The Origin of High *ortho*:*para*-Reactivity Ratios in the Reactions of Fluoronitrobenzenes with Potassium t-Butoxide in t-Butyl Alcohol

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Kinetic data for fluorine substitution of 1-fluoro-2- or 1-fluoro-4-nitrobenzene by potassium methoxide in methyl alcohol in the presence or absence of added dicyclohexyl-18-crown-6 or by potassium t-butoxide in t-butyl alcohol in the presence of the crown ether are reported. The crown ether has a negligible influence on the kinetics of the reactions of potassium methoxide where the *ortho*:*para*-activation ratio is around unity. In sharp contrast, comparison with previous data for the reactions of the same substrates with potassium t-butoxide in t-butyl alcohol shows that on addition of the crown ether (in equimolar quantities to the nucleophile, with consequent nearly total removal of potassium cation from the bulk system), the rate of reaction of the *o*-nitro-substituted substrate is increased by only a factor of three while that of the *p*-nitro-substituted substrate is increased by a factor of nearly 2000. Consequently, the *ortho*:*para*-ratio changes from $3{\cdot}6 \times 10^2$ in the absence to *ca.* 1 in the presence of the crown ether. These results show that the high value of the *ortho*:*para*-ratio obtained in t-butyl alcohol in the absence of addenda can be attributed mainly to specific stabilization of the transition state of the reaction of the *o*-nitro-substituted substrate by potassium cation bridging between the nucleophile and nitro-group oxygen atoms. This intramolecular assistance is a consequence of the low polarity and low dissociating ability of the medium used, t-butyl alcohol, and does not appear when the medium is more polar and dissociating, like methyl alcohol.

SEVERAL years ago it was suggested that *ortho* : *para*-reactivity ratios slightly lower than unity for direct substitution of chlorine from nitro-activated aryl chlorides by alkali-metal alkoxides in their lyate solvents [equations (1) and (2), X = Cl] can be mainly attributed to steric inhibition of resonance of the *o*-nitro-group in the transition state.[1] General acceptance of this idea [1] lead people to think of primary steric effects in nucleophilic aromatic substitution solely in terms of the

$$o\text{-}C_6H_4X + R\overset{-\,+}{OM} \xrightarrow{ROH} o\text{-}C_6H_4OR + \overset{+\,-}{MX} \qquad (1)$$

$$p\text{-}C_6H_4X + R\overset{-\,+}{OM} \xrightarrow{ROH} p\text{-}C_6H_4OR + \overset{+\,-}{MX} \qquad (2)$$

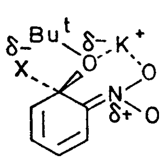
inhibition of activation of *ortho*-activating groups. Also, aza-activated substrates, because of the absence of the (supposed) great steric demand of nitro-groups, were definitely separated, in this regard, from nitro-activated substrates.

We have changed this view,[1] showing [2] that on going to a bulkier alkoxide, such as potassium t-butoxide in t-butyl alcohol, the *ortho* : *para*-ratio (*ca.* 100) [2] shifts in the direction which is opposite to that predictable on the basis of the above idea.[1] A similar trend was observed for fluorine substitution where rigorous kinetic data showed an *ortho* : *para*-ratio greater than 300.[2]

This work [2] was started on the suspicion (originating from results [3] on the reactivity of hindered amines) that the *o*-nitro-group should easily attain coplanarity with the cyclohexadiene ring in the transition state of aromatic substitution by alkoxides. However, not only were these expectations fulfilled by our results [2] but the *ortho* : *para*-ratio shifted to unpredictably large values. Errors in our work [2] were claimed by other authors.[4] However, we have rejected [5] this criticism [4] and confirmed our original [2] results.

The problem was then to rationalize such high values [2] of the *ortho* : *para*-ratio. Our idea was that such a reactivity pattern might be a consequence principally of the low polarity of the solvent used, t-butyl alcohol. In a solvent of such low polarity the polar transition state is seeking stabilization by more polar species than the solvent itself and phenomena of intramolecular assistance, favoured by the availability of the alkali-metal alkoxide only as tight ion pairs, have good chances of playing a predominant role.

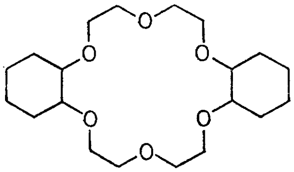
This is supported by examination of molecular models of the transition state, which is approximately represented here by the Meisenheimer addition complex,[6] as a potassium ion bridging between the alkoxide and nitro-group oxygen atoms for the reaction of the *o*-nitro-substituted substrate (1). Clearly, such an interaction of potassium ion, which simultaneously saturates the residual negative charge on the t-butoxide oxygen atom and the developing charge on the nitro-group oxygen atom, is not allowed in the reaction of the *para*-isomer. Further, a specific stabilization as in (1) should not come into play in the case of reactions of alkali-metal methoxide or ethoxide in their lyate solvents both because these are dissociated and because these media are presumably able effectively to solvate the uncomplexed transition state.



(1)

Some support to this view was obtained [7] by changing the cation from potassium to benzyltrimethylammonium. The *ortho* : *para*-ratio dropped to *ca.* 7 in accordance with the low co-ordinating ability towards oxygen expected for a tetra-alkylammonium cation.

However, a way to a more direct answer to this problem, without changing from potassium t-butoxide, is conceivable. This is by adding dicyclohexyl-18-crown-6 (2) [8a] to the reaction medium. The ether (2), and similar polyethers [8] have been shown to possess exceptionally good complexing ability for alkali-metal ions, which are held in the centre of the macroring,[9] in a variety of solvents ranging from n-hexane to water.[8,10] Typically, stability constants of *ca.* 10^6 and 10^2 for 1 : 1 complexes between ether (2) and potassium cation (from the chloride) were found in methanol and water, respectively.[10] Crown ether (2) was also shown to convert contact ions of fluorenyl alkali-metal salts into the ether-separated ion-pairs in tetrahydrofuran solutions with little accompanying dissociation into free ions.[11]



(2)

Addition of crown ether (2) to mixtures of potassium t-butoxide with *o*- or *p*-halogenonitrobenzenes in t-butyl alcohol should then remove the cause of the preferential stabilization shown in (1) while providing a more reactive t-butoxide anion. This should lead to normal *ortho* : *para*-values. On the contrary, addition of (2) should have no drastic influence on the *ortho* : *para*-ratio value for reaction of the same substrates with potassium methoxide in methyl alcohol since the alkali-metal alkoxide is already dissociated here [12] and, moreover, the medium should be able effectively to solvate the uncomplexed transition state.

That these expectations have been fulfilled is shown in

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this paper where we report kinetic data for the reactions of 1-fluoro-2- or 1-fluoro-4-nitrobenzene with potassium methoxide in methyl alcohol in the presence or absence of dicyclohexyl-18-crown-6 (2) or with potassium t-butoxide in t-butyl alcohol in the presence of the crown ether (2).

RESULTS

The reactions of potassium methoxide with 1-fluoro-2- or 1-fluoro-4-nitrobenzene in methyl alcohol in the presence or absence of dicyclohexyl-18-crown-6 (2) proceed quantitatively according to equations (1) and (2) ($R = Me$; $X = F$; $M^+ = K^+$) respectively. Formation of the respective methyl nitroaryl ethers can be followed conveniently by u.v. absorption spectroscopy because both ethers show broad intense absorptions in a region [λ_{max}^{MeOH}/nm (ε/l mol^{-1} cm^{-1}) 323 (2300) for the 2-nitro-substituted ether, and 305 (12,400) for the 4-nitro-substituted ether] where all other components of the reaction mixture are transparent. These absorptions strictly obey the Lambert–Beer law in the concentration ranges (5×10^{-5}—3×10^{-4}M for the *o*-nitro-compound and 1×10^{-5}—8×10^{-5}M for the *p*-nitro-compound) utilized. The rate data are in Table 1.

TABLE 1

Second-order[a] rate coefficient (k = Rate/[Substrate][Nucleophile]) for the reactions of 1-fluoro-2- or 1-fluoro-4-nitrobenzene with potassium methoxide or t-butoxide in the presence or absence of dicyclohexyl-18-crown-6 (2) or with benzyltrimethylammonium t-butoxide in the corresponding lyate solvents. Temperature 31 °C, unless otherwise stated

[Substrate]/M	[Nucleophile]/M	[Added crown ether (2)]/M	$\frac{10^4k}{\text{l mol}^{-1}\text{ s}^{-1}}$	k_o/k_p
o-F, 0·35	$KOBu^t$, 0·35		54[b]	$3·6 \times 10^2$
p-F, 0·44	$KOBu^t$, 0·44		0·15[b]	
o-F, 0·22	$KOBu^t$, 0·22	0·22	$1·7 \times 10^2$	0·8
p-F, 0·21	$KOBu^t$, 0·21	0·21	$2·2 \times 10^2$	
o-F, 0·33	$PhCH_2NMe_3OBu^t$, 0·32		$1·7 \times 10^2$[c]	7·4
p-F, 0·34	$PhCH_2NMe_3OBu^t$, 0·33		23[c]	
o-F, 0·24	KOMe, 0·24		5·0	1·0
p-F, 0·24	KOMe, 0·24		4·7	
o-F, 0·24	KOMe, 0·24	0·25	4·2	0·6
p-F, 0·24	KOMe, 0·24	0·25	7·0	

[a] See text. [b] Data from ref. 2, temp. 29·5 °C. [c] Data from ref. 7, temp. 28 °C.

The corresponding reactions of potassium t-butoxide in t-butyl alcohol in the presence of crown ether (2) are more complex. In our hands they cannot be exactly described by equations (1) and (2) ($R = Bu^t$; $X = F$; $M^+ = K^+$). We have been unable to avoid formation of *ca.* 20% of 2- and 4-nitrophenol at the expense of formation of the respective t-butyl nitroaryl ethers. However, neither nitrophenol arises from t-butyl nitroaryl ethers which are stable under the reaction conditions of Table 1. Thus, t-butyl 2-nitrophenyl ether (0·22M) decomposes by only *ca.* 5% after 6 h in a t-butyl alcohol solution of potassium t-butoxide (0·22M) and crown ether (2) (0·22M) at 60 °C. The same was observed for t-butyl 4-nitrophenyl ether.

Overlap of the spectra of t-butyl nitroaryl ethers with their relative nitrophenolates (and nitrophenols), coupled with the fact that t-butyl 2-nitrophenyl ether only shows a shallow relatively weak absorption with no pronounced maximum between 275 and 350 nm, does not allow the use of u.v. absorption spectroscopy to follow these reactions. As for the same reactions in the absence of crown ether (2),[2,5,7] and even more so here because formation of nitrophenols occurs to a relatively greater extent, g.l.c. is the method of choice. This allows a reliable estimate (even if not of great accuracy, which is not important for the present purposes) to be made of t-butyl nitroaryl ethers formed and of residual fluoronitrobenzenes. Disappearance of the base was determined titrimetrically and formation of nitrophenols was determined from the u.v. absorptions of the nitrophenolates.

Because of the fast competitive production of nitrophenols (whose formation practically ends before t-butyl nitroaryl ethers start forming) rate data for the formation of t-butyl nitroaryl ethers were calculated by taking as zero time that of practically complete formation of nitrophenolates. The rate data so obtained are in Table 1.

Formation of nitrophenols in larger amounts than in the same reactions run in absence of crown ether (2)[2,5,7] is also due to having used here, for solubility reasons, fluoronitrobenzenes in lower concentrations.

DISCUSSION

The rate data in Table 1 reveal several points nicely fulfilling our expectations. We first examine the reactions of potassium t-butoxide. Addition of equimolar amounts of crown ether (2), has a slight effect on the reaction of 1-fluoro-2-nitrobenzene, the rate of formation of t-butyl 2-nitrophenyl ether being increased by only a factor of three. The corresponding effect in the reaction of 1-fluoro-4-nitrobenzene is dramatic, the rate being increased by a factor of nearly 2000.

These reactions, by analogy with related ones of known mechanism and for the reasons discussed previously,[6,7] may be viewed as proceeding by an addition–elimination mechanism.[6]

The rate effect of crown ether (2) may be rationalizable in detail when it is realized that with equimolar potassium t-butoxide and crown ether (2), because of the very large association constants for such species in solvents of low polarity,[10] practically all the potassium ion must be trapped by the crown ether.

In the case of 1-fluoro-2-nitrobenzene there is little advantage for t-butoxide in reacting as highly nucleophilic, ether-separated ion pairs, $\overline{\underline{\mathrm{CK^+E}}}\mathrm{O^-Bu^t}$, rather than as tight ion pairs $K^+O^-Bu^t$ of low nucleophilicity. In fact, in the latter case intramolecular bridging of potassium ion stabilizes very effectively the transition state, which is impossible when potassium ion is encaged by the crown ether, $\overline{\underline{\mathrm{CK^+E}}}$, thus counterbalancing the lower nucleophilicity of $\mathrm{K^+O^-Bu^t}$. How effective this counterbalancing factor is, is shown by the increase of the rate by a factor of only three in the presence of crown ether (2).

With 1-fluoro-4-nitrobenzene the much higher nucleophilicity of ether-separated ion pairs $\overline{\underline{\mathrm{CK^+E}}}\mathrm{O^-Bu^t}$ than of tight ion pairs comes fully into play because in the transition state for either reaction no efficient intramolecular assistance is possible. The lack of a counterbalancing effect in the transition state of the reaction of $\mathrm{K^+O^-Bu^t}$ is reflected in the nearly 2000-fold increase in the rate on the addition of crown ether (2).

One might think of other factors as the cause of the high *ortho* : *para*-ratios in these reactions. Most appealing are London attractive dispersion forces[13] between the nucleophile and the *o*-nitro-groups in the transition state thus favouring the reaction of the presumably more polarizable nucleophile (t-butoxide, as compared with methoxide or ethoxide) with *o*-nitro-substituted as opposed to *p*-nitro-substituted substrates. The present results rule out London dispersion forces as the main cause of high *ortho* : *para*-ratios in these reactions.

Differential solvation phenomena of the type suggested[14] to rationalize the trend of *ortho* : *para* reactivity ratios (0·6—28) in the reactions of sodium methoxide, ethoxide, and isopropoxide in their lyate solvents * might also play some role in our case. However, it would be a formidable task to obtain reliable values for the activation parameters for our reactions of potassium t-butoxide in t-butyl alcohol, owing to the dependence of the second-order rate coefficient on the nucleophile concentration.[7] We also prefer to perform more direct tests based on very large variations of the quantities measured, as in the present work, rather than to attempt interpretations (which are frequently perilous because of the very intricate nature of the phenomena) of small changes in the activation parameters.

TABLE 2

Relative reactivities of some t-butoxide salts and potassium methoxide, in their lyate solvents, with 1-fluoro-2- or 1-fluoro-4-nitrobenzene (from data in Table 1)

	Cation		
Substrate	$\mathrm{K^+}$	$\overline{\underline{\mathrm{CK^+E}}}$	$\mathrm{PhCH_2NMe_3^+}$
o-$\mathrm{NO_2C_6H_4F}$	5	30	30
p-$\mathrm{NO_2C_6H_4F}$	0·03	30	5

Table 2 shows that t-butoxide salts are always more reactive (5—30 times) than potassium methoxide towards a common substrate, except in one case. This is that of the reactions of 1-fluoro-4-nitrobenzene with potassium t-butoxide [in the absence of crown ether (2)] or potassium methoxide. Here, potassium methoxide is *ca.* 30 times more reactive than potassium t-butoxide. This clearly shows that dissociated t-butoxide, or separated cation–t-butoxide ion pairs, are more reactive towards aromatic carbon than free methoxide. The reverse is true when t-butoxide is only available as tight ion pairs [potassium t-butoxide in t-butyl alcohol in the absence of crown ether (2)] unless intramolecular assistance is possible, as in the *o*-nitro-substituted substrate where, again, t-butoxide is more reactive than methoxide.

Thus, relative reactivities of alkali-metal alkoxides in their lyate solvents may in general not reflect the intrinsic nucleophilicities of these anions. Our data suggest that such anomalies disappear, and the order of the intrinsic nucleophilicities shows up, on running the reactions in the presence of a trap of the cation such as crown ether (2). This is easier than the use of tetra-alkylammonium alkoxides which are troublesome to prepare and inherently unstable[7] and more generally practicable than the use of a solvent of superior solvating ability.[7]

Both some β-eliminations[15] and some hydrogen exchanges at saturated carbon[16] by alkali-metal t-butoxides as bases in t-butyl alcohol show a peculiar stereochemistry. The preferential path seems also here dictated by the possibility of establishing intramolecular potassium ion bridges and, in accordance with this interpretation, such peculiarities disappear when either a non-co-ordinating cation, such as tetra-alkylammonium, is used[15a] or crown ether (2) is added to solutions of the potassium salt.[15,16]

Stereospecificity in β-eliminations by t-butoxide in t-butyl alcohol was considerably higher for lithium t-butoxide than for potassium t-butoxide.[15a] This suggests that the *ortho* : *para*-activation ratio by the nitro-group in aromatic substitution by lithium t-butoxide in t-butyl alcohol might well be even higher than observed[2] for potassium t-butoxide.

EXPERIMENTAL

Materials.—Reagents and products were available from a previous study. t-Butyl alcohol was purified as before.[7] Dicyclohexyl-18-crown-6 was recrystallized from light petroleum and used as a mixture of isomers.

Kinetics.—Techniques for running the reaction under dry nitrogen and for analysing for both products and reagents (g.l.c., u.v., and titrimetry) have been described.[7] Good second-order plots were observed in all cases.

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* It is peculiar that these authors[14] overlooked the results[2] for the most important member of the series, t-butoxide.

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