The Kinetics of the Reactions of Aniline with 1-Fluoro- and 1-Chloro-2,4-dinitrobenzenes in Dimethyl Sulphoxide, Dimethylformamide, Acetonitrile, and Nitromethane

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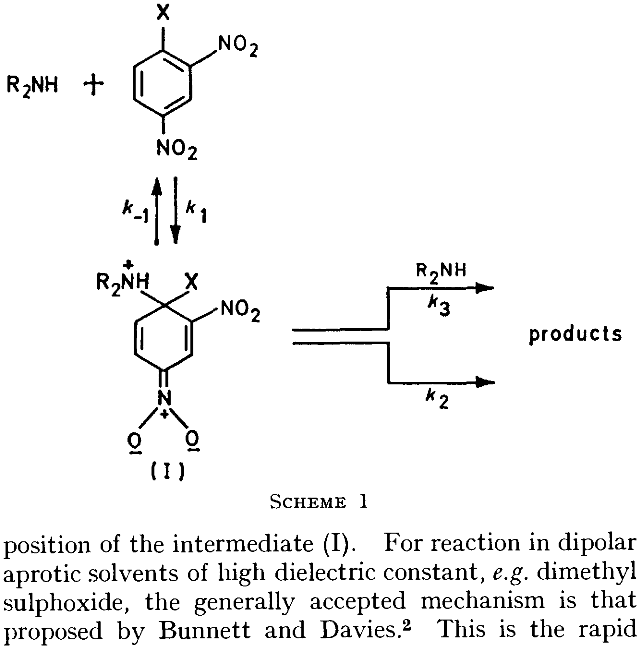
The reaction of aniline with 1-fluoro-2,4-dinitrobenzene is base catalysed in the solvents dimethylformamide, acetonitrile, and nitromethane, but not in dimethyl sulphoxide. The reaction with 1-chloro-2,4-dinitrobenzene is not base catalysed in any of these solvents. The results provide information about the mechanism of the uncatalysed decomposition of the intermediate formed in nucleophilic aromatic substitution in solvents of high dielectric constant.

THE mechanism for bimolecular aromatic nucleophilic substitution when either primary or secondary amines are the nucleophiles is given in Scheme 1. Application of the steady-state hypothesis to this mechanism gives equation (1), where k_A is the observed second-order rate constant.

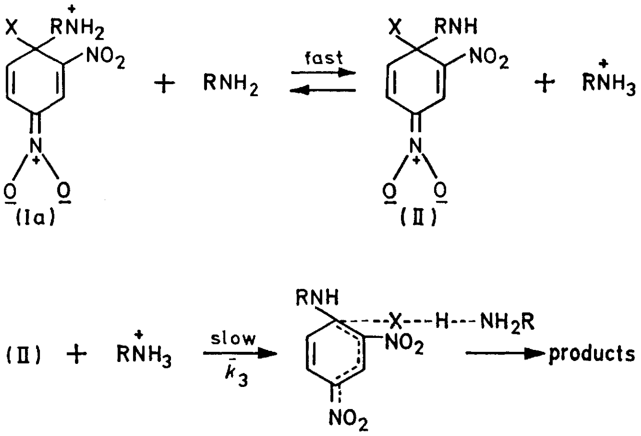
$$k_A = (k_1k_2 + k_1k_3[R_2NH])/(k_{-1} + k_2 + k_3[R_2NH]) \quad (1)$$

For the condition $k_{-1} \ll k_2 + k_3[B]$ equation (1) is reduced to $k_A = k_1$, the formation of the intermediate is rate determining, and the reaction is not base catalysed. If this condition is not obeyed, the decomposition of the intermediate is rate limiting and base catalysis is observed, the kinetic form of the catalysis depending on the relative magnitudes of k_{-1} and $k_2 + k_3[B]$. If the substrates are halogens an alternative criterion of mechanism is sometimes applied; if the rate-constant sequence F $\gg$ other halogens is observed, then breaking of the carbon–fluorine bond is not involved in the rate-determining step.[1]

Recently attention has been directed towards the nature of both the catalysed and uncatalysed decomposition of the intermediate (I). For reaction in dipolar aprotic solvents of high dielectric constant, *e.g.* dimethyl sulphoxide, the generally accepted mechanism is that proposed by Bunnett and Davies.[2] This is the rapid transformation of the first-formed intermediate into its conjugate base followed by the slow electrophilically-catalysed removal of the leaving group as shown in Scheme 2. On this interpretation k_3 [equation (1)] = $\bar{k}_3K_B$ where $K_B = ([II][R\overset{+}{N}H_3])/([I][RNH_2])$. It has been suggested [3] that the mechanism of the uncatalysed path could be similar to that of the catalysed one with a solvent molecule acting as base as shown in Scheme 3. This interpretation requires k_2 [equation (1)] = $\bar{k}_2K_S$, where $K_S = ([S\overset{+}{H}][II]/[I])$. Bernasconi and de Rossi have shown [4] that this mechanism is not tenable in hydroxylic solvents and we have shown [5] that it cannot apply to dipolar aprotic solvents when a secondary amine is the nucleophile. Our demonstration was in essence based on the fact that K_S defines the strength of the conjugate acid of an amine and it is known that the values of this can vary enormously, depending on the basicity of the solvent in which it is measured. Hence, if the Bunnett mechanism applies to both the catalysed and uncatalysed paths there should be large differences in the value of k_3/k_2 (= $\bar{k}_3K_B/\bar{k}_2K_S$) in solvents of widely differing basicity. For the reaction of 2,4-dinitrophenyl phenyl ether with morpholine [5] and piperidine [6] there was little change in this ratio when the solvent was changed from dimethyl sulphoxide to acetonitrile, and hence we concluded that the uncatalysed reaction did not take place by this mechanism, but probably proceeded unimolecularly, as first proposed by Kirby and Jencks,[7]



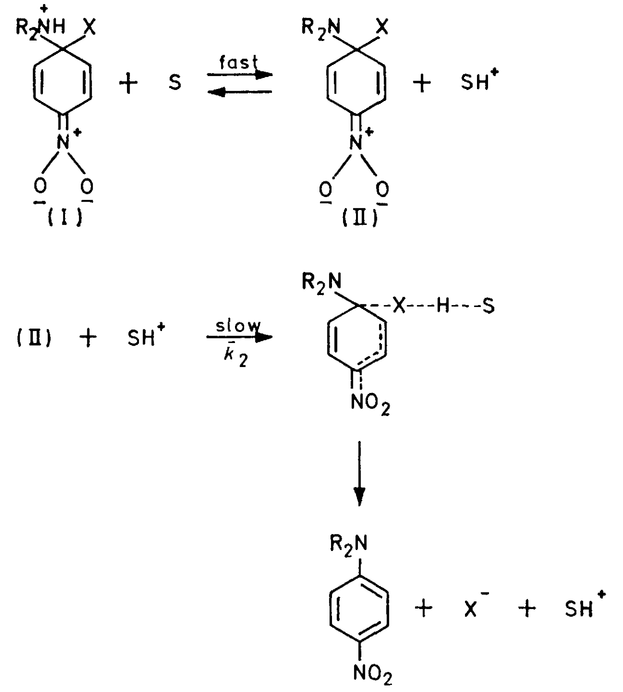
SCHEME 1



SCHEME 2

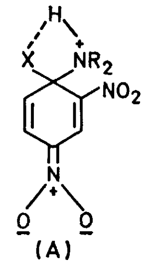
via the internally hydrogen-bonded intermediate shown in (A).

In Scheme 1, when the substrate contains an *ortho*-nitro-group then hydrogen bonding occurs in the intermediate (I) between the amino-hydrogen atoms and the oxygen atoms of the nitro-group. When the nucleophile is a secondary amine, this bond has to be broken before reaction can take place either by the Bunnett or unimolecular mechanisms. When the nucleophile is a primary amine, a second hydrogen atom is available for reaction by either mechanism without the prior breaking of the hydrogen bond, and hence the mechanism of the uncatalysed path could be different for primary and secondary amines.



SCHEME 3

In order to test this possibility a base-catalysed system involving a primary amine was required. As Kavalek, Haasova, and Sterba[8] have shown that the reaction of 1-fluoro-2,4-dinitrobenzene with aniline is base catalysed in acetonitrile we have investigated this



(A)

reaction together with the corresponding one of 1-chloro-2,4-dinitrobenzene in dimethyl sulphoxide (0),* dimethylformamide, acetonitrile (−10.13), and nitromethane (—11.9). It has been estimated[9] that dimethyl sulphoxide is approximately one pK unit more basic than dimethylformamide, and although there may be controversy[10] with respect to the absolute values of the pK_a values quoted there can be no doubt as to the relative order. Kolthoff, Chantooni, and Bhownik[11] give the values of the pK_a of the conjugate acid of aniline as 3.6 in dimethyl sulphoxide and 10.6 in acetonitrile. The rates of the reactions were followed spectrophotometrically with aniline in large enough excess to ensure first-order kinetics and with the exception of the reaction of 1-chloro-2,4-dinitrobenzene in nitromethane the experimental values of the absorbance at infinity agreed with the theoretical ones. The reaction of aniline with 1-chloro-2,4-dinitrobenzene in nitromethane is very slow and the theoretical values of the absorbances at infinity were used to calculate the rate constants. The results are given in the Table.

Rate constants (l mol^{-1} s^{-1}) for the reaction of 1-fluoro-[a] and 1-chloro-[b] 2,4-dinitrobenzenes with aniline in various solvents at 30.6 °C

Solvent	Substrate															
Me_2SO	F	10^2[aniline]/M	2	6	8	10										
		10^2k_A	2.26	2.18	2.23	2.31										
	Cl	10^2[aniline]/M	2	6		10										
		10^4k_A	4.33	4.40		4.48										
Me_2NCHO	F	10^2[aniline]/M	2	4	5	6	8	10	15	20	25	30		34		36
		10^3k_A	1.56	1.99	2.17	2.40	2.77	3.27	4.03	5.11	5.78	6.53		7.00		7.33
	Cl	10^2[aniline]/M	5	10	20	30										
		10^4k_A	1.35	1.34	1.37	1.35										
MeCN	F	10^2[aniline]/M	4	7	10	15	20	25	28	40	50	60	70	80	90	100
		10^4k_A	1.07	1.18	2.03	2.61	3.36	3.60	4.06	5.58	6.96	7.73	9.03	10.2	11.2	11.7
	Cl	10^2[aniline]/M		20			30		40							
		10^6k_A		6.75			6.93		7.07							
$MeNO_2$	F	10^2[aniline]/M	5	10	20	25	30	40	50	60	70	80				
		10^5k_A	3.77	6.73	12.8	15.5	19.0	23.0	33.2	37.7	44.4	51.9				
		$10^4k_3 = dx/dt$ [substrate] [amine]^2	7.54	6.73	6.40	6.20	6.33	5.75	6.64	6.28	6.34	6.49				
	Cl	10^2[aniline]/M	10		20		40									
		10^6k_A	2.73		2.73		2.92									

[a] Substrate concentration 2.93—3.49 × 10^{-4} mol l^{-1}. [b] Substrate concentration 3.0—4.0 × 10^{-4} mol l^{-1}.

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* Figures in parentheses are the values of the pK_a of the solvents quoted by E. M. Arnett, *Progr. Phys. Org. Chem.*, 1963, **1**, 223.

DISCUSSION

The reaction of 1-chloro-2,4-dinitrobenzene is not base catalysed in any of the solvents investigated, hence $k_A = k_1$, the rate constant for the formation of the intermediate. The value of this constant decreases from dimethyl sulphoxide through dimethylformamide and acetonitrile to nitromethane; of the 161-fold difference in rate the biggest change occurs between dimethylformamide and acetonitrile. These results are in accord with the solvating power of the solvents. On going from reactants to intermediate, charges are produced and it is well known [12] that whereas dimethyl sulphoxide and dimethylformamide solvate cations better than water, nitromethane is a very poor solvent for ions. Also as Parker [13] has observed, when amines are the nucleophiles, the transition state for bimolecular aromatic nucleophilic substitution reactions are strong hydrogen-bond donors and are solvated more strongly by basic solvents such as dimethyl sulphoxide and dimethylformamide.

The kinetic form of the reaction of 1-fluoro-2,4-dinitrobenzene with aniline varies with the solvent. In dimethyl sulphoxide the second-order rate constant is independent of the aniline concentration, in the other solvents plots (not shown) of k_A against aniline concentration are curvilinear with a definite intercept in dimethylformamide, curvilinear and passing through the origin in acetonitrile, and linear passing through the origin in nitromethane. The behaviour of this system is very different from that observed for the reactions of 2,4-dinitrophenyl phenyl ether with morpholine [5] and piperidine.[6]

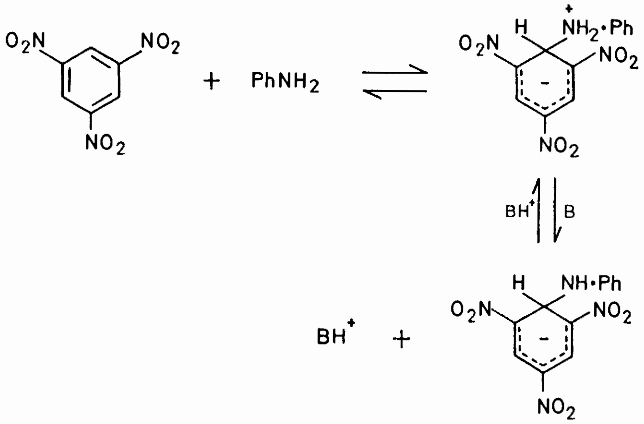
The results in dimethyl sulphoxide can be accommodated by equation (1) either by the condition $k_{-1} \ll k_2 + k[_3R_2NH]$ whence $k_A = k_1$ or by $k_2 \gg k_3[R_2NH]$ when the equation reduces to $k_A = k_1k_2/k_{-1} + k_2$ or $k_A = k_1k_2/k_{-1}$ depending on the relative magnitude of k_2 and k_{-1}. We favour the first possibility on the grounds that the reaction is not catalysed by 1,4-diazabicyclo[2.2.2]-octane and there is only a factor of *ca.* 2 between the observed k_F/k_{Cl} ratio of 50.9 and that of 103 obtained by Parker and Chapman [14] for the reactions in 99.8% ethanol at 30 °C. In dimethylformamide at low amine concentrations the kinetic form corresponds to the condition $k_{-1} \sim k_2$ and application of conventional methods of analysis [15] gives k_3/k_2, 36.1; k_{-1}/k_2, 18.1; k_{-1}/k_3, 0.50. In acetonitrile k_2 is negligible compared to k_3 and $k_{-1} \gg k_2$. The plot of $1/k_A = 1/k_1 + k_{-1}/k_1k_3$[aniline] is linear over the range of concentrations studied and the value of 4.07×10^{-3} so obtained for k_1 is in reasonable agreement with the figure of 1.83×10^{-3} l mol^{-1} s^{-1} by Kavalek *et al.*[8] at 20 °C, but our value of 2.44 for k_{-1}/k_3 is considerably greater than their value of 0.80, particularly since these authors claim that the value of the ratio is independent of temperature. Finally, the third-order kinetics observed in nitromethane corresponds to the condition $k_{-1} \gg k_3[B] \gg k_2$. Hence in going from dimethyl sulphoxide to nitromethane there is a change from $k_{-1} \ll k_2$ through $k_{-1} \sim k_2$ to $k_{-1} \gg k_2$ and although k_3/k_2 values are not known in dimethyl sulphoxide they increase from 36.1 in dimethylformamide to infinity in acetonitrile and nitromethane.

On the assumption that the base-catalysed step takes place by the Bunnett mechanism, we have already [5] examined the variation of k_3/k_2 with solvent basicity and it is clear that the present results cannot be accommodated by assuming that the uncatalysed path takes place *via* the unimolecular decomposition of the intermediate but they are compatible with it occurring by a Bunnett-type mechanism involving the solvent as base.

In the following discussion of the k_{-1}/k_2 ratio, as in the previous discussion of the k_3/k_2 ratio,[5] by 'general solvent effect' we mean all the effects of the solvent, *e.g.* those of polarity, polarisability *etc.* on the rates and positions of equilibria of a reaction with the specific exclusion of solvent basicity. The rate-determining step for the destruction of the intermediate (I) to reactants or products *via* either the unimolecular mechanism or the Bunnett-type mechanism using solvent molecules as the base involves the destruction of charge, hence general solvent effects should be in the same direction for all three processes and it is difficult to see why there should be differential effect on k_{-1} and k_2 due to this factor. If the decomposition of the intermediate to products takes place unimolecularly, then neither of the reactions for which k_{-1} and k_2 are the rate constants involves the basicity of the solvent, hence on this model there should be little change in the ratio between dimethyl sulphoxide and acetonitrile. If, however, the uncatalysed path involves a Bunnett type mechanism, then on changing from dimethyl sulphoxide to acetonitrile there is a large change in K_s which would give a corresponding large decrease in k_2.

The above discussion of the k_3/k_2 and k_{-1}/k_2 ratios has been predicated on the base-catalysed step taking place by the Bunnett mechanism. Recently however Buncel, Eggimann, and Leung [16] have shown that when 1,3,5-trinitrobenzene reacts with aniline in dimethyl sulphoxide in the presence of 1,4-diazabicyclo[2.2.1]octane to form a Meisenheimer complex as shown in Scheme 4, the rate-determining step is the abstraction of a proton from the first-formed intermediate by the base. It is possible that the base-catalysed step of the reaction of 1-fluoro-2,4-dinitrobenzene with aniline takes place by this mechanism and by analogy that the uncatalysed step proceeds by a rate-limiting transfer of the proton to a solvent. In both these processes the rate-limiting stage involves the sharing of the charge and hence although the effect of solvent change will be in the same direction as those previously discussed, their magnitude will be smaller. For true base catalysis the magnitude of the catalysis increases with increasing strength of the base, and on this basis there would be a large increase in k_3 and a large decrease in k_2 on changing from dimethyl sulphoxide to acetonitrile. As k_{-1} is independent of the basicity of the solvent, the change should result in a large increase in both k_3/k_2 and k_{-1}/k_2. A unimolecular mechanism for the uncatalysed pathway would demand as a first approximation little change of the k_{-1}/k_2 ratio with solvent change which is at variance with experimental results.

Although the solvent variation of the k_3/k_2 and k_{-1}/k_2 ratios are explicable on mechanisms involving rate-limiting proton transfers in both the catalysed and uncatalysed steps, the mechanisms would predict a very big decrease in the k_{-1}/k_3 ratio due to basicity changes in going from dimethyl sulphoxide to acetonitrile, possibly offset to a small extent by the general solvent effect. Experimentally the value of this ratio increases from 0.50 in dimethylformamide to 2.44 in acetonitrile, mitigating against the mechanism.



SCHEME 4

EXPERIMENTAL

Materials.—The purification of dimethyl sulphoxide,[17] acetonitrile,[18] aniline,[19] and 1-chloro- and 1-fluoro-2,4-dinitrobenzenes [20] has been described previously. Dimethylformaide was purified by distilling a mixture of the solvent (2 l) and benzene (400 ml) at atmospheric pressure until the vapour temperature reached 130 °C. The residue was shaken with solid potassium hydroxide and distilled under reduced pressure in an atmosphere of nitrogen. Nitromethane was purified by the method of Hoggett, Moodie, and Schofield.[21]

Kinetic Procedure.—The rates of formation of the product of the reactions were followed spectrophotometrically at 400 nm by the pipette procedure already described.[20]

[8/1417 *Received*, 31*st July*, 1978]

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