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KINETIC DEUTERIUM ISOTOPE EFFECT IN THE REACTION OF 2,4-DINITROPHENYL PHENYL ETHER WITH PIPERIDINE IN BENZENE

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In the reactions of primary or secondary amines with nitro-activated aryl fluorides or chlorides, so far examined, the change from hydrogen to deuterium at the amino nitrogen has never been found to significantly affect the rate (1, 2, 3)[*].

This lack of a significant isotope effect has been interpreted in various ways by different authors and ascribed to several causes (1, 3, 4).

In this note we wish to report some kinetic data which appear to be pertinent to this problem. These concern the reactions of 2,4-dinitrophenyl phenyl ether with piperidine[**] or N-d-piperidine in benzene, in the presence or absence of pyridine. Some of our results are collected in Table I.

Examination of the results for the reaction of piperidine (Table Ia) shows that the second-order rate coefficient increases linearly with increasing amine concentration and extrapo-

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[*] Another example is provided by fluoro-4,7-dinitronaphthalene which reacts at the same rate - within the 5% uncertanity of the experimental error - with piperidine or N-d-piperidine, at 0.043 or 0.12 M amine concentration, in benzene at 25°(10).

[**] J.F. Bunnett and R.H. Garst have found that in aqueous dioxan this reaction undergoes general base catalysis (5).

TABLE I

Reaction Rates of 2,4-Dinitrophenyl Phenyl Ether ($2.44 \times 10^{-5}\ \underline{M}$) with Piperidine or N-*d*-Piperidine in Benzene at 25°.

		(*a*) piperidine				
$10^{2} \times [C_5H_{10}NH]\ \underline{M}$		1.95	9.76	18.9	22.0	27.5
$10^{3} \times \frac{\text{Rate}}{[\text{ArX}][C_5H_{10}NH]}$	$\text{mole}^{-1}\ \text{l. sec.}^{-1}$	0.260	1.33	2.65	2.99	3.75
$10^{2} \times \frac{\text{Rate}}{[\text{ArX}][C_5H_{10}NH]^{2}}$	$\text{mole}^{-2}\ \text{l.}^{2}\ \text{sec.}^{-1}$	1.35	1.36	1.40	1.36	1.36
		(*b*) piperidine (0.0182 $\underline{M}$), pyridine				
$10 \times [\text{pyridine}]\ \underline{M}$		-	1.52	3.04	4.74	7.57
$10^{4} \times \frac{\text{Rate}}{[\text{ArX}][C_5H_{10}NH]}$	$\text{mole}^{-1}\ \text{l. sec.}^{-1}$	2.30	3.12	3.25	4.20	5.02
		(*c*) piperidine (0.178 $\underline{M}$), pyridine				
$10 \times [\text{pyridine}]\ \underline{M}$		-	2.95	4.60	6.03	
$10^{3} \times \frac{\text{Rate}}{[\text{ArX}][C_5H_{10}NH]}$	$\text{mole}^{-1}\ \text{l. sec.}^{-1}$	2.44	3.31	4.57	4.91	
		(*d*) N-*d*-piperidine				
$10 \times [C_5H_{10}ND]\ \underline{M}$		1.10	1.88	2.31	2.73	
$10^{3} \times \frac{\text{Rate}}{[\text{ArX}][C_5H_{10}ND]}$	$\text{mole}^{-1}\ \text{l. sec.}^{-1}$	1.19	2.02	2.52	2.96	
$10^{2} \times \frac{\text{Rate}}{[\text{ArX}][C_5H_{10}ND]^{2}}$	$\text{mole}^{-2}\ \text{l.}^{2}\ \text{sec.}^{-1}$	1.08	1.07	1.09	1.08	

lates to zero at zero amine concentration. The rate data are fitted satisfactorily by a third-order equation, as shown by the constancy of the third-order rate coefficient. This kinetic order behavior can not arise from a general medium effect, since in the reaction of chloro-2,4-dinitrobenzene with 2-methylpiperidine or 2,6-dimethylpiperidine in benzene (6) the order with respect to amine remains at unity at much higher amine concentration than that attained in the present reaction of the ether[*]. Thus, the reaction of the ether in benzene is piperidine catalyzed.

Piperidine catalysis appears to be base catalysis, as the addition of pyridine - which does not react appreciably with the ether under these conditions - has the effect of increasing the rate of reaction (Table Ib, c).

Furthermore, the change from piperidine to N-d-piperidine[**](about 90% deuterated) slows down the rate of reaction by a factor of 1.27[***], without changing the pattern of the kinetic orders (Table Id). This small isotope effect must be interpreted as a primary one as far as deuteration at the amino nitrogen appears to increase the nucleophilicity of amines (8).

The results of this work can be easily fitted into the intermediate complex mechanism proposed by Bunnett (9, 5) with the specializations that k_{-1} is much greater than k_B [B], and

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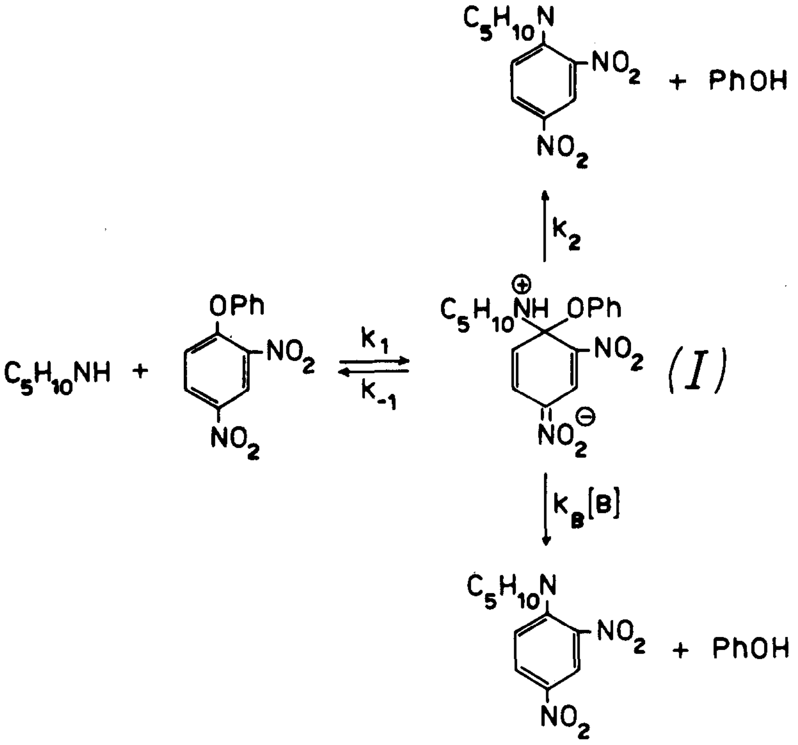
[*] See also footnote (**) in the first page of this communication.

[**] After the experiments reported in this note were completed, we learned that J.F. Bunnett and C. Bernasconi have also observed a deuterium isotope effect in this reaction in dioxan-heavy water (7).

[***] The uncertainty of the experimental error for rate data for reactions of piperidine or N-d-piperidine (Table Ia, d) is less than 4%. Rate data for reactions in the presence of pyridine (Table Ib, c) are however uncertain to about 10%.



that k_2 is in practice nil*. Here B stands for piperidine or pyridine.

The present findings refute the elaborations proposed by Suhr (11) to the above mechanism, whereby the intermediate I supposedly decomposes by a fast proton transfer to a base B to give a second intermediate which then loses the leaving group in a slow, uncatalyzed, step. In fact, such a mechanism could

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* The insignificant contribution of the uncatalyzed path does not appear to be peculiar to the displacement of phenoxide ion. In fact clean third-order kinetics have also been obtained for the displacement of fluoride ion from fluoro-4,7-dinitronaphthalene by piperidine in benzene at 25° (10).

not provide a primary isotope effect.

Moreover, there is some hint that the isotope effect arises from a rate-limiting proton transfer from the intermediate I to a base B. Thus the addition of minute amounts of methanol was found to decrease the rate of reaction of 2,4-dinitrophenyl phenyl ether with piperidine* in benzene. Thus the mechanism proposed by Bernasconi and Zollinger for the decomposition of the intermediate I in the reaction of fluoro-2,4-dinitrobenzene with piperidine in benzene (specific base - general acid catalysis) (4) does not appear to be general for reactions of this kind.

From the small magnitude of the measured isotope effect it would not be safe, at present, to draw any definite conclusion about the relative importance of bond-making and bond-breaking in the transition state of the proton transfer step. This is also due to the particular nature of the base catalyzed decomposition of intermediate I which could be reasonably conceived either as a linear three-center reaction or as a more complex, concerted β-elimination.

However, the results of this work suggest that non-linearity of transition states due to bifunctional catalysis by a second molecule of the reacting amine (12, 4) might be one of the reasons for the lack of a significant isotope effect in the reaction of the fluoro-derivatives in benzene. At present, however, there is insufficient experimental support for this hypothesis.

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* These experiments were performed at 0.018 M initial concentration of piperidine.

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REFERENCES

1. F. Pietra and A. Fava, *Tetrahedron Letters* No. **23**, 1535 (1963).
2. H. Zollinger, in *Advances in Physical Organic Chemistry* Vol.II, p. 191. Academic Press, London (1964).
3. S.D. Ross, in *Progress in Physical Organic Chemistry* Vol.I, p. 58. Interscience, N.Y. (1963).
4. C. Bernasconi and H. Zollinger, *Tetrahedron Letters* No. **16**,1083 (1965).
5. R.H. Garst, Ph.D. Thesis, Brown University, Providence, R.I. (1964).
6. F. Pietra, *Tetrahedron Letters* No. **12**, 745 (1965).
7. C. Bernasconi, personal communication.
8. For a review see E.A. Halevi, in *Progress in Physical Organic Chemistry* Vol.I, p. 180. Interscience, N.Y. (1963).
9. J.F. Bunnett and J.J. Randall, *J. Amer. Chem. Soc.* **80**, 6020 (1958).
10. F. Pietra and P. Da Re, unpublished results.
11. H. Suhr, *Chem. Ber.* **97**, 3268 (1964).
12. B. Capon and C.W. Rees, in *Ann. Reports Chem. Soc.*, (London) Vol. LX, p. 278 (1963).