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Sensitivity of Peptide Conformation to Methods and Geometrical Parameters. A Comparative ab Initio and Molecular Mechanics Study of Oligomers of α-Aminoisobutyric Acid

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ABSTRACT: The conformational behavior of α-aminoisobutyric acid has been investigated by means of ab initio and empirical methods. Empirical computations performed with fixed bond lengths and valence angles using well-known force fields show that C_5, C_7, and helical structures correspond to energy minima, but the relative stability of different conformers is strongly dependent on the parametrization. Ab initio computations performed to solve these discrepancies suggest that the three structures are essentially isoenergetic. An alternative set of net charges significantly improves the agreement between ab initio and molecular mechanics results. Complete geometry optimization using both ab initio and empirical methods does not affect the relative stabilities of C_5 and C_7 structures but significantly destabilizes the helical one. Zero point and entropy effects, although slightly destabilizing the C_7 structure, do not alter this general trend. The stabilization of helical structures with respect to C_5 and, especially, C_7 ones in polar solvents has been recovered by varying the dielectric constant governing intramolecular electrostatic interactions. Computations performed for oligomers of alanine and α-aminoisobutyric acid up to the octamer confirm the faster onset of helical structures for α-aminoisobutyric acid evidenced by experimental observations.

Introduction

The α,α-dialkylated, α-amino acid residue Aib (Aib = α-aminoisobutyric acid) extensively occurs in the transmembrane channel-forming peptide antibiotics of the alamethicin family.[1,2] As widely demonstrated by a large amount of theoretical investigation, replacement of the hydrogen atom at the C^α carbon atom in the Ala (Ala = Alanine) residue by a methyl group produces severe restriction of the conformational freedom of the resulting Aib residue.[3-6] This characteristic has stimulated many experimental studies, both in solution and in the solid state,[3,6-11] which suggest a pronounced tendency of the Aib residue to favor helical structures.

The first theoretical analyses[5,6] of the conformational space available to this residue found only small regions of the Ramachandran map energentically favorable, corresponding to helical structures of the 3_{10} ($\Phi \approx \pm 60°$, $\Psi \approx \pm 30°$) and α ($\Phi \approx \pm 55°$, $\Psi \approx \pm 45°$) types. The energy difference between the 3_{10} and α helix was small, whereas the other low-energy conformations characteristic of common protein residues were significantly less stable.[6] Subsequently, quantum mechanical calculations (using the PCILO method),[6] NMR experiments in nonpolar solvents,[7] and theoretical investigations by means of empirical functions[12,13] have, however, demonstrated that also C_5 ($\Phi \approx \Psi \approx 180°$) and C_7 ($\Phi \approx \pm 70°$, $\Psi \approx \mp 60°$) conformations are of relevant importance for this peptide.

In particular, in polar media the α-helix conformation is favored with respect to the C_7 and C_5 ones, while in apolar solvents the C_5 and C_7 structures become significantly more stable.[9]

A more recent ab initio study confirms the great stability of the helical structures, although the narrow minima corresponding to the other low-energy conformations cannot be excluded, in view of the approximate procedure and large grid used in these calculations.[14]

A critical evaluation of the above results points out the influence of the methodology for characterization of the whole conformational space for a given molecule.

Both experimental and theoretical studies have further evidenced the importance of structural parameters in determining the relative stability of the different helical structures, namely, the 3_{10} and α ones. In particular a symmetric tetrahedral geometry around the C^α atom favors the α helix, whereas an asymmetric geometry shifts the energy minimum toward the 3_{10} helix.[15] Systematic theoretical studies on the conformational properties of α,α-dialkylated peptides have then demonstrated that the overall conformational behavior of this class of molecules does not depend on the symmetry around the C^α atom, but rather on the actual values of $NC^\alpha C'$ (hereafter referred to as τ) and $C^\beta C^\alpha C^{\beta'}$ (hereafter referred to as σ) valence angles.[13,16,17] In particular small values of τ favor α helical and C_5 structures, whereas small values

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Table I
Optimized Values for the Valence and Dihedral Angles Obtained by STO-3G and AMOD Computations for F-Aib-NH_2[a]

		C_5			helix		C_7	
angle	standard	STO-3G	AMOD	F: STO-3G	STO-3G	AMOD	STO-3G	AMOD
$H_1C'_1N_2$	117.0°	111.6°	118.4°	111.4°	112.0°	118.5°	111.7°	118.3°
$O_1C'_1N_2$	124.5°	125.8°	123.2°	125.9°	125.1°	123.0°	125.8°	123.4°
$C'_1N_2C^\alpha_2$	122.2°	125.6°	127.5°	124.6°	124.0°	125.1°	126.5°	126.8°
$H_2N_2C'_1$	124.0°	121.6°	118.5°	118.2°	118.6°	117.7°	117.4°	116.9°
$N_2C^\alpha_2C'_2$ (τ)	111.1°	103.7°	105.7°	108.6°	110.8°	112.1°	109.2°	110.4°
$C^\alpha_2C'_2N_3$	116.8°	116.2°	118.1°	115.4°	114.9°	118.1°	113.4°	118.2°
$O_2C'_2N_3$	122.6°	123.1°	121.6°	122.4°	123.2°	121.3°	123.9°	121.2°
$N_2C^\alpha_2C^\beta_2$	110.5°	110.5°	110.3°	109.8°	110.5°	109.2°	111.9°	111.2°
$C^\alpha_2C^\beta_2H_2^{\beta 1}$	109.5°	109.5°	109.7°	110.1°	110.4°	110.2°	110.3°	108.8°
$C^\alpha_2C^\beta_2H_2^{\beta 2}$	109.5°	111.2°	111.0°	111.2°	110.2°	110.2°	110.2°	107.8°
$C^\alpha_2C^\beta_2H_2^{\beta 3}$	109.5°	110.7°	110.3°	110.7°	111.1°	110.4°	110.7°	108.7°
$N_2C^\alpha_2C^{\beta'}_2$	110.5°	110.5°	110.3°	107.2°	107.8°	108.2°	107.0°	107.4°
$C^\alpha_2C^{\beta'}_2H_2^{\beta' 1}$	109.5°	110.7°	110.3°	110.2°	110.2°	109.8°	111.9°	108.7°
$C^\alpha_2C^{\beta'}_2H_2^{\beta' 2}$	109.5°	111.2°	111.0°	111.3°	110.1°	110.0°	109.4°	108.8°
$C^\alpha_2C^{\beta'}_2H_2^{\beta' 3}$	109.5°	109.5°	109.7°	109.9°	110.3°	110.3°	110.0°	108.7°
$C_2N_3H_3$	120.0°	123.0°	120.3°	123.6°	122.3°	120.3°	121.6°	119.2°
$C_2N_3H'_3$	120.0°	119.8°	118.8°	119.5°	120.2°	118.6°	120.1°	119.6°
$N_2C^\alpha_2C^\beta_2H_2^{\beta 1}$	60.0°	60.8°	64.0°	59.4°	60.6°	53.7°	61.3°	54.0°
$N_2C^\alpha_2C^\beta_2H_2^{\beta 2}$	180.0°	−179.5°	−176.3°	179.0°	−179.8°	173.7°	−178.6°	173.5°
$N_2C^\alpha_2C^\beta_2H_2^{\beta 3}$	−60.0°	−58.8°	−56.5°	−60.6°	−59.8°	−66.7°	−59.3°	−67.1°
$N_2C^\alpha_2C^\beta_2H_2^{\beta 1}$	60.0°	58.8°	56.5°	62.3°	59.0°	60.9°	60.8°	59.6°
$N_2C^\alpha_2C^\beta_2H_2^{\beta 2}$	180.0°	179.5°	176.3°	−177.1°	178.5°	−179.5°	−178.6°	179.5°
$N_2C^\alpha_2C^\beta_2H_2^{\beta 3}$	−60.0°	−60.8°	−64.0°	−59.3°	−61.2°	−59.5°	−59.6°	−60.4°

[a] Standard values are discussed in the text. The labeling of the atoms is shown in Figure 1.

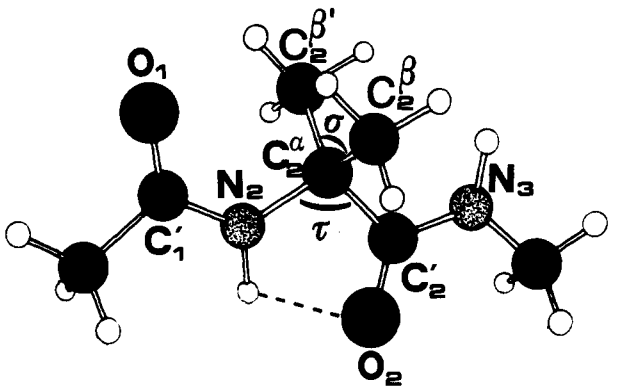

Figure 1. Schematic drawing of the C_5 conformation of Ac-Aib-NHMe and labeling of atoms.

of σ favor C_7 and 3_{10} conformers.

Another important property in characterizing biologically active peptides is the determination of a definite structural behavior for any particular amino acid present in the peptide and the rôle played in the folding process.[5]

Many proteins and peptide antibiotics are not large enough to allow formation of a central core in wich long-range hydrophobic interactions can nucleate helix folding. Instead, long-range interactions occur because intramolecular chain loops constrain residues into tightly folded conformations as in the case of peptide antibiotics like actinomycin[18] and alamethicin.[1] In all such cases, residue side chains are guided into such close proximity that steric contacts limit the number of probable conformers and this permits a unique folding.

The structural determination of the Aib-rich antibiotics points out the problem of a correct characterization of the kind (α or 3_{10}) and extension of helical domains occurring in the overall structure of these molecules, also in relation with their peculiar biological properties.

Five main points will be addressed in this study: (1) a comparison between the results obtained employing different force fields on the Aib residue in order to better define the relative stability of low-energy conformers; (2) a comparison between empirical and quantum mechanical methods; (3) an analysis of the influence of full geometry optimization on the conformational behavior of Aib; (4) a study of the role played by vibrational effects and by polar solvents in modifying the relative stability of different structures; (5) a comparison between oligomers of Aib and Ala in order to better analyze the pronounced tendency of Aib to promote the formation of helical structures.

Methods

Two different systems containing monomeric units of Aib were studied, namely, F-Aib-NH_2 (F = formyl, NH_2 = amino), hereafter referred to as model I, and Ac-Aib-NHMe (Ac = acetyl, NHMe = methylamino), hereafter referred to as model II.

The standard geometries of Scheraga and co-workers[19,20] were used for all the end groups, while the mean structure derived from X-ray data in ref 21 was used for the central part, except for the averaging of the geometrical parameters of the two β-methyl groups (see Figure 1 and Table I).

Empirical two-body potential functions were used for describing torsional, steric, electrostatic, and H-bond interactions. Conformational maps were built by the package ICER,[22,23] which, together with other appealing features, allows the use of different force fields. Three different force fields were used in the present study, namely, the latest revision[20] of the ECEPP potentials proposed by Scheraga and co-workers,[19] the potentials derived by Lifson and co-workers (hereafter referred to as L96),[24,25] and the AMBER force field proposed by Kollman and co-workers in its all-atom parametrization[26,27] and employing a dielectric constant of unity. This last force field was also used with a modified set of atomic charges (hereafter referred to as AMOD) derived by empirical rules, which avoid any preliminar quantum mechanical computation.[28] In particular the atomic charges of the backbone are always taken as constant,[27] and the total charge on each side chain was set equal to the AMBER value (0.03) for the β-hydrogens of glycine. Next, following the

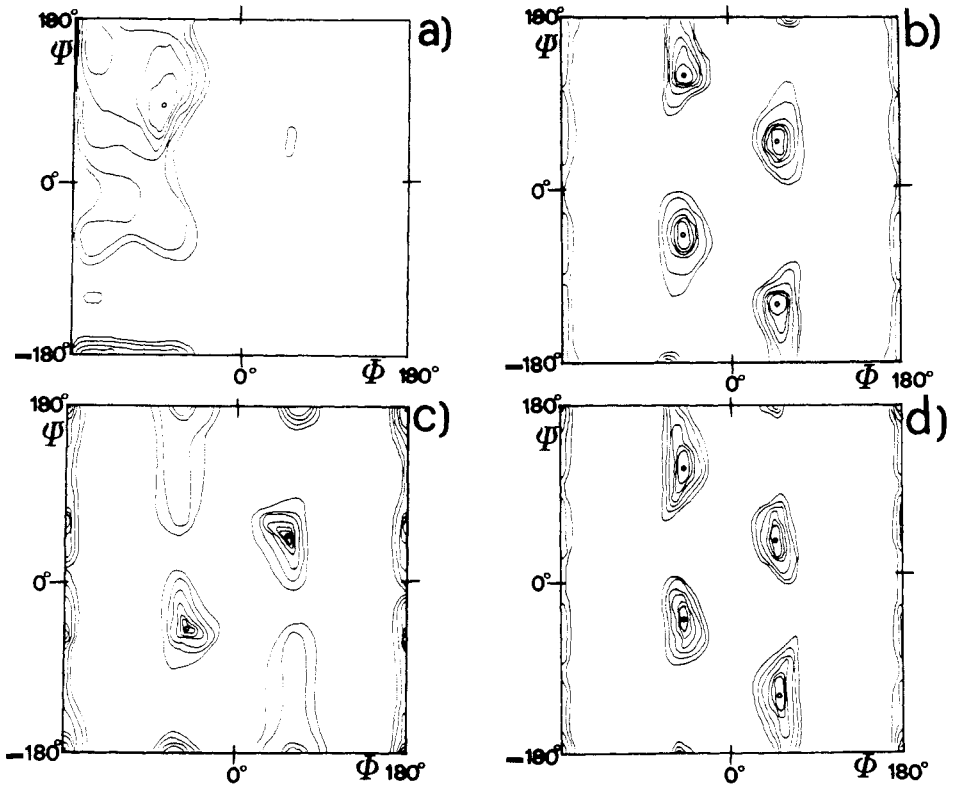

Figure 2. (Φ,Ψ) maps for different peptides obtained by empirical and ab initio computations employing rigid bond lengths and bond angles. The contour lines are spaced 5, 10, 15, 20, 30, and 40 kJ mol^{-1} over the 10° grid point of lowest energy. (a) Ac-Ala-NHMe by AMOD; (b) Ac-Aib-NHMe by AMOD; (c) F-Aib-NH_2 by STO-3G; (d) F-Aib-NH_2 by AMOD.

Table II
Dihedral Angles and Relative Stabilities with Respect to C_7 Conformations (ΔE in kJ mol^{-1}) of F-Aib-NH_2 (Model I) and Ac-Aib-NHMe (Model II) Obtained by Different Methods

	rigid geometry					flexible geometry			
	ECEPP, II	L96, II	AMOD, II	AMOD, I	STO-3G, I	STO-3G, I	AMOD, I	AMOD, II	AMBER, II
C_7 ϕ	±76°	±57°	±74°	±73°	±71°	±71°	±68°	±69°	±66°
Ψ	∓59°	∓124°	∓65°	∓63°	∓60°	∓59°	∓67°	∓66°	∓65°
ΔE	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
helix ϕ	±53°	±50°	±52°	±52°	±52°	±55°	±54°	±52°	±52°
Ψ	±40°	±48°	±39°	±38°	±40°	±38°	±32°	±34°	±35°
ΔE	-27.2	11.1	2.9	-3.8	1.7	12.6	15.5	11.7	14.6
ΔE_{Ala}	-27.2	12.1	6.7					12.5	15.1
F ϕ	±60°				±62°	±66°			
Ψ	±169°				±174°	±175°			
ΔE	10.4				13.6	20.1			
C_5 Φ	±173°	±173°	180°	±176°	180°	180°	±177°	180°	180°
Ψ	±172°	±165°	180°	±177°	180°	180°	±176°	180°	180°
ΔE	15.5	1.7	4.8	3.3	0.8	0.0	8.8	9.2	18.0

[a] The relative stabilities of the helical and C_7^{ax} conformers in Ac-Ala-NHMe (ΔE_{Ala}) are also reported.

suggestion of Lifson and co-workers,[24,25] electroneutrality was imposed on the CO, NH_2, and $NHCH_3$ moieties and constant charges were assigned to aliphatic (0.03) and amidic (0.20) hydrogen atoms. The charge on oxygen (-0.5) was the same as in AMBER, but the charges on nitrogen atoms were slightly reduced from the original values (to -0.40 and -0.34 for NH_2 and $NHCH_3$ groups, respectively) in order to enhance the agreement between empirical and ab initio results, especially concerning the relative stability of extended conformations.[23,28] Finally the value of the charge on C^α (0.08 to be compared to the AMBER value of 0.035 in glycine) allows us to always obtain neutral residues. We have, anyway, verified that reasonable modifications of net charges on aliphatic groups have essentially no effect on both structures and relative stabilities of different conformers.

The conformational space was mapped by calculating the conformational energy at 10° intervals for the Φ,Ψ angles, with Ω angles fixed at 180° and methyl groups frozen into staggered conformations.[29] Ab initio computations were performed in a similar way by using the GAUSSIAN/88 package[30] and the STO-3G basis set,[31] but with a grid of 30°.

Minimum-energy conformations were then obtained in the low-energy regions located in the above search, minimizing the energy with respect to all the dihedral angles by the ICER or GAUSSIAN/88 packages, using procedures based on analytical gradients.[26,32]

Complete geometry optimizations (i.e., including variability of bond lengths and valence angles) were performed in the same regions by using the AMBER package[26] and the complete all-atom force field of ref 27, with the original as well as with the modified net charges. In view of the negligible effect of bond length variations, only valence and dihedral angles were, instead, optimized at the STO-3G level.

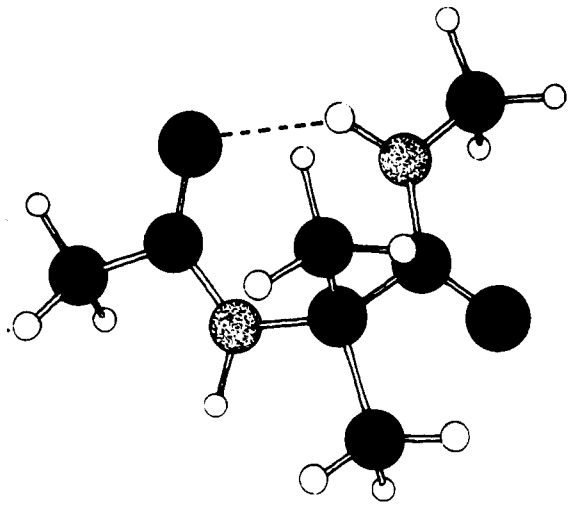

Figure 3. Schematic drawing of the C_7 conformation of Ac-Aib-NHMe.

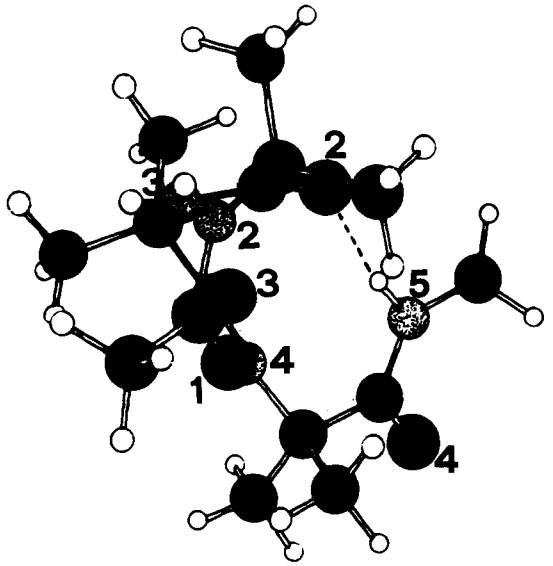

Figure 4. Schematic drawing of an incipient 3_{10} helix in Ac-$(Aib)_3$-NHMe.

Conformational energies are expressed as $\Delta E = E - E_0$, where E_0 is the energy of the most stable conformation for a given compound.

Since using complete geometry optimization allows one to readily calculate the harmonic vibrational frequencies of the molecule, the thermodynamic functions can be calculated by the standard formulas of statistical mechanics in terms of the partition function Q

$$U = E + \mathrm{ZPE} + RT^2(\mathrm{d} \ln (Q)/\mathrm{d}T)$$

$$H = U + RT$$

$$S = R[T\,\mathrm{d} \ln (Q)/\mathrm{d}T + \ln (Q)]$$

$$G = H - TS$$

where U, ZPE, H, S, and G are the internal energy, zero point energy, enthalpy, entropy, and free energy, respectively. T is the absolute temperature, R is the gas constant, and E is the conformational energy obtained from ab initio or molecular mechanics computations.

Neglecting the effects of rotation–vibration coupling, anharmonicity, and centrifugal distortion, the partition function can be written:

$$Q = Q_{tr}Q_{rot}Q_{vib}$$

$$Q_{tr} = V(mKT/2\pi h^2)^{3/2}$$

$$Q_{rot} = \pi^{7/2}[\sigma(8\pi KT/h^2)^{3/2}I_A I_B I_C]^{-1}$$

$$Q_{vib} = \sum[1 - \exp(h\nu_i/KT)]^{-1/2}$$

and

$$\mathrm{ZPE} = (1/2)\sum h\nu_i$$

In these formulas m is the mass of the molecule, h is Planck's constant, the symmetry number σ has its usual meaning, I_A, I_B, and I_C and the principal moments of inertia, and ν_i is the harmonic frequency.

Results and Discussion

As already discussed, the Aib residue differs from the Ala one for a methyl group that substitutes a hydrogen atom on the C^α position. The difference in the conformational behavior of the two molecules is well evidenced by the (Φ,Ψ) maps obtained by the AMOD force field (Figure 2a,b). The Ala residue, in contrast to Aib, does not show any energy minimum in the helical region of the conformational space, but energy minimization in the whole dihedral subspace gives helical minima for both molecules (see Table II).

The C_7^{eq} conformer represents the deepest energy minimum for Ala, but the less stable C_7^{ax} conformer provides a much better reference structure since one of the two β-methyl groups of Aib always occupies the more sterically hindered axial position. As a matter of fact the energy difference between C_7^{ax} and helical conformers of Ala (hereafter referred to as E_{Ala}) is very similar to the corresponding difference in Aib, this result being confirmed by ab initio computations as well as by all the different force fields employed in the present study (see Table II).

The Φ,Ψ maps obtained by using the AMOD force field for the two model peptides, representative of the Aib molecule, are shown in Figure 2b–d. The negligible role played by terminal groups is quite evident in view of the close similarity between the two maps. In order to investigate the dependence of the above results on the computational method, the results obtained by ab initio and different empirical calculations are collected in Table II. Since the AMOD maps indicated that the nature of the terminal groups has only a negligible effect on the conformational characteristics of Aib, ab initio computations were performed only for model I. Furthermore bond lengths were never varied in geometry optimizations in view of their constancy both in previous ab initio calculations on different peptides and in AMOD computations on Aib.

The results of Table II and Figure 2 show that the accessible conformational space of Aib is restricted to C_5, C_7, and helical structures (Figures 1, 3, and 4) irrespective of the computational method, but the relative stability of the different conformers is much more variable. At the STO-3G level Aib does not present any well-defined preferential structure, the above three regions being almost isoenergetic. A comparison between rigid geometry empirical and STO-3G (Φ,Ψ) maps (see Figure 2c,d) shows a substantial agreement on the accessible conformational space, which is restricted in both cases to the same region. The only significant difference concerns the relative stability of the C_5 conformation, which is significantly enhanced by STO-3G computations. It is noteworthy, however, that the AMOD force field represents a remarkable improvement of the AMBER one in this respect, without impairing the other good perfor-

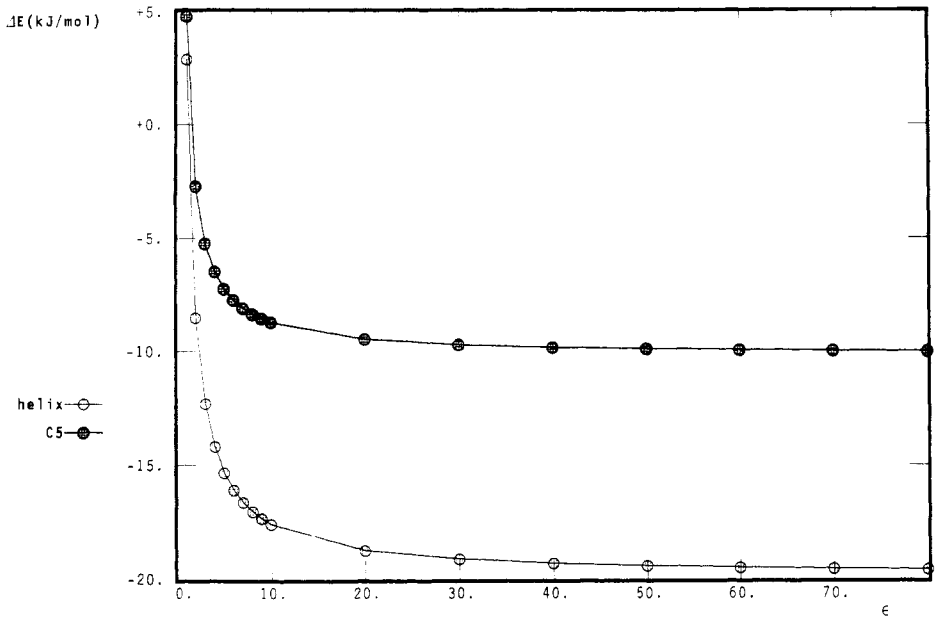

Figure 5. Relative stabilities (with respect to the C_7 structure) of helical and C_5 conformers obtained for Ac(Aib)NHMe as a function of the dielectric constant (ϵ) employing the AMOD force field with fixed bond lengths and valence angles.

Table III
Internal and Vibrational Contributions to the Relative Stabilities of Different Conformations of Ac-Aib-NHMe[a]

conformer	C_7	C_5	helix
Φ	±69°	180°	±52°
Ψ	∓66°	180°	±34°
ZPE	401.4	399.5	390.4
S	390.4	399.5	401.4
$U-E$	423.8	423.0	422.0
ΔE	0.0	9.2	11.7
ΔG	0.0	5.7	6.6

mances of the parametrization.[33]

On the other hand, the ECEPP force field, as previously suggested,[13,23] excessively stabilizes helical structures and the L96 force field gives a too large value for the Ψ angle in the C_7 conformation (124° instead of the typical value, which is around 60°). Moreover, the valence angle τ obtained for the different conformations with this latter force field relaxing the whole geometry does not show the correct behavior, τ being larger in the C_5 conformation than in the helical structures, contrary to much experimental and theoretical evidence.[16,17] This could be tentatively ascribed to an overestimation of 1–4 repulsions, which are not halved in this parametrization.[25]

The AMOD force field, therefore, provides the more balanced results, although the C_5 conformation probably remains too high in energy. In fact, although the small size of the STO-3G basis set does not allow quantitative comparisons, the underestimation of the C_5 conformer stability by molecular mechanics computations has been confirmed in the case of Gly and Ala residues by more refined ab initio computations.[34-37]

A comparison between empirical and X-ray results shows that geometrical parameters are generally well comparable and that bond lengths are essentially constant in all structures. This is not the case for valence angles, whose modification (which requires relatively low energies) is very effective in relaxing strained conformations.[23] The valence angles optimized at the STO-3G level for different conformations are compared in Table I with AMOD and experimental values. AMBER results are not reported because they are very similar to AMOD ones. The agreement is remarkable and all the trends observed at the empirical level are confirmed by ab initio computations. In particular the optimized value of the valence angle $NC^{\alpha}C'$ is reasonably narrower in the C_5 conformation. The only considerable discrepancy concerns the value of the HC'N valence angle (111–112° at the STO-3G level and 118–119° at the AMOD level), the STO-3G value being probably more reliable taking into account the experimental data for formamide (HC'N = 111.4° (STO-3G) and 112.7° (exptl)[38]). The formylic hydrogen, however, is never involved in significant contacts with other atoms in the whole conformational space. Since the trend of the $O_1C'_1N_2$ valence angle is rather well reproduced by the AMOD force field, the above discrepancy should not have any significant consequence. A more detailed analysis has not been performed because of the limited accuracy of the STO-3G basis set.

The only major effect of full geometry optimization on the conformational behavior of Aib is a significant stabilization of C_5 and C_7 structures with respect to helical ones, via relaxation of repulsive interactions involving β-methyl groups. This effect is reminiscent of the strong stabilization of the C_7^{ax} structure of Ala upon full geometry optimization,[25] the same trend being obtained by all the methods employed in the present study (see Table II).

The role played by nonpotential energy terms in modifying the relative stability of different energy minima has been also investigated. These terms stabilize both the C_5 and helical conformers with respect to the C_7 one (see Table III) but do not alter the general trends described above.

Recently it has been proposed that use of the bulk dielectric constant of water in the evaluation of electrostatic interactions mimics quite efficiently the explicit inclusion of the solvent.[39] A calculation of this kind has been also performed (see Figure 5), leading to a strong stabilization of the helical conformer, i.e., of only the energy minimum not involving any hydrogen bridge in the dipeptide model. More generally, since the hydrogen bond is essentially of electrostatic nature, any increase of the dielectric constant favors structures with the lowest number of intramolecular hydrogen bridges. This shows that contrary to previous suggestions,[40] the role of electrostatic terms is by no means negligible in the building of a reli-

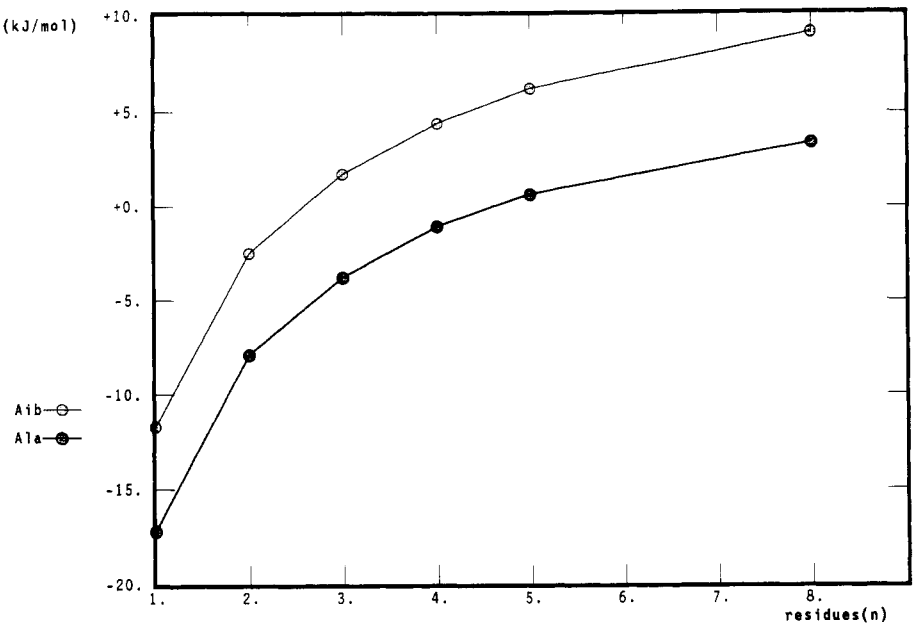

Figure 6. Energy differences (per residue) between C_7 and helical structures of Ac(Aib)$_n$NHMe and Ac(Ala)$_n$NHMe as a function of n obtained by the AMOD force field upon full geometry optimization. Positive values indicate a more stable helical structure.

Table IV
Geometric and Energetic Characteristics of Hydrogen Bonds in the C_{10} Conformations of Ac(Aib)$_n$NHMe[a]

residues	CO- -HN, Å	∠O- -H–N, deg	E_H, kJ/mol	Φ, Ψ, deg
n = 2				49, 33
4–1	1.886	166.7	1.9	50, 32
n = 3				47, 36
4–1	1.915	166.4	2.0	47, 33
5–2	1.908	160.8	2.0	51, 32
n = 4				42, 36
4–1	1.914	165.4	2.0	45, 35
5–2	1.946	161.5	2.1	48, 33
6–3	1.911	160.5	2.0	51, 31
n = 5				46, 37
4–1	1.908	165.1	2.0	45, 35
5–2	1.943	160.8	2.1	46, 35
6–3	1.956	162.0	2.1	49, 32
7–4	1.909	160.3	2.0	52, 32
n = 8				46, 37
4–1	1.908	164.6	2.0	44, 36
5–2	1.943	161.5	2.0	46, 36
6–3	1.956	162.0	2.1	47, 35
7–4	1.956	192.0	2.1	47, 34
8–5	1.955	162.1	2.1	47, 35
9–6	1.956	161.9	2.1	49, 32
10–7	1.909	160.2	2.0	52, 32

[a] E_H refers to the non-electrostatic contribution to the total hydrogen bond interaction. The different pairs of angles in the last columns refer to successive residues in each oligomer.

able potential energy surface of polar molecules.

Single-crystal X-ray diffraction data,[3,8-11] IR, and ^{1}H NMR studies[9,21,41,42] of protected (Aib)$_n$ homopeptides strongly support the view that the intramolecular H bonds of the C_{10} type, characteristic of the 3_{10} helix, are first formed at the trimer level and persist for longer oligomers. We have therefore performed full-geometry optimizations of the C_7 and helical structures of these oligomers by the AMOD force field. No evidence was found for the onset of α helices, but the geometrical parameters and NH- -OC bonding schemes reported in Table IV show the preference for the formation of incipient 3_{10} helices starting from the trimer. Repeated C_{10} H bonds become more stable than repeated C_7 ones at this same level so that the onset of helical structures is much faster than in the case of Ala (Figure 5).

The above results are in remarkable agreement with those obtained in ref 43 employing fixed bond lengths and bond angles, although the above discussion suggests the nonnegligible role of valence angle relaxation in evaluating relative stabilities of different structures.

In conclusion we think that the present study gives further insight in the rationalization of the conformational behavior of Aib oligomers and shows the potentialities of a combined quantum mechanical and empirical approach in the study of biological molecules. In particular the lack of experimental data on simple models suggests that ab initio computations are the best source of information for comparing with force fields. In this connection STO-3G computations are not sufficiently accurate for quantitative analysis and work is in progress in our laboratories to perform a full test with higher level ab initio results.[44]

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Registry No. Ac-Aib-NHMe, 42037-26-3; Ac-Ala-NHMe, 19701-83-8; F-Aib-NH$_2$, 124070-84-4; Ac-(Aib)$_2$-NHMe, 78274-11-0; Ac-(Aib)$_3$-NHMe, 78274-12-1; Ac-(Aib)$_4$-NHMe, 124070-85-5; Ac-(Aib)$_5$-NHMe, 124070-86-6; Ac-(Aib)$_8$-NHMe, 124070-87-7.

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Compatibility and Phase Behavior in Charged Polymer Systems and Ionomers

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ABSTRACT: In this paper we study the phase behavior of binary blends of charged macromolecules and ionomers. General formulas are given for the density fluctuations in the terms of the monomer and charge structure factors of the individual components, and the stability of the system is examined in detail. Coulombic and ionic interactions among the chains are shown to lead to a renormalization of the classical Flory–Huggins parameters χ_0 and χ_F. The main result is that polyelectrolytes of opposite charges are always compatible, due to the strong long-range Coulombic interaction, which can always overcome the thermodynamic repulsion. In ionomers, where the charges or dipoles are separated by a certain arc length along the chain, a micro phase separation can occur on length scales determined by the charge/ion distribution.

1. Introduction

The classical thermodynamic theory of polymer blends shows that is it extremely difficult to mix two or more polymers together, since the critical value of the so-called Flory–Huggins interaction parameter χ_0 is proportional to the inverse of the molecular weight N^{-1} of the polymers. (A physical explanation is given in the text book by de Gennes.[1]) Two polymers, A and B say, are only compatible if the thermodynamic interaction parameter χ_F between them is *less* than the critical χ_0.

It is now of great interest to modify polymers and polymer blends in such a way that the blends are more compatible over a larger range of concentration and temperature. There are basically two different ways of doing this: first, the whole blend is modified by the addition of a third component and second the polymers themselves can be modified. Consider for example a binary blend of A and B species, which is partially compatible, i.e. in a certain temperature and concentration range. In

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