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Conformation of the Helical Polyamide Poly(α-isobutyl L-aspartate)

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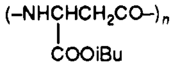
ABSTRACT: We analyze the conformation of the two forms (hexagonal and tetragonal) of the title compound with the linked-atom least-squares (LALS) methodology applied to X-ray data previously reported and with AMBER energy optimization algorithms. We conclude that both helical forms are right handed, with very similar conformational angles, and report their coordinates. The transition between both forms appears to be mainly determined by the side chain interactions.

Introduction

Some time ago we discovered[1] that the title compound could form helical structures similar to polypeptide α-helices in spite of the presence of an additional methylene group in its main chain:



$$(\text{–NH}\underset{\substack{|\\ \text{COOiBu}}}{\text{C}}\text{HCH}_2\text{CO–})_n$$

Depending on the method of sample preparation, two different crystalline forms are found: hexagonal and tetragonal.[2] The crystallographic parameters of these two forms are $a = b = 13.5$ Å and $c = 19.9$ Å, and $a = b = 13.98$ Å and $c = 4.94$ Å. An additional hexagonal form appears at high temperature which shows a lower degree of order[3] than is found in fibers pulled from chloroform solutions at room temperature. It is not clear whether the polymer main chain conformation varies in these two types of hexagonal samples.

Whereas good fiber X-ray diffraction diagrams can be obtained from hexagonal samples,[1,2,4] it has not been possible to prepare any oriented fiber for the tetragonal form in spite of the different approaches which have been attempted. Nevertheless, when fibers of poly(α-isobutyl L-aspartate) in the hexagonal form are heated at 200 °C in a nitrogen atmosphere, the resulting X-ray diffraction pattern reveals the superposition of the main reflections of both crystalline forms uniaxially oriented.[5] It is also feasible to prepare thin oriented films of the tetragonal form which are suitable for electron diffraction. We have also reported other thermal phenomena associated with transitions between these forms which have been described in detail elsewhere,[3,6] but the key features of their interconvertibility at the molecular level remain uncertain.

In principle at least four different models for each basic crystalline form are possible, as schematically indicated in Figure 1. Density and close packing analyses exclude the possibility of there being two different ways of packing the same helical form.[2] Hydrogen-bonding schemes 1 and 2 give rise to 13/4 helices which are compatible with a pseudohexagonal structure, whereas schemes 3 and 4 are suitable for the tetragonal form, since they originate 4/1 helices. Each of them may generate either right- or left-handed helices, but always one of the two (right or left handedness) is sterically forbidden due to collapse of the lateral group onto the main chain.

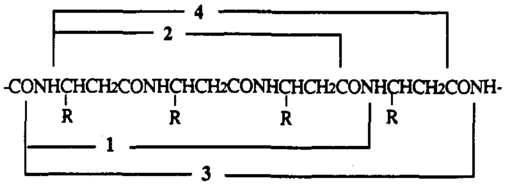


Figure 1. Different hydrogen-bonding schemes compatible with the helical conformations of poly(α-isobutyl L-aspartate).

In our previous studies[2] *we favored the left-handed form* 1 for the hexagonal crystals and the right-handed form 3 for the tetragonal crystals. As shown in Figure 1 these two models have very different topologies. Later we found that in the presence of certain solvents the transition between the two forms could take place easily.[3] Also ^{13}C NMR indicated[7] that both forms had very similar spectra in the solid state. These two observations seriously question our early model studies, and therefore we decided to study in more detail the models that we had previously proposed in order to ascertain which is the most plausible conformation of each form. With this objective in mind we have first improved our calculations on the crystalline structure of the tetragonal form, taking into account X-ray diffraction data, packing restrictions, and side chain conformation and interactions using the LALS program.[8] Both the final conformations obtained and the models revised from those previously proposed for the hexagonal form[2] were subjected to an energy optimization in order to verify that the conformations derived from X-ray diffraction analysis coincided with an energy minimum.

Methods

Approximate models with a sound stereochemistry were built and were then refined with the linked-atom least-squares (LALS) methodology[8] against the X-ray data obtained elsewhere.[2] Standard bond lengths and angles, as well as all hydrogen atoms, were introduced. Hydrogen bonds were considered to be linear with a length of 2.90 Å, but some variation was allowed during refinement. The main chain was refined first. The side chain geometry was introduced at a later state in order to minimize intra- and intermolecular contacts. In some of the models excluded, a few interatomic contacts (less than 2 Å) were found. We tried to remove them unsuccesfully by relaxing the bond angles (1–3°).

For the analysis of the tetragonal form we used powder patterns such as the one presented in Figure 3 of ref 2. The intensities were measured with a Joyce-Loebl MK III CS microdensitometer, and the integrated areas under each diffraction ring were then corrected for polarization and Lorentz factors. No absorption correction was made since the thickness of the samples used was small. Also some intensities of the reflections corresponding to the tetragonal form were measured in the oriented diagram reported by Fernández-Santín,[5] which were used to scale the contributions of individual reflections which overlap in some

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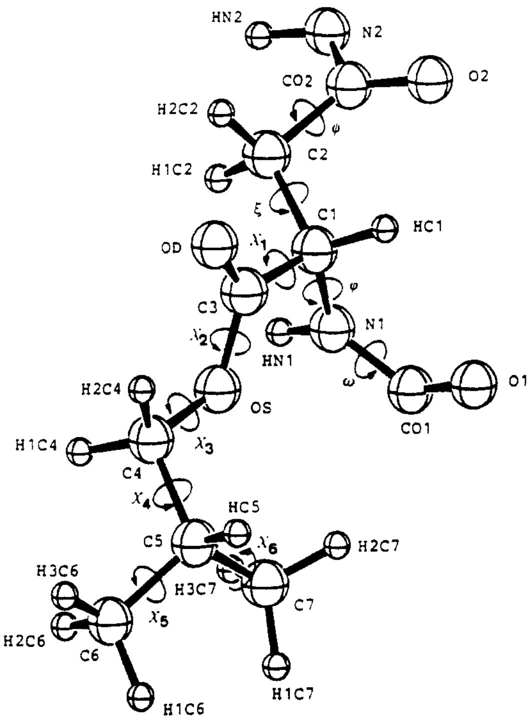

Figure 2. Schematic representation of a monomeric unit. The atom numbering and torsion angles are indicated. The amide group is repeated at both ends.

rings of the powder patterns. Thus, the observed structure factors were finally calculated. When necessary, the multiplicity of some reflections was taken into account.

The coordinates obtained from the LALS analysis were then used for energy optimization with the AMBER3a program[9] and all-atom parametrization.[10] A single chain was used in all cases. Calculations were carried out assuming a dielectric constant $\epsilon = 1$, as suggested by Hagler et al.[11,12] for anhydrous peptide crystals. In a related study[13] with another polypeptide we have indeed found that this value of the dielectric constant is the most adequate for molecular mechanics studies. Nonbonding interactions were cut off at 10 Å as suggested from the results obtained by different researchers.[14,15]

The geometry optimization process was performed in three steps. In the first step 50 cycles were carried out in order to improve the energy without a significant change of the starting geometry. If after 50 cycles the energy value improves significantly without large geometrical changes, it indicates that the structure obtained with the LALS analysis is essentially correct and close to an energy minimum. In a second step 300 additional cycles of geometric optimization with the steepest descent method were carried out in order to speed up the convergence process. Finally convergence was achieved in about 1500 cycles. The convergence criteria were that either the energy difference was smaller than 10^{-7} kcal/mol or the gradient norm was smaller than 0.1 kcal/mol for two consecutive cycles.

Results

Conformation and Crystal Structure of the Tetragonal Form. In our previous studies[2] we favored the conformation with the type 3 hydrogen-bonding scheme shown in Figure 1. However, a more detailed analysis demonstrated that there were serious clashes between some of the hydrogen atoms. Furthermore, energy optimization showed that this conformation was unstable, so that the helix geometry was destroyed after several cycles of calculations. Therefore, we decided to optimize a helix based on a type 4 hydrogen-bonding scheme, and to refine its crystal structure assuming different packing possibilities.

The monomeric unit is shown in Figure 2. As a first step a helix was built from such units with standard bond lengths and angles, according to the type 4 hydrogen-bonding scheme. For this step only the main chain torsion angles φ, ξ, and ψ were refined, while the peptide bond angle was kept in the trans conformation ($\omega = 180°$). The lateral group was simply oriented by using its first torsion angle χ_1 so as to minimize its steric interactions with the main chain. The final geometry of this isolated helix was considered satisfactory when all the contour conditions (i.e., helix continuity between succesive residues) were achieved under appropriate hydrogen-bonding geometrical restrictions. Both left-handed and right-handed helices with 4_3 or 4_1 symmetry were constructed, but it was found that only the right-handed form was stereochemically acceptable. The refined conformational angles are given in Table II. The hydrogen bond parameters in the refined helix are $b(\mathrm{HN}\cdots\mathrm{O}) = 1.85$ Å, $b(\mathrm{N}\cdots\mathrm{O}) = 2.86$ Å and $\tau(\mathrm{N}\cdots\mathrm{O{-}C}) = 178°$. No short intramolecular van der Waals contacts were found. A stereoview of the chain conformation is shown in Figure 3a.

This helical geometry was then refined against the X-ray data shown in Table I. To carry out this second step, we introduced packing constraints by means of a basic unit cell of rigid parameters $a = b = 13.98$ Å and $c = 4.94$ Å. These parameters are those experimentally observed.[2] The side chain torsion angles χ_1, χ_3, and χ_4 (the ester torsion angle was kept in the trans conformation, $\chi_2 = 180°$) were then allowed to vary as well as the X-ray scale factor and the position of each helix with respect to the unit cell axes.

In general, polymers form lamellar crystals, which require an antiparallel orientation of neighboring molecules. Therefore, different kinds of mutual arrangements of adjacent helices were considered, both in parallel and antiparallel packing directions. It was found that unexpectedly the most suitable arrangement was with parallel chains, space group $P4_1$, which gave an X-ray agreement factor $R_w = 14.3\%$ and optimal packing of side chains of adjacent molecules. Antiparallel packings gave an R factor in the range of 30.7–32.3% in the various side chain conformations, and displayed unacceptable short van der Waals contacts between side chains of neighboring molecules, in any of the arrangements considered.

A final refinement of the parallel structure was made by optimization of the position of the methyl groups and introduction of a whole unit cell temperature factor B_0. A view of the structure obtained is shown in Figure 3. The conformational parameters obtained are given in Table II and the atomic coordinates in Table III. Calculated structure factors are displayed in Table I, and final X-ray agreement and unit cell temperature factors are, respectively, $R_w = 14.2\%$ and $B_0 = 3.6$ Å^{-2}. All these calculations have been presented in greater detail elsewhere.[16]

Energy Calculations. Since the conformational optimization in the LALS methodology is rather crude from the energetic point of view, we carried out more detailed energy calculations with the AMBER program in order to assure that the conformation we used in the analysis of the crystal structure of the tetragonal form is basically correct. On the other hand, two models appeared to be stereochemically satisfactory for the hexagonal form and showed similar agreement with the X-ray data;[2] therefore, the only way we could discriminate between them was by conformational energy criteria. Since no previous charge parametrization of the isobutyl ester group had been reported, we obtained the required values with the methods used by Orozco and Luque.[17] The calculated charges were corrected with a scaling factor of 1.32, which was obtained from a correlation of the MNDO with ab initio charges.[17,18] The values obtained for the charges are similar to those

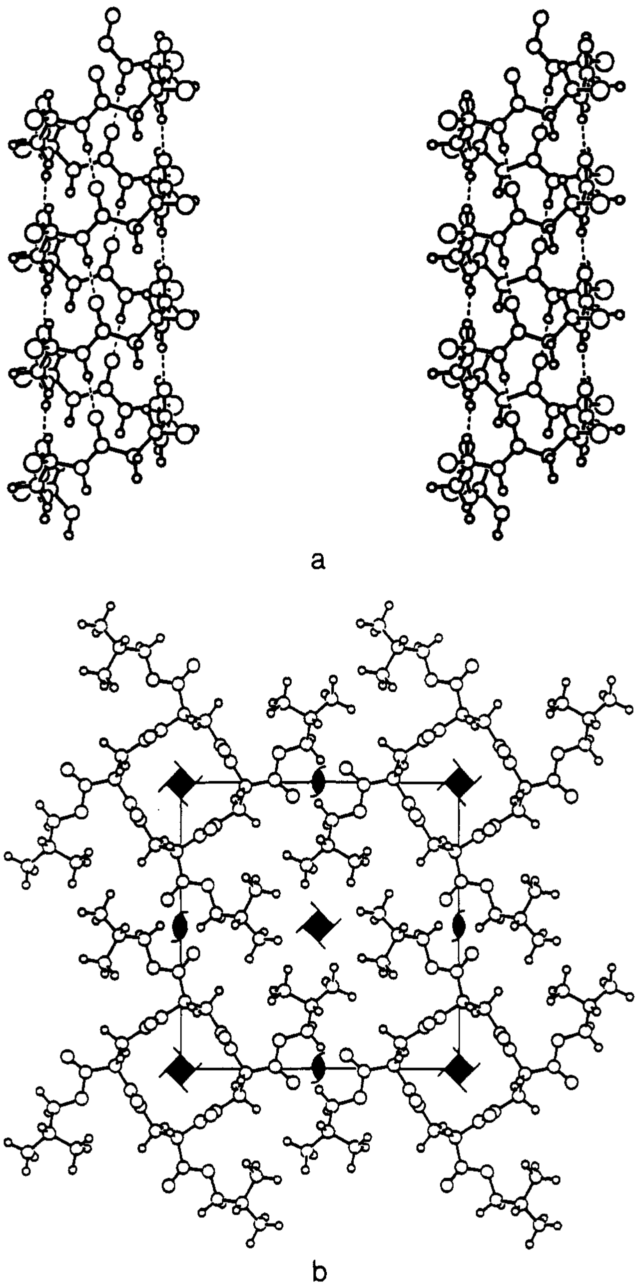

Figure 3. Diagram of the tetragonal model of poly(α-isobutyl L-aspartate) in the tetragonal form according to hydrogen-bonding scheme 4: (a) stereopair in which the lateral chains have been substituted by a single sphere; (b) equatorial projection demonstrating the interaction among side chains. The space group is $P4_1$.

Table I
Comparison of Observed and Measured Structure Factors for Poly(α-isobutyl L-aspartate) in the Tetragonal Form[a]

spot	refl	H	K	L	F(calcd)	F(obsd)	diff
1	1	1	0	0	89.43	116.71	27.28
2	2	1	1	0	47.36	52.97	5.60
3	3	2	0	0	11.56	25.94	14.39
4	4	2	1	0			
	5	1	2	0	84.93	75.95	−8.98
5	6	2	2	0	176.74	187.38	10.64
6	7	3	0	0	56.74	49.29	−7.45
7	8	1	0	1	240.26	229.90	−10.36
8	9	3	1	0			
	10	1	3	0			
	11	1	1	1	237.60	205.81	−31.79
9	12	2	0	1	76.70	98.84	22.14
10	13	3	2	0			
	14	2	3	0			
	15	2	1	1			
	16	1	2	1	164.79	163.65	−1.14
11	17	4	0	0			
	18	2	2	1	111.93	103.40	−8.53
12	19	4	1	0			
	20	1	4	0			
	21	3	0	1	141.69	138.06	−3.63
13	22	4	2	0			
	23	2	4	0			
	24	3	2	1			
	25	2	3	1	150.80	185.21	34.41
14	26	4	0	1	34.44	53.27	18.84
15	27	5	0	0			
	28	4	3	0			
	29	3	4	0			
	30	4	1	1			
	31	1	4	1	85.70	160.45	74.75
16	32	5	1	0			
	33	1	5	0			
	34	3	3	1	116.89	188.42	71.53
17	35	4	2	1			
	36	2	4	1			
	37	5	2	0			
	38	2	5	0	140.44	110.03	−30.41
18	39	4	4	0			
	40	4	3	1			
	41	3	4	1			
	42	5	0	1			
	43	1	0	2			
	44	5	3	0			
	45	3	5	0			
	46	5	1	1			
	47	1	5	1			
	48	1	1	2	195.61	202.30	6.69
19	49	6	0	0			
	50	2	0	2			
	51	6	1	0			
	52	1	6	0			
	53	5	2	1			
	54	2	5	1			
	55	2	1	2			
	56	1	2	2	153.73	178.76	25.04

[a] The model is based on a helix with four residues per turn and pitch of 4.94 Å. The helices are packed in parallel in space group $P4_1$, with $a = b = 13.98$ Å. The final R factor was 16.4% and $R_w = 14.2\%$.

used by other researchers.[10] The parametrization of the bonding terms of the ester group was carried out as described elsewhere.[19] All values are given in Table IV. These values were then introduced in the AMBER program.

The starting geometries for the hexagonal models were slightly modified with LALS methodology from those previously obtained from X-ray data and reported elsewhere.[2] For the tetragonal form the final geometry corresponding to the refined crystalline structures was used. The energy calculations were carried out with 11 residues which were blocked at the amino terminal end with an acetyl group and with an N-methyl amide at the carbonyl end. The results obtained are given in Table II. We also calculated model 3, left-handed model 4, and another tetragonal model with four residues per turn using peptide units that were alternately oriented in opposite directions. In all the latter cases, the polymer was sterically hindered and the energy calculations showed that such conformations are unstable.

In order to ascertain the influence of the side chain on the stability of the various helical forms, we carried out calculations similar to those presented in Table II, but with a single methyl group as a side chain, i.e., poly(β-aminobutyric acid). We obtained conformational angles similar to those given in Table II, with an average deviation of 11°, so that all angles were in the same conformational region. The hexagonal form 1L was again less stable than 2R by 2.5 kcal/(mol residue), but now the hexagonal form 2R was 4 kcal/(mol residue) more stable than the tetrag-

Table II
Conformational Angles and Calculated Energies of Different Models[a]

model	φ	ξ	ψ	ω	χ^1	χ^2	χ^3	χ^4	E_{tot}	E_{vdw}	E_{el}	E_{hb}	E_{bd}	n
1-L														
starting	126.6	−102.8	113.6	180.0	175.0	180.0	−101.2	114.1						3.25
50 cycles	135.4	−102.3	103.4	−179.7	−175.0	−178.2	−87.3	113.6	−101.3	−3.5	−108.2	−0.4	10.8	3.20
full ref	122.0	−80.1	101.4	164.7	−155.4	171.9	−84.1	69.6	−111.5	−9.6	−108.9	−0.5	7.5	3.05
2-R														
starting	145.2	−62.0	130.8	180.0	175.0	180.0	−101.2	114.1						3.25
50 cycles	157.4	−63.9	114.3	−174.0	−168.9	−179.9	−79.2	111.9	−112.2	−6.9	−114.0	−1.0	9.7	3.11
full ref	151.3	−59.1	118.1	180.0	−171.2	178.7	−70.7	107.7	−114.0	−8.4	−112.1	−1.1	7.7	3.14
4-R														
starting	144.2	−86.9	148.5	180.0	−179.5	180.0	−128.8	−145.8						4.0
50 cycles	153.1	−82.4	135.0	178.4	−166.2	−177.3	−161.9	171.5	−108.2	−4.0	−108.8	−1.0	5.6	3.83
full ref	148.4	−65.8	136.0	160.0	−135.3	−170.0	177.5	178.2	−119.7	−10.0	−113.5	−0.8	4.6	3.93

[a] The conformations studied correspond to those indicated in Figure 1. The letters L (left) and R (right) indicate the sense of the helix. The conformational angles correspond to those indicated in Figure 2. The different energy terms refer to one residue, where E_{tot} = total energy, E_{vdw} = van der Waals energy, E_{el} = electrostatic energy, E_{hb} = energy corresponding to the $r^{-12} - r^{-10}$ term, and E_{bd} = bonding energy. The parameter n gives the number of residues per helical turn computed from the comformational angles. The starting conformations were calculated with the LALS program taking into account the X-ray results (see text). The values given for 50 cycles and full refinement (full ref) are the average of the central four residues, which in fact differ among themselves by less than 1%.

Table III
Cylindrical Coordinates of One Residue of Poly(α-isobutyl L-aspartate) in the Tetragonal Conformation

atom	R (Å)	φ (deg)	Z (Å)
1 (O1)	2.73	−35.7	−2.13
2 (CO1)	2.73	−41.7	−0.93
3 (N1)	2.75	−22.4	0.03
4 (HN1)	2.70	−27.1	1.01
5 (C1)	3.33	2.3	−0.27
6 (HC1)	3.12	9.1	−1.27
7 (C3)	4.80	−2.2	−0.22
8 (C2)	3.26	22.2	0.76
9 (H1C2)	2.91	15.4	1.73
10 (H2C2)	4.32	25.9	0.87
11 (CO2)	2.73	48.3	0.30
12 (O2)	2.73	54.2	−0.89
13 (N2)	2.75	67.6	1.26
14 (HN2)	2.70	62.8	2.25
15 (OD)	5.71	6.0	−0.43
16 (OS)	5.25	−16.2	0.10
17 (C4)	6.69	−16.4	0.18
18 (H1C4)	7.00	−18.0	1.21
19 (H2C4)	7.15	−8.7	−0.14
20 (C5)	7.30	−25.2	−0.74
21 (HC5)	7.36	−22.1	−1.75
22 (C6)	8.74	−27.1	−0.24
23 (H1C6)	9.23	−32.1	−0.80
24 (H2C6)	8.72	−28.7	0.82
25 (H3C6)	9.37	−21.5	−0.38
26 (C7)	6.64	−36.7	−0.74
27 (H1C7)	7.44	−41.8	−1.13
28 (H2C7)	5.75	−37.3	−1.37
29 (H3C7)	6.39	−39.3	0.27
30 (orig)	0.88	4.1	0.00

Table IV
Force Field Parameters for One α-Isobutyl L-Aspartate Residue[a]

Stretching, Bending, and Torsion Parameters

atoms	K_s (kcal/Å^2)	l_0 (Å)
C3–OS	572	1.37

atoms	K_b (kcal/rad^2)	θ_0 (grad)
C1–C3–OS	45	113.1
C3–OS–C4	101	116.8
OD–C3–OS	65	118.1

atoms	$V_n/2$ (kcal/mol)	n
C4–OS–C3–C1	0.0	1
	−3.5	2
	0.0	3

Electrostatic Charges

α-isobutyl L-aspartate				NME residue		ACE residue	
atom	charge	atom	charge	atom	charge	atom	charge
O2	−0.542	C5	0.100	N	−0.694	H1C1	0.080
CO2	0.615	HC5	0.120	HN	0.330	C1	−0.347
C2	−0.302	C6	−0.371	C	0.064	H2C1	0.080
H1C2	0.163	C7	−0.371	H1C	0.010	H3C1	0.080
H2C2	0.163	H1C6	0.139	H2C	0.010	C2	0.752
C1	0.051	H2C6	0.139	H3C	0.010	CD	−0.645
HC1	0.120	H3C6	0.139				
C3	0.698	H1C7	0.139				
CD	−0.585	H2C7	0.139				
OS	−0.585	H3C7	0.139				
C4	−0.080	N1	−0.583				
H1C4	0.120	HN1	0.315				
H2C4	0.120						

[a] Bond parameters (force constants and equilibrium geometric parameters) correspond to the ester group. Electrostatic charges computed for acetyl (ACE) and N-methyl amide (NME) residues are included.

onal form 4R. These calculations allow us to reach two important conclusions: (a) The main chain conformation is not altered significantly by different side chains. (b) The side chain interactions, and therefore the packing of different molecules in the crystal, do have a significant influence on the relative energies of the various forms.

Discussion

The calculations presented here demonstrate that the title compound has a tetragonal conformation with the hydrogen-bonding scheme 4 shown in Figure 1. None of the other possible conformations appear to be suitable. In a previous paper[2] we excluded this conformation because it showed a central hole of about 3-Å diameter which we considered too large. The energy refinement shows that this hole becomes somewhat smaller (2.5-Å diameter) through some distortion of the peptide bond, which deviates 20° from planarity. Such deviation corresponds to a loss of energy of about 2 kcal/(mol residue)[20] and may be compensated by a better arrangement of the other atoms. In fact this conformation converges to the lowest energy of all those studied (−119.7 kcal/(mol residue)).

Nevertheless, the energy calculations have to be interpreted with caution, since the side chain interactions are not taken into account properly, as it is obvious from the results we have obtained with poly(β-aminobutyric acid). In the crystal the side chains tend to be rather extended since they interact with neighboring molecules (Figures 3

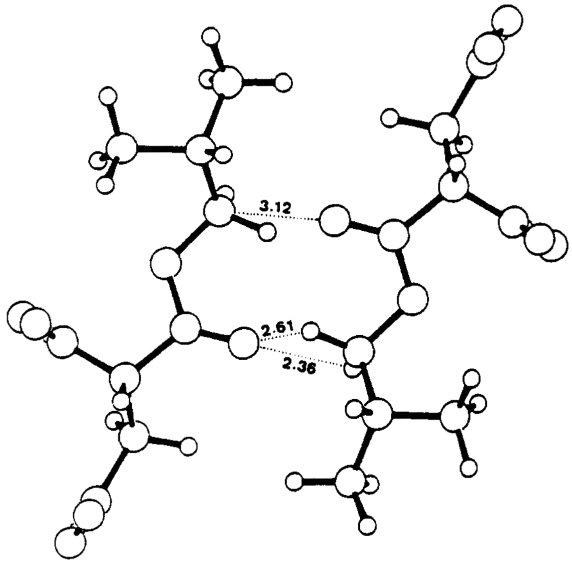

Figure 4. Side chain interaction between two neighboring molecules of poly(α-isobutyl L-aspartate) in its tetragonal form. Chains are extended to improve lateral packing. Main interatomic distances are indicated.

and 4), whereas in the energy-refined conformation the side chain tends to interact with the main chain in order to optimize the van der Waals interactions. What is clearly apparent is that all three conformations presented in Table II are energetically feasible, since after only 50 cycles of refinement a reasonable energy value is found. This observation indicates that the three conformations obtained from the LALS refinements are reasonably accurate and very close to an energy minimum. In fact the changes in conformation introduced by energy refinement cannot be considered as absolutely correct for the crystalline structures since the calculations were carried out with single chains. Intermolecular interactions were only used in the LALS procedure. Furthermore, the energy minimization does not preserve the helical parameters determined from the X-ray diffraction patterns, so that the number of residues per turn n is slightly modified, as shown in Table II.

The results presented in this paper also show that there are two conformations, 1L and 2R, compatible with the hexagonal form of the title compound. The circular dichroism results do not allow one to distinguish between these two models, since the calculated spectra are very similar for both of them.[21] On the other hand, we had previously observed that under some conditions the transition between the hexagonal and tetragonal forms takes place easily[3] and also that both forms have a very similar NMR spectrum in the solid state.[7] Since model 2R is very similar to model 4R at the main chain level, it appears that 2R is the correct model for the hexagonal phase found in fibers pulled from a concentrated chloroform solution. Furthermore, this form is 2.5 kcal/(mol residue) more stable than the 1L conformation, as shown in Table II. This form should also be the one normally found in solution.[20] It is interesting to note that models 2 and 4 have a hydrogen-bonding scheme topologically different from that found in the usual α-helix, since the peptide groups are oriented in the opposite direction with respect to the main chain. On the other hand, model 1 is topologically equivalent to the α-helix, with an additional methylene group in each monomeric unit.

Another significant difference between the protein α-helix and the helices described here results from the presence of an additional methylene group in the main chain. This methylene group gives greater freedom to the conformational angles and allows different helical conformations to appear, which may vary slightly as a function of the side chains present and of their interactions in the crystal, as we have found when the side chain is replaced by a methyl group. In fact, the β-alanine residue which constitutes the main chain of our polymer is known to have a great conformational variability, as reviewed by Pavone et al.[22]

According to the two models proposed, the transition between the hexagonal and tetragonal phases will take place easily, since it does not imply a major change in conformation (basically a slight change of the ξ and ψ torsion angles), but just a shift of one residue in the hydrogen-bonding scheme, as shown in Figure 1. Model studies[16] have shown that this kind of transition may start at any point of the molecule and then propagate itself cooperatively in both directions. Packing stability also plays a role in the transition mechanism. Whereas a tighter main chain is found in the hexagonal form, packing of the side chains is improved in the tetragonal form, as shown in Figures 3b and 4. Side chain interactions in the hexagonal form are soft and require variable conformations depending on the local packing constraints.

A final point to discuss is that according to our LALS calculations, the tetragonal phase has the polymer chains organized in a parallel fashion. This result agrees with previous observations,[3] which show that when the hexagonal crystals are transformed to tetragonal, they become much thicker, so that chain folding may be prevented. This feature of the tetragonal form may also explain the difficulties encountered to produce both oriented fibers and single crystals of this form from solution.

Polyolefins with tetragonal crystal structures show antiparallel packing in which each right-handed helix is surrounded by four left-handed helices and vice versa. Symmetry glide planes relate helices of opposite handedness. Poly(α-isobutyl L-aspartate), however, has asymmetrical carbon atoms in its main chain, so any crystalline form with symmetry planes of any kind is impossible. Furthermore, the left-handed model 4 has been calculated to be unstable. In summary the tetragonal form of the title compound has to be built of right-handed helices only, which parallel packing has revealed to be the most suitable.

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References and Notes

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