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THE NUCLEUS

March 2010 *Vol. LXXXVIII, No. 7*

Monthly Meeting

Richards Medal Award Meeting at Harvard

Richards Award to Professor Richard N. Zare

Book Review

Echoes of Life: What Fossil Molecules Reveal about Earth's History

Reviewed by Mindy Levine

Summer Scholar Report

By Rita E. Ciambra, Eva Vennmann, Katherine H. Schiavoni, and Ekaterina Pletneva

My Internship Experiences

By Rajeev Chorghade

2010 Eastern Analytical Symposium

November 15 - 18, 2010
Garden State Exhibit Center, Somerset, New Jersey

CALL FOR PAPERS

Deadline – April 15, 2010

The Eastern Analytical Symposium and Exposition is the second largest conference and exposition for laboratory science in the U.S. dedicated to the needs of analytical chemists and those in the allied sciences. We offer high quality cutting-edge technical sessions and state-of-the-art short courses, workshops and seminars. We invite you to be a part of the program by contributing a paper for oral or poster consideration. Please note that all abstracts must be submitted electronically via the EAS web site at **www.EAS.org under the Symposium tab.** The abstract submission deadline is April 15.

To submit a contributed paper for the 2010 EAS Technical Program, please submit abstracts through our web site at **www.EAS.org/asubmit** between March 1 and April 15, and follow the instructions for abstract submission.
Invited speakers must not submit abstracts to EAS until requested.

Please carefully review the following information:

- All contributed abstracts must be submitted through our web site at www.EAS.org between March 1 and April 15, 2010. No faxed, e-mailed, or mailed abstracts will be accepted.
- **Please note that no one author may submit and present more than two posters.**
- All abstracts must be a **maximum of 250 words** or less.
- All abstracts will be acknowledged via e-mail.
- The title of the presentation and the list of authors that you submit are final, and may not be changed.
- The abstract that you submit will be considered to be your final abstract that will be printed in the abstract book for the 2010 Eastern Analytical Symposium.
- Presenting authors of contributed submissions will be notified in June 2010 of the status of the abstract and its session assignment.

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Cover: *Professor Richard N. Zare of Stanford University. 2010 recipient of the Theodore Richards Medal. (Photo courtesy of Linda Cicero, Stanford News Service)*

Deadlines: *May 2010 Issue: March 11, 2010*
Summer 2010 Issue: June 15, 2010

THE NUCLEUS

The Nucleus is published monthly, except June and August, by the Northeastern Section of the American Chemical Society, Inc. Forms close for advertising on the 1st of the month of the preceding issue. Text must be received by the editor six weeks before the date of issue.

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Book Review

Echoes of Life: What Fossil Molecules Reveal about Earth's History, Susan Gaines, Geoffrey Eglinton and Jürgen Rullkötter (Oxford University Press, 2009), 376pp., ISBN: 9780195176193, $35, (hardcover)

Reviewed by Mindy Levine, Massachusetts Institute of Technology, Department of Chemistry, Cambridge, MA 02139

Where does oil come from? How did ancient cultures preserve mummies? What is the cause of deadly "red tides" in oceans?

The answers to these wildly disparate questions (and many more) are found in the book *Echoes of Life: What Fossil Molecules Reveal about Earth's History* by Susan Gaines, Geoffrey Eglinton, and Jürgen Rullkötter. The book provides an overview of the various scientific fields in which "fossil molecules" can provide key information and understanding about ancient earth. It is not, however, a rigorous scientific text; nor is it a text for the non-scientist. Rather, the book combines anecdotes about the scientists with actual stories of scientific discovery. The result is a narrative that, for the most part, succeeds in entertaining readers while conveying knowledge of an intriguing and constantly evolving scientific field, that of organic geochemistry.

The book is divided into eleven chapters:

1. Molecular Informants: A Changing Perspective of Organic Chemistry
2. Looking to the Rocks: Molecular Clues to the Origin of Life
3. From the Moon to Mars: The Search for Extraterrestrial Life
4. Black Gold: An Alchemist's Guide to Petroleum
5. Deep Sea Mud: Biomarker Clues to Ancient Climates
6. More Molecules, More Mud, and the Isotopic Dimension: Ancient Environments Revealed
7. Microbiologists (Finally) Climb on Board
8. Weird Molecules, Inconceivable Microbes, and Unlikely Environmental Proxies: Marine Ecology Revised
9. Molecular Paleontology and Biochemical Evolution
10. Early Life Revisited
11. Thinking Molecularly, Anything Goes

Each chapter covers one area in which organic geochemistry has provided an improved scientific understanding. For example, Chapter 4 investigates how the study of "fossil molecules" has improved our understanding of the source of petroleum, and how different environmental conditions can impact oil production. Chapter 5 discusses fossil molecules that have been discovered in deep-sea

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Monthly Meeting

The 904th Meeting of the Northeastern Section of the American Chemical Society

2010 ACS Richards Medal Award Meeting

Thursday – March 4, 2010

Harvard Faculty Club
20 Quincy St., Cambridge, MA

5:30 pm Social Hour

6:15 pm Dinner

8:15 pm **Richards Award Ceremony**
Mallinckrodt Building, Pfizer Lecture Hall - MB23,
12 Oxford Street, Cambridge, MA.

Dr. John McKew, NESACS Chair, Presiding

Reflections on Theodore William Richards
Prof. Roy G. Gordon, Chair, Richards Medal Committee

Introduction of the 41st Richards Medalist
Professor Mark A. Johnson, Yale University

2010 Richards Medalist
Prof. Richard N. Zare, Marguerite Blake Wilbur Professor in Natural Science, Stanford University, Palo Alto, CA. "***Theodore W. Richards Redux: Determining Isotope Ratios without Mass Spectrometers***"

Dinner reservations should be made no later than noon, Thursday, February 25, 2010. Please call or fax Anna Singer at 800-872-2054 or e-mail at secretary@nesacs.org. Please specify vegetarian. Reservations not cancelled at least 24 hours in advance must be paid. Members,$30; Non-members, $35; Retirees, $20; Students, $10.

THE PUBLIC IS INVITED

Anyone who needs special services or transportation, please call Anna Singer a few days in advance so that suitable arrangements can be made. **Free parking** in the Broadway St. Garage (3rd level or higher), enter from Cambridge Street via Felton, St.

Biography

Richard N. Zare is the Marguerite Blake Wilbur Professor in Natural Science at Stanford University with an appointment in the Department of Chemistry and a courtesy appointment in the Department of Physics. He is a graduate of Harvard University, where he received his B.A. degree in chemistry and physics in 1961 and his Ph.D. in chemical physics in 1964. In 1965 he became an assistant professor at the Massachusetts Institute of Technology, but moved to JILA, University of Colorado at Boulder in 1966, where he remained until 1969 while holding joint appointments in the Department of Chemistry, and the Department of Physics and Astrophysics. In 1969, he was appointed to a full professorship in the Department of Chemistry at Columbia University, becoming the Higgins Professor of Natural Science in 1975. In 1977 he moved to Stanford University, where he has been chair of their chemistry department since 2004. He has also been active in public service, serving on the National Science Board, the policy-setting body of the National Science Foundation, from 1992 to 1998, the last two years as its chair.

Zare has made fundamental contributions to chemical analysis. His earliest studies were on the use of laser-induced fluorescence (LIF) as a means to determine molecular structure and as a detection tool for chemical reac-

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Abstract

Theodore W. Richards Redux: Determining Isotope Ratios without Mass Spectrometers

The first American scientist to win the Nobel Prize in Chemistry was Professor Theodore W. Richards, Harvard University, who was honored "in recognition of his accurate determinations of the atomic weight of a large number of chemical elements." Richards' painstaking, careful investigations led to highly accurate atomic weights of more than 20 elements, determined in many cases to five significant figures. Richards thought that the atomic weights of the light elements were immutable constants, like the numerical values of e and π but his work on lead from different sources, radioactive and non-radioactive, helped to confirm the existence of isotopes. To quote from his 1914 Journal of the American Chemical Society article,[1] "In this paper a description is given of parallel experiments determining the equivalent weights of various samples of lead chloride obtained from different sources. It was found that all of the radioactive specimens possess a lower atomic weight than ordinary lead, as determined under identical conditions, the deficiency in one case amounting to as much as 0.75 of a unit." Since then, different isotopes, stable and radioactive, have been established to exist for all the elements. Mass spectrometers have been used to determine the most precise values of isotopic weights, abundances, and ratios, but such devices are large, costly, and require operation by experts. In this lecture, I will describe a different approach based on isotopic

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The 13th and 14th Andrew H. Weinberg Memorial Lectures

Lee Helman, MD at the 13th annual Weinberg Memorial Lecture

Despite decades of research into new drugs to treat cancer, more effort is needed to develop targeted therapies for the unique tumors of childhood and to avoid the toxic side effects of therapy. Most anti-cancer drugs were originally developed to combat adult cancer. Indeed, in the past 50 years, ***only 16*** new anti-cancer drugs that have been developed to address childhood cancer have received FDA approval for use in the U.S.

To help tackle this problem, and with the generous support of family and friends, as well as the Medicinal Chemical Group, the Northeastern Section of the American Chemical Society, and the Dana Farber Cancer Institute, the Andrew H. Weinberg Pediatric-Chemotherapy Drug Development Symposium was established in 1994. This annual symposium brings together a broad array of physicians, researchers, academicians, and political allies with one focus – the development of new therapies and approaches for the treatment of pediatric cancer.

Last year, thanks to the generosity of many individuals and corporations, the Andrew H. Weinberg Memorial Jimmy Fund Walk team raised over $5,000. This generosity allowed us on April 7th 2009 to welcome our keynote speaker, Lee Helman, M.D, a world-renowned National Cancer Institute scientist who researches new treatment strategies for battling childhood sarcomas. He discussed Ewing's sarcoma and rhabdomyosarcoma, which are driven in part by overactive growth signaling involving the insulin-like growth factor receptor (IGFR). IGFR enables cancer cells to survive and avoid cell death. He is testing antibodies that block the receptor in clinical trials. Tumors have shrunk in certain patients, but the responses have been temporary, prompting further research into this approach.

On Monday May 24, 2010, internationally renowned scientist and cancer drug developer, Stephen W. Fesik, Ph.D., of Vanderbilt University Medical Center, and formerly of Abbott Laboratories, will deliver this year's Weinberg Symposium address and meet with Dana- Farber researchers. Details of the lecture will be in the upcoming edition of *The Nucleus*. Dr. Fesik has published more than 230 papers, trained more than 27 postdoctoral fellows, has been a reviewer for the NIH Biophysical Chemistry Study Section, and has served as a member of the Editorial Boards of the *Journal of Medicinal Chemistry, Journal of Biomolecular NMR, Biophysical Journal, Molecular Cell*, *Chemical Biology & Drug Design, ChemMedChem, Molecular Cancer Therapeutics, Oncogene,* and the Highlights Advisory Panel for *Nature Reviews Cancer.*

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Announcement

The James Flack Norris and Theodore William Richards *Undergraduate Summer Research Scholarships*

The Northeastern Section of the American Chemical Society (NESACS) established the James Flack Norris and Theodore William Richards Undergraduate Summer Scholarships to honor the memories of Professors Norris and Richards by promoting research interactions between undergraduate students and faculty.

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Announcement

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Research awards of $3500 will be given for the summer of 2010. The student stipend is $3000 for a minimum commitment of ten weeks of full-time research work. The remaining $500 of the award can be spent on supplies, travel, and other items relevant to the student project.

Institutions whose student/faculty team receives a Norris/Richards Undergraduate Summer Research Scholarship are expected to contribute toward the support of the faculty members and to waive any student fees for summer research. Academic credit may be granted to the students at the discretion of the institutions.

Award winners are required to submit a report (~5-7 double-spaced pages including figures, tables, and bibliography) of their summer projects to the NESACS Education Committee by November 1, 2010 for publication in *The Nucleus*. They are also required to participate in the Northeast Student Chemistry Research Conference (NSCRC) in April, 2011.

Eligibility: Applications will be accepted from student/faculty teams at colleges and universities within the Northeastern Section. The undergraduate student must be a chemistry, biochemistry, chemical engineering, or molecular biology major in good standing, and have completed at least two full years of college-level chemistry by Summer 2010.

Application: Application forms are available on the NESACS web site at http://www.nesacs.org. Completed applications are to be submitted no later than April 2, 2010 to the Chair of the Selection Committee:

Professor Edwin Jahngen
University of Massachusetts Lowell
Chemistry Department, Room 520, Olney Hall
1 University Avenue
Lowell, MA 01854-5047

Notification: Applicants will be notified of the results by e-mail on April 23, 2010 with written confirmation to follow. ◇

NESACS Candidates for 2010 Election

From the 2010 Nominating Committee: Joseph Billo (chair), Michaeline Chen, Michael P. Filosa, Morton Z. Hoffman, Ralph Scannell

Chair-Elect (vote for 1)
Ruth Tanner

Treasurer (vote for 1)
James Piper

Auditor (vote for 1)
Anthony Rosner

Trustee (vote for 1)
Esther Hopkins
Martin Idelson

Director-at-Large (vote for 2)
John Burke
David Harris
Steve Lantos
Raeanne Napoleon

Councilor/Alternate (vote for 8)
Dora Carrico-Moniz
Mukund Chorghade
Tim Frigo
Mark Froimowitz
Tom Gilbert
Leland L. Johnson Jr.
Bob Lichter
Ken Mattes
Raj Rajur
Mary Schultz
Michael Singer
Sofia Su
Al Viola

Nominating Committee (vote for 2)
Mukund Chorghade
Ken Mattes
Raeanne Napoleon
Raj Rajur

Norris Award Committee (vote for 2)
Doris Lewis
Bob Lichter
Jason Pontrello
Mary Schultz

Petition candidates: *"Any group comprising 2 percent or more of the membership of the Northeastern Section [136 members] may nominate candidates …"*. See the NESACS website for details. ◇

My Internship Experiences

By Rajeev Chorghade, Natick High School, Natick, MA

NESACS has benefited from having countless geniuses and scientists of stature from the triad of academia, government and industry. I have been inspired by works that illustrate the pride and joy they took in research, how insatiable scientific curiosity led them to question the status quo and make groundbreaking discoveries. My scientific hero was the Nobel Laureate Robert Burns Woodward, who when questioned by a Senator about how his work would contribute to the defense of America, replied that it "would make America a lot more worth defending."

I have a fascination and passion for learning science and performing laboratory experiments. My parents and high school teachers instilled a love for the natural sciences in me at an early age. I love to delve deeper into the scientific rationale of why things work the way they do, am intellectually curious, ask numerous questions, and am the proverbial sponge for the answers. I watch cooking shows where chefs experiment with new methods and ingredients to bring out exotic flavors. I am fascinated with chefs like Heston Blumenthal, who adds unique scientific flair to the culinary world by making desserts with liquid nitrogen!

I strive for a career in research and medicine, and aspire to secure M.D. and Ph.D. degrees. I am resolved to conduct research directed at understanding causative and curative factors of sports injuries, and exploring novel options for preventive care and cure. I wanted to start research early and embarked on a quest to work in laboratories that would provide me training and intellectual stimulation. I was privileged to obtain fabulous summer internships in Cambridge, UK (Physics), California Institute of Technology (Chemistry), and Harvard Medical School (Biomedical Sciences). Stepping into these hallowed institutions where so much wonderful work was done filled me with awe and inspiration. Working with such extraordinarily distinguished scientists as Steven Ley (Fellow of the Royal Society), Robert Grubbs (Nobel Laureate), and Vikas Sukhatme (Chief Academic Officer, Harvard Medical School) were memorable experiences that have truly shaped my scientific acumen, aspirations and career goals.

I learned techniques in flow chemistry, synthetic chemistry and biomedical science, respectively. These internships provided me with unique opportunities to discuss with distinguished academicians, post-doctoral fellows and graduate students their love for science. At Caltech, I met Professors Robert Grubbs, Peter Dervan, and others who stimulated my thoughts and encouraged me by discussing how they were attracted to science. Professor Grubbs showed me the laboratories where luminaries Gilbert Lewis, Robert Millikan and Linus Pauling had worked. Seeing the laboratories where all the scientists about whom I had read in my school text books was truly a memorable experience. In Professor Grubbs' lab, I participated in projects on chiral reductions and also conducted experiments on olefin metathesis.

I was honored to work in the laboratories of Professor Steven Ley and Syrris/Dolomite Industries in Cambridge, England. Microfluidics, known as "lab-on-a-chip," enables small-scale fluid control and analysis, allowing manufacturers to develop smaller, more cost-effective, and powerful systems. I joined a team that conducted proof of concept, development, and trials for a novel plastic microcapillary flow disc (MFD) reactor. Steven Ley was extremely gracious and hospitable; his students made me feel completely at home in their midst. I was able to appreciate the history of science by visiting the fabled Cavendish laboratories where 29 Nobel Prizes were won in the early part of the last century. Seeing the laboratories where Lord Thompson discovered the electron, where Wilson invented the cloud chamber, where Lord Todd explored the chemistry of nucleic acids, and where Watson and Crick postulated the structure of DNA was a dream come true. I even saw the famous pub where Watson and Crick burst in at lunch and announced "We have now found the secret of life."

Professor Vikas Sukhatme and colleagues at the Harvard Medical School introduced me to the magical world of molecular medicine. I learned how to run cell enzyme assays to study the effects of pharmaceutical drugs on living cell lines. I felt welcome to experience the art and science of discovery, ask questions I had, and have the benefit of distinguished scholars patiently explaining the workings of the methodology. I am truly grateful to have experienced the atmosphere of these fantastic laboratories and am especially privileged to have seen them as a teenager.

These experiences led me to collaborate in establishing a Science Club at Natick High School. I insisted on taking AP Chemistry, even though it was not being offered. My teacher, Kathi Browne, a NESACS Councilor, personally mentors me and I am completing the course by independent study.

I am thankful for these exciting opportunities; few high school students have had such a stimulating introduction to science. I will use these learning experiences to optimize my academic potential, secure an M.D. and Ph.D and participate in varied activities of NESACS. ◇

Q. Exactly, how many awards and scholarships does NESACS sponsor?

a) One b) Two c) Many

www.nesacs.org/awards

Summer Internship Research Report

Christopher S. Daeffler, **Rajeev Chorghade**, Mukund Chorghade and Robert H. Grubbs
Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA

Part 1:

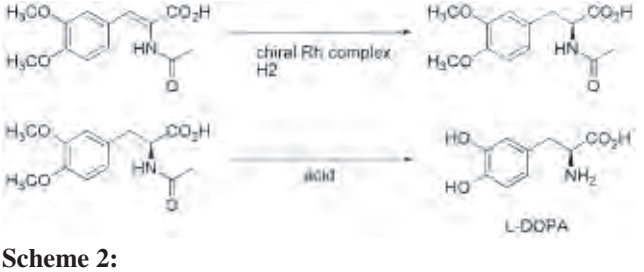
The Asymmetric Reduction of Acetophenone

The construction of chiral molecules (those which are not superimposable over their mirror image, known as an enantiomer) is an important problem in modern organic chemistry. These are known as asymmetric reactions because they provide unequal amounts of two mirror-image molecules, which are identical in every other chemical aspect. Most biomolecules are chiral, and many pharmaceuticals are as well. One good example of this is the compound L-DOPA, which is used in the treatment of Parkinson's disease (Scheme 1). In the final steps of its industrial synthesis, one of the precursor compounds is treated with a chiral rhodium catalyst and hydrogen gas. This provides one enantiomer almost exclusively. K. Barry Sharpless, Ryoji Noyori and William Knowles were awarded the 2001 Nobel Prize in Chemistry for their contributions to the field of "chirally catalyzed reactions," underlining the importance of this area.

In our project, we sought an inexpensive chiral reagent that could efficiently perform an asymmetric reaction without the need for an expensive transition metal catalyst such as the rhodium complex used in the synthesis of L-DOPA. We decided to start our investigations with the reduction of acetophenone to *sec*-phenethyl alcohol, using a combination of (-)-menthol, a readily available chiral alcohol, and lithium aluminum hydride ($LiAlH_4$), a common reducing agent. Similar methodologies are known but not well-developed.[i, ii] In the reaction mixture, (-)-menthol reacts with $LiAlH_4$ to make lithium tri-menthyloxyaluminum hydride, which then reduces acetophenone to *sec*-phenethyl alcohol. In our experiments, one enantiomer of *sec*-phenethyl alcohol was obtained in 87% enantiomeric excess (ee). Decreased temperature lowers the selectivity of the reaction (Scheme 2)

Future work will focus on the analysis of the other easily available chiral alcohols as chiral auxiliaries, such as (+)-fenchyl alcohol, (-)-borneol and (+)-isopinocampheol. These may offer a variety of steric environments that can be tailored to different substrates. With the development of a reliable set of reaction conditions, we will also test a variety of prochiral ketones to demonstrate that this technology is applicable to a wide variety of structures.

Scheme 1: Synthesis of L-DOPA



Scheme 2:
Enantioselective Reduction of Acetophenone

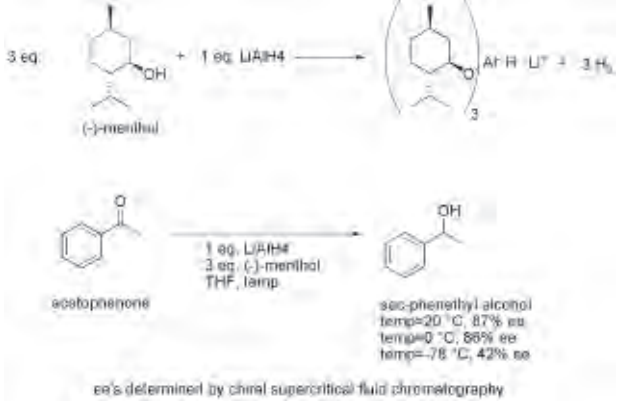
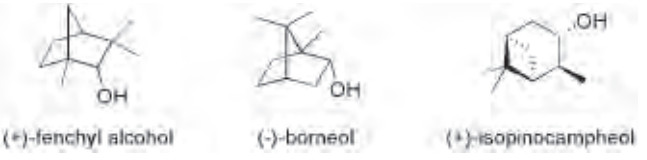


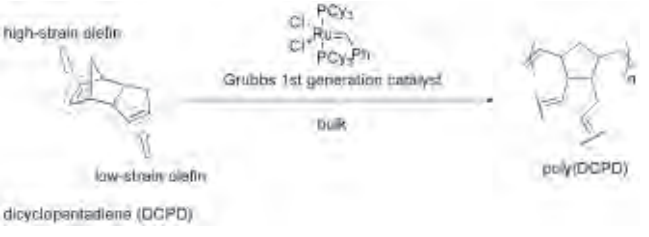
Figure 1: Inexpensive Chiral Alcohols



Part II:

Polymerization using the olefin metathesis reaction

Scheme 3: Metathesis of dicyclopentadiene



Yves Chauvin, Richard Schrock, and Robert H. Grubbs, the 2005 Nobel Prize Laureates in chemistry, have made olefin metathesis into one of organic chemistry's most important reaction. Fantastic opportunities were created for producing many new molecules, including pharmaceuticals and polymers. The word metathesis means "change-places.' In a metathesis reactions double bonds are broken and made between carbon atoms in ways that cause atom groups to change places. This happens with the assistance of special catalyst molecules.

continued on page 16

[i] Yamaguchi, S.; Kabuto, K. *Bull. Chem. Soc. Japan* **50**, 3033 (1977)
[ii] Chandrasekhar, S.; Raghunandan, R. *Tetrahedron: Asymmetry* **16**, 751 (2005)

Summer Scholar Report

Redox Reactivity, Ligand Substitution, and Conformational Changes in a *Geobacter* Heme Protein GSU0935

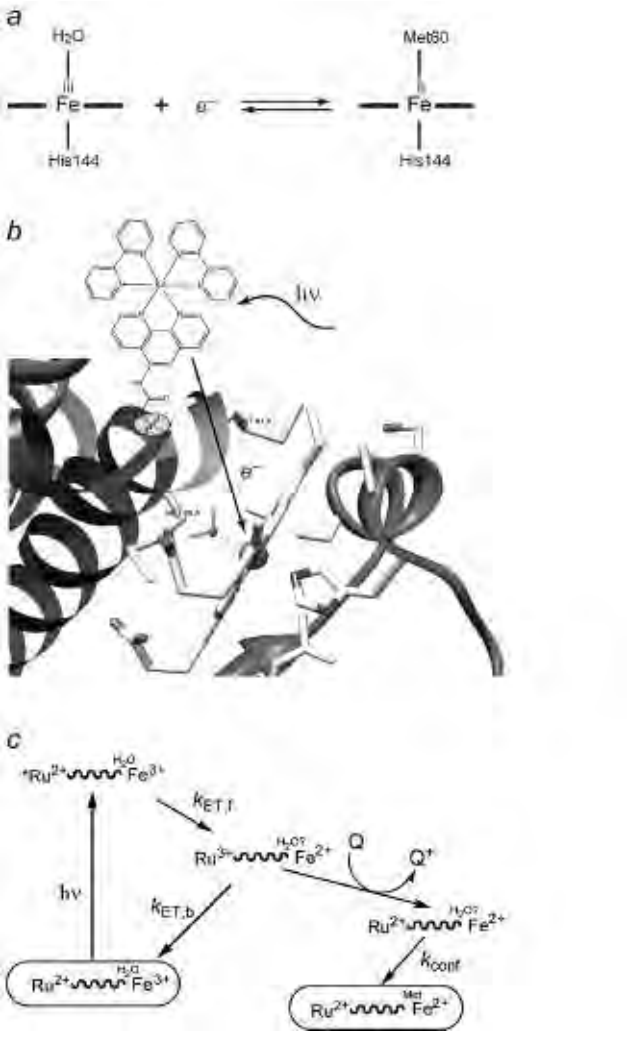
Rita E. Ciambra, Eva Vennmann, Katherine H. Schiavoni, and Ekaterina V. Pletneva,
Dartmouth College, Hanover, NH 03755

Maintaining a clean environment is a major problem facing the world today, and the continuing search for sustainable or alternative energy sources is an active area of scientific research. *Geobacter* bacteria have shown potential importance in microbial fuel cells, allowing organic compounds to be converted into electricity.[1] Additionally, *Geobacter* species can oxidize petroleum compounds into carbon dioxide, thus helping to clean up environmentally hazardous petroleum spills. These bacteria have unusually large numbers of redox metalloproteins, in particular cytochromes with *c*-type hemes. Studies of redox reactions in these metalloproteins are important for understanding chemical principles that govern *Geobacter*'s ability to remediate contaminated soil and water and to generate electricity.

A recently discovered cytochrome GSU0935 from *Geobacter sulfurreducens* switches its axial ligand H_2O to Met60 upon reduction of the heme iron (Figure 1a).[2] This change in the metal coordination environment is expected to affect the redox reactivity of the heme and could also require changes in the protein conformation. However, the reasons for ligand substitution in the redox reactions of GSU0935 and other proteins are unclear.

We have therefore designed an experimental system to examine reduction and accompanying conformational changes in GSU0935. The reduction is driven by a photoexcitation of a covalently attached Ru(II)-bipyridyl complex (Figure 1b), which creates a strong reducing agent, $*Ru^{2+}$. The $*Ru^{2+}$ species rapidly reduces the heme and the resulting conformational changes can be followed by kinetic methods (Figure 1c). We have prepared the GSU0935 mutant Gly58Cys and the cysteine-specific reagent $Ru(bipy)_2$(5-iodoacetamido-1,10-phenanthroline)$^{2+}$, $Ru(bipy)_2$phen-IA, and studied the photoinduced reduction in the Ru-bipyridyl-labeled protein.

Figure 1a-c



Materials and Methods:

Preparation of the Mutant DNA. The construct for the wild-type GSU0935 fused to the ELP purification tag[2] served as a template for the mutation Gly58Cys. The mutant DNA was prepared with a Quickchange kit from Stratagene and purified using a QIAprep Spin Miniprep Kit. The mutation was confirmed by sequencing carried out at the Molecular Biology & Proteomics Core Facility at Dartmouth College.

Protein Expression. The plasmid encoding the GSU0935 mutant (Amp^R) was cotransformed into *E.coli* SF110 together with the plasmid pEC86 (Chl^R) encoding the proteins responsible for the covalent attachment of the heme group. A single colony from the LB/Amp/Chl plate was grown in 100 mL of 2XYT media containing 100 mg/mL ampicillin and 34 mg/mL chloramphenicol. After shaking for 5 hours at 37°C, the contents of the flask were used to inoculate six 2.8 L flasks containing 2XYT media and antibiotics. These cultures were grown overnight at 250 rpm and 25°C. When the absorbance at 600nm reached 0.9-1.0, the cultures were induced with 50 μM isopropyl-beta-D-thiogalactopyranoside (IPTG). Incubation was continued overnight under the same conditions.

To harvest the protein, the cultures were centrifuged at 4,000 rpm for 25 minutes at 4°C. The pellet was then resuspended using a solution of 30% sucrose, 1 mM EDTA, 30 mM Tris (pH 8.0). The cell suspension was centrifuged at

4,000 rpm for 20 minutes at 4°C. The resulting pellet was resuspended on ice using a solution of 5 mM $MgSO_4$ and 2 mM sodium phosphate (pH 8.0). The cell suspension was centrifuged at 13,000 rpm for 60 minutes at 4°C. After centrifugation, 0.5 mM phenylmethylsulphonyl fluoride (PMSF) was added to the supernatant. The Soret peak in the absorption spectrum at 400 nm indicated the presence of the GSU0935 protein in the sample.

Protein Purification. Crystalline NaCl was added to the solution of a crude protein to a concentration of 3 M. The solution became cloudy and was centrifuged at 20,000 rpm for 90 minutes at room temperature. The red pellet formed during centrifugation was dissolved in a buffer of 50 mM Tris and 0.5 mM EDTA (pH 8.0). After dissolving, the solution was centrifuged at 14,000 rpm for 20 minutes at 4°C to remove the insoluble material. The ELP tag was cleaved overnight at room temperature with rTEV protease. Gel electrophoresis confirmed the protein cleavage, with the cleaved protein appearing at 15 kDa and the uncleaved protein at 55 kDa.

Two alternative procedures were used to further purify the protein on different occasions. The first protocol employed a HisTrap and size-exclusion chromatography as previously described.[2] The second protocol used ion exchange chromatography. The ELP tag and uncleaved proteins were precipitated with 3 M NaCl and the solution was centrifuged at 14,000 rpm for 60 minutes at room temperature. The supernatant was dialyzed overnight in a 4 L buffer solution of 10 mM Tris, 2 mM DTT (pH 8.0) at 4°C. The next day the protein was collected and the minor precipitate was removed by centrifugation at 14,000 rpm for 20 minutes at 4°C. A HiTrap Q HP column connected to GE Ätka-purifier FPLC was used to purify the protein further. Buffer A was 10 mM Tris, 2 mM DTT (pH 8.0) and buffer B was 10 mM Tris, 2 mM DTT, 1 M NaCl (pH 8.0). The protein was eluted using a 0-100% gradient of buffer B over 100 minutes and came out of the column at approximately 30% B.

Synthesis of $Ru(bipy)_2$phen-IA. 5-Iodoacetamido-1,10-phenanthroline (phen-IA) and $Ru(bipy)_2$phen-IA were synthesized according to the previously published procedure[3] with the following minor modifications. Iodoacetyl chloride instead of iodoacetic acid was used in the first step of the synthesis. The crude phen-IA product was ground to a powder and washed in a solution of 5% sodium bicarbonate. ^{1}H NMR spectra confirmed the formation of phen-IA and the final product, $Ru(bipy)_2$phen-IA.[4]

Protein Labeling. The purified protein was applied onto a PD-10 desalting column, equilibrated with 100 mM NaP*i* (pH 7.4). A ten-fold excess of tris(2-carboxyethyl)phosphine (TCEP) was added to the protein solution while it was being deoxygenated under nitrogen and stirred constantly. After deoxygenation was complete, a twenty-fold excess of $Ru(bipy)_2$phen-IA was added. The resulting solution was stirred for 5 hours in the dark. The reaction mixture was then dialyzed overnight into 10 mM sodium acetate (pH 4.5). The dialyzed protein was injected onto a HiTrap SP HP column, removing excess $Ru(bipy)_2$phen-IA in the sample. Guanidine hydrochloride (GuHCl) was necessary to fully elute the protein from the column. The protein was refolded in 10 mM Tris buffer (pH 8.0) and then applied to a HiTrap Q HP column. Buffer A was 10 mM Tris (pH 8.0) and buffer B was 10 mM Tris, 1 M NaCl (pH 8.0). The labeled protein did not bind to the resin, and unlabeled and aggregated protein eluted as the 0-50% gradient of buffer B was applied.

Spectroscopic Measurements. The steady-state absorbance and luminescence spectra were measured with Agilent 8453 UV-visible and Horiba Jobin Yvon Fluorolog 3 spectrometers, respectively. The ^{1}H NMR spectra were measured with a Varian XL-300 NMR spectrometer. Time-resolved measurements were obtained using a Continuum Minilite II Q-switched frequency-doubled Nd:YAG laser as an excitation source, which delivered 5-ns pulses at 532 nm. Transient absorbance was measured with a 75 W Xe lamp (Oriel, model 66912) as a probe source, with a secondary lens focusing the collimated light on a 2-mm aperture. Transient emission and absorbance were collected perpendicular to the excitation beam with a monochromator (Oriel, model 77200) placed after the sample. Decay of the $*Ru^{2+}$ and formation of the Fe(II) heme were monitored at 620 and 420 nm, respectively. Transient signals were measured with a Hamamatsu R928 photomultiplier tube. The current was digitized using a Lecroy Wavesurfer 64Xs oscilloscope. For each sample measurement, 500-1000 laser shots were accumulated and averaged. The traces were fitted using SigmaPlot 10.0.

Results and Discussion:

A single-cysteine mutant Gly58Cys was designed for labeling the GSU0935 cytochrome with the $Ru(bipy)_2$phen-IA reagent (Figure 1b). The estimated short Cys58-to-heme distance of 14 Å[2] and good electronic coupling[5] have suggested a possibility of fast rate of the Ru-to-heme electron transfer in this Ru-bipyridyl-labeled derivative. The mutant Gly58Cys was expressed and purified four times with an average yield of 0.05 mg pure protein per liter of media. Although the expression yield was low, adequate amounts of the protein were purified for labeling and preliminary spectroscopic experiments.

Several techniques for protein purification were explored. The first steps of purification, to the ELP-tag cleavage, were based on a previously published study.[2] Further purification of the protein was accomplished using a new protocol involving ion exchange chromatography. After purification, spectroscopic properties of the Gly58Cys mutant were examined by absorption spectroscopy. The absorption spectra of the protein were identical to that of the wild-type protein, with the Soret band at 400 nm in the oxidized state and at 418 nm in the reduced state (Figure 2a). These findings suggest that the environment of the heme group did not appreciably change upon the mutation.

The compound $Ru(bipy)_2$phen-IA was chosen for labeling because it can be linked to the protein efficiently through the cysteine-reactive iodoacetamide handle. This compound

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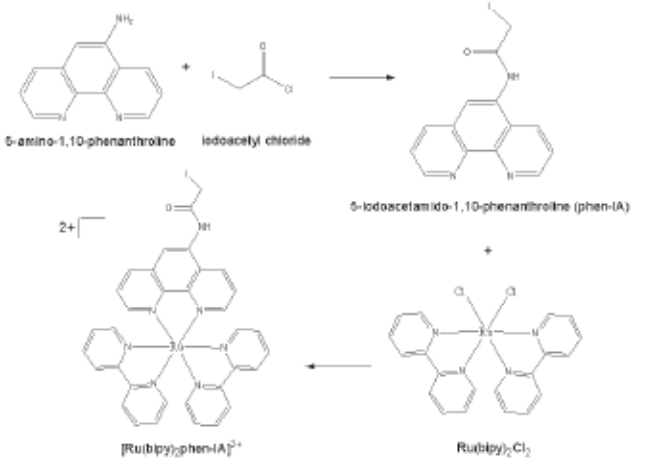
Summer Scholar

Continued from page 11

was synthesized according to Scheme 1 to give a final yield of 31%.[3] The absorption (Figure 2a) and emission spectra of $Ru(bipy)_2$phen-IA were in accord with the literature data.[3] The lifetime of the deoxygenated sample in a sodium phosphate buffer was 770 ns (Figure 2b), which is slower than that of the widely studied $Ru(bipy)_3^{2+}$.

Scheme 1



After the Gly58Cys mutant was labeled with the $Ru(bipy)_2$phen-IA reagent, it did not bind to the positively-charged Q-resin at pH 8.0. This result is consistent with the added +2 charge to the protein and contrasts with the unlabeled protein which bound to the column. Successful protein labeling was also indicated by a shoulder at 460 nm in the absorption spectrum and increase in the absorbance at 280 nm (Figure 2a). Interestingly, the Soret band in the absorption spectrum of ferric Gly58Cys also changed after labeling from 400 nm to 410 nm (Figure 2a), an observation consistent with conversion of the high- to low-spin heme state. This finding suggests the flexibility of the protein environment surrounding the heme group. We hypothesize that in this Ru-bipyridyl-labeled derivative, a Met60 ligand replaces H_2O already in the ferric protein. The attached ruthenium complex, when covalently bound in close proximity to the heme (Figure 1b), may push down the surrounding loops favoring the Met60 ligation. Future studies will verify the Met-heme coordination by examining resonance Raman spectra that are sensitive to the heme ligation as well as the 695 nm absorption band that is characteristic of the Met-Fe(III) ligation.

Photoinduced reactions in the Ru-bipyridyl-labeled derivative were followed by the decay of the excited state $*Ru^{2+}$ and by the increase in the absorption of the ferrous heme. The observed very fast reduction of approximately 15 ns (Figure 2b) suggests an efficient electron transfer process[6] and is consistent with the Ru(phen)-Cys58-Tyr59-Met60-heme through-bond pathway[5] in the Met-bound heme.

Conclusions:

We have expressed and purified the new Gly58Cys mutant of the heme protein GSU0935. The mutant was labeled with the $Ru(bipy)_2$phen-IA reagent and its photoinduced reduction was studied. The Ru-bipyridyl labeling changes the heme environment presumably by pushing Met60 to coordinate to the heme iron already in the ferric state of the protein.

Although the prepared Ru-bipyridyl-labeled derivative does not undergo H_2O-to-Met conformational switching upon reduction, it has allowed us to access the reactivity of the Met-bound heme. This derivative will become an important reference for direct comparison of the redox reactivity of the Met- and H_2O-bound hemes. A mutant lacking methionines in the coordination environment of the heme, Gly58Cys/Met60Ala/Met61Val, also labeled at the position 58, could serve as a model of the H_2O-bound heme. Further experiments to analyze conformational changes in the protein can be done with other mutants where labeling sites lie on the opposite side of the heme and away from Met60. These experiments, guided by our findings this summer, will be a direction for future research in the group.

Acknowledgements: R.E.C. (University of New Hampshire) is the recipient of The Norris-Richards Undergraduate Summer Research Scholarship. E.V. (Hamburg University) thanks the DAAD RISE program for the summer scholarship. We also thank Dr. Marianne Schiffer for providing the original GSU0935 plasmid for this work and Dr. Xiaomin Fang for her help in the initial stages of the project. These studies were supported by the ACS Petroleum Research Fund (E.V.P.).

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(3) Castellano, F. N.; Dattelbaum, J. D.; Lakowicz, J. R. "Long-lifetime Ru(II) complexes as labeling reagents for sulfhydryl

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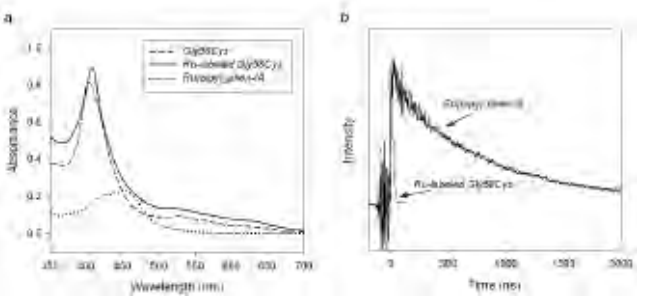
Figure 2



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Book Review

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sediments, and what such molecules indicate about the atmospheric conditions on early Earth.

A key premise of the book is stated explicitly in Chapter 9, "that a lot of genetic variation, and, presumably, evolutionary diversification can occur before it is expressed in morphological traits (page 229)." Scientists have historically studied fossils of ancient organisms in their quest to understand evolution. However, by studying ancient molecules and their prevalence throughout Earth's history, one learns that much about ancient organisms and their biochemical pathways is constantly evolving and changing. Only a small part of this change is captured successfully in morphological changes that can be detected in actual fossils.

The book is liberally sprinkled with tangential observations about scientific research. For example, scientist James Maxwell commented on how scientific research has changed since the 1960s. "Nowadays people have to focus on what they want to do because they've got to justify the money to someone who's got the whip on their back," Maxwell said, "But in those days you did what you wanted and you were just desperate to find out something new. Afterwards, in some cases – and it may have been luck, intuition, it may have been something else – it led to something. But most of the time you weren't aware of that (page 59)."

The authors highlight the sometimes-tense relationship between academic and industrial chemists. At annual Gordon Conferences, for example, the authors report that academic chemists willingly shared their research, whereas industrial chemists "would sit quietly in the back, eagerly soaking up whatever hot new ideas and information the academics had to offer, while the academics fumed because they suspected the industry scientists of harboring precisely the information and samples they needed to answer the questions at hand (page 81)."

While the book is overall a compelling read, there are a few shortcomings. First, the attempts to provide the necessary scientific background to non-scientists can verge into the overly simplistic and condescending. For example, when the authors describe the theory behind mass spectrometry, they write, "The mass spectrometer is… based on a rather juvenile impulse: the best way to see how something is put together is to break it apart (page 23)." Later in that paragraph, the authors compare mass spectrometry to shattering a tray of wine glasses, which is an analogy that may or may not hold true.

Moreover, the authors are telling a story of primarily *their* scientific discovery, of *their* encounters with other scientists, of *their* thoughts and of *their* research. The research of other scientists is covered in some detail in the various chapters, although many of these other scientists are those whom the authors know personally through various scientific conferences. As a result, the authors may completely ignore research performed by other scientists.

In particular, the chapter on meteorites, "From the Moon to Mars: The Search for Extraterrestrial Life," discusses the various amino acids found on carbonaceous meteorites such as the

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March Historical Events in Chemistry

by Leopold May, The Catholic University of America, Washington, DC

March 1, 1910
One hundred years ago, Archer J. P. Martin was born. He shared the Nobel Prize in Chemistry with Richard L. M. Synge in 1952 for their invention of partition chromatography.

March 3, 1876
Seventy-five years ago, Gregory P. Baxter and C. P. Alter determined the atomic weight of lead, which led to estimations of the age of minerals. Baxter was born on this date.

March 5, 1893
Emmett J. Culligan, who founded the world's largest water treatment organization, as well as discovering the concept of water softening, was born on this date.

March 7, 1792
John F. W. Herschel, inventor of photography on sensitized paper, was born on this day. He introduced the terms positive and negative for photography.

March 8, 1879
Otto Hahn discovered protactinium with Lise Meitner in 1917 and did research in nuclear fission with Otto Strassman. He received the Nobel Prize in Chemistry in 1944 for his discovery of the fission of heavy nuclei. He was born on this date.

March 12, 1900
Seventy-five years ago in 1935, Frédéric J. Joliot (Joliot-Curie) shared the Nobel Prize in Chemistry with his wife Irène Joliot-Curie, for production of artificial radioisotopes. In 1934, he, H. Halban, and L. W. Kowarski proved experimentally that neutron emission occurs in nuclear fission. He was born on this date.

March 13, 1733
Joseph Priestley, who was born on this date, was the discoverer of oxygen, ammonia, hydrochloric acid gas, carbon monoxide, sulfur dioxide, and oxides of nitrogen. He also made the first soda drink.

March 14, 1935
Seventy-five years ago, Julius B. Cohen died on this date. He was a researcher on the laws of aromatic substitutions and optical activity. He was born on May 6, 1859.

March 14, 1935
Seventy-five years ago, Arthur Hantszch died on this date. He was a researcher in electrical conductivity of organic compounds, organic acids and stereochemistry of nitrogen compounds. His birthdate was March 7, 1857.

March 17, 1803
In 1826, Carl Löwig was a discoverer of bromine but, because of examinations, did not publish a report, thereby allowing A. Balard to receive precedence of discovery. He was born on this date.

March 20, 1735
Two hundred and seventy-five years ago, Torbern Bergman was born on this date. He was a researcher on carbon dioxide, hydrogen sulfide and the preparation of artificial mineral water.

March 21, 1932
Walter Gilbert, researcher on the determination of deoxyribonucleic acid (DNA) base sequences; was born on this date. In 1980 he shared the Nobel Prize in Chemistry with Paul Berg and Frederick Sanger for their contributions concerning the determination of base sequences in nucleic acids.

March 22, 1788
Pierre J. Pelletier discovered quinine, strychnine, and other alkaloids; with Philip Walter, he obtained toluene by distilling pipe resin in 1836. He was born on this date.

March 23, 1962
Neil Bartlett made the first noble gas compound, XePtF6, on this date.

March 25, 1863
Simon Flexner isolated the common strain of dysentery bacillus, *Shigella dysenteriae* in 1899. He developed curative serum for cerebrospinal meningitis in 1907. He was born on this date.

March 27, 1847
One hundred years ago in 1910, Otto Wallach, a researcher on essential oils and terpenes, was awarded the Nobel Prize in Chemistry in recognition of his services to organic chemistry and the chemical industry by his pioneer work in the field of alicyclic compounds. He was born on this date.

March 28, 1861
George C. Pond, a chemistry teacher and preserver of the Priestley home in Pennsylvania, was born on this date.

March 30, 1920
Daniel E. Koshland, Jr., a researcher in the catalytic activity of enzymes and editor of *Science*, was born on this date.

March 31, 1860
One hundred and fifty years ago, Isidor Traube was born on this date. He founded capillary chemistry and did research on liquids and critical temperature, osmosis, surface tension and colloids (suspensions of nanometer-sized particles). In addition, he designed a viscometer and capillarimeter and in 1891 made the first systematic observation of the hydrophobic effect.

Additional historical events can be found at Dr. May's website, http://faculty.cua.edu/may/Chemistrycalendar.htm. ◇

Biography

Continued from page 5

tion products. He went on to use LIF for the detection of mold metabolites (aflatoxins) separated by chromatography, for detecting and quantitating analytes separated by capillary electrophoresis, and for measuring the behavior of single molecules in solutions at room temperature. He has consistently blazed new trails for chemical analysis, which has resulted in a number of awards including the National Medal of Science in 1983, the Welch Award in Chemistry in 1999, the Wolf Prize in Chemistry in 2005, and the Priestley Medal in 2010. He is also recognized for his teaching and mentoring, having received the James Flack Norris Award for Outstanding Achievement in the Teaching of Chemistry (2004), the George C. Pimentel Award in Chemical Education (2008), and the Presidential Award for Excellence in Science, Mathematics, and Engineering Mentoring (2009). ◇

Abstract

Continued from page 5

shifts in the infrared spectra of small molecules. Using the relatively new absorption technique of cavity ring-down spectroscopy, it is possible to measure the isotopic ratio of a few common elements with a precision that rivals that of mass spectrometry.[2,3] Moreover, a cavity ring-down spectrometer can be constructed that is robust, portable, inexpensive, and can run for months without calibration or maintenance. This advance opens the possibility of much more widespread applications of isotope ratio analysis for understanding the origins and provenances of chemical compounds — from geological and atmospheric to agricultural and medical samples.

1. T. W. Richards and M. E. Lembert, "The Atomic Weight of Lead of Radioactive Origin," *J. Am. Chem. Soc.* **36**, 1329-1344 (1914).
2. E. R. Crosson, K. N. Ricci, B. A. Richman, F. C. Chilese, T. G. Owano, R. A. Provencal, M. W. Todd, J. Glasser, A. A. Kachanov, B. A. Paldus, T. G. Spence, and R. N. Zare, "Stable Isotope Ratios Using Cavity Ring-Down Spectroscopy: Determination of $^{13}C/^{12}C$ for Carbon Dioxide in Human Breath," *Anal Chem.* **74**, 2003-2007 (2002).
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Book Review

Continued from page 14

Murchison meteorite, which fell in 1969. The research of marine chemist Professor Jeffrey Bada at the Scripps Institution of Oceanography is highlighted. Professor Bada investigated reports that the amino acids found on the meteorites contained some degree of L enantiomeric excess (*ee*), and concluded that such findings were likely a result of terrestrial contamination of the meteorite samples.

While this conclusion of Professor Bada's is reported in the book, the book ignores the large body of recent research that supports the opposing argument: that the amino acids found on the Murchison meteorite are extra-terrestrial in origin, and that the L *ee*'s are legitimately extra-terrestrial as well. For example, Professor Sandra Pizzarello has studied the isotopic composition of meteoritic amino acids to address this precise question; her research is not covered.

It is understood that organic geochemistry is an exciting and rapidly changing field of research, and that one book cannot cover the comprehensive body of research. However, the authors do a disservice to their readers by failing to cover both sides of this still-unsettled scientific debate.

In conclusion, this book is structured as a light-hearted narrative in the field of organic geochemistry. It is highly successful in providing an overview of organic geochemistry for the non-specialist, and is recommended for anyone interested in learning more about this exciting interdisciplinary field. ◇

Summer Internship

Continued from page 9

Professor Grubbs developed an air-stable catalyst that has found many applications. Metathesis is used daily in the chemical industry, mainly in the development of new pharmaceuticals and novel advanced plastic materials. Syntheses using olefin metathesis are:

- more efficient (fewer reaction steps, fewer resources required, less wastage),
- simpler to use (stable in air, at normal temperatures and pressures) and
- eco-friendly (non-injurious solvents, less hazardous waste products).

Poly(dicyclopentadiene)

Poly(dicyclopentadiene), abbreviated poly(DCPD), is an industrial polymer that is synthesized *via* ring-opening metathesis polymerization (ROMP) by Materia, Inc. The reaction is catalyzed by a ruthenium catalyst developed in the Grubbs research group at the California Institute of Technology. The polymerization is driven by the high ring strain of the monomer, dicyclopentadiene, causing the catalyst to irreversibly open one ring and add a new monomer unit to the chain. Also present in dicyclopentadiene is a less reactive olefin that causes individual polymer chains to crosslink into a network. This results in a high-strength material that is used in everything from tractor parts to baseball bats. I was pleased to make this polymer in the lab and learn the techniques of olefin metathesis and polymerization. ◇

Summer Scholar

Continued from page 12

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Weinberg Lectures

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March 30

Prof. Martin Burke (Univ. Illinois)
"The Prospect of Molecular Prosthetics: Small Molecules with Protein-Like Functions"
Boston College Merkert 130 4:00 pm

Prof. Purnendu Dasgupta (Univ. Texas at Arlington)
"Perchlorate, Wherefrom, Wherein and Where Do We go From Here? Re-emergence of Iodine Deficiency in the US?"
Tufts University Pearson Chemistry Building, Room P-106 4:30 pm

Mar 31

Dr. David Lambright,UMASS Medical School, Worcester,
"Structural insights into trafficking regulation by GTPases and phosphoinositides".
UMass Dartmouth, Building Group II, Room 115 4:00 pm

Notices for The Nucleus Calendar should be sent to:

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http://www.unh.edu/chemistry/seminars.html

March 2

Prof. James Whitten (Univ. Massachusetts, Lowell)
"Self-Assembled Monolayers and their Applications in Nanotechnology and Chemical Sensors"
Tufts Univ., Pearson Chemistry Building , Room P-106 4:30 pm

Barabara Li (Univ. of Melbourne)
TBA
Univ. of New Hampshire, Iddles, L103
11:10 am

Mar 3

Dr. Jane-Jane Chen, Harvard-MIT Division of Health Sciences and Technology (HST),
"Translational Control in Hemoglobin Synthesis and Erythropoiesis".
UMass Dartmouth, Building Group II, Room 115
4:00 pm

March 4

Dr. Sarah Petty (College of the Holy Cross)
Univ. New Hampshire, IddlesL 103
11:10 am

March 8

Prof. Jonathan Ellman (Univ. California, Berkeley)
"Development and Application of New Metal-Catalyzed Carbon-Carbon Bond Forming Reactions"
Boston College, Merkert 130 4:00 pm

Richard Weiss (Georgetown Univ.)
Brandeis, Gerstenzang 122 3:45 pm

March 9

Prof. Michael Best (Univ. Tennessee)
"Chemical Approaches to the Investigation of Protein-Membrane Binding Interactions using Synthetic Lipid Probes"
Boston College, Merkert 130 4:00 pm

Prof. Jonathan Ellman (Univ. Cal.,Berkeley)
Univ. of New Hampshire, Iddles, L103
11:10 am

March 10

Prof. John Caradonna (Boston Univ.)
Harvard, Pfizer Lecture Hall, MB -23
4:15 pm

Dr. Xudong Huang, Harvard Medical School/BWH ,
"Metal oxide nanoparticle exposure and Alzheimer's disease pathogenesis"
UMass Dartmouth, Building Group II, Room 115 4:00 pm

March 11

Prof. Michael Best (University of Tennessee)
"Chemical Approaches to the Investigation of Protein-Membrane Binding Interactions using Synthetic Lipid Probes"
Tufts Univ., Pearson Chemistry Building, Room P-106 4:30 pm

March 15

Jin Kim Montclare (Polytechnic Institute of NYU)
Host - Prof. Xu
Brandeis, Gerstenzang 122 3:45 pm

The Eli Lilly Symposium
Yoshito Kishi (Harvard)
TBA
Harvard, Pfizer Lecture Hall , MB-23 4:00 pm

March 18

Richmond Sarpong (Univ. California, Berkeley)
Title: TBA
MIT, 6-120 4:00 pm

March 22

Phil C. Baran (The Scripps Research Institute)
TBA
Harvard, Pfizer Lecture Hall , MB-23 4:00 pm

Paul Chirik (Columbia Univ.)
"Modern Alchemy: Base Metal Catalysis and Electron Structure"
Brandeis Gerstenzang 122 3:45 pm

March 23

Leon Wong (Univ. of Melbourne)
Univ. of New Hampshire, Iddles, L103
11:10 am

March 25

Bristol-Myers Squibb Lectures:
Andre Charette (Univ. Montreal)
TBA
Gregory Vite (Bristol-Myers Squibb)
TBA
MIT, 6-120 4:00 pm

W. E. Moerner (Stanford Univ.)
TBA
MIT, Room 6-120 5:00 pm

Prof. Guozhong Cao (Univ. Washington)
"Engineering Nanomaterials and Interfaces for Energy Conversion and Storage"
Boston College, Merkert 130 4:00 pm

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