Effects of Substituents on the Reactivity of the Pyridine Nitrogen

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Summary Consideration of the protonation equilibria and rates of quaternisation of substituted pyridines shows that dipolar electron withdrawing groups exert their influence by induction alone; this has an important bearing on the validity of the YT (Yukuwa–Tsuno) and DSP (Dual Substituent Parameter) equations in this system.

The basicity and nucleophilicity of pyridine nitrogen are highly responsive to substituent effects, forming sensitive probes much used in Brønsted and Hammett correlations.[1,2,3] Doubt has arisen, however, over the mode by which such effects should be rationalized, and its clarification becomes of importance, particularly as we wish to employ in further studies the high sensitivity of the pyridine nitrogen to investigation of substituent–solvent effects and to determination of multiple structure reactivity correlations.[4] One approach[1,5] is to use equation (1) for pyridinium ion dissociations, unless (–I–R) type substituents are present, when equation (2) applies.

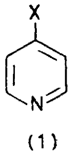
$$\log\,(K/K_0)_1 = \rho\sigma \qquad (1)$$

$$\log\,(K/K_0)_1 = \rho\sigma_I \qquad (2)$$

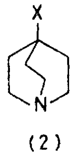
The necessity of σ_I for groups of potential (–I–R) form has also been demonstrated for quaternisations[5] and pyridine-catalysed hydrolyses of arylsulphonyl halides.[2] Equations (1) and (2) have, however, been criticised as being unrealistic in terms of chemical experience, equation (3) being put forward as the more valid approach.[6,7]

$$\log\,(K/K_0)_1 = 5{\cdot}5\sigma_I + 2{\cdot}69\sigma_R{}^{+} \qquad (3)$$

Moreover, analysis[8] of equation (3) for 4-substituted pyridines (**1**) employing recent results[9] on the protonation of 4-substituted quinuclidines (**2**) is claimed to afford strong evidence for its applicability. Nevertheless we still believe that equations (1) and (2) provide the more realistic treatment, for equation (3) fails to accommodate the fact that dipolar electron acceptors in the 4-position† influence the pK_a values by induction alone, although evidence for this appears unambiguous,[10] constituting a quite definite piece of chemical experience. Further, the pK_a values of 4-substituted quinuclidines (**2**) convincingly corroborate equations (1) and (2). Table 1 gives the relevant data.



(1)



(2)

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† These are really the only substituents on which an analysis can be based, because for resonance donors there is a correlation $\sigma_B{}^{+} = 1{\cdot}99\ \sigma_R$; $n = 9$, SD $= 0{\cdot}12$, $r = 0{\cdot}983$, so that in this case $\rho\sigma_p = \rho\sigma_I + 0{\cdot}5\,\rho\sigma_R{}^{+}$. The COMe, NO_2, CO_2Me, and CN groups make a contribution of *ca.* 0·4 pK_a units to the final (resonance) term on the r.h.s. of equation (3) well outside the limits of error in experimental pK_a determination. SD = standard deviation.

TABLE 1. Ionisation data.

4-X	σ_I	σ_R(BA)	σ_p(BA)	σ_R^+	log $(K/K_0)_1$	log $(K/K_0)_2$	R_p[a]
NMe_2	0·06	−0·83	−0·77	−4·38	−4·38	0·97	−5·35
NH_2	0·12	−0·82	−0·70	−1·61	−3·91	0·98	−4·89
NHCOMe	0·26	−0·36	−0·10	−0·86	−0·66	1·58	−2·28
OMe	0·27	−0·61	−0·34	−1·02	−1·37	1·81	−3·25
Me	−0·04	−0·11	−0·15	−0·25	−0·82	0·11	−0·91
Ph	0·10	−0·11	−0·01	−0·30	−0·14	0·94	−1·01
Cl	0·46	−0·23	0·23	−0·36	1·38	2·51	−1·29
Br	0·44	−0·19	0·25	−0·30	1·46	2·65	−1·36
I	0·39	−0·16	0·23	−0·25	1·20	2·34	−1·38

[a] Defined in text, equation (4).

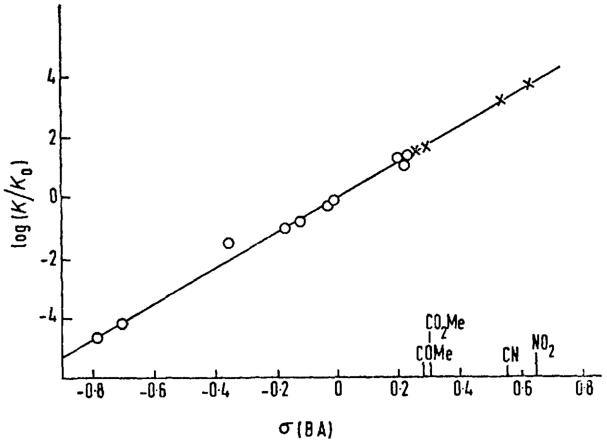

FIGURE 1. Log $(K/K_0)_1$ *vs.* σ_p using σ_I for COMe, CO_2Me, CN, and NO_2. $\rho = 5{\cdot}66$; $n = 14$, SD(ρ) = 0·12, $r = 0{\cdot}998$. Excluding OMe, $\rho = 5{\cdot}75$; $n = 13$, SD(ρ) = 0·06, $r = 0{\cdot}999$.

Figure 1 gives the plot of $\log(K/K_0)_1$ *vs.* σ(BA) or σ_I for COMe, CO_2Me, CN, and NO_2, and Figure 2 gives the plot of pK_a(1) *vs.* pK_a(2) for dipolar electron withdrawing groups.[5,8,9] For these latter substituents there is no correlation between σ_R^+ *vs.* R,[8] but there is an essentially constant ratio between log $(K/K_0)_1$ and log $(K/K_0)_2$ indicating that the same mechanism for electron withdrawal, which must be induction alone, operates in both systems, as demanded by equation (2) for pyridine. This ratio of 1·19 : 1 is a measure of the relative efficiency of induction through the two ring systems; it allows prediction of ρ for the log $(K/K_0)_2$ *vs.* σ_I correlation as 5·66/1·19 = 4·76, in close agreement with the value of 4·81 calculated for the complete range.[8] We can further predict equation (4) for the expression of resonance effects in the pyridine ring. Plotting R_p *vs.* σ_R yields $\rho = 5{\cdot}66$;

$$\log(K/K_0)_1 - 1{\cdot}19 \log (K/K_0)_2 = R_p = 5{\cdot}66\sigma_R \qquad (4)$$

$n = 9$, SD(ρ) = 0·30, $r = 0{\cdot}991$, the only point deviating markedly being OMe, as in Figure 1.‡

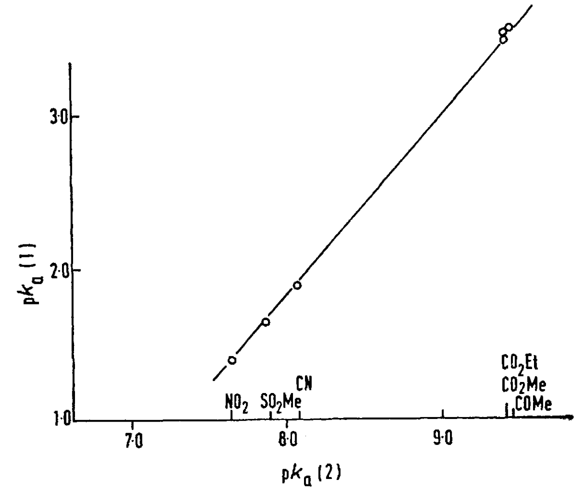

FIGURE 2. pK_a (1) *vs.* pK_a (2) for dipolar electron withdrawing groups.

TABLE 2. Influence of the COMe group on the reactivity of pyridine.

	4-COMe[a]	3-COMe[a]	H[a]	α[a]
pKa, H_2O, 25 °C	3·51[b]	3·43[c]	5·21[b]	0·96
” ” 25 °C[d]	3·62	3·26	5·31	0·82
” ” 37 °C[d]	3·58	3·21	5·35	0·83
” ” 25 °C[e]	3·52	3·26	5·27	0·88
$PhSO_2Cl$, MeOH, 25 °C[f]	1·73	1·60	2·48	0·85
EtI,[g] Me_2CO, 25 °C	0·62	0·67	1·20	1·11
” MeCN, 25 °C	0·63	0·66	1·33	1·04
” $MeNO_2$,25 °C	0·79	0·72	1·40	0·90
” $PhNO_2$, 25 °C	0·63	0·69	1·31	1·01
” ” 40 °C	1·23	1·25	1·88	1·03
” ” 50 °C	1·93[h]	1·91	2·58[h]	0·97

[a] See equation (5). [b] Ref. 5. [c] D. D. Perrin, 'Dissociation Constants of Organic Bases in Aqueous Solution,'' Butterworths, London, 1965. [d] M. R. Chakrabarty, C. S. Handloser, and M. W. Mosher, *J.C.S. Perkin II*, 1973, 938. [e] I. R. Bellobono and M. A. Monetti, *J.C.S. Perkin II*, 1973, 790. [f] Ref. 2, 2 + log *k*. [g] 6 + log *k*. [h] Ref. 5 gives 1·87 and 2·50 for 4-COMe and H, respectively.

Table 2 gives data for the influence of the COMe substituent on the reactivity of the nitrogen. The quaternisation rates were measured using a conductiometric technique. The COMe substituent was selected because the contribution of −R to its overall effect is the largest for this type of substituent (36% of its total effect; $\sigma_I = 0{\cdot}28$, $\sigma_R = 0{\cdot}16$), and therefore most readily detected, and rate determinations are not excessively slow or complicated by side reactions as for CN or NO_2.[5] The influence of the 4-COMe

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‡ If Figure 1 is used to calculate an effective σ value for OMe of 0·24, and thus a σ_R value of −0·52, then ρ becomes 5·86 for the R_p *vs.* σ_R correlation; SD(ρ) = 0·23, $r = 0{\cdot}995$.

relative to the 3-COMe group is expressed in Table 2 according to equation (5). The resultant value of α,

$$\frac{\log (k_{4-\mathrm{Ac}}/k_{\mathrm{H}}}{\log (k_{3-\mathrm{Ac}}/k_{\mathrm{H}})} = \frac{\sigma_{4-\mathrm{Ac}}}{\sigma_{3-\mathrm{Ac}}} = \alpha \qquad (5)$$

$0{\cdot}95 \pm 0{\cdot}11$, essentially constant for all conditions of reactivity, solvent, and temperature, particularly when experimental error is taken into account (see for example the several values reported for pK_a, H_2O, 25 °C) can only be logically interpreted in terms of electron withdrawal by induction alone; the COMe substituent, and presumably therefore others of (–I–R) type fail to exert their –R effect in these cases. The failure of the multiparameter approach of the form of equation (3) for the definition of pyridine pK_a's, which Topsom has interpreted as an optimum situation for its operation,[6] and in other examples[11] equally critical, cast doubt on the general validity of this approach however theoretically pertinent it may appear.[12]

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[1] G. B. Ellam and C. D. Johnson, *J. Org. Chem.*, 1971, **36**, H284.

[2] O. Rogne, *J. Chem. Soc.* (*B*), 1970, 727.

[3] See, for example, J. A. Feather and V. Gold, *J. Chem. Soc.*, 1965, 1752; J. A. Zoltewicz and L. W. Deady, *J. Amer. Chem. Soc.*, 1972, **94**, 2765.

[4] C. D. Johnson, *Chem. Rev.*, 1975, **75**, 755.

[5] A. Fischer, W. J. Galloway, and J. Vaughan, *J. Chem. Soc.*, 1964, 3591, 3596.

[6] R. T. C. Brownlee and R. D. Topsom, *Tetrahedron Letters*, 1972, 5187.

[7] S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Progr. Phys. Org. Chem.*, 1973, **10**, 1.

[8] C. A. Grob and R. W. Taft, *J. Amer. Chem. Soc.*, 1974, **96**, 1236.

[9] E. Ceppi, W. Eckhardt, and C. A. Grob, *Tetrahedron Letters*, 1973, 3627; C. A. Grob and M. G. Schlageter, *Helv. Chim. Acta*, 1976, **59**, 264.

[10] J. M. Essery and K. Schofield, *J. Chem. Soc.*, 1963, 2225 and refs. therein.

[11] C. Eaborn, R. Eastmond, and D. R. M. Walton, *J. Chem. Soc.* (*B*), 1970, 752; 1971, 127.

[12] See for example, J. S. Hine, 'Structural Effects on Equilibria in Organic Chemistry,' Wiley, New York, 1975, p. 77. Recent calculations suggest however that discrete sets of σ values may generally be appropriate: W. L. Jorgensen, *J. Amer. Chem. Soc.*, 1977, **99**, 3836. Note the correspondence between the YT and DSP equations: P. R. Wells, 'Linear Free Energy Relationship,' Academic Press, New York, 1968, p. 28.