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RESEARCH ARTICLE

The influence of steric effects on the kinetics and mechanism of S_NAr reactions of 1-phenoxy-nitrobenzenes with aliphatic primary amines in acetonitrile

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Abstract

Rate constants are reported for the reactions of 1-phenoxy-dinitrobenzenes, **3**, 1-phenoxy-dinitrotrifluoromethylbenzenes, **4**, with *n*-propylamine, and 1-methylheptylamine in acetonitrile as solvent. The results are compared with results reported previously for *n*-butylamine, pyrrolidine, and piperidine. Decreasing ring activation leads to lower values of k_1 for nucleophilic attack although this may be mediated by reduced steric congestion around the reaction centre. Specific steric effects, leading to rate retardation, are noted for the *ortho*-CF_3 group. In general, reactant-bearing *ortho*-CF_3 group were subject to base catalysis irrespective of the amine nucleophile and values of k_{Am}/k_{-1} are reduced as the size of the amine get bulkier. This is likely to reflect increases in values of k_{-1} coupled with decreases in values of k_{Am} as the proton transfer from zwitterionic intermediates to catalysing amine becomes less thermodynamically favourable.

KEYWORDS

aliphatic amines, nucleophilic aromatic substitution, steric effects, substituent effects

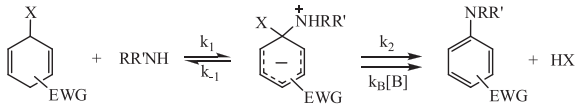
1 | INTRODUCTION

In activated aromatic nucleophilic substitution reactions (S_NAr) involving nitroaryl ethers, considerable attention has been attached to the observation of base catalysis by primary and secondary amines and its significance.[1–4] The overall mechanism of these reactions is given in Scheme 1, where EWG denotes a generalized substituent.

The presence or absence of base catalysis exerted by the nucleophile itself or by an externally added base has played an important role in deciding whether formation or decomposition of the intermediate complex is rate limiting.[5] While the factors affecting the incidence of base catalysis have been extensively discussed and in most cases substantiated experimentally, only meagre attention has been given to the effects of *ortho* substitution in the substrate. This may be due to complications arising from *ortho* effect of most substituents. Apart from the simple steric effect owing to a bulky substituent, other factors have been considered, such as the steric inhibition of resonance,[6] the field effect,[7] and the intermolecular hydrogen bonds.[8,9] Generally, steric effects are not linearly dependent in various reactions[10] but rather vary nonlinearly with the substituent, becoming suddenly appreciable at its certain size. The universal scales of steric effect therefore have no physical applicability and little practicability only in combination with other parameters. In this respect, steric effect differs from inductive and also from resonance effects.[11]

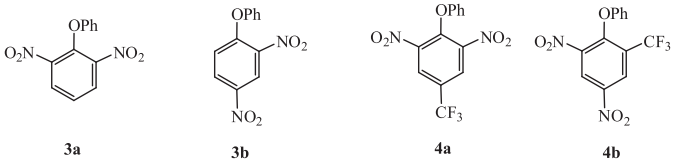
We have reported a detailed kinetic study of the reaction of 4-substituted-1-chloro-2,6-dinitrobenzenes, **1**, 6-substituted-1-chloro-2,4-dinitrobenzenes, **2**, and some of the corresponding 1-phenoxy derivatives, **3** and **4**, with *n*-butylamine, pyrrolidine, and piperidine in acetonitrile as solvent. Values of k_1, the rate constant for nucleophilic attack at the 1-position, increase with increasing ring activation but may be reduced by steric repulsion at the reaction centre, which increases in the order Cl < OPh and *n*-butylamine < pyrrolidine ~ piperidine. Also, we have extended[12] the study to the reaction of a series of

This study is dedicated to the memory of late Emeritus Professor Thomas Anthony Emokpae in honour of his immense contributions to the understanding of the mechanism of S_NAr Reactions.



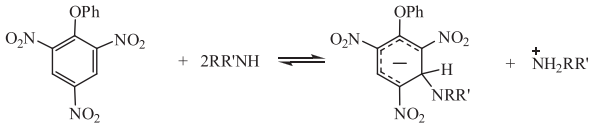
SCHEME 1 EWG, electron withdrawing groups

1-chloro-nitrobenzenes, 1-fluoro-nitrobenzenes, and 1-phenoxy-nitrobenzenes activated by CF_3 or CN groups or by ring nitrogen with *n*-butylamine, pyrrolidine, or piperidine in acetonitrile. Our results showed that the decreased ring activation in the nitroaryl ethers or pyridyl ethers leads to reductions in values of k_{Am}/k_{-1} resulting in greater susceptibility to base catalysis.[12] Rate constants k_1 for nucleophilic attack are also reduced, but steric effects due to repulsion between the incoming nucleophile and *ortho* substituents are less evident. Specific rate-retarding effects of an *ortho*-CF_3 group were observed.



3a **3b** **4a** **4b**

Reactions of the titled compounds have been performed to see how wide spread the influence of the *ortho*-CF_3 group exerts on the reaction's pathways in S_NAr reactions. Herein, the results of the kinetic studies in acetonitrile of the reactions of a selection of nitro-activated aryl phenyl ethers **3** and **4** with *n*-propylamine and 1-methylhepthylamine (also named as 2-octylamine) are reported. The results are compared with those reported for the same substrates with *n*-butylamine in acetonitrile.[12]



4f **5**

SCHEME 2

2 | RESULTS AND DISCUSSION

The reactions of parent molecules **3** and **4** with *n*-propylamine and 1-methylheptylamine in acetonitrile gave the expected products of substitution of phenoxide respectively in >95% yield. Kinetic measurements were made spectrophometrically with the concentration of amine in large excess of the parent concentration, ca 5.0×10^{-5} to 1×10^{-4} mol dm^{-3}, and first-order kinetics were observed. Previous studies[13–15] in dimethyl sulfoxide (DMSO) have shown that substitution may be preceded by the formation, under kinetic control, of adducts resulting from attack at unsubstituted ring positions. An example for **4f** is shown in Scheme 2. The values of the equilibrium constant for such processes depend on the degree of ring activation and also on the solvent. Thus, in acetonitrile, the values for the reaction in Scheme 2 are ca 10^4 smaller than in DMSO.[13–15] The dominant factor here is likely to be the greater ability of DMSO than of acetonitrile to solvate the ionic reaction products.[9]

The reaction of **4f** with amines such as pyrrolidine and *n*-butylamine in acetonitrile was shown[12] to yield the substitution products without the observation of the adduct analogous to **5**. Similarly, in the present investigation, substitution proceeded smoothly to give first-order kinetics without the observation, in spectroscopically measurable concentrations, of transient species analogous to **5** or other intermediates on the substitution pathway. Values of k_{Obs}, the first-order rate constant, are assembled in Tables 1 and 2.

For all the reactions, the UV-visible spectra (in dilute and in more concentrated solution) at the completion of the measured process were identical to those of authentic samples of

TABLE 1 Kinetic results for reaction of phenyl-2,6-dinitrophenyl ether **3a**, phenyl-2,4-dinitrophenyl ether **3b**, 4-phenoxy-3,5-dinitrotrifluoromethylbenzene **4a**, and 2-phenoxy-3,5-dinitrotrifluoromethylbenzene **4b** with *n*-propylamine in acetonitrile at 25°C

	$k_{Obs}/10^{-3}$ s^{-1}	$k_{Obs}/10^{-4}$ s^{-1}	$k_{Obs}/10^{-3}$ s^{-1}	$k_{Obs}/10^{-3}$ s^{-1}
(*n*-Propylamine)/mol dm^{-3}	**3a**	**3b**	**4a**	**4b**
0.001			4.2	0.35
0.002			8.92	1.12
0.003			13.67	2.15
0.004			18.27	3.38
0.005	1.39	1.38	22.75	4.90
0.006			28.48	6.12
0.01				11.5
0.015	4.17	4.16		
0.02	5.58	5.63		
0.03	8.08	8.53		
0.04		11.5		
0.05		14.6		

TABLE 2 Kinetic results for reaction of phenyl-2,6-dinitrophenyl ether **3a**, phenyl-2,4-dinitrophenyl ether **3b**, 4-phenoxy-3,5-dinitrotrifluoromethylbenzene **4a**, and 2-phenoxy-3,5-dinitrotrifluoromethylbenzene **4b** with 1-methylheptylamine in acetonitrile at 25°C

	$k_{Obs}/10^{-4}$ s^{-1}	$k_{Obs}/10^{-5}$ s^{-1}	$k_{Obs}/10^{-3}$ s^{-1}	$k_{Obs}/10^{-4}$ s^{-1}
(1-Methylheptylamine)/mol dm^{-3}	**3a**	**3b**	**4a**	**4b**
0.001			0.65	0.08
0.002			1.43	0.28
0.004			3.27	0.95
0.006			5.16	2.05
0.01				5.20
0.015	0.82	0.61		
0.03	2.05	1.58		
0.06	4.43	3.30		
0.1	7.59	6.03		
0.3	23.80	17.70		

the substitution products **8** dissolved in the reaction medium. A representative rapid spectrum scan is shown in Figure 1a. Our results are best interpreted by Scheme 3.

Making the usual[12] assumption that the zwitterionic adduct **6** may be treated as a steady-state intermediate (when the amine acts both as the nucleophile and as the catalysing base) leads to Equation 1.

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

The general reaction scheme for the amine substitution of 1-phenoxy compounds **3** and **4** shown in Scheme 3 indicates the possibilities for product formation by an amine (base) catalysed, k_{Am}, or uncatalysed k_2 pathways. However, here, base catalysis, as argued previously,[12–15,9] is indicative of rate-limiting proton transfer from the zwitterionic intermediates **6**, rather than general acid catalysis of phenoxide expulsion. Hence, Equation 1 applies. Limiting forms, where $K_1 = k_1/k_{-1}$, are Equation 2, when the uncatalysed pathway may be neglected, and Equation 3, when the condition $k_{-1} >> k_2 + k_{Am}[Am]$ applies.

$$k_A = \frac{K_1 k_{Am}[Am]}{1 + \frac{k_{Am}}{k_{-1}}[Am]} \quad (2)$$

$$k_A = K_1 k_{Am}[Am] + K_1 k_2 \quad (3)$$

For the reactions of the nitroaryl ethers reactants **3a**, **3b**, and **4a** with *n*-propylamine and 1-methylheptylamine, plots of k_{obs}, the first-order rate constant against the amine concentration, were essentially linear with null intercept. A representative plot of k_{obs} vs (*n*-propylamine) is shown in Figure 1b. Thus, values of the second-order rate constant, k_A, obtained from the slopes were independent of the amine concentration. This corresponds to the condition $k_2 + k_{Am}[Am] >> k_{-1}$ so that $k_A = k_1$. This is not unexpected as base catalysis with primary aliphatic amine nucleophiles has been found in a fewer cases[16–18] where factors such as the nature of the electrophilic substrate and the solvent contribute to a lowering of the ratio k_2/k_{-1}. Before discussing these data, results for **4b** will be reported.

For the reactions with *n*-propylamine and 1-methylheptylamine of **4b** carrying an *ortho*-CF_3 substituent, the plot of k_A versus (amine), shown (Figure 2), was curvilinear downwards. Values, in Table 3, gave a good fit with Equation 2.

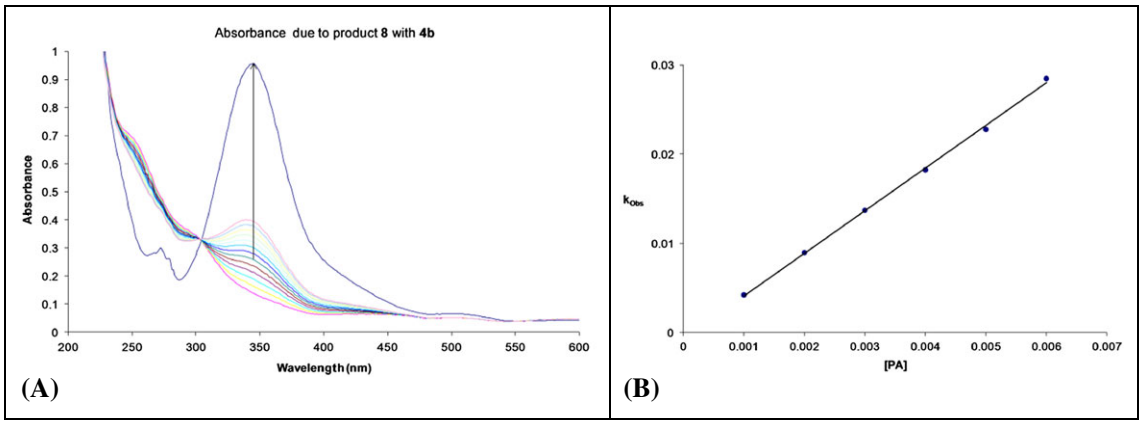
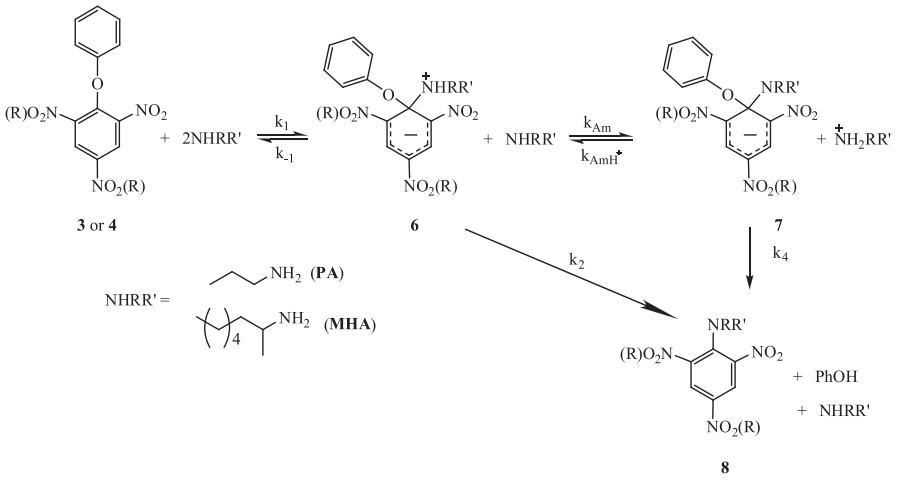


FIGURE 1 A, It shows a UV-Vis rapid scans (at 5 minutes interval for 1 hour and after several hours) for the reaction mixtures of 5.0×10^{-5} M of **4b** with 1.0×10^{-3} M (*n*-propylamine) in acetonitrile. B, This shows a representative plot of the first-order rate constant, k_{Obs}, against (*n*-propylamine, **PA**) for the reactions with **4a**



SCHEME 3

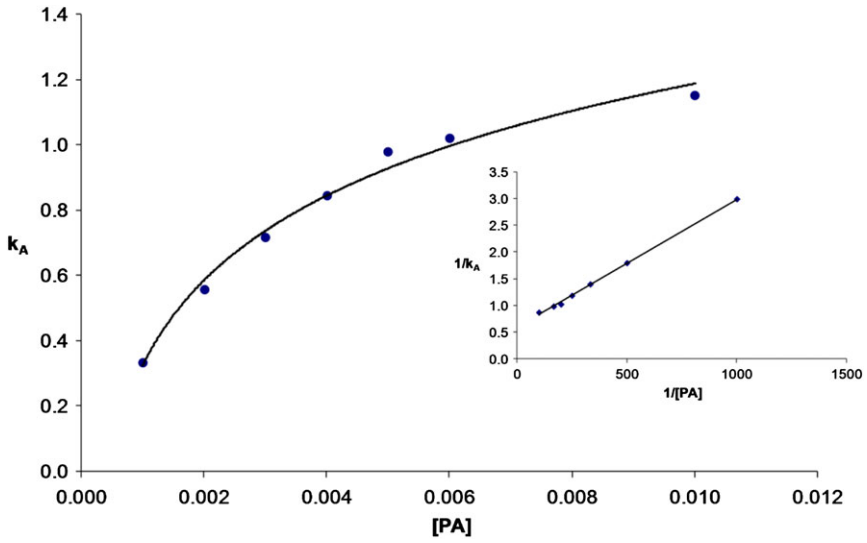


FIGURE 2 This shows a representative plot of the second-order rate constant, k_A, against (*n*-propylamine, **PA**) for the reaction with **4b** (the inset of Figure 2 shows a linear plot of $1/k_A$, against 1/(*n*-propylamine, 1/**PA**) used to obtained the rate coefficients displayed in Table 3)

A previous result for the same compound with *n*-butylamine has shown that this curvature is indicative of general base catalysis by the reaction with DABCO, a nonnucleophilic base.[12]

2.1 | Comparisons of the rate constants, k_1, for nucleophilic attack

The results in Table 3 involving nucleophilic attack at a ring carbon carrying phenoxy nucleofuge show a reactivity order for k_1 of *n*-propylamine > *n*-butylamine > 1-methylheptylamine for the less-activated compounds **3a** and **3b**. In contrast, for the more activated compounds **4a** and **4b**, the reactivity ratios in k_1 are in the order of *n*-butylamine ≈ *n*-propylamine > 1-methylheptylamine. The reactivity ratios in the values of k_1(*n*-propylamine)/k_1(1-methylheptylamine) are 33 (**3a**), 48 (**3b**), 5.3 (**4a**), and 17 (**4b**). Previous[11,12] results with a set of secondary and primary amines with the same compounds have shown a

TABLE 3 Summary of results[a] for reaction of **3** and **4** with aliphatic primary amines in acetonitrile at 25°C

Substrate, R		*n*-propylamine	*n*-butylamine[b]	1-methylheptylamine
3a 4-H	k_1/dm^3 mol^{-1} s^{-1}	0.27 (1)	4.7×10^{-2} (0.17)	8.1×10^{-3} (0.03)
3b 6-H	k_1/dm^3 mol^{-1} s^{-1}	2.9×10^{-2} (1)	4.9×10^{-3} (0.17)	6.0×10^{-4} (0.02)
4a 4-CF_3	k_1/dm^3 mol^{-1} s^{-1}	4.8 (1)	5.6 (1.17)	0.9 (0.19)
4b 6-CF_3	k_1/dm^3 mol^{-1} s^{-1}	1.70 (1)	2.0 (1.18)	9.7×10^{-2} (0.06)
	k_{Am}/k_{-1} dm^3 mol^{-1}	245 (1)	220 (0.9)	87 (0.36)
	K_1k_{Am}/dm^6 mol^{-2} s^{-1}	417 (1)	450 (1.08)	8.45 (0.02)

[a]Values in parentheses are the reactivities for a given compound relative to that for *n*-propylamine; for example, k_1(*n*-butylamine)/k_1(*n*-propylamine) and k_1(1-methylheptylamine)/k_1(*n*-propylamine).

[b]Values available from previous studies.[12]

reactivity order for k_1 of pyrrolidine > piperidine > *n*-butylamine. This is the order commonly found in nucleophilic substitution reactions[1–4] and reflects the relative basicities of the amines in acetonitrile; pKa values,[19] for the protonated amines, are pyrrolidine 19.58, piperidine 18.92, and *n*-butylamine 18.26. The superior reactivity of the secondary amines has also been attributed[20] to favourable ion-induced dipole interactions in the transition state between the partially positively charged nitrogen moiety and the polarisable alkyl substituents attached to it. The pKa values in water for *n*-propylamime, *n*-butylamine, and *n*-heptylamine are similar (approximately 10.66),[21] and in acetonitrile, the pKa value of 18.22 for *n*-propylamine is comparable with *n*-butylamine. However, pKa value in acetonitrile of 1-methylheptylamine is not available in the literature, but it is also expected to be of comparable value to these primary aliphatic amines. Hence, in the present study, the superior reactivity of *n*-butylamine and *n*-propylamine over the longer-chain aliphatic amine, 1-methylheptyamine, is not attributable to the differences in their basicities but stemmed from unfavourable steric hindrance to nucleophilic attack due to the 1-methyl group in the heptylamine nucleophile.

For compounds **3a** and **4a**, the reactivity ratios in the values of k_1, **4a/3a**, are 18 and 112 for *n*-propylamine and 1-methylheptylamine, respectively. The corresponding ratios for **4b/3b** are 58 and 162 for *n*-propylamine and 1-methylheptylamine, respectively. It is interesting to note that these reactivity ratios in the rate of nucleophilic attack is lower for compounds **4a/3a** (where the steric situation at the 1-position is constant) compared with **4b/3b**, where **4b** is carrying a 6-CF_3 group rather than hydrogen atom at the 6-position. These observed reactivity differences stem from an increase in activation in the ring rather than steric effect due to a change in the substituent group. However, a comparison of the reactivity of **4a/4b** gave a ratio of 2.8 for *n*-propylamine or *n*-butylamine and 9 for 1-methylheptylamine. This is an evidence of increased steric effects due to 6-CF_3 group in **4b**, which is more severe due to the methyl group close to the reaction centre in the reaction with 1-methylheptylamine. This is in accord with our previous results that the reactivity ratio for **4a/4b** in the rate of nucleophilic attack increases with increasing bulk of the attacking amine.[12] The steric effects of the CF_3 group in nucleophilic substitutions have been noted previously,[22] and its size has been estimated to be comparable to that of an isopropyl group.[23] Recent calculations[24] have shown that these effects may derive in part from electrostatic repulsions between the local negative charge on the trifluoromethyl group and the bulky nucleophiles. This repulsion from the trifluoromethyl, CF_3, group has been shown[24] to be stronger than that from the nitro group because of the presence of the more electronegative fluorine atom and the bigger size of the CF_3 group. Although the x-ray structure[24,12] of **4b** does not indicate any particularly large effects in the parent molecule, but kinetic results suggest that sterically, the effect of an *ortho*-CF_3 group on nucleophilic attack is greater than that of a nitro group. Thus, the current investigation reinforces the idea that the CF_3 group is sterically more demanding than the NO_2 group.

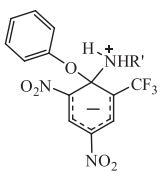
2.2 | Base catalysis

The incidence of base catalysis depends on the value of the ratio k_{Am}/k_{-1}; the lower the value, the greater the likelihood of base catalysis being observed.[13–15,25] The only compound in this study that is subject to catalysis is **4b** in all its reactions with the amines. This is likely to be due to a low value for k_{Am} due to repulsion between the *ortho*-CF_3 group in the zwitterion and the catalysing amine. There is good evidence[26–28] that with strongly activated substrates such as **3** and **4**, the zwitterionic intermediates, **6**, are more acidic than the corresponding ammonium ion, $RR'H_2N^+$, so that the proton transfer process, k_{Am}, will be in the thermodynamically "downhill" direction. Hence, values of k_{Am} may approach the diffusion limit but are known to be strongly influenced by steric factors. Thus, values are considerably decreased by steric congestion around the 1-position[28,29] and have been found to decrease with bulkier amine nucleophiles.[11,12,28,29] It must be noted that steric factors on k_{Am} differ from those involved in nucleophilic attack at the 1-position, k_1, and relate to hindrance of the approach of an amine molecule to the zwitterionic intermediates **6** to allow proton transfer to occur.

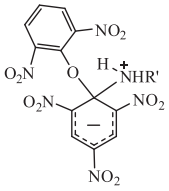
Interestingly, that the reactions with **4b** are the only reaction with all amines where base catalysis is observed is a further evidence for the large "steric" effect of the *ortho*-trifluoromethyl substituent, probably involving electrostatic repulsion by the CF_3 group of the amine base catalyst. Evidence from our report showed that values of k_{Am}/k_{-1} tend to increase with increasing electron withdrawal by the 4-substituent in the reactions of phenoxy compounds, **3**, carrying various substituent groups in the para position where the steric situation around the 1-position is similar. Since values of k_{Am} are likely to be unchanged, these increases may be attributed to decreases in values of k_{-1} as the zwitterionic intermediates, **6**, become more thermodynamically stable. It is interesting to observe from Table 3 that the values of k_{Am}/k_{-1} in the reactions with **4b** decrease by a factor of ca 3 for *n*-propylamine (or *n*-butylamine) to 1-methylheptylamine. The lower value of k_{Am}/k_{-1} for **4b** as the size of the nucleophile increases again reflects the large "steric" effects of the 6-CF_3 substituent.

It is also intriguing to recall that the reactions with the phenyl ethers **3** and **4** with aliphatic secondary amines, pyrrolidine, and piperidine are all base catalysed whereas it is only in the reactions with **4b** that such catalysis was observed with all 3 aliphatic primary amines. Here, catalysis involves rate-limiting proton transfer from the zwitterionic intermediates, **6**, to base. An additional factor to be considered in

differentiating the mechanism of S_NAr reactions with the amines is intramolecular hydrogen bonding in the zwitterionic intermediates, **6**, between an N-H proton and an *ortho*-nitro group. The presence of such hydrogen bonding, affecting the proton to be transferred, has been used[3,4] as an argument to explain differences in reactivity between primary and secondary amines. In the case of primary amines, there will always be one nonhydrogen-bonded proton available for transfer thus reducing the susceptibility to base catalysis. We have recently shown by Density functional theory (DFT) studies[24] that such hydrogen bond with either the NO_2 or the CF_3 groups may exist for compounds **4a** and **4b** in the transition state leading to the substitution products with aniline. However, this investigation as in our previous studies[12] has not found evidence for such hydrogen bonding as the differentiating factor in the dichotomy of the reactions involving **4a** and **4b** with a range of primary aliphatic amines and secondary amines of comparable basicities. In the present work, the rather similar susceptibilities to base catalysis with **4b**, of which contains an *ortho*-nitro and trifluoromethyl groups, and the observation of base catalysis in the reaction with both aliphatic primary and secondary amines affirm that such hydrogen bonding is not a major factor.



6



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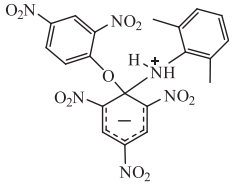

10

The observed reactivity differences and the change in mechanism from uncatalysed to catalysed reaction observed from a change in the reaction of **4a** to **4b** with these primary aliphatic amines are adequately explained in steric factors, which result in decreases in the value of k_{Am} in the order *n*-propylamine > *n*-butylamine ≫ 1-methylheptylamine. This is in contrast to the situation in which there is severe steric hindrance in the nucleofuge or the entering nucleophile. Our previous report[30] on the kinetic studies for the reactions with aniline in acetonitrile of a series of -phenyl 2,4,6-trinitrophenyl ethers (X = H, 2-, 3-, 4-CH_3, 2,4-, 2,6-$(CH_3)_2$, 2-, 3-, 4-NO_2, 2,4-, 2,6-$(NO_2)_2$) and x-ray crystal structures for X = H, 2,6-$(CH_3)_2$ and 2,6-$(NO_2)_2$ provided evidence for steric crowding around the 1-position of these molecules. With the 2,4-dinitro derivative, the uncatalysed reaction could compete with the base-catalysed pathway but the reactions with the 2,6-dinitro derivative (X = 2,6-$(NO_2)_2$) was uncatalysed, as the steric hindrance to intermolecular proton transfer from the zwitterion, **9**, to base was sufficient to make the base-catalysed pathway insignificant relative to the k_2 pathway. Similarly, the reactions of 2,4-dinitrophenyl-2,4,6-trinitrodiphenyl ethers with 12 ring-substituted anilines showed that although substituents at the 3-positions or 4-positions of the anilines have only small steric effects, alkyl substituents at the 2-position may result in considerable reductions in reactivity.[31] These effects are more pronounced for the base-catalysed pathway, and in 2,6-dimethylaniline, the uncatalysed decomposition of the zwitterionic intermediate, **10**, takes all the reaction flux.

The results from this study and our previous work[12, 26, 32] show that all phenyl trinitrophenyl ethers are sterically strained structures. Hence, steric hindrance to the steps involved in nucleophilic aromatic substitution by amine nucleophiles may become a major factor in controlling the rate-determining step in the substitution process when

- **i.** the electrophile carries a bulky *ortho*-substituent group. In this case, specific rate-retarding effects of an *ortho*-CF_3 group are observed.
- **ii.** both entering amine and leaving groups carries 2 *ortho*-substituent groups. This often results in an uncatalysed substitution.[30,31]
- **iii.** *N*-substitution in the amine nucleophile[29,32] results in considerable reduction in reactivity due to steric hindrance to the entrance of nucleophile in the formation of zwitterionic intermediate. The deactivating effect of *N*-CH_3 has been observed to be slightly higher than that of 2,6-dimethyl group in aniline nucleophiles.

3 | CONCLUSION

These results provide an interesting example of how the *ortho*-CF_3 substituent group in the substrate may give rise to a change in the nature of the rate-determining step in the substitution pathway. Steric effects appear to be less important in the determining the value of k_1, the rate constant for nucleophilic attack. However, it can, in the case of aromatic substrates bearing *ortho*-CF_3 compounds, slow the rate constants for intermolecular proton transfer to a catalysing base. The result is, for an S_NAr reactions in dipolar aprotic solvents with primary aliphatic amines and aromatic substrates, which are not prone to catalysis, a change from an *ortho*-NO_2 to the *ortho*-CF_3 substituent often changes the pathway from uncatalysed to wholly base-catalysed reaction. A situation attributed to steric-induced change in the rate-determining step in S_NAr reactions.

4 | EXPERIMENTAL

The compounds, **3** and **4** and the corresponding amine substitution products, were available from previous work.[12] Amines and acetonitrile were the purest available commercial samples. Kinetic measurements were made spectrophotometrically at the absorption maxima of the products using Varian Cary 50 or 100 UV-Vis spectrophotometers. Rate constants

were measured at 25°C under pseudo–first-order conditions with substrate concentrations of 1×10^{-4} to 1×10^{-5} mol dm^{-3} and were calculated by standard methods. Values are precise to ±3%.

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