604. *The Kinetics of Diazo-coupling and Iodination of Glyoxaline and Some Deuteroglyoxalines.*

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Diazo-coupling of glyoxaline and of 2,4,5-trideuteroglyoxaline occur at about the same rate, but in iodination of these two compounds the $k_H : k_D$-ratio is about 4·5. The iodination is catalysed by glyoxaline and anti-catalysed by iodide ions, but changes in the concentrations of these species have little effect on the $k_H : k_D$ ratio. The relative rates of iodination of 2-deutero-, 4,5-dideutero-, and 2,4,5-trideutero-glyoxaline show that the initial substitution occurs at the 4(5)-position. The mechanism of iodination is discussed in relation to recent studies of the iodination of phenol.

KINETIC studies of the diazo-coupling [1] and iodination [2] of glyoxaline have already been reported, and this work has now been extended to the deuteroglyoxalines. The preparation of 2-deutero-, 4,5-dideutero-, and 2,4,5-trideutero-glyoxaline has recently been described.[3] Analytical figures for deuterium and the proton magnetic resonance spectra of the samples used in these kinetic studies show almost complete deuteration at the stated positions. From related experiments on the deuteration of glyoxaline, it can be calculated that the exchange of deuterium between glyoxaline and the media used for diazo-coupling and iodination is negligible during a kinetic run. The full kinetic isotope effect in these substitution reactions should therefore be observed.

Deuterium-substitution at carbon atoms is known to affect acid–base equilibria at adjacent oxygen or nitrogen atoms.[4] Two such equilibria are important in the diazo-coupling and iodination reported here. The reactions are believed to involve the conjugate base of glyoxaline, and so the acidity of glyoxaline (GH) determines the concentration of the reactive form of glyoxaline (G^-) present in the solution. The basicity of glyoxaline determines the pH of the medium, for, in this work, the equilibrium $GH_2^+ \rightleftharpoons GH + H^+$ was used to buffer the solutions. The effect of deuterium substitution on the equilibrium was carefully investigated but any difference in the basicity of glyoxaline and 2,4,5-trideuteroglyoxaline is less than 0·01 pK unit, and, for our purposes, can be ignored. The same is presumably true of the acidity of the two molecules involved.

Diazo-coupling.—The reaction was carried out in aqueous solution in the presence of a large excess of glyoxaline partly neutralised with perchloric acid. Since these solutions

[1] Brown, Duffin, Maynard, and Ridd, *J.*, 1953, 3937.
[2] Ridd, *J.*, 1955, 1238.
[3] Gillespie, Grimison, Ridd, and White, *J.*, 1958, 3228.
[4] Halevi, *Tetrahedron*, 1957, **1**, 174.

were more acidic than those studied previously, and also contained a far higher concentration of glyoxaline, the kinetic form of the reaction was briefly redetermined. It seemed possible that a base-catalysed term was present in the coupling mechanism, analogous to that found in the presence of similar concentrations of glyoxaline in the kinetics of iodination.

Experiments with different initial concentrations of diazonium ions showed that the reaction was of the first-order with respect to diazonium ions and, where side-reactions could be ignored, the formation of the azo-glyoxaline followed a first-order law during a single kinetic run. Details of some kinetic runs carried out to determine the order with respect to glyoxaline and hydrogen ions are given in Table 1. The third and the fourth column indicate the initial concentrations of glyoxaline (GH) and the glyoxalinium ion (GH_2^+); these determine the hydrogen-ion concentration, and the calculated values of this are given in column 5, the dissociation constant of the glyoxalinium ion being taken as 10^{-7}. The first-order rate coefficient (k_1) is given in column 6, followed by the second-order rate coefficient (k_2) obtained by dividing k_1 by the concentration of unprotonated glyoxaline in the solution. The third-order rate coefficient (k_3) in the last column is obtained by multiplying k_2 by the hydrogen-ion concentration in the solution. The

TABLE 1. *Rate coefficients for the reaction between glyoxaline and diazotised sulphanilic acid.**

Temp.	Ionic strength	[GH] †	$[GH_2^+]$	$10^7[H^+]$	10^4k_1 (sec.$^{-1}$)	10^3k_2 (sec.$^{-1}$ mole^{-1} l.)	10^9k_3 (sec.$^{-1}$)
25°	0·030	0·030	0·030	1·00	12 ‡	4·0	4·0
25	0·030	0·020	0·020	1·00	7·3 ‡	3·6	3·6
25	0·030	0·010	0·010	1·00	3·6 ‡	3·6	3·6
0	0·052	0·033	0·027	0·82	5·5	1·67	1·37
0	0·052	0·043	0·017	0·395	13·8	3·21	1·27
0	0·052	0·073	0·047	0·64	15·4	2·11	1·35

* The concentration of diazonium ions was 5×10^{-5}M for the first three runs and 5×10^{-3}M for the remainder.

† In the work already reported [1, 2] the symbol [GH] is used in the Tables for the stoicheiometric concentration of glyoxaline; here it is used for the concentration of unprotonated glyoxaline in the solution. The latter usage conforms to that in the kinetic equations.

‡ Based on initial rates; see Experimental section.

constancy of k_3 at a given temperature indicates that k_1 is proportional to the glyoxaline concentration and inversely proportional to the hydrogen-ion concentration. The kinetic form therefore fits equation (1), in agreement with the earlier kinetic study. In particular, the first three runs in Table 1 show that there is no significant evidence of base catalysis when the pH is maintained constant.

$$\text{Rate} = k_3[GH][ArN_2^+]/[H^+] = k'[G^-][ArN_2^+] \quad . \quad . \quad . \quad . \quad (1)$$

The diazo-coupling of glyoxaline was then compared with that of 2,4,5-trideuteroglyoxaline. The spectrum of the solutions after reaction agreed with that of the 2-azo-compound apart from a small discrepancy at about 2500 Å, and the calculated concentration

TABLE 2. *Comparison of the coupling of glyoxaline and 2,4,5-trideuteroglyoxaline with diazotised sulphanilic acid at 25°.*

[GH] = 0·033M. $[GH_2^+]$ = 0·027M. $10^7[H^+]$ = 0·82M. $[ArN_2^+]$ = 0·005M.

Time (min.)	Reaction (%) $C_3H_4N_2$	Reaction (%) $C_3D_3HN_2$	Time (min.)	Reaction (%) $C_3H_4N_2$	Reaction (%) $C_3D_3HN_2$
0·0	11	9	2·0	32	30·5
0·5	18	15	2·5	36	35
1·0	23	21	3·0	40	39
1·5	29	27	3·5	43	43

of azo-compound corresponded to about 80% reaction. The details of two of the kinetic runs are given in Table 2; the difference between the initial reaction rates is almost within

the experimental error, but it may be significant because, in other pairs of runs, the deutero-compound was always the slower. However, it is clear that there is no major isotope effect in the reaction.

Iodination.—It has been shown previously [2] that the kinetics of iodination of glyoxaline by molecular iodine in an aqueous solution of potassium iodide follow equation (2); this is equivalent to equation (3) when the equilibria in the solution are taken into account. The reaction path corresponding to the first term in these equations will be referred to as the uncatalysed reaction, and that corresponding to the second as the self-catalysed reaction:

$$\text{Rate} = k\frac{[GH][I_3^-]}{[H^+][I^-]^2} + k_{cat}\frac{[GH]^2[I_3^-]}{[H^+][I^-]^2} \quad . \quad . \quad . \quad . \quad (2)$$

$$\text{Rate} = k'\,[G^-][I^+] + k'_{cat}[G^-][I^+][GH] \quad . \quad . \quad . \quad . \quad (3)$$

The kinetics of iodination of 2,4,5-trideuteroglyoxaline were studied under the same conditions but by a spectrophotometric method instead of by the titration of samples with sodium thiosulphate. The concentrations of glyoxaline (partly neutralised with perchloric acid) and of iodide ions were sufficiently large to remain effectively constant

TABLE 3. *Comparison of the iodination of glyoxaline and 2,4,5-trideuteroglyoxaline at 25°.*

$[H^+] = 10^{-7}$M. $[I^-] = 0{\cdot}01$M. $[I_2] = 0{\cdot}001$M. Ionic strength = 0·05.

	10^4k_1 (sec.$^{-1}$)		10^2k_2 (sec.$^{-1}$ mole^{-1} l.)	
[GH] * = [GH_2^+]	$C_3H_4N_2$	$C_3HN_2D_3$	$C_3H_4N_2$	$C_3HN_2D_3$
0·04	18·8	4·18	4·7	1·05
0·025	8·38	1·89	3·36	0·757
0·015	3·84	0·865	2·56	0·576
0·0075	1·29	0·317	1·72	0·422

* See footnote † to Table 1.

throughout a single kinetic run; the only variable was then the concentration of molecular iodine (present in the solution as I_3^- ions). Excellent first-order kinetics were observed and a set of first-order rate coefficients is compared in Table 3 with those obtained in the same way for the iodination of glyoxaline. From a comparison of the two sets of first-order rate coefficients, it is clear that a major isotope effect is present in the reaction.

These results enable $k_H : k_D$ ratio to be evaluated for both the uncatalysed and the self-catalysed reactions. Second-order rate-coefficients (k_2) obtained by dividing the first-order rate coefficients (k_1) by the concentration of unprotonated glyoxaline or trideuteroglyoxaline are also listed in Table 3. The values of k_2 increase linearly with the substrate concentration because of the self-catalysed term in the kinetic equation. In Fig. 1, the k_2 values are plotted against the substrate concentration (glyoxaline or trideuteroglyoxaline). The relative intercept of the graphs on the vertical axis give the $k_H : k_D$ ratio for the uncatalysed reaction, and the relative slopes of the graphs give the $k_H : k_D$ ratio for the catalysed reaction. Since both graphs can be projected to pass through almost the same point on the axis of abscissæ, it is clear that the kinetic isotope effect is very similar for the two reaction paths. Calculation gives $k_H : k_D = 4{\cdot}36$ for the uncatalysed reaction and $k_H : k_D = 4{\cdot}47$ for the self-catalysed reaction.

The concentration of iodide ions in the above kinetic runs was 0·01M. Some experiments were carried out in the absence of potassium iodide, with 50% (v/v) aqueous methanol as the reaction medium. The kinetic form of the reaction under these conditions was not investigated in detail, but the results showed that the kinetic isotope effect was almost unchanged. The variation of the optical density of the solutions arising from absorption by molecular iodine in the reaction of glyoxaline and 2,4,5-trideuteroglyoxaline under equivalent conditions is shown in Fig. 2; the initial reaction rates vary by about a factor of 4. The maximum concentration of iodide ions arising from the iodination, illustrated

in Fig. 2, cannot exceed 0·0005M. The significance of these results is discussed below with reference to recent studies on the iodination of phenol.

The iodination of glyoxaline under the conditions set out in Table 3 leads mainly to 2,4-di-iodoglyoxaline.[2] The kinetic form of the substitution, and the formation of the di-iodo-product in the presence of excess of glyoxaline, show that introduction of the first iodine atom must be the rate-determining stage. The presence of an isotope effect in the iodination makes it possible to determine the initial position of substitution. The rates

TABLE 4. *Variation of the kinetic isotope effect (at 25°) with the position of deuteration.*

$[GH] = [GH_2^+] = 0{\cdot}04$M. $[H^+] = 10^{-7}$M. $[I^-] = 0{\cdot}01$M. $[I_2] = 0{\cdot}001$M.

	Glyoxaline	2,4,5-Trideutero-	4,5-Dideutero-	2-Deutero-
$10^4 k_1$ (sec.$^{-1}$)	18·8	4·18	5·05	14·9
k_1^H/k_1^D	—	4·5	3·7	1·26

of iodination of glyoxaline and a group of deuteroglyoxalines are shown in Table 4; the large isotope effect observed with the trideutero-compound is mainly present in the

FIG. 1. *Variation of second-order rate coefficient in iodination with substrate concentration*: (○) *glyoxaline*; (●) 2,4,5-*trideuteroglyoxaline*.

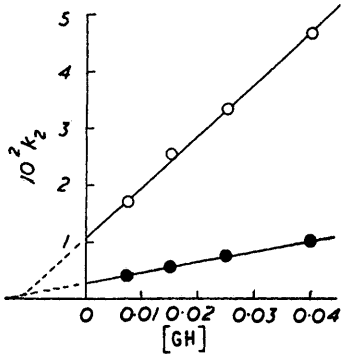
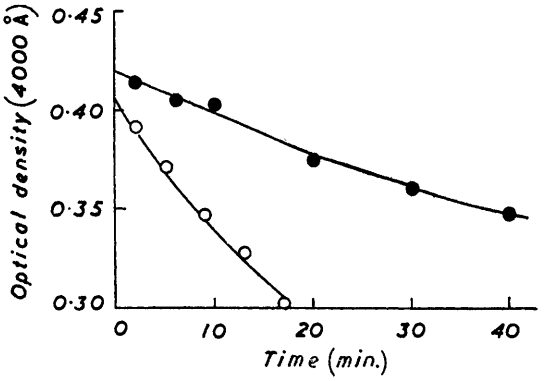


FIG. 2. *Iodination in* 50% (*v*/*v*) *aqueous methanol at* 25°; $[GH] = 0{\cdot}005$M, $[GH_2^+] = 0{\cdot}025$M; $[I_2] = 0{\cdot}0005$M; (○) *glyoxaline*; (●) 2,4,5-*trideuteroglyoxaline*.



iodination of 4,5-dideuteroglyoxaline, but almost absent in the iodination of 2-deuteroglyoxaline. This indicates that the C–H bond at the 4(5)-position is weakened in the rate-determining step, and therefore implies that, under these conditions, the initial substitution is mainly at the 4(5)-position.

The initial substitution has been previously considered to occur at the 2-position, although the evidence for this has never been conclusive and has relied mainly on the isolation of a small amount of the 2-iodo-compound under conditions where the greater part of the iodine is finally present as di- and tri-iodo-compounds.[5] This early work was carried out under strongly alkaline conditions, and a change in the pH of the medium may itself alter the orientation; this point is being investigated further. The fact that at pH 7 iodination leads to attack at the 4(5)-position while diazo-coupling leads to attack at the 2-position, is not fully understood; a possible interpretation has been given elsewhere.[6]

Comparison with Substitution in Phenol.—The above results indicate a significant correspondence between the substitution reactions of glyoxaline and of phenol. The kinetic equations for the diazo-coupling of the two substrates have the same form,[7] and those for iodination differ only in the second term.[8] In the iodination of phenol, the

[5] Pauly and Arauner, *J. prakt. Chem.*, 1928, **118**, 33.
[6] Grimison and Ridd, *Proc. Chem. Soc.*, 1958, 256.
[7] Zollinger, *Chem. Rev.*, 1952, **51**, 347.
[8] Berliner, *J. Amer. Chem. Soc.*, 1951, **73**, 4307.

second term includes a molecule of the buffer; in the iodination of glyoxaline, the second term includes an extra molecule of glyoxaline. This difference can be explained because, in the latter reaction, the concentration of glyoxaline is sufficient for glyoxaline to act as both the substrate and the buffer.[2]

The similarity in the kinetic equations extends also to the kinetic isotope effects. In the diazo-coupling of phenol,[9] as in that of glyoxaline, the $k_H : k_D$ ratio is almost unity. In the iodination of phenol the $k_H : k_D$ ratio has been recently reported[10] to be 3·97; in comparison, the value here reported for the iodination of 2,4,5-trideuteroglyoxaline is 4·5. No evidence on the variation of the $k_H : k_D$ ratio in the iodination of phenol has yet been published.

It is generally agreed that diazo-coupling and iodination of phenol involve substitution of the phenoxide ion, and the above correspondence of the kinetic equations makes it very probable that the same substitutions in glyoxaline also involve the conjugate base of the substrate. The correspondence of the kinetic isotope effects suggests that the transition state for substitution at a carbon atom in the conjugate base of glyoxaline is similar to that for substitution in the phenoxide ion.

As a result of this correspondence, the details of this kinetic study have a bearing on the mechanism of aromatic iodination. There has recently been some discussion[10,11] as to whether the kinetic equation for iodination, illustrated for glyoxaline by equations (2) and (3), results from the attack of I^+ or of H_2OI^+ on the substrate (SH) or involves the reversible formation of an intermediate (SHI^+) by the reaction $SH + I_2 = SHI^+ + I^-$. The intermediate could either lose an I^+ ion by the reverse reaction above, or lose a proton by reaction with some Brönsted base in the solution. If the reaction with iodide ions occurred more readily than that with a Brönsted base, then the proton-loss would be effectively rate-determining, and the kinetic isotope effect would be explained. However, it is then a little surprising that the $k_H : k_D$ ratio should be almost unchanged when the concentration of iodide ions at the start of the reaction is decreased from 0·01M to zero (compare the results in Figs. 1 and 2). This suggests that the isotope effect does not depend on the rapid back-reaction of any intermediate with iodide ions, although it is difficult to be certain that a minute iodide-ion concentration does not compete effectively with the reaction involving proton loss.

A further problem concerns the rôle of the base in the second term of the kinetic equation. From the results in Fig. 1 it can be seen that the $k_H : k_D$ ratio for the self-catalysed reaction is independent of the glyoxaline concentration and almost equal to the $k_H : k_D$ ratio for the uncatalysed reaction. These results are a little more consistent with the idea that the base catalyses the reactions mainly by the formation of an alternative iodinating agent rather than by participating directly in the loss of the proton. In the related iodinations of aniline derivatives the buffer-catalysis remains effective when there is no kinetic isotope effect;[12] this shows clearly that a mechanism of buffer catalysis other than by proton removal is available.

Experimental

Materials.—The glyoxaline was purified by recrystallisation and sublimation; almost all the other reagents were of "AnalaR" quality. The deuteroglyoxalines were prepared as described previously.[3] Hydrogen–deuterium analyses were as follows: 2,4,5-trideuteroglyoxaline, 75% D; 4,5-dideuteroglyoxaline 50·2% D; 2-deuteroglyoxaline, 24·5% D. Slight deuteration at unstated positions may be present in the last two compounds. The basicity measurements were carried out by taking a large number of pH readings on partly neutralised solutions of glyoxaline, a Cambridge pH meter being used in a room maintained at a constant

[9] Zollinger, personal communication of preliminary experiments.
[10] Grovenstein and Kilby, *J. Amer. Chem. Soc.*, 1957, **79**, 2972.
[11] Grovenstein and Henderson, *ibid.*, 1956, **78**, 569.
[12] Shilov and Weinstein, *Nature*, 1958, **182**, 1300.

temperature. Details are available elsewhere.[13] The azo-compound from diazotised sulphanilic acid and glyoxaline was prepared by conventional methods (Found: C, 42·0; H, 3·9; N, 22·5. Calc. for $C_9H_8O_3N_4S$: C, 42·9; H, 3·2; N, 22·2%). The absorption spectrum above 2400 Å in water consists of a single peak of $\lambda_{max.}$ 3660 Å (ε 2·2 × 10^4); in 0·1N-aqueous perchloric acid, this is changed to $\lambda_{max.}$ 3550 Å (ε 2·42 × 10^4).

Kinetic Studies of Diazo-coupling.—The kinetic runs with an initial diazonium ion concentration of 5 × 10^{-5}M were carried out in an optical cell maintained at 25° in a Unicam S.P. 500 spectrophotometer, and were followed from the increase in the optical density at 3660 Å arising from absorption by the 2-azoglyoxaline formed. Kinetic runs involving greater initial concentrations of diazonium ions were followed by extracting samples and running these into 0·1M-aqueous perchloric acid. This stopped the reaction, and the spectrum of the solution was

TABLE 5. *Details of one of the kinetic runs given in Table* 3.

[GH] = 0·04M. $[GH_2^+]$ = 0·04M. $[I^-]$ = 0·01M. $[I_2]$ = 0·001M.

Time (min.)	Optical density at 4400 Å	log (O.D. × 10)	10^4k_1 (sec.$^{-1}$)	Time (min.)	Optical density at 4400 Å	log (O.D. × 10)	10^4k_1 (sec.$^{-1}$)
0	0·520	0·716	—	10	0·169	0·228	18·8
2	0·414	0·617	19·1	12	0·134	0·127	18·9
4	0·332	0·521	18·7	14	0·105	0·021	19·1
6	0·263	0·420	19·0				
8	0·211	0·324	18·8				

then compared with that of solutions of the 2-azo-compound. The faster kinetic runs at 0° led to more than 95% of azo-coupling, but at 25° some side-reaction, presumably the decomposition of the diazonium ion, decreased the yield of azo-compound. The first-order rate coefficients were then calculated from the initial rates. Within each group of runs the ionic strength was brought to a constant value by the addition, where necessary, of sodium perchlorate.

Kinetic Studies of Iodination.—Most of the kinetic runs were carried out by adding a solution of iodine in aqueous potassium iodide at 25° to a partly neutralised solution of glyoxaline in an optical cell maintained at 25° by a thermostat. The ionic strength of the final solution was brought to 0·05 by the presence, where necessary, of sodium perchlorate. Details of a typical kinetic run are given in Table 5. For the kinetic runs illustrated in Fig. 2, this procedure was modified by dissolving the iodine in methanol and by having some methanol present in the glyoxaline solution. The extent of the reaction was determined from the absorption due to molecular iodine and tri-iodide ions at 4400 Å, a Unicam S.P. 500 spectrophotometer being used. The rate constants so calculated agreed excellently with those obtained by extracting samples and titrating the unchanged iodine with sodium thiosulphate. A product analysis carried out under conditions similar to those in the kinetic runs gave 2,4-di-iodoglyoxaline in 67% yield; no other products could be detected.

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[13] Grimison, Ph.D. Thesis, London, 1958.