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Evidence of Desulfurization in the Oxidative Cyclization of Thiosemicarbazones. Conversion to 1,3,4-Oxadiazole Derivatives

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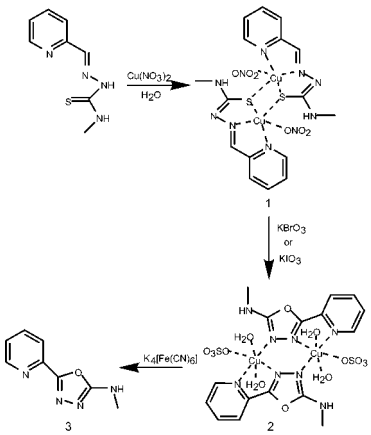
The addition of pyridine-2-carbaldehyde 4*N*-methylthiosemicarbazone ($C_8H_{10}N_4S$) to an aqueous solution of copper(II) nitrate yields [{Cu($C_8H_9N_4S$)(NO_3)}$_2$] (**1**). This complex consists of centrosymmetric dinuclear entities containing square-pyramidal copper(II) ions bridged through the sulfur thioamide atoms. The oxidation of **1** with $KBrO_3$ or KIO_3 gives rise to a compound with formula [{Cu($C_8H_8N_4O$)(H_2O)$_2$(SO_4)}$_2$]·2H_2O (**2**) ($C_8H_8N_4O$ = 2-methylamino-5-pyridin-2-yl-1,3,4-oxadiazole). The structure of **2** is made up of centrosymmetric dimers where the copper(II) ions exhibit a distorted octahedral coordination and are connected by the oxadiazole moiety. The metal ions in **2** can be removed by addition of K_4[Fe(CN)$_6$], and then the oxadiazole ligand can be isolated and recrystallized as ($C_8H_8N_4O$)·3H_2O (**3**).

1,3,4-Oxadiazoles exhibit relevant biological properties and a wide variety of applications, in particular as active compounds in both medicine and agriculture.[1] Several methods have been used for the synthesis of these kinds of compounds from acylic precursors. Some of them are the oxidative cyclizations of acyl hydrazones,[2] acyl thioureas,[3] and acyl thiosemicarbazides.[4]

The present work deals with the oxidation of a copper(II) complex with formula [{Cu($C_8H_9N_4S$)(NO_3)}$_2$] (**1**) ($C_8H_{10}N_4S$ = pyridine-2-carbaldehyde 4*N*-methylthiosemicarbazone), to give the [{Cu($C_8H_8N_4O$)(H_2O)$_2$(SO_4)}$_2$]·2H_2O (**2**) compound ($C_8H_8N_4O$ = 2-methylamino-5-pyridin-2-yl-1,3,4-oxadiazole) in which the ligand has undergone a series of reactions which have been summarized in Scheme 1.

Scheme 1



Compound **1** was synthesized by addition of $C_8H_{10}N_4S$, which was prepared following ref 5, to an aqueous solution of copper(II) nitrate. Dark green single crystals of **1** suitable for X-ray analysis were obtained by slow evaporation of an aqueous solution. The crystal structure of **1**[6] consists of centrosymmetric dinuclear molecules (Figure 1). The copper(II) ions exhibit a square-pyramidal geometry ($\tau = 0.08$) and are bridged through the sulfur thioamide atoms, in a similar way to that observed in copper(II) derivatives of pyridine-2-carbaldehyde thiosemicarbazone.[7]

The addition of potassium bromate (1 mmol, 0.17 g) to an aqueous solution of **1** (0.5 mmol, 0.32 g) gave rise to

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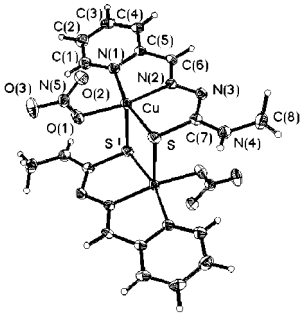

Figure 1. ORTEP plot of **1**. Selected bond distances (Å) and angles (deg): Cu−N2 1.964(2), Cu−O1 1.990(2), Cu−N1 2.028(2), Cu−S 2.2699(6), Cu−S^{I} 2.7659(6), S−C7 1.759(2), N2−C6 1.291(3), N2−N3 1.358(2), N3−C7 1.333(3), N4−C7 1.325(3), N4−C8 1.454(4), N1−Cu−S 164.77(6), N2−Cu−O1 169.78(7), N1−Cu−S′ 92.44(5), intramolecular Cu···Cu^{I} distance 3.4482(2), closest intermolecular Cu···Cu distance 5.7498(4); Cu−S−Cu^{I} 85.83(2) ($I = -x + 1, -y, -z$).

compound **2** (Scheme 1). The solution was allowed to stand at room temperature for 2 days, and green crystals of **2** appeared. Compound **2** is stable in air at room temperature for months. The crystal structure of **2**[8] is made up of centrosymmetric entities (Figure 2). The metal ions exhibit a distorted octahedral coordination and are connected by the oxadiazole moiety. Note the presence of sulfate groups in this compound which arose from the oxidation of the sulfur thione atoms.

We have also obtained oxadiazole derivatives from the oxidative attack on an analogous ligand as pyridine-2-carbaldehyde thiosemicarbazone (yield = 58%).[9] However, we were not able to obtain the same results with pyridine-2-carbaldehyde 4,4′-*N*-dimethylthiosemicarbazone. The use of potassium iodate instead of potassium bromate yielded cyclization (yield = 40%), but reactions with potassium chlorate and hydrogen peroxide were not successful. The rate of the reaction increased with heating, but the oxidation process led to the attainment of bis(pyridinecarboxylate)-copper(II) Cu(py-COO)$_2$·2H$_2$O.

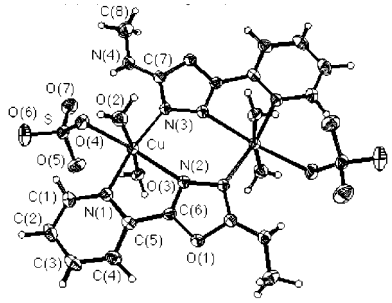

Figure 2. ORTEP plot of **2**. Selected bond distances (Å): Cu−O3 1.976(2), Cu−O2 1.998(2), Cu−N3 2.008(2), Cu−N1 2.047(2), Cu−N2 2.356(2), Cu−O4 2.368(1), S−O7 1.460(2), S−O6 1.467(2), S−O5 1.480(2), S−O4 1.489(2), O1−C7^{I} 1.358(2), O1−C6 1.376(2), N2−C6 1.282(3), N2−N3^{I} 1.391(2), N3−C7 1.322(2), N4−C7 1.308(3), N4−C8 1.453(3), intramolecular Cu···Cu^{I} distance 4.410(1), closest intermolecular Cu···Cu distance 7.226(1) ($I = -x + 1, -y, -z + 1$).

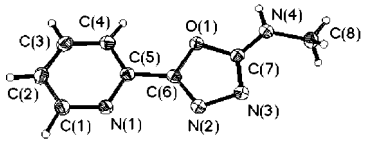

Figure 3. ORTEP plot of **3**. Selected bond distances (Å): O1−C7 1.362(2), O1−C6 1.370(2), N1−C1 1.334(2), N1−C5 1.342(2), N2−C6 1.277(2), N2−N3 1.406(2), N3−C7 1.305(2), N4−C7 1.311(2), N4−C8 1.441(2).

The reaction of K$_4$[Fe(CN)$_6$]·3H$_2$O (0.2 mmol, 0.08 g) with an aqueous solution of **2** (0.1 mmol, 0.08 g) at 0 °C yielded a dark red suspension containing the K$_2$Cu[Fe(CN)$_6$]·H$_2$O compound and a white precipitate. The latter was recrystallized from ethanol, giving rise to colorless crystals of (C$_8$H$_8$N$_4$O)·3H$_2$O (**3**) suitable for X-ray studies. The crystal structure of **3**[10] is shown in Figure 3. As in the case of the **2** derivative, a syn conformer with respect to the C(5)−C(6) bond is obtained. However, atoms C(8) and N(3) are syn with respect to the C(7)−N(4) bond in compound **3**, but they show an anti conformation in the copper(II) derivative. This conformational change is due to a steric hindrance between the methyl and the sulfate groups into the dimer.[11]

It is worth mentioning that the use of reactives different from ferrocyanide, such as NaHCO$_3$, yielded the same results

(6) Crystal data for **1**: C$_{16}$H$_{18}$Cu$_2$N$_{10}$O$_6$S$_2$, M_w = 637.60, triclinic, $P\bar{1}$ space group, a = 7.5259(5) Å, b = 8.7096(6) Å, c = 9.9215(6) Å, α = 72.734(1)°, β = 86.646(1)°, γ = 70.362(1)°, V = 584.29(7) Å^3, Z = 1, μ(Mo Kα) = 2.056 mm^{-1}, T = 298(2) K, 4140 reflections collected, 2820 were unique (R_{int} = 0.0204). Final R values: R1 [$I > 2\sigma(I)$] = 0.0350, wR2 [$I > 2\sigma(I)$] = 0.0982, R1 (all data) = 0.0376, wR2 (all data) = 0.1008. Anal. Found: C 29.8, H 2.8, N 22.0, S 10.1. Calcd for C$_{16}$H$_{18}$Cu$_2$N$_{10}$O$_6$S$_2$: C 30.2, H 2.8, N 22.0, S 10.0. Yield: 83%. Molar conductivity of 5 × 10^{-4} M solutions in water (dimethylformamide) at 25 °C: Λ_M = 91.6 (74.3) Ω^{-1} cm^2 mol^{-1}. Selected IR bands (cm^{-1}, KBr): 3390 m, 1605 m, 1586 m, 1563 m, 1518 vs, 1485 m, 1461 vs, 1447 vs, 1386 vs, 1357 sh s, 1303 s, 1234 s, 1176 s, 1023 m, 913 m, 885 m, 810 w, 776 s. EPR (X-band, solid sample): at 120 K, g_1 = 2.186, g_2 = 2.049, g_3 = 2.025.

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(8) Crystal data for **2**: C$_{16}$H$_{18}$Cu$_2$N$_8$O$_{16}$S$_2$, M_w = 779.66, monoclinic, $P2_1/c$ space group, a = 8.4426(5) Å, b = 13.1063(8) Å, c = 12.7657(8) Å, β = 91.280(1)°, V = 1412.2(2) Å^3, Z = 2, μ(Mo Kα) = 1.742 mm^{-1}, T = 298(2) K, 9746 reflections collected, 3496 were unique (R_{int} = 0.0248). Final R values: R1 [$I > 2\sigma(I)$] = 0.0288, wR2 [$I > 2\sigma(I)$] = 0.0717, R1 (all data) = 0.0400, wR2 (all data) = 0.0758. Anal. Found: C 24.4, H 3.6, N 14.3, S 8.2. Calcd for C$_{16}$H$_{28}$Cu$_2$N$_8$O$_{16}$S$_2$: C 24.6, H 3.6, N 14.4, S 8.2. Yield: 40%. Molar conductivity of 5 × 10^{-4} M solutions in water (dimethylformamide) at 25 °C: Λ_M = 211.8 (not soluble) Ω^{-1} cm^2 mol^{-1}. Selected IR bands (cm^{-1}, KBr): 3444 s,b, 1681 vs, 1624 s, 1576 m, 1559 m, 1497 m, 1389 s, 1298 m, 1109 vs,b, 789 s, 719 m, 617 vs. EPR (X-band, solid sample): in the room temperature to 120 K range, $g_{\|}$ = 2.294 and $g_{\perp}$ = 2.082.

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(10) Crystal data for **3**: C$_8$H$_{14}$N$_4$O$_4$, M_w = 230.23, crystal dimensions 0.50 × 0.35 × 0.35 mm; monoclinic, $P2_1/c$ space group, a = 12.415(1) Å, b = 7.1097(8) Å, c = 12.763(1) Å, β = 93.302(2)°, V = 1124.7(2) Å^3, Z = 4, μ(Mo Kα) = 0.110 mm^{-1}, T = 298(2) K, 6674 reflections collected, 2280 were unique (R_{int} = 0.0403). In spite of their relative instability, freshly prepared crystals were measured and no intensity decay of control reflections was observed. Final R values, R1 [$I > 2\sigma(I)$] = 0.0447, wR2 [$I > 2\sigma(I)$] = 0.1133, R1 (all data) = 0.0569, wR2 (all data) = 0.1213. Anal. Found: C 42.4, H 5.7, N 24.9. Calcd for C$_8$H$_{14}$N$_4$O$_4$: C 41.7, H 6.1, N 24.4. Yield: 45%. Mass spectrum (EMBR): m/z (%) = 176 (M$^+$, 100), 78 (py$^+$, 51). Selected IR bands (cm^{-1}, KBr): 3397 m,b, 2991 m, 1653 vs, 1548 m, 1476 m, 1424 m, 1408 s, 1153 m, 1111 m, 1077 m, 1034 s, 1000 m, 788 m, 737 m, 677 m. ^{1}H NMR(400 MHz; d_6-DMSO): δ 2.85 (3H, d, ^3J 5 Hz, CH$_3$), 8.63 (1H, dt, ^3J 5 and 1.4 Hz, H$_1$), 7.95 (1H, dt, ^3J 1.4 and 7.5 Hz, H$_4$), 7.90 (1H, td, ^3J 7 and 7.5 Hz, H$_3$), 7.78 (1H, q, ^3J 5 and 1.4 Hz, NH), 7.47 (1H, td, ^3J 5 and 7 Hz, H$_2$).

but the isolation of the ligand was more tedious. It was also possible to synthesize **3** without complexation (yield = 45%), but a certain amount of impurities was detected (e.g., the thiosemicarbazone ligand). Furthermore, compound **3** undergoes decomposition after some days; however, it is stable in air under complexation as observed in compound **2**.

As the conclusion of this work we describe a very easy route to obtain and store 1,3,4-oxadiazole unstable ligands as stable 2-methylamino-5-pyridin-2-yl-1,3,4-oxadiazole−copper(II) complexes. The starting thiosemicarbazone systems are characterized by their stability in air and aqueous solutions. Procedures for their preparation are very simple and inexpensive. Another important aspect to be considered is that, although some mechanisms of oxidative cyclization in thiosemicarbazones give rise to thiadiazoles,[12] thiadiazolines,[13] pyrazolones,[14] and 1,2,4-triazoline-5-thiones,[15] no oxadiazole complexes have been synthesized through oxidative reactions involving heterocyclic thiosemicarbazones. Furthermore, as far as we are aware, this is the first mechanism of oxidative cyclization involving desulfurization of thiosemicarbazones.

This discovery could be of importance to synthetic protocols for biologically active molecules, as well as to the preparation of active site models which are bridged by histidine moieties. Further experimental and structural details together with a discussion about the spectroscopic and magnetic properties of the complexes will be published shortly as a full paper. In the same way, the mechanism of this process and the feasibility of the desulfurization reaction of thiosemicarbazones in physiological media are under study.

Supporting Information Available: Tables of crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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