Activation of Small Molecules Using Trinuclear Copper Complexes

Tabitha Miller Literature Seminar October 11, 2016

Metalloproteins are important to the transformation of many biologically relevant molecules. Of the different metals that are often seen in these proteins, copper is one of the most abundant. Copper atoms are usually assigned as one of three different types, type 1, type 2, and type 3, based upon their coordination environment.[1] A large class of copper proteins known as multicopper oxidases (MCOs) is one that actually incorporates all three of these types of copper sites.[2] Common to all MCOs is a trinuclear copper cluster (TNC) which consists of a type 2 Cu site and the binuclear type 3 Cu site as seen in Figure 1.[2,3] This site is responsible for the reduction of O_2 to H_2O which is the main role of these proteins.[2,3] In addition to the TNC, all MCOs also possess a type 1 Cu site which is responsible for shuttling electrons to the TNC for the reduction of oxygen.[2,3] Understanding how these enzymes function and how we can take advantage of this knowledge has become a topic of study for synthetic inorganic chemistry. By using functional and structural models of enzyme active sites, chemists can gain further knowledge about metalloproteins.

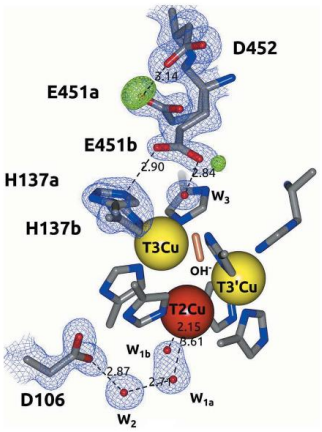


Figure 1: Trinuclear cluster from *Thermus thermophilus* HB27 multicopper oxidase

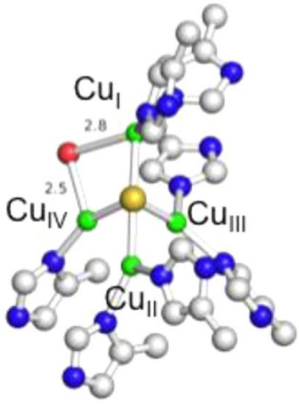
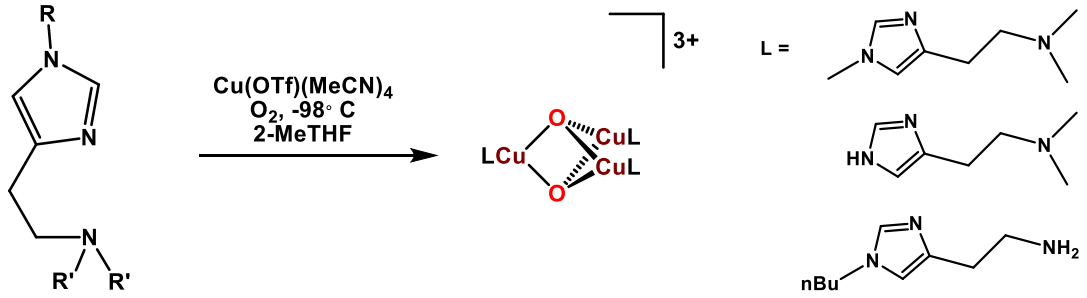


Figure 2: Tetranuclear copper cluster from *Par. denitrificans* nitrous oxide reductase

The Stack group has previously worked on modeling particulate methane monooxygenase, a dicopper protein which carries out the reduction of methane to methanol.[4,5] In their attempts to use ligands which are biologically relevant, the group chose alkylated histamine ligands.[5] In their previous work, the group focused on the synthesis of dicopper-dioxygen species by adding their ligand of choice to an already pre-synthesized dicopper-dioxygen compound.[4,5] In this current work, they modified their synthetic method by changing their reaction temperature (-125° C to -98° C) and by adding a Cu(I) salt directly to their ligand of choice in the presence of O_2 (see Scheme 1).[6] Through monitoring the reaction by UV-Vis spectroscopy, they observed a new

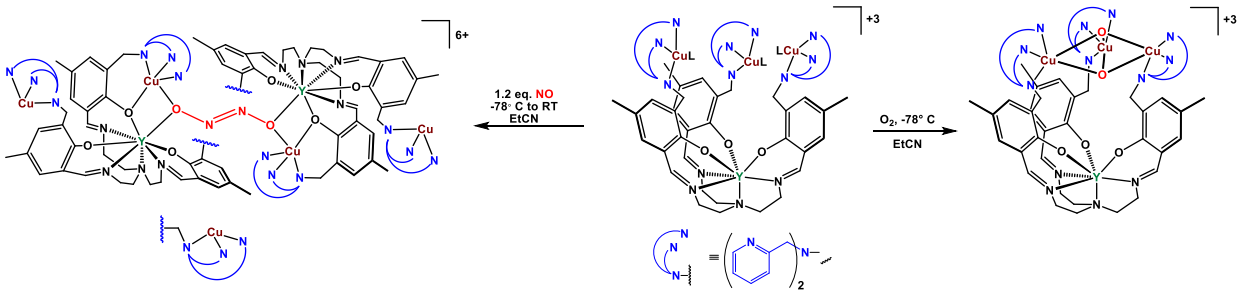
product, which after O_2 titration studies and high-resolution mass spectrometry they assigned as a tricopper-dioxygen species.[6] Due to the preference for the tricopper species at warmer



Scheme 1: Synthesis of tricopper-dioxygen complexes with alkylated histamine ligands

temperatures, they also compared the reactivity of their tricopper and dicopper species towards protonation.[6] What they found was that for the two different ligands they looked at, the dicopper species is two to six orders of magnitude faster to react.[6] However, due to the thermal instability of their products, further characterization was not possible.[6] From these studies, it is apparent that the group needs to look into making their ligand framework more rigid in order to further characterize these compounds and to continue studying oxygen activation with histamines ligands.

The Agapie group, also interested in studying oxygen activation, designed a multinucleating ligand framework with a trisphenoxide-trisimine-amine binding pocket capable of ligating a Lewis acid, as well as three dipicolylamine arms for the ligation of the three copper atoms.[7] Addition of an yttrium trialkyl species followed by three equivalents of a Cu(I) salt, resulted in the formation of a fully metallated [YCu_3] complex.[7] Crystallographic characterization of the complex confirmed that all three copper atoms were in a distorted tetrahedral geometry, with an acetonitrile solvent molecule bound.[7] Upon addition of O_2 gas the group reported the formation of a new product, as confirmed by UV-Vis spectroscopy, and by volumetric studies, they confirmed the Cu:O_2 ratio to be 3:1 (see Scheme 2).[7] In order to assess this compound as a



Scheme 2: Synthesis of dioxygen and hyponitrite [YCu_3] species

functional model of oxidase enzymes, its reactivity towards reduction and activating X-H bonds was explored. While the [YCu_3O_2] complex can oxidize TEMPO-H (BDE = 70 kcal mol^{-1}), it is

not able to activate stronger X-H bonds, such as 9,10-dihydroanthracene (BDE = 74 kcal mol^{-1}) and toluene (BDE = 88 kcal mol^{-1}).[7] In their attempt to make a functional model of a copper oxidase, the Agapie group was met with an upper limit to their complex's reactivity.

Interested in further reactivity of their tricopper complex, the Agapie group became interested in modeling the reactivity of nitrous oxide reductase (N_2OR) and nitric oxide reductase (NOR).[8] NOR proteins are coupled heme/non-heme proteins which reduce NO to N_2O, going through a proposed hyponitrite $[N_2O_2]^{2-}$ intermediate.[8] Meanwhile, N_2OR proteins have a unique tetranuclear copper active site as seen in Figure 2, where it is commonly believed that N_2O binds side-on to one of the Cu-Cu edges, where it is then reduced to N_2 and H_2O.[1] Modeling the functionality of both NOR and N_2OR in one discrete system has only been previously reported with the use of external reductants or with heterogeneous catalysts.[8]

Using their $[YCu_3]$ starting complex, the Agapie group added NO gas, and characterized their new product using ^1H NMR spectroscopy as well as x-ray crystallography.[7,8] The crystal structure of their product showed that they had isolated a trans-hyponitrite species bridging two $[YCu_3]$ complexes.[8] The bond distances for this moiety (N-N: 1.254(8) Å and N-O: 1.376(4) Å) are consistent with a N-N double bond and N-O single bond.[8] While this new complex is not the first isolated and characterized trans-hyponitrite species, it is the first biologically relevant metal to do so, where the hyponitrite moiety is generated from NO gas, and not a surrogate such as hyponitrous acid.[8] To assess whether their hyponitrite species can be reduced to generate nitrous oxide, the Agapie group added a proton source in the form of pyridinium triflate.[8] Monitoring the reaction by gas-phase IR spectroscopy, they observed the formation of N_2O gas.[8] They further corroborated this reactivity by monitoring the reduction of a ^{15}N-labelled hyponitrite complex (generated from ^{15}N-labelled NO gas) by GC-MS.[8] Interestingly, after 96 hours they also observe the formation of $^{15}N_2$, suggesting that their complex is able to further reduce *in situ* nitrous oxide to N_2, making it the first homogeneous catalyst able to do so without the need for external reductants.[8] In both of their examples of activation, the Agapie group gave no concrete reasoning for the need of a Lewis acid, beyond it binding to the hyponitrite species.[7,8] By altering their ligand framework, such that there is no longer the extra binding pocket, they could run the control reactions with just a tricopper species, proving or disproving the need for the Lewis acid.

Looking at these two examples of tricopper complexes, we have both an attempt at a structural model, in the case of Stack's work, and a functional model in the case of Agapie's work. Both have work that they need to do to further their studies, such as making a more rigid framework for Stack and doing more controls for Agapie, but they have both made significant progress in understanding and applying the fundamentals of multicopper proteins.

References:

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