derived pK values for the higher polycyclic methylarenes are down in the polyarylmethane region and should be amenable to direct equilibrium measurement. Unfortunately, with CsCHA the higher polycyclic benzenoid hydrocarbons rapidly form radical anions such that we have been unable to accomplish such direct measurement.

The present pK results may be related to the exchange rates of Ebel and Ritterbusch with lithium *N*-methylanilide at 150°.[23] Their relative deuterium exchange rates for TPM, DPM, and 9-methylphenanthrene give a Brønsted α of about 0.26 at 150°, a value that corresponds to ~0.37 at 25° if the effect is all in $\Delta H^{\ddagger}$. Hence, this reaction is much like that with LiCHA except that the anilide ion is a weaker base and higher temperatures are required for equivalent reactivities.

Aromatic Halogenation. IV.[1a] Kinetics and Mechanism of Iodination of Phenol and 2,6-Dibromophenol

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Abstract: The kinetics of iodination of phenol has been studied at 25.0° in dilute aqueous solutions of perchloric acid. From the observed dependence of rate upon the concentrations of phenol, iodine, iodide ion, and hydrogen ion, a mechanism is proposed wherein at very low iodide ion concentration molecular iodine makes a rate-determining attack upon phenoxide anion to give an intermediate iodocyclohexadienone; at high iodide ion concentration, this intermediate is formed in a reversible reaction and the rate-determining step shifts to deprotonation of the intermediate. This mechanism is confirmed by a similar study upon phenol-*2,4,6-d*$_3$. The isotope effect (k_H/k_D) increased from a value of 3.0 at an iodide ion concentration of 3×10^{-7} *M*, at which the iodination step is partially rate determining, to a limiting value of 6.2 at high iodide ion concentrations. In acetate buffers at high iodide ion concentration, acetate ion helps deprotonate the intermediate iodocyclohexadienone with an isotope effect which is about the same as that in dilute aqueous perchloric acid. In acetate buffer the isotope effect decreases with decreasing iodide ion concentration; however, the minimum value observed for the isotope effect was 3.4 at 3×10^{-7} *M* iodide ion rather than a smaller value that obtained in dilute aqueous perchloric acid solution. This unexpected result is explained on the basis of participation of acetyl hypoiodite as an iodinating agent at very low iodide ion concentration. The previously studied kinetics of iodination of adrenochrome may be explained by a mechanism similar to that proposed for phenol. Large isotope effects were observed in iodination and small isotope effects in bromination of 2,6-dibromophenol.

According to previous investigations,[2,3] the iodination of phenol in aqueous solution follows the rate expression

$$d(I_2)/dt = k[PhOH][I_2]/[H^+][I^-] + k'[PhOH][I_2][HA]/[H^+]^2[I^-] \quad (1)$$

where HA is a buffer acid such as acetic acid. Here, as in other sections of this paper, entities enclosed in brackets refer to the actual concentration of the species shown, whereas those in parentheses refer to a stoichiometric concentration, thus the concentration of iodine as determined by thiosulfate titration. On the assumption that attack of the iodinating agent upon the substrate occurs in the rate-determining step, the first term of this equation has been interpreted[2,3] to involve attack of HOI upon un-ionized phenol or, alternatively, of H_2OI^+ or I^+(aq) upon phenoxide ion; the second term to involve a general acid catalyzed attack of HOI or attack of AI (*e.g.*, acetyl hypoiodite) upon phenoxide ion. With the discovery[4] that iodination of phenol-*2,4,6-d*$_3$ occurs considerably more slowly than iodination of ordinary phenol and that, therefore, breaking of the C–H bond of phenol is part of the rate-determining step, it was recognized that the nature of the iodinating agent could not be specified since, very likely, under the kinetic conditions so far investigated, transfer of iodine cation from an iodinating agent to phenol occurs in a rapid, reversible step prior to proton loss.

While experimental verification of the mechanism of iodination of phenol remains at this indefinite stage, a detailed study[5] of the iodination of *p*-nitrophenol has revealed a mechanism in which molecular iodine attacks *p*-nitrophenol or, more readily, *p*-nitrophenoxide ion in a reversible process to give an intermediate which in a second, generally rate-determining step, loses a proton from carbon to yield, after protonation on oxygen, 2-iodo-4-nitrophenol. This mechanism was affirmed both by a kinetic study down to low iodide ion concentrations (2×10^{-5} *M*), wherein the iodination step itself became partially rate-determining, and by the decrease in the kinetic isotope effect k_H/k_D from 5.4 at 222×10^{-5} *M* iodide to 2.3 at about 1.5×10^{-5} *M* iodide.

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Similarly, Vainshtein, Tomilenko, and Shilov[6] observed that the isotope effect in the iodination of aniline fell from 3.6 at 0.125 *M* iodide ion concentration to 2.4 at no added initial iodide ion. These workers concluded that molecular iodine was the iodinating agent in a mechanism analogous to that given for *p*-nitrophenol. The kinetics of the iodination of the nickel(II) complex of imidazole[7] and of some of its derivatives[8] also seem to require molecular iodine as an iodinating agent, at least for the portion of the reaction not catalyzed by HPO_4^{2-} nor zero order in iodine.

As Berliner[9] has recently pointed out, all iodination reactions have strikingly similar kinetic characteristics, and it is tempting to draw the generalization that all aqueous iodinations involve molecular iodine as the attacking electrophile; in fact, few kinetic studies have been made at sufficiently low iodide ion concentration to establish the nature of the electrophilic reagent. Moreover, the possibility exists that at extremely low iodide ion concentrations hypoiodous acidium ion, H_2OI^+, may become the effective iodinating atent.[10-13] Furthermore, the electrophilic reagent may vary with the reactivity of the substrate.[14] For these reasons it was deemed of interest to investigate the mechanism of iodination of phenol down to much lower iodide ion concentrations than previously studied[2] (only 0.1 *M*). Preliminary studies[15] indicated that iodide ion concentrations in the range used for previous studies on *p*-nitrophenol[5] were not low enough to permit useful mechanistic distinctions to be made. The technique developed in the present work permitted kinetic studies down to 3×10^{-7} *M* iodide ion concentration.

Experimental Details[16]

Materials. Heavy water (99.5% min D_2O) was obtained from Stuart Oxygen Co. (Liquid Carbonic). Deuterium chloride was prepared as previously described.[5]

2,6-Dibromophenol from Eastman Kodak Co. was distilled *in vacuo*, and the middle fraction was recrystallized from chloroform to give crystals of mp 56–57°. Dilute solutions of iodine in water were prepared as previously described.[5] Bromine and acetic acid were purified as described elsewhere.[10] Perchloric acid was Baker Analyzed Reagent grade. Phenol was Baker Analyzed Reagent material which was purified by distillation through a 3-ft packed column; the distillate was dried at 80° overnight over anhydrous calcium sulfate and then over calcium chloride for 30 min at 50°. The phenol, after separation from drying agent by filtration while warm, was finally distilled *in vacuo* through the packed column and stored in sealed ampoules under a nitrogen atmosphere.

Sodium acetate trihydrate (1.6 kg of Baker Analyzed Reagent grade) for purification was dissolved in 4 l. of water to which was added 65 ml of 12 *M* perchloric acid and 15 ml of Chlorox (5% sodium hypochlorite). The solution was kept overnight at room temperature and then heated at 60–80° for 90 min. Upon concentration, the solution yielded crystals which were then recrystallized from water and dried to constant weight at 200° to give anhydrous sodium acetate. Sodium bicarbonate, Baker Analyzed Reagent grade, was used without purification. Sodium perchlorate from G. Frederick Smith Co. was recrystallized from water. Sodium iodide, Fisher Certified Reagent grade, was used without purification.

The water used as solvent in the kinetic runs at higher iodide ion concentrations was purified as previously described.[5] For kinetic runs at lower iodide concentrations by the spectrophotometric procedure, distilled water (from a Barnstead still) was redistilled from dilute potassium dichromate–sulfuric acid solution through a 5-ft Vigreux column and then was redistilled from dilute alkaline potassium permanganate through a 5-ft packed column.[17]

2,6-Dibromophenol-*4*-d_1 was prepared by deuterium exchange upon 2,6-dibromophenol. The phenol (14.4 g, 0.057 mol) dissolved in 100 g of heavy water containing 0.078 mol of NaOD was heated in a sealed tube under a nitrogen atmosphere at 100° for 28 days. The water was then removed under reduced pressure and replaced with fresh heavy water. The solution was then heated at 100° for 14 more days. The solution upon acidification with excess DCl in heavy water and extraction with ether yielded 2,6-dibromophenol which was purified by three sublimations *in vacuo* (yield, 8.1 g). Since upon iodination in a kinetic run at 50° at 5.6×10^{-4} *M* sodium iodide concentration this sample gave an isotope effect (k^H_{app}/k^D_{app}) of only 4.4, a portion (5.7 g, 0.022 mol) of this 2,6-dibromophenol was subjected to additional deuterium exchange with 0.039 mol of NaOD in 50 g of deuterium oxide in a sealed tube at 100° for 20 days. The product was isolated as previously described and after four sublimations *in vacuo* amounted to 3.5 g, mp 56°. This final product was used in all of the reported kinetic runs upon 2,6-dibromophenol-*4*-d_1.

Phenol-*2,4,6*-d_3 was prepared by deuterium exchange upon phenol by the general method of Ingold and coworkers.[18] Phenol (50 g, 0.521 mol) was dissolved in 200 g of heavy water containing 0.269 mol of NaOD and the solution was heated at 100° in sealed tubes under a nitrogen atmosphere for 96 hr. Sodium deuterioxide (0.269 mol) was added to neutralize the remainder of the phenol and the solution was distilled to dryness, finally *in vacuo* at 105°. Deuterium chloride (30 ml of 9.08 *M*) and 200 g of heavy water were added to the residue and the solution was heated at 100° in sealed tubes for 8 more days. The solution was then acidified with deuterium chloride solution and extracted with ether. The ether extract, after drying over anhydrous $MgSO_4$ and distillation, finally *in vacuo*, yielded 34.5 g of deuterated phenol. In a kinetic run at 25.0° at 5.0×10^{-4} *M* sodium iodide this sample reacted with iodine at a rate which yielded an isotope effect (k^H_{app}/k^D_{app}) of 5.9. This value is substantially higher than that (4.0) reported previously;[4] since the previous sample of phenol-*2,4,6*-d_3 was prepared under conditions similar to the present (except that the concentrations of phenol and sodium phenoxide were 60% of those here and the time of the second equilibration was only 4 days), a 27-g portion of the present phenol was subjected to a third equilibration with 0.162 mol of NaOD in 100 g of heavy water at 100° for 17 days and the phenol-*2,4,6*-d_3 isolated and purified as before. In a kinetic run at 25.0° in presence of 5.0×10^{-4} *M* sodium iodide, this phenol reacted with iodine at a rate 4.5% more slowly than that from the second equilibration. The isotopic purity of the phenol from the third equilibration was 99.3 mol % phenol-*2,4,6*-d_3 according to nmr analysis; this sample of phenol was used in all of the kinetic runs reported in this paper unless otherwise specified.

Kinetic Measurements. The procedure used for studying the kinetics of iodination of 2,6-dibromophenol was like that[5] previously described, as was also that[10] for bromination of this phenol. That deuterium exchange of 2,6-dibromophenol-*4*-*d* with protium in the solvent did not occur in the usual time (15 min) of a kinetic run for bromination was shown by a blank test in which 2,6-dibromophenol-*4*-*d* was dissolved in 80% acetic acid which was 2.00 *M* in HBr and the solution kept at 20° for 15 min before extraction by carbon tetrachloride. The ir spectrum of the extract was indistinguishable from that of the starting 2,6-dibromophenol-*4*-*d*.

For iodination of phenol in dilute acidic solutions, the appropriate acidity was obtained by addition of perchloric acid. The

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(17) *Cf.* A. O. Allen, "Radiation Chemistry of Water and Aqueous Solutions," Van Nostrand, Princeton, N. J., 1961, p 18.
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source of initial iodide ions in these runs was supplied by addition of sodium iodide while the ionic strength was maintained constant by use of sodium perchlorate. The kinetic procedure for iodination of phenol in acetate buffer at iodide concentrations down to 0.008 M was that of Berliner;[3,19] however, in order to avoid losses of iodine at lower concentrations of iodide ion, the multiple-flask procedure previously described for *p*-nitrophenol[5] at 50° was applied to phenol at 25.0° for iodide ion concentrations of 40×10^{-4} to 0.2×10^{-4} M and to phenol-*2,4,6-d*$_3$ for all iodide ion concentrations down to 0.2×10^{-4} M.

For iodide ion concentrations lower than this, a new kinetic procedure ("spectroscopic technique") was devised in which the iodine concentration was measured spectrophotometrically after conversion to the intensely absorbing triiodide ion. The use of a 10-cm glass-stoppered cell for absorbance measurements permitted kinetic runs at initial iodine concentrations as low as 5×10^{-7} M with initial iodide ion concentrations as low as 3×10^{-7} M. For satisfactory runs at such low iodine and iodide ion concentrations, scrupulous attention must be given to cleanliness. Each kinetic point required an individual flask. These were red low-actinic 50-ml volumetric flasks with hand-ground glass stoppers. The flasks after the usual cleaning were soaked in aqueous iodine solution of low iodide ion content in order to destroy any iodine-consuming impurities and were then flushed with the specially purified distilled water and stored filled with distilled water and protected from dust when not in use. For a kinetic run the flasks were filled with appropriate concentrations of all ingredients save iodine–iodide solution and were immersed in a constant-temperature bath at 25.0 ± 0.1° (or at 10.0 ± 0.2°) along with an iodine–iodide solution in a 250-ml red low-actinic flask. The reaction was begun by pipetting 5.00 ml of the iodine–iodide solution to each flask and shaking thoroughly the 47.0 ml total of reaction solution. To stop the reaction 3.0 ml of a sodium bicarbonate solution containing 0.38 g of sodium iodide was rapidly injected from a wide bore pipet. For reactions in 1.74×10^{-2} M perchloric acid, the quenching solution was 0.33 M in $NaHCO_3$; for less acidic solutions, the quenching solution was proportionally less concentrated in $NaHCO_3$. The addition of sodium bicarbonate was necessary since in such acidic solutions the iodide ion added to convert iodine to triiodide ion is readily oxidized to iodine (check runs showed that at the much lower iodide ion concentrations used in the kinetic runs, oxidation of iodide to iodine was undetectable). Even with the present quenching technique some oxidation of iodide to iodine occurred during quenching. This problem was solved by empirical correction which amounted in the most severe case (at highest acidity) to about 10% of the initial absorbance reading. Test experiments, with and without the presence of phenol, showed that there was no detectable consumption of iodine by phenoxide ion formed during the sodium bicarbonate–sodium iodide quenching procedure (these tests seemed necessary since if sodium bicarbonate was added to a reaction mixture prior to sodium iodide, all triiodide absorbance disappeared). For experiments at low acidity, $[H^+] = 10^{-4}$ M, or in acetic acid–sodium acetate buffer, the 3.0 ml of quench solution contained only sodium iodide generally in reduced amount (suitably 0.038 g) to retard oxidation. Background absorbance corrections were applied where necessary to remove absorbance at 3530 Å due to components in the quenched solution other than triiodide ion; the absorbance of sodium perchlorate used to adjust ionic strength was significantly reduced by double filtration through a medium porosity fritted glass filter. The iodophenol generated during iodination of phenol did not contribute detectably to the absorbance at 3530 Å. The triiodide concentrations of the quenched solutions were determined by use of a Cary 14 spectrophotometer and from these concentrations the stoichiometric concentration of iodine in the reaction solution was determined according to eq 2,

$$(I_2) = \frac{A}{\epsilon L}\left\{\frac{1 + K_I[I^-]}{K_I[I^-]}\right\}\frac{q}{r} \qquad (2)$$

where (I_2) refers to the stoichiometric concentration of iodine (the combined concentration of molecular iodine and triiodide ion), A is the corrected absorbance of the solution, ϵ is the extinction coefficient of triiodide ion which[20] is 26,400 at 3530 Å at 25.0°, L is the path length of the cell which was 10.0 cm in most of the present work, K_I is the triiodide ion formation constant which[21] is 768 M^{-1} at 25.0°, $[I^-]$ refers to the iodide ion concentration of the quenched solution, and q and r refer respectively to the volumes of the quenched solution and of the reaction solution.

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

$$k_{app} = \frac{2.303}{(b - a)t} \log \frac{a(b - x)}{b(a - x)} \qquad (3)$$

where k_{app} is expressed in units of l. mol^{-1} sec^{-1}, a is the initial molar concentration of iodine (stoichiometric concentration as calculated from eq 2), b is the initial molar concentration of phenol, and x is the stoichiometric concentration of iodine consumed at time t. A series of blank reactions containing the same concentrations of all ingredients except phenol, which was omitted, were run along with ordinary kinetic runs and were quenched at similar time intervals. A plot of iodine concentrations of blanks *vs.* time generally showed a small linear drop for reactions at the present very low iodide ion concentrations. To correct for this the value of x for eq 3 was taken as the iodine concentration in the kinetic run at time t subtracted from the iodine concentration in the blank at the same time, and a was taken as the iodine concentration in the blank at one-half time. The more sophisticated treatment of blank drop corrections developed by Berliner[22] was found to give results very similar to those from the present calculation for small blank drops (10% or less after 50% reaction in the present work).

In runs at low iodide ion concentration the iodide ion produced during the reaction caused the values of k_{app} to decrease as the extent of reaction increased. In such runs the value of k_{app} at the initial iodide ion concentration, k_{app_0}, was obtained by extrapolation back to 0% reaction. To aid in such extrapolations for runs at low iodide ion concentration (spectroscopic technique) an equation of the form

$$k_{app_0} = k_{app}\left(\frac{[I^-]_0 + 0.5x}{[I^-]_0}\right)^n \qquad (4)$$

was assumed where the value of k_{app} is that calculated from eq 3 at x stoichiometric consumption of iodine. The exponent n was estimated from a similar relationship

$$n = \log \{k_{app_I}/k_{app_{II}}\}/\log \{[I^-]_{0II}/[I^-]_{0I}\}$$

in which the average value of k_{app} in run I of initial iodide ion concentration $[I^-]_{0I}$ was used in conjunction with similar values for run II which was at some threefold higher iodide ion concentration. Another value of n was similarly estimated from a run at threefold lower iodide ion concentration than run I and the two values of n were averaged for use in eq 4 for run I. For the run at lowest iodide ion concentration, the value of n at the unmeasured threefold lower iodide ion concentration was extimated from an extrapolation based on a plot of k_{app_0} *vs.* $[I^-]_0$. Equation 4 for small values of x relative to $[I^-]_0$ and values of n of 1.0–0.37 as obtained in the present work upon phenol at $[I^-]_0$ of 27×10^{-6} to 0.3×10^{-6} implies an essentially linear variation of k_{app} with per cent reaction; eq 4 was accordingly used to estimate the slope of such plots and the best line which could be drawn through the experimental points with this slope was employed in the extrapolation to 0% reaction.

For kinetic runs at low iodide ion concentration (spectroscopic technique) in presence of appreciable acetate, insufficient data were available to use eq 4. For these runs simple graphical extrapolation[5] of k_{app} *vs.* per cent reaction was used to obtain k_{app_0}. Such extrapolation introduces some error in the values of k_{app_0}; however, the same qualitative conclusions are obtained from the data if for each run simple average k_{app} values are used in place of k_{app_0} values in the arguments in the discussion. Comparison of plots of k_{app} *vs.* per cent reaction for runs with and without sodium acetate but otherwise under similar conditions shows that the value of n in eq 4 is appreciably higher for runs with sodium acetate; this observation is in agreement with the proposed mechanism involving acetyl hypoiodite.

The k_{app_0} values are in terms of stoichiometric iodine and were corrected to rate constants k^* in terms of true iodine concentration. The true differs from the stoichiometric iodine concentration because of formation of triiodide ion (important at high iodide ion concentration) and of hypoiodous acid (important at low iodide ion concentration and low acidity). The equilibrium constant for hydrolysis of iodine[20b] was taken to be 5.4×10^{-13} at 25.0° and

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1.26×10^{-13} at 10.0° and was corrected for ionic strength by dividing by the square of the mean ionic activity coefficient (that for the species comprising the bulk of the ionic strength). The k^* values are then defined by eq 5. The iodide ion concentrations

$$k^* = k_{app_0}(I_2)_0/[I_2]_0 \quad (5)$$

were corrected for triiodide and hydrolysis equilibria just as were the iodine concentrations. In nearly all cases runs for protium and deuterium compounds under a given set of conditions were made simultaneously from the same stock solutions in order to minimize the effect of any systematic errors upon the isotope effect.

For phenol at medium (10^{-5} M) to high iodide ion concentration the value of n in eq 4 varies from near 1 to 2 as the iodide ion concentration approaches infinity because of increasing conversion of iodine to triiodide ion. For this region in which $k^*[I^-]$ is essentially constant during a kinetic run and indeed increases only some 10% from runs at lowest to runs at highest iodide ion concentration, the differential rate expression assumes closely the simple form of eq 6, which follows for a well-buffered solution from eq 1.

$$-d(I_2)/dt = k''[I_2][ArH]/[I^-] \quad (6)$$

Integration of eq 6 gives

$$k^*[I^-] \equiv k'' = \frac{\sqrt{\beta}}{t}\left\{-\frac{T^2}{2m} + A\left[\frac{T}{m} - \frac{\sqrt{\beta}}{m^2}\ln|\sqrt{\beta} + mT|\right]\right\} + \frac{C}{2\sqrt{\beta}}\left[2\alpha Q - \ln|-\sqrt{\beta}T^2 + 2\alpha T + \sqrt{\beta}|\right] - \frac{B}{\sqrt{\beta}}\left[T + \frac{\alpha}{\sqrt{\beta}}\ln|-\sqrt{\beta}T^2 + 2\alpha T + \sqrt{\beta}| - \frac{(2\alpha^2 + \beta)}{\sqrt{\beta}}Q\right]\Bigg\}_{T_{x=0}}^{T_{x=x}} \quad (7)$$

where

$$Q = \frac{1}{2\sqrt{\alpha^2 + \beta}}\ln\left|\frac{\sqrt{\alpha^2 + \beta} - (\alpha - \sqrt{\beta}T)}{\sqrt{\alpha^2 + \beta} + (\alpha - \sqrt{\beta}T)}\right|$$

$$T = (2\sqrt{\beta})^{-1}\{2x + (I^-)_0 - (I_2)_0 + \sqrt{[2x + (I^-)_0 - (I_2)_0]^2 + 4\beta}\}$$

x = stoichiometric concentration of iodine consumed at time t

$$A = (\beta^2 - m^4)/\sqrt{\beta}m(2\alpha m + \beta - m^2)$$

$$B = 2(2\alpha^2 + \beta - m^2)/(2\alpha m + \beta - m^2)$$

$$C = 2(\alpha m^2 + \alpha\beta)/\sqrt{\beta}(2\alpha m + \beta - m^2)$$

$$\alpha = (ArH)_0 + (I^-)_0/2 - (I_2)/2$$

$$\beta = (2K_1)^{-2} + [(I_2)_0 + (I^-)_0](2K_1)^{-1}$$

$$m = -(2K_1)^{-1}$$

K_1 = triiodide ion formation constant

and subscript zero refers to an initial concentration at $t = 0$.

While eq 7 was unwieldy for manual computations, it was readily handled by a Univac 1107/1108 computer. Use of this equation permitted meaningful rate constants to be obtained from runs such as that shown in Table I in which the iodide ion concentration increased so extensively with reaction that k_{app} fell too rapidly to obtain the value of k_{app_0} by an extrapolative technique. All runs for phenol at 10^{-5} M and higher iodide ion concentration were recalculated according to eq 7 to give rate constants of generally improved precision and, likely, accuracy. For the runs at 1.5–2.7 $\times$ 10^{-6} M sodium iodide in Tables II and III which were performed by the spectroscopic technique and which had a low ratio of iodine to iodide ion, the extrapolative technique described earlier gave the same value for the rate constants as obtained from eq 7.

Results and Discussion

Iodination of Phenol in Dilute Aqueous Solutions of Perchloric Acid–Sodium Perchlorate.

Table I. Kinetics of Iodination of Phenol at 25.0° [a]

Time, sec	Titer, ml	Reaction, %	k_{app}, M^{-1} sec^{-1}	$10^6k^*[I^-]$, sec^{-1}
0	8.55	0		
540	7.68	10.2	0.103	4.53
960	7.25	15.2	0.0882	4.41
1500	6.76	20.9	0.0792	4.55
5520	4.85	43.3	0.0528	4.58
7908	4.15	51.5	0.0467	4.69
10260	3.68	57.0	0.0422	4.62
				Av 4.56 ± 0.07

[a] $(PhOH)_0$ = 0.002030 M, $(I_2)_0$ = 2.17 $\times$ 10^{-4} M, $(NaI)_0$ = 0.40 $\times$ 10^{-4} M, $(HClO_4)$ = 0.0174 M, $(NaClO_4)$ = 0.2826 M; 100.0 ml of reaction mixture titrated with 0.005072 M $Na_2S_2O_3$.

The kinetic data for iodination of phenol in dilute acidic solution are given in Table II and that for phenol-*2,4,6-d*$_3$ in Table III. Since triiodide ion formation is significant only at the higher iodide ion concentrations, the rate constant k^* which has been corrected for triiodide ion formation is different from the uncorrected rate constant k_{app_0} only at higher iodide ion concentrations. The data of Table II reveal that, for comparisons at equal iodide ion concentration, the rate of iodination varies inversely with hydrogen ion concentration, *i.e.*, $k^*[H^+]$ is a constant. This result had previously been observed for phenol[2,3] at high iodide ion concentration. The data also reveal, as anticipated, that the iodination is first order both in phenol and in iodine. Since the molar ratio of phenol to iodine was 7.6 or greater, principally only monoiodination of phenol should occur under the present conditions. The same kinetic conclusions apply to phenol-*2,4,6-d*$_3$ (in Table III, $k^*[H^+][I^-]$ is fairly constant over the widely varying concentrations of all reactants).

The data of major interest in Tables II and III pertain to the variation of rate with iodide ion concentration. As the stoichiometric iodide ion concentration increases 1590-fold (or the actual iodide ion 1270-fold) the rate of iodination of phenol as measured by $k^*[H^+]$ decreases 410-fold. The rate is therefore nearly inversely proportional to iodide ion concentration. Closer inspection reveals that $k^*[H^+][I^-]$ is constant within experimental error over the range of 25–500 $\times$ 10^{-6} M iodide ion concentration. On the other hand, $k^*[H^+][I^-]$ drops rather rapidly in the range of 5 $\times$ 10^{-6} M to 0.3 $\times$ 10^{-6} M iodide ion concentration. For phenol-*2,4,6-d*$_3$ similar qualitative behavior of $k^*[H^+][I^-]$ is observed but this product decreases less rapidly than for the protium compound on lowering the iodide ion concentration. The net result of this behavior is that the kinetic isotope effect, as given by the ratio of k^*_H/k^*_D at the same hydrogen ion and iodide ion concentrations, decreases with decreasing iodide ion concentration (see Table IV).

The iodination of phenol and phenol-*2,4,6-d*$_3$ is therefore analogous to that reported previously[5] for 4-nitrophenol and 4-nitrophenol-*2,6-d*$_2$ except that some 100-fold lower iodide ion concentration is required to reduce the kinetic isotope effect for phenol to half its initial maximum value. The general mechanism of iodination of such phenols appears to be

$$ArOH \overset{fast}{\rightleftharpoons} ArO^- + H^- \quad (8)$$

$$K_2 = [ArO^-][H^+]/[ArOH]$$

Table II. Kinetic Data for Iodination of Phenol at 25.0°, μ = 0.30

10^6(NaI)$_0$, M	10^6(I$_2$)$_0$, M	10^3[H$^+$], M	10^6(ArOH)$_0$, M	k_{app_0}, M^{-1} sec^{-1}	k^*, M^{-1} sec^{-1}	10^2k^*[H$^+$], sec^{-1}	10^2k^*[H$^+$], sec^{-1} (calcd)[a]	10^8k^*[H$^+$][I$^-$], M sec^{-1}
0.315	0.647	1.30	4.89	64	64	8.3	8.3	2.63
0.315	0.647	5.21	4.89	15.1	15.1	7.9	8.3	2.48
0.315	0.701	5.21	14.4	15.9	15.9	8.3	8.3	2.61
0.315	0.701	17.4	14.4	4.7	4.7	8.2	8.3	2.57
1.21	0.606	5.21	19.8	8.5	8.5	4.5	4.2	5.4
4.83	2.45	5.21	112	2.63	2.64	1.38	1.42	6.7
10.0	133.8	17.4	1969	0.46	0.46	0.81	0.79	7.3[b]
14.9	3.94	1.30	63.2	3.60	3.64	0.47	0.50	7.1
14.8	3.79	5.21	212	0.92	0.93	0.48	0.50	7.2
14.9	3.94	17.4	63.3	0.278	0.281	0.49	0.50	7.3
19.9	89.2	17.4	1031	0.219	0.222	0.39	0.40	7.2[b]
25.0	127.6	17.4	1969	0.197	0.200	0.348	0.329	7.9[b]
27.3	5.15	5.21	222	0.49	0.50	0.262	0.277	7.1
40	217	17.4	2030	0.129	0.133	0.231	0.220	7.9[b]
40	412	17.4	2030	0.140	0.143	0.249	0.247	7.6[b]
50.0	127.6	17.4	1969	0.098	0.101	0.176	0.166	8.0[b]
100	429	17.4	2030	0.054	0.058	0.100	0.100	7.6[b]
500	421	17.4	2030	0.0089	0.0117	0.0203	0.0192	8.1[b]
500	539	17.4	1969	0.0092	0.0119	0.0207	0.0203	7.9[b]
500	517	17.4	2227	0.166	0.199	0.347		143[b,c]

[a] Calculated values based on eq 13. [b] Kinetics measured by titrimetric technique with rate constants calculated by eq 7; other runs are by photometric technique. [c] Reaction at 50.0°.

Table III. Kinetic Data for Iodination of Phenol-2,4,6-d_3 at 25.0°, μ = 0.30

10^6(NaI)$_0$, M	10^6(I$_2$)$_0$, M	10^3[H$^+$], M	10^6(ArOH)$_0$, M	k_{app_0}, M^{-1} sec^{-1}	k^*, M^{-1} sec^{-1}	10^2k^*[H$^+$], sec^{-1}	10^2k^*[H$^+$], sec^{-1} (calcd)[a]	10^8k^*[H$^+$][I$^-$], M sec^{-1}
0.315	0.529	5.21	13.7	5.2	5.2	2.7	3.0	0.85
1.21	0.606	5.21	24.0	1.92	1.92	1.00	0.95	1.21
4.83	2.45	5.21	129	0.44	0.44	0.23	0.25	1.11
10.0	127.3	17.4	2161	0.080	0.081	0.141	0.134	1.28[b]
14.8	3.79	5.21	255	0.148	0.150	0.078	0.083	1.15
25.0	127.3	17.4	2161	0.0319	0.0325	0.057	0.054	1.29[b]
27.3	5.15	5.21	207	0.082	0.084	0.044	0.045	1.19
50.0	127.3	17.4	2161	0.0156	0.0161	0.0280	0.0270	1.28[b]
500	498	17.4	2161	0.00147	0.00190	0.00330	0.00319	1.28[b]
500	517	17.4	2212	0.0302	0.0363	0.063		26.1[b,c]

[a] Calculated values based on eq 14; for other footnotes see Table II.

Table IV. Variation of Isotope Effect with Iodide Ion Concentration at 25.0°

10^6(I$^-$)$_0$, M	10^6[I$^-$], M	10^3[H$^+$], M	k_H^*/k_D^* Found	k_H^*/k_D^* Calcd[a]
0.315	0.32	5.2	3.0	2.8
1.21	1.21	5.2	4.4	4.5
4.8	4.8	5.2	6.0	5.6
10.0	9.1	17.4	5.7	5.9
14.8	14.8	5.2	6.2	6.0
25.0	22.8	17.4	6.2	6.1
27.3	27.2	5.2	6.0	6.1
50.0	46	17.4	6.3	6.2
500	383	17.4	6.2	6.2

[a] Calculated values based on eq 13 and 14.

$$ArHO^- + I_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ArHOI + I^- \quad (9)$$

$$ArHOH + I_2 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} ArHOI + H^+ + I^- \quad (10)$$

$$ArHOI + H_2O \xrightarrow{k_3} ArOI^- + H_3O^+ \quad (11)$$

In this mechanism[23a] the intermediate ArHOI from phenol is predominantly 4-iodocyclohexa-2,5-dienone since 4-iodophenol is reported as the major product of iodination with excess of phenol present.[23b] An alternative step which is kinetically indistinguishable from the process shown in eq 11 is attack of hydroxide ion upon the protonated form of iodocyclohexadienone to give directly iodophenol rather than iodophenoxide ion. Application of the steady-state approximation to the mechanism of eq 8–11 gives the general relation[5]

$$\frac{1}{k^*[H^+]} = \frac{k_{-1}[I^-]}{k_1k_3K_2} + \frac{1}{k_2[H^+] + k_1K_2} \quad (12)$$

In the case of phenol under the conditions of the present experiments the term k_2[H$^+$] is negligible relative to k_1K_2 in eq 12 since k^*[H$^+$] at constant [I$^-$] is invariant with [H$^+$]; therefore, only phenoxide ion is appreciably iodinated under the present conditions. The iodination of phenol at 25° follows the equation

$$1/k_H^*[H^+] = (13.0 \pm 0.6\ M^{-1}\ \text{sec}) \times 10^6[I^-] + 8.0\ (\text{sec}) \quad (13)$$

and accordingly k_1K_2 is 0.13 sec^{-1} and $k_1/k_3 = 1.6 \times 10^6\ M^{-1}$. That eq 13 agrees well with the kinetic data is shown by comparison of the values of k^*[H$^+$] calculated on the basis of this equation with those found (see

(23) (a) In the general mechanistic scheme the formula ArHOH is used to represent a phenol since it is important in the reaction mechanism to consider the hydrogen atom which is ultimately replaced by iodine in the iodophenol. (b) M. A. F. Holleman and M. I. J. Rinkes, *Recl. Trav. Chim. Pays-Bas*, 30, 96 (1911).

Table V. Kinetic Data for Iodination of Phenol in Acetate Buffer

$10^6(NAI)_0$, M	μ	$10^6(I_2)_0$, M	$10^6(ArOH)_0$, M	(NaOAc), M	(HOAc), M	10^2k_{app0}, M^{-1} sec^{-1}	$10^2k^*[H^+]$, sec^{-1}	$10^8k^* \times [H^+][I^-]$, M sec^{-1}	k_H^*/k_D^* [a]
				At 10.0°					
0.32[b]	0.56	0.55	2.51	0.0184	0.0426	19,700	1.84	0.58	4.5
0.32[b]	0.60	0.56	2.72	0.181	0.420	39,000	3.67	1.18	4.2
0.32[b]	1.20	0.56	2.55	0.0187	0.0427	23,100	2.53	0.84	4.8
				At 25.0°					
0.31[b]	0.30	0.60	2.70	0.000[c]	0.000[c]	73,000	7.5	2.5	3.3
0.32[b]	0.53	0.52	5.81	0.063	0.463	39,800	11.8	3.8	3.6
0.32[b]	0.67	0.48	2.12	0.176	0.490	185,000	22.2	7.3	3.4
500	0.30	503	2004	0.0500	0.500	64.3	0.0294	11.3	6.1[d]
1000	0.30	411	2004	0.0500	0.500	22.3	0.0130	10.9	
2000	0.30	497	2004	0.0500	0.500	8.6	0.00070	12.1	6.1[d]
4200	0.30	428	2004	0.0500	0.500	2.21	0.00310	12.0	
4257	0.30	1939	7933	0.0500	0.500	3.54	0.00405	11.9	
8012	0.30	1994	7978	0.0500	0.500	0.90	0.00187	11.9	
20,000	0.30	2008	8004	0.0500	0.500	0.126	0.000664	12.1	6.2[d]
60,000	0.30	2021	7990	0.0500	0.500	0.0130	0.000209	12.1	
80,000	0.30	2051	7995	0.0500	0.500	0.0071	0.000153	12.0	

[a] The general conditions for phenol-*2,4,6-d*$_3$ are as recorded for the protium compound. [b] The kinetics were followed by the spectroscopic technique; all other runs are by the titrimetric technique with use of eq 7. [c] The solution was 1.00×10^{-4} M in perchloric acid. [d] This value has been corrected for incomplete deuteration of the phenol-*2,4,6-d*$_3$; for this phenol in 500×10^{-6} M $(NaI)_0$, $(k_H^*/k_D^*)_{uncor}$ was 3.9 in the acetate buffer and was 4.0 in 0.0174 M perchloric acid.

Table II). A similar relation (eq 14) correlates the

$$1/k_D^*[H^+] = (81 \pm 5\ M^{-1}\ \text{sec}) \times 10^6[I^-] + 8.0\ (\text{sec}) \quad (14)$$

kinetics of iodination of phenol-*2,4,6-d*$_3$. Here the intercept in a plot of $1/k^*[H^+]$ *vs.* $[I^-]$ cannot be determined accurately from the available data; therefore, the value measured for the protium compound is assumed. This is equivalent to assuming the same value of k_1K_2 for phenol-*2,4,6-d*$_3$ as for ordinary phenol. On this basis $k_{-1}k_3$ for phenol-*2,4,6-d*$_3$ is 1.0×10^7 M^{-1}. Equations 13 and 14 permit calculation of the kinetic isotope effect in iodination of phenol at various iodide ion concentrations; the calculated values agree well with those found (see Table IV). The limiting isotope effect of 6.2 at high iodide ion concentration corresponds to the ratio of k_{3H}/k_{3D} according to these assumptions and the similar assumption that k_{-1} is the same for protium and deuterium compounds. The limiting isotope effect at 50° is 5.5, which is essentially the value (5.6) reported[5] for *p*-nitrophenol.

Correction of the thermodynamic ionization constant[24] of phenol (1.02×10^{-10}) at 25.0° for ionic strength (0.30) by division by the square of the mean activity coefficient of sodium perchlorate yields a value of K_2 of 2.1×10^{-10}; this result gives a value of k_1 of 6.0×10^8 M^{-1} sec^{-1}. This very high value for the rate of combination of phenoxide ion with iodine is notable; it is near the diffusion-controlled limit. Such a kinetic result does not require that the actual mechanism necessarily involves such a fast step; prior reversible combination of iodine with the much more plentiful phenol to give a weak π complex which readily loses a proton to give a second π complex which rearranges in a critical step (the counterpart of k_1) to the σ complex ArHOI is another possibility.[25] The σ complex is assumed to have the structure[4] of 4- (or 2-) iodocyclohexadienone.

The present values of k_1 and k_{-1}/k_3 for phenoxide ion at 25° are some 10^5 and 10^2, respectively, larger than the corresponding values[5] for *p*-nitrophenoxide ion at 50°. If comparisons were made at the same temperature, presumably even larger differences in relative reactivity would be observed. These differences reflect both the effect of para *vs.* ortho substitution and the effect of the nitro substituent. The value of k_1 should be greater for phenol than for *p*-nitrophenol because iodination takes place faster at the para than the ortho position of phenoxide ion[23b] but chiefly because the *p*-nitro group decreases the rate of iodination at the ortho position. The reversibility ratio k_{-1}/k_3 is larger for phenol than for *p*-nitrophenol probably because such ratios are normally[26] larger for a position para than for a position ortho to a phenolic hydroxyl. Also it may be argued that the nitro group decreases k_{-1}/k_3 because the electron-withdrawing effect of the substituent increases the acidity of the hydrogen which is removed in step k_3 more than it enhances the ease of removal of I^+ by I^- in step k_{-1}. This conclusion seems reasonable in light of the principle of soft and hard acids and bases.[27] Polar substituents on the ring ought to make the iodocyclohexadienone a harder acid and increase the reactivity toward water, a hard base, by a greater factor than toward I^-, a soft base.

Iodination of Phenol in Dilute Aqueous Solutions of Acetic Acid–Sodium Acetate. The data for iodination of phenol in acetate buffer are summarized in Table V. At constant buffer composition the product $k^*[I^-][H^+]$ is essentially constant over the range of $5\text{–}800 \times 10^{-4}$ M iodide concentration. In conjunction with the previous data for dilute aqueous perchloric acid solutions, the iodination of phenol is now demonstrated to be inverse first order in iodide ion concentration from 2.5×10^{-5} to 0.08 M iodide ion and in earlier work[2] from 0.1 to

(24) G. W. Wheland, R. M. Brownell, and E. C. Mayo, *J. Amer. Chem. Soc.*, 70, 2492 (1948); *cf.* H. C. Ko, W. F. O'Hara, T. Hu, and L. G. Hepler, *ibid.*, **86**, 1003 (1964).

(25) *Cf.* similar considerations for the nitration of aromatic amines in sulfuric acid: S. R. Hartshorn and J. H. Ridd, *J. Chem. Soc. B*, 1068 (1968).

(26) *Cf.* the larger reversibility ratio in bromodecarboxylation para to a hydroxyl group than ortho to a hydroxyl group.[10]

(27) R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967).

0.4 M iodide ion. The numerical value of $k^*[I^-][H^+]$ is somewhat larger in acetate buffer than in aqueous perchloric acid, as would be expected because of acetate ion catalysis.

Berliner[3] studied acetate ion catalysis of iodination of phenol at 25° at 0.08 M iodide ion concentration (total ionic strength adjusted to 0.3 with NaCl); from his data, eq 15 may be derived.[28] The first term in eq

$$k^*[H^+][I^-] = 8.5 \times 10^{-8}\ M\ sec^{-1} + 1.02 \times 10^{-6}\ sec^{-1}[OAc^-] \quad (15)$$

15 is similar to the value of $(7.7 \pm 0.3) \times 10^{-8}$ M sec^{-1} obtained from Table II at high iodide ion concentrations; $k^*[H^+][I^-]$ as predicted by eq 15 is some 13% higher than the value found at 0.50 M sodium acetate and high iodide ion concentrations in Table V. These small differences may arise from errors introduced by use of mean ionic activity coefficients in intercomparison of the old and new data.

Under conditions of acetate ion catalysis at high iodide ion concentration the isotope effect[30] is the same as at high iodide ion concentration in 0.0174 M $HClO_4$ (see Tables IV and V); hence, the catalytic constant for acetate ion must have about the same isotope effect as for the "uncatalyzed" term, *i.e.*, $k_H/k_D \simeq 6.2$ at high iodide ion concentrations. In related work on iodination of azulene,[1] the isotope effect was found to be essentially the same for all oxygen bases tested (but variable for nitrogen bases); a similar result was found for iodination of aniline.[6]

To account for acetate ion catalysis another step, eq 16, may be added to the previously proposed mechanism as an alternative to proton removal from the intermediate by water (eq 11). Application of the steady-state approximation to the revised mechanism then leads to eq 17. At high concentrations of iodide ion the term involving iodide ion is much larger than $1/k_2K_2$ and accordingly the latter may be neglected. Under these conditions eq 17 leads to the simplified expression (eq 18) which agrees with eq 15 found by Berliner[3] for iodination of phenol at 0.08 M iodide ion concentration. It appears then that the essential role played by acetate ion in catalysis of the iodination of phenol at high iodide ion concentration is that of a general base for removal of the proton from the intermediate σ complex to give iodophenoxide ion; a similar interpretation can be applied to the role of other bases[2,3]

$$ArHOI + AcO^- \xrightarrow{k_4} ArOI^- + AcOH \quad (16)$$

$$\frac{1}{k^*[H^+]} = \frac{k_{-1}[I^-]}{k_1K_2(k_3 + k_4[AcO^-])} + \frac{1}{k_1K_2} \quad (17)$$

$$k^*[H^+][I^-] = k_1K_2(k_3 + k_4[OAc^-])/k_{-1} \quad (18)$$

(28) In eq 15 as well as in Tables II–V and other portions of this paper the term $[H^+]$ refers to hydrogen ion concentration rather than activity. In calculations of $[H^+]$ for acetate buffers a dissociation constant of acetic acid of 1.75×10^{-5} at 25° is assumed along with appropriate values[29] for the mean activity coefficient of $NaClO_4$ or NaCl solution of the same ionic strength.

(29) H. S. Harned and B. B. Owens, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold, New York, N. Y., 1958, pp 732, 733.

(30) The value of k_H/k_D of 4.0 reported previously[4] for these conditions is now known to be low, apparently because of incomplete deuterium exchange in the phenol-*2,4,6-d*$_3$ (see Experimental Details of present paper).

in iodination of phenol at the high iodide ion concentrations which have always previously been used in such studies. Shilov, *et al.*,[6] have concluded that bases play this same role in iodination of aniline.

Since eq 18 is derived from work all at high iodide ion concentration, it was deemed of interest to test eq 17 at low iodide ion concentration such that the term $1/k_1K_2$ would be comparable in magnitude to the term involving iodide ion. Preliminary expectations would be that at 0.3×10^{-6} M iodide ion (at which the iodide ion term is about half as large as the $1/k_1K_2$ term in eq 12 and 13), acetate ion catalysis would reduce the magnitude of the iodide ion term until as a limit the value of $k^*[H^+]$ approaches, but does not exceed, the value of k_1K_2 (0.13 sec^{-1}). Acetate ion catalysis should have a similar effect upon phenol-*2,4,6-d*$_3$; hence acetate ion catalysis should reduce the magnitude of the isotope effect to the limiting value of $(k_1K_2)_H/(k_1K_2)_D$ which is thought to be near unity.

These expectations have been tested as shown in the upper portion of Table V. At 25° and 0.3×10^{-6} M sodium iodide the value of $k^*[H^+]$ increases with acetate ion concentration; however, the increase in rate at 0.176 M sodium acetate is twice as large as expected[31] and exceeds by some 75% the value found for k_1K_2. Moreover, the same trend in rate is observed for phenol-*2,4,6-d*$_3$ such that the isotope effect k_H^*/k_D^* instead of dropping to some two-thirds of the value in absence of acetate is essentially unchanged at 0.176 M acetate.[32] The same qualitative trend in rates and isotope effects is observed at 10°. It is clear therefore that eq 17 does not accurately accord with the behavior of phenol at low iodide ion concentrations in the presence of acetate ion.

According to the mechanism which has been considered in the previous discussion, at very low iodide ion concentrations the rate of iodination of the protium compound should be comparatively insensitive to acetate ion catalysis because the rate (expressed as $k^*[H^+]$) is already near the maximum value of k_1K_2; in other words at very low iodide ion concentration the attack of I_2 upon phenoxide ion (eq 9) is essentially rate determining. That appreciable acetate catalysis is nevertheless observed under these conditions implies that acetate ion can play another role in iodination of phenol. We suggest that this role is to supply a new iodinating agent, acetyl hypoiodite; thus

$$I_2 + AcO^- \rightleftharpoons AcOI + I^- \quad (19)$$

$$K_3 = [AcOI][I^-]/[I_2][AcO^-]$$

$$ArHO^- + AcOI \underset{k_{-5}}{\overset{k_5}{\rightleftharpoons}} ArHOI + AcO^- \quad (20)$$

The iodination of phenoxide ion by acetyl hypoiodite (eq 20) then provides an additinal path to the σ complex. The modified mechanism (eq 8–11, 16, 19, and 20) for iodination of phenol in acetate buffer with the usual

(31) For the purpose of testing eq 17 and 21, we take for ordinary phenol $k_1K_2k_3/k_{-1}$ to be 7.7×10^{-8} M sec^{-1} and $k_1K_2k_4/k_{-1}$ to be 86×10^{-6} sec^{-1}; for phenol-*2,4,6-d*$_3$ each of these sets of constants is divided by 6.2. Finally $1/k_1K_2$ is taken to be 8.0 sec for both phenol and phenol-*2,4,6-d*$_3$. While some uncertainty exists as to the "best" values of these constants because of the different techniques and conditions which have been employed, the conclusions reached in the text do not require precise numerical values.

(32) Since mean activity coefficients are almost constant[30] during variation of ionic strength from 0.3 to 0.7 for solutions of $NaClO_4$ and NaOAc the effect of varying ionic strength is ignored in these arguments.

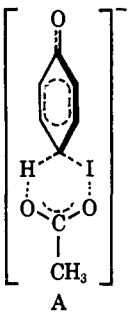
steady-state assumption gives eq 21. At zero acetate

$$\frac{1}{k^*[H^+]} = \frac{k_{-1}[I^-]}{k_1K_2(k_3 + k_4[AcO^-])} + \frac{1}{k_1K_2 + k_5K_2K_3[AcO^-]/[I^-]} \quad (21)$$

ion concentration this equation reduces to eq 12; moreover, at high iodide ion concentration in presence of acetate ion eq 18 results. The condition of present interest is low iodide ion concentration in presence of acetate ion. Solution[31] of eq 21 for k_5K_3 gives an approximate value of 1.4×10^3 sec^{-1} M^{-1}. Substitution of this value along with appropriate values[31] of the other constants for phenol-*2,4,6-d*$_3$ into eq 21 leads to inappreciable calculated drop in k^*_H/k^*_D upon acetate ion catalysis at 0.3×10^{-6} M iodide ion concentration. Additional data are needed for a more adequate test of eq 21; moreover, if K_3 is of sufficient magnitude,[33] appreciable iodine may be converted to acetyl hypoiodite and corrections for this would then need to be applied.

The concept of acyl hypoiodites as iodinating agents in aromatic halogenation was first suggested by Painter and Soper;[2] while we believe, as discussed above, that an alternative role for general bases applies to their conditions of high iodide ion concentration,[34] the general suggestion seems to have merit. Acetyl hypoiodite has been suggested recently as an iodinating agent for pentamethylbenzene in acetic acid solution containing mercuric acetate and the equilibrium constant for formation of acetyl hypoiodite has been measured spectrophotometrically.[35] We would note that while the kinetics of iodination of pentamethylbenzene are compatible with acetyl hypoiodite as an iodinating agent, the nature of the iodinating agent cannot be specified with certainty until it is proven that the iodinating agent attacks pentamethylbenzene in the rate-determining step. In other work upon the iodination of *m*-xylene in acetic acid solution with a mixture of iodine and peracetic acid, the rate is found to be proportional to the concentration of iodine and of peracetic acid but independent of the concentration of *m*-xylene; it has been suggested that the rate-determining step may involve formation of acetyl hypoiodite as the active iodinating agent.[36] The present suggestion of acetyl hypoiodite as an iodinating agent in aqueous solution therefore receives some support from experiments in acetic acid as solvent.

While the detailed mechanism of attack of molecular iodine upon phenol has been proven in the present work to involve formation of an intermediate which, at usual iodide ion concentrations, loses a proton in a subsequent rate-determining step, the same has not yet been established for acetyl hypoiodite. We wonder if the superior iodinating properties of this reagent[36] are related to a new mechanism of iodination. Acetyl hypoiodite can in principle both donate I^+ and remove H^+ in a single transition state such as A. According



A

to this proposal eq 16 and 20 of our general mechanism are fused into a single step.[37] While inadequate data are available to test this postulate at the present time, de la Mare and coworkers[38] have made a somewhat similar proposal to explain why acetyl hypochlorite is a more reactive chlorinating agent than molecular chlorine; however, for chlorination with acetyl hypochlorite no isotope effect was found and hence little cleavage of the aromatic C–H bond occurred in the transition state for the rate-determining step.

Halogenation of 2,6-Dibromophenol. To test the generality of the mechanism established for iodination of phenol and *p*-nitrophenol, the iodination of 2,6-dibromophenol was briefly studied (see Table VI). As

Table VI. Kinetic Data for Iodination of 2,6-Dibromophenol and 2,6-Dibromophenol-*4-d* at 50.0°, μ = 0.30 and (ArOH) $\simeq 5 \times 10^{-4}$ M

$10^5 \times$ (NaI)$_0$, M	10^5(I$_2$)$_0$, M	$10^2 \times$ (HClO$_4$), M	$10^2 \times (k_{app_0})_H$, M^{-1} sec^{-1}	$10^5 k_{II}$*[I$^-$], sec^{-1}	k_{II}/k_D
56.1	15.4	2.14	3.78	2.53	5.8 ± 0.5
5.0	10.2	2.14	40	1.97	4.9 ± 0.5
a	33.8	6.41	24.8		4.0 ± 0.4

[a] Run in presence of 0.0500 M thallium perchlorate which maintains[5] an iodide ion concentration of *ca.* 2×10^{-5} M.

expected for the proposed mechanism (eq 8–11), both $k^*[I^-]$ and the isotope effect decrease with decreasing concentration of iodide ion. The behavior of 2,6-dibromophenol is intermediate between that of phenol and *p*-nitrophenol, but nearer the latter, with respect to how readily $k^*[I^-]$ and the isotope effect decrease with decrease in concentration of iodide ion.

The kinetics[10] of bromination of 2,6-dibromophenol in 80% acetic acid is in agreement with a mechanism analogous to that proposed for iodination of phenol (eq 8–11) except that little of the σ complex reverts back to starting phenol at a bromide ion concentration of 0.1 M. Hence, attack of bromine rather than proton loss is primarily rate determining. The kinetics, there-

(33) If, as seems likely, the attack of acetyl hypoiodite upon phenoxide anion (k_5) occurs at near the diffusion controlled limit, *ca.* 10^{10} M^{-1} sec^{-1}, then the present value of k_5K_3 leads to a minimum value for K_3 of *ca.* 10^{-7}.

(34) From the derived values of k_1K_2 and $k_5K_2K_3$ it can readily be shown that almost exclusive attack of iodine rather than acetyl hypoiodite occurs upon phenol at the high iodide ion concentrations of previous investigators.[2,3]

(35) E. M. Chen, R. M. Keefer, and L. J. Andrews, *J. Amer. Chem. Soc.*, 89, 428 (1967).

(36) Y. Ogata and K. Aoki, *ibid.*, 90, 6187 (1968); Y. Ogata and K. Nakajima, *Tetrahedron*, 20, 43, 2751 (1964).

(37) Since acetate catalysis has been demonstrated to be significant under conditions wherein attack by acetyl hypoiodite is insignificant relative to attack by iodine, one might be led to believe that proton removal by acetate as in eq 16 is of proven mechanistic significance at low iodide ion concentrations; however, for such proof, one must compare the rate of proton removal by acetate to the rate of attack by acetyl hypoiodite. This comparison cannot be made on the basis of available data.

(38) P. B. de la Mare, I. C. Hilton, and S. Varma, *J. Chem. Soc.*, 4044 (1960).

fore, lead to the conclusion that k_H/k_D should be close to unity for such conditions. This conclusion has now been tested (see Table VII) and been found to be justi-

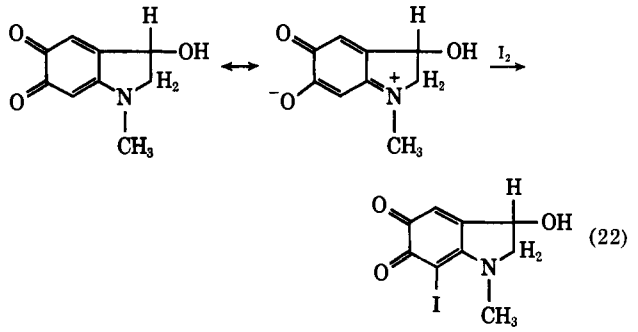
Table VII. Kinetic Data for Bromination of 2,6-Dibromophenol and 2,6-Dibromophenol-*4-d*

Solvent wt % HOAc	Temp, °C	(HBr), *M*	$(Br_2)_0$, *M*	$(k_{app})_H$, M^{-1} sec^{-1}	k_H^*, M^{-1} sec^{-1}	k_H/k_D
0.0	0.0	2.00	0.00125	4.63	185	1.19 ± 0.07[a]
80.0[b]	20.1	0.100	0.00357	1.03	10.3	1.29 ± 0.08[a]

[a] Based on duplicate runs. [b] Solvent 0.200 *M* in $LiClO_4$.

fied. The observed isotope effect, $k_H/k_D = 1.29 \pm 0.08$, is close to that expected ($k_H/k_D = 1.19$) from the observed kinetic constants[10] and the assumption that $k_{3H}/k_{3D} = 6$ in bromination as in iodination and that secondary isotope effects are negligible. The observed small isotope effect in bromination of 2,6-dibromophenol may, therefore, be largely a small primary isotope effect rather than a secondary isotope effect. Baliga and Bourns[39] have recently presented strong evidence for a similar interpretation of small isotope effects in bromodeprotonation of sodium *p*-methoxybenzenesulfonate. An attempt to confirm the present interpretation by measurement of the isotope effect in bromination in 2 *M* aqueous hydrobromic acid gave essentially the same isotope effect as in 0.1 *M* hydrobromic acid in 80% acetic acid. This experiment indicates that either the observed isotope effect is a secondary isotope effect or else that the change of solvent was so drastic that the reversibility ratio k_{-1}/k_3 of eq 12 decreased relative to the constants for bromination, $k_2[H^+]$ and k_1K_2. We favor the latter interpretation; the bromination was so much faster in water than in 80% acetic acid (in spite of the difference in HBr concentration) that the isotope effect had to be studied at 0° rather than at 20°. In previous work on bromination of phenols, Christen and Zollinger[40] reported variable isotope effects ($k_H/k_D = 1.48$–2.34) with the disodium salt of 2-naphthol-6,8-disulfonic acid while Vainshtein, Shilov, and Grishin[41] found no isotope effect in bromination of phenol.

Iodination of Adrenochrome. The iodination of adrenochrome (see eq 22) has been studied in some detail by Mattok and Wilson[42–44] at 35°. Correction[45] of their observed rate constants for triiodide formation gives values of k^*. A plot of $1/k^*$ (for data obtained[43] in 0.1 *M* acetate buffer) *vs.* $[I^-]$ gives a straight line of slope 6.8 sec and intercept (on the $1/k^*$ axis) of 1.6×10^{-2} *M* sec. If the iodination of adrenochrome follows the mechanism of eq 9, 11, and 16 analogous to that proposed for phenol, but simpler because of absence of



(22)

the ionization of eq 8, then the rate should obey eq 23.

$$\frac{1}{k^*} = \frac{k_{-1}[I^-]}{k_1k_3 + k_1k_4[OAc^-]} + \frac{1}{k_1} \quad (23)$$

Hence adrenochrome is calculated to react with molecular iodine at a rate k_1 of 62 M^{-1} sec^{-1} at 35° which is some 10^7 times slower than estimated for phenoxide ion at 25°. Also the reversibility ratio k_{-1}/k_3 is about a 1000-fold less[46] for adrenochrome than for phenoxide ion and hence the mechanism of iodination may be deduced at some 1000-fold higher iodide ion concentration than required for phenol.

What is most interesting is the dependence of the rate of iodination of adrenochrome upon the nature of the buffer and the buffer concentration. Equation 23 predicts that the maximum value of k^* (which occurs at zero iodide ion concentration or infinite acetate ion concentration) is k_1; *i.e.*, for the assumed mechanism, the maximum rate of iodination corresponds to the rate of attack of molecular iodine upon adrenochrome. It is therefore notable that[44] in a 0.6 *M* acetate buffer (pH 4.40), k^* is 231 M^{-1} sec^{-1}; in 0.033 *M* phthalate buffer (pH 5.0), 283 M^{-1} sec^{-1}; in 0.067 *M* phosphate buffer (pH 6.0), 351 M^{-1} sec^{-1}. These values are substantially larger than the estimated maximum value of 62 M^{-1} sec^{-1} obtained from the iodide dependence in eq 23. Since the rate constant for iodination of adrenochrome is said not to change significantly with variation of hydrogen ion concentration or ionic strength,[43,44,47] the data for the buffers require that the mechanism of iodination be altered; thus for acetate buffer additional steps analogous to 19 and 20 seem to be required in the mechanism such that the final kinetic equation becomes

$$\frac{1}{k^*} = \frac{k_{-1}[I^-]}{k_1k_3 + k_1k_4[OAc^-]} + \frac{[I^-]}{k_1[I^-] + k_5K_3[OAc^-]} \quad (24)$$

It may be shown that for this more complex mechanism, the previous estimate of k_1 may be too high because of neglect of acetyl hypoiodite; additional data are needed to determine accurately all of the constants. What the work of Mattok and Wilson demonstrates is that unreactive substrates such as adrenochrome as contrasted to phenoxide ion seek more reactive iodinating agents than iodine even at comparatively high iodide ion concentrations (1.7×10^{-3} *M*); in addition

(39) B. T. Baliga and A. N. Bourns, *Can. J. Chem.*, **44**, 379 (1966); see also N. Joseph and N. S. Gnanapragasam, *Curr. Sci.*, **41**, 288 (1972).
(40) M. Christen and H. Zollinger, *Helv. Chim. Acta*, **45**, 2066 (1962).
(41) F. M. Vainshtein, E. A. Shilov, and O. M. Grishin, *Zh. Vses. Khim. Obshchesi.*, **5**, 119 (1960).
(42) G. L. Mattok and D. L. Wilson, *Can. J. Chem.*, **45**, 327 (1967).
(43) G. L. Mattok and D. L. Wilson, *ibid.*, **45**, 1721 (1967).
(44) G. L. Mattok and D. L. Wilson, *ibid.*, **45**, 2473 (1967).
(45) The original workers[43] incorrectly assumed that such correction was unnecessary. We take the triiodide formation constant[21] at 35° to be 625 M^{-1}.
(46) A more precise estimate cannot be given because of difficulties in unraveling the acetate ion dependence from the limited data available.
(47) For the only experimental data quoted the ionic strength was varied from 0.1 to 0.3 by addition of sodium chloride; while the qualitative arguments are not affected, sodium chloride is an unfortuate salt to choose because it leads to formation of appreciable I_2Cl^- [see D. L. Cason and H. M. Neumann, *J. Amer. Chem. Soc.*, **83**, 1822 (1961)].

to iodine and acyl hypoiodites, the list of iodinating agents must be expanded to include $(HO)_2PO(OI)$ and/or $HOPO_2(OI)^-$. The detailed mechanism of attack of such agents is yet to be elucidated (*cf.* the discussion upon phenol in acetate buffers).

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Kinetics of the Formation of Imines from Acetone and Primary Amines. Evidence for Internal Acid-Catalyzed Dehydration of Certain Intermediate Carbinolamines[1a]

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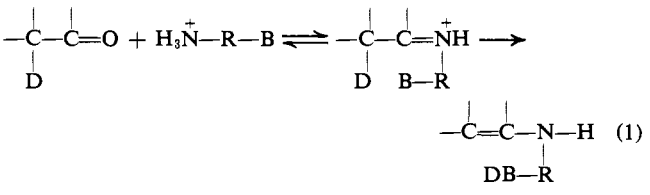
Abstract: The kinetics of the formation of imines from acetone and a number of substituted primary amines have been studied in water at 35° by a method in which trapping of the imine by hydroxylamine permitted the rate of imine formation to be determined by monitoring the rate of acetone disappearance. A plot of the logarithms of the second-order rate constants for primary *n*-alkyl amines with no substituents, ω-methoxy substituents, ω-dimethylamino substituents, and a 2-trimethylammonio substituent *vs.* the pK_a values of the corresponding primary ammonium ions gave a fairly straight line. Rate constants for the monoprotonated (at the tertiary amino group) forms of 2-dimethylaminoethylamine, 3-dimethylaminopropylamine, 4-dimethylaminobutylamine, 5-dimethylaminopentylamine, and *trans*-(2-dimethylaminomethyl)cyclopentylamine were too large to fall on this line by factors of 1000-, 12-, 3-, 2-, and 60-fold, respectively. The enhanced reactivity is attributed to internal catalysis of the dehydration of the intermediate carbinolamines by the $NHMe_2^+$ substituents in the monoprotonated diamines.

The formation of an imine is an important intermediate step in many reactions of aldehydes and ketones.[2] For example, the dedeuteration of isobutyraldehyde-*2-d* in the presence of monofunctional primary amines was found to involve the relatively rapid reversible formation of imine followed by rate-controlling attack of a base on the iminium ion.[3] Certain primary amines with basic substituents (B–R–NH_2) were found to act as bifunctional catalysts for the dedeuteration of isobutyraldehyde-*2-d*[4] and acetone-d_6[5] by the mechanism shown in eq 1. In the



(1)

case of acetone-d_6, the bifunctional catalysts had made the deuterium transfer step so efficient that imine formation had become partly rate controlling. Further increases in the efficiency of the deuterium transfer step will not be able to increase the overall rate of dedeuteration beyond the rate of imine formation. The formation of imines is known to be subject to acid catalysis.[6,7] Hence it was of interest to learn whether an acidic substituent group in a primary amine could act as an internal catalyst and increase the rate of formation of imine. Via observed such internal catalysis in the formation of imines from isobutyraldehyde and the monoprotonated forms of diamines of the type $Me_2N(CH_2)_nNH_2$, where n was 2 and 3.[8] Internal catalysis by phenolic hydroxy groups has also been suggested.[9,10] The present work is an attempt to learn whether internal catalysis can be observed in the formation of imines from monoprotonated diamines and acetone. The equilibrium constants for the formation of imines from acetone are so small that at the concentrations of reagents used only a negligible fraction of the acetone is transformed to imine at equilibrium. Hence the reaction was followed by the method of Williams and Bender, in which the imine is captured by hydroxylamine, which transforms it to acetoxime.[11]

Results

The rate of reaction of acetone with hydroxylamine

(1) (a) This investigation was supported in part by Public Health Service Grants AM 10378 from the National Institute of Arthritis and Metabolic Diseases and GM 18593 from the National Institute of General Medical Sciences; (b) National Institutes of Health Postdoctoral Fellow (No. F02 GM-41309), 1969–1971; (c) National Science Foundation Undergraduate Research Participant, Summer 1971.

(2) The imines are ordinarily formed *via* the corresponding iminium ions, but equilibrium between the two species is usually established more rapidly than any competing reaction. For this reason, we shall often use a phrase like "formation of imine" as synonomous with "formation of iminium ion" for convenience.

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(9) T. C. French, D. S. Auld, and T. C. Bruice, *Biochemistry*, **4**, 77 (1965).

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(11) A. Williams and M. L. Bender, *J. Amer. Chem. Soc.*, **88**, 2508 (1966); *cf.* E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 826 (1962).