805. *The Mechanism of the Coupling of Diazonium Salts with Heterocyclic Compounds. Part I. Glyoxaline.*

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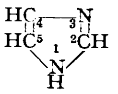
A kinetic study has been made of the coupling of diazotised sulphanilic acid with glyoxaline. It is suggested that the rate-determining step is the reaction between the diazonium ion and the glyoxaline anion, the latter being formed from glyoxaline by ionisation of the N–H bond.

The mechanism of the coupling reaction between diazonium salts and aromatic amines has been investigated by Wistar and Bartlett (*J. Amer. Chem. Soc.*, 1941, **63**, 413), who deduced that it is a bimolecular reaction between the diazonium cation and the free amine. They also concluded that the coupling with phenols arises from a bimolecular reaction between the diazonium cation and the phenoxide ion. Later work has confirmed this (Zollinger, *Chem. Reviews*, 1952, **51**, 347), and it is now accepted that diazonium coupling involves attack by the electrophilic diazonium cation.

However, this picture of the coupling reaction presents some difficulties in the case of the heterocyclic base glyoxaline (I). Glyoxaline has been shown to undergo coupling at the 2-position (Fargher and Pyman, *J.*, 1919, **115**, 217), although other common electrophilic reagents attack the 4(or the tautomerically equivalent 5)-position exclusively. Thus nitration occurs at this position, and, if the 4- and the 5-position are blocked with methyl groups, the resultant molecule is resistant to nitration (Fargher and Pyman, *loc. cit.*). Furthermore, molecular-orbital calculations for glyoxaline (Bassett and Brown, unpublished work) predict electrophilic substitution to favour strongly the 4-position, rather than the 2-position. Schofield (*Quart. Reviews*, 1950, **4**, 382) has suggested that the difference may arise because nitration and similar reactions involve strongly acid media, in which glyoxaline (here represented as GH) will undergo reaction as the cation, GH_2^+, whereas the coupling occurs in moderately alkaline solution and so will involve the neutral glyoxaline molecule. However, the molecular-orbital calculations point to the same qualitative orientation rule for GH and GH_2^+.



(I; ≡ GH)

The present investigation was therefore initiated in an attempt to resolve this anomaly in the chemistry of glyoxaline. The theoretical results do in fact suggest that electrophilic substitution would occur at the 2-position if glyoxaline were coupling through the anion, G^-. The observation that 1-methylglyoxaline does not couple with diazonium compounds (Burian, *Ber.*, 1904, **37**, 696) supports the view that ionisation of the N–H bond is a prerequisite for coupling. Attention was therefore centred on the determination of the reactive form of glyoxaline in the coupling reaction.

EXPERIMENTAL

The glyoxaline was repeatedly recrystallised from benzene until the m. p. was constant (88·5°). The sulphanilic acid, sodium nitrite, and buffer reagents were of "AnalaR" quality. The following buffer solutions were used:

			pH				pH
No. 1	0·070M-Na_2HPO_4	0·030M-KH_2PO_4	7·10	No. 4	0·038M-Na_2CO_3	0·012M-$Na_2B_4O_7$	10·00
2	0·060M-$Na_2B_4O_7$	0·040M-HCl	8·15	5	0·049M-Na_2CO_3	0·001M-$Na_2B_4O_7$	11·00
3	0·100M-$Na_2B_4O_7$	—	9·15				

The ionic strength of each was brought to 0·24 by the addition of potassium chloride.

A 0·05M-solution of sulphanilic acid was diazotised in 0·01N-hydrochloric acid, in the presence of sodium bromide to catalyse the reaction and prevent self-coupling. The diazotised solution was brought to 25°, and, after dilution, the required volume was run into a buffer solution containing glyoxaline, kept in a thermostat at the same temperature. The kinetics of coupling reactions have generally been followed by the photometric estimation of the coupled product, but, because of the pale colour of the azo-compound of glyoxaline and the possibility of further coupling, it was decided to follow the reaction from the diazonium-ion concentration. Samples were therefore extracted and run into a saturated aqueous solution of β-naphthol in 0·1N-borax. The diazonium ion coupled instantly, and was estimated colorimetrically by means of a Hilger Spekker photoelectric absorptiometer. A correction was applied for the azo-compound of glyoxaline present, by a colorimetric estimation on a sample of the reaction mixture in 0·1N-borax alone; however, for the greater part of each kinetic run, this correction was very small.

A large excess of glyoxaline was present in the buffer solution to minimise any further coupling of the monoazo-derivative. As a result, the diazonium-ion concentration decreased according to a first-order law. The first-order rate coefficients obtained were corrected for the decomposition of the diazonium compound, by carrying out runs under identical conditions except for the absence of glyoxaline. This decomposition was found to be a first-order reaction, and the rate coefficients are given in the fourth column of the Table. All rate coefficients were obtained from the slopes of lines fitted to first-order plots by the method of least squares. The corrected first-order rate coefficients for the coupling reaction are given in the sixth column of the Table, for different concentrations of glyoxaline. The appropriate second-order rate coefficients, obtained by dividing the first-order coefficients by the glyoxaline concentration, are given in the last column. The constancy of the second-order rate coefficients at a given pH shows that the reaction rate is proportional to the glyoxaline concentration.

pH	$10^5[Ar{\cdot}N_2^+]$	10^4[GH]	10^5k_1 (dec.) (sec.$^{-1}$)	10^5k_1 (obs.) (sec.$^{-1}$)	10^5k_1 (corr.) (sec.$^{-1}$)	k_2 (sec.$^{-1}$ mole^{-1} l.)
7·10	5·0	10·0	—	7·0	3·0	0·03
7·10	5·0	—	4·0	—	—	—
8·15	2·5	5·0	—	72	59	1·12
8·15	2·5	10·0	—	140	127	1·27
8·15	2·5	—	13	—	—	—
9·15	1·0	1·5	—	175	140	9·54
9·15	1·0	2·0	—	208	173	8·65
9·15	1·0	—	35	—	—	—
10·00	1·0	1·5	—	565	529	35·2
10·00	1·0	—	36	—	—	—
11·00	1·0	1·0	—	493	476	47·6
11·00	1·0	1·5	—	708	691	46·2
11·00	1·0	—	17	—	—	—

DISCUSSION

The results described in the preceding section demonstrate that the initial step in the coupling reaction is bimolecular in conformity with Wistar and Bartlett's results (*loc. cit.*) for aromatic amines. On the assumption that the diazonium ion is the reactive intermediate, the two main possibilities for the initial bimolecular step are:

$$(a)\ Ar{\cdot}N_2^+ + GH \quad \text{and} \quad (b)\ Ar{\cdot}N_2^+ + G^-$$

and these can be distinguished by comparing the experimental curve for log k_2 plotted against pH with the theoretical curves for the two mechanisms above. Calculation of the theoretical curves requires a knowledge of the equilibrium constants of the reactions:

$$GH + H^+ = GH_2^+$$
$$G^- + H^+ = GH$$
$$Ar{\cdot}N_2^+ + OH^- = Ar{\cdot}N_2{\cdot}OH$$

pK_a of the glyoxaline cation is known to be 7·0 (Albert, Goldacre, and Phillips, *J.*, 1948, 2240), and that for glyoxaline has here been taken as 12. This second pK_a is not accurately known, but some recent results from paper electrophoresis suggest that it is in the range 12—13 (Wieland and Schneider, *Annalen*, 1953, **580**, 159). Following Wistar and Bartlett, a pK of 3 has been assumed for the dissociation of the diazo-hydroxide. The fractions below have been calculated at different pH values, and the theoretical curves constructed

$$\frac{[\mathrm{GH}]}{[\mathrm{GH_2}^+]+[\mathrm{GH}]+[\mathrm{G}^-]} \qquad \frac{[\mathrm{G}^-]}{[\mathrm{GH_2}^+]+[\mathrm{GH}]+[\mathrm{G}^-]} \qquad \frac{[\mathrm{Ar{\cdot}N_2}^+]}{[\mathrm{Ar{\cdot}N_2}^+]+[\mathrm{Ar{\cdot}N_2{\cdot}OH}]}$$

by adding together the logarithms of the respective fractions. The theoretical curves for mechanisms "*a*" and "*b*" are shown in Fig. 1, and the experimental results in Fig. 2; it is evident that the experimental results agree with curve *b* and that glyoxaline therefore reacts as the anion.

This conclusion is based on the slopes of the curves in the region pH 7—10, and is very little dependent on the exact values chosen for the second and third dissociation constants.

FIG. 1.

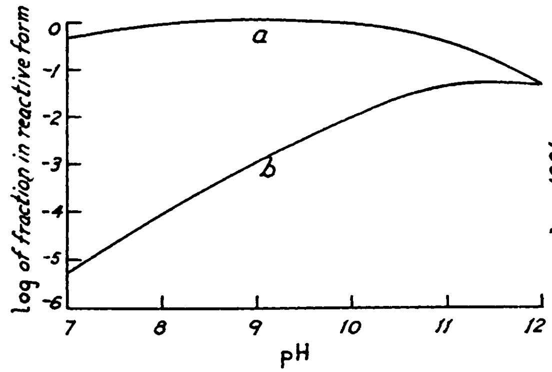
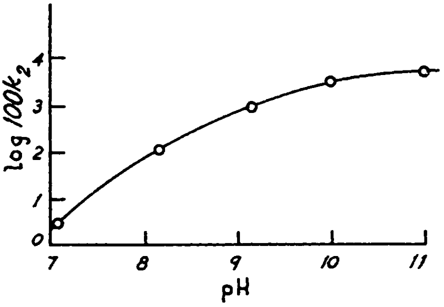


FIG. 2.



Any value greater than 12 for the pK_a of glyoxaline, and any pK below 3 for the dissociation of the diazo-hydroxide, lead to theoretical curves of the same slope. Also, any correction for the subsequent ionisation of the diazo-hydroxide into diazoate ions would depress the theoretical curves at the higher pH values, and thus could never cause curve *a* to correspond to the theoretical results.

The observed dependence of rate on pH could also be explained by assuming that the diazo-hydroxide, not the diazonium ion, is the intermediate concerned. However, this preference could only be justified if the reaction involved free radicals, and the second-order kinetics obtained make this unlikely. Also, the results with pyridine (Haworth, Heilbron, and Hey, *J.*, 1940, 349) show that the free-radical reactions of diazonium compounds lead to phenylation rather than azo-coupling. The possibility of reaction *via* the diazo-hydroxide is thus remote.

The remaining possibility of coupling between the diazonium cation and the glyoxaline anion is in agreement with all the known facts. It explains the failure of the *N*-methyl compound to react, it agrees with previous conclusions that coupling occurs through the diazonium ion, and finally it confirms the molecular-orbital indication that the anion is involved in the reaction.

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