Model Studies of Tetrathiomolybdate (TM) and its interactions with copper proteins: How does the copper antagonist drug TM interact with copper trafficking proteins?

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The biological antagonism between copper and molybdenum, first observed when cattle developed copper deficiencies after ingesting high levels of plant-born molybdenum, is currently being used in humans to treat two conditions: Wilson Disease as well as several forms of metastatic cancer. There is surprisingly little known about the interaction of the biologically active tetrathiolmolybdate ion (TM) with copper-proteins. TM has been proposed to alter copper metabolism and induce copper deficiency due to its powerful ability of chelating copper ions.

While the mechanism of how TM and copper interact in a physiological environment has not been clarified, preliminary results indicate that TM reacts quickly with the yeast copper chaperone Atx1 and with the human homologue, Hah1. Intriguingly, we find that extended reaction of TM at millimolar concentration with Cu(I)-Atx1 does not lead to copper removal or precipitation; instead, stable complexes were formed. They were robust to ultrafiltration, gel filtration by FPLC and native gel electrophoresis. Preliminary data indicates that a dimer or trimer interaction and other oligomeric complexes can be formed and isolated. Cu K-edge XANES and EPR indicate the presence of Cu(I) with a 4-coordination geometry (CuS_4) and Mo K-edge EXAFS suggests the existence of a Mo-S single scattering, satisfactorily modeled by 4 Mo-S (TM), suggesting the existence of a molybdenum – bridged CuAtx1 dimer or trimer, with a Mo-Cu interaction at 2.78 Å, which is close to Mo-Cu distances found in other biological systems. These Cu-chaperone-[MoS_4] interactions provide a starting point for understanding the interactions of TM with both intracellular and plasma-serum proteins.