REU Site: Research in Chemistry at West Virginia University
Potential Research Projects

Research Project Selection. Participants will be matched to research projects after their arrival to the REU Site with input from both participants and faculty research advisors. Initially, faculty research advisors will provide the PI with one-page descriptions of their research projects, including the societal significance, research questions to be addressed, instrumentation, procedures, and techniques to be learned, how the REU participant will contribute, and pertinent references. These one-page descriptions will be posted on the REU webpage and applicants will be referred to these materials upon receipt of their initial application and again after their acceptance of an REU offer. Upon arrival and after touring faculty research laboratories, meeting laboratory personnel (graduate students, postdocs, and advisor) and listening to and asking questions during 15-minute presentations of the available research projects, REU participants will rank their top five choices of research projects. From these rankings, and with input from faculty advisors, the PI and Co-PI will assign the research projects. This process allows REU participants to make informed decisions about their research project choices by allowing ample time for participant-faculty advisor interactions prior to project assignment. The diversity of projects in different chemistry sub-disciplines paired with more available research projects than REU participants will further facilitate this process.


Project 1: Syntheses and Structures of Carbon Nanohoops (Kung Wang, Organic) Cycloparaphenylenes (CPPs), such as Structure 1 below, represent the shortest segments of the repeating hoop-like structures of armchair carbon nanotubes. The intense current interest in CPPs is due in part to the possibility of using these hoop-like molecules as templates for growing armchair single-walled carbon nanotubes. CPPs and related carbon nanohoops can be constructed using organic synthesis reactions. This synthetic approach offers potential advantages over existing empirical methods in its ability to produce carbon nanotubes of a uniform diameter and structural arrangement, two factors of critical importance for applications in a variety of nanotechnology fields, including electronics, energy, and nanophotonic devices. REU participants will be trained to handle air- and water-sensitive materials in order to construct CPPs using contemporary organic chemistry procedures. They will be trained to operate nuclear magnetic resonance (NMR) spectrometers and infrared spectrometers (IR) and use the spectra obtained for elucidation of structural information. They will also gain experience in searching published literatures for project relevant information using online search engines.

![Structure 1](image1)

Project 2: Molecular Mechanisms of Huntingtin Interactions with Lipid Membranes (Justin Legleiter, Biophysical). There is a fundamental gap in understanding how small aggregates formed by mutant forms of the huntingtin (htt) protein with expanded polyQ tracts gain toxic biological properties causing Huntington’s disease (HD) and, more specifically, how these proteins interact with cellular surfaces comprised of lipids. Continued existence of this knowledge gap represents an important problem because these interactions may represent a fundamental step in htt-induced cellular toxicity and understanding of this phenomenon can lead to new targets for therapeutic intervention. The long-term goal of our research is to understand the physicochemical aspects and molecular mechanisms of nanoscale, pathological self-
assembly of biological macromolecules that lead to toxicity. The objective in this project is to elucidate the role of lipids on htt misfolding, aggregation, and related toxicity by determining the impact htt aggregates have on the integrity of cellular and subcellular membranous surfaces. To reach this goal, we are pursuing these specific aims: 1) identify lipid components that play a role in the binding of htt to membranes; and 2) determine how post-translational modifications (PTMs) regulate the interaction between htt and lipid membranes. Under the first aim, REU participants will use scanning probe and a variety of vesicle-based assays to characterize the endogenous interactions occurring between htt and membranes enriched with cholesterol, sphingomyelin, or GMI. Under the second aim, REU participants will use a combination of spectroscopic, mass spectrometry, and scanning probe techniques to study the role of PTMs play in modulating htt/lipid interactions.

Project 3: High Temperature Chemistry of Resonance Stabilized Radicals (Fabien Goulay, Physical)

Resonance stabilized radicals (RSRs) are characterized by delocalization of an unpaired electron in a molecular π-orbital that may encompass the entire molecule. The most common example is the propargyl radical (C₃H₃) that has two resonance structures. Figure 1 shows the propargyl-like (unpaired electron on terminal carbon) and the cyclopentadienyl-like resonance structures of the fulvenallenyl radical (C₇H₅). The true C₇H₅ structure is an intermediate between its six resonance structures. Due to their stability, RSRs can build up appreciable concentrations in combustion and interstellar environments. Recombination and cross-recombination reactions of RSRs have been proposed as a possible pathway to polycyclic aromatic hydrocarbon formation. These mechanisms are not well characterized, which leads to uncertainties about the chemical scheme governing carbon rich environments. The goal of this project is to study the kinetics and spectroscopy of RSRs at high temperature (800 K). This research project is significant because understanding the formation of combustion products will lead to improved combustion efficiency and reduced emission. The REU participant will be trained on the use of a new gas phase high temperature pulsed flow reactor to generate and investigate RSR formation and reaction. The REU participant will use laser pump-probe spectroscopy to record the kinetics and spectroscopy of reactions involving fulvenallene and other RSRs. The data will be used toward understanding the role of RSRs in combustion chemistry.

![Figure 1. Resonance structures of the fulvenallenyl radical.](image)

Project 4: Copper-Catalyzed Oxidative Decarboxylative Coupling Reactions (Jessica Hoover, Organic).

There is a need for new and alternative routes to generate complex structures from simple and readily available precursors under conditions that are benign and sustainable. Traditional cross-coupling reactions generally have poor atom- and step-economy due to the requirement for prefunctionalized organometallic reagents, noble metal catalysts, and the separation of waste products. Our work focuses on copper-catalyzed oxidative decarboxylative cross-coupling (ODC) reactions, such as C-H arylation reactions (Figure 2), as an alternative to traditional methods. Our new methodologies are significant because they represent efficient routes for the late stage functionalization of arenes to generate complex molecules of pharmaceutical interest. REU participants will evaluate new copper-catalyzed decarboxylative coupling reactions. They will perform the synthesis of starting materials, conduct and analyze new reactions, and synthesize and characterize relevant copper complexes. To carry out this work, participants will use a variety of air-sensitive techniques including Schlenk lines, high vacuum lines, a glove-box, and a solvent purification system for the handling of air- and water-sensitive materials. Participants will be trained in the use and data interpretation of a number of analytic techniques to characterize their reaction product including NMR and IR spectroscopies, and mass spectrometry.

![Figure 2. General copper-catalyzed oxidative decarboxylative cross-coupling reaction.](image)
**Project 5:** Characterizing Nt17 Peptide Oligomers with Combined Ion Mobility Spectrometry (IMS) – Gas-Phase Hydrogen-Deuterium Exchange (HDX) – Tandem Mass Spectrometry (MS/MS) Techniques. (Stephen Valentine, Analytical) Huntington’s disease (HD) is a neurodegenerative condition resulting from an expanded, glutamine-coding (CAG) repeat sequence in the huntingtin gene (HTT). The huntingtin protein (htt) contains a 17-residue, N-terminal region (Nt17) that is believed to drive protein oligomerization ultimately leading to fibril formation.\(^{13,14}\) We have recently shown that early stage oligomers of the Nt17 peptide form multiple conformations in solution that are distinguished in the gas-phase by ion mobility spectrometry (IMS) – mass spectrometry (MS) as shown in Figure 3.\(^{15}\) Molecular dynamics simulations (MDS) suggest that one conformation is relatively extended and may resemble a stacked helix assembly (Figure 2). This finding is intriguing because the oligomerization process for the Htt protein has been theorized to derive from intermolecular association of helical N-terminal regions.\(^{16,17}\) The MDS results and prior solution hydrogen deuterium exchange (HDX) studies\(^{18}\) suggest that the K6 residue may form an important stabilizing interaction. Current studies combine gas-phase HDX with IMS-MS/MS to help reveal interface regions in the oligomerization process of the Nt17 peptide. This unique combination of analytical techniques is hypothesized to reveal important interactions for a number of oligomers formed by electrospraying the Nt17 peptide as well as a number of peptides with sequence substitutions. The REU participant will work to prepare the peptide samples for the study. Next the participant will be trained in data collection on a prototype IMS-MS instrument and will conduct data analysis and interpretation of experimental results.

**Figure 3.** Drift time distributions of Nt17 [M+2H]\(^{2+}\) (upper) and [2M+3H]\(^{3+}\) (lower) ions. Lowest energy structures with matching cross sections are shown as insets next to corresponding dataset features.

**Project 6:** Forensic Chemistry (Glen Jackson, Analytical & Forensic) Dr. Jackson will use the REU program to continue to promote a strong research culture in forensic science and analytical chemistry.\(^{19}\) In one project, REU participants will use physical chemistry principles—such as vapor pressures and Antoine plots—to understand the weathering of gasoline samples under different evaporation conditions.\(^{20,21}\) Such studies will help explain how temperature affects the distributions of compounds remaining in fire debris and will be beneficial to fire investigators. In a second project, students will study the factors that affect the degradation of promethazine in forensic samples of “purple drank”.\(^{22}\) Tyler Williams (an undergraduate student on a 2015 summer research internship in the Jackson lab) has recently discovered that short-wave UV light is responsible for converting promethazine into a covalently linked dimer of promethazine. REU participants will investigate the reaction kinetics and solution chemistry conditions that influence the degradation of promethazine, which is currently causing significant problems in crime labs where “purple drank” samples are commonly seized. In a third project—recently pursued by undergraduate student Clayton Johnson (currently pursuing a PhD at Notre Dame)—REU participants will examine ways to use novel mass spectrometry methods of analysis to distinguish between the naturally occurring structural isomers tetrahydrocannabinol (THC) and cannabindiol (CBD).
Project 7: Transfer Hydrometallation using Base Metal Catalysts (Brian Popp, Organic) The hydrofunctionalization of unsaturated organic compounds is one of the most important classes of organometallic reactions since it allows small organic building blocks to be transformed into precursors of consumer products, notably pharmaceuticals. These reactions, however, have mostly necessitated precious metal catalysts, leading to higher costs and toxicity concerns. In the past decade, significant breakthroughs have allowed more cost effective and environmentally benign base metals to supplant precious metal catalysts. While base-metal-catalyzed hydrosilylation and hydroboration reactions have received significant attention, little attention has been paid to transfer hydrometallation reactions in which a simple alkyl Grignard or zinc reagent serves as the reducing source of “H-MX”. We recently discovered the first cobalt catalyst for hydromagnesiation using a bisphosphinite-pyridine (PONOP) pincer ligand (Figure 4A). The reaction is highly regioselective, providing the branched benzylic functionalized arene; however, the reaction scope of this and other iron-catalyzed reactions are limited to electron rich styrene derivatives with unsubstituted vinyl functionality. REU participants will work on complementary mechanistic and synthetic studies by carrying out kinetic studies using operando infrared spectroscopy (Figure 4B) and learning how to approach synthetic methodology development to uncover new substrate-based strategies that improve reaction generality.

Figure 4. (A) Hydromagnesiation of styrene with base metal catalysts. (B) In situ reaction timecourse of hydromagnesiation with PONOPCoCl₂ obtained with ReactIR 15. Data collected by Leandra Forte, 2015 REU participant from the College of Wooster.
References Cited


