The Kinetics and Mechanism of the Electrophilic Substitution of Heteroaromatic Compounds. Part XXXIX.[1] Transmission of Substituent Effects in the Pyridine System: Hammett-like Treatment of Hydrogen-exchange Data

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Hydrogen-exchange rate constants for pyridines and for benzenes are correlated by the same equation provided that interactions between substituents are allowed for by $\Sigma\Pi\sigma^+$. The derived equation permits the calculation of rate constants for polysubstituted benzenes and pyridines with reactivities covering 17 log units; the significance of this equation as representing something more than an empirical relationship is however in considerable doubt.

RATE constants for standard conditions[2] (pH = 0; 100°) for acid-catalysed hydrogen exchange, which provides a model for electrophilic substitution, can be applied to the direct comparison of reactions of aromatic and heteroaromatic compounds of widely differing reactivity, and can facilitate discussion of their structure–reactivity relationships. This paper is concerned with substituent effects in pyridines; there is previous evidence that substituent effects differ in different systems.[3-6]

The Hammett equation has been interpreted in the following two ways, among others. The reaction constants ρ for various reactions of electrophiles with monosubstituted benzenes vary widely,[7,8] and the magnitude of ρ measures charge development in the transition state. Olah, interpreting the Hammond postulate,[9] proposed a reactivity–selectivity relationship;[10] a low magnitude for ρ is associated with highly reactive substrates, for which 'early' transition states, with π-complex contributions, are expected. In terms of this view, ρ values characterise the positions of the transition states along the reaction co-ordinates, and whereas this proposition originally referred to different electrophiles and the same substrate series, it should hold equally for comparisons involving the same electrophile and different substrate series.[5] The scattered data hitherto available seemed to indicate less 'selective' substitutions for more reactive substrates.[5,6] However, some results are inconsistent with this hypothesis, and the incompatibility of the Hammond postulate with this interpretation of ρ values has recently been pointed out.[11]

In an alternative approach, Noyce and his coworkers[12-14] attributed the variation of ρ in different substrate series, when correlation with σ^+ was used for the solvolysis of various 1-arylethyl *p*-nitrobenzoates, to dependence on the charge distribution within each ring system. Application of a modified Dewar–Grisdale equation[15] led to a good parallelism between ρ values and delocalized charge.[14] In accord with these treatments, and indeed with that of the Hammett approach in general, a constant ρ value is assumed for a given reaction mechanism, however large the free energy changes involved within the substituent range studied, whatever implication this may have with regard to the positioning of the transition state along the reaction co-ordinate between reactant and Wheland intermediate.[11] Any deviation of effective σ values from those calculated by simple additivity is thus taken to arise from electronic interaction between substituents, steric and proximity effects, *etc.*

The ρ constant for monosubstituted benzenes is thus used in correlations with σ^+; for polysubstituted compounds, simple additivity of σ^+ values is not expected (other than for polyalkylbenzenes, for example) because the effect of each substituent depends on the mutual interactions between the substituents.[16] Experimental summations of σ^+ constants are obtained by dividing ($\log k - \log k_{\text{benzene}}$) = $\log k_{\text{rel}}$ by ρ, the resultant deviations from additivity comprising a measure of the magnitude of the interaction among and between substituents.

A quantitative treatment of substituent interactions in aromatic electrophilic substitutions of polysub-

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[1] Part XXXVIII, S. Clementi, P. P. Forsythe, C. D. Johnson, A. R. Katritzky, and B. Terem, *J.C.S. Perkin II*, 1974, 399.

[2] A. El-Anani, J. Banger, G. Bianchi, S. Clementi, C. D. Johnson, and A. R. Katritzky, *J.C.S. Perkin II*, 1973, 1065; this paper should be closely consulted for definition and explanation of methods of data appraisal employed in the present paper.

[3] (*a*) J. E. Dubois, J. J. Aaron, P. Alcais, J. P. Doucet, F. Rothenberg, and R. Uzan, *J. Amer. Chem. Soc.*, 1972, **94**, 6823; (*b*) S. I. Miller, *J. Amer. Chem. Soc.*, 1959, **81**, 101; C. D. Ritchie, *J. Phys. Chem.*, 1961, **65**, 2091; C. D. Ritchie, W. F. Sager and E. S. Lewis, *J. Amer. Chem. Soc.*, 1962, **84**, 2349.

[4] A. R. Katritzky and C. D. Johnson, *Angew. Chem. Internat. Edn.*, 1967, **6**, 608.

[5] S. Clementi and G. Marino, *J.C.S. Perkin II*, 1972, 71.

[6] M. Liler, 'Reaction Mechanisms in Sulphuric Acid and other Strong Acid Solutions,' Academic Press, London, 1971, p. 271.

[7] L. M. Stock and H. C. Brown, *Adv. Phys. Org. Chem.*, 1963, **1**, 35.

[8] O. Exner, in 'Advances in Linear Free Energy Relationships,' eds. N. B. Chapman and J. Shorter, Plenum Press, London, 1972.

[9] G. S. Hammond, *J. Amer. Chem. Soc.*, 1955, **77**, 334.

[10] G. A. Olah, *Accounts Chem. Res.*, 1971, **4**, 240.

[11] C. D. Johnson and K. Schofield, *J. Amer. Chem. Soc.*, 1973, **95**, 270.

[12] (*a*) D. S. Noyce, C. A. Lipinski, and R. W. Nichols, *J. Org. Chem.*, 1972, **37**, 2615; (*b*) D. S. Noyce and H. J. Pavez, *ibid.*, pp. 2620, 2623.

[13] D. S. Noyce and R. W. Nichols, *Tetrahedron Letters*, 1972, 3889.

[14] D. A. Forsyth and D. S. Noyce, *Tetrahedron Letters*, 1972, 3893.

[15] M. J. S. Dewar and P. J. Grisdale, *J. Amer. Chem. Soc.*, 1962, **84**, 3539, 3548.

[16] M. Godfrey, *J. Chem. Soc.* (*B*), 1971, 1545.

stituted benzenes was recently given by Dubois *et al.*[3a] following its initial development by Lewis, Miller, Ritchie, and Sager :[3b] equation (i) correlated the bromination rate constants for 44 benzene derivatives. The parameter p is considered analogous to ρ for monosubstituted benzenes and measures the charge developed in the transition state, whereas q is related to the ability of substituents to delocalize the charge in the transition state; q is denoted the interaction constant, as it characterizes the sensitivity of the reaction to substituent interactions. Both the approach of constant ρ and that of variable ρ are applied in this paper to the hydrogen-exchange rates[2] for pyridines.

RESULTS AND DISCUSSION

Variation of ρ Values with Substrate Series.—For the hydrogen exchange of benzenes, ρ appears to decrease with increase in mesomeric electron release from substituents.[6] The ρ values reported in ref. 6 were obtained under different experimental conditions for each series; recalculation gives slightly different ρ values derived from standardized[2] rate constants (k_0) for phenols and *NN*-dimethylanilines (Table 1) and comparison with those for benzene and anilines can be obtained from Table 2.

TABLE 1 [a]

Standardized rates for hydrogen exchange in H_2SO_4 of phenols [b] and *NN*-dimethylanilines [c]

Substituent	Range $-H_0$	$\frac{d[\log k(\text{stoich})]}{d(-H_0)}$ [d]	$-\log k$(stoich) at $H_0 = 0$	$-\log k$(stoich) at $H_0 = 0$, $T = 100°$	pK_a (25°) [e]	pK_a (100°)	$-\log k_0$ [f]
(i) Phenols							
p-NO_2	5·3—8·7	0·81	11·33	6·91			6·91
p-Me	0·4—3·2	1·01	7·57	3·15			3·15
p-Cl	2·8—5·2	0·86	9·23	4·81			4·81
(ii) Dimethylanilines							
H		0·00	6·21	4·39	5·47	4·21	−0·08
p-Me		0·00	6·46	4·64	6·03	4·67	−0·29
p-OMe		0·00	7·24	5·42	6·25	4·86	0·30
p-Cl		0·00	6·36	4·54	4·80 [g]	3·58	0·70
p-Br		0·00	6·39	4·57	4·63	3·51	0·80
m-Me		0·00	5·10	3·28	5·74	4·43	−1·41
m-NO_2		0·00	6·82	5·00	3·03	2·18	2·56

[a] For detailed information on general methods for calculation of data presented here, see Table 3 of ref. 2. [b] Data from V. Gold and D. P. N. Satchell, *J. Chem. Soc.*, 1955, 3609, at 25°. [c] Data from B. B. P. Tice, I. Lee, and F. H. Kendall, *J. Amer. Chem. Soc.* 1963, **85**, 329, at 65°. [d] Slopes for anilines taken equal to zero since these are free base reactions. [e] Data from D. D. Perrin, ' Dissociation Constants of Organic Bases in Aqueous Solutions,' Butterworths, London, 1965, corrected for deuteriated media. [f] Values for anilines are corrected for isotope effect. [g] At 20°.

TABLE 2

Variation of ρ values in some series of benzene derivatives

Compounds	Number of substituents	ρ	Ref.
Benzenes	14	−7·5	*a*
Phenols	3 [b]	−4·9	*c*
Anilines	4 [b]	−3·3	*d*
Dimethylanilines	7	−3·2	*c*

[a] Ref 18. [b] ρ-Values based on a small number of substituents are necessarily approximate. [c] Calculated from individual rates in Table 1. [d] Table 3.

Standardized rate constants at pH 0 and $T = 100°$ for hydrogen exchange of substituted anilines (reaction as free base) are listed in Table 3. A least squares Hammett treatment gives the reactivity at an *ortho*-position of unsubstituted aniline ($\log k_0 = -1{\cdot}24$), and a ρ value of −3·3. The standardized rates for 4-aminopyridine and 4-aminopyridine 1-oxide, reacting as monoconjugate acids, give the σ_m^+ values for the heterocyclic groups ⁚N^+H and ⁚$N^+(OH)$ as +1·92 and +2·02, respectively. This procedure was applied previously,[17] but is now repeated using the standard rates.

Using the above σ_m^+ value and $\rho = -7{\cdot}5$ for monosubstituted benzenes[18] gives $\log k_0 = -25{\cdot}4$ for the 3-position of the pyridine conjugate acid. The reactivity of a β-position of the pyridinium ion is less than that of one position of benzene by a factor of $10^{14\cdot4}$. The corresponding factor for the 1-hydroxypyridinium cation is $10^{15\cdot2}$.

Importance of the Interaction among Substituents.—Standardized k_0 values for the pyridinium and pyridinium 1-oxide cations (Table 4) give experimental summations of σ^+, denoted $\Sigma\sigma^+$(exp), by division of $\log k_{\text{rel}}$ by a ρ value of −7·5 (monosubstituted benzenes). These values are compared in Table 4 with the summations obtained, assuming additivity, by using Brown's σ^+ set (assuming $\sigma_o^+ = \sigma_p^+$ [18]) and σ_m^+ values for the heteroatoms derived above. The difference between these two quantities ($\Delta\Sigma\sigma^+$), *i.e.* the magnitude of the

TABLE 3

Reactivities at one *ortho*-position of substituted anilines [a]

4-R-anilines	$-\log k_0$	$\sigma_{m\text{-R}}^+$ [b]
4-Me	1·10	−0·066
4-OMe	1·37	0·047
4-Cl	2·38	0·399
4-NO_2	3·57	0·674
4-Aminopyridine	7·57	
4-Aminopyridine *N*-oxide	7·92	

[a] Data from ref. 2. [b] Ref. 7.

Note: k_0 refers to standard rate (*cf.* Table 1) and not specifically to the *ortho*-position.

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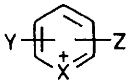
[17] G. P. Bean and A. R. Katritzky, *J. Chem. Soc.* (*B*), 1968, 864.

[18] S. Clementi and A. R. Katritzky, *J.C.S. Perkin II*, 1973, 1077.

deviation from additivity, measures the importance of interaction between substituents.

The assumption that $\sigma_o^+ = \sigma_p^+$ has been used previously by us;[18] it is nevertheless tentative. A limited list of apparently reliable σ_o^+ constants applicable to hydrogen exchange in trifluoroacetic acid has been given[19] and successfully applied to hydrogen exchange in aqueous sulphuric acid media.[20] This list is not extensive enough to be incorporated here. However, it does indicate that for $(-I + R)$-type substituents, a category into which the bulk of substituents included here fall, the assumption is not grossly incorrect: *e.g.* for OMe, $\sigma_p^+ = -0.78$, $\sigma_o^+ = -0.67$.



(1) X = NH or N(OH)

TABLE 4

Experimental and additivity $\Sigma\sigma^+$ for polysubstituted pyridines and *N*-oxides exchanging as conjugate acids

No.	Substituted pyridines	$-\log k_0$ [a]	$\Sigma\sigma^+$ (exp) [b]	$\Sigma\sigma^+$ (add) [c]	$\Delta\Sigma\sigma^+$ [d]
1	2-NH_2-3-Me	8·0	−0·40	0·54	0·94
2	2-NH_2-5-Me	8·1	−0·39	0·54	0·93
3	2-NH_2-4-Me (3)	7·8	−0·43	0·30	0·73
4	2-NH_2-4-Me (5)	7·6	−0·45	0·30	0·75
5	2-NH_2-6-Me (3)	7·4	−0·48	0·30	0·78
6	2-NH_2-6-Me (5)	6·9	−0·55	0·30	0·85
7	2-NH_2-5-Cl	9·7	−0·17	1·01	1·18
8	4-NH_2	7·6	−0·45	0·61	1·06
9	4-NH_2-2,6-Cl_2	9·1	−0·25	0·83	1·08
10	2-Pyridone	4·8	−0·83	0·32	1·15
11	3-Me-2-pyridone	4·3	−0·89	0·25	1·14
12	5-Me-2-pyridone	4·7	−0·84	0·25	1·09
13	4-Pyridone	4·8	−0·83	0·32	1·15
14	2,6-Me_2-4-pyridone (0)	2·8	−1·09	−0·30	0·79
15	2,6-Me_2-4-pyridone (+)	8·5	−0·33	0·38	0·71
16	4-OMe-2,6-Me_2	9·8	−0·16	0·52	0·68
17	2,6-Me_2	15·6	0·61	1·30	0·69
18	2,4,6-Me_3	11·9	0·12	0·99	0·87
19	1-OH-4-NH_2	7·9	−0·41	0·71	1·12
20	1-OH-2-NH_2-5-Br	9·8	−0·16	1·12	1·28
21	1-OH-2,4,6-Me_3	11·8	0·11	1·09	0·98
22	1-OH-4-OMe-2,6-Me_2	9·7	−0·17	0·62	0·79
23	1-OH-2,6-Me_2-4-pyridone (+)	8·7	−0·31	0·48	0·79
24	1-OH-2,6-Me_2-4-pyridone (0)	4·0	−0·93	−0·20	0·73

[a] Ref. 2. [b] Log k_{rel}/ρ. [c] Assuming additivity. [d] $\Sigma\sigma^+$(add) − $\Sigma\sigma^+$(exp).

Plotting log k_0 *vs.* $\Sigma\sigma^+$(add) (Figure 1) for the pyridine derivatives defines five lines for different sets of compounds of general formula (1) where X is NH or N(OH), Y is NH_2, O^-, or Me_2, and Z varies in each series. The behaviour varies according to the electron-donating ability of Y, *i.e.* the sensitivity to structural changes, as in benzenoid derivatives, depends markedly on the nature of invariant groups. Hence, just as different ρ values were found for different series of substituted benzenes (Table 2), individual ρ values (Table 5) can be calculated for amino-, hydroxy-, and dimethylpyridinium cations, as well as for amino- and dimethyl-1-hydroxypyridinium cations from the slopes of Figure 1. Table 5 also records average values for the differences (Δ) between additivity and experimental summations of σ^+ within each series.

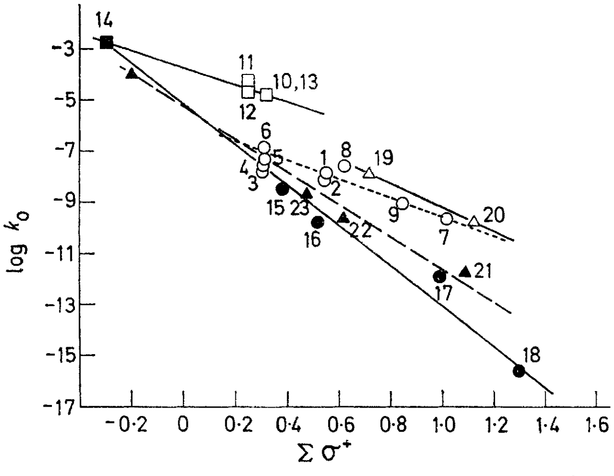


FIGURE 1 Plot of log k_0 against $\Sigma\sigma^+$ for pyridine derivatives; numbers denote compounds as in Table 4

The composite groups constituted by the azonium system and the invariant substituent Y possess σ_W^+ values (Table 5) which indicate increasing interaction with the electron-releasing ability of Y. This effect leads to an overall activating effect when Y is very powerful (NH_2 or O^-), while the presence of two methyl groups is not enough to overtake the deactivation due to the hetero-group. Interaction with an amino-group is greater for $\ddot{N}^+(OH)$ than for $\ddot{N}^+H$, and interaction with two methyl groups is similar in each case.

TABLE 5

Additivity and experimental σ^+ constants for the complex groups (X + Y) and ρ constants for different series of monosubstituted pyridinium compounds

X	Y	σ_W^+(add) [a]	$\Delta\sigma^+$ [b]	σ_W^+(exp) [a]	ρ
NH	NH_2	0·61	0·92	−0·31	−3·0
NH	O^-	0·32	1·06	−0·74	−3·2
NH	Me_2	1·30	0·75	0·55	−7·6
N(OH)	NH_2	0·71	1·20	−0·49	−4·6
N(OH)	Me_2	1·40	0·82	0·58	−6·1

[a] $\sigma_W^+ = \sigma_{m-X}^+ + \sigma_Y^+$. [b] Average value for $\Sigma\sigma^+$(add) − $\Sigma\sigma^+$(exp).

Finally, ρ for hydrogen exchange of monosubstituted pyridinium cations is obtained as −12·9 by plotting log k_0 for compounds of Table 4 where X = NH^+ and Z = H *vs.* σ_p^+ and incorporating log k_0 = −25·4 (see previously). This ρ value of −12·9 is more negative than that of −7·5 for monosubstituted benzenes, in apparent agreement with the reactivity–selectivity relationship,[10] since pyridine is *ca.* 10^{15} times less reactive than benzene. However, 4-pyridone is 10^6 times more reactive than benzene, and the reasoning just given does not account for different transition state structures,[11] since the apparent variations of ρ between series might well be explained in terms of interactions between substituents.

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[19] H. V. Ansell, J. Le Guen, and R. Taylor, *Tetrahedron Letters* 1973, 13.

[20] T. Gilbert and C. D. Johnson, *J. Amer. Chem. Soc.*, in the press.

TABLE 6

Quantitative factorization interaction treatment for partial rate factors (p.r.f.)

Compound	$\log f$(p.r.f.)	$\Sigma\sigma^{+}$ [a]	$\Sigma\Pi\sigma^{+}$	$\Delta \log k$ [b]	$\log f$(p.r.f.) $+2{\cdot}9\Sigma\Pi\sigma^{+}$	Calculated [c] $\log f$(p.r.f.)
(i) Monosubstituted benzenes						
Benzene	0	0	0	0	0	1·6
Bromobenzene	−0·6	0·15	0	0	−0·6	0·7
Toluene (*m*)	−0·4	−0·07	0	0	−0·4	2·0
t-Butylbenzene	3·2	−0·26	0	0	3·2	3·2
Toluene (*p*)	3·0	−0·31	0	0	3·0	3·6
Thiophen (β)	5·0	−0·52 [d]	0	0	5·0	4·9
Anisole	6·8	−0·78	0	0	6·8	6·5
Thiophen (α)	8·6	−0·79 [d]	0	0	8·6	6·6
Phenol	7·0	−0·92 [e]	0	0	7·0	7·4
Furan (α)	8·2	−0·93 [d]	0	0	8·2	7·5
Aniline	9·8	−1·31 [e]	0	0	9·8	9·9
NN-Dimethylaniline	11·1	−1·50 [e]	0	0	11·1	11·1
Phenolate anion	12·0	−1·60	0	0	12·0	11·7
Disubstituted benzenes: (ii) Xylenes						
m-Xylene	6·2	−0·62	0·10	0·8	6·5	5·3
p-Xylene	2·6	−0·38	0·02	0·2	2·7	4·0
(iii) Phenols						
p-Nitrophenol	4·1	−0·25	−0·62	2·2	2·3	4·5
p-Cresol	7·8	−0·99	0·06	0·4	8·0	7·7
p-Chlorophenol	6·2	−0·52	−0·37	2·3	5·1	5·7
(iv) Anilines						
p-Toluidine	9·9	−1·38	0·09	−0·4	10·2	10·1
p-Anisidine	9·6	−1·26	−0·07	0·2	9·4	9·7
p-Chloroaniline	8·6	−0·91	−0·52	1·9	7·1	8·4
p-Nitroaniline	7·4	−0·64	−0·88	2·7	4·8	7·5
(v) *NN*-Dimethylanilines						
p-Methyl	11·3	−1·57	0·11	−2·0	11·6	11·3
p-Methoxy	10·7	−1·45	−0·08	−1·7	10·5	10·9
p-Chloro	10·3	−1·10	−0·60	0·6	8·6	9·8
p-Bromo	10·2	−1·09	−0·62	0·5	8·4	9·8
m-Methyl	12·4	−1·81	0·47	−2·7	13·8	12·0
m-Nitro	8·4	−0·71	−1·19	1·6	4·9	8·6
(vi) Pyridinium cations						
2-Amino-3-methyl	3·0	0·54	−2·38	7·1	−3·9	3·2
2-Amino-5-methyl	2·9	0·54	−2·38	7·0	−4·0	3·2
2-Amino-4-methyl (3)	3·2	0·30	−1·92	5·5	−2·4	3·7
2-Amino-4-methyl (5)	3·4	0·30	−1·92	5·7	−2·2	3·7
2-Amino-6-methyl (3)	3·6	0·30	−1·92	5·9	−2·0	3·7
2-Amino-6-methyl (5)	4·1	0·30	−1·92	6·4	−1·5	3·7
2-Amino-5-chloro	1·3	1·01	−3·28	9·0	−8·2	2·1
4-Amino	3·4	0·61	−2·52	8·1	−3·9	3·2
4-Amino-2,6-dichloro	1·9	0·83	−2·95	8·3	−6·7	2·6
4-Pyridone	6·2	0·32	−3·07	8·6	−2·7	6·0
2-Pyridone	6·2	0·32	−3·07	8·6	−2·7	6·0
3-Methyl-2-pyridone	6·7	0·25	−2·88	8·6	−1·7	6·1
5-Methyl-2-pyridone	6·3	0·25	−2·88	8·2	−2·1	6·1
2,6-Dimethyl-4-pyridone (0)	8·2	−0·30	−1·53	6·0	3·8	6·7
2,6-Dimethyl-4-pyridone (+)	2·5	0·38	−1·27	5·4	−1·2	1·9
4-Methoxy-2,6-dimethyl	1·2	0·52	−1·21	5·1	−2·3	0·9
2,6-Dimethyl	−4·6	1·30	−0·91	5·2	−7·2	−4·7
2,4,6-Trimethyl	−0·9	0·99	−1·03	6·5	−3·9	−2·5
(vii) 1-Hydroxypyridinium cations						
4-Amino	3·1	0·71	−2·65	8·5	−4·6	2·7
2-Amino-5-bromo	1·2	1·12	−3·44	9·7	−8·8	1·8
2,4,6-Trimethyl	−0·8	1·09	−1·10	7·4	−4·0	−3·0
4-Methoxy-2,6-dimethyl	1·3	0·62	−1·30	6·0	−2·5	0·4
2,6-Dimethyl-4-pyridone (+)	2·3	0·48	−1·37	5·9	−1·7	1·5
2,6-Dimethyl-4-pyridone (0)	7·0	−0·20	−1·66	5·5	2·2	6·3

[a] Ref. 7 unless otherwise stated. [b] See text. [c] Using equation (iv). [d] G. Marino, *Adv. Heterocyclic Chem.*, 1971, **13**, 235. [e] S. Clementi and P. Linda, *J.C.S. Perkin II*, 1973, 1887.

Quantitative Factorization Interaction Treatment.— Rate data of Tables 1, 3, and 4 were used to test the applicability of the 'Quantitative Factorization Interaction Treatment' (QFIT) suggested[3] for polysubstituted compounds [equation (i)]. If all pyridines and disubstituted benzenes can be shown to lie on the same line with monosubstituted benzenes it is possible to formulate an equation which will predict the reactivity of any aromatic substrate towards hydrogen exchange at any position.

$$\log f(\text{p.r.f.}) = p\Sigma\sigma^{+} + q\Sigma\sigma_{X}^{+}\sigma_{Y}^{+} \qquad \text{(i)}$$

$$\Delta \log k = \log k_{\text{exp}} - \log k_{\text{add}} = \log k_{\text{exp}} + 7{\cdot}5\Sigma\sigma^{+} \qquad \text{(ii)}$$

$$\log f(\text{p.r.f.}) = p\Sigma\sigma^{+} + q\Sigma\Pi\sigma^{+} \qquad \text{(iii)}$$

Data used for QFIT are listed in Table 6. Equation (i) was first applied to pyridine, by using the approximation as proposed by Dubois *et al.*,[3a] *i.e.* utilizing the cross products of σ in the interaction term two by two only. No correlation between $\Delta \log k$ defined by equation (ii) and $\Sigma\sigma_X{}^+\sigma_Y{}^+$ was found. In equation (iii), $\Sigma\Pi\sigma^+$ includes all cross products, taken in pairs, triplets, and higher terms. Thus for the 2-amino-3-methylpyridinium cation $\Sigma\Pi\sigma^+$ is $-2{\cdot}38$, made up of the following contributions from the pairs $-2{\cdot}52$, $-0{\cdot}13$, $+0{\cdot}09$, and the triplet term $+0{\cdot}18$. A plot of $\Delta \log k$ *vs.* $\Sigma\Pi\sigma^+$ discloses a fair linear correlation for **39** polysubstituted homocyclic and heterocyclic compounds with $r = 0{\cdot}927$ and a slope (q) of $-2{\cdot}9$. A plot of $[\log f(\text{p.r.f.}) + 2{\cdot}9\, \Sigma\Pi\sigma^+]$ *vs.* $\Sigma\sigma^+$ shows for **52** compounds, including **13** monosubstituted benzenes,[18] a linear correlation ($r = 0{\cdot}986$), with a slope (p) of $-7{\cdot}1$, close to that for monosubstituted benzenes ($-7{\cdot}5$).[18] By contrast a plot of $\log f$(p.r.f.) against $\Sigma\sigma^+$ shows much greater scatter: the best line has slope $-3{\cdot}9$, intercept $4{\cdot}3$, and correlation coefficient only $0{\cdot}88$.

These results, obtained by the simple stepwise procedure outlined appear to be self-consistent as p is very close to ρ. Nevertheless, we have considerable doubts regarding the validity of the whole approach for the following reasons. A proper treatment of the results must involve multiple regression analysis, allowing independent evaluation of p and q, and this has now been carried out and gives equation (iv). The small value of p (now considerably different from ρ) and the large intercept emphasize the caution with which any conclusions concerning the nature of the transition state should be drawn. The theoretical justification is doubtful: the two variables $\Sigma\sigma^+$ and $\Sigma\Pi\sigma^+$ are not independent,[21] and q may not be a constant over different ring systems.

$$\log f(\text{p.r.f.}) = -6{\cdot}3\Sigma\sigma^+ - 2{\cdot}1\Sigma\Pi\sigma^+ + 1{\cdot}6 \quad \text{(iv)}$$

The theoretical implications of this type of treatment are far from clear, and further enquiry is necessary. Nevertheless, equation (iv) represents a very useful empirical expression for predictive purposes; although deviations from the line of Figure 2 in several cases are quite severe, overall correspondence is encouraging when the very wide range of reactivities (*ca.* 10^{16}) is taken into account, and the relationship effectively summarizes the significant progress made in quantification of pyridine reactivity in hydrogen exchange in the last decade.

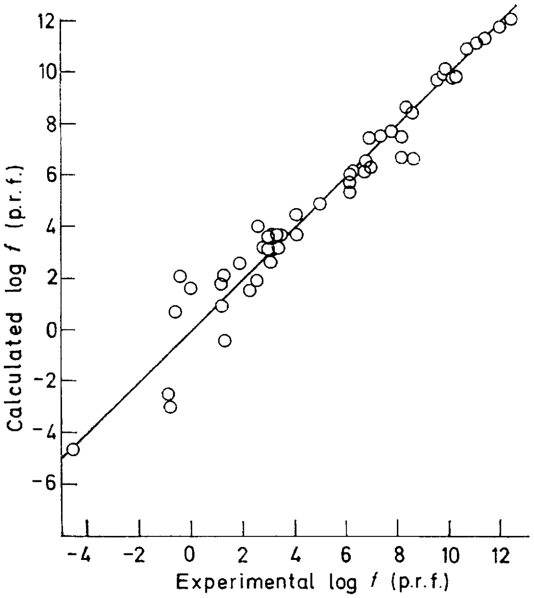

Figure 2 Plot of calculated against experimental log f(p.r.f.) values [calculations by equation (iv)]

[3/1912 *Received*, 17*th September*, 1973]

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[21] S. Clementi, unpublished results.