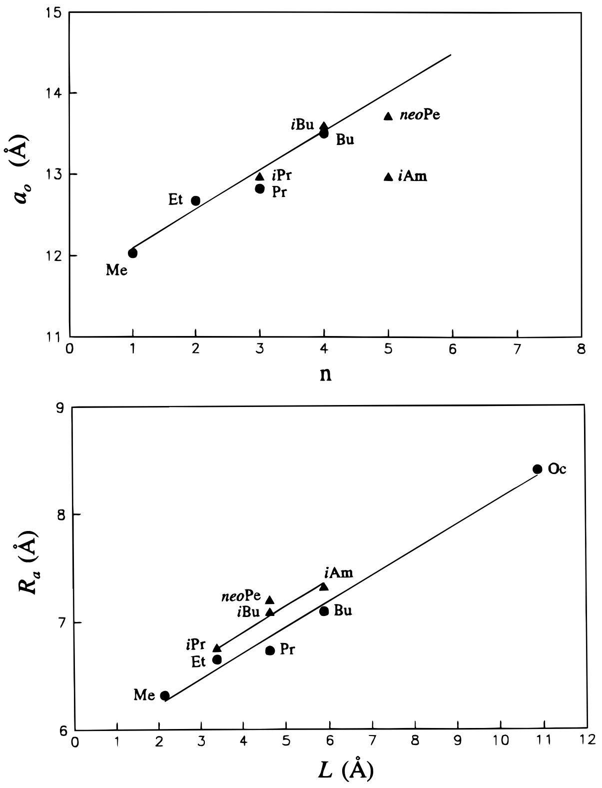


Figure 8. Helix packing in PAALA's bearing linear and branched alkyl side chains: (a) variation of the interchain distance (a_0 of the pseudohexagonal unit cell) as a function of the number of carbons contained in the alkyl side group; (b) variation of the apparent radius of the helix as a function of the length of the alkyl side group.

the space required by each new added methylene is substantially independent on branching. R_a is larger for branched derivatives revealing that side groups consisting of linear configurations interpenetrate deeper to each other. This becomes more apparent when the *n*-propyl, isobutyl, and neopentyl derivatives are compared. The side groups of these three poly(β-L-aspartate)s have the same length but different trajectory. The apparent radius increases with the degree of branching. The fact that PANPLA cannot be fitted in the line drawn for the isoalkyl members is seen as a logical consequence of the hindrance to interpenetration that can be anticipated for the highly compact neopentyl group.

A last point deserving some discussion is that concerning with the tetragonal structure made of 4/1 helices. Previous results obtained in the investigation of PAALA's suggested that the occurrence of this second helical form is disfavored for side chains composed of more than four links. The explanation for such behavior is given in terms of packing energies.[23] The longer is the side chain, the more difficult it is to occupy efficiently the interchain spaces created within the crystal. While this applies straightforwardly to linear side chain derivatives, the situation becomes more complex when branched groups are concerned. In this case the geometry of the group has be taken into account in addition to its length. The fact that the tetragonal form has been observed for PAIPLA is fully consistent with preceding observations on linear poly(β-Laspartate)s and it does not need further comments. On the contrary, the existence of such form in the case of PANPLA, which has an alkyl side group containing five carbon atoms, proves the influence that branching may have in the stabilization of the tetragonal packing. The influence of the geometry of the group is also evidenced by the fact that the tetragonal phase could not be observed for PAIALA. This does not make sense since the isopentyl group has constitutional features intermediate between the *n*-butyl group (same length) and the isobutyl group (same branching). Both of these groups have been proved to be compatible with the occurrence of a well developed tetragonal form.[3,6]

Concluding Remarks

This paper has been conceived as the third part of a research project addressed to investigate the conformation and crystal structure of poly(β-L-aspartate)s. In the first part, the structure of PAIBLA was investigated in detail and guidelines for further studies were set. The second part was devoted to the study of linear alkyl side chain derivatives. In the present paper, branched side chain poly(β-L-aspartate)s are examined with the aim of completing previous observations and outlining a comprehensive picture of the structural behavior of this family of polymers. Several remarkable conclusions have been reached.

(a) The right-handed 13/4 helix continues to be the preferred conformation among poly(β-L-aspartate)s bearing branched alkyl side chains. The novel 16/5 helical conformation that is adopted by members displaying severe restrictions in the mobility of the side group, is very close to the 13/4 helix; they have essentially the same number of residues per turn, and they share the same scheme of hydrogen bonds.

(b) The crystal lattice preferences of branched side chain derivatives are like those displayed by the linear homologues. The pseudohexagonal packing of up-and-down helices, which is formally a monoclinic lattice in the space group $P2_1$, turns out to be the most frequently observed arrangement.

(c) For a similar degree of branching, the interchain distance in the crystal increases steadily with the length of the side group. For a similar length of the side chain, members with branched side groups present a less efficient packing than their linear homologues.

(d) The hexagonal–tetragonal dimorphism characteristic of lower linear side chain poly(β-L-aspartate)s is also encountered in most of the branched side chain members. The fact that it can be obseved for the neopentyl derivative but not for its isopentyl isomer evidences the influence of geometrical factors on the relative stability of the tetragonal form.

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