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The Kinetics and Mechanisms of Aromatic Halogen Substitution. Part XXVI.[1] Confirmation of the Existence of a Solvent Deuterium Isotope Effect in the Bromination of Phenol in Acetic Acid

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The bromination of phenol in acetic acid containing lithium perchlorate and lithium bromide is faster by a factor of 1·8—1·9 than that of *O*-deuteriophenol in deuterioacetic acid containing the same salts.

In an earlier Paper,[2] we reported as a preliminary result that the bromination of phenol in acetic acid is somewhat faster than that of *O*-deuteriophenol in *O*-deuterioacetic acid. We associated this with the possibility of electron-release by H–O-hyperconjugation, and pointed out that the limiting result of this phenomenon would be proton-loss from oxygen synchronous with the first stage of bromination. Under these circumstances, the mechanism of bromination of phenol would be different from that of (*e.g.*) anisole; the former would be an S_E2' reaction followed by prototropic rearrangement, whereas the latter would be predominantly * of the S_E2 class.

Recently,[4] it has been argued that the primary isotope effect for a proton transfer from one oxygen to another accompanying cleavage of a carbon bond should be small. Consequently it has been concluded [5] that the primary isotope effect reported by us [2] seems unlikely. This current interest in our observations prompts us to report further on the experimental basis of our work and to correct our earlier numerical values, which appreciably underestimated the magnitude of the effect.

EXPERIMENTAL

Reaction of deuterium oxide with a slight excess of acetic anhydride has been used by a number of authors [cf. 6,7] for the preparation of deuterioacetic acid (CH_3CO_2D) Unfortunately, in our hands this procedure, followed by fractional distillation, gave a product which we have now shown to be unsatisfactory. Analysis by proton magnetic resonance spectroscopy showed that our second sample prepared in this way contained only 40—50% of deuterium attached to oxygen,† and this result was qualitatively confirmed by using infrared spectroscopy. Accordingly, we prepared a much more satisfactory sample by the reaction of acetyl chloride with deuterium oxide under strictly anhydrous conditions, following Linschitz, Hobbs, and Gross's method [8] as modified by Renaud and Leitch,[9] who had obtained similar evidence that the procedure involving acetic anhydride is unsound.‡ Acetyl chloride was first fractionally distilled from dimethylaniline; it had b. p. 51°. To this (300 ml.), deuterium oxide (75 g.) was added in portions with stirring under a current of dried nitrogen. Each portion was allowed to react before the next was added. The product was gently boiled under reflux to remove deuterium chloride and was then distilled and finally

* The well-known side-reaction of demethylation accompanying nitration of anisole [3] can, however, be formulated as an S_E2' reaction, a result which suggests that the balance between the rates of the two types of process may be very close.

† We thank Dr. M. D. Johnson (University College, London) for this estimate.

‡ We are indebted to Dr. A. J. Kresge for drawing our attention to this Paper.

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fractionally redistilled giving a product (60—70% yield), b. p. 119°/760 mm., f.p. 15·35°. Although this f.p. is slightly lower than that (15·66°) given by Linschitz *et al.*,[8] analysis by p.m.r. spectroscopy indicated the presence of less than 1% of protium attached to oxygen.

The rate measurements were made as before, with reagents each M/640 at 25°, and the following are the results, those for phenol in acetic acid being included for comparison.

Compound	Solvent	k_2 (l. mole^{-1} min.$^{-1}$) with added salts:				
		LiBr (M)	0·20	0·15	0·10	0·05
		$LiClO_4$ (M)	0·00	0·05	0·10	0·15
PhOH	CH_3CO_2H		32	43	65	122
PhOD	CH_3CO_2D		19	23	35	63

DISCUSSION

The results presented above confirm the existence of a substantial solvent deuterium isotope-effect on the rate of bromination of phenol in acetic acid. The magnitude of the effect ($k^{PhOH}_{CH_3CO_2H}/k^{PhOD}_{CH_3CO_2D} = 1·8$—$1·9$) is greater than was reported before, but is in the same direction. Since we now know that our previous solvent was incompletely *O*-deuterated, all our observations (involving two independent workers and three sets of measurements) support the existence of a rate-ratio of the magnitude now claimed.

A priori, four different origins could be suggested for this effect. The first is that there is a relatively large solvent isotope-effect on the equilibrium between bromide, bromine, and tribromide in this solvent. Such a large effect would theoretically be quite unexpected. Our own measurements [2] on the bromination of phenol in acetic acid without added bromide ion gave a solvent isotope-effect which was no smaller than in the presence of bromide ion. So, pending direct measurement of the equilibrium constant, we think that this effect is probably small.

The second is that there is a solvent deuterium isotope-effect on the rate of attack by bromine on the organic substrate. Such an effect would also theoretically be quite unexpected; that the solvent structure of deuterioacetic acid is very similar to that of acetic acid is shown, for example, by the similarity of their melting points, by the close relationship between their infrared spectra,[10] and by the very similar rates of third-order bromination of mesitylene in the two solvents.[7]

The third is that the observations result from a secondary isotope-effect; but for bromination, and indeed for aromatic substitution generally, " deuterium substitution for protons removed from the point of substitution does not seem to have a noticeable effect." [11] Thus for bromination of side-chain-deuterated toluene, a ratio k_H/k_D of only $1·03 \pm 0·01$ per deuterium atom has been reported.[12]

The fourth is our original proposal, which we regard as much more probable than any of the other possibilities, that H–O bond fission has made substantial progress in the transition state for bromination of phenol, so that the experimentally observed solvent isotope-effect is a normal effect on the breaking of an H–O bond. If in fact there is force in Swain, Kuhn, and Schowen's [4] argument that transfer of a proton from oxygen to oxygen should show a relatively small k_H/k_D ratio, our experimental value (1·8—1·9) may perhaps represent a situation when transfer has nearly completely loosened the proton, and transfer is half-completed; but there do not seem to be enough well-established analogies to allow this conclusion to be drawn firmly. Further work is necessary, particularly on the bromination of substrates of other kinds, and we hope to be able to put this in hand shortly.

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