# Biomimetic Modeling of Metalloenzyme Active Sites Using Computational Chemistry Methods

**Benjamin Gherman**

Department of Chemistry

College of Natural Sciences & Mathematics

- **Background:** Eubacterial proteins are synthesized with a formyl group at the N-terminus. Peptide deformylase (PDF), in a reaction catalyzed by an Fe(II) coordination complex in the active site, catalyzes the hydrolytic removal of the N-terminal formyl group from nascent proteins, making it of interest in antibacterial drug development.
- **The goal of this research** is to to find a biomimetic ligand for the enzyme active site which gives the most thermodynamically and/or kinetically favorable deformylation reaction.
- **Key result:** The imidazole ligands give the lowest $\Delta G_{rxn}$. The sulfur electron-donating group can allow for the $\Delta G^{\ddagger}$ to be lower with these ligands.

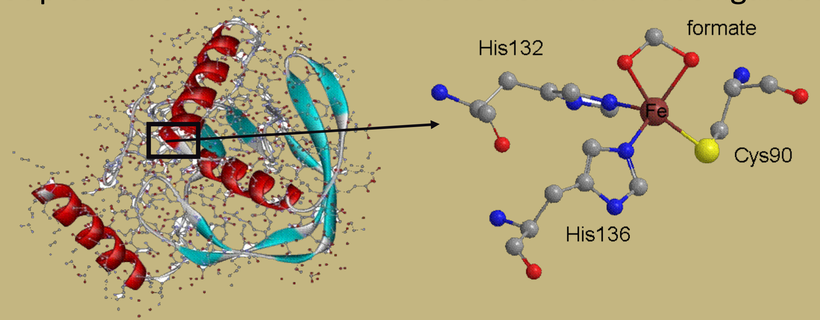
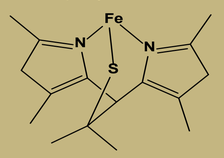


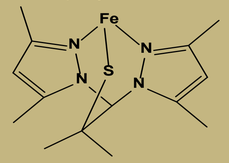

Figure 1. (left) PDF enzyme and (right) active site.

## Biomimetic Ligands

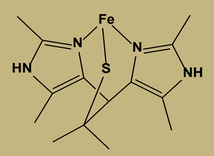
1) Pyrrole



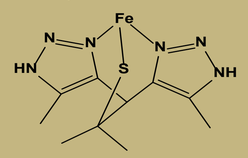

2) Pyrazole



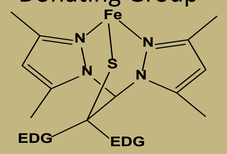

3) Imidazole



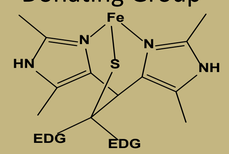

4) Triazole



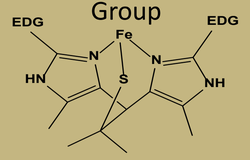

5) Pyrazole with a Sulfur Electron-Donating Group




6) Imidazole with a Sulfur Electron-Donating Group




7) Imidazole with Electron-Donating Group




- **Background:** CytC3 and SyrB2 are non-heme iron halogenase metalloenzymes that catalyze halogenation reactions of natural products. Halogenation is useful in synthesizing organic compounds; however, typical organic halogenation reactions involve toxic chemicals, posing environmental danger.
- **The goal of this research** is to determine the effect of ligand structure and metal spin state on the thermodynamics, kinetics, and chemoselectivity for the halogenation reaction catalyzed by these complexes.
- **Key result:** With the TQA ligand, reaction energetics for hydrogen atom abstraction and the overall reaction are more favorable with high-spin $Fe^{IV}$. Activation energy barriers are lower for halogenation versus hydroxylation, imparting chemoselectivity.

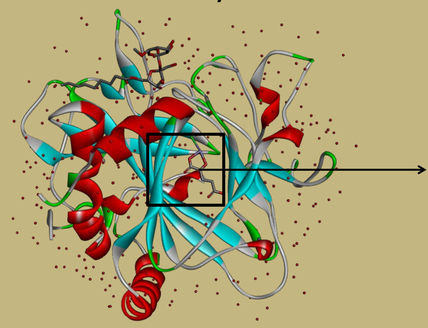
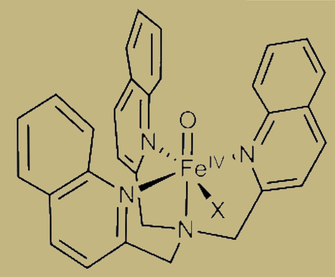
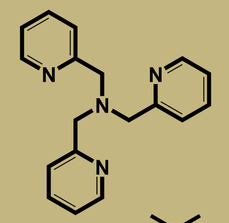



Figure 2. (left) SyrB2 enzyme and (right) active site.

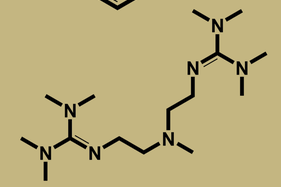
## Biomimetic Ligands




1) tris(quinolyl-2-methyl)amine (TQA)




2) tris(pyridyl-2-methyl)amine (TPA)




3) *N*-methyl-1,1-bis {2-[$N^2$-(1,1,3,3-tetramethylguanidino)]ethyl} amine ($TMG_2$dien)