Chemistry of Amidines. Part 2.[1] Substituent and Solvent Effects on Rotational Barriers in *N*′-Pyridylformamidines

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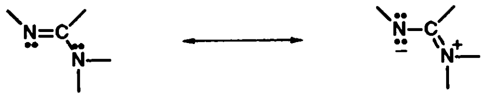
Values of $\Delta G^\ddagger$ for rotation about the carbon–dimethylamino bond in a range of substituted pyridyl formamidines have been determined by ^{1}H NMR spectroscopy in a small range of solvents. The correlation of $\Delta G^\ddagger$ with σ^- is interpreted in terms of a coplanar amidine and pyridine system. The variation of $\Delta G^\ddagger$ with solvent is interpreted in terms of hydrogen bonding to the amino lone pair of the amidine.

Amidines are compounds having the N=C–N functional group.[2] The electronic distribution over the functional group is best represented by the resonance structures **1a** and **1b**; the existence of the resonance contribution **1b** gives rise to the possibility of restricted rotation about the C–N bond. Rotational barriers about single bonds are of the order of a few tens of kJ mol^{-1}, while those about double bonds are of the order of a few hundred kJ mol^{-1}; barriers about partial double bonds such as those found in the amidine system would be expected to lie between these extremes and therefore to be suitable for determination by NMR spectroscopy.[3] Rotational barriers about carbon to nitrogen partial double bonds have been measured for many amides and values have been found to lie in the range 50–120 kJ mol^{-1}.[3,4] The height of the barrier, however, is dependent on both the nature of substituents[3a,4a,b] to the functional group and the solvent.[3a,4a,b] Barrier data for amidines are far less extensive than for amides. Values have been obtained in a variety of solvents, but mainly in CDCl$_3$, and they range from 50–80 kJ mol^{-1};[3a,c,5] smaller in general than for similar amides.[5] Simple amidines protonate on the imino nitrogen[1,6] and this results in a large increase in the barrier to rotation;[3a] few values of these barriers appear in the literature, but dimethylacetamidinium chloride has been found to show a barrier of the order of 80 kJ mol^{-1} while the unprotonated dimethyl acetamidine has a barrier too low to be determined by NMR spectroscopy.[4c] We wished to examine, more systematically, the effect of substituent and solvent on rotational barriers in amidines, and therefore undertook a study of the *N*,*N*-dimethyl-*N*′-pyridylformamidines **2**–**8**. The use of the pyridyl group was intended to introduce a general electron-withdrawing effect to the system, to produce higher and more accessible barriers, while avoiding steric effects.



1a **1b**

X
2 5-Me
3 4-Me
4 H
5 5-Cl
6 5-Br
7 4-Cl
8 5-NO$_2$

Scheme 1

Experimental

Materials.—The amidines were synthesised and purified as described previously.[1]

Spectroscopy.—All spectra were run on a Bruker AC-300 MHz NMR spectrophotometer. Solutions were generally 0.02–0.03 mol dm^{-3} in the amidine. The increasingly rapid rotation about the C–N bond as the temperature was increased was monitored by observing the coalescence of the two signals due to the methyl groups of the dimethylamino group. The difference in frequency was found not to vary during the early part of the temperature increase and $\Delta\nu$ was taken as the difference in frequency at 298 K. In most cases the coalesced peaks separated again on cooling, but for the nitro compound **8** (in D$_2$O) decomposition rapidly followed coalescence. For compound **2** in CDCl$_3$, the two methyl signals were not resolved at 25 °C and a value for $\Delta G^\ddagger$ could not be estimated. No coalescence was apparent for **8** in [^{2}H$_6$]acetone, even close to the boiling point of the solvent.

Results

The values of $\Delta G^\ddagger$ for the rotation about the carbon–dimethylamino bond were determined for some or all of the amidines in D$_2$O, [^{2}H$_6$]DMSO, CDCl$_3$, CD$_3$OD and [^{2}H$_6$]acetone. Values were calculated using eqn. (1),[3b] which is

$$\Delta G^\ddagger = -RT_c \ln[\pi h(\Delta\nu)/1.4142 k_b T_c] \qquad (1)$$

derived from $k = \pi\Delta\nu/1.4142$ and the Eyring equation. The term $\Delta\nu$ refers to the difference in frequency, without rotation, of the two non-equivalent methyl singlets on the amino group; T_c is the coalescence temperature and k is the rate constant for rotation at T_c. In D$_2$O at elevated temperatures a steady hydrolysis of the amidines was observed, but in general the methyl peaks of the amidine were still observable up to T_c. In general, uncertainties in $\Delta G^\ddagger$ are $< \pm 0.2$ kJ mol^{-1}, but for **8** in D$_2$O or where T_c is close to the boiling point of the solvent the uncertainty is $< \pm 0.6$ kJ mol^{-1}. Values in D$_2$O are collected in Table 1, and values for the other solvents are in Table 2.

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Table 1 Values of $\Delta\nu$, T_c and $\Delta G^\ddagger$ for rotation about the C–NMe$_2$ bond of the pyridyl formamidines **2–8** in D_2O

	Substituent X						
	5-Me	4-Me	H	5-Cl	5-Br	4-Cl	5-NO$_2$
$\Delta\nu$/Hz	34.3	34.3	33.0	36.3	33.3	38.3	35.4
T_c/K	317	322	323	330	329	336	356
$\Delta G^\ddagger$/kJ mol^{-1}	66.4	67.5	67.9	69.1	69.1	70.2	74.8

Table 2 Values of $\Delta\nu$, T_c and $\Delta G^\ddagger$ for rotation about the C–NMe$_2$ bond of pyridylformamidines in various solvents

Compound	$\Delta\nu$/Hz	T_c/K	$\Delta G^\ddagger$/kJ mol^{-1}
[$^2H_6$]DMSO			
2	30.2	326	68.7
3	30.1	329	69.3
5	30.8	343	72.3
8	32.6	376	79.4
$CDCl_3$			
5	4.35	306	69.2
8	7.35	340	75.9
CD_3OD			
2	23.04	319	67.9
5	23.80	332	70.7
8	22.23	>338[a]	>72[a]
[$^2H_6$]Acetone			
2	28.87	322	68.1
5	30.84	337	71.0

[a] Coalescence was advanced, but incomplete at 338 K.

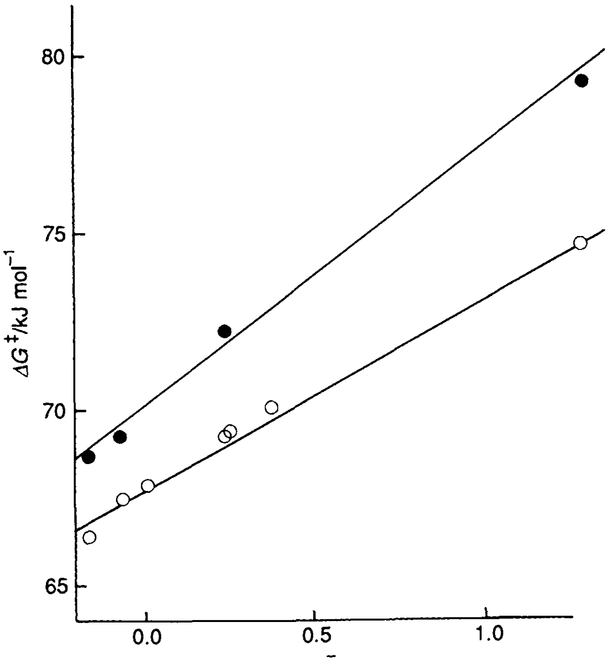

Fig. 1 Plot of values of $\Delta G^\ddagger$ for rotation about the C–NMe$_2$ bond of amidines **2–8** in D_2O (○), and amidines **2**, **3**, **5** and **8** in [$^2H_6$]DMSO (●) *vs.* σ^-

For all solvents the value of $\Delta G^\ddagger$ is seen to increase as the substituent on the pyridyl ring becomes more electron-withdrawing. For D_2O solvent a correlation of $\Delta G^\ddagger$ with σ^- is shown in Fig. 1. The correlation coefficient is 0.997; a poorer correlation (0.984) is obtained if σ is used. Since the plot is of $\Delta G^\ddagger$, rather than $\log k$, *vs.* σ^-, the slope is not directly comparable to ρ as normally defined. Using the Eyring equation to relate k to $\Delta G^\ddagger$ allows us to calculate a value of ρ (at 25 °C) of -1.0. A similar correlation for dimethyl sulphoxide (DMSO) is also better using σ^-, and has a ρ value of -1.3 (Fig. 1).

When the imino nitrogen was protonated in DCl/D_2O the value of $\Delta\nu$ for the two methyl signals increased to *ca.* 45 Hz (0.15 ppm) for all compounds, but no coalescence was observable below the b.p. of D_2O.

Discussion

We have assumed that the amidines are all in the more stable *E* configuration. Any *Z* isomer would be expected to isomerise under the conditions of the preparation.[7]

We have analysed the effect of ring substitution in terms of a linear free energy relationship, plotting $\Delta G^\ddagger$ *vs.* σ^-. The terms $\Delta H^\ddagger$ and $\Delta S^\ddagger$ are often considered to be more meaningful than $\Delta G^\ddagger$, but they are determined from the temperature variation of the rate constant for rotation using NMR spectral line-broadening measurements and the reliability of activation parameters determined in this way has been reviewed by Kessler[3b] and found to be poor. It should be stressed that $\Delta G^\ddagger$ is a temperature-dependent parameter (it includes the term $T\Delta S^\ddagger$) and that the values of $\Delta G^\ddagger$ determined in this work refer to the T_c for the particular compound as shown in the Tables. However, in the context of the reaction being considered here (rotation) it seems reasonable to assume that the entropy term is small and that the temperature dependence of $\Delta G^\ddagger$ can be neglected when considering the slope and correlation quality of the plot. Bearing in mind these considerations we can interpret the increase in the value of $\Delta G^\ddagger$ with increase in the electron-withdrawing ability of the pyridyl substituent in terms of an increased contribution from the resonance form **1b**, in which increased electron density is concentrated on the nitrogen atom bearing the pyridyl group. The correlation of $\Delta G^\ddagger$ in D_2O and [$^2H_6$]DMSO with σ^- rather than σ implies a through-resonance effect from the lone pair on the amino nitrogen to the nitro group on the pyridyl ring. Values of pK_a for imino protonation for these compounds,[1] and indeed for *N*-phenylamidines[6] are found to correlate not with σ^-, but with σ, implying that the imino nitrogen lone pair is directed at right angles to the π system on the aromatic ring. Taken together, these results show that, in solution, the amidine adopts a conformation in which the pyridine ring and the amidine system are coplanar, as shown in Scheme 1.

A comparison between our values of $\Delta G^\ddagger$ for pyridylformamidines and those for *N'*-phenylformamidines is difficult due to limited data for the latter; however, a comparison between *N,N*-dimethylamino-*N'*-(5-nitro-2-pyridyl)formamidine (**8**) and *N,N*-dimethylamino-*N'*-(4-nitrophenyl)formamidine in $CDCl_3$ shows the barrier for the former to be some 9 kJ mol^{-1} higher due to the electron-withdrawing effect of the ring nitrogen.[5]

The values of $\Delta G^\ddagger$ for the rotations in various solvents show a rather surprising distribution. It seems clear, since the height of the barrier for any given compound depends on the extent of the resonance contribution **1b**, that solvents which stabilise this dipolar form should lead to a higher barrier. Although we have insufficient data for a rigorous statistical approach to a solvent correlation, we believe that values of Z or E_T are most appropriate in defining an order of solvent polarity[8,9] in this case, since they are both based on transformations involving dipoles. Therefore we might expect barrier heights to follow the order $D_2O > CD_3OD > [^2H_6]$-DMSO $> [^2H_6]$acetone $> CDCl_3$. Based on this expectation the values for the two protic solvents, especially D_2O, appear anomalously low, and it seems reasonable to attribute this to their hydrogen-bonding ability. Hydrogen bonding to the imino nitrogen, the pyridyl nitrogen, the substituent X or to the π system of the aromatic ring would be expected in each case to favour resonance form **1b** and cannot explain the low barriers. However, hydrogen bonding to the lone pair of the amino nitrogen would be expected to lower the barrier height in these solvents by favouring form **1a**, and we believe that this is the reason for our observations. This rationalisation is also supported by noting that the value of ρ is higher in $[^2H_6]$DMSO than in D_2O, suggestive of greater delocalisation of the amino lone pair in the former solvent. It is interesting that the rotational barriers in amides are also solvent dependent, but for amides barriers appear to follow the expected pattern of solvent polarity, with the barrier for water or D_2O being higher than those for less polar solvents.[3a,4a,b] It seems likely that the lesser degree of amino lone pair delocalisation in amidines relative to that in amides allows a degree of hydrogen bonding to this atom in protic solvents.

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References

1 Part 1. I. D. Cunningham, J. S. Blanden, J. Llor, L. Muñoz and A. P. Sharratt, *J. Chem. Soc., Perkin Trans. 2*, preceding paper.
2 (*a*) *The Chemistry of Amidines and Imidates*, ed. S. Patai, Wiley, New York, 1975; (*b*) *The Chemistry of Carbon–Nitrogen Double Bond*, ed. S. Patai, Wiley, New York, 1970.
3 (*a*) L. M. Jackman and F. A. Cotton, *Dynamic NMR Spectroscopy*, Academic Press, New York, 1975, ch. 7; (*b*) H. Kessler, *Angew. Chem., Int. Ed. Engl.*, 1970, **9**, 219; (*c*) H. Kessler and D. Leibfritz, *Tetrahedron*, 1970, **26**, 1805.
4 (*a*) T. Drakenberg, K-I. Dahlqvist and S. Forsen, *J. Phys. Chem.*, 1972, **76**, 2178; (*b*) L. M. Jackman, T. E. Kavanagh and R. C. Haddon, *Org. Mag. Reson.*, 1969, **1**, 109; (*c*) R. C. Neuman, Jr. and L. B. Young, *J. Phys. Chem.*, 1965, **69**, 2570; (*d*) T. Drakenberg and S. Forsen, *J. Phys. Chem.*, 1970, **74**, 1.
5 D. J. Bertelli and J. T. Gerig, *Tetrahedron Lett.*, 1967, 2485.
6 J. Oszczapowicz and K. Ciszkowski, *J. Chem. Soc., Perkin Trans. 2*, 1987, 663, and references cited therein.
7 I. D. Cunningham and A. F. Hegarty, *J. Chem. Soc., Perkin Trans. 2*, 1986, 537.
8 E. M. Kosower, *Physical Organic Chemistry*, Wiley, New York, 1968.
9 C. Reichardt, *Solvent Effects in Organic Chemistry*, Verlag Chemie, Weinheim, 1978.

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