Helix Sense in Poly(*β*-alkyl α-L-aspartate)s

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ABSTRACT: Energy calculations have been carried out for several oligomeric peptides derived from *β*-methyl α-L-aspartate, *β*-ethyl α-L-aspartate, and *β*-propyl α-L-aspartate. *Self-consistent field* calculations have revealed the favored helix sense for such compounds, while *self-consistent reaction-field* calculations have indicated the influence exerted by the solvent on their conformational preferences. The right-handed α-helix was found to be the most favored conformation for both the ethyl and propyl derivatives. On the contrary, the conformation preferred by the methyl derivatives was the left-handed *ω*-helix. The influence of the interactions between the amide and ester groups on the helical sense preferences displayed by these compounds are discussed.

Introduction

It is widely known that helical polypeptides made up of α-amino acids in the L-configuration usually prefer the right-handed conformation.[1,2] However poly(α-L-aspartate)s (Figure 1a) deviate from the standard pattern being able to form both right- and left-handed helices. A good illustrating example is provided by poly(*β*-benzyl α-L-aspartate). This poly(α-L-amino acid) adopts the right-handed α-helical conformation in films casted from chloroform, which reverses into the left-handed one when the sample is stretched out. The left-handed sense is retained when the α-helix is converted into the *ω*-helix by heating.[3,4] On the other hand poly(*β*-alkyl α-L-aspartate)s display a conformational behavior which appears to be, in terms of helical handedness, highly sensitive to the nature of the side group.[5−9] Whereas the α-helix of both the ethyl and *n*-propyl derivatives has the expected right-handed sense, the α-helix of poly(*β*-methyl α-L-aspartate) turns out to be left-handed. Furthermore, recent studies on poly(*β*-*n*-propyl α-L-aspartate) have revealed that the sense of the α-helix made of this polymer, which is originally right-handed, may be inverted when subjected to increasing temperature.[10,11]

The peculiar behavior exhibited by poly(*β*-alkyl α-L-aspartate)s concerning the handedness of the α-helix was investigated by Scheraga and co-workers by both experimental methods[12] and force-field calculations.[13−18] In all cases except one of the polymers studied, *i.e.*, poly(*β*-ethyl α-L-aspartate), theoretical results were in agreement with experimental data. The authors found that there is a relationship between the conformation of the side chain and the preference for a given helix sense. Thus, side chain conformations were classified as either *transverse*, for which side chains wrap tangentially about the backbone at right angles to the helix axis, or *longitudinal*, for which side chains are nearly parallel to the helix axis. For poly(*β*-alkyl α-L-aspartate)s with short side chains, the *longitudinal* conformation was energetically favored, whereas for polymers with longer side chains the *transverse* conformation was preferred. However, they failed in explaining the conformational preferences of poly(*β*-ethyl α-L-aspartate).[15] This such discrepancy was attributed by the authors to the fact that side chains in poly(*β*-ethyl α-L-aspartate) stand halfway between the *longitudinal* and the *transverse* conformations.

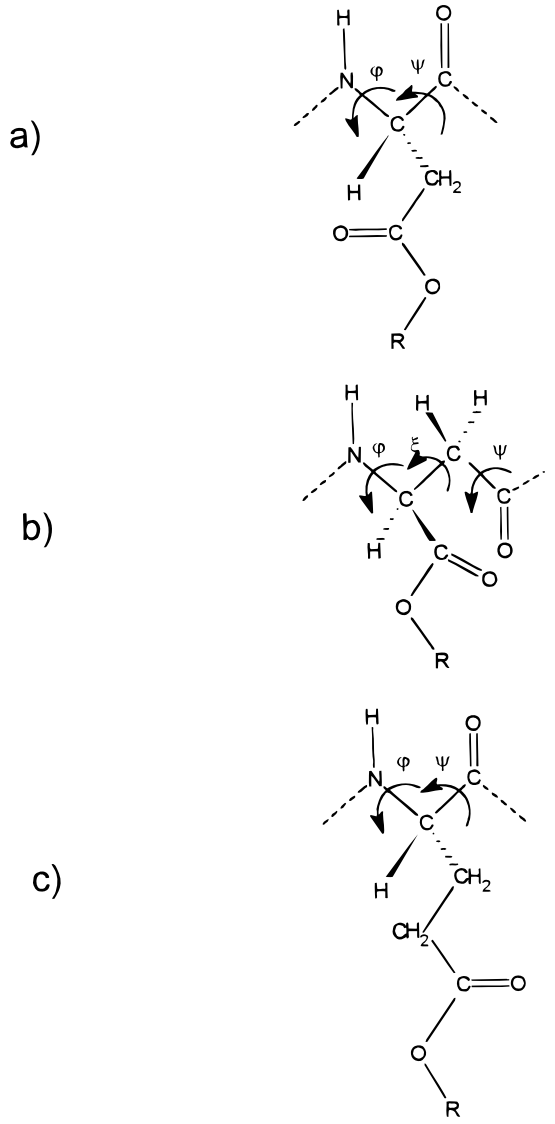

Figure 1. Repeating units of (a) poly(*β*-alkyl α-L-aspartate)s, (b) poly(α-alkyl *β*-L-aspartate)s, and (c) poly(*γ*-alkyl α-L-glutamate)s.

Poly(α-alkyl *β*-L-aspartate)s (Figure 1b) are positional isomers of the corresponding poly(*β*-alkyl α-L-aspartate)s, which are able to adopt helical structures stabi-

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lized by intramolecular hydrogen bonds with features similar to the α- and ω-helices. During the last decade, our group has carried out an extensive investigation on the conformation of these compounds by means of diffraction methods, molecular mechanics, and dynamics simulations.[19−24] As a result, several structural models, all of them based on right-handed helices, have been proposed for this family of polymers. This is striking since the spatial orientation of the side group in these helices turns to be the same as that found for the side group in a right-handed helix made up of α-amino acids in the D-configuration. Such an apparent anomaly was recently investigated by quantum mechanical calculations.[25,26] Results indicated that a right-handed helix is the conformation preferred by poly(β-L-aspartate)s due to the occurrence of additional stabilizing intramolecular interactions taking place between the amide group in the main chain and the carbonyl oxygen in the side chain.

In poly(β-alkyl α-L-aspartate)s the ester side group is spaced from the main chain by only one methylene unit. The spatial distance between the amide and the ester groups in these polypeptides is still short enough so as to be reasonable to consider intramolecular amide-ester interactions responsible, at least in part, for their helical sense preferences, in a manner similar to what happens in poly(β-L-aspartate)s. This could account for the complex conformational pattern of behavior exhibited by some poly(α-L-aspartate)s. The fact that poly(γ-alkyl β-L-glutamate)s (Figure 1c) appear to adopt invariably right-handed helices is consistent with such reasoning. In this case the ester side group is separated from the backbone carbon atom by two methylene units, making the existence of amide−ester interactions difficult.

The aim of this work is to provide a better understanding of the conformational preferences displayed by poly(β-alkyl α-L-aspartate)s as well as to disclose what the influence exerted by the different alkyl side groups on such preferences is. Quantum mechanical calculations in both the gas phase and aqueous solution were performed in order to predict the helical sense as a function of the length of the polypeptide chain. Three systems were subjected to examination, *i.e.*, methyl, ethyl and *n*-propyl derivatives, which have been abbreviated poly(βMeαAsp), poly(βEtαAsp), and poly(βPrαAsp), respectively. Although most of the experimental data and theoretical studies concerning the helical sense in poly(α-L-aspartate)s reported in the literature refers to the α-helix, some evidence in support of the stabilization of the ω-helix of poly(MeαAsp) in solution has been also published.[5,6] Due to the relevance of these observations to our study, the analysis of the ω-helix has been performed for the case of the methyl derivative.

Methods

Helical Conformations. Homopeptides were built in the right-handed α-helical conformation with the backbone dihedral angles φ and ψ fixed at −51.4 and −52.7°, respectively. The left-handed conformation was generated using the same backbone dihedral angles but with opposite sign. These values, which are close to the standard dihedral angles in the α-helix conformation, were chosen since they define good geometries for the intramolecular hydrogen bonds [d(N···O) = 3.1 Å, ∠N−H···O = 165°]. In addition, an ω-helix[27] defined by φ, ψ = −62.8, −54.9° was also considered for poly(βMeαAsp), since this is the conformation which seems to be present in solution for such compound. Homopeptides comprised of *n* residues were built for poly(βMeαAsp) and poly(βEtαAsp), with *n* ranging from 1 to 9 for the former and from 1 to 7 for the latter. Furthermore, oligopeptides with five residues were generated for poly(βPrαAsp). Note that the size of the side group is the factor limiting the number of residues of the peptide that can be subjected to quantum mechanical calculations, even at the semiempirical level.

Gas-Phase Calculations. Due to the large size of the compounds under study, quantum mechanical calculations can not be performed at the ab initio level, so they were performed at the semiempirical AM1[28] level. This is a well-known method which provides a satisfactory description of both molecular geometries and energies for helices stabilized by intramolecular hydrogen bonds.[29−31] Only the backbone dihedral angles (φ, ψ) were kept fixed at the values stated previously. Such optimization constraints were required in order to compare the residue propensity toward one or another helix sense. However, the implications associated with the use of geometry constraints were investigated for an homopeptide of poly(βMeαAsp) with six residues. For this compound the molecular geometries of the α- and ω-helices in both the right- and left-handed arrangements were fully optimized. A molecular mechanics correction was applied to the amide bond in the geometry optimizations by using the MMOK correction.

Aqueous-Phase Calculations. The free energies of solvation were determined using a semiempirical AM1 adapted version[32,33] of the SCRF developed by Miertus, Scrocco, and Tomasi (MST).[34,35] SCRF methods simulate the average effect of the solvent on the solute by means of the solvent reaction field induced by the solute molecule. These models assume that the solute is embedded inside a cavity surrounded by an infinite medium (the solvent), which is characterized by suitable physical properties like the permittivity or the thermal expansion coefficient. The AM1/MST method was parametrized to reproduce free energies of solvation in aqueous solution. The root mean square deviation with respect to experimental data was around 1 kcal/mol,[32,33] which supports the suitability of the method to describe solvation in large molecular systems. In the MST/AM1 method the free energy of solvation is given by the addition of electrostatic and steric contributions (eq 1), where the latter term was computed as the sum of cavitation and van der Waals terms.

$$\Delta G_{sol} = \Delta G_{ele} + \Delta G_{cav} + \Delta G_{vdW} \quad (1)$$

The cavitation term was determined using Pierotti's scaled particle theory,[36] while the van der Waals term was evaluated (eq 2) by means of the molecular surface area,[33] where ξ_i is

$$\Delta G_{vdW} = \Sigma \xi_i S_i \quad (2)$$

the hardness of atom *i* and S_i is the portion of the molecular surface area belonging to atom *i*.

The electrostatic term, which represents the interaction between the charge distribution of the solute and the reaction field generated by the solute in the solvent, was computed using the MST−SCRF method. In this approach, the solvent reaction field was determined from the solute electrostatic potential computed at the AM1 level using the *ortho* method. The self-consistent nature of the method stems from the mutual dependence between the solute charge distribution and the reaction field. The solute/solvent interface was determined using a molecular shape algorithm. Calculations were performed using the parametrization for the united-atom model recently developed by Orozco and co-workers.[37] Since the change in the molecular geometry upon solvation is known to have a negligible effect on the thermodynamic parameters,[30,38,39] molecular geometries optimized in the gas phase were kept fixed in SCRF calculations.

AM1 calculations were carried out with a modified version of the MOPAC[40] program. All calculations were run on a Silicon-Graphic RI-4000 at our laboratory, and on a CRAY-YMP at the Centre of Supercomputació de Catalunya (CESCA).

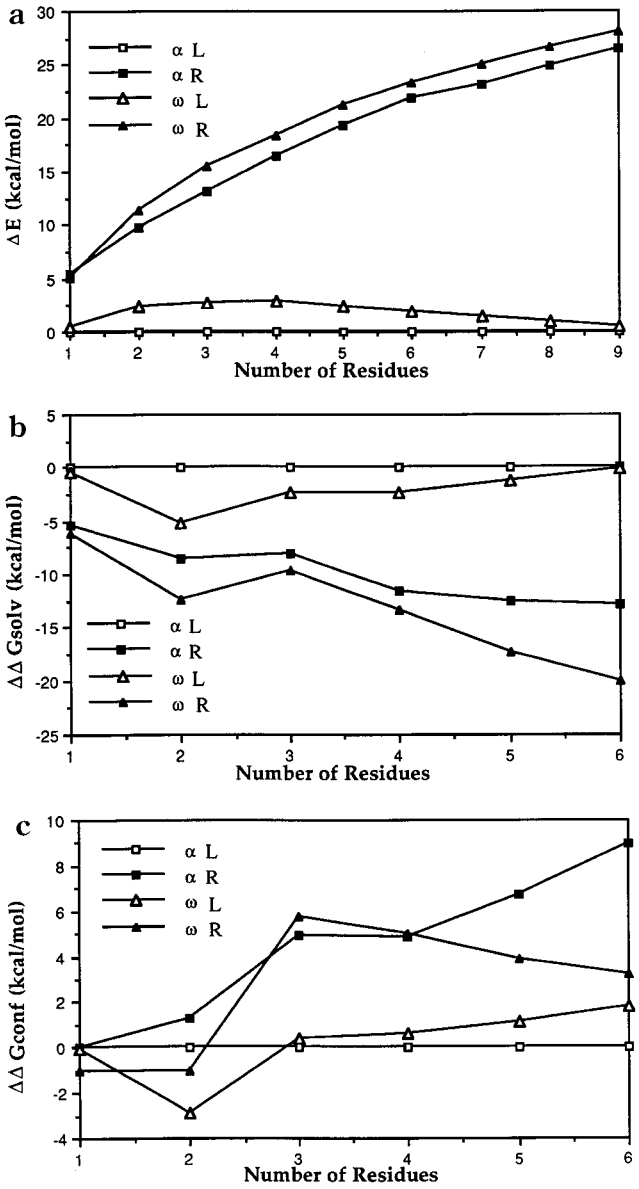

Figure 2. Enthalpies (a), solvation free energies (b), and conformational free energies (c) of the right- and left-handed α- and *ω*-helices of poly(*β*MeαAsp). The molar basis for the energies is the oligopeptide with *n* residues.Values are relative to the left-handed α-helix.

Results and Discussion

Poly(*β*-methyl α-L-aspartate). Constrained Helical Geometries. The change in gas-phase relative enthalpies obtained for helical structures as a function of the number of *β*MeαAsp residues is shown in Figure 2a. Enthalpy differences were determined relative to the enthalpy of formation of the left-handed α-helix, which was the most favored structure irrespective of the length of the peptide chain. The destabilization of the right-handed helices relative to the left-handed ones increases with the number of residues. Such effect seems to arise from the extra interaction taking place between the amide and the ester groups in the left-handed helices. Figure 3 shows both the left- and the right-handed α-helices for the oligopeptide made up of nine residues. Note that in the left-handed helix, the amide group of the *i* residue interacts with the ester group of the same residue, with an average distance between the main amide hydrogen and the carbonyl oxygen of the ester group of 3.09 Å. In contrast,

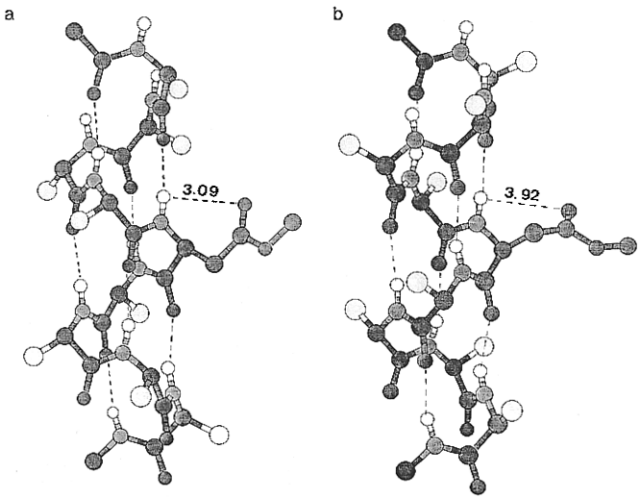

Figure 3. Left- (a) and right-handed (b) α-helices for the oligopeptide with nine residues of poly(*β*MeαAsp). For clarity aliphatic hydrogen atoms have been removed and the side chains have been substituted by a gray single sphere, with the exception of the central residue in which the amide···ester interaction is indicated.

amide···ester interactions are hindered in the right-handed helices, where the average N—H···O=C distance is 3.92 Å. Note that for the left-handed α-helix the carbonyl side groups are arranged almost parallel to the axis of the helix, while in the right-handed conformation they are oriented perpendicular to the axis of the helix. Consequently, distances between the amide and ester groups are larger in the latter than in the former. Similar results were obtained by Scheraga and co-workers,[13] who found that for this polymer the interaction of the dipole of the side ester group with the dipole of the backbone amide group is more favored for the left-handed helix than for the right-handed one.

Comparison between the relative enthalpies obtained for the left-handed α- and *ω*-helices reveals that the α-helix is favored with respect to the *ω*-helix for a small number of residues, but this preference vanishes as the length of the peptide increases. According to the trend observed for enthalpies, it may be anticipated that the relative stability of these two helices reverses for $n > 10$. A similar feature was recently found in poly(dehydroalanine),[30] a polyamide with a methylene side group on the α-carbon. In this case, the stability of the 3_{10}-helix with respect to the 2_7-ribbon structure was found to increase with the number of residues in the polypeptide. Such stabilization was attributed to the presence of the $C^{\alpha}=C^{\beta}$ double bonds, which induce significant noncovalent interactions through their negative *π*-region when the helix has an integral number of residues per turn. This situation has a parallel in the *ω*-helix of poly(*β*MeαAsp), *i.e.*, a helix with four residues per turn (Figure 4), since electrostatic interactions between the ester groups of residues *i* and $i + 4$ are expected to operate in such conformation. On the other hand the left-handed *ω*-helix presents amide···ester interactions similar to those described above for the α-helix, the average distance between the hydrogen and the oxygen atoms being 2.97 Å. These results agree with the observations on poly(*β*MeαAsp) reported by Goodman and co-workers,[5] who found that the *ω*-helix is the conformer present in both films and apolar solvents.

The changes in ΔG_{sol} with the number of residues in a chain of poly(*β*MeαAsp) are shown in Figure 2b)

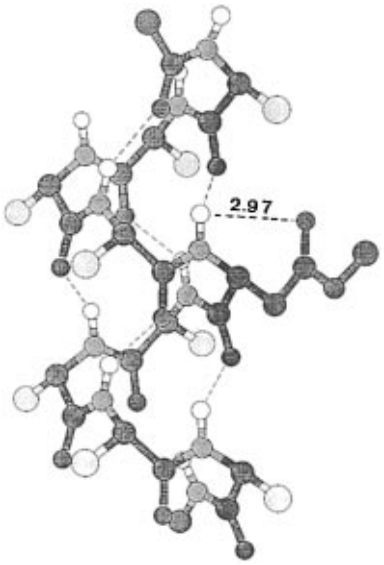

Figure 4. Equatorial projection of the left-handed ω-helix for the oligopeptide with nine residues of poly(βMeαAsp). For clarity aliphatic hydrogen atoms have been removed and the side chains have been substituted by a gray single sphere, with the exception of the central residue in which the amide···ester interaction is indicated.

Table 1. Electrostatic (ΔG_{ele}) and Steric [van der Waals + Cavitation; ΔG_{ster}] Contributions to the Free Energy of Solvation (ΔG_{sol}) in Aqueous Solution for the α- and ω-Helices (L and R Refer to Left- and Right-Handed, Respectively) of Poly(βMeαAsp) Containing 6 Residues (All Values in kcal/mol)

helix	ΔG_{ele}	ΔG_{ster}	ΔG_{sol}	$\Delta\Delta G_{sol}$[a]	$\Delta\Delta G_{conf}$[b]
α_L	−56.0	6.2	−49.8	0.0	0.0
α_R	−70.5	8.0	−62.5	−12.7	8.9
ω_L	−55.7	5.9	−49.8	0.0	1.8
ω_R	−77.6	7.7	−69.9	−20.1	3.2

[a] $\Delta\Delta G_{sol} = \Delta G_{sol}(\text{helix}) - \Delta G_{sol}(\alpha_L)$. [b] $\Delta\Delta G_{conf} = \Delta H + \Delta\Delta G_{sol}$, where ΔH refers to the gas-phase relative energy.

(relative to the left-handed α-helix). The calculations were limited to homopeptides containing up to six residues, since SCRF calculations for longer chains will require a considerable computational effort. However, the influence of solvation in aqueous solution exhibited a well-defined and continous trend when the number of residues was larger than three, making unnecessary the computation of ΔG_{sol} beyond the hexapeptide. Another feature of significance in the representation of Figure 2b is that the right-handed helices are better solvated than the left-handed ones.

Table 1 displays the different contributions to ΔG_{sol} for the homopeptide with six residues. The results disclose that the origin of the difference between the left-handed and right-handed helices lies in the electrostatic term, which clearly destabilizes the former with respect to the latter. These features can be explained on the basis of the dipole moment resulting for the different helical structures. In the homopeptide with six residues, the dipole moments of the right-handed arrangements (24.89 and 25.78 D for the α- and ω-helices, respectively) are about twice those present in the left-handed helices (13.45 and 12.22 D for the α- and ω-helices, respectively). On the other hand, the influence of the nonelectrostatic term on the relative free energy of hydration in poly(βMeαAsp) is much less noticeable (about 2 kcal/mol). Another significant feature that can be drawn from results in Table 1 and Figure 2b is the stabilization of the ω-helix with respect to the α-helix. The analysis of the different contributions to ΔG_{sol} reveals that such a trend should be also explained in terms of solute−solvent electrostatic interactions.

Table 2. Backbone Dihedral Angles (deg) and Relative Enthalpies (kcal/mol) for the Fully Relaxed α- and ω-Helices (L and R Refer to Left- and Right-Handed, Respectively) of Poly(βMeαAsp) Containing Six Residues (Relative Enthalpies (kcal/mol) Obtained from Constrained Geometry Calculations Included for Comparison)

helix	φ	ψ	ω	ΔH_r[a]	ΔH_c[a]
α_L	50.3	46.0	−172.0	0.0	0.0
α_R	−56.4	−41.6	172.3	21.5	21.8
ω_L	66.2	57.5	178.4	2.2	1.8
ω_R	−71.2	−34.7	175.7	19.2	23.3

[a] ΔH_r and ΔH_c refer to the relative enthapies computed from complete and constrained geometry optimizations, respectively.

Figure 2c shows the differences in ΔG_{conf} in aqueous solution with the number of residues relative to the values of the left-handed α-helix. It is seen that the left-handed conformations are more stable than the right-handed ones no matter what the symmetry of the helix is, provided that the number of residues is larger than three. These results agree with published optical rotatory dispersion measurements made in different polar solvents, which indicate that large oligomers and polymers derived from β-methyl α-L-aspartate adopt the left-handed conformation.[5]

Relaxed Helical Geometries. The results presented in the previous section were obtained on the assumption that the right- and left-handed helices have equal but opposite sign backbone angles. In order to ascertain the effects of such simplification on the results obtained for poly(βMeαAsp), molecular geometries were fully optimized for a homopeptide with six residues. Results for the four helical arrangements considered in the present work are listed in Table 2. Note that the absolute values of the backbone dihedral angles obtained for the right- and left-handed α-helices are very similar, the maximum deviations with respect to the values used in contrained geometry optimizations concerning the angle ψ (11.1 and 6.7° for the right- and left-handed helices respectively). On the other hand, differences between the two helical senses are considerably larger for the ω-helices than for the α-helices. Thus, although optimized values for the backbone dihedral angles of the left-handed ω-helix are very similar to those used in the constrained calculations, a large distortion occurs for the right-handed ω-helix due to its intrinsic low stability.

Enthalpy differences relative to the left-handed α-helix for both constrained and fully-relaxed geometries are included in Table 2. It is worth it to note that the effect of geometry relaxation on the results is almost negligible for the more stable conformations. Thus, the left-handed α-helix was predicted to be the most favored conformation, the left-handed ω-helix being unfavored by 2.2 kcal/mol with respect to the global minimum. On the other hand, the right-handed helices are about 20 kcal/mol less favored than the left-handed ones, in good agreement with the results obtained from constrained geometry optimizations.

Poly(β-ethyl α-L-aspartate). The results in the gas-phase for poly(βEtαAsp) obtained in a manner similar to that described above for poly(βMeαAsp) are shown in Figure 5a. Enthalpy differences were determined relative to the enthalpy of formation of the right-handed

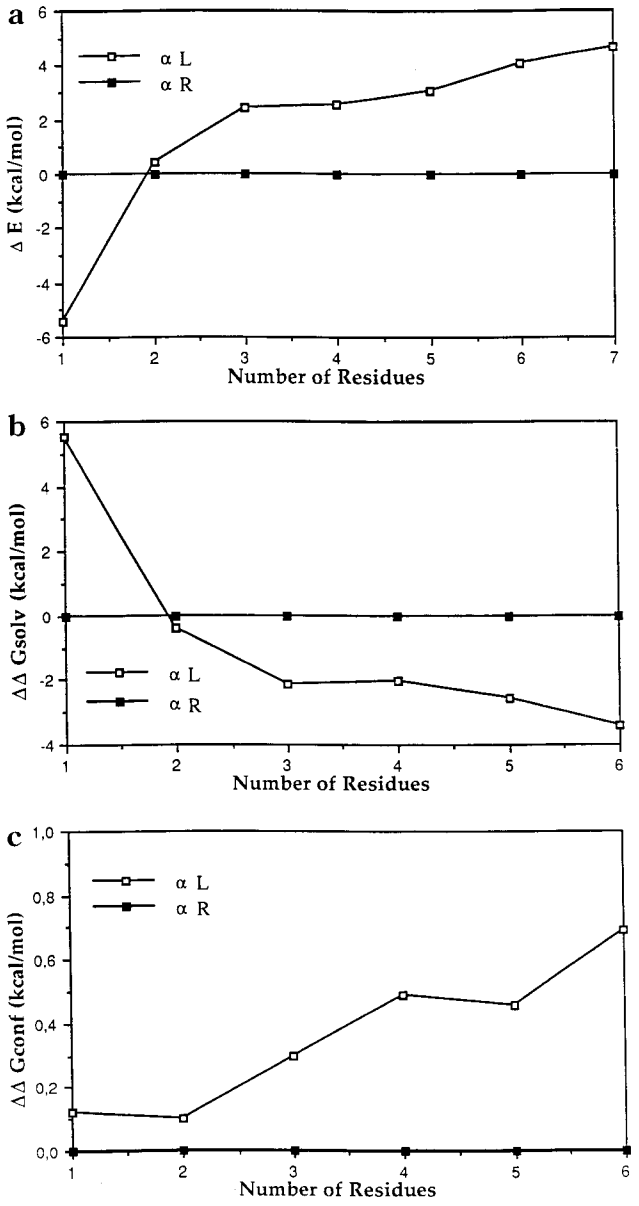

Figure 5. Enthalpies (a), solvation free energies (b), and conformational free energies (c) of the right- and left-handed α-helices of poly(βEtαAsp). The molar basis for the energies is the oligopeptide with *n* residues.Values are relative to the right-handed α-helix.

α-helix, which was the most favored structure except for the single amino acid. The destabilization of the left-handed helix was found to increase with the peptide length, but the energy differences between the two conformers are smaller than in the case of poly-(βMeαAsp). This effect seems to be due to the fact that with the ethyl side chain the extra interaction between amide and ester groups is compatible with both right and left-handed helical arrangements. The average distances between the hydrogen and oxygen atoms are 3.03 and 3.08 Å for the right- and left-handed helices, respectively. In this case the two conformations have the carbonyl side groups parallel to the axis of the helix. This means that amide···ester interaction equally operates in both helical forms. In other words, the intrinsic relative stability of the right-handed helix to the left-handed one is not altered, and the energy difference between the two conformations remains similar to that usually observed for homopeptides constituted by α-L-amino acids.[15]

Table 3. Electrostatic (ΔG_{ele}) and Steric [van der Waals + Cavitation; ΔG_{ster}] Contributions to the Free Energy of Solvation (ΔG_{sol}) in Aqueous Solution for the α-Helices (L and R Refer to Left- and Right-Handed, Respectively) of Poly(βEtαAsp) Containing Six Residues (All Values in kcal/mol)

helix	ΔG_{ele}	ΔG_{ster}	ΔG_{sol}	$\Delta\Delta G_{sol}$[a]	$\Delta\Delta G_{conf}$[b]
α_L	−56.6	4.6	−51.9	−3.4	0.7
α_R	−53.4	4.8	−48.5	0.0	0.0

[a] $\Delta\Delta G_{sol} = \Delta G_{sol}(\text{helix}) - \Delta G_{sol}(\alpha_L)$. [b] $\Delta\Delta G_{conf} = \Delta H + \Delta\Delta G_{sol}$, where ΔH refers to the gas-phase relative energy.

Table 4. Gas-Phase Relative Energy (ΔH) and Free Energy of Solvation (ΔG_{sol}) in Aqueous Solution for the α-Helices (L and R Refer to Left- and Right-Handed, Respectively) Poly(βPrαAsp) with Five Residues (All Values in kcal/mol)

helix	ΔH	ΔG_{sol}	$\Delta\Delta G_{sol}$[a]	$\Delta\Delta G_{conf}$[b]
α_L	3.0	−44.2	−0.4	2.6
α_R	0.0	−43.8	0.0	0.0

[a] $\Delta\Delta G_{sol} = \Delta G_{sol}(\text{helix}) - \Delta G_{sol}(\alpha_L)$. [b] $\Delta\Delta G_{conf} = \Delta H + \Delta\Delta G_{sol}$, where ΔH refers to the gas-phase relative energy.

Parts b and c of Figures 5 display ΔG_{sol} and ΔG_{conf} values respectively, relative to the right-handed α-helix, and Table 3 shows the different contributions to ΔG_{sol} for the homopeptide with six residues. Results indicate that the left-handed helix is better hydrated than the right-handed one. Such difference arises from the electrostatic term, which is larger for the former than for the latter. Dipole moment values agree with such variation (16.78 and 15.80 D for the left- and right-handed arrangements respectively). However, the right-handed α-helix is the favored conformation in solution since the positive value of $\Delta\Delta G_{sol}$ is not large enough to offset its intrinsic stability. Note that the stability of the right-handed helix with respect to the left-handed one increases with the peptide length. The results are in agreement with the reported experimental data, which indicate that poly(βEtαAsp) adopts the right-handed α-helical conformation at room temperature, which exchanges to the left-handed form by temperature effects.[6]

Poly(β-propyl-α-L-aspartate). No intramolecular interactions between the amide and ester groups were found after geometry optimization in either of the two helical conformations for this polypeptide. Energies (relative to the right-handed α-helix) for the oligopeptide with 5 βPrαAsp residues are displayed in Table 4. Note that in the gas phase the right-handed α-helix is favored by 3 kcal/mol with respect to the left-handed one. Although hydration slightly favors the left-handed helix, ΔG_{conf} differences clearly indicate that the right-handed conformation remains as the most stable arrangement in aqueous solution.

Poly(γ-methyl-α-L-glutamate). Gas-phase calculations were performed for the right- and left-handed α-helices of a model compound constituted by five residues of γ-methyl α-L-glutamate. The right-handed conformation was found to be favored with respect to the left-handed one by 3.4 kcal/mol. The average N—H···O═C distance between the amide and ester groups is 4.3 Å, indicating that the ester groups are too far from the main chain to introduce any energy additional contribution.

Conclusions

In this work we have presented a theoretical study on the conformational preferences of poly(βMeαAsp),

poly(βEtαAsp), and poly(βPrαAsp). The most remarkable result of this study is that concerning intermolecular interactions taking place in poly(βMeαAsp) and poly(βEtαAsp). Such interactions occur between the hydrogen atoms of the amide group and the carbonyl oxygen atoms of the ester side group. Amide···ester interactions are responsible for the stabilization of the left-handed helix in poly(βMeαAsp). In this compound the conformation of the side chain changes with the helix sense so that amide···ester interactions are precluded when the polypeptide adopts the right-handed conformation. In the case of β-ethyl α-L-aspartate oligomers, both right- and left-handed helices are able to present amide···ester interactions. On the contrary, in the case of the propyl derivative neither of the two conformations present additional interactions between the main chain and the side groups. As a consequence the right-handed helix is the stabilized conformation for both poly(βEtαAsp) and poly(βPrαAsp), as is usual in poly(α-L-amino acid)s. The conformational preferences predicted for the three compounds under study are in excellent agreement with the experimental data reported for poly(β-alkyl α-L-aspartate)s by different authors.

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