

68. *Acid Catalysis in the Iodination of Phenol. Iodination by Acyl Hypoiodites.*

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Phenol, in aqueous solutions buffered by weak acid and salt, reacts with iodine at a rate which varies inversely with the hydrogen-ion concentration and with the square of the iodide-ion concentration. This is in harmony with an interaction of hypoiodous acid with un-ionised phenol or, alternatively, of positive iodine with phenoxide ions. In addition, the rate of iodination at constant pH increases linearly with the concentration of buffer acid and this catalytic effect varies inversely as the square of the hydrogen-ion concentration. This catalytic effect is explicable in terms of an interaction of acyl hypoiodites with phenoxide ions.

A KINETIC study of the *N*-chlorination of amides (Mauger and Soper, *J.*, 1946, 71) has indicated that, in addition to chlorination by the hypochlorite ion, certain amides are also *N*-chlorinated at a rate dependent on the product of the concentrations of hypochlorous acid and of the acid present as a component of the buffer. This has been interpreted as evidence of chlorination by acyl hypochlorites. Acyl hypoiodites might be anticipated to be the most

stable of the acyl hypohalogenites, and the re-examination of the iodination of phenol (Soper and Smith, *J.*, 1927, 2757) is therefore of interest in order to determine whether the kinetic effects observed in *N*-chlorination are paralleled by similar effects in *C*-iodination.

The mechanism of the iodination of phenols was investigated by Cofman (*J.*, 1919, 115, 1040), who showed that in acid solution molecular iodine did not iodinate, whilst in alkaline solution the active iodine was equal to the concentration of hypoiodous acid calculated from the known kinetics of iodate formation (Skrabal, *Monatsh.*, 1911, 32, 171). As in acid solution the phenol is almost exclusively un-ionised, whilst in alkaline solution the highly reactive phenoxide ions would be present with possible complicating effects, the reaction was further studied by Soper and Smith (*loc. cit.*), using phosphate-buffered solutions in the near-neutral range, where the iodine existed practically entirely in the form of the tri-iodide ion. With solutions containing iodide and phenol in excess with respect to the iodine concentration, the reaction was pseudo-unimolecular. The speed, given $V = k_1 \times \text{iodine titre} = k_1[\text{I}_3^-]$, was found to be directly proportional to the phenol concentration and inversely proportional to the square of the iodide concentration. Since the concentration of free iodine will vary inversely with the first power of the iodide concentration, free iodine cannot be an iodinating agent even in the presence of the highly reactive phenoxide ions. Assuming that the pH is such that the phenol present is practically entirely in the un-ionised state, Table I shows the dependence of k_1 on the hydrogen-ion concentration of the solution according to possible mechanisms of iodination. Soper and Smith found that k_1 varied inversely with hydrogen-ion concentration more rapidly than its first power but less rapidly than its second power, and concluded that HOI reacts both with un-ionised phenol and with the phenoxide ion.

TABLE I.

Iodinating agent.	Phenolic agent.	k_1 proportional to :	Iodinating agent.	Phenolic agent.	k_1 proportional to :
HOI	PhOH	$[\text{PhOH}][\text{I}^-]^{-2}[\text{H}^+]^{-1}$	OI ⁻	PhO ⁻	$[\text{PhOH}][\text{I}^-]^{-2}[\text{H}^+]^{-3}$
HOI	PhO ⁻	$[\text{PhOH}][\text{I}^-]^{-2}[\text{H}^+]^{-2}$	I ⁺	PhOH	$[\text{PhOH}][\text{I}^-]^{-2}[\text{H}^+]^0$
OI ⁻	PhOH	$[\text{PhOH}][\text{I}^-]^{-2}[\text{H}^+]^{-2}$	I ⁺	PhO ⁻	$[\text{PhOH}][\text{I}^-]^{-2}[\text{H}^+]^{-1}$

The re-examination of the reaction has shown that at constant pH the rate of iodination is greatly affected by the concentration of the buffer, being approximately a linear function of the concentration of the buffer acid HA. Thus the unimolecular constant k_1 may be expressed by $k_1 = k_0 + k_{\text{HA}}[\text{HA}]$, *i.e.*,

$$v = k_0[\text{PhOH}][\text{I}_3^-] + k_{\text{HA}}[\text{HA}][\text{PhOH}][\text{I}_3^-]$$

The effect, at 25.0°, of acetic acid on the rate over the pH range 4.66—5.26 is shown in Fig. 1. The addition of potassium nitrate shows that the effect of increasing the buffer strength is not a salt effect. This is shown at pH 4.96 in the inset (Fig. 2). The values of k_0 , obtained by extrapolating k_1 to zero acid concentration, and the slopes of the curve which measure k_{HA} , both vary with the pH of the solution. These values of k_0 and k_{HA} are given in Table II, k_0 varying inversely as the hydrogen-ion concentration and k_{HA} inversely as the square of this concentration.

TABLE II.

pH.	$10^5[\text{H}^+]$.	k_0 .	$10^5k_0[\text{H}^+]$.	k_{HA} .	$10^{10}k_{\text{HA}}[\text{H}^+]^2$.
5.26	0.55	0.066	0.0363	3.575	1.09
5.055	0.88	0.0422	0.0372	1.42	1.10
4.96	1.10	0.0334	0.0368	0.875	1.06
4.66	2.20	0.0174	0.0383	0.220	1.07

Since the total reaction rate varies directly with the phenol concentration and inversely with the square of the iodide-ion concentration, k_0 varies as $[\text{PhOH}][\text{H}^+]^{-1}[\text{I}^-]^{-2}$ and (cf. Table I) indicates reaction between hypoiodous acid and un-ionised phenol or, alternatively, between positive iodine ions and phenoxide ions.

The term involving catalysis by acetic acid can be interpreted as showing reaction between acetyl hypoiodite and the phenoxide ion. Assuming that the concentration of the former is determined by the constant K of the equilibrium $\text{AcOH} + \text{I}_2 \rightleftharpoons \text{AcOI} + \text{H}^+ + \text{I}^-$, and that the catalysed rate is given by $v = k_{\text{cat.}}[\text{AcOI}][\text{PhO}^-]$, then, neglecting activity coefficients

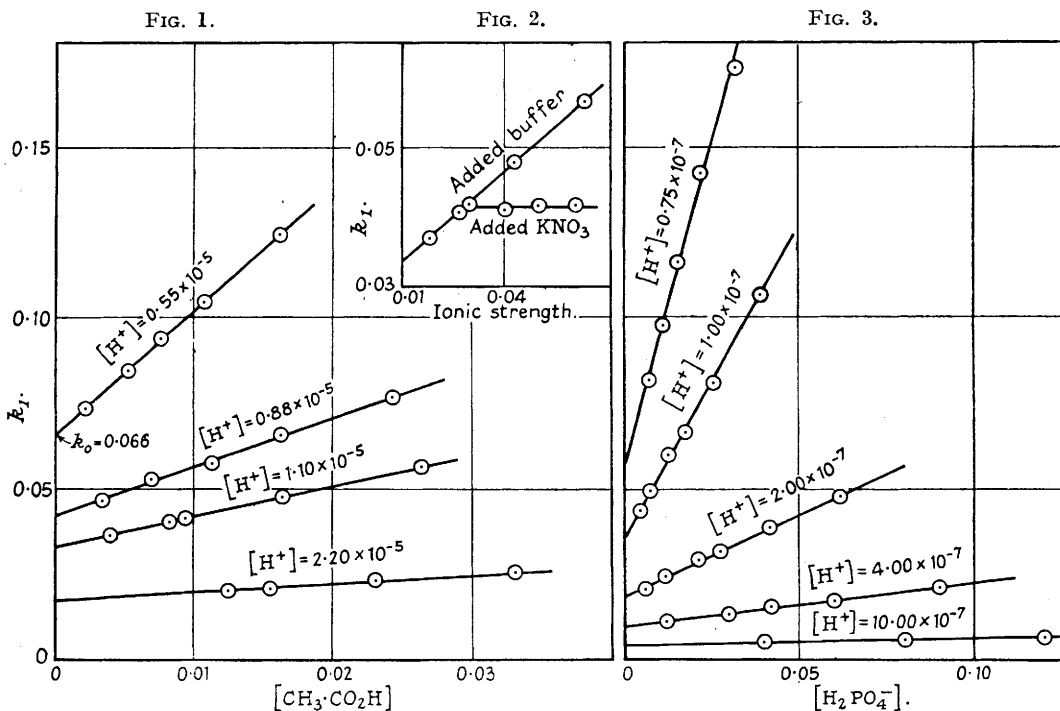
$$\begin{aligned} v &= k_{\text{cat.}} \frac{K[\text{AcOH}][\text{I}_2]}{[\text{H}^+][\text{I}^-]} \cdot \frac{K_a[\text{PhOH}]}{[\text{H}^+]} \\ &= k_{\text{cat.}} K K_{\text{I}_2} K_a \frac{[\text{PhOH}][\text{I}_3^-][\text{AcOH}]}{[\text{H}^+]^2[\text{I}^-]^2} \end{aligned}$$

where K_{I_3} is the equilibrium constant of the reaction $I_3 = I_2 + I^-$ (Bray and McKay, *J. Amer. Chem. Soc.*, 1910, **32**, 914). Comparison with $v = k_1[I_3^-] = k_0[I_3^-] + k_{HA}[AcOH][I_3^-]$ gives

$$k_{HA} = k_{cat} K K_{I_3} K_a [PhOH] / [H^+]^2 [I^-]^2$$

showing the observed dependence on hydrogen- and iodide-ion concentrations. Other possible halogenating agents have been considered whose concentration would be proportional to the concentration of the acetic acid, but only acetyl hypiodite fulfils the further required conditions of dependence of reaction rate on $[PhOH][H^+]^{-2}[I^-]^2$.

Iodination in Phosphate Buffers.—A further test of the dependence of k_0 and k_{HA} on hydrogen-ion concentration was made in phosphate buffer solutions and the results obtained at 25.0°



are shown in Fig. 3. The values of k_0 and k_{HA} deduced from the curves are given in Table III and, as before, k_0 is found to be inversely proportional to the hydrogen-ion concentration and k_{HA} inversely proportional to its square.

TABLE III.

pH.	$10^7[H^+]$.	k_0 .	$10^7k_0[H^+]$.	k_{HA} .	$10^{14}k_{HA}[H^+]^2$.
7.12	0.75	0.057	0.043	3.65	2.04
7.00	1.00	0.036	0.036	1.86	1.86
6.70	2.00	0.018	0.036	0.48	1.92
6.40	4.00	0.009	0.036	0.13	2.08
6.00	10.00	0.004	0.040	0.02	2.0

In phosphate buffers, the ion $H_2PO_4^-$ has replaced the free acid of the acetate buffers and the catalysed term can be explained in terms of an iodinating ion, iodine hydrogen phosphate, formed by $H_2PO_4^- + I_2 \rightleftharpoons HIPO_4^- + H^+ + I^-$. Such an iodinating agent reacting with phenoxide ions gives the required dependence of k_{HA} on $[PhOH][I^-]^2[H^+]^{-2}$. That the increased rate of reaction with increased phosphate buffer strength is not a salt effect was shown by increasing the ionic strength over a similar range with potassium nitrate, no appreciable alteration in k_1 being observed.

Comparison of the Catalytic Effects of Other Weak Acids.—Since the catalytic effect of the weak acid is dependent on the hydrogen-ion concentration of the solution, comparison of the

catalytic effects of dihydrogen phosphate, hydrogen maleate, hydrogen phthalate, and acetic acid was made at a constant pH of 6.0. This pH was chosen so as to minimise catalytic effects due to other acidic ions. The values obtained are given in Table IV.

TABLE IV.

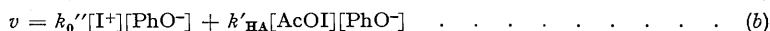
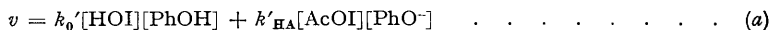
[PhOH] = 0.0100; [I⁻] = 0.100; [I₂] added = 0.001M.

	Dihydrogen phosphate.	Hydrogen maleate.	Hydrogen phthalate.	Acetic acid.
k_0	0.40	0.43	0.42	0.38
k_{HA}	0.017	0.072	0.88	1.41
$K_a \times 10^7$	0.597 *	2.6 *	39 *	186

* Second dissociation constants (see below).

In the cases of the first three acids the amounts of the un-ionised acids present at pH 6 will be negligible and the catalytic effects will be due to the ions $H_2PO_4^-$, $C_4H_2O_4 \cdot H^-$, $C_8H_4O_4 \cdot H^-$. Hence the second ionisation constants of these acids are used for purposes of comparison, and the values given are those recorded by Guggenheim and Schindler (*J. Physical Chem.*, *Chem.*, 1934, **38**, 533), Chandler (*J. Amer. Chem. Soc.*, 1908, **30**, 713), Kuhn and Wassermann (*Helv. Chim. Acta*, 1928, **11**, 44), and Lundén (*Zentr.*, 1908, I, 787). The stronger the acid the greater its catalytic effect, and hence the disturbing effect in phosphate buffers due to the weakly acidic HPO_4^{--} ion will be slight. This relation of the strength of acid to its catalytic effect parallels the observed catalytic effects of acids (Mauger and Soper, *loc. cit.*) in the *N*-chlorination of *N*-methylacetamide. The relation may be due to increasing formation of the acyl hypoiodite with increase of acid strength. Alternatively, it may be due to the greater ease of release, at the point of substitution, of the iodine from the acyl hypoiodite in the form of positive iodine.

The kinetics of the iodination conform with either (a) or (b) :



and other possible iodinating mechanisms appear to be eliminated. The uncatalysed reaction is explicable in terms either of positive iodine and phenoxide ions or of hypoiodous acid and un-ionised phenol. In mechanism (a) the hypoiodous acid attacks the un-ionised phenol in the uncatalysed reaction, but the acyl hypoiodite attacks only the phenoxide ion. Since the phenoxide ion is much more easily halogenated than un-ionised phenol (Soper and Smith, *J.*, 1926, 1582), hypoiodous acid must on this view be a more powerful iodinating agent than the acyl hypoiodite, for which some explanation is required.

In the iodination of phenol by different agents, two of the stages in the four-stage nuclear substitution process are the same, namely, the capture of the positive halogen and proton release by the carbon atom at the point of substitution. Ease of iodination by a series of iodinating agents is therefore governed by the other two stages, the ease of ionisation of the halogenating molecule into positive halogen and the ease of removal of the released proton by the residue of the halogenating molecule, the four processes blending and determining the energy of activation. If the ease of formation of positive halogen is a dominating factor, acyl hypoiodite should form a more effective iodinating agent than hypoiodous acid since nuclear release occurs more easily from the acetate ion than from the hydroxyl ion. But when hypoiodous acid iodinate, the released proton combines with hydroxyl to eliminate water whilst an acyl hypoiodite forms an acid from proton and acid ion. The much greater proton affinity of the hydroxyl ion than of the acetate ion may therefore dominate and so provide an explanation for mechanism (a). Interpretation (b), however, has formal simplicity, phenoxide ions reacting both with positive iodine in the uncatalysed reaction and with acyl hypoiodite in the acid-catalysed reaction. This simplification would receive some support by analogy with the chlorination of phenol by hypochlorous acid (Soper and Smith, *loc. cit.*) which also involves the phenoxide ions only.

EXPERIMENTAL.

Reaction mixtures were brought to thermal equilibrium at $25.0^\circ \pm 0.02^\circ$, and the reaction initiated by adding a solution of phenol to the buffered solution of iodine and iodide. Aliquot portions (10 c.c.) were examined by running them into 30 c.c. of *N*-sulphuric acid freed from oxygen by carbon dioxide,

and titrating against thiosulphate. Iodine and phenol in acid solution are stable, the iodine titre decreasing by less than 3% in 7 days. A typical run at pH 4.96 is shown below :

$$[\text{PhOH}] = 0.0100\text{M}; [\text{I}^-] = 0.0100\text{M}; [\text{I}_2] \text{ added} = 0.0010\text{M}; [\text{AcOH}] = 0.00417\text{M};$$

$$[\text{AcONa}] = 0.00832\text{M}.$$

Time, mins.	0	8.6	12.3	14.39	17.0	20.2	25.2
$[\text{I}_3^-] \times 10^4$	9.38	6.95	5.97	5.62	5.02	4.60	3.66
$k_1 \times 10^3$	—	3.48	3.67	3.56	3.67	3.53	3.73

Points shown in Figs. 1, 2, and 3 represent the mean values obtained from duplicate experiments.

Buffer solutions were prepared from 0.2M-acid and 0.2M-sodium hydroxide, and the pH given in each case refers to a solution in which the sum of the concentrations of acid and acid ion is 0.05M. Acetate and phosphate buffers were prepared from the figures quoted by Clark ("Determination of Hydrogen Ions," 1928, pp. 219, 200), and phthalate buffer from figures quoted by Reilly and Rae ("Physico-Chemical Methods," 1940, Vol. II, 482). These were checked at the standard concentration by using a Cambridge glass electrode and found to be within 0.01 unit of pH in each case. Maleic acid buffer was prepared so as to give a pH of 6.00 using the glass electrode. All buffers were shown to be stable to iodine over an examined period of 2 days, and the phenol iodinations were examined over an average period of 2 hours.

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