J. Chem. Soc. (B), 1970

# Protonation Equilibria of Amides and Related Compounds. Part III.<sup>1</sup> σ and σ<sup>+</sup> Correlations in some N-Substituted Benzamides

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The protonation equilibria in aqueous sulphuric acid of eight ring-substituted N-(2,2,2-trifluoroethyl)benzamides and eight similarly substituted N-ethylbenzamides, have been studied. The basicities of the former set are correlated best by  $\sigma^+$ , and of the latter by  $\sigma$ , substituent constants. The amides studied follow the acidity function,  $H_A$ , reasonably well, so that no separate acidity function for secondary amides is required.

THERE is evidence that amides in acid solution are protonated predominantly on the carbonyl oxygen.<sup>2</sup>



With benzamides, the resulting cation is a substituted carbonium ion in which each of the groups attached to the central carbon atom can confer stability by mesomeric interaction. The amino- or substituted aminogroup is the most effective from this point of view, and therefore can be expected to bear a good deal of the positive charge. The extent to which delocalisation of the charge in the aromatic ring is important in the stabilisation of the cation can be gauged from the effect of ring substituents; the fact that the  $pK_{\rm s}$ values of primary benzamidium cations are correlated better by  $\sigma$  than by  $\sigma^+$  substituent constants <sup>3</sup> suggests that this sort of interaction is unimportant. Three explanations have been suggested for this. (a) The extra stability to be gained by hydrogen bonding of the oxygen- and nitrogen-bound protons of the amidium ion may tend to keep the positive charge on the protonated amido-group.<sup>4</sup> This explanation is probably not satisfactory, as it has now been shown that the stability of boron trifluoride complexes of substituted benzamides <sup>5</sup> are also better correlated by  $\sigma$  constants. (b) There may be an enforced lack of co-planarity between the amido-grouping and the aromatic ring.<sup>3b</sup> (c) The supremacy of the amino-group in stabilising the protonated amide may dominate the distribution of  $\pi$ -electrons in the cation.

The effect of electron-withdrawing N-substituents should be to reduce the conjugation of the amino-group with the  $\pi$ -electron system and this could lead to increased mesomeric interaction between the central carbon atom and the aromatic ring. The behaviour with regard to protonation would then approach that of substituted benzoic acids and substituted acetophenones, where  $\sigma^+$  correlations are known to prevail.<sup>6</sup> However, if lack of co-planarity, as invoked in (b) above, is the correct explanation for the observed  $\sigma$  correlation in

<sup>4</sup> R. B. Homer and R. B. Moodie, J. Chem. Soc., 1963, 4377.

primary benzamides, then the steric factors which cause this will be more pronounced in secondary benzamides, and a  $\sigma$  correlation should remain.

We have therefore studied the protonation equilibria in aqueous sulphuric acid of eight ring-substituted N-(2,2,2-trifluoroethyl) benzamides, and for comparison a similar set of N-ethylbenzamides.

A further objective was to establish whether or not a separate acidity function is necessary for secondary amides, since previous results <sup>1,4</sup> have shown that for some secondary amides the logarithm of the ionisation ratio increases with acidity rather more rapidly than  $(-H_{\mathbb{A}}).$ 

### RESULTS

The Determination of Ionisation Ratios .--- These studies for carbonyl compounds are handicapped by the uncertainties which arise from the solvent sensitivity of the u.v. spectra 1,3,4,7 and as expected the spectra of the present compounds showed no well-defined isosbestic point. Plots of extinction coefficient at a particular wavelength against  $H_{\rm A}$  were however sigmoid, which permitted estimation by several methods. Of these we found a combination of the methods of Davis and Geissman<sup>8</sup> and of Katritzky and his co-workers 9 most satisfactory. In this method, which we will call the DGK method, the difference in extinction coefficients at two wavelengths, chosen to be the wavelengths of maximum absorption of the free base and conjugate acid respectively, were plotted against  $H_{A}$ . The upper and lower portions of the sigmoid curve so generated were approximately straight lines, and usually inclined at a slight angle to the  $H_A$  axis. These lines were extrapolated to provide values of the difference in extinction coefficients at intermediate acidities as described by Johnson, Katritzky, and their co-workers.9 We also used the latter method, and the method described by Stewart and Granger,<sup>10</sup> with data for one wavelength only. The results were similar by all three methods but the DGK method gave the smoothest sigmoid curves, and it seems likely that the partial cancellation of errors due to solution and cell preparation which is achieved in the DGK method more than offset the extra errors arising from the need for more absorbance measurements.

<sup>5</sup> B. M. J. Ellul and R. B. Moodie, J. Chem. Soc. (B), 1967, 253.

<sup>6</sup> R. Stewart and K. Yates, J. Amer. Chem. Soc., 1958, **80**, 6355; R. Stewart and K. Yates, *ibid.*, 1960, **82**, 4059. <sup>7</sup> C. C. Greig and C. D. Johnson, J. Amer. Chem. Soc., 1968,

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- and A. M. White, Tetrahedron, 1965, 21, 1055.
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<sup>&</sup>lt;sup>1</sup> Part II, V. C. Armstrong and R. B. Moodie, J. Chem. Soc.

 <sup>(</sup>B), 1968, 275.
<sup>2</sup> R. J. Gillespie and T. Birchall, Canad. J. Chem., 1963, 41, 148, 2642; A. R. Katritzky and R. A. Y. Jones, Chem. and Ind., 1961, 722.

<sup>&</sup>lt;sup>3</sup> (a) K. Yates and J. B. Stevens, *Canad. J. Chem.*, 1965, **43**, 529; (b) J. T. Edward, H. S. Chang, K. Yates, and R. Stewart, *Canad. J. Chem.*, 1960, **38**, 1518.

The ionisation ratios so obtained were fitted by the weighted least-squares method previously described  $^{1}$  to equation (2).

$$\log I = cH_{\rm A} + d \tag{2}$$

The parameters c, d, and -d/c are reported in Table 1. The values of -d/c represent  $H_{\rm A}$  values for half-protonation, and in so far as  $H_{\rm A}$  is the appropriate acidity function, and within the accuracy with which this acidity function is known,<sup>11</sup> they represent thermodynamic  $pK_{\rm a}$  values for the amidium ions. Also reported in Table 1 are values of derivatives.<sup>13</sup> We have adopted the following simple approach. Only  $\sigma$  and  $\sigma^+$  constants are considered,<sup>14</sup> and we judge which are the most appropriate by two criteria: (a) by consideration of which set of substituent constants give the higher correlation coefficient and (b) by comparison of each of the two  $\rho$ -values with the  $\rho$  value obtained with data for *meta*-substituted compounds only, the closer comparison indicating the more appropriate substituent constants.

As measures of the substituent effect we have used

TABLE 1

<b>D</b> ( ) *	
Protonation	equilibria

Substit	tuents •	Parameters in equation (2) $\log I$ in							log I in
x	Z	$\lambda_1 b/nm$	λ₂°/nm	c	$\alpha_c^d$	-d	$\alpha_{\log I}^{e}$	-d/c	53% H <sub>2</sub> SO4
н	CH.CH.	230	246	0.95	0.03	1.83	0.04	-1.92	0.76
m-Me	CH, CH,	225	252	0.90	0.04	1.70	0.06	-1.88	0.76
p-Me	CH,CH,	230	260	0.90	0.03	1.59	0.05	-1.77	0.87
m-Cl	CH,CH,	228	246	0.91	0.03	2.08	0.05	-2.28	0.41
m-Br	CH, CH,	236	249	0.99	0.03	2.37	0.04	-2.40	0.33
⊅-C1	CH, CH,	240	260	0.92	0.04	$2 \cdot 02$	0.07	-2.21	0.50
m-NO <sub>2</sub>	$CH_{2}CH_{3}$	215	231	0.79	0.01	2.01	0.02	-2.54	0.14
p-OMe	$CH_{2}CH_{3}$	255	275	1.01	0.02	1.62	0.03	-1.60	1.13
н	CH <sub>2</sub> CF <sub>2</sub>	233	253	0.96	0.05	3.20	0.07	-3.33	-0.58
m-Me	$CH_{\bullet}CF_{\bullet}$	230	258	0.88	0.04	2.83	0.08	-3.20	-0.43
⊅-Me	CH CF	240	268	1.05	0.05	3.12	0.06	-3.00	-0.28
m-Cl	$CH_{2}CF_{3}$	233	253	0.95	0.05	3.45	0.04	-3.62	-0.86
m-Br	CH, CF,	236	254	1.11	0.04	4.04	0.02	-3.64	-1.01
p-Cl	CH, CF,	<b>240</b>	266	0.98	0.03	3.32	0.05	-3.41	-0.67
m-NO <sub>2</sub>	$CH_{3}CF_{3}$	218	233	1.06	0.03	4.06	0.03	3.83	-1.16
p-OMe	$CH_2CF_3$	255	285	1.17	0.02	3.16	0.03	-2.70	+0.04

<sup>a</sup> See equation (1). <sup>b</sup> Wavelength of maximum absorption of the free base in water. <sup>c</sup> Wavelength of maximum absorption of the conjugate acid in 88-93% H<sub>2</sub>SO<sub>4</sub>. <sup>d</sup> Standard error in the slope parameter. <sup>e</sup> Standard error from the linear regression line in the log *I* direction.

log I at one common intermediate acidity  $(53.2\% H_2SO_4, H_A = -2.74)$  which are a measure of the negative logarithm of the dissociation constant of the amidium ion in this particular medium. These values were obtained by interpolation or short extrapolation using equation (2) and the parameters in Table 1.

## DISCUSSION

Secondary Amides and the  $H_A$  acidity Function.—The slope parameters, [equation (2) and Table 1], are mainly close to unity, and the range of acid concentrations covered is 16 to 78%. It is clear that there would be no justification for a separate acidity function for secondary amides and that no simple treatment of acidity function behaviour in terms of the hydrogenbonding propensity of the conjugate acid and the activity of water, as once suggested by one of us,<sup>1</sup> will be satisfactory, a conclusion which is supported by other recent work.<sup>12</sup> The secondary amides studied here follow  $H_A$  reasonably well.

The Effects of Ring Substituents on the Basicity of the Amides.—There are many ways of interpreting substituent effects in meta- and para-substituted benzene both values of -d/c (the nearest one can get to a thermodynamic  $pK_a$  value) and values of  $-\log I$  in a chosen solution of intermediate acidity (Table 1). The latter avoids uncertainties concerning the validity and appropriateness of the  $H_A$  acidity function, but in some cases depends strongly on the rather imprecise slope parameters c. The  $\rho$  values and the corresponding correlation coefficients are given in Table 2.

#### TABLE 2

## Correlations of substituent effects

#### ρ-Values (correlation coefficients in brackets)

	•		,				
	By use of $\sigma$ constants All substituents	By use of $\sigma$ constants <i>m</i> -Substituents only	By use of $\sigma^+$ constants All substituents				
N-(2,2,2-Trifluoroethyl)benzamides							
-d/c	-1.06(0.954)	-0.79(0.987)	-0.80(0.995)				
$\log I$		— 0·92(0·976)	— 0·85(0·989)				
N-Ethylbe	nzamides						
- <i>d</i> /c	-0.98(0.985)	-0.90(0.981)	-0.69(0.961)				
$\log I$	0·95(0·980)	0·85(0·990)	— 0·69(0·979)				

The N-(2,2,2-trifluoroethyl)benzamides show a better correlation with  $\sigma^+$  substituent constants, whichever

<sup>13</sup> P. R. Wells, 'Linear free energy relationships,' Academic Press, London, 1968.

<sup>14</sup>  $\sigma$  Values from D. H. McDaniel and H. C. Brown, J. Org. Chem., 1958, 23, 420.  $\sigma^+$  values from H. C. Brown and Y. Okamato, J. Amer. Chem. Soc., 1958, 80, 4979.

<sup>&</sup>lt;sup>11</sup> K. Yates, J. B. Stevens, and A. R. Katritzky, *Canad. J. Chem.*, 1964, **42**, 1957; J. F. Bunnett and F. P. Olsen, *ibid.*, 1966, **44**, 1899.

<sup>&</sup>lt;sup>12</sup> V. C. Armstrong, D. W. Farlow, and R. B. Moodie, Chem. Comm., 1968, 1362; E. M. Arnett and J. J. Burke, J. Amer. Chem. Soc., 1966, **88**, 2340.

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criterion is used. The N-ethylbenzamides on the other hand, like primary benzamides, show a somewhat better correlation with  $\sigma$  constants. In view of the uncertainties surrounding the determination of ionisation ratios of amides it is important to make sure that these conclusions are not an artifact of the chosen method. We therefore made the same comparison with ionisation ratios obtained by other methods previously mentioned. With the N-(2,2,2-trifluoroethyl)benzamides the same criteria give again  $\sigma^{\scriptscriptstyle +}$  as the better substituent constants for correlation, whilst with the *N*-ethylbenzamides, the position was not quite so clear cut, the behaviour being intermediate between a  $\sigma$  and a  $\sigma^+$  correlation. The correlation coefficients were lower than when the DGK method was used. Intermediate behaviour is, in any case, not unexpected; what is significant is that a  $\sigma^+$  correlation is observed whatever the method with the N-(2,2,2-trifluoroethyl)benzamides. This shows that possible lack of coplanarity between the amido-group and the aromatic ring<sup>3</sup> cannot be the correct explanation of the apparent lack of conjugative interaction between +M parasubstituents and the reaction centre in substituted benzamides.

The protonation equilibria of N-substituted benzamides obviously offer a method of studying in a systematic way the borderline between  $\sigma$  and  $\sigma^+$  correlations, and possibly of the validity of such treatments as that of Yukawa and Tsuno.<sup>15</sup> However, the precision of measurement of  $pK_a$  values in moderately concentrated aqueous acid is not such as to make a study of this type worthwhile at present. The protonation of N-substituted benzimidate esters, which can be studied under dilute aqueous conditions, offers more promise from this point of view.

## EXPERIMENTAL

Amides.---These, prepared by the Schotten-Baumann method from the appropriate amine and acid chloride, were recrystallised twice from aqueous methanol. In the cases of the two p-methoxy-compounds only, a contaminant, believed to be the diacylimide, was detected by t.l.c. and was separated from the product by elution with methanol from an alumina column. The product was then recrystallised twice from aqueous methanol as before. The products were: N-(2,2,2-trifluoroethyl) benzamide, m.p. 116° (lit., 16 115-116°) (Found: C, 53.0; H, 4.1; N, 6.8. Calc. for C<sub>9</sub>H<sub>8</sub>F<sub>3</sub>NO: C, 53.2; H, 3.9; N, 6.9%); m-methyl-N-(2,2,2-trifluoroethyl)benzamide, m.p. 79° (Found: C, 55.4; H, 4.7; N, 6.5. C<sub>10</sub>H<sub>10</sub>F<sub>3</sub>NO requires C, 55.4; H, 4.6; N, 6.5%); p-methyl-N-(2,2,2-trifluoroethyl)benzamide, m.p. 146° (Found: C, 54.9; H, 4.7; N, 6.7. C10H10F3NO requires C, 55.4; H, 4.6; N, 6.5%); mchloro-N-(2,2,2-trifluoroethyl)benzamide, m.p. 109° (Found: C. 45.5; H. 3.1; N. 5.9. C.H.ClF<sub>3</sub>NO requires C. 45.5; H, 2.9; N, 5.9%); p-chloro-N-(2,2,2-trifluoroethyl)benzamide, m.p. 111° (Found: C, 45.5; H, 2.9; N, 6.1. C<sub>9</sub>H<sub>7</sub>ClF<sub>3</sub>NO requires C, 45.5; H, 2.9; N, 5.9%); m-bromo-N-(2,2,2-trifluoroethyl)benzamide, m.p. 111° (Found: C, 38.3; H, 2.5; N, 5.1.  $C_{9}H_{7}BrF_{3}NO$  requires C, 38.3; H, 2.5; N, 5.0%); m-nitro-N-(2,2,2-trifluoroethyl)benzamide, m.p. 106° (Found: C, 43·4; H, 2·7; N, 11·3. C<sub>9</sub>H<sub>7</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub> requires C, 43·6; H, 2.8; N, 11.3%); p-methoxy-N-(2,2,2-trifluoroethyl)benzamide, m.p. 127° (Found: C, 51·4; H, 4·3; N, 6·1.  $C_{10}H_{10}F_3NO_2$  requires C, 51.5; H, 4.3; N, 6.0%); Nethylbenzamide, m.p. 69° (lit.,17 67°); m-methyl-N-ethylbenzamide, m.p.  $44^{\circ}$  (Found: C,  $73\cdot4$ ; H,  $8\cdot2$ ; N,  $8\cdot7$ . C<sub>10</sub>H<sub>13</sub>NO requires C,  $73\cdot6$ ; H,  $8\cdot0$ ; N,  $8\cdot6\%$ ); *p*-methyl-N-ethylbenzamide, m.p. 92° (lit., 18 90°) (Found: C, 73.7; H, 8.0; N, 8.6. Calc. for C<sub>10</sub>H<sub>13</sub>NO: C, 73.6; H, 8.0; N, 8.6%); m-chloro-N-ethylbenzamide, m.p. 69° (Found: C, 59·1; H, 5·6; N, 7·6. C<sub>9</sub>H<sub>10</sub>ClNO requires C, 58·9; H, 5.5; N, 7.6%); p-chloro-N-ethylbenzamide, m.p. 110° (lit., 18 97°) (Found: C, 59.1; H, 5.5; N, 7.7. Calc. for C<sub>9</sub>H<sub>10</sub>CINO: C, 58.9; H, 5.5; N, 7.6%); *m*-bromo-*N*-ethylbenzamide, m.p. 82° (lit., 19 82°) (Found: C, 47.8; H, 4.5; N, 6.3. Calc. for  $C_{9}H_{10}BrNO$ : C, 47.4; H, 4.4; N, 6.2%); m-nitro-N-ethylbenzamide, m.p. 122° (Found: C, 55.5; H, 5.2; N, 14.4. Calc. for  $C_{9}H_{10}N_{2}O_{3}$ : C, 55.7; H, 5.2; N, 14.4%); and p-methoxy-N-ethylbenzamide, m.p. 69° (Found: C, 67.0; H, 7.4; N, 8.1. C<sub>10</sub>H<sub>13</sub>NO<sub>2</sub> requires C, 67.0; H, 7.3; N, 7.8%).

Acid Solutions .-- These were prepared by dilution of AnalaR sulphuric acid.

Spectrophotometric Measurements .- Stock solutions of the amides were prepared in either 80% H<sub>2</sub>SO<sub>4</sub> [N-(2,2,2trifluoroethyl)benzamides] or 15% H2SO4 (N-ethylbenzamides). Aliquots (5 ml.) were then transferred to weighed 25 ml. volumetric flasks and made up to the mark using acid of appropriate concentration. The flasks were reweighed, and the final acid concentration determined from the temperature and the density. Absorbances were measured with either an S.P. 500 or Cary 16 spectrophotometer, with cells of 1 cm. path length. Solutions were normally at room temperature  $(22 \pm 3^{\circ})$ . However, for one compound (p-methoxy-N-ethylbenzamide) the spectrophotometer cells were maintained at constant temperature by a thermostatted jacket and in each case left for 30 min. to come to thermal equilibrium. Measurements at 20 and 25° gave results which were identical within experimental error, showing that accurate temperature control was not necessary.

We thank the S.R.C. for a maintenance grant (to D. W. F.).

[9/1322 Received, August 4th, 1969]

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