Conformational Properties of α-Amino Acids Disubstituted at the α-Carbon

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The conformational preferences of dipeptides from α-aminoisobutyric acid (Aib), 1-aminocyclopropane-1-carboxylic acid (Ac_3c), and 1-aminocyclobutane-1-carboxylic acid (Ac_4c) residues have been determined by ab initio quantum mechanical calculations. The results obtained evidence for the intrinsic helix-forming tendency of the Aib residue. Furthermore, the conformational preferences of Ac_3c and Ac_4c dipeptides are reported and the differences explained in terms of the size of their cyclic side chains. Finally, the large number of minima characterized for these conformationally restricted residues is explained as a function of the deformability of the molecular geometries.

Introduction

Nonstandard amino acid residues have been explicitly used in de novo approaches to peptide design.[1−3] Between them α-amino acids disubstituted at the α-carbon are of special interest since they induce severe restrictions in the backbone conformation. Thus, α,α-disubstituted amino acid residues are widely used in the synthesis of enzyme-resistant agonist and antagonist of bioactive peptides[4,5] and as scaffolding blocks in the design of protein and enzyme mimetics.[2,6]

α-Aminoisobutyric acid (Figure 1), abbreviated Aib, has been the most extensively investigated α,α-dialkylated residue due to its strong helix-inducing properties. The helical tendencies of Aib have been well characterized by numerous experimental and theoretical studies of short peptides that form 3_{10}-helices and longer helices that form mixed 3_{10}/α-helices and α-helices.[2,7−14] On the other hand, cycloaliphatic residues (Figure 1), abbreviated Ac_nc, have shown a great conformational versatility. Thus, peptides containing Ac_nc residues have been recently investigated by both experimental and theoretical methods.[15−20] The three-membered ring Ac_3c shows a remarkable preference for the "bridge" region of the conformational space ($\varphi,\psi = \pm 90°,0°$) that can be accommodated in β-bends and in 3_{10}-helices. On the contrary, the less strained residues Ac_nc with $n > 3$ display a conformational behavior similar to that of Aib.

Several theoretical studies on the intrinsic conformational preferences of Aib and Ac_nc residues are reported on the literature.[17,20,21−24] However, the highest level calculations published to date for Aib[25] (HF/6-31G(d,p) energies on HF/3-21G geometries) and Ac_nc[17] (empirical calculations using the AMBER force field) dipeptides are not sufficiently accurate to determine the conformational preferences of such conformationally restricted residues. Thus, recent studies on glycine and alanine dipeptides indicated that the HF/3-21G level is appropiate to perform the scanning of the potential energy surface, but reoptimizations at higher levels of theory and single-point calculations considering electronic correlation effects are required.[25−28] On the other hand, important discrepancies were found between ab initio and empirical results on small dipeptides, suggesting that caution must be taken when force fields are applied to such compounds.[25,27,29] In this work we present an extensive ab initio quantum mechanical study of the conformational preferences of Aib, Ac_3c, and Ac_4c dipeptides (Figure 1). The results permit an understanding of the intrinsic conformational properties of these residues providing a reliable guide for their use in the de novo peptide and protein design.

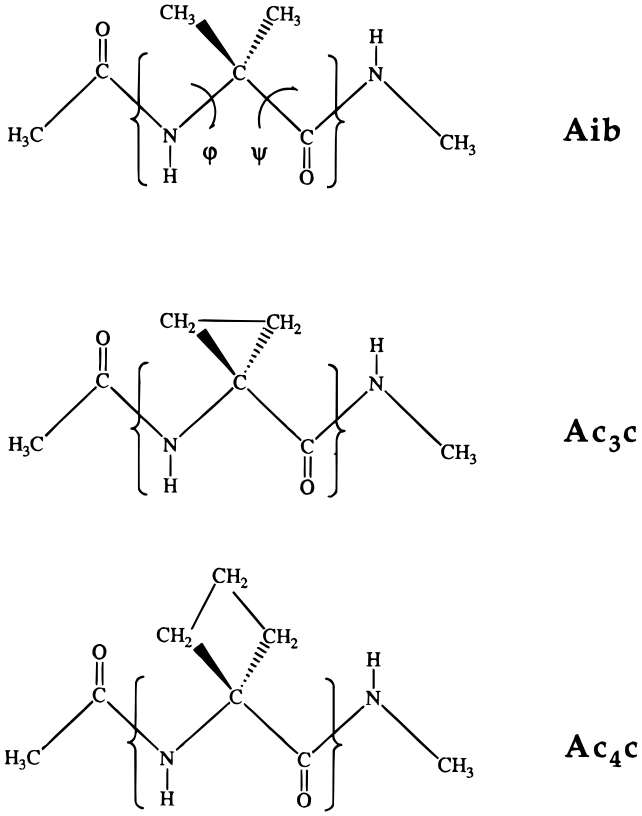

Figure 1. Aib, Ac_3c, and Ac_4c dipeptides.

Methods

The Aib, Ac_3c, and Ac_4c dipeptides are schematically shown in Figure 1. A complete exploration of the conformational space was performed in order to characterize the minimum energy structures of such compounds. Since each of the two backbone dihedral angles (φ and ψ in Figure 1) are expected to have three minima, nine minima may be anticipated for the potential energy surfaces $E = E(\varphi,\psi)$. However, due to the achiral nature of the three dipeptides, the number of expected minima can be

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TABLE 1: HF/3-21G and HF/6-31G(d) Minimum Energy Conformations[a] for Aib Dipeptide

	HF/3-21G				HF/6-31G(d)			
	ω_1	φ	ψ	ω_2	ω_1	φ	ψ	ω_2
C_5	180.0	180.0	179.9	180.0	178.5	−179.7	−179.8	180.0
C_7	−174.0	−75.0	57.5	178.6	−173.8	−75.7	58.0	179.8
α	−172.5	−63.2	−32.3	−178.4	−164.9	−65.0	−30.6	176.0
α′	−173.5	174.2	−41.6	−175.7	166.7	174.5	−33.1	−170.7
P_{II}	172.3	−57.3	136.3	179.0	166.4	−54.0	134.3	175.6

[a] Dihedral angles in degrees.

TABLE 2: HF/3-21G, HF/6-31G(d), and MP2/6-31G(d) Relative Energies[a] for Aib Dipeptide

	HF/3-21G[b]	HF/6-31G(d)[c]	MP2/6-31G(d)[d]
C_5	0.0	0.0	0.2
C_7	0.7	0.7	0.0
α	3.6	1.6	1.7
α′	4.5	3.4	3.4
P_{II}	5.8	1.7	1.9

[a] In units of kcal/mol. [b] The HF/3-21G zero of energy including ZPE and thermal corrections is −528.698 381 hartrees. [c] The HF/6-31G(d) zero of energy including ZPE and thermal corrections is −531.892 480 hartrees. [d] The MP2/6-31G(d) zero of energy including ZPE and thermal corrections at the HF/6-31G(d) level is −533.229 900 hartrees.

reduced to five. All these structures were taken as starting points in HF/3-21G[30] geometry optimizations. All the minima characterized at the HF/3-21G level were subsequently reoptimized at the HF/6-31G(d)[31] level. Frequency analyses were performed to verify the nature of the minimum state of the stationary points located during geometry optimizations, as well as to obtain zero-point energies (ZPE) and thermal corrections to the energy. Møller−Plesset perturbation treatment[32] at the MP2/6-31G(d) level was used to compute electron correlation energy.

Calculations were performed with the Gaussian-94[33] computer program. All the calculations were run on a CRAY-YMP at the Centre de Supercomputació de Catalunya (CESCA).

Results

Aib Dipeptide. Results obtained from HF/3-21G and HF/6-31G(d) geometry optimizations on Aib dipeptide are summarized in Tables 1 and 2. Note that geometry optimizations lead to five different minima, four of them (C_7, P_{II}, α, and α′) being degenerated. Table 1 indicates that the agreement between the HF/3-21G and HF/6-31G(d) structures is quite good, the largest deviations $\Delta\varphi$ and $\Delta\psi$ being 3.3° and 8.5°, respectively. Intramolecular hydrogen bond parameters for the C_5 and C_7 conformations optimized at the HF/6-31G(d) level were d(H···O) = 2.048 Å, ∠N−H···O = 111.0° and d(H···O) = 2.008 Å, ∠N−H···O = 148.4°, respectively. Interestingly, the intramolecular hydrogen bond predicted for the C_7 conformation of the Aib dipeptide is shorter than that obtained at a similar computational level for the same conformation of the Gly dipeptide (d(H···O) = 2.20 Å, ∠N−H···O = 140°).[27]

Table 2 shows the relative energies computed at different theoretical levels. Note that HF/3-21G energies are quite different from those obtained at higher levels of theory. Indeed, both HF/6-31G(d) and MP2/6-31G(d) relative energies indicate that the true surfaces are more flat than the HF/3-21G surfaces. The lowest energy minimum at the HF/6-31G(d) level is the C_5, the C_7 being 0.7 kcal/mol unfavored. However, the relative order between such conformations change on going from HF/6-31G(d) to MP2/6-31G(d), the C_7 being 0.2 kcal/mol favored with respect to the C_5 at the latter level of theory. A similar feature was recently found for the Ala and Gly dipeptide analogues.[28] On the other hand, the α minimum is only 1.7 kcal/mol less stable than the C_7 conformation at the MP2/6-31G(d) level. This small energy difference points out the intrinsic helix-forming tendency of Aib residue, which has been revealed to be larger than that of Ala residue.[11] Thus, cooperative energy differences computed on both the Aib- and Ala-based oligopeptides indicated a larger gain of energy for the former than that for the latter. Furthermore, recent calculations on the Ala dipeptide revealed that the α conformation is 4.0 kcal/mol unfavored with respect to the lowest energy minimum ($C_{7,eq}$) at the MP2/TZVP//HF/6-31G(d,p) level.[26] Thus, an energy gain of 2.3 kcal/mol appears by the addition of the second methyl group.

TABLE 3: HF/3-21G and HF/6-31G(d) Minimum Energy Conformations[a] for Ac_3c Dipeptide

	HF/3-21G				HF/6-31G(d)			
	ω_1	φ	ψ	ω_2	ω_1	φ	ψ	ω_2
C_7	−173.7	−73.3	36.0	178.7	−174.3	−78.9	31.7	172.9
β	−174.7	−95.0	2.1	178.5				
C_5	180.0	180.0	180.0	180.0	−179.9	180.0	179.9	180.0
P_{II}	167.4	−91.1	175.4	178.9	165.4	−71.2	145.6	−176.2

[a] Dihedral angles in degrees.

TABLE 4: HF/3-21G, HF/6-31G(d), and MP2/6-31G(d) Relative Energies[a] for Ac_3c Dipeptide

	HF/3-21G[b]	HF/6-31G(d)[c]	MP2/6-31G(d)[d]
C_7	0.0	0.0	0.0
β	0.3		
C_5	2.1	3.2	4.6
P_{II}	5.7	2.6	3.7

[a] In units of kcal/mol. [b] The HF/3-21G zero of energy including ZPE and thermal corrections is −527.512 798 hartrees. [c] The HF/6-31G(d) zero of energy including ZPE and thermal corrections is −530.475 626 hartrees. [d] The MP2/6-31G(d) zero of energy including ZPE and thermal corrections at the HF/6-31G(d) level is −532.045 888 hartrees.

Finally, the P_{II} and α′ minima of the Aib dipeptide are 1.9 and 3.4 kcal/mol unfavored with respect to the lowest energy minimum at the MP2/6-31G(d) level. Such relative energies are considerably lower than those estimated for the same conformations of the Ala dipeptide analogue at the MP2/6-31+G(d,p)//HF/6-31+G(d,p) level.[28] Thus, our results indicate that although Aib is a restricted amino acid due to the dimethyl substitution, its potential energy surface is similar or even flatter than those predicted for less restricted amino acids.

Ac_3c Dipeptide. Dihedral angles and relative energies for the minimum energy conformations of the Ac_3c are listed in Tables 3 and 4 respectively. Geometry optimizations at the HF/3-21G and HF/6-31G(d) levels lead to four and three minima, respectively, being all 2-fold degenerated with exception of the C_5. Intramolecular hydrogen bond geometries at the HF/6-31G(d) level for the C_5 and C_7 minimum energy conformations are d(H···O) = 2.065 Å, ∠N−H···O = 110.4° and d(H···O) = 2.162 Å, ∠N−H···O = 146.2°, respectively. These values are similar to those obtained for natural amino acids. In this case the structures obtained at the HF/3-21G level differ considerably from those obtained at the HF/6-31G(d). Thus, the β structure, which is a minimum at the lower computational level, disappears after HF/6-31G(d) geometry optimization, leading to the C_7 structure. Moreover, comparison between the dihedral angles obtained at the HF/3-21G and HF/6-31G(d) levels for the P_{II} minimum shows deviations $\Delta\varphi$ and $\Delta\psi$ of about 20°.

Relative energies indicate that the C_7 is the lowest energy minimum at all the computational levels. On the other hand, results at the HF/3-21G level indicate that C_5 is favored with respect to the P_{II} by 3.6 kcal/mol, whereas at the HF/6-31G(d) and MP2/6-31G(d) levels the latter is favored by 0.6 and 0.9

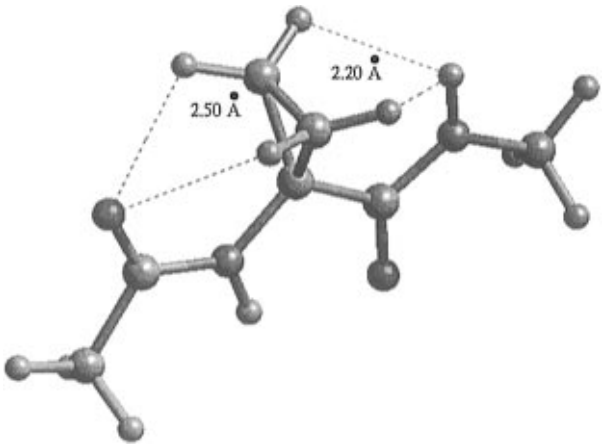

Figure 2. C_5 minimum energy conformation of the Ac_3c dipeptide.

TABLE 5: HF/3-21G and HF/6-31G(d) Minimum Energy Conformations[a] for Ac_4c Dipeptide

	HF/3-21G				HF/6-31G(d)			
	ω_1	φ	ψ	ω_2	ω_1	φ	ψ	ω_2
C_7	−174.0	−80.6	59.3	179.7	−176.0	−82.0	65.0	−178.8
C_5	180.0	180.0	180.0	180.0	180.0	180.0	180.0	180.0
α	−172.8	−75.9	−19.2	−179.4	−166.0	−74.1	−25.8	176.8
α′	174.2	173.6	−43.7	−176.3	168.7	177.2	−39.6	−170.4
P_{II}	166.8	−71.9	170.0	178.4				

[a] Dihedral angles in degrees.

kcal/mol with respect to the former, respectively. However, the more interesting finding is that the C_5 is 4.6 kcal/mol less stable than the C_7. Note that these two structures differ by less than 0.5 kcal/mol in the Gly, Ala,[25−28] and Aib dipeptide analogues. Inspection of Figure 2 indicates that the low stability of the extended conformation in the Ac_3c potential energy surface is due to the steric repulsion between the amide groups and the β-methylene hydrogen atoms. Thus, the distance between the β-methylene hydrogen atoms and the oxygen and hydrogen atoms of the amide groups are 2.50 and 2.20 Å, respectively.

On the other hand, the β structure corresponds to the conformation experimentally detected for the Ac_3c residue in the solid state. Thus, such "bridge" conformation is observed in the position $i + 2$ of the type I and type II β bends. Comparison between the C_7 and β relative energies at the HF/3-21G level suggests that the latter is only 0.3 kcal/mol unfavored with respect to the formers. Thus, the annihilation of the β minimum at the HF/6-31G(d) suggests that such conformation may be easily achieved from a distortion of about 40° in the ψ angle of the C_7. Comparison between the results obtained for the Aib and Ac_3c dipeptides suggests that the potential energy surface of the latter is more sharp and restricted than that of the former.

Ac_4c Dipeptide. Results for Ac_4c dipeptide are displayed in Tables 5 and 6. Five and four minima were found at the HF/3-21G and HF/6-31G(d) levels, respectively. Geometry optimization of the P_{II} at the HF/6-31G(d) level leads to the C_7. All the minima with exception of the C_5 are 2-fold degenerate minima. The C_5 and C_7 intramolecular hydrogen bonds are characterized at the HF/6-31G(d) level by d(H···O) = 2.050 Å, ∠N−H···O = 110.2° and [d(H···O) = 2.078 Å, ∠N−H···O = 144.5°, respectively. Deviation from the planarity of the cyclobutyl substituent is perhaps the most relevant feature concerning the molecular geometry. In all the cases the ring loses the ideally planar conformation, and the dihedral angle defined by the $C^{\alpha}-C^{\beta}-C^{\gamma}-C^{\beta'}$ atoms ranges from 8.6° (C_5) to 18.5° (C_7).

TABLE 6: HF/3-21G, HF/6-31G(d), and MP2/6-31G(d) Relative Energies[a] for Ac_3c Dipeptide

	HF/3-21G[b]	HF/6-31G(d)[c]	MP2/6-31G(d)[d]
C_7	0.0	0.0	0.0
C_5	1.3	1.8	2.8
α	3.6	1.9	2.9
α′	3.9	3.9	4.3
P_{II}	7.1		

[a] In units of kcal/mol. [b] The HF/3-21G zero of energy including ZPE and thermal corrections is −566.313 532 hartrees. [c] The HF/6-31G(d) zero of energy including ZPE and thermal corrections is −569.731 912 hartrees. [d] The MP2/6-31G(d) zero of energy including ZPE and thermal corrections at the HF/6-31G(d) level is −571.186 358 hartrees.

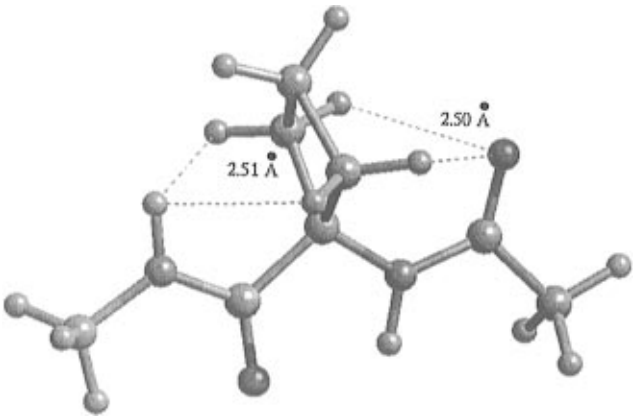

Figure 3. C_5 minimum energy conformation of the Ac_4c dipeptide.

Note that the agreement between the C_7, C_5, α, and P_{II} structures obtained at the HF/3-21G and HF/6-31G(d) levels is reasonable, the largest deviations $\Delta\varphi$ and $\Delta\psi$ being 3.6° and 6.6°, respectively. The lowest energy structure is the C_7, being that the C_5 and the α conformations are 2.8 kcal/mol and 2.9 kcal/mol less favored than the C_7, respectively. The low stability of the C_5 structure is mainly due to the interactions between the β-methylene hydrogen atoms and the oxygen and hydrogen atoms of the amide group. Figure 3 shows the C_5 structure of the Ac_4c dipeptide, where the distance between the closest atoms (2.50 Å) are indicated. Note that steric interactions in the Ac_4c dipeptide are much less repulsive than those in the Ac_3c dipeptide, the C_5 being 4.6 kcal/mol unfavored with respect to the C_7 in the latter.

The relative energy order obtained from the different theoretical levels was the same. However, the variation of the relative energy values with the computational level indicates that the effects of both polarization functions on the heavy atoms and electron correlation are needed to obtain a reliable description of the system. Thus, at the HF/3-21G level the α structure is 2.3 kcal/mol less favored than the C_5, whereas at the MP2/6-31G(d) level both structures are almost isoenergetic. Finally, the α′ conformation is about 4.3 kcal/mol unfavored with respect to the global minimum at the best theoretical level.

Discussion

The minimum energy conformations of Aib, Ac_3c, and Ac_4c dipeptides have been determined at the HF/3-21G and HF/6-31G(d) levels. In general, the structures obtained at the HF/3-21G are in reasonable agreement with the HF/6-31G(d) ones, although several minima disappear at the higher level of theory. On the other hand, relative energies computed at the HF/3-21G level differ considerably from those computed at the HF/6-31G(d) level. Correlation energy effects for relative energies were estimated at the MP2/6-31G(d) level on the HF/6-31G(d) geometries. However, electron correlation contributions were

TABLE 7: Values of the ∠N−C$^{\alpha}$−C Bond Angle[a] for the Aib, Ac$_3$c, Ac$_4$c, Gly, and Ala Dipeptides

dipeptide[b]	C_5	C_7	α	α′	P_{II}	range	ref
Aib	104.5	111.4	112.1	107.8	108.0	7.6	this work
Ac$_3$c	108.3	118.8			112.7	10.5	this work
Ac$_4$c	105.6	111.0	112.9	108.3		7.3	this work
Gly	109.4	112.8	115.7			6.3	27
Ala	107.5	109.9[c]	113.9			6.4	27
		113.1					

[a] Bond angle in degrees. [b] Molecular geometries of the Aib, Ac$_3$c, and Ac$_4$c dipeptides optimized at the HF/6-31G(d) level. Molecular geometries of the Gly and Ala dipeptides optimized at the HF/DZP level. [c] Values of 109.9° and 113.1° refer to the $C_{7,eq}$ and $C_{7,ax}$ conformers, respectively.

not large, i.e., less than 0.9, 1.4, and 1.0 kcal/mol for Aib, Ac$_3$c, and Ac$_4$c dipeptides, respectively.

The results presented in this work permit one to understand some important structural features concerning the Aib, Ac$_3$c, and Ac$_4$c residues. The first is the intrinsic helix-forming tendency of the Aib residue. It is generally assumed that the stabilization of the helical structure in polypeptides is basically due to both the formation of intramolecular hydrogen bonds and favorable van der Waals interactions between the side chains. Indeed, recently reported molecular dynamics simulations on Ala and Aib oligopeptides provided an excellent description of such interactions.[34−37] On the other hand, it is well known that in the solid state the poly-Ala can be found in both the α-helix and β-sheet conformations,[38] whereas the poly-Aib is observed only in the helical conformation.[39] These experimental observations suggest that the Aib residue has a larger intrinsic helix-forming tendency than the Ala one. Comparison between the C_5 and α minima for the Aib and Ala dipeptides can provide an estimation of the relative tendency of such residues to form helical structures, but without taking into account inter-residue interactions. The relative energies at a similar computational level are 1.7 and 4.0 kcal/mol for the Aib and Ala[26] dipeptides, respectively, indicating that the Aib residue has a larger helix propensity than the Ala one (ratio 2.3 (Aib):1.0 (Ala)).

Another interesting feature concerns the low stability of the C_5 conformation of the Ac$_3$c residue. Thus, unfavorable interactions between the β-methylene hydrogen atoms and the amide group made the C_5 of the Ac$_3$c dipeptide less stable than the global minimum by 4.6 kcal/mol. However, the results obtained for the less constrained Ac$_4$c dipeptide demonstrate that the stability of the C_5 increases when the flexibility of the side-chain ring increases. Thus, for the Ac$_4$c dipeptide the C_5 is only 2.8 kcal/mol unfavored with respect to the global minimum. The stabilization of the C_5 conformation in Ac$_4$c dipeptide is achieved by a deformation from the planarity of the cyclobutyl side chain. It is well known that cyclic groups with five or more carbon atoms have puckering displacements in a relatively free manner.[40,41] Therefore, a better adaptability of the ring to achieve favorable intramolecular interactions is expected for Ac$_n$c with $n \geq 5$.

Finally, the most striking feature observed in the present study is the large number of minima found for these restricted dipeptides. An analysis of the molecular geometries of all the minima characterized in the present work permits an understanding of this anomalous conformational behavior. The largest variation of a conformational parameter occurs for the ∠N−C$^{\alpha}$−C angle. Values for such parameters are displayed in Table 7 for all the compounds investigated in the present work. Furthermore, the ∠N−C$^{\alpha}$−C angles found for Gly and Ala dipeptides[27] are also listed for the sake of comparison. Note that the largest variation of the ∠N−C$^{\alpha}$−C angle corresponds to the Ac$_3$c, which is the more restricted residue. Thus, in the C_7 conformation the value of 118.8° is close to the expected value of 120° in a trigonal configuration. Furthermore, the range of variation of the ∠N−C$^{\alpha}$−C angle in the Aib and Ac$_4$c dipeptides is slightly larger than those computed for Gly and Ala ones. These results illustrate the large deformability of the molecular geometries in conformationally restricted residues. Thus, the adaptability of the bond parameters provides an improvement of the intramolecular interactions, allowing the existence of a large number of minimum energy conformations.

In summary, we have computed all the minima of the Aib, Ac$_3$c, and Ac$_4$c dipeptides. A large number of minima were found for each compound. The results permit us to understand some intrinsic conformational characteristics of these α,α-disubstituted amino acid residues. Molecular geometries and conformational energies derived from the present calculations can be used to derive an accurate set of force field parameters for the conformational analysis of compounds with restricted residues.

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