Chemistry of Amidines. Part 1.† Determination of the Site of Initial Protonation in *N'*-Pyridylformamidines

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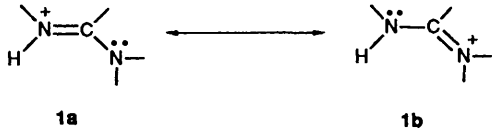
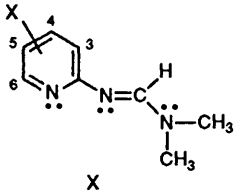
A series of substituted *N,N*-dimethyl-*N'*-pyridylformamidines has been synthesised and the pK_a values of the conjugate acids have been measured in water at 25 °C. Consideration of the pK_a values shows that initial protonation is predominantly on the imino nitrogen of the amidine system rather than on the pyridyl nitrogen. The effect of the protonation on the ^{1}H and ^{13}C NMR spectra of the amidines is discussed.

In general, protonation of the amidine functional group N=C–N occurs on the imino nitrogen (**1a**) rather than the amino



1a **1b**



X	
2	5-Me
3	4-Me
4	H
5	5-Cl
6	5-Br
7	4-Cl
8	5-NO_2

nitrogen because of resonance delocalisation of the positive charge *via* the resonance form **1b**.[1] However, when a substituent to the system is also basic the site of first protonation may not be obvious; such is the case for the pyridylformamidines **2–8**. Normally pyridines are less basic than amidines, but in the case of these compounds it was unclear to what extent the pyridine ring would effect the amidine and *visa versa*. The general electron-withdrawing effect of the pyridyl group would be expected to lower the pK_a of the imino nitrogen, while donation of either the imino or the amino nitrogen lone pairs into the pyridine ring would be expected to increase the pK_a of the pyridine nitrogen. Since pK_a values for the related *N*-phenylamidines have been found to correlate well with Hammett σ constants,[2] as have values for substituted pyridines,[3] we have used a linear free energy relationship to investigate the protonation of compounds **2–8**.

While ^{1}H NMR chemical shift values for amidines have been analysed with respect to defining additivity parameters,[4] the effect of protonation on chemical shift values for amidines does not appear to have been examined, although some NMR data are available for the guanidine–guanidinium system.[5]

Experimental

Preparation of the Aminopyridines.—2-Amino, 2-amino-5-chloro, 2-amino-4-methyl and 2-amino-5-methyl-pyridine were purchased from Aldrich and were used as supplied. 2-Amino-5-nitropyridine[6] was prepared by electrophilic nitration of 2-aminopyridine and 2-amino-5-bromopyridine[7] was prepared by electrophilic bromination of 2-aminopyridine. 2-Amino-4-chloropyridine was prepared from 2-picolinic acid by a modification[8] of the method of Graf.[9]

Table 1 M.p.s and microanalysis data for amidines **2–8**

Compound (formula)	Yield (%)	M.p./°C	Found (required) (%) C	H	N
2	69	68–71	66.7	8.0	25.8
($C_9H_{13}N_3$)			(66.2)	(7.9)	(25.7)
3	59	98–99	66.3	7.6	26.0
($C_9H_{13}N_3$)			(66.2)	(7.9)	(25.7)
4	48	29–31	—	—	—
($C_8H_{11}N_3$)		(34–36)[10]	(—)	(—)	(—)
5	45	68–69	52.0	5.6	22.8
($C_8H_{10}ClN_3$)			(52.3)	(5.4)	(22.9)
6	73	79–80	41.8	4.2	18.2
($C_8H_{10}BrN_3$)			(42.1)	(4.4)	(18.4)
7	41	78–80	52.2	5.3	22.6
($C_8H_{10}ClN_3$)			(52.3)	(5.4)	(22.9)
8	75	160–161	49.5	5.3	28.8
($C_8H_{10}N_4O_2$)			(49.4)	(5.2)	(28.9)

Preparation of Amidines.—All the amidines **2–8** were prepared by refluxing the appropriately substituted 2-aminopyridine (10 mmol) with *N,N*-dimethylformamide dimethyl acetal (Aldrich) (9 cm^3) in methanol (15 cm^3) until TLC analysis showed the reaction to be complete; generally after several hours. The amidines were recrystallised from light petroleum (b.p. 60–80 °C) to constant m.p. M.p.s and microanalyses are collected in Table 1.

Determination of pK_a.—The pK_a values were determined by potentiometric titration of 50 cm^3 of *ca.* 0.004 mol dm^{-3} solutions of amidine in water using 0.05 mol dm^{-3} hydrochloric acid in portions of 0.2 cm^3. Temperature control was maintained at 25 ± 0.5 °C by use of a reaction vessel with a water jacket supplied from a thermostatted water bath. The titration curve data obtained was processed using a 'Miniquad' computer program to calculate the pK_a.

Determination of NMR Spectra.—Spectra were run at 25 °C on a Bruker AC-300 MHz NMR spectrophotometer. Samples of the amidines (generally 14–16 mg, except where solubility was a problem in which case as little as 2 mg) were accurately weighed into an NMR tube and dissolved in D_2O before running the ^{1}H NMR spectrum; chemical shift values were

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Table 2 pK_a values for the conjugate acids of the amidines **2–8** measured in water at 25 °C

Compound	pK_a
2	7.45 ± 0.06
3	7.37 ± 0.02
4	7.20 ± 0.03
5	6.85 ± 0.03
6	6.68 ± 0.03
7	6.48 ± 0.03
8	5.37 ± 0.06

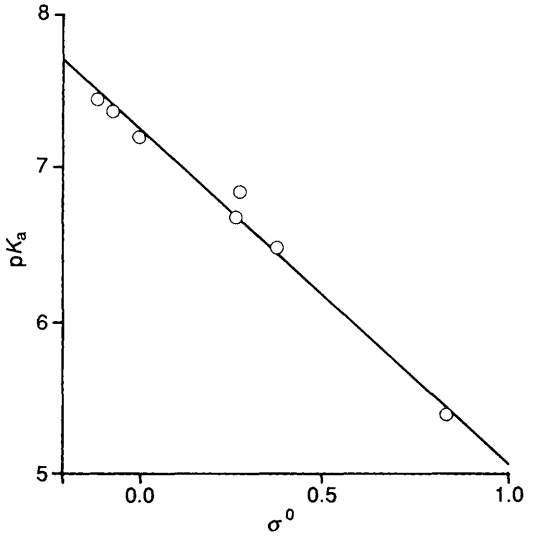

Fig. 1 Plot of pK_a values for the protonated amidines **2–8** in water at 25 °C *vs.* σ^0

ultimately referenced to dioxane (δ = 3.73 ppm). For spectra in acid a similar amount (14–16 mg) was weighed out and then, prior to running the spectrum, a quantity of 0.24 molar DCl/D_2O (generally 0.5 cm^3) sufficient to provide a 1.1:1 mol dm^{-3} excess of DCl to amidine was added to dissolve the sample. Spectra were also determined in a four- to five-fold excess of acid, by using less of the amidine. A ^1H NMR monitored titration was performed on amidine **2** by the repeated addition of small quantities (20 initially, then 50 mm^3) of 0.244 mol dm^{-3} DCl/D_2O to a solution of **2**, initially 0.052 mol dm^{-3} in amidine; dioxane was used as an internal standard. A similar titration was performed for amidine **5**. ^{13}C NMR spectra for **2** and **5** in D_2O and in DCl/D_2O were determined as above.

Results

Preparation of Amidines.—All of the amidines except **4**[10] were new compounds, and all showed IR and ^1H NMR spectra consistent with the proposed structures. All amidines were pure by TLC analysis and gave satisfactory C,H,N microanalyses (Table 1).

pK_a *Values in Aqueous Solution.*—pK_a values were measured in water at 25 °C for the amidines **2–8**. The values are collected in Table 2. In no case was any evidence found for a second pK_a above pH = 3. A Hammett plot of pK_a *vs.* σ^0 is shown in Fig. 1.[11] The plot is constructed assuming that the positional relationship of the substituents is defined relative to the amidino group. The rationale for this is given below. The value of ρ is −2.2 ± 0.1 and the correlation coefficient is >0.99. No significant difference in ρ or the correlation coefficient is found when σ is used[11] instead of σ^0. A plot in which the substituents are defined relative to the pyridyl nitrogen, and in which σ values appropriate to pyridyl protonation[3] are used also gives a ρ value of −2.2, but a correlation coefficient of 0.90.

^1H *NMR Changes on Addition of DCl.*—The ^1H NMR spectra of the amidines **2–8** in D_2O at 25 °C are given in Table 3 and are as expected for these compounds. On prolonged standing, and particularly on warming, there was evidence of slow hydrolysis, particularly of those amidines bearing electron-withdrawing substituents. Addition of 1.1 equivalents of DCl to solutions of the amidines **2–8** in D_2O caused all ^1H NMR signals to shift downfield. The magnitude of the shift of each hydrogen in each compound is given in Table 4. In general it can be seen that for most signals the change in δ is more or less independent of the substituent on the pyridyl ring, and the mean values of $\Delta\delta$ along with the standard deviations for each signal are included in the table. No significant further change in the spectra of amidines **4**, **5**, **6** and **8** was seen when further DCl (up to four-fold excess) was added. However for the 5-methylamidine **2** further changes were seen on addition of excess DCl.

Titrations of amidines **2** and **5** were monitored by ^1H NMR spectroscopy. In the case of the 5-chloroamidine **5** a steady shift in all signals was observed; by the end point of the titration all signals had shifted by an amount within ±0.02 ppm of that given in Table 4. A similar result was obtained for the 5-methylamidine **2** up to the addition of one equivalent; no further change was apparent up to the addition of almost three equivalents, but on further titration (addition of up to four equivalents) further shifts were observed for all signals. The values of $\Delta\delta$ for addition of this excess DCl are also given in Table 4. Although some broadening of some signals was observed during titrations, no significant change in coupling patterns was evident. There was no evidence of amidine hydrolysis at room temperature in acidic solutions.

^{13}C *NMR Changes on addition of DCl.*—The ^{13}C NMR spectra of amidines **2** and **5** in D_2O are given in Table 5. Signals were assigned by use of correlation tables and from C–H correlation spectra. Addition of 1.1 equivalents of DCl to solutions of amidines **2** and **5** in D_2O caused changes in the ^{13}C NMR spectra as shown in Table 5.

Discussion

The site of preferential protonation is clearly the imino nitrogen of the amidino system. This can most elegantly be seen by considering the isomeric 5- and 4-chloro-substituted amidines **5** and **7**, respectively. Since a *meta* chloro group is more electron-withdrawing than a *para* analogue, the compound whose protonation site is *meta* to the chloro group will be the less basic (lower pK_a). From Table 2 it can be seen that the 4-chloroamidine **7** is less basic than the 5-chloroamidine **5**, indicating that the imino nitrogen is the preferred site of initial protonation. A similar analysis of the methyl-substituted pair **2** and **3** also indicates imino protonation. Further evidence is provided by a consideration of the Hammett plot (Fig. 1), in which a better correlation is obtained by assuming imino protonation than by assuming pyridyl protonation. Furthermore, the slope of the correlation is close to values found for protonation of the closely related *N*-phenylformamidines,[2a,e] and appears to be typical of imino protonation. On the other hand, the slope obtained by assuming pyridyl protonation (−2.2) is very different from that expected from a consideration of more simple pyridines, where ρ values are typically −6.[3] We note that the pK_a value for the 5-nitroamidine **8** correlates better if σ^0 (or even σ) is used rather than σ^-. This has been noted in

Table 3 Values of δ (ppm) for ^{1}H NMR signals for amidines **2–8** in D_2O at 25 °C along with coupling patterns and constants in Hz

Compound	$N(CH_3)_2$		NCHN	H(3)	H(4)	H(5)	H(6)	CH_3
2	2.96 (s)	3.08 (s)	8.01 (s)	6.82 (d, 8)	7.51 (dd, 2, 8)	—	7.95 (d, 2)	2.20 (s)
3	2.92 (s)	3.04 (s)	7.97 (s)	6.70 (s)	—	6.82 (d, 6)	7.92 (d, 6)	2.21 (s)
4	2.91 (s)	3.02 (s)	7.94 (s)	6.84 (d, 6)	7.60 (t, 6)	6.94 (t, 6)	8.05 (d, 6)	—
5	3.00 (s)	3.12 (s)	8.11 (s)	6.91 (d, 9)	7.68 (dd, 2, 9)	—	8.13 (d, 2)	—
6	3.00 (s)	3.11 (s)	8.13 (s)	6.88 (d, 9)	7.82 (dd, 2, 9)	—	8.24 (d, 2)	—
7	2.97 (s)	3.10 (s)	8.04 (s)	6.89 (d, 2)	—	6.99 (dd, 2, 7)	8.00 (d, 7)	—
8	3.10 (s)	3.21 (s)	8.44 (s)	7.03 (d, 9)	8.40 (dd, 3, 9)	—	9.05 (d, 3)	—

Table 4 Change in chemical shift (ppm) of ^{1}H NMR signals due to amidines **2–8** in D_2O on addition of 1.1 equivalents of DCl at 25 °C

Compound	$N(CH_3)_2$		NCHN	H(3)	H(4)	H(5)	H(6)	CH_3
2[a]	0.28 (0.44)	0.32 (0.46)	0.69 (0.83)	0.33 (0.96)	0.25 (0.87)	—	0.15 (0.46)	0.07 (0.26)
3	0.30	0.32	0.64	0.41	—	0.32	0.17	0.18
4	0.36	0.40	0.87	0.42	0.32	0.36	0.25	—
5	0.29	0.33	0.79	0.29	0.20	—	0.20	—
6	0.28	0.33	0.78	0.27	0.20	—	0.19	—
7	0.32	0.35	0.86	0.43	—	0.36	0.26	—
8	0.28	0.31	0.73	0.37	0.20	—	0.12	—
mean $\Delta\delta$ $\pm\sigma$[b]	0.30 (0.03)	0.34 (0.03)	0.77 (0.09)	0.36 (0.06)	0.23 (0.05)	0.35 (0.02)	0.19 (0.05)	0.13 (0.06)

[a] The values in parentheses are for addition of four equivalents of DCl and are for the change in δ relative to its value in D_2O. [b] Standard deviation.

Table 5 Chemical shift values (ppm) of ^{13}C NMR signals due to amidines **2** and **5** in D_2O at 25 °C and changes on addition of 1.1 equivalents of DCl ($\Delta\delta$)

Compound	$N(CH_3)_2$		NCHN	C(2)	C(3)	C(4)	C(5)	C(6)	CH_3
2	34.4	40.7	157.1	158.8	116.3	140.1	128.4	147.2	16.7
$\Delta\delta$	2.5	3.0	−3.9	−11.2	−2.7	1.9	3.7	−1.2	0.1
5	34.6	40.9	157.4	159.8	117.3	138.8	125.4	146.0	—
$\Delta\delta$	2.8	3.5	−5.0	−12.6	−3.4	0.9	3.8	0.9	—

other imino systems[2,12,13] and can be explained by assuming that the imino *N* lone pair is at right angles to the π system of the aromatic ring and that no delocalisation into the ring takes place.

In the NMR spectra the consistency of the changes in δ for all signals and for all the amidines can be seen from Table 4 and suggests a common site of initial protonation. The protonation is reflected most significantly in the large shift of the formyl proton, and we suggest that this is characteristic of imino protonation. In the case of the 5-methylamidine **2** a second protonation is detected on addition of further acid. The ^{1}H NMR changes accompanying this second protonation are very different to those for the first; in particular, we attribute the large shift for the pyridyl protons and the small shift for the formyl proton to pyridyl protonation.

The ^{13}C NMR data is more limited and many of the shifts are rather small. Certain signals are shifted upfield on protonation suggesting an increase in electron density at these carbons. In particular the increase in electron density at the formyl carbon is probably due to increased delocalisation of the amino lone pair in the protonated form (**1a** and **1b**).

No evidence for initial protonation on the pyridyl nitrogen was found for any of the compounds **2–8**. However, it is possible that a small fraction of the protonation for any particular amidine may be at this site; the approach that we have used (using linear free energy relationships) is a rather crude one and small deviations from the correlation would not be apparent. This is particularly so at the upper (lower σ, higher pK_a) end of our range, where based on the pK_a *vs.* σ profile for simple pyridines[3] we would expect the microscopic pK_a of the pyridyl nitrogen to increase more sharply (ρ of *ca.* −6) with decreasing σ than that of the amidino nitrogen. The consistency of the ^{1}H NMR changes on protonation over the whole range supports a consistency of protonation site, but

again a small contribution from pyridyl protonation might not be detected.

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References

1 *The Chemistry of Amidines and Imidates*, ed. S. Patai, Wiley, New York, 1975.
2 (*a*) J. Vaes, F. Faubert and Th. Zeegers-Huyskens, *Can. J. Chem.*, 1975, **53**, 604; (*b*) M. J. Cook, A. R. Katritzky and S. Nadji, *J. Chem. Soc., Perkin Trans. 2*, 1976, 211; (*c*) J. Oszczapowicz, R. Orlinski and H. Walczynska, *Pol. J. Chem.*, 1979, **53**, 2531; (*d*) J. Oszczapowicz and E. Raczynska, *Pol. J. Chem.*, 1983, **57**, 419; (*e*) J. Oszczapowicz and E. Raczynska, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1643; (*f*) E. Raczynska, J. Oszczapowicz and M. Walczak, *J. Chem. Soc., Perkin Trans. 2*, 1985, 1087; (*g*) J. Oszczapowicz and K. Ciszkowski, *J. Chem. Soc., Perkin Trans. 2*, 1987, 663; (*h*) E. D. Raczynska, *J. Chem. Soc., Perkin Trans. 2*, 1987, 1117; (*i*) E. Dolecka, E. D. Raczynska and T. Drapala, *J. Chem. Soc., Perkin Trans. 2*, 1988, 257.
3 A. Fischer, W. J. Galloway and J. Vaughan, *J. Chem. Soc.*, 1964, 3591.
4 J. Oszczapowicz, W. Krawczyk, J. Osek and E. Raczynska, *J. Chem. Res. (S)*, 1985, 384.
5 H. O. Kalinowski and H. Kessler, *Org. Magn. Reson.*, 1975, **7**, 128.
6 *The Chemistry of Heterocyclic Compounds–Pyridine and its Derivatives*, ed. E. Klinsberger, Interscience, 1961, Part 2.
7 H. J. Den Herthog, *Recueil*, 1945, **64**, 85.
8 K. B. DeRoos and C. A. Salemink, *Recueil*, 1969, **88**, 1263.
9 R. Graf, *Chem. Ber.*, 1934, **64**, 21.
10 H. Brederick, F. Effenberger and A. Hofmann, *Chem. Ber.*, 1964, **97**, 61.
11 O. Exner, *Correlation Analysis in Chemistry: Recent Advances*, eds. N. B. Chapman and J. Shorter, Plenum, New York, 1978.
12 I. D. Cunningham, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1485.
13 I. D. Cunningham, G. J. Buist and S. R. Arkle, *J. Chem. Soc., Perkin Trans. 2*, 1991, 589.

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