Reaction of 2,4-Dinitrophenyl Phenyl Ether with Morpholine in Dimethyl Sulphoxide, Acetonitrile, Tetrahydrofuran, and Ethyl Acetate and of 1-Chloro-2,4-dinitrobenzene with Morpholine in Ethyl Acetate

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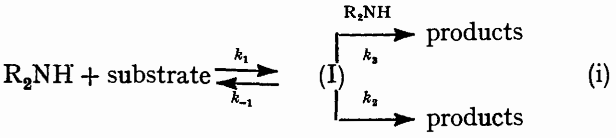
The reaction of morpholine with 2,4-dinitrophenyl phenyl ether is base-catalysed in all the solvents investigated. The values of k_3/k_2 provide information about the mechanism of the uncatalysed decomposition of the intermediate formed in nucleophilic aromatic substitution in solvents of high dielectric constant.

The reaction of morpholine with 1-chloro-2,4-dinitrobenzene in ethyl acetate is not base-catalysed. Comments are made on the mechanism of base-catalysed nucleophilic aromatic substitution in solvents of low dielectric constant and basicity.

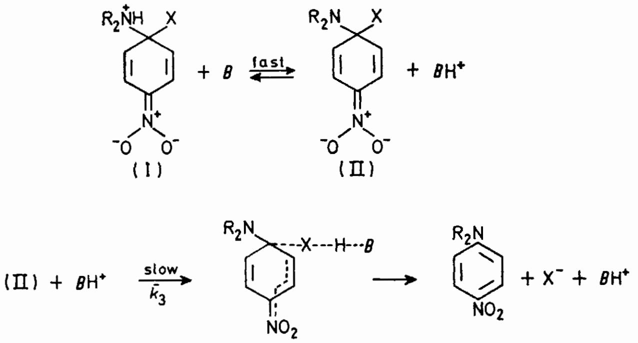
THE mechanism of bimolecular nucleophilic aromatic substitution when either primary or secondary amines are the nucleophiles can be represented by equation (i).



$$\mathrm{R_2NH} + \text{substrate} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (\mathrm{I}) \begin{cases} \xrightarrow[k_3]{\mathrm{R_2NH}} \text{products} \\ \xrightarrow{k_2} \text{products} \end{cases} \quad \text{(i)}$$

Application of the steady state hypothesis to this mechanism gives equation (ii), where k_A is the observed second-order rate constant. Considerable attention has been paid to the nature of the base-catalysed decomposition of the intermediate (I), but little is known about the mechanism of the uncatalysed pathway. For reactions in protic solvents or dipolar aprotic solvents of high dielectric constant, *e.g.* dimethyl sulphoxide, the generally accepted mechanism for the catalysed path is that proposed by Bunnett and Davies.[1] 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 1. On this interpretation, k_3 [equation (i)] = $\bar{k}_3K_B$, where $K_B = [(\mathrm{II})][B\mathrm{H}^+]/[(\mathrm{I})]\ [B]$. It has been suggested[2] that the mechanism of the uncatalysed pathway could be similar to that of the catalysed one with a solvent molecule acting as a base as shown in Scheme 2. This interpretation requires k_2 [equation (i)] $= \bar{k}_2K_S$, where $K_S = [\mathrm{SH}^+][(\mathrm{II})]/[(\mathrm{I})]$. Bernasconi and de Rossi[3] have shown that this mechanism is not tenable in hydroxylic solvents, and we now show that it cannot be applied to dipolar aprotic solvents when a secondary amine is the nucleophile.

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



SCHEME 1

We have studied the reaction of 2,4-dinitrophenyl phenyl ether with morpholine as a function of the morpholine concentration in the solvents dimethyl sulphoxide, acetonitrile, tetrahydrofuran, and ethyl acetate. The reactions were followed spectrophotometrically with morpholine in sufficient excess to give first-order kinetics. In all the solvents satisfactory results were obtained and the experimental values of the optical densities at infinity agreed with the theoretical ones. The results are given in Table 1. The reaction has been studied previously in 10% dioxan–water by Bernasconi and Schmidt.[4]

In the first three solvents listed in Table 1, there is a

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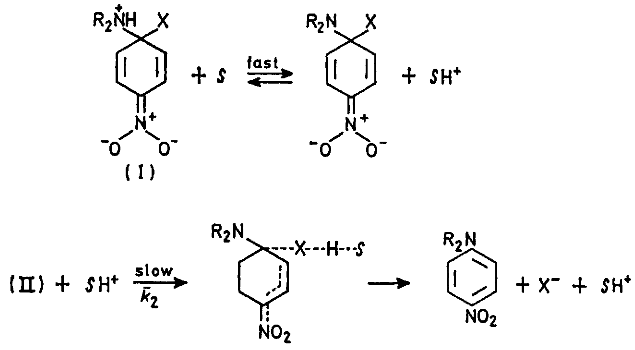
[1] J. F. Bunnett and G. T. Davies, *J. Amer. Chem. Soc.*, 1960, **82**, 655.

[2] J. A. Orvick and J. F. Bunnett, *J. Amer. Chem. Soc.*, 1970, **92**, 2417.

[3] C. F. Bernasconi and R. H. de Rossi, *J. Org. Chem.*, 1973, **38**, 500.

[4] C. F. Bernasconi and P. Schmid, *J. Org. Chem.*, 1967, **32**, 2953.

linear relationship between the observed second-order rate constant k_A and the morpholine concentration, *i.e.* $k_A = k' + k''$ [morpholine], and an almost linear dependence on the morpholine concentration was found previously in 10% dioxan–water.[4] In solvent ethyl acetate, the plot of k_A against morpholine concentration is again linear but goes through the origin, and the assumption of third-order kinetics gives steady rate constants.



SCHEME 2

TABLE 1

Rate constants (l mol⁻¹ s⁻¹) for the reaction of 2,4-dinitrophenyl phenyl ether[a] with morpholine in various solvents at 30.5 °C

Solvent									
Dimethyl sulphoxide	10^2[morpholine]/M	4.0	6.0	8.0	10.0	12.0	16.0		
	10^3k_A	1.00	1.40	1.73	2.24	2.43	3.26		
Acetonitrile	10^2[morpholine]/M	4.0	6.0	8.0	10.0	12.0	16.0		
	10^4k_A	3.38	4.57	6.50	7.58	9.42	12.3		
Tetrahydrofuran	10^2[morpholine]/M	2.0	4.0	5.6	7.4	9.1	10.4	12.7	14.8
	10^5k_A	8.2	10.2	11.9	15.8	18.4	21.7	23.1	26.2
Ethyl acetate	10^2[morpholine]/M	4.0	6.0	8.0	10.0	12.0	16.0		
	10^5k_A	7.40	10.4	15.0	17.4	21.7	29.2		
	$10^3k = \frac{dx/dt}{[\text{substrate}][\text{amine}]^2}$	1.85	1.74	1.86	1.74	1.81	1.82		

[a] Substrate concentration 2—3 × 10^{-4} mol l⁻¹.

DISCUSSION

If, in equation (ii), $k_{-1} \gg k_2 + k_3[R_2NH]$, then the equation reduces to $k_A = (k_1k_2 + k_1k_3\,[R_2NH])/k_{-1}$ and the experimentally determined $k''/k' = k_3/k_2$. Values of k_3/k_2 obtained in this way are given in Table 2 together with values from the literature.

TABLE 2

Values of k_3/k_2 at 30.5 °C in various solvents for the reaction of morpholine with 2,4-dinitrophenyl phenyl ether

Solvent	k_3/k_2
10% Dioxan–water[a]	86.7
Dimethyl sulphoxide	86
Acetonitrile	185
Tetrahydrofuran	274
Ethyl acetate	∞ (third-order reaction)

[a] At 29.4 °C; calculated from the results of ref. 4.

We have seen that the assumption of a Bunnett-type mechanism for both the catalysed and uncatalysed paths gives $k_3 = \bar{k}_3K_B$ and $k_2 = \bar{k}_2K_S$; hence $k_3/k_2 = \bar{k}_3K_B/\bar{k}_2K_S$ and for the same reaction carried in two solvents, A and D, equation (iii) applies, where the superscripts A and D refer to the rate and equilibrium constants in solvents A and D.

$$\frac{(k_3/k_2)^{\mathrm{A}}}{(k_3/k_2)^{\mathrm{D}}} = \frac{{}^{\mathrm{A}}\bar{k}_3}{{}^{\mathrm{D}}\bar{k}_3} \cdot \frac{{}^{\mathrm{A}}K_B}{{}^{\mathrm{D}}K_B} \cdot \frac{{}^{\mathrm{D}}\bar{k}_2}{{}^{\mathrm{A}}\bar{k}_2} \cdot \frac{{}^{\mathrm{D}}K_S}{{}^{\mathrm{A}}K_S} \qquad \text{(iii)}$$

In the following discussion, by a ‘general solvent effect’ we mean all the effects of solvent, *e.g.* those of polarity, polarizability, *etc.*, on the rates and positions of equilibrium of a reaction with the specific exclusion of solvent basicity. In equation (iii) K_B is the equilibrium constant for the reaction between the base and the first formed intermediate. The entities concerned are the same in both solvents; hence the ratio will only be subject to a general solvent effect, the magnitude of which will be small compared to an effect discussed later. The parameter $\bar{k}_2$ is the rate constant for the reaction between the second intermediate (II) and the conjugate acid of the solvent, SH^+. In changing from solvent A to solvent D there will be two effects: (*a*) a change in the entity from AH^+ to DH^+; we defer discussion of the effect of this change until later; (*b*) a general solvent effect on the rate constant. Now the charge types in the reactions involving $\bar{k}_2$ and $\bar{k}_3$ are the same, so the general solvent effect on reactions involving BH^+ and SH^+ should be similar, and to a first approximation k_3/k_2 should be independent of a general solvent effect.

The parameter K_S refers to the equilibrium between (I) and the solvent and defines the acid strength of (I) in a particular solvent. It is well known that the strength of an acid can vary enormously as the solvent is changed, for example the ratio of acid strengths of the tri-n-butylammonium ion in dimethyl sulphoxide and in acetonitrile[5] is $5 \times 10^9 : 1$. Hence we would expect large changes in solvent basicity to give large changes in the value of k_3/k_2. In Table 2, the first three entries refer to solvents of high dielectric constant where the Bunnett mechanism can reasonably be expected to operate. Change of solvent has little effect on k_3/k_2; in particular there is an increase of only *ca.* two-fold in changing from dimethyl sulphoxide to acetonitrile.

[5] I. M. Kolthoff, M. K. Chantooni, and S. Bhownik, *J. Amer. Chem. Soc.*, 1968, **90**, 23.

There are two ways in which the results can be explained. In changing solvents from A to D as already mentioned there is a change in the electrophilic catalyst from AH^+ to DH^+. If there were a large difference in the catalytic power of these entities, the results could be accommodated. This however is equivalent to assuming that there is an inverse relationship between the strength of the base and the catalytic power of its conjugate acid, which would imply that the catalytic effect of all bases is approximately the same. This is contrary to the general experience in base-catalysed nucleophilic aromatic substitution, where, when steric effects are negligible, the catalytic powers of bases increase with increase in their base strengths. It has been shown [4] for example that when the present reaction is carried out in 10% dioxan–water, catalysis by morpholine gives a value of k_3/k_2 of 86.7, but for catalysis by hydroxide ion the value is 7 900.

TABLE 3

Rate constants (l mol^{-1} s^{-1}) for the reaction of 1-chloro-2,4-dinitrobenzene (ClDNB) with piperidine in acetone at 30.0 °C

Initial [ClDNB] 5×10^{-5}M

10^4[amine]/M	5.00	10.0	20.0	25.0	30.0
$10k_2$	5.60	5.61	5.64	5.73	5.65

TABLE 4

Rate constants (l mol^{-1} s^{-1}) for the reaction of 1-fluoro-2,4-dinitrobenzene (FDNB) with aniline at 50.0 °C

Initial [FDNB] 3×10^{-2}M; A, values obtained in the present investigation; B, values of Banjoko, Bevan, and Hirst [9]

10^2[aniline]/M		2.00	4.00	6.00	8.00	9.00	10.0	12.0	14.0	16.0
10^4k_2	A		1.25	2.11			3.20	4.21	5.28	6.45
	B	0.62	1.28	1.89	2.44	2.86	3.29	4.29	5.11	

The alternative explanation is that the proposed mechanism is wrong. That is to say that for secondary amines in solvents of high dielectric constant the uncatalysed reaction does not proceed by a Bunnett-type mechanism.

The reaction in ethyl acetate differs from those in the other solvents in being a pure third-order reaction. Ethyl acetate has the lowest dielectric constant (ε_{25} 5.96) and with the exception of acetonitrile is the least basic of the solvents investigated. It is possible that in this solvent morpholine exists essentially in a dimeric form and that this dimer is the nucleophile. Although we considered this possibility unlikely, particularly in view of the results of Becker *et al.*[6] for the reaction of morpholine with 1-fluoro-2,4-dinitrobenzene in benzene, we decided to check it by studying the reaction of 1-chloro-2,4-dinitrobenzene with morpholine in ethyl acetate. The rationale behind this experiment was that chlorine is a very good leaving group and except in rare cases * the formation of the intermediate is rate determining; however if attack is by the dimer, this reaction too should be third-order. The results are given in Table 5. As the calculated second-order rate constants are independent of the morpholine concentration, the third-order rate law observed when the substrate is 2,4-dinitrophenyl phenyl ether cannot be due to attack by a morpholine dimer.

TABLE 5

Rate constants (l mol^{-1} s^{-1}) for the reaction of 1-chloro-2,4-dinitrobenzene (ClDNB) with morpholine in ethyl acetate at 30.5 °C

Initial [ClDNB] 3×10^{-4}M

10^2[morpholine]/M	2.00	4.00	6.00	8.00
10^2k_2	2.93	3.23	3.16	2.90

When nucleophilic aromatic substitutions are carried out in solvents of low dielectric constant it is usually assumed that the base-catalysed decomposition of the intermediate occurs with a cyclic transition state (Figure 1). This was first proposed by Capon and Rees [10] for the reaction of piperidine with 1-fluoro-2,4-dinitrobenzene in benzene. The apparent rationale behind this postulate involves (i) the need for electrophilic catalysis to assist the departure of poor leaving groups and (ii) the inability of these solvents to stabilise the ionic species required by a Bunnett-type mechanism. We explain our results in ethyl acetate on this basis, that is to say that in moving from solvents of high dielectric constants to one of low dielectric constant, there is a change of mechanism in the base-catalysed step.

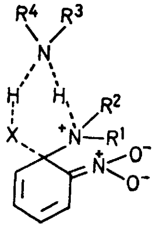


FIGURE 1

The concept of a cyclic transition state, however, requires further consideration. When the substrate

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* We have observed catalysis by piperidine in the reaction of 1-chloro-2,4-dinitrobenzene with piperidine in acetone,[7] an observation which de Rossi and Rossi [8] were unable to confirm. We have repeated our original work and the results given in Table 3 are in agreement with those of de Rossi and Rossi. At present we cannot account for our original observations. In the same paper de Rossi and Rossi criticise the results of Banjoko *et al.*[9] for the reaction of 1-fluoro-2,4-dinitrobenzene with aniline in acetone. We have reinvestigated the system and our present results, in agreement with the original observations of Banjoko *et al.*, are given in Table 4.

[6] G. Becker, C. F. Bernasconi, and Hch. Zollinger, *Helv. Chim. Acta*, 1967, **50**, 10.

[7] T. O. Bamkole and J. Hirst, *J. Chem. Soc.* (*B*), 1969, 848.

[8] R. H. de Rossi and R. A. Rossi, *J. Org. Chem.*, 1974, **39**, 3486.

[9] O. Banjoko, C. W. L. Bevan, and J. Hirst, *Nigerian J. Sci.*, 1969, **3**, 153.

[10] B. Capon and C. W. Rees, *Ann. Reports*, 1963, **60**, 279.

contains an *ortho*-nitro group, no account is usually taken of the hydrogen-bonding (Figure 2), which occurs when the intermediate is first formed. Such hydrogen-bonding has been shown[11] to stabilise Meisenheimer complexes in solvents of high polarity and basicity. In solvents of low polarity and basicity such as ethyl acetate the effect should be much greater. Even without complications due to hydrogen-bonding, the idea of a cyclic transition state leads in certain cases to conceptual difficulties.

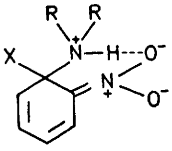

FIGURE 2

When the nucleophile is a secondary amine and the catalyst either a primary or secondary amine, unless 3-co-ordinated hydrogen is assumed the hydrogen-bond has to be broken before the cyclic transition state can be formed. For the frequently observed catalysis by tertiary amines, 3-co-ordinated hydrogen has to be assumed (Figure 3).

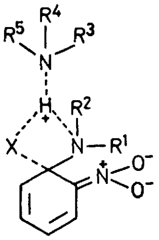

FIGURE 3

To circumvent these difficulties we propose the following modification for the base-catalysed path in solvents of low polarity. In these solvents, because of the strength and range of electrostatic forces, aggregates will be formed between the charged intermediate and any dipolar substance present in solutions, *e.g.* the nucleophile or added catalyst. With primary and secondary amines the dipoles are such that orientation can take place as shown in Figure 1. Within the aggregate, however, we do not believe that the making and breaking of bonds occur synchronously. When the nucleophile is a primary amine, as proton exchange between strong bases is a fast reaction, transfer of the proton between the two nitrogen atoms will be fast, and will be followed by the slow electrophilically catalysed breaking of the C–X bond. When the nucleophile is a secondary amine, breaking of the hydrogen bond will occur within the aggregate followed by proton exchange and the electrophilically catalysed breaking of the C–X bond.

For catalysis by tertiary amines we envisage the rapid transfer of a proton within the aggregate, followed by rearrangement inside the resulting ion-pair so that electrophilic catalysis can occur. The mechanism is essentially the Bunnett mechanism modified to fit solvents of low dielectric constant. The modifications are (i) the initial formation of suitable orientated aggregates and (ii) the occurrence of reaction within these aggregates so that the electrophilic catalyst is never produced as a separate kinetic entity.

Tetrahydrofuran has a slightly higher dielectric constant (ϵ_{25} 7.90) and is *ca.* 10^4 times more basic than ethyl acetate. The mechanism of the base-catalysed step in this solvent is most probably the same as that in ethyl acetate.

EXPERIMENTAL

Materials.—2,4-Dinitrophenyl phenyl ether, m.p. 69—70° (lit., 70°),[12] was prepared by the method of Raiford and Colbert.[13] The purification of acetonitrile[14] and dimethyl sulphoxide[15] has been described previously. Tetrahydrofuran was stored for 48 h over anhydrous sodium sulphite, dried successively with sodium hydroxide pellets and sodium wire, and then distilled. Ethyl acetate was purified by the method of Hurd and Strong.[16]

Kinetic Procedure.—All reactions were followed spectrophotometrically by the pipette procedure already described.[17]

[6/1254 *Received, 28th June,* 1976]

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[11] C. F. Bernasconi and F. Terrier, *J. Amer. Chem. Soc.*, 1975, **97**, 7458.

[12] C. F. Bernasconi, *J. Org. Chem.*, 1967, **32**, 2947.

[13] L. C. Raiford and J. C. Colbert, *J. Amer. Chem. Soc.*, 1926, **48**, 2652.

[14] J. Hirst and Khali-Ur-Rahman, *J.C.S. Perkin II*, 1973, 2119.

[15] D. Ayediran, T. O. Bamkole, and J. Hirst, *J.C.S. Perkin II*, 1974, 1013.

[16] C. D. Hurd and J. S. Strong, *Analyt. Chem.*, 1951, **23**, 542.

[17] T. O. Bamkole, C. W. L. Bevan, and J. Hirst, *Nigerian J. Sci.*, 1968, **2**, 11.