Catalysis of the Aromatic Nucleophilic Substitution Reactions of Anilines in Aprotic Solvents

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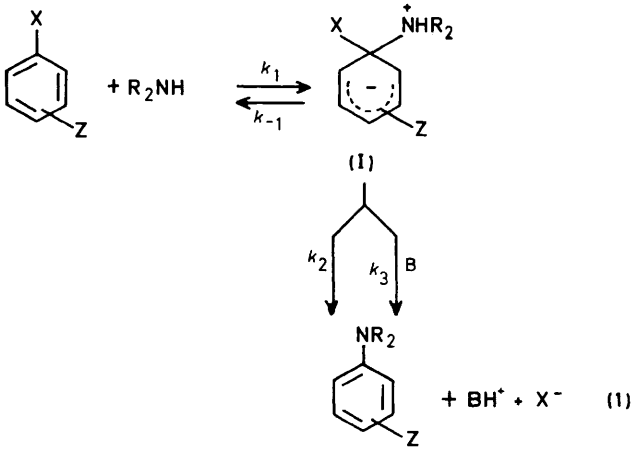
The reaction of 1-chloro-2,4-dinitrobenzene with *p*-anisidine in benzene is catalysed by the nucleophile and by tetra-n-butylammonium chloride. When the nucleophile is *N*-methyl-*p*-anisidine the reaction is not catalysed by the nucleophile, tetra-n-butylammonium chloride, DABCO, or pyridine. The reactions of both *p*-anisidine and *N*-methyl-*p*-anisidine with 1-fluoro-2,4-dinitrobenzene have been shown to be catalysed by the nucleophile, tetra-n-butylammonium chloride, and (in the case of *N*-methyl-*p*-anisidine) by DABCO and pyridine. Mechanisms are proposed to rationalize the results.

The gross mechanism of aromatic nucleophilic substitution reactions when either primary or secondary amines are the nucleophiles is given in equation (1).[1] Application of the steady-state hypothesis gives equation (2), where k_A is the observed

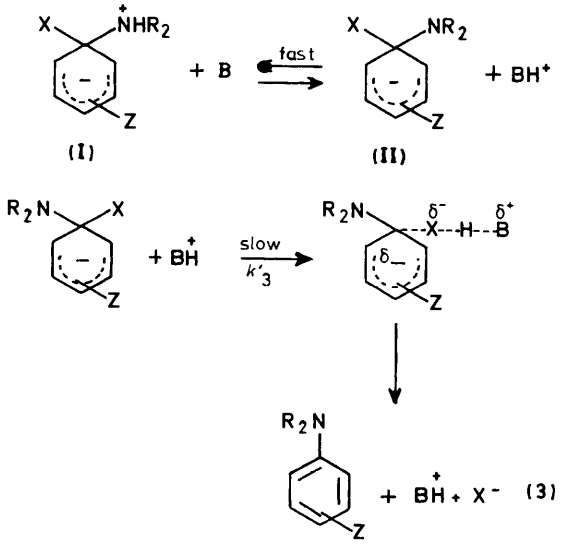


$$k_A \frac{k_1(k_2 + k_3[B])}{k_{-1} + k_2 + k_3[B]} \quad (2)$$

second-order rate constant and B is either a second molecule of the nucleophile or an added base. According to equation (2) one of three kinetic forms should be observed: (i) when $k_{-1} \ll k_2 + k_3[B]$, $k_A = k_1$ and no catalysis is observed, (ii) $k_{-1} \gg k_2 + k_3[B]$, $k_A = k_1(k_2 + k_3[B])/k_{-1}$ and k_A has a linear dependence on the concentration of B, and (iii) no simplification is possible, k_A has a curvilinear (concave downwards) dependence on the concentration of B.

In dipolar aprotic solvents of high dielectric constant such as acetonitrile the detailed mechanism of the base-catalysed decomposition to products of the intermediate formed in equation (1) is believed to be that given in equation (3).

In aprotic solvents such as benzene, however, presumably because of the inability of these solvents to stabilize the charges required by equation (3), the mechanism has been thought to be different.[2] It is only recently, though, that a difference in mechanism between the two types of solvent has been shown experimentally,[3] but the demonstration did not establish the mechanism in aprotic solvents such as benzene. Before a



systematic investigation of the mechanisms of these reactions in aprotic solvents can be undertaken there are some apparent anomalies which need to be cleared up. One of them is the reaction of 1-chloro-2,4-dinitrobenzene with *p*-anisidine in benzene.

Chloride ion is a very good leaving group and there are only two known examples of aromatic nucleophilic substitution in which the reactions of a chloro substrate is base catalysed. The first involves imidazole as a nucleophile. The reactions of 1-chloro-2,4-dinitrobenzene in chloroform and benzene[4] and of picryl chloride in chloroform[5] with this nucleophile are catalysed by imidazole and 1,4-diaza[2.2.2]bicyclo-octane (DABCO). This catalysis has been rationalized[4] as arising from special structural effects present in the imidazole molecule.

The second is the reaction between 1-chloro-2,4-dinitrobenzene and *p*-anisidine in benzene. Bernasconi and Zollinger[6] have shown that the second-order rate constant for this reaction increases linearly with increasing concentrations of *p*-anisidine, pyridine, and DABCO. The kinetic form could be explained by the reaction of a more reactive species formed in a pre-equilibrium of the type (4). As we have already shown[7] that the reaction of picryl chloride with aniline in benzene over a range of aniline concentrations (1—50 × 10^{-2}M) is not base

$$R_2NH + R'_2NH \rightleftharpoons R_2N\overset{H}{\cdots}\underset{H}{\cdots}NR'_2 \quad (4)$$

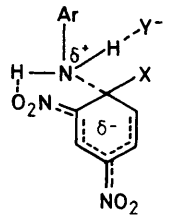


Figure 1.

Table 1. Rate constants (l mol^{-1} s^{-1}) for the reactions of 1-chloro- and 1-fluoro-2,4-dinitrobenzene with *p*-anisidine in benzene at 30.0 °C and in the presence of various additives

A 1-Chloro-2,4-dinitrobenzene[a]					
10[*p*-Anisidine]/M	1.00	2.00	2.51	3.25	4.00
$10^6 k_A$	2.09	3.11	3.63	3.98	4.73
In the presence of tetra-n-butylammonium chloride					
10^4[Bu^n_4NCl]/M	1.05	3.15	4.20	5.25	
$10^6 k_A$	8.68	22.4	29.0	34.5	
In the presence of tetra-n-butylammonium perchlorate					
10^4[$Bu^n_4NClO_4$]/M	0	1.0	4.0		
$10^6 k_A$	2.23	2.20	2.20		
B 1-Fluoro-2,4-dinitrobenzene[a]					
10[*p*-Anisidine]/M	0.5	1.0	1.5	2.0	3.0
$10^5 k_A$	2.26	6.90	14.5	22.1	50.5
In the presence of tetra-n-butylammonium chloride					
10^4[Bu^n_4NCl]/M		1.05	2.10	2.625	3.15
$10^3 k_A$		1.63	2.58	3.15	3.50

[a] Substrate concentration 2.02—2.05 × 10^{-3}M. The effect of additives was studied at a constant *p*-anisidine concentration of 1.00 × 10^{-1}M.

Table 2. Rate constants (l mol^{-1} s^{-1}) for for the reactions of 1-chloro- and 1-fluoro-2,4-dinitrobenzene with *N*-methyl-*p*-anisidine in benzene at 30.0 °C and in the presence of various additives

A 1-Chloro-2,4-dinitrobenzene[a]					
10[*N*-Methyl-*p*-anisidine]/M	1.01	2.01	3.015	4.02	
$10^6 k_A$	4.34	4.21	4.41	4.10	
In the presence tetra-n-butylammonium chloride					
10^4[Bu^n_4NCl]/M	1.05	2.10	3.15	4.20	
$10^6 k_A$	4.35	4.13	4.44	4.39	
In the presence of pyridine					
10^2[Pyridine]/M	1.00	3.01	5.01	8.01	
$10^6 k_A$	4.14	4.12	4.44	4.42	
In the presence of DABCO					
10^2[DABCO]/M	0.506	2.03	3.04	5.06	
$10^6 k_A$	4.49	4.38	4.49	4.49	
B 1-Fluoro-2,4-dinitrobenzene[a]					
10[*N*-Methyl-*p*-anisidine]/M	1.00	2.00	3.00	4.00	
$10^6 k_A$	1.30	2.60	4.10	6.24	
In the presence of DABCO					
10^3[DABCO]/M	5.06	10.1	20.3	30.4	50.6
$10^4 k_A$	1.20	2.50	4.80	7.62	11.8
In the presence of pyridine					
10^2[Pyridine]/M	0	1.00	3.01	5.01	8.00
$10^6 k_A$	1.13	1.93	3.95	5.64	8.41
In the presence of tetra-n-butylamminium chloride					
10^4[Bu^n_4NCl]/M	0	1.05	2.10	3.15	4.20
$10^6 k_A$	1.13	2.40	3.05	4.21	4.32
In the presence of tetra-n-butylammonium perchlorate					
10^4[$Bu^n_4NClO_4$]/M	0	1.00	4.00		
$10^6 k_A$	1.13	1.14	1.13		

[a] Substrate concentrations 1.98—2.23 × 10^{-3}M. The effect of additives was studied at a constant *N*-methyl-*p*-anisidine concentration of 1.00 × 10^{-1}M.

catalysed we reject this explanation, at least for the above range of aniline concentrations.

Recently[8] we have shown that the reaction of 1-chloro-2,4-dinitrobenzene with aniline in acetonitrile is catalysed by halide ions. This catalysis was shown to be due to the stabilization of the transition state of the first-formed intermediate of equation (1) by halide ions (Figure 1; Y = halide). A similar stabilization by amines when the solvent is changed to benzene would account for Bernasconi and Zollinger's results. This type of transition state has already been postulated (along with other possibilities) as an explanation of the catalysis of this reaction by Rappoport and Bunnett.[9]

This mechanism, occurring concurrently with that given in equation (1) (with $k_2 + k_3[B] \gg k_{-1}$), requires a rate equation of the form $k_A = k_0 + k[Y]$. Thus linear catalysis should be observed, irrespective of the nature of Y, and if the value for the equilibrium constant for $HCl + Cl^- \rightleftharpoons HCl_2^-$ is greater than that for amine–ammonium ion homoconjugation $BH^+ + B \rightleftharpoons (BH \cdots B)^+$ where B represents an amine, which is the case in acetonitrile, also holds in benzene, then chloride ion should be a stronger catalyst than amines. The catalysis depends on the availability of a relatively acidic hydrogen atom attached to nitrogen in the transition state. It is known that when the substrate contains an *o*-nitro group, strong hydrogen bonding occurs between it and the amino hydrogen atoms in the formation of the transition state. When the nucleophile is a primary amine there is still one amino hydrogen atom left for interaction with the catalyst, but when the amine is secondary this is not the case. Hence if the nucleophile were changed to *N*-methyl-*p*-anisidine the catalytic effect would be expected to be considerably reduced, if not eliminated entirely.

Picryl chloride is a much more reactive substrate than 1-chloro-2,4-dinitrobenzene, consequently in the reaction with amines the transition state is much earlier and the amino hydrogen atoms in it less acidic than for the 2,4-dinitro substrate. This coupled with the possibility of hydrogen bonding to two *o*-nitro groups makes picryl chloride much less susceptible to catalysis than 1-chloro-2,4-dintrobenzene.

We have studied the effect of putative catalysts on the reactions of 1-chloro-2,4-dintrobenzene with *p*-anisidine and *N*-methyl-*p*-anisidine in benzene to see how far the above predictions are realised. For comparison purposes we have studied the corresponding reactions of 1-fluoro-2,4-dinitrobenzene, reactions for which it can be safely assumed that the decomposition to products of intermediate (I) [equation (1)] is rate limiting. The results are given in Tables 1 and 2.

The second-order rate constant for the reaction at 1-chloro-2,4-dinitrobenzene with *p*-anisidine increases linearly with

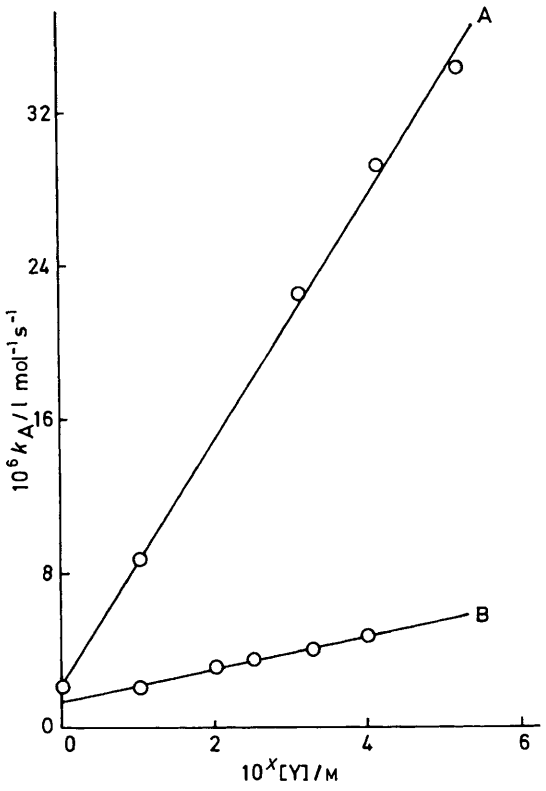


Figure 2. Plots illustrating the effect of tetra-n-butylammonium chloride and *p*-anisidine on the reaction of 1-chloro-2,4-dinitrobenzene with *p*-anisidine in benzene at 30 °C: A, tetra-n-butylammonium chloride, $x = 4$; B, *p*-anisidine, $x = 1$

increase in *p*-anisidine concentration in agreement with the results of Bernasconi and Zollinger.[6] The rate constant also has a strong linear dependence on the concentration of tetra-n-butylammonium chloride as is shown in Figure 2. Catalysis by the salt is much stronger than catalysis by the amines. At 25 °C, Bernasconi and Zollinger[6] give the slopes of the plots of k_A against catalyst as (in units of 10^6 l^2 mol^{-2} s^{-1}) *p*-anisidine 5.75; pyridine, 31.5; DABCO, 79. At 30 °C the slopes are: *p*-anisidine 8.5; tetrabutylamminium chloride, 62 000. The catalysis by tetrabutylammonium chloride cannot be due to a salt effect as addition of the corresponding perchlorate has no effect on the rate of reaction (Table 1).

As observed by Bernasconi and Zollinger[6] when the substrate is 1-fluoro-2,4-dinitrobenzene, the plot of the second-order rate constant against *p*-anisidine concentration has a pronounced upward curvature. We have already suggested an explanation of this kinetic form[3,10] as due to the electrophilic catalysis of the departure of the leaving group by the homoconjugate of the conjugate acid of the nucleophile. The reaction is strongly catalysed by tetrabutylammonium chloride. A plot of k_A against the concentration of the salt is linear with a slope of 9.1 l^2 mol^{-2} s^{-2}. In this case the observed effect is probably due not only to catalysis of the first step of the reaction, but to concurrent reactions where the salt acts as the base B in equation (3). This type of catalysis has been observed in acetonitrile.[11]

The reaction of the chloro substrate with *N*-methyl-*p*-anisidine is not catalysed by the nucleophile, pyridine, DABCO, or tetra-n-butylammonium chloride. The reaction of this nucleophile however with the fluoro substrate is catalysed by all four entities, but not by tetra-n-butylammonium perchlorate. Thus the lack of catalysis observed for 1-chloro-2,4-dinitrobenzene is not due to steric inhibition of approach to the amino hydrogen atom. It can be attributed to hydrogen bonding of this atom to the *o*-nitro group as described earlier.

The behaviour of the *p*-anisidine–*N*-methyl-*p*-anisidine pair towards the chloro and fluoro substrates is analogous to that of the aniline–*N*-methylaniline pair towards these two substrates in acetonitrile.[11] In both sets the decomposition to products of the intermediate formed by the fluoro compound is rate limiting. The lack of catalysis of the reactions of this substrate by tetra-n-butylammonium perchlorate show that accelerations produced by the chloride are not due to a salt effect and arise from it acting as the base B in equation (1), when the nucleophile is the secondary amine.

The pattern of results which we have obtained is that which would be expected if the first stage of the reaction between *p*-anisidine and 1-chloro-2,4-dinitrobenzene were catalysed and we believe that this is the explanation of the anomalous base catalysis observed by Bernasconi and Zollinger in this system. We also reinterpret the effects of aniline hydrochloride and of tetra-n-butylammonium chloride on the reactions of aniline with 1-chloro- and 1-fluoro-2,4-dinitrobenzene in acetone which we observed some time ago,[12] in a similar manner.

Experimental

The purification of 1-chloro- and 1-fluoro-2,4-dinitrobenzene,[3] pyridine,[3] DABCO,[3] benzene,[3] and tetra-n-butylammonium perchlorate[13] has already been described. Tetra-n-butylammonium chloride was purified by recrystallization from ethyl acetate followed by azeotropic distillation with benzene. *p*-Anisidine was recrystallized from water, m.p. 57 °C (lit.,[14] 55—57 °C). *N*-Methyl-*p*-anisidine was purified by distillation under reduced pressure, m.p. 37 °C (lit.,[15] 37 °C). The reaction was followed by the spectrophotometric determination of the reaction product at λ 360 (*p*-anisidine) and 386 nm (*N*-methyl-*p*-anisidine) using the pipette technique described earlier.[10]

Acknowledgements

One of us (E. T. A.) would like to thank Professor V. Horak for providing facilities in the Department of Chemistry, Georgetown University, Washington, D.C., and the International Student Exchange Program for providing support during her stay there.

References

1 J. F. Bunnett and G. T. Davies, *J. Am. Chem. Soc.*, 1960, **82**, 665.
2 B. Capon and C. W. Rees, *Annu. Rep.*, 1963, **60**, 279.
3 T. O. Bamkole, J. Hirst, and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1982, 889.
4 R. H. de Rossi, R. A. Rossi, and F. N. R. Gimenez, *J. Org. Chem.*, 1976, **41**, 3163.
5 R. Minelti and A. Bruylants, *Bull. Acad. R. Belge.*, 1970, **56**, 1047.
6 C. F. Bernasconi and Hch. Zollinger, *Helv. Chim. Acta*, 1966, **49**, 2570.
7 T. O. Bamkole and J. Hirst, *Niger. J. Sci.*, 1972, **6**, 81.
8 J. Hirst and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1984, 711.
9 Z. Rappoport and J. F. Bunnett, *Acta. Chem. Scand., Ser. B*, 1974, **28**, 478.
10 J. Hirst, G. N. Onuoha, and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1988, 971.
11 T. O. Bamkole, J. Hirst, and G. Hussain, *J. Chem. Soc., Perkin Trans. 2*, 1984, 681.
12 O. Banjoko, C. W. L. Bevan, and J. Hirst, *Niger. J. Sci.*, 1969, **3**, 153.
13 D. Ayediran, T. O. Bamkole, and J. Hirst, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1013.
14 Tse-Lok Ho and C. M. Wong, *Synthesis*, 1974, 45.
15 E. Fröhlich and E. Wedekind, *Ber. Dtsch. Chem. Ges.*, 1907, **40**, 1010.

Received 14*th December* 1987; *Paper* 7/2176