The Stabilities of Meisenheimer Complexes. Part III.[1] Specific Effects of Cations in Methanol Solution

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The stoicheiometric equilibrium constants for the formation of Meisenheimer complexes from several substituted anisoles have been measured by use of dilute solutions of potassium, lithium, and tetra-n-butylammonium methoxides in methanol. The values obtained with potassium and tetra-n-butylammonium methoxide increase with increasing base concentration, an effect which is attributed to stabilisation of the complexes by association with the cations present. With lithium methoxide no such effect is observed and it is suggested that this base may be the most suitable for measurement of thermodynamic equilibrium constants.

In concentrated solutions of the alkali-metal methoxides in methanol the basicity order at a given base concentration, as measured by the H_M acidity function,[2] is KOMe > NaOMe > LiOMe. This order has been attributed [2,3] to ion association in the metal alkoxides which results in a reduction of their activities, the effect being greatest for lithium methoxide and smallest for potassium methoxide. Nevertheless in dilute ($<0{\cdot}1$ mol l^{-1}) solutions of the three methoxides the H_M basicity has been found to be independent of the cation.[4] In addition the measured ionisation constants, governing proton abstraction from the aniline indicators by base, are independent of base concentration in these dilute solutions.[4,5]

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[1] Part II, M. R. Crampton, M. A. El Ghariani, and H. A. Khan, *J.C.S. Perkin II*, 1972, 1178.

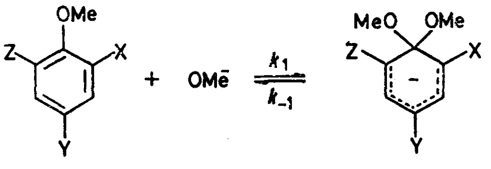
[2] C. H. Rochester, 'Acidity Functions,' Academic Press, New York, 1970.

[3] J. R. Jones, *Chem. Comm.*, 1968, 513.

[4] R. Schaal and G. Lambert, *J. Chim. phys.*, 1962, 1151.

[5] F. Terrier, *Ann. Chim. (France)*, 1969, 153.

In Part I[6] we determined rate and equilibrium constants for the addition of sodium methoxide to several highly activated anisoles in methanol where addition occurs to give Meisenheimer complexes[7] of structure (II). These equilibria define J_M acidity functions.[2] In contrast to the behaviour of the H_M indicators it was found that the stoicheiometric equilibrium constants K_C (= [complex]/[parent][NaOMe]) increased with increasing sodium methoxide concentration even in very dilute solutions. In particular the magnitude of these effects depended on the structure of the parent anisole so that no unique J_M function could be defined. A major stabilising influence on the complex was thought to be ion association with sodium ions and it was possible, making certain assumptions, to estimate ion-pair association constants.



(I) (II)

The overall increases in values of K_C were found[6] to be due to increases in the values of the rate coefficients k_1 and decreases in values of k_{-1}. Reinheimer and his co-workers[8] had previously determined salt effects on the rates of aromatic nucleophilic substitution reactions in methanol. They found that the rate coefficient for reaction of 1-chloro-2,4-dinitrobenzene with methoxide ions was increased by the addition of potassium salts and decreased by lithium salts. They noted that electrolytes could affect the reaction rate by changing the equilibrium between an ion-paired metal alkoxide and the free alkoxide ion and also considered the possibility of specific interactions of cations with nitro-groups of the substrate in the transition state. Bunton and his co-workers[9] and Fendler and his co-workers[10] have examined the effects of high salt concentrations on the rates of nucleophilic substitutions in aqueous solutions where ion-association was thought to be unimportant. They were able to separate the overall changes in rate into initial-state and transition-state effects, both of which were important.

We have now extended our measurements of Meisenheimer complex equilibria in methanol using lithium, potassium, and tetra-n-butylammonium methoxides. Our results indicate specific effects due to the cation present and are interpreted in terms of cation association with the complexes.

EXPERIMENTAL

Nitro-compounds were prepared and purified as before.[6] Lithium, sodium, and potassium methoxide solutions were prepared by dissolving clean pieces of the respective metals in pure methanol under nitrogen. Tetra-n-butylammonium methoxide was prepared by dilution with methanol of a commercial sample of tetra-n-butylammonium hydroxide in methanol. The latter solution thus contained small concentrations (0·1M) of water. However test experiments indicated that Meisenheimer complex equilibria were unaffected by the presence of small concentrations of added water. Concentrations of base solutions were determined by titration with standard acid.

Visible spectral measurements were made at 25 °C with a Unicam SP 500 instrument fitted with a thermostatted cell compartment. Solutions containing the required concentrations of reagents were prepared immediately before measurement by suitable dilution of stock solutions. It was found convenient to make kinetic measurements by the addition from a syringe of a small quantity of a concentrated solution of parent anisole to a solution of methanolic methoxide which had previously been brought to 25 °C in the measuring cell. Measurement of optical densities was begun 10 s after mixing and continued until completion of reaction. In each individual run the approach to equilibrium was an accurately first-order process and rate constants were reproducible within 5%.

Solubility Measurements.—The solubility of 2-methoxycarbonyl-4,6-dinitroanisole in methanol and in methanol solutions containing dissolved salts was determined at 25 °C (Table 1). Excess of the pure substrate was shaken with solvent for 3 h and then allowed to stand for 1 h. A sample of the solution was then diluted by a factor of 5000 with pure methanol and the absorption measured at 220 and 275 nm. The extinction coefficients at these wavelengths were measured independently and had values of 1·94 × 10^4 and 8·0 × 10^3 l mol^{-1} cm^{-1} respectively.

TABLE 1

Solubility of 2-methoxycarbonyl-4,6-dinitroanisole

Salt in methanol	Solubility/mol l^{-1}
None	0·195
0·1M-NaCl	0·180
0·1M-LiCl	0·180
0·1M-$NaClO_4$	0·20
0·1M-Na_2SO_4	0·19
KCl (saturated)	0·19
0·1M-Bu^n_4NCl	0·20

The measurements are accurate within 5% so that within experimental error there is little variation in solubility.

RESULTS AND DISCUSSION

In the presence of methoxide ions 2-methoxycarbonyl-4,6-dinitroanisole has been shown[6] to give a coloured adduct of structure (II). For this compound the attainment of equilibrium is sufficiently slow for the rate to be measured by conventional methods, and the absorption at equilibrium allows the determination of the

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

[7] For recent reviews see M. R. Crampton, *Adv. Phys. Org. Chem.*, 1969, **7**, 211; M. J. Strauss, *Chem. Rev.*, 1970, **70**, 667.

[8] J. D. Reinheimer, W. F. Kieffer, S. W. Frey, T. C. Cochran, and E. W. Barr, *J. Amer. Chem. Soc.*, 1958, **80**, 164; J. D. Reinheimer, J. T. Greig, and T. C. Cochran, *ibid.*, 1961, **83**, 2873.

[9] C. A. Bunton and L. Robinson, *J. Amer. Chem. Soc.*, 1968, **90**, 5965, 5972; *J. Org. Chem.*, 1969, **34**, 780.

[10] J. H. Fendler, E. J. Fendler, and M. V. Merritt, *J. Org. Chem.*, 1971, **36**, 2172.

stoicheiometric equilibrium constant, K_C. The individual rate coefficients could then be calculated ($k_{obs} = k_1[MOMe] + k_{-1}$). Data obtained with tetra-n-butylammonium methoxide, potassium methoxide, and lithium methoxide are in Table 2. The corresponding values for addition of sodium methoxide [6] are similar to those for potassium methoxide addition. In addition, equilibrium constants for complex formation with 4-methoxycarbonyl-2,6-dinitroanisole and 2-chloro-4,6-dinitroanisole are shown in Figures 1 and 2.

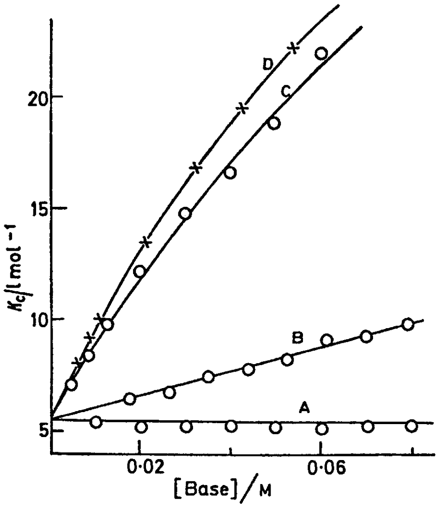

FIGURE 1 Variation of K_C with base concentration for Meisenheimer complex formation from 4-methoxycarbonyl-2,6-dinitroanisole with the following methoxides: A, lithium; B, tetra-n-butylammonium; C, sodium; and D, potassium

TABLE 2

Kinetic and equilibrium data at 25 °C for the addition of methoxide to 2-methoxycarbonyl-4,6-dinitroanisole [a] in methanol

[n-Bu$_4$NOMe]/M	Optical density at equilibrium (472 nm)	K_C/l mol^{-1}	10^2k_{obs}/s^{-1}	$10k_1$/l mol^{-1} s^{-1}	10^3k_{-1}/s^{-1}
0·0144	0·091	9·6	2·54 ±0·1	2·1	22
0·0217	0·137	10·4	2·68	2·3	22
0·0288	0·180	11·0	2·82	2·4	21
0·0360	0·22	11·6	2·92	2·4	20·5
0·043	0·26	12·5	3·15	2·5	20
0·050	0·30	13·5	3·30	2·6	19·5
0·058	0·33	13·8	3·47	2·7	19
0·50	0·745				
[LiOMe]/M					
0·010	0·054	8·3	2·7 ±0·3	2·1	25
0·020	0·100	8·3	3·2	2·2	27
0·030	0·134	7·9	3·5	2·2	28
0·040	0·170	8·0	3·6	2·2	27
0·060	0·240	8·7	4·2	2·4	27
0·080	0·285	8·6			
0·10	0·31	8·0			
0·20	0·45	9			
0·40	0·57	11			
1·0	0·70				
[KOMe]/M					
0·0044	0·038	12	1·75 ±0·05	2·0	16·5
0·0070	0·069	14	1·61	2·05	14·5
0·0108	0·121	17·5	1·54	2·3	13
0·0216	0·268	25	1·50	2·5	10
0·0323	0·39	32·5	1·77	2·8	8·5
0·043	0·48	40	1·86	2·8	7
0·054	0·54	45	2·27	3·0	6·5
0·075	0·61	56	3·27	3·5	6·3
0·81	0·76				

[a] Concentration is $3·84 \times 10^{-5}$ mol l^{-1}.

The results show certain similarities for these three nitro-compounds. In each case the value of K_C remains constant when lithium methoxide is used, but small increases are observed with tetra-n-butylammonium methoxide and larger increases with potassium and sodium methoxide. Clearly these changes are not explicable in terms of classical theories of salt effects. The changes in K_C with base concentration will depend on changes in activities of three species; the parent anisoles, the complexes, and the base. Bunton's work [9] in aqueous solutions has shown that the activities of neutral substrates may be affected by the presence of high salt concentrations. In order to test whether the activities of the parent anisoles are affected by the presence of dissolved electrolyte in methanol we measured the solubility of 2-methoxycarbonyl-4,6-dinitroanisole in methanol containing 0·1 mol l^{-1} of various salts. The results (Table 1) indicate that within experimental error the solubility, and hence activity,[11] of the substrate is unaffected by the presence of this concentration of salt. We must then look to changes in the activity of the base or the complex to account for the increases in equilibrium constant.

Our results might be interpreted in terms of a general medium effect in which the presence of dissolved electrolyte produces a favourable environment for complex formation. However no such effect is observed in the ionisation of aromatic amines used to determine the H_M acidity function.[4,5] Neither are increases in value of K_C observed [12] for complex formation of 1,3,5-trinitro-

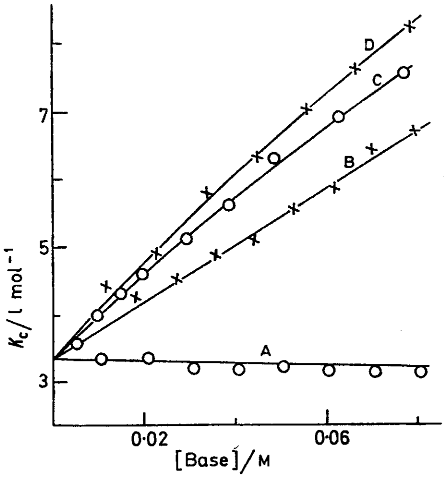

FIGURE 2 Variation of K_C with base concentration of Meisenheimer complex formation from 2-chloro-4,6-dinitroanisole with the following methoxides: A, lithium; B, tetra-n-butylammonium; C, sodium; and D, potassium

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[11] F. A. Long and W. F. McDevit, *Chem. Rev.*, 1952, **52**, 119.

[12] V. Gold and C. H. Rochester, *J. Chem. Soc.*, 1964, 1692.

benzene with sodium methoxide. In view of the fairly specific nature of the observed effects we prefer an interpretation involving stabilisation of the adduct (II) by association with the cations present. The effects of ion-association should be more pronounced in methanol than in water and we note that in aqueous solution the Meisenheimer complex from 2,4,6-trinitroanisole is apparently destabilised at high salt concentrations.[10]

In terms of the Scheme, ion association will affect the

$$\begin{tikzcd}
\mathrm{P} + \mathrm{M}^+ + \mathrm{OMe}^- \arrow[r, shift left, "K_1"] \arrow[d, shift left, "K_3"] & \mathrm{POMe}^- + \mathrm{M}^+ \arrow[l, shift left] \arrow[r, shift left, "K_2"] & \mathrm{POMe}^-, \mathrm{M}^+ \arrow[l, shift left] \\
\mathrm{P} + \mathrm{M}^+, \mathrm{OMe}^- \arrow[u, shift left] & &
\end{tikzcd}$$

SCHEME

measured equilibrium constant so that $K_\mathrm{C} = K_1(1 + K_2[\mathrm{M}^+])/(1 + K_3[\mathrm{M}^+])$. In the case of potassium ions, as with sodium ions,[6] there will probably be little association with methoxide in dilute solutions so that plots of K_C against the stoicheiometric base concentration [MOMe] should approach linearity at sufficiently low base concentrations. Our results indicate that this is the case. In fact ion association may not significantly reduce the reactivity of methoxide ions but may cause curvature in the plots by reducing the concentration of cations available for association with the complexes. The results indicate similar association of the complexes with potassium and sodium ions with association constants decreasing in the order 2-methoxycarbonyl-4,6-dinitroanisole, $K_2 = ca.$ 100 l mol^{-1}; 4-methoxycarbonyl-2,6-dinitroanisole, $K_2 = ca.$ 60 l mol^{-1}; and 2-chloro-4,6-dinitroanisole, $K_2 = ca.$ 20 l mol^{-1}.[*]

With tetra-n-butylammonium methoxide the measured values of K_C increase linearly with base concentration. The effect is independent of the particular anisole used and an enhancement in K_C by a factor of 1·5 is observed in the presence of 0·05M base over the value at zero base concentration. Association of the large diffusely charged tetra-alkylammonium ions with methoxide ions, containing a localised negative charge, is likely to be small. However tetra-alkylammonium ions are known [9,13] to interact with and stabilise large polarisable anions, such as the complexes. In this case it seems likely that the increase in K_C values result from such interactions, the effect being largely independent of the structure of the complex. The effect is smaller than that observed with sodium or potassium ions and gives a value of *ca.* 10 l mol^{-1} for K_2.

The independence of K_C values on base concentration in the case of lithium methoxide is perhaps surprising. One explanation would be that there is little association of the complexes with lithium ions. The lithium ions will be more strongly solvated than sodium or potassium ions so that their ability to form ion-pairs may be reduced. For example, the ion-pair associated constant for lithium chloride in alcoholic solvents has been found to be smaller than for the potassium or sodium salts.[14] A special argument using the idea of localised solvolysis [15] has been advanced to account for the special stability of the lithium methoxide ion-pair. It might then be expected that increasing association of the lithium and methoxide ions would result in a decrease in equilibrium constant with increasing base concentration. The case is perhaps overstated in that a methoxide ion in a lithium methoxide ion-pair would be expected to have reduced reactivity rather than no reactivity. However small rate decreases (induced by lithium ions) in nucleophilic substitution reactions have been found by Reinheimer *et al.*[8] A possible explanation in the present case is that the lithium ions associated to a similar extent with methoxide ions and with complexes so that little overall variation in equilibrium constant is obtained.

In general our results (Table 2) show that changes in K_C result from increases in value of k_1 and decreases in k_{-1} indicating that the interactions of cations with the transition state for methoxide addition are present, but to a smaller extent than with the complex.

As a consequence of our work it appears preferable to use lithium methoxide or tetra-n-butylammonium methoxide in order to measure thermodynamic equilibrium constants for Meisenheimer complex formation. Our results give the following values at 25 °C: 2-methoxycarbonyl-4,6-dinitroanisole, 8·3 (10) l mol^{-1}; 4-methoxycarbonyl-2,6-dinitroanisole 5·5 (6) l mol^{-1}; and 2-chloro-4,6-dinitroanisole 3·4 (3) l mol^{-1}. The values in parentheses were obtained previously [6] by use of sodium methoxide where the extrapolation to zero base concentration is less accurate. As a further example we give our results for the Meisenheimer complex formation of 1-methoxy-2,4-dinitronaphthalene by use of lithium methoxide (Table 3). They indicate a value of 205 l mol^{-1} for the thermodynamic equilibrium constant, compared with the previous value of 240 l mol^{-1} obtained [16] by use of sodium methoxide.

TABLE 3

Kinetic and equilibrium data for lithium methoxide addition to 1-methoxy-2,4-dinitronaphthalene ($3·84 \times 10^{-5}$ mol^{-1}) in methanol at 25 °C

[LiOMe]/ M	Optical density at equilibrium (498 nm)	$\frac{K_\mathrm{C}}{\mathrm{l\ mol^{-1}}}$	10^2k_obs/ s^{-1}	$\frac{k_1}{\mathrm{l\ mol^{-1}\ s^{-1}}}$	10^3k_{-1}/ s^{-1}
0·0038	0·39	202	0·81 ±0·02	0·93	4·6
0·0077	0·55	204	1·13	0·90	4·4
0·0096	0·60	208	1·34	0·93	4·5
0·0192	0·72	208	2·30	0·95	4·6
0·029	0·77	204	3·20	0·94	4·6
0·96	0·90				

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[*] Bivalent cations, such as Ba^{2+} or Ca^{2+}, give rise to much larger stabilising effects than the monovalent cations. Association constants K_2 are roughly two orders of magnitude greater for Ba^{2+} than for Na$^+$ (M. R. Crampton and H. A. Khan, unpublished results).

[13] E. S. Halberstadt and J. E. Prue, *J. Chem. Soc.*, 1952, 2234.

[14] J. R. Graham, G. S. Kell, and A. R. Gordon, *J. Amer. Chem. Soc.*, 1957, **79**, 2352.

[15] R. A. Robinson and H. S. Harned, *Chem. Rev.*, 1941, **28**, 419.

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