Acidity Functions and the Protonation of Weak Bases. Part VII.[1] The Protonation Behaviour of Dimethylaminopyridines and their *N*-Oxides

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The first and second pK_a values for the title compounds and some nitro-substituted derivatives are reported. First protonation occurs in all cases on the ring nitrogen (pyridines) or at the *N*-oxide oxygen (*N*-oxides), and the pK_a values are in line with predictions from the Hammett equation. The second protonation at the NMe_2 group follows the H_0''' acidity function, and thermodynamic second pK_a values calculated using the slope *m* of [BH$^+$]/[B] *vs.* H_0 are also well correlated by the Hammett equation.

In connection with a study [2] of the kinetics of their nitration, we investigated quantitatively the protonation behaviour of the dimethylaminopyridines and their *N*-oxides. The first pK_a was determined by potentiometric titration provided it fell above 2, otherwise by the u.v. method. The u.v. method was used to find H_0 values for half protonation for the second proton addition. Results are given in Table 1, which also includes the slopes *m* of log {[H_2B^+]/[HB^+]} *vs.* H_0 which are used [6] to calculate the thermodynamic second pK_a values. No second pK_a values were obtained for the following compounds for which the second protonation was incomplete in 100% H_2SO_4: 2-dimethylamino-5-nitropyridine and 2-dimethylamino-5-nitropyridine 1-oxide.

TABLE 1

Protonation data for dimethylaminopyridines and their 1-oxides

		Second proton addition					
Substituted pyridine	First pK_a [a]	Temp.	λ (nm) [b]	$H_{0\frac{1}{2}}$ [c]	*m* [d]	*n* pK_a [e] (*m* $H_{0\frac{1}{2}}$)	*r* [f]
2-N$(CH_3)_2$	6·94 ± 0·04	18	319	−8·59	1·19	−10·21	0·997
3-N$(CH_3)_2$	6·37 ± 0·04	22	270	−1·96	1·07	−2·11	0·998
			357	−1·94	1·07	−2·07	0·997
4-N$(CH_3)_2$	9·70 [g]	23	284	−6·91	1·34	−9·28	1·000
2-N$(CH_3)_2$, 3-NO_2 [h]	2·5 ± 0·3	19	300	−10·3	1·3	−13·5	0·994
			375	−10·4	1·27	−13·2	0·994
2-N$(CH_3)_2$, 5-NO_2	2·58 ± 0·04 [i]						
3-N$(CH_3)_2$, 2-NO_2	2·7 ± 0·3	25	273	−6·91	0·88	−6·09	0·998
4-N$(CH_3)_2$, 3-NO_2 [h]	5·23 ± 0·02	30	280	−8·8	1·05	−9·3	0·999
			295	−8·7	1·25	−10·9	1·000
2-N$(CH_3)_2$, 1-oxide	2·27 [j]	18	325	−4·90	0·89	−4·36	0·997
3-N$(CH_3)_2$, 1-oxide	1·92 ± 0·04	18	272	−2·72	1·05	−2·85	1·000
			356	−2·64	1·06	−2·80	1·000
4-N$(CH_3)_2$, 1-oxide	3·88 [j]	18	290	−6·60	1·02	−6·75	0·995
4-N$(CH_3)_2$, 3-NO_2, 1-oxide		18	370	−8·54	1·14	−9·77	0·999
			293	−8·50	1·17	−9·95	0·998

[a] Temperature 25 ± 2°. [b] Wavelength for determination. [c] H_0 Value at 'half-protonation' point. [d] d log *I*/d H_0. [e] For justification see ref. 3. [f] Correlation coefficient for H_0 −log *I* plot. [g] See ref. 4, p. 156. [h] See Experimental section. [i] P. J. Brignell, P. E. Jones, and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1970, 117, give 3·11 for determination in 60% EtOH. [j] See ref. 5.

Site of First Protonation.—Previous ultraviolet work has demonstrated that the site of first protonation is the cyclic nitrogen rather than the amino- (or dimethylamino)-group for 2- and 4-amino- and for 2- and 4-dimethylamino-pyridines [7,8] and that the oxygen of the *N*-oxide function is the site of first protonation for all the corresponding pyridine 1-oxides.[5] For the compounds substituted at the 3-position, the data are less complete: 3-aminopyridine is protonated first at the cyclic nitrogen; [8-10] although 3-dimethylaminopyridine has not previously been investigated, it would be expected to show similar behaviour. Jaffé [11] discussed the structure of the mono-cation (1) of 3-aminopyridine 1-oxide, using the Hammett equation, and concluded that it was an equilibrium mixture of the *O*-protonated (1a) and the *N*-protonated form (1b) in the ratio *ca.* 8 : 1. Similar treatment of the mono-cation (2) of 3-dimethylaminopyridine 1-oxide, using ρ = +3·56 for the protonation of dimethylanilines [12,13] and ρ = +2·09 for the protonation of pyridine 1-oxides, with σ_m = −0·21 for NMe_2 [14] and σ_m = +1·48 for N^+ ($-O^-$).[15] indicates that

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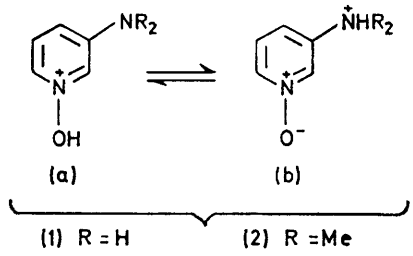
[15] (*a*) F. Cruège, G. Girault, S. Coustal, J. Lascombe, and P. Rumpf, *Bull. Soc., chim. France*, 1970 3889; (*b*) H. H. Jaffé, *J. Amer. Chem. Soc.*, 1954, **76**, 3527.

the *O*-protonated form (2a) should also predominate, in the ratio *ca.* 6 : 1. The first pK_a values have been measured and the site of first protonation of three dimethylaminopyridines discussed by Cruège *et al.*[15a] with results similar to ours.



Our own measurements confirm that the first protonation occurs preferentially at the ring nitrogen atom for all the dimethylaminopyridines and at the oxygen atom for all the dimethylaminopyridine-1-oxides. Table 2 gives the methyl chemical shifts for each species: the shift for first protonation is 0·05—0·32 p.p.m. and that for second protonation is 0·29—0·68 p.p.m.; however, for every compound (with one exception) the shift on second protonation is considerably greater—usually more than double. Protonation at the dimethylamino-group is expected to have the greater effect. The exception is 4-nitro-2-dimethylaminopyridine 1-oxide where the $\Delta\tau$ for second protonation is 0·36 and that for first protonation is 0·32: it is quite possible that the mono-cation of this compound is a mixture of O^- and NMe$_2$-protonated-forms, as the 4-nitro-group is expected to decrease the basicity at the N-oxide oxygen more than it does at the dimethylamino-group.

These conclusions are amply confirmed by the u.v. spectra for the individual species shown in Table 3. The dications have absorption maxima in the 220—270 nm region, as would be expected for nitropyridinium compounds in which conjugation with the dimethylamino-group had been effectively removed. However, the mono-cations absorb strongly above 300 nm: if the first protonation had occurred on the dimethylamino-group, the resulting chromophore should resemble 2-($\lambda_{max.}$ 269·5 and 228·5 nm, log ε 3·69, 3·80 in MeOH)[16] or 3-nitropyridine ($\lambda_{max.}$ 241 nm; log ε 3·90 in MeOH[16]).

TABLE 2

Methyl proton chemical shifts (p.p.m. on τ scale) for dimethylaminopyridines

Posn. of NMe$_2$	Other substits.	Neutral molecule			Mono-cation		Di-cation		$\Delta\tau$	
		Solvent	Std.	τ	N of H_2SO_4 solvent	τ	N of H_2SO_4 solvent	τ	*a*	*b*
2		CCl_4	Me_4Si	7·02	2·2	6·83	33·3	6·38	0·19	0·45
3		D_2O	$(Me_4N^+)_2SO_4^{2-}$	7·27	2·2	6·98	33·3	6·34	0·29	0·64
2	1-O	D_2O	HOD	7·10	2·2	6·72	33·3	6·20	0·38	0·52
3	1-O	D_2O	$(Me_4N^+)_2SO_4^{2-}$	7·13	2·2	6·95	33·3	6·27	0·18	0·68
4	1-O	D_2O	HOD	6·71	2·2	6·66	33·3	6·35	0·05	0·31
2	5-NO_2	$CDCl_3$	Me_4Si	6·70	29·3	6·58	37·4[c]	6·51[c]	0·12	0·07[c]
2	3-NO_2	CCl_4	Me_4Si	6·90	29·3	6·71	37·4	6·08	0·19	0·63
2	4-NO_2 1-O	D_2O	Me_4Si	6·91	2·2	6·59	36·4	6·23	0·32	0·36
2	5-NO_2 1-O	D_2O	HOD	6·60	29·3	6·39	37·4[c]	6·28[c]	0·21	0·11[c]

[a] τ (neutral — τ (mono-cation). [b] τ (mono-cation) — τ (di-cation). [c] Compound is incompletely second-protonated in 37·4N-sulphuric acid.

TABLE 3

U.v. data for substituted dimethylaminopyridines

NMe$_2$	Other subst.	Neutral			Monocation			Dication		
		pH	$\lambda_{max.}$	(log ε)	N of H_2SO_4	$\lambda_{max.}$	(log ε)	N	$\lambda_{max.}$	(log ε)
2	3-NO_2	7·0	235	(4·23)	26·6	213	(4·41)	Oleum	265	(4·34)
			430	(3·81)		291	(4·02)			
						374	(3·83)			
2	5-NO_2	6·8	225	(3·83)	23·5	217	(3·12)	—	—	—
			394	(3·99)		325	(3·20)			
3	2-NO_2	7·0	240	(4·06)	1·0	236	(3·82)	36·7	234 *	(3·40)
			290 *	(3·47)					273	(3·57)
			432	(3·37)						
3	1-O	8·0	246	(4·39)	1·0	227	(4·46)	27·7	225	(5·66)
			350	(4·13)		272	(4·27)			
						350	(4·14)			

* Inflection.

Nevertheless, it is noteworthy that the protonation of the pyridine ring nitrogen causes a hypsochromic shift of the $\lambda_{max.}$ of nitrodimethylaminopyridines, in contrast to the parent dimethylaminopyridines: this can be ascribed to cross-conjugation in the cations.

Acidity Function Behaviour.—Interpretation of the second pK_a values of these molecules is complicated by errors in their estimation due to approximations in

[16] G. Favini, A. Gamba, and I. R. Bellobono, *Spectrochim. Acta*, 1967, **23***A*, 89.

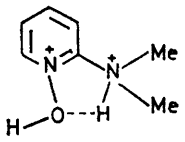
acidity function theory. The total range of slopes of H_0 *vs.* log I for the second protonations is 0·88—1·37 (Table 1). For the ions 3-dimethylamino-2-nitropyridinium and 1-hydroxy-2-dimethylaminopyridinium proximity effects might cause anomalous behaviour. The slopes for the remaining nine compounds lie in the range 1·02—1·37. The equivalent range for protonation of the tertiary amine H_0''' indicators is 1·10—1·40.[17] Despite the strong solvent interaction with positively charged pyridinium nitrogen atom, these substrates therefore in general appear to follow the acidity function demanded by the site of protonation, just as the second protonation of the aminopyridines follows the H_0 acidity function.[18]

The second pK_a values of the 3- and 4-dimethylaminopyridines obtained from the expression mH_0 (half-protonation) [3] afford a method of checking the validity of the interpretation of this expression as an approximation to the thermodynamic pK_a related to the standard state of H_2O, 25°. The ρ value for protonation of substituted dimethylanilines is 3·56,[13] and the pK_a value of dimethylaniline is 5·7; this yields values of 2·02 and 2·25 for σ_m for $\rangle\overset{+}{\mathrm{N}}\mathrm{H}$ and $\rangle\overset{+}{\mathrm{N}}\text{–}\mathrm{OH}$ respectively, and values of 4·06 and 3·49 for σ_p for $\rangle\overset{+}{\mathrm{N}}\mathrm{H}$ and $\rangle\overset{+}{\mathrm{N}}\text{–}\mathrm{OH}$ respectively. These may be compared with the corresponding values of 2·1, 2·3, 4·0, and 3·9 from dissociation of the second conjugate acids of the aminopyridines and their 1-oxides.[19] The good agreement emphasises the authenticity of the acidity function approach.

In contrast to the corresponding first pK_a values, the second pK_a values of the dimethylaminopyridines are lower than those for the corresponding aminopyridines [18] by 1·81, 0·88 and 1·63 pK units in the 2-, 3-, and 4-series, respectively. Kamlet and his co-workers [20] have observed similar behaviour for nitroanilines and their dimethyl derivatives and account for this trend by sterically sensitive solvation effects, which for the more weakly basic amines, outweigh inductive effects.

The effect of a nitro-group on the first pK_a values is in the range 3·7—4·5 units, which is in line with the usual effects of a nitro-substituent on pyridine pK_a values.[4] However, the incremental effect of a nitro-group on the second pK_a values (for protonation of the dimethylamino-group) is more variable, and is as low as 0·5 for 3-nitro-4-dimethylaminopyridine.

The increase in the basicity of the 1-hydroxy-2-dimethylaminopyridinium cation compared with the 2-dimethylaminopyridinium cation is remarkable. A possible explanation is stabilisation of the diprotonated cation in the former case by hydrogen-bonding.



(3)

EXPERIMENTAL

The dimethylaminopyridines and their *N*-oxides were prepared as described in ref. 2. The pK_a values for 2-dimethylamino-3-nitro- and 3-dimethylamino-2-nitro-pyridine showed large spreads (0·6 units), apparently not due to impurity, since the reversed variation would then have been expected,[21] nor to covalent hydration as both forward and backward titrations gave similar pH readings.[22] The preparation of aqueous sulphuric acid and measurements of the [cation]/[base] (I) ratio were as described previously.[6] Medium effects on the u.v. spectra were generally small; the H_0 values were those of Johnson, Katritzky, and Shapiro.[23] Table 4 gives typical results, for 4-dimethylamino-3-nitropyridine 1-oxide.

TABLE 4

Ionisation data for 4-dimethylamino-3-nitropyridine 1-oxide

$-H_0$	OD (293 nm)	OD (370 nm)	$\log_{10} I$ (293 nm)	$\log_{10} I$ (370 nm)
3·31	1·279	0·250		
4·32	1·261	0·239		
5·77	1·237	0·242		
6·56	1·139	0·223		
6·56	1·236	0·233		
7·42	1·139	0·216		
7·82	1·024	0·189	−0·70	−0·66
8·18	0·774	0·155	−0·21	−0·31
8·18	0·767	0·152	−0·19	−0·29
8·57	0·481	0·091	+0·25	+0·21
8·97	0·261	0·048	+0·68	+0·64
10·20	0·082	0·008		
12·0	0·035	0·003		

[1/1944 *Received*, 22*nd October*, 1971]

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