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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Apart from certain mathematical sciences, the major area of application of graph theory today is in chemistry. Although use has been made of graph-theoretical concepts by chemists for over two centuries, it is only within the last two decades that the great import of graph theory in chemistry has come to be widely recognized. The earliest applications to chemistry were in a totally implicit form, but with the passage of time increasingly explicit use has been made of graph theory. Here we review briefly several of the current major areas of application to chemistry. The

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topics covered include chemical documentation, isomer enumeration, chemical bonding theory, the study of chemical reaction networks, planning synthesis routes, macromolecules and polymers, and the use of graph invariants (so-called topological indices) for the description and prediction of chemical behavior. The latter topic is treated more fully in the paper immediately following this one. Where appropriate, the contributions of mathematicians, especially graph theorists, to the development of chemical graph theory have been highlighted. A number of the problems of a graph-theoretical nature which still confront the chemist are outlined. Key references to the relevant chemical literature are given, and all the major reviews in the field are cited. Graph theorists desirous of learning more about the chemical applications of their discipline may find the present elementary introduction a convenient point from which to start. (Keywords

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AN INTRODUCTION TO THE CHEMICAL APPLICATIONS

OF GRAPH THEORY

by

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March 6, 1987

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AN INTRODUCTION TO THE CHEMICAL APPLICATIONS OF GRAPH THEORY

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Abstract

Apart from certain mathematical sciences, the major area of application of graph theory today is in chemistry. Although use has been made of graph-theoretical concepts by chemists for over two centuries, it is only within the last two decades that the great import of graph theory in chemistry has come to be widely recognized. The earliest applications to chemistry were in a totally implicit form, but with the passage of time increasingly explicit use has been made of graph theory. Here we review briefly several of the current major areas of application to chemistry. The topics covered include chemical documentation, isomer enumeration, chemical bonding theory, the study of chemical reaction networks, planning synthesis routes, macromolecules and polymers, and the use of graph invariants (so-called topological indices) for the description and prediction of chemical behavior. The latter topic is treated more fully in the paper immediately following this one. Where appropriate, the contributions of mathematicians, especially graph theorists, to the development of chemical graph theory have been highlighted. A number of the problems of a graph-theoretical nature which still confront the chemist are outlined. Key references to the relevant chemical literature are given, and all the major reviews in the field are cited. Graph theorists desirous of learning more about the chemical applications of their discipline may find the present elementary introduction a convenient point from which to start.

Setting the Scene

The burgeoning use of graph-theoretical techniques in the physical, biological, and social sciences has led to widespread recognition that graph theory has much to offer scientists working in a remarkably broad range of disciplines. Graph theory is now being seen as an increasingly valuable tool capable of elucidating, and in some cases solving, manifold different problems. Outside of essentially mathematical sciences, such as computer science, chemistry is currently the most important client for the services of graph theory. Chemistry has made more use of graph-theoretical concepts over a longer period of time than any other science. This is perhaps hardly surprising, for graph theory is in many ways an ideal tool in the hands of the chemist. Much of the day-to-day activity of the chemist is involved with the representation, enumeration and synthesis of numerous different chemical species. Moreover, chemists are highly interested in the making and breaking of chemical bonds, i.e. in studying the myriad interactions which different types of structures can undergo. Fortunately for the chemist, both the individual structures studied and the various interactions in which they are involved can be represented very conveniently by means of chemical graphs.

It may come as something of a surprise to the reader to learn that chemists started using graphs over two centuries ago. This pioneering work is now regarded as belonging to the early development of graph theory itself [1,2]. The first use of graphs in a chemical context was made in 1769 when K_4 graphs were used to depict the forces exerted on four mutually interacting chemical species [3]. The earliest use of graphs to represent molecules was made in 1789 by William Higgins [4] - even though the concept of the molecule itself was by no means clear at the time. Beginning around the 1840s, what is now known as valence theory and structure theory began to take shape. During the next few decades the molecule was defined rigorously and many important molecular structures began to be determined [5]. The first explicit use of graph theory came in the 1870s when Sylvester and Cayley introduced chemical graphs into the mathematical literature for the respective purposes of representing [6] and enumerating [7] chemical species. Their depictions were referred to as 'graphical representations' -- a term adopted by mathematicians which in abbreviated form gave rise to the modern word 'graph'.

In the present century, graph theory has been employed extensively in both implicit and explicit ways in the elaboration of chemical bonding theory. Following the advent of quantum theory in the 1920s, chemists became increasingly fascinated with the study of the chemical bond. This work led to the evolution of numerous essentially graph-theoretical concepts and theorems [8]. There was also renewed interest in the 1930s in isomer enumeration problems following pioneering work by Henze and Blair [9,10] and the publication by Polya of his now famous Enumeration Theorem [11]. Interest by the chemical community in graph-theoretical notions has tended to be episodic: waves of great activity have usually been followed by periods of virtual neglect. A major groundswell started to make its presence felt in the late 1960s. Many chemists began to realize the great value of graph as a tool. Results obtained much earlier were often then re-evaluated and given a new, explicit graph-theoretical formulation. The continuing upsurge of interest is evidenced in the plot shown in Figure 1, in which the number of papers dealing with chemical graph theory is plotted for each of the years between 1970-1985. Assuming that the annual increase over this period of 25% continues, it can reasonably be anticipated that the annual production of papers this year (1986) will exceed 500 for the first time.
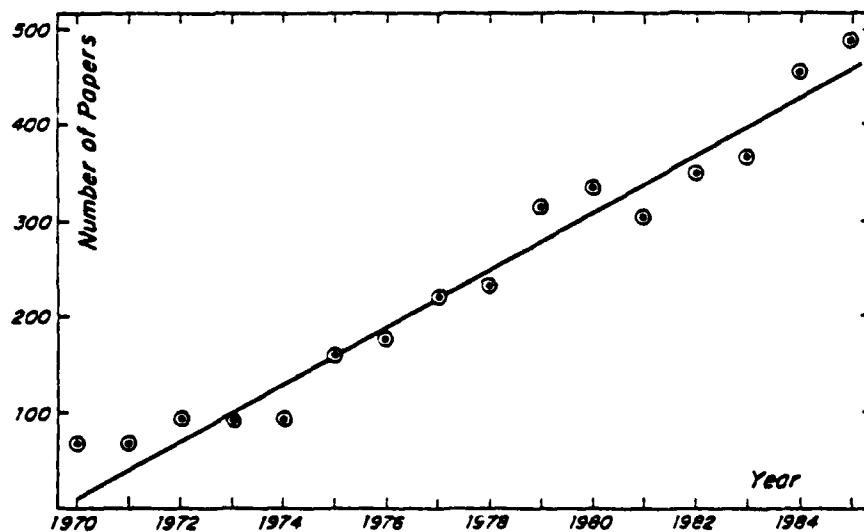

Figure 1. Plot of the annual numbers of papers treating chemical graph theory for the years 1970-1985.

The first review on the whole field of chemical applications appeared in 1971 [12]; a number of other comprehensive reviews have subsequently been published [13-16]. In very recent years, the area has become so extensive that it is scarcely possible to review in its entirety and still do justice to the subject. To prevent reviews growing to unmanageable lengths, authors have opted either to write books or to restrict the coverage of their reviews. Examples of these approaches are provided by the two-volume monograph published by Trinajstić [17], who treated many currently important themes. Recent journal review articles on the other hand have concentrated on fairly specific themes. Thus Balaban [18] built his review around the documentation and enumeration of chemical species, and Balasubramanian [19] focussed on the applications of graph theory in spectroscopy and quantum chemistry. General interest articles are also beginning to appear, such as the present author's discussions on the use of graph invariants in chemistry [20,21]. Moreover, two published conference proceedings contain papers devoted mainly to chemical graph theory [22,23]. In this presentation we outline several of the major areas of current application of graph theory to chemistry. Key references to the chemical literature are provided for readers wishing to delve further into the various topics covered here.

Chemical Documentation

The first application we discuss is one that continues to create problems for the chemist, namely the establishment of a suitable nomenclature for all known chemical species. At present, over 7 million different chemical substances have been described in the literature, and a few hundred thousand are added to this list annually. The problem of representing all known chemicals in a unique way is one that has occupied the attention of chemists for well over a century [24]. Typical examples of the representation of molecules using graphs are shown in Figure 2, which depicts the molecules of methane (CH_4), ethylene (C_2H_2), and benzene (C_6H_6). Note that in such representations the atoms are depicted as vertices whereas the covalent chemical bonds holding the molecules together are depicted as graph edges. Edges have been used to depict bonds ranging from very strong covalent bonds to very weak hydrogen bonds; an edge therefore is not associated with any particular type of bonding but indicates rather the existence of a chemical linkage between atoms. This fact can render

the use of graphs to represent molecules ambiguous on occasion.
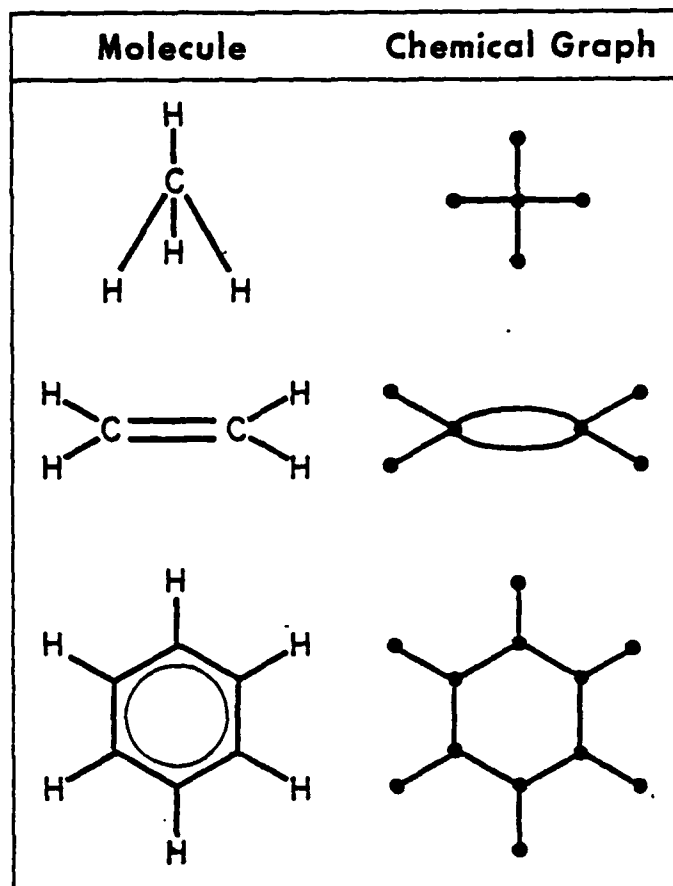
Figure 2. Chemical graphs representing the molecules of methane, ethylene, and benzene.

Chemistry is fortunate in being the best documented science and is likely to remain so for some time to come. Much useful information can be derived from structural formulas (or chemical graphs) that can be uniquely indexed or retrieved. There are problems, however, and certain of these will not be resolved until the graph isomorphism problem is solved. The really difficult problem confronting workers in this field is the representation of all the different isomeric forms a given species may assume by means of unique chemical graphs. To circumvent this problem, a number of chemical nomenclature systems have been devised. All of these operate by starting from the structural formula, performing some algorithm on it, and then obtaining as output some unique designation for the molecule in question. An example of such a designation is provided by the codes

illustrated in Figure 3, where the adjacency matrix entries for each structure are written out as a sequence. When coding in this and other ways, compromises always have to be made in practice with regard to uniqueness of the representation, length of the code, complexity of the algorithm used, etc. A set of systematic rules for optimal coding has been advanced by Read [25, 26]. Modern nomenclature systems strive to satisfy as many of these rules as possible. Certain molecules present additional problems over and above those already mentioned for structural isomers. These problems arise when the molecules have stereoisomers, chiral centers, or topological isomers. For a discussion on the special problems associated with such molecules, the reader is referred to the papers by Read [25,26], Balaban [18], and Simon [27].
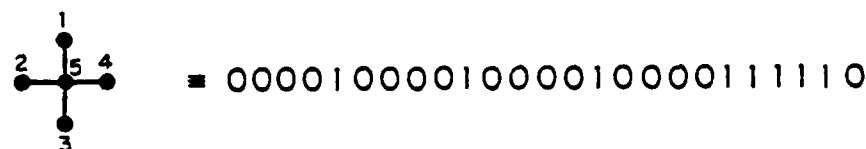
Figure 3.   Codes based on expanded adjacency matrix entries for the molecules of n-pentane, 2-methylbutane, and 2,2-dimethylpropane.

Isomer Enumeration

A molecule is said to have an isomer when another molecule has the same chemical composition but possesses a different structure. The large numbers of isomers of different types that chemists have been able to synthesize, has engendered the need to know how many are theoretically possible in each class. Accordingly, isomer enumeration problems have

held a fascination for both chemists and mathematicians for over a century. In many instances, the timely application of graph-theoretical and combinatorial techniques has resulted in a complete solution to the problem. In fact, this area of application represents one of the greatest successes of chemical graph theory. Only a comparatively small number of troublesome problems still remain, e.g. the enumeration of arene species (which is equivalent to enumerating hexagonal animals), or the enumeration of the catenanes (which is equivalent to enumerating topologically linked systems). Isomer enumeration provides a classic example of fruitful collaboration and interdisciplinary cross-fertilization between chemistry and graph theory. This mutual interaction has continued down to the present day.

Number of Carbon Atoms	Number of Alkane Isomers
1	1
2	1
3	1
4	2
5	3
6	5
7	9
8	18
9	35
10	75
20	366319
30	4111846763
40	62481801147341
50	1117743651746953270

Table 1. Isomer counts of the structural isomers for various members of the alkane homologous series.

The earliest work on isomer enumeration, by chemists such as Flavitzky [28] and mathematicians such as Cayley [7], focused on the isomers in

homologous chemical series. Homologous series are defined as sets of isomeric molecules such that members in the same set all have an identical chemical formula whereas members in adjacent sets in the series have formulas differing by a methylene (CH_2) group. A typical example of such a series is provided by the alcohols:

CH_3OH C_2H_5OH C_3H_7OH C_4H_9OH . . . . . . $C_nH_{2n+1}OH$

Methanol   Ethanol   Propanol   Butanol   General Alcohol

In the present century, two basic methods have emerged for the enumeration of isomers. These methods are founded on (i) recursion relationships between members of homologous series, such as those derived by Henze and Blair [9,10], and (ii) the well-known Enumeration Theorem of Pólya [11]. Fuller details on the application of these techniques are to be found in the review by Rouvray [29]. In more recent years, increasing use has also been made of a double coset formalism [30,31]. As a result of the labors of numerous workers [29] in the domain, virtually all important chemical series, especially the homologous series, have now been enumerated. Tabulations of some of the major results now available have recently been published [32]. To give an idea of how rapidly the numbers of isomers grow, we present in Table 1 the isomer counts for structural isomers of the alkane (C_nH_{2n+2}) homologous series.

Chemical Bonding Theory

Following the advent of quantum theory in the 1920s, it was not long before its impact began to be felt in chemistry. Fundamentally, the quantum approach entails solving the Schrödinger equation for each individual molecule of interest. Since this equation cannot in general be solved analytically, a variety of ingenious approximations have been developed. The two basic approximations widely used in chemistry today are known as the valence bond [33] and the molecular orbital methods [34]. The valence bond method describes the electron structure of a molecule in terms of wave functions constituted from products of wave functions for atom pairs, whereas the molecular orbital method uses wave function which are constructed to encompass the entire molecule. Although both methods are rather crude representations of reality -- the former overcompensates for interelectron repulsion terms while the latter virtually neglects them -- both have made

important contributions to the systematization of chemical knowledge. Traditionally, valence bond theory has been employed mainly in the study of inorganic species, and molecular orbital theory has found extensive application to organic compounds.

Hückel Matrix $\equiv$ Adjacency Matrix

$$
\begin{array}{cccccc}
 & 1 & 2 & 3 & 4 & 5 & 6 \\
1 & \alpha\text{-}E & \beta & 0 & 0 & 0 & \beta \\
2 & \beta & \alpha\text{-}E & \beta & 0 & 0 & 0 \\
3 & 0 & \beta & \alpha\text{-}E & \beta & 0 & 0 \\
4 & 0 & 0 & \beta & \alpha\text{-}E & \beta & 0 \\
5 & 0 & 0 & 0 & \beta & \alpha\text{-}E & \beta \\
6 & \beta & 0 & 0 & 0 & \beta & \alpha\text{-}E
\end{array}
\equiv
\begin{array}{cccccc}
 & 1 & 2 & 3 & 4 & 5 & 6 \\
1 & 0 & 1 & 0 & 0 & 0 & 1 \\
2 & 1 & 0 & 1 & 0 & 0 & 0 \\
3 & 0 & 1 & 0 & 1 & 0 & 0 \\
4 & 0 & 0 & 1 & 0 & 1 & 0 \\
5 & 0 & 0 & 0 & 1 & 0 & 1 \\
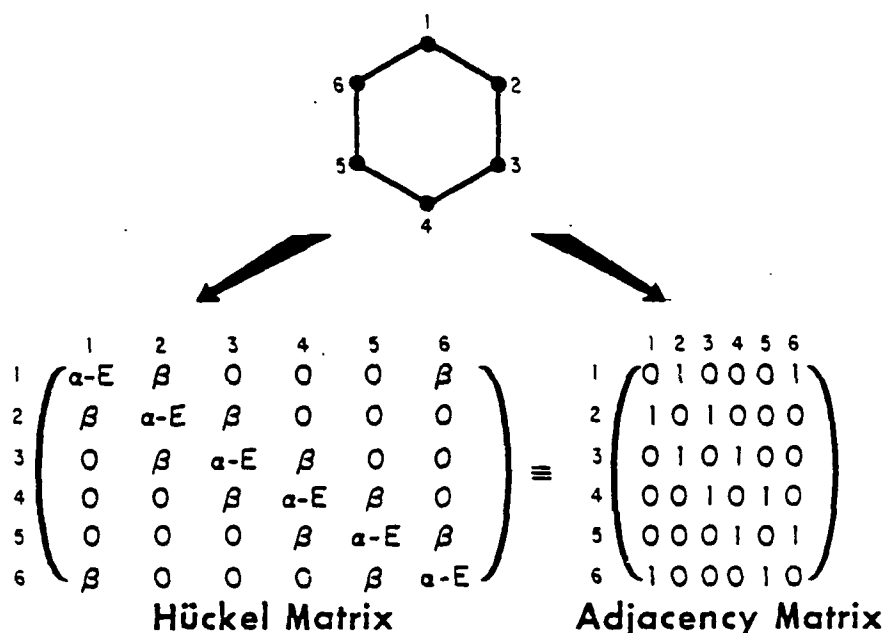6 & 1 & 0 & 0 & 0 & 1 & 0
\end{array}
$$

Figure 4. The Hückel and adjacency matrices for the graph of the benzene molecule.

Widespread use of graph theory has been made in both methods. In valence bond theory, for instance, graph-theoretical techniques have been used for enumerating the number of Kekulé structures (1-coverings) that chemical graphs possess. This information can provide interpretations of the stabilities of the molecules so represented [35]. In molecular orbital theory, a set of approximations which renders solutions for comparatively large molecules easy to obtain was put forward by Hückel [36]. The method in essence reduces to the solution of a secular determinant, an example of which is shown in Figure 4 for the molecule of benzene. The eigenvalue spectrum of this determinant yields the energy levels of the more energetic electrons which largely determine the behavior of the species. As the adjacency matrix, also shown in Figure 4, is isomorphic with the secular determinant, the molecular energy levels will differ from the eigenvalues of the adjacency matrix only by a scaling factor. This observation had led to numerous insights in bonding theory concerning

the behavior, and especially the stability, of a wide variety of molecular species [37]. A number of the results obtained using this simple theory retain their validity at higher levels of approximation. A good example of such a result is the well-known Pairing Theorem of Coulson and Rushbrooke [38], which in graph-theoretical terms states that the eigenvalues of bipartite graphs will always be paired in plus-minus pairs. This translates into the chemically significant statement that the energy levels of alternant molecules will always be distributed symmetrically about the nonbonding level.
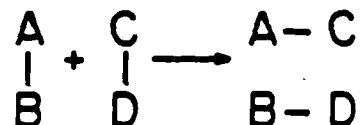
Chemical Reaction Networks

In addition to the chemical graphs described so far, which have been used to represent individual chemical species, there is another class of chemical graphs known as a reaction graphs. In these latter graphs, the vertices are now used to represent entire chemical species and the edges represent interactions or transformations that these species can undergo. The edges are referred to as the reaction routes or reaction pathways. A reaction graph thus depicts all the different possible interactions that a given chemical species can experience, subject to the prescribed reaction conditions. In a sequence of chemical transformations, the species that one begins with is known as the starting material, and the species that one finishes up with is known as the end product; species formed between these two extreme stages are referred to as intermediates. The earliest reaction graphs tended to focus on a single molecule which underwent a series of transformations based on an isomerization process or intramolecular rotation, i.e. changes in which no actual bond breaking was involved. More recently, reactions involving the breaking of chemical bonds have also been depicted by reaction graphs. The first reaction graphs were employed by Balaban et al. [39] for the first type of transformation. One spectacular success of reaction graphs was in providing plausible structures for the intermediates formed in the isomerization sequence leading to the formation of the diamantane molecule. The reaction graph had over 40,000 vertices interconnected by myriad interconversion pathways, yet, by systematically calculating the geometry and strain energy of each species and eliminating the high energy species, it was possible to work out the steps involved in the formation of the diamantane molecule [16].

Colligation

$$A + B \longrightarrow A-B$$

Cycloaddition

$$\begin{array}{ccc} A & C & A-C \\ | & + \; | & \longrightarrow \\ B & D & B-D \end{array}$$

Insertion

$$A + B-C \longrightarrow B-A-C$$

Polymerization

$$nA \longrightarrow A_n$$

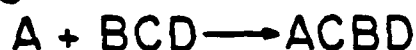## Rearrangement

$$A + BCD \longrightarrow ACBD$$

Figure 5. The five principal types of chemical bond formation and breaking.

A special class of reaction graphs concerned solely with the synthetic production of chemical substances is referred to as the class of synthon graphs [40]. In such graphs the vertices are used to represent synthons, i.e. reagent molecules or molecular fragments, and also the intermediates and target molecule. The edges represent assembly or degradation reactions. The graph as a whole depicts all the possible synthetic routes which are permitted via allowed reactions, starting from the available synthons and proceeding to the end product or target molecule. The graphs normally describe both chemical bond formation and breaking processes. The five main types of process involved are illustrated in Figure 5. In recent years in particular, synthon graphs have slowly been transforming the art of chemical synthesis into a rigorous scientific discipline. The synthon graph for the cycloaddition end product ABCD (denoted as F) might look like the graph shown in Figure 6, depending on the synthons used. The

use of reaction graphs in conjunction with sophisticated software has led
to many notable results. Corey et al. [41], for instance, succeeded in
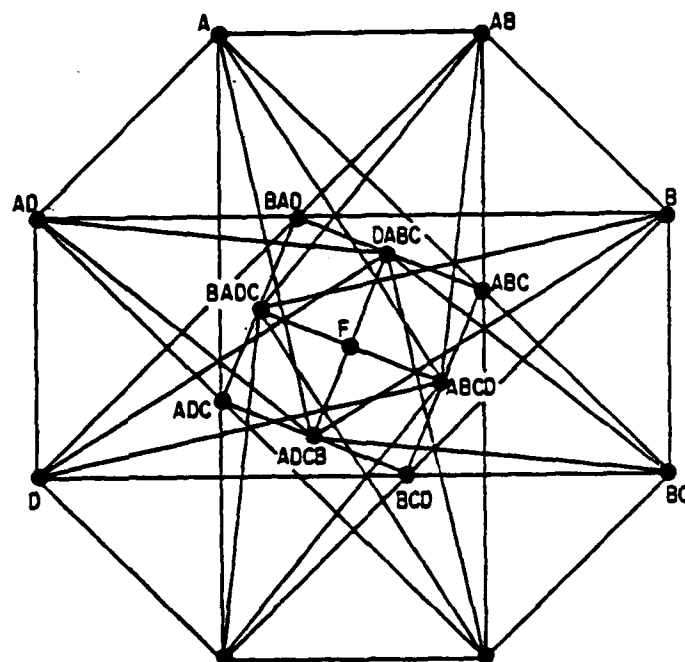the technically very demanding synthesis of prostaglandin molecules by
this method.

Figure 6. Example of a synthon graph illustrating possible routes to the
           synthesis of species F.

Macromolecules and Polymers

Many familiar materials in our everyday environment, ranging from
plastics to proteins, are composed of macromolecules, and all living
organisms in the plant and animal kingdoms are also made of such molecules.
A special group of macromolecules containing repeating sequences of groups
of atoms can be subdivided into the categories of polymers and
polycondensates. Basically, polymers are formed when small molecules link
together to yield more complex structures, whereas polycondensates result
from the reaction of sets of molecules with the concomitant splitting off
of certain small molecules such as the water molecule. The three different
types of linkage which can occur in polymerization or polycondensation
reactions are illustrated in Figure 7 for a molecule M which has f sites

of attachment for the formation of covalent bonds. The end products for f = 1 are called dimers, for f = 2 linear polymers, and for f = 3 cross-linked polymers; chemists also refer to the latter two as unidimensional and tridimensional polymers respectively. The latter terminology is misleading, however, since from the graph-theoretical standpoint all the graphs representing these systems are one-dimensional complexes.

POLYMERIZATION

Dimer (f=1)

$$2M \longrightarrow M-M$$

Linear Polymer (f=2)

$$nM \longrightarrow -M-M-M-M-$$

Cross-Linked Polymer (f=3)

$$nM \longrightarrow \begin{array}{cccc} | & | & | & | \\ -M-M-M-M- \\ | & | & | & | \\ -M-M-M-M- \\ | & | & | & | \end{array}$$
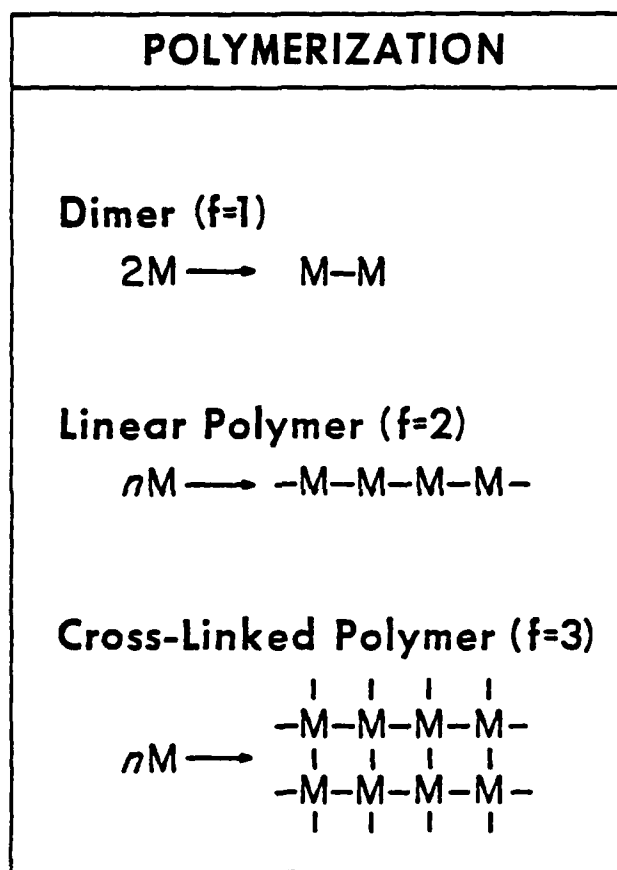
Figure 7. The three different types of linkage for a molecule having f (where $1 \leq f \leq 3$) sites of attachment.

This idea was brought out very clearly in the work of Gordon and Kennedy [42], who introduced the basic notion of 'graph-like states of matter'. Their concept arose out of studies they made on the additive properties of molecules. An additive property, P, is one that can be calculated by summing the contributing property for each of the constituents of a molecule, i.e.

$$P = \sum_i \alpha_i \cdot T_i,$$

where the α_i are coefficients which are determined either empirically or by some appropriate combinatorial technique, and the T_i are graph-theoretical invariants for the various chemical graphs under consideration. Whenever the above equality is strictly true, P is said to belong to the graph-like state of matter. An example of a T_i invariant is the number of ways in which the carbon skeleton of a given molecule can be cut out of the skeleton of some larger molecule. Gordon and Kennedy [42] concluded that all additive schemes in chemistry [43] could be reduced to an equation of this general form, and therefore that all additive parameters belong to the graph-like state of matter.

Topological Indices

In recent years, chemists and others have made widespread use of graph invariants which are numerical descriptors. The numbers yielded as a result of performing various algorithms on chemical graphs are used to characterize the structures they represent. These numerical descriptors are treated as properties of the molecules under consideration and are correlated against a variety of other, measured properties, such as the boiling point or refractive index. At present, there are over 100 graph invariants which have been put forward for this purpose, though only a handful have been used extensively in practice [20]. Many of the invariants employed by chemists can be derived from either the adjacency or distance matrix of the chemical graph. This is certainly true of the first invariant used in a chemical context. The invariant, put forward by Wiener [44] in 1947 and nowadays known as the Wiener index, can be defined as one half the sum of the entries in the distance matrix. In Figure 8 we present a schematic illustration of the derivation of this invariant. Since Wiener's early work, the invariants have come to be known to chemists as topological indices.

Topological indices have been used for the correlation and prediction of a very broad range of molecular properties. These range from the physical (e.g. boiling point), through the chemical (e.g. reactivity), the thermodynamic (e.g. heat of formation), the biochemical (e.g. biological degradability), the pharmacological (e.g. anesthetic behavior), and the
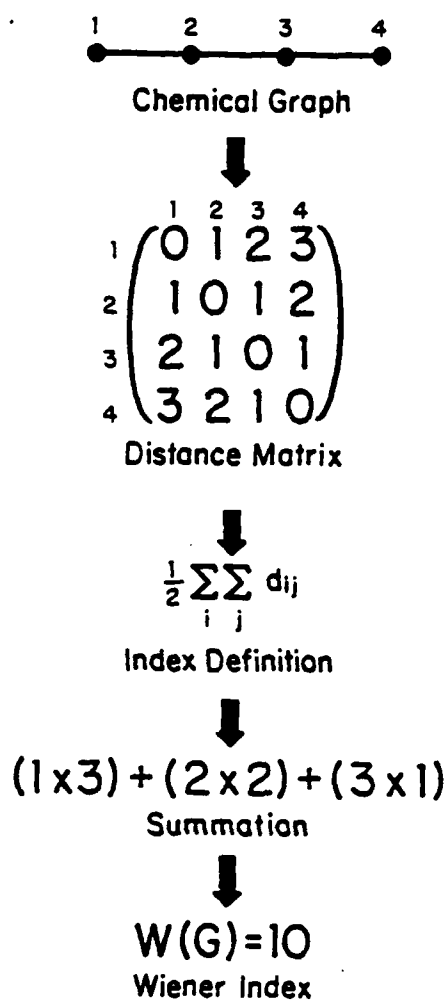
Figure 8. Schematic representation of the derivation of the Wiener index
for the molecule of n-butane.

toxicological (e.g. toxicity). Reviews on the major applications of the
indices have been published by Sabljic and Trinajstić [45], Trinajstić
[17] and Rouvray [46]. In general, the indices correlate better with
physical properties than with more biological ones; in the physical sciences
correlation coefficients in regression analyses in the region of 0.99 are
commonplace whereas in the biological sciences a value of 0.95 is regarded
as excellent. Because of the high correlation coefficients which are
attainable, the indices have found important applications in the prediction
of the properties of potential new pharmacological agents and in predicting
the degree of toxicity of major pollutant chemicals. The most successful
indices to date in terms of the range of applications are the molecular
connectivity indices of Randic [47]. A whole book has been devoted to
their use [48]. Details of these indices and their applications are to

be found in the succeeding paper [49].

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