Nucleophile Size and the *ortho*:*para* Ratio in Activation of Aromatic Substitution by the Nitro-group

By FRANCESCO PIETRA* and FRANCESCO DEL CIMA
(*Istituto di Chimica Generale, Università di Pisa, Pisa, Italy*)

REACTIONS of dilute sodium methoxide or ethoxide with halogenonitrobenzenes are known[1,2] to be slightly faster for the *para*- than for the *ortho*-isomer in the case of chlorine, but for fluorine both the same situation (for ethoxide) and the reverse one (for methoxide) have been encountered.[1] This difference has been ascribed[1] primarily to steric inhibition of resonance of the *o*-nitro-group in the transition states for the reactions of chloro-2-nitrobenzene.

We report here some results, which do not conform to this interpretation, for the reactions of both *ortho*- and *para*-isomers of fluoro- and chloro-nitrobenzenes with sublimed potassium t-butoxide in t-butanol. Formation of the ethers† and disappearance of halogenonitrobenzenes have been followed by gas chromatography (flame ionization) of the neutralized reaction mixtures. The ethers are formed by direct displacement of halogen since 3-nitrophenyl t-butyl ether† was not detected in any case. Under the kinetic conditions used, the fluoronitrobenzenes gave the corresponding ethers and nitrophenols‡ in 95 and 5% yield, respectively. In the case of chloronitrobenzenes, formation of other unidentified by-products occurred as well. Second-order rate coefficients (mole^{-1} l. sec.$^{-1}$ × 10^4) at the temperature (in parentheses) for reaction of fluoro-4-nitrobenzene with t-butoxide, both 0·44 M, are: 0·455 (39·9°),§ 1·24 (49·4°),§ 7·74 (69·7°),§ and 8·4 (70·0°). Extrapolation at 29·5° gives $k_2 = 0{\cdot}15 \times 10^{-4}$ mole^{-1} l.sec.$^{-1}$. Fluoro-2-nitrobenzene and t-butoxide, both 0·35 M, gave $k_2 = 5{\cdot}4 \times 10^{-3}$ mole^{-1} l.sec.$^{-1}$ at 29·5°. Consequently, the *ortho* : *para* ratio is about 300. Chloro-4-nitrobenzene and t-butoxide, both 0·14 M, gave at 90° the following percent of the ether at the times in parentheses: 1 (17 hr.), 4 (104 hr.), and 5 (312 hr.). Under the same conditions, percents for chloro-2-nitrobenzene are: 1 (10 min.), 3 (30 min.), 14 (3 hr.), and 60 (142 hr.). Thus, the *ortho* :*para* ratio is about 100, as can be roughly estimated from yield data at very low percent reaction where initial concentrations of the reagents are nearly unchanged.

The values found for the *ortho* :*para* ratios are unusually large for reactions of anionic nucleophiles. While their detailed interpretation requires further research, they clearly show that inhibition of resonance of the *o*-nitro-group is not pronounced in the transition states of these reactions of t-butoxide. These experiments, as far as results obtained in different solvents and with different cations of the nucleophiles can be compared, tend to rule out the above mentioned steric hypothesis[1a] of Bunnett and Morath as applied to reactions of such small nucleophiles as methoxide or ethoxide.

An important outcome of these results is to call attention to possible failures arising from the widespread usage[3] of the above hypothesis of Bunnett and Morath. In fact, general acceptance,[3] of this steric suggestion[1a] has lead to its utilization in drawing mechanistic conclusions in the reactions of alkoxides of common size with substituted pyridine *N*-oxides,[3a] with polyfluoronitro-aromatics,[3b] and with aza-activated halogeno-aromatics.[3c]

We acknowledge financial support from C.N.R., Roma.

(*Received, December 27th*, 1967; *Com.* 1376.)

---

† Satisfactory elemental analysis and ^{1}H n.m.r. spectra compatible with the assigned structures were obtained for the new ethers.

‡ Nitrophenols, determined by u.v. spectra, originated from water in the solvent (t-butyl alcohol) which was distilled from calcium hydride and then kept over molecular sieves. All sample handling was carried out in a dry-box.

§ Formation of 4-nitrophenyl t-butyl ether was followed by u.v. spectra in these runs.

[1] (a) J. F. Bunnett and R. J. Morath, *J. Amer. Chem. Soc.*, 1955, **77**, 5051; (b) J. F. Bunnett, *Quart. Rev.*, 1958, **12**, p. 9.

[2] F. Terrier, *Compt. Rend.*, 1965, **261**, 1001.

[3] To cite but a few recent references: (a) R. M. Johnson, *J. Chem. Soc.* (*B*), 1966, 1058; (b) J. G. Allen, J. Burdon, and J. C. Tatlow, *J. Chem. Soc.*, 1965, 1045; (c) G. Illuminati, *Adv. Heterocyclic Chem.*, 1964, **3**, 285, Academic Press; M. Calligaris, P. Linda, and G. Marino, *Tetrahedron*, 1967, **23**, 813; (d) A. M. Porto, L. Altieri, A. J. Castro, and J. A. Brieux, *J. Chem. Soc.* (*B*), 1966, 963.