Spectrophotometric Determination of Basicity Constants. Benzamides and Phenylureas

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

The basicity constants $K_{\mathrm{BH^+}}$ of six 4-chlorobenzamides, four 4-methoxybenzamides, ten *N*-t-butylbenzamides, 3-bromo *N*-methylbenzamide, phenylurea, and seven substituted phenylureas have been evaluated in sulphuric acid at 25 °C. The protonation equilibria follow the H_{A} acidity function.

WE are currently investigating the hydrolyses of a large number of amides and ureas. Before any interpretation of these data can be made, it is necessary to correct the rate constants of hydrolysis for the degree of protonation of the substrate, and this necessitates measurement of $K_{\mathrm{BH^+}}$, the basicity constant for reaction (1). We

$$\mathrm{B + H^+ \rightleftharpoons BH^+} \qquad (1)$$

report details of our measurements of the basicity constant $K_{\mathrm{BH^+}}$ for six 4-chlorobenzamides, four 4-methoxybenzamides, ten *N*-t-butylbenzamides (including 4-chloro- and 4-methoxy-*N*-t-butylbenzamide), and 3-bromo-*N*-methylbenzamide, and for phenylurea and seven substituted phenylureas in sulphuric acid at 25·0 °C.

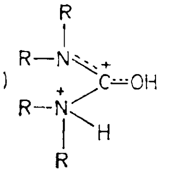
Protonation studies on carbonyl compounds are handicapped by uncertainties which arise from the solvent sensitivity of the u.v. spectra.[1-5] The benzamide series exhibit[6,7] strong solvent shifts on the absorption maxima (both $\lambda_{\mathrm{max.}}$ and $\varepsilon_{\mathrm{max.}}$) of the protonated form, and this leads to the variation in $\mathrm{p}K_{\mathrm{BH^+}}$ with wavelength.

Several procedures have been put forward to overcome the problem of medium effects in the determination of basicity constants. We have generally used a combination of the Davis–Geissman method[8] with that for the determination of ε_{B} and $\varepsilon_{\mathrm{BH^+}}$,[9] similar to that described by Farlow and Moodie.[7] Some of our results on the phenylureas have been reported briefly.[10]

The protonation of amides takes place on the carbonyl oxygen atom[11] and follows the H_{A} acidity function. No measurement has been reported on the basicity constants of ureas.

It is believed that urea, like amides, is mono-protonated in 100% sulphuric acid.[12] In super acid media the n.m.r. spectra of urea and *N*-methyl substituted ureas show the existence of diprotonation.[13,14] Cations of structure (I) have been formulated from such studies.[13]

(I)



R = Me or H

The position of the first protonation of urea and its derivatives has been the subject of much discussion,[15] but i.r., u.v., and n.m.r. data on crystalline salts of protonated urea[12,16-18] have indicated that the first protonation is on the carbonyl group.

RESULTS AND DISCUSSION

Table 1 lists the benzamides studied, their m.p.s and the wavelengths of $\lambda_{\mathrm{max.BH^+}}$ and $\lambda_{\mathrm{max.B}}$ at which measurements were made.

Table 1 also lists the values of $\mathrm{p}K_{\mathrm{BH^+}}$ obtained, together with the slopes and correlation coefficients of $\log_{10} I = \log_{10} C_{\mathrm{BH^+}}/C_{\mathrm{B}}$ against H_{A} and against H_0, and the % w/w acid composition at half protonation. The values of the slopes shown in Table 1 indicate that protonation of all the benzamides studied follows the H_{A} scale much better than the H_0 scale, and all the values of $\mathrm{p}K_{\mathrm{BH}}{}^+$ quoted were thus based on the H_{A} scale.

Table 2 lists similar data for the phenylureas studied. The values of the slopes shown in Table 2 again indicate that protonation of all the phenylureas studied follows the H_{A} scale much better than the H_0 scale and all the values of $\mathrm{p}K_{\mathrm{BH^+}}$ quoted were thus based on the H_{A} scale. This is the first time that the protonation of ureas has been studied in sufficient detail to determine their dependence on an acidity function. Armstrong and Moodie[3] found that the difference in the n.m.r. spectra of urea and its conjugate acid was too small for the $\mathrm{p}K_{\mathrm{BH^+}}$ to be measured. Farlow and Moodie[19] have

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estimated the pK_{BH^+} values for urea and ethylurea using the H_0 scale.

As can be seen from the data in Table 1, λ_{BH^+} and λ_B for 4-nitro- and 3,5-dinitro-*N*-t-butylbenzamide do not differ very much, and thus the absorbance difference was very small. For both these compounds therefore absorbance readings for the determination of $\log_{10} I$ were taken at λ_{BH^+} (262·5 and 227·5 nm respectively), and the value of I was calculated directly from equation (2).

$$I = (A - A_B)/(A_{BH^+} - A) \qquad (2)$$

Among those amides for which the slope d $\log_{10} I/$d$(-H_A)$ lies outside the range 1·05—0·95, which is considered a reasonable criterion of the base having a protonation equilibrium following H_A, thus leading to a valid[1] thermodynamic basicity constant K_{BH^+} is 3,5-dinitro-*N*-t-butylbenzamide with a slope of 0·927. This poor value is due, at least in part, to the lack of spectral changes accompanying protonation. The slope for 4-chloro-*N*-methylbenzamide lies outside the acceptable range, and again the experimental data were difficult to obtain precisely. Of the compounds whose basicity constants are listed in Table 1 only two have previously been determined in the literature, *i.e.* 4-chlorobenzamide[5] p$K_{BH^+} = -1·97$, slope 1·00 and 4-chloro-*N*-ethylbenzamide,[20] p$K_{BH^+} = -2·21$, slope = 0·92 compared with values of p$K_{BH^+} = -2·04$, slope = 0·975 and p$K_{BH^+} = -2·33$, slope = 0·993 respectively for data obtained in this investigation.

Since the protonation of ureas follows the H_A scale, it follows that any interpretation of kinetic data of ureas should be based on the H_A function. Other compounds whose protonation equilibria follow the H_A acidity function are amides,[21] pyridine 1-oxides,[22] sulphoxides,[23] carbamates,[3] and αβ-unsaturated aldehydes, ketones, and carboxylic acids.[24]

Recently Congdon and Edward[25] have measured the basicities of *N*-acetylthiourea, *N*-benzoylthioureas, and eight substituted *N*-benzoylthioureas. Thiocarbonyl protonation takes place in 35—60% sulphuric acid and

TABLE 1

Values of $\lambda_{max.BH^+}$ and $\lambda_{max.B}$ and protonation data for benzamides in sulphuric acid

Substituents	M.p./°C	$\lambda_{max.BH^+}$/nm	$\lambda_{max.B}$/nm	$-$pK_{BH^+} [a]	d $\log_{10}I/$d$(-H_A)$ [b]	Correln. coefft.	d $\log_{10}I/$d$(-H_0)$ [c]	Correln. coefft.	% w/w Acid at $C_{BH^+} = C_B$
4-Cl	179—180	250	237·5	2·04	0·975	0·999	0·626	0·999	40·0
N-Me-4-Cl	161—163	250	237·5	2·16	0·938	0·989	0·534	0·990	43·2
N-Et-4-Cl	112	250	237·5	2·33	0·993	0·992	0·558	0·982	46·5
N-Pr^i-4-Cl	146—147	252·5	237·5	2·12	0·989	0·998	0·582	0·991	42·2
N-Bu^n-4-Cl	80	252·5	237·5	2·10	0·954	0·996	0·561	0·995	42·0
N-Bu^t-4-Cl	99	250	235	1·93	0·975	0·998	0·561	0·990	38·4
N-Me-3-Br	91	242·5	230	2·16	0·973	0·996	0·579	0·999	43·2
N-Me-4-OMe	103—104	272·5	250	1·65	0·949	0·996	0·658	0·991	33·3
N-Pr^i-4-OMe	119·5—120·5	275	250	1·61	1·03	0·994	0·717	0·987	32·4
N-Bu^n-4-OMe	45	275	250	1·62	0·978	0·998	0·668	0·993	32·5
N-Bu^t-4-OMe	115	270	250	1·36	0·972	0·998	0·704	0·996	27·6
N-Bu^t-3-Cl	104	242·5	225	2·15	0·986	0·996	0·607	0·992	43·0
N-Bu^t-3,4,5-(OMe)$_3$	134—135	272·5	252·5	1·76	1·00	0·999	0·691	0·997	35·3
N-Bu^t-4-NO$_2$	160	262·5	270	2·16	1·01	0·992	0·585	0·996	43·2
N-Bu^t-4-Me	116·5—117	252·5	236	1·53	0·983	0·997	0·693	0·994	31·0
N-Bu^t-3-Me	89—89·5	242·5	230	1·73	0·997	0·996	0·701	0·992	34·6
N-Bu^t-4-F	130	242·5	227·5	1·81	0·963	0·998	0·666	0·993	36·3
N-Bu^t-3,5-(NO$_2$)$_2$	89	227·5	230	3·29	0·927	0·992	0·585	0·996	63·5
N-Bu^t-3-OMe	105	247·5	235	1·75	0·983	0·996	0·623	0·989	35·1

[a] 0·06 > S (standard deviation) > 0·02. [b] 0·043 > S > 0·009. [c] 0·045 > S > 0·011.

TABLE 2

Values of $\lambda_{max.BH^+}$ and $\lambda_{max.B}$ and protonation data for phenylureas in sulphuric acid

Substituent	M.p./°C	$\lambda_{max.BH^+}$/nm	$\lambda_{max.B}$/nm	$-$pK_{BH^+} [a]	d $\log_{10}I/$d$(-H_A)$ [b]	Correln. coefft.	d $\log_{10}I/$d$(-H_0)$ [c]	Correln. coefft.	% w/w H_2SO_4 at $C_{BH^+} = C_B$
H	146—148	227·5	235	1·30	0·942	0·998	0·671	0·995	26·2
3-Me	143	227·5	237·5	1·18	0·988	0·996	0·773	0·997	24·0
4-Me	185—187	225	237·5	1·22	0·978	0·996	0·765	0·988	24·8
4-OMe	168—169	227·5	236·5	1·05	0·748	0·996	0·619	0·937	21·5
4-OEt	173·5—175	230	236	1·15	0·801	0·996	0·645	0·991	23·4
4-F	190—191	225	235	1·18	1·04	0·994	0·891	0·989	24·0
4-Cl	213	230	241·5	1·48	0·945	0·997	0·678	0·993	29·8
4-Br	226—227	235	244	1·57	1·04	0·995	0·766	0·984	31·7

[a] 0·06 > S (standard deviation) > 0·02. [b] 0·043 > S > 0·009. [c] 0·045 > S > 0·011.

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follows the H_0 value of the solution. A second protonation, on the amide oxygen, takes place in 65—96% sulphuric acid, and follows the H_A value of the solution. The values of $-pK_{BH^+}$ and $-pK_{BH_2^{2+}}$ of *ca.* 4·5 which were obtained indicate that *N*-acylthioureas and *N*-benzoylthioureas are more weakly basic than the phenylureas we have studied.

Several of the slopes lie outside the acceptable range 1·05—0·95. The most serious discrepancies occur with 4-methoxy- and 4-ethoxy-phenylurea which have slopes of 0·748 and 0·801 respectively. In these compounds the ether substituent may have more effect on the urea group than it does on the amide group.

Ionisation ratios for the benzamides and phenylureas are listed in Supplementary Publication No. SUP 20713 (6 pp.).*

EXPERIMENTAL

Materials.—AnalaR sulphuric acid was standardised against sodium hydroxide. Solutions of the required percentage composition were prepared by dilution with deionised water by weighing.

The benzamide derivatives were obtained by treating the acid chloride (prepared by the action of phosphorus pentachloride on the corresponding benzoic acid) with the appropriate amine. The amides were recrystallised from aqueous ethanol.

Phenylurea (Fluka) and 3-methylphenylurea (Fluka) were recrystallised from ethanol. 4-Methyl-, 4-fluoro-, 4-bromo-, 4-methoxy-, and 4-ethoxy-phenylureas were made [26] by treating the appropriate aniline derivative, dissolved in acetic acid–water, with sodium cyanate. 4-Chlorophenylurea was recrystallised from acetic acid. 4-Methoxy- and 4-ethoxy-phenylureas were recrystallised from aqueous ethanol.

Kurzer [27] has shown that thermal conversion of arylureas into the corresponding diarylureas takes place extremely rapidly, even below the m.p. of the urea. This was found to be particularly true when the urea was substituted in the *para*-position. The m.p.s were often found [27] to be indefinite and corresponded to a mixture of mono- and *sym*-disubstituted urea. However, the ureas used in this investigation all melted cleanly, with m.p.s agreeing well with those in the literature.[28,29]

Method of Measurement of Basicity Constants.—The required acid (10 ml) was weighed, then mixed with 1 ml of a stock solution of the base ($2{\cdot}5 \times 10^{-3}$ g in 25 ml). The u.v. spectrum of the sample was then measured rapidly on a Cary 14 spectrophotometer. All spectra were reproducible and the spectral changes were reversible, *i.e.* no hydrolysis took place in the time taken for the basicity constant determination. All measurements were carried out at 25·0 °C.

Analysis of Basicity Data.—The pK_{BH^+} values were obtained by using a combination of the methods of Davis and Geissman [8] and Katritzky *et al.*[9] The absorbances at two wavelengths $\lambda_{max.BH^+}$ and $\lambda_{max.B}$ were measured. The difference between these two readings at the various acid concentrations was then calculated, and values of A_A and A_{BH^+} were obtained. These were substituted in equation (2), and $\log_{10} I$ was calculated. $\log_{10} I$ Values were plotted against H_A and pK_{BH^+} was obtained from the value of H_A when $\log_{10} I = 0$.

Least squares calculations were made on an IBM 1130 computer.

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* For details of Supplementary Publications see *J. Chem. Soc.* (*A*), 1970, Issue 20. Items less than 10 pp. are supplied as full size copies.

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