

Unusually High Pyramidal Geometry of the Bicyclic Amide Nitrogen in a Complex 7-Azabicyclo[2.2.1]heptane Derivative: Theoretical Analysis Using a Bottom-up Strategy

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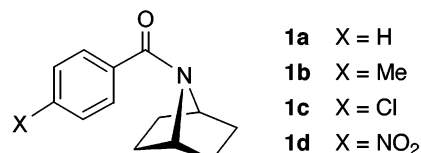
The high pyramidalization of the bicyclic amide nitrogen found in the crystal structure of a dipeptide incorporating (1*S*,2*S*,4*R*)-*N*-benzoyl-2-phenyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid has been investigated using quantum mechanical calculations. More specifically, a bottom-up strategy based on the study of model molecules of progressive complexity has been used. First, an appropriate quantum mechanical method has been selected by examining the distortion of the amide bond in three simple model molecules. Next, the amide distortion induced by the norbornane ring has been evaluated by considering three different 7-azabicyclo[2.2.1]heptane amides. After this, the suitability of quantum mechanical calculations to predict the effect of the substituents on the pyramidalization of the bicyclic amide nitrogen has been investigated by comparing experimental and theoretical parameters for a number of compounds. Finally, the factors responsible for amide distortion in the (1*S*,2*S*,4*R*)-*N*-benzoyl-2-phenyl-7-azabicyclo[2.2.1]heptane-1-carboxylic acid derivative have been elucidated using a hierarchical approach. For this purpose, several derivatives were generated by removing or modifying the substituents attached to the 7-azanorbornane system. Results have been discussed in terms of intramolecular specific interactions.

Introduction

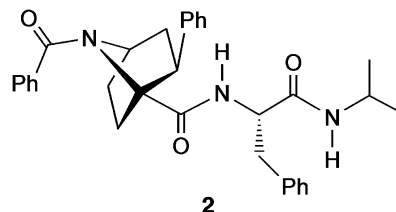
In the recent past there has been a renewed interest in the nonplanarity of the amide bond in peptides and proteins. Thus, although the distortion of amides from the planar geometry was observed many years ago,¹ the increasing number of X-ray crystal structures available has stimulated the statistical analysis of this phenomenon in the past decade.² These studies showed substantial out-of-plane deviations, which can be produced either by pyramidalization at the nitrogen atom or by simple rotation of the N–C(O) amide bond. Furthermore, it was demonstrated that in proteins this distortion is environmentally dependent, in that different secondary structure elements are characterized by different degrees of deformation of the amide bond.^{2a,c} The nonplanarity of an isolated amide has been also investigated using quantum mechanical calculations.³ In this context, particular attention was given to the deformation undergone by the acylated proline nitrogen⁴ since this residue has important implications in many biochemical processes.

Amide derivatives of the 7-azabicyclo[2.2.1]heptane (also named 7-azanorbornane) system have been recognized as being intrinsically distorted.^{5,6} Ohwada and co-workers⁶ recently reported the crystal structures of some *N*-aroyl derivatives (**1a–d**, Scheme 1) revealing a notable pyramidalization of the amide nitrogen, the sum of the valence angles around this atom (θ) ranging from 346° to 350°. In agreement with experimental data in solution, Density Functional Theory (DFT) calculations suggested a low rotational barrier for these compounds,^{6b} that

SCHEME 1



SCHEME 2



was interpreted in terms of nonplanarity of the amide bond derived from a combination of nitrogen pyramidalization and amide bond twisting.

Some of us are involved in the study of 7-azabicyclo[2.2.1]heptane derivatives that incorporate a carboxylic acid substituent at the 1-position.^{7,8} Such systems are α -amino acids, and, more specifically, they can be viewed as constrained analogues of proline. Very recently we have reported⁸ the crystalline structure of (1*S*,2*S*,4*R*)-*N*-benzoyl-2-phenyl-7-azabicyclo[2.2.1]heptane-1-carboxyl-(*S*)-*N'*-isopropylphenylalaninamide (**2**, Scheme 2). This dipeptide incorporates a norbornane proline analogue of this series linked to phenylalanine. We have shown that the replacement of proline with this bicyclic surrogate has important structural consequences, namely, the stabilization of the β 1-turn peptide conformation.⁸

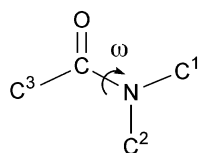
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SCHEME 3



Interestingly, the pyramidal character of the tertiary nitrogen in **2** is particularly strong ($\theta = 339^\circ$)⁸ and substantially higher than that encountered for its unsubstituted counterpart **1a** ($\theta = 350^\circ$).⁶ In fact, the θ value in **2** is closer to that expected for a nitrogen atom with sp^3 hybridization (the θ predicted⁹ for trimethylamine is 333°) than to that corresponding to a typical trigonal nitrogen with sp^2 hybridization ($\theta = 360.0^\circ$). This result clearly indicates that the nonplanarity of the amide bond in **2** is enhanced by factors that are not present in other simpler bicyclic amides (**1a–d**). Remarkably, the strong pyramidal geometry of the bicyclic nitrogen in **2** has been proposed⁸ to play a role in the stabilization of the β I-turn conformation observed in the crystal.

In the current study we have used quantum mechanical calculations to examine and understand the factors that contribute to the extremely high nitrogen pyramidalization observed for **2**. To this end, we have performed calculations on a wide number of molecules following a bottom-up strategy. First, we have selected a quantum mechanical level able to provide a quantitatively correct description of the amide bond. For this purpose, the planarity of the amide bond has been studied considering three simple acyclic amides at 25 different ab initio and DFT levels. After this, calculations on simple 7-azabicyclo-[2.2.1]heptane amides have been performed to examine the amide distortion induced by the bicycle and how it is affected by the group attached to the carbonyl moiety. Next, the ability of quantum mechanical calculations to predict the effect of bicycle substitution on amide pyramidalization has been examined by comparing experimental and theoretical geometric parameters for a number of selected compounds, whose crystal structures are available. Finally, a hierarchical approach based on the construction of model compounds of increasing complexity has been used to analyze the factors that may contribute to the unusually high pyramidalization found for the bicyclic nitrogen atom of **2**.

Methods

Computational Details. All the calculations in this work were done using the Gaussian 98¹⁰ and PC-Gamess¹¹ programs. Ab initio fully geometry optimizations were performed at the Hartree–Fock (HF), second-order Møller–Plesset perturbation (MP2), and fourth-order Møller–Plesset perturbation (MP4) levels, while DFT optimizations were performed using the Becke’s three-parameter hybrid functional¹² with nonlocal correlation provided by the Lee, Yang, and Parr functional.¹³ The double- and triple-split basis sets used in HF, MP2, and B3LYP optimizations were 6-31G(d), 6-31+G(d), 6-31+G(d,p), 6-31++G(d,p), 6-311G(d), 6-311G(d,p), and 6-311++G(d,p). MP4 optimizations were carried out with the 6-31G(d), 6-31+G(d), 6-31+G(d,p), and 6-311G(d) basis sets. Harmonic vibrational frequencies of the HF, MP2, and B3LYP optimized structures were calculated for molecules containing less than 26 heavy (non-hydrogen) atoms.

Analysis of Structural Data. The amide distortion was examined by analyzing three structural parameters. The degree of nitrogen pyramidalization was described (Scheme 3) by $\Delta\theta = 360 - \theta$ and $\Delta\alpha = |180 - \alpha|$, where θ corresponds to the sum

SCHEME 4

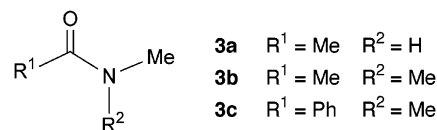


TABLE 1: Deviation from Planarity of the Amide Bond for **3a–c**^a

level	3a			3b			3c		
	$\Delta\theta$	$\Delta\alpha$	$ \omega $	$\Delta\theta$	$\Delta\alpha$	$ \omega $	$\Delta\theta$	$\Delta\alpha$	$ \omega $
HF/6-31G(d)	0.8	10.0	4.1	1.9	15.2	10.7	5.3	24.8	30.7
HF/6-31+G(d)	0.0	0.7	0.6	2.1	16.0	11.5	4.5	22.7	28.4
HF/6-31+G(d,p)	0.0	0.7	0.6	1.7	14.3	10.1	4.0	21.4	27.2
HF/6-31++G(d,p)	0.0	0.7	0.6	1.6	14.0	9.9	4.0	21.5	27.2
HF/6-311G(d)	0.9	10.9	4.5	2.6	17.8	12.6	6.2	26.7	32.7
HF/6-311G(d,p)	0.9	10.8	4.5	2.2	16.2	11.6	5.8	25.9	31.8
HF/6-311++G(d,p)	0.0	0.6	0.6	2.5	17.2	12.5	4.7	23.4	28.8
MP2/6-31G(d)	1.2	12.5	4.8	1.9	15.0	10.1	5.0	24.0	26.9
MP2/6-31+G(d)	0.9	10.6	4.2	4.6	23.3	16.2	5.4	25.2	26.7
MP2/6-31+G(d,p)	1.0	11.2	4.5	4.1	22.2	15.5	4.8	23.8	25.5
MP2/6-31++G(d,p)	1.2	12.5	5.1	4.5	23.1	16.2	5.1	24.4	25.9
MP2/6-311G(d)	2.5	18.0	7.3	3.9	21.6	15.2	6.6	27.6	29.9
MP2/6-311G(d,p)	3.5	21.0	8.9	3.8	21.4	14.7	6.5	27.4	29.6
MP2/6-311++G(d,p)	3.3	20.4	8.3	5.4	25.4	17.8	6.2	26.9	28.0
B3LYP/6-31G(d)	0.0	0.0	0.0	0.0	1.1	0.7	2.8	18.0	23.3
B3LYP/6-31+G(d)	0.0	1.6	0.6	0.3	1.2	0.8	2.7	17.8	22.7
B3LYP/6-31+G(d,p)	0.4	6.7	2.7	0.0	1.0	0.7	2.5	17.0	13.8
B3LYP/6-31++G(d,p)	0.3	6.6	2.5	0.0	1.0	0.7	2.4	16.8	21.8
B3LYP/6-311G(d)	0.0	0.2	0.1	0.0	1.0	0.7	2.8	18.0	14.9
B3LYP/6-311G(d,p)	0.0	0.0	0.0	0.0	0.9	0.7	2.4	17.0	22.4
B3LYP/6-311++G(d,p)	0.3	6.3	2.4	0.0	1.0	0.6	2.2	15.9	20.8
MP4/6-31G(d)	0.8	10.3	4.1	2.3	16.4	11.0	-	-	-
MP4/6-31+G(d)	1.0	11.5	4.8	4.6	23.5	16.5	-	-	-
MP4/6-31+G(d,p)	1.1	11.9	4.7	4.1	22.5	15.8	-	-	-
MP4/6-311G(d)	1.8	15.2	6.3	4.4	22.9	15.8	-	-	-

^a $\Delta\theta$, $\Delta\alpha$, and $|\omega|$ are in degrees. The definition of these parameters is provided in the methods section.

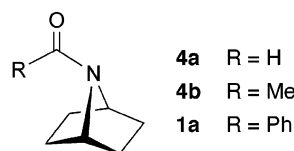
of the bond angles around the nitrogen ($\angle C(O)-N-C_1$, $\angle C(O)-N-C_2$ and $\angle C_1-N-C_2$), and α is the improper dihedral angle that defines the out-of-plane bending of the nitrogen atom, i.e., the angle formed by the planes containing the $C(O)-N-C_2$ and C_1-N-C_2 atoms. It should be noted that θ and α are 360° and 180° , respectively, for an ideally planar amide group (pure sp^2 nitrogen). On the other hand, the twisting of the $N-C(O)$ amide bond was evaluated using the absolute value of the $O-C-N-C_1$ dihedral angle, $|\omega|$. Additionally, the out of plane deformation in the amide bond was measured using the angles defined by Dunitz,¹⁴ this information being reported in the Supporting Information.

Results and Discussion

Choice of the Quantum Mechanical Method. The ability of the different theoretical levels to describe the nonplanarity of the amide bond was examined considering three simple model amides (Scheme 4): *N*-methylacetamide (**3a**), *N,N*-dimethylacetamide (**3b**), and *N,N*-dimethylbenzamide (**3c**). Table 1 shows the values of $\Delta\theta$, $\Delta\alpha$, and $|\omega|$ predicted by the different methods evaluated.

The results provided by geometry optimizations at the MP4 level, which were only performed for **3a** and **3b** due to their extremely high computational cost, are very similar to those at the MP2 level indicating that the effects of electron correlation are satisfactorily described by the latter method. However, DFT and MP results are considerably different, independently of the size of the basis set. Thus, B3LYP optimizations produced, in general, structures with a planar amide bond, while the MP2

SCHEME 5

**TABLE 2: Deviation from Planarity of the Amide Bond for 4a,b and 1a^a**

level	4a			4b			1a		
	$\Delta\theta$	$\Delta\alpha$	$ \omega $	$\Delta\theta$	$\Delta\alpha$	$ \omega $	$\Delta\theta$	$\Delta\alpha$	$ \omega $
HF/6-311G(d)	13.0	37.5	19.7	13.4	37.5	17.5	18.2	42.6	8.6
MP2/6-311G(d)	18.2	43.8	22.0	20.0	44.9	20.7	23.6	48.7	13.6

^a $\Delta\theta$, $\Delta\alpha$ and $|\omega|$ are in degrees. The definition of these parameters is provided in the methods section.

and MP4 methods predict a deviation from planarity even for these simple molecules. Inspection to Table 1 shows that the overestimation of the amide planarity provided by B3LYP calculations is particularly notable for **3a** and **3b**, although it is also appreciable for **3c**. On the other hand, HF and MP parameters are in quantitative agreement for **3b** and **3c**, but the former method tends to overestimate the planarity of the amide bond for **3a** when a basis set with diffuse functions is used. Regarding to the available experimental information, it should be noted that in the crystal environment the amino group was found to be slightly pyramidal.¹⁵ However, the crystal structure determination of **3a** indicated that the heavy atoms are coplanar, even although no clear information was given about the pyramidalization of the nitrogen atom.¹⁶

Statistical parameters, i.e. correlation coefficient, root-mean-square deviation, and relative root-mean-square deviation, comparing the results provided by the different quantum mechanical methods indicated that the HF/6-311G(d) results are able to reproduce satisfactorily the MP2/6-311++G(d,p) ones for the three molecules investigated, this feature being probably due to cancelation of errors. Accordingly, the former method, which can be applied not only to medium-size but also to large molecules, was used for the computations described henceforth. Furthermore, to examine the influence of electron correlation on larger systems, calculations on medium-size molecules have been simultaneously performed at the MP2/6-311G(d) level.

Amide Distortion Produced by the 7-Azanorbornane System. The amide distortion induced by the formation of the strained 7-azabicyclo[2.2.1]heptane system was investigated considering derivatives **4a,b** and **1a** (Scheme 5). Results are displayed in Table 2.

As expected, the out-of-plane deviation of the nitrogen atom is larger for the bicyclic amides considered than for the linear derivatives **3a–c**. Moreover, the degree of pyramidalization increases with the size of the substituent attached to the carbonyl moiety, while the twisting of the amide bond decreases. The latter feature is particularly evident in **1a** and may be related to the conjugation between the π -systems of the phenyl and amide groups. Accordingly, comparison between **4a** and **1a** allows to conclude that the *N*-benzoyl moiety increases the nitrogen pyramidalization induced by the rigid norbornane bicycle around 5°, while the amide twisting decreases about 10°. On the other hand, HF and MP2 results are fully consistent, although the amide distortion predicted by the latter method is slightly larger for all three compounds.

As mentioned in the Introduction section, Ohwada and co-workers reported the crystal structure of **1a**.⁶ The geometric parameters observed for this compound, $\Delta\theta = 10.5^\circ$, $\Delta\alpha =$

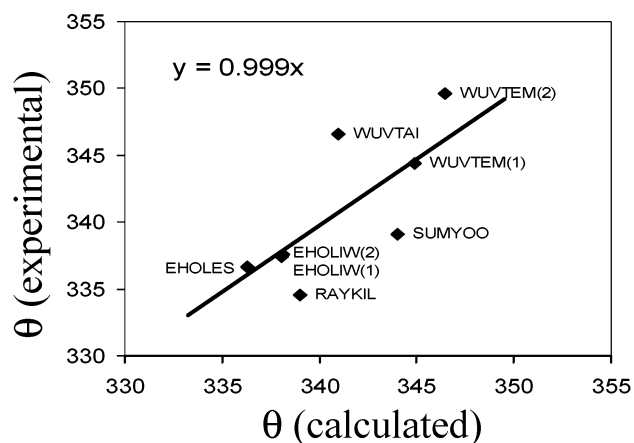


Figure 1. Graphical representation of the experimental (X-ray crystallography) vs the calculated (HF/6-311G(d) level) θ values (in degrees) for several substituted *N*-acyl-7-azabicyclo[2.2.1]heptanes available at the CSD (their CSD codes are indicated; see the Supporting Information for their structures).

26.8° and $|\omega| = 9.0^\circ$, are in qualitative agreement with the present theoretical estimations supporting the hypothesis that the deviation from planarity in *N*-benzoyl-7-azabicyclo[2.2.1]heptane systems is mainly due to nitrogen pyramidalization.⁵

N-Pyramidalization of Substituted 7-Azanorbornane Amides: Correlation between Calculated and Experimental Data. Before analyzing the factors that produce the amide distortion observed in the X-ray crystal structure of **2**,⁸ we evaluated the reliability of theoretical calculations to describe the influence of substituents on the nitrogen pyramidalization of 7-azabicyclo[2.2.1]heptane amides. For this purpose, amides containing the 7-azanorbornane skeleton were searched in the Cambridge Structural Database¹⁷ (CSD). Several significant examples, excluding compounds with complex substituents or additional cycles, were selected and optimized by means of HF/6-311G(d) calculations using as starting geometry the atomic coordinates determined by single-crystal X-ray diffraction crystallography. A total of eight independent structures corresponding to six compounds^{7b,18} were computed (in two cases, two independent molecules were characterized in the asymmetric unit, each providing a different starting geometry for our calculations). Their structures are displayed in the Supporting Information, and their coordinates are available from the CSD.

Figure 1 represents the experimental vs the calculated values of θ for the examined compounds. Results clearly show the general suitability of the quantum mechanical calculations to study the influence of the substituents on the degree of pyramidalization of 7-azanorbornane amides. Thus, not only is the correlation between the HF/6-311G(d,p) and experimental θ values good ($r = 0.77$) but the value of the scaling coefficient arising from such correlation ($y = cx$) corresponds to a very low global deviation.

Understanding the N-Pyramidalization of 2: A Hierarchical Strategy. Two different calculations were performed on **2** (Scheme 2) using as starting geometry, in both cases, the coordinates provided by X-ray crystallography.⁸ First, the molecule was partially optimized at the HF/6-311G(d) level restraining the dihedral angles of the flexible side chain of the phenylalanine residue to the experimental values, and second, the molecule was fully optimized without imposing any restriction. It should be emphasized that the conformation obtained after full geometry optimization was essentially identical to that observed in the solid state, the largest difference in a dihedral

TABLE 3: Deviation from Planarity of the Bicyclic Amide Bond for **2^a**

method	$\Delta\theta$	$\Delta\alpha$	$ \omega $
HF/6-311G(d) partially optimized	22.8	49.6	3.6
HF/6-311G(d) fully optimized	25.8	52.5	8.0
X-ray crystallography ^b	20.9	47.1	3.6

^a $\Delta\theta$, $\Delta\alpha$ and $|\omega|$ are in degrees. The definition of these parameters is provided in the methods section. ^b Reference 8.

angle being 21°. Table 3 compares the values of $\Delta\theta$, $\Delta\alpha$, and $|\omega|$ predicted for **2** with those observed in the crystal.

As can be seen, the geometric parameters obtained after the restrained geometry optimization agree very well with the experimental data. Thus, $\Delta\theta$, $\Delta\alpha$, and $|\omega|$ differ by only 1.9°, 2.5°, and 0.0°, respectively. These differences increase to 4.9°, 5.4°, and 4.4°, respectively, when the experimental and fully optimized structures are compared. The overall of these results provides an estimation of the packing effects in the crystal. Thus, comparison between the fully optimized structure and either the partially optimized or the crystalline one indicates that packing interactions tend to reduce both the pyramidalization of the nitrogen atom and the twisting of the amide group by a few degrees.

Apart from these minor differences, the fully optimized structure of **2** retains all the conformational significant features observed in the crystalline state.⁸ Thus, Figure 2a shows the terminal benzoyl C=O and isopropylamide NH sites connected by a hydrogen bond with geometrical parameters (Table 4) close to those encountered in the crystal ($d_{N\cdots O} = 2.890$ Å, $d_{H\cdots O} = 1.97$ Å, $\angle N-H\cdots O = 159^\circ$). The overall shape of the molecule corresponds to a β -turn conformation, stabilized by this N-H \cdots O=C hydrogen bond. More specifically, the β -turn type, which is defined by the orientation of the central amide moiety (involving the bicycle CO and the phenylalanine NH), corresponds to the type I. In the solid state, this β I-turn conformation has been proposed⁸ to be stabilized by a weak attractive interaction between the phenylalanine NH and the bicyclic nitrogen. Again, the structural parameters of this N-H \cdots N interaction (Figure 2a) are found to be very similar in the calculated (Table 4) and the crystalline⁸ ($d_{N\cdots N} = 2.922$ Å, $d_{H\cdots N} = 2.59$ Å, $\angle N-H\cdots N = 100^\circ$) structures of **2**. Attractive N-H \cdots N interactions have been reported for several peptides containing nonplanar tertiary amide bonds.¹⁹ In the case of **2**, the extremely high pyramidal geometry of the bicyclic nitrogen could reflect in a poor delocalization of its lone-pair electrons to the adjacent carbonyl group and, therefore, in a higher accessibility of this lone pair to participate in hydrogen bonding interactions as an acceptor site.

To understand how the specific attractive interactions observed in **2**⁸ affect the marked pyramidal character of the bicyclic nitrogen, a number of related derivatives were built by removing or modifying the substituents attached to the 7-azanorbornane system. First, calculations have been performed on compounds **5a–e** (Scheme 6) to investigate how the presence and nature of the substituents at positions 1 and 2 modulate the deformation induced by the bicycle. More specifically, we considered compounds bearing an ester (**5b** and **5d**) or an amide (**5c** and **5e**) group directly attached to position 1, while for position 2 we analyzed the influence of an exo-oriented phenyl substituent (**5a**, **5d**, and **5e**). It should be emphasized that, after geometry optimizations, no specific interaction was detected between either the COOMe or the Ph groups and the rest of the molecule, while the CONH*i*Pr group forms an N-H \cdots N interaction with the bicyclic nitrogen, as explained below.

Results are listed in Table 5. As can be seen, the parameters $\Delta\theta$, $\Delta\alpha$, and $|\omega|$ calculated for **5a** are very similar to those obtained for **1a** (Table 2), the difference being less than 0.6° in all three cases. Accordingly, we can conclude that substitution at the 2-position of the bicycle without formation of specific interactions does not amplify the distortion of the amide bond associated to the strained bicycle and the *N*-benzoyl derivatization discussed above. In contrast, substitution at the 1-position of the 7-azanorbornane system produces an enhancement of the amide pyramidalization. Thus, the values of $\Delta\theta$ and $\Delta\alpha$ predicted for **5b** are 2.8° and 3.6° larger than those obtained for **1a** at the same level of theory, even though the COOMe substituent is not involved in any specific intramolecular interaction.

On the other hand, the amide pyramidalization calculated for **5c** is notably larger than that predicted for **5b**. It should be noted that in the former compound the amide group attached to the 1-position of the 7-azanorbornane moiety forms an N-H \cdots N interaction with the pyramidal bicyclic nitrogen, which is very similar (Table 4) to that detected in the crystalline and calculated structures of **2**. The optimized structure of **5c** is displayed in Figure 2b, which shows the N-H \cdots N contact. The existence of this intramolecular interaction in **5c** increases the parameters $\Delta\theta$ and $\Delta\alpha$ by 3.0° and 3.8°, respectively, with reference to the analogous ester derivative **5b**. In summary, results on **5b** and **5c** indicate that substitution at the 1-position of the bicycle increases pyramidalization at nitrogen for sterical reasons, and this effect is more pronounced when the substituent introduced allows the nitrogen atom to act as an acceptor site in hydrogen bonding interactions. However, the twisting of the N-C(O) bond does not appear to be affected by the presence of substituents, and thus the value of $|\omega|$ is very similar for **1a** and **5a–c**.

Calculations on compounds **5d** and **5e** (Table 5, Figure 2c) reveal that simultaneous substitution at the 1- and 2-positions increases the pyramidal character of the bicyclic nitrogen atom with respect to the analogous derivatives with a single substituent at C1 (**5b** and **5c**, respectively). Indeed, the values of $\Delta\theta$, $\Delta\alpha$ and $|\omega|$ predicted for **5e** are almost identical to those calculated for **2**, indicating that all the features responsible for both nitrogen pyramidalization and amide twisting in the latter compound are also captured in the former one. Moreover, the similarity detected between **5e** and **2** indicates that the N-H \cdots O hydrogen bond characterized for **2** does not contribute to the pyramidalization of the bicyclic nitrogen atom.

Additional model compounds were built to confirm the points discussed above. Dipeptides **6–9** (Scheme 7) are long enough to adopt a β -turn conformation, stabilized by an N-H \cdots O hydrogen bond between the benzoyl oxygen and the terminal amide NH (Table 4), as found in **2**.

Compound **6** is identical to **2** but lacks the Ph group attached to the 2-position of the 7-azanorbornane system. Results obtained from full geometry optimization at the HF/6-311G(d) level for **6**, which are given in Table 6, are consistent with those discussed above. Thus, the values calculated for $\Delta\theta$ and $\Delta\alpha$ are 4.8° and 5.3°, respectively, smaller than those obtained for **2**, reflecting a decrease in the degree of pyramidalization associated to the relief of the sterical hindrance produced by the bulky phenyl substituent.

In dipeptides **2** and **6** the bicyclic moiety is followed by a phenylalanine residue, characterized by an aromatic side chain. The crystal structure of **2** shows a high proximity between the phenylalanine NH and its phenyl side chain.⁸ It should be noted

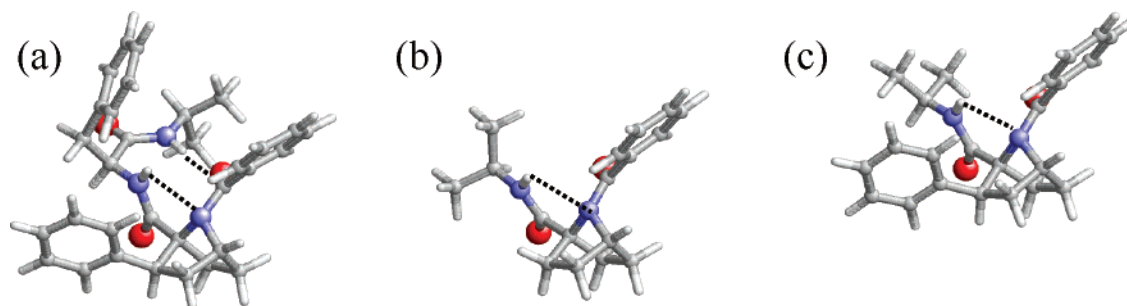


Figure 2. Geometries provided by HF/6-311G(d) calculations for: (a) **2**, (b) **5c**, and (c) **5e**. N–H···O and N–H···N hydrogen bonding interactions are indicated by dashed lines (see Table 4 for their geometry).

TABLE 4: Geometric Parameters Calculated for the Intramolecular Hydrogen Bonding Interactions^{a–c}

molecule	N–H···N			N–H···O		
	<i>d</i> (N···N)	<i>d</i> (H···N)	∠(N–H···N)	<i>d</i> (N···O)	<i>d</i> (H···O)	∠(N–H···O)
2	2.966	2.585	102.8	3.184	2.199	171.2
5c	2.922	2.508	104.8	-	-	-
5e	2.957	2.554	104.2	-	-	-
6	2.931	2.553	101.5	3.172	2.194	167.7
7	2.956	2.595	100.2	3.205	2.219	172.1
8	2.934	2.552	102.7	3.187	2.205	169.9
9	-	-	-	3.088	2.110	167.5

^a Distances in angstroms, angles in degrees. ^b Calculations at the HF/6-311G(d) level. ^c See Figure 2 for compounds **2**, **5c**, and **5e**.

SCHEME 6

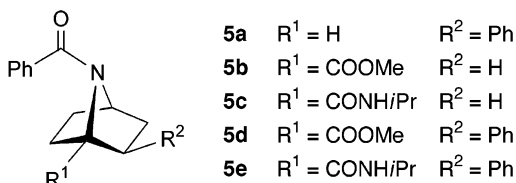


TABLE 5: Deviation from Planarity of the Amide Bond for 5a–e.^{a,b} Results Obtained for 2 Have Been Included for Comparison

molecule	specific interactions ^c	Δθ	Δα	ω
5a	-	18.6	43.1	9.1
5b	-	21.0	46.2	7.2
5c	N–H···N	24.0	50.0	8.9
5d	-	25.5	50.3	4.6
5e	N–H···N	26.1	52.7	7.2
2	N–H···N N–H···O	25.8	52.5	8.0

^a Δθ, Δα, and |ω| are in degrees. The definition of these parameters is provided in the methods section. ^b Calculations at the HF/6-311G(d) level. ^c See Figure 2 and Table 4.

that interactions between amide groups and aromatic rings have been shown to influence the conformation adopted by peptide chains.²⁰ Further calculations were carried out to analyze whether the possible interaction between the phenylalanine Ph and NH groups might affect the ability of the latter to establish an N–H···N interaction with the bicyclic nitrogen. To this end, the phenyl side chain in **2** and **6** was replaced by a hydrogen atom, i.e. the phenylalanine residue was exchanged for alanine, to give **7** and **8**, respectively. The parameters predicted for **7** and **8** (Table 6) are almost identical to those calculated for **2** and **6**, respectively, thus evidencing a negligible influence of the phenylalanine aromatic side chain on the pyramidalization of the bicyclic nitrogen.

A further modification was considered. Compound **9** was generated by replacing the alanine NH in **8** with an oxygen atom. As a consequence, the possibility for an N–H···N interaction was eliminated, and compound **9** only retains the

SCHEME 7

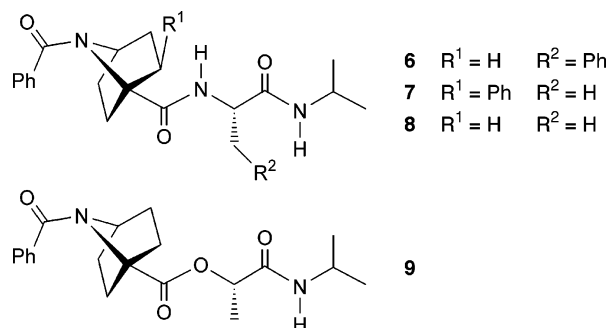


TABLE 6: Deviation from Planarity of the Amide Bond for 6–9.^{a,b} Results Obtained for 2 Have Been Included for Comparison

molecule	Δθ	Δα	ω
6	21.0	47.2	3.6
7	25.2	51.8	8.0
8	21.1	47.1	3.6
9	19.5	44.9	8.4
2	25.8	52.5	8.0

^a Δθ, Δα, and |ω| are in degrees. The definition of these parameters is provided in the methods section. ^b Calculations at the HF/6-311G(d) level.

N–H···O hydrogen bond typical of the β-turn conformation (Table 4). The replacement of the amide group in **8** by the ester group in **9** resulted in a lower pyramidalization of the bicyclic nitrogen (Table 6), supporting that the N–H···N interaction enhances the nonplanar character of this nitrogen, as deduced above from the study of compounds **5b–e**. Moreover, comparison of the latter series of compounds with **9** confirms that this enhancement is maintained in the presence of the N–H···O hydrogen bond, which does not seem to affect the nitrogen geometry.

Finally, a point that deserves special consideration is the dependence between the amide nitrogen geometry and the length of the N–C(O) bond. In the crystalline structure of **2**, the marked pyramidal character of the bicyclic nitrogen is accompanied by a notable lengthening of the N–C(O) bond (1.38 Å)⁸ with respect to the standard amide bond length (1.33 Å).²¹ This effect was attributed to a poor delocalization of the nitrogen lone pair to the carbonyl group. Figure 3 shows the correlation between the Δθ values and N–C(O) bond lengths predicted for all the bicyclic compounds calculated in this work at the HF/6-311G(d) level. As can be seen, the bond length increases with Δθ, i.e. with the out-of-plane deviation of the nitrogen atom. The Pearson correlation coefficient *r* = 0.85 reveals a good fitting between the two geometrical parameters indicating that calculations are able to capture the relationship between nitrogen pyramidalization and electronic delocalization.

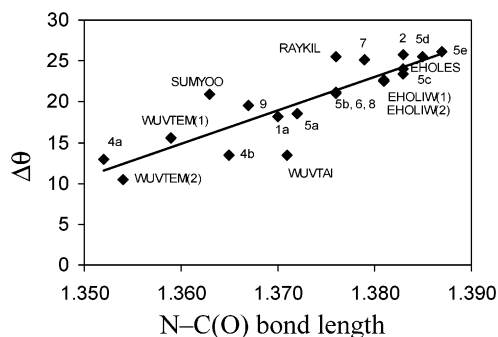


Figure 3. Graphical representation of the relationship between the calculated $\Delta\theta$ value (in degrees) and N–C(O) bond length (in Å). Data correspond to all the bicyclic compounds computed in this work at the HF/6-311G(d) level.

Conclusions

The distortion of the bicyclic amide bond found in the crystal structure of **2** has been investigated using quantum mechanical methods through a bottom-up strategy. Calculations on simple linear amides indicated that HF/6-311G(d) calculations provide a satisfactory description of both amide nitrogen pyramidalization and N–C(O) twisting. Although a small degree of distortion was found even for the linear amides considered, calculations on a number of bicyclic model compounds with a norbornane skeleton allows to conclude that the unusually high amide nitrogen pyramidalization found in **2** is due to the sum of the following factors:

- The incorporation of the nitrogen atom at the 7-position of the strained bicyclo[2.2.1]heptane system.
- The conjugative effects between the carbonyl and phenyl groups of the benzoyl moiety.
- The simultaneous substitution at the 1- and 2-positions of the bicycle.
- The attractive N–H...N interaction involving the bicyclic nitrogen as an acceptor site.

Finally, it should be noted that calculations predict the amide pyramidalization in **2** to be even higher than that observed in the crystal. Thus, packing interactions seem to reduce the nonplanarity of the nitrogen atom by a few degrees.

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Supporting Information Available: Tables S1–S6 list the optimized coordinates for all the compounds calculated in this work. Table S7 lists the internal parameters proposed by Dunitz to describe the out of plane deformation of the amide bond. The structures of *N*-acyl-7-azabicyclo[2.2.1]heptanes selected from a search in the CSD are displayed in Figure S1. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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