Novel Methods for determining Substrate Basicity Properties and Kinetic Parameters from Kinetic Data for Reactions in Strong Acid Solutions

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Many compounds react in strong mineral acid solutions by fast equilibrium protonation followed by a slow, rate-determining reaction of the cation. In mechanistic studies involving the variation with acidity of the rates of such reactions it is necessary to separate the effect of changing acidity on the reactivity of the cation from its effect on the amount of cation present. This latter factor is normally studied by a static determination of the compound's basicity. We now show that such determinations can be unnecessary, and that suitable treatment of plots of kinetic data against acidity can define both the static basicity behaviour of the compound and the kinetic behaviour of the cation. These novel methods have been applied to existing kinetic data for cyclohexadienone rearrangements and for amide hydrolyses. For the latter, a mechanism involving reaction through a single, most abundant, cation gives excellent correlation with the experimental results.

THE rates of reactions of many compounds in acidic solutions [see reactions (1) and (2)] have been correlated with acidity in attempts to define the mechanisms involved.[1-3] Frequently, plots have been made of the logarithm of the observed rate constant, log k_{obs} against the Hammett acidity function, H_0. According to the Zucker–Hammett hypothesis,[4] a linear graph with gradient -1 implied a unimolecular reaction of the monopronated substrate in the rate-determining step.

$$\mathrm{S} + \mathrm{H}^+ \overset{\text{fast}}{\rightleftharpoons} \underset{(1)}{\mathrm{SH}^+} \xrightarrow{\text{slow}} \text{Transition state } \ddagger \longrightarrow \text{Products} \quad (1)$$

$$\mathrm{S} + \mathrm{H}^+ \overset{\text{fast}}{\rightleftharpoons} \underset{(1)}{\mathrm{SH}^+} \xrightarrow[\text{slow}]{r\mathrm{H_2O}} \ddagger \xrightarrow{\text{fast}} \text{Products} \quad (2)$$

Although many such plots are linear, their gradients can differ markedly from -1 [1,2,4b] and the hypothesis lost much of its theoretical backing when it was shown that the protonation equilibria of many substrates do not follow the H_0 function. More recently, Bunnett and Olsen have used plots against (H_0 + log [H$^+$]) which frequently give better correlations.[5]

The variation of rate with acidity is due to the variation of the proportion of substrate which is present in the form of the reactive cation (1) [defined by the protonation equilibria of equations (3)] and of the inherent reactivity of this cation which can be expressed by equations (5).† In practice, it is necessary to separate out the effect of the basicity equilibrium of the substrate in order to define the kinetic parameters for the reactive cation. Although u.v. or n.m.r. spectroscopy can give rate data and, by extrapolation of the readings to zero time, also give points which allow a basicity determination, it is necessary in many cases for the kinetic experiments to be completely separate from those which provide basicity data (*e.g.* refs. 9—11). The acquisition of accurate data for basicity determinations is frequently made difficult by effects such as heat of mixing which can cause curvature of kinetic plots over the first few minutes and render uncertain the extrapolations to zero time, or by the need to correct for medium effects on spectra, and by the high accuracy and precision required in measurements, even for compounds which react slowly or not at all.[1,12] For compounds which react rapidly, for example for some of the cyclohexadienones we have studied which react with half-lives <10 s, the difficulties are considerable, or direct measurement of basicities is impossible. In many cases in the literature, basicity parameters have had to be assumed by analogy,[13] or chosen to provide good straight-line plots of kinetic data against acidity,[5] or measured at one temperature and used to interpret results obtained at a different temperature.[9,10]

I now suggest that the information provided by kinetic studies over a sufficient range of acidity contains the basicity data which are required, as well as the kinetic parameters characteristic of the cation. When these data have been extracted by simple graphical methods they may be re-inserted into the defining equations, and a simple programme run on an electronic calculator can be used to simulate the full range of kinetic points and check their fit against experiment.

Equations.—The equations upon which the methods are based are first given for the A-1 mechanism [reaction (1)]. They are given in terms of H_s, the acidity function appropriate to the substrate, and H_0. The indicator equations (3a and b) are standard; $m_s(H_s)_{\frac{1}{2}}$ is taken as the best estimate of the pK, and if H_s is strictly the appropriate acidity function $m_s = 1$ and $(H_s)_{\frac{1}{2}}$ is the pK: in that case, $m_0(H_0)_{\frac{1}{2}}$ is a poorer estimate of the pK. Equation (4) relates the observed rate constant k_{obs} to that of the reacting cation, k_1. Equations (5) have been discussed before;[6] $k_1{}^0$ is the value of k_1 extrapolated to a zero value of the acidity function, $k_{1,s}{}^0$ being the value at $H_s = 0$.

$$\log\,[\mathrm{SH^+}]/[\mathrm{S}] = m_s[(H_s)_{\frac{1}{2}} - H_s] \quad (3a)$$

$$= m_0[(H_0)_{\frac{1}{2}} - H_0] \quad (3b)$$

$$\begin{aligned} \mathrm{d[stoicheiometric\ substrate]/d}t &= -k_{\text{obs.}}\,\text{(stoicheiometric substrate)} \\ &= -k_1\ [\mathrm{SH^+}] \end{aligned}$$

$$\therefore \mathrm{d[S + SH^+]/d}t = -k_{\text{obs}}\,[\mathrm{S + SH^+}]$$

$$\therefore k_1 = k_{\text{obs}}\,\{1 + [\mathrm{S}]/[\mathrm{SH^+}]\} \quad (4)$$

$$\log k_1 = cH_s + \log k_{1,s}{}^0 \quad (5a)$$

$$= dH_0 + \log k_{1,0}{}^0 \quad (5b)$$

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† The applicability of equations (5) has been established for the cations of a range of cyclohexadienones [6-8] and will be discussed later.

Thus $\log k_{\mathrm{obs}}$

$$= cH_{\mathrm{s}} + \log k_{1,\mathrm{s}}^{0} - \log \{1 + [\mathrm{S}]/[\mathrm{SH}^{+}]\} \quad (6a)$$

$$= dH_{0} + \log k_{1,0}^{0} - \log \{1 + [\mathrm{S}]/[\mathrm{SH}^{+}]\} \quad (6b)$$

These equations apply at all acidities. In the 'low acidity' region, where the substrate is very little protonated, $[\mathrm{S}]/[\mathrm{SH}^{+}] \gg 1$ and equations (6) simplify to (7). Substitution from equation (3) then gives (8). At 'high acidities', $k_{\mathrm{obs}} = k_1$ and equations (5) apply directly.

At 'low acidity'

$$\log k_{\mathrm{obs}} = cH_{\mathrm{s}} + \log k_{1,\mathrm{s}}^{0} - \log [\mathrm{S}]/[\mathrm{SH}^{+}] \quad (7)$$

$$= \log k_{1,\mathrm{s}}^{0} + m_{\mathrm{s}}(H_{\mathrm{s}})_{\frac{1}{2}} + H_{\mathrm{s}}(c - m_{\mathrm{s}})$$

$$= \log k_{1,\mathrm{s}}^{0} + \mathrm{p}K + H_{\mathrm{s}}(c - m_{\mathrm{s}}) \quad (8a)$$

$$\doteqdot \log k_{1,0}^{0} + \mathrm{p}K + H_{0}(d - m_{0}) \quad (8b)$$

because $$m_{\mathrm{s}}(H_{\mathrm{s}})_{\frac{1}{2}} = \mathrm{p}K \text{ and } m_{0}(H_{0})_{\frac{1}{2}} \doteqdot \mathrm{p}K \quad (9)$$

Method 1.—The procedure requires that k_{obs} for the reaction be measured over a range of acidities, and that $\log k_{\mathrm{obs}}$ be plotted against an acidity function. If the acidity function appropriate to the substrate, H_{s}, is known, or guessed at on the basis of analogy, it should be used. The procedure tests this choice. Otherwise Hammett's H_0 can be used, and has the advantage of being reliably defined for the largest range of acids and temperatures. The equations show that the experimental curve [equation (6a or b)] resembles two straight lines, one at 'low acidity' (defined as giving very little protonation of the substrate), and the other at 'high acidity' (defined as giving almost complete protonation), joined by a curved region which falls around the pK of the substrate. In practice, one straight line is constructed through the 'low acidity' points, preferably using the least squares method, and another through the 'high acidity' points (see later, also). From equations (5a) and (8a), the gradient of the former is $(c - m_{\mathrm{s}})$, and of the latter c: the difference gives m_{s}. Thus if the appropriate acidity function H_{s} is used, the two gradients will differ by 1.0. The intercept of the former line, at $H_{\mathrm{s}} = 0$ is $(\log k_{1,\mathrm{s}}^{0} + \mathrm{p}K)$, and of the latter $(\log k_{1,\mathrm{s}}^{0})$: the difference is then the pK. If the H_0 acidity function is used instead of H_{s}, the parameters are those given in equations (5b) and (8b), in direct analogy. If kinetic data are available over the entire range of 'low' to 'high acidity,' this is the method of choice. The straight line constructions should be checked as in Method 2, and the parameters should then be refined, if possible, as outlined later.

Method 2.—Consideration of equations (5) and (6) shows that the deviation of the experimental curve from the extrapolated straight line of 'high acidity' readings is $\log \{1 + [\mathrm{S}]/[\mathrm{SH}^{+}]\}$. Measurement of these deviations allows the values of $[\mathrm{S}]/[\mathrm{SH}^{+}]$ and of $\log [\mathrm{S}]/[\mathrm{SH}^{+}]$ to be deduced, and standard 'basicity' plots can be made according to equations (3) to provide values of m_{s} and $(H_{\mathrm{s}})_{\frac{1}{2}}$ or m_0 and $(H_0)_{\frac{1}{2}}$. Similarly, the experimental curve deviates from the extrapolated straight line of 'low acidity' readings by $\log \{1 + [\mathrm{S}]/[\mathrm{SH}^{+}]\} - \log [\mathrm{S}]/[\mathrm{SH}^{+}]$, which equals $\log \{1 + [\mathrm{SH}^{+}]/[\mathrm{S}]\}$. Measurement of these deviations allows values of $[\mathrm{SH}^{+}]/[\mathrm{S}]$ to be deduced, and 'basicity' plots can again be made according to equations (3).

A further important result is obtained by extrapolating the 'high' and 'low acidity' straight lines, constructed above, to their intersection point. Solution of the simultaneous equations (5) and (8) shows this to be at an acidity $(H_{\mathrm{s}})_{\frac{1}{2}}$ or $(H_0)_{\frac{1}{2}}$, *i.e.* the half-protonation acidity for the substrate, and to be uniquely at a $\log k_{\mathrm{obs}}$ value 0.30 above the experimental curve. This allows a valuable check on the straight line constructions. Moreover, if the kinetic data are limited, for example, due to extreme speed or slowness at high or low acidities, it may still be possible to cover one or other 'straight line' portion and some or all of the curved portion of the plot of $\log k_{\mathrm{obs}}$ *versus* acidity. In this case, the deviations of the curve from the extrapolated 'straight lines' can give the basicity parameters, and a check on the acidity of half-protonation. This method can be particularly valuable when a compound reacts too quickly at high extents of protonation for Method 1 to be used or for the cation to be accessible for a conventional basicity determination. The parameters which are deduced should be refined to give the best fit to experiment (see later).

It is important to define the experimental points which can be used to construct the straight lines at 'low' and 'high' acidities. Ideally, points would be taken at least $2H_{\mathrm{s}}$ units from the pK, so that protonation is $<1\%$ or $>99\%$ complete, but this may drastically limit the available data. In practice, one can use 'first-try' straight lines drawn through points away from the curved part of the plot, with the '0.30 deviation' concept, to estimate the half-protonation acidity. Then, if the appropriate acidity function is being used, one may take points to within xH_{s} units of this acidity to obtain a $y\%$ error in the gradient, where x and y have the values (1.5,1.3%), (1.7,0.8%), (1.9,0.5%).* These points may be used to redefine $(H_{\mathrm{s}})_{\frac{1}{2}}$ and the cycle may be repeated.

Refinement of Parameters.—The parameters $(H)_{\frac{1}{2}}$, m, c or d, and $\log k_1^0$ derived from the experimental plots can be used to calculated 'simulated' values of $\log k_{\mathrm{obs}}$ at any chosen values of the acidity function H using equations (3) and (6). The sum of the squares of the differences between the experimental and simulated values is calculated, to test the quality of fit. By varying the parameters within the limits allowed by uncertainties in the data and graphical Methods 1 and 2 the quality of fit can be optimised. The equations can be handled by computer, and the necessary variations made automatically. For routine tests a programmable calculator allows very fast and easy refining of parameters.

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* The error estimates result from substituting various values of $H_{\mathrm{s}} - (H_{\mathrm{s}})_{\frac{1}{2}}$ into equation (6) to define values of $\log (k_{\mathrm{obs}} - \log k_1^{0})$ The gradients of lines linking pairs of such points are compared with those defined by equation (8).

Treatment of Data for A-2 *Reactions*.—The linear relationship between $\log k_1$ and H_s [equations (5)] for A-1 reactions implies [6] a linear relationship between the acidity functions appropriate to the transition state, $H_‡$ and the protonated substrate, H_s. This agrees with the general finding [14] that H_0 and many other acidity functions are related in an approximately linear manner. For reaction (2), in which r molecules of water and the protonated substrate are involved in the rate-determining step, the kinetic scheme must be modified. Acidity function definitions for $S \rightleftharpoons SH^+$ give equations (10), and equation (11) for the pseudo-equilibrium between S, SH^+, rH_2O, and the transition state. Equation (12) follows. The kinetic equation (13) combined with the Brönsted equation (14) and equation (12) gives (14). Provided $H_s - H_‡$ is proportional to H_s (*i.e.* that $H_‡$ is proportional to H_s) as in the A-1 reactions, equation (15) has the same form as (6) and the same procedure can be used. It should be noted that the transition state includes r molecules of water and

$$H_s = -\log a_{H^+} - \log f_s/f_{SH^+} \qquad (10)$$

$$H_‡ = -\log a_{H^+} - r \log a_{H_2O} - \log f_s/f_‡ \qquad (11)$$

$$\therefore H_‡ - H_s = \log f_‡/f_{SH^+} - r \log a_{H_2O} \qquad (12)$$

$$k_{obs}[S + SH^+] = k_2[SH^+]a^r_{H_2O}$$

$$\therefore \log k_{obs} = \log k_2 + r \log a_{H_2O} - \log (1 + [S]/[SH^+]) \qquad (13)$$

$$\log k_2 = \log k_0 + \log f_{SH^+}/f_‡ \qquad (14)$$

$$\therefore \log k_{obs} = \log k_0 + H_s - H_‡ - \log \{1 + [S]/[SH^+]\} \qquad (15)$$

this assumption of proportionality cannot be generally true. The validity of the assumption should be reflected in a good linear plot of $\log k_{obs}$ ($= \log k_2$) in the region of complete protonation. If the value of r is known, perhaps from other studies of closely related compounds,[14] the plots may be of ($\log k_{obs} - r \log a_{H_2O}$) against H_s or H_0, which directly reflect the change in the ionisation ratio [equations (6), with $c = d = 0$]. The physical basis of this approach is that used by Yates in his 'r treatment',[14] that $\log f_{SH^+}/f_‡$ does not vary much with acidity and can be assumed constant. An alternative procedure, which does not require knowledge of r, uses the Bunnett and Olsen equations.

Use of Bunnett and Olsen's Equations.—Bunnett and Olsen published equations relating protonation equilibria

$$H_0 + \log [SH^+]/[S] = \phi_e(H_0 + \log [H^+]) + pK \qquad (16)$$

$$\log k_1 = \log k_0 + \phi_k(H_0 + \log [H^+]) \qquad (17)$$

$$\therefore \log k_{obs} = \log k_0 + \phi_k(H_0 + \log [H^+]) - \log \{1 + [S]/[SH^+])\} \qquad (18)$$

[equations (16)] and rate constants [equations (17)] * to acidity.[5,15] These presuppose a different relationship between activity coefficients, and therefore between acidity functions, from that implied by equations (6), and have been suggested [16] to be of more general applicability. The methods outlined earlier can be used with slight modification.

The plots now use ($H_0 + \log [H^+]$) as the measure of acidity, instead of H_s or H_0. Equation (18) relates k_{obs} to acidity, with the values of $[S]/[SH^+]$ defined by equation (16), and replaces equation (6). A plot of $\log k_{obs}$ is a curve which, at 'high acidities' becomes the straight line of equation (19). This defines $\log k_0$ and ϕ_k

At high acidity:

$$\log k_{obs} = \log k_0 + \phi_k(H_0 + \log [H^+]) \qquad (19)$$

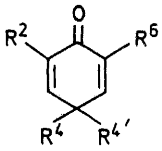
At low acidity, $[S]/[SH^+] \gg 1$:

$$\log k_{obs} + H_0 = (\phi_k + \phi_e)(H_0 + \log [H^+]) + \log k_0 + pK \qquad (20)$$

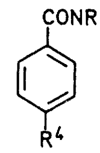
as in ref. 5). A *separate* plot must be made of ($\log k_{obs} + H_0$), which is again a curve but becomes the straight line of equation (20) at 'low acidity'. This yields values of ($\phi_k + \phi_e$) and of ($\log k_0 + pK$), which are used with the values of $\log k_0$ and ϕ_k to define ϕ_c and pK. This replaces Method 1. The deviation of either curve from its extrapolated straight line portion can be used directly for Method 2, as shown earlier. The derived values of $[S]/[SH^+]$ are then used in a plot according to equation (16). The parameters derived by the graphical procedures should be refined, or their limits defined, using a program similar to that described earlier.

DISCUSSION

Our new procedures have been applied to the data for rearrangement of cyclohexadienones (I), which are known to follow an A-1 mechanism.[6-8] The results are given in Table 1, which lists the pK, m_0, and/or $(H_0)_{\frac{1}{2}}$ values derived, and the kinetic parameters d and $\log k_1{}^0$. Comparison with the results of the previous determinations of basicity shows the agreement to be good. For compounds (I; $R^4 = R^{4'} = Me$) and (I; $R^4 = Me$, $R^{4'} = Et$) there are insufficient data available for low acidities, and the 'low acidity' straight line of equation (8b) could not be defined for Method 1; for the former compound we supplemented our data with those of Vitullo and Grossman,[17] but the combined results are not quite as uniform as usual. The case of (I; $R^2 = Br$, $R^4 = R^{4'} = Me$) [18] is of particular note because the very fast rearrangement in concentrated acids makes a normal basicity determination difficult and uncertain.



(I)



(II)

The basicity measurements published for the dienones (I) [6-8] were related primarily to the amide acidity func-

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* The subscripts in ϕ_e and ϕ_k are used to emphasise the equilibrium (basicity) or kinetic significance of these quantities.

TABLE 1

Kinetic and basicity parameters derived for cyclohexadienones (I) from their rearrangements in aqueous sulphuric acid at 25.0 °C

Compound	Line, equation (8b) [a]		Line, equation (5b)							
	Intercept [b]	Gradient [c]	Intercept log k_1^0	Gradient [d]	$m_0(H_0)_{\frac{1}{2}}$ [e] = pK	m_0 [f]	$(H_0)_{\frac{1}{2}}$ [g]	$(H_0)_{\frac{1}{2}}$ [h]	$(H_0)_{\frac{1}{2}}$ [i]	$(H_0)_{\frac{1}{2}}$ [j]
(I; R^4 = Me, $R^{4'}$ = Et) [8]	[k]	[k]	−4.08 [l]	−0.36	[m]					−3.0
(I; R^4 = Me, $R^{4'}$ = Pr^n) [8]	−6.57	−1.12	−3.71	−0.26	−2.86 [n]	0.86	−3.32	−3.3	−3.4	−3.3
(I; R^4 = $R^{4'}$ = Me) [6b]	−8.08	−1.17	−5.23	−0.29	−2.85 [o]	0.88	−3.24	−3.25	−3.3	−3.1
(I; R^2 = R^4 = $R^{4'}$ = Me) [7]	−7.04	−1.00	−4.52	−0.25	−2.52 [p]	0.75	−3.36			−3.4
(I; R^2 = R^4 = $R^{4'}$ = R^6 = Me) [7]	−7.50	−1.16	−3.24	−0.13	−4.26 [q]	1.03	−4.13	−4.15	−3.9	−4.4
(I; R^2 = Br, R^4 = $R^{4'}$ = Me) [17]	−9.15	−1.08	−4.00	−0.25	−5.15 [r]	0.83	−6.20	−6.2	−6.2	−6.2

[a] ' Low acidity ' straight line. [b] Intercept = log $k_1^0 + m_0(H_0)_{\frac{1}{2}}$. Closest estimate to log k_1^0 + pK. [c] Gradient = $d - m_0$. [d] ' High acidity ' straight line. [e] Difference in intercepts of ' low acidity ' and ' high acidity ' lines, equations (8b) and (5b). [f] Difference in gradients of ' high acidity ' and ' low acidity ' lines, equations (5b) and (8b). [g] H_0 at half-protonation by dividing preceding two columns. [h] H_0 value at which ' low acidity ' and ' high acidity ' lines, equations (8b) and (5b), intersect. [i] H_0 value at which ' low acidity ' line, equation (8b), lies 0.30 above the experimental curve of log k_{obs} *versus* H_0. [j] H_0 value at which ' high acidity ' line, equation (5b), lies 0.30 above the experimental curve. [k] Too few points available. [l] The point at highest acidity is omitted. [m] Lit. data [8] $(H_0)_{\frac{1}{2}}$ −2.96 ± 0.10, m_0 0.65 ± 0.15, pK −2.26 ± 0.10, log k_1^0 −4.00, d −0.337. [n] Lit. data [8] $(H_0)_{\frac{1}{2}}$ −3.32 ± 0.24, m_0 0.54 ± 0.04, pK −2.43 ± 0.12, log k_1^0 −3.89, d −0.30. [o] Lit. data [6] $(H_0)_{\frac{1}{2}}$ −3.15, m_0 0.53 ± 0.03, pK −2.37 ± 0.03, log k_1^0 −5.09, d −0.267. [p] Lit. data [7] $(H_0)_{\frac{1}{2}}$ −3.27 ± 0.12, m_0 0.69 ± 0.03, pK −2.7 ± 0.2, log k_1^0 −4.53 ± 0.05, d −0.25. [q] Lit. data [7] $(H_0)_{\frac{1}{2}}$ −4.20 ± 0.07, m_0 1.01 ± 0.03, pK −4.2 ± 0.1, log k_1^0 −3.35 ± 0.06, d −0.15. [r] Lit. data [18] pK −4.1 ± 0.15 on the H_A scale corresponding to half protonation in (74.3 ± 1.8)% H_2SO_4. Our present determination corresponds to half-protonation in 72.3% H_2SO_4.

tion, H_A, as determined by Yates *et al.*[19] It is difficult to refine properly the parameters deduced from Methods 1 and 2 when this acidity function is used. This is because H_A was assumed to coincide with H_0 at low acidities and then to diverge at higher acidities.[19] This assumption is not made in a recent re-determination of H_A[20] which allows better correlations with equations (6). Figure 1 shows the experimental points and the derived curve, based on the parameters deduced by Method 1, for (I; R^4 = Me, $R^{4'}$ = Pr^n, R^2 = R^6 = H).

Our procedures have also been applied to some recent data on the acid hydrolysis at 100.7 °C of substituted benzamides. We first assume that equations (6) apply directly to these reactions (see the earlier discussion of *A*-2 reactions), as evidenced by the good linearity of the ' high acidity ' straight lines. For example, for the two amides for which most kinetic points are reported at high acidities, 4-chlorobenzamide and 4-chloro-*N*-methylbenzamide, these lines have correlation coefficients 0.9986 and 0.9991, respectively, in the plots against H_0

TABLE 2

Kinetic and basicity parameters derived from hydrolyses of substituted benzamides (II) in aqueous sulphuric acid at 100.7 °C, using the H_A acidity function

Compound	Line, equation (8a) using H_A scale [a]		Line, equation (5a) H_A scale [d]							
	Intercept [b]	Gradient [c]	Intercept log k_1^0	Gradient [c]	$m_A(H_A)_{\frac{1}{2}}$ = pK [e]	m_A [f]	$(H_A)_{\frac{1}{2}}$ [g]	$(H_A)_{\frac{1}{2}}$ [h]	$(H_A)_{\frac{1}{2}}$ [i]	$(H_A)_{\frac{1}{2}}$ [j]
(II; R = R^1 = R^4 = H) [10,k]	−3.40	−0.40	−1.85	0.72	−1.55	1.12	−1.38	−1.4	−1.6	−1.2
(II; R = R^4 = H, R^1 = Me) [10,l]	−4.52	−0.43	−3.00	0.64	−1.52	1.07	−1.42	−1.4	−1.4	−1.4
(II; R = R^1 = Me, R^4 = H) [10,m]	−3.90	−0.40	−2.60	0.70	−1.30	1.10	−1.18	−1.2	−1.2	−1.2
(II; R = R^1 = H, R^4 = Cl) [9,n]	−3.40	−0.55	−1.36	0.86	−2.04	1.41	−1.45	−1.45	−1.4	−1.5
(II; R = H, R^1 = Me, R^4 = Cl) [9,o]	−4.75	−0.88	−2.94	0.61	−1.79	1.49	−1.20	−1.2	−1.2	−1.2

The H_A scale is that of ref. 20.

[a] ' Low acidity ' straight line. [b] Intercept = log $k_1^0 + m_A(H_A)_{\frac{1}{2}}$; closest estimate to log k_1^0 + pK. [c] Gradient = $c - m_A$. [d] ' High acidity ' straight line. [e] Difference in intercepts of ' low acidity ' and ' high acidity ' lines, equations (8a) and (5a). [f] Difference in gradients of ' high acidity ' and ' low acidity ' lines, equations (5a) and (8a). [g] H_A at half-protonation, by dividing preceding two columns. [h] H_A value at which ' low acidity ' and ' high acidity ' lines, equations (8a) and (5a), intersect. [i] H_A value at which ' low acidity ' line, equation (8a) lies 0.30 above the curve of log k_{obs} *versus* H_A. [j] H_A value at which ' high acidity ' line, equation (5a) lies 0.30 above the experimental curve. [k] Lit. data,[10] pK −1.84, m_A 1.03, corresponding to pK −1.51 on the H_A scale used by us. [l] Lit.[10] pK −1.7, corresponding to −1.37 on our scale. [m] Lit.[10] pK −1.4, corresponding to −1.07 on our scale. [n] Lit.[9] pK −2.04, corresponding to −1.72 on our scale. The use of the H_0 scale determined [21] at 90 °C gave entries −3.58, −0.55, log k_1^0 −1.70, d 0.54, pK −1.88, m_0 1.09, and $(H_0)_{\frac{1}{2}}$ estimates of −1.72, −1.73, −1.7, and −1.7. [o] Lit.[9] pK −2.16, m_A 0.938, corresponding to pK −1.84 on our scale. The use of the H_0 scale determined [21] at 90 °C gave entries −4.83, −0.87, log k_1^0 −3.23, d 0.38, pK −1.60, m_0 1.25, and $(H_0)_{\frac{1}{2}}$ estimates of −1.28, −1.27, −1.3, and −1.3.

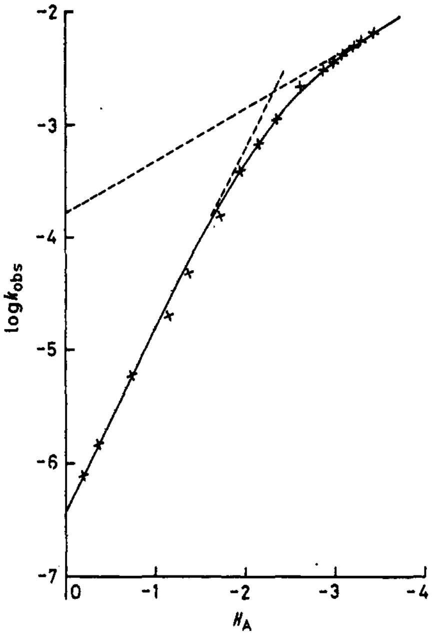

FIGURE 1 Plot of log k_{obs} against H_A for 4-methyl-4-n-propylcyclohexa-2,5-dienone. The line is calculated using equation (6a); log $k_1^0 = -3.76$, $c = -0.466$, $m_A = 1.154$, $(H_A)_{\frac{1}{2}} = -2.32$; the points are experimentally determined,[8] and the H_A scale is that of ref. 20

(using H_0 data for 90 °C). The plots were primarily made using Edward and Wong's H_A function,[20] with the results shown in Table 2. When the differences between this scale and the previous one [19] are allowed for, the agreement between our basicity data and those reported from static basicity determinations is very good. It is clear, however, that exact adherence to the H_A scale is not found, particularly for 4-chlorobenzamide. This is presumably because the H_A scales were determined at 25 °C, whereas the kinetic measurements were made at *ca.* 100 °C. The data for two amides were also plotted against H_0 as determined at 90 °C (the closest available to 100 °C),[21] with the results shown in footnotes *n* and *o* to Table 2. They suggest that at 100.7 °C the Hammett H_0 function applies better than does the 25 °C H_A function.

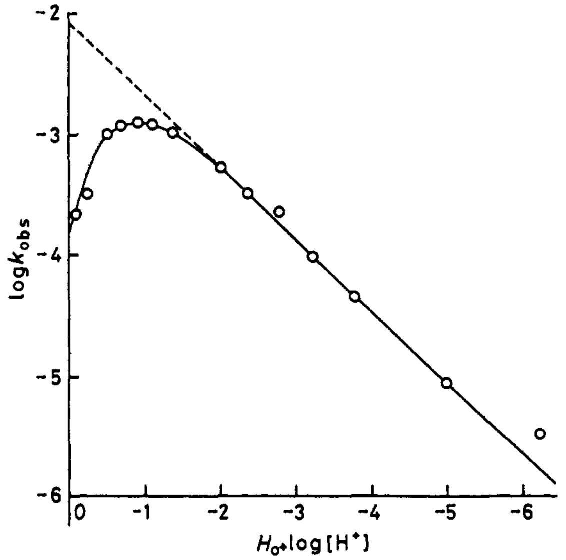

FIGURE 2 Plot of log k_{obs} against (H_0 + log [H$^+$]) for 4-chlorobenzamide. The line is calculated using equation (18), and log $k^0 = -2.06$, $\phi_k = 0.60$, and the pK and ϕ_e values derived from Figure 3. The points are from ref. 9

A measure of the quality of correlation of data to equations (6) is given by the results for 4-chlorobenzamide. The experimental values of log k_{obs} at each value of H_0 were reproduced with deviations between zero and 0.08, with a root mean square error of 0.029, which is less than twice the estimated error for each experimental point. The root mean square error for the correlation against H_A, using the parameters quoted in Table 2, is 0.014.

Our procedures using Bunnett and Olsen's equations are shown in Figures 2 and 3 for 4-chlorobenzamide, using the kinetic data of ref. 9. Insufficient data are available to define a 'low acidity' straight line according to equation (20), so Method 2 is used to give the values of pK and ϕ_e (Figure 3). The 'high acidity' line defines ϕ_k and log k_1^0 (Figure 2). The experimental results are compared with those calculated using equation (19) in Figure 2. Again, the correlations are excellent and the near-zero value of ϕ_e shows the compound to be close to a Hammett base.

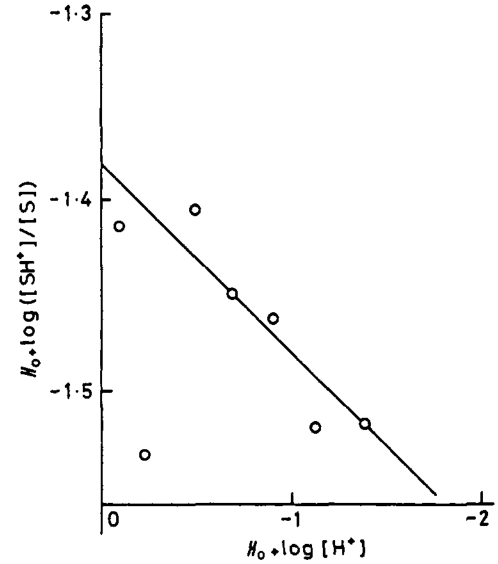

FIGURE 3 Use of Method 2, with Bunnett and Olsen's equations, for 4-chlorobenzamide. Deviations of the curve from the straight line in Figure 2 give log (1 + [S]/[SH$^+$]). The derived values of log [SH$^+$]/[S] are plotted here according to equation (16). The least-squares straight line (ignoring the single deviant point) gives p$K = -1.38 \pm 0.02$, $\phi_e = 0.10 \pm 0.02$

The implication for the mechanism of amide hydrolysis is that a mechanism involving a single reactive cation allows an excellent correlation of rates over the entire range of acidity studied. This kinetically active cation has a very similar pK to that studied in static basicity measurements, and is presumably the same, *O*-protonated cation. It does not seem to be necessary, in these cases, to postulate[9] reaction *via* a minor, *N*-protonated cation or *via* a mixture of *O*- and *N*-cations.

Note added in proof: Computer programs are available which optimise the fit of calculated to experimental data (see p. 1030). Written in ANSI Fortran IV, they use a direct grid search method and vary the constants in equations (6), or (16) and (18), to minimise the sum of squares of deviations of the calculated from the experimental rate constants. The program KINBASIC correlates rates with H_0 and H_A, and BOKINBASIC fits them to Bunnett and Olsen's equations. Copies of the program listings are available from the author.

[8/491 *Received*, 17*th March*, 1978]

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