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30th NATIONAL ORGANIC CHEMISTRY SYMPOSIUM



Under the auspices of the Divisions of Organic Chemistry
of the American Chemical Society and the Canadian Society for Chemistry,
and the University of British Columbia

June 21-25, 1987

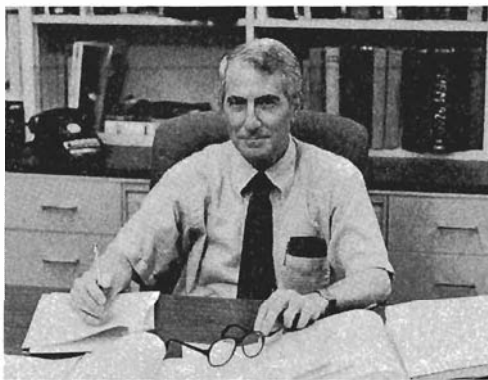
Vancouver, British Columbia

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 medal and an honorarium of ten 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 Jerome A. Berson of Yale University. His award address is entitled "Structure, Spin, and Reactivity of π -Conjugated non-Kekulé Molecules".



Jerome A. Berson

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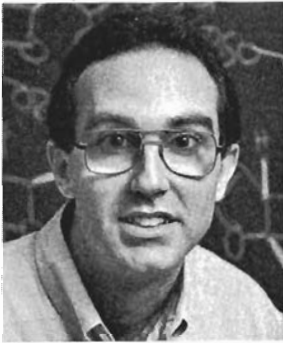
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Department of Chemistry, University of British Columbia

Speakers



Stuart L. Schreiber



Ronald Breslow



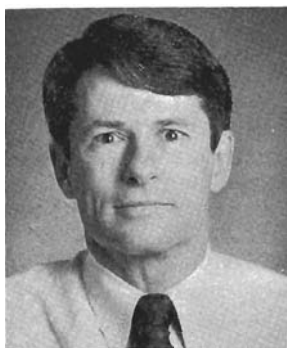
Jeremy R. Knowles



Samuel Danishefsky



E. Thomas Kaiser



C. Dale Poulter



Paul G. Gassman



David Dolphin



Gilbert Stork



K.C. Nicolaou

Program

Monday, June 22

- 8:30 AM Welcome, Announcements, and Opening of the Symposium
- 9:00 AM **Stuart L. Schreiber**, "Chemistry Relevant to Several Compounds of Biological Interest"
- 10:30 AM **Ronald Breslow**, "Mimics of Functionalizing Enzymes"
- 7:30 PM **Jeremy R. Knowles**, "The Evolution of Enzyme Function"
- 8:45 PM Poster Discussions and refreshments

Tuesday, June 23

- 9:00 AM **Samuel Danishefsky**, "Synthesis and Natural Products"
- 10:30 AM **E. Thomas Kaiser**, "The Design of Biologically Active Peptides and Proteins from Hormones to Enzymes"
- 7:30 PM **Jerome A. Berson**, *Adams Award Address*: "Structure, Spin, and Reactivity of π -Conjugated non-Kekulé Molecules"
- 8:45 PM Poster Discussions and refreshments

Wednesday, June 24

- 8:30 AM **C. Dale Poulter**, "Biosynthetic Tactics: Construction of Carbon-Carbon Bonds in the Isoprenoid Pathway"
- 10:00 AM **Paul G. Gassman**, "The Use of ESCA in the Characterization of Stable and Transient Metal Complexes"
- 11:15 AM **David Dolphin**, "Synthetic Heme Protein Active Sites"

Thursday, June 25

- 9:00 AM **Gilbert Stork**, "Radical Cyclizations in Natural Products Synthesis"
- 10:30 AM **K.C. Nicolaou**, "New Synthetic Technology and the Total Synthesis of Natural Products"
- 12 Noon Closing Remarks

All lectures will take place in IRC #2; posters will be set up in the IRC foyer

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Chemistry Relevant to Several Compounds of Biological Interest

Stuart L. Schreiber

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Natural products have played a prominent role in many of the successes attributed to the field of organic chemistry. The number of new reactions that have been discovered or developed in the course of a natural product synthesis is large. The elucidation of reaction mechanisms and the formulation of stereochemical and conformational constructs have resulted from some of the more momentous ventures in this area.¹

Of course, the significant biological properties that are characteristic of some natural products have attracted considerable attention. The formulation of new structures, based on natural product models, of compounds with increased efficacy and diminished toxicity constitutes an important challenge. Many biologically active natural products have been isolated with guidance from assays that detect a property of the compound relevant to the goals of improved human health and welfare. Traditionally, these assays measured, either directly or indirectly, cellular (e.g., microbial) or viral toxicity. Biochemical and pharmacological studies that shed light on the mechanism of action of these compounds have fostered efforts to develop stereochemical models of structure-function relationships. More recently, isolation methods have employed assays based on the measurement of enzyme inhibition or receptor binding.² Significantly, these "mechanism of action" assays also provide a shortcut to information necessary for the development of the structure-function models. Fermentation science serves as a more direct link to the organic chemist with an interest in formulating new structures with biological activity as the interest in this type of assay increases. Through synthesis, new materials have been prepared and tested for their intended function. Negative results have led to the refinement or abandonment of the model. Positive results have provided new materials with promise in medicine and utility in biology and chemistry. Needless to say, these activities offer the same opportunities for providing advances in reaction development and mechanism that the natural products syntheses present.

POLYFUNCTIONAL ENZYME MODELS

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There are two good reasons to prepare and study enzyme models. First of all, such models may contribute new chemical understanding that is relevant to the enzyme itself. In this situation chemistry is assisting biochemistry. The second reason for constructing enzyme models is to build artificial enzymes, which can catalyze chemical reactions with enzyme-like specificity and speed. To the extent that information about natural enzymes helps in the design of such novel catalysts, biochemistry is assisting chemistry.

In this presentation we will describe examples of both situations. First I will discuss a study of the cleavage of RNA by imidazole buffer, which is the simplest "enzyme model" imaginable. We have devised [1] a novel assay technique to follow RNA cleavage, using enzymatic hydrolysis as one of the assay steps. With this assay we studied [2] the cleavage of RNA by imidazole and imidazolium cation, the two principal catalytic groups in the enzyme ribonuclease.

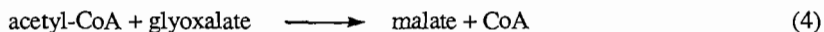
We observed a bell-shaped rate vs. pH profile, as expected for bifunctional catalysis. Ribonuclease itself shows a similar pH vs. rate profile, as does a cyclodextrin bis-imidazole we prepared some years ago as a ribonuclease mimic [3]. However, in the current study the rate was strictly

SYNCHRONEITY AND CONCERT IN ENZYME-CATALYZED REACTIONS

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The convention of the curly arrow is an invaluable shorthand that chemists use to summarize mechanistic pathways. When this convention is combined with the view that enzymes must surely exploit all imaginable chemical devices to achieve the extraordinary rate acceleration that they mediate, we are often led to the view that the combination of "push" and "pull" in a catalyzed reaction will result in a concerted (if not actually a synchronous) reaction. Most seductive to the chemist, of course, are those reactions that involve (or seem to involve) six-membered cyclization states. In this lecture, we shall examine several examples of enzyme-catalyzed reactions for which concerted transition states have been suggested. In so doing, a number of different methods for the unambiguous distinction between stepwise and concerted reactions will be illustrated. These include stereochemical approaches (which we have used to investigate the reaction catalyzed by phosphoenolpyruvate carboxylase (eq. 1) and the ATP-dependent carboxylation of biotin (eq. 2)), and use of the double isotope fractionation method (which we have used to probe the carboxylation of pyruvate by carboxy-biotin (eq. 3), and the Claisen reaction catalyzed by malate synthase (eq. 4)):



It will become evident that concerted processes are rare in enzymology, and that the pathway of lowest free energy seems often to involve explicit enzyme-bound reaction intermediates.

SYNTHESIS AND NATURAL PRODUCTS

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The study of the total synthesis of natural products has attracted the attentions of organic chemists almost from the dawn of the subject.² Early on, there was doubt as to whether a natural product could, in principle, be obtained in the laboratory. Perhaps there was a difference in essence between "natural" and "unnatural" products. In a later development, synthesis was seen to provide the ultimate proof of structure of the target. It was felt that a total synthesis exercise could not succeed unless the structural hypothesis was correct. Still another incentive arose from the possibility that through synthesis, practical access to the "natural" product could be improved. In a variation of this theme, it has been properly argued that a successful total synthesis opens up routes to the preparation of analog structures of a type which might not be accessible from retro fitting of the parent structure itself.

With the maturation of organic chemistry into a fully respectable, intellectual endeavor, a new dimension of synthesis grew in importance. Increasingly synthesis came to be seen as an important arena for testing new ideas, for discovering new reactions and for ascertaining the feasibility limits of "known" reactions. Moreover, it has become appreciated that the strategy of a synthesis has, in itself, heuristic implications which enrich the science. As the power and reach of separation sciences, spectroscopy and crystallography increase, the sophistication of identifiable structures coming off nature's assembly lines continues to grow. New challenges to the acumen of the chemist emerge. More importantly, the existence of such complex structures challenges the current limits of the strategic capacity of the field and, by implication, the outer reaches of chemical theory itself.

When viewed through such prisms and against the standard of what "ought to be" rather than what has already been accomplished, that fascinating science-art form which we call total synthesis is properly perceived to be in a rather primitive state. Though the strides and accomplishments of biotechnology in synthesis have indeed been formidable and will become even more so, they do not yet address the serious intellectual issues which must be mastered in a laboratory synthesis of a complex, non-repetitive³ natural product.

THE DESIGN OF BIOLOGICALLY ACTIVE PEPTIDES FROM HORMONES TO ENZYMES

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Several years ago when we decided to begin to design biologically active peptides and proteins we divided our efforts into two approaches. In one approach we took existing folded structures, tertiary structures like those in enzymes, and introduced new catalytic groups either by chemical modification (semisynthetic enzymes)¹⁻³ or by genetic engineering (site-directed mutagenesis)^{4,5}. In the other, because our ability to predict folding patterns or tertiary structure from primary amino acid sequences was not developed, we undertook to design the structural regions of biologically active peptides and proteins where to a first approximation we could neglect folding^{6,7}. In other words, we concentrated on designing systems where secondary structural features played a major role in determining the biological and physical properties of the peptides and proteins. It is the latter approach focusing on secondary structural elements that I shall discuss primarily in my lecture.

In searching for peptides and proteins to model where we would not have to concern ourselves initially with folding problems we were drawn to surface active molecules that bind at membrane interfaces. We proposed that the biological and physical properties of peptides and proteins binding in amphiphilic environments like those of membranes often depend on the

STRUCTURE, SPIN, AND REACTIVITY OF PI-CONJUGATED NON-KEKULE' MOLECULES

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Theoretical Introduction: Non-Kekule' (ref. 1) pi-conjugated molecules contain enough atoms but not enough bonds to satisfy the standard rules of valence (ref. 2). Nevertheless, a number of such compounds exist, and their properties, in some cases at least, are reasonably well understood.

One might imagine that Nature would impose a condign penalty on any rash enough to violate so basic a concept as the structural theory of organic chemistry. Indeed, the study of non-Kekule' molecules is burdened with an unavoidable complexity, which originates in the need to specify the electronic spin state and configuration. However, this challenge motivates the search for predictability through an interplay of theory and experiment.

At a low level of theory, for example, in the Hückel approximation, the two electrons from the (conceptually) broken bond of a non-Kekule' molecule occupy a degenerate pair of molecular orbitals (MOs). In these circumstances, the customary application of one form of Hund's rule (ref. 3) leads to the prediction that the triplet spin state will be favored over the singlet. More generally, the state of highest multiplicity will be the lowest energy state of a given electronic configuration.

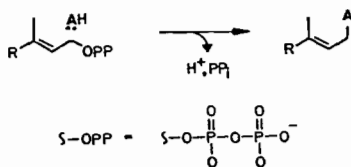
Nevertheless, good theoretical reasons support the conjecture that Hund's rule may not apply to certain pi-conjugated non-Kekule' molecules. This was first recognized by E. Hückel as long ago as 1936 (ref. 4) in a discussion of two non-Kekule' hydrocarbons of Schlenk and Brauns (refs. 5 and 6), 1 and 2. The connectivity patterns in the two molecules are fundamentally disparate. Because the carbon atoms at the 2-forming union have zero HMO coefficients (the sites are "inactive" (ref. 7)), the exchange energy vanishes at this level of approximation, and the normal basis for the application of Hund's rule vanishes with it.

BIOSYNTHETIC TACTICS: CONSTRUCTION OF CARBON-CARBON BONDS IN THE ISOPRENOID PATHWAY

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The isoprene pathway is one of nature's most versatile schemes for the construction of naturally occurring molecules. Parts or all of several thousand organic compounds with a myriad of functions are produced during isoprenoid metabolism. Some of the more well known classes are plant mono-, di-, and sesquiterpenes, sterols, carotenoids, ubiquinones, and dolichols.

The building reactions in the central part of the pathway are unique. The substrates lack carbonyl groups, and construction of carbon-carbon bonds does not rely on the aldol and Claisen chemistry commonly encountered in the fatty acid, polyketide, glycolytic, and many other major pathways. Instead, the skeleta of isoprenoids are assembled by a series of prenyl transfer reactions. These are bisubstrate processes that involve an isoprenoid allylic



diphosphate ester and an electron-rich acceptor and result in alkylation of the acceptor by the hydrocarbon portion of the allylic substrate, loss of inorganic pyrophosphate from the allylic residue, and loss of a proton from either the allylic or acceptor moieties.¹ The most common example of prenyl transfer is the sequential 5-carbon extension of isoprenoid chains using

THE USE OF ESCA (XPS) IN THE CHARACTERIZATION
OF STABLE AND TRANSIENT TRANSITION METAL COMPLEXES

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X-Ray photoelectron spectroscopy (XPS, ESCA) has been utilized primarily by analytical chemists and physical chemists. As a result, relatively little use has been made of this spectroscopic method by organic or inorganic chemists. This is unfortunate because ESCA can provide information which is not available through other techniques. This is especially true when this technique is applied to the broad area of organometallic chemistry.

This presentation will outline the application of ESCA to a variety of studies in organometallic chemistry. These studies will include the characterization of active catalysts in olefin metathesis,¹ the quantitative assessment of the electronic effects of certain ligands on the electronic properties of various transition metals,² the correlation of electrochemically evaluated properties (valence shell electrons) with ESCA evaluated properties (inner shell electrons),² the synthesis and evaluation of new ligands,³ and lastly, a detailed look at the application of our newly developed techniques to the

SYNTHETIC HEME PROTEIN ACTIVE SITES

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Heme proteins play many varied functions in living systems. Hemoglobin and myoglobin bind, transport and store molecular oxygen, and the cytochromes carry out the same roles with electrons. Catalases and peroxidases control and consume hydrogen peroxide. In both cases an initial oxidation of the porphyrin macrocycle, by peroxide, precedes a subsequent substrate oxidation¹ (peroxide in the case of catalase, phenols and aromatic amines for the peroxidases). Most aerobic organisms employ for the last step in respiration a cytochrome oxidase which, with a high thermodynamic efficiency, brings about a four electron reduction of dioxygen to water, without the release of peroxide. The cytochromes P-450 include a similar reduction of dioxygen but, being monooxygenases, a two electron reduction gives water and an oxidant so powerful that, under physiological conditions, the hydroxylation of unactivated C-H bonds is achieved.² Lignin makes up 25% of this planet's total annual biomass, but it was only in 1983 that ligninases, which depolymerize lignin, were isolated; they are, of course, heme proteins.³

With but minor modifications all of these heme proteins use heme (iron protoporphyrin (1)) at their active sites. How is such diverse chemistry controlled by the same porphyrin? Clearly the protein must play a major role in modulating the enzymatic chemistry. We plan to show, using synthetic model porphyrins, what some of the roles of the proteins are and how, having understood the enzymatic mechanisms,

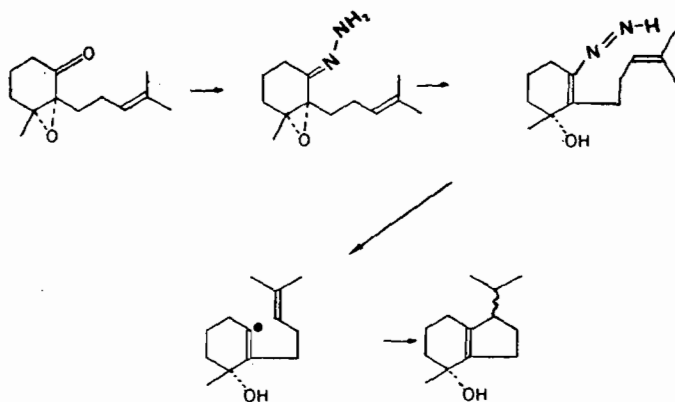
RADICAL CYCLIZATION IN NATURAL PRODUCT SYNTHESIS

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A number of years ago we realized that radical cyclization reactions might become an important addition to the methods available for the synthesis of carbon frameworks of some complexity. There had been some earlier effort, largely by Marc Julia and his group in France, starting around 1960, who studied the radical-mediated cyclization of certain cyanoacetic ester derivatives. These interesting cyclizations did not develop into general synthetic tools, perhaps because of the uncertainty which resulted from apparent reversibility, at least under the relatively high temperatures often required to initiate them. Interest in radical cyclizations then became the province of physical organic chemists. Walling in the United States, Beckwith in Australia, and Ingold in Canada made especially important contributions by their studies of stannane-initiated cyclizations of 6-bromohexene and related systems. Their work unraveled the rates of the various competing reactions, and demonstrated the kinetic preference for five-membered ring formation which is normally shown by these particular radical cyclizations.

Our interest in the synthetic potential of radical cyclization processes was aroused by the study of the reactions by which certain α,β -epoxyketones bearing an apposite double bond undergo cyclization upon reaction with hydrazine in methanol.¹ It occurred to us that this type of cyclization might involve the formation of vinyl radicals as intermediates and that, should the cyclization of vinyl radicals be generally feasible, a radical cyclization process of



NEW SYNTHETIC TECHNOLOGY AND TOTAL SYNTHESIS

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The brevetoxins are a new class of marine natural products produced by the dinoflagellates *pytchodiscus brevis* (*Gymnodinium breve*) Davis which flourish during the so called "red tide" catastrophes and cause massive fish and other marine life destructions¹. The structures of the two most prominent and potent members of this group of compounds, brevetoxins B² and A³, have recently been established by spectroscopic and X-Ray crystallographic techniques.

These remarkable structures provide unique synthetic challenges in that they stand at the limits of current synthetic technology. Particularly challenging are the plethora and variety of stereogenic centers and oxarings, present in their molecular frameworks. They, therefore, provide excellent opportunities for the development of new synthetic processes and strategies and for contributions in biological areas relating to their biosynthesis and mode of action. Our synthetic efforts in this area will be the topic of this lecture.

A number of new reactions have been devised to address the various subunits of the brevetoxins. These include:

1. Regio- and stereocontrolled formation of tetrahydropyran systems via activation of *endo* over *exo* epoxide openings by π -orbital participation (**Scheme 1**)⁴.
2. New Synthetic technology for the construction of oxocenes by intramolecular trapping of sulfonium species with hydroxyl groups (**Scheme 2**)⁵.
3. New synthetic technology for the construction of *cis*- and *trans*-fused oxapolycyclic systems by bridging of macrocycles to bicycles (**Scheme 3**)⁶, and
4. New synthetic technology for the construction of medium and large ring ethers via nucleophilic additions to thionolactones (**Scheme 4**)⁷.

These and other new synthetic reactions and strategies and their application to projected total syntheses of brevetoxins B and A will be discussed.