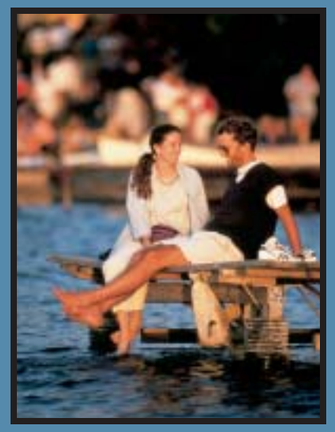
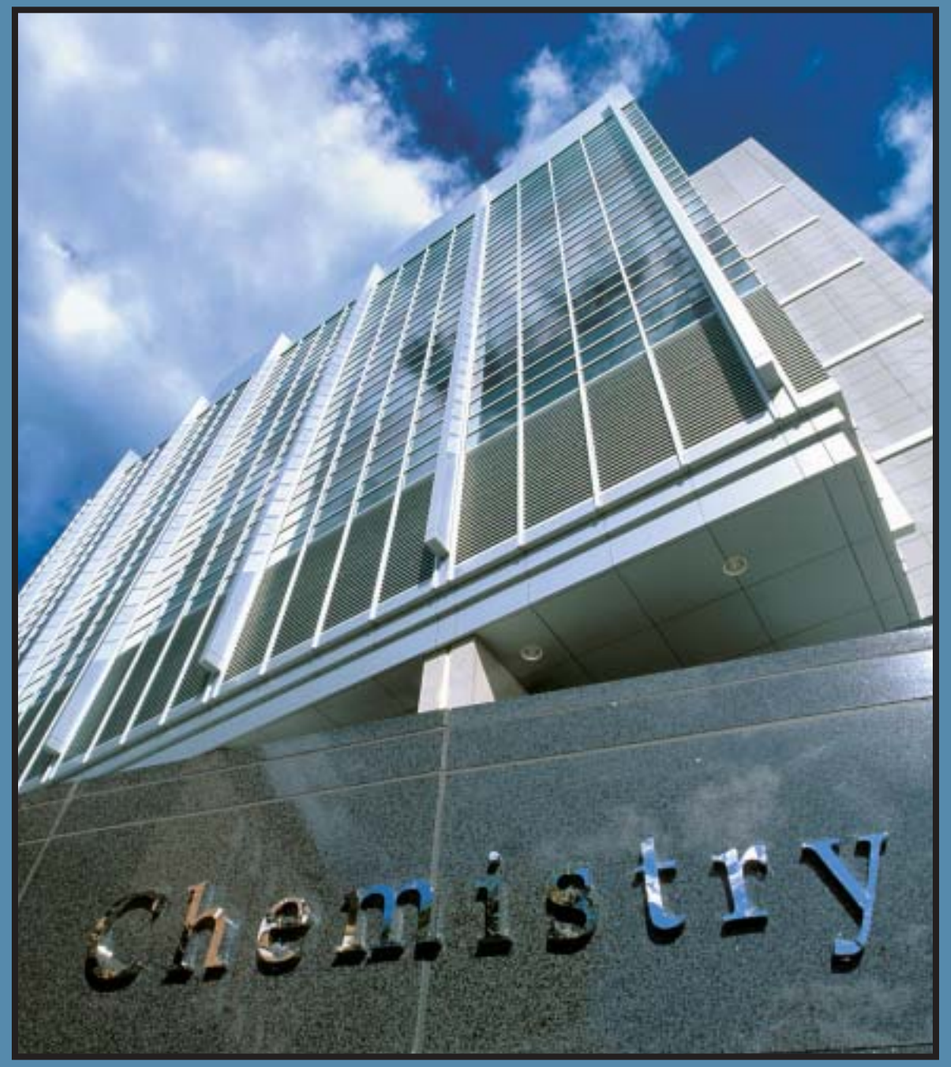


THE UNIVERSITY of WISCONSIN MADISON

Graduate Studies In

Chemistry



UNIVERSITY OF WISCONSIN–MADISON

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Why Wisconsin?

The University and the Department

The University of Wisconsin–Madison is the premier public research university in the United States. Among all universities, public and private, Wisconsin ranks in the top 5 in recent evaluations of research activity and expenditures for research and development (almost $600 million in 2001–02). Among doctoral programs in the US, fifteen UW–Madison departments, *including chemistry*, are ranked in the top 10. Five Nobel Prizes have been awarded to current or former UW–Madison faculty. Twelve Nobel prizes have been awarded to UW–Madison alumni. Seventeen Pulitzer Prizes have been awarded to Wisconsin faculty and alumni. Fifty-eight of the UW–Madison faculty are members of the National Academy of Science or the National Academy of Engineering.

For decades, Chemistry at Wisconsin has attracted outstanding graduate students, faculty, postdoctoral associates and visiting scholars. The long and continuing tradition of excellence in our Department has many direct and indirect benefits for graduate students. In addition to having a broad choice of high quality courses, seminars, and research projects, you will benefit from informal interactions with exceptional research scientists at all levels of experience. The reputation for excellence in our department is recognized locally and nationally by funding agencies and corporate research sponsors. This facilitates the establishment and maintenance of first-rate instrumentation, library, shops and laboratories.

In 2001, Chemistry Department research expenditures were in excess of $8 million. Most of this research support comes from federal agencies such as the National Science Foundation, the National Institutes of Health, and the Department of Energy, among others.

The UW–Madison campus is continuing an extensive capital improvement program. Recent projects in support of scientific research include the Biotech Center, a new Biochemistry building, and a new Chemistry building. The new Chemistry wing completed in 2000 has increased research space by 35%. The new Engineering Centers Building was dedicated Oct. 18, 2002, and renovations to the Mechanical Engineering Building are underway. The Biostar project will add over $300 million in construction and major renovations in Biotech, Biochemistry, Microbial Sciences, and Interdisciplinary Biology.

Whether you expect to pursue an academic, industrial or government career, a Wisconsin Chemistry Ph.D. will be of great value. Literally hundreds of graduates of our programs have distinguished themselves as professors, research scientists, and administrators. The reputation of Wisconsin graduates in industry is evidenced by the fact that numerous companies send recruiters each year to conduct placement interviews right in our Department. This is a significant career advantage for Wisconsin graduate students.

The research atmosphere at Wisconsin, especially in Chemistry, is a distinctive feature. Collegiality and interactiveness are the rule. Two or more research groups typically combine for research and literature seminars, broadening students' exposure to a variety of viewpoints and techniques. This free intellectual and technical exchange, together with talent and enthusiasm for science, affords a very stimulating environment.

You will note that Chemistry, Biochemistry, Pharmacy and Chemical Engineering are separate departments at Wisconsin. Each, on its own, enjoys national top ten status among competing doctoral programs. Interaction and collaboration between students and faculty in these departments are common, and you are encouraged to take advantage of these wider opportunities in your course work and research.

Faculty Awards

The research and teaching accomplishments of the faculty in our department have been recognized with numerous national and international awards. Within the past ten years, current faculty have won nine American Chemical Society Awards, eight National Science Foundation Presidential Young Investigator or Faculty Fellow Awards, and six awards from the Dreyfus Foundation. Election to the National Academy of Sciences, the American Association for the Advancement of Science, or the American Physical Society are notable distinctions earned by eleven chemistry professors active at Wisconsin now. Seventeen faculty have been named Fellows of the Alfred P. Sloan Foundation, nine have received Alexander von Humboldt Senior Scientist Awards, and five have been J. S. Guggenheim Fellows. Twenty additional corporate, foundation and international awards have recently been given to Wisconsin chemistry faculty.

These, together with numerous appointments to editorial advisory boards

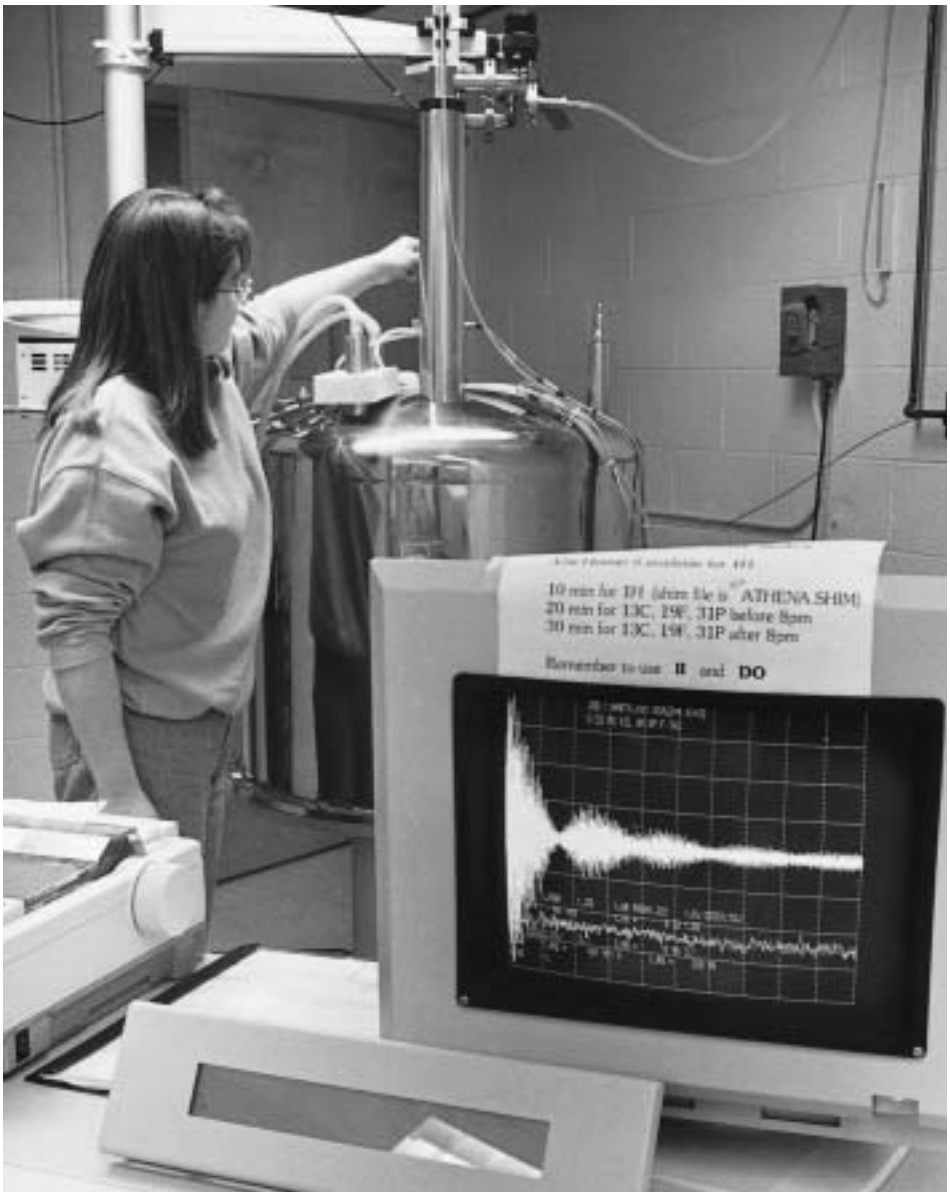
and federal funding review panels, underscore the reputation and achievements of our faculty. The scientific accomplishments of our students are directly acknowledged as the basis for this recognition.

Research Opportunities and Course Opportunities

Graduate students at Wisconsin major in one of the classical fields of chemistry: analytical, inorganic, materials, organic, or physical. These broad designations do not convey, however, the richness of research opportunities that exist. The following subdisciplines, which often overlap one or more of the classical fields, are currently represented among the research groups at Wisconsin.

Astrochemistry
Bioanalytical Chemistry
Bioinorganic Chemistry
Bioorganic Chemistry
Biophysical Chemistry
Biotechnology
Catalysis
Chemical Education
Computational Chemistry
Electrochemistry
Instrumentation
Laser Chemistry
Macromolecular Science
Molecular Dynamics
Molecular Self-Assembly
Natural Products
Organometallic Chemistry
Pharmaceutical Chemistry
Photochemistry
Physical Organic Chemistry
Quantum Chemistry
Reaction Mechanisms
Solid State Chemistry
Spectroscopy
Structural Chemistry
Surface Science
Synchrotron Radiation
Synthetic Chemistry
Theoretical Chemistry
X-Ray Crystallography

More information about these topics is contained in the descriptions of the individual faculty members' research programs.



First-year graduate students select from a nucleus of fundamental courses given each year in areas such as thermodynamics, organic reaction mechanisms, quantum mechanics, spectroscopy, kinetics, transition metal chemistry, instrumental analysis, MO theory of organic systems, organic synthesis, and so on. More specialized courses at the advanced level are also given, and vary from year to year. Depending on a student's major area, the actual program varies widely. Students are required to take four courses in areas outside their thesis specialization (the "minor" requirement). Course work in the major area is described in more detail under seven categories (analytical, inorganic, materials, organic, physical, chemistry, theoretical chemistry, and the chemistry-biology interface). However, there is much variation even within these categories, especially after the first year. For example, the advanced courses taken by physical chemists specializing in theoretical chemistry often will differ from those taken by their colleagues in spectroscopy or macromolecular chemistry. Similarly, organic chemists may choose to place emphasis on synthesis or on physical methods of structural characterization.

For students with research interests that extend into other fields bordering chemistry there are opportunities for

course work, collaborative research, and seminars presented by experts from throughout the world in many other departments. Upon approval by the thesis adviser and any other faculty members involved, collaboration is possible with the Enzyme Institute, the Molecular Biology program, the Biophysics program, the School of Pharmacy, the Departments of Bacteriology, Biochemistry, Genetics, Mathematics, Physics, and Computer Sciences, and the College of Engineering.

Facilities

The Chemistry Department occupies a modern, air-conditioned building. All of the graduate course activities are in the same building, as is the extensive chemistry library. Graduate students receive a key to the library for access at all hours. Research facilities are among the best in the country. The machine shop can produce anything from microware to a huge vacuum chamber, and the glassblowing shop and the electronics shop are equally impressive. Many research instruments have been built there, and students have a special area for their own shop work and electronics projects. Access to shop service and specialized equipment makes the most sophisticated construction projects possible.

Chemistry Instrument Center

The UW–Madison Chemistry Department maintains a comprehensive research instrumentation facility that is open and accessible to students. The Paul Bender Chemical Instrumentation Center (CIC) provides Chemistry Department researchers with state-of-the-art instrumentation in the areas of magnetic resonance (NMR and ESR), mass spectrometry, and x-ray crystallography. Each area is headed by a Facility Director. These individuals, all Ph.D. chemists, advise and work with students on the experiments and on the science. Two highly skilled electronics engineers attend to instrument maintenance and upgrades. Interested students will get hands-on access to most departmental instrumentation, an experience that is intended to be an integral part of a Wisconsin education. Practical training in NMR is provided in formal courses, taught by the NMR staff, while individual instruction is provided for more complex techniques. Qualified student operators have key privileges and around-the-clock access to instruments.

Nuclear Magnetic Resonance Spectroscopy

Eight research spectrometers constitute the state-of-the-art nuclear magnetic resonance facility in our Department. Routine proton, carbon, fluorine and phosphorus spectra are obtained on two Bruker 300 MHz NMR instruments, and all common nuclei and variable temperature are accessible on a Bruker 250 MHz spectrometer. Much of the NMR research investigating organometallic compounds is performed on a new Bruker AVANCE 360 MHz instrument. A very wide range of temperatures and multinuclear capability is provided on this instrument, as well as on our recently upgraded UNITY–500 MHz spectrometer. New Varian INOVA–500 and 600 MHz spectrometers provide the highest field strengths for the most complex and demanding experiments. High-resolution magic-angle spinning capability is available on the INOVA–500, allowing liquid-like spectra to be obtained from combinatorial chemistry compounds synthesized on solid-supports. All of this equipment is available for student use, and extensive training in the theoretical and experimental aspects of modern NMR spectroscopy is provided both through formal courses (Chemistry 636 and 637) and when appropriate by individual tutorial. Dr. Charles Fry, Director of the NMR Facility, is available to help in the interpretation of spectra, and to assist in the design and implementation of more sophisticated experiments such as those involving pulsed-field gradients, selective excitation, and multiple dimensional NMR.

Also available in the facility is a Bruker ESP–300E ESR Spectrometer. This equipment can be used for solution, powder, and single crystal X-band studies. The spectrometer is connected to the department ethernet and includes a PC based off-line data station for ESR data reduction and plotting. Several irradiation sources are available, as are variable temperature capabilities to run spectra between 4 K and 325 K.

Mass Spectrometry

Five mass spectrometers are located in the Mass Spectrometry Laboratory in the new wing of building. Three different ionization techniques are available on the

different instruments. Three of the instruments are normally in electrospray ionization mode, one in matrix-assisted laser desorption/ionization mode (MALDI), and one in electron impact mode. This allows a wide range of samples to be characterized. The 2002 Nobel Prize in Chemistry (Fenn and Tanaka) recognized the importance of having electrospray ionization and laser desporption/ionization in a modern laboratory. The prize also points up the necessity of continuously upgrading analytical instrumentation to give Wisconsin students opportunities to make state-of-the-art measurements.

As of this writing, the mass spectrometers in the lab are a Micromass LCT (orthogonal electrospray ionization, reflectron time-of-flight analyzer), a Bruker Reflex II (MALDI, reflectron, time-of-flight analyzer, delayed extraction, 337 nm nitrogen lazer), a Shimadzu LCMS–2010 (electrospray ionization, single quadrupole analyzer, autosampler, photoarray detector, fraction collector), a Micromass AutoSpec (electron impact ionization, magnetic sector analyzer), and a Finnegan TSQ700 (electrospray ionization, triple quadrupole analyzer). Both the Bruker Reflex II and the Shimadzu LCMS–2010 are operated by graduate students who have been trained by the Laboratory Director, Dr. Martha M. Vestling. To get experience in the operation of all the instruments, graduate students are urged to consider becoming a mass spectrometry TA.

Chemistry 638, Introduction to Mass Spectrometry, is a one-credit course team taught by Dr. Vestling and Dr. Amy Harms, Biotechnology Center Mass Spectrometry Laboratory, to promote the design of good experiments for our instruments. It provides information on the various mass spectrometers, on how to prepare samples, and how to analyze the data. Dr. Vestling and assistants work closely with individual students and faculty in the Department on specific research projects.

A GCMS is available in the Advanced Analytical Chemistry teaching laboratory.

X-Ray Crystallography

The Molecular Structure Laboratory, located on the second floor of the new building, is supervised by its Director, Dr. Ilia Guzei. The lab has a full array of single crystal diffraction equipment for structural characterization of crystalline materials. The results provided by an X-ray single crystal experiment include coordinates of atoms in the unit cell in the lattice, atomic connectivity, and interatomic distances and angles. Structural data allow three-dimensional analysis of the molecular geometry which can enable a researcher to understand or explain properties of the compound. Data are collected on two state-of-the-art Bruker diffractometers with CCD area detectors and a Siemens P4 diffractometer with a point detector, using either Mo or Cu sealed-tube generators. The diffractometers are independently controlled by PC computers and fitted with nitrogen-streaming low temperature devices. Data collections are routinely conducted at 173(2) K which allows handling of air- and moisture-sensitive samples in addition to air-stable crystals. The data are analyzed on one of seven PC computers situated in the X-ray computer laboratory. The Bruker SHELXTL program package is most often used for structure solution and refinement. The Cambridge Structural Database containing the results of nearly all published structures of organic and organometallic compounds is also available and can be searched with program ConQuest. Dr. Guzei works closely with students and faculty in the preparation of manuscripts reporting structural experiments.

Library

The Chemistry Library, located in the Daniels wing of the Chemistry Building, is available to you 24 hours per day. Two librarians and several part-time employees staff the library. The Chemistry Library's collection covers all major areas in chemistry and includes approximately 17,000 books, 26,000 bound serial volumes, 200 current print journal subscriptions, and electronic access to a variety of full-text journals and indexes to the chemical literature. Instruction in the use of any Library resource is available. Drop-in workshops are periodically scheduled in the library. The Madison campus maintains 35 general and research libraries with over 6 mil-

lion volumes. Other campus libraries of interest to chemists include Health Sciences, Life Sciences, Physics, Pharmacy, and Engineering Libraries.

Financial Support

Graduate students are supported by teaching appointments, research assistantships, traineeships and fellowships. Generally, most first-year students have teaching assistantships. This teaching experience is valuable, as it strengthens the mastery of the subject matter taught and develops poise and maturity in working with individuals and groups. Students with fellowships benefit by doing some teaching, and can usually supplement their stipend. However, there is no required teaching at Wisconsin. In later years, students in the Ph.D. program are usually supported as research assistants by their thesis adviser. Summer support for Ph.D. candidates is routinely available.

Fellowship awards are made by the Graduate School in mid February. Students applying for graduate school in the following year who are awarded fellowships may activate their awards in June or September. A limited number of summer teaching positions is also available from the Department for exceptional new students who have accepted the Department's offer for the following year. Information on the fellowship programs can be obtained from the Graduate Admissions Office.

Opportunities for Minority Graduate Students

The Chemistry Department welcomes applications for graduate study from members of minority groups. Financial assistance for minority students is available through the University of Wisconsin Graduate School. Details can be obtained from Dr. Matt Sanders, Department of Chemistry.

Departmental Web Access

Because of anticipated recruitment of new faculty members and the sometimes rapidly changing nature of the research being performed in the Department, this brochure is meant to serve as a guide only; it will not have the most recent information. The Chemistry Department maintains an active web site at *http://www.chem.wisc.edu*. Interested students are encouraged to consult the website for recent information about the Department, and an on-line application process designed by Mary Kay Sorenson in the Graduate Admissions Office (http://www.chem.wisc.edu/areas/admissions).

Teaching Opportunities for Graduate Students

Teaching is an important part of the Wisconsin experience. Several of our faculty have won University teaching awards, eight graduate teaching assistants have been recognized for outstanding teaching by College and University awards in recent years, and the Department received the first Chancellor's Award for Teaching Excellence in 2000. Graduate teaching assistants are responsible for supervision of undergraduate laboratories, and also are in charge of recitation sessions. Their duties vary depending on whether they are involved with analytical, inorganic, organic, physical, or gen-

eral chemistry courses. The general chemistry program is by far the largest.

Each year more than 5,000 students enroll in general (first-year) chemistry courses at Wisconsin. The course format consists of weekly lectures, discussion sessions, and laboratory periods. Typically, each lecture section has about 300 students while each discussion-laboratory section has no more than 22 students. Graduate teaching assistants (TAs) are assigned to teach discussion-laboratory sections under the guidance and supervision of a lecture professor.

Numerous efforts are made to enhance the role of graduate students as TAs and to make their participation in teaching both effective and rewarding. Early in the fall, chemistry TAs participate in an intensive training program aimed at preparing them to successfully fulfill the responsibilities of their teaching assignments. Different sessions dealing with how to lead discussion, how to prepare and grade quizzes, how to be a laboratory instructor, *etc.* are organized and conducted by faculty and a group of experienced TAs. Safety rules and precautions are discussed in a special session of this TA training program.

During weekly staff meetings ample opportunities are available for lecture professors to discuss with their TAs both course content and teaching strategies. Pre-lab videotapes are normally previewed during staff meetings and all aspects of the laboratory are discussed with Dr. Gordon Bain, Director of General Chemistry Laboratories. At the end of the semester, a formal evaluation of TAs is conducted which includes student opinions as well as ratings by the lecture professor. Outstanding performance is rewarded by cash prizes.

Interested students may also participate in graduate seminars on teaching in chemistry and participate in the activities of the Institute for Chemical Education.

Orientation programs are also used for analytical, organic, and physical chemistry TAs. Since these courses are considerably smaller and have fewer TA recitation sessions, the orientation emphasizes proper supervision of laboratory experiments and safety. Also, an opportunity to become more familiar with the specialized laboratory instrumentation is provided.

Wisconsin continues to strengthen its commitment to excellence in undergraduate instruction and graduate research by ensuring that qualified graduate students are properly guided and rewarded for their performance as TAs. In many respects the graduate student's stint as a TA complements the challenging and rich experience of doing basic research and completing course work toward the Ph.D. degree.

Analytical Sciences at Wisconsin

The Analytical Sciences Ph.D. program emphasizes the development and application of state-of-the-art scientific tools, techniques, and methodologies for chemical and biological analysis. While the fundamental core of the program lies in the science of *measurement*, much of the excitement of this field comes from the fact that good, quantitative analytical methods are the "enabling technologies" for advances in rapidly-expanding fields such as bioanalytical chemistry and nanotechnology. What you'll find here is not old-fashioned analytical chemistry, but a group of researchers focused on new types of measurement, such as:

- Development of new methods for screening, imaging, analyzing, and understanding the behavior of biological molecules in vivo and in vitro, often at the single-molecule level.
- DNA Computing: Using DNA molecules for computing and problem-solving
- Nonlinear optical spectroscopies for dissecting complicated infrared spectra and for probing intra- and intermolecular interactions.
- Linking biomolecules (DNA, proteins) with nanoscale objects such as dendrimers and carbon nanotubes to develop new nanoscale architectures, methods of nanoscale chemical analysis, and single-molecule electrical measurements and detection.
- Tracking transport of specific proteins in live cells in three dimensions with 10 nm spatial resolution.
- Bioelectronics: Using electrical signals to directly detect and control biological binding events.
- Creation of novel optical detection systems, scanning probe microscopies, and microfluidic delivery systems for biomolecular sensors on gold, silicon and diamond surfaces.
- Creation of high fidelity attachment chemistries and fabrication strategies for DNA and protein microarrays.
- Development of new chemical and instrumental approaches to biological mass spectrometry at the single cell level.

- Enzymology and single-pair protein-DNA interactions on surfaces.

Much of the research is interdisciplinary, linking chemistry with biology/biotechnology, nanotechnology, materials science, and geological/environmental sciences. One of Wisconsin's greatest strengths is the strong collaborative research environment. Many analytical research projects involve multiple groups working together, with each group providing its special expertise in order to achieve a more far-reaching goal. In addition to being recognized authorities in analytical chemistry, the faculty are also active in related fields such as physical chemistry, chemical physics, genetics, biochemistry and molecular biology, materials science, and macromolecular science. This environment gives students a unique opportunity to work with multiple faculty members and to craft individualized research projects, tailored to their interests and goals.

While students in the Analytical Science Ph.D. program can do research under the supervision of any chemistry faculty member (or even faculty outside of chemistry, with appropriate arrangements), faculty in the chemistry department who have a strong interest in analytical sciences include:

Robert M. Corn — David Schwartz (also Dept. of Genetics)
Thomas C. Farrar — Lloyd M. Smith
Robert J. Hamers — James Weisshaar
Lingjun Li (also Dept. of Pharmacy)
John L. Schrag — John C. Wright

Inorganic Chemistry at Wisconsin

World class fundamental research programs in a wide variety of subject areas are available to the graduate student majoring in inorganic chemistry. The internationally renowned faculty are involved in cutting edge research that involves virtually all areas of inorganic chemistry and many related disciplines.

General research areas include synthetic inorganic and organometallic chemistry, physical inorganic and organometallic chemistry, theoretical inorganic and organometallic chemistry, bioinorganic chemistry, metalloenzyme chemistry, solid state chemistry, and materials science. In these research areas there are many different types of investigations involving, among others, metal ring and/or cluster molecules, homogeneous and heterogeneous catalysis, photochemistry, inter- and intra-molecular dynamics, computer modeling, and the elucidation of reaction mechanisms.

Serving as inorganic division faculty are:

Thomas C. Brunold — Judith N. Burstyn
Charles P. Casey — Lawrence F. Dahl
Arthur B. Ellis — Clark R. Landis
Robert J. McMahon — Bassam Z. Shakhashiri
Shannon Stahl — Paul M. Treichel

In addition, Emeritus Professors Donald Gaines and Robert C. West continue research programs in the Department.

Current research interests of the individual faculty are detailed in following pages. Many graduate students devise their own research projects, and may be closely associated with several research groups simultaneously. Interdisciplinary research involving other groups within and outside the department is an important and expanding part of the inorganic research program.

The major objective of the inorganic faculty is to maintain the highest intellectual atmosphere and to provide the best physical facilities so that every graduate student can achieve his or her greatest creative research potential. To this end, students are encouraged to play a very active role in developing their graduate programs, including the selection of the thesis adviser, research projects, and courses that will address their particular educational needs.

We urge inorganic graduate students to interview the divisional faculty and join a research group during their first semester. In this way new students are rapidly integrated into the research community that is the essential core of each research group. Weekly departmental inorganic seminars bring together all the inorganic students and faculty. Seminar speakers include visiting chemistry faculty from other universities, visiting industrial chemists and our own advanced graduate students, faculty, and post-doctoral research associates.

Graduate students in inorganic chemistry take a core curriculum that includes several courses in descriptive inorganic chemistry and physical inorganic chemistry. The courses are evolving constantly to address the growth of the various disciplines within inorganic

chemistry. At the present, incoming graduate students take survey courses during the first year in transition metal chemistry, inorganic structure and bonding, and spectroscopic methods. In addition there are a variety of more specialized courses that may be elected. Among the offered courses are bioinorganic chemistry, solid-state chemistry, organometallic chemistry, photochemistry, structural chemistry, and theoretical inorganic chemistry. Typically a graduate student takes courses that complement his or her chosen research area. Many students enroll in additional courses in areas removed from their primary research interests in order to develop a more comprehensive view of the chemical world. In the interests of encouraging a broad perspective, all chemistry graduate students must complete a minor that typically consists of several courses outside the major chemistry field. These may be in a specific chemical area outside inorganic chemistry or in another department, or in a combination of areas or departments.

The inorganic division provides a stimulating environment in which graduate students can develop truly creative research capabilities. The success of our program is amply illustrated by the placement of our Ph.D. graduates in virtually every type of chemical industry and in colleges and universities throughout the world.

Prospective inorganic chemistry graduate students are urged to contact the chemistry department or individual divisional faculty members for additional information about any aspect of our inorganic program. If possible, you should visit the department to see at first hand the support provided for our graduate program.

Organic Chemistry at Wisconsin

As a graduate student majoring in organic chemistry, you can expect to participate in one of the strongest organic programs in the world. Our approach to graduate education is to combine well-organized academics (courses, seminars, cumulative exams, proposal) with world-class research. The goal of the organic program is to give the Ph.D. student the most modern of backgrounds in preparation for an independent career. Graduate education involves learning the latest theoretical treatments of organic reactions, the development of synthetic expertise, the ability to analyze critically physical-organic and reaction mechanism problems, and the art of structure elucidation.

We encourage students to join research groups before the end of their first semester. Early involvement in a research group is a good idea because experienced students in the group can be the best source of information about the department, coursework, and other important matters. Early participation in research group seminars is especially valuable and helps provide a sense of camaraderie and intellectual stimulation.

At Wisconsin you will have an unusually large number of top-flight research groups to choose from for your dissertation studies. All organic research areas of current interest, including synthetic, mechanistic, bioorganic, organometallic, combinatorial, materials, catalytic, structural, and computational chemistry are represented, usually by multiple research groups. With such an extensive selection available, you should be readily able to match your interests and goals to an appropriate research advisor. A distinguishing feature of the research environment at Wisconsin is the degree of interaction and collaboration between groups. This will enhance your exposure to all of the research areas, and broaden your experience. The instrumental support for your research at Wisconsin is unsurpassed, with numerous NMR, mass spec, x-ray, and computational facilities for your use. Everyone is strongly encouraged to acquire hands-on experience with these state-of-the-art instruments which are so crucial for first-class research.

New students with a strong background can finish all of the course requirements during the first academic year. As few as six courses can satisfy all requirements, two of which are specified: CHEM 641 (a course in reaction mechanisms and physical organic) and CHEM 841 (organic synthesis and synthetic methods). Four other courses can be chosen from a wide selection to satisfy the minor requirement. Most often, choices include CHEM 605 (Spectroscopic Methods; structure elucidation by use of the most modern of organic techniques) plus selections from such topics as biochemistry, transition metal chemistry, MO theory, kinetics, pharmacology, computer science, and so forth. An informal problem-solving course, CHEM 647, is also taken by organic majors to refine their "arrow pushing" ability on a variety of

reactions and molecular rearrangements. The details of a student's program depend on research area and career plans, and are arranged through discussions with the thesis advisor.

A series of advanced courses is available with changing content. This CHEM 800 series consists of special topics courses in areas such as bioorganic, synthetic, organometallic, materials, structural, computational, and mechanistic chemistry, among others. All students sit in on some of these courses for their own benefit and attend the numerous special lectures by distinguished visiting scientists.

The success of our approach to graduate education is reflected in the fact that Wisconsin ranks as one of the largest and most respected sources of Ph.D. organic chemists for academic and industrial positions. Most major college chemistry departments have organic faculty members who have studied at Wisconsin, and dozens of companies come to Madison each fall to recruit our students. Many of our graduates have reached the highest levels of national and international distinction in their independent careers.

Members of the Chemistry Department primarily involved in organic chemistry are:

P.J. Belshaw†
H.E. Blackwell
S.D. Burke
C.P. Casey
S.H. Gellman
L.L. Kiessling†
D. Lee
S. Mecozzi*
S.F. Nelsen
R.T. Raines†
H.J. Reich
D.H. Rich*
Ben Shen*
S.S. Stahl
D. Lynn+
R.J. McMahon
H.W. Whitlock
H.E. Zimmerman

*Joint appointments with the School of Pharmacy
†Joint appointments with the Department of Biochemistry
+Joint appointment with the Department of Chemical Engineering

If you would like to know more about the research groups at Wisconsin, please contact members of our staff directly, or go to the Organic Divisional Website at *http://www.chem.wisc.edu* via the link, Research.

Physical Chemistry at Wisconsin

Physical chemistry at Wisconsin offers a graduate student the benefits of a strong and diverse faculty, outstanding facilities for research support, and a program that emphasizes both depth in one's thesis topic and breadth of chemical knowledge and experience. Faculty research interests span the remarkable range of topics addressed by modern physical chemistry: theory, gas phase spectroscopy and dynamics, condensed phase structure and dynamics, macromolecular and biophysical chemistry. The faculty in these broad categories are:

Theoretical Chemistry:

P. R. Certain
Q. Cui
J. E. Harriman
E. L. Sibert
J. L. Skinner
F. A. Weinhold
A. Yethiraj

Spectroscopy, Structure and Dynamics:

S. Cavagnero
F. F. Crim
M. D. Ediger
R. J. Hamers
G. Nathanson
R. C. Woods
H. Yu
M. T. Zanni

Macromolecular and Materials:

R. M. Corn
M. D. Ediger
R. J. Hamers
G. Nathanson
M. T. Record
H. Yu

Biophysical Chemistry:

T. Brunold
S. Cavagnero
R. M. Corn
M. T. Record
J. C. Weisshaar
M. T. Zanni

We continue to benefit from the active involvement of our Emeritus Professors C. D. Cornwell, C. F. Curtiss, T. C. Farrar and W. E. Vaughan.

Students specializing in physical chemistry may also choose to do research with faculty in other traditional divisions. Other portions of this booklet describe the research interests of these groups.

The Ph.D. in physical chemistry is a research degree. The doctoral thesis demonstrates the student's ability to master a specialized field in depth and conduct original research. We encourage students to become acquainted with the available research opportunities and to select a research group as soon as possible, usually in the first semester. Early involvement with a group permits rapid progress in independent research and provides an academic base as well as a source of ideas, advice, and encouragement. Most entering physical chemistry students take a course in thermodynamics/equilibrium statistical mechanics and a course in quantum mechanics during the first semester. Students choose additional courses according to their individual needs and interests.

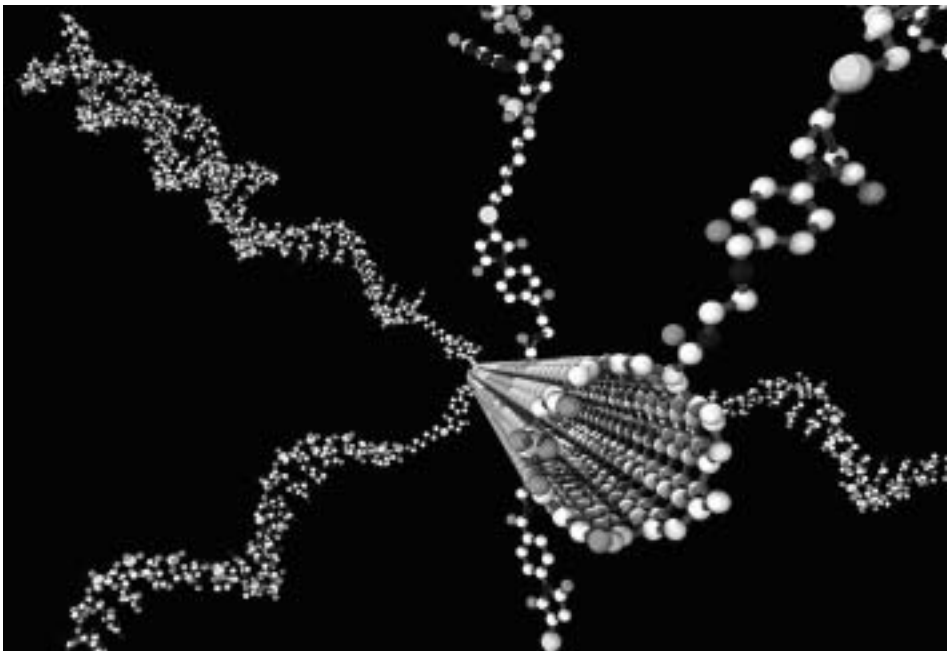
Breadth of experience in our program comes from coursework, from research seminars, and from group meetings, often held jointly with other research groups. In the second year, two

requirements encourage good early progress on a well-defined thesis project. They also provide experience in the important skills of presenting scientific ideas orally and of using the scientific literature. The first of these is a pair of Literature Topic Exams during the fall semester of the second year. They consist of a written examination on a paper from the current physical chemistry literature. Students receive the paper ten days prior to the examination and, often, work together to master the topic and the associated background material. The second is a Thesis Background Exam in February, where the student presents a formal seminar on research plans and answers questions from a faculty committee. With few exceptions, students move smoothly through these exams and begin to concentrate full time on research.

Research in theoretical chemistry is described in the following section on the Theoretical Chemistry Institute.

Gas phase physical chemistry at Wisconsin has a strong chemical flavor. One active research area in gas phase spectroscopy and dynamics is the study of highly vibrationally excited molecules prepared by tunable laser pulses. Nanosecond and picosecond lasers probe vibrational structure and dissociation dynamics of polyatomic molecules. These techniques have revealed bond-specific photodissociation and bimolecular reaction. Another area uses sophisticated detection schemes to provide highly sensitive and specific probes of reaction species important in plasma processing.

Research in condensed phase structure and dynamics includes new molecular beam-liquid surface scattering experiments. This research directly probes fundamental gas-liquid interactions at the molecular level. Very little is known about the trapping and solvation of gas phase molecules by a liquid surface, not to mention chemical reaction mechanisms. One can also explore molecular structures and dynamics through vibrational motions and couplings. To accomplish this, sophisticated ultra-fast multi-dimensional spectroscopies are being developed that correlate vibrational modes and measure frequency fluctuations. New ultra-fast laser techniques are also being developed with the goal to follow the flow of energy within a molecule directly and study vibrationally driven reactions in liquids.



The physical chemistry of polymers is an area of great traditional strength at Wisconsin. Experiments in our Department probe the dynamics of polymer motions on time scales ranging from picoseconds to days! State-of-the-art techniques include fast laser pulse pump-probe experiments, neutron and light scattering, transient grating spectroscopy, and viscoelasticity and flow birefringence measurements. The systems of interest are bulk polymers, polymer solutions, and glasses.

Some of nature's most fascinating problems yield best to an *interdisciplinary* approach grounded in the rigorous methods of physical chemistry. Modern biophysical research at Wisconsin combines state-of-the-art measurements with the powerful methods of molecular biology and with sophisticated theoretical modeling to solve complex problems. This multi-faceted approach can elucidate biomolecular *energetics*, *mechanisms*, and *dynamics* at an unprecedented level of detail. Biophysical studies range from bulk to surfaces to single molecules. Particularly active areas of investigation at Wisconsin include: DNA-protein interactions; metalloenzyme spectroscopy and dynamics; interactions of proteins, nucleic acids, and carbohydrates with model membranes and with chemically tailored surfaces; secretory vesicle transport phenomena in live cells; and protein folding mechanisms, both *in vitro* and in conditions approaching those of a live cell. Experimental tools include novel vibrational and electronic spectroscopies using *cw* and femtosecond lasers; high-field, multi-dimensional NMR; other magnetic spectroscopies, such as EPR and MCD; scanning probe microscopies, including AFM, STM and SEM; and optical microscopies, including surface plasmon resonance and ultra-sensitive fluorescence methods.

Biophysical students typically augment physical chemistry coursework with selections offered by departments around the campus, consistent with the interdisciplinary nature of this rapidly growing field. Interested students should also consult the following section of this brochure, "Research at the Chemistry-Biology Interface", for related information.

The Chemistry Department research support facilities are outstanding. In our machine shop, electronics shop, and glass shop a skilled staff construct highly sophisticated specialized equipment and provide design assistance. The well-equipped student machine and electronics shops allow graduate students to work on their own projects with the guidance of expert machinists and technicians. Departmental facilities include state-of-the-art NMR, ESR, X-ray, photoelectron and mass spectrometers, as well as a network of computers. The University of Wisconsin Physical Sciences Laboratory operates the Synchrotron Research Laboratory, a national resource providing high

intensity vacuum ultraviolet and soft X-ray radiation for a wide variety of research projects.

Prospective physical chemistry students should inquire about further details of the graduate program. Individual faculty members can provide additional information about their research programs. We encourage prospective students to visit Madison to gain a first-hand impression of the city, the Chemistry Department, our faculty, and our graduate students.

Theoretical Chemistry Institute

The Theoretical Chemistry Institute (TCI) is part of the Physical Chemistry Division and interacts with the Physics, Mathematics, Computer Science, and various Engineering departments as well as other divisions in Chemistry. Our students ordinarily work toward Ph.D. degrees in physical chemistry or physics, in an environment that emphasizes interactions among all theoretical research groups and faculty. The shared facilities include the TCI Library (with an outstanding collection of theoretical monographs and principal research journals), seminar and conference rooms, and computational resources. Proximity and easy access to the Departmental Computer Center (state-of-the-art workstation clusters and supercomputers, with many installed software utilities for theoretical work) and close interaction with groups having primarily experimental interests strongly enhance the environment for theoretical research.

Each year the Theoretical Chemistry Institute awards the internationally recognized Hirschfelder Prize in Theoretical Chemistry. The prize winner spends a week visiting the department and presents three lectures during this stay. In addition, TCI has an active Visitor Program, which funds visits by theorists from around the world.

The members of TCI are:

Ludwig A. Bruch*
Phillip R. Certain
Qiang Cui
Charles F. Curtiss+
John E. Harriman
Edwin L. Sibert
James L. Skinner, Director
Frank A. Weinhold
Arun Yethiraj

*Professor of Physics
+Emeritus Professor

Theoretical chemistry seeks to explain quantitatively the physical and chemical properties of condensed matter, to relate these macroscopic properties to the properties of the individual molecules, and to predict the structure and properties of the individual molecules. Since the discovery of quantum mechanics, the required fundamental laws of nature appear to be sufficiently well known to account for the phenomena of molecular physics and chemistry, at least at low energy. Theoretical chemistry uses computers and analytic methods for applying the fundamental laws to describe complex molecules, clusters, and condensed phases. No longer restricted to small idealized prototype systems, theoretical chemists are increasingly to be found, in active collaboration with experimentalists, at the forefront of contemporary investigations of the structure and dynamics of complex chemical systems.

Research at the Chemistry-Biology Interface

Many exciting research problems in science today lie at the interfaces between disciplines. The interface between chemistry and biology is particularly rich, and research groups in all four divisions in the Chemistry Department at UW–Madison have substantial efforts that interweave ideas from chemistry and biology to solve important problems. Our faculty is helping to define this evolving approach to science, and accordingly, UW–Madison is one of the strongest centers for research at the chemistry-biology interface in the world.

Chemistry-biology interfacial research at UW–Madison is exceptionally broad in scope, extending from the design and synthesis of organic compounds that bind and modulate the function of specific proteins, to the spectroscopic study of metalloprotein structure, to the construction and use of high density DNA arrays for data storage and retrieval, to the development of new polymeric vehicles for drug delivery. In general, research groups are either synthesizing compounds and materials with novel biological activity, developing new experimental and spectroscopic techniques to characterize biomolecules and biological phenomena, or combining both of these approaches in their laboratories. As this type of research is inherently collaborative, many faculty have joint projects with other members of the Chemistry Department and with researchers in other departments on the UW–Madison campus. In our interactive environment, sharing specialized equipment and facilities, and continually exploring new research opportunities across campus is standard practice for both faculty and students.

Active research areas include:

- Combinatorial library synthesis and screening
- Elucidation of protein-, nucleic acid-, carbohydrate-, and small molecule-protein interactions with biophysical and chemical tools
- Design and synthesis of protein and receptor mimics
- Natural product biosynthesis and metabolic pathway engineering
- Spectroscopic study of biomolecular structure, including but not limited to NMR, IR, resonance Raman, EPR, and mass spectrometry techniques
- Chemical approaches to signal transduction
- Design of new polymers with well-defined folding properties (“foldamers”)
- Multi- and monolayer assembly of biomolecules at surfaces
- Chemical glycobiology
- New polymeric materials for gene and drug delivery
- Enzyme mechanism and synthesis of enzyme inhibitors
- Single nucleotide polymorphism (SNP) analyses
- Integration of biological molecules with novel materials for nanoscale chemical sensing and bio-electronic integration
- Computational approaches to protein structure and function
- Whole genome “shotgun” optical mapping
- Spectroscopic analysis of *in vitro* and *in vivo* protein folding by multidimensional NMR

- Development of new chemical and instrumental approaches to biological mass spectrometry at the single cell level
- *In vivo* fluorescence and single molecule dynamics

The interdisciplinary research projects listed above are supported by the outstanding facilities at UW–Madison. High field NMR spectrometers (600 and 500 MHz) equipped with sophisticated triple resonance and magic angle spinning probes are housed in the Chemistry Department. Along with the other excellent instrumentation located within the Department, the recent addition of the Keck Center for Chemical Genomics to the UW campus provides additional state-of-the-art instrumentation that will fuel research at the chemistry-biology interface for years to come. The Keck Center, which has a facility located in the Chemistry Department, serves to integrate chemical synthesis and surface science for the investigation of biological systems. The Center includes equipment for high throughput screening (liquid handling robotics, plate readers, etc), for the automated chemical synthesis of small molecule libraries, and for the fabrication and characterization of surfaces (atomic force microscopy, surface plasmon resonance, etc). Additionally, UW–Madison is home to a National Magnetic Resonance Facility (NMRFAM), which houses 900, 800, 750, 600 (3), 500 (2), and 400 MHz NMR spectrometers, along with the BioMagResBank (BMRB), which is the worldwide repository for data from NMR spectroscopy on proteins, peptides, and nucleic acids. Finally, open access to state-of-the-art facilities at the Biophysics Instrumentation Facility (located nearby in the Biochemistry Department), the Biotechnology Center, and School of Pharmacy, coupled with exceptional campus-wide bioinformatics and computational capabilities, creates a world class environment to engage in research at the chemistry-biology interface.

Graduate students pursuing research at the chemistry-biology interface at UW–Madison typically fulfill the requirements of one of the four traditional divisions and use the distributed minor option for more specialized coursework appropriate to their own research. Weekly seminars and semester-long graduate-level courses in the areas of chemical biology, bioorganic chemistry, bioinorganic chemistry, and biophysical chemistry are currently offered and can be used to fulfill the minor requirement. Qualified students can be nominated prior to or during their first year for prestigious graduate fellowships supported by the NIH that include interdepartmental training in the Chemistry-Biology Interface, Biotechnology, Molecular Biophysics, and Bioinformatics. These programs provide unparalleled interdisciplinary training opportunities for students and encourage participation in seminar courses and off-campus summer internships. There is a large biological community at UW–Madison outside of the Chemistry Department that is actively involved in these training grant programs, including faculty from Biochemistry, Bacteriology, and Chemical Engineering along with the Medical School and School of Pharmacy. Students who are accepted into the Chemistry graduate program can join any of these laboratories but must be co-advised by a faculty member with an appointment in the Chemistry Department.

Further information on these training grant programs and the faculty currently involved can be found at the following websites:

http://www.pharmacy.wisc.edu/CBITraining/

http://www.bact.wisc.edu/Biotech/orientbook2/toc1.html

http://virology.wisc.edu/biophysics/molecularbiophysics/info.html

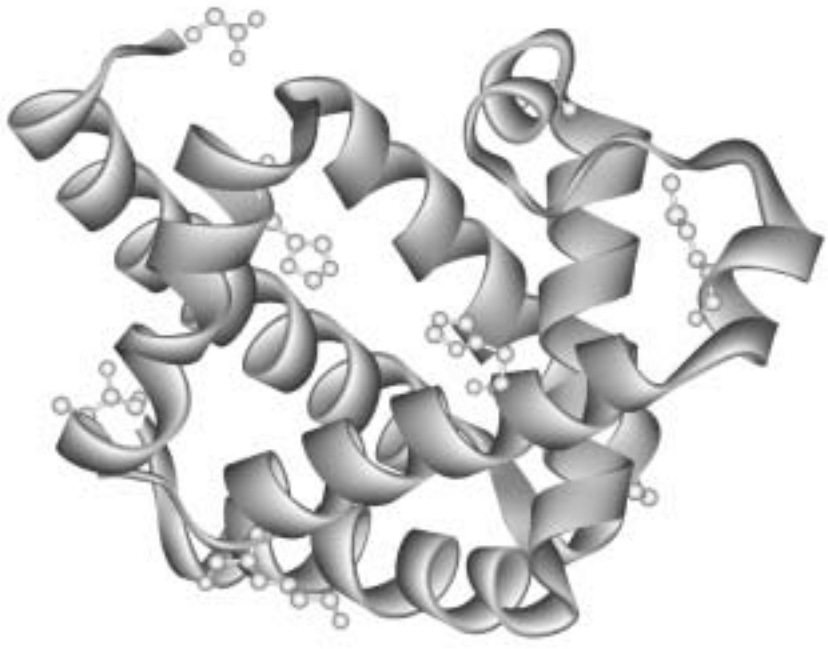
Chemistry Department faculty with biological interests are conducting research in diverse areas, some of which are represented in the broad classifications below:

Chemical Biology

Peter J. Belshaw
Helen E. Blackwell
Samuel H. Gellman
Laura L. Kiessling
Daesung Lee
Ronald T. Raines
Daniel H. Rich
Ben Shen

Protein Structure & Function

Peter J. Belshaw
Helen E. Blackwell
Thomas C. Brunold
Judith N. Burstyn
Silvia Cavagnero
Qiang Cui
Samuel H. Gellman
Laura L. Kiessling
Lingjun Li
Ronald T. Raines
M. Thomas Record
Daniel H. Rich
Ben Shen
James C. Weisshaar
Martin T. Zanni



Protein & Receptor Mimics

Helen E. Blackwell
Steven D. Burke
Judith N. Burstyn
Samuel H. Gellman
Sandro Mecozzi
Daniel H. Rich
Howard W. Whitlock

Biomaterials & Surface Science

Robert M. Corn
Robert Hamers
Laura L. Kiessling
David M. Lynn
Sandro Mecozzi
Lloyd M. Smith
Shannon S. Stahl
Hyuk Yu

Biophysical Chemistry

Thomas C. Brunold
Silvia Cavagnero
Robert M. Corn
Qiang Cui
Samuel H. Gellman
Robert Hamers
Lingjun Li
Sandro Mecozzi
M. Thomas Record
Lloyd M. Smith
James C. Weisshaar
Hyuk Yu
Martin T. Zanni

Genomics, Proteomics & Bioinformatics

Peter J. Belshaw
Lingjun Li
David C. Schwartz
Ben Shen
Lloyd M. Smith

Metalloenzymes & Bioorganometallics

Thomas C. Brunold
Judith N. Burstyn
Qiang Cui
Shannon S. Stahl

If you would like to learn more about research at the chemistry-biology interface at Wisconsin, we encourage you to contact the faculty directly, or go to their individual and group web pages at the UW–Madison Chemistry Department web site: http://www.chem.wisc.edu

Materials Chemistry at Wisconsin

The Materials Chemistry Program is a Ph.D. program within the department of chemistry that is targeted toward students whose interests span the traditional divisions of chemistry, and who are interested in the chemistry of materials.

"Materials Chemistry" can be defined as the branch of chemistry aimed at the preparation, characterization, and understanding of substances/systems that have some specific useful function (or potentially useful function). It involves 4 primary components: preparation/synthesis ("How are materials made?"), structure ("How are they put together?"), characterization ("How do they behave?") and applications ("What are they good for?"). It integrates elements from all four classical areas of chemistry, but puts an intellectual focus on the fundamental scientific issues that are unique to materials. Materials Chemistry largely involves the study of chemistry of condensed phases (solids, liquids, polymers, nanomaterials) and interfaces between different phases (e.g., bio-materials interfaces). Because many of these materials have direct technological applications, materials chemistry has a strong link between basic science and many existing and newly-emerging technologies. While chemistry-focused, the Materials Chemistry Program also serves as a bridge between chemistry and the engineering and life sciences.

Some examples:
Here are just a few examples of some of the many materials chemistry projects that are ongoing in our department.

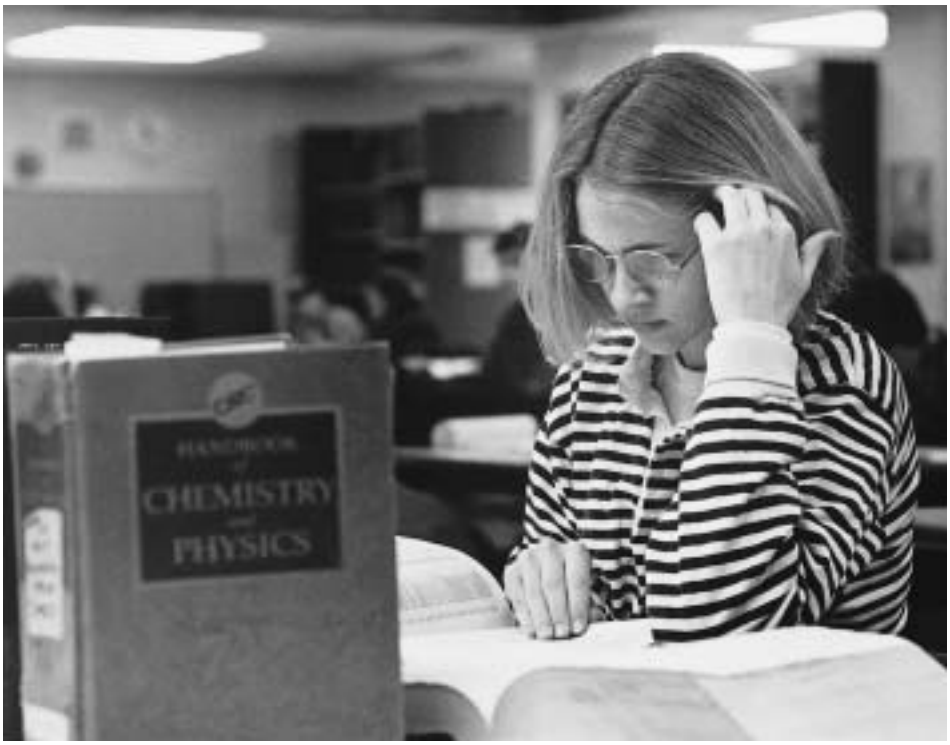
- Development of new surface-based methods for detecting and manipulating biological molecules (bio-chips, bio-electronics)
- Surface/interface chemistry of micro-electronic materials (silicon, diamond, gold)
- DNA computing (using DNA molecules as molecular computers or memory devices)
- Molecular electronics (using individual molecules or ensembles of molecules as wires, switches, diodes, and transistors)
- Nanotubes and nanowires as single-molecule chemical and biological sensors.
- Structure and dynamics of polymers (experiment and theory)
- Photonics
- Synthesis and characterization of organic non-linear optical materials
- Quantum dots (nanometer-sized assemblies of atoms)

The Materials Chemistry Ph.D. degree program is a relatively new program that is designed to provide a flexible way of meeting the needs and interests of students who are working in materials chemistry. While the program is chemistry-centered, much of the research is interdisciplinary, and students with bachelor's degrees in related fields such as physics, biochemistry, chemical engineering, and materials science and who are interested in moving into chemistry will also find the materials chemistry program quite attractive.

Students in the materials chemistry program are free to do their research with any faculty member in the department as their Ph.D. adviser. It is also possible to arrange for a Ph.D. adviser in another department. Chemistry faculty with research interests in materials chemistry include:

Robert M. Corn
Mark D. Ediger
Robert J. Hamers
Max Lagally (Dept. of Materials Science and Engineering)
Robert J. McMahon
Gilbert M. Nathanson
John L. Schrag (*emeritus*)
James L. Skinner
Lloyd Smith
Robert West (*emeritus*)
R. Claude Woods
John C. Wright
Arun Yethiraj
Hyuk Yu

Institute for Chemical Education (ICE) and Project SERAPHIM



The Institute for Chemical Education is one of several highly respected programs in chemical education research and development at the University of Wisconsin–Madison. ICE is national in scope and has led the drive to help teachers revitalize science in schools throughout the United States. Its efforts include: **research in chemical education; development of new materials, demonstrations, and hands-on activities; in-service workshops for teachers; laboratory programs for school children and dissemination via a major publications program.**

More than 3000 teachers and students have attended ICE workshops at the UW–Madison headquarters and at Field Centers across the country. ICE Affiliates at other colleges and universities have been trained to carry out similar workshops.

Project SERAPHIM began in 1982 as a clearinghouse for technology-based instructional materials in chemistry. Since then, SERAPHIM has collected more than 700 computer programs for chemistry instruction from teachers throughout the country, and it has disseminated more than 100,000 floppy disks of software. Its workshop leaders have taught more than 5000 teachers how to make effective use of computers, videodiscs, and computer-interfaced experiments in their classrooms.

The publications program includes written materials and kits, developed to provide what teachers and students need and can afford. Examples include: *Fun with Chemistry: A Guidebook of K–12 Activities*, which lists 53 hands-on science activities; *The Hole in the Ozone Layer*, one of a series called *Topics in Chemistry* that provides teachers with important information about everyday chemistry; *Memory Metal*, which describes the properties of shape-memory alloys and provides a sample for demonstration purposes; the Color LED Strip Kit, which includes half a dozen experiments that enable students to discover the properties of LEDs and light; and handbooks that tell how to carry out ICE-like programs. SERAPHIM software is now available via the World Wide Web, as is more information about ICE.

ICE and SERAPHIM attract visiting faculty Fellows from all over the country; ICE Fellows helped develop our very popular solid-state model construction kit and SERAPHIM Fellows have created software, video, and multimedia materials that exemplify appropriate uses of new technology.

Journal of Chemical Education: Print, Software, Online, Books

The *Journal of Chemical Education* is the premier journal in chemical education in the world. In 1996 John Moore was appointed its seventh editor, making the *Journal* a part of the Chemistry Department. The University has made available an annex around the corner known as Journal House, where most of the *Journal*'s staff of twelve work. All facets of the *Journal*'s operation take place in the department—from the receipt of manuscripts through the production of fully designed pages that are conveyed digitally to the printing company. The *Journal* appears monthly and is sent to subscribers all around the world; all subscribers receive both print and full online access to *JCE Online*.

The *Journal of Chemical Education* is a peer-reviewed journal founded in 1924 by Neil Gordon and published by the ACS Division of Chemical Education, Inc. *JCE* publishes papers on all aspects of chemical education from elementary school through graduate level. Competition for space in its pages is very keen. The *Journal's* section headings provide an indication of its breadth: Chemical Education Today; In the Classroom; In the Laboratory; Chemistry for Everyone; Information, Textbooks, Media, Resources; and Research: Science and Education. The *Journal*'s readership of 13,000 worldwide makes it one of the largest chemistry journals.

JCE Software, founded in 1988, publishes computer programs for Windows and Macintosh, digitized video and software on CD-ROMs, and videotapes. Descriptions of the many publications of *JCE Software* can be found at http://jchemed.chem.wisc.edu/JCESoft.

Web-based *JCE Online* publishes not only the complete content of the print *Journal* but many additional items: abstracts of all published papers, laboratory supplements, video supplements, and spreadsheets. Of particular interest is *Only@JCE Online*, which publishes articles that require the dynamic online medium—check the animation of a hydrogen atom 1s to 2s transition, for example.

The *Journal* continues to publish a variety of other materials that are useful to those who teach chemistry—including the popular Handbook for Teaching Assistants and monthly Classroom Activities for high school teachers. Current information about all of the *Journal*'s operations is available at http://jchemed.chem.wisc.edu or by sending an email to jce@chem.wisc.edu.

Journal of Chemical Education Digital Library Project

The *Journal of Chemical Education* is a major participant in an endeavor that is likely to transform education in the U.S. Called the National Science Digital Library (NSDL), it is a collection on the World Wide Web of exemplary teaching materials in all areas of science, engineering, mathematics, and technology. Funded by the National Science Foundation, the NSDL involves more than 100 projects in all science, engineering, and technology disciplines as well as mathematics.

The NSDL is collecting high quality multimedia and other digitized learning materials, and it aims to make them easy to find and convenient to use for a broad audience that includes teachers, librarians, students, and the general public. It is a very ambitious undertaking whose goal is to bring the services one would normally find in a library to the desktop computers and homes of all U.S. citizens. We are proud to be one of only four collection projects in the NSDL that involve chemistry. We expect that our participation will bring new opportunities in chemical education to all students in the department.

Specific new NSDL collections that involve *JCE* are

- *DigiDemos*, a digital library of chemical demonstrations that will include *JCE* articles describing demos, images showing setups and apparatus, and videos showing how a demo is done, as well as up-to-date information about safety and waste disposal;
- Documents for Mathcad and other computer algebra systems that enable students to carry out complicated mathematics easily, promoting exploration and discovery;
- Web-deliverable questions for homework and student assessment that can incorporate images, sound, and digitized video; and
- *JCE* WebWare, an eclectic collection of short but useful Java applets, dynamic HTML (DHTML) pages, virtual reality (VRML) documents, QuickTime and Flash movies, animated gifs, and other interactive items that will help students learn chemistry.

These will be added to the rich collections of laboratory experiments, instructional software, and videos of chemical reactions and laboratory techniques that *JCE* has already created. Attached to each item in the collection is what the NSDL calls "metadata"—information that will enable others to retrieve specific items of interest from a vast digital collection.

Participating in the National Science Digital Library project is an exciting prospect for *JCE* and for our department. We expect to be able to make major contributions to the project and derive major benefits from participating in it.

Wisconsin Initiative for Science Literacy

Developing a science literate and science friendly citizenry is essential to Wisconsin's and the nation's success in this technological age. Increasingly, scientific issues are also political and social issues. For the sake of our democratic institutions, it's important that all citizens develop an appreciation of science and technology, be able to judge their potential risks and benefits, and make informed decisions.

The Wisconsin Initiative for Science Literacy (WISL) at the University of Wisconsin–Madison aims to promote literacy in science, mathematics, and technology among the general public; and to attract future generations to careers as the researchers, entrepreneurs, and teachers on whom the nation' s continuing economic health and security will depend.

WISL aims specifically to improve science teaching; to put more under-represented groups on a track to becoming tomorrow's scientists and science teachers; and to explore and establish new links between science, the arts ,and humanities. The Wisconsin Initiative for Science Literacy also wants to locate and promote pockets of excellence in educational or other community settings, where parents and teachers, along with business, professional and civic leaders, come together to successfully cultivate science literacy.

Among WISL's programs is a popular series of discussions called **Conversations in Science** that enable local middle and high school teachers to interact with UW–Madison's cutting edge scientists and engineers and take new ideas back to the classroom. Another is a series of special Saturday morning science sessions for middle school and high school students in Madison and Milwaukee as part of our **Science in the City** program. These stimulating programs require that parents attend and participate in the hands-on experiments too, furthering WISL's goal of cultivating and involving the family and community in supporting science education, particularly in inner cities. The **Women in Science** program targets girls and women, encouraging their participation in science through a variety of activities.

WISL is uncovering rich new terrain in the **Science, the Arts and Humanities** program in which faculty–scientists, artists and humanists–explore areas where their disciplines overlap and then share their discoveries and new perspectives through public outreach activities. For example, WISL organized a symposium in 2003 on the element oxygen. This free program of discussions, lectures, and impressive demonstrations, aimed at the general public, accompanied the staging of the play *Oxygen,* a drama that explores the culture of science and asks who really discovered oxygen.

Besides these new programs, WISL director–chemistry professor Bassam Z. Shakhashiri–and staff continue to take the popular **Science is Fun** programs of spectacular chemical demonstrations out into the community to communicate the wonders of science and the basic principles of chemistry. WISL also reaches a statewide audience through **Science on the Radio**, a Wisconsin Public Radio feature in which Prof. Shakhashiri responds directly to listeners' questions about chemicals in everyday life; and through the WISL website, popular for its informative feature, "Chemical of the Week." WISL also has helped chemistry teachers for many years with a popular **four-volume series of workbooks** describing how to present effective chemical experiments and demonstrations. Called *Chemical Demonstrations, a Handbook for Teachers of Chemistry*, the texts are now translated into several languages.

WISL programs always promote the teaching of chemistry and science in ways that capture the audience's imagination, regardless of their academic background, and make them think and wonder and question. The participation of graduate students, post-doctoral fellows and faculty in WISL is welcomed. It not only enriches the quality of the programs, but is an opportunity for individuals to enhance their own professional development.

The Campus and Its Environs

The University stretches about 1.5 miles along one of Madison's three lakes and its campus is certainly one of the country's prettiest. At one end is the Memorial Union, a popular place for lunch, sailing, concerts, and other leisure activities. At the other end is Picnic Point, with its wooded pathways, which stretches a quarter mile into the lake between the campus and the married student housing area.

Madison itself has been selected as one of the ideal cities for living. Although large enough to have excellent shopping and cultural opportunities, Madison has few of the problems of large cities. There is little industry here, and rolling countryside and lakes are never far away. With excellent air connections to a number of major cities, Madison combines the convenience of urban living with the advantages of a manageable, progressive community.

Housing

More than a thousand apartments in an attractive location next to Lake Mendota are operated by the University for graduate students and their families. An unusually large selection of more expensive modern apartments can be found within five miles of the campus, and excellent Madison bus service is available to the university. Many students combine to rent apartments or houses within walking distance, but these are harder to find. May is a good time to look. There is also a graduate dormitory three blocks from the Chemistry Building. For campus housing information, please contact the University Housing Office, Slichter Hall, University of Wisconsin–Madison, Madison, WI 53706.

Publication of this brochure is made possible . . .

. . . by numerous individual, foundation and company donations to the Department. The annual *Badger Chemist* newsletter contains a complete listing of Department funds and donors. The Chemistry Department is grateful to all of its friends and donors for the support we receive.

CHEMISTRY
UNIVERSITY OF WISCONSIN - MADISON

1. Access the latest, up-to-date information about Chemistry department faculty on our website at:

http://www.chem.wisc.edu/people/profiles/faculty.php

2. The profiles which follow were dated for March 2003 and may not be current.

Peter J. Belshaw

Assistant Professor of Chemistry and Biochemistry
B.Sc. 1990, University of Waterloo, Ontario, Canada
Ph.D. 1996, Harvard University

Our research interests lie at the interface of Chemistry and Biology with the broad goals of investigating and manipulating biological systems with both chemical and genetic approaches.

1. **Chemical synthesis of combinatorial libraries of natural product variants and the screening of these libraries to identify compounds with novel biological activities.** Such compounds will be useful as pharmacological probes of the proteins (or other cellular molecules) whose cellular function is modified upon binding to the compound, thus providing tools for cell biology investigations. We are particularly interested in identifying compounds which disrupt protein-protein interactions. If any of these compounds ultimately prove useful as medicinal agents, it should be possible to genetically program a microorganism to biosynthesize them directly using methods developed in 2.

2. **Mechanism of natural product biosynthesis.** Many natural products fall into two classes: polyketides and nonribosomal peptides. Examples of polyketides include erythromycin, rapamycin, FK506 and avermectin. Nonribosomal peptides include penicillin, cyclosporin and vancomycin. In recent years it has been discovered that these compounds are biosynthesized in microorganisms in a template directed fashion by enormous enzymes (up to 1,500,000 Da). These enzymes are composed of repeating modules, where each module effects the incorporation of a single building block into the growing structure of the natural product. For polyketides, the building blocks are acetate, propionate and butyrate. For nonribosomal peptides the building blocks are amino acids. There are also hybrid polyketide/nonribosomal peptide synthetases which incorporate both types of monomers into the natural product. We are interested in developing methods to genetically reprogram nonribosomal peptide synthetases to biosynthesize new variants of natural products.

Organic Chemistry

Natural Product Biosynthesis; Combinatorial Chemistry; Protein Evolution

(608) 262–2996. belshaw@chem.wisc.edu.

http://belshaw.chem.wisc.edu/

1. Aminoacyl-CoAs as Probes of Condensation Domain Selectivity in Nonribosomal Peptide Synthesis. P. J. Belshaw, C. T. Walsh, and T. Stachelhaus, *Science* **284**(5413), 486–489 (1999).

2. Thiazole and oxazolepeptides: biosynthesis and molecular machinery. R. Sinha Roy, A. M. Gehring, J. C. Milne, P. J. Belshaw, and C. T. Walsh, *Natural Product Reports* **16**(2), 249–263 (1999).

3. Regioselectivity and chemoselectivity analysis of oxazole and thiazole ring formation by the peptide-heterocyclizingmicrocin B17 synthetase using high-resolution MS/MS. N. K. Kelleher, P. J. Belshaw, and C. T. Walsh, *J. Am. Chem. Soc.* **120**, 9716–9717 (1998).

4. Kinetics and Regioselectivity of Peptide to Heterocycle Conversions by Microcin B17 Synthetase. P. J. Belshaw, R. Sinha Roy, N. L. Kelleher, and C. T. Walsh, *Chemistry and Biology* **5**, 373–384 (1998).

5. Cell-specific calcineurin inhibition by a modified cyclosporin. P. J. Belshaw, S. L. Schreiber, *J. Am. Chem. Soc.* **119**, 1805–1806 (1997).

6. Oligomerization activates c-raf–1 through a ras-dependent mechanism. Z. J. Luo, G. Tzivion, P. J. Belshaw, D. Vavvas, M. Marshall, and J. Avruch, *Nature* **383**, 181–185 (1996).

7. Functional analysis of Fas signaling in vivo using synthetic dimerizers. D. M. Spencer, P. J. Belshaw, L. Chen, S. N. Ho, F. Randazzo, G. R. Crabtree, and S. L. Schreiber, *Current Biology* **6**, 839–847 (1996).

8. Controlling programmed cell death with a cyclophilin-cyclosporin-based chemical inducer of dimerization. P. J. Belshaw, D. M. Spencer, G. R. Crabtree, and S. L. Schreiber, *Chemistry & Biology* **3**, 731–738 (1996).

9. Controlling protein association and subcellular localization with a synthetic ligand that induces heterodimerization of proteins. P. J. Belshaw, S. N. Ho, G. R. Crabtree, and S.L. Schreiber, *Proc. Natl. Acad. Sci. USA.* **93**, 4604–7 (1996).

10. Rational Design of Orthogonal Receptor-Ligand Combinations. P. J. Belshaw, J. G. Schoepfer, K.-Q. Liu, K. L. Morrison, and S. L. Schreiber, *Angew. Chem. Int. Ed. Engl.* **34**, 2129–32 (1995).

Helen E. Blackwell

Assistant Professor of Chemistry
B.A. 1994, Oberlin College
Ph.D. 1999, California Institute of Technology

Organic Chemistry

Organic synthesis; Combinatorial chemistry; Green chemistry; Chemical biology.

(608) 262–1503. blackwell@chem.wisc.edu.

1. "A One-Bead, One-Stock Solution Approach to Chemical Genetics: Part 1" H. E. Blackwell, L. Pérez, R. A. Stavenger, J. A. Tallarico, E. C. Eatough, M. A. Foley, and S. L. Schreiber. *Chemistry & Biology* **2001**, *8*, 1167–1182.

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We are developing an integrated chemical biology research program that uses complex molecules derived from organic synthesis to probe important problems in biology, particularly in the areas of cancer and photobiology. In the process, we seek to advance new chemical platforms for high-throughput, yet environmentally responsible synthesis. The realization of our research program requires an interdisciplinary team of researchers with a diverse skill set, including organic synthesis, combinatorial library design, structure elucidation techniques, molecular biology, and assay and technology development. Below are summaries of three ongoing research projects:

Microwave-Enhanced Synthesis on Planar Solid Supports. There remains a need for the development of efficient, inexpensive, and low tech approaches to the synthesis and biological screening of small molecule libraries. We believe that spatially segregated SPOT-synthesis on planar cellulose supports, coupled with dramatic reaction rate enhancement using microwave irradiation, will permit straightforward compound isolation, the outgrowth of environmentally benign synthetic methodology, and extremely rapid library synthesis (~1–2 h total). We are currently developing efficient methods to both functionalize planar cellulose surfaces and to quantitate these surface functionalization reactions. As SPOT synthesis requires markedly reduced quantities of reagents and solvents, pairing this technique with the reduced energy demands of microwave enhanced chemistry produces a synthesis platform in tune with today's needs for "greener" chemistry. This platform is the present foundation for new methodology development, library construction and biological screening efforts in our lab.

Directed Synthesis and Identification of Peptoid p53/Hdm2 Antagonists. Protein-protein interactions are pivotal to intra- and intercellular communication. One highly relevant protein-protein interaction is the binding of the p53 tumor suppressor protein to Hdm2 as it is implicated in numerous human cancer pathways. Thus, the synthesis and screening of small molecules that can disrupt this interaction could uncover compounds useful as both biological probes and potential frameworks for therapeutics. This project involves the design and synthesis of helical, non-peptide (*peptoid*) ligands that mimic the conformation and functional display of the Hdm2 binding domain of p53. Functionalized cellulose membranes and microwave-enhanced synthetic methodology developed in-house is being used for the efficient SPOT-synthesis of complex peptoid libraries

with α-chiral, aromatic side chains. Our ability to conduct ELISA assays directly on the solid support bound peptoid arrays facilitates the rapid preliminary screening for those that abrogate of the p53/Hdm2 protein-protein interaction. Solution phase NMR experiments coupled with molecular modeling are our primary tools for elucidation of peptoid secondary structure, both alone and in peptoid/protein complexes.

Exploration of Plant Photomorphogenesis with Small Molecule Developmental Screens. How plants grow and respond to their light environment during early development is a complex and poorly understood process. This project involves the systematic use of small molecule screens to explore light-dependent development, or photomorphogenesis, in plants. Targeted libraries of small molecules synthesized using in-house SPOT technology are being screened for their effects on photomorphogenesis in the model plant *Arabidopsis thaliana* and in the algal flagellates *Euglena gracilis* and *Chlamydomonas reinhardtii*. The vibrant plant biology community here at UW–Madison provides an unparalleled environment for us to pursue this highly interdisciplinary project. Straightforward spectrophotometric assays for small molecules that affect chlorophyll biosynthesis and chloroplast biogenesis are being developed, in conjunction with solid phase protein-binding assays targeted at certain photoreceptor kinases (i.e. the phytochromes, the red/far-red light receptors in plants). Simultaneously, we are also interested in examining the effects of naturally occurring plant growth regulators (e.g., auxin, ethylene, abscisic acid, and gibberellic acid) on light-dependent development in *Arabidopsis* using small molecule suppressor and enhancer phenotypic screens.

Thomas C. Brunold

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Ph.D. 1996, University of Bern, Switzerland

Our research is aimed at unraveling metalloenzyme and cofactor structure/function relationships through combined experimental and computational studies of key enzymatic states and synthetic inorganic model complexes. Experimental techniques used in our studies include electronic absorption, circular dichroism, magnetic circular dichroism, resonance Raman, and electron paramagnetic resonance. Spectroscopic data are complemented by density functional theory, semi-empirical INDO/S-CI, and combined quantum mechanics/molecular mechanics electronic structure calculations to develop experimentally-calibrated bonding descriptions. This approach permits us to selectively probe the geometric and electronic structures of catalytically active metal centers and allows us to explore structures and reactivities of catalytic intermediates that are not accessible by X-ray crystallography.

One area of our research is devoted to the study of enzymes and cofactors that form reactive metal–carbon bonds in their catalytic cycles. Despite the fact that these bio-organometallic species catalyze a wide range of biological reactions and transformations, they employ only three different catalytically active metal ions: Fe, Co, and Ni. This observation indicates that while the metal center defines the range of possible reactions, the ligands determine the chemistry that actually occurs. Thus, bio-organometallic species constitute excellent systems through which to explore basic structure/function relationships in metalloenzymes and cofactors. Current studies focus on CO dehydrogenase (oxidation of CO to CO_2), acetyl-CoA synthase (synthesis of acetyl-CoA from CO, CoA, and a methyl group), Ni-F_{430} dependent methyl-CoM reductase (methane formation from methyl-CoA and CoBSH), and the biochemistry of the Co-B_{12} cofactor adenosylcobalamin. Knowledge gained in these studies should significantly sharpen our understanding of the principles by which these bio-organometallic species achieve their high reaction rates, exquisite selectivity, and chemically challenging transformations under ambient conditions.

Another project aims at exploring the effects of the second coordination sphere on metalloprotein function. Significantly, families of enzymes are known with virtually identical active site structures but strikingly different metal specificities, indicating that the second coordination sphere (comprising amino acids that are not directly bound to the metal ion) can also have a crucial effect on catalytic activity. These effects are poorly understood, however, because they are difficult to evaluate by crystallography and typically too challenging to be addressed by model studies. We address this problem using our combined spectroscopic/computational approach to study families of related enzymes with identical active site ligands but distinct metal specificities. Current studies focus on the strictly Fe- and Mn-specific superoxide dismutases (SODs) that catalyze the dismutation of the superoxide radical anion, a major cytotoxic agent that has been implicated in a wide variety of human diseases (e.g., Parkinson's disease, amyotrophic lateral sclerosis (ALS), and AIDS). By studying the native and metal-substituted SODs we aim at exploring essential geometric and electronic factors for SOD activity and their relation to the strict metal specificities of these enzymes. Knowledge gained in these studies may also provide the insight necessary for the rational design of SOD mimics for pharmaceutical applications.

Inorganic Chemistry.

Bioinorganic and physical inorganic chemistry; application of spectroscopic and computational methods to study metalloenzyme structure and function.

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8. Jackson, T. A.; Yikilmaz, E.; Miller, A.-F.; Brunold, T. C. "Spectroscopic and Computational Study of a Non-Heme Iron $\{Fe\text{-}NO\}^7$ System: Exploring the Geometric and Electronic Structures of the Nitrosyl Adduct of Iron Superoxide Dismutase", submitted to *J. Am. Chem. Soc*.

9. Stich, T. A.; Brooks, A. J.; Brunold, T. C. "Spectroscopic and Computational Studies of Co^{3+}-Corrinoids: Spectral and Electronic Properties of the B_{12} Cofactors and Biologically Relevant Precursors", submitted to *J. Am. Chem. Soc*.

Steven D. Burke

Professor
B.S. 1973, University of Wisconsin–Eau Claire
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Organic and Bioorganic Chemistry

Synthesis of biologically active natural products; design, synthesis, and study of biomimectic, unnatural ion transport systems; supramolecular self-assembly; molecular recognition in solution and in the solid state; computational molecular modeling; catalytic asymmetric synthetic methods; synthesis and study of templated biological recognition elements.

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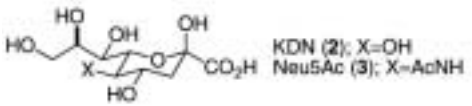
Our research encompasses a broad range of synthetic and bioorganic projects. Natural products total synthesis and synthetic methods development continue to be areas of pursuit for us. Increasingly, we have become involved in the design, construction and study of novel, unnatural molecules to function as artificial receptors or conduits for molecular and ionic substrates.

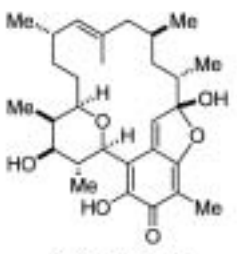
Molecules that exhibit important biological activity, challenging structural features, and low natural abundance are attractive synthetic targets. Discovery, development and application of new reactivities, strategies and methods are important aspects of these efforts.

Halichondrin B (1) is a structurally complex substance isolated from a Pacific sponge. Potent cytotoxicity *in vivo* against leukemias and solid tumors in mice combines with extreme scarcity to encourage laboratory synthesis of this and analogous structures for development as clinical anticancer agents. Recent efforts from our labs toward the halichondrins are described in references 2, 4 and 9.

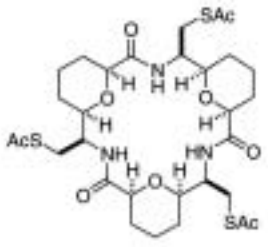


KDN (**2**); X=OH
Neu5Ac (**3**); X=AcNH

Very short and efficient synthetic routes to simpler biologically-active molecules are also being developed. For example, the sialic acids KDN (2) and *N*-acetylneuraminic acid [Neu5Ac, (3)] have been synthesized using Ru-catalyzed ring-closing metathesis (RCM) in key steps, as described in references 1, 6, and 8. Application of the general strategy of converging subunits with simple ketalization reactions and establishing rings via catalytic RCM has also led to the development of a conceptually new route to spiroketals (reference 5), which are important structural elements of numerous anticancer and antibiotic agents. Further application of this strategy is

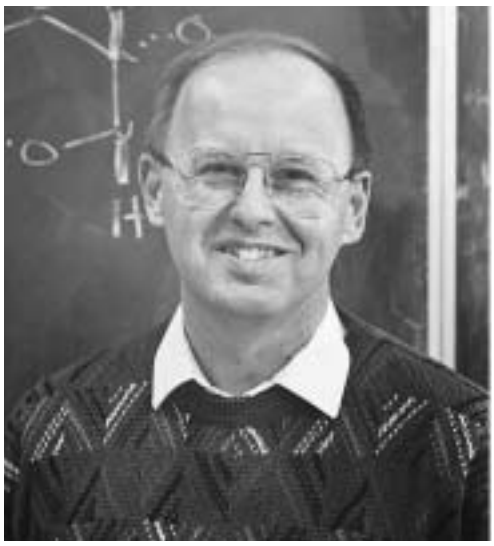


Kendomycin (**4**)



5

C_2-Symmetric Synthetic Scaffold for Enzyme Mimic or Protein Model



underway for the synthesis of kendomycin (4), a recently characterized ansa macrocyclic quinone methide with antibacterial and anticancer activities, and other biologically important natural products.

We have been involved in the design, synthesis and study of a new class of macrocyclic ligands and scaffolds that are symmetric cyclooligomers of hydropyran subunits (references 3, 10, and 12). These molecules have rigidified structures with open cavities and appendages oriented perpendicular to the plane of the macrocycle (e.g. 5). These trivalent templates are being used to display biological recognition elements for probing protein-carbohydrate and protein-protein interactions. They are also being developed for the study of protein structure (collagen) and for the inhibition of viral infectivity via polyvalent inhibitor displays. The trithiol derived from compound 5 is being studied as a transacylation catalyst for cyclodepsipeptide synthesis, with the goal of mimicking the functional activity of megasynthetase enzymes.

Central to all of our projects is the ability to build, purify and characterize exotic organic structures. Diverse exposure to mechanistic, analytical, computational, spectroscopic and chromatographic techniques will be part of your training. Organometallic and biological chemistry are also pertinent to these studies. If you are interested in a career in pharmaceutical drug discovery and development, the research background available through these projects is considered to be ideal.

Judith N. Burstyn

Professor of Chemistry and Pharmacology, Born 1959
B.A. 1980, Cornell University
Ph.D. 1986, University of California, Los Angeles

My research group studies bioinorganic chemistry, the role of the inorganic elements in biological systems. In our laboratory we explore the function of metalloproteins in gas sensing, studying how the interaction of a gas molecule with a metal center alters the structure and function of the protein. We use our understanding of the proteins we study as guides in the design and synthesis of inorganic molecules that act as gas sensors or hydrolysis catalysts.

Metalloproteins serve as sensors and signal transducers in a number of important biological processes. For example, NO regulates blood pressure by interacting with the heme protein soluble guanylyl cyclase. Bacteria use heme proteins to sense gases such as O_2, CO, and NO in their environment, and plants use copper metalloproteins to detect ethylene, a hormone that regulates plant development. One focus of our research involves understanding how gas sensing occurs at a metal center, and how changes in the coordination chemistry at the metal center are coupled to allosteric conformational changes in the protein. Through our studies of the mammalian NO-sensor soluble guanylyl cyclase and the bacterial CO-sensor CooA, we have learned that interactions of the gas molecules with the heme centers induce changes in the coordination geometry, and these changes correlate with functional changes in the proteins. Our current work aims to elucidate the mechanisms by which the coordination changes are communicated throughout the proteins. In addition to studying the gas-sensing capabilities of soluble guanylyl cyclase, we study the mechanism by which the enzyme catalyzes its metal-dependent transesterification reaction. Recently, we have applied our knowledge of heme proteins to the enzyme cystathionine—β–synthase, a protein implicated in a variety of neurological disorders. The discovery of the heme cofactor in this enzyme has led to our investigation of its possible function as an allosteric regulator. We utilize a variety of biochemical and biophysical tools to probe the structure-function relationships in these proteins. Techniques include enzyme kinetics, protein modification or mutagenesis, and electronic absorption, EPR, resonance Raman, CD, MCD and fluorescence spectroscopies.

Another area of interest is the development of metal-based gas sensors and hydrolysis catalysts. We have investigated the mechanisms of copper(II) triazacyclononane-mediated hydrolysis of phosphodiesters and amides and we have generated molecules capable of hydrolyzing the stable backbones of DNA, RNA, and protein. New and exciting research is aimed at modeling the copper center in the plant ethylene receptor and developing both small molecule and polymer-based sensors for ethylene. In sensing applications, we take advantage of the high sensitivity of luminescence and the high affinity of metal centers for gas molecules to create novel molecules and materials that respond to gas binding. We make use of inert atmosphere synthetic techniques to prepare complexes and we detect gas binding by laser-induced emission. We study the interaction of ethylene with our newly prepared materials using Raman and IR spectroscopies.

Students with a wide variety of interests participate in these projects. Some students focus on biophysical characterizations of proteins; others create new variant proteins using molecular biological techniques and carry out biochemical studies. Students with interests in more chemical projects synthesize and characterize small molecules or materials and evaluate their function as catalysts or gas sensors.

Inorganic Chemistry.

Bioinorganic chemistry, gas-sensing metalloproteins, biochemistry of NO, CO and ethylene, inorganic sensor design, metal-mediated hydrolysis in chemical and biological systems.

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1. "Analysis of the L116K variant of CooA, the heme-containing CO sensor, suggests the presence of a novel heme ligand resulting in unusual activity" Hwan Youn, Robert L. Kerby, Marc V. Thorsteinsson, Robert W. Clark, Judith N. Burstyn, Gary P. Roberts *J. Biol. Chem.* **2002**, *277*. 33616–33623.

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Charles P. Casey

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B.S. 1963, St. Louis University
Ph.D. 1967, Massachusetts Institute of Technology

Organic and Inorganic Chemistry.

Mechanisms of organometallic reactions; homogeneous hydrogenation and hydroformylation catalysis; carbene complexes; metallocene polymerization catalysts; new synthetic methods using organometallic compounds.

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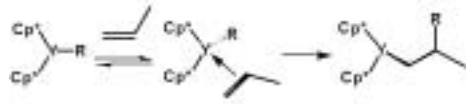
My research group is interested in studying the mechanisms of organometallic reactions and in developing an understanding of homogeneous catalysis. In addition, we are trying to design organometallic reagents for synthesis and new catalysts.

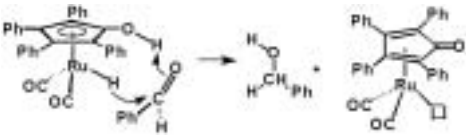
d^0 Transition Metal-Alkyl-Alkene Complexes: Models for a Key Intermediate in Metallocene Catalyzed Alkene Polymerization

The key intermediate in the generally accepted mechanism for Ziegler-Natta alkene polymerization is a d^0-metal-alkyl-alkene complex but because of its high reactivity, this intermediate has never been detected in a catalytic system and no model compounds were seen until we prepared the first in this class. We first prepared neutral chelated d^0 yttrium-alkyl-alkene complexes and determined the kinetics of alkene dissociation ($\Delta G^{\ddagger}$ = 7 kcal mol^{-1}) and the thermodynamics of alkenes binding to d^0 metals ($\Delta H°$ = 4 kcal mol^{-1}). Next, we observed a non-chelated yttrium alkyl-alkene complex and succeeded in measuring the rate of alkyl migration to the coordinated alkene. This is the first measure of the rate of the key carbon-carbon bond forming process in alkene polymerization. We are extending our studies to cationic zirconium-alkyl-alkene complexes which are more closely related to industrially important metallocene catalysts.



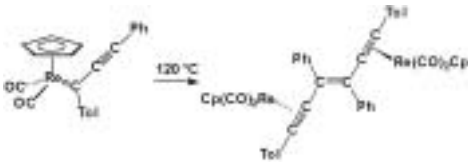
Reductions Catalyzed by Metal Complexes with Both Hydridic and Acidic Hydrogens.

We are studying catalysts that simultaneously deliver a hydride and a proton to polar molecules. $(C_5Ph_4OH)Ru(CO)_2H$ has an electronically coupled acidic OH unit and a hydridic RuH unit and we have shown that it reduces aldehydes by simultaneous transfer of H^+ from OH and H^- from RuH; this occurs outside the coordination sphere of the metal. We are now studying the mechanism of regeneration of the active reducing agent with H_2 and are devising improved catalysts based on our mechanistic insight.



Alkynyl Carbene Complexes

Fundamental studies of alkynyl carbene complexes such as $Cp(CO)_2Re{=}C(Ph)C{\equiv}CTol$ led to the unexpected dimerization that involves coupling at the terminal alkyne carbons and a [1,1.5] migration of the metal to form ene-diyne complexes. We are extending this discovery to more economical manganese systems that offer a novel route to enediynes.



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An important prerequisite for the correct functioning of all living cells is the biosynthesis of their protein and nucleic acid components. However, the mere formation of the proper number of covalent bonds is not sufficient to produce functional biomolecules. These are only created when formation of the correct array of intramolecular interactions, i.e., a proper *three-dimensional folding,* takes place. How exactly is this process taking place and what is driving it? The answer to this is one of the most fascinating and unsolved questions in modern biology.

Our group focuses on exploring the *fundamental principles that govern the folding and misfolding of proteins and RNA*. We specifically address both mechanistic and structural aspects and employ a variety of biophysical methods ranging from ultrarapid mixing to nuclear magnetic resonance (2D and 3D experiments, selective labeling), mass spectrometry and computational techniques. The ability of these tools to follow *time-resolved events* is exploited and further developed in our lab.

This interdisciplinary research uses the tools of modern physical chemistry to solve problems at the chemistry-biology interface. Our studies provide an ideal benchmark for students interested to address and solve intellectually-challenging scientific questions while, at the same time, testing theoretical principles and acquiring valuable practical experience in state-of-the-art biophysical spectroscopy. Our research program focuses on the following two areas:

I. The Chain Length Dependence of Protein Folding: Mechanisms of Cotranslational Folding and Misfolding in the Cell. The time required for the *in vivo* biosynthesis of proteins typically ranges from a few seconds to minutes. On the other hand, formation of high propensity secondary structure in isolated peptides is known to occur on submillisecond timescales. It is therefore not surprising that some degree of folding and(or) misfolding can occur cotranslationally in proteins. This makes the study of *biosynthetic* protein folding extremely interesting from both the theoretical and practical perspective. The goal of this project is to systematically dissect the physical principles that govern the chain length dependence of folding, as it pertains to achieving a better understanding of *in vivo* protein folding and misfolding. Our approach is based on employing minimalist model systems suitable to model and follow, at the amino acid-specific level, the timecourse of cotranslational folding of simple cytoplasmic proteins bearing simple secondary and tertiary structure motifs. Comparison between our working mechanistic hypotheses, experimental results and theoretical models developed in our lab play and essential role in this research. The function of ribosomal RNA and chaperones within the cotranslational machinery is also separately being investigated.

II. Kinetic Traps and Chaperones in RNA Folding. One of the most intriguing properties of RNA is its tendency to populate misfolded species on its way to the bioactive conformation. As a consequence, mechanistic steps corresponding to escape from kinetically trapped conformations are often rate-determining in RNA folding. We are particularly interested in the implications that this bears on protein translation, ribosomal assembly and retrovirus maturation. Understanding the kinetic and structural role of RNA chaperones in these processes is an important step in working out the rules that govern RNA folding. Additionally, it may prove an invaluable tool in directing future efforts aimed at the development of therapeutic agents able to control key-steps of the above processes. The Cavagnero group focuses on using a combination of biophysical techniques, particularly Nuclear Magnetic Resonance, to achieve a detailed understanding of the molecular mechanisms that enable certain proteins and polypeptides to serve as RNA chaperones. Systems of particular interest are those that assist RNA to achieve its bioactive conformation in the context of viral and ribosomal folding/assembly events.

Biophysical and Physical Chemistry.

Biomolecular NMR Spectroscopy; Isotope-Filtered Multidimensional NMR; NMR Pulse Sequence Development; Ultrafast Mixing; Mechanisms of Cotranslational Protein Folding and Misfolding; Kinetic Channeling in RNA Folding.

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2.Cavagnero S., Debe D., Zhu Z.H., Adams M.W.W., Chan S.I. *Biochemistry* **37**, 3369–3376 (1998) 'Kinetic Role of Electrostatic Interactions in the Unfolding of Hyperthermophilic and Mesophilic Rubredoxins'.

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Analytical and Physical Chemistry.

Surface Chemistry, Surface Spectroscopy, Surface Biochemistry

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1. Greta J. Wegner, Hye Jin Lee and Robert M. Corn, "Characterization and Optimization of Peptide Arrays for the Study of Epitope-Antibody Interactions Using Surface Plasmon Resonance Imaging," *Anal. Chem.* **74**, 5161–5168 (2002).

2. Emily A. Smith, Motoki Kyo, Hiroyuki Kumasawa, Kazuhiko Nakatani, Isao Saito, and Robert M. Corn, "Chemically Induced Hairpin Formation in DNA Monolayers," *J. Am. Chem. Soc.* **124**, 6810–6811 (2002).

3. Ming Li, Hye Jin Lee, Anne E. Condon and Robert M. Corn, "A DNA Word Design Strategy for Creating Sets of Non-Interacting Oligonucleotides for DNA Microarrays," *Langmuir* **73**, 805–812 (2002).

4. Hye Jin Lee, Terry T. Goodrich and Robert M. Corn, "Surface Plasmon Resonance Imaging Measurements of 1D and 2D DNA Microarrays Created from Microfluidic Channels on Gold Thin Films," *Analytical Chemistry* **73**, 5525–5531 (2001).

5. Emily A. Smith, Matt J. Wanat, Yufei Cheng, Sergio V. P. Barreira, Anthony G. Frutos and Robert M. Corn, "Formation, Spectroscopic Characterization and Application of Sulfhydryl-Terminated Alkanethiol Monolayers for the Chemical Attachment of DNA onto Gold Surfaces," *Langmuir* **17**, 2502–2507 (2001).

6. Bryce P. Nelson, Timothy E. Grimsrud, Mark R. Liles, Robert M. Goodman, and Robert M. Corn, "Surface Plasmon Resonance Imaging Measurements of DNA and RNA Hybridization Adsorption onto DNA Microarrays," *Analytical Chemistry* **73**, 1–7 (2001).

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The chemistry of interfaces impacts a wide variety of important scientific and technological areas such as heterogeneous catalysis, electrochemistry, energy conversion and storage, tribology, chemical sensors, and biological membranes. In each of these systems, a very small number of molecules at the surface can often control the macroscopic properties and direct the overall reactivity of the entire device or structure. For this reason, chemists are acutely interested in creating well defined chemical and physical structures for the control of biopolymer adsorption. Our research efforts have been dedicated to the development and application of the chemical systems and spectroscopic tools necessary to study biomolecular interactions at condensed phase interfaces.

1. Biopolymer Adsorption onto Self-Assembled Monolayers and Multilayers at Metal Surfaces.

We are interested in developing chemical modification strategies for controlling the specific and non-specific adsorption of biopolymers (e.g., synthetic polypeptides, proteins, DNA and RNA) onto metal surfaces. The formation of biologically active biopolymer monolayers at metal surfaces is an essential step in the fabrication of a number of important bioanalytical devices. The surface-sensitive spectroscopic method of polarization-modulation FTIR reflection absorption spectroscopy (PM-FTIRRAS) is used as the primary spectroscopic method the study of the chemical structure of self-assembled monolayers and multilayers.

2. Surface Plasmon Resonance (SPR) Methods for the Detection of Biopolymer Adsorption.

A second area of biopolymer adsorption that we are exploring is the creation of high density DNA and polypeptide microarrays on metal surfaces. We use the technique of Surface Plasmon Resonance (SPR) imaging to detect the adsorption of DNA, RNA and proteins of specific DNA onto the chemically modified metal surface. The multi-element SPR adsorption biosensor arrays are a novel, label-free detection method that can be used for antibody screening assays, DNA diagnostics, and rapid protein characterization measurements.

3. Liquid/Liquid Interfaces and Ultrathin Biopolymer Films

The formation of adsorbed monolayers at liquid/liquid interfaces frequently plays a central role in many natural and synthetic chemical systems. One particular type of liquid/liquid interface which we have studied is the interface between two immiscible electrolyte solutions (ITIES). Recently we have extended our spectroscopic studies to ultrathin liquid/liquid systems composed of ultrathin biopolymer films at metal surfaces.

4. DNA Computing at Surfaces

This research project is aimed at the development and characterization of complex mixtures of DNA molecules attached to surfaces. The attachment chemistry, hybridization chemistry and enzymatic activity of the adsorbed DNA molecules will be characterized by a variety of spectroscopic and biochemical methods, and subsequently optimized for use in (i) the manipulation of DNA sequences in molecular computing strategies and (ii) the high density storage and retrieval of information by DNA hybridization chemistry.

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Our group is studying the molecular dynamics of reactions and photodissociation with the goal of understanding the essential features of chemistry in both gases and liquids. The key to all of our experiments is preparing molecules in vibrationally excited states and spectroscopically monitoring their subsequent behavior. Because laser excitation is a particularly attractive means of preparing molecules in specific internal states, our strategy is to excite molecules with a laser pulse and use time-resolved spectroscopy to follow their subsequent behavior. We are able to remove the averaging that is usually present in chemical reactions by preparing molecules with particular vibrations and monitoring the reaction or photodissociation products. We use high resolution lasers in some experiments and lasers producing ultrashort pulses of about 100 fs duration in others. The two approaches often provide complementary information and allow us to explore a host of processes.

We use a variety of excitation and detection techniques, such as laser induced fluorescence or resonant multiphoton ionization in molecular beams and time-resolved transient absorption or non-linear spectroscopy in liquids. The molecular beam experiments provide an extremely detailed view of the chemical dynamics of isolated, well-characterized molecules. We have recently exploited our understanding of the behavior of vibrationally excited molecules to *control* the course of a chemical reaction, using laser excitation to cleave a particular bond selectively in both photodissociation and bimolecular reaction. New ultrafast laser techniques now allow us to follow the flow of energy *within* a molecule directly and study vibrationally driven reactions in liquids. Discovering the controlling aspects of chemical reactions at a fundamental level is the central focus of our research. The attached list gives a few representative publications. There is a current list of all publications at our group website.

Physical Chemistry.

Molecular Dynamics. State-to-state chemical reactions, photodissociation, and molecular energy transfer.

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1. *An Experimental and Theoretical Study of the Bond-Selected Photodissociation of HOD*. R. L. Vander Wal, J. L. Scott, F. F. Crim, K. Weide, and R. Schinke, J. Chem. Phys. **94**, 3548 (1991).

2. *Controlling Bimolecular Reactions: Mode and Bond Selected Reaction of Water with Hydrogen Atoms*. A. Sinha, M. C. Hsiao, and F. F. Crim, J. Chem. Phys. **94**, 4928 (1991).

3. *Vibrationally Mediated Photodissociation: Exploring Excited State Surfaces and Controlling Decomposition Pathways*, F. F. Crim, Ann. Rev. Phys. Chem. **44**, 397 (1993).

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5. *Bond-Selected Chemistry: Vibrational State Control of Photodissociation and Bimolecular Reaction*, F. Fleming Crim, J. Phys. Chem. **100**, 12725 (1996) *(Centennial Issue)*.

6. *Vibrational State Control of Bimolecular Reactions: Discovering and Directing the Chemistry*, F. Fleming Crim, Acc. Chem. Res. **32**, 877 (1999).

7. *Transient Electronic Absorption of Vibrationally Excited CH_2I_2: Watching Energy Flow in Solution*. Dieter Bingemann, Andrew M. King, and F. Fleming Crim, J. Chem. Phys. **113**, 5018 (2000).

8. *CH_2I_2 Fundamental Vibrational Relaxation in Solution Studied by Transient Electronic Absorption Spectroscopy.* Christopher M. Cheatum, Max M. Heckscher, Dieter Bingemann, and F. Fleming Crim, J. Chem. Phys. **115**, 7085 (2001).

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10. *Relaxation of the C-H Stretching Fundamental Vibrations of CHI_3, CH_2I_2, and CH_3I in Solution.* Max M. Heckscher, Leonid Sheps, Dieter Bingemann, and F. Fleming Crim, J. Chem. Phys. **117**, 8917 (2002).

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1. The functional specificities of Methylglyoxal Synthase (MGS) and Triosephosphate Isomerase (TIM): A combined QM/MM analysis, X. Zhang, D. H. T. Harrison, Q. Cui, *J. Am. Chem. Soc*. In press (2002).

2. A coarse-grained block normal mode approach for macromolecules: an efficient implementation and application to Ca^{2+}-ATPase, G. Li, Q. Cui, *Biophys. J.* **83**, 2457 (2002).

3. An implicit solvation model in the combined QM/MM framework, Q. Cui, *J. Chem. Phys*. **117**, 4720 (2002).

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5. Combining *ab initio* and density functional theory with semi-empirical methods, Q. Cui, H. Guo, M. Karplus, *J. Chem. Phys*. **117**, 5617 (2002).

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7. QM/MM Studies of the Triosephosphate isomerase (TIM) Catalyzed Reactions: The effect of geometry and tunneling on proton transfer rate constants, Q. Cui, M. Karplus, *J. Am. Chem. Soc.* **124**, 3093–3124 (2002).

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10. The spin-forbidden reaction $CH(^2\Pi)+N_2 \rightarrow HCN+N(^4S)$ revisited. II. Nonadiabatic transition state theory and application, Q. Cui, K. Morokuma, J. M. Bowman, S. J. Klippenstein, *J. Chem. Phys.* **110**, 9469–9482 (1999).

Understanding complex molecular systems using experiments alone is difficult. Computer simulations based on physical and chemical principles can complement experiments and provide novel insights into the behavior of these systems at an atomic level. Our research targets the development and applications of state-of-the-art computational tools that explore the underlying mechanisms of complex molecular systems. Enzymes and other biological macromolecules, along with bio-inorganic ligands, are of primary interest.

Simulation of complex molecular machines in bio-energy transduction

Biological systems involve many fascinating "molecular machines" that transform energy from one form to the other. Important examples are F_1-ATP synthase and calcium pump; the former utilizes the proton motive force to synthesize ATP, while the latter employs the free energy of ATP binding and hydrolysis to transport calcium ions across the membrane. With the recent developments in crystallography, cyro-EM and single molecule spectroscopy, the working mechanisms of these nano-machines are being discovered. In order to understand the energy transduction process at an atomic level, our group is developing and applying state-of-the-art computational techniques to analyze the detailed mechanisms of several large molecular complexes including: myosin, RNA polymerase and the calcium pump. Questions of major interest include: (i). What are the functionally relevant conformational flexibilities of these complexes? (ii). How are the chemical events (e.g., ATP binding and hydrolysis) coupled to the mechanical (e.g., conformational transition) process? (iii). How is the efficiency for energy transduction regulated?

Understanding the catalytic mechanism of enzymes

Enzymes overshadow most chemical catalysts because they are extremely efficient and highly reaction-specific. Our group is developing and applying novel computational methods to explore the physical and chemical mechanisms behind the catalytic efficiency and specificity of several fascinating enzymatic systems. These include enzymes that exploit transition metal ions (copper chaperones), electronically excited states (aequorin), and radical intermediates (cholesterol oxidase). In addition to their important biological implications, an underlying theme for these systems is catalysis modulated by protein motion. Our studies will not only provide insights into the fundamental working mechanisms of enzymes, but may also lead to the *rational* design of enzymes (methyl glyoxal synthase, polyketide synthase) with improved or even altered functions.

Developing computational techniques and theoretical models for complex systems

A substantial amount of research activity in our group is geared toward developing novel computational techniques to make the simulation of complex biomolecular systems possible. One major area involves improving the efficiency and accuracy of combined quantum mechanical and classical mechanical methods, such that bond-breaking and bond-formation (chemistry!) can be studied in detail for realistic biological environments. Another area is related to the development of coarse-grained normal mode and molecular dynamics approaches, such that insights into the thermodynamics and kinetics of long time-scale processes (e.g., large-scale conformational transitions) can be obtained computationally. Finally, phenomenological models will also be developed to make connections between microscopic MD simulations (e.g., potential of mean force) and macroscopic observables (e.g., calcium flux across the membrane).

Interfacing biology and material science

The last decade has seen the thrilling developments in the science of materials at the nanometer scale. Nano-materials with tailored electrical, optical or mechanical properties have been synthesized. An exciting direction that has been recently recognized is that biomolecules can be used to provide control in organizing technologically important (non-biological) objects into functional nano-materials. The interaction between biomolecules and inorganic materials is fundamental to these applications, and we are using computational techniques to investigate this aspect. These studies are expected to play a guiding role in the design of novel hybrid materials and new sensors for biological molecules.

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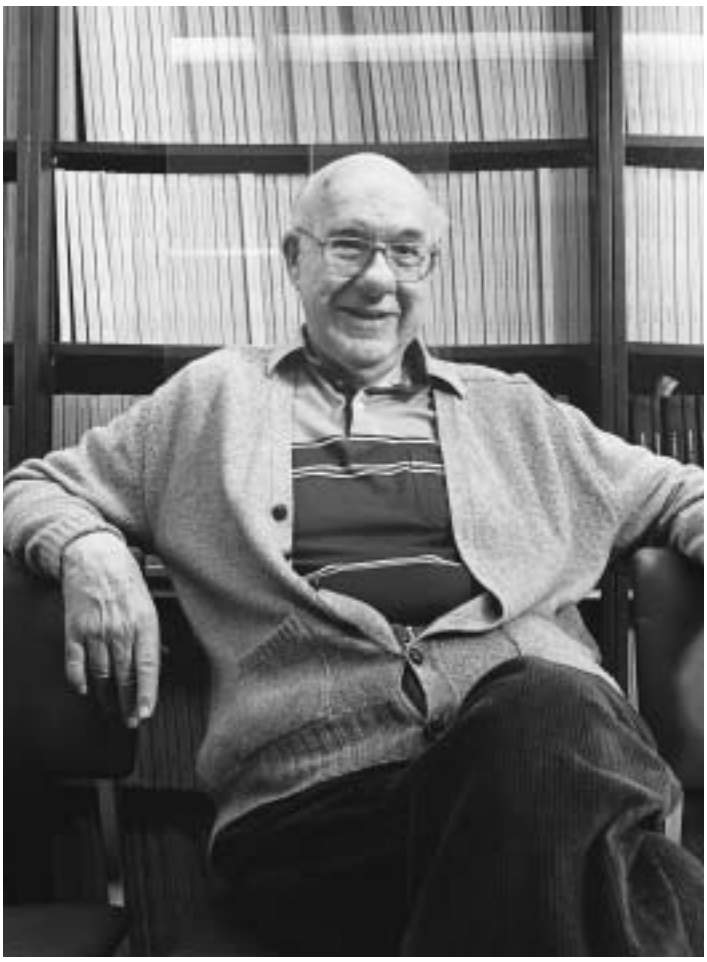

The phenomena of diffusion, viscosity, and thermal conductivity are associated with the transport of mass, momentum, and energy, respectively, through a material, and hence are referred to, collectively, as transport phenomena. In the gas phase, the transport is due primarily to the tendency of the random Brownian motion of the molecules to mix the molecules of one region with those of another. The effect of collisions is to slow down this process by limiting the distance through which a molecule may move without encountering another. That is, the larger the molecule the shorter the mean distance between collisions and hence the less easily the three properties may be transported through the gas. Elementary ideas of kinetic theory lead directly to simple expressions for the transport coefficients of a gas of rigid spheres.

Of course, real molecules interact according to a soft potential. They attract each other at large separation distances and the molecular cores lead to repulsion at shorter distances. It is often assumed that the intermolecular potential depends only on the distance between the molecules, i.e., that the molecules are spherically symmetric. This is true, of course, for the rare gas atoms but for few, if any, real molecules.

The study of transport phenomena in systems involving nonspherical molecules is developing rapidly. The theoretical study of molecular scattering cross sections has developed to a point that it is now possible to predict transport coefficients of gases of nonspherical molecules.

The theory of transport phenomena in the liquid phase is more complex in that each molecule is always interacting with several others and isolated two body collisions do not occur. Polymeric systems, both solutions and pure polymers are particularly interesting. The viscoelastic, or rheological, properties of such systems are non-linear at easily attained conditions. This is in strong contrast to the behavior of gaseous systems in which the behavior becomes non-linear only at extreme conditions, such as those occurring in shock waves.

The theory of the rheological behavior of polymeric systems is based on the same underlying concepts as that of gaseous systems. Although the development of the theory differs significantly, in detail, many of the mathematical techniques of the gaseous theory have been generalized and used in the study of polymeric systems.

Physical Chemistry.

Theory of transport phenomena in gases; theory of molecular collisions; rheology of polymeric solutions and melts.

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1. Hirschfelder, J.O., Curtiss, C.F. and Bird, R.B. "Molecular Theory of Gases and Liquids," John Wiley, New York, 1954, 1964.

2. Bird, R.B. and Curtiss, C.F. "Fascinating Polymeric Liquids," *Physics Today, 37*, 36 (1984).

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4. Curtiss, C.F. "Intermolecular Contributions to the Stress Tensor of Polymeric Systems," *J. Chem. Phys., 95*, 1345 (1991).

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6. Curtiss, C.F. and Bird, R.B. "Statistical Mechanics of Transport Phenomena in Polymeric Liquid Mixtures", Advances in Polymer Science, Volume 125. Springer (1996).

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Giant-Sized Homometallic/Heterometallic Carbonyl Clusters: Synthesis, Structure/Bonding and Physical/Chemical Characterization

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1. Tran, N.T.; Kawano, M.; Powell, D.R.; Hayashi, R. K.; Campana, C. F.; Dahl, L.F., "Isostructural $[Au_6Pd_6(Pd_{6-x}Ni_x)Ni_{20}(CO)_{44}]^{6-}$ and $[Au_6Ni_{32}(CO)_{44}]^{6-}$ Clusters Containing Corresponding Nonstoichiometric $Au_6Pd_6(Pd_{6-x}Ni_x)Ni_{20}$ and Stoichiometric Au_6Ni_{32} Nanosized Cores", *J. Am. Chem. Soc.*, **1999**, *121*, 5945–5952.

2. Tran, N.T.; Kawano, M.; Powell, D.R.; Dahl, L.F., "High-Nuclearity $[Pd_{13}Ni_{13}(CO)_{34}]^{4-}$ Containing a 26-atom $Pd_{13}Ni_{13}$ Core With an Unprecedented Five-Layer Close-Packed Triangular Stacking Geometry", *J. Chem. Soc., Dalton Trans.*, **2000**, 4138–4144.

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6. Tran, N. T.; Kawano, M., Dahl, L.F. "High-Nuclearity Palladium Carbonyl Trimethylphosphine Clusters Containing Unprecedented Face-Condensed Icosahedral-Based Transition-Metal Core-Geometries", *J. Chem. Soc., Dalton Trans.*, **2001**, 2731–2748.

7. Zhang, J.; Dahl, L. F., "First-Known High-Nuclearity Silver-Nickel Carbonyl Cluster: Nanosized $[Ag_{16}Ni_{24}(CO)_{40}]^{4-}$ Possessing a New 40-Atom Cubic T_d Closed-Packed Metal-Core Geometry", *J. Chem. Soc., Dalton Trans.*, **2002**, 1269–1274.

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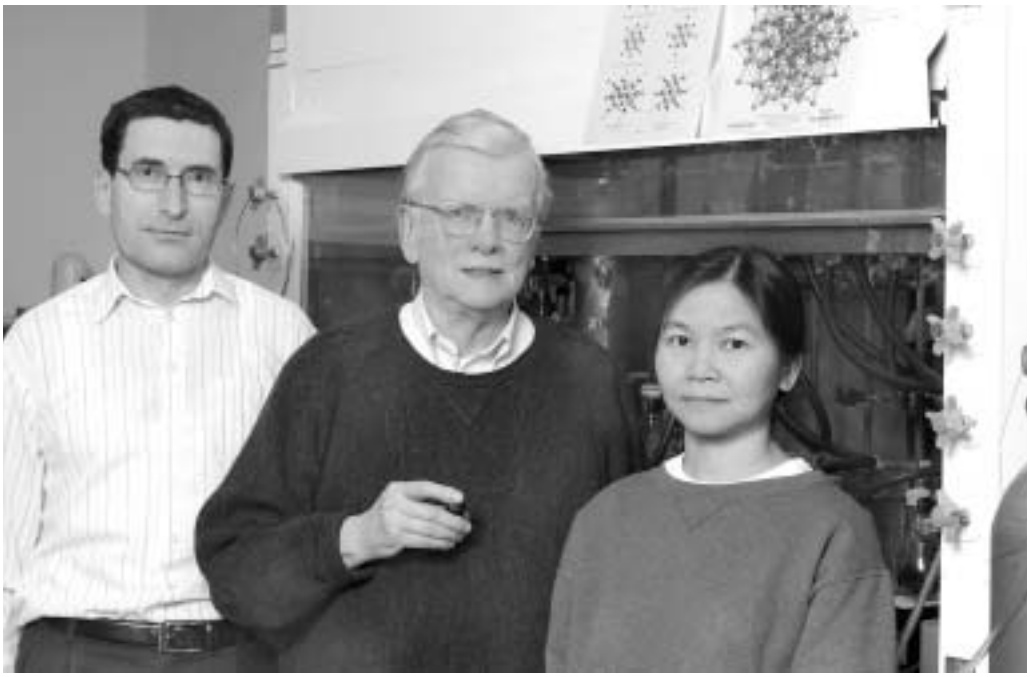
Research in our group continues to focus mainly on high-nuclearity homometallic and heterometallic carbonyl clusters: namely, those with at least 10 metal-core atoms containing primarily Group 10 (Ni, Pd, Pt) and Group 11 (Cu, Ag, Au) metals that form direct metal-metal bonds. It combines the art of synthesis (involving Schlenkware, preparative vac-line, and drybox techniques) with structural/bonding analyses and physical/chemical charaterization studies. Modern physical methods utilized include CCD X-ray diffraction, spectroscopic (IR, UV-Vis-near IR, multinuclear NMR, ESR), mass spectrometric, magnetic susceptibility, and electrochemical measurements.

Because most of these giant-sized metal clusters possess well-defined stoichiometries and precise geometries, detailed investigations of their physical behaviors should produce insight into the onset of metallic-like character with increasing metal-core size (especially for clusters with interior atoms within their metal cores). It will be important to correlate their physical properties (e.g., variable-temperature magnetic moments and specific heats) with those of naked and ligand-stabilized nanoparticles with non-uniform size distributions. These clusters are possible precursors of new materials with useful catalytic, electronic, magnetic, optical and/or photochemical/electrochemical properties.

Recent work has given rise to a considerable number of remarkable new nanosized clusters such as: 1) isostructural 38-atom trimetallic Au-M-Ni (M=Pd, Pt) and bimetallic Au-Ni carbonyl clusters of pseudo-D_{3d} symmetry with substitutional M/Ni (M=Pd, Pt) crystal-disorder occurring at only six equivalent metal sties (coloring problem); 2) two crystallographically superimposed Au-Ni carbonyl clusters of pseudo-D_{4d} symmetry containing the same 26-atom gold cage (with either one or two interior Au prisoners) surrounded by 40 Ni atoms that are ligated by 56 COs; and 3) a three-shell palladium carbonyl phosphine cluster of pseudo-icosahedral symmetry containing 55 interior Pd atoms in the first two shells encapsulated by a 60-vertex 3rd shell polyhedron (a geometrical metalloisomer of C_{60} buckyball) with 30 additional capping Pd atoms.

The diversity of research, in which coworkers are encouraged to develop and broaden their own research projects and to carry out "operational tests" of their hypotheses in the laboratory, generates a highly stimulating environment with extensive cross-fertilization of ideas and much give-and-take interactions occurring between group members. The publications illustrate some of our research.



Mark D. Ediger

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The properties of materials depend to a considerable extent upon the dynamics of the atoms and molecules that comprise them. Our research attempts to develop a molecular-level understanding of dynamics in polymeric materials and low molecular weight glass formers. What is it about the structure of the material and the potentials which govern the interaction of the atoms which makes dynamics fast or slow in a given system? How does the presence of a nearby interface alter the dynamics? As devices move closer to the nanometer length scale, the knowledge obtained from our molecular level experiments will become more and more essential to the correct functioning of these devices.

Polymer dynamics in multicomponent systems. Almost all applications of polymers utilize polymer blends or composites. Miscible polymer blends are a good starting point for understanding the properties of these composite systems; they are also technologically important and have flow properties that cannot currently be predicted. In polymer blends, the segmental dynamics of each component are modified from the values that they have as pure components and in general are not equal to each other. Statistical composition fluctuations thus lead to spatial variations in the mobility of the blend. NMR measurements have a special role to play in the study of polymer blends, since isotopic labeling allows each component to be selectively interrogated. An essential feature of our approach is the comparison with large scale molecular dynamics computer simulations.

Supercooled liquids/diffusion in thin films. If crystallization is avoided upon cooling, a liquid will become more viscous and eventually transform into a glass. Part of the interest in this process is that a new type of matter results by a purely kinetic process, *i.e.*, the glass transition does not result from changes in structure. Glasses of many types (polymeric, low molecular weight organic, inorganic, saccharide,...) play important roles in technologies.

In the last few years, we have shown that, as the glass transition is approached, dynamics become increasingly spatially heterogeneous, *i.e.*, the dynamics in one region of the sample may be orders of magnitude faster than the dynamics a few nanometers away. Our current work involves vapor deposition of thin films of deuterated and hydrogenous glass formers onto a cold substrate, followed by subsequent thermal cycling leading to interdiffusion. These experiments have extended the range of measured diffusion coefficients by 6 orders of magnitude and shown that diffusion near the glass transition is qualitatively different than in "normal" liquids. Our current work, in combination with theory by other groups, aims to quantitatively predict transport at low temperatures.

Dynamics near polymer interfaces. In many situations dynamics near a glassy polymer surface are important. For example, polymer structures with dimensions less than 100 nm are projected to be routinely prepared by lithography within 6 years. These small structures are weaker than would be expected based on the properties of larger polymer samples; this weakness will interfere with many possible applications. Our current hypothesis is that this weakness results from dynamics near free surfaces being orders of magnitude faster than those away from the interface. We use confocal microscopy to measure the dynamics of dye molecules covalently linked to surfactants that localize the dyes near an interface. The rotational and translational motion of the dyes can be quantitatively related to the polymer dynamics near the surface. In collaboration with groups in Engineering, we are investigating schemes to strengthen small polymer structures.

Physical Chemistry

Molecular-level description of dynamics in materials and the influence of dynamics on material properties; polymer blends; low molecular weight glass formers; polymer nanostructures; the glass transition; translational and rotational diffusion; diffusion in thin films and near surfaces; NMR spectroscopy; time-resolved optical spectroscopy.

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Physical and Inorganic Chemistry; Materials Science.

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Our research program focuses on nanoscale materials and devices. In collaboration with colleagues in the College of Engineering, we are investigating the preparation and characterization of nanoscale shape memory alloys. Bulk samples of these materials undergo solid-state phase changes that allow them to be mechanically deformed, yet recover their original shape when heated through the phase transition temperature. They can thus be used as switches and actuators. Production of nanoscale versions of these alloys is being pursued through chemical and electrochemical synthetic routes. Characterization methods include X-ray diffraction, scanning probe microscopy, electron microscopy, and surface analytical methods.

We are actively involved in the creation of nanotechnology instructional materials through the UW–Madison Materials Research Science and Engineering Center on Nanostructured Materials and Interfaces, http://www.mrsec.wisc.edu/edetc.

Ellis is on detail through June, 2004 at the National Science Foundation, where he is serving as Director of the Division of Chemistry.

Thomas C. Farrar

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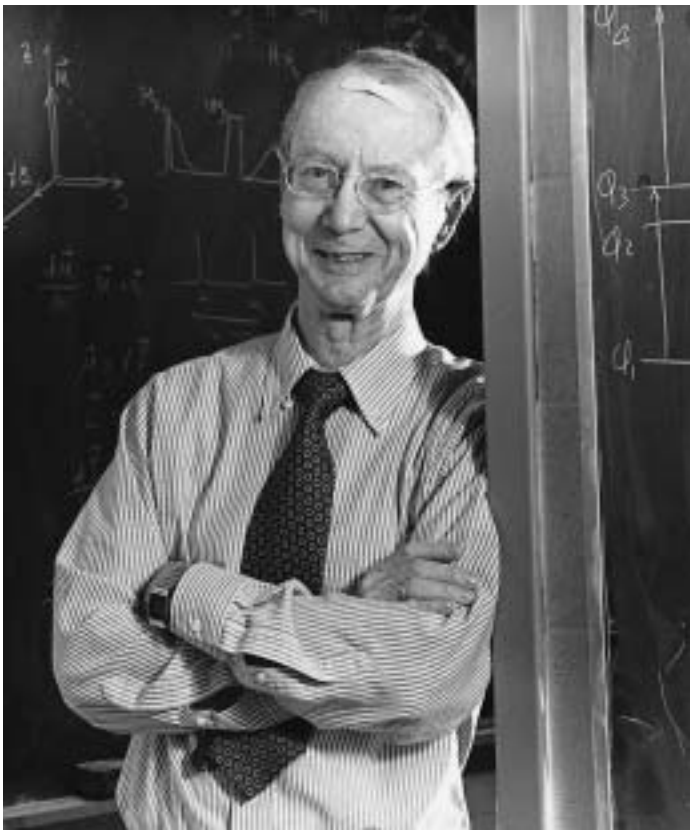
Our research group is interested in the molecular structure and dynamics of liquids. We are especially interested in hydrogen bonded liquids and the forces that drive molecular self-assembly of such liquids. It is now quite clear that simple alcohols and alcohol-water binary solutions form supramolecular structures. There are still questions, however, about the size, shape, dynamics and the lifetimes of these supramolecular structures.

To study these systems we use a variety of experimental and theoretical methods. High resolution nuclear magnetic resonance (NMR)and NMR relaxation time studies provide a wealth of information about molecular size, molecular shape and molecular dynamics. Infrared studies complement the information available from the NMR studies. We have recently developed new experimental/theoretical methods for the accurate measurement of nuclear quadrupole coupling constants (qcc) in the liquid state. This makes it now possible to obtain accurate values for rotational correlation times of nuclei such as deuterium, nitrogen and oxygen. This experimental data for the rotational correlation times of several molecular vectors in a molecule provides important information about the molecular dynamics. It also provides important bench mark information that is important for the testing of the validity of the force fields used in molecular dynamics (MD) simulations.

The combination of the Gaussian 98 suite of theoretical programs, molecular dynamics simulations, experimental NMR and infrared experiments is providing new insights about the structure and dynamics of liquids. For example, experimental data and theoretical calculations provide powerful evidence that liquid ethanol consists primarily of cyclic hexamers with an average lifetime at room temperature of about 10 picoseconds. At low temperatures the population of the cyclic hexamers increases significantly and the lifetimes increase by several orders of magnitude. The azeotropic mixture of ethanol and water (80 mole percent ethanol and 20 mole percent water) consists of cyclic pentamers composed of four ethanol molecules and one water molecule. This structure seems to be especially stable and long lived. Work under way includes further work on neat alcohols and ethanol-water binary mixtures. Studies of water, urea and formamide along with binary mixtures of these molecules are also in progress.



Analytical and Physical Chemistry.

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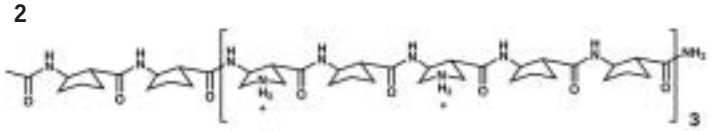
1. Design of new oligomers and polymers with well-defined folding properties ("foldamers"). We are trying to design new repetitive backbones that adopt highly ordered conformations, like those of proteins. Once we have identified backbones that display long-range conformational order in solution, it should be possible to generate recognition and/or catalytic functions via combinatorial synthesis and screening methods.

Our efforts to date have focused on oligomers of b-amino acids ("β-peptides"). β-Peptide secondary structures appear to be very stable. We have shown, for example, that β-peptides containing just six residues (e.g., **1**)

1

adopt very stable helical conformations in aqueous solution. Current goals include creation of β-peptide tertiary structure and identification of β-peptides with useful biological activities. Our first success in the latter area has involved development of β-peptides with potent and selective antibacterial properties (e.g., **2**). We

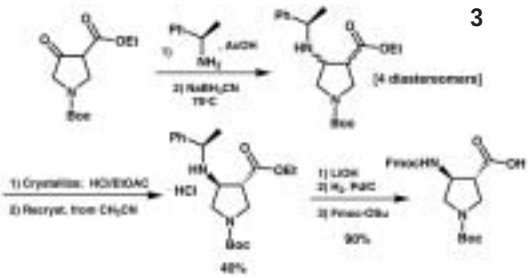
2



are also trying to use foldamers to disrupt specific protein-protein interactions.

Foldamer research requires mastery of a number of different skills. Asymmetric synthesis is critical, because foldamer building blocks must be available in enantiomerically pure form via short routes (e.g., the synthesis of protected β-amino acid **3**). Individual β-peptides are synthesized via solid-phase methods, and we are currently trying to identify the most efficient strategies for preparing β-peptide libraries. Structural analysis is also critical in foldamer research. We rely heavily on two-dimensional NMR techniques. We are increasingly turning to biological methods to evaluate foldamer activity.

3



2. Protein design: minimal increments of secondary and tertiary structure. At the level of secondary structure, proteins are dominated by just a couple of motifs, e.g., α-helix and β-sheet. The factors that control α-helix stability are well understood because appropriate model systems have long been available. In contrast, β-sheet model systems that fold in water have appeared only recently. We have developed a powerful strategy for design of small β-sheets, and we are using these molecules to probe the network of forces that control β-sheet conformational stability.

We are beginning to extend our design efforts to the tertiary level, which requires the development of new strategies for identifying minimal increments of tertiary folding. These strategies should allow us to create heterogeneous tertiary structures, in which conventional secondary structural elements pack against unnatural units (e.g., β-peptide segments).

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Professor
B.S. 1980, University of Wisconsin–Madison
Ph.D. 1986, Cornell University

Our research is focused on understanding and manipulating chemistry to control, with atomic precision, the chemistry at solid surfaces and interfaces. We refer to this area as "interfacial architecture" because we are interested in understanding the physical properties of molecular building-blocks and using this information to design, build, and understand more complex structures with precisely-tailored functional properties. We are especially interested in interfaces that link organic/biological molecules with inorganic materials that have good electrical properties, such as silicon, diamond, and carbon nanotubes. These hybrid organic/inorganic systems are of increasing importance in emerging areas such as organic and molecular electronics, bio-electronics, biosensing, and nanotechnology. We are also interested in complex interfaces found in the environment and how reactions at these interfaces affect the environment.

Our group studies interfaces under a range of conditions, from ultrahigh vacuum to solid-liquid interfaces, and from very fundamental studies of small molecules all the way to fabricating structures and devices with direct practical application.

Some of our ongoing projects include:

1) Organic-inorganic interface chemistry: Organic molecules have great potential as active elements in microelectronic devices and even as "single-molecule" devices, but little is known about how to control the interfaces between organic molecules and other materials. We are investigating mechanistic aspects of surface chemical reactions of organic molecules and the use of well-defined surface chemistry to enable fabrication of organic electronic devices on micro- and nano- length scales.
2) Bioelectronic interfaces: Linking biological molecules with microelectronic materials has the potential for new types of chemical sensors and actuators providing real-time, label-free detection of biological molecules. We have develop new chemical modification schemes on silicon and diamond that lead to very stable interfaces, and are developing new electronic detection methods for sensing biological molecules using entirely electronic means.
3) Nanotechnology and Interface Architecture: We are developing new methods for chemically modifying carbon nanotubes and nanowires, and using these to develop new types of surface architectures and as tiny chemical/biological sensors. By linking nanotubes with biological molecules such as DNA we are using biochemical interactions to control how nanotubes assemble into more complex structures and are working toward nanotubes/nanowires as chemical/biological sensors down to the single-molecule level.
4) Environmental Interfaces: Interfaces between minerals and aqueous phase play crucial roles in human health and the environment. We are studying geochemical transformations and binding of molecules to mineral surfaces, and how these processes are affected by biological systems.

To carry out these studies, our laboratories are equipped with a wide variety of state-of-the-art instruments for characterizing the chemical, electrical, and optical properties of interfaces. These include dedicated instruments for scanning tunneling microscopy, atomic force microscopy, sub-monolayer infrared spectroscopy, core-level and valence-band photoemission spectroscopy, and optical spectroscopy. These instruments provide a comprehensive picture of the physical and chemical structure of surfaces and interfaces. For more complex interfaces (such as those involving various biological molecules), these methods are further augmented by techniques such as fluorescence microscopy, electrochemical impedance spectroscopy, and novel microwave-frequency electrical measurements.

Some of these projects involve collaborations with other researchers at UW, at other institutions, and at national and/or industrial laboratories. Students in the group come from a variety of backgrounds, including analytical chemistry, materials chemistry, physical chemistry, inorganic chemistry, the cross-campus "Materials Science Program," and the Department of Physics. The interdisciplinary nature of the research is especially well-suited for students whose interests extend beyond the individual sub-disciplines of chemistry.

Analytical, Materials, and Physical Chemistry

Chemistry at solid surfaces and interfaces. Hybrid interfaces of inorganic materials (silicon, diamond, nanotubes/nanowires) with organic and biological materials for electronics, sensing, and actuation. Nanotechnology and molecular assembly. Bioelectronics and electronic/electrical characterization of biological interfaces. Chemistry at environmentally-relevant surfaces and interfaces.

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The goal of research in this group is to gain a better understanding of the electronic structure of molecules by use of reduced density matrices. Methods include formal extensions of the theory, calculations of good quality for specific systems and the graphical presentation of results, and investigations of simple models.

State-of-the-art electronic wave functions may involve millions of coefficients, which never get out of the computer. Fortunately, such a wave function contains much more information than is needed. Reduced density matrices and densities in coordinates, momenta, or both provide a way of concentrating our attention on the relevant information. Densities provide less information than density matrices, and the relationships among these quantities is of interest. Not only is the formal theory of these objects of interest itself, but an analysis in terms of them can aid us in the calculation and understanding of properties such as correlation of various types, spin density distributions, etc.

In a formal sense, densities and density matrices are elements of vector spaces; we can investigate their geometric properties. Some of the relationships among these spaces depend on the basis set used. Others are determined by symmetry. One of our goals is to learn as much as we can of the properties of reduced density matrices and densities that are determined by symmetry, basis set, and general requirements of quantum mechanics, so that when we look at results for a particular system we can concentrate on those aspects specific to it, and thus providing information about it.

It has long been a goal of density matrix theory to calculate the simpler reduced density matrix directly, without involving the more complicated wave function. This has been difficult because of the need to impose appropriate boundary conditions: the "n-representability problem." Recent methods involving contracted Schrodinger equations or constraints seem promising and we are interested in justification of or problems with these methods.

In addition, many of the formal results of density matrix theory with a basis set are directly applicable to magnetic resonance theory and to formally similar problems arising in laser experiments. We are interested in applying what we have learned to these problems.

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Cell Surface Binding Interactions; Carbohydrate – Protein Complexation; Organic Synthesis of Natural and Non-Natural Bioactive Compounds Cells require the ability to sense ligands, such as hormones, nutrients, and toxins, in their environments so that they can respond appropriately to those signals. The complexation of ligands to cell surface receptors is a crucial step in regulating the responses of cells to external stimuli. The Kiessling research group is focused on the synthesis and identification of compounds that regulate cellular responses through their interactions with cell surface receptors. The underpinning of our studies is the use of synthetic organic chemistry to generate the ligands necessary to elucidate the biological recognition events of interest.

Protein – Carbohydrate Interactions. The cell surface oligosaccharides are a class of ligands that has been a focus of Kiessling group research. Oligosaccharides play important roles in development, immune system function, inflammation and host – pathogen interactions; yet, compounds that can modulate – carbohydrate interactions are rare. The Kiessling group is using parallel synthesis to generate libraries of molecules from which active compounds can be identified. They are mining compounds that either interact with carbohydrate-binding proteins or that interfere with saccharide biosynthesis. Protein targets under investigation include the selectins, receptors that play critical roles in inflammation and are implicated in cancer metastasis, and UDP-galactofuranose mutase, which is an essential enzyme in cell wall biosynthesis in mycobacteria (e.g., those that cause tuberculosis) and parasites (e.g., those that cause sleeping sickness). It is this interest in devising molecules that modulate protein – carbohydrate interactions that has led the Kiessling group to investigate multivalent ligands in cell surface recognition.

Multivalent Ligand Inhibitors. Most research on receptor – ligand interactions focuses on the interaction of molecules with single receptor binding sites. Ligands that can occupy multiple protein binding sites simultaneously because they display multiple copies of recognition elements are termed multivalent. The Kiessling group is investigating multivalent as well as monovalent ligands as modulators of biological activities. For example, the Kiessling group has shown that multivalent carbohydrate displays are highly effective (10^{5-6}-fold more potent) at blocking cell agglutination mediated by carbohydrate-binding proteins. The potencies of these ligands rest in their abilities to interact with the target receptors through molecular recognition

processes not available to monovalent ligands. Specifically, many multivalent ligands function by clustering receptors in solution or on the surface of a cell. Molecules with this activity can serve not only as inhibitors but also as effectors.

Multivalent Ligand Effectors. As with inhibitor design, strategies to design effector ligands (i.e., ligands that promote rather than inhibit a biological response) have focused primarily on identifying molecules that could occupy a single receptor binding site (agonists). The finding that ligand-promoted receptor clustering can trigger signaling pathways has led to the generation of synthetic multivalent ligands that promote protein dimerization or oligomerization and, therefore, signal transduction. For example, we found that multivalent ligands can lead to the loss L-selectin, an important mediator of the inflammatory response, from the cell. Moreover, we have found that multivalent ligands can be used to tune a cellular response. Specifically, ligands of different valencies have different potencies as chemoattractants for bacteria. By varying ligand valency, we can systematically vary the chemotactic responses of bacteria. These changes may arise from differences in receptor clustering at the membrane. Our data indicate that the most potent chemoattractants are ligands that can cluster the chemoreceptors through non-covalent interactions. These strategies may prove useful in controlling signal transduction events in the immune system and in stem cell biology.

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Our research centers on catalysis involving transition metal complexes. The approach is multidisciplinary: synthesis, kinetics, development of novel instrumentation, sophisticated NMR spectroscopy, theory, and computations all are brought to bear on contemporary issues in homogeneous catalysis. Themes in our current research include the creation of highly selective and active catalysts, the exploration of large scale screening methods for catalyst discovery, developing fundamental mechanistic understanding of commercial catalytic processes, and the interplay of experiment and computation in understanding catalytic processes and designing new catalysts.

Mechanisms of Catalytic Reactions

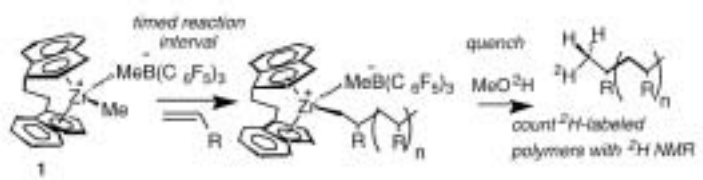
One of the largest commercial applications of homogeneous catalysts is the metallocene-catalyzed polymerization of simple alkenes to make polyethene, polypropene, polystyrene, etc. New homogeneous metallocenes catalysts based on Ti and Zr have revolutionized this industry, making possible new polymeric materials through exquisite control of polymer molecular weights and microstructure. Surprisingly, characterization of rate laws for the fundamental steps (initiation, propagation, and termination) of metallocene-catalyzed polymerization and a fundamental understanding of how various activators and co-catalysts affect the rates, stereospecificity, and molecular weights of catalytic polymerizations are underdeveloped. Our research encompasses the development of new methods for determining the number of catalyst sites that are producing polymers (i. e., active site counting), new instrumentation for measuring very fast reaction rates, and new approaches to probing the influence of ion-pairing dynamics on the polymerization activity. We are using rapid kinetics instrumentation developed in our laboratory to achieve complete characterization of rate laws for initiation, propagation, and termination for the catalytic polymerization of 1-hexene in the presence of, [(*rac*-C_2H_4(1-Ind)$_2$)ZrMe]$^+$[MeB(C_6F_5)$_3$]$^-$. We are in the process of extending these studies to other novel polymerization catalysts of commercial importance.

Ligands for Large Scale Catalyst Screening

The key attribute of homogeneous catalysts is selectivity. The potential of harnessing such selectivity for cost effective, "greener" manufacturing of pharmaceuticals and fine chemicals drives modern research in homogeneous catalysis. Chiral phosphine ligands attached to catalytically active metal centers result in enzyme-like rates and enantioselectivities for the hydrogenation of some substrates. The scope of highly selective catalytic transformations can increase as a result of coupling rapid catalyst screening methods with the synthesis of diverse arrays of ligands, especially chiral phosphine ligands. Our current research focuses on the creation of diverse arrays of chiral phosphine ligands. We have developed new synthetic methods for the rapid construction of chiral diazaphospholanes. Large arrays of this new class of chiral phosphine ligand are being synthesized and employed in screening studies aimed at creating new, highly enantioselective catalytic transformations.

Computation and Theory in Catalysis

Computations are a valuable complement to both catalyst design and mechanistic studies. Our use of computational methods spans the ab initio through the empirical (such as molecular mechanics). Our goals are to (1) develop a "Valence Bond" perspective of bonding in transition metal complexes (2) create new molecular mechanics software based on this perspective and (3) apply high level, hybrid quantum mechanics/molecular mechanics methods to explore the origin of selectivity control in homogeneous catalysis. A recent example involves the use of hybrid methods as implemented on parallel supercomputers to elucidate the origin of enantioselectivity in asymmetric hydrogenation of dehydroamino acids, a process which has been commercialized for the production of the anti-Parkinson's drug, L-DOPA.



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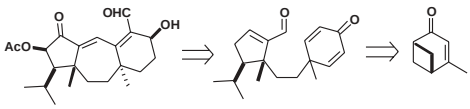
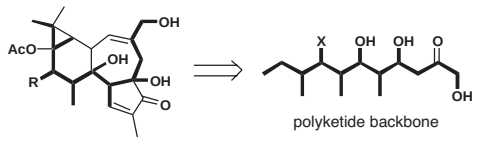
The main focus of our research lies in the development of new synthetic methods and their application to the synthesis of biologically active natural compounds. Specific research goals are the development of (a) strategies for the construction of carbocycles containing quaternary carbon centers and its application to the synthesis of guanacastepene A; (b) a new approach for the stereoselective construction of cyclic terpene structures and its application to the synthesis of tumor promoter-related compounds, such as phorbol and prostratin; (c) new general method for the construction of tetrahydropyrans and its application to the synthesis of lasonolide A and zampanolide.

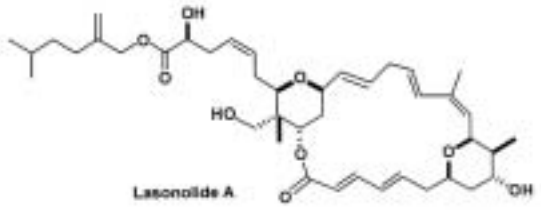
Guanacastepene synthesis: We are engaged in the total synthesis of the newly isolated diterpene antibiotic guanacastepene A, which has shown antibiotic activity against two of the most drug-resistant pathogens of concern, *Staphylococcus aureus* and *Enterococcus faecalis*. In this effort, we are developing a novel and general strategy to build the two critical ring-junction quaternary methyl groups via alkylidene carbene insertion chemistry and a diastereoselective reductive coupling between enal and enone.

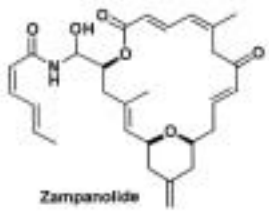


Prostratin synthesis: We want to develop a new concept for the synthesis of polyoxygenated multi-ring containing terpene structures such as phorbol and prostratin from polyketide-like linear molecules. This non-traditional retrosynthetic analysis is possible due to the advancement of acyclic stereocontrol via the development of stereoselective C–C bond-forming methods.



New methods for pyran synthesis and its application to lasonolide A and zampanolide: The tetrahydropyran is a ubiquitous functionality found in many macrolide natural products possessing antitumor activity. For the purpose of synthesizing these compounds, we are developing an efficient synthetic methodology for the construction of tetrahydropyran moieties. Our strategy is particularly attractive because the starting building blocks are readily available in both enantiomeric forms and the stereochemistry of the starting material is stereospecifically translated into that of tetrahydropyran products. Therefore, not only the thermodynamically more favorable 2,6-*cis*-disubstituted tetrahydropyrans but also 2,6-*trans*-disubstituted pyrans are available with equal efficiency. We are planning to use this synthetic method for the synthesis of lasonolide A and zampanolide.





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Our research program lies at the interface between analytical chemistry and cellular neurobiology and involves two interlinked aspects. First, we plan to develop and implement an array of enabling mass spectrometric tools coupled with front-end microseparation strategies that are capable of global analysis of peptides and proteins in complex biological matrices in a high throughput and high sensitivity manner. Second, using several well-defined crustacean neuronal networks as model systems, we aim to obtain a complete catalog of the diverse assortment of peptides contained within these neuronal networks and expand our fundamental understanding of cotransmission and neuromodulation at the molecular level.

The crustacean stomatogastric nervous system is an excellent model system for studying the neural basis of rhythmic behavior and it is also an ideal system to investigate neuromodulation in a well-defined neural network. These central pattern-generating networks found in crabs and lobsters are responsible for controlling the rhythmic movement of food through the foregut. This is an attractive preparation because of the limited number of neurons whose electrophysiological properties can be readily assessed and yet an amazingly large number of peptide neuromodulators are involved in this small neural network. However, we are far from having a complete description of "full cast of modulatory players" and their pattern of colocalization in inputs to the stomatogastric ganglion, which is crucial for understanding the mechanisms by which this hard-wired, pattern-generating circuitry is functionally modulated. Because the electrophysiology and rhythmic patterns of the circuit are well-characterized, the neuromodulatory effect of any newly-discovered peptides on the network can be readily probed, thus directly connecting the biochemical nature of peptide modulators to their functional roles.

Given the previous knowledge of several peptide families suggested by immuno-reactivities and the high chemical complexity of the crustacean stomatogastric nervous system, we will develop proteomics-based strategies that couple front-end immunoaffinity isolation and capillary separation with various mass spectrometric instrumentation, including a 7 Tesla Fourier transform mass spectrometer, an ESI ion trap mass spectrometer and a MALDI time-of-flight mass spectrometer. Furthermore, to address the challenge of discovering novel peptides and

characterizing full complement of neuropeptides in the absence of genomic sequence of these model systems, we will develop a new hybrid strategy to use the partial sequence information obtained by *de novo* MS/MS sequencing in combination with database search via homology of genomes from other related species. Finally, nanoscale-sampling techniques will be developed to allow peptide detection at the single cell and even subcellular level under different physiological conditions.

In summary, our research will (a) develop improved MS-based methods of neuropeptide and protein analysis both at large-scale and micro-scale and (b) provide essential information on understanding the mechanisms of neuromodulation of behaviorally relevant neural circuits and peptide evolution and peptide regulation. The research program can be generally described as bioanalytical, but combining aspects of analytical mass spectrometry, protein chemistry, microseparations, neurobiology, immunochemistry, and bioinformatics. We expect that by developing new tools that combine greatly improved sensitivity and chemical selectivity, significant gains can be made to advance our knowledge of how networks of neurons interact in both healthy and diseased systems.

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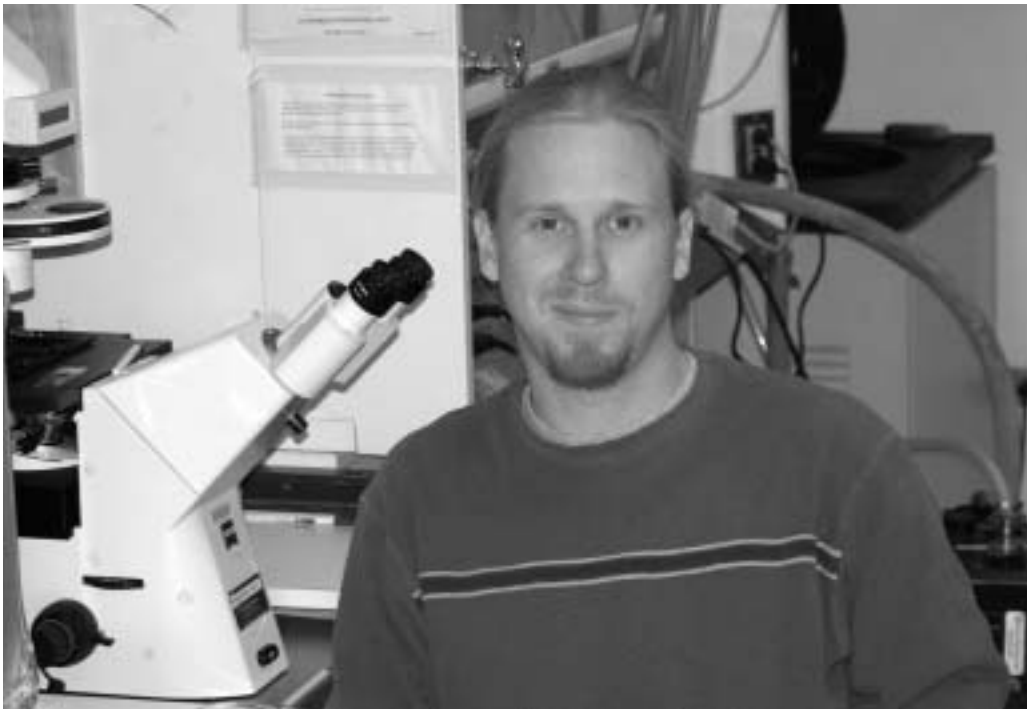
Our group uses the principles of chemistry, engineering, and biology to design materials-based approaches to important problems in the biomedical, pharmaceutical, and health-related fields. Our research is conducted in a highly interdisciplinary and collaborative environment that provides opportunities for students with backgrounds and/or interests in chemistry, engineering, biology, materials science, medicine, and the pharmaceutical sciences.

We use new concepts in chemical synthesis and polymer science to design new materials for biomedical applications such as gene delivery, controlled release, and tissue engineering. Traditionally, biomaterials research has relied heavily on materials developed for non-biomedical applications. More recently, the design of materials that are specifically tailored to meet the needs of individual applications has helped to fuel the enormous growth seen in the health care industry. As one example, the sales of controlled-release pharmaceutical formulations alone (which have depended heavily on the development of new functional, biocompatible materials) now exceed $20 billion a year.

Within the context of a particular problem, we seek to understand: 1) how control over structure at the molecular level influences material properties, and 2) how subtle changes in material properties affect interactions with biological systems. The first goal takes advantage of advances in the chemical sciences, particularly in the areas of organic chemistry, polymer synthesis, and materials characterization. Toward the second goal, we are actively engaged in the *in vitro* and *in vivo* evaluation of our materials in our own laboratory and work closely with other groups and members of the biotech industry to identify new strategies and opportunities.

How do subtle changes in polymer structure affect the efficiency or mechanism through which cells internalize and process nanoparticles for gene delivery? How does the structure of a material affect the release rates of encapsulated drugs, or influence the attachment, proliferation, and differentiation of different cell types? A fundamental understanding of materials properties and the structure/activity relationships that characterize new biomaterials is essential to the design, engineering, and application of new therapeutic systems. We use a mixture of hypothesis-driven and discovery-oriented techniques to synthesize new classes of polymers and develop approaches that could accelerate the rate at which new materials are discovered for clinical applications.

While our interests lie broadly at the interface of materials with biological systems, the techniques, materials, concepts, and approaches we use frequently spill over into projects in adjacent areas of chemistry, engineering, and materials science.



Organic Chemistry.

Polymer synthesis; Biomaterials; Functional materials; Gene and drug delivery; Controlled release; Parallel synthesis and screening.

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Organic, Inorganic and Materials Chemistry

Organic and organometallic photochemistry; generation and characterization of reactive intermediates; thermal and photochemical rearrangement mechanisms of organic and organometallic compounds; mechanisms of intramolecular C-H bond activation in organometallic complexes; design, synthesis, and evaluation of new materials with nonlinear optical properties.

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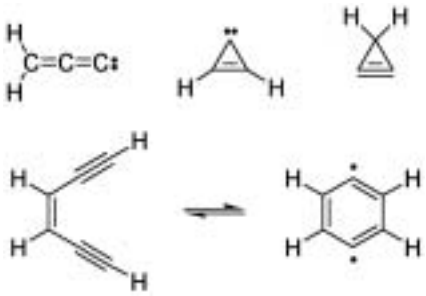
Our research program focuses on bringing insights from mechanistic chemistry to bear on diverse scientific problems. Our interests range from mechanistic organic and organometallic chemistry to the fundamental chemistry underlying important problems in materials science.

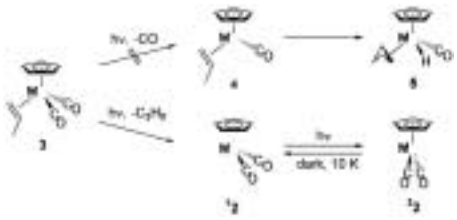
Mechanistic Organic Chemistry

The organic chemistry of interstellar space represents one of the research frontiers in mechanistic organic chemistry. Our recent research efforts focus on elucidating the structure, photochemistry, and spectroscopy of organic species that play a role in the chemistry of the interstellar medium. Understanding the chemistry interstellar clouds represents a significant challenge in mechanistic organic chemistry-both in terms of identifying new organic species in the clouds and in terms of investigating the chemical processes that govern the formation and destruction of these organic species. Recent investigations from our laboratory illustrate the role that physical-organic chemistry plays in addressing important chemical problems in astronomy and molecular spectroscopy.



Mechanistic Organometallic Chemistry

The most fundamentally important rearrangement pathway of many coordinatively-unsaturated organometallic intermediates involves intramolecular hydrogen migration. Because the rates of these rearrangements are so rapid, and because the intermediates are so elusive, almost no quantitative rate data or detailed structure-reactivity correlations exist at the present time. Using sophisticated low-temperature NMR methods and matrix-isolation techniques, we became the first to 1) directly observe an intramolecular oxidative-addition reaction, and 2) characterize an allyl hydride complex of a first-row transition metal.



A deeper understanding of these exceptionally reactive species may lead to new insights concerning C-H bond activation catalysts and mechanisms of metal-catalyzed alkene isomerization.

Nonlinear Optical Materials

Strange optical processes (frequency doubling, holographic effects) occur when intense laser light interacts with certain organic and inorganic compounds; these effects are generically referred to as nonlinear optical phenomena. Many of these unusual phenomena are tremendously important in emerging high-technology areas such as erasable optical information storage, optical computing, and optical communication. By synthesizing and studying new compounds, we seek to 1) understand the molecular and bulk properties that govern nonlinear optical response, and 2) develop more efficient nonlinear optical materials. Research in this area involves elements of molecular design, synthesis, molecular orbital calculations, laser spectroscopy, and materials chemistry.

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Our research efforts focus on fundamental studies of non-covalent interactions and the application of the resulting findings to biochemical and biomedical problems. We use the predictive value of advanced computational techniques in conjunction with the power of chemical synthesis to generate molecules that are able to recognize each other through intermolecular forces. The study of these complexes allows us to explore a variety of different chemical and biological phenomena. These include the nature of specific intermolecular forces in condensed phase, the origin of the peculiar fluorous phase behavior in highly fluorinated materials and the interaction between short RNAs and small molecules.

The Fluorous Phase.
The introduction of fluorine substituents into an organic molecule can radically change the physico-chemical properties of that molecule. High performance materials and polymers, vectors for drug delivery, anesthetics, fluorine-containing drugs, perfluorinated solvents for organic reactions are only a few examples of the practical uses of fluorinated molecules. Extensive perfluorination of organic molecules generates a new phase of liquid matter known as the fluorous phase. This phase does not mix with either polar or non-polar hydrogenated phases. The formation of a fluorous phase is at the basis of the unusual behavior of heavily fluorinated molecules and polymers. While the applications and the uses of fluorinated compounds are constantly increasing, the origin of their unusual properties is currently not completely understood. It is not known what exactly drives the formation of a fluorous phase.

We are currently investigating the nature of the fluorous phase by synthesizing and analyzing some self-assembling fluorinated amphiphilic molecules bearing water solubilizing groups and variously fluorinated functionalities.

We are also performing molecular dynamics simulations on mixtures involving water, hydrocarbons, and a variety of fluorinated molecules. The purpose of these simulations is to establish first what kind of intermolecular forces can explain the formation of three phases and then identify the minimum number of fluorine atoms that are necessary for generating a fluorous phase.

The Nature of Intermolecular Interactions
We focus our studies on understanding the basic principles behind weak, yet biologically and energetically significant non-covalent forces. Our most recent studies have focused on using the recognition events between enzymes and their inhibitors to study the energetics of specific intermolecular interactions. We have recently designed and synthesized new inhibitors of HIV–1 protease where we have replaced groups known to hydrogen bond to the protein backbone by groups that bear non-classical hydrogen-bonding functionalities. The general purpose of this work is to measure the energetic contributions by these new hydrogen bonds. This approach can be fruitfully used to study a variety of different intermolecular interactions and, at the same time, to achieve a deeper understanding of the enzymes' inner machinery. These experimental studies are complemented by high level *ab initio* calculations on simple complexes. Natural Bond Orbital theory is also used to chemically understand the origin of the interactions.

Short RNA-Small Molecules Complexes
Our research in this field focuses on finding the minimal RNA sequences able to bind small organic molecules with high selectivity and affinity. Our own approach starts from the analysis of the crystal structure of RNA aptamer–small molecule complexes. We then computationally model these complexes to study the effect of nucleotide deletion and spatial rearrangement on the overall energetics. This approach allows us to computationally design short RNAs that are able to specifically bind small molecules. The complexation thermodynamics is then studied by microdialysis. We are also currently pursuing a dynamic combinatorial approach to this problem.

Organic Chemistry

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Chemical Education.

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11. "Getting By" J. W. Moore, Editorial, *Journal of Chemical Education*, **1998**, 75(3), 255.

12. "Has Chemical Education Reached Equilibrium?" J. W. Moore, Editorial, *Journal of Chemical Education*, **1997**, 74(6), 613.

Current research aims at improving teaching and learning of chemistry by expanding the use of interactive, student-oriented means of instruction. We are exploring the potential of a variety of media through which students can obtain chemical knowledge and intuition, and examining each medium to determine how it can make the greatest contribution to the chemistry curriculum. Unique opportunities are available for students who are seriously interested in teaching of chemistry to broaden that interest by working on a project in chemical education.

Instructional technology, both current and future, can provide richer, more diverse environments within which students can learn chemistry than have ever before been available. Many technologies permit, even encourage, an inductive, experimental approach to the subject—students are led to try things, develop hypotheses, and proceed on the basis of their observations, ideas, and conclusions. That is, they are encouraged to act as scientists would act.

Opportunities are available for work on new computer software, interactive multimedia materials, computer-based laboratories, chemical demonstrations, and hands-on chemistry activities aimed at both college and pre-college students. Examples of recent work are

- "Periodic Table Live," a multimedia hypertext about the elements and their properties that includes video images of the reaction of each with air, water, acids, and base; and includes fifty chemical and physical properties of 103 elements;
- "ChemPages Laboratory," a multimedia encyclopedia of laboratory procedures and techniques that students can access via the World Wide Web;
- Web-based multimedia quizzes and homework assignments that allow students to be examined using digitized video, sound, and computer animations;
- "Chemistry Comes Alive!" a series of CD-ROMs that provide nearly instant random access to still pictures, action video sequences, and animations showing a large number of chemical demonstrations and laboratory techniques close up so that the chemistry is the center of attention; and
- "ChemPages Netorials," a set of Web-based tutorials on all aspects of introductory chemistry and biochemistry.

The *Journal of Chemical Education* (*JCE*), the Institute for Chemical Education (ICE), and Project SERAPHIM provide for interaction with a wide variety of persons who are interested in problems associated with education in chemistry. Each year we host visiting faculty and postdoctoral Fellows who provide many new perspectives on chemical education and good contacts for students. ICE is a national center that works to revitalize the teaching of chemistry at all educational levels by forming partnerships among academic, government, and industrial chemists. Project SERAPHIM develops new kinds of software and new applications of technology in teaching.

The editorial offices of the *Journal of Chemical Education* moved to Madison in 1996. This provides additional opportunities for interactions with a wide variety of people interested in chemical education. *Journal of Chemical Education Software*, a branch of the *Journal of Chemical Education*, is the first scientific journal to publish computer software in electronic form—on floppy disks, videodiscs, CD-ROMS, and the Internet. It too contributes to the very strong chemical education component of UW–Madison.

Gilbert M. Nathanson

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Molecular beam scattering experiments have blossomed into a universal technique for understanding and controlling reactions in the gas phase and on solid surfaces. Our research confronts a third frontier: the microscopic structure and reactivity of liquid surfaces. We use molecular beam techniques to explore collisions and reactions of gas molecules with liquids ranging from crude oils, fluorinated lubricants, and liquid metals to glycerol, sulfuric acid, and molten sodium hydroxide. These liquids are important industrially and in the atmosphere, where sulfuric acid aerosols play a role in ozone destruction.

The questions we ask are simple: what does the surface of a liquid "look like" atom by atom and "feel like" during the short time scale of a gas-liquid collision? How does an acidic molecule such as HCl dissolve and dissociate in the neutral liquid glycerol or in supercooled sulfuric acid? What are the interfacial analogs of bulk solvation, hydrogen bonding, the "like dissolves like" rule, proton exchange, and acid-base reactions?

Molecular beam scattering experiments can answer these questions. We direct a highly collimated and nearly monoenergetic beam of molecules at the surface of a continuously renewed, low vapor pressure liquid inside a vacuum chamber. These gases range from inert atoms to alcohols, carboxylic acids, and hydrogen halides. After striking the liquid, the molecules either scatter from the liquid or stick and dissolve, perhaps reacting with solvent molecules in the interfacial or bulk regions of the liquid. A fraction of the reaction products may then desorb into the vacuum. The identity of the recoiling and desorbing molecules and their direction and velocity are monitored by a mass spectrometer. In many cases, we also measure interfacial and bulk reaction probabilities and the residence times of the gas molecules in the liquid. The data allow us to develop a "blow-by-blow" description of the ways in which these gas molecules bounce off, dissolve in, and react with each liquid.

Our studies bring together the most recent advances in chemical kinetics and theories of liquid structure and dynamics. By carrying out controlled collisions between a gaseous solute molecule and a liquid solvent, we are helping to construct an intimate picture of the chemistry of gas-liquid interfaces.

Physical Chemistry.

Molecular beam studies of gas-liquid collisions and reactions; atmospheric heterogeneous chemistry; structure and reactivity of the surfaces of pure liquids, acidic and basic solutions, and soluble and insoluble monolayers.

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1. "Collisions of DCl with Liquid Glycerol: Evidence for Rapid, Interfacial D-H Exchange and Desorption", Bradley R. Ringeisen, Annabel H. Muenter, and Gilbert M. Nathanson, *Journal of Physical Chemistry B* **106**, 4999 (2002).

2. "Collisions of HCl, DCl, and HBr with Liquid Glycerol: Gas Uptake, Proton Exchange, and Solution Thermodynamics", Bradley R. Ringeisen, Annabel H. Muenter, and Gilbert M. Nathanson, *Journal of Physical Chemistry B* **106**, 4988 (2002).

3. "Surface Tensions and Surface Segregation of n-Butanol in Sulfuric Acid", Ryan D. Torn and Gilbert M. Nathanson, *Journal of Physical Chemistry B* **106**, 8064 (2002).

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10. "Kinetics and Dynamics at the Gas-Liquid Interface", Gilbert M. Nathanson, Paul Davidovits, Douglas Worsnop, and Charles E. Kolb, *Centennial Issue of the Journal of Physical Chemistry* **100**, 13007 (1996).

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Organic Chemistry.

Preparation of theoretically significant molecules; electron transfer reactions and radical ion/radical chemistry; lone pair and _,π interactions; organic electrochemistry; application of physical methods to the study of molecular geometry and electronic interactions.

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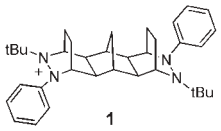
Much of our research involves the design of the proper molecules to study, through modeling of the effects of structural changes on molecular properties and electronics. We are especially interested right now in the design and study of "intervalence compounds" of the general structure **M-B-M**$^+$, that have identical but separated sites for the "hole" that results from loss of an electron [**M** is a charge-bearing unit and **B** a bridge between the **M**s]. These are the simplest electron transfer systems, and their study provides the most stringent tests for the validity of the assumptions used in theories of electron transfer. The intervalence concept was developed for transition metal centered compounds, and virtually all the compounds that had been studied before our work had either coordination compounds or aromatic compounds as the **M**. Our principal contribution has been to design compounds for which the electron transfer rate constant can be measured by employing specially designed **M** units that slow electron transfer enough to measure its rate using ESR.[1] The role of the bridge in facilitating electron transfer is being studied in both systems with saturated bridges, such **1**, and unsaturated ones such as **2**. The simplest Marcus-Hush



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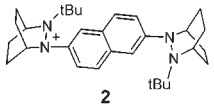
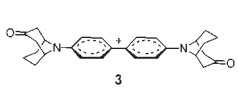


2

"two parabola" theory that uses only a vertical reorganization energy (λ) and an electronic coupling through the bridge (H_{ab}), both obtained from the charge transfer band in the optical spectrum of an intervalence compound, predicts the thermal electron transfer rate constants for several of these compounds much better than I think anyone predicted. We improved the prediction by actually fitting the optical charge-transfer band instead of pretending that the diabatic surfaces are perfect parabolas (they are not).[1] These studies showed that although simplest theory fits many compounds well,[4] the way that solvent contributions to λ are being estimated fails badly.[8] Just changing the bridge from the naphthalene of **2** to anthracene makes the simple model fail badly,[2] and we are designing both experimental systems and theoretical analysis that properly test how to handle these situations, which we suggest will prove to be common. There is great current interest in "almost delocalized" intervalence compounds that have only a tiny electron transfer barrier,[2,5] and we hope to provide experimental answers as well as theoretical predictions by the preparation and study of properly designed systems. We have shown that inserting a single oxygen in the

bridge in going from **3**, which is strongly delocalized, to **4** results in charge localization



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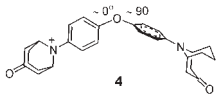

4

because of the big difference in twist at the oxidized and reduced **M** groups, but electron transfer in **4** remains very fast because twisting at the O-aryl bond increases electronic coupling.[7] Recent improvements in computation should allow much better treatments of optical absorption spectra and electron transfer dynamics than the semiempirical calculations we have been using to save computational time,[2,6,7] and we hope be able to use *ab initio* calculations for such questions in the future. We have recently shown that DFT calculations, which offer great time-savings over *ab initio* methods for many purposes, do not work for intervalence compounds because they incorrectly fail to get significant geometry differences between oxidized and reduced **M** units.

We are also actively studying intermolecular ET reactions.[9] Modern electron transfer theory predicts that the simple analysis of such reactions we use should not work because H_{ab} should be very sensitive to structure. But experimentally it is not, and we now have a consistent picture for both intra-[8] and intermolecular[9] electron transfers. There is a small (about 0.01 kcal/mol) and quite constant H_{ab} for intermolecular electron transfers for all but the least sterically hindered systems. In the near future we hope to extend our studies to determining what factors are important in achieving coupled electron and proton transfer. Such processes are very important in biochemistry: ATP formation is based upon it. No simple model systems that will allow probing coupled e^-,H^+ ET are currently available. We expect the high reorganization energies of hydrazines to allow such studies.

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The amino acid sequence of a protein encodes its three-dimensional structure, and this structure manifests itself in biological function. Using techniques that range from synthetic chemistry to cell biology, we are illuminating in atomic detail both the chemical basis and the biological purpose for protein structure and protein function. Our efforts are leading to insights into the relationship between amino acid sequence and protein function (or dysfunction), as well as to the creation of novel molecules with desirable properties. Our work is now focused on the following problems.

Protein Chemistry—The complete sequence of the human genome is now known. This information is a powerful raw material for developing new cures for disease. The human genome encodes nearly 100,000 proteins, including 5,000 or so new drug targets. Mining this raw material for new therapies requires producing the encoded proteins. We have developed new methodology for assembling proteins from their component amino acids. Our method can be automated to enable the production of any protein. Other advantages include great speed, facile purification, and the ease of incorporating modified, unusual, or even nonnatural amino acid residues. Automated protein assembly can be used to produce either large quantities of a single protein (for detailed analyses) or small amounts of many proteins (for drug discovery using combinatorial chemistry).

Protein Folding—The formation of disulfide bonds is a critical step during the folding of many proteins. We are creating new proteins and small-molecules that are efficient catalysts of disulfide bond formation both in vitro and in vivo.

Protein Stability—Collagen is the most abundant protein in animals. We have discovered a simple collagen derivative that is much more stable than normal collagen. This discovery is spawning new biomaterials for a variety of medical procedures.

Protein Function—We are revealing the molecular basis for the special biological activities of two ribonucleases: onconase (which is toxic to tumor cells) and angiogenin (which promotes neovascularization).

These research projects are designed to reveal how biological phenomena can be explained and manipulated by using chemical principles. Our hypotheses are far-reaching, and testing them requires the use of techniques and ideas from diverse disciplines. For example, members of the group learn (1) to synthesize simple organic molecules as well as peptides, nucleic acids, and their derivatives; (2) to create well-defined mutant proteins and mutant microorganisms; (3) to evaluate structure-function relationships in atomic detail by using modern biophysical methods; and (4) to acquire pertinent data in vivo. This broad/deep training is appropriate for scientists who want to perform innovative and meaningful research at the widening chemistry – biology interface.

Organic Chemistry

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M. Thomas Record

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Specificity, stability and mechanisms of formation of protein-nucleic acid complexes; biophysical studies of the *E. coli* cytoplasm; polyelectrolyte properties of nucleic acids and their complexes.

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Site specific interactions between DNA binding proteins and their target sequences govern the expression and replication of genetic information. To understand these central noncovalent binding processes, our effort is focused on quantifying the thermodynamics (energetics) and kinetics of interaction between DNA and three bacterial proteins: RNA polymerase, *lac* repressor, and "integration host factor" (IHF). All these systems are unified by a common theme: large conformational changes and other coupled processes in the proteins and/or their target DNA sites occur in binding. To initiate transcription from promoter DNA sites, RNA polymerase opens more than 10 base pairs of the DNA helix in the vicinity of the transcription start site, and in the process creates the catalytic site for NTP binding and synthesis of the RNA transcript. *Lac* repressor folds alpha helices in the minor groove of its target DNA sequence and wraps or loops flanking DNA regions to act as an on-off switch for transcription of genes for growth on the sugar lactose. To wrap and package DNA, IHF induces a large bend (>160°) in its specific binding site.

We use a wide range of biophysical and biochemical measurements to characterize these conformational changes and to quantify the amount of biopolymer surface they expose to or remove from solvent and solutes. From thermodynamic and kinetic studies, we determine the balance between driving forces and free energy costs for these conformational changes, and characterize the sequence of mechanistic steps by which they occur. We also study the DNA binding behavior of oligocations and model proteins to dissect contributions from individual components of the overall protein-DNA binding surface, and do computational and analytic theory to describe the behavior of these simpler systems.

The series of conformational changes orchestrated by RNA polymerase to form the open promoter complex and the transcription bubble occur in a minimal three step mechanism. From our kinetic studies and low resolution structural data for the intermediates (from chemical and enzymatic footprinting) we propose large scale changes in each step including DNA wrapping, kinking, unpairing and unstacking as well as protein folding and hinge bending (jaw closing). In particular, we deduce that the first kinetically-significant intermediate (I1) has a sharp bend upstream of the transcription start site which puts the downstream DNA in the jaws of polymerase prior to opening, as drawn below into Prof. S. Darst's structure of free RNA polymerase:

Current work in our lab is characterizing these conformational changes and coupled processes (including coupling of disruption of protein surface salt bridges to DNA wrapping) by thermodynamic, kinetic and footprinting methods, using selected protein structural variants and DNA sequence variants and analyses based on the recent crystal structures of eucaryotic, prokaryotic and phage RNA polymerases.

Other projects in the laboratory include the characterization of the bacterium *E. coli* as a chemical and osmotic system, and the thermodynamic and molecular characterization of interactions of cytoplasmic solutes (e.g. potassium glutamate, glycine betaine) and common biochemical solutes (e.g. urea, glycerol) with biopolymers and of effects of these solutes on biopolymer processes.

Graduate students from Chemistry, Biochemistry and Biophysics are conducting this research. The broad range of backgrounds and interests of these students has been a key factor in our research successes and contributes to a stimulating research environment. Many of my students have gone on to academic positions in chemistry and biochemistry departments; many others are engaged in research at chemical, pharmaceutical and biotechnology companies.

Hans J. Reich

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Our research effort is directed towards the study of organometallic and organometalloid compounds. The goal of the work is to deepen our understanding of these compounds and thus improve and extend their chemistry, as well as to discover new reactions of value for synthetic chemistry.

Most carbon-carbon bond forming processes involve the interaction of carbanionic centers with carbon electrophiles like carbonyl compounds, epoxides, aziridines, alkyl halides, activated alkenes and many others. Organolithium reagents are probably the single most important source of carbanionic species, and they have long played an important role in synthetic organic chemistry. A vast literature provides many complex recipes for preparing and utilizing them. However, the basis for much of what we do in the laboratory when we prepare and use lithium reagents is empirical rather than based on firm mechanistic and structural insights. We are trying to replace the "art" in the chemistry of these organometallic reagents with science.

The first step in unraveling these complexities lies in understanding the organolithium reagents themselves: What are their structures in solution and how do these change with solvent? What is the configurational stability of organolithium reagents and can we make optically active ones? How do they invert configuration, and can we control the process? How do chelating appendages affect structure and reactivity? We have developed multinuclear NMR spectroscopic tools for gaining detailed insights into the structures of lithium reagents in solution to provide answers to these and other questions.

Some of the reactivity issues we are interested in are the following: What determines whether a 1-substituted allyl or allenyl metal reacts at the α- or γ-position? What determines whether an organometallic reagent adds 1,2 or 1,4 to an α,β-unsaturated carbonyl compound?

Why do lithium halides sometimes have such dramatic effects on organolithium reactions? What role does catalysis by lithium cation play in reactions? What species are formed when organolithium species are transmetalated to organocerium, manganese, titanium and other organometallics?

Coordinating solvents and co-solvents such as THF, TMEDA, HMPA, crown ethers and others play important roles in fine tuning the chemistry of organolithium reagents. Rates of reactions as well as stereochemical and regiochemical selectivity are profoundly affected by such additives, but we do not understand the origin of these changes. We are developing a rapid-injection NMR apparatus for studying fast reactions at very low temperatures which we anticipate will provide insights into such effects at the molecular level.

Organic Chemistry.

Main group organometallic chemistry: structure, stereochemistry, mechanism and synthetic applications of organic compounds containing lithium, tin, silicon, sulfur, selenium, tellurium and other metals and metalloids; NMR spectroscopy.

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Organic Chemistry.

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1. Designing Non-Peptide Peptidomimetics in the 21st Century: Inhibitors Targeting Conformational Ensembles. M.G. Bursavich and D.H. Rich, *J. Med. Chem*., *45*, 542–558 (2002).

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7. Total Synthesis of the Cyclic Biphenyl Ether peptides K–13 and OF–4949 via SNAr Macrocyclization of Peptidyl Ruthenium Arene Complexes, J.W. Janetka and D.H. Rich, *J. Amer. Chem. Soc*., 119, 6488–6495 (1997).

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9. Solid Phase Synthesis of Cyclosporin Peptides. Y.M. Angell, T.L. Thomas, G.R. Flentke, and D.H. Rich, *J. Amer. Chem. Soc*, 117, 7279–7280 (1995).

My group is interested in the chemistry and bioorganic chemistry of natural products derived from peptides. All target molecules are biologically active; many are protease inhibitors and the rest bind to well-characterized receptor molecules. Each inhibitor contains at least one novel structural feature, usually a unique, highly functionalized amino acid, that is essential for the biological activities of the inhibitor. Our goals are to understand how this component stabilizes binding to the receptor molecule, characterize the catalytic mechanisms of the affected enzymes, and devise selective inhibitors of related, therapeutically important enzymes.

We select natural products because many of them possess novel structural features that are essential for efficient inhibition of the target enzyme and which appear to function as transition-state analog inhibitors but whose mechanisms are not well understood. For example, our synthesis of analogs of pepstatin and the characterization of their mode of binding to pepsins by various methods provided a general strategy for designing inhibitors of this class of enzyme that has been used to develop several therapeutic agents, including inhibitors of renin, HIV protease, and most recently, β-secretase.

Today, the conformations of ligands bound to target proteins can be determined by X-ray and NMR methods, but what is needed are ways to identify possible lead structures based only on the knowledge of the enzyme's ligand binding site, and to select from the many potential inhibitors those that are likely to exhibit the pharmacodynamic properties needed to obtain drugs. My group is testing various approaches for designing or creating novel inhibitors of therapeutically important enzymes, e.g. β-secretase and botulinum toxin metallo protease. The long-term goal is to discover ways to exploit the precise structural information contained in high resolution structures of enzyme-inhibitor complexes in order to develop non-peptide structures that mimic the parent peptide. By use of computerized structure-generating programs, thousands of potential mimics of the inhibitor are grown in the active site of the enzyme, one atom at a time. Some of these are synthesized by my students and tested to see how well they inhibit the target enzyme. We have actually "taught" the computer to "discover" known pepsin inhibitors, and now are embarked on a program to synthesize novel inhibitors. This strategy is being applied to a variety of enzymes that have therapeutic potential.

Botulinum toxin metallo protease is one of the most selective peptidases known and needs to recognize at least 35 amino acids in a protein in order to cleave the substrate sequence. This class of peptidase represents a particularly challenging target for which to attempt rational drug design. There are no known natural inhibitors of these enzymes and traditional approaches employed to inhibit related enzymes fail with this one. Recently we obtained the first non-peptide, low molecular weight inhibitor of BoNT/B peptidase. We are actively trying to modify this lead using structure-based design and combinatorial chemistry in hopes of obtaining clinically useful lead structures.

John L. Schrag

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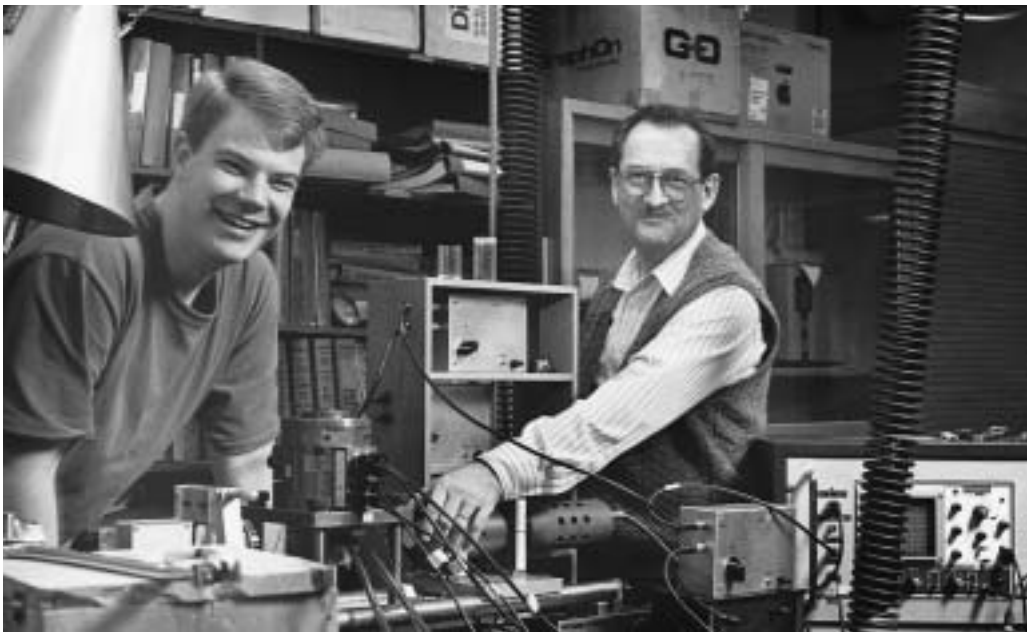
Our research activities have had two major goals: first, to determine experimentally the influence of specific chemical structure, as well as polymer-solvent and polymer-polymer interactions, on the conformational dynamics of macromolecules; second, to explore the utility of such dynamics information for polymer analysis and characterization. The first aspect of our work has been an attempt to explore the ranges of applicability to motional dynamics of various simple mechanical models of macromolecules to provide experimental guidance for the development of more complete motional modeling for such systems.

The second has been an attempt to apply dynamics methods to obtain characterization information (degree of long chain branching, for example) that is difficult to obtain by other less direct methods. The instrumental techniques employed have measured oscillatory flow birefringence or viscoelastic properties of polymer solutions and have made possible studies over the entire motional scale of importance in chain dynamics in high viscosity solvents. It has also been possible to extrapolate to infinite dilution to obtain isolated molecule properties.

Additional experiments—such as oscillatory flow dichroism and time-resolved light scattering and Raman spectroscopy of solutions undergoing time-varying flows—have been explored, and several new birefringence and viscoelasticity instruments capable of operation to higher frequencies—as well as over much wider frequency ranges than commercially available systems—have been developed that enable studies of macromolecules in low viscosity solvents so that more polymer-solvent systems could be examined, especially ones of biological importance for which water-based solvents generally must be employed.

Recent studies have addressed the following questions: what roles do side groups play in chain dynamics; do weak but significant intra- and intermolecular association forces exist in polymer solutions; what causes the apparent modification of moderately long range forces in chlorinated biphenyl solvents when small amounts of polyisoprene or polybutadiene are present; does the presence of polymer significantly modify solvent properties for polymer/solvent systems; what is the concentration dependence of oscillatory flow birefringence, viscoelastic properties, and chain relaxation times; what is the influence of induced internal electric fields on birefrigence measurements; what influence do the number and length of arms have on the observed conformational dynamics behavior of branched polymers; what dilute solution birefringence and viscoelastic properties are shown by block copolymer solutions; how can the combination of oscillatory flow birefringence and viscoelastic studies be used to examine aggregation in rigid molecule systems; and can detailed helix coil transition information be obtained by oscillatory flow birefringence studies?



Analytical and Physical Chemistry.

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1. "Studies of Solvent Modification by Polymer in Dilute Solution", C. C. White and J. L. Schrag, *Polym. Prepr.* (Am. Chem. Soc., Div. Polym. Chem.) **34** (1993) 552–553.

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Reduction of experimental scale terminates at the single molecule level. Single molecules are the ultimate analyte, since they represent the pinnacle of minaturization, and when sytematically analyzed as ensembles, offer the greatest advantages for the generation large-scale data sets. Such large and often complex datasets have become the currency of modern biological analysis. In this regard, our laboratory has pioneered the first single molecule system for large-scale genome analysis—Optical Mapping. This system uses automated fluorescence microscopy to image thousands of individual of "biochemically marked" DNA molecules. Generally speaking our research centers on the development of new genome analysis systems, which exploit novel macromolecular phenomena, with clear goals set to answer important biological problems. In this regard, Optical Mapping was used to construct whole genome maps of many microrganisms, which included *Yersinia pestis (black plague*) and *Plasmodium falciparum* (the major causative agent of malarial disease) without the use of PCR, electrophoresis, or clones. Curently, the system is being used for comparative genome studies in microbes and human populations. Such studies are forming the basis for rational approaches to solving difficult problems in pharmacogenomics.

Our systems are a complex mix of principles derived from nano/microfluidics, surface science, biochemistry, optics, genetics, polymer science and bioinformatics. The generality of our approaches to effectively analyze single molecules has spawned several other related systems. Optical Sequencing is based on the imaging of DNA polymerase action on individual DNA Molecules absorbed to Optical Mapping surfaces. Transchip is an *in vitro* transcription message display system designed to elucidate the biochemistry of transcriptional action over entire genomes, using ensembles of single DNA molecules. Future work in this direction will incorporate our advancements in nanofluidics and surface science to enable the development of "cell on a chip" systems.

Single molecule technologies underlie the basis of many cytogenetic techniques, yet access to these individual molecules is hindered by nucleoprotein complexes. These complexes serve to package DNA yet reduce the usable information available to cytogeneticists. Using newly developed high-throughput Optical Mapping systems, we are characterizing, at high resolution, genome alterations linked to human malignancies, on a whole genome basis. Special interest is given to heterochromatic regions, which compose centromeric and telomeric regions on most chromosomes. Current approaches cannot readily analyze such chromosomal regions for basic structural details and putative coding regions. The ultimate plan is to further this analysis to cover large populations, and to discern mutations which are representative of different tumor types.

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Communicating science, especially to non-scientists, is an important responsibility. Those who are scientifically literate must devote proper efforts to enhance the level of science literacy among non-scientists. This is true more so now than ever as the level of science literacy in the United States and elsewhere around the world continues to drop and the gap between scientists and the general population is widening at an alarming rate. My efforts to improve science literacy are in five major areas:

1. Pursuit of the understanding of chemical phenomena and development of lecture demonstrations/experiments for communicating chemistry in the classroom and to the general public (e.g., the television program, ONCE UPON A CHRISTMAS CHEERY IN THE LAB OF SHAKHASHIRI and the Science is Fun Outreach programs for students, teachers and the public at large).

2. Other scholarly work resulting in publication of laboratory manuals, topical booklets, audio-tutorial lessons, computer-based instructional management and laboratory videotapes.

3. Investigation of creative ways to enhance the quality of teaching chemistry by faculty and by teaching assistants and to increase the effectiveness of the teaching and learning environment.

4. Creation of structures, such as the Institute for Chemical Education (which I founded in 1983 and in which I served as first director through June of 1984), to carry out extensive research and development in chemistry education at the Kindergarten through graduate school levels and to promote wide-spread dissemination through workshops, short courses, publications, *etc*.

5. Development of national policies and implementation of strategies at the federal and state levels to revitalize and restructure science, mathematics, and engineering education at all levels (from 1984 to 1990 I served in Washington, D.C. as Assistant Director of the National Science Foundation for Science and Engineering Education).

Presently my major focus is on expanding the programs of the Wisconsin Initiative for Science Literacy (WISL) which I launched in the Fall of 2002. The programs aim to promote literacy in science, mathematics, and technology among the general public; and to attract future generations to careers as researchers, entrepreneurs,

and teachers. WISL's current thrusts are to improve the quality of science teaching; to put more under-represented groups on a track to becoming tomorrow's scientists and science teachers; and to explore and establish new links between science, the arts, and humanities.

Among WISL's programs is a popular series called Conversations in Science that enable local middle and high school teachers to interact with UW–Madison's cutting edge faculty and to take new ideas back to the classroom. Another is a series of Saturday morning science sessions for middle school and high school students and their parents in Madison and Milwaukee. This is part of WISL's Science in the City program which focuses on science education in urban settings. The Women in Science program targets girls and women to encourage their participation in science by making them aware of role models and offering them chances to "try out" science in fun and supportive science sessions. WISL is uncovering rich new terrain in the Science, the Arts and Humanities program in which faculty–scientists, artists and humanists–explore areas where their disciplines overlap with science; they then share their discoveries and new perspectives through public outreach activities.

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Microorganisms produce a large variety of biologically active substances representing a vast diversity of fascinating molecular architecture not available in any other systems. Our research centers on the chemistry, biochemistry and genetics of the biosynthesis of these secondary metabolites. Blending organic chemistry, biochemistry, and molecular biology, we take a multidisciplinary approach to study the secondary metabolism by asking the following questions: what reactions are available in nature, what are the enzymatic mechanisms of these reactions, how are these reactions linked to produce complex structures, what are the regulatory mechanisms of these pathways, and, ultimately, how can we manipulate nature's biosynthetic machinery for the discovery and development of new drugs. The followings are brief summaries of current projects.

Engineered biosynthesis of polyketide and peptide hybrid antibiotics: We study the biosynthesis of bleomycin, phleomycin, oxazolomycin, and leinamycin as model systems for hybrid peptide-polyketide metabolites to decipher the mechanism of how nonribosomal peptide synthetase (NRPS) and polyketide synthase (PKS) can be hybridized into a functional system to make novel anticancer drugs from amino acids and short fatty acids.

Cloning and genetic engineering of enediyne biosynthesis in *Streptomyces*: We study the biosynthesis of C–1027 and neocarzinostatin to develop a biological approach to the synthesis of the enediyne family of antibiotics—the most potent, highly active antitumor agents ever discovered.

Novel polyketide synthases: We study the biosynthesis of macrotetrolides, dorrigocin/migrastatin, and lactimidomycin to search for PKSs with novel structure and mechanism—the macrotetralide PKS functions independent of acyl carrier protein and catalyzes both C-C and C-O bond formation, and the dorrigocin/migrastatin and lactimidomycin PKSs exhibit modular structure but lack the cognate acyltransferase domain.

Biosynthesis of aromatic polyketides: We study the biosynthesis of tetracenomycin and fredericamycin as model systems to elucidate how type II PKSs determine the chain length during the biosynthesis of an aromatic polyketide from the malony CoA precursors.

Members of our group gain broad training spanning organic chemistry, biochemistry, microbiology and molecular biology, a qualification that is becoming essential for the modern bioorganic chemists who seek career opportunity in both academia and pharmaceutical and biotechnology industry.

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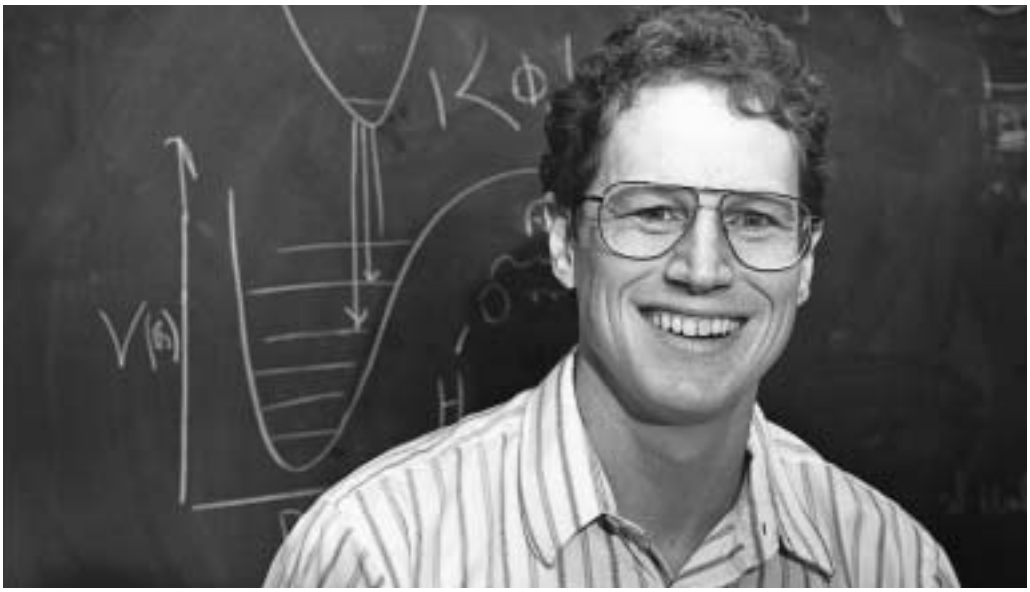
The long term goal of our research is to develop predictive theories for the vibrational dynamics of small molecules in order that we may determine both the products and rates of laser initiated chemical events. Working towards this goal our current research focuses on theoretically describing the dynamics and spectroscopy of polyatomic molecules in both the gas and condensed phases. In the gas phase, we are primarily interested in understanding and elucidating the mechanisms and pathways of intramolecular energy flow over wide ranges of energy. In the liquid phase we are investigating vibrational relaxation of CH and OH stretches due to the interplay of solvent-solute interactions and intramolecular couplings.

At low energies the dynamics in the gas phase is well understood. The rotational and vibrational motions are separable, and the vibrations consist of independent normal mode harmonic oscillators. At higher energies, that are relevant to chemical dynamics, the coupling between these motions becomes appreciable; mixing occurs as Fermi and Coriolis resonance interactions become prevalent. The resultant energy flow between the normal modes can be both rapid and complex. At yet higher energies, descriptions of the dynamics once again can be simplified, and statistical descriptions such as random matrix theory can be used.

The exact quantum mechanical solutions to the dynamics over a wide range of energies, using standard basis set methodologies, are intractable for systems with more than three degrees-of-freedom; hence alternative routes to their solutions must be explored and developed. One approach, that we have successfully pursued, is the implementation of perturbation theory to reduce the complexity of the problem. This approach not only allows us to describe many experimental spectra, but it also enables us to understand the spectra in terms of features in the classical phase space structures. With these methods we have begun to understand the dynamics of molecules whose energies span from the normal mode regime to the statistical region.

Vibrational relaxation in the condensed phase is relevant to many aspects of chemistry, physics, and biology. It is involved in thermal chemistry, shock-induced chemistry, electron transfer, photochemistry, and biological processes such as vision and photosynthesis. Moreover, vibrationally excited solute molecules relax due to solvent-solute interactions; hence the rate of energy transfer can be used as a probe of these interactions. At present we are investigating the role of the CH stretch relaxation in neat chloroform in order to unravel the multiple relaxation pathways that are available to this molecule and to develop the theoretical tools that will enable us to combine quantum descriptions of the solvent with classical descriptions of the solute.



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Theoretical Chemistry.

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My group is interested in the structure and dynamics of condensed phase systems, and in particular, in the theory of time-dependent phenomena in liquids, supercritical fluids, crystalline and amorphous solids, on surfaces, and in proteins. We typically use the methods of classical and quantum nonequilibrium statistical mechanics to investigate these phenomena.

Experimentally, one important avenue for determining the structure and dynamics of condensed matter involves the spectroscopy of dilute probe molecules. Typically, vibrational or optical spectroscopy contains information about the probe's local environment, whose extraction, however, usually requires theoretical models and their solutions. For some time we have been developing and solving theoretical models for the spectroscopy of probe molecules in crystals, amorphous solids, liquids, and in proteins, and have applied our research to a number of different types of experiments. Examples include: single-molecule spectroscopy in crystals, glasses and biopolymers, hole-burning spectroscopy in proteins, and ultrafast optical and vibrational spectroscopy in liquids, supercritical fluids, and proteins.

Relaxation processes are important for the understanding of chemical reaction dynamics, electron transfer reactions, NMR spectroscopy, solid-state laser design, and many other fields. We have been involved with developing theories of relaxation processes in condensed phases. Our interests range from fundamental issues in nonequilibrium quantum statistical mechanics, to calculations of multi-phonon relaxation in crystals, and to theories of vibrational energy relaxation in liquids.

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Two of the most dynamic research areas in analytical biotechnology today are mass spectrometry and DNA arrays. The Smith group makes fundamental contributions to these techniques using an interdisciplinary and collaborative approach. Three current projects are described below.

Mass Spectrometry. The recent completion of the Human Genome Sequence, archived in widely accessible databases, has permitted the identities of proteins in complex mixtures to be rapidly and automatically determined by mass spectrometric analysis. Nanobore liquid chromatography coupled to a new generation of mass spectrometers have made it possible to analyze extremely complex mixtures of proteins, even entire proteomes of model organisms. This revolution in mass spectrometry of very large biomolecules such as nucleic acids and proteins is attributable to the twin techniques of Matrix-Assisted Laser Desorption/Ionization (MALDI) and Electrospray Ionization (ESI) Mass Spectrometry (MS), which were developed in the late 1980s. Nonetheless, as powerful as this technology has become, we believe that the field of biological mass spectrometry is still in its infancy.

Mass spectrometry as it currently exists is a relatively inefficient process, in which typically only one out of 10^7 to 10^{10} molecules in a sample being analyzed actually gives rise to a detection event. This is because of ion losses that occur throughout a mass spectrometry system; in the ion source, the mass analyzer, and at the detector. Although the resolution for low m/z species can be extremely high, at larger m/z values corresponding to low charge states of large biomolecules and biomolecular complexes, both resolution and detection efficiency are extremely poor. The major focus of our mass spectrometry group is the development of a new generation of mass spectrometers that will address these issues, extending the useful mass range of biological mass spectrometry well out into the megadalton range and beyond. This work requires the study and understanding of fundamental mechanisms in mass spectrometry, as well as the design and construction of novel instrumentation. These advances will comprise a next generation of mass spectrometers of unparalleled power for dissecting biological and chemical complexity in the post-genomic era.

DNA Computing. To perform a computation one must have the ability to store information, and then manipulate that stored information. Nature provides us with an elegant medium for information storage and manipulation namely, DNA and enzymes. The complex arrangement of the four basic nucleotides into a DNA molecule yields a large storage capacity that can be manipulated with naturally occurring enzymes and

probed (read) by hybridization. Our group is collaborating with the groups of Professor Robert Corn, also in the Chemistry Department, and Professor Anne Condon, of the University of British Columbia, Department of Computer Science, to develop a scalable implementation of DNA-based computing. By immobilizing the information-encoding DNA molecules to a solid support, it becomes a simple matter to purify them between the various steps of the DNA computation. We have demonstrated the feasibility of this approach in solving a small example of the SATISFIABILITY problem, in which the values of Boolean variables satisfying a series of clauses are determined, and in present efforts we are extending this approach to larger problems.

Surface Invader. In the aftermath of the Human Genome Project, attention has turned back to the difficult question of understanding the functions and interactions of the protein products. A powerful tool for analyzing this area is, as it has always been, Genetics. Mendel was the first to show that phenotypes (observable changes in the characteristics of an organism) were governed by changes in molecules, and today that approach remains the most powerful tool available to biologists. The most common type of variation in the genome is the single nucleotide polymorphism, or SNP. We are developing a new technology in which hundreds of thousands of such genetic variations can be determined rapidly and easily in a single step. The approach is to use a highly specific nucleic acid cleavage technology in conjunction with high complexity photolithographically manufactured DNA arrays. The development and characterization of new surface attachment chemistries and surface enzymatic reactions are important aspects of the work.

Analytical Chemistry.

Development and application of novel bioanalytical tools.

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Organic, Inorganic and Biological Chemistry.

Research Interests:

- Development of environmentally benign, catalytic reactions that use molecular oxygen in the selective oxidation of organic substrates
- Investigation of organic, organometallic and inorganic reaction mechanisms that underlie catalytic transformations
- Study of catalytic transformations of carboxamides for the preparation of amide-based heteropolymers.

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1. Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766–767. "Mechanistic Study of Alcohol Oxidation by the $Pd(OAc)_2/O_2$/DMSO Catalyst System and Implications for the Development of Improved Aerobic Oxidation Catalysts."

2. Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 164–166. "Efficient Intramolecular Oxidative Amination of Olefins through Direct Dioxygen-Coupled Palladium Catalysis."

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4. Stahl, S. S.; Thorman, J. L.; Nelson, R. C.; Kozee, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7188–7189. "Oxygenation of Nitrogen-Coordinated Palladium(0): Synthetic, Structural and Mechanistic Studies and Implications for Aerobic Oxidation Catalysis."

5. Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem. Int. Ed.* **1998**, *37*, 5000–5012. "Homogeneous Oxidation of Alkanes by Electrophilic Late Transition Metals."

We are broadly interested in the development and study of catalytic reactivity, ranging from new synthetic methodology for organic chemistry to fundamental inorganic and organometallic transformations. Our efforts divide into two main areas: (1) development and investigation of new catalysts for the selective oxidation of organic substrates by molecular oxygen and (2) investigation of new catalytic methods for the manipulation of carboxamide-based molecules.

Selective Oxidation Catalysis

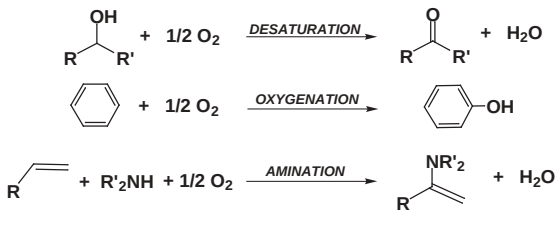
There is a dramatic need for environmentally benign oxidation chemistry in the pharmaceutical and chemical industries. Dioxygen represents an ideal alternative to stoichiometric transition metal oxidants such as CrO_4^{2-} and MnO_4^- that are used extensively in industry; however, the scope of dioxygen-coupled oxidation reactions is presently quite limited.

We are currently investigating a series of new transition-metal-catalyzed reactions for the selective oxidation of organic substrates by dioxygen. Reactions of interest encompass a wide range of transformations, including desaturation (e.g., alcohol oxidation), oxygenation (e.g., arene hydroxylation), and oxidative amination. Formally, these reactions proceed by a two stage catalytic cycle: (1) oxidation of the substrate by an oxidized transition metal catalyst and (2) regeneration of the oxidized catalyst by dioxygen (Scheme I).

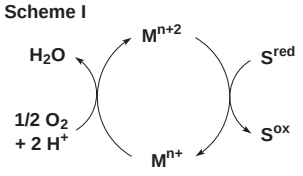
Our interests in this area range from the development of useful synthetic methodologies for organic chemistry (*synthetic organic chemistry*) to the elucidation of mechanistic principles that underlie dioxygen-coupled catalysis (*physical organic, inorganic and organometallic chemistry*). Mechanistic studies often include the preparation of key catalytic intermediates (*synthetic inorganic and organometallic chemistry*) and investigation of their fundamental reactivity through kinetics, isotope effects, and other mechanistic tools.

Catalytic Amide Metathesis

Polyamides are ubiquitous in chemistry and biology, ranging from synthetic materials based on relatively simple monomers, e.g., nylon 6 and Kevlar, to biological enzymes. We are developing and investigating new catalytic methods to manipulate amide-based molecules. The methodology that we are developing will provide new opportunities to prepare functional heteropolymers with a new material and chemical properties. Numerous applications may be envisioned for such molecules, and in collaboration with the group of Professor Samuel Gellman the biocompatibility and bioactivity of such molecules are being investigated.



Scheme I



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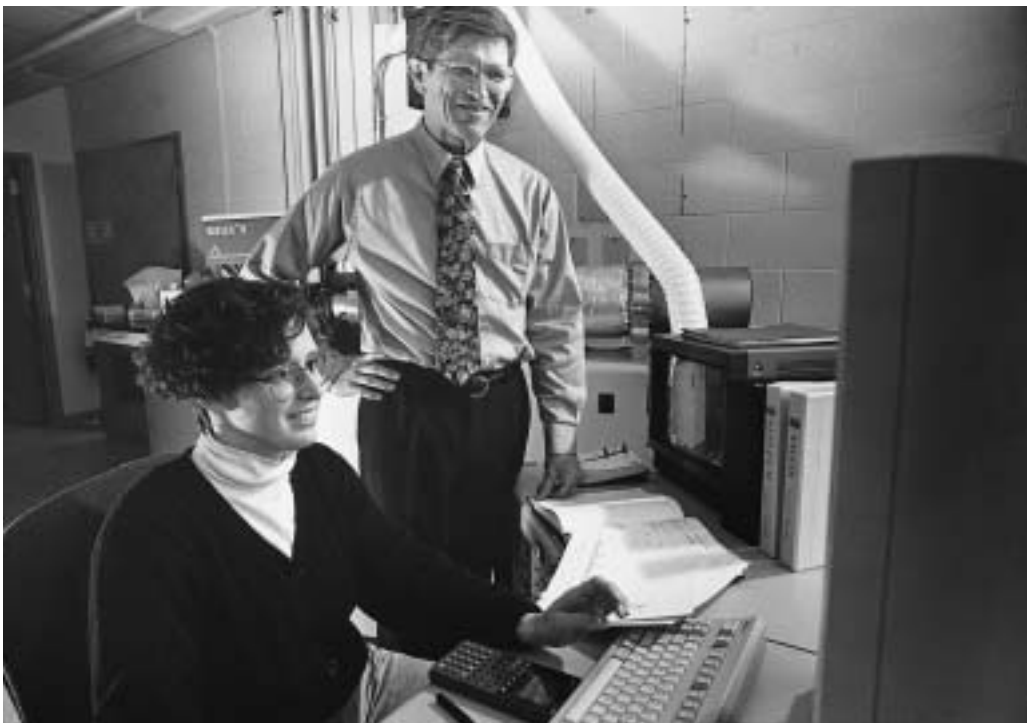

Our current research centers on the development of synthetic methodology for small (electron precise) metal clusters and the synthesis of new and interesting compounds. Our major recent activities have been focused on rhenium (III) compounds. Two papers describing syntheses, on rhenium chalcogenide clusters ($[Re_3Cl_9A]^{2-}$ A = S, Se, Te) and on clusters containing acetamidate ligands (such as $[Re_3Cl_{10}(HNCOCH_3)]^{2-}$) and $[Re_3Cl_8(HNCOCH_3)_2]^-$), are cited in the publication list on the margin of this page. The former species are remarkable in their simplicity, with a core of three metals and a chalcogenide atom. The acetamidate ligand in the latter species forms by hydrolysis of a coordinate acetonitrile ligand.

An interesting development in our research efforts has been the use of MALDI and ESI mass spectrometry. For the kind of compounds that we have targeted, traditional instrumental techniques of IR and NMR are of little value. We have found these two modern mass spectrometric methods allow us to monitor chemical reactions and to characterize new products. The acetamidate project began with our obtaining ESI MS spectra of $Cs_3Re_3Cl_{12}$ in acetonitrile.

Our background and experience in mass spectroscopy has led to a collaboration with food scientists, from which several papers have now appeared.

A synergy has developed between my research and teaching that I have been able to share with my students. Arising out of our interests in mass spectrometry was the cited paper in J. Chem. Ed. analyzing masses and relative abundances in the envelope of parent mass peaks for large molecules. In addition, over the past decade, I have been involved in the teaching of scientific ethics, an interest that extends over both undergraduate and graduate teaching.

Inorganic Chemistry.

Current research: Synthesis and characterization of small metal cluster species; Use of mass spectrometry, especially MALDI, LDI, and ESI, in inorganic synthesis. Recent studies have concentrated on rhenium chemistry. Other research interests: Organometallic chemistry, including synthesis of new compounds and studies on chemical reactivity. Research on metal carbonyls, phosphine and isonitrile complexes, species with sulfur containing ligands, and hydrocarbon complexes. Teaching interests: Scientific Ethics, General Chemistry, Inorganic Chemistry.

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Physical Chemistry.

Dynamics in condensed phases. Nonequilibrium statistical mechanics, dielectric relaxation.

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1. Hill, N.E., Vaughan, W.E., Price A. and Davies, M. "Dielectric Properties and Molecular Behavior," London: Van Nostrand Reinhold (1969).

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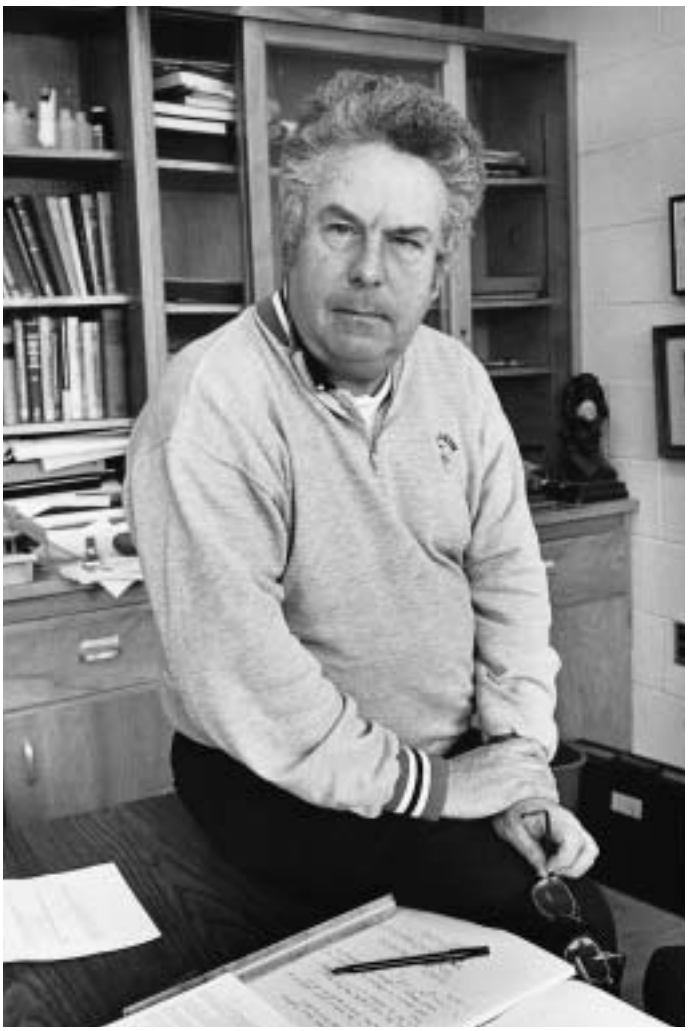

Our research interests are in the area of the response of condensed matter to time varying electric fields. Microscopic models of the dynamics including intermolecular forces are analyzed via statistical mechanics to provide predictions for the measured macroscopic response (especially the dielectric behavior). We have characterized the influence of the long range dipole-dipole forces on the reorientational motion of molecules in liquids and the role of barriers to internal rotation on the dynamics of conformational change. Automated apparatus has been constructed to measure the dielectric response. We are currently using our apparatus and formalism to study counterion dynamics on and near the surface of DNA restriction fragments. The results will help elucidate the dynamics of protein binding to DNA and contribute to an understanding of the role of DNA in gene expression.

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Our work focuses on development and application of *ab initio* molecular quantum mechanics to advance understanding of chemical structure and reactivity. We study a broad range of phenomena (including organic, inorganic, and biophysical systems [1]), employing techniques applicable to molecules, supramolecular clusters, and condensed phases. The ultimate goal is development of unifying chemical concepts that build on powerful modern technology for solving Schrödinger's equation to improve the scope, accuracy, and usefulness of chemical theory.

A foundation of our research program is Natural Bond Orbital (NBO) analysis [2]. NBO-based methods were developed in our group, providing a general bridge to describe complex numerical wavefunctions in the familiar language of chemical bonding theory. These methods lead to a mathematically rigorous "Lewis structure" representation of the wavefunction, with associated bonds, hybrids, and other valence descriptors determined in optimal fashion. The NBOs thereby provide a "chemist's basis set" that can be used to compare, contrast, and comprehend many levels of *ab initio* and density functional theory in a rigorous and consistent manner. The current NBO 5.0 program [3] is widely incorporated in modern electronic structure packages (including Gaussian, Jaguar, ADF, GAMESS, Columbus, Q-Chem, NWChem, PQS) and used by computational chemistry researchers throughout the world.

NBO-based techniques have demonstrated particular effectiveness in elucidating resonance-type stereoelectronic and steric factors in covalent and noncovalent phenomena, including the torsional and H-bonding interactions that underlie protein folding processes [4–6]. Recently, new NBO-based analysis methods have been developed for NMR properties, including J-coupling and chemical shielding, providing important new insights into structure and function of complex biomolecules [7–9]. In collaboration with the Landis group, NBO-based methods are also being employed to extend localized bonding and hybridization concepts in transition metal species, leading to a coherent and comprehensive pedagogical picture of Lewis-like bonding patterns in main-group and transition group chemistry [10]. NBO-based methods are also being extended to analysis of photoexcited and radical species [11]. A particular focus of current research involves the remarkable class of "pi-star" charge-transfer complexes, exemplified by nitrosyl cation (NO^+) complexation with aromatics.

We are also engaged in ongoing theoretical and experimental investigations of the nature of hydrogen bonding and related types of supramolecular association. The key theoretical tool is Quantum Cluster Equilibrium (QCE) theory, a method developed in our group to determine equilibrium cluster distributions and phase properties of strongly associated liquids and solids [12,13]. QCE theory combines the rigorous methods of *ab initio* quantum chemistry for the cluster partition functions with the standard machinery of quantum statistical thermodynamics for the equilibrium cluster populations at chosen temperature and pressure. A fully *ab initio* treatment of cluster energetics allows QCE to incorporate the important nonpairwise-additive "cooperative" effects of donor-acceptor interactions that are commonly neglected or misrepresented in empirical simulation potentials.

Physical and Theoretical Chemistry.

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1. F. Weinhold and C. R. Landis, *Valency and Bonding: A Natural Bond Orbital Donor-Acceptor Perspective* (Cambridge U. Press, 2003).

2. F. Weinhold, "Natural Bond Orbital Methods," in *Encyclopedia of Computational Chemistry.* P. v.R. Schleyer et al. (Eds.), (John Wiley & Sons, Chichester, UK, 1998), Vol. 3, pp. 1792–1811.

3. NBO 5.0 website: http://www.chem.wisc.edu/~nbo5

4. F. Weinhold, "News & Views: A New Twist on Molecular Shape," *Nature* **411**, 539–541 (2001).

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Physical and Analytical Research at the Chemistry-Biology Interface.

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1. C.F. Weise and J.C. Weisshaar, Conformational Analysis of Alanine Dipeptide from Dipolar Couplings in a Water-based Liquid Crystal, J. Phys. Chem. B, submitted (2002).

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The work of the cell is carried out in large part by assemblies of specific proteins with highly coordinated moving parts that operate in precise sequence—protein machines! While x-ray crystallography and NMR provide critically important "snapshots" of stable structures, new techniques in fluorescence microscopy allow us to watch *single and multiple protein molecules in motion in real time.* The Weisshaar group studies the motions and interactions of proteins and DNA in live cells, in lipid bilayers, and tethered to surfaces. The experimental method uses widefield imaging in an inverted microscope with laser illumination of the sample by total internal reflectance (TIR). A fast ccd camera records particle motion in all three dimensions. Fluorescence resonance energy transfer (FRET) monitors changes in the distance between two dye molecules based on the color of emission, allowing us to observe specific changes in protein or DNA conformation with time.

Protein-DNA interactions. In solution DNA is a stiff, negatively charged biopolymer, yet it adopts bent, compact conformations in many real biological systems such as chromatin. *Integrated host factor* (IHF) is an architectural protein that bends double-stranded DNA by 160° at a specific recognition sequence! Our goal is to observe the dynamics of non-specific binding and specific binding (and bending) in real time using FRET. RNA polymerase (RNAP) is a complex, multi-sub-unit machine that transcribes DNA into messenger RNA, which in turn instructs protein synthesis. We are designing experiments that will monitor specific sequences of events in the early stages of transcription initiation using fluorescence labels to report on conformational motion both within the protein and within DNA itself.

Membrane Proteins. A substantial fraction of the surface of a cell comprises membrane proteins responsible for transport of small molecules and ions across the membrane and for signaling or triggering of biochemical events. Membrane protein machines are typically homo- or hetero-aggregates. Single-molecule methods can study the assembly of a working machine from its constituent parts in real time by literally *counting* the fluorescence intensity. In these experiments, we form lipid bilayers on a clean glass substrate by depositing vesicles from a buffer solution or using Langmuir-Blodgett methods. We are studying aggregation of the protein synaptotagmin (Syt) in the presence of Ca^{2+} and of negatively charged phosphatidylserine (PS) lipid head groups. Syt may be the protein that triggers *exocytosis* of neuropeptide-containing secretory vesicles that spill their contents across the synapse when nerve cells fire. Many soluble

transmembrane proteins and peptides must insert themselves across the lipid bilayer prior to aggregation and function. We plan to study insertion of monomers and assembly of working ion channels, such as the heptameric α-hemolysin, in real time.

Nanoscale Protein Trafficking in Live Cells. The new family of fluorescent proteins such as green and yellow fluorescent protein (GFP and YFP) can be attached to a natural protein by inserting the appropriate piece of DNA into the cell's transcription machinery. This makes it possible to use fluorescence to track a specific membrane protein in a live cell from its synthesis in the endoplasmic reticulum, through its packaging in a vesicle and transport to the plasma membrane, to its functioning in a signaling complex. This is the analytical chemistry of a live cell!

We are monitoring the motion of secretory vesicles in PC12 cells with unprecedented spatial and time resolution. Trajectories reveal directed motion, oscillatory motion, and trapping in 100 nm diameter sites. Remarkably, we are able to locate the center of bright vesicles to a spatial resolution of 5–10 nm on a 30 ms timescale, revealing a new regime of vesicle dynamics. The goal is to understand how the vesicles are transported through the dense filaments of the actin cortex to the plasma membrane for docking and exocytosis. The mechanism appears to be a combination of passive (diffusive) transport among obstacles and active transport driven by motor proteins.

This interdisciplinary work combines the traditional strengths of physical and analytical chemistry—innovative experimental methods, careful quantitative analysis of data, detailed comparison with specific physical models—with the methods of modern molecular biology. Many important biological problems are amenable to this approach.

Robert West

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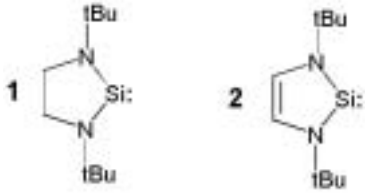
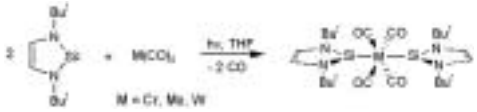
B.A. 1950, Cornell University
A.M. 1952, Harvard University
Ph.D. 1954, Harvard University

Research in our group is devoted to organosilicon chemistry. Although silicon is the second most abundant element (after oxygen), making up 27% of the earth's crust, its chemistry has not been carefully explored. The first compound containing a silicon-silicon double bond, tetramesityldisilene, synthesized in our group in 1981, has led to a broad new area of organosilicon chemistry. However, triply-bonded compounds of silicon (-SiSi-, -SiC-, SiN) are all still unknown, and we are now trying to synthesize them.

Under active investigation here is the chemistry of stable divalent silicon compounds, silylenes. Structures of the first two examples of this type, **1** and **2**, are shown below:



The silylenes, like the analogous carbenes of organic chemistry, have a rich reaction chemistry. They are isolobal with phosphines, and so can form transition metal complexes, some of which have catalytic properties. Some examples are shown below:

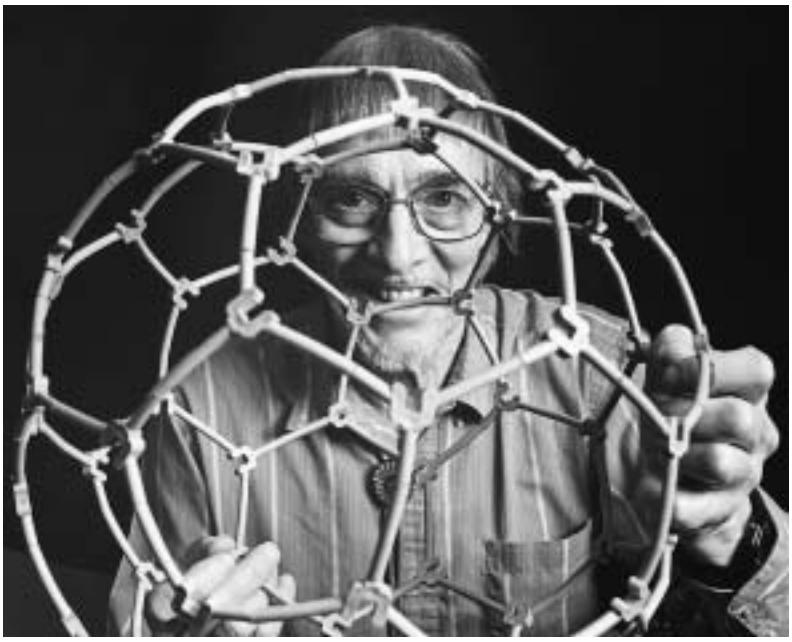


Organosilicon polymers are also under active investigation, including both polysiloxanes (silicones, **3**) and polysilanes (**4**). The "designer polysiloxanes" made here bind lithium ions, and have the highest conductivity yet reported for polymer electrolytes. They are now being tested in lithium batteries.

The polysilanes, with long linear chains of silicon atoms, behave as one-dimensional molecular wires. They are promising materials as organic semiconductors and as organic light-emitting diodes. We are studying their synthesis, and the effect of substituents and conformation on the electron delocalization.

Silicon derivatives of C_{60}, buckminsterfullerene, are also being studied in our group. We find that Si-H bonds add readily to C=C bonds in C_{60} to give silicon-containing molecules. These silylated fullerenes can be converted to polymers in which the C_{60} units are part of the polymer framework.

Our research is now mainly under the Organosilicon Research Center, with corporate and federal support. The mission of OSiRC is to carry out fundamental research, providing the groundwork for the organosilicon industry 10 to 15 years in the future.



Organic and Inorganic Chemistry.

Director, Organosilicon Research Center. Organosilicon and organogermanium chemistry, including multiply bonded silicon and germanium compounds, stable divalent molecules R_2Si and R_2Ge, and aromatic rings containing Si and Ge; polysilane and polysiloxane high polymers; and silicon derivatives of buckminsterfullerene, C_{60}.

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1. Terphenyltrifluorosilanes: Reduction Products and Possible Formation of a Disilyne, R. Pietschnig, R. West, D. R. Powell, Organometallics **19**, 2724 (2000).

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4. Electronic and Steric Properties of Stable Silylene Ligands in Metal (0) Carbonyl Complexes, M. Haaf, T. A. Schmedake, B.J. Paradise, A. J. Millevolte, D. R. Powell, R. West, J. Organometal. Chem. **636**, 17 (2001).

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6. Structure and Chemistry of 1-Silafluorene Dianion, its Derivatives and an Organosilicon Diradical Dianion, Y. Liu, T. C. Stringfellow, D. Ballweg, I. A. Guzei, R. West, J. Am. Chem. Soc. **124**, 49 (2002).

7. Halophilic Reactions of a Stable Silylene with Chloro and Bromocarbons, D. F. Moser, T. Bosse, J. Olson, J. L Moser, I. A. Guzei, R. West, J. Am. Chem. .Soc. **124**, 4186 (2002).

8. Chemistry of the Aromatic 9-Germafluorene Dianion and some Related Silicon and Carbon Species, Y. Liu, D. Ballweg, T. Mueller, I. A. Guzei, R. W. Clark, R. West, J. Am Chem. Soc. **124**, 12174 (2000).

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Organic Chemistry.

Synthesis and chemistry of interesting molecules; artificial intelligence and its application or organic chemistry; computers; stacking complexes; artificial enzymes.

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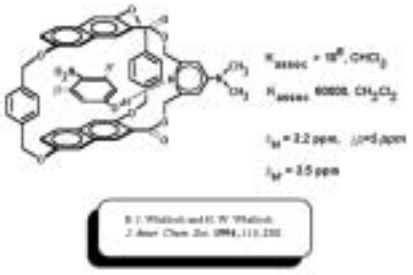
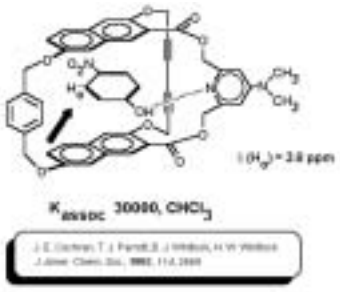
1. Brown, A.B. and Whitlock, H.W. "Inversion Topologies of n.8.81(2,1,4) Cyclophanes; Effects on Host Cavity Stereodynamics," *J. Am. Chem. Soc.*, *111*, 3640 (1989).

2. Whitlock, H.W., "On the Iconic Nature of Conformational Pictures and Their Recognition," *J. Org. Chem.*, *56*, 7297 (1991).

3. Cochran, J.E., Parrott, T.J., Whitlock, B.J. and Whitlock, H.W. "Pi Hydrogen Bonds as a Design Principal in Molecular Recognition," *J. Am. Chem. Soc.*, *114*, 2269 (1992)

We are currently engaged in the synthesis and study of doughnut-shaped molecules possessing hydrophobic cavities. A particular example recently synthesized is shown in the structures. The interest in these molecules lies in the observation that they form hydrophobic complexes of appreciable stability (K_{assoc} 10^4N^{-1}) with aromatic guest molecules. Exploitation of this cavity binding property as a basis of artificial enzyme construction is under active investigation.





R. Claude Woods

Professor, Born 1940
B.S. 1961, Georgia Institute of Technology
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Microwave spectroscopy is a technique in which the absorption of radiation in rotational transitions of small molecular species is detected and the resonant frequencies are measured to great accuracy (8 to 9 significant digits). Using quantum mechanics the frequency data can be fit to a model Hamiltonian, and the molecular structure and other molecular properties can be determined with great precision. Intensities and widths of microwave lines provide concentrations and dynamical information. We have applied this technique in laboratory discharge plasmas to transient species like the CN radical, the HNC unstable molecule, the a^3P metastable electronic state of CO, and especially to molecular ions like CO^+, HCO^+, HOC^+, HNN^+, HCS^+, KrD^+, XeH^+, SO^+, H_2D^+, SiF^+, or PO^+. Many of these species are of great importance in the chemistry of the interstellar medium and have been detected by radioastronomy (actually microwave astronomy), in some cases with our active participation. A great deal of information on the chemistry and dynamics of the interstellar medium has been obtained by radioastronomical study of species like these. The chemistry and dynamics of the laboratory discharges themselves is also of great interest and only partially understood. We are trying to improve this understanding using microwave spectroscopy and other techniques at our disposal. The latter include quadrupole mass spectrometry, a high resolution ultraviolet-visible emission spectroscopy, and computer controlled Langmuir probes. We are also carrying out large scale quantum chemical calculations of the structures and other properties of small ions and molecules. Many species have been treated with large basis sets (80–100 contracted orbitals) and correlated *ab initio* methods like CI-SD, MP4-SDQ, CEPA–1, and CASSCF. Results are used to facilitate spectroscopic searches for new ions and also to compare against our experimentally determined spectroscopic constants. Another part of our research involves active participation in the Engineering Research Center for Plasma Aided Manufacturing. Plasma etching and deposition are crucial steps in the manufacture of almost all semiconductor devices, and we are working to understand the details of the chemistry and physics of the plasmas used. Diagnostics like ultra-high resolution infrared diode laser spectroscopy and laster induced fluorescence spectroscopy, laser induced fluorescence spectroscopy, and microwave spectroscopy are being used to probe plasmas in RF (13 MHz) discharge and microwave (2450 MHz) electron cyclotron resonance (ECR) plasma reactors.

Physical Chemistry.

Microwave spectroscopy of ions and other transient species; plasma chemistry in discharge plasmas; optical emission spectroscopy, quadrupole mass spectrometry; *ab initio* calculations on small molecules, plasma etching; infrared diode laser spectroscopy; laser induced fluorescence; microelectronics processing.

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10. Y. Pak and R. C. Woods, "Coupled Cluster Calculations of the Potential Energy Surfaces and spectroscopic Constants of SiF_2, PFs(+,2), SO2, POs(-,2), and ClOs(+,2)", *J. Chem. Phys.* **104**, 5547 (1996).

11. R. C. Woods, "Infrared Diode Laser Absorption Spectroscopy as a Plasma Chemical Diagnostic" in **Handbook of Thin Film Process Technology**, D. A. Glocker and S. I. Shah, eds. (1996).

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Analytical Science and Physical Chemistry.

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1. W. Zhao and J. C. Wright, *Physical Review Letters* **83**, 1950–1953 (1999). "Measurement of $^{(3)}$ for Doubly Vibrationally Enhanced Four Wave Mixing Spectroscopy".

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4. W. Zhao, K. M. Murdoch, D. M. Besemann, N. J. Condon, K. A. Meyer, and J. C. Wright, *Appl. Spectrosc.***54**, 1000 (2000). "Two Dimensional Vibrational Spectroscopy by Doubly Vibrationally Enhanced Four Wave Mixing."

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8. D. M. Besemann, N. J. Condon, K. M. Murdoch, K. A. Meyer, W. Zhao, and J. C. Wright, Chem. Phys. **266**, 177–196 (2001). "Interference, Dephasing and Vibrational Coupling Effects Between Coherence Pathways in Doubly Vibrationally Enhanced Nonlinear Spectroscopies."

9. K. A. Meyer and J. C. Wright, Analy. Chem. **73**, 5020–5025 (2001). "Detection Limits For Time-Resolved Coherent Two-Dimensional Vibrational Spectroscopy."

10. K. M. Murdoch and J. C. Wright, J. Chem. Phys. **116**, 5717–5724 (2002). "Infrared Spectroscopy of Ethanol Clusters in Ethanol-Hexane Binary Solutions."

11. J. C. Wright, Int. Rev. Phys. Chem. **21**, 185–255 (2002) "Coherent Multidimensional Vibrational Spectroscopy."

12. Kyungwon Kwak, Sangyob Cha, Minhaeng Cho, and John C. Wright, J. Phys. Chem. 117, 5675–5687 (2002). "Vibrational Interactions of Acetonitrile: Doubly Vibrationally Resonant IR-IR-Visible Four-Wave-Mixing Spectroscopy."

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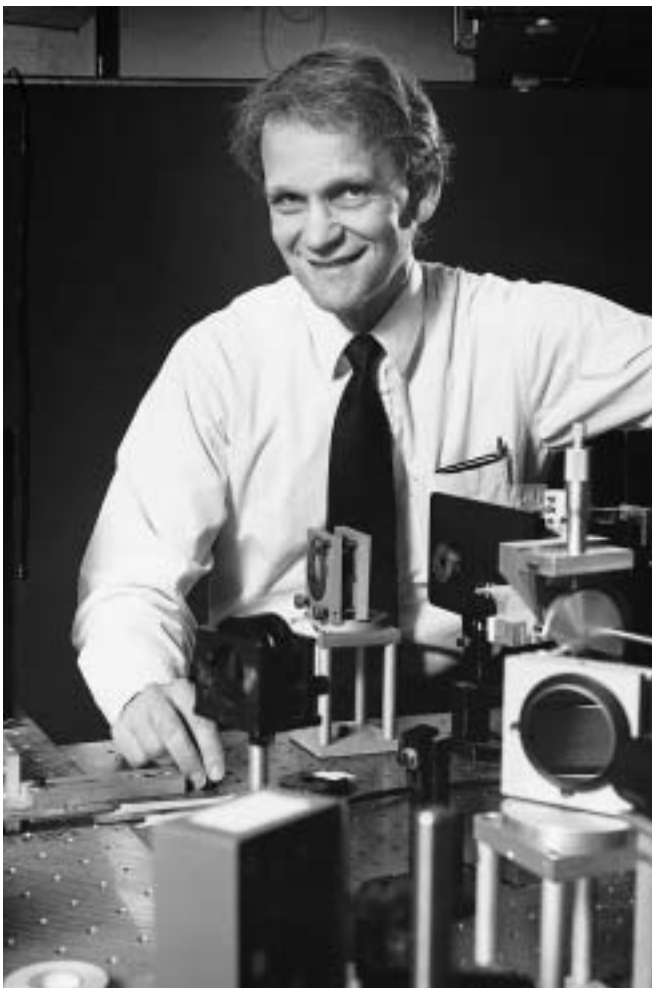
Our group has pioneered the development of a new family of highly selective analytical spectroscopies that use nonlinear optical processes to provide unique capabilities for measuring the intra- and intermolecular interactions in chemical systems. In particular, we have created laser techniques where multiple coherent beams excite different molecular resonances. The excitation of a particular resonance perturbs all the molecular resonances that are coupled to it by intra- or intermolecular interactions. This coupling gives rise to cross-peaks between resonances that form the basis for multidimensional vibrational and electronic spectra.

The methods have a close relationship to multidimensional NMR methods. Instead of generating higher order spin coherences by carefully controlled $\pi/2$ and π pulses, higher order vibrational and optical coherences are generated by intense, ultrafast laser excitation. The coherences radiate new beams in directions and frequencies that are fingerprints of all the different possible $\pi/2$ and π pulses. One spatially and spectrally selects the particular coherence sequence of interest.



The multidimensional nonlinear family includes a rich and diverse set of members that differ in the number of pulses, the pulse delay sequences, the polarizations, and the relative phases. The family includes high order and cascaded lower order processes, homodyne and heterodyne detection, and frequency and time domain methods as well as "noisy spectroscopy", a hybrid of both. Methods based on an even number of excitation pulses are inherently surface selective and those based on an odd number are universally applicable. These methods are closely related to photonic devices and quantum computing which use the same coherences for information processing. They are also closely related to coherent control methods where the judicious choice of frequency and phase of the strong electric fields of light can control the motion and reactivity of molecules.

Our group's mission is to both continue developing this exciting new family of spectroscopies and applying the methods to chemical measurement and coherent control of hydrogen bonding, electron transfer dynamics, chemical analysis, surface spectroscopy, protein-protein, protein-DNA, and DNA-DNA interactions, and environmentally important problems. We expect coherent multidimensional nonlinear methods will take their place beside multidimensional NMR as one of our most powerful structural tools for studying chemical and biochemical systems.

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B.Tech. 1985, Indian Institute of Technology, Bombay
M.S. 1987, Louisiana State University
Ph.D. 1991, North Carolina State University

Our research focuses on theoretical studies of condensed matter, especially macromolecules. Traditionally, polymeric fluids have been treated using coarse grained (e.g. lattice) models, motivated by the reasoning that most of the properties of interest depend largely on the long-range structure, allowing one to neglect chemical details on short length scales. In recent years it has become increasingly clear that the short-range structure plays an important role in many cases such as, for example, the phase behavior of mixtures and the behavior of polymers at surfaces. These systems can be best understood, therefore, if one incorporates molecular features on all length scales. We are interested in employing theory and computer simulation to study a variety of problems with the final aim of predicting the properties of real polymers using chemically realistic models. Our research has two components: the development of methods and the application of these methods to understand the structure and dynamics of condensed phases. Some areas of current interest are:

Polyelectrolyte solutions. In order to make polymers dissolve in water, something that is of considerable technological interest, it is necessary to add charged groups along the hydrophobic backbone. These charged macromolecules display a rich variety of properties not found in neutral polymers and are therefore of considerable interest from a basic scientific standpoint. Our understanding of polyelectrolyte solutions is in its infancy, and there are many issues that are far from resolved. These include the conformational properties, self-diffusion, viscosity, and adsorption behavior. We are using computer simulation and liquid state theory to establish the importance of solvent effects, counterion correlations, and polymer architecture on the behavior of polyelectrolytes in solution. The methods we develop and the knowledge we obtain should be useful in the study of other complex fluids including surfactants, biological macromolecules, and gels.

Confined Liquids. The behavior of fluids at surfaces and in confinement can be qualitatively different from that of bulk fluids. This is particularly true of polymers because a modest surface-fluid interaction per segment translates to a large surface-fluid interaction per molecule. There is considerable interest in obtaining an understanding of the adsorption behavior of fluids and the segregation to the surface of one component from a mixture of polymers, because of the importance of these phenomena in polymer processing. The dynamic properties of confined liquids are also of interest and significance. For example, the surface can induce dynamics reminiscent of entangled polymers,

and the transport properties can be vastly different from bulk fluids. We are studying the behavior of confined polymers using theory and simulation. Using density functional theory, we are investigating the adsorption behavior and the segregation of polymers. We have recently developed an algorithm for the simulation of liquids in planar oscillatory flow, and devised a technique for the extraction of viscosity via analysis of the simulation results using continuum mechanics. We are in the process of performing extensive non-equilibrium molecular dynamics simulations of confined liquids.

Fluids in disordered media. The behavior of macromolecules in disordered materials is of importance in a number of practical applications including adsorption in porous media, separation processes, drug delivery, electrophoresis, and crowding behavior in cells. Fascinating transport processes arise in many of these areas of nano-scale research. In living cells, for example, transport plays an important role in neurotransmission and protein secretion. Advances in experimental techniques have allowed the imaging of trajectories of vesicles inside the cell as they move from the Golgi apparatus to the cell membrane. We are interested in understanding the mechanism of this transport while at the same time developing methods for the analysis of the dynamical trajectories of complex molecules in complex environments. We are doing this via molecular dynamics simulations of model liquids and macromolecules in random disordered materials. The system consists of fluid particles and (fixed) media particles and we are generating trajectories of the fluid particles and analyzing these using a variety of correlation functions. The goal is to obtain an understanding of the mechanism of molecular motion in complex environments. For example, how does the distribution of the media particles and their interaction with the fluid affect the diffusion of the fluid particles? It is hoped that we will obtain an understanding of these dynamic phenomena that will provide us with a theoretical standard against which experimental data may be compared.

Theoretical Chemistry.

Liquid state theory and computer simulation; Physical Chemistry of polymers; polymer alloys; colloidal dispersions; polyelectrolytes; liquid crystals; polymer/solid interfaces.

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1. K. Miyazaki and A. Yethiraj, "Entanglement Effects in Mode-coupling Theories of Polymers", *J. Chem. Phys.* **117**, 10448 (2002).

2. K. Jagannathan, R. Chang, and A. Yethiraj, "A Monte Carlo Study of the Self-Assembly of Bacteriorhodopsin", *Biophysical Journal* **83**, 1902 (2002).

3. A. Yethiraj, "Integral Equations for Polymers in Quenched Random Media", *J. Chem. Phys.* **116**, 5910 (2002).

4. C.-Y. Shew and A. Yethiraj, "Integral Equation Theory for the Structure of DNA Solutions", *J. Chem. Phys*. **116**, 5308 (2002).

5. R. W. Chang and A. Yethiraj, "Brownian Dynamics Simulations of Salt-free Polyelectrolyte Solutions", *J. Chem. Phys.* **116**, 5284 (2002).

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8. R. W. Chang and A. Yethiraj, "Solvent Effects on the Collapse Dynamics of Polymers", *J. Chem. Phys.* **114**, 7688 (2001).

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10. A.Yethiraj, H. Fynewever, and C.-Y. Shew, "Density Functional Theory for Pair Correlation Functions in Polymeric Liquids", *J. Chem. Phys*. **114**, 4323 (2001).

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B.S. 1955, Seoul National University, Korea
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Physical Chemistry.

Interfacial dynamics and viscoelasticity of amphiphiles and polymers; surface modification of polymers for biocompatibility; biomembrane mimetic surfaces and their functions; enzyme kinetics on phospholipid monolayers and their modulation by compatible polymers.

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1. Keiji Tanaka and Hyuk Yu, "Polymer-Modulated, Diffusion-Controlled Enzyme Kinetics on Monolayers" in *Biocatalysis in Polymer Science, ACS Symposium Series,* Eds. R. Gross & C. N. Cheng, Oxford University Press, 2002.

2. Danny G. Miles, Jr., Zhihao Yang and Hyuk Yu, "Surface Light Scattering Adopted to the Advanced Undergraduate Laboratory", J. Chem. Edu .79, 1007–1012 (2002).

3. Keiji Tanaka and Hyuk Yu, "Lipase Activity on Lipid/Polymer Binary Monolayers: Lateral Diffusion-Controlled Enzyme Kinetics", Langmuir, 18, 797–804 (2002).

4. Thorsteinn Adalsteinsson and Hyuk Yu, "Lipid Lateral Diffusion in Multyi-Bilayers, and in Monolayers at the Air/Water and Heptane/Water Interfaces", Langmuir 16, 9410–9413 (2000).

5. Alan R. Esker, Lanhui Zhang, Bryan B. Sauer, Woongki Lee and Hyuk Yu, "Dilational viscoelastic Behaviors of Homopolymer Monolayers: Surface Light Scattering Analysis", Colloids Surf. A 171, 131–148 (2000).

6. Keiji Tanaka, Steven P. Mecca, and Hyuk Yu, "Lipase Catalysis on Monolayers at the Air/Water Interface. 2. Diffusion-Controlled Kinetics on Quasi-Two-Dimension", Langmuir 16, 2672–2676 (2000).

7. Keiji Tanaka, Patricia A. Manning, and Hyuk Yu, "Lipase Catalysis on Monolayers at the Air/Water Interface. 1. Kinetic Rate Constants on Quasi-Two-Dimension", Langmuir 16, 2665–2671 (2000).

8. Zhihao Yang, Jeffrey A. Galloway and Hyuk Yu, "Protein Interactions with Poly(ethylene glycol) Self-Assembled Monolayers on Glass Substrates: Diffusion and Adsorption", Langmuir 15, 8405 (1999).

9. Zhihao Yang and Hyuk Yu, "Biomembrane Mimetic Surfaces by Phospholipid Self-Assembled Monolayers on Silica Substrates", Langmuir 15, 1731 (1999).

10. Keiji Tanaka, Patricia A. Manning, Victor K. Lau and Hyuk Yu, "Lipid Lateral Diffusion in Dilauroylphosphatidyl choline/Cholesterol Mixed Monolayers at the Air/Water Interface", Langmuir 15, 600 (1999).

Our research is concerned with macromolecules of synthetic and biological origins. What distinguishes macromolecules most strikingly from small molecules is the multiplicity of internal degrees of freedom by virtue of a large number of atoms linked together in macromolecules, giving rise to many different chain configurations which are in turn mainfested in a whole host of physical properties not found in small molecule systems in condensed state. Most notable among them is the viscoelasticity in bulk state and concentrated solutions. This also appears in thin films and monolayers. The focus of this group is to understand this distinct feature of macromolecules by examining their chain transport properties since the multiplicity of chain configuration is exhibited through the molecular transport properties to the viscoelasticity. Conversely, we probe many different complex media including physical and chemical gels by the chain transport properties of test macromolecules dispersed in the media. Depending on the size of the test chain, we can probe the media in various length scales from 0.1 nm to 100 nm.

On the interfacial properties of amphiphiles and polymers, we make use of thermally generated or externally stimulated surface capillary waves to probe the interfaces of vapor/liquid and liquid/liquid by means of the propagation and damping characteristics of these waves. Main purpose is to understand the viscoelasticity of monolayers and thin films of amphiphilic molecules and surface active macromolecules on the air/water and oil/water interfaces, and the interfacial properties of polymer/polymer either in solutions or in bulk state. In addition, we examine the lateral transport properties at the interfaces.

Our experimental techniques are those of scattering and diffraction of electromagnetic radiations, mostly in visible range. These include elastic and quasi-elastic light scattering, a transient optical grating technique called forced Rayleigh scattering, and surface fluorescence photobleaching and recovery method. Aside from these optical techniques. we synthesize our own polymer samples by anionic initiation methods with the breakseal technique, and label polymer samples with appropriate dyes for the transient optical grating experiments. In dealing with biological macromolecules, we extract DNA from various sources and fractionate them by ourselves.

Although the group is broadly partitioned into the two areas, each student's research project is related to those of others in parallel. Thus, the individual project neither requires nor is isolated from others, so that sufficient room is allowed for the individual style and progress in performing research while the active interactions among the members are maximized. During the graduate study, development of interaction skills and creative input to the thesis research are insisted upon.

Martin T. Zanni

Assistant Professor
B.S. 1994, University of Rochester
Ph.D. 1999, University of California, Berkeley

Research in the Zanni group is aimed at exploring molecular structures and dynamics through vibrational motions and couplings. To accomplish this, sophisticated ultrafast multi-dimensional spectroscopies are being developed that correlate vibrational modes and measure frequency fluctuations. Emphasis is placed on understanding the molecular vibrations of complex biomolecules with regards to structure and function.

Two-color 2D IR spectroscopy - 2D IR spectroscopy is a newly emerging technique that is similar in ways to 2D NMR spectroscopy. In 2D IR spectroscopy, multiple femtosecond infrared pulses drive coherences between vibrators that then emit a free induction decay whose time-dependence depends on the structures and dynamics of the system. The resulting 2D IR spectrum has a diagonal peak for each vibrational mode and cross peaks between coupled modes. The cross peak splittings are related to the distances and orientations between the coupled vibrators and hence the relative molecular structures.

Structure and dynamics of protein solvents - Hydrophobic forces are one of the most important interactions responsible for protein folding and stability and are often studied using chemical denaturants. In conjunction with isotope labeling and de novo peptide design, the vibrational coupling between specific amino acid groups and nearby solvent molecules are being measured and models are being developed to relate the coupling to the solvent angles, distances and dynamics. Because 2D IR spectroscopy has femtosecond time resolution, new insights into protein hydration and chemical denaturation are expected.

DNA vibrational couplings and structure - Linear infrared spectroscopy has been used for decades to monitor the structures of DNA and has revealed evidence that the double bond vibrations amongst DNA bases are strongly coupled, but is insufficient to understand the structural origins of the spectra. The approach in the Zanni group is to use modern DNA sequencing methods, synthetic bases, and 2D IR spectroscopy to measure the inter- and intra-strand couplings between DNA strands. The results are providing information on the molecular vibrations of DNA, assisting in interpretation of FTIR studies, and laying the groundwork for DNA structural studies using 2D IR spectroscopy.

Physics of molecular vibrations - Many fundamental physical chemistry problems are being investigated to advance our understanding of the basic physics behind molecular vibrations such as condensed phase vibrational relaxation, coupling, rotational motion, frequency fluctuations, inhomogeneous broadening, and correlation between fluctuations. Sophisticated polarization, phase control, and phase-matching geometries are being incorporated into the experiment that will advance state-of-the-art laser technology. The results are testing theoretical models and encouraging further development of spectroscopically accurate potentials.

Physical Chemistry.

Ultrafast multi-dimensional infrared spectroscopy; biomolecular structures and dynamics; vibrational relaxation, coupling and dephasing; peptide and oligonucleotide synthesis; isotope labeling.

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The research of my students and myself ranges from the synthesis of unusual organic molecules at one extreme to theoretical organic chemistry at the other. In between are reaction mechanisms, the study of unusual organic species, organic photochemistry, and the application of quantum mechanics and MO theory to organic chemistry. One rewarding research topic for us these days is solid-state photochemistry, where reactivity is determined by the shape of molecular cavities in which a molecule reacts. Some students become an expert in all areas while some prefer to concentrate at one end of the spectrum. An advantage of having a stimulating research group interested in a wide range of scientific topics is keeping all members of the group in contact with a variety of hot areas of chemistry.

One particularly exciting area we enjoy is mechanistic and exploratory organic photochemistry. We seem to encounter an endless number of intriguing and new photochemical rearrangements. Many are synthetically useful; many are superb challenges for detailed molecular study.

Some of the tools we are presently using are single photon counting, computation of x-ray structures, energy surfaces for reaction mechanisms, and more.

Our photochemical calculations generally provide an understanding of the observed reactivity. The reactions are often simply predicted by an MO expert and an organic "electron pusher." Our approach is to design molecules chosen to test some mechanistic hypothesis. Our tools and techniques are both organic and physical.

The emphasis of my research students has been towards an academic career. I think what I particularly like about the bright and energetic students working with me is that they keep me concentrating on the next challenging problem. We have a lot of "give and take" in our group with continual debate about chemistry. I tend to spend a lot of time working with my students.

I'm pleased that 81 of my former students have gone into academic life and most have earned tenure. Additionally some very fine students have gone into good industrial jobs. I can always send out a complete bibliography, but I'm selecting the following papers as typifying my research interests.