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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 Aliphatic Amines in Acetonitrile

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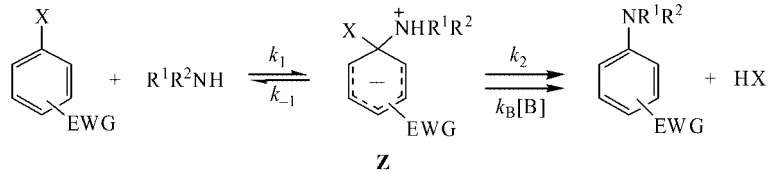
Rate constants are reported for reaction of 4-substituted 1-chloro-2,6-dinitrobenzenes **1**, 6-substituted 1-chloro-2,4-dinitrobenzenes **2**, and some of the corresponding 1-phenoxy derivatives, **3** and **4**, with *n*-butylamine, pyrrolidine and piperidine in acetonitrile as solvent. Values of k_1, 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. *ortho*-Substituents may also have adverse steric effects, and those of the trifluoromethyl group are particularly serious. X-ray crystal structures of phenyl 2,4-dinitro-6-trifluoromethylphenyl ether and phenyl 2,6-dinitro-4-trifluoromethylphenyl ether are reported. Base catalysis in the 1-phenoxy derivatives is attributed to rate-limiting proton transfer from the zwitterionic intermediates **6** to base. Values of rate constants for this process decrease with increasing steric congestion at the reaction centre and in the order *n*-butylamine > pyrrolidine > piperidine.

Introduction

The study of mechanisms and reactivity in aromatic nucleophilic substitution reactions has interested chemists for some years[1,2] and continues to attract attention.[3–6] The general mechanism for reactions involving amine nucleophiles is shown in Scheme 1, and early studies 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, the rate-limiting proton transfer may be from the zwitterionic intermediate **Z** to base, the RLPT mechanism; or, it may involve general acid catalysis, by BH^+, of the expulsion of the leaving group from the deprotonated form of **Z**, the SB-GA mechanism.

The latter mechanism has been shown to apply to substrates such as alkyl ethers carrying poor leaving groups.[7–10] However, there is good evidence that for substrates containing good leaving groups, such as phenyl ethers, the RLPT mechanism applies.[11–15] The absence of base catalysis implies[1] that the initial nucleophilic attack, k_1 step, is rate limiting.

Several previous studies have reported the effects of varying the electron-withdrawing substituents in the aromatic ring and/or the nature of the amine.[1,2] Electronic, steric and hydrogen-bonding effects have been identified as important factors influencing reactivity. However these studies have often been piecemeal in nature rather than encompassing an extended range of compounds.[16–20] Here we report kinetic studies of the reactions in acetonitrile of a series of 4-substituted 1-chloro-2,6-dinitrobenzenes **1**, 6-



Scheme 1.

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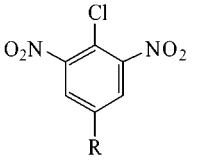
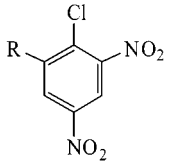
substituted 1-chloro-2,4-dinitrobenzenes **2**, and some of the corresponding 1-phenoxy derivatives **3** and **4** with *n*-butylamine, pyrrolidine and piperidine. Our aims were to (i) examine the relative activating power of substituents at positions *ortho* and *para* to the reaction centre, and (ii) compare the values of rate constants for the individual steps in the reaction pathway.



1



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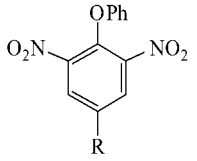

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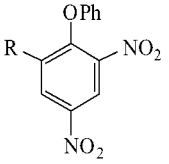


4

a R = H
b R = CF_3
c R = CO_2Me
d R = CN
e R = ring N
f R = NO_2

Results and Discussion

The reactions of parent molecules **1**–**4** with *n*-butylamine, pyrrolidine or piperidine in acetonitrile gave the expected products of substitution of chloride or phenoxide, respectively, in >95% yield. Kinetic measurements were made with the concentration of amine in large excess of the parent concentration, ca. $1 \cdot 10^{-4}$ mol dm^{-3}, and first-order kinetics were observed. Previous studies[11] in 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 **3f**, 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.[11] The dominant factor here is likely to be the greater ability of DMSO than of acetonitrile to solvate the ionic reaction products. The reaction of **4e** with pyrrolidine in acetonitrile was shown[21] to yield the substitution products without the observation of the adduct analogous to **5**. In the present work, reactions of the most strongly activated substrates **1c**,**d** and **2e**,**f** were measured in the presence of a low concentration, 0.001 mol dm^{-3}, of the perchlorate salt of the amine under investigation to remove the possibility of reaction at unsubstituted ring positions, while in the reactions of **3b**,**c**,**d** and **4b**,**e** amine concentrations were $\leq$ 0.05 mol dm^{-3}. Under these conditions substitution proceeded smoothly to give first-order kinetics without the observation, in spectroscopically measurable concentrations, of transient species analogous to **5** or of intermediates on the substitution pathway.

Making the usual assumption that the zwitterionic adduct **Z** 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).

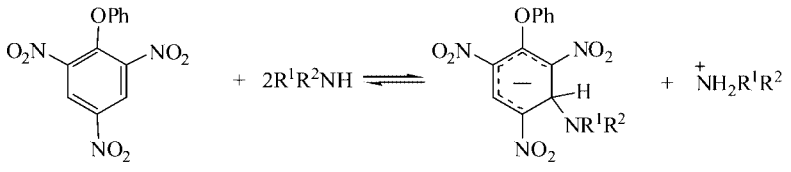
$$k_A = \frac{k_{obs}}{[Am]} = \frac{k_1(k_2 + k_{Am}[Am])}{k_{-1} + k_2 + k_{Am}[Am]} \quad (1)$$

For the 1-chloro-substituted reactants **1** and **2** values of the second-order rate constant, k_A, 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 chloride ion as the leaving group has only been found in a few special cases,[22] where factors such as the nature of the entering amine and the solvent contribute to a lowering of the ratio k_2/k_{-1}. Values of k_{obs}, the first-order rate constant, are available as supplementary information in Tables S1–S6 (for supporting information see also the footnote on the first page of this article), and the second-order rate constants giving values of k_1 are collected in Table 1 and Table 2. Before discussing these data, results for **3** and **4** will be reported.

Table 1. Values of rate constants, k_1 [dm^3 mol^{-1} s^{-1}], for reaction[a] of **1** and **2** with aliphatic amines in acetonitrile at 25 °C.

Substrate, R	*n*-Butylamine k_1 [dm^3 mol^{-1} s^{-1}]	Pyrrolidine	Piperidine
1a, 4-H	0.015(1)	0.055(3.7)	0.023(1.5)
1b, 4-CF_3	3.3(1)	21.6(5.5)	10.8(3.3)
1c, 4-CO_2Me	4.1(1)	29.7(7.2)	16.4(4.0)
1d, 4-CN	26.1(1)	233(8.9)	106(4.1)
1f, 4-NO_2	86(1)	1000(11.6)	640(7.4)
2a, 6-H	0.0089(1)	1.31(147)	0.52(58)
2b, 6-CF_3	0.50(1)	2.85(5.7)	0.85(1.7)
2e, ring N	32.5(1)	5690(175)	1880(58)
2f, 6-NO_2	86(1)	1000(11.6)	640(7.4)

[a] Values in parentheses are the reactivities for a particular compound relative to that for *n*-butylamine; i.e. k_1(pyrrolidine)/k_1(*n*-butylamine) and k_1(piperidine)/k_1(*n*-butylamine).



3f **5**

Scheme 2.

Table 2. Effects of ring-substituents on the relative reactivities, k_1 values, of **1** and **2** with aliphatic amines in acetonitrile at 25 °C.[a]

Substrate, R	*n*-Butylamine	Pyrrolidine	Piperidine
1a, 4-H	1	1	1
1b, 4-CF_3	220	393	470
1c, 4-CO_2Me	273	540	732
1d, 4-CN	$1.7\cdot10^3$	$4.2\cdot10^3$	$4.6\cdot10^3$
1f, 4-NO_2	$5.7\cdot10^3$	$1.8\cdot10^4$	$2.8\cdot10^4$
2a, 6-H	1	1	1
2b, 6-CF_3	56	2.2	1.6
2e, ring N	$3.6\cdot10^3$	$4.3\cdot10^3$	$3.6\cdot10^3$
2f, 6-NO_2	$9.7\cdot10^3$	760	$1.2\cdot10^3$

[a] For a given amine values are compared to the reactivity with **1a**, and **2a**, respectively.

The general reaction scheme for the 1-phenoxy compounds is shown in Scheme 3. However, base catalysis, as argued previously,[11–13,15] is indicative of rate-limiting proton transfer from the zwitterionic intermediates **6**, in contrast to general acid catalysis of phenoxide expulsion. Hence Equation (1) applies. Limiting forms, where $K_1 = k_1/k_{-1}$, are Equation (2), if the uncatalysed pathway can be neglected, and Equation (3) if the condition $k_{-1} >> k_2 + k_{Am}[Am]$ applies.

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

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

Reactions with *n*-butylamine of **3a**–**d** and **4a**,**e** gave values of k_{obs} which increased linearly with the amine concentration, indicating that nucleophilic attack, the k_1 step, is rate limiting. Conditions used are given in Table S7. However, for **4b** carrying an *ortho*-CF_3 substituent the plot of k_A vs. [amine], not shown, was curved. Values, in Table 3, gave a good fit with Equation (2). That this curvature is indicative of general base catalysis is shown by the catalysis of the reaction by DABCO (Table 3).

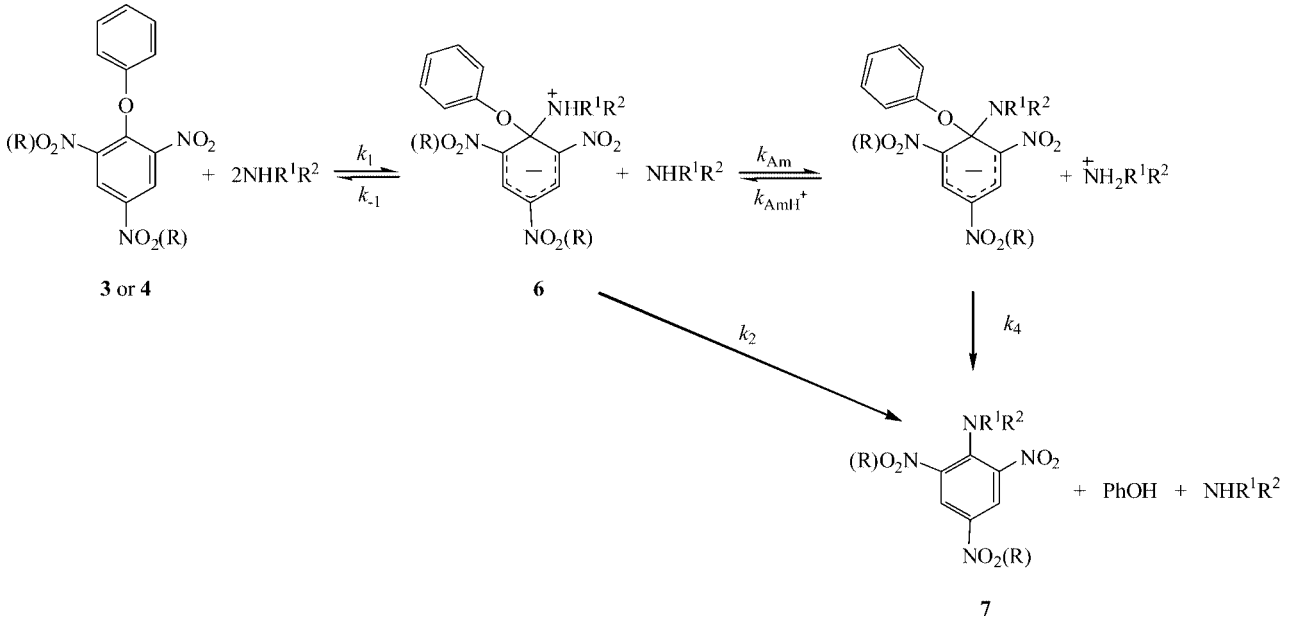
Table 3. Kinetic results[a] for the reactions of **4b** with *n*-butylamine in acetonitrile at 25 °C.

[*n*-Butylamine] [10^{-3} mol dm^{-3}]	[DABCO] [10^{-3} mol dm^{-3}]	k_A [dm^3 mol^{-1} s^{-1}]	k_A[b] [c] (calcd.) [dm^3 mol^{-1} s^{-1}]
1.0	–	0.35	0.37
1.5	–	0.54	0.51
2.0	–	0.64	0.63
2.5	–	0.75	0.73
3.0	–	0.86	0.81
3.5	–	0.89	0.89
4.0	–	0.97	0.96
6.0	–	1.15	1.16
2.0	3.0	0.98	0.94
2.0	5.0	1.10	1.08
2.0	10	1.27	1.30
2.0	15	1.43	1.44
2.0	20	1.52	1.53

[a] Measured at 345 nm. [b] Values calculated with Equation (2) with K_1k_{Am} 450 dm^6 mol^{-2} s^{-1} and k_{Am}/k_{-1} 220 dm^3 mol^{-1}. [c] Values in the presence of DABCO calculated with Equation (4) with K_1k_{Am} 450 dm^6 mol^{-2} s^{-1}, k_{Am}/k_{-1} 220 dm^3 mol^{-1}, K_1k_{DABCO} 280 dm^6 mol^{-2} s^{-1} and k_{DABCO}/k_{-1} 140 dm^3 mol^{-1}.

The reactions with pyrrolidine gave evidence for base catalysis. Plots of values of k_A vs. amine concentration, not shown, were, except for **4b**, curved and gave good fits with Equation (2). Specimen results are in Table 4 and other data are in supplementary Table S8. For **4b** the plot was linear through the origin indicating that the value of k_{Am}/k_{-1} is relatively low (< 5 dm^3 mol^{-1}).

The progression from pyrrolidine to piperidine resulted in lower values for the parameter k_{Am}/k_{-1}, so that for **3a**–**d** and **4b** Equation (3) was applicable. Linear plots of k_A vs. [piperidine] yielded values of K_1k_{Am}. Only in the case of **3a**



Scheme 3.

Table 4. Kinetic data[a] for reactions of **3** and **4** with pyrrolidine in acetonitrile at 25 °C.

[Pyrrolidine] [10^{-3} mol dm^{-3}]	**3b** k_A [dm^3 mol^{-1} s^{-1}]	$k_{calcd.}$	**3c** k_A [dm^3 mol^{-1} s^{-1}]	$k_{calcd.}$	**4a** k_A [dm^3 mol^{-1} s^{-1}]	$k_{calcd.}$
1.0	0.12	0.12	0.35	0.34	0.025	0.024
1.5	0.18	0.17	–	–	–	–
2.0	0.23	0.23	0.70	0.67	0.041	0.045
2.5	0.29	0.29	–	–	–	–
3.0	0.33	0.34	0.99	0.99	0.059	0.064
4.0	–	–	1.2	1.3	0.075	0.081
5.0	0.55	0.56	1.5	1.6	0.087	0.096
8.0	0.88	0.87	–	–	–	–
10	1.06	1.07	2.9	2.9	0.16	0.15
20	–	–	5.5	5.0	0.23	0.22
30	–	–	6.8	6.6	0.27	0.25

[a] Values of $k_{calcd.}$ were calculated using Equation (2) with the values collected in Table 5.

Table 5. Summary of results[a] for reaction of **3** and **4** with aliphatic amines in acetonitrile at 25 °C.

Substrate, R		*n*-Butylamine	Pyrrolidine	Piperidine
3a 4-H	k_1 [dm^3 mol^{-1} s^{-1}]	0.047(1)	0.024(0.51)	–
	k_{Am}/k_{-1} [dm^3 mol^{-1}]	–	3.5	–
	K_1k_{Am} [dm^6 mol^{-2} s^{-1}]	–	0.083	0.0011
	K_1k_2 [dm^3 mol^{-1} s^{-1}]	–	–	$6\cdot10^{-5}$
3b 4-CF_3	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
3c 4-CO_2Me	k_1 [dm^3 mol^{-1} s^{-1}]	9.3(1)	17.5(1.9)	–
	k_{Am}/k_{-1} [dm^3 mol^{-1}]	–	20	–
	KK_1k_{Am} [dm^6 mol^{-2} s^{-1}]	–	350	10.2
3d 4-CN	k_1 [dm^3 mol^{-1} s^{-1}]	45(1)	450(10)	–
	k_{Am}/k_{-1} [dm^3 mol^{-1}]	–	7	–
	K_1k_{Am} [dm^6 mol^{-2} s^{-1}]	–	3200	112
4a 6-H	k_1 [dm^3 mol^{-1} s^{-1}]	$4.9\cdot10^{-3}$(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	0.80
4b 6-CF_3	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
4e ring N[b]	k_1 [dm^3 mol^{-1} s^{-1}]	0.95(1)	85(90)	24(25)
	k_{Am}/k_{-1} [dm^3 mol^{-1}]	–	1300	100
	K_1k_{Am} [dm^6 mol^{-2} s^{-1}]	–	$1.1\cdot10^5$	2440
4f 6-NO_2[c]	k_1 [dm^3 mol^{-1} s^{-1}]	183(1)	2400(13)	650(3.6)
	k_{Am}/k_{-1} [dm^3 mol^{-1}]	–	55	8
	K_1k_{Am} [dm^6 mol^{-2} s^{-1}]	–	$1.3\cdot10^5$	5200

[a] Values in parentheses are the reactivities for a given compound relative to that for *n*-butylamine; i.e. k_1(pyrrolidine)/k_1(*n*-butylamine) and k_1(piperidine)/k_1(*n*-butylamine). [b] Values for reaction with pyrrolidine from ref.[21]. [c] Values from ref.[13].

did the plot have an intercept indistinguishable from zero, indicating that here the uncatalysed decomposition of the intermediate, k_2 step, contributed to the reaction flux. Values of k_A are available in Table S9 and results are collected in Table 5. For **4a** and **4e**, carrying no bulky substituent at the 6-position, values of k_{Am}/k_{-1} were larger so that the data in Table 6 gave a good fit to Equation (2).

X-ray Crystal Structures: Our results for **4b** indicate unusual effects which may be due to the presence of the *ortho*-trifluoromethyl group. Hence the X-ray structure of **4b** was determined and compared with that for **3b** where the CF_3 group is in the *para* position. The structure of **4f**, which has been briefly reported previously,[6] is shown in Figure 1.

Compound **3b** crystallises in a chiral space group $P2_12_12_1$. The asymmetric unit comprises two molecules, shown in Figure 2; in both the CF_3 groups show rotational disorder which we have rationalised as two orientations in a 9:1 ratio. In each molecule, the two nitro groups and the PhO group are inclined to the plane of the tetra-substituted ring A in a propeller-like fashion. The sense of the twist is opposite in the two independent molecules which are thus, roughly, mirror images of each other. The O(1) atom is slightly tilted out of the ring A plane, to the opposite side from the phenyl group B.

Compound **4b** crystallises in a non-centrosymmetric, albeit not chiral, space group *Pc*, with two molecules per asymmetric unit, shown in Figure 3. Interestingly, these molecules are related by a pseudo-inversion centre (½ ¼ ½), as shown in Figure 3 (d). Although this operation applies only to the approximate positions of the molecule as a whole, rather than individual atomic positions, it produces pseudo-systematic absences characteristic of the space

Table 6. Kinetic results[a] for reaction of **4a** and **4e** with piperidine in acetonitrile at 25 °C.

[piperidine]/ 10^{-3} mol dm^{-3}	**4a** k_A [dm^3 mol^{-1} s^{-1}]	$k_{calcd.}$	**4e** k_A [dm^3 mol^{-1} s^{-1}]	$k_{calcd.}$
1.0	–	–	2.2	2.2
3.0	–	–	6.1	5.6
4.0	0.0031	0.0031	–	–
5.0	–	–	8.1	8.1
8.0	0.0059	0.0061	–	–
10	–	–		
12	0.0088	0.0089	12.1	12.2
15	–	–	14.8	14.6
20	0.015	0.014	16.4	16.3
40	0.026	0.026	–	–
60	0.037	0.036	–	–
80	0.047	0.045	–	–
100	0.055	0.053	–	–

[a] Values calculated using Equation (2) with the values given in Table 5.

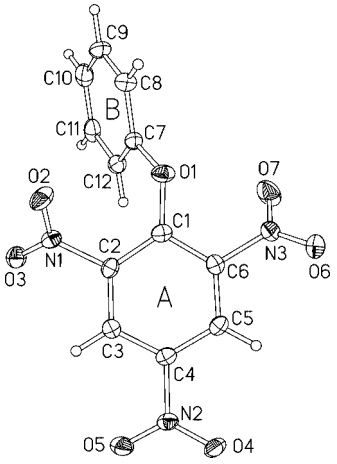


Figure 1. Molecular structure of **4f**. Henceforth the atomic displacement ellipsoids are drawn at the 50%% probability level.

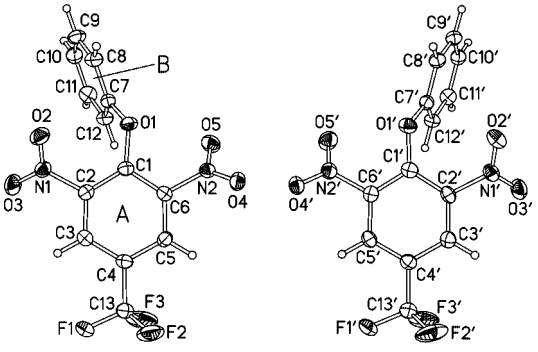


Figure 2. Independent molecules I (left) and II in the structure of **3b**, projected on the plane of ring A. Minor (10%) orientations of the CF_3 groups are not shown.

group $P2_1/c$: reflections $0k0$ with odd k are present but weaker than the average by a factor of 10. One of the independent molecules is disordered between two conformations, which differ by a rotation of the entire $C_6H_2(NO_2)_2$-CF_3 moiety by 180° around the O(1)···N(2) vector, so that superpositions of nitro and CF_3 substituents are observed at both C(2) and C(6). With 85% probability, the nitro group is attached to C(2) and the CF_3 group to C(6), with 15% vice versa. The phenyl group B is tilted more towards the *ortho*-nitro group and away from the CF_3 group. Selected bond lengths and angles are listed in Table 7.

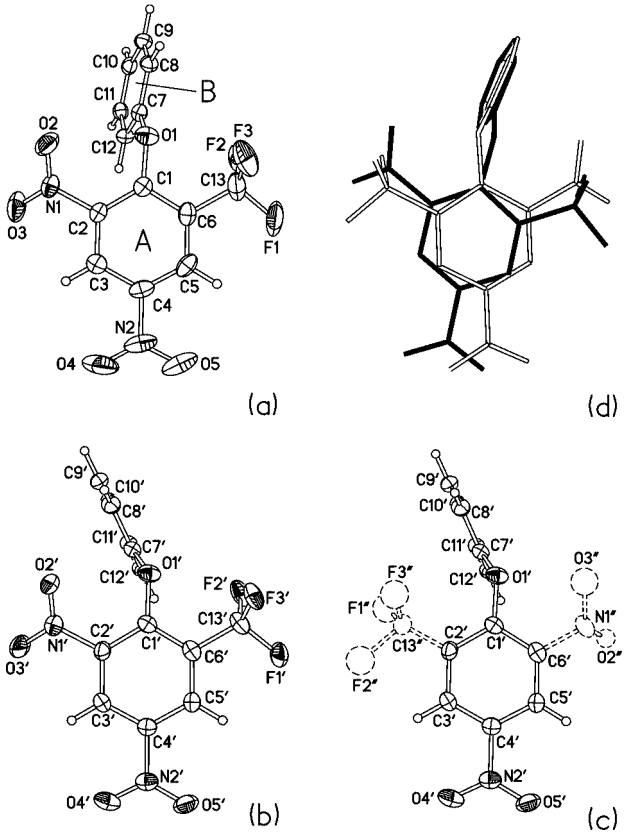


Figure 3. (a) Ordered molecule I in the structure of **4b**; (b) major and (c) minor orientations of the disordered molecule II; (d) overlap of molecules I and II by the pseudo-inversion symmetry.

Molecular geometry can be compared with those of recently studied sterically less encumbered analogues, diphenyl ether **8**,[23] and *p*-nitrophenyl phenyl ether **9**.[24] In two different polymorphs of **8**, the dihedral angle between the benzene rings is similar, 87.6 and 88.4° (cf. 67.7° predicted by ab initio calculations[23]), in **9** it is reduced to 63.2°. The C–O–C angles, varying from 117.9 to 119.7°, agree with our results. In **9** the C–O bond to the nitro-substituted ring is shorter than the other [1.378(2) vs. 1.396(2) Å], which can be explained by electron-withdrawing effect of NO_2. However, similar difference was observed in **8**, viz. 1.381(2) vs. 1.392(2) Å in the monoclinic form, 1.379(2) vs. 1.394(2) in the orthorhombic. Rather, the C–O distance correlates with the C–C–O–C torsion angle, which is close to 90° for the former ring (88.0 and 87.2°, respectively) and close to 0 for the latter (3.6 and 4.8°). Thus, shorter C–O distance reflects the conjugation of the oxygen lone pair with the ring. Nevertheless, in **3b**, **4b** and **4f** the difference between C(1)–O(1) and C(7)–O(1) distance is much larger than in **8** and **9** and show no correlation with

Table 7. Selected bond lengths and angles.

	3b, I	**3b**, II	**4b**, I	**4b**, II	**4f**[b]
O(1)–C(1) [Å]	1.357(2)	1.357(3)	1.369(4)	1.364(4)	1.349(3)
O(1)–C(7) [Å]	1.410(2)	1.409(2)	1.411(4)	1.411(4)	1.407(2)
C(1)–O(1)–C(7) [°]	117.7(2)	118.7(2)	117.9(2)	117.7(2)	120.1(2)
dihedral angles [°]					
ring A/2-nitro group	38.1	37.1	27.2	29.1	46.1
ring A/6-nitro group	53.1	42.3	–	42[a]	46.3
ring A/4-nitro group	–	–	6.6	10.9	15.4
ring A/ring B	77.3	74.7	75.6	89.7	66.0
O(1)–C(1) tilt from plane A [°]	2.7	3.8	0.9	1.9	4.3
torsion angles [°]					
C(2)–C(1)–O(1)–C(7)	–60.1(3)	62.9(3)	–79.7(4)	–69.0(4)	–58.3(3)
C(1)–O(1)–C(7)–C(12)	–32.4(3)	23.3(3)	6.5(4)	–37.0(4)	–17.0(3)

[a] Minor position of the disordered group. [b] Ref.[6].

the torsion angles, indicative of the strong p-π conjugation with the strongly electron withdrawing dinitro-substituted ring.

The steric interactions in **3b**, **4b** and **4f** are accommodated by rotation of the *ortho*-nitro group(s) from the ring plane and by a twist between the planes of the two aromatic rings. In each structure there is evidence of steric crowding around the 1-position, which is at least as severe in **4b** as in **3b** and **4f**.

Comparisons

Rate Constants, k_1, for Nucleophilic Attack: The results in Table 1 involving nucleophilic attack at a ring-carbon carrying chlorine show a reactivity order for k_1 of pyrrolidine > piperidine > *n*-butylamine. This is the order commonly found in nucleophilic substitution reactions[1,2] and reflects the relative basicities of the amines in acetonitrile; pK_a values,[25] for the protonated amines are: pyrrolidine 19.58, piperidine 18.92, *n*-butylamine 18.26. The superior reactivity of the secondary amines has also been attributed[8] 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.

For compounds **2a** and **2e** the pyrrolidine/*n*-butylamine reactivity ratios are 147 and 175, respectively. These compounds carry hydrogen or ring-nitrogen at the 6-position so that steric interaction at the reaction centre with the incoming nucleophile will be minimised. We note that a pyrrolidine/*n*-butylamine ratio of ca. 100 was found[3] for reaction with 2-bromo-5-nitro-3-substituted thiophenes, where steric effects should also be small. However, for compounds **1a**–**f**, carrying a nitro group at the 6-position, and for **2b**, with a 6-CF_3 group, the pyrrolidine/*n*-butylamine ratio decreases dramatically to values in the range 3.7–11.6. This decrease is likely to reflect steric hindrance to approach of the secondary amine to the reaction centre. We note also that the ratio increases consistently from 3.7 for **1a**, the least activated compound, to 11.6 for **1f**, the most activated. This increase may reflect a shift to a somewhat "earlier" transition state, involving rather less steric interaction, as the thermodynamic stability of the zwitterionic intermediate increases. The pyrrolidine/piperidine reactivity ratio for all the compounds in Table 1 is fairly constant, varying only between 1.6 to 3.3, indicating that here piperidine is not sterically disadvantaged relative to pyrrolidine.

The values in Table 5 show that for compounds **3** and **4**, carrying a phenoxy group at the position of nucleophilic attack, values of the pyrrolidine/*n*-butylamine ratio are generally lower than those for correspondingly activated **1** and **2**. For example, for **3a** and **1a** the ratios are 0.51 and 3.7, respectively. These reductions may be attributed to increases in the difficulty of approach to the 1-position by the amine nucleophiles in **3** and **4**, carrying a phenoxy group, compared with corresponding attack on **1** and **2**, carrying chlorine. Since the steric requirements of the secondary amine are higher than those of the primary amine, the effect is more serious for pyrrolidine (and piperidine) than for *n*-butylamine.

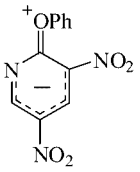
It is also instructive to compare k_1 values for similarly activated chloro and phenoxy compounds, in terms of the ratio of k_1(Cl) to k_1(OPh), which we have called "Cl/OPh" in Table 8. For *n*-butylamine, where steric effects are likely to be small, values of Cl/OPh are, with two exceptions, in the range 0.25–0.6, indicating rather faster attack at the phenoxy-substituted carbon atom than at the chloro-substituted carbon atom. For pyrrolidine, the values are higher (generally ca. 2). This is attributable to the greater steric requirements of phenoxy than of chloro and of pyrrolidine than of *n*-butylamine groups. The two notable exceptions

Table 8. Relative reactivities[a] of similarly activated 1-chloro- and 1-phenoxy compounds in their reactions with *n*-butylamine and with pyrrolidine in acetonitrile.

Substrates, R	Cl/OPh *n*-butylamine	pyrrolidine
1a/3a, 4-H	0.3	2.3
1b/3b, 4-CF_3	0.6	1.8
1c/3c, 4-CO_2Me	0.4	1.7
1d/3d, 4-CN	0.6	0.5
2a/4a, 6-H	1.8	3.5
2b/4b, 6-CF_3	0.25	–
2e/4e, 6 ring N	34	67
2f/4f, 6-NO_2	0.5	0.4

[a] Ratios compare k_1 values, k_1(Cl)/k_1(OPh).

are compounds **2a** and **4a** and **2e** and **4e** which lack a bulky substituent at the 6-position. Here the 1-chloro derivatives are more reactive than the 1-phenoxy derivatives. This can be reasonably ascribed to reduced reactivity of the phenoxy derivatives due to ground-state stabilisation involving resonance interaction as shown in **10** and **11**. Such stabilisation has previously been demonstrated in σ-adduct-forming reactions of ring-activated alkyl ethers.[2,26]



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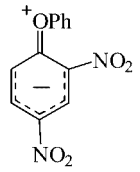


11

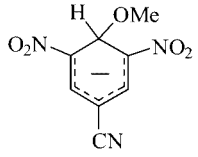
A similar but less pronounced effect has been noted in the corresponding phenyl ethers.[21,27] Because this interaction involves p-π overlap between oxygen and the electron-deficient ring, it will be greatly reduced, or eliminated, by the presence of a bulky 6-substituent which increases the steric congestion around the 1-position.

Effects of Ring-Activation: For compounds **1a**–**f** the steric situation at the reaction centre is similar, and the data in Table 2 show that for each amine values of k_1 increase regularly with increasing electron withdrawal of the 4-substituent. Hammett plots, not shown, vs. σ^- are reasonably linear with slopes, ρ, of ca. 3.5 indicating that bond formation is fairly well developed in the transition state for nucleophilic attack. However, there is some evidence for downward curvature in the Hammett plots as electron-withdrawal by the 4-substitutents increases, and this may be indicative (as referred to earlier) to a shift towards an "earlier" transition state. The same trends are followed by the 2,6-dinitro-1-phenoxy compounds **3a**–**d** and **4f** where again the steric situation at the 1-position is constant.

For compounds **2a**–**f** the bulk of the 6-substituent as well as its activating effect clearly has to be considered. The results in Table 2 show that for each amine the reactivity order is ring-N > CF_3 > H. However, for *n*-butylamine the 6-NO_2 group is more activating than the ring-nitrogen, while this order is reversed for the secondary amines. This may be attributed to the steric effect of the 6-NO_2 group, which is more serious in reactions with the secondary amines. The data for **2b** indicate that the 6-CF_3 group has a serious steric effect for the secondary amines. Thus with pyrrolidine and piperidine **2b** is only slightly more reactive than **2a**. The steric effects of the CF_3 group in nucleophilic substitutions have been noted previously,[20] and its size has been estimated to be comparable to that of an isopropyl group.[28] Recent calculations[29] 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. Although the X-ray structure of **4b** does not indicate any particularly large effects in the parent molecule the kinetic results suggest that sterically the effect of an *ortho*-CF_3 group on nucleophilic attack is greater than that of a nitro group.

The effects of ring activation in the series **4a**–**f** are complicated by the reduced reactivity of **4a** and **4e** due to the ground-state stabilisation referred to earlier.

It is also worth considering the relative activating effects of groups *ortho* and *para* to the reaction centre. Results reported[2] for methoxide addition to 1-cyano-3,5-dinitrobenzene and 3,5-dinitro-1-(trifluoromethyl)benzene show that there is kinetic preference for reaction at the 4-position to give adducts **12** and **13**, respectively, while the isomeric adducts formed by addition at the 2-position have greater thermodynamic stabilities. Hence, in the absence of steric effects, reactions with nucleophiles of **1a** may be expected to be faster than those of **2a**. The results in Table 1 show that this is observed for reaction with *n*-butylamine.



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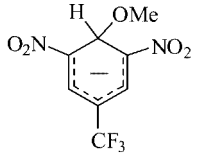

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However, for secondary amines steric effects become important and this order is reversed. Nevertheless, for all three amines the reactivity of **1b** is higher than that of **2b**, i.e. reaction is faster at the position between the nitro groups than at a position *ortho* to nitro and trifluoromethyl groups. This again bears witness to the large steric effect of the CF_3 group.

Incidence of Base Catalysis: The observation of base catalysis in the 1-phenoxy compounds **3** and **4** depends on the value of the ratio k_{Am}/k_{-1} and becomes more likely as the value of the ratio decreases. There is good evidence[13,14,30] 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[9,11,13,14,31] and have been found to decrease in the order *n*-butylamine > pyrrolidine > piperidine.[11,13,30] 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, in the present work the only reaction involving *n*-butylamine where base catalysis is observed is with **4b**. This is 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.

The reactions of all the phenoxy compounds with pyrrolidine are base-catalysed. The results in Table 5 show that for compounds **3a**–**d** and **4f**, where the steric situation around the 1-position is similar, values of k_{Am}/k_{-1} tend to increase with increasing electron-withdrawal by the 4-substituent. 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. The low value of k_{Am}/k_{-1} for **4b** again reflects the large "steric" effects of the 6-CF_3 substituent. The relatively high values of k_{Am}/k_{-1} for **4a** and **4e**, carrying hydrogen or ring-nitrogen at the 6-position, respectively, can be attributed to a combination of increases in value of k_{Am} and decreases in value of k_{-1} as the steric strain decreases.

Work with related systems[9,11,30,32] has shown that values of k_{Am} are likely to be lower by a factor of ca. ten for piperidine than pyrrolidine. For compounds **3a**–**d** and **4b** these decreases result in the condition $k_{-1} >> k_{Am}[Am]$ so that Equation (3) applies and proton transfer is fully rate-determining. For the most activated compound **4f** the expected reduction in value of k_{-1} allows a value for k_{Am}/k_{-1} to be measured, and for **4a** and **4e**, where steric hindrance is reduced, values are also measurable.

The only system where the uncatalysed decomposition pathway makes a measurable contribution is for reaction of **4a** with piperidine. The k_2 step is likely[1,2] to involve intramolecular proton transfer within the zwitterionic adduct **6** coupled with movement of electrons away from the anionic ring. Because **4a** is the substrate with lowest ring activation such movement of electrons should be easier than for other substrates. This coupled with the relatively low value expected for k_{Am} for reactions involving piperidine allows competition of the uncatalysed with the catalysed pathway.

An additional factor to be considered 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[1,2] as an argument to explain differences in reactivity between primary and secondary amines. In the case of primary amines there will always be one non-hydrogen bonded proton available for transfer thus reducing the susceptibility to base catalysis. However, previous studies[15,30] have not found evidence for such hydrogen bonding. Our results for the systems studied in the present work are adequately explained in terms of steric factors which result in decreases in value of k_{Am} in the series *n*-butylamine, pyrrolidine, piperidine.

Conclusions

Our study has identified the following as major factors in determining values of k_1 for nucleophilic attack for the systems studied in acetonitrile:

(a) **Ring activation** – values increase with increasing electron withdrawal by ring substituents. However substituents, notably the CF_3 group, at *ortho* positions can have deleterious steric effects.

(b) **Steric effects at the reaction centre** – values decrease with increasing congestion at the 1-position; effects increase in the order Cl < OPh and *n*-butylamine < pyrrolidine ≈ piperidine.

(c) **Ground-state stabilisation** – as shown in **8** and **9** may decrease reactivity.

The incidence of base catalysis depends on values of the ratio k_{Am}/k_{-1}. Values of k_{Am} decrease in the order *n*-butylamine > pyrrolidine > piperidine, and with increasing steric congestion in the zwitterionic adducts, **6**; e.g. *ortho*-substitution decreases k_{Am}. Steric congestion in the zwitterions may also increase k_{-1} values.

Although previous studies[1,2] have considered these and other factors, we have succeeded in making quantitative measurements using a range of substrates and amines.

Experimental Section

The 1-chloro compounds **1** and **2** were, apart from **1c**, the purest available commercial samples. Compound **1c** was prepared by esterification of the corresponding benzoic acid with methanol; m.p. 102 °C, (ref.[33] 106°). **1c**: calcd. C 36.9, H 1.93, N 10.7; found C 36.5, H 1.93, N 10.3. ^{1}H NMR (200 MHz, CD_3CN): δ = 8.63 (s, 2 H), 3.95 (s, 3 H) ppm. The 1-phenoxy compounds **3b**–**d** and **4b** were prepared by reaction at 45 °C 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. Data are given in Table 9. The following compounds were available from previous work, **3a** and **4a**,[11] **4e**,[21] **4f**.[15] Amines and acetonitrile were the purest available commercial samples. ^{1}H NMR spectra were measured with a Varian Mercury 200-MHz instrument. Kinetic measurements were made spectrophotometrically at the absorption maxima of the products using Perkin–Elmer Lambda 2 or Shimadzu UV PC spectrometers or an Applied Photophysics SX-17 MV stopped-flow spectrometer. Rate constants were measured at 25 °C under first-order conditions with substrate concentrations of $1 \cdot 10^{-4}$ mol dm^{-3} and were evaluated by standard methods. Values are precise to ±3%.

Table 9. Analytical data for **3b**–**d** and **4b**.

	M.p. [°C]	% C, H, N (found) % C, H, N (calcd.)	^{1}H NMR shifts[a]
3b	83	47.4, 2.12, 8.4 47.5, 2.15, 8.5	8.59 (s, 2 H), 7.37 (t, 2 H) 7.18 (t, 1 H), 6.98 (d, 2 H)
3c	105	53.2, 3.16, 8.9 52.8, 3.17, 8.8	8.83 (s, 2 H), 7.35 (t, 2 H) 7.15 (t, 1 H), 6.99 (d, 2 H), 3.95 (s, 3 H)
3d	160	54.7, 2.44, 14.7 54.7, 2.47, 14.7	9.08 (s, 2 H), 7.35 (t, 2 H) 7.15 (t, 1 H), 7.02 (d, 2 H)
4b	68	47.1, 2.10, 8.6 47.5, 2.15, 8.5	8.99 (s, 1 H), 8.85 (s, 1 H) 7.38 (t, 2 H), 7.19 (t, 1 H), 6.95 (d, 2 H)

[a] Spin coupling, J = 7–8 Hz, was observed between *ortho*-hydrogen atoms. **3b** and **4b** were in CD_3CN and **3c** and **3d** in [D_6]DMSO.

X-ray Crystallography: Light yellow crystals of **3b** and **4b** were grown from ethanol at room temperature. X-ray experiments were carried out on Bruker SMART 3-circle diffractometers with CCD area detectors 1 K (for **4b** and **4f**) or 6 K (for **3b**), using graphite-monochromated Mo-K_α radiation ($\bar{\lambda}$ = 0.71073 Å) and Cryostream (Oxford Cryosystems) open-flow N_2 gas cryostats. The structures were solved by direct methods and refined, by full-matrix least-squares against F^2 of all reflections, using SHELXL programs.[34] Non-hydrogen atoms were refined with anisotropic displacement parameters, except the minor positions of the disordered atoms

which were refined in isotropic approximation. All H atoms were "riding" in idealised positions. The absolute structures of **3b** and **4f** could not be determined in the absence of atoms with substantial anomalous scattering, therefore all $\Delta f''$ were set to 0 and all Friedel equivalents merged. The crystal data and experimental details are listed in Table 10. CCDC-285790 (for **3b**), -285791 (for **4b**) and -285694 (for **4f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 10. Crystal data.

Compound	**3b**	**4b**	**4f**
Formula	$C_{13}H_7F_3N_2O_5$	$C_{13}H_7F_3N_2O_5$	$C_{12}H_7N_3O_2$
M	328.21	328.21	305.21
Temp. [K]	120	120	120
Crystal system	orthorhombic	monoclinic	orthorhombic
Space group	$P2_12_12_1$ (#19)	Pc (#7)	$P2_12_12_1$ (#19)
a [Å]	5.6276(6)	15.779(3)	7.6597(15)
b [Å]	13.238(1)	5.5901(9)	9.6982(19)
c [Å]	35.711(2)	15.736(3)	17.107(3)
β, [°]	90	108.80(1)	90
V [Å^3]	2660.4(4)	1313.9(4)	1270.8(4)
Z	8	4	4
$D_{calcd.}$ [g/cm^3]	1.249	1.659	1.595
μ [mm^{-1}]	0.21	0.16	0.14
Refls. measured	30794	14213	14483
Refls. unique[a]	3531	3044	1690
Refls. with $I \geq 2\sigma(I)$[a]	3338	2875	1530
R_{int}	0.031	0.043	0.046
$R[I \geq 2\sigma(I)]$	0.031	0.043	0.034
w$R(F^2)$, all data	0.077	0.103	0.074

[a] Friedel equivalents merged.

Supporting Information (see footnote on the first page of this article): The Supporting Information in Tables S1 to S9 contains kinetic data as detailed in the main text.

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