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On History of the Randić Index and Emerging Hostility toward Chemical Graph Theory

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Dedication: This article is dedicated to "Good Editors" of scientific journals that I knew or know: **Alexandru T. Balaban** (*Polycyclic Aromatic Compounds*), **Erkki Brändas** (*International Journal of Quantum Chemistry*), **David C. Clary** (*Chemical Physics Letters),* **Ante Graovac** (*Croatica Chemica Acta* – guest editor), **John Gladys** (*Chemical Reviews*), **Ivan Gutman** (*MATCH Communication in Mathematical and in Computer Chemistry*)**, John Hancock** (*Journal of Proteome Research*), **Paul G. Mezey** (*Journal of Mathematical Chemistry*), **George W. A. Milne** (*Journal of Chemical Information and Computer Sciences*), **Yngve Öhrn** (*International Journal of Quantum Chemistry*), **Robert G. Parr** (*Journal of American Chemical Society*), **J. W. Stout** (*Journal of Chemical Physics*), **Božo Težak** (*Croatica Chemica Acta*), **Nenad Trinajstić** (*Croatica Chemica Acta*), **Wendy Warr** (*Journal of Chemical Information and Computer Sciences & Journal of Chemical Information and Modeling*).

I apologize to those not named, with whom I may have but limited contacts as an author or referee – who together with the above named make a visible minority in the scientific community of journal editors – but the minority that gives us hope for the continuing progress in science.

> "*Unfortunately, now there are too few theoretical chemists with sufficient vision to take a giant step of exploring completely new techniques. Instead, scientists in the 1980s get so immersed in a maze of computational detail that they lose sight of the simple, elegant theories*."
>
> J. O. Hirschfelder [1]

Prologue

Dedications of scientific publications are not unknown. I made my share of such dedications over my past 35 years of publishing activity, including among others: (in chronological order): **V. Prelog**, **E. Clar**, **O. E. Polansky**, **C. A. Coulson**, **P-O Löwdin**, **H. Hauptman**, **L. Pauling**, **M. Eigen**, **F. Harary**, **H. Kroto**, and **J. A. Pople**. For complete listing and more details see Appendix 1.

Occasionally festschrifts and even books are dedicated to select scientists, occasionally for 70-th anniversary or such, and I have contributed to some such, like a special issue of *Journal of Physical Chemistry*, festschrift dedicated to Professor E. Bright Wilson (edited by D. Herschbach) [2], a book dedicated to Professor R. G. Parr [3], special issue of *Croatica Chemical Acta* [4] and *Journal of Chemical Information and Modeling* [5] dedicated to Professor Nenad Trinajstić. Not long ago even I was honored by a special issue of *Croatica Chemical Acta* [6] and Internet Electronic Journal of Molecular Design [7] on the "occasion of my 70th birthday." To this list I would like to add, what may appear at the first sight a somewhat unusual dedication – the first of a kind as far as I know, a paper by Sheriff E-Basil, "Dedicated to Professor Milan Randić on the occasion of his 72 birthday" [8]. However, in contrast to other contributions "on the occasion of my 70 birthday" (e.g. [6, 7]), which were all two years "late," Sheriff El-Basil was the only person who could count straight!

Inspiration for the above dedication came by recalling the article "Fast and permanent changes in preparative and pharmaceutical chemistry through multicomponent reactions and their "libraries"," which was published in *Proceedings of the Estonian Academy of Sciences* [9].

"*Dedicated in the 65th year of Ivar Ugi to the 85th, 80th, 75th, 70th, 65th and 60th birthdays of his admired colleagues, professors . . .*

The list continues with two dozen names gathered in the same age group, including the following (I listed only those that I knew, knew of, or know):

75th: Sir Derek H. R. Barton, Jacques Emile Dubois, Rolf Huisgen;
70th: Albert Eschenmoser, Joshua Lederberg;
65th: Frank Albert Cotton, Milan Randiç, Paul von Ragué Schleyer;
60th: Nikolai S. Zefirov

Ivar Ugi ended his dedication with:

and also in fond memory of the ingenious mathematician James Dugundji, who passed away 10 years ago in 1985, and the life of Hans Fischer and his important role in chemistry, that ended 50 years ago."

My name, as one can see was slightly misrepresented by use of "ç" instead of "ć", which wood looks OK if I were Croatian living "Down Under" (Australia), rather than USA. This minor typographic issue reminds me of my first day in Cambridge, England when I arrived in 1954 to start work on my Ph. D. thesis. On arrival I was immediately advised to report to the local Police Station to obtain a local ID document (which when necessary I would show instead of using my passport). I came to the Police Station and at a small window reported my presence. The police officer handed me a small piece of paper and asked to spell my name. I have written: "Milan Randić" and gave him. He looked at it then tore it to parts and handled another piece of paper and said: "No accents." I said: "That was not an accent, that was a diacritical mark. Accents you put on vowels." He looked at me for a moment and said: "If you cannot write your name in English characters put a sign of cross." As is known, the sign of cross is worldwide used as a "signature" of illiterate – which would be a bad sign for someone enrolling for a graduate study! I immediately realized that one does not argue with police in England, (a democratic country) just as I already knew that one does not argue with police in (then my native) Communist Yugoslavia. Ever since any "c", with "accent" or without, or any modification of it, I have been accepting as legitimate. Such modifications allow me to pretend that I am multinational, next best to being international.

Speaking of the first impressions when visiting other countries I encountered some "official" misunderstanding also soon on my arrival to United States, this time not with police, but the Johns Hopkins university administration. My first six months in 1971 I spent in the Department of Chemistry at Johns Hopkins in the group of Professor R. G. Parr, where I shared an office with Vlasta Bonačić (now Professor at Humboldt University in Berlin, Germany), my former student, whom I sent to Johns Hopkins to get her Ph. D. with Professor Parr. On my arrival at the Johns Hopkins, Professor Parr sent me to the secretary of the Department to complete some paperwork formalities. When I came to her office the young secretary started to ask me lot of questions, like when and where I was born, etc. Then she asked me what my religion was. I was a bit surprised and even today I don't know what has this to do with chemistry. This may be the first time in my life that someone asked me what my religion is. I consider this very a private question because I may have none or I may have several. Later it occurred to me that I could have answered the question by saying that my religion is science, but whether she would believe may depend on her religion! The next question surprised me even more: "*What is your color*?" As I was standing in front of her, she was sitting at her desk, I put my hands on the edge of the desk, looked at them and said "*Pink*." Indeed when my hands hang down for a while they become pinkish. She looked at me and her eyes were widely open, almost to fell out. At the very moment that I said "pink" I realized that, coming from then a Communist country, the word has an additional meaning. "Pink" has been the label for people leaning towards Communism or following Communists. So I was worried and immediately went to see Professor Parr to apologize. I tried to explain the incident, because of possible political implications (after all, this was the time of the cold war). I even mentioned to Professor Parr that it was only in the time of Nazi occupation of Yugoslavia (when I was 10-14 years old) that questions on religion and race were asked. Professor Parr was also upset about this incident and told me that this secretary was specifically warned and asked <u>not to ask such questions</u> and that she is

deliberately disobeying instructions. He then asked me to write a letter to the President of the Johns Hopkins University, Milton Eisenhower (the brother of Dwight Eisenhower, the President of United States) about the incident. I was so happy that my "pink" coloration was not a problem and somehow convinced Professor Parr that perhaps the best is to do nothing – and the best would be to forget the whole incident. Part of my problem was then (as it may still be now) that writing in correct English for me has been an art, and I am not in art, I am in science.

* * *

To some this article may appear as my "rambling" about the past, which in a way I am. I took the opportunity offered by the Editor to say something about the connectivity index, which I did, adding also few historical comments. But I took the opportunity to speak not only about the hostility towards the connectivity indices, which have been going for over 25 years, and while subsiding significantly, has not fully evaporated, but also about hostility towards Chemical Graph Theory, the nonsense that continues and does not show signs of subsiding. It is a sad sign for Theoretical Chemistry that this hostility toward Chemical Graph Theory can last for such a long time. Where are the voices of those leading authorities in the Theoretical Chemistry Establishment to stop the nonsense? Or are they unaware of it?

Who is to blame for this absurd situation that a sizable constellation of Quantum chemists (mostly anonymous), some Physical chemists, and some Medicinal chemists, continue to negate, marginalize, ignore, overlook, minimize, misrepresent and trash Chemical Graph Theory? On the other hand Chemical Graph Theory has the support of many illustrious chemists such as Nobel laureates: **Elias Corey, Dudley Herschbach, Roald Hoffmann, Jerome Karle, Harry Kroto, Joshua Lederberg, Rudolf Marcus, George Olah, late Vladimir Prelog, and Ahmed Zewail**. The first (but not the only) to blame are the editors of scientific journals, who are in the position to ask questions and promote dialog between authors (who understand what they are doing) and reviewers (who often and for most part do not understand what authors are doing). Compare the difference between politicians (and in particular Presidents of states) and scientists, in particular Editors of journals. While good Presidents (like the late J. F. Kennedy) will surround themselves with outstanding advisors, most Editors of Journals surround themselves with their "copies," scientists who have similar views on most issues, instead of inviting advice of those with whom they may not agree. This leads to what one may refer to "scientific" incest, which results in mediocre views on areas viewed as non-traditional chemistry, be it Chemical Graph Theory or Density Functional Theory.

There are worthy exceptions (the "Good Editors," to whom this article is dedicated). I have listed those with whom I had occasional or prolonged contacts but I am sure there are others, and other scientists may wish to point to them – because good editors are heroes of our "unheroic times." I am using here a phrase that was part of the title of an exhibition of the great Croatian sculptor Ivan Meštrović, which he used for his exhibition in Paris in 1924. At the end of this article I gave some justification for my selection for most of the named "Good editors." I am sure the current scientific

"nonsense" will fade away sooner or later, but if this article can facilitate that it be sooner, I would have accomplished more than I hoped for.

Introduction

During 1974/75, after spending a year at Harvard as a faculty guest, I was visiting Tufts University in Medford Massachusetts (a part of Boston area) where I came to consider the problem of characterization of molecules from the positions of Graph Theory. During a relatively short time there I published four papers that received visible attention in years to come. The first was the paper "On Molecular Branching" published in *J. Am. Chem. Soc*. in 1975 [10] and the second was a brief note in *Chemical Physics Letters* [11] followed by two full length articles, one in *Tetrahedron* on resonance energies in polycyclic conjugated hydrocarbons [12] and another in *J. Am. Chem. Soc*. on Aromaticity and Conjugation [13]. I came to Tufts University after spending a year as Faculty Guest at the Harvard University where I was associated with Professor E. Bright Wilson, and outstanding experimental and theoretical scientist, well known (among other things) for an introductory book on use of Quantum Mechanics in Chemistry, co-authored with the illustrious Linus Pauling [14], the development of the FG matrix method for calculation of normal coordinates and molecular vibrational frequencies [15, 16], for theoretical and experimental developments of microwave spectroscopy, and for his book "*Introduction to Scientific Research*" [17] (that he was asked by a government official to prepare in order to facilitate after WW II the science development in USA, where science was dominated by European "imports" many of whom were scientists endangered directly or indirectly by growing Nazi threats).

During my year at Harvard in 1973/74 I had the opportunity to attend many seminars, including a seminar by Alexandru Balaban, a Rumanian chemist, on "Solved and Unsolved Problems of Chemistry" where Graph Theory as a tool has considerable potential. Immediately after that seminar I decided to drift into this interesting and intriguing area of theoretical chemistry that was neither widely known nor appreciated. The next day with Professor Balaban we copied some 20 reprints and preprints - which was almost all of the available literature on the topic of application of Graph Theory to Chemistry, that incidentally included few papers of my former students, Nenad Trinajstić, Ante Graovac and Tomislav Živković, as well as Ivan Gutman, who joined my former Group of Theoretical Chemistry at the Institute Rudjer Bošković, after I already left for USA. So this is my initiation into Chemical Graph Theory. I should add that I had founded the Theoretical Chemistry Group at the Rudjer Bošković Institute in 1960, after returning from Cambridge, England, where I had obtained my Ph. D degree in 1958 working on high resolution infrared spectroscopy (under supervision of Norman Sheppard, a well-known leading authority on IR spectroscopy). However, I should not take the credit for initiation of Quantum Chemistry in ex-Yugoslavia. The idea came from Professor Ivan Supek, Professor of Theoretical Physics at the University of Zagreb, Croatia, a former student of Werner Heisenberg; I was one of his few students. When the time came to work on "Diploma Work," an essay on a topic that one is not taught during the four years of the study of Theoretical Physics, in 1953, I was informally told that there are enough of "atomic physicists" in Yugoslavia and that I should get into

chemistry. Maybe even it was mentioned that "chemistry is too difficult for chemists, so physicists have to get into it." This may be one of reasons why Max Born [18] suggested to his students Heitler and London [19], who of course were theoretical physicists, to study the H_2 molecule – which not only removed the "mystery" of so-called "chemical forces" (characterized by: (1) short distance interaction; (2) directional properties; and (3) saturation), but opened a new theoretical discipline: Quantum Chemistry. Incidentally the "rumor" that chemistry is too difficult for chemists may have been stimulated by a statement of the outstanding German mathematician on the turn of the 20-th century, David Hilbert, who said: "*Physics is too important to be left to physicists*" [20].

Be it as it may, Professor Supek gave me Linus Pauling's book "*The Nature of the Chemical Bond"* [21] and asked me prepare my diploma work on some topic of chemistry. My first thoughts were that I am not good enough for nuclear physics and thus I have been sacrificed to chemistry, but upon reading the book of Pauling I was fascinated by possibilities of applying notions of Quantum Mechanics to Chemistry – and never since then I regretted that fate, and consider I myself being a winner of fortunate combinations of "accidents" that led me to study for Ph. D in Cambridge and listen to lectures by H. C. Longuet-Higgins, S. F. Boys, J. A. Pople, G. Hall, attending a number of lectures of Dirac (in the Mathematics Department), while being in the company of D. Buckingham (from Australia) and J. N. Murrell, among other students of Theoretical Chemistry at that time who later emerged as early researchers in Theoretical Chemistry in England.

My first days in Cambridge were hectic, because I was "sent" to work under Professor Norrish who was involved in fast reaction photochemistry – a field in which I was totally lost. Within a week of desperation I was advised by someone (maybe David Buckingham, as we belonged to the same Corpus Christi College and lived in the same set of houses assigned to graduate students) to transfer to Sheppard, and work on molecular spectroscopy. Sheppard was willing to "take" me if Professor Norrish agreed. Structural chemistry and vibrational spectroscopy are definitely closer to physics then fast chemical reactions and a better field for a "transition" from physics to chemistry. Professor Norrish gracefully "released" me and thus I was on my road of exploring molecular structure – which I travel even today, over 50 years later.

Fascination with Graph Theory

My first paper that belongs to Chemical Graph Theory was published in the *Journal of Chemical Physics* [22]. I have written it while at Harvard University in 1973/74. I soon found out that the paper was well received. I have reproduced in the Appendix 2 two paragraphs from article "Toward chemical topology," written for the section "News and Views" by *Nature*'s molecular sciences correspondent, in which this first graph theoretical paper of mine is described [23]. In that paper I have outlined two algorithms for arriving at the canonical labels for vertices in molecular graphs, for which the adjacency matrix, when its rows are read from the left to the right and from the top to the bottom as a single binary code gives the smallest possible number. One of the two

algorithms was deficient, in that it could lead to local minimum, which warranted further clarifications [24-26].

In 1974/75, while at Tufts University, I published the two papers [10, 11] that opened two important areas of Chemical Graph Theory. These two papers have had a distinction of being widely known among many scientists involved in structure-property activity studies on one hand [10], and theoretical organic chemists interested in aromaticity on the other hand [11]. What has not been widely unknown is that these two papers may well be among the least "expensive" research papers. At that time I was unpaid, awaiting possible offers for a job or visitation. Due to unforeseen health problems in the family around that time, we decided to leave Boston and go to Iowa. Though personally I considered the paper on "conjugated circuits" [11] a greater result, the interest in the paper on "molecular branching" [10], with over 1400 citations, appears to be at least about three times more "popular." I am afraid, I cannot take a full credit for the "popularity" of this work – which owes its visibility mostly due to an immediate interest in it (even before the paper was published) by Kier and Hall. As it is widely known, already in 1976 Kier and Hall published their first book on the use of molecular connectivity indices [27], and continued for years to expand the use of the connectivity indices in QSAR (Quantitative Structure-Activity Relationship). In 1986 Kier and Hall have written their second book on application of connectivity indices in structure-activity studies [28], and followed with their third book on the closely related topic of Atomic Electrotopological State indices [29]. Moreover, on the occasion of the 25th anniversary of the "Randić (branching) index," or the connectivity index, L. H. Hall and L. B. Kier have organized within the Division of Computers in Chemistry a Symposium: Molecular Connectivity – The First Quarter Century at the 220th Meeting of the American Chemical Society in Washington, D. C. (August 20-24, 2000). Proceedings of this two-day Symposium were published in *Journal of Molecular Graphics and Modelling* in 2001, which also included my article "The connectivity index 25 years after" [30] in which I reviewed the developments following the introduction of the connectivity indices as molecular descriptors in multiple linear regression analysis for structure-property-activity studies.

So the credit for "popularizing" the connectivity index goes without doubt to Kier and Hall, who immediately realized the merits of the connectivity index. Before I give more details on the very early stages of this research let me comment on some parts of the history of the connectivity index, which I overlooked to mention at the symposium on the 25th anniversary of the connectivity index.

Let me add here that 25th anniversary of the connectivity index has been noticed also by others. I. Gutman, O. Araujo and J. Rada have written three papers [31-33]: "An identity for Randić's connectivity index and its application," "Justifying Randić's definition of the Randić index," and "Randić index of benzenoid systems and phenylenes," which are "dedicated to Professor Milan Randić on the occasion of the 25th anniversary of the discovery of the connectivity index." There have been many other "gentleman and scientists" who have honored me by dedicating their papers to me and let me here mention only here only the "early birds" of this class: 25 years ago Sheriff El-Basil dedicated three of his papers on "Novel graph-theoretical approach to estimating

the relative importance of individual Kekulé valence structures" to me [34-36] and 20 years ago Denis H. Rouvray dedicated to me a paper: "The prediction of biological activity using molecular connectivity indices" [37].

The Connectivity Index

Kier and Hall learned of the connectivity index when I was invited to give a seminar at the Massachusetts Pharmacy School on invitation from Professor L. B. Kier. Kier and I had met a couple of weeks earlier in Buffalo, New York, where I was visiting for a year the Chemistry Department at SUNY at Buffalo (on invitation of theoretical chemist Professor J. W. McIver) and where I met in the Department of Biophysics Professor Robert Rein, with whom I would meet weekly. I may add here that Professor J. W. McIver, though younger than me, was a well accomplished theoretical chemist. His paper [38]: "*Structure of transition states in organic reactions. General theory and an application to the cyclobutene-butadiene isomerization using a semiempirical molecular orbital method*" published in 1972, is listed among "The 125 Most-Cited JACS Publications" [39] (during the 125 years of existence of JACS (*Journal of American Chemical Society).*

Rein was originally from former Yugoslavia, of Hungarian and Jewish origin, coming form Vojvodina, a part of Austro-Hungary which after WWI was allotted to Yugoslavia. He was fortunate to escape the Nazi terror by hiding and merging with other population (his sister was married and lived in Belgrade, a fact which helped his survival). He left Yugoslavia in 1948 for Israel, when for the first time Communist Yugoslavia let Jewish people to emigrate (non-Jewish people could not leave the country). From Israel he soon immigrated to USA and was faculty at the SUNY at Buffalo, NY. Professor Rein had a Ph. D student from Israel and needed two "outside" examiners for the Ph. D. thesis of this student and asked L. B. Kier and me to join the "process." During the "coffee break" immediately after Ph. D. thesis was defended, hearing that he came from Boston, I told Professor Kier that every other week I spend a few days in Boston. At that time my family lived in Boston, where my wife was Professor at the Tufts University Medical School in Boston. Upon hearing this, Professor Kier promised to invite me to give a seminar at his Pharmacy School of Boston.

My seminar at the Pharmacy School of Boston was on the "molecular branching index." In the audience, besides Lemont Kier, was also Lowell Hall, who was spending his sabbatical leave (from Eastern Nazarene College in the Boston area) working with L. B. Kier. There was a lively discussion and my willingness to continue to discuss the topic was taken up. I was invited again to visit Kier, Hall, and Dr. Murray (from the Medical School of the University of Nebraska in Omaha, Nebraska, who was a visitor in Kier's laboratory at the time) at the Pharmacy School of Boston. These two visits resulted in two publications: *Molecular Connectivity. I. Relationship to non-specific local anesthesia* [40], which is the first publication on use of the connectivity index in QSAR; and *Molecular connectivity V. Connectivity series concept applied to density* [41], in which the concept of the "higher order" connectivity indices was introduced.

Let me take this opportunity to clarify an occasional confusion between "Randic indices" and "Kier indices" of different order – a terminology which is for example embedded in the widely used program CODESSA of Katritzky, Lobanov and Karelson [42]. The initial important contribution of Kier and Hall was, among other, to recognize the merit of the branching index as potential index for QSAR. Let us be reminded of a quote of E. B. Wilson, from his "*Introduction to Scientific Research*" [17]:

"*The most rewarding work is usually to explore a hitherto untouched field. These are not easy to find today. However, every once in a while, some new theory or new experimental method or apparatus makes it possible to enter a new domain. Sometimes it is obvious to all that this opportunity has arisen, but in other cases recognition of the opportunity requires more imagination*."

Kier and Hall clearly had the imagination to recognize the novelty of this "hitherto hardly touched field," which remained to be a misunderstood field by too many for too long a time. All this despite the Pleiades of outstanding scientists and contributors to Chemical Graph Theory, people like: **A. T. Balaban**, **E. Estrada**, **I. Gutman**, **H. Hosoya**, **D. J. Klein**, **N. Trinajstić**, and others. Pleiades, what need not be necessarily widely known, are in Greek mythology the seven daughters of Atlas and Pleione, who were pursued by Orion and set by Zeus among the stars to escape. In astronomy Pleiades are a loose cluster of hundreds of stars in the constellation of Taurus, six or seven of which are blue-white giants clearly visible to ordinary sight, hence the above list of pioneers of Chemical Graph Theory is limited to seven, six visible to naked eye, as is with Pleiades in the sky, the seventh "invisible" one for readers to discover.

Soon after the first papers on application of the connectivity indices, Kier and Hall proposed an important generalization, the concept of valence connectivity indices [43] that will differentiate carbon atoms from heteroatoms in a molecule. The stage was thus set for wide applications of these simple mathematical descriptors to structure-property and structure-activity studies and molecular drug design. I may also add that the name "connectivity index," to replace my original term "the branching index," originated with Kier, who also introduced the "zero" connectivity index. The label "connectivity index" is a much better label; in view that one can calculate the "branching index" also for "monocyclic ring structures" and linear "unbranched" molecular skeletons, which have no branching atoms.

25th Anniversary of Kekulé Benzene Formula

Before continuing with a few comments on construction of the connectivity indices, let me add a general comment on an unexpected, and rather rare, celebration of the 25th anniversary of scientific papers. I have not researched the history of Chemistry and there may be a few such similar celebrations, but I know of only one other chemistry paper, the 25th anniversary of which was honored and celebrated by a Symposium. That is the case with the August Kekulé's paper on the ring structure of benzene, on the 25th anniversary of which the German Chemical Society organized a Symposium in Berlin

[44]. This was the occasion on which Kekulé told the audience how, while riding a bus in London, he dreamed a snake biting its tail, which suggested a ring structure for benzene. Recently Wotiz and Rudolfsky [45] went so far to accuse Kekulé of scientific misconduct. According to Wotiz: "*The dream itself was very clever misconduct*." accusing Kekulé of even being "*a German super nationalist who invented the dream how he wouldn't have to cite previous work in the field by researchers from Austria, France, and Scotland*." However, August Kekulé was not German, he was Czech who lived and worked in Germany. So accusing Kekulé of being a German "super nationalist" is, to say the least, not plausible. This agrees with Rocke [46], who took to defend Kekulé and expose flaws in the arguments of Wotiz. All this has been described in more detail by S. Borman in an article "*19th-Century chemist Kekulé charged with scientific misconduct*" [47]. This whole episode raises a question: Isn't questioning someone's scientific integrity (based solely on speculations) itself a Scientific Misconduct?

May I add here that undocumented opinions of those who are attacking research in chemical graph theory and by implication "questioning someone's scientific integrity base solely on speculations" is just another illustration of abrasive Scientific Misconduct.

In contrast to the emergence of Chemical Graph Theory, Kekulé's celebrated work belongs to those scientific results that are immediately recognized by chemists as very significant – which add to their greatness. In other words one doesn't need much imagination to recognize the merits of the work of Kekulé. Apparently, in contrast, one does need imagination to recognized merits of the role that Graph Theory plays in chemistry. I may add that Kekulé was "recognized not only by chemists" because the mathematician Silvester, the first professor of mathematics at the Johns Hopkins University in Baltimore, MD and the founder of the *American Mathematical Journal*, in his papers "*Chemistry and Algebra*" [48] and "*On application of the new atomic theory to the graphical representation of the invariants and covariants of binary quantics*" [49] refers to the Kekulé benzene structure.

I expect that there may have been several other similar celebrations of 25th anniversary of significant scientific results but it appears that such events are rare. Does this not tell us something sinister or at best something selfish about science and scientists? Have you heard of celebration of the 25th anniversary of the work of Heitler and London [19]? Have you heard of celebration of the 25th anniversary of the work of S. F. Boys on *ab initio* calculations [50, 51]? Have you heard of the 25th anniversary of the work of Pariser, Parr and Pople on what is now known as PPP method [52-56]? Have you heard of the 25th anniversary of the work of Hauptman and Karle on solving the inverse problem of X-ray crystallography [57]? Have you heard of the 25th anniversary of the work of Woodward and Hoffmann about their rules that govern the formation of products during certain types of organic reactions [58]? And how about a celebration of the 25th anniversary of the work of Linus Pauling on the hybridization of atomic orbitals [21] or the celebration of the 25th anniversary of the work of Erich Hückel [59, 60] (another physicist who "invaded" chemistry)? We could go on and on. Just look at the list of 125 most cited papers published in *J. Am. Chem. Soc*. during its past 125 years of existence [39] to find many additional illustrations. Incidentally, I could add here that my

paper on the connectivity index is at the position 94 in that list, which also includes a paper by McIver with whom I was associated during my visit to Buffalo, NY.

What we are missing in science is a special brand of "outstanding gentlemen" among "outstanding scientists." Scientists are very busy people, and by definition, if one has too much time for other activities outside science, one may be working to some degree against "self." So do not expect that your work will be recognized for its inherent merits, it is more likely to be noticed for occasional mistakes. When R. Pariser and R. G. Parr were presenting their meritorious and exciting work on the PP(P) method many years ago at a meeting in Chicago, the only comment came from Professor Mulliken who said: "*This is interesting*" [61] (see Appendix 3). Often even less is said.

Scientists and Gentlemen

I have been fortunate to have met during my 50 years of "wandering over the Globe" a dozen "great scientists" and "great gentlemen" and would like to list these names and ask others to do similarly. I am listing these gentlemen and scientists in an approximate chronological order as I met them: **Charles A. Coulson** (Oxford University, Oxford, England); **Hermann Hartmann** (the founder and first editor of *Theoretica Chimica Acta*, Frankfurt, Germany); **Oskar E. Polansky** (the founder and the first editor of *MATCH*, Institut für Strahlenchemie, Mülheim, Germany); **Robert G. Parr** (then at the Johns Hopkins University, Baltimore, MD); **E. Bright Wilson** (Harvard University, Cambridge, MA); **Alexandru T. Balaban** (Bucharest Polytechnic University, Romania), **Per Olov Löwdin** (Director of Sanibel Island Conferences in Florida and Uppsala, Sweden); **Robert S. Hansen** (Director of Ames Laboratory, Ames, IA); **Roald Hoffmann** (Cornell University, Ithaca, NY), **Ivar Ugi** (Technische Universität München, Germany), **Alan Katritzky** (Florida State University, Gainesville, FL), and **Dudley Herschbach** (Harvard University, Cambridge, MA). I am sure others who traveled and had close contacts with more scientists could expand such listing – I have been blessed enough.

I have also met some unpleasant scientists – I guess that is unavoidable, because there are many. Apparently most of them tend to be unpleasant only anonymously, through their comments as referees. I am sure others have similar experience with abuse of the peer-review systems, which can take different forms, including occasional misbehavior of editors of journals. Very few scientists tend to speak of such unpleasant experiences publicly, but some do – and I am one to join the "club." I have written a paper "20th Century Clouds Over the Chemical Graph Theory" [62] (now in press), in which I listed a number of "orchestrated" and "non-orchestrated" attacks on Chemical Graph Theory. I am not to disclose the journal till the paper appears, in order to hinder possible "interventions" of those who may anticipate that I do not have much respect for their skepticism towards Chemical Graph Theory and their non-scientific meddling in things that they do not understand. The title of this article was inspired by the title of an article of Lord Kelvin [63] on the turn of the century: "19th Century Clouds Over the Dynamical Theory of Heat and Light," but while Lord Kelvin was addressing difficulties

of the Classical Physics, that have led to the then unknown Relativity of Albert Einstein and the Quantum Theory of Max Planck, the clouds of the 20th century were far from that fundamental issue of science (physics). In contrast, the "new" 20th century clouds try to cloud over what is known, in an effort by some to discredit legitimate science as being primitive, outdated, and irrelevant.

Mathematicians and the Connectivity Index

Before reviewing some other topics of Chemical Graph Theory let me point to considerable interest that mathematicians apparently expressed for the connectivity index, or better, its mathematical properties. The connectivity index has attracted attention even of the legendary Paul Erdös. I do not recall how this interest was stimulated, except that I am aware of Siemion Fajtlowicz, a mathematician form the University of Houston, and his work on "Graffiti" [64], in which several conjectures relating to the connectivity index were reported. "Graffiti" is a computer program developed by Fajtlowicz, which it generates conjectures. According to Fajtlowicz the basic idea of "Graffiti" is that generates various formulas involving graph invariants and evaluates them for a small set of representative graphs. If the formula is true it is considered to be a conjecture. If the conjecture is later shown to be false, the counterexample which disproves the conjecture is added to the library of "representative" graphs. In Appendix 4 there is a brief outline on "Graffiti" written by Barry A. Cipra for *Science* [65] in which two conjectures concerning the Randić index are mentioned. One of the two conjectures mentioned by B. A. Cipra remained at the time of writing that article (year 1989) unresolved – and may still be unresolved, but in view of the passed time those challenged by the conjecture are strongly advised to contact Siemion Fajtlowicz (math0@bayou.uh.edu) and inquire, before investing their time in such an adventure.

I have collected in Table 1 a number of papers by mathematicians considering some mathematical issues connected to the Randić index. The list is showing just as a "tip of an iceberg," a very small portion of such works, but at least it shows some aspects of the Randić index that were of interest to mathematicians. For more on this topic one should consult the recent book by X. Li and I. Gutman: "*Mathematical Aspects of Randić-type Molecular Structure Descriptors*" [66], as well as the review article by I. Gutman "*Chemical Graph Theory – The Mathematical Connection*" [67], where besides a section on the Randić (connectivity) index there are sections on other connections between Discrete Mathematics and Chemistry. Finally I may mention that the connectivity index has even appeared in a mathematical textbook. José Luis Carlavilla and Gabriel Fernández have written a lovely 140 page booklet *Aventuras topólogicas* [68] in which there is a short section "Graphos y Quimica," which mentions the connectivity index. In Appendix 5 I have reproduced half a page from this book describing the connectivity index – for those reading Spanish or willing to learn Spanish. This book also mentions the Wiener index [69], the first non-trivial graph theoretical molecular descriptor and the Balaban's J index [70], which one may say is the first highly

discriminating molecular descriptor. It shows degeneracy starting with alkane isomers with n=12 atoms, there being 551 trees with 12 vertices. Later several highly "powerful" (discriminating) graph theoretical indices have been reported. One of these is the Molecular ID number [71], which could discriminate all trees with 14 and less vertices but for n = 15, as demonstrated by Knop *et al*., [71], it fails among 7741 trees to discriminate between a pair of trees (show in Fig. 1). The "prime number-based Molecular ID" [73], which is based on connectivity index model with the prime-number weights, is even more "powerful" in discrimination of trees. The smallest pair of trees which show degeneracy occur, as again demonstrated by Szymanski et al., for n=20 [74], which is one pair of graphs (trees) in 823,065.

Table 1 Mathematical papers on the Randić index

Authors	Title	Journal
D. A. Morales & O. Araujo	The relationship between the connectivity index and the number and types of carbon atoms in a structure	*J. Mol. Struct*. (*Theochem*) 417 (1997) 241-246.
O. Araujo & J. A. de la Pena	Some bounds for the connectivity index of a chemical graph	*J. Chem. Inf. Comput. Sci*. 38 (1998) 827-831
O. Araujo & J. A. de la Pena	The connectivity index of a weighted graph	*Lin. Alg. Appl*. 283 (1998) 171-177.
B. Bollobás & P. Erdös	Graphs of extremal weights	*Ars Combinatoria* 50 (1998) 225-233.
I. Gutman, O. Miljković, G. Caporossi & P. Hansen	Alkanes with small and large Randić connectivity index	*Chem. Phys. Lett*. 306 (1999) 366-372.
I. Gutman, O. Araujo & J. Rada	An identity for Randić connectivity index and its application	*Acta Chim. Hung. – Models in Chemistry* 137 (2000) 653-658.
I. Gutman, O. Araujo & D. A. Morales	Estimating the connectvity index of saturated hydrocarbon	*Indian J. Chem*. 39 A (2000) 381-385.
I. Gutman, O. Araujo & D. A. Morales	Bounds for the Randić connectivity index	*J. Chem Inf. Comput. Sci.* 40 (2000) 593-598.
O. Araujo & J. Rada	Randić index and Lexicographic order	*J. Math. Chem*. 27 (2000) 201-211.
J. Rada, O. Araujo and I. Gutman,	Randić index of benzenoid systems and phenylenes	*Croat. Chem. Acta* 74 (2001) 225-235.
O. Araujo & J. Rada	Vertex and edge type relations of Randić index for chemical trees	*Ars Combinatoria* 62 (2002) 65-78.
J. Rada and O. Araujo	Higher order connectivity index of starlike trees	*Discrete Appl. Math*. 119 (2002) 287-295
I. Gutman, O. Araujo and J. Rada	Justifying Randić's definition of the Randić index	*Chem. Phys. Lett*.
J. Rada and O. Araujo	A recursive formula for the Randić index of a tree	*MATCH Commun. Math. Comput. Chem*. 49 (2003) 15-21
H. Liu, M. Lu & F. Tian	On the Randić index	*J. Math. Chem*. 38 (2005) 345-354

D. Repovš, V. Bobrovskij & E. Muranova	On the Randić connectivity index and physical properties of alkanes	
L.-Z. Zhang, M. Lu & F. Tian	Maximum Randić index on trees with k-pendent vertices	*J. Math. Chem.* 41 (2006) 161-171.
H. Hua & H. Deng	On unicycle graph with maximum and minimum zeroth-order general randić index	*J. Math. Chem.* 41 (2006) 173-181.

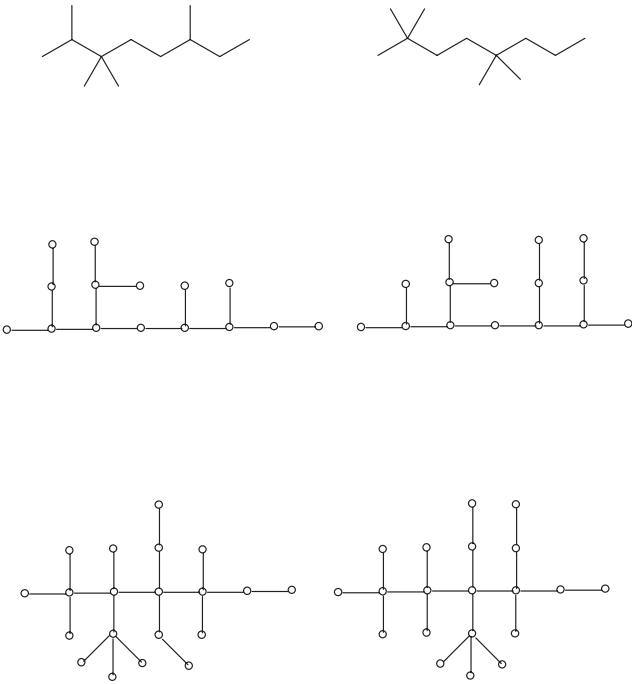


Fig. 1 The smallest trees having the same Balaban's J index (n=12), having the same molecular ID number (n=15) and having the same "prime number" ID (n=20)

Let us also mention that the Hosoya topological index Z [75] has interesting mathematical properties and has been featured in a book by Koshy "*Fibonacci and Lucas Numbers with Applications"* [76] and in the book by Cvetković, Doob and Sachs "*Spectra of Graphs*" [77].

"Primitive" Conjugated Circuits

The word "primitive" in fact has been used to characterize polycyclic conjugated systems based on the conjugated circuit method. Z. B. Maksić in one of his publications [78] refers to conjugated circuits as primitive, leaving no doubt from the context that here the adjective was used as derogatory label. When recently I confronted him, he was trying to say that it was not a derogatory comment. Maybe my English and his English are different, but according to the Funk and Wagnalls Dictionary [79] "primitive has only two meanings (besides anthropological and biological meaning that do not apply here): 1. Pertaining to the beginning or origin; earliest, primary; not derived. 2. Resembling the manners or style of early times; simple; crude. Both of these may apply to "conjugated circuits." The first, clearly is complimentary, and the "conjugated circuit method" deserves such characterization. The second, in reference to scientific methods is not complimentary and is offensive on verge of being vulgar, which the "conjugated circuit method" does not deserve. Which one to choose? I have neither seen nor heard Dr. Maksić to have said or written anything complimentary about Chemical Graph Theory and why should he here made an exception?

Anyone can make an error, or errors. Recall: "*Errare humanum est*." (of Saint Jerome c. 347 - c. 420). Perhaps Dr. Maksić made an error in judgment, being unfamiliar with the model and graph theory as its background. There is a difference, of course, between an error and a mistake. "It is a mistake not to correct an error" so let us wait and see if Dr. Maksić, when he referred to the conjugated circuit method as "primitive," has made an error or mistake. Meanwhile, those who are less familiar with the model of conjugated circuits and have no time to read the lengthy review "*Aromaticity of Polycyclic Conjugated Hydrocarbons*," [80], or look into the original publications [11-13] can browse through more recent accounts of this model and see how it is related to advanced quantum chemical computations. I have collected some 20 publications of Professor D. J. Klein (Texas A&M at Galveston) that span over 15 years in which Klein and coworkers have considered "primitive" conjugated circuit model [81-98]. Professor Klein got his Ph. D. degree with the late Professor F. A. Matsen, theoretical physicist and recognized authority on Quantum Theory. It suffices just to read the titles of the papers of Klein and coworkers in order to get an idea on the relevance of conjugated circuits in theoretical chemistry. They include titles such as: Conjugated circuit theory for graphite [83], Foundations of conjugated-circuits models [85], The conjugated-circuit model revisited [86], The conjugated-circuit model [87], Conjugated circuits computations for conjugated hydrocarbons [89], Many-body conjugated circuit computations [86], Aromaticity via Kekulé structures and conjugated circuits [93], Conjugated circuits computations on two-dimensional carbon networks [94], and Conjugated circuits for polymers [95]. Would Professor D. J. Klein and some dozen of his co-authors waste time (over 15 year period) on a "primitive" model if it does not deserve such attention?. Hence, the model does deserve attention of serious theoretical chemists. Whether those who think differently are unaware of such work or are not serious, is for them to find out.

Because there is such a volume of abuse against contributions coming from applications of Graph Theory to chemical problems, which I have experienced, I am currently writing another manuscript on abuses in science. It is entitled "*Adversaries in*

Search" [99], the title being inspired by an article of Professor R. G. Parr, today's leading authority in theoretical chemistry though in his early 80's. His article "*Companions in the Search"* [100], starts with a list of some 80 scientists with whom he has been associated. The list includes myself even though we have no joint publication. The article outlines Professor Parr's rich research experience over many years of activity. In contrast my article speaks of difficulties that I encountered in my scientific career, which prompted me to paraphrase the well known adage (of unknown origin [101]): "*Publish or Perish*" into "*Publish and Perish*" [102, 103].

Let me list a few publications by scientists who had the courage to publicly talk about their mistreatment by the "Establishment," about misuse of the peer- review system and the refereeing process in general, and such. The list includes the Nobel laureate in Medicine John C. Eccles [104], mathematicians D. V. Lindley [105] and R. T. Thompson [106], and chemist E. T. Strom [107]. I may add that the above are papers that I came across more-less "accidentally" and I am sure there are many additional such contributions worth exploring and citing. I take this opportunity to encourage colleagues in science to do the same: to records abuses in science and make their misgiving public – because that appears to be the only way to reduce some of the misconduct in science, which is currently tolerated by the Establishment.

Unwarranted Confrontations

Scientists are, just like ordinary people, of different types: some are kind and helpful, genuine "gentlemen (and ladies of course) in science." I have already listed a short list of these that I was fortunate to have met. Some may be stubborn and perhaps quarrelsome - a category to which, perhaps, I belong. Some are disagreeable, abrasive, arrogant and obnoxious, to various degrees, in short: unpleasant. Such people are making unwarranted comments, meddle in things that are not their concern (often in matters that they think that they understand but in reality do not), they promote hostility, raise problems where there are none, or interfere in affairs that are not their business. I had my share of meeting such types, which of course one avoids whenever possible. I will mention here two such incidents: **Z. B. Maksić** (from Institute Rudjer Bošković, Zagreb) and **P. Coppens** (from Chemistry Department of State University of New York at Buffalo), the two being of different kinds.

Last summer I accidentally met Z. B. Maksić during a coffee break at an NMR Conference in Ljubljana, Slovenia on the occasion of their National Institute of Chemistry acquiring an 800 MHz NMR machine. I shook hands with his wife (an experimental chemist) but when extending my hand to him, he refused to shake hands. From a brief exchange of views apparently he is upset that I was, according to him, circulating a "pamphlet" (his characterization of my letter, which mentions him, sent to a dozen people). Well, if he knew of such a "pamphlet" why he did not ask me to send him the letter? But he did not. Does one need a permission of a third party when writing letters to friends and acquaintances? In the letter I was essentially complaining how among chemists in Croatia (Zagreb in particular) there is a lack of appreciation for

Chemical Graph Theory, despite that Nenad Trinajstić with his work in Chemical Graph Theory has made Zagreb visible on the "Chemistry" map of Europe. The letter was, of course, implying a continual "messing" of Z. B. Maksić with Chemical Graph Theory, and his efforts to trash this branch of Theoretical Chemistry.

Let me continue with comments on a brief verbal "exchange" with Maksić who, while I was maintaining the significance of Chemical Graph Theory (implying of course the important role that was contributed by the work of Nenad Trinajstić and myself), obviously had contrary opinion. When I mentioned how our work is cited his comment was: "*You cite Trinajstić and he cites you*." That is true but can this explain over 11,000 citations that I have? In Fig. 2 are shown my citations for each year since my first paper was published in 1959 years and number of papers published in each year. The publications of the last seven years were made after my formal retirement form the Drake University. These bar-type figures are reproduced as they appeared in "Web of Science," which also gives as the total number of my publications: 394; the total number of citations: 11,088; the average citation per publication: 28.14 and the h-index: 51. When I mentioned to Maksić that my paper on the connectivity index has 1400 citations (the number has increased since last summer to over 1450) he congratulated me (what else could he say?). As one can see from Fig. 2 after year 2000 on average I have about 600 citations per year. I am sure this number includes a number of citations from Nenad Trinajstić, but how can Trinajstić produce 600 citations per year to my citation List? And I can mention that the book of Nenad Trinajstić "*Chemical Graph Theory*," has as of today more than 1500 citations. If I would be responsible for the citations of the book of Trinajstić's "*Chemical Graph Theory*" I would have to cite his book over five times in each of my 300 papers on application of graph theory in chemistry. I have not counted how many times I cited his book, but I would be surprised if it is even close to 50. So Maksić has to account for the difference of 1450 citations of this, the only single-author, monograph on chemical graph theory. All this only illustrates that critics of Chemical Graph Theory, like Maksić, do not even bother to collects facts and do their homework – before engaging themselves in trying to disparage their perceived opponents!

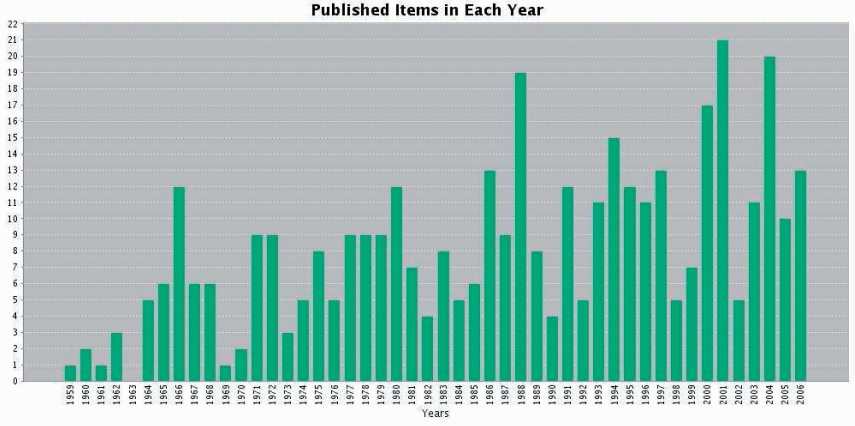
When I mentioned that Professor Parr, and he well knows that Professor Parr is the leading theoretical chemist in USA and beyond, in a recent letter (Appendix 3) gave a high opinion on Chemical Graph Theory, his response was: "*Ah, Parr is 80 years old*." This demonstrates his intention to dismiss the view of Professor Parr on Chemical Graph Theory. I was stunned. If this is not despicable, what is? As if people in their eighties are necessarily of limited mental abilities. All this insinuation just because Maksić did not like what Parr has said about Chemical Graph Theory – so Professor Parr has to be discredited! If one doesn't like facts, as is the case with Maksić here, the best tactics appear to claim that facts are fiction. This reminds me of an ostrich, which in danger, buries its head in sand – no to see the facts! But Maksić is not in danger, it is my reputation in Croatia as being a *bona fide* accomplished theoretical chemist that has been endangered, and for a considerable period of time, some 30 years. Be it as it may, as we will see later, Professor Parr expressed favorable views on Chemical Graph Theory already 15 years ago – at the age that he was younger than the time when Maksić uttered his thoughtless and tasteless remark on Professor Parr. There is no need to argue about

the mental agility of Professor Parr but there is no better way to nullify the fantasy of Maksić on "unreliability" of good views that professor Parr expressed about Chemical Graph Theory than to cite the view on Graph Theory that Professor Parr expressed over 15 years (*vide infra).*

In Appendix 6 is copy of a letter of Michael R. Ferrari, President of Drake University, to the Honorable Terry E. Branstad, Governor of Iowa, in which he nominated me for Iowa Governor's Science Medal. The letter includes two brief quotes concerning Graph Theory, one by Professor Parr and another one by Roald Hoffmann, from which follows that these outstanding scientists had favorable views on Chemical Graph Theory. Part of the nomination letter has been reproduced in "On Campus" – Drake University Newspaper (April 14, 1989) in which is added: "*Randic was the subject of an article in Scientific American, a popular science journal, in September 1986. He has written more than 200 articles for scientific and technical journals. In addition, he is one of the founding editors of the Journal of Mathematical Chemistry and is the first president of the International Society for Mathematical Chemistry*." I have no idea who has written the above, but may up-date the information by saying that "He has written more than 400 articles for scientific journals" and that "in addition, he is one of founder of the International Academy of Mathematical Chemistry, and is its current Vice-President." The title of the article in *Scientific American* mentioned above was "Predicting Chemistry from Topology" and was written by Dennis H. Rouvray [108]. Other outstanding chemists who supported my nomination for Governor's Science Medal were E. Bright Wilson, Per-Olov Löwdin and Kurt Mislow. Could so many people be wrong and fool Governor Branstad, who accepted their nomination?

And what about qualifications of Dr. Z. B. Maksić to raise such questions? Should those who don't know what Graph Theory is and don't know that they don't know, be tolerated to challenge the inclusion of the Chemical Graph Theory in Theoretical Chemistry? Chemical Graph Theory is legitimate part of Theoretical Chemistry, neither above nor below, but aside, as other fields of theoretical chemistry. Such are quantum chemistry (which besides MO also includes VB computations and DFT), statistical mechanics, molecular spectroscopy, chemoinformatics, bioinformatics and others. Perhaps Fig. 3 (which I am reproducing from my review article on aromaticity of polycyclic conjugated systems [80]), which depicts the mutual relationship between MO theory, the VB theory and GT (graph theory) can clarify situation for those willing to listen.

Is there a learning message for others in the above described incident? Yes, there is a message for many quantum chemists, most of which (including Dr. Z. B. Maksić)



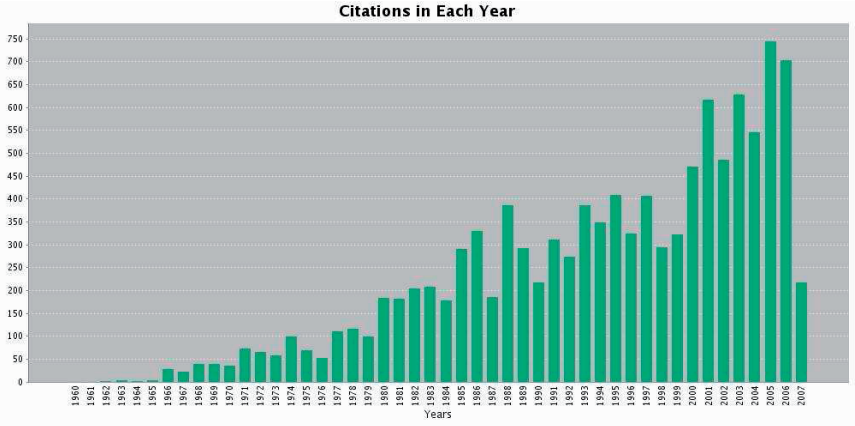


Fig. 2 Papers of M. Randić and citations during the past 20 years

should be referred more properly to as "MO chemists" (MO = Molecular Orbitals). The message is in a form of questions: How many MO chemists are aware of *ab-initi*o VB calculations? How many of MO chemists know what else is there in Theoretical Chemistry outside Gaussian MO computations? Would have the Density Functional Theory (DFT) of Kohn, Parr, Mezey, and others had difficulties had it not been that the quantum chemical education of many theoretical chemists limited to MO calculations? It took the Nobel Prize given to Kohn [109, 110] for acceptance of the density functional theory (DFT) by MO-dominated Quantum Chemistry Establishment! It is time for most MO chemists to get out form their cocoon and as a first step I would suggest they became more familiar with VB methods, including more recent *ab-initio* VB computations on

benzenoid hydrocarbons [111, 112], then became more familiar with DFT, and eventually became more familiar with CGT (Chemical Graph Theory).

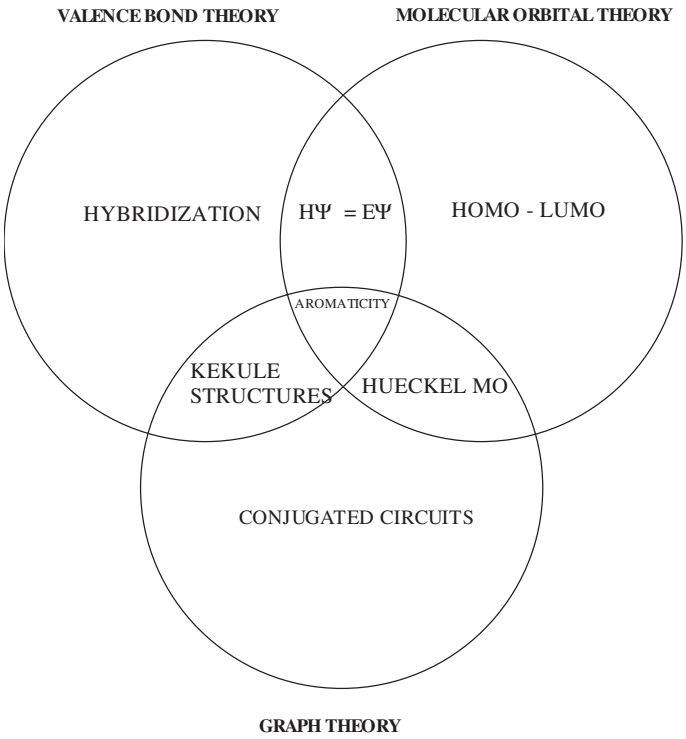


Fig. 3 Overlap of Valence Bond Theory, Molecular Orbital Theory and Graph Theory

Science is not about anonymity. These "invisible enemies" prefer to remain anonymous, but scientific journals, including in particular the *Journal of Chemical Physics*, are not, and their editors are not anonymous. Good editors will be remembered, bad ones will be forgotten. "Editors come and go . . ." as Professor Parr mentioned in his letter. Some may not take the view on Graph Theory of Professor Parr seriously, as is Maksić dismissing Professor Parr's complimentary letter about Chemical Graph Theory.

But then whose opinions would they trust if not of the "masters" of theoretical chemistry, the people mentioned, who supported my nomination for Iowa Science Medal, for research that was exclusively only about application o graph theory to chemistry? May I add, for those who do not know well Professor Per Olov Löwdin, that he signed his letter with, among other titles, "Secretary of Nobel Committee for Physics 1970-1980," and we already mention that physicists know of Graph Theory.

The unpleasant incident that I had at SUNY Buffalo is a confrontation with Professor of Physical Chemistry, a crystallographer, Philip Coppens, which is of a totally different nature, and is a relatively short story. I spent the academic year 1974/75 at the Chemistry Department of SUNY at Buffalo after prior meeting two younger of their chemistry faculties: Professors James W. McIver and Harry F. King, both accomplished theoretical chemists, both pleasant persons. I may add that more recently I found that a publication of J. W. McIver from 1972 is listed among the 125 most cited publication in *Journal of American Chemical Society* published during its 125 years of existence. About till half way through my stay at the department Professor Coppens, a crystallographer, confronted me with an unpleasant comment that the department pays me and I doing nothing for the department (i.e., I am not giving lectures). I replied: "*I am not paid to give lectures."* To this he said something like he has to give lectures. I said: "*You are paid to give lectures, and I am not*." His salary, I guess, was at least three times more than my stipend (not mentioning other benefits, like pension contributions and health insurance contributions). Soon after the Chair of the Department (whose name I do not recall) ask me to come to his office, to which I obliged. I told the Chairman that when arrangements were made about my visit earlier in the summer of 1974 I talked with James W. McIver and Harry F. King about my visit, and Professor Coppens was not involved in these conversations at all. I have added that I have no problem to leave tomorrow if there is misunderstanding about my visit. To this the Chairman responded that there was no need for me to leave and that I stay and continue my visit.

I had neither additional confrontation with Coppens nor do I recall even seeing him in the Department till some times later during a visit of Professor F. A. Cotton, from Texas A&M at College Station, TX to the Chemistry Department of the SUNY at Buffalo. The Chemistry Department has invited Professor Cotton for a 3-day visit trying to entice him to join their faculty as an Einstein Professor of Chemistry (a title for distinguished professors throughout the SUNY system). At the evening of his arrival there was a "welcome party" for Cotton at the department to which everybody was invited. While drinking beer I had an opportunity of a five-minute conversation with Al Cotton. I mentioned that we met once in Basel, Switzerland during a break in the conference, attended by some 4000 chemists. We met in fact during the conference lunch break when 4000 people converged on a roasted bull placed in the middle of a huge garden to be served as a meal. He did not recall and asked me what I am scientifically doing. I said that I am a theoretical chemist, to which Cotton made a comment "*Ah, another quantum chemist*," and from his gesture it was obvious that he has not been impressed with many of them. I replayed: "*No, I am not doing quantum chemistry, I am in graph theory."* He immediately replied: "*This is very interesting – we have to talk."* Then he took his 3-day schedule out of his pocket, looked at his very "busy" schedule

and told me: "*Milan, be in your office tomorrow at 10:00 AM and we will talk. I am scheduled from 10:00 – 11:00 to meet students of Coppens, and I will first come to talk to you and then I will visit students of Coppens*."

Next day I was in my office and Al Cotton appeared exactly at 10:00 to learn more about my research interests. We were sitting across each other at my desk, with me looking directly to the open door of the office (It is customary in USA universities to have doors open if one is in office). I do not recall details of the conversation but among other Cotton was interested to hear if I would be willing to come to Texas A&M as a faculty. In fact he even suggested dates for my first visit. Some ten minutes after 10:00 a student of Coppens, standing at the door, interrupted our conversation to remind Cotton that at this time he has appointments with them. Cotton turned to the student and told him that he will come in a short time. Five minutes later I see Professor Coppens at my door, interrupting and telling Al Cotton that his students are waiting on him. On this, Cotton turned toward Coppens and told him: "*Let them wait. This man is more important to me than your students. I will come*." I said nothing but was glad that it was clear that it was not me who was keeping Cotton in my office but it was Cotton. Soon after Cotton apologized that he has now to go and left. I have met Cotton again at my scheduled visit to Texas A&M at College Station. It turned out that there was no "vacancy" for theoretical chemists in the department of chemistry and that the influence and attempt of Al Cotton to secure such a position apparently did not materialize. Nevertheless, for me it was somewhat amusing to see that while the Department of Chemistry of SUNY Buffalo was trying to hire Professor Cotton, at the same time Cotton was trying to hire me to join him at Texas A&M.

The incident between Professor Cotton and Professor Coppens is instructive for all of us: When you have as a visitor, an outstanding scientist, a *dignitary*, treat him/her with *dignity*!

On the Design of the Connectivity Index

Let me return back to the connectivity index and continue this reminiscence on the "old times," by emphasizing an important aspect of the connectivity index which is not often mentioned. I have heard comments as how "lucky" I was to "guess" the right "combinations" and construct such a still very useful molecular descriptor. Well, luck, guessing and combining things are all well known ingredients for success in science, but I have to admit that in this case the *luck* was to meet Robert Rein in Buffalo, who catalyzed a meeting with Monty Kier. There has been also some *guessing* (testing of possible forms for various bond contributions as a solution to the constructed inequalities, *vide infra*), but this can also be viewed as a rational approach to a design of a *successful* molecular descriptor for studies of structure-property relationships. Thus, while many may have been surprised how well the "branching index" works, in numerous structure-property studies, I have not been surprised at all. I would have been surprised if it would not work so well, at least for alkanes, for which it was initially constructed! Why? Well, first I have *ordered* isomers of hexane and heptane according to their boiling points. I

expressed their bonding types in the form of bond additive terms, which are characterized by the graph theoretical "valence" of carbon atoms forming bonds. In chemical terms that meant to differentiate the role of primary, secondary, tertiary and quaternary carbon atoms.

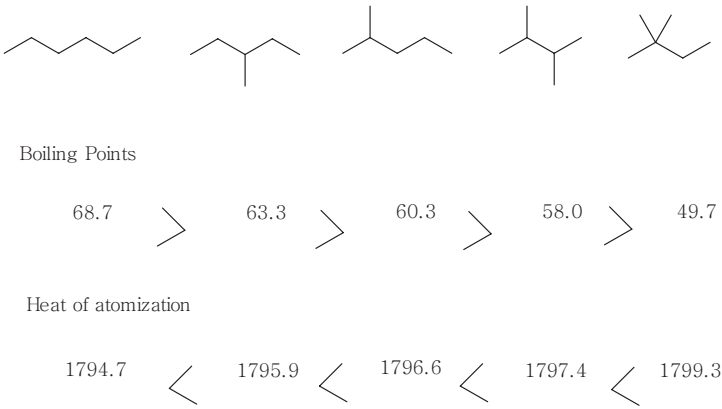
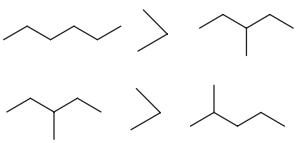


Fig. 4 The five isomers of n-hexane, their boiling points and heats of atomization

Consider the five isomers of hexane (Fig. 4), which when ordered with respect to their boiling points:

$$\text{n-hexane} > \text{3-methyl-}C_5 > \text{2-methyl-}C_5 > \text{2,3-dimethyl-}C_4 > \text{2,2-dimethyl-}C_4$$

lead to the following four inequalities:



$$2(1,2) + 3(2,2) > 2\,(1,2) + (1,3) + 2(2,3)$$

$$2(1,2) + (1,3) + 2(2,3) > (1,2) + 2(1,3) + (2,2) + (2,3)$$

$$(1,2) + 2(1,3) + (2,2) + (2,3) > 4(1,3) + (3,3)$$

$$4(1,3) + (3,3) > (1,2) + 3(1,4)+(2,4)$$

Here the bond types (m, n) where m, n = 1 through 4, indicate the bond between carbon atoms having m and n nearest neighbors. Observe that when one orders hexane isomers relative to their boiling points 3-methylpentane dominates 2-methylpentane. Similarly in the case of heptane isomers 3-methylhexane dominates 2-methylhexane, and so on. This, however, is not often the case with many topological indices, including the Wiener index [69]. The Hosoya Z index [75] is one of few exceptions.

By trial and error I found as a simple solution (m, n) = $1/\sqrt{(m \times n)}$ that satisfies all the inequalities that one can write for hexane and heptane isomers. Among other possibilities I tested also (m, n) = $1/(m \times n)$, which defines one of the Zagreb indices [113-115]. I discarded it, because it does not satisfy the inequalities considered. Indices that do not satisfy the above inequalities when combined in an MRA (multiple regression analysis), will continue to predict incorrectly the relative magnitudes for the corresponding physico-chemical properties that satisfy the ordering of isomers.

I should mention here the variable connectivity index. It has been around for over 15 years [116-135], but has been receiving limited, or at best, a modest attention (for a review and recent applications see [136, 137]). The variable connectivity index can be constructed from the adjacency matrix of a graph by replacing the zeros on the main diagonal with variables x, y, etc. The variables x, y, etc., discriminate atoms of different kind (such as carbon, oxygen [117], nitrogen [118], sulfur [122], chlorine [116]), or the same atom in different local environments [129]. In Table 2 is illustrated a construction of the variable connectivity index for 2-methy-1-pentanol. The row sums of the adjacency matrix, which are now augmented with the variable x or y, give the "revised" degrees for each vertex of molecular graph. The row sums can be used for construction of the connectivity index in an analogous approach of Balaban for construction of his J index [70], which is derived from the row sums of the distance matrix. Balaban J index was the first "highly" discriminating molecular descriptor. It is interesting to add that by varying x and y for x, $y \geq 0$ the relative order of the three derivatives n-alkane, 3-methyl and 2-methyl derivatives remains the same, but for some values x, $y < 0$ this may change to: n-alkane, 2-methyl and 3-methyl derivatives.

There is no doubt the novel methodology in regression analysis associated with the variable connectivity index, and variable topological indices in general, will be better appreciated in the future. This approach offers a search for the best descriptors of a given type by varying the relative weights of terms that constitute the molecular descriptor considered (here "the best" is used in the sense of producing regressions with the smallest standard error). This "variability" should be distinguished from another type of optimization of graph descriptors in which the *functional form* that defines an index is varied. Such variations have been explored by Randić, Hansen and Jurs almost 20 years ago [138]. These authors have showed that by varying the exponent in the Wiener index,

the Hosoya index and the connectivity index one can “straighten” a curved correlation into a linear one. Trinajstić and collaborators [139], and collaborators without Trinajstić [140] reported more recently on varying the exponent of the Wiener index and Zagreb indices, respectively.

Table 2 Augmented adjacency matrix for 2-methy-1-pentanol

	1	2	3	4	5	6	7	Row sum
1	x	1	0	0	0	0	1	2 + x
2	1	x	1	0	0	1	0	3 + x
3	0	1	x	1	0	0	0	2 + x
4	0	0	1	x	1	0	0	2 + x
5	0	0	0	1	x	0	0	1 + x
6	0	1	0	0	0	x	0	1 + x
7	1	0	0	0	0	0	y	1 + y

Bond contributions:

1 – 2 $1/\sqrt{(2 + x)(3 + x)}$

1 – 7 $1/\sqrt{(2 + x)(1 + y)}$

2 – 3 $1/\sqrt{(3 + x)(2 + x)}$

2 – 6 $1/\sqrt{(3 + x)(1 + x)}$

3 – 4 $1/\sqrt{(2 + x)(2 + x)} = 1/(2 + x)$

4 – 5 $1/\sqrt{(2 + x)(1 + x)}$

The variable connectivity index $\chi(x, y)$ is:

$$2/\sqrt{(2 + x)(3 + x)} + 1/\sqrt{(1 + x)(3 + x)} + 1/(2 + x) + 1/\sqrt{(1 + x)(2 + x)} + 1/\sqrt{(1 + x)(3 + x)}$$

There appears to be some confusion about variable molecular descriptors when it comes to comparisons of their performance with the performance of the standard (non-variable) descriptors. Randić and Pompe have shown on a regression of the boiling points

of 100 smaller alcohols [128] that a single variable connectivity index gave a better regression than the use of four descriptors (out of pool of 56 descriptors) obtained from CODESSA. In this particular application two variables were used, one for carbon and one for oxygen, and the optimal weights found were: $x = 0.10$ for carbon and $y = -0.92$ for oxygen. Such outstanding performance of the variable connectivity index may have prompted some to speculate that they involve some "hidden" descriptors, which contribute to their success, and that a single variable connectivity index may not be "single" [141]. If one is interested in "predictive" power of descriptors it does not matter if one has a "single" descriptor, or perhaps "married" descriptors (if this would be a suitable analogy to refer to the ambiguous association of variable connectivity index having single or more variables, and even including cases of polygamy?). However, from a pure mathematical point of view it does matter. Nevertheless, I claim that "hidden variables" are fiction and that the *number of coefficients* in the regression equation determines *how many descriptors* are used.

Another matter is how one selects descriptors. CODESSA, for example, is a software that can evaluate some 400 descriptors, and then using some statistical criteria selects about half a dozen best. While this will generate sets of useful combinations of descriptors, the process, nevertheless, may overlook successful combinations of simple descriptors which individually do not show meaningful correlation, but together span the structure-property space [142]. In the case of variable connectivity index in order to find optimal weights typically one calculates some 40-50 combinations of the variables x, y *during* the process of search (starting with $x = 0$, $y = 0$, which is the standard connectivity index). Hypothetically one could in advance select 20 values for x and 20 values for y and calculate a pool of 400 (augmented non-variable) connectivity indices, and then select the best, using an analogous procedure to CODESSA. Thus what is the difference between variable and non-variable indices? There is no difference, because once *selected,* the variable index becomes non-variable! The difference is in how one *arrives* at the best descriptor or a small subset of best descriptors from 400 alternatives, the choice is (1) to use pool of 400 (or subset of these) descriptors; or (2) to *construct* them by changing variables along the process of the search for best descriptors.

Hostility toward Chemical Graph Theory

Let us recall the statements of E. B. Wilson concerning scientific research [17]:

"*The most rewarding work is usually to explore a hitherto untouched field . . .*"

"*. . . it is almost always worthwhile to explore a region which is really new. Unexpected results can generally be relied upon under these circumstances . . .* "

"*No one can be so obstructive of progress as the "expert" who has worked all his life on a single subject.*"

Perhaps the above expressions summarize the basis for unwarranted considerable hostility towards the connectivity indices (and other topological indices in general) in

some circles of physical and medicinal chemistry. The above clearly indicates a possibility of increased productivity for those involved in new fields. But "new" approaches may endanger the interest of those who do not welcome novelty, circles of scientists who may be trying to protect their past "investments" and try to reserve certain areas of science as their "turf." New approaches may require new understanding of what others do in science, which may involve besides hard labor "more imagination" – and this commodity is not necessarily part of everyone's ability. For example, when the second book of Kier and Hall: "*Molecular Connectivity in Structure-Activity Analysis*," which appeared ten years after their first book, a book review of S. H. Unger characterized it as "numerology" [143]. We quote here part of the message or "wisdom" of Unger, addressed to his colleagues and those equally unfamiliar with Discrete Mathematics and its potential in Chemistry:

"*Molecular connectivity is certainly not a fundamental variable of nature and does not code for 3-D properties; it is a highly concocted bit of numerology and is often applied with total lack of rationale. The vast number of possible indices, their squares, cubes, reciprocal, cross-products, etcetera, can only leave one with the feeling that there is a lot of fiddling going on, either intentional or out of complete naiveté.*

One wonders to what degree the "blindness" of S. H. Unger and such critics towards the connectivity indices may reflect conscious or unconscious concerns how to preserve the monopoly in an applied area of medicinal and physical chemistry at the time of the emergence of mathematical molecular descriptors. Most of the QSAR (Quantitative Structure-Activity Relationship) was dominated with approaches in which molecular properties are used as molecular descriptors. Hence, correctly the area should be refereed to as QPAR (Quantitative Property-Activity Relationship). As with time the use of the connectivity indices (and other topological indices) in the structure-property-activity studies grew, another line of direction of those trying to stop the "intruders" into QSAR (that is the connectivity indices and other graph theoretical molecular descriptors) became evident. According to J. T. Edwards, [144] the connectivity indices may be OK for use in structure-property relationships (that is limited to correlations of various physico-chemical properties of molecules), but they are inadequate QSAR. Taylor [145], as quoted in the same book, goes even further by stating: ". . . *there has been some tendency, therefore, to use molecular connectivity in context for which it is unsuitable . . .*" and then continues to express his opinion by stating that he "*regards molecular connectivity as an irrelevance which has had unfortunate effect of diverting attention from the real work that needs doing.*" Time has shown what is *irrelevant*: the view of Taylor and such on the connectivity index – except that the news apparently has not reached the author of the book! It suffices to mention here but a single application of topological indices that will disqualify views of Taylor and such – the work of Lahana and coworkers [146] on the synthesis of a new immunosuppressive drug. These workers constructed a combinatorial library of decapeptides having over 280,000 virtual compounds based on a lead decapeptide. Then they used two dozen molecular descriptors, half of which were various topological indices, including also the connectivity index, and set for each descriptors selected a narrow "band" of allowed values. Because of interdependence of various descriptors they settled for a dozen

descriptors used to filter the combinatorial library and find structures that satisfy the constraints imposed. Appling the screening they ended with some two dozen virtual compounds which have been more closely examined by elaborate computations and five of which have been selected for synthesis. In this way at the end they found a decapeptide which has been approximately two orders of magnitude more potent than the initial lead compound. To arrive at a drug that is twice as potent as the starting drug would be hailed as an impressive success, but Lahana and coworkers synthesized and tested the compound and found it about 100 times more potent! So let us not waste time on Taylor and such – let them argue irrelevance of topological descriptors with Lahana and his coworkers.

We agree with the part of Taylor's comment that: ". . . *there has been some tendency . . . to use molecular connectivity in context for which it is unsuitable . . .*" and will offer a specific illustration. Recall that the connectivity index has been designed for characterization of bond-additive molecular properties. However, Dunn and coworkers [147] applied the connectivity index to try to describe differences between ortho, meta, and para substituted derivatives of benzene, and by failing to get satisfactory answer concluded that connectivity index failed – while in fact they failed in not listening to the advice of their colleague Taylor! Clearly the differences between ortho-meta-para substituted derivatives go beyond molecular bond additivity. For more on misunderstanding of topological indices one should consult a chapter "QSPR/QSAR by graph theoretical descriptors beyond frontiers" by Estrada and Molina in a book *QSPR/QSAR Studies by Molecular Descriptors* [148].

Such claims are absurd – and that it is reprinted in a QSAR monograph [149] twenty years after is even greater absurd. But just as this is not enough misrepresentation of use and usefulness of topological indices in QSAR continues. In year 2000 A. B. Richon and S. S. Young ended their 25 page article "An Introduction to QSAR Methodology" [150] with the following paragraph:

"*In general, topological approaches start with a very different graph theoretic representation of molecular structure in which atoms are represented by vertexes and bonds by edges. Numerical indexes for the structure are then defined which abstract information including atom descriptors (atom types, atomic weight, atomic number, ratio of valence electrons to core electrons, etc.) and sub-group descriptors. In addition, a series of indexes (the χ indexes) are developed which describe the molecule as a set of fragments of varying size and complexity. Regression analysis of equations which have chi indexes as parameters has been used to correlate chemical structure to physicochemical behavior in applications such as chromatographic retention times, molar refractivity, ionization potential and heats of atomization. While the application of topological indices has been widely reported in QSAR[47-49], the utility of these methods has been limited to predicting structure-property relationships for polymers and hydrocarbons*." (Underlined by MR)

Let me first mention that with this last statement the authors (A. B. Richon and S. S. Young) contradict themselves, because just half a dozen lines above this paragraph

they write: "*Because no single method works for all cases, many groups are examining alternative approaches to developing SAR equations including electronic based descriptors and topological indices*." Surely SAR (Structure-Activity Relationship) is not about "polymers and hydrocarbons." I have been familiar with two of the three references listed: a paper by Balaban on application of graph theory to chemistry [151], and a paper by Hall and Kier on the molecular connectivity chi indexes and kappa shape indexes in structure-property modeling [152]. Both articles are brief reviews, the first one on a very broad topic of Graph Theory in Chemistry and the second on very narrow topic of molecular shape descriptors – thus neither relating to SAR.

The article of Balaban appeared in a special issue introduced by the editor T. L. Isenhour as: "The Silver Anniversary Issue of the *Journal of Chemical Information and Computer Science*, is presented both as a review of the past 25 years of its subject and as predictor of the future." Authors have been selected and invited, each reviewing multitude of topics that this journal has been covering over the past 25 years. Among those invited we find articles by Herman Skolnik [153], the founder of the journal, Eugine Garfield on citation indexes [154], N. Lozac'h on organic nomenclature [155], Stephen R. Heller on Spectral Databases [156], Sun-ichi Sasaki on structure elucidation [157], William J. Wiswesser on development of chemical notations [158], T. L. Isenhour on robotics in laboratory [159], Peter C Jurs and collaborators on molecular structure-biological activity relationship [160], D. L. Massart and P. K. Hopke on chemometrics [161] Jacques-Emile Dubois and Yves Sobel on artificial intelligence in chemistry [162], and Alexandru T. Balaban on Graph Theory in Chemistry [151]. As we see this is a special "historic" issue of selected topics of applications of methods of Discrete mathematics to chemistry. Balaban was writing about Graph Theory in Chemistry, not in SAR. If A. B. Richon and S. S. Young wanted a reference on SAR why they did not cite the paper of Peter C. Jurs and collaborators on molecular structure-biological activity relationship [160]? In that paper Jurs et al., consider SAR of 122 anti-inflammatory steroids and 152 retinoid compounds and for both sets among selected descriptors are the connectivity indices. Does this sound like "*structure-property relationships for polymers and hydrocarbons*"? In fact, the title of the article in which the debut of the connectivity index occurred was: "Molecular connectivity. I. Relationship to non-specific local anesthesia". Does this sound like "*structure-property relationships for polymers and hydrocarbons*"? Obviously the concluding remark of the article of Richon and Young is simply – just propaganda – an effort that may confuse those who know less about topological indices than Richon and Young, while at the same time telling those who know and use topological indices how much Richon and Young are unfamiliar with the subject.

If connectivity indices correlate well with properties, and properties are used as descriptors for correlation with activity it seems plausible to expect that a selection of properties will also correlate with activities – as they do. In fact there is here a paradoxical situation: QSAR structure-activity people have been using molecular (bulk) properties to correlate with biological activity, which is a manifestation of interactions at individual molecular levels; while QSPR structure-property people have been using individual molecular properties (topological indices) to correlate with molecular

properties, which are manifestation of interactions at bulk levels. So the situation is just opposite of what Edwards and others have been advocating. From purely theoretical point of view, graph theoretical descriptors should be used for structure-activity studies, while property-property correlations represent another logical research domain. What is intriguing is that topological indices correlate also with properties. Instead of trying to scorn them, the traditional QSAR researchers should praise topological indices because by the fact that these descriptors of *individua*l molecules are also good at correlations with bulk molecular properties is a justification for medicinal chemists to use bulk molecular properties in their Hansch-type analyses for correlation between *individual* drug molecule and *receptor* [163,164].

Complimentary Evaluations of Chemical Graph Theory

The traditional QSAR field has been lacking for years new ideas and higher mathematical involvement, but when new ideas arrived, as we have seen from the views of S. Unger [143] and opinions of Kubinyi [149] about connectivity indices, they appear the first to not let it grow. Before we confront their "views and opinions" with views and opinions of users, let me add that the above comment about a view expressed by a lack of new ideas in QSAR is not my construction, though I fully subscribe to it! It is (*vide infra*) an anonymous referee of a paper that myself and C. L. Wilkins submitted to *J. Am. Chem. Soc*. writing to E. R. Davison, the editor of to *J. Am. Chem. Soc.* for theoretical chemistry:

Dear Dr. Davidson,

I have read the revised manuscript entitled, "A Graph Theoretical Approach to Quantitative Structure-Activity Correlations" by Milan Randic and Charles L. Wilkins, and find it most acceptable for publication in the Journal of American Chemical Society. The authors in reworking the manuscript, have produced a much more readable and interesting report of their new research which should be of great interest to much of the chemical community. . . . .

I feel this paper may stimulate increased activity in a field where there hasn't been a good idea for a number of years. I don't necessarily feel that the authors' approach, as presented in the paper, will be used directly as stated, but the new ideas offered should stimulate additional research in the structure-activity area.

Below is a comment on the connectivity indices by M. J. M. Wells and C. R. Clark [165] from the introductory part of their paper that also appeared about ten years after the "branching index":

"*In a treatise "On Characterization of Molecular Branching" (1) a topological branching index was proposed for the study of molecular graphs. In bench mark articles (2-4) the concept of molecular connectivity as an indexing system was expanded and refined. Now, some 10 years later, the predictions form the original paper (1) describing*

the utility of molecular connectivity as (1) " providing an accurate and precise scheme for predicting a particular property" and (2) "revealing novel relationships among unsuspected quantities and discerning the topological nature of others: has been realized.

Molecular connectivity refers to a collection of indexes that provide quantitative information abut molecular structure, Derived form the structural features of "connectedness" of a chemical graph, the indexes of chi terms ($^{m}\chi_{t}$) are dimensionless and encode information about the number of atoms, connections, unsaturation, cyclization, and heteroatom types in a molecule (5, 6).

Molecular connectivity is useful in establishing quantitative structure-property and structure-activity relationships. . . . . "

The references (1) – (6) are as follows:

(1) M. Randic, *J. Am. Chem. Soc*. 97 (1975) 6609
(2) L. B. Kier, L. H. Hall, W. J. Murray, M. Randic, *J. Pharm. Sci*. 64 (1975) 1971
(3) L. H. Hall, L. B. Kier, W. J. Murray, *J. Pharm. Sci*. 64 (1975) 1974
(4) W. J. Murray, L. H. Hall, L. B. Kier, *J. Pharm. Sci*. 64 (1975) 1978
(5) L. B. Kier and L. H. Hall, *Molecular Connectivity in Chemistry and Drug Research*; Academic Press: New York, 1976
(6) L. B. Kier, L. H. Hall, Eur. *J. Med. Chem.* 12 (1977) 307.

This is not an isolated view. There are QSAR circles where the connectivity indices have been well received. For example, Reiner Franke in his book on "*Theoretical Drug Design Methods*" (1984) wrote [166]:

". . . *the advantage of* χ *is that its calculation for practically any structure is easy and straightforward . . . The use of the connectivity can be recommended especially in such cases where relatively large structural variations are present in a series of compounds and where the primary goal of a QSAR analysis is data description rather than interpretation."*

I may add here a kind of different "recognition" that I have received several years ago, that is related to my "invention" of the connectivity index. In Maribor, Slovenia, every year in September there are "chemical festivities," a two-day meeting, known as "Chemical Days," during which there are numerous presentations of research in chemistry divided between various sections, with a few invited plenary lectures. I have attended several of these events, including one in the year 2000 on which Professor Allan Katritzky delivered an invited plenary lecture: "Understanding how chemical structure determines physical properties" in front of about 350 participants. Professor Jure Zupan, Dr. Marjana Novič, Dr. Marjan Vračko and myself (all from the Chemometrics Laboratory of the National Institute of Chemistry in Ljubljana) traveled to Maribor by train, which unfortunately was late. When we arrived to attend the Plenary Lecture, Professor Katritzky was already speaking, probably for 5-10 minutes. We sneaked in the front part of the side rows to least disturb the event. It took another 5-10 minutes when

Professor Katritzky, who was walking while taking, spotted me in the audience of 300-400 persons. He continued to lecture as he was approaching our row of seats and then came quite close, stopped lecture briefly and extended his hand for shaking my hand, asking how I am. After my response (that I am fine) he continued with his lecture for another half an hour or longer. I have been very much pleasantly startled with his kindness, and I am still, and I believe most of the chemists in the audience have been surprised with this not often seen mannerism. Professor Katritzky, who enjoys an outstanding reputation as one of the leaders in heterocyclic chemistry was here publicly acknowledging his appreciation for the connectivity indices and Chemical Graph Theory – of which I have been one of its visible ambassadors.

Emotional Hostility

An illustration of emotional hostility to connectivity indices is a pamphlet: "*Use of Molecular Connectivity indices in Socio-Historical and Business Management Studies*" [167], which was circulated among chemometricians. It came to my attention by courtesy of Yoshikatsu Miyashita from Toyohashi University, Japan, during my first visit to Japan in the summer of 1986. In this pamphlet it is admitted that the connectivity indices apparently do correlation slightly better than the traditional descriptors of QSAR, but then the main point of the pamphlet is to discredit the connectivity indices as a meaningless artifact that can correlate anything against anything - and to make them ridiculous. Instead, they made themselves ridiculous by concocted an absurd regression between telephone numbers of a select group of people in a small town in Sweden and connectivity indices for seven heptane isomers – which they assigned to individual persons. "We have chosen alkanes, because of their presence in gasoline . . . ". They assigned to each person one isomer "and matched them in sequence against the telephone numbers." They found an excellent correlation. This was to demonstrate the absurdity of the connectivity indices that can correlate with whatever nonsense one can think of. Aside from the ill-motivation, this pamphlet also points to a lack of innate logic. If indeed the connectivity indices produced good correlation for these essentially random data, then the same holds for the traditional QSAR descriptors, which according to Wold *at a*l. are only a little less successful! Hence, while trying to discredit the molecular connectivity indices the authors incriminate also themselves in discrediting their own type of QSAR descriptors! One need not be surprised at this "suicidal" act, because, according to Road Hoffmann [168], most chemists are not trained in formal logic and are not familiar with its laws. I found for the first time that English language, which claims over 500,000 words, is not rich enough to properly characterize this level of arrogance by a single word. Attribute that is perhaps close but still not quite close to characterize this kind of arrogance is: "fatuous." One can even speculate that intent of this pamphlet was to characterize the connectivity indices as an idiotic contraption. The word "idiotic" has several meaning including "an offensive term that deliberately insults somebody else's intelligence." Be as it may, the authors of the pamphlet and the editors of "Graph Theory Day" have overlooked the fact that the pamphlet also reflects on their attitude and their values of research of others, whether they understand it or not.

To me the pamphlet was mislabeled, as it is not a reflection on "*Use of Molecular Connectivity Indices in Socio-Historical and Business Management Studies*" but rather a reflection on "*Use of Molecular Connectivity Indices in Socio-Hysterical Studies*." One has to be careful in choosing words and obviously the authors of the pamphlet failed. According to *Funk & Wagnalls Standard Desk Dictionary* [79] the adjective "historical" has five meanings: 1. Constituting, belong to, or of the nature of history; 2. Pertaining to, concerned with, or treating the events of history; 3. Of, pertaining to, or based on known facts as distinct from legendary or fictitious accounts; 4. serving for the source for knowledge of the past; 5. Historic. The adjective "historic" is explained in the same dictionary few lines above as: 1. Important or famous in history; 2. Memorable; significant; 3. Historical. Well the pamphlet of John T. Edward, Erik Johansson and Svante Wold does not constitute, belong to, or has a nature of history, does not treat the event of history, is not based on known facts, is not source for knowledge of the past, neither is important or famous in history, nor is memorable and significant – hence misuse of the word "Historical." However the adjective "hysterical" suits the title of the pamphlet much better, I would say perfectly. The same dictionary describes "hysterical" and "hysteria" as follows: hysterical (adjective): 1. Resembling hysteria; uncontrolled, violent; 2. Characterized or caused by hysteria; 3. Inclined to hysteria. Hysteria, (aside its medical meaning as psychoneurotic condition characterized by violent emotional disturbances, which is here of no interest) is defined as: Abnormal excitement; wild emotionalism, frenzy. Again we have to exclude frenzy, which is related to a medical condition: A state of extreme excitement or agitation suggestive of or bordering on delirium or insanity, (again according to *Funk & Wagnalls* dictionary). So we are left with "Abnormal excitement; wild emotionalism," which fully fits the content of the pamphlet.

Had this incident remained just at the level of circulation of a pamphlet among hostile scientists – then it would not be worth mentioning it. People, including scientists, can do what they want in private contact, make fool of themselves, be arrogant, and display a lack of familiarity with Discrete Mathematics and Chemical Graph Theory, as well as logic. However, the pamphlet became not a private slander but a public event – and that is why it is mentioned here (and elsewhere [62],[99]).

Discrete Applied Mathematics is a very respectful journal for applied mathematics edited by Peter Hammer, Professor at Rutgers University, New Brunswick, NJ, (Romanian by origin). I do not recall how and when it came to my attention that there will be a special issue of this journal with guest editors Luis V. Quintas and J. W. Kennedy (from Pace University, New York) dealing with papers in Chemical Graph Theory. Neither do I recall how nor when I learned that the pamphlet of Wold et al., had been accepted for publication in that special issue of the *Discrete Applied Mathematics* edited by L. V. Quintas and J. W. Kennedy. I vaguely remember that the first author, the Canadian John Edward, may have informed me and may even have sent a copy of the article after the "pamphlet" was accepted in *Discrete Applied Mathematics.* I already had a copy of the article from my visit to Japan and could not imagine that such nonsense can be considered for publication. I was shocked – not because of the attack on the connectivity indices, but because of un-scientific mode and tone of this pamphlet, which

has no place in scientific literature. I immediately alerted a few colleagues, and in particular D. J. Klein (at Texas A & M University at Galveston, TX) and S. C. Basak, at the Natural Resources Research Institute of the University of Minnesota in Duluth, MN). Professor Klein informed me that he has written a strong letter of disapproval to Louis V. Quintas and J. W. Kennedy, the guest editors of the *Discrete Applied Mathematics*, and indicated that he will withdraw his article already accepted in that special issue of *Discr. Appl. Math*., if the article of Wold et al. is to appear in the same issue. Dr. Basak, who was asked to review the "pamphlet," in very strong terms, rejected the paper as scientific nonsense. Dr. Basak sent me his report, portions of which I reproduced in the Appendix 7a and 7b. In part (a) is the "Referee's Evaluation form" which lists the "Criteria for inclusion of manuscript" in the *Discrete Applied Mathematics Special issue* while part (b) has criticism of the manuscript of Edwards, Johansson and Wold. I may add that very recently I. Gutman [67] in his article on "mathematical" connections between mathematical and chemical models characterized (quite correctly) this "pamphlet" of John T. Edward, Erik Johansson and Svante Wold [167] as a lampoon. I was not quite familiar with this word despite living five years in England, one year in Canada and 35 years in USA. I had to consult *Funk & Wagnalls Standard Desk Dictionary* [79], which for lampoon says: "A scurrilous, but often humorous attack in prose or verse directed against a person." Then I had to look for "scurrilous," another word with which I was not familiar. I found that it stands for "grossly and offensively abusive." That is, what this pamphlet is: *grossly and offensively abusive*. As William Shakespeare wrote: *All is well that ends well* – so I have to admit that the "pamphlet" had some positive values – it enriched my English vocabulary by two words. Most likely I will hardly use these words, except when recalling John T. Edward, Erik Johansson and Svante Wold or Louis V. Quintas and J. W. Kennedy. I must admit that I was somewhat surprised that I have not come across the two words before, particularly as I like to read dictionaries, a hobby that I have in common with the President Abraham Lincoln, as I later learned.

After such responses from Klein and Basak (and possibly others?), Kennedy and Quintas withdrew the paper of Wold et al., from the journal of *Discrete Applied Mathematics*. However, they published it in a skinny journal (one issue of which appears annually) *Graph Theory Notes of New York*, of which they are the sole editors. Publishing a "pamphlet" in *Graph Theory Notes of New York* is an illustration of editorial "suicide," editors hurting themselves and the journal, for no good reasons. This happens, but usually because of editorial ignorance and/or reviewers' incompetence. In this case the "suicide" is not a result of an editorial ignorance but editorial arrogance and foolishness. The whole matter reminds one of the statuette of three monkeys, one keeps hands over its eyes, one over its ears, and one over its mouth – don't see, don't hear, don't speak. But the guest editors, who apparently did not see (or did not want to see) and did not hear (or did not want to hear) – nevertheless decided to speak!

An Epilog to the Hostility

As the epilog let me add that at one of the Sanibel conferences where I was invited to present a lecture, after my lecture during the coffee break, a young tall

participant addressed me speaking in soft voice about something that I could not immediately relate to. Then I realized that he is apologizing because he was the third author of the infamous pamphlet. He said that he was a young student, working for his Ph. D and was in company of senior advisors (Wold and Edwards), and he had little choice. I believe more properly, he should have said that he had no choice! I was telling him to forget the incident, and that there is no need for apology. Not only from him but also from senior authors – after all, people have the right to make mistakes. In my view the only persons who should apologize are the editors of *Graph Theory Notes of New York* (J. W. Kennedy a chemist, and L. V. Quintas, mathematician). However, the apology should not be addressed to me but to the readers of *Graph Theory Notes of New York*, a journal which unnecessarily got stained for life!

To strengthen my statement that indeed Johansson, the young co-author, was in a no-win situation when co-opted as co-author of the pamphlet, let me recall an editorial of Isenhour [169], in *J. Chem. Documentation*. He described an incident in his department. Briefly, while walking behind two senior professors in the department, he overheard their comments on a candidate for new faculty. One said: Have you seen his (long) list of publications? On this, the other replied: "But have you seen in what kind of journals he published"? – presuming inferior journals, if there are such (there are inferior papers but they can also appear in reputed journals!). To this Isenhour was tempted to tell the senior faculties: "But have you read the papers"? but then he remembered that he had not yet got tenure – and wisely remained silent – as an untenured faculty should, unless he/she can afford to be unemployed.

The incident with this pamphlet illustrates one of not so uncommon traits with scientists, who are obviously experts in their own narrow field of activity, but could have superficial knowledge or are totally ignorant of other areas. In particular this is the case when scientists give opinions in scientific fields in which they have no formal education.

Learn Graph Theory

It is known that most quantum chemists and physical chemists have no formal education in Discrete Mathematics, which includes Graph Theory. The situation may change in the future as the significance of the role of Discrete Mathematics gets better known. However, at this time comments made by quantum chemists and physical chemists on applications of Discrete Mathematics to chemistry and Chemical Graph Theory remain irrelevant. One wonders how many of those quantum chemists, who were unwise to make public comments on Chemical Graph Theory, had training in Discrete Mathematics? The same can be stated about those quantum chemists and physical chemists who hide themselves behind the anonymity of the peer-review process. Have they seen even an introductory book on Graph Theory, such as the lovely book of Robin Wilson [170]? One may mention other books on Graph Theory that can be highly recommended and that such ought to consider. These include the well-known textbooks, such as the widely known "*Graph Theory*" of F. Harary [171], or that of Bondy and Murty [172], considered by some as the best books on Graph Theory. How many of

those fictional "experts" have looked in the book of König: "*Theorie der endlichen und unendliched Graphen*" *with subtitle: Kombinatorische Topologie der Streckenkomplexe* [173], the first book on Graph Theory? This was one of many German and European books allowed to be fully reprinted in U. S. A., during WWII and after, by an act of Congress, which allowed legally reprinting of books from "enemy countries" without compensating publishers and authors. Incidentally the two-volume books of Eric Clar: *Polycyclic Aromatic Hydrocarbons* [174] is another illustration of this war "piracy" [175]. Finally I may add a "*Graph Theory*" book of R. Gold [176], which is divided in ten chapters covering paths, cycles, planarity, matching, independence, and special topics with numerous applications, for which I have written a book review [177]. Last but not least is to be recommended the outstanding book of N. L. Biggs, E. K. and R. J. Wilson, *Graph Theory 1736 – 1936*, which is much more than merely a worthy historical review of Graph Theory throughout its 200 years of existence [178]. Even browsing the entertaining book of Rouse Ball *Mathematical Recreations* [179] (updated by Coxeter) would be instructive to a novice in Graph Theory!

In an article in the *Indian Journal of Chemistry* I published a paper "*Chemical Graph Theory: Fact and Fiction*" [180] in which I have listed 60 questions, most of which everyone ever publishing in Chemical Graph Theory will have no difficulty to answer. Answers are also provided in the paper for those unfamiliar with Chemical Graph Theory and Discrete Mathematics, that is, the majority of quantum chemists, physical chemists and medicinal chemists. For example, Z. B. Maksić, in an editorial to a book on theoretical chemistry [181] identified Graph Theory with Hückel MO theory! Well, anyone who even has not heard of Graph Theory can judge the lack of the validity of such a misconception by looking through the table of content of the book on 200 years of Graph Theory [178], which has ten chapters, none of which deals with HMO. In fact one of the ten chapters is titled "Chemical Graphs," but the chapter considers Kekulé valence structures, not Hückel MO.

So how can one identify Graph Theory with Hückel MO, which is related only to part of Graph Theory dealing with spectral properties of graphs [77, 182-184] (and let me hasten to add that "spectra" in Graph Theory is not the same as "spectra" in HMO theory!). The case of Maksić illustrates unfamiliarity of many quantum chemists with Graph Theory, which to them becomes a "disguised" HMO theory. Of course, there are notable exceptions to the overwhelming unfamiliarity of quantum chemists with Graph Theory. They include on one side H. Primas, H. H. Günthard, K. Ruedenberg, E. Heilbronner, R. G. Parr, P-O. Löwdin, and others, and on the other side a few theoretical chemists who had or have interest in both, the Quantum Chemistry and application of Graph Theory to chemistry and published work in both sub-disciplines of Theoretical Chemistry. Such are, O. Sinanoğlu, K. Balasubramanian, M. Vračko, D. J. Klein, T. G. Schmalz, W. A. Seitz, G. E. Hite, Y. Jiang, T. Živković, and F. E. Harris, and other theoretical chemists, with whose background I may not be well acquainted. All these theoreticians have published works not only in Quantum Chemistry (including *ab initio* computations) but also in Chemical Graph Theory.

K_2 Graphs

During the biannual Brijuni Conference in 2004 [185], there was another public "incident" with Z. B. Maksić concerning Chemical Graph Theory. At that conference I presented some of my latest results of extending graph theoretical methods from molecules to the characterization of DNA. I started to be involved in developing numerical characterization DNA since the year 2000, after attending a seminar on graphical representation of DNA by Ashes Nandy, from Calcutta, India. Both of us at that time were visiting Dr. Subhash C. Basak at the Natural Resources Research Institute of the University of Minnesota at Duluth, MN. By "joining forces" we arrived at a numerical characterization of DNA [186]. This has been the first paper in Bioinformatics of this kind, which has opened a novel direction for research on quantitative comparative studies of DNA. Hence, formally my presentation at the Brijuni Conference belongs to Bioinformatics – not Chemical Graph Theory. Nevertheless, after my lecture, as a part of discussion, Maksić, who was in the audience, raised a question which essentially boiled down to: "*How can Graph Theory be useful in Chemistry when all diatomic molecules have the same graph*"? His question, of course, implied (his) answer that Graph Theory is useless for Chemistry. My first thought was to respond with a question: How a fork can be useful for eating a soup? As if "Chemistry" stands for "Quantum Chemistry", and Quantum Chemistry stands for "Molecular Orbital" calculations, and "soup" is the only food we eat. But the solemnity of the conference asked for a more appropriate answer so I replied by stating that when one considers 3-4 particles in a box one does not use Statistical Mechanics. In other words one chooses a tool having in mind the problem considered. If one is interested in bonding in diatomic molecules (or molecules in general) one uses Quantum Theory. If one is interested in complexities involved with adsorption of diatomic molecules of lattice surfaces one uses Graph Theory.

It is not difficult to construct questions similar to that raised by Maksić, the answers to which are obvious. For example how about the question like: "How can Molecular Weight (MW) be useful in Chemistry when all isomers have the same MW"? And of course, the number of isomers exceeds the limited number of diatomic molecules. Of course, chemists know that MW is a highly useful quantity. The question posed by Maksić at the conference in 2004 was not new, because already in 1990 Maksić in a Prologue to a book "*Atomic Hypothesis and the Concept of Molecular Structure*" [181] of which he was the Editor wrote the following paragraph (to which I added underlines):

"*There is an abundance of graph-theoretical indices which are purely mathematical constructions and yet they are correlated by some researchers with various molecular properties implicitly suggesting a deeper meaning of these indices than is justified. In our opinion they belong to the realm of hypothesis. They might be true, but they are not. In graph theory <u>as applied to chemical bonding</u> the level of abstraction is exaggerated so that the whole physics disappeared. One should just recall that hundreds of diatomic have the same molecular graph – two vertices connected by an edge. The same holds for larger molecules too. Generally speaking, ad hoc assumptions that certain mathematical structures should have a semblance to molecular properties is arbitrary. This could have been an excellent theoretical model framework in the time of Couper and Kekulé in the*

last century, but today it is obvious to almost everyone that the notion of orbitals, their overlapping, their charge populations and hybridization is pivotal. They represent irreducible subunits of models in quantum chemistry. This conjecture does not imply that graph theory is completely outdated. It has been shown that graph theory is equivalent to Hückel MO model in its simplest form . . . "

This quote tells it all – some quantum chemists like Maksić do not know what Graph Theory is. They are vocal, mostly anonymous and I am afraid, numerous. The above misrepresentation neither deserves time nor space for rebuttal, but is quite widespread. These "critics" of Graph Theory remind me of the "Flat Earth Society," consisting of people who *think* that they know without knowing facts. The same is true with what we may refer to as "Graph Theory = HMO Society" even if not formally constituted. There are hundreds (mostly anonymous) members among quantum chemists of which apparently Maksić has chosen to be one of few visible. By writing the above I recollected the well known statement of Archimedes: Give me a fixed point and I will move the Earth. In the above context: Find me a single publication in which Graph Theory is applied to bonding of diatomic molecules – and I will start eat soup with a fork!

RE: the underlines in the above extract from the Prologue of Z. B. Maksić:

(1) Graph theory is not about chemical bonding but connectivity. Even when Graph Theory is applied to the Hückel MO model, a topic I never had much interest in, except for the occurrence of isospectral graphs, excessive eigenvalue degeneracy in HMO, and multiple occurrence of eigenvalues in different systems – topics of some mathematical interest, not chemical interest. However, my colleagues Nenad Trinajstić, Ivan Gutman and Ante Graovac made a number of interesting contributions in that department. But what most quantum chemists misunderstood about their work is that they wanted to show that the early success of HMO is not due to quantum chemistry (and they were not reviving HMO when it already served its role as viable model), but due to recognition (by Nenad Trinajstić, Ivan Gutman, Ante Graovac and others applying Graph Theory to Chemistry) that many properties of HMO are merely a consequence of molecular topology and connectivity. Thus the famous Hückel 4n+2 rule is not a consequence of quantum chemistry and chemical bonding in monocyclic polyenes, but a consequence of graph theory and molecular connectivity. In a similar fashion the famous Woodward-Hoffmann Orbital Rules are also consequence of connectivity (graph theory) and not quantum chemistry.

(2) Here Maksić identifies Quantum Chemistry with MO Model. What about Valance Bond Model and Density Functional Theory? Are they not part of Quantum Chemistry?

(3) Graph Theory is Graph Theory and not HMO.

One way to find out what is Chemical Graph Theory is to review publications in which Graph Theory has been applied to Chemistry. That in itself is not a small task, so let us just review the topics of chemical graph theory covered with 70+ publications of this author listed in Appendix 1, which represents about 1/4 of graph theoretical publications of this author. They involve diverse topics of chemistry such as: Study of symmetry of

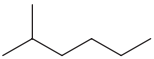
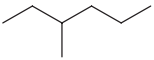
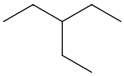
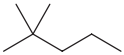
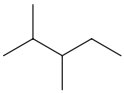
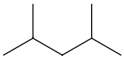
graphs representing degenerate isomerizations; Local aromatic properties of Benzenoid hydrocarbons; Expressions for Resonance energies of conjugated polycylic hydrocarbons; Characterization of atoms by random walks; The graph center concept; On evaluation of characteristic polynomial; Nonempirical approach to structure-activity studies; Statistical approach to resonance energies of large molecules; Generalized Wheland polynomials (related to enumeration of "excited" valence structures); Search for pharmacophore in structure-activity relationship; Isospectral multi-trees; Kekulé structure count and algebraic structure counts; The conjugated circuit model; Construction of orthogonal molecular descriptors; Representation of graphs by set of "basic graphs"; Novel molecular descriptors; Curve-fitting paradox; On characterization of fullerenes; Graphical bond orders; Molecular profiles: novel geometry-dependent molecular descriptors; Molecular shape profiles; Molecular bonding profiles; Higher order Fibonacci numbers; Resonance energy in giant benzenoids; Linear combination of path numbers as molecular descriptors; Hierarchical orthogonalization of descriptors; On characterization of molecular surfaces; On structural ordering and branching of acyclic saturated hydrocarbons; Clar polynomials; Graph theoretical descriptors of 2-D chirality; On molecular complexity; On complexity of transitive graphs representing degenerate rearrangements; Graphical Matrices; Characterization of 2-D proteome maps; Atlas of Kekulé valence structures of Buckminsterfullerene; On canonical numbering of fullerenes.

If this is not enough I can continue with topics not covered in the above list, which includes construction of various graph matrices, including the Distance/Distance or D/D matrix in which matrix elements are given as the quotient of graph theoretical and Euclidean distance between atoms; Molecular shape indices (given by quotients of the count of paths and walks; Anticonnectivity (in which some atoms or bonds suppress molecular dominant additivity property); Graphical enumeration of n-alkane conformations (rotamers); On graphical construction of Clar's aromatic π-sextet formulas; Numerical Kekulé valence structures and π-electron ring partition; and one of the latest papers on classification of the π-electron ring partitions. Then there is a list of topics from Bioinformatics, which besides numerical characterization of graphical representations of DNA includes publications on: Novel graphical representations of DNA; Graphical representation of proteins; Graphical alignment of DNA sequences and Graphical alignment of proteins" On alternative numerical characterization of proteomics maps, On characterization of proteome; On characterization of dose-response of proteome and successfully detecting the presence of the hormesis (known for years to characterize the dose-response for whole organism) at the cellular level! This last mention work was published in the Journal of Proteome Research (with impact factor about 7) jointly with E. Estrada [187] under the title: "Order from chaos: Observing hormesis at the proteome level," and was accompanied with a brief one sentence reviewer's report: "This paper will be highly cited – publish as is."

Have you seen any HMO paper listed above? Except for the topic of isospectral graphs and a single paper on graph theoretical search for benzenoid polymers with zero energy gap, which can be related to HMO (and again from the point of view of graph theory not quantum chemistry) none of plentitude of topics listed has anything to do with

HMO. I should add that I have not exhausted all the topics of Graph Theory in which I have been involved in, even less the topics considered by a number of people with whom I collaborate including: A. T. Balaban, K. Balasubramanian, S. C. Basak, M. V. Diudea, E. Estrada, A. Graovac, X. Guo, I. Gutman, D. J. Klein, H. V. Kroto, M. Novič, T. Pisanski, D. Plavšić, M. Pompe, N. Trinajstić, D. Vikić-Topić, D. Vukičević, J. Zupan. Then there is a pleiades of outstanding contributors to chemical graph theory, people like: J.-i. Aihara, D. Bonchev, J. R. Dias, S. El-Basil, S. Fujita, J. Galvez, H. Hosoya, O. Ivanciuc, Y. Jiang, E. Kirby, I. Lukovits, L. Pogliani, Ch. and G. Rücker, S. Tratch, N. Zefirov, to mention few who are still very active in the field. Then we could continue by adding contributors to QSAR and QSPR involved in developing and using (among other) graph theoretical molecular descriptors, people like: F. Burden, L. H. Hall, P. C. Jurs, M. Karelson, A. R. Katritzky, L. B. Kier, R. Todeschini. Even all the people mentioned do not completely cover areas of Graph Theory of interest in chemistry, one should not overlooked a fine class of mathematicians who have contributed much to Chemical Graph Theory and mathematical Chemistry in general, people like: O. Araujo, D. Cvetković, T. Došljić, J. Dugundji, S. Fajtlowicz, E. Flappan, C. D. Godsil, F. Harary, D. Janežič, E. John, A. Kerber, S. Klavžar, J. V. Knop, E. K. Lloyd, D. Marušič, B. Mohar, R. C. Read, H. Sachs, A. J. Schwenk, D.L. Sumners, D. Svrtan, I. Tomescu, D. Veljan, J. Žerovnik. That physicists would support expanse of Graph Theory in Chemistry is understandable – after all there are number of theoretical physicists who already "invaded" chemistry, which included half of my former students: besides Z. B. Maksić, also T. Živković, A. Graovac, S. Bosanac and Vlasta Bonačić-Koutecky. This may be a reflection of the saying that "Chemistry is too difficult for chemists, so physicist have to join," which appears as paraphrasing what Hilbert said about physics. There is one additional important (if not, beside mathematics, the most important) branch of science – Medicine that is likely to welcome Graph Theory, even though currently there are too few bridges at the horizon connecting Mathematics and Medicine. I made an "excursion" towards medicine following a paper that tried to characterize branching in neurons [188] by an alternative approach based on count of paths [189]. On the other hand, J. Lederberg, 1958 Nobel laureate in Physiology and Medicine, for: "*for his discoveries concerning genetic recombination and the organization of the genetic material of bacteria,"* considered use of trivalent planar graphs and the fact that they most of them have a Hamiltonian cycle to upgrade chemical nomenclature [190-193]. In a correspondence with Professor Lederberg, he let me know that some of this work (which earlier he sent me as a preprint) he could not publish in chemical journals. Reflecting about this I think that I may know the answer – Chemists prefer "men made" (or I should say "committee made") chemical names to those "God given" (and "men discovered") names, for which one needs some imagination. I may add that at one time it was believed that all trivalent planar graphs have Hamiltonian cycle, but Tutte [194] succeeded to construct a trivalent (three-connected) planar graph which has no Hamiltonian cycle. Graph is three-connected if removing of any two vertices leaves the graph connected, but removal of three vertices may result in a disconnected graph.

Table 3 "Men made" and "God Given" names of Heptane isomers

Heptanes	**"Men made"**	**"God Given"**
	n-heptane	6, 5, 4, 3, 2, 1
	2-methylhexane	6, 6, 4, 3, 2
	3-methylhexane	6, 6, 5, 3, 1
	3-ethyl pentane	6, 6, 6, 3
	2,2-dimethylpentane	6, 8, 4, 3
	2,3-dimethylpentane	6, 7, 6, 2
	2,4-dimethylpentane	6, 7, 4, 4
	3,3-dimethylpentane	6, 8, 6, 1
	2,2,3-trimethylbutane	6, 9, 6

If Chemical Graph Theory is Chemical Nonsense (that is, it has no bearing on "real" chemistry – as come "critics" would like to be the case) how would so many scientists be fooled? On an occasion, in defending the late M. Razinger, who was criticized by President of University of Ljubljana (a heterocyclic chemist) about the topic of the Ph. D. thesis that he supervised as being "un-chemical," being concerned with graph theoretical characterization of molecular structure Bill Milne summarized his letter of support expressing the thought that "*It seems unlikely that the many scientists who work on the utility of graph theory in chemistry have misjudged its possibilities*."

To Know Graphs Is not the same as to Know Graph Theory

By being about half way through the manuscript perhaps I should say for whom this manuscript is written. It is not written for Z. B. Maksić and such, it is not written for S. Wold and such, it is not written for J. W. Kennedy and such, it is not written for H. Kubinyi and such, it is not written for S. Unger and such, and it is not written for anonymous conspirators or lone sharks, who have no courage and conviction to come out publicly against topological indices and Chemical Graph theory in general and prefer to remain anonymous. It is not written because, as Professor E. Pretsch from ETH (Zurich), once said [195]:

"*You cannot convince an illiterate about the relevance of writing and in the same way you cannot persuade an innumerate about the relevance of counting*."

This "history" of hostility towards Chemical Graph Theory is written for open minded chemists, experimental and theoretical, mostly for chemists outside the field of Chemical Graph Theory, including theoretical chemists, physical chemists and medicinal chemists, who made no prejudgment about application of Discrete Mathematics in Chemistry. Most of them may have been unaware of the difficult and trying times we in Chemical Graph Theory had to endure, the amount of abuse, mistreatment, arrogance, scurrility (to take an advantage of a word that I learned in the process of writing this manuscript) that we are receiving, mostly from anonymous (and incompetent I should add) reviewers of our manuscripts – which despite their obstruction eventually get published in the same or some other journals. The intent of this manuscript is to expose scientific misconduct of a different kind, not one involving forging experimental data and results of a research, but one involving blocking legitimate research results to appear in press. Is it not a scientific misconduct to harshly attack someone's work anonymously and then when, despite such attacks, the paper appears in press, not come out opening a debate and expressing the opposing views? Who is afraid of Graph Theory? If anonymous reviewers are so convinced in their righteousness why do they not speak? I am sure that the editor of this journal, and possibly other journals, would welcome exchange of views on the role of Graph Theory in Chemistry. So come on and tell us what is wrong with graph theoretical papers on chemistry topics – or stop this anonymous nonsense of pretending to be an expert in the field in which you never made any scientific contribution.

To know graphs is not the same as to know graph theory just as to know numbers is not to know Algebra. Algebra is more than numbers, and Graph Theory is more than graphs. Algebra is rich in ideas, procedures, theorems, etc. Everybody knows numbers but how many know Algebra? Consider a selection of concepts of Algebra such as: Algebraic function, Association algebra, Binomial Theorem, Cardano formulas, Determinants and minors, Discriminant, Distributive lattice, Factorization, Immanent of a matrix, Pfaffian, Irreducible polynomials, Isomorphism, Lattice (order), Permanent, Complex numbers, Quaternions, Rational root theorem, Symmetric difference, etc.

Similarly Graph Theory is more than graphs, and is rich in ideas, procedures, theorems, etc. Consider a few: Algorithms (e.g., Dijkstra's algorithm for finding the shortest path); Canonical labeling, Clarke theorem, Clique, Regular graphs, Zero-symmetric graphs, Complete graphs, Kuratowski theorem, $K_{3,3}$ and K_5 graphs, Bipartite and Complete bipartite graphs, Planarity, Embeddings, Graphical enumeration, Hamiltonian path, Euler graphs, Homomorphism, Independent set, k-factors, Minimum spanning tree, cages, including Petersen's graph, Ulam subgraphs, Graph reconstruction conjecture, Coxeter graph, Tutte graph, etc.

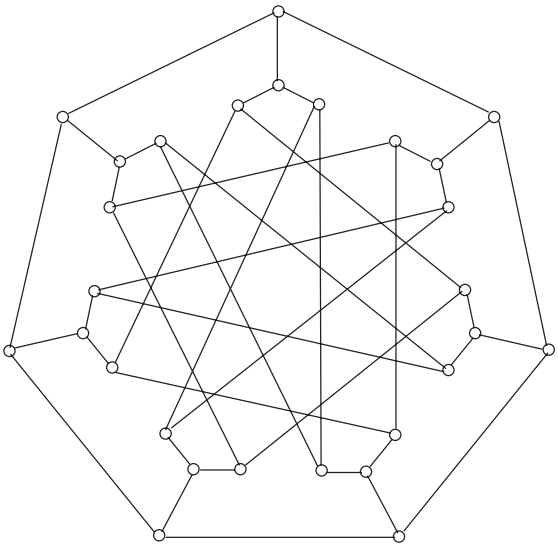


Fig. 5 On 25th anniversary of: "The Coxeter graph as drawn by Milan Randić" (reproduced from paper of H. S. M. Coxeter in *Congressus Nemerantium,* p. 332; Received Sept. 15, 1981)

Why these "pundits" who are speaking of Graph Theory, some even offering advice on what we in Chemical Graph theory should do(!), themselves do not look for Graph Theory in Wikipedia at the internet to find out how little they know of Graph Theory. There on pages and pages (free of charge) one finds an outline of the basic concepts of Graph Theory. Alternatively they can consult a glossary of basic definitions of graph theory compiled by Essam and Fisher [196] (published in *Reviews of Modern Physics* over 35 years ago!). There they will find among dozen pages but a single line: "Spectral Graph Theory studies relationship between the properties of the graph and its

adjacency matrix." Adjacency matrix is but one of two dozen and more matrices associated with graphs. A most recent review on most of graph matrices can be found in a book by D. Janežič, A. Miličević, S. Nikolić and N. Trinajstić [197], that has just appeared in a series of books on Mathematical Chemistry, initiated by Ivan Gutman, the Editor of *MATCH*. See also "Matrices and structure descriptors computed from molecular graph distances," by O. Ivanciuc and T. Ivanciuc in: *Topological Indices and Related Molecular Descriptors in QSAR and SAR*, edited by J. Devillers and A. T. Balaban [198]. And matrices are just a section of Graph Theory.

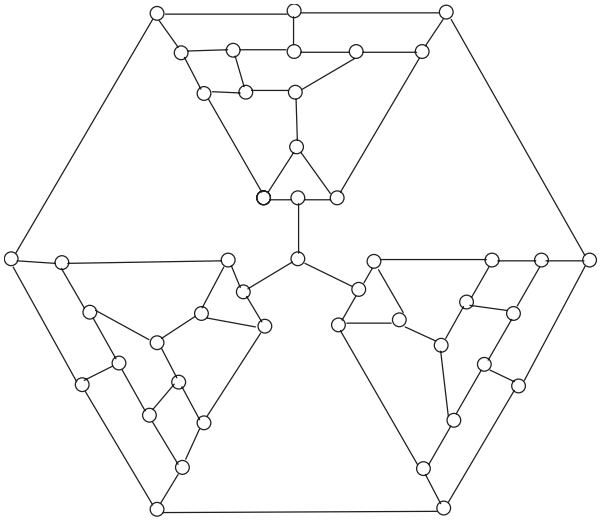


Fig. 6 The Tutte graph: Trivalent, planar, non-hamiltonian and three-connected

In Fig. 5 and Fig. 6 we illustrate the Coxeter graph and the Tutte graph, merely to illustrate for chemists a pair of "mathematical" graphs, to broaden somewhat their horizon on what non-chemical graphs may look like. I included the Coxeter graph in part of its "silver anniversary." For additional nice graphs interested readers can consult a chapter: "Bridges between Geometry and Graph Theory" [199] and for not so nice graphs, perhaps the article "Blanuša Double," which besides Blanuša graph [200] and its double considers embedding of snarks having 20 vertices on torus and double torus [201].

I should add also that chemical graphs, including molecular graphs, can sometimes have somewhat unusual and. unexpected look. Consider, for example, an alternative view of the graph of Buckminsterfullerene, usually shown as Schlegel

projection. In contrast in Fig. 7, it is shown with on of its Hamiltonian circuits displayed on its periphery.

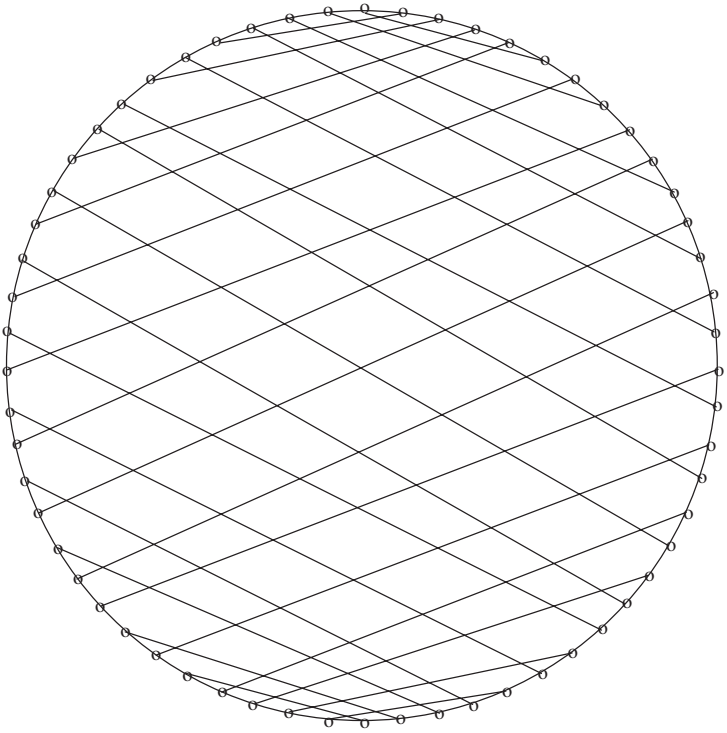


Fig. 7 Molecular graph of Buckminsterfullerene C_{60} displaying Hamiltonian cycle

Connectivity versus Bonding

Chemical Graph Theory is not about chemical *bonding* but about chemical *structure*! More specifically it is about combinatorial and topological properties of chemical structure! So how can Graph Theory be outdated? Diatomic molecules have no complexity tied to their combinatorial and topological properties, therefore one does not use graph theory to solve problems of single diatomic molecules. But counting ways of placing dimers (diatomic molecules) over a hexagonal (graphite) grid is a very complex problem, known in graph theory as dimer covering. It has received attention in

graph theory (considered often as an application of graph theory in physics rather then chemistry) [202-213]. The mistakes that Maksić made about Graph Theory are his problems not ours, fortunately his mistaken views are without consequence on the progress of Chemical Graph Theory. They remain his personal views – and scientists have the right to retain opinions, be stubborn and uninformed (without ever realizing their misfortune). As to the opinions, it may be appropriate to remind readers of what Lynn Margulis, a scientist, has said about scientists and their opinions [214]:

"*So I don't see how people can have strong opinions . . . Let me put this way: opinions aren't science. There is no scientific basis! It is just opinion*!"

Recall also (anonymous?):

People with the least expertise have the most opinions.

It remains to be seen if characterization of the "Conjugated Circuit" model by Maksić as "primitive" will be shared by others. Would one refer to Pauling's hybridization model and the Pauling bond orders as primitive models? Had Maksić followed a good practice in science, to contact authors when possible prior to making public comments on their work, he could have saved himself future embarrassments when comments are found inappropriate – as has been in this case. Be it as it may, such behavior hurts the messenger and not the audience, and has no effects on publication activity or research in Chemical Graph Theory. It is apparent that some quantum chemists see only molecular orbitals and nothing else – so I offer them a figure of the overlap (to use the word quantum chemists understand) of Molecular Orbitals Theory, Valence Bond Theory and Chemical Graph Theory. I already published this figure in my "giant" review article on aromaticity in polycyclic conjugated hydrocarbons [80]. For some people who see only molecular orbitals as a tool of theoretical chemistry this figure may be an eye opener – if they choose to open their minds.

Much more serious are negative statements about Chemical Graph Theory by anonymous reviewers of publications, who mostly communicate with editors of journals, who also are mostly ignorant of Chemical Graph Theory. Unfortunately today in many journals authors are viewed as the least competent scientists on the subject of their publication, instead of the opposite. There is too much interference of reviewers and editors when it comes to publishing research papers. Historically, scientific journals started as a vehicle for exchanging views among scientists, but are driven today as a tool for strengthening views of the Establishment. I wonder how many editors have read the papers by James V. Bradley "*Pernicious Publication Practice*" [215] and "*Editorial Overkill*" [216]. I enclosed the abstract of these two publications as Appendix 8 at the end of this brief reminiscence of unwarranted difficulties that many of us in Chemical Graph Theory encountered over the past 30 years. In this respect, the comments of Maksić represent a kind of editorial propaganda. Recall what John Warcup Cornforth (who shared the Nobel Prize in Chemistry in 1975 with Vladimir Prelog) said about "propaganda":

"*Propaganda is that sort of art of lying that consists in deceiving your friends without deceiving your enemies."*

Perhaps the above "definition" of "propaganda," which clearly applies to politicians, needs be somewhat modified when one speaks of scientists. This can be done by replacing two words: "art" with "craft" and "lying" by "fantasy." The difference between politicians and scientists is clear: while politicians most of the time know when they are lying, scientists sometimes do not know that they are fantasizing. The Prologue of Z. B. Maksić illustrates a case of what one may refer to as "Editorial Suicide." As is known, most suicides produce little damage, except to the nearest of kin.

Reviewers and Editorial Incompetence

Let me continue with a single illustration of the abrasiveness, arrogance and ignorance of anonymous reviewers when it comes to Chemical Graph Theory. In one of my papers I used canonical labels to establish the symmetry of one of Balaban's isomerization graphs (see Appendix 9). A reviewer of the prestigious *Journal of Chemical Physics* commented that if all that I did was determining the symmetry of that graph, then not only that is trivial, but it reminded him about what his ten-year old son was doing.

I was appalled with ignorance and arrogance of a reviewer of such distinguished journal so I have written a brief letter (enclosed as Appendix 9) stating the facts and sought views of scientists whom I knew that they know better. I have contacted several leading mathematicians in graph theory and a number of outstanding chemists familiar with graph theory, including: H. S. M. Coxeter, F. Harary, R. Frucht, E. K. Lloyd among mathematicians, K. Mislow, D. Herschbach, P. G. Mezey, A. T. Balaban, Hs. H. Günthard, H. Primas, M. Gielen, and A. Mead, among chemists. From each of them I received a supportive response. Professor Coxeter, at that time the President of the Mathematical Society of Canada, known to readers of *Scientific American* as "Mr. Geometry," widely respected as the leading authority in Combinatorial Geometry sent a brief letter (dated July 25, '82), which may be viewed as a summary for all other responses:

"*Dear Dr. Randic,*
Thanks for your letter about the 15-point graph. I find it interesting and consider the referee to be incompetent; *he should not have called your conclusion 'obvious'. It took me about ten minutes to see how to name the 15 vertices with the pairs of 6 symbols so that two of them are joined iff they have no common symbol in common.*
Best regards,
HSM Coxeter "

I sent the responses to the Editor of *J. Chem. Phys*. introducing Professor Coxeter as "the leading mathematician in this area." I got response that "It took only 15 minutes for the leading mathematician in this area to solve the problem." To this I replied: ". . .

No, I solved the problem, professor Coxeter verified and found the solution correct. To see the difference here is cubic equation $x^3 - 2x^2 - x + 2 = 0$. Try to solve it using Cardano formulas and it may take you 10-15 minutes, but if I tell you that the solutions are $x = \pm 1$ and $x = 2$, you can verify that this is correct in a few seconds." (I did not elaborate that cubic equations with simple coefficients can be often solved fast by other methods). This whole correspondence took some time and meanwhile I published this "simplistic" (or should I say "childish") paper (in collaboration with M. I. Davis) elsewhere [217]. The Editor apparently overlooked the difference between *solution* and *verification*, as others may also have. The problem of determining the symmetry of graphs is an NP problem (involving non-polynomial algorithms), while the verification of the same problem is P (polynomial in nature). At that time most theoretical chemists had not heard that NP ≠ P [218] and knew little about complexity of computations, the subject with which computational scientists were well familiar then and now.

I have, however, to express my respect for the then Editor of *J. Chem. Phys*., because he was not only kind enough to continue the correspondence, but was taking appropriate measure to get better appraisal of my work. My next paper in the series on the symmetry of isomerization graphs (in all there were ten papers) that I sent to him was accepted for publication. Unfortunately, a change of editors occurred and the new editor did not respect the decision of his predecessor, but sent the already accepted manuscript to a "new" reviewer. After receiving his report, the essential part of which was that this paper reminds him of the geometrical puzzle that his ten-year old son was solving, the new Editor rejected the paper! Here are a few passages form the letter of the "new" referee to the new Editor:

"*Dear John:*

Here are my comments on Randic's paper and a general assessment of this line of research.
The reasons why the Journal has generally declined to publish this sort of things are pretty clear after even a quick run through this manuscript. Firstly there is precisely little here of any chemical substance at all. There is a fair bit of hand waving, dressed up for the occasion with plenty of graph theorist's jargon. . . . Secondly, and this point transcends the first, graph theory at present does not have the mathematical tools to do many of the things we'd want it to do. So the discussion for example which starts on page 9 uses 'trial-and-error' or ' "educated guess" ' (his " ") type approaches to the problem of finding alternative graphical descriptions. This happens to be a fundamental part of the paper and in terms of pecking order of intellectual endeavors this must rank pretty near the bottom. It frankly reminds me of the geometrical puzzles my 10-year old does. To answer one of your questions, there is nothing incorrect in this paper, just not much of any depth at all. . . . "

At that point I decided to break "diplomatic relations" with the *Journal of Chemical Physics*, never sending anything there nor giving them benefits of my advice. Let those who want to be in darkness remain in darkness. My only comment was that

maybe the 10-year olds is a genius, but the father is ignorant of Graph Theory. Yet he is arrogant enough to continue his report to John (the Editor):

"*After such an assault on this particular paper, let me outline some areas where graph theory is and has been important and has allowed significant inroads into chemical problems . . .* "

Then he continues to suggest topics of HMO, which to me even then belonged to the least important and the least relevant topic of quantum chemistry. When a blind leads a blind, both will fall in a ditch – says an English proverb. Do we who have been developing Chemical Graph Theory over years need instructions from outsiders on what to do? Let me end this wandering of mine at the bottom"*of pecking order of intellectual endeavors*" by reproducing (in the Appendix 10) a sizable part of a letter from Professor Coxeter relating to canonical labels (that I used for determining the symmetry of graphs). At least being at the "bottom" of the "Scientific Ocean," I am in company of very outstanding mathematician! In his letter Coxeter referred to the "monster graph": *You are indeed bold to study a monster graph with 10!/3 vertices.* The "Monster graph" depicts degenerate rearrangements of bullvalene, $C_{10}H_{10}$, that Doering and Roth [219] thought of as an interesting possible molecule in which CC bonds would continually interchange connecting adjacent carbon atoms. This is how they described their brain child:

"*By virtue of its potentially extraordinary properties, tricyclo[3.3.2.0^{4,6}]deca-2,7,9-triene of "Bullvalene," as it has been colloquially named deserves mention even though it is at present no more than an hypothetical molecule . . . it will of necessity be a molecule in which no two carbon atoms remain bonded to each other, and all ten carbon atoms inevitably wander over the surface of a sphere in ever changing relationship to each other. Such a fluxional structure will have no precedent in organic chemistry*."

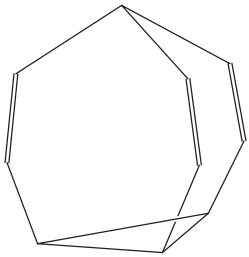


Fig. 8 Bullvalene $C_{10}H_{10}$

In Fig. 8 we illustrated bullvalene. We may add that equally amazing as bullvalene is, is the fact that already the next year G. Schröder [220] in Germany succeeded in synthesizing this molecule and proved that predictions of Doering and Roth

were correct. Ten years later Schröder and coworkers [221] listed a few properties of the bullvalene rearrangement graph, a trivalent graph having 10!/3 = 1,209,600 vertices, pointing that the shortest cycle in the graph has 14 points. Later we found that this is not correct and that the shortest cycle in the graph has 12 points (see ref. 15 in [222]). To see this one designates carbon atoms of bullvalene by code: (*abc*) (*dg*) (*eh*) (*fi*) (*j*), with the *abc* being in the C_3 ring, *j* at the apex and *dg* a CC double bond adjacent to atom *a*, then successive permutations $(AB)^6$ with *A* producing (*jih*) (*gd*) (fc) (*eg*) (*a*) and *B*: (*ijg*) (fc) (*he*) (*da*) (*b*) from the initially given code will close to a 12-membered cycle.

We wanted to characterize the bullvalene rearrangement "Monster graph", but the available computer had no enough memory for our project, so we turned our attention to "Baby Monster graph" trivalent graph associated with "only" 7!/3 = 1680 vertices (and 2520 edges), which we successfully characterized [222]. The Baby Monster graph is representing the degenerate rearrangement of P_7^{3-} which represents an analogue system to bullvalene but now in inorganic chemistry. To use the characterization of Doering for bullvalene one can say of P_7^{3-}, synthesized by M. Baudler in 1982 [223], that

"*. . . it will of necessity be a molecule in which no two phosphorus atoms remain bonded to each other, and all seven phosphorus atoms inevitably wander over the surface of a sphere in ever changing relationship to each other. Such a fluxional structure will have no precedent in inorganic chemistry*."

Below we show the count and distribution all neighbors at various distances for the Baby Monster graph, with the maximal distance of 14:

1, 3, 6, 12, 24, 45, 81, 147, 255, 365, 350, 231, 116, 37, 7

Let's end with a comment on monster graphs by pointing out that Tomislav Živković [224] succeeded in obtaining the count and distribution all neighbors at various distances for the Monster graph – without use of large computers, which is quite an accomplishment. The count of the distribution all neighbors at various distances for the Monster graph, with the maximal distance at 30:

1, 3, 6, 12, 24, 48, 93, 177, 339, 651, 1242, 2327, 4341, 8040, 14682, 26343, 46446, 79021, 126085, 183648, 231607, 232096, 163373, 70564, 16343, 1848, 125, 21, 3, 1

Adding all these numbers one obtains 10!/3. We feel that a comparison of the two list of neighbors at different distances fully justified the referring to the two graphs as the "baby Monster" and "the Monster Graph," respectively. For a comparison, the list of neighbors at different distances for molecular graph of buckminsterfullerene (depicted in Fig. 7 in somewhat unusual representation), with the maximal distance of 10, is:

1, 3, 6, 8, 10, 10, 9, 6, 6, 1

the total being 60. The above sequence, already in comparison with the sequence of neighbors for the "Baby Monster" graph, can at best be referred as "embryonic monster" graph.

We shall Overcome

Despite a mountain of negative reports and attitudes against Chemical Graph Theory that this author and others have accumulated we shell overcome. I have heard of difficulties of several colleagues, including A. T. Balaban and H. Hosoya. Balaban recalls that he had sent a manuscript "Chemical Graphs. 3. Reactions with cyclic six-membered transition states" to *Angewandte Chemie International Edition in English*, but the paper was turned down. He then published this work in Revue Roumanie de Chemie [225]. To his surprise, several years later *Angewandte Chemie International Edition in English* published a paper by J. B. Hendrickson [226] (a well-known author of the organic chemistry textbook co-authored with D. J. Cram and J. S. Hammond), which has essentially the same ideas and content. After being contacted by Balaban, Professor Hendrickson apologized for not having known about the *Rev. Roum. Chim*. Paper. Clearly the editor of *Angewandte Chemie* is to blame for rejecting a paper, which however, when it comes under different name and different address is acceptable. As a protest Balaban never again submitted his paper to *Angewandte Chemie*. Hosoya has even written about problems that he encountered [227]. It is from his publication that I adopted the expression "invisible enemies." These are but few, but I am sure that there is hardly any researcher in Chemical Graph Theory who has not his/her share of abused that they experience with ignorant or suspicious reviewers of Graph Theory for otherwise often their outstanding work. For instance, the first graph theoretical contribution of Haruo Hosoya, a note that has written about his now celebrated Z index, was rejected by *Chemical Physics Letters.* It appeared a year later in the *Bulletin of Chemical Society of Japan,* despite the fact that even for this journal "*at least two persons refused to referee*" the paper. This is how Haruo Hosoya has summarized his experiences ". . . *except for a few papers, I had to fight my graph-theoretical papers against invisible enemies, i., e., ignorant and offensive referees and editors, inside and outside the country*."

Let me continue by saying that despite the terror against graph theory (terror in the sense of an intolerable nuisance – see Funk & Wagnalls's dictionary for an informal meaning of terror), there have been a number of very positive evaluations of our work. I will mention but a few. Let us start with how was one of my papers on Graph Theoretical Approach to Conjugation [12] (one of the three papers mentioned at the very beginning of this article) evaluated by an anonymous reviewer of *Tetrahedron*:

"*This paper presents a novel and impressively revealing application of graph theory to chemistry. I am amazed how the simple concept of conjugated circuits is utilized to provide a wealth of qualitative and quantitative information about conjugated hydrocarbons. The contribution is timely in view of the widespread interest in structure-stability-reactivity relationships. The manuscript is lucidly written . . .*"

On the three leading questions accompanying the letter sent to referees:

1. Does this article incorporate novel and original organic chemistry – theoretical or experimental?
2. Will the paper be read with interest and enjoyment by a sizable group of organic chemist?
3. Does the paper describe a substantial, definitive piece of work?

The anonymous referees answered with 7 on the scale 1-7 (7 being the best).

I sent copies of the work on conjugated circuits to Linus Pauling and got soon a reply. I thank his son Dr. Linus Pauling, Jr. for permission to reproduce the letter, which I did in my "giant" review paper on Aromaticity in Polycyclic Conjugated Hydrocarbons, published in Chemical Reviews in 2003). Here is a part of it (dated 24 March 1976):

"*Dear Professor Randic:*

I was pleased to receive your letter and your paper, which I have examined with interest. I agree with you that it is better to make rather simple calculations, such as yours, than the very complicated ones.

Your work on conjugated circuits reminds me of a paper that I wrote on the diamagnetic anisotropy of aromatic molecules, Journal of Chemical Physics 4, 673 (1936). . . .

Again let me thank you for writing to me.

Sincerely,
Linus Pauling"

That much for the "primitive" method of Conjugated Circuit. Let continue with a report on the paper by I. Gutman and myself "A correlation between Kekulé valences structures and conjugated circuits," which appeared in *Chemical Physics* [228] (European "equivalent of the *Journal of Chemical Physics*) after the following evaluation (dated January 5, 1979):

> "*Although I have not checked the mathematics carefully, I suspect it is correct. I find this to be a very interesting, stimulating, and a clear paper about a subject that few would have thought contained such plums. I recommend publication*."

Let me explain for those less familiar with English idioms that "plum" besides the well known label for a common fruit and its tree has also idiomatic meaning: "The best or most choice part of anything" (e.g., see *Funk & Wagnalls Desk Dictionary* [79]). This is particularly proper to mention because in many regions of Balkan (which produces about 80 % of plums in the World) "plum" is not a complement (but Slivovitz is appreciated!). In a free translation one could use the word "pearl" instead of "plum," for example when speaking of Dubrovnik (Croatia) "as the pearl of Adriatic" and Merida (Venezuela) as

"the pearl of Andes." That "plums" and "pearls" are viewed as gems is evident from the Preface to the book "*Mathematical Plums*" [229], edited by Ross Honsberger, in the series "Dolciani Mathematical Expositions" of The Mathematical Association of America. There R. Honsberger starts his Preface with: "*MATHEMATICAL PLUMS extends Dolciani collection of mathematical gems with ten independent essays . . . In keeping with the preceding volumes in the series, the present volume stems from the desire to share the wonder and excitement of ingenious mathematical work at the elementary level . . .*"

The manuscript "A correlation between Kekulé valences structures and conjugated circuits" was initially sent to the *Journal of Chemical Physics*, but with a letter of Editor of November 14, 1978, after the editor "*consulted an additional referee as to the suitability*" he continued with "*I must confirm the earlier decision that it [the paper] is not suitable for the Journal of Chemical Physics*." In Appendix 11 one can find reproduced one of the opinions on which the paper was rejected – because it is not only very instructive and informative of those who do not know that they do not know (and who are according to Confucius dangerous and should be avoided) but because the identical report also received by Professor Balaban for one of his graph theoretical papers (on topological indices). Thus we have an "expert" (who needs a colleague to support his view) who has a "master" copy of his "evaluation" and an editor who either is unaware of the "industrial" production of "opinions" of papers in chemical graph theory or who trusts and tolerates those who do not deserve either. It appears as almost that this referee tries to re-invent Henry Ford's mass production and automatization – but in the field of science evaluations!

Another letter of encouragement came from D. Hellwinkel of Heidelberg (of March 1977):

"*I just came from reading your most interesting paper on Aromaticity and Conjugation (JACS 99 (1977) 444). I think that your extension of the Hückel Rule provides a most important improvement in the understanding of the properties of polynuclear conjugated systems. This even more so because your method of dividing fused systems formally into cyclic conjugated sub-entities can be understood and performed by every student without sophisticated theoretical/mathematical background. Personally I think that always these theories are the best ones which allow simple quantifications of inherent chemical intuitions. And this is exactly the case with your elegant substructure counting and weighting procedure. I am sure that these ideas will find very broad (and grateful) acceptance in chemical world . . .*"

Dog Barks while Caravan Passes By *(an Arab proverb)*

Now let me reproduce in full the "second" opinion, on whose basis the freshly appointed Editor of *J. Chem. Phys*. has rejected the already accepted paper which,

according to a European view has been characterized as "*a very interesting, stimulating, and a clear paper about a subject that few would have thought contained such plums"*:

I do not believe this paper should be published in J. Chem. Phys. The use of graph theory (to enumerate the numbers and types of polycyclic systems, to single out parts of valence structures where there is alternation of single and double bonds, and to predict resonance energies) has been Dr. Randic's main concern for the past few years. He has published a large number of papers and notes on this method, some of which have presented interesting insights into the concept of resonance. I am afraid I do not believe that the present paper lives up to that criterion. The present paper presents the proof of three theorems, one of which (g), is used to find all Kekulé structures for coronene from the examination of a single Kekulé structure; and then the idea of disjoint conjugated circuits is discussed in relation to Clar's sextet idea. While these are amusing, they do not, in my opinion, contain enough physics or chemistry to make them of interest to the chemical physics community (or even to a significant fraction of that community).

I realize that this is an opinion, not a fact, and that Dr. Randic will not like it any better than the other referee's report; however, I think that he realizes that most of the scientists interested in chemical bonding in aromatic polycyclic molecules do <u>not</u> find this approach very fruitful, and it is up to the practitioners of this method (Dr. Randic, for example) to convince rest of the error of their judgment. This paper does not do that.

This report is not only a "classic" illustration of pernicious editorial practices and editorial overkill, but is also accompanied by undocumented assertions, phrases that reviewers want to *impress* the editor, instead *informing* him or her, like *that most of scientists interested in chemical bonding in aromatic polycyclic molecules do <u>not</u> find this approach fruitful.* Well, how does he know? Whom has he asked? What about scientists not interested in chemical *bonding* but interested in chemical *structure* as a whole? I can list, besides the anonymous referee of *Chemical Physics*, where eventually this paper has been published, a dozen interested scientists who expressed their interest in this graph theoretical approaches to chemical structure, people like D. Hellwinkel, F. Boschke, K. Hafner, G. Kraus, M. Krygowski, M. Zander, and E. Clar, the doyen of the chemistry of polycyclic aromatic compounds, to mention a few outside of the chemical graph theory community. This is a brief excerpt from a letter of E. Clar of May 1974:

"*Thank you very much for your interesting letter of 7th March. I find your work most interesting and I should be grateful for any information of the progress of your publications and for reprints of them . . . I hope you have been treated not too badly by the Establishment and your papers will be published unaltered, as they deserve it. Perhaps Tetrahedron may be the best journal for your papers. The broad minded and liberal influence of Sir Robert Robinson can still be active there . . .*"

In March of 1977 I received the following letter:

Springer
Springer-Verlag
Berlin Heidelberg New York

Dr. Milan Randić
Energy and Mineral Resources
Research Institute
Ames, Iowa 50011 / USA

March 1, 1977
Be/Hei

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
"Aromaticity and Conjugation"

Dear Dr. Randić,

It was with the greatest pleasure that I have studies the above mentioned article.

I am scientific advisor for chemistry at Springer-Verlag and have recently founded the series "Lecture Notes in Chemistry" (see enclosure).

As I feel that the material you presented in the ACS Journal may be of interest to the readers of this new series, I would like to ask you whether you would be willing to treat this subject in "Lecture Notes in Chemistry"?

Hoping for your soon and favorable reply,
I am with kind regards
Yours Sincerely,

Dr. F. Boschke

Encl.

Unfortunately, in 1977 I was still without job and was only helped by the kindness of the Director of Ames Laboratory, Professor Robert Hansen with having an office and about getting $ 3,000 per year from Director's Discretion Fund, for attending conferences, buying reprints and books. This support continued for more than ten years, even later when I joined the faculty of Drake University. This stipend from Ames Laboratory made it possible for me to regularly attend and enjoy the Sanibel Symposia organized yearly by the late professor Per Olov Löwdin. Apparently not everyone was happy or approving of "spending money" on "nobody," because on one occasion in the afternoon (a day before traveling to Florida) when I approached the Secretarial Office of Ames Laboratory to collect my travel tickets, I was sent to see the Deputy Director of Ames Laboratory (Professor Hansen was not in the town). He informed me that my ticket was impounded. My English was somewhat limited and this was the first time that I cam across the word "impounded," so I asked what this meant. I was told that Ames Laboratory should not be spending money on my travel. Well, I returned home and stopped preparations for a 7-days travel to St. Augustine, FL in the vicinity of which the Sanibel Conference was to be

held. Then late in the evening, between 10-11 PM I got a phone call from Professor Hansen, who just returned from his travel to inform me that I should be ready tomorrow at 6:00 AM, that a government car would come to take me to the Des Moines Airport (which is one hour drive, some 40 miles south of Ames) and that the chauffeur will bring me my air tickets. It is needless to say that when Professor R. S. Hansen retired, my support from Ames Laboratory was stopped. The new director told me that the support I was receiving over a dozen years was "illegal." I was not convinced, because if a fund is discretionary, it is up to the Director to decide how to spend it – and obviously Professor R. S. Hansen, who was Professor of Physical Chemistry, appreciated my work in Chemical Graph Theory.

That this is the case confirms the request of Professor R. S. Hansen that I take one of his former M. Sc. students, Stuart C. Grossman, a professor at a High School in Omaha, NE, and asked me to lead him to Ph. D. thesis (at Iowa State University), which I happily accepted. However, because the Chemistry Department at the Iowa State University requested that S. G. Grossman enroll to numerous courses during the work on his Ph. D. thesis (which would take a lot of precious time) I suggested that he register his Ph. D. thesis with the University of Zagreb. There people with Master of Science (his was in Mathematics) have first to send an "Abstract" on the topic of the research for thesis, and if that is approved, they have to submit a thesis and come in person to defend it and prove that this is their work – by answering questions of three examiners. Professor Nenad Trinajstić, who was appointed by the University to follow the case, approved the topic of the thesis and about two years later S. C. Grossman defended his thesis (written in English and the examination being in English, of course). A few years later Mr. N. Hideyuki Narumi, a former student of Haruo Hosoya, also defended his thesis in the area of Chemical Graph Theory at the University of Zagreb. During my association with Ames Laboratory I have published about 60 "illegal" papers, some of which are highly cited!

Unfortunately I could not accept the kind offer from Springer to write a book for "*Lecture Notes in Chemistry*" because on one hand at the time I was engaged and investing much time in looking for more durable employment, and on the other hand had additional obligations related to the brain surgery of my eight-year old son – but the Letter from Dr. Boschke was valuable encouragement in the time when a flood of disapproval of Chemical Graph Theory was in fashion.

Catch 22

But let us return to the question: How can one *"convince* the *rest of the error of their judgment"* when one is prevented to communicate the message? In courts in civilized countries person is innocent till proven guilty. In science it appears to be just the opposite; it looks like that scientists have to prove that their work is worthy of publication, instead of the burden of proof being on referees and editors. How can one demonstrate that *most of scientists* would be interested in one's work? This is an illustration of Catch 22!

And then why should one care about *most of the scientists*? Were the famous papers of Einstein published in 1905 understood and appreciated by "most" or even a "significant fraction" of the scientific community? I can understand that this may be an issue with commercial scientific journals but the *Journal of Chemical Physics* is not commercial (while *Chemical Physics*, which is published by Elsevier, hence commercial, has accepted the paper!).

Finally as my response to the "amusing" character of the paper I will quote physicist Stephen Weinberg, a Nobel laureate [230]: "*Our mistake is not that we don't take theories seriously enough, but that we do not take them seriously*."

Is there a way to prevent, or at least curtail, the urge of scientists "who don't know that they don't know" to spread disinformation about those areas of science which is outside their own research activity? One answer that relates to curtail of foolishness in science has been known to ancient Greeks as displayed by the motto on the portal of Plato's Academy: "LET NO ONE IGNORANT OF MATHEMATICS ENTER HERE." Perhaps editors of journals, instead of writing anonymous pamphlets [231] on what graph theoretical papers they would consider "worthy" of accepting, ought to ask their reviewers whether they had formal or informal education in the Discrete Mathematics? That ought to disqualify about 90 % of referees of papers on chemical graph theory and cut the nonsense 90 %. For example, two of the six reviewers of a paper of mine that I have recently submitted to the *Journal of Chemical Information and Modeling* did not know the difference between graphical and graph theoretical! Hence, not only did they have no idea about Discrete Mathematics but they also put their knowledge of the "classical" mathematics in question. Apparently most chemists have, at best, a limited awareness of the substance of the Discrete Mathematics. Discrete Mathematics need better visibility among chemists, excepting those with a fair experience in computer algorithms. Perhaps the recently founded International Academy of Mathematical Chemistry should accept as its motto: "LET NO ONE IGNORANT OF DISCRETE MATHEMATICS ENTER HERE."

Intolerance

> *If a man does not keep a pace with his companions, perhaps it is because he hears a different drummer. Let him step to the music he hears, however measured or far away.*
>
> H. D. Thoreau

The above quote is taken from *Walden* of Henry David Thoreau (1817-1862), American essayist and philosopher known for his libertarian views. We have illustrated cases of **ignorance** and cases of **arrogance** that accompany scientists who indulge in "criticizing" scientific contributions that are outside the area of their competence. What is their motivation – is for them to explain. It can vary from personal animosities to

convictions that they are the only true "prophets" in science and those who depart from their views are "infidels." Be it as I may, such an unscientific behavior of these "fundamentalists" is accompanied with high dose of **intolerance** – a vile that is not so strange to politicians but has no place in science.

Researchers in Chemical Graph Theory have seen a lot of ignorance, arrogance and intolerance, most from anonymous sources. But when detected in public it calls for response. Because of the space limitations we will mention only a single case: "QSAR Preaching" of Hugo Kubinyi. Here is the first paragraph of his article "Validation and predictivity of QSAR models" [232] for illustration:

"*When QSAR started about 40 years ago [1], the quantitative description of structure-activity relationships (SARs) was in foreground; prediction played only a minor role. A few physicochemical parameters, i.e., lipophilicity, expressed by log P or π values, electronic properties, expressed by σ, molar refractivity MR, steric properties, and/or parabolic lipophilicity terms were used in the correlations. Later, quantum chemical and geometrical parameters, connectivity values, electrotopological state parameters, WHIM parameters, and many other were tested (see e.g., [2,3]), whether they are suited to explain SARs in a quantitative manner and whether the resulting models are capable to predict the activities of new analogs. As a consequence of so many (artificial) parameters and despite the fact that the use of too many parameters has been criticized already thirty years ago [4],* ***the literature is now spoiled with, most probably, thousands of meaningless chance correlations***." (bold emphasis by MR)

The references cited above are:

[1] C. Hansch and T. Fujita, ρ-σ-π Analysis. A method for the correlation of biological activity and chemical structure. *J. Am. Chem. Soc*. 86 (1964) 1616-`626.

[2] R. Todeschini and V. Consonni, *Handbook of Molecular Descriptors* (Methods and Principles in Medicinal Chemistry, Vol. 11, R. Mannhold, H. Kubinyi, H. Timmerman, Eds.) Wiley-VCH: Weinheim, 2000

[3] R. Todescini, Program DRAGON; www.disat.unimib.it/chm/Dragon.htm.

[4] J. G. Topliss and R. J. Costello, Chance correlations in structure-activity studies using multiple regression analysis, *J. Med. Chem*. 15 (1972) 1066-1068.

This is, of course, not the first time that Kubinyi and such people complain about "artificial" molecular descriptors, which, according to them, lack physico-chemical interpretation. What apparently bothered Kubinyi and such is that their preferred "physico-chemical parameters, log P or π, σ, MR etc." have been in "thousands" of correlations supplemented or replaced by alternative structural and mathematical descriptors – the success of which they cannot deny and as a measure of desperation want to discredit – perhaps in a more "civilized" manner, in comparison to the language of S. Unger and S. Wold used 30 years ago. But where are the arguments to "hand-waving" accusations of the literature being "spoiled" and "meaningless" correlations? I leave to statisticians, such as Hawkins, who has published a paper entitled: "QSAR with few

compounds and many features" [233], to respond to comments on "meaningless chance correlations" and use of regressions models with many descriptors (about which Kubinyi complains in the second paragraph of his article). But there are simple tests against chance correlations: One should randomize the input data (the property to be correlated) and use the same set of the descriptors and see if this leads to a good correlation – if it does that, this means that regression is over-fitted and is meaningless, but if it does not, the regression is meaningful, as is the case with at least hundreds of regressions using the connectivity indices (and I expect with others of the thousands allude to), that Kubinyi is trying to disqualify. I am confining attention to regressions using half a dozen descriptors or less (such as for instance generated by CODESSA [42] and similar software) – as I had no interest and have no experience with regression using large number of descriptors.

Intolerance manifests itself in different guises. One of these is the belief that the "reality" of chemical models has to have "physico-chemical" interpretation. Thus topological indices are "artificial" or "artifact," because at least most of them may lack a "physico-chemical" interpretation. But the same is with most quantum chemical concepts, yet their "reality" has not been questioned. What is, for example "physico-chemical" interpretation of Kekulé valence structure? What is "physico-chemical" interpretation of "Configuration interaction"? What is "physico-chemical" interpretation of "maximum overlap hybridization" or "molecular orbitals"? All these concepts, including the widely accepted notion of bond dipoles, have a clear interpretation within the model in which they are used, be it VB model, MO model and even GT (Graph Theory) model. To insist that quantum chemical and graph theoretical concepts have to have "physico-chemical" interpretation is manifestation of science intolerance, or if you will, to use more updated political language, manifestation of science fundamentalism. This is, for instance, what Maksić, in the Prologue in book that he was editing "Atomic Hypothesis and the concept of molecular structure" stated about structure-property regressions:

"*Mathematical fitting of data without underlying physical picture is not a model because of the lack of interpretive ability . . . there is abundance of graph-theoretical indices which are purely mathematical constructions and yet they are correlated . . . with various molecular properties implicitly suggesting a deeper meaning of these indices than is justified*."

Justified by whom or by what? It appears that "the lack of interpretive ability" for physical chemists means "physico-chemical" interpretability and for quantum chemists means "quantum-chemical" interpretability – because they cannot *tolerate* the presence of chemical models which are neither physico-chemical nor quantum chemical. Graph theoretical indices should have structural and graph theoretical interpretability, most of which they have, and not physico-chemical and quantum chemical interpretability, which some may have but in general need not. Consider the case of Coulson bond orders [234] and Pauling bond orders [235], both widely known and respected concepts of MO and VB quantum chemical models. Both these quantities are "purely mathematical constructions," in fact both are "pure graph theoretical" products but most quantum

chemists don't know it, don't want to know it, or don't want to hear it! Both are used for correlating with molecular properties (bond lengths) – and according to Maksić, such correlations do not support a "deeper meaning" for these quantities. The concept of "bond orders" extends beyond the initial HMO calculations and applies to Pariser-Parr-Pople (PPP) calculations and even more advanced computational models. For instance, one of the first research papers of this author [236] considered differences between Coulson bond orders and PPP bond orders (when this author was unaware of Graph Theory, though quantum chemical veterans like Klaus Ruedenberg and Hans Primas were aware that HMO structural matrix is the graph theoretical adjacency matrix). An interesting finding of my first research paper (which was outside the subject of my Ph. D. Thesis, which was on high resolution IR spectra, supervised by Norman Sheppard and submitted to Cambridge University in 1958) was that the difference between the two models in case of benzenoid hydrocarbons points to Fries structures [237], Kekulé valence structures with the maximal number of benzene rings having three CC double bonds, this connecting MO and VB models in an unexpected way. I may add here that there are other unexpected connections between VB and MO models, some known already in the time of HMO (like that the square root of the determinant of HMO matrix give the number of Kekulé valence structures of a benzenoid hydrocarbons), some not – and interested readers should consult a book of N. Trinajstić "*Chemical Graph Theory*" [238] for more details.

Speaking of this book, and in general on "reactions" of certain circles of physical chemists and medicinal chemists to Chemical Graph theory, it may be of interest to remind readers that the first edition of this book published in 1986 [239], which had two volumes, was well received in mathematical circles (see half a page book review this book of Mathematical Reviews [240]. This overview is complemented with a review of a book "*Mathematical and Computational Concepts in Chemistry"* [241] (edited by N. Trinajstić), which was written by Erkki Brändas [242], quantum chemists, and current editor of the *International Journal of Quantum Chemistry*. I have reproduced in Appendix 12 major part of his evaluation. Both mentioned reviews on books on Chemical Graph theory have been written over 20 years ago – but "critics" of topological indices and numerous other concepts of chemical graph theory are apparently dismissing views that may question their anti-graph campaign. Both views are of interest because they came outside the circle of chemical graph theorists, and are thus are more likely to be balanced. The excerpts from the review of Errki Brändas have been included here in particular, not as an attempt to change the views of Maksić, Unger, Wold and such but to change views of people who have been mislead, people who have been listening to false prophets, like Maksić, Unger, Wold and such. The positive views on Chemical Graph Theory by mathematicians and isolated quantum chemists mentioned in this article, may also help chemists, who by being themselves uniformed of the subject, may have taken seriously for too long those who should have not been taken seriously. Unfortunately, many of those have apparently forgotten about benefits and the practice of listening to one side only. If they want to be serious about their "scientific health" they better seek a "second" opinion and listen to specialists who may have alternative explanations.

If this is not enough of "independent views" I can direct readers to a five page article by Jeffrey L. Fox [243]: "Use of Mathematical Tool in Chemistry Yield Insights" with subtitle: "Chemists are using topology and graph theory to classify molecules and their properties and to describe molecular structures and reaction paths," which appeared in *Chemical & Engineering News*, a chemistry journal with over 100,000 subscribers. The article gives a report on a symposium "Chemical Applications of Topology and Graph Theory, organized by Professor R. Bruce King of University of Georgia, Athens and sponsored by the Office of Naval Research of Washington, D. C. The article even depicts my figure of the central part of the "monster graph" (representing degenerate rearrangement of bullvalene $C_{10}H_{10}$). In Appendix 13 I reproduced a small part of this article, which represents a small fraction of the whole "movement" of applying Discrete Mathematics to chemistry. Let me cite here the last paragraph of the article of Fox:

The whole movement, according to Yale University chemistry professor Oktay Sinanoğlu, another participant at the University of Georgia conference, "is perhaps a watershed for practicing chemistry more rationally, applicable to all the chemists out there working with test tubes."

It would be amusing were it not damaging that Chemical Graph Theory, which is about *rational* approach to chemistry – is receiving so intense *irrational* reception in some circles of self-imposed "guardians of rational science."

I have been concerned with continuous attempts to misrepresent mathematical invariants of molecular structure or molecular graph as "artificial" parameters, implying thus presumably lack of their connection to the "real world" (the phrase which is often on the lips of the "invisible enemies" of Chemical Graph Theory). But let us turn to another aspect of "interpretations" of chemical models that tends to be overlooked (deliberately?). Consider the "classical" physico-chemical parameters of the Hansch QSAR – which uses as molecular descriptors the already mentioned log P or π, σ, MR etc., molecular properties. What do properties say about molecular structure of compounds considered? Not much, because they are properties of a structure – and as a consequence QSAR, quantitative structure-activity relationship is, to say the least, an illustration of language misuse. This was OK some 30-40 years ago, when little was known of molecular structural parameters – mathematical invariants of chemical structures – but today the use of label QSAR for Hansch-type approach is an anachronism, which should be tolerated merely on historical grounds. To "preach," by Kubinyi, Taylor and such, that this is the only theoretical approach that will lead to meaningful regressions is an illustration of a narrow view on science by those who expect that everyone should follow in their own footsteps and do not tolerate the sounds coming from people who hear "different drummers." This may remind us of one of the quotes of E. B. Wilson to be found in his "*Introduction to Scientific Research* [17]:

No one can be so obstructive of progress as the "expert" who has worked all his life on a single subject.

I should add here that Corwin Hansch, the "father" of the "Hansch Approach" himself has a much broader outlook on QSAR than some of his zealous followers. This is what

he stated in one of his review articles [244]: Towards a deeper understanding of chemico-biological interactions" concerning molecular descriptors used in QSAR:

"*At present two broad approaches to QSAR are evolving. One is the "traditional" method using experimental parameters for substituent effects; that is, Hammett constant (and sometime MO parameters] for electronic effects, molar refraction, molar volume or Verloop et al., sterimol parameters (or ES) for steric effects, topological indices and partition coefficients first used by Meyer and Overton for hydrophobic interactions . . . The alternative approaches are with parameters, which provide one with little insight in terms of chemical thinking as we know it*."

Because of the complexity of chemico-biological interactions it appears prudent to follow Hansch advice and approach, and combine the use of experimental parameters (such as Hammett constant, molar refraction and molar volume, geometrical parameters (sterimol parameters or ES), quantum chemical parameters (some MO parameters, like HOMO-LUMO separations), physical chemistry parameters (partition coefficients) and graph theoretical parameters (topological indices) – but who is listening?

Apparently there are critics of the connectivity index and hundreds of other topological and topographic molecular descriptors who are "obsessed" with the lack of physico-chemical meaning of various topological indices – as if molecular descriptors have to have physico-chemical meaning! They do not, but some may. What they have to have – is some useful structural interpretation – and while some have, the full interpretation of some may still be obscured. Recently Randić and Zupan have addressed this issue and suggested a general approach for interpretation of some less "transparent" topological indices [245, 246]. They described a somewhat general approach how can various topological indices be partitioned to bond contributions. However there are alternative interpretations worth consulting. For example, the connectivity index χ has been interpreted in terms of the accessibility of individual atoms [247, 248]

We should add that while an interpretation of molecular descriptors may in some cases be difficult, this is a lesser problem than the problem of interpretation of the regression equations, whether it is of Hansch-type, based on quantum chemical descriptors, based on topological indices, or combinations of all of these. The difficulty here results from mutual correlation of descriptors, which cause the well-known instability of the regression equations with introduction of additional descriptors. It was pointed out that a way out of this quagmire is to orthogonalize molecular descriptors before constructing the regression equation [249, 250], to use stepwise regression accompanied with extraction of correct coefficients [251, 252], or to apply retro-regression [253, 254]. The tool has been available for some time – but apparently too few are taking advantage of it. As Roald Hoffmann has pointed out some time ago [255] (reflecting on theoretical computations, which equally applies to QSAR):

In many interesting areas of chemistry we are approaching predictability, but . . . I would claim, not understanding.

Understanding the connectivity indices, the variable connectivity indices, topological indices in general, and Chemical Graph Theory, may require not only willingness to accept this area of theoretical chemistry as legitimate, and some imagination, but also some knowledge of Discrete Mathematics, which most theoretical chemists and physical chemists lack. This ignorance, combined by arrogance and intolerance has produced views on connectivity indices, and Chemical Graph Theory in general, which border with tragic-comical opinions of "critics" that they cannot see just as color-blind people cannot see colors. As Professor Lynn Margulis has said: *Opinions aren't science*. There is one more thing that these critics cannot see and that is that their views are irrelevant for Chemical Graph Theory. Among those applying Graph Theory to chemistry these self proclaimed "experts" on Chemical Graph Theory, a subject that they never contributed to, or to say the least, never studied and never even had introductory books in hand, are ignored. Their opinions may be important to them and those like them, but outside their narrow circles are fully ignored today, will be ignored in the future, as they have been ignored in the past 30 years. And here is a question for them: How would they go around screening of virtual libraries without "artificial" descriptors?

Let me return to the remark "***the literature is now spoiled with, most probably, thousands of meaningless chance correlations***." If that is the case I wonder whether a thought may have occurred to these skeptical pundits that perhaps the correlations are not chance and not meaningless but that they cannot capture the meaning and understanding of what is going on there. How much one can understand of anything often may depend on how much background information one was able to grasp on the subject considered. With a widespread misunderstanding of Graph Theory among chemists, one should expect a widespread misunderstanding of the connectivity index (which has even entered an elementary topology book (see Appendix 4), and widespread misunderstanding of the rest of Chemical Graph Theory – the opposite would be miracle. Thus the level of understanding depends on the amount of time one spends in learning about the subject. Some obviously think that they know graph theory without learning – but at best they may know something about graphs, not Graph Theory. We have seen chemists who do not know the difference between "graphical" and "graph theoretical!" All this will be clearer if instead of learning science one speaks of learning languages. For example, in my case, I understand Russian, almost being fluent (and reading Solzhenitsyn and my favorite Chekhov in original); I know some German and can read technical material without consulting dictionaries. I even understand a little of Italian, but have to admit that I am ignorant of French (accept to the degree that French overlaps with English, or I should say more correctly, the opposite, how much English overlaps with French). There is some explanation about my language abilities, or better said inabilities. I have been six months under Mussolini (in 1941 while living in Split, part of Croatia which was under Italian occupation), then I was four years in part of Croatia that was under Hitler (and his cronies, while living in Zagreb), to the end after WWII with some 25 years indirectly under Stalin and Russian influence (even though Tito managed gradually to dissociate Yugoslavia of Soviet domination) – but I am afraid, Napoleon was not in my time, which may explain my lack of French acquaintance.

Well, the same is with Chemical Graph Theory. If you spent six months with it you will know little, if you spent four years, you will be able to follow most of technical stuff, but it takes 25 years before you will be fluent with Chemical Graph Theory – hence either start get engaged or shut up (for your own benefit)! The fuss that has been going on about topological indices could have been raised about most quantum chemical non-observables, such as Coulson and Pauling bond orders, molecular orbitals, hybridization, resonance energies etc. etc. – but it was not, because these non-observables are "dressed" in the respectable language (model) of quantum chemistry, while connectivity indices, Wiener number, Hosoya Z index, molecular ID numbers, conjugated circuits, π-electron ring partitions [256] are "dressed" in "foreign" language for most chemists. From mathematical points of view there is no difference between the two – both are just illustration of mathematical *invariants* of chemical structure. Most (but not all) quantum chemical non-observables are invariants of Calculus, while most (but not all) graph theoretical non-observables are invariants of Discrete Mathematics. So before one wants to criticize a message in a foreign language shouldn't one first learn the language? And just as there are occasional overlaps of different languages so there are occasional overlaps not only between different branches of theoretical chemistry, like MO, VB and GT illustrated in Fig. 3 but also between Theoretical Chemistry, Physical Chemistry and even Medicinal Chemistry.

Consider, for example, the case of ^{13}C Chemical Shift Sums [257]. Chemical shifts are highly important NMR experimental quantities that tell much about an immediate local atomic environment and is an extremely valuable tool used in particular by synthetic organic chemists for identification of molecular structures, products and by-products of chemical reactions. Clearly they qualify as "atomic" properties of a molecule, but if one adds chemical shifts for all atoms in a molecule one formally obtains an NMR "molecular" property. That would appear to be a trivial result and hardly worth comments were it not that graph theoretical analysis of ^{13}C Chemical Shift Sums in alkanes had not shown important regularities in chemical shift sums: Chemical shift sums show a regular increase with the increase in the number of paths of length two and paths of length three [258].

Paths as elementary structural parameters have been advocated by Platt over 50 years ago [259] but have been mostly overlooked till the revival of Chemical Graph Theory in early 1970s. As Randić and Wilkins [260, 261] have demonstrated among alkane isomers (already in 1979), most physicochemical molecular properties (boiling points, heats of formation, heats of atomization, molar volumes, entropy, density, etc.,) show regularity, the increase or decrease of their magnitudes with increase or decrease of the paths of length two and length three (isomers, of course have all the same number of paths of length one, that is bonds). So is the ^{13}C Chemical Shift Sum of a molecule a physico-chemical property or a graph theoretical property?

The above mentioned regularities in variations of a collection of physico-chemical properties of isomers with the number of paths p_2 and p_3 confirm the sound intuition of Platt [259] regarding path numbers as potentially useful molecular descriptors and justify referring to path numbers of molecules as "God Given" names for molecule (see Table 3

for illustration). Along those lines, I can then refer to my "shape" molecular descriptors [262], which lead to amazingly satisfactory regressions for numerous properties of octane isomers (see Table 4), which are given as the quotient of the path numbers and walk numbers, as being the result of "divine" inspiration.

Table 4 Dozen physico-chemical properties of octanes correlated against "atomic" and "molecular" shape indices

	Atomic		Molecular	
Property	Regression coefficient	Standard error	Regression coefficient	Standard error
steric	0.9781	0.394	0.9729	0.438
Boiling points	0.9141	5.45	0.9340	2.33
Entropy	0.9503	1.50	0.9541	1.57
DH	0.9542	0.123	0.9899	0.078
R^2	0.8538	0.100	0.8547	0.100
density	0.9908	0.0017	0.9887	0.0018
Heat of vapor.	0.9520	0.660	0.9705	0.520
Critical temperature	0.9098	3.88	0.9039	4.00
Critical pressure	0.9868	0.208	0.9840	0.229
^{13}C Sums	0.9115	8.17	0.9685	4.95
Acentric	0.9197	0.013	0.9879	0.005
Molar refraction	0.9948	0.020	0.9927	0.024

Good Editors – Bad Editors

What is the difference between good editors and bad editors? Good editors ask questions and facilitate exchange of conflicting views between reviewers and reviewers and authors. For example, Bill Milne would send to reviewers the views of other referees involved as well as his decision concerning accepting or rejecting an article. In this way an incompetent referee can see that other experts involved disagree with him, and this may help him/her to correct his deficiencies. By contrast, here is an illustration of an attitude, which I would characterize as "bad editorial attitude," as written in a letter of 17th June 1980 by D. A. Young, Editor of *Faraday Transactions*:

Professor M. Randic
Ames Laboratory – U. S.
Department of Energy
Iowa State University
Ames
Iowa 50011
U. S. A.

Dear Professor Randic.

Paper No. 0/653

Thank you for your letter, I quite understand that you are chagrined by my apparent inability to quote chapter and verse for the reasons why we cannot accept your paper, However, in order to obtain advice at all on graph-theoretical papers I have to approach individual scientists on a personal basis, when their opinions are given informally and must remain confidential.

The very strong trend of opinion against graph theoretical papers appearing in chemical journals is manifested to me in a continuous series of refusals even to referee papers in this subject. Since my colleagues in physical chemistry and chemical physics are not even prepared to read papers seriously it is, I fear, quite out of order for me to accept them.

In the circumstances it would perhaps be best if you were to turn your attention to journals of mathematical methods or theoretical chemistry per se.

Yours sincerely,

D. A. Young
Editor
Faraday Transactions

First observe that the editor is not hostile to graph-theoretical papers, but his advisors are! He is in effect in a difficult situation, but he opts for a way out that does not help authors. This situation can be compared with a similar situation that faced Professor Božo Težak, the Editor of *Croatica Chemica Acta*, in mid 1960's. He had a manuscript at hand in the area of colloid science (written by his colleague Professor Mirnik) that several referees refused to review. One of the reviewers, while refusing to review the article, indicated that if the article is to be published he is willing to send his comment expressing contrary views. This was just about the time that I was going for a visit to Sheffield University (to collaborate with Professor J. N. Murrell), so Professor Težak, asked if I could consult someone in England to see how should he proceed with this matter. Observe manners of good editors, here Professor Težak – they don't make decisions lightly, they asking questions. On my arrival in Sheffield I contacted Professor Hojtink, the first editor of the now well-known journal *Chemical Physics Letters*, and

explained the situation. Professor Hojtink had no hesitations at all to tell me that the paper should be published, regardless whether or not it will be followed by comments of others.

I feel the same policy should apply to *Faraday Transactions* or any other journal in similar situation. If critics, who are protected as reviewers by remaining anonymous, cannot even "quote chapter and verse" then there is "something rotten in the state of Denmark! Scientist have right to refuse to review papers, but should state their reasons, otherwise refusal is tantamount to boycott. If those who are ready to boycott research of others cannot articulate their reasons they deserve to be ignored, and not those they boycott against.

Consider another letter, written to the Editor of *Molecular Physics* which precedes the above letter by 15 years, and deserves a short comment:

Professor I. M. Mills,
Editor: Molecular Physics,
Department of Chemistry,
University of Reading,
Reading RG6 2AD

18th September 1974

Dear Ian

M. P. 4. 9/276

I am unenthusiastic about the application of graph theory to conjugated hydrocarbons. I have not yet seen a publication on this subject which has increased chemical knowledge so that perhaps the first point that might be made to Milan Randic is that we would not like Molecular Physics to be the accepted depository of papers on graph theory.

Regarding the present paper, I found it very readable and dealing with an interesting intellectual question. Notwithstanding my previous comments I am therefore going to recommend it for publication as I believe that many readers of Molecular Physics would enjoy it.

I had the opportunity last year of hearing a lecture from one of the authors and he led me to believe that most developments in graph theory at the present time were being carried out by chemists, so I am recommending the paper on the assumption that the work has not been published by mathematicians in a journal unfamiliar to me

Yours sincerely,

The manuscript was about isospectral graphs. From the letter apparently an anonymous reviewer identifies graph theory with HMO – just as others did at that time

and some, including Maksić, do still today. The reviewer is unenthusiastic about re-visitation of the Hückel MO from the graph theoretical standpoints – and he/she is entitled to his/her views and opinions. While there may be some who may have different opinions, he speaks "we would not like." Hence, there is a conspiracy! Such attitudes can be contrasted to those who do not necessarily share such limited approach to science. For example, compare the above with the statement of legendary physicist Richard P. Feynman (1918-1988) [263]:

"*The formulation is mathematically equivalent to the more usual formulation. There are therefore, no fundamentally new results. However, there is a pleasure in recognizing old things from a new point of view*."

And this is precisely what was going on with the application of Graph Theory to Benzenoid Hydrocarbons at that time. I should add that "a new point of view" has also brought some new insights that have been overlooked during the time of dominance of the HMO model in quantum chemistry. In 1973 (just about the time the letter was written) T. Živković identified 1,4-divinylbenzene and 2-phenybutadiene as isospectral, that is, that they have all eigenvaleus of HMO identical [264]. It was unheard of before that two molecules can have identical eigenvalues. Živković found this by browsing through the widely available book of C. A. Coulson and A. Streitwieser, Jr.: "*Dictionary of π-Electron Calculations*" [265]. This "bible" book was available for full eight years – without any one else noticing it!

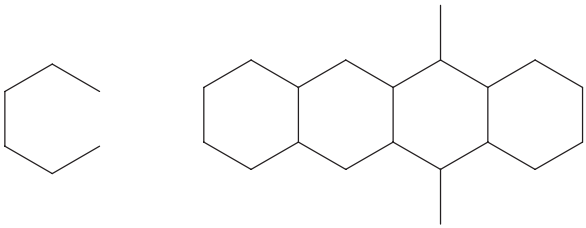


Fig. 9 Illustration of subspectral graphs: All the (HMO) eigenvalues of smaller graph (hexatriene, at the left) are contained in the set of the eigenvalues of the larger graph (tetracene derivative, at the right). Why?

The Graph Theoretical approach to HMO clarified few additional characteristics of Hückel MO calculations, such as the occurrence of high degeneracy of certain eigenvalues that could not be attributed to molecular symmetry, or the occurrence of common eigenvalues in different molecular systems. Consider, for illustration the two conjugated hydrocarbons of Fig. 9 [266-268]. One may refer to them as a subspectral pair, because one finds that the all the HMO eigenvalues of the smaller molecules are

also the eigenvalues of the larger molecule. Why? Early Quantum Chemistry was not even aware of such situations and does not offer answers. You can challenge your quantum chemist colleagues with this problem as an intellectual exercise (in view that HMO is today of limited interest). I doubt that those not familiar with Graph Theory will make any progress in answering the question, and if they do – most likely they will be applying graph theoretical approaches without knowing it.

Much of the present misconceptions about Chemical Graph Theory, and other "unpopular" subjects such as was the case with DFT (density functional theory), could be resolved with adequate Editors - Reviewers - Authors interactions. The present misconceptions about Chemical Graph Theory will continue to be perpetuated with a lack of Editors - Reviewers – Authors dialog. Since Editors have here initiative and the leading role they are responsible for the dialog. On that outcome it is not difficult to evaluate editors as "outstanding," "good," "not so good," bad" and "very bad." Recently, one of my papers was evaluated "acceptable" by one reviewer, according to the second reviewer it needing a "minor revision," while the third reviewer, in choosing between "major revision" and "rejection" was "leaning to rejection." The Editor, without waiting a response from authors sided with the third reviewer and requested "major revisions," which will require the manuscript to be submitted for subsequent re-evaluation. In contrast another Editor of the same journal (*JCICS*), Wendy Warr, was in a similar situation with two reports, one in favor and the other against. She contacted the two reviewers (I was one in favor), sent them both reviews, and asked for clarification and advice. That is what makes the difference between good editors and not so good editors, good editors ask questions and not so good editors are not asking questions.

I could continue with similar illustrations to justify my individual selection of "good" editors to whom this article is dedicated. For example, Professor Stout of the *Journal of Chemical Physics* has shown unusual patience (over a number of years in which I communicated with him) and was *responding* to questions and comments, while his successor was reversing his decision without ever explaining why in the first place an accepted paper needed to be re-evaluated. Authors, just as referees, need sometime some protection. Professor Hancock of *Journal of Proteome Research* (impact factor around 7.0) is to be commended on that count. I have been recently very disappointed with an evaluation of my paper in which I described a totally new approach to the problem of protein alignment (which is customarily dealt by use of available computer software). I have described how this problem can be approaches purely graphically – and to my amazement received a report that there is nothing new in the manuscript! I have reacted in my response to the reviewer with strong words, but the Editor returned my response and asked that I confine response to answering point-by-point to the objections of the reviewer. After "cooling down" and some reflection I realized that this is the right and pragmatic approach. My expressed views on lack of reviewers competence need not be explicitly stated, they may be "hidden" in my point-by-point response to his/her objections. After my response the paper was accepted, but when the referee continued to insist debating some issues, my answers to his request "to continue the dialog" was to withdraw the article already accepted, which was sent to Journal of Mathematical Chemistry, where it will appear. I do not wish to continue a dialog with an anonymous

scientist – he/she should wait till the paper is published and then raise questions and continue the dialog.

Another similar incident I had recently with a related short paper on an alternative graphical representation of proteins that I submitted to *Chemical Physics Letters*. Having a fresh lesson from the *Journal of Proteome Research*, this time when I received a very negative opinion of a reviewer, who was essentially complained of seeing some 70 papers of this kind in the literature (papers on graphical and numerical characterization of DNA, proteins, and proteomics maps) in which "there is no biology," I decided to immediately withdraw the paper. It would be waste of time to argue with reviewer about his limitations. Moreover, why should I spend my time to educate an anonymous and hostile scientist? What for? However, because the "attack" was on a broader area of bioinformatics in which other people (with some of whom I collaborate) were involved, I felt obliged to explain to the Editor my reasons for withdrawing the article. I wrote a letter to the Editor of *Chemical Physics Letters* (Professor J. Clary) to point to gross misrepresentations and misinformation that this reviewer is spreading about this kind of work. The anonymous reviewer obviously does not like that mathematics enters biology, despite that it did over 50 years ago with the pioneering work of Nicolás Rashevsky [269, 270]). Shortly afterwards sending my letter I got a message from Professor Clary secretary, asking me to reconsider withdrawal and return the manuscript, which will be sent to another reviewer, what I did. Editors at large should balance views of *their* reviewers and the views of *their* authors – as J. Clary did. Professor Parr, when retiring as the editor for theoretical chemistry papers for the *Journal of American Chemical Society*, mentioned in his letter to a pool of 600 people who helped him over years with evaluation of papers, that it is a lesser mistake to publish a mediocre article than not published exceptional work. This attitude is a sign of good editorship!

I could continue with illustrations of good editorship for all good editors to whom this article has been dedicated but I have to apologize to other good editors to whom this article has been dedicated who have not been here mentioned in person. I also have to heed to the advice of the good editor of this journal, Ivan Gutman, to keep the article short, if possible.

The final comment on bad editors is the *bias* of their editorial attitude to some fragments of science, like Chemical Graph Theory. This bias is evident from the editorial "alert" sent to reviewers about graph theoretical manuscripts submitted to the *Journal of Chemical Information and Computer Science* (see Appendix 13). Do they send similar "Alerts" when manuscripts from other branches of theoretical chemistry are considered? This particular "Alert" implies that hitherto published papers in this journal in the area of graph theory should have not be published. If that is so, in the tradition of "one is innocent until proven guilty" I demand that editors (with help of their advisors if necessary) make a list and point to individual graph theoretical publications that trivial and do not deserve to be published. To make their work easier they may start with my own publications in their journal, and if that is too much work, they may start with a single issue of their Journal (the issue of May-June 2001, in which I have published 13 papers, as contributions from lectures and posters at the Second Indo-U. S. Workshop on

Mathematical Chemistry, Duluth, MN, May 2000) if my work in Chemical Graph Theory induces them to write their "Alert." I have my reasons to published 13 papers in a single issue of a journal, just as Joseph Michel has his reasons (which he told me) for publishing 18 papers in a single issue of the *Journal of American Chemical Society* some years ago, but this is not the place to elaborate. I only want to add an observation: Soon after publishing his 18 papers Joseph Michel was promoted to be Editor of Chemical Reviews (impact factor around 22), but soon after I published my 13 papers in the *Journal of Chemical Information and Computer Science* Editors of that journals were issuing their "Alerts" about their policy to prevent mediocre Chemical Graph Theoretical papers! One does not issue an "Alert" if a single "bad" paper appears in a journal. If numerous graph theoretical papers hitherto published in JCICS are *mediocre* than Editors have to point to such papers and tells us what is wrong with them – and if they cannot that Editors judgment about graph theoretical papers is *mediocre* and not graph theoretical papers! Which is the case?

To circulate an "Alert" that insinuates that graph-theoretical papers have not been "truly innovative," may lack "unique ideas and thus could not make major advance in graph theory applied to chemical systems" by those who have no formal education in Discrete Mathematics" is to say the least – preposterous. To continue and claim that so far published graph theoretical modeling in chemistry "have not used graph theory to make large scientific advancement" implies that all other "non-graph theoretical" papers published in JCICS have produced "large scientific advancement." I challenge the Editors of JCICS to come out and tell us which "non-graph theoretical" paper published in JCICS made which "large scientific advancement." Science progresses most of the time in small steps - "large scientific advancement" are occurring, are rare, and are usually recognized by Nobel Prize!

The insinuations stated in the "Alert" are serious accusations, undocumented and anonymous! According to my Roget's Thesaurus [271] "insinuate refers to conveying something, usually unpleasant, in a covert manner that suggest underhandedness" and that is what this "Alert" is. And to make sure that I am not misusing words I consulted another dictionary [272] to verify my feelings about "underhandedness" as being something sinister I found that adjective "underhand" stands for "**secret and dishonest** done secretively and dishonestly or with the intention to deceive and cheat somebody." That they went about this "Alert" in secrecy is clear, since authors have not been alerted to this neither before submitting manuscripts nor after papers being accepted or rejected. It is not clear whom they wanted to deceive and cheat – except themselves! The "alert" is also pretentious in assuming that reviewers (particularly those outside the community of Chemical Graph theory) are competent to discern "major advances in graph theory applied to chemical systems." If that is the case, if they have those abilities, they should have been long ago part of Chemical Graph Theory community! "Alert" is just an additional illustration of lack of understanding of Graph Theory by those who think that they know but don't know that they do not know and is merely an illustration of an additional editorial propaganda.

I challenge readers, reviewers and editors of JCICS and JCIM to point out which are those "bad papers" that apparently have appeared in their journal and have caused them to issue the "alert" against graph theoretical contributions submitted to their journal. As I said, clearly this could not be a single paper and a single author, but even if that would be the case, speak up, let everyone know what is wrong with such papers, be it a single paper of many. I recall many years back an incident, when a quantum chemical paper was published in *J. Chemical Physics* which was erroneous. More than a dozen readers who recognized the mistake of the author wrote to the Editor. The editor then combined their response into a single multi-author "Letter to the Editor," which appeared in the following issues of *J. Chemical Physics*. Let aside that in this particular case it was the reviewer of the journal who failed miserably, not the young author, who in trying a novel type of wavefunction made a numerical error, which was not difficult to detect by others. Unfortunately he applied his "trial" wavefunction to a case for which the exact solution was known – and he did not reproduce it. From this incident we see, besides learning of an incompetent reviewer, that when wrong and unworthy result is reported in a scientific journal there are routes to correct the situation without need to initiate secretive editorial "alerts." Those (including editors) who detected a "misuse" of a journal, that is articles reporting "trivial" results, lacking novelty and fresh ideas, or lacking applicability to chemical problems, etc. should write a Letter to the Editor, or a full article if necessary and tell the readers (not the Editors) what is wrong or why the particular publication should have not been published. If readers (and that includes reviewers and editors) cannot or are not willing to comment in public (on what is already by being published a public knowledge), then Editors should not take sides, even less "develop" new editorial policy. Will we ever hear on what grounds, whose initiative, and what scientific findings has such new policy been installed? This "Alert" of the Editorial Board of *JCICS* should have been published in the journal, and after hearing views of those concerned, should have been withdrawn with apology to readers and in particular to Chemical Graph Theory community.

May I add that one of my latest papers to be considered by JCICS, in the frenzy of anti-graph theoretical attitude of some circles around JCICS, was sent to six reviewers, two were in favor, four against. The paper was an elaboration of an interesting *graphical* approach of Klavžar at al., [273] to enumerate Clar's π-aromatic sextets [274] in cata-condensed benzenoids. As I already mentioned of the four reviewers who recommended rejection of the manuscript at least two did not know the difference between *graphical* and *graph theoretical*! This was apparent from their reports, when they stated that in view of the new JCICS policy on *graph theory* manuscript they think . . . . bla-bla-bla . . . . to reject the manuscript. Those accepting such unworthy reports (who may have been behind composing the JCICS "Alert") and could not detect the absurdity of mixing "graphical" with "graph theoretical" are also likely not to know the difference between the two. My paper will appear in coming issue of the *Journal of Mathematical Chemistry* (now in print [275]) and anyone interested can judge whether the particular article is *graphical* (as I claim) or *graph theoretical* (as claimed by those who do not know the difference between graphical and graph theoretical).

Apparently there are many chemists who have been overlooking the fact that **to know graphs is not to know graph theory** (this became one of my "quotes" from my collection of statements about the science and scientists [103]). But that there is a difference between knowing graphs and knowing graph theory chemists have been "alerted" exactly 30 years ago. Vlado Prelog, an outstanding organic chemist, graph theorist, and Nobel laureate, has written a Foreword for the first monograph on *Applications of Graph Theory to Chemistry*. I have reproduced the relevant portion of this Foreword in Appendix 14. This outstanding book, edited by Professor A. T. Balaban, has contributions from a dozen prominent chemists and mathematicians, and is still a good start to become better acquainted with Graph Theory and Chemical Graph Theory [276]. Despite all this there is a strange paradox about attitudes of many towards use of Graph Theory in chemistry:

Graph Theory is widely appreciated and widely acknowledged in physics;

Graph Theory is widely appreciated and widely acknowledged in biology;

But

Graph Theory is hardly appreciated and hardly acknowledged in certain established circles in chemistry.

Why?

Who is afraid of Graph Theory?

The problem is that part of the Chemical Establishment and a sizable group of quantum chemists and physical chemists lack basic education in Discrete Mathematics and are thus in no position to appreciate and acknowledge the role of Graph Theory in Chemistry. I am repeating what Professor E. Pretsch has said:

"You cannot convince an illiterate about the relevance of writing and in the same way you cannot persuade an innumerate about the relevance of counting."

The Establishment realizes that there is part of Theoretical Chemistry that is not under their "control." This they then interpret (considering themselves to know all that is worth knowing in Theoretical Chemistry) to mean not to be important for "solving problems in chemistry" (to use the phrase from the *JCICS* editorial "Alert). I recall years back a comment made to me by the late Mike Zerner (at the time one of the editors of the *International Journal of Quantum Chemistry*) about graph theoretical papers submitted to that journal: "Milan, you in graph theory are all refereeing papers of each other." "Yes, I replied, so are you in quantum chemistry." – And that is how it should be. The idea that JICSC tried to promote that people *outside* graph theory should review papers on graph theory is – to say the least – unprofessional! It would be the same as giving manuscripts on organic synthesis to inorganic chemists, but with the distinction that most inorganic chemists know that they are not competent to evaluate work on complex organic synthetic reactions, allowing, of course for exceptions. One such exception, of course, is Roald Hoffmann, whose Nobel Lecture had the title: "Building Bridges between

inorganic and organic chemistry" [277]. Just as most inorganic chemists are unaware of details of organic chemistry multi-step synthetic routes to be able to evaluate and offer useful comments to such manuscripts of organic chemistry, most quantum chemists and other "outsiders" of Chemical Graph Theory are not aware of subtleties of chemical graph theory to be able to evaluate and offer useful comments to such manuscripts. To make it worse, they are not aware that they are not competent to evaluate manuscripts on application of graph theory to chemistry.

It is not surprising that editors of some journals have had difficulties to find reviewers for papers on chemical graph theory, because, being themselves unfamiliar with the subject, they do not know whom to ask for advice. When many years back I had a problem with the rejection of my paper on symmetry of graphs by the *Journal of Chemical Physics* I easily found about 20 chemists and mathematicians who responded to my concerns, because I knew whom to ask. Those writing the "Alert" on Graph Theory obviously did not want to ask those who know better, which in itself is symptomatic. There have been more than a dozen leading authorities in chemical graph theory on the editorial board of *JCICS* over its past 20 years! Why not ask them? Why not open a public debate on this issue? Why not have a special conference and invite those who are pro and those who are contra to as dialog? The least that can be done is to open pages of *JCICS* to a "paper" conference on the topic – that would allow everyone to participate in the debate without incurring expenses. But the alternative, to ask those who are outside the area of Chemical Graph Theory for evaluation of works in the field for which they lack often the most basic education is – non-professional, non scientific and bound to fail. As Sigmund Freud (1856-1939) has said:

"*The voice of intellect is a soft one, but it does not rest until it has gained a hearing. Ultimately, after endless rebuffs, it succeeds. This is one of the few points in which one may be optimistic about the future of mankind*."

My voice may to some appear not soft enough, but let me assure everybody that in comparison to the damage, humiliation, suffering, pain, distress, hinder, impediment, frustration, obstructions, and anguish, accompanied with a lack of support for research, and all this extending over three decades, with no of yielding, let me assure you that my voice has been too soft.

The time for action is now – either one follows those who do not know that they don't know (and who are for the most part anonymous to the general chemistry public) or one follows the pioneers and the masters of chemical graph theory – who are well known and have been mentioned and indicated directly or indirectly in this article, enough to be identified. The outcome is predictable, and has been spelled out some 2500 years ago by Confucius (Chinese philosopher, moralist, administrator and social reformer, around 551 – 479 B. C):

Who does not know, and does not know that he does not know
Is dangerous, avoid such

Who does not know, and knows that he does not know
Is child, teach such

Who knows, and does not know that he knows
Sleeps, awake such

Who knows, and knows that he knows
Is wise, follow such.

We started this review with a quote of Joseph O. Hirshfelder [1] and we will end with an up-date on the very same quote, which shows how little has changed in theoretical chemistry during the past 20 years:

> "*Unfortunately, now there are too few theoretical chemists with sufficient vision to take a giant step of exploring completely new techniques. Instead, scientists in the 21st millennium get so immersed in a maze of computational detail that they lose sight of the simple, elegant theories*."

Perhaps some may have forgotten that:

Theoretical Chemistry includes and goes beyond the Quantum Chemistry;

Quantum Chemistry includes and goes beyond the Study of Molecules;

Study of Molecules includes and goes beyond the Chemical Bonding; and

Chemical Bonding includes and goes beyond the Molecular Orbitals.

Returning back to the main theme of this article – the connectivity index χ – let me mention that this index, which has attracted unprecedented attention in the structure-property-activity community, has also attracted considerable attention in mathematical community, as witnessed by the recent book of Li and I. Gutman, *Mathematical Aspects of Randic-Type Molecular Structure Descriptors* [66]. The interested readers can find there an extended bibliography on *Randic-type* indices. The current interest in explorations of mathematical properties of this index and its derivatives (see Table 1) continue to flourish at considerable pace that may render the book of Li and Gutman prematurely to "old" and in a need to be up-dated. Here we end with listing 37 mathematical references on Randic-type indices [352-388], that appeared in 2005 and after. They include over 40 mathematicians as authors and co-authors, and their articles may be viewed as the first "up-date" of the bibliography of the book of Li and Gutman. I am grateful to Professor I. Gutman for sending me this latest list of mathematical publications on the Randic-type indices.

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Appendix 1 List of persons to whom various graph theoretical papers of mine have been dedicated

Person	**Dedication**	**Year**	**Ref.**
Vladimir Prelog	Dedicated to Professor Vladimir Prelog	1977	278
Vladimir Prelog	Dedicated to Professor Vladimir Prelog	1979	279
Eric Clar	Dedicated to Professor Eric Clar, doyen of benzenoid chemistry, whose work inspired much of the recent graph theoretical interest in aromaticity	1980	280
Linus Pauling	This paper is dedicated to Professor Linus Pauling	1980	281
Jeremy Musher	Dedicated to the memory of Jeremy Musher	1980	282
Alexandru T. Balaban	Dedicated to Professor A. T. Balaban for his pioneering work in reviving interest in chemical graph theory	1980	283
Oskar E. Polansky	Dedicated to Professor Oskar E. Polansky on the occasion of his 60^{th} birthday	1980	284
Oskar E. Polansky	Dedicated to Professor Oskar E. Polansky for his enthusiastic support, participation, and promotion of chemical graph theory at the times an understanding is decisive	1981	285
Charles A. Coulson	Dedicated to the memory of Charles A. Coulson who appreciated the role of graph theory in chemistry and made contribution to the field at the time most of us were unaware of graph theory	1982	286
John R. Platt	Dedicated to professor J. R. Platt for his pioneering insights into the significance of topological factors in molecular additivities	1983	287
Franz Sondheimer	This work is dedicated to the memory of Franz Sondheimer	1983	288
Per-Olov Löwdin	Dedicated to Quantum Encyclopeadist, Professor Per-Olov Löwdin	1984	289
Kurt Mislow	Dedicated to Professor Kurt Mislow of Princeton University	1985	290
Vladimir Prelog	Dedicated to Professor Vladimir Prelog on the occasion of his 80^{th} birthday	1986	291
Edgar Heilbronner	Dedicated to Professor Edgar Heilbronner in recognition of his work on the structure of topological MOs	1986	292
Massimo Simonetta	Dedicated to the memory of Professor Massimo Simonetta, an early contributor to Mathematical Chemistry	1986	293
F. Albert Cotton	This contribution is dedicated to Professor F. A. Cotton for his prolonged support and appreciation of chemical graph theory	1986	222

Corwin Hansch	This paper is dedicated to Prof. Corwin Hansch for his leading role in developing the discipline of QSAR	1986	294
Roald Hoffmann	This work is dedicated to Professor Roald Hoffmann for his many contributions in extending theoretical chemistry beyond H_2 molecule	1987	295
George W. Wheland	This contribution s dedicated to the memory of the late Professor George W. Wheland, a brilliant scientist who was prematurely incapacitated and deprived of the opportunities to elaborate on his many pioneering contributions	1987	296
Michael J. S. Dewar	Dedicated to Professor Michael J. S. Dewar on the occasion of his 70^{th} birthday	1987	297
Harry Wiener	Dedicated to Dr. Harry Wiener, a pioneer of graph-theoretical modeling of structure-property relationship	1987	298
Joseph O. Hirschfelder	Dedicated to Professor Emeritus Joseph O. Hirschfelder	1998	299
Basil E. Gillam	Dedicated to Basil E. Gillam, Professor Emeritus of the Department of mathematics and Computer Science at Drake University	1988	300
Bernard Pullman	Dedicated to Professor Bernard Pullman	1988	301
W. J. Orville-Thomas	Dedicated to Professor W. J. Orville-Thomas, who has always been a great supporter of mathematical chemistry	1989	302
Melwyn S. Newman	This paper is dedicated to Professor Emeritus Melwyn S. Newman, the founder of helicene chemistry	1989	303
Herbert Hauptman	Dedicated to Herbert Hauptman (Nobel Prize in Chemistry, 1985) for making mathematical chemistry visible	1990	304
Dušan Hadži	This paper is dedicated to Professor Dušan Hadži from Boris Kidrič Institute in Ljubljana, Slovenia, Yugoslavia*	1991	116
R. W. Taft	This contribution is dedicated to Professor R. W. Taft	1991	305
Charles F. Wilcox	This work is dedicated to professor C. F. Wilcox, Jr. for his inspiring work in the chemistry of unusual conjugated hydrocarbons	1991	306
Denis H. Rouvray	Dedicated to Denis H. Rouvray, one of the foremost promoters of chemical graph theory	1991	307
Linus Pauling	Dedicated to Linus Pauling (Nobel Prize for Peace 1954 and Nobel Prize for Chemistry 1962) in appreciation of his outstanding contributions to structural chemistry and untiring efforts to end war	1992	308
Manfred Eigen	Dedicated to Professor Manfred Eigen (Nobel Laureate in Chemistry, 1967)	1992	309
Lemont B. Kier	This paper is dedicated to Professor L. B. Kier for his	1993	310

	untiring explorations of the use of the connectivity indices in structure-property-activity studies		
W. J. Orville-Thomas	We dedicate this paper to Professor W. J. Orville-Thomas, who founded the journal and has led it successfully through the Scyllas and Charybdises of editing a journal to this Golden Number	1993	311
Tibor Škerlak	In memory of Professor T. Škerlak, University of Sarajevo (Department of Physical Chemistry), killed by sniper fire February 1993 in Sarajevo	1993	312
Frank Harary	Dedicated to dedicated graph theorist, Frank Harary, for his continuous promotion of graphs, graph theorems, graph enumerations, graph constructions, graph algorithms and graph applications	1993	267
Norman Sheppard	Dedicated to Professor Norman Sheppard, FRS, Norwich, East Anglia	1993	313
Yngve Öhrn	This article is dedicated to dedicate Swede, Professor Yngve Öhrn, who continues to enrich us with advances in mathematical physics and mathematical chemistry	1994	314
Harry W. Kroto	This paper is dedicated to Harry W. Kroto who dreamed the right structure at the right time!	1994	315
John A. Pople	Dedicated to John A. Pople, a builder of chemical models	1994	316
Tibor Škerlak	Dedicated to the memory of Professor Tibor Škerlak**	1994	317
Roald Hoffmann	Dedicated to Roald Hoffmann, whose theoretical rules are central to experimental chemistry	1995	318
George W. A. Milne	This contribution is dedicated to George W. A. Milne, the Editor of the Journal of Chemical Information and Computer Science, whose enthusiasm and professionalism has transformed a “peripheral” chemistry journal into one of the more highly visible chemical documents	1995	319
Douglas J. Klein	This paper is dedicated to Professor D. J. Klein (Texas A & M at Galveston), a pioneer of the overlapping areas of group theory, graph theory and quantum theory	1995	320
Alexandru T. Balaban	Dedicated to Professor A. T. Balaban (Bucharest), the winner of the ACS Division of Chemical Information 1994 Hermann Skolnik Award	1995	321
Norman Allinger	Dedicated to Norman S. Allinger, the Master of Molecular Mechanics	1995	322
Ronald C. Read	Dedicated to a leading graph theorist, Professor R. C. Read, for sharing his mathematical talents on chemical structures	1996	323
Stanko Borčić	Dedicated to the memory of Professor Stanko Borčić	1996	324

Marko Razinger	This paper is dedicated to the memory of Marko Razinger, a friend and colleague, whose death in July of this year was both unexpected and untimely.	1996	325
Nenad Trinajstić	This paper is dedicated to Professor Nenad Trinajstić who pioneered chemical studies using graph theory	1996	326
Haruo Hosoya	Dedicated to Professor Haruo Hosoya of Ochanomizu University, Tokyo, Japan, on the occasion of 25 years of the topological index Z	1996	327
Klaus Müllen	Dedicated to Professor Klaus Müllen, the pioneer of giant hydrocarbons	1997	328
Lionel Salem	Dedicated to Professor L. Salem	1997	329
Jean-Louis Calais	Dedicated to the memory of Jean-Louis Calais	1997	330
Jean-Louis Calais	In memory of Professor Jean-Louis Calais, the editor of *Int. J Quantum Chem*.	1997	331
Mrs. Per-Olov Löwdin	Dedicated to Mrs. Per-Olov Löwdin, gracious companion of the Sanibel Symposia	1997	332
Danail Bonchev	Dedicated to Danail Bonchev	1997	333
Norman March	Dedicated to Professor Norman March, an old friend of Mathematical Chemistry	1998	334
Maximilian Zander	This paper is dedicated to Professor Maximilian Zander in appreciation of his long-life devotion to chemistry of polycyclic aromatic compounds	1998	335
William C. Herndon	This paper is dedicated to Professor W. C. Herndon, one of the pioneers of chemical graph theory	1999	336
George G. Hall	Dedicated to Professor George G. Hall	1999	337
Ivar Ugi	Dedicated to Professor Ivar Ugi (München), a pioneer in Combinatorial Chemistry	2001	338
Robert S. Hansen	Dedicated to the memory of Professor Robert S. Hansen (1918-1998), former Director of Ames Laboratory, Ames, IA, gracious supporter of Chemical Graph Theory in the time of need	2001	339
Drago Kollar	This paper is dedicated to the memory of Professor Drago Kolar	2001	130
Smiljko Ašperger	Dedicated to Professor Smiljko Ašperger on the occasion of his 80th birthday	2001	340
F. Albert Cotton	This paper is dedicated to Professor F. A. Cotton, on the occasion pf his 70th birthday	2001	253
Alexandru T. Balaban	On the occasion of his 70th anniversary this paper is dedicated to Professor A. T. Balaban, one of few chemists of today who continues to share his time between the theoretical research in mathematical chemistry and synthesis of novel organic compounds	2001	341
Robert G. Parr	Contribution to 2 Volume book: A Celebration of the contributions of Robert G. Parr	2002	342
George G. Hall	This article is dedicated to Professor George G. Hall	2003	343

W. G. A. Milne	This article is dedicated to W. G. A. Milne, on the occasion of his retirement after serving for 15 years as the Editor-in Chief of the *Journal of Chemical Information and Computer Sciences*	2004	344
W. G. A. Milne	Dedicated to Dr. George W. A. Milne who friendly supported the MCC meetings throughout the years and helped to collect and edit the papers presented there	2004	345
Nenad Trinajstić	Dedicated to Professor Nenad Trinajstić, one of the pioneers of chemical graph theory	2004	346
Nenad Trinajstić	Dedicated to Academician Nenad Trinajstić, one of the most distinguished Croatian scientist	2004	347
Edward C. Kirby	Dedicated to Dr. Edward C Kirby in happy celebration of his 70th birthday	2005	348
Edward C. Kirby	Dedicated to Dr. Edward C Kirby on the occasion of his 70th birthday	2005	349
Ivan Gutman	This paper is honoring Professor Ivan Gutman, a dedicated warrior for a better recognition of Clar's insights into the nature of benzenoids	2007	350
Jerome Karle	This paper is dedicated to Dr. Jerome Karle, Nobel Laureate (1985), a staunch supporter of Mathematical Chemistry	2007	351

* By 1991 Yugoslavia became extinct (except in name, which lingered on for a while). This paper was submitted in November of 1989 and accepted July 1980, while Yugoslavia still existed

** Professor of Physical Chemistry in the University of Sarajevo, a Slovene by nationality, a colleague upon whose invitations I delivered series of lectures on Quantum Chemistry for graduate students at the University of Sarajevo in the late 1960s

Appendix 2 From "Towards chemical topology" (*Nature*, Vol. 252 November 15, 1974):

The uninitiated, faced with the awesome variety of organic chemistry, its peculiar cryptonymous nomenclature and its tendency to produce publications in twenty of thirty parts, might be excused for finding there more to excite the wonder of the natural historian than rigors of mathematics. Neither is the practitioner sketching formulae in the odorous intimacy of the laboratory likely to ascribe much abstract significance to the ciphers which he learns to manipulate as by second nature. Yet the business of classifying and labeling complicated ring and branched structures which figure so prominently in the modern subject has been recognized in recent years to involve to involve far more than simple book-keeping; in fact some of the problems which arise, when stripped to their abstract essentials, connect with as yet unresolved difficulties in the area of finite mathematics usually termed graph theory.

Consider, for example, the following: can a coding system be devised which not only leads to the systematic reconstruction of an arbitrary carbon skeleton but which is essentially independent of the particular way adopted for labeling individual atoms or other distinguishing features? Alternatively, if a certain labeling system is adopted (usually, of course, that of attaching sequential numbers to the carbon atoms present) can coded representations be found which the topological identity of two differently numbered version of the same N-carbon structure can immediately be inferred. (Other, that is, than by investigation of all possible N! permutations of labeling).

This problem, which shares its graph-theoretical content with several others in statistical mechanics and the theory of disordered structures, has been taken up in a number of recent papers, most notably by M. Randić of the University of Zagreb writing in the Journal of Chemical Physics (60, 3920; 1974). Professor Randić advances no rigorous proofs but suggests an ingenious algorithm by which a binary number code is assigned to each possible labeling of a given structure, the lowest number obtainable under systematic rearrangements providing both a canonical numbering scheme and an immediate comparison test for the identity of different networks of bonds. The method given seems to fall short of guarantying the discovery of the minimal labeling but seems to work well when tried on common systems of saturated and benzenoid hydrocarbons. Needless to say the canonical numbering system s come out differently from those traditionally adopted. (It is notable, and amusing, that the basic tool of the Randić method – the adjacency matrix for comparable structures – is now familiar part of O-level mathematics (see Schools Mathematics Project Book Y, 55; Cambridge University Press, 1973) though likely to seem formidable to many research chemists educated in an earlier era.)

. . . . . .

Appendix 3 Letter from Professor Parr (February 28, 2004) to Milan Randić

Dear Milan: I thank you very much for noting the NAS award. Of course I am happy about it. But I know full well that such things are mainly luck. Good genes, good family, good teachers, good friends, good coworkers, and a great deal of luck!.....Your own career, and your own work, are to be admired, and I congratulate you for them. In reply to your own ruminations about them, I offer a few remarks. Most important, you should realize, and you should rejoice that, chemical graph theory in fact has succeeded famously. It in no way is being passed by; rather, it is here to stay and you personally are in large part responsible. Your remarks about the subject are not the major contribution; it is the body of research you have produced or stimulated within the subject. How various elements of the population have reacted to the field is of no essential importance, for it is established, permanently, by the substantial publications in journals around the world, and there is a significant number of persons active in the field. It makes not a whit of difference whether the initials for a journal are JCP or something different. And editors come and go; they die. .....

Three stories from my own experience illustrate how science and scientists in fact operate. (1) Founding of JCP. [An interesting event described in detail, in a book by a historian of chemistry (name forgotten) I saw recently]. In the very early 1930s the leading young American physical chemists got very upset by the disdain for quantum mechanics, molecular spectroscopy, and the like, shown toward such subjects by the editor of the then Journal of Physical and Colloid Chemistry (later JPC), a chap named Bancroft, and the fact that the chemical leadership in the country would not force a change. They {Harold Urey, Joe Mayer, John Kirkwood, Robert Mulliken, others} went to the American Physical Society, and there soon followed the founding of JCP. Take a look at issue 1, volume 1, of JCP, and you will amazed by the high quality. It took forty years or so for JPC to recover (perhaps one should say "be born again"). (2) The development of quantum chemistry immediately after WWII. Having already had a preliminary shot at the subject, the senior American leaders in chemical physics decided that there was no point in pursuing quantitative electronic structure theory past three or four electrons. I vividly recall sitting in the audience at an ACS meeting in Pittsburgh, perhaps in '49 or '50, as the speaker, a great chemical physicist of the day [great except for this attitude],declared this opinion to an audience of a hundred or more. Mulliken, Slater, and my professor, Bryce Crawford, knew better. Bright Wilson was not so antagonistic, but neither was he optimistic. Examine the faculty lists at Harvard, Stanford, MIT, Berkely, Caltech, and you will see how slowly the new quantum chemistry began to be accepted as useful. (3) Acceptance of DFT by chemists. Closer to the present day, think how slowly, after properly turning back Slater's appeal to accept X-alpha as a cure-all, the quantum chemists themselves (much less the broader chemical community) accepted DFT as a useful, lasting tool. Few of the leaders in the subject (Lowdin, yes, but many others) were positive.

Conclusion.
This is all mainly to say, the story of Chemical Graph Theory is not unusual but typical. It is the way of science. We must be skeptical, critical, slow to applaud, open minded but super questioning. In June of 1952, Robert Mulliken was sitting in the right-back of an auditorium while Rudy Pariser and I gave a two-part double-talk on PP(P) theory. John Platt was presiding [I share what I read as your high opinion

of Platt]. When we finished, Platt (saying nothing else) asked for questions. Robert Mulliken quickly stood up. What he said was, "This is very interesting". Then he sat down. That is the way of science, and that is the way of scientists. .... Just as a child wants a parent to express approval (or better, applause), a scientist (perhaps especially a scientist in a new country in a new language, surrounded by other scientists hardly noticing him) wants at least one or two of the others to commend him for his work. "Interesting" is likely to be as much as they will ever say. What I say now, Milan (and hope I have said before), is Bravo, friend, for good, interesting science, well done!
All the best,

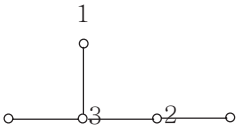
Bob

Appendix 4 Extract from "*Aventuras Topológicas*" by J. L. Caralvilla and G. Fernandez p.103

Existen otros tipos de indices llamados de concetividad, uno de los más utlizados es el de Randic, R, definido mediante:

$$R = \Sigma\, (1/mn)^{1/2}$$

donde la sumatoria esta extendida a todos las aristas, siendo m y n los grados de los vértices unidos por una arista. En al siguiente ejemplo se ilustra su cálculo en uno caso concreto:



$$R = (1/3 \times 1)^{1/2} + (1/3 \times 1)^{1/2} + (1/3 \times 2)^{1/2} + (1/2 \times 1)^{1/2} = 2.2701$$

Se han encontrado buenas correlaciones entre R y propiedades fisicas como la densidad, solubilidad an agua y calor de evaporación. También permite establecer correlaciones con determinadas propriedades biológicas de la moléculas, como la tedencia a actuar como anestésicos, narcóticos o alucinógenos.

Appendix 5 Excerpt from "Research News" in *Science* 19 May 1989 in which B. A. Cipra in article [65]: Do Mathematicians still do Math? refers to "Graffiti" and the Randic index:

"*Invariants of a graph are numbers that don't change if the graph is redrawn or relabeled. They range from geometrical data, such as the graph's diameter (determined by finding the shortest path between each pair of vertices), to algebraic information, such as the number of positive eigenvlaues of the graph's adjacency matrix. While some are purely mathematical concoctions, other invariants seem to have real physical meaning. One called the Randic index, for instance, is used to predict boiling points of hydrocarbons.*

Graffiti's conjectures all say that one invariant is less than or equal to another invariant (or combinations of invariants). For instance, Graffiti conjectured (correctly) that the Randic index is never more than the number of vertices; Graffiti also claims that the average distance between vertices is never more than the Randic index, a conjecture that remains to be settled. So far Graffiti boasts a respectable batting average: of the conjectures that have been settled, roughly a third have been proved correct."

Appendix 6 Letter of President of Drake University nominating Milan Randić for the 1988 Governor's Science Medal in Science Achievement

Drake University

Office of the President

October 31, 1988

Dear Governor Branstad:

I am honored to nominate Dr. Milan Randić, Ellis and Nelle Levitt Professor of mathematics at Drake University, for the 1988 Governor's Science Medal in Science Achievement.

The enclosed letters of support from several internationally-acclaimed scientists provide testimony to Professor Randić's pioneering research in the mathematical analysis of chemical structures. He has been singularly instrumental in the growth of this area, and the applications of his original work have been recognized by scientists in America and abroad as well as by the pharmaceutical industry and the Environmental Protection Agency.

Perhaps Dr. Robert Parr, Keenan Professor of Theoretical Chemistry at the University of North Carolina at Chapel Hill and the premier theoretical chemist I the world , placed in perspective best the research of Milan Randić: "Through a long series of imaginative and incisive papers, he has almost single-handedly established a whole new subdiscipline: graph theory as it applies to chemistry. His studies range from fists proofs of mathematical theorems to interesting applications to chemical problems."

Nobel Prize winner, Roald Hoffmann of Cornell University, commented that "Milan Randić is, of course, one of this country's outstanding theoretical chemists and mathematicians . . . Dr. Randić has invented ways pf characterizing these graphs, ways which have allowed pharmaceutical chemists to classify, understand, even occasionally to predict the activity of drugs. This work is very important, on an absolute scale, and certainly deserves the highest recognition of the State of Iowa."

These comments and similar praise from others make clear that our State and Drake University are fortunate indeed to have a scientist of such stature. Milan Randić is worthy of the honor symbolized by the Governor's Science Achievement Award.

The fact that he has earned international recognition for his original theoretical achievements at a university that does not have a major scientific research focus is also of significance. To recognize the major scientific breakthroughs associated with the research of Milan Randić the state sends a clear signal to the entire science community of the considerable depth that exists at Drake and in several private colleges in Iowa.

As a President of Drake University, I am proud to recommend Milan Randić to you for consideration as the 1988 recipient of the Science Achievement Award.

Sincerely.

Michael R. Ferarri
President

MRF/wt

The Honorable Terry E. Branstand
Governor of Iowa
State Capitol
Des Moines, Iowa 50319

Appendix 7a Blank Referee form for Discrete Applied Mathematics

PACE UNIVERSITY

Discrete Applied Mathematics
Special Issue: Applications of Graph Theory in
Chemistry and Physics

Referee's Evaluation form

Title:

Authors:

Criteria for inclusion of manuscript:

A. The paper must exhibit a significant content in both graph theory and either chemistry or physics. Exceptionally, a paper containing only one of the content requirements may be accepted where it has special relevance to the other requirement.

B. The paper must be clearly written and must be intelligible to the wide audience suggested by the title of the special issue. In particular language should be minimized and, when used, clearly defined in the paper.

Please reply to the following questions:

1). Does the paper meet the above criteria? Yes ____ : No ____
2). Is the title appropriate? Yes ____ : No ____
3). Is the summary adequate? Yes ____ : No ____
4). Should the paper be accepted for publication?
Yes ____ : With Minor Revision ____ : With Major Revision ____ No ____

Please use the following space to suggest revisions, give criticisms or state reasons for rejection of paper (as appropriate).

(continue on a separate sheet if necessary).

The anonymity of the referee will be strictly preserved, The following information is for the files of the editors only.

Referee: *Signature:*
Date:

Appendix 7b Dr. S. C. Basak evaluation of the manuscript "Use of molecular connectivity indices in socio-historical and business management studies" by J. T. Edward, E. Johanson & S. Wold for special issue of Discrete Applied Mathematics

To the question (1) to (4) Dr. Basak answered "No" except for (3) his answer was N/A, No summary.
His response is dated February 26, 1988.

Here are excerpts from his 2 ½ page response:

The content of the paper neither deals with significant aspect of graph theory nor any area of chemistry or physics. Therefore, according to criterion A for the inclusion of a paper in the special issue of Discrete Applied Mathematics, I strongly feel that the paper by Edward, Johanson and Wold should not be accepted for publication in the special issue of the journal.

The primary purpose of the paper seems to ridicule some applications of a set of graph invariants which have been very popular among practitioners of molecular modeling both in academia and industry. This is particularly evident from the last paragraph of the paper. I believe that this is contradictory to the ethics of good scientific practice. The statement "Rather, we see the theory as giving rise to an endless flood of papers, written by university professors and helping them to earn tenure and promotion, without ever producing an amphetamine or a thalidomide" does not contain anything but a tendency towards denigration and vilification of research published, mostly in peer-reviewed and international scientific journals. Such statements may find place in low-grade political pamphlets but never in an esteemed journal like Discrete Applied Mathematics.

The authors demonstrate a miserable lack of understanding of the Structure-property similarity principle – the central paradigm of structure-activity relationship (SAR) studies. Let me try to clarify this point . . . .

Constructive and valid criticism of any scientific approach is always welcome. Conjecture and refutation are the means of scientific development (K. R. Popper, The Logic of Scientific Discovery, Basic Book, New York, 1959). Consequently, applications of graph theory (or any other mathematical theory) to chemistry are not immune to criticism. The authors may receive good education by reading a paper by Balaban and Harary (J. Chem. Doc. 11 (1971) 259) where the authors refuted Spialter's (J. Chem. Doc. 4 (1964) 261; J. Chem. Doc. 4 (1964) 269; J. Am. Chem. soc. 85 (1963) 2012) conjecture. Although some individual scientist may dislike certain development in Science, we should not forget Bacon's dictum: "Truth emerges more readily from error than from confusion." Publication of this paper in Discrete Applied Mathematics (or any other scientific journal) will, in my opinion, have two distinct effects: 1) shock those who

believe in the ethical practice of science, and 2) confuse those who are less critical. Neither will serve any positive purpose.

In conclusion, I find no logico-mathematical or scientific content in the paper by Edward, Johanson and Wold. Consequently, I have no hesitation to say that this paper should not be published in Discrete Applied Mathematics.

Appendix 8 Abstracts of two articles on abuse of editorial role in sceince

James V. Bradley "Pernicious publication practices," *Bulletin of the Psychonomic Society*, 18 (1981) 31-34;

Abstract

Although apparently approving of the peer-review system in general, university professors answering a mail questionnaire were often critical of specific features. In the peer review of their latest revised and published articles, 76 % encountered pressure to conform to the strictly subjective preferences of the reviewers, 73 % encountered false criticisms (and 8 % made changes in the article to conform to reviewers' comment they knew to be wrong), 67% encountered inferior expertise, 60 % encountered concentration upon trivia, 43% encountered treatment by referees as inferior, and 40% encountered careless reading by referees. At some time in their general experience with the peer-review system, 65% believed that referees' comments were contrived to impress the editor, 53% felt that the editor regarded their knowledge and opinion about the reported research as less important than that of the referees, 44% felt they were being treated like supplicant, and 47% accepted a referee's suggestion against their better judgment.

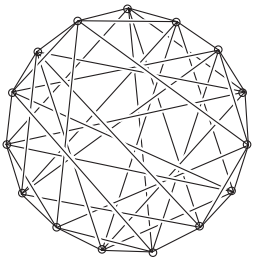
James V. Bradley "Editorial overkill", *Bulletin of the Psychonomic Society*, 19 (1982) 271-274.

Abstract

Mandatory revision in accordance with reviewers' comments has apparently become the norm for articles published in certain quarters. Of the regular articles published in the 9-year period 1972-1980 by a sample of highly reputable journals (*British Journal of Psychology, Econometrica* and the *Journal of the American Statistical Association*) 68%

to 99% had to be revised subsequent to submission. These high rates of coerced revision place enormous power in the hands of reviewers to enforce conformity to their values while largely escaping responsibility, or accountability, for their actions. This situation is conducive to a variety of abuses that detract from the efficiency of the peer-review system and therefore constitute editorial overkill. These abuses are extensively discussed and illustrated.

Appendix 9 Letter to colleagues about calculating the symmetry of a graph



Dear Colleague:

Recently I analyzed the graph shown here (which arises in a study of isomerizations) and established to have automorphism group S_6. A referee of a distinguished journal finds my finding – obvious – but has not forwarded explanation. I determined the symmetry (automorphism) using canonical labels in a process which is neither obvious nor trivial. As you know, the determination of symmetry of graphs (as is also case with related problem of graph isomorphism) is NP-complete, generally viewed as intractable problems, not trivial.
Do you find the problem and the solution obvious?
Please, send your brief comment to:
Milan Randić
3225 Kingman Rd.,
Ames, Iowa 50014

First Day of Summer 1982

P. S.
One refers to a problem as intractable if it is so hard that no polynomial time algorithm can possibly solve it.

With kind regards
Milan Randić

Appendix 10 Letter from Professor Coxeter:

University of Toronto
Toronto, Canada
M5S 1A1

Department of Mathematics

17 Feb. '81

Dear Dr. Randić,

Thank you for your interesting letter of Jan. 31 about symmetry properties of graphs. By an amazing coincidence, you ask about what Bondy & Murty call the "Coxeter Graph" just after I have submitted a 45 page paper on that very subject to the London Math. Society (and I am still waiting to hear whether their referees have found it publishable) ! I enclose copies of some pages, showing my version of a canonical numbering, and why it has the same group as the Heawood graph (which appears in my paper as "Figure 4"). I like your idea of drawing it with concentric heptagons. I have tried some modifications in an attempt to reduce the number of crossings. . . .*

Your pentagonal version (A – 5) of the Folkman graph is very pretty; so is Hamiltonian version of Grünbaum (A – 6). I find Szekeres (A – 7) less interesting because it is not edge-transitive (Is it even vertex-transitive?)

You are indeed bold to study a monster graph with 10!/3 vertices.
My Ph. D. student, Mrs. Weiss, believes she has found a trivalent 3-regular graph with 40 vertices, different from Foster's. Its group is S5 × C4. Is this, by any chance, in your own collection?

I have been invited to a conference in Israel next month. I enclose a copy of my abstract,

Yes, I hope we can meet when you visit your friend in Waterloo,

Sincerely
HSM Coxeter

** Sorry I forgot to bring these; I will send them next week. C*

Appendix 11

REFEREES REPORT File: 1363A8

Title: A correlation between Kekulé valence structures and conjugated circuits

Authors: Ivan Gutman and Milan Randic

My colleague, , and I have examined the above paper. We have decided not to referee it in the usual sense of providing an analysis of strengths and weaknesses because we feel that, being about neither chemistry nor physics, it is not appropriate for the JCP. This paper is representative of a genre which has grown up over the past few years in which various numbers are associated with a molecular structure (usually derived by simply counting the number of members of some class of substructures) and then correlations are sought between these numbers and some other molecular property, frequently a number resulting from another exercise of the same kind. These studies are usually coached in the language of graph theory but they do not lead to any deeper insights into the mathematics of structure, in fact they tend to be mathematically quite unsophisticated.

Since papers of this class contain no physics, negligible chemistry and near-trivial mathematics it is hard to say where they might find a home in the scientific literature. (Unfortunately a few of them have found their way into JCP and few other journals of similarly high standards). Many of these papers have been published in Croat. Chem. Acta, Rev. Roum. Chem., Bull. Chem. Soc. Japan and Mathematical Chemistry; while I am not personally familiar with any of these journals, perhaps one of them would be appropriate place.

Appendix 12 Excerpts from the Book Review: *Mathematics and Computational Concepts in Chemistry* (edited by N. Trinajstić), Wiley 1985.

This book contains invited and special lectures presented at the International Symposium on the Applications of mathematical Concepts to Chemistry held in Dubrovnik, Croatia, September 2-5, 1985. In the preface the recognition of a new filed, Mathematical Chemistry, is emphasized. The "new" used here is in fact a misnomer, since the topics of the conference that is used to constitute the filed of mathematical chemistry have had a long tradition in Yugoslavia in general and in Croatia in particular.

Even if the history and the present status of mathematical chemistry as well as its influence on other aspects of chemistry are well expressed in the opening chapters of the book, the prospective reader may wonder, as he digests the remaining chapters, how to define the field. Is it a collection of topics like application of graph theory to organic chemistry, molecular topology, or algebraic chemistry? Or can one define the mathematical goals more specifically and then in terms of some underlying fundamental principle?

To aid and prepare the reader for the role of mathematical concepts in chemistry, the Nobel Prize winners for chemistry of 1975, John Warcup Cornforth and Vladimir Prelog, contribute in the introductory chapters, the latter with a well-motivated prologue and the former with a communicated work-up list of minimum requirements mathematics needed for a good organic chemist.

With some overlap the following lectures consist of 14 well-written contributions on the application of graph theory, including one by the "father of the topological index," Haruo Hosoya, and the lecture by the pioneer Milan Randic, 11 chapters of quantum chemistry, and 9 other applications ranging from molecular topology and transition state theory to master equations and subdynamics. The list of topics s impressive, the presentations of high quality and the topical "mix" very interesting. The represent book is warmly recommended to everybody on at least a graduate level of chemistry, physics, and mathematics. . . . .

Erkki Brändas

Int. J. Quantum Chem. 30 (1986) p. 867.

Appendix 13 False "Alert" about graphs and graph theory: Editorial "Alert" to reviewers about graph theoretical manuscript submitted to the *Journal of Chemical Information and Computer Science*

The JCICS Policy on Graph Theory Manuscripts

The Journal of Chemical Information and Computer Sciences is adopting a new policy concerning papers in the area of graph theory. To be publishable, a manuscript must now have truly innovative and unique ideas that make major advances in graph theory applied to chemical systems, or, it must use graph theory in a way as to make a large scientific advancement.

Accordingly, if the manuscript you are reviewing: (1) is presenting a trivial advance in graph theoretical methodology and lack any application to a chemical problem of significance (the significance of the work needs to be clearly delineated in the author's manuscript) or if it is of purely graph theory that should be published in a mathematical journal, we are asking you to note this in your review or (2) if the manuscript has no clearly stated scientific hypothesis that are being proved or disproved, i.e., if the work is simply yet another GT study of some system that is narrow in scope, or if the manuscript simply compares its methodology to existing GT methods without attempting to show its general applicability to solving problems in chemistry and informatics, we ask that you also indicate this in your review.

Appendix 14 A true "Alert" about graphs and graph theory: Part of the Foreword of V. Prelog to a first monograph on Chemical Graph Theory (edited by A. T. Balaban)

Pictorial representations of graphs are so easily intelligible that chemists are often satisfied with inspecting and discussing them without paying too much attention to their algebraic aspects, but it is evident that some familiarity with the theory of graphs is necessary for deeper understanding of their properties.

Vlado Prelog