Acidity Functions and the Protonation of Weak Bases. Part VI.¹ The Amide Acidity Function: its Extension and Application to N-Oxides

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The protonation of pyridine 1-oxides of low basicity in aqueous sulphuric acid solutions is correlated by the amide acidity function rather than the Hammett acidity function. The H_A-scale has been extended by measurements of the second protonation of phenazine 5,10-dioxide.

THE quantitative study of the nitration of pyridine 1-oxides² revealed anomalous behaviour which was most simply explicable on the basis that the concentration of free base species decreased with increasing acidity less rapidly than calculated for a Hammett base. Contrary to our previous conclusion,³ this implied that pyridine 1-oxides did not satisfy equation (1) with n = 1.

$$H_0 = pK_a - n \log_{10} \frac{[\text{cation}]}{[\text{base}]} \tag{1}$$

In our previous work,³ only the α -substituted pyridine 1-oxides had values of n significantly different from unity, and this deviation was attributed to steric hindrance to protonation. Critical examination of the results (see Table 2 of ref. 3) showed, however, that these α -substituted compounds were the weakest bases of the oxides studied; many of the others undergo significant amounts of protonation in the pH range. Pyridine 1-oxides carrying several electron-withdrawing substituents, both with and without α -substituents, have now been investigated to clarify their base behaviour.

Preparation of Compounds.-3,5- and 2,6-Dichloropyridine were smoothly converted into N-oxides; direct nitration yielded the 4-nitro-derivatives (I and II). The orientations were proved by the singlet n.m.r. spectra obtained (chemical shifts for trifluoroacetic acid solutions indicated in the formulae). For the 2,6-dichloro-derivative, similar results were published by Rousseau and Robins⁴ since our work was completed. The other compounds were prepared by published methods.

EXPERIMENTAL

3,5-Dichloro-4-nitropyridine 1-Oxide. 3,5-Dichloropyridine was converted by the standard peracetic acid procedure (cf. ref. 5) into the 3,5-dichloropyridine 1-oxide (95%), which separated from light petroleum as needles, m. p. 109-110°, after sublimation at 100°/15 mm. (Found: C, 36·4; H, 1·7; N, 8·3. C₅H₃Cl₂NO requires C, 36·6; H, 1.8; N, 8.5%).

The oxide $(4 \cdot 1 \text{ g.})$ in sulphuric acid $(22 \text{ ml.}, d 1 \cdot 84)$ and nitric acid (12 ml., $d \cdot 1 \cdot 5$) was heated for $1\frac{1}{2}$ hr. at 10° . The whole was poured on ice and sodium carbonate was added until neutral. Chloroform-extraction gave the nitro-derivative (79%), which separated from ethanol as pale yellow plates, m. p. 155°, turning pink on extended exposure to light (Found: C, 29.0; H, 1.0; N, 13.3. $C_5H_2Cl_2N_2O_3$ requires C, 28.7; H, 1.0; N, 13.0%).

2,6-Dichloropyridine 1-oxide [m. p. 139-140°; lit.,4 m. p. 139.5-140.5° (Found: C, 36.6; H, 2.3; N, 8.3. Calc. for C₅H₃Cl₂NO: C, 36.6; H, 1.8; N, 8.5%), prepared (75%) by the method ⁶ used previously for the 2,6-dibromoanalogue] was similarly converted into the 4-nitro-derivative (92%) which formed yellow plates, m. p. 177-178° (lit.,4 m. p. 177-178.5°).

⁴ R. J. Rousseau and R. K. Robins, J. Heterocyclic Chem., 1965, 2, 196.

 ⁶ E. Ochiai, J. Org. Chem., 1953, 18, 534.
⁶ R. F. Evans, M. van Ammers, and H. J. den Hertog, Rec. Trav. chim., 1959, 78, 408.

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Nitration of 3,5-dimethylpyridine 1-oxide yielded the 4-nitro-derivative (64%) as yellow plates, m. p. 177-178° (lit.,⁷ 174-175°). The n.m.r. spectra in trifluoroacetic acid showed singlets at $\tau 1.2$ and 7.5 of relative area 1:3.

The preparation of aqueous sulphuric acid solutions, and measurements of the [cation]/[base] ratio, were as before.3

RESULTS AND DISCUSSION

The H_0 values 8 for half protonation and values of n determined from equation (1) are in Table 1. Clearly,

the pyridine N-oxides (unlike many other weak bases 8,9) do not follow the H_0 function in their protonation behaviour, and are thus not Hammett bases. However, it was found that these protonations were correlated satisfactorily by the $H_{\mathbb{A}}$ function,¹⁰ as indicated by the straight-line plots of Figure 1 and by the n values of near unity (Table 1) calculated by use of equation (2).

$$H_{\rm A} = pK_{\rm a} - n \log_{10} \frac{[\text{cation}]}{[\text{base}]}$$
(2)

TABLE 1			
Substituted	pyridine	1-oxides	

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		Wavelength for determination	From eq	ın. (1)	From e	qn. (2)	
	Substituents	(mµ)	$\mathbf{p}K_{\mathbf{a}}$	п	$\mathbf{p}K_{\mathbf{a}}$	n	р <i>Ка</i> ^в
I	3,5-Dimethyl-4-nitro-	270	-0.59	0.98	-0.59	0.96	-0.59
II	2-Chloro-	255	-0·81 ª	1·30 ª	-0.83	1.00	
III	3,5-Dichloro-	265	-1.01	1.30	-0.94	1.04	-0.95
IV	2,6-Dimethyl-4-nitro-	320	-1.10	1.22	-1.02	0.98	-1.00
v	2-Cyano-	268	-2.08	1.23	-1.75	0.92	
VI	3,5-Dimethoxy-2-nitro-	255	-2.16	1.30	-1.95	0.90	-1.97
\mathbf{VII}	2-Nitro-	245	-2.71	1.44	-2.13	0.94	
VIII	3,5-Dichloro-4-nitro-	275	-2.82	1.79	-2.23	0.92	-2.29
\mathbf{IX}	2,6-Dichloro-	290	-3.10	1.66	-2.31	0.90	-2.41
х	2,6-Dichloro-4-nitro-	320	- 3.90	1.70	-2.76	0.91	-2.85

^a Figures reassessed from previous data (see ref. 4). ^b pK_a values by 'overlap' method.



FIGURE 1 Plots of indicator ratios against the H_A acidity scale (numbering of compounds refers to Table 1)

TABLE 2

[cation]

Log10 [base]

-0.99

-0.62

-0.73

-0.48

- 0.30

--0.18 -0.15

-0.00

+0.24

+0.21

+0.65

Ionisation ratios of phenazine 5,10-dioxide

Sulphuric acid

(% w/w) 74·06

79.00

80.00

80.90

84.13

84.30

84.66 86.00

87.50

88.50

91.97

TABLE	3
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Extended $H_{\rm A}$ values

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huric acid	
% w/w)	$-H_{A}$
82.00	4.74
84.00	4.91
86.00	5.12
88.00	5.34
90.00	5.57
92.00	5.79
93.00	5.90

The H_0 values for half-protonation (Table 1) are therefore not true pK_a values for the N-oxides, and

⁷ J. M. Essery and K. Schofield, J. Chem. Soc., 1960, 4953. ⁸ M. J. Jorgenson and D. R. Hartter, J. Amer. Chem. Soc., 1963, 85, 878.

⁹ L. P. Hammett and A. J. Deyrup, J. Amer. Chem. Soc., 1932, 54, 2721. ¹⁰ A. R. Katritzky, J. B. Stevens, and K. Yates, Canad. J. Chem., 1964, 42, 1957.

cannot be used to calculate [cation]/[base] ratios in acids of other strengths. However, the H_A values for halfprotonation (Table 1) do represent pK_a values, which are anchored in the pH range (see, however, recent work by Bunnett and Olsen¹¹), and are reasonable approximations to the thermodynamic pK_a values, and can be used to calculate [cation]/[base] ratios. Application of Bunnett and Olsen's treatment ¹¹ to our values {plotting $\log([\text{cation}]/[\text{base}]) + H_0$ against $H_0 + \log[\text{H}^+]$ gave values of ϕ (the slope) which are in the same range as they have recorded for amides.



FIGURE 2 Plots of indicator ratios against concentration of sulphuric acid for (A) *m*-nitrobenzamide, (B) 2,3,6-trichloro-(D) 2,4,6benzamide (C) 2,4-dichloro-3,5-dinitrobenzamide, trinitrobenzamide, and (E) phenazine 5,10-dioxide

The $H_{\rm A}$ -scale previously extended only to 80% sulphuric acid, whereas our work on nitration of pyridine 1-oxides has been carried out in higher concentrations of sulphuric acid. Substituted pyridine 1-oxides of still lower basicity, required to investigate the H_A acidity scale in acidities greater than 83% sulphuric acid, were not available. Although pyridine 1-oxide $(pK_a \ 0.79)$ is a much weaker base than pyridine $(pK_a \ 0.79)$ 5.23), substituents have a considerably greater effect on basicity in the latter series $(\rho = -5.8)^{12}$ than in the former $(\rho = -1.9)$.¹³ Attemps failed to convert pentafluoro- and pentachloro-pyridine (kindly donated by Dr. C. Clayton of Imperial Chemical Industries Limited, Mond Division, Runcorn) into their N-oxides. (The protonation behaviour of pentachloropyridine

¹¹ J. F. Bunnett and F. P. Olsen, Canad. J. Chem., 1966, 44, 1899.

1-oxide, a sample of which was generously denoted by Dr. H. Suschitzky, is now being studied.) We therefore extended the H_{Λ} -scale by studying phenazine 5,10-dioxide. The ionisation ratios for the second protonation of this compound are in Table 2. Figure 2 shows the indicator-ratio plots compared with those of the four most weakly basic amides previously studied.¹⁰ The second pK_a of phenazine 5,10-dioxide (-5.12) was calculated by use of the usual overlap method, and $H_{\rm A}$ values thence established for the 80–93% sulphuric acid range (Table 3).

The H--scale ¹⁰ involves the assumption that His coincident with H_0 for acidities up to $16\cdot1\%$ H₂SO₄, while Bunnett and Olsen¹¹ further point out that the use of pyrrole-2-carboxamide as an indicator may have introduced further errors. We have now shown that pyridine 1-oxides follow the H-scale. The more strongly basic compounds (I, III, and IV; cg. Table 1) thus enable a pyridine 1-oxide acidity function to be thermodynamically anchored (Table 4, column 3).

TABLE 4

The amide and pyridine 1-oxide acidity functions

Amides (H_A)	Pyridine 1-oxides
-0.29	-0.53
-0.70	-0.68
-1.00	-0.95
-1.25	-1.22
-1.50	-1.46
-1.74	-1.77
-2.00	-2.04
	$\begin{array}{r} \text{Amides } (H_{\text{A}}) \\ -0.29 \\ -0.70 \\ -1.00 \\ -1.25 \\ -1.50 \\ -1.74 \\ -2.00 \end{array}$

This procedure demonstrates that the original Hscale is a valid description of the protonation behaviour of both amides and pyridine 1-xodes (cf. Table 4, columns 2 and 3); Bunnett and Olsen's ¹¹ estimate of it being too negative by 0.3 units is not confirmed.

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12 H. H. Jaffé and H. Lloyd Jones, "Advances in Heterocyclic Chemistry," ed. A. R. Katritzky, Academic Press, New York and London, 1963, vol. 3, p. 209. ¹³ H. H. Jaffé, J. Org. Chem., 1958, **23**, 1790.