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Special issue dedicated to Professor Lemont B. Kier on the occasion of the 75th birthday

My Journey Through Structure: The Structure of My Journey

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Abstract

I describe here, my adventures in science as a journey in the realm of structure. This is focused on the structures of atoms, groups, molecules and molecular systems within the vast hierarchy of all systems in nature. I have explored structure at the atom level with molecular orbital theory and the electrotopological state. My exploration of structure at the group and molecule levels was with molecular connectivity. My journey through molecular systems was done with cellular automata. No interesting journey is taken alone and so I speak here of many who have shared my travels. As in any scientific endeavor, the hypotheses and theories created are ephemeral, and so the journey has no end. But the excitement and satisfaction keeps us traveling and so I hope to be a passenger for many more years. ALL ABOARD!

Keywords. Topological indices; electrotopological state indices; cellular automata; quantitative structure–activity relationships; QSAR.

1 OVERTURE

I am honored and very pleased to receive this attention to my 75th year. Being 75 is a new experience for me. It is a point in time where you look back with memories, look at today with pleasure and look ahead with anticipation. But of course, we can do that at any age. In this passage I would like to focus on some memories that are associated with my career in research. It is a journey that has a structure which is varied and interesting. It is about structure. At the same time I would like to highlight a few incidents that were pivotal in my career. Some of these are worth mentioning to newly–minted PhD's, post–docs and new faculty. I think that those of us with a few years experience have the responsibility to mentor the new people coming along in science. So I will sprinkle in some of my observations and nuggets of wisdom. Many people impacted on my career. Scientific research is not done in a cave, we encounter many who influence us. I can't mention them all so I apologize to those whom I have overlooked.

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2 BEGINNINGS

I was born, along with my twin sister Judy, on 13 September, 1930, in the hospital at Western Reserve University in Cleveland Ohio. A few hundred meters from that building, in 1887, Mickelson and Morley performed their famous experiment along the railroad tracks. They found that light was propagated at the same velocity in any direction, dispelling the hypothesis that there existed an "ether' through which it traveled. My father had a chemistry degree and so there were some books around the house that eventually led to my browsing. My mother was an artist, an ability that later surfaced among my interests. It was a very happy childhood with Judy, and caring and interesting parents. Later I had a younger sister, Myra, who was also close to me in my adult years.

An early interest in geography surfaced, particularly the stories of the discoveries in the Arctic and Antarctic and remote places on the planet. I imagined how wonderful these adventures must be, coming across an undiscovered mountain, island, lake or what ever, realizing that it was new to common knowledge. Along with that interest came a similar vicarious thrill when reading about the discoveries of the elements in my Dad's Handbook of Chemistry and Physics. These readings fueled my sense of curiosity and a keen interest in the process of discovery. These emotions have stayed with me and have grown over the years.

An important event occurred at Christmas in my tenth year. My father bought me a child's chemistry set. This sealed my fate for the next 65 years. It was really fun doing some of the experiments as written in the directions, but then straying away and doing things just to "see what happens". I guess I have been doing that ever since. Out of these early experiences, I came to the conclusion that I wanted to be a chemist and I wanted to be a professor of that subject and I wanted to make discoveries. It all turned out that way.

3 EDUCATION

I did not have a strong preference as to where I wanted to go to college. I knew that I wanted eventually to go to graduate school. I also was interested in a varied social life that was to be found at major state universities, and so I enrolled at The Ohio State University as a chemistry major in 1948. The studies were interesting, as was the social life, but I found that I was interested in the biological aspects of chemistry. In particular I became interested in the role of drug molecules in living systems. After three years of study I realized that I would fulfill my interests more actively by transferring into the Pharmacy program. This was an important decision, one that shaped my career in a very positive way. At the same time I met and later married my wife, Martha. Since then we have raised five children. My intention remained, to go on to graduate school and this intent was reinforced by the interest shown in me by Prof. John Wagner. *How very significant and indelible is*

the interest of a teacher, *in their students*. This lesson was not lost as my academic career evolved.

Upon graduation in 1954, I received an Army commission in the Medical Service Corps. I was called to active duty but this was postponed because I was accepted into the graduate program at the University of Minnesota as a teaching assistant. The years at Minnesota were as interesting as those at Ohio State. In spite of some cold weather, we enjoyed the university and the ambience of the twin cities. We always hoped that summer would come on a weekend. I had the great fortune of having a wonderful major professor, Taito O. Soine. He was knowledgeable, enthusiastic, humorous, and very interested in my education and career. He became a very good friend and model for many years after I graduated. *Directing a graduate student is an awesome responsibility deserving of every ounce of care and attention*. Years later I had the privilege, as department chairman at VCU, to be able to hire his son, William, as a faculty member.

My research introduced me to the world of molecular structure. My goal was to elucidate the structure of alkaloids in a poppy plant, my first real entry into the adventure of discovery. At that time there was no NMR, IR, automated chromatography, and only a primitive UV. All of the discovery had to be done with chemical reactions. I reached conclusions about the structures of two alkaloids and then received my Ph.D. degree in 1958. The structures turned out to be wrong as found by NMR analysis five years later, a humbling experience for a newly minted Ph.D., but that's the way science is. Following graduation I served on active duty at the Brooke Army Medical Center, San Antonio, Texas, in an officer training program followed by a few months in a clinical laboratory.

4 INTO THE ACADEMY

At this time there were many academic jobs open and so eligible applicants could make decisions on a number of bases. I applied for several beginning positions and decided that the University of Florida offered the best opportunity plus an interesting place to live. My academic career started in January 1959 in Gainesville, Florida, as an Assistant Prof. of Pharmaceutical Chemistry in the College of Pharmacy. My research continued in the pathway started at Minnesota. I followed leads about plants with alleged biological activities, processing the raw material, extracting what was presumably the active molecule and doing structure analyses using chemical and physical techniques.

My first graduate student, Krishnan Kaistha was a few years older than I. He was a very hard working student and I valued his colleagueship as well as his good research. Other graduate students were Devindra Dawan and Tom Stewart. I continued my reductionist approach to structure elucidation, chemically decomposing molecules to parts and then identifying them, followed by recombination to predict the whole molecule structure.

5 MESOIONIC HETEROCYCLES

A seminal event occurred one day in 1960. I ran into a young chemistry graduate student, Marion Miles, who asked me if I had heard his seminar. I confessed that I had missed it so he gave me the handout with a summary. The topic was mesoionic compounds with emphasis on the sydnones. Looking at these structures ignited a very strong attraction to their potential for biological activity. Today we would say that they looked "drug–like". My research interests took a right–angle turn at this time. The lesson here is *attend seminars and be prepared to receive new ideas*. My graduate students and I synthesized compounds from several types of mesoionic heterocycles, summarized in a review article [1]. Again, it was the structure of these compounds that attracted my interest. It was novel in the sense of not being describable with a single canonical structure and it had a variety of polar atoms yet it was relatively hydrophobic.

6 MOLECULAR ORBITAL THEORY

In 1963 I joined the Pharmacy faculty at The Ohio State University and continued my research on the mesoionics. I had an outstanding young graduate student at that time, Ted Roche. I have been very proud of his achievements over the forty years since his graduation. One day Ted came into my office after his class and drew some things on my board. He wrote down the structure of ethylene and then some numbers in a matrix followed by some diagonal products. He ended up with a number at each carbon. I asked what all of this was. He said it was Hückel molecular orbital theory that could, through computation, derive numerical values interpreted as electron densities at an atom and the energies of molecules. I was astounded that such information could be obtained without going into the lab and cooking up stuff. This produced another right–angle turn in my research career. Almost immediately I turned to molecular orbital theory to calculate attributes such as electron densities, energies and preferred conformations. The lesson is *listen to your graduate students*. Ted did a beautiful dissertation on the molecular orbital analyses of mesoionic compounds. The idea that theoretical calculations could lead to predictions of properties with high validity really opened up in my mind a whole new paradigm of structure elucidation and molecule design. There were several people who had introduced M.O. theory into more practical realms including Bernard and Alberte Pullman [2], Andrew Streitwieser [3], Charles Coulson [4], and others who greatly influenced my studies and research.

In the decade of the 1960's, there formed two distinct approaches to relating molecular attributes with biological activity. The first approach was the development of physical property relationships to biological activity, pioneered by Corwin Hansch [5]. This approach was described under the label of quantitative structure–activity relationships (QSAR). The method did not produce structure information, interpretable by the synthetic chemist, but it related a biological property with a physical property. The alternative approach to molecular definition using properties, was based on

the structure of a molecule, as available through models such as molecular orbital theory. Pioneering efforts in this decade contributed to the ability to calculate these parameters and to model molecular activities and properties. These included the first attempt at an all–valence electron M. O. method by Del Re in 1958 [6], the first all–valence electron method capable of predicting conformational preferences by Hoffmann in 1963 [7], and the first all–valence electron method giving reasonable charges by Pople in 1967 [8].

The early work using these M.O. methods was largely focused on chemical reactions and interactions. Several symposia were held during this decade. These included the Menton, France symposiums sponsored by the Pullmans, the Jerusalem symposia begun in 1967, Gordon Conferences devoted to quantum mechanical calculations, and the Sanibel Island Conferences. The main focus of these meetings was M.O. development and applications primarily in chemical reactivity. At each symposium, there was always one or two invited biologically oriented scientists who would describe their calculations relating the theoretical methods to biological phenomena. I found myself in this role on several occasions. Presentations relating structure to drug activity were usually on the last day of the meeting and it would appear as the last chapter in the symposium volume.

There were a number of scientists, impressed by the work of the Pullmans and Streitwieser who ventured into the drug molecule structure–activity realm using these methods. Some interesting work was published in the 60's by a handful of investigators but it was not warmly received at that time by the medicinal chemists, the quantum people or the property–activity modelers. The beginning of my contribution occurred in 1967 when I reported the first M. O. calculation of the preferred conformation of a drug molecule, acetylcholine [9]. The prediction was later confirmed experimentally. My studies on other transmitters and drugs led the way to the predictions of the salient molecular structures producing the activity, that I called the pharmacophore. I referred to this strategy as "receptor mapping". The prediction of preferred conformation is now an automatic procedure that modelers accomplish by clicking on an icon to "minimize".

I organized the first symposium devoted primarily to applications of M.O. studies on drug molecules in 1969 at the Battelle Center in Seattle. Most of the investigators using M.O. in QSAR studies at that time were in attendance. The speakers included: Art Cammarata, Bill Purcell, Soloman Snyder, Jack Green, Brock Neely, Arnie Wohl, Bernard Pullman, Robert Rein, Jim Hoyland, and myself. Other contributors during the 60's included Joyce Kauffman and Gilda Lowe. At this symposium the latest work in structure–based QSAR was presented. The symposium book from this meeting, the first book dealing with drug QSAR, was published the following year [10]. The QSAR studies in the 60's using molecular orbital theory were summarized in a book on the

subject that I wrote in 1971 [11]. The use of more sophisticated molecular orbital methods followed these pioneering efforts and so the state of this approach has passed into the realm of standard procedures, de rigueur, of modeling, today.

Along with the study of conformational structure, I became interested in the potential for a molecule to interact with another, through non–covalent bonds. This attribute of structure finds fruition in the prediction of possible encounters of molecules as in the interaction of pharmacophores with receptors. Working with Jim Hoyland and Jack George, in the early 70's, we crafted a general equation computing the potential for electrostatic, dipolar and dispersion forces between molecules, modeling pharmacophore–receptor interactions. We called these, "model interaction energy calculations". This approach is now referred to as "docking" studies, extensively developed by Garland Marshall. One of the more interesting outcomes of our research was a study of the currently postulated pharmacophore for the sweet taste. My conformation studies led to the extension of the existing model to include a third, hydrophobic binding site, imparting an explanation for the steriospecificity of some sweet–tasting molecules [12]. The Shellenburger, Acree and Kier theory of the sweet–tasting pharmacophore is still valid today. One lesson learned form this period was the value of collaborations with colleagues. My message here is *don't hesitate to collaborate with competent*, *compatible*, *colleagues*. The social side of science is extremely rewarding both professionally and personally.

In 1972 I accepted a professorship and an administrative position at the Massachusetts College of Pharmacy in Boston. This was and still is a wonderful city in which to live and work. My time there was extremely interesting and productive. I entered into a period where I had a number of very good and interesting sabbatical fellows. These included, Hans–Dieter Höltje from Germany, Therese DiPaolo from Canada, and Michael Tute from England. From the US I enjoyed the colleagueship of Wally Murray, Haven Aldrich and Lowell Hall. I experienced very stimulating exchanges with each of these, especially with Lowell Hall, which was to be the beginning of a collaboration and a close friendship that has continued for the past 32 years.

7 MOLECULAR CONNECTIVITY

Another seminal event in my journey through structure occurred in the opening week of 1975. I had a visit from Milan Randić, a scientist that I had recently met during a visit with Robert Rein. He described to Lowell, Wally Murray and I, a scheme he had worked out, to encode, numerically, the branching patterns of alkane isomers [13]. It was based on counts of bonded neighbors, other than hydrogen, to each carbon atom. These indices appeared to rank alkane isomers according to an intuitive degree of branching, but they also closely ranked them according to boiling point.

The possibilities appeared to us to be very great. Here was a simple algorithm, based on counts,

not selected basis sets or arbitrary assumptions, that could encode important structural attributes of atoms in molecules and whole molecules. We saw the potential for the encoding of structure to include unsaturation, aromaticity, heteroatoms, electronegativity, and relative volume. Calling the system molecular connectivity, Lowell and I expanded the simple parameter scheme to encode information about other hybrid states and atoms other than carbon, which led to valence state indices. We also introduced multiple bond molecular dissection to produce higher order fragment indices. This greatly expanded the original algorithm, making it possible to encode the structures of molecules of biological interest. A series of papers followed that developed these attributes [14–16]. Within a year, Lowell and I published a book on the subject [17]. A large effort was put forward in the application of molecular connectivity to the creation of QSAR models. Lowell wrote a computer program that disseminated molecular connectivity to a wide audience in industry, the academy and government agencies. It has become a very widely used methodology in compound design.

In 1977 I accepted the chair of Medicinal Chemistry at Virginia Commonwealth University. My studies on molecular connectivity continued with Lowell Hall, leading to another book on the subject in 1986 [18]. An important paper came out of our studies in 1981 [19]. In the examination of the parameters for the simple atom structure, δ, and the valence based atom structure, δ^v, it became obvious that there were close relationships between these delta values and the Mulliken–Jaffe valence state electronegativities of atoms in molecules. From this we derived a relationship closely predicting this, which is now called the Kier–Hall electronegativity. A simplified form using the periodic table columns and rows gives the same result, which is useful in teaching this important concept to beginning students.

In the 80's I became interested in a structural attribute that can be interpreted as shape. This led to a scheme to calculate such indices using topological structure, that I called the kappa indices [20]. One of these drew on the Shannon information index, a description used in molecular structure analyses by Danail Bonchev in his book [21]. He later joined with me in some studies and is now a colleague.

8 THE ELECTROTOPOLOGICAL STATE

I had for some time been interested in the attribute of electronegativity. As a learning tool it is superb, but often neglected in early chemistry courses. Reading Sanderson's book, [22], and other publications, led me to explore its potential to produce an atom–in molecule structure descriptor. This interest was a return to the atom level of structure that I had studied a decade earlier with molecular orbital theory. Using the information revealed by the delta values [19] it became apparent that a simple scheme could be written down that encoded the relative electronegativity of an atom in a molecule. This became the Kier–Hall electronegativity:

$$X_{KH} = \frac{\delta^v - \delta}{N^2} \quad (1)$$

where N is the principal quantum number, δ^v, is the count of sigma, pi and lone pair electrons other than to hydrogen, and δ is the count of sigma electrons other than those bonding hydrogen. The expression reduces to the count of pi and lone pair electrons, modified by the N value. The value of this electronegativity can be quickly calculated by the simple expression

$$X_{KH} = \frac{\text{The periodic table column} - \text{The number of bonded neighbors}}{(\text{The periodic table row})^2} \quad (2)$$

This atom centered index encodes electron–richness at an atom in a molecule. We can add to that information by introducing a description of the topological state, an attribute that plays a strong role in the intermolecular accessibility of an atom. To encode the topological state of an atom, we looked to the simple delta value. The reciprocal of the delta value, $1/\delta$, is a large number ($1/\delta = 1.0$) for a mantle atom as is found in the methyl group. In contrast, the central atom of neopentane has a low value ($1/\delta = 0.25$).

To derive an expression the encodes both the electron richness at an atom due to electronegativity and the topological accessibility of the atom, we wrote an expression that is a function of these two attributes:

$$I = \frac{\delta^v - \delta}{\delta} \quad (3)$$

To avoid zero values for C sp^3 atoms and to produce values above 1.0 we algebraically modified the expression to

$$I = \frac{\delta^v + 1}{\delta} \quad (4)$$

This combination of attributes was called the intrinsic state, I. To encode the effect of electronegativity equalization due to all of the other atoms in the molecule, we created an algorithm to reflect these effects. In essence the effect of all other atoms on a particular atom is due to the differences in their intrinsic states, modified by their distance, expressed as the square if the number of atoms separating the atom from its perturbing neighbor. This leads to a modified intrinsic state that is a function of the relationship of all other atoms in the molecule. This modification puts the index beyond the reductionist frame of molecular connectivity and other topological indices. It expresses the structure as an emergent attribute in a complex system (the molecule) arising from the complex contributions of the agents (atoms). This modified intrinsic state is called the electrotopological state, S, or E–State for short:

$$S_i = I_i + \sum (I_i - I_j)/r^2 \quad (5)$$

where r is the count of atoms separating i and j including these two atoms.

The E–State index and the variants that we have created are finding wide use in QSAR analyses, database searches and similarity applications. Lowell and I wrote a book on the E–State in 1999 [23]. The use and value of the E–State coupled with other indices was described in our article on bioisosterism in 2004 [24].

9 CELLULAR AUTOMATA MODELS

In 1989 a young graduate student from India, Nikhil Joshi, joined me to pursue a Ph.D. in theoretical molecule description. He is a brilliant scholar and he did a masterful piece of research on aspects of the E–State. One day he came into my office and gave me a book he was reading. It was "Chaos" by James Gleick. I read it learning something about complexity, chaos, fractals and … cellular automata. This later subject triggered a strong response as to its possibilities and thus produced another right angle turn in my focus on structure. Here was a dynamic system that could model the structure of systems of agents (molecules) with great ease and with a visual component. I foresaw the possibility of modeling and understanding some of the attributes of large numbers of molecules such as water, solutions and other interacting ensembles of molecules at the system level. I immediately focused on this possible application of this paradigm, developed a half–century earlier by John Von Neumann [25]. It had been used very little in chemistry at the molecular system level.

Working with Chao–Kun Cheng, in Computer Science at VCU, we crafted a series of programs using cellular automata dynamics to model water, solutions, hydrophobic effects and many other molecular systems [26]. I later collaborated with Bernard Testa and also with Paul Seybold on a variety of studies with these models. I published a book on the subject in 2005 with Seybold and Cheng [27].

Another significant event occurred in 1989. I was invited to spend three months at the University of Lausanne, Switzerland, studying with Bernard Testa. I have been invited every year since as a visiting professor, receiving the University of Lausanne Chair of Honor in 1992. I shared many research projects with Bernard, one of which was in the area of the emergence of complex systems by a process that Bernard defined as dissolvence. We published several papers on structure and molecular–level complexity [28,29].

In 2002 I participated in the founding of the Center for the Study of Biological Complexity in the Life Sciences Structure at the Virginia Commonwealth University. I am a Senior Fellow and a member off the staff responsible for programs and fellows. In 2004 I was presented with the Commonwealth of Virginia Life Achievement Award in Science.

My recent studies have focused on modeling the structure of water under the influence of protein surfaces. This has led to a theory of the passage of ligands over the protein landscape around

receptors and enzyme active sites. Invoking the hydrophobic and hydrophic effects of side chains on surface water, I predicted the presence of passageways, I called chreodes through this surface water. Ligands experience a facilitated two–dimensional diffusion to and away from these effectors, through these chreodes, leading to familiar phenomena. [30]. A consequence of this theory was my theory of the mechanism of the non–specific general anesthetic effect [31].

10 LOOKING AHEAD

Looking back, I have devoted my research career to pursuing the elusive attributes called structure; modeling it, using it, encoding information about atoms, fragments, molecules and systems of molecules. All of these are essential for any insight into the relation between structure and properties. This generalizes to the relation between form and function. What a molecule does in response to any interaction (function) is of great importance for any progress in technology. What a molecule is (form) is an essential ingredient in the creation of understanding in science. In both activities we depend also on the interdependence between form and function. To define form we employ function (experiment). To explain function we employ form (information).

Looking ahead I see an increasing appreciation for and the value of dynamic modeling of complex systems. I hope to remain active in this arena, with research, books and courses taught in the CSBC and Life Sciences. Perhaps you will ask me to write something for my 80th birthday. Thank you all again for this honor and remembrance.

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