Spectrophotometric Determination of Basicity Constants. Part III.[1] Phenylureas

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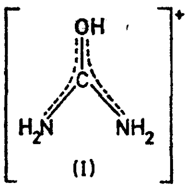
The basicity constants K_{BH^+} of seven substituted phenylureas have been evaluated in sulphuric acid at 25°. The protonation equilibria follow the H_A acidity function and $-pK_{BH^+}$ of 12 substituted phenylureas correlate well with Hammett σ. The site of protonation is discussed.

It is believed [2] that urea is monoprotonated in 100% H_2SO_4 (as are other amides). Urea, more than ordinary amides, would be expected to undergo *O*-protonation because of the very favourable resonance possibilities in the conjugate acid (I). I.r., u.v. and n.m.r., evidence have shown that urea and its derivatives are *O*-protonated, and thiourea and its derivatives are *S*-protonated.[3-5]



(I)

I.r. spectra have been quoted as evidence for both *O*- and *N*-protonation of amides. Direct i.r. evidence for *O*-protonation of amides has been obtained by Gompper and Altreuther [6] who prepared fixed cations of the type $RC(OR)=\overset{+}{N}R_2$ and $RCO\cdot\overset{+}{N}R_3$. They showed that the i.r. spectrum of protonated benzamide closely resembles that of the former cation but not that of the latter. Similar results were reported by Cook.[7] The evidence in support of *N*-protonation comes from a consideration of the shift in the C=O frequency as the amide is protonated, the direction and magnitude of the shift being dependent on the degree of double bond character in the carbonyl bond. Strong bands, assumed to be carbonyl bands, have been found for several amide cations at frequencies higher than those for the carbonyl band of the parent amide, and this has been used as an argument to support *N*-protonation.[8] Davies and Hopkins [9] and Spinner [8] also observed higher $\nu_{C=O}$ frequencies for urea and derivatives of urea, and similarly considered this to be diagnostic of *N*-protonation. Subsequently, Stewart and Muenster [10] prepared ^{18}O labelled dicyclohexylurea and its toluene-*p*-sulphonate salt; the $\nu_{C=O}$ band in the labelled urea shows the expected shift to lower frequency (*i.e.* 1 628 to 1 611 cm^{-1}), but on formation of the toluene-*p*-sulphonate salt a band at 1 669 cm^{-1} appears and is unaffected by isotopic substitution. It is obviously not a carbonyl stretching frequency and indicates that the urea cation is *O*-protonated. Janssen [5] has reinterpreted Spinner's data and explained the apparent upward displacement of the carbonyl band on protonation by reassignment of this frequency to $>C=\overset{+}{N}<$ in the protonated form.

Bryden's [11] *X*-ray structure analysis of *N*-methylurea nitrate revealed oxygen as the site of protonation. Janssen [12] has also studied the i.r. spectrum of tetramethylthiourea and deduced that steric hindrance of mesomerism occurs. He has suggested that for tetramethylurea and tetramethylthiourea the *N*-protonated form exists in equilibrium with the *O*-protonated form and he has assigned bands in the i.r. spectrum accordingly.

In concentrated acid solutions evidence has been presented for the diprotonation of urea. Tetraethylurea was found to be diprotonated to the extent of 10% in 100% H_2SO_4.[13] Birchall and Gillespie [14] have studied the n.m.r. spectra of urea and 1,3-dimethylurea in fluorosulphuric acid and in fluorosulphuric acid containing 10% antimony pentafluoride. For these two compounds they found no peaks corresponding to NH or OH protons in either acid and this was attributed to diprotonation of the bases rendering these protons highly acidic and leading to rapid exchange with solvent protons. Olah and White [15] have studied the n.m.r. spectra of urea and various methylated derivatives in the superacid system, 1 : 1 molar FSO_3H-SbF_5 and have shown that all these compounds are diprotonated in this system. For asymmetrically substituted urea in which two possible sites for *N*-protonation exist,

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[1] Part II, C. J. Giffney and C. J. O'Connor, *J.C.S. Perkin II*, 1975, 706.

[2] G. S. Holstead, A. H. Lamberton, and P. A. H. Wyatt, *J. Chem. Soc.*, 1953, 3341.

[3] W. Kutzelnigg and R. Mecke, *Spectrochimica Acta*, 1961, **17**, 4530.

[4] C. R. Redpath and J. A. S. Smith, *Trans. Faraday Soc.*, 1962, **58**, 462.

[5] M. J. Janssen, *Spectrochimica Acta*, 1961, **17**, 475.

[6] R. Gompper and P. Altreuther, *Z. Analyt. Chem.*, 1959, **170**, 205.

[7] D. Cook, *Canad. J. Chem.*, 1962, **40**, 2362.

[8] E. Spinner, *Spectrochimica Acta*, 1959, **15**, 95.

[9] M. Davies and L. Hopkins, *Trans. Faraday Soc.*, 1957, **53**, 1563.

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[11] J. H. Bryden, *Acta Cryst.*, 1957, **10**, 714.

[12] M. J. Janssen, *Rec. Trav. chim.*, 1960, **79**, 454.

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[14] R. J. Gillespie and T. Birchall, *Canad. J. Chem.*, 1963, **41**, 2642.

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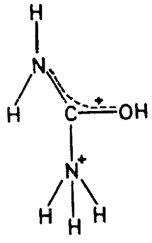
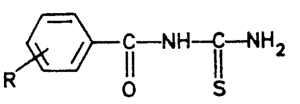
protonation was found to occur at the least substituted nitrogen, the result of a combination of steric and electronic factors.[15,16] The structure of diprotonated urea is represented as (II).

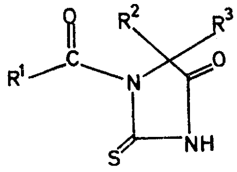
Congdon and Edward [17] have studied the basicities of



(II)



(III)



(IV)

N-acetylthiourea and various substituted N-benzoylthioureas (III) using u.v. spectrophotometry. They observed that these compounds were protonated in 35—60% H_2SO_4 and followed the H_0''' [18] scale and they attributed this to a thiocarbonyl protonation. A second protonation takes place in 65—96% (w/w) H_2SO_4 and follows the H_A [19] value of the solution; this was attributed to protonation of the amide oxygen. Similarly, Congdon and Edward [20] have studied the mono- and diprotonation of a series of 1-acyl-2-thiohydantoins (IV). They found that over the range 50—80% H_2SO_4 a protonation takes place on the thiocarbonyl sulphur, the extent of protonation depending on the H_0 [21] value of the solution. As the acid concentration is increased above 90% H_2SO_4 a second protonation begins to take place on the carbonyl oxygen. In 100% acid 2-thiohydantoin is about half-converted into the diprotonated species.

TABLE 1

Values of $\lambda_{\max.B}$ and $\lambda_{\max.BH^+}$ used in the evaluation of basicity constants of substituted (X) phenylureas

X	4-Pr^i	4-Bu^n	4-F	3-NO_2	4-NO_2	4-MeO	4-EtO
$\lambda_{\max.B}$/nm	237.0	237.0	230.0	234.5	326.0	236.5	236.0
$\lambda_{\max.BH^+}$/nm	226.0	229.0	217.5	225.0	295.0	229.4	230.0

TABLE 2

Comparison of pK_{BH^+} values of substituted (X) phenylureas obtained by acidity function and l.f.e.r. methods

X	m_A	$-H_A^{\frac{1}{2}}$	$-m_AH_A^{\frac{1}{2}}$	m_0	$-H_0^{\frac{1}{2}}$	$-m_0H_0^{\frac{1}{2}}$	ϕ	$-pK_{BH^+}$ (l.f.e.r.)	$-c$ [a]	$-(m_0H_0^{\frac{1}{2}} + m_Ac)$ [b]
4-Pr^i	0.97	1.14	1.10	0.77	1.29	1.00	0.35	0.99	0.13	1.12
4-Bu^n	0.96	1.16	1.11	0.75	1.31	0.98	0.37	0.99	0.13	1.11
4-F	0.99	1.37	1.35	0.72	1.52	1.10	0.40	1.12	0.20	1.30
3-NO_2	1.02	1.94	1.98	0.62	2.41	1.50	0.45	1.64	0.38	1.89
4-NO_2	1.04	2.18	2.26	0.60	2.78	1.66	0.47	1.83	0.50	2.18
4-MeO	1.05	0.94	0.92	0.89	0.96	0.85	0.18	0.84	0.10	0.95
4-EtO	0.94	0.88	0.88	0.78	1.03	0.81	0.34	0.80	0.10	0.90

[a] c Is the intercept in the equation $H_A = mH_0 + c$. [b] See Discussion section of Part II.[1]

The first spectrophotometric studies on phenylureas showed [22] that the protonation equilibria followed the H_A [19] acidity function.

We have recently reported [1] an extensive investigation on the protonation equilibria of acetanilides and report below further data on the basicity constants of phenylureas. The theory and methods of calculation of pK_{BH^+} were detailed in Part II.[1]

The nature of the spectral changes observed for the present set of compounds makes it clear that O-protonation is observed.

RESULTS AND DISCUSSION

In the measurement of the pK_{BH^+} values of the phenylureas the positions of maximum absorbance of the protonated and unprotonated species were found to be well separated. The methods of Davis and Geissman [23] and Stewart and Granger [24] were therefore used to calculate the values of $\log_{10}I$. The positions of $\lambda_{\max.}$ of

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the protonated and unprotonated forms are given in Table 1. The ionisation data obtained from plots of $\log_{10}I$ *vs.* H_A and $\log_{10}I$ *vs.* H_0 and the results obtained from substituting the data into the Bunnett–Olsen linear free energy relationship (l.f.e.r.)[25] are given in Table 2. In all these plots the standard deviations s in slope and intercept were in the range $0.01 < s < 0.09$.

We previously reported[22b] that the slopes of $\log_{10}I$ against H_A for 4-methoxy- and 4-ethoxy-phenylureas (0.748 and 0.801 respectively) were outside the acceptable range, 1.05—0.95, required for the value of pK_{BH^+} obtained to be considered of thermodynamic importance,[19] and were not able to account for these serious discrepancies.

Re-examination of the experimental curves for these two compounds revealed solvent effects due to hydrogen bonding of the alkoxy-groups in moderately concentrated acid solutions, effects similar to those observed in the spectra of 4-methoxy and 4-ethoxyacetanilides.[1] These solvent effects had previously been included in the evaluation of $\lambda_{max.BH^+}$ and in the subsequent values of $A = A_{\lambda BH^+} - A_{\lambda B}$, thus leading to erroneous values of $\log_{10}I$ and $m_A H_A^{\frac{1}{2}}$. These values of pK_{BH^+} have therefore been recalculated and the results are given in Table 2.

For phenylureas it is apparent that agreement between the values of $m_0 H_0^{\frac{1}{2}}$ and $m_A H_A^{\frac{1}{2}}$, and between these values and the pK_{BH^+} values obtained from the Bunnett–Olsen l.f.e.r. is only fair. The discrepancies increase as the base becomes weaker, *i.e.* as the acidity at which the base is half-protonated increases.

Although the relationship between H_A and H_0 is not linear, we have found it convenient to use the form (1)

$$H_A = mH_0 + c \qquad (1)$$

where m and c are, respectively, the slope and intercept of the line drawn tangent to the curve of $-H_A$ *vs.* $-H_0$. Using this relationship we derived equation (2) for

$$m_A H_A^{\frac{1}{2}} = m_A c + m_0 H_0^{\frac{1}{2}} \qquad (2)$$

calculating $m_A H_A^{\frac{1}{2}}$. The results of $m_A H_A^{\frac{1}{2}}$ derived from equation (2) for the phenylureas we have studied are given in the last column of Table 2 and it can be seen that these results show a much improved agreement with $m_A H_A^{\frac{1}{2}}$ than do those of uncorrected values of $m_0 H_0^{\frac{1}{2}}$.

The difference between the values of pK_{BH^+} (l.f.e.r.) and $m_A H_A^{\frac{1}{2}}$ are of the same order and direction as observed previously.[1,25,26] Bases having a $pK_{BH^+} > -1.4$ show excellent agreement between $m_0 H_0^{\frac{1}{2}}$ and pK_{BH^+} (l.f.e.r.). For weaker bases the discrepancy increases as the base weakens, because the accuracy of pK_{BH^+} depends on the slope ϕ remaining constant, where ϕ becomes more positive with increasing acid concentration, thus introducing a larger error in pK_{BH^+}.

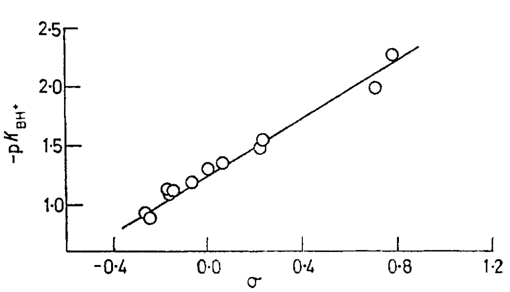
Ionisation ratios are listed in Supplementary Publication No. SUP 21393 (3 pp.).*

The Hammett Equation.—The Hammett equation (3)

$$\log_{10}k = \log_{10}k^0 + \sigma\rho \qquad (3)$$

has been applied to the dissociation constants, pK_{BH^+}, determined in this investigation and also to the results for phenylureas previously determined.[22b] These latter values of $H_A^{\frac{1}{2}}$ have been corrected to values of $m_A H_A^{\frac{1}{2}}$ before substitution into (3) and the corrected values are given in parentheses: 4-methyl- (1.18), 3-methyl- (1.16), 4-chloro- (1.40), and 4-bromo- (1.63) phenylurea, and phenylurea (1.22).

The results obtained from plots of $\log_{10}K_{BH^+}$ *vs.* σ[27] and σ^+[28] gave values of $\rho = 1.15 \pm 0.06$ and 0.86 ± 0.08 respectively. As for acetanilides,[1] there is a much better correlation with σ (0.984) than with σ^+ (0.961); the value of $\rho = 1.15$ is very similar to that obtained[29] for correlation of pK_{BH^+} values of substituted benzamides with σ substituent constants (ρ 0.92).



Hammett plots of $-pK_{BH^+}$ *vs.* σ for substituted phenylureas

The Figure shows the plot of $-pK_{BH^+}$ *vs.* σ for all the substituted phenylureas we have studied.

We have recently shown[30] that the chemical shifts (δ_{NH} and δ_{NH_2}) of phenylureas also correlate well with Hammett σ.

EXPERIMENTAL

Materials.—All measurements were made in AnalaR sulphuric acid solutions which were prepared as previously described.[1]

The preparation and purification of 4-methyl-, 4-methoxy-, 4-ethoxy-, 4-fluoro-, 4-chloro-, and 4-bromo-phenylurea have been described.[22b]

Phenylurea (Fluka) and 3-methylphenylurea (Fluka) were recrystallised from ethanol, m.p.s. 146—148 and 143°, respectively. 4-Isopropyl- and 4-n-butyl-phenylureas were

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* For details of Supplementary Publications see *J.C.S. Perkin II*, 1974, Index issue. Items less than 10 pp. are supplied as full-size copies.

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prepared by the method of Vogel.[31] The appropriately substituted aniline was dissolved in acetic acid–water and to this solution was added a hot solution of sodium cyanate in water; the phenylureas precipitated out and were recrystallised from aqueous ethanol.

m- and *p*-Nitrophenylurea were prepared using the method of Wheeler and Walker.[32] The appropriately substituted aniline (5 g) was dissolved in warm glacial acetic acid (25 ml) and to this was added powdered sodium cyanate (4 g). The hot solution was quickly filtered and poured into an excess of cold water. Both *m*- (Found: C, 46.55; H, 4.05; N, 23.15. $C_7H_7N_3O_3$ requires C, 46.4; H, 3.85; N, 23.2%) and *p*-nitrophenylureas were recrystallised from hot aqueous acetic acid. The m.p.s of 4-isopropyl-, 4-n-butyl-, and 3-nitro-phenylurea were 157.0—158.5, 126.0—126.5, and 189.5—191.0°, respectively (Reichert microscopic m.p. apparatus). For 4-nitrophenylurea it was necessary to use a Kofler graduated hot bench in order to obtain a clean m.p., 227.5—228.0°. When 4-nitrophenylurea was slowly heated on the Reichert apparatus it was observed to undergo a change in structure which began to take place at temperatures below the m.p. Increasing the temperature by a further 50° beyond the m.p. (measured by the alternative method) did not cause the sample to melt. The change in structure is undoubtedly due to the conversion of the arylurea into the symmetrical diarylurea, a conversion which has often been observed for substituted ureas with high m.p.[33,34] Davis *et al.*[35,36] showed that equations (4)—(6) accounted for the production of symmetrical diarylureas.

$$\begin{tikzcd} & \mathrm{ArNH_2 + HNCO} \qquad (4) \\ \mathrm{ArNHCONH_2} \arrow[ur, "\Delta"] \arrow[dr, "\Delta"'] & \\ & \mathrm{ArNCO + NH_3} \qquad (5) \end{tikzcd}$$

$$\mathrm{ArNH_2 + ARNCO} \longrightarrow \mathrm{ArNHCONHAr} \qquad (6)$$

Method of Measurement of Basicity Constants and Analysis of Basicity Data.—These were similar to those already described.[1, 22(b)] All measurements were made at 25°. Least squares calculations were made on a Burroughs B6700 computer.

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