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HALOGEN MOBILITY IN ACTIVATED AROMATIC NUCLEOPHILIC SUBSTITUTION (1).

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It is a textbook notion (2) that the usual halogen mobility order in activated aromatic nucleophilic substitution is F>> Cl∼Br∼J, while the reverse order is less frequently encountered (2,3,4). However, the factors determining such an inversion are still not well understood (5,6).

We wish to report here some kinetic data which appear to be pertinent to this problem. These concern the reactions of piperidine with fluoro-4- or fluoro-2-nitrobenzene in benzene (Table I).

Examination of the results for the reaction of fluoro-4-nitrobenzene** (Table I,a) shows that the second-order rate coefficient increases linearly with increasing piperidine concentration and extrapolates to zero at zero piperidine concentration. The reaction is third-order overall (second-order in amine), as shown by the constancy of the third-order rate coefficient.

It can be excluded that this kinetic order behaviour originates from a general medium effect since in the reaction of chloro-4-nitrobenzene with piperidine in benzene the second-order rate coefficient increases but slightly with increasing piperidine concentration (8). Thus, the reaction of fluoro-4-nitrobenzene is piperidine catalyzed. Whether this is bifunctional or pure base catalysis is still an open question (9).

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[**] Rate data for this reaction at 25° have already been reported (7). Owing to the scanty precision associated with the very low reactivity at that temperature, the rates have been now more precisely measured at 85°. However, it proved impossible, by the ultraviolet technique used, to obtain good rate data at 85° or at higher temperatures when the concentration of piperidine was made lower than 0.176 M. This was due to the formation, with the long reaction times required, of by products interfering with the ultraviolet analysis.

TABLE I

Reaction Rates of Piperidine, PIP, with Fluoronitrobenzenes in Benzene.

(*a*) Fluoro-4-nitrobenzene 2.52×10^{-5} *M* ; temp. 85°*

10x[PIP], *M*	1.76	2.56	3.60	4.37	5.22	6.00
10^6xRate/[ArF][PIP], $\text{mole}^{-1}\text{l.sec.}^{-1}$	8.73	12.5	17.7	20.8	25.1	29.2
10^5xRate/[ArF][PIP]^2, $\text{mole}^{-2}\text{l}^2\text{sec.}^{-1}$	4.96	4.88	4.92	4.76	4.81	4.87

(*b*) Fluoro-2-nitrobenzene 3.21×10^{-4} *M* ; temp. 25°

10x[PIP], *M*	0.326	0.652	1.34	1.96	2.67	3.26	4.01	6.68
10^4xRate/[ArF][PIP], $\text{mole}^{-1}\text{l.sec.}^{-1}$	5.61	5.68	5.97	6.12	6.43	6.58	6.77	7.60

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* These experiments were carried out under nitrogen.

Scrutiny of the results for the reaction of fluoro-2-nitro-benzene (Table I,b) shows that the second-order rate coefficient increases but slightly with increasing piperidine concentration (10). The rate data are fitted satisfactorily by equation I

$$\mathrm{Rate}/[\mathrm{ArF}][\mathrm{PIP}] = k + k_{\mathrm{PIP}}[\mathrm{PIP}] \qquad (\mathrm{I})$$

Linear regression analysis gives $k=5.52\times10^{-4}$ mole^{-1}l.sec.$^{-1}$ and $k_{\mathrm{PIP}} = 3.15\times10^{-4}$ mole^{-2}l.^{2}sec.$^{-1}$. Therefore, one obtains $k_{\mathrm{PIP}}/k = 0.57$ mole^{-1}l..

Rate data for the reaction of chloro-2-nitrobenzene with piperidine in benzene give $k_{\mathrm{PIP}}/k = 0.10$ mole^{-1}l. at 100° (8).

These results can be fitted into the intermediate complex mechanism proposed by Bunnett (11). Thus, piperidine catalysis for breakdown of the intermediate to products, which is essential in the reaction of fluoro-4-nitrobenzene, is scarcely, if at all, required in the reaction of fluoro-2-nitrobenzene. Here, the transition state for this reaction step is stabilized by interaction between the ammonium proton and the oxygen of the ortho-nitro group[*].

These findings make it clear that in the reactions of ortho-nitro substituted substrates the ratio $k_{\mathrm{ArF}}/k_{\mathrm{ArCl}}$ of the second-order rate coefficients extrapolated to zero piperidine concentration [about 200 in the reaction of 2-nitrophenylhalides (13) and 7 in those of 2,4-dinitrophenylhalides (7)] is not a measure of the relative mobility of fluorine and chlorine. What is observed in such circumstances is, in fact, the ortho-nitro group assisted elimination of the ammonium proton and fluoride ion.

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[*] Consistently with this interpretation, the reaction in benzene of piperidine with fluoro-4,7-dinitronaphtalene is wholly piperidine catalyzed (12), while that of fluoro-2,4-dinitrobenzene is not (7,9). However, the finding that piperidine catalysis is relatively more pronounced in the reaction of fluoro-2,4-dinitrobenzene ($k_{\mathrm{PIP}}/k = 600$ mole^{-1}l.) (7,9) than in that of fluoro-2-nitrobenzene requires some comment. We offer the plausible explanation that in the reaction of fluoro-2,4-dinitrobenzene the stabilizing interaction between the ammonium proton and the oxygen of the ortho-nitro group is diminished, relative to that in the reaction of fluoro-2-nitrobenzene, owing to dispersal of the negative charge over two nitro groups.

When the relative leaving group ability is properly computed as the above ratio for the reactions of the para-nitro substrates, the result comes out that fluorine is much less mobile than chlorine.

Kinetic data for the reactions of bromo- or iodo-4-nitrobenzene with piperidine in benzene (14) show that bromine and iodine are about as mobile as chlorine.

The change from a non-polar aprotic solvent, like benzene, to dipolar aprotic or protic ones has a dramatic influence on the kinetics of the reactions of fluoro-4- or chloro-4-nitrobenzene with piperidine. Thus, second-order overall kinetics and the reactivity order ArF>> ArCl are observed both in dimethyl sulfoxide (15 a,b) and in methanol (16,17). The conclusion that fluorine is more mobile than chlorine in these media is warranted, however, only if the two reactions proceed through the same mechanism. While this seems to be the case for dimethyl sulfoxide (18) it is certainly not so for protic solvents where catalysis by the solvent is present only in the reaction of the fluoro compound (7,9).

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