The Iodination of Glyoxaline.

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A kinetic study has been made of the iodination of glyoxaline, by iodine in aqueous solution, at about pH 7. The rate equation consists of two terms, one suggesting the reaction of the glyoxaline anion with I^+ or H_2OI^+, and the other, involving dependence on the square of the glyoxaline concentration, indicating self-catalysis by glyoxaline.

The position of electrophilic substitution in glyoxaline appears to depend on the substituting agent; *e.g.*, iodination (Pauly and Arauner, *J. pr. Chem.*, 1928, **118**, 33) and diazo-coupling (Fargher and Pyman, *J.*, 1919, **115**, 217) lead to substitution at the 2-position, while bromination (Balaban and Pyman, *J.*, 1922, **121**, 947) leads to substitution at the 4(5)-position. It has been suggested that this is due to a difference in mechanism, the glyoxaline anion reacting initially at the 2-position, and the neutral molecule at the 4(5)-position (Brown, Duffin, Maynard, and Ridd, *J.*, 1953, 3937; Bassett and Brown, *J.*, 1954, 2701). The kinetics of the iodination have therefore been studied to determine whether they are consistent with the prior formation of the glyoxaline anion.

The iodination of the glyoxaline ring in histidine has already been studied kinetically by Li (*J. Amer. Chem. Soc.*, 1944, **66**, 225). However, this is an unsuitable guide to the behaviour of glyoxaline, for the amino-acid side chain greatly alters the reactivity of the glyoxaline ring, making it very resistant to iodination. Brunings (*ibid.*, 1947, **69**, 205) was thus unable to prepare *C*-iodohistidines under Li's kinetic conditions, obtaining only highly coloured compounds of uncertain composition. Li found that the reaction was buffer-catalysed, but did not separate the catalysed and the uncatalysed rate.

In the work now reported, catalysis by extraneous buffers has been avoided by using a large excess of glyoxaline, partially neutralised with perchloric acid, to buffer the solution. A solution of iodine in potassium iodide was added to this, and the reaction was followed by estimating the iodine concentration. The concentrations of glyoxaline and iodide ions were at least twenty times the iodine concentration, and so remained effectively constant during a kinetic run, in spite of the formation of iodide ions in the reaction. The reaction was then found to be of the first-order with respect to stoicheiometric iodine. Table 1

Table 1.*

10^2[GH]	10^2[$HClO_4$]	10^2[I^-]	10^3k_1	$10k_2$	10^2[GH]	10^2[$HClO_4$]	10^2[I^-	10^3k_1	$10k_2$
6·0	3·0	2·0	0·282	0·094	5·0	2·5	1·0	0·845	0·338
4·0	2·0	2·0	0·144	0·072	3·0	1·5	1·0	0·384	0·256
2·0	1·0	2·0	0·0492	0·0492	1·5	0·75	1·0	0·138	0·184
7·0	3·5	1·5	0·652	0·186	5·0	2·5	0·75	1·435	0·574
5·0	2·5	1·5	0·384	0·152	3·0	1·5	0·75	0·626	0·417
3·0	1·5	1·5	0·173	0·115	2·0	1·0	0·75	0·329	0·329
8·0	4·0	1·0	1·880	0·470	1·5	0·75	0·75	0·218	0·291

* Throughout, units of k_1 are $sec.^{-1}$; units of k_2 are $sec.^{-1}$ $mole^{-1}$ l.

gives details of a batch of kinetic runs, carried out under buffered conditions giving constant hydrogen-ion concentration, so that the order with respect to glyoxaline and iodide ions could be determined. In all runs, the temperature was 25°, and the ionic strength was brought to 0·05 by addition of sodium perchlorate. The concentrations of glyoxaline (here represented as GH), perchloric acid, and iodide ions are given in cols. 1—3; col. 4 gives the observed first-order rate coefficients (k_1), and the last column gives the second-order rate coefficients (k_2), obtained by dividing k_1 by the concentration of free glyoxaline in the solution.

Since k_2 is not constant at a single iodide-ion concentration, the reaction cannot be of first order with respect to the glyoxaline. In Fig. 1, k_2 is plotted against the free glyoxaline concentration in the solution. At each iodide-ion concentration, the values fall on a straight

line intersecting the axis, [GH] = 0, at a point above the origin. This shows that the reaction rate can be expressed as the sum of two terms, one of first order with respect to glyoxaline, and the other of second order: these will be referred to as the uncatalysed and the self-catalysed reaction respectively. The relative slopes and intercepts show that the rates of both reactions vary approximately as the inverse square of the iodide-ion concentration. When the logarithms of the slopes are plotted against log [I^-], the order is given as −2·1. The same value is obtained from a logarithmic plot of the intercepts, for iodide-ion concentrations of 0·01—0·02M, but the value for the 0·0075M-solutions lies below the line, and the order calculated from the two lowest iodide-ion concentrations is −1·4. For simplicity, subsequent experiments were restricted to iodide-ion concentrations equal to or above 0·01M, so that the inverse-square relation could be used.

FIG. 1.

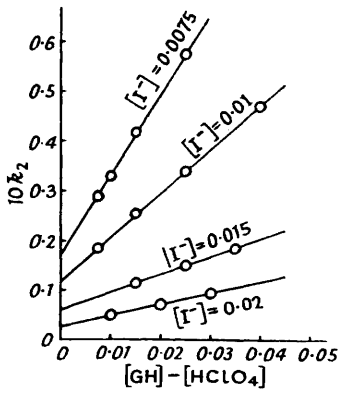

FIG. 2.

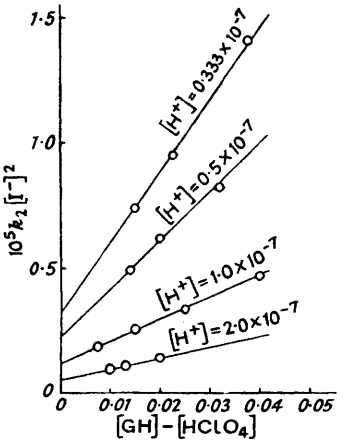

Table 2 gives the results of a number of runs carried out to determine the variation of k_2 with the hydrogen-ion concentration. The values quoted for [H^+] are calculated from the ratio [GH_2^+] : [GH], 10^{-7} being taken as the dissociation constant of the glyoxalinium cation (Albert, Goldacre, and Phillips, *J.*, 1948, 2240); however, this value is not critical, since the conclusions depend only on the relative hydrogen-ion concentrations. The second-order rate coefficients are calculated as in Table 1, and rendered independent of the iodide-

TABLE 2.

10^2[GH]	10^2[$HClO_4$]	10^2[I^-]	10^7[H^+]	10^3k_1	$10k_2$	10^5k_2[I^-]^2
5·0	1·25	2·0	0·333	1·323	0·353	1·412
3·0	0·75	2·0	0·333	0·536	0·238	0·952
2·0	0·5	2·0	0·333	0·278	0·185	0·740
4·8	1·6	1·5	0·5	1·174	0·367	0·826
3·0	1·0	1·5	0·5	0·553	0·276	0·621
2·1	0·7	1·5	0·5	0·307	0·219	0·493
6·0	4·0	1·0	2·0	0·274	0·137	0·137
4·0	2·66	1·0	2·0	0·141	0·106	0·106
3·0	2·0	1·0	2·0	0·095	0·095	0·095

ion concentration by multiplying by [I^-]^2. The values of k_2[I^-]^2 in the last column are plotted against the free glyoxaline concentration in Fig. 2, together with those values from Table 1 for [I^-] = 0·01. Since Table 1 refers to half-neutralised glyoxaline solutions, these values correspond to [H^+] = 10^{-7}. From the relative slopes and intercepts, it is found that both the self-catalysed and the uncatalysed reaction rate are inversely proportional to the hydrogen-ion concentration. When the logarithms of the slopes and intercepts are plotted against log [H^+], the order with respect to hydrogen ions is given as −1·0 for both. The full kinetic equation for the iodination is thus:

$$\text{Rate} = k[GH][I_3^-]/[H^+][I^-]^2 + k'[GH]^2[I_3^-]/[H^+][I^-]^2$$

Discussion.—Berliner's work on the iodination of aniline (*J. Amer. Chem. Soc.*, 1950, **72**, 4003) and phenol (*ibid.*, 1951, **73**, 4307) provides a guide to the interpretation of the kinetic equation. He showed that two reaction paths are present in buffered solutions, one involving iodination by I^+ or H_2OI^+, and the other being buffer-catalysed, possibly by the formation of alternative iodinating agents. Previously the neutral hypoiodous acid molecule had been considered as the iodinating species, but this should be a poor electrophilic reagent, and the results can be re-interpreted in favour of I^+ or H_2OI^+ (Ingold, " Structure and Mechanism in Organic Chemistry," Bell and Sons, London, 1953, p. 290). The species I^+ and H_2OI^+ are here considered as equivalent.

In the solutions used here, the stoicheiometric iodine is mainly present as I_3^-, so that the molecular iodine concentration varies as $[I^-]^{-1}$, and the concentrations of I^+ and H_2OI^+ as $[I^-]^{-2}$. The kinetics of the uncatalysed reaction, and, in particular, the order with respect to $[H^+]$ and $[I^-]$, agree with iodination by I^+ or H_2OI^+ on the glyoxaline anion, and rule out predominant iodination by molecular iodine. The reaction of the glyoxaline molecule through the anion is consistent with the mechanism of diazo-coupling (Brown *et al.*, *loc. cit.*) and with M.O. calculations on the position of substitution (Bassett and Brown, *loc. cit.*).

The self-catalysed reaction is clearly a special example of the general buffer catalysis of iodination. Such catalysis has the kinetic form expected from the formation of alternative iodinating agents by the substitution of I^+ for H^+ in the buffer acid. Thus in acetic acid, the kinetics fit iodination by IOAc, and in solutions buffered by HPO_4^{2-} and $H_2PO_4^-$, the buffer catalysis fits iodination by $IHPO_4^-$ (Painter and Soper, *J.*, 1947, 342). In these glyoxaline solutions, the buffer acid is GH_2^+, so the analogous iodinating agent is the *N*-iodo-cation GHI^+; and the kinetics are consistent with the interaction of this with the glyoxaline anion. Thus, as a result of the following equilibria:

$$I_3^- = I^- + I_2 \quad \ldots \quad (1)$$

$$I_2 + H_2O = H_2OI^+ + I^- \quad \ldots \quad (2)$$

$$GH = G^- + H^+ \quad \ldots \quad (3)$$

$$GH + H_2OI^+ = GHI^+ + H_2O \quad \ldots \quad (4)$$

the equation for the reaction rate can be rewritten in the form

$$\text{Rate} = k[G^-][H_2OI^+] + k'[G^-][GHI^+]$$

where k and k' now include the equilibrium constants for reactions (1)—(4).

If this interpretation is correct, the *N*-iodoglyoxalinium ion must be rapidly formed in a small equilibrium concentration. This presumably occurs by iodination at the unsubstituted " pyridine " nitrogen atom, to form a cation which can then attack the glyoxaline anion in the same way as any other carrier of I^+. However, this self-catalysed reaction is of special interest since its relative importance increases with the glyoxaline concentration, so that under preparative conditions it must largely determine the reaction rate and the position of substitution.

The foregoing discussion refers to the formation of the monoiodo-compound. However, analysis shows that even with a twenty-fold excess of glyoxaline, the main product is a di-iodoglyoxaline; hence the initial reaction must be rapidly followed by a second iodination. This implies that the observed rate coefficients are twice those of the initial reaction; however, the relative values, and hence the mechanistic discussion, are unaffected. The fact that the kinetics are of first order with respect to iodine (as I_3^-) shows that the rate-determining step is the formation of a monoiodo-compound. The rapid iodination of the monoiodo-compound can be understood if this also reacts through the anion, for while the ionised fraction is small, the greater concentration of the iodoglyoxaline anion can more than compensate for its lower reactivity.

Doak and Corwin (*J. Amer. Chem. Soc.*, 1949, **71**, 159) have shown that iodination of substituted pyrroles, in the presence of much greater iodide-ion concentrations, goes through molecular iodine. The relative importance of the I_2 and the H_2OI^+ mechanism

would be expected to depend jointly on the reactivity of the substrate and the iodide-ion concentration, so this is, in part, understandable. In our work, the deviation observed at the lowest iodide-ion concentration cannot be ascribed to a contribution from this mechanism, for the relative equilibrium concentrations of I_2 and H_2OI^+ do not then favour iodination by molecular iodine.

The kinetics of iodination of glyoxaline may be too complex to admit of a unique interpretation. Thus the uncatalysed reaction could be an internal rearrangement of a *N*-iodoglyoxaline to a *C*-iodo-product, and the catalysis by glyoxaline observed could be due to assisted proton loss in this transition state. However, there are a number of points in favour of the anion interpretation; it agrees with the diazo-coupling results, it is consistent with other studies on iodination, it explains the unreactivity of the *N*-methyl compound (Pauly and Gundermann, *Ber.*, 1908, **41**, 3999), and it provides a reason for the apparent change in the initial point of attack.

Experimental

The glyoxaline, recrystallised three times from benzene, had m. p. 89°. The iodine, potassium iodide, perchloric acid, and sodium thiosulphate were "AnalaR" reagents. The sodium perchlorate was dried at 120°, and stored in a vacuum desiccator.

Aqueous solutions of the reagents were prepared and diluted as required for the kinetic runs. The reaction was started by adding a solution of iodine in a twenty-fold excess of potassium iodide to a solution of glyoxaline partially neutralised with perchloric acid and containing, where necessary, sodium perchlorate and more potassium iodide. The solutions were kept in a thermostat at 25°, before and after mixing. The final volume was 100 ml., and the final iodine concentration was 0·0005M, except in the runs where $[I^-] = 0·0075$, where the iodine concentration was reduced to 0·000375. Samples (10 ml.) were withdrawn at suitable intervals and run into N-sulphuric acid (20 ml.), which stopped the reaction. They were immediately titrated with 0·002N-thiosulphate solution, with starch as an indicator. Good first-order kinetics were obtained, the rate constants being calculated from the slope of a logarithmic plot of the titre against time.

The analysis of the products was carried out on ten times the kinetic scale, and with the substitution of hydrochloric acid for perchloric acid, to prevent precipitation of potassium perchlorate on evaporation. The following concentrations were used : [GH] = 0·05, [HCl] = 0·025, $[I^-] = 0·05$, $[I_2] = 0·0025$. After two days the solution was evaporated to 50 ml., cooled, and filtered. The precipitate, after recrystallisation from water, had m. p. 182° (Found : C, 11·6; H, 0·8; N, 9·1; I, 80·0. Calc. for $C_3H_2N_2I_2$: C, 11·3; H, 0·6; N, 8·8; I, 79·4%).

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