Stereoelectronic Properties of Metalloenzymes. 4. Bis(imidotetraphenyldithiodiphosphino-*S*,*S'*)copper(II) as a Tetrahedral Model for Type I Copper(II)

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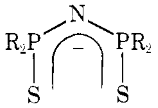
Abstract: The preparation and characterization of bis(imidotetraphenyldithiophosphino-*S*,*S'*)copper(II) is reported. This intensely colored blue complex is proposed as a potential model for type I copper(II) sites in metalloenzymes. The spin Hamiltonian parameters ($A_{\parallel} = 121$ G, $A_{\perp} = 20.2$ G, $\langle a \rangle$ 48.6 G, $g_{\parallel} = 2.107$, $g_{\perp} = 2.030$, and $\langle g \rangle = 2.055$) are consistent with a rather covalent pseudotetrahedral environment. The intense optical electronic transitions at 407 (ϵ 4100) and 575 nm (ϵ 3600) are assigned as $M \rightarrow S(\sigma)$ and $M \rightarrow S(\pi)$ charge transfer bands. Weaker features at 923 nm (ϵ 400) and 1350 nm (very weak) are similar to those reported for type I copper and are assigned as ligand field transitions for the D_{2d} complex. The complex is unstable to autoreduction to copper(I) at room temperature in the solid state and solution. An interpretation of the electron spin resonance parameters and optical absorption values along with a comparison to both type I copper(II) as well as other copper(II) complexes thought to exist in a similar coordination geometry is presented.

Our recent interest has centered not only on the characterization of copper(II) sites in metalloenzymes but also on the design and preparation of copper(II) complexes which mimic aspects of the chemistry and/or physical properties of these copper(II) sites.[2-7] While this "model-building" is a difficult task at best, we have recently reported model complexes which mimic aspects of the optical and electron spin resonance parameters (ESR) for type I[5] and type II[3] copper(II) as well as some chemical features.[7]

Type I copper(II) is thought to exist in a pseudo-tetrahedral environment involving coordination to at least one sulfur atom.[8] Few examples of such a coordination geometry *in solution* exist.

It has been shown recently that imidotetramethyl(phenyl)-dithiodiphosphinate ($SPR_2NPR_2S^-$) forms bis-coordinated



complexes with divalent metals (Mn, Fe, Co, or Ni),[9,10] which have a MS_4 tetrahedral core.[11,12] Churchill et al.,[11] when they reported the crystal structure of the Ni(II) complex where R = methyl, emphasized that the tetrahedral coordination geometry of the complex was *not* the result of steric crowding. It is obviously interesting to pursue this system further, especially if the copper(II) complex could be isolated. An attempt to prepare the copper(II) complex was reported by Davison and Switkes but only a "white" presumably copper(I) product resulted.[9] We have prepared $Cu[SP(C_6H_5)_2NP(C_6H_5)_2S]_2$ by the reaction of the potassium salt of the ligand with $CuCl_2$ in methanol at −78 °C. The resulting dark blue complex is reported as are its physical parameters.

Experimental Section

Materials. All chemicals and solvents were reagent grade and were used without further purification. $ClP(C_6H_5)_2$ and $NH[Si(CH_3)_3]_2$ were obtained from Aldrich Chemical Company.

H(SPh$_2$PNPPh$_2$S). A solution of 20.2 g of $ClP(C_6H_5)_2$ (91.8 mmol) and 7.2 g of $NH[Si(CH_3)_3]_2$ (46.1 mmol) in 80 ml of toluene was stirred and heated to 90 °C for 3 h. During this time $ClSi(CH_3)_3$ (bp 56 °C) was distilled from the reaction flask. The solution was cooled to room temperature and 3.0 g of sulfur (93.5 mmol) was added. The reaction mixture was reheated to 90 °C for 3 h. Upon cooling, the product which precipitates was removed by filtration and was washed by toluene, carbon disulfide, and petroleum ether, respectively, and allowed to dry in air. The yield of product was 14.7 g (70% mp 212–214 °C, lit.[13] 213.5–214.5 °C).

K(SPh$_2$PNPPh$_2$S). The potassium salt of the $(SPPh_2NPPh_2S)^-$ anion was prepared by the published procedures.[13]

Cu(SPh$_2$PNPPh$_2$S)$_2$. A slurry of 1.00 g of $K(SPh_2PNPPh_2S)$ (2.05 mmol) in 20 ml of CH_3OH and a solution of 0.50 g of $CuCl_2 \cdot 2H_2O$ in 4 ml of CH_3OH were mixed at −78 °C with stirring. Upon mixture, a dark blue precipitate formed immediately. The mixture was stirred for a total of 10 min at −78 °C and filtered with a sintered-glass filter which has previously been covered with approximately 0.5 in. of Celite pad. After filtration, the precipitate was washed with cold methanol and recrystallized in the following manner.

The precipitate was covered with a layer of liquid nitrogen and the sintered glass filter was placed on a new receiving flask which contained hexane at −78 °C. After the liquid nitrogen had boiled from the precipitate, cold diethyl ether was added to the precipitate. The resulting solution passed through the Celite pad into the hexane upon sunction and a blue precipitate re-formed immediately. This product was filtered on another sintered-glass filter, washed with two portions of petroleum ether (first portion wash was at −78 °C, second portion was at 25 °C), and air dried, yield 0.30 g, 25%.

Anal. Calcd for $Cu(SPh_2PNPPh_2S)_2$: C, 60.00; H, 4.20; N, 2.92. Found: C, 59.70; H, 4.06; N, 2.96.

The product was stable at room temperature in the solid state for several days. Significant decomposition can be observed after a week. Nonaqueous (CH_2Cl_2) solutions are fairly unstable. A solution at approximately 10^{-3} m will decompose slowly at room temperature. This reaction appears to be first order ($K \cong 2 \times 10^{-3}$ min^{-1}).

Analyses. All analyses were determined by Atlanta Analytical Laboratories, Atlanta, Ga.

Spectroscopy Measurements. Optical spectra were obtained on methylene chloride solutions employing a Cary 14. Spectra were recorded as soon after dissolving a freshly prepared sample as possible and at known times thereafter. An extrapolation of the change in ϵ as a function of time to $t = 0$ (sample dissolution) yielded ϵ for the optical transitions. Optical spectra of mulls in Nujol did not give all the well-resolved peaks obtained in solution but in one case a rather broad asymmetric band near 900 nm. Infrared spectra were determined in Lubinol mulls on a Perkin-Elmer Model 467 spectrometer. X-Band electron spin resonance spectra were determined as before.[3]

Results and Discussion

The optical spectrum of $Cu(SPh_2PNPPh_2S)_2$ in methylene chloride consists of two intense bands at 407 (24 600 cm^{-1}) and 575 nm (17 400 cm^{-1}). The extinction coefficients for

Table I. Spin Hamiltonian Values for $Cu(SPh_2PNPPh_2S)_2$[a]

$g_\parallel = 2.107$ $A_\parallel = 121$ $\langle a \rangle = 46.8$
$g_\perp = 2.030$ $A_\perp = 20.2$ $\langle g \rangle = 2.055$
$\langle g \rangle_{cal}^{+} = 2.050$ $\langle a \rangle_{cal} = 53.8$
$^{+}\langle g \rangle = \frac{1}{3}(g_\parallel + 2g_\perp)$ $\langle a \rangle_{cal} = \frac{1}{3}(A_\parallel + 2A_\perp)$

[a] Values for A in gauss (G).

these two bands are 4100 and 3610, respectively. A distinct band also occurs at 920 nm (10 800 cm^{-1}) with $\epsilon = 400$. A diffuse absorption spectrum in this region of a mulled sample shows a more assymmetric band which might include more than one peak. Near 1380 nm (7250 cm^{-1}) a weak shoulder occurs in both the solution and mulled spectrum but no extinction coefficient could be assigned this feature.

The electron spin resonance parameters for this complex in a frozen methylene chloride glass and solution are given in Table I and shown in Figure 1. The most striking value is the low value of both $A_\parallel$ and $g_\parallel$. All complexes of Cu coordinated to four S atoms previously studied have $A_\parallel$ values in a range of 175–195 G.[14] At the same time, complexes of Cu(II) where a pseudotetrahedral environment is thought to exist as judged by low $A_\parallel$ values envariably yield high $g_\parallel$ values (2.3–2.5).[5,15-17] Such a low $A_\parallel$ value and a low $g_\parallel$ value can result only in a system which is nearly tetrahedrally coordinated and a very covalent system as well.

Assuming therefore that a pseudotetrahedral environment is present, the optical spectrum can be explained in the following manner. The crystal field effect of sulfur ligation is almost always high spin complexes. That is, sulfur coordination, regardless of the type of sulfur ligand, is weak field. We would expect therefore, that the "d–d" bands would be low in energy. An estimation of their value can be obtained by inspecting the single crystal polarized optical spectrum of $Cu(bpy)_2^{2+}$ where pseudotetrahedral coordination is known to exist from the crystal structure.[18] All of the "d–d" bands assigned in this complex occur between 10 and 18 kK. However, the ligand field strength of bipyridyl is nearly twice that of sulfur type ligands. Thus, we would expect that the maximum band arising from "d–d" transitions in this complex would be around 10 kK. This comparison works well in "guessing" the d–d bands in tetrahedral $CuCl_4^{2-}$ where the optical data are also available.[19] Without regard to symmetry considerations, one would suspect that the more covalent bonding normally encountered in M–S complexes would result in more intense transitions than M–N or M–O systems. Thus, the band at 10 kK in this complex is both reasonable in intensity and position to be the highest ligand field transition. *If* a T_d ligand field existed (which is not possible because of Jahn-Teller distoration), this would be the $^2T_2 \rightarrow {}^2E$ transition. However, the weak feature near 7.4 kK suggests a lower local symmetry. The exact nature of this symmetry can only be guessed, however.

More important, however, is that the bands at 575 and 423 nm are too intense and too high in energy to be ligand field in nature. The band at 575 which accounts for the blue color of the complex is probably due to $n \rightarrow \pi^*$ charge transfer resulting from low lying π^* orbitals available on the sulfur. This transition band is not present at this intensity in other complexes which are also pseudotetrahedral but do not contain sulfur.[5,20] The other band at 423 nm is probably due to $n \rightarrow \sigma^*$ charge transfer resulting from low lying σ^* orbitals on the sulfur.

The infrared spectrum of this complex consists of these bands associated with the ligand[13] and new bands at 390, 500, and 650 cm^{-1}. While some of these might be associated with Cu–S stretches, it is difficult to assign those which are M–S and an assignment of symmetry based on these data alone is dangerous.

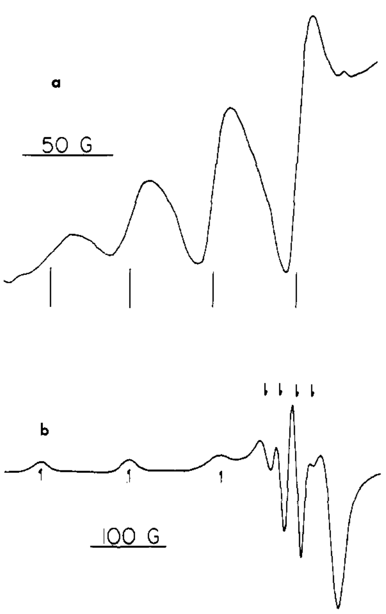


Figure 1. (a) Electron spin resonance spectrum of $Cu(SPh_2PNPPh_2S)_2$ in CH_2Cl_2 at 77 K. (b) Electron spin resonance spectrum of $Cu(SPh_2PNPPh_2S)_2$ in CH_2Cl_2 at room temperature.

Numerous reports of attempts to prepare copper(II) in pseudo-tetrahedral environments or to study Cu(II) atoms in similar solid state environments exist in the recent literature. The overriding goal has been to understand and duplicate physical and chemical properties of type I copper(II) atoms in metalloenzymes. This complex possesses two properties of the type I atoms. (1) An intense optical transition near 600 nm found in all metalloproteins containing a type I copper(II) atom. (2) A low value of $A_\parallel$, which while not below the "magic number" of 100 G which is the upper limit found in proteins, is, when compared to $g_\parallel$, exactly on the ratio of $g_\parallel/A_\parallel$ found for type I atoms. This is not true for other model complexes.

We,[5] as well as others,[21,22] have postulated that the intense band near 600 nm in blue copper proteins was probably charge transfer in nature and probably involved a sulfur ligand atom. It has also been shown that a Cu–S vibrational band exists in type I systems.[8] The complex reported here is the *first* example of pseudotetrahedral environment with sulfur ligation to copper(II). As such, the presence of the intense band at 575 nm which is certainly charge transfer in nature offers strong support to the contention that blue copper proteins are "blue" because of sulfur ligation.[21,22]

A great deal of importance has also been given to the ability to obtain low values for $A_\parallel$ in coordinate complexes of copper(II). At the same time, a compilation of all the spin Hamiltonian parameters for type I copper(II) atoms shows a linear relationship between $g_\parallel$ and $A_\parallel$. The complex studied also lies on the same line at a lower $g_\parallel$ value and a higher $A_\parallel$ value. Other complexes with low $A_\parallel$ values have extremely high $g_\parallel$ values. While the low $A_\parallel$ values and high $g_\parallel$ values are not outside the range found for type I copper(II) atoms, the two values together are inconsistent with the relationship found for the proteins. For example, we recently reported a complex with a coordination environment of 2N and 2Cl atoms. While this complex almost certainly possesses a pseudotetrahedral environment, the $g_\parallel$ value of near 2.3 would require an $A_\parallel$ value of less than 50 G.[5] A value of 90 G was found. Thus, the low value of $A_\parallel$ itself is not a sufficient criteria for duplication of the spin Hamiltonian parameters for blue copper.

We have also shown earlier that the addition of more ionic type ligand atoms (N or O) for sulfur would be expected to lower $A_\parallel$ in a D_{2d} environment without significantly changing the coordination geometry.[5] It can be reasonably assumed that such a change will raise the $g_{\|}$ value at the same time. Since a value of 120 G for $A_{\|}$ is high for a realistic model for type I copper(II), then an environment made up of sulfur(s) and nitrogen(s) atoms is a probable coordination environment. A guess of one sulfur and three nitrogen atoms seems most reasonable based on this work and the recent conclusion of Spiro that a C_3 local symmetry axis existed at the copper center.[8]

One very interesting aspect of this work is simply the observation that the $Cu(SPh_2PNPPh_2S)_2$ complex is redox unstable in the solid state and in solution. At room temperature, the reaction is apparently first order in complex concentration with $K \cong 2 \times 10^{-3}$ min^{-1}, and a half life of ~300 min. It is substantiated that type I copper(II) is involved in a redox mechanism where copper(II) is reduced to copper(I).[23] It is obvious that simple sulfur ligation does not significantly change the Cu(II) → Cu(I) redox couple since square planar CuS_4 complexes are stable. A change in coordination geometry seems required. That fact alone offers a strong argument for the tetrahedral coordination geometry of this complex.

Further studies of this and similar complexes are underway especially with regard to the kinetic properties. Hopefully, a more refined model will include spin Hamiltonian parameters nearer to type I copper(II) as well as an incorporation of the redox couple for these systems.

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Kinetics of Copper(II)-Glycylglycyl-L-histidine Reactions. Acid Decomposition and Proton-Assisted Nucleophilic Displacement by Triethylenetetramine

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Abstract: The presence of histidine as the third amino acid residue in tripeptide complexes of Cu(II) drastically decreases their susceptibility to nucleophilic attack. The rate constant for triethylenetetramine (trien) reaction with $Cu(H_{-2}glyglyhis)^-$ is only 0.5 $M^{-1}\ s^{-1}$ whereas the unprotonated ligand reacts more than 10^7 times faster with $Cu(H_{-2}glyglygly)^-$. However, a previously unobserved pathway is found involving the combined reaction of H^+ and H_2trien^{2+} with $Cu(H_{-2}glyglyhis)^-$ (the value of the third-order rate constant is $1.7 \times 10^9\ M^{-2}\ s^{-1}$). This proton-assisted nucleophilic reaction becomes the major pathway between pH 6.5 and 8.5 even at low trien concentrations. At higher trien concentrations a rate, limited by proton transfer to the peptide nitrogen, is reached and this reaction is general-acid catalyzed. Acid dissociation reactions in the absence of trien require uptake of two protons and the rate changes from a second-order $[H^+]$ dependence at pH 5 to a zero-order $[H^+]$ dependence at pH 1. This is due to the rapid formation of an "outside" protonated species in which the peptide oxygens have protonation constants of $10^{4.2}$ and $10^{2.3}$. These dissociation reactions are limited by metal-peptide bond cleavage and are not general-acid catalyzed.

The displacement of tripeptides from copper(II) complexes of the type $Cu(H_{-2}tripeptide)^-$ has been shown to occur by two general mechanisms involving either acid attack on the deprotonated ligand or nucleophilic attack on the metal ion.[1-4] When histidine is the third amino acid residue in the tripeptide, as in glycylglycyl-L-histidine (glyglyhis), the reactivity of the complex via both these pathways is reduced greatly and a new reaction pathway is found. This new pathway proceeds by a proton-assisted nucleophilic mechanism with the novel feature that the tripeptide displacement is initiated at a non-terminal position.[5]

Histidine is the third amino acid residue in serum albumin (human, bovine, and rat) and it has been proposed that Cu(II) binds preferentially at the amino terminal of serum albumin with coordination of an amino group, two deprotonated peptide nitrogens, and an imidazole nitrogen[6-9] similar to the coordi-