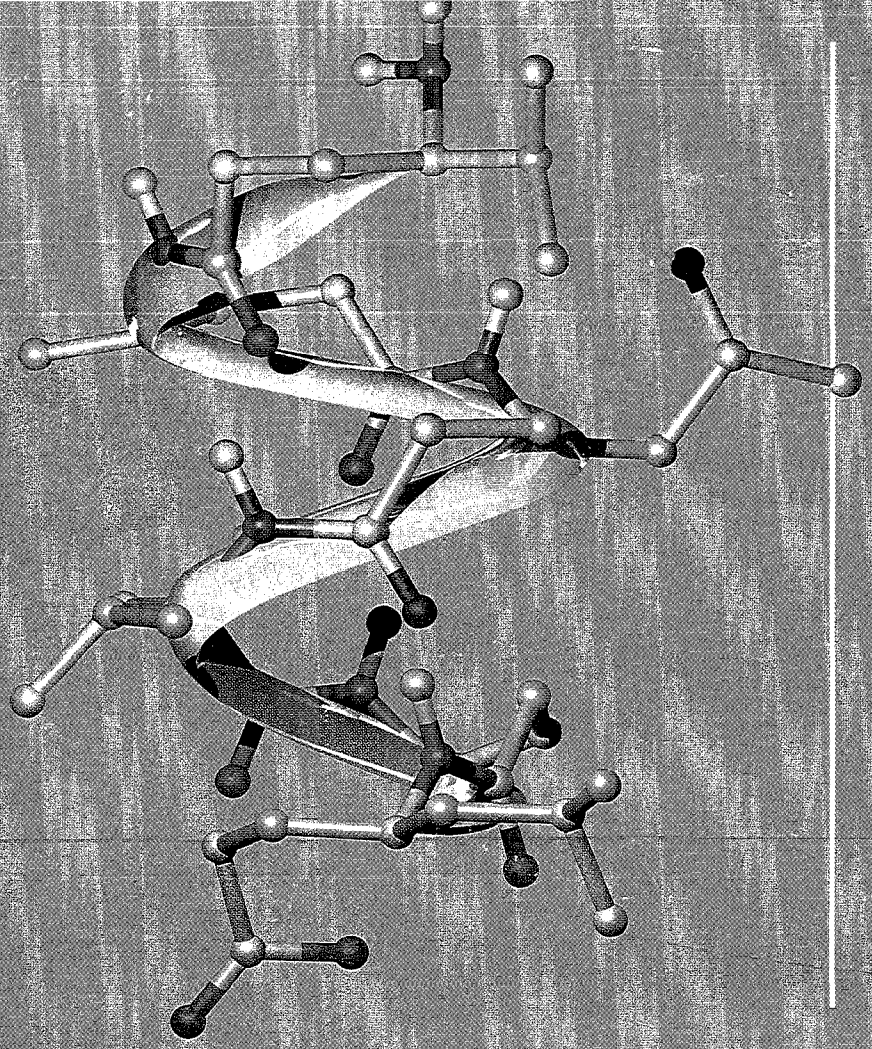
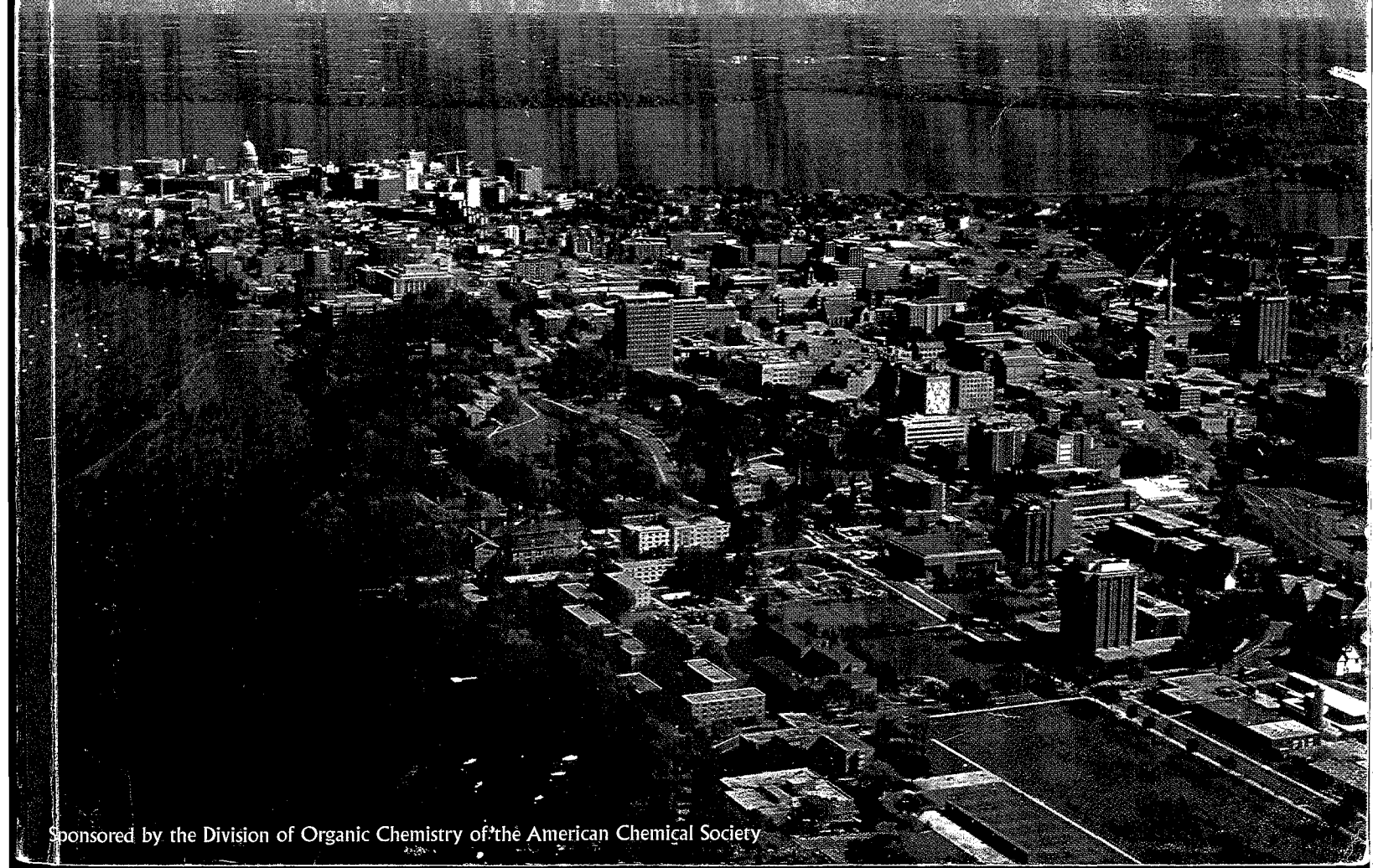


36th National ORGANIC CHEMISTRY SYMPOSIUM

University of Wisconsin-Madison
June 13-17, 1999



Sponsored by the Division of Organic Chemistry of the American Chemical Society

Ed Fenton

36th National Organic Chemistry Symposium

June 13 – 17, 1999
University of Wisconsin
Madison, Wisconsin

Table of Contents

Symposium Program

Throughout this program, the numbers listed below the poster sessions refer to the **abstract** number in the book. Platform Session will be held in the **Union Theater**. Poster Sessions will be held in **Great Hall**.

Sunday, June 13

11:00 - 8:00 p.m.	Registration	North Buffet Room-Gordon Commons
7:00 p.m.	Dinner	Lakefront Cafeteria
8:30 p.m. - Midnight	**Opening Mixer & Poster Session I** See Abstracts 1-78	Great Hall

Monday, June 14

7:30 a.m - Noon	Registration continues	Union Theater Lobby
8:00 - 5:00 p.m.	Milwaukee Zoo	Outside Memorial Union-Langdon St.
8:30 - 12:30 p.m.	City Tour of Madison	Outside Memorial Union-Langdon St.
8:30 - 9:00 a.m.	Opening Remarks	Union Theater
9:00 - 10:00 a.m.	**Elias J. Corey** Harvard University Adventures in Enantioselective Synthesis Page 1	Union Theater
10:00 - 10:15 a.m.	Questions	
10:15 - 10:45 a.m.	Break	Union Theater Lobby
10:45 - 11:45 a.m.	**Sheila DeWitt** Orchid Biocomputer *Synthesis in Chips* Page 7	Union Theater
11:45 a.m. - Noon	Questions	
12 Noon	Lunch	Lakefront Cafeteria
1:00 - 5:00 p.m.	City Tour of Madison	Outside Memorial Union-Langdon St.
2:00 - 4:00 p.m.	NIH/NSF Grantsmanship Workshop *John Schwab (NIH), Ron Dubois (NIH), George Rubottom (NSF), and other panelists*	Room to be announced
4:00 - 6:00 p.m.	UW-Chemistry Alumni and Friends Reception	Pyle Center 702 Langdon St. Pyle Alumni Lounge
5:30 p.m.	Dinner	Lakefront Cafeteria

7:30 - 8:30 p.m.	**Gregory Fu** Massachusetts Institute of Technology *Asymmetric Catalysis with "Planar-Chiral" Heterocycles* Page 15	Union Theater
8:30 - 8:45 p.m.	Questions	
8:45 - 9:45 p.m.	**Samuel Gellman** University of Wisconsin-Madison *Heteropolymer Folding: Proteins and Beyond* Page 20	Union Theater
9:45 - 10:00 p.m.	Questions	
10:00 p.m. - Midnight	**Mixer & Poster Session II** See Abstracts 79-157	Great Hall

Tuesday, June 15

9:00 - 10:00 a.m.	**Robert Grubbs** California Institute of Technology *Ruthenium-Based Olefin Metathesis Catalysts* Page 25	Union Theater
10:00 - 10:15 a.m.	Questions	
10:15 - 10:45 a.m.	Break	Union Theater Lobby
10:45 - 11:45 a.m.	**Chaitan Khosla** Stanford University *Assembly Line Synthesis using Modular Enzymes* Page 32	Union Theater
11:45 a.m. - Noon	Questions	
12 Noon	Lunch	Lakefront Cafeteria
1:00 - 4:00 p.m.	The International Crane Foundation	Outside Memorial Union-Langdon St.
1:00 - 4:30 p.m.	Village of Cambridge Tour	Outside Memorial Union-Langdon St.
1:30 - 4:30 p.m.	ACS Tutorial on Managing an Effective Job Search *James D. Burke, Ph. D.* Rohm and Haas Co. and ACS Career Consultant	Room to be announced
5:30 p.m.	Dinner	Lakefront Cafeteria
7:30 - 9:00 p.m.	**Dieter Seebach** ETH (Zurich), *Roger Adams Award Address:* *Organic Synthesis-as central as ever:* *Excursions to the Chemistry of Polymers and Oligomers* Page 36	Union Theater
9:00 p.m. - Midnight	**Mixer & Poster Session III** See Abstracts 158-235	Great Hall

Wednesday, June 16

8:30 - 9:30 a.m.	**Jeffrey Moore** University of Illinois at Urbana-Champaign *Folding Non-biological Oligomers into Barrel-Like Architectures* Page 45	Union Theater
9:30 - 9:45 a.m.	Questions	
9:45 - 10:15 a.m.	Break	Union Theater Lobby
10:15 - 11:15 a.m.	**Gregory Petsko** Brandeis University *The Catalytic Pathway of Cytochrome P450 at Atomic Resolution* Page 52	Union Theater
11:15 - 11:30 a.m.	Questions	
11:30 - 12:30 p.m.	**Daniel Singleton** Texas A&M University *Organic Reaction Mechanisms from Experimental Transition States* Page 57	Union Theater
12:30 - 12:45 p.m.	Questions	
12:30 p.m.	Lunch	Lakefront Cafeteria
1:00 - 5:00 p.m.	Mount Horeb and Botham Winery Tour	Outside Memorial Union-Langdon St.
3:30 - 5:30 p.m.	Discussion of Planning and Building New UW-Chemistry Research Labs *Professor Robert McMahon*	Room to be announced
5:30 - 8:00 p.m.	Outdoor Lakeside Picnic Lakeside Residence Halls (A short walk from the Union)	Tripp Hall Lawn
8:00 - 9:00 p.m.	**Ralph Hirschmann** University of Pennsylvania *Peptide-Related Research: Its Genesis and Some Current Research* Page 61	Union Theater
9:00 - 9:15 p.m.	Questions	
9:15 p.m. - Midnight	**Mixer & Poster Session IV** See Abstracts 236-314	Great Hall

Thursday, June 17

9:00 - 10:00 a.m.	**Masakatsu Shibasaki** University of Tokyo *Recent Progress in Multifunctional Asymmetric Catalysis* Page 64	Union Theater
10:00 - 10:15 a.m.	Questions	
10:15 - 10:45 a.m.	Break	Union Theater Lobby
10:45 - 11:45 a.m.	**Stuart Schreiber** Harvard University *Challenges for Organic Synthesis in Forward & Reverse Chemical Genetic Research* Page 68	Union Theater
11:45am - Noon	Questions & Closing Remarks	
12 Noon	Lunch	Lakefront Cafeteria

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Listed below are the thirty-seven advanced graduate students who were awarded Division of Organic Chemistry Graduate Fellowships in the past two years. Many of these students are here at the Symposium with poster presentations. Also listed are the names of their institutions, faculty research advisors, and the companies that sponsored these awards. The Division is pleased to honor these extraordinary students and to gratefully acknowledge the substantial financial support provided by the generous sponsors.

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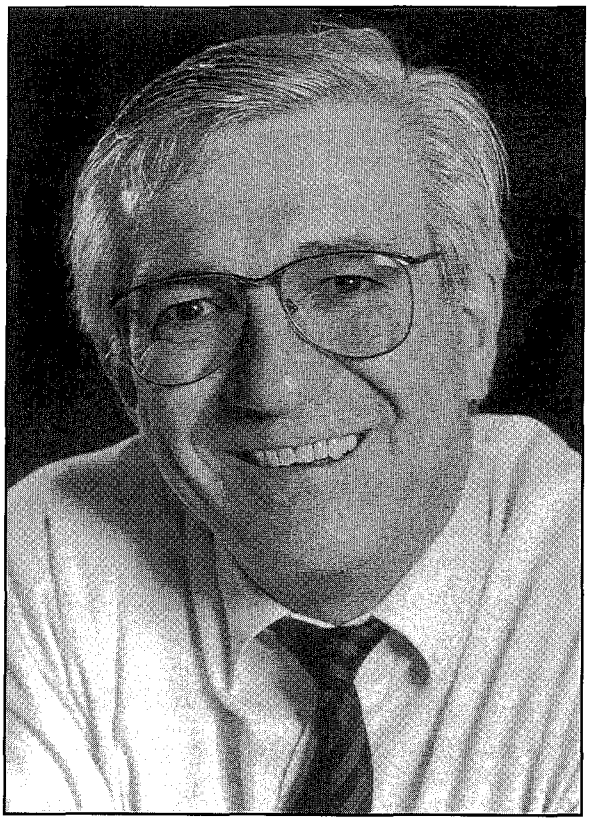
The Roger Adams Award in Organic Chemistry

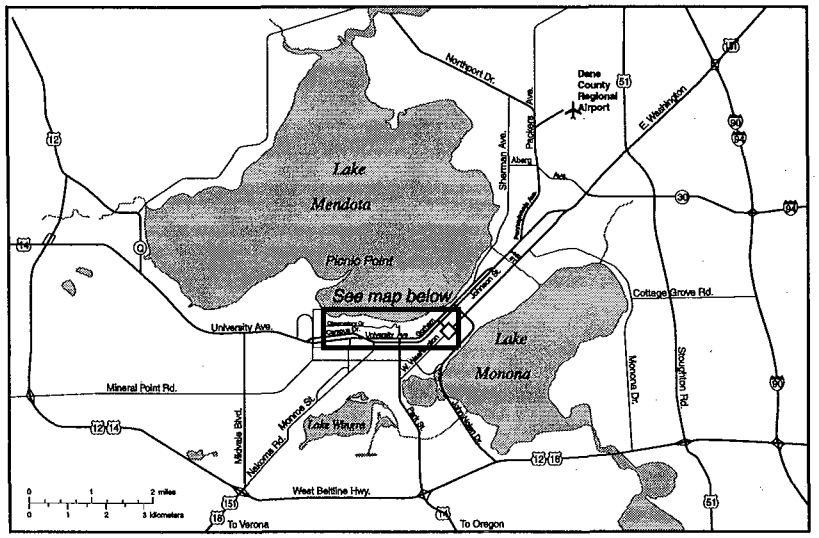
The Roger Adams Award in Organic Chemistry is sponsored jointly by the American Chemical Society, Organic Reactions, Inc., and Organic Syntheses, Inc. The award recognizes the distinguished career of Roger Adams, who played a vital role in each of these three organizations. He was Chairman of the Board of Directors as well as President of the American Chemical Society, and he co-founded *Organic Syntheses* and *Organic Reactions*.

The award is made biennially to an individual, without regard to nationality, for outstanding contributions to research in organic chemistry. The award consists of a gold medal, a sterling silver replica of the medal, and an honorarium of twenty-five thousand dollars. It is presented at the biennial National Organic Chemistry Symposium of the Division of Organic Chemistry of the American Chemical Society. The awardee is a featured lecturer in the program of the symposium.

The recipient of this year's Roger Adams Award is Professor Dieter Seebach of the Eidgenössische Technische Hochschule (ETH), Zurich. His award address, entitled "Organic Synthesis – as Central as Ever: Excursions to the Chemistry of Polymers and Oligomers," will be delivered on Tuesday evening, June 15.



Dieter Seebach



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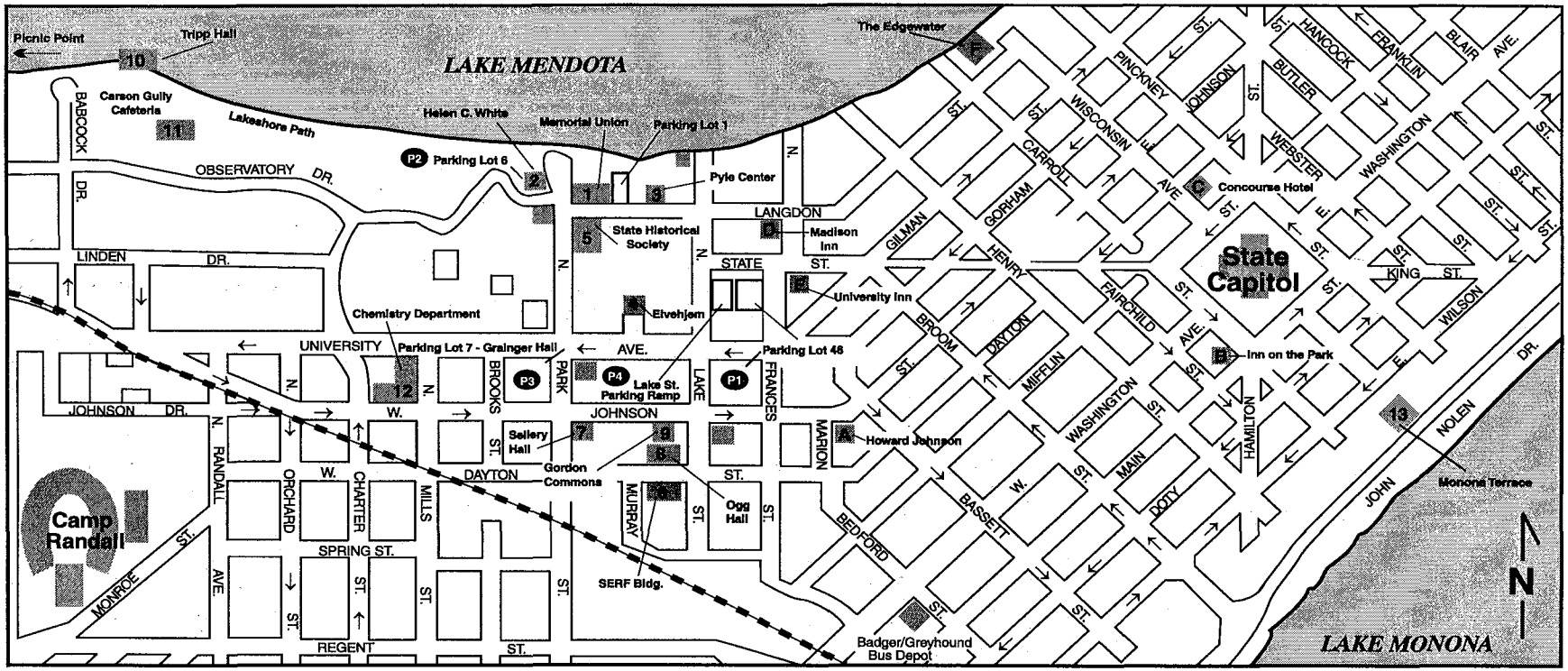
- P1 Parking Lot 46
- P2 Parking Lot 6
- P3 Parking Lot 7 - Grainger Hall
- P4 Lake Street Parking Ramp

UNIVERSITY BUILDINGS

1. Memorial Union
2. Helen C. White Library Computer Lab
3. Pyle Center
4. Elvehjem Museum
5. State Historical Society
6. Serf Building (Athletic Facility)
7. Sellery Hall
8. Ogg Hall
9. Gordon Commons
10. Tripp Hall Lawn-Picnic (Follow Lakeshore Path)
11. Carson Gully Cafeteria (Rain Location for Picnic)
12. Chemistry Department
13. Monona Terrace

HOTELS

- A Howard Johnson
- B Best Western Inn on the Park
- C Madison Concourse Hotel & Governor's Club
- D Madison Inn
- E University Inn
- F The Edgewater



University of Wisconsin, Madison, Wisconsin

36th National Organic Chemistry Symposium:

Platform Sessions
- Union Theater

Slide Preview Room
- Winkler Lounge

Poster Room
- Great Hall

Exhibitor Room
- Great Hall /Reception Room

Lunch/Dinner
- Lakefront Cafeteria

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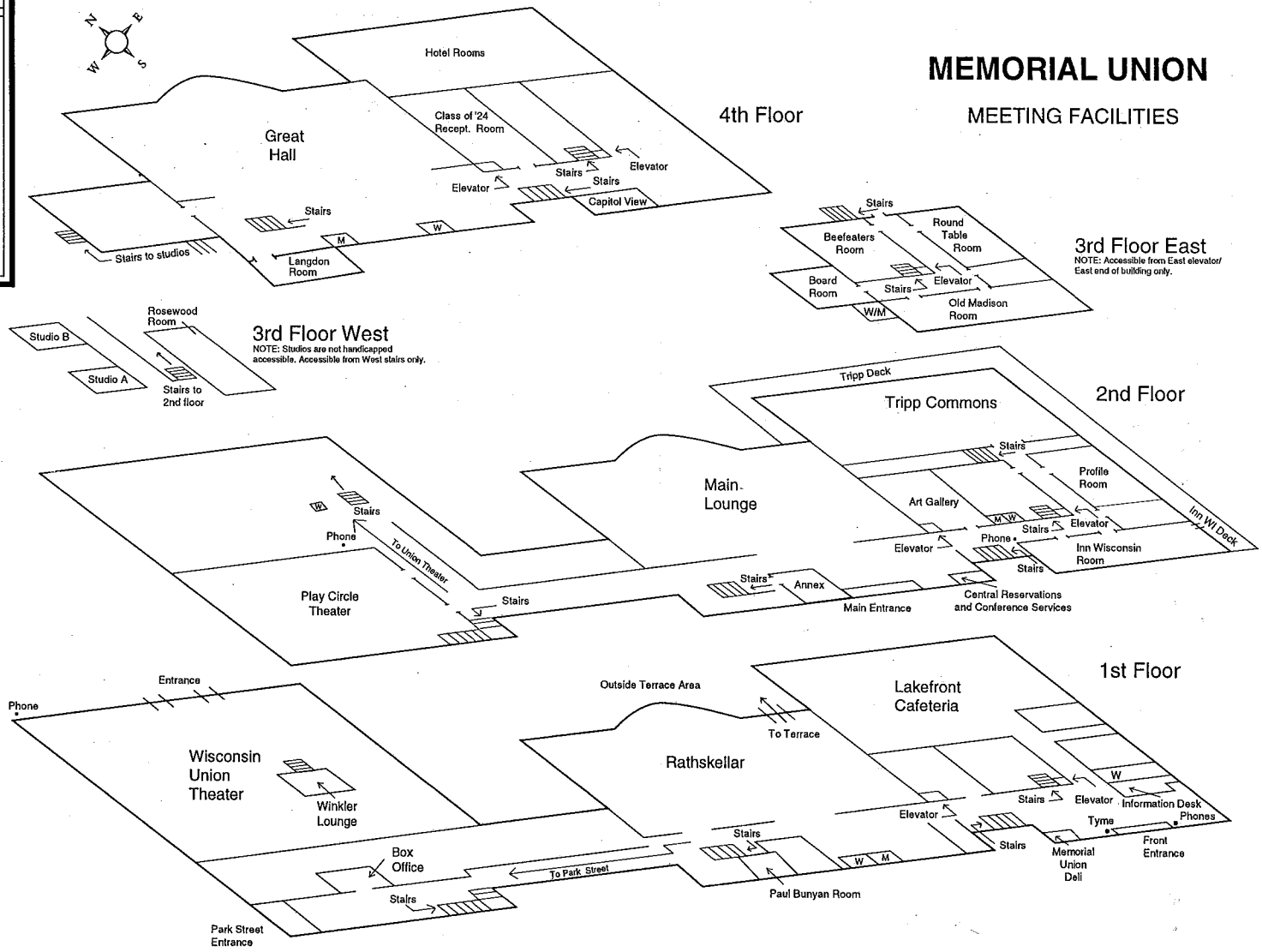


ADVENTURES IN ENANTIOSELECTIVE SYNTHESIS

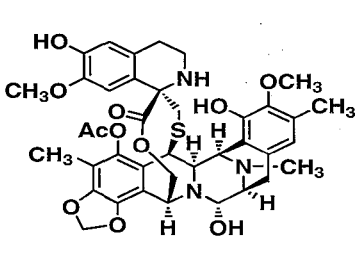
E. J. Corey

Department of Chemistry & Chemical Biology, Harvard University, Cambridge, Massachusetts, 02138

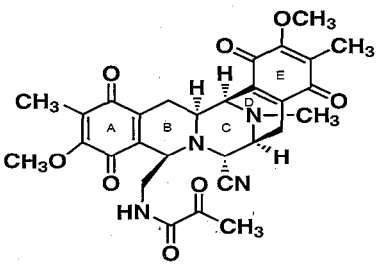
Much of the recent research effort of my group at Harvard has been devoted to the chemical synthesis of important biologically active molecules and to the development of new methods and strategies of synthesis which are crucial to the efficient and successful execution of such multistep processes. This lecture collects several related projects and illustrates the close relationship between synthetic strategy and design, on the one hand, and the development of powerful new tools for synthesis, on the other. These projects also exemplify the close relationship of synthetic chemistry to medicine and biology.

Ecteinascidin 743 (Et 743) is an exceedingly potent and rare marine-derived antitumor agent which is currently in Phase 2 clinical trials for a variety of cancers.[1] The first part of this lecture will deal with the development of efficient enantioselective syntheses of this complex structure which are suitable for large scale commercial development.[2] The same key intermediates have been applied to an effective enantiocontrolled total synthesis of saframycin A (Sf A).[3,4]

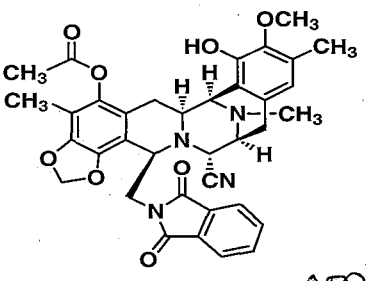
Modeling studies of the Et 743 molecule, its possible mode of interaction with double-stranded DNA, and studies of the antitumor activity of a few selected derivatives of some of the pentacyclic intermediates on the pathway to Et 743, led to the design of a new series of antitumor agents of simpler structure than Et 743. The second of these to be synthesized, phthalascidin 650 (Pt 650) was found to be an exceedingly active antitumor agent against a wide range of cell types.[5] The potency of Pt 650 is essentially identical to that of Et 743 and



Ecteinascidin 743



Saframycin A



Phthalascidin

mol wt Rowland Mass Spec!

650 mol wt

Synthesis in Chips

Sheila H. DeWitt, Ph.D.

Orchid Biocomputer, Inc. 303 Washington Rd
Princeton, NJ 08540 Phone: 609-750-2209
Fax: 609-750-2250
sdewitt@orchidbio.com
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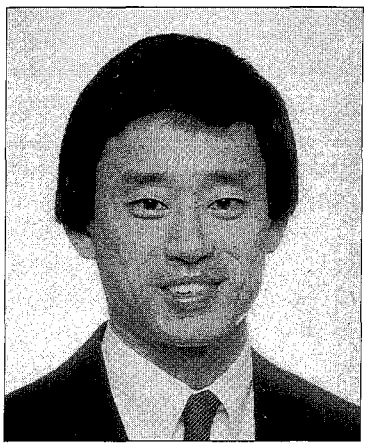
Summary

The advances of the past few years in microreactors have demonstrated that the miniaturization of chemistry has significant advantages in cost, safety, throughput, kinetics, and scale-up [1-2]. The use of chemical microreactors for catalytic oxidations [3] and heterocyclic syntheses [4] has illustrated the utility and benefits for both chemical discovery and chemical development applications.

Introduction

Recently, the heightened interest in microreactors and associated operations has been in response to pressures from two separate but related disciplines - preclinical drug discovery and chemical development / manufacturing. The economic pressures on the pharmaceutical industry to provide higher quality therapeutics in a shorter amount of time at a reduced cost has driven the adoption of several new technologies and components thereof, including combinatorial chemistry and high throughput screening. In the past five years, efforts to increase the efficiency and productivity of chemical synthesis efforts have leveraged parallel reactor systems and automation for both medicinal chemistry and process optimization [5-7]. A promising means to decrease time and costs further is through miniaturization in several application areas, including the use of microreactors to execute chemical synthesis. The miniaturization of chemical reactors has demonstrated numerous benefits for synthesis, including:

- Decreased reagent and processing costs,
- Improved process conditions (i.e. increased heat transfers),
- Improved conversion and selectivity,
- Prevention of thermal run-away reactions,
- Control of free radical branching reactions,

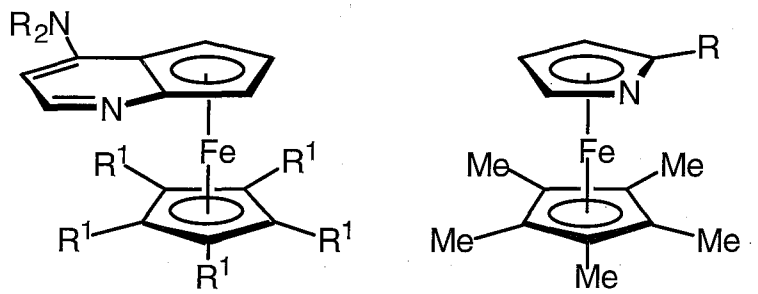


Asymmetric Catalysis with "Planar-Chiral" Heterocycles

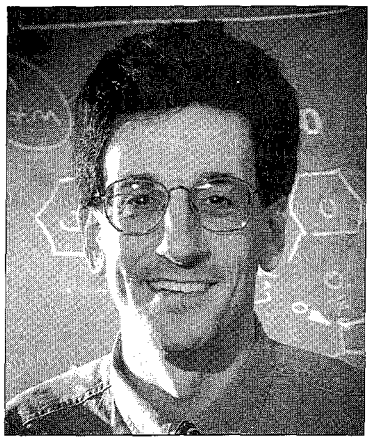
Gregory Fu

Massachusetts Institute of technology

Many useful organic reactions are catalyzed by nucleophiles such as DMAP, DABCO, and PPh_3. Surprisingly, little work has been reported on asymmetric variants of these processes using *chiral* nucleophiles. We are exploring the chemistry of "planar-chiral" π-complexes of heterocycles with transition metals, a class of compounds that had not previously been examined in the context of nucleophilic (or asymmetric) catalysis.



We have established that these complexes serve as effective chiral catalysts for a number of interesting processes, including the addition of alcohols to ketenes, the rearrangement of *O*-acylated enolates to β-dicarbonyls, and the kinetic resolution of secondary alcohols.



HETEROPOLYMER FOLDING: PROTEINS AND BEYOND

Samuel H. Gellman

Department of Chemistry, University of Wisconsin - Madison

The remarkable molecular functions displayed by living systems (e.g., catalysis) are carried out largely by heteropolymers that adopt compact and specific conformations. Proteins are responsible for most of these sophisticated activities, but RNA, too, can perform complex tasks. Because function and macromolecular folding are intimately linked, chemists have long sought to elucidate the origins of biopolymer conformational preferences. Recently, organic chemists have become increasingly interested in the prospect that unnatural oligomers ("foldamers") can be induced to fold specifically, and that the resulting structures can be endowed with complex activities.[1]

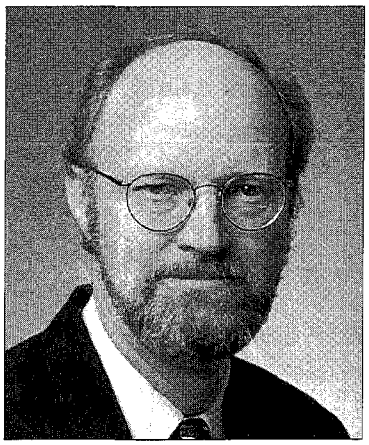
Our work has straddled the border between natural and unnatural molecular backbones, i.e., between a subject traditionally viewed as part of biophysics and the sort of extrapolation from natural systems that has always been the domain of the organic chemist. In order to elucidate the forces that determine protein folding preferences, we have developed a new class of β-sheet model systems.[2] These models allow us to probe the relationship between α-amino acid sequence and conformational stability at the secondary structure level. In a parallel effort, we have explored the folding behavior of oligomers of β-amino acids ("β-peptides").[1]

β-Sheet model systems. Only two types of secondary structure with long-range order are observed in proteins, helices (α and 3_{10}) and sheets (parallel and antiparallel). The α-helix has been extensively examined with model systems, because there are well-established rules for designing peptides that adopt helical conformations in solution. In contrast, relationships between β-sheet stability and sequence, length, or other factors are poorly understood, because, until recently, it has been difficult to generate peptides that adopt β-sheet conformations without aggregating in aqueous solution.

In the past few years, several laboratories including ours have learned how to create small linear peptides that adopt antiparallel β-sheet conformations in aqueous solution.[2] The smallest increment of β-sheet is the "β-hairpin," which contains two antiparallel strands

University of Wisconsin, Madison, Wisconsin

Possum Trot, KY
U. of Gainsville BS
Columbia PhD (Breslow)
Coleman



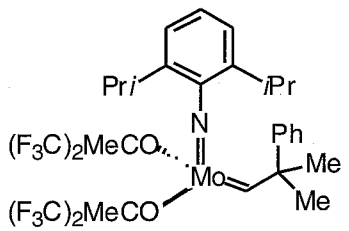
Ruthenium-Based Olefin Metathesis Catalysts

Robert H. Grubbs, Matthias Scholl, Tina M. Trnka, and John P. Morgan

California Institute of Technology

Over the past few years the olefin metathesis reaction has emerged as a powerful tool for the formation of C-C bonds in complex molecules[1]. Ring closing metathesis (RCM) has seen the broadest applications with cross metathesis (XMET) finding an increasing role. Key to these advances is the availability of well-defined alkylidene-metal complexes for this transformation that include the alkoxy imido molybdenum complex **1**[2] and the benzylidene ruthenium complex **2**[3]. The molybdenum complex **1** is more reactive towards a broad range of substrates with many steric or electronic variations;[4] however, it also suffers from high sensitivity to air and moisture and decomposition upon storage. To increase the activity and selectivity of the ruthenium family new derivatives of **2** have been prepared. These derivatives of **2** include bidentate salicylaldimine ruthenium complexes[5], binuclear ruthenium complexes[6], and ruthenium complexes with a family of imidazolinylidene ligands[7]. These designs are based on the mechanistic studies that demonstrated that the activity of the system was related to the large cone angle and basicity of the cyclohexylphosphine[8]. The basic steps of RCM shown below define the improvements needed and those that have been made in the catalyst systems.

Cy = cyclohexyl



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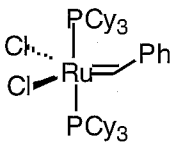
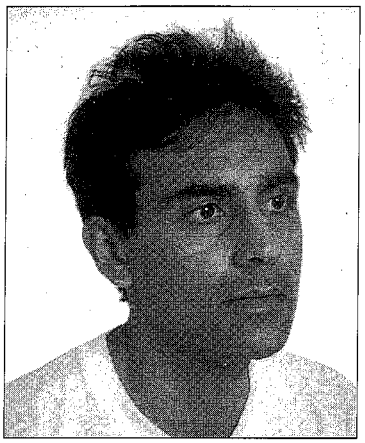


2

Since the instantaneous ratio of concentrations of the desired and oligomeric product is defined by the following equation, the yield of RCM can be controlled by the concentration



Assembly Line Synthesis Using Modular Enzymes

BS Indian Inst Tech
PhD Chem Eng Cal Tech
UK. post doc

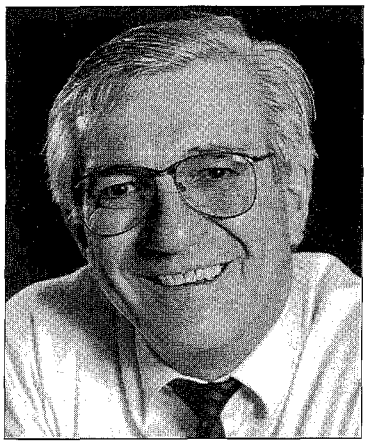
Chaitan Khosla

Departments of Chemistry and Chemical Engineering, Stanford University, Stanford CA 94305-5025

Many natural products are synthesized by modular multi-enzyme assemblies through non-template mechanisms. Polyketides are one such family of structurally diverse and medicinally important natural products. They are synthesized by multifunctional polyketide synthases (PKSs) which catalyze repeated decarboxylative condensations between acyl-thioesters. In addition to varying chain length, choice of primer and extender units, stereochemistry, and the degree and regiospecificity of reduction of the polyketide backbone, PKSs introduce structural variability into the product by catalyzing regiospecific cyclizations of nascent polyketide chains. There is considerable interest in exploiting the modularity of PKSs for the engineered biosynthesis of "unnatural" natural products. A combination of genetic, biochemical, and chemical tools is proving to be extremely powerful towards this end. Examples will be presented that illustrate the scope and potential of biosynthetic engineering for the controlled generation of novel natural product-like molecules. On one hand "unnatural" natural products yield new insights into how PKSs control their catalytic specificities. At the same time, they serve as potentially useful tools for biochemical research.

My presentation will include results drawn from our studies on the molecules shown below. Key background references from the recent literature can be found in the following review articles.

1. Khosla, C., Harnessing the biosynthetic potential of modular polyketide synthases., *Chem. Rev.*, 97, 2577-2590, 1997.
2. Cane, D. E., Walsh, C. T., and Khosla, C. Harnessing the biosynthetic code. Combinations, permutations, mutations., *Science*, 282, 63-68, 1998.



Organic Synthesis – as central as ever: Excursions to the Chemistry of Polymers and Oligomers

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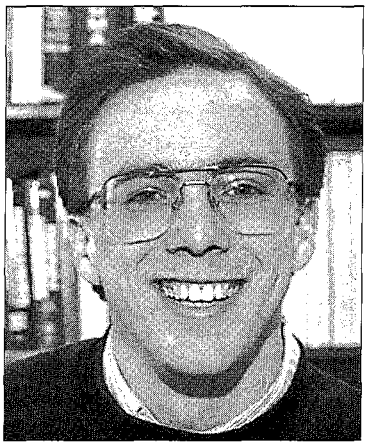
The lecture will cover three areas of ongoing research in our group, common to which is the prerequisite that polymers and oligomers have to be prepared. In this abstract both, the background and the most recent results in these areas are alluded to, and referenced, while the lecture will focus on current work.

TADDOLs for Catalysis and for New Materials

In order to be able to compare polar main-group (Li) with early-transition-element organometallic compounds we began to study ***titanium derivatives***, twenty years ago. Transmetalation of RLi or RMgX with $ClTi(OCHMe_2)_3$ furnished highly functional-group-selective and stereoselective new reagents.[1,2] From dramatic effects of the R'O groups in R-$Ti(OR')_3$ on the reactivity we quickly turned to chiral derivatives, and we tested several readily available enantiopure alcohols R'OH to form titanate reagents. To reduce the aggregation tendency we prepared a bulky diol from tartrate acetonide and phenyl Grignard reagent which became the prototype of a large family of chiral ligands for metal centers (Li, Mg, Al, Ti, Zr, Rh, Pd, Cu, Zn), *the* ***TADDOLs*** (abbreviation of the full name: α,α,α',α'-**t**etra**a**ryl-1,3-**d**ioxolan-4,5-**d**imetha**nol**). Some reactions mediated by TADDOL derivatives are presented in the upper part of Scheme 1; a short review article[3] covers the literature up to mid 1994. Most recently, we have prepared styryl-substituted TADDOLs for copolymerization with styrene and preparation of polymer-bound complexes.[4] The **dendritic cross-linkers** shown on the bottom of Scheme 1 gave polymers with unique material properties and performance in multiple uses of the corresponding Ti complexes.[5] – Besides being versatile chiral ligands for metals, TADDOLs can also be used as chiral NMR shift reagents,[6] for enantiomer-differentiating crystallization of inclusion compounds,[7] and as chiral dopants for converting achiral liquid-crystals into cholesteric phases.[8]



Folding Non-biological Oligomers into Barrel-Like Architectures

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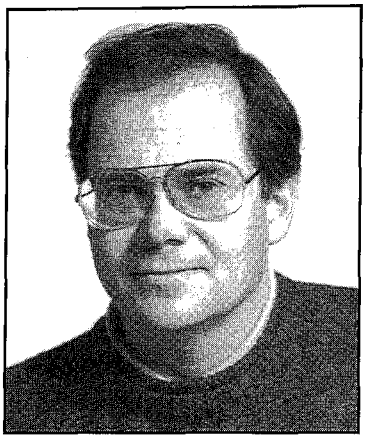
Biology's complex molecular machinery is based on simple chain molecules of linear monomer sequences that adopt well-defined conformations in solution. In a similar way, learning to fold non-biological polymers promises simple routes to sophisticated materials (e.g., molecular recognition, catalysis, or stimuli-responsive polymer gels). While ordered solution conformations are commonplace among biopolymers, only recently have significant strides been made with synthetic chain molecules.[1-4] This talk will summarize efforts in our laboratory involving amphiphilic oligomers that are driven to fold into "barrel-like" architectures by solvophobic forces. The choice of this particular target is motivated by the notion that the folded conformation creates a three-dimensional pocket with information-rich surfaces that can be used for molecular recognition.

Learning to control the conformation of chain molecules in solution is a problem that can be thought of as supramolecular chemistry, intramolecular style. In other words, target folds are to be realized by engineering favorable non-covalent interactions between segments within a single chain (positive design). Moreover, to achieve the challenging goal of conformational uniqueness, unwanted folded structures must also be "designed away" by introducing destabilizing interactions (negative design). While the individual interactions that stabilize or destabilize a particular conformation may be quite weak, a large collection of coupled interactions can become energetically significant. Because the interacting segments in a chain molecule are coupled through constraints imposed by the backbone's covalent connectivity, the conformational transitions can exhibit high cooperativity. Cooperativity provides a powerful design principle well suited to chain molecules, as will be emphasized throughout the talk.

We have recently shown that phenylene ethynylene oligomers (e.g., **1**) can be driven to fold into helical conformations by solvophobic forces alone (Figure 1).[3,5] On the basis of molecular modeling studies, we proposed that a key parameter in the design of solvophobically folded oligomers is *the molecular contact area per degree of conforma-*



The Catalytic Pathway of Cytochrome P450 at Atomic Resolution

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Cytochrome P450 enzymes are ubiquitous heme-containing monooxygenases named after their absorption band at 450 nm when complexed to carbon monoxide. They are the biological equivalent of a propane torch: they carry out the addition of oxygen to simple carbon compounds such as alkanes and aromatics. However, these enzymes can perform this difficult chemistry at room temperature, stereospecifically and with great substrate selectivity. Various members of the P450 family are involved in the biosynthesis of steroids or lipids and the degradation of xenobiotics [1,2]. The mechanism by which these enzymes are able to activate oxygen to carry out the hydroxylation of unactivated carbon compounds has been investigated for decades, yet many details remain uncertain. In particular, the nature and geometry of the various oxygen species bound to the heme iron at different stages of the P450 reaction cycle have never been established.

The best-characterized P450 is the soluble P450cam that allows Pseudomonas putida to use D-camphor as a sole carbon source. P450cam catalyzes the regio- and stereospecific hydroxylation of camphor to 5-exo-hydroxycamphor. The structures of the reduced enzyme, the bound dioxygn complex and the activated oxygen intermediate have only been inferred from model compound studies and by analogy with other heme proteins.

P450cam was the first member of the P450 family whose three-dimensional structure was determined by X-ray crystallography [3]. This structure was that of the enzyme-substrate complex (P450cam+camphor) with the oxidized cofactor (FeIII). Later, the structures of the met (aquo) form of the enzyme and of the enzyme-product complex (P450cam+5-exo-

Organic Reaction Mechanisms from Experimental Transition States

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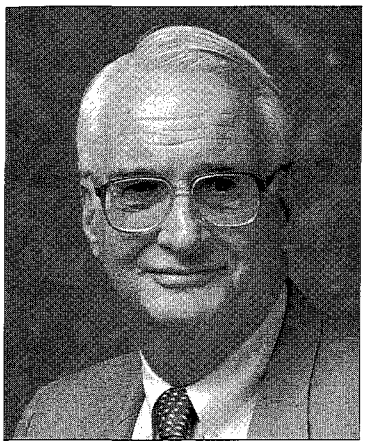
It has been said that organic chemistry is just ten million isolated facts without mechanistic theory. Physical organic and mechanistic analysis underlies all understanding of organic chemistry, and is used at some level in virtually all efforts to invent and control new reactions. However, the broad mechanistic understanding ordinarily used by organic chemists as the basis for their intuition gives way to a host of intricacies in reality. Real organic reactions are complex. Tremendous advances have been made in the understanding of organic reactions, but the finer mechanistic details of even venerable organic reactions are often uncertain, and each new reaction presents new questions. Unfortunately, mechanistic study is difficult, with years of work often failing to resolve controversies. As a result, organic chemists regularly make due with limited understanding of reactions of interest.

Our goal has been to develop methodology for the study of organic reactions that is both powerful and *fast*. A first step was the development of methodology for the high precision combinatorial determination of small isotope effects at natural abundance.[1] Any reaction at natural abundance is a competition reaction between all of the possible isotopically-substituted isomers (isotopomers). As a reaction proceeds, the product becomes enhanced in the faster reacting isotopomers and the starting material becomes enhanced in the slower reacting isotopomers. Thus, any reaction inherently provides mechanistic information about all possible kinetic isotope effects. We obtain this information by taking advantage of the isotope- and position-specific information inherent in NMR techniques. Consequently, the complete set of isotope effects (^{13}C, ^{2}H, ^{17}O, or in principle any minor NMR active nuclei) may be obtained from a single reaction at natural abundance.

With the rapid availability of kinetic isotope effects, the challenge shifts to their interpretation. Because isotope effects show what atoms are undergoing significant bonding changes in the rate-limiting step, their classical application is in making choices among highly divergent mechanistic possibilities. Such qualitative interpretations of isotope ef-

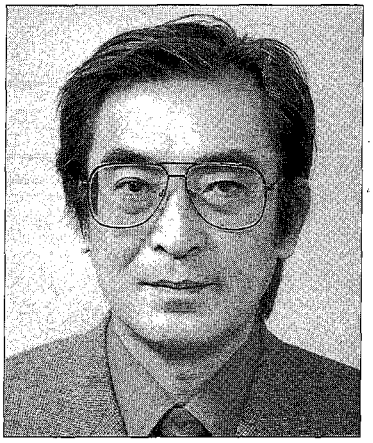


Peptide-Related Research: Its Genesis and Some Current Research at the University of Pennsylvania

Ralph Hirschmann

University of Pennsylvania

Peptide Chemistry had its beginning nearly one hundred years ago. In 1902, at a meeting in Karlsbad, Germany, Emil Fischer and Franz Hofmeister reported independently that proteins are made up of amino acids. Fischer even coined the term "peptide bond" to describe the linker. In this historical overview, I will discuss some arbitrarily selected breakthroughs in peptide research which have occurred during the 20th century. For example, the combination of activation of amino acids via azide formation (Curtius 1902) with the invention of the first urethane protecting group (Bergmann 1932) permitted the sequential addition of amino acids without epimerization about 60 years ago. Such milestones as the isolation and later the characterization and synthesis of biologically active peptides, the automation of both peptide synthesis (Merrifield) and peptide sequencing will be mentioned. The significance of the fact that Sanger determined the amino acid sequence of insulin at about the same time as Crick and Watson's discovery of the triplet code will be mentioned. Some highlights of collaborative peptide-related research at the University of Pennsylvania with Smith and Nicolaou will conclude the lecture.



Recent Progress in Multifunctional Asymmetric Catalysis

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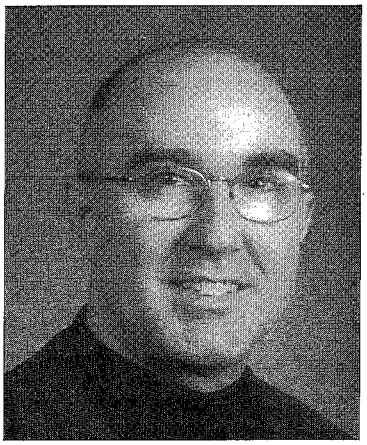
This lecture focuses on a new concept in catalytic asymmetric synthesis, which was first realized by the use of heterobimetallic complexes. Since these complexes function at the same time as both a Lewis acid and a Brønsted base, similar to enzymes, they make possible a variety of efficient catalytic asymetric reactions. This "heterobimetallic" concept has proven to be applicable to a variety of new asymmetric catalyses. We have already succeeded in carrying out asymmetric nitroaldol reactions catalyzed by the $LaLi_3$tris(binaphthoxide) complex (LLB), and asymmetric Michael reactions catalyzed by the $LaNa_3$tris(binaphthoxide) complex (LSB). Now, the LLB catalyst can also be applied efficiently to the tandem inter-and intramolecular asymmetric nitroaldol reaction, affording a synthetically usefull bicyclic product with four newly generated chiral carbons, in one pot. Furthermore, we have succeeded in the first direct asymmetric aldol reaction of aldehydes with unmodified ketones (up to 94% ee), using a catalytic amount of LLB. The LSB or $SmNa_3$tris (binaphthoxide) complex (SmSB) catalyzed Michael addition is even successful when thiols are used as the nucleophile. The SmSB catalyst was also found to be quite efficient for asymmetric protonation in the Michael reaction. While LLB was also effective in the hydrophosphonylation of aldehydes, asymmetric hydrophosphonylations of imines were efficiently catalyzed by the LnK_3tris(binaphthoxide) complex (LnPB:Ln = rare earch metal such as La, Yb) (up to 96% ee). Alkali metal free lanthanum complexes prepared from $Ln(O\text{-}i\text{-}Pr)_3$ (Ln = La or Yb), and 1,1' -binaphthol (BINOL) or 3-hydroxymethyl-BINOL, were excellent catalysts for the asymmetric epoxidation of α,β,-unsaturated ketones (up to 94% ee).

We also developed another type of heterobimetallic catalyst featuring group 13 elements, such as Al or Ga, as a central metal. Among them, the AlLibis (binaphthoxide) complex (ALB) is an effective catalyst for asymmetric Michael reactions of malonates or Horner-Wadsworth-Emmons reagents (up to 99% ee), and for asymmetric tandem Michael-aldol reactions. Applications of this catalytst to syntheses of biologically important



Challenges for Organic Synthesis in Forward & Reverse Chemical Genetic Research

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Natural products are known and have been synthesized that either inactivate or activate protein function, and some have recently been shown to do so with extraordinary specificity, equaling that of a gene deletion mutation. To extend the "chemical genetic"[1, 2] approach in the directions of both forward and reverse genetics, we are integrating methods from stereoselective synthesis, molecular cell biology, and miniaturization science. Conceptually, one would like to access through synthesis the many millions of presumed, "transient" natural products that were evolutionarily de-selected along the billion year paths that led to the natural products produced today. Using a far greater array of building blocks than used in nature, we are synthesizing millions of natural product-related compounds and assessing their properties by using rationally designed assays that can explore many facets of human biology not sampled during the selection of natural products.

Transcription profiling using cDNA microarrays allows the specificity of small molecules to be assessed in a semi-quantitative way for the first time. We have used this method to show that the specificity of a small molecule approaches that of a deletion mutant, where the gene encoding the small molecule receptor is inactivated. We have undertaken two approaches to generalize chemical genetics. The first uses small molecule dimerizers[3], and it allows the approach to be used to study the function of proteins for which small molecule ligands are not known. The second uses our ability to emulate many aspects of genetic principles to discover small molecule ligands, in the limit leading to a small molecule partner for every gene product[4]. My lecture will focus on the latter studies. I will present new syntheses of natural product-like compounds and two methods for analyzing these compounds – one using small molecule printing (for reverse chemical genetics) and the other using cytoblots (for forward chemical genetics).