

IN SEARCH OF STRUCTURAL INVARIANTS*

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Abstract

Graph theory has been used for modeling chemical structures, that is, chemical compounds, intermediates, changes, reactions and mechanisms. Among the most important such applications are: (1) structure–property relationships (SAR); (2) design of compounds of desired properties; (3) enumeration and construction of compounds of certain classes; (4) unique representation of compounds (for documentation needs). Here, we outline selected accomplishments of the past, show some current efforts and point to directions which may lead to further advancements in chemical graph theory.

1. Introduction

We will briefly review selected topics in chemical graph theory, in particular being concerned with the use of graphs for modeling chemical structure. This article is intended primarily for those who are not familiar with chemical graph theory, including also mathematicians who, while familiar with graph theory, wish to learn of its applications in chemistry. We must here at the beginning emphasize the distinction between graphs and molecules, and also mention that graphs model other chemical structures besides molecules. When one interprets vertices as atoms and edges as bonds, graphs show only the connectivities within a molecule. This particular structural element is exceedingly important and it is of considerable interest to find all the results of a particular connectivity. Hence, graphs will remain the important models of chemical compounds. There are several additional structural features that "decorate" chemical compounds and require some generalization of simple graphs. These include:

- (1) occurrence of multiple connections, which can be modeled by multigraphs;
- (2) presence of distinct atoms, which may be modeled by introducing loops at selected vertices, or by coloring vertices;

*Dedicated to Linus Pauling (Nobel Prize for Peace 1962 and Nobel Prize for Chemistry 1954) in appreciation of his outstanding contributions to structural chemistry and his untiring efforts to end war.

- (3) possibility of existence of different geometrical forms for the same connectivity, which can be modeled by embedding graphs on qualified coordinate grids.

These more generalized objects, graphs with multiple connections, with loops and embedded on selected grids, still belong to the domain of graph theory. Chemical bonding, a result of Coulombic interactions as governed by the laws of quantum mechanics, is rich in variations. Clearly, all the details of the chemical bond cannot be represented by models based on graphs. Because of this, many chemists, who are well aware of the delicacies of chemical structure, sensitivities of electron energetics to fine details in geometric variations of nuclei positions, never expressed much interest in graphs as a mathematical object of interest in chemistry. Of course, graphs are not substitutes for molecules; graphs represent a model.

“Modeling is a ubiquitous and often misunderstood enterprise . . .” wrote M.C. Kohn [1] in an enlightening article on mathematical modeling in biology and chemistry. Models are built and developed to answer specific questions, and no model will answer all the questions that one may pose. Moreover, different models may equally well account for the same property of an object [1]:

“It is unusual for only one model to be compatible with the experimental observations. Often the data are not sufficiently extensive to discriminate among rival models and new experiments must be designed to answer outstanding questions. The statistical, graph theoretical, and sensitivity analysis methods can identify the areas for further investigation that are likely to produce significant new results.”

Chemical graph theory does not compete with quantum chemistry, statistical mechanics or group theory – rather, it is complementary. Hence, chemists should be aware of the kind of questions that graph theory can answer. Those who continue to identify chemical graph theory with the Hückel MO model [2] fail to appreciate connectivity as a structural element. Besides occurrence in the simple pi-electron models, connectivity plays a critical role in such diverse contexts as: enumeration of isomers, bond additivities, Kekulé valence structures, molecular similarity, molecular complexity, degenerate isomerizations, etc. Equally, graph theorists who continue to refer to graph spectra as electron orbital energies fail to accept the limitations of the “nearest-neighbor approximation” of Felix Bloch [3]. This approximation has been immortalized in chemistry by Hückel's early applications to benzene and other large organic compounds.

In table 1, we summarize the roles of distinct mathematical disciplines as they relate to application in chemistry, particularly to questions concerning chemical structure. In table 2, we list several questions that are of interest in chemistry. They are classified according to the appropriate mathematical discipline which offers the most *efficient* route to the answer. Tables 1 and 2 should not be taken very rigidly; they illustrate a convenient classification of questions of interest in chemistry and the

Table 1

Distinct mathematical branches as applied in theoretical chemistry.

Calculus	Probability
Differential equations	Statistics
Linear algebra	
	Classical statistical mechanics
Quantum theory	Maxwell
Planck	Boltzmann
Heisenberg	Gibbs
Schrödinger	Quantum statistical mechanics
Dirac	Fermi, Dirac
	Bose, Einstein
Quantum chemistry	
Qualitative: Heitler and London	
Pauling	Sequential events:
Mulliken	Markov
Coulson	Kolmogorov
Quantitative: Parr	Monte Carlo:
Pople	Ulam
	Chaos:
	Feigenbaum
Group theory	
Lie algebra	Graph theory
Point groups	
Fluxional groups	Enumerations
Hougen	Cayley
Longuet-Higgins	Polyá
Symmetric group	Networks
Weyl	Kirchhoff
Wigner	
Unitary group	Isomerizations
Moshinsky	Balaban
Paldus	Mislow
Matsen	
Space groups	
Schonflies	
Seitz	
Color groups	
Shubnikov	Topology
Dynamic groups	Hückel

... continued

Table 1 (continued)

Topology	Miscellaneous
Gauge theory	Fractals
Weyl	Mandelbaum
Geometric phase	Lattices
Berry	
Knotted molecules	Partial order
Walba	Muirhead
	Ruch
Catastrophy theory	Factor analysis
Thom	Hotelling

Table 2

Various questions of interest in chemistry and corresponding mathematical disciplines involved in solving questions.

Questions concerning:	Domain:
Molecular geometry	Quantum chemistry
Molecular spectra – transitions	Quantum chemistry
– intensities	Quantum chemistry and statistical mechanics
Splitting of degeneracy	Group theory
Periodic table	Group theory and quantum statistics
Isomer count	Graph theory
Bond additivities	Graph theory
Molecular similarity	Graph theory
Comparison of molecules	Graph theory
of molecular fragments	Graph theory
Random structures statistics and graph theory	
Zero matrix elements (selection rules)	Group theory and graph theory
Thermodynamic properties	Statistical mechanics

tools available. There are other mathematical disciplines of interest in chemistry, such as coding theory and cryptanalysis, linear programming, number theory, theory of category, topology and knot theory, etc.

The same questions may sometimes be answered by using different mathematical approaches. For example, to find the splitting of a degeneracy of atomic levels in a crystal field or to find the number of isomers, or number of conformers (that is, the

Table 3

Important concepts and novel structural features in chemistry.

Concept/Compound	Author	Year
Homologous series	Gerhardt	1845
Valency	Frankland	1852
Isomers	Butlerov	1860
Structural formulas	Crum Brown	1864
Benzene structure – delocalized bond	Kekulé	1865
Tetrahedral carbon	van's Hoff and LeBel	1874
Optical isomers	Pasteur	
Isoprene rule	Wallech	1887
Coordination compounds	Werner	1893
Conjugation	Thiele	1899
Bond dipoles	Langevin	1905
Electron dot diagrams	Lewis	1916
Hydrogen bond	Latimer and Rodebush	1920
Atom and bond additivity	Fajans	1920
Diborane – electron deficient system	Dilthey	1921
Pi sextets – pi-electrons description	Armit and Robinson	1922
Donor–acceptor bond – transition metals	Sidgwick	1923
Bredt's rule – bridge head restrictions	Bredt	1924
Hybridization	Pauling	1928
Ferrocene – sandwich molecules	Pauson	1951
Fast polymerization	Ziegler	1953
Isotactic polymers	Natta	1953
Double helix – DNA structure	Crick and Watson	1954
	protein coding	
Xenon compounds – supposed not to exist!	Bartlett	1962
Bulvalene – fluxional molecules	Doering	1963
Hafner hydrocarbon – relatively unstable	Hafner	1963
Orbital following – cyclization rules	Woodward and Hoffmann	1965
Antiaromaticity	Breslow	1966
Möbius–Hückel concept	Zimmermann	1966
Catenenes – interlocked rings	Wasserman, Schill	1964
Resonant sextets	Clar	1972
Van der Waals molecules	Herschbach	
Metal clusters		
Knotted molecules	Walba	1983
Buckminsterfullerene – unusually stable	Kroto and Smaley	1985
Retrosynthesis – synthesis analysis	Corey	

number of possible embeddings of, say, a chain molecule on a diamond grid) one can in principle use the quantum mechanics and ignore the group theory and the graph theory, respectively. The distinction between "in principle" and "in practice" may make in many applications the distinction between "to remain ignorant" and "to know". This is of crucial importance to chemists, even if belittled by physicists or mathematicians. It is over sixty years since Dirac's famous statement in the introductory paragraph of his paper on quantum mechanics of many-electron systems [4]:

“The underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only in that the exact application of these laws leads to equations much too complicated to be soluble. It therefore becomes desirable that approximate practical methods of applying quantum mechanics should be developed, which can lead to an explanation of the main features of complex atomic systems without too much computation.”

Since that time, important developments in chemistry have occurred (table 3 reviews some old and more recent developments), crowned by some 100 Nobel Prize laureates. These include Pauling (1954), Mulliken (1966), Prelog (1975), Lipscomb (1976), Hoffmann (1981), Karle and Hauptman (1985), and Corey (1990), who made important contributions to mathematical chemistry by advancing the theoretical, computational and/or conceptual content of chemistry.

2. Concepts and ambiguities

When we confine interest to chemical structure, the basic difference between quantum chemistry and chemical graph theory can be summarized as follows: Quantum chemistry is interested in "The Nature of the Chemical Bond" [5], while chemical graph theory is interested in "The Nature of Chemical Structure" [6]. The distinction is important: in the first case, the focus is on the results of short-range interactions of electrons and nuclei which result in a stable system – a molecule. In the latter case, one accepts (as input information) a particular bonding and the focus is on the results of the connectivity. Quantum chemistry can in principle (and for relatively small molecules in practice) produce quite accurate information on molecular geometry and electron energetics (spectra). One can even simulate composite systems, such as properties of a molecule surrounded by layers of other smaller (solvent) molecules. Computations can tell, for example, that the central bond in naphthalene is the shortest CC bond in that compound, that phenanthrene is more stable than anthracene (fig. 1). Similarly, at least in principle, computations can predict that the boiling point of 3-methylhexane is greater than that of 2-methylhexane. However, quantum chemistry does not tell us *why* the above are the cases.

The above questions imply comparisons, such as comparison of different molecular fragments, bonds included, comparison of different molecular parts, or comparison

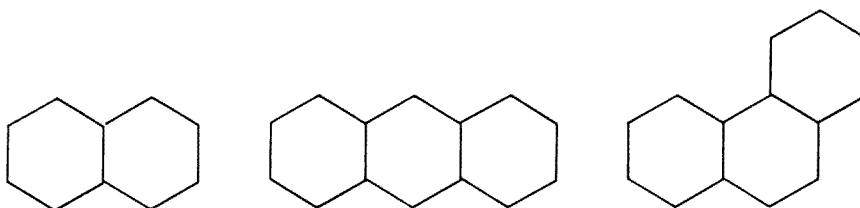


Fig. 1. Molecular skeletons (graphs) for naphthalene, anthracene and phenanthrene (carbon atoms only).

of different molecules. Comparison as a mathematical operation is not part of quantum mechanics' axiomatic basis. Typically, comparisons between molecules are made by considering various structural invariants, but invariants of interest in structural chemistry are not necessarily observables of interest in the quantum theory. To answer questions that imply comparisons between structures, one needs to introduce concepts that can illuminate a particular structural property of interest in the comparison. In table 4,

Table 4

Common chemical concepts which qualify as nonobservables.

Nonobservables – common chemical concepts	
Kekulé valence structure	Bond dipole
Resonance energy	Hybridization
Pi-electron sextets	Hybrids
Atomic orbitals	Free valency
Molecular orbitals	Potential curve
Equivalent and localized orbitals	Equipotential contours
Orbital energies	Electrostatic potential
HOMO–LUMO separation	Jahn–Teller "effect"
Bond order	Force constants
Atom–atom polarizabilities	Molecular surface
Atom–bond polarizabilities	Molecular volume

we list several concepts used in chemistry which do not represent observables in the strict sense of quantum mechanics. Many of these concepts have been introduced in the early developments of the quantum chemistry. To those not initiated in the graph theory they may appear as the legitimate quantum chemistry concepts. The label "quantum" is, however, more historical than substantive and many of the concepts of table 4 are today recognized as essentially graph theoretical in nature or as equivalent to selected graph theoretical concepts.

Table 5

Ambiguous concepts of chemistry	
Structure	Characterization
Size	Sensitivity
Shape	Similarity
Fragment	Functionality
Component	Hierarchy
Complexity	Domination
Stability	Aromaticity
Reactivity	Antiaromaticity
Profile	

In table 5, we list several widely used concepts in chemistry that yet remain to be better characterized. We may view the items in table 5 as a motivation for a continuous search for appropriate graph invariants and structural invariants that may help clarification of some such concern. We have deliberately crossed out Aromaticity, which has been one of the central concepts of organic chemistry for over a century. The reason is that this concept has been successfully resolved (*vide infra*) using the graph theoretical analysis of Kekulé valence structures in terms of conjugated circuits [7]. Clarification of the important chemical concepts of table 5 may be considered as "open challenges" or "open problems" of the chemical graph theory. Resolving some of these problems is likely to result in the advancement of chemical science. One may be reminded of a quote of William Thompson (Lord Kelvin) [8]:

“When you measure what you are speaking about, and express it in numbers, you know something about it; but when you cannot measure it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind: it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of science.”

However, one should not overlook that a qualitative character of some concepts in chemistry may be more desirable, at least for the time being. Hence, one should not insist on metrics at all costs. It is only when a concept reaches a phase of full maturity that a quantitative description may be more productive than a qualitative one. This is likely to be the case today with the concept of similarity, sensitivity and complexity, for example, but not necessarily with concepts such as shape or profile. Ambiguities of such concepts have served their purpose, and there is a danger that too rigid a definition may hinder rather than help and even lead to an unproductive direction. Hence, the problem is not in arriving at a solution at any cost, but to arrive at a characterization which is more useful than the hitherto used qualitative notion.

It is appropriate to end this section on the distinctive role of quantum chemistry and graph theory in chemistry with a courageous quote from a paper by Gordon and Kennedy [9], even though it relates specifically to the problem of bond additivities of some molecular properties:

“The theory of graphs, a rapidly developing mathematical discipline, is immensely useful in chemistry. Using quite elementary concepts and terms of graph theory, a single systematic definition of about 50 words, contains as special cases, practically all that is useful in previously proposed additivity schemes for predicting standard thermodynamic data. The customary calculation from standard enthalpies of substantial delocalization energies in the form of "steric corrections" is criticized as being biased. It is doubtful whether quantum theory had so far contributed significantly to the results of analyzing enthalpy data on alkanes.”

The past twenty years have seen an unusually fruitful expansion of chemical graph theory, growth in number of investigators, publication of many reviews [10], several books [11], including the first monograph on chemical graph theory [12], proceedings of regular conferences where chemical graph theory is a central subject [13], and two journals with the major content being chemical graph theory [14].

3. Separation of factors

In modeling, it is natural to simplify the problem when possible. In particular, in mathematical analyses it is desirable to reduce the dimensionality of a problem when possible. Thus, typically in quantum chemistry, the total molecular wave function is "broken down" gradually into various factors. Such a factorization, of course, is approximate only and under certain conditions may not be satisfactory. In table 6, we illustrate the situation for a representative polyatomic molecule. The bottom line summarizes the outcome; various factors can then be considered separately:

$$\begin{pmatrix} \text{electron} \\ \text{motion} \end{pmatrix} \begin{pmatrix} \text{nuclear} \\ \text{vibration} \end{pmatrix} \begin{pmatrix} \text{molecular} \\ \text{rotation} \end{pmatrix} \begin{pmatrix} \text{electron} \\ \text{spin} \end{pmatrix} \begin{pmatrix} \text{nuclear} \\ \text{spin} \end{pmatrix}$$

Transitions:

UV	IR	MW	ESR	NMR
Ultraviolet	infrared	microwave	electron	nuclear
			magnetic	resonance

When the Born–Oppenheimer approximation [15] fails (for example, the case of the hydrogen bond), we can no longer separate nuclear motion from electronic motion. Another manifestation of the failure of the separation of electronic and nuclear motion is manifested in the dynamic Jahn–Teller "effect" [16]. Similarly,

Table 6

Common simplifying steps in the theoretical analysis of various molecular properties.

Born–Oppenheimer approximation: $\Psi_{\text{molecule}} = \Psi_{\text{nuclei}} \Psi_{\text{electrons}}$

Failures:

Jahn–Teller "effect": molecule takes less symmetrical shape if electronic state is degenerate;

Fluxional molecules: due to low barrier nuclei continuously change relative positions

Vibrational–Rotational separation: $\Phi_{\text{nuclear motion}} = \Phi_{\text{vibration}} \Phi_{\text{rotation}}$

Breakdown:

Coriolis coupling: causes distinct rotational fine structure in vibrational bands associated with degenerate vibrations;

Centrifugal distortion: high rotational levels associated with stretching of some bonds

Independent particle model: $F(1, 2, 3, \dots, n) = a(1)b(2)c(3) \dots x(n)$

Many electron wave function \rightarrow antisymmetrized product function

Corrections:

Configuration "interaction"

Electron correlation

Space–spin separation

Breakdown:

Spin–orbit coupling

the effect of Coriolis forces is a manifestation of the limitations of separation of vibration and rotation, which results in apparently different rotational constants in vibration–rotation spectra in the infrared [17]. Another illustration of the difficulties with the separation of vibration and rotation occurs in fluxional molecules.

Is there a similar useful separation of molecular structure which will allow various structural features of a molecule to be examined separately, at least in prevailing instances? In applications of the graph theory to complex molecules it would help if one could "dissect" a molecule and focus attention on individual selected structural features, rather than consider the molecule, as is typically the case, as a whole. Recently [18], we suggested the following resolution of a structure:

$$\left(\text{size}\right) \left(\text{shape}\right) \left(\text{function}\right).$$

Here, "size" basically will depend on the number of atoms in a compound. "Shape" is somewhat less clearly defined, but essentially it discriminates among molecules

of the same size but different geometry. Finally, "function" involves variations in the atomic composition, that is, the presence of heteroatoms. The role of heteroatoms becomes more clear when a molecule is situated in a proper environment. For example, the same molecule in a solution, or adsorbed on a surface, or in the vicinity of another macromolecule, such as occur in modeling drug–receptor systems, will act differently. Quantitative studies extending the structure–property relationship to drug–receptor interactions is known as QSAR (Quantitative Structure–Activity Relationship) [19]. In this field, of particular interest are the solubility of compounds, the transport through membranes, the resistance to degradation, etc. With such applications in mind, we can further factor "functionality" of molecules, following [20], and arrive at:

$$\left(\text{size} \right) \left(\text{shape} \right) \left(\begin{array}{c} \text{field/inductive} \\ \text{effect} \end{array} \right) \left(\begin{array}{c} \text{resonance} \\ \text{effect} \end{array} \right) \left(\text{polarizability} \right).$$

The above separation helps one to focus attention on a single structural variable at a time. If under "shape" we understood "isomeric variations", that is, the variations in connectivity within isomers, such as the eighteen isomers of octane illustrated in fig. 2, we could study the mutual correlation among various molecular properties for these compounds by excluding the dominant role that size plays [18]. The same physico-chemical properties, when octanes are examined separately, show a much lesser degree of interrelatedness than that found for alkanes as a whole [21]. Clearly, "size" as a variable obscures the role of "shape" as a variable, which only becomes more clear when the dominant role of the molecular shape is eliminated (by restricting the analysis to molecules of the same size). The formal separation of a chemical structure in "size" and "shape" factors results in an additive decomposition of appropriate molecular descriptors. The descriptor for the size is constant for molecules of the same size, while other variables may critically depend on the shape, that is, will change among isomers (and conformers).

4. Similarity

Among the "ambiguous" concepts of table 5, we will only briefly comment upon similarity. The importance of this concept for chemical application is clear if one recollects the universally accepted paradigm that similar molecules have similar properties. A recent book on "Concepts and Applications of Molecular Similarity" offers a fair introduction to the topic [22]. One of the earliest recognitions of this postulate can be traced to Emil Fisher [23], who modeled drug–receptor interaction by a "lock and key" analogy. The postulate on similarity, or what may be more appropriate to refer to it, following E.B. Wilson [24], as one of the "emergent laws", is underlying much of QSAR methodology. It can be formulated in alternative forms, for example, as the Principle of Graduality [25]:

"The changes in Nature are gradual",

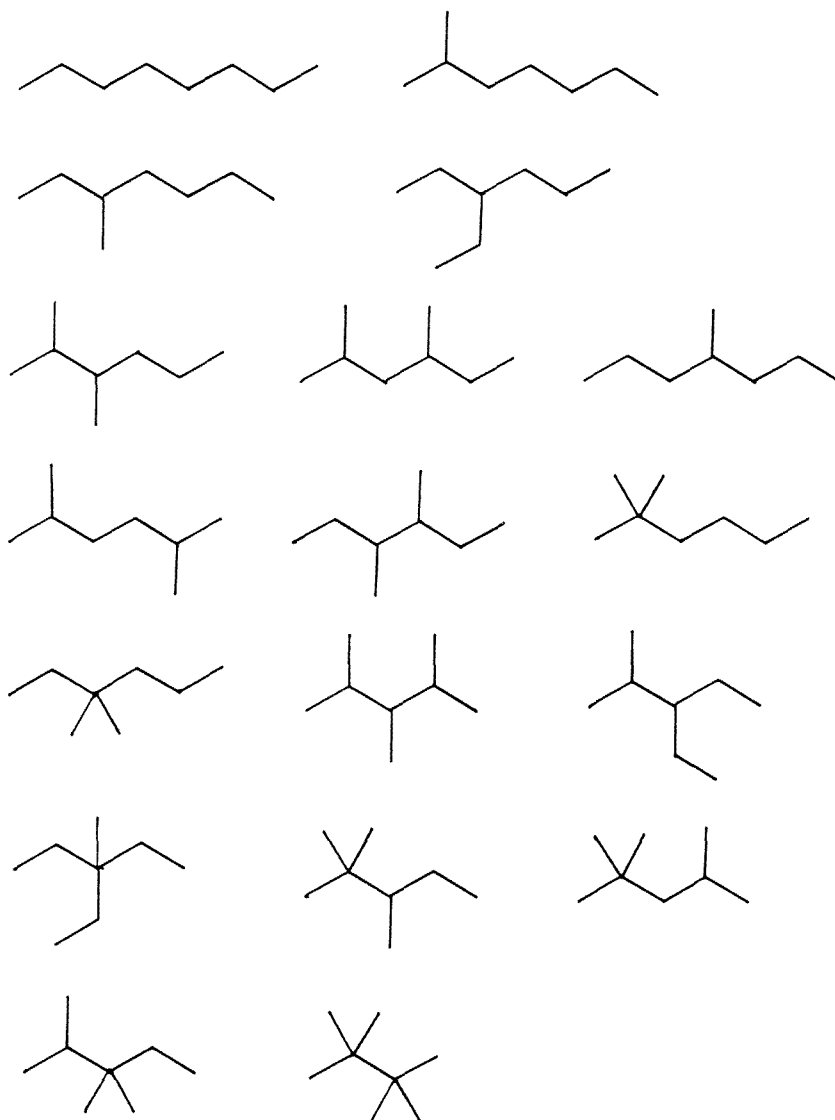


Fig. 2. Molecular skeletons (graphs)
for octane isomers (carbon atoms only).

which may be recognized as a paraphrase of Aristotle's "*Natura non facit saltus*" (Nature does not make jumps). With discrete objects, clearly there is a break of the traditional concept of the continuity; however, the above principles state that the concept of **vicinity**, which is defined for discrete objects, is somewhat similar to **neighborhood**, the basic concept of topology and the continuum. Thus, we can speak of close points (structures) and more distant points (structures) in a structure—

space which consists of clustering of disconnected points if we can arrive at a useful characterization of structures and an adequate metric. Perhaps a more pragmatic and less philosophical approach follows from a formation of the similarity principle as follows:

“Structures or systems that differ little in the mathematical **invariant** properties will differ little also in their physical, chemical, and biological properties.”

In the above quote, taken from ref. [26], we inserted the attribute **invariant** to emphasize a distinction between properties that are independent of conventions (such as an assumed labeling of atoms, or an orientation of a coordinate system adopted). This was necessitated to avoid ambiguities in a statement on "all mathematical properties" because mirror images of chiral objects are mathematically the same, yet they may be differentiated. For instance, one might identify unimodular determinants to mirror image coordinate systems with the Jacobian determinants taking values +1 and -1 for the right- and left-handed cases, respectively. The above immediately reveals a strategy to attack the problems of structure–property relationship. Rather than directly trying to relate a property to structure, we may instead investigate different mathematical properties (invariants) of a structure and then follow with property–property correlations in which relatively simpler mathematical properties are used to express more complicated or convoluted physico-chemical and biological properties.

Before considering specifics, let us emphasize the **qualitative** nature of the above similarity postulate. Deliberately, we use the attribute "little" without specifying how small little is. Neither do we qualify which mathematical properties are to be used, nor do we say what measure of similarity may be most suitable. Also, we have to emphasize that "structure" or "system" in the above postulate is the totality of atoms or molecules that mutually interact. A chiral object and its mirror image, viewed separately and isolatedly, will have all mathematical properties the same. This is analogous to the time dependence of a mechanical system in physics which under the reversal of time does not yield a distinguished description of the motion. It is the presence of another object that discriminates between chiral antipodes; hence, when chirality is manifested one has to take a whole system, the chiral molecule and its environment of all interacting parts, as "the structure".

It should also be clear that the similarity, even when one selects the metrics, is not an absolute quantity. Recently, however, an attempt to define an absolute similarity between a pair of structures was considered [27]. The idea behind such an absolute measure is the notion of a complete, or almost complete, basis of molecular descriptors that is analogous to a complete (or almost complete) basis of infinite vector spaces. While a search for an "almost complete basis" of invariants for a characterization of chemical structures is of considerable interest, for the time being similarity will continue to be confined to selected molecular descriptors.

Hence, similarity should be qualified by the appropriate attribute. Two molecules may be of similar size, of similar shape, of similar functionality, they may be similar with respect to path content, with respect to cyclic structure, with respect to selected components, etc. They may be similar in some properties but not in others. The need for such diversification is that for many molecular properties, not the molecule as a whole but parts of a molecule are responsible. Similarity satisfies axioms analogous to those for a metric, that is,

- (1) $S(A, B) > 0$, i.e. to every pair (A, B) one assigns a non-negative quantity S ;
- (2) $S(A, B) = S(B, A)$, i.e. similarity does not depend on the order of comparison.

Similarity is not transitive, that is, if A is similar to B and B is similar to C , it does not necessarily follow that A is similar to C (within the prescribed margins for a quantitative measure of similarity). That this is the case one can recognize by ordering a dozen structures so that successive structures differ little. The accumulative effect of gradual changes will, however, result in considerable differences between the initial and the final structure. Therefore, contrary to a distance function, neither the triangular inequality needs to hold, nor does $S(X, Y) = 0$ imply $X = Y$. In addition to the most customary Euclidean distance, there are other similarity coefficients that have found application in structure–property–activity studies.

5. Useful invariants

We will here briefly review a dozen graph invariants that have found *use* in various chemical applications. Emphasis here is on use, which is interpreted broadly. In some cases it leads to structural insights, in some cases to predictive qualitative or quantitative models. In some applications it may lead to a resolution of practical questions, such as the discrimination of non-isomorphic structures.

5.1. WIENER NUMBER – A MEASURE OF A MOLECULAR VOLUME

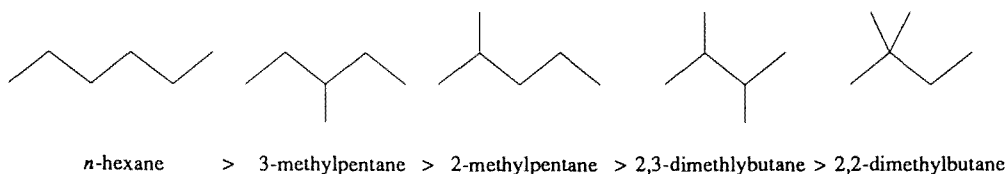
Wiener was intrigued by unqualified statements that molecular branching is the critical parameter which determines the relative magnitude of various molecular thermodynamic properties [28]. He therefore tried to quantify such correlations and in doing this, introduced a purely graph theoretical descriptor W defined, for trees only, as [29]:

“The path number W is defined as the sum of the distance between any two carbon atoms in the molecule, in terms of carbon–carbon bonds. Brief method of calculation: Multiply the number of carbon atoms on one side of any bond by those on the other side; W is the sum of these values for all bonds.”

Platt [30], immediately recognizing the importance of such descriptors, tried to rationalize their interpretation. He has shown that W relates to the overall molecular volume. Several very successful linear regressions by Wiener involved yet another graph theoretical descriptor P , the count of paths of length three. With these two descriptors, Wiener obtained regressions for various molecular properties for several families of compounds (alkanes, alcohols, fatty acids, amines) [31].

5.2. THE CONNECTIVITY INDEX

Can one characterize molecular branching by a single structural descriptor? This problem was considered in the mid 1970's by the present author [32] and resolved successfully. By first ordering isomers, such as the following hexanes:



and by decomposition of the corresponding hydrogen suppressed molecular graphs into bond components, such that one discriminates among C–C bond types (m, n) , where m, n signify the valences of the end vertices, we obtain:

$$\begin{aligned}
 2(1, 2) + 3(2, 2) &> 2(1, 2) + (1, 3) + 2(2, 3) > (1, 2) + 2(1, 3) + (2, 2) \\
 &+ (2, 3) > 4(1, 3) + (3, 3) > (1, 2) + 3(1, 4) + (2, 4).
 \end{aligned}$$

Construction of a descriptor requires finding a solution to the above set of inequalities. Inequalities of course may have an infinite number of particular solutions. A solution will guarantee that a bond additive property following the same relative sizes for the above compounds (and other smaller alkanes used to have enough number of inequalities) will produce a correlation of high quality. As outlined in [32], a simple prescription: $(m, n) = 1/\sqrt{m \cdot n}$ leads to numerical weights for different bond types that produce a correct relative ordering of isomers of small alkanes. Thus, by summing the contributing $1/\sqrt{m \cdot n}$ over all bonds, we obtain a single-number descriptor designed to yield good correlations for selected molecular properties. This defined the connectivity index ${}^1\chi$, which has found wide application in structure–property–activity studies [32,33]. Later, the connectivity index ${}^1\chi$ was generalized to "higher" connectivity indices ${}^m\chi$ [35] and to graphs representing hetero-molecules [36].

5.3. PATHS OF DIFFERENT LENGTHS

Platt [37] anticipated that path numbers may become useful descriptors of molecules. However, not until the late 1970's have paths been shown as useful descriptors. In a series of papers, Randić and Wilkins [38] have shown that short paths, in particular paths of length 2 and 3, suffice to order isomers in a hierarchical way and that the same ordering reflects upon the relative sizes of several of their physico-chemical properties. Later, the same authors have shown that paths offer a practical basis for a quantitative measure of molecular similarity of interest in structure–activity studies. The result of such comparisons is the partial order for the structures based on the considered property [39].

It should be pointed out that examination of molecular paths has led to a recognition of novel molecular properties. Carbon-13 NMR chemical shifts offer a direct probe into atomic environments of carbon atoms and probably represent one of the currently most valuable tools to study molecular structure and conformations. However, the variation of the sums of all carbon-13 chemical shifts among isomers, such as alkanes, shows pronounced regularities [40] and thus qualifies as an interesting molecular property, even though it represents a mathematical construction. Very successful correlations of ^{13}C chemical shift sums in alkanes were proposed using a single parameter based on a combination of path numbers [41].

5.4. WEIGHTED PATHS

Clearly, paths of shorter length are of interest as molecular descriptors in multivariate regressions as potential dominant components in structure–property correlations. Longer paths supply information of interest in comparisons of structures, for clustering, ranking and similarity analysis. Because typically there are many paths of intermediate length, they may obscure the role of shorter paths. For this reason, a weighting procedure that assigns to each bond a factor less than 1 should be considered. Such weights will weaken the contributions of longer paths and give prominence to the role that shorter paths play. It was found that the weighting factor $1/\sqrt{m \cdot n}$, introduced in the connectivity index, offers a suitable weighting procedure. In table 7, we illustrate weighted paths for a fragment of clonidine, a molecule of interest in QSAR [42].

5.5. ATOMIC ID

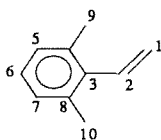
If weighted paths for each atom are added, one obtains a single-number representation for each atom (vertex) in a graph. Such atomic parameters were called atomic identification numbers, or atomic IDs, because typically non-equivalent atoms in a molecule will in this way be assigned different numerical values [26]. Moreover, atoms in different molecules also show distinct ID numbers. Thus, atomic ID numbers are characteristic of atomic environments. Significantly similar atomic

Table 7

Weighted path numbers for a 10-atom fragment of clonidine derivatives^{a)}. Each row gives information for individual atoms, the last row gives the results for the whole fragment (molecule).

Atom	p_1	p_2	p_3	p_4	p_5	p_6	p_7	Atomic ID
1	0.817	0.272	0.181	0.179	0.037	0.019	0.008	2.516
2	1.150	0.222	0.219	0.045	0.023	0.001	0.001	2.674
3	1	0.020	0.136	0.068	0.028	0.016		3.177
4, 8	1.319	0.426	0.302	0.064	0.049	0.001		3.170
5, 7	0.908	0.622	0.193	0.175	0.032	0.16		2.945
6	1	0.408	0.372	0.091	0.082			2.953
9, 10	0.577	0.428	0.246	0.175	0.037	0.029		2.497
Molecule								Molecule ID
	4.788	2.392	1.195	0.605	0.203	0.071	0.013	19.271

a)



environments are associated with numerical values for atomic ID which are similar. This regularity is the basis for the use of atomic ID in QSAR [43].

5.6. MOLECULAR ID

Similar to atomic ID is the molecular ID number [44] defined as the sum of all weighted paths in a molecule. Again, after examining the numerical values for molecular ID for several molecules, one sees that similar molecules show numerically similar ID numbers. Thus, ID numbers clearly capture considerable structural information. Therefore, they may be of interest in structure–property–activity studies. For example, a collection of therapeutically useful antihistamines, anticholinergics, antihypnotics, antidepressants, anticonvulsants and analgesics, which are apparently similar, have been clustered into various subclasses solely based on molecular ID numbers [45]. This shows the potential of ID numbers as a molecular descriptor.

5.7. PRIME ID NUMBERS

Molecular ID numbers apparently condense important structural features into a single numerical parameter that parallels some molecular properties. On the other hand, we see also that different molecules have distinct ID values. Szymanski and collaborators [46] undertook to examine the degree of uniqueness of ID numbers for alkane graphs, that is, cyclic graphs with a maximal valency of four. An exhaustive

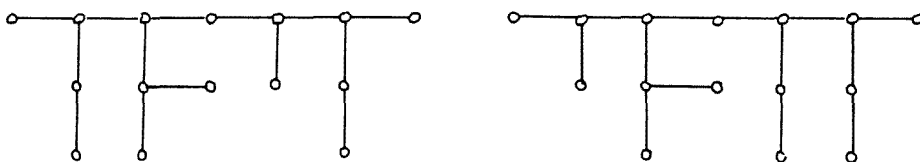


Fig. 3. The smallest graphs with the same molecular identification numbers (i.e. same sum for all weighted paths in a molecular graph).

(and efficient) computer search revealed the smallest pair of nonisomorphic trees (fig. 3) for pairs of graphs having $n = 15$ vertices as the smallest such duplicate graphs with the same ID numbers. This represents a pair of graphs among some 7500 graphs, which was an hitherto unheard of power of discrimination. Balaban's J index [47], which was so far the most discriminatory, produced duplications when $n = 10$, which is in the field of "only" 150 acyclic graphs. Despite the failure of the ID numbers to be unique in such high resolution power, hitherto not even approached by other topological indices [48], the ID numbers remain of interest because they lead to numerically similar entries for apparently similar structures and thus may serve a purpose in screening large data bases.

One should bear in mind, however, that the two goals: (i) design of a useful descriptor for QSAR, and (ii) design of a useful descriptor for documentation do not parallel one another. For the latter purpose, one wants to maximally discriminate among structures. Hence, if ID numbers are to be used in documentation, one should introduce as many different weights as there are different bond types. Hence, rather than using the algorithm $1/\sqrt{(m \cdot n)}$, one can assign to various (m, n) bond types successive prime numbers and construct similar weights as $1/\sqrt{(p_i p_j)}$, where p_i and p_j are the corresponding prime numbers. In this way, one reduces the chance of accidental duplication of ID numbers [49]. Indeed, as Szymanski and co-workers [50] have shown, the revised prime number IDs (based on the prime number weighting procedure as outlined in ref. [49]) results in even greater discrimination among alkane graphs – the first duplicate occurs for $n = 20$, about one graph in 600,000. While nonunique labels are of no particular interest in mathematics as such, in practice a scheme which leads to such high resolution among structures, as prime ID numbers do, may nevertheless be of considerable interest in chemistry.

5.8. DISTANCE MATRIX ANALOGS OF χ

The connectivity index ${}^1\chi$ derived in a bond-additive fashion by discriminating various (m, n) bond types was extended by Balaban [47] to distance matrices. Here, one uses the entries (x, y) of the distance matrix D of a graph as the source for construction of the bond-additive quantity J using the same algorithm $1/\sqrt{(x, y)}$ to which a normalizing factor was attached. Balaban and Quintas [51] examined the smallest graphs with the degenerate index J . Each such study tells something about

the capabilities of a single-number representation of graphs; however, the index J has not yet found much practical application in QSAR.

5.9. THE HOSOYA INDEX Z

Hosoya [52] introduced an important index Z for graphs defined as the sum $\sum p(G, k)$, where $p(G, k)$ is the number of ways in which k nonadjacent edges are chosen from a graph G . By definition $p(G, 0) = 1$, and trivially $p(G, 1) = E$, the number of edges in a graph. The summation extends to $[N/2]$, N being the number of vertices and the Gaussian brackets $[]$ represent the greatest integer function. Z was introduced initially as a "newly proposed quantity characterizing the topological nature of structural isomers of saturated n hydrocarbons", intended to be a "topological index as a sorting device for coding chemical structures" [53]. However, soon it was found to be of interest in structure–property studies since it shows correlations with several thermodynamic properties [54]. Note that similarly the DARC system by Dubois [55] and the codes for characterization of structures by Willett [56] were both initially designed as documentation-oriented systems, but soon were applied to the study of structure–property relationships. Because of the structural basis of such systems, they often adequately reflect various structural factors of a molecule and hence become of potential interest in the structure–property applications. One may say that interest in initial studies "switched" the priorities, and such studies became oriented toward coding that is of interest in property studies rather than being solely confined to interests of chemical documentation.

Hosoya's Z index, called the topological index (although in fact it would be more appropriate to call it the graph theoretical index), was the first index deliberately introduced to represent a structure (graph) by a single number. Today, the term "topological index" has become generic and stands for any single-number representation of a graph.

5.10. KEKULÉ STRUCTURE COUNT K

An important class of organic compounds, the cyclic conjugated hydrocarbons, received considerable attention in theoretical chemistry. In fig. 4, we illustrate carbon skeletons of a number of polycyclic conjugated hydrocarbons. A convenient classification of such is:

- (1) benzenoids = systems composed of fused hexagons (and having $K \neq 0$);
- (2) alternants = nonbenzenoids having in addition to benzene (hexagons) rings also $4m$ membered rings;
- (3) nonalternants = systems having (besides even rings) also odd rings.

Cyclic systems (without exocyclic CC bonds such as in triphenylmethyl, or even more stable tris(biphenyl)methyl) with $K = 0$ are typically hypothetical, being non-

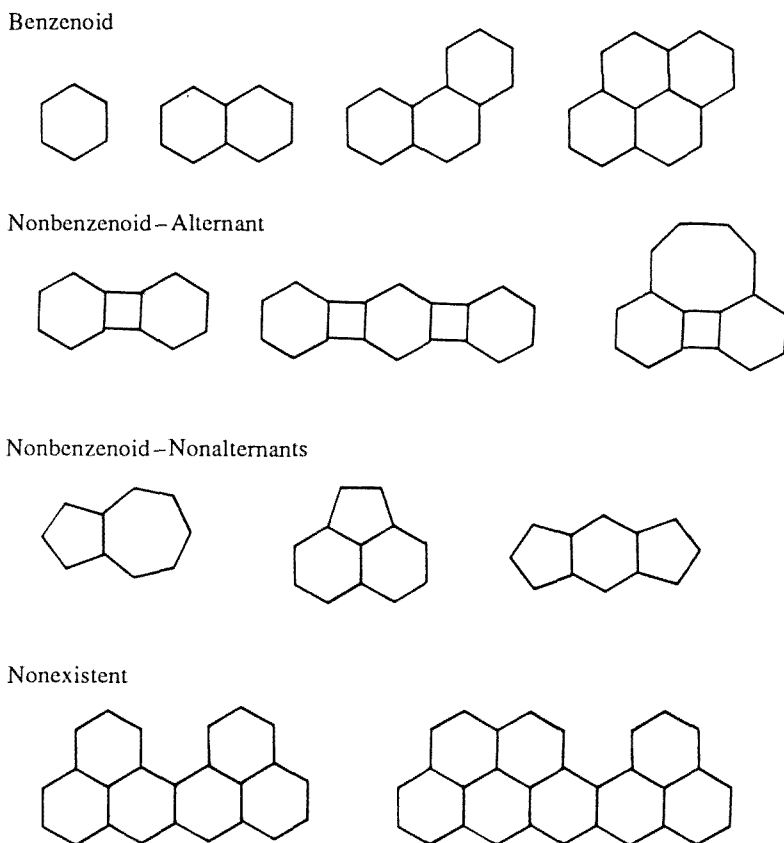


Fig. 4. Conjugated hydrocarbons: small benzenoid systems (top row); alternant nonbenzenoids (i.e. systems with even cycles only) (next row); nonalternants (systems with odd rings) (third row); and nonexistent (last row).

existent or at least highly reactive. Empirically, it was found that among structures of similar size, those with larger K are more stable [57]. K , the number of Kekulé valence structures of chemistry, is equivalent to the number of perfect 1-matchings for the corresponding graphs in mathematics. In fig. 5, we illustrate eleven Kekulé valence structures of benzopyrene. There is considerable literature in chemical graph theory on the enumeration of Kekulé valence structures [58–60]. In particular, considerable attention was given to benzenoid systems (that is, systems built from fused benzene rings). An early elegant algorithm by Gordon and Davison [61] was generalized to nonbenzenoid chains of fused rings [62], to branched catacondensed benzenoids [63], and to lattices of benzenoids [64]. Finally, John and Sachs [65] produced an elegant determinantal form for deriving K for a generalized benzenoid system.

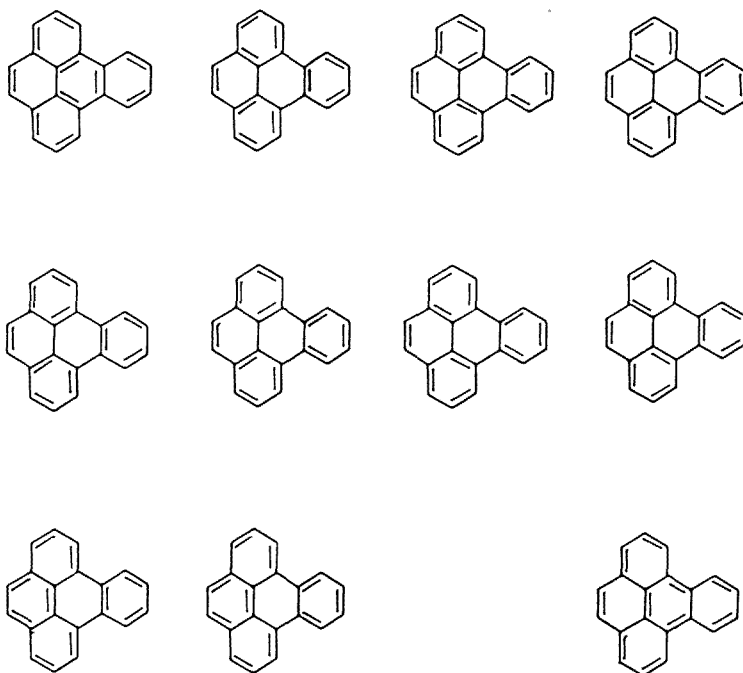


Fig. 5. All Kekulé valence structures of benzopyrene.

6. Conjugated circuits and aromaticity

We will end the review of selected molecular descriptors by considering conjugated circuits. Despite the long history of Kekulé valence structures and an intensive use thereof in the early valence bond (VB) calculations, the conjugated circuits as structural invariants were overlooked for a long time! Conjugated circuits are defined for individual Kekulé valence structures. In fig. 6, we illustrate them

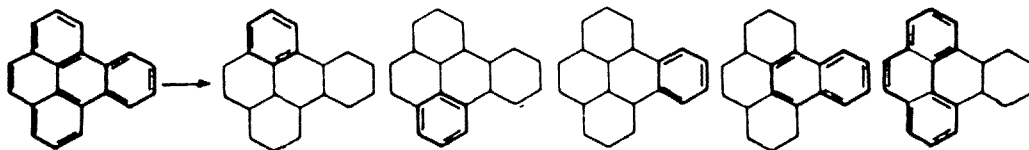


Fig. 6. Conjugated circuits within a single Kekulé valence structure (one of the eleven Kekulé valence structures shown in fig. 5).

for one of the eleven Kekulé valence structures of benzopyrene of fig. 5. A circuit in a valence structure in which there is a regular alternation of CC single and CC

double bonds defines a conjugated circuit. They are necessarily even and can be of size $4n + 2$ and $4n$, labeled R_n and Q_n , respectively. Hence, while a conjugated system can be viewed as a superposition of Kekulé valence structures, each Kekulé valence structure can be decomposed into conjugated circuits. Hence, we can view a conjugated system as a superposition of various conjugated circuits. In systems having essentially single C–C bonds (or essentially double C=C bonds), such a superposition does not change the singular nature of these bonds which are part of the conjugated framework. The decomposition of Kekulé valence structures of conjugated systems into contributing conjugated circuits has proved very useful in various applications:

(1) The average contribution of Kekulé valence structures yields an expression for molecular resonance energy (RE) [7, 66–68]. RE can be defined as that part of the molecular energy that makes a cyclic system more stable compared to an appropriate corresponding noncyclic standard. That is, RE represents a deviation in molecular energy from bond additivity. The expressions of RE in R_n and Q_n show that this deviation of the energy of a cyclic system itself is circuit-additive, but only the conjugated circuits make a contribution.

(2) The $4n + 2$ conjugated circuits make a positive contribution (i.e. add to the stability of a molecule), while $4n$ conjugated circuits destabilize the structure. On the basis of this empirical fact, one can classify cyclic conjugated systems into the following [66]:

- (i) Those having only $4n + 2$ conjugated systems, hence most stable. This class is by definition considered as aromatic.
- (ii) Those having only $4n$ conjugated circuits, hence most unstable. This class by definition represents so-called antiaromatic systems, the concept introduced by Breslow [69].
- (iii) Systems having both $4n + 2$ and $4n$ conjugated circuits, which will show various degrees of aromaticity, depending on the relative role of R_n and Q_n contributions.

In fig. 7, we illustrate carbon skeletons of several aromatic and antiaromatic cyclic conjugated hydrocarbons. Considerable literature on conjugated circuits followed the initial work of Randić and collaborators [7, 66, 67]. In particular, this includes the relationship of the conjugated circuit model to the approach to the VB Resonance Theory by Herndon [70], the enumeration of conjugated circuits, the parametrization of the R_n and Q_n , their statistical treatment, etc. [71]. In addition to offering a simple computational approach to the molecular RE, the concept of conjugated circuits is to be noticed for important conceptual developments. It gives insights into the important distinction between various polycyclic conjugated systems. A simple geometrical classification of cyclic conjugated systems into alternants and

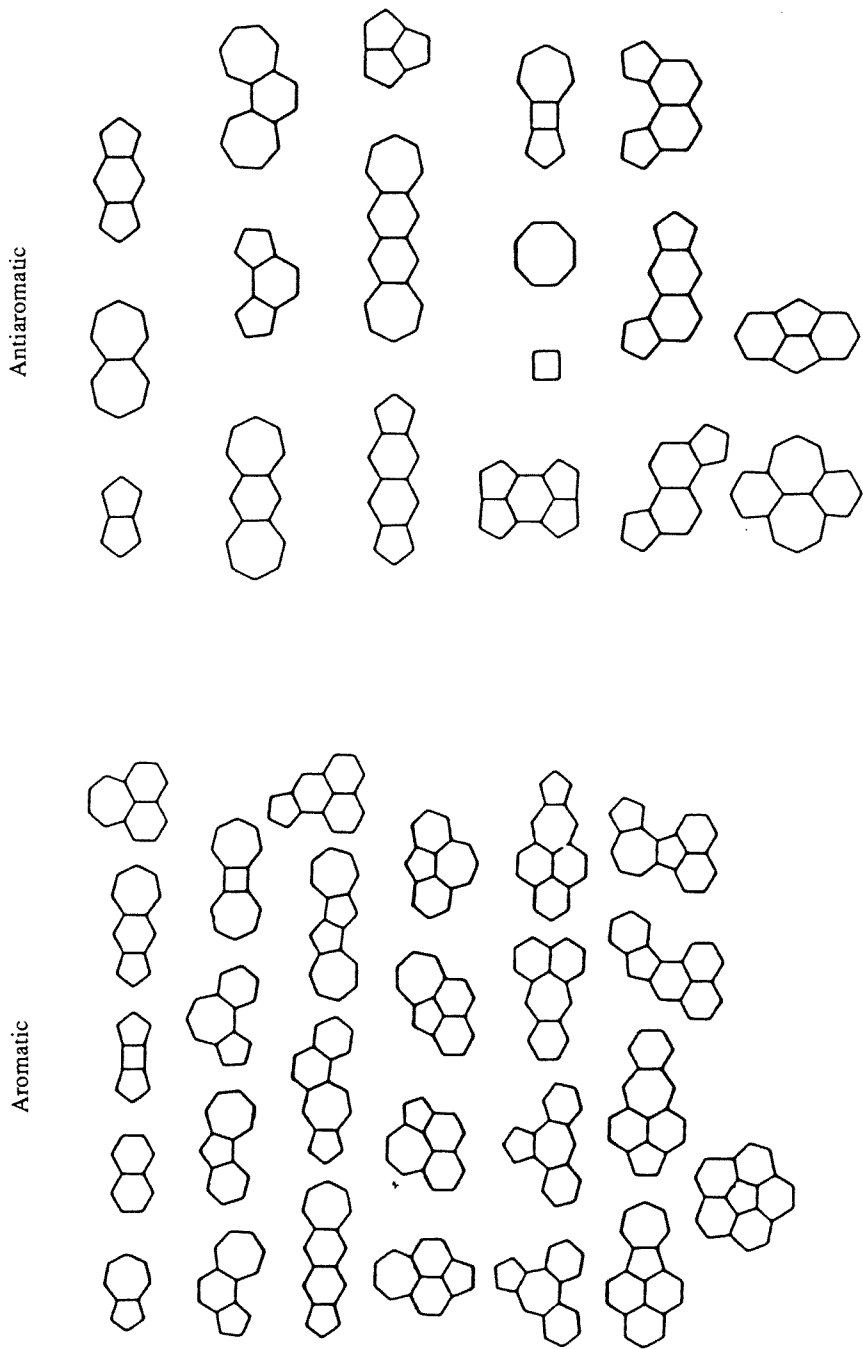
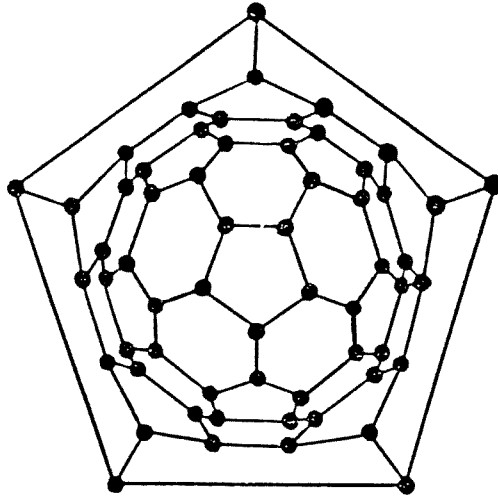
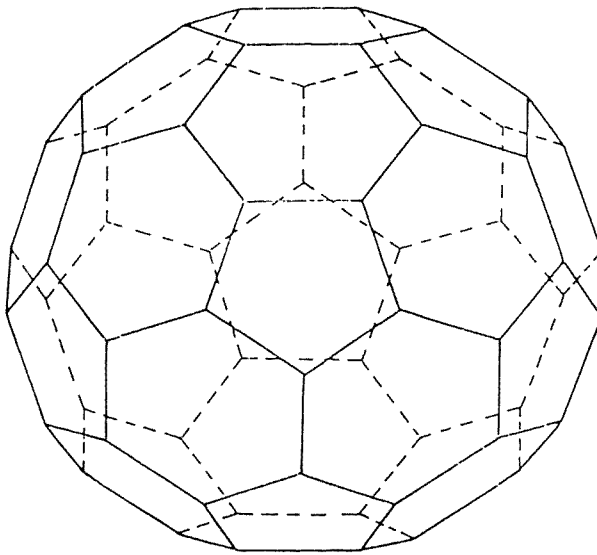


Fig. 7. Aromatic systems (having only $4n + 2$ conjugated circuits (left-hand side), and antiaromatic systems (having only $4n$ conjugated circuits) (right-hand side).



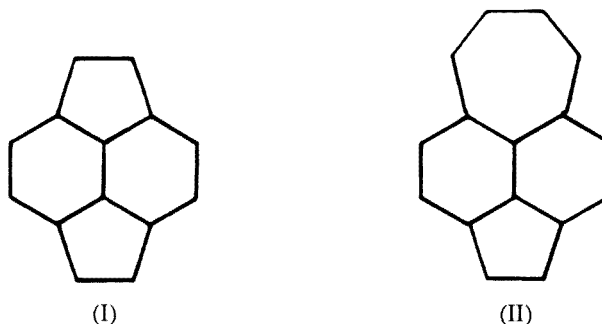
(a)



(b)

Fig. 8. Buckminsterfullerene graph (a) and projection (b).

nonalternants does not highlight the fundamental distinction between apparently similar azupyrene (I) and acepleiadylene (II):



However, the decomposition of the Kekulé valence structures of the two polycyclic hydrocarbons in conjugated circuits immediately shows a basic distinction between the two. We obtain the following expression for their respective molecular RE [67]:

$$\text{azupyrene:} \quad (4R_1 + 2R_2 + 6Q_3)/4;$$

$$\text{acepleiadylene:} \quad (4R_1 + 2R_2 + 6R_3)/4.$$

Thus, the former is by far less stable, while the latter should show considerable similarity in properties to typical benzenoid hydrocarbons even though it is formally classified as a nonbenzenoid. The presence of Q_n contributions makes the corresponding hydrocarbons more elusive in synthesis. Hafner [72] was the first to synthesize some of these more elusive cyclic conjugated hydrocarbons.

As another illustration of the use of conjugated circuits, consider buckminsterfullerene (fig. 8), a carbon C_{60} cage which has recently received considerable attention. Klein and coworkers [73] were the first to report that this unusually stable cage has 12,500 Kekulé valence structures. Later, they were able to count conjugated circuits (using the transfer matrix approach [74] and taking advantage of the fivefold symmetry axis of the molecule), not only in this particular cage but also in all cages built from fusions of five, six and seven rings [75]. They reported the corresponding RE, which clearly shows that buckminsterfullerene C_{60} is visibly more stable. No other theoretical approach could lead to such a reliable estimate of the molecular stability.

7. Polynomials as a source for invariants

The coefficients of graph polynomials offer a route to a characterization of graphs. We will briefly mention half a dozen of such, although the use of most of the polynomials in structure–property applications remains yet to be proved.

7.1. CHARACTERISTIC POLYNOMIAL

This is by far the most widely known and discussed polynomial in graph theory as well as in chemical graph theory. Various methods of deriving the characteristic polynomial $Ch(G;x)$ for graph G are known [76], clearly those based on the trace of the adjacency matrix being sufficiently efficient [77]. Factoring of the characteristic polynomial was reported [78] and alternative representations in Chebyshev polynomials have been shown to have some interesting properties [79].

Graph spectra [80] (eigenvalues of the adjacency matrix) also received considerable attention in the chemical literature. In particular, this relates to isospectral and subspectral graphs [81]. Belatedly, however, graph spectra were recognized as equivalent to pi-electron molecular orbital energies of the so-called HMO (Hückel molecular orbital model) [2]. Belatedly, because by early 1970 the HMO model was no longer a preferred tool. Today the HMO model serves primarily as an educational tool, although neither its historic value nor its interpretation as a topological model for complex molecules can be denied [82]. It is still occasionally found of interest [83].

7.2. ACYCLIC OR MATCHING POLYNOMIAL

Lieb [84] was the first to investigate the polynomial that for trees coincides with the characteristic polynomial. The acyclic polynomial can be derived for a general graph either from Hosoya's $p(G, k)$ numbers or, alternatively, from a decomposition of a graph into characteristic subgraphs consisting of disjoint edges and disjoint cycles only [85]. The acyclic polynomial $Ac(G;x)$, usually referred to in the mathematical literature as the matching polynomial, has all roots real [86]. Another intriguing property of the acyclic polynomial was outlined by Godsil and Gutman [87]. They have shown that the acyclic polynomial appears as a factor of a characteristic polynomial of an augmented acyclic graph. The augmented acyclic graph [88] is constructed by depicting all paths in a cyclic graph, as illustrated in fig. 9. This property aids in obtaining acyclic (matching) polynomials for many smaller graphs [89]. The construction of acyclic polynomials for large complex graphs can be unusually tedious, but if graphs have periodicity, such as systems built of fused benzene rings, the transfer matrix approach helps. The construction of acyclic polynomials using the transfer matrix was shown on several examples [90]. In fig. 10, we show the results for smaller benzenoids expressed in matrices I, J, K outlined by Randić, Hosoya and Polansky [91]. It is of some interest to see that such matrices on the one hand may be viewed as a nomenclature device. However, on the other hand, by a proper interpretation they become operators. This illustrates the power of mathematical nomenclature which allows algebraic manipulations.

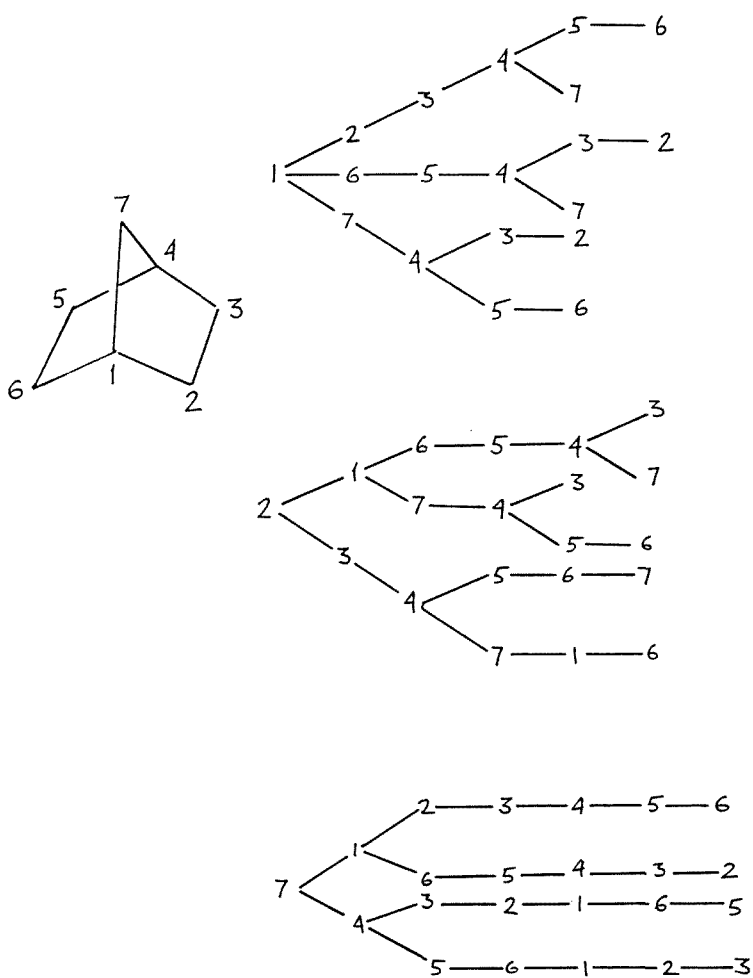


Fig. 9. Graphs depicting all paths for the graph of norborane. Only nonequivalent vertices are considered.

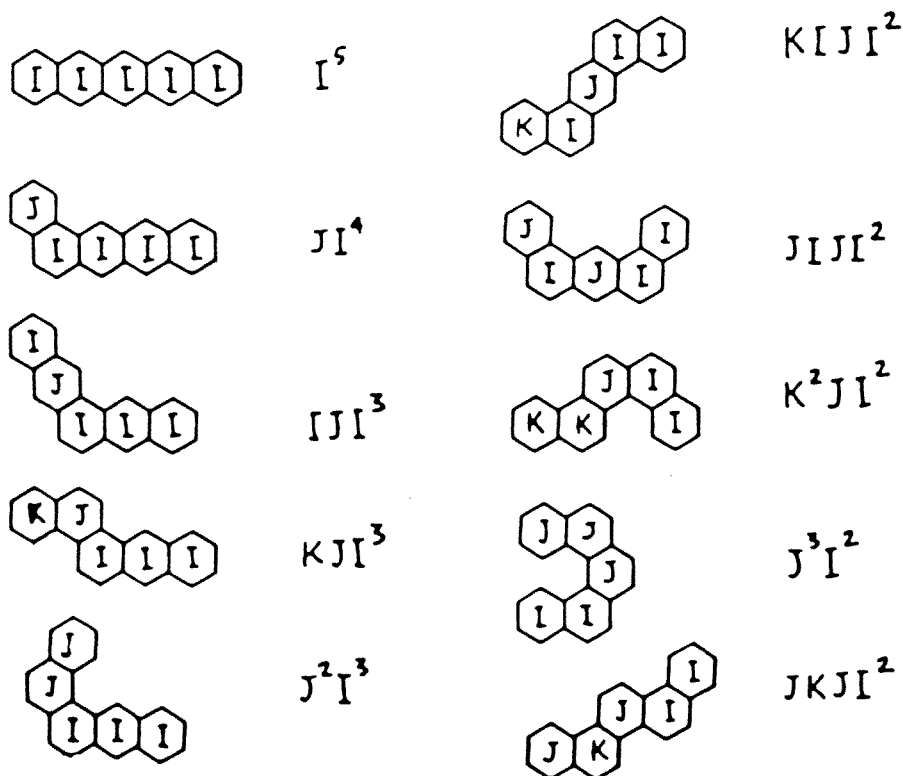


Fig. 10. Smaller benzenoids with labeling which identifies the form of the transfer matrix that will produce acyclic (matching) polynomials.

7.3. THE ALTENBURG POLYNOMIAL

Altenburg [92] proposed a polynomial for acyclic graphs, the coefficients of which count paths of different length, or alternatively, count pairs of vertices a distance p apart. When extended to cyclic structures, as outlined by Hosoya [52], such a polynomial gives the population of a given topological distance in a graph. From the coefficients of such a polynomial, Altenburg constructed sums $W = \sum C_k k$ (not being aware that the result gives the Wiener number) and has shown a linear correlation of W/N^2 (which defines squared radii of an alkane) with ${}^1\chi$.

7.4. DISTANCE POLYNOMIAL

Similar to the characteristic polynomial which is derived from the adjacency matrix, one can consider the distance matrix and its characteristic polynomial [93]. Hosoya and coworkers [94] considered the distance polynomial, from which an index Z' similar to the Hosoya Z index constructed for acyclic polynomials can be

constructed as the sum of the absolute values of the coefficients of the polynomial. In view of the relatively large values of the coefficients, it is less likely that two graphs will have the same distance polynomial or the same Z' .

7.5. TERMINAL POLYNOMIAL

An important, even if not sufficiently well known, theorem for trees by Zaretskii [95] states that a tree is uniquely characterized by a distance matrix in which only entries for terminal vertices are included. In table 8, we list terminal polynomials for some smaller trees. Kleiner and Randić [96] examined the properties

Table 8

Illustration of terminal polynomials of some smaller trees.

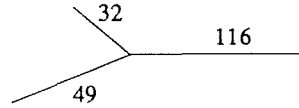
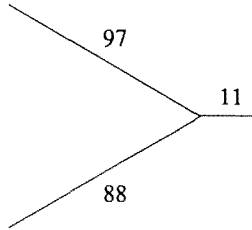
Terminal matrix	Terminal polynomial	Graph
$\begin{pmatrix} 0 & 2 & 3 & 5 \\ 2 & 0 & 3 & 5 \\ 3 & 3 & 0 & 4 \\ 5 & 5 & 4 & 0 \end{pmatrix}$	$x^4 - 88x^2 - 376x - 416$	
$\begin{pmatrix} 0 & 2 & 4 & 5 \\ 2 & 0 & 4 & 5 \\ 4 & 4 & 0 & 3 \\ 5 & 5 & 3 & 0 \end{pmatrix}$	$x^4 - 95x^2 - 404x - 444$	
$\begin{pmatrix} 0 & 2 & 5 & 5 \\ 2 & 0 & 5 & 5 \\ 5 & 5 & 0 & 2 \\ 5 & 5 & 2 & 0 \end{pmatrix}$	$x^4 - 108x^2 - 400x - 384$	
$\begin{pmatrix} 0 & 3 & 4 & 5 \\ 3 & 0 & 3 & 4 \\ 4 & 3 & 0 & 3 \\ 5 & 4 & 3 & 0 \end{pmatrix}$	$x^4 - 84x^2 - 384x - 476$	

of associated characteristic polynomials, with a particular interest in the occurrence of isospectral trees for Zaretskii matrices. An extensive computer search among trees with three terminal vertices, each branch having up to 30 vertices, for isospectral cases has revealed none. However, by examining the structure of the polynomials, it was possible to construct a pair of trees with isospectral terminal polynomials, shown in table 9 [97]. It is not known whether this particular pair is the smallest such pair.

Table 9

Isospectral terminal polynomials

$$T(G; x) = x^3 - x_{1,2^2} + x_{1,3^2} + x_{2,3^2}x - 2(x_{1,2} x_{1,3} x_{2,3})$$



$$x_{1,2} = 97 + 88$$

$$x_{1,3} = 97 + 11$$

$$x_{2,3} = 97 + 88$$

$$x_{1,2} = 32 + 116$$

$$x_{1,3} = 32 + 49$$

$$x_{2,3} = 116 + 49$$

$$\begin{aligned} T(G_1; x) &= x^3 - [(185)^2 + (108)^2 + (99)^2]x - 2(185)(108)(99) \\ &= x^3 - 55,690x - 3,956,040 \end{aligned}$$

$$\begin{aligned} T(G_2; x) &= x^3 - [(148)^2 + (81)^2 + (165)^2]x - 2(148)(81)(165) \\ &= x^3 - 55,690x - 3,956,040 \end{aligned}$$

7.6. BIPARTITE POLYNOMIAL

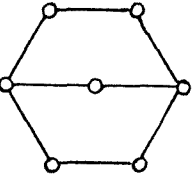
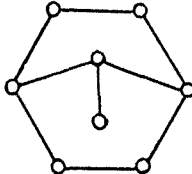
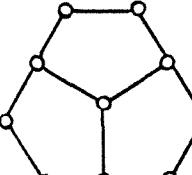
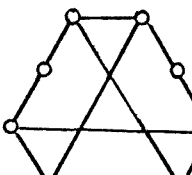
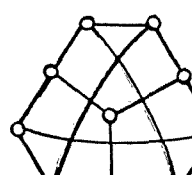
One can derive the acyclic polynomial from the characteristic polynomial by counting only contributions to the polynomial arising from disjoint edges. This is precisely entailed in Hosoya's construction of his *Z* index. If one includes, besides isolated edges, also contributions of even cycles, but not odd cycles, one obtains a novel polynomial named the bipartite polynomial [98]. Bipartite polynomials coincide with the characteristic polynomial of bipartite graphs (that is, graphs with only even cycles) as acyclic polynomials coincide with the characteristic polynomial for trees. So far, we know little about the bipartite polynomials, including the question of whether their roots are always real. In table 10, we illustrate bipartite polynomials for selected graphs.

7.7. VICINAL POLYNOMIAL

Another polynomial that may be a source of useful invariants is derived from a vicinal matrix, a matrix the entries of which count the occurrence of paths (i, j) in a qualified graph. Such a matrix was mentioned in a work of Zefirov and

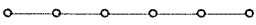
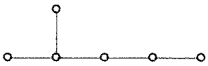
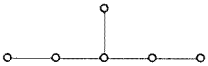
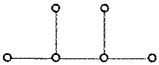
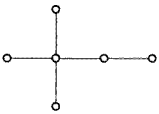
Table 10

Illustration of bipartite polynomials for the Petersen graph and some of its subgraphs.

Graph	Bipartite polynomials
	$x^7 - 8x^5 + 17x^3 - 10x$
	$x^8 - 9x^6 + 23x^4 - 19x^2 + 4$
	$x^{10} - 12x^8 + 48x^6 - 75x^4 + 39x^2 - 3$
	$x^9 - 12x^7 + 45x^5 - 66x^3 + 24x$
	$x^{10} - 15x^8 + 75x^6 - 165x^4 + 120x^2 - 6$

collaborators [99], but it was not considered separately. Rather, it was combined with the adjacency matrix in an attempt to arrive at a novel topological index. Recently, however, the vicinal matrix received some attention [100]. While the coefficients of the associated characteristic polynomial show a wide variation in size among isomers, nevertheless the first eigenvalue (the largest positive eigenvalue) of vicinal matrices shows some regularities in isomeric variations (table 11).

Table 11
Illustration of vicinal polynomials.

Graph	Vicinal polynomial	First eigenvalue
	$x^6 - 406x^4 - 24560x^3 - 15715x^2 - 4200x + 37375$	24.809
	$x^6 - 304x^4 - 2671x^3 - 6360x^2 - 577x + 3415$	21.094
	$x^6 - 270x^4 - 2130x^3 + 4050x^2 - 2400x + 2375$	19.703
	$x^6 - 209x^4 - 1424x^3 - 2801x^2 - 2160x - 575$	17.345
	$x^6 - 198x^4 - 1162x^3 - 1620x^2 - 540x + 115$	16.559

7.8. GENERALIZED WHELAND POLYNOMIAL

We end this section on polynomials by considering the generalized Wheland polynomial. Wheland [101] introduced a counting polynomial having the recursion:

$$Wh(G; x) = Wh(G - E; x) + (1 - x)Wh(G - EE; x),$$

where $G - E$ is a graph with edge E deleted and $G - EE$ is a graph with deleted edge E and its incident edges. $Wh(G; x)$ counts the "valence structures of different degrees of excitation" [101], which are of interest in VB calculations. Unfortunately, $Wh(G; x)$ is not a graph or structural invariant. The form of the polynomial depends on the

selection of the canonical valence structures and these in turn depend on the assumed numbering of vertices, as discussed at some length by Ohkami and Hosoya [102]. However, if the Wheland polynomial is generalized so that it counts not only canonical valence structures but *all* the valence structures, we obtain polynomials $GW(G; x)$, a generalized Wheland polynomial. GW stands for George Wheland, a brilliant scientist who was prematurely incapacitated [103]. The coefficients of the generalized Wheland polynomial represent invariants, and hence may offer useful molecular descriptors. Properties of $GW(G; x)$ polynomials received some attention [104].

8. Matrices as a source of invariants

Although there have been many efforts to enlarge the pool of molecular descriptors by considering various *ad hoc* constructions, generalized matrices as a source of graph invariants have been for too long overlooked. Even before 1940, Balandin [105] advocated the use of matrices in studies of molecular properties. He constructed various matrices by substituting selected molecular properties as matrix entries. If one restricts such considerations to mathematical properties, which can always be derived accurately and made available, rather than using experimental properties which are often inaccurate or unavailable, one would immediately enlarge the pool of structural invariants enormously. Such an approach has recently been advocated [6], and we will follow by briefly listing a few of such more general matrices of potential interest.

8.1. TWO-DIMENSIONAL TOPOGRAPHIC MATRICES

Consider a regular hexagonal lattice (honeycomb or graphite lattice) and graphs embedded on such a lattice. The same graph (up to isomerism) can now occur in different conformations, as illustrated in fig. 11, for the carbon atom

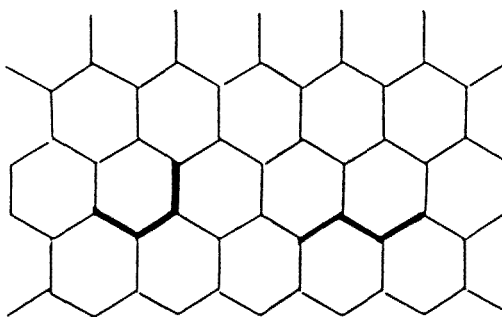


Fig. 11. Graphite (honeycomb) lattice with two distinct embeddings of a butadiene (chain of four carbon atoms, with hydrogens suppressed).

skeletons of cis- and trans-butadiene. If we assume a standard CC bond length of 1, the two cases lead to different distance matrices [106]:

cis-butadiene	trans-butadiene
$\begin{pmatrix} 0 & 1 & \sqrt{3} & 2 \\ 1 & 0 & 1 & \sqrt{3} \\ \sqrt{3} & 1 & 0 & 1 \\ 2 & \sqrt{3} & 1 & 0 \end{pmatrix}$	$\begin{pmatrix} 0 & 1 & \sqrt{3} & \sqrt{7} \\ 1 & 0 & 1 & \sqrt{3} \\ \sqrt{3} & 1 & 0 & 1 \\ \sqrt{7} & \sqrt{3} & 1 & 0 \end{pmatrix}$

One now expects that many invariants derived from these two different matrices will in general be different. Hence, such topographic matrices (with idealized molecular geometries enforced by embedding on a regular hexagonal grid) will lead to molecular descriptors which will discriminate among conformers of the same molecular graph.

8.2. THREE-DIMENSIONAL TOPOGRAPHIC MATRICES

The same approach can be extended to alkanes and other related saturated compounds by replacing a two-dimensional honeycomb grid by a three-dimensional diamond grid (fig. 12) [107]. In table 12, we illustrate such a matrix for the all-trans

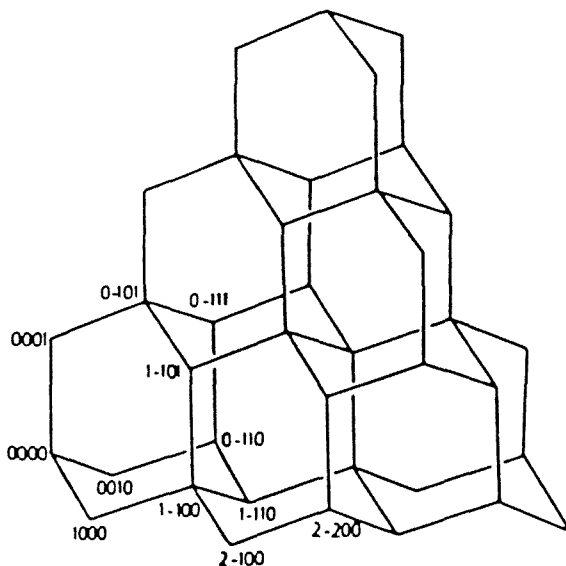
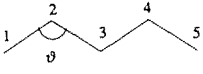


Fig. 12. Diamond lattice characterized by tetrahedral angle. The four directions lead to coordinates x, y, z, u (indicated for several points close to the origin $(0, 0, 0, 0)$).

Table 12

The geometry matrix and the weighted paths obtained from this matrix for *n*-pentane (a straight chain of five carbon atoms with tetrahedral angle of $109^{\circ}28'$ between the adjacent bonds).

Graph	Geometry matrix				
 $\vartheta = 109^{\circ}28'$	0	1	1.6330	2.5166	3.2660
	1	0	1	1.6330	2.5166
	1.6330	1	0	1	1.6330
	2.5166	1.6330	1	0	1
	3.2660	2.5166	1.6330	1	0
Atom	Paths				Atomic ID
1	1.1222	0.7442	0.3348	0.0748	3.2761
2	0.9301	0.7004	0.3676	0.0898	3.0879
3	0.8421	0.6953	0.3509	0.1002	2.9886
Molecule	2.4734	1.7924	0.8779	0.2147	10.3583

rotational isomer (rotamers) of *n*-pentane. The ALLPATH program [108], which counts all paths (or alternatively, all weighted paths), has been changed to count paths in topographic matrices. Since matrices are no longer sparse, the computational time required to count all paths increases considerably. As the size of such matrices increases, eventually the computations will not be practical after a certain size.

8.3. GEOMETRY-DISTANCE MATRIX

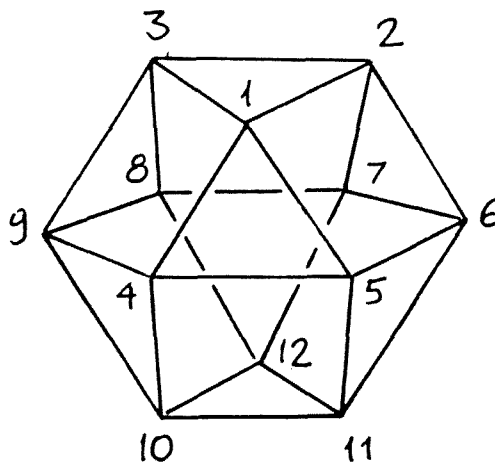
Of course, many molecular geometries do not involve a simple trigonal hybridization (angle of 120°) associated with the graphite lattice or tetrahedral hybridization (angle $109^{\circ}28'$) associated with the diamond grid as are ubiquitous in carbon chemistry. Hence, a matrix in which entries show Euclidean distances between atoms may be considered. Such a geometric matrix, as well as other matrices with no zero off-diagonal entries, considerably increase the computational time when all paths are to be enumerated. Hence, some truncated form of such matrices may become desirable if the analysis is to be extended to larger compounds.

8.4. GEODESIC MATRIX

In polyhedra, geodesic distances may be of interest, measured over the surface of the polyhedra, rather than geometric distance measured "through space". If one restricts distances only between vertices having a common face (that is, the nearest neighbors and vertices with a common face), one obtains simple matrices, i.e. matrices with several zero entries. Such matrices nevertheless contain the essential information for a reconstruction of the polyhedron. In table 13, we illustrate such a facial matrix for the graph shown [109].

Table 13

Illustration of a polyhedron and its adjacency matrix in which only distances for vertices belonging to the same face are included.

$$\begin{pmatrix}
 0 & 1 & 1 & 1 & 1 & \sqrt{2} & 0 & 0 & \sqrt{2} & 0 & 0 & 0 \\
 1 & 0 & 1 & 0 & \sqrt{2} & 1 & 1 & \sqrt{2} & 0 & 0 & 0 & 0 \\
 1 & 1 & 0 & \sqrt{2} & 0 & 0 & \sqrt{2} & 1 & 1 & 0 & 0 & 0 \\
 1 & 0 & \sqrt{2} & 0 & 1 & 0 & 0 & 0 & 1 & 1 & \sqrt{2} & 0 \\
 1 & \sqrt{2} & 0 & 1 & 0 & 1 & 0 & 0 & 0 & \sqrt{2} & 1 & 0 \\
 \sqrt{2} & 1 & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 1 & \sqrt{2} \\
 0 & 1 & \sqrt{2} & 0 & 0 & 1 & 0 & 1 & 0 & 0 & 0 & 1 \\
 0 & \sqrt{2} & 1 & 0 & 0 & 0 & 1 & 0 & 1 & \sqrt{2} & 0 & 1 \\
 \sqrt{2} & 0 & 1 & 1 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & \sqrt{2} \\
 0 & 0 & 0 & 1 & 2 & 0 & 0 & \sqrt{2} & 1 & 0 & 1 & 1 \\
 0 & 0 & 0 & \sqrt{2} & 1 & 1 & 0 & 0 & 0 & 1 & 0 & 1 \\
 0 & 0 & 0 & 0 & 0 & \sqrt{2} & 1 & 1 & \sqrt{2} & 1 & 1 & 0
 \end{pmatrix}$$


8.5. WILSON'S G^{-1} MATRIX

An alternative to the geometry matrix is the G^{-1} matrix of Wilson [17] and Eliashevich [110] which incorporates, in addition to geometrical features, also the masses of the atoms involved.

8.6. BOND FUNCTION MATRICES

Since entries of a matrix correspond to pairs (i, j) of vertices, any function $F(i, j)$ will, in general, lead to an associated matrix F . If (i, j) represents force constants in a potential function, F becomes the F matrix of Wilson's FG matrix method for the calculation of normal coordinates of molecules [17]. $F(i, j)$ can represent rather arbitrary quantities, in which case we will obtain a family of F -matrices with the corresponding interpretation. Let us mention a few choices only:

- (a) F represents Pauling bond order [111];
- (b) F represents Coulson bond orders [112];
- (c) F represents generalized bond order (*vide infra*) [113].

9. Novel approaches and novel invariants

From what is outlined above, we see that the only limit to the design of invariants is the imagination and resourcefulness of investigators. Hence, a proliferation of structural invariants is to be expected. While some may be alarmed by such a prospect others, including this author, welcome such developments provided some rules in the game of designing new invariants are observed. The situation is similar to a search for a system of codes and a design of codes for chemical structures in particular. There, too, rules have to be obeyed if one is interested in developing a system of nomenclature that has promise for practical use. In table 14, we summarize a few of the more important desired properties for codes, due to Read [114]. Analogous rules for the construction of invariants (topological indices in particular) that this author has advanced [115] are also listed in table 14. Balaban similarly listed some requirements for a satisfactory topological index [116]. Such descriptors are mainly to be used in multiple regressions, where the prime criterion for a successful correlation can be summarized in two commands:

- (1) use as few descriptors as possible; and
- (2) use descriptors with a direct structural interpretation.

The first command ensures a viable *statistics* (reliability) and the second a viable *interpretation* (insight, understanding). With a recently introduced approach to multivariate regression based on the construction of orthogonal molecular

Table 14

Requirements for codes according to Read and analogous requirements for structural invariants of potential interest in structure–property–activity studies.

Requirements for codes as proposed by Read	Desirable attributes for topological indices
1 Codes should be linear strings of symbols	1 Direct structural interpretations
2 Codes should be unique	2 Good correlation with at least one property
3 Reconstruction algorithm should be defined	3 Good discrimination of isomers
4 Codes should be simple (preferably made by hand)	4 Locally defined
5 Decoding should be possible, preferably by hand	5 Generalizable to "higher" analogues
6 Nonsystematic (trivial) names should not be used	6 Linearly independent
7 Properties should not be used	7 Simplicity
8 Codes should be brief	8 Not based on physico-chemical properties
9 Codes should be pronounceable	9 Not trivially related to other indices
10 Codes should be easily understood	10 Efficiency of construction
11 Familiar symbols only should be used	11 Based on familiar structural concepts
12 Coding and decoding should be efficient	12 Show a correct size-dependence
13 Similar structures should have codes of similar length (proposed by Randić)	13 Gradual change with gradual change in structures

descriptors [117], it may be possible to extract the dominant descriptors from a given initial set of descriptors. The methodology of orthogonal descriptors can also be applied to compact relevant structural information in fewer descriptors [118]. It thus appears that more attention ought to be given to the *interpretation* of descriptors rather than merely to generating descriptors, the interpretation of which becomes more and more involved. In this respect, for instance, one may view eigenvalues (graph spectra) as convoluted, although conceptually not involved. That is, for given graphs, most often one cannot simply by inspection (by examining various fragments present, etc.) in general say much about their spectra. In contrast, in many instances one may, by inspection, derive several simple topological indices, such as Hosoya's Z , the Wiener number or the connectivity index ${}^1\chi$. In this way, one may try to interpret differences between the structures to differences between the descriptors. For this reason, we view the former as convoluted and the latter as explicit.

There are graph theoretical invariants considered in the mathematical literature that have not yet been tested for possible chemical applications. Such may or may not be of interest in chemistry, but without testing we will not know. If some existing mathematical invariants, and others yet to be suggested in unrelated mathematical analyses, are shown to correlate with some of the known molecular properties (even if it is for a special class of compounds), the findings may be of considerable interest for chemistry – not only because such invariants may offer a novel predictive tool in structure–property studies, or an alternative route to a

certain molecular property, but they may give additional insight into structure–property relationships. Finally, such results may show novel mathematical concepts of use in chemistry. In addition to the pragmatic aspects of such for QSAR, and structure–property analysis in general, it is of considerable interest, at least to some of us, to find out what kind of mathematics is hidden in chemistry – even if this in some instances may merely represent an alternative to a well-understood relationship. To quote Feynman [119]:

“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.”

10. An illustration: Generalized bond orders

Consider the already discussed molecular descriptors Z (total number of nonadjacent edges), W (total number of graph distances), and P (the total number of paths in a graph), given by integers or the descriptors χ and J given as real numbers. One way of arriving at novel invariants using the existing ones is to consider novel concepts yet applied on old invariants. One such approach recently outlined [115] is to consider local invariants and combine them into a global invariant. For example, if in a graph G we erase an edge E we can evaluate for the graph $G - E$ a selected invariant X ($X = Z, W, P, \chi, J$, etc.). If we refer to the derived value for the invariant as X' , which is a bond function, then X' or X'/X can be viewed as entries in the matrix $F(i, j)$ mentioned before. In this way, additional matrices for a graph G can be composed. If one adds all bond values of X'/X for a graph, one obtains a novel single-number representation of a graph G , a novel topological index. This outlines yet another approach to novel invariants based on the use of existing graph invariants. Balaban and coworkers [120] recently described a general approach to the construction of local graph invariants. The descriptors X'/X may be viewed as a modification of their more general scheme in that the fragment used is a single edge rather than a fragment. However, in constructing X'/X , we add the contributions rather than combining them in a multiplicative fashion as advocated by Balaban and coworkers.

Again, we must emphasize that a construction of a novel invariant that shows no advantages in structure–property or structure–activity analyses over the existing descriptors will produce little interest in chemical circles. In another study [121], Balaban and coworkers outlined a very general prolific approach for obtaining novel invariants based on multiplication of matrices with suitably selected vectors. Hence, it is not difficult to come across novel invariants. However, if such constructions do not yield a simple **structural** interpretation, even if successful in a regression analysis, we will be left in the dark as to which structural elements are essential for the particular property. Therefore, if a successful regression is not based on

structurally meaningful descriptors, at best it solves half the problem; it produces a regression of better statistical qualities. However, that is not the sole goal in structure–property–activity studies. A better multivariate regression will undoubtedly lead to more accurate predictions, but will tell us little about the structural factors that dominate a property. We know that the total wave function suffices to compute selected molecular properties. Hence, from accurate wave functions for two molecules we can in principle, if not in practice, compute selected properties and find that molecule *A*, say, has greater total energy or greater binding energy than molecule *B*. However, why this is the case we do not know because accurate wave functions are so convoluted that auxiliary quantities (often nonobservables such as orbital populations, orbital energies, bond orders, etc.) have to be invoked. Here is an opportunity for the chemical graph theory to come forward with adequate structural invariants that can rationalize small differences in properties of similar molecules by quantities which are conceptually simple and structurally unambiguous.

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