[CONTRIBUTION FROM THE MARION EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE, BRYN MAWR, PENNA.]

The Iodination of 2,4,6-Trideuterioanisole by Iodine Monochloride[1]

BY ERNST BERLINER

RECEIVED APRIL 23, 1960

The kinetics of iodination of 2,4,6-trideuterioanisole by iodine monochloride has been studied in water containing perchloric acid and chloride ions. The reaction has an isotope effect of about 3.8, which is independent of the hydrogen ion (0.1 to 0.0001 *M*) and the chloride ion (0.3 to 0.9 *M*) concentrations. A change from H_2O to D_2O slows down the reaction by about 30%. Experiments were carried out which showed that the isotope effect persists to very low chloride ion concentrations, and it is concluded that of the various possible mechanisms, the one which involves H_2OI^+ as the substituting agent is the more likely.

The kinetics of iodination by iodine monochloride of fairly reactive compounds, such as *p*-chloroaniline,[2] 2,4-dichlorophenol and anisole,[3] is in agreement with two different mechanisms, involving different substituting agents (Schemes A and B). In Scheme A the substituting agent is H_2OI^+, which is formed by hydrolysis of ICl, and in Scheme B it is ICl itself, which is in equilibrium with an aromatic intermediate. The substitution process in Scheme A may proceed in the customary two-step sequence, as written, or it may be a one-step reaction with simultaneous bond-breaking and making. Scheme A is very similar, kinetically and mechanistically, to one proposed also for aqueous iodination by iodine itself,[4] while Scheme B is also similar to one suggested for molecular iodinations, by analogy with certain bromodecarboxylations.[5] In support of Scheme B, the important observation was made that iodination of phenol by iodine has a kinetic isotope effect of about 4, as demanded by this scheme.[6] Since that time, an isotope effect of similar magnitude has also been observed for iodination by iodine of glyoxaline[7] and of aniline.[8,9] The characteristic feature common to both Schemes A and B is the inverse dependence of the rate on chloride ion concentration (or iodide ion, in case of iodination by iodine), and this is experimentally observed. In the previous study on iodinations with ICl, a decision between the two alternatives could not be made, although preference was expressed for Scheme A. In order to arrive at a possible distinction between the two mechanisms, it was essential also to study iodination by ICl for a possible deuterium isotope effect. The two-step Scheme A may or may not have an isotope effect, depending on which step is rate-determining; Scheme B demands an isotope effect (see, however, the later discussion). Of the previously studied compounds, anisole was chosen for further investigation, because, if the iodination of anisole showed an isotope effect, it is very likely that *p*-chloroaniline and 2,4-dichlorophenol would do likewise. This should be so, because of the three, anisole may be expected to form the least stable intermediary species, and a certain stability is required for the postulated intermediate in Scheme B to be present in equilibrium or stationary concentrations. The results are reported below.

$$\mathrm{ICl} + \mathrm{H_2O} \rightleftarrows \mathrm{H_2OI^+} + \mathrm{Cl^-} \qquad \text{Scheme A}$$

$$\mathrm{ArH} + \mathrm{H_2OI^+} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathrm{ArHI^+} + \mathrm{H_2O} \qquad k_{-1} \gg k_2 \text{ or}$$

$$\mathrm{ArHI^+} \xrightarrow{k_2} \mathrm{ArI} + \mathrm{H^+} \qquad k_2 \gg k_{-1}$$

$$\mathrm{ArH} + \mathrm{ICl} \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \mathrm{ArHI^+} + \mathrm{Cl^-} \qquad \text{Scheme B}$$

$$\mathrm{ArHI^+} \xrightarrow{k_2} \mathrm{ArI} + \mathrm{H^+} \qquad k_{-1} \gg k_2$$

Experimental.—Deuterioanisole was prepared from anisole and deuteriosulfuric acid by a procedure similar to one described,[10] except that 50 mole % of D_2SO_4 led to extensive sulfonation, and 40 mole % acid was employed instead. The acid was made from stabilized SO_3 (Sulfan B of Baker and Adamson) and deuterium oxide (99.5% of the Stuart Oxygen Co.).[11] The final acid assayed for 39 mole % of D_2SO_4. About 15 ml. of the previously purified sample of anisole[3] was shaken in a glass-stoppered bottle with 30 ml. of D_2SO_4 for 12 hours. After that time the layers were separated, and the anisole was shaken twice more for 16 hours each with fresh D_2SO_4. At each treatment with D_2SO_4 the organic layer decreased by about 5 to 10%. After working up, the deuterioanisole was distilled twice from metallic sodium and boiled at 153.2–153.4° (751.7 mm.), $n^{25}\mathrm{D}$ 1.5143. A final yield of 25% was obtained. The deuterioanisole was analyzed through n.m.r. by Varian Associates, Palo Alto, Calif., and was found to be "about 92% 2,4,6-trideuterioanisole. Probably the greatest part of the remaining 8% is 2,3,4,6-tetradeuterioanisole."[12] The sample of anisole was put through exactly the same procedure, except that light sulfuric acid was used, in order to make the two samples as much comparable as possible; b.p. 154° (756 mm.), $n^{25}\mathrm{D}$ 1.5149. All other materials were best reagent grade chemicals, as described before.

The kinetic procedure was exactly as described before. All data for anisole are new, except those for calculating activation energies. They agree with the previous values[3] within a few %. Precision of the data and agreement of duplicate runs was also the same as before. A typical run for deuterioanisole is reproduced below. In the runs with 0.05 *M*, 0.01 *M* and no initial chloride ions, the total volume was 25 ml., sufficient for two 10-ml. samples. The concentration of reactants and the ionic strength was kept low in order to slow down the reaction. Reaction was started by adding 1 ml. of the ICl stock solution from a fast

---

(1) Kinetics of Aromatic Halogenation. VII. Previous publication, E. Berliner, *Chemistry & Industry*, 177 (1960).

(2) E. Berliner, THIS JOURNAL, **78**, 3632 (1956).

(3) E. Berliner, *ibid.*, **80**, 856 (1958).

(4) E. Berliner, *ibid.*, **72**, 4003 (1950); **73**, 4307 (1951); B. S. Painter and F. G. Soper, *J. Chem. Soc.*, 343 (1947).

(5) E. Grovenstein, Jr., and U. V. Henderson, Jr., THIS JOURNAL, **78**, 569 (1956); see also L. G. Cannell, *ibid.*, **79**, 2927, 2932 (1957).

(6) E. Grovenstein, Jr., and D. C. Kilby, *ibid.*, **79**, 2972 (1957).

(7) A. Grimison and J. H. Ridd, *Proc. Chem. Soc.*, 256 (1958).

(8) E. Shilov and F. Weinstein, *Nature*, **182**, 1300 (1958).

(9) An isotope effect is also observed in the iodination of anisole by ICl in glacial acetic acid (ref. 1) and by I_2 in water (unpublished results by Dr. E. Grovenstein, Jr.). I am greatly indebted to Dr. Grovenstein for this private communication.

(10) C. K. Ingold, C. G. Raisin and C. L. Wilson, *J. Chem. Soc.*, 1637 (1936).

(11) E. F. Jenny and J. D. Roberts, THIS JOURNAL, **78**, 2005 (1956).

(12) Letter from Varian Associates, April 1, 1959.

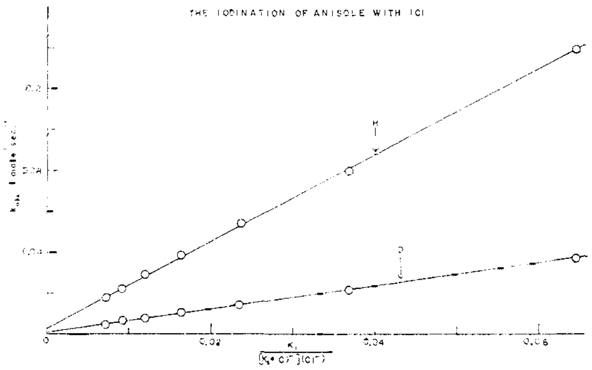

Fig. 1.—The dependence of the rate on the chloride ion concentration: upper line, anisole; lower line, 2,4,6-trideuterioanisole.

running pipet calibrated for blow-out, to 24 ml. of a solution containing the other reagents and immediately withdrawing the first 10-ml. sample. Time was recorded when the pipet was half emptied. The initial ICl concentration was determined by several blank determinations. Points were taken at least in duplicate, but usually three or four times. In a typical run for anisole with no initial chloride, the % reaction after 20 sec. was 74.9, 75.2, 76.2 and 74.9, and for deuterioanisole after 125 sec. 79.2, 81.1 and 81.4%. Halfway through these determinations the two samples were redistilled from sodium, but the results did not change.

TABLE I

A KINETIC RUN IN THE IODINATION OF 2,4,6-TRIDEUTERIOANISOLE WITH IODINE MONOCHLORIDE AT 25°

2,4,6-Trideuterioanisole 0.004089 M, $HClO_4$ 0.1 M, NaCl 0.3 M, $NaClO_4$ 0.6 M, ICl $\simeq$ 0.001 M

Time, min.	0.02 N thiosulfate, ml.	$10^2 k_{obs}$, l. mole^{-1} sec.$^{-1}$
0	1.004	
10	0.918	3.69
20	.838	3.76
30	.770	3.72
41	.702	3.70
53	.636	3.69
65	.580	3.65
82	.504	3.68
2880	...	

Results and Discussion

Deuterioanisole, prepared from anisole and deuteriosulfuric acid, was 100% deuterated in the 2,4,6-positions. The kinetics of its iodination was carried out exactly as before,[3] in water which contained perchloric acid and excess chloride ion, in order to prevent too rapid hydrolysis and disproportionation of ICl, to slow down the reaction to measurable speeds, and to minimize the effect of chloride ions formed during substitution. The kinetics of iodination of anisole itself was repeated, and for a given set of conditions runs were always conducted with both anisole and deuterioanisole. Under all sets of conditions, which included changes in acid and chloride ion concentration as well as in temperature, and a change to D_2O, the reaction has a pronounced isotope effect, and anisole reacts about 3.8 times faster than trideuterioanisole at 25°. The variations in conditions and their possible bearing on a distinction between the two mechanisms are discussed in order.

The Effect of Chloride Ions.—The chloride ion concentration was varied from 0.9 to 0.3 M at a constant total salt concentration of 1.0 M. Within these variations the isotope effect is practically unchanged, although the rates vary by a factor of about 8 (Table II). As shown before,[3] the observed rate constants are proportional to the expression $K_1/(K_1 + Cl^-)(Cl^-)$, where K_1 is the equilibrium constant for iododichloride dissociation according to $ICl_2^- \rightleftarrows ICl + Cl^-$. The least square slope for the straight line obtained on plotting k_{obs} for anisole against the above expression has the value 2.10 ± 0.012, and the intercept is $(2.95 \pm 0.39) \times 10^{-3}$ (Fig. 1). The previous values were 2.12 and 3.47×10^{-3}, respectively. For deuterioanisole the slope is 0.555 ± 0.0032 and the intercept $(0.951 \pm 0.098) \times 10^{-3}$. A possible meaning of the positive intercept has been discussed before.[2] The ratio of the slopes is 3.78.[13] The fact that the relationship is observed strictly means that in Scheme B, if operative, the intermediate must be in actual equilibrium with the reactants within the investigated range of chloride ions. It is also noteworthy that within that range, the isotope effect is constant. More will be said about this later.

TABLE II

THE EFFECT OF CHLORIDE IONS

$ArOCH_3 \simeq 0.004$ M, $HClO_4$ 0.1 M, ICl $\simeq$ 0.001 M, T 25°, μ 1 M[a]

NaCl, mole/l.	$k_H \times 10^2$, l. mole^{-1} sec.$^{-1}$	$k_D \times 10^2$, l. mole^{-1} sec.$^{-1}$	k_H/k_D
0.90	1.77	0.477	3.71
.80	2.18	.598	3.65
.70	2.89	.763	3.79
.60	3.79	1.025	3.70
.50	5.40	1.44	3.75
.40	7.94	2.16	3.67
.30	14.0	3.70	3.78

[a] The ionic strength was maintained with $NaClO_4$.

The Effect of Hydrogen Ions.—Within a variation of $HClO_4$ of 0.1 to 0.0001 M at a constant ionic strength, the rates, as well as the isotope effect, are the same (Table III). When isotope effects occur, rates and isotope effects usually depend on pH,[14] because the rate-controlling step involves a proton loss. In the present case, the only base present, other than the perchlorate or the chloride

TABLE III

THE EFFECT OF HYDROGEN IONS

$ArOCH_3 \simeq 0.004$ M, NaCl 0.5 M, ICl $\simeq$ 0.001 M, μ 0.6 M,[a] T 25°

$HClO_4$, mole/l.	$k_H \times 10^2$, l. mole^{-1} sec.$^{-1}$	$k_D \times 10^2$, l. mole^{-1} sec.$^{-1}$	k_H/k_D
0.1	3.87	1.05	3.69
.01	3.94	1.08	3.65
.001	3.99	1.07	3.73
.0001	3.97	1.07	3.71

[a] The ionic strength was maintained with $NaClO_4$.

---

(13) The slopes are equal to $k_1k_2K_2/k_{-1}$ for Scheme A (where K_2 is the equilibrium constant for ICl hydrolysis as written) and k_1k_2/k_{-1} for Scheme B. The ratio is only equal to $k_2(H)/k_2(D)$ if the pre-equilibria are not affected by isotopic substitution.

(14) K. B. Wiberg, *Chem. Revs.*, **55**, 713 (1955); F. A. Long and D. Watson, *J. Chem. Soc.*, 2019 (1958).

ions, is the water, the concentration of which is practically constant over the range of acid concentration. For this reason, neither the rates nor the isotope effects vary, although the final step must involve an acid–base reaction.

The Effect of Temperature.—Activation energies for iodination of deuterioanisole were determined from measurements of rate constants at four different temperatures (Table IV). The activation energy is 15.5 ± 0.17 kcal., log A is 9.37 ± 0.12 l. mole^{-1} sec.$^{-1}$ and ΔS^* is -17.6 e.u. For anisole itself the figures were[3] 14.7 kcal., 9.33 and -17.8 e.u. It is gratifying that all of the difference in rate due to the isotope effect is caused by the greater activation energy for iodination of deuterioanisole; the entropies are identical within the experimental errors.

TABLE IV

THE EFFECT OF TEMPERATURE

$ArOCH_3 \simeq 0.004$ M, NaCl 0.5 M, $HClO_4$ 0.05 M, $NaClO_4$ 0.05 M, ICl $\simeq 0.001$ M

T, °C.	$k_H \times 10^2$,[a] l. mole^{-1} sec.$^{-1}$	$k_D \times 10^2$, l. mole^{-1} sec.$^{-1}$	k_H/k_D
38.0	10.84	3.085	3.51
32.0	6.95	1.90	3.66
25.0	4.02	1.075	3.74
18.0	2.14	0.553	3.87

[a] Data from ref. 3.

Experiments in D_2O.—In D_2O the rate of iodination of anisole is about 30% less than in water (Table V). This is a reasonable value for reactions in which the proton loss is rate-determining,[14] and is expected on the basis of the presumed lower base strength of D_2O compared to H_2O. Deuterioanisole also reacts about 30% slower in D_2O than in H_2O, and hence about 5.3 times slower than anisole in water. The effects of changing the hydrogens in the substrate to deuterium, and those of changing the solvent from H_2O to D_2O, are therefore additive and independent of each other. No new mechanistic significance regarding the problem at hand can therefore be gained from these experiments.

TABLE V

THE EFFECT OF D_2O

$ArOCH_3 \simeq 0.004$ M, NaCl 0.5 M, $HClO_4$ 0.002 M, ICl $\simeq$ 0.001 M, T 25°

	H_2O	D_2O	$k(H_2O)/k(D_2O)$
H-Anisole	3.44	2.44	1.41
D-Anisole	0.899	0.647	1.39
k_H/k_D	3.83	3.77	

The Mechanism.—The kinetic evidence so far considered makes it impossible to distinguish Scheme A, with the second step rate-determining ($k_{-1} \gg k_2$), from Scheme B.[15] This obviously is due to the identity of the transition states for the two schemes. The transition state must approach a configuration in which the iodine is already attached to the ring and the proton is being stretched. It is far removed from the reactants and closer to the products. The bulk reagent for either scheme is ICl, and the kinetics cannot tell, within the above range of conditions, where the iodine came from, or how many, if any, pre-equilibria preceded the transition state.[16] Furthermore, a change of solvent to D_2O will affect the energy of the bulk reagents, ICl and the solvent, to the same extent for each scheme, and the lowering of the rate on going from H_2O to D_2O is the only effect that might have been expected. This being the case, one may ask if it makes any sense to inquire where the iodine came from, from H_2OI^+ or from ICl, and if the question can be decided on kinetic grounds. Iodine monochloride and the conjugate acid of hypoiodous acid are certainly different compounds, and the question, which of the two carries the iodine into the aromatic ring, is therefore justified.

It seemed feasible to arrive at a distinction between the two schemes by considering the effect of chloride ion concentration on the isotope effect. An inspection of the two mechanisms shows that in Scheme A the isotope effect should be independent of the chloride ion concentration, because the chloride ion is formed in a pre-equilibrium, which has nothing to do with the substitution step. In mechanism B, a lowering of the chloride ion concentration should eventually lead to a situation where the back reaction in the first step becomes negligible, and the first step should become rate determining, in which case the isotope effect would disappear. This becomes clear when the expression for k_{obs} for the steady-state treatment for Scheme B is considered; that is, it is assumed that the intermediate is present in a small, stationary concentration (and does not accumulate); k_{obs} then becomes $k_1k_2K_1/(K_1 + \text{Cl}^-)[k_2 + k_{-1}(\text{Cl}^-)]$. In the extreme case, as the chloride ion concentration becomes zero, K_1 and k_2 will cancel, so that the expression becomes $k_{obs} = k_1$, and the reaction should have no isotope effect. At intermediate concentrations of chloride ions, intermediate values for k_D might be expected. It has been shown already that in the range of 0.9 to 0.3 M chloride ion, the isotope effect is unchanged (Table II). Within this range, the two mechanisms are not distinguishable, as has been stressed by Grovenstein and co-workers.[6] But at concentrations much less than 0.3 M chloride ion, the rates become too fast for exact measurements by the conventional sampling technique which was employed. Ridd and Grimison, in studying the iodination of glyoxaline by I_2, have recently succeeded, by measuring initial rates, in conducting the reaction with no added initial iodide ions, and, having found an undiminished isotope effect, have concluded that the scheme analogous to A is the more reasonable.[17]

We have followed a similar procedure and have first lowered the chloride ion concentration to 0.05 M and 0.01 M. In the first case, the rate is

---

[15] In previous publications (ref. 2, 3) it was assumed that the first step in Scheme A was rate determining and specific rate constants for iodination by H_2OI^+ were calculated on this basis (for instance, Table V in ref. 3). These values are now seen to be incorrect, because the observed rate constants not only depend on k_1, but also on k_{-1} and k_2.

[16] See the discussion in P. B. D. de la Mare and J. H. Ridd, "Aromatic Substitution," Butterworth Scientific Publications, London, 1959, Chapter III.

[17] I am greatly indebted to Dr. Ridd for telling me of this work prior to publication; see A. Grimison and J. H. Ridd, *J. Chem. Soc.* 3019 (1959).

about 10 times, and in the second case about 100 times faster than at a 0.3 *M* chloride ion concentration. Some results, expressed in terms of percentage reaction, are reproduced in Table VI. For the same amount of reaction, deuterioanisole takes approximately four times longer to react than anisole, and the isotope effect persists down to these low chloride ion concentrations. Rate constants calculated for these reactions fall off, partly because of the accumulation of chloride ions and partly because of possible di-iodination on lowering the anisole concentration. If these "constants" are averaged, the ratios k_H/k_D for 0.05 *M* chloride ion is 4.3 and for 0.01 *M* it is 3.6. These ratios are only approximate and somewhat arbitrary, because the two compounds were not compared over exactly the same extent of reaction, *and the comparison of times for equal amounts of reaction is more meaningful.* Finally, the reaction was conducted with no added initial chloride ions present, but in a solution 4% in glacial acetic acid, in order to make the ICl sufficiently soluble. Under these conditions, about 75% of anisole, but only about 45% of deuterioanisole, has reacted in 20 sec. Using a standardized technique, the reaction percentages were well reproducible, and again, for an equal amount of reaction, deuterioanisole takes about four times longer to react (last entries in Table VI). Actually, the isotope effect appears to be somewhat larger and to increase with time. The reason probably is that some di-iodination occurs, as a result of keeping the anisole concentration, and hence the speed of the reaction, low, and this gives rise to an additional isotope effect for deuterioanisole because of *ortho*-iodination. The important point is that at 0.05 *M*, 0.01 *M* and with no added initial chloride ion concentrations, the reaction has qualitatively the same isotope effect, and that it appears to be the same also quantitatively.

TABLE VI

RUNS AT LOW CHLORIDE ION CONCENTRATIONS AT 25°

Time, sec.	Reaction, %	
	H-Anisole	D-Anisole
(A) ArOCH$_3$ 0.002 *M*, NaCl 0.05 *M*, HClO$_4$ 0.04 *M*, ICl $\simeq$ 0.00077 *M*		
20	7.73	
50	15.2	
65		4.82
80	20.2	
125	27.8	
305	51.3	19.6
485		27.1
1205		50.3
1805		62.1
(B) ArOCH$_3$ 0.0012 *M*, NaCl 0.01 *M*, HClO$_4$ 0.04 *M*, ICl $\simeq$ 0.00076 *M*		
20	30.5	
40	45.2	
50	51.0	
65		28.7
95	66.0	
125		40.7
140	74.1	
185		49.6
365		67.1
545		75.6
(C) ArOCH$_3$ $\simeq$ 0.00098 *M*, NaCl (initial) O, HClO$_4$ 0.04 *M*, ICl 0.000622 *M*, HAc 4%		
20	75.3	45.7
25	79.6	
35	83.7	58.1
50	88.5	67.2
65	89.7	70.8
95		76.5
125		80.6
185		84.0
305		86.4

H-Anisole, sec.	Reaction, %	D-Anisole, sec.
15[a]	69.4–70.8	65
20	75.3–76.5	95
25	79.6–80.6	125
35	83.7–84.0	185

[a] Only one determination.

From what has been said before, these experiments point to Scheme A as the more probable mechanism. But the proof cannot be considered unique, because there is always some chloride ion present as reaction proceeds, and also from hydrolysis of ICl, and in favor of Scheme B it can be argued that even the lowest chloride ion concentration is sufficient to reverse the initial step.[18] While Scheme A is therefore not a certainty, the least that can be stated is that it is more likely, on the basis of these experiments, than Scheme B. Of the two possible Schemes A, the two-step one is favored, by analogy with the accepted mechanism of substitution reactions which do not show an isotope effect, although the one-step sequence is a possibility.[19] In either case, the substituting agent would be H_2OI^+. By implication, the same substituting agent would then also be involved in the iodination by ICl of the other two compounds mentioned in the introduction.

Acknowledgment.—This work was supported by National Science Foundation Grant No. G-4474, which is gratefully acknowledged.

---

[18] The use of silver ions to keep the concentration of the chloride ions produced by the reaction to a minimum was contemplated, but proved unfeasible, because ICl reacts immediately with silver nitrate solution.

[19] G. S. Hammond, THIS JOURNAL, **77**, 334 (1955).