## Graduate Study in Chemical Biology at UCI

The University of California, Irvine Department of Chemistry offers the opportunity to study Chemical Biology in a multi-disciplinary environment while earning a Ph.D. degree in chemistry. At UCI, graduate study in Chemical Biology is designed to provide students with expertise in both chemistry and biology, while training students to communicate effectively and perform research at the chemistry-biology interface.

Students with Bachelor's degrees in the biological sciences have a unique perspective to tackle Chemical Biology research, and are especially welcome to pursue graduate studies in our program. Students with Biology degrees enter the Department during the summer prior to their first year of graduate studies and participate in a program of classes and laboratory rotations. During this summer period, two courses, *Advanced Organic Chemistry* and *Chemical Biology,* will be offered. Participants in this summer program will be fully supported. The program starts at the beginning of July.

## The Curriculum

Our graduate curriculum is noteworthy for its strength, breadth and quality. Students choose from a variety of courses that provide a strong background with which to tackle problems at the interface between chemistry and biology. These courses include:

Advanced Organic Chemistry
Organic Reaction Mechanisms I
Organic Reaction Mechanisms II
Organic Spectroscopy
Organic Synthesis I
Organic Synthesis II
Organometallic Chemistry
Metallobiochemistry
Chemical Biology
Bioorganic Chemistry
Natural Products Chemistry
Polymer Chemistry
Molecular Modeling

## The Doctor of Philosophy in Chemistry

The Department of Chemistry at UCI prides itself on the outstanding quality of its Ph.D. graduates. A doctorate in chemistry from UCI is an excellent starting point for a career as an independent scientist. Many of UCI's Ph.D. graduates pursue careers in the pharmaceutical industry. Listed below are a few recent graduates, their year of graduation, and their current positions.

Dr. Steven Govek (2002) Merck; Dr. Mark Rosen (2002) Johnson and Johnson; Dr. Alec Lebsack (2002) Merck; Dr. Lewis Pennington (2002) Array Biopharma; Dr. Fred Cohen (2001) Genentech, Inc.; Dr. Amy Lew (2001) Exelixis, Inc.; Dr. Olga Fryszman (2001) Triad Therapeutics; Dr. Garrick Packard (2001) Abbott Laboratories; Dr. Dean Phillips (2001) Ligand Pharmaceuticals; Dr. Brian Bear (2001) Bayer; Dr. David Kopecky (2001) Tularik; Dr. Connie Tong (2000) Knobbe, Martens, Olson, and Dear, LLP; Dr. Rong Lin (2000 Dionex; Dr. James Tsai (2000) Arena Pharmaceuticals, Inc.; Dr. Chi Nguyen (2000) US Patent Office; Dr. Adam Tomasi (2000) Cytokinetics; Dr. Alex Buckmelter (2000) Array Biopharma; Dr. Brian Ridgway (2000) Wyeth-Ayerst; Dr. Brian Stearns (2000) Merck; Dr. David Carter (2000) Roche Bioscience; Dr. Shawn Stachel (1999) Merck; Prof. John Chisholm (1999) Syracuse University; Prof. Linda Schechinger (1999) Cerritos College.

# David A. Brant

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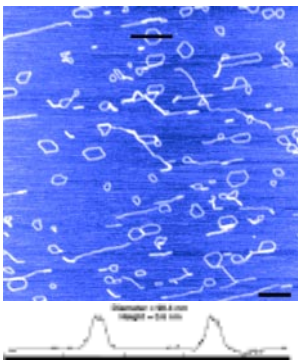
**Professor Brant received his B.S. degree from Yale University in 1958 and his Ph.D. degree from the University of Wisconsin in 1962. Prior to joining the UCI faculty in 1965, he was an NIH Postdoctoral fellow at Stanford University. Professor Brant has held Guggenheim and NIH-French CNRS Research Fellowships and received the UCI Distinguished Teaching Award in 1977. He is a member of the editorial advisory boards of *Biopolymers, Carbohydrate Research*, the *International Journal of Biological Macromolecules*, and the *Journal of Carbohydrate Chemistry*.**

Carbohydrates have experienced a great revival of chemical and biological interest. They occur in profusion on the surfaces of the cells of all higher organisms and are now known to be intimately involved in many of the processes of biological recognition, signaling, and adhesion that occur within and at the boundaries of cells. The term glycobiology has recently been coined to encompass the study of carbohydrates at the juncture of molecular and cellular biology. Our research program has its focus specifically on high molecular-weight carbohydrate polymers. Given the variety of sugars available in nature and the multiple sites of hydroxyl functionality at which modification or chain

branching can occur, there is a large potential for structural and conformational diversity. Cell surface carbohydrates are now known to serve as important sites for biological information storage.

My group has sought a fundamental physical chemical description of the relationship between polysaccharide primary structure and the distribution of three-dimensional molecular shapes that is implied by the primary sequence and modulated by the environment of the chain. About half our effort is devoted to considerations of the dynamics of change in molecular shape. Experimental methods include scattering and rheological methods for characterizing the long range (global) conformational features of polysaccharides. NMR is used as a probe of shorter-range structural features and also as a window on macromolecular motions on the nanosecond time scale. Computer simulations at the atomistic level are used to assist in data interpretation and to model behaviors that are not subject to direct observation.

Electron microscopy and scanning force microscopy have taken on increasing importance in our research program. A major theme of our current work involves studies of the nature and strength of the carbohydrate-carbohydrate interactions that stabilize the double-and triple-stranded ordered helical forms characterizing many microbial polysaccharides. In one polysaccharide system of interest for its immunostimulatory properties, we are studying the equilibrium between a very stiff linear triple-stranded helix and a highly unusual circular version of the same molecule. The linear and circular forms are readily distinguished experimentally by electron and atomic force microscopic probes. The adjacent figure shows an atomic force micrograph of the mixture of linear and circular forms produced by annealing the single-stranded random coil molecules at 70 °C.



**Representative Publications**


"Observations of the (1,3)-β-D-Glucan Linear Triple Helix to Macrocycle Interconversion Using Noncontact Atomic Force Microscopy." McIntire TM, Brant DA *J. Am. Chem. Soc.* **1998**, *120*, 6909.

"The Equilibrium Spatial Distribution of Aqueous Pullulan: Small Angle X-Ray Scattering (SAXS) and Realistic Computer Modeling." Liu JH-Y, Brant DA, Kitamura S, Kajiwara K, Mimura M. *Macromolecules* **1999**, *32*, 8611.

"Novel Approaches to Analysis of Polysaccharide Structures." Brant DA *Curr. Opin. Struct. Biol.* **1999**, *9*, 556.

"Conformational Analysis of Aqueous Pullulan Oligomers: An Effective Computational Approach." Liu JH-Y, Brameld KA, Brant DA, Goddard WA 3rd *Polymer* **2002**, *43*, 509.

"Rheology of Concentrated Isotropic and Anisotropic Xanthan Solutions: 2. A Semiflexible Wormlike Intermediate Molecular Weight Sample." Lee HC, Brant DA *Macromolecules*, **2002**, *35*, 2223.

"Rheology of Concentrated Isotropic and Anisotropic Xanthan Solutions: 3. Temperature Dependence." Lee HC, Brant DA *Macromolecules*, **2002**, *35*, 742.

# A. Richard Chamberlin

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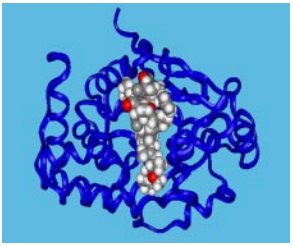
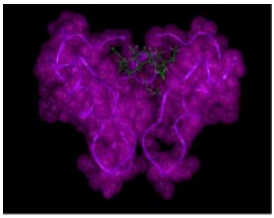
**Professor Chamberlin received his B. S. from Stanford University in 1971 and his Ph.D. from the University of California, San Diego in 1978. After spending two years at Harvard University as an NIH Postdoctoral Fellow, he joined the UCI Chemistry Department in 1980. He was an Eli Lilly Grantee and has won the UCI Physical Sciences Distinguished Teaching Awards and an NIH Research Career Development Award in neuroscience.**

Enzymes, receptors, and other proteins work in concert to control most cellular functions. How they do so is often not well understood. An important method for studying proteins is to use small molecules, generally in the molecular weight range of 100-1000, as probes. These probes can be crosslinkers, "reporters," or conformer mimics that provide information about structures of ligand binding sites in receptors or enzymes, protein-protein binding domains, electron transfer pathways, and so on. The key to such studies is careful design by computer modeling, followed by synthesis. Biologically active natural products often provide important leads because they have evolved to bind tightly to specific proteins; our synthesis efforts, however, are focused on producing new compounds that can provide information that the natural products cannot. Our synthetic targets thus encompass—in addition to the natural products—many non-natural amino acids, toxins, and even proteins. The sections below summarize four different projects of this type.


*Glutamate Receptor Binding Site Mapping with Synthetic Amino Acids.* Receptors in the brain that are activated by the neurotransmitter L-glutamate are crucial for normal cognitive function. Using a combination of computer design, synthesis, and collaborative testing, we are attempting to determine the steric and electronic properties of the binding sites of glutamate receptors and transporters in the central nervous system.



*Design and Synthesis of Serine-Theonine Phosphatase Inhibitors.* Signals are sent to various destinations within the cell in response to neurotransmitter binding and other ligands to the extracellular domains of membrane bound receptors. The resultant trafficking inside the cell is mediated in part by protein phosphorylation reactions that are induced by kinases and reversed by phosphatases. We are using the structures of naturally occurring serine-threonine phosphatase inhibitors, such as the microcystins, tautomycin, and cantharidine, to design and synthesize non-natural inhibitors that provide a better understanding of the intracellular signaling in which they participate.



*A Combinatorial Approach to Potassium Ion Channel Blockers.* Potassium ion channels—proteins embedded in cell membranes that control the passage potassium ions—are found in neurons and other cells. Using computer models of specific channels, we are designing new potential inhibitors of the flow of potassium ions through these channels. Combinatorial libraries will be synthesized in hopes of maximizing the potency of the designed inhibitors.

*Protein Structure-Function Studies with Non-coded Amino Acids.* We are exploiting a general method developed in our lab and several others of introducing non-natural amino acids into proteins without resorting to total synthesis or non-selective post-translational modification. This new protein engineering technique allows us to modify proteins in ways not possible with conventional site-directed mutagenesis. Currently, we are preparing mutants designed to study such diverse problems as (1) electron transfer pathways in heme proteins, (2) molecular recognition in protein-protein binding, and (3) protein folding.

**Representative Publications**


"Differing Effects of Substrate and Non-substrate Transport Inhibitors on Glutamate Uptake Reversal." Anderson CM, Bridges RJ, Chamberlin AR, Shimamoto K, Yasuda-Kamatani Y, Swanson RA *J. Neurochem.* **2001**, *79*, 1207.

"5'-Alkyl-benzothiadiazides: A New Subgroup of AMPA Receptor Modulators with Improved Affinity." Phillips D, Sonnenberg J, Arai AC, Vaswani R, Krutzik P, Kleisli T, Kessler M, Granger R, Lynch G, Chamberlin AR *Bioorg. Med. Chem.* **2002**, *10*, 1229.

"Total Synthesis of Dysiherbaine." Phillips D, Chamberlin AR *J. Org. Chem.* **2002**, *67*, 3194.

"The Microcystins and Nodularins: Cyclic Polypeptide Inhibitors of PP1 and PP2A." Gulledge B, Aggen JB, Huang H-B, Nairn AC, Chamberlin AR *Curr. Med. Chem.* **2002**, in press.

"Methylation of L-trans-2,4-Pyrrolidine Dicarboxylate Converts the Glutamate Transport Inhibitor from a Substrate to a Non-substrate Inhibitor." Esslinger CS, Titus JL, Koch HP, Bridges RJ, Chamberlin AR *Bioorg. Med. Chem. Lett.* **2002**, in press.

# Patrick J. Farmer

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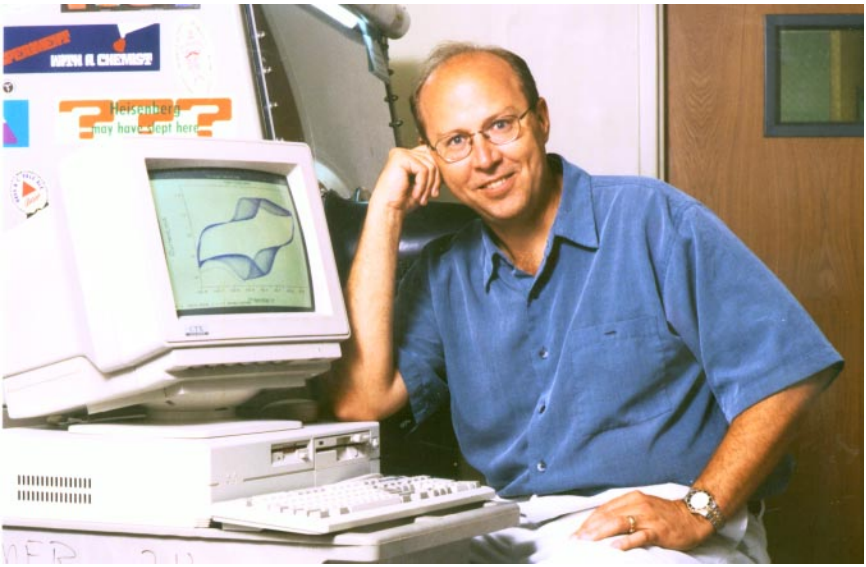
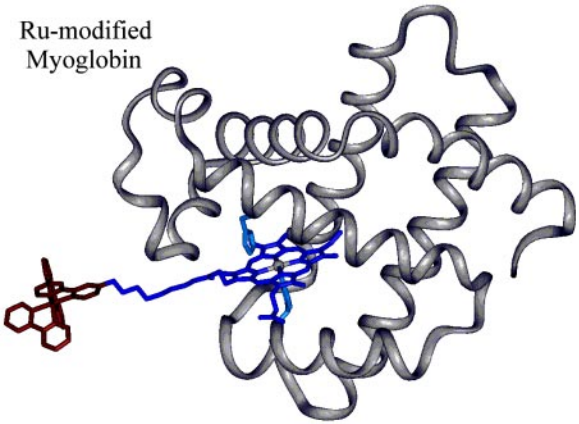
**Professor Farmer received his B.S. degree from University of Texas at San Antonio and his Ph.D. degree from Texas A&M University in 1993. He was a National Science Foundation NATO Postdoctoral Fellow at the Ecole Normale Supériore in Paris and National Science Foundation Post-doctoral Fellow at the California Institute of Technology.**

Energy transduction in biological systems, from photosynthesis to oxygen metabolism, is based on the organized transfer of electrons. Metallo-enzymes have a unique role as manifolds for electron transfers (like batteries and wires), and as catalytic sites for redox-coupled reactions. Nature has amazing control over these electron transfers; redox sites are typically oriented so as to "aim" the electron towards its acceptor site, often gating the electron flow to a specific chemical event. Like nature, we try to exploit directed electron transfer to initiate redox-catalysis in hybrid enzymes.

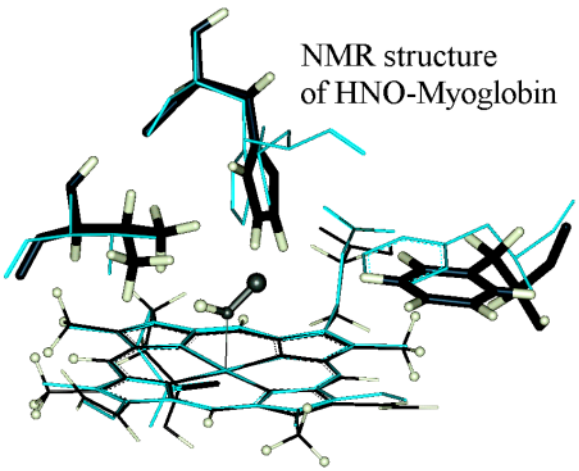
We have focused on the chemistry of oxidoreductases, like the cytochromes P450 and the nitrite reductases, which catalyze multistep, proton-coupled reductions. We can control electron flow into the active site by two methods, the first is to contain the enzyme within a film construct on an electrode surface. This allows rapid electrochemical measurements and information on






sequential steps in complicated reactions. Using the simple heme protein myoglobin as a model oxido-reductase, we can induce several bio-mimetic reactions that model transformations important to the global nitrogen cycle.

An alternative method of controlling redox chemistry within a protein is to bind a Ru complex to a protein surface; this allows us to photo-initiate redox transformations within the protein active-site and follow the reactivity of short-lived intermediates in catalytic reactions. Ultimately, we hope to make our own tailor-made enzymes to perform a number of useful chemical transformations driven simply by electricity or light.




**Representative Publications**

"Electrochemical Reduction of NO by Myoglobin in Surfactant Film: Characterization and Reactivity of the Nitroxyl ($NO^-$) Adduct." Bayachou M, Lin R, Cho W, Farmer PJ *J. Am. Chem. Soc.* **1998**, *120*, 9888.

"Catalytic Two-electron Reductions of $N_2O$ and $N_3^-$ by Myoglobin in Surfactant Film." Bayachou M, Elkbir L, Farmer PJ *Inorg. Chem.* **2000**, *39*, 289.

"The HNO Adduct of Myoglobin: Synthesis and Characterization." Lin R, Farmer PJ *J. Am. Chem. Soc.* **2000**, *122*, 2393.

"Electron Transfer in the Ruthenated Heme Domain of Cytochrome P450BM-3." Sevrioukova IF, Immoos CE, Poulos TL, Farmer PJ *Isr. J. Chem.* **2000**, *40*, 47.

"O-Atom Transfer from Nitric Oxide Catalyzed by Fe(TPP)." Lin R, Farmer PJ *J. Am. Chem. Soc.* **2001**, *123*, 1143.

"Redox Regulation in Human Melanocytes and Melanoma." Meyskens FL, Farmer PJ, Fruehauf J *J. Pigm. Cell Res.* **2001**, *14*, 148.

"Metal Binding by Melanins: Studies of Colloidal DHI-Melanin, and its Complexation by Cu(II), and Zn(II) Ions." Szpoganicz B, Kong P, Farmer PJ *J. Inorg. Biochem.* **2002**, *89*, 54.

# Zhibin Guan

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**Professor Guan received his B.S. degree from Peking University in 1987 and his Ph.D. degree from University of North Carolina at Chapel Hill in 1994, where he was awarded the Dobbins Fellowship. After completing post-doctoral research at California Institute of Technology, he joined DuPont Central Research in 1995 as a Research Chemist and was promoted to Senior Research Chemist in 1999 before joining the UCI faculty in 2000. He received the Accomplishment Award at DuPont in 1997 and was honored with the Beckman Young Investigator Award and the DuPont Young Professor Award in 2001 and the 3M Non-Tenured Faculty Award and the National Science Foundation CAREER Award in 2002.**

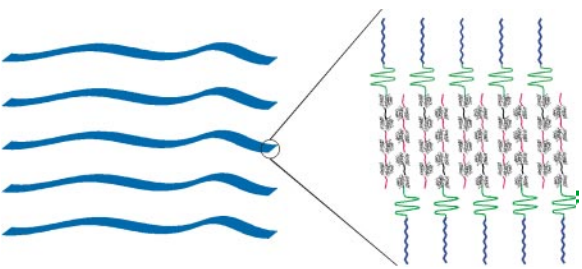
Biological soft and hard tissues, such as muscle and seashell, exhibit a remarkable combination of functions and properties. Recent single-molecule studies of muscle proteins and seashells have revealed that their combined high strength and toughness appear to derive from their modular structures comprising a linear array of domains, in which each domain is held together by secondary interactions, e.g. hydrogen-bonding, hydrophobic, and van der Waals interactions, etc. Our research program focuses on the design, synthesis and studies of organic macromolecules and organic/inorganic nano-composites that mimic the structures and functions of these natural soft and hard tissues.

*Macromolecules with multiple domains to mimic muscle.* A few strategies will be used to construct macromolecules with multiple domains to simulate the muscle protein

Macromolecule with multiple domains

*titin*. For example, synthetic and natural protein subunits with well-defined tertiary structures will be linked as domains into macromolecules. Both synthetic and genetic approaches will be applied to tune the structures of protein subunits. The structure-property correlation of the constructed macromolecule will be investigated at the single-molecule level by atomic force microscopy (AFM). A potential biomedical application of these synthetic macromolecules is as artificial muscle.

*Organic/inorganic nano-composites to mimic seashell.* The synthetic macromolecule with multiple domains will be further functionalized for use as matrix in the synthesis of organic/inorganic nano-composite materials by mimicking the strategy of biomineralization, the process used in biological systems for formation of nano-composites such as bones and seashells. A tri-block macromolecule, which contains a block with multiple domains, a soft linkage block, and a peptide block at the end for inducing mineralization, will be constructed using organic synthesis. It will self-assemble in aqueous solution to form ordered lamellar phase, which is used as matrices to induce mineralization to form hierarchically ordered organic/inorganic nano-composites. Combinatorial peptide synthesis will be used to select peptides that can induce crystallization of various minerals. A potential application of these synthetic nano-composites is as artificial bone.


Lamellar matrix formed by self-assembly (left), with a close view of the matrix (right)

**Representative Publications**

"Synthesis of Fluoropolymers in Supercritical Carbon Dioxide." DeSimone JM, Guan Z, Elsbernd CS *Science* **1992**, *257*, 945.

"Glucose Sensing Polymers." Chen G, Guan Z, Chen CT, Fu L, Sundaresan V, Arnold FH *Nature Biotechnology* **1997**, *15*, 354.

"Chain Walking – A New Strategy to Control Polymer Topology." Guan Z, Cotts PM, McCord EF, McLain SJ *Science* **1999**, *283*, 2059.

"A Remarkable Visible Light Effect on Atom Transfer Radical Polymerization." Guan Z, Smart BE *Macromolecules* **2000**, *33*, 6904.

"Novel Branching Topology in Polyethylenes as Revealed by Light Scattering and NMR." Cotts PM, Guan Z, McCord EF, McLain SJ *Macromolecules* **2000**, *33*, 6945.

"Control of Polymer Topology by Chain Walking Catalysts." Zhibin G *Chem. Eur. J.* **2002**, *8*, 3086.

"Control of Polymer Topology through Transition Metal Catalysis. Synthesis of Hyperbranched Polymers by Cobalt-Mediated Free Radical Polymerization." Zhibin G *J. Am. Chem. Soc.* **2002**, *124,* 5616.

# James S. Nowick

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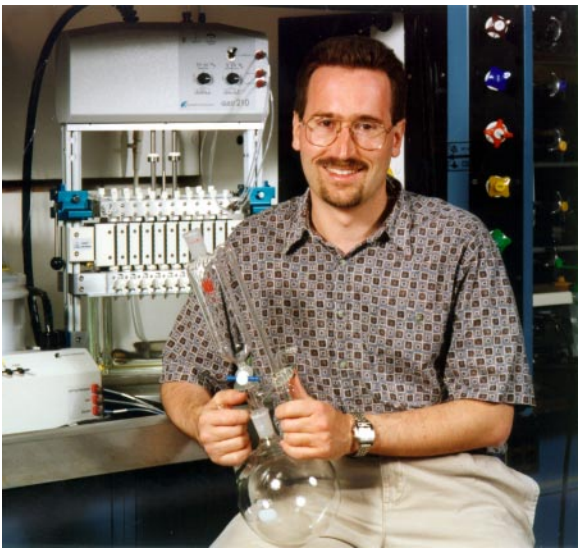
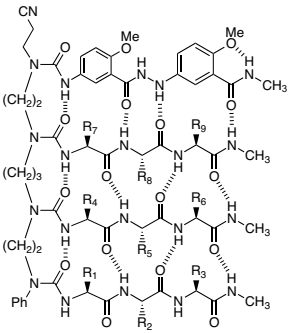
**Professor Nowick received his A.B. degree from Columbia University in 1985 and his Ph.D. from M.I.T. in 1990. He was a postdoctoral fellow at M.I.T. before joining the UCI faculty in 1991. Professor Nowick has received the following honors and awards: NSF Graduate Fellowship, an ACS Division of Organic Chemistry Graduate Fellowship, a NSF Postdoctoral Fellowship in Chemistry, Camille and Henry Dreyfus Foundation award for distinguished newly appointed faculty, American Cancer Society Junior Faculty Research Award, NSF Young Investigator Award, Arnold and Mabel Beckman Foundation Young Investigator Award, Presidential Faculty Fellow Award, Camille Dreyfus Teacher-Scholar Award, Alfred P. Sloan Research Fellowship, American Chemical Society Arthur C. Cope Scholarship.**

Molecules that mimic proteins can help teach us about proteins and lead to new drugs. Our research program focuses upon the design, synthesis and evaluation of organic molecules that mimic the structures and interactions of proteins. As an integral part of these endeavors, we seek to contribute to organic synthesis through the development of new synthetic methods.

*Unnatural Oligomers.* Unnatural oligomers that mimic polypeptides and other biopolymers are emerging as important targets in drug discovery and other areas. With the goals of developing compounds with useful structural and biological properties, we are inventing new unnatural oligomers and developing efficient methods for synthesizing them. Once we develop efficient syntheses of these unnatural oligomers, we evaluate their properties using techniques such as NMR spectroscopy and X-ray crystallography, and we incorporate them into designed complex molecules.

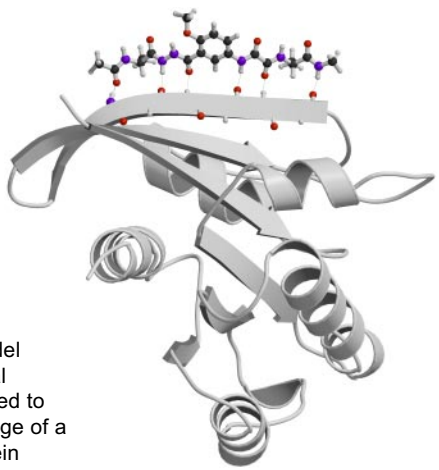


*Designed Complex Molecules.* Our unnatural oligomers serve as building blocks for more complex molecules that we design to have protein-like structures and properties. One such class of targets mimics protein β-sheets; we have termed these molecules artificial β-sheets. Once we synthesize our targets, we study them by NMR spectroscopy and molecular modeling to determine whether they achieve the anticipated structures and properties.



artificial β-sheet

*Biological Applications.* Among the most interesting and important properties of our unnatural oligomers and designed complex molecules is the ability to interact with biological systems. Right now, we are particularly excited about developing molecules that can mimic and block β-sheet interactions between proteins. β-Sheet interactions between proteins are involved in protein dimerization, recognition between different proteins, and protein aggregation and play key roles in diseases ranging from AIDS to cancer to Alzheimer's disease. Compounds that mimic β-sheets may be used to block these interactions and may ultimately lead to new drugs to treat these diseases.



Molecular model of an unnatural oligomer docked to the β-sheet edge of a Ras oncoprotein

**Representative Publications**


"Chemical Models of Protein β-Sheets." Nowick JS *Acc. Chem. Res.* **1999**, *32*, 287.

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"An Unnatural Amino Acid that Mimics a Tripeptide β-Strand and Forms β-Sheetlike Hydrogen-Bonded Dimers." Nowick JS, Chung DM, Maitra K, Maitra S, Stigers KD, Sun Y *J. Am. Chem. Soc.* **2000**, *122*, 7654.

"A Triply Templated Artificial β-Sheet." Nowick JS, Cary JM, Tsai JH *J. Am. Chem. Soc.* **2001**, *123*, 5176.

"Three-Stranded Mixed Artificial β-Sheets." Nowick JS, Smith EM, Ziller JW, Shaka AJ *Tetrahedron* **2002**, *58*, 727.

"An Unnatural Amino Acid that Induces β-Sheet Folding and Interaction in Peptides." Nowick JS, Lam KS, Khasanova TV, Kemnitzer WE, Maitra S, Mee HT, Liu R *J. Am. Chem. Soc.* **2002**, *124*, 4972.

# A. J. Shaka

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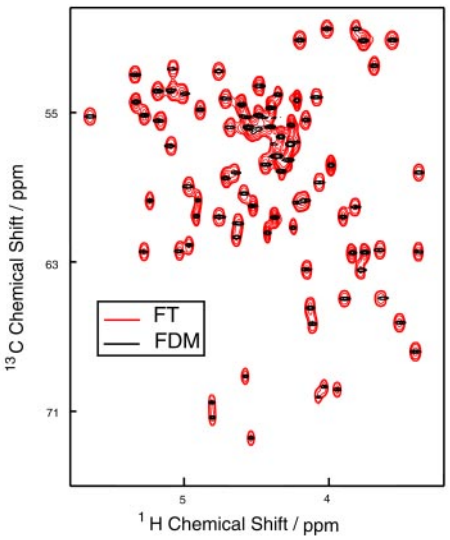
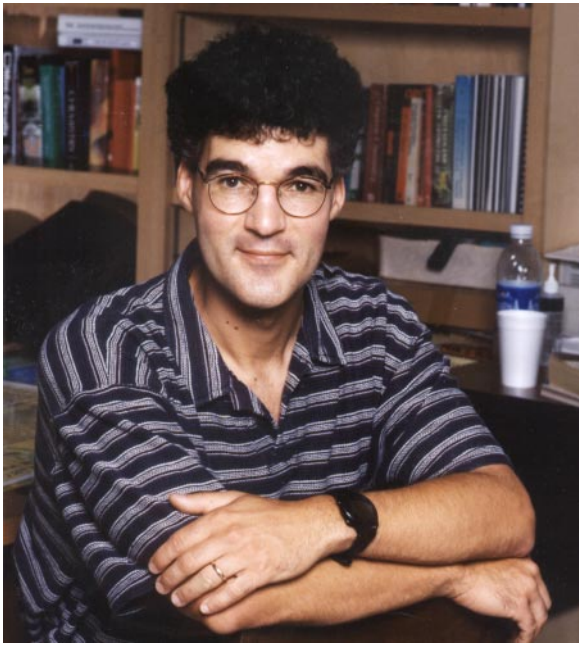
**Professor Shaka received his B.S. degree from Harvey Mudd College in 1980 and his Ph.D in 1984 from Oxford University on a Rhodes Scholarship. He joined the UCI faculty in 1988 after a year as a Junior Research Fellow at St. John's College, Oxford, and two years as a Miller Research Fellow at the University of California, Berkeley. He received a Beckman Foundation Young Investigator award, a School of Physical Sciences Distinguished Teaching award, and was named one of thirty National Science Foundation Presidential Faculty Fellows in 1992. He was honored with a UCI Alumni Association Distinguished Teaching Award in 1994 and is currently a Dreyfus Foundation Teacher Scholar, an Alfred P. Sloan Foundation Fellow, and a Rolex Achievement Award recipient.**

Nuclear magnetic resonance (NMR) spectroscopy provides a powerful tool for the study of biomolecular structures and interactions. Our main interest lies in the development of new techniques in NMR and their application to experiments for the structure determination of molecules in solution. We have recently developed, in collaboration with Professor Mandelshtam of this department, an alternative to the tried-and-true Fourier transformation, the conventional way to obtain an NMR spectrum from the measured time-domain data. Our alternative, called the Filter Diagonalization Method (FDM) is an exciting advance for protein NMR, and we are currently the only group in the world who can do it.

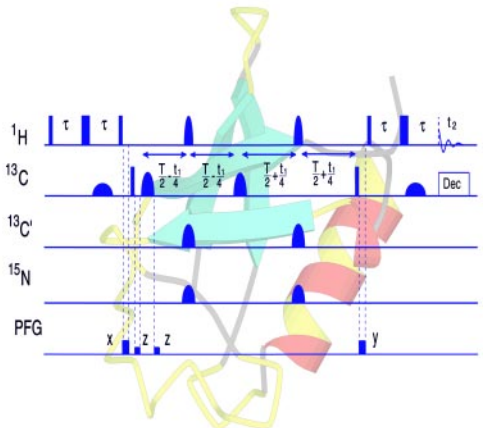
As an example, a "constant time" CH correlation of the C-alpha region of a 9.5 kDa protein is shown, with a variation of the pulse sequence used to obtain the data.





The FT data is too blurry to be useful in this crowded region, but FDM neatly resolves all the peaks. For aficionados, the total constant time was 2T = 8.3 ms, a factor of three shorter than used in this experiment before. This short time makes relaxation loss much less of a problem.

FDM will greatly improve a whole host of useful NMR experiments, with the most exciting applications yet to come.




**Representative Publications**


The Multidimensional Filter Diagonalization Method." Hu H, De Angelis AA, Mandelshtam VA, Shaka AJ *J. Magn. Reson.* **2000**, *144*, 357.

"Regularization of the Two-Dimensional Filter Diagonalization Method: FDM2K." Chen J, Mandelshtam VA, Shaka AJ *J. Magn. Reson*. **2000**, *146*, 363.

"RRT: The Regularized Resolvent Transform for High-Resolution Spectral Estimation." Chen JH, Shaka AJ, Mandelshtam VA *J. Magn. Reson.* **2000**, *147*, 129.

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# Douglas J. Tobias

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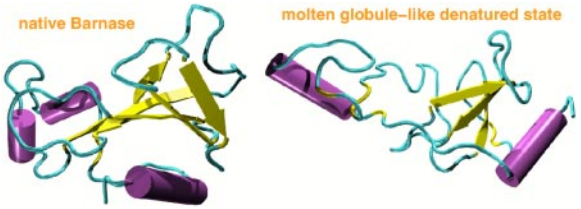
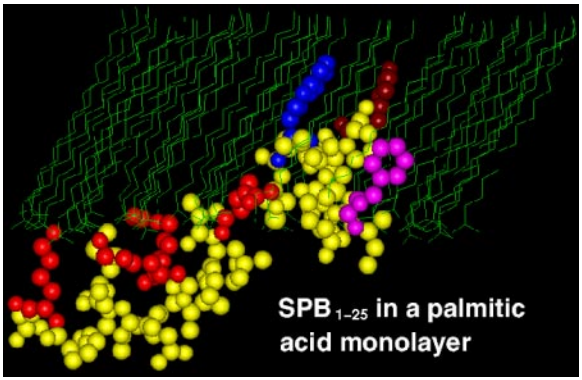
**Professor Tobias received his B.S. and M.S. degrees from University of California at Riverside in 1984 and 1985 respectively, and his Ph.D. degree from Carnegie Mellon University in 1991. Prior to joining the UCI faculty in 1997, he was a National Institutes of Health postdoctoral fellow at the University of Pennsylvania and a guest researcher at the NIST Center for Neutron Research.**

Atomic-scale computer simulations based on classical and quantum mechanics are used in our research to study the structures and dynamics of biological molecules. We devote some of our efforts to developing new simulation technology, and we collaborate extensively with experimentalists. Subjects of current interest include:



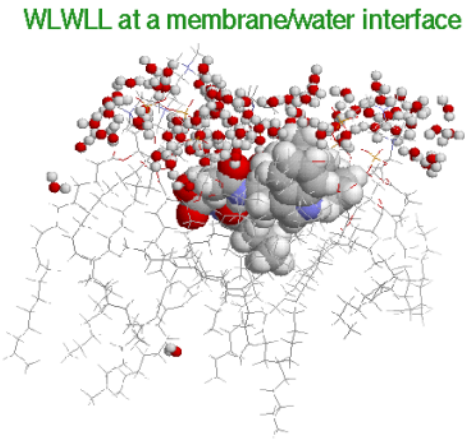

*Interactions of peptides and proteins with lipid membranes.* Membrane proteins comprise roughly 30% of the genome and 90% of pharmaceutical targets, but only a few structures of membrane proteins are known. In order to be able to predict their structures, we need to understand how membrane proteins interact with membranes. We are modeling peptides and proteins in lipid bilayers, and developing methods for using simulations to refine structures of membrane proteins determined by X-ray and neutron diffraction.

*Structure and function of pulmonary surfactant proteins.* Pulmonary surfactant (PS) is a mixture of proteins and lipids that resides at the alveolar air/water interface and keeps the surface tension low during breathing, thereby providing stability to the expanding




and contracting alveoli. We are simulating native and mutant PS proteins in lipid monolayers to predict their structures and to elucidate the role of specific residues in their function. The resulting insight should prove useful in the design of synthetic replacement surfactants to treat respiratory diseases associated with the lack of PS proteins.

*Protein dynamics.* We are using molecular dynamics simulations to study several fundamental aspects of protein dynamics related to function and folding: the transition from an inactive, glassy state at low temperature to the active, liquid-like state at higher temperatures, and the role of the solvent in affecting this transition; the storage and dissipation of vibrational energy in heme proteins; the dynamics of proteins and water molecules in denatured states.




**Representative Publications**

"Amplitudes and Frequencies of Protein Dynamics: An Analysis of Discrepancies Between Neutron Scattering and Molecular Dynamics Simulations." Tarek M, Martyna GJ, Tobias DJ *J. Am. Chem. Soc.* **2000**, *122*, 10450.

"The Dynamics of Protein Hydration Water: A Quantitative Comparison of Molecular Dynamics Simulations and Incoherent Neutron Scattering Experiments." Tarek M, Tobias DJ *Biophys. J.* **2000**, *79*, 3244.

"Membrane Simulations," in *Computational Biochemistry and Biophysics*, Tobias DJ (eds.: OM Becker, AD MacKerell, Jr., B Roux, & M Watanabe) Marcel Dekker, New York, pp. 465-496 (2001).

"Short Wavelength Collective Dynamics in Phospholipid Bilayers: a Molecular Dynamics Study." Tarek M, Tobias DJ, Chen S-H, Klein ML *Phys. Rev. Lett.* **2001**, *87*, art. no. 238101.

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# David L. Van Vranken

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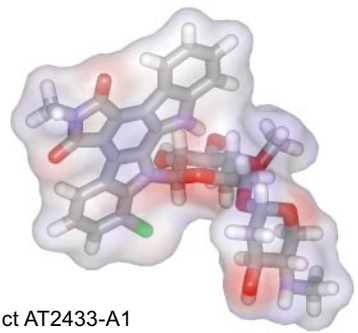
**Professor Van Vranken received his B. S. from the University of Texas at Austin in 1987 and his Ph.D. from Stanford University in 1991. He was a postdoctoral fellow at the University of California, Berkeley before joining the UCI faculty in 1994. Professor Van Vranken has received the following honors and awards: NSF Graduate Fellowship, NSF Postdoctoral Fellowship, Camille and Henry Dreyfus Foundation New Faculty Award, NSF CAREER Award, Glaxo Wellcome Chemistry Scholarship, Eli Lilly Faculty Grantee, Alfred P. Sloan Research Fellowship, Arthur C. Cope Scholarship.**

Organic synthesis is a precision tool for engineering molecules and the Van Vranken group is using organic synthesis to construct complex molecules: bioactive natural products, models of cross-linked proteins, and probes of biological function.

Proteins are chemically reactive. Two biologically important patterns of reactivity are (i) the formation of carbon-carbon bonds between aromatic sidechains, and (ii) the covalent attachment of carbohydrates to protein sidechains. These reactions of peptides and proteins are an important guide for the construction of complex natural products and we have used them in the synthesis of the tjipanazoles, the peronatins, and the AT2433 antitumor natural products.

As we continue to harness the reactions of amino acids for organic synthesis, we are also interested in the biological consequences of these reactions. Ditryptophan crosslinks can enforce 90° turns in peptide chains and induce peptides to crystallize in antiparallel beta sheets. In the defensin indolicidin, a ditryptophan crosslink confers protease resistance without diminution of the biological activity. The profound effects of ditryptophans have inspired us to look at the effects of dityrosine crosslinks, which are commonly found in long-lived structural human proteins.

Why synthesize complex molecules? In the best of cases, complex molecules can serve as powerful tools for exploring

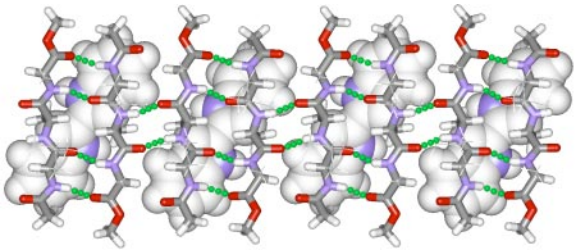


antitumor natural product AT2433-A1

biology and modulating biological function. The ability of tryptophan dimers to stereoselectively trap complex carbohydrates provides an efficient route to indolocarbazole glycoside natural products. Under physiological conditions, similar reactions graft glucose molecules onto human proteins, without the benefit of enzymatic control. These reactions are believed to contribute to the long-term consequences of diabetes: blindness, kidney failure, and amputation.

Every major protein component of the blood is known to react with glucose, but nothing is known about the membrane-bound targets of glucose. For the skilled synthetic chemist, such information is easily within reach. By constructing tagged glucose molecules, it should be possible to fish out those proteins that react fastest with glucose under physiological conditions.

The natural product bakuchiol, isolated from the Chinese herbal medicine buguzhi has been shown to reduce hyperglycemia in the db/db mouse model. Nothing is known about the origin of this important effect. Our group has developed a powerful iron-catalyzed reaction for constructing the hindered quaternary center of bakuchiol and related meroterpenoids. The structure and biological effects of bakuchiol resemble those of retinoids, suggesting a possible effect on transcriptional control.



Crystal structure of ditryptophan peptide dimers

**Representative Publications**


"A Caveat in the Application of the Exciton Chirality Method to *N*,*N*-Dialkylamides. Synthesis and Structural Revision of AT2433-B1." Chisholm JD, Golik J, Krishnan B, Matson JA, Van Vranken DL *J. Am. Chem. Soc.* **1999**, *121*, 3801.

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"Synthesis of (±)-Madindolines and Chemical Models Studies of Chemical Reactivity." McComas CC, Perales JB, Van Vranken DL *Org. Lett.* **2002**, *4*, 2337.

# Gregory A. Weiss

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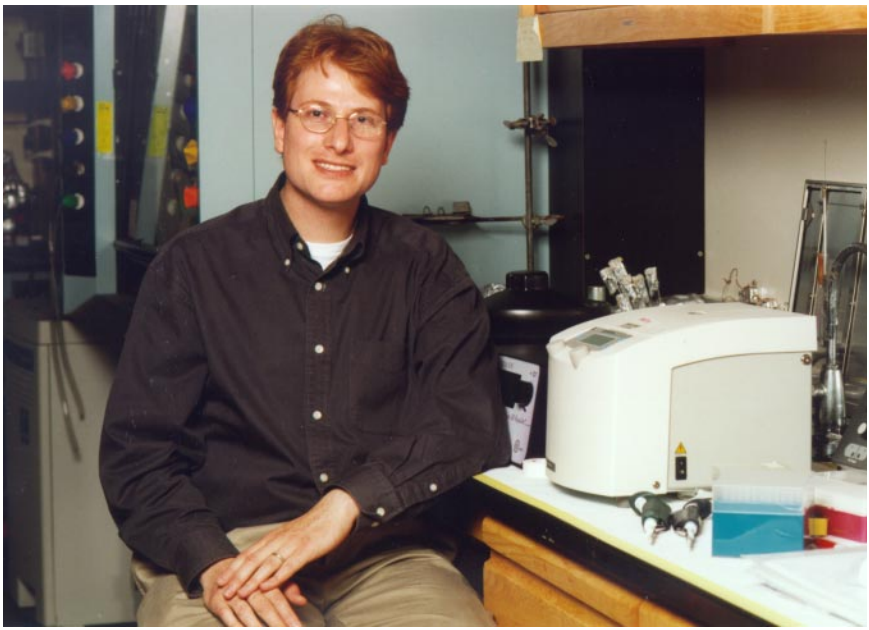
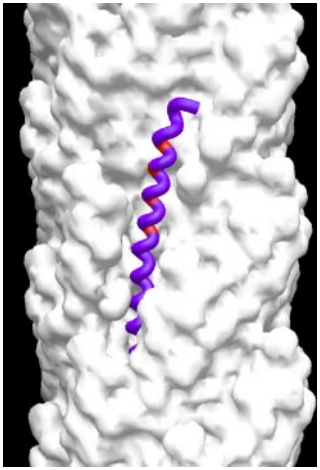
**Professor Weiss received his B.S. degree from University of California at Berkeley in 1992 and his Ph.D. degree from Harvard University in 1997. Prior to joining the UCI faculty in 2000, he was a postdoctoral fellow at Genentech, Inc. and was awarded an NIH Postdoctoral Fellowship. He received the Arnold and Mabel Beckman Young Investigator Award in 2002.**

Living cells are complicated reaction vessels—thousands of different proteins barraged by hundreds of chemical modification reactions and innumerable potential binding interactions. Research in the Weiss laboratory dissects how cells manage such complexity. Currently, our dissections apply a form of molecular evolution in a test tube called phage display to explore the chemistry and biology of cells. From vast libraries of greater than a trillion different polypeptides, we select unique protein functions and activities. This strategy of in vitro Darwinian evolution is used to explore the following areas of chemical biology.

*Molecular Recognition.* Some protein-protein binding combinations are more productive than others, as though the proteins can speak a complementary language to each other. To decipher this communication, my laboratory



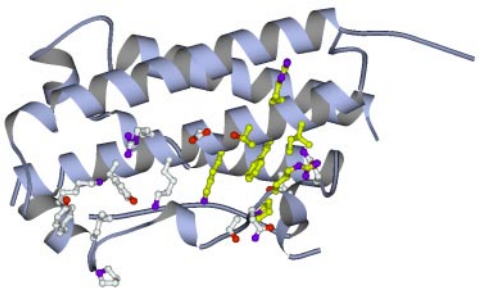


Detail of the phage coat with residues conserved during selection for high copy protein display highlighted in red

applies shotgun scanning, combinatorial libraries of alanine mutations, to rapidly map how receptors bind ligands.

*Post-translational Modification Reactions.* After synthesis by the ribosome, proteins can undergo transformation by numerous chemical modification reactions. To examine the organic chemistry of these post-translational modification reactions, my laboratory synthesizes vast protein libraries for in vitro selections of the ideal reactant. Our goal is to elucidate the organic chemistry underlying each post-translational modification reaction, by observing trends in the reactivity of starting materials.

*Enzyme Engineering.* From exceptionally large protein libraries ($>10^{12}$), we can select enzymes with powerful new capabilities.



Shotgun scanning of human Growth Hormone (above) identifies a conserved hot spot (yellow residues)

**Representative Publications**


"High Copy Display of Large Proteins on Phage for Functional Selections." Sidhu SS, Weiss GA, Wells JA *J. Mol. Biol.* **2000**, *296*, 487.

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## The Department of Chemistry

The UCI Department of Chemistry consistently ranks amongst the top programs in the country; for example, the organic chemistry program ranked ninth nationally according to a recent *U.S. News & World Report.* With 43 faculty members, 200 graduate students, and 50 postdoctoral research associates, the Department prides itself on its ability to provide vigorous research programs with international reputations in a friendly, informal atmosphere. The Department has the instrumentation needed to support these high quality research programs, including an NMR facility housing six high-field instruments, an X-ray facility equipped with two diffractometers, and four mass spectrometers that can analyze molecules as light as gases or as massive as proteins and polymers.

Research in the Department is supported by six Ph.D.–level staff scientists and three technicians, fully staffed glass and machine shops, and a chemical stockroom that never closes. In 2002, a state-of-the-art Chemical Biology building (Natural Sciences 1) opened with lab space to support research groups from both Chemistry and Biological Sciences. Natural Sciences 1 includes a NIH-funded parallel synthesis facility and organic compound archive in addition to space for very high field NMRs. Laboratory space is optimized for Chemical Biology research, including extensive 8-foot fume hoods, cold, warm, and tissue culture rooms.

## The University

The University of California at Irvine is one of the leading research universities in the United States. UCI receives almost $200 million annually from federal, state, and private agencies for the support of basic and applied research. This high level of research activity is a critical component of the educational process, particularly at the graduate level, and UCI faculty members have achieved national and international recognition for their work.

## Living on the Southern California Coast

UCI's location offers the cultural, recreational, and economic resources of a major urban area and direct access to some of the most scenic parts of California. Five miles from the Pacific Ocean, 40 miles south of Los Angeles, and 90 miles north of San Diego, the University is nestled in 1,489 acres of coastal foothills near Newport Beach. Campus buildings encircle a 21-acre central park, and the campus itself is an arboretum planted with trees and shrubs from all over the world. UCI is surrounded by beautiful coastal rangeland and is adjacent to the San Joaquin Freshwater Marsh Reserve, home to a wide variety of wildlife. The campus has an open, almost rural feel even though it lies in a dynamic, rapidly growing area of high technology development. Within a few miles of campus are many stores and boutiques, dozens of outstanding restaurants, major hotels, the Orange County Airport, movie theaters, repertory theaters, performance halls, art galleries, museums, and sports stadiums. A wide variety of affordable housing is available in the UCI area. Many of our graduate students live in Verano Place or Palo Verde, convenient on-campus apartments communities within walking distance to the Department of Chemistry.