STABILITY CONSTANTS

and

OXIDATION-REDUCTION POTENTIALS

of

COPPER COMPLEXES

Thesis

submitted for the

Degree of Doctor of Philosophy

in

The Australian National University

by

Clifford John Hawkins

Department of Medical Chemistry
John Curtin School of Medical Research
The Institute of Advanced Studies
The Australian National University

The work described in this thesis is the candidate's own, except where otherwise expressly stated.

C. J. Hawkins
Several important oxidising enzymes, such as tyrosinase, contain copper and depend for their activity on the reversible oxidation and reduction of this metal ion which is bound to the apoenzyme. Discussion of the magnitude of the oxidation-reduction potentials of such systems is rendered difficult by the lack of knowledge of factors that govern them and by the paucity of values for model systems. Also, little is known concerning the co-ordination chemistry of the copper(I) ion. For these reasons the present study was undertaken.

The ease with which hydrated Cu⁺ undergoes disproportionation limits the methods of investigation and the types of ligands that can be used. Further, copper(I) and copper(II) complexes of many ligands, such as the heterocyclic and aliphatic nitrogen donors reported in Chapter 2, tend to dissociate under the conditions of the experiments so that their oxidation-reduction potentials have to be calculated from stability constant data.

Where relatively stable complexes are formed, potentials can be determined by direct potentiometric measurements. Results are given in Chapter 3 for 2,9-dimethyl- and 2-chloro-1,10-phenanthroline complexes over a range of temperatures. These, in turn, have enabled the thermodynamic quantities, enthalpy and entropy, to be obtained.
In the course of this work, further information was sought on the metal-binding ability of some of the groups met with in biological systems. Thus, stability constants of copper(II) complexes of some carboxylic acids are given in Chapter 4 and the equilibria in systems of the type, cystine-copper(II), are described in Chapter 5. The latter study, which was aimed at a partial elucidation of the equilibria involved in the cystine-cysteine, copper(II)-copper(I) system, has shown the overriding importance of polynuclear complex formation in the system.

Finally, in Chapter 6 the general factors that govern oxidation-reduction potentials of copper complexes are discussed and theories are put forward to rationalise the values obtained in this work.

Publications based wholly or in part on the work described in this thesis are listed below:


This work has been carried out in the Department of Medical Chemistry of the John Curtin School of Medical Research under the supervision of Dr. D.D. Perrin. I am most grateful to Dr. Perrin for his helpful supervision and interest throughout this project. Grateful acknowledgement is also made to the Australian National University for the award of a Scholarship.
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Appendix 1

The presence of copper in plants was first reported independently by Fleschel (1815) and Neusen (1817) and its presence in animal tissues was discovered a few years later by Bouligny (1875). Copper is essential both in animal (including human) metabolism (McIlroy and Glass, 1950; Scheinberg, 1961), and as a micronutrient for the growth of plants (Arson, 1950; Steinberg, 1950). It is universally distributed throughout the animal kingdom, vertebrates and invertebrates alike, as well as throughout the various forms of plant life.

In recent years, a number of copper metalloproteins have been isolated and purified, and their chemical and physical properties examined (Dawson and Mallevlo, 1945; McIlroy and Glass, 1950; Singer and Karpav, 1954; Scheinberg, 1961; Westerfeld, 1961). The copper-containing proteins, summarised in Table 1.01, include a number of aerobic oxidases which depend for their activity on the ability of the copper to undergo reversible oxidation and reduction. In the resting state of the enzyme the copper is usually divalent, whereas, upon oxidation of the substrate, the copper is reduced to its univalent state. Molecular oxygen completes the cycle by
CHAPTER 1

INTRODUCTION

1.1 The Biological Significance of Copper

The presence of copper in plants was first reported independently by Bucholz (1816) and Meissner (1817) and its presence in animal tissue was discovered a few years later by Boutigny (1833). Copper is essential both in animal (including human) metabolism (McElroy and Glass, 1950; Scheinberg, 1961), and as a micronutrient for the growth of plants (Arnon, 1950; Steinberg, 1950). It is universally distributed throughout the animal kingdom, vertebrates and invertebrates alike, as well as throughout the various forms of plant life.

In recent years, a number of copper metalloproteins have been isolated and purified, and their chemical and physical properties examined (Dawson and Mallette, 1945; McElroy and Glass, 1950; Singer and Kearney, 1954; Scheinberg, 1961; Westerfeld, 1961). The copper-containing proteins, summarised in Table 1.01, include a number of aerobic oxidases which depend for their activity on the ability of the copper to undergo reversible oxidation and reduction. In the resting state of the enzyme the copper is usually divalent, whereas, upon oxidation of the substrate, the copper is reduced to its univalent state. Molecular oxygen completes the cycle by
### Table 1.01

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<td>?</td>
<td>ND</td>
<td>a</td>
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</table>

ND - Not Demonstrated.

converting the copper back to its original valency. This action is diagrammatically represented below,

\[
\begin{align*}
\text{AH}_2 & \quad \text{P-Cu}^{2+} \quad \text{H}_2\text{O} \\
\text{A} & \quad \text{P-Cu}^+ \quad \text{O}_2
\end{align*}
\]

where \(\text{AH}_2\) is the substrate and \(\text{P-Cu}^{2+}\) is the oxidase.

Haemocyanin in its oxygenated form, oxyhaemocyanin, has been found to be responsible for oxygen-transport in the blood of molluscs and arthropods; the copper is univalent in both forms of the protein (Redfield, 1950; Nakamura and Mason, 1960). Further, the formation in vivo of haemoglobin, the oxygen-carrier in human blood, is somehow dependent on the presence of copper (Cartwright, 1950). The remainder of the copper proteins have had no particular function ascribed to them.

In biological systems, copper is also of importance because of the bactericidal and fungicidal action of certain of its complexes. For example, the copper(II) complex of 8-hydroxyquinoline is toxic to the fungus, \(\text{Aspergillus niger}\), and to the bacterium, \(\text{Staphylococcus aureus}\), whereas 8-hydroxyquinoline, per se, is inactive (Albert, 1960). Mice injected with various copper complexes have been protected against such malignancies as Ehrlich carcinoma and Crocker sarcoma (Albert, 1961). The protective effect of isatin-\(\beta\)-thiosemicarbazone against
vaccinia virus infection of mice is thought to be due to the formation of a stable copper complex; vaccinia virus belongs to the pox group of viruses, which are known to be associated with copper in vivo (Albert, 1961).

![Chemical Structures]

8-Hydroxyquinoline  Isatin-β-thiosemicarbazone

A more detailed understanding of the role of copper in biological systems must await an increase in fundamental knowledge of the way in which copper is bound, both in its univalent and divalent states, to various donor atoms. For this reason, a physico-chemical study of complex compounds of both states of copper in aqueous solution has been undertaken by the determination of their oxidation-reduction potentials and stability constants.

1.2 Oxidation-Reduction Potentials and their Determination

(i) Definitions

The thermodynamically reversible system,

$$ML_x^{m+} + (m-n)e \rightleftharpoons ML_x^{n+},$$

will impress upon an inert electrode inserted into the equilibrium mixture a potential, $E$, which is given by the Nernst equation,
\[ E = E^0_{ML_x^{m+},ML_x^{n+}} - \frac{RT}{(m-n)F} \ln \left( \frac{a_{ML_x^{n+}}}{a_{ML_x^{m+}}} \right), \quad (1.01) \]

where \( a_i \) is the activity of the species, \( i \), and \( E^0_{ML_x^{m+},ML_x^{n+}} \) is the standard oxidation-reduction potential for the \( ML_x^{m+}-ML_x^{n+} \) couple and is the potential when both species are at unit activity. Replacement of activities by concentrations gives the formal oxidation-reduction potential, \( E^0_f(ML_x^{m+},ML_x^{n+}) \), as defined in eqn.1.02.

\[ E = E^0_f_{ML_x^{m+},ML_x^{n+}} - \frac{RT}{(m-n)F} \ln \left( \frac{[ML_x^{n+}]}{[ML_x^{m+}]} \right), \quad (1.02) \]

where \([\cdot]\) indicates concentration. Standard and formal oxidation-reduction potentials are temperature-dependent. The latter also depend on the ionic medium; hence they are somewhat limited in their usefulness.

Since it is not possible to determine the absolute potential of an isolated half-cell, the potential must be referred to some standard. By convention, this standard is the hydrogen electrode which, for hydrogen gas at one atmosphere in equilibrium with hydrogen ions at unit activity, has a potential defined as zero at all temperatures.

(ii) The Equivalence Method

According to eqn. 1.02, if the two complexes are fully formed and do not dissociate significantly under the
conditions employed, the formal oxidation-reduction potential of the couple can be determined by measuring the potential impressed upon an inert electrode by a solution containing equal concentrations of the two species. It is also possible to determine the standard oxidation-reduction potential in this way by making measurements at varying ionic strengths. Thus, eqn. 1.01 can be expanded to the expression,

\[ E = E^0 \frac{ML_x^{m+}ML_x^{n+} - RT \ln [ML_x^{n+}] - RT \ln f_{ML_x^{n+}}}{(m-n)F} - RT \frac{\ln f_{ML_x^{m+}}}{(m-n)F} \]

where \( f \) is the activity coefficient of the species indicated. According to Guntelberg (1926), the mean activity coefficient of an electrolyte, XY, is given approximately by eqn. 1.04.

\[ -\log f^+ = A \frac{|z_Xz_Y| I^{1/3}}{1 + I^{1/3}} , \]

where \( A \) is a constant, \( I \) is the ionic strength of the solution and \( z \) is the ionic charge. For a particular ion, \( i \),

\[ -\log f_i = A z_i^2 I^{1/3} \frac{1}{1 + I^{1/3}} . \]

The Guntelberg expression is a good approximation at ionic strengths less than 0.1 (Robinson and Stokes, 1959). By combining eqns. 1.03 and 1.05, it is possible to express...
the measured potential, $E$, as a function of ionic strength:

$$E = E^0_{\text{ML}^\text{m+}, \text{ML}^\text{n+}} - \frac{RT}{(m-n)F} \ln \left[\frac{\text{ML}^\text{n+}}{\text{ML}^\text{m+}}\right] - 2.303RTA(m+n)I_1^\frac{3}{2}. \quad (1.06)$$

Hence the plot of the measured potential, $E$, against $I^\frac{3}{2}/(1+I^\frac{3}{2})$ gives the standard oxidation-reduction potential as intercept of a straight line, slope $-2.303RTA(m+n)/F$, with the potential axis.

(iii) The Stability Constant Ratio Method

If, because of dissociation, the concentration of the complexes which form the couple are not known, the potential is best obtained from the stability constants of the complexes. The theory of the method is as follows. In a solution containing a metal ion, $M$, and a complexing species, $L$, the following equilibria occur.*

$$M + L \rightleftharpoons \text{ML}$$

$$\text{ML} + L \rightleftharpoons \text{ML}_2$$

$$\ldots \ldots \ldots$$

$$\text{ML}_{p-1} + L \rightleftharpoons \text{ML}_p$$

(*Charges omitted here and elsewhere for clarity.)

The equilibrium constant, $K_x$, for any of the above reactions is known as the "thermodynamic" formation constant of the complex, $\text{ML}_x$, and is given by the expression,
\[ t_{K_x} = \frac{a_{ML_x}}{a_{ML_{x-1}} \cdot a_L} \]  

(1.07)

where \( x \) can vary from 1 to \( P \), the maximum number of molecules of \( L \) that bind with the metal ion, \( M \). The overall constant, \( t\beta_x \), where

\[ t\beta_x = \frac{a_{ML_x}}{a_M \cdot a_L} \]  

(1.08)

is known as the "thermodynamic" stability constant of the complex, \( ML_x \), and is also given by

\[ t\beta_x = t_{K_1} t_{K_2} \ldots t_{K_x} \]  

(1.09)

The constants determined in this project are concentration equilibrium constants, defined by

\[ K_x = \frac{[ML_x]}{[ML_{x-1}][L]} \]  

(1.10)

\[ = \frac{t_{K_x} \cdot f_{ML_{x-1}} \cdot f_L}{f_{ML_x}} \]

and

\[ \beta_x = \frac{[ML_x]}{[M][L]^x} \]  

(1.11)

\[ = \frac{t\beta_x \cdot f_M \cdot f_L^x}{f_{ML_x}} \]

(1.14)
Such concentration constants are valid only for a solution of a particular composition. For this reason, in the present work, the activity coefficients were kept constant throughout an experiment by the use of media of constant ionic strength. If the complex is polynuclear, say $M_aL_b$, the concentration stability constant, $\beta_{a,b}$, is given by

$$\beta_{a,b} = \frac{[M_aL_b]}{[M]^a[L]^b} \quad (1.12)$$

Now, in the equilibrium system,

$$M^{m+} + xL \rightleftharpoons ML_x^{m+}$$

$$+(m-n)e \quad \longleftrightarrow \quad +(m-n)e$$

$$K' \quad \quad \quad \quad K''$$

$$M^{n+} + xL \rightleftharpoons ML_x^{n+}$$

the standard oxidation-reduction potential for the couple, $ML_x^{m+}-ML_x^{n+}$, is given by the equation,

$$E^0_{ML_x^{m+},ML_x^{n+}} = \frac{RT \ln K''}{(m-n)F} \quad (1.13)$$

Eqn. 1.13 can be expanded according to eqn. 1.08 to give the expression,

$$E^0_{ML_x^{m+},ML_x^{n+}} = E^0_{M^{m+},M^{n+}} + \frac{RT}{(m-n)F} \ln \frac{t\beta_x^N}{t\beta_x^M} \quad (1.14)$$
where $\rho$ is the activity coefficient quotient, $f(ML_{x}^{n+})f(M^{m+})/\rho f(M^{n+})f(ML_{x}^{m+})$. The standard oxidation-reduction potential can therefore be calculated from eqn. 1.14 if the "thermodynamic" stability constants for the respective complexes and the standard potential for the corresponding aquo couple are known. If the ligand is neutral, it can be assumed that

$$f_{ML_{x}^{n+}}^{n+} = f_{M^{n+}}^{n+} \text{ and } f_{ML_{x}^{m+}}^{m+} = f_{M^{m+}}^{m+},$$

and hence the standard potential can be obtained from eqn. 1.15 by setting $\ln \rho$ equal to zero.

The application of this technique to obtain oxidation-reduction potentials requires accurate stability constant determination for copper(I) and copper(II) complexes.

1.3 Methods of Stability Constant Determination

(i) Copper(II)

The study of equilibria in solutions of metal complexes has been greatly stimulated by the work of Bjerrum (1941) and Leden (1941) who independently developed general methods for computing stepwise formation constants. These
methods have been applied to a large number of experimental techniques (see, for example, Rossotti and Rossotti, 1961). In the present study, two methods, both of which are potentiometric, have been applied to complexes of copper(II).

The pH-titration method, the more widely used technique, was developed by Bjerrum (1941), and the experimental procedure was modified by Calvin and Wilson (1945). It is applicable to systems in which there is competition for the ligand between metal ions and protons. A solution containing a known concentration of Cu$^{2+}$, ligand and, usually, acid is titrated with alkali of known concentration. The hydrogen ion concentration of the solution is determined throughout the titration and, with a knowledge of the acid dissociation constants of the ligand, the stability constants can be calculated.

The second technique utilises the copper-amalgam electrode as a convenient means of determining the activity of free Cu$^{2+}$ ions in a solution; the potential of the electrode is dependent upon the activity of these ions in the solution.

$$E = E^0_{Cu^{2+}/Cu-Hg} + \frac{RT \ln a_{Cu^{2+}}}{2F}$$

Stability constant studies of copper(II) complexes using the copper-amalgam electrode have included work by Bjerrum (1934), Bjerrum and Nielsen (1948), Fronaeus (1948),
Perrin (1961) and Sandell (1961). The scope of the method is limited to those complexes where the equilibrium,

$$\text{Cu}L_x^{2+} + \text{Cu(Hg)} + xL \rightarrow 2\text{CuL}_x^+,$$

is unimportant. In the present investigation the electrode was in the form designed by Dawson and Nair (1950). The stability constants were calculated from a knowledge of the composition of the solution, the acid dissociation constants of the ligand, the standard oxidation-reduction potential, $E^0(\text{Cu}^{2+}/\text{Cu-Hg})$, and the activity of the $\text{Cu}^{2+}$ ions as measured by the electrode.

(ii) Copper(I)

The investigation of copper(I) complexes in aqueous solution is difficult for two reasons. The hydrated $\text{Cu}^+$ ion tends to disproportionate, and it is difficult to obtain the copper(I) complex in solution free of interfering species such as chloride, bisulphite, or mercurous ions.

In the literature, studies have been mainly by solubility and potentiometric (including polarographic) techniques (Bjerrum et al., 1957; Bjerrum et al., 1958). The two most important investigations have been by Bjerrum (1934) who studied the copper(I)-ammonia system by a potentiometric method, based on the equilibrium,

$$\text{Cu}L_x^{2+} + \text{Cu} + xL \rightarrow 2\text{CuL}_x^+,$$

and by James and Williams (1961) who also used a potentiometric
technique to determine a number of copper(I) stability constants. However, it is difficult to assess the accuracy of constants obtained by the latter method, in which solid copper(I) chloride was added to the system, and in which, presumably, there was competitive complex formation for copper(I) ion between the chloride ions and the other ligand; chloride ion forms a number of relatively stable complexes with copper(I) (Bjerrum et al., 1958), but the stability constants of these have not been determined sufficiently accurately for corrections to be applied.

In the present work, copper(I) complexes have been prepared both by chemical reduction of corresponding copper(II) complexes and by electrolytic oxidation of copper metal in the presence of the ligand. Thus, substituted 1,10-phenanthroline complexes with copper(I) have been prepared by the first method, using crystallisation to effect separation from any undesirable species. The stability constants of these complexes can be determined according to eqn. 1.15 from the values for the copper(II) complexes and \( E^0(\text{CuL}_x^{2+}, \text{CuL}_x^+) \), as determined by the equivalence method. The second method, electrolytic oxidation of copper metal, was first used by Náray-Szabó and Szabó (1933) for the study of the copper(I)-chloride system. In theory, the electrolysis of copper in
a solution of a ligand produces both copper(I) and copper(II) complexes according to the equilibrium,

\[
\text{Cu} + xL + \text{CuL}_x^{2+} \rightleftharpoons 2\text{CuL}_x^+.
\]

Once formed, the complexes can be titrated with acid and the resulting changes in the copper(I)-copper(II) equilibrium system in the absence of copper metal can be followed by measurement of the pH of the solution and the e.m.f. of the cell,

\[
\text{Au (Pt)} / \text{Cu}^{2+}, \text{Cu}^+, \text{ligand} // \text{sat. cal.},
\]

where \text{sat. cal.} is the saturated calomel electrode. In practice, however, the method is restricted to those cases where the above equilibrium is in favour of the univalent copper complex to such an extent that sufficient of this complex is present, following electrolysis, to allow an accurate estimation of the stability constants to be made. Independent knowledge of the stability constants of the copper(II) complexes is required.

1.4 An Historical Review of Oxidation-Reduction Potentials of Copper Ions in Aqueous Solution

(i) Aquo Couples

The standard electrode potential of cuprous ion, \(E^0(\text{Cu}^+/\text{Cu})\), has been investigated by a number of workers. The value most commonly taken, 522 mv at 25°, was determined by Fenwick in 1926 from studies on equilibrium,
and is about the average of the values published more recently (Gmelin, 1955).

Numerous attempts have been made over the last sixty years to determine the standard electrode potential of cupric ion, $E^0(Cu^{2+}/Cu)$. The major problem has been the preparation of a copper electrode which is free of surface defects and occluded hydrogen, and which is capable of producing reproducible and accurate results. Lewis and Lacey (1914), and Denham and Pennycuick (1923) claimed that the spongy copper electrode was both constant and reproducible. Getman (1930) found that his results with a single unstrained copper crystal (0.3475 v at 25°) agreed with those which Lewis and Lacey had obtained with the spongy copper electrode. However, Nielsen and Brown (1928) and Newbery (1929) found the latter electrode unsatisfactory due to what they thought was occlusion of hydrogen. The single unstrained copper crystal was later used by Adams and Brown (1937) whose value for the electrode (0.3472 v at 25°) agreed very closely with that of Getman (1930).

Other attempts have been made to determine $E^0(Cu^{2+}/Cu)$, the values varying over the range 343-348 mv at 25° (Gmelin, 1955).

Another approach to the determination of this electrode potential has been to find the value for $E^0(Cu^{2+}/Cu-Hg)$
and to make a correction for the activity of copper in the amalgam. A number of workers have investigated the Cu\(^{2+}\)/Cu-Hg couple, the results obtained being spread over a range of about 10 mv. After applying a correction of -4 mv to the copper-amalgam potential, the range of values for the desired potential, E\(^0\)(Cu\(^{2+}\)/Cu), was found to be 335 - 346 mv (Gmelin, 1955).

Fenwick (1926) obtained the value 167 mv for the standard oxidation-reduction potential, E\(^0\)(Cu\(^{2+}\), Cu\(^+\)), at 25\(^\circ\), and most other workers have found values which do not differ markedly from this value (Gmelin, 1955).

(ii) Complex Couples

Few values for the oxidation-reduction potentials of corresponding pairs of copper(II) and copper(I) complexes in aqueous solution have so far been published. Thus a recent review (Perrin, 1959) listed only four potentials that were considered to be reasonably reliable, namely those for the 1:2-complexes with ammonia, imidazole, and ethylenediamine, and for the sulphides. Subsequently, James and Williams (1961) confirmed to within 20 mv the values for the first three of these and also reported potentials of 1:2-copper complexes in water with morpholine, piperidine, some 1,10-phenanthrolines, 2,2'-bipyridines and \(\alpha\)-aminoacids. They also studied a more extensive series of 1:2-complexes with 1,10-phenanthrolines and
2,2'-bipyridines in 50% dioxan-water, but the relation of the values so obtained to potentials in water is uncertain; in the four cases where aqueous values are also known they are from 84 to 131 mv less positive. The potential determined by James and Williams (1961), \( E^*(\bar{n}_{II}:\bar{n}_I) \), is the measured potential of a system containing equal concentrations of copper(I) and copper(II) when the degrees of formation, \( \bar{n} \), of both copper complexes are the same. Such potentials would correspond to the formal oxidation-reduction potentials if both complexes were fully formed or, more generally, if the stability constants were such that, at \( \bar{n} = x \), both states were mainly in the 1:x-form so that \( [\text{CuL}_x^{2+}]/[\text{CuL}_x^+] = 1 \). Usually, neither of these assumptions can be taken as warranted. Nevertheless, in the absence of data enabling accurate standard potentials to be obtained, values of \( E^*(\bar{n}_{II}:\bar{n}_I) \) provide useful indications of what these potentials might be. For this reason, such values for corresponding pairs of complexes are listed in Table 1.02. Standard potentials calculated from published stability constants using eqn. 1.15 are given in Table 1.03.
Table 1.02
Oxidation-Reduction Potentials of Copper(II)-Copper(I) Couples in Water

<table>
<thead>
<tr>
<th>Ligand</th>
<th>$E_f^* (2:2)$ (v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonia</td>
<td>0.308</td>
</tr>
<tr>
<td>Ethylenediamine</td>
<td>-0.360</td>
</tr>
<tr>
<td>Glycine</td>
<td>-0.160</td>
</tr>
<tr>
<td>Alanine</td>
<td>-0.130</td>
</tr>
<tr>
<td>Sarcosine</td>
<td>-0.130</td>
</tr>
<tr>
<td>Pyridine</td>
<td>0.304$^b$</td>
</tr>
<tr>
<td></td>
<td>0.300$^c$</td>
</tr>
<tr>
<td>2,2'-Dipyridyl</td>
<td>0.120</td>
</tr>
<tr>
<td>4,4'-Dimethyl-2,2'-dipyridyl</td>
<td>0.091</td>
</tr>
<tr>
<td>4,4'-Dicarboxy-2,2'-dipyridyl</td>
<td>0.150</td>
</tr>
<tr>
<td>3,3'-Dicarboxy-2,2'-dipyridyl</td>
<td>0.213$^d$</td>
</tr>
<tr>
<td>2,2', 2''-Terpyridyl</td>
<td>-0.080$^d$</td>
</tr>
<tr>
<td>Morpholine</td>
<td>0.250</td>
</tr>
<tr>
<td>Piperidine</td>
<td>(?0.145)</td>
</tr>
<tr>
<td>Imidazole</td>
<td>0.317</td>
</tr>
<tr>
<td>1,10-Phenanthroline</td>
<td>0.174</td>
</tr>
<tr>
<td>2-Chloro-1,10-phenanthroline</td>
<td>0.400</td>
</tr>
<tr>
<td>2-Methyl-1,10-phenanthroline</td>
<td>0.337</td>
</tr>
<tr>
<td>2,9-Dimethyl-1,10-phenanthroline</td>
<td>0.594</td>
</tr>
</tbody>
</table>

$^a$At 25$^\circ$ and $I = 0.3$, from James and Williams, 1961.
$^b$ $E_f^* (3:3)$; $^c$ $E_f^* (4:4)$; $^d$ $E_f^* (1:1)$. 
**Table 1.03**

Standard Oxidation–Reduction Potentials of Copper Complexes in Water at 20°

<table>
<thead>
<tr>
<th>Ligand</th>
<th>(E^0_{2:2}(v))</th>
<th>(E^0_{2}^*(2:2)(v))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ammonia</td>
<td>0.33</td>
<td>0.308</td>
</tr>
<tr>
<td>Ethylenediamine</td>
<td>-0.38</td>
<td>-0.360</td>
</tr>
<tr>
<td>Imidazole</td>
<td>0.35</td>
<td>0.317</td>
</tr>
</tbody>
</table>

\(E^0_{2:2} = E^0_{CuL_2^{2+},CuL_2^{+}}\), \(E^0_{Cu^{2+},Cu^{+}} = 0.167 \text{ V at } 25^{\circ}\)

\(E^0_{2}^* = 0.162 \text{ V at } 18^{\circ}\)

- \(a\) At 25° and \(I = 0.3\), from James and Williams, 1961 (included for comparison).
- \(b\) At 18° and \(I = 2\), from \(\log \beta_2^I = 10.86\) (Bjerrum, 1934) and \(\log \beta_2^{II} = 7.98\) (Bjerrum, 1931).
- \(c\) At 25° and \(I = 1\), from \(\log \beta_2^I = 10.8\) and \(\log \beta_2^{II} = 20.07\) (Bjerrum and Nielsen, 1948).
- \(d\) At 25° and \(I = 0.15\), from \(\log \beta_2^I = 10.8\) (Li et al., 1954) and \(\log \beta_2^{II} = 7.67\) (Mickel and Andrews, 1955).
- \(e\) Fenwick, 1926.
- \(f\) Corrected for temperature difference with literature value for \(\Delta S^0\) (Hugus, 1951; Wagman, 1951; Latimer, 1952).
Amongst the functional groups that are thought to act as sites for complex formation in biological systems, the amino group is one of the most important, mainly because of its presence in α-amino acids and in proteins containing lysine residues. The imidazole group, by co-ordination through one of its nitrogen atoms, can also form metal complexes (see, for example, Li et al., 1954). This property confers metal-binding ability on the histidine moieties of proteins. It also enhances complex-formation by individual molecules of histidine. Another important complexing group is the carboxylate anion which is found, for example, in all amino acids, in proteins containing glutamic and aspartic acid residues, and in components of many important metabolic cycles. The mercapto- and phosphate groups (in cysteine and nucleotides, respectively) as well as the above three functional groups, acting singly or in various combinations, probably account for most of the metal ion-binding in "labile" biological complexes (that is, complexes which exist in dynamic equilibrium with their components, in contrast to "robust" complexes, such as the metallo-porphyrins, which require high activation energies to bring about dissociation). Their effects are likely to be
modified to some extent by co-operative activity with weaker or less-common binding groups such as the methylthio group of methionine and the phenate ion derived from tyrosine and its derivatives.

A number of aliphatic and heterocyclic amines were chosen for investigation with the copper system. The selection of ligands was aimed mainly at discovering the effects that are operative in determining the magnitude of oxidation-reduction potentials for copper-amine complexes. The standard potentials were obtained by the stability constant ratio method. For the copper(II) complexes, stability constants were obtained by the pH-titration technique, whereas for copper(I), the method used was based on the electrolytic oxidation of solid copper in the presence of ligand.

2.1 Ligands

"Analar" pyridine (from British Drug Houses Ltd.) which had been kept over potassium hydroxide pellets for three months was distilled yielding a fraction with b.p. 113.5°/714 mm. (Weissberger et. al., 1955) give 113.65°/714 mm.).
4-Methylpyridine (from B.D.H. Ltd.) was refluxed over barium oxide for 4 hr and distilled; the fraction boiling at 141.5°/714 mm (Lange (1956) gives 143.1°/760 mm.) was collected.

Imidazole (from Messrs. L. Light and Co.) was decolorised with charcoal, recrystallised three times from benzene and dried at 40° in vacuo, m.p. 89° (Lange (1956) gives 89 - 90°).

Benzimidazole (from B.D.H. Ltd.) was decolorised with charcoal, recrystallised four times from aqueous ethanol and dried at 100° for 12 hr, m.p. 169° (Lange (1956) gives 170°).

2-Methylthioethylamine, prepared by the method of Brighton and Reid (1943) and repeatedly distilled, had b.p. 145.5°/720mm. (Brighton and Reid (1943) give 146.8°/760mm.).

A-Grade L-Methionine (from California Corporation for Biochemical Research) was dried at 110° for 2 hr, m.p. 282°d. (Lange (1956) gives 283°d.).
2.2 Acid Dissociation Constants

The pKₐ values in Table 2.01 were determined by potentiometric titration and calculated using the complete Henderson-Hasselbalch equation,

\[
pK_a = rH + \log \frac{[BH^+] + [OH^-]}{[B] - [OH^-]} \quad (\text{for } rH > 7)
\]

\[
= rH + \log \frac{[BH^+] - [H^+]}{[B] + [H^+]} \quad (\text{for } rH < 7),
\]

where \(rH = -\log [H^+]\), B is the base and BH⁺ is the conjugate acid. The acid dissociation constants are concentration constants; the concentration of H⁺ was obtained from pH-measurements by using an activity coefficient determined from a titration of the inert medium (0.15M-sodium perchlorate) with acid of known concentration.

2.3 Copper(II) Stability Constants

(i) Reagents

A stock copper perchlorate solution (0.0277M) was prepared as described by Perrin (1960) and standardised both by cation exchange (I.R.-120,H⁺)– the liberated acid being titrated with standard alkali– and by EDTA-murexide.

\[
\text{Adenine (from Messrs. L. Light and Co.) was recrystallised three times from water and dried at } 110^\circ.
\]
titration (Schwarzenbach, 1957). A stock solution of
0.1M-sodium hydroxide (carbonate-free) was prepared by
ion exchange. Sodium perchlorate (B.D.H. Ltd.), purified
by recrystallisation from aqueous ethanol, was dried at
room temperature \textit{in vacuo}. All other reagents were of
"AnalaR" grade. (Throughout this thesis, the reagents,
unless otherwise specified, are of this quality).

(ii) Apparatus

The titration-cell was a cylindrical glass vessel
of about 200 ml capacity, closed by a rubber stopper through
which passed a glass electrode, a gas-bubbler, a thermometer
and fine-bore polythene tubing attached to an "Agla" micro-
meter syringe. The cell was connected to an external
saturated calomel electrode by an ammonium nitrate-sodium
nitrate-agar salt-bridge (Perrin, 1958a). An inert
atmosphere was maintained in the vessel by continuously
passing scrubbed nitrogen through the solutions, which
were stirred by a magnetic stirrer. All pH measurements
were made at 20 \pm 0.1^\circ on a Cambridge bench model pH meter,
taking as standard, 0.05M-potassium hydrogen phthalate,
pH 4.00 at 20^\circ, and as a secondary standard, 0.05M-sodium
borate, pH 9.23 at 20^\circ.

(iii) Experimental

The titrations were performed by adding 0.1M-sodium
hydroxide (carbonate-free) in small portions from a micro-
meter syringe to the solutions, which contained Cu^{2+} ions,
ligand in excess, and an equivalent amount of acid, and which were adjusted to an ionic strength of 0.15 by the addition of sodium perchlorate. A typical titration curve is plotted in Fig. 2.01.

The determination of stability constants was based on three independent equations, namely those for total concentrations of metal species, total concentrations of ligand species, and total charges. For an uncharged ligand, L, these equations become, respectively

\[ [\text{Cu}]_T = [\text{Cu}^{2+}] + \sum_{x=1}^{P} [\text{CuL}_x^{2+}] \quad (2.02) \]

\[ [L]_T = [L] + [\text{HL}^+] + \sum_{x=1}^{P} x[\text{CuL}_x^{2+}] \quad (2.03) \]

\[ [\text{H}^+] + [\text{HL}^+] + [\text{Na}^+] + 2[\text{Cu}]_T = [\text{ClO}_4^-] + [\text{OH}^-] \quad (2.04) \]

where \( P \) is the maximum number of ligand molecules complexed to a copper(II) ion.

However, \([\text{Na}^+] = [\text{NaOH}] + [\text{NaClO}_4] \quad (2.05)\]

and \([\text{ClO}_4^-] = [\text{NaClO}_4] + [\text{HClO}_4] + 2[\text{Cu}]_T \quad (2.06)\]

Thus, from eqn. 2.04, 2.05 and 2.06,

\[ [\text{HL}^+] = [\text{HClO}_4] + [\text{OH}^-] - [\text{NaOH}] - [\text{H}^+] \quad (2.07) \]

The concentration of free ligand (uncomplexed and unprotonated), \([L]\), is expressed in terms of the acid dissociation constant, \( K_a \), of the ligand in eqn. 2.08.

\[ [L] = (K_a/[\text{H}^+])[\text{HL}^+] \quad (2.08) \]
The degree of complex formation, \( \bar{n} \), is defined by eqn. 2.09.

\[
\bar{n} = \frac{x=P}{\sum_{x=1}} x[CuL_x^{2+}] / [Cu]_T .
\]  
(2.09)

According to eqn. 2.03,

\[
\bar{n} = \frac{([L]_T - [L] - [HL^+]^0)}{[Cu]_T} .
\]  
(2.10)

From eqns. 1.11, 2.02 and 2.09, \( \bar{n} \) can be expressed by

\[
\bar{n} = [Cu^{2+}] \sum_{x=1}^{x=P} \beta_x [L]^x .
\]  
(2.11)

Thus, by rearranging,

\[
\bar{n} = \sum_{x=1}^{x=P} (x - \bar{n}) \beta_x [L]^x ,
\]  
(2.12)

and

\[
\frac{\bar{n}}{1-\bar{n}} = \frac{K_1 + \beta_2 (2-\bar{n}) [L]}{(1-\bar{n})} + \frac{\beta_3 (3-\bar{n}) [L]^2}{(1-\bar{n})^2} + \ldots.
\]

(2.13)

If, for a particular ligand, \( P \) is 2,

\[
\bar{n} = \frac{K_1 + \beta_2 (2-\bar{n}) [L]}{(1-\bar{n})} ,
\]  
(2.14)

and \( K_1 \) and \( \beta_2 \) are determined from a plot of \( \bar{n} / (1-\bar{n}) [L] \) against \( (2-\bar{n}) [L] / (1-\bar{n}) \) (Irving and Rossotti, 1953). However, if \( P \) is greater than 2, the stability constants are determined by successive approximations based on eqn. 2.13.
For \( P = 4 \), \( K_1, \beta_2, \beta_3, \) and \( \beta_4 \) are determined from eqns. 2.14, 2.15 and 2.16.

\[
\left( \frac{n}{(1-n)[L]} - K_1 \right) \left( \frac{1-n}{(2-n)[L]} - \beta_2 \right) \left( \frac{2-n}{(3-n)[L]} - \beta_3 + \frac{\beta_4(4-n)[L]}{(3-n)} \right) = K_1 + \frac{\beta_2(2-n)[L]}{(1-n)}.
\]

The maximum co-ordination number, \( N \), of copper(II) in aqueous solution is usually taken to be 4 although, in the presence of a large excess of ligand, copper(II) can become hexaco-ordinate (see Chapter 6). Thus, for monodentate ligands \( P \), the maximum number of ligand molecules complexed to a copper(II) ion is taken to be 4; contributions from the possible species, \( \text{CuL}_5^{2+} \) and \( \text{CuL}_6^{2+} \), are assumed to be unimportant under the conditions of the experiments. Similarly, \( P \) is assumed to be 2 for bidentate chelates.

Results of calculations based on the typical titration curve, Fig. 2.01, for imidazole are reported in Table 2.02, and the final graphs from which the stability constants were determined are plotted in Figs. 2.02 and 2.03.

Methionine (HL) co-ordinates to \( \text{Cu}^{2+} \) through the anion, \( L^- \). For this bidentate anion, the equations for total concentrations of copper species, total concentrations of ligand species and total charges are given by eqns. 2.17,
2.18 and 2.19, respectively. Any contribution the methylthio group may make to the binding will not affect these equations because this group is not concerned in any equilibria involving protons.

\[
[Cu]_T = [Cu^{2+}] + [CuL^+] + [CuL_2].
\] (2.17)

\[
[L]_T = [L^-] + [HL] + [H_2L^+] + [CuL^+] + 2[CuL_2].
\] (2.18)

\[
[H^+] + [H_2L^+] + 2[Cu^{2+}] + [CuL^+] + [Na^+] = [ClO_4^-] + [OH^-] + [L^-].
\] (2.19)

From eqns. 2.17 and 2.18,

\[
[L]_T - 2[Cu]_T = [L^-] + [HL] + [H_2L^+] - 2[Cu^{2+}] - [CuL^+].
\] (2.20)

Combining eqns. 2.05, 2.06, 2.19 and 2.20 gives

\[
2[H_2L^+] + [HL] = [L]_T + [OH^-] + [HClO_4] - [H^+] - [NaOH],
\] (2.21)

from which the concentration of free ligand is obtained since

\[
[H_2L^+] = \frac{[H^+]^2[L^-]}{K_{a1}K_{a2}} \quad \text{and} \quad [HL] = \frac{[H^+][L^-]}{K_{a2}}.
\]

For this system, \( \bar{n} \) is given by

\[
\bar{n} = ([L]_T - [H_2L^+] - [HL] - [L^-]) / [Cu]_T.
\] (2.22)

Stability constants for the copper(II) - methionine system were calculated from the experimental data in Table 2.03 according to eqn. 2.14 (see Fig. 2.04).
The stability constants of the copper(II)-amine complexes are summarised in Table 2.04. The values for the copper(II) complexes of pyridine and 4-methylpyridine diverge increasingly from those of Bruehlman and Verhoek (1948), which appear to be based on Bjerrum's approximations (not valid here because differences in the series $K_1 > K_2 > K_3 > K_4$ are not great) that the reciprocals of ligand concentration at $\tilde{n} = 0.5, 1, 1.5$ and 2 are equal, respectively, to $K_1$, $\beta_2^{1/3}$, $\beta_3^{1/3}$ and $\beta_4^{1/4}$.

2.4 Copper(I) Stability Constants

(i) Apparatus

The electrolysis- and titration-cell was a cylindrical glass vessel of about 200 ml capacity, closed by a rubber stopper through which passed "Quickfit" ground-glass sockets carrying three electrodes (bright platinum foil, gold foil and glass), a platinum wire supporting a cylindrical copper anode 1 cm high and 2 cm in diameter (constructed from "AnalaR" copper foil and freshly scoured with steel wool to remove the oxide coating), ancillary attachments (an "Agla" micrometer syringe, thermometer, gas-inlet tube and gas-outlet tube through a water-trap), and an alumina thimble. This thimble, which was sealed with a coating of calcium silicate except for an annular strip near its base, contained 0.05M-sodium sulphate, acidified with sulphuric acid, into which dipped a platinum gauze electrode which was the cathode during electrolysis.
The Electrolysis- and Titration-Cell:  A - cell;  B - alumina thimble containing acidified Na₂SO₄ (0.05M);  C - platinum gauze electrode (cathode for electrolysis);  D - platinum wire supporting cylindrical copper electrode (anode for electrolysis);  E - gold (bright platinum) foil electrode;  F - glass electrode;  G - gas-inlet tube;  H - gas-outlet tube;  I - salt-bridge;  J - sat. calomel electrode;  K - magnetic stirrer.
In addition, the cell was connected to an external saturated calomel electrode by an ammonium nitrate-sodium nitrate-agar salt-bridge (Perrin, 1958a). The potentiometer was a Tinsley instrument (type 4046B), easily readable to 0.1 mv, and was used with a Pye "Scalamp" galvanometer. pH measurements were made on a Cambridge bench-model pH-meter, with 0.05M-potassium hydrogen phthalate (pH 4.00 at 20°) as standard and 0.05M-sodium borate (pH 9.23 at 20°) as a secondary standard. The solution in the cell was stirred magnetically. Before the electrolysis, oxygen was removed from the system by bubbling nitrogen (commercial "oxygen-free", passed through Fieser's solution and potassium hydroxide, then washed with water) through the solution for 1 hr. For the remainder of the experiment a slight positive pressure was maintained by passing the nitrogen over the surface of the solution. A gas coulometer, which could be read to 0.01 ml, giving an accuracy of about 1:1000 over the working range, was used to follow the electrolysis.

(ii) Experimental

The following experimental procedure for the copper(I) complexes was based on the principle that, if $E^0$ for $\text{Cu}^I L_x/\text{Cu}^0$ is less positive than $E^0$ for $\text{Cu}^{II} L_x/\text{Cu}^0$, copper(I) complexes will be formed in solution by the anodic electrolysis of copper in a solution of the ligand (cf. Chapter 6.1). A neutral or weakly acid solution of
The Gas Coulometer

A - water jacket;  B - bright platinum plate electrodes;  
C - graduated tube for measuring volume of gas evolved;  
D - sulphuric acid solution (1M).

the ligand in sulphuric acid was adjusted to an ionic strength of 0.15 by the addition of sodium sulphate. Copper(I) and copper(II) ions were generated in the solution by electrolysis, the quantity, \([\text{Cu}^+] + 2[\text{Cu}^{2+}],\) being known from the gas coulometer. The copper anode was then lifted out of the solution. The potential of the
platinum and gold electrodes (with respect to the saturated calomel electrode) and the pH of the solution were recorded as the solution was titrated with standard 0.05M-sulphuric acid. Because differences between potentials with the platinum and gold electrodes never exceeded 0.4 mv, the average of the two readings at each point was used in the subsequent calculations. Measurements were made at 20° ± 0.1°.

Calculations of stability constants for the copper(I) complexes are based on the Nernst equation,

\[ E = E^0_{\text{Cu}^{2+}, \text{Cu}^+} - \frac{(RT/F) \ln (a_{\text{Cu}^+}/a_{\text{Cu}^{2+}})}{\text{Cu}^2+, \text{Cu}^+} + E_j \]  

(2.23)

(where \( E_j \) is the liquid junction potential), and the expressions,

\[ \frac{1}{[\text{Cu}^+]} = \frac{(1 + K_1 \text{I}[L] + \beta_2 \text{I}[L]^2 + \ldots)}{[\text{Cu}^\text{I}]_T}, \]  

(2.24)

\[ \frac{1}{[\text{Cu}^{2+}]} = \frac{(1 + K_1 \text{II}[L] + \beta_2 \text{II}[L]^2 + \ldots)}{[\text{Cu}^\text{II}]_T}, \]  

(2.25)

which were derived from eqns. 1.11, 2.02 and the corresponding equation for copper(I). From the identities, 2.23, 2.24 and 2.25, we have

\[ E = E^0_{\text{Cu}^{2+}, \text{Cu}^+} - \frac{RT \ln [\text{Cu}^\text{I}]_T}{F} - \frac{RT \ln f_{\text{Cu}^+}}{[\text{Cu}^\text{II}]_T} - \frac{RT \ln f_{\text{Cu}^{2+}}}{F} + \frac{RT \ln (1 + K_1 \text{I}[L] + \beta_2 \text{I}[L]^2 + \ldots)}{F} \]  

\[ \frac{1}{(1 + K_1 \text{II}[L] + \beta_2 \text{II}[L]^2 + \ldots)} \]  

(2.26)
If \([\text{Cu}^I]_T/\text{[Cu}^{II}]_T\) and the activity coefficient ratio remain constant, then

\[
E = E_T + \frac{RT \ln (1 + K_1^{I}[L] + \beta_2^{I}[L]^2 + \ldots)}{F} ,
\]

(2.27)

where \(E_T\) is a constant. Eqn. 2.27 can be written in the form,

\[
\frac{r}{s} = s + t[L] + u[L]^2 + \ldots
\]

(2.28)

where

\[
r = (1 + K_1^{II}[L] + \beta_2^{II}[L]^2 + \ldots) \exp \left(-\frac{FE}{2.3026RT}\right) ,
\]

(2.29)

\[
s = \exp \frac{FE_T}{2.3026RT} ,
\]

(2.30)

\[
t/s = K_1^{I} ,
\]

(2.31)

\[
u/s = \beta_2^{I} ,
\]

(2.32)

etc.

If \(K_1^{II}, \beta_2^{II}, \ldots, \) and \([L]\) are known, \(r\) can be evaluated at each point of the titration. The set of points, \(r_1, [L]_1, [L]^2_1, \ldots\) so obtained have to be fitted to the surface described by eqn. 2.28. This is done by minimising the quantity,

\[
\sum (r_i - r)^2 = \sum (r_i - s - t[L]_i - u[L]^2 - \ldots)^2 ,
\]

(2.33)

as in the method of least squares, to give the simultaneous equations,

\[
\sum \left< (s - r_1) + t[L]_1 + u[L]^2_1 + \ldots \right> = 0 ,
\]

(2.34)
\[ \sum \langle (s - r_1) [L]^i + t[L]^2 + u[L]^3 + \ldots \rangle = 0, \quad (2.35) \]
\[ \sum \langle (s - r_1) [L]^2 + t[L]^3 + u[L]^4 + \ldots \rangle = 0, \quad (2.36) \]

which can be solved to give \( s, t, u, \ldots \), and hence, \( E_T, K_1^I, \beta_2^I, \ldots \). The expression,

\[ \frac{1}{[L]} \left( \frac{r}{s} - 1 \right) = K_1^I + \beta_2^I [L] + \ldots, \quad (2.37) \]

(derived from eqns. 2.28, 2.31 and 2.32), provides an internal check on the calculations since, if the species, \( Cu^I[L]^3 \) and \( Cu^I[L]^4 \), are unimportant, a plot of \( (1/[L]) \langle (r/s) - 1 \rangle \) against \([L]\) should yield a straight line from which \( K_1^I \) and \( \beta_2^I \) can be calculated.

Values for the free ligand concentration for uncharged ligands and the anion of methionine are calculated from eqns. 2.38 and 2.39, respectively,

\[ [L] = \left( \frac{K_a}{[H^+]} \right) \left( 2[H_2SO_4] - [H^+] - ([Cu^I]_T + 2[Cu^{II}]_T) \right), \quad (2.38) \]
\[ [L^-] = \left( \frac{K_a}{[H_2SO_4]} \right) \left( 2[H^+]^2 + [H^+]K_a \right) \left( 2[H_2SO_4] + [L]_T - [H^+] \right) - \left( ([Cu^I]_T + 2[Cu^{II}]_T) \right), \quad (2.39) \]

these equations being derived in a manner similar to eqns. 2.08 and 2.21.

Details of a typical experiment for an uncharged ligand (pyridine) are set out in Table 2.05, and a graph of eqn. 2.37 based on these results is presented in Fig. 2.05.
Determination of $\beta_3^I$ and $\beta_4^I$ for the pyridine system was attempted using the values of $K_1^I$ and $\beta_2^I$ (which had previously been obtained) at points in the titration where $[H_2SO_4]<1.8 \times 10^{-2}M$ (these points have not been included in Table 2.05). However, no accurate results could be obtained because the calculations were dependent upon small differences between relatively large quantities.

Complex formation between copper(I) and the anion of methionine was studied in both sulphate and perchlorate media in the presence of a relatively large excess of ligand to limit the formation of polynuclear complex species (the metal:ligand molar ratios for both experiments were different). The experimental data for both are listed in Table 2.06. The stability constant, $K_1$, was determined from a plot of $<(r/s - 1)>$ against $[L]$ according to eqn. 2.37 (Fig. 2.06). A straight line which passed through the origin was obtained, thus showing the absence of the species, $CuL_2^-$. The agreement of the results for the two metal:ligand molar ratios (1:12 and 1:20) suggests that, under the conditions of these experiments, polynuclear complex formation is unimportant.

The stability constants of the copper(I) complexes are listed in Table 2.07.

Laufer and Charney (1945) have reported that purine compounds possessing an unsubstituted imino nitrogen form
copper(I) complexes. It was hoped to be able to examine the copper(I) complex of the biologically important purine, adenine, which belongs to the above classification, by the usual potentiometric method. However, for an aqueous solution containing adenine ($5 \times 10^{-4}\text{M}$) and $[\text{Cu}^\text{I}]_T + 2[\text{Cu}^\text{II}]_T = 7 \times 10^{-5}\text{M}$ (at $I = 0.15$, $\text{Na}_2\text{SO}_4$), the measured potential did not vary significantly over the pH-range 6 to 4.5. This could possibly be due either to insufficient formation of copper(I) during electrolysis or to precipitation of copper(I) as an insoluble adenine complex. The former is unlikely because it is possible to prepare the copper(I) complex by reduction of the corresponding copper(II) complex.

2.5 Oxidation-Reduction Potentials

Standard oxidation-reduction potentials for corresponding pairs of copper(II) and copper(I) complexes were calculated from the stability constant data according to eqn. 1.15. Since methionine co-ordinates as its anion, the term, $p$, in eqn. 1.15 was not equal to unity; it had to be calculated from eqn. 1.05. The potentials are given in Table 2.08 together with literature values where available.

Results in Tables 1.02, 1.03 and 2.08 indicate that in aqueous solution all saturated monodentate amines (with the doubtful (James and Williams, 1961) exception of
piperidine) preferentially stabilise copper(I) in 1:1 and 1:2 complexes.

Frequently, the stability constants of a cation with a series of related ligands follow the relationship,

\[ \log \beta_x = a \cdot pK_a + b, \]

(2.40)

where \( a \) and \( b \) are constants. This is true, for example, for \( \text{Ag}^+ \) in 1:1 complexes with primary amines (Bruehlman and Verhoek, 1948) with \( a \approx 0.25 \). Comparable generalisations might be expected for \( \text{Cu}^+ \). Hence, the closeness of the \( \log K_1^I \) and \( \log \beta_2^I \) values for the copper complexes with ammonia and 2-methylthioethylamine, in conjunction with the similarity of their \( pK_a \) values, \( (pK_a = 9.40 \text{ (Bates and Pinching, 1949), 9.56;} \log K_1^I = 5.93 \text{ (Bjerrum, 1934), 5.65;} \log \beta_2^I = 10.86 \text{ (Bjerrum, 1934), 10.98, respectively}), \) strongly suggests that, in its 2-methylthioethylamine complexes, copper(I) is co-ordinated only through the amino group. By similar reasoning, ethylenediamine \( (pK_a = 10.17, 7.49, \log \beta_2^I = 10.8 \text{ (Bjerrum and Nielsen, 1948)}) \) behaves towards univalent copper as a monodentate ligand. In the copper(II) series, \( \log K_1^{II} \) and \( \log \beta_2^{II} \) for the complexes with 2-methylthioethylamine are about 1 and 2 logarithmic units higher than for ammonia \( \text{(log } K_1^{II} = 4.31, \log \beta_2^{II} = 7.98 \text{, from Bjerrum, 1931), because rather weak chelation, involving ring formation by the metal through the sulphur and nitrogen atoms, can occur. The very strong chelation} \)
of Cu$^{2+}$ by ethylenediamine ($\log K_1^{\text{II}} = 10.72$, $\log \beta_2^{\text{II}} = 20.03$, from Bjerrum and Nielsen, 1948) causes the marked increase in $\log \beta_2^{\text{II}}$ of over 12 logarithmic units relative to ammonia. Because of this effect, $E^0$ for the 1:2 copper complexes of 2-methylthioethylamine is only 0.09 v less positive than for the ammonia complexes, but $E^0$ for the ethylenediamine complexes is less positive by 0.71 v. The value of $-0.160$ v for $E_f^*$ corresponding to the 1:2 copper-glycine complexes (James and Williams, 1961), together with $\log \beta_2^{\text{II}} = 15.1$ for the copper(II) complex (Bjerrum et al., 1957) and $E_f^0(\text{Cu}^{2+},\text{Cu}^+) = 0.148$ v (James and Williams, 1961), leads to $\log \beta_2^{\text{I}} = 9.9$ and suggests that here, too, copper(I) is co-ordinated only through the amino group. It can readily be seen, however, by comparing the values of $\log K_1^{\text{I}}$ for methionine ($pK_a = 9.20$, $\log K_1^{\text{I}} = 7.0$), ammonia, and 2-methylthioethylamine that methionine does not co-ordinate with copper(I) simply through an amino group. Since an $\alpha$-aminoacid group appears unable to chelate copper(I), the results suggest that methionine forms a 6-membered chelate ring through the nitrogen and sulphur atoms. On the other hand, Cu$^{2+}$ forms methionine complexes through the aminoacid group and the sulphur atom (see Chapter 5); the greater stability of this type of bonding makes $E^0(1:1)$ less positive than $E^0(\text{Cu}^{2+},\text{Cu}^+)$. 
### Table 2.01

Acid Dissociation Constants at $20^\circ$ and $I = 0.15$

(Mean ± maximum deviation)

<table>
<thead>
<tr>
<th>Compound</th>
<th>$pK_a$ ± deviation</th>
<th>lit.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridine</td>
<td>5.32 ± 0.00</td>
<td>5.45$^a$</td>
</tr>
<tr>
<td>4-Methylpyridine</td>
<td>6.19 ± 0.02</td>
<td>6.26$^a$</td>
</tr>
<tr>
<td>Imidazole</td>
<td>7.20 ± 0.03</td>
<td>7.11$^b$</td>
</tr>
<tr>
<td>Benzimidazole</td>
<td>5.68 ± 0.02</td>
<td>5.58$^c$</td>
</tr>
<tr>
<td>2-Methylthioethylamine</td>
<td>9.56 ± 0.02</td>
<td>9.45$^d$</td>
</tr>
<tr>
<td>L-Methionine</td>
<td></td>
<td>2.20$^e$</td>
</tr>
<tr>
<td></td>
<td>9.20 ± 0.02</td>
<td>9.34$^e$</td>
</tr>
</tbody>
</table>

$^a$ At $25^\circ$ and $I = 0.5$, from Bruehlman and Verhoek, 1948.

$^b$ At $22.5^\circ$ and $I = 0.16$, from Edsall et al., 1954.

$^c$ At $25^\circ$ and $I = 0.16$, from Lane and Quinlan, 1960.

$^d$ At $30^\circ$ and $I = 1.0$, from Gonick et al., 1954.

$^e$ At $20^\circ$ and $I = 0.01$, from Albert, 1950.

---

### Table 2.02

Titration with carbonate-free sodium hydroxide (0.0999M) of an aqueous solution of copper perchlorate (5 x $10^{-3}$M), imidazole (6 x $10^{-2}$M) and perchloric acid (6 x $10^{-2}$M), adjusted to $I = 0.15$ with sodium perchlorate.
Table 2.02 (cont.)

<table>
<thead>
<tr>
<th>pH</th>
<th>(\bar{n})</th>
<th>([L] \times 10^4, M)</th>
<th>pH</th>
<th>(\bar{n})</th>
<th>([L] \times 10^4, M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.33</td>
<td>0.0970</td>
<td>0.0761</td>
<td>5.04*</td>
<td>1.6321</td>
<td>3.1506</td>
</tr>
<tr>
<td>3.41</td>
<td>0.1208</td>
<td>0.0908</td>
<td>5.11*</td>
<td>1.7209</td>
<td>3.6324</td>
</tr>
<tr>
<td>3.48</td>
<td>0.1482</td>
<td>0.1062</td>
<td>5.18*</td>
<td>1.8078</td>
<td>4.1874</td>
</tr>
<tr>
<td>3.61</td>
<td>0.2095</td>
<td>0.1419</td>
<td>5.25*</td>
<td>1.8933</td>
<td>4.8151</td>
</tr>
<tr>
<td>3.73*</td>
<td>0.2757</td>
<td>0.1861</td>
<td>5.37@</td>
<td>2.0595</td>
<td>6.2660</td>
</tr>
<tr>
<td>3.84*</td>
<td>0.3458</td>
<td>0.2363</td>
<td>5.50@</td>
<td>2.2176</td>
<td>8.0738</td>
</tr>
<tr>
<td>3.94*</td>
<td>0.4180</td>
<td>0.2979</td>
<td>5.62@</td>
<td>2.3646</td>
<td>10.3310</td>
</tr>
<tr>
<td>4.06*</td>
<td>0.4727</td>
<td>0.3843</td>
<td>5.73@</td>
<td>2.5030</td>
<td>12.9150</td>
</tr>
<tr>
<td>4.16*</td>
<td>0.6046</td>
<td>0.4781</td>
<td>5.84@</td>
<td>2.6262</td>
<td>16.1330</td>
</tr>
<tr>
<td>4.26*</td>
<td>0.6992</td>
<td>0.5912</td>
<td>5.93@</td>
<td>2.7453</td>
<td>19.4660</td>
</tr>
<tr>
<td>4.35*</td>
<td>0.7941</td>
<td>0.7174</td>
<td>6.03@</td>
<td>2.8709</td>
<td>23.4670</td>
</tr>
<tr>
<td>4.44*</td>
<td>0.8889</td>
<td>0.8708</td>
<td>6.11@</td>
<td>2.9443</td>
<td>27.6430</td>
</tr>
<tr>
<td>4.52</td>
<td>0.9839</td>
<td>1.0448</td>
<td>6.19</td>
<td>3.0307</td>
<td>32.1700</td>
</tr>
<tr>
<td>4.60*</td>
<td>1.0782</td>
<td>1.2389</td>
<td>6.26@</td>
<td>3.1185</td>
<td>36.5710</td>
</tr>
<tr>
<td>4.68*</td>
<td>1.1724</td>
<td>1.4687</td>
<td>6.41@</td>
<td>3.2313</td>
<td>47.7190</td>
</tr>
<tr>
<td>4.76*</td>
<td>1.2661</td>
<td>1.7214</td>
<td>6.53@</td>
<td>3.3408</td>
<td>58.6430</td>
</tr>
<tr>
<td>4.83*</td>
<td>1.3587</td>
<td>2.0174</td>
<td>6.64@</td>
<td>3.4254</td>
<td>70.2110</td>
</tr>
<tr>
<td>4.90*</td>
<td>1.4508</td>
<td>2.3485</td>
<td>6.74@</td>
<td>3.4979</td>
<td>81.8930</td>
</tr>
<tr>
<td>4.97*</td>
<td>1.5420</td>
<td>2.7197</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

where * indicates points for Fig. 2.02, and @ points for Fig. 2.03.
Table 2.03

Titration with carbonate-free sodium hydroxide (0.1012 M) of an aqueous solution of copper perchlorate (1 x 10^{-3} M), L-methionine (5 x 10^{-3} M) and perchloric acid (5 x 10^{-3} M), adjusted to $I = 0.15$ with sodium perchlorate.

<table>
<thead>
<tr>
<th>$[\text{NaOH}] \times 10^{-3}, \text{M}$</th>
<th>pH</th>
<th>$\bar{n}$</th>
<th>$[\text{L}] \times 10^8, \text{M}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.9475</td>
<td>2.95</td>
<td>0.1607</td>
<td>0.191</td>
</tr>
<tr>
<td>3.7048</td>
<td>3.13</td>
<td>0.2585</td>
<td>0.301</td>
</tr>
<tr>
<td>4.2651</td>
<td>3.33</td>
<td>0.3654</td>
<td>0.477</td>
</tr>
<tr>
<td>4.6351</td>
<td>3.49</td>
<td>0.4884</td>
<td>0.685</td>
</tr>
<tr>
<td>4.8190</td>
<td>3.59</td>
<td>0.5619</td>
<td>0.856</td>
</tr>
<tr>
<td>5.0936</td>
<td>3.76</td>
<td>0.7024</td>
<td>1.239</td>
</tr>
<tr>
<td>5.1848</td>
<td>3.82</td>
<td>0.7578</td>
<td>1.408</td>
</tr>
<tr>
<td>5.2758</td>
<td>3.88</td>
<td>0.8177</td>
<td>1.616</td>
</tr>
<tr>
<td>5.3666</td>
<td>3.96</td>
<td>0.8775</td>
<td>1.898</td>
</tr>
<tr>
<td>5.4573</td>
<td>4.02</td>
<td>0.9493</td>
<td>2.171</td>
</tr>
<tr>
<td>5.6381</td>
<td>4.18</td>
<td>1.0951</td>
<td>3.033</td>
</tr>
<tr>
<td>5.7283</td>
<td>4.27</td>
<td>1.1734</td>
<td>3.619</td>
</tr>
<tr>
<td>5.8182</td>
<td>4.36</td>
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</tr>
<tr>
<td>5.9080</td>
<td>4.46</td>
<td>1.3392</td>
<td>5.368</td>
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</table>

Table 2.04

Stability Constants of Copper(II) Complexes in Water at 20° and $I = 0.15$
<table>
<thead>
<tr>
<th>Ligand</th>
<th>$\log K_1^{II}$</th>
<th>$\log \beta_2^{II}$</th>
<th>$\log \beta_3^{II}$</th>
<th>$\log \beta_4^{II}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridine</td>
<td>2.65</td>
<td>4.86</td>
<td>6.90</td>
<td>8.45</td>
</tr>
<tr>
<td></td>
<td>2.52$^a$</td>
<td>4.38$^a$</td>
<td>5.69$^a$</td>
<td>6.54$^a$</td>
</tr>
<tr>
<td>4-Methylpyridine</td>
<td>2.56</td>
<td>5.39</td>
<td>7.66</td>
<td>9.54</td>
</tr>
<tr>
<td></td>
<td>2.82$^a$</td>
<td>4.97$^a$</td>
<td>6.58$^a$</td>
<td>7.74$^a$</td>
</tr>
<tr>
<td>Imidazole</td>
<td>4.26</td>
<td>7.87</td>
<td>10.73</td>
<td>12.98</td>
</tr>
<tr>
<td></td>
<td>4.20$^b$</td>
<td>7.67$^b$</td>
<td>10.51$^b$</td>
<td>12.51$^b$</td>
</tr>
<tr>
<td></td>
<td>4.36$^c$</td>
<td>7.93$^c$</td>
<td>10.78$^c$</td>
<td>12.84$^c$</td>
</tr>
<tr>
<td>Benzimidazole</td>
<td>3.56</td>
<td>6.34</td>
<td>9.00</td>
<td>10.97</td>
</tr>
<tr>
<td></td>
<td>3.43$^d$</td>
<td>6.41$^d$</td>
<td>8.92$^d$</td>
<td>10.92$^d$</td>
</tr>
<tr>
<td>2-Methylthioethylamine</td>
<td>5.30</td>
<td>9.68</td>
<td></td>
<td>10.68$^e$</td>
</tr>
<tr>
<td>L-Methionine</td>
<td>8.00</td>
<td>15.23</td>
<td></td>
<td>14.7$^f$</td>
</tr>
</tbody>
</table>

$^a$ At 25° and $I = 0.5$, from Bruehlman and Verhoek, 1948.
$^b$ At 25° and $I = 0.135$, from Mickel and Andrews, 1955.
$^c$ At 22.5° and $I = 0.16$, from Edsall et al., 1954.
$^d$ At 25° and $I = 0.16$, from Lane and Quinlan, 1960.
$^e$ At 30° and $I = 1.0$, from Gonick et al., 1954.
$^f$ At 20° and $I = 0.01$, from Albert, 1950.

Table 2.05

Determination of Stability Constants of Copper(I)-Pyridine Complexes at 20° and $I = 0.15$
An aqueous solution of pyridine \((4.108 \times 10^{-2} \text{M})\) containing sulphuric acid \((1.642 \times 10^{-2} \text{M})\) was adjusted to \(I = 0.15\) with sodium sulphate. Copper ions were added by electrolysis, giving \(\left[\text{Cu}^+\right]_T = 2\left[\text{Cu}^{II}\right]_T = 4.476 \times 10^{-4} \text{M}\). The solution was then titrated with \(0.0497\text{M}-\text{sulphuric acid}\).

<table>
<thead>
<tr>
<th>([\text{H}_2\text{SO}_4] \times 10^2, \text{M})</th>
<th>pH</th>
<th>(-E (\text{mv}))</th>
<th>([\text{L}] \times 10^3, \text{M})</th>
<th>(x)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8511</td>
<td>3.97</td>
<td>40.2</td>
<td>1.539</td>
<td>0.3796</td>
</tr>
<tr>
<td>1.8539</td>
<td>3.95</td>
<td>41.7</td>
<td>1.471</td>
<td>0.3490</td>
</tr>
<tr>
<td>1.8569</td>
<td>3.92</td>
<td>43.3</td>
<td>1.391</td>
<td>0.3181</td>
</tr>
<tr>
<td>1.8598</td>
<td>3.90</td>
<td>44.9</td>
<td>1.315</td>
<td>0.2903</td>
</tr>
<tr>
<td>1.8627</td>
<td>3.87</td>
<td>46.4</td>
<td>1.243</td>
<td>0.2662</td>
</tr>
<tr>
<td>1.8656</td>
<td>3.85</td>
<td>47.9</td>
<td>1.176</td>
<td>0.2445</td>
</tr>
<tr>
<td>1.8685</td>
<td>3.82</td>
<td>49.7</td>
<td>1.111</td>
<td>0.2221</td>
</tr>
<tr>
<td>1.8714</td>
<td>3.79</td>
<td>51.4</td>
<td>1.038</td>
<td>0.2019</td>
</tr>
<tr>
<td>1.8742</td>
<td>3.77</td>
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<td>0.981</td>
<td>0.1838</td>
</tr>
<tr>
<td>1.8771</td>
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<td>54.7</td>
<td>0.928</td>
<td>0.1698</td>
</tr>
<tr>
<td>1.8800</td>
<td>3.71</td>
<td>56.4</td>
<td>0.867</td>
<td>0.1547</td>
</tr>
<tr>
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<td>58.1</td>
<td>0.801</td>
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</tr>
<tr>
<td>1.8857</td>
<td>3.66</td>
<td>59.9</td>
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<td>0.1294</td>
</tr>
<tr>
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<td>61.7</td>
<td>0.715</td>
<td>0.1181</td>
</tr>
<tr>
<td>1.8915</td>
<td>3.60</td>
<td>63.0</td>
<td>0.676</td>
<td>0.1103</td>
</tr>
<tr>
<td>1.8943</td>
<td>3.57</td>
<td>64.6</td>
<td>0.632</td>
<td>0.1017</td>
</tr>
<tr>
<td>1.8971</td>
<td>3.54</td>
<td>66.2</td>
<td>0.590</td>
<td>0.0938</td>
</tr>
<tr>
<td>1.9000</td>
<td>3.51</td>
<td>67.7</td>
<td>0.551</td>
<td>0.0870</td>
</tr>
</tbody>
</table>
Table 2.05 (cont.)

<table>
<thead>
<tr>
<th>[H$_2$SO$_4$] x 10$^2$, M</th>
<th>pH</th>
<th>-E(mv)</th>
<th>[L] x 10$^3$, M</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9028</td>
<td>3.49</td>
<td>69.1</td>
<td>0.521</td>
<td>0.0813</td>
</tr>
<tr>
<td>1.9056</td>
<td>3.46</td>
<td>69.9</td>
<td>0.492</td>
<td>0.0778</td>
</tr>
</tbody>
</table>

r is defined by eqn. 2.29. From these results, the following values were obtained: $s = 2.761 \times 10^{-2}$, $t = 40.980$, $u = 1.213 \times 10^5$. Hence, log $K_1^I = 3.17$, and log $\beta_2^I = 6.64$.

... ... ...

Table 2.06

Determination of Stability Constants of Copper(I) - L-Methionine Complexes at 20° and I = 0.15.

(i) An aqueous solution of L-methionine ($4.989 \times 10^{-3}$M) was adjusted to I = 0.15 with sodium sulphate. Copper ions were added by electrolysis, giving $[\text{Cu}^I]_T + 2[\text{Cu}^{II}]_T = 4.082 \times 10^{-4}$M. The solution was then titrated with 0.0497M-sulphuric acid.

<table>
<thead>
<tr>
<th>[H$_2$SO$_4$] x 10$^4$, M</th>
<th>pH</th>
<th>E(mv)</th>
<th>[L] x 10$^8$, M</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.149</td>
<td>4.38</td>
<td>-9.2</td>
<td>5.859</td>
<td>8.8141</td>
</tr>
<tr>
<td>0.497</td>
<td>4.22</td>
<td>-0.6</td>
<td>3.925</td>
<td>7.3653</td>
</tr>
<tr>
<td>0.992</td>
<td>4.06</td>
<td>8.3</td>
<td>2.865</td>
<td>7.3097</td>
</tr>
<tr>
<td>1.487</td>
<td>3.96</td>
<td>13.9</td>
<td>2.261</td>
<td>7.1595</td>
</tr>
<tr>
<td>1.980</td>
<td>3.84</td>
<td>18.2</td>
<td>1.736</td>
<td>6.6787</td>
</tr>
<tr>
<td>2.473</td>
<td>3.76</td>
<td>21.4</td>
<td>1.431</td>
<td>6.4862</td>
</tr>
</tbody>
</table>
Table 2.06 (cont.)

<table>
<thead>
<tr>
<th>$[\text{H}_2\text{SO}_4] \times 10^4, \text{M}$</th>
<th>pH</th>
<th>E(mv)</th>
<th>$[\text{L}] \times 10^8, \text{M}$</th>
<th>$r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.964</td>
<td>3.69</td>
<td>24.0</td>
<td>1.221</td>
<td>6.4000</td>
</tr>
<tr>
<td>3.944</td>
<td>3.56</td>
<td>27.6</td>
<td>0.903</td>
<td>6.0933</td>
</tr>
<tr>
<td>4.921</td>
<td>3.45</td>
<td>30.1</td>
<td>0.707</td>
<td>5.9009</td>
</tr>
<tr>
<td>7.345</td>
<td>3.28</td>
<td>33.9</td>
<td>0.471</td>
<td>5.7776</td>
</tr>
</tbody>
</table>

From these results, $s = 5.575$, $t = 6.26 \times 10^7$. Thus, $\log K_{1}^{I} = 7.05$.

(ii) An aqueous solution of L-methionine ($2.504 \times 10^{-3}\text{M}$) containing perchloric acid ($1.468 \times 10^{-5}\text{M}$) was adjusted to $I = 0.15$ with sodium perchlorate. Copper ions were added by electrolysis, giving $[\text{Cu}^{I}]_T + 2[\text{Cu}^{II}]_T = 1.288 \times 10^{-4}\text{M}$.

The solution was titrated with perchloric acid ($0.1468\text{M}$).

<table>
<thead>
<tr>
<th>$[\text{HClO}_4] \times 10^4, \text{M}$</th>
<th>pH</th>
<th>E(mv)</th>
<th>$[\text{L}] \times 10^8, \text{M}$</th>
<th>$r$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1468</td>
<td>4.43</td>
<td>18.1</td>
<td>3.437</td>
<td>13.187</td>
</tr>
<tr>
<td>0.2935</td>
<td>4.35</td>
<td>21.9</td>
<td>2.825</td>
<td>12.334</td>
</tr>
<tr>
<td>0.4403</td>
<td>4.28</td>
<td>25.2</td>
<td>2.432</td>
<td>12.035</td>
</tr>
<tr>
<td>0.7336</td>
<td>4.17</td>
<td>30.1</td>
<td>1.888</td>
<td>11.506</td>
</tr>
<tr>
<td>1.0269</td>
<td>4.08</td>
<td>34.0</td>
<td>1.515</td>
<td>11.167</td>
</tr>
<tr>
<td>1.4665</td>
<td>3.95</td>
<td>38.2</td>
<td>1.131</td>
<td>10.658</td>
</tr>
<tr>
<td>2.0523</td>
<td>3.83</td>
<td>42.0</td>
<td>0.854</td>
<td>10.438</td>
</tr>
<tr>
<td>2.9301</td>
<td>3.69</td>
<td>45.8</td>
<td>0.613</td>
<td>10.288</td>
</tr>
</tbody>
</table>

From these results, $s = 9.737$, $t = 8.25 \times 10^7$. Thus $\log K_{1}^{I} = 6.93$. 
### Table 2.07

Stability Constants of Copper(I) Complexes at 20° and I = 0.15.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>log $K_1^I$</th>
<th>log $\beta_2^I$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridine</td>
<td>3.17</td>
<td>6.64</td>
</tr>
<tr>
<td>4-Methylpyridine</td>
<td>3.90$^a$</td>
<td>6.60$^a$</td>
</tr>
<tr>
<td>Imidazole</td>
<td>4.30</td>
<td>7.65</td>
</tr>
<tr>
<td>2-Methylthioethylamine</td>
<td>5.78</td>
<td>10.98</td>
</tr>
<tr>
<td>L-Methionine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ At 25° and I = 0.3, from James and Williams, 1961.

$^b$ At 25° and I = 0.15, from Li et al., 1954.

### Table 2.08

Standard Oxidation-Reduction Potentials of Copper(II)-Copper(I) Couples in Water at 20°.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>$E^{o}_{1:1}(v)$</th>
<th>$E^{o}_{2:2}(v)$</th>
<th>$E^*<em>f(\bar{n}</em>{II}:\bar{n}_I)(v)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridine</td>
<td>0.194</td>
<td>0.267</td>
<td>0.304$^a$</td>
</tr>
<tr>
<td>4-Methylpyridine</td>
<td>0.265</td>
<td>0.295</td>
<td>0.300$^b$</td>
</tr>
<tr>
<td>Imidazole</td>
<td>0.252</td>
<td>0.345</td>
<td>0.317$^c$</td>
</tr>
</tbody>
</table>

$^a$ At 25° and I = 0.3, from James and Williams, 1961.

$^b$ At 25° and I = 0.15, from Li et al., 1954.

$^c$ At 25° and I = 0.15, from Li et al., 1954.

$^d$ At 25° and I = 0.15, from Li et al., 1954.
**Table 2.08 (cont.)**

<table>
<thead>
<tr>
<th>Ligand</th>
<th>$E_0^{1:1}(v)$</th>
<th>$E_0^{2:2}(v)$</th>
<th>$E_f^*(\bar{n}<em>{II}-\bar{n}</em>{I})(v)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzimidazole</td>
<td>0.217</td>
<td>0.361</td>
<td></td>
</tr>
<tr>
<td>2-Methylthioethylanine</td>
<td>0.184</td>
<td>0.240</td>
<td></td>
</tr>
<tr>
<td>L-Methionine</td>
<td>0.081</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E^0$</td>
<td>0.167 V at 25°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$Cu^{2+},Cu^+$</td>
<td>0.164 V at 20°</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- $E_f^*(3:3)$, at 25° and $I = 0.3$, from James and Williams, 1961.
- $E_f^*(4:4)$, at 25° and $I = 0.3$, from James and Williams, 1961.
- $E_f^*(2:2)$, at 25° and $I = 0.3$, from James and Williams, 1961.
- see Table 1.03.
- Fenwick, 1926.
- Corrected for temperature difference with literature value for $\Delta S^0$ (Hugus, 1951; Wagman, 1951; Latimer, 1952).
**Fig. 2.01.** Titration Curve for Copper(II)-Imidazole System. The titration with CO₂-free sodium hydroxide (0.0999 M) of an aqueous solution of copper perchlorate (5x10⁻³ M), imidazole (6x10⁻² M) and perchloric acid (6x10⁻² M), adjusted to I=0.15 with sodium perchlorate.
Fig. 2.02. Determination of $K_1$ and $\beta_2$ for Copper(II)-Imidazole System. Using $\beta_3 = 5.4 \times 10^{10} \text{M}^{-3}$ and $\beta_4 = 9.45 \times 10^{12} \text{M}^{-4}$ (from prior approx.) gives $K_1 = 1.80 \times 10^4 \text{M}^{-1}$ and $\beta_2 = 7.46 \times 10^7 \text{M}^{-2}$ (see eqn. 2.16).
Fig. 2.03. Determination of $\beta_3$ and $\beta_4$ for Copper(II)-Imidazole System. Using $K_1 = 1.80 \times 10^4 M^{-1}$ and $\beta_2 = 7.46 \times 10^7 M^{-2}$ (from Fig. 2.02) gives $\beta_3 = 5.4 \times 10^{10} M^{-3}$ and $\beta_4 = 9.45 \times 10^{12} M^{-4}$ (from eqn. 2.15).
Fig. 2.04. Determination of $K_1$ and $\beta_2$ for Copper(II) - Methionine System. From graph, $K_1 = 1.0 \times 10^8 \text{M}^{-1}$ and $\beta_2 = 1.7 \times 10^{15} \text{M}^{-2}$ (from eqn. 2.14).
Fig. 2.05. Copper(I) - Pyridine System: an internal check on the titration and stability constants. According to eqn. 2.37, $\log K_1^I = 3.17$, and $\log \beta_2^I = 6.64$. 
Fig. 2.06. From graph (according to eqn. 2.37), $K_1 = 1 \times 10^7 \text{M}^{-1}$ for the copper(I) - methionine system.

- $\circ$ - titration (i); $\Phi$ - titration (ii).
CHAPTER 3

SUBSTITUTED 1,10-PHENANTHROLINE LIGANDS

3.1 Introduction

Rigidity of the 1,10-phenanthroline molecule and its formation of metal complexes by co-ordination through two N atoms make it a possible model compound for considering metal-porphyrin complexes (James et al., 1962). In the copper complexes this analogy must not be carried too far because, whereas in porphyrins the four nitrogen atoms must be in a plane, in the phenanthroline complexes steric interactions involving the hydrogen atoms at positions 2 and 9 in the phenanthroline nucleus prevent the complexes from being planar.

2,9-Dimethyl-1,10-phenanthroline (DMP) has more interest for biologists than the unsubstituted compound. Its metal complexes have been claimed to possess fungistatic activity (Geigy, 1952). Further, a copper(II)-DMP solution has been used as a model for the copper metallo-enzymes, polyphenoloxidase and uricase, in a study of the oxidation of the biologically important substrates, 3,4-dihydroxyphenylalanine and uric acid (Isaka, 1960). Also DMP and related compounds are important analytical reagents for the determination of copper as copper(I) (Smith and McCurdy, 1952).

Determination of the temperature dependence of the
standard oxidation-reduction potentials for the copper systems with DMP and 2-chloro-1,10-phenanthroline (ClP) has allowed the calculation of the contributions of enthalpy and entropy to these potentials. Such a study has not been previously reported in the literature for a copper(II)-copper(I) complex couple.

Crystalline mono- and bis-DMP complexes of both copper(II) and copper(I) have recently been characterised (Hall et al., 1962). However, the reported analytical data for the bis-DMP-copper(I) sulphate complex do not agree with the postulated trihydrate: the figures for carbon and hydrogen are consistent with values for a pentahydrate, but the nitrogen results appear to contain an arithmetical error.

3.2 Experimental
(i) Reagents:— ClP was prepared according to Halcrow and Kermack (1946) and purified by recrystallisation from
benzene giving pale fawn needles, m.p. 130° (Halcrow and Kermack (1946) give 130°). (Found: C, 67.22; H, 3.29; N, 12.96. Calc. for C_{12}H_{7}N_{2}Cl : C, 67.14; H, 3.29; N, 13.05%). "Puriss" grade DMP.H_{2}O (Fluka) was used without further purification.

(ii) Bis(2,9-dimethyl-1,10-phenanthroline)copper(I) sulphate pentahydrate:- Copper(II) sulphate pentahydrate (0.86 g), dissolved in water (5 ml), was added to a suspension of DMP.H_{2}O (1.5 g) in water (100 ml). The mixture was stirred until solution was complete. Sodium sulphite (0.9 g of Na_{2}SO_{3}.7H_{2}O in 5 ml of water) was added dropwise, with stirring, to the green solution. The solution's colour changed to orange-red, and orange-red needles of the copper(I) complex precipitated. Recrystallisation from 10% aqueous ethanol gave the bis-DMP-copper(I) sulphate (1.37 g). (Found: C, 58.85; H, 5.15; N, 9.69. C_{56}H_{48}N_{8}O_{4}SCu_{2}.5H_{2}O requires C, 58.68; H, 5.10; N, 9.78%).

(iii) Bis(2-Chloro-1,10-phenanthroline)copper(I) sulphate pentahydrate:- A solution of copper sulphate (0.87 g) and ClP (1.5 g), treated with a sodium sulphite solution as described above for the DMP complex, yielded dark-red plates of bis-ClP-copper(I) sulphate (1.4 g), which were recrystallised from 50% aqueous ethanol. (Found: C, 49.31; H, 3.28; N, 9.59. C_{48}H_{28}N_{8}Cl_{4}O_{4}SCu_{2}.5H_{2}O requires C, 49.20; H, 3.27; N, 9.56%).
(iv) Redox apparatus:— The cell was a cylindrical glass flanged beaker of about 200 ml capacity, closed by a rigid polythene top which was sealed to the beaker with soft petroleum jelly and clipped in position to make the vessel air-tight. Through the polythene top passed "Quickfit" ground-glass sockets carrying two gold electrodes (cleaned with concentrated nitric acid to which had been added a drop of concentrated hydrochloric acid), an adjustable glass rod from which was hung a platinum cage, a thermometer, an "Agla" micrometer syringe, gas-inlet tube, and gas-outlet tube passing through a water-trap. In addition, the cell was connected to an external saturated calomel electrode (E.I.L.) by a 0.1M-potassium chloride salt-bridge, the ends of which were plugged with tightly-rolled Whatman 542 filter paper. The potentiometer, a Tinsley instrument (type 4046B) easily readable to 0.1 mv, was used with a Cambridge spot galvanometer.

(v) Standard oxidation-reduction potentials:— The solid copper(I) complex was weighed in a small platinum boat which was placed in the platinum cage in the 'up' position. After the solution of copper sulphate and the ligand had been deoxygenated in the cell by passing oxygen-free nitrogen through the solution for 1 hr, the platinum cage was lowered into the solution and the copper(I) complex dissolved with the aid of stirring (magnetically) and gentle warming. The cell was brought to the desired temperature
and the electrodes were inserted. For ionic strengths greater than 0.01, sodium sulphate was incorporated in the original solution of copper sulphate and ligand; otherwise, the ionic strength of the solution was varied by adding oxygen-free 0.1M-sodium sulphate solution. After each addition, the solution was stirred by bubbling nitrogen through it. It was then allowed to come to equilibrium with the electrodes for 10 mins. Nitrogen was passed continuously over the surface of the solution. Readings were taken immediately after the insertion of the salt-bridge, which was then withdrawn from the solution. (Before inserting the salt-bridge, its outside was thoroughly washed and dried). The process was repeated at 5 min intervals until constancy was obtained; usually, two measurements were sufficient. The potentials for the two gold electrodes at each reading agreed to within 0.1 mv. Details of experiments are shown in Figs. 3.01 and 3.02. The standard oxidation-reduction potentials were determined by the equivalence method using eqn. 1.06. The slopes of the lines in Figs. 3.01 and 3.02 (0.084 at 10°, 0.089 at 20°, 0.092 at 30°) are the theoretical values from eqn. 1.06 (using A = 0.4989 at 10°, 0.5070 at 20° and 0.5161 at 30°, from Robinson and Stokes, 1959ii). Formal potentials at I = 0.15 for both couples, and at I = 0.075 for the DMP couple, also lie on these lines.
(vi) Calibration of the calomel electrode:— The potential for the saturated calomel electrode, including a liquid-junction potential for the 0.1M-potassium chloride salt-bridge, was measured against a 0.01M-hydrochloric acid-quinhydrone electrode, allowing at least 40 hr for electrode equilibration at each temperature. The potential, $E_q$, of the quinhydrone electrode was calculated from the equation,

$$E_q = E^0_q + \frac{RT}{F} \ln a_{H^+}, \quad (3.01)$$

using published values for $E^0_q$ (Clark, 1960) and $f^+$(HCl) (Harned and Owen, 1950). Details are summarised in Table 3.01.

### 3.3 Results

Values for the standard oxidation-reduction potentials, determined from Figs. 3.01 and 3.02 according to eqn. 1.06, and the formal potentials at $I = 0.15$ are given in Table 3.02. The formal oxidation-reduction potentials obtained by James and Williams (1961) at $I = 0.3$ are included for comparison.

Changes of standard entropy, $\Delta S^0$, and enthalpy, $\Delta H^0$, for the redox equilibria have been calculated from

$$\Delta G^0 = \Delta H^0 - T \Delta S^0, \quad (3.02)$$

where $\Delta G^0 = -FE^0$. For both the DMP and ClP couples the changes of standard entropy are small ($\Delta S^0 = 1.8$, and
0 e.u., respectively), indicating that the oxidation-reduction potentials are due mainly to enthalpy terms. The change of standard enthalpy for the first of these couples, -13.88 kcal, is 3 kcal more negative than that for the second, -10.76 kcal.

The stability constant for the bis-DMP-copper(I) complex at 20° and I = 0.15 was calculated from eqn. 1.15 (log β_2^I = 19.54; cf. at 25° and I = 0.3, log β_2^I = 19.1, from James and Williams, 1961). The value for the corresponding copper(II) stability constant at 20° and I = 0.15 (Na_2SO_4) (log β_2^{II} = 11.63; cf. at 25° and I = 0.3, log β_2^{II} = 11.7, from James and Williams, 1961) was determined by the pH-titration technique. The value of log β_2^I for the copper(I)-DMP complex is greater than for similar complexes with 2-chloro-, 2-methyl-, and unsubstituted-1,10-phenanthroline (James and Williams, 1961), as expected from the greater basicity of the ligand.
### Table 3.01

Potential of the Saturated Calomel Electrode, $E_{s.c.}^0$, with a 0.1M-Potassium Chloride Salt-Bridge

<table>
<thead>
<tr>
<th></th>
<th>$10^\circ$</th>
<th>$20^\circ$</th>
<th>$30^\circ$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E^0_q$</td>
<td>0.71073</td>
<td>0.70343</td>
<td>0.69607</td>
</tr>
<tr>
<td>$f_\pm$ (0.01M-HCl)$^b$</td>
<td>0.9055</td>
<td>0.9052</td>
<td>0.9034</td>
</tr>
<tr>
<td>$2.3026RT/F$</td>
<td>0.056182</td>
<td>0.058165</td>
<td>0.060149</td>
</tr>
<tr>
<td>$E_{s.c.}^0$ (with 0.1M-KCl salt-bridge)</td>
<td>0.3312</td>
<td>0.3292</td>
<td>0.3240</td>
</tr>
</tbody>
</table>


### Table 3.02

Standard and Formal Oxidation-Reduction Potentials of 1:2-Copper Complexes of DMP and ClP

<table>
<thead>
<tr>
<th>Ligand</th>
<th>$E^0(v)$</th>
<th>$E^0_f(v)$</th>
<th>$E^*_f(v)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMP</td>
<td>0.6233</td>
<td>0.6248</td>
<td>0.5992</td>
</tr>
<tr>
<td>ClP</td>
<td>0.4668</td>
<td>0.4666</td>
<td>0.4412</td>
</tr>
</tbody>
</table>

$^a$ James and Williams, 1961.
Fig. 3.01. Determination of Standard Oxidation-Reduction Potential for the 1:2 copper complexes of DMP (using eqn. 1.06). The ionic strength of an aqueous solution of copper sulphate (5 x 10^{-5} M), bis-DMP-copper(I) sulphate (2.5 x 10^{-5} M) and DMP (2 x 10^{-4} M) was adjusted with sodium sulphate (0.1 M).
Although the carboxylate anion forms relatively weak complexes with copper(II) (Frouin, 1961; Ferrin, 1961), it is thought to be biologically important as a co-ordinating group; especially as a metal group in hydroxy complexes. Hydrolysis would not interfere with its function if it is assumed that the degree of hydrolysis of copper(II) ion is dependent on the concentration of the copper(II) ion (Frouin, 1961) and, at low concentrations of copper(II) and at pH values as are set within biological systems, the degree of hydrolysis of copper(II) ion would be small. However, in studying complex formation in the investigations of copper(II) ion are necessary. This implies that possible copper complexes can be investigated.

\[ E + RT \ln \frac{[CuL_2^+]}{[CuL_2^{2+}]} \]

\[ (v) \]

\[ 0.21 \]

\[ 0.20 \]

\[ 0.04 \]

\[ 0.08 \]

\[ \frac{I^+}{(1 + I^+)} \]

**Fig. 3.02.** Determination of Standard Oxidation-Reduction Potential for the 1:2 Copper Complexes of ClP (using eqn. 1.06). The ionic strength of an aqueous solution of copper sulphate \((2.5 \times 10^{-5} \text{M})\), ClP \((1.25 \times 10^{-4} \text{M})\) and bis-ClP-copper(I) sulphate \((\Theta - 1.25 \times 10^{-5} \text{M}; \odot - 6.25 \times 10^{-6} \text{M})\) was adjusted with sodium sulphate \((0.1 \text{M})\).
CO-ORDINATION OF DONOR GROUPS WITH COPPER(II): COMPLEXES OF SUBSTITUTED CARBOXYLIC ACIDS

Although the carboxylate anion forms relatively weak complexes with copper(II) (Fronaeus, 1948, 1951; Perrin, 1961; Sandell, 1961), it is thought to be biologically important as a co-ordinating group, especially in conjunction with the amino group in α-aminoacids. Hydrolysis of Cu$^{2+}$ would not interfere with its forming a complex with -COO$^-$ under biological conditions; the degree of hydrolysis of Cu$^{2+}$ is dependent on the concentration of the copper(II) ion (Perrin, 1960) and, at the low concentrations of Cu$^{2+}$ and at pH 7 such as are met with in biological systems, the degree of hydrolysis of copper(II) ion would be small. However, in studying complex formation in the laboratory, higher concentrations of copper(II) ion are necessary. This limits the possible pH range over which complexes can be investigated quantitatively and, in the present case, leads to the pH-titration method being unsatisfactory for work on complex formation between Cu$^{2+}$ and most of the carboxylic acids studied (glycine is an exception). The copper amalgam electrode does not suffer from this disadvantage and was used in the present investigations.
4.1 Reagents

Acetic and propionic acids (Laboratory Reagent grade, from B.D.H. Ltd.) were purified by fractional distillation. Phenylacetic (Laboratory Reagent grade, from B.D.H. Ltd.) and glycollic (from L. Light & Co. Ltd.) acids were recrystallised from light petroleum (80°-110°) and ether, respectively, and dried in vacuo. Sodium glycollate (Laboratory Reagent grade, from B.D.H. Ltd.) was recrystallised from water and dried in vacuo.

4.2. Apparatus

The apparatus was as described for the pH-titration technique (see Section 2.3(ii)) with the following additions:

(a) A copper amalgam electrode of a modified Dawson and Nair (1950) design was included in the titration-cell assembly. This type of electrode is superior to the more usual pool electrode because the surface of the electrode can be renewed for each measurement.

(b) A Tinsley potentiometer (type 4046B), readable to 0.01 mv, was used with a Pye "Scalamp" galvanometer.

4.3 Standard Electrode Potential, \( E^0(Cu^{2+}/Cu-Hg) \)

The method adopted for the calculation of stability constants for the copper(II)-carboxylate complexes requires the standard electrode potential, \( E^0(Cu^{2+}/Cu-Hg) \), to be known. A value for the potential was obtained from eqn. 1.16.
by measuring the potential impressed upon the copper amalgam electrode by a series of solutions with varying activity of Cu$^{2+}$. The activity coefficient of Cu$^{2+}$ was calculated from the Davies' (1938) modification of the Debye-Hückel equation,

$$-\log f_1 = A z_1^2 \left( I^{1/2}/(1+I^{1/3}) - 0.2I \right). \tag{4.01}$$

Details of experiments are given in Fig. 4.01: the value obtained for $E^0(Cu^2+/Cu-Hg)$, 0.1028 v vs sat. cal., includes a liquid-junction potential for the ammonium nitrate-sodium nitrate-agar salt-bridge.

**The Copper Amalgam Electrode**

A - glass reservoir; B - acidified CuSO$_4$ solution to prevent deterioration of amalgam; C - two-phase copper amalgam(1-2%) prepared according to Dawson and Nair (1950); D - stopcock; E - platinum contact-wire; F - glass capillary.
4.4 Copper(II) - Carboxylate Stability Constants

The following experimental procedure was adopted for the determination of stability constants for copper(II) complexes with all the acids except glycine:

(a) A good approximation for the activity coefficient of \( \text{Cu}^{2+} \) in a perchlorate medium with \( I = 1.0 \) was obtained from eqn. 1.16 by measuring the potential impressed upon the copper amalgam electrode by a solution of copper perchlorate of known concentration which had been acidified with perchloric acid to prevent hydrolysis of \( \text{Cu}^{2+} \).

(b) The ionic strength of a solution containing copper perchlorate of the same concentration as that in (a), and containing also the carboxylic acid and its sodium salt in such a ratio as to ensure a buffered pH of approximately the same value as that of the solution in (a), was adjusted to \( I = 1.0 \) with sodium perchlorate.

(c) The carboxylic acid solution was added stepwise to the first solution. The pH of the solution and the potential impressed on the copper amalgam electrode were measured.

The stability constants were calculated from the equation,

\[
\frac{([\text{Cu}]_T /[\text{Cu}^{2+}] - 1)/[\text{L}^-]}{[\text{L}^-]} = K_1 + \beta_2 [\text{L}^-],
\]  

(4.02)

the derivation of which is based on the expression for the total concentrations of metal species,

\[
[\text{Cu}]_T = [\text{Cu}^{2+}] + \sum_{x=1}^{x=P} [\text{CuL}_x^{(2-x)^+}].
\]

(4.03)
A general equation (4.04) corresponding to eqn. 4.02 is obtained from eqn. 4.03 by substituting expressions for the concentrations of the individual complex species according to eqn. 1.11.

\[
\frac{[Cu]_T/[Cu^{2+}] - 1}{[L^-]} = \sum_{x=1}^{\infty} \beta_x [L^{-}]^x - 1.
\] (4.04)

Experimental conditions were so selected that species with \(x\) greater than 2 were unimportant.

Values for \([Cu^{2+}]\) and \([L^-]\) were obtained from eqns. 1.16 and 4.05, respectively.

\[
[L^-] = \frac{K_a}{[H^+]} ([HL]_T + [HClO_4]_T + [OH^-] - [H^+]).
\] (4.05)

The latter equation for the concentration of free ligand was derived, as usual, from the equations for total concentrations of metal species, total concentrations of ligand species, and total charges (cf. derivation of eqn. 2.07). Details of a typical experiment are given in Table 4.01 and Fig. 4.02.

The experimental procedure for the copper(II) - glycinate system differed from the above in that the ligand solution was added as one portion and the resulting solution was titrated with alkali. Equations for the calculations were as before except that the concentration of free ligand was obtained from the equation,

\[
[L^-] = \frac{K_{a1} K_{a2}}{[H^+](2[H^+] + K_{a1})} ([HL]_T + [HClO_4]_T + [OH^-] - [H^+] - [NaOH]_T),
\] (4.06)
which is an extension of eqn. 2.21. Details of an experiment for the glycine system are given in Table 4.02 and Fig. 4.03.

Stability constants for the copper(II)-carboxylate complexes investigated with the copper amalgam electrode are given in Table 4.03. Literature values for the constants determined under comparable conditions are included for comparison. Stability constants for copper(II) complexes with other carboxylic acids have been reported in the literature and are given in Table 4.04.

4.5 Effect of Substituents on a Carboxylic Acid as a Ligand

The approximate straight-line relationship between the pKₐ values for a series of closely related ligands and their stability constants with a metal ion is well known. For the "carboxylic acid series", when only the carboxylate group is involved in complex formation, (see Fig. 4.04)

\[ \log K_1 = 0.38 \, pK_a + b. \]  

(4.07)

It is difficult to evaluate the constant, b, accurately from the available data, but it is approximately 0. It has been suggested previously (Jones et al., 1958) that b is a measure of the \( \pi \)-character of the metal-ligand bond. Thus, there is no tendency for copper(II) to donate electrons to the ligand. This is to be expected as there
are no suitable orbitals on the ligand to receive the electrons.

The failure of a number of ligands to satisfy the straight-line relationship is probably due to the tendency of these ligands to chelate. The ratio, $K_1/K_{1\text{ (est.)}}$, where $K_{1\text{ (est.)}}$ is the stability constant predicted from eqn. 4.07, is a measure of the stabilising effect of the substituent. Values of this ratio for copper complexes which show enhanced stability are given in Table 4.05. They indicate that the co-ordinating tendencies of the substituents for copper(II) ion lie in the sequence,

$$-\text{NH}_2 > -\text{SR} > -\text{OH} > -\text{OR}.$$  

The greater tendency for a thioether than for an ether to co-ordinate has also been observed by Tichane and Bennet (1957) for the copper(II) complexes with $X(\text{CH}_2\text{COO}^-)_2$. Sandell (1961) has suggested from a comparison of the stability constants of copper(II) with acetate, alkoxyacetate and ethylthioacetate that alkoxyacetate does not act as a chelate, but, in the ethylthioacetate complex, "the sulphur atom is strongly bound to the central atom". Bjerrum (1941), Fronaeus (1948) and Ahrland (1953) used purely statistical reasoning to conclude that, if chelates are formed, the ratios between the successive formation constants, $K_n/K_{n+1}$, should be greater than in a system where chelates are not formed. Thus, from a comparison of
his values for $K_1/K_2$ for the acetate and glycollate systems, Fronaeus (1948) postulated that the glycollate ion chelates with Cu$^{2+}$. However, according to Table 4.06, if this criterion for chelate formation were to be used, only glycine would be considered to behave as a chelate. The statistical reasoning that Bjerrum (1941) and the other authors (Fronaeus, 1948; Ahrland, 1953) have used is based on the assumption that a monodentate ligand when complexed does not influence the position at which a second ligand molecule will complex. However, it is doubtful whether this assumption is valid, especially for an anionic ligand. For a square-planar complex (4-coordinate copper(II) complexes usually are square-planar (see Section 6.3ii)), the second anion will co-ordinate in a position trans to the first ligand due to such effects as ionic repulsions. If this is taken into account, statistical arguments similar to those of Bjerrum (1941) give $K_1/K_2$ the value, 8, for both mono- and bidentate ligands, which is in good agreement with most of the values in Table 4.06. However, statistical arguments are not the only factors that govern the value of this ratio (Rossotti, 1960). Thus, $K_1/K_2$ is not constant for all the "carboxylic acid series". (No doubt experimental inaccuracies also contribute to the variations in the values for $K_1/K_2$. )
Tanaka and Kato (1960) have recently studied the formation of copper(II)-acetate complexes over a 20° temperature range. Entropy (ΔS = 23.3 e.u.) and enthalpy (ΔH = 4.6 kcal) terms obtained from their results show that the copper(II) - carboxylate bond owes what stability it does have to the favourable change of entropy on complex formation; the change in enthalpy, which is composed of both hydrational and ligational factors, is positive and thus opposes complex formation.

Little is known concerning the ability of the carboxylate anion to co-ordinate with copper(I). However, it is not expected that such a complex would be any more stable than the corresponding copper(II) complex. Sandell (1961) observed that solutions of copper(II) with either ethylthioacetate or thiodiacetate reacted with metallic copper or copper amalgam giving, in the case of ethylthioacetate, a yellow precipitate, presumably the copper(I) - ethylthioacetate complex. However, it is not known whether complex formation is through the sulphur, carboxylate, or both.

Because of the relatively weak co-ordination between the carboxylate anion and copper, this group is not expected to be important in biological redox systems involving copper, but it could take part in such systems in conjunction with another donor group through chelation.
Determination of Stability Constants for the Copper(II)–Acetate System in a Perchlorate Medium, $I = 1.0$, at $20^\circ$.

A solution of acetic acid ($1.685\text{M}$), sodium acetate ($0.997\text{M}$) and copper perchlorate ($1 \times 10^{-3}\text{M}$) was added stepwise to a solution of copper perchlorate ($1 \times 10^{-3}\text{M}$), sodium perchlorate ($0.997\text{M}$) and perchloric acid ($2.87 \times 10^{-5}\text{M}$).

\[
\begin{array}{cccc}
[\text{HL}]_T (\times 10^3, \text{M}) & \text{pH} & E(\text{mv}) & [\text{HL}]_T (\times 10^3, \text{M}) & \text{pH} & E(\text{mv}) \\
0.000 & 4.32 & 11.62 & 13.380 & 4.34 & 7.85 \\
1.683 & 4.33 & 11.10 & 15.030 & 4.34 & 7.45 \\
3.362 & 4.33 & 10.60 & 16.680 & 4.34 & 7.03 \\
5.375 & 4.33 & 10.02 & 19.980 & 4.34 & 6.26 \\
8.050 & 4.33 & 9.27 & 26.540 & 4.34 & 4.78 \\
9.385 & 4.33 & 8.90 & 29.800 & 4.34 & 4.10 \\
10.710 & 4.34 & 8.52 & 33.030 & 4.34 & 3.40 \\
12.040 & 4.34 & 8.16 & & & \\
\end{array}
\]

Results give $f_{\text{Cu}^{2+}} = 0.733$. 


Table 4.02

Determination of Stability Constants for the Copper(II) - Glycinate System in a Perchlorate Medium, I = 1.0, at 20°.

A solution of copper perchlorate \((5 \times 10^{-4} \text{M})\), glycine \((1 \times 10^{-2} \text{M})\), perchloric acid \((2.287 \times 10^{-4} \text{M})\) and sodium perchlorate \((0.9983 \text{M})\) was titrated with carbonate-free sodium hydroxide \((0.1002 \text{M})\).

<table>
<thead>
<tr>
<th>([\text{NaOH}] \times 10^4, \text{M} )</th>
<th>pH</th>
<th>(-E (\text{mv}))</th>
<th>([\text{NaOH}] \times 10^4, \text{M} )</th>
<th>pH</th>
<th>(-E (\text{mv}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.000</td>
<td>3.80</td>
<td>12.61</td>
<td>4.368</td>
<td>4.13</td>
<td>21.28</td>
</tr>
<tr>
<td>@ 0.399</td>
<td>3.83</td>
<td>13.14</td>
<td>4.763</td>
<td>4.16</td>
<td>22.41</td>
</tr>
<tr>
<td>0.797</td>
<td>3.85</td>
<td>13.78</td>
<td>5.158</td>
<td>4.21</td>
<td>23.71</td>
</tr>
<tr>
<td>@ 1.201</td>
<td>3.87</td>
<td>14.46</td>
<td>5.552</td>
<td>4.25</td>
<td>25.09</td>
</tr>
<tr>
<td>1.593</td>
<td>3.90</td>
<td>15.08</td>
<td>5.946</td>
<td>4.29</td>
<td>26.58</td>
</tr>
<tr>
<td>@ 1.990</td>
<td>3.93</td>
<td>15.88</td>
<td>6.340</td>
<td>4.34</td>
<td>28.22</td>
</tr>
<tr>
<td>2.389</td>
<td>3.96</td>
<td>16.62</td>
<td>6.734</td>
<td>4.40</td>
<td>29.96</td>
</tr>
<tr>
<td>2.784</td>
<td>3.99</td>
<td>17.40</td>
<td>7.127</td>
<td>4.45</td>
<td>31.77</td>
</tr>
<tr>
<td>3.180</td>
<td>4.01</td>
<td>18.22</td>
<td>7.913</td>
<td>4.57</td>
<td>36.26</td>
</tr>
<tr>
<td>3.576</td>
<td>4.05</td>
<td>19.14</td>
<td>8.893</td>
<td>4.75</td>
<td>43.10</td>
</tr>
<tr>
<td>3.972</td>
<td>4.09</td>
<td>20.22</td>
<td>9.872</td>
<td>4.95</td>
<td>52.27</td>
</tr>
</tbody>
</table>

© Points omitted from Fig. 4.03 to simplify presentation.

Activity coefficient was found to be \(f_{\text{Cu}^2+} = 0.730\).
### Table 4.03

Stability Constants for Copper(II)-Carboxylate Complexes in a Perchlorate Medium, \( I = 1.0 \), at 20°.

<table>
<thead>
<tr>
<th>Acid</th>
<th>( pK_a )</th>
<th>( \log K_1 )</th>
<th>( \log \beta_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic</td>
<td>4.54</td>
<td>1.62</td>
<td>2.37</td>
</tr>
<tr>
<td></td>
<td>4.61(^a)</td>
<td>1.62(^a)</td>
<td>2.60(^a)</td>
</tr>
<tr>
<td></td>
<td>4.61(^b)</td>
<td>1.65(^b)</td>
<td>2.65(^b)</td>
</tr>
<tr>
<td>Propionic</td>
<td>4.69</td>
<td>1.66</td>
<td>2.41</td>
</tr>
<tr>
<td>Phenylacetic</td>
<td>4.16</td>
<td>1.54</td>
<td>2.24</td>
</tr>
<tr>
<td>Glycollic</td>
<td>3.45</td>
<td>2.19</td>
<td>3.49</td>
</tr>
<tr>
<td></td>
<td>3.63(^a)</td>
<td>2.34(^a)</td>
<td>3.70(^a)</td>
</tr>
<tr>
<td>Glycine</td>
<td>2.41(^c), 9.76(^c)</td>
<td>8.35</td>
<td>15.41</td>
</tr>
<tr>
<td></td>
<td>2.43(^d), 9.62(^d)</td>
<td>8.38(^d)</td>
<td>15.25(^d)</td>
</tr>
</tbody>
</table>

\( ^a \) Fronaeus, 1948. \(^b\) Fronaeus, 1951. \(^c\) Perrin, 1958b. \(^d\) At 25° and \( I = 0.1 \) (NaCl\(_4\)), Basolo and Chen, 1954.
### Table 4.04

Stability Constants for Copper(II)-Carboxylate Complexes at 20° and with I = 1.0.

<table>
<thead>
<tr>
<th>Acid</th>
<th>$pK_a$</th>
<th>log $K_1$</th>
<th>log $\beta_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroacetic</td>
<td>2.66$^a$</td>
<td>0.91$^b$</td>
<td>1.09$^b$</td>
</tr>
<tr>
<td>2,4-Dichlorophenoxyacetic</td>
<td>2.78$^c$</td>
<td>0.8$^c$</td>
<td></td>
</tr>
<tr>
<td>4-Chlorophenoxyacetic</td>
<td>2.91$^c$</td>
<td>1.1$^c$</td>
<td></td>
</tr>
<tr>
<td>2,4-Dimethylphenoxyacetic</td>
<td>3.08$^c$</td>
<td>0.9$^c$</td>
<td></td>
</tr>
<tr>
<td>Methoxyacetic</td>
<td>3.37$^d$</td>
<td>1.82$^d$</td>
<td>2.81$^d$</td>
</tr>
<tr>
<td>Ethoxyacetic</td>
<td>3.46$^d$</td>
<td>1.79$^d$</td>
<td>2.87$^d$</td>
</tr>
<tr>
<td>Ethylthioacetic</td>
<td>3.61$^d$</td>
<td>2.56$^d$</td>
<td>4.76$^d$</td>
</tr>
<tr>
<td>a-Naphthylacetic</td>
<td>4.04$^c$</td>
<td>1.4$^c$</td>
<td></td>
</tr>
<tr>
<td>Indole-3-acetic</td>
<td>4.36$^c$</td>
<td>1.7$^c$</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4.05**

Measure of Enhanced Stability in "Carboxylic Acid Series".

<table>
<thead>
<tr>
<th>Acid</th>
<th>Substituent</th>
<th>$\log K_1$(est.)</th>
<th>$K_1/K_1$(est.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycine</td>
<td>-NH$_2$</td>
<td>0.86</td>
<td>3.1 x 10$^7$</td>
</tr>
<tr>
<td>Ethylthioacetic</td>
<td>-S-C$_2$H$_5$</td>
<td>1.30</td>
<td>18.2</td>
</tr>
<tr>
<td>Glycollic</td>
<td>-OH</td>
<td>1.24</td>
<td>8.9</td>
</tr>
<tr>
<td>Methoxyacetic</td>
<td>-O-CH$_3$</td>
<td>1.21</td>
<td>4.1</td>
</tr>
<tr>
<td>Ethoxyacetic</td>
<td>-O-C$_2$H$_5$</td>
<td>1.25</td>
<td>3.5</td>
</tr>
</tbody>
</table>

**Table 4.06**

Ratio of Successive Formation Constants for Copper(II)-Carboxylic Acid Complexes.

<table>
<thead>
<tr>
<th>Acid</th>
<th>$K_1/K_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetic</td>
<td>7.4</td>
</tr>
<tr>
<td>Propionic</td>
<td>8.1</td>
</tr>
<tr>
<td>Phenylacetic</td>
<td>6.9</td>
</tr>
<tr>
<td>Glycollic</td>
<td>7.8</td>
</tr>
<tr>
<td>Ethoxyacetic</td>
<td>5.2</td>
</tr>
<tr>
<td>Methoxyacetic</td>
<td>6.8</td>
</tr>
<tr>
<td>Ethylthioacetic</td>
<td>2.3</td>
</tr>
<tr>
<td>Glycine</td>
<td>19.5</td>
</tr>
</tbody>
</table>
Fig. 4.01. Determination of $E^0(Cu^{2+}/Cu-Hg)$. The ionic strength of a solution of copper perchlorate ($\Theta = 3 \times 10^{-4} M$; $O = 6 \times 10^{-4} M$) acidified with perchloric acid ($1 \times 10^{-3} M$) (to prevent hydrolysis of $Cu^{2+}$) was varied by adding a sodium perchlorate-copper perchlorate ($\Theta = 3 \times 10^{-4} M$; $O = 6 \times 10^{-4} M$) solution. The straight line (the slope, 0.0291, is the theoretical according to eqn.1.16) gives $E^0(Cu^{2+}/Cu-Hg) = 0.1028 \text{ v vs sat. cal.}$
Fig. 4.02. Determination of Stability Constants for the Copper(II) - Acetate System. (pKₐ for acetic acid = 4.54)

From eqn. 4.02 and data in Table 4.01, log $K_1 = 1.62$ and log $\beta_2 = 2.37$. 
Fig. 4.03. Determination of Stability Constants for the Copper(II) - Glycinate System. For glycine, pKₐ₁ = 2.41 and pKₐ₂ = 9.76 (Perrin, 1958b). From eqn. 4.02 and data in Table 4.02, log K₁ = 8.35 and log β₂ = 15.41.
Fig. 4.04. Relationship between pKₐ values of substituted carboxylic acids (R-CH₂COOH) and log K₁ for their copper(II) complexes. Data for the diagram are given in Tables 4.03 and 4.04.
5.1 Introduction

Although it would be of some biochemical interest, no extensive and quantitative study of equilibria in the aqueous copper(II)-cystine system appears to have been made. This is probably due, in part, to the sparing solubilities of the ligand and the copper(II)-cystine complex and, in part, to the complicated nature of the problem. Kolthoff and Stricks (1951) concluded from polarographic evidence that complex formation between copper(II) and cystine was not significant in ammoniacal solution. On the other hand, Hamaguchi and Kamamoto (1960) explained polarographic observations by the slow formation of a mononuclear complex, in which (as previously postulated by Ray and Bhaduri (1950) and Scaife (1959)) the two amino-acid groupings were co-ordinated to the same metal ion. However, Leybold atomic models show that simultaneous complex formation by both ends of the cystine anion to the same copper(II) ion is sterically impossible. This restriction also applies to the structurally related bis-(aminoacid), 2,7-diaminosuberic acid. The observation that the copper(II)-cystine complex could be crystallised as long fibres led Kahler and his co-workers (1952) to suggest that in the solid state the complex is a straight-
chain polymer.

The copper(II)-cystine system was studied by the pH-titration technique and, as a preliminary to this investigation, similar studies were carried out on equilibria in aqueous solution between hydrated copper(II) ion and a number of substances which are closely related to cystine.

5.2 Reagents and Apparatus

(i) Ligands

L-Cystine (Laboratory Chemical, from B.D.H. Ltd.) was purified by repeated solution in hydrochloric acid and reprecipitation by dropwise addition of alkali. The final product was dried at 100° for 2 hr and at room temperature in vacuo for 16 hr.

2,7-Diaminosuberic acid (DAS), prepared according to the method of Simmonds (1954), was recrystallised from water to give colourless crystals, m.p. > 360°. (Found: C, 46.94; H, 7.97; N, 13.79. Calc. for C₈H₁₆O₄N₂: C, 47.05; H, 7.90; N, 13.72%.)

Bis(2-carboxyethyl) disulphide (BCED), prepared from 3-mercaptopropionic acid (Westerman and Rose, 1927), was recrystallised from water to give colourless plates,
m.p. 156°. (Found: C, 34.14; H, 4.91; S, 30.41. Calc. for C₆H₁₀S₂O₄: C, 34.27; H, 4.79; S, 30.50%.)

Bis(2-aminooethyl) disulphide (BAED) was prepared from 2-mercaptopoethylamine (Mills and Bogert, 1940), isolated as the di-perchlorate by adding excess concentrated perchloric acid to a cold alcoholic solution of the free base, and the salt purified by recrystallisation from ethanol to give colourless plates, m.p. 124° (d.). (Found: C, 13.36; H, 3.96; N, 7.81. C₄H₁₄O₈N₂Cl₂S₂ requires C, 13.60; H, 4.00; N, 7.93%.)

3-(2-Aminooethylthio)-L-alanine (AEDA) was prepared as its hydrochloride according to the method of Schoberl and Grafje (1958) via the thiosulphinate ester of bis(2-aminooethyl) disulphide. It was purified by dissolving the product in a minimum of water and fractionally precipitating the compound by adding acetone dropwise with stirring and chilling to give colourless crystals, m.p. 171-172°. (Found: N, 11.81; S, 27.47. Calc. for C₅H₁₃O₂N₂ClS₂: N, 12.03; S, 27.55%.)
(ii) Apparatus:- The apparatus was as described for the pH-titration technique (Section 2.3(ii)).

5.3 Acid Dissociation Constants

The overlapping pK\textsubscript{a} values were obtained from potentiometric titrations; a graphical method similar to that of Speakman (1940) was used for the calculations. Thus, eqns. 5.01 and 5.02 were applicable to the acid and alkali titrations of a bis(aminoacid), AH\textsubscript{2}.

\[
\frac{(2a - b)[H^+]}{(b - a)} = K_{a1} + K_{a1}K_{a2} \cdot \frac{b}{[H^+](b - a)}, \quad (5.01)
\]

\[
\frac{c[H^+]^2}{(2a - c)} = K_{a3}K_{a4} + K_{a3} \cdot \frac{(c - a)[H^+]}{(c - 2a)}, \quad (5.02)
\]

where \(a\) is the total concentration of the aminoacid, \(b = [\text{acid}] + [\text{OH}^-] - [H^+], \quad c = [\text{Na}^+] + [H^+] - [\text{OH}^-], \text{ and,}

omitting charges, \(K_{a1} = [\text{AH}_{(4-1)}][H^+]/[\text{AH}_{(5-1)}], \text{ where}

\(i = 1, 2, 3, 4.\)

Eqn. 5.02 was derived from the total concentration of aminoacid and total charge equations (eqns. 5.03 and 5.04, respectively) for the alkali titration of AH\textsubscript{2},

\[
a = [\text{AH}_2] + [\text{AH}^-] + [A^{2-}], \quad (5.03)
\]

\[
[\text{Na}^+] + [H^+] = 2[A^{2-}] + [\text{AH}^-] + [\text{OH}^-], \quad (5.04)
\]

by expressing each as a function of \([A^{2-}], \text{ equating and} \]
rearranging. The corresponding equations for acid titration gave eqn. 5.01. Typical titration data and results are given in Figs. 5.01 and 5.02 for the alkali titration of DAS.

Similarly equations were derived for the titrations of BCED, BAED and AEDA. Because of the low solubility of cystine in water, the values for $pK_{a1}$ and $pK_{a2}$ could not be obtained. By dissolving the aminoacid in two equivalents of alkali and back-titrating, values for $pK_{a3}$ and $pK_{a4}$ were found. Although these values are probably only accurate to within about ±0.10 because the solution, on back-titration, was supersaturated, they agree within experimental error with the literature values (see Table 5.01). The acid dissociation constants are given in Table 5.01. In compounds of the type, $+H_3N-R-CH(NH_3^+)-COO^-$, the highest $pK_a$ value is assigned to the basic amine group (Albert, 1952). Hence, in AEDA, $pK_{a3} = 9.30$ relates to the amine group and $pK_{a2} = 8.28$ to the aminoacid nitrogen.

5.4 Copper(II) and Bis(2-carboxyethyl) Disulphide

Leybold atomic models show that both ends of BCED (a complex-forming species of type HLRLH) are capable of simultaneous complex formation with the same metal ion and so, also, is the -S-S- group. Although the complexing ability of the latter, per se, is probably weak, the stabilising effect associated with 5- and 6- membered chelate
ring formation would be expected to favour the formation of
the 1:1 complexes,

\[
\text{(A)} \quad \text{CO} \quad \text{Cu}^+ \quad \text{CH}_2\text{CH}_2\text{S}-\text{S}-\text{CH}_2\text{CH}_2\text{COOH}
\]

\[
\text{(B)} \quad \text{CO} \quad \text{Cu}^+ \quad \text{CH}_2\text{CH}_2\text{S}-\text{S}-\text{CH}_2\text{CH}_2
\]

Because B is a planar terdentate structure, the stability
of the 1:2 complex would be much less than that of the 1:1
complex (cf. thiodiacetate system (Tichane and Bennet, 1957;
Sandell, 1961)) and so it is possible to select conditions
under which formation of the 1:2 complex is unimportant,
and the relevant equilibria in acid solution are

\[
\text{Cu}^2+ + \text{HLRLH} \rightleftharpoons \text{HLRLCu}^+ + \text{H}^+
\]

and

\[
\text{Cu}^2+ + \text{HLRLH} \rightleftharpoons \text{LRLCu} + 2\text{H}^+
\]

In the system where copper(II) ion is added to a solution
of BCED and titrated with standard alkali, the equations
for total concentrations of metal species, total con-
centrations of ligand species, and total charges become,
respectively,

\[
[\text{Cu}]_T = [\text{Cu}^2+] + [\text{HLRLCu}^+] + [\text{LRLCu}]
\]

\[
= [\text{Cu}^2+] + K_1[\text{Cu}^2+][\text{HLRL}^-] + K_1K_2[\text{Cu}^2+][\text{HLRL}^-]/[\text{H}^+], \quad \text{(5.05)}
\]

\[
\ldots \ldots \text{(5.06)}
\]
where $K_1$ and $K'_1$ are the stability constants of $HLRLCu^+$ and $[LRLCu]$,

$$[HLRLH]_T = [HLRLH] + [HLRL^-] + [LRL^{2-}] + [HLRLCu^+] + [LRLCu^-],$$  \hspace{1cm} (5.07)

$$2[Ca^2+] + [HLRL^-] + 2[LRL^{2-}] = [Na^+] + [H^+] + 2[Ca^{2+}] + [HLRLCu^+].$$  \hspace{1cm} (5.08)

Hence, by subtracting eqn. 5.05 from eqn. 5.07 and rearranging

$$[Cu^{2+}] = a[HLRL^-] - ([HLRLH]_T - [Ca^2+_T]),$$  \hspace{1cm} (5.09)

where $a = 1 + [H^+]/K_{a1} + K_{a2}/[H^+]$. From eqns. 5.05 to 5.09 it can be deduced that

$$aK_1[HLRL^-]^2 + \left<(2a-b) - K_1([HLRLH]_T - [Ca^2+_T])\right>[HLRL^-] + ([Na^+] + [H^+] - 2[HLRLH]_T) = 0,$$  \hspace{1cm} (5.10)

where $b = 1 + 2K_{a2}/[H^+]$.

Selecting two arbitrary points - one at the beginning and the other at the end of the titration (i) in Fig. 5.03 - and using an iterative procedure to solve eqns. 5.06, 5.09 and 5.10, $K_1$ and $K'_1$ were evaluated. This value of $K_1 = 3.5 \times 10^2 M^{-1}$ was then used in eqns. 5.09 and 5.10 to obtain $[Ca^{2+}]$ and $[HLRL^-]$ at each point in the titration, so that, by substitution in eqn. 5.06, the corresponding values of $K_1'$ could be calculated. The
average over titration (i) was $K'_1 = 1.04 \pm 0.12 \times 10^3 \text{M}^{-1}$, the maximum deviation being $0.23 \times 10^3 \text{M}^{-1}$. Arbitrarily selected points from titration (ii) (as indicated in Fig. 5.03) gave the values for $K'_1$ listed in Table 5.02(ii). These values agreed, within experimental error, with the value for $K'_1$ from titration(i). The consistency of $K'_1$ over the two titrations, in which both the total concentrations of metal and ligand were different, strongly supports the above interpretation.

According to Fig. 4.04, the value of $\log K'_1 = 2.54$ for the copper(II) complex with the carboxylic acid, BCED ($pK_a = 3.88$), is much greater than would be expected for a simple carboxylic acid of similar $pK_a$ ($\log K_1\text{est.} = 1.40$). The additional stabilisation ($K'_1/K_1\text{est.} = 13.8$) is attributed to the contribution of the disulphide group to the co-ordination. A similar effect is found for the sulphide group in the copper(II) complex with ethylthioacetate where $\log K'_1 = 2.56$, $pK_a = 3.61$, and $K'_1/K_1\text{est.} = 18.2$ (see Section 4.5).

5.5 Copper(II) and Bis(2-aminoethyl) Disulphide

In BAED (which is a ligand of the type, LRL) both amino groups can complex to the same metal ion. For reasons similar to those discussed for BCED, the important equilibria with copper(II) in acid solution can be assumed to be
The sparing solubility of the complex limits the accessible range of experimental conditions. Taking two arbitrarily selected points - one at the beginning and the other at the end of the titration in which the metal:ligand ratio was 1:5 - the corresponding equations give $K_1$ and $K'_1$ as $6.15 \times 10^{-3} \text{M}^{-1}$ and $5.02 \times 10^{-6} \text{M}^{-1}$, respectively, where

$$K_1 = \frac{[+\text{HLRLCu}^2+] / [\text{Cu}^2+] [\text{LRLH}^+] \text{, and}}{K'_1 = \frac{[\text{LRLCu}^2+] / [\text{Cu}^2+] [\text{LRL}]\text{.}}$$

Values of $K'_1$ at other points in the titration (obtained using $K_1 = 6.15 \times 10^{-3} \text{M}^{-1}$) are included in Table 5.03. The average over the titration was $K'_1 = 4.97 \pm 0.10 \times 10^{-6} \text{M}^{-1}$, the maximum deviation being $0.16 \times 10^{-6} \text{M}^{-1}$.

As in the BCED system, it is proposed that the disulphide group contributes to the co-ordination. Knoblock and Purdy (1961) have claimed that BAED does not form a complex with copper(II) at pH 7.4, but this is not consistent with the present experimental results.

5.6 Copper(II) and 3-(2-Aminoethylldithio)-L-alanine

AEDA has four different groups potentially capable of complex formation with copper(II). These comprise the amine, the disulphide, and the amino and carboxyl groups of
the aminoacid. However, the experimental results (Fig. 5.04) were unable to satisfy equations derived on the assumption that both the amine and aminoacid groups (with or without any contribution from the disulphide) were attached to the same copper ion. If only one of these groups were involved, the much greater complex-forming ability of an aminoacid group than that of a simple amine (Bjerrum et al., 1957) would make the former the more likely binding site in copper complexes with AEDA.

Comparison of the stability constants for the copper(II) complexes of L-methionine with those of simple aminoacids indicates that in the complexes of methionine the sulphur atom contributes to the co-ordination. Thus, although the pKₘ of methionine is 0.65 units less than that of glycine, the stability constants of their copper complexes are similar (log K₁ = 8.00, log β₂ = 15.23, pKₘ = 9.20 for methionine; cf. glycine (Irving et al., 1954), log K₁ = 8.12, log β₂ = 15.03, pKₘ = 9.85). In the 1:2-methionine complex the sulphur atoms probably occupy remote positions in a typical distorted octahedral structure. Therefore, by comparison, it also appears probable that, as in the BCED and BAED systems, the disulphide group in AEDA would contribute to its co-ordination with copper(II).

Results from Fig. 5.05, calculated according to eqn. 2.14 (where L is the species LRLH⁺ in which the amine, but not the aminoacid nitrogen, is protonated) on the
assumption that the aminoacid grouping, but not the
terminal amine group, is involved in complex formation
between Cu$^{2+}$ and AEDA, show that in acid solutions
different metal:ligand molar ratios lead to the same
values of $\log K_1 = 7.08$ and $\log \beta_2 = 13.80$. In neutral
and alkaline solutions the amine group can no longer be
taken to be completely protonated. Under these conditions
the titration curves in Fig. 5.04 are reproduced quanti-
tatively using the above values of $\log K_1$ and $\log \beta_2$ if
$pK_a = 8.2$ is assigned to this amine group in the copper-
AEDA complexes. This decrease of 1.1 from the $pK_a$ value
in AEDA is probably due mainly to the tendency of the
amine group to co-ordinate with the copper ion.

5.7 Copper(II) and 2,7-Diaminosuberic Acid

The anion of DAS is a ligand of the general type,
$LRL_2^2-$, where $R$ is a group that prevents simultaneous
complex formation by both ends of the ion with a single
metal ion. This restriction gives rise to the formation
of polynuclear species with metal ions in aqueous solution.
Thus, Schwarzenbach (1952) observed a tendency for ligands
related to ethylenediaminetetra-acetic acid to form poly-
nuclear complexes with various metal ions as the length
of the methylene chain increased. Although numerous
polynuclear complexes have been isolated from solution
(Bailar, 1956), no extensive quantitative investigation
has previously been made of the types of species present
in solutions of metal ions and polydentate ligands to which the above restriction applies.

The difference of 0.66 between $pK_{a3}$ and $pK_{a4}$ for DAS agrees, within experimental error, with the factor, $0.60 = \log 4$, predicted on statistical grounds for consecutive $pK_a$ values of identical, non-interacting groups attached to the same molecule. (Compare $pK_{a3} = 8.02 \pm 0.03$, $pK_{a4} = 8.71 \pm 0.03$, difference 0.69 ± 0.06, for cystine, from Greenstein et al., 1939). This agreement implies that the electrostatic interaction between the two ends of the DAS molecule is negligible. Hence the aminoacid groups in DAS should act independently of each other in metal complex formation, with the restriction, as shown by Leybold atomic models, that it is sterically impossible for all four donor atoms of any given DAS molecule to be co-ordinated with the same metal ion. (So long as metal complex formation can occur in which the two aminoacid groups from any DAS molecule are able to complex with different metal ions, the energetically less-favoured binding through one aminoacid grouping and the other amino or carboxyl group of a DAS molecule, although possible, is unlikely to be significant).

It can readily be seen that, because of its preference for a co-ordination number of four in its aminoacid complexes ($\log K_3$ for the copper(II) - glycine system is less than 1 (Bjerrum et al., 1957)), the kinds of
complexes that copper(II) can form with DAS are limited to the four polynuclear series,

\[ \text{HLRL-}(\text{CuLRL})_{n-1}\text{-Cu}^+, \quad (A'), \quad n \geq 1, \]

\[ +\text{(CuLRL)}_{n-1}\text{-Cu}^+, \quad (B'), \quad n \geq 2, \]

\[ \text{HLRL-}(\text{CuLRL})_n\text{-H}^-, \quad (C'), \quad n \geq 1, \]

and

\[ \text{HLRL-}(\text{CuLRL})_{n-1}\text{-Cu}, \quad (D'), \quad n \geq 2, \]

where HLRLH represents neutral (including zwitterionic) DAS. In each member of the linear series, A', B' and C', the end groups are, respectively, a free aminoacid and a copper ion, two copper ions, and two free aminoacids. When at least two DAS molecules and two copper ions are present in a complex, ring formation can also occur, to give the cyclic complexes which comprise series D'. The extent of formation of any complex in any of the above series will be governed by stepwise equilibrium constants.

These considerations indicate, and the experimental results confirm, that the simple Bjerrum-type treatment of the system as one containing only 1:1 and 1:2 complexes is not applicable. Instead, they imply that the extent of complex formation between Cu\(^{2+}\) and one specified end of a DAS molecule should be essentially independent of whether the other end is uncharged, ionised, or complexed to another copper(II) ion. A similar comment applies to further complex formation by a copper ion which is already
complexed to one end of a DAS molecule. Thus, in the copper-DAS system, one or other of the usual stepwise formation constants,

\[ K_1 = \frac{[\text{HLRLCu}^+]}{[\text{Cu}^{2+}][\text{HLRL}^-]}, \]
\[ K_2 = \frac{[\text{Cu(LRLH)}_2]}{[\text{HLRLCu}^+][\text{HLRL}^-]}, \]
refers to each step in the general equilibria,

\[ \text{X-LRL}^- + \text{Cu}^{2+} \rightleftharpoons \text{X-LRL-Cu}^+ \quad (K_1) \]
\[ \text{X-LRL}^- + \text{Cu-LRL-Y} \rightleftharpoons \text{X-LRL-Cu-LRL-Y} \quad (K_2) \]
\[ \text{Y-LRL}^- + \text{Cu-LRL-X} \rightleftharpoons \text{X-LRL-Cu-LRL-Y} \]

independently of the nature of X and Y.

The concentrations of all complexes in series A to D, expressed as functions of \( K_1, K_2, K_{a3}, [\text{H}^+], [\text{Cu}^{2+}] \) and \([\text{HLRL}^-]\), are given by eqns. 5.11, 5.12, 5.13 and 5.14.

\[ [\text{HLRL-(CuLRL)}_{n-1}-\text{Cu}^+] = K_1^n K_2^{n-1} K_{a3}^{n-1} [\text{Cu}^{2+}]^n [\text{HLRL}^-]^n / [\text{H}^+]^{n-1}. \]
\[ \ldots \quad (5.11) \]
\[ [\text{+(CuLRL)}_{n-1}-\text{Cu}^+] = K_1^n K_2^{n-2} K_{a3}^{n-1} [\text{Cu}^{2+}]^n [\text{HLRL}^-]^{n-1}/4[\text{H}^+]^{n-1}. \]
\[ \ldots \quad (5.12) \]
\[ [\text{HLRL-(CuLRL)}_{n-1}-\text{H}] = K_1^n K_2^n K_{a3}^{n-1} [\text{Cu}^{2+}]^n [\text{HLRL}^-]^{n+1} / [\text{H}^+]^{n-1}. \]
\[ \ldots \quad (5.13) \]
\[ [\text{LRL-(CuLRL)}_{n-1}-\text{Cu}] = K_1^n K_2^n K_{a3}^{n} [\text{Cu}^{2+}]^n [\text{HLRL}^-]^n / 2n[\text{H}^+]^n. \]
\[ \ldots \quad (5.14) \]
The numerical factors are statistical in origin.

The principles involved in deriving these equations are demonstrated in the following examples of stepwise equilibria:

\[
\text{HLRL}^- + \text{Cu}^{2+} \rightleftharpoons \text{HLRCLCu}^+ ,
\]

\[
^+\text{CuLRLH} \rightleftharpoons ^+\text{CuLRL}^- + \text{H}^+ ,
\]

\[
^+\text{CuLRL}^- + \text{Cu}^{2+} \rightleftharpoons ^+\text{CuLRLCu}^+ ,
\]

\[
\text{HLRL}^- + ^+\text{CuLRLCu}^+ \rightleftharpoons \text{HLRCLCuLRLCu}^+ .
\]

Thus,

\[
[\text{HLRCLCu}^+] = K_1 [\text{Cu}^{2+}] [\text{HLRL}^-] , \quad (5.15)
\]

\[
[^+\text{CuLRL}^-] = K_{a_3} [\text{HLRCLCu}^+] / 2[\text{H}^+] , \quad (5.16)
\]

\[
= K_1 K_{a_3} [\text{Cu}^{2+}] [\text{HLRL}^-] / 2[\text{H}^+] , \quad (5.17)
\]

the factor of \(\frac{1}{2}\) being due to \(\text{HLRCLCu}^+\) having only one site from which a proton can dissociate whereas in \(\text{HLRLH}\) there are two.

\[
[^+\text{CuLRLCu}^+] = K_1 [\text{Cu}^{2+}] [^+\text{CuLRL}^-] / 2 \quad (5.18)
\]

\[
= K_1^2 K_{a_3} [\text{Cu}^{2+}] [\text{HLRL}^-] / 4[\text{H}^+] . \quad (5.19)
\]

Here the new factor of \(\frac{1}{2}\) arises because there is only one way in which the complex can form from \(\text{Cu}^{2+}\) and \(^+\text{CuLRL}^-\), whereas there are two ways in which it can dissociate to give these species. Similarly,

\[
[\text{HLRCLCuLRLCu}^+] = 4K_2[^+\text{CuLRLCu}^+][\text{HLRL}^-] \quad (5.20)
\]
the factor of 4 entering because the complex can be formed in either of two ways from its components but, once formed, it can only dissociate in one way to give the species from which it is derived, whereas the 1:2 mononuclear complex can be formed from the 1:1 complex in only one way while it can dissociate in either of two ways.

Thus, in spite of the complexity of the system, quantitative interpretation of the potentiometric titration data depends on values assigned to only two adjustable parameters, namely $K_1$ and $K_2$.

In the system where a copper(II) salt is added to a neutral DAS solution and titrated with standard alkali the three independent equations for total concentrations of metal species, total concentrations of ligand species, and total charges become, respectively,

$$
[Cu]_T = [Cu^{2+}] + \sum_{n=1}^{\infty} \left( nK_1^{n}K_2^{n-1}K_3^{n-1}[Cu^{2+}]^{n}[HLRL^-]^n/[H^+]^{n-1} \right)
$$

$$
+ \sum_{n=2}^{\infty} \left( nK_1^{n}K_2^{n-2}K_3^{n-1}[Cu^{2+}]^{n}[HLRL^-]^{n-1}/4[H^+]^{n-1} \right)
$$

$$
+ \sum_{n=1}^{\infty} \left( nK_1^{n}K_2^{n}K_3^{n-1}[Cu^{2+}]^{n}[HLRL^-]^{n+1}/[H^+]^{n-1} \right)
$$

$$
+ \sum_{n=2}^{\infty} \left( K_1^{n}K_2^{n}K_3^{n}[Cu^{2+}]^{n}[HLRL^-]^n/2[H^+]^n \right),
$$

(5.22)
\[ [\text{HLRLH}]_T = [\text{H}_2\text{LRLH}_2^{2+}] + [\text{HLRLH}_2^+] + [\text{HLRLH}] + [\text{HLRL}^-] + [\text{LRL}^{2-}] \]

\[ + \sum_{n=1}^{\infty} \frac{nK_1nK_2n^{-1}K_{a_3}}{n-1} [\text{Cu}^{2+}]^{n} [\text{HLRL}^-]^n / [\text{H}^+]^{n-1} \]

\[ + \sum_{n=2}^{\infty} \frac{(n-1)K_1nK_2n^{-2}K_{a_3}}{n-1} [\text{Cu}^{2+}]^{n} [\text{HLRL}^-]^{n-1} / 4[\text{H}^+]^{n-1} \]

\[ + \sum_{n=1}^{\infty} \frac{(n+1)K_1nK_2nK_{a_3}}{n-1} [\text{Cu}^{2+}]^{n} [\text{HLRL}^-]^{n+1} / [\text{H}^+]^{n-1} \]

\[ + \sum_{n=2}^{\infty} \frac{K_1nK_2nK_{a_3}}{n-1} [\text{Cu}^{2+}]^{n} [\text{HLRL}^-]^{n} / 2[\text{H}^+]^{n}. \quad (5.23) \]

\[ 2[\text{Cu}]_T + [\text{OH}^-] + [\text{HLRL}^-] + 2[\text{LRL}^{2-}] \]

\[ = [\text{H}^+] + [\text{Na}^+] + 2[\text{H}_2\text{LRLH}_2^{2+}] + [\text{HLRLH}_2^+] + 2[\text{Cu}^{2+}] \]

\[ + \sum_{n=1}^{\infty} \frac{K_1nK_2n^{-1}K_{a_3}}{n-1} [\text{Cu}^{2+}]^{n} [\text{HLRL}^-]^n / [\text{H}^+]^{n-1} \]

\[ + 2 \sum_{n=2}^{\infty} \frac{K_1nK_2n^{-2}K_{a_3}}{n-1} [\text{Cu}^{2+}]^{n} [\text{HLRL}^-]^{n-1} / 4[\text{H}^+]^{n-1}. \]

\[ \ldots \quad (5.24) \]

Each of the summations is of a binomial series, the sums of which lead to the equations,

\[ [\text{Cu}]_T = [\text{Cu}^{2+}] + \frac{x}{(1-x)^2} \left[ \frac{[\text{H}^+] + [\text{HLRLH}] + (2-x)K_1[\text{Cu}^{2+}]}{K_2K_{a_3}^4K_2} \right] \]

\[ + \frac{x^2}{2(1-x)}, \quad (5.25) \]
Using an iterative procedure, values of $K_1 = 1.08 \times 10^8 M^{-1}$ and $K_2 = 1.47 \times 10^6 M^{-1}$ were obtained by simultaneous solution of eqns. 5.25, 5.26 and 5.27 at two arbitrarily selected points – one at the beginning and the other at the end of the titration curve for the copper: DAS molar ratio of 1:5 (see Fig. 5.06). Comparison of the stability constants for the mononuclear complexes with those of simple aminoacid-copper(II) complexes shows that the ligand from DAS acts as a simple aminoacid bidentate chelate ($\log K_1 = 8.03$, $\log \beta_2 = 14.20$, $pK_a = 9.23$ for DAS; for glycine (see Table 4.03) $\log K_1 = 8.35$, $\log \beta_2 = 15.41$, $pK_a = 9.76$).
Knowing $K_1$ and $K_2$, it was then possible to test the quantitative correctness of the above discussion by solving eqns. 5.25 and 5.26 at each point in the series of potentiometric titrations of copper(II) and DAS shown in Fig. 5.06. Values for $[Cu^{2+}]$ and $[HLRL^-]$ obtained in this way were then used to evaluate the right-hand side of eqn. 5.27 to provide a comparison with the already-known value of $2[CU]_T$. Because of the inherent mathematical complexity, solution of eqns. 5.25 and 5.26 at each point was carried out on an IBM 1620 Digital Computer using Fortran (the program, which was not developed by the author, is given in the Appendix), the machine being required to find by an incremental method unique values of $[Cu^{2+}]$ and $[HLRL^-]$ at any point, $i$, lying within the limits,

$$[Cu]_T \geq [Cu^{2+}]_{i-1} \geq [Cu^{2+}]_i \geq 0,$$

$$[HLRL^-]_T \geq [HLRL^-]_i \geq [HLRL^-]_{i-1} \geq 0,$$

and satisfying eqns. 5.25 and 5.26. These values are listed in Table 5.04 for the titrations with $[Cu]_T:[HLRLH]_T$ molar ratios of 1:5, 2:5 and 1:1, the corresponding total copper concentrations being 1, 2 and $5 \times 10^{-4}\text{M}$. The average deviation of the computed values of $2[CU]_T$ from the experimental values was less than $\pm 0.9\%$; in no case did it exceed $1.8\%$. This agreement strongly suggests that equilibria in the $Cu^{2+}$ - DAS system are correctly
represented by the statistical distribution of complexes of the types postulated. The mathematical analysis is very sensitive to the values assigned to log $K_1$ and log $K_2$; changes of 0.04 in either (or both) values produce, in the computed $2[Cu]_T$ values, systematic deviations exceeding 1%.

The concentration of each of the complexes represented by the general eqns. 5.11 to 5.14 can be calculated throughout the titrations, and hence their individual significance in the system can be assessed. Results for titrations with metal:ligand molar ratios of 1:1 and 1:5 are shown in Figs. 5.07 and 5.08; results for the 2:5 ratio lie between them. The species, $HLRLCu^+$, $Cu(LRLH)_2$, $^+CuLRLCu^+$ and $(CuLRL)^*$ (where the asterisk denotes a ring-type complex belonging to series D'), account for more than 97% of all copper present in the complexes.

Although polynuclear complex formation was expected in the $Cu^{2+}$ - DAS system, the major importance of the binuclear species, $(CuLRL)^*$, especially over the second half of each titration, was surprising. This complex is, because of its definition, bis-$\mu$-(2,7-diaminosuberato) di-copper(II) and has the structure shown below.
Bis-µ-(2,7-diaminosuberato) Dicopper(II).

The trans-trans structure is shown, but there is no evidence to discriminate between this and the cis-cis configuration; both are sterically possible. In the structure each copper forms part of two five-membered rings which, in turn, are linked in pairs by two tetramethylene bridges. Dimers with structures analogous to this have been demonstrated cryoscopically for the copper(II) complexes of substituted disalicylidenebenzidine, disalicylidene-p-phenylenediamine and disalicylidene-m-phenylenediamine (Pfeiffer and Pfitzner, 1936).

Overall stability constants of the various species can be expressed as functions of $K_1$ and $K_2$ by substituting the expressions for their concentrations into the usual stability constant equations. Values obtained in this way for the more important species are given in Table 5.05.
A crystalline copper(II)-DAS complex was prepared by mixing equimolar amounts of 2,7-diaminosuberic acid and copper(II) sulphate pentahydrate in 1M-hydrochloric acid, heating the solution to near boiling, and adding a dilute ammonia solution dropwise until the solution was neutral. The blue, finely-crystalline precipitate was extremely insoluble; no solvent was found that would dissolve it in the cold or on boiling. Therefore it is probable that in the titrations (especially over the later stages of the titrations), in spite of the low concentrations used, the solutions were supersaturated with respect to the insoluble complex; precipitation slowly occurred when the final solutions were allowed to stand. Analysis of the blue crystals indicated a 1:1 copper:DAS ratio in the complex. (Found: Cu, 22.43; C, 34.02; H, 5.55; N, 9.90. Cu(C₈H₁₄N₂O₄). H₂O requires Cu, 22.39; C, 33.86; H, 5.68; N, 9.87%). The complex could well be bis-µ-(2,7-diaminosuberato) dicopper(II), which is the main species present in solution under the experimental conditions and which would be expected to be only sparingly soluble because of its non-ionic character. Chemical analysis is consistent with this structure, but its molecular weight could not be determined because of its insolubility. The magnetic moment of 1.91, determined by the Gouy method, is typical of simple aminoacid - copper(II) complexes (cf. µ = 1.93 for bis(glycinato)copper(II) mono-
hydrate, from Ray and Sen, 1948) and indicates the absence of Cu-Cu $\delta$-bonding in this compound.

5.8 Copper(II) and Cystine

The naturally-occurring $\alpha$-aminoacid, L-cystine, resembles DAS in being unable for steric reasons to coordinate both of the aminoacid portions in any molecule with the same metal ion. As discussed earlier for DAS this leads to polynuclear complex formation with $\text{Cu}^{2+}$; the kinds of complexes that can be formed are again limited to the series, A', B', C', D'.

The method of calculation described for the DAS-copper(II) system - with the added assumption that, under the experimental conditions, the concentrations of the species, $\text{HLRLH}_2^+$ and $\text{H}_2\text{LRLH}_2^+$, are insignificant - enabled values of $K_1$ and $K_2$ to be obtained for the formation constants of the mononuclear species, $\text{HLRLCu}^+$ and $\text{Cu(LRLH)}_2^+$, respectively. Two arbitrarily selected points in the titration of a solution containing copper and cystine with a molar ratio of 1:3 gave $K_1 = 1.0 \times 10^7 \text{M}^{-1}$ and $K_2 = 5.3 \times 10^6 \text{M}^{-1}$. These constants were inserted into the program (see Appendix) for an IBM 1620 Digital Computer so that concentrations of free metal ion and free complexing species could be computed at each point in a number of titrations (Fig. 5.09) in which the metal:ligand molar ratio, and the total copper and ligand concentrations
were varied. The values for $[\text{Cu}^{2+}]$ and $[\text{HLRL}^-]$ are listed in Table 5.06. The average deviation of the computed values of $2[\text{Cu}]_T$ from the experimental values was less than $\pm 1\%$ for points where copper(II) was up to 90% complexed. This range represents an uncertainty of a little less than $\pm 0.05$ in $\log K_1$ and $\log K_2$. The largest deviations, 2.1%, 3.5%, and 4.5%, occurred at the end of the 1:1 titration. This agreement strongly suggests that equilibria in the copper(II)-cystine system are correctly represented by a statistical distribution of complexes of the types postulated.

From the computed values of $[\text{Cu}^{2+}]$ and $[\text{HLRL}^-]$, knowing $K_1$, $K_2$ and $K_a^3$, the concentrations of all of the complexes represented by the general formulae, $A^- - D^+$, can be calculated throughout the titrations using eqns. 5.11 to 5.14. Hence their individual significance in the system can be assessed. The concentrations of the principal species, expressed as percentage of total copper, are plotted against pH in Figs. 5.10 and 5.11 for the 1:1 and 1:3 cases; results for the 1:2 case follow similar trends. The species, $\text{Cu}^{2+}$, $\text{HLRLCu}^+$, $\text{Cu}(\text{LRLH})_2$ and $(\text{CuLRL})^*$, account for more than 97% of all the copper present. The mononuclear complex, $\text{HLRLCu}^+$, and, surprisingly, the straight-chain dimer, $^+\text{CuLRLCu}^+$, are less important than they were in the DAS-copper(II) system. However, as in the DAS case, the binuclear complex, $(\text{CuLRL})^*$, is the
major species, especially over the second half of each titration. By definition, this complex is di-μ-cystinato dicopper(II).

Overall stability constants of the various species can be expressed as functions of $K_1$ and $K_2$ by substituting the expressions for their concentrations (eqns. 5.11 to 5.14) into the usual stability constant equations; the constants for the more important species are given in Table 5.07.

Comparison of the stability constants for the mononuclear complexes of copper(II) and cystine with those of AEDA strongly suggests that these two closely related ligands form their complexes through the same groups. (Note: The agreement in the stability constants for the copper(II) complexes with AEDA and cystine, which have very similar structures (and $pK_a$ values) and hence would be expected to form mononuclear complexes of similar stability, is indirect evidence in support of the validity of the method of calculation for the copper(II)-cystine system since the constants for the AEDA complexes were determined by conventional means.) Thus, in its mononuclear complexes, cystine is co-ordinated with copper through one of the aminoacid groups and also through the disulphide group. The ratio, $K_1/K_2 = 2$, for the copper complexes of cystine and AEDA, and the ratio $K_1/K_2 = 6$ for
the methionine-copper(II) system are much lower than that for the DAS ($K_1/K_2 \approx 70$) and other aminoacid-copper(II) complexes (Bjerrum et al., 1957). These differences are probably due to the bonding of the sulphur atoms. The co-ordination to sulphur would be greater in the 1:2 than in the 1:1 complexes, so that $K_2$ would be increased relative to $K_1$. This is a consequence of the reduction in net positive charge on the copper ion with progressive co-ordination of electron-donating amino and carboxyl groups, thereby increasing the tendency of $d$-electrons on copper(II) to be donated into vacant $d$-orbitals of sulphur atoms ("back-bonding"). The disulphide group would be expected to contribute to the co-ordination in the polynuclear, as well as the mononuclear, complexes and hence the important polynuclear species, di-μ-cystinato dicopper(II), would have the structure as shown below. In this structure each copper forms part of three five-membered rings while at the same time both coppers are linked in a multi-membered ring. Leybold atomic models confirm that this structure is possible, but provide no information about the stereochemistry of the bond between the copper and the -S-S- groups. Appreciable vertical movement can occur for the -S-S- group when it is located above a copper atom, and sufficient lateral displacement is possible so that bonding could be through either sulphur atom or through a $\pi$-bond involving one of their shared orbitals.
A blue, finely-crystalline complex was prepared by the method of Ray and Bhaduri (1950). It was extremely insoluble in all solvents that were tried. Thus, it is probable that in the titrations (especially over the later stages of the titrations), in spite of the low concentrations used, the solutions were supersaturated with respect to the insoluble complex; precipitation slowly occurred when the final solutions were allowed to stand. The complex which was isolated from solution contained copper and cystine in an equimolar ratio. (Found: Cu, 19.75; C, 22.76; H, 3.69; N, 8.85; S, 20.19. Calc. for Cu(C$_6$H$_{10}$N$_2$S$_2$O$_4$)$_3$H$_2$O: Cu, 19.87; C, 22.53; H, 3.78; N, 8.76; S, 20.05%). It is possible that this complex is di-µ-cystinato dicopper(II), which is the form in which most of the copper is present in solution under the experimental conditions; this species would be expected to be only sparingly soluble because of its non-ionic...
character. Chemical analysis is consistent with this structure, but its molecular weight could not be determined because of its insolubility. The suggestion of Kahler and his co-workers (1952) that the complex is a straight-chain polymer is another possibility because, although such a complex is not a major species in aqueous solution under the conditions of the experiment, the solubility product of the high molecular weight compound could favour its precipitation. The magnetic moment of 1.91, determined by the Gouy method, is identical with that for the corresponding DAS complex. Thus, there is no Cu-Cu $\sigma$-bonding in this compound.

Stricks and Kolthoff (1951) have postulated that cysteine forms polynuclear complexes of the type, $\text{Cu(RSCu)}_x^+$, with copper(I). However, there is no evidence concerning the copper(I)-cystine system, but it is expected that polynuclear complexes are also of importance in this system. The complicated nature of the copper(II)-copper(I)-cystine system has not allowed the oxidation-reduction potential to be determined.
### Table 5.01

Acid Dissociation Constants at 20° and I=0.15 (Sodium Perchlorate)

<table>
<thead>
<tr>
<th>Compound</th>
<th>pK(_{a1})</th>
<th>pK(_{a2})</th>
<th>pK(_{a3})</th>
<th>pK(_{a4})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystine</td>
<td>&lt; 1(^a)</td>
<td>2.1(^a)</td>
<td>8.02(^a)</td>
<td>8.71(^a)</td>
</tr>
<tr>
<td>DAS</td>
<td>1.84</td>
<td>2.62</td>
<td>9.23</td>
<td>9.89</td>
</tr>
<tr>
<td>BCED</td>
<td>3.88</td>
<td>4.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAED</td>
<td>8.82</td>
<td>9.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEDA</td>
<td>8.28</td>
<td>9.30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) At 35° and I = 0.1, from Greenstein et al., 1939.

### Table 5.02

Copper(II) and Bis(2-carboxyethyl) Disulphide (Calculated from titration curves given in Fig. 5.03, taking \(K_1 = 3.5 \times 10^{-2} M^-1\).)

(i) \([Cu]_T = 1.0 \times 10^{-3} M, [HLRLH]_T = 5.0 \times 10^{-3} M\).

<table>
<thead>
<tr>
<th>[Cu(^{2+})] (x10^4, M)</th>
<th>[HLRL(^-)] (x10^4, M)</th>
<th>(K_1) (x10^{-3}, M^-1)</th>
<th>[Cu(^{2+})] (x10^4, M)</th>
<th>[HLRL(^-)] (x10^4, M)</th>
<th>(K_1) (x10^{-3}, M^-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.942</td>
<td>9.898</td>
<td>1.14</td>
<td>5.168</td>
<td>16.166</td>
<td>1.21</td>
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<tr>
<td>6.769</td>
<td>10.818</td>
<td>(0.93)</td>
<td>4.974</td>
<td>16.819</td>
<td>1.21</td>
</tr>
<tr>
<td>6.547</td>
<td>11.670</td>
<td>0.93</td>
<td>4.913</td>
<td>17.583</td>
<td>1.03</td>
</tr>
<tr>
<td>6.270</td>
<td>12.434</td>
<td>1.08</td>
<td>4.563</td>
<td>18.633</td>
<td>1.06</td>
</tr>
<tr>
<td>6.107</td>
<td>13.341</td>
<td>0.95</td>
<td>4.473</td>
<td>19.160</td>
<td>0.98</td>
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</table>
### Table 5.02 (cont.)

<table>
<thead>
<tr>
<th>[Cu$^{2+}$] x10$^4$, M</th>
<th>[HLRL$^-$] x10$^4$, M</th>
<th>$K'_1$ x10$^{-3}$, M$^{-1}$</th>
<th>[Cu$^{2+}$] x10$^4$, M</th>
<th>[HLRL$^-$] x10$^{-3}$, M$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.886</td>
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<td>0.97</td>
<td>4.301</td>
<td>19.993</td>
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<tr>
<td>5.542</td>
<td>14.691</td>
<td>1.27</td>
<td>3.861</td>
<td>20.453</td>
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<tr>
<td>5.387</td>
<td>15.497</td>
<td>1.17</td>
<td>3.644</td>
<td>20.678</td>
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</tbody>
</table>

(ii) $[\text{Cu}]_T = 5.0 \times 10^{-4}$ M, $[\text{HLRLH}]_T = 2.506 \times 10^{-3}$ M.

### Table 5.03

#### Copper(II) and Bis(2-aminoethyl) Disulphide

$[\text{Cu}]_T = 5.0 \times 10^{-4}$ M, $[\text{LRL}]_T = 2.505 \times 10^{-3}$ M, $K_1 = 6.15 \times 10^3$ M$^{-1}$

<table>
<thead>
<tr>
<th>[NaOH] x10$^4$, M</th>
<th>pH</th>
<th>[Cu$^{2+}$] x10$^4$, M</th>
<th>[LRLH$^+$] x10$^5$, M</th>
<th>$K'_1$ x10$^{-6}$, M$^{-1}$</th>
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</thead>
<tbody>
<tr>
<td>1.011</td>
<td>6.45</td>
<td>4.410</td>
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<td>(5.02)</td>
</tr>
<tr>
<td>1.213</td>
<td>6.50</td>
<td>4.302</td>
<td>1.010</td>
<td>5.13</td>
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<tr>
<td>1.415</td>
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<td>1.128</td>
<td>5.00</td>
</tr>
<tr>
<td>1.617</td>
<td>6.59</td>
<td>4.089</td>
<td>1.230</td>
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<td>1.342</td>
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</tr>
<tr>
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<tr>
<td>3.630</td>
<td>6.87</td>
<td>3.068</td>
<td>2.205</td>
<td>(5.02)</td>
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Table 5.04

Computed Concentrations for Titrations of Copper Perchlorate and DAS with 0.1M Sodium Hydroxide

(i) $1 \times 10^{-4}\text{M}$ copper perchlorate and $4.984 \times 10^{-4}\text{M}$ DAS

<table>
<thead>
<tr>
<th>pH</th>
<th>$[\text{Cu}^{2+}] \times 10^5\text{M}$</th>
<th>$[\text{HLRL}^-] \times 10^8\text{M}$</th>
<th>pH</th>
<th>$[\text{Cu}^{2+}] \times 10^5\text{M}$</th>
<th>$[\text{HLRL}^-] \times 10^8\text{M}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.48</td>
<td>5.568</td>
<td>0.693</td>
<td>4.96</td>
<td>2.763</td>
<td>1.957</td>
</tr>
<tr>
<td>4.52</td>
<td>5.358</td>
<td>0.749</td>
<td>5.04</td>
<td>2.340</td>
<td>2.321</td>
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<tr>
<td>4.54</td>
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<td>1.951</td>
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<td>4.57</td>
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<td>0.845</td>
<td>5.18</td>
<td>1.629</td>
<td>3.194</td>
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<td>4.60</td>
<td>4.854</td>
<td>0.903</td>
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<td>3.726</td>
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<td>4.64</td>
<td>4.580</td>
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<td>4.387</td>
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<td>3.190</td>
<td>1.664</td>
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</table>

(ii) $2 \times 10^{-4}\text{M}$ copper perchlorate and $5.029 \times 10^{-4}\text{M}$ DAS

<table>
<thead>
<tr>
<th>pH</th>
<th>$[\text{Cu}^{2+}] \times 10^5\text{M}$</th>
<th>$[\text{HLRL}^-] \times 10^8\text{M}$</th>
<th>pH</th>
<th>$[\text{Cu}^{2+}] \times 10^5\text{M}$</th>
<th>$[\text{HLRL}^-] \times 10^8\text{M}$</th>
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<tr>
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Table 5.04 (cont.)

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<th>$[\text{HLRL}^-]$</th>
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<th>$[\text{Cu}^{2+}]$</th>
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<tr>
<td></td>
<td>$\times 10^5, \text{M}$</td>
<td>$\times 10^8, \text{M}$</td>
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<td>$\times 10^5, \text{M}$</td>
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<td>1.667</td>
<td>5.72</td>
<td>0.486</td>
<td>8.143</td>
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</table>

(iii) $5 \times 10^{-4} \text{M}$ copper perchlorate and $5.034 \times 10^{-4} \text{M}$ DAS

<table>
<thead>
<tr>
<th>pH</th>
<th>$[\text{Cu}^{2+}]$</th>
<th>$[\text{HLRL}^-]$</th>
<th>pH</th>
<th>$[\text{Cu}^{2+}]$</th>
<th>$[\text{HLRL}^-]$</th>
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<td>0.780</td>
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<td>0.071</td>
<td>1.936</td>
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</table>
**Table 5.05**

Stability Constants for Copper(II)-DAS Complexes at 20°
and I = 0.15

<table>
<thead>
<tr>
<th>Species</th>
<th>Products</th>
<th>Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLRLCu⁺</td>
<td>Cu²⁺ + HLRL⁻</td>
<td>log β₁:₁ = 8.03</td>
</tr>
<tr>
<td>HLRLCuLRLCu⁺</td>
<td>2Cu²⁺ + LRL²⁻ + HLRL⁻</td>
<td>log β₂:₂ = 22.83</td>
</tr>
<tr>
<td>HLRLCuLRLH</td>
<td>Cu²⁺ + 2HLRL⁻</td>
<td>log β₁:₂ = 14.20</td>
</tr>
<tr>
<td>HLRLCuLRLCuLRLH</td>
<td>2Cu²⁺ + LRL²⁻ + 2HLRL⁻</td>
<td>log β₂:₃ = 29.00</td>
</tr>
<tr>
<td>CuLRLCu⁺</td>
<td>2Cu²⁺ + LRL²⁻</td>
<td>log β₂:₁ = 16.06</td>
</tr>
<tr>
<td>(CuLRL)₂⁺</td>
<td>2Cu²⁺ + 2LRL²⁻</td>
<td>log β₂:₂ = 29.00</td>
</tr>
</tbody>
</table>

**Table 5.06**

Computed Concentrations for Titrations of Copper Perchlorate
and Cystine with 0.1M-Sodium Hydroxide

(i) 1x 10⁻⁴M copper perchlorate and 2.996 x 10⁻⁴M cystine.

<table>
<thead>
<tr>
<th>pH</th>
<th>[Cu²⁺] x10⁵ M</th>
<th>[HLRL⁻] x10⁸ M</th>
<th>pH</th>
<th>[Cu²⁺] x10⁵ M</th>
<th>[HLRL⁻] x10⁸ M</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.14</td>
<td>4.970</td>
<td>2.775</td>
<td>4.42</td>
<td>2.150</td>
<td>4.669</td>
</tr>
<tr>
<td>4.19</td>
<td>4.455</td>
<td>3.012</td>
<td>4.50</td>
<td>1.637</td>
<td>5.415</td>
</tr>
<tr>
<td>4.24</td>
<td>3.893</td>
<td>3.299</td>
<td>4.58</td>
<td>1.177</td>
<td>6.440</td>
</tr>
<tr>
<td>4.29</td>
<td>3.312</td>
<td>3.650</td>
<td>4.69</td>
<td>0.751</td>
<td>8.123</td>
</tr>
<tr>
<td>4.36</td>
<td>2.693</td>
<td>4.122</td>
<td>4.85</td>
<td>0.390</td>
<td>11.389</td>
</tr>
</tbody>
</table>
Table 5.06 (cont.)

(ii) $2 \times 10^{-4}$M copper perchlorate and $4.000 \times 10^{-4}$M cystine.

<table>
<thead>
<tr>
<th>pH</th>
<th>$[Cu^{2+}]$ x10$^5$M</th>
<th>$[HLRL^-]$ x10$^8$M</th>
<th>pH</th>
<th>$[Cu^{2+}]$ x10$^5$M</th>
<th>$[HLRL^-]$ x10$^8$M</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.94</td>
<td>11.970</td>
<td>2.218</td>
<td>4.26</td>
<td>5.427</td>
<td>3.659</td>
</tr>
<tr>
<td>3.97</td>
<td>11.330</td>
<td>2.327</td>
<td>4.30</td>
<td>4.780</td>
<td>3.907</td>
</tr>
<tr>
<td>4.00</td>
<td>10.670</td>
<td>2.441</td>
<td>4.34</td>
<td>4.117</td>
<td>4.214</td>
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<td>4.02</td>
<td>10.120</td>
<td>2.538</td>
<td>4.39</td>
<td>3.524</td>
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</tr>
<tr>
<td>4.05</td>
<td>9.466</td>
<td>2.658</td>
<td>4.44</td>
<td>2.894</td>
<td>5.027</td>
</tr>
<tr>
<td>4.08</td>
<td>8.822</td>
<td>2.783</td>
<td>4.50</td>
<td>2.307</td>
<td>5.619</td>
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<tr>
<td>4.11</td>
<td>8.186</td>
<td>2.914</td>
<td>4.57</td>
<td>1.756</td>
<td>6.434</td>
</tr>
<tr>
<td>4.15</td>
<td>7.469</td>
<td>3.076</td>
<td>4.66</td>
<td>1.244</td>
<td>7.633</td>
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<tr>
<td>4.18</td>
<td>6.782</td>
<td>3.460</td>
<td>4.76</td>
<td>0.800</td>
<td>9.510</td>
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<tr>
<td>4.22</td>
<td>6.041</td>
<td>3.659</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

(iii) $3 \times 10^{-4}$M copper perchlorate and $2.990 \times 10^{-4}$M cystine.

<table>
<thead>
<tr>
<th>pH</th>
<th>$[Cu^{2+}]$ x10$^4$M</th>
<th>$[HLRL^-]$ x10$^8$M</th>
<th>pH</th>
<th>$[Cu^{2+}]$ x10$^4$M</th>
<th>$[HLRL^-]$ x10$^8$M</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.90</td>
<td>2.159</td>
<td>1.364</td>
<td>4.35</td>
<td>1.034</td>
<td>1.845</td>
</tr>
<tr>
<td>3.95</td>
<td>2.033</td>
<td>1.440</td>
<td>4.42</td>
<td>0.900</td>
<td>1.883</td>
</tr>
<tr>
<td>4.00</td>
<td>1.889</td>
<td>1.517</td>
<td>4.51</td>
<td>0.757</td>
<td>1.922</td>
</tr>
<tr>
<td>4.06</td>
<td>1.743</td>
<td>1.586</td>
<td>4.60</td>
<td>0.621</td>
<td>1.955</td>
</tr>
<tr>
<td>4.11</td>
<td>1.598</td>
<td>1.649</td>
<td>4.70</td>
<td>0.502</td>
<td>1.982</td>
</tr>
<tr>
<td>4.17</td>
<td>1.431</td>
<td>1.713</td>
<td>4.84</td>
<td>0.375</td>
<td>2.006</td>
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<tr>
<td>4.22</td>
<td>1.321</td>
<td>1.752</td>
<td>5.03</td>
<td>0.248</td>
<td>2.022</td>
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<tr>
<td>4.28</td>
<td>1.183</td>
<td>1.799</td>
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</table>
Table 5.07
Stability Constants for Copper(II)-Cystine Complexes at 20° and I = 0.15

<table>
<thead>
<tr>
<th>Species</th>
<th>Products</th>
<th>Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLRLCu⁺</td>
<td>Cu²⁺ + HLRL⁻</td>
<td>log β₁:₁ = 7.00</td>
</tr>
<tr>
<td>HLRLCuLRLCu⁺</td>
<td>2Cu²⁺ + LRL²⁻ + HLRL⁻</td>
<td>log β₂:₂ = 21.33</td>
</tr>
<tr>
<td>HLRLCuLRLH</td>
<td>Cu²⁺ + 2HLRL⁻</td>
<td>log β₁:₂ = 13.72</td>
</tr>
<tr>
<td>HLRLCuLRLCuLRLH</td>
<td>2Cu²⁺ + LRL²⁻ + 2HLRL⁻</td>
<td>log β₂:₃ = 28.05</td>
</tr>
<tr>
<td>(CuLRL)₂⁺</td>
<td>2Cu²⁺ + 2LRL²⁻</td>
<td>log β₂:₂ = 28.05</td>
</tr>
</tbody>
</table>

Table 5.08
Stability Constants for Copper(II) Complexes at 20° and I=0.15

<table>
<thead>
<tr>
<th>Ligand</th>
<th>pKₐ</th>
<th>log K₁</th>
<th>log β₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Cystine</td>
<td>8.03</td>
<td>7.00</td>
<td>13.72</td>
</tr>
<tr>
<td>AEDA</td>
<td>8.28</td>
<td>7.08</td>
<td>13.80</td>
</tr>
<tr>
<td>DAS</td>
<td>9.23</td>
<td>8.03</td>
<td>14.20</td>
</tr>
<tr>
<td>L-Methionine</td>
<td>9.20</td>
<td>8.00</td>
<td>15.23</td>
</tr>
</tbody>
</table>
Fig. 5.01. Titration Curve for the Determination of $pK_{a3}$ and $pK_{a4}$ for DAS. An aqueous solution of DAS ($1.002 \times 10^{-3}$M) and sodium perchlorate (0.15M) was titrated with carbonate-free sodium hydroxide (0.1012M). For convenience of presentation, points marked with * have been omitted from Fig. 5.02.
Fig. 5.02. Determination of $pK_a_3$ and $pK_a_4$ for DAS using eqn. 5.02 and data from Fig. 5.01. From the graph, $pK_a_3 = 9.23$ and $pK_a_4 = 9.89$. 
Fig. 5.03. Titration Curves for the Copper(II)-BCED System.

(i) $1 \times 10^{-3}$ M copper perchlorate and $5.0 \times 10^{-3}$ M BCED - O;
(ii) $5 \times 10^{-4}$ M copper perchlorate and $2.506 \times 10^{-3}$ M BCED - O.

Arrows indicate points referred to in Table 5.02(ii).

Asterisk denotes points that have not been used for the calculations due to insignificant complex formation.
Fig. 5.04. Titration Curves for the Copper(II)-AEDA System.

- O - $2 \times 10^{-4}\text{M}$ copper perchlorate and $4.971 \times 10^{-4}\text{M}$ AEDA hydrochloride;
- Θ - $5 \times 10^{-4}\text{M}$ copper perchlorate and $4.995 \times 10^{-4}\text{M}$ AEDA hydrochloride.
Fig. 5.05. Evaluation of $K_1$ and $\beta_2$ for Copper(II)-AEDA Complexes. From graph (using eqn. 2.14 and data from Fig. 5.04), $\log K_1 = 7.08$ and $\log \beta_2 = 13.80$. 

\[
\frac{\overline{n}}{(1-n) [L]} x 10^{-7}, \text{M}^{-1}
\]

\[
\frac{(2-n)[L]}{(1-n) x 10^7, \text{M}}
\]
Fig. 5.06. Titration Curves for the Copper(II) - DAS System.

(i) ○ - $1 \times 10^{-4}$M copper perchlorate and $4.984 \times 10^{-4}$M DAS;
(ii) □ - $2 \times 10^{-4}$M copper perchlorate and $5.029 \times 10^{-4}$M DAS;
(iii) ◯ - $5 \times 10^{-4}$M copper perchlorate and $5.034 \times 10^{-4}$M DAS.
Fig. 5.07. Distribution of copper species (as % total copper) for the copper(II)-DAS system in which $[Cu]_T = 5 \times 10^{-4} M$, $[DAS] = 5.034 \times 10^{-4} M$. $a - Cu^2+; b - HLRLCu^+; c - (CuLRL)_2; d - +CuLRLCu^+$. 
Fig. 5.08. Distribution of copper species (as % total copper) for the copper(II)-DAS system in which $[\text{Cu}]_T = 1 \times 10^{-4} \text{M}$, $[\text{DAS}] = 4.984 \times 10^{-4} \text{M}$. $a$ - $\text{Cu}^{2+}$; $b$ - $\text{HLRLCu}^+$; $c$ - $\text{(CuLRL)}_2$; $d$ - $^+\text{CuLRLCu}^+$; $e$ - $\text{Cu(LRLH)}_2$. 
Fig. 5.09. Titration Curves for Copper(II)-Cystine System.

(i) ○ - 1 x 10^{-4} M copper perchlorate and 2.996 x 10^{-4} M cystine. (ii) ○ - 2 x 10^{-4} M copper perchlorate and 4.000 x 10^{-4} M cystine. (iii) ○ - 3 x 10^{-4} M copper perchlorate and 2.990 x 10^{-4} M cystine.
Fig. 5.10. Distribution of copper species (as % total copper) for the copper(II)-cystine system, in which $[Cu]_T = 3 \times 10^{-4} \text{M}$ and $[\text{cystine}] = 2.990 \times 10^{-4} \text{M}$. a - Cu$^{2+}$. b - (CuLRL)$^*$. c - HLRLCu$^+$. d - Cu(LRLH)$_2$. 
Fig. 5.11. Distribution of copper species (as % total copper) for the copper(II)-cystine system, in which $[Cu]_T = 1 \times 10^{-4}\text{M}$ and $[\text{cystine}] = 2.996 \times 10^{-4}\text{M}$. 

- a - $\text{Cu}^{2+}$
- b - $(\text{CuLRL})^*$
- c - $\text{HLRLCu}^*$
- d - $\text{Cu(LRLH)}_2$

Note: $\Delta G^\circ$ is the change in standard free energy of the overall equilibrium.
6.1 Free Energy - Oxidation State Diagrams

Frost (1951) and Tarsey (1954) have designed Free Energy - Oxidation State Diagrams that are useful in discussing valence states of metals that can form ions of more than one oxidation state. In these diagrams, the change of standard free energy, $\Delta G^0$, in forming a certain species from the uncharged (zerovalent) metal is plotted against the oxidation state of the metal ion in that species. The standard oxidation-reduction potential of a particular couple is numerically equal to the slope of the line which joins the individual species that form the couple. Fig. 6.01 shows such a diagram for copper(0)-copper(I)-copper(II) systems.

To obtain this diagram, the equilibrium for the formation of the complex, $\text{CuL}_x^{m+}$,

$$\text{Cu}^0 + x\text{L} \rightleftharpoons \text{CuL}_x^{m+} + \text{me} \quad \left( \Delta G^0 \right)_{\text{CuL}_x^{m+}}$$

can be divided into two separate equilibria,

$$\text{Cu}^0 \rightleftharpoons \text{Cu}^{m+} + \text{me} \quad \left( \Delta G^0 \right)_{\text{Cu}^{m+}}$$

and

$$\text{Cu}^{m+} + x\text{L} \rightleftharpoons \text{CuL}_x^{m+} \quad \left( \Delta G^0^* \right)_{\text{CuL}_x^{m+}}$$

The change in standard free energy of the overall equilibria,
\( \Delta G^0(\text{CuL}_x^{m+}) \), is equal to the sum of the changes in standard free energy for the two individual steps.

\[
\Delta G^0_{\text{CuL}_x^{m+}} = \Delta G^0_{\text{Cu}^{m+}} + \Delta G^0_{\text{CuL}_x^{m+}}. 
\]

These energy changes, \( \Delta G^0(\text{Cu}^{m+}) \) and \( \Delta G^0(\text{CuL}_x^{m+}) \), can be calculated from the standard oxidation-reduction potential, \( E^0(\text{Cu}^{m+}/\text{Cu}^0) \), and the stability constant, \( t\beta_x^M \) (or \( \beta_x^M \) for an uncharged ligand), according to eqns. 6.02 and 6.03, respectively.

\[
\Delta G^0_{\text{Cu}^{m+}} = mFE^0_{\text{Cu}^{m+}/\text{Cu}} , \tag{6.02}
\]

\[
\Delta G^0_{\text{CuL}_x^{m+}} = -RT \ln t\beta_x^M . \tag{6.03}
\]

The diagram (Fig. 6.01) makes it easy to see the conditions under which the disproportionation reaction,

\[
2\text{Cu}^+ \rightleftharpoons \text{Cu}^{2+} + \text{Cu} ,
\]

becomes important. Thus, if \( E^0(\text{CuL}_x^{+/\text{Cu}}) \) is more positive than \( E^0(\text{CuL}_x^{2+/\text{Cu}}) \), the complex of copper(I) will disproportionate to a greater or less extent into the divalent species and copper. If, on the other hand, \( E^0(\text{CuL}_x^{+/\text{Cu}}) \) is less positive than \( E^0(\text{CuL}_x^{2+/\text{Cu}}) \), disproportionation of copper(I) is negligible. This corresponds to a point, A, which represents the copper(I) complex on the diagram, Fig. 6.01, lying below the line joining the points representing
the free copper and the divalent species, $B$.

The univalent copper state is said to be stabilised relative to the divalent if the stability constant of the copper(I) complex is greater than that of the corresponding copper(II) complex. This stabilisation of copper(I) is represented quantitatively by the oxidation-reduction potential, $E^0(\text{CuL}_x^{2+}, \text{CuL}_x^+)$, which is numerically equal to the slope of the line which joins the two species (in Fig. 6.01) that form the couple. If this potential is more positive than the potential for the simple hydrated species, $E^0(\text{Cu}^{2+}, \text{Cu}^+)$, the univalent state is said to be stabilised. It does not necessarily follow that under these conditions $\text{CuL}_x^+$ will not disproportionate. Disproportionation will be negligible only if $E^0(\text{CuL}_x^{2+}/\text{Cu})$ is equal to, or less positive than, $E^0(\text{Cu}^{2+}, \text{Cu}^+)$. Conversely, the conditions that $E^0(\text{CuL}_x^{2+}/\text{Cu})$ is equal to, or less positive than, $E^0(\text{Cu}^{2+}, \text{Cu}^+)$, and $\text{CuL}_x^+$ does not disproportionate do not necessarily imply that the copper(I) state has been stabilised. For example, in Fig. 6.01, the univalent species, $A$, does not readily disproportionate although it has not been stabilised relative to $B$.

Appreciable formation of the complex, $\text{CuL}_x^+$, by reduction of $\text{CuL}_x^{2+}$ requires that $E^0(\text{CuL}_x^+/\text{Cu})$ be less positive than $E^0(\text{CuL}_x^{2+}/\text{Cu})$. If this condition does not hold, reduction of $\text{CuL}_x^{2+}$ will lead ultimately to complete conversion to the free metal. Similarly, electrolytic
oxidation of solid copper in the presence of ligand will favour the formation of $\text{CuL}_x^+$ only if $E^0(\text{CuL}_x^+/\text{Cu})$ is less positive than $E^0(\text{CuL}_x^{2+/\text{Cu}})$.

6.2 Factors Governing Oxidation-Reduction Potentials

The factors contributing to the oxidation-reduction potential of a particular couple can be ascertained from the following equilibrium scheme:

$$
\begin{align*}
\Delta G^0_{2,1}(g) \\
\text{Cu}^{2+}(g) + e(g) &\rightleftharpoons \text{Cu}^+(g) \\
+xL(g) &\rightleftharpoons +xL(g) \\
\Delta G^0_2(g) &\rightleftharpoons \Delta G^0_1(g) \\
\text{CuL}_x^{2+}(g) &\rightleftharpoons \text{CuL}_x^+(g) \\
\Delta G^0_{2(aq)} &\rightleftharpoons \Delta G^0_1(aq) \\
\text{CuL}_x^{2+}(aq) + e(g) &\rightleftharpoons \text{CuL}_x^+(aq),
\end{align*}
$$

where $\Delta G^0$ is the change in standard free energy for the reduction of the copper(II) complex to the copper(I) complex in solution, $\Delta G^0_{2(aq)}$ and $\Delta G^0_1(aq)$ are the standard free energies of hydration of $\text{CuL}_x^{2+}$ and $\text{CuL}_x^+$, $\Delta G^0_2(g)$ and $\Delta G^0_1(g)$ (the ligational standard free energies) are the changes of standard free energy for the formation of the complexes, and $\Delta G^0_{2,1}(g)$ is the change in standard free energy associated with the reduction of $\text{Cu}^{2+}$ to $\text{Cu}^+$ in the gaseous phase and is constant for all couples. The standard
The free energy of hydration of the complexes is given by the equation,

$$\Delta G^0_{(aq)} = n^2 e^2 (1 - 1/D)/2r$$  \hspace{1cm} (6.04)

where \(r\), in angstroms, is the radius of the cavity the ion occupies in the solution, \(D\) is the dielectric constant of water, and \(n e\) is the ionic charge (Born, 1920). Thus, for a series of complexes, as the radius of the ion increases the significance of \(\Delta G^0_{(aq)}\) decreases asymptotically.

The overall contribution of solvation to \(\Delta G^0\) is given by

$$\Delta G_1(aq) - \Delta G_2(aq) = e^2 (2r_1 - \frac{1}{2} r_2) (1 - 1/D)/r_1 r_2.$$  \hspace{1cm} (6.05)

Since \((2r_1 - \frac{1}{2} r_2)\) is generally positive, as the dielectric constant of the solvent is decreased the difference in the free energies of solvation becomes less positive, and hence the contribution from solvation increasingly favours the univalent state. Thus, Nelson and his co-workers (1961) have observed a two-step polarographic reduction of Cu\(^{2+}\) in non-complexing, non-aqueous solvents whereas in aqueous solution the Cu\(^{2+}\) ion is reduced by only one step to Cu\(^0\).

From the cycle, \(\Delta G^0\) can be resolved into the other free energy terms by eqn. 6.06.

$$\Delta G^0 = \Delta G^0_{2,1(g)} + (\Delta G^0_{1(g)} - \Delta G^0_{2(g)}) + (\Delta G^0_{1(aq)} - \Delta G^0_{2(aq)}).$$  \hspace{1cm} (6.06)
\( \Delta G^0 \) is related to the standard oxidation-reduction potential, \( E^0(\text{CuL}_x^{2+}, \text{CuL}_x^+) \), by eqn. 6.07.

\[
\Delta G^0 = -F(E^0_{\text{CuL}_x^{2+}, \text{CuL}_x^+} + E^0_{\text{H}^+, \frac{1}{2}\text{H}_2})
\]

where \( E^0(\text{H}^+, \frac{1}{2}\text{H}_2) \) is the absolute potential of the standard hydrogen electrode.

Free energy terms can be expressed as their enthalpy and entropy components according to eqn. 3.02. The ligational enthalpy, which is a measure of the strength of the metal-ligand bond, is composed of a number of factors, including

(a) Ion-dipole (or ion-ion) interactions. This electrostatic force is dependent on the charge on the metal ion, the dipole moment (or charge) of the ligand, and the distance between the charges.

(b) \( \sigma^- \) overlap of the metal and ligand orbitals.

(c) Polarisation of the ligand by the metal ion and subsequent overlapping of orbitals. This effect depends on the polarisability of the ligand and the polarising power of the metal ion.

(d) Polarisation of the metal ion by the ligand and subsequent overlapping of orbitals. This effect depends on the polarising power of the ligand and the polarisability of the metal ion.

(e) "Back-donation" of electrons from metal to ligand.

For this to occur three conditions must be satisfied:
(i) the metal ion must have available electrons in suitable d-orbitals, (ii) the ligand must have empty orbitals which can be made available to receive these d-electrons, and (iii) the sizes of the orbitals on the metal ion and ligand must be such as to ensure effective overlap.

(f) Energy level stabilisation term. This includes such factors as crystal-field stabilisations.

The above forces largely control the stereochemistry and co-ordination number of copper complexes. These factors, in turn, profoundly influence the oxidation-reduction potentials of copper complex couples.

6.3 The Co-ordination Number and Stereochemistry of (i) Copper(I)

Complexes of copper(I) are usually 4-co-ordinate with tetrahedral structures. Examples where such structures have been found by X-ray analysis include the copper(I) complexes with chloride (Brink and MacGillavry, 1949; Brink et al., 1954), thioacetamide (Cox et al., 1936; Truter and Rutherford, 1962), thiourea (Knobler et al., 1959), triethylarsine (Mann et al., 1936), and 1-diethylphosphino-2-diethylarsinobenzene (Cochran et al., 1957). The energy level diagram for copper(I) in a tetrahedral complex is given in Fig. 6.02. However, copper(I) can also be 2-co-ordinate in some of its complexes. Bjerrum (1934) has shown that in the aqueous ammonia system no
more than two ligands complex with Cu⁺. Foerster and Blankenberg (1906) and Nast and Schultze (1961) have, in fact, isolated the diammine complex as its sulphate and iodate. Subsequently, Brown and Dunitz (1961) have confirmed the expected linear structure of a 2-co-ordinate copper(I) complex by the X-ray analysis of diazoamino-benzencopper(I), which exists as a dimer in the solid state.

Two explanations have been proposed for the tendency of copper(I) to form the different types of complexes. James and Williams (1961) attempted to rationalise the observed co-ordination numbers by dividing ligands into two classes: (i) saturated ligands which are strong σ-donors but weak π-acceptors (2-co-ordinate), and (ii) strong π-acceptors (4-co-ordinate). The extra energy required to co-ordinate the additional two ligands in the 4-co-ordinate complexes was gained from the
increased π-bond formation which is possible in a tetrahedral configuration. Although the importance of back-donation of electrons in copper(I) complexes has been questioned by Nyholm (1961) and Griffith (1962), the ability of copper(I) to form complexes with alkynes (Blake et al., 1959), alkenes (Hendra and Powell, 1962), and ligands with donor atoms from periods other than the first (Ahrland et al., 1958) suggests that back-bonding could well be of importance as has been stressed by Chatt and his coworkers (see Ahrland et al., 1958). Dunitz and Orgel (1960) have proposed that the formation of 2- and 4-coordinate complexes is governed by the degree of covalent character of the metal-ligand bond. Formation of 2-coordinate linear complexes is explained by postulating an admixture of s and d$_{z^2}$ orbitals; the lowest d$^9$s state is only 2.7 e.v. above the d$^{10}$ level. Such a separation is sufficiently small for the two electrons which occupy the d$_{z^2}$ orbital to be placed in the (s - d$_{z^2}$) hybrid orbital, thus removing charge from the z axis and transferring it to the xy plane, and leading to very strong bonds along the z axis. For this hybridisation to take place, the metal-ligand bond must have a high degree of covalent character. Since the covalent character of the metal-ligand bond increases with increasing electron donor properties of the ligand, strongly basic ligands such as ammonia tend to form 2-co-ordinate linear complexes. An
(i) $d_{z^2}$ orbital, (ii) $s$ orbital, (iii) $(s + d_{z^2})$ hybrid orbital, (iv) $(s - d_{z^2})$ hybrid orbital.

Energy level diagram for such a complex, based on Orgel's theory, is given in Fig. 6.03. Where the ligand is not strongly basic, highly polarising, or easily polarised, and hence the metal-ligand bond is not very covalent, there is no tendency for promotion and hybridisation to occur. For complexes with these ligands, copper(I) would be expected to be 4-co-ordinate with a regular tetrahedral structure.

(ii) Copper(II)

Until recently copper(II), which has the $3d^9$ electronic configuration, was thought to have the characteristic maximum co-ordination number of 4 in aqueous solution (Bjerrum et al., 1954). It is now realised that the most common co-ordination number is 6, the complexes having a distorted octahedral configuration, the regular octahedron rarely, if ever, occurring (Orgel and Dunitz,
The distortion arises from crystal field effects on the $3d^9$ configuration (see Fig. 6.04). The theory of these distortions, the Jahn-Teller stabilisations, has been discussed fully in the literature (Griffith and Orgel, 1957; Dunitz and Orgel, 1960).

Although 4-co-ordinate copper(II) has been found to have either the square planar or the tetrahedral configuration, the latter is very rare (Felsenfeld, 1956; Orgel and Dunitz, 1957) and usually would only occur when the ligand demands sterically that the bonds are not planar (e.g. 2,2'-bis(salicylideneamino)-6,6'-dimethyl-diphenyl, Lions and Martin, 1957), or when there is undue electrostatic interaction in a square planar complex (e.g. chloride ion, Felsenfeld, 1956). Nyholm (1961) has postulated that strongly covalently bound copper(II) complexes have a tetrahedral structure. He suggests that in $\text{CuCl}_4^{2-}$ the chloride ion is highly polarised by $\text{Cu}^{2+}$, thus making the copper-chloride bond covalent in nature and the tetrachlorocuprate(II) ion tetrahedral. The square planar configuration can be regarded as a limiting case of the Jahn-Teller effect, the two ligands on the $z$ axis having been removed completely from the primary co-ordination sphere of the central metal ion.

Although copper(II) complexes possessing a maximum co-ordination number of 5 are unknown in aqueous solution,
they have been reported in non-aqueous solution and 5-co-
ordinate copper(II) complexes have been isolated from
solution (Corbridge and Cox, 1956; Graddon, 1959; Barclay
and Kennard, 1961; Harris et al., 1961; Mori et al.,
1961). The structures of iodo-bis(2,2'-dipyridyl)-copper-
(II) iodide (Barclay and Kennard, 1961), bis-chloro-
terpyridylcopper(II) (Corbridge and Cox, 1956) and the
pentachlorocuprate(II) ion (Mori et al., 1961) have been
shown by X-ray analysis to be trigonal bipyramidal.

6.4 The Copper - Amine Complexes

From the foregoing discussion of factors that
govern the oxidation-reduction potentials of copper
complexes, especially the influence of co-ordination number
and stereochemistry, it is possible to give reasons for
the magnitude of the potentials that have been obtained.

The preferential stabilisation of the copper(I)
state in 1:1 and 1:2 complexes with saturated monodentate
amines could be due to polarisation effects. Because of
differences in the size and charge of the copper(I) and
copper (II) ions, the amino group polarises the former
more than the latter, leading to greater orbital overlap
and stronger covalent-bond formation in copper(I)-amine
complexes than in the corresponding copper(II) complexes.
Further, since the saturated amines are, in general,
highly basic, there is a tendency for hybridisation of the
$\text{d}_{2z^2}$ and $\text{g}$ copper(I) orbitals to occur. This confers
additional stability on the univalent state and also leads to the formation of linear complexes. However, with ligands such as ethylenediamine, 2-methylthioethylamine, and α-aminocarboxylic acids, the effect of this stabilisation, in favouring linear complexes, is to oppose the formation by copper(I) of bidentate chelates. (Leybold atomic models confirm that these ligands would be unable to span the linear metal ion to form a 5-membered chelate ring.) Because these ligands can chelate with the square planar copper(II) ion, the absence in the corresponding copper(I) complexes of this effect means a greatly enhanced relative stability of the copper(II) complexes. For this reason, the oxidation-reduction potentials of the copper complexes with ethylenediamine, 2-methylthioethylamine and α-aminocarboxylic acids are less positive than the corresponding complexes with monodentate amines.

Methionine, an α-aminocarboxylic acid, would tend to form a linear copper(I) complex because of the basic nature of the amino group. From a comparison of the stability constants for the copper(I) complexes of methionine, ammonia and 2-methylthioethylamine it has been postulated that methionine co-ordinates as a bidentate chelate with copper(I). Since the α-aminoacid grouping is unable to span the linear complex, methionine must be attached to copper(I) by the sulphur atom and the amino group.
Further evidence for this bidentate character of methionine in a linear copper(I) complex is gained from the reluctance of Cu$^+$ to form a 1:2 complex with the ligand. Although chelation has resulted in additional stabilisation for the copper(I) complex, the corresponding copper(II) complex is relatively more stable because of the bonding in this complex of the aminoacid grouping as well as the sulphur atom. Thus, the oxidation-reduction potential for the 1:1 copper-methionine system is less positive than that for the simple hydrated copper ions.

The Free Energy - Oxidation State Diagram for the ammonia, 2-methylthioethylamine and ethylenediamine systems (Fig. 6.05) illustrates part of the above discussion. Whereas all the copper(I) complexes have been stabilised relative to Cu$^+$ by similar amounts, only the ethylenediamincopper(I) complex has a tendency to disproportionate. Fig. 6.05 also indicates that the 2-methylthioethylamine-copper(I) complex could be examined by a polarographic technique (cf. the ammonia system, von Stackelberg and von Freyhold, 1940); CuL$_2$$^{2+}$, the major copper(II) species in solution in the presence of excess ligand, would be reduced polarographically in the two steps,

$$\text{CuL}_2^{2+} + e \rightleftharpoons \text{CuL}_2^+ ,$$

$$\text{CuL}_2^+ + e (+ \text{Hg}) \rightleftharpoons \text{Cu(Hg)} + 2\text{L} .$$
On the other hand, ethylenediaminecopper(I) could not be investigated polarographically; Laitinen and his co-workers (1949) have observed a simple one step reduction (copper(II)-copper(0)) for the ethylenediamine system.

Li and his co-workers (1954) have shown that imidazole forms its complexes through the N(3) nitrogen. According to X-ray analysis, the tetrakis(4-methylimidazole)-copper(II) ion has a square-planar configuration; steric strains in the complex due to interactions of the four imidazole rings are relieved by rotation of the rings out of the plane (Montgomery and Lingafelter, 1960). The copper(I)imidazole complex is 2-co-ordinate (Li et al., 1954); the 1:1 and 1:2 complexes (which presumably are linear) are more stable than the corresponding copper(II) complexes. This stabilisation of the univalent state could be due, in part, to the favourable polarisation of the copper(I) ion by the polar ligand (electric dipole moment = 3.84 D, from Jensen and Friediger, 1943) and, in part, to the basicity of imidazole (pK_a = 7.20). However, the acid dissociation constant of imidazole is not a good indication of the basicity of the compound since the increased resonance on protonation due to the structures,
contributes to the $pK_a$ value although it is not related to the basicity of the $N(3)$ nitrogen. Hydrational effects could well be of importance in the imidazole complexes, the $N(1)$ atom providing a centre of charge on the periphery of the complex ions. However, the extent to which this would influence the potential is difficult to assess.

James and Williams (1961) have shown that the copper(I)-pyridine complex has a maximum co-ordination number of 4. Hence, the 4-methylpyridine-copper(I) complex is also probably 4-co-ordinate. On the other hand, there is, at present, no direct evidence to indicate whether the benzimidazole-copper(I) complex is 2- or 4-co-ordinate. Benzimidazole forms more stable copper(I) and copper(II) complexes than 4-methylpyridine although both ligands have similar basicities. The differences of 2.08 and 0.95 logarithmic units between the values of $\log \beta_2^I$ and $\log \beta_2^{II}$, respectively, could be due to the difference in the polarising power of the ligands. (The electric dipole moments are 4.0 D for benzimidazole (Wesson, 1948) and 2.57 D for 4-methylpyridine (Leis and Curran, 1945)). Differences in hydrational effects for the two complexes due to the presence of the $N(1)$ atom in benzimidazole might also contribute to the observed differences in the stability constants. It is possible that the more highly polar nature of benzimidazole, and the subsequent covalent binding
in its complexes, is sufficient for hybridisation of the copper(I) ion's $d_z^2$ and $s$ orbitals to impose a 2-coordinate linear structure on the benzimidazole-copper(I) complex. The failure of pyridine to form a linear complex can be explained in terms of its relatively low basicity and dipole moment (2.2 D, from Wesson, 1948). The increase of $pK_a$ from pyridine to 4-methylpyridine is reflected in the higher stability constants of the copper(I) and copper(II) complexes of 4-methylpyridine.

According to Leybold atomic models, steric interactions prevent four pyridine rings being planar with the square-plane of copper(II) in tetrakis(pyridine)copper(II). Thus, as in the imidazole case, the pyridine rings must be rotated out of the plane if steric strains are to be relieved. Since there is no extraordinary lowering of formation constants when more than two ligands are complexed in the copper(II) systems with pyridine, 4-methylpyridine, imidazole and benzimidazole, it would appear that this rotation of the rings does not seriously affect the complex formation. Back-donation of electrons from the $d_{zx}$ and $d_{zy}$ orbitals of copper(II) to the $\pi$-orbitals of the ligands would necessitate the four rings being in the plane of the copper(II). As this is impossible, it is improbable that "back-donation" is of importance in these copper(II) complexes.

The complexes for the four heterocyclic ligands are
compared diagrammatically in Fig. 6.06. The curves for the CuL$_4^{2+}$ - CuL$_2^+$ couples, with imidazole and benzimidazole as ligands, show that polarography could be used to study the copper(I) complexes even when conditions are such that the copper(II) complexes are 4-co-ordinate; Li and his coworkers (1954) have, in fact, observed the CuL$_4^{2+}$ - CuL$_2^+$ step for imidazole.

Because complexes of the same oxidation state for the 2,9-dimethyl- and 2-chloro- 1,10-phenanthroline couples are of similar size and charge, hydrational effects are unlikely to contribute significantly to the difference of 3 kcal in $\Delta H^0$ values for the redox equilibria. This leaves ligational enthalpy as the major factor in accounting for the difference, which is probably due, mainly, to differences in steric interactions in the copper(II) complexes. Divalent metal ions of the first transition series are believed to exist in aqueous solution essentially in the form, M(H$_2$O)$_6^{2+}$, in which six water molecules are disposed octahedrally around the metal ion. In the hydrated cupric ion, however, this structure is vertically distorted because of the Jahn-Teller effect. Formation of bis-complexes, ML$_2$, with bidentate ligands such as 1,10-phenanthroline may result in configurations designated as cis and trans.
Leybold atomic models show that the hydrogen atoms at positions 2 and 9 of pairs of 1,10-phenanthroline molecules are in contact in the trans form of bis(1,10-phenanthroline)-copper(II), and Jørgensen (1955) has postulated, on spectroscopic evidence, that this complex exists in the cis configuration. Steric hindrance is greatly increased by the introduction of 2- and 9-substituents (Irving et al., 1953), preventing trans complex formation. The bulkiness of the chloro- and methyl- groups limits the number of ways in which 2-chloro- and 2-methyl- 1,10-phenanthroline can be disposed in their cis complexes and (according to atomic models) formation of the cis complex of 2,9-dimethyl-1,10-phenanthroline with copper(II) ion is prevented. Bis(2,9-dimethyl-1,10-phenanthroline)copper(II) probably has a configuration intermediate between cis-octahedral and tetrahedral.

It had been thought that steric effects would be unimportant in the formation of 1:1 metal complexes of DMP.
If so, the stability constants of these complexes might be expected to be greater than those of 1,10-phenanthroline, itself. This is because, in related ligands, \( \log K_1 \) usually increases with the \( pK_a \) of the ligand. Thus, Banks and Bystroff (1959) found that for 1:1 iron(II) complexes of some 5-substituted-1,10-phenanthrolines

\[
\log K_1 \approx 0.6 \ pK_a + 2.93.
\]

Perrin (1962) has recently determined stability constants for 2,9-dimethyl-1,10-phenanthroline complexes with divalent copper, iron and zinc; these constants are summarised in Table 6.01. The experimental values of \( \log K_1 \) for the ferrous complexes of 2-methyl-1,10-phenanthroline (\( pK_a = 5.42, \log K_1 = 4.2 \), from Irving et al., 1953) and 2,9-dimethyl-1,10-phenanthroline (\( pK_a = 5.79, \log K_1 = 2.8 \)) indicate stabilities of only one hundredth and one three-thousandth of those predicted by the equation. Similarly, the 1:1 copper(II) and zinc(II) complexes of 2,9-dimethyl-1,10-phenanthroline have values of \( \log K_1 \) about 3 logarithmic units less than for the unsubstituted-phenanthroline complexes (Banks and Bystroff, 1959). Atomic models suggest that this drop is due to a steric effect; the methyl groups need to occupy positions round the metal ion, which are normally filled by water molecules. Thus, with phenanthrolines unsubstituted in positions 2 and 9, only two water molecules have to be removed in forming a 1:1 complex according to the equation,
leaving two water molecules in the plane of the organic ligand. With 2-methyl- and 2-chloro-1,10-phenanthroline, one of these water molecules, and with 2,9-dimethyl-1,10-phenanthroline, both of these water molecules, must be displaced in forming a 1:1 complex. In the latter case, it is possible that one of these water molecules may remain in an intermediate position in the plane, giving a trigonal bipyramidal structure. According to Basolo and Pearson (1958) the enthalpy change for the equilibrium,

\[
M(H_2O)_6^{2+} + L \rightleftharpoons ML(H_2O)_4^{2+} + 2H_2O,
\]

assuming a trigonal bipyramidal structure for \(Fe(H_2O)_5^{2+}\), is 25 kcal. This unfavourable enthalpy change would be a contributing factor in lowering the value of \(\log K_1\) for the iron(II) - 2,9-dimethyl-1,10-phenanthroline complex.

That \(\log K_2\) for the zinc complex of 2,9-dimethyl-1,10-phenanthroline is greater than \(\log K_1\) accords with results for the zinc ammines, where a similar increase has been attributed to increasing relative stability of the tetrahedral configuration as one passes from the octahedral \(Zn(H_2O)_6^{2+}\) ion (Orgel, 1960). For copper(II) ion, whereas formation of the 1:1 complex of 2,9-dimethyl-1,10-phenanthroline involves unfavourable hydrational energy change, formation of the 1:2 complex leads to gross distortion
from an octahedral structure. Thus, both steps in copper complex formation include energetically-unfavourable processes, and hence lead to lower stability constants than would be expected. The temperature dependence of \( \log K_1 \) and \( \log K_2 \) for these copper(II) complexes shows that little net entropy change (\( \Delta S = 0\pm5, 4\pm5 \text{ e.u.} \), respectively) occurs in these reactions. The steric strains discussed above are unimportant in tetrahedral structures, which are presumably adopted in the 1:2 complexes of zinc and copper(I). Thus, the copper(I) complex of 2,9-dimethyl-1,10-phenanthroline is stabilised relative to the copper(II) complex and the oxidation-reduction potential is high.

In the light of the present investigations, some comments can be made on the bonding of copper in metalloproteins, including, particularly, the oxidases.

Imidazole residues have been suggested as sites for attachment of copper in a number of proteins (Tanford, 1952; Dawson, 1960; Williams, 1961). Dawson (1960) proposed that copper is bound by several (2 or 4) imidazole groups in ascorbic acid oxidase, while Williams (1961) pointed out that the oxidation-reduction potential of plastocyanin, \( E^0 = 0.390 \text{ v at pH = 7} \) (Katoh, 1960), is comparable with the potential for the copper-imidazole system. Further, Malmström and Wannström (1960) postulated from ESR studies that copper is bound to nitrogen in laccase.
which has been found to have a potential of 0.415 v at pH = 7 (Nakamura, 1958). Also, azurin, another copper protein, has recently been found to have an oxidation-reduction potential of 0.395 v (Sutherland and Wilkinson, 1962).

The copper(I)-imidazole complex is 2-co-ordinate and the potential of the copper(II)-copper(I) couple is about 0.35 v for the pairs of 1:2 copper-imidazole complexes. Hence, if a copper protein were to have a potential of about 0.4 v and the copper were to be bound to imidazole residues, it would be expected that the protein would be attached to the copper ion by two linear bonds. If more than two imidazole residues were bound to copper(II), the potential would be considerably lower than 0.4 v. However, it does not necessarily follow that a potential around 0.4 v implies bonding to imidazole residues. Complexing to amino groups could lead to an oxidation-reduction potential of this order of magnitude. The potential of a simple 1:2 copper-amine complex is approximately 0.33 v, and the observed differences in biological systems may well be due to steric strains in the copper(II)-protein complexes.

In summary, the following general observations can be made concerning the design of ligands to confer high or low oxidation-reduction potentials on the copper(II)-copper(I) couple. Copper(II) complexes will be favoured
(low values of $E^0$) in the following circumstances:

(i) When the ligand is multidentate and constrained to be planar. For this reason, for example, potentials of copper-porphyrins are likely to be so low as to render them unimportant in biological redox systems.

(ii) When the ligand is bidentate and strongly basic, especially if 5-membered ring formation is involved. The ligand may be a diamine (such as ethylenediamine), a monoamine (such as 2-methylthioethylamine), or a zwitterion (such as glycine).

Copper(I) complexes will be favoured (high values of $E^0$):

(i) when steric factors permit a tetrahedral arrangement of ligand molecules around a copper(I) ion while at the same time preventing the adoption of a square-planar configuration around a copper(II) ion,

(ii) when the ligand has donor atoms from periods other than the first (e.g. sulphur),

(iii) when the ligand is monodentate and forms a highly covalent copper(I)-ligand bond.

- - - - -

Table 6.01

Thermodynamic Stepwise Formation Constants of Metal Complexes of 2,9-dimethyl-1,10-phenanthroline

(At low ionic strengths and assuming $-\log f_1 = \text{Ar}^2$)

<table>
<thead>
<tr>
<th>Cation</th>
<th>pH range</th>
<th>$T$, in °C</th>
<th>$\log K_1$</th>
<th>$\log K_2$</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu$^{2+}$</td>
<td>3.39 - 4.63</td>
<td>0.43 - 1.24</td>
<td>15</td>
<td>6.36</td>
<td>5.49</td>
</tr>
</tbody>
</table>
Table 6.01 (cont.)

<table>
<thead>
<tr>
<th>Cation</th>
<th>pH range</th>
<th>$\bar{n}$</th>
<th>T, in °C</th>
<th>$\log K_1$</th>
<th>$\log K_2$</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu$^{2+}$</td>
<td>3.67 - 5.09</td>
<td>0.50-1.39</td>
<td>20</td>
<td>6.19</td>
<td>5.36</td>
<td>b</td>
</tr>
<tr>
<td>Cu$^{2+}$</td>
<td>3.31 - 4.46</td>
<td>1.06-1.66</td>
<td>20</td>
<td>6.28</td>
<td>5.58</td>
<td>c</td>
</tr>
<tr>
<td>Cu$^{2+}$</td>
<td>3.84 - 4.67</td>
<td>0.56-1.17</td>
<td>30</td>
<td>5.99</td>
<td>5.31</td>
<td>b</td>
</tr>
<tr>
<td>Cu$^{2+}$</td>
<td>3.97 - 4.98</td>
<td>0.59-1.27</td>
<td>42</td>
<td>5.82</td>
<td>5.09</td>
<td>b</td>
</tr>
<tr>
<td>Fe$^{2+}$</td>
<td>4.69 - 6.36</td>
<td>0.04-0.32</td>
<td>20</td>
<td>2.79</td>
<td>-</td>
<td>d</td>
</tr>
<tr>
<td>Zn$^{2+}$</td>
<td>4.32 - 5.72</td>
<td>0.13-1.25</td>
<td>20</td>
<td>3.40</td>
<td>4.43</td>
<td>e</td>
</tr>
</tbody>
</table>

Thermodynamic Acid Dissociation Constant$^f$(mean ± max. deviat.)

<table>
<thead>
<tr>
<th></th>
<th>15°</th>
<th>20°</th>
<th>30°</th>
<th>42°</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.81 ± 0.03</td>
<td>5.79 ± 0.03</td>
<td>5.72 ± 0.04</td>
<td>5.60 ± 0.03</td>
</tr>
</tbody>
</table>

$^a$ Perrin, 1962.

$^b$ 5 x $10^{-5}$M - copper nitrate, 10$^{-4}$M in total ligand, titrated with 0.1M-HClO$_4$.

$^c$ 5 x $10^{-4}$M - copper nitrate, 10$^{-3}$M in total ligand, 5 x $10^{-4}$M - sulphuric acid, titrated with 0.1M-potassium hydroxide. $pK_a$ of H$_2$SO$_4$ was taken as 1.87.

$^d$ 4 x $10^{-4}$M - ferrous sulphate, 10$^{-3}$M in total ligand, titrated with 0.1M - hydrochloric acid. Log $K_1$ was constant within ± 0.08 over the accessible range of $\bar{n}$ (hydrolysis occurs in less acid solution) so that no estimate of $K_2$ could be obtained.

$^e$ 5 x $10^{-4}$M - zinc perchlorate, 10$^{-3}$M in total ligand, titrated with 0.1M - hydrochloric acid.

$^f$ By titration of 10$^{-3}$M solution; evaluated over 9/10ths of the titration using the complete Henderson-Hasselbalch equation with activity coefficient corrections.
Fig. 6.01. Free Energy – Oxidation State Diagram for the Copper(II) – Copper(I) – Copper(0) System.

Fig. 6.02. Energy Level Diagram for Tetrahedral Copper(I) Complex. $\sigma$ – Cu$^+$ orbitals. $\pi$ – Cu$^0$ orbitals in a tetrahedral field. $\gamma$ – orbitals for tetrahedral copper(I) complex. $\delta$ – ligand orbitals.
Fig. 6.02. Energy Level Diagram for Tetrahedral Copper(I) Complex. 
a - Cu⁺ orbitals. 
b - Cu⁺ orbitals in a tetrahedral field. 
c - Orbitals for tetrahedral copper(I) complex. 
d - Ligand orbitals.
Fig. 6.03. Energy Level Diagram for Linear Copper(I) Complex.

- **a** - Cu$^+$ orbitals.
- **b** - Cu$^+$ orbitals in linear field.
- **c** - hybridisation of s and d$_{z^2}$ orbitals.
- **d** - orbitals for linear copper(I) complex.
- **e** - ligand orbitals.
Fig. 6.04. Energy Level Diagram for Copper(II) in a Distorted Octahedral Complex. a - regular. b - distorted. c - orbitals for distorted octahedral copper(II) complex.
Fig. 6.05. Free Energy - Oxidation State Diagram for 1:2 Copper-Amine Complexes. ○ - ammonia. Θ - 2-methylthio-ethylamine. ◊ - ethylenediamine.
Fig. 6.06. Free Energy - Oxidation State Diagram for Copper Complexes with Nitrogen Heterocyclic Compounds. A circle indicates a 1:2 complex and a square indicates a 1:4 complex. 

- pyridine.
- 4-methylpyridine.
- imidazole.
- benzimidazole.
REFERENCES


Edsall, J.T., Felsenfeld, G., Goodman, D.S. and Gurd, F.R.N.


Foerster, F. and Blankenberg, F. (1906). Ber., 39, 4428.
Fronaeus, S. (1948). "Komplexsystem hos koppar", Gleerupska-
Universitets-Bokhandeln, Lund.
(of. Chem.Abs., 1954, 48, 12184 b.)
Gmelin (1955). "Gmelins Handbuch der Anorganischen Chemie,
8. Auflage. System-nummer 60, Kupfer Teil A", Verlag
Chemie, GMBH, Weinheim/Bergstrasse, pp.1053 - 1058.
Chem.Soc., 76, 4671.
1374.
1850, 1857.


76, 6219.
1273.
McElroy, W.D. and Glass, B. (1950), eds. "Copper Metabolism",
The Johns Hopkins Press, Baltimore.
216, 625.
Mallette, M.F. (1950). In "Copper Metabolism", McElroy, W.
D. and Glass, B., eds., The Johns Hopkins Press,
Baltimore, p.48.
183, 321.
118.
1503.
77, 5291.
1173.


(a) Mathematical Derivation of Eqs. 5.25, 5.26 and 5.27 (see Section 5.7). (Derived in collaboration with Dr. P. B. Feringa.)

The equations for the total concentrations of metal species and ligand species, and for the total charges (eqns. 5.22, 5.23 and 5.24, respectively) include the summations of binomial series. Eqns. 5.29, 5.26 and 5.27 are obtained from the previous equations by performing the summations and rearranging as follows.

Put $x = \frac{K_{d}x_{0}x_{0}}{K_{d}x_{0}x_{0} + [Cu^{2+}]^{2}[NTA]^{-2}/[NTA]^{2}}$, where $x_{0}$ and $x_{0}$ are the stepwise formation constants for the formation of the 1st and 142 copper(II) complexes and $K_{d}$ is the third acid dissociation constant for the bis(carboxylate).

Then,

$$\sum_{i=1}^{n} (nK_{d}x_{0})^{i-1}[Cu^{2+}]^{i}[NTA]^{2-}/[NTA]^{2}$$

$$= \frac{[H^{+}]^{i-2i}}{1K_{d}x_{0}^{2i-2}} \sum_{i=1}^{n} (nK_{d}x_{0})^{i-1}[Cu^{2+}]^{i}[NTA]^{2-}/[NTA]^{2}$$

$$= \frac{[H^{+}]^{i-2i}}{1K_{d}x_{0}^{2i-2}} \sum_{i=1}^{n} (nK_{d}x_{0})^{i-1}[Cu^{2+}]^{i}[NTA]^{2-}/[NTA]^{2}$$

$$\left| \frac{[H^{+}]^{i-2i}}{1K_{d}x_{0}^{2i-2}} \sum_{i=1}^{n} (nK_{d}x_{0})^{i-1}[Cu^{2+}]^{i}[NTA]^{2-}/[NTA]^{2} \right| < 1$$

(3a)

Similarly,
APPENDIX

Polynuclear Complex Formation

(a) Mathematical Derivation of Eqns. 5.25, 5.26 and 5.27 (see Section 5.7). (Derived in collaboration with Dr. D. D. Perrin.)

The equations for the total concentrations of metal species and ligand species, and for the total charges (eqns. 5.22, 5.23 and 5.24, respectively) include the summations of binomial series. Eqns. 5.25, 5.26 and 5.27 are obtained from the previous equations by performing the summations and rearranging as follows.

Put \( x = \frac{K_1 K_2 K_3 [Cu^{2+}][HLRL^-]}{[H^+]}, \) where \( K_1 \) and \( K_2 \) are the stepwise formation constants for the formation of the 1:1 and 1:2 copper(II) complexes and \( K_{a3} \) is the third acid dissociation constant for the bis(aminoacid).

Then,

\[
\sum_{n=1}^{\infty} (nK_1 K_2 K_{a3}^{n-1}) [Cu^{2+}]^n [HLRL^-]^n / [H^+]^{n-1}
\]

\[
= \frac{[H^+]^{n=\infty}}{K_2 K_{a3}} \sum_{n=1}^{\infty} (nx^n)
\]

\[
= \frac{[H^+] x}{K_2 K_{a3} (1-x)^2} \quad (|x| < 1) \quad (Ia)
\]

Similarly,
\[ \sum_{n=2}^{\infty} (nK_1 nK_2 n^{-2} K_{a3}^{-1} [Cu^{2+}]^n [HLRL^-]^{n-1}/4[H^+]^{n-1}) \]

\[ = \frac{[H^+]}{4K_2^2 K_{a3} [HLRL^-]} \sum_{n=2}^{\infty} (nx^n) \]

\[ = \frac{[H^+]}{4K_2^2 K_{a3} [HLRL^-]} \cdot \frac{x^2 (2-x)}{(1-x)^2} \quad (|x| < 1) \]

\[ = \frac{K_1 [Cu^{2+}] x (2-x)}{4K_2 (1-x)^2} , \quad (IIa) \]

\[ \sum_{n=1}^{\infty} (nK_1 nK_2 n^{-1} K_{a3}^{-1} [Cu^{2+}]^n [HLRL^-]^{n+1}/[H^+]^{n-1}) \]

\[ = \frac{[HLRL^-][H^+]}{K_{a3}} \sum_{n=1}^{\infty} (nx^n) \]

\[ = \frac{[HLRL^-][H^+] x}{K_{a3} (1-x)^2} \quad (|x| < 1), \quad (IIIa) \]

and

\[ \sum_{n=2}^{\infty} (K_1 nK_2 nK_{a3}^{-1} [Cu^{2+}]^n [HLRL^-]^{n+1}/2[H^+]^n \]

\[ = \frac{1}{2} \sum_{n=2}^{\infty} (x^n) \]

\[ = \frac{1}{2} \frac{x^2}{(1-x)} \quad (|x| < 1). \quad (IVa) \]

From eqn. 5.22,

\[ [Cu]_T = [Cu^{2+}] + \frac{x[H^+]}{K_2 K_{a3} (1-x)^2} + \frac{K_1 [Cu^{2+}] x (2-x)}{4K_2 (1-x)^2} + \frac{[HLRL^-][H^+] x}{K_{a3} (1-x)^2} \]
\[
\begin{align*}
&= [\text{Cu}^{2+}] + \frac{x}{(1-x)^2} \left( \frac{[\text{H}^+]}{K_{2K_a}} + \frac{(2-x)K_1[\text{Cu}^{2+}]}{4K_2} + \frac{[\text{H}^+][\text{HLRL}^-]}{K_a^3} \right) \\
&\quad + \frac{x^2}{2(1-x)}.
\end{align*}
\]

Further,
\[
\sum_{n=2}^{\infty} \left( (n-1)K_1 K_2 n^{-2} K_a^3 n^{-1}[\text{Cu}^{2+}]^n [\text{HLRL}^-]^n / 4[\text{H}^+]^{n-1} \right)
\]
\[
= \frac{[\text{H}^+] x^2}{4K_2 K_a^3 (1-x)^2} \quad (|x| < 1)
\]

and
\[
\sum_{n=1}^{\infty} \left( (n+1)K_1 K_2 n K_a^3 n^{-1}[\text{Cu}^{2+}]^n [\text{HLRL}^-]^{n+1} / [\text{H}^+]^{n-1} \right)
\]
\[
= \frac{[\text{HLRL}^-][\text{H}^+]}{K_a^3} \cdot \frac{n=\infty}{\sum_{n=1}} \langle (n+1)x^n \rangle
\]
\[
= \frac{[\text{HLRL}^-][\text{H}^+] x(2-x)}{K_a^3 (1-x)^2} \quad (|x| < 1). \quad (\text{V1a})
\]

From eqn. 5.23,
\[
[\text{HLRLH}]_T = g[\text{HLRL}^-] + \frac{[\text{H}^+]x + K_1[\text{Cu}^{2+}]x}{K_2K_a3(1-x)^2} \frac{K_2}{4K_2(1-x)^2}
\]
\[+ \frac{[\text{HLRL}^-][\text{H}^+]x(2-x) + \frac{x^2}{K_a3(1-x)^2}}{2(1-x)}
\]
where \( g = 1 + \frac{[\text{H}^+]^2 + [\text{H}^+]^3 + K_{a4}}{K_a3 K_a2 K_a3 K_a1 K_a2 K_a3} \).

That is
\[
[\text{HLRLH}]_T = g[\text{HLRL}^-] + \frac{x}{(1-x)^2} \frac{[\text{H}^+] + K_1[\text{Cu}^{2+}]}{K_2K_a3} \frac{K_2}{4K_2}
\]
\[+ \frac{(2-x)[\text{HLRL}^-][\text{H}^+]}{K_a3} \]
\[+ \frac{x^2}{2(1-x)} \]  

Also,
\[
\sum_{n=1}^{\infty} \left( K_1 K_2 K_3^{-1} \frac{[\text{Cu}^{2+}]^n [\text{HLRL}^-]^n}{[\text{H}^+]^{n-1}} \right) = \frac{[\text{H}^+]x}{K_2K_a3(1-x)} \quad (|x| < 1), \quad (VIIa)
\]

and
\[
\sum_{n=2}^{\infty} \left( K_1 K_2 K_3^{-1} \frac{[\text{Cu}^{2+}]^n [\text{HLRL}^-]^{n-1}}{4[\text{H}^+]^{n-1}} \right) = \frac{[\text{H}^+]}{4K_2^2K_a3[\text{HLRL}^-]} \cdot \sum_{n=2}^{\infty} (x^n)
\]
From eqn. 5.24,

\[
\frac{\text{[HLRL\textsuperscript{-}]}_T - [\text{Cu}]_T}{K_a} = \frac{[\text{Cu}^{2+}]}{4K_2} \quad (|x| < 1)
\]

= \frac{[\text{HLRL\textsuperscript{-}}]}{4K_2K_a}(1-x)

= K_1[\text{Cu}^{2+}]x/4K_2(1-x) \quad (\text{VIIIa})

From eqn. 5.24,

\[
2[\text{Cu}]_T = [\text{H}^+] + [\text{Na}^+] + 2[\text{H}_2\text{LRLH}_2^{2+}] + [\text{HLRLH}_2^{+}] + 2[\text{Cu}^{2+}]
\]

+ \frac{[\text{H}^+]x}{K_2K_a(1-x)} + \frac{K_1[\text{Cu}^{2+}]x}{2K_2(1-x)} - \frac{[\text{HLRL}^{-}]}{2} - 2[\text{LRL}^{2-}]

= \frac{[\text{H}^+] + [\text{Na}^+] + 2[\text{Cu}^{2+}] + x}{(1-x)} \left( \frac{[\text{H}^+]}{K_2K_a} \right)

+ \frac{[\text{H}_2\text{LRLH}_2^{2+}] + [\text{HLRLH}_2^{+}] - [\text{HLRL}^{-}] - 2[\text{LRL}^{2-}]}{K_2K_a(1-x)}

- [\text{OH}^{-}] \quad \text{(5.27)}

(b) Basis for Program for IBM 1620 Digital Computer

From eqns. 5.25 and 5.26,

\[
[\text{HLRLH}]_T - [\text{Cu}]_T = A = g[\text{HLRL}^{-}] - [\text{Cu}^{2+}] + \frac{x}{(1-x)} \left( \frac{[\text{H}^+][\text{HLRL}^{-}]}{K_a} \right)
\]

= \frac{[\text{HLRL}^{-}] - [\text{Cu}^{2+}] + k_4[\text{HLRL}^{-}][\text{Cu}^{2+}]}{(1-k_4[\text{HLRL}^{-}][\text{Cu}^{2+}]})

\text{where } k_4 = \frac{K_1K_2K_a}{[\text{H}^+]}.
Expanding this equation gives

\[
[Cu^{2+}]^2 \left( k_4[HLRL^-](K_1/4K_2 - l) \right) + [Cu^{2+}](1 - k_4A[HLRL^-]) + k_4[HLRL^-]^2j + (A - g[HLRL^-]) = 0 \quad (\text{Ib})
\]

where \( j = g - [H^+]/K_a3 \).

From which

\[
a = k_4[HLRL^-](K_1/4K_2 - l)
\]

\[
\beta = 1 - k_4A[HLRL^-] + k_4[HLRL^-]^2j
\]

\[
\gamma = A - g[HLRL^-]
\]

\[
[Cu^{2+}] = \frac{-\beta \pm \sqrt{\beta^2 - 4a\gamma}}{2a}
\]

(To simplify the program the approximation, \( g = 1 + [H^+] / K_a3 \), was made).

Eqn. 5.25 can be expanded to give

\[
4K_a3K_2([Cu]_T - [Cu^{2+}])(1 - k_4[HLRL^-][Cu^{2+}])^2
\]

\[
= k_4[HLRL^-][Cu^{2+}](4[H^+] + 4K_2[H^+][HLRL^-])
\]

\[
+ 2K_1K_a3[Cu^{2+}] - k_4K_1K_a3[HLRL^-][Cu^{2+}]^2
\]

\[
+ 2k_4K_2K_a3[Cu^{2+}][HLRL^-]
\]

\[- 2k_4^2K_2K_a3[HLRL^-]^2[Cu^{2+}]^2 \] (\text{IIb})

Also eqn. 5.27 can be rewritten as

\[
2[Cu]_T = [H^+] + [Na^+] + 2[Cu^{2+}] + X + Y + C[HLRL^-] - [OH^-]
\]

\[ \ldots \] (\text{IIIb})
where \( X = \frac{x[H^+]}{(1-x)K_2K_a^3} \),

\[
Y = \frac{xK_1[Cu^{2+}]}{2(1-x)K_2} = \frac{xK_1}{2K_2[HRL^+]},
\]

and \( C = 2[H^+]^3/K_a1K_a2K_a3 + [H^+]^2/K_a2K_a3 - 1 - 2K_a4/[H^+] \).

Values of \([Cu^{2+}]\) and \([HLRL^-]\) which satisfy eqns. Ib and IIb can be obtained at any point, \( i \), of a titration by an iterative procedure using arbitrary values for \( K_1 \) and \( K_2 \) and the limits,

\[
[Cu]_T \geq [Cu^{2+}]_{i-1} \geq [Cu^{2+}]_i > 0,
\]

\[
[HLRLH]_T \geq [HLRL^-]_i \geq [HLRL^-]_{i-1} > 0,
\]

\[
1 > K_4[HLRL^-][Cu^{2+}] > 0 \quad \text{(i.e. } 1 > x > 0)\).
\]

(In the program a lower limit of \( 1 \times 10^{-10} M \) was imposed on \([HLRL^-]\).) To check the correctness of the selected values of \( K_1 \) and \( K_2 \), values of \([HLRL^-]\) and \([Cu^{2+}]\) were determined at two widely-separated points in a titration and substituted into eqn. IIIb. The procedure was repeated with different values of \( K_1 \) and \( K_2 \) until eqns. Ib, IIb, and IIIb were satisfied.

(c) Program (developed by Miss E. Reid) for IBM 1620 Digital Computer using FORTRAN:

1 FORMAT(E15.8)
2 FORMAT(I4)
3 FORMAT(E15.8,E15.8,E15.8)

ACCEPT TAPE 1,CKA,CK1,CK2
18 PAUSE

ACCEPT TAPE 2,N
ACCEPT 1,FM
BL=1.OE-10
DO 20 I = 1,N
ACCEPT TAPE 3, TOTM ,H,A
23 CK4=CKA*CK1*CK2/H
6 ALPHA=CK4*BL*(CK1/(4.*CK2)-1.)
IF(ALPHA)4,5,4
5 BL=BL+1.OE-11
GO TO 6
4 BETA=1.-CK4*A*BL+CK4*BL*BL
GAMMA=A-BL-(H*BL/CKA)
Z=BETA*BETA-4.*ALPHA*GAMMA
IF(Z)5,8,8
8 BM=(-BETA+SQRT(Z))/(2.*ALPHA)
IF(BM)9,9,7
7 IF(BM-FM)10,9,9
9 BM=(-BETA-SQRT(Z))/(2.*ALPHA)
IF(BM)5,5,12
12 IF(BM-FM)10,5,5
10 IF(CK4*BL*BM)5,5,11
11 IF(CK4*BL*BM-1.)13,5,5
13 ALHS=4.*CKA*CK2*(TOTM-BM)*(1.-CK4*BL*BM)**2
RHS=4.*H+4.*CK2*H*BL+2.*CK1*CKA*BM-CK1*CK4*CKA*BL*BM**2
RHS=RHS+2.*CK2*CK4*CKA*BM*BL-2.*CK2*CK4**2*CKA*BL**2*BM**2
RHS = RHS * CK4 * BM * BL
DIFF = ALHS - RHS
IF (DIFF) 14, 14, 5
14 IF (SENSE SWITCH 3) 21, 15
15 IF (SENSE SWITCH 1) 22, 20
20 BL = BL + 1.0E-11
PRINT 19
19 FORMAT (16H SET SWITCH 3 ON)
PAUSE
ACCEPT 3, ANAOH, BL
24 ACCEPT 3, FM, CK1, CK2
GO TO 23
21 CK4 = CKA * CK1 * CK2 / H
D = CK4 * BL * BM
X = H * D / (CKA * CK2 * (1. - D))
Y = X * D / (2. * CK2 * BL)
ACCEPT 1, C
FNTN = ANAOH * 1.0E-04 - 2.*TOTM + H * C * BL + X + Y + 2.*BM
IF (SENSE SWITCH 2) 29, 28
29 PRINT 1, FNTN
28 IF(FNTN)24,25,25
25 PRINT 26, BM, BL, CK1, CK2
26 FORMAT(E15.8,E20.8,E20.8,E20.8)
   PRINT 27
27 FORMAT(24H TURN SENSE SWITCHES OFF)
   PAUSE
   GO TO 18
   END

Symbols
CKA = $K_{a3}$
CK1 = $K_1$
CK2 = $K_2$
N = No. of data sets in each experiment
FM = Maximum limit of $[Cu^{2+}]$
BM = $[Cu^{2+}]$
TOTM = $[Cu]_T$
BL = $[HLRL^-]$
H = $[H^+]$
A = $[HLRLH]_T - [Cu]_T$
ANAOH = $[NaOH] \times 10^4$
C = $\frac{2[H^+]^3}{K_{a1}K_{a2}K_{a3}} + \frac{[H^+]^2}{K_{a2}K_{a3}} + \frac{1 - 2K_{a4}}{[H^+]}$

...