

Intermediates in Nucleophilic Aromatic Substitution. Part XV.¹ Thermodynamic Stabilities of Hydroxy and Methoxy Meisenheimer Complexes of Substituted Arenes²

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Considering available thermodynamic data on the interaction of hydroxide and methoxide ions with substituted arenes, relative free energies of Meisenheimer complex stabilization have been calculated for given substituents at different positions on the benzene and naphthalene ring as well as those for benzo-fusion. Using these values stabilities of Meisenheimer complexes can be predicted. Excellent agreement has been obtained between the predicted and experimentally determined stabilities for 116 pairs of Meisenheimer complexes. Satisfactory correlations have also been obtained between rate and equilibrium constants for the formation and decomposition of σ -complexes and the sums of appropriate substituent constants. Additionally, stabilization of Meisenheimer complexes by dipolar aprotic DMSO and DMF have been shown to be independent of the number and type of substituents on the aromatic nucleus, on the attacking nucleophile, or on the co-solvent. The significance of these results is that they provide a coherent framework for the mechanistic discussion of nucleophilic aromatic substitution.

DATA for the stabilities of Meisenheimer complexes, formed from di-, tri-, and tetra-nitrosubstituted naphthalenes have been detailed in previous Parts. Combination of all the available information, obtained by us^{1,3-7} and others⁸⁻¹¹ allows a critical discussion of the factors which influence the thermodynamic stabilities of activated σ -complexes. Thermodynamic stabilities, following Strauss' suggestion,¹² will be calculated by the use of equation (1) where K_A and K_B are equilibrium

$$\delta\Delta G = 2.3RT\log K_A/K_B \quad (1)$$

constants for the formation of Meisenheimer complexes A and B. Equation (1) assumes, of course, that differences in the free energies of the reactants forming A and B are negligible. Attention will be focused on the entering nucleophile ($-\text{OH}$ and $-\text{OCH}_3$), on the number and kind of nitro and other electron-withdrawing groups, on the aromatic nucleus, and on the role of dipolar aprotic co-solvents. Special emphasis will be placed on comparing kinetic and thermodynamic parameters for the stabilities of complexes formed on rehybridization of a carbon atom constituting a benzene and a naphthalene ring. Transmission of electron delocalization across the two rings of naphthalene will be elucidated. The relative stabilizing power of individual nitro-groups, located at different positions on the naphthalene ring will be assessed by comparing equilibrium constants among appropriate pairs of complexes. These data will extend and substantiate those previously determined.¹²

¹ Part XIV, W. L. Hinze, L.-J. Liu, and J. H. Fendler, preceding paper.

² For recent reviews on Meisenheimer complexes and their relevance in nucleophilic aromatic substitution see (a) R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, 1966, **16**, 61; (b) E. Bunzel, A. R. Norris, and K. E. Russell, *Quart. Rev.*, 1968, **22**, 123; (c) P. Buck, *Angew. Chem. Internat. Edn.*, 1969, **8**, 120; (d) J. Miller, 'Aromatic Nucleophilic Substitutions,' Elsevier, New York, 1968; (e) M. J. Strauss, *Chem. Rev.*, 1970, **70**, 667.

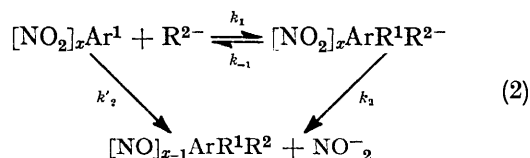
³ J. H. Fendler, E. J. Fendler, and C. E. Griffin, *J. Org. Chem.*, 1969, **34**, 689.

⁴ J. H. Fendler, E. J. Fendler, W. E. Byrne, and C. E. Griffin, *J. Org. Chem.*, 1968, **33**, 977.

⁵ J. H. Fendler and E. J. Fendler, *J. Org. Chem.*, 1970, **35**, 3378.

Knowledge of the stabilizing powers of the substituents and of benzo-fusion will allow calculations of equilibrium constants for the formation of Meisenheimer complexes. These predicted values will be compared with those obtained experimentally. Additionally, thermodynamic stabilities will be correlated with ¹H n.m.r. chemical shifts.

Experimental data are summarized in Table I for substitution (2) at a carbon atom in phenyl (1)—(5)



and naphthyl (6)—(12) derivatives. Symbols a—c refer to hydroxy-, methoxy-, and dimethoxy-complexes *i.e.* $\text{R}^1, \text{R}^2 = \text{H}, \text{OH}$, $\text{R}^1, \text{R}^2 = \text{H}, \text{OMe}$, and $\text{R}^1, \text{R}^2 = (\text{OMe})_2$, respectively.

Stabilities of 1-Hydroxy-, 1-Methoxy-, and 1,1-Dimethoxy-cyclohexadienylides.—Meisenheimer complexes, formed in the interaction of methanolic methoxide ion with polynitro-substituted anisoles, (3c), (6c), and (7c) are factors of 1 090, 2 550, and 2 100 more stable than the corresponding 1-methoxycyclohexadienylides (3b), (6b), and (7b) (Table 1). Using equation (1) for these data a $\delta\Delta G$ value of 4.2 kcal mol⁻¹ is calculated for the additional stabilization of Meisenheimer complexes by a methoxy-group covalently attached to the 1-position. The greater stability of the 1,1-dimethoxy-

⁶ E. J. Fendler and J. H. Fendler, *J.C.S. Perkin II*, 1972, 1403.

⁷ J. H. Fendler, E. J. Fendler, and L. M. Casilio, *J. Org. Chem.*, 1971, **36**, 1749.

⁸ C. F. Bernasconi, *J. Org. Chem.*, 1968, **90**, 4982; *J. Amer. Chem. Soc.*, 1970, **92**, 4682.

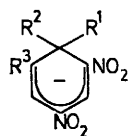
⁹ M. R. Crampton and M. El Ghariani, *J. Chem. Soc. (B)*, 1970, 391.

¹⁰ M. R. Crampton and V. Gold, *J. Chem. Soc. (B)*, 1966, 893.

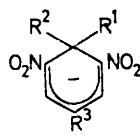
¹¹ F. Terrier, P. Pastour, and R. Schaal, *Compt. rend.*, 1965, **260**, 5783.

¹² R. M. Murphy, C. A. Wulff, and M. J. Strauss, *J. Amer. Chem. Soc.*, 1974, **96**, 2678.

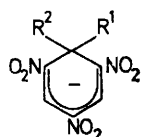
cyclohexadienyliides, compared with the 1-methoxy-cyclohexadienyliides, is a consequence of differences in the rate constants for both the formation (k_1) and decomposition (k_{-1}) of the appropriate complexes. Thus, methoxide ion reacts faster with hydrogen bearing aromatic carbon atoms than with anisoles. Ratios of



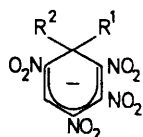
- (1) $R^3 = H$
 (16) $R^3 = CN$
 (20) $R^3 = CO_2CH_3$
 (21) $R^3 = CF_3$
 (23) $R^3 = Cl$
 (24) $R^3 = F$



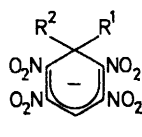
- (2) $R^3 = H$
 (13) $R^3 = CN$
 (14) $R^3 = CO_2CH_3$
 (15) $R^3 = CF_3$
 (22) $R^3 = Cl$
 (25) $R^3 = SCH_3$
 (26) $R^3 = CONHCH_2CH_3$
 (27) $R^3 = I$
 (28) $R^3 = SO_2CH_3$



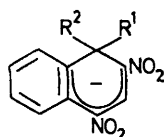
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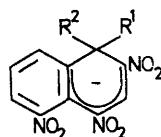
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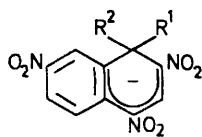
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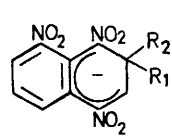
(6)



(7)



(8)



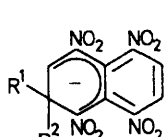
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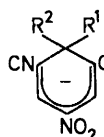
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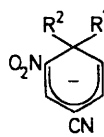
(11)



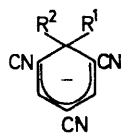
(12)



(17)



(18)



(19)

k_1 for (3b)/(3c), (6b)/(6c), and (7b)/(7c) are 407, 12, and 9, respectively. Differences in decomposition rates are, however, more significant: ratios of k_{-1} for (3b)/(3c), (6b)/(6c), and (7b)/(7c) are 3.1×10^5 , 3.2×10^4 , and 2.0×10^4 , respectively. The methoxy-group in polynitro-substituted anisoles is sterically crowded. Enhanced stabilities of (3c), (6c), and (7c) are explicable in terms of the relief of steric strain upon rehybridization

¹³ M. R. Crampton, *J.C.S. Perkin II*, 1973, 2157.

¹⁴ C. F. Bernasconi and H. S. Cross, *J. Org. Chem.*, 1974, **39**, 1064.

of the sp^2 to an sp^3 carbon atom in which the methoxy-groups are located above and below the plane of the aromatic ring. Additionally, effective charge delocalization is an important factor as manifested by the biggest difference in k_{-1} for the trinitro-substituted complexes [(3b)/(3c) as compared with (6b)/(6c) and (7b)/(7c)]. Driving force for enhanced stabilization of (3c), and (6c), primarily originate in differences in enthalpies of activation. This decomposition of (3c) and (7c) requires 9.2 and 7.1 kcal mol⁻¹ more energy of activation than those for (3b) and (7b).

Comparisons of the stabilities of 1-hydroxy- with 1-methoxy-cyclohexadienyliides is less straight forward, since the media for the former is water while the latter is formed in methanol. Equilibrium constants for the formation of hydroxy Meisenheimer complexes are factors of 1.5—4.0 greater than those for 1-methoxy-cyclohexadienyliides with the notable exception of those formed from 1,3,5-trinitrobenzene (Table 1). Once again stability differences are the consequence of the greater reactivity of methoxide than hydroxide ion as well as the slower rate of decomposition of the hydroxy- than methoxy-adducts.

Effects of the Added Aromatic Ring.—Comparison of (1) and (6) affords the assessment of the free energy contribution of the added aromatic ring (benzo-fusion) to the stabilization of Meisenheimer complexes. Treating the equilibrium constants for the formation of (6b) and (1b) according to equation (1), a value of 7.02 kcal mol⁻¹ is obtained as being due to the free energy of stabilization of the added aromatic ring. This value should be compared with that of 7.2 kcal mol⁻¹ obtained on calculating free energy differences for (6c) and (1c). Similarly, there is a 7.4 kcal mol⁻¹ free energy difference between the stabilities of cyclic Meisenheimer complexes formed from 1-(β -hydroxyethoxy)-2,4-dinitro-benzene and -naphthalene.^{13,14} Good agreement among these relative free energy differences may imply that the electron-withdrawing power of the added phenyl ring is independent, at least for polynitro-substituted arenes, on the nature of the lyate ion and of the solvent. A value of 7.2 kcal mol⁻¹ is assigned, therefore, for benzo-fusion. Dewar has calculated that the formation of cyclohexadienyl intermediates from substituted benzenes requires a 10 kcal mol⁻¹ loss in resonance energy, whereas the resonance energy difference between naphthalene and the 1,1-disubstituted naphthalene σ -complex is only 2 kcal mol⁻¹.¹⁵ The theoretical value for the difference in resonance energy loss for the formation of Meisenheimer complexes from substituted benzenes and naphthalenes (*i.e.* 10—2 kcal mol⁻¹) agrees well, therefore, with the experimentally determined free energy difference due to benzo-fusion. Using a value of 7.2 kcal mol⁻¹ for benzo-fusion affords, therefore, a means of estimating equilibrium constants for the formation of Meisenheimer complexes whose stabilities preclude their experimental investigation. Using 7.2 kcal mol⁻¹ for

¹⁵ M. J. Dewar, 'The Electronic Theory of Organic Chemistry,' Oxford University Press, London, 1949, p. 177.

benzo-fusion the equilibrium constant for the formation of (1a), for example, is estimated to be $1 \times 10^{-6} \text{ l mol}^{-1}$. This value is in the expected range if equilibrium constant ratios for (6a)/(6b), (3a)/(3b) and (1a)/(1b) are considered.

The free energy difference due to benzo-fusion is the consequence of changes in enthalpies of activation for both formation and decomposition as well as those in entropies of activation for the decomposition of the complexes. ΔE_1 and ΔE_{-1} for (1c) and (6c) are 3.6 and $-4.7 \text{ kcal mol}^{-1}$, while $\delta\Delta S_1^\ddagger$ and $\delta\Delta S_{-1}^\ddagger$ for (1c) and (6c) are -0.4 and $+6.0 \text{ cal mol}^{-1} \text{ K}^{-1}$. The appreciable decrease in the entropy of activation for the decomposition of (6c) compared with that of (1c) is attributable to the increase of solvent orderliness around the bulkier naphthalene Meisenheimer complex.

phile and of the solvent. Taking the mean of these three ratios the free energy of stabilization due to an additional nitro-group in the 5-position is calculated [by equation (1)] to be $2.9 \text{ kcal mol}^{-1}$.

A comparison of the equilibrium constants for the formation of (8c) with that of (6c) yields $3.6 \text{ kcal mol}^{-1}$ for the free energy of stabilization due to an added nitro-group in the 7-position. This value is nicely substantiated by comparing the stabilities of (11a) with that of (7a). This latter comparison also gives a $\delta\Delta G$ value of $3.6 \text{ kcal mol}^{-1}$ for stabilization by the nitro-group at the same position. Comparison of the equilibrium constants for the formation of (11b) with that for (7b) results, however, in a $\delta\Delta G$ value (*ca.* $3.8 \text{ kcal mol}^{-1}$) which is in fair agreement with those obtained on comparing (11a) with (7a) and (8c) with (6c). This slight

TABLE I
Kinetic and thermodynamic parameters for polynitro-substituted Meisenheimer complex formation ^a

Meisenheimer complex	$k_1/\text{l mol}^{-1} \text{ s}^{-1}$	k_{-1}/s^{-1}	$K/\text{l mol}^{-1}$	$E_1/\text{kcal mol}^{-1}$	$\Delta S_1^\ddagger/\text{cal mol}^{-1} \text{ K}^{-1}$	$E_{-1}/\text{kcal mol}^{-1}$	$\Delta S_{-1}^\ddagger/\text{cal mol}^{-1} \text{ K}^{-1}$	Ref.
(1b) ^b			5×10^{-7}					10
(1c)	1×10^{-2}	42.0	2.7×10^{-4}	17.4 ± 0.5	-17.4	11.8 ± 0.5	-12.1 ± 1.7	8
(2b)			$(0.5-1.0) \times 10^{-6}$					16
(2c) ^b			9.8×10^{-20}					11
(3a) ^c	37.5	9.8	3.73	16.1 ± 0.8	1.1 ± 2.7	7.9 ± 0.8	-29.8 ± 2.7	8
(3b)	7 050	305	15.6	10.8 ± 0.8	-6.7 ± 2.7	9.8 ± 0.8	-16.3 ± 2.7	8
(3c)	17.3	1×10^{-3}	17 000	13.5 ± 1.0	-9.4 ± 2.0	19.0 ± 1.0	-4.8 ± 2.0	3
(4a)			24 000					9
(5a)			<50					9
(6a) ^d	0.29 ± 0.05	1.12 ± 0.2	0.26 ± 0.05					1
(6b) ^e	11.2 ± 0.5	124 ± 4	0.09 ± 0.01					1
(6c)	0.90	3.9×10^{-3}	230	13.8 ± 0.8	-17.0 ± 2.0	16.5 ± 0.8	-18.0 ± 2.0	4
(7a)	3.8 ± 1.1	0.12 ± 0.05	43 ± 15	14.2 ± 1.9^f	-9.4 ± 1.8^f			1
(7b)	304 ± 6	22 ± 3	13.8 ± 2	12.2 ± 1.3	-7.9 ± 0.5	11.5 ± 1.0	-15.0 ± 1.0	1
(7c)	32.8	1.1×10^{-3}	29 300	12.2 ± 0.3	-12.5 ± 2.0	18.6 ± 0.8	-11.7 ± 2.0	5
(8c)			1.09×10^5					6
(9a) ^d	0.08 ± 0.02	0.018 ± 0.01	7.0 ± 5.0					1
(9b)			1.5					1
(10a)	12.8 ± 1	2×10^{-2}	640 ± 20					1
(10b)	7 900	18.0	438	9.6 ± 2.0	-10.4 ± 1.5	13.0 ± 4.0	-11.1 ± 5	1
(11a)	250	0.23	11 000					7
(11b)	2.3 ± 10^4	(≤ 3)	$\geq 7 700$	8.2 ± 0.5	-11.8 ± 1.0			1
(12a) ^d	40 ± 10	0.10 ± 0.02	320 ± 100					1
(12b)	1 820	10.0	182	7.25 ± 1.5	-21.1 ± 2.0	12.0 ± 1.5	-15.7 ± 2.0	1

^a At 25.0°, solvent for R¹,R² = H, OH is water and R¹,R² = H, OMe or R¹,R² = (OMe)₂ is methanol, unless stated otherwise.
^b Determined *via* the J_{M} acidity function. ^c In H₂O-dioxan 90:10 (v/v). ^d Extrapolated values from mixtures of H₂O-dioxan.
^e Extrapolated values to zero NaOCH₃ concentrations. ^f In H₂O-dioxan 95:5 (v/v).

Effects of Nitro-groups.—The order of Meisenheimer complex stabilities, (4) > (11) > (10) > (12) > (8) > (7) > (3) > (9) > (6) > (1) > (2), reflects the electron-withdrawing powers of the substituents on the parent compounds and extent of electron delocalization in the complexes. Quantitatively the effects of adding an additional nitro-group at a given ring position may be assessed by comparing appropriate free energies of activation [equation (1)].

Effect of an added nitro-group in the 5-position of a substituted naphthalene on the stability of the Meisenheimer complex can be estimated by comparing equilibrium constants for the formation of (7) and (6). The fair agreement among the equilibrium constant ratios for (7c)/(6c), (7b)/(6b), and (7a)/(6a), 127, 153, and 165, indicate an independence on the nature of the nucleo-

discrepancy is explicable in terms of the uncertainties involved in obtaining values for k_{-1} for the decomposition of (11b) (Table 1).¹ The more pronounced effect of Meisenheimer complex stabilization by an added nitro-group in the 7- than in the 5-position of the naphthalene ring can be rationalized on the basis of both electronic and steric considerations. Since the nitro-group in the 7-position is closer to the seat of substitution, it can more efficiently create a relatively large electron deficiency at the site of nucleophilic attack than when it is in the 5-position. Additionally, steric hindrance of the 5-nitro-group in these polynitronaphthalenes leads to some loss of coplanarity and hence to decreased conjugation as compared to the lesser hindered 7-nitro-group.

¹⁶ M. R. Crampton and H. A. Khan, *J.C.S. Perkin II*, 1973, 710.

Comparing the equilibrium constants for the formation of (12b) with (9b) and that of (12a) with (9a) results in a $\delta\Delta G$ value of 2.4 kcal mol⁻¹ for the free energy of stabilization due to the addition of a nitro-group at the 8-position. Similarly, comparing the equilibrium constants for the formation of (10b) with (9b) and that of (10a) with (9a) affords a value of 2.9 kcal mol⁻¹ for the free energy of stabilization of the 6-nitro-group. These estimations of free energies of stabilization due to 6- and 8-nitro-groups may be somewhat in error since the point of nucleophilic attack is no longer at the 1-position (see structures in Table 1).

Effects of additional nitro-groups in the 2- and 4-positions on the stabilization of cyclohexadienylides are, not unexpectedly, considerably greater than those in other positions. Thus a comparison of the equilibrium constants for the formation of (1c) with (2c) and (1b) with (2b) yields a $\delta\Delta G$ value of 21 kcal mol⁻¹ for the 4-nitro-group. This large value for stabilization by a nitro-group *para* to the seat of substitution is fully expected and is substantiated by extensive data on a variety of systems. Comparisons of the equilibrium constant for the formation of (3c) with (1c), (3b) with (1b), and (3a) with (1a) yield 10.3 kcal mol⁻¹ for the free energy of stabilization due to a 2-nitro-group. Apparently an added nitro-group *ortho* to the seat of substitution is more effective than benzo-fusion. Equilibrium constants for the formation of (1), (3), and (6) also demonstrate this trend.

Finally, treating the equilibrium constants for the formation of (4a) and (3a) according to equation (2) results in a $\delta\Delta G$ value of 5.2 kcal mol⁻¹ for the effect of an additional nitro-group in the 3-position.

Table 2 summarizes the relative stabilizing powers for

Relative stabilizing powers of nitro groups and of benzo-fusion	
Effect of	$\delta\Delta G/\text{kcal mol}^{-1}$ ^a
Benzo-fusion	-7.2 (-7)
2-NO ₂	-10.3 (-9)
3-NO ₂	-5.2
4-NO ₂	-21.0 (-30)
5-NO ₂	-2.9 (-2.8)
6-NO ₂	-2.9
7-NO ₂	-3.6 (-3.8)
8-NO ₂	-2.4

^a Values in parentheses are from a previous and less complete estimation.¹²

Meisenheimer complexes of benzo-fusion and of nitro-groups in the different positions.

Equilibrium constant differences for pairs of Meisenheimer complex stabilities depends, of course, on differences in k_1 and k_{-1} values. Ratios of k_1 and k_{-1} for

(7c)/(6c) agrees well with those for (7b)/(6b) and (7a)/(6a) (Table 1) indicating that rate constant ratios remain essentially independent of the attacking and leaving groups and of the solvent as functions of additional nitro-groups. Generally, for pairs of complexes whose free energy changes of stabilization are relatively small [(7)/(6), (8)/(6), and (11)/(6)], effects on the rate constants for the formation of the complexes is greater than those on their decomposition. Conversely, free energies of stabilization due to additional nitro-groups in the 2-position is the consequence of considerably more pronounced effects on the k_{-1} than those on the k_1 ratios.

Effects of Other Electron-withdrawing Groups.—The remarkable consistency of $\delta\Delta G$ values obtained from comparisons of equilibrium constants for the formation of appropriate sets of Meisenheimer complexes warrants the extension of this approach to estimating free energies of stabilization due to other electron-withdrawing groups. Table 3 summarizes the available rate and equilibrium constants.

TABLE 3
Kinetic and thermodynamic parameters for Meisenheimer complex formation^a

Meisenheimer complex	$k_1/l \text{ mol}^{-1} \text{ s}^{-1}$	k_{-1}/s^{-1}	$K/l \text{ mol}^{-1}$	Ref.
(13b)			1—1.9	17
(13c)	6.1	0.22	280	3
(14b)			$(2.9-8.5) \times 10^{-3}$	18, 19
(14c)	0.36	6.0×10^{-2}	6.0	18
(15b)			1.2×10^{-2}	16
(15c)			2.0	20
(16c)	18.8	7.2×10^{-3}	2 600	3
(17c)	12.0	3.7×10^{-1}	34	21
(18c)	2.0	0.198	10	21
(19c)			0.4	22
(20c)	0.22	2.2×10^{-2}	10	22
(21c)			14	20
(22c)			4.3×10^{-3}	23
(23c)	0.18	6.0×10^{-2}	2.5—7.8	20, 24
(24c)			0.3	23
(25b)			3.9×10^{-5}	16
(26b)			1.1×10^{-4}	16
(27b)			8.9×10^{-4}	16
(28b)			0.5	16

See note a in Table 1.

The free energy of stabilization due to a 2-cyano-group may be estimated, by comparing equilibrium constants for pairs of complexes which differ only in that one (or two) of the nitro-groups has been replaced by cyano group(s) at the 2- (and 6-)positions. Thus, for example, taking equilibrium constant ratios for (19c)/(18c) a free energy difference of 1.9 kcal mol⁻¹ is calculated. This value, assigned to $\delta\Delta G_{2-\text{NO}_2} - \delta\Delta G_{2-\text{CN}} = 1.9$ kcal mol⁻¹, gives 8.4 kcal mol⁻¹ for stabilization by an additional cyano-group in the 2-position. Analogous comparisons of free energies of stabilizations between (18c)

¹⁷ E. J. Fendler, J. H. Fendler, N. L. Arthur, and C. E. Grifftin, *J. Org. Chem.*, 1972, **37**, 819.

¹⁸ M. R. Crampton and H. A. Khan, *J.C.S. Perkin II*, 1972, 1173.

¹⁹ M. R. Crampton and H. A. Khan, *J.C.S. Perkin II*, 1971, 733.

²⁰ F. Terrier, *Ann. Chim. (France)*, 1969, **4**, 153.

²¹ E. J. Fendler, J. H. Fendler, C. E. Grifftin, and S. W. Carsen, *J. Org. Chem.*, 1970, **35**, 287.

²² E. J. Fendler, W. Ernsberger, and J. H. Fendler, *J. Org. Chem.*, 1971, **36**, 2333.

²³ M. R. Crampton, M. A. El Ghariani, and H. A. Khan, *J.C.S. Perkin II*, 1972, 1178.

²⁴ F. Terrier, F. Millot, and R. Schaal, *J.C.S. Perkin II*, 1972, 1192.

and (17c), between (17c) and (16c), between (16c) and (3c), between (17c) and (3c), and between (19c) and (13c) results in $\delta\Delta G$ values of 8.3, 7.7, 9.2, 8.5, and 8.4 kcal mol⁻¹, respectively. The mean of these values, 8.4 kcal mol⁻¹, is considered to be due to the stabilization of the Meisenheimer complex by an additional 2-cyano-group. Free energies of stabilization due to the 4-cyano-group were estimated from comparisons of ΔG values for (13b) with (3b), (13c) with (3c), (19c) with (17c), and (18c) with (16c). Similarly, $\delta\Delta G$ values for 4-Cl, 4-CF₃, and 4-CO₂CH₃ were taken as mean values from comparing stabilities of (22c) and (3c), (22c) and (13c); (15c) and (3c), (15b) and (3b), (15c) and (13c), (15b) and (13b); and (14b) and (3b), (14c) and (3c). Values for the 2-Cl, 2-CO₂CH₃, and 2-CF₃ were estimated from single pairs of free energies of stabilization, (23c) and (3c), (20c) and (3c), (21c) and (3c), respectively. The calculated values for the free energies of stabilization due to these substituents are summarized in Table 4.

TABLE 4

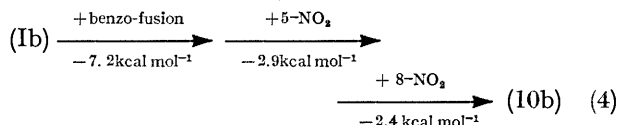
Relative stabilizing power of substituents

Substituent	$\delta\Delta G/\text{kcal mol}^{-1}$
1-OCH ₃	-4.2
2-CN	-8.4
4-CN	-18.5
2-CO ₂ CH ₃	-6.0
4-CO ₂ CH ₃	-16.2
2-CF ₃	-6.2
4-CF ₃	-15.9
2-Cl	-5.6
4-Cl	-12.1

Estimation of Free Energies of Meisenheimer Complex Stabilization.—The utility of the derived values for free energies of stabilization due to benzo-fusion, and to electron-withdrawing groups (Tables 3 and 4) is that it allows the prediction of Meisenheimer complex stabilities. For example, considering process (3), a knowledge



of the equilibrium constant for the formation of (1b) (5×10^{-7} l mol⁻¹) allows the prediction of that for (10b) by the use of appropriate $\delta\Delta G$ values as shown in process (4). The predicted value (12.5 kcal mol⁻¹) compares well



with that determined experimentally (12.1 kcal mol⁻¹). Table 5 compares predicted and experimentally determined relative free energies of stabilization for 116 pairs of Meisenheimer complexes. The excellent agreement between the calculated and predicted equilibrium constants justifies the assumed additivity, and the lack of importance of ground state effects lends credence to this method of predicting complexes formed in nucleophilic substitution.

Quantitative Treatment of Substituent Effects.—The success of predicting free energies of stabilization of

TABLE 5

Comparison of predicted and experimentally determined relative free energies of Meisenheimer complex stabilizations

Conversion	$\delta\Delta G/\text{kcal mol}^{-1}$	
	Predicted	Experimental
(1b) \longrightarrow (13b)	-7.8	-8.8
(1c) \longrightarrow (13c)	-7.8	-8.2
(1b) \longrightarrow (13c)	-12.0	-11.9
(1c) \longrightarrow (13b)	-3.6	-5.0
(6c) \longrightarrow (13c)	-0.6	-0.1
(6c) \longleftarrow (13b)	-3.6	-3.0
(6b) \longrightarrow (13b)	-0.6	-1.7
(6b) \longrightarrow (13c)	-5.2	-4.7
(7b) \longrightarrow (13c)	-1.9	-1.8
(7b) \longleftarrow (13b)	-2.3	-1.3
(7c) \longleftarrow (13b)	-6.5	-5.8
(7c) \longleftarrow (13c)	-2.3	-2.7
(8c) \longleftarrow (13b)	-7.2	-6.9
(8c) \longleftarrow (13c)	-3.0	-3.5
(13c) \longrightarrow (3c)	-2.5	-2.4
(13c) \longrightarrow (3b)	-1.7	-1.7
(13b) \longrightarrow (3c)	-6.7	-5.5
(13b) \longrightarrow (3b)	-2.5	-1.4
(13c) \longrightarrow (16c)	-0.6	-1.3
(13c) \longleftarrow (17c)	-1.3	-1.2
(13c) \longleftarrow (18c)	-1.9	-2.0
(13c) \longleftarrow (19c)	-3.8	-3.9
(16c) \longleftarrow (17c)	-1.9	-2.5
(16c) \longleftarrow (18c)	-2.5	-3.3
(16c) \longleftarrow (19c)	-4.4	-5.2
(17c) \longleftarrow (18c)	-0.6	-0.7
(17c) \longleftarrow (19c)	-2.5	-2.6
(18c) \longleftarrow (19c)	-1.9	-1.9
(3c) \longleftarrow (16c)	-1.9	-1.1
(3c) \longleftarrow (17c)	-3.8	-3.7
(3c) \longleftarrow (18c)	-4.4	-4.4
(3c) \longleftarrow (19c)	-6.3	-6.3
(6c) \longrightarrow (16c)	-1.2	-1.4
(6c) \longrightarrow (17c)	-0.7	-1.1
(6c) \longrightarrow (18c)	-2.3	-1.8
(6c) \longrightarrow (19c)	-3.2	-3.7
(7c) \longrightarrow (16c)	-1.7	-2.0
(7c) \longrightarrow (17c)	-3.6	-4.0
(7c) \longrightarrow (18c)	-4.2	-4.7
(7c) \longrightarrow (19c)	-6.1	-6.6
(8c) \longrightarrow (16c)	-2.4	-2.2
(8c) \longrightarrow (17c)	-4.3	-4.7
(8c) \longrightarrow (18c)	-4.9	-5.5
(8c) \longrightarrow (19c)	-6.8	-7.4
(1c) \longrightarrow (16c)	-8.4	-9.5
(1b) \longrightarrow (16c)	-12.6	-13.1
(1c) \longrightarrow (17c)	-6.5	-6.9
(1b) \longrightarrow (17c)	-10.7	-10.6
(1c) \longrightarrow (18c)	-5.9	-6.2
(1b) \longrightarrow (18c)	-10.1	-9.9
(1c) \longrightarrow (19c)	-4.0	-4.3
(1b) \longrightarrow (19c)	-8.2	-8.0
(3b) \longrightarrow (16c)	-2.3	-3.0
(3b) \longrightarrow (17c)	-0.4	-0.5
(18c) \longrightarrow (3b)	-0.2	-0.3
(19c) \longrightarrow (3b)	-2.1	-2.2
(1c) \longrightarrow (20c)	-6.0	-6.2
(1b) \longrightarrow (20c)	-10.2	-9.9
(20c) \longrightarrow (3c)	-4.3	-4.4
(20c) \longrightarrow (3b)	-0.1	-0.3
(20c) \longrightarrow (6c)	-1.2	-1.8
(6b) \longrightarrow (20c)	-3.0	-2.9
(20c) \longrightarrow (7c)	-4.1	-3.4
(20c) \longrightarrow (7b)	-0.1	-0.2
(20c) \longrightarrow (8c)	-4.8	-5.5
(1b) \longrightarrow (14b)	-5.5	-5.4
(1c) \longrightarrow (14c)	-5.5	-5.9
(3b) \longrightarrow (14b)	-4.8	-4.4
(3c) \longrightarrow (14c)	-4.8	-4.7
(14b) \longrightarrow (3c)	-9.0	-8.9
(14b) \longrightarrow (6b)	-1.7	-1.6
(14c) \longrightarrow (6c)	-1.7	-2.1

TABLE 5 (Continued)

Conversion	$\delta\Delta G/\text{kcal mol}^{-1}$	
	Predicted	Experimental
(14b) \longrightarrow (7b)	-4.6	-4.7
(14c) \longrightarrow (7c)	-4.6	-5.0
(14b) \longrightarrow (7c)	-8.8	-9.2
(14c) \longrightarrow (7b)	-0.4	-0.5
(14c) \longrightarrow (8c)	-5.3	-5.8
(14c) \longrightarrow (13c)	-2.3	-2.3
(14b) \longrightarrow (13b)	-2.3	-3.4
(1c) \longrightarrow (21c)	-6.2	-6.4
(1b) \longrightarrow (21c)	-10.4	-10.1
(21c) \longrightarrow (3c)	-4.1	-4.2
(21c) \longrightarrow (3b)	-0.1	-0.1
(21c) \longrightarrow (6c)	-1.0	-1.6
(21c) \longrightarrow (7c)	-3.9	-4.5
(21c) \longrightarrow (8c)	-4.6	-5.3
(20c) \longrightarrow (21c)	-0.2	-0.2
(1b) \longrightarrow (15b)	-5.2	-5.9
(1c) \longrightarrow (15c)	-5.2	-5.6
(15b) \longrightarrow (3b)	-5.1	-4.2
(15c) \longrightarrow (3c)	-5.1	-5.3
(15c) \longrightarrow (6c)	-2.0	-2.8
(15b) \longrightarrow (6b)	-2.0	-1.1
(15b) \longrightarrow (7b)	-5.0	-4.2
(15c) \longrightarrow (7c)	-5.0	-5.6
(15c) \longrightarrow (8c)	-5.7	-6.4
(15b) \longrightarrow (14b)	-0.3	-0.6
(1c) \longrightarrow (23c)	-5.6	-5.8
(1b) \longrightarrow (23c)	-9.8	-9.5
(23c) \longrightarrow (3c)	-4.7	-4.4
(23c) \longrightarrow (3b)	-0.5	-0.6
(23c) \longrightarrow (6c)	-1.6	-2.3
(23c) \longrightarrow (7c)	-4.5	-5.1
(23c) \longrightarrow (8c)	-5.2	-5.9
(15c) \longrightarrow (23c)	-0.6	-0.5
(23c) \longrightarrow (14c)	-0.4	-0.1
(23c) \longrightarrow (13c)	-2.8	-2.4
(1c) \longrightarrow (22c)	-1.4	-1.6
(22c) \longrightarrow (3c)	-8.9	-8.9
(22c) \longrightarrow (3b)	-4.7	-4.8
(22c) \longrightarrow (6c)	-5.8	-6.4
(22c) \longrightarrow (7c)	-8.7	-9.3
(22c) \longrightarrow (8c)	-9.4	-10.0
(22c) \longrightarrow (14c)	-4.1	-4.3
(22c) \longrightarrow (15c)	-3.8	-3.6
(22c) \longrightarrow (13c)	-6.4	-6.5

Meisenheimer complexes rests upon the additivity of $\delta\Delta G$ values attributed to given electron-withdrawing substituents and benzo-fusion. This additivity can also be expressed in terms of a linear free energy correlation between the equilibrium constant for σ -complex formation and the corresponding substituent constant.

Table 6 lists the substituent constants utilized. For *ortho*-substituents in the benzene nucleus, as customary, Taft's σ^* values were used.²⁵ Substituent constants for electron-withdrawing groups attached to the naphthalene ring were obtained from the dissociation constants of appropriate α - and β -naphthoic acids.^{27,28} Values for the benzo-fusion were obtained from differences in dissociation constants between corresponding naphthoic and benzoic acids. The sum of substituent constants for a given Meisenheimer complex, σ^s , are simply obtained from summation of the appropriate individual substituent constants given in Table 6. For example, σ^s for (3c) is equal to the sum of the substituent

constants due to the nitro groups in the 2-, 4-, and 6-positions and that due to the methoxy-group in the 1-position, *i.e.* $2 \times 0.78 + 1.24 + 0.40 = 3.20$. Similarly σ^s for (6c) is the sum of the substituent constants due to nitro-groups in the 2- and 4-positions, that due to the 1-methoxy-group and that due to benzo-fusion, *i.e.* $0.78 + 1.24 + 0.40 + 0.56 = 2.98$.

Utilizing all the available data (Tables 1 and 3) there are indeed good correlations between the logarithms of Meisenheimer complex stability and σ^s values (Figure 1). The larger body of data is for the interaction of methoxide ion with polynitroarenes in methanol. Data for the interaction of hydroxide ion with polynitroarenes in water fall on a parallel line. The mean difference between these two lines, *ca.* 0.25 σ^s unit, is attributable to a composite substituent constant representing the hydroxy-group and the change of solvent from methanol to water. The slope of the lines in Figure 1, 5.8, indicate

TABLE 6

Substituent constants		
Substituent ^a	Substituent constant	Reference
2-NO ₂	0.78	25
3-NO ₂	0.63	25, 26
4-NO ₂	1.24	27, 28
2-CN	0.50	25
3-CN	0.56	28
4-CN	1.00	27
2-Cl	0.20	25
3-Cl	0.41	28
4-Cl	0.23	29
2-F	0.24	25
4-F	0.06	29
4-SO ₂ CH ₃	1.05	27
4-SCH ₃	0.16	29
4-I	0.27	29
3-NH ₂	-0.16	29
3-N(CH ₃) ₂	-0.21	29
4-CF ₃	-0.74	27
5-NO ₂	0.39	28
6-NO ₂	0.34	28
7-NO ₂	0.44	28
8-NO ₂	0.49	28
4-NO ₂ ^b	0.58	28
5-NO ₂ ^b	0.37	28
6-NO ₂ ^b	0.52	28
7-NO ₂ ^b	0.34	28
8-NO ₂ ^b	0.48	28
1-OCH ₃ ^c	0.40	
<i>ortho</i> -Benzo-fusion ^c	0.56	
<i>meta</i> -Benzo-fusion ^c	0.60	

^a Using the naphthalene numbering system. For substituents at a benzenoid carbon atom position 5 = 3 and 6 = 2.

^b Obtained from the ionization constants of β -naphthoic acids and used for complexes where rehybridization occurs at a position other than C-1. ^c See Discussion section.

the pronounced stabilization of Meisenheimer complexes by electron withdrawing groups.

An alternative way to test the additivity is to plot the derived $\delta\Delta G$ values against σ^s . The observed satisfactory linear relationship (Figure 2) substantiates the assumptions of our method. It is worthwhile to note that the $\delta\Delta G$ value attributed to benzo-fusion, -7.2

²⁵ J. Hine, 'Physical Organic Chemistry,' McGraw-Hill, New York, 1962, p. 98.

²⁶ M. J. S. Dewar and P. J. Grisdale, *J. Amer. Chem. Soc.*, 1962, **84**, 3552.

²⁷ S. M. Shein and L. A. Kozorez, *Org. Reactivity*, 1966, **3**, 315.

²⁸ A. Bryson, *J. Amer. Chem. Soc.*, 1960, **82**, 4862.

²⁹ D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420.

kcal mol⁻¹, corresponds to 0.55 on the σ^s scale. This thermodynamically derived substituent constant agrees well with that obtained from comparing pK_a values of naphthoic and benzoic acids (see later).

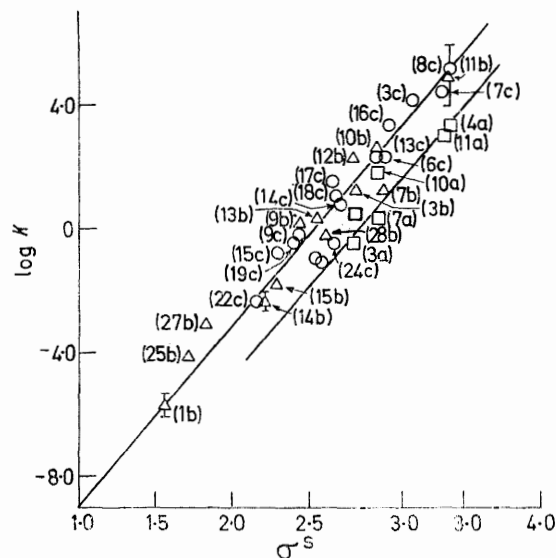


FIGURE 1 Plot of $\log K$ against σ^s

Available data on rate constants for the formation, k_1 , and decomposition, k_{-1} , of Meisenheimer complexes are less extensive than those on the equilibrium constants. Nevertheless satisfactory linear free energy correlation can be obtained on plotting $\log k_1$ and $\log k_{-1}$ against σ^s (Figure 3). The slopes of these lines, as expected, are positive for the formation and negative for the decomposition of the Meisenheimer complexes. Some rate constants fit rather poorly on the correlation. This is not entirely surprising since in their extensive

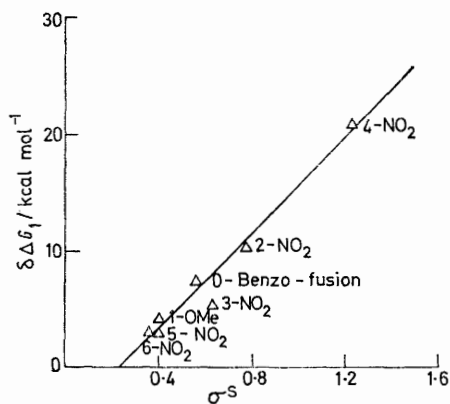


FIGURE 2 Plot of free energies of Meisenheimer complex stabilization due to different substituents and to benzo fusion against σ^s values

linear free energy correlations Shein and Kozorez have shown that ρ values for attack by a given nucleophile on a series of monosubstituted benzenes decrease with the

introduction of additional nitro groups.²⁶ Nevertheless the linear free energy correlations for rate (Figure 3) and equilibrium (Figure 1) constants for the attack of hydroxide and methoxide ions on polysubstituted arenes are potentially useful for predicting unknown reactivities.

Effects of Dipolar Aprotic Solvents.—Stabilities of σ^s -complexes are considerably enhanced by the addition of dipolar aprotic solvents. Indeed several correlations have been observed between rate (or equilibrium) constants for Meisenheimer complex formation and decomposition and solvent polarities. The origin of these solvent effects have been discussed in terms of increased basicity of the nucleophiles. It is more appropriate,

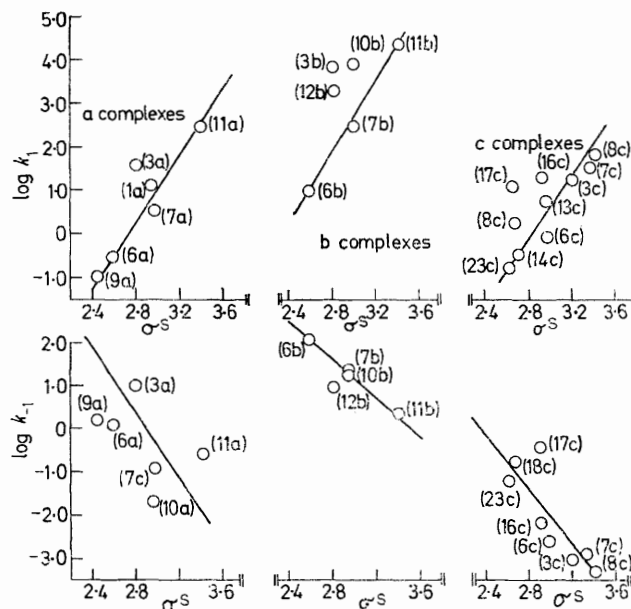


FIGURE 3 Plots of the rate constants for the formation (k_1) and decomposition (k_{-1}) of Meisenheimer complexes against σ^s values

however, to consider the effects of solvents on the relative activity coefficients of the reactants and transition states both for the formation and decomposition of Meisenheimer complexes. In view of this complex situation no physical significance should be attached to the frequently observed linear relationships between rates and solvent composition. It is even more surprising that relative free energies of stabilization ($\delta\Delta G = \Delta G^{\text{DMSO}} - \Delta G^{\text{CH}_3\text{OH}}$; or $\Delta G^{\text{DMSO}} - \Delta G^{\text{H}_2\text{O}}$ or $\Delta G^{\text{DMF}} - \Delta G^{\text{H}_2\text{O}}$) by DMSO or DMF are independent of substrate. Figure 4 illustrates the unexpectedly good correlation between $\delta\Delta G$ values for 10 structurally different Meisenheimer complexes and the molar concentration of the dipolar aprotic solvents. Effects of DMSO on the rate constants for the formation and decomposition of some Meisenheimer complexes are also additive. Plots of these rate constants against percentages of DMSO result in a family of parallel curves,²⁴ implying that relative rate constants, $k_1^{\text{DMSO-CH}_3\text{OH}}/k_1^{\text{CH}_3\text{OH}}$ or $k_{-1}^{\text{DMSO-CH}_3\text{OH}}/k_{-1}^{\text{CH}_3\text{OH}}$, are independent of the nature of the

parent aromatic compound or that of its σ complex. Such correlations are, of course, of substantial value in predicting rate and equilibrium constants for nucleophilic aromatic substitutions at given co-solvent concentrations.

¹H N.m.r. Chemical Shift Correlations.—An expected consequence of the additivity of substituent constants and of the observed correlation between Meisenheimer complex stability and σ^s (Figure 1) is that the ¹H n.m.r. chemical shift of the parent polynitronaphthalenes also correlate with equilibrium constants for Meisenheimer complex formation. This is indeed the case. In view of the complexity involved in chemical shift values in substituted naphthalenes³⁰ the observed correlation (Figure 5) is considered satisfactory. Similar correlation has been reported previously between the chemical shifts of the 3- and 5-H resonances for the Meisenheimer

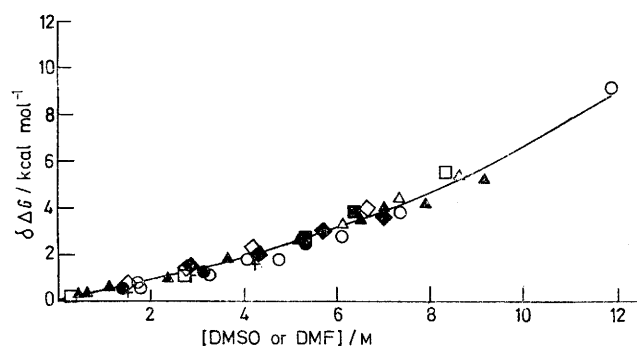


FIGURE 4 Plot of free energies of Meisenheimer complex stabilization against molar concentration of DMSO or DMF in protic-dipolar aprotic co-solvent systems: (\blacktriangle) (3a) in DMF-H₂O; (\triangle) (6b) in DMSO-MeOH; (\circ) (23c) in DMSO-MeOH; (\bullet) methoxy-complex of 3,5-dinitropyridine in DMSO-MeOH; (\square) cyclic Meisenheimer complex of 1-(β -hydroxy-ethoxy)-2,4-dinitrobenzene; (\blacksquare) hydroxy-complex of 3,5-dinitropyridine in DMSO-H₂O; (\diamond) methoxy-complex of 3,5-dinitrobenzotrile in DMSO-MeOH; (\blacklozenge) (6a) in DMSO-H₂O; (+) (17c) in DMSO-MeOH; (\times) (3a) in DMSO-MeOH

complexes of cyanodinitro-, dicyanonitro-, and tricyano-anisoles.²² Poor relationships have been observed, however, in plotting the 3- and 5-H chemical shifts of the parent anisoles. Apparently anisotropy and other

factors, in addition to electron density, also contribute to the observed chemical shifts. Due care, therefore, needs to be exercised in the utilization of chemical shifts

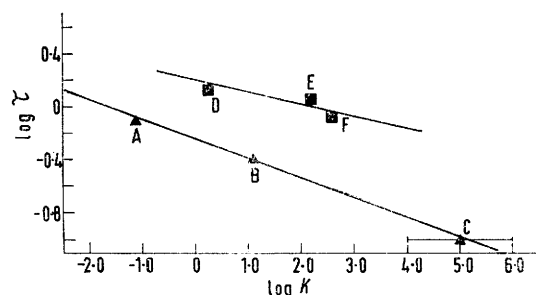


FIGURE 5 Plots of chemical shifts of 2-H for 1,3-dinitronaphthalene (A), 1,3,8-trinitronaphthalene (B), and 1,3,6,8-tetranitronaphthalene (C) and those of 6-H for 1,4,5,7-tetranitronaphthalene (D), 1,4,5,8-tetranitronaphthalene (E), and 1,3,5,8-tetranitronaphthalene (F) against the logarithm of the stabilities of the corresponding methoxy Meisenheimer complexes

of Meisenheimer complexes or their parent molecules for predicting complex stabilities.

Conclusions.—Ample evidence has been presented for the utilization of the derived free energies of stabilization due to the different substituents as well as that of sums of individual substituent constants for predicting Meisenheimer complex stabilities. Sums of individual substituent constants also correlate with the rate constants for the formation and decomposition of the intermediates formed in nucleophilic aromatic substitutions. Surprisingly, even the effects of dipolar aprotic solvents on relative free energies of complex stabilization is independent of the nature of polysubstituted arenes. The success of these correlations is extremely encouraging since it allows a more rational mechanistic treatment of nucleophilic aromatic substitutions than that previously available.

Support of this work by the Robert A. Welch Foundation is gratefully acknowledged.

[4/2691 Received, 23rd December, 1974]

³⁰ P. R. Wells, *J. Chem. Soc.*, 1963, 1967; P. R. Wells and P. G. E. Alcorn, *Austral. J. Chem.*, 1963, **16**, 1108; P. R. Wells, *ibid.*, 1964, **17**, 967.