Kinetics of Nucleophilic Aromatic Substitution in Concentrated Solutions of Alkali Metal Methoxides in Methanol†

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The kinetics of nucleophilic aromatic substitution by methoxide ion on 11 substituted arenes have been studied at 20 °C using alkali metal (Li, Na, K) methoxides in methanol. Rate constants show a linear correlation with the excess basicity functions X for the three media, thus proving the applicability of the method to the interpretation of rate profiles in basic systems. The slopes $m^*_\ddagger$ are shown to depend on the solvation of the transition state leading to the Meisenheimer complex intermediates. The relationship between $m^*_\ddagger$ and standard state reactivities ($\log k_0$) is discussed. The inversion in the relative reactivities of 2- and 4-chloronitrobenzene with increasing base concentration is explained.

Nucleophilic aromatic substitution reactions (S_NAr) have been the subject of a large number of studies which have elucidated their various mechanistic aspects and exploited their synthetic utility. Several excellent reviews are available on this topic and on the closely related chemistry of Jackson–Meisenheimer σ-complexes.[1–7]

It is generally accepted that S_NAr reactions of activated arenes (*i.e.* containing electron-withdrawing groups, usually nitro), proceed *via* a Meisenheimer complex intermediate, as indicated in eqn. (1).

$$\mathrm{ArX} + \mathrm{Y}^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [\mathrm{ArXY}]^- \xrightarrow{k_2} \mathrm{ArY} + \mathrm{X}^- \qquad (1)$$

As is well known, suitable substrates (lacking a good leaving group and possessing two or three nitro groups) lead to complexes which are sufficiently stable to be studied spectroscopically or even isolated; rate and equilibrium constants for the reversible formation of such complexes are available.[1–7]

Normally, the formation of the σ-complex is the rate-determining step; however, if the substrate ArX is weakly or moderately activated (*e.g.* mononitroarenes) the reaction may be a one-step process in which the complex is actually a transition state.[1] Likewise, additions to unactivated arenes do not occur.

Kinetic basicity dependences in concentrated basic systems (mostly methanol and DMSO) have also been reviewed.[8] Most studies in these media have tackled the problems encountered in acidic media,[8–10] *i.e.* the correlation of reaction rates with acidity functions and the derivation of mechanistic criteria, transition state structure and solvation from rate–basicity profiles.[8,11,12] However, the limitations and lack of generality inherent in the acidity function approach, which have been thoroughly recognized and discussed for acidic media,[9,10,13] also apply to basic media. On the other hand, the treatment of kinetic data in acid solutions by means of the modern Bunnett–Olsen or excess acidity treatments has been shown to be a valuable tool in elucidating reaction mechanisms and in estimating the solvation of transition states.[9,10]

Recently, we have determined the basicity of concentrated solutions of alkali metal methoxides in methanol in terms of excess basicity functions (X), along with equilibrium constants for the deprotonation equilibria of various weak nitrogen acids and the addition of methoxide ion to nitroanisoles.[14] The activity coefficient behaviour of the AH/A$^-$ pair, expressed by the slope parameter m^*, was found to be related to the solvation energy of A$^-$ and to depend on chemical structure in the same way previously found for onium ions BH$^+$.[14]

This formulation of acid–base equilibria in strongly basic solutions gives us access to the approaches developed for acid-catalysed reactions in strongly acidic media. In the present paper, we have applied the above principles to the study of the rates of methoxide addition to nitro-substituted arenes in methanol solution.

General Treatment.—The reaction of a weakly acidic substrate AH can be described as shown in eqns. (2a and b), where the rate-determining step is either the deprotonation (*e.g.*, by MeO$^-$) or the decomposition of the deprotonated substrate, respectively.

$$\mathrm{AH} + \mathrm{MeO}^- \xrightarrow{\text{slow}} [\ddagger] \longrightarrow \text{products} \qquad (2a)$$

$$\mathrm{AH} + \mathrm{MeO}^- \rightleftharpoons \mathrm{A}^- + \mathrm{MeOH} \xrightarrow{\text{slow}} [\ddagger] \longrightarrow \text{products} \qquad (2b)$$

The pseudo-first-order rate constant k_{obs} is expressed by eqn. (3), where c_{AH} is the stoichiometric concentration ($c_{\text{AH}} = [\mathrm{AH}] + [\mathrm{A}^-]$), and ‡ refers to the transition state for the rate-determining step.

$$\text{rate} = k_{\text{obs}}\, c_{\text{AH}} = k[\ddagger] \qquad (3)$$

The kinetic basicity dependence of reactions (2a and b) can be analysed using the formalism adopted for the interpretation of acid-catalysed reactions in moderately concentrated acids.[15] Even though there is evidence that most S_NAr reactions proceed through a rate-determining addition of the nucleophile, we have developed equations which account for the two cases of (*a*) rate-determining deprotonation and (*b*) rate-determining decomposition of the deprotonated substrate formed in a pre-equilibrium.

(a) *Rate-determining deprotonation.* Assuming equilibrium between the reactants and the transition state, we can expand

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† Presented in part at the 10th IUPAC Conference on Physical Organic Chemistry, Haifa, Israel, August 5–10th, 1990.

eqn. (2a) to give eqn. (4), so that an equilibrium constant ($K_‡$) can be defined as in eqn. (5).

$$\mathrm{HA} + \mathrm{MeO}^- \rightleftharpoons [‡] \rightleftharpoons \mathrm{A}^- + \mathrm{MeOH} \qquad (4)$$

$$K_‡ = ([‡]\gamma_‡)/([\mathrm{AH}][\mathrm{MeO}^-]\gamma_{\mathrm{AH}}\gamma_{\mathrm{MeO}^-}) \qquad (5)$$

Thus, if $c_{\mathrm{AH}} \approx [\mathrm{AH}]$ (*i.e.*, the anionic form is consumed in the subsequent fast process), we can combine eqns. (3) and (5) to yield eqn. (6):

$$k_{\mathrm{obs}} = k_0[\mathrm{MeO}^-]\gamma_{\mathrm{AH}}\gamma_{\mathrm{MeO}^-}/\gamma_‡ \qquad (6)$$

where $k_0 = kK_‡$. The activity coefficient term in eqn. (6) can be evaluated by recalling that the activity coefficient term for an acid–base pair AH/A$^-$ is linearly related to the same term for a reference acid AH* through a slope parameter m^* [eqn. (7)].[9,13,14]

$$\log(\gamma_{\mathrm{AH}}\gamma_{\mathrm{MeO}^-}/\gamma_{\mathrm{A}^-}) = m^*\log(\gamma_{\mathrm{AH}^*}\gamma_{\mathrm{MeO}^-}/\gamma_{\mathrm{A}^{*-}}) = m^*X \qquad (7)$$

Assuming the transition state to behave like any anionic species, we have eqn. (8).*

$$\log(\gamma_{\mathrm{AH}}\gamma_{\mathrm{MeO}^-}/\gamma_‡) = m^*_‡\log(\gamma_{\mathrm{AH}^*}\gamma_{\mathrm{MeO}^-}/\gamma_{\mathrm{A}^{*-}}) = m^*_‡X \qquad (8)$$

By combining eqns. (6) and (8) and taking logarithms, we derive eqn. (9), which describes the kinetic basicity dependence of reaction (2a). This is the equivalent of the $A_{SE}2$ mechanism in acid-catalysed reactions.[10,15]

$$\log k_{\mathrm{obs}} - \log[\mathrm{MeO}^-] = m^*_‡X + \log k_0 \qquad (9)$$

It must be noted that this formulation does not distinguish between the addition–elimination and one-step mechanisms, the rate-determining step being the same.

(b) *Pre-equilibrium.* In this case the reaction course is described by eqn. (10), and the expression for the equilibrium constant is given by eqn. (11).

$$\mathrm{AH} + \mathrm{MeO}^- \rightleftharpoons \mathrm{A}^- + \mathrm{MeOH} \rightleftharpoons [‡] \rightleftharpoons \text{products} \qquad (10)$$

$$K_‡ = ([‡]\gamma_‡)/([\mathrm{A}^-]\gamma_{\mathrm{A}^-}) \qquad (11)$$

Thus, combining eqns. (3), (10) and (11) and taking logarithms, we obtain eqn. (12).

$$\log k_{\mathrm{obs}} - \log([\mathrm{A}^-]/c_{\mathrm{AH}}) = \log(\gamma_{\mathrm{A}^-}/\gamma_‡) + \log k_0 \qquad (12)$$

Recalling eqns. (7) and (8), the activity coefficient term can be written as eqn. (13). Combining this with eqn. (12) we obtain the final rate expression as eqn. (14), equivalent to the A1 mechanism.

$$\log(\gamma_{\mathrm{A}^-}/\gamma_‡) = (m^*_‡ - m^*)X \qquad (13)$$

$$\log k_{\mathrm{obs}} - \log([\mathrm{A}^-]/c_{\mathrm{AH}}) = (m^*_‡ - m^*)X + \log k_0 \qquad (14)$$

Use of this equation requires the simultaneous knowledge of kinetic and equilibrium (m^*, $[\mathrm{A}^-]/c_{\mathrm{AH}}$) data, which may not be available. It can be simplified[15] in the two limiting cases of AH undergoing the reaction in a basicity range where (*i*) it is not appreciably deprotonated (weak acid) or (*ii*) it is completely deprotonated (strong acid). In case (*i*), $[\mathrm{AH}] \approx c_{\mathrm{AH}}$, so that the expression $[\mathrm{A}^-]/c_{\mathrm{AH}}$ is equal to the ionization ratio for the deprotonation equilibrium of AH ($I = [\mathrm{A}^-]/[\mathrm{AH}]$), for which the excess basicity equation (15) holds.[14]

$$\log I - \log[\mathrm{MeO}^-] + \log a_{\mathrm{MeOH}} = m^*X - \mathrm{p}K_\mathrm{a} \qquad (15)$$

Thus eqn. (14) becomes eqn. (16):

$$\log k_{\mathrm{obs}} - \log[\mathrm{MeO}^-] + \log a_{\mathrm{MeOH}} = m^*_‡X + \log k_0 - \mathrm{p}K_\mathrm{a} \qquad (16)$$

In the case (*ii*), $[\mathrm{A}^-] \approx c_{\mathrm{AH}}$ and eqn. (17) holds.

$$\log k_{\mathrm{obs}} = (m^*_‡ - m^*)X + \log k_0 \qquad (17)$$

Alternatively, eqn. (14) can be approximately calculated if equilibrium data are available for a similar species, recalling that $[\mathrm{A}^-]/c_{\mathrm{AH}} = I/(I + 1)$.

The above treatments can be also be applied to S_NAr reactions, where the substrate undergoes addition of a nucleophile (MeO$^-$) to give a Meisenheimer complex which eventually gives the substituted product [eqn. (1)]. All the above considerations apply, replacing AH with ArX, A$^-$ with ArXOMe$^-$ and pK_a with pK_M.[14] The new activity coefficient term ($\gamma_{\mathrm{ArX}}\gamma_{\mathrm{MeO}^-}/\gamma_‡$) can be calculated assuming that the activity coefficient terms pertaining to addition equilibria of MeO$^-$ to nitroanisoles behave in the same way as simple deprotonation reactions, *i.e.* $\log(\gamma_{\mathrm{ArX}}\gamma_{\mathrm{MeO}^-}/\gamma_‡) = m^*X$.[14]

Experimental

All substrates used, except 3,4- and 2,5-dinitroanisole, were commercial products purified by standard methods; the anisoles were prepared by nitration of 3-nitroanisole in fuming HNO_3.[16] The preparation and handling of the methoxide salts were carried out as described previously.[17] The kinetics were studied at 20 °C by UV spectrometry under pseudo-first order conditions, which were found to hold up to at least 99% reaction. Rate constants were obtained by monitoring the changes in absorbance at a suitable wavelength. The values of the X functions of MeOLi, MeONa and MeOK solutions were calculated as described previously.[14]

Results

We have studied the kinetics of nucleophilic aromatic substitutions in concentrated solutions of Li, Na and K methoxides in MeOH on the following substrates: 4-nitropyridine *N*-oxide (**1**), 2,5- and 3,4-dinitroanisole (**2** and **3**), 3,4-dinitrotoluene (**4**), 2- and 4-chloronitrobenzene (**5** and **6**), 1-chloro- and 1-iodo-2,4-dinitrobenzene (**7** and **8**), 2-chloro-5-nitro- and 2-chloro-3-nitropyridine (**9** and **10**) and 1,4-dinitronaphthalene (**11**). In all cases, only substitution products are found, with no occurrence of species deriving from the reduction of the nitro group *via* single-electron transfer processes, which have been observed in similar systems.[18] The products obtained from **5**–**10** derive from halogen substitution. For the others, substitution of one nitro group is observed: in the case of **2**–**4** the nitro group *meta* to the methoxy group is lost exclusively. Data in MeONa and MeOK are available for all compounds, while, due to the low solubility and weaker basicity of MeOLi solutions,[14] only the most reactive substrates (**1**, **7**, **9** and **10**) have been studied in the latter medium. All substrates react at convenient rates in a

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* Cox has suggested[10] expressing the slope parameter $m^*_‡$, which appears in eqn. (8), as the product of the equilibrium value (m^*) and of a coefficient ($m^‡$) describing the degree of advancement of the reaction (for proton transfer reactions, this would be the Brønsted coefficient, α_A). Thus the two treatments are formally identical, with $m^*_‡ = m^‡m^*$.

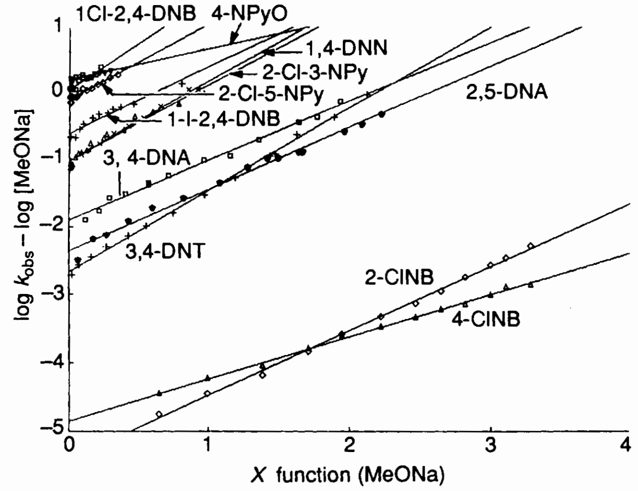

Fig. 1 log k_{obs} − log[MeONa] *vs.* the excess basicity function X

base concentration range < 3 mol dm^{-3}, except **5** and **6** (up to 5.3 mol dm^{-3}, which is close to saturation).[14]

The occurrence of the pre-equilibrium mechanism [eqns. (14), (16), (17)] can be ruled out by the following considerations. Case (*ii*) [eqn. (17)] would require linearity of original data, which is not the case, because the plots of log k_{obs} *vs.* log[MeO$^-$] or X are highly curved. Because of the wide basicity range employed, case (*i*) might not be appropriate, but the general eqn. (14) can be tested against equilibrium data for the formation of Meisenheimer complexes from dinitroanisoles.[14] For these, in MeOK, the average values of m^* and pK_M are 1.0 and 2.3, respectively; thus we can approximately calculate this value from the excess basicity eqn. (15) and apply eqn. (14). When this is done, sharply non-monotonic curves are observed.

Therefore, following eqn. (9), $m^*_\ddagger$ values have been obtained from plots of log k_{obs} − log[MeO$^-$] *vs.* X. The plots of eqn. (9) are linear, apart from some plots for [MeOK] < *ca.* 0.6 mol dm^{-3}. The data fitted refer to the high-concentration branch where better linearity is attained. The results are collected in Table 1 and plotted in Fig. 1.

Discussion

The slope $m^*_\ddagger$ of the lines describing the rate profiles [eqn. (9)] is formally analogous to the m^* parameter of acid–base equilibria [eqn. (7)], which describes the sensitivity of the equilibrium to medium changes.[14] In fact, eqn. (7) can be rewritten as eqn. (18).

$$\log \gamma_{\mathrm{MeO}^-} - \log(\gamma_{\mathrm{A}^-}/\gamma_{\mathrm{AH}}) = m^*[\log \gamma_{\mathrm{MeO}^-} - \log(\gamma_{\mathrm{A}^{*-}}/\gamma_{\mathrm{AH}^*})] = m^*X \quad (18)$$

Measurements for cations in acidic media[19] and for anions in aprotic solvents[20] have shown that the activity coefficients (which represent free energies of transfer, *i.e.*, of solvation) of charged species are higher than those of neutral species, and increase with charge localization and strength of hydrogen bonding to the solvent: thus, for example, $\gamma_{\mathrm{MeO}^-} > \gamma_{\mathrm{A}^-} > \gamma_{\mathrm{AH}}$ and phenoxide > amide > fluorenide. If $\gamma_{\mathrm{A}^-} \gg \gamma_{\mathrm{AH}}$, the ratio $\gamma_{\mathrm{A}^-}/\gamma_{\mathrm{AH}}$ will be large, and the left-hand side of eqn. (18) will be small relative to the right-hand side, with $0 < m^* < 1$. Conversely, $m^* > 1$ when $\gamma_{\mathrm{A}^-} \approx \gamma_{\mathrm{AH}}$. The case $m^* < 1$ will occur when A$^-$ has a more localized, highly solvated charge than the reference A^{*-} and *vice versa.* As expected, m^* values follow the trend $ArNH^- < Ar_2N^- < Ar_2CH^-$, and $R_2OH^+ < ArNH_3^+ < R_2SH^+ < Ar_3C^+$.[9,14] The observed value stems from a balance between internal and external stabilization due to the substituents and the solvent, respectively. From a more practical point of view, the higher the value of m^*, the steeper the increase of the ionization ratio with increasing acidity (or basicity).

Thus m^* can be interpreted in terms of the solvation requirements of the charged species (A$^-$ or BH$^+$) relative to a reference compound, for which $m^* = 1$ by definition.[9,14] Likewise, the $m^*_\ddagger$ parameter reflects the solvation of the transition state involved in the rate-determining step [eqn. (8)].[15] This interpretation allows one to explain medium and structural effects on relative reactivities.

Medium Effects.—In general, $m^*_\ddagger$ values decrease somewhat in the order Li > Na > K, but in many cases the differences are barely outside experimental errors; the data in MeONa and MeOLi solutions tend to be levelled with respect to MeOK. The few data in MeOLi solutions are affected by the lower accuracy of the X function,[14] so this trend cannot be fully assessed, though it seems analogous to those of equilibrium data and can be similarly explained.[14]

The values of the intercepts (log k_0) measure the reactivities at $X = 0$, *i.e.* in ideal solutions, where all media should behave identically; in fact a fair agreement among them is found.

Structural Effects.—In the deprotonation of various weak nitrogen acids in MeO$^-$/MeOH solutions, the major factor affecting m^* is the number of nitro and aryl groups available to delocalize the negative charge.[14] The substrates studied can be divided into two categories, according to the transition state structure, *i.e.* substrates whose transition states are stabilized by (*a*) one or (*b*) two nitro or aza groups besides that undergoing substitution. It can be seen from Table 1 that **1**–**6** belong to (*a*), while **7**–**10** belong to (*b*). Compound **11** may also be tentatively assigned to group (*b*) in consideration of the second aromatic ring. The results in Table 1 are consistent with our expectation that transition states of group (*a*) should be more solvated than (*b*); $m^*_\ddagger$ values for **1**–**6** are lower than for **7**–**11**. Moreover, it is significant that mono- and di-nitro derivatives have significantly different $m^*_\ddagger$ values, despite the expected levelling effect of nitro groups. Interestingly, **1** has a very low $m^*_\ddagger$ value, which is probably related to a highly solvated structure in which the negative charge is localized on the oxygen atom of the *N*-oxide group.

Correlation between $m^*_\ddagger$ *and* log k$_0$.—The possibility of a relationship between transition state solvation and substrate reactivity has previously been considered by Bowden.[12c,d] As Bowden pointed out (implicit in Cox's treatment[10]), $m^*_\ddagger$ contains two contributions: (*a*) the degree of advancement (bond breaking) of the reaction, which influences solvation through different degrees of charge build-up at the reaction site, and (*b*) the solvation of the transition state due to structural effects (substituents). Both factors are somehow related to the intrinsic reactivities (log k_0). We recognize the individual behaviour of the activity coefficients appearing in the definition of $m^*_\ddagger$, especially when one considers large structural variations, and therefore we do not expect a precise correlation. Nevertheless, the following considerations can be made. (*a*) In general, lower reactivity corresponds to a more product-like (late) transition state. If we assume it resembles the Meisenheimer complex intermediate, this will be more solvated because of the greater charge built on it. Thus we generally expect log k_0 to be proportional to $m^*_\ddagger$. (*b*) Assuming the influence on $m^*_\ddagger$ due to (*a*) to be constant, changes in the solvation of the transition state will be mostly due to different stabilizations by substituents. If this is true, we expect that better solvation (lower $m^*_\ddagger$) corresponds to higher reactivity. Thus the contributions (*a*) and (*b*) are in opposition.

Table 1 Kinetic data for methoxide addition at 20 °C[a]

	Substrate	Li		Na		K	
		$m_{\ddagger}^{*}$	$\log k_0$	$m_{\ddagger}^{*}$	$\log k_0$	$m_{\ddagger}^{*}$	$\log k_0$
1	4-Nitropyridine *N*-oxide	1.2 (0.21)	1.89 (0.02)	0.47 (0.06)	1.95 (0.01)	0.52 (0.05)	2.02 (0.01)
2	2,5-Dinitroanisole			0.91 (0.02)	−0.58 (0.02)	0.68 (0.01)	−0.29 (0.02)
3	3,4-Dinitroanisole			0.88 (0.02)	−0.12 (0.02)	0.65 (0.01)	0.11 (0.02)
4	3,4-Dinitrotoluene			1.22 (0.01)	−0.89 (0.02)	0.83 (0.01)	−0.62 (0.02)
5	2-Chloronitrobenzene			0.94 (0.01)	−3.63 (0.03)	0.56 (0.01)	−3.24 (0.03)
6	4-Chloronitrobenzene			0.61 (0.01)	−3.06 (0.02)	0.45 (0.01)	−2.93 (0.02)
7	1-Chloro-2,4-dinitrobenzene	1.23 (0.08)	1.78 (0.01)	1.4 (0.11)	1.80 (0.01)	1.3 (0.10)	1.86 (0.01)
8	1-Iodo-2,4-dinitrobenzene			0.89 (0.03)	1.21 (0.01)	1.05 (0.07)	1.20 (0.03)
9	2-Chloro-5-nitropyridine	1.29 (0.09)	1.64 (0.01)	1.05 (0.05)	1.67 (0.01)	1.05 (0.03)	1.71 (0.01)
10	2-Chloro-3-nitropyridine	0.91 (0.03)	0.69 (0.01)	1.03 (0.04)	0.81 (0.02)	1.03 (0.04)	0.83 (0.02)
11	1,4-Dinitronaphthalene			1.19 (0.02)	0.75 (0.01)	1.11 (0.03)	0.79 (0.02)

[a] Rate constants in $dm^3 mol^{-1} s^{-1}$. Standard deviations are given in brackets.

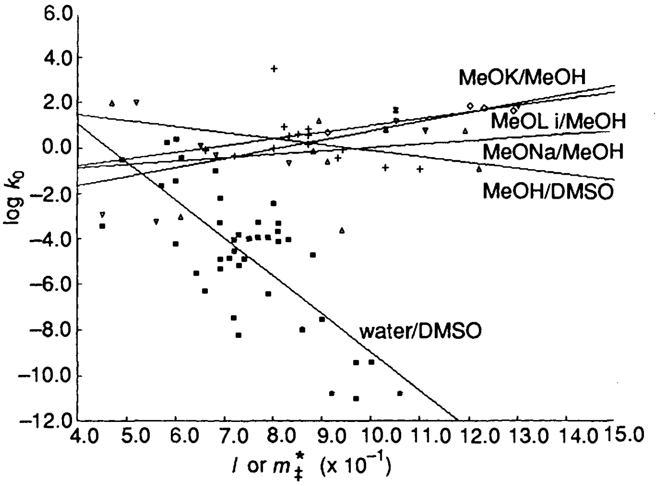

Fig. 2 Correlation of $\log k_0$ and $m_{\ddagger}^{*}$ for various substrates in MeOLi–Na–K/MeOH (this work), MeOH–DMSO and water–DMSO (ref. 12). Slopes are 3, 1.5, 4, −3 and −17, respectively.

Bowden *et al.* have analysed kinetic data for various substrates, similar to ours, in aqueous or methanolic DMSO containing fixed amounts of Me_4NOH (1.1×10^{-2} mol dm^{-3}) or MeONa (0.1 mol dm^{-3}) by plotting $\log k_{obs}$ *vs.* ($H_- + \log a_{solv}$).[12] These data allow us to test our predictions by comparing medium effects on reactivities in other solvents.

From the definition of the H_- acidity function (*e.g.* in MeOH)[8] [eqn. (19)] it follows that, if the base concentration is fixed, the expression ($H_- + \log a_{MeOH}$) differs from m^*X by a constant term [eqn. (20)]. Therefore the slope l of those correlations is related to $m_{\ddagger}^{*}$, and the constant c to $\log k_0$ through eqn. (21).

$$H_- = -\log(a_{H^+}\gamma_{A^-}/\gamma_{AH}) = pK_{MeOH} - \log a_{MeOH} + \log(\gamma_{AH}\gamma_{MeO^-}/\gamma_{A^-}) + \log[MeO^-] \quad (19)$$

$$H_- + \log a_{MeOH} = m^*X + (\log[MeO^-] + pK_{MeOH}) \quad (20)$$

$$\log k_{obs} = l(H_- + \log a_{MeOH}) + c = lm^*X + l(\log[MeO^-] + pK_{MeOH}) + c \quad (21)$$

Thus Bowden's data can be converted to $m_{\ddagger}^{*}$ and $\log k_0$ values considering that the acidity function used (H_-) is based on the same indicators used for determining X;[14] therefore $m^* = 1$ and $m_{\ddagger}^{*} = l$. Recalling that $pK_w = 14$, $pK_{MeOH} = 16.86$ and $\log(1.1 \times 10^{-2}) = -1.96$, we obtain eqns. (22a and b).

$$\log k_0 = c + 12.04l + 1.96 \text{ (water–DMSO)} \quad (22a)$$

$$\log k_0 = c + 15.86l + 1.00 \text{ (MeOH–DMSO)} \quad (22b)$$

Incidentally, we note that **1** yields the lowest l value despite differences in medium, conditions and treatment. This further supports our results, and sets this compound apart from the others because of the unique factors affecting its solvation.

In order to test the above considerations, we have plotted $\log k_0$ *vs.* $m_{\ddagger}^{*}$ for our data and those recalculated from Bowden's values of l and c by means of eqns. (22a and b) (see Fig. 2). All data sets in the three media* (MeOH, and MeOH–DMSO and water–DMSO) include similar substrates which encompass large changes in structure, reactivity and solvation. The data in MeOH/MeO$^-$ define a positive average slope (3), while those in MeOH/DMSO exhibit a negative slope of −3; the data in water–DMSO show a much larger negative slope (−17). No meaningful conclusion could be drawn from the behaviour of single substrate families.

While there is a large scatter in the correlations, due to the essentially individual behaviour displayed by the substrates (also because other factors, like steric effects, are not considered), they do establish some trends. In water the main factor affecting reactivities is the solvation of the transition state, while in MeOH (where solvation energies are lower) the two factors approximately balance, with little, if any, correlation.

Relative Reactivities of 2- *and* 4-*Chloronitrobenzene*.—It has long been known that, for reactions with primary or secondary amines, the *ortho* isomer is more reactive than the *para* ($k_{para} < k_{ortho}$), while for reactions with anionic nucleophiles the reverse is generally true ($k_{para} > k_{ortho}$).[4] Relative reactivities with amines have been explained as due to either intramolecular hydrogen bonding[4] or an electrostatic interaction ('built-in solvation')[4,21] between the nitro and N–H groups in the transition state, this stabilizing interaction accounting for the higher reactivity of the *ortho* isomer.

The data obtained by Bowden in water–DMSO (addition of OH$^-$) are consistent with the above findings.[12a] On the other hand, in methoxide solutions of varying concentration, the behaviour is as stated before ($k_{para} > k_{ortho}$) only in dilute solutions, while at base concentrations greater than *ca.* 3 mol dm^{-1} the behaviour reverses, and matches that found towards amines ($k_{para} < k_{ortho}$).[22] This inversion of reactivity is apparent

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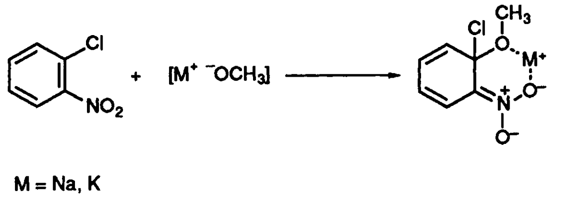
* The data sets in MeOH/MeO$^-$ and MeOH–DMSO are separated only for convenience, as the values of $\log k_0$ refer to the same reference solvent (MeOH); the data in MeOLi, MeONa and MeOK give negligibly different results.

in Fig. 1, which shows a steeper increase of rate constant for the *ortho* isomer. From the data in Table 1 we note that $m^{*}_{\ddagger}$ (*ortho*) > $m^{*}_{\ddagger}$(*para*) both in MeONa and MeOK. This implies a lower solvation of the transition state leading to the *ortho* isomer, and can be explained by an interaction with the metal cation, as shown in Scheme 1. This interaction stabilizes the transition state, thus reducing external stabilization by the solvent; the effect is more marked for the smaller Na^+ cation. A similar reasoning was applied in the interpretation of the relative reactivities in the presence of crown ethers capable of effectively removing the K^+ ion from the reaction site.[23,24] It is interesting to note that $m^{*}_{\ddagger}$ is also sensitive to these interactions, which are not directly related to electronic effects of substituents on hydrogen bonding.



Scheme 1

In the water–DMSO system, the base concentration range in which the kinetics can be conveniently studied is such that inversion does not occur, and it happens to lie in an interval where 'normal' behaviour is observed. Similar inversions of relative acidity and basicity induced by solvation have often been found in acid–base equilibria.[9,14,25]

Acknowledgements

Financial assistance from the Ministero della Pubblica Instruzione (Finanziamento 60% and Finanziamento 40%) is gratefully acknowledged.

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Paper 0/04688D
Received 18*th October* 1990
Accepted 29*th November* 1990