

Modeling the Active Sites of Thiolate-Coordinated Metalloenzymes

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A number of metalloenzymes have active-site coordination environments incorporating thiolate ligands, including the iron and cobalt nitrile hydratases (NHase) and the A-cluster of CO Dehydrogenase/Acetyl CoA Synthase (CODH/ACS). In recent years, we have developed a methodology for the incorporation of thiolate coordination to transition metals using 2,2'-dithiodibenzaldehyde (DTDB) as a source for the thiolates. This reagent obviates the need for protection/deprotection of the thiolate moiety, since the thiolate is masked as a disulfide. Reaction of DTDB with metal complexes containing coordinated primary amines results in concomitant Schiff-base condensation and cleavage of the disulfide to form the thiolate. We have applied this methodology to the synthesis of synthetic analogs for the active sites of the enzymes mentioned above.

The NHase active site consists of a trivalent metal with octahedral coordination by two deprotonated amide N atoms (from the peptide backbone), one cysteine thiolate, two oxidized cysteine thiolates, and an exogenous hydroxide ligand. The A-cluster of CODH/ACS consists of an Fe₄S₄ cubane bridged by a single cysteine thiolate to a dinuclear nickel cluster. The proximal Ni is coordinated by an exogenous diatomic ligand and two additional cysteine thiolates which bridge it to the distal Ni, whose coordination sphere is completed by two deprotonated amide ligands. The structural similarities between the two sites include coordination by thiolate ligands as well as the unusual coordination by deprotonated amide ligands.

Using the DTDB methodology, we have synthesized and structurally characterized an octahedral Co complex of a pentadentate N₂S₃ ligand which reproduces the protein-derived donor atoms at the active site of Co NHase, as well as a bis(thiolate)-bridged Ni dimer which serves as a symmetric first-generation model for the dinuclear nickel portion of the CODH/ACS A-cluster. This poster will enumerate advances that we have made in synthesizing model complexes which more closely duplicate the active-site structures.