The Interaction of Thiols with Copper(II): an Electron Spin Resonance Study

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While electron spin resonance (ESR) spectroscopy has been used extensively for the characterization of nitrogen and oxygen donor ligand complexes of copper(II) [1–3] studies involving the interaction of thiol ligands with copper(II) are not well documented. These latter systems have relevance not only for the insight that they may give to the nature of the Cu–S bond in blue copper proteins [4], but also for the growing awareness of the importance of the effects that millimolar cellular thiol concentrations have on the viability of new copper(II) containing drugs [5].

The synthesis and characterization by single crystal X-ray crystallography of copper(II)–thiolate complexes is limited because of the reduction of copper(II) by the thiolate ligand [6]:

$$[Cu^{II}RS]^{+} \longrightarrow Cu^{I} + \tfrac{1}{2}RSSR$$

However it is possible to detect unstable transient copper(II)–thiolate species in frozen solutions by ESR spectroscopy. In this study we have surveyed the interaction of a range of thiols (see Table I) with copper(II) using ESR. By concentrating on the $g_{\|}-|A_{\|}|$ parameter relationship [2, 3] and the distinctive spectral profiles arising from the different coordination spheres we find it is possible to distinguish between 'CuS_4', 'CuS_2O_2' and '$CuSO_3$' donor sets.

Experimental

Electronic and ESR spectra were recorded as previously described [7]. Copper(II)–thiol solutions were prepared using the reactant molar ratios indicated in Table I and immediately frozen in ESR tubes to −160 °C before recording the spectra. The copper salts were either $CuCl_2 \cdot 2H_2O$ or $Cu(CH_3COO)_2 \cdot 1H_2O$.

Results and Discussion

The ESR parameters for the thiol–copper(II) solutions are presented in Table I. The spectra (see Fig. 1) are typical of an approximately axial environment about the copper(II) [1] in that they show a four line $g_{\|}$ region and a strong $g_{\perp}$ region at higher field in the first derivative presentation. The typically low $g_{\|}$ values which can arise when several S donor ligands bind to copper(II) [3] causes an overlapping of the fourth, and often the third, lines (derived from the $M_I = -3/2$ and $M_I = -1/2$ states respectively) with the more intense perpendicular line. In solution therefore, it can be assumed that the complexes formed adopt an approximately tetragonal coordination geometry in which solvent molecules complete the ligand sextet. The discussion that follows will concentrate on the equatorial or in-plane ligands. Blumberg–Peisach plots [2] of $g_{\|}$ *versus* $|A_{\|}|$ for the thiol–copper(II) solutions listed in Table I indicate a clustering into three distinct regions (Fig. 2).

The assignment of the ligand donor sets (*viz.* 'S_4', 'S_2O_2' and 'SO_3') which give rise to the diagonal

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TABLE I. ESR Spectral Parameters for the Copper(II)–Thiol Complexes

Thiol	Thiol:Cu(II) ratio on mixing	Solvent	$g_{\|}$	$10^4 \times \|A_{\|}\|$ (cm^{-1})	$g_{\perp}$	Proposed donor set
2,3-Dimercaptopropane sulphonic acid	2:1	H_2O	2.093	143	2.024	S_4
2,3-Dimercaptosuccinic acid	2:1	MeOH	2.097	151	2.031	S_4
1,2-Dimercaptoethane (disodium salt)	20:1	EtOH	2.094	165	2.015	S_4
4-Mercaptopyridine	4:1	H_2O	2.092	158	2.015	S_4
2-Mercapto-3-pyridinol	2:1	EtOH	2.175	195	2.035	S_2O_2
Thiomalic acid	2:1	H_2O	2.177	169	2.047	S_2O_2
N-(2-Mercaptopropionyl)glycine	2:1	H_2O	2.194	161	2.049	S_2O_2
2,3-Dimercaptopropane sulphonic acid[a]	1:1	H_2O	2.357	155	2.075	SO_3
Cysteamine hydrochloride	1:1	H_2O	2.360	156	2.073	SO_3
Cysteine hydrochloride	1.43:1	H_2O	2.333	149	2.084	SO_3
Penicillamine	1:1	0.1 M HCl	2.335	161	2.095	SO_3

[a]Spectrum shows some 2:1 complex also present.

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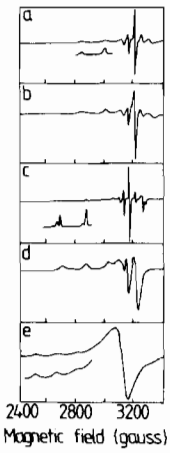

Fig. 1. ESR spectra of thiol–Cu(II) frozen solutions. (a) 1,2-dimercaptoethane/Cu(II) 20:1 (disodium salt). (b) 4-mercaptopyridine/Cu(II) 4:1. (c) 2-mercapto-3-pyridinol/Cu(II) 2:1. (d) *N*-(2-mercaptopropionyl)glycine/Cu(II) 2:1. (e) cysteamine hydrochloride/Cu(II) 1:1.

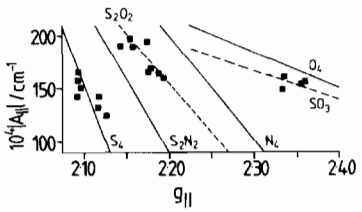

Fig. 2. Plots of $|A_{\|}|$ *vs.* $g_{\|}$ for Cu(II) centres with 'S_4', 'S_2N_2', 'S_2O_2', 'N_4', 'SO_3' and 'O_4' donor sets. Data from this work and refs. 8–11 and 13.

regions in Fig. 2 was made by comparison of the spectra with the few well characterized examples available from the literature coupled with the rationalization of the value of $g_{\|}$ on the basis of the number of equatorial oxygen or sulphur donor atoms. The diagonal line for the 'S_4' donor set is taken from Sakaguchi and Addison [3] as are the 'N_2S_2', 'N_4' and 'O_4' lines which are included for comparison. The 'S_2O_2' and 'SO_3' lines are derived from the present study and in the former case the plot includes examples from other types of Cu(II)–'S_2O_2' complexes [8–11]. In all cases lines only approximate the centres of the $g_{\|}$–$|A_{\|}|$ regions as a function of ligand donor type.

While the details of the spectral profiles can vary somewhat depending on the solvent used some general comments are worth noting. In particular if the spectra are well resolved the $I_{Cu} = 3/2$ coupling, due to ^{63}Cu and ^{65}Cu isotopes, is evident on the $g_{\|}$ line. In principle this should allow 'S_2N_2' and 'S_2O_2' donor sets to be differentiated. Nitrogen donor systems do not show this coupling as a result of N-superhyperfine coupling interactions, which may give rise to a distinctive pattern of lines, dependent on the number of N donor atoms, or simply cause a broadening of the $g_{\|}$ component [1]. The ESR spectrum of the copper(II)/2-mercapto-3-pyridinol solution in ethanol shows an unusual splitting in the $g_{\|}$ region of the $M_I = 3/2$ and 1/2 lines into three and two parts respectively (Fig. 1). The same observation has been noted by Murray *et al.* [8] for another 'S_2O_2' system, bis(*N*-methylformothiohydroxamato)-copper(II), and was ascribed to the solvation of some of the chelate molecules only thus giving rise to two different species with slightly different ESR parameters. Credence to this explanation comes from an earlier study by Brown and West [11] who made similar observations for spectra of the 'S_2O_2' complex, bis(2-thiopyridine *N*-oxide)copper(II), recorded in the presence of amine donors. Thiomalic acid and *N*-(2-mercaptopropionyl)glycine copper solutions also show ESR spectra assignable to 'S_2O_2'–copper moieties. The latter spectrum is similar to that obtained by Sugiura *et al.* [12] under acid conditions (pH 2–4) and with a copper to *N*-(2-mercaptopropionyl)glycine molar ratio of 1:1.

To our knowledge there have been no previous reports of ESR data for Cu(II)–'SO_3' coordination spheres. Nonetheless the positioning of the points on the Blumberg–Peisach plot in relation to other more established donor sites lends credence to such an assignment for the compounds so listed in Table I. Thiol–copper(II) coordination in these compounds is implicated by the appearance of intense electronic spectral bands (e.g. $\lambda_{max} = 642$ nm for copper(II)/2,3-dimercaptopropane sulphonic acid and 517 nm for copper(II)/cysteamine hydrochloride) attributable to sulphur to copper charge transfer transitions [6]. Potential nitrogen coordination by the thiols giving rise to the 'SO_3' systems has been prevented by using hydrochloride salts or performing the reaction in dilute HCl.

As previously mentioned, the 'S_4' line is taken from the literature [3] and the points for copper(II) complexes in this work with proposed 'S_4' donor sets fall near this line. Also included on the graph, to show the general usefulness of such plots to characterize transient copper(II) species, are points from some thiourea–copper(II) systems {tetramethylthiourea–Cu(II) $g_{\|}$ 2.117, $|A_{\|}|$ 131 × 10^{-4} cm^{-1}, di-*o*-tolylthiourea–Cu(II) $g_{\|}$ 2.118, $|A_{\|}|$ 143 × 10^{-4} cm^{-1}, *N*,*N*-dimethyl-*N'*-*p*-tolylthiourea–Cu(II) $g_{\|}$ 2.126, $|A_{\|}|$ 125 × 10^{-4} cm^{-1}} [13]. The transient red species were said to be probably complexes between copper(II) and thioureas. The positioning of these points close to the 'S_4' delineator indicates that indeed this is so and in fact 'S_4' donor sets are clearly implicated. Furthermore the points for the thiourea–Cu(II) complexes fall further down the 'S_4' line than the thiol complexes suggesting that the thiourea–'CuS_4' chromophores suffer some distortion towards tetrahedral [3].

Conclusions

The present study has shown that ESR spectroscopy can be used to detect unstable copper(II)–thiol complexes and from plots of the $g_{\|}$ *versus* $|A_{\|}|$ parameters in-plane atom donor sets (e.g. 'S_4', 'S_2O_2' and 'SO_3') can be assigned with reasonable certainty.

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