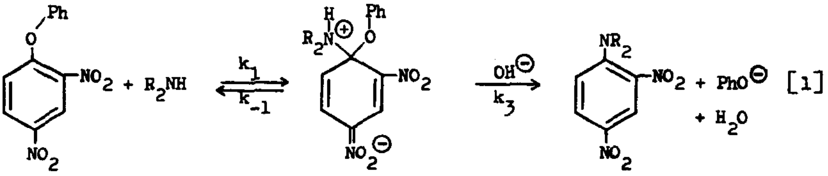
Tetrahedron Letters No.26, pp. 2995-3002, 1966. Pergamon Press Ltd.
Printed in Great Britain.

KINETIC OXYGEN AND HYDROGEN ISOTOPE EFFECTS IN THE HYDROXIDE ION CATALYZED REACTION OF 2,4-DINITROPHENYL PHENYL ETHER WITH PIPERIDINE IN AQUEOUS DIOXANE

C. R. Hart and A. N. Bourns
Department of Chemistry, McMaster University,
Hamilton, Ontario, Canada

(Received 18 April 1966)

The intermediate complex mechanism for aromatic nucleophilic substitution reactions of activated compounds is indicated by a variety of evidence much of which has been provided by the work of Bunnett and coworkers (1). The concerted S_N2 mechanism has continued to have its proponents, however, particularly for the reaction of halonitrobenzenes with amines in hydroxylic solvents (2). Strongest support for the intermediate complex mechanism is found in Bunnett's recent study (3) of the kinetic form of the base catalysis of the reaction of 2,4-dinitrophenyl phenyl ether with piperidine in aqueous dioxane. The observation that the second order rate constant, k_A, for the formation of 2,4-dinitrophenylpiperidine shows a curvilinear dependence on hydroxide ion concentration is in accord with the scheme of eq. [1],



since, depending upon the concentration of the catalyzing base, either the formation or decomposition of the intermediate may be rate limiting.

In studies on aromatic electrophilic substitution the strongest evidence for the intermediate complex mechanism has been provided by the observation of a change in the magnitude of the leaving-group isotope effect with changing concentration of some reagent. In the diazo coupling reaction this reagent was a base which catalyzes the decomposition of the intermediate to products (4); in halogenation it was halide ion which influences the rate of return of the intermediate to reactants (5). A similar study can have equal significance in establishing the mechanism of aromatic nucleophilic substitution, but has not been reported because, until Bunnett's recent work (3), no suitable system for the application of this "variable kinetic isotope effect" criterion has been known.

In this Communication we wish to report kinetic oxygen isotope effect results for the reaction of 2,4-dinitrophenyl phenyl ether with piperidine at 0° in 40% water-60% dioxane by volume in the presence of varying concentrations of hydroxide ion. Also, data on the dependence of the deuterium solvent isotope effect on hydroxide ion concentration is presented and discussed in relation to the mechanism of the base-catalyzed step of the process.

Under the conditions chosen for this study, nucleophilic attack of hydroxide ion giving 2,4-dinitrophenol accounts for less than two per cent of the total reaction. Furthermore, neither uncatalyzed nor piperidine catalyzed processes make a significant contribution over the range of hydroxide ion concentration used in the isotope effect experiments*.

Applying the steady-state approximation to eq. [1], the following kinetic expression may be derived:

$$\frac{1}{k_A} = \frac{k_{-1}}{k_1 k_3} \frac{1}{[OH^-]} + \frac{1}{k_1} \qquad [2]$$

---

*This is shown by the linearity of the plot of $1/k_A$ vs $1/[OH^-]$, Fig. 1. The basis of this test is set out in ref. (3).

It follows that a plot of $1/k_A$ vs $1/[OH^-]$ should give a straight line the slope of which is k_{-1}/k_1k_3 and the intercept $1/k_1$. This linearity was observed by Bunnett (3) and is shown in Fig. 1 for reaction under our conditions in both undeuterated and deuterated solvent. The slope/intercept ratio represents k_{-1}/k_3 and is found to have a value of 3.6×10^{-2} mole $\ell.^{-1}$ for reaction in H_2O:dioxane and 6.7×10^{-2} mole $\ell.^{-1}$ for reaction in deuterated solvent. The corresponding values for k_1 are 5.6×10^{-3} $\ell.$ mole^{-1} sec.$^{-1}$ and 5.35×10^{-3} $\ell.$ mole^{-1} sec.$^{-1}$.

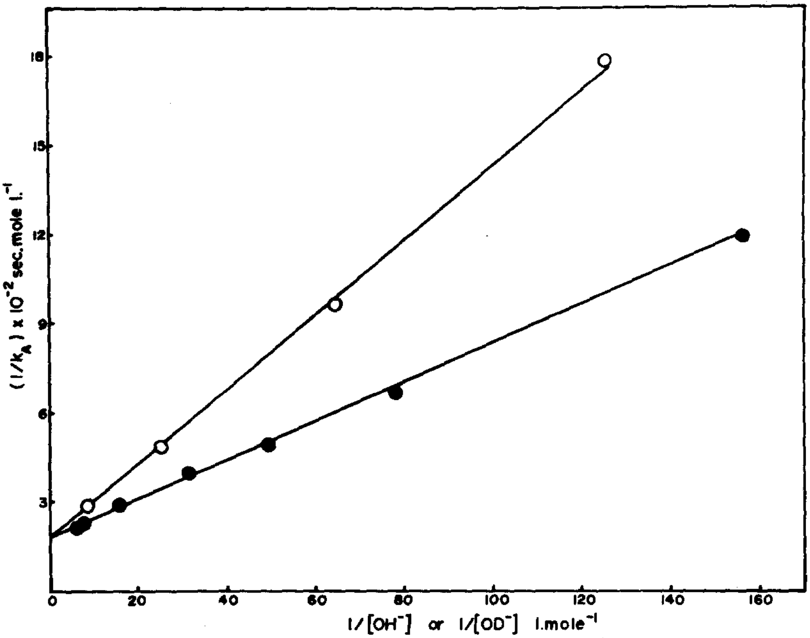


FIG. 1

Hydroxide Ion Catalyzed Reaction of 2,4-Dinitrophenyl Phenyl Ether with Piperidine at 0° in Aqueous Dioxane with Electrolyte Concentration 0.2 M: Solid Circles, 40% H_2O:60% Dioxane; Open Circles, 40% D_2O:60% Dioxane.

Oxygen isotope effect measurements have been made at three hydroxide ion concentrations: 0.005 M, 0.033 M and 0.149 M. Assuming that the reaction follows the pathway represented by eq. [1], it can be seen that $k_{-1}/k_3[OH^-]$, which is the ratio of the rate of return of the intermediate to reactants to its rate of conversion to products, will have values of 7.2, 1.1 and 0.24, respectively. It follows that at the lowest hydroxide concentration used almost nine of every ten intermediate-complex molecules which are formed will return to reactants and hence the step involving carbon-oxygen bond rupture will be mainly rate limiting. A primary oxygen isotope effect, therefore, should result. At the highest hydroxide ion concentration, on the other hand, only about one in five of the intermediate species will return to reactants and now the overall rate will be determined mainly by the rate of the first step. The oxygen isotope effect, therefore, should be very small (k_A^{16}/k_A^{18} very close to unity). Finally, an isotope effect having an intermediate value is predicted for reaction at 0.033 M sodium hydroxide since at this $[OH^-]$ the complex will partition itself about equally between reactants and products. The intermediate complex mechanism, therefore, requires a decrease in the leaving-group isotope effect with increasing concentration of the catalyzing base. In a one-step S_N2 process, on the other hand, the oxygen isotope effect will have a value which is independent of the concentration of hydroxide ion.

The oxygen isotope effects were determined by comparing the ratio $O^{16}:O^{18}$ in the product, phenol, formed from a reaction carried to completion to that of the product of reactions carried to some known extent ranging from 10 to 34 per cent. The reactant contained approximately five per cent O^{18} in the ether position. Isotopic analyses were made on phenol itself using a simultaneous collection mass spectrometer. The results, shown in Table I, are in complete accord with the predictions of the intermediate complex mechanisms.

It was not convenient for experimental reasons to measure the isotope effect at a sufficiently high hydroxide ion concentration such that the formation of the intermediate is completely rate limiting. Since, however, the effect is only 1.002 when as much as 20 per cent of the intermediate returns to reactants, it can be assumed that k_1^{16}/k_1^{18} is unity. Assuming also that k_{-1}^{16}/k_{-1}^{18} is also unity, it is possible to calculate k_3^{16}/k_3^{18}, the isotope effect for the carbon-oxygen bond rupture step, from the observed isotope effect at any given hydroxide ion concentration. The values so obtained for the two base concentrations at which the observed effect is appreciable are shown in the last column of the Table. The agreement, which is well within experimental error, lends further support for the mechanism upon which the calculations have been based.

TABLE I

Kinetic Oxygen Isotope Effects in the Reaction of

2,4-Dinitrophenyl Phenyl Ether with Piperidine

in 40% Water - 60% Dioxane at 0° *

[NaOH] M	$k_{-1}/k_3[OH^-]$	k_A^{16}/k_A^{18} (observed) **	k_3^{16}/k_3^{18} (calc.)
0.005	7.23	1.0109 ± 0.0014	1.0124
0.033	1.08	1.0070 ± 0.0007	1.0133
0.149	0.24	1.0024 ± 0.0017	

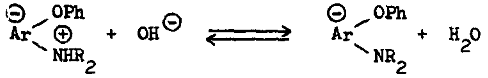
* Ether concentrations ranged from 0.0013 to 0.0051 M; piperidine concentrations from 0.0051 to 0.051 M. Total electrolyte concentration was maintained at 0.2 M by addition of NaCl.

**The result shown at each hydroxide concentration is the average of four determinations. Precision limits are given as standard deviations.

In accordance with the predictions of this mechanism, Bunnett (3) has found that the solvent isotope effect, k_A^H/k_A^D, for reaction in 90% water:10% dioxane at 29.4° decreases with increasing concentration of hydroxide ion.

A similar result has been observed in the present study, as is seen from Fig. 1. From the values of k_1 and k_{-1}/k_3 obtained from the plots in this Fig. (*vide supra*), the isotopic ratios, $k_1^H/k_1^D = 1.03$ and $k_{-1}^D k_3^H/k_{-1}^H k_3^D = 1.80$, are calculated. If it is now assumed that the isotope effect associated with the return of the intermediate to reactants is very small, as seems reasonable since the transition state for the first step should closely resemble this complex (6), then it follows that the isotope effect for the conversion of the intermediate to products, k_3^H/k_3^D, is also about 1.8.

It is difficult to account for an isotope effect as large as this by any mechanism for the conversion of the intermediate to products which does not involve proton transfer in a rate limiting step since the equilibrium isotope effect, K^H/K^D, for the process



I II [3]

would be expected to be *ca* 0.4*. This places in question the validity of Swain's "solvation rule" (7) which states that "a proton being transferred in an organic reaction from one oxygen (or nitrogen) to another should lie in an entirely stable potential at the transition state".

Several mechanisms for the conversion of the intermediate to products are in accord with the observation of primary leaving group and hydrogen isotope effects. One, favoured by Bunnett (3), involves pre-equilibrium proton transfer, eq. [3], followed by a concerted transfer of a proton from a water molecule to the ether oxygen and rupture of the carbon-oxygen bond. This pathway cannot be general, however, since there is no electrophilic

---

* For this equilibrium $K^H/K^D = K_b^D/K_b^H$, where the K_b's are the basic dissociation constants for the intermediate II in H_2O and D_2O, respectively. This ratio is considered to be the same as that for piperidine (3).

catalysis by methanol when the reaction is carried out in benzene (8). A second possibility is a multicenter process in which the oxygen of hydroxide ion accepts a proton from nitrogen and at the same time donates a proton to the ether oxygen as the bond of this oxygen to carbon is broken (9). This pathway also cannot be general since it does not account for catalysis by tertiary amines in fluoride displacement reactions (10). Finally, the intermediate may decompose by concerted removal of a proton from nitrogen and rupture of the carbon-oxygen bond, as in an E2-type elimination.

ACKNOWLEDGMENTS

The authors wish to express their thanks to Professor J. F. Bunnett who suggested the reaction for this study and furnished kinetic data in advance of publication. The financial support of the National Research Council of Canada is also acknowledged.

REFERENCES

1. J. F. Bunnett, Quart. Rev. (London) 12, 1 (1958).
2. R. E. Parker and T. O. Read, J. Chem. Soc. 1962, 9, 3149; R. E. Parker, Adv. Fluorine Chem. 3, 63 (1963); S. D. Ross, Progr. Phys. Org. Chem. 1, 31 (1963).
3. J. F. Bunnett and R. H. Garst, J. Am. Chem. Soc. 87, 3875 (1965); J. F. Bunnett and C. Bernasconi, ibid 87, 5209 (1965).
4. H. Zollinger, Experientia 12, 165 (1956).
5. E. Grovenstein, Jr., and N. S. Aprahamian, J. Am. Chem. Soc. 84, 212 (1962); F. M. Vainshtein, E. I. Tomilenko and E. A. Shilov, Kinetika i Kataliz 4, 357 (1963); B. T. Baliga and A. N. Bourns, Can. J. Chem. 44, 363, 379 (1966).
6. G. S. Hammond, J. Am. Chem. Soc. 77, 334 (1955).

7. C. G. Swain, D. A. Kuhn and R. L. Schowen, J. Am. Chem. Soc. **87**, 1553 (1965).

8. F. Pietra, Tetrahedron Letters, No. 28, 2405 (1965).

9. B. Capon and C. W. Ries, Ann. Rept. Progr. Chem., **60**, 278 (1964).

10. C. Bernasconi and H. Zollinger, Tetrahedron Letters, No. 16, 1083 (1965).