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A theoretical study of the influence of nitrogen angular constraints on the properties of amides: rotation/inversion barriers and hydrogen bond accepting abilities of *N*-formylaziridine and -azirine

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Theoretical calculations at the MP2/6-311++G** level have been carried out on three compounds: *N*,*N*-dimethylformamide (**1**), *N*-formylaziridine (**2**) and *N*-formylazirine (**3**). The barriers to rotation and inversion have been calculated, together with the properties of the nitrogen and oxygen atoms of these amides as hydrogen bond acceptors. The results provide a quantitative picture of the influence of ring strain on the properties of amides, with special emphasis on the effects associated with nitrogen pyramidalization.

Introduction

This paper corresponds to an attempt to quantify some intuitive ideas using high level computation. The possibility that calculations disprove the simplifications chemists usually assume in their qualitative thinking cannot *a priori* be excluded, but we can anticipate that it is not the case in the present work.

The idea we wanted to test is the existence of a simple relationship between the non-planar geometry of the nitrogen atom in amides and some properties of these compounds such as inversion and rotation barriers, on one side, and hydrogen bond acceptor properties, on the other. We will use the acronyms HB, HBA and HBD for hydrogen bond, hydrogen bond acceptor and hydrogen bond donor, respectively.

Instead of using a simple compound, like formamide, and progressively deforming its geometry, we have preferred to select some particular molecules and determine their stationary points (minima and transition states), verifying their nature by means of frequency analysis.

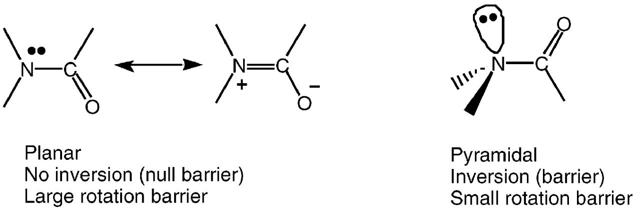
What are the above-referred qualitative predictions?

(i) *Concerning the inversion/rotation processes*, it is assumed that, on going from an sp^2-like nitrogen of a normal amide, like *N*,*N*-dimethylformamide (DMF, **1**), to the sp^3-like nitrogen of a pyramidal amide, the following behavior will be observed (Scheme 1): the more pyramidal the nitrogen atom, the higher the inversion barrier and the lower the rotation barrier.

(ii) *Concerning the HBA properties of the N and O atoms*, the more pyramidal the nitrogen, the better HBA this N atom should become (Scheme 2) and, reciprocally, the typical HBA character of the O atom will decrease.

Similar considerations to those of Scheme 1 can be found in previous works on the structure of amides.[1–8] and particularly in ref. 9. A theoretical and experimental approach to the intermolecular hydrogen bonding ability of tertiary amides as HBAs has been published but it concerns only the O atom.[10]

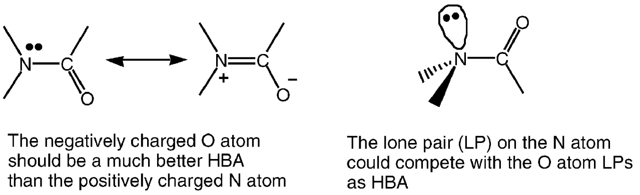
We have studied three compounds (Scheme 3): *N*,*N*-dimethylformamide (**1**), *N*-formylaziridine (**2**) and *N*-formylazirine (**3**). It is known that aziridine derivatives are the most strained amides.[3,8,11] We must note here that compounds **1** and **2** are essentially reference compounds that have been selected to test our calculations with reference to those of other authors, while compound **3** has never been considered before. The stress on the HB abilities of these compounds is original of the present work.



Scheme 1 Amide inversion and rotation barriers.

Results and discussion

The minimum energy structures are called **a**, the transition states (TSs) of the inversion process, TS1, are called **b** (obviously, the planar DMF has not a TS of type **1b**), and the TSs corresponding to the rotation process, TS2, are **c** (synperiplanar) and **d** (antiperiplanar), depending on the relative positions of the oxygen atom and the substituents on the nitrogen.



Scheme 2 Hydrogen bond acceptor (HBA) abilities of oxygen and nitrogen atoms in amides.

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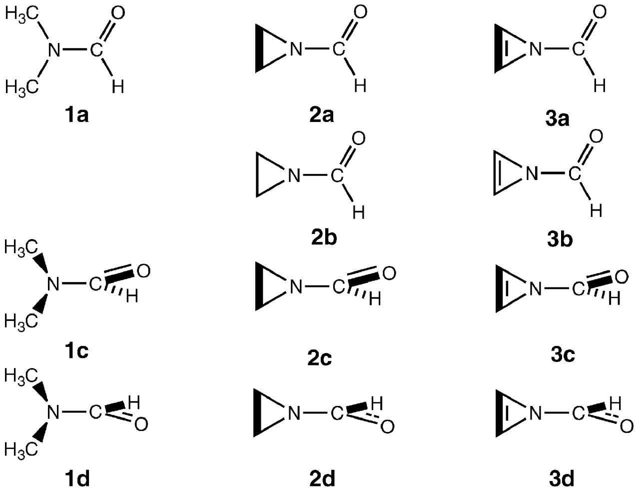


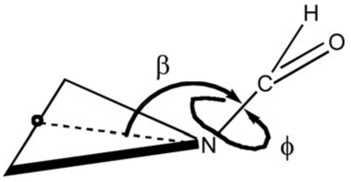
Scheme 3 The calculated eleven stationary points of structures **1–3**.

Geometry and barriers

The most relevant geometrical parameters of the structures depicted in Scheme 3 at the MP2/6-311++G** level are reported in Table 1 (ΣN is the sum of the angles about the N atom), together with the TS energies. The barriers have also been calculated at the G3 level, verifying that the values are very similar to the MP2 ones.

The experimental rotation barrier of DMF (**1**) is 91.2 kJ mol^{-1} in solution[12] and 85.8 kJ mol^{-1} in the gas-phase,[13] which compares well with our values (either **1c** or **1d**). Many theoretical studies have been published where values close to the experimental ones have been reported.[6,14]

The experimental information about *N*-acylaziridines is not abundant; moreover, there is no data, either experimental or calculated, about *N*-acylazirines. Anet and Osyany reported that no barrier can be measured on *N*-acetylaziridine (**4**) even at −160 °C, and this was interpreted in terms of a slow nitrogen inversion.[15] Boggs and Gerig[16] tried to measure the barrier of *N*-benzoylaziridine (**5**) only to reach the conclusion that the inversion barrier should be less than 25 kJ mol^{-1} and that the barrier of **4** should be "significantly lower than 25 kJ mol^{-1}". At that time, the assignment of the barrier to an inversion or a rotation process should be considered tentative at the best. According to the calculations reported in Table 1 for compound **2**, the experimental barrier of compounds **4** and **5** should correspond to a rotation process.



2

In more recent studies, Rademacher and Würthwein have carried out a 3-21G study of compound **2**.[17] They defined two angles β (inversion) and ϕ (rotation); their minimum structure **2a** corresponds to β = 134.4° and ϕ = 75.2° (in our case, β = 125.4° and ϕ = 76.6°) and calculated three barriers: inversion 6.0 kJ mol^{-1}, rotation **c** (ϕ = 0°) 11.9 kJ mol^{-1} and rotation **d** (ϕ = 180°), 33.4 kJ mol^{-1}. Rauk *et al.*[18] have calculated these three barriers at the MP2/6-31G* level, obtaining, after ZPVE correction, respectively inversion 25.1 kJ mol^{-1} (in Table 1, 25.5 kJ mol^{-1}), rotation **c** 13.0 kJ mol^{-1} (in Table 1, 16.5 kJ mol^{-1}) and rotation **d** 26.7 kJ mol^{-1} (in Table 1, 23.9 kJ mol^{-1}). Both Rademacher[17] and Rauk[18] have pointed out that the **d** TS lies much higher than the **c** TS in the case of **2**. Ohwada *et al.* have calculated,[8] at the B3LYP/6-311G** level, the rotation barrier of **5**, obtaining a value of 12.6 kJ mol^{-1}, lower than our TS2 for **2** (16.5 kJ mol^{-1}, Table 1).

Table 1 Some relevant distances (in Å) and angles (°) of **1a–3d** and the TS energies (in kJ mol^{-1}) calculated at the MP2/6-311++G** level. The G3 barriers are also given

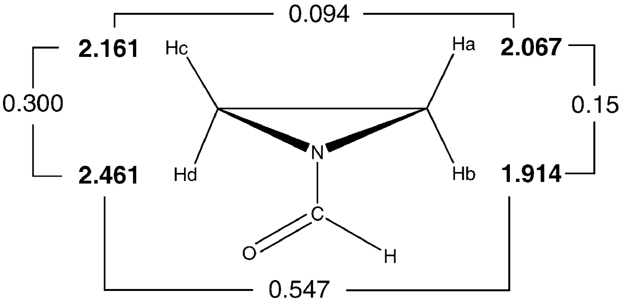
Compound		1	2	3
Minimum **a**	d_{CN}	1.365	1.397	1.429
	d_{CO}	1.222	1.214	1.211
	ΣN	360.0	301.5	269.6
Inversion TS1 **b**	d_{CN}	—	1.359	1.345
	d_{CO}	—	1.218	1.229
	ΣN	—	360.0	360.0
	Barrier	0.00	25.46	63.95
	Barrier G3	0.00	24.61	55.91
Rotation TS2 **c**	d_{CN}	1.441	1.432	1.444
	d_{CO}	1.210	1.211	1.210
	ΣN	330.4	283.1	268.4
	Barrier	80.18	16.46	4.45
	Barrier G3	80.97	16.71	4.48
Rotation TS2 **d**	d_{CN}	1.434	1.429	1.442
	d_{CO}	1.205	1.203	1.203
	ΣN	326.9	281.2	268.2
	Barrier	79.89	23.89	7.47
	Barrier G3	80.14	23.36	8.10

Since Anet recognized that the difficulty in measuring a barrier on **4** should be related to "a small value for ν_{AB}" (the difference in chemical shifts on the signals that coalesce),[15] we have carried out a GIAO calculation of the four aziridine protons of **2** in its minimum **2a** (Scheme 4).

The absolute shieldings (σ, ppm) have been transformed into chemical shifts (δ, ppm) using the average value reported by Anet for the four protons in *N*-acetylaziridine (2.15 ppm) and other empirical fittings.[15,19] The most different proton is Hd, which is close to the carbonyl oxygen and for this reason deshielded. An inversion process exchanges the north/south protons (on average ν = 0.226 ppm) while a rotation process exchanges the east/west protons (on average ν = 0.320 ppm). The difference is too small to decide which process will be observed first by VT ^{1}H NMR spectroscopy.

The TSs of Table 1 are related, if one assumes that the inversion barrier of DMF is 0. Eqn (1) shows that when TS2 **c** (rotation) increases, TS1 **b** (inversion) decreases, but the relationship is not linear [a linear dependence is observed for (TS1 **b**)$^{0.2}$]. On the other hand, both rotational barriers are linearly related, eqn (2).

$$\text{TS1 } \mathbf{b}\ (\text{kJ mol}^{-1}) = (53 \pm 17) - (0.70 \pm 0.37)\text{TS2 } \mathbf{c}\ (\text{kJ mol}^{-1}),\ n = 3,\ r^2 = 0.78 \qquad (1)$$



Scheme 4 Calculated chemical shifts of aziridine **2a**.

$$\text{TS2 } \mathbf{d} \text{ (kJ mol}^{-1}) = (5.7 \pm 3.1) + (0.93 \pm 0.06)\text{TS2 } \mathbf{c} \text{ (kJ mol}^{-1}),\ n = 3,\ r^2 = 0.995 \qquad (2)$$

The geometrical parameters are also related, although still not linearly: when d_{CN} increases, d_{CO} and ΣN decrease, and when d_{CO} increases, ΣN also increases. According to Scheme 1, the barriers should be related to the geometries, the most characteristic being ΣN, but in the inversion process, $\Sigma N = 360°$ for the three molecules, so we have used d_{CN} (**b**) in this case (for **1b** we have used d_{CN} = 1.365 Å, the distance of **1a**).

$$\text{TS1 } \mathbf{b} \text{ (kJ mol}^{-1}) = (4260 \pm 467) - (3118 \pm 344)d_{CN}\ \mathbf{b} \text{ (Å)},\ n = 3,\ r^2 = 0.988 \qquad (3)$$

$$\text{TS2 } \mathbf{c} \text{ (kJ mol}^{-1}) = -(334 \pm 30) + (1.25 \pm 0.10)\Sigma N\ \mathbf{c}\ (°),\ n = 3,\ r^2 = 0.993 \qquad (4)$$

$$\text{TS2 } \mathbf{d} \text{ (kJ mol}^{-1}) = -(322 \pm 2) + (1.232 \pm 0.007)\Sigma N\ \mathbf{d}\ (°),\ n = 3,\ r^2 = 1.000 \qquad (5)$$

Eqn (3) shows that when the CN bond length decreases, *i.e.* the more close to an sp^3 hybridization becomes the N atom in the minimum, the energy of TS1 **b** (the inversion barrier) increases. Similarly, the rotation barriers increase when ΣN increases, *i.e.* the less sp^3 becomes the N atom. Although less good, the relationships corresponding to eqn (6)–(8), are more intuitive because they correspond directly to Scheme 1:

$$\text{TS1 } \mathbf{b} \text{ (kJ mol}^{-1}) = (239 \pm 62) - (0.67 \pm 0.20)\Sigma N\ \mathbf{a}\ (°),\ n = 3,\ r^2 = 0.92 \qquad (6)$$

$$\text{TS2 } \mathbf{c} \text{ (kJ mol}^{-1}) = -(236 \pm 57) + (0.87 \pm 0.18)\Sigma N\ \mathbf{a}\ (°),\ n = 3,\ r^2 = 0.96 \qquad (7)$$

$$\text{TS2 } \mathbf{d} \text{ (kJ mol}^{-1}) = -(218 \pm 2) + (0.82 \pm 0.11)\Sigma N\ \mathbf{a}\ (°),\ n = 3,\ r^2 = 0.98 \qquad (8)$$

Geometry and hydrogen bonding properties

The HB interaction energies (Table 2) correspond to the situations depicted in Scheme 5 (we have not reported the situation where the HF molecule bonds to the "internal" oxygen LP because there is some supplementary interaction with the three-membered ring). The HBD is always a molecule of hydrogen fluoride.

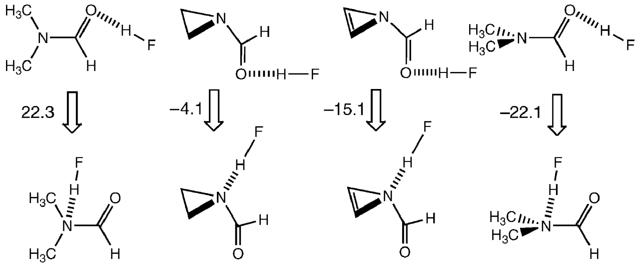
The HBA properties of amides in relation to their basicity have been the subject of many studies. For instance, Bagno *et al.* have studied the *O*- *vs.* *N*-protonation of simple amides, concluding that *O*-protonation is always favored.[20] Several authors have examined the effect of highly twisted amides on N pyramidalization and basicity.[21] Indeed, the subject of twisted amides, like Kirby's amide that protonates on the nitrogen, is of continuous interest.[21]

The HB basicity of the nitrogen atom of the azirine derivative **3a** (−51.8 kJ mol^{-1}) is larger than that of the aziridine **2a** (−43.9 kJ mol^{-1}) proving that the ring strain overcomes the conjugation effects present in "enamine" **3a**. At the same level of calculation, the thermodynamic basicity of parent azirine is 21.6 kJ mol^{-1} greater than that of aziridine.

In its TS (**1c**), DMF becomes a strong HBA by its N atom, which is notably pyramidal (Table 1), to the point that the N atom behaves as a better HBA than the O atom (compare with the protonation results in twisted amides).[21,22] *N*-Formylaziridine (**3a**) also shows a greater preference for HF by the N than by the O atom. The differences in the O/N interaction energies for the four structures considered (Table 2) are linearly related to the C=O distances of the isolated compounds (Table 1). Eqn (9) reflects the fact that the shorter the CO bond, the less conjugated the amide and the higher the preference of HF for the N over the O atom.

Table 2 Interaction energies, E_I, with regard to the separated parts in kJ mol^{-1}

Compound	E_I (O···HF)	E_I (N···HF)	Difference
1a	−49.7	−27.4	22.3
2a	−39.8	−43.9	−4.1
3a	−36.7	−51.8	−15.1
1c	−34.3	−56.4	−22.1



Scheme 5 HB energy differences (in kJ mol^{-1}) for structures **1a**, **2a**, **3a** and **1c**.

$$\text{Difference (kJ mol}^{-1}) = -(4340 \pm 275) + (3570 \pm 226)d_{CO} \text{ (Å)},\ n = 4,\ r^2 = 0.992 \qquad (9)$$

Conclusions

The simple ideas the chemists use every day have a lot of accumulated experience behind them. Therefore, it was not surprising that the calculated and the intuitive models agree. However, only calculations give a quantitative picture. In this sense, we have followed Kant's counsel that there is no science without mathematization ("…*jeder besonderen Naturlehre nur so viel Wissenschaft angetroffen werden könne, als darin Mathematik anzutreffen ist*").[23] It has not escaped our notice that the model we have used could be immediately extended to the real situation found in some peptides exhibiting highly pyramidalized amide bonds.[24]

Computation section: MP2, G3 and GIAO calculations

The geometry of the isolated monomers and hydrogen bonded complexes have been fully optimized at the B3LYP/6-31G* computational level,[25,26] with the Gaussian 03 package.[27] In the case of the transition state structures, C_s symmetry has been imposed. The minimum and transition state structures have been confirmed by frequency calculation at the same computational level. Further optimizations have been carried out at the MP2/6-311++G** and G3 computational levels.[28,29] The chemical shieldings have been evaluated at the MP2/6-311++G** level using the GIAO method.[30]

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