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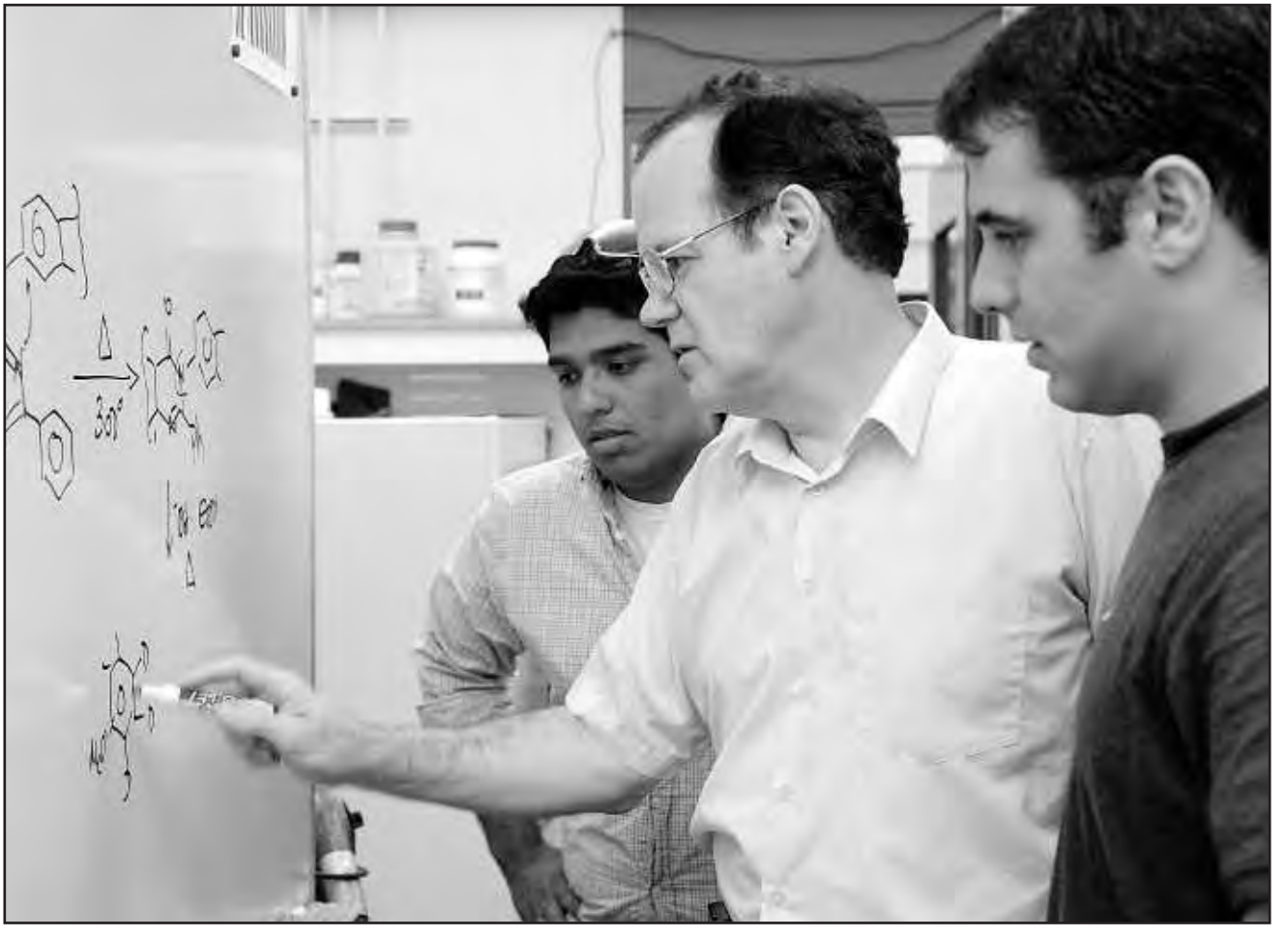
NESACS

THE NUCLEUS

April 2008 *Vol. LXXXVI, No. 8*



Monthly Meeting

Esselen Award Meeting at Harvard
Awardee: Professor John A. Katzenellenbogen

Richards Award Address

By Michael D. Pluth, Robert G. Bergman and Kenneth N. Raymond

Interviewing in the Bio-Pharma Industry

Part 1 - The Telephone Screen by Megan Driscoll

12th Andrew H. Weinberg Memorial Lecture

"The Evolution of Cancer Therapeutics" by David R. Parkinson, M.D.

Interviewing in the Bio-Pharma Industry

By Megan Driscoll, President, PharmaLogics Recruiting
www.PharmaLogicsRecruiting.com
www.MeganDriscoll.com

1st of a 4 part series:

Part 1 - The Telephone Screen
Part 2 - The Face-to-Face Interview
Part 3 - The Scientific Presentation
Part 4 - The Offer Stage

The Telephone Screen
Hiring Managers are evaluating you in 3 main areas during a phone interview:

1st - Your technical fit for the position

2nd - Your personality and fit for the group

3rd - Your verbal communication skills

How is the hiring manager assessing your technical fit for the position?

Hiring managers need to know that each candidate possesses the relevant technical skills necessary for the position. The keys to the technical questions that will be asked are in the job description.

Prior to the phone interview familiarize yourself with the bullets from the required skills section of the job description. Highlight the points in the job description where you see the words required and preferred and begin thinking of examples where you have experience with those skills. Write your answers out and keep them near the phone for your call. You will be asked about the required skills set, so don't be caught off guard about these inevitable questions.

If there are required skills listed in the job description that you do not have experience with, don't worry. Simply state that you are familiar with that skill and a quick learner, and that you are genuinely interested in developing that experience. Many hiring managers will overlook a lacking skill set if they are convinced the candidate is a fast learner and has a genuine interest in acquiring the knowledge in question.

How is the hiring manager evaluating personality?

50% of any job interview process is focused on a candidate's personality fit into the group. Although this will be more of a focus in a face-to-face interview, the interviewer will certainly be trying to get a feeling about personality over the phone.

Coming across likable over the phone can be difficult. In order to do this you must:

1- Match the style of the interviewer
2- Exhibit enthusiasm for the position and the company

Matching Style

The cue to the hiring manager's style will be in the way the person starts the conversation. If the interviewer gets right to business very quickly on the phone, you are dealing with someone who is matter-of-fact and possibly very busy. Do not try to lighten the call, just simply respond with the same serious approach to your answers.

If on the other hand the interviewer sounds very upbeat and starts the call by discussing personal matters, return the favor and try and open up a bit. If you feel high energy in the voice of the interviewer, you will want to be upbeat as well.

Show Enthusiasm

First, make sure you tell the interviewer that you are interested and excited about the position. Many candidates forget to actually say this during a phone interview.

Additionally, prior to the phone interview, at a minimum, go to the company website and look at the product portfolio. Familiarize yourself with not only the job description, but also how that position might fit in to the company's overall drug development pipeline. After viewing the product pipeline, scan the company's recent news section as well and work that information into the call. This will show you have done your homework.

continued on page 7

The Northeastern Section of the American Chemical Society, Inc.

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Contents

Cover: *Professor John A. Katzenellenbogen, 2008 Gustavus J. Esselen Award recipient, with two of his students (Photo courtesy of Professor Katzenellenbogen)*

Deadlines: *Summer 2008 Issue: June 16, 2008*
September 2008 Issue: July 14, 2008

THE NUCLEUS

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NESACS Election

Candidates for 2008

Candidate Statements will appear in the May Issue of the Nucleus.

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Trustee:

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May Meeting

Medicinal Chemistry Symposium

"Cost, Speed and Quality: Drug Discovery Outsourcing in Asia"

The May Medicinal Symposium titled "Cost, Speed and Quality: Drug Discovery Outsourcing in Asia." Will be held on May 14th (Wednesday, 8:30am ~ 5:30pm) at the Holiday Inn in Woburn, Massachusetts.

The costs associated with discovering and developing novel therapeutics have driven many companies to look for ways to trim costs without sacrificing the quality of the science behind their products. One avenue for achieving this goal has been to turn to contract research organizations (CROs) in Asia, who can do many (if not all) of jobs typically done here in the United States at a fraction of the cost and in a timely manner. Quite a few of the CROs in Asia are led by native scientists who received their formal training in the United States and worked in big/small Pharma or Biotech prior to returning to Asia. This shift in resources toward Asia is not surprising, given the large number of Asian scientists who work in the pharmaceutical industry, and has led to Asia becoming a research hub not unlike the United States and Europe. What are the drawbacks to this paradigm shift and what are the long-term benefits? These are some of the questions we would like to address on May 14th.

For the symposium we are bringing in speakers from local biotech and pharmaceutical companies doing business in Asia, and also bringing in some of the CROs from Asia, they are using. Dr. Ge Li, CEO of WuXi PharmaTech will be the key note speaker. Confirmed speakers include Dr. Michael Song of Beijing PharmaScience, Dr. C. S. N. Murthy of Aurigene Discovery Technologies, Dr. Rashmi H. Barbhaiya of Advinus Therapeutics Pvt Ltd, Mr. John V. Oyler of Bioduro, Dr. Aravind Y. Merwade, of Wockhardt Ltd, Dr. Chun-Lin Chen of MPI-Medicilon Research, and Dr. Kerry Spear from Sepracor in Marlborough, Massachusetts. ◇

Corporate Patrons ($2000+)

Abbott Laboratories
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Astra-Zeneca R&D Boston
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ZINK Imaging
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PCI Synthesis
Royal Society of Chemistry
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New Members

Invitation to attend a meeting

You are cordially invited to attend one of our upcoming Section meetings as a guest of the Section at the social hour and dinner preceding the meeting.

Please call Marilou Cashman at 800-872-2054, 508-653-6329 or: Mcash(at)aol.com by noon of the first Thursday of the month, letting her know that you are a new member. ◇

Looking for seminars in the Boston area?

Check out the NESACS Calendar

www.nesacs.org/seminars

Monthly Meeting

The 887th Meeting of the Northeastern Section of the American Chemical Society

Esselen Award Meeting

Thursday, April 17, 2008

Harvard University, Cambridge, MA
Harvard Faculty Club, 20 Quincy Street

5:30 pm Social Hour

6:30 pm Dinner

8:15 pm **Award Meeting**, Mallinckrodt Building, 12 Oxford Street
Pfizer Lecture Hall (MB23), Ground Floor

Dr. Marietta Schwartz, NESACS Chair, presiding

Welcome - Joseph A. Lima, Chair, Esselen Award Committee

The Esselen Award - Dr. Myron S. Simon, Founding Member of the Esselen Award Committee

Introduction of the Award Recipient - Dr. Elias J. Corey, Sheldon Emery Research Professor of Chemistry, Harvard University

Presentation of the Award - Gustavus J. Esselen, IV

Estrogens and Estrogen Receptors as a Nexus of Chemistry and Biology in Health and Disease - Dr. John A. Katzenellenbogen, Swanlund Professor of Chemistry, University of Illinois at Champaign-Urbana

Dinner reservations should be made no later than noon, Friday, April 11. Please call or fax Marilou Cashman at (800) 872-2054 or e-mail at MCash0953(at)aol.com. Reservations not cancelled at least 24 hours in advance must be paid. Members, $30.00; Non-members, $35; Retirees, $20; Students, $10.

THE PUBLIC IS INVITED

Anyone who needs special services or transportation, please call Marilou Cashman a few days in advance so that suitable arrangements can be made.

Free Parking in the Broadway Street Garage (3rd level or higher), enter from Cambridge Street via Felton Street. Directions to the Harvard Faculty Club can be found at http://www.hfc.harvard.edu/ .

Next Meeting: Education Night, May 20, 2008 ◇

Biography

John A. Katzenellenbogen graduated with an A.B. degree in chemistry from Harvard University in 1966 and continued at that institution for his graduate studies with Professor E. J. Corey, receiving his Ph. D. degree in 1969. He began and has continued his academic career at the University of Illinois at Urbana-Champaign, where he is now the Swanlund Chaired Professor of Chemistry.

Dr. Katzenellenbogen's research spans chemistry, biology, and medicine, and involves analysis of steroid receptor structure and function, and use of receptors and their ligands in various bioanalytical and biomedical applications. He prepared the first affinity labels and subtype-specific agents for estrogen receptors, and he has developed an extensive series of steroid receptor-based agents for imaging receptor-positive breast and prostate tumors by positron emission tomography (PET). He obtained the first PET images of breast and prostate tumors based on their content of steroid receptors, and he developed PET imaging-based hormone challenge tests to predict breast cancer patient response to endocrine therapies. He collaborates extensively with other researchers, both at the University of Illinois at Urbana-Champaign and elsewhere in the US and internationally. He has trained more than 100 doctoral and postdoctoral students and published more than 400 articles.

In service to the scientific community, Dr. Katzenellenbogen has been

continued on page 6

Abstract

Estrogens and Estrogen Receptors as a Nexus of Chemistry and Biology in Health and Disease

Estrogens are steroidal and non-steroidal hormones that have diverse actions in both reproductive and non-reproductive tissues, regulating both normal physiological processes and pathologies, including breast cancer. These hormones act through the estrogen receptor, which is a ligand-modulated transcription factor that regulates hundreds of genes in target tissues. When estrogens bind to the estrogen receptor, they stabilize specific conformations that reflect their size and shape. The rigidified external surface features of the ligand-receptor complex then serve as specific docking sites for coregulators, thereby altering the rates of target gene transcription and controlling cell phenotypic properties.

Using X-ray crystallography and molecular modeling as a guide, we have developed modular methods for the synthesis of non-steroidal estrogens, adaptable to combinatorial approaches, through which we have prepared a number of estrogens of novel structure that are highly selective

continued on page 6

Biography

Continued from page 5

a member of the Editorial Boards of *Biochemistry*, the *Journal of Medicinal Chemistry*, the *Journal of Receptor and Signal Transduction Research*, *Bioconjugate Chemistry*, the *Journal of Organic Chemistry*, *Molecular Endocrinology*, and the *Journal of Korean Medicinal Chemistry*. He is currently an Associate Editor of *Steroids* and the *Journal of Nuclear Medicine*. He has served on and chaired grant review panels for the National Institutes of Health, the Department of Energy, and the U.S. Army Medical Research Command. He serves on the National and Midwest Councils of the American Academy of Arts and Sciences.

His honors include Fellow of the American Association for the Advancement of Science, Fellow of the American Academy of Arts and Sciences, three NIH MERIT awards, the Paul C. Aebersold Award from the Society of Nuclear Medicine, Cope Scholar Award from the American Chemical Society, Roy O. Greep Lectureship Award from The Endocrine Society (jointly with Benita S. Katzenellenbogen), and the E. B. Hershberg Award for Important Discoveries in Medicinal Chemistry from the American Chemical Society.◇

Abstract

Continued from page 5

for only one of the two estrogen receptor subtypes, ERa or ERb. Because these receptors have different tissue distributions and different biological functions, these selective ligands are proving to be useful as pharmacological probes of the functions of the two different ERs. We have also diversified the structure and elemental composition of ER ligands, introducing three-dimensional core elements and replacing a carbon-carbon double bond with a boron-nitrogen bond. Some of these ligands have unexpected biological selectivities that could be medically important. We have also prepared dendrimer-bound estrogens that can be used to activate selectively rapid non-genomic estrogen signaling.

Elevated levels of steroid receptors are found in many tumors, and these receptors serve as key targets for endocrine therapies that can often be very effective, with minimal side effects. We have designed high affinity receptor ligands, labeled with the positron-emitting radionuclide fluorine-18, for positron emission tomographic (PET) imaging of these tumor receptors. This non-invasive determination of receptor levels in the tumors provides valuable information in selecting both breast and prostate cancer patients most likely to benefit from endocrine therapy. In addition, a hormone challenge test which images hormone-induced changes in tumor metabolism is proving highly predictive of response to endocrine therapies in breast cancer.

These chemical, biochemical, and structural studies on estrogen receptors and their ligands are providing new insights into the broad functions of these receptors in biology and medicine.◇

Call for Papers

NSCRC

Northeast Student Chemistry Research Conference 2008

Open to undergraduates, graduates, and postdoctoral fellows in all areas of chemical research

Saturday, April 19th, 2008

MIT

The Ray and Maria Stata Center

Visit the NESACS YCC website for more details at www.nsycc.org .

Abstracts will be accepted on this site. There is no registration fee.

Students are invited to present a poster or a 15 minute oral presentation.

Deadlines:
Oral presentation: April 8th, 2008
Poster presentations: April 10th, 2008◇

Interviewing

Continued from page 2

How is the hiring manager assessing your communication skills?

Verbal communication is a key component of the phone screen evaluation. The two questions a hiring manager is asking are: Can you answer questions clearly and concisely? Are you able to give more than just yes and no answers?

Be mindful of rambling, but make sure that every answer you give is elaborated on. I often hear from hiring managers that when a candidate answers in solely yes or no's, they automatically question their aptitude. Conversely, if you do all the talking and some of it seems aimless, hiring managers will also question your aptitude. The best way to avoid this is to have prepared examples of your skills written out and next to the phone. This should keep you on point and prevent you from being too verbose.

Final Points:

- As a rule, listen more than you talk.
- Try to find a private place where you are not worried about others listening to your conversation. If you are in a cube, this may mean that you would need to schedule calls before or after the work day. Interviewers would rather accommodate a time before or after work than deal with cryptic or half answers.
- Know that a call from HR will be very different than a call from a hiring manager. The HR call will be more about you personally, while the hiring manager will be more about your technical background.
- Try to take the call from a land line. Cell phone usage has become very popular, but cell coverage is still inconsistent and the clarity of a cell line is not yet as clear as a land line. There is nothing more annoying than to be speaking to someone and have it be broken up or, worse, disconnected.

If you are interested in learning more interviewing techniques, please visit www.megandriscoll.com, ◇

Fifth Annual Northeast Student Chemistry Career Fair

Thursday, April 24, 2008

3PM – 7PM

Brookline Holiday Inn

1200 Beacon Street, Brookline, MA

Register to participate:

ACS Career Services workshops on resume writing and interviewing skills will be performed on-site. Have your resumé reviewed.

Job Fair –
Meet with representatives from companies in the Northeast about employment opportunities. Hand deliver your resumé to company scientists and HR representatives.

Last Year
Over 110 resumé submissions
12 companies recruiting new hires
Come, network with your future colleagues

Corporate sponsorship inquiries: 617-304-6474, Leland Johnson leland.johnson(at)nyscc.org.

FREE ONLINE REGISTRATION
(Returnable Deposit): ***Please register*** *at the Northeastern Section Younger Chemists Committee website: www.nsycc.org*

Participating companies *and all* ***details*** *will be listed.*

April Historical Events In Chemistry

by Leopold May
The Catholic University of America, Washington, DC 20064

April 2, 1877
Carl L. Alsberg, who was born on this date, was a researcher in the chemistry of food.

April 5, 1827
Joseph Lister, who introduced antiseptics, such as carbolic acid (phenol), was born on this date.

April 6, 1927
Edmond H. Fischer, who was born on this date, is a researcher on protein phosphorylation as a biological regulatory mechanism. In 1992, he shared the Nobel Prize in Medicine with Edwin G. Krebs for their discoveries concerning reversible protein phosphorylation as a biological regulatory mechanism.

April 8, 1911
Melvin Calvin, who received the Nobel Prize in Chemistry in 1961 for his research in photosynthesis, was born on this date.

April 10, 1863
Paul Louis Toussaint Héroult, born on this date, discovered the electrolytic aluminum process in 1886, the same year that Charles Martin Hall discovered the same process for isolating aluminum, which is called the Hall-Heroult process. In 1900, He invented the electric arc furnace for steel, which replaced some giant smelters for the production of a variety of steels.

April 11, 1799
Humphry Davy discovered nitrous oxide, laughing gas on this date.

April 12, 1773
Thomas Thompson, who was born on this date, invented the instrument known as Allan's saccharometer. He identified a zeolite mineral named thomsonite; promoted Dalton's atomic theory and Prout's hypothesis in his journal *Annals of Philosophy* and his book *System of Chemistry*.

April 14, 1969
NASA's Nimbus III weather satellite made the first civilian use of nuclear batteries on this day.

April 16, 1838
Ernest Solvay, born on this date, developed the Solvay process for making commercial soda cheaply.

April 18, 1924
Quantum Chemical incorporated as National Distillery Products Corp. on this day.

April 19, 1912
Fifty years ago in 1958, Glenn T. Seaborg codiscovered nobelium. He was born on this date and shared the Nobel Prize in Chemistry in 1951 with Edwin M. McMillan. He also co discovered americium, 1944, berkelium, 1950, californium, 1950, curium, 1944, einsteinium, 1952, fermium, 1953, mendelevium, 1955, plutonium, 1940, and element 106, 1974.

April 21, 1970
The first Earth Day was founded by Sen. Gaylord Nelson, Father of Earth Day and organized by Denis Hayes and celebrated on this day. It is celebrated by ACS on April 22.

April 23, 1858
One hundred and fifty years ago, Max K. E. L. Planck was born on this date. In 1900, he introduced the quantum theory and was awarded the Nobel Prize in Physics in 1918 in recognition of the services he rendered to the advancement of Physics by his discovery of energy quanta.

April 25, 1900
Wolfgang Pauli, who was born on this day, received the Nobel Prize in Physics in 1945 for the discovery of the Exclusion Principle, also called the Pauli Principle.

April 26, 1775
Antoine L. Lavoisier reported that heating mercury in air forms red calx, HgO, while the air is reduced in volume and no longer supports combustion. He heated red calx to liberate oxygen.

April 28, 1941
K. Barry Sharpless, born on this date, discovered and developed many catalytic oxidation processes for stereoselective oxidation. He shared the Nobel Prize in Chemistry in 2001 with William S. Knowles and Ryoji Noyori for their work on chirally catalyzed hydrogenation reactions

April 29, 1904
Nashua incorporated as Nashua Card, Gummed & Coated Paper on this day.

April 30, 1958
Fifty years ago, Albert Ghiorso, et al., announced the discovery of mendelevium based upon research done at the University of California, Berkeley.

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

The 12th Annual Andrew H. Weinberg Memorial Lecture

This annual event highlights the achievements and focuses on the development of new strategies for the treatment of cancer patients

David R. Parkinson, M.D.

President and CEO, Nodality, Inc.

The Evolution of Cancer Therapeutics

Wednesday, April 9th, 2008, 4:00pm

Sponsored by the Andrew H. Weinberg Endowment at Dana-Farber, Team Andrew, the Jimmy Fund Walk
and in part by the Medicinal Chemistry Group, Northeastern Section of the American Chemical Society

Dana-Farber Cancer Institute
1 Jimmy Fund Way, Smith Building, room 308/309
Boston, MA 02115

For more information, please contact Caleb King at 617-632-2072 or caleb_king@dfci.harvard.edu

Abstract

The Evolution of Cancer Therapeutics

The development of improved cancer therapy remains a slow, inefficient and risky process, despite the remarkable ongoing advances in our understanding of cancer biology as well as improvements in the industry's ability to create novel biologically-targeted novel therapeutic agents. This situation will continue until our concept of clinical therapeutics development evolves into a more complete set of biological characterizations of individual patient's relevant tumor biology with the measured effects of particular therapies on that biology, linked with clinical outcome. Only with this manner of approach, which requires fundamental changes in how clinical trials are designed, resourced, executed, and analyzed, will we learn incrementally more from each patient studied in each trial. The increased information obtained per patient allows for changed study designs and should result in more efficient focused therapeutics development and drug approvals based on greater clinical activity of drugs in biologically appropriate patients, with improved therapeutic index. Recent examples of the benefits of such an approach and the perils of not proceeding in this manner will be reviewed. The implications of this new "personalized" approach on malignancy classification, therapeutics development strategy, academic and industry approaches to the organization, resourcing, and conduct of clinical research, together with regulatory and reimbursements, will be considered. The promise of this new approach, where strategic intent transcends classical "translational medicine" activities, promises the more rapid development of agents more predictably effective in patients with cancer.◇

Biography

David Parkinson is President and CEO of Nodality, a South San Francisco-based biotechnology company focused on the biological characterization of signaling pathways in patients with malignancy to enable more effective therapeutics development and decision-making. Until recently Dr. Parkinson was Senior Vice President, Oncology Research and Development at Biogen Idec. At Biogen he oversaw all oncology discovery research efforts and the development of the oncology pipeline. Previously he had served as Vice President, Oncology Development, at Amgen and Vice President, Global Clinical Oncology Development at Novartis. During his tenures at Amgen and Novartis, Dr. Parkinson was responsible for clinical development activities leading to a series of successful global drug registrations for important cancer therapeutics, including Gleevec, Femara, Zometa, Kepivance, and Vectibix.

Dr. Parkinson worked at the National Cancer Institute from 1990 to 1997, serving as Chief of the Investigational Drug Branch, then as Acting Associate Director of the Cancer Therapy Evaluation Program, before leaving for Novartis. He has also held academic positions at the M.D. Anderson Cancer Center, University of Texas and New England Medical Center of Tufts University School of Medicine.

He received his M.D. as gold medalist from the University of Toronto Faculty of Medicine in 1977, with Internal Medicine and Hematology/Oncology training in Montreal at McGill University and in Boston at New England Medical Center. Dr. Parkinson is a past Chairman of the Food & Drug Administration (FDA) Biologics Advisory Committee and is a recipient of the FDA"s Cody Medal. He is a past President of the Interna-

continued on page 18

Richards Award Address

Selective Organic and Organometallic Reactions in Water-Soluble Host-Guest Supramolecular Systems

Michael D. Pluth, Robert G. Bergman and Kenneth N. Raymond
Department of Chemistry, University of California, Berkeley, and
Division of Chemical Sciences, Lawrence Berkeley National Laboratory, Berkeley, CA 94720-1460 USA

Introduction

Carbon-hydrogen (C-H) bond activation has become a major area of research activity in both organometallic and synthetic organic chemistry. Our group's research in this area dates from initial experiments in the early 1980's, and in the intervening time, extensive studies have been carried out designed to explore the scope of metal-mediated C-H activation and to understand its mechanism.

One goal of C-H activation research has been not simply to find new C-H activation reactions, but to obtain an understanding of them that will allow the development of reagents capable of *selective* transformations of C-H bonds into more reactive functionalized molecules. Some selectivity in C-H bond activation occurs due to the inherent nature of the bonds being cleaved. Although authors in this field often refer to C-H bond dissociation energy (BDE) as a potential selectivity-controlling factor, one can make the case that either acidity or the strength of the metal-carbon bond that is formed upon activation are more important factors in determining the relative rates of activation of different types of C-H bonds. An example of this is the long-known fact that aryl and vinyl C-H bonds, which are known to have much higher BDE's than alkyl C-H bonds, are often activated more readily by transition metal reagents.

Furthermore, the inherent selectivity-determining properties of C-H bonds are often weak, leading to mixtures of products that typically form in many C-H bond activation reactions. Accordingly, many workers, especially those seeking synthetically useful applications, have turned to the directing effects of neighboring functional groups as a means of making C-H activation reactions more selective, especially in catalytic processes. However, this approach poses many problems in itself, not the least of which is the requirement for installing the directing group at the specifically required position in the molecule to be activated.

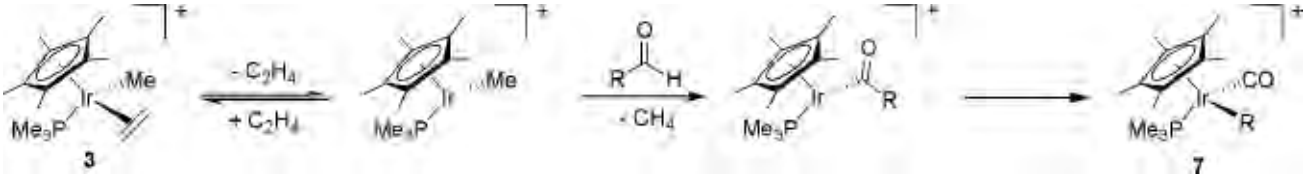
A different approach to obtaining selectivity in C-H activation reactions, which is potentially generalizable to other types of reactions, is to utilize a binding pocket in a host molecule which has an appropriate size and/or shape to achieve reactivity between different molecules and even between different locations in the same molecule. This principle is the one that nature employs, using enzymes to activate otherwise unreactive compounds or to functionalize particular positions in molecules (in some cases, by activating C-H bonds) in remarkable ways; two examples are cytochrome P450 and methane mono-oxygenase.

Inspired by the efficiency and selectivity of enzymes, synthetic chemists have designed and prepared a wide range of host molecules that can bind smaller molecules with their cavities; this area has become known as "supramolecular" or "host-guest" chemistry. Pioneered by Lehn, Cram, Pedersen, and Breslow,[1-3] and followed up by a large number of more recent investigators, it has been found that the chemical environment in each assembly – defined by the size, shape, charge, and functional group availability – greatly influences the guest-binding characteristics of these compounds.[4-9]

In contrast to the large number of binding studies that have been carried out in this area, the exploration of chemistry – especially catalytic chemistry - that can take place inside supramolecular host cavities is still in its infancy. For example, until the work described here was carried out, very few examples of organometallic reactivity inside supramolecular hosts were known, especially in water solution. For that reason, our group and the group directed by Kenneth Raymond decided to take advantage of our complementary expertise and attempt to carry out metal-mediated C-H bond activation reactions in water-soluble supramolecular systems. This article begins by providing background from the Raymond group in supramolecular coordination chemistry and the Bergman group in C-H bond activation. It goes on to report the results of our combined efforts in supramolecular C-H activation reactions, followed by extensions of this work into a wider range of intracavity transformations.

Coordination chemistry of tetrahedral supramolecular cluster systems

In the last decade, the Raymond group has made efforts toward understanding how encapsulation of molecules within a synthetic host molecule affects the selectivity and reactivity of the guest. A number of host molecules of the stoichiometry M_4L_6 (M = Ga^{III} (**1**), Al^{III}, In^{III}, Fe^{III}, Ti^{IV}, or Ge^{IV}, L = *N,N-bis*(2,3-dihydroxybenzoyl)-1,5-diaminonaphthalene) (Figure 1) have been developed.[10-13] The M_4L_6 assembly is a well-defined, self-assembling tetrahedron formed from metal-ligand interactions with the ligands spanning each edge and the metal ions occupying the vertices. The *tris*-bidentate coordination of the catechol amides at the metal vertices makes each vertex a stereocenter and the rigid ligands transfer the chirality of one metal vertex to the others, thereby forming the homochiral $\Delta\Delta\Delta\Delta$ or $\Lambda\Lambda\Lambda\Lambda$ configurations.[14, 15] While the -12 overall charge imparts water solubility, the interior cavity is defined by the naphthalene walls, thereby providing a hydrophobic environment that is isolated from the bulk aqueous solution. Initial studies of host formation and guest encapsulation focused on small tetra-alkylammonium cations such as NEt_4^+. Making use of the hydrophobicity and polyanionic



Scheme 1 Mechanism for C-H bond activation of aldehydes by **3**.

charge of **1**, a number of highly reactive cations have been kinetically stabilized by encapsulation. These include tropylium,[16] iminium,[17] diazonium,[18] and reactive phosphonium species,[19] all of which decompose rapidly in water and are normally stable only under anhydrous or highly acidic aqueous conditions.

Figure 1 Left: A schematic of the M_4L_6 assembly with only one ligand shown for clarity. Center: A model of **1** with encapsulated NEt_4^+. Right: A space-filling model of **1** as viewed down the aperture coincident with the 3-fold axis.

Although thermodynamically stable within **1**, encapsulated guests are able to exchange with other guests in solution.[20, 21] The activation barrier for guest ejection is dependent on the size of the guest. Despite the hemi-labile coordination of the catechol oxygens at the metal vertices, the assembly remains intact during the guest exchange process. During this process, the apertures coincident with the 3-fold axis of **1** dilate to allow for guest ingress and egress.

As will be discussed in this article, the fundamental host-guest chemistry of **1** has been elaborated to include both stoichiometric and catalytic reactions. The constrained interior and chirality of **1** allows for both size– and stereo– selectivity.[22-26] Additionally, **1** itself has been used as a catalyst for the sigmatropic rearrangement of enammonium cations[27, 28] and the hydrolysis of acid-labile orthoformates and acetals.[29, 30] The assembly itself is used to catalyze reactions that either require preorganization of the substrate or contain high energy reactive species that can be stabilized in **1**.

Chemistry of Organometallic Guests

To explore the possibility of carrying out organometallic chemistry inside the cavity of the clusters discussed above, we initially targeted the iridium-mediated C-H activation reactions of the complex [Cp*(PMe_3)Ir(Me)OTf] (**2**), which have been developed and extensively studied by the Bergman group.[31-35] This complex thermally activates C-H bonds of a variety of molecules such as aldehydes, ethers, and hydrocarbons, including methane. Dissociation of the labile triflate ligand from **2** gives the reactive monocationic intermediate [Cp*(PMe_3)Ir(Me)]$^+$ (Scheme 1). This cationic species or its solvent adduct should be an ideal candidate for encapsulation in **1**. However, addition of **2** to an aqueous solution of **1** did not afford a host-guest complex, presumably because the aquo species Cp*(PMe_3)Ir(Me)(OH_2)$^+$ is too highly solvated. In order to circumvent this problem, the more hydrophobic olefin species Cp*(PMe_3)Ir(Me)(h^2-olefin)$^+$ (olefin = ethylene (**3**), *cis*-2-butene (**4**)) were prepared and introduced to **1**. These species formed host-guest complexes [**3** Ì **1**]$^{11-}$ (**5**) and [**4** Ì **1**]$^{11-}$ (**6**), stabilized by the higher hydrophobicity of these guests as well as the potential π-π interactions between the coordinated olefin and the π-basic naphthalene walls of **1**.

In order to generate the active iridium species, dissociation of the coordinated olefin was required. Gentle heating of the host-guest complex (45 °C for **6**, 75 °C for **5**) facilitated olefin dissociation and allowed for C-H bond activation of the substrates to occur. Upon addition of acetaldehyde to the iridium host-guest complex, new resonances corresponding to the encapsulated [Cp*(PMe_3)Ir(CO)(Me)]$^+$ complex (**7,** R = Me) were observed. A variety of aldehydes were added to the host-guest complex to probe the reactivity inside **1**. Interestingly, both size and shape selectivity are observed. Small aldehydes, such as acetaldehyde, are readily activated whereas large aldehydes, such as benzaldehyde, are too large to fit inside the cavity. In the absence of **1**, both acetaldehyde and benzaldehyde undergo C-H bond activation. However, when the same experiment is performed with the encapsulated complex, only acetaldehyde undergoes C-H bond activation while benzaldehyde remains unreacted, confirming that the reaction is occurring in **1**.

A representative range of aldehydes activated by **4** in **1** is shown in Table 1.[24, 25]

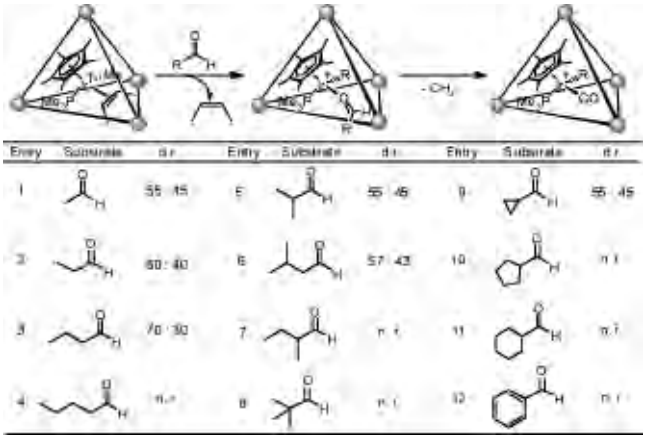


Table 1 Diastereoselectivites for C-H bond activation of aldehydes by **6**.

continued on page 12

Richards Award

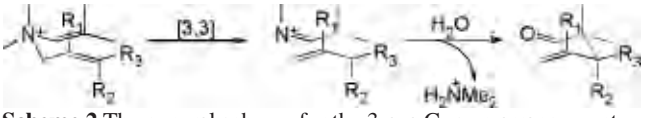
Continued from page 11

In addition to the expected size effects, small changes in the shape of the aldehydes have a dramatic influence on the reactivity with the encapsulated host-guest complex (Table 1). For example, the host-guest complex reacts with isobutyraldehyde (entry 5) with a lower diastereoselectivity than with butyraldehyde (entry 3). This may be due to the more spherical shape of the isobutyraldehyde complex when compared to the butyraldehyde complexes. Even more striking is the fact that 3-methylbutyraldehyde reacts easily with **1**, whereas no reaction is observed with its 2-methyl isomer (entries 6 and 7), in spite of the fact that these two molecules have the same molecular weight.

The Assembly as a Catalyst: Electrocyclic Rearrangements

Two possible approaches to the use of assemblies such as **1** as a catalyst are to encapsulate a catalyst in the cavity, or to use the synthetic host molecule itself as the catalyst. The latter approach draws direct inspiration from enzyme catalysis, and it is the one that we have made most progress on so far. One benefit of binding substrates in a finite cavity is the increased encounter frequency of the bound molecules, which may also be thought of as an increased local concentration. For example, Rebek and co-workers have observed a 200-fold rate acceleration through encapsulation in the Diels-Alder reaction of benzoquinone with cyclohexadiene mediated by a hydrogen bonded, self-assembled "softball."[36, 37] Unfortunately, a problem that often plagues such systems is that the high binding affinity of the product for the cavity prevents catalytic turnover. In cases where such product inhibition is observed, choosing different reactants can often lower the binding affinity of the product. For example, in the Rebek system, the use of a different dienophile, 2,5-dimethyl-thiophene dioxide, provided a product with a lower binding affinity than the substrate, thereby allowing for catalytic turnover.[38] Similarly, Fujita and co-workers have used organopalladium cages to affect the reactivity and selectivity of Diels-Alder reactions occurring within the molecular host.[39, 40]

In order to use **1** itself as a catalyst, a chemical transformation of a monocationic substrate which is compatible with the supramolecular host needed to be identified. Ideally, the reaction would either produce a weakly bound product or a product that could undergo further reaction in solution to prevent its re-encapsulation in **1**. The utility of tetra-alkyl ammonium cations as guests prompted a search for similar but more chemically reactive guests. An attractive class of candidates is enammonium cations associated with the 3-aza Cope rearrangement.[41-43] The 3-aza Cope (or aza Claisen) reaction is a member of the [3,3] class of sigmatropic rearrangements and occurs thermally in *N*-allyl enamine systems with varying degrees of ease. Neutral allylic enamines thermally rearrange to δ-ene imines at elevated temperatures (170-250 °C); however, the corresponding quaternized molecules require much milder conditions (20-120 °C).[44-46] The subsequent iminium product undergoes spontaneous hydrolysis in water to the corresponding γ,δ-unsaturated aldehydes. Since neutral molecules are only very weakly bound by **1**, hydrolysis of the iminium product should circumvent product inhibition and allow for catalytic turnover (Scheme 2).



Scheme 2 The general scheme for the 3-aza Cope rearrangement. The enammonium cation undergoes a [3,3] sigmatropic rearrangement to form an iminium cation which can be hydrolyzed in water to the associated aldehyde and dimethyl ammonium.

In order to determine if encapsulation in **1** affected the rate of the unimolecular rearrangement, a variety of enammonium cations were prepared and the rates of rearrangement were measured for the free and encapsulated reactions. Encouragingly, in all cases, the encapsulated substrates rearranged faster than in the un-encapsulated reaction with the largest rate acceleration reaching almost three orders of magnitude (Table 2).[27, 28] Interestingly, intermediately sized substrates appear to be an "optimal fit" in **1** and show the largest rate accelerations. Larger or smaller substrates are still accelerated by **1** but to a lesser extent. As was also observed in the C-H bond activation of aldehydes, both shape and size selectivity are observed. For example, com-

Table 2 Substrate scope and rate constants for the free (k_{free}) and encapsulated (k_{encaps}) rearrangements.

Entry	Substrate	Product	k_{free} (s^{-1})	k_{encaps} (s^{-1})	$\frac{k_{encaps}}{k_{free}}$
1			3.49×10^{-5}	16.3×10^{-3}	5
2			7.61×10^{-5}	198×10^{-5}	26
3			3.17×10^{-5}	446×10^{-5}	141
4			4.04×10^{-5}	135×10^{-4}	90
5			1.69×10^{-5}	74.2×10^{-5}	150
6			0.37×10^{-5}	316×10^{-5}	44
7			3.97×10^{-5}	222×10^{-5}	854
8			0.033×10^{-5}	1.17×10^{-5}	56
9			6.3×10^{-5}	331×10^{-5}	35
10			3.48×10^{-4}	16.3×10^{-2}	53

Richards Award

Continued from page 12

paring the Z- and E- substitution isomers (entries **3, 4** and **5, 6** in Table 2) shows an increased acceleration for the E- isomers.

Having established that **1** catalyzes the unimolecular rearrangement, the origin of this acceleration was investigated. Addition of a strongly-binding guest, NEt_4^+, to **1** inhibited the catalysis suggesting that the interior of **1** was catalyzing the reaction. Control experiments of the rearrangement in different solvents showed no dependence on solvent polarity, suggesting that the hydrophobic interior of **1** was not the primary contributor to the acceleration. The prospect that the high negative charge of **1** was causing the rate acceleration was ruled out by adding salt (2 M KCl) in the absence of the assembly, which did not result in a notable increase in rate for the free rearrangement.

In order to probe the kinetics of the reaction in **1**, the activation parameters were measured for three substrates for the free and the encapsulated rearrangements (Table 3). The obtained parameters for the free rearrangement of the ethyl-substituted substrate, for example, are ($D\mathit{H}^{\ddagger}$ = 23.1(8) kcal/mol and $D\mathit{S}^{\ddagger}$ = -8(2) eu) and are similar to those reported in the literature for related systems. This negative entropy of activation suggests an organized transition state is required for the rearrangement. To ensure that this negative entropy of activation was not an artifact of solvation changes specific to the aqueous medium, the activation parameters for this material were also measured in C_6D_5Cl, again revealing a negative entropy of activation. The encapsulated reaction in water gave an identical enthalpy of activation ($D\mathit{H}^{\ddagger}$ = 23.0(9) kcal/mol); however, the entropy of activation differed remarkably by almost 10 eu ($D\mathit{S}^{\ddagger}$ = +2(3) eu), suggesting preorganization of the encapsulated substrate by **1**.

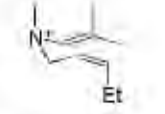
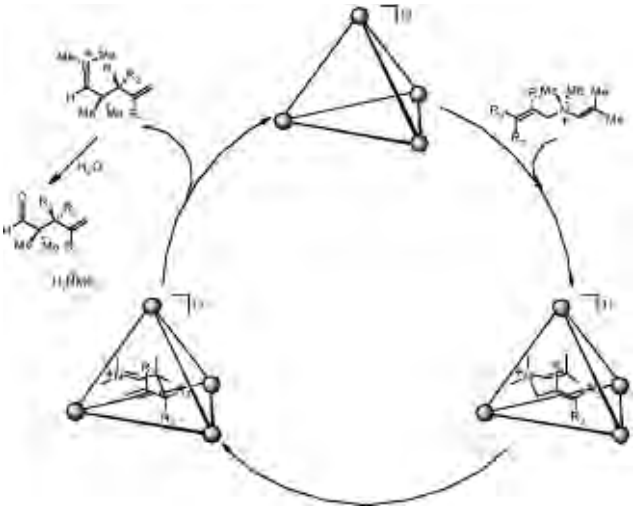
Entry	Substrate	solvent	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal mol^{-1} K^{-1})
1		D_2O	23.1(8)	-8(2)
2		C_6D_5Cl	23.4(5)	-5(2)
3		encaps.	23.0(9)	+2(3)
4		D_2O	23.0(4)	-10(1)
5		encaps.	21.8(7)	-5(2)
6		D_2O	23.6(3)	-11(1)
7		encaps.	22.6(9)	-1(2)

Table 3 Summary of activation parameters for the sigmatropic rearrangement of free and encapsulated substrates.

Analysis of the activation parameters for the different encapsulated substrates reveals that the source of catalysis is more complex than simply a reduction of the entropy of activation, since different effects are observed for these substrates. While the rate acceleration in entry 1 was exclusively due to lowering the entropic barrier, for entries 2 and 3; a decrease in the enthalpic barrier for rearrangement is observed in addition. It is possible that, for entries 2 and 3, binding into the narrow confines of the metal-ligand assembly induces some strain on the bound molecules, thereby raising their ground-state energies compared to those of the unbound substrates. The changes in $D\mathit{S}^{\ddagger}$ suggest that encapsulation selects a preorganized conformation of the substrate which facilitates the rearrangement as shown in the mechanism for rearrangement and hydrolysis in **1** (Scheme 3). The space-restrictive host cavity allows for encapsulation of only tightly packed conformers that closely resemble the conformations of the transition states. The predisposed conformers, which have already lost several rotational degrees of freedom, are selected from an equilibrium mixture of all possible conformers, causing the entropic barrier for rearrangement ro decrease. The lower enthalpic barrier for rearrangement in **1** is realized by the added strain that is induced by squeezing the ground state into the tight cavity. The strain becomes more significant for the larger substrates, allowing for a noticeable decrease in $D\mathit{H}^{\ddagger}$ when the optimal fit of the reactant transition state in the host cavity is exceeded, the rate accelerations become attenuated as seen in entries 8 and 9 of Table 2.



Scheme 3 Mechanism for the [3,3] aza-Cope rearrangement of enammonium substrates in **1**. Hydrolysis of the iminium product leads to catalytic turnover.

Analysis of 2D NOESY spectra of encapsulated enammonium substrates in **1** also suggests that the host assembly can selectively bind preorganized, reactive conformations of the substrates. The hypothesis of substrate preorganization upon encapsulation was further investigated using quantitative NOE growth rate experiments which allowed for the conformation of the encapsulated substrates to be determined.[47] These studies, carried out on the ions shown in Fig. 2, and revealed that the ground state conformations of the substrate in **1** resembled the chair-like transition state for the rearrangement (Figure 2), thereby confirming the lowered entropic activation barrier for the rearrangement of the

Richards Award

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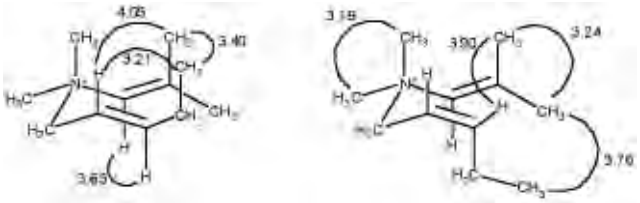


Figure 2 Intramolecular distances as determined by NOE buildup studies. Distances between methyl groups refer to a pseudoatom located at the average location of the three hydrogen atoms.

encapsulated substrate is to the preorganization of the substrate upon encapsulation.

Stabilization of Conjugate Acids of Phosphines and Amines by Encapsulation.

Following the successful use of **1** as a catalyst for the unimolecular rearrangement of enammonium substrates, the further potential of **1** as a catalyst was explored. Given the propensity of **1** to preferentially bind cations over neutral guests, it was hoped that **1** could catalyze reactions that contained a cationic transition state. An ideal candidate for this type of reaction is the class of hydrolysis reactions that occur through an acid-catalyzed pathway. The subsequent protonated substrate or high-energy species on the reaction coordinate should be stabilized by **1**, hopefully leading to catalysis. Extension to this class of reactions would be significant because it would allow for catalysis of neutral substrates, thereby greatly increasing the potential scope of possible substrate for catalysis.

A common method used by nature to activate otherwise unreactive compounds is the precise arrangement of hydrogen-bonding networks and electrostatic interactions between the substrate and adjacent residues of the protein.[48] Electrostatic interactions alone can greatly favor charged states and have been responsible for large pK_a shifts of up to 5 pK_a units, as seen in acetoacetate decarboxylase.[49] A number of reports in the literature have documented synthetic chemists' approaches to mimicking such pK_a shifts. Synthetic host molecules such as cyclodextrins and crcurbiturils have produced pK_a shifts of up to two units.[50-53] The breadth of work utilizing monocations as guests prompted our investigation of the ability of **1** to encapsulate protonated guest molecules.

To test the hypothesis that protonation of neutral guests can facilitate their encapsulation, *bis*(dimethylphosphinomethane) (Figure 3) was added to **1** and new upfield resonances corresponding to the encapsulated phosphine were observed both in the ^{1}H NMR and ^{31}P NMR spectra. A ^{31}P{^{1}H} NMR spectrum in H_2O revealed a singlet and an un-decoupled spectrum gave $^1J_{HP}$ = 490 Hz corresponding to a one-bond P-H coupling, thus confirming protonation. In D_2O a $^1J_{DP}$ = 74 Hz was observed, which confirmed deuteration. After establishing that protonation of phosphines allows for encapsulation in **1**, a number of potential amine guests were screened (Figure 3).[54]

Primary amines, either monodentate or chelating, are not encapsulated. This is presumably because primary amines are more highly solvated in water and the enthalpy loss during encapsulation from desolvation is disfavored. Similarly, pyridine-based amines are not encapsulated, which is likely due either to their inherently low basicity or to shape incompatibility with **1**. More exotic guests such as pro-azaphosphatrane suberbases[55-58] can also be encapsulated in **1**.

To probe the thermodynamics of amine encapsulation, the binding affinities for different protonated amines for **1** were investigated. By studying the stabilization of the protonated form of encapsulated amines, the feasibility of stabilizing protonated intermediates in chemical reactions could be assessed. The thermodynamic cycle for encapsulation of hypothetic substrates (S) is shown in Scheme 4. The acid-base equilibrium of the substrate is defined by K_1 and is the binding constant of the protonated substrate in **1** is defined by K_2. Previous work has shown that neutral substrates can enter **1**; however, the magnitude of this affinity (K_4) remains unexplored. Although neutral encapsulated amines were not observable in the study of protonated substrates, the thermodynamic cycle can be completed with K_3, which is essentially the acid-base equilibrium inside of **1**.

All of the protonated amines encapsulated in **1** remained encapsulated even when the pH of the bulk solution was higher than the pK_a of the protonated amine, which suggest that **1** significantly stabilizes the encapsulated guest. In order to confirm that **1** was not acting as a kinetic trap for

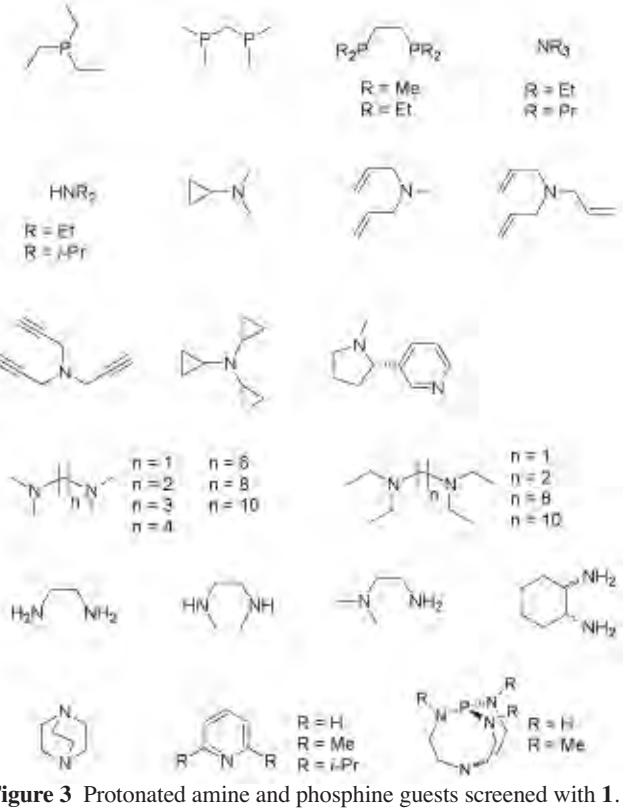
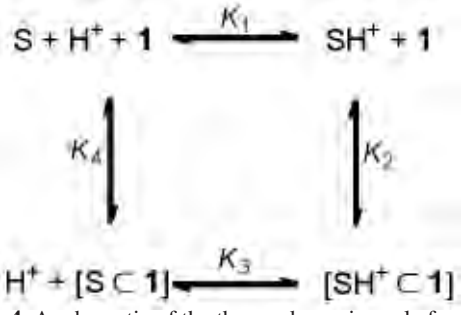


Figure 3 Protonated amine and phosphine guests screened with **1**.

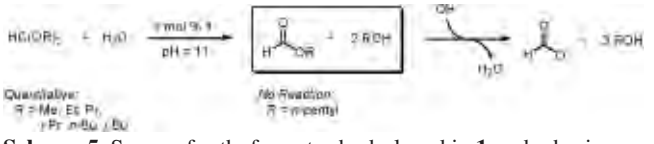


Scheme 4 A schematic of the thermodynamic cycle for encapsulation of protonated guests in **1**.

the encapsulated guests, the self-exchange rates were measured for the protonated amines using the selective inversion recovery (SIR) method.[59-61] All of the protonated amines encapsulated in **1** were found to exchange quickly on the NMR time scale, confirming that the stabilization of the encapsulated substrates was thermodynamic rather than kinetic. In order to determine the magnitude of the stabilization of the protonated amines in **1**, guest encapsulation was monitored as a function of pH, allowing for determination of the binding constants (K_{eff}). The product of the ammonium ion pK_a and its binding constant in **1** gives the effective basicity of the encapsulated amine (pK_{eff}) The pK_a shifts observed for the protonated amines were typically 3 to 4 pK_a units. These are the largest pK_a shifts observed in synthetic host molecules and approach those observed in enzymes.

Orthoformates and Acetals in Basic Solution

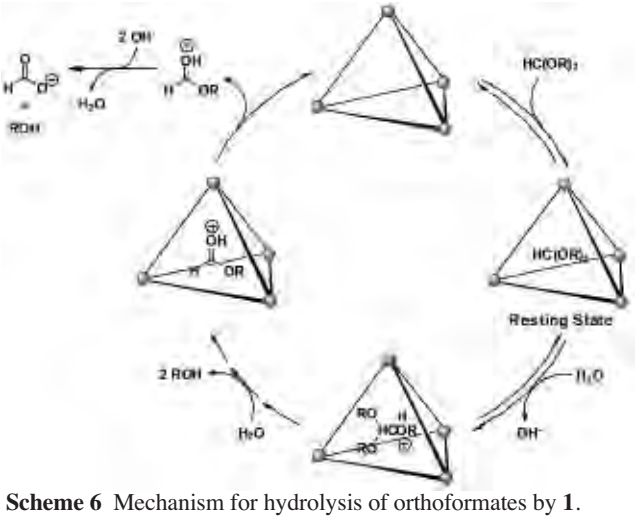
Nature often exploits large pK_a shifts in enzymes to effect chemical catalysis. This prompted us to explore whether the large shifts in effective basicities of encapsulated guests discussed above could be applied to reaction chemistry. Initial studies focused on the hydrolysis of orthoformates, a class of molecules responsible for much of the formulation of the Brønsted theory of acids almost a century ago.[62] While orthoformates are readily hydrolyzed in acidic solution, they are exceedingly stable in neutral or basic solution.[63] However, in the presence of a catalytic amount of **1** in basic solution, small orthoformates are quickly hydrolyzed to the corresponding formate ester, which after extrusion from the cavity undergo further base-catalyzed hydrolysis to carboxylates.[29] Addition of NEt_4^+ to the reaction inhibited the cluster catalysis but did not affect the hydrolysis rate measured in the absence of **1**. With a limited volume in the cavity of **1**, substantial size selectivity was observed in the orthoformate hydrolysis. Orthoformates smaller than tripentyl orthoformate are readily hydrolyzed with 1 mol% **1**, while larger substrates remain unreacted (Scheme 5).



Scheme 5 Scope of orthoformates hydrolyzed in **1** under basic conditions.

Having established that **1** catalyzes the hydrolysis of orthoformates in basic solution, the reaction mechanism was probed. Mechanistic studies were performed using triethyl orthoformate as the substrate at pH 11.0 and 50 °C. First-order substrate consumption was observed under stoichiometric conditions. Working under saturation conditions (0^{th} order in substrate), kinetic studies revealed that the reaction is also first-order in [H^+] and in [**1**]. When combined, these mechanistic studies establish that the rate law for this catalytic hydrolysis of orthoformates by host **1** obeys the overall termolecular rate law: *rate* = k[H^+][Substrate][**1**] which reduces to *rate* = k¢[H^+][**1**] at saturation.

We conclude that the neutral substrate enters **1** to form a host-guest complex, leading to the observed substrate saturation. The encapsulated substrate then undergoes encapsulation-driven protonation, presumably by deprotonation of water, followed by acid-catalyzed hydrolysis inside **1** during which two equivalents of the corresponding alcohol are released. Finally, the protonated formate ester is ejected from **1** and further hydrolyzed by base in solution. The reaction mechanism (Scheme 6) shows direct parallels to enzymes that obey Michaelis-Menten kinetics due to the initial pre-equilibrium followed by a first-order rate-limiting step.



Scheme 6 Mechanism for hydrolysis of orthoformates by **1**. The formate ester product is further hydrolyzed by base to formate anion and corresponding alcohol.

Lineweaver-Burk analysis using the substrate saturation curves afforded the corresponding Michaelis-Menten kinetic parameters of the reaction; V_{max} = 1.79 x 10^{-5} M s^{-1}, K_M = 21.5 mM, k_{cat} = 8.06 x 10^{-3} s^{-1} for triethyl orthoformate, and V_{max} = 9.22 x 10^{-6} M s^{-1}, K_M = 7.69 mM, k_{cat} = 3.86 x 10^{-3} s^{-1} for its tri-isopropyl analogue. These parameters demonstrate substantial rate acceleration over the background reaction with k_{cat}/k_{uncat} for triethyl orthoformate and triisopropyl orthoformate being 560 and 890 respectively. Assuming a fast pre-equilibrium with respect to k_{cat}, K_M is essentially the dissociation constant of the encapsulated neutral substrate. The specificity factor k_{cat}/K_M can be used to compare the

Continued on page 16

Richards Award

Continued from page 15

efficiency of hydrolysis by **1** for the two substrates. This constant corresponds to the second-order proportionality constant for the rate of conversion of the pre-formed host-guest complex to the product. Interestingly, the triethyl and triisopropyl ortho esters have specificity factors of 0.37 M^{-1} s^{-1} and 0.50 M^{-1} s^{-1} respectively, showing that the latter more hydrophobic is more efficiently hydrolyzed by **1**.

Also characteristic of enzymes that obey Michaelis-Menten kinetics is that suitable inhibitors can compete with the substrate for the enzyme active site, thus impeding the reaction. If the inhibitor binds reversibly to the enzyme active site, then the substrate can compete for the active site and at suitably high concentrations will completely displace the inhibitor, leading to competitive inhibition. In order to test for competitive inhibition for the hydrolysis of orthoformates by **1**, the rates of hydrolysis of triethyl orthoformate were measured in the presence of a varying amount of the strongly-binding inhibitor NPr_4^+ ($K_a = 10^{2.0(2)}$ M^{-1}). By varying the concentration of substrate for each amount of inhibitor, the resulting saturation curves were compared using an Eadie-Hofstee plot (Figure 4).[64, 65] The saturation curves intersect on the *y*-axis, signifying that at infinite substrate concentration the maximum reaction velocity is independent of the amount of inhibitor, which confirms that competitive inhibition is indeed present.

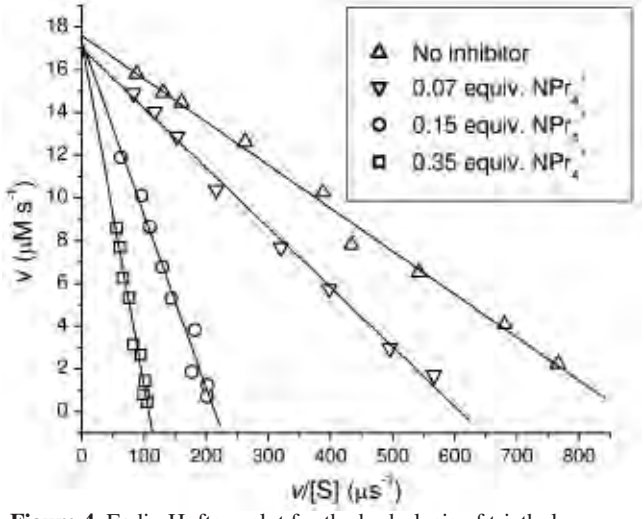
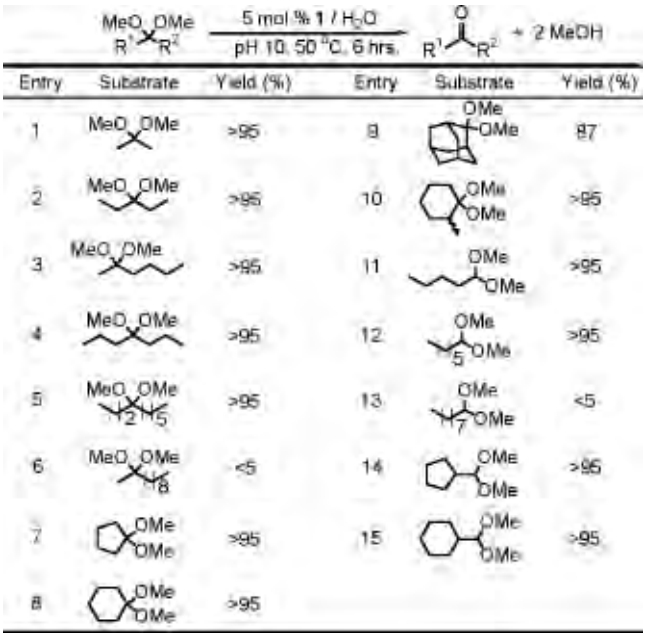


Figure 4 Eadie-Hoftsee plot for the hydrolysis of triethyl orthoformate in **1**, pH 11, 100mM K_2CO_3, 50 °C, using NPr_4^+ as a competitive inhibitor

Expanding the substrate scope for hydrolysis reactions catalyzed by **1,** the deprotection of acetals was investigated. Acetals are among the most commonly used protecting groups for aldehydes and ketones in organic synthesis due to their ease of installation and resistance to cleavage in neutral or basic solution.[66] Traditionally, aqueous acids, organic solutions acidified with organic or inorganic acids, or Lewis acids have been used for the reconversion of the acetal to



Entry	Substrate	Yield (%)	Entry	Substrate	Yield (%)
1		>95	9		87
2		>95	10		>95
3		>95	11		>95
4		>95	12		>95
5		>95	13		<5
6		<5	14		>95
7		>95	15		>95
8		>95			

Table 4 Scope of acetals and ketals hydrolyzed by **1** in basic solution.

carbonyl functionality.[67-71] However, a number of recent reports have documented a variety of strategies for acetal cleavage under mild conditions[72-81] including the first acetal deprotection in basic solution using cerium ammonium nitrate at pH 8 in a water-acetonitrile solution.[82]

Addition of 2,2-dimethoxypropane to a solution of **1** in H_2O at pH 10 quickly yielded hydrolysis products (acetone and methanol). The hydrolysis reactions were screened by mild heating (50 °C) of 5 mol % of **1** with respect to the acetal substrate at pH 10 in H_2O in sealed NMR tubes. To examine the reaction scope, a variety of alkyl acetals and ketals were screened (Table 4). Smaller substrates, which are able to fit into the cavity of **1**, are readily hydrolyzed. However, larger substrates, such as 2,2-dimethoxyundecane (entry 6) or 1,1-dimethoxynonane (entry 13), remain unreacted, suggesting that they are too large to enter the interior cavity of **1**. In all cases, addition of a strongly binding inhibitor for the interior cavity of **1**, such as NEt_4^+, inhibits the overall reaction, confirming that **1** is the active catalyst. For smaller acetals, the encapsulated substrate is not observed although the host resonances broaden, suggesting that the substrates are exchanging quickly on the NMR time scale. However, for larger acetals, broad guest resonances are observed upfield, suggesting a more slowly exchanging guest. For very bulky substrates, such as 2,2-dimethoxyadamantane (entry 9), the substrate is observed to be cleanly encapsulated in a 1:1 host-guest complex indicating slow guest ingress and egress on the NMR time scale (Figure 5). By monitoring the ^1H NMR spectrum of this reactant during the course of the reaction, new peaks corresponding to the encapsulated product, 2-adamantanone, were observed.

With the observation that both the substrate and product were encapsulated, the binding affinities of both molecules

Richards Award

Continued from page 16

within **1** were investigated in order to help explain the catalytic turnover. The total substrate, both free in solution and encapsulated, was monitored as a function of the concentration of **1**. The concentration of free substrate in solution was kept constant by always maintaining the presence of solid or liquid substrate in the system, which insured a uniform activity of the substrate throughout the experiments. The total amount of substrate in solution can be defined as shown in the equation in Figure 5, where S_t is the total substrate concentration, s_0 is the constant concentration of free substrate in solution, $\mathbf{1}_t$ is the total concentration of **1** and K_a is the association constant for the host-guest complex.[83]

Using this equation, the binding constants, K_a, for the substrate 2,2-dimethoxyadamantane and its hydrolysis product 2-adamantanone were determined from the data (Figure 5). Monitoring the encapsulation of both compounds over a concentration range from 2.8 mM to 40 mM **1**, in a 25:1 H_2O:D_2O solution buffered to pH 10 with 100 mM carbonate, yielded binding constants of 3100 M^{-1} and 700 M^{-1} for 2,2-dimethoxyadamantane and 2-adamantanone, respectively. As expected, the hydrolysis product is bound less tightly by **1** and is much less soluble in water than the substrate, which allows for the observed catalytic turnover.

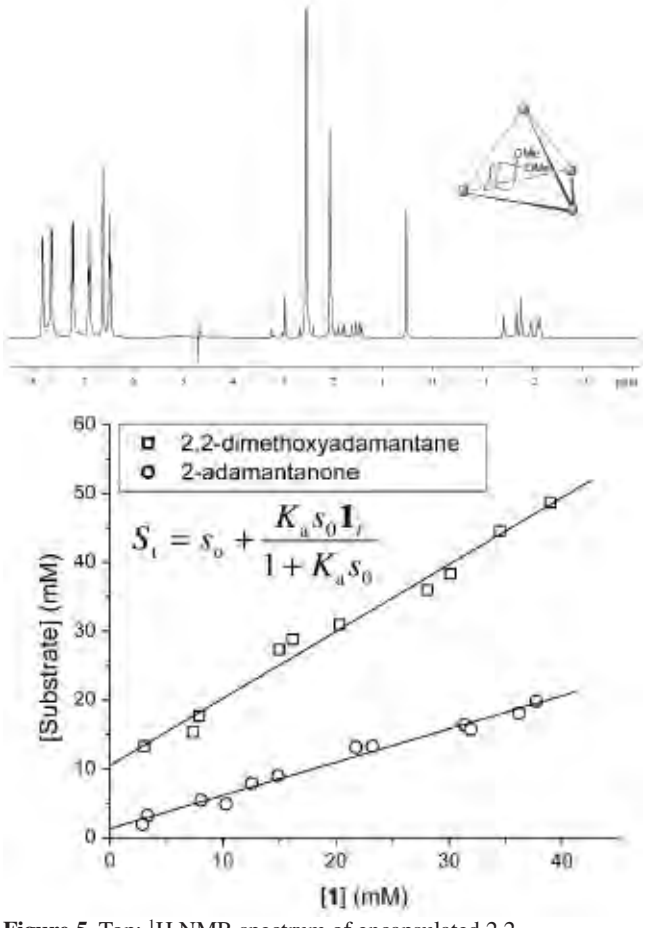


Figure 5 Top: ^{1}H NMR spectrum of encapsulated 2,2-dimethoxyadamantane in **1**. Bottom: Binding constant determination from the equation shown for 2,2-dimethoxyadamantane and 2-adamantanone in **1** in a 25:1 H_2O:D_2O solution buffered to pH 10 with 100 mM carbonate, measured at 298K

Conclusions and Outlook

The chemistry of a water-soluble, chiral supramolecular assembly has been explored over the last decade. Understanding the fundamental host-guest chemistry of the assembly **1**, such as the mechanism of guest exchange and the preference of monocationic guests, has allowed for the chemistry of **1** to be expanded into the field of catalysis. In hopes of using the chirality of **1** as a chiral environment for encapsulated guests, reactive monocationic organometallic guests were encapsulated in **1**. Chiral-at-metal iridium cationic complexes were encapsulated, and the C-H bond activation of aldehydes was carried out with diastereoselectivies of up to 70:30. Furthermore, **1** itself was used as a catalyst for the [3,3] sigmatropic rearrangement of enammonium cations with rate accelerations of up to 10^3. Encapsulation of a substrate in **1** locks the substrate in a reactive conformation, thereby reducing the entropic penalty in the transition state of the rearrangement. The preference for cationic substrates was exploited by using **1** to stabilize the cationic intermediate species, allowing for the catalysis of neutral substrates as shown by the hydrolysis of orthoformates and acetals in basic solution.

As the field of supramolecular chemistry grows and the complexity of synthetic structures increases, the basic understanding of the host-guest chemistry is of utmost importance in the development of new chemistry. As synthetic chemists begin to emulate Nature's ability to carry out complex reactions in the confined cavities of enzymes, fundamental understanding of the contributing forces to such reactivity is paramount. Key understandings in the solvation effects, both upon encapsulation and in the self-assembly process of host molecules themselves, as well as the contributions of encapsulation to entropic concerns of the reaction are all important frontiers that remain underexplored. The field of supramolecular chemistry allows chemists to uniquely examine how weak forces can interact to produce spectacular results and is poised to contribute to our understanding of enzyme mimicry and catalysis as a whole.[30]

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continued on page 20

The Andrew H. Weinberg Symposium

Few events can generate emotional turmoil in parents the way learning that their child has been diagnosed with cancer does. Despite major improvements in cancer treatments over the last few decades, cancer is still one of the most common causes of childhood death. Unlike many adult cancers, which are frequently associated with smoking or other exposures, the reason for most childhood cancer remains a mystery. In 1993, one family experienced the anguish of having a child diagnosed with rhabdomyosarcoma, a rare form of muscle tumor. In spite of aggressive attempts at a cure, Andrew H. Weinberg passed away shortly before his 3rd birthday.

The tragedy faced by the Weinberg family is relived daily around the world. While children remain innocent victims of this disease, there is still insufficient effort made to identify the cause or treatment of childhood cancer. Because children make up a small portion of cancer victims when compared to adults, little effort is exerted to address their specific issues or problems. As such, only two drugs have been approved for use in pediatric cancer patients since 1979 and only ~16 drugs have been approved over the last 50 years.

The Dana-Farber Cancer Institute and Children's Hospital have been leaders in the fight against childhood cancer dating back to the 1940's, when Dr. Farber achieved the first remission in childhood cancer. That commitment to identifying active agents that will impact childhood cancer continues to this day.

With the generous support of family and friends, as well as the Medicinal Chemical Group of the Northeastern Section of the American Chemical Society, and the Dana Farber Cancer Institute, a fund was created in 1994 and endowed in 2001. The Andrew H. Weinberg Memorial Endowment Fund is dedicated to bringing researchers together from the field of chemotherapy development with those in the medical community helping foster an environment for synergy and new approaches for cancer research.

The success of the Weinberg Symposium is evidenced by the large and enthusiastic turnout for past speakers.

Previous speakers have included:

Ken Bair, Ph.D.
Bruce Chabner, M.D.
Nicholas Dean, Ph.D.
Judah Folkman, M.D.
Stephen H. Friend, M.D., Ph.D.
Peter Ho, M.D., Ph.D.
John Hohnecker, M.D.
Peter Houghton, Ph.D.
Senator Edward M. Kennedy
David Kessler, M.D.
Richard Klausner, M.D.
David Parkinson, M.D.
Charles Pratt, M.D., Ph.D.
Malcom Smith, M.D., Ph.D.
Daniel Von Hoff, M.D.
Steven Weitman, M.D., Ph.D.

Special gratitude is extended to:

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Procyon Pharmaceuticals, Inc.
Schering-Plough Research Institute
Vertex Pharmaceuticals, Inc.
The Dover Church
Jon O. Lee
James S. Weinberg◇

Parkinson Biography

Continued from page 9

tional Society of Biological Therapy, and past Editor of the Journal of Immunotherapy. He currently serves on the National Cancer Policy Forum of the Institute of Medicine and is a member of the FDA's Science Board. He was recently elected to the Board of Directors of the American Association of Cancer Research, and continues to serve as Chairman of the AACR Finance Committee.◇

February NESACS Meeting

Photos by Morton Z. Hoffman

Valerie Wilson (Brown University), James Phillips (Waters Corporation), Dorothy Phillip (Waters Corporation), Joyce Foster (Williams College), Wilton Virgo (MIT), Patrick Gordon (Simmons College)

(l-r) Valerie Wilson (Brown University), Marietta Schwartz, NESACS Chair (University of Massachusetts Boston), Joyce Foster (Williams College)

Historical Notes

Herbert O. Hultin 1934-2007

Herbert O. Hultin passed away on December 10, 2007, just short of his 74th birthday. He was born in Quincy, MA on January 1, 1934 .

His academic training was in the Food Science Department at MIT, where he earned the Bachelor of Science, the Master of Science degrees in 1956, and the Ph.D. Degree in 1959.

His first appointment was at the University of Massachusetts in the Department of Food Science and Technology, 1959-1963, with leave for a post-doctorate fellowship at the Institute for Enzyme Research at University of Wisconsin, 1962-3.

He returned to the University of Massachusetts for the rest of his career, progressing to Professor in 1969, and Director of the University's Marine Foods Laboratory and the Marine Station in Gloucester, MA,, form 1979 to December, 2007.

Professor Hultin's 214 refereed publications and some 140 other presentations and publications on the biochemistry of seafood led to major progress in the understanding of lipid oxidation and protein solubility. (It is interesting to note that he was exposed to the problem of protein solubilization in 1956 when he worked for the Woburn Process Company.)

He was the recipient of many research awards, including the S.C. Prescott Award of the Institute of Food Technologists,1968, the E.P.McFee Award of the Atlantic Fisheries Technologists, 1985, Award of the Division of Agricultural and Food Chemistry, American Chemical Society, 1988, the Outstanding Researcher Award from the University of Massachusetts, 2003, and the Stephen S. Change Award for Lipid Chemistry, 2004 .

He was founding editor of the Journal of Food Biochemistry, 1977-1986. I am grateful to Editor N.F. Haard for much of the information in this report. Professor Hultin is survived by his wife, Marie, and five children

Frederick J. Viles, Jr 1915-2007

We report the passing on June 9, 2007 in Mashpee, MA of **Frederick J. Viles**, Jr, at the age of 91. He was born August 16, 1915 to Anna and Frederick Viles, the first of their six children.

His academic training led to a B.S. degree from M.I.T, and an M.S. degree in Industrial Hygiene from Harvard in 1947. He was a founding member of the American Industrial Hygiene Association in 1939, and numbered the Air Pollution Control Association and the American Chemical Society among his other professional societies.

He was a Research Fellow at Harvard for four years and worked as an Industrial Hygienist at Liberty Mutual Insurance Company, Harvard and M.I.T. In addition he was a consultant to more than 50 companies, published 36 professional papers and four U.S. Patents. He was a visiting lecturer at both Harvard School of Public Health and Northeastern University

Viles served in the Navy 5 years during WWII. He is survived by his wife Elsie R. Praetsch Viles, two daughters, a brother, a sister, grandchildren, and great grandchildren.

M.S.S.

We present here short biographies of chemists and chemical engineers whose deaths have been reported to us during the past year. We thank members of the Northeastern Section who have sent us obituary notices appearing in newspapers we do not see. ◇

Richards Award

Continued from page 17

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April 01

Prof. Lealon Martin (Rensselaer Polytechnic Institute)
"Rational Design of Photocatalytic Oxidation Processes for Water Treatment Applications through Systems Engineering"
Tufts University, Pearson Chemistry, P106
4:30 pm

Rory Waterman (Univ.Vermont)
"Mechanistic Variety in Zirconium-Catalyzed Bond Formation"
Univ. of New Hampshire, Iddles, L103
11:10 am

April 02

Dr. Ira Laurie (U.S. DEA Lab, Special Testing and Research)
"Use of Liquid Phase Separations for the Analysis of Seized Drugs"
Northeastern, 129 Hurtig Hall
12:00 Noon

April 03

Anna Mapp (Univ. Michigan)
TBA
MIT, 6-120
4:00 pm

Prof. Wafaa Fawzy (Colby College)
"Determination of the Molecular Structure and the Long Range Intermolecular Potential Energy Surfaces of Weakly-Bonded Open-Shell Complexes Toward Obtaining a Molecular Based Level of Understanding of the Role of Free Radicals in Chemical Reactions in the Atmosphere and in Biological Systems"
Univ. New Hampshire, Iddles, L103
11:10 am

April 07

Prof. James M. Mayer (Univ. Washington)
TBA
Boston Univ., Life Science and Engineering Building Auditorium (B01)
4:00 pm

April 14

Eli Lilly Symposium
Andrew Phillips (Univ. Colorado, Boulder)
TBA
Harvard, Pfizer Lecture Hall
3:30 pm

Boston University YCC Colloquium
Professor David Evans (Harvard Univ.)
TBA
Boston Univ., Life Science and Engineering Building Auditorium (B01)
4:00 pm

April 15

Prof. Peter G. Wolynes (U. C., San Diego)
"Landscapes of the Sciences"
Boston College, Merkert 127
4:00 pm

Prof. Chuck Merryman (Venter Institute)
"Towards a Synthetic Cell"
Tufts Univ., Pearson Chemistry, P106
4:30 pm

Yvon Durant (UNH Materials Science)
"Synthesis of Multifunctional Nanoparticles for Biomedical Applications"
Univ. of New Hampshire, Iddles, L103
11:10 am

April 16

Prof. Peter G. Wolynes (U. C., San Diego)
"Energy Landscapes and the solved Protein Folding Problems"
Boston College, Merkert 127
4:00 pm

ADL Seminar in Physical Chemistry
Carlos Bustamante (U. C., Berkeley)
MIT, 6-120
4:00 pm

April 17

ADL Seminar in Physical Chemistry
Carlos Bustamante (U. C., Berkeley)
TBA
MIT, 6-120
4:00 pm

Prof. Peter G. Wolynes (U. C., San Diego)
"Beyond Protein Folding"
Boston College, Merkert 127
4:00 pm

Prof. Lei Zhu (U. Conn.)
"Self-Assembled Biodegradable Block Copolymers"
Univ. of New Hampshire, Kingsbury, S145
11:10 am

April 18

ADL Seminar in Physical Chemistry
Carlos Bustamante (U. C. Berkeley)
TBA
MIT, 6-120
4:00 pm

April 22

Dr. Donald Eigler (IBM Almaden Research Center)
"Spin Excitation Spectroscopy"
Tufts Univ., Pearson Chemistry, P106
4:30 pm

Walter Shortle (USDA Forest Service)
"Use of Dendrochemistry to Monitor and Evaluate Environmental Change"
Univ. of New Hampshire, Iddles, L103
11:10 am

April 23

Barbara Finlayson-Pitts (U.C., Irvine)
Iddles Lecture Series
"Air Pollution and Climate Change from the Lower 48 to the Arctic"
Univ. of New Hampshire, Iddles L101
3:10 pm

April 24

Darrell G. Schlom (Pennsylvania State)
TBA
Harvard, Pfizer Lecture Hall
4:00 pm

Barbara Finlayson-Pitts (U. C., Irvine)
Iddles Lecture Series
"Heterogeneous Chemistry in the Lower Atmosphere from Particles to Parking Lots"
Univ. of New Hampshire, Iddles L103
11:10 am

April 28

Dr. Steve Bruner (Boston College)
TBA
Brandeis Univ., Gerstenzang 122
3:45 pm

Gilbert Stork, Columbia University
Gilbert Stork Day
Harvard, Pfizer Lecture Hall
4:15 pm

April 29

Prof. Neil Kelleher, University of Illinois
"Quantitative Studies of Human and Yeast Chromatin Using Ultra-High Resolution Tandem Mass Spectrometry"
Tufts Univ., Pearson Chemistry, P106
4:30 pm

April 29-30

AD Little Lecture in Inorganic Chemistry:
Michael Graetzel (Institute of Physical Chemistry, EPFL)
MIT, 6-120
4:00 pm

Notices for The Nucleus Calendar of Seminars should be sent to:

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