Amherst College
Department of Chemistry

Faculty Research Abstracts
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Note: Not all of the above faculty will be taking thesis students in the 2023-2024 academic year.
Research in the Bishop lab:

Target-specific control of protein tyrosine phosphatase activity

The research interests of the Bishop laboratory are predominantly focused at the interface between organic chemistry and molecular biology. We use a combination of chemical and biochemical approaches to study complex biological processes such as cellular signal transduction. Some ongoing projects of the lab are described in greater detail below.

Protein tyrosine phosphatases (PTPs) are enzymes that help to send cellular messages by enzymatically removing phosphate groups from other proteins. When cellular phosphate removal goes awry, so do the basic regulatory mechanisms of the cell, and improperly regulated PTP activity has been implicated as a causative agent in a range of human diseases, including cancer, diabetes, and neurodegenerative disorders. Research in the Bishop lab focuses on the design of small-molecule PTP inhibitors and activators that achieve selectivity by covalently engaging non-conserved cysteine residues within the target PTPs of interest.

One particular PTP, Src-Homology-2-domain-containing PTP 2 (SHP2), represents a striking example of the connection between aberrant PTP activity and pathogenesis, as SHP2 mutations cause the developmental disorders Noonan syndrome and LEOPARD syndrome, and elevated SHP2 activity has been strongly associated with the development of human cancers. Many of our efforts center on the discovery of selective inhibitors and activators of SHP2 and its disease-associated cysteine mutants, providing direct leads for SHP2-directed pharmaceutical development.

In a project that focuses on a different PTP, we seek to discover allosteric inhibitors of T-cell protein phosphatase (TCPTP). TCPTP has recently emerged as an intriguing drug target, as disruption of TCPTP activity substantially increases the effectiveness of cancer-fighting immunotherapeutic strategies. However, few TCPTP-directed inhibitor studies have been carried out and no TCPTP-selective allosteric or covalent inhibitors have been previously identified. We are working to develop selective covalent TCPTP inhibitors that engage a cysteine residue within TCPTP’s catalytic domain. These studies will expand the range of PTP-domain cysteines that can be targeted for potent and selective allosteric control of PTP activity and will provide a novel strategy for increasing the efficacy of anti-cancer immunotherapy.
Hybrid materials that combine organic and inorganic components at the smallest of length scales are appealing because of the potential for combining the unique properties of the different constituents, such as the flexible or moldable character and the chemical functionality of polymers and the hardness or magnetic properties of minerals. In biogenic hybrid minerals such as bones, teeth, and shells, integration of organic macromolecules (proteins) in very low concentrations (typically no more than a few percent by weight) imparts remarkable enhancements in mechanical properties compared to the analogous minerals of non-biogenic origin, calcium phosphate and calcium carbonate (limestone or chalk). In synthetic hybrid materials such as polymer–clay composites, addition of a few weight percent of clay can enhance the mechanical strength, thermal stability, and barrier properties of a polymer, but only if the individual, nanometer-thick layers of the clay are well dispersed in the polymer matrix. Manipulation of the interactions at the interface between the organic and inorganic components, which may not be inherently compatible or prone to integration, is the key challenge in the preparation of hybrid materials that exhibit “best of both worlds” property enhancements rather than “worst of both worlds” results.

Efforts in the Burkett lab are directed toward a novel route to polymer–clay nanocomposites that uses synthetic layered hybrid materials as substrates for the controlled growth of end-tethered polymer chains (“brushes”); recent work has involved magnesium organosilicates (Mg₃Si₃R₆O₁₀(OH)₆) as initiating substrates for the controlled growth of the biocompatible polymer polycaprolactone. This research involves inorganic and organic synthesis as well as the use of numerous instrumental techniques for compositional and structural characterization at multiple length scales, with an emphasis on solution- and solid-state NMR techniques. The modular approach to the synthesis of components and composites accommodates a variety of linkage motifs that permit the synthesis of different types of polymer brushes of controlled length and packing density. The resulting nanocomposites are of interest for their unique materials properties and as model systems for elucidating fundamental features of polymer–clay nanocomposite structure and polymer chain dynamics. Nanocomposites of this type may find applications as lightweight, high-performance, flame-resistant materials in the airline and automotive industries or as components of medical implants and drug delivery systems in the biomedical arena.
The Durr Group: Catalyst Design for Next Generation Polymeric Materials

Research in the Durr group is centered around developing and understanding next generation polymeric materials. This includes discovering new inorganic catalysts, as well as new techniques. One of the advantages of this research is that there is something to be found in it for every type of chemist. Whether you are interested in inorganic, organic, physical, analytical, and biological chemistry you will be able to contribute to these projects and learn something new along the way.

Photoswitchable Catalysts
How do we match nature’s accuracy and precision in polymer synthesis? Nature routinely makes perfectly sequenced polymers which act as the basis for life. DNA, which is a polymer made up of four repeating monomers, encodes vast amounts of data while proteins, which are polymers made up of ~20 different monomers, are applied in numerous roles throughout living systems. Synthetic polymer chemistry is always striving for, but has thus far failed to achieve, such accuracy.

Our group hopes to achieve accurate polymer sequencing through the development of switchable catalysts. A switchable catalyst is one which polymerizes a particular monomer, A, until a stimulus is applied (oftentimes this is a redox reagent or a temperature change) and then it prefers to polymerize a different molecule, B. If we can oscillate the stimulus back and forth we can achieve sequence control of the final polymer which allows us to tune how the final material melts, moves, assembles, and physically behaves. The current challenge in this field is based around efficiently adding and removing the stimulus. Our group aims to tackle this problem by using light to switch between monomers, where the catalyst polymerizes A in the dark, and B in the light (Figure 1).

Degradable Polymers
Many of the plastics we use every day are not biodegradable – once they are used and disposed of, they will persist in our environment long after we’re gone. There are polymers that can degrade over time, but there are relatively few commercial examples compared to traditional, non-degradable, plastics. Our goal is to discover new families of polymers that will be both environmentally friendly and useful to our society. (Figure 2) This means finding new routes of degradation as well as new monomers that are capable of this
chemistry. In all cases we will be searching for catalysts that can efficiently produce such materials.

**Figure 2.**

**Bio-medical Materials**
We will be looking to utilize the catalysts we make in the production of polymers that are capable of drug delivery, medical imaging and tissue scaffolding. By controlling the composition and architecture of the polymers we produce we can influence their material properties such as crystallinity, degradation rate, strength etc. (Figure 3)

**Figure 3.**
Hansen Group—Research Abstract

If you have any questions about the projects described below or would like more information, please don’t hesitate to e-mail Professor Hansen at dehansen@amherst.edu.

Early in 2007, the Sanders group reported the serendipitous discovery of a unique class of self-assembling, helical, organic nanotubes [Pantoş, G.D.; Pengo, P.; Sanders, J.K.M. “Hydrogen-Bonded Helical Organic Nanotubes,” *Angew. Chem. Int. Ed.* 2007, 46, 194–197]. In these structures, as shown in the figure to the right, amino-acid functionalized naphthalene diimide (NDI) derivatives serve as the building blocks. Each turn of the helical nanotube consists of three NDI subunits, precisely oriented through hydrogen-bonding interactions between the carboxylic acid functionalities. The Sanders nanotubes can also serve as receptors and will complex “a string of” C$_{60}$ molecules [Pantoş, G.D.; Wietor, J.-L.; Sanders, J.K.M. “Filling Helical Nanotubes with C$_{60}$,” *Angew. Chem. Int. Ed.* 2007, 46, 2238–2240]. Although this system is remarkably elegant and the requisite NDI subunits are readily prepared, the nanotubes that form in solution are heterogeneous in length, dynamically disassembling and reforming. **The first goal of work in the Hansen lab is thus to design and synthesize NDI constructs that will assemble into nanotubes of uniform length.**

The Sanders group then reported a remarkable additional finding in spring 2008: In the presence of C$_{70}$, their NDI derivatives self-assemble not into nanotubes but rather into discrete capsules containing six NDI subunits—that is, capsule formation is templated by C$_{70}$ [Wietor, J.L.; Pantoş, G.D.; Sanders, J.K.M. “Templated Amplification of an Unexpected Receptor for C$_{70}$,” *Angew. Chem. Int. Ed.* 2008, 47, 2689–2692]. In this capsule, as shown in the figure to the left, the NDI subunits associate by forming a hydrogen-bonding network quite distinct from that in the helical nanotube. **Again, this capsule forms only in the presence of the template C$_{70}$ and thus the second goal of the work in the Hansen lab is the generation of NDI capsules that form in the absence of a template molecule.**

The broad strategy employed by the Hansen lab to achieve both of the above goals is the synthesis of NDI dimers and trimers in which the NDI monomers are preorganized through covalent tethers. For some specifics, please see our first publication on this work: Olsen, J.-C.; Batchelder, N.A.; Raney, J.H.; Hansen, D.E. “Naphthalenediimide dimers and trimers form self-assembling hydrogen-bonded nanotubes of enhanced stability,” *Supramol. Chem.* 2012, 24, 841–850. And in work not yet published, we have recently succeeded in synthesizing a tethered NDI trimer that spontaneously dimerizes to form a capsule in the absence of C$_{70}$. Further analysis of this untemplated capsule will undoubtedly be a focus of future work in the Hansen lab.
The Jaswal Lab: Unfolding proteins to learn the secrets of function and stability in Nature’s origami
https://www3.amherst.edu/~sjaswal/index.html

Proteins are the molecules that carry out the vast majority of the jobs necessary to keep cells functioning, including breaking down and synthesizing nutrients, carrying messages and cargo, providing structural support, and raising the alarm and defending against attack. The code by which sets of three nucleotides in DNA specify the 20 chemical building blocks known as amino acids that comprise the alphabet of proteins was deciphered long ago. With the explosion of genome sequencing, the order in which amino acids need to be strung together to make each and every protein that is found in nearly 200 different organisms, including humans, is now known. There is tremendous potential within this wealth of sequence information to contribute to better understanding of biology and to improve medicine by pinpointing differences in proteins from different samples – for example between healthy and tumor cells. However, this contribution is currently limited because protein chemists like us have yet to solve the 2nd half of the genetic code that truly links protein sequence to biological function.

The missing link arises because proteins function not as linear chains of amino acids, but rather each protein folds into a specific compact three-dimensional structure whose shape is the key to its ability to carry out its particular tasks. Cracking the code for this molecular origami – how an amino acid sequence specifies the correctly folded structure and the pathway for reaching it – is the fundamental “Protein Folding Problem” that has captivated protein chemists for decades. Our lab is interested in how Nature has solved the related “Protein Function Problem”: balancing the specific demands of the protein’s job within a three-dimensional structure that also possesses the stability and longevity to remain active despite (sometimes extreme) challenges of its working environment. Not only do these problems highlight a fundamental chemical puzzle, but aspects of folding and stability are incorporated into a protein’s biological role, and protein misfolding and destabilization have been linked to aging and an ever-increasing number of diseases – including neurodegeneration, cancer, and HIV infection – over the past two decades. (Fig.1)
The Jaswal Lab studies mechanisms of protein stabilization using an array of biophysical, biochemical, and computational approaches. Because some proteins spontaneously find their way back to the same folded structure after being unfolded in the test-tube, investigators have found clues into the folding process by “interrogating” proteins through heating or adding chemicals to the protein sample, and watching them unfold, then refold when returned to less harsh conditions. The principles derived from studies of refolding small proteins place the folded, or native, protein at the global energy minimum (Fig. 2A) and have entered textbooks and guided the development of models to predict and refine structure. While the harsh conditions of traditional folding methods yield insight into folding for model proteins that are “well-behaved” and resilient to being harassed by heat and chemicals, most proteins do not recover and little information about their folding is gained through such treatment. We focus on “folding-challenged” proteins that are very different from most model proteins studied. These rogue proteins are characterized by an extremely high energy barrier (Fig. 2B & C) that prevents the folded structure from unfolding, which may be a feature common to proteins involved in diseases such as Alzheimer’s and Parkinson’s as well.

**Figure 2. Simple models for protein stabilization.** With thermodynamic stabilization (A), equilibration of the native state (N) with partially and unfolded states (U) continuously exposes the protein to aggregation and proteolysis. In kinetic stabilization (B and C), the large kinetic barrier to unfolding prevents equilibration with vulnerable states, effectively isolating the functional landscape of the protein during its lifetime to the native side of barrier or transition state (‡, TS). Even if the native state is more thermodynamically stable (B) than the unfolded state, the mechanism of stabilization is still dependent on the height of the barrier and thus kinetic.

We are also developing a milder technique that uses conditions closer to physiological and allows the proteins to remain in their native state to probe folding that exploits mass spectrometry to expand the range of proteins accessible to folding investigations. The ability to explore the full diversity of mechanisms for coupling protein folding to biological function will be crucial for understanding the pathology of these diseases as well as for developing novel design strategies for therapeutic and engineering purposes.
Intermolecular interactions: unraveling their nature and employing them in chiral analysis

Research in the Leung Lab

Although they are much weaker than chemical forces, the immense number of pairwise interactions due to intermolecular forces is responsible for the structures and functions of chemical and biological systems. Furthermore, they have been shown to have a profound influence on reaction rates and product distributions. Through rotational spectroscopy of molecular complexes bound solely by these interactions (and with the guidance of theoretical calculations), we determine the structures of the complexes, from which the nature of the intermolecular forces can be inferred.

One of our several projects is to understand how halogen substituted ethylenes interact with other species. With the presence of both electron withdrawing and electron donating functionalities in the ethylenes, the manner in which they bind to protic acids (such as HF, HCl, HCCH, each with an electropositive hydrogen and an electron rich region) reveals not only the delicate balance between attractive and repulsive forces, but also the nature of these forces. For example, the protic acids bind to vinyl fluoride, 1,1-difluoroethylene, and trans-1,2-difluoroethylene in a similar motif (“top-binding”, Fig. a) but the mode of binding changes for 1,1,2-trifluoroethylene (“side-binding”, Fig. b). These complexes are all planar, and a careful analysis of the structural parameters reveals that steric effects dominate in the “top-binding” configuration, while electrostatics is prevalent in the “side-binding” motif.

Fluorine exerts its effects primarily through inductive electron withdrawal, and we have extended our work to chlorine substitution to open the possibility of contributions from resonance donation of electron density. Our findings so far have been surprising. Unlike vinyl fluoride complexes where different protic acids bind to the substituted ethylene in the same manner (“top-binding”), vinyl chloride–HF and vinyl chloride–HCCCH have different planar configurations (Figs. c and d). The binding mode of vinyl chloride–HCl is even more extraordinary; it is nonplanar (Fig. e). In fact, when F and Cl are present in the ethylene subunit, a variety of binding configurations, including “unusual” ones, have been observed. The elucidation of the structures of additional complexes (including an expansion to propene-acid complexes) is yielding a wealth of information about the competition among electrostatic interactions, dispersion forces, and steric factors.

Using non-convalently bound molecular complexes, we are forging a new direction to advance chiral analysis. Many pharmaceuticals are small, chiral molecules. It is, therefore, important to develop a precise method to determine qualitatively the absolute stereochemistry (not just the connectivity among atoms) of a chiral compound as well as determine quantitatively the purity of a mixture of this compound and its enantiomer. Current commercial implementations of these analyses are either difficult or inefficient. In our lab, we tackle these problems by using an enantiopure complexing agent (“tag”) to convert enantiomers into diastereomers, which have different structures and thus different rotational spectra. We have examined several potentially useful chiral tags as shown here:

One of them (“TFO”, Fig. f) has been used for chiral tagging experiments in forming (TFO)₂ and TFO-styrene oxide. We are continuing our efforts to identify additional chiral tags and employ them in further chiral tagging experiments.
Experimental and Theoretical Approaches to Determining Molecular Structure

Research in the Marshall Lab

Molecular structures are the basis for understanding much of chemistry, from theories of chemical bonding, to intermolecular interactions, to reaction mechanisms, to properties of materials, and even to biochemistry. Often structures of smaller systems are taken as models for larger ones, and it is essential to have the tools available to determine the molecular geometries. Microwave, rotational spectroscopy provides some of the most precise structural data available for small molecules, especially when combined with appropriate theoretical methods. In my lab, we seek to apply state-of-the-art instrumentation with innovative applications of theory to a variety of molecular systems.

Microwave spectroscopy is performed using a chirped-pulse, Fourier transform microwave (CP-FTMW) spectrometer that allows a broad region of the microwave spectrum of a molecule to be obtained in a short time. Shown below on the left is a diagram indicating the frequency content of a typical 4 μs pulse of 1500 MHz microwave power (narrow spike) and the wider spectrum from a 4 μs pulse generated using new technology that allows the frequency to be “chirped” from 1000 to 2000 MHz. In fact, we are able to generate chirps spanning 5000 MHz and centered at any frequency we desire.

Theoretical tools include the ability to solve the electronic Schrödinger equation as a function of molecular geometry using the commercial quantum chemistry package, Gaussian 16. This can provide, for example, the interaction potential energy surface between two chemical species. Shown above on the right is a relaxed scan of the interaction potential between acetylene and vinyl chloride. In the scan, the angular orientation of the vinyl chloride molecule (θ_{vc}) is varied from 5° to 355° in 10° steps, and the distance between the two subunits (R) and the orientation of the acetylene (θ_{HCCH}) are optimized at each step. We can see two possible geometries (minima on the curve) predicted by theory for this complex.

Recent developments in rotational spectroscopy also have the potential to meet the measurement challenges in the analysis of chiral species. The two mirror-image forms of a chiral molecule, or enantiomers, have nearly identical physical properties. However, when one chiral molecule interacts with another, the handedness of the two species is of critical importance. Often the desired action of a bioactive chiral molecule is associated with only one enantiomeric form. For small drug pharmaceuticals, most of which are chiral, there is a general goal of producing the final active pharmaceutical ingredient in an enantiopure form to improve drug potency and safety. Thus, the analysis of chiral mixtures, that is, mixtures containing both enantiomers of a compound, to determine the relative amounts of each and the absolute configuration of each is of key importance to the pharmaceutical industry, but currently used methods suffer from significant drawbacks. By using an enantiopure complexing agent to convert enantiomers into diastereomers with different rotational spectra the absolute configuration of the analyte can be determined. Furthermore, the relative intensities of transitions due to the different diastereomers can be used to determine the enantiomeric excess of the sample.
Biological molecules interact with each other at the molecular level in a dynamic molecular dance fueled by thermal energy, with atoms shaking, bonded atoms vibrating and twisting, side groups rotating, and larger helical units breathing and bending. In some systems, those dynamical motions provide insight into biological function, revealing the normally obscured active site of an enzyme when an inhibitory peptide transiently moves away or presaging a structural transition when a large helix bends as a side group rotates, thus shifting the register of noncovalent interactions that stabilize one of the states. Our lab’s interest is in studying these interactions both in solution and at the single molecule level. Solution studies permit measurements of large populations of molecules. Single molecule spectroscopy allows for the detection of structures that might get averaged out in typical ensemble measurements or are intermediates in the transition from one state to the next.

Three biomolecular systems are currently of interest.

- the chaperone protein alpha crystallin (αX), that is faced with the challenging task of not only keeping itself from forming opaque precipitates in the ultra-dense human lens but preventing other proteins from doing the same.
- the small protein calmodulin (CaM) that uses a variety of strategies to regulate cellular processes in response to a calcium signal.
- The large estrogen receptor (ER), in charge of responding to extracellular hormonal signals by binding to it in the cytoplasm, undergoing structural changes that lead to its dimerization, migrating to the nucleus and then locating a particular genetic locus where its job is to turn on and off sets of genes that could change the cell’s developmental fate.

At the core of our research is the application of fluorescence spectroscopy to determine the conformational dynamics that relate to protein function by using some of the techniques below:

- Förster Resonance Energy Transfer (FRET) is the non-radiative transfer of energy between two fluorescent molecules. Excitation of the donor molecule by a light source, in our case a 532nm laser, creates an excited state. Energy is then transferred to an acceptor molecule in a distance dependent manner. Ensemble FRET measurements have successfully been used to determine distances between DA pairs on a protein.
- Single molecule FRET (smFRET) allows individual molecules to be observed. As a molecule passes through the focal volume the donor is excited by a laser and emitted light (from the D or A) is recaptured by the objective and transmitted to detectors equipped with optics such that each detects wavelengths associated with D or A emission. The D/A ratio of photons is calculated and used to build up a histogram of individual FRET efficiencies.
- Fluorescence Correlation Spectroscopy (FCS) requires one detector and analyzes fluctuations in the photon count using an autocorrelation function. Depending on the time scale of these fluctuations, parameters such as fluorescence lifetime (τ) and diffusion time (τD) can be determined. Note that this function is maximized when N = 1 molecule. Diffusion of particles in and out of the focal volume happens on ~ms timescale for our systems, and can be related to the mass of the diffusing molecule.
We are interested in understanding and harnessing photo-initiated charge and energy transfer in nanoscale systems, with a focus on nanocrystal-organic molecule conjugates. This research has broad implications for technologies as diverse as artificial photosynthesis, bio-imaging, and quantum computation.

**Photoexcited charge transfer from quantum dots.** Quantum dots (QDs) are semiconducting nanocrystals that have quantum confined charges (like a particle-in-a-box) and size-tunable band gaps. Additionally, robust optical properties and surface tunability make QDs promising light-absorbers and emitters in a variety of applications ranging from solar energy conversion to displays (e.g. QLED TVs). Photoexcited charge and energy transfer plays a key role in many of these applications, motivating us to expand the fundamental mechanistic understanding of this process. We are especially interested in experimental model systems composed of QDs covalently linked to molecular charge acceptors. To glean mechanistic information from charge transfer processes, we can alter the identity of the charge donor or acceptor (QD or molecule), and see how this affects charge transfer rate constants. We also explore effects of solvent, temperature, and concentration.

**Photocatalytic CO₂ reduction.** Quantum dots can be used as light absorbers in photocatalytic CO₂ reduction schemes that use light energy to photocatalytically convert CO₂ to usable fuels in a process akin to photosynthesis. We are exploring ways to increase the efficiency of this process.

**Photogenerated spin qubit pairs.** Photoexcitation and subsequent charge separation results in a state composed of a radical cation and a radical anion. While the charge separated state persists, it possesses unique properties. Specifically, the two unpaired electron spins associated with the two radicals (anion and cation) will be correlated and in a well-defined quantum state. These photogenerated states have been termed spin qubit pairs (SQP) since they have the potential to find applications in quantum computation. We hope to use electron paramagnetic resonance techniques to detect these SQPs in systems composed of zinc oxide QDs and appended molecular charge donors.

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a) Quantum dots are semiconducting nanocrystals with confined charges and size tunable band gaps. b) They are stabilized in solution with organic ligands and can also be functionalized with molecular charge acceptors and c) can act as photosensitizers for photocatalytic CO₂ reduction; d) can host spin qubit pairs (SQP) for quantum applications.
The Wiscons group focuses on studying the effects of defect structures on the performance of crystalline molecular electronics with the goal of developing new approaches to optimize lightweight, chemically tunable, and solution processible technologies. Dopant inclusion and solid solution formation are routine performance-engineering strategies within the context of inorganics that enable modern electronics; however, the roles that analogous defect structures have on the performance of organics is underexplored. The Wiscons group uses diffuse X-ray scattering techniques to study defect structures in this material class. We are actively researching in two project areas: data storage approaching the single-molecule limit using bowl-shaped molecules and spin-polarized semiconduction in charge-transfer helicene crystals.

**Data Storage Approaching the Single-Molecule Limit**

Investigation of organic materials for practical information storage applications has long been precluded by the lack of organic ferroelectric systems that operate at or near room temperature. Ferroelectricity in organic crystals arises from collective movement of molecules in the solid-state in response to an applied electric field. We are exploring a new class of organic ferroelectrics that exploits the conformational inversion of bowl-shaped molecules for ferroelectric switching, allowing tunability of ferroelectric performance through molecular design. Students working on this project will gain experience in multi-step synthesis, learning to execute air-free and water-free reactions, as well as NMR spectroscopy and X-ray crystallography.

**Exciton Recombination in Quasiracemates of Helical Small Molecules**

Solar energy technologies are promising alternatives to conventional carbon-based fuels but lack the combination of high power conversion efficiency and cost-effectiveness necessary for widespread adoption. Currently, organic photovoltaics are limited by a balancing act between shrinking the exciton diffusion length and slowing the recombination rate of photoexcited charges. This project explores the unique ways in which broken molecular symmetry and crystallographic pseudosymmetry in quasiracemates affect the spin state and recombination kinetics of photoexcited electron-hole pairs using helical small molecules as model systems. Students working on this project will be focusing on the multi-step synthesis of the helical small molecules, involving an I$_2$-mediated oxidative photocyclization. The photocyclization reaction requires the use of a photoreactor, which has been designed and constructed by research students.