The Origins of the Dichotomy of Amine Effects in Aromatic Nucleophilic Substitution Reactions

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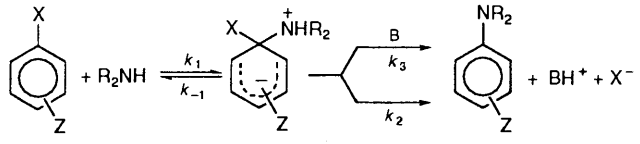
The reactions of 2-trifluoromethyl- and 2-cyano-4-nitrofluoro-benzenes with piperidine, *n*-butylamine and benzylamine in acetonitrile are not base catalysed, but the reactions with morpholine are catalysed. In benzene, the reactions of the 2-cyano-substrate with all four nucleophiles are catalysed. In acetonitrile, the reaction of 2-cyano-4-nitrophenyl phenyl ether with piperidine is base catalysed, whereas that of *n*-butylamine is not. In benzene, the reactions of this substrate with both nucleophiles are catalysed. The reasons why the reactions of secondary amines in aromatic nucleophilic substitution reactions are more prone to base catalysis than the corresponding reactions with primary amines of the same basicity are discussed.

In aromatic nucleophilic substitution reactions when substrates containing an *ortho*-group, particularly an *ortho*-nitro group react with primary and secondary amines of the same basicity quite often the reactions of the secondary amines are base catalysed while those of the primary amines are not. The mechanism of these reactions is given in Scheme 1 and application of the steady-state hypothesis gives eqn. (1) where k_A is the observed second-order rate constant and B is either a



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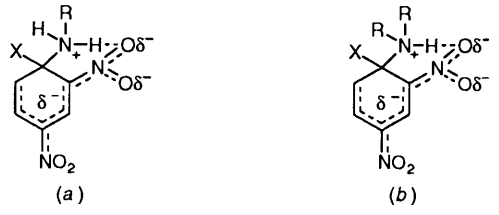
Scheme 1

$$k_A = \frac{k_1(k_2 + k_3[B])}{k_{-1} + k_2 + k_3[B]} \quad (1)$$

second molecule of the nucleophile or an added base. If $k_{-1} \ll k_2 + k_3[B]$, then $k_A = k_1$, the formation of the intermediate is rate-limiting and the reaction is not base catalysed. If this condition does not hold, decomposition of the intermediate to products is rate-limiting and the reaction is base catalysed.

Originally[1] the difference in behaviour between primary and secondary amines was attributed to steric compressions in the intermediate **I**, which, because of the greater bulk of secondary amines were greater for secondary than for primary amines. In the transition state for reversion to reactants this strain is partially released and the relief is greater for secondary than for primary amines leading to greater k_{-1} values for the former. While this and other[2] steric effects almost certainly play a role in the dichotomy of amine effects, subsequent attention has been focussed on the role of hydrogen-bonding known to occur[3,4] between the ammonio hydrogen atoms of the intermediate complex and the oxygen atoms of the *ortho*-nitro group as shown in Fig. 1. Briefly, the argument[5,6] is that hydrogen-bonding stabilises the intermediate with the following consequences: (*a*) k_{-1} is decreased because reversion to reactants involves breaking of the hydrogen-bond in addition to the C–N bond. The effect should be about equal for primary and secondary amines and (*b*) as there is a free transferable proton for primary amines, Fig. 1(*a*), whereas for secondary amines the hydrogen-bond in Fig. 1(*b*) has to be broken before further reactions to products can take place, the ratio (k_2 +



(*a*) (*b*)

Fig. 1

$k_3[B])/k_{-1}$ is smaller for secondary amines than for primary ones of approximately the same basicity, thus making the reactions of the former more prone to base catalysis than the latter. There is a considerable amount of experimental evidence in support of the hypothesis,[2,7] but there is a paucity of evidence for the contribution of purely steric/stereoelectronic effects to the dichotomy of amine effects in these reactions. The purpose of this paper was to look for that evidence.

The cyano group is linear and much smaller[8] than either the nitro or trifluoromethyl groups. In *ortho*-cyanoanilines geometry prevents the formation of intramolecular hydrogen-bonds from the amino group to the lone-pair orbital of the nitrogen atom of the cyano group. Instead weak interaction takes place with the π-electrons of the triple bond.[9] Models show that similar geometric inhibition to hydrogen-bonding with the lone-pair electrons exists in the intermediate **I** when a cyano, not a nitro group is *ortho* to the reaction site. Although the nitro and trifluoromethyl groups have the same 'width',[8] the nitro group is planar and, when *ortho* to a fluorine atom, 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 the nitro group. From its E_s value, its steric bulk is greater than that of the isopropyl group.[10] Fluorine attached to carbon is a very poor hydrogen bond acceptor. Christen[11] could not find evidence of hydrogen-bonding in *ortho*-fluoroaniline and Smith[12] found little or no evidence for intramolecular hydrogen-bonding in *ortho*-fluorophenol. Hibbert and Emsley[13] state that perfluorocarbons are among the weakest hydrogen-bonding substances known. Because of these properties, the reactions in acetonitrile of 2-cyano- and 2-trifluoromethyl-4-nitrofluorobenzenes with *n*-butylamine and piperidine [pK_a(acetonitrile)[14] 18.26, 18.92], benzylamine and morpholine [pK_a(acetonitrile)[14] 16.76, 16.62] were studied and their kinetic form compared with those of the corresponding reactions of 2,4-dinitrofluorobenzene already recorded in the literature,[15] thus allowing com-

Table 1 Rate constants ($dm^3\ mol^{-1}\ s^{-1}$) for the reactions of 2-cyano- and 2-trifluoromethyl-4-nitrofluorobenzenes and 2-cyano-4-nitrophenyl phenyl ether with some amines in aprotic solvents at 30 °C

Solvent	Substrate	Nucleophile	c/mol dm^{-3}	k_A	k''/k' [a]
Acetonitrile	2-Trifluoromethyl-4-nitrofluorobenzene	Piperidine	5.0×10^{-2}	1.48×10^{-3}	14.9
			6.0×10^{-2}	1.60×10^{-3}	
			8.0×10^{-2}	1.85×10^{-3}	
			10×10^{-2}	2.11×10^{-3}	
		n-Butylamine	1.0×10^{-2}	4.29×10^{-3}	6.0
			1.5×10^{-2}	4.41×10^{-3}	
			1.6×10^{-2}	4.58×10^{-3}	
			2.0×10^{-2}	4.53×10^{-2}	
			2.5×10^{-2}	4.68×10^{-3}	
		Morpholine	5.0×10^{-2}	2.06×10^{-5}	
			10×10^{-2}	3.61×10^{-5}	
			15×10^{-2}	4.86×10^{-5}	
			20×10^{-2}	5.85×10^{-5}	
			25×10^{-2}	6.84×10^{-5}	
			30×10^{-2}	7.77×10^{-5}	
			40×10^{-2}	9.53×10^{-5}	
			50×10^{-2}	10.8×10^{-5}	
		Benzylamine	4.0×10^{-2}	3.95×10^{-4}	1.2
			6.0×10^{-2}	3.88×10^{-4}	
			8.0×10^{-2}	3.98×10^{-4}	
			10×10^{-2}	4.04×10^{-4}	
			15×10^{-2}	4.45×10^{-4}	
			20×10^{-2}	4.54×10^{-4}	
	2-Cyano-4-nitrofluorobenzene	Piperidine	8.0×10^{-4}	4.55×10^{-1}	
			10.0×10^{-4}	4.60×10^{-1}	
			12.0×10^{-4}	4.60×10^{-1}	
			14.0×10^{-4}	4.70×10^{-1}	
			100×10^{-4}	4.30×10^{-1}	
		n-Butylamine	4.0×10^{-3}	9.95×10^{-2}	
			6.0×10^{-3}	10.9×10^{-2}	
			8.0×10^{-3}	10.4×10^{-2}	
			10.0×10^{-3}	9.53×10^{-2}	
			20.0×10^{-3}	10.0×10^{-2}	
		Morpholine	8.0×10^{-3}	3.46×10^{-3}	
			10.0×10^{-3}	3.88×10^{-3}	
			20.0×10^{-3}	4.87×10^{-3}	
			40.0×10^{-3}	7.03×10^{-3}	
			60.0×10^{-3}	9.45×10^{-3}	
			80.0×10^{-3}	11.8×10^{-3}	
			100×10^{-3}	13.3×10^{-3}	
			150×10^{-3}	17.7×10^{-3}	
		Benzylamine	4.0×10^{-2}	1.72×10^{-2}	1.9
			6.0×10^{-2}	1.73×10^{-2}	
			8.0×10^{-2}	1.83×10^{-2}	
			10.0×10^{-2}	1.90×10^{-2}	
Dimethylsulfoxide [b]		Morpholine	4.0×10^{-4}	1.47	
			6.0×10^{-4}	1.56	
			8.0×10^{-4}	1.50	
			10.0×10^{-4}	1.54	
			12.0×10^{-4}	1.31	
			14.0×10^{-4}	1.46	
			20.0×10^{-4}	1.52	
		Benzylamine	1.0×10^{-3}	3.40×10^{-1}	
			2.0×10^{-3}	3.25×10^{-1}	
			2.5×10^{-3}	3.30×10^{-1}	
			5.0×10^{-3}	3.36×10^{-1}	
			10.0×10^{-3}	3.47×10^{-1}	

Table 1 (*continued*)

Solvent	Substrate	Nucleophile	c/mol dm^{-3}	k_A	k''/k' [a]
Benzene		Piperidine	6.0×10^{-3}	0.867×10^{-2}	1.05×10^{3}
			8.0×10^{-3}	1.12×10^{-2}	
			10.0×10^{-3}	1.30×10^{-2}	
			20.0×10^{-3}	2.57×10^{-2}	
			30.0×10^{-3}	3.80×10^{-2}	
		n-Butylamine	4.0×10^{-2}	0.86×10^{-3}	408
			6.0×10^{-2}	1.26×10^{-3}	
			8.0×10^{-2}	1.70×10^{-3}	
			10.0×10^{-2}	2.06×10^{-3}	
			20.0×10^{-2}	4.11×10^{-3}	
		Morpholine	5.0×10^{-2}	1.57×10^{-3}	233
			6.0×10^{-2}	1.90×10^{-3}	
			8.0×10^{-2}	2.45×10^{-3}	
			10.0×10^{-2}	3.01×10^{-3}	
			12.0×10^{-2}	3.64×10^{-3}	
		Benzylamine	1.0×10^{-1}	3.09×10^{-4}	
			2.0×10^{-1}	6.50×10^{-4}	
			3.0×10^{-1}	10.3×10^{-4}	
			4.0×10^{-1}	14.1×10^{-4}	
			5.0×10^{-1}	19.1×10^{-4}	
	2-Cyano-4-nitrophenyl phenyl ether	Piperidine	3.0×10^{-1}	2.11×10^{-5}	
			4.0×10^{-1}	3.25×10^{-5}	
			5.0×10^{-1}	4.36×10^{-5}	
			6.0×10^{-1}	5.55×10^{-5}	
			7.0×10^{-1}	5.97×10^{-5}	
			8.0×10^{-1}	7.06×10^{-5}	
		n-Butylamine	2.0×10^{-1}	0.835×10^{-6}	∞
			3.0×10^{-1}	1.24×10^{-6}	
			4.0×10^{-1}	1.44×10^{-6}	
			5.0×10^{-1}	2.14×10^{-6}	
			6.0×10^{-1}	2.57×10^{-6}	
Acetonitrile		Piperidine	5.0×10^{-2}	3.00×10^{-5}	123
			7.5×10^{-2}	3.88×10^{-5}	
			10.0×10^{-2}	5.50×10^{-5}	
			20.0×10^{-2}	11.2×10^{-5}	
			25.0×10^{-2}	13.1×10^{-5}	
			30.0×10^{-2}	15.1×10^{-5}	
		n-Butylamine	1.0×10^{-1}	0.975×10^{-5}	5.4
			2.0×10^{-1}	1.42×10^{-5}	
			3.0×10^{-1}	1.72×10^{-5}	
			4.0×10^{-1}	2.03×10^{-5}	
			5.0×10^{-1}	2.46×10^{-5}	
			6.0×10^{-1}	2.77×10^{-5}	

[a] See the text. [b] At 29 °C.

parisons of the nitro group with a smaller group with weaker hydrogen-bonding accepting ability on the one hand and with a more bulky group with negligible hydrogen-bonding acceptor properties on the other. The results are given in Table 1* and the kinetic form of the reactions summarised in Table 2.

Discussion

In acetonitrile the reactions of 2-cyano-4-nitrofluorobenzene with piperidine and *n*-butylamine are not base catalysed. Those of benzylamine together with the reactions of piperidine, *n*-butylamine and benzylamine with 2-trifluoromethyl-4-nitrofluorobenzene have a linear dependence on the nucleophile concentration. When the condition $k_{-1} \ll k_2 + k_3[B]$ does not hold in eqn. (1), the reaction is base catalysed and can have one of two possible kinetic forms. If no simplification of the equation can be made, *i.e.* $k_{-1} \sim k_2 + k_3[B]$, then k_A has a curvilinear, concave downward dependence on base concentration. For the condition $k_{-1} \gg k_2 + k_3[B]$ eqn. (1) has the form given in eqn. (2) and there is a linear dependence of k_A on

$$k_A = k^1 + k''[B] \quad (2)$$

catalyst concentration (for B = nucleophile, $k''/k^1 = k_3/k_2$). In many aromatic nucleophilic substitution reactions small linear increases of k_A with increasing nucleophile (on more generally, added base) concentration are observed. The values of k''/k^1 are small and the accelerating effect of the bases bears no relationship to their base strength. According to Bunnett [1] this does not represent true base catalysis, the formation of the

* The isolation of products corresponding to aminodefluorination and the agreement between theoretical and experimental values of the absorbances at infinite time show that no irreversible attack of the nucleophiles on the cyano group occurs.

Table 2 Kinetic form of some of the reactions in Table 1 and other relevant reactions. The curvatures refer to the shapes of the plots of k_A *vs.* nucleophile concentration

		Nucleophile			
Solvent	Substrate	Piperidine	*n*-Butylamine	Morpholine	Benzylamine
Acetonitrile	2,4-Dinitrofluorobenzene[a]	Not catalysed	Not catalysed	Curvilinear	Not catalysed
	2-Cyano-4-nitrofluorobenzene	Not catalysed	Not catalysed	Curvilinear	Not catalysed
	2-Trifluoromethyl-4-nitrofluorobenzene	Not catalysed	Not catalysed	Curvilinear	Not catalysed
	2,4-Dinitrophenyl phenyl ether[b]	Linear with intercept	Not catalysed		
	2-Cyano-4-nitrophenyl phenyl ether	Linear with intercept	Not catalysed		
Benzene	2,4-Dinitrofluorobenzene	Linear with intercept[c]	Curvilinear[d]		
	2-Cyano-4-nitrofluorobenzene	Linear	Linear	Linear	Upward curvature
	2,4-Dinitrophenyl phenyl ether	Linear through origin[e]	Curvilinear through origin[f]		
	2-Cyano-4-nitrophenyl phenyl ether	Linear with negative intercept	Linear through origin		

[a] Data from ref. 15. [b] Data from ref. 6. [c] Data from ref. 20. [d] Data from ref. 21. [e] Data from F. Pietra, *Tetrahedron Lett.*, 1965, 2405. [f] Data from ref. 30(*a*).

intermediate is rate-determining in these reactions and the small increases are due to some unspecified effect. In other reactions increase in base concentration has a powerful accelerating effect, the value of k''/k^1 is high (> 50) and the catalytic effect increases with increase in strength of the base. These reactions are regarded as base catalysed and the decomposition of the intermediate is rate-limiting. For the reaction of 2-cyano-4-nitrofluorobenzene with benzylamine the k''/k^1 value is 1.9 and for the trifluoromethyl substrate the values of the ratio are 6.0 (*n*-butylamine), 14.9 (piperidine) and 1.2 (benzylamine). According to Bunnett's criteria these low values do not represent true base catalysis and we take the measured k_A values as being those of k_1, the rate constant for the formation of the intermediate.

The data in Table 1, together with the k_A values of the corresponding reactions of 2,4-dinitrofluorobenzene in acetonitrile[15] allows an assessment of the relative effects of *ortho* trifluoromethyl, cyano and nitro groups on the reactivity of 4-nitrofluorobenzene. For primary amines, the two sets of relative rate constant ratios for the *ortho*-CF_3:CN:NO_2 groups of $1:24.8:2.2 \times 10^3$ (*n*-butylamine) and $1:42.2:5.7 \times 10^3$ (benzylamine) are very similar and their values much less than the corresponding sequence of $1:539:1.7 \times 10^5$ obtained for the secondary amine piperidine. In aromatic nucleophilic substitution reactions where formation of the intermediate is rate-determining, secondary amines are usually better nucleophiles than primary ones of the same basicity. In the present series this is examplified by the ratio of the rate constants for piperidine and *n*-butylamine (k_A^{Pip}/k_A^{Bu}) of 15.5 and 4.5 for the *ortho*-nitro and -cyano substrates, respectively. When the *ortho* group is trifluoromethyl the value of this ratio is 0.2, *i.e.*, the secondary amine is less reactive than the primary one. We believe that this, together with the greater span of the reactivity in the sequence discussed above of piperidine compared with primary amines constitutes good evidence for the operation of a primary steric effect in the attack of piperidine on 2-trifluoromethyl-4-nitrofluorobenzene. Morpholine and piperidine have similar bulk, hence this element should also be present when morpholine attacks this substrate, and, by the principle of microscopic reversibility, increase k_{-1}, the rate constant for the reversion of the ensuing Meisenheimer complex to reactants.

The rate constants for the reactions of morpholine with both the 2-cyano- and 2-trifluoromethyl-substrates have a curvilinear dependence on the nucleophile concentration. Thus the reactions of these two substrates with benzylamine and morpholine together with those of 2,4-dinitrofluorobenzene with this amine pair for which analogous kinetic forms have already been demonstrated,[15] give further examples of the dichotomy of amine effects. The interpretation of these results for the cyano group for which both steric and intramolecular hydrogen-bonding effects are considerably reduced compared with those of the nitro group, is not clear cut. For the trifluoromethyl group, whose steric effects are at least as great and most probably greater than those of a nitro-group and whose hydrogen-bonding effects are negligible, the interpretation is clear, particularly as it has already been demonstrated that k_{-1} for morpholine is enhanced with respect to k_{-1} for benzylamine by release of steric strain present in the intermediate. The difference in the behaviour of the two amines is due at least in part to a greater relative value for k_{-1} for morpholine originating in a greater relief of steric strain for the secondary amine when the intermediate reverts to reactants.

Further information can be obtained by a consideration of the k_2/k_{-1} and k_3/k_{-1} ratios which, as the rate constants for the reactions of morpholine have a curvilinear dependence on nucleophile concentration, can be obtained by conventional analysis[16] and are given in Table 3. In the course of this analysis the values of 4.29×10^{-2} and 2.82×10^{-4} $dm^3\ mol^{-1}\ s^{-1}$ were obtained for the values of k_1 for the attack of morpholine on the cyano- and trifluoromethyl-substrates, respectively. These give $k_1^{morpholine}/k_1^{benzylamine}$ values of 2.8 and 0.7 for the cyano and trifluoromethyl compounds, thus confirming the existence of a steric effect in the attack of morpholine on the trifluoromethyl substrate as was deduced earlier. The factors that affect the k_2/k_{-1} and k_3/k_{-1} ratios are (*i*) activation: Bernasconi and de Rossi[2] state that increased activation should increase both k_2 and k_3 but the effect is greatest for k_3 and Kaválek and Štěrba[17] have shown experimentally that although k_2/k_{-1} values are relatively insensitive to activation, k_3/k_{-1} ratios increase strongly with increase in activation; (*ii*) hydrogen-bonding: a decrease in the strength of the hydrogn bond to the *ortho* group gives an increase in k_{-1}, reducing both k_2/k_{-1} and k_3/k_{-1}; (*iii*) steric effects: these can be divided into two, (*a*) repulsion: as the bulk of the nucleophile is greater than that of the fluorine atom, the greatest relief of steric strain is obtained by expelling the nucleophile, thus increasing the steric requirements of the *ortho*-group increases k_{-1} relative to k_2 and k_3, (*b*) stereoelectronic

Table 3 Values of k_2/k_{-1} and k_3/k_{-1} ($dm^3\ mol^{-1}$) for the reactions of 2-X-4-nitrofluorobenzenes with morpholine in acetonitrile at 30 °C

X	k_2/k_{-1}	k_3/k_{-1}
NO_2[a]	0.50	260
CN	0.04	4.35
CF_3	0.02	1.22

[a] Calculated from data in ref. 15.

effects:[2,18,19] greater steric effects of the *ortho*-substituent will reduce k_2 and k_3, thus reducing the values of k_2/k_{-1} and k_3/k_{-1}. Hence both steric effects (*a*) and (*b*) act in the same direction.

The values of the ratios for the cyano- and trifluoromethyl-substrates are of the same order of magnitude and differ considerably from those of the nitro-substrate. Compared with the results of Kaválek and Štěrba the decreases in the values of the cyano- and trifluoromethyl-ratios with respect to those of the nitro-group seem too large to be due to a decrease in activation, and the relative decreases nitro/cyano, cyano/trifluoromethyl do not accord with the relative activating powers of the groups. The results are best interpreted as being primarily due to loss of hydrogen-bonding to the *ortho* group combined with decreased activation, the combined effects swamping those of purely steric origin. If this interpretation is correct it supports the hypothesis that the dichotomy in behaviour of morpholine and benzylamine towards the cyano substrate arises principally from differential steric effects.

Aromatic nucleophilic substitution reactions are more prone to base catalysis in aprotic solvents of low permittivity than in dipolar aprotic ones[5] and it is already known that the reactions of 2,4-dinitrofluorobenzene with both piperidine[20] and *n*-butylamine[21] are catalysed when the solvent is benzene. Consequently as the reactions proceeded at convenient rates, the rate constants for the reactions of the cyano-substrate with all four nucleophiles in benzene were determined and are given in Table 1 and the kinetic form of the reactions together with those of 2,4-dinitrofluorobenzene are displayed in Table 2. When the nucleophile is benzylamine, plots of the second-order rate constants against nucleophile concentration have an upward curvature, a kinetic form that is observed quite frequently in aromatic nucleophilic substitution reactions in solvents of low permittivity. At present there is controversy[22] as to the origin of this curvature, but for our purpose it is sufficient to note that it arises from an additional mode of decomposition of the intermediate to products to those given in Scheme 1, usually when the condition $k_{-1}[\mathbf{I}] \gg \Sigma$ rates of decomposition to products, obtains.

For the reactions of both the nitro- and cyano-substrates with all four nucleophiles the change of solvent from acetonitrile to benzene results in an increase of k_{-1} relative to $(k_2 + k_3[B])$. In the case of 2,4-dinitrofluorobenzene, superimposed on this general solvent effect is a differential effect between primary and secondary amines. Thus for piperidine the change from acetonitrile to benzene changes the condition $k_{-1} \ll k_2 + k_3[B]$ to $k_{-1} \gg k_2 + k_3[B]$, whereas for both *n*-butylamine and benzylamine the change is from $k_{-1} \ll k_2 + k_3[B]$ to $k_{-1} \sim k_2 + k_3[B]$. This is due to the increased strength in benzene of the hydrogen-bonding between the ammonio proton and the *ortho*-nitro group leading to a decrease in k_{-1}. For the secondary amine this is offset by a decrease in k_2 which does not occur with primary amines. This difference in behaviour between the two types of amine is not observed when the substrate is 2-cyano-4-nitrofluorobenzene. For this substrate for piperidine, *n*-butylamine and benzylamine, the change is from $k_{-1} \ll k_2 + k_3[B]$ to $k_{-1} \gg k_2 + k_3[B]$. This is in agreement with the proposal that when the *ortho*-group is cyano, hydrogen-bonding to it from the ammonio proton in the intermediate is either very weak or negligible.

Another way of increasing the susceptibility of a sytem to base catalysis is to decrease the nuclofugacity of the leaving group. Thus the reaction of 2,4-dinitrophenyl phenyl ether with piperidine in acetonitrile is catalysed[6] while the corresponding reaction with *n*-butylamine[6] is not and provides another example of the dichotomy of amine effects. The second-order rate constants for the reaction of 4-nitro-2-cyanophenyl phenyl ether with both piperidine and *n*-butylamine in acetonitrile have a linear dependence on the nucleophile concentration. For piperidine the value of the k''/k^1 ratio is 123 whereas that for *n*-butylamine is 5.4, indicating, according to Bunnett's criteria,[1] that the piperidine reaction is catalysed while that with *n*-butylamine is not, again demonstrating the difference between the reactions of primary and secondary amines of the same basicity. The fact that the dichotomy is observed when the *ortho*-group is cyano, for which it has been demonstrated there is little or no hydrogen-bonding between it and the ammonio group of the σ-complex, indicates that its origin must be steric.

As indicated earlier, the steric effects could be either steric compressions in the σ-complex resulting in an increase in k_{-1} or a stereoelectronic effect giving a reduction in k_2 and k_3, in which *ortho*-substituents interfere with the unshared electrons on the nucleophile attaining an antiperiplanar position with respect to the bond breaking in the transition state for the departure of the nucleofuge from the σ-complex. The cyano group is small and there is no evidence for any appreciable steric compressions arising from the reactions of secondary amines when this group is in a position *ortho* to the leaving group. For the reaction of 2-cyano-4-nitrofluorobenzene in acetonitrile the k_1^{Pip}/k_1^{Bu} ratio is 4.5 and by measuring the rates of reaction of this substrate with morpholine and benzylamine in dimethyl sulfoxide, a solvent in which neither reaction is base catalysed (*cf.* Table 1), a value of 4.4 for $k_1^{morpholine}/k_1^{benzylamine}$ was obtained. Even for the more bulky *ortho*-nitro group k_1 for secondary aliphatic and alicyclic amines are invariably greater than those of their primary counterparts. In the present series the k_1^{Pip}/k_1^{Bu} ratio for the fluoro-substrate in acetonitrile is 15.5. We conclude that the steric effects which give rise to the dichotomy of amine effects in 4-nitro-2-cyanophenyl phenyl ether and 2-cyano-4-nitrofluorobenzene do not arise from differential steric compressions between primary and secondary amines in the σ-complexes formed in these reactions.

There is no evidence at present which demonstrates the existence of a stereoelectronic effect involving an *ortho*-cyano-group, what evidence there is pertains to the nitro group. Bunnett[18] has shown that in the reactions of pyrrolidine and piperidine with 2,4-dinitro-1-naphthyl ethyl ether in dimethyl sulfoxide, the rate of nucleofuge detachment is 11 000 times faster for pyrrolidine than for piperidine and Hasegawa[23] observed a very large difference between the two reagents for the ratio of detachment of methoxide when the substrate was methyl 4-methoxy-3,5-dinitrobenzoate. Bernasconi[5] has drawn attention to the enormous increase in k_2/k_{-1} which occurs when the nucleophile is changed from piperidine to pyrrolidine in the reactions of 2,4-dinitrophenyl phenyl and methyl ethers in aqueous dioxane which Bunnett and Cartão[24] ascribe to stereoelectronic inhibition of the detachment of the nucleofuge when piperidine is the nucleophile. A similar difference between piperidine and pyrrolidine has been observed by Consiglio,[25] and given the same rationalisation, in the aminodemethoxylation reactions of 2-methoxy-3-nitrothiophene, a substrate in which steric effects of substituents *ortho* to the reaction site are minimised. Hence there are precedents for a stereoelectronic effect involving piperidine at reaction sites where the steric effects are not too demanding. Crampton[26] has explained the huge reduction in the rate of acid-catalysed nucleofuge

expulsion from the Meisenheimer complexes formed from 2,4,6-trinitrophenetole in dimethyl sulfoxide when the nucleophile is changed from primary amines to piperidine as, at least in part, the same effect. In this explanation of the difference in behaviour of primary and secondary amines both k_2 and k_3 are reduced when the nucleophile is a secondary amine.* An alternative, but less likely explanation is that only k_3 is reduced owing to congestion at the reaction site.

Nudelman and Cerdeira[27] have shown that the > 100 fold reduction in rate in the reaction of isopropylamine with *p*-nitrofluorobenzene in toluene compared with that of *n*-propylamine is due to a large reduction in the rate of the base-catalysed step for isopropylamine. Crampton[26] has demonstrated that for Meisenheimer complex formation in dimethyl sulfoxide, increased crowding at the reaction centre caused by change from primary amines to piperidine results in rate reductions of proton transfer from the zwitterionic intermediate to the amine catalyst and Hirst[19] has shown how these results[26,28] on Meisenheimer reactions can be used to demonstrate steric inhibition to the electrophilic catalysis of the expulsion of the leaving group in aromatic nucleophilic substitution reactions. In this case values of the ratio k_3/k_2 would be expected to be lower for secondary amines than for the corresponding primary ones except where hydrogen-bonding can take place between a group *ortho* to the reaction site and the ammonio hydrogen atoms of the intermediate. The selective lowering of k_2 for secondary amines would lead to increases in their k_3/k_2 values relative to primary amines and the interpretation of the relative values would be ambiguous. For the reactions of 2-cyano-4-nitrofluorobenzene with *n*-butylamine and piperidine in benzene, for which we believe hydrogen-bonding to the cyano group to be negligible in the intermediates, the values of k_3/k_2 of 408 (*n*-butylamine) and 1.05×10^3 (piperidine) militate against selective steric inhibition of the base-catalysed step being the dominant factor in the difference in behaviour of the two amines.

The effect of change of solvent from acetonitrile to benzene on the reactions of the phenyl ether series parallels that observed in the fluoro-series with reduced k_2/k_{-1} values. When the reagent is *n*-butylamine, the reaction of the nitro-substrate changes from one that is not catalysed to one in which plots of k_A against nucleophile concentration have a curvilinear dependence on nucleophile concentration and pass through the origin; for the cyano-substrate the change is from a non-catalysed reaction to one in which the plot is linear and passes through the origin.† For piperidine the change for the nitro-substrate is from one in which the plot of k_A against piperidine concentration is linear with a definite positive intercept to one in which the plot is linear and passes through the origin. In the case of the cyano-substrate the change is from a plot which is linear with a positive intercept to one which is linear with a definite negative intercept. This last kinetic form is well known in S_NAr reactions in benzene,[29] and is usually attributed to a term third order in the nucleophile concentration. The mechanistic interpretation of this term is however controversial.[22] The lowering of the k_2/k_{-1} relative to k_3/k_{-1} ratios when the leaving group is phenoxide compared with those when the nucleofuge is fluoride is in accord with the mechanism advocated by Hirst[30] for the S_NAr reactions of ethers with amines in aprotic solvents of low relative permittivity.

Finally the uncatalysed reactions of *n*-butylamine with the 2-nitro- and 2-cyano-substrates in acetonitrile show a large increase in the $k_1^{NO_2}/k_1^{CN}$ ratio from 89 to 856 when the leaving group is changed from fluorine to phenoxide. This is due to the greater relative stabilisation of the ground state of the cyano-compared with the nitro-substrate in the ethers. The cyano group is small and linear and is not subject to steric inhibition of resonance by neighbouring groups when attached to a benzene ring[31] whereas it is well known that steric interactions occur between nitro-groups and bulky *ortho*-substituents with resulting loss of resonance.

Experimental

The purification of acetonitrile,[32] benzene[33] and dimethyl sulfoxide[34] has been described already. 2-Fluorobenzonitrile, obtained from 2-fluoroaniline by the Sandmeyer reaction, on nitration with fuming nitric acid at 0 °C gave 2-cyano-4-nitrofluorobenzene, m.p. 74–75 °C (ethanol) (lit.,[35] 74–75 °C). 2-Trifluoromethyl-4-nitrofluorobenzene, b.p. 105–106 °C/25 mmHg (lit.,[36] 105–106 °C/25 mmHg, was obtained from 2-trifluoromethyl-4-nitrochlorobenzene which was heated with anhydrous potassium fluoride in dimethylformamide at 160 °C for 4 h. 2-Cyano-4-nitrophenyl phenyl ether was prepared by refluxing an aqueous alcoholic solution of sodium phenoxide and 2-cyano-4-nitrofluorobenzene, m.p. 125 °C (lit.,[37] 125–126 °C). The spectrophotometric determination of the rate constants has been described already.[38] The wavelengths used for the various nucleophiles were: piperidine, 370 nm for all substrates; *n*-butylamine, 350 nm for both cyano substrates and 370 nm for the trifluoromethyl substrate; morpholine, 360 nm (cyano), 365 nm (trifluoromethyl); benzylamine, 350 nm (cyano), 360 nm (trifluoromethyl).

References

1 J. F. Bunnett and R. H. Garst, *J. Am. Chem. Soc.*, 1965, **87**, 3875.
2 C. F. Bernasconi and R. H. de Rossi, *J. Org. Chem.*, 1976, **41**, 44.
3 C. F. Bernasconi, *J. Phys. Chem.*, 1971, **75**, 3636.
4 C. F. Bernasconi and F. Terrier, *J. Am. Chem. Soc.*, 1975, **97**, 7458.
5 C. F. Bernasconi, *M.T.P. International Reviews of Science*, 1973, Series 1, Butterworth, London, Vol. 3, p. 33.
6 D. Ayediran, T. O. Bamkole, J. Hirst and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1580.
7 I. Onyido and C. I. Ubochi, *J. Chem. Soc., Perkin Trans. 2*, 1987, 563.
8 W. A. Sheppard, in *The Chemistry of Functional Groups. The Chemistry of the Cyano Group*, ed. Z. Rappoport, Interscience, New York, 1970, p. 209.
9 J. Grundnes and P. Klaboe, *The Chemistry of Functional Groups. The Chemistry of the Cyano Group*, ed. Z. Rappoport, Interscience, New York, 1970, p. 123.
10 B. E. Smart, in *The Chemistry of Functional Groups. The Chemistry of the Carbon–Halogen Bond, Supplement-D. The Chemistry of Halides, Pseudo-halides and Azides*, ed. S. Patai and Z. Rappoport, Wiley, New York, 1983, p. 603.
11 D. Christen, *J. Mol. Struct.*, 1977, **41**, 315.
12 J. W. Smith, in *The Chemistry of Functional Groups. The Chemistry of the Carbon–Halogen Bond, Part 1*, ed. S. Patai, Wiley, London, 1973, p. 265.
13 F. Hibbert and J. Emsley, *Adv. Phys. Org. Chem.*, 1990, **26**, 255.
14 J. F. Coetzee, *Prog. Phys. Org. Chem.*, 1967, **4**, 45.
15 D. Ayediran, T. O. Bamkole and J. Hirst, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1396.
16 J. F. Bunnett and C. Bernasconi, *J. Am. Chem. Soc.*, 1965, **87**, 5209.

* A referee has suggested that as morpholine and piperidine are stereochemically similar and the major difference between them is in their pK_a values, the differences in kinetic form of the reactions of the two nucleophiles with the fluoro-substrates in acetonitrile is due to a change in mechanism whereby proton transfer from the intermediate I in Scheme 1 becomes rate-limiting when the reagent is morpholine. The change from an uncatalysed to a base-catalysed reaction with decrease in basicity of the nucleophile is well known in aromatic nucleophilic substitution reactions for both primary and secondary amines[5,13] and has been ascribed[5] to an increase in k_{-1} with decreasing basicity of the nucleophile.

† A plot of k_A against *n*-butylamine concentration gives a small negative intercept. Linear regression analysis however shows that the standard deviation of the intercept is more than ten times its estimated value and the assumption that the reaction is second order in nucleophile concentration gives good rate constants.

17 J. Kaválek and V. Štěrba, *Collect. Czech. Chem. Commun.*, 1973, **38**, 884.
18 J. F. Bunnett, S. Sekiguchi and L. A. Smith, *J. Am. Chem. Soc.*, 1981, **103**, 4865.
19 T. A. Emokpae, P. U. Uwakwe and J. Hirst, *J. Chem. Soc., Perkin Trans. 2*, 1993, 125.
20 C. F. Bernasconi and Hch. Zollinger, *Tetrahedron Lett.*, 1965, 1083.
21 F. Pietra and D. Vitali, *J. Chem. Soc. B*, 1968, 1200.
22 D. Ayediran, T. O. Bamkole, J. Hirst and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1977, 597; O. Banjoko and P. Otiono, *J. Chem. Soc., Perkin Trans. 2*, 1981, 399; N. S. Nudelman and D. Palleros, *J. Org. Chem.*, 1983, **48**, 1607.
23 Y. Hasegawa, *J. Org. Chem.*, 1985, **50**, 649.
24 J. F. Bunnett and A. V. Cartãno, *J. Am. Chem. Soc.*, 1981, **103**, 4861.
25 G. Consiglio, C. Arone, D. Spinelli and R. Noto, *J. Chem. Soc., Perkin Trans. 2*, 1982, 721.
26 M. R. Crampton and P. J. Routledge, *J. Chem. Soc., Perkin Trans. 2*, 1984, 573.
27 N. S. Nudelman and S. Cerdeira, *J. Chem. Soc., Perkin Trans. 2*, 1986, 695.
28 M. R. Crampton, P. J. Routledge and P. Golding, *J. Chem. Soc., Perkin Trans. 2*, 1984, 329.
29 O. Banjoko and C. Ezeani, *J. Chem Soc., Perkin Trans. 2*, 1986, 531.
30 (*a*) E. T. Akinyele, I. Onyido and J. Hirst, *J. Phys. Org. Chem.*, 1990, **3**, 41; (*b*) T. A. Emokpae, P. U. Uwakwe and J. Hirst, *J. Chem. Soc., Perkin Trans. 2*, 1991, 509.
31 W. C. Spitzer and G. W. Wheland, *J. Am. Chem. Soc.*, 1940, **62**, 2995.
32 J. Hirst and Kahli-Ur-Rahman, *J. Chem. Soc., Perkin Trans. 2*, 1973, 2119.
33 T. O. Bamkole, J. Hirst and I. Onyido, *J. Chem. Soc., Perkin Trans. 2*, 1982, 889.
34 D. Ayediran, T. O. Bamkole and J. Hirst, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1013.
35 J. F. K. Wilshire, *Aust. J. Chem.*, 1967, **20**, 1663.
36 G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc.*, 1956, **78**, 6034.
37 C. F. Bernasconi, R. H. de Rossi and P. Schmid, *J. Am. Chem. Soc.*, 1977, **99**, 4090.
38 T. A. Emokpae, J. Hirst and P. U. Uwakwe, *J. Chem. Soc., Perkin Trans. 2*, 1990, 2191.

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