Hydrolysis of Phenylureas. Part II.[1] Hydrolysis in Acid and Aqueous Solutions

By **C. Janet Giffney** and **Charmian J. O'Connor,*** Chemistry Department, University of Auckland, Private Bag, Auckland, New Zealand

The rate constants of hydrolysis of 4-methyl-, 4-methoxy-. 4-ethoxy, 4-isopropyl-, 4-n-butyl-, 4-chloro-, 4-bromo-. 4-nitro-. and 3-nitro-phenylurea have been measured in aqueous H_2SO_4 (0.5—98% w/w) at 101.0°. The rate profiles exhibit a bell shape up to intermediate acidities. followed by a localised minimum, and then an increase in rate. In acidities up to the minimum application of the standard criteria of mechanism for hydrolysis of the *O*-protonated conjugate acid have proved unsatisfactory. The rate constants of hydrolysis of 4-chloro- and 4-methyl-phenylurea have also been measured in 2.5—37% (w/w) HCl and 5—60% (w/w) $HClO_4$ and in mixtures of LiCl–HCl at 101.0°. Results show that there is a strong dependence on water activity but that the counter anion has little effect. Rate constants of hydrolysis of 4-fluoro- and 3-methyl-phenylurea. the phenylureas listed above. and also phenylurea have been measured in water (pH 6.48). and these differ little from the ' acid-catalysed ' rate constants. A new mechanism of hydrolysis is postulated, for which water acts as a proton transfer agent to either the unprotonated species or the minor *N*-protonated conjugate acid. Solvent deuterium isotope effects and Hammett ρ constants support the new mechanism. Electron donating substituents cause sulphonation in >70% (w/w) H_2SO_4 and a mechanism of hydrolysis at these higher acidities is postulated as *A*-1 decomposition of the *O*-protonated conjugate acids.

IN contrast to the wealth of information available on acid hydrolysis of amides, there is a paucity of data for ureas. Moreover, existing postulates are conflicting. Shaw and Walker[2] proposed that ureas decompose *via* intramolecular hydrogen transfer and dissociation of the activated complex according to Scheme 1, which specifically involves an *N*-bound proton in decomposition. Moodie *et al.*[3] originally postulated that the rate-determining step in the unimolecular decomposition of urea and ethylurea involved the free base at low acidities and the conjugate acid at high acidities, but this mechanism which allowed reaction to take place by paths which are independent of water activity did not fit the data for hydrolysis of phenylurea and its 3-Me and 4-F derivatives.[1] The values of log*A* obtained by Moodie *et al.*[3] for ureas did not support a unimolecular mechanism and later Farlow and Moodie[4] suggested that the reaction at intermediate acidities, 60—85% (w/w) H_2SO_4, is a bimolecular one between water and the diprotonated ureas. In contrast to the profiles exhibited by urea, *NNN'N'*-tetramethylurea and *O*-methylisourea, for which a shallow maximum was found in the range 60—85% (w/w) H_2SO_4,[3,4] those for the phenylureas[1] were

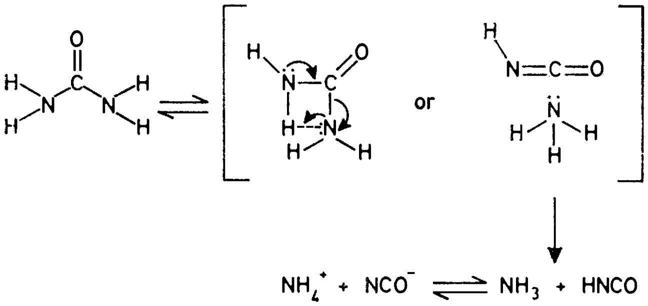
---

[1] Part I, C. J. O'Connor and J. W. Barnett, *J.C.S. Perkin II*, 1973, 1457.

[2] W. H. R. Shaw and D. G. Walker, *J. Amer. Chem. Soc.*, (*a*) 1956, **78**, 5769; (*b*) 1957, **79**, 2681; (*c*) p. 3683; (*d*) p. 4329; (*e*) 1958, **80**, 5337.

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

[4] D. W. Farlow and R. B. Moodie, *J. Chem. Soc.* (*B*), 1971, 407.



Scheme 1

found to have a sharp maximum at *ca.* 12.5% (w/w) H_2SO_4. Moreover, up to 45% (w/w) H_2SO_4 the values of E_a and $\Delta S^\ddagger$ remain essentially constant and are typical of a unimolecular mechanism. In 50% and 60% (w/w) H_2SO_4 the values of E_a and $\Delta S^\ddagger$ decrease markedly in the direction expected for a change to a bimolecular reaction mechanism. We have measured the basicity constants, K_{BH^+}, of a series of phenylureas [5,6] and have found that the extent of *O*-protonation, which follows the H_A acidity function, is dependent on the substituent (Hammett ρ 1.15).[5] This present study using bases of differing strengths was undertaken in an attempt to examine the present controversies. It had been hoped that the stronger bases would confirm the postulate of a change in mechanism by allowing it to occur in more dilute acid.

RESULTS AND DISCUSSION

Hydrolysis of Phenylureas.—4-Methyl-, 4-ethoxy-, 4-methoxy-, 4-isopropyl-, 4-n-butyl-, 4-chloro-, 4-bromo-, 3-nitro-, and 4-nitro-phenylurea have been hydrolysed in aqueous sulphuric acid solutions (0.5—98% w/w) at 101.0°. The rate constants of hydrolysis, k_ψ, are given in Table 1, and Figure 1 shows typical rate profiles.

The above phenylureas as well as 4-fluoro- and 3-methyl-phenylurea and phenylurea have been hydrolysed in water (pH 6.48), and the rate constants of hydrolysis, k_ψ, are given in Table 1.

The rate constants of hydrolysis of 4-methyl- and 4-chloro-phenylureas have also been measured in 2.5—37% (w/w) HCl and 5—60% (w/w) $HClO_4$ at 101.0° and are given in Table 2. The rate profiles for the hydrolysis of 4-methylphenylurea in H_2SO_4, HCl, and $HClO_4$ are given in Figure 2, the rates being plotted against the water activity, a_w, in order to compare the catalytic effectiveness of the three acids. Similar profiles are obtained for 4-chlorophenylurea. At a given a_w there is little difference in the rate constants of hydrolysis in the different acids, although k_ψ decreases in the order HCl $\geqslant H_2SO_4 > HClO_4$. This trend is similar, but much less marked than that observed in the *A*-2 hydrolysis of

Table 1

Rate constants of hydrolysis of substituted phenylureas in sulphuric acid and water at 101°

					$10^5\ k_\psi/s^{-1}$				
C_{H^+}/M	4-Cl	4-Br	3-NO_2	4-NO_2	4-MeO	4-EtO	4-Me	4-Pr^i	4-Bu^n
0.058	9.00	8.65	6.32	5.60	10.9	10.5	11.3		
0.11	9.39	8.85	6.53	5.90	12.8	12.5	12.2		
0.28	10.4	10.3	7.50	6.08	14.6	14.1	15.6		
0.55	11.9	12.6	8.06	6.40	17.0	16.7	18.1	19.3	18.7
0.71					17.7	17.3	19.7		
1.08	13.5	15.0	9.92	7.52	17.4	17.7	19.7	21.1	20.8
1.37	14.9				16.5	16.7	18.7		
1.68	15.8	16.0			14.4	15.2	17.5	19.5	19.3
2.01	16.0	16.3							
2.38	16.2	16.4	12.7	11.6	11.7	12.4	15.4	16.6	15.7
2.71	16.1	16.4							
3.06	15.2	16.1			9.56	9.96	13.2	13.9	13.8
3.78	13.9	14.4	17.4	18.2	7.29	7.68	10.5	11.7	11.6
4.52	12.7	12.9	19.1		5.30	5.86	8.06		
5.33	10.4	10.8	20.1	24.0	3.81	4.03	5.61	6.03	5.93
6.21	8.60	8.98	20.7	28.1	2.71	3.04	4.13		
7.15	7.06	7.24	20.2	31.2	1.92	2.19	2.88	3.11	2.99
8.10			18.8	34.8					
9.15	4.07	4.80	17.0	38.6	1.03	1.35	1.35	1.33	1.47
10.30				39.8					
11.33	2.04	1.58	11.8	39.6	1.01	1.25	0.78	0.81	0.92
12.72				38.2	1.16	1.14	1.06		
14.07	0.86	0.91	8.56	37.0	1.20	1.09	2.75	2.87	3.07
15.40	0.68	0.85		37.2	1.24	0.98	6.95	7.74	7.32
16.65	0.63	0.72	5.44	42.2	1.84	1.76	8.92	10.9	9.02
18.3	3.90	3.92	4.75	82.7	4.36	3.94	10.8	13.1	10.6
pH 6.48 *	4.99	5.12	5.31	4.22	3.98	4.03	4.24	4.26	4.31
	3-Me	H	4-F						
pH 6.48 *	4.36	4.38	4.73						

* k_w was evaluated from spectra after addition of acid. Rate constants of hydrolysis evaluated from spectra before addition of acid were $\leqslant \pm 7\%$ of these values.

---

[5] C. J. Giffney and C. J. O'Connor, *J.C.S. Perkin II*, 1975, 1206.

[6] J. W. Barnett and C. J. O'Connor (*a*) *J.C.S. Chem. Comm.*, 1972, 653; (*b*) *J.C.S. Perkin II*, 1973, 1331.

carbamates,[7] anhydrides,[8] amides,[9] esters,[10] nitrones, and oxaziridines.[11] In all these latter cases the rates decrease in the order HCl > H_2SO_4 > $HClO_4$ and the salt effects are, at least in part, caused by the fact that electrolytes have specific effects upon the activity coefficient, f_s, of the substrate.[12,13]

Since the rates in acid solution seem to be influenced largely by decreasing water activity and are almost independent of anion effect, the effect of decreasing water activity was studied on the hydrolysis of 4-methyl- and 4-chloro-phenylureas in aqueous and in hydrochloric acid solutions with added lithium chloride. The water activity in these lithium chloride solutions was taken as being equal to the water activity in hydrochloric acid solutions of equivalent concentration.[14] Values of k_ψ and corresponding values of a_w are given in Table 3 and indicate that the addition of small amounts of lithium chloride to aqueous solutions does not affect the reaction rate. But over a wider range of lithium chloride concentrations the rate of reaction decreases. This indicates that the unprotonated substrate decomposes by a mechanism which involves the water activity.

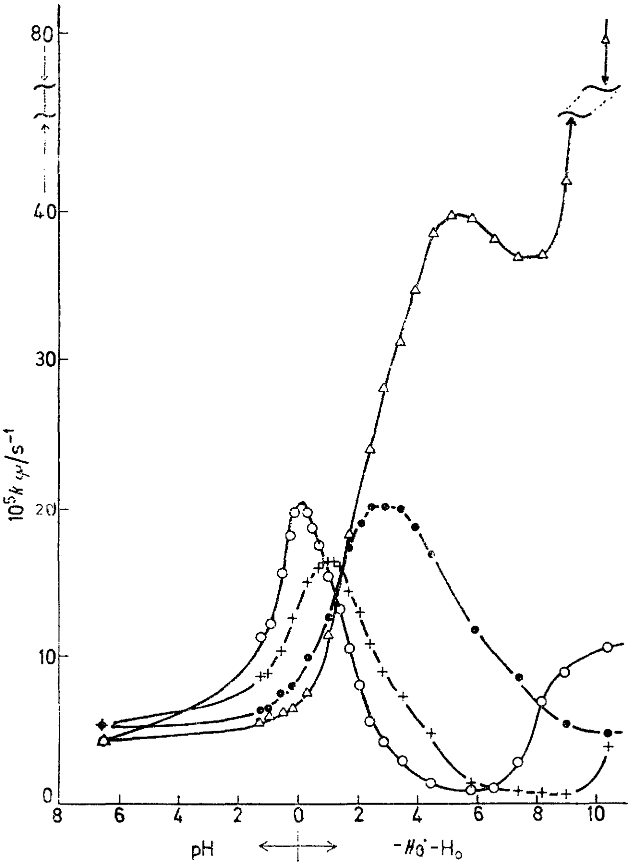


FIGURE 1 Typical profiles for rate constants of hydrolysis, k_ψ, against acidity for substituted (X) phenylureas in H_2SO_4 at 101.0°: ○, X = 4-Me; +, X = 4-Br; ●, X = 3-NO$_2$; Δ, X = 4-NO$_2$

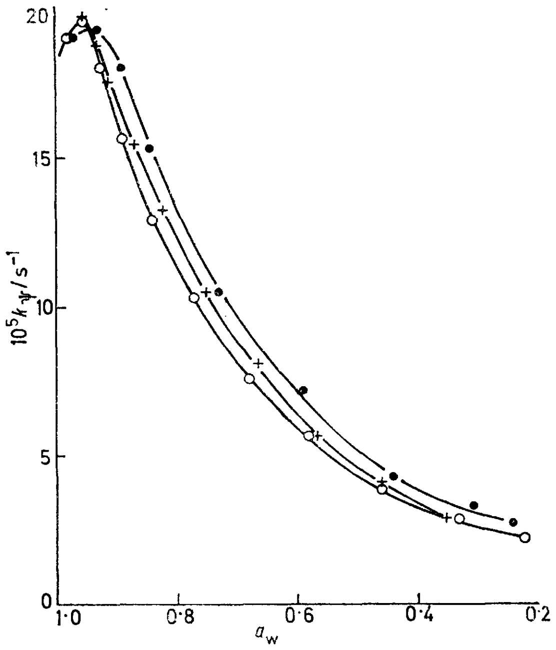


FIGURE 2 Profiles for rate constants of hydrolysis, k_ψ, against water activity, for hydrolysis of 4-methylphenylurea in: +, H_2SO_4; ●, HCl; and ○, $HClO_4$ at 101.0°

TABLE 2

Rate constants of hydrolysis of 4-methyl- and 4-chloro-phenylureas in HCl and $HClO_4$ at 101.0°

HCl and $HClO_4$ at 101.0°

C_{HCl}/M	$10^5k_\psi/s^{-1}$		C_{HClO_4}/M	$10^5k_\psi/s^{-1}$	
	4-Me	4-Cl		4-Me	4-Cl
0.71	19.0	13.3	0.51	19.0	11.4
1.40	19.3	16.0	1.05	19.6	14.4
2.11	18.0	16.9	1.62	18.0	16.1
2.87	15.3	16.9	2.23	15.7	16.3
4.43	10.5	15.5	2.88	12.9	15.0
6.06	7.20	12.7	3.58	10.3	13.7
7.65	4.30	9.63	4.30	7.54	12.1
9.41	3.31	7.84	5.15	5.62	11.1
10.57	2.71	6.99	6.02	3.83	9.11
11.68	2.42	6.22	6.98	2.85	7.06
			8.01	2.20	6.26
			9.13	1.73	4.19

We have recently measured [5,6] the basicity constants of all the phenylureas whose rate constants of hydrolysis we now report. Values of $pK_{BH^+} = m_AH_A^{\frac{1}{2}}$ (where m_A is the slope of a plot of $\log_{10}C_{BH^+}/C_B$ against H_A, and $H_A^{\frac{1}{2}}$ is the value of H_A when $C_{BH^+} = C_B$) enable us to calculate the fraction of *O*-protonated conjugate acid, $a = h_A/(K_{BH^+} + h_A)$, of the substrate, or alternatively the fraction $(1 - a)$ of unprotonated substrate.

---

[7] R. B. Moodie and R. Towill, *J.C.S. Perkin II*, 1972, 184.

[8] C. A. Bunton and J. H. Fendler, *J. Org. Chem.*, 1966, **31**, 3764.

[9] 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.

[10] C. A. Bunton, J. H. Crabtree, and L. Robinson, *J. Amer. Chem. Soc.*, 1968, **90**, 1258.

[11] C. J. O'Connor, E. J. Fendler, and J. H. Fendler, *J.C.S. Perkin II*, 1973, 1744.

[12] F. A. Long, F. B. Dunkle, and W. F. McDevit, *J. Phys. Colloid. Chem.*, 1951, **55**, 829.

[13] F. A. Long and D. McIntyre, *J. Amer. Chem. Soc.*, 1954, **76**, 3243.

[14] R. A. Robinson and R. H. Stokes, 'Electrolyte Solutions,' Butterworths, London, 1959.

In contrast to the acid-catalysed hydrolysis of amides[15] where the maximum in the rate profile is 10^4 times greater than the uncatalysed rate, for phenylureas the maximum rate of k_ψ (Table 1) is less than one order of magnitude greater than the uncatalysed rate, k_w, at pH 6.48 (Table 1). Therefore before any attempt at deducing the mechanism of the acid-catalysed reaction can be attempted the contribution to total k_ψ of the reaction by unprotonated substrate must be allowed for using equation (1).

TABLE 3

Rate constants for the hydrolysis of 4-methyl- and 4-chloro-phenylurea in aqueous and HCl solutions with added LiCl at 101.0°

	H_2O			C_{HCl} 0.71M		C_{HCl} 1.40M		C_{HCl} 7.63M	
		$10^5k_\psi/s^{-1}$		$10^5k_\psi/s^{-1}$		$10^5k_\psi/s^{-1}$		$10^5k_\psi/s^{-1}$	
LiCl added (mol)	a_w	4-Me	4-Cl	4-Me	4-Cl	4-Me	4-Cl	4-Me	4-Cl
0	1.00	4.24	4.99	19.0	13.3	19.3	16.0	4.30	9.63
0.5	0.98	4.25	4.98						
1.0	0.96	4.16	4.99	17.6	12.6	16.9	14.4	3.73	8.65
1.5	0.94	3.98							
2.0	0.92	3.94	4.41	16.3	12.0	15.0	13.3	3.38	7.54
4.0	0.80	3.05	3.55	13.4	10.2	11.6	11.4	2.34	6.49
6.0	0.68	2.16	2.56	12.1	9.60	10.8	11.3		

$$k' = k_\psi - k_w a_w(1 - a) \qquad (1)$$

Plots of k' against acidity are very similar to those shown in Figure 1. All substrates exhibit a bell shaped profile from low to intermediate acidities, followed by a localised minimum (except for 3-nitrophenylurea) and a subsequent increase in rate with increasing acid concentration. Maximum values of k' and k_ψ are observed to occur at the same acidity, although $k'_{(\max.)}$ is 19% smaller than $k_{\psi(\max.)}$ for the most strongly basic substrate, 4-methoxyphenylurea, but only 4% smaller for the most weakly basic substrate, 4-nitrophenylurea. In the past such profiles have been interpreted in terms of an *A*-2 reaction of the conjugate acid over the region of the bell-shaped profile, followed by an *A*-1 reaction of the conjugate acid at higher acidities after the localised minimum. Thus rate constants of hydrolysis of amides,[9,16] esters,[17] *N*-acylthioureas,[18] and of acetanilides[15] were interpreted cleanly as above by using the Yates r modification[19] of the Bunnett w criterion[20] of mechanism and also by using the Bunnett–Olsen linear free energy relationship (l.f.e.r.).[21] Certainly our original hope that the basicity of the substrate would influence the position of the maximum and minimum in the profiles has been realised. The more basic the substrate, the lower are the acidities at which the maximum and minimum occur, and *vice versa*. But correction of k' for degree of *O*-protonated substrate [in acidities up to *ca.* 50% (w/w) H_2SO_4] and application of the Yates r and Bunnett–Olsen criteria of mechanism according to standard formulations for moderately basic substrates[22] lead to curved plots and values of r and ϕ cannot be evaluated. Indeed the only criterion of mechanism which gives linear plots is the Zucker–Hammett *A*-1 equation, $[\log_{10}k' - \log_{10}(1 - a)]$ against H_A, for which linear correlation coefficients of 0.98 ± 0.01 were obtained, but the slopes were only 0.3 ± 0.1 and thus do not satisfy the criterion of unit value. The usual explanation of bell-shaped profiles, *i.e.* of an *A*-2 reaction of the *O*-protonated conjugate acid is therefore not validated for phenylureas.

We must conclude that the *O*-protonated conjugate acid is not decomposed at low to intermediate acidities. Nevertheless, the shape of the profiles leads us to believe that, contrary to Scheme 1, a protonated species is involved. We therefore suggest that it is the *N*-protonated urea which is the reactive entity. As for the *O*-protonated urea, an initial increase in acid concentration at low acidities will increase the concentration of the minor *N*-protonated urea, according to equilibrium (2).

$$H^+ + PhNHCONH_2 \overset{K_N}{\rightleftharpoons} PhNHCO\overset{+}{N}H_3 \qquad (2)$$

The concentration of *N*-protonated urea will, however, reach a maximum and any further increase in acid concentration will cause a decrease in concentration of *N*-protonated urea as the equilibria involving K_N and K_{BH^+} are shifted to favour 100% *O*-protonation in concentrated acid.[23] Two possibilities for *N*-protonation exist, (a) $PhNHCO\overset{+}{N}H_3$ and (b) $Ph\overset{+}{N}H_2CONH_2$. (b) will be less abundant than (a),[24,25] but subsequent expulsion of $PhNH_3^+$ would be easier than expulsion of NH_4^+. Nevertheless, a mechanism involving (b) cannot be reconciled with the formation of carbamic acids.

When the phenylureas were hydrolysed in water it was observed that the reaction had reached completion without the formation of the corresponding aniline, *i.e.* although there was a decrease in the absorbance of the carbonyl peak as the reaction progressed, this absorbance

---

[15] C. J. Giffney and C. J. O'Connor, *J.C.S. Perkin II*, in the press.

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

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

[18] W. I. Congdon and J. T. Edward, *J. Amer. Chem. Soc.*, 1972, **94**, 6099.

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

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

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

[22] C. K. Rochester, 'Acidity Functions,' Academic Press, New York, 1970, p. 113.

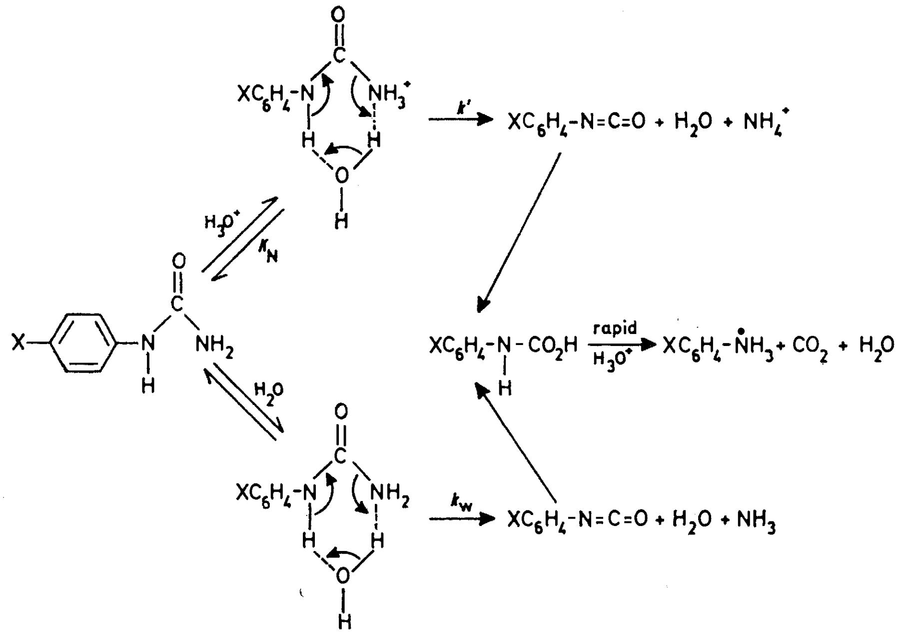
[23] S. Rysman de Lockerente, O. B. Nagy, and A. Bruylants, *Org. Magnetic Resonance*, 1970, **2**, 179.

[24] G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, 1968, **90**, 6087.

[25] L. C. Martinelli, C. DeWitt Blanton, and J. F. Whidby, *J. Amer. Chem. Soc.*, 1971, **93**, 5111.

did not tend to zero, but towards a new value of $\varepsilon_{\text{max.}}$ at a slightly different value of $\lambda_{\text{max.}}$. When a few drops of acid were added to the infinity sample the carbonyl peak collapsed immediately to give the spectrum of the corresponding aniline. Thus, in the absence of acid there is a build-up of a product which has been identified as the corresponding carbamic acid. In acid solutions carbamic acids are very unstable and are known to decompose rapidly to form aniline and carbon dioxide.

We cannot measure the amount of the minor *N*-protonated conjugate acid, but it is related to the fraction of unprotonated substrate according to the equilibrium, K_N, and the amount of protonation will follow an unknown acidity scale H_N. Therefore, before applying the various criteria of mechanism, we should correct k' for the degree of unprotonated substrate $(1 - a)$. When this is done Yates r plots [19] (correlation coefficients 0.94—0.97, slopes r —1.2 to —2.9) and Bunnett–Olsen l.f.e.r. plots [21] (correlation coefficients 0.981—0.996, slopes ϕ —0.29 to —0.75) provide good linear fits. Moreover the negative values of r and ϕ are consistent with a mechanism in which water is not involved as a nucleophile in the rate-determining step. Plots of $(\log_{10}k' - \log_{10}a)$ against $-H_0$ (the Zucker–Hammett *A*-1 plot for substrate not *O*-protonated) gave good linear fits (correlation coefficients 0.97—0.98) but the slopes 0.3—0.7 cannot be interpreted since the correct plot should have been against the appropriate acidity function H_N and not H_0.



SCHEME 2

We are not able to draw any conclusions about the mechanism by comparison of the rates over the wide range of acidities in HCl, H_2SO_4, and $HClO_4$.

Solvent Isotope Effects.—The rate constants for the hydrolysis of 4-chloro- and 4-methyl-phenylurea in deuteriated solvents [D_2O; 10.8% (w/w) D_2SO_4–D_2O and 41.0% (w/w) D_2SO_4—D_2O] have been measured and are given in Table 4 together with the corresponding values of k_H/k_D. The values of k_H/k_D are all >1.0 and reflect a normal solvent isotope effect. We realise that isotope effects can nearly always be rationalised in a variety of ways, but the normal effect we observe is compatible with Scheme 2 in which there is a slow cyclic transfer of protons within an already (pre-equilibrium) proton acid substrate *via* a water molecule. At least three isotope effects are involved: (i) on the pre-equilibrium protonation of N, (ii) on N–H bond breaking, and (iii) on N–H bond formation.

TABLE 4

Solvent isotope effects on the rates of hydrolysis of 4-methyl- and 4-chloro-phenylureas

	H_2O or D_2O		10.8% (w/w) H_2SO_4 or D_2SO_4		41.0% (w/w) H_2SO_4 or D_2SO_4	
	4-Me	4-Cl	4-Me	4-Cl	4-Me	4-Cl
$10^5k_H/s^{-1}$	4.24	4.99	19.4	14.0	5.18	10.1
$10^5k_D/s^{-1}$	1.75	2.45	15.0	12.1	2.44	5.99
k_H/k_D	2.42	2.04	1.29	1.15	2.12	1.68

Hammett Plots.—In Scheme 2, electron-donating groups on the benzene ring would be expected to favour the protonation of the substrate, while the rate of the following proton-transfer step, k' or k_w, might be slightly increased by electron-withdrawing groups. There is, however, an additional complication since ureas are predominantly *O*-protonated and electron-donating groups will increase the concentration of the *O*-protonated cation and decrease the concentration of free base available for hydrolysis. Application of the Hammett equation [26] to plots of $k'/(1-\alpha)$ (in 5% w/w H_2SO_4) and of

---

[26] L. P. Hammett (*a*) *J. Amer. Chem. Soc.*, 1937, **59**, 96; (*b*) *Trans. Faraday Soc.*, 1938, **34**, 156.

k_w (in H_2O at pH 6.48) against σ gave slightly concave downwards plots with slopes over the main linear regions of ρ -0.85 (substituents 4-Me to 4-NO_2) and $+0.20$ (substituents 4-MeO to 4-Br) respectively.

Schreck [27] has studied a variety of non-linear Hammett relationships and found that this phenomenon of concave downwards plots is common in reactions involving the carbonyl group.

Concave downwards Hammett plots have also been observed in the formation of semicarbazone from substituted benzaldehydes [28] and in the reaction of aromatic aldehydes with n-butylamine to form substituted benzylidene-n-butylamines, under acid-catalysed and neutral conditions.[29] In the former example there is a change in the Hammett plot as the pH at which the reaction is carried out is varied from 1.75 to neutral pH.

From the relative values of ρ, evaluated from reactions governed by k' and k_w, we are able to deduce that the substituent effect on pre-equilibrium protonation overrides the small substituent effect on the slow cyclic transfer of protons. The ρ values are therefore consistent with the proposed mechanism. But the main effect observed with changing substituents has been to shift the position of the maximum in the bell-shaped profile to higher acidities with decreasing basicity.

Mechanism of Hydrolysis.—Scheme 2 summarizes the reaction paths outlined above. The uncatalysed rate, k_w, occurs because water acts as a proton transfer agent in a six-membered cyclic transition state, thus forming an aryl isocyanate after bond cleavage. The acid-catalysed rate, k', occurs through a similar path involving the minor *N*-protonated conjugate acid. Phenyl isocyanates are readily attacked by water to form the corresponding carbamic acids and these decompose instantly to the corresponding aniline salt on addition of mineral acid.

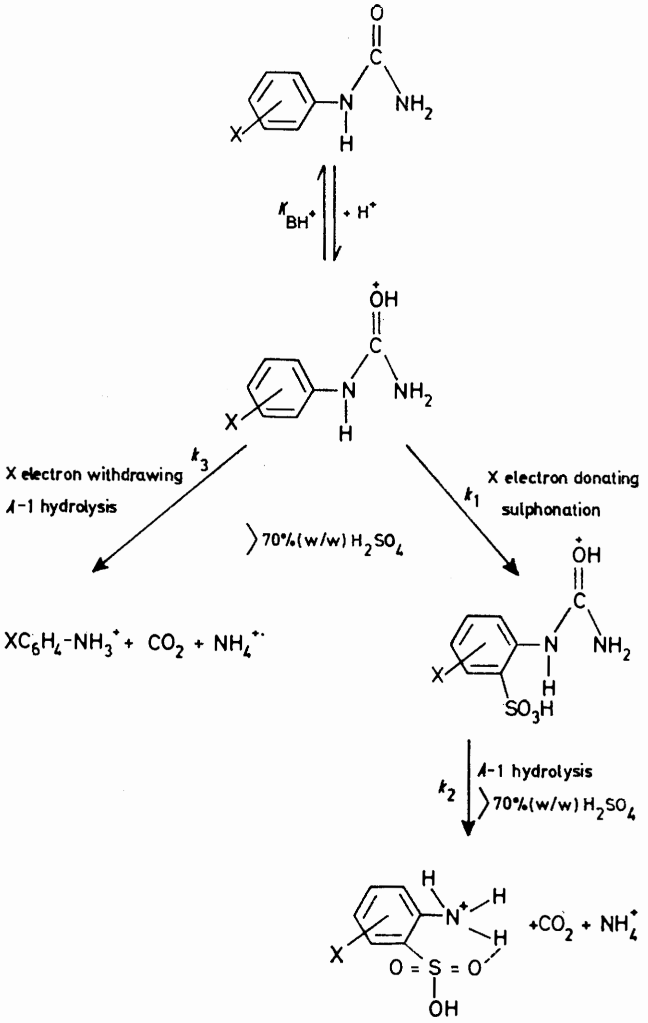
Arrhenius parameters [1] earlier led us to believe that ureas did not hydrolyse by a bimolecular mechanism involving nucleophilic water attack, at least at acidities covered by the initial bell-shaped profile. The mechanism we propose in Scheme 2 is consistent with this conclusion. Beyond the localised minimum in the profiles, at least in H_2SO_4, a new mechanism takes over and we have been unable to confirm the introduction [3,4] of a bimolecular mechanism at intermediate acidities.

Reactions in More Concentrated Sulphuric Acid.—Phenylurea and 3-methylphenylurea have been found to undergo sulphonation at high sulphuric acid concentration,[1] and it is these sulphonated derivatives which hydrolyse in $>70\%$ (w/w) H_2SO_4. The increase in the rate of hydrolysis of urea in $>90\%$ (w/w) H_2SO_4[4] has also been attributed to a sulphonation similar to that described by Bieber [30] for the reaction of urea and 1,3-dimethylurea with oleum.

As we have observed for substituted acetanilides,[15] phenylureas (except 3-nitrophenylurea) have a minimum in their rate profiles in concentrated acid and a subsequent increase in rate with increasing acid concentration.

In $>75\%$ (w/w) H_2SO_4 all the phenylureas having electron-donating substituents attached to the benzene ring, *i.e.* 4-Me, 4-MeO, 4-EtO, 4-Pr^i, and 4-Bu^n, undergo a shift in absorption maximum prior to hydrolysis and, since the ureido group ($NHCONH_2$) is activating towards electrophilic substitution, this shift is undoubtedly due to sulphonation of the phenylurea. For 4-methylphenylurea $\lambda_{max.}$ (C=O) shifted from 237.0 to 241.0 nm on sulphonation. Proof of sulphonation is outlined below.

We know that at acidities beyond the minimum in the profiles that all the other phenylureas studied are essentially fully monoprotonated on oxygen and we can assume that the sulphonated ureas formed with electron-donating substituents will also be essentially fully *O*-protonated at these acidities. There is also likely to be some concentration of diprotonated urea in these very concentrated



SCHEME 3

---

[27] J. O. Schreck, *J. Chem. Educ.*, 1971, **48**, 103.

[28] B. M. Anderson and W. P. Jencks, *J. Amer. Chem. Soc.*, 1960, **82**, 1773.

[29] T. I. Crowell, C. E. Bell, jun., and D. H. O'Brien, *J. Amer. Chem. Soc.*, 1964, **86**, 4973.

[30] T. I. Bieber, *J. Amer. Chem. Soc.*, 1953, **75**, 1405.

acids. The rate increases we observe beyond the minimum for the unsulphonated and sulphonated phenylureas are consistent with a change in mechanism from that postulated over the region of the bell shape. By analogy with other systems [31] this new mechanism could well be an *A*-1 hydrolysis of the mono-*O*-protonated urea or perhaps of the diprotonated urea, but we have insufficient data to validate this hypothesis. Scheme 3 summarizes the suggested mechanism for the monoprotonated species.

EXPERIMENTAL

Materials.—AnalaR sulphuric, perchloric, and hydrochloric acids were standardised against AnalaR sodium hydroxide and diluted, by weighing, with distilled water to produce acids of the required percentage composition.

Deuteriosulphuric acid (Merck; 96—98% w/w; 99% D_2SO_4) was diluted, by weighing, with D_2O (MC and B; 99.5%) to produce the acids of required composition. All diluted solutions were restandardised against AnalaR sodium hydroxide.

The identity of the hydrolysis product in aqueous solution was confirmed as follows. A sample of phenyl isocyanate was warmed in water for a few minutes in order to form the carbamic acid. The solution was filtered and the u.v. spectrum of the carbamic acid formed was compared with the u.v. spectrum of a sample of phenylurea hydrolysed to infinity in aqueous solution. The details of the two spectra are given in Table 6.

Sulphonation.—A sample of 4-methylphenylurea was hydrolysed in 90% (w/w) sulphuric acid until the reaction had reached completion; the product aniline was precipitated out by adding a small amount of water to the hydrolysed solution. The product was filtered and recrystallised from boiling water. The i.r. spectrum of this compound indicated the presence of a sulpho-group, $\nu_{max.}$ 630s and 1 130s (S=O) and 3 380mbr cm^{-1} (N–H). The n.m.r. spectrum (in deuteriated DMSO) revealed that there were aromatic protons and a time-averaged peak (3H) which is, presumably, due to rapid exchange between the two amino-protons and the proton of the sulpho-group. On addition of D_2O this latter peak exchanged out (Found: C,44.8; H,4.95; N,7.5; S,16.75. $C_7H_9NO_3S$ requires C,44.9; H, 4.8; N, 7.5; S, 17.1%).

TABLE 5

Spectrophotometric data for the hydrolysis of substituted (X) phenylureas in sulphuric acid solution

X	4-MeO	4-EtO	4-Me	4-Pr^i	4-Bu^n	4-H	3-Me	4-F	4-Cl	4-Br	3-NO$_2$	4-NO$_2$
$\lambda_{max.}$/nm [a]	236.0	236.0	237.0	238.0	238.0	235.5	237.5	231.5	242.0	244.5	237.5	220.0 328.0
$\lambda_{max.}$/nm [b]	220.5	221.0							215.5	219.0	258.0	258.0
λ/nm [c]	222.5	223.5							221.5	224.5	255.0 210.5	238.0 281.5

[a] Phenylurea. [b] Amine. [c] Isosbestic point.

Anhydrous LiCl (May and Baker) was used in the measurement of salt effects. The method of preparation, purification and m.p.s of the ureas are given in refs. 5 and 6.

Measurements of Rate Constants of Hydrolysis.—The urea (*ca.* 10^{-3}g) was dissolved in the appropriate acid (10 ml). Aliquot samples were removed from the thermostat bath at *ca.* 0,1/3, 2/3, 1, 1.5, 2, and 2.5 half-lives of the reaction and an infinite time sample was removed after heating for 8—10 half-lives. The hydrolysis reaction was quenched by placing the sample in an ethanol–dry ice slurry. Aliquot portions (1 ml) of the hydrolysed solution were diluted with deionised water to 10 ml for spectrophotometric analysis. The rate constant for hydrolysis was calculated from the slope of a plot of $\log_{10}(A_t - A_\infty)$ against time, where A is the absorbance of the urea at $\lambda_{max.}$ of urea. The error in k_ψ is $\pm 2\%$.

The spectrophotometric data for the hydrolysis of substituted phenylureas in dilute and moderately concentrated acid solutions are given in Table 5.

When the phenylureas were hydrolysed in water it was observed that the carbonyl peak did not tend to zero absorbance as the reaction proceeded towards infinity. Instead, the peak underwent a comparatively small decrease in absorbance maximum accompanied by a hypsochromic shift in spectrum. It was possible to evaluate the rate constant, k_w, from these spectra, but the results were less reliable than those evaluated from spectra measured after addition of a few drops of 20% (w/w) H_2SO_4 to each sample to decompose the carbamic acid formed as product in neutral solution to the corresponding aniline.

The results indicate that the product is 2-amino-5-methylbenzenesulphonic acid. The presence of hydrogen bonding between the amino-proton and the oxygen of the sulpho-group is indicated by the fact that in the i.r. spectrum the N–H stretch is a rather broad peak.

Product Analysis.—On hydrolysis, phenylureas produce the substituted aniline, ammonia, and carbon dioxide.[3] The anilines were identified by comparing the spectra of the pure anilines with those obtained after hydrolysing the corresponding phenylureas in solutions 10—20 times more concentrated than those used for kinetic investigation.

TABLE 6

Comparison of the u.v. spectrum of carbamic acid and the u.v. spectrum of a sample of phenylurea hydrolysed to infinity in aqueous solution

Substrate	$\lambda_{max.}$/ nm (1)	$\lambda_{max.}$/ nm (2)	$\lambda_{min.}$/ nm (1)	$\lambda_{min.}$/ nm (2)
Phenylurea + $H_2O \xrightarrow{\Delta} \infty$	230.5	280.5	212.0	260.5
$PhNCO + H_2O \xrightarrow{\Delta} PhNHCO_2H$	231.0	280.5	212.5	261.0

Apparatus.—The oil-bath was maintained at the required temperature by using a Gallenkamp contact thermometer, Klaxon stirrer, and a heating element. Spectrophotometric measurements were carried out on a Unicam SP 800 spectrophotometer, i.r. spectra were measured on a Shimadzu IR 27G, and n.m.r. spectra on a Varian T60 recording spectrophotometer. Least-squares analyses were carried out on a Burroughs B6 700 computer.

We are indebted to the referees for helpful comments.

[4/2297 *Received*, 5*th November*, 1974]

---

[31] J. W. Barnett and C. J. O'Connor, *J.C.S. Perkin II*, 1972, 3278.