A General Method for the Determination of Copper(I) Equilibria in Aqueous Solution

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Copper(I) equilibrium constants can, for the first time, be studied routinely in aqueous solution by potentiometric titration using Cu^{I} solutions produced by reduction of Cu^{II} with an excess of copper and stabilized by chloride.

The importance of copper in biochemistry and physiology is beyond dispute.[1–3] To date, however, most studies of the solution chemistry of copper have focused on the common Cu^{II} oxidation state. For example, in one large database[4] there are over 3000 equilibrium constants for Cu^{II}, most determined by the popular potentiometric titration method, whereas there are only about 100 constants for Cu^{I}, many of them estimated. Yet there is substantial indirect evidence that Cu^{I} complexes are not only significant but may actually be the predominant low molecular mass copper species in a variety of biofluids. For example, both glutathione and cysteine, which are readily and irreversibly oxidized by Cu^{II}, have been strongly implicated in the *in vivo* metabolism of the 'softer' metal ions such as Pb, Hg, Ag and Zn.[2,5] Such species would also be expected to interact strongly with the 'soft' Cu^{I}.[3] Further evidence comes from the redox potentials of certain biofluids. In blood plasma, for example, even though the redox potential is difficult to determine exactly, it is undoubtedly negative (*vs.* the standard hydrogen electrode) and possibly as low as −200 mV, judging from the known ratios of reduced to oxidized forms of species such as cysteine/cystine and ascorbate/dehydroxyascorbate.[6,7] In cell cytoplasm the redox potential is even more negative as evidenced by the particularly high concentrations of the reduced form of glutathione.[7]

Copper(I) certainly has a well established, albeit limited, coordination chemistry[3] and Cu^{I} species are important in mineral processing either because they are present in copper ore bodies[8] or because they appear during extraction.[9] The best known example of the latter is the interference of Cu^{I}/CN^{-} species with the recovery of gold from copper-rich ore bodies using the usual cyanide leaching process.[9]

There is, clearly, a marked contrast between the known or implied importance of Cu^{I} species and their quantitative study. The explanation for this lies in the difficulty of studying Cu^{I} complexes in aqueous solution because of the ease of oxidation of Cu^{I} [$E^{\circ}(Cu^{II}/Cu^{I}) = 0.168$ V][3,10] and its tendency to disproportionate: $2Cu^{I} \rightleftharpoons Cu^{II} + Cu^{0}$ (*K ca.* 10^{5}).[10] Nevertheless, it is well known that the relative stability of Cu^{I} can be manipulated by the addition of suitable ligands or by changes in solvent.[3,10,11]

We have found with appropriate experimental precautions, Cu^{I} can be prepared and maintained in aqueous 1 mol dm^{-3} NaCl in a manner suitable for the determination of its formation constants with a wide variety of ligands by conventional potentiometric titration or other methods. The relatively high chloride concentration is necessary to stabilize Cu^{I} sufficiently relative to Cu^{II}. This concentration is higher than the 0.15 mol dm^{-3} (Na)Cl medium often used for modelling biofluid equilibria purposes but it is close to that found in seawater and in many industrial contexts and has routinely been used in our laboratories to study a wide variety of equilibria.[12] Certainly, this procedure produces constants that are more immediately relevant for modelling most aqueous solutions than those obtained in mixed solvents,[11] and avoids the need for more complicated approaches such as *in situ* generation of Cu^{I}.[13]

Of course, constants obtained in chloride media may be regarded as conditional. A full description of ternary Cu^{I}/Cl^{-}/ligand systems is necessary for comparison with equilibrium constants in (notionally) non-complexing media. However, this is beyond the scope of the present paper. More to the point, these 'conditional' constants are more appropriate for modelling in chloride media as noted above.

Cu^{I} stock solutions were prepared by allowing a suitable concentration of Cu^{II} (*ca.* 50 mmol dm^{-3}) to stand for several days over an excess of copper metal in slightly acidified $I = 1.0$ mol dm^{-3} (Na)Cl solution under thoroughly deoxygenated argon. The disappearance of Cu^{II} can be monitored spectrophotometrically or electrochemically. The final concentration of Cu^{I} and H^{+} in the stock solution are determined by aerial oxidation to Cu^{II} of appropriate aliquots followed by standard ethylenediamminetetraacetic acid and NaOH titrations, respectively. For potentiometric titrations a suitable quantity of ligand in slightly acidic 1.0 mol dm^{-3} Na(Cl) solution is placed in an air-tight, thermostatted titration vessel.[14] The vessel and solution are then thoroughly degassed by scrubbed, pre-humidified, high purity argon while the electrodes come to equilibrium. An appropriate aliquot of the (analysed) Cu^{I} stock solution is then injected into the vessel solution and after stabilization the solution is titrated with deoxygenated NaOH [I = 1.0 mol dm^{-3} (Na)Cl] in the conventional manner. Titrations can be performed using any high precision titrator system.

To test our procedures a thorough study has been made of the Cu^{I}/CN^{-} system, one of the few Cu^{I} systems for which reasonably reliable formation constants are available.[15] The results obtained are summarized in Table 1 and, taking into account the differences in media, can be seen to be in good agreement with the literature values. Full details of this work will be published elsewhere.[16]

Given their probable medical importance,[17] we have also studied the equilibrium constants of Cu^{I} with the cupruetic drug penicillamine. The results are summarized in Table 2; again, full information will reported elsewhere.[18] Penicillamine has been widely used as an anti-inflammatory agent and is known to cause a dramatic increase in the urinary excretion of copper for treatment of Wilson's disease.[17,19] Various mechanisms for this effect, including the formation of a mixed valence Cu^{II}/Cu^{I} complex, have been proposed but none is convincing.[19] The data in Table 2 will be useful in the computer simulation of biofluids and may help to establish whether Cu^{I} chelation provides an explanation, although it can be seen that the complexes are not unusually strong. The detection of a '430' species, *i.e.* Cu_4L_3 [L = $^{-}OOC(NH_2)$–CH–CMe_2S^{-}], is noteworthy since a number of complexes containing a tetrahedron of Cu^{I} atoms held together by sulfur or chloride bridges are known in the solid state.[10] We searched for other polynuclear species[11,13] but no evidence was found; details are given elsewhere.[18] Our results are in broad agreement with those of Österberg *et al.*[13] measured in 0.5 mol dm^{-3} $NaClO_4$ but differ in detail as might be expected due to the presence of chloride.

The range of Cu^{I} complexes, which can be studied by this procedure is extremely broad and a variety of systems are already under investigation in our laboratories including the important *S*-amino acids cysteine and glutathione.[16,18] Although we have restricted ourselves to potentiometry in this communication, the extension to other standard techniques for the study of formation constants, such as spectrophotometry, is straightforward. It is of particular significance that the method is readily applicable to glass electrode potentiometry, by far the most common technique for equilibrium constant measurement. It is anticipated that our understanding of the biochemistry and physiology of copper will undergo a dramatic transformation as more formation constants of Cu^{I} become available.

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Table 1 Equilibrium (formation) constants for Cu^{I}/CN^{-} complexes[a] I = 1.0 (Na)Cl, 25 °C

	log [β_n/(mol dm^{-3})$^{-n}$]		log (K_n/dm^3 mol^{-1})	
	This work[b]	Lit.[c]	This work	Lit.[c]
$n = 1$[d]	16.33	—	16.33	—
$n = 2$	23.97 (0.01)	23.72	7.64	—
		21.7 (0.2)		
$n = 3$	29.40 (0.04)	26.8 (0.2)	5.43 (0.04)	5.30 (0.04)
$n = 4$	31.78 (0.02)	27.9 (0.2)	2.38(0.04)	1.5 (0.2)

[a] Data given as overall [β_n: $Cu^{+} + nCN^{-} \rightleftharpoons Cu(CN)_n^{1-n}$] and stepwise [$K_n$: $Cu(CN)_{n-1}^{2-n} + CN^{-} \rightleftharpoons Cu(CN)_n^{1-n}$] constants to facilitate comparisons with literature data from different sources.[15] [b] Constants were determined by glass electrode potentiometry from 16 titrations (1900 points) assuming pK_a(HCN) = 8.968 (0.003).[16] Numbers in parentheses are calculated standard deviations. [c] Literature data; conditions are *I ca.* 0, 25 °C.[15] Numbers in parentheses are estimated errors.[15] [d] The $CuCN^{\circ}_{aq}$ complex is not normally detected in this type of measurement;[15] the value given is estimated.

Table 2 Equilibrium constants for Cu^{I}–D-penicillamine complexes[a] I = 1.0 (Na)Cl, 25 °C

p	q	r	log [β_{pqr}/(mol dm^3)$^{1-p-q-r}$]
1	1	0	12.25 (0.02)
1	1	1	18.34 (0.01)
1	2	0	15.44 (0.03)
4	3	0	49.15 (0.07)

[a] Data are given as overall formation constants (β_{pqr}: $pCu^{+} + qL + rH^{+} \rightleftharpoons Cu_pL_qH_r^{1-p-q-r}$) and are based on eight glass electrode potentiometric titrations (655 points) assuming pK_w = 13.732, and ligand protonation constants: log β_{011} = 10.495, log β_{012} = 18.48, log β_{013} = 20.48. Numbers in parentheses are calculated standard deviations.

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