271. *The Mechanisms of* N-*Substitution in Glyoxaline Derivatives. Part I. Introduction, and Study of Prototropic Equilibria involving* 4(5)-*Nitroglyoxaline.*

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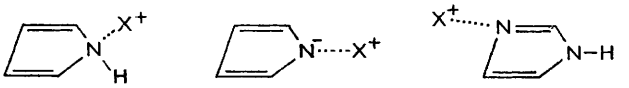
The orientation of *N*-substitution in glyoxaline derivatives is discussed in terms of the reaction mechanism and the tautomeric equilibria involved. A spectrometric study of acid–base equilibria in aqueous solutions of 4(5)-nitroglyoxaline and its *N*-methyl derivatives is reported. The basicity of the 1,5-methyl derivative is greater than that of 4(5)-nitroglyoxaline, but the basicity of the 1,4-isomer is less; these results are related to the position of tautomeric equilibrium in the parent compound.

The mechanisms and orientation of *N*-substitution in glyoxaline derivatives were last discussed in detail by Pyman and his collaborators as part of the general problem of *N*-substitution in amidines.[1] Their studies of *N*-methylation led to empirical rules for predicting the orientation, but their theoretical discussion of the results was limited by a lack of knowledge of the prototropic equilibria involved and by absence of kinetic information on the reaction mechanism. In consequence, the various factors that lead to the observed orientation are not fully understood.[2] This group of papers is concerned with the prototropic equilibria involved in the *N*-methylation of 4(5)-nitroglyoxaline and with the dependence of the reaction mechanism on the acidity of the medium. In Part III, the conclusions drawn from this analysis are extended to other substituted glyoxalines and to substituted benzimidazoles.



(I) S_E2 (II) S_E2cB (III) S_E2'

(1) *Mechanisms of* N-*Substitution.*—The possible mechanisms of *N*-substitution in these compounds have not been classified previously. In any conjugated heterocyclic compound containing an imino-group, there are two mechanisms of *N*-substitution that must be generally available. One involves the attack of an electrophilic species (X^+) on the π-electrons of the conjugated system, leading to a transition state of type (I) (to simplify this discussion, proton transfers are not considered to be rate-determining). The rate of such a reaction should be related to the energy required to localise two π-electrons on the nitrogen atom. The other general mechanism involves the ionisation of the N–H bond followed by reaction of the conjugate base with the electrophilic reagent (transition state II). This mechanism presumably involves the σ-electrons of the nitrogen atom. Further mechanisms are possible in derivatives of glyoxaline. One involves the attack by the electrophilic reagent at the tertiary nitrogen atom of the ring, followed by proton loss from the imino-group (transition state III). These transition states (I), (II), and (III) above have the characteristics designated in other connections by S_E2, S_E2cB, and S_E2' respectively.[3] Another possible mechanism of substitution in glyoxaline derivatives would be by an S_E2-type transition state involving the conjugate acid of the substrate (mechanism S_E2cA). However, no evidence for this mechanism, or for other mechanisms

[1] Pyman, (*a*) *J.*, 1922, **121**, 2616; (*b*) *J.*, 1923, **123**, 367; (*c*) *ibid.*, p. 3359; (*d*) Hazeldine, Pyman, and Winchester, *J.*, 1924, **125**, 1431.

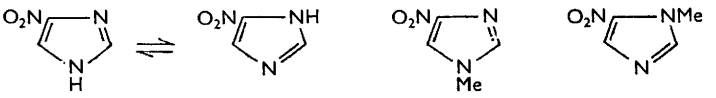
[2] Hofmann, "Imidazole and its Derivatives, Part I," Interscience Publ. Inc., New York, 1953, p. 29.

[3] Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, Chap. 6, 8, and 10.

involving the conjugate acids of the substrates, has been found in this work and they will not be considered further.

The S_E2' mechanism appears to occur much more readily than the S_E2 mechanism for substitution in derivatives of glyoxaline. One illustration of this is the relative reactivity of pyrrole and glyoxaline towards methyl iodide. Substitution by the S_E2 mechanism can occur in both substrates, although it should occur more slowly in glyoxaline because of the deactivating effect of the second nitrogen atom. However, glyoxaline reacts very readily with methyl iodide at room temperature,[4] giving the *N*-methyl derivative: pyrrole reacts much more slowly giving mainly *C*-methyl derivatives.[5] For methylation, the energy barrier for S_E2 substitution at nitrogen appears comparable with that for substitution at carbon. Reactions by the mechanisms S_E2 and S_E2' have the same kinetic form but, because of the apparent difficulty in observing the S_E2 reaction on nitrogen, this kinetic form in the methylation of 4(5)-nitroglyoxaline is taken as evidence of the S_E2' mechanism.

For substitution in a glyoxaline derivative, it is easy to show that the orientation should depend on the mechanism involved. The preferred position of substitution by the S_E2cB mechanism should be at the most nucleophilic nitrogen atom in the conjugate base. In substitution by the S_E2' mechanism the problem is more complex; substitution must occur at an unprotonated nitrogen atom but the substrate will exist as a mixture of two tautomeric forms and the expected relation between the basicity of a nitrogen atom and its nucleophilic power suggests that the tautomer present in lower concentration will have the higher rate coefficient for this mechanism of substitution. Because of the importance of the tautomeric and acid–base equilibria, the study of the methylation of 4(5)-nitroglyoxaline was preceded by an examination of the equilibria involved.



(IVa) (IVb) (V) (VI)

(2) *The Acidity and Basicity of* 4(5)-*Nitroglyoxaline.*—The neutral molecule of 4(5)-nitroglyoxaline exists in solution as an equilibrium mixture of two tautomeric forms (IVa and IVb), both of which can add or lose a proton to form the common conjugate acid and conjugate base. The spectrum of 4(5)-nitroglyoxaline was investigated in ethanol and in a range of aqueous solvents varying in acidity from 0·1M-sodium hydroxide to 5M-perchloric acid. There is one main absorption band whose maximum varies from 350 to 270 mμ as the acidity is increased. The spectrum in ethanol is very similar to that in aqueous solutions at pH 5, and this was taken to be the spectrum of the neutral nitroglyoxaline molecule. In buffer solutions at pH values between 8 and 10, the spectra correspond to an equilibrium between the neutral molecule and the conjugate base, although below 250 mμ the extinction coefficients were unexpectedly high. Conversion into the conjugate base appeared to be complete in 0·1M-sodium hydroxide. The pK of the neutral molecule was calculated from the equation: [6]

$$\mathrm{pH} = \mathrm{p}K + \log\{(\varepsilon_{obs} - \varepsilon_{G^-})/(\varepsilon_{GH} - \varepsilon_{obs})\}$$

where ε_{obs}, ε_{G^-}, and ε_{GH} are the extinction coefficients, at the same wavelength, of the mixture, the conjugate base, and the neutral molecule respectively. Details are given in the Experimental section and the result is included in Table 1.

[4] Wallach, *Ber.*, 1882, **15**, 644.
[5] Elderfield, " Heterocyclic Compounds," Wiley, New York, 1950, Vol. I, pp. 295—299.
[6] Andon, Cox, and Herington, *Trans. Faraday Soc.*, 1954, **50**, 918.

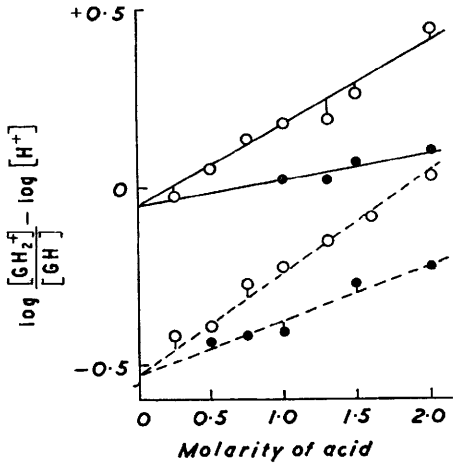
In acidic solutions the spectrum changes in a way consistent with an equilibrium between the neutral molecule(GH) and the conjugate acid(GH_2^+), conversion into the latter being effectively complete in 5M-perchloric acid. The pK of the conjugate acid was first calculated from the concentration ratio $[GH_2^+]/[GH]$ and the H_0 acidity function of

TABLE 1. *The main absorption band and acid–base equilibria.*

Compound	Medium	Form *	$\lambda_{max.}$ (mμ)	$10^{-3}\varepsilon$	pK
4(5)-Nitroglyoxaline	0·1M-NaOH	CB	350	10·19	9·30
	Buffer pH 4·7	N	297	6·40	
	5M-$HClO_4$	CA	269	7·04	−0·05
1-Methyl-5-nitroglyoxaline	H_2O	N	303	8·37	2·13
	M-$HClO_4$	CA	266	6·42	
1-Methyl-4-nitroglyoxaline	H_2O	N	300	7·27	−0·53
	5M-$HClO_4$	CA	269	7·16	

* CB, as conjugate base; N, as the neutral molecule; CA, as conjugate acid.

the medium, but the pK values in hydrochloric acid and perchloric acid did not agree and a more detailed investigation showed that the protonation of 4(5)-nitroglyoxaline in hydrochloric acid deviated significantly from that predicted by the H_0 acidity function. The pK was therefore determined by plotting log ($[GH_2^+]/[GH]$) − log $[H^+]$ against the molarity of the acid and extrapolating to zero concentration (cf. ref. 7). The linear extrapolation to obtain the pK is shown in the Figure, and details of the indicator ratios are given in



Plot for the determination of pK_a *values for* 4(5)*-nitroglyoxaline and* 1*-methyl-4-nitroglyoxaline from measurements in perchloric acid and hydrochloric acid.*

4(5)*-Nitroglyoxaline* ———.
1*-Methyl-4-nitroglyoxaline* – – – –.
Perchloric acid ○.
Hydrochloric acid ●.

Table 2. The pK value obtained (−0·05) agrees with the measurements in both hydrochloric and perchloric acid.

After this work had been completed, values were reported for these two equilibrium constants which had been determined by a potentiometric method.[8] The value obtained for the acidity of the neutral molecule (pK 9·1) is in fair agreement with our work, but that obtained for the acidity of the conjugate acid (pK 1·5) is not, and the discrepancy is far greater than the experimental error of our method. This discrepancy presumably arises from the known difficulties of potentiometric methods in studying the protonation of very weak bases.

(3) *The Basicity of the* N*-Methylnitroglyoxalines.*—Substitution by a methyl group at either of the ring nitrogen atoms has little effect on the spectrum (Table 1) but it does change the basicity. 1-Methyl-4-nitroglyoxaline (V) (pK_a −0·53) is a little less basic than

[7] Long and Paul, *Chem. Rev.*, 1957, **57**, 1.
[8] Bruice and Schmir, *J. Amer. Chem. Soc.*, 1958, **80**, 148.

4(5)-nitroglyoxaline; the protonation was followed in the same way and the results are included in the Figure. 1-Methyl-5-nitroglyoxaline (VI) (pK_a 2·13) is much more basic than 4(5)-nitroglyoxaline and the equilibrium was therefore studied in buffer solutions.

The change in basicity of 2 pK units as a result of methylation is unusually large (for example, the pK's of glyoxaline and *N*-methylglyoxaline differ by less than 0·1 unit [9]) but it can be understood if the predominant tautomeric form of the parent compound has structure (IVa). Then the comparison of the basicities of 1-methyl-5-nitro- and 4(5)-nitro-glyoxaline relates to different nitrogen atoms, and the large substituent effect of the methyl group can be explained by the fact that it releases the more basic nitrogen atom for protonation.

The decrease in the basicity arising from substitution at the other nitrogen atom was unexpected, but it can be shown to be consistent with the above assumption and with the behaviour of glyoxaline. The basicities of glyoxaline and *N*-methylglyoxaline are almost identical,[9] but the interpretation of this fact is complicated by a statistical factor; the glyoxalinium ion has two equivalent ionisable protons, but the conjugate acid of *N*-methylglyoxaline has only one. This factor alone would cause the dissociation constant of the *N*-methylglyoxalinium ion to be half that of the unsubstituted compound; the pK_a should therefore increase by 0·3 unit on methylation. Since this is not observed in the basicity of *N*-methylglyoxaline, the methyl group must effectively reduce the basicity of the other nitrogen atom by this amount. If, as assumed above, 4(5)-nitroglyoxaline in solution has structure (IVa), then, in the conjugate acid of 4(5)-nitroglyoxaline, the two ionisable protons are far from equivalent and in the comparison of the basicities of (IVa) and (V) the statistical factor is absent. It is reasonable therefore that the decrease in the basicity of the other nitrogen atom should be directly observed.

This decrease in basicity is probably a consequence of the decreased solvation of the conjugate acid when an NH group is replaced by an NMe group (cf. ref. 10). It seems probable that this effect should operate about equally for substitution at the two nitrogen atoms, so that the acidity of the conjugate acids of the two *N*-methyl isomers should be proportional to the acidity of the respective protons in the conjugate acid of 4(5)-nitroglyoxaline. If so, then the ratio of the concentrations of the two tautomeric forms of 4(5)-nitroglyoxaline will be the ratio of the dissociation constants of the two *N*-methyl isomers. This argument suggests that in solutions of 4(5)-nitroglyoxaline structure (IVa) predominates by a factor of 400 over structure (IVb). This method of calculating tautomer ratios should be more accurate than the method based on the pK_a of the unsubstituted compound and the pK_a of one of the methyl derivatives.[11]

The greater stability of structure (IVa) than of (IVb) can be related to the qualitative theory of organic chemistry by considering the acidity of the two protons in the common conjugate acid. The electron-withdrawal by the nitro-group would be expected to cause the nearer imino-group to be the more acidic. This presumably outweighs any differential stability of the linear conjugated system in (IVb) over the branched conjugated system in (IVa).

(4) *Correlation of Protonation Equilibria with* H_0.—The extent to which the protonation of substituted glyoxalines follows the acidity function H_0 is of interest because glyoxalines are very different in structure from the aniline derivatives used in establishing the H_0 scale. Some values of the indicator ratios in the protonation of 4(5)-nitro- and 1-methyl-4-nitro-glyoxaline are given in Table 2. These indicator ratios can be compared with those calculated from the pK_a values in Table 1 and the appropriate H_0 values.[7] From such comparisons it seems that the protonation of 4(5)-nitroglyoxaline follows H_0 in perchloric acid, but deviates appreciably from H_0 in hydrochloric acid. In both acids, the protonation of 1-methyl-4-nitroglyoxaline increases more rapidly with acidity than

[9] Bender and Turnquest, *J. Amer. Chem. Soc.*, 1957, **79**, 1656.
[10] Hall, *J. Amer. Chem. Soc.*, 1957, **79**, 5441.
[11] Albert, " Heterocyclic Chemistry," Univ. of London, 1959, p. 59; cf. Mason, *J.*, 1958, 674.

does that of 4(5)-nitroglyoxaline. There is some evidence that *N*-methylation in aniline derivatives increases the dependence of the indicator ratio on the acidity of the medium; *e.g.*, in the comparison of 2,4-dinitroaniline and *NN*-dimethylpicramide.[7]

TABLE 2. *Protonation of 4(5)-nitroglyoxaline and 1-methyl-4-nitroglyoxaline in mineral acids.*

	log ([GH_2^+]/[GH])			
	4(5)-Nitroglyoxaline		1-Methyl-4-nitroglyoxaline	
Molarity of acid	$HClO_4$	HCl	$HClO_4$	HCl
0·25	−0·63	—	−1·02	—
0·50	−0·25	—	−0·69	−0·75
0·75	−0·05	—	−0·40	−0·54
1·0	0·18	0·02	−0·23	−0·40
1·3	0·30	0·13	−0·04	—
1·5	0·44	0·24	—	−0·09
1·6	—	—	0·12	—
2·0	0·74	0·43	0·34	0·08
2·5	0·90	0·67	0·53	0·25
3·0	1·20	—	0·75	0·40

EXPERIMENTAL

Materials.—4(5)-Nitroglyoxaline (m. p. 309°) was prepared by the method of Fargher and Pyman.[12] It was repeatedly crystallised from acetic acid and dried *in vacuo* at 100° for several hours. 1-Methyl-5-nitroglyoxaline (m. p. 55°) was prepared by a modification of the method of Hazeldine, Pyman, and Winchester,[1d] but with repeated crystallisation from light petroleum (b. p. 40—60°) replacing purification through the picrate. 1-Methyl-4-nitroglyoxaline (m. p. 133°) was prepared by the method of Allsebrook, Gulland, and Story,[13] and was repeatedly crystallised from benzene.

pH *Measurements.*—These were carried out with a Doran pH meter and conventional electrodes. Solutions were brought to 25° before use, and measurements were made by using an insulated cell in an air-jacket at the same temperature. Borate and carbonate buffer solutions were used at about pH 9, and partly neutralised mono-, di-, and tri-chloroacetic acid solutions were used at about pH 2.

Spectrometric Measurements.—These were carried out on a Unicam S.P. 500. In the measurements on buffer solutions, the cells were thermostatically maintained at 25°. The pK values for 4(5)-nitroglyoxaline at about pH 9 were based on optical densities at 340 and 360 mμ; the pK values for 1-methyl-4-nitroglyoxaline at about pH 2 were based on optical densities at 260 and 310 mμ. A small ionic-strength correction was made to obtain the thermodynamic pK values listed in Table 1. Most of the measurements involving mineral acids were carried out at room temperature (~20°); comparative experiments showed that the difference between these results and those at 25° was negligible. The values of the indicator ratios in Table 2 are based on optical densities at 300 and 310 mμ. The spectra of the neutral molecules and the conjugate acids used in these calculations were obtained under the conditions listed in Table 1, except that a small correction was applied to the spectrum of 1-methyl-4-nitroglyoxaline in 5M-perchloric acid, because about 2% of the neutral molecule should then be present.

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[12] Fargher and Pyman, *J.*, 1919, **115**, 217.
[13] Allsebrook, Gulland, and Story, *J.*, 1942, 232.