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Editorial

Introduction and foreword to the Special Issue commemorating the 25th anniversary of molecular connectivity as a structure description system

Introduction

Two names are synonymous with the subject of molecular connectivity. These names are Lemont B. Kier and Lowell H. Hall. It is my pleasure to welcome them as Guest Editors of this special issue.

The groundwork for this issue was laid at the American Chemical Society (ACS) national meeting in April 2000 when Professors Hall and Kier requested that papers from the symposium they were organizing for the August 2000 ACS national meeting be published in this journal. The proposal was readily welcomed. Their Molecular Connectivity symposium was accepted part of the Computers in Chemistry Division (COMP) program. Since this journal affiliated with COMP, it is an excellent venue for publishing papers from thematic COMP symposia where the number of papers is not large enough to warrant production of an entire book in the ACS symposium series. As has been the standard editorial practice for this journal, all the papers in this issue were subjected to vigorous refereeing and revision.

Molecular connectivity is a subject that capitalizes on information inherent in a chemical structural diagram, i.e. what atoms are present and how they are connected by covalent bonds. The subject has been developed over the last 25 years by a small but intensely devoted coterie of computational chemists. Their research has led to highly inventive mathematical prescriptions for an astounding array of quantities reflective of molecular structure. Molecular connectivity descriptors have been extensively used in looking for quantitative structure–activity and structure–property relationships (QSAR and QSPR). The descriptors have the advantage of being adaptable to extremely rapid algorithms on small computers. The arrival of combinatorial chemistry about 10 years ago and the resultant need to design combinatorial compound libraries provided a research environment where interest in rapidly computable descriptors including molecular connectivity could flourish. The descriptors can help the chemist measure and conceptualize compound space. Now many pharmaceutical companies use these descriptors, along with a large number of others including those related to Lipinski's "Rule-of-Five". All these various descriptors are being tested and employed in drug discovery efforts worldwide.

Dr. Hall is Professor of Chemistry at Eastern Nazarene College in the Boston suburb of Quincy, MA. He served as head of the Chemistry Department from 1967–1996 and as chairman of the college's Division of Natural Sciences and Mathematics from 1976–1999. Dr. Hall's association with the college began with his undergraduate studies there which led to his B.S. degree in 1959. His interest in physical chemistry took him to Johns Hopkins University where he obtained his Ph.D. in 1963. Following postdoctoral research at the National Bureau of Standards and teaching at Florida Atlantic University, he returned to Eastern Nazarene as a faculty member in 1967 and has been teaching there for 34 years.

Dr. Hall wrote the MOLCONN-Z program which is widely used for research in academia and industry. The software has been written for various platforms including VAX, PC, and Apple Macintosh. Dr. Hall has published over 100 papers. His first book, on "Group Theory and Symmetry in Chemistry", was published in 1969. He and Professor Kier have co-authored four books, in addition to many journal articles. Their latest book, "QSAR Development with QsarIS", which is scheduled for publication in 2001, is co-authored with Dr. Hall's son, L. Mark Hall. The book is designed to accompany SciVision's new software product for data entry, QSAR analysis, graphics, and interpretation of topological indices.

Dr. Kier has been Professor of Medicinal Chemistry in the School of Pharmacy at Virginia Commonwealth University in Richmond since 1977. He obtained his B.S. degree in pharmacy at Ohio State University in 1954 and a Ph.D. in medicinal chemistry from the University of Minnesota 4 years later. Based on duty in the Reserve Officers Training Corps at Ohio State, he served in the US Army, and rose to the rank of Major before retiring from the Reserve

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in 1969. Dr. Kier's military bearing is still evident after 30 years. Like Dr. Hall, he began his teaching career in Florida. Following 4 years at the University of Florida, he returned to Ohio State as an assistant professor in l963 and, staying in Columbus, Ohio, joined Battelle Institute in 1966. He was on the faculty at Massachusetts College of Pharmacy in Boston for the years 1972–1977. There his collaboration with Dr. Hall began in 1974 when Dr. Hall came for a sabbatical. In 1977, Dr. Kier moved south to VCU to serve as Chairman of the Medicinal Chemistry Department for 10 years.

One of the pioneers in QSAR since the mid-1960s, Dr. Kier has written over 230 articles and book chapters. Among his publications are two chapters in *Reviews in Computational Chemistry* (1991 and 2001). He edited a book on molecular orbital theory in drug research in 1970 and then wrote his own book on this subject in 1971. He has written four additional books, all with Professor Hall. Dr. Kier is frequently invited to present talks at scientific meetings and has served as consultant to various companies. His recognition in the scientific community has led to his appointment to the editorial boards of four journals or book series. Since 1989 he has been a visiting professor at the University of Lausanne in Switzerland.

We appreciate the interest and support that Professors Hall and Kier have shown in the ACS Computers in Chemistry Division (COMP) and in this journal.

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Foreword

A new general approach to molecular design emerged in the 1960s and has become a major method in medicinal and pharmaceutical chemistry. At the heart of this approach are the correlations that have been found between a wide variety of molecular properties and mathematical descriptions based on molecular structure. The statistical models describe a relationship between a function (biological activity or physical properties) of a molecule and a form (structure) of a molecule. The models, thus, created constitute quantitative structure-activity relationships (QSAR). Given these correlations, the computational chemist is in a position to evaluate structure designs and to make predictions on which designs to synthesize for the purpose of enhancing a target property.

Modeling information to describe molecules comes from one of two very different sources: measured physical properties and numerical values derived from counts of attributes or probabilities of occurrences of states of modeled structures. The former approach to a QSAR model has proven to be successful; however, the approach depends on an indirect final step in the prediction process, that is, the conversion of property-based information (such as lipophilicity) into structure information to guide the synthetic chemist in creating new molecules. The second approach, based on a structure model, creates information that does not require intermediary experimental data when being used to design new molecules.

The first structural descriptors employed in creating QSAR models were based upon values calculated by molecular orbital methods, including partial charges, dipole moments, or energy levels. Subsequently, there were forays into the areas of topology and graph theory in a direct attempt to encode molecular structure information. These early efforts reached a climatic point when Milan Randic published a seminal paper in 1975 describing an algorithm quantifying the branching of alkanes. This method provided a branching index that correlated closely with several physical properties of these alkanes.

That same year a series of papers by Kier and Hall recognized the huge potential that the Randic algorithm afforded for quantifying structure in a chemically useful way. We added to the basic algorithm the capability to quantify a variety of substructure types and to encode the presence and valence states of atoms other than carbon. A structure system, molecular connectivity, emerged from these efforts and is now widely used in industry to design new molecules and in academia to understand the influences of structure. The widespread use of molecular connectivity comes from its intrinsic quality and the foresight of Lowell Hall in writing a computer program and making it available two decades ago. At the same time, other investigators participated in the development, notably Alexandru Balaban and Donail Bonchev. These developments were followed by contributions from Subhash Basak and Paul Seybold. More recently, innovations by Jorge Galvez, Alexander Tropsha, Lionello Pogliani, and Ernesto Estrada have added greatly to the value of molecular connectivity.

As a new decade and a new millennium approached, we realized that an anniversary was upon us: the 25th year since the creation of the molecular connectivity system. We decided to bring together the principal participants in the origin and development of molecular connectivity at a symposium. The American Chemical Society meeting in Washington, DC, in August of 2000 afforded such an opportunity. All of those mentioned above attended and each presented some historical aspect or brought to the meeting their newest contribution to molecular connectivity. This special issue is comprised mainly of these presentations.

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Chemistry, Chemical Computing Group, EduSoft, Hall Associates Consulting, Molecular Design Limited, Molecular Simulations Inc., SciVision, SemiChem, and Tripos. Acknowledgment is also made to the Donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this symposium.

It is our hope that a 50th Anniversary Symposium of Molecular Connectivity can be held in 2025. Finally, we extend thanks to the Editor, Donald Boyd, for his offer to develop this special issue.

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