DOI: 10.1002/ejoc.200600968

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

Michael R. Crampton,*[a] Thomas A. Emokpae,[b] and Chukwuemeka Isanbor*[b]

Keywords: Nucleophilic aromatic substitution / Reactivity–substituent effects / Amines

Rate constants are reported for the reactions of a series of 1-chloro-, 1-fluoro- and 1-phenoxy-nitrobenzenes activated by CF_3 or CN groups or by ring-nitrogen with *n*-butylamine, pyrrolidine or piperidine in acetonitrile. The results are compared with results reported previously for more strongly ring-activated compounds. 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, is noted for the *ortho*-CF_3 group. The 1-phenoxy compounds are subject to base catalysis and values of k_{Am}/k_{-1} are reduced relative to more strongly activated compounds. 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.
(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2007)

Introduction

Nucleophilic substitution in the reactions of activated aromatic compounds with amines usually involves the S_NAr mechanism[1,2] as shown in Scheme 1. When the second step is rate limiting then general base catalysis may be observed.

Mechanisms and reactivity in these systems continue to attract attention[3–5] and we have recently made a comparison of the displacement by aliphatic amines of chloride and phenoxide from strongly activated compounds **1** and **2** (X = Cl, OPh) carrying at least two nitro groups.[6] This study identified the following as major factors affecting values of k_1 for nucleophilic attack:

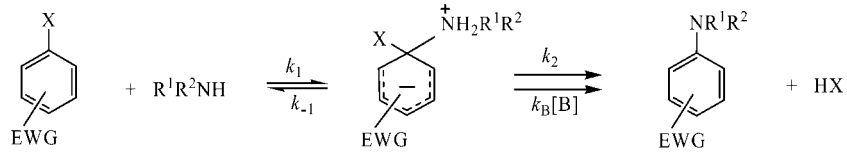
(a) *Ring activation* – values increase with increasing electron withdrawal by ring substituents but *ortho* substituents, notably the CF_3 group, can have serious steric effects.

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

(c) *Ground-state stabilisation* – involving resonance interactions between the phenoxy group and the ring may decrease reactivity.

The observation of base catalysis, dependent on the value of the ratio k_B/k_{-1}, was interpreted in line with previous evidence[7] in terms of rate limiting proton transfer from the zwitterionic intermediate, **Z**, to base.

Here, we report rate data for the substitutions of a series of less activated compounds, **3**–**7**, carrying only one nitro group, so that the reaction centre is less sterically crowded than in **1** and **2**. The effects of changing the nature of the leaving group from chloride, to fluoride and to phenoxide and of the amine from *n*-butylamine to pyrrolidine and to piperidine are examined.

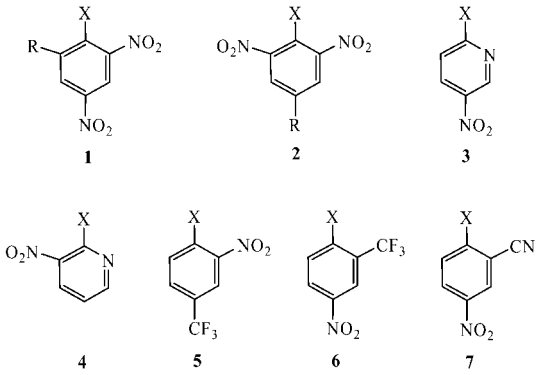


EWG = electron-withdrawing groups

Scheme 1.

[a] Chemistry Department, Durham University, Durham, DH1 3LE, UK
[b] Chemistry Department, University of Lagos, Lagos, Nigeria
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

© 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



1 **2** **3** **4** **5** **6** **7**

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

Results and Discussion

The reactions of **3**–**7** with the amines studied in acetonitrile gave the expected products of substitution of halide or phenoxide in >95% yield. Kinetic measurements were made spectrophotometrically with the concentration of amine in large excess of the parent concentration, ca. $1\cdot10^{-4}$ mol dm^{-3}, and first-order kinetics were observed. Previous studies[8] with more strongly activated compounds have shown the possibility of the initial formation of σ adducts resulting from attack at unsubstituted ring-positions. However here with less-activated compounds such adducts were not observed.

Making the usual assumption[1,2] that the zwitterionic adduct in Scheme 1 may be treated as a steady-state intermediate leads, when the amine acts as both the nucleophile and the catalysing base, to Equation (1).

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

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, $k_{Am}[Am] >> k_2$.

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

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

For the 1-chloro compounds **3a**–**5a** and **7a** plots of $k_{obsd.}$ vs. the amine concentration were linear, the slopes giving values of k_1 for nucleophilic attack. Values of $k_{obsd.}$ are available as Supporting Information in Tables S1–S3 and the values obtained for k_1, together with previously reported[6] values for **1a**, R = H and **2a**, R = H, are in Table 1. It should be noted that **6a** was too unreactive for satisfactory measurement. Similarly for the 1-fluoro compounds **1b**, R = H and **5b** linear plots of $k_{obsd.}$ vs. [amine] yielded values of k_1. For **6b** linear plots were again obtained with *n*-butylamine and with pyrrolidine, however with piperidine the plot showed distinct concave curvature indicative of base catalysis and data were fitted to Equation (4) with K_1k_{Am} 0.043 dm^6 mol^{-2} s^{-1} and k_{Am}/k_{-1} 20 dm^3 mol^{-1}. Combination of these values gives k_1 0.0022 dm^3 mol^{-1} s^{-1}. Interestingly results have been published previously[9] for reaction of **6b** with morpholine, albeit at 30 °C, and fitting of this data to Equation (4) gave values of K_1k_{Am} $4.8\cdot10^{-4}$ dm^6 mol^{-2} s^{-1}, k_{Am}/k_{-1} 2.4 dm^3 mol^{-1} and k_1 $2.0\cdot10^{-4}$ dm^3 mol^{-1} s^{-1}. Results are summarised in Table 1, together with literature data for **7b** and values of $k_{obsd.}$ are available in Table S4–S6. It is worth noting at this point the severe rate-retarding effects of the *ortho*-CF_3 group in **6b**, but detailed discussion of the results will be delayed until results for the 1-phenoxy compounds have been reported.

Table 1. Values of k_1 [dm^3 mol^{-1} s^{-1}] for reactions[a] of 1-chloro and 1-fluoro compounds with aliphatic amines in acetonitrile at 25 °C.

Substrate	*n*-Butylamine k_1 [dm^3 mol^{-1} s^{-1}]	Pyrrolidine	Piperidine
1a, R = H[b]	$8.9\cdot10^{-3}$ (1)	1.3 (146)	0.52 (58)
2a, R = H[b]	$1.53\cdot10^{-2}$ (1)	$5.5\cdot10^{-2}$ (3.4)	$2.3\cdot10^{-2}$ (1.5)
3a	$3.84\cdot10^{-4}$ (1)	$7.3\cdot10^{-2}$ (190)	$3.3\cdot10^{-2}$ (87)
4a	$6.1\cdot10^{-4}$ (1)	0.175 (287)	0.035 (57)
5a	$7.0\cdot10^{-5}$ (1)	$9.9\cdot10^{-3}$ (140)	$2.8\cdot10^{-3}$ (40)
7a	$9.0\cdot10^{-5}$ (1)	$1.2\cdot10^{-2}$ (130)	$5.8\cdot10^{-3}$ (64)
1b, R = H	8.9 (1)	570 (64)	150 (17)
5b	0.12 (1)	5.0 (42)	2.1 (18)
6b	$3.6\cdot10^{-3}$ (1)	$2.2\cdot10^{-2}$ (6)	$2.2\cdot10^{-3}$ (0.6)[d]
7b[c]	0.10 (1)	–	0.46 (4.6)

[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 from ref.[6]. [c] Values calculated from results at 30 °C in ref.[9]. [d] This reaction is base-catalysed.

The 1-phenoxy compounds showed greater susceptibility to base catalysis than the corresponding 1-halogeno derivatives. In the case of **3c** and **4c** plots, for each amine, of $k_{obsd.}$ vs. [amine] showed concave curvature and the data gave good fits with Equation (4), yielding values of K_1k_{Am}, k_{Am}/k_{-1} and hence k_1. For **5c** in reaction with *n*-butylamine there was no evidence of base catalysis while the results with pyrrolidine and piperidine gave good fits with Equation (3) but not Equation (4). Base catalysis in the reaction with pyrrolidine was confirmed by the linear increase in values of k_A with increasing concentration of Dabco. **6c** was too unreactive for satisfactory measurements to be made. Results are reported in Table 2, Table 3, and Table 4 and are summarised in Table 5 which for comparison includes values reported[6] previously for **1c**, R = H and **2c**, R = H, and recalculated literature data[9] at 30 °C for **7c**.

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 2. Kinetic results[a] for reaction of **3c**, **4c** and **5c** with *n*-butylamine in acetonitrile at 25 °C.

n-Butylamine, conc. [mol dm^{-3}]	**3c** k_A [10^{-4} dm^3 mol^{-1} s^{-1}]	**4c** k_A [10^{-5} dm^3 mol^{-1} s^{-1}]	**5c** $k_{obsd.}$[b] [10^{-6} s^{-1}]
0.02	–	–	0.86
0.04	–	–	1.54
0.1	–	3.4 (3.3)	4.38
0.15	–	3.9 (3.75)	6.86
0.2	0.089 (0.089)	4.0 (4.0)	9.25
0.3	0.111 (0.112)	–	14.80
0.4	0.126 (0.129)	4.3 (4.4)	–
0.5	0.138 (0.141)	–	–
0.6	0.151 (0.151)	4.5 (4.6)	–
0.8	0.168 (0.166)	4.6 (4.7)	–

[a] Values in parentheses were calculated from Equation (4) using the values given in Table 5. [b] First-order rate constants, $k_{obsd.}$.

Table 3. Kinetic results for reaction of **3c**, **4c** and **5c** with pyrrolidine in acetonitrile at 25 °C.

Pyrrolidine, conc. [mol dm^{-3}]	**3c** k_A[a] [10^{-4} dm^3 mol^{-1} s^{-1}]	**4c** k_A[a] [10^{-4} dm^3 mol^{-1} s^{-1}]	**5c** k_A[b] [10^{-4} dm^3 mol^{-1} s^{-1}]
0.02	–	5.9 (4.9)	4.2 (4.2)
0.03	–	–	5.3 (5.3)
0.04	1.4 (1.4)	8.9 (8.9)	6.2 (6.4)
0.06	1.9 (2.0)	11.3 (12.2)	–
0.08	2.5 (2.5)	14.3 (15.1)	10.6 (10.9)
0.1	3.0 (3.0)	16.3 (17.5)	13.2 (13)
0.15	–	–	–
0.2	5.3 (5.0)	25.7 (26.0)	–

[a] Values in parentheses were calculated using Equation (4) with the values given in Table 5. [b] Values in parentheses were calculated using Equation (3), and the values given in Table 5. Values of k_A with 0.04 mol dm^{-3} pyrrolidine increased linearly with increasing [Dabco], 0–0.06 mol dm^{-3}, yielding a value for K_1k_{Dabco} of 0.033 dm^6 mol^{-2} s^{-1}.

Table 4. Kinetic results for reaction of **3c**, **4c** and **5c** with piperidine in acetonitrile at 25 °C:.

Piperidine, conc. [mol dm^{-3}]	**3c** k_A[a] [10^{-4} dm^3 mol^{-1} s^{-1}]	**4c** k_A[a] [10^{-4} dm^3 mol^{-1} s^{-1}]	**5c** k_A[b] [10^{-4} dm^3 mol^{-1} s^{-1}]
0.075	–	–	0.65 (0.75)
0.1	0.49 (0.49)	0.45 (0.45)	0.67 (0.68)
0.15	–	–	0.91 (0.90)
0.2	0.88 (0.90)	0.81 (0.84)	1.16 (1.12)
0.3	1.23 (1.24)	1.19 (1.17)	1.57 (1.56)
0.4	1.56 (1.54)	1.50 (1.46)	2.01 (2.00)

[a] Values in parenthesis were calculated from Equation (4) with the value given in Table 5. [b] Values in parenthesis calculated from Equation (3) with the values in Table 5.

Comparisons

The reaction centre in compounds **3**–**7** is less sterically crowded than in the compounds **1** and **2** (apart from **1**, R = H) that we have studied previously[6] because there is at most one bulky substituent at an *ortho* position. A consequence is that the results in Table 1 for the 1-chloro compounds indicate little steric hindrance to nucleophilic attack. Reactivity ratios decrease in the order pyrrolidine > piperidine > *n*-butylamine with pyrrolidine/*n*-butylamine ratios in excess of one hundred. The ratios are those normally associated with attack at an unhindered ring-position.[1,2,10,11] By comparison amine reactivity ratios are much reduced in **2a**, R = H indicating the considerably greater steric requirements of pyrrolidine and piperidine relative to *n*-butylamine.

The results in Table 1 also allow comparison of similarly activated 1-fluoro and 1-chloro compounds. For **1** (R = H), **5** and **7** the F/Cl ratios are high consistent with rate limiting nucleophilic attack.[1,2] For reactions with *n*-butylamine the ratio is greater than one thousand, but is notably lower for reactions with pyrrolidine and piperidine. This can be seen from the *n*-butylamine: pyrrolidine: piperidine reactivity ratios which, for example, for **5a** are 1:140:40 and for **5b** 1:42:18. The generally higher reactivity of the fluoro compounds derives from the higher electronegativity of fluorine than of chlorine resulting in strong polarisation of the carbon–fluorine bond, $C^{\delta+}$–$F^{\delta-}$. While encouraging attack at carbon this may give rise to electrostatic repulsion between the negative charge density on fluorine and the incoming nucleophile which is more severe with bulky nucleophiles.

Although **6a** was too unreactive for measurement, results were obtained for **6b**, 1-fluoro-2-trifluoromethyl-4-nitrobenzene, and deserve special mention. Here the *n*-butylamine: pyrrolidine: piperidine reactivity ratios are un-

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 5. Summary of results[a] for reactions of 1-phenoxy compounds with aliphatic amines in acetonitrile at 25 °C.

Substrate		*n*-Butylamine	Pyrrolidine	Piperidine
1c, R = H[b]	k_1 [$dm^3 mol^{-1} s^{-1}$]	$4.9 \cdot 10^{-3}$ (1)	0.37 (76)	0.16 (33)
	k_{Am}/k_{-1} [$dm^3 mol^{-1}$]	–	70	5.0
	$K_1 k_{Am}$ [$dm^6 mol^{-2} s^{-1}$]	–	26	0.8
2c, R = H[b]	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	–
	$K_1 k_{Am}$ [$dm^6 mol^{-2} s^{-1}$]	–	0.083	–
	$K_1 k_2$ [$dm^3 mol^{-1} s^{-1}$]	–	–	0.0011
3c	k_1 [$dm^3 mol^{-1} s^{-1}$]	$2.3 \cdot 10^{-5}$ (1)	$1.47 \cdot 10^{-3}$ (64)	$5.3 \cdot 10^{-4}$ (23)
	k_{Am}/k_{-1} [$dm^3 mol^{-1}$]	3.1	2.6	1.0
	$K_1 k_{Am}$ [$dm^6 mol^{-2} s^{-1}$]	$7.2 \cdot 10^{-5}$	$3.8 \cdot 10^{-3}$	$5.4 \cdot 10^{-4}$
4c	k_1 [$dm^3 mol^{-1} s^{-1}$]	$5.0 \cdot 10^{-5}$ (1)	$5.0 \cdot 10^{-3}$ (100)	$5.7 \cdot 10^{-4}$ (11)
	k_{Am}/k_{-1} [$dm^3 mol^{-1}$]	20	5.4	0.86
	$K_1 k_{Am}$ [$dm^6 mol^{-2} s^{-1}$]	$1.0 \cdot 10^{-3}$	$2.7 \cdot 10^{-2}$	$4.9 \cdot 10^{-4}$
5c	k_1 [$dm^3 mol^{-1} s^{-1}$]	$4.5 \cdot 10^{-5}$	–	–
	k_{Am}/k_{-1} [$dm^3 mol^{-1}$]	–	<1	–
	$K_1 k_{Am}$ [$dm^6 mol^{-2} s^{-1}$]	–	$1.1 \cdot 10^{-2}$	$4.4 \cdot 10^{-4}$
	$K_1 k_2$ [$dm^3 mol^{-1} s^{-1}$]	–	$1.95 \cdot 10^{-4}$	$2.4 \cdot 10^{-5}$
7c[c]	k_1 [$dm^3 mol^{-1} s^{-1}$]	$4 \cdot 10^{-5}$	–	–
	k_{Am}/k_{-1} [$dm^3 mol^{-1}$]	3	–	–
	$K_1 k_{Am}$ [$dm^3 mol^{-1} s^{-1}$]	$1.25 \cdot 10^{-4}$	–	$5.3 \cdot 10^{-4}$

[a] Values in parentheses are the values of k_1 for a given compound relative to the value for *n*-butylamine. [b] Values from ref.[6]. [c] Values calculated from data at 30 °C given in ref.[9].

usually low, so that the value of k_1 for *n*-butylamine is higher than that for piperidine. This may be attributed to the large "steric" effect of the *ortho*-CF_3 group.[6,9] There is evidence[12,13] that this is not simply a size effect but results partly from electrostatic repulsion between the local negative charge on the CF_3 group and bulky nucleophiles. Our results show that this effect still operates in **6b** where there is an *ortho*-CF_3 group but no other *ortho* substituent.

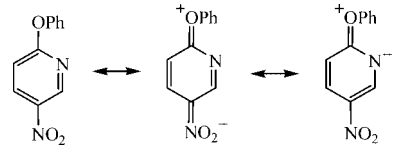
The relative reactivities of 1-chloro- and 1-phenoxy compounds are compared in Table 6. The results are interpretable in terms of two major effects: resonance stabilisation in the parent phenoxy compounds, and the greater steric requirements of the phenoxy group compared with chlorine.

Table 6. Relative reactivities[a] of similarly activated 1-chloro and 1-phenoxy compounds.[b]

Reactants	*n*-Butylamine	Pyrrolidine	Piperidine
3a/3c	17	50	62
4a/4c	12	35	61
5a/5c	1.4		
1a/1c, R = H	1.8	3.5	3.3
2a/2c, R = H	0.33	2.3	

[a] Ratios compare k_1(Cl)/k_1(OPh). [b] Data for **1** and **2**, from ref.[6]

Resonance stabilisation in the phenoxy-compounds as indicated in Scheme 2 will reduce their reactivity and hence increase the Cl/OPh ratio. The results in Table 6 show that this resonance can be inhibited by the presence of bulky *ortho* substituents particularly, as in **2**, R = H, when there are substituents at both the 2- and 6-ring positions. The relatively high Cl/OPh ratio for **4** indicates that ring nitrogen at an *ortho* position can effectively participate in this stabilising resonance interaction. For all substrates the Cl/OPh ratio increases in the order *n*-butylamine < pyrrolidine < piperidine showing that irrespective of ring substituents there is some unfavourable steric interaction between the phenoxy group and bulky attacking nucleophiles.



Scheme 2.

Effects of Ring Substituents

The effect of changing the nature or positioning of ring substituents on rate constants for nucleophilic attack are compared in Table 7. The first four rows compare values for compounds in which the *ortho* substituent is varied in compounds carrying a *para*-nitro group. The results show that the activating effects of the *ortho* substituents decrease in the order NO_2 > ring N > CN > CF_3. In general the ratios do not depend significantly on the nature of the amine. However the **6b/1b**, R = H ratios decrease substantially as the bulk of the amine is increased from *n*-butylamine to pyrrolidine and to piperidine. This reinforces the idea that the CF_3 group is sterically more demanding than the NO_2 group. Further evidence comes from the low values for the **6b/5b** ratio and the fact that these values decrease with increasing bulk of attacking amine.

The final row in Table 7 allows the comparison of the effects of a nitro group *ortho* or *para* to the reaction centre in 2-chloropyridines. The *ortho*/*para* ratios are slightly higher than unity as reported by Bunnett and Morath[14] for the reactions of chloronitrobenzenes with amines. They attributed this to favourable electrostatic interaction be-

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 7. Effects[a] of ring substituents on values of k_1 for nucleophilic attack.

	n-Butylamine	Pyrrolidine	Piperidine
3a/1a (R = H)	0.043	0.056	0.063
7a/1a (R = H)	0.010	0.009	0.011
7b/1b (R = H)	0.011	–	0.003
6b/1b (R = H)	$4.0 \cdot 10^{-4}$	$3.9 \cdot 10^{-5}$	$1.5 \cdot 10^{-5}$
6b/5b	0.030	0.0044	0.0011
4a/3a	1.6	2.4	1.1

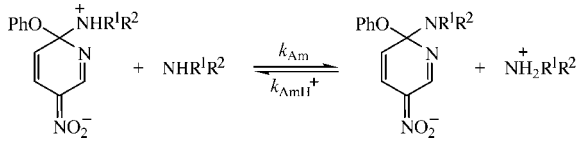
[a] Values given are the ratios for k_1 values.

tween the developing positive and negative centres in the transition state for the reaction of the *ortho* compound. In fact studies of σ adduct formation[1] in 1-substituted 3,5-dinitrobenzene have shown that there is a kinetic preference for nucleophilic attack at the 4-position, between the nitro groups, while the adducts formed by addition at the 2-position have greater thermodynamic stabilities. However *ortho* activation is not always favoured relative to *para* activation as shown by the reactivities of 2-chloro-3-nitro- and 2-chloro-5-nitropyridines with aryloxide ions in methanol.[15] Here, the *ortho*/*para* ratios are less than unity possibly due to steric interaction in the *ortho*-substituted compound.

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. The only halogeno compound to show catalysis is **6b** in its reaction with piperidine. 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.

The results for the phenoxy compounds **3c** and **4c** in Table 5 show that base catalysis is observed with all three amines studied. There is a difference here with the more strongly activated compounds studied previously,[6] for example **1c** and **2c**, where catalysis is not observed with *n*-butylamine. The higher values of k_{-1} in **3c** and **4c** where there is less activation by ring substituents is likely to be a major factor. However the reduction in ring-activation may also lead to reduced values of k_{Am}. There is strong evidence[8,16,17] 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. Hence values of k_{Am} may approach the diffusion limit but are reduced by steric factors and have been shown to decrease in the order *n*-butylamine > pyrrolidine > piperidine. However, in the less activated compounds studied in the present work the electron-withdrawing power of the ring in the zwitterions will be reduced so that the proton transfer process, k_{Am}, may not be thermodynamically favoured. The process involved for **3c** is shown in Scheme 3. A consequence of this is that values of k_{Am} will be influenced not only by steric factors but also by the basicities of the amines; pK_a values[18] for the protonated amines are: *n*-butylamine 18.26, pyrrolidine 19.58, piperidine 18.92. The results in Table 5 for **3c** and **4c** show that the k_{Am}/k_{-1} ratio is higher for *n*-butylamine than for the secondary amines, but not dramatically so. This difference from the behaviour with more strongly ring-activated compounds[6] may reflect reductions in the values of k_{Am} which are largest for reactions involving *n*-butylamine.



Scheme 3.

In **5c** the electron-withdrawing power of the ring is further reduced. We were surprised that the reaction with *n*-butylamine is not base-catalysed. However, the reactions with the secondary amines follow Equation (3) showing that proton transfer is fully rate-determining. Here 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 reduced ring activation. Some literature data[9] for **7c** also show the occurrence of base catalysis.

The possibility of intramolecular hydrogen bonding in the zwitterionic intermediates between an N–H proton and an *ortho*-nitro group must also be considered. Such hydrogen bonding, which affects the proton to be transferred, has been used[1,2] to explain the differences in reactivity between primary and secondary amines. However, our previous studies[6,17,19] have not found evidence for the effects of such hydrogen bonding. In the present work the rather similar susceptibilities to base catalysis of **3c** and **4c**, only one of which contains an *ortho*-nitro group, and the observation of base catalysis in the reaction of piperidine with **6b**, but not with **5b**, indicates that such hydrogen bonding is not a major factor.

Conclusions

Our results show that the decreased ring activation in compounds **3**–**7**, 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 attack are also reduced but steric effects due to repulsion between the incoming nucleophile and *ortho* substituents are less evident. However, as previously,[6] the specific rate-retarding effects of an *ortho*-CF_3 group are observed.

Experimental Section

The 1-halogeno compounds were the purest available commercial samples. The 1-phenoxy compounds **3c**, **4c** and **5c** were prepared by reaction at 45 °C for 2 h 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

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

solid formed was recrystallised from ethanol. Analytical data for **3c** and **4c** were in agreement with the expected structures and melting points agreed with those previously reported: **3c** m.p. 92 °C (ref.[20] 93 °C); **4c** m.p. 88 °C (ref.[21] 89 °C). Data for **5c**: M.p. 32 °C. $C_{13}H_8F_3NO_2$ (283.2): calcd. C 55.1, H 2.85, N. 4.9, F 20.1; found C 54.7, H 2.74, N 4.9, F 19.7. ^{1}H NMR (200 MHz, CD_3CN): δ = 8.31 (s, 1 H), 7.86 (d, 1 H), 7.51 (t, 2 H), 7.37 (t, 1 H), 7.16 (m, 3 H) ppm.

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. Absorption maxima for the products from **1**, **3**, **6** and **7**, which carry a *para*-nitro group, were 370 ± 10 nm, and for **2**, **4** and **5**, which carry an *ortho*-nitro group, were 420 ± 10 nm. Rate constants were measured at 25 °C under first-order conditions with substrate concentrations of ca. $1 \cdot 10^{-4}$ mol dm^{-3} and were evaluated by standard methods. Values are precise to ±3%.

Supporting Information (see also the footnote on the first page of this article): Tables S1–S6 contain kinetic data, $k_{obsd.}$ values, as detailed in the text.

Acknowledgments

C. I. thanks the Royal Society of Chemistry for the award of a J. W. T. Jones Travel Grant to allow him to spend time in Durham University, U. K.

[1] F. Terrier, *Nucleophilic Aromatic Displacement*, VCH Publishers, New York, **1991**.
[2] C. F. Bernasconi, *MTP Int. Rev. Sci. Org. Chem. Ser. 1* **1973**, *3*, 33–63.
[3] O. Banjoko, I. A. Babatunde, *Tetrahedron* **2004**, *60*, 4645–4654.
[4] P. M. Mancini, G. G. Fortunato, L. R. Vottero, *J. Phys. Org. Chem.* **2004**, *17*, 138–147.
[5] M. R. Crampton, T. A. Emokpae, C. Isanbor, *J. Phys. Org. Chem.* **2006**, *19*, 75–80.
[6] M. R. Crampton, T. A. Emokpae, C. Isanbor, A. S. Batsanov, J. A. K. Howard, R. Mondal, *Eur. J. Org. Chem.* **2006**, 1222–1230.
[7] R. A. Chamberlin, M. R. Crampton, *J. Chem. Soc., Perkin Trans. 2* **1995**, 1831–1838.
[8] M. R. Crampton, S. D. Lord, *J. Chem. Soc., Perkin Trans. 2* **1997**, 369–376.
[9] R. E. Akpojivi, T. A. Emokpae, J. Hirst, *J. Chem. Soc., Perkin Trans. 2* **1994**, 443–449.
[10] a) G. Consiglio, V. Frenna, S. Guernelli, G. Macaluso, D. Spinelli, *J. Chem. Soc., Perkin Trans. 2* **2002**, 965–970; b) G. Consiglio, V. Frenna, S. Guernelli, G. Macaluso, D. Spinelli, *J. Chem. Soc., Perkin Trans. 2* **2002**, 971–975.
[11] J. F. Bunnett, S. Sekiguchi, L. A. Smith, *J. Am. Chem. Soc.* **1981**, *103*, 4865–4871.
[12] T. Katagiri, S. Yamaji, M. Handa, M. Irie, K. Uneyama, *Chem. Commun.* **2001**, 2054–2055.
[13] T. Nagai, G. Nishioka, M. Koyama, A. Ando, T. Miki, I. Kumadaki, *J. Fluorine Chem.* **1992**, *57*, 229–238.
[14] J. F. Bunnett, R. J. Morath, *J. Am. Chem. Soc.* **1955**, *77*, 5051–5055.
[15] A. A. El-Bardan, *J. Phys. Org. Chem.* **1999**, *12*, 347–353.
[16] C. F. Bernasconi, M. C. Muller, P. Schmid, *J. Org. Chem.* **1979**, *44*, 3189–3196.
[17] M. R. Crampton, B. Gibson, *J. Chem. Soc., Perkin Trans. 2* **1981**, 533–539.
[18] J. F. Coetzee, *Progr. Phys. Org. Chem.* **1967**, *4*, 45–92.
[19] C. Isanbor, T. A. Emokpae, M. R. Crampton, *J. Chem. Soc., Perkin Trans. 2* **2002**, 2019–2024.
[20] T. Talik, Z. Talik, *Prace Naukowe Akademii Ekonomicznej imienia Oskara Langego we Wroclawice* **1987**, *398*, 99–109.
[21] H. Alsaidi, R. Gallo, J. Metzger, *Synthesis* **1980**, 921–924.

Received: November 6, 2006
Published Online: January 17, 2007

 © 2007 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim