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Functionalized Thiosemicarbazone Clusters of Copper(I) and Silver(I)

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Reaction of $[Cu(MeCN)_4]^+$ with thiosemicarbazones bearing groups such as phenol, pyridine, or ferrocene gives tetranuclear or hexanuclear clusters with functional substituents; analogous air stable fluorescent clusters can also be prepared with Ag(I).

Thiosemicarbazide and thiosemicarbazone complexes of copper have attracted particular attention over the past decade in the context of their wide spectrum of biological activity and applications as radiopharmaceuticals.[1,2] Thiosemicarbazones such as $\mathbf{L^2}$H (Figure 1) are known antitumor compounds, but their copper complexes show enhanced biological activities and are potent cytotoxic agents as well as inhibitors of DNA synthesis.[1] It is thought that the antitumor activity of the copper thiosemicarbazone complexes is due to their ability to inhibit DNA topoisomerase-II (topo-II), an enzyme that regulates the topology of DNA.[2] Very recently analogues of $\mathbf{L^2}$H have been successfully radiolabeled with ^{64}Cu.[3] The resulting compounds showed high uptake in L1210 tumor line cells, which are known to express high levels of topo-II. It is possible that the cellular retention of these compounds involves intracellular reduction of the Cu(II) to a Cu(I) species that may or not be stable inside the cell.[4,5]

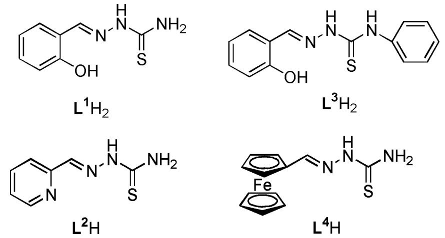

Figure 1. Thiosemicarbazone ligands.

Also, Cu(II) complexes of certain bis(thiosemicarbazones) show high selectivity for hypoxic cells, and this has led to their radiolabeled analogues being used for the positron emission tomography (PET) imaging of tumor hypoxia and radiotherapy.[4,5] Despite the fact that the stability and structure of the Cu(I) species formed in cells is crucial to the hypoxic selectivity and the biological activity of topo-II inhibitors, there are few reports of structurally characterized Cu(I) thiosemicarbazone complexes.[5,6] Also, surprisingly, there have been no structure determinations on Ag(I) thiosemicarbazone complexes although their stoichiometries were first reported more than 20 years ago.[7]

The Cu(II) complex of the thiosemicarbazone of salicylaldehyde ($\mathbf{L^1}H_2$) (Figure 1) can exist both in a monomeric solvated 4-coordinate form and as a phenolic oxygen bridged dimer where each copper is 5-coordinate. The thiosemicarbazone ligand is SNO bound via 5- and 6-membered chelate rings.[8] However, reaction of $\mathbf{L^1}H_2$ with $[Cu(MeCN)_4]PF_6$ in DMF in the presence of triethylamine resulted in the formation of complex **1**.[9] A representation of the structure of **1** appears in Figure 2 together with pertinent bond lengths.[10] The structure consists of 6 copper atoms and 6 thiosemicarbazone ligands which are each singly depro-

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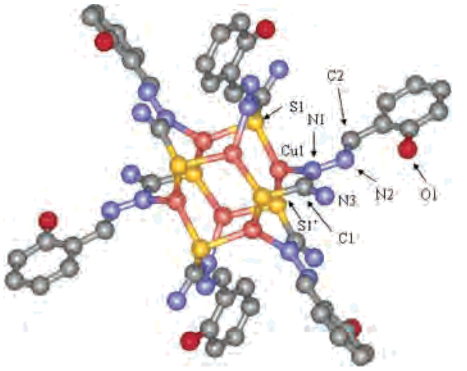

Figure 2. A representation of the X-ray crystal structure of **1** with partial labeling scheme for one of the six symmetry related units. Hydrogen atoms and solvent molecules are omitted for clarity. Selected bond lengths (Å): Cu(1)−N(1), 2.005(2); Cu(1)−S(1), 2.505(7); Cu(1)−S(1)′, 2.389(7); S(1)−C(1), 1.764(3); C(1)−N(1), 1.317(4); N(1)−N(2), 1.395(3); N(2)−C(2), 1.284(4).

tonated. Each copper(I) is considered to be 3-coordinate, coordinated to two thiolate sulfur atoms and one hydrazinic nitrogen, with all six metal atoms in a Cu_6S_6 central core, and each thiolate sulfur bridging two copper atoms. The deprotonation of the ligand on coordination is evident in the observed bond lengths in the cluster. The C−S bond distance increases from 1.689(4) Å in the $\mathbf{L^1}H_2$ to 1.764(3) Å in **1**, and there is also a decrease in length of the C1−N1 bond from 1.346(4) to 1.317(4) Å, indicating that the −N═C−S− thiolate resonance form predominates in the complex. The N−N bond length of 1.395(3) Å suggests little multiple bond character, and there does not appear to be delocalization of electron density as found for other thiosemicarbazone complexes.

The two 6-membered Cu_3S_3 rings are in a chair configuration stacked one above the other and linked together by 6 bridging NCS units of the $\mathbf{L^1}H$ ligands. The six unbound NCC_6H_4OH-2 groups lie alternately to each side of the double ring to give the overall Ferris wheel appearance. The 6 copper atoms are disposed in a compressed octahedral array with two triangles of coppers (Cu−Cu distance 3.226(6) Å) staggered with respect to one another to give an inter-ring Cu−Cu distance of 2.8501(5) Å. The hexameric units lie on a site with crystallographic symmetry 3 (point group S_6). Within the ring systems the Cu−Cu distances are 2.2389(7) and 2.2505(7) Å, indicating slightly asymmetric bridging by the bridging sulfur. Each copper within the Cu_3S_3 rings has approximately trigonal planar coordination with the copper lying 0.27 Å out of the NS_2 plane.

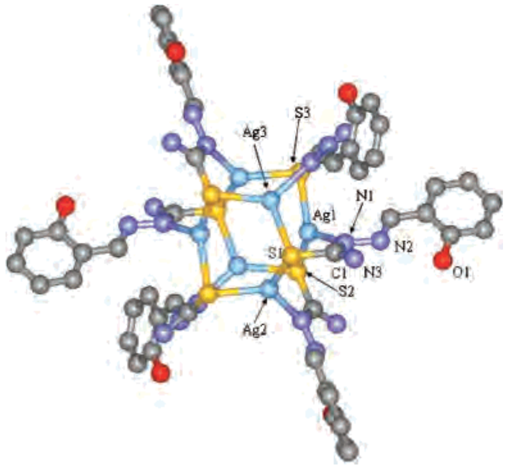

Figure 3. A representation of the X-ray crystal structure of the silver complex, **4**. Hydrogen atoms and solvent molecules are omitted for clarity. Selected bond lengths (Å): Ag(1)−N(1), 2.274(4); Ag(1)−S(2), 2.4799(12); Ag(1)−S(3), 2.5107(11).

This structural motif appears to be highly reproducible, remaining the major product even when the reaction mixture contains a large excess of thiosemicarbazone ligand. Presenting the Cu(I) with an alternative to the phenoxyl donor in the form of a softer donor such as a pyridyl nitrogen, $\mathbf{L^2}H$, did not prevent the formation of an analogous structure, **2**, which retains the Cu_6S_6 core with essentially the same bond distances and angles.[11] Substitution of the thiosemicarbazone with a phenyl group ($\mathbf{L^3}H_2$) and reaction under the same conditions also gave an analogous structure **3**, once again with a similar Cu_6S_6 core showing that the system appears to be tolerant, at least to some extent, to substitution of the NH_2 group.[11] It appears that the high stability of the Cu_6S_6 core and the coordination preferences of Cu(I) provide the driving force for this unusual coordination mode for thiosemicarbazones.

The reaction of $AgBF_4$ with $\mathbf{L^1}H_2$ under the same conditions gives the analogous silver complex, $[Ag_6(\mathbf{L^1}H)_6]$, **4** (Figure 3).[12] Single crystal X-ray crystallography reveals that the silver compound once again contains the same structural motif and the silver compounds provide oxygen-stable alternatives to the copper complexes which rapidly oxidize in the presence of oxygen to give copper(II) complexes. The hexameric silver complex is situated on a crystallographic center of inversion, so the asymmetric unit contains three Ag atoms, three molecules of the ligand, and three molecules of DMF. The complex has a similar connectivity to the Cu analogue, but the geometry is less regular, as illustrated by the wide range of Ag···Ag distances. The "long" distances vary from 3.3913(5) to 3.7202(5) Å

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(9) $[Cu_6(\mathbf{L^1}H)_6](\mathbf{1}\cdot 6DMF\cdot Et_2O)$ (**1**): $[Cu(MeCN)_4]PF_6$ (80 mg, 0.256 mmol) was added under N_2 to a degassed solution of $\mathbf{L^1}H_2$ (50 mg, 0.256 mmol) and Et_3N (36 μL, 0.256 mmol) in DMF (1 mL). The solution was layered with Et_2O, and after 24 h yellow crystals of **1** were obtained (60%). Calcd for $C_{70}H_{100}N_{24}O_{13}S_6Cu_6$: C 40.8, H 4.9, N 16.3. Found: C 40.4, H 5.0, N 16.6. ^1H NMR (300 MHz, d_6-DMSO, 25 °C): δ 1.2 (tr, 6 H; Et_2O), 2.8 (s, 18 H; DMF), 2.9 (s, 18 H; DMF), 6.8 (tr, 6 H; Ar), 6.9 (d, 6 H; Ar), 7.2 (tr, 6 H; Ar), 7.9 (d, 6 H; Ar), 8.0 (s, 6 H; DMF), 8.8 (s, 6 H; HC═N), 10.0 (s, 6 H; OH).

(10) $\mathbf{1}\cdot 6DMF\cdot Et_2O$ ($C_{70}H_{100}Cu_6N_{24}O_{13}S_6$, $M_w = 2059.35$): crystal dimensions 0.20 × 0.26 × 0.26 mm, rhombohedral (obverse trigonal setting), $R\bar{3}$, $a = 20.1483(5)$ Å, $b = 20.1483(5)$ Å, $c = 19.0249(5)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 120°$, $V = 6688.5$ Å^3, $Z = 3$, $\rho_{calcd} = 1.534$ mg m^{-3}, $F(000) = 3192.987$. Radiation: λ(Mo Kα) = 0.71073 Å, $T = 150$ K, reflections collected/unique 15927/3379 ($R_{int} = 0.041$). $R = 0.0346$, $wR = 0.0416$, GOF = 1.0684, max/min residual density 0.88, −0.86 e Å^{-3}. CCDC-215653.

(11) See Supporting Information.

(12) $[Ag_6(\mathbf{L^1}H)_6](\mathbf{4}\cdot DMF\cdot Et_2O)$ (**4**): As for complex **1**[9] except using $AgBF_4$ (50 mg, 0.256 mmol), $\mathbf{L^1}H_2$ (50 mg, 0.256 mmol) and Et_3N (36 μL, 0.256 mmol). **4** was isolated as a yellow crystalline product (63%). Calcd for $Ag_6C_{55}N_{19}S_6O_8H_{65}$: C 33.7, H 3.3, N 13.6. Found: C 34.0, H 3.9, N 13.5. ^1H NMR (300 MHz, d_6-DMSO, 25 °C): δ 2.7 (s, 6 H; DMF), δ = 2.9 (s, 6 H; DMF), 6.7 (tr, 6 H; Ar), 6.8 (d, 6 H; Ar), 7.2 (tr, 6 H; Ar), 7.7 (br, 12 H; Ar and NH_2), 7.9 (s, 2 H; DMF), 8.1 (s, br, 6 H; NH_2), 8.5 (s, 6 H; HC═N), 10.1 (s, 6 H; OH).

(mean 3.5511 Å), while the "short" distances vary from 2.9358(4) to 3.0230(5) Å (mean 2.9923 Å). The bond distances within the ligand are similar to the same distances in the copper analogue. The larger atomic radii of Ag result in longer Ag−N (2.236(4)−2.274(4) Å) and Ag−S ("short" 2.4588(11)−2.4818(11) Å, "long" 2.5050(12)−2.5189(11) Å) bond distances when compared to the copper analogue so the silver complex can be considered as a somewhat expanded analogue of the copper complex.[13] The electrospray mass spectrum of the silver analogue, **4**, in DMF showed a single peak corresponding to the hexameric "Ferris wheel" cluster at $m/z = 1813$. This shows that the silver complex retains its structural integrity in DMF solutions. The complex is fluorescent with an emission at 480 nm (excitation at 380 nm) in DMSO solution.

Reaction of the ferrocenyl−thiosemicarbazone, $\mathbf{L^4}$H, with $AgCF_3SO_3$ under the same conditions resulted in the isolation of an analogous hexameric ferrocenyl substituted cluster, **5**.[14] Cyclic voltammetry measurements in DMF with a platinum working electrode show that this complex undergoes a reversible oxidation at $E_{1/2} = +0.70$ V (vs SCE) with a peak separation of 110 mV. This suggests that the ferrocene units oxidize simultaneously and are not electronically coupled. While similar M_6S_6 cores have been previously reported for Cu(I) and Ag(I),[15] these are the first structurally characterized examples containing thiosemicarbazones with functional substituent groups.

In contrast to the other complexes reported here, complex **6**, isolated from reaction of $\mathbf{L^4}$H with $[Cu(MeCN)_4]PF_6$, gives a completely different tetrameric structure (Figure 4).[16] Once again, the copper atoms are 3-coordinate with a $CuNS_2$ coordination sphere and each ligand is singly deprotonated with each sulfur bridging two copper centers.[17] The tetrahedron of Cu atoms is compressed along a 2-fold axis such that there are two "long" Cu···Cu distances and four "short" distances. The S bridging is more symmetrical than in **1**, and the Cu−S distances are significantly shorter. Unlike **5** the oxidation processes for the ferrocenyl groups are not reversible, presumably as the ferrocenium centers produced are reduced by the Cu(I) centers.

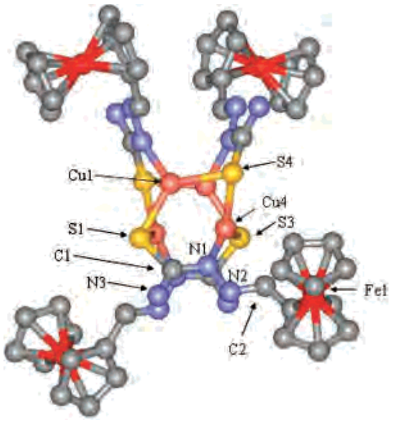

Figure 4. A representation of the X-ray crystal structure of **6**, with partial labeling scheme and hydrogen atoms and solvent molecules omitted for clarity. Selected bond distances (Å): Cu(4)−N(1), 1.997(3); Cu(1)−S(1), 2.2718(9); Cu(4)−S(4), 2.2858(9); Cu(4)−S(3), 2.2687(9); C(1)−S(1), 1.767(3); C(1)−N(1), 1.305(4); N(1)−N(2), 1.411(4); N(2)−C(2), 1.278(4).

The formation of these bicyclic M_6S_6 clusters for both Cu(I) and Ag(I) generates a unique triply bridged bonding mode for the thiosemicarbazone ligands. The Cu(I) complexes, which can be synthesized directly from Cu(I) or by reduction of the Cu(II) complexes, are of interest since the antitumor activity of the Cu(II) complexes could involve intracellular reduction to Cu(I) species. It is also possible to functionalize the thiosemicarbazone ligands to provide donor sites at the cluster periphery with the potential to bind additional metal ions. We are currently exploring the coordination of other metal ions at the peripheral binding sites.

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Supporting Information Available: Experimental details and CIFs. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) $\mathbf{4}\cdot6DMF$ ($Ag_6C_{66}H_{90}N_{24}O_{12}S_6$, $M_w = 2251.18$): crystal dimensions 0.18 × 0.20 × 0.24 mm^3, monoclinic, $P2_1/n$, $a = 15.4658(2)$ Å, $b = 18.2708(3)$ Å, $c = 15.7568(3)$ Å, $\alpha = 90°$, $\beta = 92.5355(7)°$, $\gamma = 90°$, $V = 4448.1$ Å^3, $Z = 2$, $\rho_{calcd} = 1.681$ mg m^{-3}, $F(000) = 2244.598$. Radiation: λ(Mo Kα) = 0.71073 Å, $T = 150$ K, reflections collected/unique 47214/10434 ($R_{int} = 0.064$). $R = 0.0333$, $wR = 0.0377$, GOF = 1.0612, max/min residual density 0.73/−0.71 e Å^{-3}. CCDC-215656.

(14) $[Ag_6(\mathbf{L^4})_6](\mathbf{5}\cdot2DMF)$ (**5**): As for complex **1**[7] except using $AgCF_3SO_3$ (45 mg, 0.175 mmol), $\mathbf{L^4}$H (50 mg, 0.175 mmol), and Et_3N (25 μL, 0.175 mmol). Red crystals of **5** were obtained (74%). Calcd for $Ag_6Fe_6C_{78}N_{20}S_6O_2H_{86}$: C 37.3, H 3.5, N 11.2. Found: C 37.8, H 3.8, N 11.4. ^{1}H NMR (300 MHz, d_6-DMSO, 25 °C): δ 2.8 (s, 12 H; DMF), 2.9 (s, 12 H; DMF), 4.3 (s, 30 H, π-C_5H_5), 4.4 (s, 12 H; π-C_5H_5), 4.7 (s, 12 H; π-C_5H_5), 6.9 (s, 6 H; NH_2), 7.4 (s, 6 H; NH_2), 8.0 (s, 4 H; DMF), 8.2 (s, 6 H; HC=N).

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(16) $[Cu_4(\mathbf{L^4})_4](\mathbf{6}\cdot Et_2O)$ (**6**): As for complex **1**[9] except using $[Cu(MeCN)_4]PF_6$ (60 mg, 0.175 mmol), $\mathbf{L^4}$H (50 mg, 0.175 mmol), and Et_3N (25 μL, 0.175 mmol). Red crystals of **6** were obtained (79%). Calcd for $Cu_4Fe_4C_{52}N12S_4OH_{58}$: C 42.4, H 4.0, N 11.4. Found: C 42.0, H 4.6, N 12.0. ^{1}H NMR (300 MHz, d_6-DMSO, 25 °C): δ 2.7 (s, 6 H; DMF), 2.9 (s, 6 H; DMF), 4.2 (s, 20 H; π-C_5H_5), 4.4 (s, 8 H; π-C_5H_5), 4.7 (s, 4 H; π-C_5H_5), 4.8 (s, 4 H; π-C_5H_5), 7.2 (s, 4 H; NH_2), 7.6 (s, 4 H; NH_2), 7.9 (s, 2 H; DMF), 8.4 (s, 4 H; HC=N).

(17) $\mathbf{6}\cdot3Et_2O\cdot DMF$ ($C_{63}H_{85}Cu_4Fe_4N_{13}O_4S_4$, $M_w = 1694.25$): crystal dimensions 0.22 × 0.22 × 0.26 mm, monoclinic, $P2_1/n$, $a = 12.4351(2)$ Å, $b = 12.3172(2)$ Å, $c = 46.2731(3)$ Å, $\alpha = 90°$, $\beta = 94.4412(3)°$, $\gamma = 90°$, $V = 7066.17$ Å^3, $Z = 4$, $\rho_{calcd} = 1.592$ mg m^{-3}, $F(000) = 3490.924$. Radiation: λ(Mo Kα) = 0.71073 Å, $T = 150$ K, reflections collected/unique 16659/15934 ($R_{int} = 0.056$). $R = 0.0337$, $wR = 0.0389$, GOF = 1.0430, max/min residual density 0.61/−0.44 e Å^{-3}. CCDC-215657.