Acid Catalysed Hydrolysis of *N*-Alkyl-4-chlorobenzamides. Part II.[1]

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Rate constants of hydrolysis for 4-chloro-*N*-n-propyl- and *N*-isobutyl-benzamides have been measured in sulphuric acid at 100.7°. Existing criteria of mechanism have been applied to the rate data. Taft parameters have been applied to the chemical shifts, δ_{NH}, the basicity constants, K_{BH^+}, and the rate constants of hydrolysis, k_ψ, in sulphuric acid at 100.7° of a series of *N*-alkyl-4-chlorobenzamides.

We recently reported[1] the rate constants of hydrolysis for a number of *N*-substituted 4-chlorobenzamides and analysed the data in terms of the existing criteria of mechanism. We have now extended these studies and have studied the effect of changing alkyl substituent on the chemical shift of NH, δ_{NH}, the basicity constants, K_{BH^+}, and the rate constants of hydrolysis, and have applied the data to the Taft equation.[2] The rate data have also been applied to existing criteria of mechanism.

N.m.r. Spectra.—We have recently found[3] that the chemical shifts δ_{NH} and δ_{NH_2} of phenylureas and δ_{NH} and δ_{CH_3} of acetanilides correlate well with Hammett σ constants.[4] In Table 1 we give the chemical shift δ_{NH} of a series of *N*-alkyl-4-chlorobenzamides. These values fit well a Taft plot of δ_{NH} against E_s' for which we found $\delta_{NH} = (0.38 \pm 0.04)E_s' + (8.61 \pm 0.04)$. The data are plotted in Figure 1.

TABLE 1

Chemical shifts, δ_{NH}, of *N*-alkyl-4-chlorobenzamides in $(CD_3)_2SO$

Alkyl	H	Me	Et	Pr^n	Pr^i	Bu^n
δ_{NH}	7.87	8.50	8.52	8.52	8.28	8.51
	Bu^t	Bu^i	Ph	CH_2Ph	C_6H_{11}	
	7.84	8.55	10.31	9.16	8.27	

Basicity Constants.—The pK_{BH^+} values of 4-chloro-*N*-propyl- and -*N*-isobutyl-benzamides were found spectrophotometrically to be 2.11 ± 0.04 and 2.00 ± 0.04 respectively, using $\lambda_{max.}$ 250 nm for the first and 237 nm for the second. d $\log_{10}I/d(-H_A) = 1.0$ [as against d $\log_{10}I/d(-H_0) = 0.6$] showing, as expected, that H_A[5] was the more appropriate acidity scale. The Bunnett–Olsen treatment[6] gave pK_{BH^+} values of 1.77 ± 0.02 and 1.69 ± 0.01 respectively and ϕ values (0.47 and 0.45) between 0.42 and 0.55, as expected for amide protonation.[6,7]

The constants, pK_{BH^+}, of all the *N*-alkyl-4-chlorobenzamides which we have measured[8] are best fitted by the Taft equation $\log_{10}K_{BH^+} + E_s = \rho^*\sigma^* + \text{const.}$ for which $\rho^* = -3.1 \pm 0.3$. The data are plotted in Figure 2.

Kinetic Data.—The pseudo-first-order rate constants of hydrolysis (k_ψ) of 4-chlorobenzamide, and 4-chloro-*N*-methyl-, -*N*-ethyl, -*N*-n-butyl-, -*N*-isopropyl-, and -*N*-t-butyl-benzamides in sulphuric acid at 100.7° have been previously reported.[1] Those for 4-chloro-*N*-isobutyl- and -*N*-n-propyl-benzamides are given in Table 2.

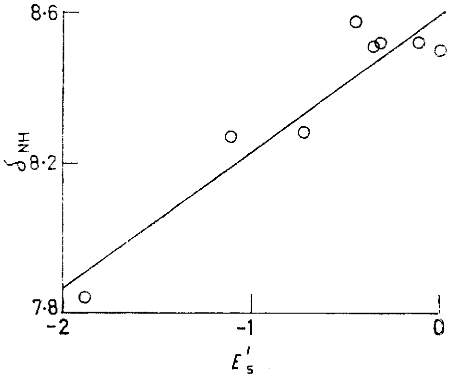

FIGURE 1 Taft plot of δ_{NH} against E_s' for *N*-alkyl-4-chlorobenzamides

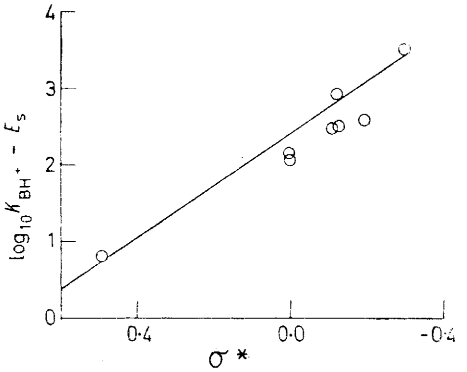

FIGURE 2 Taft plot of $\log_{10}K_{BH^+} - E_s$ against σ* for *N*-alkyl-4-chlorobenzamides

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[1] Part I, C. J. Hyland and C. J. O'Connor, *J.C.S. Perkin II*, 1973, 1402.

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[5] K. Yates, J. B. Stevens, and A. R. Katritzky, *Canad. J. Chem.*, 1964, **42**, 1957.

[6] J. F. Bunnett and F. P. Olsen, *Canad. J. Chem.*, 1966, **44**, 1899.

[7] J. W. Barnett and C. J. O'Connor, *Austral. J. Chem.*, 1973, **26**, 2083.

[8] J. W. Barnett and C. J. O'Connor, *J.C.S. Perkin II*, 1973, 1331.

Table 3 shows the correlation coefficients and slopes (r) for plots of ($\log_{10}k_\psi - \log_{10}\alpha$) against $\log_{10}a_w$ (Yates r modification [9] of Bunnett w function [10]) and the correlation coefficients and slopes (ϕ) for plots of ($\log_{10}k_\psi - \log_{10}\alpha$) against ($H_0 + \log C_{H^+}$) [Bunnett–Olsen linear free energy relationship (l.f.e.r)] [11] for these two amides. The Yates r plots for these two amides are curved as previously found for this series of compounds,[1] while the correlation coefficients for the Bunnett–Olsen l.f.e.r. are quite reasonable.

TABLE 2

Rate constants for the hydrolysis of 4-chloro-N-n-propyl- and -N-isobutyl-benzamides in sulphuric acid at 100.7°

C_{H^+}/mol l^{-1}	1.09	2.35	3.07	3.76	4.52
10^5k_ψ/s^{-1} (Pr^n)	1.73	3.96	4.95	5.89	5.76
10^5k_ψ/s^{-1} (Bu^i)	1.21	2.17	2.87	3.31	3.29
C_{H^+}/mol l^{-1}	5.33	7.10	9.16	11.48	14.07
10^5k_ψ/s^{-1} (Pr^n)	4.63	2.49	1.23	0.62	0.19
10^5k_ψ/s^{-1} (Bu^i)	2.94	1.45	0.66	0.28	0.15

TABLE 3

Analysis of rate data for hydrolysis of N-alkyl-4-chlorobenzamides in H_2SO_4 at 100.7° by existing criteria of mechanism

	Yates r plot		Bunnett–Olsen l.f.e.r.		Equation (2) slope		Equation (3) slope	
Alkyl	correln. coefft.	r	correln. coefft.	ϕ	10^5k_N/l mol^{-1} s^{-1}	correln. coefft.	10^4k_O/s^{-1}	correln. coefft.
Pr^n	0.927	1.45 ± 0.19	0.983	0.58 ± 0.04	1.62 ± 0.06	0.994	13.5 ± 0.4	0.996
Bu^i	0.912	1.37 ± 0.20	0.977	0.56 ± 0.04	1.10 ± 0.04	0.992	10.3 ± 0.4	0.992

We previously reported [1,12] that the rate constants of hydrolysis of aromatic amides were excellently fitted by an empirical rate law (1) which allowed the acid hydrolysis

$$k_\psi = k_N(1 - \alpha)C_{H^+}a_w + k_O\alpha a_w \qquad (1)$$

to proceed by two distinct mechanistic paths, possibly involving O- and N-protonated transition states. Table 3 shows the results of applying this law to the present rate data plotted in two forms [equations (2) and (3)].

$$k_\psi/\alpha a_w = k_N(1 - \alpha)\ C_{H^+}/\alpha + k_O \qquad (2)$$

$$k_\psi/(1 - \alpha)\ C_{H^+}a_w = k_N + k_O\alpha/(1 - \alpha)\ C_{H^+} \qquad (3)$$

As found previously,[1,12] the fits are excellent. Moodie *et al.*[13] have criticised this two term rate law because the assumption made that the activity coefficient of the free amides and activity coefficient ratios of ions of like charge are medium independent is not well founded. Smith and Yates [14] also considered that the idea of a dual mechanism was inconsistent with their observed lack of medium dependence of $\Delta H_p^\ddagger$.

We now find that the good correlations are in fact misleading. The plots are not linear but steeply curved. The slopes of equations (2), k_N, and (3), k_O, for 4-chlorobenzamide [1] have been substituted back into the two-term rate equation (1) in an attempt to reproduce the experimental rate profile. The result is shown in Figure 3. Although the two-term rate equation (1) predicts the shape of the curve, it does not accurately predict the values of the rate constants of hydrolysis.

The development and application of a rate equation involving only an N-protonated cation, which is well fitted by 59 sets of rate data for hydrolysis of benzamides and acetanilides will be the subject of a forthcoming publication. Both Moodie *et al.*[13] and Smith and Yates [14] have considered the possibility that hydrolysis takes place *via* the $A_N{}^D2$ (acid-catalysed, bimolecular, N-protonated cation, direct displacement) mechanism.

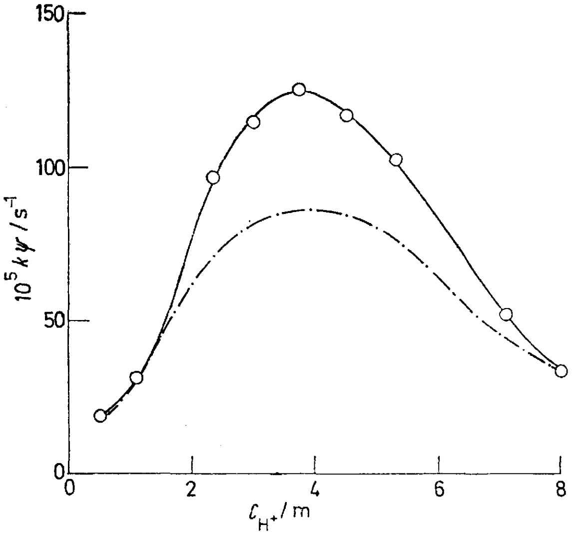

FIGURE 3 Rate profiles for hydrolysis of 4-chlorobenzamide in H_2SO_4 at 100.7°: ○, experimental values; —·—·—, theoretical profile calculated from two-term rate equation (1) involving both O- and N-protonated transition states

The observed rate constants for the hydrolysis of the N-substituted 4-chlorobenzamides at 20 and 50% (w/w)

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[9] K. Yates and J. B. Stevens, *Canad. J. Chem.*, 1965, **43**, 529.

[10] J. F. Bunnett, *J. Amer. Chem. Soc.*, 1961, **83**, 4956, 4968, 4973, 2978.

[11] J. F. Bunnett and F. P. Olsen, *Canad. J. Chem.*, 1966, **44**, 1917.

[12] C. A. Bunton, C. J. O'Connor, and T. A. Turney, *Chem. and Ind.*, 1967, 1835; C. A. Bunton, S. J. Farber, A. J. G. Milbank, C. J. O'Connor, and T. A. Turney, *J.C.S. Perkin II*, 1972, 1869; J. W. Barnett, C. J. Hyland, and C. J. O'Connor, *J.C.S. Chem. Comm.*, 1972, 720.

[13] V. C. Armstrong, D. W. Farlow, and R. B. Moodie, *J. Chem. Soc.* (*B*), 1968, 1099.

[14] C. R. Smith and K. Yates, *J. Amer. Chem. Soc.*, 1971, **93**, 6578.

H_2SO_4 have been corrected for the degree of protonation, ($k_p = k_\psi/\alpha$) and applied to the Taft equations.

In contrast to the work of Bolton,[15] we find that there is little difference between the plots obtained using the E_s, E_s', and E_s^c steric parameters. Correlation coefficients were *ca.* 0.94 ± 0.04. Figure 4 shows typical plots against E_s for 20 and 50% (w/w) H_2SO_4 respectively.

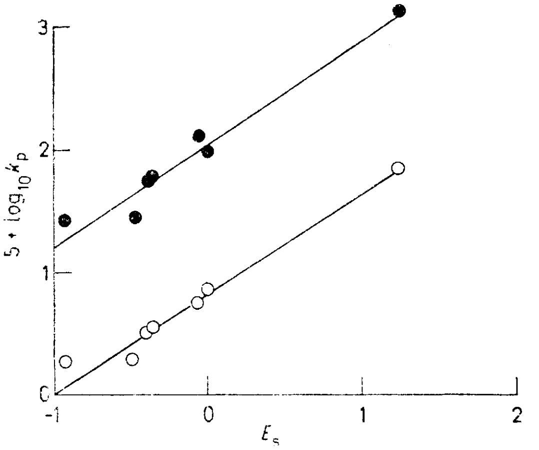

FIGURE 4 Taft plots of $5 + \log_{10}k_p$ against E_s for hydrolysis of *N*-alkyl-4-chlorobenzamides in 20% (w/w) H_2SO_4, ●; and in 50% (w/w) H_2SO_4, ○

For the hydrolysis of the series of *N*-substituted acetamides Bolton[15] found a much better correlation with E_s^c and E_s' than with E_s; a similar result might, therefore, have been expected here. We realise, however, that any interpretation of results obtained from application of the Taft plots to our data is obviously limited by the rather narrow range of substituents whose rate profiles we have measured. We plan to extend this range to include electron-withdrawing groups substituted on the amide nitrogen.

But in general, the Taft analysis, its equations and parameters have not been subjected to the extensive refinement applied to the Hammett equation.[16] The very nature of the species studied, *i.e.* the proximity of substituents and reaction sites, places an uncertainty on the general applicability of the substituent parameters.

EXPERIMENTAL

Materials.—4-Chloro-*N*-n-propyl-, -*N*-isobutyl-, -*N*-phenyl-, -*N*-benzyl-, and -*N*-cyclohexyl-benzamides were prepared by treating 4-chlorobenzoyl chloride (prepared by the action of phosphorus pentachloride on 4-chlorobenzoic acid) with the appropriate amine. The amides were recrystallized from aqueous ethanol and had m.p. 98.5—99.5, 96.5—98.0, 200, 230, and 163—164° respectively. The last three 4-chlorobenzamides were too insoluble to allow basicity constant or kinetic measurements to be made on them.

The other amides used in this investigation were prepared and purified by Barnett and O'Connor.[8]

Concentrated AnalaR sulphuric acid was standardised against sodium hydroxide and was diluted with deionised water by weighing to give solutions of the required composition.

[$^2H_6$]Dimethyl sulphoxide (B.D.H. 99.5%) was used for measurement of n.m.r. spectra.

Method of Measurement of Basicity Constants.—The required acid (10 ml) was weighed, then mixed with 1 ml of a stock solution of the base (2.5×10^{-3} g in 25 ml). The u.v. spectrum of the sample was then measured rapidly on a Cary 14 spectrophotometer. All spectra were reproducible and the spectral changes were reversible, *i.e.* no hydrolysis took place in the time taken for the basicity constant determination. All measurements were carried out at 25.0°.

Analysis of Basicity Data.—The pK_{BH^+} values were obtained by using a combination of the methods of Davis and Geissman[17] and Katritzky *et al.*[18] The absorbances at two wavelengths, $\lambda_{max.BH^+}$ and $\lambda_{max.B}$, were measured. The difference between these two readings at the various acid concentrations was then calculated, and values of A_B and A_{BH^+} were obtained. These were substituted in equation (4) and $\log_{10}I$ was calculated. $\log_{10}I$ Values were plotted

$$I = (A - A_B)/(A_{BH^+} - A) \qquad (4)$$

against H_A and $pK_{BH}{}^+$ was obtained from the value of H_A when $\log_{10}I = 0$.

Ionisation ratios for 4-chloro-*N*-isobutyl- and -*N*-n-propyl-benzamide in H_2SO_4 at 25° are listed in Supplementary Publication No. SUP 21394 (2 pp.).*

Measurement of Reaction Rates.—Hydrolysis reactions at 100.7 ± 0.2° were carried out in an oil-bath maintained at the required temperature by using a Gallenkamp contact thermometer, Klaxon stirrer, and heating element.

The amides (*ca.* 10^{-3} g) were dissolved in the appropriate acid (10 ml). Aliquot portions (1 ml), sealed in ampoules, were removed at intervals and after quenching the reaction by rapid cooling to room temperature were diluted 10 times before undertaking spectrophotometric analysis of the change in absorbance between 210 and 250 nm using a Unicam SP 800A recording spectrophotometer. (Freezing the quenched sample or allowing it to stand at room temperature for any length of time caused precipitation of 4-chlorobenzoic acid.) Values of k_ψ, calculated at two or three wavelengths from slopes of plots of $\log_{10}(A_t - A_\infty)$ against t (where A_t and A_∞ are the absorbances at time t and at infinite time respectively) generally agreed within ±2% and the average value of k_ψ is quoted in Table 2. For the slower runs the accuracy decreased to ±5% and these rates are quoted to only two significant figures in Table 2.

Least-squares analyses were carried out on a Burroughs B6700 computer.

N.m.r. spectra were measured on a Varian T60 recording spectrophotometer.

We are grateful to Mr D. J. Calvert for technical assistance.

[4/2077 *Received, 7th October,* 1974]

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* For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1974, Index issue. Items less than 10 pp. are supplied as full-size copies.

[15] P. D. Bolton, J. Ellis, R. D. Frier, and P. C. Nancarrow, *Austral. J. Chem.*, 1972, **25**, 303.

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[18] C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, N. Shakir, and A. M. White, *Tetrahedron*, 1965, **21**, 1055.