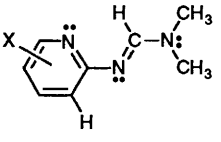
Chemistry of Amidines. Part 4.[1] Analysis of Conformation for a Series of *N'*-Pyridylformamidines by ^{1}H NMR Spectroscopic, Molecular Mechanical and Semi-empirical Molecular Orbital Methods

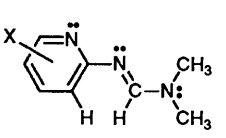
Ian D. Cunningham,* Juan Llor† and Luis Muñoz‡
Department of Chemistry, University of Surrey, Guildford, UK, GU2 5XH

The results of NOE measurements for a series of *N'*-pyridylformamidines and their conjugate acids have been interpreted with the aid of molecular mechanical and semi-empirical molecular orbital calculations. Conformations about the pyridyl–N_{im} and the C_f–N_{am} bonds are determined by delocalisation of the N_{am} lone pair, dipolar interactions, steric interactions and, in the conjugate acids, long range interaction between the pyridyl N and the electron-deficient formyl H.

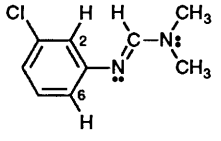
While several papers in recent years have dealt with conformation about the C–N_{am} partial double bond of amidines (R–N_{im}=C–N_{am}–) where rates of rotation are appropriate to variable temperature NMR analysis,[2] investigation of conformation about other amidine bonds, where rotation is faster, is more difficult. In a recent communication[1] we have reported the use of NOE (Nuclear Overhauser Effect) for analysis of conformation about the pyridyl-N_{im} (C2-N_{im}) bond of *N'*-(2-pyridyl)-*N*,*N*-dimethylformamidines (**1**) and their conjugate



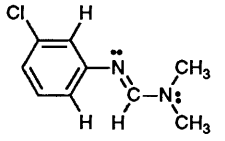
1a



1s



2a



2s

acids in $CDCl_3$ and [$^2H_6$]DMSO. In this paper we wish to present some additional NOE results for these compounds and to consider a conformational analysis based on molecular mechanical (MM) and semi-empirical molecular orbital (SMO) calculations. NOE has been used to a rather limited extent for conformational analysis of small molecules[3,4] and while MM has been used to support NOE results[5] it has so far found little use in analysis of amidines. Several papers[6] report studies of amidines by *ab initio* or MNDO methods, but consider only relatively simple amidines, although a study of *N*-phenylformamidine is of relevance to our work.[6c] Protonated amidines have not been studied to any great extent by these methods.

Experimental

The amidines were prepared as previously described.[7] Spectra were run at 25 °C on a Bruker AC 300 MHz NMR spectrometer. The conjugate acids were formed *in situ* by the addition of a slight molar excess of trifluoroacetic acid (TFA) to solutions of the free amidine or by dissolving the free amidine in a D_2O/DCl solution the strength of which was calculated to give a slight molar excess of DCl.

MM calculations were performed with the MM2(85) program, a PC version of MM2 Allinger MM program;[8a] parameters not available in this program were taken from the 1987 version of MM2(87).[8b]

SMO calculations were performed on the University of Surrey's MicroVax system using a locally modified version[9a] of the MOPAC package[9b] with the AM1[9c] hamiltonian.

Results

The ^{1}H NMR spectra of the amidines and their conjugate acids involved in this study in D_2O have been described previously;[7] spectra in other solvents were similar although δ for H_f varied by up to 0.4 ppm and the separation of the NMe_2 signals was solvent dependent.[2a]

NOE of Amidines and their Conjugate Acids.—The NOEs for the various ^{1}H signals were determined for the amidines, **1** (X = 5-NO_2, 5-Cl, 4-CH_3 and 5-CH_3) in $CDCl_3$, **1** (X = 5-NO_2, 5-Cl, H, 4-CH_3 and 5-CH_3) and **2** in [$^2H_6$]DMSO and **1** (X = 5-Br, 5-Cl, H, 4-CH_3 and 5-CH_3) in D_2O. Some of these results have been presented in general terms previously,[1] but are shown in more detail in Table 1 where the signals being irradiated are in the vertical column and those receiving enhancement are in the horizontal rows; the figures quoted are percentage enhancements in the area under the peak relative to that for the unenhanced signal. Where a range is shown the trend is from the amidine bearing the most electron-withdrawing substituent to that bearing the most electron-donating. Results for the conjugate bases **3** and **4**, of **1** and **2** respectively, in the same solvents with added TFA or DCl are given in Table 2.

In D_2O small enhancements were observed for the H_f/H3 pair for most **1**, although in this solvent the H_f signal is very close to the H6 signal. For all **1** in [$^2H_6$]DMSO and D_2O (and for the 5-NO_2 amidine in $CDCl_3$) the low field methyl signal of the NMe_2 pair showed a larger enhancement than did the high field signal upon irradiation at H_f, with the difference decreasing as X becomes more electron-donating from 3% and 0% (X = 5-NO_2, [$^2H_6$]DMSO) to almost 1% and 1% (X = 5-CH_3, D_2O). Complementary behaviour was observed on irradiation at each methyl signal; as X was made more electron-donating (particularly in D_2O) irradiation of one resulted in partial, but increasing suppression of the other. For **3** the results of the NOE experiments were complex in that small enhancements of H3 were observed on irradiation of H_f (and *vice versa*) to an extent depending on solvent and substituent. In $CDCl_3$/TFA a mutual

† *Present address:* Departamento de Quimica Fisica, Universidad de Granada, Granada, Spain.
‡ *Present address:* Departamento de Quimica Pura y Aplicada, Facultad de Ciencias, Universidad de Vigo, Vigo, Spain.

Table 1 Nuclear Overhauser enhancements for selected signals for amidines **1** in $CDCl_3$, [$^2H_6$]DMSO and D_2O, and for amidine **2** in [$^2H_6$]DMSO

1 in $CDCl_3$	H_f	H3	N–CH_3(a)[a,c]	N–CH_3(b)[b,c]
H_f	—	0	1	
H3	0	—	0	
N–CH_3(a)[a,c] N–CH_3(b)[b,c]	8 ± 1	0	—	

1 in [$^2H_6$]DMSO	H_f	H3	N–CH_3(a)	N–CH_3(b)
H_f	—	0	3–1	0–1
H3	0	—	0	0
N–CH_3(a)	8 ± 1	0	—	—
N–CH_3(b)	0–7	0	—	—

1 in D_2O	H_f	H3	N–CH_3(a)	N–CH_3(b)
H_f	—	1–3	3–1	2–1
H3	1–3	—	0	0
N–CH_3(a) N–CH_3(b)	12 ± 4[d]	0	—	—

2 in [$^2H_6$]DMSO	H_f	H2	H6	N–CH_3(a)	N–CH_3(b)
H_f	—	6	3	1	1
H2	4	—	—	0	0
H6	3	—	—	0	0
N–CH_3(a) N–CH_3(b)	12	0	0	—	—

[a] Low field methyl singlet. [b] High field methyl singlet. [c] Signals insufficiently resolved. [d] See text.

Table 2 Nuclear Overhauser enhancements for selected signals for protonated amidines **3** in $CDCl_3$/TFA, [$^2H_6$]DMSO/TFA and D_2O/DCl, and for **4** in [$^2H_6$]DMSO/TFA

3 in $CDCl_3$/TFA	H^+	H_f	H3	N–CH_3(a)	N–CH_3(b)
H^+	—	—	1–3	0	1
H_f	—	—	0–1	2	0
H3	—	0–1	—	0	0
N–CH_3(a)	0	6 ± 1	0	—	—
N–CH_3(b)	—[a]	0	0	—	—

3 in [$^2H_6$]DMSO/TFA	H_f	H3	N–CH_3(a)	N–CH_3(b)
H_f	—	0–3	1–2	0
H3	0–3	—	0	0
N–CH_3(a)	6 ± 1	0	—	—
N–CH_3(b)	2–0	0	—	—

3 in D_2O/DCl	H_f	H3	N–CH_3(a)	N–CH_3(b)
H_f	—	1–6	2–5	0
H3	2–4	—	0	0
N–CH_3(a)	10 ± 3	0	—	—
N–CH_3(b)	2 ± 1	0	—	—

4 in [$^2H_6$]DMSO/TFA	H_f	H2	H6	N–CH_3(a)	N–CH_3(b)
H_f	—	7	3	3	0
H2	5	—	—	0	0
H6	3	—	—	0	0
N–CH_3(a)	8	0	0	—	—
N–CH_3(b)	0	0	0	—	—

[a] Enhancement was difficult to measure due to variable peak width; values were ≤8%.

enhancement of <1% was observed only for **3** (X = 4-CH_3); in [$^2H_6$]DMSO/TFA small enhancements of <1% for this pair were seen for most **3** (except for X = NO_2) with a value of 3% for **3** (X = 4-CH_3), while in D_2O/DCl larger enhancements were observed for all **3** with 6% for X = 4-CH_3.

In contrast to the amidines **1** mutual NOEs between H_f and the low field NMe_2 methyl signal only were observed, and (in $CDCl_3$) between 'H^+' and the high field methyl signal only.

Molecular Mechanics Calculations.—An MM calculation was performed on the two co-planar structures **1a** and **1s** (X = H) and on the analogous structures **2a** and **2s**. For the amidine **1** the calculations give the *anti* conformer **1a** as the more stable by over 14 kJ mol^{-1}. The calculations are most appropriate to a gas phase analysis, but changing the relative permittivity in the calculation to simulate a more polar (solution-like) environment reduces the difference to less than 8 kJ mol^{-1}. The MM calculations identify a steric interaction between H3 and H_f in

Table 3 Summary of MOPAC calculations for the structure **1**, **3a**, **3s**, **5a** and **5s**

	1	**3a**	**3s**[a]	**5a**	**5s**
ΔH_f*anti–syn* /kJ mol^{-1}	—	15.8 ± 1.1		−3.6 ± 0.9	
ΔH_f**3a–5s** /kJ mol^{-1}	—	31.5–6.0	—	—	31.5–6.0
ΔH_f**1–3a** /kJ mol^{-1}	608–554		—	—	—
C2–N_{im} bond order	1.10–1.05	0.95 ± 0.01	0.94 ± 0.01	1.31–1.21	1.30–1.20
N_{im}–C_f bond order	1.71–1.61	1.31–1.36	1.33–1.37	1.34–1.44	1.34–1.43
C_f–N_{am} bond order	1.17–1.10	1.44–1.38	1.43–1.39	1.42–1.34	1.42–1.34
C3–C2–N_{im}–C_f dihedral angle	174 ± 1°	180 ± 1°	50 ± 3°	160 ± 3°	18 ± 2°
H3–H_f distance/Å	4.63 ± 0.01	4.65 ± 0.01	2.41 ± 0.05	4.56 ± 0.03	2.16 ± 0.05
H3–H^+ distance/Å	—	2.36 ± 0.01	3.62 ± 0.02	—	—

[a] No data for 5-CH_3O-substituted compound.

1s resulting in the C3–C2–N_{im}, C2–N_{im}–C_f and N_{im}–C_f–H_f bond angles being 125°, 124° and 125°, respectively. A similar interaction between an *ortho*-H and CH_3 has been proposed for phenylacetamidines.[2d]

Calculations on the two conformers **2a** and **2s** give a difference in energy of only 0.25 kJ mol^{-1} and variation of the relative permittivity makes little difference to this value.

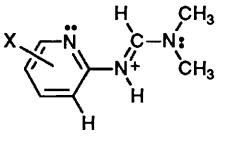
The structures generated by MM give the H_f–H3 distance in **1s**, the H_f–H6 distance in **2s**, and the H_f–H2 distance in **2a** as 2.10 Å, and the distances between the same hydrogens in **1a**, **2a** and **2s**, respectively, as 4.60 Å.

Semi-empirical Molecular Orbital Calculations.—The calculations were performed using the MOPAC program for the amidines **1** bearing substituents 5-NO_2, 4-NO_2, 5-Br, 4-Br, 5-Cl, 4-Cl, H, 5-CH_3, 4-CH_3, 5-CH_3O and 4-CH_3O on the pyridine ring. For each compound only the *anti* conformer **1a** was considered and the results are collected in Table 3; where a range of values is shown, a steady trend from the most electron-withdrawing to the most electron-donating is implied, while a single figure implies a constant value within the confines of the stated standard deviation. The calculated structures are essentially planar; in particular we note that the bond order about the C2–N_{im} bond is >1 with the C3–C2–N_{im}–C_f bond angle calculated to be 174°.

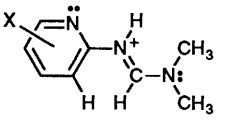
The calculations were performed for the protonated amidines bearing the same substituents. For each substituted amidine four structures were considered: namely the *syn* and *anti* N_{im}-protonated amidines, **3s** and **3a**, respectively, and the *syn* and *anti* N_{py}-protonated amidines, **5s** and **5a**, respectively. For all compounds the N_{im}-protonated *anti* form, **3a**, was calculated to have the lowest enthalpy of formation; in particular, the difference between the *anti* conformer **3a** and the *syn* **3s** is 13.6–17.6 kJ mol^{-1} (with no clear trend evident) over the range of compounds studied.

The relevant results are collected in Table 3 and the geometries resulting from calculations on structures **3a** and **3s** for the unsubstituted amidine (X = H) are shown in Fig. 1 along with relevant bond angles, bond lengths and interatomic distances.

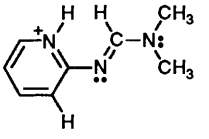
Some of the entries in Table 3 can be compared with experimental data. For example, the C_f–NMe_2 bond orders appear appropriate given the known rotational barriers.[2a] The calculation of the N_{im}-protonated form as being more stable than the N_{py}-protonated form is in agreement with our findings;[7] further, a good correlation (r = 0.999, n = 6) is obtained when the pK_a values[7] for the amidines analysed by NMR



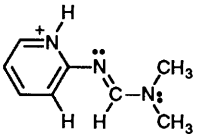
3a



3s



5a



5s

spectroscopy in this study are plotted against the difference in the heat of formation between **3a** and **1** [$\Delta H_{f(\mathbf{3a}-\mathbf{1})}$] (Table 3).

Discussion

Amidines.—The NOE results with respect to conformation about the C2–N_{im} bond have been discussed in an earlier paper;[1] they show that conformation **1a** is favoured in all cases and this was rationalised in terms of dipole repulsion.[1] The MM and SMO results also predict **1a** as the more stable, with the MM suggesting an additional, steric, destabilisation of **1s** and SMO calculations giving a co-planar pyridine ring and amidine system. This contrasts with the case of *N*-phenylformamidine[6c] where the twist angle of the phenyl group has been calculated to be 123°, presumably owing to the steric interaction between the H_f and the phenyl *ortho*-hydrogens. In contrast to results in $CDCl_3$ and [$^2H_6$]DMSO, the evidence in D_2O of a H_f/H3 interaction suggests an increased proportion of the *syn* conformation **1s**. In this more polar solvent dipole effects are likely to be less significant, reducing the energy difference between *syn* and *anti* (as modelled by MM). In addition, there is evidence from our work[2a] and that of others[2b] that delocalisation of the NMe_2 lone pair is reduced in D_2O and this may, in turn result in a relatively low degree of C2–N_{im} double-bond character in D_2O. With respect to rotation about the C_f–N_{am} bond, the relative strengths of the interaction between H_f and the low and high field methyls (Table 1) are related to the rate of rotation, with a $\Delta G^{\ddagger}$ value of about 68 kJ mol^{-1} (X = 5-CH_3)[2a] resulting in equal NOEs for both methyls and a $\Delta G^{\ddagger}$ of about 79 kJ mol^{-1} (X = 5-NO_2)[2a] resulting in an NOE for one

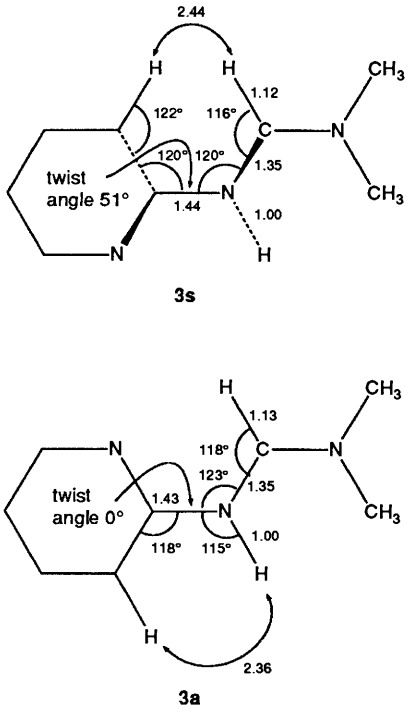


Fig. 1 Calculated structure for **3a** and **3s**

only. The differential NOEs allow the assignment of the lower field methyl singlet to that group nearer H_f.

Protonated Amidines.—The MO calculations (most appropriate to gas phase) show the *anti* conformer of the N_{im}-protonated amidine **3a** to be more stable than the *syn* **3s** and the NOE results are in agreement with this to the extent that the H_f/H3 interaction, likely to be strong for the *syn* conformer **3s**, is absent or small for the least polar solvent $CDCl_3$. MOPAC calculates the C2–N_{im} (pyridyl to N_{im}) bond order in both N_{im}-protonated forms **3** to be less than 1 (typically 0.95) for all substituents. This implies that conformation about the C2-N_{im} bond is controlled by factors other than partial double-bond character. It seems clear that the H3/H_f steric interaction will destabilise the *syn* form **3s** and consideration of the figure shows that MOPAC calculates it to be far from planar. However even when twisted out of plane by 51° the structure is still less stable by some 13 kJ mol^{-1} than the *anti* form **3a** which has been calculated to be planar and which appears to be favoured over all others, planar or non-planar. MOPAC calculates the H_f in **3** to be highly electron-deficient (excess charge 0.25 compared to 0.27 for 'H^+' of N_{im}–H) and, therefore, we propose that a small stabilisation of the *anti* conformer **3a** arises from interaction of H_f with the pyridine lone pair despite the calculated distance between this N and H_f of 2.44 Å.

The small increase in the H_f/H3 NOE on going from $CDCl_3$ to the more polar [$^2H_6$]DMSO and D_2O suggests a decrease in the predominance of conformer **3a**; we explain this as resulting from suppression of the above interaction as the electron-deficient H_f becomes solvated.

We propose that the significant H_f/H3 NOE for X = 4-CH_3 is due to a contribution from the **5s** structure. Although **5s** is calculated in all cases to be less stable than **3a**, the difference in enthalpy of formation between these two forms does decrease as the substituents become more electron donating with respect to the N_{py} atom. In addition it must be remembered that protonation is a process likely to be much influenced by solvent effects which are beyond the scope of our MOPAC analysis. In earlier work we used a linear free energy relationship to propose that the site of first protonation for the amidines **1** is N_{im}; that analysis does not preclude a contribution from a small amount of N_{py}-protonated form particularly for compounds bearing suitably positioned electron-donating groups.

The specificity of the various NOEs involving H_f, H^+ and CH_3 reflects the much higher barriers for rotation about the C_f–NMe_2 bond in the protonated amidines relative to the free amidine. The MO calculations also reflect this in terms of greatly increased bond orders relative to the unprotonated amidines (Table 3).

Conclusions

Our NMR, MM and SMO analysis shows that the amidines exist predominantly in the *anti* form **1a** because of C2–N_{im} partial double-bond character, the need to minimise the dipole moment, and the need to avoid a H_f/H3 steric interaction. For the N_{im}-protonated amidines **3** an additional factor is the stabilisation provided by a long range interaction between the N_{py} lone pair and the electron-deficient H_f; this effect may be reduced in more polar solvents and electron-donating groups may introduce a contribution from the N_{py}-protonated *syn* form **5s**. Restricted rotation about C_f–NMe_2 bond in both free and protonated amidines is reflected in the unequal NOE interaction of H_f with each methyl group; for the amidines the NOEs can be related to barrier height.

We believe that the present study, involving amidines, can be a model for other compounds where changes in chemical and/or biological activity are associated with conformational change due to the effect of substituent or solvent.

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References

1 Part 3. I. D. Cunningham, J. Llor and L. Muñoz, *J. Chem. Soc., Perkin Trans. 2*, 1992, 331.
2 (*a*) Part 2. I. D. Cunningham, J. Llor and L. Muñoz, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1751; (*b*) I. Wawer, *Magn. Reson. Chem.*, 1989, **27**, 1031; (*c*) I. Wawer, *J. Mol. Liq.*, 1988, **38**, 1; (*d*) I. Wawer, *Magn. Reson. Chem.*, 1988, **26**, 601; (*e*) I. Wawer, *Magn. Reson. Chem.*, 1987, **25**, 514; (*f*) M. Drobnič-Košoroc, S. Polanc, B. Stanovnik, M. Tišler and B. Verček, *J. Heterocycl. Chem.*, 1978, **15**, 1105; (*g*) M. Zupan, V. Pirc, A. Pollak, B. Stanovnik and M. Tišler, *J. Heterocycl. Chem.*, 1974, **11**, 525.
3 D. Neuhaus and M. Williamson, *The Nuclear Overhauser Effect in Structural and Conformational Analysis*, VCH, New York, 1989.
4 C. Landis and V. S. Allured, *J. Am. Chem. Soc.*, 1991, **113**, 9493.
5 B. Giraud, R. Nouguier, C. Jaime and A. Virgili, *Magn. Reson. Chem.*, 1992, **30**, 133.
6 (*a*) W. Kinasiewicz, A. Les and I. Wawer, *J. Mol. Struct. (Theochem.)*, 1988, **168**, 1; (*b*) J. Oszczapowicz, C. A. Regelmann and G. Hafelinger, *J. Chem. Soc., Perkin Trans. 2*, 1990, 1551; (*c*) I. Wawer. *Magn. Reson. Chem.*, 1989, **27**, 577.
7 I. D. Cunningham, J. S. Blanden, J. Llor, L. Muñoz and A. P. Sharratt, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1747.
8 (*a*) N. I. Allinger, MM2(85)-PC. Molecular Design Ltd., San Leandro, CA: Athens, GA, 1985; (*b*) N. L. Allinger, Operating Instructions for MM2(87). Quantum Chemistry Program Exchange, Department of Chemistry, Indiana University, Bloomington, IN, 1987.
9 (*a*) S. Olivella, *QCPE Bull.*, 1984, **4**, 10. Extended by S. Olivella and J. M. Bofill, 1990; (*b*) J. J. P. Stewart, *QCPE Bull.*, 1983, **3**, 101; (*c*) M. J. S. Dewar, E. G. Zoebisch, E. F. G. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1984, **107**, 3902.

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