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On the Planarity of Amide Nitrogen. Intrinsic Pyramidal Nitrogen of N-Acyl-7-Azabicyclo[2.2.1]heptanes

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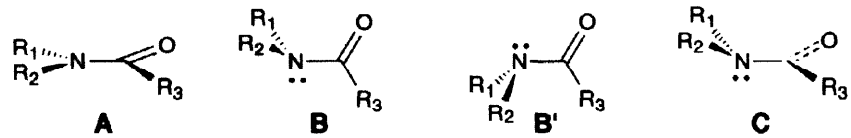
Abstract

Simple amides of 7-azabicyclo[2.2.1]heptane free from steric bias, including the parent N-benzoyl 7-azabicyclo[2.2.1]heptane, are nitrogen-pyramidal amides in the crystalline state. It was suggested that pyramidalized amide nitrogen is a general feature and intrinsic to the 7-azabicyclo[2.2.1]heptane motif.

An amide bond is the fundamental linkage in the structures of peptides and proteins.[1] Nitrogen atoms in amides (**A**) are believed to be planar-trigonal due to conjugation with the carbonyl group.[1] Since this notion has been emphasized in organic and biochemical textbooks, it was generally believed that few peptides contain non-planar amides, and the rigid planarity of the amide linkage is prerequisite for encoded protein folding and many



other chemical and biological processes.[1a] In the isomerization process between planar *trans*-amides and *cis*-forms (**A**),[2] the nitrogen-pyramidalized amide (**B** and **B'**) is presumed to be involved as a transition structure, or structure **C** has also been postulated in calculations.[3]

Non-planar amides *in the ground state* will highlight the significance of the planarity and rigidity of the peptide linkage, and also decode the transition structures involved in the *trans-cis* amide isomerization which is also relevant to structural alteration of amides in chemical and biological processes.[1f,7a] Although several examples of amides which are non-planar (**B** and **C**) in the ground state have been reported, including aziridine amides and bridgehead bicyclic lactams,[3-6] pyramidal nitrogen of amides is still an exceptional phenomenon, and the structural motif is limited. Aziridine amides are the most strained.[3,7] The structure, energy and reactivity of medium-sized bridgehead bicyclic lactams have been studied, although the parent bridgehead bicyclic lactam, 1-azabicyclo[2.2.2]octan-2-one (2-quinuclidone) remains unknown.[5] Most of them suffer from facile hydrolysis.

Here we will show that pyramidal amide nitrogen exists in sterically non-biased amides of 7-azabicyclo[2.2.1]heptane, including the parent N-benzoyl-7-azabicyclo-[2.2.1]heptane, in the ground state and may be a general feature intrinsic to the 7-azabicyclo[2.2.1]heptane motif. These compounds are stable under

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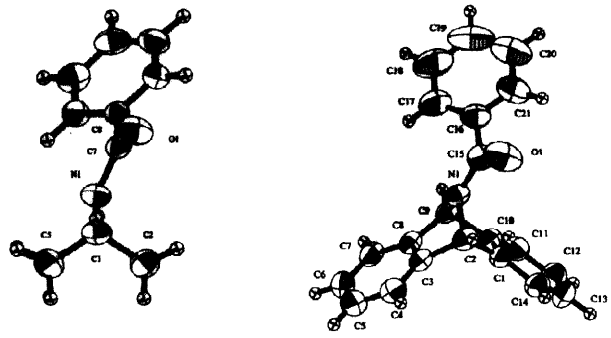
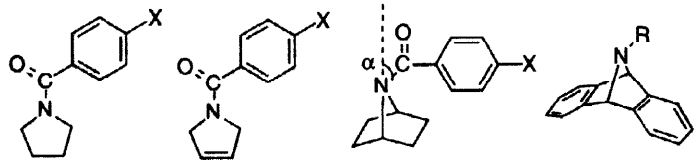


3a 4

Figure 1 ORTEP Diagrams Showing 50 % Probability Displacement Ellipsoids

usual synthetic conditions, and are amenable to modification and identification. The sysnthetic utility of the 7-azabicyclo[2.2.1]heptane motif has been examined in studies on the epibatidine alkaloids.[8]

The planarity of amide nitrogen can be represented in terms of two angle parameters, the summation of the three valence angles around the nitrogen (θ), and the out-of-plane angle (α) of the N-substituent (i.e., the carbonyl carbon atom) with respect to the plane defined by the nitrogen atom and the two adjacent carbon atoms (Table 1). The single crystal structure of N-(*p*-nitrobenzoyl)pyrrolidine **1** and N-(*p*-nitrobenzoyl)-3-pyrroline **2** confirm the essentially planar nature of their amide nitrogen: θ=359.3 and α=7.5 for **1**; θ=357.4 and α=14.8 for



1 X=NO_2 **2** X=NO_2 **3a** X=H **3b** X=NO_2 **4** R=COPh

2.[9,10] The angle θ of the ideal trigonal planar nitrogen atom is 360 °. The angle α is a direct measure of the tilting of a substituent on the nitrogen atom, its range being between 0 ° and 54.7 °.[11] Our single crystal structure determination of N-benzoyl-7-azabicyclo[2.2.1]heptane (**3a**), shown in Figure 1, revealed significant pyramidalization of the amide nitrogen atom: θ=349.5 and α=26.8 (Table 1).[9,10]

The Cambridge Structural Database contains four examples of the crystal structures of amide derivatives of 7-azabicyclo[2.2.1]heptane, **5**,[12] **6**,[12] **7**,[13] and **8**.[14] Although these structures are the early examples of pyramidalized nitrogen in amide derivatives of 7-azabicyclo[2.2.1]heptane, this important phenomenon is not well documented or widely recognized,[12-14] probably because these examples (**6**-**8**) are sterically biased (sterically unsymmetric) molecules with a bulky appendant or an additional ring structure, i.e.,the pyramidalization seems to be strongly dependent on the structures. Table 1 also includes the structural parameters of the four previously known amide derivatives of 7-azabicyclo[2.2.1]heptane (**5**-**8**). The angle θ of **3a**, as well as that of benzoyl-substituted **5**, apparently indicates intermediate character of the nitrogen atom between sp^3 (ideally, 328.4 °) and sp^2 (ideally, 360 °). The mean values of the summation of the three valence angles around the nitrogen (θ) for 126 examples of N-benzoyl secondary amines (only amides), and 35 examples of N-(substituted benzoyl)pyrrolidine fragments (without pyrroles) in the Cambridge Structural Database are 355.9(8)° and 357.0(8)°, respectively.[15] The N-C(O) bonds of **3a** (1.356(3) Å) and **5** (1.353(8) Å) seem to be slightly elongated as compared with the mean value of N-(substituted benzoyl)pyrrolidines (1.345(2) Å) and those of **1**

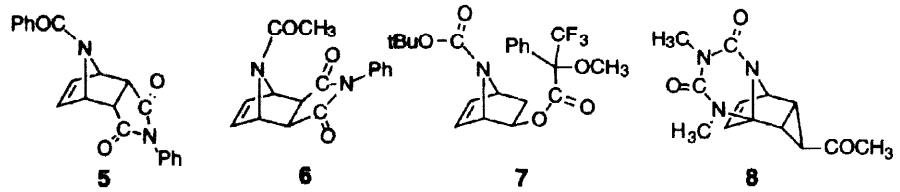
Table 1 Nitrogen Pyramidalization of Amides [a]

	angles around N θ (deg.)	out-of-plane angle α (deg.)	N-C bond length (Å)
1	359.3 (0.2)	7.5	1.337 (0.002)
2	357.4 (0.3)	14.8	1.345 (0.003)
3a	349.5 (0.2)	26.8	1.356 (0.003)
3b[b]	347.1 (0.3)	29.8	1.354 (0.004)
	350.1 (0.3)	26.2	1.350 (0.004)
4	347.5 (0.3)	29.4	1.343 (0.004)
5[c]	343.7 (0.5)	33.4	1.353 (0.008)
6[c]	351.2 (0.4)	24.3	1.374 (0.007)
7[d]	339.1	39.1	1.357
8[e]	328.7	47.9	1.382

a) Standard deviations are shown in parentheses. b) Two kinds of molecule are involved in a unit cell. c) Reference 12. The code of **5** and **6** in the Cambridge Structural Database are DELYOI and DELYUO, respectively. d) Reference 13. The code of **7** in the Cambridge Structural Database is SUMYOO. e) Reference 14.The code of **8** in the Cambridge Structural Database is FUFLUN.

(1.337(2) Å) and **2** (1.345(4) Å).

The *para*-nitro substituent (**3b**), which might be expected to strengthen amide resonance, does not enhance amide planarity (Table 1). Nitrogen pyramidalization is also found in N-benzoyldibenzo-7-azabicyclo-[2.2.1]heptadiene **4** (θ=347.5, α=29.4) (Figure 1).[9] Thus, the pyramidalization of the "symmetrical" amide groups of **3a**,**3b** and **4** is not induced by conventional steric effects.



5 **6** **7** **8**

Nitrogen pyramidalization can be accompanied with twisting of the amide bond. The torsion angles $\omega_1(R_3CNR_2)$ and $\omega_2(OCNR_1)$ (see **A**) are as follows[4a,b]: **1**, (+11.6(0.3); +0.6(0.3)); **2**, (+9.7(0.3); -8.6(0.6)); **3a**, (+40.0(0.3); -9.0(0.3)); **3b**, (+38.7(0.4); -12.7(0.5)), (+29.1(0.5); -15.4(0.5)); **4**, (+35.9(0.5); -14.2(0.6)). The torsion angles of the bicyclic amides **3a**, **3b** and **4** are larger than those of the monocyclic counterparts **1** and **2**. Therefore, the values of the twist angle |τ| of the amide plane, defined by the torsion angles ω_1 and ω_2,[4b,6c] of the bicyclic amides **3a** (15.3(0.3)), **3b** (13.0(0.5); 6.9(0.5)) and **4** (10.8(0.6)) are distinctly larger than those of the monocyclic amides **1** (6.1(0.3)) and **2** (0.6(0.5)). On the other hand, the carbonyl carbons of the amides of 7-azabicyclo[2.2.1]heptane **3** and **4**, as well as the monocyclic amides **1** and **2**, are perfectly trigonal-planar, as judged from the summation of the three valence angles around the carbonyl carbon (data not shown). Therefore, the non-planarity of the amide groups embedded in the 7-azabicyclo[2.2.1]heptane motif, **3** and **4**, stems mainly from the pyramidalization of the amide nitrogen.

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9) Crystal data for **1** ($C_{11}H_{12}N_2O_3$); monoclinic, space group P $2_1/n$, a =12.5540(8), b=6.138(1), c=14.6228(7) Å, β =111.312(4) °, V=1049.7(2) Å^3, Z=4, D_x =1.393 Mgm^{-3}, λ(Cu Kα_1)=1.54050 Å, T=296 K, R=0.042 for 1556 unique reflections. Crystal data for **2** ($C_{11}H_{10}N_2O_3$); triclinic, space group P 1, a =7.959(1), b=9.3506(8), c=7.8732(9) Å, α=92.430(8), β =118.719(9), γ=82.679(9) °, V=509.5(1) Å^3, Z=2, D_x =1.422 Mgm^{-3}, λ(Cu Kα_1)=1.54050 Å, T=296 K, R=0.063 for 1555 unique reflections. Crystal data for **3a** ($C_{13}H_{15}NO$); monoclinic, space group P $2_1/n$, a =6.217(2), b=13.380(2), c=13.258(2) Å, β =92.48(2) °, V=1101.8(4) Å^3, Z=4, D_x =1.213 Mgm^{-3}, λ(Cu Kα_1)=1.54050 Å, T=296 K, R=0.042 for 1453 unique reflections. Crystal data for **3b** ($C_{13}H_{14}N_2O_3$); monoclinic, space group C 2/c, a =47.660(5), b=6.9459(9), c=14.622(1) Å, β =90.135(8) °, V=4840.4(9) Å^3, Z=16, D_x =1.352 Mgm^{-3}, λ(Cu Kα_1)=1.54050 Å, T=296 K, R=0.042 for 2362 unique reflections. Crystal data for **4** ($C_{21}H_{15}NO$); monoclinic, space group P $2_1/a$, a =15.541(3), b=6.1350(7), c=16.801(2) Å, β =91.45(1) °, V=1601.3(4) Å^3, Z=4, D_x =1.233 Mgm^{-3}, λ(Cu Kα_1)=1.54050 Å, T=296 K, R=0.048 for 1635 unique reflections. Further details of the crystallographic data will be discussed in a full paper.

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15) The 126 examples of N-benzoyl secondary amines include 20 cases of pyramidalized nitrogen amides (θ: 339.9 ° (mean)), of which most are N-benzoyl aziridines (4 cases) and N-benzoyl cyclic amides bearing an adjacent bulky *tert*-butyl group (11 cases) (see reference 6). The mean value (θ) of the remaining 106 examples is 358.9 °. The 126 examples include only amide compounds among N-benzoyl secondary amines (150 cases) , that is, excluding ureas and urethanes. The mean values of the summation of the three valence angles around the nitrogen (θ) and the N-C(O) bonds for all examples of N-benzoyl secondary amines (including ureas and urethanes, 150 cases) in the Cambridge Structural Database are 355.6(8) ° and 1.382(3) Å, respectively. The 35 examples include N-(substituted benzoyl)pyrrolidines and 3-pyrrolines and **5**, excluding pyrroles. The mean values of the summation of the three valence angles around the nitrogen (θ) and the N-C(O) bonds for 34 examples of N-(substituted benzoyl)pyrrolidines and 3-pyrrolines (excluding **5** from the 35 examples) in the Cambridge Structural Database are 357.4(7)° and 1.345(2) Å, respectively.