Chemical Synthesis of Acetyl Coenzyme A Synthase Active Site

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During the Fall 2005 semester I have been working on Dr. Hegg's acetyl coenzyme A synthase project. This enzyme plays a vital role in the global carbon cycle by forming and removing greenhouse and poisonous gases in the atmosphere. The structure of the ACS has been discovered only recently. This finding revealed a never before seen hexameric three-component ACS active site containing a FeS4 protein cluster bridged to a binuclear center consisting of Ni-Ni active site. A lot of important questions about the catalytic mechanisms and electronic properties of this polynuclear active site have not been answered yet. Different kinds of catalytic mechanisms of ACS have been proposed by many scientists, but there’s still no consensus on which of the mechanisms is the true one. In order to answer this question, the Hegg lab is working to synthesize model complexes that would mimic the active sites of the ACS. It has proven to be very difficult to bridge the two Ni centers of ACS together. My project suggests a different, an "outside the box" way to bridge the two nickel ions. It can be achieved by ligating one Ni to a third thiolate that is attached to an extension coming off of the ligand surrounding the other Ni. This may ensure the bridging of the first Ni so that a dinuclear Ni-Ni complex could form and only minor alterations from the "real-life" active site would be present.

The ligand that could "hold" the two Ni ions since the beginning of the Fall semester I have been working on synthesizing this ligand by literature methods. I have not been able to construct this molecule, but I have come very close to doing so: one last peptide coupling reaction needs to be carried out under the right conditions in order to separate this ligand. After this is done, I will try to bridge the two Ni ions in order to get the dinuclear Ni-Ni complex. Then I can study the properties of the metal complex and propose a mechanism according to the observed properties.