Acid Catalysed Hydrolysis of Substituted Acetanilides.   Part II[1]

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The rate constants of hydrolysis of 12 *para*-substituted acetanilides have been measured in 5—98% (w/w) H_2SO_4 at 100.1°.   In H_2SO_4 (<65% w/w) the data are reasonably well fitted by the Yates *r* and Bunnett–Olsen criteria for an *A*-2 mechanism, and correlate well with Hammett σ.   Acetanilides with electron-donating substituents in the 4-position, *i.e.* OH, Me, MeO, and EtO are sulphonated in >70% (w/w) H_2SO_4 and these substituted intermediates and the other acetanilides studied are hydrolysed in concentrated (>70% w/w) H_2SO_4 by an *A*-1 mechanism.

THE rate constants of hydrolysis of acetanilide[2] have previously been measured over a wide range of acidities in HCl, H_2SO_4, and $HClO_4$ at 25.0 and 80.0°, those of *N*-acetylsulphanilic acid[1] over a wide range of acidities (H_2SO_4) and temperatures, and those for seven substituted acetanilides[1] in >50% (w/w) H_2SO_4 at 100°.

N-Substituted amides hydrolyse by either an *A*-2 or an *A*-1 mechanism depending on the medium acidity. Evidence for a changeover in mechanism has been found for substituted acetanilides.[1,3-6]

We have now extended the studies on hydrolysis of substituted acetanilides to include 12 acetanilides over a wide range of acidities in H_2SO_4.

RESULTS AND DISCUSSION

Basicity Constants.—The ionisation ratios $I = C_{BH+}/C_B$ have been previously reported[8] and plots of $\log_{10} I$ against $-H_A$[9] were linear with slopes (m_A) near unity. Values of $pK_{BH+} = m_A H_A^{\frac{1}{2}}$, where $H_A^{\frac{1}{2}}$ is the value of H_A at half protonation, are given in Table 1.   We have used

TABLE 1

Rate constants for the hydrolysis of 4-X-acetanilides in H_2SO_4 at 100.1°

Concentration (M)	$10^3 k_\gamma / s^{-1}$											
	H	F	Cl	Br	I	NH₂	Me	MeO	EtO	OH	CO₂H	NO₂
	1.58*	1.70*	1.88*	2.01*	2.07*	2.37*	1.28*	1.27*	1.22*	1.02*	2.20*	2.59*
0.55	1.38	1.21				1.75	1.06	0.93	0.93	1.13	2.64	5.14
1.09	2.84	2.38	2.92	3.07	2.51	3.58	2.14	1.67	1.77	1.68	5.48	6.99
1.68	4.16	3.30	4.94	5.50	4.74	5.49	2.89	2.41	2.43	2.38	8.13	11.6
2.00		4.00	5.60	6.11	5.26		3.20	2.69	2.80			
2.35	5.13	4.31	6.22	7.12	6.08	7.02	3.74	2.88	2.95	2.70	10.4	15.7
2.70		4.70	6.93	7.50	6.72		3.91	3.02	3.09			
3.07	5.85	4.78	7.45	7.98	7.37	7.89	4.00	3.06	3.22	2.77	13.8	20.8
3.40		4.84	7.81	8.02	7.49	8.64	3.97	2.99	3.14			
3.76	5.70	4.82	7.69	7.84	7.46	9.00	3.81	2.92	2.99	2.65	16.6	24.6
4.13		4.62	7.28	7.48	6.99	9.40	3.50	2.76	2.83			
4.52	4.91	4.42	6.84	7.23	6.58	9.59	3.21	2.54	2.61	2.31	17.2	26.2
4.92		4.04	6.38	6.68	5.99	9.37						
5.33	3.67	3.65	5.58	6.00	5.24	8.94	2.42	1.80	1.90	1.74	15.9	25.3
5.78						8.00						
6.21	2.67	2.44	4.30	4.64	4.47	7.45	1.58	1.18	1.27	0.99	11.5	23.1
7.10	1.50	1.44	2.48	2.61	2.49	4.71	0.97	0.70	0.71	0.66	8.85	18.7
8.05	0.69	0.70	1.24	1.33	1.31	2.92	0.42	0.32	0.32	0.34	5.70	13.0
9.16	0.25	0.25	0.46	0.51	0.51	1.27	0.13	0.13	0.14	0.12	2.67	6.89
10.30	0.091	0.098	0.20	0.20	0.24	0.39	0.044	0.047	0.043	0.053	1.04	3.12
12.75						0.035	0.0050	0.010	0.010	0.012	0.22	0.66
14.07		0.0038	0.0058	0.0065	0.016							
15.40						0.033	0.0054	0.0066	0.0057	0.0049	1.24	1.62
16.65		0.0018	0.0044	0.0045	0.037	0.049	0.014	0.012	0.014	0.013	3.88	3.49
18.3		0.0072	0.013	0.011	0.141	0.079	0.036	0.055	0.058	0.055	25.5	12.7

* Value of $-pK_{BH+}$.

3-Hydroxy- and 4-methyl-acetanilide[1] and acetanilide[7] are sulphonated in concentrated H_2SO_4 and it is the sulphonated intermediates (3-hydroxy-4-sulpho- and 4-methyl-2-sulpho-acetanilide   and   *N*-acetylsulphanilic acid) which undergo subsequent hydrolysis.[1,6]

these values in our calculations of α (the fraction of protonated substrate) $= h_A/(K_{BH+} + h_A)$ which were necessary for analysing the rate data.

Kinetic Data.—The rate constants of hydrolysis, k_ψ, of a series of *para*-substituted acetanilides (4-OH, -Me,

[1] Part I, J. W. Barnett and C. J. O'Connor, *J.C.S. Perkin II*, 1972, 2378.
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[8] C. J. Giffney and C. J. O'Connor, *J.C.S. Perkin II*, 1975, 706.
[9] K. Yates, J. B. Stevens, and A. R. Katritzky, *Canad. J. Chem.*, 1964, **42**, 1957.

-MeO, -EtO, -H, -F, -Cl, -Br, -I, -NH$_2$, -NO$_2$, and -CO$_2$H) have been measured in 5—98% (w/w) H$_2$SO$_4$ at 100.1°. The data are given in Table 1. The hydrolysis of acetanilide was also carried out in water at 100.1° and *the rate* constant obtained ($k_\psi = 6.82 \times 10^{-7}\text{s}^{-1}$) indicates that this hydrolysis is enhanced by a factor of 10^4 by acid solutions.

When 4-hydroxy-, 4-methyl-, 4-methoxy-, and 4-ethoxy-acetanilides were hydrolysed in >70% (w/w) H$_2$SO$_4$ the positions of $\lambda_{max.}$ underwent a bathochromic shift (Table 2) followed by a decrease in absolute ab-

TABLE 2

Positions of $\lambda_{max.}$ before [a] and after [b] the sulphonation of acetanilides having electropositive substituents (X) on the benzene ring

X	4-OH	4-Me	4-MeO	4-EtO
$\lambda_{max.}$/nm [a]	244.0	241.5	244.0	244.0
$\lambda_{max.}$/nm [b]	247.0	246.0	248.0	248.5

sorbance. Similar shifts have previously been observed and interpreted in terms of formation of sulphonated intermediates.[1,6] By analogy, the final hydrolysis products in the four cases above are assumed to be 2-amino-5-hydroxy-, 2-amino-5-methyl-, 2-amino-5-methoxy-, and 2-amino-5-ethoxy-benzenesulphonic acids.
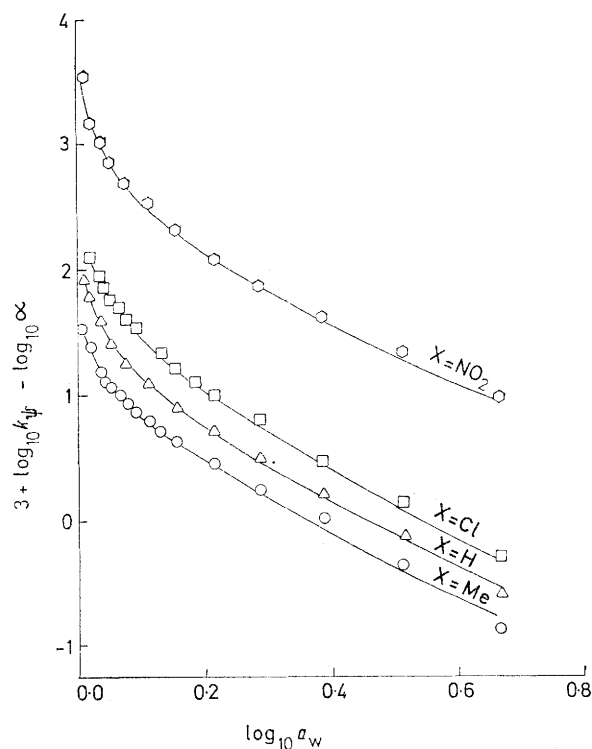

FIGURE 1   Typical plots of Yates r function [11] for 4-X-acetanilides in H$_2$SO$_4$ at 100.1°

The rate profiles of all the acetanilides studied have a minimum in the observed rate constants in concentrated

acid solutions, followed by an increase in rate with further increase in acid concentration. Minima in the rate profiles of other acetanilides [1,3,5,6] and of esters [10] have previously been observed and have been attributed to a
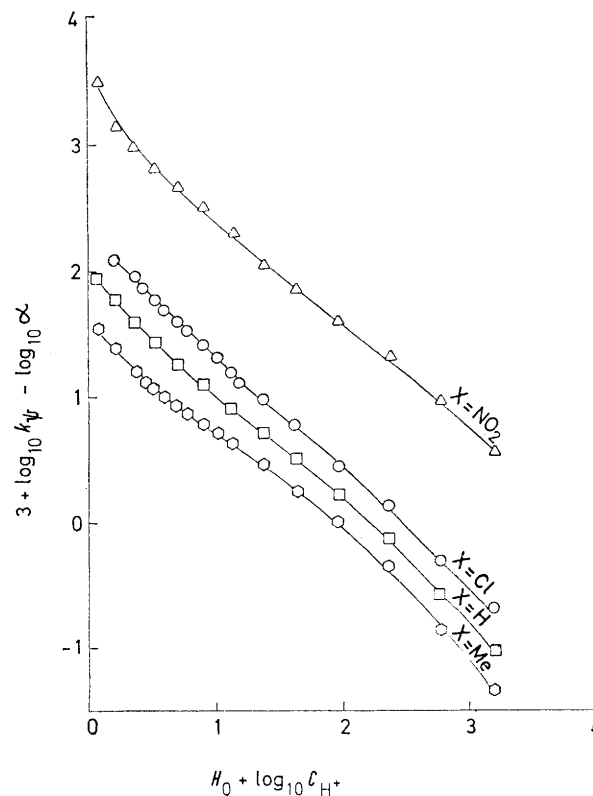

FIGURE 2   Typical plots of Bunnett–Olsen linear free energy relationship [12] for 4-X-acetanilides in H$_2$SO$_4$ at 100.1°

changeover from an A-2 to an A-1 mechanism and a similar explanation is proposed here.

The kinetic data for the hydrolysis of the 4-X-acetanilides in 5—65% (w/w) H$_2$SO$_4$ has been analysed according to the standard criteria of mechanism. Typical plots of Yates r function [11] (log k_ψ — log α) against $\log_{10} a_w$, correlation coefficients 0.97—0.99, slopes (r) 2.8—3.5 ($\pm$0.2), and of the Bunnett–Olsen linear free energy relationship [12] ($\log_{10} k_\psi$ — $\log_{10}\alpha$) against ($\log_{10} C_{H^+} + H_0$), correlation coefficients 0.995—0.999, slopes (ϕ) 0.79—0.91 ($\pm$0.02) are given in Figures 1 and 2 respectively and show slight curvature. As we found previously for acetanilides [1,2] the fit of these criteria involving only a one term mechanistic pathway is quite good; indeed the values of r obtained indicate that water is involved as a nucleophile in the rate-determining step [11,13] and suggest that there are three water molecules involved in going from the ground to the transition state in this acid-catalysed hydrolysis. This is similar to the results obtained by Yates and Stevens [14] and by Moodie *et al.*[15]

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[12] J. F. Bunnett and F. P. Olsen, *Canad. J. Chem.*, 1966, **44**, 1917.
[13] J. F. Bunnett, *J. Amer. Chem. Soc.*, 1961, **83**, 4956, 4968, 4973, 4978.
[14] K. Yates and J. B. Stevens, *Canad. J. Chem.*, 1965, **43**, 529.
[15] R. B. Moodie, P. D. Wale, and T. J. Whaite, *J. Chem. Soc.*, 1963, 4273.

for the hydrolysis of a variety of amides. In addition a value of r *ca.* 3.0 was obtained for nine acetanilides and nicotinamides studied by Hashmi in H_2SO_4 at 25 °C,[16] his data being analysed using values of pK_{BH^+} measured in this laboratory,[8] (where applicable), or those calculated from his ionisation data [16] using the amide acidity scale, H_A, and the value of $m_A H_A^{\ddagger}$.

The rate data obtained in this study has also been analysed according to the two term rate equation (1) of

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

Bunton *et al.*[17] which allows hydrolysis to occur concurrently by two distinct paths, involving both N- and O-protonated cations, but the results were unsatisfactory. Equation (1) has previously been found to be applicable only to aromatic amides.[18]

Hammett Plots.—The rates of hydrolysis of the unsulphonated acetanilides in 90% (w/w) H_2SO_4 have been applied to the Hammett equation.[19] The correlation of $\log_{10}k_p$ (where $k_p = k_{\psi}$ as all the acetanilides will be fully protonated in this concentrated acid), with both σ [20] (correlation coefficient = 0.867) and σ^+ [21] (correlation coefficient = 0.893) is only reasonable, but the values of ρ obtained (5.08 and 4.39 respectively) indicate that the reaction is very definitely favoured by electron-withdrawing groups. Indeed, electronegative substituents on the benzene ring attached to the nitrogen would be expected to assist in the unimolecular fission of the carbonyl–nitrogen bond, this being the mechanism previously proposed for the hydrolysis of other acetanilides in concentrated acid.[3] The positive values of ρ indicate that the positive charge has decreased on the nitrogen atom in the transition state, and are consistent with an A-1 reaction occurring through the O-protonated form, and not the minor N-protonated form. Amides are fully O-protonated in 100% H_2SO_4,[22,23] and although the concentration of N-protonated amide is related to the fraction, α, of the amide that is protonated on oxygen, when the fraction of unprotonated substrate becomes <0.1 the stability of the N-protonated cation is markedly reduced and the protonation equilibria shift to favour formation of the O-protonated cation.[24]

The Hammett equation has also been applied to the kinetic data obtained in 20 and 50% (w/w) H_2SO_4, the observed rate constants being corrected for the degree of protonation of the substrate ($k_p = k_{\psi}/\alpha$) and the values of $\log_{10}k_p$ being plotted against σ and σ^+. The results are given in Table 3. The plots of $\log_{10}k_p$ against σ are shown in Figure 3.

The A-2 reaction mechanism at moderate acidities is also favoured by electron withdrawal ($\rho > + 1.0$) but it is significant that the mechanism in highly acidic media is much more dependent on electron withdrawal and this supports the identification as A-1. A central issue in amide hydrolysis is whether the actual hydrolyses proceed *via* the N- or the O-protonated conjugate acid. We
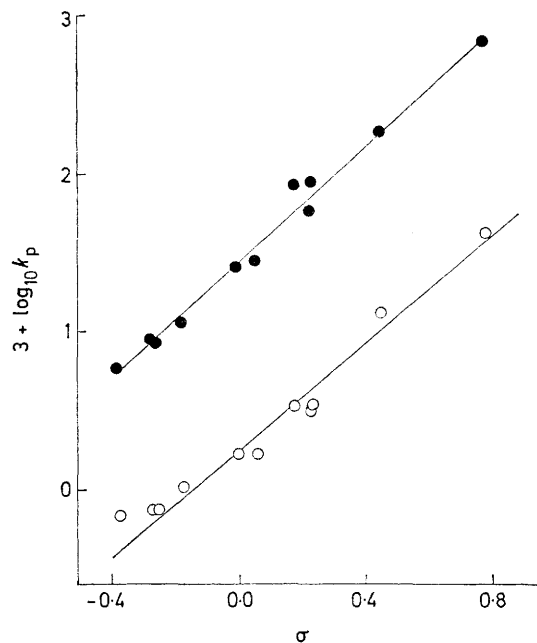

FIGURE 3 Hammett plot of $3 + \log_{10}k_p$ against σ for the hydrolysis of 4-X-acetanilides in 20% (w/w) H_2SO_4; ●, and in 50% (w/w) H_2SO_4, ○

TABLE 3

Analysis of rate data of 4-X-acetanilides in 20% (w/w) H_2SO_4 [a] and in 50% (w/w) H_2SO_4 [b] by the Hammett equation

Ordinate of of plot	σ Values		σ⁺ Values	
	correln. coefft.	ρ	correln. coefft.	ρ
$\log_{10}k_p$ [a]	0.993	1.87 ± 0.07	0.956	1.18 ± 0.12
$\log_{10}k_p$ [b]	0.982	1.60 ± 0.09	0.917	0.96 ± 0.14

have shown (see above and ref. 18) that the postulate of a two-term mechanistic pathway is not viable for acetanilides. Comparison of these present data with those for hydrolysis of 4-chlorobenzamides [25] under comparable conditions leads us to favour an A-2 reaction mechanism in which water attacks the N-protonated conjugate acid in the rate determining step. Both Moodie *et al.*[26] and Smith and Yates [27] have considered the possibility that

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[21] H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, 1958, **80**, 4979.
[22] R. J. Gillespie and T. Birchall, *Canad. J. Chem.*, 1963, **41** (a) 148; (b) 2642.
[23] M. Liler, *J.C.S. Perkin II* (a) 1972, 816; (b) 1974, 71.
[24] C. J. Giffney and C. J. O'Connor, unpublished results.
[25] C. J. Giffney and C. J. O'Connor, *J.C.S. Perkin II*, 1975, 1203.
[26] V. C. Armstrong, D. W. Farlow, and R. B. Moodie, *J. Chem. Soc. (B)*, 1968, 1099.
[27] C. R. Smith and K. Yates, *J. Amer. Chem. Soc.*, 1971, **93**, 6578.

hydrolysis takes place *via* the A_N^D2 (acid catalysed, bi-molecular, *N*-protonated cation, direct displacement) mechanism.

EXPERIMENTAL

Materials.—Concentrated AnalaR sulphuric acid was standardised against sodium hydroxide, and diluted with distilled water by weighing to give solutions of the required molarity.

Preparation, purification, and m.p.s of the acetanilides have been previously described.[1,8]

Measurement of Reaction Rates.—The acetanilides were hydrolysed using the method previously described.[1,2] The error in estimate of k_ψ is generally within $\pm 2\%$. For the slower runs the accuracy decreased to $\pm 5\%$ and these rates are quoted to only two significant figures in Table 1.

As the reaction proceeded the absorbance maximum of the carbonyl peak for acetanilide and the 4-Me, 4-F, and 4-NH$_2$ derivatives tended towards zero, while the position of $\lambda_{max.}$ remained unaltered. For the other acetanilides studied $\lambda_{max.}$ (aniline), the product, differed from that of $\lambda_{max.}$ (acetanilide) and a constant isosbestic point was noted throughout a kinetic run.

The hydrolysis of substituted acetanilides, in dilute and moderately concentrated acid, yields the corresponding anilines and these were identified by u.v. spectroscopy. The other product in the hydrolysis of these acetanilides is acetic acid.

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