Acid Catalysed Hydrolysis of *N*-Substituted 4-Chlorobenzamides

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The hydrolysis of 4-chlorobenzamide, and 4-chloro-*N*-methyl-, -*N*-ethyl-, -*N*-isopropyl-, -*N*-n-butyl-, and -*N*-t-butyl-benzamides have been carried out over a wide range of acidities (10—90% w/w) in sulphuric acid at 100·7 °C. Interpretation of the rate data by use of the Bunnett criterion of mechanism has been found unsatisfactory, and by the Bunnett–Olsen criterion only reasonable; however, the data do fit an empirical two-term rate equation. The rate of hydrolysis of 4-chloro-*N*-t-butylbenzamide shows a sudden reversal of the general trend of decreasing rate with increasing chain length.

We recently reported[1] that the mechanism for the acid catalysed hydrolysis of aromatic amides appeared to differ from that of aliphatic amides. Whereas the latter gave linear Bunnett w[2] and Bunnett–Olsen linear free energy relationship (l.f.e.r.)[3] plots, the former followed

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[1] J. W. Barnett, C. J. Hyland, and C. J. O'Connor, *J.C.S. Chem. Comm.*, 1972, 720.

[2] J. F. Bunnett, *J. Amer. Chem. Soc.*, 1961, **83**, 4956, 4968, 4973, 4978.

[3] J. F. Bunnett and F. Olsen, *Canad. J. Chem.*, 1966, **44**, 1899, 1917.

an empirical two-term rate law.[4] However, the limited number of rate data reported for hydrolysis of aromatic amides[5,6] restricted the analysis to only three compounds, benzamide, *N*-methylbenzamide, and *NN*-dimethylbenzamide. We have now extended the analysis to hydrolysis of 4-chlorobenzamide and five *N*-substituted 4-chlorobenzamides which have been studied over the range 10—90% w/w H_2SO_4. The results confirm our earlier postulate.

TABLE 1

Hydrolysis of *N*-R-4-chlorobenzamides at 100·7 °C in sulphuric acid. Values of $10^5k_\psi/s^{-1}$

% w/w H_2SO_4	R H	Me	Et	Bu^n	Pr^i	Bu^t
5·0	18·5					
10·0	31·2	2·41	1·76	1·45	0·90	12·6
20·0	96·9	6·05	4·73	3·81	1·86	76·0
25·0	115	8·76	7·26	5·11	2·72	101
30·0	126	10·4	7·64	5·31	3·24	105
35·0	117	9·35	7·01	4·93	3·15	98·6
40·0	103	7·87	5·23	3·76	2·57	86·4
50·0	51·9	5·02	3·35	2·26	1·30	41·7
55·0	33·6	3·31	2·22	1·50	1·09	29·8
60·0	21·9	2·21	1·21	1·15	0·84	17·4
65·0	9·52	1·23	0·92	0·72	0·52	8·36
70·0	4·49	0·81	0·67	0·54	0·36	3·81
80·0	0·91	0·26	0·24	0·22	0·20	0·82
90·0	0·33	0·084	0·081	0·069	0·063	0·27

TABLE 2

Analysis of rate data for hydrolysis of *N*-R-4-chlorobenzamides in H_2SO_4 at 100·7 °C by use of Bunnett *w* and Bunnett–Olsen l.f.e.r.

	Bunnett *w*	Bunnett–Olsen l.f.e.r.		
R	Correlation coefficient	ϕ [a]	$-\log_{10}k_2^0/s^{-1}$ [b]	Correlation coefficients
H	0·933	0·67	1·67	0·992
Me	0·924	0·57	2·85	0·986
Et	0·897	0·59	2·79	0·972
Pr^i	0·894	0·49	3·44	0·970
Bu^n	0·899	0·52	3·19	0·973
Bu^t	0·951	0·62	1·95	0·993

[a] 0·04 > Standard deviation (*s*) > 0·02. [b] 0·11 > *s* > 0·05.

TABLE 3

Analysis of rate data for hydrolysis of *N*-R-4-chlorobenzamides in H_2SO_4 at 100·7 °C by use of a two-term rate equation

R	$10^5k_N/$ l mol^{-1} s^{-1}	$10^5k_O/s^{-1}$	Correlation coefficient
H	34·2	165	0·997
Me	2·28	40·0	0·997
Et	1·74	40·0	0·997
Pr^i	0·76	30·0	0·997
Bu^n	1·34	35·0	0·997
Bu^t	40·2	135	0·997

RESULTS AND DISCUSSION

Table 1 gives the pseudo-first-order rate constants of hydrolysis of 4-chlorobenzamide, and 4-chloro-*N*-methyl, -*N*-ethyl-, -*N*-n-butyl-, -*N*-isopropyl-, and -*N*-t-butylbenzamides in sulphuric acid at 100·7 °C.

The rate profiles given in Figure 1 show the typical bell shape usually found for amides,[7] but there are very marked differences in the values obtained for 4-chlorobenzamide and 4-chloro-*N*-t-butylbenzamide on the one hand, and 4-chloro-*N*-methyl-, *N*-ethyl, -*N*-n-butyl-, and -*N*-isopropyl-benzamides on the other. We have previously shown[8] that the basicities of these same amides first decrease and then increase with increasing chain length of the substituent on nitrogen. This trend is reflected in the rate profiles of hydrolysis, as shown by the values of $k_{\psi(\max.)}$. The reversal is most marked for 4-chloro-*N*-t-butylbenzamide. (Yates[9] has shown that the hydrolysis behaviour of t-butyl acetate differs markedly from that of other acetates.) The observed order of hydrolysis, primary > secondary, is similar to that observed for benzamides[5,6] and acetamides.[10]

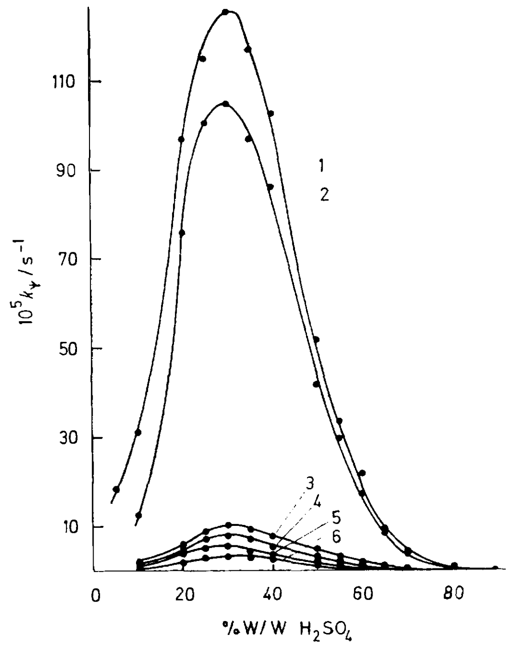

FIGURE 1 Rate profiles for hydrolysis of *N*-R-4-chlorobenzamides in H_2SO_4 at 100·7 °C: 1 R = H; 2 R = Bu^t; 3 R = Me; 4 R = Et; 5 R = Bu^n; 6 R = Pr^i

Amides are moderately basic substrates and therefore the rate constants of hydrolysis must be corrected for the degree of protonation of the substrate, $\alpha = h_A/(h_A + K_{BH^+})$, before any attempt at kinetic analysis is made. Values of $-pK_{BH^+}$ (given in parentheses) for 4-chlorobenzamide (2·04), and 4-chloro-*N*-methyl- (2·16), -*N*-ethyl- (2·33), -*N*-isopropyl- (2·12), -*N*-n-butyl- (2·10), and -*N*-t-butyl-benzamides (1·93) have been obtained[8] and used in the calculations which follow.

Values of h_A, the amide acidity function, have been

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[4] C. A. Bunton, C. J. O'Connor, and T. A. Turney, *Chem. and Ind.*, 1967, 1835.

[5] 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.

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

[7] C. J. O'Connor, *Quart. Rev.*, 1970, **24**, 553.

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

[9] K. Yates, *Accounts Chem. Res.*, 1971, **4**, 136.

[10] P. D. Bolton, *Austral. J. Chem.*, 1966, **19**, 1013; 1972, **25**, 303.

evaluated in H_2SO_4 at 25 °C.[11] Values of H_0 in H_2SO_4 at 90 °C [12] and values of a_w calculated from vapour pressures of water in H_2SO_4 at 100 °C have also been substituted into the calculations. Substitution of parameters, measured at temperatures different from that of the rate data, into these calculations introduces some error but it is not regarded as significant.

Table 2 shows the correlation coefficients for plots of $(\log_{10}k_\psi - \log_{10}\alpha)$ against $\log_{10}a_w$ (Bunnett *w* function) [2] and the slopes (ϕ), intercepts ($\log_{10}k_2{}^0$), and correlation coefficients for plots of $(\log_{10}k_\psi - \log_{10}\alpha)$ against $(H_0 + \log_{10}C_{H^+})$ (Bunnett–Olsen l.f.e.r.).[3] The Bunnett *w* plots (Figure 2) are curved but those for 4-chlorobenzamide and 4-chloro-*N*-t-butylbenzamide are more nearly linear than those of the other amides. Smith and Yates [6] have noted that *N*-methylbenzamide and *NN*-dimethylbenzamide possess similar curves for Bunnett *w* plots, but that these differ significantly (and are more curved) from that for benzamide. They suggested that there may be two classes of reaction for unsubstituted and *N*-substituted amides, and with one exception our results agree with their hypothesis. The correlation coefficients for the Bunnett–Olsen l.f.e.r. are generally reasonable, and for the unsubstituted and *N*-t-butyl substituted amides are good. Values of ϕ for these two amides, however, are >0·58, the upper limit suggested by Bunnett and Olsen for reactions in which water is involved as a nucleophile in the rate-determining step. Our experience suggests that limits for this mechanism for amides should be $0{\cdot}47 \leqslant \phi \leqslant 0{\cdot}98$.

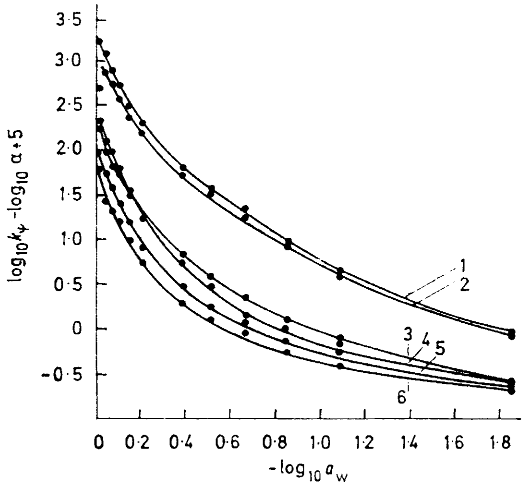

FIGURE 2 Bunnett *w* plots for hydrolysis of *N*-R-4-chlorobenzamides in H_2SO_4 at 100·7 °C: 1 R = H; 2 R = Bu^t; 3 R = Me; 4 R = Et; 5 R = Bu^n; 6 R = Pr^i

The lack of correlation of the rate data for hydrolysis of benzamide, *N*-methylbenzamide, and *NN*-dimethylbenzamide in acid solution with the Bunnett [2] and Bunnett–Olsen [3] criteria of mechanism, led to the formulation [4,5] of an empirical rate law, $k_\psi = k_N(1 - \alpha)C_{H^+}a_w + k_O\alpha a_w$, which suggests that the acid hydrolysis of amides proceeds by two distinct mechanistic paths, possibly involving *O*- and *N*-protonated transition states. Table 3 shows the results of applying this law to our rate data. The fit is invariably excellent. If this law were viable, then substitution on nitrogen should have relatively much more effect on the values of k_N than on those of k_O, and analysis of the rate data does indeed confirm the existence of this effect. The contribution to the rate made by the *N*-protonated path is very much greater for 4-chlorobenzamide and 4-chloro-*N*-t-butylbenzamide than for the other amides and must be partially responsible for the large value of $k_{\psi(\max.)}$ observed for these two amides (Figure 1). At present we cannot offer an explanation of their unusual reactivity, but the effect of R = H and R = Bu^t is being further investigated on other substrates.

EXPERIMENTAL

Materials.—The preparation and purification of the amides are described in ref. 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.

Measurement of Reaction Rates.—Hydrolysis reactions at 100·7 ± 0·2 °C 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 10 ml of the appropriate acid. Aliquot portions (1 ml), sealed in ampoules, were removed at timed intervals, and after quenching the reaction by rapid cooling, 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. 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 1. For the slower runs the accuracy decreased to ±5% and these rates are quoted to only two significant figures in Table 1.

Least-squares analyses were carried out on an IBM 1130 computer.

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

[12] C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.*, 1969, **61**, 6654.