JOC*Note*

N-Acetyl-*N*′-methylamide Derivative of (2*S*,3*S*)-1-Amino-2,3-diphenylcyclopropanecarboxylic Acid: Theoretical Analysis of the Conformational Impact Produced by the Incorporation of the Second Phenyl Group to the Cyclopropane Analogue of Phenylalanine

Jordi Casanovas,*,† Ana I. Jiménez,‡ Carlos Cativiela,‡ Juan J. Pérez,§ and Carlos Alemán*,§

Departament de Química, Escola Universitària Politècnica, Universitat de Lleida, c/Jaume II No. 69, 25001 Lleida, Spain, Departamento de Química Orgánica, ICMA, Universidad de Zaragoza-CSIC, 50009 Zaragoza, Spain, and Departament d'Enginyeria Química, E.T.S. d'Enginyers Industrials de Barcelona, Universitat Politècnica de Catalunya, Diagonal 647, 08028 Barcelona, Spain

jcasanovas@quimica.udl.es; carlos.aleman@upc.es

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Abstract: The intrinsic conformational preferences of (2*S*,3*S*)-1-amino-2,3-diphenylcyclopropanecarboxylic acid, a phenylalanine cyclopropane analogue bearing two phenyl substituents, have been examined theoretically. For this purpose, its *N*-acetyl-*N*′-methylamide derivative, Ac-(2*S*,3*S*)-$c_3$diPhe-NHMe, has been investigated by using ab initio HF and DFT methods. Results have been compared with those previously reported for other cyclopropane analogues of phenylalanine, and with experimental data available for $c_3$diPhe-containing peptides.

α,α-Dialkylated amino acids have been widely used to reduce the flexibility of peptide chains.[1] Thus, the (φ,ψ) conformational space allowed to the simplest α,α-dialkylated residue (α-aminoisobutyric acid, Aib) is drastically reduced with reference to its unmethylated counterpart (alanine, Ala).[1,2] In the cyclic homologue of Aib (1-aminocyclopropanecarboxylic acid, Ac_3c) the restrictions imposed by α,α-dialkylation are modulated by the peculiar stereoelectronic properties of the cyclopropane ring.[1a,c,2a]

The incorporation of selectively oriented side substituents to conformationally restricted amino acids should also be considered in the design of peptide analogues with controlled fold in the backbone, given the possible influence of the side chain disposition on the main chain conformation.[3] In this context, we are interested in the incorporation of one or more phenyl groups to the cyclopropane ring of Ac_3c. The amino acids thus obtained, which can be viewed as phenylalanine analogues, are valuable systems for these studies due to the rigidity of the three-membered ring and the rich electronic properties of the phenyl group.

We have investigated the conformational propensities of the different stereoisomers of 1-amino-2-phenylcyclopropanecarboxylic acid (c_3Phe) by using both experimental[4] and theoretical[5] methodologies. Results indicate that steric and electronic interactions between the rigidly held aromatic side chain and the main chain affect the conformational preferences of the latter to an extent that depends on the side chain orientation, i.e. on the c_3Phe stereochemistry.

Recently, an Ac_3c derivative incorporating two vicinal phenyl substituents in a trans relative disposition ($c_3$diPhe) has been synthesized[6] and each of the two enantiomers has replaced phenylalanine in a derivative of the RNase A *C*-peptide, leading to either the stabilization or the disruption of the helical conformation accommodated by the parent peptide.[6b] Moreover, preliminary studies on model peptides containing $c_3$diPhe[7] present this highly constrained phenylalanine analogue as a promising candidate for the stabilization of peptide secondary structures, in particular, the γ-turn conformation.[8] Notably, a model peptide incorporating $c_3$diPhe has been shown to adopt a distorted γ-turn by X-ray diffraction crystallography.[7a] This amino acid could have wide applications in peptide design and, therefore, an understanding of its conformational features from a theoretical point of view is important to anticipate its value in the induction of peptide secondary structures.

In this note, we describe the intrinsic conformational preferences of one of the $c_3$diPhe enantiomers investigated with quantum mechanical calculations. A conformational analysis of Ac-(2*S*,3*S*)$c_3$diPhe-NHMe (Figure 1) has allowed us to identify and characterize all the minimum energy conformations and to examine their relative stability in different environments. Results have been compared with literature data on $c_3$diPhe-containing peptides, as well as with the behavior theoretically predicted for Ac-(1*S*,2*S*)c_3Phe-NHMe and Ac-(1*R*,2*S*)c_3-Phe-NHMe.[5] It should be noted that (2*S*,3*S*)$c_3$diPhe can be viewed as a combination of (1*S*,2*S*)- and (1*R*,2*S*)c_3Phe, incorporating a cis and a trans phenyl substituent, respectively (Figure 1).

* To whom correspondence should be addressed.
† Universitat de Lleida.
‡ Universidad de Zaragoza-CSIC.
§ Universitat Politècnica de Catalunya.

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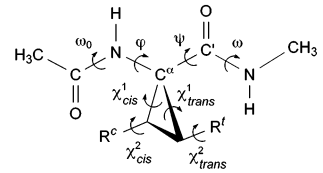
TABLE 1. Dihedral Angles[a] for the Conformational Energy Minima of the (2*S*,3*S*)c$_3$diPhe Amino Acid Derivative at the HF/6-31G(d) and B3LYP/6-31G(d) Levels

	ω_0	φ	ψ	χ^1_{cis}	χ^1_{trans}	χ^2_{cis}	χ^2_{trans}	ω
HF/6-31G(d)								
1	−177.4	−82.3	47.0	7.0	−140.1	80.3/−100.9	80.0/−102.1	174.7
2	162.9	−75.4	167.8	10.1	−139.2	79.0/−102.8	71.7/−111.4	−178.8
3	165.4	68.7	27.2	7.6	−135.3	77.7/−105.0	71.0/−112.3	−174.2
4	−167.9	58.9	−131.1	7.3	−139.0	73.6/−110.1	63.9/−119.6	175.2
B3LYP/6-31G(d)								
1	−174.7	−78.5	46.3	7.2	−139.8	78.7/−101.9	80.5/−101.1	175.8
2	162.2	−81.8	166.3	10.7	−138.2	120.7/−59.1	73.3/−109.5	−179.4
3	167.4	67.1	26.5	7.8	−132.1	73.8/−108.6	115.3/−66.1	−175.2
4	−173.2	63.3	−115.1	5.6	−139.6	73.7/−109.6	63.5/−120.0	173.4

[a] In degrees; see Figure 1 for definition.



Ac-Ac$_3$c-NHMe	$R^c = R^t$ = H
Ac-(1*S*,2*S*)c$_3$Phe-NHMe	R^c = Ph R^t = H
Ac-(1*R*,2*S*)c$_3$Phe-NHMe	R^c = H R^t = Ph
Ac-(2*S*,3*S*)c$_3$diPhe-NHMe	$R^c = R^t$ = Ph

FIGURE 1. Chemical structure of the Ac-(2*S*,3*S*)c$_3$diPhe-NHMe monopeptide investigated in the present work. The phenylalanine cyclopropane analogues with a single phenyl substituent (c$_3$Phe) and the unsubstituted parent compound (Ac$_3$c) are also shown for comparison. The α-carbon corresponds to position 1, while positions 2 and 3 refer to the *β*-carbons. The phenyl substituents are considered cis (*c*) or trans (*t*) according to their disposition relative to the N-terminus. Dihedral angles are defined as suggested by the IUPAC-IUB Commission (*Biochemistry* **1971**, *9*, 3471).

The conformational properties of Ac-(2*S*,3*S*)c$_3$diPhe-NHMe have been investigated with use of the Gaussian 98 program[9] package. It was considered that this amino acid derivative retains the restrictions imposed by the cyclopropane ring to the backbone conformation of Ac-Ac$_3$c-NHMe. Thus, the three minima characterized for Ac-Ac$_3$c-NHMe at the HF/6-31G(d) level [(φ,ψ) = (i) (−79°,32°); (ii) (180°,180°); (iii) (71°,-146°)][2a,5] were used to generate the starting structures for ab initio geometry optimizations. Furthermore, minima (i) and (iii) were 2-fold degenerated [$E(\varphi,\psi) = E(-\varphi,-\psi)$] for Ac-Ac$_3$c-NHMe, but this does not hold true for the (2*S*,3*S*)c$_3$diPhe derivative because of the chiral nature of the compound. Regarding the side chain disposition, the values of χ^1_{cis} and χ^1_{trans} are fixed by the cyclopropane system (Table 1), whereas the dihedral angles χ^2_{cis} and χ^2_{trans}, defining the orientation of the phenyl planes, are flexible and three minima (trans, gauche$^+$, and gauche$^-$) are expected. Accordingly, 45 minima can be anticipated for the potential energy hypersurface $E = E(\varphi,\psi,\chi^2_{cis},\chi^2_{trans})$ of Ac-(2*S*,3*S*)c$_3$diPhe-NHMe, i.e. (2 × 2) + 1 backbone minima × 3 minima for χ^2_{cis} × 3 minima for χ^2_{trans}. These structures were built and taken as starting points in HF/6-31G(d)[10] geometry optimizations. The HF/6-31G(d) minimum energy conformations were fully reoptimized at the B3LYP/6-31G(d)[11] level. Frequency analyses were additionally employed to compute the conformational free energies in the gas phase (ΔG^{gp}_{conf}) at 298 K, using the standard statistical formulas. Furthermore, single-point energy calculations were performed at the B3LYP/6-311G(d,p) level on the B3LYP/6-31G(d) minima.

On this basis, only four minima were characterized for Ac-(2*S*,3*S*)c$_3$diPhe-NHMe at the HF/6-31G(d) and B3LYP/6-31G(d) levels. As can be seen in Table 1, both methods provide similar backbone conformations. However, the side chain disposition of minima **2** and **3** largely depend on the computational method.

Relative energies (ΔE_{gp}) and free energies (ΔG^{gp}_{conf}) computed at three different levels of theory are listed in Table 2. In all cases the same ordering of conformers is obtained. The ΔE_{gp} and ΔG^{gp}_{conf} values predicted at the HF/6-31G(d) level are underestimated by 1.2 kcal/mol, on average, with respect to the B3LYP/6-31G(d) ones. On the other hand, comparison between the B3LYP/6-31G(d) and B3LYP/6-311G(d,p) results reveals that the influence of the basis set expansion is small in relation to that of electron correlation. Furthermore, previous studies on small model peptides indicated that energies are relatively insensitive to the inclusion of diffuse functions.[12]

Conformer **1** (Figure 2a) is the lowest energy minimum and corresponds to an equatorial C_7 (seven-membered hydrogen bonded ring) or γ-turn conformation, with hydrogen bonding parameters d(H···O) = 1.967 Å and ∠N−H···O = 150.6°. This conformation is additionally stabilized by an attractive interaction between the c$_3$-diPhe N−H and the π cloud of the cis phenyl group.[13] The distance between the amide hydrogen and the center

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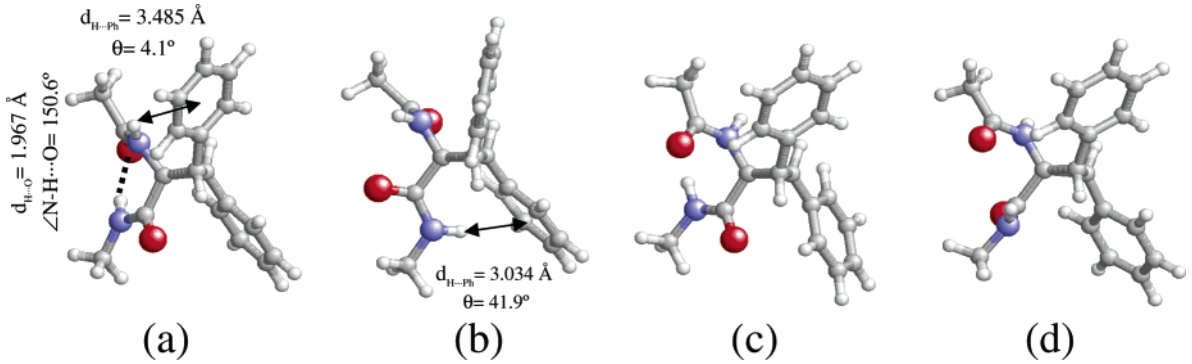

FIGURE 2. Minimum energy conformations of Ac-(2*S*,3*S*)$c_3$diPhe-NHMe obtained at the B3LYP/6-31G(d) level: (a) **1**, (b) **2**, (c) **3**, and (d) **4**. Hydrogen bonding distances (H···O) and angles (N−H···O), as well as the parameters associated with the interactions between the N−H bonds and the phenyl rings (H···Ph center distance, d_H···Ph; N−H···Ph angle, θ), are indicated.

TABLE 2. Relative Energies[a] (ΔE_{gp}) and Conformational Free Energies[a] (ΔG^{gp}_{conf}; at 298 K) for the Minima of the (2*S*,3*S*)$c_3$diPhe Amino Acid Derivative in the Gas Phase

level[b]		1	2	3	4
HF/6-31G(d)//	ΔE_{gp}	0.0[c]	2.5	4.5	4.7
HF/6-31G(d)	ΔG^{gp}_{conf}	0.0[d]	2.6	4.4	5.0
B3LYP/6-31G(d)//	ΔE_{gp}	0.0[e]	3.6	5.0	6.5
B3LYP/6-31G(d)	ΔG^{gp}_{conf}	0.0[f]	4.0	5.5	6.3
B3LYP/6-311G(d,p)//	ΔE_{gp}	0.0[g]	3.3	4.7	5.9
B3LYP/6-31G(d)	ΔG^{gp}_{conf} [h]	0.0[i]	3.8	5.2	5.6

[a] In kcal/mol. [b] Level of energy calculation//level of geometry optimization. [c] $E = -989.790774$ au. [d] $G = -989.462062$ au. [e] $E = -996.032030$ au. [f] $G = -995.731231$ au. [g] $E = -996.289831$ au. [h] Vibrational corrections obtained at the B3LYP/6-31G(d) level are included. [i] $G = -995.989032$ au.

of the ring is 3.485 Å, with a parallel arrangement between the N−H bond and the phenyl plane ($\theta = 4.1°$, Figure 2a). The C_{7eq} structure was also identified as the global minimum for both Ac-(1*S*,2*S*)c_3Phe-NHMe and Ac-(1*R*,2*S*)c_3Phe-NHMe,[5] a similar N−H···π interaction ($d_{H···Ph} = 3.396$ Å, $\theta = 9.1°$) being detected for the cis derivative. This conformation was also predicted as the most stable disposition for *p*-BrBz-(2*S*,3*S*)$c_3$diPhe-NH^{i}Pr by using energy calculations based on classical potentials.[7b] Moreover, a γ-turn has been observed in the crystalline structure of ^{t}BuCO-L-Pro-(2*R*,3*R*)$c_3$diPhe-NH^{i}Pr[7a] (in this case, the enantiomeric C_{7ax} arrangement is adopted). This result is noteworthy because, to the best of our knowledge, this structure has never been found among the X-ray structures of peptides incorporating Ac_3c or c_3Phe. As a matter of fact, the C_7 conformation is generally predicted as the lowest energy minimum for Ac-Xaa-NHMe monopeptides,[14] but is very rarely found in the crystalline form.[15]

Interestingly, the ψ dihedral angle predicted for **1** (Table 1) is about 25° smaller than that expected for an ideal γ-turn ($\psi \sim 70°$).[13] This feature, which was already detected in our previous calculations on Ac_3c[2a,5,14c] and c_3Phe[5] derivatives, can be attributed to hyperconjugation between the lone pairs of the $c_3$diPhe carbonyl oxygen and the adjacent σ^* $C^\beta-C^{\beta'}$ molecular orbital, which is optimal when the C=O bond bisects the $C^\beta-C^\alpha-C^{\beta'}$ angle ($\psi = 0°$).[16] Moreover, the distortion of the ψ dihedral predicted theoretically is in agreement with the scarce crystallographic data available for γ-folded cyclopropane residues.[7a,17,18]

It is also noteworthy that, even if small ψ values are a general trend of the C_7 conformation for cyclopropane residues, the side substituents are able to modulate the backbone geometry. Thus, at the B3LYP/6-31G(d) level, the ψ angle predicted for the C_{7eq} minimum of both Ac-Ac_3c-NHMe[5] and Ac-(1*S*,2*S*)c_3Phe-NHMe[5] lies close to 36°, whereas for the derivatives incorporating (1*R*,2*S*)-c_3Phe[5] and (2*S*,3*S*)$c_3$diPhe (Table 1) ψ values around 46° are obtained. This difference can be ascribed to the trans phenyl substituent present in the two latter compounds, which introduces severe repulsions with the carbonyl oxygen when ψ approaches 0°.

Minima **2** (Figure 2b) and **4** (Figure 2d) correspond to polyproline II (P_{II}) conformations of opposite handedness and are respectively 3.8 and 5.6 kcal/mol less stable than the global minimum (Table 2). These semiextended structures are not intramolecularly hydrogen bonded. In minimum **2** a stabilizing interaction between the terminal methylamide N−H and the π orbitals of the trans aromatic substituent is established ($d_{H···Ph} = 3.034$ Å), with a tilted arrangement between the N−H bond and the phenyl plane ($\theta = 41.9°$). An N−H···π interaction with almost identical geometrical parameters was also present in the P_{II} minimum energy conformation characterized for Ac-(1*R*,2*S*)c_3Phe-NHMe at (φ,ψ) = (−83°,-169°).[5] Although a φ angle in the −80° region should allow an additional interaction between the $c_3$diPhe amide hydrogen and the cis phenyl group, as described above for minimum **1**, in the case of **2** the amide bond involving this NH exhibits a significant deviation from planarity ($\omega_0 = 162°$, Table 1) and this deformation increases the distance between the amide hydrogen and

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the phenyl ring center to 4.102 Å, too large for an efficient N−H···π interaction. In minimum **4**, both $d_{H\cdots Ph}$ distances exceed 4.95 Å, thus precluding the existence of amide−aromatic interactions, a factor that could contribute to the higher energy predicted for **4** in relation to **2**. Conformation **4** was identified as a potential energy minimum for Ac-(1*S*,2*S*)c_3Phe-NHMe at the HF/6-31G(d) level [(φ,ψ) = (60°,-129°)], but it was annihilated by the inclusion of electron correlation effects through the B3LYP method.[5] The P_{II} conformation has been observed in the solid state for several *N*-acyl derivatives of Ac_3c with a carboxylic acid or a methyl ester functionality at the C-terminus.[18] However, as far as we know, only one diamide derivative of a cyclopropaneamino acid has been reported to adopt such a semiextended structure in the crystal state.[7b]

Minimum **3** (Figure 2c) corresponds to a left-handed 3_{10}-/α-helical conformation and is 5.2 kcal/mol less stable than the global minimum (Table 2). No stabilizing intramolecular interaction either of the N−H···π or of the hydrogen bond type is present in this structure. It was characterized as an energy minimum for Ac-(1*R*,2*S*)c_3-Phe-NHMe, but not for the (1*S*,2*S*)c_3Phe and Ac_3c monopeptides.[5] Remarkably, the (φ,ψ) angles of minimum **3** [(67°,27°), Table 1] are almost identical with those found for the $c_3$diPhe residue in the crystal structures of ^{t}BuCO-L-Pro-(2*S*,3*S*)$c_3$diPhe-NH^{i}Pr [(67°,25°)][7a] and Bz-$c_3$diPhe-OMe [(67°,26°)].[6a] The solid state conformation reported for *p*-BrBz-(2*S*,3*S*)$c_3$diPhe-NH^{i}Pr [(φ,ψ) = (65°,44°)][7b] also lies in the helical region of the conformational map.

It should be noted that the minimum characterized for Ac-(1*R*,2*S*)c_3Phe-NHMe [(φ,ψ) = (86°,16°)][5] deviates slightly toward the spatially close *bridge* region [(φ,ψ) = (±90°,0°)][19] with reference to the (φ,ψ) values of minimum **3**. However, this small difference seems to have an important conformational impact, since most Ac_3c and c_3Phe residues incorporated into small peptides actually accommodate backbone dispositions in the *bridge* rather than in the helical region.[1a,c,4a,18]

The results described evidence that the conformational preferences of (2*S*,3*S*)$c_3$diPhe are marked by the simultaneous presence of a cis and a trans phenyl substituent, which limit respectively the values accessible to φ and ψ both by steric factors and by electronic interactions with the amide groups. Thus, the incorporation of a second phenyl group to the c_3Phe derivatives results in the disappearance of some minimum energy conformations (such as the fully extended and the axial C_7 structures respectively characterized for (1*R*,2*S*)- and (1*S*,2*S*)c_3Phe)[5] as well as in the modification of the energy and geometry of other minima. Remarkably, all four crystalline structures reported in the literature for $c_3$diPhe derivatives[6a,7] exhibit backbone conformations in excellent agreement with the theoretical predictions.

The effect of the solvent on the conformational preferences of Ac-(2*S*,3*S*)$c_3$diPhe-NHMe was estimated by using the MST model,[20] which is a continuum method based on the PCM originally developed by Miertus, Scrocco, and Tomasi.[21] Three different solvents were considered: water,[20a] chloroform,[20b] and carbon tetrachloride.[20c] MST calculations were performed in the framework of the semiempirical AM1 method (MST/AM1).[20] The conformational free energies in solution (ΔG^{sol}_{conf}) were estimated by adding the ΔG_{sol} provided by MST calculations to the ΔG^{gp}_{conf}. MST/AM1 calculations were performed using a modified version of MOPAC.[22]

TABLE 3. Free Energies of Solvation[a,b] (ΔG_{sol}) and Conformational Free Energies in Solution[a,c] (ΔG^{sol}_{conf}; at 298 K) for the Minima of the (2*S*,3*S*)$c_3$diPhe Amino Acid Derivative in CCl_4, $CHCl_3$, and Aqueous Solutions

	ΔG_{sol}			ΔG^{sol}_{conf}		
	CCl_4	$CHCl_3$	H_2O	CCl_4	$CHCl_3$	H_2O
1	−15.3	−19.2	−12.1	0.0	0.0	0.0
2	−15.3	−19.3	−12.8	3.8	3.7	3.1
3	−15.5	−20.0	−15.1	5.0	4.4	2.2
4	−15.0	−19.2	−13.9	5.9	5.6	3.8

[a] In kcal/mol. [b] ΔG_{sol} values were computed with the MST/AM1 model. [c] ΔG^{sol}_{conf} values were estimated by adding $\Delta\Delta G_{sol}$ to the ΔG^{gp}_{conf} computed at the B3LYP/6-311G(d,p)//B3LYP/6-31G(d) level (Table 2).

Table 3 reports the ΔG_{sol} and ΔG^{sol}_{conf} values determined for conformations **1**−4 in aqueous, $CHCl_3$, and CCl_4 solutions. As expected, solvation in organic solvents, especially in $CHCl_3$, is better than that in water. On the other hand, the effect of the environment on the relative stability of the different structures clearly increases with the polarity of the solvent.

Our calculations indicate, therefore, that the C_7 conformation is the most favored disposition not only in the gas phase but also in CCl_4, $CHCl_3$, and water solutions. However, solvation by water introduces significant changes in the relative stability of the conformers, namely the energy gap between the global minimum and the other conformations is reduced, and conformation **3** becomes the second energy minimum. The strong stabilization predicted for this structure when intermolecular interactions are considered could explain the high tendency exhibited by $c_3$diPhe to adopt helical conformations in the crystal state,[6a,7] where the intramolecular hydrogen bond that stabilizes the C_7 structure can be compensated by intermolecular hydrogen bonding.

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Supporting Information Available: The coordinates of the minimum energy conformations obtained at the HF (Table 1S) and B3LYP (Table 2S) levels for Ac-(2*S*,3*S*)$c_3$diPhe-NHMe. This material is available free of charge via the Internet at http://pubs.acs.org.

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