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An Unusual Dimeric Structure of a Cu(I) Bis(thiosemicarbazone) Complex: Implications for the Mechanism of Hypoxic Selectivity of the Cu(II) Derivatives

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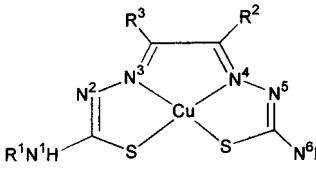
Transition metal complexes of bis(thiosemicarbazone) (btsc) ligands (Figure 1, which also shows standard abbreviations) have been studied for nearly 50 years.[1−3] Subsequent interest has focused on the redox properties, structures and biological activity of such complexes.[4] In particular bis(thiosemicarbazone) complexes of copper(II) have been know for some time to be anti-tumor agents.[5,6] However, it is the hypoxic selectivity of certain copper bis-(thiosemicarbazones) and their use as vehicles for the delivery of radioactive copper isotopes to tumors[7,8] or leucocytes[9] that has attracted much recent attention[10] through the work of Welch and Fujibayashi and co-workers. This is exemplified by a very recent report that [^{64}Cu(II)(ATSM)] significantly improves the survival times of animals bearing human GW38 colon cancer tumors.[11] The general topic of copper-based radiopharmaceuticals has also been reviewed relatively recently.[12] The hypoxic selectivity is strongly dependent on the substituents on the carbon backbone ([Cu(ATSM)] shows good hypoxic selectivity whereas [Cu(GTS)] exhibits none), and we have studied the chemistry of these systems in some detail in an effort to understand the mechanism of hypoxic selectivity more fully.

The mechanism of hypoxic selectivity of [Cu(btsc)] complexes has been discussed in terms of the redox potentials for reduction of the Cu(II) complexes to Cu(I),[13] the most selective complexes being those that are most difficult to reduce. The redox potentials are markedly dependent on the backbone substituents, and it was suggested that this variation accounted for the range of hypoxic selectivity observed. Trapping of the complexes within the cells was assumed to occur by virtue of the formation of the charged anion. The reported redox potentials were measured in dry DMF, and under these conditions two completely Nernstian reversible processes are observed, one corresponding to reduction to Cu(I) and that at positive potentials to oxidation to Cu(III). However, hypoxic cells are mildly acidic,[14] and Cu(II) btsc complexes are known to protonate. A [Cu(II)(btsc)] complex has been reported to have pK_a values of 2.75 and ca. 0.8.[15] Reduction of the Cu(II) complex will further enhance the basicity of the coordinated btsc ligand. We have observed that the CVs of the Cu(II) complexes in the presence of aqueous acid are dramatically different from those in anhydrous DMF, and coupled protonation and reduction clearly cannot be neglected in the medium likely to be found within hypoxic cells. This suggests strongly that a Cu(I) anionic complex is unlikely to be formed in the reduction of the [Cu(II)(btsc)] complexes in the mildly acidic aqueous environment of hypoxic cells.

The structure of [Cu(II)(ATSM)] has been determined for the first time and is shown in Figure 2. The complex comprises square



$R^1 = R^2 = R^3 = H$, GTS
$R^2 = R^3 = Me$, $R^1 = Me$, ATSM
$R^2 = Me$, $R^3 = H$, $R^1 = Me$, PTSM

Figure 1. Structures and abbreviations for Cu(II) bis(thiosemicarbazones).

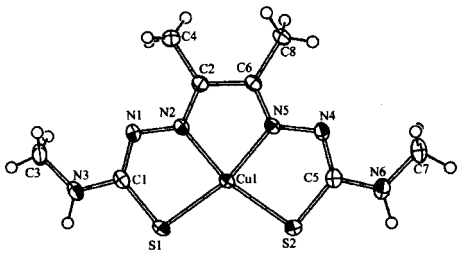


Figure 2. Crystal structure of [Cu(II)(ATSM)].

planar units which are loosely associated into dimers by long Cu−S interactions. The long Cu−S interactions have been reported in the very few earlier structure determinations for Cu(btsc) complexes.[16] However there is an interesting difference for the structure of the d^{10} Zn complex of ATSM which is unequivocally dimeric with five-coordinate square pyramidal Zn.[17] This suggested that the corresponding hypothetical Cu(I) anion, postulated as the species responsible for the selective trapping of Cu in hypoxic cells, might have the same structure. However, it now appears that at the concentrations used for synthesis that it is probable that this species if formed, protonates rapidly and rearranges to the dimeric species (**1**).

We have attempted to isolate the Cu(I) species by reaction of the btsc ligands with a Cu(I) precursor. Reaction of [$Cu(MeCN)_4$]-[PF_6] with $ATSMH_2$ in MeCN unexpectedly yielded the novel dimeric species $[Cu_2(ATSMH_2)_2]^{2+}$, isolated as the $[PF_6]^-$ salt (**1**). All attempts to isolate an anionic species by the addition of strong base failed, suggesting that it may not in fact be stable even in aprotic media. It also proved impossible to isolate any Cu(I) species with GTS. The X-ray crystal structure of (**1**) (Figure 3) revealed a dimeric structure with each of the btsc ligands acting as a bidentate N−S donor to each Cu(I) ion to generate a novel helical structure which is unprecedented for bis(thiosemicarbazone) complexes. The Cu−Cu distance of 3.561 Å suggests little interaction between the two metal ions. The two components of the dimer are related by a crystallographic two-fold axis that bisects the C−C bond. Each of the ligands is twisted substantially at the C−C bond (torsion angles: N(2)−C(2)−C(2)′−N(2)′ = 51.1°, N(4)−C(6)−C(6)′−

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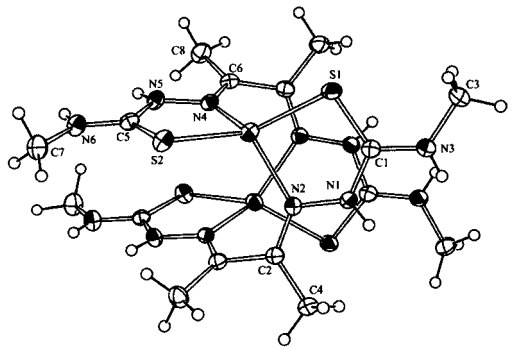

Figure 3. Structure of the dication present in complex (**1**).

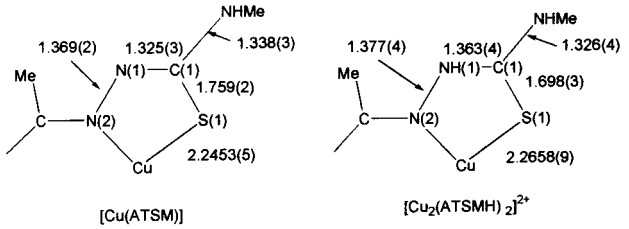

Figure 4. Bond distances in Å for the Cu(II) and Cu(I) ATSMH complexes (ring selection is arbitrary, but parameters differ little).

N(4)′ = 51.8°) The geometry about each Cu(I) is strongly distorted tetrahedral with the dihedral angle between the N(2)−Cu(1)−S(1) and N(4)−Cu(1)−S(2) planes being reduced to 75.1°. The Cu−N and Cu−S distances for (**1**) are within the normal range found for Cu−N and Cu−S (thione) bonds. Each asymmetric unit contains two DMF molecules of crystallization and one $[PF_6]^-$ anion. Each pair of N−H bonds forms H-bonds to the oxygen of a single DMF solvent molecule. The N−H protons were located successfully and refined.

Figure 4 summarizes the differences in bond lengths in the five-membered chelate rings in the Cu(I) and Cu(II) species. Planarity of the ring system is maintained on protonation, and the most significant bond distance changes occur for the C−S bonds with smaller changes for the C−N bonds.

DMF solutions of (**1**) in air are oxidized rapidly and quantitatively back to the Cu(II) species. This was confirmed by UV/visible spectroscopy and the isolation of crystals from the oxidized DMF solution which were used for the structure shown in Figure 1.

This raises the question as to whether the dimer (**1**) is actually formed in cells during labeling. The CV studies above show clearly that reduction of the [Cu(II)(ATSM)] complex in the mildly acidic aqueous environment inside a cell will be accompanied by protonation and generate an unstable diprotonated Cu(I) cation. The Cu(I) ion has a strong preference for tetrahedral geometry, and this drives distortion of the complex. The ligand is unable to accommodate tetrahedral Cu(I) by a small rotation about the C−C bond of the backbone, and partial dissociation occurs with the btsc ligand bound by only one S and one N. This is facilitated by the shift on protonation to the thione form with weakening of the C−S bond. The local concentration of the η^2-btsc species inside cells during labeling is unknown, but may well be too low for formation of (**1**), and the vacant coordination sites may then be occupied by water or other potential ligands in the interior of the cell. Whatever the precise identity of this species, it is retained, possibly by virtue of the *positive* charge, and is rapidly reoxidized by oxygen in oxic cells to regenerate the planar Cu(II) ATSM complex which diffuses out of the cell. The protonated Cu(I) GTS species appears to be significantly less stable and decomposes to species which cannot be reoxidized to Cu(II)(GTS). This may relate to the significantly shorter C−C bond length in the backbone of the GTS system[17] and the lack of steric repulsions due to substituents that reduces the tendency for rotation about C−C and formation of an η^2-bound intermediate.

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Supporting Information Available: Crystallographic data (CIF) and characterization data for complex (**1**) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org

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