THE NUCLEUS

March 1997 *Of the Northeastern Section of the American Chemical Society* *Vol. LXXV, No. 7*

Monthly Meeting

Hans van Willigen on magnetic resonance studies

Book Review

"Symmetry Through the Eyes of a Chemist" by I. And M. Hargittai

Meeting Report

"Tuberculosis Now and Then" from the January meeting

Summer Scholar

Report on Modeling Using Atom Type Electrotopological State Indices

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THE NUCLEUS

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Board of Directors

Notes of Meeting of December 12, 1996

Officer's Reports

Chair: Dr. Samuel relayed a request from National for mentors for the ACS Scholars Program, especially from industry. Annual Reports are due! The Annual meeting of the board will meet January 9, 1997, followed by the regular monthly board meeting.

Secretary: Dr. Hearn mentioned the excellent program on Carbohydrate Mass Spectrometry held at the Boston Univ. School of Medicine and hosted by C. Costello.

Treasurer: Dr. Piper presented the budget report. It was VOTED to accept the report.

Archivist: Dr. Simon asked for assistance in obtaining copies of complete Annual Reports, starting with 1990.

Standing Committees:

Bd. Of Publications: Advertising income is well ahead of projections. Policies concerning the new web site were discussed.

Editor: The January NUCLEUS will have 20 pages, including about six pages of advertising.

Chemistry Education: Dr. Hoffman announced the new Chair of the committee: Dr. Ruth Tanner (UMassLowell). The Annual College Research Symposium will be held April 26 at Boston University. A number of Grants-in-Aid will permit some Section students to attend the National ACS meeting in San Francisco in April.

Professional Relations:

Employment Services: Ted and Arlene Light recenly attended an ACS Local Section Career Program on efforts to help unemployed chemists. Copies of their report are at the Section Office.

Old Business: Nominated by the Nominating Committee, the following were elected to fill vacancies in the list of Alternate Councilors: Charles Blank, Don Rickter; and in the list of Directors-at-Large: Phyllis Brauner and Bonnie Carr. For the Nominating Committee (Board Members), Wallace Gleekman and Mike Strem were elected. The Board approved the following bylaws amendment of Bylaw III, Sec. 11: The Local Arrangements Committee shall, in cooperation with the Program Committee, arrange for the accommodation of speakers. It shall also arrange for the greeting of new members, for the meeting site and for all social functions of the Northeastern Section.

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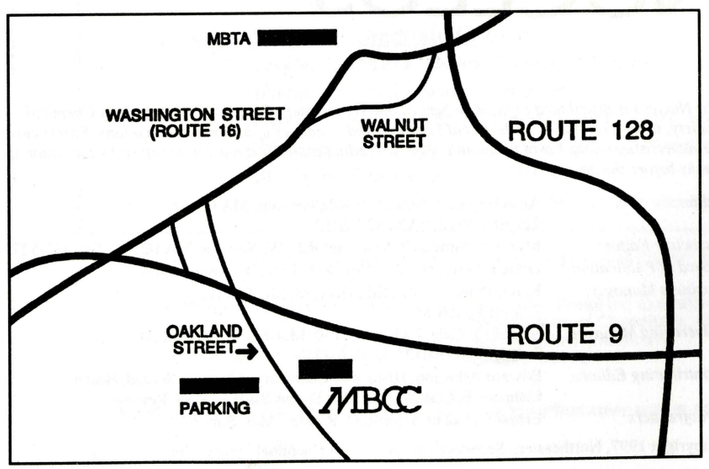
The Section Handbook is to reflect the cooperation between the Program and Local Arrangements Committee.

New Business: Dr. Light announced that at the next meeting a recommendation concerning the Employment Services Committee will be made. ◇



Directions

From the North South or East: Take Rte. 128 to Rte. 9 West. On Rte. 9, drive about 1 ½ miles . Take the ramp to Rte. 16 East, which is the "Oakland St./Mass Bay" exit just before the Rte. 16 overpass. Take the second right , Oakland St., following the green Mass Bay signs. Cross Rte. 9 and proceed to the college. Parking is on the right, the college building on the left.

From the West: Take Rte. 9 East. After going under the Rte. 16 overpass turn right at the first traffic signal into Oakland St. and proceed to the college, as above. ◇

Monthly Meeting

The 787th Meeting of the Northeastern Section of the American Chemical Society

Thursday, March 13, 1997

Massachusetts Bay Community College, 50 Oakland St., Wellesley, Mass. Library Atrium

5:30 Social Hour

6:30 Dinner

8:00 Evening Meeting, Dr. Martin Idelson, Chair
Dr. Hans van Willigen, University of Massachusetts Boston:
Magnetic Resonance Studies of Photochemical Reactions: A Window on Spin Effects on Chemical Kinetics

Refreshments will be served after the program.

Dinner reservations should be made no later than noon, March 6. Please call or fax Marilou Cashman at (800) 872-2054. The entree will be chicken. Those who wish a vegetarian entree, please so specify when making the reservation. Reservations not canceled at least 24 hours in advance must be paid. Members, $25.00; Non-members, $28.00; Retirees, $15.00; Students, $8.00. THE PUBLIC IS INVITED.

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

Next meeting on APRIL 3 (note the change in date), Esselen Award to Dr. Arangaswamy Srinivasan (UVTech Associates, Ossining, NY) "The Friendly Ultraviolet Laser Is Etching It's Way Into Our Lives". At Harvard University, 5:30 Social hour and dinner, (Harvard Faculty Club), 8:00 evening meeting (Harvard Undergraduate Science Center, 1 Oxford St.)

Abstract

Interest in the use of solar energy has stimulated the application of a variety of instrumental methods in the study of mechanisms of photochemical reactions. Among these, Electron Paramagnetic Resonance(EPR) has proven to be a valuable source of information.This presentation concerns the detection of short-lived free radicals formed in pulsed laser initiated reactions relevant to solar energy utilization with Fourier Transform (FT) EPR. FT EPR investigations contribute to the understanding of reaction mechanisms by identifying paramagnetic intermediates with lifetimes in the microsecond time domain and by providing data on kinetics of formation and decay. Magnetic resonance spectra show that electron and nuclear spins can play an important role in chemical dynamics, providing a mechanism by which weak magnetic fields can affect biochemical reactions. These "spin chemistry " effects are an important source of mechanistic information, as well. Among FT EPR applications that will be discussed are the photochemistry of C60, a potential photocatalyst in solar energy conversion schemes, and 4-chlorophenol, a pollutant that can be degraded photochemically. ◇

Biography

Dr. van Willigen was born in The Netherlands. He received his undergraduate and graduate education at the University of Amsterdam. After being awarded the doctorandus (master's) degree in 1963, he spent two years in the research group of Professor S. I. Weissman at Washington University. Work performed during that period formed the basis for his doctoral dissertation that earned him the Ph.D. from the University of Amsterdam in 1965. From 1965 to 1969 van Willigen held a faculty position at the University of Nijmegen in The Netherlands. In 1969 he moved back to the United States, where, after a year as visiting scientist at the University of California at Riverside, he assumed the position of Associate Professor at the University of Massachusetts at Boston, where he is now Professor of Chemistry. During his tenure at UMB he has been associated with a number of other institutes, working as visiting scientist at the magnet laboratories of MIT and Argonne National Laboratory and as visiting professor at the Freie Universität Berlin, Jyvaskyla University (Finland), Trondheim University (Norway) and as Fulbright Research Professor at the Institute of Science, Bangalore (India). Dr. van Willigen's research interests are in the field of the application of magnetic resonance to the study of chemical structure and reactivity. Topics of research have included magnetic field effects on reaction kinetics and the study of chemical structure with electron nuclear double resonance. Currently his work is concerned with the application of pulsed electron paramagnetic resonance techniques in studies of photochemical reactions. His main hobby is running. He has completed the Boston Marathon some 15 times and has participated in ultra-marathon trail running events in California, Colorado and Alaska. ◇

ACS News

Local Section Career Program

Truman and Arlene Light attended the Local Section Career Program conference at the Belmont Conference Center (ACS, Maryland) Nov. 8-10, 1996.

These conferences are being presented to representatives of all 180 local sections by the ACS Department of Career Services at the request of the ACS Board of Directors who allocated a sum of money to "... provide programs and activities to facilitate the career development of chemical professionals". This has been in response to the present era of cutbacks, downsizing and forced retirement resulting in one of the highest unemployment rates in the history of the ACS. (3.0% unemployed on 3/1/96; 7.8% unemployed and seeking during past year, 5.0% experienced unemployment within year).

Re-engineering the Corporation—for increased competitiveness seems to be an euphemism for both downsizing and lay-offs. Very good statistics are collected by the ACS.

Total chemist jobs are forecast to be up in 10 years (2005).

The Conference was held at the ACS Belmont Conference Center on 600 acres in Maryland. Herds of deer were roaming the roadway and grounds.

In attendance were 16 people from 15 local sections; (So. Calif. to Northeastern). 14 attendees, 1 employer rep. (Ted Logan, P&G, possible speaker for Prof. Relations night, Oct. 1997), 1 Director (Region 1, Jim Bennett.)

We were given demographics of the Northeastern Section (NESACS): 5,227 members (as of 2/16/96), 76% male, 22% female, bal. n/a; 43% Ph.D., 16% M.S., 33% B.S., 10% Chem. Engineers, also include demographics by age, fields etc.

There were tutorials given on the facilities and programs available at National ACS and Suggestions were made for detailed plans that Local Sections might implement to meet the unemployment and downsizing conditions currently existing. A box of materials covering a broad spectrum of employment needs was received by each attendee to be used by the Local Section. The Northeastern Section was singled out as being a pioneer in offering employment and career services to their members.

Suggestions were also given for creating Internet access and creating a local section homepage. Again we were able to report that the NESACS had already accomplished this [as had been announced at the previous Board meeting]. In conjunction with this topic, there was much discussion concerning the appropriateness of publishing on the Internet the positions available and resumes of candidates. Because of legal implications, Mary Funke stated that she wanted to seek legal counsel and advised us not to implement such a course of action, as yet. ◇

Board Elects

Alternate Councilors: Charles Blank and Don Rickter to fill the two vacancies, both for a one-year terms, ending December 31, 1997.

Members-at-Large of Board: Phyllis Brauner (one year term) and Bonnie Carr (one year term) join Lisa Corbett (two year term), Yigong Gao (two year term), James A. Kaufman (three year term) and Mary Ann Solstad (three year term)

Nominating Committee:
Wallace Gleekman and Michael Strem were elected as the Board of Director representatives on the Nominating Committee.

Professional Relations Committee:
D. Rickter (chair) (correction of previous listing.)◇

Meeting Report

Tuberculosis Today.- Chemical Perspectives on the Resurgence of the White Plague

Michael J. Hearn
Department of Chemistry
Wellesley College
Wellesley, MA 02181 USA

Tuberculosis Then and Now

When New York Giants second baseman Laughing Larry Doyle left the Trudeau Tuberculosis Sanatorium in 1954, he was one of the last of many thousands of tuberculosis patients to leave such institutions and return to society to lead normal lives, thanks to the development of modern chemotherapeutic methods. Often spending years in medical confinement, Doyle and others like him had been committed to treatments involving rich diets, bed rest, sunshine and plenty of clean fresh air. In advanced cases, patients had been required to endure painful surgical procedures to help improve their prognosis. All of this began to change radically about the year 1950, when effective tuberculosis antimicrobials became available to physicians, and the sanatoria were no longer necessary. The new drugs came from natural sources in some cases and were derived from coal tar in others. They could be dispensed conveniently as tablets, syrups or injections and brought the patient to a healthy non-infectious state, eliminating the need for quarantine. They were truly "miracle drugs."

No respecter of persons, tuberculosis had been well-known and characterized as a disease throughout human history, afflicting people of all walks and stages of life. John Harvard, Samuel Johnson, Henry David Thoreau, John Keats, Frederick Chopin, Emily and Charlotte Bronte and Robert Louis Stevenson are among the many lucent figures from intellectual history who were victims of the disease. Tuberculosis was known as "phthisis" (from the Greek meaning "wasting away") or "consumption", not only because of the general wasting syndrome associated with the disease, but also because it seemed quite literally to consume the substance of its prey. Increases in population densities in Western Europe during the Middle Ages, coupled with degradation of the urban environment, are thought to have led to a centuries-long epidemic of tuberculosis (called the White Plague from the condition of the expectorant of infected persons), culminating in the mid-nineteenth century, by which time about one in four deaths could be attributed to the disease.

Although treatment regimens have been extant since at least the Hellenistic period, modern methods are said to have begun with the sanatorium movement at the end of the nineteenth century. Edward Livingston Trudeau, a young physician himself infected with the disease, found that his physical condition and mental outlook were greatly improved with the benefits of rest, country diet and fresh air during a three month stay near Lake Saranac in New York. Seeking to bring the benefits of his personal discovery to others, Trudeau established a cottage sanatorium and tuberculosis research laboratory and devoted the remainder of a long and productive life to the study and treatment of the disease. The strong research efforts of the Trudeau Institute continue to this day.

At the same time, the recognition of the infectious nature of the disease and the identification of the tubercle bacillus by microscopy gave rise to the public health movement in the United States. The knowledge that the causative agent of the disease is an airborne inhaled pathogen made public health officials focus on education and social welfare approaches toward arresting its spread. Regulations were put into place concerning the reporting of incidents of the disease by medical professionals, coughing and spitting in public, food handling procedures, and quarantine for those with active infection.

Although rest, diet, attentive medical care and fresh air probably improved the condition of nearly all the patients, many were not so fortunate as to be cured by the sanatorium methods. Before the advent of chemotherapy, for example, the mortality rate for tuberculosis patients admitted to New York State sanatoria still ranged as high as about 70%. This picture brightened enormously in the years immediately following the Second World War, however, with the introduction of new and highly potent drugs. The first among these, streptomycin, is an antitubercular natural product derived from a soil microorganism, the Actinomycete *Streptomyces griseus*. The research team which isolated, characterized and learned to harvest streptomycin on a large scale was led by Professor Selman Waxman of Rutgers University, who was later awarded the Nobel Prize. A structurally complex amino glycoside, streptomycin has since been the subject of a successful total synthesis. Streptomycin, it can be fairly said, truly revolutionized the treatment of tuberculosis. Within several years, the additional application of the new drug isonicotinic acid hydrazide (isoniazid, INH), a purely synthetic material, had equally startling results in bettering the condition of tuberculosis patients. Many of those who had failed to respond to the most attentively applied rest treatments or the most drastic surgical procedures were cured, particularly when isoniazid was used in combination with streptomycin. Other powerful drugs were concurrently introduced, and it seemed to many that the conquest of tuberculosis was at hand. Medical professionals, public health workers and scholars were confident the decline in the incidence and mortality of the disease would continue. This confidence appeared justified until the mid-1980's.

In 1985, the hopeful trend had reversed and the Center for Disease Control (CDC) estimates that more than 50,000 new cases have been documented since that time in the United States alone. The World Health Orga-

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nization indicates that there are now about three million deaths per year worldwide from tuberculosis, and the disease remains the foremost infectious cause of death. Disturbing to health care workers is the fact that many of the new cases are occasioned by bacteria which are unexpectedly virulent.

Infectious Disease on the Rise

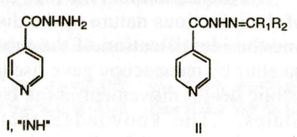
The increase in the number of cases of active infectious tuberculosis can be attributed to several factors. The rapid pace of international commerce and the convenience of swift air travel are two of these. It is now possible for an infected individual residing in a part of the world where the disease is endemic to become a vector for the spread of tuberculosis on another continent in a matter of a few hours. The CDC estimates that approximately one-third of recent arrivals in the United States have active infectious tuberculosis. The breakdown of public health measures has been another contributory factor. The abandonment of public health facilities in the face of fiscal deficits, the collapse of adequate reporting methods and the lack of basic medical care for those often least able to afford it have not been without their own quiet but drastic consequences, posing risks not only for the afflicted individuals but for society at large. Other important issues concern the unplanned and unregulated development of land and water resources, the prevalence of alcoholism and the problem of homelessness. The emergence of bacteria resistant even to the application of combination therapy involving as many as twelve different anti-tuberculosis drugs is of special concern.

New Approaches to Drug Design and Analysis

In spite of the efficacy of streptomycin, rifampin, ethambutol, INH and other tuberculostatic drugs[1], the sharp rise in the number of new cases of tuberculosis world-wide and the emergence of drug-resistant strains of *Mycobacterium tuberculosis*[2,3] have made clear the pressing need for the evolution of newer and more powerful drugs, the re-examination and re-evaluation of older drugs, and --- perhaps above all--- the detailed elucidation of the specific modes of action of antimycobacterial compounds. These matters represent a stern challenge to the research community. The lack of widespread and vigorous research on tuberculosis in the past thirty years has meant that much lost ground will have to be regained on the part of public health officials, medical professionals, microbiologists and chemists. Certain areas have become lost art and will have to be rediscovered.

Our own exploratory investigations of the chemistry of organic hydrazines,[4,5,6] have recently led us to become interested in the elaboration of dependable means for the preparation of tuberculostatic derivatives of INH (I) in such quantity and purity as to be fitting for further biological evaluation. Side by side with this objective in synthetic organic chemistry has been the need for a quick and easy method of analyzing the progress of our preparations. The analysis should be robust and should require minimal procedural effort.

We have thus found that near infrared spectroscopy (NIR) provides a practical method for the analysis of INH and its derivatives and allows us to detect the reactions of INH with suitable reagents to form tuberculostatic Schiff bases (II). In compounds II, the particular choices of substituent groups



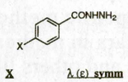
I, "INH" II

R_1 and R_2 have allowed us to form materials displaying many times the useful range of applicability of current drugs such as isoniazid and rifampin in the pertinent bacteriological protocols. The groups R_1 and R_2 are chosen in such a way as to enhance the lipophilicity of II or to increase the number of tuberculostatic moieties built into a single molecule.

The benefits of NIR spectroscopy include ease of sample preparation and readiness of quantification.[7-10] In this way the NIR spectra permit a better understanding and control of preparative conditions in organic synthesis. NIR is closely allied to other forms of vibrational spectroscopy, including the traditional mid-range infrared (IR) methods familiar to most organic chemists. The practice of NIR, however, is largely concerned with the higher energy vibrational transitions corresponding to overtones and combinations. It may also include the analysis of weak electronic transitions.

TABLE. NEAR-INFRARED SPECTRA OF ACID HYDRAZIDES

Entry	λ (ε) symm	λ (ε) antisymm
1.	1558 (0.72)	1518 (0.096)



Entry	X	λ (ε) symm	λ (ε) antisymm
2.	H	1560 (0.86)	1518 (0.25)
3.	Cl	1553 (0.81)	1517 (0.36)
4.	Br	1560 (0.56)	1518 (0.26)
5.	CH_3	1561 (0.64)	1518 (0.25)
6.	CH_3O	1561 (0.59)	1518 (0.30)
7.	NO_2	1558 (0.51)	1518 (0.21)

Absorption maxima in nm in DMF.
Absorptivities in liters $mol^{-1}cm^{-1}$.

The table (Entry 1) lists the observed absorption maxima and absorptivities for INH near 1500 nm in the first overtone region. The data were determined for 0.30 M solutions of INH in dimethylformamide, conveniently prepared using straightforward quantitative techniques. The data for INH are similar to ones measured under similar conditions for a family of related benzoic acid hydrazides (Entries 2-7) and do not show much variability with changes in structure under these conditions. The main features of the first overtone spectra of the acid hydrazides include a peak corresponding to the symmetrical mode of the N-H stretching vibration near 1558 nm and a considerably weaker peak for the

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counterpart antisymmetric mode at 1518 nm.[11-15]

The Schiff base derivatives II do not absorb at 1558 nm. This permits ready non-destructive analysis of our preparative reactions while they are in progress by examining the disappearance of the 1558 nm peak of INH. From the slope of a plot of corrected absorbance versus time, it is possible to obtain estimates of initial pseudo first order rate constants for our preparative procedures. We find that less electrophilic reagents react somewhat more slowly with INH, as might be expected.[16]

Conclusions

We can anticipate that the future will continue to challenge the ingenuity of chemists and those in related disciplines in renewing the effort to achieve control over tuberculosis. Near infrared spectroscopy provides a ready method for the quantification of INH I and for following its reactions in the preparation of effective tuberculostatic Schiff bases II. We hope that the simplicity of the NIR spectra in the 1558 nm region and the technical ease with which measurements can be made will promote use of the first overtone of the N-H stretch for the analysis of preparations of these anti-tuberculosis substances.

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Book Review

Symmetry Through the Eyes of a Chemist,

by István and Magdolna Hargittai, second edition
(Plenum Press, 1995, 469 pp., $39.50 paperback, $85.00 hard cover)

Reviewed by Dennis J. Sardella
(Department of Chemistry, Boston College)

There is something about symmetry and symmetrical objects that is inherently appealing to people. Perhaps it is because symmetry provides an organizing principle that can help to bring order out of chaos, or because it hints at the underlying existence of regularity in an inherently irregular world. Whatever the reason, symmetry has always featured prominently in decoration and design and, of course, in science. Jacob Bronowski, in one of the episodes of his monumental Public Television series "The Ascent of Man," discusses the preoccupation of medieval Arab mathematicians and artists with symmetry as the central component of their art, using as an illustration tiling patterns found in the Alhambra, the great Moorish castle in Spain. He points out that the importance of symmetry goes beyond the merely aesthetic:

It brings us face to face with something which is hard to remember, and that is that we live in a special kind of space — three-dimensional, flat — and the properties of that space are unbreakable. In asking what operations will turn a pattern into itself, we are discovering the invisible laws that govern our space. There are only certain kinds of symmetries which our space can support, not only in man-made patterns, but in the regularities which nature herself imposes upon her fundamental, atomic structures.[1]

For Bronowski, the appreciation and analysis of symmetry is not simply an aesthetic experience or an abstruse mathematical study, but the beginning of a journey into an appreciation of the mysteries that lie at the heart of the physical world.

This realization is really the principle upon which the second edition of "Symmetry Through The Eyes of a Chemist," by István and Magdolna Hargittai, is based: that an educated appreciation of symmetry both sensitizes us to the beauty of the world around us, and enhances our effectiveness as scientists by providing a powerful tool for the qualitative analysis of a wide variety of physical and chemical phenomena. The book is a significantly updated and extensively illustrated version of the authors' highly successful first edition, published in 1986. Although the overall length of the book has not changed much, the authors have clearly made a major attempt to include material from the recent literature. As one indication of the currency of the book, 25-30% of the literature references in most chapters are to material published since 1985.

The book begins with a greatly expanded introductory chapter that gives an overview of the importance of symmetry, particularly in the area of chemistry, with the authors pointing to fullerenes and quasicrystals as particularly significant areas of development. This is followed by an enjoyable descriptive chapter on simple and combined symmetries in which the concepts are made very accessible by the large number of photos, including examples from architecture, flowers and trees, the human form, molecular structures, musical scores and sculpture. Three points I found particularly interesting

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[1] Jacob Bronowski, "The Ascent of Man," Little, Brown & Company (Boston, 1973), p. 174.

Book review

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were an analogy between snowflake growth and dendrimer chemistry, a discussion of enantiomerically pure drugs and asymmetric synthesis, and an elegant example of the classic "coupe du roi" parlor trick drawn from organic synthesis.

The book becomes discernibly more chemical in focus in the third chapter, entitled "Molecules: Shape and Geometry." Fairly standard material on assignment of molecular point groups and VSEPR theory is extensively illustrated with examples taken from the literature, including sections on the structures of polycyclic systems, such as fullerenes, polycyclic hydrocarbons and rapidly rearranging permutational isomerism in dicarboranes. One of the longest chapters in the first edition, it has been shortened significantly by the deletion of numerous examples of structures and distortions in the VSEPR section.

Chapters 4 through 7 are fairly "traditional," corresponding roughly to material covered in the first edition of Cotton's "Chemical Applications of Group Theory." Chapter 4 presents a fairly standard and unexceptional introduction to matrix mathematics and its application to group theory, relieved somewhat by an enjoyable pictorial section on antisymmetry. Nonmathematically oriented readers may find it unappealing and can probably skip over it without much loss, focusing primarily on the concepts of reducible and irreducible representations, which are central to much of what follows in subsequent chapters.

Chapters 5 and 6 illustrate the application of group theory to the discussion of molecular vibrations and the electronic structures of atoms and molecules. They are essentially unchanged from the previous edition. Both rely heavily on chapter 4.

In contrast, much of Chapter 7 ("Chemical Reactions") will be familiar and easily understandable to anyone who has taken a contemporary introductory organic chemistry course, since it is almost completely non-mathematical and deals largely with Woodward-Hoffmann rules and the concepts of aromatic and antiaromatic transition states applied to reaction dynamics. It also introduces the second-order Jahn-Teller Effect and contains a very neat final section on the application of Hoffmann's "isolobal" analogy to the structures of organometallic systems.

In the two concluding chapters the authors' focus shifts from finite systems (isolated molecules and transition states) where use of point groups is appropriate, to a discussion of the symmetries of systems exhibiting periodic symmetry, such as polymers and crystals. Chapter 8 introduces space group symmetries, again in conjunction with numerous illustrations, while the final chapter discusses crystal symmetries. It concludes with a discussion of the need for a more general formulation of symmetry to accommodate cases, such as hypersymmetry (local symmetry due to interacting, nonequivalent molecules within a unit cell, but which is unrelated to the crystal symmetry) and quasicrystals (quasiperiodic structures containing more than one unit call), where space groups are insufficient to describe the symmetry properties.

In reading this book, I could not help recalling with pleasure my introduction as a graduate student to the use of symmetry applications through Cotton's "Chemical Applications of Group Theory." There is, in fact, more than a casual connection between the two books, since they cover much of the same material (particularly the latest edition of Cotton's book, which includes space groups). At the same time they are more complementary than competitive, with Hargittai and Hargittai beginning at the descriptive and aesthetic level and ending with illustrations of how symmetry can be applied to chemical problems, while Cotton begins with group theory and presents much more detailed discussions of its applications.

Hargittai and Hargittai's combination of scientific competence and artistic sensibility is refreshing and all too rarely encountered in scientific writing. My only regret is that some of the photographs could not have been in color. Nonetheless, I found "Symmetry Through the Eyes of a Chemist" enjoyable and informative and recommend it, whether the reader chooses to work through the technical sections or skim them. ◇

Member News

Charles E. Kolb is the recipient of the 1997 *ACS Award for Creative Advances in Environmental Science & Technology.* Dr. Kolb, was Chairman of this Section in 1991 and has contributed several articles to the *NUCLEUS*. Our congratulations! *(C&EN, Jan. 13, 1997)*

Student Awards:

Karl Hansen, fourth year student at Harvard, working under Prof. Eric N. Jacobsen has received a *Boehringer Ingleheim Pharmaceutical Fellowship* on chiral (salen) Cr-III catalyzed ring opening of meso epoxides.

Craig Masse, third-year student at Boston University under **Prof. James S. Panek** has received an *Organic Syntheses Fellowship*. He will be expanding the synthetic utility of chiral *(E)*-crotylsilanes. *(C&EN, Nov. 25, 1996)*

Christopher B. Murray, a graduate student working for **Prof. Moungi G. Bawendi** at MIT, has received the *1997 Nobel Laureate Signature Award for Graduate Education in Chemistry* for work on nanocrystals, opening a promising new branch of materials science. *(C&EN, Dec. 23, 1996).*

Michele Randall, a fourth-year student at Boston College under **Prof. Marc L. Snapper** has received a *Proctor & Gamble Fellowship*. Her research will be on selective ring opening cross-metatheses between strained acyclic olefins and acrylic olefins. *(C&EN, Nov. 25, 1996)* ◇

Summer Scholar Report

The Development of Models of Chemical Properties Using the Atom Type Electrotopological State Indices

Timothy A. Vaughn† and Lowell H. Hall (Faculty Advisor)

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Eastern Nazarene College
Quincy, Massachusetts 02170

The development of mathematical models which relate molecular structure to a property value are useful for two reasons. The estimation of the properties of new compounds is desirable because it saves the time and costs of synthesis, purification, characterization, and the measurement of the property. A rational selection of compounds that are most likely to be useful is possible through estimating properties. It is especially helpful if the structure descriptors in the model are readily calculated for all anticipated molecular structures. Models may also provide insight into the mode of action of a compound. An understanding of a mechanism is of great interest because it is beneficial in designing new compounds with a more desirable effect. The availability of data and a new set of structure descriptors for structure-activity modeling brought us to examine several data sets using the newly developed atom type electrotopological state indices and quantities from semi-empirical quantum mechanical calculations.

In 1990 a new atom level topological index, called the electrotopological state index (E-state), was introduced[3]. Most other topological indices deal with the whole molecule as a sum over subgraphs of the hydrogen-suppressed molecular graph. In the development of the E-state, the index is computed as a graph invariant for each atom in the molecular graph. This atom level index combines the electronic state of the bonded atom with its topological nature in the context of the whole molecular skeleton. The E-state indices have been used for a variety of QSAR studies[3].

An extension of the E-state indices, called the atom type E-state, has recently been introduced[4]. In this extended approach, each atom in the molecule is categorized in a valence state classification scheme. All the atoms of the same type are grouped and their E-state values summed to make the new atom type E-state index for that atom type. This atom type index lends itself to a use similar to the group additive scheme in which an index appears in a QSAR model for each atom type in the molecule. In some cases, only a few atom type indices may be required for a particular investigation, particularly in a biological study in which only a few atom types are required to represent the structure-activity relation. However, for several biological QSARs reported to date, a type of skeletal superposition has been used so that the individual E-state values for corresponding atoms were entered as variables in regression analysis[3,5-11]. This most recent development of atom type E-state values provides the basis for application to a wider range of problems to which the E-state formalism is applicable without the need for superposition.

Much like the atom-type E-state index, a calculated quantity, such as the partial charge of an atom or the vibrational frequency of a carbon-hydrogen bond, can be entered as a variable in regression analysis or an artificial neural network. With programs such as AMPAC[15], semi-empirical quantum mechanical calculations can quickly provide numerical values for these quantities. The quantity may contribute significantly to a model.

In this paper the anesthetic potency and toxicity of the 42 halocarbons of the Davies et al[1] data set is modeled. The models of anesthetic potency and toxicity provide insight into the significance of the halogens on these properties. In this study, regression analysis provides an excellent model. Also, the toxicity of 50 phenols, from the data set of Jurs et al[2], are modeled using regression analysis and artificial neural networks. Another study involving the prediction of the solubility of compounds in water is currently under way using similar descriptors and statistical methods.

Method

Structure Descriptors. The main descriptors used for both studies are the atom type electrotopological state indices. These indices are calculated with the software MolconnZ[13]. Some examples of the E-states used are as follows: SsCH3, SssCH2, SsssCH, SssssC, SsF. These represent the methyl carbon, the methylene carbon, the methine carbon, the quaternary carbon and the fluorine E-states, respectively. In this notation the 'S' stands for the sum of the E-state values for a particular atom. The set of bonds connected to the atom is given by the string of lower case letters after the 'S' An 's' represents a single bond, a 'd' a double bond, a 't' a triple bond, and an 'a' represents an aromatic bond. For example, SaaCH would represent the carbons of benzene. In the Davies et al study, the first order valence molecular connectivity index was also used, $^{1}\chi^{v}$ [12]. Several descriptors were also used from semi-empirical quantum mechanical calculations done on AMPAC. In addition, an index developed by Davies et al describing the hydrogen bond donating ability, HBond, was used. Structure input for the 42 halocarbons was done using SMILES code and for the 50 phenols using the Molconn format. The Molconn format allows indices to be used that describe the structurally

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† 1996 James Flack Norris and Theodore William Richards Summer Research Scholar

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invariant portion of the structures in the data set.

Data Set. The anesthetic potency [log (AD_{50})] and the toxicity [log (LD_{50})] of the 42 halocarbons are taken from Davies et al. The toxicity [log BR] of the 50 phenols is taken from Jurs et al.

Statistical Method. The SAS System[16] was used to carry out multiple linear regression for both studies. In the Jurs et al study the program Neuralyst(14) was used to model with artificial neural networks.

Results

Halocarbon Anesthetic Potency and Toxicity. For the anesthetic potency seven of the atom type electrotopological state indices were used as well as $^1\chi^v$ and the Hbond descriptor developed by Jurs et al. Two descriptors were taken from AMPAC semiempirical quantum mechanical calculations. These quantities include the partial charge of the carbon attached to the most weakly acidic hydrogen and the highest frequency of a carbon-hydrogen vibration, usually the symmetric stretch, which represent the weakly acidic carbon-hydrogen bond. The RSQUARE statement of SAS[16] was used to examine models with 1 to 5 variables. A four-variable model produced a standard error close to the estimated experimental error. The coefficients and the variables of the best model and all of the related statistics are in Table I. Figure 1 shows the calculated anesthetic potency versus the observed potency. A graph of the residuals versus the observed potency (not shown) shows no trends and appears to be random.

An identical strategy was used for developing a model for the toxicity of the halocarbons. However, the AMPAC descriptors were not used in this RSQUARE procedure. The results appear in Table I. The best model for toxicity uses five variables. This model produced a standard error close to the estimated experimental error. Figure 2 shows the calculated toxicity versus the observed toxicity. A graph of the residuals

	For log (AD_{50})			For log (LD_{50})		
Variable	Coefficient	Standard Deviation	Percent Contribution	Coefficient	Standard Deviation	Percent Contribution
$^1\chi^v$	-1.90	0.043	62.1	-1.00	0.172	47.9
HBond	-0.84	0.028	17.9	-0.57	0.051	18.1
SsF	0.036	0.002	14.9	0.022	0.005	13.6
SsCl	-0.067	0.006	5.2	-0.13	0.019	14.3
SsBr	-.-	-.-		-0.31	0.075	6.1
intercept	5.76	0.116		5.37	0.229	
r^2	0.988			0.955		
s	0.13			0.24		
F	889.			149.		
n	42.			42.		
r^2_{press}	0.986			0.937		
s_{press}	0.15			0.28		

Table I. The results of multiple linear regression analysis for the anesthetic potency and toxicity of 42 halocarbons using the atom type E-state indices.

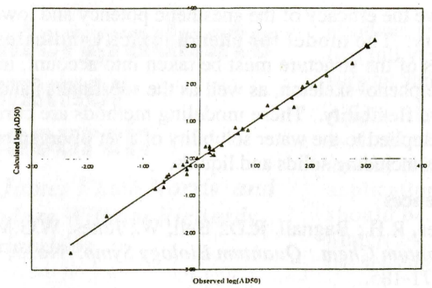

Figure 1. The calculated versus observed anesthetic potency, log(AD_{50}), based on the equation using, $^1\chi^v$, Hbond, SsF, SsCl. See Table I.

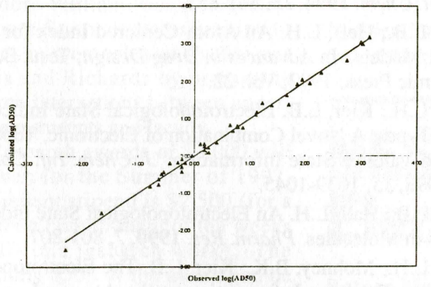

Figure 2. The calculated versus observed toxicity, log(LD_{50}), based on the equation using $^1\chi^v$, Hbond, SsF, SsCl, SsBr. See Table I.

versus the observed toxicity (not shown) shows no trends and appears to be random.

The relationship between the anesthetic potency and the toxicity was also explored. The equation found by regression analysis is

$$\log (LD_{50}) = 0.812\ (\pm 0.034) \log (AD_{50}) + 1.213\ (\pm 0.046)$$
$$r^2 = 0.876,\ s = 0.27,\ F = 584,\ n = 42. \qquad (1)$$

Phenol Toxicity. The phenol toxicity was regressed against several atom type E-state indices and the E-state indices for the structurally invariant portions of the phenol subskeleton. Also, an index which represents the flexibility of the compound, ϕ_α, was used[13]. The positions are labeled by the number given to that atom in Molconn fortnat. The RSQUARE procedure of SAS[16] was used to obtain the best nine variable models. The standard error of this model only differs from the model developed by Jurs et al by 0.8%. A plot of the calculated toxicity versus the observed toxicity (not shown) shows a tight line. A graph of the residuals versus the observed toxicity (not shown) shows no trends and appears to be random.

A model was also developed for the toxicity using an artificial neural network. Software developed by the Chesire Engineering Corporation, Neuralyst, was used to set up the network. The same indices were used as inputs into the network. For the run with the best results, the *MAE* for the whole set, training set, and testing set are 0.047, 0.037, and 0.136, respectively. The architecture of the network is 11:4:1. Typical runs of the network took 15,000 to 30,000 epochs. These measures of

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error indicate that the model is making predictions near the estimated experimental error.

Discussion

The QSAR models developed for halocarbon anesthetic potency and toxicity are satisfying because they yield results close to the estimated experimental data[1]. The press statistic indicates that these models are also reliable for prediction. For the anesthetic potency, s_{press} is only increased by 15% over the standard error in the regression model for the whole data set. Likewise, the s_{press} for the toxicity data set is increased by 17%. These results indicate that these models are definitely reliable for prediction.

These models also provide insight into the structure-activity relationship. The bromine atom type E-state is not a significant contributor to the anesthetic potency model whereas it is necessary for a quality model for toxicity. The bromine contribution to the toxicity model is small, 6.1%, but not negligible. Bromine seems to effect toxicity more directly than anesthetic potency. The model also indicates that an increase in SsCl will increase the potency, and a decrease in SsF will increase the potency.

The largest contributor to each model is the first order valence chi index. The $^1\chi^v$ index contributed 62.1% for the potency and 47.9% for the toxicity. Compared to the atom type E-state, $^1\chi^v$ encodes information about the whole molecule. The negative coefficient indicates that an increase in $^1\chi^v$ will increase the anesthetic potency. The $^1\chi^v$ index increases with skeletal branching, with increasing number of atoms; further, it increases more with chlorine and bromine atoms, than with carbon and fluorine atoms.

This study also shows a close relationship between anesthetic potency and toxicity. Eq.1 indicates that the mechanism of toxicity is closely related to the mechanism evoking anesthetic activity.

The variables that proved to be important in modeling the phenol toxicity are ϕ_α, Ss26, Ss35, Ss7, Hs4, Hs26, SssCH2, SsssCH, ShalnF, SsF, and SHarom. Ss26, Ss35, and Ss7 represent the E-state for the ortho position, the meta position, and the position attached to the hydroxyl group for the phenol substructure, respectively. Hs4 and Hs26 represent the hydrogen E-states for the para and ortho positions, respectively. ShalnF is the sum of the atom type E-states for all of the halogens excluding fluorine. Fluorine is represented by SsF. SHarom is an E-state that represents the aromatic character of the phenol. The coefficient on the flexibility index, ϕ_α, indicates that a more flexible alkyl substitution leads to higher toxicity. The variables represent all of the sections of the phenol substructure. There is not one section of the molecule that seems to influence the toxicity more than another.

Conclusions

Topological indices are a basis for useful models to relate structure to properties for the data sets examined. The models for halocarbon anesthetic potency and toxicity have provided insight into possible changes that can be made to improve the efficacy of the anesthetic potency and lower the toxicity. The model for phenol toxicity indicates that aspects of the structure must be taken into account, including the phenol skeleton, as well as the substituents and their relative flexibility. These modeling methods are currently being applied to the water solubility of a set of organic compounds including solids and liquids.

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[13]Molconn-Z (Molconn-X ver.3.0); Hall Associates, 2 Davis Street, Quincy, MA 02170.

[14]Neuralyst; Chesire Engineering Corp.: 650 Sierra Madre Villa Avenue, Pasadena, CA 91107.

[15]AMPAC (ver.5.0); Semichem; 7128 Summit, Shawnee, KS 66216.

[16]SAS Institute, Cary, NC ◇

Undergraduate Summer Research

The James Flack Norris and Theodore William Richards Scholarships

The Northeastern Section of the American Chemical Society established the James Flack Norris and Theodore William Richards Undergraduate Summer Scholarships to honor the memories of Professors Norris and Richards by promoting research interactions between undergraduate students and faculty.

Research awards of $3,000 will be given for the Summer of 1997. The student stipend is $2,500 (for a minimum commitment of ten weeks of full-time research work). The remaining $500 of the award can be spent on supplies, travel, faculty support, and other items relevant to the student project.

Institutions whose student/faculty team receive a Norris/Richards Undergraduate Summer Research Scholarship are expected to contribute toward the support of the faculty members and to waive any student fees for summer research. Academic credit may be granted to the students at the discretion of the institutions.

Award winners are required to submit a report (5-7 double spaced pages, including figures, tables, and bibliography) of their summer projects to the Education Committee by November 1, 1997, for publication in The Nucleus. They are also expected to participate in the NESACS Undergraduate Research Symposium in April, 1998.

Eligibility: Applications will be accepted from student/faculty teams from colleges and universities within the Northeastern Section, The undergraduate student must be a chemistry, biochemistry, chemical engineering, or molecular biology major in good standing, and have completed at least two full years of college-level chemistry by Summer, 1997.

Application: Application forms are available from departmental chairs and the NESACS office. Completed applications with two photocopies should be submitted no later than March 24, 1997 to the Chairman of the Selection Committee:

Professor Edwin Jahngen
Department of Chemistry
University of Massachusetts-Lowell
Lowell, MA 01854

Notification: Applicants will be notified of the results by April 23, 1997. ◇

NESACS Elections

Before May 1, ballots for electing officers, councilors/alt. councilors and other elected positions will be mailed, to be returned by June 1. The list of nominees will be in the next issue, to be mailed March 21. Nominations by petition are due March 23 at the NESACS Office. ◇

NESACS Website

You may have noticed the website listing on page 3. The Section has maintained this website since November through the kind offices of Dr. Arthur Obermayer, who is serving as the Webmaster. A subcommittee of the Board of Publications will have the responsibility for overseeing this operation. Also notice the ad for an Assistant Webmaster in the February *NUCLEUS* and in this issue.

The website address is: **http://www.tiac.net/users/obermayr/nesacs**

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February 20

Dr. Phaedon Avouris (IBM Watson Res. Ctr.)
"Atomic and Nanometer Scale Modification of Materials Using Proximal Probes"
Mass. Inst. of Technology
Room 8-120, at 5:00 PM

February 24

Prof. Michael Ward (Univ. of Minnesota)
"Crystal Engineering with Robust Hydrogen-bonding Networks: Rational Design of Layered Materials and Nonaporous Solids"
Brandeis University
Room 122, Gerstenzang, at 4:00 PM

Prof. Gregory Fu (Mass. Inst. of Technology)
"Asymmetric Catalysis with Planar-Chiral Heterocycles"
Harvard University
Pfizer Lect. Hall, Mb-23, 12 Oxford St., at 4:00 PM

February 25

Prof. JoAnne Stubbe (Mass. Inst. of Technology)
"Bleomycins: Structure and Function"
Tufts University
Pearson Hall, Rm. 106, at 4:30 PM

February 26

Prof. Lila Gierasch (Univ. Mass., Amherst)
"Folding of a Predominantly Beta-Sheet Protein with a Hole in the Middle"
Brandeis University
Room 122, Gerstenzang, at 4:00 PM

February 27

Prof. George W. Flynn (Columbia Univ.)
"Imaging Molecules at the Liquid-Solid Interface Using Scanning Tunneling Microscopy:
Desperately Seeking STM Chromophores"
Boston College
Merkert Chem. Ctr., Room 127, at 4:00 PM

Sir John Meurig Thomas (The Royal Inst., ENG)
"Designed Solid Inorganic Catalysts"
Harvard University
Pfizer Lect. Hall, Mb-23, 12 Oxford St., at 5:00 PM

March 3

Prof. Lisa Pfefferle (Yale Univ.)
"Catalytic Combustion of Methane using Pd-based Catalysts"
Tufts University
AV Room, Science & Technol. Ctr., at 2:30 PM

March 4

Prof. Vincent Rotello (Univ. Mass., Amherst)
"Modulation of Cofactor Redox Potentials through Specific Interactions:
Synthetic Models of the Flavoenzymes"
Tufts University
Pearson Hall, Rm. 106, at 4:30 PM

March 5

Prof. Jacob Israelachvill (Univ. California, Santa Barbara)
"Measuring Surface Forces and Other Interfacial Phenomena with the Surface Forces Apparatus"
Harvard University
Pfizer Lect. Hall, Mb-23, 12 Oxford St., at 4:00 PM

March 11

Prof. John Wright (Univ. Wisconsin, Madison)
Eddy Lecture: "Is there Credible Evidence that Active Learning Works?"
Tufts University
Pearson Hall, Rm. 106, at 4:30 PM

March 12

Prof. Laurie Butler (Univ. of Chicago)
"Understanding Chemical Reaction Dynamics and Product Branching When the Born-Oppenheimer Approximation Breaks Down"
Harvard University
Pfizer Lect. Hall, Mb-23, 12 Oxford St., at 4:00 PM

Prof. John Wright (Univ. Wisconsin, Madison)
"Research Opportunities at High Laser Intensities - New Optical Materials
Based on Fullerenes and New Spectroscopies Based on Multiresonant Vibrational Transitions"
Tufts University
Pearson Hall, Rm. 106, at 4:30 PM

March 17

Prof. Edward Solomon (Stanford Univ.)
"Oxygen Intermediates in Multicopper Enzymes"
Harvard University
Pfizer Lect. Hall, Mb-23, 12 Oxford St., at 4:00 PM

March 19

Prof. Emily Carter (Univ. California, Los Angeles)
"Ab Initio Molecular Dynamics and Kinetics of Gaseous and Gas-Surface Reactions"
Harvard University
Pfizer Lect. Hall, Mb-23, 12 Oxford St., at 4:00 PM

Dr. Charlene Mello (Army Natick Labs)
"Forced Molecular Evolution: The Development of Microorganisms with Novel Degradative Capabilities"
UMass Dartmouth
Sci. & Eng. Bldg., Rm. 228, at 4:00 PM

March 20

Dr. Frank H. Stillinger (AT&T Bell Laboratories)
"Living in a Metastable World: A Theoretical Perspective"
Boston College
Merkert Chem. Ctr., Room 127, at 4:00 PM

March 24

Prof. Larry Overman (Univ. of California, Irvine)
"New Ring-Forming Methods and Their Application in Natural Products Total Synthesis"
Harvard University
Pfizer Lect. Hall, Mb-23, 12 Oxford St., at 4:00 PM

Prof. Alan Engleman (Dana Farber Cancer Inst.)
"Stereo Chemistry and HIV-I Integration"
Tufts University
AV Room, Science & Technol. Ctr., at 2:30 PM

March 25

Prof. David Kane (Brown Univ.)
"TBA"
Boston College
Merkert Chem. Ctr., Room 127, at 4:00 PM

Prof. David Kaplan (Tufts University)
"Spider Silk - A New Paradigm for Material Sciences"
Tufts University
Pearson Hall, Rm. 106, at 4:30 PM

Notices for the Nucleus Calendar should be sent to:

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