Acid-catalysed Hydrolysis of Substituted Acetanilides

By **J. W. Barnett** and **Charmian J. O'Connor,*** Department of Chemistry, University of Auckland, New Zealand

The rate of hydrolysis of *N*-acetylsulphanilic acid has been measured over a wide range of acidities and temperatures in H_2SO_4. In H_2SO_4 (<75% w/w) the data fit well the Bunnett and Bunnett–Olsen criteria of an *A*-2 mechanism. In more concentrated acid Arrhenius parameters indicate a change to an *A*-1 mechanism and the rate increases with increasing acidity. Seven other substituted acetanilides exhibit this behaviour in H_2SO_4, and 2,4,6-tribromoacetanilide does so also in $HClO_4$. Evaluation of *w* and ϕ values confirm the existence of an *A*-1 mechanism.

WE recently reported[1] that the hydrolysis profile of *N*-acetylsulphanilic acid exhibited a maximum at 30—35% w/w H_2SO_4 and also[2] that the phenomenon of increasing rate with increasing acidity (>75% w/w H_2SO_4) was not uncommon with substituted acetanilides. Such behaviour has previously been observed for amides only in the case of the nitro-derivatives of acetanilide,[3,4] but it is well known in the hydrolysis of esters.[5,6]

RESULTS AND DISCUSSION

Basicity Constant.—We have determined the ionisation ratio $I = C_{BH^+}/C_B$ for *N*-acetylsulphanilic acid in sulphuric acid at 25 °C (Table 1). Using the relationship $C_{BH^+}/C_B = (A - A_B)/(A_{BH^+} - A)$ where A, A_B, and A_{BH^+} are the absorbances of the solution, unprotonated, and fully protonated substrate respectively at 251·5 nm (the absorbances all refer to the same total concentration of substrate), we have found that a plot of log I against $-H_A$[7] was linear (slope = 0·96, correlation coefficient = 0·997) and the value of pK_{BH^+}

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TABLE 1

Ionisation data for *N*-acetylsulphanilic acid in sulphuric acid at 25·0 °C

$C_{H_2SO_4}$ (mol l^{-1})	1·51	2·14	2·79	3·49
$\log_{10}I$	−0·970	−0·716	−0·519	−0·247
$-H_A$	0·58	0·88	1·13	1·39
$C_{H_2SO_4}$ (mol l^{-1})	4·88	6·51	7·41	
$\log_{10}I$	0·200	0·602	1·00	
$-H_A$	1·87	2·33	2·58	

(equal to H_A at half protonation) = −1·63 and we used this value in our calculations of α (the fraction of protonated substrate) = $h_A/(K_{BH^+} + h_A)$ which were necessary for analysing the rate data. A Bunnett and Olsen[8a] linear free-energy relationship (l.f.e.r.) plot [$(\log I + H_0)$ against $(\log C_{H^+} + H_0)$] of the same data gave a value of $pK_{BH^+} = -1·36$, $\phi = 0·44$ (correlation coefficient = 0·990). The values of pK_{BH^+} thus obtained differ by 0·27 log unit, in agreement with the hypothesis[8a] that the H_A function is too negative by *ca.* 0·3 log unit. Homer and Johnson[9] have suggested a lowering of the H_A scale by using pyridine 1-oxides to reanchor it, but this modification has not yet been used in a kinetic investigation.

TABLE 2

Hydrolysis of *N*-acetylsulphanilic acid in sulphuric acid. Values of 10^5k_ψ/s^{-1}

H_2SO_4 (% w/w)	t/°C							
	100·0	95·3	90·0	86·3	80·0	40·0	30·0	25·0
5·34	202							
9·94	392							
15·1	639							
20·0	785		334			7·21	3·65	2·30
25·1	830		420		223	9·60	5·04	3·05
30·1	854		492		255	11·7	6·65	3·32
35·0	859		528		255	10·9	6·24	3·27
40·0	815		502		249	9·29	5·12	2·54
44·9	756		420		187	6·48	3·14	1·58
50·2	541		266		160	3·91	1·75	
55·0	309		163		77·2	1·74	0·681	
60·0	128		64·9		34·2	0·609	0·218	
65·1	62·8		22·6		10·2		0·051	
70·0	16·3	8·99	5·71	3·64	1·81			
75·7	12·0	5·62	3·22	1·50	0·472			
80·0	14·2	7·36	5·03	2·09	1·78			
84·9		10·1	7·12	2·94	1·82			
90·0	44·5	26·1	18·0	7·80	4·05			
96·6	99·6	52·0	30·9	15·5	6·43			

Table 2 summarises the results obtained for the pseudo-first-order rate constants of hydrolysis, k_ψ, of *N*-acetylsulphanilic acid in sulphuric acid at various temperatures. The rate profiles are smooth curves with little scatter, and show a maximum between 30 and 35% w/w followed by a local minimum at *ca.* 77% w/w H_2SO_4. Table 3 shows the results of plotting $(\log_{10}k_\psi - \log_{10}\alpha)$ against $\log_{10}a_w$ (Bunnett *w* function)[10] and against $(\log_{10}C_{H^+} + H_0)$ (Bunnett–Olsen linear free energy relationship),[8b] for the data up to the local minimum. (The values of a_w were calculated at each temperature from water vapour pressures[11] by use of $a_w = P/P_0$ where P_0 is the vapour pressure of water at t °C and P that over the system, and values of H_0 were taken from measurements made up to 90 °C[12] at the nearest appropriate temperature to that of the rate data.) Both these criteria of mechanism give good correlations. The values of *w* increase with decreasing temperature but all lie in the range 1·2—3·3 said to be characteristic of water acting as a nucleophile in the rate-determining step. However, the values of ϕ are all >0·58, and therefore fall in the region of water acting as a proton-transfer agent. As we have previously observed[13] it seems that the limits of Bunnett's original classifications will have to be extended as more experimental data become available.

TABLE 3

Analysis of rate data for hydrolysis of *N*-acetylsulphanilic acid in sulphuric acid (<75% w/w) by use of Bunnett *w* and Bunnett–Olsen linear free energy relationships

	Bunnett *w*		Bunnett–Olsen l.f.e.r.	
t/°C	w[a]	Correlation coefficient	ϕ[b]	Correlation coefficient
100·0	2·41	0·985	0·70	0·992
90·0	2·36	0·999	0·74	0·983
80·0	2·41	0·997	0·75	0·979
40·0	2·57	0·999	0·70	0·987
30·0	2·77	0·999	0·77	0·987
25·0	2·86	0·999	0·60	0·993

[a] Standard deviation ≤0·03. [b] Standard deviation ≤0·05.

Table 4 gives the Arrhenius parameters for the hydrolysis of *N*-acetylsulphanilic acid as a function of acidity. Over the region of the maximum in the profile there is a

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slight increase in the values of E_a and $\log_{10}A$ but beyond the local minimum these values increase rapidly. (The data for 75·7% H_2SO_4 appear badly out of line with results for neighbouring acidities, and the difference is much greater than the experimental accuracy. This discrepancy is discussed later.) Similar, but less marked, increases in the values of E_a have been reported for the hydrolysis of some nitroacetanilides,[3,4] and were interpreted as indicative of a change from *A*-2 to an *A*-1 mechanism, but the details of the suggested mechanisms differed.

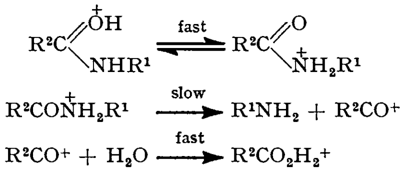
TABLE 4

Arrhenius parameters for hydrolysis of *N*-acetylsulphanilic acid in sulphuric acid

H_2SO_4 (% w/w)	20·0	25·1	30·1	35·0	40·0	44·9	50·2	55·0
E_a/kcal mol^{-1}	16·7	16·3	16·1	16·5	17·1	18·1	18·8	19·8
$\log_{10}A$/s^{-1}	8·58	8·42	8·39	8·59	8·98	9·50	9·76	10·1

H_2SO_4 (% w/w)	60·0	65·1	70·0	75·7	80·0	84·9	90·0	96·6
E_a/kcal mol^{-1}	20·9	22·6	28·2	38·7	28·2	28·1	31·8	35·6
$\log_{10}A$/s^{-1}	10·4	11·0	13·7	19·8	13·7	16·3	16·3	18·8

Duffy and Leisten[3] showed that beyond 70% w/w H_2SO_4 *p*-nitro- and 3,5-dinitro-acetanilide were completely converted into their conjugate acids and underwent hydrolysis according to the Scheme.



SCHEME

Vinnik *et al.*[4] state that in the range 70—100% w/w H_2SO_4 the concentration of un-ionised *o*-nitroacetanilide and 2,4-dinitroacetanilide will decrease, but that their conjugate acids and undissociated sulphuric acid molecules are reactive. The activated complex would thus incorporate the BH^+ ion and H_2SO_4.

From our measured value of pK_{BH^+}, *N*-acetylsulphanilic acid is 99% converted into its conjugate acid at 70% w/w H_2SO_4. Beyond this acidity we are therefore justified in treating *N*-acetylsulphanilic acid as a strong base (*i.e.*, $C_{BH^+} \gg C_B$) and by analogy with literature pK_{BH^+} values for other amides, it seems likely that the other substituted acetanilides we have used would be fully protonated beyond *ca.* 75% w/w H_2SO_4.

Table 5 shows the rate data for hydrolysis of a number of substituted acetanilides in >50% w/w H_2SO_4 and for 2,4-dinitro- and 2,4,6-tribromo-acetanilides in >50% w/w $HClO_4$.

In the series 4-fluoro-, 4-chloro-, 4-bromo-, and 4-iodo-acetanilides the magnitude of the increase in rate with increasing acidity increases along the series, and also the position of the local minimum shifts to lower acidity.

In >70% w/w H_2SO_4, the position of maximum absorbance for 3-hydroxy- and 4-methyl-acetanilide shifted rapidly to higher wavelength and then decreased. The final hydrolysis products were identified as 4-amino-2-hydroxybenzenesulphonic acid and 2-amino-5-methylbenzenesulphonic acid respectively. The sulphonated intermediates 3-hydroxy-4-sulpho- and 4-methyl-2-sulpho-acetanilide showed increasing rates of hydrolysis with increasing acidity.

The most dramatic increase in rate with increasing acidity in H_2SO_4 occurred for the hydrolysis of 2,4,6-tribromoacetanilide and we have found that the occurrence of a local minimum is not a specific property of sulphuric acid, since this substrate also shows an increasing rate with increasing acidity in perchloric acid. By contrast, such an increase was not observed for hydrolysis of 2,4-dinitroacetanilide in $HClO_4$ although its rate increase in H_2SO_4[4b] is the largest of those so far reported. 2,4-Dinitroacetanilide ($pK_{BH^+} = -4{\cdot}15$ on an H_0 scale)[4b] would not be fully protonated in 70% w/w $HClO_4$ and cannot therefore be considered a strong base.

Table 6 shows the results of plotting ($\log_{10}k_\psi - H_0$) against $\log_{10}C_{H^+}$ (Zucker–Hammett *A*-2 hypothesis modified for hydrolysis of a fully protonated substrate), $\log_{10}k_\psi$ against $\log_{10}a_w$ (Bunnett *w*), ($\log_{10}k_\psi - \log_{10}C_{H^+} - H_0$) against $\log_{10}a_w$ (Bunnett *w**), and $\log_{10}k_\psi$ against ($\log_{10}C_{H^+} + H_0$) (Bunnett–Olsen l.f.e.r.) for those substrates where the rate increases were sufficiently large over an adequate range of acidity to justify mathematical analysis. Although the correlation coefficients for the Zucker–Hammett *A*-2 hypothesis and the Bunnett *w** plots are overall better than for Bunnett *w* and Bunnett–Olsen l.f.e.r. plots, the values of the slopes of the Zucker–Hammett plots (17—35) are meaningless and the values of *w** (with the exception of the reaction in $HClO_4$) are all > -2 and are therefore indicative of water acting as a proton-transfer agent. The correlation coefficients for Bunnett *w* and Bunnett–Olsen l.f.e.r. plots are however generally quite good, and moreover the values of *w* and ϕ are all negative and fit clearly into the classification of water not being involved in the rate-determining step in these hydrolyses. It seems that an *A*-1 mechanism similar to that postulated by Duffy and Leisten is operative in this acid region and that *w* and ϕ values will prove to be useful supporting evidence to Arrhenius parameters in identifying *A*-1 mechanisms in amide hydrolyses.

In the region 70—80% w/w H_2SO_4 there are two mechanisms occurring in parallel, at comparable rates. The simple Arrhenius equation may not then be valid, and this may account for the anomalous values of E_a and $\log_{10}A$ for data of *N*-acetylsulphanilic acid in 75·7% w/w H_2SO_4 (Table 4).

EXPERIMENTAL

Materials.—Concentrated AnalaR sulphuric and perchlorid acids were standardised against sodium hydroxide, and were diluted with deionised water by weighing to give solutions of the required molarity. 4-Fluoroacetanilide (Koch–Light), recrystallised from aqueous ethanol, had m.p. 152 °C.

4-Chloro-, 4-bromo-, 4-iodo-, 3-hydroxy-, 4-methyl-, and 2,4,6-tribromo-acetanilides were prepared by acetylating the corresponding aniline (1 g) with acetic anhydride (20 ml) and concentrated sulphuric acid (2 drops) and were recrystallised respectively from aqueous acetic acid (m.p. 179 °C), ethanol (m.p. 168 °C), water (m.p. 184 °C), aqueous ethanol (m.p. 168 and 148 °C), and ethanol (m.p. 236 °C).

TABLE 5

Hydrolysis of substituted acetanilides in concentrated solutions of mineral acids

		$10^5k_\psi/\mathrm{s}^{-1}$							
		Sulphuric acid (% w/w)							
t/°C	Substituent	50·2	60·0	70·0	75·7	80·0	84·9	90·0	96·6
100·0	4-Fluoro		23·8	2·00		0·332		0·259	0·540
100·0	4-Chloro	222	23·5	1·93		0·449		0·477	1·12
105·0	4-Chloro		43·5	2·57		0·930		0·980	2·47
100·0	4-Bromo	179	31·9	2·23		0·574		0·921	1·44
105·0	4-Bromo		52·4	2·93		1·55		1·61	4·09
100·0	4-Iodo (II)	187	23·6	2·05	1·73	2·29	2·31	4·96	11·9
100·0	3-Hydroxy	116	26·3	13·5					
100·0	3-Hydroxy-4-sulpho (III)				25·6	44·5	103	189	297
100·0	4-Methyl	102	9·90	0·859					
100·0	4-Methyl-2-sulpho					0·905		1·83	4·31
100·0	2,4,6-Tribromo (IV)		97·3	170		258	310		578

		Perchloric acid (% w/w)		
		50·0	60·0	70·0
100	2,4,6-Tribromo (IV)	128	282	551
25	2,4-Dinitro	30·6	11·4	<0·1

TABLE 6

Analysis of rate data for hydrolysis of *N*-acetylsulphanilic acid (I) and other substituted acetanilides in H_2SO_4 (>75% w/w) by use of Zucker–Hammett, Bunnett w and w^*, and Bunnett–Olsen linear free-energy relationships

		Zucker–Hammett		Bunnett w		Bunnett w^*		Bunnett–Olsen l.f.e.r.	
Substrate [a]	t/°C	Slope	Correlation coefficient	w	Correlation coefficient	w^*	Correlation coefficient	ϕ	Correlation coefficient
(I)	100·0	28·3	0·991	−0·48	0·998	−1·70	0·999	−0·39	0·999
(I)	95·3	28·9	0·991	−0·52	0·987	−1·73	0·999	−0·41	0·980
(I)	90·0	28·4	0·993	−0·43	0·978	−1·56	0·997	−0·38	0·975
(I)	86·3	30·2	0·992	−0·49	0·988	−1·69	0·998	−0·40	0·981
(I)	80·0	28·3	0·990	−0·34	0·968	−1·62	0·999	−0·26	0·951
(II)	100·0	33·2	0·993	−0·51	0·997	−1·65	0·999	−0·45	0·993
(III)	100·0	28·4	0·997	−0·44	0·957	−1·64	0·992	−0·37	0·968
(IV)	100·0	20·9	0·991	−0·21	0·997	−1·57	0·992	−0·15	0·997
(IV) [b]	100·0	17·8	0·979	−0·52	0·990	−3·76	0·999	−0·16	0·995
(V) [c]	65·0	34·5	0·999	−0·48	0·994	−1·50	0·995	−0·47	0·999
(VI) [d]	25·0	29·8	0·999	−0·49	0·969	−1·51	0·968	−0·48	0·999

[a] See Table 5 for (II)—(IV). [b] In $HClO_4$ (>50% w/w). [c] (V) = 3,5-Dinitroacetanilide (ref. 3). [d] (VI) = 2,4-Dinitroacetanilide (ref. 4*b*).

N-Acetylsulphanilic acid was prepared by the method of Kloftz and Melchoir,[14] 2,4-dinitroacetanilide by the method of Duffy and Leisten [3] (m.p. 120 °C from ethanol).

Ionisation Spectra.—The changes in the spectrum of *N*-acetylsulphanilic acid in increasing concentrations of sulphuric acid at 25·0 °C were measured on a Cary 14 spectrophotometer ($\lambda_{max.}$ 251·5 nm).

Measurement of Reaction Rates.—The hydrolyses were carried out in sealed ampoules in constant-temperature baths. 2,4,6-Tribromoacetanilide does not have a suitable spectrum for direct spectrophotometric analysis and aliquot samples were therefore analysed by a modification of the diazonium method used by Duffy and Leisten.[3]

The hydrolyses of the other substituted acetanilides were followed spectrophotometrically by use of spectra recorded in the region of the $\lambda_{max.}$, *i.e.*, 4-fluoro (237 nm), 4-chloro (245 nm), 4-bromo (248 nm), 4-iodo (251 nm), 3-hydroxy (243 nm), 4-methyl (243 nm), and 2,4-dinitro (347 nm).

3-Hydroxy- and 4-methyl-acetanilides undergo rapid sulphonation in preference to hydrolysis in >70% w/w sulphuric acid. We observed this behaviour during the hydrolysis of acetanilide.[15] These sulphonations are accompanied by a shift in maximum absorbance to that of the intermediates 3-hydroxy-4-sulphoacetanilide ($\lambda_{max.}$ 251 nm) and 4-methyl-2-sulphoacetanilide ($\lambda_{max.}$ 244 nm), and the hydrolyses of these intermediates were followed at their $\lambda_{max.}$. Intermediates and products of the hydrolyses were identified as before.[15]

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

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