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Investigating metalloenzymes

Ferman Chavez focuses his research on oxalate-degrading manganese enzymes. Elevated oxalate concentrations in humans (hyperoxaluria) has been implicated in a number of pathological conditions such as the formation of calcium oxalate stones in the kidney (urolithiasis), renal failure, cardiomyopathy, and cardiac conductance disorders. Oxalate is associated with pathogenesis in several plants. Accumulation in leafy plants, for example spinach, causes nutritional stress as these plants lack the ability to catabolize oxalate.

Oxalate oxidase (OxOx) is expressed by plants and turns the manganese-dependent oxidative decarboxylation of oxalate to carbon dioxide and hydrogen peroxide, protecting plants from the toxic effects of this organic acid. The active site of this enzyme consists of manganese(II) bonded to a glutamate and three histidine residues. Oxalate decarboxylase (OxDC) is also a manganese-dependent enzyme and catalyzes the conversion of oxalate to formate and carbon dioxide. The active site structure of OxDC is similar to OxOx. OxDC and OxOx have been used in the clinical assay of oxalate in blood and urine. Other potential applications for these enzymes and their synthetic functional models are in the removal of oxalate from food sources. Despite the detailed structural knowledge for both OxOx and OxDC, very little is known about the catalytic mechanism for these enzymes. In their current work, Chavez and his coworkers are engaged in the synthesis of the manganese active site of OxOx and OxDC. They will use these model compounds to test conditions which lead to either OxOx or OxDC activity and gain insight into how these enzymes perform their function.

Chavez's team also is studying iron containing cysteine dioxygenase. Mammalian cysteine dioxygenase (CDO) catalyzes the irreversible oxidation of cysteine to cysteine sulfinate, which is important to human health. This reaction is required for a variety of critical metabolic pathways. Clinical evidence indicates that a block in cysteine catabolism, thought to be a CDO, leads to an altered cysteine-to-sulfate ratio that is associated with sulfate depletion and other adverse effects. The prevalence of impaired cysteine catabolism has been reported to be increased in patients afflicted with rheumatoid arthritis, liver diseases, Parkinson's disease, Alzheimer's disease, motor neuron disease, and systemic lupus erythematosus. Large doses of cysteine or cystine have been shown to be toxic in several species. The function of CDO has been studied most thoroughly in mammals, where it is expressed primarily in liver hepatocytes. Several crystal structures of CDO were recently solved. A deeper understanding of this enzyme will help in elucidating how it can be enhanced/modified in patients with CDO-related disease.

Chavez's research also applies to the development of polymer electrolyte membranes for fuel cells, DNA cleaving agents, and the synthesis of nitric oxide donor compounds. The structural and physical properties of new coordination compounds containing biologically relevant ligands also are of ongoing interest.

Representative Recent Publications

1. Chavez FA, Hamdi H. 2009. Nanomaterials for fuel cell proton exchange membranes. In: *Nanomaterials for Energy Storage Applications*, Nalwa HS, Ed., American Scientific Publishers: Valencia, California.

2. Pawlak PL, Malkhasian AYS, Sjlivic B, Tiza MJ, Kucera BE, Loloee R, Chavez FA. 2008. Synthesis, structure, and magnetic properties of a new binuclear Ni(II) complex supported by 1,4,8-Triazacycloundecane. *Inorg Chem Commun* 11:1023-1026.

3. Malkhasian AYS, Finch ME, Pawlak PL, Anderson JM, Brennessel WW, Chavez FA. 2008. Synthesis, structure, and characterization of Dichloro-(1-Benzyl-4-Acetato-1,4,7-Triazacyclononane)Iron(III). *Z Anorg Allg Chem* 634:1087-1092.

4. Malkhasian AYS, Finch ME, Nikolovski B, Menon A, Kucera BE, Chavez FA. 2007. N,N'-dimethylformamide-derived products from catalytic oxidation of 3-hydroxyflavone. *Inorg Chem* 46:2950-2952.

5. Malkhasian AYS, Nikolovski B, Kucera BE, Loloee R, Chavez FA. 2007. Synthesis, structure, and properties of Iron(II) and Manganese(II) Bis[Tris(1-Ethyl-4-Methylimidazolyl-κN)Phosphine] complexes. *Z Anorg Allg Chem* 633:1000-1005.

6. Chavez FA, Que L Jr. 2005. Iron: models of proteins with dinuclear active sites. In: Encyclopedia of Inorganic Chemistry, 2nd Ed, Crabtree RH, Ed. Wiley: Chichester.