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Nucleophilic Aromatic Substitution Reactions in Dipolar Aprotic Solvents: The Remarkable Effect of Trifluoromethyl Group on the Reactivity of Nitrophenyl Ethers with Nucleophiles.

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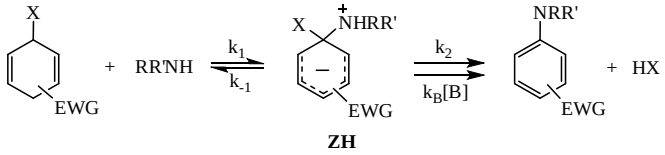
ABSTRACT

Rate constants are reported for the reactions of 4-phenoxy-3-nitrobenzotrifluoride **3c**, 2-phenoxy-5-nitrobenzotrifluoride **4c** and 1-phenoxy-2,4-dinitrobenzene **5c** activated by trifluoromethyl (CF_3) or nitro (NO_2) groups with *n*-butylamine, pyrrolidine and piperidine in DMSO. The results are compared with results reported previously for same reactants and with the more strongly ring-activated compounds 4-phenoxy-3,5-dinitrobenzotrifluoride **1c** and 2-phenoxy-3,5-dinitrobenzotrifluoride **2c** in acetonitrile. A change in reaction medium from acetonitrile to DMSO leads to a reduction in values of k_{Am}/k_{-1} as the proton-transfer from zwitterionic intermediates to catalysing amine becomes less thermodynamically favourable. Overall, the reactivity order is **5c** > **3c**> **4c** and decreasing ring-activation in the 1-phenoxy compounds **1c** - **5c** leads to lower values of k_{Am}/k_{-1} resulting in greater susceptibility to base catalysis. Specific steric effects leading to rate-retardation, is noted for the *ortho*-CF_3 group. The higher reactivity of *para*-CF_3 group in compounds **3c** compared to **4c** has been attributed partly to the more effective polar hyperconjugative activation by the CF_3 group in **3c** and to a possible participation of unfavourable electrostatic repulsion for the *ortho*-CF_3 group between the electronegative fluorine atoms in **4c** and the incoming nucleophiles.

Keywords: Trifluoromethyl group, Proton transfer mechanism, Stereoelectronic effects, Nucleophilic aromatic substitution.

1.0 INTRODUCTION

Mechanisms and reactivity of aromatic nucleoplilic substitution (S_NAr) reactions continue to attract attention [1-4] and recent studies show the continued synthetic utility of S_NAr strategies in the development of pharmaceuticals and other functional materials. S_NAr reactions of activated aromatic compounds with amines usually involves the Bunnett-type mechanism [5-7] shown in Scheme 1. When the second step is rate limiting then general base catalysis may be observed.



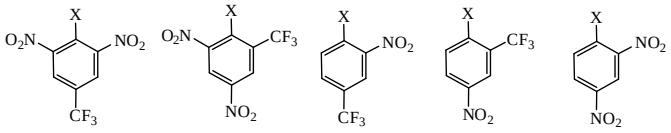
EWG = electron withdrawing groups

Scheme 1

Early studies [8] were concerned with discerning the mechanism of the general base catalysed step, $k_B[B]$. It is now recognised that in dipolar aprotic solvents, such as dimethyl sulfoxide (DMSO) and acetonitrile (MeCN), the rate limiting proton transfer may be from the zwitterionic intermediate **ZH** to base, the rate-limiting proton transfer (RLPT) mechanism; or, it may involve general acid catalysis, by BH^+, of the expulsion of the leaving group from the

deprotonated form of **ZH**, the specific base – general acid (SB-GA) mechanism [9]. The latter mechanism has been shown to apply to substrates such as alkyl ethers carrying poor leaving groups [10, 11]. However there is good evidence that for substrates containing good leaving groups, such as phenyl ethers the RLPT mechanism applies [12-15]. The absence of base catalysis implies that the initial nucleophilic attack, k_1 step, is rate limiting [5-7].

Steric and electronic effects due to substituent groups on the kinetics of organic reactions in solution are very useful tools for probing reaction mechanism [16]. In previous publications [17-20] we have shown that in the field of nucleophilic aromatic substitution, kinetic data obtained by varying the steric and electronic properties of the electrophilic substrates **1**-**5** can provide valuable information on the mechanism of S_NAr processes in aprotic and dipolar aprotic solvent. Our results showed that in the reaction carried out in toluene and MeCN as solvent, the decreased ring-activation in compounds **3**-**5**, compared to compounds **1**, **2**, leads to reductions in values of k_{Am}/k_{-1} resulting in greater susceptibility to base catalysis. Rate constants k_1 for nucleophilic attacks are also reduced but steric effects due to repulsion between the incoming nucleophile and *ortho*-substituents are less evident in **3-5**. These studies also revealed remarkable rate-retarding effects of an *ortho*-CF_3 group in compound **2** [17,19].



1 **2** **3** **4** **5**

a X = Cl
b X = F
c X = OPh

Fluoroorganic compounds are known to have unique chemical, physicochemical and biological properties continue to attract attention [21,22]. Hence, we have extended our interest in the S_NAr reactions of these compounds to obtain additional information about the effects of changing reaction medium and the relative position of CF_3 substituent in the phenoxy derivatives **3c** and **4c**, on the of base-catalyzed (k_3[B]) and uncatalyzed (k_2) pathways in Scheme 1 and to elucidate further the mechanism of base catalysis in these chemical systems. Herein rate data for the substitutions of compounds, **3c**, **4c** and **5c** with the amine *n*-butylamine, pyrrolidine and piperidine in DMSO are reported. The effect of changing the solvent medium from MeCN to DMSO and the comparison of the relative activation and stereoelectronic effects due to *ortho*-nitro and *ortho*-trifluoromethyl groups in these compounds are examined.

2.0 EXPERIMENTAL

The phenoxy compounds **3c**, **4c** and **5c** were prepared by reaction at 45ºC for two hours of the appropriate 1-chloro compound (1 equiv.) with potassium hydroxide (1 equiv.) in an excess of phenol in aqueous ethanol. On completion water was added and the solid formed was recrystallised from ethanol. Analytical data for **3c-5c** have been reported previously [17-19].

Amines and DMSO were the purest available commercial samples. Kinetic measurements were made spectrophotometrically at the absorption maxima of the products using Shimadzu UV PC spectrometer. Rate constants were measured at 25ºC under first-order conditions with substrate concentrations of *ca*. 1×10^{-4} mol dm^{-3} and were evaluated by standard methods. Values are precise to ±3%.

3.0 RESULTS AND DISCUSSION

3.1. Kinetic data

UV-vis measurements of the reaction of substrates **3c** $5.0x10^{-5}\,mol\,dm^{-3}$ in DMSO containing ($0.001\text{-}0.2\,mol\,dm^{-3}$) amine showed in each case a single process. Spectra at the completion of the reactions were identical to those of the authentic samples of the products dissolved in the reaction medium. At the concentration of the amines used, the rapid reversible reactions leading to the formation of adducts at the 3-position were not observed. The

results are therefore interpreted in terms of Scheme **2**. In all cases, substitution of the phenoxy group by amine to give the corresponding amine substituted derivatives occurred without the appearance in spectroscopically observable concentration, of intermediate **7** on the reaction pathway. Failure to observe such an intermediate is attributed to its rapid cleavage by loss of phenoxide ion [23, 24].

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

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

If nucleophilic attack is rate-limiting, corresponding to the condition $k_2 + k_{Am}[Am] >> k_{-1}$ then Equation (1) reduces to Equation (2)

$$k_A = k_1 \quad (2)$$

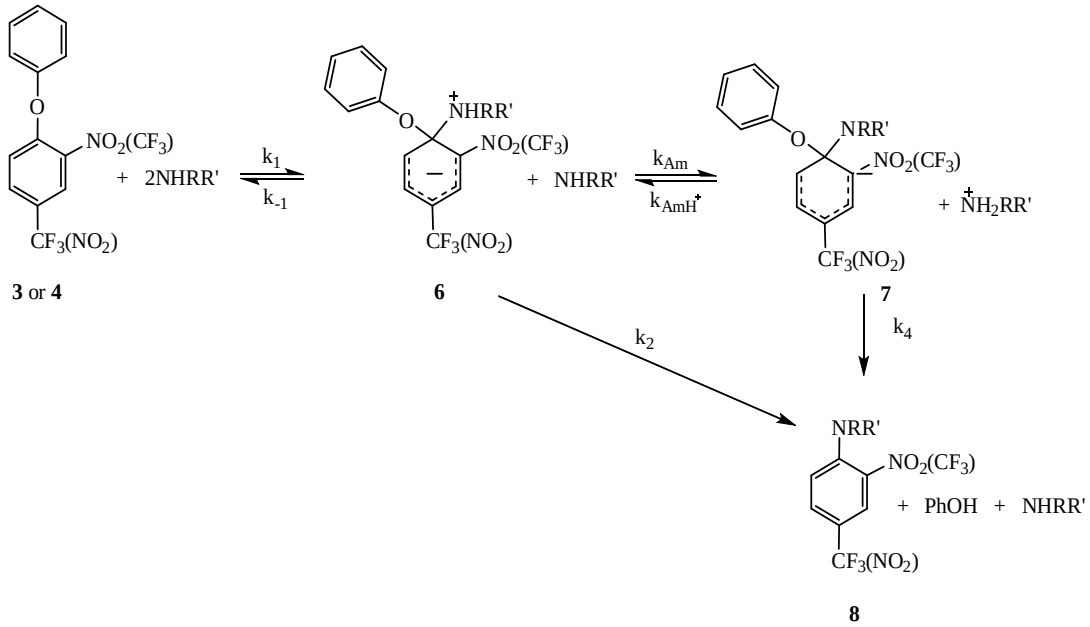
Other limiting forms of Equation (1) are Equation (3) when $k_{-1} >> k_2 + k_{Am}[Am]$, and Equation (4) when the uncatalysed pathway may be neglected, $k_{Am}[Am] >> k_2$.

$$k_A = K_1k_2 + K_1k_{Am}[Am] \quad (3)$$

$$k_A = \frac{K_1k_{Am}[Am]}{1 + \frac{k_{Am}[Am]}{k_{-1}}} \quad (4)$$

Rate data for the reactions of **3c** with *n*-butylamine and with piperidine are displayed in Table I. For the reaction of **3c** with *n*-butylamine, values of the second order rate constant, k_A, in Table I were independent of the amine concentration. This corresponds to the condition $k_2 + k_{Am}[Am] >> k_{-1}$ so that equation 2 applies.

Rate data for the corresponding reaction of **3c** with piperidine are also displayed in Table 1 but the corresponding reactions with pyrrolidine are in Table 2. In both cases, the plots of k_A versus amine concentration shown in Figures 1 (a and b) had a distinct intercept. Hence equation (3) applies, indicating that the contribution of both the base-catalysed and the uncatalysed pathway is significant to the overall reaction flux.



Scheme 2

Table 1. Kinetic results[a] for reaction of **3c** with *n*-butylamine and with piperidine in DMSO at 25°C.

[Amine]/ 10^{-2} mol dm^{-3}	***n*-Butylamine**		**Piperidine**	
	$k_{obs}/10^{-5}$ s^{-1}	$k_A/10^{-4}$ dm^3 mol^{-1} s^{-1}	$k_A/10^{-4}$ dm^{3}mol^{-1} s^{-1}	$k_{Acalc}10^{-4}$ dm^3 mol^{-1} s^{-1}
1.2	0.65	5.41	-	-
1.6	0.71	4.44	-	-
4.0	1.90	4.75	-	-
6.0	-		0.72	0.71
8.0	4.07	5.09	0.78	0.77
10.0	4.68	4.68	0.83	0.83
20.0	8.81	4.41	1.17	1.15
40.0	-		1.85	1.80
50.0	-	-	2.12	2.10

a) k_{Acalc} (Values calculated using equation 3 with the values given in Table 3)

Table 2. Kinetic results[a] for reaction of **3c** and **4c** with pyrrolidine in DMSO at 25°C

[Pyrrolidine]/ 10^{-2} mol dm^{-3}	**3c**		**4c**	
	$k_A/10^{-2}$ dm^3 mol^{-1} s^{-1}	$k_{Acalc}/10^{-2}$ dm^3 mol^{-1} s^{-1}	$k_A/10^{-5}$ dm^3 mol^{-1} s^{-1}	$k_{Acalc}/10^{-5}$ dm^3 mol^{-1} s^{-1}
1.0	1.32	1.42	-	-
2.0	1.51	1.54	-	-
8.0	2.30	2.26	-	-
20	3.64	3.70	1.44	1.60
30	-	-	2.16	2.10
50	-	-	3.12	3.20

a) Values calculated using equation 3 (for **3c**) and equation 4 (for **4c**) with the values given in Table 3.

Table 3. Summary of results[(a)] for reactions of 1-phenoxy-nitrobenzenes with aliphatic amines in DMSO at 25ºC.

Substrate			*n*-Butylamine	Pyrrolidine	Piperidine
3c	4-CF_3	k_1/ dm^3 mol^{-1} s^{-1}	4.4×10^{-4}	-	-
		K_1k_{Am}/ dm^6 mol^{-2} s^{-1}	-	0.12	3.0×10^{-4}
		K_1k_2/dm^3 mol^{-1} s^{-1}	-	0.013	5.0×10^{-5}
4c	6-CF_3	k_1/dm^3 mol^{-1} s^{-1}	-	1.52×10^{-4}	1.64×10^{-5}
		k_{Am}/k_{-1} dm^3 mol^{-1}	-	0.53	0.173
		K_1k_{Am}/dm^6 mol^{-2} s^{-1}	-	8.1×10^{-5}	2.83×10^{-6}
5c[b]	4-NO_2	k_1/dm^3 mol^{-1} s^{-1}	4.2×10^{-2}(1)	1.15(27)	0.6(14)
		k_{Am}/k_{-1} dm^3 mol^{-1}	-	37	1.3
		K_1k_{Am}/dm^6 mol^{-2} s^{-1}	-	43	0.8
		K_1k_2/dm^{3}mol^{-1} s^{-1}	-	-	5.0×10^{-3}

a) Values in parentheses are the values of k_1 for a given compound relative to the value for *n*-butylamine

b) Values obtained from ref. [18]

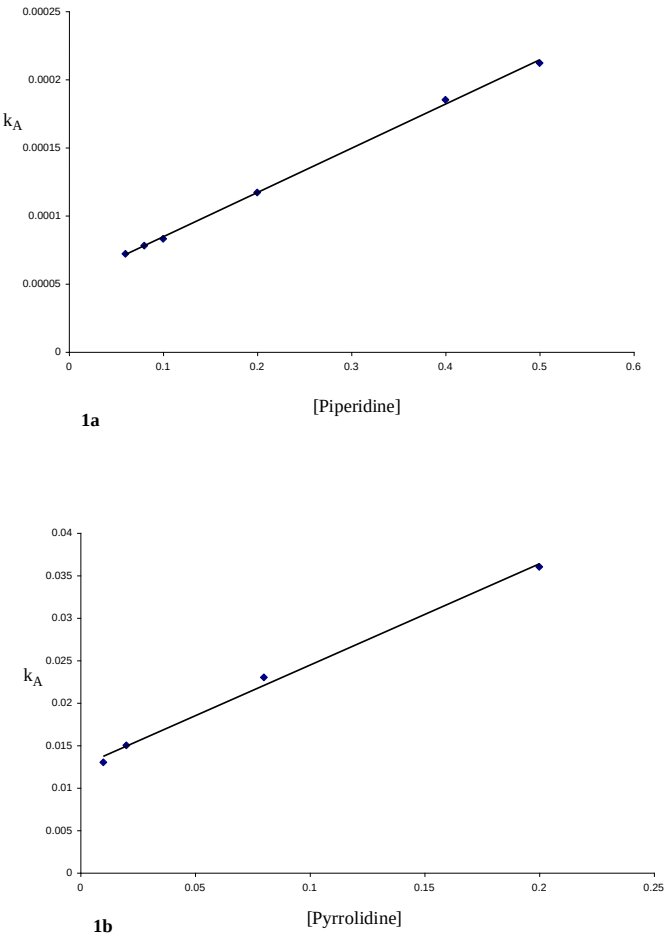


Figure 1. Plots of the second order rate constant, k_A, against [amine] for the reactions of **3c** with piperidine (1a) and pyrrolidine (1b) in DMSO.

Unexpectedly, the corresponding substitution involving the reactions of **4c** with low to high concentrations of *n*-butylamine in DMSO were extremely slow for kinetic measurement. However reactions of **4c** with high concentrations 0.2- 0.5 mol dm^{-3} of piperidine and pyrrolidine, the more basic amine are considerably faster and gave the expected amine substitution products in >90% yield. Kinetic data are displayed in Table 2 and showed evidence for base catalysis. Plots of values of k_A versus amine concentration, not shown, are curved and the alternate plot of the inverse of k_A *vs* 1/[amine] gave good fit with equation (4). Values of rate coefficient obtained from kinetic plots are assembled in Table 3.

3.2 Comparison

The S_NAr reaction centres in compounds **3** and **4** are less sterically crowded than the previously studied compounds **1** and **2** (apart from **1**, R=H) since there is at most one bulky substituent at an *ortho*-position. The comparison of the reactivity ratio displayed in Table 4 gives a quantitative measure for the effects of changing the positions of the ring substituents on rate constants for the individual steps in Scheme 2 for compounds **3-5**, in which either the *ortho* or *para*-substituent is varied by either carrying a nitro or CF_3 groups. Although the compounds showed varying kinetic forms but comparison is possible where same rate coefficients are available. The rate coefficients reflects the activating power of the substituents and decrease in the order NO_2 > CF_3. However, a comparison of the influence of an *ortho*: *para* ratio for **3c**/**4c**, with activating CF_3 group gave over a 100 fold higher reactivity for *para*-CF_3 compared to *ortho*- CF_3. This is far in excess of the *ortho:para* ratio observed when the change in position of the substituent involved only a nitro group [18]. Interestingly, the reactivity ratios for all the parameters k_1, k_{Am}/k_{-1}, K_1k_{Am}, K_1k_{Am} displayed in Table 4, show small decrease as the bulk of the amine is increased from pyrrolidine to piperidine and particular severe for compounds **4c** bearing *ortho*-CF_3. Reactivity ratios (Table 3) decrease in the order pyrrolidine > piperidine > *n*-butylamine.

Interestingly, the k_1 pyrrolidine/k_1 piperidine ≈ 10 obtained for the reaction with **4c** is in sharp contrast to a value of ca. 2 for the same reactions with **5c**; a ratio normally associated with attack at an unhindered ring-position [5-7, 25, 26]. Comparison using previously reported data in Table 5 for similar reactions in acetonitrile, show that the amine reactivity ratios are much reduced in **2a**, R=H indicating the considerably greater steric requirements to nucleophilic attack for pyrrolidine and piperidine relative to *n*-butylamine. Reactions in both DMSO and acetonitrile indicate that compound **3c** is more reactive than **4c**.

Table 4. Relative reactivities[(a)] of similarly activated 1-phenoxy- compounds **3-5** in DMSO.

Reactants	Rate coefficient	*n*-Butylamine	Pyrrolidine	Piperidine
5c/**3c**	k_1	96	-	-
	K_1k_{Am}/dm^6 mol^{-2} s^{-1}	-	358	2.67×10^3
	K_1k_2/dm^{3}mol^{-1} s^{-1}	-	-	100
5c/**4c**	k_1	-	7.56×10^3	3.65×10^4
	k_{Am}/k_{-1} dm^3 mol^{-1}	-	64	8
	K_1k_{Am}/dm^6 mol^{-2} s^{-1}	-	5.31×10^5	2.83×10^5
3c/**4c**	K_1k_{Am}/dm^6 mol^{-2} s^{-1}	-	1.48×10^3	106

a) The more reactive substrate as the denominator.

Table 5. Summary of results [(a)] for reactions of 1-phenoxy compounds with aliphatic amines in acetonitrile[(b)] at 25ºC.

Substrate			*n*-Butylamine	Pyrrolidine	Piperidine
1a	4-CF_3	k_1/dm^3 mol^{-1} s^{-1}	220	393	470
1c		k_1/dm^3 mol^{-1} s^{-1}	5.6(1)	12(2.1)	-
		k_{Am}/k_{-1} dm^3 mol^{-1}	-	10	-
		K_1k_{Am}/dm^6 mol^{-2} s^{-1}	-	120	3.3
2a	6-CF_3	k_1/dm^3 mol^{-1} s^{-1}	56	2.2	1.6
2c		k_1/dm^3 mol^{-1} s^{-1}	2.0(1)	>2(>1)	-
		k_{Am}/k_{-1} dm^3 mol^{-1}	220	<5	-
		K_1k_{Am}/dm^6 mol^{-2} s^{-1}	450	11.3	0.30
3a	4-CF_3	k_1/dm^3 mol^{-1} s^{-1}	7.0×10^{-5}(1)	9.9×10^{-3}(140)	2.8×10^{-3}(40)
3b		k_1/dm^3 mol^{-1} s^{-1}	0.12(1)	5.0(42)	2.1(18)
3c		k_1/ dm^3 mol^{-1} s^{-1}	4.5×10^{-5}	-	-
		k_{Am}/k_{-1} dm^3 mol^{-1}	-	<1	-
		K_1k_{Am}/ dm^6 mol^{-2} s^{-1}	-	1.1×10^{-2}	4.4×10^{-4}
		K_1k_2/dm^3 mol^{-1} s^{-1}	-	1.95×10^{-4}	2.4×10^{-5}
4b	6-CF_3	k_1/dm^3 mol^{-1} s^{-1}	3.6×10^{-3}(1)	2.2×10^{-2}(6)	2.2×10^{-3}(0.6)[d]
4c		k_1/dm^3 mol^{-1} s^{-1}	-	-	-
5a		k_1/dm^3 mol^{-1} s^{-1}	8.9×10^{-3} (1)	1.3(146)	0.52(58)
5b		k_1/dm^3 mol^{-1} s^{-1}	8.9(1)	570(64)	150(17)
5c		k_1/dm^3 mol^{-1} s^{-1}	4.9×10^{-3}(1)	0.37(76)	0.16(33)
		k_{Am}/k_{-1} dm^3 mol^{-1}	-	70	5.0
		K_1k_{Am}/ dm^6 mol^{-2} s^{-1}	-	26	0.8

(a) Values in parentheses are the values of k_1 for a given compound relative to the value for *n*-butylamine.
(b) Values from reference [17, 18].

This presumably is polar in origin and may involve hyperconjugative activation in the substrate **3c** and stabilization in the intermediate **6c** by the trifluoromethyl group which is more effective from the *para*- than from the *ortho* position [27, 28]. Another possible contributory effect is the unfavourable repulsive forces at the *ortho* position between the electronegative fluorine atoms in **4c** and the incoming nucleophiles [17, 18]. Although the nitro group imparts a greater ionic polar component to the C-NO_2 bond i.e δ^+ C- δ^- NO_2 compares to δ^+ C - δ^- CF_3 bond but the repulsive steric effects of the CF_3 group are larger. The steric effects of the CF_3 group in nucleophilic substitutions have been noted previously [29], and its size has been estimated to be comparable to that of an isopropyl group [30]. Recent calculations [31] have shown that these effects may derive in part from electrostatic repulsions between the local negative charge on the trifluoromethyl group and the incoming nucleophile.

3.3 Solvent effects

The ratio in the value of k_1(DMSO) : k_1(MeCN), the rate constant for the nucleophilic attack for the reactions with butylamine were ≈10 and 4 for the reactions with **3c** and **4c** or **5c** respectively. This reflect a higher reactivity in DMSO > MeCN. The major factor influencing reactivity difference in these solvents medium is likely to be the greater ability of DMSO than acetonitrile to solvate the charged species, **6**, which are the products of reaction at the 1-position [32, 33].

In contrast, the ratio of k_{Am}/k_{-1}(DMSO): k_{Am}/k_{-1} (MeCN) are ≈ 0.52 and 0.26 for the reaction of pyrrolidine and piperidine with **5c** respectively. Previous work has shown that rate constants for proton transfers between nitrogen atoms may be considerably lower, by a factor of 10^4, in DMSO than in acetonitrile [11-13, 15, 23, 24]. This has been attributed to the excellent hydrogen-bond acceptor properties of DMSO so that acidic ammonium protons [34], in $-\overset{+}{N}HR^1R^2$ groups, will be H-bonded to the solvent thus reducing rate constants for their transfer. This will be expected to reduce values for k_{Am} in DMSO relative to acetonitrile. However, the results suggest that values of the overall rate for nucleophilic substitution process in DMSO are faster than those in acetonitrile.

3.4 Mechanism of Substitution

Reaction of the phenyl ethers (**3c - 5c**), with *n*-butylamine are first order in amine indicating that nucleophilic attack is rate limiting, $k_{Am} >> k_{-1}$. This is likely to be a consequence, in terms of the mechanism in Scheme 2 of relatively high values of k_{Am}, the rate constant for proton transfer and low values of k_{-1}, the rate constant for the decomposition of the zwitterion to reactants. In contrast, reactions with pyrrolidine and piperidine with the same compounds show clear evidence of base catalysis. In compound **5c**, the electron-withdrawing power of the ring is further reduced and although surprisingly, the reaction with *n*-butylamine is not base catalysed but the reactions with the secondary amines follow Equation 3 showing that proton transfer is fully rate-determining. While the reactions with the secondary amines with **4c** were wholly base catalysed, those of **3c** and **5c** show that the k_2 pathway, involving intramolecular proton transfer within the zwitterion coupled with leaving group expulsion, may compete with the k_{Am}[Am] pathway. This is likely to reflect the lower values of k_{Am} associated with the reduce ring activation. There is strong evidence that in strongly activated compounds, e.g. **1c** and **2c**, the zwitterionic intermediates, **Z**, are more acidic than the corresponding ammonium ions $R^1R^2NH_2^+$ so that the proton transfer process, k_{Am}, is in the thermodynamically "downhill" direction [17, 35]. Hence values of k_{Am} may approach the diffusion limit but are reduced by steric factors which have been shown to decrease in the order *n*-butylamine > pyrrolidine > piperidine.

The reactivity ratio for **5c**/**3c** in the values K_1k_{Am} (NO_2): K_1k_{Am} (CF_3) in Table 4 for the reactions with pyrrolidine and piperidine are 358 and 2.67×10^3 respectively. In contrast, the ratios for **3c**/**4c** are 1.48×10^3 and 106 for the reactions with pyrrolidine and piperidine

respectively. Interestingly, values for the reactivity ratios in k_{Am}/k_{-1} for **5c**/**4c** are 69 and 7.5 respectively for the reaction of pyrrolidine and piperidine respectively. Our previous reports [17-20] show that changes in ring activation from the *para* remote position in the substrate has little effect on the base catalysed pathway. Hence, these reactivity ratios reflect the reduction in the values of k_{Am} due to effect of the trifluoromethyl group as the size of the nucleophile get bigger. Although the nitro and the trifluoromethyl group have the same width [36], the nitro group is planar and when *ortho* to most leaving groups, its plane is in the plane of the benzene ring, whereas the trifluoromethyl group approximates to a hemisphere and its thickness is considerably greater than that of a nitro group. There is evidence that the steric bulk of CF_3, especially in nucleophilic reaction is comparable to that of an isopropyl or *tert*-butyl groups [37]. This unexpected large steric effect of CF_3 has been attributed to a possible participation of electrostatic repulsion. The k_{-1} for the trifluoromethyl group is therefore likely to be more enhanced than that of nitro group by release of steric strain present in the intermediate, such as **6**. Hence, the rate constants for proton transfer from the zwitterionic intermediates **6** are largely determined by steric factors in accord with the proton transfer (RLPT) mechanism in S_NAr reactions [10-19].

4.0 CONCLUSION

Our results show that the decreased ring-activation in compounds **3-5**, compared to compounds **1**, **2**, leads to reductions in values of k_{Am}/k_{-1} resulting in greater susceptibility to base catalysis. Also a change in reaction medium from acetonitrile to DMSO showed a reduction in values of k_{Am}/k_{-1} as the proton-transfer from zwitterionic intermediates to catalysing amine becomes less thermodynamically favourable. Reactions in both DMSO and acetonitrile indicate a higher reactivity of **3c** than **4c**, i.e. reaction is faster at the position with the nitro-group *ortho* to the nucleofuge than at a position *ortho* to trifluoromethyl-groups. This bears witness to the large steric effect of the CF_3 group. Thus, the specific rate-retarding effect of an *ortho*-CF_3 group has been attributed partly to the effects of polar hyperconjugative activation by the trifluoromethyl group and unfavourable repulsive forces at the *ortho* position between the electronegative fluorine atoms and the incoming nucleophiles.

REFERENCES

1. M. Gazitu, R.A. Tapia, R. Contreras and P. R.Campodónico (2018), Mechanistic pathways of aromatic nucleophilic substitution in conventional solvents and ionic liquids, *New J. Chem*., **42**, 260-264.
2. M. S. Mayo, X. Yu, X. Feng, Y.Yamamoto and M. Bao **(**2015), Isoquinolone Synthesis through S_NAr Reaction of 2-Halobenzonitriles with Ketones Followed by Cyclization, *J. Org. Chem.,* ***80*** (8), 3998-4002.
3. N.R. Lee, F. Gallou and B.H. Lipshutz (2017**)**, S_NAr Reactions in Aqueous Nanomicelles: From Milligrams to Grams with No Dipolar Aprotic Solvents Needed, *Org. Process Res. Dev.*, **21**(2), 218-221.
4. *N.A. Isley, R. T.H. Linstadt, S.M. Kelly, F. Gallou and B.H. Lipshutz (*2015**),** Nucleophilic Aromatic Substitution Reactions in Water Enabled by Micellar Catalysis, *Org. Lett*., **17** (19), 4734-4737.
5. O. Banjoko and I.A. Babatunde (2004**)**, Rationalization of the conflicting effects of hydrogen bond donor solvent on nucleophilic aromatic substitution reactions in non-polar aprotic solvent: reactions of phenyl 2,4,6-trinitrophenyl ether with primary and secondary amines in benzene-methanol mixtures, *Tetrahedron*., **60**, 4645-4654.
6. P.M. Mancini, G.G. Fortunato and L.R. Vottero (2004**)**, Kinetics of the reactions between 1-fluoro-2,6-dinitrobenzene and pyrrolidine and piperidine in binary solvent systems: Influence of the nucleophile structure, *J. Phys. Org. Chem*., **17**, 138-147.
7. F.Terrier (2013**),** Nucleophilic Aromatic Substitution. Wiley-VCH; Germany:
8. C.F. Bernasconi (1973**)**, Mechanisms and Reactivity in Aromatic Nucleophilic Substitution Reactions, *MTP International Reviews of Science Org. Chem*. Ser. 1 Butterworths, London, , **3**, 33-63.

9. C. F. Bernasconi and P. Schmid (1977), Changing views on the mechanism of base catalysis in nucleophilic aromatic substitution. Kinetics of reactions of nitroaryl ethers with piperidine and with *n*-butylamine in aqueous dioxane, *J. Am. Chem. Soc*., , 99, 4090-4096.
10. M. R. Crampton, T.A. Emokpae and C. Isanbor (2006), Electronic and Steric Effects in the S_NAr Substitution Reactions of Anilines with 2,4-Dinitrophenyl 2,4,6-trinitrophenyl ether in Acetonitrile , *J. Phys. Org. Chem*., **19**, 75-80.
11. R.A. Chamberlin and M.R. Crampton (1995**)**, Mechanism of base catalysis in the reactions of phenyl aryl ethers with aliphatic amines in dimethyl sulfoxide, *J. Chem. Soc, Perkin Trans. 2.*, 1831-1838.
12. M.R. Crampton and S.D. Lord (1997**)**, Kinetic and equilibrium studies of σ-adduct formation and nucleophilic substitution in the reactions of trinitro-activated benzenes with aliphatic amines in acetonitrile, *J. Chem. Soc, Perkin Trans. 2*, 369-376.
13. M.R. Crampton and P. Routledge (1984) The stabilities of Meisenheimer complexes. Part 34. Kinetic studies of σ-adduct formation and nucleophilic substitution in the reactions of 2,4,6-trinitrophenetole with aliphatic amines in dimethyl sulphoxide, *J. Chem. Soc, Perkin Trans. 2*, 573-581.
14. Y. Hasegawa (1985), Kinetics of the formation of the 1,3-complex and on the formation and decomposition of the intermediate complex. Reaction of 2,4,6-trinitroanisole with n-butylamine in dimethyl sulphoxide, *J. Chem. Soc, Perkin Trans. 2*, 87-92.
15. M.R.Crampton and B.Gibson (1981), The stabilities of Meisenheimer complexes. Part 25. Kinetic studies of the reaction of 1,3,5-trinitrobenzene with aliphatic amines in dimethyl sulphoxide, *J. Chem. Soc, Perkin Trans. 2*., 533-539.
16. S. Böhm and O. Exner (2007). Steric effects of the alkyl groups: evaluation on isolated molecules by means of isodesmic reactions, *Org. Biomol. Chem*., **5**, 2081- 2086.
17. M.R. Crampton, T.A. Emokpae, C. Isanbor, A.S. Batsanov, J.A.K. Howard and R. Mondal (2006), Effects of *Ortho*- and *Para*-Ring Activation on the Kinetics of S_NAr reactions of 1-Chloro-2-nitro- and 1-Phenoxy-2-nitro-benzenes with Aliphatic Amines in Acetonitrile, *Eur. J. Org. Chem*., 1222-1230.
18. M.R. Crampton, T.A. Emokpae and C. Isanbor (2007), The Effects of Ring Substituents and Leaving Groups on the Kinetics of S_NAr Reactions of 1-Halogeno- and 1-Phenoxy-nitrobenzenes with Aliphatic Amines in Acetonitrile, *Eur.J. Org.Chem*., 1378-1383.
19. C. Isanbor and A. I. Babatunde (2009**)** The Kinetics of S_NAr Reactions of 1-Phenoxy-nitrobenzenes with Aliphatic Amines in Toluene: Ring Substituent and Solvent Effects on the Reaction Pathways. *J. Phys. Org. Chem*., 22, 1078-1085.
20. O. Oloba-Whenu and C. Isanbor (**2015**), Computational studies of the Effects of *ortho*- and *para*-Ring Activation on the Kinetics of S_NAr Reactions of 1-Chloro-2-nitro- and 1-phenoxy-2-nitrobenzenes with Aniline, *J. Phys. Org. Chem*., 28, 57-67.
21. K. Ishizawa, H. Nagai, Y. Shimizu and M. Kanai (2018), Boron-Catalyzed Carboxylic Acid-Selective Aldol Reaction with Trifluoromethyl Ketones, *Chem. Pharm. Bull*., **66**, 231-234.
22. [a] M. Zanda, (2004**),** Trifluoromethyl group: an effective xenobiotic function for peptide backbone modification , *New J. Chem*. **28**, 1401-1411 [b] P. Jeschke (2004**)**, The unique role of fluorine in the design of active ingredients for modern crop protection. *ChemBioChem*., **5**, 570-5789
23. M.R, Crampton, T.A. Emokpae, J.A.K. Howard, C. Isanbor and R. Mondal (2003**),** Kinetic and Equilibrium Studies of σ-adduct Formation and Nucleophilic Substitution in the Reactions of 2-Phenoxy-3, 5-dinitropyridine and 2-Ethoxy-3,5-dinitropyridine with Aliphatic Amines in Dipolar Aprotic Solvents, *Org. Biomol. Chem*., **1**, 1004-1011.
24. M.R. Crampton, L.M. Pearce, and L.C. Rabbitt (**2002**), Kinetic and equilibrium studies of the reactions of 4-nitrobenzofurazan and some derivatives with sulfite ions in water. Evidence for the Boulton–Katritzky rearrangement in a σ-adduct, *J. Chem. Soc, Perkin Trans. 2*., 257-261.
25. J.F. Bunnett, S. Sekiguchi and L.A. Smith (1981), Kinetics of reactions of cyclic secondary amines with 2,4-dinitro-1-naphthyl ethyl ether in dimethyl sulfoxide solution. Spectacular difference between the

behavior of pyrrolidine and piperidine, *J. Am. Chem. Soc*., **103**, 4865-4871.

26. G. Consiglio, V. Frenna, S. Guernelli, G. Macaluso and D. Spinelli (2002), Analysis of substituent effects: the reactions of some 2-L-5-nitro-3-X-thiophenes with primary and secondary amines in methanol, *J. Chem. Soc*, *Perkin Trans. 2*., 965-970.
27. J.F. Bunnett and R.J Morath (1955), The ortho: para Ratio in Activation of Aromatic Nucleophilic Substitution by the Nitro Group, *J. Am. Chem. Soc*., **77**, 5051- 5055.
28. F. R. Leroux, B. Manteau, J. Vors and S. Pazenok (2008), Trifluoromethyl ethers--synthesis and properties of an unusual substituent, *Beilstein J. Org. Chem*., **4** (13), 1-15.
29. S. V. Druzhinin, E. S. Balenkova and V. G. Nenajdenko (2007) Recent advances in the chemistry of α, β-unsaturated trifluoromethylketones, *Tetrahedron*, **63**, 7753-7808.
30. T. Katagiri, S. Yamaji, M. Handa, M. Irie and K. Uneyama (2001), Diastereoselectivity controlled by electrostatic repulsion between the negative charge on a trifluoromethyl group and that on aromatic rings, *Chem. Commun*., 2054-2055.
31. T. Nagai, G. Nishioka, M. Koyama, A. Ando, T. Miki and I. Kumadaki (1992, Reactions of trifluoromethyl ketones. IX. Investigation of the steric effect of a trifluoromethyl group based on the stereochemistry on the dehydration of trifluoromethyl homoallyl alcohols, *J. Fluorine Chem*., **57**, 229-238.
32. C.F. Bernasconi, M.C.Muller, P. Schmid (1979), Intermediates in nucleophilic aromatic substitution. 20. Rate-limiting proton transfer in the formation of Meisenheimer complexes between 1,3,5-trinitrobenzene and amines. The effect of dimethyl sulfoxide on proton-transfer rates. Relative leaving-group abilities of amines and alkoxide ions, *J. Org. Chem*., **44**, 3189-3196.
33. C. Isanbor, T.A. Emokpae and M.R. Crampton (2002), Steric and Electronic Effects on the Mechanism of Nucleophilic Substitution (S_NAr) Reactions of some Phenyl-2,4,6-trinitrophenyl Ethers with Aniline and *N*-methylaniline in Acetonitrile and Dimethyl sulfoxide, *J. Chem. Soc*, *Perkin Trans. 2*, 2019-2024.
34. J.F. Coetzee (1967), Ionic Reactions in Acetonitrile , *Progr. Phys. Org. Chem*.**,** **4**, 45-92.
35. R.A. Chamberlin and M.R. Crampton (1994), Kinetic studies of the reactions of some phenyl aryl sulfides with aliphatic amines in dimethyl sulfoxide; the mechanism of base catalysis, *J. Chem. Soc.*, *Perkin Trans. 2*, 425-432..
36. W.A. Sheppard (1970). The Chemistry of Functional Groups. The Chemistry of Cyano group. Ed. Z-Rappoport, Interscience New York**,** 209
37. B.E. Smart (1983). The Chemistry of Carbon-Halogen Bond, Supplement D, The Chemistry of Halides, Pseudo-Halides and Azides. Ed. S. Patai and Z-Rappoport, Wiley, New York, 603-655.