A Conformational Study of the α-L-Aspartate-Containing Dipeptide

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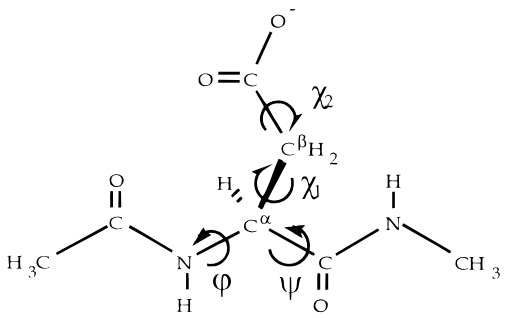
The conformational preferences of the α-L-aspartate-containing dipeptide were investigated by ab initio calculations. The structures of the minima were generated by full geometry optimization at the HF/6-31G(d) and HF/6-31+G(d) levels of 27 starting geometries, resulting from the systematic combination of the three minima associated with the flexible dihedral angles φ, ψ, and χ_1. The energies of the resulting minima were computed at the MP2/6-31+G(d) level. Selected minima were used as starting points for geometry optimization at the MP2/6-31+G(d) level. The conformational behavior of this compound was markedly different from that of the model dipeptides composed of common α-amino acids. Thus, the charged side chain produces substantial changes in the potential energy hypersurface with respect to those observed in other compounds with neutral polar side chains, such as the L-asparagine-containing dipeptide.

Introduction

The theoretical study of the potential energy hypersurface (PEHS) of model dipeptides has become a topic of interest in recent years. This is because such studies allow one to answer satisfactorily two fundamental issues: (i) the intrinsic conformational preferences of the amino acids contained in the dipeptide, i.e., those associated with the amino acid by itself without considering long-range interactions, and (ii) the changes induced by the interaction between the side chain and the backbone in the PEHS. The glycine- and L-alanine-containing dipeptides have been extensively investigated,[1] as they were chosen as the most simple model systems for representing the conformational preferences of the common substituted amino acids. However, the conformational preferences of model dipeptides composed of other amino acids, such as some of the remaining 18 common amino acids,[2] α,α-dialkylated amino acids,[3] β-amino acids,[4] etc., have also been investigated. These works have provided evidence that polar side chains have a strong influence on the conformational preferences of peptide systems.[2,4a,4c]

Among the amino acids with polar side chains, those with ionizable side groups are particularly relevant, as they are involved in salt bridges. These interactions have been thoroughly studied because of the important and often quite specific biological functions played by ion pairs.[5] Nevertheless, despite their importance, the intrinsic conformational preferences of the amino acids involved in salt bridges remain unknown at the present moment. In this work, the PEHS of the L-aspartate-containing dipeptide (**1**) has been investigated, allowing a comparison with the results obtained for other model dipeptides.

The compound of interest was chosen because, in addition to the charged side chain, it presents a sequence of atoms with special conformational properties. This is the C(=O)−C^{α}−C^{β}−C(=O) moiety, in which two carbon atoms with sp^3 hybridization are situated between two carbonyl groups. It was recently found that, in this sequence, the carbonyl group induces rotation toward the gauche conformation of the C^{α}−C^{β} bond.[6] This folding has been observed in a variety of compounds involving such a sequence like amides,[6a,6b] ketones,[6c] and esters,[6d] as well as the L-asparagine-containing dipeptide (**2**).[2c] According to the similarities between **1** and **2**, i.e., both dipeptides contain a polar side group and the C(=O)−C^{α}−C^{β}−C(=O) sequence, a special emphasis has been given to the comparison of their PEHSs.



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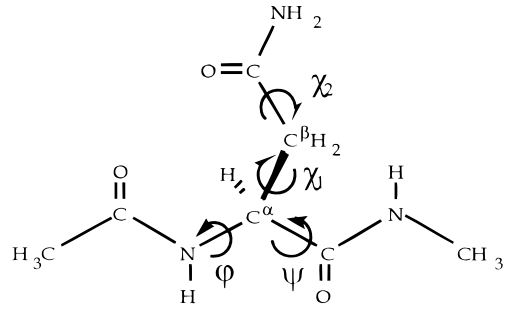

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Methods

All ab initio calculations were carried out using the Gaussian 94 molecular orbital package.[7] A systematic exploration of the conformational space was performed in order to characterize

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TABLE 1: Minima[a] Obtained from HF/6-31G(d) Geometry Optimizations

structure	ω_1	φ	ψ	ω_2	χ_1
α_R/g^+	179.8	−97.6	−49.2	−172.1	50.7
C_5/t	177.7	−153.5	168.0	173.8	−165.7
P_{II}'/t	160.4	−78.9	168.5	174.6	−161.5
α_R/g^-	−161.0	−71.2	−31.2	174.0	−53.1
C_{7eq}/g^-	161.6	−86.7	73.3	−172.5	−48.9
C_{7eq}/g^+	−176.2	−84.8	46.6	173.0	47.6
P_{II}/t	−157.6	66.6	−177.4	−175.4	−148.3
C_{7ax}/g^-	150.5	73.9	−39.5	−175.3	−56.8
α_L/g^-	153.3	60.1	39.1	−170.0	−57.2
α_L/g^+	136.4	37.7	1.5	−176.6	57.3

[a] Dihedral angles in units of degrees.

the minimum energy conformations of **1**. Because each of the three flexible dihedral angles φ, ψ, and χ_1 is expected to have three minima, 27 minima can be anticipated for the PEHS $E = E(\varphi,\psi,\chi_1)$. The dihedral angle χ_2 was initially considered in the trans conformation. All of these structures were taken as starting points in HF/6-31G(d) geometry optimizations.[8] The resulting structures were reoptimized at the HF/6-31+G(d) level[9] of theory to explore the effect of added diffuse functions for heavy atoms on both molecular geometries and conformational energies. Frequency analyses were performed to verify the nature of the minimum state of the stationary points located during both the HF/6-31G(d) and the HF/6-31+G(d) geometry optimizations, as well as to obtain zero-point energies and thermal corrections to the energy. To explore the effects of electron correlation on the conformational energies, single-point calculations at the MP2/6-31+G(d) level[10] were performed on both the HF/6-31G(d) and the HF/6-31+G(d) minima. Furthermore, selected structures were also reoptimized at the MP2/6-31+G(d) level.

Results and Discussion

Influence of the Level of Theory on the Molecular Geometries and Conformational Energies. Geometry optimizations at the HF/6-31G(d) level provided 10 minima, whose dihedral angles are displayed in Table 1. These structures were labeled according to the backbone and side chain conformations associated with such dihedral angles. As is common in the conformational studies of model dipeptides,[1−3] the backbone conformations were classified as follows: $C_{7,eq}$ (seven-membered intramolecular hydrogen-bonded ring; φ, $\psi \approx -60°$, 60°), $C_{7,ax}$ (φ, $\psi \approx 60°$, −60°), C_5 (five-membered intramolecular hydrogen-bonded ring; φ, $\psi \approx 180°$, 180°), α_L (φ, $\psi \approx$ 60°, 60°), α_R (φ, $\psi \approx -60°$, −60°), P_{II} (φ, $\psi \approx 60°$, 180°), and P_{II}' (φ, $\psi \approx -60°$, 180°). The side chain conformation was described as gauche$^+$ (g^+), skew$^+$ (s^+), trans (t), skew$^-$ (s^-), or $^-$ (g^-) depending on the value of the dihedral angle χ_1. As can be seen in Table 1, only 4 of the 10 minima are stabilized by interactions between the two backbone amide groups (C_5/t, C_{7eq}/g^-, C_{7eq}/g^+, and C_{7ax}/g^-). The remaining minima correspond to helical (α_R/g^+, α_R/g^-, α_L/g^-, and α_L/g^+) and semiextended (P_{II}'/t and P_{II}/t) structures.

The HF/6-31G(d) structures were used as starting points for full optimization at the HF/6-31+G(d) level, with the resulting stationary points being minima, as above. The dihedral angles of the HF/6-31+G(d) minima are listed in Table 2. As can be seen, the HF/6-31+G(d) results are extremely close to the HF/6-31G(d) results. Thus, the mean change in the dihedral angles is less than 3°, and the largest change, which corresponds to the α_L/g^+ minimum, is 10.1°.

The conformational energies obtained at different levels of theory for both the HF/6-31G(d) and the HF/6-31+G(d) minima are listed in Table 3. It is worth noting that the structures optimized with the 6-31G(d) and 6-31+G(d) basis sets provide very similar relative energies at both the HF/6-31+G(d) and MP2/6-31+G(d) levels. Accordingly, it can be concluded that the additional diffuse function led to very small changes in the molecular geometries. However, such a diffuse function plays an essential role in the conformational energies, which is even greater than that of electron correlation. Thus, the difference between the HF/6-31G(d) and HF/6-31+G(d) energies is larger than the difference between the HF/6-31+G(d) and MP2/6-31+G(d) energies. It is also clear from Table 3 that electron correlation does not introduce major changes in the energy order of the different structures. Thus, there is only one change that occurs between the α_R/g^- and C_{7eq}/g^- minima.

TABLE 2: Minima[a] Obtained from HF/6-31+G(d) Geometry Optimizations

structure	ω_1	φ	ψ	ω_2	χ_1
α_R/g^+	−179.8	−98.2	−48.7	−172.7	51.2
C_5/t	177.3	−150.3	166.5	173.2	−166.3
P_{II}'/t	162.7	−81.9	166.0	173.9	−162.8
α_R/g^-	−161.7	−72.7	−28.9	174.5	−51.8
C_{7eq}/g^-	−165.3	−84.9	73.2	−173.5	−48.9
C_{7eq}/g^+	−175.4	−85.5	44.9	172.8	46.8
P_{II}/t	−159.7	67.3	−175.9	−175.1	−146.9
C_{7ax}/g^-	153.9	73.1	−44.3	174.5	−51.8
α_L/g^-	154.5	60.7	37.2	−171.2	−57.5
α_L/g^+	146.5	29.8	−4.6	−174.9	54.6

[a] Dihedral angles in units of degrees.

TABLE 3: Conformational Energies[a] at Different Levels of Theory for the Structures Obtained from HF/6-31G(d) and HF/6-31+G(d) Optimizations

	HF/6-31G(d) minimum[b]			HF/6-31+G(d) minimum[c]	
structure	HF/ 6-31G(d)	HF/ 6-31+G(d)	MP2/ 6-31+G(d)	HF/ 6-31+G(d)	MP2/ 6-31+G(d)
α_R/g^+	0.0	0.0	0.0	0.0	0.0
C_5/t	2.7	2.1	2.6	2.1	2.6
P_{II}'/t	3.7	3.0	4.0	3.0	4.2
α_R/g^-	5.5	4.7	5.1	4.7	5.0
C_{7eq}/g^-	6.1	5.6	5.1	5.0	4.3
C_{7eq}/g^+	6.9	6.3	6.0	6.4	6.1
P_{II}/t	8.2	8.1	8.5	8.1	8.5
C_{7ax}/g^-	9.4	8.7	8.4	8.6	8.4
α_L/g^-	10.0	9.4	9.6	9.3	9.7
α_L/g^+	22.9	22.6	21.7	22.4	21.4

[a] Conformational energies in units of kcal/mol. Reference energies (in hartrees): HF/6-31G(d)//HF/6-31G(d) = −679.710525; HF/6-31+G(d)//HF/6-31G(d) = −679.741180; MP2/6-31+G(d)//HF/6-31G(d) = −681.705294; HF/6-31+G(d)//HF/6-31+G(d) = −679.741914; and MP2/6-31+G(d)//HF/6-31+G(d) = −681.706479. [b] Zero-point energies and thermal corrections computed at the HF/6-31G(d) level are included. [c] Zero-point energies and thermal corrections computed at the HF/6-31+G(d) level are included.

To ascertain the influence of electron correlation on molecular geometries, the five most stable structures were optimized at the MP2/6-31+G(d) level. The resulting dihedral angles and conformational energies are displayed in Table 4. It is clear from the results of Tables 2−4 that the inclusion of electron correlation using the MP2 method does not produce significant changes in either the molecular geometries or the conformational energies. Thus, the largest change in the dihedral angles was 6°, and the largest change in the conformational energy was 0.3 kcal/mol. Given the very small differences between the results obtained at the MP2/6-31+G(d)//HF/6-31+G(d) and MP2/6-31+G(d)//MP2/6-31+G(d) levels, the remaining structures were not computed at the latter level of theory.

Molecular Structures and Intramolecular Interactions. The molecular structures of the 10 minima characterized at the

TABLE 4: Minima[a] Obtained from MP2/6-31+G(d) Geometry Optimizations

structure	ω_1	φ	ψ	ω_2	χ_1	ΔE^b
α_R/g^+	179.5	−99.8	−49.4	−172.9	51.5	0.0
C_5/t	175.8	−148.4	168.8	171.9	−168.3	2.7
P_{II}'/t	159.8	−76.4	167.3	172.7	−164.0	4.1
α_R/g^-	−167.8	−69.7	−28.6	171.9	−51.4	4.7
C_{7eq}/g^-	−166.3	−83.4	70.8	−172.3	−47.3	4.0

[a] Dihedral angles in units of degrees. Conformational energies in units of kcal/mol. Reference energies (in hartrees): MP2/6-31+G(d)//MP2/6-31+G(d) = −681.716008. [b] Zero-point energies and thermal corrections computed at the HF/6-31+G(d) level are included.

HF/6-31+G(d) level are displayed in Figure 1. All of the structures, with exception of α_L/g^+, which is the highest-energy structure, present an intramolecular interaction between one of the two backbone amide groups and the carboxylate side group (Figure 1). The geometric parameters for such interactions, as well as for the amide···amide interactions of the C_5 and C_7 structures, are listed in Table 5.

The lowest-energy conformation is the helical minimum α_R/g^+. This is a striking result because, for dipeptides based on α-amino acids, the lowest-energy conformation usually corresponds to either the C_5 or the C_7 conformation.[1−3] However, statistical analyses of both proteins[11] and rotamer libraries[12] indicate that Asp is frequently found forming helices. The second minimum corresponds to the C_5/t, which is about 2.7 kcal/mol disfavored with respect to the global minimum. As can be seen in Table 5, the geometric parameters for the backbone···side chain interaction are better for C_5/t than for α_R/g^+. Accordingly, the larger stability of the latter is due not to the intramolecular interaction but to the favorable interactions between the carboxylate side chain and the two peptide bond dipoles (Figure 2).

The third and fourth minima are the P_{II}'/t and α_R/g^-, respectively. These structures are close in energy, being about 4−5 kcal/mol less stable than the global minimum. The energy difference between the α_R/g^+ and α_R/g^- minima reveals the large influence of the side chain conformation on the stability of the helical conformation. The next minima are the C_{7eq}/g^- and C_{7eq}/g^+, the former being about 1.8 kcal/mol less stable than the latter. Accordingly, the side chain conformation plays a less important role in the stability of the C_{7eq} structure than in that of the α_R structure. Finally, the P_{II}/t, C_{7ax}/g^-, α_L/g^-, and α_L/g^+ are disfavored by at least 8.4 kcal/mol with respect to the global minimum. As can be noted from Table 5, the α_L/g^+ conformation does not present any intramolecular interaction. Accordingly, the difference between the energies of the α_L/g^- and α_L/g^+ minima provides an estimation of the strength of the interaction between the carboxylate side group and the backbone amide group. This is 11.7 kcal/mol, which is about twice the strength of a hydrogen bond between noncharged groups.[13]

It is well established that poly(α-L-amino acid)s usually prefer the right-handed conformation.[14] However, poly(*β*-alkyl-α-L-aspartate)s deviate from such a standard pattern, being able to form both right- and left-handed helices.[15] Thus, the conformational behavior of this family of polypeptides appears to be, in terms of helical handedness, highly sensitive to the nature of the side group. To examine the helical preferences of the α-L-aspartate residue, the α_R and α_L minima have been compared. The two α_R minima are energetically favored with respect to the α_L minima, indicating that, for this residue, the right-handed helical conformation is more stable than the left-handed conformation.

The energies of the α_R/g^+ and α_L/g^+ structures cannot be properly compared because the intramolecular interaction between the carboxylate side group and the backbone amide group does not appear in the latter conformation. However, the α_R/g^- structure is about 4.7 kcal/mol more favored than the α_L/g^- structure. This result is in excellent agreement with those recently obtained for different oligopeptides of poly(*β*-ethyl-α-L-aspartate).[16] Thus, it was predicted that, for a compound containing only one residue, the α_R is about 5 kcal/mol more stable than the α_L. These results, together with those obtained in our previous work,[16] indicate that the unusual conformational behavior observed in some poly(*β*-alkyl-α-L-aspartate)s must be related only to the alkyl group and not to the α-L-aspartate residue.

It should be emphasized that the present work reports the conformational preferences of **1** in the gas-phase and that very

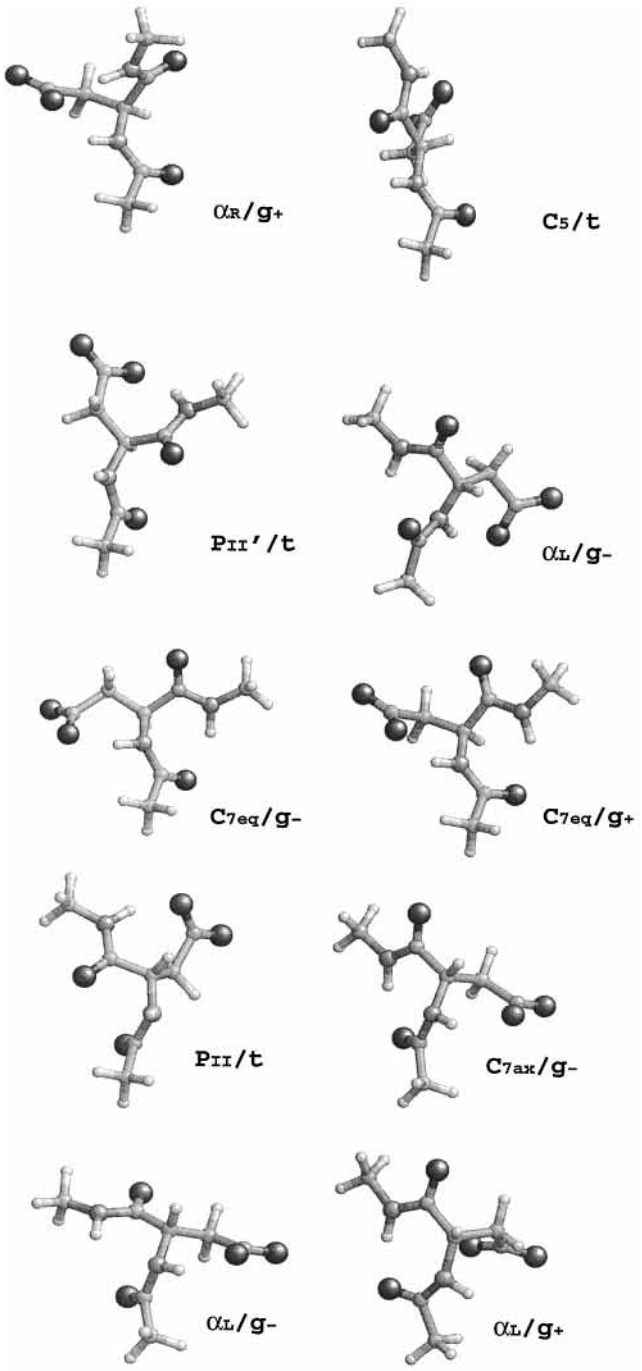

Figure 1. Minimum-energy conformations obtained at the HF/6-31+G(d) level for the α-L-aspartate-containing dipeptide. The intramolecular interactions are represented by dashed lines.

TABLE 5: Geometric Parameters[a] for the Interactions between the Carboxylate Side group and the backbone amide group, and between the two backbone amide groups

	amide···carboxylate		amide···amide	
structure	*d*(H···O)	∠N−H···O	*d*(H···O)	∠N−H···O
α_R/g^+	1.963	148.8	-	-
C_5/t	1.818	152.6	2.127	107.5
P_{II}'/t	1.867	151.1	-	-
α_R/g^-	1.818	142.1	-	-
C_{7eq}/g^-	1.859	139.4	2.005	146.5
C_{7eq}/g^+	1.798	138.5	2.152	148.1
P_{II}/t	1.807	155.4	-	-
C_{7ax}/g^-	1.882	152.4	2.158	117.5
α_L/g^-	2.022	125.7	-	-
α_L/g^+	-	-	-	-

[a] Distances and angles in units of angstroms and degrees, respectively. Molecular geometries optimized at the HF/6-31+G(d) level (Figure 1).

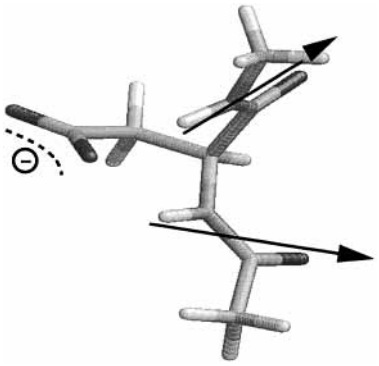

Figure 2. Schematic representation of the interaction between the charged side group and the peptide bond dipoles (solid arrows) in the α_R/g^+ conformation.

TABLE 6: Dihedral Angle[a] C(═O)−Cα−Cβ−C(═O) and Conformer Population[b] for the Minima Obtained from HF/6-31+G(d) Geometry Optimizations

structure	C(═O)−Cα−Cβ−C(═O)	*P* (%)
α_R/g^+	−75.3	99.7
C_5/t	74.6	0.1
P_{II}'/t	76.1	0.1
α_R/g^-	−176.2	0.0
C_{7eq}/g^-	−171.5	0.1
C_{7eq}/g^+	−80.5	0.0
P_{II}/t	85.7	0.0
C_{7ax}/g^-	168.5	0.0
α_L/g^-	171.9	0.0
α_L/g^+	−83.5	0.0

[a] Dihedral angle in units of degrees. [b] Population of the 10 minima at 298 K considering the energies obtained at the MP2/6-31+G(d)//HF/6-31+G(d) level (Table 3).

different results should be expected in a polar environment like an aqueous solution. Previous studies indicated that the solvent strongly modifies the conformational behavior of peptides, favoring structures without intramolecular hydrogen bonds.[2c,4,17] Thus, the latter interactions are usually replaced by solute−water hydrogen bonds. Furthermore, it should be also expected that solvation would flatten the gas-phase surface, reducing the energy gap between the different structures.[2c,4,17]

Folding of Methylene Units. The dihedral angle C(═O)−Cα−Cβ−C(═O) and the conformer population for the 10 minima characterized at the HF/6-31+G(d) level are displayed in Table 6. The conformer populations were estimated at 298 K by considering that the molar ratio of a given conformation to the most stable conformation is $\exp(-\Delta E/RT)$, where ΔE corresponds to the relative energy at the MP2/6-31+G(d)//HF/6-31+G(d) level (Table 3).

The number of minima in which the sequence C(═O)−Cα−Cβ−C(═O) adopts a trans conformation is lower than that for a folded conformation, i.e., gauche$^+$ and gauche$^-$. Furthermore, the first three minima present a folded conformation for such a sequence, i.e., one gauche$^-$ and two gauche$^+$. The population analysis indicates that only the global minimum, which presents a gauche$^-$ conformation, can exist at room temperature for **1**, as the energies of all of the other minima are too high.

Comparison with the Asparagine Dipeptide. Geometry optimizations at the HF/6-31G(d) level of the 27 minima that can be anticipated for the PEHS $E = E(\varphi,\psi,\chi_1)$ of **2** resulted in 17 minima.[2c] The lowest-energy conformation at the MP2/6-31G(d)//HF/6-31G(d) level was the C_{7eq}/g^+ conformation. The next minima was the C_5/s^-, which was 0.4 kcal/mol less stable than the global minimum. The remaining minima were destabilized with respect to the C_{7eq}/g^+ by at least 3.6 kcal/mol. The polar side chain exerts a strong influence on the conformational preferences of **2**; however, some essential structural features of the most common amino acids, like glycine and alanine, are retained. Thus, glycine- and alanine-containing dipeptides present the C_7 and C_5 as the most favored conformations.[1] Conversely, for **1**, these conformations are disfavored with respect to the global minimum by more than 2.7 kcal/mol.

On the other hand, the lowest-energy minimum for **1** is the α_R/g^+ conformation. This structure was not characterized as an energy minimum on the PEHS of **2**, the most similar minimum being the α_R/g^-. This conformation was 7.0 kcal/mol less stable than the global minimum. Accordingly, the helical conformations were strongly disfavored for **2**, in good agreement with the results found for glycine- and alanine-containing dipeptides.[1] Overall, these results indicate that the effect of the side chain on the conformational preferences of **1** is dramatic. Thus, the charged side chain strongly perturbs the conformation of this compound, its effect being significantly greater than that observed in other dipeptides with neutral polar side chains such as **2**.[2]

Conclusions

The conformational preferences of **1** have been determined by theoretical calculations at different ab initio levels. The minimum-energy conformations of this compound obtained at the HF/6-31G(d) and HF/6-31+G(d) levels are consistent with the minima optimized at the MP2/6-31+G(d) level. However, significant changes are observed in the conformational energies upon inclusion of both the additional diffuse function and the electron correlation corrections. Comparisons between the MP2/6-31+G(d)//HF/6-31+G(d) and MP2/6-31+G(d)//MP2/6-31+G(d) results indicate that the former is a suitable level of theory to study the conformational behavior of **1**.

The results obtained from ab initio calculations offer new insights into the influence of charged side chains on the conformational preferences of peptide structures. The lowest-energy minimum of **1** corresponds to the helical conformation α_R/g^+ rather than to the C_5 or C_7 structures usually found in α-amino acid-containing dipeptides. The second minimum is about 2.7 kcal/mol less stable than the global minimum, indicating the large stability of the latter. This and other distinctive structural features displayed in the previous section point out that the conformational behavior of **1** is quite different from those predicted for other dipeptides composed of α-amino acids, even from those containing polar side chains such as L-asparagine. Accordingly, it can be concluded that insertion

of a charged side chain into a peptide structure is not conformationally neutral and produces substantial changes in the peptide structure.

On the other hand, the relative energies predicted in this work for the minimum-energy conformations of **1** could be used to calibrate molecular mechanical potential functions. Thus, torsional potentials can be modified according to differences in the molecular mechanical and quantum mechanical relative energies, allowing the derivation of an improved parameter set for a protein force field.[18]

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