Pyridine Nitrogen Reactivity [1]

By **C. David Johnson,*** **Ian Roberts,** and **Peter G. Taylor,** School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ

Pyridinium pK_a values and rates of quaternization with ethyl iodide in various solvents are used to evaluate the effect of substituents on the pyridine nitrogen reactivity. Substituent effects on nitrogen reactivity are found to be intrinsic properties of the pyridine system independent of specific reaction type or solvent. The relevance of hydrogen-bonding in methanol and its influence on pyridine quaternization is discussed. The influence of potential resonance acceptors is shown to be due to their inductive effect alone, and the general question of the applicability of the dual substituent parameter equation to substituent effects on nitrogen reactivity in pyridine is considered.

THE pyridine system is a potentially good model for the quantitative investigation of substituent effects in nucleophilic substitution and addition reactions. Transmission of electronic effects between substituent and reaction site is more efficient than in a comparable benzenoid series, because the nucleophilic centre is present within the ring framework, and therefore tends to exhibit a far greater sensitivity to substituent effects. At the same time, the similarity of the two systems leads one to hope that pyridine reactions can be realistically described in terms of substituent constants already defined for benzenoid reactions, thus avoiding further additions to the already extensive lists of such constants. Moreover, logarithmic rates of quaternization [2-5] and sulphonation [6] measured in a variety of different solvents for series of 3- and 4-substituted pyridines, as detailed later, correlate with one another, and with pK_a values [7-13] and hydrogen-bonding free energies [14] measured both in aqueous solution and in the gas phase, so that substituent effects in this nucleus appear to be intrinsic properties, and not artefacts arising from a specific solvent effect or reaction mode. These factors, taken in conjunction with the general ease of synthesis of substituted pyridines, make such systems appealing for the investigation and discussion of structure–reactivity correlations.

EXPERIMENTAL [15]

Substituted pyridines and other compounds were available commercially or prepared by standard methods. All were distilled or recrystallised before use. A commercial sample of ethyl iodide was dried with calcium chloride, then sodium, fractionally distilled, and stored over mercury in a dark bottle. Solvents acetonitrile, dichloromethane, acetone, dimethylformamide, methanol, nitromethane, and nitrobenzene were commercial samples dried and purified by recommended procedures. Rates of quaternization of pyridines by ethyl iodide were measured conductometrically on a Wayne-Kerr autobalance universal bridge B641. The conductivity cells were of a standard type having an internal volume of 10 ml and a distance of 4 cm between the two disc platinum electrodes. Pyridine stock solution (*ca.* 1 ml) made up in the appropriate solvent (10^{-2}M; prepared within the previous 48 h) was syringed into the preweighed conductivity cell, made up to 10 ml with solvent, and the cell reweighed. The cell was equilibrated at 25.00 ± 0.05° for 0.5 h, and the reaction then initiated by introduction of ethyl iodide (*ca.* 1 ml); the properties of each solvent are thus modified by this significant quantity of ethyl iodide. Conductivity readings were taken at appropriate time intervals. Finally reweighing of the cell enabled the exact amount of ethyl iodide added to be determined.

Blank runs with solvent and ethyl iodide in the absence of base showed random variations or a drift, in all cases far too small to affect the rate measurements, with the exceptions explained below.

The pseudo-first order rate constant was evaluated from the kinetic expression $(\chi_\infty - \chi_t) = \chi_\infty e^{-kt}$ as described by Wiberg [16] (χ is conductivity), and the true second-order rate constant obtained by dividing by the molar concentration of ethyl iodide. For concentrations above 3×10^{-3}M in pyridine, deviations from a linear conductivity–concentration relationship were observed, and even in the concentrations described here, small deviations at higher amounts of reaction were found, probably due to ion-pairing. For this reason, all reactions were followed to the extent of 40%, giving correlation coefficients for rate plots which were invariably 0.999 or better, and almost always 0.9999—1.0000; the rate constants thus obtained differed only slightly however from those calculated by following the reaction over three or more half-lives. All runs were repeated at least once, and usually several times, and reproducibility was found to be ±3% at maximum, with the exception of those in dichloromethane (±5%), and in methanol (±10%; probably due to ethyl iodide methanolysis, see later).

Rates could be followed for the more reactive pyridines in dimethylformamide (see Table 1), but levelled off for reaction with the methylpyridines and less reactive compounds due to secondary reaction of the ethyl iodide with the solvent. Rate studies in dimethyl sulphoxide, acetone–water mixtures, and ethyl acetate were also complicated by side-reactions or low conductivities.

N-Ethylpyridinium iodide was prepared by dissolving the substituted pyridine in ethyl iodide, allowed to crystallise out, and filtered and dried. Samples made up in appropriate solvents had the same conductivity as the equivalent kinetic runs of the same concentration at their end-points.

In some solvents, pyridine substituted with electron-withdrawing substituents, particularly 4-nitro, did not yield good first-order plots, probably due to the instability of the quaternary salt.

RESULTS AND DISCUSSION

Solvent Effects.—The rate data for the quaternization reactions are collected in Table 1 and the data summar-

TABLE 1

Second-order rate constants for reaction between substituted pyridines and ethyl iodide in various solvents.

				Rate constant [a]					
Substituent	$MeNO_2$	CH_2Cl_2	MeOH	$HCONMe_2$	Me_2CO	MeCN		$PhNO_2$ [b]	
4-NMe	649	787	1.47	622	379	420	639	2140	8050
$4-NH_2$	300	379	1.32	400	577	366	593	1570	7050 [c]
4-OEt	65.0	117	1.15	25.7		53.5	65.5	238	762 [c]
4-OMe	59.7	140							
$3-NH_2$	95.6	64.9	1.13	98.2	81.4	79.1	114	466	1420 [c]
$4-CHMe_2$	55.4	62.5	1.17			40.1	41.8	150	
4-Me	47.0	89.1	1.21	21.3	26.6	37.6	45.1	167	
4-Et	55.3	60.6	1.15	20.1	28.0	40.6	42.6	148	624 [c]
4-SEt	36.3	48.1				24.7	31.5	98.4	473
3-Me	40.6	48.4	1.17	21.7	22.2	30.9	43.1	151	625 [c]
4-Pyrrol-1-yl [d]	22.3	39.8					18.7	61.4	482
H	25.6	32.9	1.12	19.8	16.0	21.4	20.5	76.7	383 [c]
4-Ph [e]	31.4				11.9	21.1	26.3	89.6	414 [c]
4-COMe	5.82	9.44	1.07		4.64	4.28	4.30	17.0	85.7 [c]
$4-CO_2Et$	5.81	9.17			2.50	4.66	3.58	12.1	63.1
3-COMe	5.60	7.80	1.03		4.64	4.62	4.90	17.7	81.2
$3-CO_2Et$	5.33	6.45				3.09	3.26	11.7	52.6
$3-CONH_2$	6.99	7.94							
3-Br	3.07	4.49	1.09				1.84	9.63	
4-CN	1.42	2.36							
$4-SO_2Et$	1.63	1.75						6.03	21.3
3-CN	0.955	1.59							
3-Aza	0.893	1.66						3.94	18.9
4-Aza	1.33							4.27	22.1

[a] $10^6\ k/l\ mol^{-1}\ s^{-1}$, measured at 25° unless stated otherwise. [b] Measured at 25, 40, and 60°, respectively. [c] Ref. 4 gives the following rate constants: $4-NH_2$, 5070; $3-NH_2$, 1490; 4-Me, 665; 4-Ph, 345; H, 315; 4-MeCO, 74; 4-OMe, 820; 3-Me, 635. [d] The effective σ value for 4-pyrrolyl is thus 0.00 ± 0.03. [e] The effective σ value for 4-Ph is thus 0.03 ± 0.02, including also in this calculation the value derived from pyridinium pK_a values.[7]

ised in the form of Brønsted plots in Table 2 (really pseudo-Brønsted plots, because the equilibrium conditions are not those of the reactions). Generally linearity is good, and the conclusion must be that substituent effects on the pK_a values closely conform to those on reactivity. In polar solvents however the 3-amino-group appears consistently to enhance the rate by a log factor of 0.42 ± 0.07 above that predicted by the pK_a (see footnote *e* in Table 2). Exactly the same effect was found in other quaternization studies,[4] while a rate enhancement for 3-alkoxy-substituents in the reaction of pyridine derivatives with allyl bromide in nitromethane [3] has also been observed.

The attenuation factor for effects in the alkylation reactions compared with those in the protonation equilibria appears to be about one-third, with the exception of the results for methanol, where substituents do not appear to influence the reaction rate at all. We are worried about complications arising from side reactions between ethyl iodide and methanol, although the pseudo-first order reaction in the absence of pyridine was about two orders of magnitude slower than the quaternization reaction. The methanolysis second-order rate constant is $5 \times 10^{-10}\ l\ mol^{-1}\ s^{-1}$. In agreement with this, the second-order rate constant for methyl iodide with methanol (25°) is $1.3 \times 10^{-10}\ l\ mol^{-1}\ s^{-1}$.[17] The solvolysis reaction thus seems too slow to interfere with the pyridine rate measurements, and certainly our rate constant for ethylation of pyridine itself in methanol at 25°, $1.12 \times 10^{-6}\ l\ mol^{-1}\ s^{-1}$, is similar to but not coincident with, values found by other workers.[18]

A possible explanation for this apparent lack of substituent-induced rate variation in methanol is that the hydrogen-bonded species may be considered as in equilibrium with the free pyridine molecules, and that reaction only occurs on the latter. The Scheme may thus be constructed.

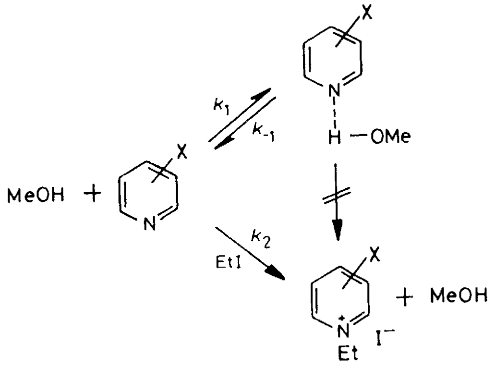
Assuming the concentration of the hydrogen bonded form predominates strongly over the free form, equation (1) holds where k_{obs} is the observed second-order rate

TABLE 2

Brønsted plots ($6 + \log k = mpK_a + c$) for quaternization of 3- and 4-substituted pyridines with ethyl iodide

Solvent	T/°C	Substituents [a]	$6 + \log(k_H/l\ mol^{-1}\ s^{-1})$	m	c	r [c]	S.d. [d]	S.d.(m)
$MeNO_2$	25	1—4, 6—24 [e]	1.41	0.332	−0.368	0.995	0.085	0.008
CH_2Cl_2	25	1—11, 13—23	1.52	0.330	−0.219	0.994	0.092	0.009
MeCN	25	1—3, 6—10, 12, 13—17 [e]	1.33	0.334	−0.492	0.994	0.077	0.011
Me_2CO	25	1, 2, 7, 8, 10, 12, 15—17 [e]	1.20	0.356	−0.688	0.988	0.126	0.019
$PhNO_2$	25	1—3, 6—17, 19 [e]	1.31	0.378	−0.686	0.994	0.087	0.012
$PhNO_2$	40	1—3, 6—17, 19, 21, 23, 24 [e]	1.88	0.335	0.124	0.992	0.104	0.010
$PhNO_2$	60	1—3, 8—17, 21—23 [e]	2.58	0.323	0.826	0.993	0.103	0.011
MeOH	25	1—3, 5—8, 10, 14, 16, 19	0.05	0.019	−0.041	0.923	0.018	0.003

[a] Substituent and pyridinium pK_a: 1, $4-NMe_2$ 9.61; 2, $4-NH_2$ 9.12; 3, 4-OEt 6.67; 4, 4-OMe 6.58; 5, $3-NH_2$ 6.04; 6, $4-CHMe_2$ 6.04; 7, 4-Me 6.03; 8, 4-Et 6.03; 9, 4-SEt 5.94; 10, 3-Me 5.67; 11, 4-pyrrol-1-yl 5.41; 12, 4-Ph 5.35; 13, H 5.21; 14, 4-COMe 3.51; 15, $4-CO_2Et$ 3.45; 16, 3-COMe 3.43; 17, $3-CO_2Et$ 3.35; 18, $3-CONH_2$ 3.35; 19, 3-Br 2.85; 20, 4-CN 1.86; 21, $4-SO_2Et$ 1.62 22, 3-CN 1.35; 23, 3-aza 1.23; 24, 4-aza 1.10. [b] pK_a Values taken from ref. 7 if available, otherwise ref. 8. [c] Correlation coefficient. [d] Standard deviation. [e] $3-NH_2$ deviated markedly from plot. Rate enhancement factors $\Delta \log k$ were as follows: $MeNO_2$, 0.35; MeCN, 0.37; Me_2CO, 0.46; $PhNO_2$ (25°), 0.48; $PhNO_2$ (40°), 0.54; $PhNO_2$ (60°), 0.38.



SCHEME

constant for quaternization, and $K_E = k_1/k_{-1}$ = [hydrogen-bonded complex]/[free pyridine][MeOH]. In terms of the Hammett equation, this may be written as

$$\log k_{obs} = \log k_2 - \log K_E - \log[\text{MeOH}] \quad (1)$$

$$\log k_{obs} = \rho(\rho_2 - \rho_E) + \log(k_2/K_E)_{X=H} - \log[\text{MeOH}] \quad (2)$$

(2). If $\rho_2 = \rho_E$, *i.e.* the substituent effect on the hydrogen-bonding reaction is equal to that on alkylation, then the observed rate constant will be the same for all 3- and 4-substituted pyridines [equation (3)]. K_E Is

$$\log k_{obs} = \log(k_2/K_E)_{X=H} - \log[\text{MeOH}] \quad (3)$$

2.31 [19] (although this is in carbon tetrachloride rather than methanol solution), enabling an estimate of k_2 for pyridine of 65×10^{-6}.

TABLE 3

α Values [a]

Reaction series	MeCO	CO_2Et	CO_2Me	NO_2	Substituent CN	PhCO	$CONH_2$	CF_3	aza	aza-H⁺
σ_p/σ_m	1.32	1.22	1.22	1.10	1.18	1.28	1.36	1.26	1.48	1.13
pK_a–H_2O–25°	0.96	0.95	0.81	0.95	0.87	0.92	0.86	0.94	1.04	0.94
EtI–$MeNO_2$–25°	0.98	0.96			0.88				0.88	
EtI–CH_2Cl_2–25°	0.87	0.79			0.87					
EtI–MeCN–25°	1.04	0.79								
EtI–Me_2CO–25°	1.09									
EtI–$PhNO_2$–25°	1.10	0.95								
EtI–$PhNO_2$–40°	1.03	0.98							0.97	
EtI–$PhNO_2$–60° [b]	0.97	0.91			0.83	1.10			0.95	
CH_2:$CHCH_2Br$–$MeNO_2$–40° [c]		0.93								
CH_2:$CHCH_2Br$–$MeNO_2$–60°C [c]		0.93								
$ArSO_2Cl$–H_2O–25° [d]	0.86				0.86					
Gas-phase basicities–25° [e]					0.93			0.96		
Gas-phase hydration–127° [f]					0.75					
Mean values	0.98	0.91	0.81	0.95	0.86	1.01	0.86	0.95	0.96	0.94

[a] For definition, see text. [b] See also ref. 4. [c] Ref. 3. [d] Ref. 6. [e] Ref. 12. [f] Ref. 14.

Rewriting equation (1) in the form (4) permits the calculation of m_2 if m_e is known. The latter value is *ca.*

$$\log k_{obs} = m_{obs}\text{p}K_a + \text{constant} = (m_2 - m_e)\text{p}K_a + \text{constant} \quad (4)$$

0.20,[*] so that m_2 becomes 0.22, a slightly lower value than for other solvents. The increased rate for quaternization of pyridine in methanol compared with that for other media, together with the decreased value of m, may possibly be due to the relative polarity of this solvent.[†]

Substituent Effects.—The pK_a values of 3- and 4-substituted pyridinium ions correlate well with Hammett σ values, provided σ_I is used for potential resonance acceptors in the 4-position.[1,7] Such substituents thus appear able to exert only an inductive effect and not a resonance-demanding effect, in the pyridine nucleus (defining resonance as the effect due to π-orbital overlap and induction as the total effect remaining when that overlap is removed, by twisting of substituents out of the plane of the aromatic ring, or by consideration of saturated systems). To illustrate this, we define a parameter $\alpha = (\log k_4 - \log k_H)/(\log k_3 - \log k_H)$, previously calculated for the acetyl substituent; the averaged value of 0.95 could only logically be interpreted in terms of electron withdrawal by induction alone.[1] These results are now supplemented by the values shown in Table 3 for a wide variety of such substituents, and in all cases α falls close to 0.95. Variations from this value are small, and could well be due predominantly to experimental error. The α values are certainly all significantly lower than the appropriate ratio of σ values shown in the first row of Table 3.

The following results are also relevant. Experiments on the effect of twisting the 4-nitro-group out of the plane of the pyridine ring by 3,5-dimethyl groups showed that the former group influenced the pK_a values by induction alone.[20] pK_a Measurements on extensive series of methyl substituted picolinium ions gave a $\rho_p : \rho_m$ ratio of 0.96.[21] Magnetic circular dichroism measurements [22] demonstrated that the 4-aza-substituent exerts only inductive effects in the pyridine series. Substituent analysis [23] showed σ_I to be the most appropriate for the description of 4-CO_2R, 4-CN, 4-Ac, and 4-NO_2 on pyridinium pK_a values. I.r. intensity measurements [24] revealed

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[*] See Figure 2 of ref. 19.

[†] We emphasise that this analysis is only tentative. For example, a referee suggests that other explanations may be considered for the lack of substituent-induced variation in methanol, since if the free pyridine is reactive the Brønsted plot should be the same as that for a high dielectric constant, non-solvating solvent. It is possible that the rate-determining step involves displacement of hydrogen-bonded methanol by ethyl iodide, bond breaking and making at pyridine nitrogen being synchronous, so substituent effects are small.

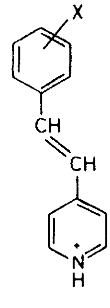
that quaternization of the pyridine nitrogen does not increase its resonance acceptor power, and that electron-accepting substituents conjugate far less effectively with the 4-position of the pyridine ring than with benzene. Finally, pK_a values of 4-substituted pyridinium ions plot linearly against the pK_a values of the correspondingly substituted 4-quinuclidines.[1, 25, *]

The dual substituent parameter (DSP) equation suggested by other workers [26-30] to account best for substituent effects on pyridinium ion ionisation [equation

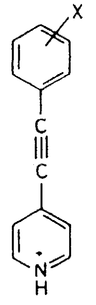
$$\log K/K_0 = \rho_I\sigma_I + \rho_R\sigma_R^+ = 5.15\sigma_I + 2.69\sigma_R^+ \quad (5)$$

(5)] does not therefore give satisfactory correlation for such substituents, because as detailed previously,[1] the resonance factor $2.69\sigma_R^+$ contributes *ca.* 0.4 pK_a units to the predicted value, a contribution well outside experimental error. Equation (5) could however be legitimate for resonance donors. Indeed, it might theoretically be favoured over the straightforward Hammett equation, since the lack of success experienced by resonance acceptors in drawing resonance stabilisation from the pyridine system could indicate a strong tendency of that system to extract a resonance contribution from resonance donors best measured in terms of σ_R^+. One factor which argues against this however is the negligible influence of 4-Ph on the reaction rates, and on pyridinium pK_a values, since it is a substituent which has a σ value about zero, but an appreciably negative σ^+ value [31] (see footnote *e* in Table 1).

A further, more general argument, against the use of equation (5) may be developed as follows. The inductive effect is generally assumed to be a polar or field effect and thus it will die away with distance; this is considered [32, 33] to be the reason why the inductive component in equation (5) is greater than the resonance component as compared with the defining benzenoid side-chain reaction, for which there is a greater distance from substituent site to reaction probe. (Other workers have suggested alternative values for ρ_I and ρ_R allowing them to vary from one set of results to another,[25] and even from one substituent type to another,[34] but this would appear to us to mask rather than emphasise the general correspondence demonstrated in this paper between one reaction at pyridine nitrogen and another.) One difficulty in testing the DSP treatment in the form of equation (5) is that for resonance donors $\rho\sigma = \rho\sigma_I + (\rho/2)\sigma_R^+$ to well within the limits of experimental error. There are however results extant [35] on the pK_a values of related systems (1)—(3) which appear in some measure to deny the validity of the reasoning behind equation (5). Using the terminology introduced by Godfrey,[36] these molecules have the same source and probe as pyridine, but a different core region.



(1)



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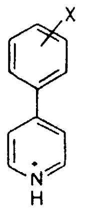

(3)

The Figure shows plots of pyridinium pK_a values against those for correspondingly substituted styrylpyridinium (1), phenylethynylpyridinium (2), and phenylpyridinium (3). The slopes of the plots show the expected attenuation of effects, but the linearity is quite reasonable, and points to the same blend of inductive and resonance effects within the four systems. We have in hand experiments in which the effect of a wider variety of substituent types including positive and negative poles, in both *m*- and *p*-positions, are studied for various reactions at nitrogen, but the present results lend general support to other experiments [37, 38] which point to the constancy of balance between inductive and resonance effects, and in consequence cast doubt on theories involving separate and independent contributions.

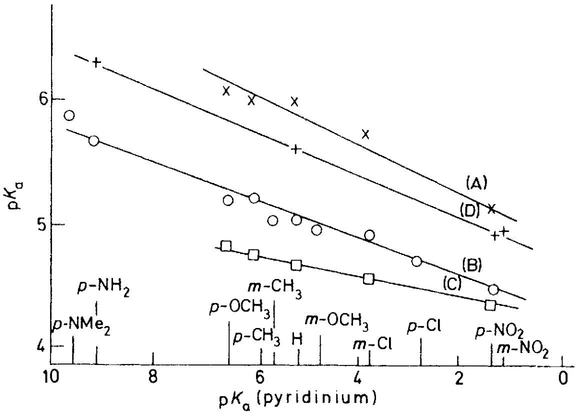

FIGURE Plots of pK_a values of systems (1)—(3) against pK_a values of correspondingly substituted pyridinium compounds. The slopes and correlation coefficients are as follows: (A), (1), H_2O, 0.17 ± 0.02, 0.986; (B), (1), 50%, aqueous ethanol, 0.16 ± 0.01, 0.986; (C), (2), H_2O, 0.09 ± 0.01, 0.991; (D), (3), H_2O, 0.17 ± 0.01, 0.999

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[*] Ref. 25 suggests that this linear plot is also explicable in terms of a constant resonance demand from NO_2, CN, CO_2R, COMe, and SO_2Me. It is true that $\sigma_R(= \sigma_R^+)$ is approximately constant for these groups, but although Charton claims this makes the right-hand side of equation (9) in his paper constant, substitution of relevant figures into the expression shows this is not so, because the size of the resonance component relative to the inductive component is different from one group to another.

For example, taking $L_Q = L_P = 5.17$, $D = 4.23$ (Set 1 in Table II of ref. 25), equation (9) yields 1.20 and 1.47 for the right-hand side expression for NO_2 (σ_I 0.65, $\sigma_R = \sigma_R^+ = 0.15$)[26] and MeCO ($\sigma_I$ 0.28, $\sigma_R = \sigma_R^+ = 0.16$ [26]), respectively. Moreover, the $\rho_R(D_p)$ value of 4.23 calculated by Charton is quite different to that of 2.69 used by Taft [26-30] for the same data.

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