

## The Acid-catalysed Hydrolysis of Acetanilide

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The rate of hydrolysis of acetanilide has been measured over a wide range of acidities in HCl, H<sub>2</sub>SO<sub>4</sub>, and HClO<sub>4</sub>. In H<sub>2</sub>SO<sub>4</sub> ≥ 80% (w/w) acetanilide undergoes sulphonation in preference to hydrolysis. Application of the Bunnett criteria of mechanism fit the data in HCl and H<sub>2</sub>SO<sub>4</sub> well, whereas the data in HClO<sub>4</sub> are fitted by an empirical two-term rate equation. A revised value of the constant  $-pK_{AH^+}$  has been determined in each acid.

THE nitro-derivatives of acetanilide all show a rate minimum<sup>1,2</sup> in their hydrolysis profiles between 70 and 80% (w/w) H<sub>2</sub>SO<sub>4</sub> and this has been attributed to a change in mechanism from A-2 to A-1. These substituted anilides are quite weakly basic and consequently this change in mechanism occurs only in very concentrated acid. If this were a general phenomenon then acetanilide with a reported  $-pK_{AH^+}$  value of  $-0.61$ <sup>3</sup> should have displayed a unimolecular mechanism in

relationship (1)<sup>4</sup> where Abs, Abs<sub>A</sub>, and Abs<sub>AH<sup>+</sup></sub> are the absorbances of the solute in its partially protonated,

$$[AH^+]/[A] = (\text{Abs} - \text{Abs}_A)/(\text{Abs}_{AH^+} - \text{Abs}) \quad (1)$$

unprotonated, and fully protonated forms, respectively, at  $\lambda_{\text{max}, AH^+}$ . At the concentration of acetanilide used ( $7.4 \times 10^{-5}M$ ) these varied from Abs<sub>A</sub> = 0.665 to Abs<sub>AH<sup>+</sup></sub> = 0.543. Equation (1) does not take account of minor medium effects and impurity errors, and it is not

TABLE I

Ionisation ratios for acetanilide ( $7.4 \times 10^{-5}M$ ) in hydrochloric, sulphuric, and perchloric acids calculated using absorbances measured at 238 nm

Hydrochloric acid			Sulphuric acid			Perchloric acid		
$-H_A$	$c_{H^+}$	$\log_{10} I$	$-H_A$	$c_{H^+}$	$\log_{10} I$	$-H_A$	$c_{H^+}$	$\log_{10} I$
0.46	1.41	-0.757	0.48	1.31	-1.009	0.325	0.95	-0.811
0.73	2.00	-0.506	0.63	1.62	-0.794	0.57	1.50	-0.487
0.84	2.30	-0.165	0.87	2.18	-0.354	0.91	2.07	-0.233
1.34	2.87	-0.207	1.18	2.90	0.009	1.13	2.65	-0.014
1.44	4.00	0.201	1.38	3.49	0.059	1.36	3.28	0.218
1.55	4.45	0.247	1.62	3.98	0.139	1.89	4.70	0.791
1.86	5.50	0.635	2.30	6.10	1.006			
2.31	7.00	1.065						

reasonably dilute acid. Although the hydrolysis of acetanilide does show a rate minimum in concentrated solutions of sulphuric acid, this is caused by preliminary sulphonation to *N*-acetylsulphanilic acid. Measurement of the basicity constant of acetanilide shows the literature value<sup>3</sup> to be in error.

### RESULTS AND DISCUSSION

**Basicity Constant.**—We have determined the ionisation ratio  $I = [AH^+]/[A]$  for acetanilide in hydrochloric, sulphuric, and perchloric acids (Table I) by use of the

<sup>1</sup> J. A. Duffy and J. A. Leisten, *J. Chem. Soc.*, 1960, 853.

<sup>2</sup> M. I. Vinnik, I. M. Medvetskaya, L. R. Andreeva, and A. E. Tiger, *Russ. J. Phys. Chem.*, 1967, **41**, 128; M. I. Vinnik and I. M. Medvetskaya, *ibid.*, p. 947.

easy to specify a systematic error which could be due to such effects when one has very small differences between extinction coefficients of the two forms of an indicator. However, the spectra appeared very clean, reproducible, and reversible, and we believe that the u.v. spectrophotometric changes we observed represent the equilibrium protonation of acetanilide, and are not an artifact of medium effects, as was observed for the spectra of benzonitrile in acid solution.<sup>5</sup>

<sup>3</sup> I. Heilbron, 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, 1937, vol. 1, p. 3, as quoted by J. A. Duffy and J. A. Leisten (Ref. 1).

<sup>4</sup> K. Yates and J. B. Stevens, *Canad. J. Chem.*, 1965, **43**, 529.

<sup>5</sup> C. J. Hyland and C. J. O'Connor, *J.C.S. Perkin II*, following paper.

Table 2 shows the results of plotting  $\log_{10} I$  against  $-H_A$ .<sup>6</sup> Only values of  $\log_{10} I$  within the range  $\pm 1$  were substituted in these plots. The slopes are close to unity, and thus the values of  $-\text{p}K_{\text{AH}^+} = -H_A$  at  $\log_{10} I = 0$  can be regarded as valid functions within the limitations of the basic uncertainties discussed above. The limits on  $-\text{p}K_{\text{AH}^+}$  given in Table 2 were obtained from least-squares plots, but bearing in mind the small difference

TABLE 2

Values of  $-\text{p}K_{\text{AH}^+}$  of acetanilide in hydrochloric, sulphuric, and perchloric acids at 25.0 °C

Acid	$-\text{p}K_{\text{AH}^+}$	Slope of $\log_{10} I$ vs. $-H_A$	Correln. coefft.
HCl	$1.23 \pm 0.02$	$0.97 \pm 0.04$	0.993
H <sub>2</sub> SO <sub>4</sub>	$1.32 \pm 0.02$	$1.04 \pm 0.07$	0.989
HClO <sub>4</sub>	$1.12 \pm 0.01$	$1.00 \pm 0.03$	0.998

in absorbance and the limitation of the spectrophotometer ( $\pm 0.002$  absorbance units), more realistic error

( $H_0 + \log_{10} c_{\text{H}^+}$ ) (Bunnett-Olsen linear free-energy relationship).<sup>9</sup> Both these criteria of mechanism give good correlations for the data in HCl and H<sub>2</sub>SO<sub>4</sub>. The values of  $w$  generally lie in the range 1.2–3.3 said to be characteristic of water acting as a nucleophile in the r.d.s., but the values of  $\phi$  are all  $\geq 0.58$ , and therefore fall in the region indicative of water acting as a proton-transfer agent. It would seem that the limits of Bunnett's original classifications will have to be extended as more experimental data becomes available.

The data in HClO<sub>4</sub> do not correlate well with these criteria of mechanism. We have previously found a similar lack of correlation for rates of hydrolysis of benzamide, *N*-methylbenzamide, and *NN*-dimethylbenzamide in HCl, H<sub>2</sub>SO<sub>4</sub>, and HClO<sub>4</sub>.<sup>7</sup> We have found, however, that all these data correlate very well with a rate equation<sup>7,10</sup> which allows the acid hydrolysis of amides to proceed by two distinct mechanistic paths involving both oxygen- and nitrogen-protonated

TABLE 3

Hydrolysis of acetanilide in concentrated solutions of mineral acids

Hydrochloric acid 25.0 °C		Hydrochloric acid 80.0 °C		Sulphuric acid 25.0 °C		Sulphuric acid 80.0 °C		Perchloric acid 25.0 °C		Perchloric acid 80.0 °C	
$c_{\text{H}^+}$	$10^5 k_{\psi}/\text{s}^{-1}$	$c_{\text{H}^+}$	$10^5 k_{\psi}/\text{s}^{-1}$	$c_{\text{H}^+}$	$10^5 k_{\psi}/\text{s}^{-1}$	$c_{\text{H}^+}$	$10^5 k_{\psi}/\text{s}^{-1}$	$c_{\text{H}^+}$	$10^5 k_{\psi}/\text{s}^{-1}$	$c_{\text{H}^+}$	$10^5 k_{\psi}/\text{s}^{-1}$
1.42	0.416	1.40	70.3	1.10	0.394	1.48	82.2	1.05	0.287	0.50	25.8
2.74	0.880	2.13	97.7	1.72	0.669	1.18	93.3	1.62	0.403	1.06	48.3
4.45	0.951	2.95	126	2.33	0.745	2.40	112	2.23	0.440	2.25	80.7
6.05	0.572	3.75	147	3.02	0.781	3.15	117	2.88	0.431	3.60	59.3
7.67	0.270	4.61	138	3.72	0.735	3.83	116	3.58	0.358	5.20	36.6
9.45	0.129	5.25	118	4.51	0.594	4.53	106	4.34	0.266	7.10	17.2
		6.05	101	5.32	0.343	6.25	60.8	5.15	0.210		
		7.70	79.5	6.19	0.203	7.11	31.6				
		10.1	18.4			9.16	9.16				

limits of  $-\text{p}K_{\text{AH}^+}$  would be approximately  $\pm 0.1$ . However, it does seem that the values of  $-\text{p}K_{\text{AH}^+}$  obtained differ for the three mineral acids, as do the basicity constants of benzamide, *N*-methylbenzamide, and *NN*-dimethylbenzamide.<sup>7</sup>

Table 3 summarises the results obtained for the hydrolysis of acetanilide in acid solutions. The pseudo-first-order rate constants of hydrolysis,  $k_{\psi}$ , must be corrected for the fraction,  $\alpha$ , of protonated substrate before an attempt at kinetic analysis is made. Equations

$$\alpha = [\text{AH}^+]/([\text{AH}^+] + [\text{A}]) = h_{\text{A}}/(K_{\text{AH}^+} + h_{\text{A}})$$

applicable to hydrolysis of moderately basic substrates have been used in the application of the data in Table 3 to the criteria of mechanism which follow. Where the data are available, values of  $H_0$  and  $a_w$  appropriate to the temperature of the rate measurements have been substituted into the equations of criteria of mechanism. This method has been described previously.<sup>7</sup>

Table 4 shows the results of plotting  $(\log_{10} k_{\psi} - \log_{10} \alpha)$  against  $\log_{10} a_w$  (Bunnett  $w$  function)<sup>8</sup> and against

TABLE 4  
Analysis of rate data for hydrolysis of acetanilide by use of Bunnett  $w$  and Bunnett-Olsen l.f.e.r. relationships

Acid	$t/^\circ\text{C}$	Bunnett $w$		l.f.e.r.	
		$w$	Correln. coefft.	$\phi$	Correln. coefft.
HCl	80.0	2.46	0.990	0.58	-2.17
	25.0	2.88	0.996	0.65	-4.32
H <sub>2</sub> SO <sub>4</sub>	80.0	2.67	0.987	0.67	-2.00
	25.0	3.95	0.989	0.71	-4.14
HClO <sub>4</sub>	80.0	2.86	0.892	0.58	-2.33
	25.0	4.37	0.971	0.70	-4.52

transition states. Table 5 shows the fit of this equation (2) for the hydrolysis data of acetanilide. We have

$$k_{\psi} = k_{\text{N}}(1 - \alpha)c_{\text{H}^+}a_w + k_{\text{O}}\alpha a_w \quad (2)$$

plotted the data in two forms

$$k_{\psi}/\alpha a_w = k_{\text{N}}c_{\text{H}^+}(1 - \alpha)/\alpha + k_{\text{O}} \quad (3)$$

and

$$k_{\psi}/c_{\text{H}^+}(1 - \alpha)a_w = k_{\text{N}} + k_{\text{O}}\alpha/c_{\text{H}^+}(1 - \alpha) \quad (4)$$

<sup>8</sup> J. F. Bunnett, *J. Amer. Chem. Soc.*, 1961, **83**, 4956, 4968, 4973, 4978.

<sup>9</sup> J. F. Bunnett and F. P. Olsen, *Canad. J. Chem.*, 1966, **44**, 1899.

<sup>10</sup> C. A. Bunton, C. J. O'Connor, and T. A. Turney, *Chem. and Ind.*, 1967, **43**, 1385.

<sup>6</sup> (a) K. Yates, J. B. Stevens, and A. R. Katritzky, *Canad. J. Chem.*, 1964, **42**, 1957; (b) K. Yates and J. C. Riordan, *ibid.*, 1965, **43**, 2328; (c) K. Yates, personal communication.

<sup>7</sup> 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.

where equation (3) gives a more reliable value of  $k_N$  (the rate constant for hydrolysis by the  $N$  protonated path) and equation (4) a more reliable value of  $k_O$  (the rate constant for hydrolysis by the  $O$  protonated pathway).

TABLE 5

Analysis of rate data for hydrolysis of acetanilide by use of a two-term rate equation

Acid	$t/^\circ\text{C}$	Equation (3)		Equation (4)	
		$10^5 k_N / \text{mol}^{-1} \text{s}^{-1}$	Correln. coefft.	$10^5 k_O / \text{s}^{-1}$	Correln. coefft.
HCl	80.0	47.5	0.960	62.3	0.914
	25.0	0.321	0.929	0.341	0.975
$\text{H}_2\text{SO}_4$	80.0	62.1	0.982	33.3	0.923
	25.0	0.403	0.982	0.177	0.738
$\text{HClO}_4$	80.0	50.1	0.998	45.3	0.994
	25.0	0.310	0.999	0.172	0.992

Only the data in  $\text{HClO}_4$  give good correlations of these plots.

We have recently shown<sup>11</sup> that, generally, rate constants for acid hydrolysis of amides which do not fit the well accepted criteria of reaction mechanism<sup>8,9</sup> seem to fit this empirical two-term rate equation. We do not, however, suggest that equation (2) should be applied to all acid-catalysed amide hydrolysis data.

**Sulphonation.**—In  $\text{H}_2\text{SO}_4 > 70\%$  (w/w) (11.5M) the position of maximum absorbance shifted rapidly from 238 to 252 nm to form an intermediate identified as  $N$ -acetylsulphanilic acid, which then hydrolysed to 4-aminobenzenesulphonic acid. Details of this sulphonation reaction<sup>12</sup> and a report on the acid-catalysed hydrolysis of the intermediate<sup>13,14</sup> have been published.

#### EXPERIMENTAL

**Materials.**—Acetanilide (B.D.H.) was recrystallised from hot water (m.p. 113.5–114.0 °C).

Concentrated AnalaR hydrochloric, sulphuric, and perchloric acids were standardised against sodium hydroxide, and were diluted with deionised water by weighing to give solutions of the required molarity.

**Ultraviolet Spectra.**—The changes in the spectrum of acetanilide,  $7.4 \times 10^{-5}\text{M}$ , in increasing concentrations of

hydrochloric, sulphuric, and perchloric acids at 25.0 °C were measured on a Shimadzu QV.50 spectrophotometer at 238 nm. The value of  $\text{Abs}_A$  was taken as the value in water and the value of  $\text{Abs}_{\text{AH}^+}$  was the constant absorbance value obtained in solutions  $\geq 25\%$  (w/w) hydrochloric acid,  $\geq 60\%$  (w/w) sulphuric acid and in solutions of  $\geq 55\%$  (w/w) perchloric acid. At  $\lambda_{\text{max}} = 238 \text{ nm}$   $\log_{10} \epsilon_A = 3.95$  and  $\log_{10} \epsilon_{\text{AH}^+} = 3.86$ . It should be noted that the extinction coefficient of protonated acetanilide is less than that for acetanilide. This is opposite from the normal behaviour of amides, but similar behaviour has been found with ureas.<sup>15</sup> However, the measurements relate to a true equilibrium situation since 1 ml samples of stock solution ( $7.4 \times 10^{-4}\text{M}$ ) in water and 70% (w/w)  $\text{HClO}_4$  gave identical spectra when diluted to 10 ml of 20% (w/w)  $\text{HClO}_4$  with acid and water respectively.

**Measurement of Reaction Rates.**—Hydrolysis reactions at  $80.0 \pm 0.1$  °C were carried out in an oil-bath maintained at the required temperature by using a Gallenkamp contact thermometer, Klaxon stirrer, and a heating element. The hydrolysis reactions at  $25.0 \pm 0.1$  °C were carried out in a water-bath fitted with a Tecam (Techne, Cambridge) temperature unit.

Acetanilide (*ca.*  $7 \times 10^{-4}\text{M}$ ) was dissolved in 10 ml of the appropriate acid. 1 ml aliquots, sealed in ampoules, were removed at time intervals and were diluted 10 times before spectrophotometric analysis of the decrease in absorbance between 235 and 245 nm. Values of  $k_p$ , calculated at several wavelengths from slopes of plots of  $\log_{10} (\text{Abs}_t - \text{Abs}_\infty)$  against  $t$  (where  $\text{Abs}_t$  and  $\text{Abs}_\infty$  are the absorbances of the aliquots at time  $t$  and at infinite time respectively) agreed within  $\pm 2\%$ .

**Product Analysis.**—On hydrolysis, acetanilide produces the anilinium ion,  $\lambda_{\text{max}} = 204 \text{ nm}$  ( $\epsilon_{\text{max}} = 7500$ ) and acetic acid,  $\lambda_{\text{max}} = 204 \text{ nm}$  ( $\epsilon_{\text{max}} = 60$ ). Under the conditions of the hydrolysis reactions, it was not possible to identify the products. Therefore solutions of acetanilide ten times more concentrated than under the kinetic conditions were heated for the time required for complete hydrolysis in solutions of hydrochloric acid [5–35% (w/w)], perchloric acid [10–70% (w/w)], and sulphuric acid [10–75% (w/w)]. Peaks were then observed at 260.5, 254.6, 248.7, and 249 nm and these agreed well with the spectrum of pure aniline. It was not possible to identify acetic acid under these conditions.

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<sup>11</sup> J. W. Barnett, C. J. Hyland, and C. J. O'Connor, *Chem. Comm.*, 1972, 720.

<sup>12</sup> J. W. Barnett and C. J. O'Connor, *Chem. and Ind.*, 1970, 36, 1172.

<sup>13</sup> J. W. Barnett and C. J. O'Connor, *J.C.S. Perkin II*, 1972, 2378.

<sup>14</sup> J. W. Barnett and C. J. O'Connor, *Tetrahedron Letters*, 1971, 2164.

<sup>15</sup> J. W. Barnett and C. J. O'Connor, unpublished results.