A Theoretical Investigation of the Chemical Reactivity of Glyoxaline.

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From a theoretical investigation of the glyoxaline molecule by the molecular-orbital approximation, undertaken in an attempt to elucidate the orientations observed in electrophilic susbtitutions, it is concluded that electrophilic substitutions in acidic media, such as nitration, bromination, and sulphonation, occur in the glyoxaline molecule itself, or in the glyoxalinium cation. In alkaline solution however the substitution must occur in the glyoxaline anion wherever the substitution occurs preferentially in the 2-position. This mechanism applies to diazonium coupling, and is suggested here for the iodination of glyoxaline.

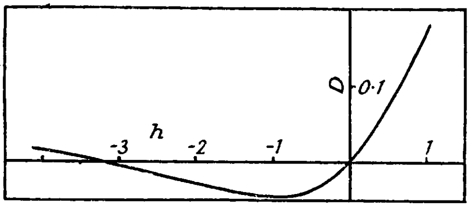
THE chemistry of glyoxaline and its derivatives has been studied in some detail but hitherto the interpretation of some of the observations has proved difficult. In particular it has been difficult to reconcile the facts that nitration and sulphonation occur exclusively, and bromination preferentially, in the 4-position, while diazonium compounds preferentially attack the 2-position, because these reactions are now recognised to be electrophilic substitutions (Ingold, " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, 1953, pp. 269, 297). Schofield (*Quart. Reviews*, 1950, **4**, 382) suggested that the difference might arise if the glyoxalinium cation were involved in the nitration (*i.e.*, under strongly acid conditions) while coupling occurred in the uncharged glyoxaline molecule. Dewar (" The Electronic Theory of Organic Chemistry," Oxford Univ. Press, 1949, p. 193) has also made some theoretical speculations on the reactivity of glyoxaline. A detailed theoretical study has therefore been undertaken of the reactivity of glyoxaline, in terms of the LCAO molecular-orbital procedure.

The two nitrogen atoms, and carbon atoms 4 and 5, were taken to be equivalent by symmetry so far as the system of six π-electrons is concerned. This should be an acceptable assumption if the secondary nitrogen is hybridized sp^2, as in pyrrole (Wilcox and Goldstein, *J. Chem. Phys.*, 1952, **20**, 1656). The resonance integrals of all bonds were taken to have the standard value β, in conformity with previous practice (*e.g.*, Brown, *Quart. Reviews*, 1952, **6**, 63); the carbon atoms were assigned standard coulomb integrals, α, and the nitrogen atoms $\alpha + h\gamma$, h thus being an index of the difference in electronegativity of carbon and nitrogen. All calculations included a standard overlap integral $S = 0{\cdot}250$. Attention was centred on the way in which electron densities and atom-localization energies vary as the relative electronegativity parameter, h, is varied over a wide range of values.

Electron Densities.—The π-electron densities for the various positions in glyoxaline and for various values of h are tabulated in an Appendix. For the discussion of chemical reactivity it is more convenient to consider the quantity $D = q_4 - q_2$ since our main interest is the relative reactivities of the 2- and the 4-position towards electrophilic reagents. Insofar as the charge densities reflect the chemical reactivity, electrophilic substitution would be expected preferentially at position 4 when D is positive, and at position 2 when D is negative. A plot of D as a function of the relative electronegativity parameter, h (Fig. 1), shows that the sign of D changes with varying h : D is positive for positive h, tending to 1 as h tends to $+\infty$, but is negative for h in the range $(-3{\cdot}07, 0)$, and then positive again for h less than $-3{\cdot}07$, passing through a maximum at $-7{\cdot}4$, then tending asymptotically to zero as h tends to $-\infty$. Some details of the technique employed for obtaining these data are given in the Appendix.

These results suggest an interpretation of the observed electrophilic substitutions in glyoxaline. The implication is that electrophilic substitutions in acidic media, such as nitration, sulphonation, and bromination, involve a form of glyoxaline such that nitrogen is more electronegative than carbon (*i.e.*, h is positive), while diazonium coupling involves another form of glyoxaline for which nitrogen is less electronegative than carbon [and h lies in the range $(-3{\cdot}07$ to $0)$]. Now in neutral molecules nitrogen atoms are recognised to be more electronegative than carbon; further, if a nitrogen becomes positively charged, *e.g.*, by protonation, this will enhance its electronegativity and render it still more electronegative than a neutral carbon atom. If however the nitrogen gains a negative charge, such as would arise by the ionization of the proton on a secondary nitrogen atom, this will result in a decrease in electronegativity. Little seems to be known about the magnitude of the change in electronegativity of an atom arising from a change in its formal charge, but it seems possible that a negatively charged nitrogen atom might be *less* electronegative than a neutral carbon atom. The present results imply that diazonium coupling in glyoxaline proceeds through the glyoxaline anion, in which each nitrogen atom carries a formal half electronic charge, and that this is sufficient to make them less electronegative than the ring carbon atoms, corresponding to h in the range -3 to 0. This results in direction of the coupling to the 2-position, whereas nitration occurs through either the neutral glyoxaline molecule or the glyoxalinium cation, for either of which the appropriate value of h is surely positive, resulting in a directive influence favouring the 4-position.

FIG. 1.



The mechanism of diazonium coupling suggested above has recently been confirmed by kinetic studies (Brown, Duffin, Maynard, and Ridd, *J.*, 1953, 3937.). A similar mechanism appears to apply for the iodination of glyoxaline in alkaline solution, in which the 2-position is preferentially attacked. Such iodinations are known to proceed by way of electrophilic substitution by I^+ (or its hydrated form H_2OI^+) (Ingold, *op. cit.*, p. 291). The preferential attack on the 2-position indicates that in the alkaline solutions employed the reaction proceeds through the glyoxaline anion. It is significant also that only glyoxalines with a free imino-group are iodinated. The mechanism suggested by Brunings (*J. Amer. Chem. Soc.*, 1947, **69**, 205), involving initial *N*-iodination and subsequent rearrangement, does not explain why the final product is 2-iodoglyoxaline rather than the 4-isomer.

A further consequence of the above results is that nucleophilic substitution might be expected to be directed in a complementary manner. In the neutral molecule attack would be expected at the 2-position, while the 4-position would be more reactive in the anion. However, the negative charge on the latter would probably completely inhibit any attack by the usual nucleophilic reagents.

Atom Localization Energies.—The values of the atom localization energies, A_e' and A_n', are tabulated in the Appendix for various values of h. The differences, $\Delta A_e' = A_e'(2) - A_e'(4)$, and $\Delta A_n' = A_n'(2) - A_n'(4)$, are plotted against h in Figs. 2 and 3. It emerges that for all values of h, except in the very small range of (0, 0·35), $\Delta A_e'$ is positive (however, values of h greater than +3, for which it appears that $\Delta A_e'$ might become negative, were not investigated because such values do not seem to be physically reasonable, even for positively charged nitrogen). Thus for virtually all values of h it is easier to localize two π-electrons at the 4-position than at the 2-position. It is interesting that Dewar (*op. cit.*) deduced precisely the contrary on the basis of symmetry arguments, so the present results demonstrate the dangers of such qualitative speculations about π-electron energies.

FIG. 2.

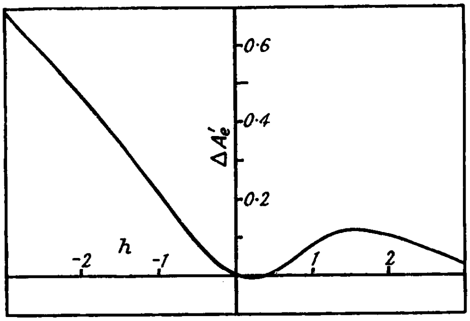
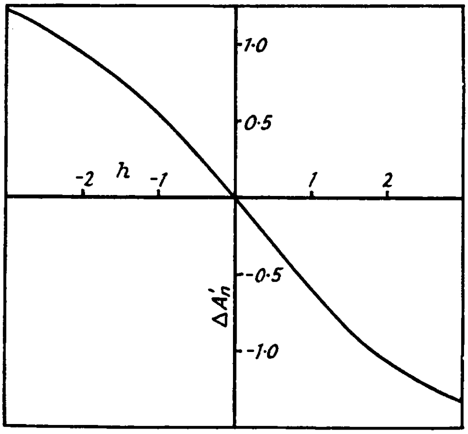


FIG. 3.



For moderate positive values of h, then, both the localization energies and the charge densities indicate that the 4-position would be preferred by electrophilic reagents. The contradiction in the h range (0, 0·35) is trivial because the difference in the two localization energies here is physically quite insignificant, and the actual relative reactivities of the 2- and the 4-position would be expected to lie between those indicated by the localization energies and those indicated by the relative electron densities. So the 4-position would still be expected to be more reactive in this range of h.

Fig. 3 indicates that the nucleophilic localization energies agree with the electron densities, indicating preferential nucleophilic substitution at the 2-position for positive h.

For negative h in the range (—3, 0) the electron densities and localization energies lead to different predictions of orientation for electrophilic substitution. This means (cf. Brown, *loc. cit.*) that the theoretical potential energy curves for the two positions cross somewhere along the reaction co-ordinate. The fact that the charge densities can be made to agree with the observed orientation, and the localization energies cannot, shows that the energy curves cross at a degree of localization between that appropriate for the activated complex and complete localization.

The nucleophilic localization energies are however in agreement with the electron densities for h in the range $(-3, 0)$. Values of h less than -3 are not likely to be physically important, so they do not call for discussion here.

APPENDIX

Electron densities

Position	h: ∞	1	0	-1	-2	-3	-4	$-\infty$
1	2	1·502	1·200	0·903	0·660	0·489	0·375	0
2	0	0·884	1·200	1·429	1·578	1·675	1·740	2
4	1	1·056	1·200	1·383	1·551	1·674	1·755	2

Calculation of dD/dh *for Location of Maximum.*—Several methods suggest themselves for this purpose. Thus a contour integral expression which may be derived for q can be differentiated under the integral and the resultant integral evaluated numerically. Alternatively the residues at the poles within the contours may be evaluated numerically and summed. Another possibility is to differentiate the secular equations with respect to h, and solve the resultant linear equations in the $\mathrm{d}c_r/\mathrm{d}h$ by standard methods, making use of the values of the c_r and $\mathrm{d}x_j/\mathrm{d}h$. Trials showed that the three methods involved similar computational labour. The method of differentiating the secular equations was preferred, however, because the calculations can be made self-checking, while the alternative methods do not offer this advantage.

h	-1	-4	-5	-6	-7	$-7·5$	-8
$10^3\mathrm{d}D/\mathrm{d}h$	+0·64	$-12·15$	$-5·79$	$-2·30$	$-0·45$	+0·084	+0·45

Atom localization energies $(-\gamma)$

	Position	h: -3	-1	$-0·5$	$-0·1$	0	+0·2	0·5	1	1·5	2	3
A_e	2	0·7827	1·1626	1·2947	1·4058	1·4332	1·4862	1·5566	1·6281	1·6215	1·5558	1·4166
	4	0·0969	0·9475	1·2152	1·3970	1·4332	1·4920	1·5434	1·5482	1·5013	1·4469	1·3838
A_n	2	8·0981	4·4655	3·6502	3·0407	2·8952	2·6135	2·2160	1·6281	1·1433	0·7656	0·3018
	4	6·8663	3·9151	3·3606	2·9812	2·8952	2·7339	2·5173	2·2202	1·9943	1·8297	1·6440

$$\text{At } h = 0,\ \mathrm{d}\Delta A_e'/\mathrm{d}h = -\ 0·0690\ (-\ \gamma)$$
$$\mathrm{d}\Delta A_n'/\mathrm{d}h = -\ 0·5979\ (-\ \gamma).$$

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