Modified CNDO/2 calculations were carried out using a modified CNDO/2 program supplied by H. Bock and described in ref 15. The geometry of imidazole was taken from ref 16.

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Substituent Effects on Pyridine Nitrogen Reactivity

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The observations of Johnson, Roberts, and Taylor which were interpreted to indicate that electron acceptor substituents exert only a localized (field and/or inductive) effect can be accounted for by a constant delocalized (resonance) effect. Contrary to the claim of Johnson et al. and in accord with the observations of Ehrenson, Brownless, and Taft, the LD (extended Hammett) equation is much more effective in describing substituent effects on pyridine nitrogen reactivity than is the simple Hammett equation. This conclusion is based on correlations obtained with both equations for 13 sets of 4-substituted pyridine acidity data and 5 sets of rate constants for their reaction with alkyl halides.

In a recent publication, Johnson, Roberts, and Taylor[1] have made an important claim. They state that substituents which are electron acceptors by both the localized (field and/or inductive) and delocalized (resonance) electrical effects (LaDa groups) exert only a localized effect upon the reactivity at the nitrogen atom of substituted pyridines. On the basis of the evidence they cite in support of this claim, they have come to two important conclusions. They are:

1. The validity of multiparameter correlation equations such as the LD (extended Hammett) equation and the Yukawa–Tsuno equation is in doubt. The former equation in the form

$$(Q_X/Q_H) = L\sigma_{IX} + D\sigma^*_{RX} \tag{1}$$

was reported by Ehrenson, Brownlee, and Taft[2] to be the best choice for the correlation of reactivity of substituted pyridines.

2. The best equation for correlating data for substituted pyridine reactivities is the Hammett equation

$$Q_X = \rho\sigma_X + h \tag{2}$$

When eq 2 is applied, σ_I constants are used for LaDa groups and σ_m or σ_P constants for all other groups.

The first of these conclusions is of the utmost importance. An enormous number of correlations of chemical reactivities, physical properties, and biological reactivities have been carried out with multiparameter equations. It is therefore of great importance to determine whether the conclusions of Johnson et al. are warranted. The arguments cited in favor of the conclusions are: The equation

$$\frac{\log (k_X/k_H)_P}{\log (k_X/k_H)_Q} = c \tag{3}$$

where P refers to the ionization of pyridinium ions, Q refers to the ionization of quinuclidinium ions, X may be any LaDa substituent, H is the hydrogen point, the k's are ionization constants, and c is a constant, is obeyed. The equation

$$pK_{a(X,P)} = a_1[pK_{a(X,Q)}] + a_0 \tag{4}$$

is obeyed when only LaDa groups are considered. The only LaDa groups available for study were NO_2, CN, CO_2Me, and Ac. The quantity defined by the equation

$$\frac{\log (k_{4(Ac)}/k_H)}{\log (k_{3(Ac)}/k_H)} = \frac{\sigma_{4(Ac)}}{\sigma_{3(Ac)}} = \alpha \tag{5}$$

has a value of 0.95 ± 0.11. This value was obtained by examination of a number of reactions. A correlation of pK_a data for 4-substituted pyridinium ions with eq 2 using σ_I for LaDa groups and σ_P constants for all other groups gave excellent results with $r = 0.998$ and $s\gamma = 0.12$.

Examination of the σ^+_R values[3] for all the LaDa groups we have studied shows that they have a mean value of 0.104 with a standard error of 0.0262. The groups considered by Johnson et al., CN, NO_2, Ac, and CO_2Me, have a σ^+_R value of 0.0875 with a standard error of 0.0222. It follows then, that for the groups studied σ^+_{RX} is constant, and therefore eq 1 may be rewritten as

$$\log (k_X/k_H)_P = L_p\sigma_{IX} + C^* \tag{6}$$

where

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Table I. Data Used in the Correlations

1. pK_a, 4-$XC_5H_4NH^+$ in water at 25 °C[a]
H, 5.21; Me, 6.03; Et, 6.03; Pr, 6.05; *i*-Pr, 6.04; MeO, 6.58; NH_2, 9.12; Cl, 3.83; Br, 3.75; Bz, 3.35; CN, 1.86; NO_2, 1.39; $PhCH_2$, 5.59; Ph, 5.35; Ac, 3.51; CO_2Me, 3.49
2. pK_a, 4-$XC_5H_4NH^+$ in water at 20 °C
H, 5.278;[h] NH_2,[b] 9.2524; Me,[i] 6.10; MeO,[d] 6.62; NO_2,[g] 1.61; SMe,[3] 5.97; SO_2Me,[f] 1.62
3. pK_a, 4-$XC_5H_4NH^+$ in water at 25 °C[b]
H, 5.229;[h] NH_2,[b] 9.1141; Me,[c] 6.03; MeO,[c] 6.58; Br,[c] 3.68; CN,[c] 1.48; NO_2,[c] 1.23; Cl,[c] 3.83; Ac,[c] 3.505
4. pK_a, 4-$XC_5H_4NH^+$ in water at 25 °C[j]
Ac, 3.58; NH_2, 9.19; Br, 3.96; Cl, 4.09; CN, 2.14; Me, 5.88; H, 5.35
5. pK_a, 4-$XC_4H_4NH^+$ in water at 25 °C[k]
H, 5.14; Me, 5.95; Br, 3.74; Cl, 3.79; $CONH_2$, 3.43; CO_2Et, 3.30; CN, 1.83
6. pK_a, 4-$XC_5H_4NH^+$ in 9.0 mol % aqueous MeOH at 25 °C[k]
H, 4.92; Me, 5.72; Br, 3.55; Cl, 3.58; $HOCH_2$, 5.14; $CONH_2$, 3.24; CO_2Et, 3.10; CN, 1.66
7. pK_a, 4-$XC_5H_4NH^+$ in 19.4 mol % aqueous MeOH at 25 °C[k]
H, 4.59; Me, 5.45; Br, 3.24; Cl, 3.28; $HOCH_2$, 4.87; $CONH_2$, 7.95; CO_2Et, 2.78; CN, 1.41
8. pK_a, 4-$XC_5H_4NH^+$ in 27.2 mol % aqueous MeOH at 25 °C[k]
H, 4.37; Me, 5.20; Br, 2.99; Cl, 3.04; $HOCH_2$, 4.63; $CONH_2$, 2.73; CO_2Et, 2.55; CN, 1.24
9. pK_a, 4-$XC_5H_4NH^+$ in 36.0 mol % aqueous MeOH at 25 °C[k]
H, 4.14; Me, 4.96; Br, 2.71; Cl, 2.75; $HOCH_2$, 4.46; $CONH_2$, 2.59; CO_2Et, 2.32; CN, 1.10
10. pK_a, 4-$XC_4H_4NH^+$ in 51.1 mol % aqueous MeOH at 25 °C[k]
H, 3.81; Me, 4.61; Br, 2.40; Cl, 2.44; $HOCH_2$, 4.17; $CONH_2$, 2.31; CO_2Et, 2.03; CN, 0.9
11. pK_a, 4-$XC_5H_4NH^+$ in 69.2 mol % aqueous MeOH at 25 °C[k]
H, 3.63; Me, 4.43; Br, 2.22; Cl, 2.23; $HOCH_2$, 4.04; $CONH_2$, 2.21; CO_2Et, 1.96
12. $\delta\Delta G_i$, 4-XC_5H_4N proton affinity, gas phase[l]
NMe_2, 14.6; OMe, 6.7; Me, 4.0; H, 0; Cl, −3.1; CF_3, −7.8; CN, −10.5
13. $10^{-3}kr$, deprotonation of 4-$XC_5H_4NH^+$ in strongly acid aqueous solution[m]
NMe_2, 0.008156; NH_2, 0.0131; *t*-Bu, 3.42; Me, 3.07; H, 32.0; Cl, 563; Br, 528; CO_2H, 1570; CO_2Me, 1230; CN, 71900
21. 10^4kr, 4-XC_5H_4N in EtI in $PhNO_2$ at 60 °C[n]
H, 3.15; Me, 6.65; NH_2, 50.7; MeO, 8.20; CN, 0.107; Bz, 0.755; $PhCH_2$, 4.46; *i*-Pr, 6.02; Ph, 3.45; Ac, 0.740
22. kr, 4-XC_4H_4N + *n*-$C_{12}H_{25}Br$ in DMF at 50 °C[o]
NH_2, 6.76; Me, 5.05; Et, 4.85; H, 2.94; Bz, 2.17; CO_2Me, 1.76; CO_2Et, 1.52; CN, 1.29
23. 10^5kr, 4-XC_5H_4N + *n*-$C_{12}H_{25}Br$ in MeOH at 50 °C[o]
NH_2, 3.03; Me, 0.874; Et, 0.847; H, 0.500; Bz, 0.339; CO_2Me, 0.384; CO_2Et, 0.329; CN, 0.253
24. 10^5kr, 4-XC_5H_4N + *n*-$C_{12}H_{25}Br$ in MeOH at 75 °C[o]
NH_2, 27.4; Me, 8.82; Et, 9.02; H, 5.65; Bz, 4.23; CO_2Me, 4.54; CO_2Et, 3.86; CN, 2.72
25. 10^5kr, 4-XC_5H_4N + *n*-$C_{12}H_{25}Br$ in MeOH at 100 °C[o]
NH_2, 194; Me, 61.3; Et, 67.4; H, 48.3; Bz, 37.8; CO_2Me, 35.9; CO_2Et, 29.4; CN, 21.9

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$$C^* = D_P\sigma^+_R \quad (7)$$

For quinuclidinium ionization constants only the localized electrical effect can occur, thus

$$\log (k_X/k_H)_Q = L_Q\sigma_{IX} \quad (8)$$

Then

$$\frac{\log (k_X/k_H)_P}{\log (k_X/k_H)_Q} = \frac{L_P}{L_Q} + \frac{C^*}{L_Q\sigma_{IX}} \quad (9)$$

We have correlated rate and equilibrium data for a number of sets of 4-substituted pyridines and pyridinium ions with the LD equation in the form

$$Q_X = L\sigma_{IX} + D\sigma^+_{RX} + h \quad (10)$$

The data used in the correlations are given in Table I. Values of $100R^2$ are given in Table II. Complete results are given in Table I of the supplementary material. From the D value given in Table I, set 1 in supplementary material, we may calculate values of C^* for each X group. The average value of $C^*/L_Q\sigma_{IX}$ can now be obtained. We find a value of 0.212 for this quantity with a standard error of 0.085. The values range from 0.128 to 0.286. Then, $C^*/L_Q\sigma_{IX}$ is essentially constant, and as L_P and L_Q are constant, eq 9 reduces to eq 3. Thus, eq 3 can be accounted for quite nicely by a constant value of σ^+_R. It is interesting to note that the value for C of 1.19 reported by Johnson et al. would, if their arguments were correct, imply that the pyridinium skeletal group is much more effective at transmitting the localized effect than is the quinuclidinium skeletal group. This is difficult to account for by either a field effect mode of transmission or by an inductive mode of transmission. In the field effect mode, L_P/L_Q should be about 1; in the inductive mode, the quinuclidinium skeletal group has three pathways for transmission compared with two in the pyridinium group, and the available evidence suggests that transmission by the inductive mode is not strongly dependent on the hybridization of the carbon atoms which constitute the path. From the L_P value in Table I of the supplementary material for pyridinium ionization (set 1) we find a value of −5.17 which combined with an L_Q value[3] of −5.28 results in L_P/L_Q = 0.98, in agreement with the above discussion. If we then substitute in eq 8 a value of 0.98 for L_P/L_Q and of 0.21 for $C^*/L_Q\sigma_{IX}$, we obtain a value of C of 1.19, in agreement with that reported by Johnson and his group.

If we write for the pK_as of 4-substituted pyridinium and 4-substituted quinuclidinium ions the equations

$$pK_{a(X,P)} = L_P\sigma_{IX} + D_P\sigma^+_{RX} + h_P \quad (11)$$

and

$$pK_{a(X,Q)} = L_Q\sigma_{IX} + h_Q \quad (12)$$

respectively, and we rearrange eq 12 to obtain

$$\sigma_{IX} = \frac{pK_{a(X,Q)} - h_Q}{L_Q} \quad (13)$$

We obtain on combining eq 7, 11, and 13

Table II. Values of $100R^2$, $100r^2$, and Δ

set	$100R^2$ [a]	$100r^2$ [b]	Δ
1	99.53	99.56	−0.03
2	99.78	99.22	0.56[c]
3	99.61	99.54	0.07
4	99.82	99.17	0.65[c]
5	99.66	99.83	−0.17
6	99.71	97.89	1.87[c]
6A	99.67	99.84	−0.17
7	99.78	97.57	2.19[c]
7A	99.77	99.83	−0.06
8	99.85	97.41	2.44[c]
8A	99.87	99.69	0.18
9	99.70	96.36	3.34[c]
9A	99.86	99.24	0.46[c]
10	99.52	95.58	3.94[c]
10A	99.84	98.95	0.89[c]
11	98.67	92.32	6.35[c]
11A	99.51	98.51	1.00[c]
12	98.87	99.70	−0.83[d]
13	97.91	97.94	−0.03
13A	96.79	97.81	−1.02[d]
21	98.76	98.15	0.61[c]
22	99.21	87.68	11.53[c]
23	98.40	95.65	2.75[c]
24	97.93	96.63	1.30[c]
25	97.42	95.88	1.54[c]

[a] For correlation with eq 10. [b] For correlation with eq 2. [c] Best correlation with eq 10. [d] Best correlation with eq 2. The quantities $100R^2$ and $100r^2$ are measures of the percent of the variance of the data accounted for by the regression equation.

$$pK_{a(X,P)} = \left(\frac{L_P}{L_Q}\right) pK_{a(X,Q)} + C + h_P - \frac{L_P h_Q}{L_Q} \qquad (14)$$

which is equivalent to eq 4 with $a_1 = (L_P/L_Q)$ and $a_0 = C^* + h_P - (h_Q/L_Q)$. Thus, once more, we can account for the evidence reported by Johnson et al. in terms of a constant σ^+_R term.

The third line of evidence proposed by Johnson is based on the constancy of α which was defined in eq 5. If we write eq 6 for 3-substituted and 4-substituted pyridinium ions we obtain, after writing $D_{3(P)} = b_0 D_{4(P)}$

$$\frac{\log (K_{4(X)}/K_H)}{\log (K_{3(X)}/K_H)} = \frac{L_{4(P)}\sigma IX + C^*}{L_{3(P)}\sigma_{IX} + b_0 C^*} \qquad (15)$$

or when X = Ac, for example

$$\alpha = (L_{4(P)}\sigma_{IX} + C^*)/(L_{3(P)}\sigma_{IX} + b_0 C^*) \qquad (15a)$$

Then

$$(\alpha L_{3(P)} - L_{4(P)})\sigma_{IX} = C^*(1 - \alpha b_0) \qquad (16)$$

We may write $L_{4(P)} = \alpha L$. Then

$$1/\alpha = \left(\frac{L_{3(P)} - L^*}{C^*}\right)\sigma_{IX} + b_0 \qquad (17)$$

or

$$1/\alpha = b\sigma_{IX} + b_0 \qquad (18)$$

For any given choice of X, σ_{IX} is constant and $b\sigma_{IX} + b_0$ is therefore constant. Then, α must be constant. Thus, once again the conclusion of Johnson and his group can be accounted for in terms of a constant σ^+_R value for LaDa groups. We may now proceed to a test of the Johnson conclusion that correlation with the simple Hammett equation (eq 2) using σ_{IX} constants for LaDa groups and σ_{PX} constants for all other groups gives better results than does the use of eq 10. We have carried out correlations with eq 2 using the substitutent constants as proposed by Johnson. The data used are the sets given in Table I. Values of $100r^2$ are presented in Table II. Complete results are given in Table II of the supplementary material. In sets 6 to 11 the CH_2OH group occurs. In set 13, the CO_2H group is found. As substituent constants for these groups are suspected of having a large dependence on the medium, correlations have been carried out both with and without these groups. The sets from which they were excluded are designated by the letter A. The best choice of a statistic for comparison of the correlations with eq 2 and 10 is $100r^2$ (eq 2) and $100R^2$ (eq 10). This statistic represents the percent of the variance of the data accounted for by the correlation equation. We regard a difference in $100r^2$, Δ, defined by

$$\Delta = 100R^2 - 100r^2 \qquad (19)$$

of less than 0.25 as insignificant. Values of Δ are given in Table II. All of the data sets were chosen because they included at least two LaDa groups. The results show clearly that (whether the CH_2OH and CO_2H groups are included or excluded) the best results are almost always obtained by correlation with eq 10. Thus, when the suspected groups were included, 13 sets gave the best results with eq 10, 1 set gave the best results with eq 2, and 4 sets showed no significant difference. When the suspected groups were excluded, 10 sets gave the best results with eq 10, 2 sets gave the best results with eq 2, and 6 sets showed no difference. A comparison of the *L*, *D*, and H values for sets including the CH_2OH group (sets 6–11) with those for sets excluding the CH_2OH group (sets 6A–11A) indicates that there are no significant differences between them. There may be some slight effect in sets 9–11, but there is certainly no effect in sets 6–8. This is reasonable as the σ_I and σ^+_R constants were obtained from pK_a data in water. The σ_P value for CH_2OH was also calculated from a pK_a value determined in water. It is somewhat surprising, then, that the correlations of sets 6–8 with eq 2 are so comparatively poor.

Our results show very clearly that *the conclusions of Johnson, Roberts, and Taylor are unwarranted*. In fact, Ehrenson, Brownlee, and Taft[2] and Topsom[4] are quite correct in their assertion that reactivities of pyridinium ions are best correlated with some form of eq 10.

Supplementary Material Available: Complete statistics for the correlation of the data in Table I with eq 2 and 10 (3 pages). Ordering information is given on any current masthead page.

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