The Origin of Primary Steric Effects in Aromatic Substitution: Reactions by Alkoxides or Amines as Nucleophiles

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Kinetics of the reactions of potassium or benzyltrimethylammonium t-butoxide with 1-fluoro-2- or 1-fluoro-4-nitrobenzene in t-butyl alcohol and of the reactions of piperidine with 2- or 4-nitrophenyl phenyl ether and 2,4-dinitrophenyl phenyl or 2,4-dinitrophenyl cyclohexyl ether in dimethyl sulphoxide are reported. Less quantitative data of similar scope are also reported for the reactions of potassium t-butoxide with the above halogenonitrobenzenes in dimethyl sulphoxide and in some aprotic dipolar solvents or with 1-chloro-2- or 1-chloro-4-nitrobenzene in t-butyl alcohol and for the piperidinodecyclohexyloxylation of 2- or 4-nitrophenyl cyclohexyl ether in neat piperidine. The *ortho* : *para* ratio is *ca.* unity for reactions with piperidine and greater than unity for reactions with t-butoxide. 2,4-Dinitrophenyl phenyl ether is appreciably more reactive than its cyclohexyl analogue but markedly less than was previously found for reactions carried out in benzene. It is shown that in the transition states of these reactions neither inhibition of the resonance of the *o*-nitro-group nor repulsions between the entering and leaving group occur to any appreciable extent, while the *o*-nitro-group is markedly rotated out of the plane of the benzene ring both in the starting substrates (chloro-compounds or ethers) and products. These results confirm and extend previous ideas about the origin of primary steric effects in aromatic nucleophilic substitution and their possible implications are discussed.

MUCH recent mechanistic research in aromatic nucleophilic substitution reactions has been concerned with kinetic steric effects.[1] Apart from a unique example concerning methoxydechlorination of phenanthridine derivatives, where the observed steric acceleration was attributed to the release, on going to the transition state, of non-bonding interactions in a position far from the reaction centre,[2] most such studies have dealt with primary steric retardation resulting from increased crowding around the reaction centre in the transition state.

For reactions of primary or secondary amines with 2,4-dinitro-activated benzene derivatives it was established [3] that α-branching to the nitrogen in the reacting amine brings about a steric retardation. More recently it has been established that such a rate retardation originates from steric compression in the transition state among substituents in the α-position to the amine nitrogen and the benzene carbons and hydrogens (this term is used for simplicity even if the transition state is better described by a cyclohexadienoid rather than by a benzenoid structure) and does not involve to any great extent either an *ortho*-activating (nitro) group or the leaving group (fluoride or chloride).[4] This is clearly a consequence of the tetrahedral, or nearly so, geometry at the reaction centre in the transition state.[4]

As regards reactions by anionic nucleophiles, a study [5] of the replacement of halogen from 6-halogenobenzothiazoles by mercaptide ions in a common solvent, methanol (reactions which, like their analogous on benzenoid substrates are viewed [5] to proceed through the addition–elimination mechanism) also revealed that branching at the α-position to the nucleophilic atom in the nucleophile results in a rate retardation whose magnitude is nearly independent of the size of the halogen displaced. Moreover, such rate retardations [5] do not differ markedly in magnitude from those observed [6] for reactions by primary alkylamines with 1-chloro-2,4-dinitrobenzene. These findings, in our opinion, do not support the original conclusions [5] that in aromatic nucleophilic substitution (*a*) steric retardation results mainly from repulsions between the entering and leaving group in the case of anionic nucleophiles, and (*b*) the extent of bond formation between the entering group and the electrophilic site of the substrate at the rate-determining transition state is substantially smaller in reactions by anionic nucleophiles than in reactions by protic amines. Rather, such observations [5] for reactions by anionic nucleophiles can be more satisfactorily rationalised on the same basis as the amine reactions [4] discussed above. (The fear of these authors [5] that in the study of the origin of steric effects in aromatic substitution by protic amines one can be misled by the second stage of the reaction [1] becoming rate-limiting is also unwarranted as far as the reactions discussed above [3,4,6] are concerned. There is in fact unequivocal proof that the first-stage is rate-determining in such cases.[4,6])

Such reinterpretation is further supported by the fact that in reactions at a benzenoid carbon the change from methoxide to t-butoxide as nucleophiles in their respective lyate solvents does not bring about any appreciable inhibition of resonance of an activating *o*-nitro-group in the case of either fluoride or chloride as a leaving group.[7] In fact, in the case of halogenomononitrobenzenes the change from sodium methoxide or ethoxide to potassium t-butoxide in the corresponding lyate solvents brings about a change of the *ortho* : *para* reactivity ratio from *ca.* unity (fluorine) or 0·1 (chlorine) for the first two reagents to about 300 (fluorine) or 100 (chlorine) for t-butoxide. This, other than contradicting the idea (*a*), is exactly the opposite of what could have been expected were steric inhibition of resonance of the

[1] F. Pietra, *Quart. Rev.*, 1969, **23**, 504.
[2] B. R. T. Keene and G. L. Turner, *Chem. Comm.*, 1967, 221.
[3] O. L. Brady and F. R. Cropper, *J. Chem. Soc.*, 1950, 507.
[4] F. Pietra and F. Del Cima, *J. Org. Chem.*, 1968, **33**, 1411.
[5] G. Bartoli, L. Di Nunno, and P. E. Todesco, *Tetrahedron Letters*, 1968, 2369.
[6] F. Pietra and D. Vitali, *J. Chem. Soc.* (*B*), 1968, 1200.
[7] F. Pietra and F. Del Cima, *Chem. Comm.*, 1968, 216.

o-nitro-group responsible, as was suggested,[8] for the low *ortho* : *para* ratios for reactions of methoxide or ethoxide with chloromononitrobenzenes.

However, it could be argued that our findings for amine reactions[4,7] cannot be directly compared with those for methoxide or ethoxide in the corresponding lyate solvents.[8a] This, for reactions by protic amines, may be due to freezing, by hydrogen bonding, of that conformation of the transition state which holds the piperidine substituents (in an α-position to the nitrogen) away from the *o*-nitro-group.[4] (We use here the term 'hydrogen bonding'[9] as an equivalent of 'built-in solvation'[8] in contrast with recent literature[10] where the two terms are referred to two different theories. The first term was originally used by Bishop, Cavell, and Chapman[9] and the second by Bunnett and Morath[8a] to rationalise the greater reactivity of *o*-nitro- than *p*-nitro-substituted substrates towards protic amines. A careful reading of the original papers[8,9] shows that the 'built-in solvation' idea is not meant to exclude the 'hydrogen bonding' idea. If anything, the original authors[8a] considered the hydrogen bond to have a predominantly electrostatic character.)

A similar objection could also be raised about our t-butoxide reactions[7] as the t-butyl carbons can be held away from the *o*-nitro-group in the transition state by bridging of the potassium ion between the nucleophile and nitro-group oxygens. Although such interactions are unimportant in the case of alkali-metal cations for rate processes in polar solvents,[11] they may well be involved when a solvent of such low polarity as t-butyl alcohol,[12] where potassium t-butoxide is largely associated,[13] is used.

In order to minimise the weight of such presumed bridged structures, we made the appropriate[13,14] change to a tetra-alkylammonium t-butoxide in t-butyl alcohol or, maintaining potassium as the cation, we changed to a dipolar aprotic solvent. The results of such investigations are reported here. We report here also the results of an extension of our investigation of the factors determining the *ortho* : *para* ratio in activation by the nitro-group to cover leaving groups other than fluoride and chloride, such as phenoxide and cyclohexyloxide, in reactions by protic amines.

RESULTS

Reactions of Benzyltrimethylammonium t-Butoxide with 1-Halogeno-2- or 1-Halogeno-4-nitrobenzenes in t-Butyl Alcohol.—Under the conditions of Table 1 benzyltrimethylammonium t-butoxide in t-butyl alcohol replaces fluorine from either 1-fluoro-2- or 1-fluoro-4-nitrobenzene with good yields (*ca.* 95%), the lacking 5% being 2- or 4-nitrophenol, respectively. At lower concentrations of either fluoro-compound we obtained instead ethers and nitrophenols in an about 1 : 1 ratio.

It is admitted that moisture, in spite of care in purifying and handling materials, is responsible for nitrophenol formation. In fact nitrophenols do not originate from subsequent reaction of the ethers as a 0·08M-solution of either 4- or 2-nitrophenyl t-butyl ether remained unchanged in the presence of 0·08M-benzyltrimethylammonium t-butoxide in t-butyl alcohol at such a temperature and for a time where the corresponding fluoro-compound would have completely reacted.

TABLE 1

Second-order[a] rate coefficient (k = Rate/[Substrate]-[Nucleophile] (l. mole^{-1} sec.$^{-1}$) for the reactions of potassium[b] or benzyltrimethylammonium (BTMA) t-butoxide with 1-fluoro-2- or 1-fluoro-4-nitrobenzene in t-butyl alcohol at 29·5 or 28 °C for KOBu^t or BTMAOBu^t, respectively

Substrate (M)	Nucleophile (M)	10^4k	k_o/k_p
p-F, 0·44	KOBu^t, 0·44	0·15[b]	360
o-F, 0·35	KOBu^t, 0·35	54[b]	
p-F, 0·084	BTMAOBu^t, 0·076	3·3	26
o-F, 0·076	BTMAOBu^t, 0·071	85	
p-F, 0·34	BTMAOBu^t, 0·33	23	7·4
o-F, 0·33	BTMAOBu^t, 0·32	170	

[a] See text. [b] Data from ref. 7.

The rate data for the above reactions, where 3-nitrophenyl t-butyl ether was not formed in any detectable (by v.p.c.) amount, are collected in Table 1 together with previous[7] data for the corresponding reactions of potassium t-butoxide.

Change of the leaving group from fluoride to chloride proved to be dramatically detrimental to ether yields, particularly in the case of benzyltrimethylammonium t-butoxide. Although we have not investigated the nature of the competing reactions, nitrophenols alone did not account for all material balance. Even lower yields of ethers were obtained in the case of benzyltrimethylammonium t-butoxide on raising the temperature owing, presumably, to a greater activation energy for nucleophile decomposition than for aromatic substitution (alkalimetric titration showed that our freshly prepared 0·08M-benzyltrimethylammonium t-butoxide in t-butyl alcohol decomposed by *ca.* 20% in 47 hr. at 30 °C, while *ca.* 70% decomposition occurred after only 1 hr. at 73 °C). Therefore rigorous kinetic data for displacement of chlorine could not be obtained. However we report (Table 2) yields obtained under such conditions that relative reactivities can be satisfactorily estimated (see Discussion section). Under the conditions of Table 2, v.p.c. analysis showed that 3-nitrophenyl t-butyl ether was never formed in appreciable amount.

Reactions of Potassium t-Butoxide with 1-Halogeno-2- or 1-Halogeno-4-nitrobenzenes in Dipolar Aprotic Solvents.—Title reactions (halogen = fluorine or chlorine) were examined in truly aprotic dipolar solvents[15] like dimethylform-

[8] (*a*) J. F. Bunnett and R. J. Morath, *J. Amer. Chem. Soc.*, 1955, **77**, 5051; (*b*) J. F. Bunnett, *Quart. Rev.*, 1958, **12**, 1.
[9] R. R. Bishop, E. S. A. Cavell, and N. B. Chapman, *J. Chem. Soc.*, 1952, 437.
[10] J. Burdon, I. N. Rozhkov, and G. M. Perry, *J. Chem. Soc.* (*C*), 1969, 2615.
[11] C. A. Bunton and L. Robinson, *J. Amer. Chem. Soc.*, 1968, **90**, 5965.
[12] Ch. Reichart and K. Dimroth, *Fortschr. Chem. Forsch.*, 1968, **11**, (1), 1.
[13] W. H. Saunders, D. G. Bushman, and A. F. Cockerill, *J. Amer. Chem. Soc.*, 1968, **90**, 1775.
[14] D. H. Hunter and Y. T. Lin, *J. Amer. Chem. Soc.*, 1968, **90**, 5921.
[15] J. I. Brauman and N. J. Nelson, *J. Amer. Chem. Soc.*, 1968, **90**, 491.

TABLE 2

Yield data for the reactions of potassium or benzyl trimethylammonium (BTMA) t-butoxide with 1-chloro-2- or 1-chloro-4-nitrobenzene in t-butyl alcohol

A.[a] *p*-C_6H_4·NO_2·Cl 0·14M[b]; $KOBu^t$ 0·14M[b]; temp. 90 °C

Time (hr.)	17	104	312
p-C_6H_4·NO_2·Cl (%)[c]	75	44	
$KOBu^t$ (%)[c]	79	45	
p-C_6H_4·NO_2·OBu^t (%)[d]	1	4	5

B.[a] *o*-C_6H_4·NO_2·Cl 0·14M[b]; $KOBu^t$ 0·14M[b]; temp. 90 °C

Time (hr.)	0·17	0·50	3	142
o-C_6H_4·NO_2·Cl (%)[c]	99	97		30
$KOBu^t$ (%)[c]	94	92		0·5
o-C_6H_4·NO_2·OBu^t (%)[d]	1	3	14	60

C. *p*-C_6H_4·NO_2·Cl 0·13M[b]; $BTMAOBu^t$ 0·11M[b]; temp. 30 °C

Time (hr.)	5·2	21·1	30	46	148
p-$C_6H_4NO_2$·Cl (%)[c]	98	96	94	93	85
$BTMAOBu^t$ (%)[c]	95	78	75	72	50
p-C_6H_4·NO_2·OBu^t (%)[d]	0·16	0·35	0·38	0·46	1·1

D. *o*-C_6H_4·NO_2·Cl 0·14M[b]; $BTMAOBu^t$ 0·087M[b]; temp. 30 °C

Time (hr.)	5	20·8	30	46	148
o-$C_6H_4NO_2Cl$ (%)[c]	98	96	95	94	84
$BTMAOBu^t$ (%)[c]	92	77	72	70	41
o-C_6H_4·NO_2·OBu^t (%)[d]	0·3	0·6	0·8	1·0	2·0

[a] Part of these data have been reported [7]. [b] Initial concentrations. [c] Percentage with respect to the initial concentration. [d] Percentage with respect to the expected theoretical amount for quantitative reaction.

amide, hexamethylphosphoramide, or in dimethyl sulphoxide. A deep red-brown colour developed immediately on mixing the reagents in such non-degassed solvents at room temperature. The colour became yellow on dilution with water and neutralisation with aqueous hydrogen chloride (after 5 min. from the mixing of the reagents the strong alkali was only a few % of the initial amount). V.p.c. showed that, with initially 0·1M-reagents, in every case the starting halogenonitrobenzene had largely disappeared whereas percentages of the corresponding ethers were 66, 66, 9, and 15 for 1-fluoro-4-, 1-fluoro-2-, 1-chloro-4-, or 1-chloro-2-nitrobenzene, respectively, in dimethylformamide.

Neither here nor in the following cases was 3-nitrophenyl t-butyl ether detectable in the mixtures.

When the reactions were run in dimethyl sulphoxide no appreciable amount of ethers was obtained from either chloro-compound (t.l.c. of the reaction mixtures in the case of 1-chloro-2-nitrobenzene revealed the presence of a variety of products besides unchanged substrate), whereas percentages of the corresponding ethers were 19 and 43 for 1-fluoro-4- or 1-fluoro-2-nitrobenzene, respectively.

Addition of t-butyl alcohol (80%) to dimethyl sulphoxide slowed the reaction of the chloro-compounds. However, at 70 °C yields of ethers were poor (though greater from the *ortho*-compounds) while the starting reagents had extensively decomposed.

In the case of reactions run in hexamethylphosphoramide, where only the *para*-compounds were examined, 4-nitrophenyl t-butyl ether was formed in 89 and 15% yield from 1-fluoro- or 1-chloro-4-nitrobenzene, respectively. We found also that in (non-degassed) amide containing potassium t-butoxide nitrobenzene disappears rather rapidly (v.p.c.) at room temperature.

Reactions of Piperidine with Some Nitrophenyl Phenyl or Nitrophenyl Cyclohexyl Ethers in Dimethyl Sulphoxide.—The reactions of piperidine with a number of ethers like 2- or 4-nitrophenyl phenyl ether and 2,4-dinitrophenyl phenyl or 2,4-dinitrophenyl cyclohexyl ether in dimethyl sulphoxide were examined in a range of amine concentrations at various temperatures. Quantitative substitution of the phenoxy-group for the first three ethers and of the cyclohexyloxy-group for the fourth by piperidine were observed under the conditions of the kinetic experiments reported in Table 3. In the last case (Table 3, D) a rather high concentration of substrate (*ca.* 0·1M) was necessary. At lower concentrations, in fact, the formation of coloured by-products of unidentified origin interfered with the u.v. analysis of the *N*-2,4-dinitrophenylpiperidine produced.

TABLE 3

Second-order rate coefficient (k = Rate/[Substrate][Piperidine], l. mole^{-1} sec.$^{-1}$) for the reactions of piperidine (PIP) with: (A) 2-nitrophenyl phenyl ether; (B) 4-nitrophenyl phenyl ether; (C) 2,4-dinitrophenyl phenyl ether; (D) 2,4-dinitrophenyl cyclohexyl ether in dimethyl sulphoxide

A. 2-Nitrophenyl phenyl ether (initial concn. *ca.* 10^{-2}M); temp. 69·8 °C, unless otherwise stated

10[PIP]	2·50	5·08	9·97	10·1	10·5	10·5	15·0	20·0
10^6k	4·71	4·70	4·81	4·81	2·12[a]	9·85[b]	4·92	4·93

B. 4-Nitrophenyl phenyl ether (initial concn. *ca.* 7 × 10^{-4}M); temp. 69·8 °C, unless otherwise stated

10[PIP]	2·50	5·02	10·1	10·1	10·1	15·2
10^6k	5·94	6·11	6·53	12·4[b]	21·4[c]	6·27

C. 2,4-Dinitrophenyl phenyl ether (initial concn. *ca.* 2·3 × 10^{-5}M); temp. 25 °C, unless otherwise stated

10^2[PIP]	2·26	2·30	2·47	3·39	3·73	3·73	4·28
10^2k	2·48[d]	2·98[e]	2·34	2·94	3·94[d]	4·49[e]	3·91
10^2[PIP]	4·52	4·60	4·95	6·78	7·12	7·47	9·05
10^2k	4·56[d]	5·18[e]	4·48	5·60	7·80[e]	7·25[d]	8·33[e]
10^2[PIP]	9·20	9·87	12·3	14·3	17·1	20·6	24·0
10^2k	9·58[e]	7·88	9·40	10·5	12·3	13·3	15·0

D. 2,4-Dinitrophenyl cyclohexyl ether (initial concn. *ca.* 0·1M); temp. 55 °C, unless otherwise stated

10[PIP]	4·35	5·01	5·01	9·80	10·1
10^5k	1·71	2·64[f]	3·47[g]	3·15	4·12[f]
10[PIP]	10·1	14·5	14·8	14·8	
10^5k	5·95[g]	4·21	6·11[f]	8·67[g]	

[a] At 54·5 °C. [b] At 85·0 °C. [c] At 98·4 °C. [d] At 34·4 °C. [e] At 48·2 °C. [f] At 69·8 °C. [g] At 84·8 °C.

The uncertainty of the experimental error is *ca.* 5% for rate data at A and B, *ca.* 2% for rate data at C, and *ca.* 10% for rate data at D.

Experiments not reported here showed that, as expected,[1] all the above reactions are of the first order with respect to the starting ether. It can also be seen from the data of Table 3, A, B, that the reactions of either 2- or 4-nitrophenyl phenyl ether are nicely of the first order with respect to the amine.

In the case of the cyclohexyl ether (Table 3, D) the second-order rate coefficient (k = Rate/[Substrate][Piperidine]) increases with increasing piperidine concentration, according to equation (1), where PIP stands for piperidine.

$$k = k_0 + k_{PIP}[PIP] \quad (1)$$

At 69·8 °C k_0 is 7·4 × 10^{-6} l. mole^{-1} sec.$^{-1}$ and k_{PIP} 3·5 × 10^{-5} l.^{2} mole^{-2} sec.$^{-1}$. Therefore, k_{PIP}/k_0 is *ca.* 5 l. mole^{-1}. Similar values of the last ratio were obtained at the other two temperatures investigated.

TABLE 4

Activation parameters * (determined from second-order rate coefficients unless otherwise stated) for the reactions of piperidine with 2- or 4-nitrophenyl phenyl ether and with 2,4-dinitrophenyl phenyl or 2,4-dinitrophenyl cyclohexyl ether in dimethyl sulphoxide

Substrate	$\Delta H^{\ddagger}$ (kcal. mole^{-1})	$-\Delta S^{\ddagger}$ (e.u.)
2-Nitrophenyl phenyl ether	10·8	52
4-Nitrophenyl phenyl ether	9·9	54
2,4-Dinitrophenyl phenyl ether	2·3 [a]	61 [a]
	1·4 [b]	63 [b]
2,4-Dinitrophenyl cyclohexyl ether	4·2 [c]	66 [c]
	4·3 [d]	66 [d]
	5·1 [e]	65 [e]

* Determined at piperidine concn. (M): [c] 0·5; [e] 1·0; [f] 1·5. [d] Calculated from k_0 terms (equation 1). [e] Calculated from k_{PIP} terms (equation 1).

In the case of 2,4-dinitrophenyl phenyl ether data at 25 °C (Table 3, C) are fitted by equation (1) only up to *ca.* 0·01M-piperidine and k_{PIP}/k_0 is *ca.* 1 l. mole^{-1}. On further increase of the piperidine concentration a levelling off of the rate is observed.

Activation parameters for the above reactions are listed in Table 4.

Either 2- or 4-nitrophenyl cyclohexyl ether remained unchanged after 90 hr. in the presence of 2M-piperidine in dimethyl sulphoxide at 150 °C. However, piperidinolysis at 160 °C afforded some cyclohexanol from either ether (Table 5). Under such conditions neither cyclohexene nor *N*-cyclohexylpiperidine was formed in any appreciable amount.

TABLE 5

Piperidinolysis of 2- or 4-nitrophenyl cyclohexyl ether; cyclohexanol yield after 168 hr. at 160 °C

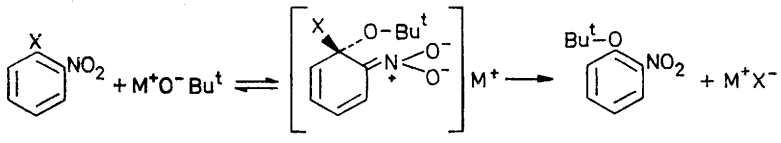
o-NO_2·C_6H_4·OC_6H_{11} (M) [a]	p-NO_2·C_6H_4·OC_6H_{11} (M) [a]	$C_6H_{11}OH$ (%) [b]
0·0982		11
	0·066 [b]	1 [c]

[a] Initial concentrations. [b] Percentage with respect to the expected theoretical amount for quantitative reaction. [c] The starting ether is still about 99% unchanged (by u.v. analysis).

DISCUSSION

Reactions of Alkoxides as Nucleophiles.—3-Nitrophenyl t-butyl ether, an expected product from a benzyne mechanism,[1,16] is never formed in the reactions by t-butoxide as a nucleophile investigated here. Therefore these reactions may be viewed, by analogy with related ones of known mechanism,[1] to proceed through the addition–elimination mechanism [shown in equation (2) for an *o*-nitro-substituted substrate] with fast decomposition of the tetrahedral addition-intermediate (I) into products.

It seems profitable to examine the *ortho* : *para* activation ratio by the nitro-group obtained here for reactions by a tetra-alkylammonium t-butoxide. Rigorous kinetic data for displacement of fluorine show (Table 1) that the *ortho* : *para* ratio is higher than unity. In the case of the chloro-compounds, where rigorous kinetic data could not be obtained, the *ortho* : *para* ratio can be satisfactorily estimated from ether yields obtained under such conditions that the concentrations of the starting materials had changed little. Table 2 thus shows that even for displacement of chlorine the *ortho* : *para* ratio by the nitro-group is higher than unity.*



(I) (2)

Tables 1 and 2 reveal that the values of the *ortho* : *para* activation ratio by the nitro-group, though always higher than unity, depend appreciably on the nature of the cation of the nucleophile. Thus, in displacement of fluorine, the *ortho* : *para* ratio is more than one order of magnitude greater for potassium than for tetra-alkylammonium t-butoxide at the same concentrations (Table 1). In the latter case, where the influence of the nucleophile concentration has been investigated, Table 1 shows also that the *ortho* : *para* ratio increases appreciably with decreasing nucleophile concentration. This is because, although rigorous second-order kinetics were obtained for any single run, the apparent second-order rate coefficient increases with increasing stoicheiometric nucleophile concentration, the trend being more pronounced for the *p*-nitro- than for the *o*-nitro-substituted substrate.

Increase of the apparent second-order rate coefficient had already been noticed for reactions of *o*-nitrohalogenobenzenes with tetra-alkylammonium methoxide in various solvents [11,17] and clearly [11] attributed to the stabilising action of this cation on the large activated complex. In the displacement of chlorine the *ortho* : *para* activation ratio by the nitro-group increases from a little more than unity for the tetra-alkylammonium t-butoxide to more than 100 for potassium t-butoxide (Table 2). With the potassium salt 1-chloro-2-nitrobenzene affords the minimum assayable amount of

* *Added in proof:* This conclusion is justified by the fact that (*a*) 2-nitrophenyl t-butyl ether (0·08M) in the presence of potassium t-butoxide (0·13M) in t-butyl alcohol remained unaltered after 3·5 hr. at 70° and decomposed by only 12% after 24 hr. at 90°, (*b*) 4-nitrophenyl t-butyl ether (0·11M) also remained unaltered after 40 hr. at 90° in the presence of potassium t-butoxide (0·13M) in t-butyl alcohol (F. Pietra and F. Del Cima, *Chem. Comm.*, 1970, 769).

[16] J. D. Roberts, C. W. Vaughan, L. A. Carlsmith, and D. A. Semenow, *J. Amer. Chem. Soc.*, 1956, **78**, 611.

[17] W. Hostetler and J. D. Reinheimer, *J. Org. Chem.*, 1968, **33**, 3510, and previous papers in the series.

ether (1%) in one hundredth of the time required by its *para*-isomer at the same temperature (Table 2, A, B). The *ortho* : *para* activation ratio must however be even higher than 100 as, under the above conditions, 1-chloro-4-nitrobenzene had already decomposed by more than 20% (Table 2, A).

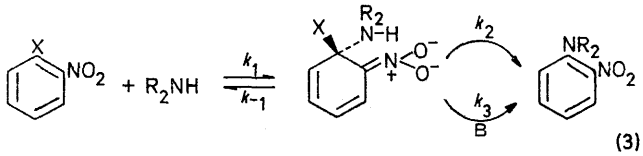
The large increase of the *ortho* : *para* activation ratio observed here on changing from a cation of low co-ordinating ability towards electronegative atoms, like a tetra-alkylammonium cation, to one that, like potassium, displays a good co-ordinating ability towards such atoms [14] gives some hint that the exceptionally high values of the *ortho* : *para* ratio observed in the case of potassium t-butoxide may reflect a specific stabilisation of the transition state of the reactions of the *o*-nitro-substituted substrates by potassium cation bridging between the nucleophile and a nitro-group oxygen. [Another case that bears at least some formal resemblance to the present one is the methoxydefluorination of pentafluoronitrobenzene by sodium methoxide in methanol–ethyl ether,[18] where the *ortho* : *para* ratio increases appreciably with increasing percentage of the less polar solvent (ethyl ether) in the mixture.[18]

The fact that the enhanced reactivity of benzyltrimethylammonium t-butoxide with respect to the corresponding potassium salt is more pronounced in the case of reactions with *p*- than with *o*-nitro-substituted substrates (Table 1) might also be rationalised along the same lines. In fact, while a greater reactivity for a largely dissociated salt (benzyltrimethylammonium t-butoxide in t-butyl alcohol [13]) with respect to a largely associated one (potassium t-butoxide in t-butyl alcohol [13]) can be attributed to the generally higher nucleophilicity of free anions than of paired anions,[19] such a less pronounced trend in the case of *o*-nitro-substituted substrates might reflect some extra stabilisation of the transition state in the latter case.] Although this is no more than a (reasonable) hypothesis in the absence of information on the free energies of the reactants,[11] the above data for the reactions of benzyltrimethylammonium t-butoxide, owing to the low co-ordinating ability of the cation towards electronegative atoms,[14] definitely show that in the transition state for displacement of either fluorine or chlorine by t-butoxide no appreciable inhibition of resonance of an *o*-nitro-group occurs.

Therefore these data refute the suggestion [8] that *ortho* : *para* activation ratios slightly smaller than unity for displacement of chlorine by either methoxide or ethoxide in their lyate solvents reflect inhibition of resonance of the *o*-nitro-group in the transition state. This present conclusion is not affected by the reported [20] dependence of the steric requirement of alkoxide ions on the solvent nature. In fact, in the case of methoxide as a nucleophile it is believed [20] that the steric requirement of the alkoxide increases on changing from methanol to t-butyl alcohol as solvent.

The unsuitability of either dimethyl sulphoxide or truly aprotic dipolar solvents for the above reactions is attributable, as we have shown, to the presence of a nitro-group in the substrate. These are uncommon examples of nucleophilic substitutions which, contrary to the norm,[21] are not helped by the use of dipolar aprotic solvents. When the substrate is not substituted by a nitro-group, as in the case of halogenobenzenes, substitution of the halogen by t-butoxide is enormously faster in dimethyl sulphoxide than in t-butyl alcohol.[22] However, at least in the case of bromobenzene, the reaction probably occurs *via* a benzyne intermediate.[23]

Reactions of Amines as Nucleophiles.—The commonly accepted addition–elimination mechanism can be written as in equation (3) for reactions by a secondary amine as a nucleophile taking an *o*-nitro-substituted substrate as an example. Here k_2 may represent either the rate coefficient for the unassisted,[1] the solvent-assisted,[1] or the *o*-nitro-group-assisted [24] decomposition of the addition intermediate (II) into products while k_3 represents the rate coefficient for a catalysed (by a basic,[1] an



(II) (3)

acidic,[25] or a bifunctional [25] catalyst) pathway to products.

The reactions reported here are reasonably interpretable in terms of the mechanism of equation (3) with fast decomposition of the intermediate (II) into products. This, for reactions by 2- or 4-nitrophenyl phenyl ether, is immediately clear since, over a broad range of amine concentrations, first-order kinetics with respect to piperidine are observed.

The same conclusion can be arrived at even for the reactions of either phenyl or cyclohexyl 2,4-dinitrophenyl ether. In fact, the k_{PIP}/k_0 ratio, which can be taken as a measure of the extent of piperidine catalysis,[26] is much too low to be attributable to piperidine catalysis. Moreover, should the slight acceleration by piperidine of the reaction of 2,4-dinitrophenyl phenyl ether with piperidine represent base catalysis by piperidine, one would have expected that the corresponding reaction of 4-nitrophenyl phenyl ether be even more powerfully

[18] J. Burdon, D. Fisher, D. King, and J. C. Tatlow, *Chem. Comm.*, 1965, 65.
[19] S. Winstein, L. G. Savedoff, S. Smith, I. D. R. Stevens, and J. S. Gall, *Tetrahedron Letters*, 1960, **9**, 24; R. G. Burns and B. D. England, *J. Chem. Soc.* (*B*), 1966, 864.
[20] R. D. Chambers, D. Lomas, and W. K. R. Musgrave, *J. Chem. Soc.* (*C*), 1968, 625.
[21] A. J. Parker, *Quart. Rev.*, 1962, **16**, 163.
[22] D. J. Cram, B. Rickborn, and G. R. Knox, *J. Amer. Chem. Soc.*, 1960, **82**, 6412.
[23] M. Kise, T. Asari, N. Furukawa, and S. Oae, *Chem. and Ind.*, 1967, 276.
[24] F. Pietra and F. Del Cima, *Tetrahedron Letters*, 1967, 4573.
[25] F. Pietra and D. Vitali, *J. Chem. Soc.* (*B*), 1968, 1318.
[26] J. F. Bunnett and R. H. Garst, *J. Amer. Chem. Soc.*, 1965, **87**, 3875.

accelerated by piperidine, contrary to what has been observed here. In fact, the *o*-nitro-group is known to be able to exert an intramolecular base catalysis in reactions of this class.[24]

Therefore the slight accelerations by piperidine of displacements of phenoxy- or cyclohexyloxy-groups observed here can be either attributed to some stabilisation of unclear origin of the transition state leading to the intermediate (II) [26] or might reflect a solvent effect on the initial state, an increasing piperidine content in the dimethyl sulphoxide–piperidine solvent mixture possibly diminishing its solvating ability towards the aromatic substrate.

The levelling off of the rate for displacement of the phenoxy-group observed here is also likely to have the same origin and cannot have anything to do with phenomena of the change of the rate-limiting step with changing the catalyst concentration.[1]

Displacement of either phenoxy- [27] or cyclohexyloxy-groups [28] from 2,4-dinitrophenyl substrates by piperidine are fully piperidine-catalysed processes when the reactions are run in benzene. In the case of displacement of the phenoxy-group piperidine behaves as a pure base catalyst.[27]

Similar observations concerning displacement of fluorine by piperidine from aromatic substrates in either dimethyl sulphoxide or benzene as solvent have already been made.[29] Some authors [29a] interpreted the rate enhancement and the change of the pattern of the kinetic orders from second- to first-order in piperidine observed on changing from dimethyl sulphoxide to benzene to the sulphoxide's behaving as a base in the abstraction of a proton from the intermediate (II). However, other authors [29b] showed that such state of affairs results from a general medium effect by dimethyl sulphoxide.

This solvent effect of dimethyl sulphoxide is enormously more pronounced when the substrate does not bear an *o*-nitro-group. Thus, a mechanistically sound comparison of the extent of rate enhancement brought about by dimethyl sulphoxide relative to benzene can be done only through the k_0 [equation (1)] terms. Such an analysis for the piperidinodefluorinations of both 1-fluoro-2- and 1-fluoro-4-nitrobenzene discloses that the rate enhancement due to a change from benzene to dimethyl sulphoxide is only *ca.* 50 in the former case [4,24] while in the latter [4,24] a very large value is obtained. (Difficulty in giving a precise value reflects the difficulty experienced in obtaining a precise value of k_0 for reaction of the *p*-nitro-substrate in benzene, such reaction being described, within the limits of the experimental error, as of the second-order with respect to piperidine.) These results reflect again the anchimeric role [24] of the *o*-nitro-group in piperidinodefluorination of 1-fluoro-2-nitrobenzene in benzene.

The fact that the *ortho* : *para* activation ratio by the nitro-group for replacement of the phenoxy-group by piperidine is *ca.* unity clearly shows that no appreciable inhibition of the resonance of the *o*-nitro-group is involved in the transition state. This conclusion is firmly established owing to a similarity of the activation data for the two reactions compared.

The same conclusion can also be drawn for piperidinodecyclohexyloxylation under the presumption (which, on the basis of the above data seems reasonable) that the two reactions compared are of the same kinetic order with respect to piperidine. In fact, the yield of cyclohexanol from the less reactive (*para*) isomer has been obtained under conditions that no appreciable side decomposition of the starting compound has occurred.

With the 2,4-dinitro-activated substrates, the reactivity ratio between the reactions of 2,4-dinitrophenyl phenyl ether and its cyclohexyl analogues with piperidine is much greater in benzene [28] than in dimethyl sulphoxide. This might be because in benzene decomposition of the addition-intermediate (II) into products is rate-limiting; [27,28] therefore, probably, some stretching of the bond to the leaving group occurs in the transition state.[27,30] If so, lower bond energy [31] should favour the phenyl over the cyclohexyl ether. (This is only a tentative rationalisation. In fact, while it has been shown that piperidine catalysis of the reaction of 2,4-dinitrophenyl phenyl ether with piperidine in benzene is pure base catalysis,[27,28] the origin of piperidine catalysis of the reaction of 2,4-dinitrophenyl cyclohexyl ether with piperidine in benzene is much less understood.[28] In the latter case, the stronger basic nature of the leaving group might well require a kinetically important solvation by piperidine.) In dimethyl sulphoxide, on the contrary, decomposition of the intermediate (II) is not kinetically important and therefore the phenyl ether is favoured by only about 2 kcal. mole^{-1} of activation energy (Table 4).

We conclude that even in the case of 2,4-dinitro-activated ethers there is no appreciable inhibition of resonance of the *o*-nitro-group in the transition state. Previously, when kinetic data for only the cyclohexyl ether in benzene [28] were available, this was not obvious.[28]

As regards the relative bulk of cyclohexyl and phenyl groups, results from conformational equilibrium data on cyclohexane systems point to a similarity of the relative 'sizes,' [32] while results of the stereospecific reduction of phenyl cyclohexyl ketone could be interpreted in terms of a greater steric bulk of the cyclohexyl than of the phenyl group.[33]

It is surprising that all cyclohexyl ethers examined here fail to react appreciably with piperidine at the

[27] F. Pietra, *Tetrahedron Letters*, 1965, 2405.
[28] F. Pietra, D. Vitali, and (in part) S. Frediani, *J. Chem. Soc.* (*B*), 1968, 1595.
[29] (*a*) H. Suhr, *Ber. Bunsenges. phys. Chem.*, 1963, **67**, 893; (*b*) C. F. Bernasconi, M. Kaufmann, and H. Zollinger, *Helv. Chim. Acta*, 1966, **49**, 2563.
[30] C. R. Hart and A. N. Bourns, *Tetrahedron Letters*, 1966, 2995.
[31] J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, 1968; p. 217.
[32] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Wiley, New York, 1965.
[33] E. Parker Burrows, F. J. Welch, and H. S. Mosher, *J. Amer. Chem. Soc.*, 1960, **82**, 880.

cyclohexyl moiety even under the very drastic conditions used for the mononitro-ethers. Nucleophilic substitution at the aliphatic (methyl) carbon with either 2,4-dinitrophenoxide [34] or 2,4,6-trinitrophenoxide [35] as a leaving group and nucleophilic substitution or β-elimination at the cyclohexyl system with 2,4,6-trinitrophenoxy (either axial or equatorial) as a leaving group [36] are in fact well known. Moreover, 2,4-dinitrophenyl t-butyl ether gives easily isobutene on treatment with piperidine in benzene.[37]

Conclusions.—Full activating power of the *o*-nitro-group in the transition state of aromatic nucleophilic substitution, as found here, requires the *o*-nitro-group to be coplanar with the benzene carbons and hydrogens in the transition state and is a clear consequence of the tetrahedral nature of the latter at the reaction centre. Relief of repulsive interactions is then obtained by insertion of the *o*-nitro-group between the entering and leaving group in the transition state which must then be close to the addition intermediate (I) or (II). This requires that both in the present and previous cases [4,7] there is no appreciable repulsion in the transition state between the entering and leaving group.

When such a favourable situation of the transition state is not attainable, as in both the reactants and the products of our reactions, either the entering or the leaving group is sufficiently bulky to prevent coplanarity of the *o*-nitro-group with the benzene ring. This is shown by diffraction experiments on *o*-nitrochlorobenzenes [38] and is also clearly indicated by the comparatively (with respect to the *p*-nitro-substituted isomer) low intensity of the long-wave u.v. absorption band for *N*-2-nitrophenylpiperidine,[4] and for t-butyl, phenyl, or cyclohexyl 2-nitrophenyl ether (Table 6).

TABLE 6

Wavelength (λ, mμ) and molar absorptivity (ε l. mole^{-1} cm.$^{-1}$) at the maximum of the long-wave absorption of some ethers

Compound		$10^{-3}\varepsilon$
[a] 2-NO_2·C_6H_4·OBu^t	[b]	*ca.* 1·2 (at 300 mμ)
[a] 4-NO_2·C_6H_4·OBu^t	295	8·79
[c] 2-NO_2·C_6H_4·OPh	305	2·06
[c] 4-NO_2·C_6H_4·OPh	311	10·3
[c] 2-NO_2·C_6H_4·OC_6H_{11}	322	1·31
[c] 4-NO_2·C_6H_4·OC_6H_{11}	311	10·3

[a] In t-butyl alcohol. [b] Shallow absorption between 275 and 350 mμ with no pronounced maximum. [c] In benzene.

[A comparatively similar situation exists when type (I) intermediates are compared with initial substrates. This has been done directly by *X*-ray diffraction.[39]]

Clearly, however, coplanar geometry is essential to the transition state when the nitro-group must accept electrons from the nucleophile, but not for *o*-nitrophenyl substrates.[4,8a] It is therefore perhaps also conceivable that this planarity requirement will be the less stringent the farther is the transition state from the addition-intermediate along the reaction co-ordinate. If so, studies like the present ones cannot be a precise test for the position of the rate-determining transition state along the reaction co-ordinate.

These results confirm and extend our ideas [4,7] that neither inhibition of resonance of the *o*-nitro-group nor repulsion between the entering and leaving group in aromatic nucleophilic substitution can be so frequent as previously believed.[5,8,40] However, it is to be expected that in particular cases, which we would consider to be out of the norm, an appreciable repulsion between the entering and leaving group can occur in the transition state of nucleophilic aromatic substitution and this may reflect itself in inhibiting coplanarity of the *o*-nitro-group with the benzene carbons and hydrogens in the transition state.

The literature contains such claims which cannot be refuted at present. These include amination of 1-fluoro-2,4-dinitrobenzene in water where the reactivity order dimethylamine > methylamine > trimethylamine was attributed to steric effects (not better defined) in the transition state.[41] This conclusion was drawn from the fact that in the case of a substrate having no *o*-nitro-substituent, like 6-chloropurine ribonucleoside, the amine reactivity order for chlorine displacement was trimethylamine > dimethylamine > methylamine.[41]

Another case is provided by the reactions of triethylenediamine with 1-chloro-2- or 1-chloro-4-nitrobenzene in benzyl alcohol where the *ortho* : *para* ratio is 0·004.[42] This very low ratio was attributed to steric inhibition of resonance of the *o*-nitro-group in the transition state and was judged [42] to lend further support to the idea [8,9] that *ortho* : *para* ratios greater than unity in reactions by protic amines as nucleophiles reflect a specific stabilisation of the transition state for the reaction of the *o*-nitro-substituted substrate by intramolecular hydrogen bonding between the ammonium proton and a nitro-group oxygen. These results are however contradicted by the more recent report that another non-protic amine, like pyridine, replaces chlorine from 1-chloro-2-nitrobenzene much more quickly than from the *para*-isomer in dimethyl sulphoxide.[43] It would be desirable that the origin of such disagreement [42,43] should be assessed.

[34] J. F. Bunnett and R. H. Garst, *J. Org. Chem.*, 1968, **33**, 2320.
[35] R. S. Cahn, *J. Chem. Soc.*, 1931, 1121; M. Kohn and F. Grauer, *Monatsh.*, 1913, **34**, 1751; E. Hertel and H. Lührmann, *Z. Elektrochem.*, 1939, **45**, 405; L. B. Clapp, H. Lacey, G. G. Bechwith, R. M. Srivastava, and N. Muhammad, *J. Org. Chem.*, 1968, **33**, 4262.
[36] M. L. Sinnott and M. C. Whiting, *Chem. Comm.*, 1968, 1617.
[37] F. Pietra and D. Vitali, unpublished work.
[38] See, *e.g.*, C. M. Gramaccioli, R. Destro, and M. Simonetta, *Chem. Comm.*, 1967, 331.
[39] H. Ueda, N. Sakabe, J. Tanaka, and A. Furusaki, *Nature*, 1967, **215**, 956; R. Destro, C. M. Gramaccioli, and M. Simonetta, *Acta Cryst.*, 1968, B, **24**, 1369.
[40] E. S. Lewis and H. Suhr, *J. Amer. Chem. Soc.*, 1960, **82**, 862; B. O. Coniglio, D. E. Giles, W. R. McDonald, and A. J. Parker, *J. Chem. Soc.* (*B*), 1966, 152.
[41] B. T. Walsh and R. Wolfenden, *J. Amer. Chem. Soc.*, 1967, **89**, 6221.
[42] S. D. Ross and M. Finkelstein, *J. Amer. Chem. Soc.*, 1963, **85**, 2603.
[43] H. Suhr, *Annalen*, 1967, **701**, 101.

Still another case is perhaps provided by the observed decreased reactivity of methoxydealkylsulphonylation from 2-alkylsulphonylquinoxalines on increasing the size of the alkyl residue from methyl to t-butyl.[44] In the opinion of the original authors [44] such a rate decrease cannot be entirely attributed to electronic factors and steric effects must also be involved. However, the authors [44] did not make clear whether they intended to advocate a steric repulsion between the entering and leaving group or rather a repulsion between the leaving group and the benzene carbons and hydrogens in the transition state. In the latter, the steric effect would conform to the norm.

It has also been suggested [45] that in reactions of 4-halogenopyridines with lithium piperidide in piperidine the shift of mechanism from the addition–elimination to the hetharyne mechanism observed [45] on changin from chloride to bromide and to iodide as leaving groups can be attributed to increased steric repulsions between the entering and the leaving group in the transition state for the direct substitution of halogen.

In view of our findings and arguments we suggest that the above claims for either inhibition of resonance of the *o*-nitro-group or steric repulsion between the entering and leaving group in the transition state should be further examined by means of reactions of compounds of appropriate structures.

EXPERIMENTAL

M.p.s were determined on a Kofler hot stage apparatus and are uncorrected. V.p.c. was with a Perkin-Elmer 810 GC instrument with flame ionisation detector. ^{1}H N.m.r. spectra were recorded on a Varian DA-60 IL spectrometer (10% solutions, $SiMe_4$ as internal standard, unless otherwise specified; room temperature). U.v. spectra were taken on a Beckman DU or a Unicam SP 800 spectrophotometer with 10 mm. quartz cuvettes.

Materials. t-Butyl alcohol was recrystallised several times and then distilled over calcium hydride.[46] Dimethylformamide was distilled from P_2O_5 under nitrogen. Piperidine and dimethyl sulphoxide were purified as before.[4] Cyclohexanol, cyclohexene, mesitylene, and hexamethylphosphoramide were fractionally distilled (the latter at 0·5 mmHg). 1-Fluoro-2, 1-chloro-2-, 1-fluoro-4-, and 1-chloro-4-nitrobenzene were recrystallised several times from absolute ethanol. *N*-Cyclohexylpiperidine,[47] 2- [48] or 4-nitrophenyl phenyl ether,[48] 2- [49] or 4-nitrophenyl cyclohexyl ether,[49] and 4-nitrophenyl t-butyl ether [49] were prepared as in the literature and purified. The ^{1}H n.m.r. spectrum for the latter compound ($CDCl_3$, hexamethyldisiloxane as internal standard), supports the structure showing absorptions attributed to the 9-proton of the t-butyl group (sharp at δ 1·40) and the 4-proton (A_2X_2 system,[50] δ_A 8·05, δ_A 6·93, J_{AX} 9 Hz) of the aromatic ring. *N*-2- [4] or *N*-4-Nitrophenylpiperidine,[4] *N*-2,4-dinitrophenylpiperidine,[4] and cyclohexyl [28] and phenyl 2,4-dinitrophenyl ether [27] are from previous work. Potassium t-butoxide was twice sublimed.[51] Benzyltrimethylammonium t-butoxide was prepared in a dry-box on mixing a 0·08M solution in t-butyl alcohol of recrystallised dry benzyltrimethylammonium chloride with an equimolar solution of potassium t-butoxide in t-butyl alcohol. KCl precipitated as a gel and was centrifuged out. More concentrated solutions, owing to the low solubility of benzyltrimethylammonium chloride, were obtained by distilling off some of the solvent from a solution obtained as above and centrifuging again. These solutions darkened rather rapidly (as already noticed for the corresponding methoxide salt [52]) and were used immediately. *2-Nitrophenyl t-butyl ether* was prepared by the method used for its 4-isomer.[49] Careful fractional distillation (80°/0·05 mmHg) afforded the desired compound as a light yellow oil (yield 70%) (Found: C, 61·8; H, 6·87; N, 7·23. $C_{10}H_{13}NO_3$ requires C, 61·5; H, 6·71; N, 7·18%). The suggested structure is supported by the ^{1}H n.m.r. spectrum (CCl_4) which shows absorptions attributed to the 9-proton (sharp δ 1·38) of the t-butyl group and to the 4-proton (complex pattern δ 6·8—7·7) of the aromatic ring. *3-Nitrophenyl t-butyl ether* was prepared by shaking a mixture of 3-nitrophenol (4·8 g.), anhydrous diethyl ether (12 ml.), conc. sulphuric acid (0·02 ml.), and dry isobutene (10 g.) in a steel bomb for 24 hr. Then 2M-sodium hydroxide was added and the mixture was ether-extracted. The ether layer was dried (Na_2SO_4) and evaporated and the residue was fractionally distilled at 0·02 mm. (bath temperature 85°). The desired compound was obtained (0·13 g.) as a light yellow oil (Found: C, 61·2; H, 6·50; N, 7·33%). The ^{1}H n.m.r. spectrum ($CDCl_3$) supports the suggested structure showing absorptions attributed to the 9-proton of the t-butyl group (sharp δ 1·42) and to the 4-proton (complex pattern δ 7·1—8·0) of the aromatic ring.

U.v. Spectra.—Data for the u.v. long-wave absorption band of t-butyl, phenyl, and cyclohexyl 2-nitrophenyl ether and for their 4-isomers are in Table 6.

Kinetics.—Kinetics of the reactions of piperidine with 2- or 4-nitrophenyl phenyl ether and phenyl or cyclohexyl 2,4-dinitrophenyl ether were determined by following the increase of u.v. absorption of the resulting amines at the maximum of their absorption band where the Lambert–Beer law is strictly followed.[4] At such wavelengths absorption of the starting materials was negligible. The sealed ampoule method or, when necessary, methods for faster reactions,[4] were utilised. The same technique was also used for the reaction of potassium t-butoxide with 1-fluoro-4-nitrobenzene in t-butyl alcohol. (U.v. data are in Table 6, at which wavelength the Lambert–Beer law is strictly followed at least for the concentration range 10^{-5}—10^{-4}M). In any case, the u.v. absorption of the reaction mixture after the appropriate number of half-lives agreed with that of the expected products.

Results by the last method agreed with those by a v.p.c. analysis of the ethers produced (together with v.p.c. determination of the residual substrate and acidimetric determination of the residual strong base). A measured

[44] G. B. Barlin and W. V. Brown, *J. Chem. Soc.* (*B*), 1969, 333.
[45] T. Kaufmann and R. Nürnberg, *Chem. Ber.*, 1967, **100**, 3427.
[46] H. C. Brown and R. L. Klimisch, *J. Amer. Chem. Soc.*, 1966, **88**, 1425.
[47] J. F. Bunnett and J. Lovendahl Marks, *J. Amer. Chem. Soc.*, 1949, **71**, 1587.
[48] M. J. Rarick, R. Q. Brewster, and F. B. Dains, *J. Amer. Chem. Soc.*, 1933, **55**, 1289.
[49] K. Bowden, and P. N. Green, *J. Chem. Soc.*, 1954, 1795.
[50] Ref. 4, footnote 31.
[51] S. M. McElvain and A. N. Bolstad, *J. Amer. Chem. Soc.*, 1951, **73**, 1988.
[52] D. Bethell and A. F. Cockerill, *J. Chem. Soc.* (*B*), 1966, 913.

volume (1 ml.) of the reaction mixture was placed in a calibrated (5 ml.) flask and after addition of water (0·5 ml.) and Thymol Blue as indicator it was exactly neutralised with 2M-hydrochloric acid added from a microsyringe (any large excess of acid is to be avoided as it leads to decomposition of 4-nitrophenyl t-butyl ether during v.p.c. analysis). Biphenyl was then added as an internal standard, the flask filled to the mark with t-butyl alcohol, and the solution injected into the v.p.c. apparatus. Concentration was determined through a calibration curve made with the appropriate products in t-butyl alcohol with diphenyl as internal standard (column: 15% Apiezon L on Chromosorb W, 80—100 mesh, 2 m. × 2 mm.). The column temperature must not exceed 150 °C in the case of *o*-nitro-compounds (at higher temperatures 2-nitrophenyl t-butyl ether decomposes extensively during v.p.c. analysis) which requires a high pressure (2·6 atm.) of carrier gas, N_2. In the case of *p*-nitro-compounds, the column temperature was raised to 160 °C without any appreciable decomposition of 4-nitrophenyl t-butyl ether. Under the above conditions retention times (min.) were: 1-chloro-2-nitrobenzene (7), 2-nitrophenyl t-butyl ether (15), biphenyl (17·5); 1-chloro-4-nitrobenzene (5·5), biphenyl (11), 4-nitrophenyl t-butyl ether (17·5). Fluoro-compounds showed shorter retention times than their corresponding chloro-compounds. In any case a rapid ageing of the column was observed on injecting solutions containing even slight quantities of dimethyl sulphoxide.

Cyclohexanol produced from the reactions of either 2- or 4-nitrophenyl ethers with piperidine was determined by v.p.c. [column, 2 m. × 2 mm., 15% poly(propylene glycol) UC oil LB-550-X on Chromosorb W, 80—100 mesh, N_2 1 atm.; temp. 110°, mesitylene as an internal standard]. Under such conditions retention times were (min.): cyclohexanol (15), mesitylene (13). Cyclohexene or *N*-cyclohexylpiperidine can easily be detected by v.p.c. Cyclohexene [column, 2 m. × 2 mm., 15% poly(propylene glycol) UC oil LB-550-X on Chromosorb W, 80—100 mesh, N_2 0·8 atm.; temp. 70 °C] had a retention tim of 4 min. and *N*-cyclohexylpiperidine (column, 2 m. × 2 mm., 10% silicon gum nitrile GE-XE-60 on Chromosorb G, 80—100 mesh, N_2 2·2 atm.; temp. 120°) 42 min.

In all cases good first- or second-order plots were obtained up to at least 80% reaction.

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