The Influence of Some Steric and Electron Effects on the Mechanism of Aromatic Nucleophilic Substitution (S_NAr) Reactions in Nonpolar Solvent

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ABSTRACT: Kinetic studies are reported for the reactions with aniline in benzene of a series of X-phenyl 2,4,6-trinitrophenyl ethers [X = H; 2-, 3-, 4-CH_3; 2,4-, or 2,6-$(CH_3)_2$] **1a–f**, and the results compared with those of the corresponding nitro derivatives. In the methyl series, kinetic data show that increasing substitution reduces drastically the rates of reactions indicative of the operation of some kind of steric effect. The unfavorable steric congestion at the reaction center appears to be unimportant in determining the kinetic order of the reactions. In general, the second-order rate constants k_A depend linearly on the square of nucleophile concentration. The change in the kinetic form observed in the nitro derivatives may be largely due to the electron-withdrawing effect of the group. With the 2,6-dinitro derivative, however, the uncatalyzed pathway k_2 takes all the reaction flux. Steric hindrance to intermolecular proton transfer from base to the ethereal oxygen of the intermediate is sufficient to make the base-catalyzed pathway insignificant relative to the k_2 pathway. © 2005 Wiley Periodicals, Inc. Int J Chem Kinet 37: 744–750, 2005

INTRODUCTION

Bernasconi [1] has discussed the various factors responsible for the incidence of base catalysis in S_NAr reactions, and in most cases they have been well substantiated experimentally. However, the effects of ortho-substituents in such reactions are complex. In the process of obtaining additional data which would provide further evidence for the cyclic transition state mechanism for reactions in nonpolar aprotic solvents, Banjoko and Ezeani [2] have shown for the reactions in

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benzene of aniline with 2,4,6-trinitrodiphenyl ether and derivatives containing a nitro group in the 2-, 3-, and 4-positions of the leaving group that the second-order rate constant k_A had a linear dependence on [aniline]^2. A similar dependence on nucleophile concentration for the 4-nitro derivative was obtained by Emokpae et al. [3] when the nucleophile was the secondary amine, *N*-methylaniline. Banjoko and Ezeani [2] also observed that with exception of the 2′,6′-dinitro isomer, when the leaving group contained two nitro groups, k_A had a linear dependence on the aniline concentration, i.e. the transition state for the decomposition of the intermediate to products only contained two molecules of aniline. The 2′,6′-dinitro derivative was not base catalyzed and so was first order in both substrate and nucleophile. The lack of catalysis observed in the 2′6′-dinitro isomer was attributed to an interplay of electronic effects and steric compressions in the δ-complex.

In order to better assess the role played by these effects on the uncatalytic behavior of the 2′,6′-dinitro isomer, the investigations of the nitro series **2b–f** have been extended to a series of mono- and di-methyl-substituted phenyl-2,4,6-trinitrophenyl ethers **1a–f**. Capon and Chapman [4] have shown that while the polar effect of a methyl group is small, the steric effect of an ortho-methyl group is appreciable. The electronic effects of methyl substituents as reflected in the values of the p*K*a of the corresponding phenols in water [5] (Table I) are almost identical. In benzene, the differences between the values of the p*K*a are not likely to be magnified. The nucleofugalities of the leaving groups will therefore be nearly identical. Similarity in the kinetic form of the reactions of **1a–f** would show that steric effects are relatively insignificant while a change in the kinetic order would indicate the importance of steric effects in determining the kinetic form of the reactions of mono- and di-methyl-substituted phenyl-2,4-6-trinitrophenyl ethers with aniline in benzene. The results, unlike those of the nitro series **2a–f**, show that there is no dramatic change in the behavior from the 2,6-dimethyl derivative. Although steric effects certainly caused rate decreases in the reactions of methyl-substituted trinitrophenyl ethers **1a–f** with aniline in benzene, there was no change in the kinetic order. The plots of k_A/[amine] versus [aniline] were all linear.

EXPERIMENTAL

Diphenyl ethers **1a–f** were prepared by the reaction of picryl chloride with 1 equivalent of base in the presence of an excess of the appropriate phenol in aqueous ethanol. Recrystallization was from ethanol. The reaction product, 2,4,6-trinitrodiphenylamine **V** was prepared by reaction of picryl chloride with excess aniline in ethanol. All substrates had m.p.s in satisfactory agreement with published values [2,6,7]. The details for the purification of aniline and the spectroscopic determination of the rate constants have already been given [2,3,6].

RESULTS AND DISCUSSION

Aniline reacted with the substrates in benzene to give the expected *N*-(2,4,6- trinitrophenyl) aniline in quantitative yield. With concentration of aniline (0.1–0.8 mol dm^{-3}) in large excess of the concentration of the diphenyl ethers, (10^{-4} mol dm^{-3}), excellent first-order kinetics were observed; the reactions proved to be first order in the substrates, and division of the pseudo-first-order rate coefficients k_{obs} by the appropriate concentration of aniline gave second-order rate constants k_A. The data are gathered in Table II.

The Methyl Series, 1a–f

The values of the second-order rate coefficient k_A increased rapidly with aniline concentration. A typical plot, in this case for the 2,4-dimethylphenyl substrate, of k_A versus aniline concentration is given in Fig. 1. It shows a line with an upward curvature and with intercept on the *y*-axis statistically indistinguishable from zero. This indicates that the contribution of k_2, the uncatalyzed pathway, is insignificant. Similar plots were obtained for all the other methyl substrates**.** Plots (not shown) of the quotient k_A/[aniline] against aniline concentration however were linear (correlation coefficient >0.9990) consistent with reactions being third order in the rate law.

The kinetic data are analyzed in terms of Scheme 1. The reactions are expected to proceed through three routes: (a) an uncatalyzed pathway involving the

Table I p*K*a Values of the Substituted Phenols in Water for the X-phenyl 2,4,6-trinitrophenyl ethers [X = H; 2-, 3-, 4-CH_3; 2,4-, 2,6-$(CH_3)_2$] **1a–f** and [X = 2-, 3-, 4-NO_2; 2,4-, 2,6-$(NO_2)_2$] **2b–f**

1a	1b	1c	1d	1e	1f	2b	2c	2d	2e	2f
10.00	10.28	10.08	10.14	10.40	10.60	7.23	7.10	7.15	4.11	3.15

Table II Kinetic Results for the Reactions of X-phenyl-2,4,6-trinitrophenyl Ethers (X = 4-H,2-, 3-, 4-CH_3, 2,4-, 2,6-$(CH_3)_2$) **1a–f** with Aniline in Benzene at 30°C

	k_A ($\times 10^{-4}$ dm^3 mol^{-1} s^{-1})					
[Aniline] (mol dm^{-3})	4-H	2-CH_3	3-CH_3	4-CH_3	2,4-CH_3	2,6-CH_3
0.10			1.60	1.96		
0.15	5.3		3.15	3.9		
0.20	8.3		5.0	6.95		
0.25	13.0		7.63	10.44		
0.30	18.0	1.75	10.85	14.80	0.60	0.0115
0.35	23.5		14.63	20.0		
0.40	30.0	2.61			1.02	0.0191
0.50		3.72			1.48	0.0294
0.60		5.11			2.08	0.042
0.65						0.0497
0.70		6.73			2.80	0.057
0.80		8.53			3.65	

formation of a four-membered ring (II), (b) a catalytic route involving the formation of a six-membered ring (III) due to the participation of one molecule of amine, and (c) a catalytic route involving the formation of a eight-membered ring (IV) due to the participation of two amine molecules.

The assumption that these intermediates may be treated as steady-state intermediates leads to Eq. (1)

$$k_A = \frac{k_1k_2 + k_1k_3[B] + k_1k_4[B]^2}{k_{-1} + k_2 + k_3[B] + k_4[B]^2} \qquad (1)$$

From Fig. 1, it can be seen that $k_A = 0$ at null base concentrations, the $k_1k_2/k_{-1} + k_2$ must therefore be

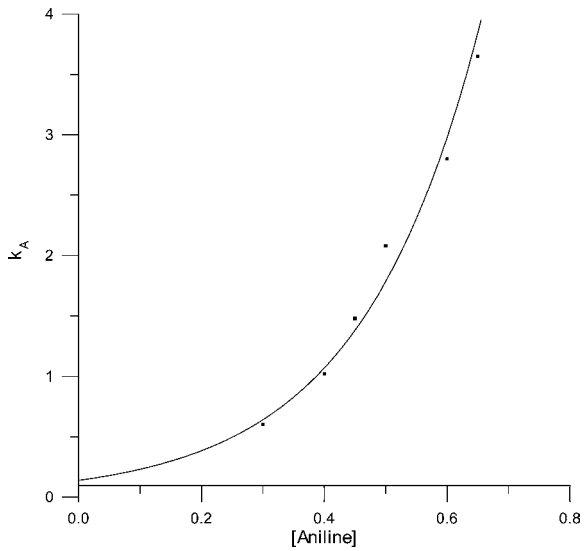


Figure 1 Plot of k_A vs. [aniline] in benzene at 30°C for the reaction of 2,4-dimethylphenyl-2,4,6-trinitrophenyl ether (**1e**) with aniline.

zero. Since k_1 measures the rate of monomer attack, it is reasonable to assume that its value is not negligible; so most probably k_2 is zero i.e. the uncatalyzed pathway, route (a) is unimportant. With this assumption, Eq. (1) simplifies to Eq. (2)

$$k_A = \frac{k_1k_3[B] + k_1k_4[B]^2}{k_{-1} + k_3[B] + k_4[B]^2} \qquad (2)$$

Our results which provide evidence for base catalysis indicate that the condition $k_{-1} \gg k_3[B] + k_4[B]^2$ applies so that Eq. (2) reduces to Eqs. (3) and (4)

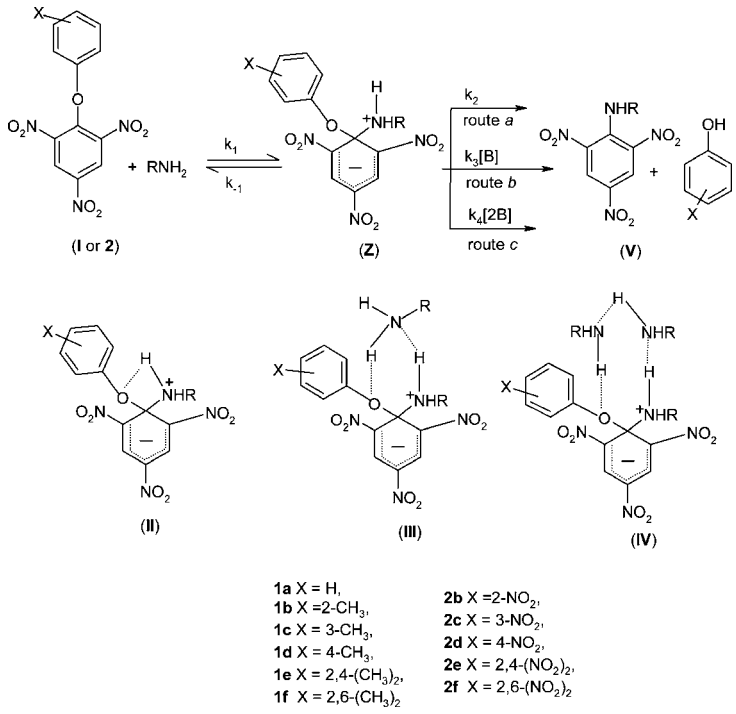
$$k_A = \frac{k_1k_3[B]}{k_{-1}} + \frac{k_1k_4[B]^2}{k_{-1}} \qquad (3)$$

$$\frac{k_A}{[B]} = \frac{k_1k_3}{k_{-1}} + \frac{k_1k_4[B]}{k_{-1}} = k' + k''[B] \qquad (4)$$

Equation (4) agrees with the experimental results of the linear dependence of $k_A/[B]$ on $[B]$ observed for all the reactions.

Nitro Series, 2b–f

For the mononitro derivatives, the behavior was qualitatively similar to that for the methyl isomers; values of k_2 were negligibly small, and data in Tables III conform to Eqs. (1) and (4). Banjoko and Ezeani [2] had shown that the plot of k_A versus aniline concentration for **2e**, the 2,4-dinitro derivative gave an excellent straight line. The sizable intercept on the y-axis represents reaction by uncatalyzed pathway, while the positive slope indicates the presence of a base-catalyzed route. For **2f**, the 2,6-derivative, the values of k_A were independent of aniline concentration; the reaction was therefore not base catalyzed.



Scheme 1

Table III Kinetic Results for the Reactions of X-phenyl-2,4,6-trinitrophenyl Ethers (X = 4-H; 2-, 3-, 4-NO_2, 2,4-, 2,6-$(NO_2)_2$) with Aniline in Benzene at 30°C

	k_A (10^{-4} dm^3 mol^{-1} s^{-1})					
[Aniline] (mol dm^{-3})	4-H[a]	2-NO_2[b]	3-NO_2	4-NO_2[a]	2,4-NO_2[b]	2,6-NO_2[b]
						99.6
						99.6
						99.6
0.01					4.45	99.6
0.02		2.05			8.25	
0.03					12.0	
0.04		33.0			15.75	
0.05			4.0	5.0		
0.06		53.3				
0.08		81.4				
0.10			16.5	18.0		
0.12			24.0	25.0		
0.15	5.3		36.0	39.0		
0.18			50.3	55.0		
0.20	8.3		62.0	68.0		
0.25	13.0					
0.30	18.0					
0.35	23.5					
0.40	30.0					

[a] Data from present work.
[b] Data from [2].

Base Catalysis

The origin of the upward curvature of the plot of k_A against base concentration has generated a lot of interest and active discussion. Initially this was ascribed to "unspecific solvent effects," but more recently three major explanations of the abnormal behavior have been given and they have enjoyed varied degree of acceptances:

(i) *Dimer mechanism*: Nudelman and Palleros [8–10] have suggested association of the nucleophile with the base prior to attack on the substrate followed by the base-catalyzed decomposition of the intermediate.

(ii) The *cyclic transition state mechanism* modified by Banjoko et al. [2,11,12] in which there is an initial attack of an amine molecule on the substrate followed by the decomposition of the resulting intermediate via on eight-membered ring involving three molecules of the amine.

(iii) *Homo/heteroconjugate mechanism*: Ayediran et al. [13] have proposed that because of the low relative permittivity of aprotic solvents and the consequent range of electrostatic forces, aggregates are formed within which mechanisms such as those proposed by Bunnett and Davies [14] can operate. They explained [15] the upward curving plots as due to electrophilic catalysis of the expulsion of the leaving group by homo- and hetero-conjugate acid of the nucleophile. It was stressed [16] however that because of the range of electrostatic forces and the importance of hydrogen bonding in these solvents, several mechanisms could operate, the relative importance of which would depend not only on the entities employed, but also on their concentration. Recently, the mechanism was strongly supported by Jain et al. [17] in their investigation of ammolysis reactions of *o*-aryl oximes with aliphatic primary and secondary amines in benzene. Akinyele et al. [18] had given plausible mechanism for the formation of cyclic transition state for aromatic nucleophilic substitution reactions in all solvents of low relative permittivity. The concept was developed by Emokpae et al. [3] to rationalize reactions proceeding through cyclic transition states containing either two or three molecules of amines.

An eight-membered transition state is more effective in removing the nucleofuge than a six-membered transition state. This was confirmed by Gandour [19] who showed from the study of structural requirements for intramolecular proton transfer that the highest possibility for proton transfer would occur when the cyclic transition state involved could accommodate a linear arrangement of donor–proton–acceptor of appropriate length. This easily occurs when the ring size is eight. Most of the conceptual difficulties associated with the cyclic intermediates in S_NAr reactions pertain to catalyses by tertiary amines because of the unlikelihood of the formation of three hydrogen bonds in a single step. There is now evidence for bifurcated hydrogen bonds in both small crystal structures [20,21] and if formation of hydrogen bonds of weak to moderate strength is an electrostatic phenomenon, they should also exist in solution of solutes in solvents of low relative permittivity. Hirst has recently advanced convincing reasons that if three-centered hydrogen bonding is allowed, then the distinction between cyclic and homo-/heteroconjugate mechanisms becomes blurred [22]. For the present reactions, we prefer to interpret our results in terms of the cyclic state mechanism.

COMPARISON

Since the reactions of **1a–f** have the same kinetic form, we can assess the relative rates of their reactions. Comparison of the second-order rate constants k_A under the same experimental conditions shows that the reactivity of the substrates decreases in the order

$$\mathbf{1a} > \mathbf{1d} > \mathbf{1c} > \mathbf{1b} > \mathbf{1e} > \mathbf{1f}.$$

This can be rationalized in terms of the nucleofugality of the leaving groups. The expulsion of the leaving group involves the breaking of the C—O bond in the zwitterionic intermediate **Z** which then generates a negative charge on the oxygen atom of the phenoxide ion. The departure of the nucleofuge would be facilitated if it is stabilized by delocalization of the negative toward the benzene ring of the phenoxide ion through conjugation. This is certainly aided by substituents which are election withdrawing and retarded by those that are election donating. All the mono- and di-methyl substituted groups decreased the nucleofugality of the leaving group and consequently reduced the rates of the reactions. Specifically, a 4-methyl group in the nucleofuge decreased the rate constant by a factor of 1.2, while a 2-methyl group gave a 10-fold reduction. The 2,6-dimethyl group also reduced the rate constant by a factor of ca. 1600. While the effect of the 2-methyl group may be regarded as small, that of 2,6-dimethyl group is enormous, indicative of the operation of some kind of steric effect. This was reinforced recently by X-ray crystal structures of **1a**, **1f**, and **2f** which provide evidence of steric crowding around the 1-position of

these molecules [23]. Our kinetic data, however, show that this unfavorable steric crowding at the reaction center does not change the kinetic order. It only reduces the rates of the reactions. It is worth noting that in acetonitrile [23] such increase crowding at the reaction center did not sterically inhibit attack by the nucleophile, and an "early" transition state was suggested.

In reactions in which the decomposition of the intermediates to reactants is rate limiting, steric effects may in principle be reflected in all elementary rate constants in Scheme 1. There are various sources of these effects. The first is steric compression in the intermediate between the amine and the aromatic ring plus ortho-substituents. On reverting to reactants, the steric strain is partially released since the transition state is "looser" than the intermediate. This enhances k_{-1} and therefore decreases k_2/k_{-1}. The transition state for the decomposition **Z** to reactants is the same as for its formation, and according to the Hammond postulate it is structurally close to the intermediate. Steric compressions will therefore be expected in the transition state, and these should be manifested in a reduction in k_1. A second is due to the fact that when the leaving group X leaves the intermediate, the incoming group must move from the "tetrahedral" position to a position in the plane of the benzene ring. Any interference with this motion by other groups in the molecule would lead to a reduction in k_2 and k_3. Other related effects that may cause reduction in the values of k_2 and k_3 have been discussed exhaustively by Bernasconi and de Rossi [24]. Despite these factors which reduce k_2/k_{-1} or k_3/k_{-1}, the role of steric effects in bringing about the incidence of base catalysis is not clear-cut. They are only a few unambiguous examples of steric effect influencing the occurrence of base catalysis. The reaction of 2,4-dinitrodiphenyl ether with pyrrolidine which was insensitive to catalysis by NaOH [25] responded linearly to catalysis by NaOH when the substrate was changed to the 6-methyl derivative [26]. Similarly, in acetonitrile and in dimethyl sulfoxide, the introduction of 6-methyl group changed the kinetic form of the reaction of 2,4-dinitrophenyl phenyl ether with *n*-butylamine from an uncatalyzed one to one in which there was a linear dependence of the rate constant k_A on nucleophile concentration [27]. Another example where change in the rate-limiting step was induced by the steric effect of an ortho-methyl group was the reactions of substituted aniline with 2,4-dinitrofluorobenzene in dimethyl sulfoxide [28]. The introduction of 2-methyl group into aniline changed the kinetic form of the reaction from an uncatalyzed one to one in which there was a curvilinear dependence of the rate constant k_A on nucleophile concentration. The rate of the reaction was reduced to a factor of ca. 200 when the methyl substituent was moved from the para- to the ortho-position in the nucleophile. This change in the rate-limiting step for the same reactions brought about changing the steric properties of the nucleophile was recently confirmed by the determination of leaving group fluorine kinetic isotope effects [FK1Es]. The large FKIE [1.0119 ± 0.0037] for 2-methylaniline suggests rate-limiting leaving group departure for the sterically more hindered nucleophile, whereas the insignificant FKIE (1.0005 ± 0.0030] for the less sterically hindered 4-methyl aniline indicates rate-limiting addition of the nucleophile [29]. Interestingly, the reaction of 1-bromo 3,5-dinitrobenzene with 2-methyaniline in dimethyl sulfoxide was not base catalyzed. The introduction of a 6-bromo-substituent into 1-fluoro 2,4-dinitrobenzene caused the mechanism of its reactions with 2-methylaniline to revert to a rate-determining formation of zwitterions [28].

The kinetic data for the series **1a–f** are different from those of the **2b–f**. The nitro group enhances the departure ability of the leaving group by facilitating delocalization of negative charge due to its electron-withdrawing effect. In the nitro series **2b–f**, there was a change in the kinetic form for the reactions of aniline with ethers containing unsubstituted or mono nitro substituted leaving groups from a third-order dependence on aniline concentration to a second-order dependence for leaving groups containing 2,4-, 3,4-, and 2,5-dinitro group to $k_A = k_1$ for the 2,6-dinitrophenoxy group. The change was ascribed to changes in the transition states for the decomposition of the intermediate from eight- to six- to four-membered rings (containing two, one, and no molecules of aniline respectively) brought about by increases in the leaving group ability of the nucleofuge. This is readily explicable as the introduction of a second nitro group will reduce the basicity of the ethereal oxygen in the zwitterionic intermediate **Z** and decrease the population of species hydrogen bonded to it and thus the livelihood of the attainment of a third molecule of the nucleophile. The favorable electronic effect of the nitro groups therefore outweighs their adverse steric effect.

With **2f**, the 2,6-dinitro derivative, the steric hindrance to intermolecular proton transfer from the base to the ethereal oxygen in the intermediate is sufficient to make the base-catalyzed pathway insignificant relative to the k_2 pathway. There is general agreement that in aprotic solvent such as cyclohexane and benzene, the uncatalyzed decomposition of the intermediate to products takes place unimolecularly via a hydrogen-bonded intermediate (Fig. 2). Since this involves intramolecular proton transfer, steric effects are unlikely to be important. In acetonitrile, the reaction of **2f**, the 2,6-dinitro derivative was also not catalyzed by the nucleophile [23].

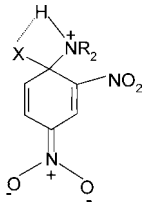


Figure 2 Hydrogen bonding in the uncatalyzed decomposition of the intermediate to products.

CONCLUSION

Our results reveal that steric crowding at the reaction center does not play a major role in the determination of the kinetic order of the reactions of aniline with methyl-substituted trinitrodiphenyl ethers in nonpolar aprotic solvent. It however retards the rates of such reactions. The change in the kinetic form observed in the nitro derivatives must have arisen from the basicity of the phenolic-leaving group. It is only with **2e** and **2f** derived from the least phenoxides that the uncatalyzed reaction could compete with the base-catalyzed pathway. With the 2,6-dinitro derivative, the main reaction flux occurs through the uncatalyzed pathway. Steric hindrance to intermolecular proton transfer from base to the ethereal oxygen is sufficient to make the base-catalyzed pathway insignificant relative to the k_2 pathway.

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