TWENTY-FOURTH NATIONAL ORGANIC CHEMISTRY SYMPOSIUM of the AMERICAN CHEMICAL SOCIETY

AUSPICES OF THE DIVISION OF
ORGANIC CHEMISTRY
and
COLORADO STATE UNIVERSITY

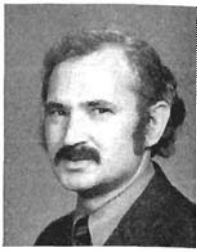
June 22-26, 1975
Fort Collins, Colorado

TWENTY-FOURTH NATIONAL ORGANIC CHEMISTRY SYMPOSIUM of the AMERICAN CHEMICAL SOCIETY

SPEAKERS AT THE TWENTY FOURTH NATIONAL ORGANIC CHEMISTRY SYMPOSIUM

R. G. Bergman

J. E. Baldwin



A. J. Bard

E. J. Corey

J. P. Collman

P. Deslongchamps

E. L. Eliel

C. R. Johnson

J. R. Knowles

A. A. Lamola

R. V. Stevens

N. J. Turro

PROGRAM

SUNDAY, June 22

Registration: Braiden Residence Hall, 6:00–9:00 p.m.

MONDAY, June 23

Registration: Student Center, 2nd Floor Lobby, 8:00 a.m.
Meetings: Student Center, Main Ballroom

9:00 A.M. Welcome. A. R. CHAMBERLAIN, President of Colorado State University.
Response. JEREMIAH P. FREEMAN, Chairman Division of Organic Chemistry, ACS.

9:30 A.M. ANGELO A. LAMOLA, "Molecular Mechanisms in a Human Photosensitivity Disease."

10:45 A.M. ROBERT V. STEVENS, "Studies on the Synthesis of Corrins and Related Ligands. An Approach to the Total Synthesis of Vitamin B-12."

8:00 P.M. ELIAS J. COREY, "Synthetic Routes to Prostaglandins."

TUESDAY, June 24

8:45 A.M. ALLEN J. BARD, "Organic Electrochemistry."

10:00 A.M. ROBERT G. BERGMAN, "Thermal and Cobalt-catalyzed Transformations of Organic Compounds."

11:15 A.M. PIERRE DESLONGCHAMPS, "Stereoelectronic Control in the Cleavage of the Tetrahedral Intermediate in the Hydrolysis of Amides."

8:00 P.M. ROLF HUISGEN, "Electrocyclic Ring Opening Reactions of Ethylene Oxides."

WEDNESDAY, June 25

8:45 A.M. JAMES P. COLLMAN, "Synthetic Models for the Oxygen Binding Hemoproteins

10:00 A.M. JACK E. BALDWIN, "The Oxidation of Peptides Related to the β-Lactam Antibiotics."

11:15 A.M. JEREMY R. KNOWLES, "The Energetics of Enzyme Catalysis: Evolution to Perfection?"

8:00 P.M. ERNEST L. ELIEL, "Twenty-five Years of Conformational Analysis."

THURSDAY, June 26

8:45 A.M. NICHOLAS J. TURRO, "Chemiluminescent Organic Reactions."

10:00 A.M. CARL R. JOHNSON, "New Synthetic Methods Involving Sulfur Reagents."

THE ROGER ADAMS AWARD IN ORGANIC CHEMISTRY

The Roger Adams Award in Organic Chemistry has been established with joint sponsorship by the American Chemical Society, Organic Reactions, Inc., and Organic Syntheses, Inc. 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. The presentation of the award is made at the biennial National Organic Chemistry Symposium of the Division of Organic Chemistry of the American Chemical Society, and the recipient delivers a lecture as part of the program of the Symposium.

The award recognizes the distinguished career of Roger Adams who played such a vital role in each of the three organizations sponsoring the award, having been Chairman of the Board of Directors as well as President of the American Chemical Society and co-founder of Organic Syntheses and Organic Reactions.

The recipient of this year's award is Professor Rolf Huisgen of the Institute for Organic Chemistry at the University of Munich. His award address is entitled "Electrocyclic Ring Opening Reactions of Ethylene Oxides."

R. Huisgen

ORGANIZING COMMITTEES

The plans and program for the 24th National Organic Chemistry Symposium have been developed by the members of the Executive Committee of the Division of Organic Chemistry who have served during the past two years.

	1973–74	1974–75
Chairman	E. L. Eliel	J. P. Freeman
Chairman-elect	J. P. Freeman	H. E. Simmons
Secretary	E. M. Burgess	E. M. Burgess
National Symposium Executive Officer	C. D. Gutsche	C. D. Gutsche
Executive Committee	M. C. Caserio	M. C. Caserio
	C. J. Collins	E. L. Eliel
	H. L. Goering	H. L. Goering
	N. A. LeBel	N. A. LeBel
	J. G. Moffatt	J. G. Moffatt
	W. A. Sheppard	J. H. Prager
	H. J. Shine	H. J. Shine
	A. M. Trozzolo	A. J. Speziale
		A. M. Trozzolo

The local arrangements have been handled by a committee consisting of A. I. Meyers (Chairman), K. E. DeBruin, L. S. Hegedus, L. I. Miller, and F. R. Stermitz who are members of the Department of Chemistry, Colorado State University.

CONTENTS

MOLECULAR MECHANISMS IN A PHOTOSENSITIVITY DISEASE

Angelo A. Lamola

Bell Laboratories

Murray Hill, N.J.

Erythropoietic Protoporphyria (EPP)

The predominant early symptom of the rare hereditary metabolic disorder erythropoietic protoporphyria (EPP) is severe cutaneous photosensitivity which is disabling under bright sunlight conditions (Magnus, 1940). The disease is characterized by a large elevation over normal of the concentration of acid-extractable protoporphyrin (PP) in the red blood cells (rbc), plasma, and feces. The elevated rbc PP causes these cells to fluoresce brightly. The action spectrum for the enhanced erythemal response of the skin matches the absorption spectrum of PP (Magnus).

A characteristic of the rbc of the EPP patients is the facile *in vitro* photohemolysis they undergo, a feature of some diagnostic value but of unknown clinical importance (Harber, 1964). This photohemolysis requires molecular oxygen and has a porphyrin-like action spectrum; membrane lipids become oxidized, and antioxidants and quenchers of singlet oxygen are inhibitory (Goldstein and Harber, 1972, Schothorst et al. 1972).

For an organic photochemist the most fascinating aspect of EPP is, perhaps, the impressive effectiveness of orally

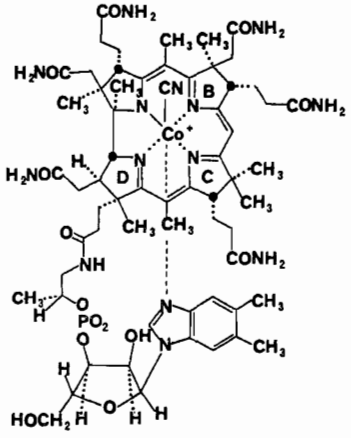
STUDIES ON THE SYNTHESIS OF CORRINS AND RELATED LIGANDS. AN APPROACH TO THE TOTAL SYNTHESIS OF VITAMIN B-12

Robert V. Stevens

Rice University

Houston, Texas

Any synthetic investigation whose ultimate goal is the total synthesis of vitamin B-12 must ultimately rely on a reliable method for construction of the macrocyclic "corrin" ligand.



Vitamin B_{12}

In consonance with this fact we have been developing methodology [J.A.C.S. 93, 6629, 6637 (1971)] which utilizes isoxazole ñũclei as equivalent synthons for the crucial ring bridging vinylogous amidine chromophores found in both the corrin and corphin ligands.

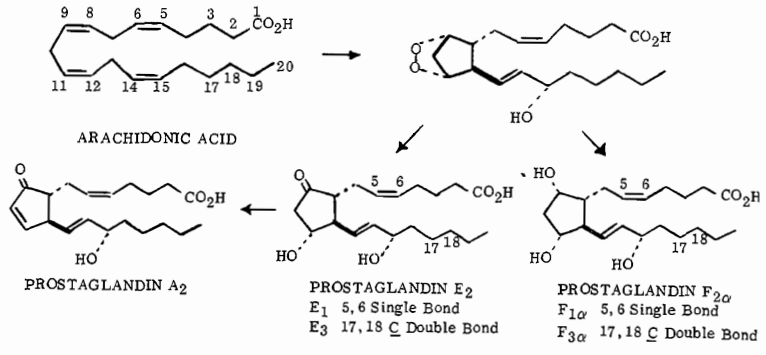
SYNTHETIC ROUTES TO PROSTAGLANDINS

Elias J. Corey

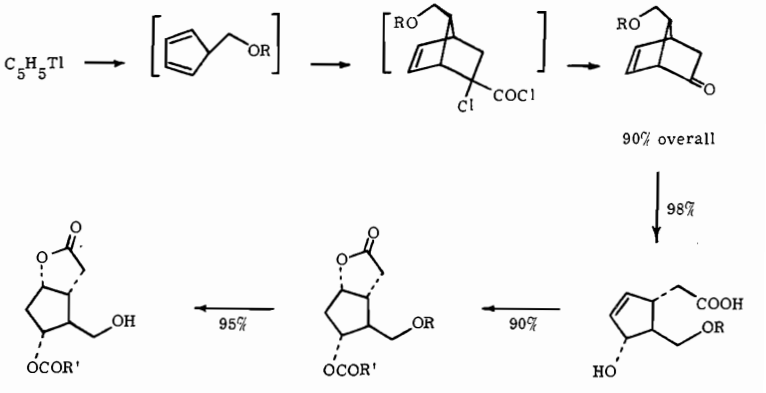
Harvard University

Cambridge, Mass.

STRUCTURE/BIOSYNTHESIS OF PROSTAGLANDINS



General PG Synthesis (1969-73)



R = CH_3, $CH_2C_6H_5$, CH_2CCl_3

R' = CH_3, p-$C_6H_5C_6H_4$, p-$C_6H_5C_6H_4NH$

Facile resolution achieved for R = CH_3, CH_2CCl_3, and $CH_2C_6H_5$.

ORGANIC ELECTROCHEMISTRY

Allen J. Bard

University of Texas

Austin, Texas

Introduction

The field of organic electrochemistry has undergone rapid expansion in recent years, as evidenced by the appearance of a number of books and review articles in this area.[1-4] Several reasons can be given for the recent advances in this area. The use of aprotic solvents, especially in conjunction with vacuum line and glove box techniques, allowed observation of reactive intermediates (e.g. radical ions) and simplification of the overall reaction mechanisms. These studies permitted correlations of the electrochemical results with spectroscopic and MO data so that a molecular basis of electrochemical reactions of aromatic compounds could be established. A number of new electrochemical techniques have been devised and rigorous theoretical treatments for the elucidation of complex reaction schemes using these methods have been reported. Modern instrumentation for applying these techniques has become commercially available; the application of three electrode cells, especially when used in conjunction with positive feedback resistance compensation circuits have made precise measurements possible, even in highly resistive organic solvents. Finally the realization that electrochemical methods allow the generation and study of short-lived species, with the acquisition of accurate thermodynamic and kinetic data about the reactions of these species, has produced numerous studies, especially in the area of radical ion chemistry.

This lecture will discuss several topics in organic electrochemistry based on recent research in our laboratory mainly to illustrate the types of problems that can be attacked and the kinds of information obtainable by electrochemical

THERMAL AND COBALT-CATALYZED TRANSFORMATIONS OF ORGANIC COMPOUNDS

Robert G. Bergman

California Institute of Technology
Pasadena, California

The carbon-carbon triple bond has an unusually high heat content, and this makes the large majority of reactions which involve the conversion of acetylenes into olefinic or saturated molecules highly exothermic. The large exothermicity of simple acetylene oligomerization reactions is illustrated by the examples shown below. Benzene is, of course, a very stable molecule, and so its formation from three acetylene molecules releases a great deal

	$\Delta H°$ (kcal/mole)	$-T\Delta S°$ (kcal/mole. r.t.)
3 HC≡CH ⟶ 	-143	+25
2 HC≡CH ⟶ 	-51?	+10
2 HC≡CH + CO ⟶ 	-80	+22

of energy. However, even in the (hypothetical) cycloaddition of two acetylenes to cyclobutadiene, an estimate of the enthalpy of reaction indicates a relatively large exothermicity, and the same is true of cyclopentadienone formation. In each case, the room temperature entropy tends to increase the free energy of reaction, but not by a large enough value to make these processes thermodynamically inaccessible.

These considerations led us to the idea that acetylenic molecules should be ideal precursors in the synthesis of highly strained or otherwise energetic organic molecules, if appropriate conditions or catalysts for such

STEREOELECTRONIC CONTROL IN THE CLEAVAGE OF THE TETRAHEDRAL INTERMEDIATE IN THE HYDROLYSIS OF AMIDES

Pierre Deslongchamps

University of
Sherbrooke
Sherbrooke, Canada

We have recently described a new theory of stereoelectronic control for the cleavage of tetrahedral intermediates which are formed during the hydrolysis of esters (1) and amides (2, 3).

This work originated from our previous study of the oxidation of acetals by ozone (4). In this new approach, the precise conformation of the tetrahedral intermediate plays a major role in determining the products formed. It is postulated that the precise conformation of the tetrahedral intermediate is transmitted into the products of the reaction and that the specific decomposition of such intermediate is controlled by the orientation of the lone pair orbitals of the heteroatoms. Stereoelectronic cleavage of a tetrahedral intermediate is defined in the following way: specific cleavage of a carbon-oxygen or a carbon-nitrogen bond which occurs when two heteroatoms (oxygen or nitrogen) of the tetrahedral intermediate each have an orbital oriented antiperiplanar to the departing O-alkyl or N-alkyl leaving-group.

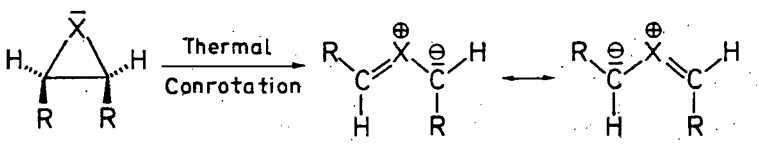
A study of the basic hydrolysis of several imidate salts having either a *syn* or an *anti* conformation will first be described. The stereoelectronic theory predicts that an imidate salt having an *anti* conformation such as 1A will react with hydroxide ion to give the tetrahedral conformer 2A (Figure 1). Conformer 2A can be cleaved with stereoelectronic control to yield the ester-amine products. The theory implies that when a tetrahedral intermediate can break down in a stereoelectronically controlled fashion, the energy barrier for its cleavage is much lower than that for rotation to give other conformers. So, there is no need to consider other conformers

ELECTROCYCLIC RING OPENING REACTIONS OF ETHYLENE OXIDES

Rolf Huisgen

University of Munich
Munich, Germany

Electrocyclic ring opening reactions of aziridines and oxiranes have been known for ten years ; they are of preparative importance and theoretical interest.[1] The azomethine ylides and carbonyl ylides, which occur in thermal or photochemical equilibrium with the three-membered heterocycles, undergo 1,3-dipolar cycloadditions to many multiple-bond systems producing a variety of five-membered heterorings. Substituted aziridines were shown



X = N-R : Aziridine ⇌ Azomethine ylide

X = O : Oxirane ⇌ Carbonyl ylide

to undergo the thermal conrotation and photodisrotation[2] predicted by Woodward and Hoffmann for the isoelectronic system cyclopropyl anion → allyl anion.[3] An ensemble of kinetic methods revealed the total energy profile of ring opening, rotation and ring closure of trisubstituted aziridines.[4]

Much less is known mechanistically of the oxirane ring opening which was discovered by Linn and Benson in 1965.[5] However, the tetracyanoethylene oxide used cannot give information on the steric mode of ring opening.

SYNTHETIC MODELS FOR THE OXYGEN BINDING HEMOPROTEINS

James P. Collman

Stanford University

Palo Alto, California

Metalloproteins often exhibit structural, physical, and chemical properties which have no counterparts among synthetic metal complexes. Until recently, this was the case with the oxygen binding hemoproteins, hemoglobin (Hb), myoglobin (Mb), and cytochrome P-450. In each of these substances a protein encompasses a ferrous protoporphyrin IX providing an environment that reversibly binds (Hb and Mb) or activates (P-450) molecular oxygen. In these cases the protein provides a protective oxygen binding cavity and donates the appropriate axial base (a histidyl imidazole in the case of Hb and Mb). The manner by which the protein stabilizes the iron-dioxygen complex towards irreversible oxidation, the structural features of coordinated dioxygen, and the nature of the axial base in P-450 have long been points of controversy. Some of these questions have been clarified by the synthesis, isolation, structural characterization, and spectroscopic study of model iron porphyrins and their dioxygen complexes[1].

Simple iron(II) porphyrin complexes react irreversibly with oxygen affording μ-oxo iron(III) complexes. This reaction is

$$4B_2Fe(TPP) + O_2 \rightarrow 2(TPP)Fe\text{-}O\text{-}Fe(TPP) + 4B$$

TPP = mesotetraphenylporphyrin, B=imidazole, etc.

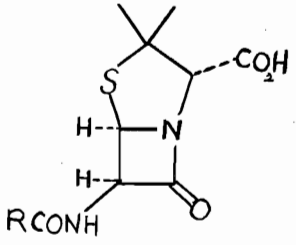
retarded by lowering the temperature[2], decreasing the iron concentration, and increasing the concentration of axial base, B. Even mild proton acids catalyze this

THE OXIDATION OF PEPTIDES RELATED TO THE β-LACTAM ANTIBIOTICS

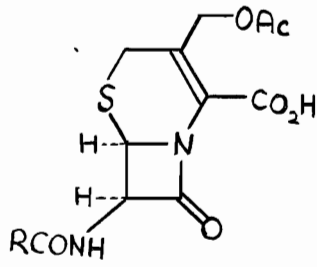
Jack E. Baldwin

Massachusetts
Institute of
Technology
Cambridge, Mass.

The detailed biosynthetic pathway to the β-lactam antibiotics penicillin (1) and cephalosporin (2) is essentially unknown. For the past four years we have been engaged on a joint biosynthetic

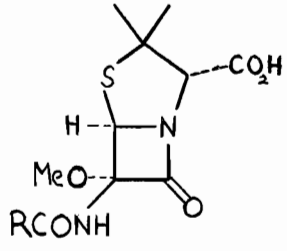


(1)



(2)

and chemical synthesis program designed to clarify this problem and to make available new members of this class. Some of our results will be presented. Early work from our group demonstrated the first stereospecific functionalization of C-6 and then the first direct methoxylation of C-6 and C-7 in the penicillins (3) and cephalosporins (4) respectively. These latter compounds are active antibiotics:-



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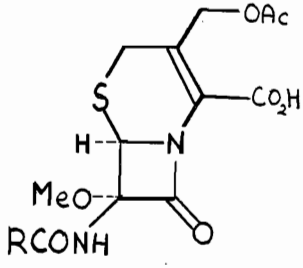


(4)

THE ENERGETICS OF ENZYME CATALYSIS: EVOLUTION TO PERFECTION?

Jeremy R. Knowles

Harvard University

Cambridge, Mass.

The mechanistic description of an enzyme-catalyzed reaction requires the synthesis of both kinetic and structural information, showing how the static structure that is observed crystallographically, leads to the particular sequence of dynamic events. With the promise of solutions to high resolution of the crystal structures both of the enzyme triose phosphate isomerase and of its complex with substrate, (D. C. Phillips, Oxford), it has been our aim to solve the energetics of this catalyzed reaction and to describe all the kinetically significant transition states and intermediates. This has proved possible by virtue of the remarkably fine balance amongst the rates of the different elementary steps, and has revealed--as an unexpected bonus--that this enzyme appears to have arrived at the end of its evolutionary development.

The interconversion of the two triose phosphates involves the breaking (and making) of the

TWENTY-FIVE YEARS OF CONFORMATIONAL ANALYSIS

Ernest L. Eliel

University of
North Carolina
Chapel Hill, N.C.

The chair shape of cyclohexane was first recognized by H. Sachse in 1890, the principle of rapid ring inversion was appreciated by E. Mohr in 1918, experimental evidence for the chair form was provided by H. G. Derx, P. Hermans and W. Hückel in 1922-25 and the axial and equatorial positions were distinguished spectroscopically by Dickinson and Bilicke (1928) and by Kohlrausch (1936). Yet, the conformational behavior of cyclohexane began to become clear only in the early 1940's when O. Hassel [Tidskr. Kjemi Bergvesen Met., 3, 32 (1943)] discussed conformational equilibria in monosubstituted cyclohexanes on the basis of electron diffraction data. And it was only in 1950 that D. H. R. Barton [Experientia, 6, 316 (1950)] coined the term "conformational analysis", introduced the subject to organic chemists and, almost immediately, brought home its enormous importance in predicting stability, reactivity and physical properties in such widely occurring molecules as steroids and terpenoids and some alkaloids. This work, which led to the award of the Nobel Prize in Chemistry for 1969 to Barton and Hassel, is properly considered the origin of conformational analysis and so, in 1975, we are celebrating the 25th anniversary of this important subject.

Our own interest in the subject was aroused by Barton's lectures in the United States in early 1950 and we turned to the mobile systems studied earlier by Hassel. The first case we examined concerned the rates of nitrobenzoylation of the menthols, studied earlier by J. Read. [E. L. Eliel, Experientia, 9, 91 (1953)]. This

CHEMILUMINESCENT ORGANIC REACTIONS

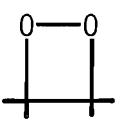
Nicholas J. Turro

Columbia University

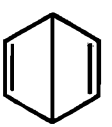
New York, N.Y.

CHEMILUMINESCENCE : THE PHENOMENON

The visual observation of light streaming out of an object (which is apparently at ambient temperatures) is a curious sight. The phenomenon of chemiluminescence has intrigued scientists for centuries. Until relatively recently, however, very little was known about the molecular details of the chemiluminescence sequence involving organic molecules. We shall consider here both the mechanisms of some chemiluminescent reactions and the application of chemiluminescence to study the mechanism of photochemical reactions. In particular, chemiluminescent pericyclic reactions involving 1,2-dioxetanes and the valence isomers of benzene will be discussed.

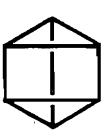


1,2-DIOXETANE



DEWAR BENZENE

BENZVALENE



PRISMANE

BIS-CYCLOPROPENYL

NEW SYNTHETIC METHODS INVOLVING SULFUR REAGENTS

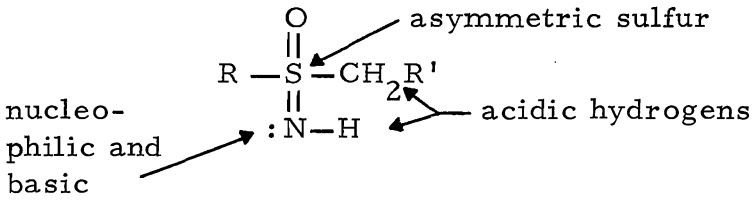
Carl R. Johnson

Wayne State University

Detroit, Michigan

SULFOXIMINE REAGENTS

The sulfoximine functional group is uncommonly versatile. It has acidic hydrogens on carbon and nitrogen, it is basic and nucleophilic at nitrogen and it is potentially asymmetric.



As a model system and as a starting point for much of our work we have utilized S-methyl-S-phenylsulfoximine (1). The most practical methods for the synthesis of 1 and its derivatives are illustrated in Scheme I.

Our work, which commenced in 1968, has focused on the utilization of sulfoximines and their derivatives as reagents for organic synthesis. Besides novelty, these compounds have great potential for synthetic applications; they enable things to be done easily which are difficult or impossible by other methods.