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Synthesis, Characterization, and Reactivity of New Copper(II) Complexes of 2-Methylthio-*N*-(2-pyridylmethyl)acetamide

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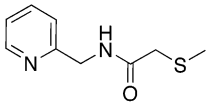
Copper(II) complexes were prepared with the new N_2S(thioether) ligand 2-methylthio-*N*-(2-pyridylmethyl)acetamide (2-HL^{N2S}). [Cu(2-L^{N2S})Cl(MeOH)], which formed in the presence of excess triethylamine, is a distorted square pyramidal complex containing the ligand with the amide nitrogen deprotonated. The structurally analogous complex, [Cu(2-HL^{N2S})Cl_2], which formed in the absence of triethylamine, contains 2-HL^{N2S} in the tautomeric imidic acid form. Neutral copper(II) N_2S(thioether)S(thiolate) species were generated by addition of alkyl or aromatic thiolates to [Cu(2-L^{N2S})Cl(MeOH)] and an unusual decomposition pathway was discovered.

The coordination chemistry of copper with sulfur-containing ligands has attracted considerable interest because of its relevance to bioinorganic chemistry. Copper thiolate and thioether complexes are of particular interest because of their key roles in a number of ubiquitous metalloproteins such as the type 1 copper electron transfer sites found in cupredoxins.[1] Type 1 copper centers contain a copper ion coordinated by a distorted tetrahedral arrangement of His_2-CysMet (e.g., plastocyanin[2]), an axially elongated trigonal bipyramidal array of His_2CysMetGly (e.g., azurin[3]), or a distorted trigonal planar array of His_2Cys (e.g., azurin mutants[3]). In each case, the cysteine residue donates a thiolate sulfur atom to copper, and in the first two cases methionine donates a thioether sulfur atom. In what can be described as a binuclear version of the type 1 copper center, the Cu_A electron transfer site, found in both cytochrome *c* oxidase (CcO)[4] and nitrous oxide reductase (N_2OR),[5] contains two copper ions bridged by two cysteine thiolates.[6] Copper metallothioneins contain copper(I) ions coordinated exclusively by cysteine thiolate ligands.[7] A methionine thioether sulfur atom and two histidines coordinate to the copper ion in Cu_B from the peptidylglycine α-hydroxylating monooxygenase (PHM) domain of peptidylglycine α-amidating monooxygenase (PAM).[8] And finally, inorganic sulfide is found in the unprecedented catalytic Cu_Z site from N_2OR.[9] The diverse and plentiful copper−sulfur chemistry in these systems has inspired us to investigate the chemistry of copper complexes of a new thioether-containing ligand. Herein we report preliminary results of an investigation into the synthesis and characterization of mixed thiolate/thioether copper(II) complexes with pyridyl/amide/thioether supporting ligands. We have synthesized new N_2S(thioether) ligands and their copper(II) complexes, probed their thiolate reactivity, and discovered an unusual redox decomposition pathway.



2-HL^{N2S}

The new ligand 2-methylthio-*N*-(2-pyridylmethyl)acetamide (2-HL^{N2S}) was synthesized by DCC-mediated coupling of methylthioacetic acid to 2-picolylamine.[10−12] Ligand 2-HL^{N2S}, which is reminiscent of the N_3S(thioether) tetra-

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(1) Solomon, E. I.; Szilagyi, R. K.; George, S. D.; Basumallick, L. *Chem. Rev.* **2004**, *104*, 419−458.
(2) Freeman, H. C.; Guss, J. M. In *Handbook of Metalloproteins*; Wieghardt, K., Ed.; Wiley: Chichester, 2001; Vol. 2, pp 1153−1169.
(3) Kolczak, U.; Dennison, C.; Messerschmidt, A.; Canters, G. W. In *Handbook of Metalloproteins*; Messerschmidt, A., Huber, R., Poulos, T., Wieghardt, K., Eds.; Wiley: Chichester, 2001; Vol. 2, pp 1170−1194.
(4) Tsukihara, T.; Aoyama, H.; Yamashita, E.; Tomizaki, T.; Yamaguchi, H.; Shinzawa-Itoh, K.; Nakashima, R.; Yaono, R.; Yoshikawa, S. *Science* **1995**, *269*, 1069−1074.
(5) Brown, K.; Tegoni, M.; Prudêncio, M.; Pereira, A. S.; Besson, S.; Moura, J.; Moura, I.; Cambillau, C. *Nat. Struct. Biol.* **2000**, *7*, 191−195.
(6) Farrar, J. A.; Neese, F.; Lappalainen, P.; Kroneck, P. M. H.; Saraste, M.; Zumft, W. G.; Thomson, A. J. *J. Am. Chem. Soc.* **1996**, *118*, 11501−11514.
(7) Henkel, G.; Krebs, B. *Chem. Rev.* **2004**, *104*, 801−824.
(8) Prigge, S. T.; Eipper, B. A.; Mains, R. E.; Amzel, L. M. *Science* **2004**, *304*, 864−867.
(9) (a) Alvarez, M. L.; Ai, J. Y.; Zumft, W.; Sanders-Loehr, J.; Dooley, D. M. *J. Am. Chem. Soc.* **2001**, *123*, 576−587. (b) Ghosh, S.; Gorelsky, S. I.; Chen, P.; Cabrito, I.; Moura, J. J. G.; Moura, I.; Solomon, E. I. *J. Am. Chem. Soc.* **2003**, *125*, 15708−15709.
(10) DCC = 1,3-dicyclohexylcarbodiimide. DCC-mediated coupling of amines with carboxylic acids was used previously in our laboratory to synthesize ligand−peptide conjugates. Mondal, A.; Klein, E. L.; Khan, M. A.; Houser, R. P. *Inorg. Chem.* **2003**, *42*, 5462−5464.
(11) See Supporting Information for synthetic details and characterization.
(12) The 3- and 4-substituted isomers, 2-methylthio-*N*-(3-pyridylmethyl)-acetamide (3-HL^{N2S}) and 2-methylthio-*N*-(4-pyridylmethyl)acetamide (4-HL^{N2S}), have also been synthesized. Their syntheses, characterization, and coordination chemistry will be reported elsewhere.

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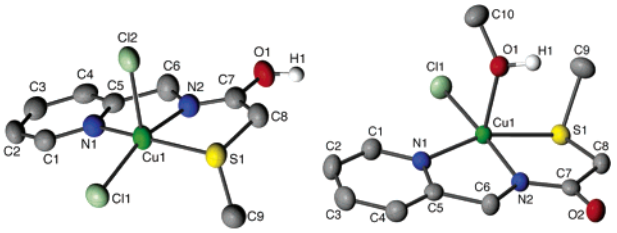

Figure 1. X-ray crystal structure of **1** (left) and **2** (right) as 50% thermal ellipsoids. Only the imidic acid H1 (**1**, left) and the methanol H1 (**2**, right) hydrogen atoms are shown for clarity.

Table 1. Bond Lengths (Å) for **1** and **2**

	1	**2**
Cu1−N1	2.015(3)	2.0194(12)
Cu1−N2	1.950(3)	1.9316(11)
Cu1−S1	2.3670(9)	2.3322(4)
Cu1−Cl1	2.2369(9)	2.2382(4)
Cu1−Cl2[a]	2.6479(10)	
Cu1−O1[b]		2.3293(10)
C7−O1[a]/C7−O2[b]	1.318(4)	1.2519(16)
C7−N2	1.277(4)	1.3176(17)

[a] Complex **1** only. [b] Complex **2** only.

dentate ligand *N*-(2-pyridylmethyl)-2-((2-aminoethyl)thio)-acetamide (pygeH),[13] contains pyridyl and thioether functional groups connected by an amide linkage, providing up to four potential ligand donor atoms: N(py), N(amide), O(amide), and S(thioether). Indeed, in the case of copper complexes of the closely related *N*-(2-pyridylmethyl)acetamide (2-HL^{N2}), the ligand coordinates through all three potential donor atoms, N(py), N(amide), and O.[14]

The reaction of 2-HL^{N2S} with $CuCl_2 \cdot 2H_2O$ in methanol resulted in tautomerization of the ligand amide bond to its corresponding imidic acid form upon coordination to copper(II), generating deep blue [Cu(2-HL^{N2S})Cl$_2$] (**1**).[11] The X-ray crystal structure of **1** (Figure 1, left)[15] reveals that the copper ion is coordinated by 2-HL^{N2S} via its N(py), N(amide), and S(thioether) donors in three basal plane positions of the square pyramidal complex ($\tau = 0.02$),[16] while the fourth basal position and one axial position are occupied by chloride ligands. The imidic acid form of 2-HL^{N2S} is evident in the C7−N2 and C7−O1 bond distances (Table 1), as well as in the presence of the hydrogen atom H1 bonded to O1.

When the reaction of 2-HL^{N2S} with $CuCl_2 \cdot 2H_2O$ is carried out in the presence of excess of triethylamine, 2-HL^{N2S} is deprotonated to [2-L^{N2S}]$^-$ and [Cu(2-L^{N2S})Cl(MeOH)] (**2**) is obtained.[11] The structure of **2** (Figure 1, right)[15] is similar to that of **1** in that the ligand coordinates to copper(II) in the three basal plane positions of the distorted square-pyramidal complex via its N(py), N(amidate), and S(thioether) donors, but while 2-HL^{N2S} is neutral in **1**, the amide group in **2** is deprotonated and [2-L^{N2S}]$^-$ is anionic. Consequently, only one chloride, located trans to N2, is found coordinated in **2**, while the axial coordination site is occupied by MeOH. With the exception of the axial ligands, the bond distances and angles around the copper atoms in **1** and **2** are remarkably similar (see Table 1). The axial Cu1−O1 bond distance in **2** is more than 0.3 Å shorter than the Cu1−Cl2 distance in **1**. This shorter axial bond length in **2** is accompanied by a shifting of the copper atom out of the basal plane, giving rise to a larger τ value of 0.21.[16] The tautomeric relationship of the ligands in **1** and **2** is illustrated quantitatively by the C−N and C−O bond distances highlighted in Table 1, which support the assignment of the imidic acid form of the ligand in **1** and the amidate form of the ligand in **2**. It is noteworthy that **2** is structurally and spectroscopically similar to [Cu(pyge)Br].[13c] With the exception of the axial Cu(II)−ligand bond and the Cu(II)−halide bonds, the solid state structural parameters for **2** and [Cu(pyge)Br] are nearly identical. However, while the structure of **2** is a slightly distorted square pyramid ($\tau = 0.21$), [Cu(pyge)Br] has a τ value of 0.01,[13c] making it a nearly ideal square pyramid.

The similarity of the N_2S(thioether) ligand set in **2** to the His_2Met ligands of the type 1 copper site in azurin prompted us to attempt the synthesis of thiolate complexes of **2**. Methanol solutions of **2** were treated at −80 °C with thiols 2,6-dimethylthiophenol (HSAr) or triphenylmethylmercaptan ($HSCPh_3$), in the presence of triethylamine to deprotonate the thiols in situ. Alternatively, **2** was treated with the sodium thiolate salts of HSAr and $HSCPh_3$, producing the same products. The reactions occur spontaneously and are accompanied by dramatic color changes of scarlet red for **2**(SAr) and intense green for **2**($SCPh_3$). While solutions of both **2**(SAr) and **2**($SCPh_3$) are stable at −80 °C, they decompose rapidly at room temperature (vide infra), thwarting recrystallization attempts.

The spectroscopic properties of **2**(SAr) and **2**($SCPh_3$) support their formulation as copper(II) thiolate species. The EPR spectra of both **2**(SAr) and **2**($SCPh_3$) differ considerably from the EPR of **2** alone,[11] suggesting significant geometric and electronic changes in the coordination sphere around the copper ion. Furthermore, the UV−vis spectra of **2**(SAr) and **2**($SCPh_3$) are dominated by strong absorptions at 496 and 428 nm, respectively [see Supporting Information for **2**(SAr) and Figure 2 for **2**($SCPh_3$)]. These absorptions have been tentatively assigned as S(thiolate) → Cu(II) LMCT transitions. Additionally, the copper(II) d−d transition is shifted upon thiolate coordination from 642 nm for **2** to 555 nm for **2**($SCPh_3$) along with an increase in intensity ($\epsilon = 500$ M^{-1} cm^{-1}).

(13) (a) Toscano, P. J.; Marzilli, L. G. *Inorg. Chem.* **1983**, *22*, 3342−3350. (b) Toscano, P. J.; Belsky, K. A.; Engelhardt, L. M.; Fordon, K. J.; White, A. H. *Inorg. Chem.* **1990**, *29*, 1357−1359. (c) Toscano, P. J.; Fordon, K. J.; Macherone, D.; Liu, S.; Zubieta, J. *Polyhedron* **1990**, *9*, 2375−2383.

(14) Mondal, A.; Li, Y.; Khan, M. A.; Ross, J. H., Jr.; Houser, R. P. *Inorg. Chem.*, in press.

(15) X-ray data collection was performed on a Bruker Apex CCD diffractometer with Mo Kα radiation (0.71073 Å) at 153 K for **1** and 120 K for **2**. X-ray data for **1**: $C_9H_{12}Cl_2CuN_2OS$, $M = 330.71$, trigonal, space group $P3_1$, $a = 6.9560(8)$ Å, $c = 21.791(5)$ Å, $V = 913.1(3)$ Å^3, $Z = 3$, $\rho_{calcd} = 1.804$ g/cm^3, R1 = 0.025, wR2 = 0.062, GOF = 1.023. X-ray data for **2**: $C_{10}H_{15}ClCuN_2O_2S$, $M = 326.29$, triclinic, space group $P1$, $a = 7.3002(3)$ Å, $b = 8.2461(4)$ Å, $c = 10.8430(5)$ Å, $a = 78.0590(10)°$, $b = 80.3540(10)°$, $c = 84.5680(10)°$, $V = 628.36(5)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.725$ g/cm^3, R1 = 0.020, wR2 = 0.051, GOF = 1.051.

(16) $\tau = (\beta - \alpha)/60$. Addison, A. W.; Rao, T. N.; Reedijk, J.; van Rijn, J.; Verschoor, G. C. *J. Chem. Soc., Dalton Trans.* **1984**, 1349−1356.

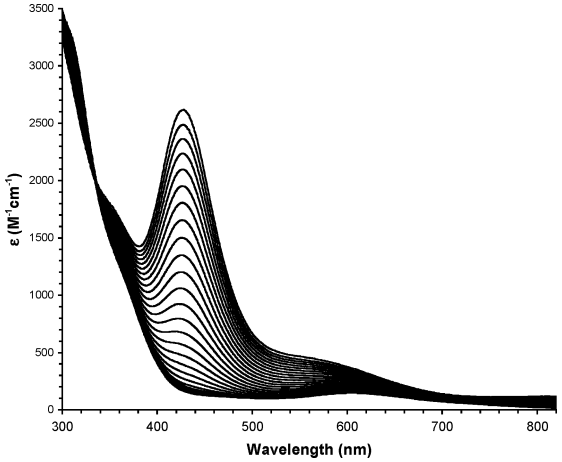

Figure 2. Decomposition of **2**($SCPh_3$) in THF at room temperature. Scans were collected every 10 min.

With the notable exceptions of several stable copper(II)[17] and mixed valence thiolate complexes,[18] copper(II) thiolates are readily reduced to copper(I) with concomitant oxidation of thiolate to disulfide.[19] However, our preliminary experiments suggest that the decompositions of **2**(SAr) and **2**($SCPh_3$) proceed by way of an alternate pathway. When solutions of **2**($SCPh_3$) or **2**(SAr) are allowed to equilibrate at room temperature, their color surprisingly changes back to the blue color of the starting material, **2**. The decomposition of **2**($SCPh_3$) was followed by UV−vis spectroscopy in THF (Figure 2) and was observed to proceed cleanly as per the isosbestic point at 338 nm. While the S(thiolate) → Cu(II) LMCT band at 428 nm completely diminishes, the 555 nm d−d band undergoes a red shift of about 50 nm, with the final spectrum corresponding to the spectrum of **2** in the same solvent. The amount of **2** was quantified by UV−vis spectrometry, corresponding to exactly half of the original amount of **2**. Furthermore, the identity of the blue species was verified by X-ray crystallographic analysis of **2** recrystallized from the decomposition solution. A white precipitate with the empirical formula [Cu($SCPh_3$)] was also isolated and quantified gravimetrically, accounting for 50% of the copper ions and half of the $HSCPh_3$.[20] A mixture of organic products, including the other half of the $HSCPh_3$ in the form of disulfide and ligand products, was isolated from the decomposition solution by flash column chromatography.[21]

From these observations, it is apparent that only half of the copper(II) is reduced, leaving the remainder unchanged as **2**. Furthermore, only half of the thiolate is oxidized to disulfide. When 2 equiv of thiolate is added to **2**, all of the Cu(II) is reduced, as indicated by the complete bleaching of the solution and formation of [Cu($SCPh_3$)].[20] The absence of any observable features in the UV−vis or EPR of this decomposition solution confirms the absence of any detectable quantities of Cu(II). These data are consistent with the reactions illustrated in eqs 1 and 2, where the slow redox formation of Cu(I) is followed by a fast step where the Cu(I) sequesters the thiolate from the remaining $Cu^{II}(2\text{-}L^{N2S})(SR)$ species, producing $Cu^{I}(SR)$ and $Cu^{II}(2\text{-}L^{N2S})$. Thus, 2 equiv of thiolate are required to reduce the copper(II) since 1 equiv of thiolate is sequestered by $Cu^{I}(SR)$.

$$Cu^{II}(2\text{-}L^{N2S})(SR) \xrightarrow{\text{slow}} Cu^{I} + RSSR + 2\text{-}HL^{N2S} \quad (1)$$

$$Cu^{I} + Cu^{II}(2\text{-}L^{N2S})(SR) \xrightarrow{\text{fast}} Cu^{I}(SR) + Cu^{II}(2\text{-}L^{N2S}) \quad (2)$$

In summary, we have synthesized a new ligand, $2\text{-}HL^{N2S}$, that was used to synthesize copper(II) complexes. Thiolate species were identified spectroscopically and decompose by an unusual pathway. We are currently investigating this reaction as well as the coordination chemistry of the related ligands 3- and $4\text{-}HL^{N2S}$.[12]

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Supporting Information Available: X-ray structural information for **1** and **2** (CIF). Full experimental details for $2\text{-}HL^{N2S}$, **1**, and **2**. UV−vis and EPR spectra for **1**, **2**, **2**(SAr), and **2**($SCPh_3$) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

IC049136E

(17) (a) John, E.; Bharadwaj, P. K.; Potenza, J. A.; Schugar, H. J. *Inorg. Chem.* **1986**, *25*, 3065−3069. (b) Kitajima, N.; Fujisawa, K.; Tanaka, M.; Moro-oka, Y. *J. Am. Chem. Soc.* **1992**, *114*, 9232−9233. (c) Houser, R. P.; Halfen, J. A.; Young, V. G., Jr.; Blackburn, N. J.; Tolman, W. B. *J. Am. Chem. Soc.* **1995**, *117*, 10745−10746. (d) Holland, P. L.; Tolman, W. B. *J. Am. Chem. Soc.* **1999**, *121*, 7270−7271. (e) Holland, P. L.; Tolman, W. B. *J. Am. Chem. Soc.* **2000**, *122*, 6331−6332.

(18) Houser, R. P.; Young, V. G.; Tolman, W. B. *J. Am. Chem. Soc.* **1996**, *118*, 2101−2102.

(19) Downes, J. M.; Whelan, J.; Bosnich, B. *Inorg. Chem.* **1981**, *20*, 1081−1086.

(20) The white precipitate, [Cu($SCPh_3$)], was characterized in THF-d_8 by ^1H and ^{13}C NMR and by elemental analysis. Anal. Calcd for $C_{19}H_{15}CuS$: C, 67.33; H, 4.46; N, 0.00; S, 9.46. Found: C, 67.58; H, 4.85; N, 0.17; S, 9.43.

(21) Organic products were separated from the inorganic products and analyzed by GC/MS.