Pyrazolylborate Models of Zinc Enzymes

Andrew C. Dunbar Literature Seminar November 29, 2005

Model studies of enzymes can provide insight into how the coordination environment around the metal center affects activity. Model studies can also help improve the design of possible inhibitors for the enzyme in question. Inhibitors with specific affinity for a particular enzyme are potential therapeutic agents for diseases in which the enzyme is implicated. Zinc enzymes play important biochemical functions and therefore are also involved in certain disease states. For example, carbonic anhydrase can contribute to increased intraocular pressure resulting in the onset of glaucoma.[1] In addition, the inhibition of β-lactamase could potentially lead to a revival of β-lactam based drugs because an inhibitor would disable the bacteria's defense mechanism against β-lactam-based drugs. Model studies of alcohol dehydrogenase have been used to determine how the coordination environment around the zinc center affects the activity of the model. To this end, researchers have constructed active zinc enzyme mimics utilizing the pyrazolylborate ligand family developed in the 1960's by Swiatoslaw Trofimenko (Figure 1).[2] Tris(pyrazolyl)borate ligands bind facially to a metal center, and substitution of the pyrazole ring at the 3 and 5 positions adds steric bulk and affects the electronic properties of the metal center.[3]

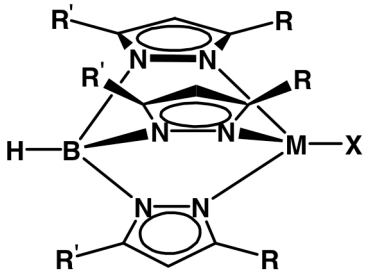
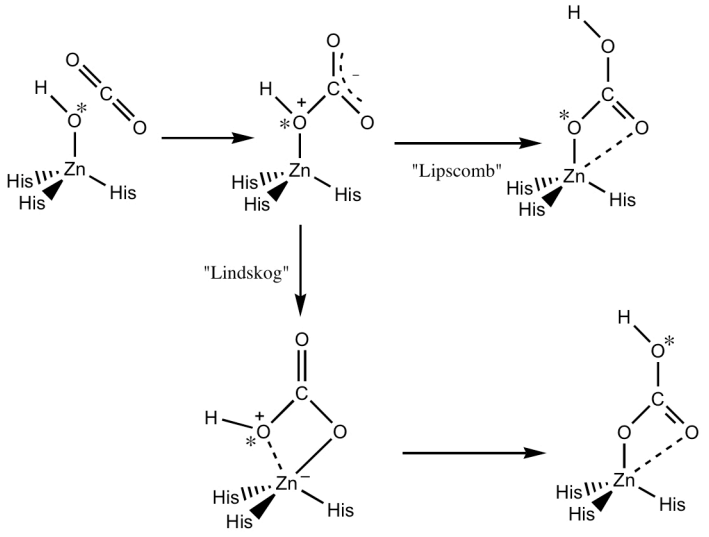


Figure 1: The tris(pyrazolyl)hydroborato ligand system, ([$Tp^{RR'}$]MX).[2]

Carbonic anhydrase is one of the most extensively studied zinc enzymes. Carbonic anhydrase catalyzes the conversion of CO_2 to HCO_3^- and is characterized by a tetrahedral zinc center bound by three histidine residues and a water molecule.[4] Deprotonation of the aqua ligand is essential to initiating the catalytic cycle.[5] Lipscomb[6] and Lindskog[7] have proposed different mechanisms for the rearrangement that is the last step in the conversion of carbon dioxide to bicarbonate (Scheme 1).[8,9] Lipscomb has suggested this rearrangement occurs by an internal proton transfer, whereas Lindskog has suggested that it involves an η^1-η^2-η^1 sequence. Tris(pyrazolyl)borate zinc hydroxide complexes are being investigated as models for carbonic anhydrase to provide insight into how carbonic anhydrase works.

β-Lactamase is a zinc enzyme that enables bacteria to develop resistance towards β-lactam antibacterial agents such as penicillin. Specifically, the enzyme catalyzes the opening of the β-lactam ring in penicillin, thus rendering the drug inactive (Figure 2).[10] The active site of *Bacteroides fragilis* β-lactamase consists of two zinc centers, and the enzyme requires both zinc



Scheme 1: Two proposed mechanisms of the carbonic anhydrase catalytic cycle.[8,9]

centers for full catalytic activity. The first zinc is bound to three histidine residues, and the fourth site is occupied by a water ligand that bridges to the second zinc which has a coordination sphere consisting of an aspartate, cysteine, histidine, and water. Model zinc complexes with pyrazolylborate ligands are not sufficiently nucleophilic to cleave the amide bond of the β-lactam substrate unless the amide bond is activated by attaching electron-withdrawing groups to the nitrogen atom.[11]

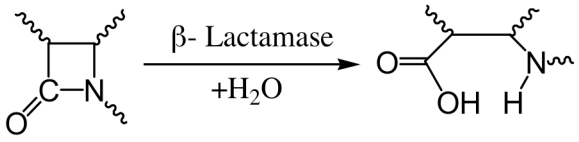


Figure 2: Enzymatic action of β-Lactamase.[8]

Alcohol dehydrogenase is a binuclear zinc enzyme responsible for converting primary and secondary alcohols into the corresponding aldehydes and ketones. One of the zinc centers is not catalytically active; its role in the enzyme is strictly structural. This zinc is bound by four cysteine residues in a tetrahedral geometry. The catalytically active zinc atom, which is also in a tetrahedral coordination environment, is bound to two cysteine residues, one histidine residue, and a water molecule.[5] Alcohol dehydrogenase requires a cofactor, nicotinamide adenine dinucleotide (NAD^+), which acts as a hydride abstracting agent. The resulting product, NADH, is also a key component in the biological process of gluconeogenesis. The catalytic cycle of alcohol dehydrogenase involves displacement of the bound aqua ligand with alcohol, followed by hydride transfer to NAD^+, to afford in a zinc alkoxide complex. Alkoxide formation in the alcohol dehydrogenase model is extremely sensitive to the electronic properties of the alcohol.[12]

References

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