Kinetics and Mechanism of Iodination of 8-Hydroxyquinoline

By **Alan A. Humffray** * and **Darryl R. Schroeter**, Department of Physical Chemistry, University of Melbourne, Parkville 3052, Australia

Kinetic measurements on the reaction of iodine with 8-hydroxyquinoline (oxine) are consistent with a reaction between molecular iodine and oxinate anion, through a cyclohexadienone intermediate, *i.e.* a mechanism similar to that observed for iodination of phenol, but different from that proposed for bromination of oxine. The enthalpy of activation is also very similar to that observed for phenol. Catalysis by acetate ion is observed, and both the catalytic rate coefficient and that for the 'uncatalysed' reaction are about 300 times those for phenol at 25°.

DETAILED kinetic studies, including isotope effect measurements,[1-4] have led to a reasonable understanding of the mechanism of iodination of monocyclic phenols, but no comparable studies on annulated aromatic systems have been reported. In continuation of our studies on electrophilic substitution in the naphthalene ring [5] we have performed some kinetic measurements on the reactions between iodine and 1- and 2-naphthol,[6] but the interpretation of the results is complicated by the occurrence of oxidative dimerization [7] instead of (or accompanying) iodination. At the same time we sought a comparison with a related heterocyclic phenol, 8-hydroxyquinoline (oxine) which is known to undergo iodination,[8] but for which no kinetic investigation has been performed. Gershon and his co-workers [9] concluded that the product distributions for a range of iodinating agents and reaction conditions were inconsistent with theoretical predictions (based on localization energies), although good agreement was observed for chlorination and bromination; they suggested that the mechanism of iodination might be different from that of chlorination and bromination. Since a kinetic study of the bromination of oxine has been reported,[10] kinetic measurements on the iodination make possible a direct comparison of the mechanisms of the two halogenation reactions, as well as providing an opportunity to investigate the effects of annulation on the reactivity and mode of reaction of a phenol.

EXPERIMENTAL

AnalaR oxine (BDH) and resublimed iodine (May and Baker) were used without further purification. 5-[11] and 7-iodo-oxine [12] were prepared and purified by published methods. Kinetic solutions were prepared in triple distilled water, all other chemicals being AnalaR grade. Because of the low solubility of oxine in water, stock solutions were prepared in *ca.* 0.04M-acetic acid (2.5 cm^3 acetic acid per dm^3 solution).

Kinetic Procedure.—In a 100 cm^3 water-jacketted beaker, which was thermostatted by water circulating through the jacket, was placed 25.0 cm^3 of oxine stock solution, and aliquot portions of stock solutions of potassium iodide, sodium acetate, acetic acid, and potassium nitrate as required to maintain the ionic strength at 0.40M, and water to a total volume of 45.0 cm^3. The solution was stirred at 750 r.p.m. by a glass stirrer and the reaction initiated by addition of 5.0 cm^3 of a stock solution of iodine (2×10^{-4}M) in potassium iodide (0.1M). The oxine concentration was at least 50 times the analytical iodine concentration initially, so that pseudo-first-order conditions prevailed, and polysubstitution was minimised. The stoicheiometric iodine concentration, $[I_2]_{st} = [I_2] + [I_3^-]$, was monitored as a function of time by recording the diffusion current between two platinum electrodes in the solution at an applied potential difference of *ca.* 100 mV (the 'dead stop' technique [13]). A Varian G10 recorder with chart speeds of 1 and 16 in min^{-1} was employed, and independent measurements verified the proportionality between analytical iodine concentration and recorder reading, and that no other components of the kinetic solutions produced a recorder deflection, *i.e.* the 'infinity reading' was zero. Pseudo-first-order rate constants k_{obs} were obtained from linear plots of log (recorder reading) against time, and converted to second order rate constants k_2 by dividing by the oxine concentration.

Equilibrium constants K_1 and K_2 for the reactions $H_2A^+ \overset{K_1}{\rightleftharpoons} H^+ + HA$ and $HA \overset{K_2}{\rightleftharpoons} H^+ + A^-$ (where HA = oxine) were measured spectrophotometrically at 25 and 40° in phthalate and borax buffers at wavelengths of 350, 360, 370, and 380 nm, using a Hilger H700 Uvispek spectrophotometer fitted with an electronically controlled constant temperature cell block. Good agreement was observed at each wavelength, and mean values of K_1 and K_2 were used in subsequent calculations. A Cambridge pH meter with a Titron combined glass–calomel electrode was used to measure the pH of each kinetic solution at reaction temperature.

The sole product of the reaction was identified as 5-iodo-oxine by steam distillation to remove excess of oxine, then i.r. analysis, using a Unicam SP 1200 spectrophotometer, of a chloroform extract. It was found possible to detect, in synthetic mixtures, as little as 5% of 7-iodo-oxine in the 5-isomer.

---

[1] E. Grovenstein, N. S. Aprahamian, C. J. Bryan, N. S. Gnanapragasam, D. C. Kilby, J. M. McKelvey, and R. J. Sullivan, *J. Amer. Chem. Soc.*, 1973, **95**, 4261.

[2] E. Berliner, *J. Amer. Chem. Soc.*, 1951, **73**, 4307.

[3] B. S. Painter and F. G. Soper, *J. Chem. Soc.*, 1947, 342.

[4] F. G. Soper and G. E. Smith, *J. Chem. Soc.*, 1927, 2757.

[5] R. L. Bruce and A. A. Humffray, *Austral. J. Chem.*, 1971, **24**, 1085.

[6] A. A. Humffray and R. L. Bruce, unpublished results.

[7] M. Francois and L. Seguin, *Bull. Soc. chim. France*, 1933, **53**, 711, 718.

[8] R. G. W. Hollingshead, 'Oxine and its Derivatives,' Butterworths, London, 1956, vol. III, pp. 677, 731.

[9] H. Gershon, M. W. McNeil, and S. G. Schulman, *J. Org. Chem.*, 1971, **36**, 1616.

[10] G. S. Kozak, Q. Fernando, and H. Frieser, *Analyt. Chem.*, 1964, **36**, 296.

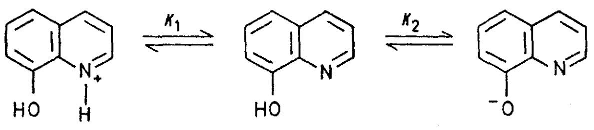
[11] F. Pirrone and A. Cherubino, *Gazzetta*, 1935, **65**, 743.

[12] H. Gershon, M. W. McNeil, and A. T. Grefig, *J. Org. Chem.*, 1969, **34**, 3268.

[13] C. W. Foulk and A. T. Bawden, *J. Amer. Chem. Soc.*, 1926, **48**, 2045.

RESULTS AND DISCUSSION

Spectrophotometric measurements led to the following pK values for the equilibrium (1). At 25°, p$K_1 = 5.10$ and p$K_2 = 9.88$; at 40°, p$K_1 = 4.87$ and p$K_2 = 9.68$. The values at 25° are in reasonable agreement with those quoted by Hollingshead;[14] values at other temperatures appear not to have been previously reported, although Näsänen[15] gave a value for the temperature coefficient of pK_2, in reasonable agreement with the value quoted above.



(1)

H_2A^+ HA A^-

All kinetic measurements were performed in acetate buffers, in the pH range 4.3—5.8 and, at fixed ionic strength, pH, buffer, and iodide ion concentrations, the reaction was found to be first order with respect to both stoicheiometric oxine and iodine concentrations, *i.e.* rate $= k_2[\mathrm{Ox}]_{\mathrm{st}}[\mathrm{I}_2]_{\mathrm{st}}$, where $[\mathrm{Ox}]_{\mathrm{st}} = [\mathrm{H_2A^+}] + [\mathrm{HA}] + [\mathrm{A^-}]$. It is evident from the pK values that oxine in such solutions exists mainly in the forms HA and H_2A^+. Considerations of the equilibria involved lead to values for the ratios R and S given in equations (2) and (3). Here

$$R = \frac{[A^-]}{[\mathrm{Ox}]_{\mathrm{st}}} = \frac{K_1K_2y_0}{(a_{\mathrm{H}})^2y_0 + K_1a_{\mathrm{H}}y_1 + K_1K_2y_0} \approx \frac{K_1K_2}{(a_{\mathrm{H}})^2 + K_1a_{\mathrm{H}}y_1} \qquad (2)$$

$$S = \frac{[\mathrm{HA}]}{[\mathrm{Ox}]_{\mathrm{st}}} = \frac{K_1a_{\mathrm{H}}y_1}{(a_{\mathrm{H}})^2y_0 + K_1a_{\mathrm{H}}y_1 + K_1K_2y_0y_1} \approx \frac{K_1a_{\mathrm{H}}y_1}{(a_{\mathrm{H}})^2 + K_1a_{\mathrm{H}}y_1} \qquad (3)$$

a_{H} is the hydrogen ion activity, y_0 the activity coefficient of an uncharged species, HA, and y_1 that of a univalent cation, H_2A^+, or anion, A^-, assumed equal.

The simplified approximate expressions (2) and (3) are adequate under the experimental conditions employed, since K_1K_2 is negligible compared to $(a_{\mathrm{H}})^2$ or K_1a_{H} and $y_0 \approx 1$. Furthermore, since the tri-iodide ion formation constant K_3 is 768 at 25 and 574 l mol^{-1} at 40,[16] and the lowest iodide ion concentrations employed were 0.05M at 25° and 0.10M at 40 °C, the ratio (4) applies and the simplified approximate expression (4) is adequate under the experimental conditions employed.

$$[\mathrm{I_2}]/[\mathrm{I_2}]_{\mathrm{st}} = 1/(1 + K_3[\mathrm{I^-}]) \approx 1/K_3[\mathrm{I^-}] \qquad (4)$$

Three mechanisms have been proposed[1-4] for the iodination of monocyclic phenols at reasonably high iodide ion concentrations.

Mechanism (I).—A pre-equilibrium reaction exists between molecular iodine and phenolate ion to give a cyclohexadienone type intermediate, which undergoes rate-determining proton loss (5). For this mechanism,

$$\mathrm{I_2} + \mathrm{A^-} \overset{K_4}{\rightleftharpoons} \underset{\substack{+\\ \mathrm{I^-}}}{\mathrm{AI}} \xrightarrow{k} \text{products} \qquad (5)$$

if applicable to oxine,* we obtain equations (6)—(9) with the last at fixed [I⁻], pH, and buffer concentration.

$$\text{rate} = k\,[\mathrm{AI}] \qquad (6)$$

$$= k\,K_4\,[\mathrm{I_2}][\mathrm{A^-}][\mathrm{I^-}]^{-1} \qquad (7)$$

$$= k\,K_4\,R[\mathrm{Ox}]_{\mathrm{st}}[\mathrm{I_2}]_{\mathrm{st}}[\mathrm{I^-}]^{-2}/K_3 \qquad (8)$$

$$= k_2\,[\mathrm{Ox}]_{\mathrm{st}}[\mathrm{I_2}]_{\mathrm{st}} \qquad (9)$$

Mechanism (II).—Rate-determining reaction (10) between phenolate ion and an iodine cation occurs, for which equations (12), (13), and (9) apply with the last at fixed [I⁻], pH, and buffer concentration.

$$\mathrm{I_2} \overset{K_5}{\rightleftharpoons} \mathrm{I^+} + \mathrm{I^-} \qquad (10)$$

$$\mathrm{I^+} + \mathrm{A^-} \xrightarrow{k} \text{products} \qquad (11)$$

$$\text{rate} = k[\mathrm{I^+}][\mathrm{A^-}] \qquad (12)$$

$$= k\frac{K_5R}{K_3{y_1}^2}[\mathrm{Ox}]_{\mathrm{st}}[\mathrm{I_2}]_{\mathrm{st}}[\mathrm{I^-}]^{-2} \qquad (13)$$

Mechanism (III).—Rate-determining reaction (15) between HOI and molecular phenol occurs, for which equations (16)—(19) apply since $S/y_1\,a_{\mathrm{H}} = R/K_2$ and,

$$\mathrm{I_2} + \mathrm{H_2O} \overset{K_6}{\rightleftharpoons} \mathrm{HOI} + \mathrm{H^+} + \mathrm{I^-} \qquad (14)$$

$$\mathrm{HOI} + \mathrm{HA} \xrightarrow{k} \text{products} \qquad (15)$$

$$\text{rate} = k[\mathrm{HOI}][\mathrm{HA}] \qquad 16)$$

$$= k\,\frac{K_6S}{K_3a_{\mathrm{H}}y_1}[\mathrm{Ox}]_{\mathrm{st}}[\mathrm{I_2}]_{\mathrm{st}}[\mathrm{I^-}]^{-2} \qquad (17)$$

$$= k\,\frac{K_6R}{K_2K_3}[\mathrm{Ox}]_{\mathrm{st}}[\mathrm{I_2}]_{\mathrm{st}}[\mathrm{I^-}]^{-2} \qquad (18)$$

again, at constant [I⁻], pH, and buffer concentration we have equation (9).

From the above treatment, constancy of the ratio $k_2[\mathrm{I^-}]^2/R$ as pH and iodide ion concentration are varied at constant buffer concentration and ionic strength implies a process compatible with any of the above mechanisms; for a monohydric phenol, the analogous constant expression is $k_2[\mathrm{I^-}]^2a_{\mathrm{H}}y_1/K_{\mathrm{a}}$, as can be deduced from the work of Berliner[2] and Soper.[3,4] (Berliner performed all

---

* Base catalysis is considered later.

[14] Ref. 8, pp. 21—33.

[15] R. Näsänen, P. Lumme, and A. L. Mukula, *Acta Chem. Scand.*, 1951, **5**, 1199.

[16] M. Davies and E. Gwynne, *J. Amer. Chem. Soc.*, 1952, **74**, 2748.

his measurements at a constant iodide ion concentration, 0.08M in acetate buffers, and neglected activity coefficients in his calculations, so he used constancy of the quantity $k_2[H^+]/K_a$ as his criterion for the mechanism.)

Arguments against mechanisms (II) and (III) have been presented,[17] and mechanism (I) certainly appears most plausible. Results presented in Tables 1 and 2 indicate satisfactory constancy at both 25 and 40° of the ratio $k_2[I^-]^2/R$ when the buffer concentration is constant. In evaluating R, Davies' modified equation [18] was used to calculate y_1. It should be noted that the relation between a_H and R is such that, *e.g.* in Table 2, when the extreme pH values correspond to a change in a_H by a factor of *ca.* 30, R changes by a factor of almost 150.

As has been previously observed for other phenols,[1-4] catalysis by acetate ion occurred, since, at constant pH, ionic strength and iodide ion concentration, the values of k_{obs} and k_2 increased when the acetate ion concentration was increased. Thus the quantities $k_2[I^-]^2/R$ listed in Tables 1 and 2 are all of the form (19) k_{cat} being

$$k_2[I^-]^2/R = k_0 + k_{cat}[OAc^-] \qquad (19)$$

the catalytic coefficient for acetate ion catalysis, and k_0 the 'uncatalysed' rate coefficient. Table 3 lists mean values for the quantities $k_2[I^-]^2/R$ at various acetate ion concentrations, together with the values of k_0 and k_{cat} evaluated by least squares from (19).

TABLE 1

Iodination of oxine at 25°

[oxine] 1—4 × 10^{-3}M; ionic strength 0.40M

pH	10^5R	$[OAc^-]$/M	$[I^-]$/M	k_2/ l mol^{-1} s^{1}	R^{-1}/ mol l^{-1} s^{-1}
5.63	5.49	0.05	0.30	0.122	200
5.66	5.99	0.10	0.10	1.72	287
5.66	5.99	0.10	0.15	0.749	282
5.66	5.99	0.10	0.20	0.435	290
5.66	5.99	0.10	0.25	0.272	284
5.66	5.99	0.10	0.30	0.193	290
5.48	3.48	0.10	0.10	1.02	293
5.48	3.48	0.10	0.15	0.475	307
5.48	3.48	0.10	0.20	0.262	301
5.34	2.21	0.10	0.10	0.601	272
5.34	2.21	0.10	0.15	0.285	290
5.34	2.21	0.10	0.20	0.144	261
5.54	4.19	0.15	0.10	1.48	354
5.51	3.78	0.20	0.10	1.67	442
5.01	0.689	0.20	0.10	0.289	420
4.81	0.317	0.20	0.10	0.138	435
4.58	0.124	0.20	0.10	0.0549	443

Berliner's results for the iodination of phenol in acetate buffers at 25° in 0.08M-KI can be represented by the equation $k_2[H^+]/K_a = 7.1 \times 10^3$ l mol^{-1} min^{-1} + 8.3 × 10^4 l^2 mol^{-2} min^{-1}$[OAc^-]$. To convert into a form suitable for comparison with the results presented above, it is necessary to correct for the iodide ion effect, by multiplying by $[I^-]^2$, for activity coefficients by multiplying by y_1^2, and dividing by 60 to convert from min^{-1} to s^{-1}. This procedure leads to equation (20). The left hand side of this equation is then the quantity analogous to $k_2[I^-]^2/R$ in (19), hence the coefficients on the right hand side of (20) may be compared with those obtained from (19) in Table 3, *viz.* 1.2 × 10^2 l mol^{-1} s^{-1} and 1.57 × 10^3 s^{-1} respectively; the coefficients for oxine are then *ca.* 300 times those for phenol.

$$k_2 a_H y_1[I^-]^2/60\ K_a = 0.41\ \mathrm{l\ mol^{-1}\ s^{-1}} + 4.8\ \mathrm{s^{-1}}[OAc^-] \qquad (20)$$

In terms of mechanism (I) above, this implies that the product kK_4 for oxine is *ca.* 300 times as great as for phenol; it should be noted, however that the oxine results refer to an ionic strength of 0.40M and the phenol results to 0.3M. Berliner found [2] for phenol a decrease of *ca.* 10% in rate when the ionic strength was increased from 0.3 to 0.4M.

TABLE 2

Iodination of oxine at 40°

[oxine] 1—4 × 10^{-3}M; ionic strength 0.40M; $[I^-]$ 0.10—0.30M

pH	10^5R	$[OAc^-]$/M	$10^2k_2[I^-]^2$/ mol l^{-1} s^{-1}	$k_2[I^-]^2$ R^{-1}/mol l^{-1} s^{-1}
5.31	3.93	0.10	4.69	1 195
4.64	0.377	0.10	0.485	1 288
4.33	0.107	0.10	0.136	1 276
5.49	6.70	0.15	9.23	1 378
4.77	0.621	0.15	0.849	1 368
4.64	0.377	0.15	0.509	1 352
5.61	9.40	0.20	15.1	1 607
4.89	0.966	0.20	1.59	1 645
4.78	0.644	0.20	1.06	1 646
5.71	12.34	0.25	21.1	1 710
4.99	1.38	0.25	2.38	1 727
4.71	0.494	0.25	0.864	1 749
5.79	15.26	0.30	30.2	1 980
5.07	1.81	0.30	3.78	2 087
4.79	0.669	0.30	1.28	1 914

The values of k_0 at 25 and 40° lead to an approximate enthalpy of activation $\Delta H^\ddagger$ of 99 kJ mol^{-1}, comparable to the value of 105 kJ mol^{-1} found for phenol by Berliner, from measurements at 25 and 35°.[2] These values include the enthalpy changes for the tri-iodide and any other equilibria involved, *e.g.* that associated with K_4.

TABLE 3

Buffer catalysis of oxine iodination at 25 and 40°

$[OAc^-]$/M	0.05	0.10	0.15	0.20	0.25	0.30
k_{25} [a]/l mol^{-1} s^{-1}	195	287	354	435		
k_{40} [a]/l mol^{-1} s^{-1}		1 253	1 366	1 633	1 729	1 994

At 25°, equation (19) gives $k_0 = 121 \pm 9$;[b] $k_{cat} = 1\,570 \pm 65$ [b] (r 0.998); at 40°, equation (19) gives $k_0 = 857 \pm 68$;[b] $k_{cat} = 3\,690 \pm 318$ [b] (r 0.989).

[a] $k = k_2[I^-]^2/R$. [b] Standard deviation.

The results in Tables 1 and 2 are consistent with the mechanism of iodination of oxine being similar to that for phenol. In spite of the similarity in the $\Delta H^\ddagger$ values for iodination of phenol and of oxine, comparison of the k_0 and k_{cat} values indicates a significantly greater reactivity for oxine, as was found [10] for bromination at low pH, although the mechanism proposed for bromination involved reaction of molecular bromine with unionised

---

[17] E. Berliner, *J. Chem. Educ.*, 1966, **43**, 124.

[18] C. W. Davies, 'Ion Association,' Butterworths, London, 1962, 41.

oxine. Evaluation of the bromination rate constant is complicated by the occurrence of disubstitution, but the treatment employed[10] appears sound; the results presented are certainly not compatible with a reaction between molecular bromine and the oxinate anion. Because of the low rate of iodination of oxine in acetate buffers, and the high rate of bromination in 0.1M-perchloric acid, it is unlikely that a direct comparison of the two halogenations could be effected under similar conditions. In its greater reactivity than phenol in both these halogenation reactions, oxine shows more resemblance, not unexpectedly, to α-naphthol. Kozak *et al.*[10] reported the rate of bromination of α-naphthol to be too high to be measured under conditions similar to those employed for oxine and phenol;[19] the difficulties in measuring the rate of iodination of α-naphthol have been mentioned above.

On the evidence available, it appears that the mechanism for bromination and iodination of oxine are different, in agreement with the suggestion of Gershon *et al.*[9] These authors predicted, however, from localization energies, that reaction of oxine as the anion should lead to substitution in position 7, and that 5-substitution would result from reaction as HA or H_2A^+. Bromination and iodination both lead to 5-substituted products, so the observed orientation is compatible with the mechanism proposed[10] for bromination, but not for iodination. A possible explanation is that localization energies are perhaps inappropriate measures of reactivity for reactions proceeding through a cyclohexadienone intermediate [mechanism(I)], where the rate-determining step is proton removal.

Our thanks are due to S. Maccarrone for performing some initial kinetic measurements at 25°.

[5/929 *Received*, 16*th May*, 1975]

---

[19] G. S. Kozak and Q. Fernando, *Analyt. Chim. Acta*, 1962, **26**, 541.