Copper(II) Complexes of Histamine and Cysteine Produced by Thiosulfate-Assisted Synthesis Using Copper(I) Cyanide. The in Situ Formation of the Thiocyanate Anion and the 2-Amino-2-thiazoline-4-carboxylic Acid Ligand

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Introduction

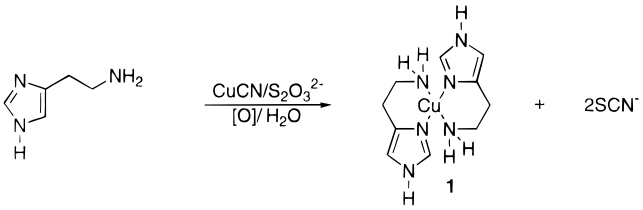
In 1996 we reported a new method for preparing crystalline copper(I) cyanide complexes using thiosulfate-assisted synthesis. Those reports described the preparation of new complexes of thioamides, including thioacetamide[1] and a family of thioureas.[2] Subsequently, while using the new method to prepare a family of crystalline CuCN/imidazole complexes,[3] we subjected both histamine and histidine to the aqueous CuCN/$S_2O_3^{2-}$ reaction medium. Contrary to the course of previous reactions, the reaction solutions with both of these substances rapidly took on a deep blue color that indicated the production of Cu(II). In the histamine reaction solution, a crystalline product was produced after slow evaporation. The X-ray crystal structure revealed the presence of thiocyanate anion, which accounted for the presence of a strong infrared absorption in the 2050 cm^{-1} region. The reaction is shown in Scheme 1.

Given its structure, it seemed almost certain that **1** could be synthesized from histamine and CuSCN. This was easily accomplished after dissolving the CuSCN in $S_2O_3^{2-}$ solution.

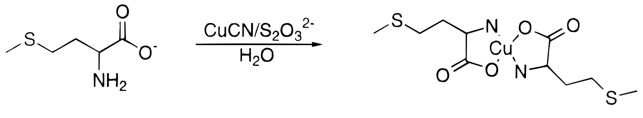
Certain histidine/copper(II) complexes have been shown to have important biological roles. The active site in hemocyanin is believed to comprise histidine units complexed to Cu.[4] A copper(II)−histidine complex has been used as a treatment for Menkes disease, a rare neurological disorder that can afflict young children.[5] Histidine was reacted with CuCN/$S_2O_3^{2-}$ and, although rapid development of a deep blue color was observed, no crystalline product was produced. Subsequently reactions were attempted with several other amino acids.[6] Reaction with methionine produced bis(methioninato)copper(II), which had been prepared using $Cu(OH)_2$ and aqueous methionine by McAuliffe and co-workers in 1966.[7] The crystal structure was reported in 1969.[8] Our synthesis is outlined in Scheme 2.

The reaction of cysteine was unusual in that blue crystals were obtained from a colorless solution. This phenomenon occurred at the solution/air interface. From the X-ray crystal structure it could be seen that the 2-amino-2-thiazoline-4-carboxylic acid (atca) ligand had been produced. The reaction for the synthesis of $Cu(atca)_2(H_2O)$ (**2**) is shown in Scheme 3.

Scheme 1

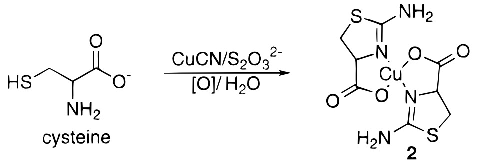


Scheme 2



bis(methioninato)copper(II)

Scheme 3



Experimental Section

General. Commercial chemicals were used without further purification. Infrared spectra were recorded as KBr pellets with a Perkin-Elmer model 1430 spectrophotometer. UV−vis spectra were recorded on a Beckman DU 7400 diode array spectrophotometer. Elemental analyses were determined by Galbraith Laboratories, Knoxville, TN. The crystal structures were determined by the X-ray Service Laboratory, Department of Chemistry, University of Minnesota (Minneapolis, MN).

Preparation of $Cu(SCN)_2(hista)_2$ 1. a. From CuCN. To a solution of 7.446 g (30 mmol) of $Na_2S_2O_3 \cdot 5H_2O$ in 90 mL of distilled water was added 810 mg (9 mmol) of CuCN. Stirring for a few minutes resulted in a clear colorless solution, to which was added 666 mg (6 mmol) of histamine (free base). The stirred solution soon took on a blue color and a greenish precipitate appeared. The latter, which failed to dissolve when the solution was heated on a steam bath, was removed by filtration. The hot filtrate became cloudy upon cooling. The flask was stoppered and set aside for several days. After the first day the solution had become dark blue and was covered with a shiny thin film of green colored material. After the fifth day the blue solution was filtered again, removing the amorphous material which under the microscope looked like glassy plates with black or dark blue particles attached. The blue solution was placed in an evaporating dish and set aside. Eight days later the solution was decanted from a crusty surface coating which prevented evaporation. The following day a good crop of royal blue needles was present which was collected by suction filtration, and washed quickly with a small amount of ice-cold distilled water. Care was taken not to expose the water soluble crystals to excessive washing. The yield was 321 mg (17.7%). IR (KBr): 3305 w, 3200 w, 3122 s, 3035 w, 2960 w, 2910 m, 2060 m, 2040 s, 1597 s, 1584 m, 1498 w, 1475 m, 1460 s, 1435 m, 1400 w, 1350 m, 1322 m, 1270 s, 1233 m, 1197 w, 1180 m, 1137 s, 1090 s, 1065 w, 1017 m, 933 m, 880 w, 830 w, 775 s, 710 w, 650 m, 620 s, 505 w, 475 w, 370 m, 345 w cm^{-1}. UV−vis (H_2O): λ_{max} (ϵ_M) 597 nm (84.6). Anal. Calcd for $C_{12}H_{18}CuN_8S_2$: C, 35.85; H, 4.51; Cu, 15.81; N, 27.87; S, 15.95. Found: C, 35.03; H, 4.51; Cu, 17.68; N, 27.59; S, 15.76.

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[1] Stocker, F. B.; Troester, M. A. *Inorg. Chem.* **1996**, *35*, 3154.

[2] Stocker, F. B.; Troester, M. A.; Britton, D. *Inorg. Chem.* **1996**, *35*, 3145.

[3] Stocker, F. B.; Troester, M. A.; Britton, D. Unpublished work.

[4] Gaykema, W. P. J.; Hol, W. G. J.; Vereijken, N. M.; Soeter, N. M.; Bak, H. J.; Beintema, J. J. *Nature* **1984**, *309*, 23.

[5] Sarkar, B. *J. Pediatrics* **1993**, *123*, 828.

[6] These included alanine, arginine, cysteine, cystine, and methionine.

[7] McAuliffe, C. A.; Quagliano, J. V.; Vallarino, L. M. *Inorg. Chem.* **1966**, *5*, 1996.

[8] Veidis, M. V.; Palenik, G. J. *J. Chem. Soc., Sect. D* **1969**, 1277.

10.1021/ic9814118 CCC: $18.00

b. From CuSCN. To a solution of 2.482 g (10 mmol) of $Na_2S_2O_3 \cdot 5H_2O$ in 30 mL of distilled water was added 242 mg (2 mmol) of CuSCN, which dissolved slowly (~0.5 h with magnetic mixing) producing a clear colorless solution. Histamine (free base, 222 mg, 2 mmol) was added, and the solution rapidly took on a blue color and produced a greenish precipitate. The precipitate darkened over the next half hour until it was gray to black. The precipitate was removed by filtration after 2 h, leaving a deep blue solution. The solution was allowed to undergo slow evaporation over a one week period. Twice during that time a surface crust was removed by filtration. One the eighth day deep blue needles were present. The product (47 mg, 5.8%) was collected by suction filtration and washed quickly with ice-cold distilled water. The IR spectrum was identical to that of the product produced by method **a** above. Found: C, 34.14; H, 4.67; Cu, 15.45; N, 27.51.

Preparation of Cu(atca)$_2$(H$_2$O) 2. To a solution of 7.746 g (30 mmol) of $Na_2S_2O_3 \cdot 5H_2O$ in 90 mL of distilled water was added 810 mg (9 mmol) of CuCN. Stirring for a few minutes resulted in a clear colorless solution, to which were added in succession (magnetic mixing continued throughout the additions), 504 mg (6 mmol) of $NaHCO_3$, and 473 mg (3 mmol) of cysteine·HCl. Within the first 2 h, the clear solution darkened, passing through a faint yellow color, a rich golden color, and finally it took on a brown, opaque appearance. The flask was stoppered and set aside. By the next day a brown precipitate was evident and more brown precipitate continued to form over the next 3 days. Four days after mixing, the fine, fluffy brown precipitate was removed using a retentive grade of filter paper. The now colorless solution was transferred to a set of 6″ test tubes which were covered with filter paper to prevent entry of dust while allowing evaporation and admission of oxygen. Two days later the content of each test tube was filtered again to remove small amounts of brown precipitate. During this filtration, as the solutions percolated through the filter paper, they showed fleeting signs of pale blue color. The solutions were returned to clean test tubes and again covered with filter paper. Three days later blue crystals were observed in the colorless solutions, with most of the crystals floating on the surface while a few had settled to the bottom. Two days hence (11 days since the reaction was started) the product was collected by suction filtration. The combined product from the test tubes amounted to 95 mg (17.0%). IR (KBr): 3470 sh w, 3350 s, 3310 sh w, 3110 m, 2850 w, 1645 s, 1618 sh w, 1565 m, 1440 w, 1403 w, 1365 s, 1310 m, 1280 m, 1228 w, 1135 w, 1100 m, 1018 w, 917 w, 815 m, 750 w, 708 m, 635 w, 590 br w, 525 br w, 460 w, 390 w, 335 w, 305 w cm^{-1}. Anal. Calcd for $C_8H_{12}CuN_4O_5S_2$: C, 25.84; H, 3.25; Cu, 17.09; N, 15.07; S, 17.24. Found: C, 24.20, 25.39; H, 3.48, 3.30; Cu, 16.86; N, 14.77; S, 17.65, 16.81.

X-ray Structure Determinations. Data for **1** were collected on an Enraf-Nonius CAD-4 diffractometer. The intensities of three representative reflections, measured every 100 minutes of X-ray exposure time remained constant throughout data collection; no decay corrections were necessary. Data for **2** were collected on a Siemens SMART system. The fifty frames of data collected at the start of the data collection were re-collected at the end and showed no significant changes; again no decay corrections were necessary. Crystallographic data for **1** and **2** are presented in Table 1. Both structures were solved by direct methods, **1** using the programs MITHRIL[9] and DIRDIF,[10] and **2** using the program SHELXS.[11] The final refinements for both structures were made with full-matrix least-squares refinement on F^2 using the program SHELXL.[11]

Table 1. Summary of X-ray Diffraction Data[a]

	Cu(SCN)$_2$(hista)$_2$ (**1**)	Cu(atca)$_2$(H$_2$O) (**2**)
empirical formula	$C_{12}H_{18}CuN_8S_2$	$C_8H_{12}CuN_4O_5S_2$
fw	401.99	371.88
space group	$P\bar{1}$ (No. 2)	$P2_12_12_1$ (No. 19)
a, Å	8.552 (2)	7.9578 (2)
b, Å	9.254 (2)	8.1505 (2)
c, Å	11.624 (2)	19.5206 (6)
α, deg	87.81 (2)	90.0
β, deg	85.74 (2)	90.0
γ, deg	66.93 (2)	90.0
V, Å^3	844.0 (7)	1266.11 (6)
Z	2	4
D_{calcd}, g/cm^3	1.582 (1)	1.951 (1)
temp, °C	24 (2)	−100 (2)
μ, cm^{-1}	15.44	20.80
transm factors	0.73−0.88	0.59−0.85
R^b	0.044	0.0201
w$R2^c$	0.051	0.0485

[a] Radiation: Mo Kα (graphite monochromated, $\lambda = 0.710\,73$ Å). [b] $R = \sum||F_o| - |F_c||/\sum|F_o|$. [c] $wR2 = \{\sum[w(Fo^2 - F_c{}^2)^2/\sum[w(F_o{}^2)^2]\}^{1/2}$.

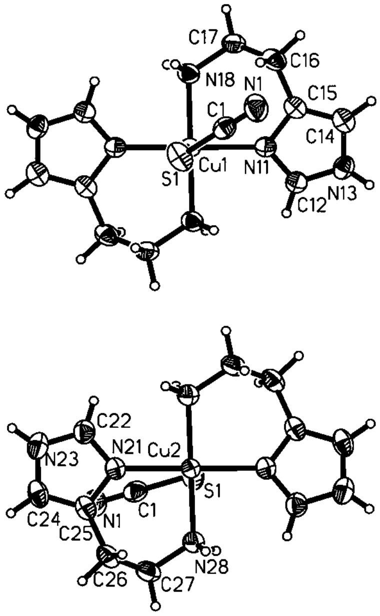

Figure 1. ORTEP plots of Cu(SCN)$_2$(hista)$_2$ (**1**), showing the atom labeling and 50% probability ellipsoids. Hydrogen atoms have been given arbitrary radii. (Top) Cation **1** viewed perpendicular to the CuN$_4$ plane plus one of the two thiocyanate ions to which it is bonded. (Bottom) Similar view for cation **2**, which is shown with the same thiocyanate ion. The other thiocyanate ion, which is not close to either Cu atom, is not shown.

Non-hydrogen atoms were refined anisotropically; hydrogen atoms were included at idealized positions with isotropic displacement parameters 20% greater than the B_{eq} values of the atom to which they were bonded, except for the water H in **2**, which were refined with isotropic displacement parameters. The neutral atom scattering factors used include a correction for the real and imaginary components of the effect of anomalous dispersion.[12]

Discussion

Complex **1** crystallizes in space group $P\bar{1}$ with two molecules in the unit cell. However, there are two crystallographically independent Cu(hista)$_2^{2+}$ ions, each located at a crystallographic center of symmetry. The labeling and anisotropic displacement ellipsoids are shown in Figure 1. Selected bond lengths and angles are given in Table 2. The center of symmetry requires that the CuN$_4$ fragment is exactly planar. The octahedral coordination around the Cu atom is completed by formation of two long (weak) bonds to S. Both Cu atoms bond to S1 so that

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(9) MITHRIL: Gilmore, C. J. *J. Appl. Crystallogr.* **1984**, *17*, 42.

(10) DIRDIF: Beurskens, P. T. Technical Report 1984/1 Crystallography Laboratory: Toernooiveld, 6525 ED Nijmegen, The Netherlands, 1984.

(11) Both SHELXS and SHELXL are included in SHELXTL, Version 5.0, by Sheldrick, G. M. Siemens Analytical X-ray Instruments, Inc., Madison, WI, USA 1994.

(12) (a) Cromer, D. T.; Waber, J. T. *International Tables for X-ray Crystallography*; The Kynoch Press: Birmingham, England, 1974; Vol. IV, (a) Table 2.2A; (b) Table 2.3.1.

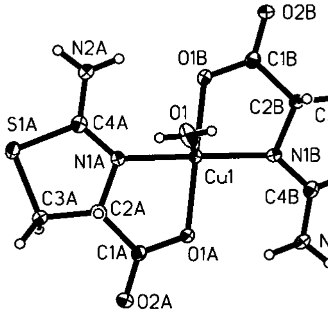


Figure 2. ORTEP plot of Cu(atca)$_2$(H$_2$O) (**2**), showing the atom labeling and 50% probability ellipsoids. Hydrogen atoms have been given arbitrary radii. The view is normal to the mean plane of the CuN$_2$O$_2$ atoms.

Table 2. Selected Bond Lengths (Å) and Angles (deg)

	Cu(SCN)$_2$(hista)$_2$ (**1**)		
Cu1−N11	2.028(3)	Cu2−N21	2.031(3)
Cu1−N18	2.014(3)	Cu2−N28	2.005(3)
Cu1−S1	3.021(1)	Cu2−S1	3.055(1)
N11−Cu1−N18	91.33(12)	N21−Cu2−N28	92.05(12)
N11−Cu1−S1	84.57(8)	N21−Cu2−S1	90.73(9)
N18−Cu1−S1	95.43(8)	N28−Cu2−S1	86.67(10)
Cu1−S1−Cu2	146.12(4)		
	Cu(atca)$_2$(H$_2$O) (**2**)		
Cu1−N1A	1.930(2)	Cu1−N1B	1.929(2)
Cu1−O1A	2.013(2)	Cu1−O1B	2.011(2)
Cu1−O1	2.417(2)		
N1A−Cu1−O1A	82.47(8)	N1B−Cu1−O1B	82.89(8)
N1A−Cu1−N1B	178.57(9)	O1A−Cu1−O1B	165.37(8)
N1A−Cu1−O1	86.71(9)	N1B−Cu1−O1	94.65(9)
O1A−Cu1−O1	109.19(8)	O1B−Cu1−O1	85.39(8)

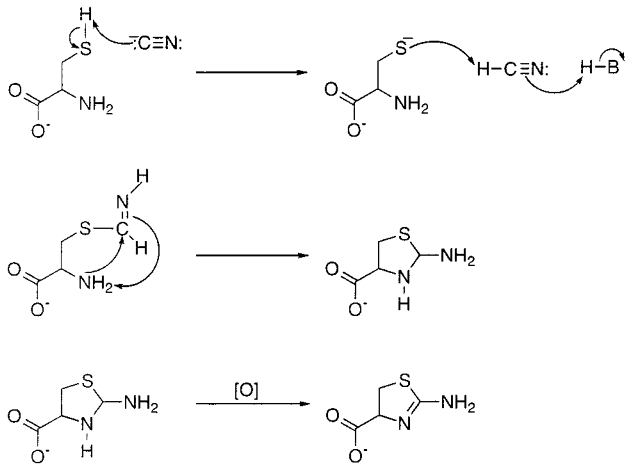
infinite chains Cu1···S1···Cu2···S1 are formed parallel to the *c* axis. The other SCN$^-$ ion is not coordinated to Cu.

The labeling and anisotropic displacement ellipsoids for **2** are shown in Figure 2. Selected bond lengths and angles are given in Table 2. The molecule has no required crystallographic symmetry; it has a five-coordinate Cu ion with a geometry closer to square pyramidal than to trigonal bipyramidal. The water molecule, at the apex of the square pyramid, has a longer (weaker) bond to Cu.

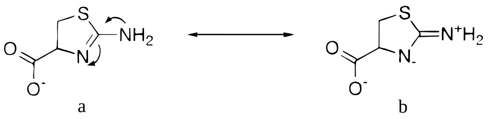
The production of the thiocyanate anion evidently occurs via nucleophilic attack by cyanide ion on thiosulfate ion. This transformation is similar to the reaction of cyanide ion with S$_8$ that produces thiocyanate ion, as outlined by Cotton and Wilkinson.[13] Either histamine or Cu^{2+} must promote this reaction because thiocyanate ion has not been observed in dozens of other preparations using CuCN/S$_2$O$_3$$^{2-}$ and ligand.

The creation of the 2-amino-2-thiazoline ring system from cysteine and cyanide ion is shown in Scheme 4.

Scheme 4



Scheme 5



An acid−base reaction between cyanide ion and the thiol produces HCN and the thiolate ion. Nucleophilic addition of the thiolate ion to the carbon−nitrogen triple bond, followed by proton transfer, generates a thioimidate. Nucleophilic addition of the amino nitrogen atom to the carbon−nitrogen double bond leads to formation of the saturated heterocycle, which is oxidized to the unsaturated analogue by molecular oxygen. During the preparation of **2**, the blue crystalline product appears at the surface of the colorless reaction solution, suggesting that oxygen from the air plays the role of the oxidizing agent. Only one citation appears in the literature for 2-amino-2-thiazoline-4-carboxylic acid, namely, a German patent that reports its synthesis from H$_2$NC(:NH)SCH$_2$CHClCO$_2$H by dehydrochlorination using aqueous ammonia and heat.[14]

From the relative stabilities of the contributing forms to the resonance hybrid of 2-amino-2-thiazoline (Scheme 5), the differences in C−N bond lengths can be understood. Resonance form **a** contributes more to the hybrid because it has none of the destabilizing effects of the charge separation in **b**.

The observed ring C−N bond length is 1.299 (3) Å, whereas the observed exocyclic C−NH$_2$ bond length is 1.334 (4) Å, both in accord with the predicted character of the hybrid. A typical C═N bond length (sp^2−N) is about 1.28 Å (oximes, imines), whereas a typical C−N (sp^2−N) is about 1.38 Å (formamide).[15]

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Supporting Information Available: X-ray crystallographic files for structures **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed.; John Wiley and Sons: New York, 1988; p 498.

(14) Togo, K.; Tamura, F.; Yasuda, N.; Ichikawa, T.; Sano, K.; Matsuda, K.; Mitsugi, K. The conjugate addition of thiourea to methyl choloroacrylate produced the precursor. Ger. Offen. DE 2650783, 1977.

(15) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley and Sons: New York, 1992; p 21.