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1-Amino-2-Phenylcyclopentane-1-carboxylic Acid: A Conformationally Restricted Phenylalanine Analogue

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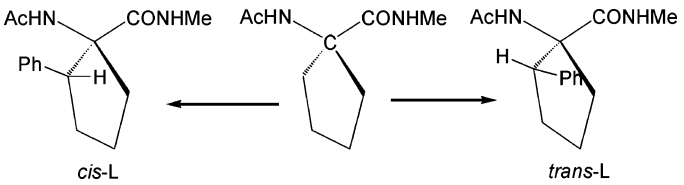

DFT calculations at the B3LYP/6-311G(d,p) level have been used to investigate the intrinsic conformational preferences of 1-amino-2-phenylcyclopentane-1-carboxylic acid (c_5Phe), a constrained analogue of phenylalanine in which the α and *β* carbons are included in a cyclopentane ring. Specifically, the *N*-acetyl-*N*′-methylamide derivatives of the *cis* and *trans* stereoisomers, where *cis* and *trans* refer to the relative position between the amino group and the phenyl ring, have been calculated. Solvent effects have been examined using a self-consistent reaction field (SCRF) method. Results indicate that the conformational space of the *cis* stereoisomer is much more restricted than that of the *trans* derivative both in the gas phase and in solution.

Introduction

Conformationally restricted α-amino acids are widely used in the construction of peptide analogues with controlled fold in the backbone. Among the α-amino acids whose structural rigidity can be exploited in the design of restricted peptides are α,α-dialkylated (also called *quaternary*) amino acids. Tetrasubstitution at C^{α} introduces severe constraints in the backbone torsion angles, thus stabilizing particular elements of peptide secondary structure.[1]

The simplest α,α-dialkylated amino acid is α-aminoisobutyric acid (Aib), that is, α-methylalanine. Replacement of the α hydrogen in alanine (Ala) by a methyl group results in a drastic reduction of the conformational space available. Theoretical and experimental studies[1−3] have demonstrated the strong tendency of Aib to induce folded structures in the 3_{10}-/α-helical region

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($\varphi,\psi \approx \pm 60°, \pm 30°$), while semi-extended or fully extended conformations are extremely rare for this residue. In comparison, Ala is easily accommodated in folded or extended structures.

For higher homologues of Aib with linear side chains (diethylglycine, dipropylglycine, dibutylglycine, etc.), the stability of helical structures decreases as the side-chain length increases and thus these residues have been shown to prefer fully extended conformations.[1] Conversely, their cyclic analogues (1-aminocycloalkane-1-carboxylic acids, Ac$_n$c) exhibit an overwhelming tendency to adopt folded conformations.[1] Among the Ac$_n$c series, the conformational propensities of the cyclopropane (Ac$_3$c),[1,4] cyclobutane (Ac$_4$c),[1,4b,5] cyclopentane (Ac$_5$c),[1,5b,6] and cyclohexane (Ac$_6$c)[1,5b,7] members have been deeply investigated and shown to strictly parallel those of Aib (with some distortion in the case of Ac$_3$c, which prefers the spatially close *bridge* region, $\varphi,\psi \approx \pm 80°, 0°$).

The preparation and subsequent structural study of conformationally restricted synthetic amino acids, which usually involves complex synthetic routes, is a topic of great interest in bio-organic chemistry. The conformational preferences of symmetrically α,α-dialkylated α-amino acids have been extensively investigated, whereas chiral residues have been much less studied due to synthetic difficulties. We are involved in a research project aimed at the preparation and the structural analysis of amino acids obtained by incorporating a phenyl ring at one of the β positions of the different Ac$_n$c residues ($n = 3-6$). The compounds thus obtained can be considered as phenylalanine (Phe) analogues, and we denote them as c$_n$Phe, with *n* referring to the size of the cycle, as in Ac$_n$c. Since the α and β carbons in c$_n$Phe are connected through an alkylidene bridge, rotation about the $C^{\alpha}-C^{\beta}$ bond is prohibited and the orientation of the aromatic side chain is therefore dictated by both the bridge length, that is, the ring size (*n*), and the stereochemistry at C^{α} and C^{β}. The additional phenyl substituent can be incorporated in a *cis* or a *trans* relative disposition with respect to the amino moiety (respectively giving rise to *cis*- or *trans*-c$_n$Phe derivatives), and therefore, four stereoisomeric forms are possible for each residue, namely, a *cis* and a *trans* analogue for both L- and D-Phe.

Thus, the different c$_n$Phe stereoisomers can be regarded as a series of phenylalanine analogues with different well-defined side-chain orientations. Since side chains are directly involved in molecular recognition processes, their three-dimensional arrangement is crucial for adequate peptide−receptor interactions. Moreover, the conformation of the peptide backbone may be modulated, to a certain extent, by the side-chain orientation, and the different members of the c$_n$Phe family are excellent tools to investigate this effect since the aromatic substituent may interact with the peptide backbone not only sterically but also electronically through the aromatic π orbitals.

We have developed synthetic methodologies[8] to obtain all enantiomerically pure stereoisomers of each c$_n$Phe residue for $n = 3-6$ and studied the conformational propensities of the cyclopropane (c$_3$Phe)[9] and cyclohexane (c$_6$Phe)[10] derivatives using both theoretical and experimental methods. The phenylalanine cyclopropane analogues exhibit a certain ability to influence the peptide conformation in solvents of low polarity,[9b,c] while the different c$_6$Phe stereoisomers are able to stabilize different types of turns according to the phenyl side-chain orientation and independently of the environment.[10a,c] Remarkably, the addition of a further phenyl substituent to c$_3$Phe has allowed us to study the helical peptide handedness in the absence of chirality at the α carbon,[11] to stabilize tubular nanostructures based on β-helical proteins,[12] and to characterize the first example of an incipient 2.2_7-helix (a double γ-turn).[13]

All stereoisomers of the cyclopentane derivative 1-amino-2-phenylcyclopentane-1-carboxylic acid (c$_5$Phe) have been recently synthesized,[8c] but in spite of the potential structural interest, no information about their intrinsic conformational preferences is available yet. In this work, we report a conformational study of the *N*-acetyl-*N*′-methylamide derivatives of the L enantiomer of *cis*-c$_5$Phe and *trans*-c$_5$Phe, hereafter denoted as Ac-*c*-L-c$_5$Phe-NHMe and Ac-*t*-L-c$_5$Phe-NHMe, respectively (Figure 1). Density functional theory (DFT) calculations at the B3LYP/6-311G(d,p) level have been used to locate and

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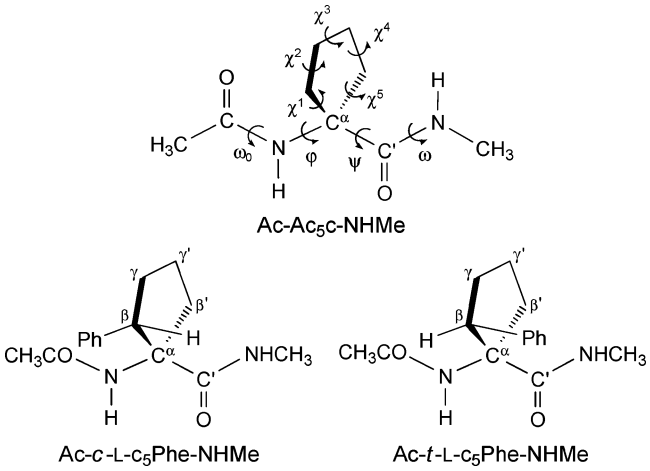

FIGURE 1. Structure of the dipeptides investigated, Ac-*c*-L-c_5Phe-NHMe and Ac-*t*-L-c_5Phe-NHMe. The backbone and side-chain dihedral angles are indicated for the unsubstituted Ac-Ac_5c-NHMe derivative, studied in a previous work.

characterize the minimum energy conformations, this theoretical method being identical to that applied in our previous study on the unsubstituted counterpart Ac-Ac_5c-NHMe.[6a] Furthermore, a previously reported conformational study on Ac-Ac_3c-NHMe, in which results obtained using different theoretical levels were compared, indicated that B3LYP calculations provide a reliable description of this kind of bio-organic molecules from both qualitative and quantitative points of view.[9a] The influence of the solvent polarity on the conformational preferences of the c_5Phe dipeptides has been examined using a self-consistent reaction field (SCRF) method.

Methods

The conformational properties of Ac-*c*-L-c_5Phe-NHMe and Ac-*t*-L-c_5Phe-NHMe have been investigated using the GAMESS computer program.[14] The conformational search was performed considering that these dipeptides retain the restrictions imposed by the cyclopentane ring on the backbone in Ac-Ac_5c-NHMe. Thus, the five minimum energy conformations characterized for Ac-Ac_5c-NHMe in ref 6a were used to generate the starting structures for Ac-*c*-L-c_5Phe-NHMe and Ac-*t*-L-c_5Phe-NHMe. Although for Ac-Ac_5c-NHMe such five minima were two-fold degenerated due to the symmetry of the molecule, that is, $\{\varphi,\psi,\chi^i\} = \{-\varphi,-\psi,-\chi^i\}$, the chiral nature of the two c_5Phe derivatives under study requires explicit consideration of both $\{\varphi,\psi,\chi^i\}$ and $\{-\varphi,-\psi,-\chi^i\}$ possibilities. The arrangement of the phenyl side group is defined by the flexible dihedral angle ξ, which is expected to exhibit three different minima: *trans* (180°), *gauche*$^+$ (60°), and *gauche*$^-$ (−60°). Consequently, 5 (minima of Ac-Ac_5c-NHMe) × 2 (chiral nature of the c_5Phe-containing dipeptides) × 3 (minima of ξ) = 30 minima can be anticipated for the potential energy hypersurface (PEH) $E = E(\varphi,\psi,\chi^i,\xi)$ of each c_5Phe-containing dipeptide. All these structures were used as starting points for subsequent full geometry optimizations.

All geometry optimizations were performed using the B3LYP functional[15,16] combined with the 6-311G(d,p) basis set.[17] Frequency analyses were carried out to verify the nature of the minimum state of all the stationary points obtained and to calculate the zero-point vibrational energies (ZPVE) and both thermal and entropic corrections. These statistical terms were then used to compute the conformational Gibbs free energies in the gas phase at 298 K (ΔG_{gp}).

To obtain an estimation of the solvation effects on the relative stability of the different minima, single-point calculations were conducted on the optimized structures using a SCRF model. Specifically, the polarizable continuum model (PCM) developed by Tomasi and co-workers[18] was used to describe water, chloroform, and carbon tetrachloride as solvents. The PCM model represents the polarization of the liquid by a charge density appearing on the surface of the cavity created in the solvent. This cavity is built using a molecular shape algorithm. PCM calculations were performed in the framework of the B3LYP/6-311G(d,p) level using the standard protocol and considering the dielectric constants of water ($\epsilon = 78.4$), chloroform ($\epsilon = 4.9$), and carbon tetrachloride ($\epsilon = 2.2$) to obtain the free energies of solvation (ΔG_{solv}) of the minimum conformations. Within this context, it should be emphasized that previous studies indicated that solute geometry relaxations in solution and single-point calculations on the optimized geometries in the gas phase give almost identical ΔG_{solv} values.[19,20] The conformational free energies in solution (ΔG^{conf}) at the B3LYP/6-311G(d,p) level were estimated using the classical thermodynamics scheme $\Delta G^{conf} = \Delta G_{gp} + \Delta G_{solv}$.

Results and Discussion

Using as starting points the 30 structures described in the Methods section, geometry optimizations at the B3LYP/6-311G(d,p) level led to the characterization of 8 and 10 minimum energy conformations, respectively, for Ac-*c*-L-c_5Phe-NHMe and Ac-*t*-L-c_5Phe-NHMe. This indicates that the steric and/or electronic interactions induced by the aromatic substituent produce the annihilation of many of the minima anticipated for the PEH $E = E(\varphi,\psi,\chi^i,\xi)$. Thus, the phenyl ring plays a significant role in the conformational preferences of the compounds under study.

Figure 2 represents the backbone φ,ψ angles of all the minimum energy conformations characterized for Ac-*c*-L-c_5Phe-NHMe and Ac-*t*-L-c_5Phe-NHMe. All minima are distributed around the C_5 (fully extended; $\varphi,\psi \approx \pm 180°,\pm 180°$), C_7^{eq} (equatorial C_7 or inverse γ-turn; $\varphi,\psi \approx -60°,60°$), C_7^{ax} (axial C_7 or classical γ-turn; $\varphi,\psi \approx 60°,-60°$), α_R (right-handed α-helix; $\varphi,\psi \approx -60°,-60°$), and α_L (left-handed α-helix; $\varphi,\psi \approx 60°,60°$) regions of the Ramachandran map. These results are fully consistent with those previously obtained for Ac-Ac_5c-NHMe,[6a] indicating that the backbone minimum energy conformations found for the unsubstituted amino acid (Ac_5c) are not significantly altered, as far as the geometry is concerned, by the incorporation of the phenyl side group. However, as shown below, the relative stability of such minima is strongly influenced by the presence and relative disposition (*cis*/*trans*) of the phenyl substituent, to the point that the aromatic side chain is responsible for the annihilation of the minima in the α_R region for Ac-*c*-L-c_5Phe-NHMe and of the α_L type for Ac-

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TABLE 1. Backbone and Side-Chain Dihedral Angles[a] and Relative Energies in the Gas Phase (ΔE) for the Minimum Energy Conformations of Ac-*c*-L-c$_5$Phe-NHMe Characterized at the B3LYP/6-311G(d,p) Level

	backbone dihedral angles				cyclopentane dihedral angles					Ph	
conformer	ω_0	φ	ψ	ω	χ^1	χ^2	χ^3	χ^4	χ^5	ξ	ΔE^b
$C_7^{eq}/_\beta E$	−175.4	−73.7	45.4	175.2	39.5	−37.2	19.9	5.2	−27.6	80.5/−99.8	0.0[c]
$C_7^{eq}/_\alpha E$	−172.6	−76.5	62.0	−179.1	−33.7	15.9	8.1	−29.3	39.2	101.0/−79.0	1.8
$C_7^{ax}/_\alpha E$	171.4	72.3	−62.1	178.1	−41.4	31.9	−10.6	−15.9	35.9	101.4/−80.0	2.5
$C_7^{ax}/_\beta E$	168.9	53.1	−22.5	−176.4	41.9	−36.3	16.1	10.7	−32.2	88.9/−92.0	6.3
$C_5/^\gamma E$	−173.9	−175.8	165.4	177.6	16.7	−36.7	42.9	−32.1	9.3	87.2/−92.8	2.8
$C_5/^{\gamma'} E$	−178.7	−164.5	172.2	174.5	−3.1	24.1	−36.3	34.2	−19.0	89.8/−91.6	6.4
$\alpha_L/^{\beta'} E$	166.4	60.3	35.2	−177.1	−15.5	−9.2	30.8	−40.7	34.8	110.0/−70.8	5.2
$\alpha_L/^\alpha E$	165.6	50.5	37.3	−173.2	39.7	−32.3	11.7	13.6	−32.9	87.6/−92.4	7.2

[a] In degrees; see Figure 1 for definition. [b] In kcal/mol. [c] $E = -843.351999$ au.

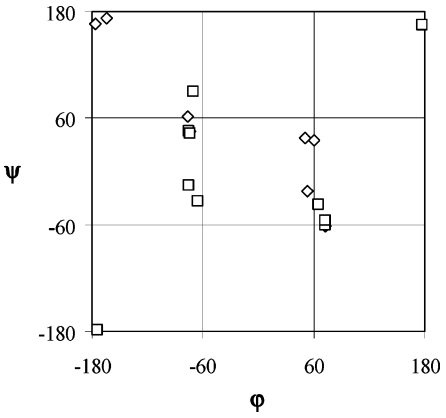

FIGURE 2. Distribution on the Ramachandran map of the minimum energy conformations characterized at the B3LYP/6-311G(d,p) level for the two c$_5$Phe-containing dipeptides. Diamonds and squares correspond to Ac-*c*-L-c$_5$Phe-NHMe and Ac-*t*-L-c$_5$Phe-NHMe, respectively.

t-L-c$_5$Phe-NHMe (Figure 2). In the absence of the phenyl ring (that is, for the unsubstituted Ac$_5$c derivative), the α_L and α_R structures are indistinguishable.[6a]

Ac-*c*-L-c$_5$Phe-NHMe. Table 1 lists the backbone and side-chain dihedral angles and the relative energies (ΔE) of all minima obtained for Ac-*c*-L-c$_5$Phe-NHMe in the gas phase. The eight minima are distributed as four pairs of conformations located at the C_7^{eq}, C_7^{ax}, C_5, and α_L regions of the Ramachandran map (Figure 2), the main difference within each pair being the arrangement of the cyclopentane ring. Inspection of the ΔE values in Table 1 reveals that only the two equatorial C_7 conformers are energetically accessible, the other six being destabilized with respect to the lowest energy conformation by more than 2.5 kcal/mol. In comparison, the five minima characterized for Ac$_5$c[6a] in the gas phase were found to lie within an energy range of 3.1 kcal/mol. All these facts together clearly indicate that the conformational space available to *cis*-c$_5$Phe is severely restricted due to the presence of the phenyl substituent.

The global minimum of Ac-*c*-L-c$_5$Phe-NHMe corresponds to $C_7^{eq}/_\beta E$ (Figure 3a), in which the terminal CO and NH groups form an intramolecular hydrogen bond [d(H···O) = 1.917 Å, <N−H···O = 154.5°], defining a seven-membered cycle (C_7 or γ-turn conformation), and the cyclopentane ring adopts a C^β-exo envelope ($_\beta$E) arrangement. This geometry combined with the *gauche*$^+$ orientation of the phenyl ring allows the formation of a stabilizing interaction between the π electron density of the aromatic side chain and the amino group of *cis*-c$_5$Phe. Both the distance between the NH hydrogen atom and the center of the phenyl ring ($d_{H\cdots Ph}$ = 3.352 Å) and the angle defined by the N−H bond and the plane of the aromatic ring (θ = 14.7°) are appropriate for the existence of this attractive interaction. As a matter of fact, interactions of the N−H···π-type have been frequently cited as stabilizing factors in the structure of peptides and proteins[21] and were invoked to explain the conformational preferences experimentally observed in small peptides containing the cyclopropane[9b] and cyclohexane[10c] analogues of phenylalanine.

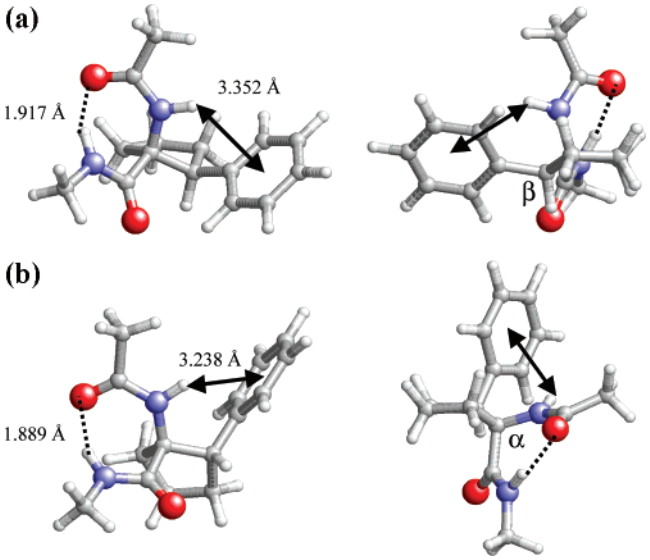

FIGURE 3. Lowest minimum energy conformations of Ac-*c*-L-c$_5$Phe-NHMe obtained from B3LYP/6-311G(d,p) calculations: (a) $C_7^{eq}/_\beta E$ and (b) $C_7^{eq}/_\alpha E$ conformers (see Table 1 for geometry). Two different views are depicted for each minimum to show the intramolecular N−H···O and N−H···π interactions (left) and the arrangement of the cyclopentane ring (right). Distances associated with the N−H···O hydrogen bonds (dashed lines) and N−H···π interactions (double arrows) are given. The carbon atom of the cyclopentane moiety deviating out of the plane (envelope conformation) has been labeled for clarification.

The $C_7^{eq}/_\alpha E$ conformation (Figure 3b) is 1.8 kcal/mol less stable than the global minimum. The peptide backbone also forms a seven-membered intramolecularly hydrogen-bonded ring [d(H···O) = 1.889 Å, <N−H···O = 151.2°], while the cyclopentane moiety adopts a C^α-exo envelope ($_\alpha$E) arrange-

(21) (a) Steiner, T.; Koellner, G. *J. Mol. Biol.* **2001**, *305*, 535. (b) Worth, G. A.; Wade, R. C. *J. Phys. Chem.* **1995**, *99*, 17473. (c) Mitchell, J. B. O.; Nandi, C. L.; McDonald, I. K.; Thornton, J. M. *J. Mol. Biol.* **1994**, *239*, 315. (d) Mitchell, J. B. O.; Nandi, C. L.; Ali, S.; McDonald, I. K.; Thornton, J. M. *Nature* **1993**, *366*, 413.

ment. This minimum is also stabilized by an N−H···π interaction between the phenyl ring and the methylamide group, with parameters ($d_{H\cdots Ph}$ = 3.238 Å, θ = 17.6°) similar to those found for the global minimum.

Comparison of the geometrical data listed in Table 1 and the pictures displayed in Figure 3 reveals that the only difference between the $C_7^{eq}/_{\beta}E$ and $C_7^{eq}/_{\alpha}E$ minima corresponds to the arrangement of the cyclopentane ring. Specifically, in the former, the β carbon bearing the bulky aromatic substituent is arranged in exo, with the axial position being occupied by the hydrogen atom attached to it, whereas in the $C_7^{eq}/_{\alpha}E$ minimum the α carbon is exo and the −CONHMe peptide fragment is oriented axially. Accordingly, this $_{\beta}E$-to-$_{\alpha}E$ transition leads to a destabilization by 1.8 kcal/mol.

The relative energies of the other six minima characterized for Ac-*c*-L-c$_5$Phe-NHMe range from 2.5 to 7.2 kcal/mol (Table 1), and therefore, their relative populations in the gas phase can be considered as negligible. Interestingly, for each backbone conformation, two different arrangements are found for the cyclopentane ring, as described above for the C_7^{eq} structure. In all cases, the five-membered cycle adopts an envelope conformation, and the flap of the envelope is occupied by one of the substituted carbons (C^{α} or C^{β}), with the exception of the C_5 minima, in which case it is the γ or γ' carbon that deviates out of the plane. Minima exhibiting C_7^{ax} or C_5 backbone dispositions are stabilized by intramolecular hydrogen bonds, at variance with the two minima located in the α_L region. On the other hand, analysis of the relative orientation between the NH and phenyl groups reveals that none of these six minima exhibit N−H···π interactions.

Comparison of the present results with those previously reported for Ac-Ac$_5$c-NHMe[6a] provides evidence for the strong influence that the aromatic substituent exerts on the conformational equilibrium of the cyclopentane ring, which, in turn, affects the conformational preferences of the peptide backbone. This effect is clearly illustrated when comparing the disposition accommodated by the cyclopentane moiety in the C_7 minima characterized for the Ac$_5$c and *cis*-c$_5$Phe dipeptides.

For the Ac$_5$c derivative,[6a] the peptide backbone was found to prefer a C_7 conformation (no distinction can be established in this case between the axial and equatorial dispositions), with two minima being located for the C^{α}-endo ($C_7/^{\alpha}E$) and C^{α}-exo ($C_7/_{\alpha}E$) envelope arrangements of the cyclopentane moiety. The former, in which the sterically more demanding substituent (−CONHMe) exhibits an equatorial orientation, was found to be favored by only 0.4 kcal/mol. Moreover, even if minima were located for only two dispositions of the five-membered ring, computation of the relative energy of the C_7 conformation as a function of the phase angle of pseudorotation of the cyclopentane system showed[6a] all the pseudorotational states to be accessible at room temperature for this backbone structure, with the highest barrier not exceeding 0.8 kcal/mol.

This situation differs notably from that encountered for *cis*-c$_5$Phe and described above. In the case of this nonsymmetrical molecule, the equatorial and axial C_7 backbone conformations are not equivalent and, for both of them, minima were found for the C^{β}-exo and C^{α}-exo envelope arrangements of the five-membered ring ($C_7^{eq}/_{\beta}E$, $C_7^{ax}/_{\beta}E$, $C_7^{eq}/_{\alpha}E$, $C_7^{ax}/_{\alpha}E$). The C^{α}-endo envelope disposition, which was preferred in the Ac$_5$c derivative, does not appear in any of the *cis*-c$_5$Phe minima. Moreover, the relative energies of the four C_7 minima characterized for the *cis*-c$_5$Phe dipeptide (Table 1) show that the flexibility of the cyclopentane ring is strongly limited by the presence of the phenyl substituent. When the cyclopentane moiety accommodates a C^{α}-exo envelope, an energy difference of 0.7 kcal/mol is observed between the C_7^{eq} and C_7^{ax} minima ($C_7^{eq}/_{\alpha}E$ and $C_7^{ax}/_{\alpha}E$, respectively). In comparison, a much higher energy cost is associated with the $C_7^{eq}/_{\beta}E$-to-$C_7^{ax}/_{\beta}E$ transition, with the latter conformation being destabilized by 6.3 kcal/mol (Table 1). This situation is in sharp contrast with the almost flat profile obtained for the pseudorotation of the five-membered ring in Ac-Ac$_5$c-NHMe[6a] and should be ascribed to unfavorable interactions between the phenyl ring and the substituents at the α carbon, whose relative disposition—for a given backbone conformation—is defined by the cyclopentane shape.

TABLE 2. Relative Conformational Gibbs Free Energies[a] at 298 K for the Minimum Energy Conformations of Ac-*c*-L-c$_5$Phe-NHMe in the Gas Phase (ΔG_{gp}), Carbon Tetrachloride (ΔG_{TEC}^{conf}), Chloroform (ΔG_{CHL}^{conf}), and Aqueous Solution (ΔG_{WAT}^{conf}) Characterized at the B3LYP/6-311G(d,p) Level

conformer	ΔG_{gp}	ΔG_{TEC}^{conf}	ΔG_{CHL}^{conf}	ΔG_{WAT}^{conf}
$C_7^{eq}/_{\beta}E$	0.0[b]	0.0	0.0	0.0
$C_7^{eq}/_{\alpha}E$	1.3	2.2	2.0	2.1
$C_7^{ax}/_{\alpha}E$	3.8	4.4	4.3	4.3
$C_7^{ax}/_{\beta}E$	5.6	6.1	5.7	5.8
$C_5/^{\gamma}E$	2.8	3.0	2.8	2.8
$C_5/^{\gamma'}E$	7.3	7.7	7.5	7.6
$\alpha_L/^{\beta'}E$	6.3	6.5	6.1	6.5
$\alpha_L/^{\alpha}E$	5.7	6.1	5.9	6.3

[a] In kcal/mol. [b] G = −843.066067 au.

Table 2 shows the conformational Gibbs free energies of all eight minima characterized for Ac-*c*-L-c$_5$Phe-NHMe in the gas phase at 298 K (ΔG_{gp}). As can be seen, addition of the ZPVE, thermal, and entropic contributions to the energies listed in Table 1 does not alter substantially the main conformational trends outlined above. Thus, the $C_7^{eq}/_{\beta}E$ and $C_7^{eq}/_{\alpha}E$ continue to be the only significant conformations, the ΔG_{gp} difference between them being 1.3 kcal/mol. Table 2 also compares the ΔG_{gp} values with the conformational free energies estimated in carbon tetrachloride, chloroform, and aqueous solutions at the same temperature. These data reveal that the strength of the solute−solvent interactions, which depends on the solvent polarity, does not alter the stability order obtained in the three solvents, which is identical to that observed in the gas phase. Interestingly, solvation seems to increase the stability of the global energy minimum, and indeed, according to a Boltzmann distribution, the population at room temperature of the $C_7^{eq}/_{\beta}E$ conformation increases from 90% in the gas phase to ∼97% in solution, while that of $C_7^{eq}/_{\alpha}E$ decreases from 9 to ∼3%. This behavior differs substantially from that observed before for Ac-Ac$_5$c-NHMe,[6a] for which the environment proved crucial to the relative stability of the different minima. Thus, in the gas phase, minimum energy conformations located in the α region were found to be destabilized by about 3 kcal/mol with respect to the global minimum, $C_7/^{\alpha}E$, whereas they became isoenergetic in aqueous solution.[6a]

Ac-*t*-L-c$_5$Phe-NHMe. In this compound, the phenyl ring is situated in a *trans* relative disposition with respect to the amino substituent. Therefore, the interactions between the aromatic side chain and the rest of the molecule (peptide backbone and cyclopentane ring) are expected to be different from those existing in *cis*-c$_5$Phe. Table 3 lists the main dihedral angles and the ΔE values of all 10 minima characterized in the gas phase for Ac-*t*-L-c$_5$Phe-NHMe.

TABLE 3. Backbone and Side-Chain Dihedral Angles[a] and Relative Energies in the Gas Phase (ΔE) for the Minimum Energy Conformations of Ac-*t*-L-c$_5$Phe-NHMe Characterized at the B3LYP/6-311G(d,p) Level

	backbone dihedral angles				cyclopentane dihedral angles					Ph	
conformer	ω_0	φ	ψ	ω	χ^1	χ^2	χ^3	χ^4	χ^5	ξ	ΔE[b]
$C_7^{eq}/_{\alpha}E$	−175.3	−75.1	45.3	174.5	−43.7	28.3	−1.6	−25.9	42.2	77.5/−103.6	0.0[c]
$C_7^{eq}/_{\alpha}E$-(b)	−173.5	−73.8	43.2	175.4	−41.2	25.9	−0.2	−25.6	41.0	179.2/−3.7	2.6
$C_7^{eq}/^{\alpha}E$	175.6	−70.4	89.5	−171.3	43.5	−31.4	7.5	20.1	−39.5	85.0/−97.4	4.2
$C_5/_{\gamma}E$	176.2	−174.1	−179.1	176.8	−18.8	36.1	−39.5	27.5	−5.2	126.7/−55.7	0.6
$C_5/_{\gamma'}E$	−176.5	177.6	164.2	173.0	0.9	−23.5	37.4	−36.7	22.0	99.8/−80.9	2.5
$C_7^{ax}/^{\alpha}E$	176.8	73.1	−55.9	−178.7	38.4	−27.2	5.7	18.9	−35.8	77.9/−103.3	1.0
$C_7^{ax}/_{\beta}E$	179.1	72.3	−60.0	−178.6	33.8	−39.6	30.2	−8.5	−15.9	43.6/−139.2	1.6
$C_7^{ax}/_{\alpha}E$	172.6	64.9	−37.7	−175.7	−38.5	32.5	−13.3	−11.7	31.1	71.8/−111.6	3.3
$\alpha_R/_{\alpha}E$	−172.7	−75.5	−15.4	179.9	−40.1	34.4	−14.9	−10.5	30.9	74.6/−105.7	1.5
$\alpha_R/^{\alpha}E$	−171.3	−65.4	−33.3	175.7	39.3	−25.7	2.6	22.4	−38.5	82.5/−98.6	5.2

[a] In degrees; see Figure 1 for definition. [b] In kcal/mol. [c] $E = -843.357832$ au.

Classification of these minima according to the backbone disposition is as follows (Figure 2): three C_7^{eq}, three C_7^{ax}, two C_5, and two α_R. Thus, each backbone conformation was found to be compatible with two or three different arrangements of the cyclopentane ring. Inspection of the ΔE values reveals that in this case five minima are energetically accessible, that is, four local minima are destabilized with respect to the lowest energy conformation by less than 1.6 kcal/mol. Moreover, the ΔE values of the less favored minima are significantly smaller than those obtained for the *cis* derivative. Thus, the ΔE of the least favored conformation characterized as a minimum is 5.2 and 7.2 kcal/mol for Ac-*t*-L-c$_5$Phe-NHMe (Table 3) and Ac-*c*-L-c$_5$Phe-NHMe (Table 1), respectively. The overall conclusion of these results indicates that the presence of a phenyl group in the neighborhood of the carbonyl group (*trans*-c$_5$Phe) imposes less severe conformational constraints than those produced when the phenyl substituent is close to the amino moiety (*cis*-c$_5$Phe).

The lowest energy structure found for Ac-*t*-L-c$_5$Phe-NHMe is a $C_7^{eq}/_{\alpha}E$ conformer (Figure 4a), with φ,ψ angles −75.1°, 45.3° and hydrogen-bonding parameters $d(H\cdots O) = 1.915$ Å and $<N-H\cdots O = 153.2°$. Additionally, the NH and phenyl substituents of *trans*-c$_5$Phe form a stabilizing N−H$\cdots\pi$ interaction ($d_{H\cdots Ph} = 3.605$ Å, $\theta = 9.1°$). This attractive interaction is allowed because the cyclopentane ring and the phenyl group accommodate C$^{\alpha}$-exo envelope ($_{\alpha}E$) and *gauche*$^+$ ($\xi = 77.5°$) dispositions, respectively, which leads to an almost parallel arrangement between the N−H bond and the aromatic ring plane.

Two additional minimum energy structures with an equatorial C_7 backbone conformation were detected. In $C_7^{eq}/_{\alpha}E$-(b), the cyclopentane ring also adopts a C$^{\alpha}$-exo envelope arrangement and, indeed, the only difference with respect to the global minimum is the orientation of the phenyl ring plane, which assumes a *trans* ξ dihedral angle ($\xi = 179.2°$), thus precluding the formation of any N−H$\cdots\pi$ interaction. Consequently, the $C_7^{eq}/_{\alpha}E$-(b) structure is 2.6 kcal/mol less stable than the global minimum. Similarly, no N−H$\cdots\pi$ interaction was detected for the $C_7^{eq}/^{\alpha}E$ minimum even when the aromatic side chain exhibits a *gauche*$^+$ disposition. Moreover, in this case, the C$^{\alpha}$-endo envelope ($^{\alpha}E$) arrangement accommodated by the cyclopentane moiety increases the proximity between the phenyl ring and the carbonyl oxygen of *trans*-c$_5$Phe, which leads to a destabilization of 4.2 kcal/mol with respect to the global minimum.

On the other hand, three minima with the backbone arranged in an axial C_7 conformation were characterized. Two of them, $C_7^{ax}/^{\alpha}E$ (Figure 4c) and $C_7^{ax}/_{\beta}E$ (Figure 4d), are relatively close in energy to the global minimum ($\Delta E = 1.0$ and 1.6 kcal/mol, respectively), whereas the $C_7^{ax}/_{\alpha}E$ minimum is destabilized by 3.3 kcal/mol. Thus, for a C_7^{ax} backbone arrangement, the change from an envelope C$^{\alpha}$-endo ($^{\alpha}E$) to a C$^{\alpha}$-exo ($_{\alpha}E$) disposition produces a destabilization of 2.3 kcal/mol.

Two minima with the backbone exhibiting a fully extended conformation were also located. In the $C_5/_{\gamma}E$ minimum (Figure 4b), the cyclopentane adopts a C$^{\gamma}$-exo envelope ($_{\gamma}E$) conformation and the amide moieties form a five-membered intramolecularly hydrogen-bonded ring with parameters $d(H\cdots O) = 1.990$ Å and $<N-H\cdots O = 113.3°$. This structure is destabilized with respect to the global minimum by only 0.6 kcal/mol.

An energetically accessible minimum was also found in the α_R helical region. Thus, the $\alpha_R/_{\alpha}E$ structure (Figure 4e) is 1.5 kcal/mol above the global minimum, which is quite a low ΔE value in the gas phase considering that no stabilizing intramolecular interaction either of the N−H$\cdots\pi$ or of the hydrogen bond type is present. Moreover, this ΔE value is significantly lower than that encountered for the α-helical conformations of Ac-Ac$_5$c-NHMe[6a] and other α,α-dialkylated amino acids with bulky side chains.[9a,22] The other α_R minimum located for the *trans*-c$_5$Phe dipeptide ($\alpha_R/^{\alpha}E$) differs from the $\alpha_R/_{\alpha}E$ conformer in the arrangement of the cyclopentane ring, and this change is associated with an energy difference of 3.7 kcal/mol. In comparison, a quite flat profile was obtained for the cyclopentane ring pseudorotation in Ac-Ac$_5$c-NHMe for an α-helical backbone structure.[6a] Thus, the phenyl ring in *trans*-c$_5$Phe does induce profound alterations in the conformational states accessible to the cyclopentane system. It is indeed remarkable that the largest energy gaps in Table 3 are observed between different dispositions of the cyclopentane ring for a given backbone conformation rather than being associated with changes in the peptide backbone structure. This behavior is completely different from that expected for a proteinogenic amino acid, where the orientation of the side chain influences the conformational preferences of the peptide backbone in a more subtle way.[23]

The ΔG_{gp} values reported in Table 4 indicate that the addition of ZPVE, thermal, and entropic corrections does not affect significantly the conformational profile of *trans*-c$_5$Phe presented above. According to these results, Ac-*t*-L-c$_5$Phe-NHMe can be

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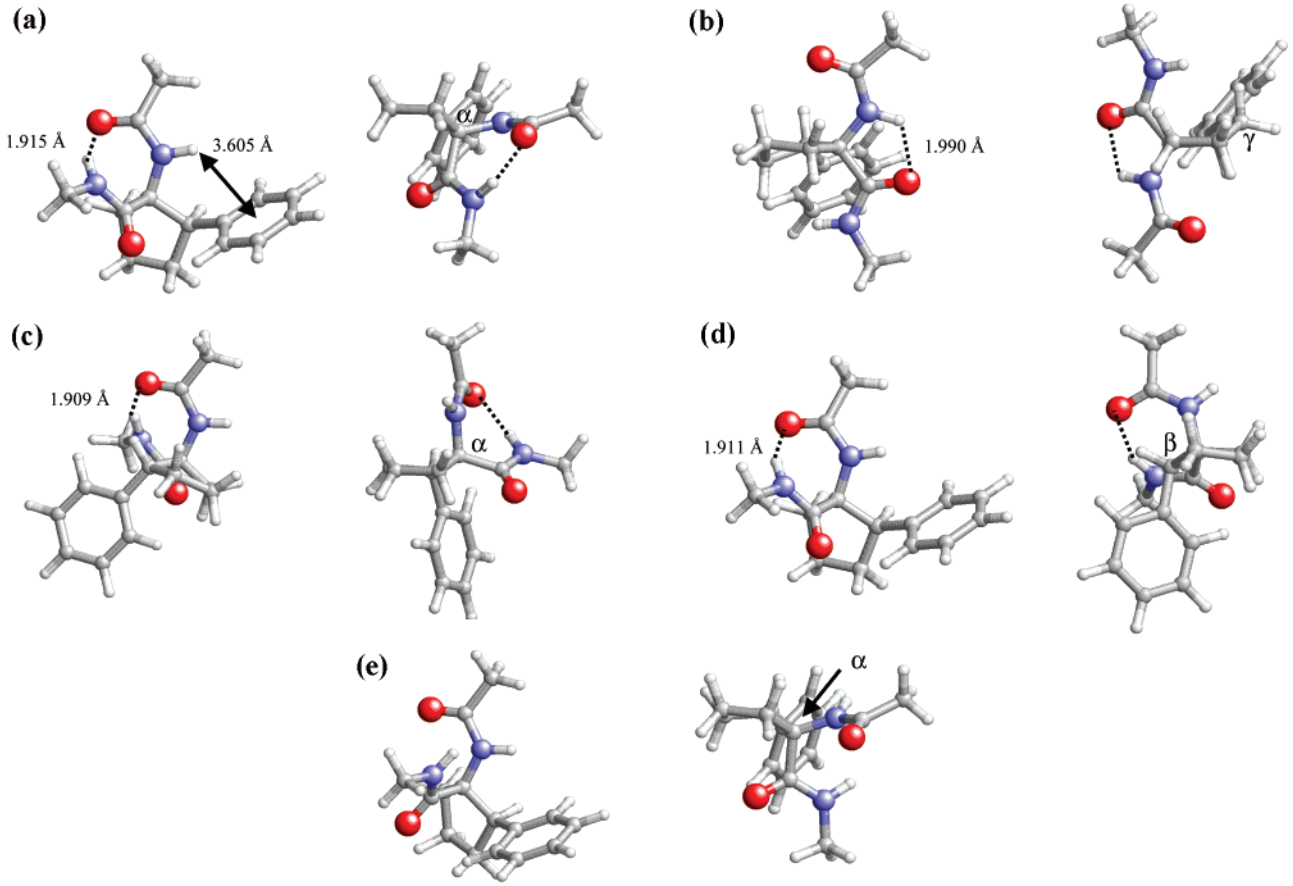

FIGURE 4. Lowest minimum energy conformations of Ac-*t*-L-c_5Phe-NHMe obtained from B3LYP/6-311G(d,p) calculations: (a) $C_7^{eq}/_{\alpha}E$, (b) $C_5/_{\gamma}E$, (c) $C_7^{ax}/^{\alpha}E$, (d) $C_7^{ax}/_{\beta}E$, and (e) $\alpha_R/_{\alpha}E$ conformers (see Table 3 for geometry). Two different views are depicted for each minimum to show the intramolecular N−H···O and N−H···π interactions (left) and the arrangement of the cyclopentane ring (right). Distances associated with the N−H···O hydrogen bonds (dashed lines) and N−H···π interactions (double arrows) are given. The carbon atom of the cyclopentane moiety deviating out of the plane (envelope conformation) has been labeled for clarification.

TABLE 4. Relative Conformational Gibbs Free Energies[a] at 298 K for the Minimum Energy Conformations of Ac-*c*-L-c_5Phe-NHMe in the Gas Phase (ΔG_{gp}), Carbon Tetrachloride (ΔG_{TEC}^{conf}), Chloroform (ΔG_{CHL}^{conf}), and Aqueous Solution (ΔG_{WAT}^{conf}) Characterized at the B3LYP/6-311G(d,p) Level

conformer	ΔG_{gp}	ΔG_{TEC}^{conf}	ΔG_{CHL}^{conf}	ΔG_{WAT}^{conf}
$C_7^{eq}/_{\alpha}E$	0.0[b]	0.0	0.0	0.0
$C_7^{eq}/_{\alpha}E$-(b)	2.6	2.0	1.8	1.6
$C_7^{eq}/^{\alpha}E$	4.3	3.4	3.0	2.6
$C_5/_{\gamma}E$	0.8	0.6	0.4	0.2
$C_5/_{\gamma'}E$	2.2	2.2	1.9	1.8
$C_7^{ax}/^{\alpha}E$	1.6	1.1	0.7	0.4
$C_7^{ax}/_{\beta}E$	1.4	1.2	0.9	0.7
$C_7^{ax}/_{\alpha}E$	2.5	2.8	2.5	2.5
$\alpha_R/_{\alpha}E$	0.8	0.8	0.5	0.6
$\alpha_R/^{\alpha}E$	4.2	3.4	2.9	3.2

[a] In kcal/mol. [b] $G = -843.062158$ au.

described in the gas phase at room temperature by six minimum energy conformations that present non-negligible Boltzmann populations: 55% $C_7^{eq}/_{\alpha}E$, 15% $\alpha_R/_{\alpha}E$, 14% $C_5/_{\gamma}E$, 5% $C_5/_{\gamma'}E$, 5% $C_7^{ax}/_{\beta}E$, and 4% $C_7^{ax}/^{\alpha}E$, while the remaining four conformations contribute by about 2%. Data in Table 4 indicate that the environment alters the conformational description from a quantitative point of view but not qualitatively. The relative stability of all local minima is enhanced in solution, and the magnitude of these stabilizations increases with the polarity of the solvent. For example, the Boltzmann populations obtained for the more significant minima in aqueous solution are 32% $C_7^{eq}/_{\alpha}E$, 23% $C_5/_{\gamma}E$, 16% $C_7^{ax}/^{\alpha}E$, 11% $C_7^{ax}/_{\beta}E$, and 11% $\alpha_R/_{\alpha}E$, whereas the other five conformations contribute about 7% altogether. Thus, the population of the $C_7^{eq}/_{\alpha}E$ conformer decreases from 55% in the gas phase to 32% in water. This shows that the stereoisomer with a *trans* phenyl group is more sensitive to solvent polarity than that with the aromatic ring in a *cis* disposition.

Conclusions

Quantum mechanical calculations at the B3LYP/6-311G(d,p) level have been used to explore the conformational preferences of Ac-*c*-L-c_5Phe-NHMe and Ac-*t*-L-c_5Phe-NHMe. Results allow us to draw the following conclusions about the intrinsic conformational preferences of these cyclopentane analogues of phenylalanine: (i) The energy minima characterized for the two c_5Phe dipeptides show backbone geometries similar to those previously found for the unsubstituted Ac-Ac_5c-NHMe. However, the phenyl side group affects significantly the relative stability of these conformations and produces the annihilation of some of the expected minima. The aromatic substituent gives rise to steric and electronic interactions with the contiguous −CONHMe and −NHCOMe peptide fragments, which depend on the *cis*/*trans* stereochemistry and the conformation adopted by the peptide backbone. Moreover, the cyclopentane ring

puckering is also strongly affected by the aromatic substituent. (ii) The lowest energy minima of Ac-*c*-L-c_5Phe-NHMe and Ac-*t*-L-c_5Phe-NHMe are $C_7^{eq}/_{\beta}E$ and $C_7^{eq}/_{\alpha}E$, respectively. These structures are stabilized by both hydrogen bond and N−H$\cdots\pi$ intramolecular interactions and differ only in the arrangement of the cyclopentane ring. (iii) The conformation of Ac-*c*-L-c_5-Phe-NHMe in the gas phase at room temperature can be described using only the lowest energy minimum ($C_7^{eq}/_{\beta}E$), while six minima with populations ranging from 55 to 4% are required to represent the *trans*-c_5Phe derivative. These results indicate that the conformational restrictions imposed by the phenyl substituent are significantly more severe in the former dipeptide. (iv) Although the solvation effects have been found to be more intense for the *trans*-c_5Phe stereoisomer, the environment does not alter substantially the conformational preferences observed in the gas phase for any of the c_5Phe dipeptides. This behavior is in high contrast to that described before for Ac-Ac_5c-NHMe.

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Supporting Information Available: Coordinates and energy of the minimum energy conformations characterized for Ac-*c*-L-c_5Phe-NHMe and Ac-*t*-L-c_5Phe-NHMe. This material is available free of charge via the Internet at http://pubs.acs.org.

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