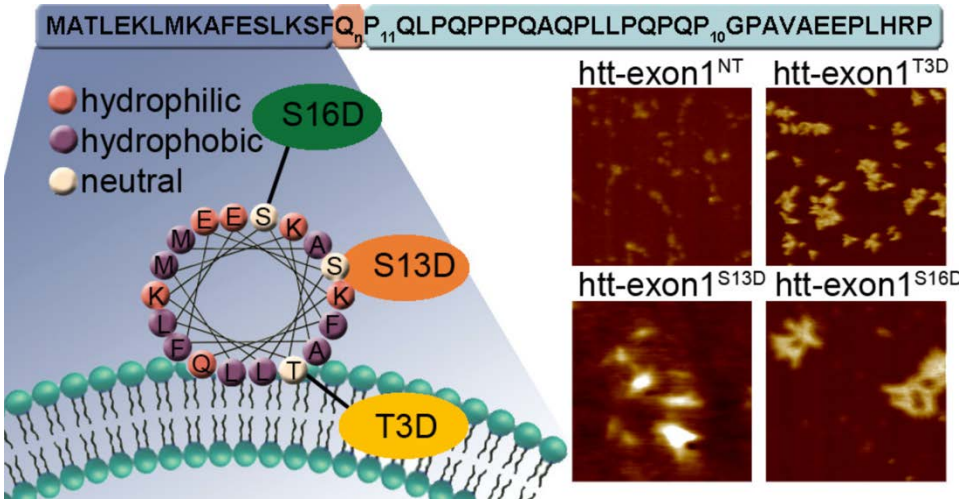
CHEMISTRY SEMINAR

The Effect of Phosphomimetic Mutations on Huntingtin Aggregation Using Various Model Lipid Membranes

By Andrea Brazyte, Chemistry '24

11:30 am **Thursday, September 28, 2023** **Science Center Room 300**

Abstract:
Huntington's disease (HD) is a neurodegenerative disease that causes motor, cognitive, and behavioral defects in patients. HD is caused by an expansion of CAG triplet repeats in the huntingtin gene (htt) that lead to an abnormally elongated polyglutamine (polyQ) region. Directly preceding the polyQ region is the first 17 N-terminal amino acids of htt (Nt17) which are believed to be involved in htt aggregation and its interaction with lipid membranes. Nt17 can form amphipatic alpha helical structures with the help of a binding partner which then can associate into oligomers. These alpha helix oligomers can increase fibril formation by having the polyQ domains of different htt proteins interact, which results in aggregation. Additionally, these alpha helices can also bind htt-exon1 to lipid membranes. Post-translational modifications of Nt17, such as phosphorylation, have been investigated as they are believed to impact htt's function and interactions with its environment. Therefore, three residues, threonine 3, serine 13, and serine 16, in Nt17 were phosphorylated to explore this phenomena. The model lipid membranes utilized were total brain lipid extract (TBLE), 1-Palmitoyl-2-oleoyl-glycero-3-phosphatidylcholine (POPC) and 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phospho-1′-*rac*-glycerol (POPG). The phosphomimetic mutations caused changes in htt's interaction with and aggregation in the presence and absence of lipids, however, this was due to the various model systems used.



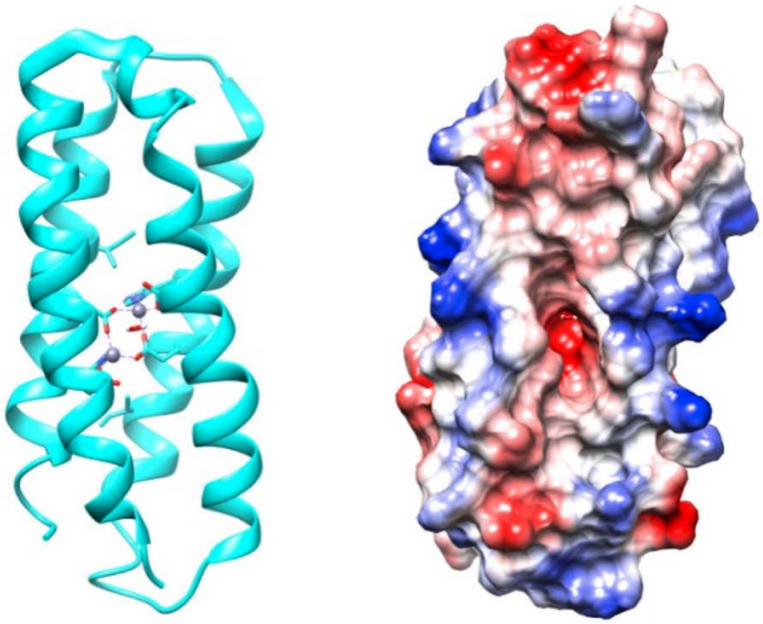
CHEMISTRY SEMINAR

Biophysical Characterization of Metal Binding to de novo Due Ferri proteins

By Ethan Clare, Chemistry '25

11:30 a.m. **Thursday, September 28, 2023** **Science Center Room 300**

Abstract:
Uncontrolled hydrolysis is the ultimate enemy when trying to work around the unwanted aqueous chemistry of abundant metals like titanium and vanadium. These metals, often used in industrial settings, are not seen much in biological environments because of their propensity to undergo this uncontrolled hydrolysis. However, nature has found ways around unwanted hydrolysis in many metals, including iron. Using this as a model, a metalloprotein system has been developed that stabilized Ti and V in an aqueous setting, thus functionalizing them to cleave DNA. The Due Ferri single chain (DFsc) protein has two iron binding sites and is modeled from natural proteins. The family encompasses many different proteins with unique modifications to the binding site. The focus of this project is biophysically characterizing the metal binding of a set of DFsc proteins with a tyrosine substitution near the active site (DY, DFY, G4Y) to better understand the structure-function relationships in these enzymes. We are interested in how the substitution of tyrosine changes metal stabilization and the binding interactions of the DFsc variants compared to proteins without tyrosine. We focused on titanium, vanadium, and zinc binding to these proteins, and were able to monitor the secondary structural of the protein associated with metal binding with circular dichroism spectroscopy. We are also monitoring binding using Inductively Coupled Plasma Optical Emission and fluorescence spectroscopies. Isothermal titration calorimetry to develop a thermodynamic profile of metal binding to protein. Using these instruments, new binding information was collected with the tyrosine proteins and a variety of metals of interest



DFsc

CHEMISTRY SEMINAR

Redox Applications of the Iron(tetraphenylcyclopentadienone) Catalyst

By Sneha Jayaram, Chemistry '25

11:30 am **Thursday, September 28, 2023** **Science Center Room 300**

Abstract:
The catalytic transfer dehydrogenations of alcohols offer a safe, green alternative to stoichiometric oxidations. Following the scheme of an Oppenauer oxidation, earth-abundant (tetraphenylcyclopentadienone)iron tricarbonyl complexes can be employed as catalysts in the oxidation of alcohols using a suitable hydrogen acceptor. Acetone, though an attractive option for the hydrogen acceptor as it doubles as the solvent, has a low reduction potential and therefore limits the substrate scope. Through previous work in this lab, furfural, having a higher reduction potential than acetone, was found to be an optimal hydrogen acceptor. Here, a comparison of three reaction conditions, varying by choice of hydrogen acceptor and temperature, was performed with a substrate scope of primary and secondary alcohols (Fig. 1). A general trend of higher yields was observed for products obtained from reactions conducted in furfural versus acetone, though no clear trend for products obtained from acetone at reflux versus 80C could be discerned.

Due to the susceptibility of aldehydes to air oxidation, giving rise to carboxylic acids, special care must be taken for their storage. The formation of bisulfite adducts offers a shelf-stable storage alternative for reactive aldehydes. The iron(tetraphenylcyclopentadienone) complexes, known to effectively catalyze carbonyl reductions, were used to conduct preliminary experiments on the direct reduction of the bisulfite adduct of 4-methylbenzaldehyde to determine the conditions under which the reaction occurs. Under the conditions described in Fig. 2, the reduction to its corresponding alcohol was observed in the presence of base. A small base screen was performed as a first step toward optimizing the reaction.

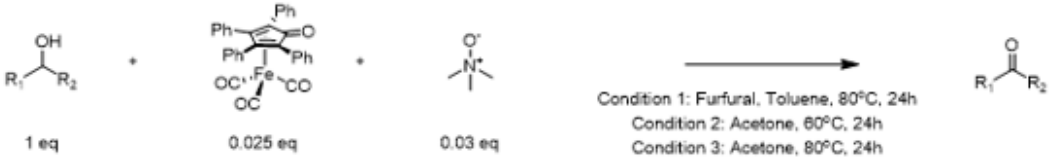


Fig. 1. Alcohol oxidations using the iron(tetraphenylcyclopentadienone) catalyst

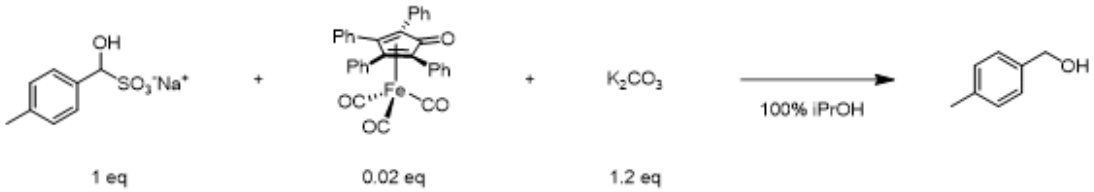


Fig. 2. Iron(tetraphenylcyclopentadienone) catalyzed reduction of an aldehyde/bisulfite adduct