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Edited by

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Advances in Physical Organic Chemistry

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Editor's preface

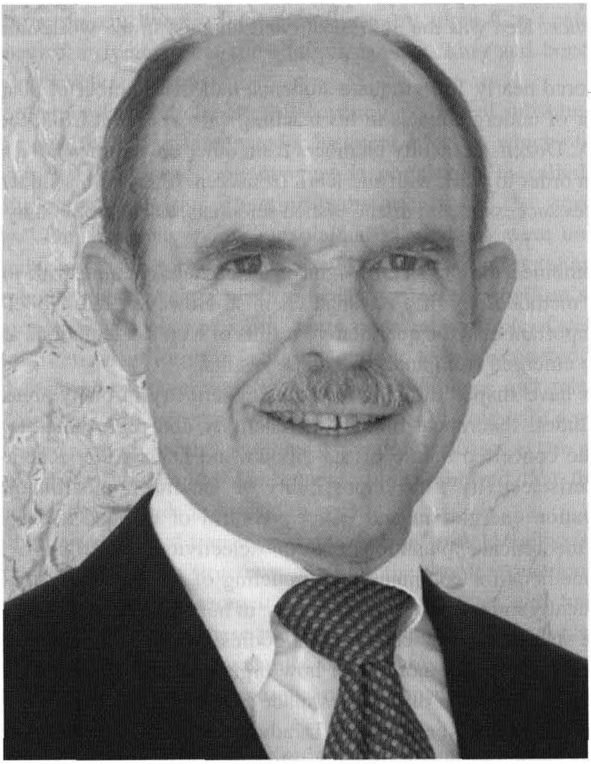
The speed of computers has increased exponentially during the past 50 years and there is no sense that an upper limit has been reached. This has resulted in a continuous assessment of the quality of the agreement between chemical experiments and calculations, and signs that the perpetual confidence of computational chemists in the significance of their calculations will eventually be fully justified, if this is not already the case. The interplay between computational and experimental chemists can be painful. It is sometimes diffcult for experimentalists to avoid the uncongenial and uncharitable view of computational chemists as dilettantes, with little interest in coming to grips with the tangled web of experimental work as needed to evaluate the agreement between theory and calculation and, consequently, no sense of the reactivity of real molecules and the mechanisms by which they react. Computational chemists may fee certain reservations regarding the abilities of experimentalists who become embroiled in interminable and unfathomable controversies about the interpretation of their data. It is understandable that they might view a world where experiments are rendered obsolete by computational infallibility as desirable. A degree of sympathy and mutual respect can be achieved through collaborations between experimental and computational chemists directed towards solving problems of common interest.

The question of the scope of Physical Organic Chemistry is often raised by those who recognize that this field is regarded by some as unfashionable, and who are concerned by the limited attention paid to problems that first spurred its development – Hammett relationships; reactive intermediates; proton-transfer at carbon; polar reaction mechanisms; and so forth. Those who identify with Physical Organic Chemistry have little choice but to work to expand its scope, while preserving a sense of coherence with earlier work. Computational chemistry is fully developed subdiscipline of chemistry; and, computational chemists who publish on problems of long-standing interest to physical organic chemists may shape reports of their work to emphasize either the computational methods, or the reactions being investigated. This monograph provides an audience for those who wish to report advances in physical organic chemistry that have resulted from well-designed computational studies.

Volume 38 of *Advances in Physical Organic Chemistry* is a testament to advances that can result through the thoughtful application of computational methods to the analysis of mechanistic problems not fully solved by experiment. It has been dedicated to Kendall Houk on the occasion of his 60th birthday by the chapter authors, former coworkers of Ken's who have written about problems of mutual interest. Ken's contributions to chemistry and his personality are recounted in opening remarks by Wes Bordon. In a broader sense, this volume recognizes the scope of Ken's contributions; and, his active mind and gracious personality which are central to an ability to convey a knowledge of Chemistry and an enthusiasm for its study to colleagues of all ages.

John P. Richard

Kendall N. Houk at Age 60



It is hard to believe that Ken Houk turned 60 on February 27, 2003. Ken continues eagerly to tackle new challenges, both professional and personal. As an example in the latter arena, last year Ken learned to ride a unicycle – a 59th birthday present from his wife Robin Garrell.

In addition, despite his magnificent contributions to chemistry and the many awards that he has won for them, Ken still has not learned to take himself seriously. This summer he and Robin convulsed an audience of quantum chemists by dressing and acting like movie stars on Oscar night when they presented the award for best poster at an international conference. People who meet Ken are amazed to discover that a chemist as famous as he can be so easy going and so funny. Nevertheless, Ken really is one of the people who helped to transform physical organic chemistry from the study of reaction mechanisms in solution to the much broader field that it is today.

Ken has been a leader in the development of rules to understand chemical reactivity and selectivity and in the use of computers to model complex organic and biological reactions. Ken's theoretical work has stimulated numerous experimental tests of predictions made by him, and some of these tests have been performed by his own research group. Ken has not only shown organic chemists how to use calculations to understand chemistry, but his papers and his lectures have also inspired experimentalists to use calculations in their own research.

Ken has published prolifically. He has authored or co-authored nearly 600 articles in refereed journals, an average of 10 papers/year since his birth in Nashville in 1943. The majority of his papers have appeared in *JACS*, but a smattering have been published in *Angew. Chem.*and in *Science*. Ken was the 35th most cited chemist in the world during the last two decades.

Ken has mentored nearly 150 graduate students, half that number of postdocs, and many times that number of undergraduates in his teaching career, first at LSU, then at Pittsburgh, and now at UCLA. Dozens of faculty members from other universities have spent sabbaticals in Ken's group, in order to work with and learn from Ken. Many of his students and postdocs are now themselves successful and distinguished scientists, as exemplified by the contributors to this volume.

In Ken are combined the physical insight of an organic chemist with the sophistication in computational methodology of a physical chemist. However, like Nobel Laureate Roald Hoffmann, less important than the quantitative results of Ken's calculations are the qualitative insights that have emerged from analyzing these results.

Ken's insights have shaped thinking in organic chemistry in many areas. The list of his contributions includes: theoretical models of reactivity and regio- and stereoselectivity in cycloadditions, the concerted nature of 1,3-dipolar and Diels-Alder reactions, the concept and theory of "periselectivity", the impossibility of "neutral homoaromaticity", the origin of negative activation energies in and entropy control of carbene addition reactions; the phenomenon and theoretical explanation of "torquoselectivity"; the origins of stereoselectivity in and practical methods for computational modeling of the transition structures of a wide variety of synthetically important reactions, gating in host-guest complexes, and mechanisms of transition state stabilization by catalytic antibodies. Many of the contemporary concepts that permeate organic chemists' notions of how organic reactions occur and why they give particular products originated in discoveries made in the Houk labs.

Like Roald Hoffmann and Ken's own Ph.D. adviser, R. B. Woodward, Ken seems to enjoy making up erudite-sounding names for new phenomena that he discovers. In addition to "periselectivity" and "torquoselectivity", Ken has added "theozyme" to the chemical lexicon.

In the beginning, Ken created a frontier molecular orbital (FMO) theory of regioselectivity in cycloadditions. In particular, his classic series of papers showed how FMO theory could be used to understand and predict the regioselectivity of 1,3-dipolar cycloadditions. Ken's generalizations about the shapes and energies of frontier molecular orbitals of alkenes, dienes, and 1,3-dipoles, are in common use today; and they appear in many texts and research articles.

In a very different area of organic chemistry Ken produced a series of landmark theoretical papers on carbene reactions. He developed a general theory, showing how orbital interactions influence reactivity and selectivity in carbene additions to alkenes. Ken also showed how entropy control of reactivity and negative activation barriers in carbene addition reactions could both be explained by a new, unified model.

With great insight, Ken pointed out that even if such reactions have vanishingly small enthalpic barriers, they still do involve very negative changes in entropy. The $-T\Delta S^{\ddagger}$ term in the free energy of activation produces a free energy barrier with an entropic origin. The position and height of this barrier both depend on how rapidly the enthalpy and entropy each decrease along the reaction coordinate and also on the temperature. Ken's theory has had a pervasive impact on the interpretation of fast organic reactions.

The name "Houk" has become synonymous with calculations on the transition states of pericyclic reactions. For two decades, as increasingly sophisticated types of electronic structure calculations became feasible for such reactions, Ken's group used these methods to investigate the geometries and energies of the transition structures. Ken's calculations showed that, in the absence of unsymmetrical substitution, bond making and bond breaking occur synchronously in pericyclic reactions.

In his computational investigations of electrocyclic reactions of substituted cyclobutenes, Ken discovered a powerful and unanticipated substituent effect on which of the two possible modes of conrotatory cyclobutene ring opening is preferred. He called this preference for outward rotation of electron donating substituents on the scissile ring bond "torquoselectivity." On this basis many unexplained phenomena were understood for the first time. The prediction that a formyl group would preferentially rotate inward, to give the less thermodynamically stable product, was verified experimentally by Ken's group at UCLA. The concept of torquoselectivity has blossomed into a general principle of stereoselection, and experimental manifestations of torquoselectivity continue to be discovered.

In a study of reactivity and stereoselectivity in norbornenes and related alkenes, the observation of pyramidalized alkene carbons led Ken to the discovery of a general pattern — alkenes with no plane of molecular symmetry pyramidalize so as to give a staggered arrangement about the allylic bonds. Subsequent studies showed that there is a similar preference for staggering of bonds in transition states.

Ken pioneered the modeling of transition states with force field methods. Before modern tools existed for locating transition structures in all but the simplest reactions, his group used *ab initio* calculations to find the geometries of transition states and to determine force constants for distortions away from these preferred geometries. These force constants could then be used in standard molecular mechanics calculations, in order to predict how steric effects would affect the geometries and energies of the transition structures when substituent were present.

Another series of publications from Ken's group compared kinetic isotope effects, computed for different possible transition structures for a variety of reactions, with the experimental values, either obtained from the literature or measured by Singleton's group at Texas A&M. These comparisons established the most important features of the transition states for several classic organic reactions — Diels-Alder cycloadditions, Cope and Claisen rearrangements, peracid epoxidations, carbene and triazolinedione cycloadditions and, most recently, osmium tetroxide bis-hydroxylations. Due to Ken's research. the three-dimensional structures of many transition states have become nearly as well-understood as the structures of stable molecules.

Ken has continued to explore and influence new areas of chemistry. For example, he has recently made an important discovery in molecular recognition. His finding that a conformational process ("gating") is the rate-determining step in complex formation and dissociation in Cram's hemicarceplexes has produced a new element in host design. Ken's investigations of the stabilities and mechanisms of formation of Stoddart's catenanes and rotaxanes have already led to discovery of gating phenomena in and electrostatic stabilization of these complexes.

Ken's calculations on catalytic antibodies provide a recent example of the fine way that he utilizes theory to reveal the origins of complex phenomena. His computations have led to the first examples of a quantitative understanding of the role of binding groups on catalysis by antibodies.

Ken's research has been recognized by many major awards. Among these some of the most significant are an Alexander von Humboldt U.S. Senior Scientist Award from Germany, the Schrödinger Medal of the World Association of Theoretically Oriented Chemists, the UCLA Faculty Research Lectureship, a Cope Scholar Award and the James Flack Norris Award of the American Chemical Society, the Tolman Award of the Southern California Section of the American Chemical Society, and an Honorary Degree ("Dr. honoris causa") from the University of Essen, Germany in 1999. In 2000, he was named a Lady Davis Professor at the Technion in Israel and received a Fellowship from the Japanese Society for the Promotion of Science. Last year Ken was elected to the American Academy of Arts and Sciences, and he has won the 2003 American Chemical Society Award for Computers in Chemical and Pharmaceutical Research.

Ken has gotten into his share of controversies. Among the most prominent of his sometime scientific adversaries have been Michael J. S. Dewar, Ray Firestone, George Olah, Fred Menger, Tom Bruice, and Arieh Warshel. However, Ken's sense of humor and refusal to take anything too seriously, including himself, has allowed him to remain good friends with (almost) all of these chemists at the same time they were having intense scientific disagreements.

Ken's long-term scientific friends outnumber his sometime scientific foes by at least two orders of magnitude. He has collaborated with an amazingly large number of the world's most outstanding chemists; and in my capacity as an Associate Editor of *JACS*, I have found that at least half of the organic theoreticians whose manuscripts I handle suggest Ken as a Referee. I am sure that they respect his critical judgement, but I suspect that they also believe that Ken is too nice a person to suggest that their manuscripts be rejected. Of course, I cannot possibly comment on whether or not they are right, but I can state that Ken unfailingly and promptly writes insightful reports on the comparatively small fraction of those manuscripts that I actually do send him.

However, Ken's service to the chemical community extends far beyond his willingness to referee promptly and thoroughly manuscripts that I send him. Ken has served as Chair of the Gordon Conferences on Hydrocarbon Chemistry and Computational Chemistry, two Reaction Mechanisms Conferences, and a recent Symposium honoring the life and chemistry of Donald Cram. He has also been Chair of the Chemistry and Biochemistry Department at UCLA, and for two years he was the Director of the Chemistry Division at the National Science Foundation.

I have known Ken for forty years, since we were both undergraduates at Harvard. He played trumpet in a jazz band, and I heard him perform on several occasions. I, as a Miles Davis wannabe (but one with no musical talent), noted with envy that, when Ken played, he adopted the same, highly characteristic posture as Miles. However, this was probably the last time in his life that Ken imitated anybody.

As Harvard graduate students, I with E. J. Corey and Ken with R. B. Woodward, we nodded politely at each other when we passed in the hall; but it was not until many years later, when we met at a conference, that I remember actually talking to Ken. In addition to both being theoretically inclined organic chemists, whose groups also did experiments, we discovered that we had other interests in common, interests which we still sometimes discuss but no longer pursue.

Through the years Ken and I have collaborated on several projects, all of them concerned with the Cope rearrangement. Some idea of the non-scientific side of Ken can be gleaned from his contributions to the late-night email messages we exchanged a few years ago in which the goal was to think of different words or phrases that incorporated "Cope" but had nothing to do with this pericyclic reaction. A few examples of Ken's creativity include "Cope ascetic", "Cope a cabana", and "Cope Ernie cuss".

However, I think Ken was at his creative best fifteen years ago when we coauthored an invited review on "Synchronicity in Multibond Reactions" for *Annual Reviews of Physical Chemistry*. This review was written to refute Michael Dewar's assertion in a *JACS* paper that "synchronous multibond reactions are normally prohibited". The review provided a rare occasion when Ken and I could each write on this subject without having to respond to a three-page, single-spaced, report from an "anonymous" Referee, which usually wound up by claiming that, if we weren't ignorant, then we must be scientifically dishonest in asserting that multibond reactions actually could be synchronous.

Given the freedom to include whatever we wished in this review, Ken suggested that we conclude with some comments on synchronicity from the non-scientific literature. Thus it was that our review ended with an excerpt from the song "Synchronicity" by Sting — "Effect without cause, Subatomic laws, Scientific pause, Synchronicity."

It has been my good fortune to know Ken for forty years as a friend, collaborator, and one of the most important and influential physical-organic chemists of the twentieth century. I have no doubt that, if Ken's unicycle does not put an untimely end to his brilliant career, his seminal contributions to chemistry will continue well into this century.

Wes Borden

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Contents

Orbital interactions and long-range electron transfer

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Preamble

Professor Houk and I are coevals and we embarked on our research careers at about the same time. In the beginning of the 1970s, both he and I were independently working on mechanistic aspects of pericyclic reactions, using a combination of experiment, simple perturbational MO theory and semi-empirical MO calculations. My published work in this area was of variable quality whereas Ken's was uniformly outstanding. I was due for sabbatical study in 1980. Although, by that time, I had begun my investigations into electron transfer, a story which is told below, I considered it daft not to spend 1980 with Ken, who was clearly on track to becoming one of the great American physical organic chemists. So I went to LSU in January, 1980, to become a member of "Houk's hordes", as they were then affectionately called. That year was the most rewarding, most exciting, and happiest year of my professional career. We did great work together, with Nelson Rondan, solving all sorts of challenging problems concerning π-facial stereoselectivity, using John Pople's spanking new GAUSSIAN 80 program that actually located stationary points automatically, thereby banishing for all time that dreadful axial iterative method for optimising molecular geometries! Over the intervening years, Ken and I have kept up our friendship and we even occasionally collaborate on projects of mutual interest. Although my interests have diverged somewhat from Ken's, I always read his papers for, like Roald Hoffmann's papers, Ken's are not only of the highest quality but they are also elegantly written. I respect and admire Professor Houk, not only for his chemical brilliance, but also for his humanity – his generosity, his great sense of humour, his liberal views and his tolerance of other people's points of view. So, I am absolutely delighted to have been invited to contribute an article to this volume in honour of Professor Houk's 60th birthday.

1 Introduction

This article is a semi-personal account of how we, and others, solved one of the outstanding problems in the electron transfer (ET) field, namely, the distance dependence of long-range, non-adiabatic, ET dynamics, and how this distance dependence varies with the nature and configuration of the medium between the redox couple (chromophores). There are two main reasons why the issue of the distance dependence of ET dynamics was (and continues to be) so significant. Firstly, ET is the most fundamental of all chemical reactions and is pervasive throughout chemistry and biology; it behoves us, therefore, to understand fully, the mechanistic characteristics of such a fundamental process, and the distance dependence of ET dynamics is a pivotal characteristic. Secondly, it has been known for some time that ET in proteins and DNA double helices may take place over very large distances, often exceeding 50 Å,[1] and so a detailed mechanistic knowledge of biological ET necessarily entails an understanding of its distance dependence.

There are three principal modes of ET, namely, thermal, optical and photoinduced ET, and these are shown schematically in Fig. 1. Optical ET differs from photoinduced ET in that ET in the former process results from direct electronic excitation into a charge transfer (CT) or intervalence band, whereas photoinduced ET takes place from an initially prepared locally excited state of either the donor or acceptor groups. Photoinduced ET is an extremely important process and it is widely studied because it provides a mechanism for converting photonic energy into useful electrical potential which may then be exploited in a number of ways. The most famous biological photoinduced ET reaction is, of course, that which drives