Acid Hydrolysis of Phenylurea, 4-Fluorophenylurea, and 3-Methylphenylurea

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The rate constants of hydrolysis of phenylurea and 4-fluorophenylurea have been measured over the acid range 2·5—60·1% and 2·5—70·0% w/w H_2SO_4 respectively at five temperatures in the range 70·0—110·4 °C: those of 3-methylphenylurea have been measured over the acid range 2·5—60·1% w/w H_2SO_4 at 100·1 °C. Attempts to correlate the rate data with Bunnett w and w^*, Bunnett–Olsen linear free energy relationship, and Zucker–Hammett criteria of mechanism have proved unsatisfactory. Application of a two-term equation and high activation parameters provide evidence that these phenylureas hydrolyse by an *A*-1 mechanism. Rate constants of hydrolysis of the sulphonated derivatives of phenylurea and 3-methylphenylurea are reported over the range 70·0—95·0% w/w H_2SO_4 at 100·1 °C.

THE hydrolysis of ureas has not been subjected to the extensive kinetic studies which have been carried out on esters[1] and amides.[2] Early workers[3,4] observed the reactions in very low acid and alkali concentrations, *i.e.* in the pH range $^{1-12}$ Moodie and his co-workers[5,6] have followed the reaction of several aliphatic ureas over a wide range of sulphuric acid concentrations, and in methanesulphonic acid, in order to investigate the possibility of sulphonation occurring in sulphuric acid. Shaw and Walker[3] found that mono-, di-, and trimethylthioureas underwent decomposition rather than hydrolysis. Tetramethylthiourea does not decompose but appears to hydrolyse.[3e] This was taken as confirmation of hydrogen bonding to the nitrogen atom in the decomposition of the three thioureas previously studied.

The hydrolysis of urea in dilute aqueous acid does not involve acid catalysis[3e] and the decrease in observed rate constants has been attributed to a decrease in concentration of the unprotonated form.[5] Moodie *et al.*[5] established that a shallow maximum (corresponding to diprotonation of urea) occurred at *ca.* 70% w/w H_2SO_4. The behaviour of ethylurea[6] was similar and values of E_a for ethylurea hydrolysis decreased from 114 kJ mol^{-1} at 39·9% w/w H_2SO_4 to 99 kJ mol^{-1} at 79·9% w/w H_2SO_4. The results for urea[5] were well fitted by equation (1) which allowed for decomposition of the free base and of the conjugate acid (k_{up} = specific first-order rate constant

$$k_1 = k_{up}[K_a/K_a + h)] + k_p[h/(K_a + h)] \qquad (1)$$

of unprotonated base, k_p = specific first-order rate constant of protonated base, and h = appropriate acidity function).

The hydrolysis of urea shows an increase in rate beyond 90% w/w H_2SO_4, and this is due to a sulphonation reaction.[5]

The data for hydrolysis of *NNN'N'*-tetramethylurea and *O*-methylisourea were interpreted in terms of a bimolecular reaction between water and diprotonated urea. The onset of a rate maximum (at *ca.* 70% w/w H_2SO_4), at considerably lower acidities than those at which substantial protonation (in this case diprotonation) occurs is not uncommon for *A*-2 reactions,[7] and merely means that the decreasing activity of water is more important than the increasing acidity of the medium.

Recently Congdon and Edward[8] hydrolysed nine *N*-acylthioureas in sulphuric acid. The rate profiles showed a sharp maximum at *ca.* 43% acid, and then a minimum at *ca.* 72% acid. This behaviour indicated a change from a bimolecular (*A*-2) mechanism involving water as a nucleophile in the rate-determining step in 0—70% acid, to a unimolecular (*A*-1) mechanism involving an intermediate acyl cation in 70—100% acid. The change in mechanism was supported by Arrhenius parameters (E_a increased from 67 kJ mol^{-1} at 25·2% acid to 92 kJ mol^{-1} at 96·9% acid), Hammett ρ, Bunnett w,[9] and Bunnett–Olsen ϕ[10] values.

We report below the rate constants of hydrolysis of phenylurea and 4-fluorophenylurea measured over the acid range 2·5—60·1% and 2·5—70·0% w/w H_2SO_4 respectively over the temperature range 70·0—110·4 °C, and of 3-methylphenylurea over the acid range 2·5—60·1% w/w H_2SO_4 at 100·1 °C. Phenylurea and 3-methylphenylurea are sulphonated rapidly at high acidities and we report the rate constants of hydrolysis of their sulphonated derivatives at $\geqslant$70% w/w H_2SO_4 at 100·1 °C.

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

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

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

[4] G. Travagli, *Gazzetta*, 1952, **82**, 528; 1953, **83**, 806; 1957, **87**, 673; 1958, **88**, 1129.

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

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

[7] P. W. C. Barnard, C. A. Bunton, D. Kellerman, M. M. Mhala, B. Silver, C. A. Vernon, and W. A. Welch, *J. Chem. Soc.* (*B*), 1966, 227.

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

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

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

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

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

RESULTS AND DISCUSSION

The rate constants of hydrolysis are given in Tables 1—4.

Figure 1 shows rate profiles for the hydrolysis of phenylurea, 4-fluorophenylurea, and 3-methylphenylurea and the sulphonated derivatives of phenylurea and 3-methylphenylurea at 100·1 °C. The most notable observation is that the position of the sharp rate maximum (corresponding to monoprotonation) at *ca.* 12·5% w/w H_2SO_4, occurs at an acidity intermediate between that of aliphatic ureas[5] and *N*-acylthioureas,[8] in agreement with intermediate values of the basicity constant K_{BH^+}.[11]

We have recently measured the basicity constants of phenylurea and seven substituted phenylureas.[11] pK_{BH^+} Values of —1·30 for phenylurea, —1·18 for 4-fluorophenylurea, and —1·18 for 3-methylphenylurea, all based[11] on the H_A acidity scale,[12] have been used to correct the observed rate constants for the degree of protonation, α, of the substrate. $\alpha = h_A/(K_{BH^+} + h_A)$.

TABLE 1

Rate constants of hydrolysis of phenylurea in sulphuric acid

	t/°C				
	110·4	100·1	90·0	80·0	70·0
% w/w H_2SO_4	$10^5\ k_\psi/s^{-1}$				
2·53	39·5	11·6	4·37	1·42	0·416
5·02	49·6	13·2	5·79	1·72	0·505
7·49	53·7	16·4	6·01	2·14	0·588
10·0	54·0	17·0	6·42	2·47	0·671
12·5		18·2	6·35	2·03	0·626
15·0	52·6		6·14	1·86	0·587
17·5	51·9	17·0	5·74	1·82	0·539
20·0	50·4	15·4	5·29	1·62	0·520
25·1	44·2	11·7	4·36	1·55	0·479
30·0	38·3	9·62	3·52	1·39	0·394
35·0	30·3	8·06	3·13	0·922	
40·0	24·9	4·99	2·62	0·652	0·217
45·0	18·5		2·04	0·553	0·189
50·7		3·01	1·39	0·371	0·128
60·1		1·93	0·769	0·320	0·077

TABLE 2

Rate constants of hydrolysis of 4-fluorophenylurea in sulphuric acid

	t/°C				
	110·4	100·1	90·0	80·0	70·0
% w/w H_2SO_4	$10^5k_\psi/s^{-1}$				
2·53	30·9	11·7	3·10	1·18	0·364
5·02	37·7	15·5	4·11	1·43	0·420
7·49	42·2	18·1	4·84	1·56	
10·0	44·7	19·9	4·98	1·58	0·474
12·5		19·4	4·97	1·56	0·475
15·0	44·2	18·7	4·66	1·47	0·460
17·5		16·9		1·38	0·454
20·0	40·5	14·8	4·14	1·24	
25·1	37·7	11·7	3·84	1·13	0·350
30·0	28·8	9·62	3·39	0·883	0·330
35·0	24·5	8·06	2·79	0·722	0·257
40·0	19·3	4·99	2·11	0·551	0·185
45·0	13·7	4·46	1·56	0·341	
50·7	10·3	3·01			
60 1	9·46	1·97			
70·0		0·878			

Table 5 shows the results of plotting ($\log_{10}k_\psi$ — $\log_{10}\alpha$) against $\log_{10}a_w$ (Bunnett *w*),[9] and against (H_0 + $\log_{10}C_{H^+}$) (Bunnett–Olsen linear free energy relationship) (l.f.e.r.);[10] [$\log_{10}k_\psi$ — $\log_{10}C_{H^+}/h_0$ + K_{BH^+})] against $\log_{10}$-a_w (Bunnett *w**);[9] and [$\log_{10}k_\psi$ — $\log_{10}(1 - \alpha)$] against H_0 (Zucker–Hammett *A*-1 relationship for a moderately basic substrate)[13] and against $\log_{10}C_{H^+}$ (Zucker–Hammett

TABLE 3

Rate constants of hydrolysis of 3-methylphenylurea in sulphuric acid at 100·1 °C

% w/w H_2SO_4	$10^5k_\psi/s^{-1}$	% w/w H_2SO_4	$10^5k_\psi/s^{-1}$
2·53	11·3	20·0	15·9
5·02	15·8	25·1	14·1
7·49	17·1	30·0	10·9
10·0	19·4	35·0	8·90
12·5	18·8	40·0	6·96
15·0	18·2	50·7	3·97
17·5	17·5	60·1	2·39

TABLE 4

Rate constants of hydrolysis of sulphonated phenylurea and 3-methylphenylurea in concentrated sulphuric acid at 100·1 °C

	$10^5k_\psi/s^{-1}$	
% w/w H_2SO_4	Phenylurea	3-Methylphenylurea
70·0	2·96	5·24
80·0	10·3	8·24
90·0	10·7	11·0
95·0	9·04	7·22

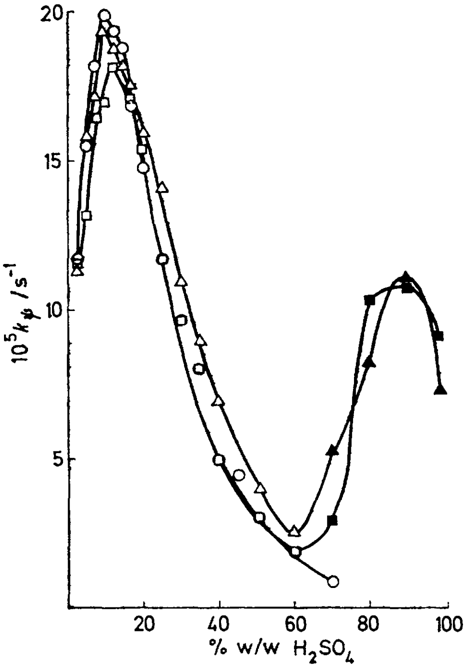

FIGURE 1 Rate constants of hydrolysis of phenylurea, 4-fluorophenylurea, 3-methylphenylurea, and sulphonated phenylurea and 3-methylphenylurea in sulphuric acid at 100·1 °C. □ phenylurea; ○ 4-fluorophenylurea; △ 3-methylphenylurea; ■ sulphonated phenylurea; ▲ sulphonated 3-methylphenylurea

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

A-2 relationship for a moderately basic substrate)[13] for the data shown in Tables 1—3.

TABLE 5

Analysis of rate data for hydrolysis of phenylureas in sulphuric acid by use of Bunnett *w* and *w**, Bunnett–Olsen l.f.e.r., and Zucker–Hammett relationships

		Bunnett *w*	Bunnett *w* *	Bunnett–Olsen l.f.e.r.	Zucker–Hammett *A*-1		Z–H *A*-2
Urea	t/°C	Correln. coefft.	Correln. coefft.	Correln. coefft.	Slope [a]	Correln. coefft.	Correln. coefft.
Phenylurea	110·4	0·866	0·620	0·949	0·206	0·989	0·935
	100·1	0·821	0·365	0·929	0·196	0·963	0·869
	90·0	0·825	0·306	0·929	0·216	0·977	0·877
	80·0	0·820	0·287	0·926	0·205	0·944	0·835
	70·0	0·842	0·334	0·956	0·204	0·967	0·895
4-Fluorophenylurea	110·4	0·815	0·094	0·926	0·267	0·993	0·911
	100·1	0·827	0·308	0·931	0·218	0·970	0·884
	90·0	0·883	0·595	0·955	0·251	0·992	0·954
	80·0	0·885	0·683	0·960	0·178	0·987	0·942
	70·0	0·830	0·671	0·960	0·196	0·976	0·951
3-Methylphenylurea	100·1	0·834	0·164	0·936	0·257	0·986	0·942

[a] $0{\cdot}014 > s$(standard deviation) $> 0{\cdot}008$.

The best fit of the experimental data with these criteria of mechanism is obtained with the Zucker–Hammett *A*-1 hypothesis, which has correlation coefficients in the range 0·944—0·993. However the slopes of these plots do not satisfy the Zucker–Hammett postulate of unit value, but lie in the range **0·178—0·267**. (A similar situation occurred for the *A*-1 hydrolysis of acetanilide derivatives in strong acid media.[14]) The correlation coefficients for the Bunnett *w* and Bunnett–Olsen l.f.e.r. plots are not good and therefore *w* and ϕ parameters do not hold any significance. Figure 2 shows the curved Bunnett *w* plot for phenylurea at 100·1 °C.

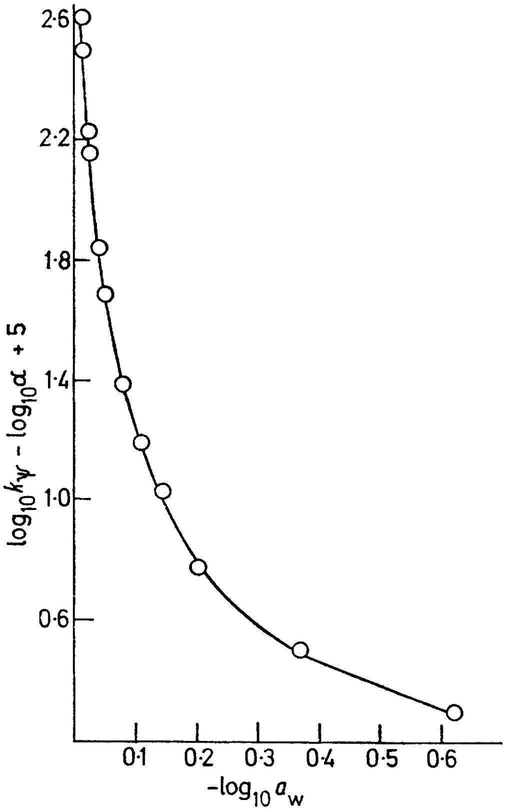

FIGURE 2 Bunnett *w* plot for hydrolysis of phenylurea in sulphuric acid at 100·1 °C

We have substituted our data into equation (1) of Moodie *et al.*[5] which allows for the hydrolysis to take place by paths which are independent of the water activity and the hydrogen ion concentration. Equation (1) may be rearranged into two forms (2) and (3).

$$k_1/\alpha = k_{up}(1 - \alpha)/\alpha + k_p \qquad (2)$$

$$(k_1/(1 - \alpha) = k_p\alpha/(1 - \alpha) + k_{up} \qquad (3)$$

The results are given in Table 6. The results obtained by plotting equation (3) over a wide range of acidities, 0—60% w/w H_2SO_4 ($0{\cdot}01 < \alpha < 0{\cdot}98$), are better than any obtained by the standard criteria of mechanism (Table 5). Plotting equation (2) does not yield such good correlation coefficients, and this incompatibility parallels that found on reversing the two-term equation

TABLE 6

Analysis of rate data for hydrolysis of phenylureas in sulphuric acid by use of equations (2) and (3)

		Equation (2)		Equation (3)	
Urea	t/°C	10^5k_p/s^{-1}	Correln. coefft.	10^5k_{up}/s^{-1}	Correln. coefft.
Phenylurea	110·4	15·3	0·965	40·7	0·991
	100·1	16·5	0·988	11·8	0·991
	90·0	0·683	0·964	4·58	0·988
	80·0	0·284	0·994	1·47	0·986
	70·0	0·681	0·978	0·429	0·989
4-Fluorophenylurea	110·4	5·86	0·978	31·7	0·994
	100·1	1·74	0·984	12·3	0·981
	90·0	1·37	0·956	3·21	0·983
	80·0	0·266	0·921	1·22	0·992
	70·0	0·152	0·951	0·368	0·996
3-Methylphenylurea	100·1	2·17	0·981	11·8	0·979

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[14] J. W. Barnett and C. J. O'Connor, *J.C.S. Perkin II*, 1972, 2378.

for amides.[15] When the equations are reversed one axis tends to become distorted.

There is, however, a serious inconsistency in the conclusions which can be drawn from this analysis. For example, the observed rate constants for phenylurea at 100·1 °C are thus interpreted as the sum of contributions from the free base (medium independent specific rate constant $11{\cdot}5 \times 10^{-5}$ s^{-1}) and the conjugate acid (medium independent specific rate constant $16{\cdot}5 \times 10^{-5}$ s^{-1}). If this were so, a plot of the observed rate constant against H_A should follow a sigmoid curve, rising from a plateau at $11{\cdot}5 \times 10^{-5}$ s^{-1} at low acidities to a plateau at $16{\cdot}5 \times 10^{-5}$ s^{-1} at high acidities. Table 1 shows that this is clearly not the case.

It seems that the best interpretation that can be placed on the data is that of a single mechanism, unimolecular decomposition of the free base, the *specific* rate constant for which rises slowly with decreasing water activity as with other unimolecular decompositions in aqueous acids. The observed rate constant at first rises, and then falls because of decreasing concentration of the free base. This mechanism is in accord with the observed activation parameters (*vide infra*), and the same as that observed with urea itself at low acidities.[5] We cannot unequivocally rule out a small contribution of reaction through the mono- or di-protonated urea at the highest acidities and this aspect is being investigated further using substrates of varying basicities.

Table 7 lists the activation parameters obtained for hydrolysis of phenylurea, and those obtained for hydrolysis of 4-fluorophenylurea are shown in Table 8. The most noteworthy feature of the values of E_a and $\log_{10}A$ is their insensitivity to changes in acidity. For phenylurea $E_a = 123 \pm 5$ kJ mol^{-1} and for 4-fluorophenylurea 127 ± 5 kJ mol^{-1} and this scatter is only just outside the experimental accuracy. These values are higher than any previously obtained for hydrolysis of ureas and are consistent with an *A*-1 mechanism. The occurrence of such a mechanism for the related carbonyl compounds, amides [14,16] and esters,[17] is rare and generally occurs at much higher acidities than found in this investigation.

TABLE 7

Arrhenius parameters for hydrolysis of phenylurea in sulphuric acid

% w/w H_2SO_4	E_a/kJ mol^{-1}	$\log_{10}(A/s^{-1})$	Correln. coefft.
2·53	123	14·3	0·999
5·02	123	14·4	0·997
7·49	121	14·2	0·999
10·0	117	13·7	0·998
12·5	120	14·0	1·00
15·0	123	14·5	0·999
17·5	123	14·7	0·999
20·0	125	14·7	0·999
25·1	121	14·1	0·997
30·0	121	14·0	0·996
35·0	128	14·9	0·997
40·0	126	14·5	0·992
45·0	127	14·5	0·999

TABLE 8

Arrhenius parameters for hydrolysis of 4-fluorophenylurea in sulphuric acid

% w/w H_2SO_4	E_a/kJ mol^{-1}	$\log_{10}(A/s^{-1})$	Correln. coefft.
5·02	125	14·5	0·998
7·49	134	16·0	0·998
10·0	127	15·0	0·998
12·5	131	15·5	0·998
15·0	128	15·1	0·998
17·5	130	15·4	0·998
20·0	132	15·1	0·999
25·1	128	15·0	0·999
30·0	123	14·2	0·998
35·0	126	14·7	0·998
40·0	126	14·4	0·997

Phenylurea and 3-methylphenylurea both undergo sulphonation at high sulphuric acid concentrations. This property has not been subjected to the extensive investigation given the formation and hydrolysis behaviour of *N*-acetylsulphanilic acid.[14,18] However, sulphonation does occur at a lower acidity than the corresponding acidity at which sulphonation occurs for the acetanilide derivatives.[14] The rate of hydrolysis of the sulphonated ureas so formed, show a maximum in their rate profiles at high acidities as shown in Figure 1 and Table 4. The hydrolysis of 4-fluorophenylurea at 100·1 °C was also studied at high acidities, but no evidence of sulphonation was observed, nor was there any increase in rate similar to that observed for the acetanilide derivatives.[14] Instead the rate continued to decrease until it became too slow to measure easily.

4-Fluoroacetanilide showed the least increase in rate with increasing acidity ($>70\%$ w/w H_2SO_4) of all the acetanilide derivatives studied.[14] We are therefore extending this work to hydrolysis of some phenylureas corresponding to the acetanilide derivatives which changed their mechanism of hydrolysis markedly as the acidity increased, in order to investigate the possibility of a similar phenomenon existing for phenylureas.

EXPERIMENTAL

Materials.—AnalaR sulphuric acid was standardised against sodium hydroxide and diluted with deionised water by weighing to give solutions of the required percentage composition.

The method of preparation and m.p.s of the ureas are given in ref. 11.

Measurement 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 approximately 0, 1/3, 2/3, 1, 1½, 2, and 2½ times

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

[16] J. W. Barnett and C. J. O'Connor, *J.C.S. Chem. Comm.*, 1972, 525.

[17] K. Yates and R. A. McClelland, *J. Amer. Chem. Soc.*, 1967, **89**, 2686.

[18] J. W. Barnett and C. J. O'Connor, *Chem. and Ind.*, 1970, 1172; *Tetrahedron*, 1971, 2161.

the half-life of the reaction and an infinite time sample was removed after heating for 8—10 times the half-life. 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 wavelengths used were 235 (phenylurea), 231 (4-fluorophenylurea), and 237 nm (3-methylphenylurea).

Table 9

Spectrophotometric data for the hydrolysis of sulphonated phenylureas

Urea	% w/w H_2SO_4	$\lambda_{max.}$/nm
Phenylurea	70	235
	$\geqslant 80$	250
3-Methylphenylurea	60	237
	$\geqslant 70$	250

Phenylurea and 3-methylphenylurea undergo initial sulphonation before hydrolysing in more concentrated solutions of sulphuric acid. The formation of a sulphonated intermediate was accompanied by a shift in absorption maximum. Table 9 summarises the results.

Product Analysis.—On hydrolysis, phenylureas produce the substituted aniline, ammonia, and carbon dioxide.[5] The anilines were identified by comparing the spectra of the pure anilines with those obtained after hydrolysing the corresponding phenylureas in solutions more concentrated than those used for kinetic investigation. Spectral data are given in Table 10.

Table 10

Product analysis; spectral data measured after complete hydrolysis of phenylurea, 4-fluorophenylurea, and 3-methylphenylurea

	λ_1/nm	λ_2/nm	λ_3/nm	λ_4/nm
Aniline	260·5	254·6	248·7	249
4-Fluoroaniline	267	261	256	253·5s
3-Methylaniline	275	267	260s	

Apparatus.—All oil baths were maintained at the required temperature by using Gallenkamp and Heju contact thermometers, Klaxon stirrer, and a heating element. Spectrophotometric measurements were carried out on a Shimadzu QV.50 spectrophotometer. Least-squares analyses were carried out on an IBM 1130 computer.

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