# *The Stabilities of Some Metal Complexes of* 8-*Hydroxyquinoline and Related Substances.*

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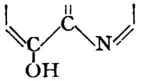
Dissociation constants of 8-hydroxyquinoline (and its 2-, 5-, 6-, and 7-methyl derivatives), 1 : 2 : 3 : 4-tetrahydro-10-hydroxyacridine, 8-hydroxycinnoline (and its 4-methyl derivative), 8-hydroxyquinazoline (and its 2 : 4-dimethyl- and 4-methyl-2-phenyl derivatives), and 5-hydroxyquinoxaline, and the stability constants of the complexes they form with $Mg^{++}$, $Zn^{++}$, $Ni^{++}$, $Cu^{++}$, and $UO_2^{++}$ ions have been measured in 50% v/v aqueous dioxan at 20°. Some factors affecting the stability of these complexes are discussed. Absorption spectra of 8-hydroxyquinazoline and 5-hydroxyquinoxaline and of their derivatives have been measured in acidic, neutral, and alkaline solution to provide further evidence for the position of the basic nitrogen atom in these compounds.

The importance of 8-hydroxyquinoline (" oxine ") and its derivatives in analytical chemistry (cf. Welcher, " Organic Analytical Reagents," van Nostrand, 1947, Vol. 1, Chap. XIII, XIV) has stimulated several quantitative studies of the stabilities of such reagents (*e.g.*, Maley and Mellor, *Austral. J. Sci. Res.*, *A*, 1949, **2**, 92, 579; Albert, *Proc. Biochem. Soc.*, 1950, 47, xxvii; Näsänen *et al.*, *Acta Chem. Scand.*, 1951, **5**, 1199, 1293; 1952, **6**, 352, 837; 1953, **7**, 1261; *Suomen Kem.*, 1953, **32**, 11; Johnston and Freiser, *J. Amer. Chem. Soc.*, 1952, **74**, 5240). These measurements have been made under very different conditions of solvent composition and of ionic strength, and there is little coherent information on which to base a discussion of the effect of substituents in the oxine ring system on the stability of the corresponding metal complexes. The present work aims at a study of the variation in the stability of metal complexes with change in the environment of the functional group (inset). The chelating power of this group is modified by changing the inductive effects on the nitrogen atom and hydroxyl group, both by introducing substituents in the oxine skeleton, and by replacing one –CH= in the heterocyclic ring by –N=. Steric effects due to substituents near the functional group (*e.g.*, in the 2- and the 7-position in oxine) must also be considered.



*Scope of the Work.*—Stability constants, $K_1$ and $K_2$, where $K_n = [ML_n]/[ML_{n-1}][L]$, have been determined for the available reagents with the following bivalent ions selected for diversity of size and electronic configuration: $Mg^{++}$, $Zn^{++}$, $Ni^{++}$, $Cu^{++}$, and $UO_2^{++}$.

Measurements were made in 50% v/v aqueous dioxan, as many of the reagents and complexes are very sparingly soluble in water. A salt background of 0·3M-sodium perchlorate was used throughout, since in this mixed solvent the rate of change of activity coefficient with ionic strength is likely to be small at this concentration (Harned and Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publ. Corp., New York, 1950, p. 548).

*Methods.*—Stability constants of metal complexes were determined by the Calvin–Bjerrum pH-titration technique (Calvin and Wilson, *J. Amer. Chem. Soc.*, 1945, **67**, 2003), and the dissociation constants of the reagents were determined by pH titration in the absence of metal ions. Typical titration curves obtained for oxine are shown in Fig. 1. Formation curves derived from these titrations appear in Fig. 2. The calculation of the dissociation constants and stability constants from the titration curves and the possibility of converting these values into thermodynamic constants is discussed in the preceding paper. All the values reported here are stoicheiometric concentration constants, valid only for the conditions of solvent and ionic background under which they were obtained.

*The Dissociation Constants of the Reagents.*—The stoicheiometric dissociation constants obtained at 20° in 50% v/v aqueous dioxan (0·3M-sodium perchlorate) are given in Table 1 together with the values of the dissociation constants in water, where these are known.

TABLE 1. *Dissociation constants of organic reagents at 20° in 50% v/v aqueous dioxan.*

| | | Aqueous solution | | | 50% Aqueous dioxan | | |
|---|---|---|---|---|---|---|---|
| No. | Reagent | $pK_{OH}$ | $pK_{NH}$ | Ref. | $pK_{OH}$ | $pK_{NH}$ | Ref. |
| 1 | 8-Hydroxyquinoline | 9·85 | 5·00 | 2 | 10·80 | 4·48 | 3 |
| | | | | | 11·54 | 3·97 | 4 |
| 2 | 8-Hydroxy-2-methylquinoline | 10·31 | 5·54 | 5 | 11·01 | 5·01 | 3 |
| | | | | | 11·69 | 4·51 | 4 |
| 3 | 8-Hydroxy-5-methylquinoline | — | — | — | 11·11 | 4·71 | 3 |
| 4 | 8-Hydroxy-6-methylquinoline | — | — | — | 10·71 | 4·76 | 3 |
| 5 | 8-Hydroxy-7-methylquinoline | — | — | — | 11·31 | 4·26 | 3 |
| 6 | 1 : 2 : 3 : 4-Tetrahydro-10-hydroxyacridine | — | — | — | 11·39 | 5·49 | 3 |
| 7 | 8-Hydroxycinnoline | 8·20 | 2·70 | 6 | 8·84 | 1·77 | 3 |
| | | 8·13 | 2·86 | 7 | | | |
| 8 | 8-Hydroxy-4-methylcinnoline | 8·67 | 3·28 | 7 | 9·00 | 2·59 | 3 |
| 9 | 8-Hydroxyquinazoline | 8·65 | 3·41 | 6 | 9·59 | 3·30 | 3 |
| | | 8·54 | 3·36 | 8 | | | |
| 10 | 8-Hydroxy-2 : 4-dimethylquinazoline | 9·41 | 3·79 | 8 | 10·14 | 3·15 | 3 |
| 11 | 8-Hydroxy-4-methyl-2-phenylquinazoline | — | — | — | 10·33 | $<1$ | 3 |
| 12 | 5-Hydroxyquinoxaline | 8·65 | 0·9 | 6 | 9·29 | $<1$ | 3 |
| | | 8·56 | 0·97 | 9 | | | |
| | | 7·98 | 3·05 | 8 | | | |

(1) $pK_{OH} = \log [HA]/[H^+][A^-]$; $pK_{NH} = \log [H_2A^+]/[HA][H^+]$, where HA represents the neutral species. Thus $pK_{OH} = \log {}^{C}K_1{}^{H}$ and $pK_{NH} = \log {}^{C}K_2{}^{H}$ in the terminology of the preceding paper. Thermodynamic dissociation constants for the acids $H_2A^+$ and HA will be given by $\log {}^{T}K_1 = -pK_{NH}$ and $\log {}^{T}K_2 = -(pK_{OH} + 0{\cdot}74)$, $f_{\pm HCl}$ being taken as 0·43 by interpolation from data given by Harned and Owen (*op. cit.*). (2) Irving, Ewart, and Wilson, *J.*, 1949, 2672: thermodynamic constants obtained spectrophotometrically at room temperature. (3) Present authors: stoicheiometric constants obtained at 20° ± 0·2° and ionic strength 0·3M. (4) Johnston and Freiser (*loc. cit.*): Brønsted constants obtained at 25° by pH-titrations at unspecified ionic strength. (5) Phillips, *J. Amer. Chem. Soc.*, 1952, **74**, 552: Brønsted dissociation constants obtained spectrophotometrically at 25° ± 3° and ionic strength 0·1M. (6) Albert and Hampton, personal communication: Brønsted constants obtained by pH-titration at 20° and unspecified ionic strength. (7) Alford, Irving, Marsh, and Schofield, *J.*, 1952, 3009: thermodynamic constants obtained spectrophotometrically at 14° ± 3°. (8) Freeman and Spoerri, *J. Org. Chem.*, 1951, **16**, 438: no details given. (9) Irving and (Mrs.) Rossotti, unpublished work: thermodynamic constants obtained spectrophotometrically at 14° ± 3°.

It will be seen that $pK_{OH}$ is increased by alkyl substitution in the 2-, 5-, and 7-positions of the oxine system, but is almost unchanged by a 6-methyl substituent. This is in accordance with the expected inductive effect. Methyl substitution also increases $pK_{OH}$ in the aza-oxines studied. The observed lowering of $pK_{OH}$ by aza-substitution has also been reported for some 4-hydroxyazaquinolines (Keneford, Morley, Simpson, and Wright, *J.*, 1949, 1356) and may be attributed to the electron-attracting power of the nitrogen atom.

As expected from the inductive effect, $pK_{NH}$ is increased by alkyl substitution in the 2-, 5-, and 2 : 3-positions in oxine, the 4-position of 8-hydroxycinnoline (I), and the 2 : 4-positions of 8-hydroxyquinazoline (II). The very low value of p$K_{NH}$ of 8-hydroxy-4-methyl-2-phenylquinazoline may be attributed to blocking of the basic nitrogen atom by the large phenyl group (cf. Craig, *J.*, 1946, 534). The lowering of p$K_{NH}$ in oxine by substitution of a methyl group in the 7-position may be due to a displacement of the hydroxyl group by the methyl group towards the basic nitrogen atom, thus hindering the approach of protons. The order of values of p$K_{NH}$ for oxine and its aza-derivatives is the same as that established for the parent heterocyclics (Albert, Goldacre, and Phillips, *J.*, 1948, 2240) and, with the exception of 5-hydroxyquinoxaline (III), corresponds with that deduced from the calculations of relative charge distribution made by Longuet-Higgins and Coulson (*J.*, 1949, 971). The very low value obtained for 5-hydroxyquinoxaline differs widely from that reported by Freeman and Spoerri (*loc. cit.*) but is in good agreement with that of Albert and Hampton (*loc. cit.*) and compatible with the very low value of p$K_{NH}$ for the parent quinoxaline for which, following Albert, Goldacre, and Phillips (*loc. cit.*), we postulate very favourable resonance possibilities for the neutral molecule compared with those for the cation :

FIG. 1. *The titration of* 8-*hydroxyquinoline and metal–oxine complexes in* 50% *v/v aqueous dioxan at* 20°.

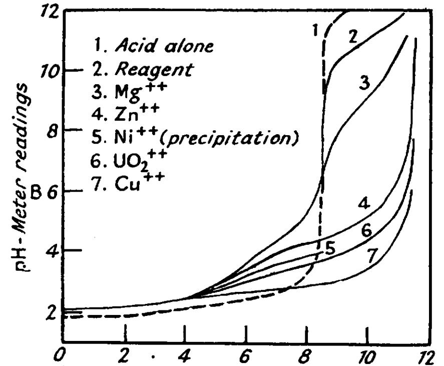
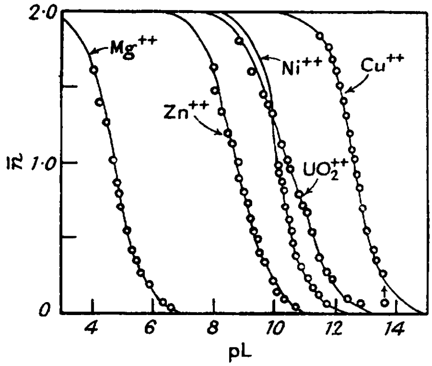
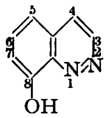


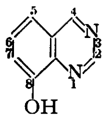
FIG. 2. *The formation curves of metal–oxine complexes in* 50% *v/v aqueous dioxan at* 20°.



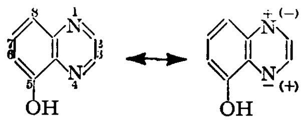
*Full curves are those calculated from values of* $K_1$ *and* $K_2$ *obtained from the experimental points* (*open circles*).



(I)



(II)



(III)

Such resonance would be less likely for cinnolines where the unlike charges would be less well separated. It would be impossible for quinazolines.

The increase in p$K_{OH}$ observed on changing from water to a mixed solvent has frequently been noted for compounds in which a hydroxyl group dissociates (cf. Harned and Owen, *op. cit.*, p. 529; Van Uitert, Haas, Fernelius, and Douglas, *J. Amer. Chem. Soc.*, 1953, **75**, 455). The similar decrease in p$K_{NH}$ has been reported for N–H dissociation in piperidine (Wynne-Jones and Salomon, *Trans. Faraday Soc.*, 1938, **34**, 1321) and in substituted anilines (James and Knox, *ibid.*, 1950, **46**, 1358). The increase in p$K_{OH}$ and concomitant decrease in p$K_{NH}$ with increasing organic content of a mixed solvent has previously been reported for oxine (Maley and Mellor, *loc. cit.*) but without comment, and it considerably complicates any quantitative prediction of the effect of solvent composition upon the stability of metal complexes derived from this type of reagent. An approach to a thermodynamic treatment of this problem will be discussed by the authors elsewhere.

The strengths of the –OH and $>\overset{+}{N}$–H bonds in the acids conjugate to oxine and its alkyl derivatives should be some index of the order of stability of the corresponding metal complexes and, in the absence of steric and other complicating factors, a quantitative relationship between the stabilities of the metal–ligand and proton–ligand complexes might be expected (Calvin and Wilson, *loc. cit.*; Fernelius *et al.*, *J. Amer. Chem. Soc.*, 1953, **75**, 457, 3862; Bruehlman and Verhoek, *ibid.*, 1948, **70**, 1401). Since $\Delta F_n = -2{\cdot}303\boldsymbol{R}T \log_{10} K_n$, the stability constants are really a measure of free-energy changes in the reaction and not simply of changes in the heats of bonding. The significance of entropy changes in complex formation has been discussed by Irving and Williams (*J.*, 1953, 3192).

The influence of $pK_{NH}$ on complex formation in azaoxines is somewhat obscured by lack of conclusive evidence for the position of the more basic nitrogen (to which $pK_{NH}$ refers) which might no longer be that one adjacent to the hydroxyl group.

*The Position of the More Basic Nitrogen Atom.*—Longuet-Higgins and Coulson's calculations (*loc. cit.*) indicate that, for the parent heterocyclic systems, the basic centre will be $N_{(1)}$ in both cinnoline and quinazoline, but in the latter the distribution of charge on the two nitrogen atoms is very similar and the position of the more basic centre might be changed by the presence of substituents. The parent quinoxaline is symmetrical. It has been found (Atkinson and Simpson, *J.*, 1947, 808; Simpson, *ibid.*, p. 1653) that $N_{(1)}$ is the basic centre in 4-methyl- and 4-amino-cinnoline. The large increase in $pK_{NH}$ produced by the substitution of a methyl group in the 4-position of 8-hydroxycinnoline (Alford *et al.*, *loc. cit.*) also indicates that the more basic nitrogen atom is in the $\gamma$-position to the 4-substituent. In the quinazoline derivatives quaternary-salt formation takes place at $N_{(3)}$ in the parent (Gabriel and Colman, *Ber.*, 1904, **37**, 3643) and at $N_{(1)}$ in some 4-substituted derivatives (Morley and Simpson, *J.*, 1948, 360; 1949, 1354).

The absorption spectra of oxine, of 8-hydroxyquinazoline and its available derivatives, and of 5-hydroxyquinoxaline were studied in the hope of elucidating this problem. Measurements of optical absorption were made in alkali ($pH > pK_{OH} + 2$), in alcohol, and in acid ($pH < pK_{NH} - 2$) to give the spectra of the anion, neutral molecule, and cation respectively. The main features of the spectra, together with relevant data from the literature, are given in Table 2.

TABLE 2. *Absorption spectra.*

| In 0·01N-HCl | | In 95% MeOH | | In 0·01N-NaOH | |
|---|---|---|---|---|---|
| λ (mμ) | log ε | λ (mμ) | log ε | λ (mμ) | log ε |
| 8-Hydroxyquinoline [1] | | | | | |
| 252 * | 4·76 | 243 * | 4·54 | 252 * | 4·49 |
| 270 | 2·47 | 275 | 3·13 | 290 | 2·91 |
| 310 * | 3·21 | 310 * | 3·40 | 335 * | 3·45 |
| 315 | 3·20 | | | 345 | 3·44 |
| 320 * | 3·22 | | | 352 * | 3·46 |
| 327 | 3·08 | | | | |
| 358 * | 3·25 | | | | |
| 8-Hydroxycinnoline [2] | | | | | |
| 252 * | 4·62 | 245 * | 4·53 | 236 * | 4·04 |
| 290 | 3·00 | 269 | 2·66 | 240 | 3·95 |
| 300 * | 3·07 | 302 * | 3·03 | 255 * | 4·41 |
| 335 | 2·62 | 306 | 3·01 | 290 | 2·74 |
| 430 * | 3·31 | 315 * | 3·03 | 330 * | 3·43 |
| | | 320 | 3·01 | 356 | 2·94 |
| | | 362 * | 3·43 | 425 * | 3·49 |
| 8-Hydroxy-4-methylcinnoline | | | | | |
| 250 * | 4·39 | 245 * | 4·44 | 255 * | 4·40 |
| 290 | 3·03 | 268 | 2·68 | 288 | 2·76 |
| 305 * | 3·14 | 310 * | 3·09 | 330 * | 3·45 |
| 335 | 2·46 | 320 | 3·05 | 360 | 3·02 |
| 420 * | 3·43 | 360 * | 3·50 | 420 * | 3·59 |
| 8-Hydroxyquinazoline | | | | | |
| 242 | 3·67 | 242 * | 4·39 | 255 * | 4·42 |
| 258 * | 3·83 | 265 | 2·83 | 285 | 2·92 |
| 280 | 3·48 | 325 * | 3·41 | 338 * | 3·56 |
| 298 * | 3·72 | | | | |
| 8-Hydroxy-2 : 4-dimethylquinazoline | | | | | |
| 234 | 3·78 | 244 * | 4·54 | 255 * | 4·38 |
| 254 * | 4·39 | 275 | 3·23 | 285 | 2·87 |
| 280 | 3·23 | 330 * | 3·51 | 335 * | 3·59 |
| 300 * | 3·41 | | | | |
| 325 | 2·94 | | | | |
| 365 * | 3·17 | | | | |
| 8-Hydroxy-4-methyl-2-phenylquinazoline [3] | | | | | |
| 280 * | 4·39 | 270 * | 4·66 | 248 | 4·15 |
| 315 | 3·58 | 300 | 3·68 | 275 * | 4·51 |
| 335 * | 3·67 | 330 * | 3·76 | 310 | 3·29 |
| | | | | 350 * | 3·83 |
| 5-Hydroxyquinoxaline [4] | | | | | |
| 264 * | 4·32 | 252 * | 4·53 | 245 | 4·15 |
| 290 | 2·74 | 288 | 2·96 | 265 * | 4·51 |
| 340 * | 3·65 | 325 * | 3·38 | 298 | 2·92 |
| 361 | 2·69 | | | 320 * | 3·02 |
| 420 * | 2·96 | | | 351 | 2·72 |
| | | | | 415 * | 3·21 |

* Indicates maximum, otherwise minimum.

[1] Cf. Ewing and Steck's diagram, *J. Amer. Chem. Soc.*, 1946, **68**, 2181.

[2] Alford, Irving, Marsh, and Schofield, *loc. cit.*

[3] 0·2N-Hydrochloric acid used in place of 0·01N.

[4] 5N-Hydrochloric acid used in place of 0·01N.

The bathochromic shift and slight decrease in the intensity of the long wave-length band shown by the cations of 8-hydroxy- and 8-hydroxy-4-methyl-cinnoline relative to the spectra of the neutral molecule are very similar to those observed for oxine and may be taken as further indication that $N_{(1)}$ is the more basic centre in these compounds. Similar shifts occur in 8-hydroxy-2 : 4-dimethyl- and -4-methyl-2-phenyl-quinazoline, but the spectrum of the cation of the parent 8-hydroxyquinazoline shows a hypsochromic shift relative to the neutral molecule and a slight increase in intensity. These observations support the suggestion that the more basic centre is $N_{(1)}$ in some 4-substituted quinazolines, but is at $N_{(3)}$ in other quinazoline derivatives. In acidic solutions the absorption spectrum of 5-hydroxyquinoxaline is very similar to that of oxine, but the assignment of the basic centre to $N_{(4)}$ is necessarily tentative in the absence of further data. Thus in all the reagents studied except 8-hydroxyquinazoline, p$K_{NH}$ may always be taken as referring to that nitrogen atom which takes part in the chelation process.

*Stabilities of the Metal Complexes.*—Concentration stability constants for the various metal complexes at 20° in 50% v/v aqueous dioxan (0·3M-sodium perchlorate) are given in Table 3.

TABLE 3. *Stability constants of metal complexes at 20° in 50% v/v aqueous dioxan.*[1]

|  | $Mg^{++}$ | $Zn^{++}$ | $Ni^{++}$ | $Cu^{++}$ | $UO_2^{++}$ |
|---|---|---|---|---|---|
| 8-Hydroxyquinoline |  |  |  |  |  |
| log $K_1$ | 5·04 | 9·34 | 10·43 | 13·03 | 11·25 |
|  | (6·38) [2] | (9·96) | (11·44) | (13·49) |  |
| log $K_2$ | 4·29 | 8·22 | 9·97 | 12·35 | 9·64 |
|  | (5·43) | (8·90) | (9·94) | (12·73) |  |
| 8-Hydroxy-2-methylquinoline |  |  |  |  |  |
| log $K_1$ | 3·73 | 8·66 | 8·52 | 10·22 | $\simeq$9·4 |
|  |  | (10·10) | (9·50) | (13·00) |  |
| log $K_2$ | 3·13 | 8·10 | 7·96 | 9·32 | $\simeq$8·0 |
|  |  | (9·07) | (8·50) | (11·64) |  |
| 8-Hydroxy-5-methylquinoline |  |  |  |  |  |
| log $K_1$ | 5·21 | 9·46 | * | 13·55 | 11·25 |
| log $K_2$ | 4·47 | 8·40 | — | 12·35 | 9·52 |
| 8-Hydroxy-6-methylquinoline |  |  |  |  |  |
| log $K_1$ | 5·09 | * | * | * | 10·89 |
| log $K_2$ | 4·31 | — | — | — | 9·26 |
| 8-Hydroxy-7-methylquinoline |  |  |  |  |  |
| log $K_1$ | 4·64 | 9·31 | * | * | 11·28 |
| log $K_2$ | 4·12 | 8·11 | — | — | 9·78 |
| 1 : 2 : 3 : 4-Tetrahydro-10-hydroxyacridine |  |  |  |  |  |
| log $K_1$ | 3·98 | 8·80 | * | 11·78 | 10·10 |
| log $K_2$ | 3·56 | 7·86 | — | 10·40 | 8·20 |
| 8-Hydroxycinnoline |  |  |  |  |  |
| log $K_1$ | 3·02 | 6·93 | 8·25 | 9·48 | 8·68 |
| log $K_2$ | 2·18 | 5·80 | 7:23 | 8·59 | 7·16 |
| 8-Hydroxy-4-methylcinnoline |  |  |  |  |  |
| log $K_1$ | 3·66 | 7·22 | ~8·5 | * | 9·00 |
| log $K_2$ | 2·58 | 6·47 | ~8·2 | — | 7·30 |
| 8-Hydroxyquinazoline |  |  |  |  |  |
| log $K_1$ | 3·89 | 7·48 | * | 10·56 | 8·99 |
| log $K_2$ | 2·91 | 6·96 | — | 9·54 | 7·70 |
| 8-Hydroxy-2 : 4-dimethylquinazoline |  |  |  |  |  |
| log $K_1$ | 3·81 | 7·77 | 7·88 | 10·26 | 8·77 |
| log $K_2$ | 3·09 | 7·01 | 7·00 | 9·74 | 7·33 |
| 8-Hydroxy-4-methyl-2-phenylquinazoline |  |  |  |  |  |
| log $K_1$ | 0 | 7·03 | * | 8·83 | 8·53 |
| log $K_2$ | — | 5·87 | — | 8·31 | 7·85 |
| 5-Hydroxyquinoxaline |  |  |  |  |  |
| log $K_1$ | 3·44 | 7·07 | 7·79 | 9·66 | 8·40 |
| log $K_2$ | 2·95 | 5·71 | 7·02 | 8·84 | 7·51 |

* = Insoluble.

[1] The values quoted are concentration constants valid for a 0·3M-sodium perchlorate salt background. $f_{\pm \text{HCl}}$ being taken as 0·43 (interpolation from data by Harned and Owen, *op. cit.*), thermodynamic stability constants can be calculated from log ${}^{T}K_1$ = log ${}^{C}K_1 + 1·48$, and log ${}^{T}K_2$ = log ${}^{C}K_2 + 0·74$.

[2] Values in parentheses are those reported by Johnston and Freiser (*loc. cit.*), obtained by pH-titration at 25°. Although there is a systematic variation between the two sets of stability constants obtained for oxine complexes, there is little agreement between Johnston and Freiser's values and those we now report for 8-hydroxy-2-methylquinoline complexes.

The relation between the dissociation constant of a reagent and the stability of its metal complexes has been considered by Calvin and Wilson (*loc. cit.*), Fernelius *et al.* (*loc. cit.*), and Bruehlman and Verhoek (*loc. cit.*) but no quantitative treatment has been proposed. For a given metal and a series of reagents of similar type it can be shown * that the free energy of formation of the metal–ligand complex should be a linear function of the free energy of formation of the proton-ligand complex; the plot of log $K_1$ against p$K$ for the reagent

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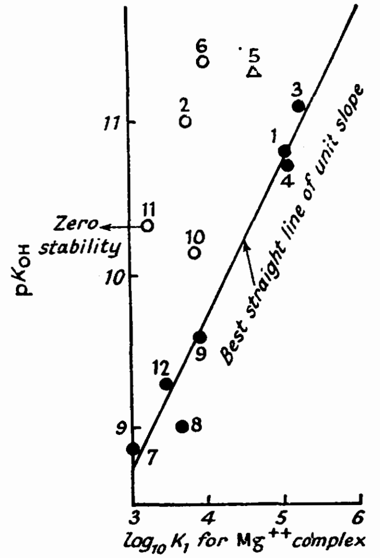
* A full discussion of the thermodynamic derivation of this and related equations will be published shortly (Irving and Rossotti, in preparation).

should be a straight line of unit slope. The plot for magnesium complexes is shown in Fig. 3 together with the best straight line of unit slope.

There are two types of deviation from the theoretically predicted behaviour. (*a*) Major deviations, where log $K_1$ is always smaller than predicted. These are invariably associated with reagents having substituents adjacent to the chelating nitrogen atom, and the stabilities of the metal complexes are clearly decreased by steric hindrance (cf. Irving, Butler, and Ring, *J.*, 1949, 1489). There is no evidence of complex formation between magnesium ions and 8-hydroxy-4-methyl-2-phenylquinazoline.

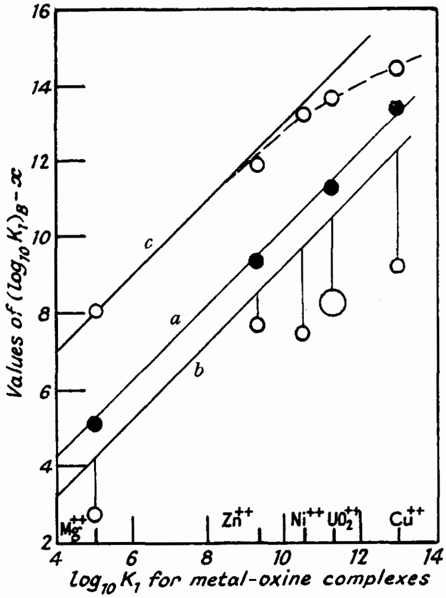
(*b*) Minor deviations, in which log $K_1$ may be either smaller or greater than predicted. Since both oxygen and nitrogen atoms are involved in complex formation, the magnitude of p$K_{OH}$ is not the only factor which influences log $K_1$. The observed minor deviations may well be due to differences in the co-ordinating powers of the nitrogen atoms in the various reagents for which p$K_{NH}$ forms a measure.

FIG. 3.



*Open circles refer to reagents with substituents adjacent to the chelating nitrogen atom. The open triangle refers to the reagent with a substituent adjacent to the chelating oxygen atom. The numbers of the reagents are those given in Table* 1.

FIG. 4. *Intercomparisons of the stability of metal complexes analogous to those of* 8-*hydroxyquinoline.*



*The ordinates represent values of the first stability constants of metal chelates of* (a) 8-*hydroxy*-5-*methylquinoline*; $x = 0$. (b) 8-*Hydroxy*-2-*methylquinoline*; $x = -1{\cdot}0$. (c) 8-*Hydroxycinnoline*; $x = +5{\cdot}0$. *The straight lines have the theoretical slopes and intercepts* (*see text*).

Data for zinc, nickel, and uranyl complexes when plotted in the same way resemble Fig. 3 in displaying large negative deviations for sterically hindered metal complexes; but the minor deviations are more marked than in the case of magnesium and it seems probable that the value of p$K_{NH}$ for the reagent has a greater influence on the stability of complexes formed by these ions, which may form fairly strong metal–nitrogen bonds, than on those of magnesium, which forms only weak links to nitrogen. Indeed, if the metal ion is very strongly bonded to one of the chelating atoms it may appreciably modifiy the inductive effects on the other, so that any simple theoretical prediction of stability based upon the values obtained for the unchelated hydrogen complexes, *i.e.*, upon p$K_{OH}$ and p$K_{NH}$ may be unjustified. Such an effect would be most noticeable among copper complexes where, in fact, a small increase in p$K_{OH}$ gives rise to an abnormally large increase in the stability of the metal complex, and the slope of the best straight line in a plot of log $K_1$ against p$K$(reagent) is 2·2.

Any tendencies towards "specific" behaviour in reagents may be disclosed by comparing the stabilities of complexes formed by a series of cations with different pairs of ligands, A and B. If, for a given cation, the stability of the complex depended only on the strength of the corresponding ligand–hydrogen bond, then the plot of (log $K_1)_A$ against (log $K_1)_B$ for a series of cations should give a straight line of unit slope and of intercept p$K_A$ − p$K_B$.* Some plots of this type, together with the theoretically predicted lines, are shown in Fig. 4, *a*, *b*, *c*, where the abscissæ represent values for log $K_1$ for oxine complexes in every case.

In Fig. 4, *a*, where values of log $K_1$ for 8-hydroxy-5-methylquinoline complexes are plotted as the ordinates, the experimental points fall closely on the theoretical line, as might be expected for reagents which differ only slightly in structure and in their values of p$K_{NH}$. A similar plot (not reproduced) is obtained for complexes of 8-hydroxy-6-methylquinoline but, somewhat unexpectedly, complexes of 8-hydroxy-7-methylquinoline are consistently somewhat less stable than predictable from the values for oxine itself. This may be due either to the lower p$K_{NH}$ of the reagent or to steric effects. Since the deviation occurs even with magnesium complexes, the latter seems more likely. It is noteworthy that the sensitivity of the reactions of 7-methyloxine towards a variety of metal ions was found to be significantly greater than those of oxine itself (Irving, Butler, and Ring, *loc. cit.*).

The ordinates in Fig. 4, *b* are values of log $K_1$ for 8-hydroxy-2-methylquinoline complexes, all of which are seen to be less stable than the p$K_{OH}$ of the reagent would suggest. This is undoubtedly due to steric effects, and it is especially marked for the small magnesium and (presumably) planar nickel ions. Similar plots (not reproduced) are obtained for the pairs of reagents 8-hydroxyquinoline and 1 : 2 : 3 : 4-tetrahydro-10-hydroxyacridine; 8-hydroxyquinazoline (II), and 8-hydroxy-2 : 4-dimethylquinazoline or 8-hydroxy-4-methyl-2-phenylquinazoline. The decrease in stability is most noticeable with the last pair of reagents on account of the size of the 2-phenyl substituent. While steric hindrance to chelation of successive molecules of reagent to a metal ion should be reflected in abnormally large values of the ratios log $K_1/K_2$, log $K_2/K_3$, etc., the lower values of log $K_1$ observed for complexes of every 2-substituted reagent as compared with those for the parent reagent and the same metal provide clear evidence that steric factors are operative even in the chelation of a single molecule of reagent. This supplements results recently reported for the chelation of 1 : 10-phenanthroline and its 3-methyl derivative to ferrous iron (Irving, Cabell, and Mellor, *J.*, 1953, 3417) and for the chelation of ethylenediamine and its *N*-alkyl derivatives to various transition metals (Irving and Griffiths, *J.*, 1954, 213).

Values of log $K_1$ for complexes of 8-hydroxycinnoline form the ordinates in Fig. 4, *c*. The stability constant of the magnesium complex lies on the theoretical line, that for the copper complex lies well below it. Points for other cations are in intermediate positions. The low value of p$K_{NH}$ for 8-hydroxycinnoline compared with the value for oxine would be expected to reduce the stability of its copper complex but to have little effect on that with magnesium. Similar plots (not reproduced) are obtained if values of log $K_1$ for 8-hydroxyquinazoline, 5-hydroxyquinoxaline, or 8-hydroxy-4-methylcinnoline are used as ordinates. If values of log $K_1$ for these reagents are plotted severally against those for 8-hydroxycinnoline, the experimental points lie much nearer to the theoretical line than when 8-hydroxyquinoline complexes are made the basis of comparison as in Fig. 3. Doubtless this is because the variation in p$K_{NH}$ among these reagents is smaller.

The differences log $K_1$ − log $K_2$ for the various metal complexes studied do not indicate a purely statistical addition of the second ligand (Bjerrum, "Metal Ammine Formation in Aqueous Solution," P. Haase and Son, Copenhagen, 1941, p. 40). The differences observed show no definite trend, and it seems probable that the cation is so modified by the addition of the first ligand—not least so far as its solvation sheath is concerned—that the forces leading to the interaction of the singly charged 1 : 1 complex with a further molecule of ligand are of quite a different type and order from those operating between the solvated bivalent ion and the first molecule of ligand (cf. Fernelius *et al.*, *J. Amer. Chem. Soc.*, 1953,

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* See footnote, p. 2914.

**75**, 2739, 3862). In none of the complexes investigated is $K_2 > K_1$. The values of $K_1/K_2$ are consistently high for all uranyl complexes.

Irrespective of the nature of the ligand the stability of these metal complexes always follows the order $Mg^{++} < Zn^{++} < Ni^{++} < UO_2^{++} < Cu^{++}$ whether steric hindrance occurs or not. The only exception is 2-methyloxine where the nickel complex is slightly weaker than the zinc complex. The extent of steric hindrance to complex formation (as estimated by deviations from the theoretical straight lines of Fig. 4) cannot be simply related to any properties of the ions or ligands investigated. Thus the order of increasing deviation is $Zn^{++} < Mg^{++} < UO_2^{++} < Cu^{++}$ for 1 : 2 : 3 : 4-tetrahydro-10-hydroxyacridine, $Zn^{++} < Mg^{++} < Ni^{++} \cong UO_2^{++} < Cu^{++}$ for 2-methyloxine, but $Mg^{++} < Zn^{++} < Ni^{++} \cong UO_2^{++} < Cu^{++}$ for 8-hydroxy-2 : 4-dimethylquinazoline, and $Zn^{++} < UO_2^{++} < Cu^{++} < Ni^{++}$ for 8-hydroxy-4-methyl-2-phenylquinazoline.

## EXPERIMENTAL

*Materials.*—Solutions of metal ions were prepared by weighing out " AnalaR " sulphates (or " AnalaR " uranyl nitrate) into " AnalaR " perchloric acid standardised against carbonate-free sodium hydroxide. Pure anhydrous sodium perchlorate was obtained from a good commercial specimen by repeated recrystallisation from water (Fronaeus, Diss., Lund, **1948**, p. 21). " AnalaR " dioxan was used without further treatment and all water was redistilled from an all-Pyrex still. Carbonate-free sodium hydroxide was prepared as described by Vogel (" Quantitative Inorganic Analysis," Longmans, Green and Co., London, 1951, p. 234) and standardised against " AnalaR " potassium hydrogen phthalate, dried at 115°.

Pure oxine was available and the methyl-substituted oxines and the specimen of 1 : 2 : 3 : 4-tetrahydro-10-hydroxyacridine had been previously prepared in this laboratory (Irving, Butler, and Ring, *loc. cit.*). We are indebted to Dr. K. Schofield, of University College, Exeter, for the cinnoline and quinazoline derivatives, and to Prof. A. Albert, of the Australian National University, for the gift of 5-hydroxyquinoxaline.

*Apparatus.*—Titrations were carried out at 20·0° ± 0·2° in a double-walled Pyrex-glass cell of total capacity 25 ml. Water from a thermostat circulated through the outer jacket. Alkali was added from an " Agla " micrometer syringe (capacity 0·5 ml.) fitted with a capillary glass nozzle bent at right angles to the barrel. The barrel was mounted horizontally and the micrometer screw advanced mechanically by a motor and reduction gear which gave 8 rev./min., equivalent to 0·08 ml./min. The syringe was calibrated by weighing, using mercury, and one large division was found to represent 0·01992 ± 0·00014 ml. The contents of the titration vessel were stirred by a stream of nitrogen freed from carbon dioxide and pre-saturated with solvent. A Doran " Alkacid " sealed glass electrode and a Pye dip-type microcalomel electrode with a fibre liquid junction were used. The pH-meter readings were measured to 0·01 unit with a Cambridge bench-type pH-meter, standardised before, and checked after, each titration with buffer solutions of pH 4·01 and 9·20 at 20° prepared from " Soloid " tablets (Messrs. Burroughs and Wellcome, Ltd.).

*Titration Procedure.*—The carbonate-free alkali was about 1·1N for all titrations. Solutions for the titration of metal complexes were prepared by pipetting 5·00 ml. of 0·0394N-perchloric acid containing 0·6M-sodium perchlorate and 0·006M-metallic salt into the titration vessel and adding 5·00 ml. of dioxan containing 0·012M-reagent. Titration of the reagent alone was carried out by using similar solutions but omitting the metallic salt, and titrations of the acid alone by omitting both metal and reagent. In some systems titrations were also carried out with half the metal concentration prescribed above, but the stability constants thence obtained did not differ by more than 0·02 unit from those determined at the higher metal concentration.

The change in volume on mixing water and dioxan was determined by measuring the densities of the pure liquids and of the mixture. The final volume was found to be 9·850 ± 0·004 ml. instead of 10·000. The concentrations of the reactants were calculated with allowance for this contraction and also for volume changes due to the addition of alkali during the titration (see preceding paper).

*Calculations.*—The method used for computing the formation curves for the various metal complexes (Bjerrum, *op. cit.*) from titration measurements has been described and discussed in the preceding paper. Thence stability constants were obtained by the " correction term " method (Irving and Rossotti, *J.*, 1952, 3397).

*Spectrophotometric Measurements.*—Absorption spectra were measured with a Beckman D.U.

Spectrophotometer using minimum slit widths and matched 1 cm. silica cells. Spectra of cations were obtained by using 5N-hydrochloric acid with 5-hydroxyquinoxaline, 0·2N for 8-hydroxy-4-methyl-2-phenylquinazoline, and 0·01N-hydrochloric acid for all other reagents. Spectra of the neutral molecules were measured in " 95% " methanol prepared by adding 5 ml. of distilled water to 95 ml. of redistilled methyl alcohol previously tested for its optical transparency. The spectra of the anions were obtained in 0·01N-sodium hydroxide. Concentrations of the reagents were varied from $10^{-3}$M to $10^{-5}$M depending upon the part of the spectrum under investigation. All reagents were shown to obey Beer's law in the three solvents in this concentration range.

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