Cupric Complexes Produced from the Reaction of Cupric Nitrate Trihydrate with S-2-Pyridyl Thioates

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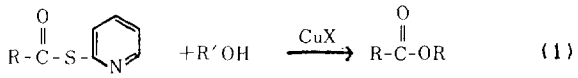
The reaction of cupric nitrate trihydrate with S-2-pyridyl thioates in acetonitrile was studied. The major products were the corresponding carboxylic acids and $[Cu(NO_3)(C_5H_4NS)(C_5H_5NS)]$ (Complex A). Sometimes $[Cu(NO_3)_2(C_5H_4NS)_2(H_2O)]$ was also obtained in addition to Complex A. When Complex A was recrystallized in dimethylsulfoxide, $[Cu(NO_3)_2(C_5H_4NS)_2\{(CH_3)_2SO\}_2]\cdot 2H_2O$ was crystallized. The structures of these copper complexes and the role of cupric nitrate in the hydrolysis of S-2-pyridyl thioates are discussed.

Introduction

Recently some of us reported a rapid and convenient preparation of sterically hindered esters by the reaction of S-2-pyridyl thioates with alcohols in the presence of cupric bromide or chloride.[1]



(1)

During this work we noted formation of an orange precipitate when S-2-pyridyl thioate and cupric bromide were mixed in acetonitrile. The precipitate, when characterized, may shed some light on the role of the copper complex in this reaction. However, the infrared spectrum of the precipitate differed slightly each time it was prepared, indicating that the precipitate was a mixture of several species. In addition, the precipitate did not show any electron paramagnetic resonance (EPR) spectrum. The absence of EPR indicates that the major species are not mononuclear cupric complexes, but either cuprous or multinuclear cupric complexes. We have found that cupric nitrate trihydrate reacts with S-2-pyridyl thioate to produce mononuclear cupric complexes that can be easily characterized. In this paper we report the copper complexes thus obtained and discuss the role of cupric nitrate in the hydrolysis of S-2-pyridyl thioates.

Experimental

Preparation of Compounds. Complex A. An acetonitrile solution of S-2-pyridyl mesitothioate (0.50 mmol) was added to cupric nitrate trihydrate (0.25 mmol) in acetonitrile at room temperature. Yellow-green precipitate was formed in a few hours. The precipitate was collected and washed with acetonitrile several times. Anal.[2] Calcd for $[Cu(NO_3)_2(C_5H_4NS)_2(C_5H_5NS)]$: Cu, 18.2; C, 34.7; H, 2.6; N, 8.1. Found: Cu, 17.1; C, 33.2; H, 2.2; N, 8.27. The same result was obtained when S-2-pyridyl caprylothioate or benzothioate was used instead of mesitothioate.

Complex B. Sometimes needle-shaped crystals grew on top of the precipitate of Complex A. These crystals were separated from the precipitate and analyzed.[2] Calcd for $[Cu(NO_3)_2(C_5H_4NS)_2(H_2O)]$: C, 23.7; H, 2.37; N, 5.50. Found: C, 22.7; H, 2.6; N, 5.82.

Complex C. Complex A was dissolved in warm dimethylsulfoxide, and the solution was set aside for several days. Blue crystals were collected and analyzed. Calcd for $[Cu(NO_3)_2(C_5H_4NS)_2(C_5H_5NS)_2\{(CH_3)_2SO\}_2]\cdot 2H_2O$: Cu, 11.8; C, 31.2; N, 5.2. Found: Cu, 11.9; C, 31.4; N, 5.3.

Spectral Measurements. Infrared spectra were obtained from KBr discs on a Shimadzu IR-440 spectrometer, and EPR spectra were recorded on a Bruker EPR(Model ER 200E) spectrometer operating at 9.4 GHz at 150K.

Results and Discussion

Infrared Spectra. The infrared spectra of Complexes A, B, and C are quite similar as shown in Figure 1. Many bands match closely those of 2-pyridinethione (2-pyt),[3] indicating the presence of 2-pyt and/or the 2-pyridinethiolate anion in the complexes. A coordinated nitrate anion in $Cu(2\text{-pyt})_3(NO_3)_2$ was reported[4] to show two bands at 1460 and 1280 cm^{-1}. Thus the band at 1465 cm^{-1} may be assigned to the coordinated nitrate group. In the region 1250 - 1300 cm^{-1} there are three overlapped bands, two of which may be identified with the bands (observed at 1240 and 1260 cm^{-1}) of 2-pyt.[3] The remaining band may be ascribed to the coordinated nitrate group. The broad bands at 3400 and 1600 cm^{-1} in the spectra of Complexes B and C indicate the presence of either coordinated or lattice water molecule(s). Although the elemental analysis and the mass spectrum show the presence of dimethylsulfoxide molecules in Complex C, the band due to the S=O stretching could not be identified.

EPR Spectra. The frozen solution EPR spectrum of Complex C is characteristic of a mononuclear cupric ($I = 3/2$)[5] complex; see Figure 2(b). The frozen solution spectrum of Complex A dissolved in dimethylsulfoxide shows two sets of four parallel lines, indicating the presence of two species; see figure 2(a). One set matched the spectrum of Complex C, which has two dimethylsulfoxide molecules in addition to the ligands that

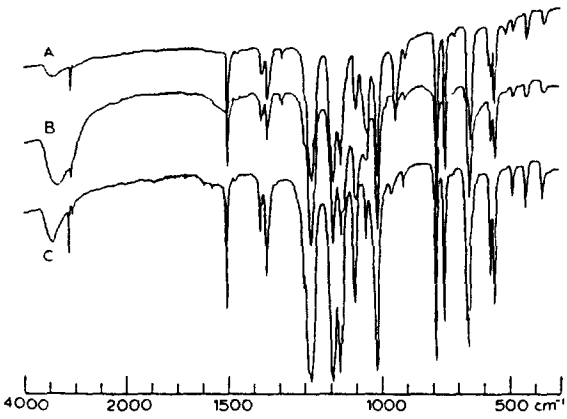


Figure 1. The infrared spectra of Complexes A, B, and C.

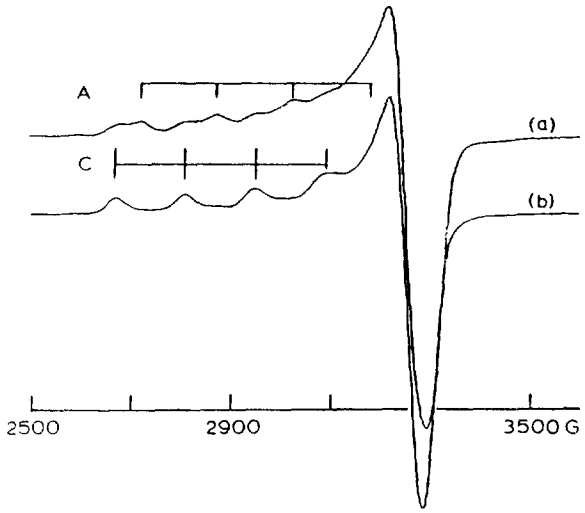


Figure 2. (a) The frozen solution EPR spectrum of Complex A in dimethylsulfoxide at 150 K. Two different species ascribed to Complex A and Complex C are detected. (b) The frozen solution EPR spectrum of Complex C in dimethylsulfoxide. See the text for the chemical formulae of these complexes.

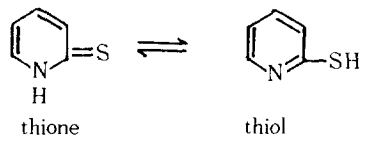
Complex A has. So this set may be ascribed to a species where two dimethylsulfoxide molecules are axially coordinated to Complex A. The other set may be ascribed to Complex A, a square planar cupric complex. It is known that some solvent molecules can coordinate at the axial positions of the square planar cupric complexes.[6]

The spectra have been analyzed by using the following equation:[7]

$$h\nu = g_{11}\beta B + Am + \frac{B^2}{2h\nu}\{I(I+1) - m^2\} \quad (2)$$

An approximate $g_\perp$ value was calculated from the position of the maximum absorption in the spectrum. The resulting parameters are $g_{11}=2.08$, $g_\perp=2.08$, and $|A|=163\times10^{-4}$ cm^{-1} for Complex A and $g_{11}=2.337$, $g_\perp=2.08$, and $|A|=154\times10^{-4}$ cm^{-1} for Complex C. These parameters are in agreement with the theoretical consideration showing that g_{11} increases and $|A|$ decreases when a square planar cupric complex is further coordinated at the axial sites.[6]

Modes of Coordination. Complex A has three different ligands: 2-pyt, the 2-pyridinethiolate anion, and the nitrate anion. In solution 2-pyt can exist in equilibrium with a thiol tautomer.



thione thiol (3)

However, it was shown that the thione tautomer is the dominant form in solution,[8] and that it coordinates to the cuprous ion through the sulfur atom.[9] The same type of coordination is quite likely in Complex A.

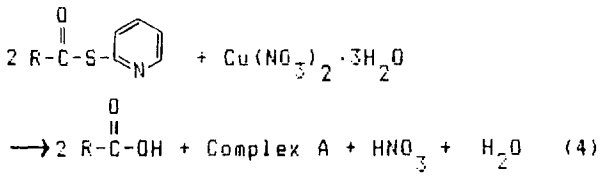
No copper complex with the 2-pyridinethiolato ligand has been reported so far. It is known that the anion coordinates to ruthenium(II) as a bidentate lighand.[10] If it coordinates to the cupric ion as a bidentate ligand, superhyperfine lines due to the nitrogen (I = 1) atom are expected in the EPR spectrum. We have tried to find such superhyperfine lines in both solution and frozen solution spectra without success. Thus we believe that it coordinates to the cupric ion through the sulfur atom only. This conclusion is not unreasonable, for the spatial arrangement of nitrogen and sulfur atoms are unfavorable for the 2-pyridinethiolate ion to become a bidentate ligand.

The cupric ion is most likely to form a square planar complex with four ligand atoms in the absence of steric hindrance. Since 2-pyt and the 2-pyridinethiolate anion occupy only two coordination sites, the nitrate ion should coordinate as a bidentate ligand to form a square planar complex.

When Complex A is dissolved in dimethylsulfoxide, the solvent molecules are expected to axially coordinate to the copper ion without much change in the square plane. Such a species is believed to be Complex C. It is known that dimethylsulfoxide coordinates to copper ions through the oxygen atom.[11]

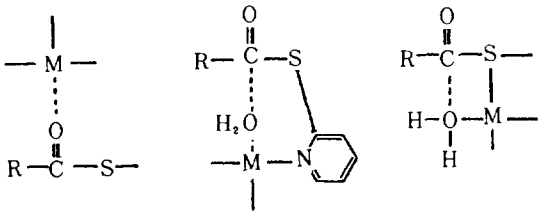
Complex B is a species in which the 2-pyridinethione ligand in Complex A is replaced by a water molecule.

Reaction of Cupric Nitrate Trihydrate with S-2-Pyridyl Thioate. The organic product from the reaction of cupric nitrate trihydrate with S-2-pyridyl thioate was found to be a carboxylic acid.[12] Thus the overall reaction may be written as follows:



(4)

This reaction being a hydrolysis of a thiol ester, the mechanisms proposed for the metal ion catalyzed hydrolysis of esters may apply to this reaction. The role of the metal ion in ester hydrolysis is interpreted in terms of (1) the electrophilic activation of the carbonyl moiety by the metal ion (Scheme 1) and/or (2) the nucleophilic attack of a metal-bound water molecule.[13,14] For the latter mechanism, the substrate molecule must coordinate to the metal ion in such a way that the metal-bound water molecule can easily attack the carbon atom. S-2-pyridyl thioate has two such ligand atoms, namely nitrogen (Scheme 2a) and sulfur (Scheme 2b).



Scheme 1 **Scheme 2a** **Scheme 2b**

If either Scheme 1 or 2a is followed, the next step will be the C-S cleavage. The leaving group, the 2-pyridinethiolate anion, will be either coordinated to the cupric ion or protonated first and then coordinated to the cupric ion. This picture is in accordance with the structure of Complex A, a major product of the reaction. However, there is one serious problem in these mechanisms.

It is known[15] that cupric nitrate is reduced by 2-pyt in ethanol, but that the cuprous complex, $Cu(2\text{-pyt})_3(NO_3)$, can be oxidized to $Cu(2\text{-pyt})_3(NO_3)_2$ by adding cupric nitrate. These reactions may be explained by assuming that the cupric ion is reduced by the thiol tautomer, but not by the coordinated thione tautomer. Since we could not find any evidence for the reduction of the cupric ion in our reaction system, we believe that the cupric ion is attached to the sulfur atom prior to the C-S cleavage and the 2-pyridinethiolate anion is protonated in a coordinated state.

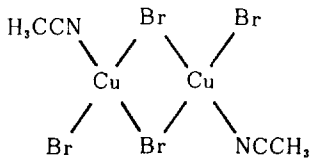
Since two coordination sites of the cupric ion are occupied already by the bidentate nitrato ligand, only two sites are avaiable for the coordination of sulfur atoms. (The axial sites will not be considered, for the copper complexes produced are square planar complexes.) The ligation of the first sulfur atom to the cupric ion and the following hydrolysis may be explained by Scheme 2b.

After the C-S cleavage and loss of the water molecule, the cupric complex has only one vacant coordination site. When it carries a water molecule at this site, it is Complex B. When the second sulfur atom is coordinated at this site, Scheme 2b cannot be applied; a free water molecule must attack the carbon atom. Thus the hydrolysis of the second molecule is expected to be much slower than that of the first one.

An alternative pathway after attachment of the cupric ion to a sulfur atom is the C-S cleavage and formation of an acylium ion, which is rapidly hydrolyzed. So for we have not been able to find an experimental method which can distinguish clearly between the acylium and the non-acylium mehcnaisms.

Our original work was concerned with the esterification of S-2-pyridyl thioates with alcohols in the presence of cupric halide.[1] It was noted that approximately two moles of a thioate were esterified by one mole of cupric halide at room temperature. And the reaction time needed until 95% of S-2-pyridyl mesitothioate was converted into ester was dependent on the mole ratio of the thioate and cupric bromide: 10 min. for 1:1 mixture and 90 min. for 2:1 mixture. For the 2:1 mixture, the first mole was esterified at a much faster rate than the second mole.

These results suggest that the copper complex responsible for the esterification has two coordination sites available for the substrate molecules. One likely species is a binuclear cupric complex with two bridging and two terminal bromo ligands and two acetonitrile ligands, which is known to be formed when cupric bromide is dissolved in acetonitrile.[16]



Since the acetonitrile and the terminal bromo ligands can be easily substituted by other ligands, such a species can use two coordination sites per copper atom to bring a thioate molecule and an alcohol molecule together. If the same mechanism as was proposed above for the hydrolysis is assumed, the first thioate molecule will be esterified rapidly. When one coordination site is occupied by a 2-pyridinethiolato ligand, and the second thioate molecule is coordinated to the cupric ion, the substrate must be attacked by a free alcohol molecule to be esterified. Thus the second thioate molecule will be esterified at a much slower rate than the first one. And the final cupric complex is expected to be diamagnetic due to a strong ferromagnetic interaction between the two cupric ions. These conclusions are in accordance with our observations on the reaction rates and the EPR inactivity of the isolated cupric complex.

However, the difference in the reaction rates of the first and second equivalents of the thioate can also be explained by the acylium mechanism. Here the rate-determining step must be the coordination of the thioate molecule at the axial position of the copper complex leading to the ligand substitution. The charge of the mononuclear moiety of the copper complex is 0 when the first thioate molecule is coordinated, while it is -1 when the second thioate molecule is coordinated. Consequently the second thioate molecule will coordinate to the cupric complex and thus be esterified at a much slower rate than the first one.

In this paper we have speculated on the role of some cupric complexes in the hydrolysis and the esterification of S-2-pyridyl thioates on the basis of the cupric complexes isolated and some observations on the reaction rates. Further work is needed to distinguish between the acylium and the non-acylium mechanisms considered here.

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Theoretical Study on the Role of Water in Anesthesia

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There are lipid phase theories and aqueous phase theories among the theories of anesthesia. For water clusters induced by anesthetizing molecules, the interaction energies are calculated using an empirical potential function and correlated with the anesthetizing partial pressures for mice. A good agreement was obtained with the theory that the water clusters around anesthetics play an important role on the anesthetic actions.

Introduction

General anesthetics don't possess any common physical or chemical feature. Thus, it is thought that only the simplest intermolecular interactions are involved in anethetic actions.

The mechanism of general anesthesia is not known fully yet. Among the physico-chemical theories of anesthesia, there are lipid phase theories[1-4] and aqueous phase theories.[5,6] Lipid phase theories showed good correlations between anesthetic potencies and physical properties as solubility of anesthetics at lipid phase, and suggested that anesthetics act in the lipid region of nerve membrane.

On the other hand, aqueous phase theories were proposed independently by Pauling[5] and Miller.[6] The Pauling theory[5] is that the hydrate microcrystals of anesthetics involving the protein side chains and other charged groups would be formed and interfere with the central nervous system. While Miller[6] proposed that the hydrate microcrystals would not be formed in the body, but the anesthetics would induce the ordering referred to as icebergs in the neighboring water molecules. Pauling[5] pointed out that approximately the same correlation would be found between the anesthetizing partial pressure of non-hydrogen-bonding anesthetic agents and any property involving an intermolecular interaction energy, but water containing ions and proteins with charged side chains is expected to be largely involved in the consciousness actions. Claussen *et al.*[7] suggested that the water structures which constitute the icebergs would be the same water structures surrounding the voids in the hydrates. Therefore it is thought that anesthetizing molecules are enclosed by the hydrate-like structures in the aqueous phase in the body.

In this work, the interaction energies were evaluated for the systems composed of sereval anesthetizing molecules and the surrounding water framework using an empirical potential function.[8] The resulting interaction energies were correlated with the anesthetizing pressures of the anesthetics.

Model System

Small molecules such as xenon(Xe), kripton(Kr), argon(Ar), helium(He), hydrogen(H_2), nitrous oxide(N_2O), and carbon tetrafluoride (CF_4) are surrounded by the water framework composed of 20 water molecules having the structure of pentagonal dodecahedron. Slightly larger molecules such as chloroform ($CHCl_3$), dichlorodifluoromethane(CCl_2F_2), and cyclopropane ($c\text{-}C_3H_6$) are surrounded by the water framework composed of 28 water molecules having the structure of hexakaidecahedron. The water frameworks enclosing no anesthetizing molecule are referred to as the reference water frameworks.

X-ray crystallographic results for gas hydrates[9,10] were used as the initial geometry of water frameworks for energy calculations. The center of each anesthetizing molecule[11] is taken as the center of the water framework enclosing the anesthetic molecule. The geometry of water molecule is taken from the experimental values,[12] *i.e.*, r(O-H) = 0.9572 Å and $\angle HOH = 104.52°$.

Potential Function[8]

The total interaction energy consists of electrostatic, nonbonded, hydrogen-bonding, and polarization energies.

$$E_{tot} = \sum_{i,j \neq hb} \sum (E_{el} + E_{nb}) + \sum_{i,j \neq hb} \sum E_{hb} + \sum_{i,j} \sum E_{pol} \quad (1)$$

Where the first summation is the interaction energy for atoms