

Catalysis by Amine Salts of Some Aromatic Nucleophilic Substitution Reactions

Jack Hirst* and Ikenna Onyido

Department of Chemistry, University of Ibadan, Ibadan, Nigeria

The reaction of 1-chloro-2,4-dinitrobenzene with aniline in acetonitrile is catalysed by R_4NY where Y is Cl, Br, I, or toluene-*p*-sulphonate, but not by 1,4-diazabicyclo[2.2.2]octane (DABCO). When the nucleophile is changed to *n*-butylamine or morpholine, addition of tetraethylammonium chloride has only a small effect; the reactions of all three nucleophiles are not catalysed by tetraethylammonium perchlorate. The reaction of 1-fluoro-2,4-dinitrobenzene with aniline is strongly catalysed by tetraethylammonium chloride, to a lesser extent by the bromide and toluene-*p*-sulphonate and also by trimethylamine hydrochloride, but not by tetraethylammonium perchlorate. The reactions of morpholine with 1-fluoro-2,4-dinitrobenzene and piperidine with 2,4-dinitrophenyl phenyl ether are not catalysed by amine salts. The results are consistent with the formation and stabilisation of the intermediate formed in aromatic nucleophilic substitution reactions by the anions of the salts, when the nucleophile is aniline.

Base catalysis in aromatic nucleophilic substitution reactions when the nucleophile is a primary or secondary amine is usually explained in terms of the mechanism given in Scheme 1. Application of the steady state hypothesis gives equation (1) where k_A is the observed second-order rate constant. Either the formation or decomposition to products of the

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

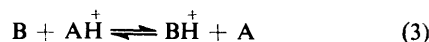
intermediate (I) can be rate determining. If $k_{-1} \ll k_2 + k_3[B]$ then $k_A = k_1$, the formation of the intermediate is rate determining and no base catalysis is observed. If this condition does not hold, decomposition to products is rate limiting and the kinetic form depends on the relative magnitudes of k_{-1} and $k_2 + k_3[B]$. If $k_{-1} \gg k_2 + k_3[B]$ equation (1) simplifies to $k_A = k' + k''[B]$. Many cases are known, however, in which there are slight linear increases in k_A with the concentration of the catalysts for which k''/k' is small and the effectiveness of the catalyst bears no relationship to its base strength. In these cases true base catalysis is believed not to occur and the increases are due to some unspecified effect.¹ Where no simplification of equation (1) can be made a curvilinear dependence of k_A on the concentration of the base is obtained.

When the reactions are carried out in dipolar aprotic solvents the intimate mechanism for the catalysed decomposition of the intermediate is believed to be that proposed by Bunnett and Davies² and given in Scheme 2. In this mechanism the first formed intermediate is rapidly and reversibly converted into its conjugate base from which the slow electrophilically catalysed expulsion of the leaving group takes place. As is shown by equation (2) there is no order with

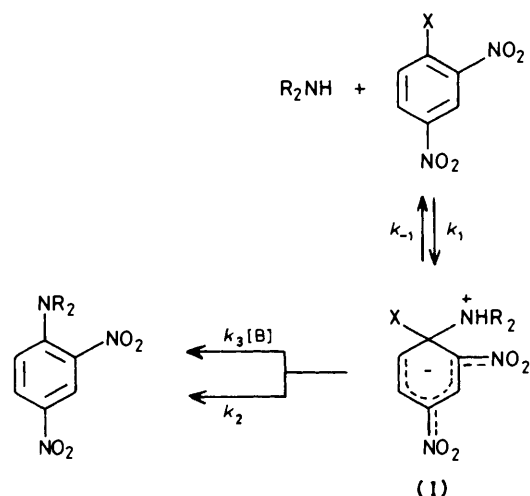
$$\frac{d}{dt} [\text{products}] = k'_3[(\text{II})][\text{BH}^+] = k'_3K[(\text{I})][\text{B}] \quad (2)$$

$$\text{where } K = \frac{[(\text{II})][\text{BH}^+]}{[(\text{I})][\text{B}]}$$

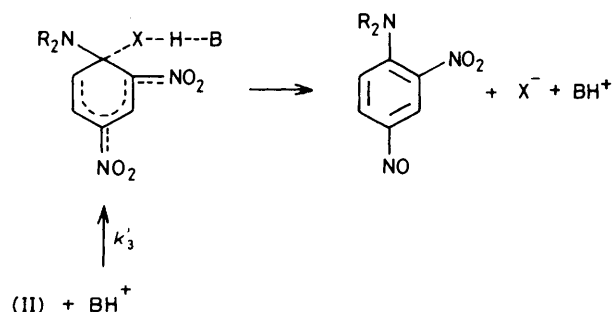
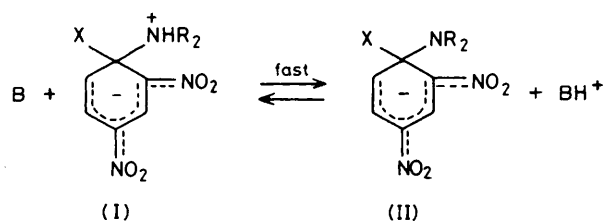
respect to the conjugate acid of the base, but the addition of other electrophiles should give a measurable kinetic effect. As in this type of solvent the base B is almost invariably an amine, usually a second molecule of the nucleophile, the addition of other amine salts AH^+ results in equilibrium (3),



a second nucleophile is introduced into the system and the



Scheme 1.



Scheme 2.

kinetics are difficult to interpret. Although this latter effect can be overcome by using trimethylamine salts, because the nucleophilic reactions of trimethylamine with 2,4-dinitrobenzene substrates are extremely slow at *ca.* 30 °C, corrections still have to be applied in the majority of cases for the existence of the equilibrium. The different basicities of aniline pK_a 10.56 and trimethylamine pK_a 17.61³ in acetonitrile is sufficient for the equilibrium to be almost entirely in the aniline direction and, as we have already shown⁴ that in this solvent the reaction between aniline and 1-fluoro-2,4-dinitrobenzene is base catalysed, we studied the effect of trimethylamine hydrochloride on this reaction. Although catalysis was found, the observation of a much greater catalytic effect by tetraethylammonium chloride led us to a more extensive study of the effect of amine salts on the aminodehalogenation of 1-fluoro- and 1-chloro-2,4-dinitrobenzenes. The results are given in the Table.

We have shown previously⁴ that the reaction of 1-chloro-2,4-dinitrobenzene with aniline in acetonitrile is not catalysed by aniline and the present results show it is not catalysed by

Table. Effect of the addition of amine salts on the rate constants ($l\ mol^{-1}\ s^{-1}$) at 30 °C of some aromatic nucleophilic substitution reactions in acetonitrile

1 Reaction of 1-chloro-2,4-dinitrobenzene^a with aniline^b

A In the presence of tetraethylammonium chloride (Et_4NCl)

$10^3[Et_4NCl]/M$	5.94	11.9	27.0
10^6k_A	7.03	17.7	27.6 51.7

B In the presence of tetraethylammonium bromide (Et_4NBr)

$10^3[Et_4NBr]/M$	5.44	10.6	23.7
10^6k_A	7.03	9.75	12.0 17.3

C In the presence of tetraethylammonium iodide (Et_4NI)

$10^3[Et_4NI]/M$	8.95	19.5	50.5
10^6k_A	7.03	9.23	17.7 33.5

D In the presence of tetramethylammonium toluene-*p*-sulphonate (Me_4NT)

$10^3[Me_4NT]/M$	3.58	8.74	18.5
10^6k_A	7.03	8.31	9.52 12.2

E In the presence of DABCO

$10^2[DABCO]/M$	1.54	3.46	5.86
10^6k_A	7.03	7.82	8.84 9.72

F In the presence of water (at 30.3 °C)

$10^4[H_2O]/M$	3.56	8.88	17.8
10^6k_A	7.33	7.47	7.45

G In the presence of tetraethylammonium perchlorate (Et_4NClO_4)

$10^3[Et_4NClO_4]/M$	6.03	19.4	32.3
10^6k_A	7.03	7.28	7.50 7.78

^a $[Cloro]_0$ 3.12—4.28 $\times 10^{-4}M$. ^b $[PhNH_2]_0$ 1.00 $\times 10^{-1}M$.

2 Reaction of 1-chloro-2,4-dinitrobenzene^a with morpholine^b

A In the presence of tetraethylammonium chloride (Et_4NCl)

$10^3[Et_4NCl]/M$	5.31	11.7	21.3
10^2k_A	4.89	5.02	5.22 5.51

B In the presence of tetraethylammonium perchlorate (Et_4NClO_4)

$10^3[Et_4NClO_4]/M$	5.29	21.1	32.4
10^2k_A	4.89	4.92	4.95 4.91

^a $[Cloro]_0$ 3.30 $\times 10^{-4}M$. ^b $[Morpholine]_0$ 2.04 $\times 10^{-2}M$.

Table (continued)

3 Reaction of 1-chloro-2,4-dinitrobenzene^a with *n*-butylamine^b

A In the presence of tetraethylammonium chloride (Et_4NCl)

$10^3[Et_4NCl]/M$	5.97	14.0	30.9
10^2k_A	1.26	1.36	1.40 1.59

B In the presence of tetraethylammonium perchlorate (Et_4NClO_4)

$10^3[Et_4NClO_4]/M$	8.31	16.4	29.6
10^2k_A	1.26	1.21	1.25 1.27

^a $[Cloro]_0$ 3.02 $\times 10^{-4}M$. ^b $[Bu^oNH_2]_0$ 2.07 $\times 10^{-2}M$.

4 Reaction of 2,4-dinitrophenyl phenyl ether^a with piperidine^b

A In the presence of tetraethylammonium chloride (Et_4NCl)

$10^3[Et_4NCl]/M$	4.81	8.88	20.2	30.1
10^3k_A	6.52	6.44	6.46	6.34 6.62

^a $[Ether]_0$ 2.99 $\times 10^{-4}M$. ^b $[Piperidine]_0$ 8.59 $\times 10^{-3}M$.

5 Reaction of 1-fluoro-2,4-dinitrobenzene^a with morpholine^b

A In the presence of tetraethylammonium chloride (Et_4NCl)

$10^3[Et_4NCl]/M$	3.33	11.4	26.7
$10k_A$	6.48	6.57	6.41 6.40

B In the presence of tetraethylammonium bromide (Et_4NBr)

$10^3[Et_4NBr]/M$	6.57	12.6	20.1
$10k_A$	6.74	6.81	6.75 6.79

C In the presence of tetramethylammonium toluene-*p*-sulphonate (Me_4NT)

$10^3[Me_4NT]/M$	6.48	10.4	16.5
$10k_A$	6.74	6.80	6.58 6.80

^a $[Fluoro]_0$ 5.14 $\times 10^{-5}M$. ^b $[Morpholine]_0$ 5.50—5.62 $\times 10^{-4}M$

6 Reaction of 1-fluoro-2,4-dinitrobenzene^a with aniline^b

A In the presence of trimethylamine hydrochloride (Me_3NHCl)

$10^3[Me_3NHCl]/M$	5.49	13.1	25.3	31.1	42.8
10^4k_A	2.02	3.64	5.71	7.95	9.80 12.4

B In the presence of aniline hydrochloride ($PhNH_3Cl$)

$10^3[PhNH_3Cl]/M$	1.47	3.21 ^c
10^4k_A	2.02	2.00 2.15

C In the presence of tetraethylammonium chloride (Et_4NCl)

$10^3[Et_4NCl]/M$	5.60	9.49	15.9	24.1	36.0
10^4k_A	2.02	9.25	13.9	21.4	28.1 30.7

D In the presence of tetraethylammonium bromide (Et_4NBr)

$10^3[Et_4NBr]/M$	5.80	9.96	20.5	22.2
10^4k_A	2.02	3.07	3.61	5.53 5.87

E In the presence of tetramethylammonium toluene-*p*-sulphonate (Me_4NT)

$10^3[Me_4NT]/M$	2.14	4.27	6.40	10.7	17.9
10^4k_A	2.02	2.26	2.91	3.34	4.47 6.30

F In the presence of tetraethylammonium perchlorate (Et_4NClO_4)

$10^3[Et_4NClO_4]/M$	7.18	16.0	32.6
10^4k_A	2.02	1.92	1.91 1.92

^a $[Fluoro]_0$ 3.21 $\times 10^{-4}M$. ^b $[PhNH_2]_0$ 0.10M. ^c Limit of solubility of aniline hydrochloride.

1,4-diazabicyclo[2.2.2]octane (DABCO). The very slight linear increase in the rate constant with the addition of DABCO gives a value of k''/k' *ca.* 0.15 and cannot be interpreted as

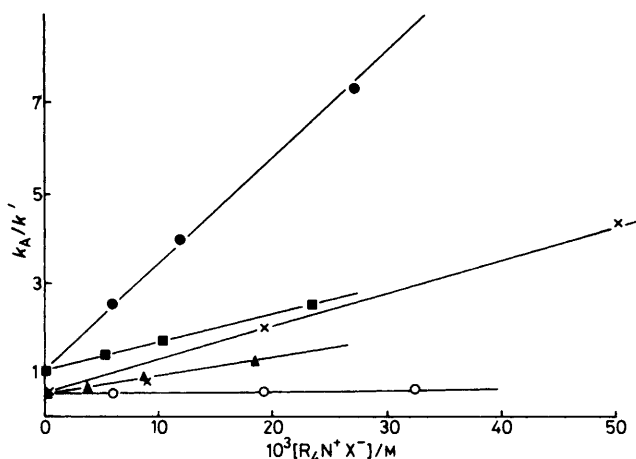


Figure 1. Plots illustrating the influence of added quaternary ammonium salts $\text{Et}_4\text{N}^+\text{Y}^-$ on the reaction of aniline with 1-chloro-2,4-dinitrobenzene in acetonitrile at 30 °C. $\text{Y} = \bullet, \text{Cl}^-; \blacksquare, \text{Br}^-; \times, \text{I}^-; \blacktriangle, p\text{-MeC}_6\text{H}_4\text{SO}_3^-; \circ, \text{ClO}_4^-$. Values of k_A/k' for $\text{Y} = \text{I}^-, p\text{-MeC}_6\text{H}_4\text{SO}_3^-$, and ClO_4^- are depressed by 0.5 unit

base catalysis. Figure 1 shows that the addition of quaternary ammonium salts ($\text{R}_4\text{N}^+\text{Y}^-$) produces substantial linear accelerations for $\text{Y} = \text{Cl}$ ($k''/k' 240$), Br ($k''/k' 62.5$), I ($k''/k' 75$), and toluene-*p*-sulphonate ($k''/k' 40$), but not for $\text{Y} = \text{ClO}_4$. When the nucleophile is changed to morpholine or *n*-butylamine, addition of tetraethylammonium perchlorate again has no effect on the rate constant, but now the addition of the chloride has only a small effect, k''/k' values of *ca.* 8 (morpholine) and 10 (*n*-butylamine). It has been shown previously⁵ that the reaction of the substrate with both these nucleophiles is not base catalysed.

In the anilinodechlorination reaction, the lack of catalysis by aniline and by DABCO indicates that the formation of the intermediate is rate determining, and the insensitivity of the reaction to the addition of small amounts of water shows that the accelerations observed on addition of quaternary ammonium salts are not due to any traces of water associated with these salts. The absence of catalysis by tetraethylammonium perchlorate shows that they are not due to ionic-strength effects on reactions between two neutral reagents proceeding *via* a charged transition state. The most likely explanation is that the anion of the salt stabilises the transition state for the formation of the first intermediate by hydrogen bonding, as is shown in Figure 2, one of the amino hydrogen atoms hydrogen bonds with the *ortho*-nitro group and the other with the anion. That a termolecular process is quite likely under the conditions used and accounts satisfactorily for the known facts is demonstrated below.

The mechanism given in Scheme 3, occurring concurrently with that in Scheme 1 (with $k_2 + k_3[\text{B}] \gg k_1$) gives a rate equation of the form given in equation (4), which requires a

$$k_A = k_0 + k[\text{Y}^-] \quad (4)$$

linear dependence of the measured rate constant on the anion concentration, as is found experimentally.* The transition state for these reactions is believed to be very close to the zwitterionic intermediate.⁷ Bernasconi *et al.*⁸ have shown that

* In Figure 1 relative rates are plotted against the concentrations of quaternary ammonium salts. Grimsrud and Kratochvil have shown⁶ that 10^{-3}M solutions of $\text{Et}_4\text{N}^+\text{Cl}^-$ in acetonitrile are *ca.* 99% dissociated, hence $[\text{Et}_4\text{NCl}] \text{ca. } [\text{Cl}^-]$.

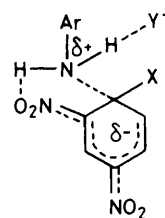
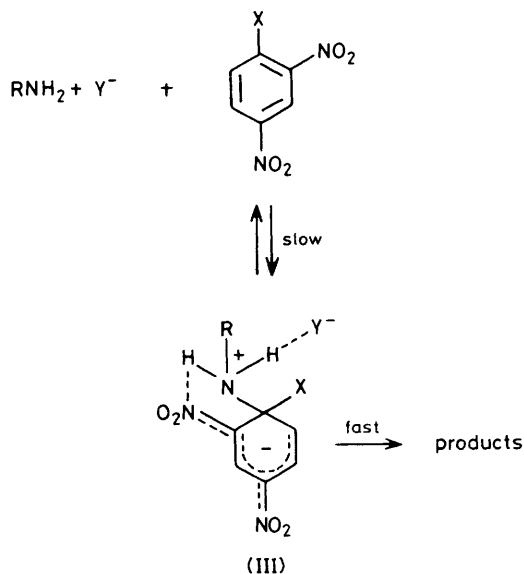


Figure 2. Stabilisation of transition state for formation of first intermediate by hydrogen bonding



Scheme 3.

the Meisenheimer complexes formed from 1,3,5-trinitrobenzene and primary and secondary amines are 100–400 times less basic than the nucleophiles from which they are derived and a difference of at least this order of magnitude would be expected between (II) and the nucleophile. As the $\text{p}K_a$'s of HCl ³ and aniline in acetonitrile are 8.9 and 10.56, respectively, intermediate (I) is probably more acidic than HCl and as the equilibrium constant for $\text{HCl} + \text{Cl}^- \rightleftharpoons \text{HCl}_2^-$ is 200,⁹ (I) will be very largely hydrogen bonded to chloride ion at equilibrium. The equilibrium constants for amine–ammonium ion homoconjugation $\text{BH}^+ + \text{B} \rightleftharpoons (\text{BH} \cdots \text{B})^+$, where B represents the amine, are at least ten times smaller, indicating that chloride ion is a much better hydrogen-bond acceptor than amines. Bromide, iodide, and toluene-*p*-sulphonate ions are all less basic than chloride ion and their catalytic effect would be expected to be less.

When morpholine and *n*-butylamine are the nucleophiles, the values of their $\text{p}K_a$'s in acetonitrile³ of 16.6 and 18.26 indicate that their amino hydrogen atoms are very much less acidic in the transition state than those of aniline and consequently their reactions are much less prone to catalysis. With morpholine, hydrogen bonding in the transition state between its only amino hydrogen atom and the *ortho*-nitro group also occurs, and when the nucleophile is *N*-methyl-aniline, where this type of bonding has been postulated to be strong,¹⁰ k''/k' values of 8.9 and 4.1 have been obtained¹¹ for tetraethylammonium chloride and perchlorate, indicating that any catalysis by chloride ion, if indeed it does occur, is slight.

Hydrogen bonding has been postulated by Ross¹² to

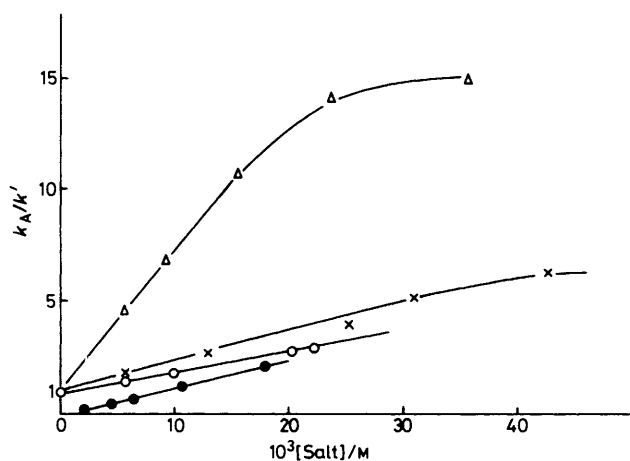


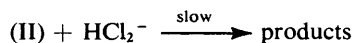
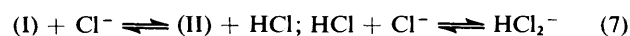
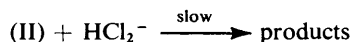
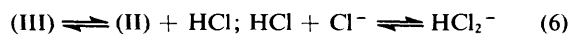
Figure 3. Plots illustrating the influence of added alkylammonium salts on the reaction of aniline with 1-fluoro-2,4-dinitrobenzene in acetonitrile at 30 °C: Δ , $\text{Et}_4\text{N}^+\text{Cl}^-$; \times , $\text{Me}_3\text{NH}^+\text{Cl}^-$; \circ , $\text{Et}_4\text{N}^+\text{Br}^-$; \bullet , $\text{Me}_4\text{N}^+-\text{O}_3\text{SC}_6\text{H}_4\text{Me-}p$. Values of k_A/k' for $\text{Me}_4\text{N}^+-\text{O}_3\text{SC}_6\text{H}_4\text{Me-}p$ are depressed by 1 unit

explain the mild catalysis he observed by *n*-butylamine and benzyltrimethylammonium nitrate of the reaction of *n*-butylamine with 1-chloro-2,4-dinitrobenzene in chloroform. He believed that this may have arisen from equilibrium (5),



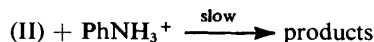
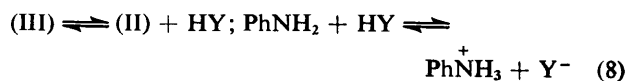
giving a hydrogen bonded complex that would be a better nucleophile than the amine itself. In the present system we specifically reject the idea of a pre-equilibrium as we know of no evidence for complex formation between halide ions and unprotonated amines. Bernasconi and Zollinger¹³ reported that the reaction of 1-chloro-2,4-dinitrobenzene with *p*-anisidine in benzene is strongly catalysed by DABCO, and Lamm and Lammert¹⁴ extended the study to include the leaving groups Br^- , PhSO_2^- , and MeSO^- . Both groups of workers interpreted the effect of DABCO as base catalysis of the reaction of intermediate to products. Rappoport and Bunnett,¹⁵ however, have pointed out that among other interpretations, the results could signify a rate-determining initial step that is catalysed by DABCO hydrogen-bonding with the acidic hydrogens of the anisidine amino group in the transition state. We believe, however, that the present results are the first clear demonstration of strong catalysis of the first step of an aromatic nucleophilic substitution reaction.

Figure 3 shows that the addition of tetraethylammonium chloride catalyses the reaction of 1-fluoro-2,4-dinitrobenzene with aniline in a curvilinear fashion, a kinetic form that is not explicable in terms of Scheme 3. The reaction is known to have a curvilinear dependence on both aniline⁴ and DABCO¹⁶ concentrations indicating that the decomposition of intermediate to products is rate limiting. As chloride ion is not very much of a weaker base than aniline in acetonitrile, the curvature can be accounted for by either of the two mechanisms (6) and (7). Most probably these mechanisms and the one given in Scheme 2 occur concurrently.



A similar abstraction of a proton from a tetrahedral intermediate by chloride ion has been suggested by Kevill and Foss¹⁷ to explain the large acceleration produced by the addition of tetraethylammonium chloride on the rate of reaction of methanol with *p*-nitrobenzoyl chloride in acetonitrile.

When the anion of the tetraethylammonium salt is changed to bromide or toluene-*p*-sulphonate, the catalysis is a linear function of the concentration of the salt. This requires that the rate-determining breakdown to products of the catalytically formed intermediate proceeds by the mechanisms given in sequence (8). This change in mechanism when the



anion of the salt is changed, the absence of catalysis by tetraethylammonium salts when the nucleophile is morpholine,* and the reaction of piperidine* with 2,4-dinitrophenyl phenyl ether are explicable in terms of the equilibrium $\text{BH}^+ + \text{Y}^- \rightleftharpoons \text{B} + \text{HY}$.

The $\text{p}K_a$ values of morpholine, piperidine, hydrogen bromide, and toluene-*p*-sulphonic acid in acetonitrile of 16.6,³ 18.9,³ 5.5,³ and approximately 7, respectively, are such that when B is morpholine or piperidine for all Y and when B is aniline and Y is Br or toluene-*p*-sulphonate, the equilibrium lies almost entirely on the left and the only effective electrophilic catalyst is the amine salt. These are examples of the phenomenon, to which we have drawn attention,¹⁶ that in acetonitrile, catalysis by an added base B is not observed if B is a much weaker base than the nucleophile.

The big difference in the catalytic effects of tetraethylammonium chloride and trimethylamine and aniline hydrochlorides is due to the large decrease in the degree of dissociation that occurs in acetonitrile when the alkyl groups of quaternary ammonium salts are replaced by hydrogen. The investigation of the very slight catalytic effect of aniline hydrochloride could not be extended to higher salt concentrations because of the low solubility of this compound in acetonitrile.

Experimental

Details of the purification of the substrates, nucleophiles, DABCO, and acetonitrile and the procedure for the spectrophotometric determination of the rates of formation of the products of the reaction have already been given.¹⁶ When runs were carried out in the presence of tetraethylammonium iodide, the reaction was stopped by dilution with methanol instead of the usual sulphuric acid-methanol mixture to avoid the formation of iodine, which occurs rapidly under acidic conditions.

Tetramethylammonium toluene-*p*-sulphonate was prepared by shaking an aqueous solution of a commercial sample of tetramethylammonium bromide with excess of silver(I) oxide. The solution was filtered and the filtrate titrated with aqueous toluene-*p*-sulphonic acid to a phenolphthalein endpoint and then evaporated almost to dryness. The solid was recrystallised twice from 1 + 1 methanol-acetonitrile mixture and dried *in vacuo* at 79 °C. Tetraethylammonium bromide

* In acetonitrile, the reaction of 1-fluoro-2,4-dinitrobenzene with morpholine is catalysed by morpholine⁵ and DABCO¹⁶ and that of the ether with piperidine is catalysed by both piperidine¹⁸ and DABCO.¹⁶

was prepared by refluxing ethyl bromide with triethylamine in acetone and recrystallised twice from a 1 + 1 methanol-ether mixture. The preparation and purification of tetraethylammonium chloride and iodide have already been described.¹⁹ Tetraethylammonium perchlorate and triethylamine hydrochloride were commercial samples recrystallised twice from a methanol-ether solvent mixture.

Acknowledgements

We thank Professors P. Ahlberg, C. A. Bunton, and C. D. Ritchie for most helpful communications.

References

- 1 J. F. Bunnett and R. H. Garst, *J. Am. Chem. Soc.*, 1965, **87**, 3875.
- 2 J. F. Bunnett and G. T. Davies, *J. Am. Chem. Soc.*, 1960, **82**, 665.
- 3 J. F. Coetzee, *Prog. Phys. Org. Chem.*, 1967, **4**, 45.
- 4 T. O. Bamkole, J. Hirst, and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1317.
- 5 D. Ayediran, T. O. Bamkole, and J. Hirst, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1396.
- 6 E. P. Grimsrud and B. Kratochvil, *J. Am. Chem. Soc.*, 1973, **95**, 4477.
- 7 J. Hirst and Khali-Ur-Rahman, *J. Chem. Soc., Perkin Trans. 2*, 1973, 2119.
- 8 C. F. Bernasconi, M. C. Muller, and P. Schmid, *J. Org. Chem.*, 1979, **44**, 3189.
- 9 I. M. Kolthoff, S. Bruckenstein, and M. K. Chatooni, Jr., *J. Am. Chem. Soc.*, 1961, **83**, 3927.
- 10 J. Kavalek, J. Kubies, and V. Sterba, *Collect. Czech. Chem. Commun.*, 1972, **37**, 4041.
- 11 T. O. Bamkole, J. Hirst, and G. Hussain, unpublished work.
- 12 S. D. Ross, *Tetrahedron*, 1969, **25**, 4427.
- 13 C. F. Bernasconi and H. Zollinger, *Helv. Chim. Acta*, 1966, **49**, 2570.
- 14 B. Lamm and J. Lammert, *Acta Chem. Scand., Ser. B*, 1973, **27**, 191.
- 15 Z. Rappoport and J. F. Bunnett, *Acta Chem. Scand., Ser. B*, 1974, **28**, 478.
- 16 T. O. Bamkole, J. Hirst, and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1982, 889.
- 17 D. N. Kevill and F. D. Foss, *J. Am. Chem. Soc.*, 1969, **91**, 5054.
- 18 D. Ayediran, T. O. Bamkole, J. Hirst, and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1580.
- 19 T. O. Bamkole, J. Hirst, and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1981, 1201.

Received 6th April 1983; Paper 3/536