838. *Protonation Equilibria in Amides.*

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The protonation equilibria of a number of primary, secondary, and tertiary amides in aqueous sulphuric acid solutions have been investigated by a spectrophotometric method. For each amide the logarithm of the ionisation ratio, $\log c_{\mathrm{AmH}^+}/c_{\mathrm{Am}}$, increases with acidity less rapidly than the Hammett acidity function, H_0. This behaviour is discussed in terms of the hydration of the conjugate acids. An explanation is suggested for the lack of conjugation between the protonated amide group and the aromatic nucleus in substituted benzamides.

It is now well known that the unit-slope linear correlation between the logarithm of the ionisation ratio of a base B, $\log c_{\mathrm{BH}^+}/c_{\mathrm{B}}$, and the Hammett acidity function, H_0, is not always observed.[1-5] Recent work suggests that the discrepancies are at least partly due to the different hydration requirements of the conjugate acids of the various bases. Increasing acid concentration is accompanied by decreasing availability of water. It follows that those bases whose conjugate acids require the greatest hydration are those for which the ionisation ratio increases least rapidly with acidity.

Bases such as azulenes,[1] trialkoxybenzenes,[2,6] and olefins,[7] whose conjugate acids have no protons bound to positively charged oxygen or nitrogen atoms and are therefore not strongly hydrogen-bonded to water molecules, show the most rapid increase of the ionisation ratio with acidity. A new acidity function, H_R', was recently developed for these compounds.[2] Perceptible differences in behaviour between the Hammett indicators themselves have been observed, and attributed to differences in the number of hydrogen-bonding protons on the conjugate acids.[3]

Propionamide[4] and substituted benzamides[5] have ionisation ratios which increase more slowly with acid concentration than those of the Hammett indicator bases. In this paper, similar behaviour in a group of nine primary, secondary, and tertiary amides is reported and discussed.

Experimental

The amides were prepared from the acids by standard methods. M. p.s agreed with published values.

4-Nitro-1-naphthylamine[8] was obtained from 1-nitronaphthalene and converted into the acid[9] through the nitrile.[10] Reaction of the acid chloride with aqueous methylamine gave N-*methyl*-4-*nitro*-1-*naphthamide*, m. p. 179° (from ethanol) (Found: C, 62·2; H, 4·5; N, 11·7. $C_{12}H_{10}N_2O_3$ requires C, 62·6; H, 4·4; N, 12·2%).

The aqueous solutions of " AnalaR " sulphuric acid were standardised by titration against 0·1N-sodium hydroxide. The corresponding H_0 and $\log a_{\mathrm{H_2O}}$ values were read off large scale plots of the published data.[11]

The solutions of the amides were prepared by making up 0·1 ml. of a methanol solution of the amide to 20 ml. with the appropriate acid.

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[1] Long and Schulze, *J. Amer. Chem. Soc.*, 1961, **83**, 3340.

[2] Kresge and Chiang, *Proc. Chem. Soc.*, 1961, 81; Kresge, Barry, Charles, and Chiang, *J. Amer. Chem. Soc.*, 1962, **84**, 4344.

[3] Taft, *J. Amer. Chem. Soc.*, 1960, **82**, 2965.

[4] Edward and Wang, *Canad. J. Chem.*, 1952, **40**, 966.

[5] Katritzky, Waring, and Yates, *Tetrahedron*, 1963, **19**, 465; Moodie, Wale, and Whaite, *J.*, 1963, 4273.

[6] Schubert and Quacchia, *J. Amer. Chem. Soc.*, 1962, **84**, 3778.

[7] Deno, Groves, Jaruzelski, and Lugasch, *J. Amer. Chem. Soc.*, 1960, **82**, 4719.

[8] *Org. Synth.*, 1948, **28**, 80.

[9] Friedlaender and Weisberg, *Ber.*, 1895, **28**, 1838.

[10] Goldstein, Mohr, and Blezinger, *Helv. Chim. Acta*, 1935, **18**, 813.

[11] Paul and Long, *Chem. Rev.*, 1957, **57**, 1; Shankman and Gordon, *J. Amer. Chem. Soc.*, 1939, **61**, 2370.

Spectra were measured in stoppered 4 cm. silica cells with a Unicam S.P. 500 spectrophotometer, and the cell compartment was maintained at 25° ± 0·1°. Optical densities were measured at 2 mμ intervals; the complete spectrum was recorded within 30 min. of preparation of the solution, hydrolysis in this time being negligible.

RESULTS AND DISCUSSION

Spectra of the Amides, and Determination of the Ionisation Ratios.*—The complete spectrum of each amide was obtained at various acidities. A typical set of spectra, *viz.*, those for *N*-methyl-1-naphthamide, is shown in Fig. 1. The absorption maxima of the protonated and unprotonated forms of each amide are recorded in Table 1. In most cases the spectrum of the protonated amide shifted to longer wavelengths at higher acidities. Before the ionisation ratio could be obtained from eqn. (1) it was therefore usually necessary, as described by Flexser *et al.*,[12] to move the spectrum of the protonated amide up to 4 mμ toward shorter wavelengths; the curve then passed through a moderately well-defined isosbestic point. These shifts, and the wavelengths used for the subsequent calculation of the ionisation ratio, are given in Table 1. The greatest accuracy is obtained

$$c_{\mathrm{AmH}^+}/c_{\mathrm{Am}} = I = (\varepsilon_{\mathrm{Am}} - \varepsilon)/(\varepsilon - \varepsilon_{\mathrm{AmH}^+}). \qquad (1)$$

when I is near to unity. Only results for which $-1{\cdot}2 < \log I < 1{\cdot}2$ are included in this report.

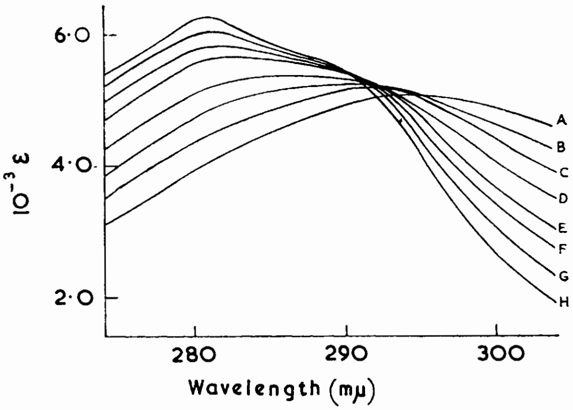

FIG. 1. The spectrum of *N*-methyl-1-naphthamide at various acidities (% H_2SO_4).

A 62·7, B 52·5, C 45·8, D 39·4, E 33·7, F 26·5, G 20·1, H 0·5%.

TABLE 1.

Spectra of the amides.

	Free base *		Conj. acid †		λ (mμ) used for detmn. of I	Shift (mμ)
	$\lambda_{\max.}$ (mμ)	$10^{-3}\varepsilon$	$\lambda_{\max.}$ (mμ)	$10^{-3}\varepsilon$		
1-Naphthamide	278	6·15	310	4·85	310	0
N-Methyl-1-naphthamide	278	6·56	295	5·09	278	2
NN-Dimethyl-1-naphthamide	279	6·70	288	4·99	304	2
2-Naphthamide	280	6·40	299	6·82	299	0
N-Methyl-2-naphthamide	279	6·06	287	8·32	288	4
NN-Dimethyl-2-naphthamide	278	5·50	283	6·50	286	1
p-Phenylbenzamide	270	23·5	299	21·2	299	0
N-Methyl-*p*-phenylbenzamide	268	23·0	290	20·9	296	2
NN-Dimethyl-*p*-phenylbenzamide	263	21·2	279	19·1	279	0
4-Nitro-1-naphthamide	337	4·35	339 ‡	4·36 ‡		
N-Methyl-4-nitro-1-naphthamide	337	4·42	337	4·45		

* In methanol. † In 65% H_2SO_4. ‡ In 80% H_2SO_4.

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* The choice of amides was dictated by other studies of the acidity of sulphuric–acetic acid mixtures.

[12] Flexser, Hammett, and Dingwall, *J. Amer. Chem. Soc.*, 1935, **57**, 2103.

The Basicity of the Amides.—The pK's of weak bases are usually measured from eqn. (2).

$$\mathrm{p}K = H_0 + \log I. \qquad (2)$$

For the amides studied, $H_0 + \log I$ is not a constant. No pK can therefore be derived by the use of eqn. (2). The most convenient measure of basicity is the H_0 value for half-protonation. These values (Table 2) were derived in two ways. Method (A) is that suggested by Davies and Geissmann.[13] The difference in extinction coefficient at two selected wavelengths was plotted against H_0. The point of inflection of the sigmoid curve so obtained gave the H_0 value for half-protonation. This method, which involves no arbitrary curve-shifting and is reasonably insensitive to the wavelengths chosen for measurement (see Table 3), is considered the more accurate. In method (B), the value derived by the conventional least-squares calculation of the empirical parameters a and b in eqn. (3) was used.[2] The value of a/b gives the H_0 value for half-protonation. Fair

$$\log I = a - bH_0 \qquad (3)$$

agreement is obtained between the two methods.

TABLE 2.

The H_0 values for half-protonation, and the parameters in eqns. (3) and (8).

	No. of pts.	Parameters in eqn. (3)			H_0 for $I = 1$ Method †		
		a	b	σ *	(A)	(B)	m ‡
1-Naphthamide	9	−1·61	0·638	0·984	−2·73	−2·52	5·2
2-Naphthamide	9	−1·58	0·600	0·988	−2·50	−2·63	5·2
p-Phenylbenzamide	7	−1·47	0·645	0·990	−2·15	−2·28	4·9
N-Methyl-1-naphthamide	7	−1·59	0·749	0·985	−2·20	−2·13	4·2
N-Methyl-2-naphthamide	11	−1·58	0·741	0·987	−2·11	−2·14	4·2
N-Methyl-*p*-phenylbenzamide	11	−1·57	0·715	0·983	−2·15	−2·19	4·2
NN-Dimethyl-1-naphthamide	9	−1·20	0·634	0·997	−1·93	−1·89	
NN-Dimethyl-2-naphthamide	10	−0·98	0·578	0·999	−1·67	−1·70	
NN-Dimethyl-*p*-phenylbenzamide					−1·30		

* Least-squares correlation coefficient. † See text. ‡ Parameter in eqn. (8).

TABLE 3.

H_0 values for half-protonation of *NN*-dimethyl-1-naphthamide, derived by method (A), using different wavelengths.

Wavelengths used (mμ)	272, 306	278, 300	280, 302
H_0 for half-protonation	−1·95	−1·90	−1·93

An Explanation for the Lack of Conjugation Between the Protonated Amide Portion and the Aromatic Nucleus.—The basicities of substituted benzamides have been shown to give better correlation with σ than with σ^+ substituent constants.[14] The data above for *p*-phenylbenzamide and 2-naphthamide support this conclusion (σ and σ^+ constants were obtained from refs. 15 and 16). The correlation with σ constants indicates a lack of conjugation between the protonated amide portion and the aryl group.[14] Recent work leaves little doubt that benzamides,[17] like benzoic acids,[18] are protonated predominantly on the carbonyl-oxygen atom. The lack of conjugation is not therefore due to N-protonation. We suggest that the presence of a full positive charge in the protonated amide portion will increase stabilisation due to hydrogen-bond formation to solvent water molecules, and the extra

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[13] Davis and Geissmann, *J. Amer. Chem. Soc.*, 1954, **76**, 3507.

[14] Edward, Chang, Yates, and Stewart, *Canad. J. Chem.*, 1960, **38**, 1518.

[15] Jaffe, *Chem. Rev.*, 1953, **53**, 191.

[16] Brown and Inukai, *J. Amer. Chem. Soc.*, 1961, **83**, 4825.

[17] Gillespie and Birchall, *Canad. J. Chem.*, 1963, **41**, 148; Jones and Katritzky, *Chem. and Ind.*, 1961, 722.

[18] Stewart and Yates, *J. Amer. Chem. Soc.*, 1960, **82**, 4059.

stability gained in this way is greater than would be obtained by conjugation with the aromatic nucleus and consequent delocalisation of the positive charge. The opposite behaviour is observed in benzoic acids,[18] which are measurably protonated only at higher acid concentrations. Here, the low water activity precludes extensive hydration, and so conjugation with the aromatic ring is favoured.

This explanation requires that protonated amides are extensively hydrated in the acid solutions in which their basicities are measured. Evidence for this is presented below. Experience with protonated acids, indicates that conjugation in protonated benzamides should be restored at higher acidities, where extensive hydration can no longer occur. The change in the spectrum of protonated benzamide at high acidities[19] may be explained in this way.

Hydration of Protonated Amides.—Each of the amides studied gave straight-line plots of log I against H_0. The values of a and b (eqn. 3) and least-squares correlation coefficients are given in Table 2. In all cases the slope, b, is significantly less than unity. This behaviour, which is common to all amides so far studied,[4,5] indicates that the conjugate acids require more extensive hydration than the protonated Hammett indicators.

The treatment below is similar to that used by Edward and Wang,[4] but here H_R' is used as the reference acidity function,[2] since it is derived from indicator equilibria where hydration is presumably unimportant. The neutral amide molecule is also assumed not to be hydrated; this is believed to be justified in solutions more acid than 35% sulphuric acid (1 mole of H_2SO_4 to 10 moles of water) because here the species must compete for the available water with the $H_9O_4^+$ ion, and the latter is capable of forming relatively stable hydrogen bonds to a further six water molecules.[20]

For a triarylmethanol, ROH,

$$\mathrm{R}^+ + (n+1)\mathrm{H_2O} = \mathrm{ROH} + \mathrm{H}^+(\mathrm{H_2O})_n;$$

$$K_{\mathrm{R}^+} = a_{\mathrm{H}^+}a_{\mathrm{H_2O}}^{-n-1}a_{\mathrm{ROH}}/a_{\mathrm{R}^+}; \qquad (4)$$

$$h_{\mathrm{R}}' = a_{\mathrm{H}^+}a_{\mathrm{H_2O}}^{-n}\,\gamma_{\mathrm{ROH}}/\gamma_{\mathrm{R}^+} = K_{\mathrm{R}^+}a_{\mathrm{H_2O}}c_{\mathrm{R}^+}/c_{\mathrm{ROH}}. \qquad (5)$$

For an amide base, Am,

$$\mathrm{Am}^+(\mathrm{H_2O})_m + (n-m)\mathrm{H_2O} = \mathrm{Am} + \mathrm{H}^+(\mathrm{H_2O})_n;$$

$$K_{\mathrm{AmH}^+} = a_{\mathrm{H}^+}a_{\mathrm{H_2O}}^{m-n}a_{\mathrm{Am}}/a_{\mathrm{AmH}^+}. \qquad (6)$$

Activities, activity coefficients, and concentrations refer to hydrated species. If we write I for $c_{\mathrm{AmH}^+}/c_{\mathrm{Am}}$ and H_{R}' for $-\log h_{\mathrm{R}}'$, eqns. (5) and (6) lead to eqn. (7).

$$H_{\mathrm{R}}' + \log I = \mathrm{p}K_{\mathrm{AmH}^+} + \log(\gamma_{\mathrm{R}^+}\gamma_{\mathrm{Am}})/(\gamma_{\mathrm{ROH}}\gamma_{\mathrm{AmH}^+}) + m\log a_{\mathrm{H_2O}}. \qquad (7)$$

If m is constant, the assumption that the activity-coefficient term in eqn. (7) is invariant with acidity leads to eqn. (8). However, if m changes, then so does K_{AmH^+} (eqn. 6) and

$$\mathrm{d}(\log I + H_{\mathrm{R}}')/d(\log a_{\mathrm{H_2O}}) = m. \qquad (8)$$

eqn. (8) no longer holds. Fig. 2 shows graphs of $(\log I + H_{\mathrm{R}}')$ against $\log a_{\mathrm{H_2O}}$. Most of the curves are linear above 40% sulphuric acid ($-\log a_{\mathrm{H_2O}} > 0{\cdot}25$), and where this occurs values of m have been derived and are recorded in Table 2. The values suggest hydration numbers for the protonated primary and secondary amides, in the region 40—55% sulphuric acid, of 5 and 4, respectively. In the same region of acidity, hydration numbers for the

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[19] Edward and Meacock, *J.*, 1957, 2000.

[20] Grahn, *Arkiv Fysik*, 1962, **21**, 13.

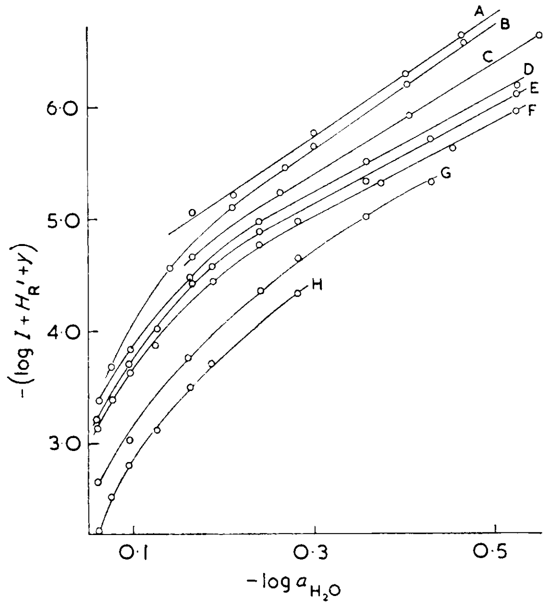
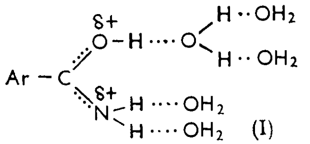


FIG. 2. Graphs of ($\log I + H_R'$) against $-\log a_{H_2O}$; the constant y is used to adjust the ordinate.

A 1-Naphthamide ($y = 0{\cdot}9$), B 2-naphthamide ($y = 0{\cdot}7$), C *p*-phenylbenzamide ($y = 0{\cdot}7$), D *N*-methyl-1-naphthamide ($y = 0{\cdot}7$), E *N*-methyl-2-naphthamide ($y = 0{\cdot}6$), F *N*-methyl-*p*-phenylbenzamide ($y = 0{\cdot}4$), G *NN*-dimethyl-1-naphthamide ($y = 0{\cdot}2$), H *NN*-dimethyl-2-naphthamide ($y = 0$).

conjugate acids of primary and secondary anilines of 3 and 2, respectively (one water molecule for each hydrogen-bonding proton), have been derived by a similar method.[3]



(I)

This difference between protonated anilines and protonated amides provides further evidence for *O*-protonation in amides, since an *N*-protonated amide and an anilinium ion would both form hydrogen bonds through the NH_3^+ group. The most reasonable structure for the hydrated primary amide conjugate acid at these acidities is (I). The protonated secondary amide has one less hydrogen-bonding proton attached to nitrogen and therefore one less water molecule of hydration.

The greater basicity of the di-methylamides precluded accurate measurements of the ionisation ratio at high acidities. The plot (Fig. 2) was non-linear, and under these conditions, as explained above, eqn. (8) no longer holds and values of *m* cannot be derived. Attempts to overcome this problem by the study of 4-nitro-1-naphthamide and its methylated derivatives failed because of the lack of spectral change of these compounds on protonation (Table 1). *p*-Nitroacetanilide and 4-nitrofuramide were also examined but were too unstable at the acid strengths used.

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