Discussion of Standard Nitration Rates for Benzenoid and Heteroaromatic Compounds †

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Standard log k_0 values for nitration are compared with previous partial rate factors. log k_0 Values for monosubstituted benzenes are correlated by σ^+ with ρ −9.7, but for polysubstituted derivatives and heterocyclic analogues much scatter is shown which is not improved by a correction term of type $\pi\sigma^+$ for substituent–substituent interactions. Comparison of relative reactivities of individual substrates towards nitration and to hydrogen exchange shows that there is no simple unique scale of substrate reactivity toward electrophilic substitution.

EVALUATION of standard nitration rates [2] (25°; H_0 − 6.6 in aqueous H_2SO_4) permits discussion of substrate reactivities under the same conditions. Previous comparisons between the nitration rates of compounds of widely differing reactivity have required a stepwise procedure.[3a] Such procedures carry the implicit assumption that partial rate factors do not vary appreciably with acidity, and the absence of any uniquely defined procedure introduces ambiguities in the results.

Comparison with Previous Work.—A comparison of our derived standard log k_2° values with the previously reported partial rate factors is given in Figure 1. The sources of the literature data used in Figure 1 are listed [Table (i)] in Supplementary Publication No. SUP 21466 (8 pp.).‡ The plot includes 70 points and shows a fairly good relationship (r 0.98, slope 0.97), but a large scatter (s.d. 0.61). We believe that standard rates expressed by log k_2° are preferable for proper comparison of relative substrate reactivities as log k_2°. Values are uniquely defined whereas no unique definition for f is generally accepted and f could vary with temperature and acidity. Figure 1 also includes some reactivities in media other than aqueous H_2SO_4 ($MeNO_2$ or Ac_2O) from Stock and Brown's compilation.[4] These apparently fall on the same regression line as the data for aqueous H_2SO_4.

Monosubstituted Benzenes.—Figure 2 is a Hammett plot for the nitration of monosubstituted benzenes from the data of Table 1. The ρ value for nitration in mixed media was evaluated by Stock and Brown as −6.0,[4] and recalculated by Schofield and his co-workers as −6.2.[3b] For reactions in aqueous H_2SO_4 the same plot was already reported using log f,[5] but no conclusions on the ρ value were drawn. Figure 2 shows a linear relationship with ρ −9.7 for unsubstituted benzene and deactivated derivatives (15 points).§ Reactivities for benzenes containing activating substituents level off at log k_2° *ca.* 2. This is attributed to the reaction proceeding at the encounter rate, 40 times higher than the rate constant of benzene.[3,6,¶]

Attempted Hammett Correlation for Polysubstituted Derivatives.—The standard rate constants relative to that of benzene for 59 mono- or poly-substituted compounds are listed in Table (ii) (in SUP 21 466) and plotted in Figure 3 against $\Sigma\sigma^+$. Only those substrates with substituents for which the σ^+ values are well established are included. For the many cases where nitration occurs at a position *ortho* to a substituent we took $\sigma^+_o = 0.86\sigma^+_p$.[7] Although the additivity plot shows considerable scatter the points do not appear to be random. As previously

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† The Kinetics and Mechanism of the Electrophilic Substitution of Heteroaromatic Compounds. Part XLIV.[1]

‡ For details of Supplementary Publications see Notice to Authors, No. 7, in *J.C.S. Perkin II*, 1974, Index Issue. Items less than 10 pp. are supplied as full-size copies.

§ For Figure 2, r (correlation coefficient) is 0.934, S_{est} (or SD, standard deviation) is 0.963, but S_b (standard error in slope) is 1.03, and therefore t_8 (Student test) is 9.44, which gives a very high confidence level.

¶ This figure refers to 69% H_2SO_4; at 75% H_2SO_4 (H_0 −6.6) log k_2 (encounter) is *ca.* 3.

[1] Part XLIII, A. R. Katritzky, O. H. Tarhan, and B. Terem, *J.C.S. Perkin II*, 1975, preceding paper.

[2] A. R. Katritzky, B. Terem, E. V. Scriven, S. Clementi, and H. O. Tarhan, *J.C.S. Perkin II*, 1975, 1600.

[3] J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, 'Nitration and Aromatic Reactivity,' Cambridge University Press, Cambridge, 1971 (*a*) p. 123; (*b*) p. 194.

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

[5] R. G. Coombes, D. H. G. Crout, J. G. Hoggett, R. B. Moodie, and K. Schofield, *J. Chem. Soc.* (*B*), 1970, 347.

[6] R. G. Coombes, R. B. Moodie, and K. Schofield, *J. Chem. Soc.* (*B*), 1968, 800.

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

found for the hydrogen exchange data,[8] several individual lines could be drawn on the plot for various limited substrate series in which the molecular structure is kept constant except for the variation of one substituent parameter. Thus, pyridones exhibit a higher slope than the main regression line (involving homocyclic compounds and pyridines), whereas the five-membered heterocycles and the methoxy-substituted compounds lie on lines exhibiting a lower ' selectivity '. A least square analysis on the 43 points for which the reactivity is less than that of benzene gives ρ — 5.55, intercept −1.89, and r 0.72. Application of the modified Dubois equation[9] (1) which

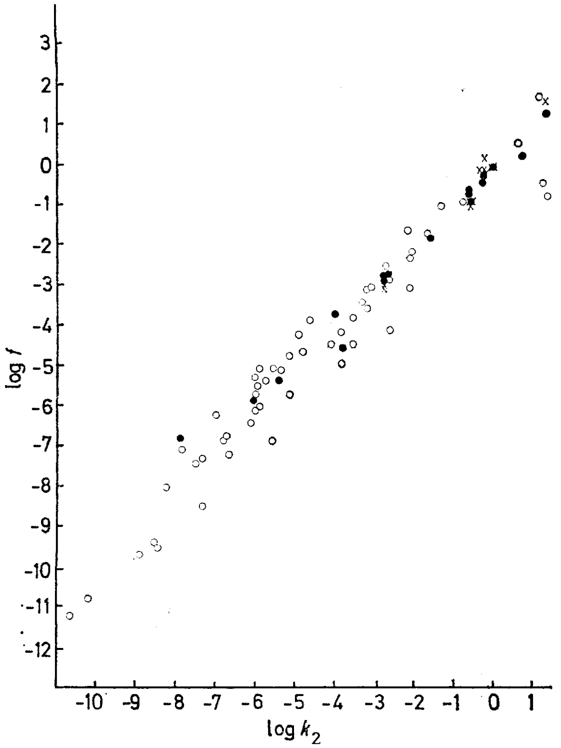

FIGURE 1 Comparison of previously evaluated partial rate factors with standard nitration rates. Plot of log f against log k_2° (rel): ●, monosubstituted benzenes in H_2SO_4; ○, polysubstituted benzenes and heterocycles in H_2SO_4; ×, monosubstituted benzenes in $MeNO_2$ or Ac_2O

TABLE 1

Standard nitration rates of monosubstituted benzenes

Substituent	log k_2° [a]	σ^+ [b]
α-S	1.68	−0.79 [c]
p-OMe	2.37	−0.78
o-OMe	1.73	−0.67 [d]
2,5-Me_2	1.65	−0.34 [e]
p-Me	1.82	−0.31
o-Me	1.73	−0.27 [d]
m-Me	0.26	−0.07
p-F	0.23	−0.07
H	0.45	0
m-CH_2OMe	−0.86	0.02 [f]
p-Cl	−0.15	0.11
p-I	0.21	0.13
p-Br	−0.15	0.15
m-F	−2.22	0.35
m-COMe	−3.35	0.38 [f]
m-Cl	−2.29	0.40
m-COOH	−3.60	0.40 [f]
m-Br	−2.30	0.41
m-CN	−6.36	0.56
m-NH_3^+	−5.59	0.63 [f]
m-NO_2	−7.46	0.67

[a] Ref. 2. [b] Ref. 4 unless otherwise stated. [c] S. Clementi, P. Linda, and G. Marino, *J. Chem. Soc.* (*B*), 1970, 1153. [d] Ref. 7. [e] Assuming additivity. [f] σ_m values: see C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, 1964, **2**, 323.

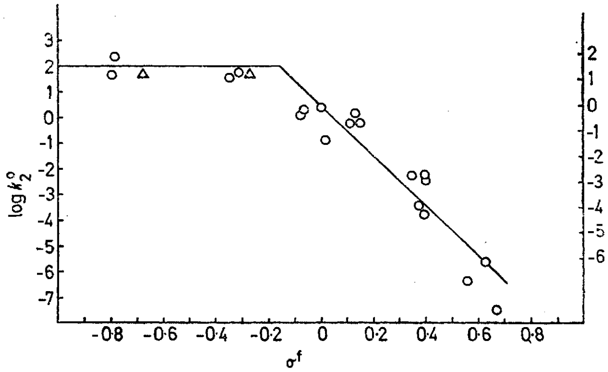

FIGURE 2 Hammett plot for nitration of monosubstituted benzenes at standard conditions

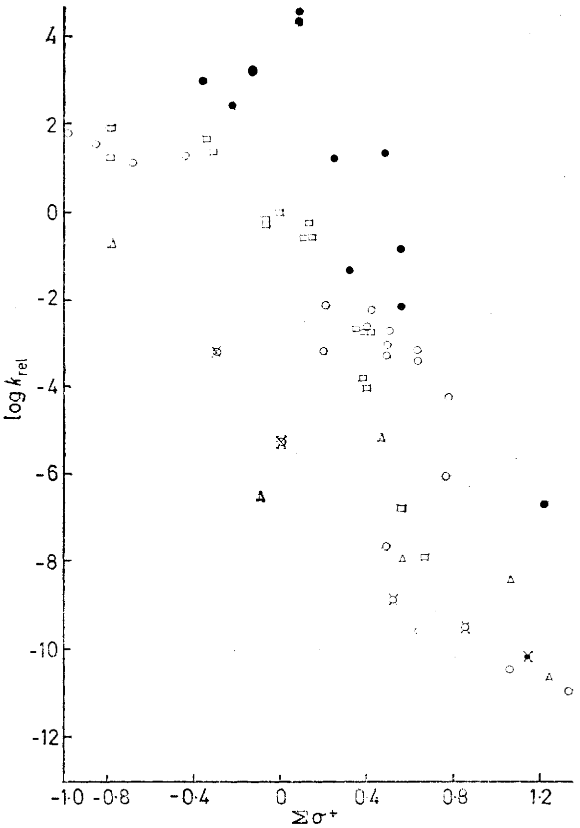

FIGURE 3 Additivity plot: □, monosubstituted benzenes; ●, pyridones (✱ as CA); ☆, five-membered rings; △, methoxy-derivatives

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[8] S. Clementi, C. D. Johnson, and A. R. Katritzky, *J.C.S. Perkin II*, 1974, 1294.

[9] J. E. Dubois, J. J. Aaron, P. Alcais, J. P. Doucet, F. Rothenberg, and R. Uzan, *J. Amer. Chem. Soc.*, 1972, **94**, 6823.

correlated the reactivities of polysubstituted compounds towards hydrogen exchange [8] gives poor results for the present nitration data: multiple regression analysis leads to $p - 5.73$, $q - 0.22$, intercept -1.98, and R (multiple correlation coefficient) 0.725. Although the explanatory variables are not strictly correlated (partial correlation coefficient ≈ 0.2), corrections of type $\pi\sigma^+$ for interactions between substituents do not improve the $\Sigma\sigma^+$ relationship, possibly because of non-negligible steric effects for *ortho*-nitration. Use of the figures obtained as regression parameters from this multiple correlation for recalculating the relative rates gives very large errors (see Table 2).

$$\log k_{\text{rel}} = p\Sigma\sigma^+ + q\Sigma\Pi\sigma^+ + c \qquad (1)$$

Comparison of Hydrogen Exchange and Nitration.—Table 2 and Figure 4 compare the standard rates of individual substrates towards hydrogen exchange and nitration. The points in no way fall on a unique line and it follows that there is no unique scale of reactivity valid for electrophilic substitution reactions. Each class of closely related compounds falls on a different line; above the appropriate level reactivities level off because of the encounter rate limitation. Since the standard rates for hydrogen exchange [10] also obey the Hammett equation ($\rho - 7.5$) [11] all points for monosubstituted benzenes should lie on the line drawn in Figure 4, the slope of which (0.77) is equal to the ratio of the two ρ constants. This is apparently the case except where the reactivities of activated benzenes in nitration are limited by the encounter rate.

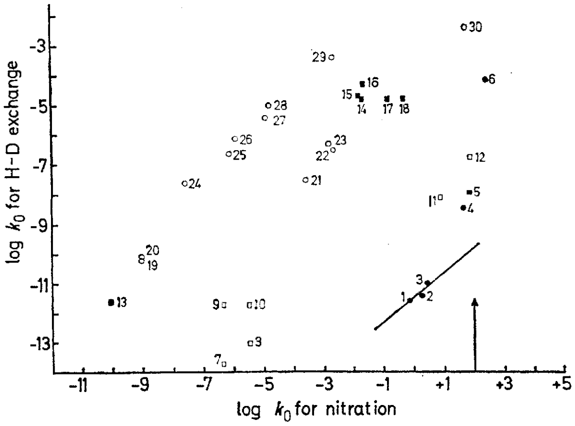

FIGURE 4 Plot of rates for hydrogen exchange against rates for nitration for ●, substituted benzenes (1: PhBr at *p*; 2: PhMe at *m*; 3: C_6H_6; 4: *p*-$C_6H_4Me_2$ at 2; 5: PhMe at *p*; 6: PhOMe at *p*). □, Bicyclic compounds (7: quinolinium cation at 8; 8: isoquinolinium cation at 8; 9: quinolinium cation at 5; 10: isoquinolinium cation at 5; 11: naphthalene at 2; 12: naphthalene at 1). ■, Heteroaromatics with six-membered rings (13: 2,4,6-trimethylpyridinium cation at 3; 14: 4-pyridone at 3; 15: 5-methyl-2-pyridone at 3; 16: 3-methyl-2-pyridone at 5; 17: 2-pyridone at 5; 18: 2-pyridone at 3). ○, Heteroaromatic compounds with five-membered rings (19: 2,3,5-trimethylisothiazolium cation at 4; 20: 3,5-dimethylisothiazolium cation at 4; 21: isothiazole at 4; 22: 3-methylisothiazole at 4; 23: 5-methylisothiazole at 4; 24: 1-methylpyrazolium cation at 4; 25: 1,5-dimethylpyrazolium cation at 4; 26: 1,3-dimethylpyrazolium cation at 4; 27: 1,2,3,5-tetramethylpyrazolium cation at 4; 28: 1,3,5-trimethylpyrazolium cation at 4; 29: 3,5-dimethylisoxazole at 4; 30: thiophen at 2)

All points for heterocyclic compounds, which are considered here as polysubstituted benzenes, fall above this line, *i.e.* the reactivity of heterocyclic substrates is much lower towards nitration than would be expected if their rate of hydrogen exchange were taken as a model for electrophilic substitution. This is presumably due to different substituent interactions in the transition states of the two reactions. The transition state for the nitration reaction appears to be less advanced along the reaction co-ordinate than that for hydrogen exchange, possibly implying some π-complex character.

TABLE 2

Comparison between standard rates for nitration and hydrogen exchange

Compound (position)	log k_2° [a] (nitration)	log k_0 [b] (hydrogen exchange)
Benzene	0.45	−11.00
Toluene (*meta*)	0.26	−11.42
Toluene (*para*)	1.82	−7.95
Bromobenzene (*para*)	−0.15	−11.58
Anisole (*para*)	2.37	−4.17
p-Xylene	1.65	−8.44
Naphthalene (α)	1.85	−6.75 [c]
Naphthalene (β)	0.85	−8.11 [c]
Thiophen	1.68	−2.39
2,4,6-Trimethylpyridine	−10.03	−11.60 [d]
4-Pyridone	−1.69	−4.80 [d]
2-Pyridone (3)	−0.37	−4.80 [d]
2-Pyridone (5)	−0.85	−4.80 [d]
3-Methyl-2-pyridone	1.70	−4.30 [d]
5-Methyl-2-pyridone	1.83	−4.70 [d]
1-Methylpyrazole	−7.60 [e]	−7.60 [f]
1,3-Dimethylpyrazole	−5.94 [e]	−6.10 [f]
1,5-Dimethylpyrazole	−6.16 [e]	−6.60 [f]
1,3,5-Trimethylpyrazole	−4.79	−5.00 [f]
1,2,3,5-Tetramethylpyrazolium cation	−4.93	−5.40 [f]
3,5-Dimethylisoxazole	−2.72	−3.40 [g]
Isothiazole	−3.82 [h]	−7.50 [g]
3-Methylisothiazole	−2.66 [h]	−6.50 [g]
5-Methylisothiazole	−2.94 [h]	−6.30 [g]
3,5-Dimethylisothiazole	−9.03	−10.10 [g]
2,3,5-Trimethylisothiazolium cation	−9.03	−10.20 [g]
Quinoline (5)	−6.28	−11.70 [d]
Quinoline (8)	−6.36	−11.50 [d]
Isoquinoline (5)	−5.46	−11.70 [d]
Isoquinoline (8)	−5.46	−13.00 [d]

[a] Ref. 2. [b] Ref. 11 unless otherwise stated. [c] Calculated from data given in J. Banger, C. D. Johnson, A. R. Katritzky, and B. R. O'Neill, *J.C.S. Perkin II*, 1974, 394. [d] Ref. 10. [e] H. O. Tarhan, unpublished results. [f] S. Clementi, P. P. Forsythe, C. D. Johnson, and A. R. Katritzky, *J.C.S. Perkin II*, 1973, 1675. [g] S. Clementi, P. P. Forsythe, C. D. Johnson, A. R. Katritzky, and B. Terem, *J.C.S. Perkin II*, 1974, 399. [h] Ref. 1.

Individual Reactivities.—The log k_0 values for individual substrates are listed in Table 9 of ref. 2, and the effects of change of substituents or ring heteroatoms may be deduced from them by comparison. We take pyridine as an example.

It is not possible to compare k_0 values directly for cor-

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[10] A. El-Anani, J. Banger, G. Bianchi, S. Clementi, C. D. Johnson, and A. R. Katritzky, *J.C.S. Perkin II*, 1973, 1065.

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

responding benzenes and pyridines, because rates are only available for those pyridines where the correspondingly substituted benzenes react at the encounter rate. In the methoxy- and trimethyl derivatives, the retardation by the pyridinium NH^+ is seen to be $>10^{12}$. However, the reactivity of the parent pyridinium cation can be estimated in at least two different ways. The ρ value for monosubstituted benzenes and the $\sigma_m{}^+$ constant for the $-\overset{+}{N}H=$ group gives log $k_2{}^\circ$ -18.6. A Hammett plot relying on reactivities of pyridones and dimethylaminopyridines gives a ρ value for nitration of pyridinium cations as -11.4, and log $k_2{}^\circ$ for the unsubstituted compound as -18.2. The pyridinium cation appears therefore to be some 10^{19} times less reactive than benzene towards nitration at standard conditions.

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