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Aromatic Halogenation. II. The Kinetics and Mechanism of Iodination of 4-Nitrophenol and 4-Nitrophenol-2,6-d_2[1]

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The kinetics of iodination of 4-nitrophenol has been studied in aqueous solution at 50.0°. At constant hydrogen and iodide ion concentrations the iodination is first order in the concentration of both 4-nitrophenol and of iodine. At the higher range of iodide ion concentrations studied, the rate of iodination, after correction for formation of unreactive triiodide ion is inversely proportional to the concentration of iodide ion but appears to become independent of the concentration of iodide ion as the latter becomes very small. Throughout the higher range of iodide ion concentrations studied, the iodination of 4-nitrophenol is inverse first order in the concentration of hydrogen ion while in the lower range of iodide ion concentrations the order in hydrogen ion concentration becomes less than unity. The kinetics of iodination of 4-nitrophenol-2,6-d_2 has also been studied. An isotope effect, $k_H/_D$, of 5.4 was obtained at 22×10^{-4} M iodide ion concentration. This isotope effect diminished with decreasing iodide ion concentration until a value of 2.3 was obtained at about 0.15×10^{-4} M iodide concentration. A similar small isotope effect (2.6 ± 0.4) was found for iodination in presence of 0.050 M thallous perchlorate. These data are interpreted in terms of a mechanism in which molecular iodine attacks 4-nitrophenol or, more readily, 4-nitrophenoxide ion in a reversible process to give an intermediate which appears to have the structure of 6-iodo-4-nitrocyclohexa-2,4-dienone. In a second, generally rate-determining, step the intermediate loses a proton from carbon to give after protonation on oxygen the final product, 2-iodo-4-nitrophenol.

Since our preliminary communication[2] concerning the occurrence of a kinetic isotope effect in the iodination of phenol-2,4,6-d_3 ($k_H/k_D \simeq 4$), similar isotope effects have been observed in the iodination of aniline, and some, but not all, of its derivatives[3a] in the iodination of phenol-3-sulfonic acid[3b] and in the iodination of glyoxaline.[4] In all of these experiments molecular iodine was the added reagent. In the halogenation of anisole, isotope effects have been found with iodine[5] and with iodine monochloride,[6] but no appreciable isotope effect was observed with bromine.[6] Similarly no isotope effect was observed in the bromination of benzene by hypobromous acid[7a] or by bromine with iodine catalyst.[7b] Bromination of phenol[3b] likewise gave no detectable isotope effect while bromination of 2-naphthol-6,8-disulfonic acid[8] and of dimethylaniline[9] gave appreciable isotope effects ($k_H/k_D \backsimeq 2$). A large isotope effect was found in bromination of 1,3,5-tri-t-butylbenzene ($k_H/k_T \backsimeq 10$)[10] and evidently a smaller isotope effect in bromination of 3-bromodurene ($k_H/k_D > 1.4$)[11].

The presence of a large isotope effect in aromatic halogenation demands that breaking of the aromatic carbon–hydrogen bond be of kinetic significance in the rate-determining step of the reaction. This result could be explained[12,13] on the basis of a concerted termolecular mechanism of substitution (eq. 1., which is written without regard to charge).

$$E + ArH + B{:}\ \text{—}[E\ldots Ar\ldots H\ldots B]\rightarrow Ar\text{—}E + B\text{—}H \qquad (1)$$

transition state

Here the electrophile E and the base B: attack the aromatic nucleus in a single stage to give the products. According to the kinetics of iodination of phenol[14] the one-stage termolecular mechanism could consist of attack of H_2OI^+ (or I^+) upon phenoxide anion with proton removal being assisted by solvent (water); for the general base-catalyzed reaction, the general base (A^-) could replace the solvent for the proton removal or it might be joined to the iodinating agent (as A—I or as $A\text{—}H\ldots\overset{H}{\overset{|}{O}}\text{—}I$). However, the termolecular mechanism of electrophilic aromatic substitution appears *never* to have been established, although it cannot be said to have been disproved in all cases; instead the two-stage mechanism (eq. 2 and 3) appears to be generally operative.[8,13] In this mechanism an

$$E + ArH \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} E\text{—}Ar\text{—}H \qquad (2)$$

$$E\text{—}Ar\text{—}H + B{:} \xrightarrow[k_2]{} Ar\text{—}E + B\text{—}H \qquad (3)$$

electrophilic reagent E attacks the aromatic nucleus to give an intermediate E–Ar–H which in a second step loses a proton to a base B: . To account for a large kinetic isotope effect, $k_{-1} >> k_2(B{:})$; while if $k_2(B) >> K_{-1}$, no isotope effect is observable. If the former possibility holds, however, the first step of the reaction must be at or very near equilibrium. From kinetic data under such conditions the nature of the electrophilic reagent *cannot be specified*[2]; in particular, molecular iodine is not excluded as the electrophile.[15]

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[1] Presented in part at the Southeastern Regional Meeting of the Am Chem. Soc., Durham, N. C., Nov. 14, 1957. For more complete experimental details see the Ph.D. thesis of N. S. Aprahamian, Georgia Institute of Technology, October, 1960.

[2] Paper I, E. Grovenstein, Jr., and D. C. Kilby, *J. Am. Chem. Soc.*, **79**, 2972 (1957).

[3] (a) E. A. Shilov and F. Weinstein, *Nature*, **182**, 1300 (1958); F. M. Vainstein and E. A. Shilov, *Dolkady Akad. Nauk S.S.S.R.*, **123**, 93 (1958) [*C. A.*, **53**, 3852 (1959)]. We are indebted to Dr. Shilov for kindly communicating to us some of his results before publication. (b) F. M. Vainstein, E. A. Shilov and O. M. Grishin, *Zhur. Vsesoyuz. Khim. Obshch. D. I. Mendeleeva*, **5**, 119 (1960).

[4] A. Grimison and J. H. Ridd, *Proc. Chem. Soc.*, 256 (1958); *J. Chem. Soc.*, 3019 (1959).

[5] Unpublished experiments of the present authors.

[6] E. Berliner, *J. Am. Chem. Soc.*, **82**, 5435 (1960); *Chemistry & Industry*, 177 (1960). We are indebted to Dr. Berliner for kindly communicating to us his results before publication.

[7] (a) P. B. D. de la Mare, T. M. Dunn and J. T. Harvey, *J. Chem. Soc.*, 923 (1957); (b) L. Melander, *Arkiv. Kemi*, **2**, 211 (1950).

[8] H. Zollinger, *Experientia*, **12**, 165 (1956).

[9] P. G. Farrell and S. F. Mason, *Nature*, **183**, 250 (1959).

[10] P. C. Myhre, *Acta Chem. Scand.*, **14**, 219 (1960).

[11] E. Baciocchi, G. Illuminati and G. Sleiter, *Tetrahedron Letters*, **No. 23**, 30 (1960).

[12] G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).

[13] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 279 ff.

[14] (a) B. S. Painter and F. G. Soper, *J. Chem. Soc.*, 342 (1947); F. G. Soper and G. F. Smith, *ibid.*, 2757 (1927); (b) E. Berliner, *J. Am. Chem. Soc.*, **73**, 4307 (1951).

The purpose of the present investigation was to try to distinguish between the one-stage (termolecular) and the two-stage mechanisms for iodination of 4-nitrophenol and to try to find out what molecular species constitutes the iodinating agent. Our approach was to take some of the techniques which have proved useful in the study of bromodecarboxylation[15,16] and bromodesulfonation[17] and apply these to iodination.[18]

Experimental Details

Reagents.—Heavy water (99.5% min. D_2O) was obtained from Stuart Oxygen Co. (Liquid Carbonic). Deuterium chloride was prepared[19] by reaction of heavy water with purified[20] thionyl chloride and was separated from sulfur dioxide by passage through two traps cooled with solid carbon dioxide–acetone.

Carbon tetrachloride from Dow Chemical Co. was purified by distillation over potassium permanganate. The distillate was extracted with a 10% solution of sodium hydroxide and then with dilute sulfuric acid and, after drying over $CaCl_2$, was redistilled. Iodine was Merck & Co., Inc., resublimed U.S.P. grade and was purified as described in the section on kinetic measurements. 4-Nitrophenol from Eastman Kodak Co. was recrystallized six times from water to give pale yellow needles of m.p. 113.5–114° uncor. (recorded[21] m.p. 114°). Perchloric acid was Baker Analyzed reagent grade. Sodium iodide, J. T. Baker analyzed reagent grade, was dried *in vacuo* at 80° before use in the kinetic runs; however, Merck U.S.P. sodium iodide was used to stop kinetic runs. Sodium perchlorate was obtained from Amend Drug & Chemical Co. and from G. Fredrick Smith Chemical Co. or was prepared by neutralization of perchloric acid with sodium hydroxide; this salt was dried *in vacuo* at 130–140° before use. Thallium(-ous) perchlorate, C.P. grade from City Chemical Corp., N. Y., was dried at 80° *in vacuo* before use.

The water used as solvent in the kinetic runs was distilled water which was redistilled over $KMnO_4$ and NaOH and was then deoxygenated by bubbling nitrogen through it for 1 hour.

4-Nitrophenol-2,6-d_2 was prepared by deuterium exchange upon 4-nitrophenol by a method somewhat similar to that used by Ingold[22] and co-workers for phenol-2,4,6-d_3. 4-Nitrophenol (28 g., 0.20 mole) was partially neutralized with sodium deuteroxide which had been prepared from 2.54 g. (0.11 g. atom) of freshly cut sodium metal and 171 g. of heavy water (93% D_2O). The resulting solution was sealed under a nitrogen atmosphere in Pyrex glass tubes and was heated in a boiling water-bath for 15 days. The tubes were then opened and the solvent removed by distillation under vacuum. To the solid residue was added 150 g. of heavy water (99.5% min. D_2O) and the solution was sealed and heated as before for 18 days. The solution was then made just acidic to litmus with 3.7 M DCl in heavy water and was evaporated almost to dryness to give after filtration 22 g. of crude product. A portion of this product (4.0 g.) was sublimed at a bath temperature near 135° and a pressure of 0.03 mm. and gave 2.6 g. of deuterated 4-nitrophenol (called sample A) of m.p. 113.5–114.0° (uncor.) with the remainder of the material being a non-volatile residue. To the remainder of the crude product was added 100 g. of heavy water (99.5% min. D_2O) which had been previously treated with 1.9 g. (0.083 g. atom) of sodium metal. The solution was sealed in tubes containing an atmosphere of nitrogen and was heated in a boiling water-bath for 32 days. The product (sample B) was isolated and purified as for sample A and weighed 4.2 g. and had m.p. 113.5–114.0° (uncor.).

Kinetic Measurements.—Dilute iodine solutions for kinetic measurements were prepared as follows. A saturated stock solution of iodine in purified carbon tetrachloride (200 ml.) was extracted with three 150-ml. portions of water. These aqueous extracts were discarded while the fourth and subsequent extracts were used for the kinetic runs. This procedure for preparing iodine solutions was repeated each day with the same stock iodine–carbon tetrachloride solution, which was stored over crystalline iodine. This procedure was used in order to eliminate, as far as possible, spurious iodide in the aqueous iodine solutions.

Kinetic runs were ordinarily carried out in 50-ml. or 100-ml. red, low-actinic, volumetric flasks fitted with ground-glass stoppers which were lightly lubricated with silicone grease. To the flasks was added first a stock solution containing sodium iodide and perchloric acid along with enough sodium perchlorate to make the final ionic strength 0.300 M. Next the iodine solution was added and finally 5.0 ml. or 10.0 ml. of a solution of 4-nitrophenol. The flask was then shaken vigorously. Zero time for the reaction was taken when one half of the solution of 4-nitrophenol had drained into the flask. All stock solutions and reaction flasks were kept in a water-bath set at 50.0 ± 0.1° and which maintained a constant temperature to ±0.02°. To stop the reactions, a freshly prepared saturated solution of sodium iodide (1 ml. per 50 ml. of reaction mixture) was injected into the reaction flasks with a syringe, the time was recorded, and the flask was shaken vigorously. The contents of the reaction flasks were rinsed into erlenmeyer flasks and titrated to a starch end-point with sodium thiosulfate solution (generally 0.006 M) delivered from a 10-ml. biuret. Kinetic runs with the most dilute solutions of iodine (0.0001 M) were run in 200-ml. flasks and were titrated with 0.012 M sodium thiosulfate. Nine reaction flasks were usually prepared for each kinetic run. Three of these flasks contained all of the reactants except 4-nitrophenol and were used as blanks in order to determine the initial stoichiometric concentration of iodine. These blanks were determined at time intervals near the beginning, middle and end of the kinetic runs; the general constancy of the blanks demonstrated that iodine was not being lost by volatilization nor being formed or lost by chemical reactions among components of the blanks.

Kinetic runs with thallium ions were run in 50-ml. flasks in a similar manner to the above except that the stock solution of perchloric acid and sodium perchlorate contained thallium perchlorate instead of sodium iodide. To the reaction flasks containing this stock solution was added enough sodium iodide to make the solution $2.00 \times 10^{4-}$ M in iodide ion (save for the precipitation of thallium iodide) and then iodine solution was added (of such concentration that the final-concentration of iodine would be below 3.3×10^{-4} M). These reactants were then allowed to equilibrate for about 0.5 hour before addition of 5.0 ml. of 4-nitrophenol. The reaction was stopped by pouring the contents of the flask into an erlenmeyer flask containing an excess of standardized sodium thiosulfate solution. The contents of the reaction flask were rinsed into the erlenmeyer flask with water and then 2.0 ml. of a saturated solution of sodium iodide in water was added. The flask was allowed to stand

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(15) E. Grovenstein, Jr., and U. V. Henderson, Jr., *J. Am. Chem. Soc.*, **78**, 569 (1956).

(16) E. Grovenstein, Jr., and G. A. Ropp, *ibid.*, **78**, 2560 (1956).

(17) L. G. Cannell, *ibid.*, **79**, 2927, 2932 (1957).

(18) A recent admirable investigation of the kinetics of iodination of 2,4-dichlorophenol [W. C. Buss and J. E. Taylor, *J. Am. Chem. Soc.*, **82**, 5991 (1960)] has emphasized that all published data still leave the detailed mechanism of iodination of phenols uncertain. While we are in full accord with this general view, some criticism of specific mechanistic claims made in this paper appears proper. In the first place, one of us never stated that the iodination of phenol "must proceed by a similar mechanism" to that proposed for bromodecarboxylation of 3,5-dibromo(2 or 4)-hydroxybenzoic acid; it was merely pointed out that a similar mechanism would accommodate all the known facts.[15] In the second place we do not understand how the statement "*There is then no experimental proof of the quinoid complex* [in bromodecarboxylation and bromodesulfonation]" can be made in light of the published record on bromodecarboxylation[15,16] and bromodesulfonation.[17] The experimental methods which were offered in support of quinoid intermediates in these brominations are very similar to those which were used to establish quinoid intermediates in azo-coupling reactions[8] and are rather similar to some of the techniques used for establishing the intermediacy of carbonium ions (see ref. 13, pp. 360–371) and methylenes [J. Hine, "Physical Organic Chemistry," McGraw–Hill Book Co., New York, N. Y., 1956, pp. 131–133] in reactions of alkyl halides.

(19) A. Langseth and A. Klit, *Kgl. Danske Videnskab. Selskab, Mat.-fys. Medd.*, XV, No. 13, 7 (1937).

(20) E. L. Martin and L. F. Fieser, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 570.

(21) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 326.

(22) C. K. Ingold, C. G. Raisen and C. L. Wilson, *J. Chem. Soc.*, 1637 (1936); A. P. Best and C. L. Wilson, *ibid.*, 28 (1938).

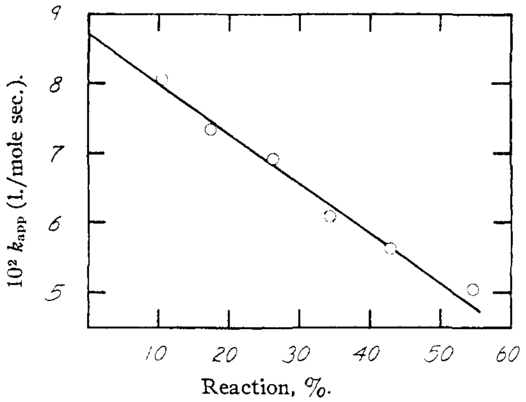

Fig. 1.—Integrated second-order rate constants *vs.* percentage reaction for 4-nitrophenol in aqueous solution at 50.0°; $(NaI)_0 = 0.250 \times 10^{-4}$ *M*, $(I_2)_0 = 1.396 \times 10^{-4}$ *M*, $(HClO_4) = 0.00982$ *M*, $(NaClO_4) = 0.290$ *M*.

for a few minutes to ensure complete precipitation of thallium iodide and the solution was filtered through two medium porosity filter papers on a Büchner funnel under mild vacuum. The clear or pale yellow solution was then back titrated in presence of starch with a standardized iodine–sodium iodide solution (0.005 *M*) until a pale blue-green color was attained and then back titrated to a colorless solution with sodium thiosulfate. If more than a few drops of thiosulfate solution had to be added, the end-point was not always sharp.

Apparent second-order rate constants (k_{app}) for disappearance of iodine were calculated by use of the integrated rate equation

$$k_{app} = \frac{2.303}{(b - a)t} \log \frac{a(b - x)}{b(a - x)}$$

where k_{app} is expressed in units of liter mole^{-1} second^{-1}, *a* is the initial molar concentration of 4-nitrophenol, *b* is the initial molar concentration of iodine (stoichiometric concentration as determined by thiosulfate titration) and *x* is the molar concentration of iodine reacted at time *t*.

Results and Discussion

Kinetics of Iodination.—On the basis of the reported data for iodination of phenol,[14] it was to be anticipated that in an aqueous solution of constant hydrogen and iodide ion concentration the rate of disappearance of titrimetric iodine would be proportional to the stoichiometric concentration of both 4-nitrophenol and iodine; therefore, apparent second-order rate constants (k_{app}) were calculated on this basis. That this relationship holds is indicated by the data of Table I, especially the runs at 1.000 *M* NaI and 0.00982 *M* HClO₄ which cover a tenfold change of concentration of 4-nitrophenol and a 2.5-fold change of concentration of iodine. The molar ratio of phenol to iodine was always at least 3.7 and was generally some 25 in the present work in order that principally only monoiodination of 4-nitrophenol occur.[23] Since hydrogen iodide is a product of the reaction, frequently the iodide ion concentration and sometimes the hydrogen ion concentration vary appreciably during a kinetic run. If such is the case, then k_{app} falls as reaction proceeds and the values of k_{app} recorded in Table I were obtained by extrapolation to zero per cent. reaction (thus see Fig. 1). Where both the initial hydrogen ion and the iodide ion concentrations were sufficiently high, the values of k_{app} were satisfactorily constant throughout a kinetic run (for an example see Table II). For a more detailed treatment of the reaction kinetics of individual runs see the Appendix.

TABLE I

KINETIC DATA FOR IODINATION OF 0.00770 *M* AQUEOUS SOLUTIONS OF 4-NITROPHENOL AT 50.0°, $\mu = 0.300$ *M*

$10^4 \times (NaI)_0$, moles/l.	$10^4 \times [I^-]_0$, moles/l.	$10^4 \times (I_2)_0$, moles/l.	$10^3 k_{app}$, l./mole sec.	$10^3 k^*$, l./mole sec.	$10^7 k^* \times [I^-]_0$, sec.$^{-1}$
		$[HClO_4] = 0.001091$ *M*			
1.000	0.918	1.914	348	364	334
2.000	1.842	1.914	197	215	396
2.000	1.754	3.11	193	210	368
3.00	2.67	2.89	130	147	392
6.00	5.43	2.70	56.0	70.9	385
8.00	7.21	3.01	43.0	58.2	420
		$[HClO_4] = 0.00327$ *M*			
0.500	0.437	3.01	169	172	75.2
1.000	0.872	3.12	117	122	106
2.50	2.21	2.93	49.0	54.3	120
5.00	4.51	2.68	24.9	30.4	138
25.0	21.4	6.96	3.24 ± 0.12[a]	6.64	142
		$[HClO_4] = 0.00982$ *M*			
0.250	0.234	1.396	87.5	88.5	20.7
.500	.455	2.07	66.0	67.5	30.7
.500	.436	3.06	64.0	65.4	28.5
1.000	.914	2.02	40.0	41.8	38.2
1.000	.825	4.49	40.4	42.0	34.7
1.000	.812	4.90	41.0	42.6	34.6
1.000	.910	2.10	39.0[b]	40.7[b]	37.1[b]
1.000	.910	2.10	39.0[c]	40.7[c]	37.1[c]
2.50	2.12	4.06	17.9	19.8	41.9
5.00	4.25	4.33	8.70	10.5	44.7
12.00	10.73	3.69	2.78	4.24	45.6
25.0	22.3	5.12	1.095 ± 0.029[a]	2.29	51.2
25.0	22.3	5.25	1.118 ± .030[a]	2.34	52.0
65.0	61.6	4.57	0.199 ± .004[a]	0.798	49.1
125.0	121.6	3.98	0.0617 ± .0011[a]	0.430	52.2
		$[HClO_4] = 0.0491$ *M*			
0.500	0.444	2.65	15.9	16.2	7.21
1.000	0.890	2.63	9.65	10.1	8.96

[a] Average value of k_{app} and mean deviation; values of k_{app} for which no mean deviation is given were obtained by extrapolation of k_{app} to zero per cent. reaction. [b] $(4\text{-Nitrophenol})_0 = 0.000770$ *M*. [c] $(4\text{-Nitrophenol})_0 = 0.00257$ *M*.

TABLE II

KINETIC DATA FOR IODINATION OF 4-NITROPHENOL IN WATER AT 50.0°

$(O_2NC_6H_4OH)_0 = 0.00770$ *M*, $(I_2)_0 = 0.0003984$ *M*, $(NaI)_0 = 0.01250$ *M*, $(HClO_4)_0 = 0.00982$ *M*, $(NaClO_4) = 0.2777$ *M*; 50.0 ml. of reaction mixture titrated with 0.005991 *M* $Na_2S_2O_3$.

Time × 10^{-3}, sec.	Titer, ml.	$k_{app} \times 10^5$, l./mole sec.	Reaction, %
0	6.65		0
249.1	5.95	6.02	10.5
503.0	5.26	6.09	20.9
850.4	4.41	6.33	33.6
1372	3.45	6.30	48.1
1803	2.88	6.13	56.6
	Av.	6.17 ± 0.11	

The variation of k_{app} with initial concentration of iodide ion has been studied in some detail as recorded in Table I. In the first place k_{app} would be expected to decrease with increasing concentration of iodide ion because of the conversion of iodine into

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[23] *Cf.* W. Körner, *Jahresber. Fortschr. Chem.*, 616 (1867); *Z. Chem., N.F.*, **4**, 324 (1868); Beilstein's "Handbuch der Organischen Chemie," 4th ed., Verlag von Julius Springer, Berlin, 1923, Vol. VI, p. 228.

comparatively unreactive[14,24] triiodide ion. Correction can be made for this reaction by use of the equilibrium constant K_1 for triiodide formation.

$$K_1 = [\mathrm{I}^-_3]/[\mathrm{I}_2][\mathrm{I}^-] \quad (1)$$

At 50°, K_1 has been reported[25] to be 490 l. mole^{-1} and this constant has been used to calculate the values of k^* reported here. The quantity k^* is defined by the relation

$$k^* = k_{\mathrm{app}} \frac{(\mathrm{I}_2)}{[\mathrm{I}_2]} \quad (2)$$

Here, as in other sections of this paper, entities enclosed in brackets refer to the actual concentration of the species shown, while those in parentheses refer to the stoichiometric concentration, in this case the concentration of iodine as determined by thiosulfate titration. The quantity k^* should remain constant with variation of iodide ion concentration at constant hydrogen ion concentration if the iodination is first order in the species I_2 and zero order in I^-. According to Table I while k^* is less variable than k_{app}, both quantities decrease rapidly with increasing iodide ion concentration. The quantity k^* $[\mathrm{I}^-]$ should remain constant with variation of iodide ion concentration at constant hydrogen ion concentration if the iodination is first order in the species I_2 and inverse first order in I^-. According to Table I while $k^*[\mathrm{I}^-]$ is much less variable than k^*, $k^*[\mathrm{I}^-]$ at a hydrogen ion concentration of 0.00982 M increases some 2.5-fold as the stoichiometric iodide concentration increases from 2.5 × 10^{-5} M to 1250 × 10^{-5} M. In fact k^* $[\mathrm{I}^-]$ is essentially constant in the range of $[\mathrm{I}^-]$ of 250 × 10^{-5} M to 1250 × 10^{-5} M but decreases ever more rapidly with decrease in iodide concentration below this range. The iodination of 4-nitrophenol is, therefore, first order in $[\mathrm{I}_2]$ and inverse first order in $[\mathrm{I}^-]$ at the higher range of iodide ion concentrations studied, but the order in $[\mathrm{I}^-]$ appears to approach zero as the concentration of iodide ion becomes very small.

The variation of k_{app} with the concentration of hydrogen ion has been studied as summarized in Table III. At high iodide concentrations, thus at $[\mathrm{I}^-]$ of 22 × 10^{-4} M, $k^*[\mathrm{H}^+]$ remains constant as the hydrogen ion concentration is tripled. The same relationship appears to hold at $[\mathrm{I}^-]$ near 2 × 10^{-4} M over a ninefold change of $[\mathrm{H}^+]$. At $[\mathrm{I}^-]$ of 0.9 × 10^{-4} M, however, while k^* $[\mathrm{H}^+]$ is essentially constant as the hydrogen ion concentration is increased from 1.09 × 10^{-3} M to 9.82 × 10^{-3} M, a further increase to 49.1 × 10^{-3} M produces some 20% increase in k^* $[\mathrm{H}^+]$. Finally at an iodide ion concentration of 0.44 × 10^{-4} M, $k^*[\mathrm{H}]^*$ appears to increase with increasing $[\mathrm{H}^+]$ throughout the range of the experiments. Throughout the higher range of iodide ion concentration studied, therefore, the iodination of 4-nitrophenol is inverse first order in $[\mathrm{H}^+]$ while at the lower range of iodide ion concentration the order in $[\mathrm{H}^+]$ becomes less than unity.

In conclusion, at the high concentrations of iodide ion used in the present work the pattern of kinetics for 4-nitrophenol is like that reported for phenol[14] at still higher concentrations of iodide ion (0.1 to 0.4 M). However, at low concentrations of iodide ion, the kinetics of iodination of 4-nitrophenol changes to a complex form which is of non-integral order in both iodide ion and hydrogen ion concentrations. Similar but less extensive kinetic results were obtained with 4-nitrophenol-2,6-d_2 and are recorded in Table IV. The kinetic pattern for iodination of 4-nitrophenol resembles that reported earlier for bromodecarboxylation[15] of 3,5-dibromo-4-hydroxy- and 3,5-dibromo-2-hydroxy-benzoic acids.

TABLE III

VARIATION OF $k^*[\mathrm{H}^+]$ WITH $[\mathrm{H}^+]$ FOR IODINATION OF 4-NITROPHENOL IN WATER AT 50.0°

$[\mathrm{I}^-]$ × 10^4, moles/l.	$[\mathrm{H}^+]$, moles/l.	$k^*[\mathrm{H}^+]$ × 10^4, sec.$^{-1}$	$[\mathrm{I}^-]$ × 10^4, moles/l.	$[\mathrm{H}^+]$, moles/l.	$k^*[\mathrm{H}^+]$ × 10^4, sec.$^{-1}$
0.444	0.0491	7.97	2.12	0.00982	1.94
.445	.00982	6.53	2.21	.00327	1.78
.437	.00327	5.63	1.75	.00109	2.29
.890	.0491	4.95	2.66	.00109	1.60
.914	.00982	4.11	4.25	.00982	1.03
.872	.00327	3.99	4.51	.00327	1.00
.918	.001091	3.97	22.3	.00982	0.227
			21.4	.00327	0.217

TABLE IV

KINETIC DATA FOR IODINATION OF 0.00770 M AQUEOUS SOLUTIONS OF 4-NITROPHENOL-2,6-d_2 AT 50.0°, $\mu = 0.300$ M, $[\mathrm{HClO}_4] = 0.00982$ M

10^4 × $(\mathrm{NaI})_0$, moles/l.	10^4 × $[\mathrm{I}^-]_0$, moles/l.	10^4 × $(\mathrm{I}_2)_0$, moles/l.	$10^3 k_{\mathrm{app}}$, l./mole sec.	$10^3 k^*$, l./mole sec.	$10^7 k^*$ × $[\mathrm{I}^-]_0$, sec.$^{-1}$
0.250	0.236	1.238	26.2	26.5	6.25
0.500	.453	2.17	15.8	16.1	7.32
1.000	.906	2.22	8.67	9.05	8.20
5.00	4.39	3.47	2.00	2.43	10.7
5.00	3.95	6.47	2.08[a]	2.48[a]	9.81[a]
25.0	22.2	5.29	0.206 ± 0.006[b]	0.431	9.58
25.0	22.0	5.75	0.255[a]	.530[a]	11.7[a]
65.0	59.9	6.84	0.0495[a]	.195[a]	11.7[a]

[a] 4-Nitrophenol-2,6-d_2 was of partially deuterated sample A. Unless otherwise indicated the 4-nitrophenol-2,6-d_2 was of sample B. [b] Average value of k_{app} and mean deviation; values of k_{app} for which no mean deviation is given were obtained by extrapolation of k_{app} to zero per cent. reaction.

Interpretation of the Kinetics of Iodination.—The mechanism of iodination of 4-nitrophenol (ArHOH) cannot consist simply of the attack of hypoiodous acidium ion ($\mathrm{H}_2\mathrm{OI}^+$) or iodine cation ($\mathrm{I}^+$) upon 4-nitrophenol anion (ArHO^-) as has been proposed for phenol[14] since such a mechanism (I), regardless of whether or not it is concerted or two stage, demands that the rate of reaction after correction for formation of triiodide anions (*i.e.*, k^*) be inversely proportional to the concentration of iodide ion at low as well as high iodide ion concentrations or that $k^*[\mathrm{I}^-]$ be constant.

Another possible mechanism (II) is that 4-nitrophenol or 4-nitrophenoxide anion undergoes rate-determining attack either by a concerted or two-stage mechanism both by molecular iodine and by hypoiodous acidium ion (or other species of similar iodide ion dependence such as HOI or I^+). At constant hydrogen ion concentration this mechanism has the kinetic form

$$\text{rate} = k[\mathrm{ArHOH}][\mathrm{I}_2] + k'[\mathrm{ArHOH}][\mathrm{I}_2]/[\mathrm{I}^-] \quad (3)$$

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[24] E. Berliner, *J. Am. Chem. Soc.*, **72**, 4003 (1950).

[25] M. Davies and E. Gwynne, *ibid.*, **74**, 2748 (1952).

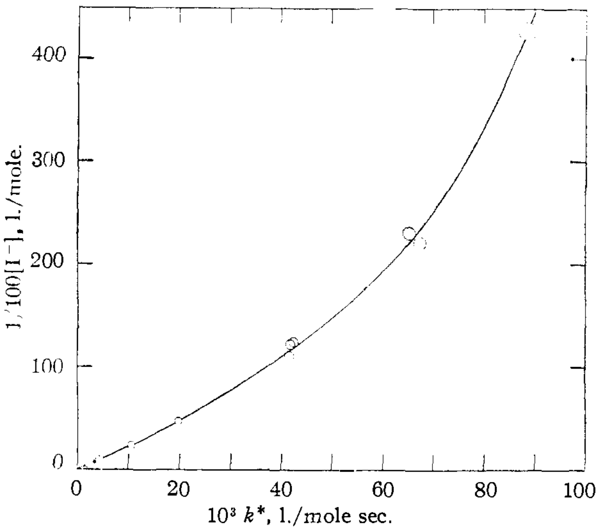


Fig. 2.—Variation of k^* with $1/[I^-]$ for 4-nitrophenol in 0.00982 M perchloric acid at 50.0°.

An analogous mixed mechanism has been proposed to account for the kinetics of iodination of tyrosine,[26] histidine[27] and certain pyrroles.[28] As a test for this mechanism for 4-nitrophenol, since by definition of k_{app}

$$\text{rate} = k_{app}(\text{ArHOH})(\text{I}_2) \tag{4}$$

and since under the present conditions of acidity to a good approximation (ArHOH) = [ArHOH], then

$$k_{app}\,(\text{I}_2)/[\text{I}_2] \equiv k^* = k + k'/[\text{I}^-] \tag{5}$$

According to this equation at sufficiently high iodide ion concentration (where $k'/I^- \ll k$), k^* should become almost independent of the iodide ion concentration, while at sufficiently low iodide ion concentration k^* should become inversely dependent on the iodide ion concentration. However our results are just the opposite of this—at high iodide ion concentrations k^* was inversely proportional to the iodide ion concentration while as the iodide ion concentration decreased k^* approached zero order dependence in concentration of iodide ion. Alternatively the failure of eq. 5 to fit our data for 4-nitrophenol can be demonstrated by the failure of a plot of k^* *vs.* $1/[\text{I}^-]$ to give a straight line (see Fig. 2).

To account for the observed iodide ion and hydrogen ion dependency of k_{app}, the following mechanism (III) is proposed for 4-nitrophenol

$$\text{ArHOH} \overset{\text{fast}}{\rightleftharpoons} \text{ArHO}^- + \text{H}^-; \quad K_2 = \frac{[\text{ArHO}^-][\text{H}^+]}{[\text{ArHOH}]} \tag{6}$$

$$\text{ArHO}^- + \text{I}_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{ArHOI} + \text{I}^- \tag{7}$$

$$\text{ArHOH} + \text{I}_2 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \text{ArHOI} + \text{H}^+ + \text{I}^- \tag{8}$$

$$\text{ArHOI} + \text{H}_2\text{O} \xrightarrow{k_3} \text{ArOI}^- + \text{H}_3\text{O}^+ \qquad (9)^{29}$$

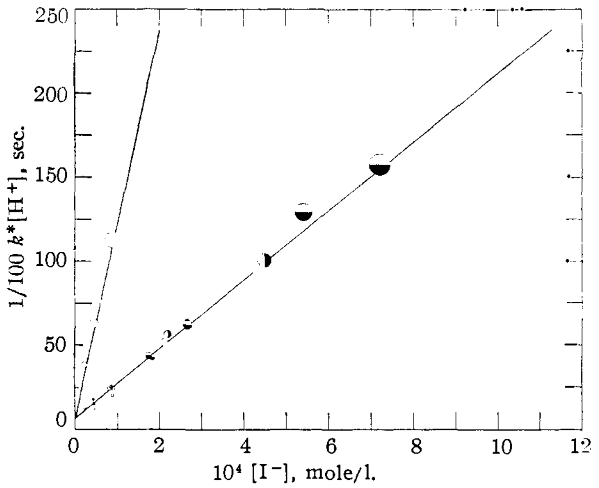
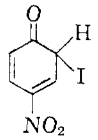


Fig. 3.—$[\text{I}^-]$ *vs.* $1/100k^*[\text{H}^+]$ for 4-nitrophenol-2,6-d_2 (upper curve) and 4-nitrophenol (lower curve) at $[\text{HClO}_4]$ equal 0.0491 M (□), 0.00982 M (○), 0.00327 M (◑) and 0.001091 M (◒); points drawn with radius equal 4% of $1/100k^*$ $[\text{H}^+]$ and the curves drawn so as to minimize the deviation for all of the kinetic runs of Tables I and IV at $[\text{HClO}_4]$ equal 0.00982 M.

where ArHOI is a reactive intermediate which is presumed to have the structure I.



I

This intermediate is assumed to be formed in small concentration relative to that of 4-nitrophenol. Application of the steady-state approximation gives

$$k_1[\text{ArHO}^-][\text{I}_2] + k_2[\text{ArHOH}][\text{I}_2] = k_{-1}[\text{ArHOI}][\text{I}^-] + k_{-2}[\text{ArHOI}][\text{H}^+][\text{I}^-] + k_3[\text{ArHOI}] \tag{10}$$

Substitution for $[\text{ArHO}^-]$ from 6 and solving for [ArHOI] gives

$$[\text{ArHOI}] = \frac{k_1K_2[\text{ArHOH}][\text{I}_2] + k_2[\text{ArHOH}][\text{I}_2][\text{H}^+]}{\{k_{-1}[\text{I}^-] + k_{-2}[\text{H}^+][\text{I}^-] + k_3\}\ [\text{H}^+]} \tag{11}$$

Since

$$\text{rate} = k_3[\text{ArHOI}] = k_{app}\,(\text{ArHOH})(\text{I}_2) \tag{12}$$

substitution of 11 into 12 gives

$$k_{app}\frac{(\text{I}_2)[\text{H}^+]}{[\text{I}_2]} = k^*[\text{H}^+] = \frac{k_1K_2 + k_2[\text{H}^+]}{(k_{-1})/k_3)[\text{I}^-] + (k_{-2}/k_3)[\text{H}^+][\text{I}^-] + 1} \tag{13}$$

Application of equilibrium statistics and the principle of microscopic reversibility[30] to reactions 6, 7 and 8 leads to the relationship

$$k_1K_2/k_{-1} = k_2/k_{-2} \tag{14}$$

which must hold even away from equilibrium. From 13 and 14 there may be obtained

$$\frac{1}{k^*[\text{H}^+]} = \frac{k_{-1}[\text{I}^-]}{k_1k_3K_2} + \frac{1}{k_2[\text{H}^+] + k_1K_2} \tag{15}$$

According to 15 a plot of $1/k^*[\text{H}^+]$ *vs.* $[\text{I}^-]$ should give a series of parallel straight lines for each

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[26] C. H. Li, *J. Am. Chem. Soc.*, **64**, 1147 (1942); **66**, 228 (1944).

[27] C. H. Li, *ibid.*, **66**, 225 (1944).

[28] K. W. Doak and A. H. Corwin, *ibid.*, **71**, 159 (1949).

[29] This step is presumed to be subject to general base catalysis. Conceivably the un-ionized form of the phenol is produced directly in this step by simultaneous proton addition to oxygen and proton withdrawal from carbon.

[30] A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 202.

hydrogen ion concentration. Such a plot is shown in Fig. 3; however, the data for 4-nitrophenol fall reasonably well upon a single straight line. Such a result might be expected from eq. 15 either at high iodide ion concentrations (which could make the first term on the right-hand side of 15 large compared to the second term) or at low hydrogen ion concentrations where $k_2[\mathrm{H}^+] \ll k_1K_2$. At low iodide ion and high hydrogen ion concentrations deviations from the single straight line drawn for 4-nitrophenol in Fig. 3 are to be expected with the points at a constant iodide concentration lying at larger values of $1/k^*[\mathrm{H}^+]$ the smaller the hydrogen ion concentration. Some of the deviations of the points from the line in Fig. 3 at low iodide ion concentration can be explained in this manner, but because of the compressed scale in Fig. 3 for data at low iodide ion concentration the relationship is more clearly presented by Table III. The trend here in the values of $k^*[\mathrm{H}^+]$ with changes in hydrogen ion concentration for runs at constant iodide ion concentration are as expected from eq. 15. The slope of the line for 4-nitrophenol in Fig. 3 corresponds to a value for $k_{-1}/k_1k_3K_2$ of $205 \pm 9 \times 10^5$ sec. l./mole and the intercept gives the value for $1/\{k_2[\mathrm{H}^+] + k_1K_2\}$ of 660 ± 60 sec. at $[\mathrm{H}^+] = 0.00982$ *M*.[31] From the latter value and similarly derived values from Table I, the individual values of k_2 and k_1K_2 are calculated to be approximately 0.051 l. mole^{-1} sec.$^{-1}$ and 0.0010 sec.$^{-1}$, respectively. From these data and the ionization constant of 4-nitrophenol which is reported[32] to be 12.7×10^{-8} at 50°, it is estimated that k_1/k_2 is 2×10^5, which represents the reactivity of 4-nitrophenoxide ion relative to 4-nitrophenol. The reversibility ratio k_{-1}/k_3 is computed to be about 2.0×10^4 l. mole^{-1}; according to this ratio at an iodide ion concentration of 10^{-4} *M* some two times as much of the intermediate I reverts back to 4-nitrophenoxide ion as passes on to final product. Finally the reversibility ratio k_{-2}/k_{-3} is estimated to be 1.0×10^6 l.^{2}/mole^2 and, therefore, at an iodide ion concentration of 10^{-4} *M* and a hydrogen ion concentration of 10^{-2} *M* intermediate I reverts to 4-nitrophenol at about the same rate as it passes on to final product. Hence under the specified conditions only some 25% of the intermediate I goes directly to final product.

In conclusion, the two-stage mechanism III is able to account for the detailed dependence of the rate of iodination of 4-nitrophenol upon both the iodide ion and the hydrogen ion concentrations. In order to verify this mechanism the kinetics of iodination of 4-nitrophenol-2,6-d_2 has also been investigated.

Isotope Effect in Iodination.—The kinetic data for iodination of 4-nitrophenol-2,6-d_2 in aqueous solution is summarized in Table IV. In this table sample A is 4-nitrophenol which was equilibrated with heavy water two times while sample B was equilibrated for a third time for a period equal to that of the first two equilibrations. The near similarity of rate constants of samples A and B, the high value of the isotope effect (see discussion below) and the constancy of k_{app} at high iodide ion concentrations for sample B provide evidence that sample B is equilibrated at positions 2 and 6 with respect to deuterium and therefore contain 99% or more deuterium in these positions.

The dependence of rate of iodination of 4-nitrophenol-2,6-d_2 upon iodide ion concentration has been studied in some detail. This dependence is similar to that found for 4-nitrophenol except that k^* increases some 61-fold for the deuterium compound and only 38-fold for the protium compound as the iodide ion concentration increases 95-fold (from 0.235×10^{-4} *M* to 22.3×10^{-4} *M*). This trend is qualitatively expected on the basis of mechanism III since k_3 should be appreciably smaller for the deuterium compound than the protium compound because of a primary isotope effect; therefore eq. 7 and 8 of mechanism III are expected to be more nearly at equilibrium down to lower iodide ion concentrations for the deuterium compound. For a more quantitative comparison a plot of $1/k^*[\mathrm{H}^+]$ *vs.* $[\mathrm{I}^-]$ is given in Fig. 3 for both the protium and deuterium compounds. It is of interest to note that the two lines have, as nearly as can be judged, about the same intercept but differ widely in slope. The same intercept corresponds to a similar value of $k_2[\mathrm{H}^+] + k_1K_2$ and this is to be expected at identical values of $[\mathrm{H}^+]$ because k_2 and k_1K_2 should differ little from protium to deuterium compound since secondary isotope effects are generally small. On the other hand, the slopes of these plots correspond to values of $k_{-1}/k_1k_3K_2$ and the ratio of the slope of the line for the deuterium compound to that of the protium compound, which from Fig. 3 is 5.6, corresponds to $k_{3\mathrm{H}}/k_{3\mathrm{D}}$ if the isotope effects upon k_{-1}, k_1 and K_2 are negligible in comparison with the primary isotope effect upon k_3.

The effect of iodide concentration upon the magnitude of the apparent deuterium isotope effect is given in Table V. The apparent deuterium isotope effect is taken as the ratio of k^* of the protium compound to k^* of the deuterium compound ($k^*_{\mathrm{H}}/k^*_{\mathrm{D}}$). It is seen that this isotope effect varies from

TABLE V

VARIATION OF ISOTOPE EFFECT WITH IODIDE ION CONCENTRATION AT 50.0°, $[\mathrm{HClO_4}] = 0.00982$ *M*, $\mu = 0.300$ *M*

$[\mathrm{I}^-] \times 10^4$, moles/l.	$k^*_{\mathrm{H}} \times 10^3$, l./mole sec.	$k^*_{\mathrm{D}} \times 10^4$, l./mole sec.	($k^*_{\mathrm{H}}/k^*_{\mathrm{D}}$) Found	($k^*_{\mathrm{H}}/k^*_{\mathrm{D}}$) Calcd.
60	0.798	0.155[a]	5.2[a]	5.6
22.2	2.31	.430	5.4	5.5
		.422[a]	5.5[a]	
4.2	10.5	2.43	4.3	5.3
		1.90[a]	5.5[a]	
0.90	43.3	9.06	4.8	4.4
.45	66.4	16.2	4.1	3.7
.235	88.5	26.5	3.3	3.1
.095	129[b]	56[b]	2.3[b]	2.1

[a] Value of k^*_{D} from 4-nitrophenol-2,6-d_2 of sample A corrected for presence of 6% non-deuterated 4-nitrophenol or an equivalent amount (11%) of 4-nitrophenol-2-*d*. [b] Values of k_{app} ($\simeq k^*$) at 10% reaction at which percentage reaction the $[\mathrm{I}^-]$ had climbed from 0.095×10^{-4} to 0.21×10^{-4} *M*.

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[31] Because of limitations of space it is not practical to show all of the data of Table I in Fig. 3. Moreover the slope and intercept which are drawn in Fig. 3 and cited in the discussion were most accurately obtained by numerical calculations which gave the intercept which corresponds to the smallest average deviation in slope for all the pertinent data of Table I.

[32] H. Lunden, *J. chim. phys.*, **5**, 586 (1907).

5.4 to 2.3 as the iodide ion concentration decreases from 22.3×10^{-4} M to about 0.15×10^{-4} M. This variation of isotope effect with iodide ion concentration is in fair quantitative accord with expectations based upon mechanism III. Thus on the assumption that an appreciable isotope effect exists only for the step involving k_3 (which will be designated $k_{3\mathrm{H}}$ and $k_{3\mathrm{D}}$ for the protium and deuterium compounds, respectively), division of eq. 15 for the deuterium compound by the same equation written for the protium compound gives

$$\frac{k^*_{\mathrm{H}}\,[\mathrm{H}^+]_{\mathrm{H}}}{k^*_{\mathrm{D}}\,[\mathrm{H}^+]_{\mathrm{D}}} = \frac{k_{-1}[\mathrm{I}^-]_{\mathrm{D}}\,/k_{3\mathrm{D}}\,k_1K_2 + 1/(k_2[\mathrm{H}^+]_{\mathrm{D}} + k_1K_2)}{k_{-1}[\mathrm{I}^-]_{\mathrm{H}}\,/k_{3\mathrm{H}}\,k_1K_2 + 1/(k_2[\mathrm{H}^+]_{\mathrm{H}} + k_1k_2)} \tag{16}$$

If values of k^*_{H} and k^*_{D} are compared always at the same value of $[\mathrm{H}^+]$ and $[\mathrm{I}^-]$ for the deuterium and protium compounds and if as from previous considerations $k_{3\mathrm{H}}/k_{3\mathrm{D}} = 5.6$, eq. 16 simplifies to

$$\frac{k^*_{\mathrm{H}}}{k^*_{\mathrm{D}}} = \frac{5.6[\mathrm{I}^-]k_{-1}/k_{3\mathrm{H}}\,k_1K_2 + 1/(k_2[\mathrm{H}^+] + k_1K_2)}{[\mathrm{I}^-]k_{-1}/k_{3\mathrm{H}}\,k_1K_2 + 1/(k_2[\mathrm{H}^+] + k_1K_2)} \tag{17}$$

All the constants in eq. 17 are known from the slope and intercept of the plot of the protium compound in Fig. 3. Equation 16 or 17 therefore permits, from a detailed study of the kinetic dependence of the protium compound upon the iodide ion concentration, prediction to be made of the apparent isotope effect (or of k^*_{D}) at any iodide ion concentration provided that one measurement of k^*_{D} has been made previously at a sufficiently high iodide concentration to permit calculation of $k_{3\mathrm{H}}/k_{3\mathrm{D}}$. The results of such calculation of $k^*_{\mathrm{H}}/k^*_{\mathrm{D}}$ are presented in the right-hand column of Table V. The calculated values on the whole compare favorably with those determined by experiment. This agreement of calculated and experimental values provides additional evidence for mechanism III.

Kinetic Studies in Presence of Thallous Ion.—To provide confirmation of the drop of the apparent isotope effect with decreasing iodide ion concentration, some kinetic studies of iodination of 4-nitrophenol and 4-nitrophenol-2,6-d_2 were made in presence of thallium ions. Thallium ions in large excess are expected to keep the iodide ion concentration nearly constant throughout a kinetic run by precipitation of the iodide ion which is formed as a thallium iodide. The chemistry of thallium iodide–iodine solutions has been studied at 25° in aqueous solution by Maitland and Abegg.[33] These workers found that at concentrations of iodine below 0.76×10^{-5} M TlI precipitated, at iodine concentrations $> 0.76 \times 10^{-5}$ M but $< 3.3 \times 10^{-4}$ M $\mathrm{Tl_6I_8}$ precipitated, while at iodine concentrations above 3.3×10^{-4} M $\mathrm{TlI_3}$ precipitated. However, the present kinetic studies were at 50°, the initial concentration of iodine was below 3.3×10^{-4} M and the final concentration of iodine was well above 0.76×10^{-5} M; therefore $\mathrm{Tl_6I_8}$ is evidently the composition of the thallium iodide precipitate formed. The solubility of TlI has been measured[34] in the temperature range of 0 to 25°; extrapolation of these data to 50° gives a value of 10^{-6} mole^2/l.^{2} for the solubility product, $[\mathrm{Tl}^+][\mathrm{I}^-]$, of thallium iodide. From this value at a thallous ion concentration of 0.05 M, a solution saturated with TlI should have an iodide ion concentration of 0.2×10^{-4} M. The formation of $\mathrm{Tl_6I_8}$ if this occurs at the same limiting concentration as at 25°, would reduce this iodide ion concentration by a factor of only about one-half; but considering the approximations involved (especially the neglect of the effect of ionic strength which would be expected to have the opposite effect), this effect is negligible. However, the formation of $\mathrm{Tl_6I_8}$ makes the iodide ion concentration somewhat dependent on the iodine concentration; it can be calculated that a reaction which starts with an initial iodine concentration of 3×10^{-4} M increases in iodide ion concentration by about 30% at the attainment of 60% reaction. Examination of Table I shows that such an increase in iodide ion concentration would be expected to decrease the reaction rate constant by less than 30% for 4-nitrophenol; an even smaller decrease is expected for the integrated constant k_{app} since the integrated value would pertain to some sort of mean iodide ion concentration. It is therefore not surprising that k_{app} is almost constant for iodination of 4-nitrophenol in presence of 0.0500 M $\mathrm{TlClO_4}$ (see Table VI). The average value of k_{app} from four such runs up to 50% reaction is $2.37 \pm 0.15 \times 10^{-2}$ l./mole sec.; the corresponding average value of k_{app} from two runs upon 4-nitrophenol-2,6-d_2 is 0.90 ± 0.08. These values of k_{app} are not readily comparable to other values which have been obtained because the formation of $\mathrm{Tl_6I_8}$ makes the kinetically effective iodine concentration different from the titrimetric value. Because of the almost identical conditions for protium and deuterium compounds the correction factor for this effect will cancel in the ratio of $(k_{\mathrm{app}})_{\mathrm{H}}/(k_{\mathrm{app}})_{\mathrm{D}}$ which is here 2.6 ± 0.4. Since the iodide ion concentrations are the same, this ratio must be essentially identical with that of $k^*_{\mathrm{H}}/k^*_{\mathrm{D}}$. Therefore, kinetic investigations in presence of 0.0500 M Tl^+ give an isotope effect which is intermediate between that found near 0.15×10^{-4} and 0.234×10^{-4} M iodide ion concentration (see Table V). This reasonable result lends support to the previous conclusion that the apparent kinetic isotope effect ($k^*_{\mathrm{H}}/k^*_{\mathrm{D}}$) diminishes with decrease in iodide ion concentration.

TABLE VI

KINETIC DATA FOR IODINATION OF 4-NITROPHENOL IN AQUEOUS SOLUTION OF 0.0500 M $\mathrm{TlClO_4}$ AT 50°

$(\mathrm{O_2NC_6H_4OH})_0 = 0.00770$ M, $(\mathrm{I_2})_0 = 0.000260$ M, $(\mathrm{NaI})_0 = 0.00020$ M, $(\mathrm{HClO_4}) = 0.0491$ M, $(\mathrm{NaClO_4}) = 0.201$ M; 50.0 ml. of reaction mixture titrated with 0.006019 M $\mathrm{Na_2S_2O_3}$.

Time, sec.	Titer, ml.	$k_{\mathrm{app}} \times 10^2$, l./mole sec.	Reaction, %
0	4.32		0
692	3.83	2.26	11.3
1275	3.42	2.39	20.8
2105	2.96	2.34	31.5
2776	2.43	2.48	41.0
3773	2.16	2.24	47.6
5478	1.71	2.10	58.5
7520	1.20	(1.72)	70.9
		Av. 2.30 ± 0.12	

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[33] W. Maitland and R. Abegg, *Z. anorg. Chem.*, **49**, 341 (1906).

[34] F. Kohlrausch, *Z. physik. Chem.*, **64**, 129 (1908); G. Jones and W. C. Schumb, *Proc. Am. Acad. Arts Sci.*, **56**, 199 (1921).

Conclusions.—The one-stage termolecular mechanism (see eq. 1 and mechanisms I and II) involving any likely iodinating agent or combination thereof is unable to explain the kinetics of iodination of 4-nitrophenol, in particular the dependence of rate upon hydrogen and iodide ion concentrations and the variation of isotope effect with iodide ion concentration.

The two-stage mechanism (eq. 2 and 3) is capable of explaining all of the presently known data if the electrophilic reagent is iodine and if the mechanism is modified according to the scheme designated as mechanism III (eq. 6-9). The most novel feature of this mechanism is that it accounts for the iodide ion dependency on the basis of interaction of iodide ion with an intermediate to regenerate starting components rather than interaction of iodide ion with a suspected iodinating agent. Mechanism III is closely similar to the mechanisms proposed for bromodecarboxylation[15,16] and bromodesulfonation[17] and is similar in its general features to the mechanism of the azo-coupling reaction.[8] All of these mechanisms have in common the formation of an intermediate which, in what may be the rate-determining step, loses a proton, carbon dioxide or sulfur trioxide to give the final substituted phenol.

The chief uncertainty in mechanism III for iodination of 4-nitrophenol appears to be the structure of the intermediate. The kinetic data show merely that the intermediate consists of 4-nitrophenoxide ion and iodine cation (I^+). It cannot be said, on the basis of present evidence, whether or not water molecules are also bound in the intermediate. The simplest structure for the intermediate is that of 6-iodo-4-nitrocyclohexa-2,4-dienone (I). This structure is analogous to that of known isolable halogen derivatives of 2,4,6-trisubstituted phenols.[35] It is also similar to that of the intermediate produced during the *para* Claisen rearrangement[36] and to intermediates produced during participation of 4-aryl oxide groups in some nucleophilic substitutions.[37] The first proposal that an intermediate of this type was formed during halogenation of phenols appears to have been made by Lapworth[38] in 1901 for bromination of phenol.

Appendix

In the interpretation of the data above it was necessary to extrapolate apparent second-order rate constants to zero per cent. reaction. At the lowest iodide concentration tested (0.100×10^{-4} M) such extrapolations are apt to be inaccurate. In order to avoid this difficulty and to make more complete use of all the kinetic data from a particular run, it is necessary to solve the differential rate equation for each likely mechanism. An important simplifying assumption which is rather closely valid at low iodide ion concentration is that throughout a particular kinetic run the ratio of actual to stoichiometric iodide ion concentration is constant, *i.e.*

$$[I^-]/(I^-) = \text{constant} = B \qquad (18)$$

Thus in a run at an initial iodide ion concentration of 0.100×10^{-4} M, B has and initial value of 0.947 and rises to 0.972 at 48% reaction; and in another run at 0.250×10^{-4} M initial iodide ion concentration, B has an initial value of 0.937 and rises to 0.971 at 54.7% reaction. From eq. 18 it may be shown that

$$[I_2] = (I_2)_0 + (B - 1)(I^-)_0 + (B - 2)x \qquad (19)$$

where the subscript zeros refer to the initial concentration of a reactant or product and x is the molar concentration of iodine which has reacted at time t. If it is further assumed, as is nearly true in the runs of interest, that the concentrations of 4-nitrophenol and hydrogen ion remain constant during a kinetic run, then substitution of eq. 19 into eq. 11 and of the resultant expression into eq. 12 gives for mechanism III

$$\frac{dx}{dt} = \frac{(B - 2)[\text{ArHOH}]\,\{k_1k_3K_2 + k_2k_3[H^+]\}\left\{\dfrac{(I_2)_0 + (B - 1)(I^-)_0}{(B - 2)} + x\right\}}{B[H^+]\,\{k_{-1} + k_{-2}[H^+]\}\left\{x + (I^-)_0 + \dfrac{k_3}{B\,\{k_{-1} + k_2[H^+]\}}\right\}} \qquad (20)$$

Integration of eq. 20 leads to

$$gt = x + (h - c)\ln\left(\frac{c + x}{c}\right) \qquad (21)$$

where

$$g = \frac{(B - 2)}{B}\,\frac{k_1k_3K_2}{k_{-1}}\,\frac{[\text{ArHOH}]}{[H^+]}$$

$$c = \frac{(I_2)_0 + (B - 1)(I^-)_0}{(B - 2)}$$

$$h = (I^-)_0 + \frac{k_1k_3K_2}{k_{-1}\,B\,\{k_2[H^+] + k_1K_2\}}$$

In eq. 21 the value of c is known while g and h involve two unknown sets of constants, namely $k_{-1}/k_1k_3K_2$ and $1/\{k_2[H^+] + k_1K_2\}$. These sets of constants are the same as those which appear in eq. 15 and have been previously evaluated from the slope and intercept of the plot in Fig. 3. For the purpose of checking the applicability of eq. 21, the value of $k_{-1}/k_1k_3K_2$ was taken as 2050×10^4 sec. l./mole as derived previously and the value of $1/\{k_2[H^+] + k_1K_2\}$ was calculated for each kinetic point by use of eq. 21. Some of the results are shown in Table VII. The values of $0.1/\{k_2\,[H^+] + k_1K_2\}$ are close to that (66 sec.) obtained previously from the intercept of the plot in Fig. 3; however, a duplicate run at 0.100×10^{-4} M NaI gave a value of 47 ± 5. The value of $1/\{k_2[H^+] + k_1K_2\}$ is not greatly dependent on the value of B which is chosen; thus a 1% increase in B decreases the numerical result by less than 0.4%. Also a 5% increase in $k_{-1}/k_1k_3K_2$ decreases $1/\{k_2\,[H^+] + k_1K_2\}$

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(35) Thus see G. M. Coppinger and T. W. Campbell, *J. Am. Chem. Soc.*, **75**, 734 (1953); L. E. Forman and W. C. Sears, *ibid.*, **76**, 4977 (1954); J. A. Price, *ibid.*, **77**, 5436 (1955); L. Denivelle and R. Fort *Compt. rend.*, **235**, 1514, 1658 (1952); L. Denville, R. Fort, and J. Favre, *ibid.*, **237**, 340 (1953); E. A. Shilov and A. A. Yašnikov, *Acta Chim. Acad. Sci. Hung.*, **21**, 63 (1959) [*C. A.*, **54**, 20942 (1960)].

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TABLE VII

KINETICS OF IODINATION OF 4-NITROPHENOL IN WATER AT 50.0°

$(O_2NC_6H_4OH)_0$ = 0.00770 *M*, $(HClO_4)$ = 0.00982 *M*, $(NaClO_4)$ = 0.2902 *M*; 200.0 ml. of reaction mixture titrated with 0.01204 *M* $Na_2S_2O_3$.

Time, sec.	Titer, ml.	Reaction, %	$k_{app} \times 10^2$, l./mole sec.	$0.1/\{k_2[H^+] + k_1K_2\}$, sec.	$k^*[I^-] \times 10^6$, sec.$^{-1}$
$(NaI)_0 = 0.100 \times 10^{-4}$ *M*, $(I_2)_0 = 0.0001144$ *M*, $B = 0.950$					
0	3.80	0	(15.2)[a]	(47)[a]	(1.45)[a]
120	3.40	10.5	12.1	52	1.87
219	3.19	16.1	10.4	59	1.94
435	2.84	25.2	8.71	67	2.11
687	2.58	32.1	7.35	79	2.10
992	2.24	41.1	6.95	74	2.40
1249	1.95	48.0	6.96	67	2.70
			Av.	66 ± 7	
$(NaI)_0 = 0.250 \times 10^{-4}$ *M*, $(I_2)_0 = 0.0001396$ *M*, $B = 0.947$					
0	4.64	0	(8.75)[a]	(67)[a]	(2.07)[a]
180	4.15	10.6	8.04	62	2.52
342	3.83	17.5	7.32	65	2.64
575	3.42	26.3	6.90	59	2.96
900	3.05	34.3	6.07	66	2.98
1299	2.65	42.9	5.61	64	3.17
2061	2.10	54.7	5.02	62	3.40
			Av.	63 ± 2	

[a] Value obtained by extrapolation of k_{app} to zero per cent. reaction.

by about an equal percentage for the run at 0.100×10^{-4} *M* iodide. On the other hand, attempts to apply eq. 21 to 4-nitrophenol-2,6-d_2 have not been very successful because, in view of the some six-fold larger value of $k_{-1}/k_1k_3K_2$, $1/\{k_2[H^+] + k_1K_2\}$ is obtained as a small difference between large numbers and is therefore highly susceptable to change due to small experimental errors or to the value chosen for $k_{-1}/k_1k_3K_2$.

For mechanism I, which consists of the attack of I^+ or H_2OI^+ upon 4-nitrophenol or 4-nitrophenoxide anion by either a concerted or two-stage mechanism, on the basis of the same simplifying assumptions as used to derive eq. 21, the following integrated rate expression may be derived

$$k^*[I^-] = \frac{Bx}{(B-2)[\text{ArHOH}]t} + \frac{B[(I^-)_0 - c]}{(B-2)[\text{ArHOH}]t} \times \ln\left(\frac{c+x}{c}\right) \quad (22)$$

where all the symbols are as defined previously. For mechanism I the product k^* $[I^-]$ should be constant during a run and from run to run provided that the hydrogen ion concentration is constant. The failure of this product to remain constant in Table VII provides additional evidence against mechanism I.

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Diphenylcyclobutadienoquinone. II. Ring Opening Reactions[1]

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The earlier report on the tendency for diphenylcyclobutadienoquinone (I) to undergo ring opening, in ethanol, to give diethyl α,α'-diphenylsuccinate prompted us to examine the behavior of the diketone I in reactions with other nucleophilic reagents. With *o*-phenylenediamine it was found that the reaction with compound I was complex. In only one of the sets of experimental conditions, upon refluxing compound I in ethanol together with sodium acetate, was there formed a product which comprised the combination of one mole of each reactant. This product was shown to be a rearranged quinoxaline, 3-phenylacetyl-2-phenylquinoxaline (III). The oxime of this ketoquinoxaline when subjected to conditions which might be expected to give a typical Beckmann rearrangement cyclized to 2-benzylquino[3,4-b]quinoxaline. Methanolic sodium hydroxide also effected ring opening of the diketone I to give, as isolable products, benzaldehyde and α-keto-β,γ-diphenyl-γ-butyrolactone.

The synthesis and structure of diphenylcyclobutadienoquinone (I) prepared by the sulfuric acid hydrolysis of 1,2-diphenyl-3,3,4,4-tetrafluorocyclobutene has been described[3] together with the observation that opening of the cyclobutene ring of the diketone I occurs in ethanol solution at room temperature to give a mixture of *meso* and *racemic* diethyl α,α'-diphenylsuccinate, probably *via* a bis-phenylketene intermediate. The chemistry of this highly unsaturated compound is now discussed further; in particular, the results of reactions of the diketone I with *o*-phenylenediamine and with sodium hydroxide are presented. With these reagents cleavage of the four-membered ring also occurs.

A possible straightforward way in which to transform the diketone I into a diphenylcyclobutadiene derivative[4] would be by its reaction

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[1] This is the thirteenth publication on the chemistry of small carbon rings. For the preceding paper in this series see A. T. Blomquist and D. J. Connolly, *J. Org. Chem.*, **26**, 2573 (1961). For preliminary communications of portions of this particular investigation see: (a) Abstracts of Papers Presented at the National Meeting of the American Chemical Society in Boston, Mass., April, 1959, p. 54-O; (b) Abstracts of Papers Presented at the Sixteenth National Organic Chemical Symposium of the American Chemical Society, Seattle, Wash., June 15–17, 1959, p. 11.

[2] Support by funds from the Sage Fellowship, Summer, 1957; Procter and Gamble Fellow, Summer, 1958; American Cyanamid Fellow, Summer, 1959; Allied and Chemical and Dye Fellow, 1959–1960.

[3] A. T. Blomquist and Eugene A. LaLancette, *J. Am. Chem. Soc.*, **83**, 1387 (1961).

[4] An early envisaged method of transforming compound I into such a derivative was modeled after the photo-chemical work of Schönberg and Mustafa[5] in which it has been shown that addition of