Chemistry Department
Faculty Research Abstracts

February 6, 2015
The following chemistry faculty will be supervising thesis students for the 2015-16 academic year:

Anthony Bishop
Sandra Burkett
David Hansen
Sheila Jaswal
Helen Leung
Mark Marshall
Patricia O’Hara
Elizabeth Young
Research in the Bishop Lab:

*Using small molecules to control the activities of important cell-signaling enzymes*

Broadly, the research focus of the Bishop lab lies at the interface of bioorganic chemistry and molecular biology, with a particular emphasis on the field "chemical biology"—the use of chemical tools to elucidate the cellular functions of biological macromolecules. A central challenge of the field of chemical biology is the development of small-molecule tools that can be used to study protein function very specifically, and much of our work focuses on meeting that challenge for the protein tyrosine phosphatases (PTPs), enzymes that catalyze the hydrolytic dephosphorylation of tyrosine residues on protein substrates.

Mammalian cells utilize a variety of chemical transformations to send communicative signals from one cellular location to another. The most widespread of such chemical signals is the phosphate group; the phosphorylation or dephosphorylation of a given protein can dramatically alter its enzyme activity, protein-protein interactions, or cellular localization. PTPs are therefore key regulators of signal transduction, and a complete understanding of cell signaling and signaling-based pathologies will require a full accounting of PTP function.

Small-molecule ligands that can specifically inhibit or activate individual PTPs would be valuable tools for dissecting protein-phosphorylation networks. However, the size of the PTP superfamily—roughly 100 are encoded in mammalian genomes—and the common architecture of PTP active sites impede the discovery of selective PTP ligands via conventional medicinal chemistry. The Bishop lab uses protein-engineering strategies for generating inhibitor-sensitive and activator-sensitive PTPs: engineered phosphatases whose activities are uniquely responsive to cell-permeable biarsenical small molecules. The crux of our approach resides in the introduction of ligand-binding motifs that are not present in wild-type PTPs. The engineered motifs are designed to confer either PTP inhibition or activation upon binding of the ligands, which do not affect the activities of wild-type PTPs. In a cellular context, chemical control over the activity of a single PTP of interest can be achieved by adding the ligand to cells that express the sensitized PTP.

A significant advantage of these engineered-sensitivity approaches to controlling PTP activity is that they can potentially yield general strategies for targeting multiple members of a large protein family—the amino-acid residues identified for sensitization are often present across the protein family, eliminating the need to redesign a protein/ligand interface for each new PTP target. Once highly sensitizing mutations are discovered on model PTPs, primary-sequence alignments allow for the identification of the corresponding positions in other PTPs, enabling the design, expression, and analysis of an array of sensitized PTPs for target-specific inhibition and activation. The long-term objectives of this research are to generate target-specific ligands for a substantial fraction of the PTP superfamily; to validate the potency and selectivity of target-specific PTP control in living cells; and to use the PTP inhibitors and activators in mammalian cell-signaling experiments toward the delineation of PTP functions in signaling cascades, as well as the validation of PTPs as therapeutic targets.
Hybrid Materials
Burkett Research Group

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 (Mg$_{6}$Si$_{x}$R$_{y}$O$_{16}$(OH)$_{x}$) and magnesium-aluminum layered double hydroxide clays ([Mg$_{1-x}$Al$_{x}$(OH)$_{2+}$]$_{n}$R$^{+}$)$_{m}$·nH$_{2}$O) as initiating substrates for the controlled growth of the biocompatible polymer poly(caprolactone). 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.

layered magnesium organosilicate (Mg$_{6}$Si$_{x}$R$_{y}$O$_{16}$(OH)$_{x}$)
tethered polymer chains

low polymer content
high polymer content

polymer brush–clay nanocomposites
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 dhansen@kecksci.claremont.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 untemplate 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/~jaswal/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.
Unraveling the Nature of Intermolecular Interactions

Helen O. Leung

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, we determine the structures of the complexes, from which the nature of the intermolecular forces.

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 they bind to protic acids (such as HF, HCl, HCCH, each with a 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 “side-binding” motif.

![Diagrams](image)

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–HCCH have different planar configurations (Figs. c and d). The binding mode of vinyl chloride–HCl is even more extraordinary; it is nonplanar (Fig. e). It appears that the less electronegative, more polarizable chlorine in vinyl chloride allows the competing intermolecular forces to manifest much more subtly than those in fluoroethylenes and that London dispersion forces play a significant role in stabilizing the complex.

In our studies of complexes where both F and Cl are present in the ethylene subunit, a protic acid prefers to bind to the F atom. The binding mode of 1-chloro-1-fluoroethylene–HF, 1-chloro-1-fluoroethylene–HCCH, and (E)-1-chloro-2-fluoroethylene–HF is similar to that of 1,1-difluoroethylene–HF (“top-binding”) whereas the binding mode of (E)-1-chloro-1,2-difluoroethylene–HF is similar to that of 1,1,2-trifluoroethylene–HF (“side-binding”). Thus, on the surface, it appears that the substitution of an F atom in a fluoroethylene complex by Cl does not change the manner it interacts with a protic acid. It is, therefore, unexpected for Nazir Khan ’15 to have found that HCCH binds to the Cl atom of (Z)-1-chloro-2-fluoroethylene. The elucidation of the structure of this complex will yield a wealth of information about the competition between electrostatic and steric factors.

In addition to using protic acids, we also use Ar as a binding partner to a halogen substituted ethylene. Ar is structureless and interacts with the ethylene through dispersion forces; thus, it is an effective probe of electron density away from the molecular plane of the ethylene. Hannah Tandon ’16 has worked on Ar-(E)-1-chloro-1,2-difluoroethylene. Her results are consistent with Ar binding in the FCCl cavity, which, therefore, has a higher electron density than the FCCF cavity or the CICCH cavity despite the presence of π electrons.

We will continue our work on complexes of halogen substituted ethylenes in the next academic year. Please visit my website for a more complete list of complexes studied in our lab.
Experimental and Theoretical Approaches to Determining Molecular Structure and Dynamics

Mark Marshall

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. Show 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 09. 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 ($\theta_{\text{CC}}$) is varied from 5° to 355° in 10° steps, and the distance between the two subunits ($R$) and the orientation of the acetylene ($\theta_{\text{HCCH}}$) are optimized at each step. We can see two possible geometries (minima on the curve) predicted by theory for this complex.

With the interaction potential energy surface in hand, it is important to understand the nature of molecular motion on that surface. In other words, is the molecular structure a fairly rigid one, with the atoms only moving slightly from their equilibrium positions, or is the molecule “floppy” without a well-defined structure at all? We are implementing a novel means of solving the vibrational Schrödinger equation that does not require the tedious evaluation of integrals over the potential energy surface. Called the discrete variable representation (DVR), the method provides both vibrational energy levels and wave functions. Using this method, Jessica Mueller ’13 was able to explore the quantum mechanical tunneling phenomenon in the argon-cis-1,2-difluoroethylene complex. The picture shown here indicates that, quantum mechanically, the argon atom is equally likely to be found either above or below the difluoroethylene plane, and in fact, “tunnels” between the two locations 532,000 times per second, despite not having enough energy, in the classical sense, to be found in a planar configuration. Gillian Lupinsky ’15 and Jimmy Yu ’15 are working to implement the DVR method in spherical polar coordinates for application to the lower symmetry complex formed between the argon atom and vinyl chloride, for which there is also experimental evidence for tunneling behavior.
Several projects will be available for students in the O’Hara lab for the 2015-2016 academic year. Due to my travel schedule, it will not be possible for me to direct the research of senior thesis writers until my settling back on campus in September.

The first potential thesis project is the examination of the regulation and activation of the estrogen receptor by a host of different spectroscopic techniques. You may know that estrogen is a powerful hormone that binds and activates an intracellular cytosolic receptor resulting in the complex being translocated into the nucleus where it turns on gene expression. Regulation studies seek to understand the details of that activation, looking for both small and large molecule activators and repressors. We also wish to learn the molecular details of how other compounds known as xenoestrogens (man made compounds) or phytoestrogens (plant made compounds) can also bind to the estrogen receptor, sometimes activating and other times blocking gene expression. We use fluorescence techniques such as polarization binding assays, multifrequency phase fluorometry, single molecule fluorescence, and yeast based GFP gene expression systems for our analysis.

The second potential thesis project is to develop fluorescence techniques that can be used to monitor degradation, rancidity, and fraudulent production in olive oil. Olive oil contains small amounts of many fluorescent materials including chlorophyll and its derivatives and polyphenolic compounds. These compounds provide a fingerprint for the particular cultivars and a time stamp as they continue to change post harvest. Analysis of the fluorescence of the oil can provide both producers and consumers with rapid, low cost method to judge the integrity of the oil. In its initial phase, this project would involve photophysical multicomponent analysis of the complex spectra of the oil and the development of methods for inexpensive and simple field analysis.
Research in the Young Lab

The scientific interests of the Young Lab lie in understanding the way in which electrons move from one molecular species to another. Indeed, this research is rooted in the two concepts you have all covered during CHEM-161: thermodynamics and kinetics. Recall that thermodynamics tells us if there is energy available to a system to perform a reaction, in this case, an electron transfer. And, kinetics is used to describe how fast this process happens. In the Young Lab, we explore the relationship between the thermodynamic tendency for electron transfer and the kinetics of the electron transfer event.

Why study electron transfer?

Electron transfer (ET) is ubiquitous in all of chemistry. In fact, chemical reactions are, at their core, electron rearrangements. Many other processes (some of which are outlined in the figure to the right) involve ET.

By studying ET, scientists hope to identify intermediates in chemical transformations, answer questions about how charge transfer occurs in biological systems (where movement of electrons involves movement of protons), develop theories to help predict movement of electrons (and electron movement coupled to protons), and understand the function of man-made devices (ET in solar cells, batteries, fuel cells) to improve their efficiency.

Research in the Young Lab focuses on three specific areas: i) biologically-inspired charge transfer reactions, ii) electron transfer involved in molecular systems designed for energy conversion in man-made, solid-state devices and iii) kinetics of charge transfer in thin film materials for organic solar cells (see poster by Sean Rodriguez).

Biologically-inspired electron (and energy) transfer

In biological systems, ET in proteins and peptides occurs along well-defined pathways. However, the electron cannot move alone. Charge balance must be maintained, meaning that movement of an electron along a pathway is coupled to shorter movements of protons in a mechanism known as proton-coupled electron transfer (PCET). We have employed a ferrocenyl-amidinium (Fcam) molecule to explore how its spectroscopic and electrochemical properties depend on the protonation state of the acid functionality. We have shown that this through-bond energy transfer occurring between Fcam and a ruthenium polypyridyl complex is dependent on the protonation state of the Fcam in the same way we might expect ET to depend on protonation state. In future work, we will incorporate a phlorin molecular scaffold to study charge transfer through hydrogen bonds.

Electron transfer in energy conversion

In engineered, solid-state devices, ET is the fundamental process in device operation. The generation, transport and storage of charge in solid state devices are crucial to addressing global energy concerns. In organic solar cells (OSC), charge generation occurs in a semiconductor material that consists of molecules in the solid state. Understanding the generation, transport and collection of charge in devices using such molecules is critical to understanding their operation and helping to guide design of improved devices. We are currently working on the electrochemical and spectroscopic characterization of a family of BIODPY-based molecules. Our work and work characterizing their performance in OSC will be combined to determine correlations between molecular properties and device performance.