Samford University
Howard College of Arts and Sciences

Chemistry and Biochemistry Department

Faculty Sponsored Student Research

2021-2022

Significant experiential learning opportunities for students are available in the Department of Chemistry and Biochemistry via one-on-one faculty-guided research in chemistry and biochemistry. Research participation expands and builds on the knowledge and skills students acquire in their coursework, allowing students to develop higher order technical proficiency that substantially improves their ability to compete for graduate or professional opportunities. The range of research projects available in the department is wide and covers the sub-disciplines of analytical chemistry, biochemistry, inorganic chemistry, organic chemistry, and physical chemistry. In fact, many of the projects are cross-disciplinary, overlapping with several of these sub-disciplines.

This brochure is intended to provide students with a snapshot of some of the research projects that are currently underway in the department. Readers are encouraged to contact individual faculty should they have questions about the research in this brochure. Any other questions regarding department research opportunities not answered in this brochure should be directed toward the Department Chair.

There are two general mechanisms by which students can become involved in departmental research:

DURING THE ACADEMIC YEAR

Students who are interested in participating in research during the semester (fall or spring) can do so by enrolling in a particular faculty member's section of CHEM 440. Students who do enroll in CHEM 440 are expected to devote three hours a week for each credit hour earned. Some faculty may specify a minimum of six hours a week (two credit hours) for participating in their CHEM 440 section. Each student will undergo laboratory safety training in the faculty member's lab prior to beginning any laboratory work.

To initiate this process, it is strongly recommended that students first pick up an *Application for Research* form from the departmental office (also online). This form instructs students to arrange for individual interviews with at least three research-active faculty with whom they are considering working. The discussion during those interviews will likely focus on ongoing projects within each faculty member's research group and whether there are available positions within their group. After completing the interviews, the student should rank their first, second, and third choice for faculty mentor, attach a copy of their weekly schedule for the semester, and return the form to the departmental office. Students must complete these interviews by the due date listed on the form. The faculty will then compile the application forms and try to match each student with one of their faculty mentor choices. Afterwards, students will be contacted by their assigned faculty mentors and given details about the section of CHEM 440 they should register into.

DURING THE SUMMER

Students who are interested in participating in research during the summer and have not participated previously in CHEM 440 are strongly recommended to pick up an *Application for Summer Research* form from the departmental office and to arrange for individual interviews with at least three research-active faculty, in a process that is formally identical to the one discussed above for CHEM 440. Students must complete these interviews by the due date listed on the form. If selected, students will be contacted by their assigned faculty mentors in order to discuss the details associated with their participation in the summer program. The number of summer research positions that become available may vary from year to year and will depend on the level of department and extramural funding that exists.

Students who have previously enrolled in CHEM 440 with a faculty member (and have already participated in individual interviews with faculty) and who wish to participate in summer research need only fill out an *Application for Summer Research* form and list the name of their faculty mentor. It will also be necessary for these students to discuss with their faculty mentor their intention to apply for the summer program well in advance of the indicated due date for the application.

Dr. Brian W. Gregory — Analytical

Research in the Gregory group generally focuses on topics that have applications in nanotechnology or surface science. Many of these projects are directed toward studying the structure and properties of novel surface films and layers that have advanced technological applications. These films often involve the formation of ultrathin organic layers (1-10 nm thick) deposited onto metal or semiconductor surfaces through self-assembly processes or other molecular layer deposition methods. The structure and properties of these nanoscale materials are currently being investigated using *infrared reflection spectroscopy*, *electrochemistry*, *mass spectrometry*, *X-ray photoelectron spectroscopy*, and other surface-sensitive techniques. Undergraduate researchers in the Gregory group receive direct, hands-on experience with most of these techniques in their projects, and the majority have become co-authors on peer-reviewed scientific publications. Some of the recent projects in the Gregory research group are briefly described below.

PROJECT 1: CONSTRUCTION OF AN OLIGO(ETHYLENEGLYCOL)-BASED SELF-ASSEMBLED SCAFFOLD USING N-HYDROXYSUCCINIMIDE CONJUGATION CHEMISTRY FOR THE CHEMICAL ATTACHMENT OF ENZYMES TO GOLD SURFACES

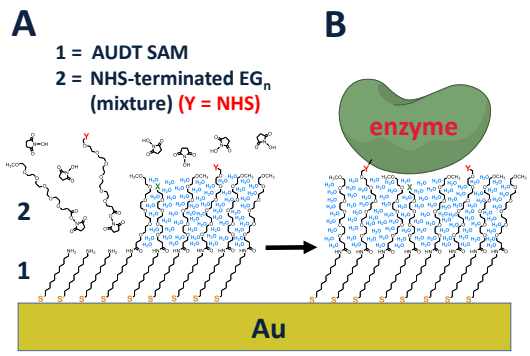


Figure 1. Multilayer mixed films for covalent immobilization of enzymes. Y = NHS ester. X = Internal standard.

One of our recent projects is focusing on the formation of bilayer films on gold that may be employed for the covalent immobilization of enzymes (**Fig. 1**). These bilayer scaffolds are being constructed from α,ω-functional reagents using self-assembly and surface conjugation methods in a "layer-by-layer" approach. Current efforts employ (1) a compact inner layer formed by a self-assembled monolayer (SAM) of 11-amino-undecane-1-thiol (AUDT) on gold, and (2) a less compact outer layer formed by surface conjugation of N-hydroxy-succinimidyl ester derivatized oligo(ethylene-glycol) reagents (NHS-EG_n-Y, n > 1). Conjugation of EG_n-Y to the terminal primary amines on the SAM is expected to result from reaction between the α-NHS of the EG_n–Y precursor, resulting in amide bond formation. To bind the enzyme and minimize non-specific adsorption, the composition of the outer layer will necessarily contain two or more ω-functional NHS-EG_n-Y reagents. Initial depositions of the overlayer have been performed from aqueous solution or from THF (in order to suppress the binding of interfacial water within the EG_n layer). *Infrared reflection-absorption spectroscopy* (IRRAS), *super grazing angle reflection spectroscopy* (SuGARS) and *X-ray photoelectron spectroscopy* (XPS) are being used to investigate AUDT SAMs on gold as well as bilayer scaffolds formed by coupling either CH_3-EG_n-NHS or NHS-EG_n-NHS to AUDT SAMs.

PROJECT 2: THE USE OF A DICATIONIC PAIRING REAGENT TO DETECT ALKYLSULFONIC ACIDS AT LOW CONCENTRATION BY PAIRED-ION ELECTROSPRAY IONIZATION MASS SPECTROMETRY

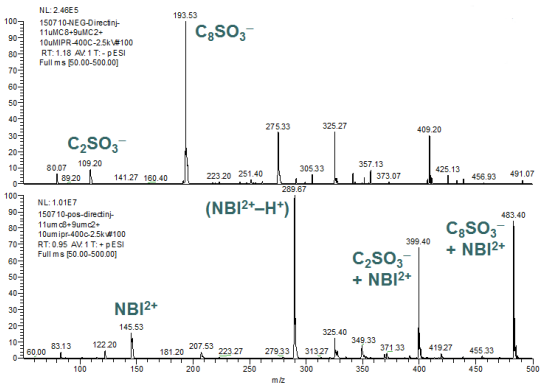


Figure 2. Top: Negative-mode ESI-MS spectrum of 9.3 μM $C_2SO_3^-$ (ethansulfonate) + 11 μM $C_8SO_3^-$ (octanesulfonate) + 10 μM NBI^{2+}; Bottom: Positive-ion mode PIESI-MS spectrum of same solution.

Another recent project in the Gregory research group has focused on improving both the limit of detection and the reproducibility for quantitative analyses of alkylsulfonic acids by mass spectrometry. Alkylsulfonic acids are the most stable oxidation products that result when alkanethiol self-assembled monolayers (SAMs) are desorbed from metal surfaces when exposed to a strong oxidant such as H_2O_2. Our approach has been to apply a relatively new technique entitled *paired ion electrospray ionization mass spectrometry* (PIESI-MS) in a novel way to a highly demanding application: to detect the ultralow concentrations of alkylsulfonic acids that result when a SAM is oxidatively removed from the surface into solution. To do this, we are introducing a dicationic *ion pairing reagent* (IPRs) to the solutions which bind singly charged anions to produce a complex ion having a net +1 charge. The product species are cationic and have a larger mass, which improves the probability of mass spectral detection (**Fig. 2**).

Recent Publication:

(1) S. Beck, E. Berry, S. Duke, A. Milliken, H. Patterson, D.L. Prewett, T.C. Rae, V. Sridhar, N. Wendland, B.W. Gregory, C.M. Johnson. Characterization of Trametes versicolor laccase-catalyzed degradation of estrogenic pollutants: Substrate limitation and product identification. *International Biodeterioration & Biodegradation* **2018**, *127*, 146-159.

Dr. Corey M. Johnson — Biochemistry

Enzymology

Enzymes are fascinating biological catalysts which mediate most of the biochemical reactions found in nature. In addition, enzymes, along with cell surface receptors, are most often the target of designed drugs. Research projects in my lab use a broad spectrum of biochemical methods to understand how enzymes work and how that knowledge can be exploited for the development of new therapies or industrial applications.

Enzyme Function and Antibiotic Development

Rapid development of antibiotic resistance is an increasing problem for treatment of life-threatening bacterial infection. Therefore, there is a great need to identify new targets and develop innovative, new approaches to the design of antibiotic drugs. The diaminopimelate pathway (DAP) for the biosynthesis of L-lysine in gram-negative bacteria and mycobacteria has been identified as a target for antibacterial agents because it produces *two* metabolites necessary for bacterial growth, survival and pathogenicity; the amino acid L-lysine, and its precursor, *meso*-diaminopimelate (used in construction of the bacterial peptidoglycan (PG) cell wall). L-Tetrahydrodipicolinate *N*-succinyltransferase (DapD) is an enzyme that catalyzes the first committed step in the pathway. Structural, kinetic and chemical mechanistic studies of this enzyme will enable an informed drug design to inhibit this clinically relevant target.

Enzyme Immobilization and Biosensors

In a collaborative project with Dr. Brian W. Gregory, we are studying the immobilization of enzymes to surfaces. This technology is useful for the development of biosensors and biofuel cells. Enzymatic systems offer a number of advantages in the development of industrial catalysts (mild conditions, cost, safety, sustainability). Unfortunately, immobilization of the enzyme often results in decreased catalytic efficiency. To investigate the enzyme-surface interface, we are studying the interactions between a model immobilized enzyme and a variety of surfaces. The model enzyme used in this project is laccase, a multi-copper oxidase of great interest as an industrial catalyst. Laccase catalyzes the oxidation of phenolic substrates with concomitant reduction of oxygen to water. We previously characterized laccase from fungal sources in bioremediation applications. This work resulted in two publications with Samford undergraduates (Beck *et al*., 2018; Eldridge *et al.*, 2017). Goals for this bionanotechnology project include achieving controlled, covalent attachment and surface coverage of the immobilized enzyme, as well as optimal enzymatic activity for the given application conditions.

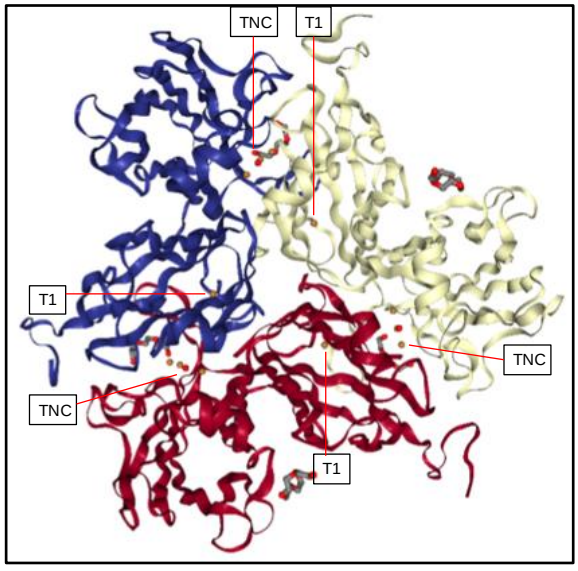


Figure. Small laccase from *Streptomyces coelicolor* is an enzyme important to industrial applications. The trimeric, functional form of the enzyme is shown here. The T1/TNC sites indicate locations of copper ion cofactors that participate in the oxidation/reduction reactions catalyzed by the enzyme. This image was generated using protein database PDB ID: 3CG8. (Skalova *et al*., 2009)

Recent Publications:

Beck, S., Berry, E., Duke, S., Milliken, A., Patterson, H., Prewett, D., Rae, C., Sridhar, S., Wendland, N., Gregory, B.W. and Johnson, C.M. (**2018**) Characterization of *Trametes versicolor* laccase-catalyzed oxidation of estrogenic pollutants: substrate inhibition and product identification. *International Journal of Biodeterioration and Biodegradation.* 127: 146-159.

Eldridge, H.C., Milliken, A., Farmer, C., Hampton, A.-S., Wendland, N., Coward, L., Gregory, D.J. and Johnson, C.M. (**2017**) Efficient Remediation of 17alpha-ethinylestradiol by *Lentinula edodes* (shiitake) Laccase. *Biocatalysis and Agricultural Biotechnology.* 10: 64-68.

Dr. Molly M. Lockart — Biochemistry

Research in my lab combines techniques from molecular biology, chemistry, and physics to better understand enzymes that are important in human health and disease. Specifically, we focus on enzymes that are gatekeepers to the human immune response to pathogens, DNA damage, and tumors. Projects in my lab will include interdisciplinary skills such as cloning, enzymology, spectroscopy, data analysis, and programming in Python and MATLAB.

Exploring cGAS and its Role in the Human Immune Response

The recognition of foreign DNA is a cornerstone of host cell defense across various forms of life. In mammals, one of the key pathways is mediated by cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS for short). This enzyme (shown in **Figure 1**) binds double-stranded DNA in the cytosol of cells. While DNA is typically in the nucleus, cytosolic DNA can occur in the case of viral or bacterial pathogens, DNA damage, or tumor formation. Despite its importance in human health and disease, there are still many questions regarding cGAS structure and activity. Research in my lab will use a biophysical approach to look at the structure and function of cGAS. Specifically, our research will focus on addressing open questions related to cGAS activation and regulation.

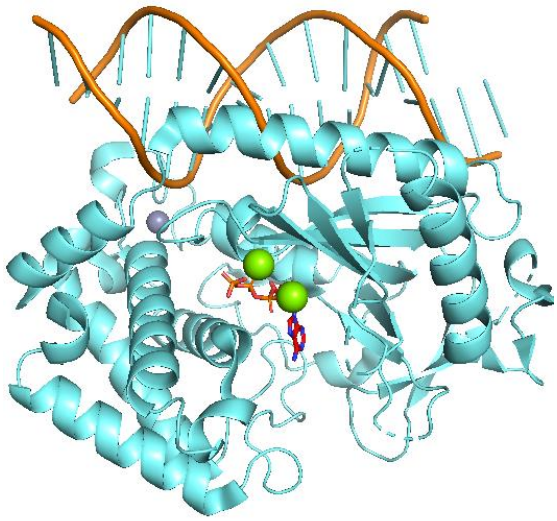


Figure 1: Crystal structure of human cGAS-DNA complex with ATP. PDB entry: 6CTA (Zhou, *et al*., 2018).

The initial project in my lab will be to explore a recently discovered alternative pathway of cGAS activation. Typically, cGAS uses Mg(II) as its catalytic cofactor. However, Mn(II) also binds to and activates cGAS. Interestingly, Mn(II) is released into the cytosol as an innate response to viral infections, and it increases cGAS' sensitivity to DNA. We will use enzymology and spectroscopy to look at how Mn affects cGAS structure and activity. A more in-depth understanding of how Mn(II) activates cGAS will provide new insight into cGAS-mediated antiviral responses.

In addition to looking at alternate activation pathways in cGAS, we will explore how cGAS is regulated towards self-DNA. The function of cGAS is to bind foreign DNA and to start an immune response. However, cGAS binds DNA regardless of the DNA sequence. Therefore, regulatory functions are in place to prevent it from binding self-DNA and causing an unwanted immune response. We will explore the structural components of cGAS that might be part of this self-regulation using a variety of spectroscopic techniques. In addition, we will generate variants of cGAS that are missing parts of the regulatory structure to better understand how activity towards self-DNA is prevented. Collectively, this project will provide new details about the components of cGAS that regulate its activity and how these regulatory domains are related to autoimmune responses.

Recent Publications

Lockart, M. M.; Edwards, K. C.; Vincent, J. B.; Pierce, B. S. Electron Paramagnetic Spectrum of Dimanganic Human Serum Transferrin. *Polyhedron*. **2021**, *203*, 115224.

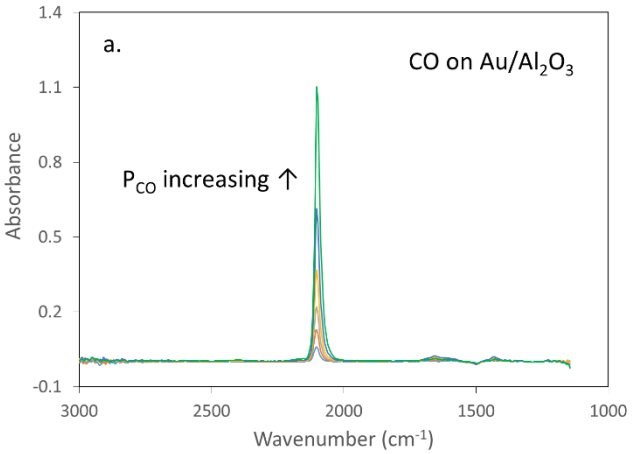
York, N. J.; **Lockart, M. M.**; Sardar, S.; Khadka, N.; Shi, W.; Stenkamp, R. E.; Zhang, J.; Kiser, P. D.; Pierce, B. S. Structure of 3-mercaptopropionic acid dioxygenase with a substrate analog reveals bidentate substrate binding at the iron center. *J. Biol. Chem*. **2021**, *296*, 100492.

Lockart, M. M.; Butler, J. T.; Mize, C. J.; Fair, M. N.; Cruce, A. A.; Conner, K. P.; Atkins, W. M.; Bowman, M. K., Multiple drug binding modes in Mycobacterium tuberculosis CYP51B1. *J. Inorg. Biochem.* **2020**, *205*, 110994.

Dr. Chris Pursell — Physical Chemistry

Infrared Spectroscopic Studies of Adsorption

Infrared spectroscopy is a fundamental experimental technique for probing the vibrational energy levels in molecules. Measurement of the infrared frequency that a molecule absorbs provides information about (1) the unique vibrational energy of the molecule (and helps identify the molecular species), and (2) the molecular environment; while measurement of absorbance provides information about the number of molecules present. Our research laboratory uses infrared spectroscopy to probe the adsorption of gas-phase molecules onto solid surfaces, thereby learning something about the interaction of the molecule with the surface and the physical and chemical properties of the surface. An example is shown below for the adsorption of CO gas on Au/Al_2O_3 catalyst. One project that we are presently pursuing is briefly discussed below.



Infrared spectra for the adsorption of CO gas onto Au/Al_2O_3 catalyst at room temperature. The different spectra represent different pressures of CO gas. The infrared frequency "peak" at 2100 cm^{-1} is unique for the CO molecule adsorbed on gold nanoparticles, while the absorbance measurement represents the number of CO molecules adsorbed.

Physical and Chemical Properties of Nanoparticle Metal Catalysts

Fundamental studies of the unique physical and chemical properties of metal nanoparticle catalysts are an important area of scientific research. An important aspect of these catalysts concerns the interaction of the metal nanoparticles with the underlying support. This is especially true for reducible metal oxide supports. The literature contains many examples that demonstrate how electronic metal – support interactions (EMSI) between metal nanoparticles and the support material are very important as they control electronic transfer and catalytic transformations that occur at the catalytic active site.

Understanding the mechanisms that control charge transfer and the activation of reactive species at specific sites can therefore aid in the design of more efficient and selective catalysts. This project therefore concerns fundamental EMSI studies examining adsorbate-induced charge transfer: from adsorbate to metal nanoparticle to the support.

Our research goals are: (1) to provide a deeper understanding of electronic metal – support interactions for these catalysts; and (2) to develop greater knowledge of the mechanism associated with hydrogen adsorption and dissociation, including hydrogen spillover. The ultimate outcome of these studies will be the further development of our understanding of metal nanoparticle catalysts.

Recent Publications:

CO Oxidation Kinetics over Au/TiO_2 and Au/Al_2O_3 Catalysts: Evidence for a Common Water-Assisted Mechanism, Johnny Saavedra, Christopher J. Pursell, Bert D. Chandler, *Journal of the American Chemical Society*, **2018**, 140, 3712-3723.

CO Adsorption on Au/TiO_2 Catalysts: Observations, Quantification, and Explanation of a Broad-Band Infrared Signal, Camilah D. Powell*, Arthur W. Daigh*, Meagan N. Pollock*, Bert D. Chandler, and Christopher J. Pursell, *Journal of Physical Chemistry – C*, **2017**, 121 (44), 24541-24547.

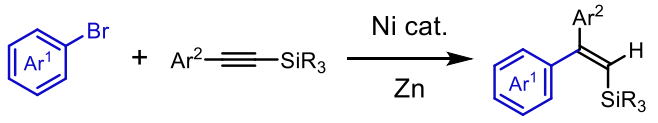
Dr. Dale Wilger — Organic Chemistry & Catalysis

Developing New Ni-Catalyzed C–C Bond-Forming Reactions

Research in my group focuses on the catalytic chemistry of the first-row transition metals. The first-row transition metals provide the perfect balance of properties, allowing for new reaction modalities with practicality and ease of operation. While modern organic chemistry has developed into an incredibly advanced field, numerous challenges still exist. A brief survey of the chemical compounds which are produced on the industrial scale by human technology indicates an overarching level of structural simplicity when compared to the architectural and biologically active molecules synthesized by organisms. At the same time, the human population and its consumption of natural resources are both growing exponentially. Organic chemistry is still one of mankind's primary instruments for converting natural resources into medicines, fuels, food additives, agrochemicals, and advanced materials such as plastics. Modern organic chemistry will only continue to advance if our synthetic capabilities are significantly enhanced. At the same time, an emphasis has to be placed on practicality, scalability, and sustainability.

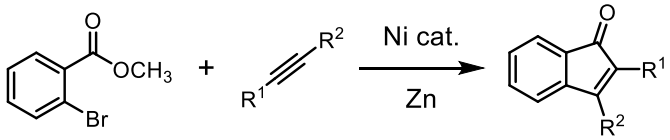
My group has recently been focused on two distinct types of Ni-catalyzed cross-coupling reaction. **Project 1** involves Ni-catalyzed alkyne hydroarylation reactions as a route towards stereoselective alkene synthesis. Alkenes are extremely useful as chemical building blocks. Several different types of alkenes are themselves included within the structures of important medicines such as Tamoxifen. Our undergraduate research group recently published a paper (*J. Org. Chem.* **2019**, *84*, 11612) which describes a Ni-catalyzed alkene synthesis with unique and sought after *anti* stereoselectivity. Within that paper we also describe a detailed account of the catalytic reaction mechanism. This will be important for developing future reactions which can improve upon this success. Five different Samford University students were authors on that paper. Our second major research **Project 2** relates to Ni-catalyzed indenone synthesis. Indenones represent an important subset of organic compounds which frequently display advanced biological activity. Indenone and indanone core structures are present in a variety of antibiotics, antivirals, anticancer agents, and in treatments for neurodegenerative disorders. Reactions which rely on Pd catalysts to construct indenones have been around for years, but many still suffer severe limitations in terms of what types of indenones can be synthesized. Our group specializes in synthesizing indenones with aliphatic and silyl substituents.

Project 1 - *Ni-Catalyzed Alkyne Hydroarylation*:



- Highly Scalable
- Entirely Air-Stable Catalysts/Reagents
- Unusual *Anti* Selectivity

Project 2 - *Ni-Catalyzed Indenone Synthesis*:



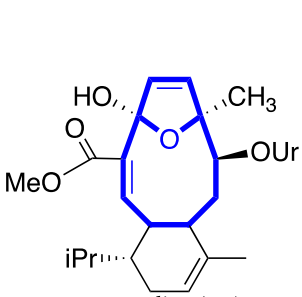
- Rare Indenone Synthesis with Esters
- Previously Unreported Aliphatic Indenones

Recent Publication:

Nickel-Catalyzed Hydroarylation of Alkynes under Reductive Conditions with Aryl Bromides and Water, E. R. Barber, H. M. Hynds, C. P. Stephens, H. E. Lemons, E. T. Fredrickson, and D. J. Wilger, *Journal of Organic Chemistry* **2019**, *84*, 11612-11622.

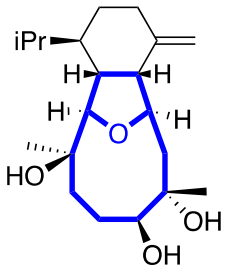
Dr. Paul Wiget Synthetic Methodology & Physical Organic Chemistry

Synthetic Methodology. How do we make a molecule consistently, efficiently, cheaper, safer, etc.? The development of new synthetic methods is an essential part of organic chemistry. Nature has its limitations, often not producing the most potent form of a drug, producing it in too small quantities to be useful, or does not produce it all. Furan-bridged ring systems (outlined in blue) are found in a number of biologically active compounds found in marine-derived natural products. These compounds have yet to find use clinically due to their lengthy and expensive syntheses. As it would be beneficial to develop a general reaction method to produce this important structural motif, our approach utilizes the stereospecific power of the [3+4] cycloaddition reaction to create four stereocenters in a single step. Having accomplished this, we are currently screening oxidation conditions for the Baeyer-Villiger (Y=O) oxidation or Beckman rearrangement (Y=NR_1). Numerous conditions exists for the solvolysis of the resulting esters and amides.



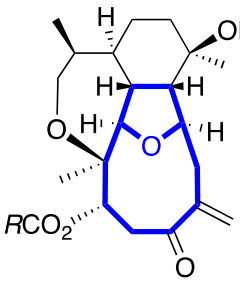
sarcodictyin A

lung, breast, ovarian, & renal cancers



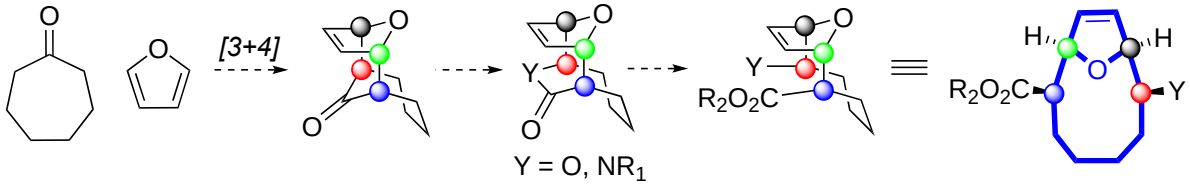
sclerophytin A
a cladiellin

leukemia

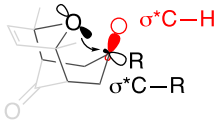


brairellin F
(R=n-heptyl)

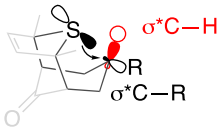
malaria



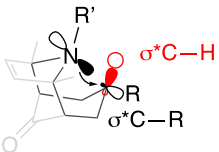
Physical Organic Chemistry. What is the relationship between structure and reactivity or properties? This is the question that drives the field of physical organic chemistry. How do we answer this question? We synthesize molecules to study specific phenomena, then we compare experimental results with previously studied systems, computational models or other theoretical predictions. The [3+4] cycloadducts mentioned above display very interesting spectroscopic properties. We have discovered the largest through-space interaction between two atoms in a single molecule. We then change the donor atom (eg. O, S, N, C) and observe the outcome. These studies have proved most fruitful in that as we attempt to build natural product scaffolds, we are always able to study and publish interesting artifacts about the molecules themselves.



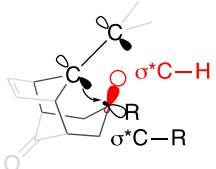
ether series
discovered remote hyperconjugation



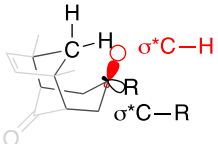
sulfide series
size and polarization on remote hyperconjugation



amine series
effect of electronegativty and sterics in remote hyperconjugation



fulvene series
bound electrons as donors in remote hyperconjugation



methylene series
control group

Recent Publication: Electronic Donation or Steric Contraction: A Spectroscopic and Structural Analysis of Medium-Sized Constrained Rings for Potential Long-Range Hyperconjugation. Robert Lee, Bryan Bashrum, Ethan C. Cagle, Jillian Walters, Jake Massey, Monica Zanghi, Carolyn Birchfield, David French, Jessica Joy, Gabriel dos Passos Gomes, and Paul A. Wiget. *Journal of Organic Chemistry*. **2019**, 84, 9897−9906. DOI: 10.1021/acs.joc.9b00979