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MECHANISMS OF AROMATIC NUCLEOPHILIC SUBSTITUTION REACTIONS IN ETHYL ACETATE AND TETRAHYDROFURAN

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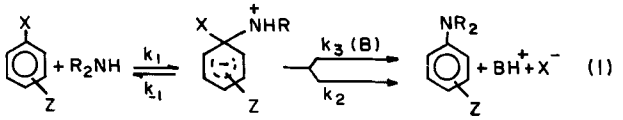
The kinetics of the reactions of 1-chloro-, 1-fluoro- and 1-phenoxy-2,4-dinitrobenzene with piperidine, n-butylamine and benzylamine, and in the case of the ether, morpholine were studied as functions of nucleophile, DABCO and pyridine concentrations in tetrahydrofuran and ethyl acetate. The reactions of the ether with n-butylamine and benzylamine in benzene were also studied as functions of nucleophile, DABCO and pyridine concentrations. A comparison with results in the literature indicated that the reactions in tetrahydrofuran and ethyl acetate resemble those in dipolar aprotic solvents when primary amines are the nucleophiles and those in aprotic solvents when the nucleophile is a secondary amine. An explanation is suggested for the observation that whereas the reactions of 1-phenoxy-2,4-dinitrobenzene with piperidine and morpholine in both tetrahydrofuran and ethyl acetate are strongly catalysed by the nucleophiles, they are not catalysed by pyridine and there is either extremely weak or no catalysis by DABCO.

INTRODUCTION

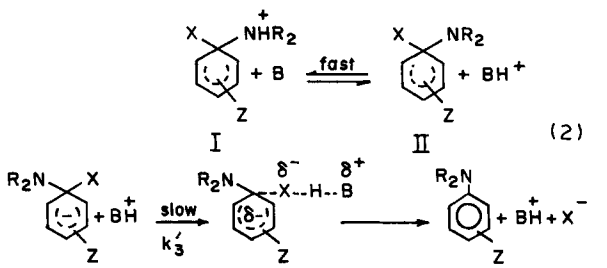
The general mechanism of aromatic nucleophilic substitution reactions when either primary or secondary amines are the nucleophiles is shown in equation (1). In dipolar aprotic solvents of high dielectric constant such as dimethyl sulphoxide, the detailed mechanism of the base-catalysed decomposition to products of the intermediate (I) is believed to be that given in equation (2), and when secondary amines are the nucleophiles the uncatalysed path is thought to proceed unimolecularly through an internally hydrogen-bonded intermediate as in structure 1.



(1)

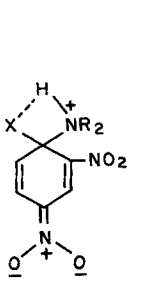
I

In aprotic solvents such as benzene and cyclohexane, Capon and Rees[1] proposed that the base-catalysed decomposition of the intermediate I takes place via a cyclic intermediate (**2**). It is only fairly recently[2] that



(2)

experimental evidence for a difference in mechanism for these reactions in the two types of solvent has been obtained, and the mechanism of the reactions in aprotic solvents is still under investigation.[3,4]



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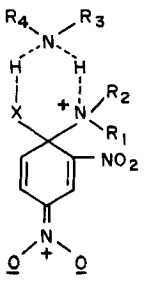

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The effect of solvent basicity on the mechanism of aromatic nucleophilic substitution reactions in dipolar aprotic solvents of high dielectric constant has been investigated,[5] but there are a group of solvents such as ethyl acetate and tetrahydrofuran, which have appreciable basicity but low dielectric constants, in which the mechanisms of these reactions have not been systematically investigated. A study has been made of several typical aromatic nucleophilic substitution reactions in tetrahydrofuran and ethyl acetate in an attempt to assess the effect of dielectric constant on their mechanisms by comparing the results in these solvents with those in acetonitrile and dimethyl sulphoxide and, where possible, benzene. As the pK_a of ethyl acetate is $-6{\cdot}5$[6] and that of tetrahydrofuran is $-2{\cdot}04$[7] but their dielectric constants are similar (ε_{25}: THF 7·58, EtOAc 6.02),[8] it was hoped that information could be obtained on the effect of solvent basicity in solvents of low dielectric constant.

RESULTS AND DISCUSSION

The results are given in Tables 1–3.

Application of the steady-state hypothesis to I in equation (1) gives

$$k_A = \frac{k_1(k_2 + k_3[B])}{k_{-1} + k_2 + k_3[B]} \qquad (3)$$

where k_A is the observed second-order rate constant and B is either an added base or a second molecule of the nucleophile. If $k_{-1} \ll k_2 + k_3[B]$, then equation (3) reduces to $k_A = k_1$, the formation of the intermediate is rate determining and the reaction is not base catalysed. If either (a) $k_{-1} \gg k_2 + k_3[B]$ when equation (3) reduces to the form $k_A = k' + k''[B]$ or (b) no simplifying assumptions can be made, then base catalysis is observed and the decomposition of the intermediate is rate limiting. Condition (a), however, requires further amplification. In many aromatic bimolecular nucleophilic substitution reactions, small linear increases in the second-order rate constant with increasing amine (or, more generally, added base) concentration are observed. The values of the ratio k''/k' are small (<5) and the accelerating effect of the bases bears no relationship to their base strength. According to Bunnett and Garst,[9] this does not represent true base catalysis, but rather the formation of the intermediate is rate determining in these reactions and the small increases are due to some unspecified effect. In other reactions an increase in base concentration has a powerful accelerating effect, the value of k''/k' is high (>50) and the catalytic effect increases with increase in strength of the base. These reactions are regarded as base catalysed and the decomposition of the intermediate is rate limiting. Although we are in general agreement with these conclusions, we believe that in solvents of low dielectric constant the criterion of the magnitude of the k''/k' ratio should be applied cautiously, as relatively low values of the ratio may still indicate base catalysis.

The reactions of 1-chloro-2,4-dinitrobenzene with piperidine, n-butylamine, morpholine[10,11] and benzylamine in tetrahydrofuran and ethyl acetate are not base catalysed, nor are the reactions of n-butylamine and benzylamine with 1-fluoro- and 1-phenoxy-2,4-dinitrobenzene. The slight linear increases in k_A with increasing nucleophile concentration observed for the reaction of 1-chloro-2,4-dinitrobenzene with benzylamine in ethyl acetate ($k''/k' = 2{\cdot}13$) and n-butylamine with the phenoxy substrate in the same solvent ($k''/k' = 4.58$) have very low values of k''/k' and are not regarded as being due to base catalysis. In all these reactions the addition of 1,4-diazabicyclo[2·2·2·]octane (DABCO) and pyridine has no effect on the rate. In this respect the two solvents are similar to dimethyl sulphoxide and acetonitrile, but differ from the present results in benzene in which reactions of the phenoxy substrate with both n-butylamine and benzylamine are base catalysed and the reactions of the fluoro substrate with these two nucleophiles are already known[12,13] to be catalysed in this solvent.

When the reactions are not base catalysed, $k_A = k_1$ and the effect of solvent variation on the rate constant for the formation of the intermediate I can be obtained. We have already shown[14] that the value of k_1 in dimethyl sulphoxide is much greater than that in acetonitrile. Comparison of the present results in tetrahydrofuran with those in acetonitrile[15,16] shows that the values in the two solvents are approximately the same, and those in tetrahydrofuran are slightly greater than in ethyl acetate by factors ranging from 1·5 to 3.

In contrast, the fluoro substrate with piperidine exhibits a strong linear dependence on the piperidine concentration in both solvents [$k''/k' = 2{\cdot}24 \times 10^3$ (THF) and $1{\cdot}55 \times 10^3$ (ethyl acetate); Nudelman *et al.*[17] give $k''/k' = 426$ for this reaction in ethyl acetate and 698 in THF at 15 °C]. This behaviour is similar to that observed in benzene[18] but differs from that in acetonitrile, where the reaction is not base catalysed.[15,17] Bamkole *et al.*[11] have shown that for the reaction of this substrate with morpholine in the two solvents k_A has a strong linear dependence on the concentration of the nucleophile. Again this is similar to the behaviour in benzene,[4,19] but differs from that in dimethyl sulphoxide, where the reaction is not base catalysed,[5] and acetonitrile, where a curvilinear dependence on the morpholine concentration has been observed.[15] The reaction between the fluoro substrate and piperidine is strongly catalysed by DABCO in both solvents [$k''/k' = 74{\cdot}3$ (THF) and 138 (ethyl acetate)] and shows a linear dependence on pyridine concentration [$k''/k' = 9{\cdot}0$ (THF) and 7.0 (ethyl acetate)]. Although the k''/k' values for pyridine are small, similar accelerations are not observed when the substrate is 1-chloro-2,4-dinitrobenzene, hence they are

Table 1. Nucleophilic substitutions on dinitrophenyl substrates ArX in THF at 30° C

Substrate/nucleophile	Base varied	[B] (M)	k_A (l mol^{-1} s^{-1})
X=Cl[a]/piperidine	Piperidine[b]	$1\cdot01-5\cdot05\times10^{-3}$	$3\cdot68\times10^{-1}$
	Pyridine[c]	$1\cdot0-5\cdot0\times10^{-2}$	$3\cdot80\times10^{-1}$
	DABCO[c]	$2\cdot0-5\cdot0\times10^{-3}$	$3\cdot67\times10^{-1}$
X=Cl[d]/n-BuNH$_2$	n-BuNH$_2$	$1\cdot12-6\cdot50\times10^{-2}$	$1\cdot02\times10^{-2}$
	Pyridine[e]	$5\cdot0-20\cdot0\times10^{-2}$	$1\cdot24\times10^{-2}$
	DABCO[e]	$0\cdot50-2\cdot0\times10^{-2}$	$1\cdot18\times10^{-2}$
X=Cl[d]/benzylamine	Benzylamine	$1\cdot02-5\cdot08\times10^{-2}$	$3\cdot56\times10^{-3}$
	Pyridine[e]	$5\cdot0-30\cdot0\times10^{-2}$	$3\cdot54\times10^{-3}$
	DABCO[e]	$0\cdot50-2\cdot0\times10^{-2}$	$3\cdot43\times10^{-3}$
X=F[f]/n-BuNH$_2$	n-BuNH$_2$[g]	$4\cdot0-12\cdot0\times10^{-4}$	$9\cdot41$
	Pyridine[h]	$5\cdot0-20\times10^{-3}$	$10\cdot2$
	DABCO[h]	$2\cdot0-30\cdot0\times10^{-4}$	$10\cdot2$
X=F[f]/benzylamine	Benzylamine[g]	$4\cdot0-14\cdot0\times10^{-4}$	$2\cdot88$
	Pyridine[i]	$5\cdot0-20\cdot0\times10^{-3}$	$3\cdot10$
	DABCO[i]	$5\cdot0-30\cdot0\times10^{-4}$	$3\cdot13$
X=F[f]/piperidine	Piperidine[g]	10^4[B]: 4·0 6·0	8·0 10·0 12·0 14·0 16·0
		k_A: 1·92 2·36	2·94 3·30 3·68 4·24 4·67
	Pyridine[j]	10^2[B]: 0·5 2·0	3·0 5·0
		k_A: 2·50 2·90	3·23 3·48
	DABCO[j]	10^3[B]: 0·4 1·0	2·0 3·0
		k_A: 2·58 2·63	2·93 3·02
X=OPh[k]/n-BuHN$_2$	n-BuNH$_2$[l]	$2\cdot0-10\cdot0\times10^{-2}$	$5\cdot27\times10^{-3}$
	Pyridine[m]	$1\cdot0-3\cdot0\times10^{-1}$	$5\cdot37\times10^{-3}$
	DABCO[m]	$2\cdot0-5\cdot0\times10^{-2}$	$5\cdot26\times10^{-3}$
X=OPh[k]/benzylamine	Benzylamine[l]	$1\cdot0-4\cdot25\times10^{-1}$	$1\cdot47\times10^{-3}$
	Pyridine[n]	$1\cdot0-3\cdot0\times10^{-1}$	$1\cdot49\times10^{-3}$
	DABCO[n]	$2\cdot0-8\cdot0\times10^{-2}$	$1\cdot47\times10^{-3}$
X=OPh[k]/piperidine	Piperidine[l]	10^2[B]: 3·34 5·04	6·0 7·06 8·0 10·0
		10^3k_A: 1·94 2·62	3·48 3·73 4·10 5·30
	Pyridine[o]	$5\cdot0-20\cdot0\times10^{-2}$	$2\cdot64\times10^{-3}$
	DABCO[o]	$3\cdot5-9\cdot8\times10^{-2}$	$2\cdot76\times10^{-3}$
X=OPh/morpholine[p,q]	Morpholine	10[B]: 1·0 2·0	3·0 4·0
		10^4k_A: 1·30 2·62	3·58 4·71
	Pyridine[r]	$5\cdot0-20\cdot0\times10^{-2}$	$1\cdot31\times10^{-4}$
	DABCO[r]	10^2[B]: 0 3·5	8·0
		10^4k_A: 1·30 1·45	1·62

[a] [Substrate]$_0 = 1\cdot31\times10^{-5}$ M.
[b] At 28·2 °C.
[c] [Piperidine] $= 3\cdot03\times10^{-3}$ M.
[d] [Substrate]$_0 = 5\cdot01-5\cdot03\times10^{-4}$ M.
[e] [Nucleophile] $= 3\cdot0\times10^{-2}$ M.
[f] [Substrate]$_0 = 1\cdot0-1\cdot30\times10^{-5}$ M.
[g] At 28·2 °C.
[h] [n-BuNH$_2$] $= 4\cdot0\times10^{-4}$ M.
[i] [benzylamine] $= 8\times10^{-4}$ M.
[j] [Piperidine] $= 6\cdot0\times10^{-4}$ M.
[k] [Substrate]$_0 = 1\cdot2-1\cdot5\times10^{-5}$ M.
[l] At 28·2 °C.
[m] [n-BuNH$_2$] $= 4\cdot0\times10^{-2}$ M.
[n] [Benzylamine] $= 1\cdot0\times10^{-1}$ M.
[o] [Piperidine] $= 5\cdot0\times10^{-2}$ M.
[p] [Substrate]$_0 = 5\cdot4\times10^{-4}$ M.
[q] At 32·0 °C.
[r] [Morpholine] $= 1\cdot0\times10^{-1}$ M.

tentatively ascribed to base catalysis. If this is so, the behaviour of this reaction in tetrahydrofuran and ethyl acetate resembles that in benzene rather than acetonitrile.[2]

The reaction between 1-phenoxy-2,4-dinitrobenzene and piperidine is strongly catalysed by piperidine in both tetrahydrofuran and ethyl acetate. In both solvents a plot of k_A against piperidine concentration is linear and passes through the origin, that is, the reactions are third order, as was observed by Pietra[20] when the reaction was carried out in benzene. Values of 461 and 542 have been recorded[16] for k''/k' for the reactions in dimethyl sulphoxide and acetonitrile, respectively. The observations of Ayediran *et al.*[10] on the reactions of morpholine with this substrate in the two solvents have been confirmed. A plot of k_A against morpholine concentration is linear and passes through the origin in ethyl acetate, but in tetrahydrofuran there is a small intercept, giving a k''/k' value of 43·4* at 32 °C. The values[10] of k''/k' for this reaction in dimethyl sulphoxide and acetonitrile are 86 and 185 and in benzene a plot of k_A against nucleophile concentration has an upward curvature and passes through the origin.[2]

* A value of 274 was mistakenly given for k''/k' at 30·5 °C in Ref. 10. The correct value is 31·6.

Table 2. Nucleophilic substitutions on dinitrophenyl substrates ArX in ethyl acetate at 30 °C

Substrate/nucleophile	Base varied	[B] (M)		k_A (l mol^{-1} s^{-1})				
X=Cl[a]/n-BuNH$_2$	n-BuNH$_2$	$2\cdot0 - 8\cdot0 \times 10^{-2}$		$4\cdot47 \times 10^{-3}$				
	Pyridine[b]	$5\cdot03-20\cdot0 \times 10^{-2}$		$4\cdot37 \times 10^{-3}$				
	DABCO[b]	$5\cdot15-20\cdot6 \times 10^{-3}$		$4\cdot41 \times 10^{-3}$				
X=Cl[a]/piperidine	Piperidine	$3\cdot12- 9\cdot0 \times 10^{-3}$		$2\cdot45 \times 10^{-1}$				
	Pyridine[c]	$1\cdot0 - 5\cdot0 \times 10^{-3}$		$2\cdot60 \times 10^{-1}$				
	DABCO[c]	$1\cdot0 - 5\cdot0 \times 10^{-3}$		$2\cdot50 \times 10^{-1}$				
X=Cl[a]/benzylamine	Benzylamine	10^2[B]: 2·0	4·0	6·0	8·0			
		$10^3 k_A$: 1·20	1·23	1·30	1·34			
X=F[d]/n-BuNH$_2$	n-BuNH$_2$	$3\cdot02- 8\cdot67 \times 10^{-4}$		$5\cdot06$				
	Pyridine[c]	$0\cdot5 - 5\cdot0 \times 10^{-2}$		$5\cdot01$				
	DABCO[c]	$0\cdot5 - 5\cdot0 \times 10^{-3}$		$5\cdot01$				
X=F[d]/benzylamine	Benzylamine	$3\cdot2 - 8\cdot85 \times 10^{-4}$		$1\cdot87$				
	Pyridine[f]	$5\cdot0 -30\cdot0 \times 10^{-3}$		$1\cdot89$				
	DABCO[f]	$0\cdot5 - 3\cdot0 \times 10^{-3}$		$1\cdot92$				
X=F[d]/piperidine	Piperidine	10^4[B]: 3·08	5·01	6·00	8·10	10·0	12·3	
		k_A: 3·60	4·35	4·87	5·44	6·46	7·07	
	Pyridine[g]	10^2[B]: 0·5	1·0	3·0	5·0			
		k_A: 3·67	3·86	4·35	4·81			
	DABCO[g]	10^3[B]: 0·5	1·0	3·0	5·0			
		k_A: 3·73	4·22	5·05	6·07			
X=OPh[h]/nBuNH$_2$	n-BuNH$_2$	10^2[B]: 2·0	4·0	6·0	8·0			
		$10^3 k_A$: 2·27	2·60	2·72	2·88			
	DABCO[i]	$1\cdot0- 8\cdot0 \times 10^{-2}$		$1\cdot99 \times 10^{-3}$				
X=OPh[h]/benzylamine	Benzylamine	$0\cdot6- 3\cdot0 \times 10^{-1}$		$4\cdot83 \times 10^{-4}$				
X=OPh[h]/piperidine	Piperidine	10^2[B]: 1·0	2·0	3·0	4·0	5·0	6·0	8·0
		$10^3 k_A$: 0·39	0·96	1·54	2·27	2·66	2·87	4·31
	Pyridine[j]	$0\cdot5-3\cdot0 \times 10^{-1}$		$1\cdot47 \times 10^{-3}$				
	DABCO[j]	10^2[B]: 1·0	3·0	5·0	8·0			
		$10^3 k_A$: 1·39	1·48	1·54	1·67			
X=OPh[h]/morpholine	Morpholine	10[B]: 1·0	2·0	3·0	4·0			
		$10^4 k_A$: 1·52	3·13	4·52	5·83			
	Pyridine[k]	$5\cdot0-20 \times 10^{-2}$		$1\cdot51 \times 10^{-4}$				
	DABCO[k]	$1\cdot0- 8\cdot0 \times 10^{-2}$		$1\cdot52 \times 10^{-4}$				

[a] [Substrate]$_0 = 3\cdot05-50\cdot3 \times 10^{-5}$ M.
[b] [n-BuNH$_2$] $= 4\cdot0 \times 10^{-2}$ M.
[c] [Piperidine] $= 3\cdot12 \times 10^{-3}$ M.
[d] [Substrate]$_0 = 3\cdot03-3\cdot39 \times 10^{-5}$ M.
[e] [n-BuNH$_2$] $= 3\cdot02 \times 10^{-4}$ M.
[f] [Benzylamine] $= 5\cdot20 \times 10^{-4}$ M.
[g] [Piperidine] $= 3\cdot08 \times 10^{-4}$ M.
[h] [Substrate]$_0 = 5\cdot0 \times 10^{-4}$ M.
[i] [n-BuNH$_2$] $= 2\cdot0 \times 10^{-2}$ M.
[j] [Piperidine] $= 3\cdot0 \times 10^{-2}$ M.
[k] [Morpholine] $= 1\cdot0 \times 10^{-1}$ M.

The effects of pyridine and DABCO on the reactions of the phenoxy substrate are surprising. The reactions with piperidine and morpholine are not catalysed by pyridine in either solvent. The reaction of piperdine in tetrahydrofuran is not catalysed by DABCO and in ethyl acetate k''/k' for this additive is only 2·9. DABCO does not catalyse the reaction with morpholine in ethyl acetate and in tetrahydrofuran its k''/k' ratio has the low value of 3.1. The lack of catalysis by DABCO cannot be due to a change of condition in equation (3) to $k_1 \ll k_2 + k_3[B]$ giving $k_A = k_1$, as the value of k_A in the presence of the catalyst would be the maximum value possible, which is not the case. It cannot be due to the operation of adverse steric effects, as both the substrate–piperidine and substrate–morpholine systems are strongly catalysed in acetonitrile.[2] The relative values of the base strengths of the nucleophiles and catalysts in tetrahydrofuran and ethyl acetate are not known but the lack of catalysis cannot be due to the relative base strengths of DABCO and nucleophile[2] as the reaction between 1-fluoro-2,4-dinitrobenzene and piperidene is strongly catalysed by DABCO in both solvents.

In the past[2,4,10] we have emphasized the importance of internuclear forces and hydrogen bonding on reactions taking place in solvents of low dielectric constant. Of the nucleophiles and catalysts used in this investigation, only the nucleophiles are capable of acting as

Table 3. Nucleophilic substitutions on 2,4-dinitrophenyl phenyl ether[a] in benzene at 30 °C

Nucleophile	Base varied	[B] (M) and k_A (l mol^{-1} s^{-1})					
n-$BuNH_2$	n-$BuNH_2$	10^2[B]:	2·0	4·0	6·0	8·0	18·0	30·0
		10^4k_A:	0·625	1·16	1·52	1·96	3·30	4·37
	Pyridine[b]	10^2[B]:	5·0	10·0	20·0	30·0		
		10^4k_A	1·82	2·22	3·15	3·95		
	DABCO[b]	10^2[B]:	1·0	3·0	5·0	8·0		
		10^4k_A:	1·62	2·25	2·53	2·80		
Benzylamine	Benzylamine	10^2[B]:	5·0	10·0	20·0	30·0		
		10^5k_A:	1·97	4·06	7·10	8·63		
	Pyridine[c]	10^2[B]:	5·0	10·0	20·0	30·0		
		10^5k_A:	4·76	5·69	7·51	9·89		
	DABCO[c]	10^2[B]:	1·0	3·0	5·0	8·0		
		10^5k_A:	4·19	5·84	6·49	7·02		

[a] $\{Substrate\}_0 = 5·0 \times 10^{-4}$ M.
[b] $[n\text{-}BuNH_2] = 4·0 \times 10^{-2}$ M.
[c] [Benzylamine] = $1·0 \times 10^{-1}$ M.

hydrogen-bond donors. In solvents of low dielectric constant a molecule of the nucleophile can become strongly hydrogen bonded to the ethereal oxygen of the intermediate I formed in these reactions when an ether is the substrate. When the substrate contains an *ortho*-nitro group, hydrogen bonding occurs in the intermediate I between the amino hydrogen atoms of the complex and the oxygen atoms of the nitro group. When secondary amines are the nucleophiles, this is the only amino hydrogen atom present and must be removed in the base-catalysed pathway. Proton transfer in hydrogen-bonded species is believed to occur in two stages:[21] first the hydrogen bond is broken, followed by proton abstraction by base. If this process occurs in the Meisenheimer complex, then a second molecule of the nucleophile, anchored on the leaving group, is most favourably situated for proton abstraction, possibly to the exclusion of all other catalysts. This effect should not occur when the substrates are fluorides as organic fluorides do not form hydrogen bonds.[22] It should be observed for similar aromatic nucleophilic substitution reactions with secondary amines in all solvents of low dielectric constant. The rate constant for the reaction of 1-phenoxy-2,4-dinitrobenzene with morpholine in benzene increases linearly with the concentration of DABCO;[2] the value of k''/k' is only 6·7, however, Spinelli *et al.*[23] concluded that they could not safely say that DABCO catalyses the reaction of piperidine with 2,4-dinitrophenyl 4-nitrophenyl ether in benzene. Their results indicate a value of k''/k' of approximately 1.5. The rate constants for the reactions of 2-methoxy-3-nitrothiophene with perhydroazepine, pyrrolidine and piperidine in benzene increase linearly with increasing DABCO concentration.[24] The k''/k' values for this catalyst are 7·7 (perhydroazepine), 4·4 (pyrrolidine) and 7·5 (piperidine).

If the uncatalysed decomposition of the intermediate I takes place unimolecularly as in structure **1**, then hydrogen bonding of the nucleophile to the leaving group should enhance k_3 at the expense of k_2, giving rise to large values of k_3/k_2 ($=k''/k'$ when the base is the nucleophile). Generally, this is observed. Plots of k_A against nucleophile concentrations pass through the origin in the following reactions: 2,4-dinitrophenyl cyclohexyl ether with piperidine in benzene;[25] 2-phenoxy-1,3,5-triazene with piperidine in isooctane;[26] 2-methoxy-3-nitrothiophene with piperidine[27] and perhydroazepine[24] in benzene; 1-phenoxy-2,4,6-trinitrobenzene with morpholine in benzene;[28] 1,3-dinitro-2-phenoxybenzene with piperidine and morpholine in benzene;[29] 3,5-dinitro-2-phenoxypridine with morpholine in benzene;[29] 1-methyl-3,5-dinitro-2-phenoxybenzene with piperidine and morpholine in benzene;[29] and 2,4,6,4′-tetranitrodiphenyl ether with *N*-methylaniline in benzene.[29] Consiglio *et al.*[24] give $k_2/k_{-1} = 0$ and $k_3/k_{-1} = 0·70$ l mol^{-1} for the reaction of pyrrolidine with 2-methoxy-3-nitrothiophene in benzene, and $k''/k' = 579$ for the reaction of 1-phenoxy-2,4,6-trinitrobenzene with piperidine in benzene.[28] Comparatively low values of the ratio are known. Apart from the value of 43·9 recorded above for the reaction of 1-phenoxy-2,4-dinitrobenzene with morpholine in tetrohydrofuran, the value for the reaction of 2,4-dinitrophenyl 4-nitrophenyl ether with piperidine in benzene is given as 44.[23]

The above arguments apply to secondary amines but may not have the same force when the nucleophile is a primary amine. In secondary amines, as there is only one amino hydrogen atom available which is hydrogen bonded to the *ortho*-nitro group, this must necessarily be the one which is eliminated. With primary amines a second amino hydrogen atom is available and it is pos-

sible that the requirements of amino group–*ortho*-nitro group hydrogen bonding result in conformers in which this second hydrogen atom is poorly placed for attack by a molecule of the nucleophile attached to the oxygen atom of the leaving group and thus is available for elimination by tertiary (and other) bases. For secondary amines the proposal gives a plausible mechanism for the formation of the cyclic transition state that is often postulated for the base-catalysed path of aromatic nucleophilic substitution reactions in aprotic solvents.

The comparisons of the kinetic forms of the reactions in tetrahydrofuran and ethyl acetate with those in dipolar aprotic and aprotic solvents indicate that these solvents resemble dipolar aprotic solvents when primary amines are the nucleophiles and aprotic solvents when the reagent is a secondary amine. We have presented evidence[14] that in dipolar aprotic solvents, when primary amines are the nucleophiles, the mechanism of the uncatalysed decomposition of the intermediate I to products is similar to that given in equation (2), with a molecule of solvent replacing that of base. Tetrahydrofuran and ethyl acetate are probably sufficiently basic to overcome the effect of decreasing dielectric constant and allow this mechanism to operate, with the condition $k_{-1} \ll k_2 + k_3[B]$.

The results for secondary amines can be accommodated by assuming that the value of k_2/k_{-1} decreases with decreasing dielectric constant. If, for these amines, the uncatalysed decomposition of the intermediate I takes place via the cyclic transition state given in structure **1**, k_2 would be relatively insensitive to changes in solvent compared with k_{-1} which refers to a process in which an appreciable decrease in charge has taken place in the transition state and will be accelerated by decrease in dielectric constant.

EXPERIMENTAL

Tetrahydrofuran was treated successively with sodium sulphite, sodium hydroxide and sodium wire and then distilled, the fraction with b.p. 64 °C being collected. Ethyl acetate was washed with 5% sodium carbonate, then saturated with sodium chloride solution and dried initially over potassium carbonate followed by phosphorus pentoxide. Distillation from phosphorus pentoxide gave a fraction with b.p. 77 °C, which was collected. The purification of all other materials has been described previously.[4,16]

The kinetics of the slower reactions were investigated using a pipette technique,[30] in which aliquots of the reaction mixture were pipetted into calibrated flasks containing methanol 1·0 M in sulphuric acid. The volume was made up to the mark and the absorbance measured at the appropriate wavelength. Faster reactions were followed in the thermostated cell compartment of either an SP 30 or SP-8-400 spectrophotometer. The concentrations of the nucleophiles in all instances were at least ten times those of the substrates and the reactions were followed to 60–70%. The first-order rate constants so obtained had a standard error not greater than 2%.

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