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Effects of Aqueous and Organic Solvents on the Conformational Properties of the Helix-Forming α-Methyl-*β*-L-aspartamyl Residue

Juan José Navas, Carlos Alemán,* and Sebastián Muñoz-Guerra

Departament d'Enginyería Química, E. T. S. d'Enginyers Industrials, Universitat Politècnica de Catalunya, Diagonal 647, Barcelona E-08028, Spain

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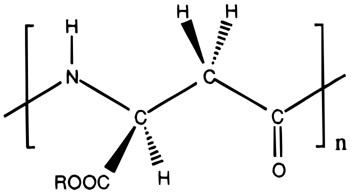
The conformational preferences of *N*-acetyl-*N*′-methyl-α-methyl-*β*-L-aspartamide, which is the model compound for helical poly(*β*-L-aspartate)s, have been determined by ab initio SCF-MO computations. Two driving patterns have been found for the existing 13 minimum energy conformations: (i) intramolecular hydrogen bonding interactions of both amide−amide and amide−ester type; and (ii) repulsive interactions between the four oxygen atoms contained in the molecule. Self-consistent reaction-field (SCRF) calculations based on the method proposed by Miertus, Scrocco, and Tomasi have been performed in order to evaluate the effect of the solvent on the conformational preferences of the compound subject of study. Water and carbon tetrachloride were the solvents chosen for this purpose, and results have been discussed and interpreted on the basis of their electronic structures. The conclusions drawn from this study are of assistance to understand some features of the conformational transitions experimentally found in poly(*β*-L-aspartate)s.

Introduction

Poly(α-alkyl-*β*-L-aspartate)s are nylon 3 derivatives bearing an alkoxycarbonyl group on the third carbon atom of the repeating unit.



The outstanding feature of these novel polyamides is their ability to adopt helical conformations stabilized by intramolecular hydrogen bonds similar to the familiar α-helix of polypeptides and proteins.[1] This represents a departure from the characteristic behavior traditionally observed for non-polypeptidic polyamides that may have interesting technological applications. Indeed, certain properties arising from the stiff helical nature of the macromolecule, such as formation of liquid crystal phases[2,3] and piezoelectricity,[4] have been observed for some of these polymers.

The crystal structure of poly(*β*-L-aspartate)s in the solid state has been extensively studied by us during the last decade. A pseudohexagonal crystal form composed of right-handed 13/4 helices has been found to be the structure most frequently assumed by these polyamides.[5−8] In addition, a second crystal form consisting of a tetragonal packing of right-handed 4/1 helices has been observed for some members of the series, like ethyl, *n*-butyl, and isobutyl derivatives.[5,7,8] In such cases, the form in which the polymer crystallizes depends upon the method of preparation, and the transition between the two crystal forms may be induced by effect of heating or upon the action of certain solvents.[7,9]

In spite of the structural significance of this family of polyamides, the conformational properties of the *β*-aspartamyl residue has not been examined so far. Such a study is highly desirable because the crystal dimorphism displayed by these polymers is most likely determined by the conformational preferences of the monomeric unit. The study should include solvent effects since some authors have recently demonstrated that they may reverse the conformational preferences of a molecule by modifying the stability of dipole−dipole interactions.[10−14]

In this paper we have carried out a detailed and systematic ab initio study of the potential energy hypersurface of *N*-acetyl-*N*′-methyl-α-methyl-*β*-L-aspartamide (Figure 1), which is taken as the appropriate molecule for modeling poly(*β*-L-aspartate)s. This is a reasonable choice because *N*-acetyl and *N*-methyl derivatives of α-amino amides are the most frequent model compounds used in ab initio calculations. Although the space available for the α-methyl-*β*-L-aspartamyl residue might be slightly different in the polyamide chain as it is in the dipeptide, the conclusions to be drawn from this study will be essentially valid for the polymer as well.

The effect of the solvent has been also explored by means of a self-consistent reaction-field (SCRF) method.

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Two different solvents, water and CCl_4, were chosen to analyze the influence of the environment on the molecular system. While a large number of methods have been developed to simulate aqueous solutions,[15−20] little attention has been devoted so far to modeling solvation in nonaqueous media[21,22] which is of great importance in organic and macromolecular chemistry. The SCRF methodology used in the present work was developed to simulate neutral solutes in CCl_4 with high precision.[22] By these means, a complete picture of the conformational preferences of *N*-acetyl-*N*′-methyl-α-methyl-*β*-L-aspartamide, including three different media, gas-phase, aqueous solvent, and apolar solvent, is provided.

Methods

Gas-Phase Calculations. Ab initio SCF-MO geometry optimizations have been carried out using the Gaussian-92 program[23] with the 3-21G[24] and 6-31G(d)[25] basis sets. Frequency analysis was performed to verify the nature of the minimum state of the stationary points located during geometry optimizations, as well as to obtain the Zero Point Energies (ZPE) and the thermal corrections to the energy. The calculations comprised a total of 152 and 222 basis functions at the 3-21G and 6-31G(d) levels, respectively. To investigate the effect of the electron correlation, single-point calculations at the MP2/6-31G(d) level were performed on the minima characterized at the HF/6-31G(d) level.

Polymer calculations were performed at the SCF-MO level on a model compound containing six residues of α-methyl-*β*-L-aspartamyl. Since ab initio calculations on such a large molecular system are not possible, AM1[26] semiempirical calculations were carried out on all the conformations considered for this compound.

Solvent Phase Calculations. The free energies of solvation (ΔG_{solv}) were determined using a semiempirical AM1 adapted version of the SCRF developed by Miertus, Scrocco, and Tomasi (MST/AM1). According to this method, the ΔG_{solv} was determined as the addition of electrostatic and steric contributions (eq 1). The steric component was computed as the sum of the cavitation and van der Waals terms.

$$\Delta G_{solv} = \Delta G_{elec} + \Delta G_{cav} + \Delta G_{vdW} \qquad (1)$$

The cavitation term was determined using Pierotti's scaled particle theory,[27] while the van der Waals term (eq 2) was evaluated by means of a linear relation with the molecular surface area:[15a,c,16]

$$\Delta G_{vdW} = \sum_i \xi_i \, S_i \qquad (2)$$

where S_i is the portion of the molecular surface area belonging to atom *i* and ξ_i is the hardness of atom *i*. Parameters defining the hardness of the different atom types in H_2O and CCl_4 solvents were determined in previous parametrizations.[15c,22]

The electrostatic interaction between the solute and the solvent was computed using the MST-SCRF approach, in which the solvent is represented as a continuous dielectric, which reacts against the solute charge distribution generating a reaction field (V_R). The effect of the solvent reaction field on the solute is introduced as a perturbation operator in the solute hamiltonian (eq 3).

$$(H^0 + V_R)\psi = E\psi \qquad (3)$$

The perturbation operator is computed in terms of a set of point charges located at the solute/solvent interface, *i.e.* the solute cavity (eq 4).

$$V_R = \sum_i q_i/|r_o - r| \qquad (4)$$

Such imaginary charges were determined by solving the Laplace equation at the solute/solvent interface. The electrostatic potential of the solute was computed at the AM1 level using the *ortho* method.[28]

In all cases the solute/solvent interface was determined using a molecular shape algorithm.[15,16,19,20] Standard van der Waals radii (C = 1.5 Å; N = 1.5 Å; O = 1.4 Å; H = 1.2 Å; H(bound to polar atoms) = 0.8 Å) were used.[15b,c] Since the change of the molecular geometry upon solvation has a negligible effect on the thermodynamic parameters only gas-phase optimized geometries were used.[29] Previous studies indicated that the root mean square deviations between experimental and MST/AM1 ΔG_{solv} are 1 and 0.40 kcal/mol for aqueous[16] and CCl_4[22] solutions, respectively. Calculations were performed with an adapted version of MOPAC93 Revision 2,[30] which permits MST calculations with H_2O and CCl_4 solvents.

Results and Discussion

Gas Phase Conformations. The *N*-acetyl amino acid *N*′-methylamides of natural amino acids are frequently used in ab initio calculations as diamide systems to model polypeptides.[31−35] In this work the *N*-acetyl-*N*′-methyl-α-methyl-*β*-L-aspartamide stands for the model com-

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Table 1. Conformational Angles (in degrees) and Relative Energies (in kcal/mol) for the Minimum Energy Structures Characterized at the HF/3-21G Level of *N*-Acetyl-*N*′-methyl-α-methyl-L-aspartamide

no.	ω_1	φ	ξ	ψ	ω_2	χ_1	χ_2	ΔE^{a}	$\Delta E_{\mathrm{ZPE+TC}}{}^{a,b}$
1	177.4	67.2	64.0	−154.3	−177.4	−171.0	172.3	0.0	0.0
2	175.1	112.7	62.8	−177.5	−179.3	−169.4	179.6	1.0	1.5
3	177.9	72.3	−133.0	56.7	179.2	176.0	177.9	1.9	2.7
4	175.6	155.9	60.3	100.5	−176.9	−174.5	−173.8	2.4	3.1
5	−171.5	63.5	55.8	88.5	−177.9	−175.7	−175.2	4.1	4.7
6	−176.2	−64.6	−66.6	161.3	177.7	−165.4	−178.7	4.2	4.7
7	175.5	63.2	−160.3	−154.7	−176.7	−168.8	−177.3	5.0	5.5
8	−172.7	−63.3	−155.4	−152.2	−178.0	−158.2	−177.8	5.4	5.2
9	−171.0	172.7	−51.5	−99.5	177.9	171.5	−179.0	5.4	6.1
10	−172.7	90.7	−54.2	−86.3	166.9	174.7	178.5	5.8	6.3
11	177.0	48.2	−96.5	149.6	−179.2	−175.8	−177.1	6.0	6.5
12	177.4	102.9	−133.5	−49.5	179.5	173.9	178.9	7.3	7.8
13	176.6	144.6	−70.5	154.4	177.0	179.1	−177.3	7.8	8.0
14	172.4	97.1	−69.6	87.6	−169.9	175.7	179.4	7.8	8.2
15	−164.9	−63.9	−75.1	45.1	178.1	−173.3	−179.4	8.9	9.5
16	167.1	−80.0	44.8	93.5	−170.0	−133.5	−179.8	9.0	9.5
17	−170.0	−59.5	−163.6	59.9	179.8	−176.1	175.2	12.1	12.3

[a] Computed at the HF/3-21G//HF/3-21G level. [b] Includes corrections for zero point energy and for translational, rotational, and vibrational energies at the HF/3-21G//HF/3-21G level.

Table 2. Conformational Angles (in degrees) and Relative Energies (in kcal/mol) for the Minimum Energy Structures Characterized at the HF/6-31G(d) Level of *N*-Acetyl-*N*′-methyl-α-methyl-L-aspartamide

no.	ω_1	φ	ξ	ψ	ω_2	χ_1	χ_2	ΔE^{a} (HF/6-31G(d))	$\Delta E_{\mathrm{ZPE+TC}}{}^{a,b}$ (HF/6-31G(d))	ΔE^{c} (MP2/6-31G(d))	$\Delta E_{\mathrm{ZPE+TC}}{}^{a,b}$ (MP2/6-31G(d))
1	171.8	77.6	63.2	−149.6	−179.9	−174.4	177.7	0.0	0.0	0.0	0.0
3	176.3	74.2	−136.1	58.9	176.0	171.4	177.0	1.8	2.1	1.2	1.5
4	168.6	161.4	62.7	121.5	−178.9	169.8	−178.1	1.8	2.0	1.5	1.7
6	−162.8	−59.5	−52.0	114.2	−175.2	−173.4	−178.0	3.0	3.3	2.9	3.2
8	−166.0	−70.3	−156.4	−149.2	178.8	−150.9	−177.0	3.8	3.8	4.1	4.1
9	−179.9	177.0	−56.9	−105.0	177.6	149.5	−179.7	3.4	3.5	3.5	3.6
10	−172.5	91.1	−52.5	−88.2	167.9	162.3	177.6	3.4	3.4	3.1	3.1
11	174.1	57.0	−102.1	138.7	−174.7	178.4	−178.0	4.2	4.4	4.4	4.5
13	167.3	160.3	−67.8	135.5	175.3	165.1	−179.7	4.7	4.6	6.1	6.0
14	166.7	105.9	−73.1	92.5	−169.7	167.4	178.6	4.8	4.9	4.6	4.7
15	−160.7	−71.9	−73.6	41.6	174.1	−164.7	−177.3	7.5	7.6	6.6	6.7
16	168.4	−80.1	44.7	96.9	−169.9	−131.2	179.8	7.7	7.8	4.6	4.7
17	−163.3	−66.6	−155.7	56.1	172.3	−165.5	−179.3	9.7	9.7	9.7	9.7

[a] Computed at the HF/6-31G(d)//HF/6-31G(d) level. [b] Includes corrections for zero point energy and for translational, rotational, and vibrational energies at the HF/6-31G(d)//HF/6-31G(d) level. [c] Computed at the MP2/6-31G(d)//HF/6-31G(d) level.

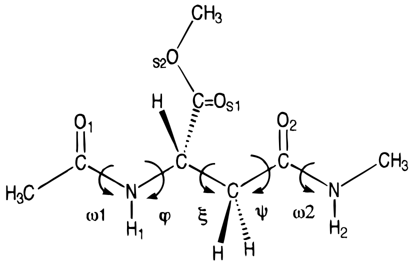

Figure 1. Schematic representation of the *N*-acetyl-*N*′-methyl-α-methyl-L-aspartamide. The torsion angles and atom labeling are indicated.

pound of poly(β-L-aspartate)s. Since each of the three backbone torsional angles (φ, ξ, and ψ in Figure 1) are expected to have 3 minima,[36] 27 minima may be anticipated for the potential energy hypersurface $E = E(\varphi,\xi,\psi)$ of this compound according to the conformational multidimensional analysis developed by Csizmadia and coworkers.[36,37] All these structures were taken as starting geometries in HF/3-21G geometry optimizations. Side chain dihedral angles (χ_1 and χ_2 in Figure 1) were initially considered in *all-trans* conformation, as they are usually observed in poly(β-L-aspartate)s.[5-8] All the minima characterized at the HF/3-21G level were subsequently reoptimized at the HF/6-31G(d) level. Tables 1 and 2 display the conformational angles and energies for all the minima found at the HF/3-21G and HF/6-31G(d), respectively, which were characterized as such from frequency analyses. In order to obtain a more accurate estimation of the gas-phase relative energies, single point calculations at the MP2/6-31G(d) level were performed on the 13 minima found at the HF/6-31G(d) level. These results are included in Table 2.

A comparative inspection of the results listed in Tables 1 and 2 reveals some important features. First, 4 of the 17 minima found at the HF/3-21G level dissapeared upon geometry optimization at the HF/6-31G(d) level, indicating that such structures are not real minima. This fact suggests that the HF/3-21G level is appropiate to perform the scanning of the potential energy surface, but reoptimizations at higher levels of theory are required. Similar conclusions have been reached by other authors for glycine and alanine dipeptides.[10,32] Second, a comparison of the φ, ξ, and ψ dihedral angles for a given minimum in Tables 1 and 2 suggest that the agreement

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Table 3. Hydrogen Bonding Geometries (distances in Å and angles in degrees) for the Minimum Energy Conformation of *N*-Acetyl-*N*′-methyl-α-methyl-L-aspartamide Obtained at the HF/6-31G(d). Labels for the Donor and Acceptor Atoms are Displayed in Figure 1

no.	atoms	*d*(H···O)	*d*(N···O)	<N−H···O
1	N1−H1···OS1	2.24	2.67	104.5
3	N1−H1···O2	2.21	3.15	155.8
4	N1−H1···O2	2.17	2.89	127.4
9	N1−H1···O2	2.24	2.93	124.9
10	N1−H1···OS1	2.44	2.71	94.8
11	N1−H1···OS1	2.16	2.63	107.3
14	N1−H1···OS1	2.24	2.68	104.8
16	N2−H2···OS2	2.36	3.15	135.8

between the HF/3-21G and HF/6-31G(d) optimized structures are quite good, the largest deviation being ≈11°. Thus, although HF/3-21G is found to overestimate the number of minima, it provides an acceptable description of the molecular geometries. However, the agreement between HF/3-21G and HF/6-31G(d) relative energies is not good, the relative energy of most minima is lower at the HF/6-31G(d) level than at the HF/3-21G level. Furthermore, single point calculations at the MP2/6-31G(d) level point out the crucial role of electron correlation in relative energies. This effect is specially remarkable in **15** and **16**. Overall, these results suggest that the true surface of *N*-acetyl-*N*′-methyl-α-methyl-β-L-aspartamide is more flat than that predicted at the HF level.

The most striking feature of the potential energy hypersurface $E = E(\varphi,\xi,\psi)$ of *N*-acetyl-*N*′-methyl-α-methyl-β-L-aspartamide is the existence of two well-defined forces driving the folding of the backbone dihedral angles to the different minima. These forces are (i) the hydrogen bonds between the amide groups and the oxygen atoms of either amide or ester groups; and (ii) the minimization of the repulsive electrostatic and steric interactions between the four oxygen atoms contained in the model molecule. Intramolecular hydrogen bonds are present in 8 out of the 13 energy minima characterized at the HF/6-31G(d) level. Hydrogen bond parameters for such conformations are shown in Table 3. As can be noted, only three minima are stabilized by amide−amide interactions, the hydrogen bonding with the oxygen atoms of the side chain being the most frequent interaction. Indeed, the lowest energy conformation, which is shown in Figure 2a, is clearly stabilized by an amide−ester interaction. This conformation has a strong C_5 interaction (five-membered intramolecular hydrogen-bonded ring) between the NH group of the α-methyl-β-L-aspartyl residue and carbonyl oxygen atom of the ester group. Therefore, the C_5 interaction between the amide−ester groups seems to have an stabilizing effect similar to that observed between the amide−amide groups in the extended conformation of α-amino acids.[31−35] This result is in excellent agreement with recent high-level ab initio calculations,[38] which reveal that the more favorable interaction between amide−ester groups occurs with the carbonyl oxygen of the ester group. Thus, this strongest form of the amide−ester hydrogen bonding appeared to be of similar strength as the amide−amide interaction. On the other hand, repulsive interactions between the oxygen atoms seem to be the primary driving force in the stabilization of the minima labeled **6**, **8**, **13**, **15**, and **17**. The minimum energy conformation of this second set of conformers, *i.e.* conformation number **6**, is shown in Figure 2b, where the shortest distance between two oxygen atoms is 3.40 Å. This conformation is 3.2 kcal/mol less stable than the absolute minimum. Thus, the combination of these driving forces seems to be the responsible for the lossing of 14 out of 27 minima anticipated on the basis of multidimensional analysis. In all cases, side-chain dihedral angles kept a conformation close to the *all-trans*.

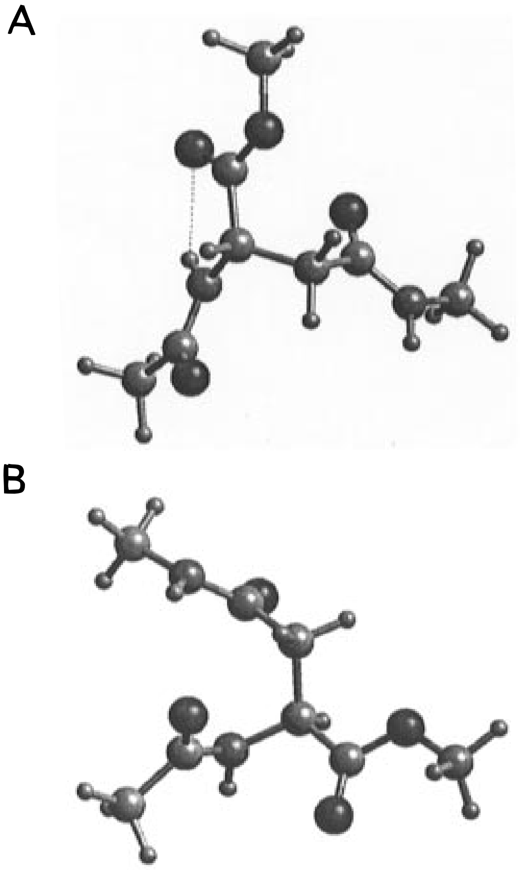

Figure 2. (a) Global energy minimum conformation (**1** in Table 2) of the *N*-acetyl-*N*′-methyl-α-methyl-L-aspartamide. (b) The lowest energy conformation stabilized by the minimization of the repulsive interactions between the oxygen atoms (**6** in Table 2) of the same compound.

Effect of the Aqueous Solvent. The $\Delta\Delta G_{hyd}$ computed at the AM1/MST level for the 13 minima characterized at the HF/6-31G(d) level is shown in Table 4, where the electrostatic (ΔG_{elec}) and steric ($\Delta G_{cav}+\Delta G_{vdW}$) contributions are also displayed. Results indicate that the electrostatic term provides the most important contribution to ΔG_{hyd} in all cases, whereas the steric one has a unfavorable contribution to ΔG_{hyd}. The polarizable nature of water makes this solvent to be highly structured, and therefore generation of cavity is difficult from an energy point of view. This unfavorable contribution is not compensated by the van der Waals interactions, which, due to the small size of the cavity, are not attractive enough. As can be seen, the largest value of $\Delta\Delta G_{hyd}$ is 5.2 kcal/mol (minimum **3**) reflecting the strong influence of the aqueous solvent on the potential energy hypersurface $E = E(\varphi,\xi,\psi)$ of *N*-acetyl-*N*′-methyl-α-methyl-L-aspartamide.

A noticeable result is that the lowest values resulting for the $\Delta\Delta G_{hyd}$ (minima **13** and **17**) correspond to conformations with minimal repulsive interactions between

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Table 4. MST/AM1 Free Energies of Solvation in Water (ΔG_{hyd} in kcal/mol) for the 13 Minima of the *N*-Acetyl-*N′*-methyl-α-methyl-L-aspartamide. Relative Values ($\Delta\Delta G_{hyd}$; in kcal/mol) Are Also Displayed. The SCRF Free Energy is Decomposed into Electrostatic (ΔG_{elec}; in kcal/mol) and Steric ($\Delta G_{cav} + \Delta G_{vdW}$; in kcal/mol) Terms

no.	ΔG_{elec}	$\Delta G_{cav} + \Delta G_{vdW}$	ΔG_{hyd}	$\Delta\Delta G_{hyd}$
1	−17.0	4.2	−12.8	2.8
3	−14.8	4.4	−10.4	5.2
4	−17.0	4.5	−12.4	3.2
6	−17.0	4.4	−12.7	2.9
8	−18.2	4.3	−13.9	1.7
9	−18.1	4.6	−13.5	2.1
10	−16.1	4.2	−11.9	3.7
11	−15.9	4.2	−11.7	3.9
13	−19.9	4.4	−15.6	0.0
14	−17.1	4.3	−12.8	2.8
15	−17.6	4.4	−13.2	2.4
16	−16.4	4.1	−12.3	3.3
17	−19.2	4.2	−15.0	0.6

Table 5. MST/AM1 Free Energies of Solvation in CCl$_4$ (ΔG_{CCl4} in kcal/mol) for the 13 Minima of the *N*-Acetyl-*N′*-methyl-α-methyl-L-aspartamide. Relative Values ($\Delta\Delta G_{CCl4}$; in kcal/mol) Are Also Displayed. The SCRF Free Energy is Decomposed into Electrostatic (ΔG_{elec}; in kcal/mol) and Steric ($\Delta G_{cav} + \Delta G_{vdW}$; in kcal/mol) Terms

no.	ΔG_{elec}	$\Delta G_{cav} + \Delta G_{vdW}$	ΔG_{CCl4}	$\Delta\Delta G_{CCl4}$
1	−1.5	−9.1	−10.6	0.9
3	−1.4	−9.0	−10.4	1.1
4	−1.7	−9.0	−10.7	0.8
6	−1.5	−8.8	−10.3	1.2
8	−1.6	−8.9	−10.5	1.0
9	−1.8	−9.2	−11.0	0.5
10	−1.3	−8.8	−10.1	1.4
11	−1.4	−8.9	−10.4	1.1
13	−2.1	−9.4	−11.5	0.0
14	−1.7	−9.0	−10.8	0.7
15	−1.8	−9.0	−10.8	0.7
16	−1.5	−8.1	−9.6	1.9
17	−1.9	−8.9	−10.8	0.7

oxygen atoms. This is a very reasonable result since such conformations have a dipole moment larger than those stabilized by intramolecular hydrogen bonds. Thus, the alignment of the amide and ester dipoles is unfavored in the gas-phase due to the repulsive electrostatic interactions between pairs of atoms with charges of equal sign. However, the large molecular dipole moment obtained by the alignment of the bond dipoles provide a more favorable electrostatic interaction with the solvent.

A rough estimation of the decisive effect of the aqueous solvent on the conformational preferences of the model compound can be attained by adding ΔG_{hyd} to the in vacuo energy for each conformation. The major changes correspond to the ordering of the conformers with a gas-phase relative energy ranging between 3 and 6 kcal/mol (minima from **6** to **16**). Furthermore, the results displayed in Table 3 revealed the hydrophobic character of the hydrogen bond, such as has been recently pointed out by some authors.[10,11,39] The hydrophobic character of the hydrogen bond has been recently investigated in small model complexes.[39] Results indicated that fragments are better hydrated than complexes, suggesting a poor tendency to form molecular associations in the aqueous phase. On the other hand, recent SCRF calculations in model dipeptides indicated that the ΔG_{hyd} in conformations without intramolecular hydrogen bonding is more favorable than in conformations involving this type of interactions.[10,11]

Effect of the CCl$_4$ Solvent. Results computed at the AM1/MST level for the model compound in CCl$_4$ solution are shown in Table 5. Comparison with results obtained for aqueous solution reveals significative differences. Thus, the electrostatic contribution is the leading term in aqueous solution, whereas in CCl$_4$ solution it accounts for only 20% of ΔG_{CCl_4}. Furthermore, the steric term in CCl$_4$ solution is attractive whereas in aqueous solution provides a repulsive contribution. The reason of this behavior must be attributed to the electronic structure of CCl$_4$ molecules. Thus, the bigger size and the higher polarizability of CCl$_4$ makes this solvent to be less structured than water.

The larger value of $\Delta\Delta G_{CCl_4}$ is 1.9 kcal/mol, which suggest that the CCl$_4$ solvent has a small influence on the the potential energy hyperfurface of *N*-acetyl-*N′*-methyl-α-methyl-L-aspartamide. To our knowledge, this is the first study in which the effect of CCl$_4$ solvent on the conformational preferences of a dipeptide is investigated using a SCRF method. Therefore, no comparison with other model compounds can be performed since recent Monte Carlo-free energy perturbation simulations (MC-FEP) demonstrate that force fields do not give accurate estimations of the electrostatic contributions.[22] Thus, MC-FEP simulations usually underestimate the polarization effects giving an underestimation of ΔG_{elec}. However, it must be pointed out that some force-fields have been recently designed to include polarization effects.[40] On the other hand, several strategies have been designed to consider the solvent effects in the parametrization of electrostatic parameters.[41] In summary, the present results indicate that the change from gas-phase ($\epsilon = 1$) to CCl$_4$ solution ($\epsilon = 2.228$ at 298 K) does not introduce any significant change on the conformational preferences of the solute, whereas the change to aqueous solution ($\epsilon = 78.5$ at 298 K) introduces a dramatic alteration in the ordering of the relative energies.

Implications for Poly(β-L-aspartate)s. The torsional angles of conformer **13** ($\varphi = 160.3°$, $\zeta = -67.8°$, $\psi = 135.5°$) appear to be the closest one to those describing the conformation assumed by the asymmetric unit of poly(β-L-aspartate)s in the hexagonal ($\varphi = 146.2°$, $\zeta = -59.8°$, $\psi = 128.8°$) and tetragonal ($\varphi = 144.4°$, $\zeta = -87.2°$, $\psi = 148.1°$) crystal forms. However, this conformation is energetically unfavored by 6.0 kcal/mol with respect to the global minimum in the gas-phase. The apparent stabilization achieved by this structure with the number of residues can be rationalized in terms of the energy gain associated with the formation of intramolecular hydrogen bonds between backbone amide groups. In this regard it is worthy to note that if torsional angles of conformer **13** were used to generate an infinite polymer chain, a right handed 7/2 helix having 3.5 residues per turn would result. Such a helix is approximately halfway between the 13/4 helix of the hexagonal form and the 4/1 helix of the tetragonal form. The three helical arrangements are schematically compared in Figure 3, where the intermediate character of the 7/2 helix is clearly evidenced. This strongly suggests that the sta-

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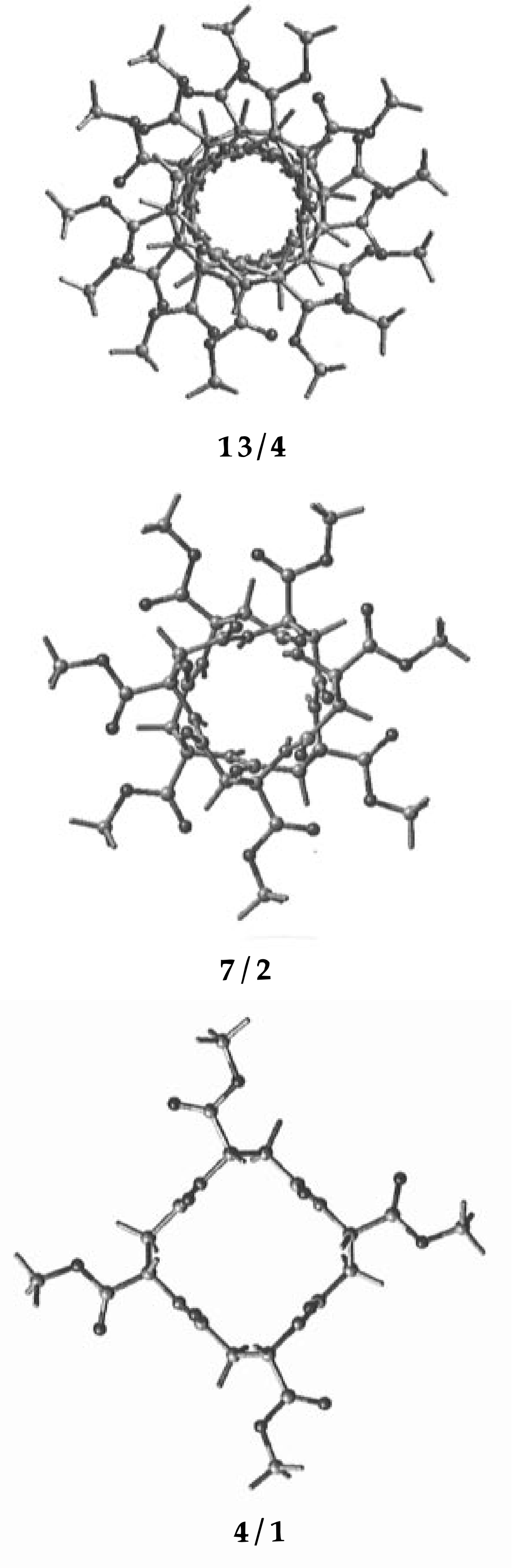

13/4

7/2

4/1

Figure 3. Equatorial projection of the 13/4-, 7/2-, and 4/1-helices of poly(β-L-aspartate)s.

bilization of the potential energy surface of the residue may be attained by evolving toward either of the two helices. The option to be chosen will be determined by environmental conditions.

Table 6. Torsional Angles (in degrees) and Relative Energies (in kcal/mol of residue) Associated with a Residue in the Hexagonal and Tetragonal Conformations of the Poly(β-L-aspartate)s

	helix	φ	ξ	ψ	ΔE	$\Delta\Delta G_{hyd}$	$\Delta\Delta G_{CCl_4}$
hexagonal	13/4	146.2	−59.8	128.8	0.0	4.0	0.5
tetragonal	4/1	144.4	−87.2	148.1	1.2	0.0	0.0

The great influence of the solvent on conformational equilibrium is a well known fact. However, as can be seen in Tables 4 and 5, the magnitude of $\Delta\Delta G_{solv}$ is very different depending on the nature of the solvent. The magnitude of the solvent effect in conformation **13**, as determined with respect to the lowest energy minimum in the gas-phase ($\Delta\Delta G_{solv} = \Delta G_{solv,1} - \Delta G_{solv,13}$), is −2.8 and −0.9 kcal/mol for aqueous and CCl_4 solutions, respectively. Water tends to estabilize the helical conformation of *N*-acetyl-*N′*-methyl-α-methyl-L-aspartamide in a similar way to that found for dipeptides of natural α-amino acids. Conversely, CCl_4 does not seem to have any significant effect on such conformation.

These features are fully consistent with the hexagonal-to-tetragonal transition observed in poly(β-L-aspartate)s when the polymer is soaked in low molecular weight alcohols. The tetragonal form will display more favorable electrostatic interactions in contact with polar solvents than the hexagonal one because of its larger molecular dipole moment. In order to have a more accurate description of this feature, we computed the energy associated with a residue in both the hexagonal and tetragonal conformations for the three environments considered in this work. For this purpose, we use a general procedure according to which the difference between the energy of the blocked compounds with one and two repeating units of poly(β-L-asparate)s can be associated with the increment of energy in one residue.[42,43] Results achieved by this procedure are displayed in Table 6. As can be seen, the hexagonal conformation turns to be 1.2 kcal/mol favored over the tetragonal one in absence of solvents. The energy gained by the tetragonal helix when it interacts with apolar solvents is not sufficient to outweight its inherent unstability. On the contrary, the stabilization provided by the interaction with polar solvents clearly compensates such a difference. These results evidence the effect exerted by the solvent in the transition from hexagonal to tetragonal.

The effect of hydrogen bonding interactions along the polymer chain has been recently investigated by means of molecular mechanics calculations on helices of poly(α-isobutyl-β-L-aspartate) and poly(α-*n*-butyl-β-L-aspartate), abbreviated PAIBLA and PANBLA, respectively.[8] Results were in agreement with experimental data in both cases. The most favored conformation is the 4/1-helix in PAIBLA, whereas the 13/4- and 4/1-helices are almost isoenergetic. These results permit one to explain the fact that the hexagonal-to-tetragonal transition taking place in PAIBLA by heating cannot be observed in PANBLA.[8] However, such calculations do not permit one to explain the crystal phase conversion readily induced in both polymers by effect of alcohols.

In order to understand the effect of the polarity of the environment on the stability of the different helices,

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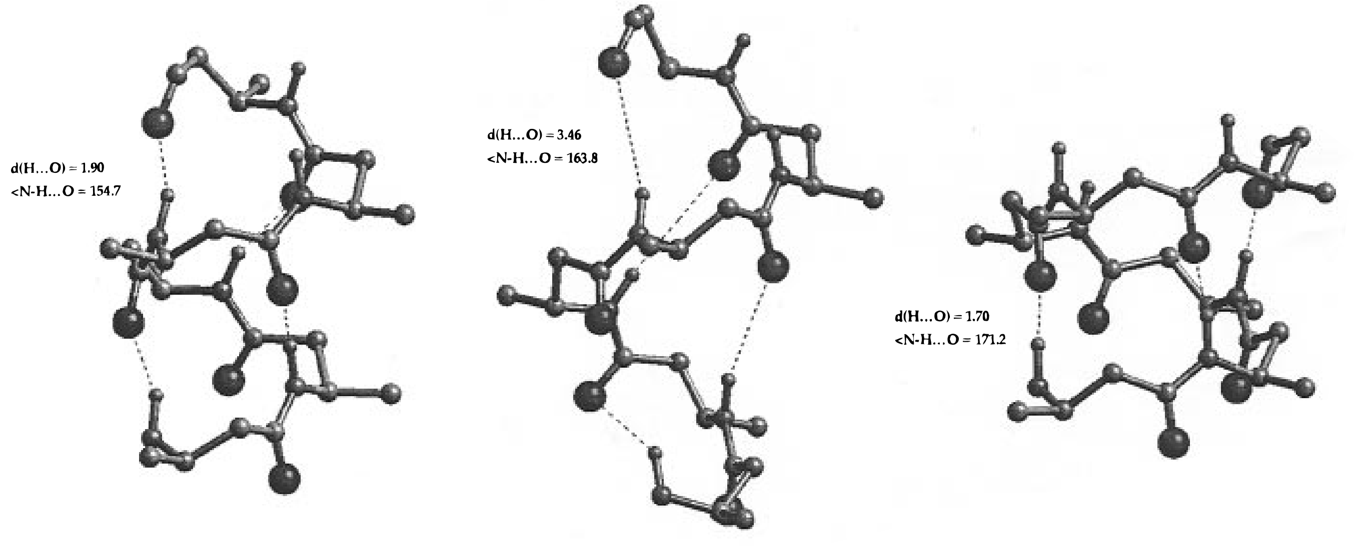

13/4 **7/2** **4/1**

Figure 4. Axial projection and hydrogen bond parameters of the 13/4-, 7/2-, and 4/1-helices of poly(*β*-L-aspartate)s. Side chains have been replaced by a single sphere.

Table 7. Relative Energies (in kcal/mol of residue) of the 13/4-, 7/2-, and 4/1-Helices of Poly(α-isobutyl-*β*-L-aspartate) (PAIBLA) and Poly(α-*n*-butyl-*β*-L-aspartate) (PANBLA). Three Different Environments were Considered: Gas-Phase, CCl_4, and Aqueous Solution. Energies Were Estimated by Means of SCRF Calculations Using a Recently Developed United Atom Parametrization of the MST/AM1 Method

	PAIBLA			PANBLA		
helix	gas-phase	CCl_4	H_2O	gas-phase	CCl_4	H_2O
13/4	0.5	0.7	1.0	0.0	0.0	0.0
7/2	3.2	2.7	1.6	3.2	2.9	1.8
4/1	0.0	0.0	0.0	0.2	0.3	0.7

SCRF calculations were performed on small oligopeptides mimicking both PANBLA and PAIBLA. Such oligopeptides were composed of five residues and blocked at the amino terminal end with an acetyl group and with a *N*-methylamide group at the carbonyl end. Calculations were done using a recently developed united-atom parametrization of the MST/AM1 method.[44] Results are shown in Table 7. It is noteworthy to note that the stability of the 7/2-helix increases with the polarity of the environment, giving a similar variation for the two polymers. This can be attributed to the weakening of the hydrogen bonding interactions in both the 13/4- and 4/1-helices by effect of the polarity of the environment. A molecular drawing of the three helices is given in Figure 4, showing their essential hydrogen bond parameters. As can be seen, the 7/2-helix adopts a hydrogen bonding scheme which is at half-way between those of the 13/4- and 4/1-helices. In summary, the present results reveal that an increment of the polarity of the medium stabilizes the 7/2-helix with respect to the 13/4- and 4/1-helices.

Conclusions

The results of the present work clearly indicate that the stabilization of the different minima of *N*-acetyl-*N*′-methyl-α-methyl-L-aspartamide is due to two driving forces: (i) intramolecular hydrogen bonds and (ii) repulsive interactions between oxygen atoms. These interactions permit characterization of 13 minima on the potential energy hypersurface $E = E(\varphi,\xi,\psi)$ at the HF/6-31G(d) level. Single point calculations at the MP2/6-31G(d) level indicate that in this model compound the helical conformation usually found in poly(*β*-L-aspartate)s is 6.0 kcal/mol less stable than the global minimum.

SCRF calculations using the MST/AM1 model permit one to estimate the effects played by the aqueous and CCl_4 solvents on the conformational preferences of *N*-acetyl-*N*′-methyl-α-methyl-L-aspartamide. Results indicate that the potential energy hypersurfaces in both gas-phase and CCl_4 solution are very similar, whereas polar solvents have a dramatic effect on the conformational energy of the solute. The different behavior of the solvents has been rationalized in terms of the electronic structure of the H_2O and CCl_4 molecules. The quantification of the solvent effects on the conformational energy of the basic unit of poly(*β*-L-aspartate)s provides useful insights that help us to understand the conformational transitions observed in this family of polyamides. Moreover, calculations on small oligopeptides of both PAIBLA and PANBLA enable us to rationalize in part the occurrence of the transition induced by the action of low molecular weight alcohols.

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