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WHAT CHEMISTS COULD NOT SEE WITHOUT MATHEMATICS - DEPENDENCE OF TOTAL π-ELECTRON ENERGY ON MOLECULAR STRUCTURE

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ABSTRACT. Total π-electron energy E (as computed within the Hückel molecular orbital approximation) is a quantum chemical characteristic of unsaturated conjugated compounds whose dependence on molecular structure can be deduced and analyzed by means of algebraic graph theory. It is shown that E depends - in a perplexed, but mathematically well-defined manner - on a large number of molecular structural features. The mathematical representations of these structural features are the so-called Sachs graphs. Some of these Sachs graphs correspond to familiar chemical notions: bonds, rings, Kekulé structures. Most of them, however, represent structural features whose chemical significance was not anticipated by chemists. Thus we are faced with a case of structure-property relation that could not be deduced and rationalized without the use of modern mathematical methods. In the article are outlined the basic results achieved along these lines, illustrated with concrete chemical applications.

INTRODUCTION

Most chemists are of the opinion that mathematics is of little importance and of almost no value in their science, including "theoretical chemistry". The undeniable fact is that most chemist can successfully do their work or conduct their research (up to winning a Nobel prize) without utilizing any form of mathematics that goes beyond simplest calculus. As a consequence, being chemist often means being ignorant in mathematics.

The aim of this article is to demonstrate that, in some cases at least, the lack of mathematical way of reasoning makes chemists blind to certain aspects of their work. We are aiming at one of the central objectives of chemistry: finding connections between molecular structure and molecular properties.

It is one of the paradigms of chemistry that molecular structure determines the (physical, chemical, pharmacological, ...) properties of the corresponding substance, provided, of course, that this substance consists of molecules. Thus, from the known molecular structure, the

properties of substances should be predictable. Although much success along these lines has been achieved and much knowledge accumulated, we are still very far from the complete solution of the problem. [In contemporary chemical literature two acronyms are often encountered: QSPR = *Quantitative Structure Property Relations* and QSAR = *Quantitative Structure Activity Relations*. Under "property" are meant the physical and chemical properties, whereas "activity" refers to pharmacological, biological, medicinal and similar properties.]

In this article we consider a special problem in QSPR research, namely the finding of the (quantitative) connection between the structure of a polycyclic conjugated hydrocarbon and its total π-electron energy E. Although E cannot be directly measured, it is known to be reasonably well related to the experimentally accessible thermodynamic data (Gutman, 1992, Gutman and Polansky, 1986, Schaad and Hess, 1972, 2001).

The total π-electron energy considered here is computed by means of the tight-binding Hückel molecular orbital (HMO) approximation and, as usual, expressed in the units of the carbon-carbon resonance integral β. Details of HMO theory are found, e. g., in the books (Coulson et al., 1978, Yates, 1978). Within the HMO model it is possible to employ the mathematical apparatus of graph spectral theory; for applications of graph spectral theory in molecular orbital theory see the books (Dias, 1993, Graovac et al., 1977) and the articles (Dias, 1987, 1992, Gutman, 2003, Gutman and Trinajstić, 1973).

For the present considerations the actual value of the parameter β is not important, except that its value is negative. We nevertheless mention that for thermochemical purposes the recommended value of β is -137.00 *kJ/mol* and that the heats of atomization computed by the HMO method are accurate to 0.1%, implying that E is accurate up to ±0.005 β units (Schaad and Hess, 1972). Thus, the greater is E, the higher is the thermodynamic stability of the respective compound; structural factors increasing (resp. decreasing) the value of E increase (resp. decrease) the thermodynamic stability.

GRAPH THEORETICAL PREPARATIONS

In order to be able to present the results on the structure-dependence of E, we must specify a few basic notions of graph theory and graph spectral theory. More details can be found in the books (Graovac et al., 1977, Gutman, 2003a , Gutman and Polansky, 1986).

A conjugated hydrocarbon is represented by its molecular graph. The construction of such a graph should be evident from the example shown in Fig. 1.

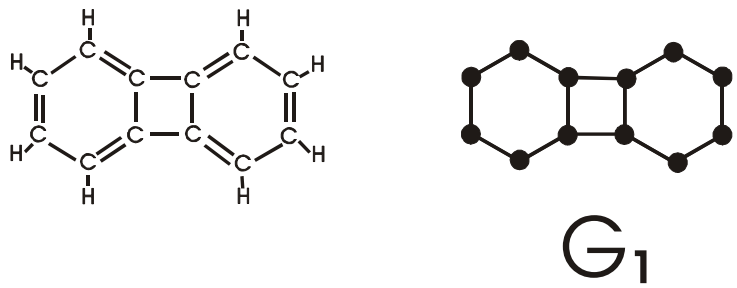

Figure 1. The structural formula of biphenylene and the corresponding molecular graph G_1. The graph G_1 has n=12 vertices and 14 edges. The vertices of G_1 represent the carbon atoms, whereas its edges represent the carbon-carbon bonds of biphenylene.

The number of vertices of a molecular graph G is denoted by n. Two vertices connected by an edge are said to be adjacent.

If the vertices of the graph G are labeled by $v_1, v_2,..., v_n$, then the structure of G can be represented by the adjacency matrix $\boldsymbol{A} = \boldsymbol{A}(G) = ||A_{ij}||$. This is a square matrix of order n, whose elements A_{ij} are defined so that $A_{ij}=A_{ji}=1$ if the vertices v_i and v_j are adjacent, and $A_{ij}=0$ otherwise. For an example see Fig. 2.

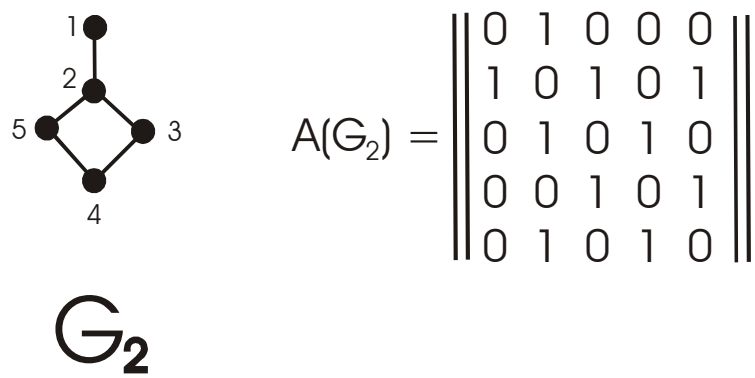

Figure 2. A graph G_2 and its adjacency matrix $\boldsymbol{A}(G_2)$. It can be computed (but not easily) that the characteristic polynomial of G_2 is $\Phi(G_2,x) = x^5 - 5x^3 + 2x$. The solutions of the equation $x^5 - 5x^3 + 2x = 0$ are $x_1=[(5 + \sqrt{17})/2]^{1/2} = 2.13578$, $x_2=[(5 - \sqrt{17})/2]^{1/2} = 0.66215$, $x_3=0$, $x_4=-[(5 - \sqrt{17})/2]^{1/2} = -0.66215$ and $x_5=-[(5 + \sqrt{17})/2]^{1/2} = -2.13578$. These five numbers are the eigenvalues of the graph G_2 and form the spectrum of G_2.

The characteristic polynomial of the graph G, denoted by $\Phi(G,x)$ is equal to the determinant $det(x\boldsymbol{I}-\boldsymbol{A})$ where $\boldsymbol{I}$ is the unit matrix. It can be shown that $\Phi(G,x)$ is a polynomial in the variable x, of degree n. For an example see Fig. 2.

The numbers $x_1, x_2,...,x_n$, obtained by solving the equation $\Phi(G,x)=0$, are the eigenvalues of the graph G. These eigenvalues form the spectrum of G. For an example see Fig. 2.

SOME RESULTS FROM THE THEORY OF TOTAL π-ELECTRON ENERGY

Anticipating that the majority of the readers of this article will not be interested in the perplexed mathematical details of the theory of total π-electron energy, and will not be willing to spend time on apprehending them, in what follows we give only a few master formulae that the non-interested reader may skip and go straight to the next section. Those who are interested to learn the entire theory should, first of all, consult chapter 8 of the book (Gutman and Polansky, 1986).

It can be shown (Graovac et al., 1977, Gutman and Trinajstić, 1973) that, in the majority of chemically interesting cases, the total π-electron energy is related to the eigenvalues of the molecular graph as

$$E = 2\sum x_i \qquad (1)$$

where the summation goes over the positive-valued eigenvalues of the molecular graph. Another neat way in which Eq. (1) can be written is

$$E = \sum_{i=1}^{n} |x_i| \qquad (2)$$

where now the summation embraces all graph eigenvalues.

Thanks to the symmetric form of Eq. (2), the HMO total π-electron energy E is particularly suitable for mathematics-based investigations. The first significant result in this area was obtained by the British mathematician and theoretical chemist Charles Coulson, good 30 years before other chemists started to use graph spectral theory (Coulson, 1940). Coulson found a connection between E and the characteristic polynomial of the molecular graph, an expression that may look frightening to chemists:

$$E = \frac{1}{\pi}\int_{-\infty}^{+\infty}\left[n - \frac{ix\Phi'(G,ix)}{\Phi(G,ix)}\right]dx \qquad (3)$$

In formula (3), Φ' stands for the first derivative of the characteristic polynomial, and i for the imaginary unit, $i=\sqrt{-1}$.

A quarter of century later, the German mathematician Horst Sachs discovered the way in which the characteristic polynomial of a graph depends on its structure. His result, nowadays referred to as the Sachs theorem (Gutman, 2003b), reads as follows:

$$\Phi(G,x) = x^n + \sum_S (-1)^{p(S)} 2^{c(S)} x^{n-n(S)} \qquad (4)$$

where the summation goes over all so-called Sachs graphs of the graph *G*. These Sachs graphs, essential for the present considerations, are defined as follows.

By K_2 is denoted the graph consisting of two vertices, connected by an edge. By C_n is denoted the cycle possessing *n* vertices, *n*=3,4,5,..., see Fig. 3.

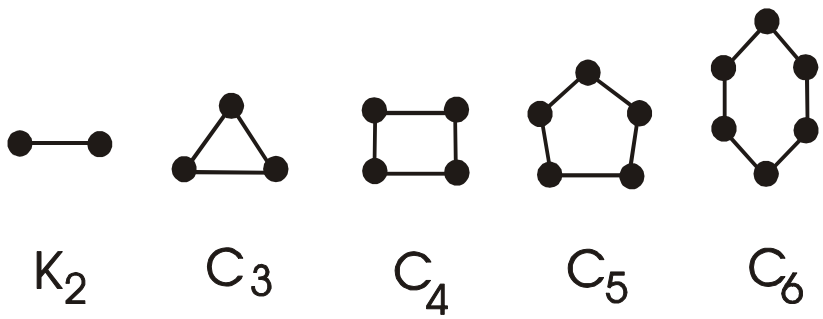

Figure 3. Components of the Sachs graphs. Any Sachs graph consists of components that are K_2 and/or C_3 and/or C_4 and/or ... , see Fig. 4.

A graph in which each component is K_2 or C_3 or C_4 or C_5 or ... is called a Sachs graph. Some of these Sachs graphs are contained in the molecular graph; examples are found in Fig. 4.

In formula (4), *p(S), c(S)* and *n(S)* are the number of components, cyclic components and vertices, respectively, of the Sachs graph *S*. For instance, the Sachs graphs S_1, S_4, S_7 and S_9 (depicted in Fig. 4), have, respectively, 1, 6, 3 and 2 components, 0, 0, 1 and 2 cyclic components, and 2, 12, 10 and 12 vertices.

When formulae (3) and (4) are combined, one arrives at an explicit expression, connecting the total π-electron energy with molecular structure (Gutman, 1977, Gutman and Trinajstić, 1976):

$$E = \frac{1}{\pi} \int_{-\infty}^{+\infty} x^{-2} \ln \left| 1 + \sum_{S} (-1)^{p(S)} 2^{c(S)} x^{n(S)} \right| dx \qquad (5)$$

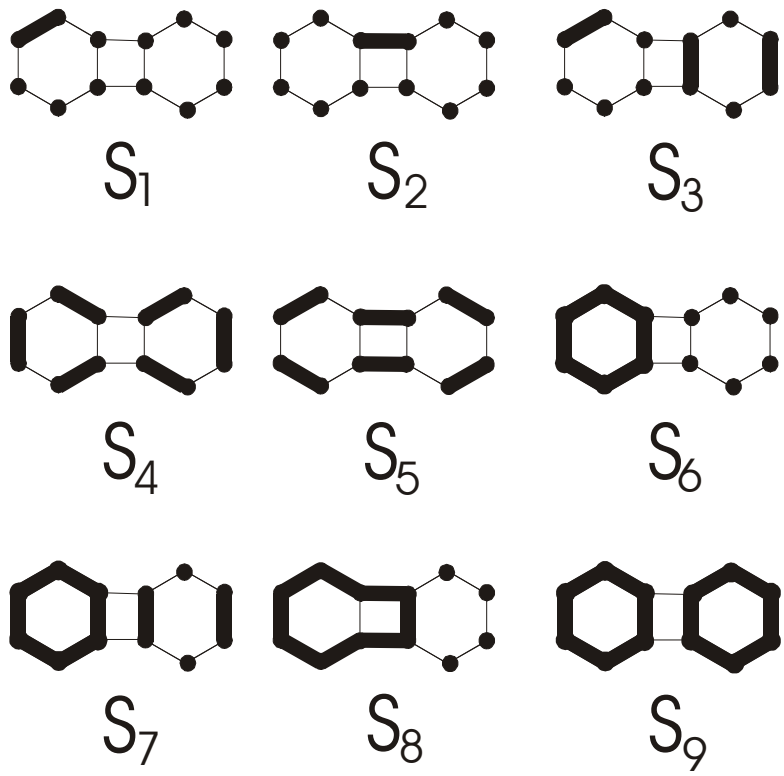

Figure 4. Examples of Sachs graphs (indicated by tick lines) contained in the biphenylene graph G_1. The biphenylene graph contains a total of 514 Sachs graphs. Each of these graphs can be understood as representing a structural feature of the respective molecule.

THE CHEMICAL SIGNIFICANCE OF FORMULA (5)

Each Sachs graph can be understood as representing a particular structural detail of the underlying molecule. Some of these structural details are those familiar to every chemist. For instance, S_1 and S_2 in Fig. 4 pertain to two distinct carbon-carbon bonds of biphenylene, S_6 corresponds to one of its six-membered rings, S_4 and S_6 can be viewed as representing two of its Kekulé structural formulae. However, most Sachs graphs have no usual chemical interpretation. For instance, hardly any non-mathematical chemist has ever thought of structural details such as S_3 (three mutually non-touching carbon-carbon bonds) or S_7 (a six-membered ring and two non-touching carbon-carbon bonds, not belonging to this ring), etc. etc. Yet, all such structural details play role in determining the magnitude of the total π-electron energy, and thus are responsible for the thermodynamic stability of the respective molecule.

Formula (5) is really awkward, but it represents the mathematically complete solution of the structure-dependence problem of a molecular property, in this particular case - of the HMO total π-electron energy. There exist very few QSPR results of this kind.

What can we learn from formula (5)?

First: The relation between total π-electron energy and molecular structure is extremely complicated. [In our opinion, the true relation between any molecular property and molecular structure is extremely complicated, only usually we are not aware of this fact.]

Second: Formula (5) precisely identifies all structural details that influence the total π-electron energy. As already mentioned, some of these are familiar: bonds, rings, Kekulé structures. Most of them are exotic, never anticipated by "intuitively thinking" chemists. Formula (5) reveals the plenitude of (relevant) information contained in a molecular structure, most of which chemist would never recognize without utilizing graph spectral theory.

Third: Formula (5) shows the precise mathematical form in which each structural feature influences the value of E. Thus from it we could make quantitative inferences. The effect of various structural details on E is far from being linear (what chemist prefer because of the simplicity of the linear mathematical expressions).

Fourth: In principle, any question concerning the structure-dependence of E can be answered by means of formula (5). In reality, we encounter serious mathematical difficulties. Therefore, research in the theory of total π-electron energy continues until the present days (Gutman et al., 2004, Zhou, 2004) and will, most probably, go on also in the foreseen future. One particular problem that has been completely resolved is the effect of cycles on E (Gutman, 1984, Gutman and Bosanac, 1977, Gutman et al., 1993, Gutman and Polansky, 1981). We outline the details of this topic in the subsequent section.

Applications: Effects of Cyclic Conjugation

Long time ago chemists have recognized that cyclic π-electron systems exhibit very large stabilization or destabilization relative to their acyclic analogs. The pairs benzene vs. hexatriene (stabilization) and cyclobutadiene vs. butadiene (destabilization) are textbook examples. Already in the 1930s Hückel formulated his *4m+2* rule, claiming that monocyclic conjugated systems are stable if they possess *4m+2* (i. e., 2, 6, 10, 14, ...) π-electrons, and are unstable if the number of π-electrons is *4m* (i. e., 4, 8, 12, ...). That this is an energy-based effect was demonstrated in the 1960s (Breslow and Mohácsi, 1963).

Extending the Hückel rule to polycyclic conjugated molecules became possible only after graph theory was applied in molecular orbital theory, more precisely: after Eq. (5) was discovered.

Using the fortunate fact that the total π-electron energy depends on Sachs-graph-type structural features, and that (some) Sachs graphs consist of cycles, it was possible to express the effect of a particular cycle C, contained in the molecular graph G, on the respective E-value (Gutman, 1984, Gutman and Bosanac, 1977, Gutman et al., 1993, Gutman and Polansky, 1981):

$$ef(G,C) = \frac{1}{\pi}\int_{-\infty}^{+\infty} \ln\left|\frac{\Phi(G,ix)}{\Phi(G,ix)+2\Phi(G-C,ix)}\right| dx \qquad (6)$$

In Eq. (6) G-C denotes the subgraph obtained by deleting the cycle C from the graph G. Whenever *ef(G,C)* is positive, the cycle C stabilizes the molecule; negative *ef*-values imply destabilization.

In Fig. 5 are given the energy-effects of two typical polycyclic conjugated systems.

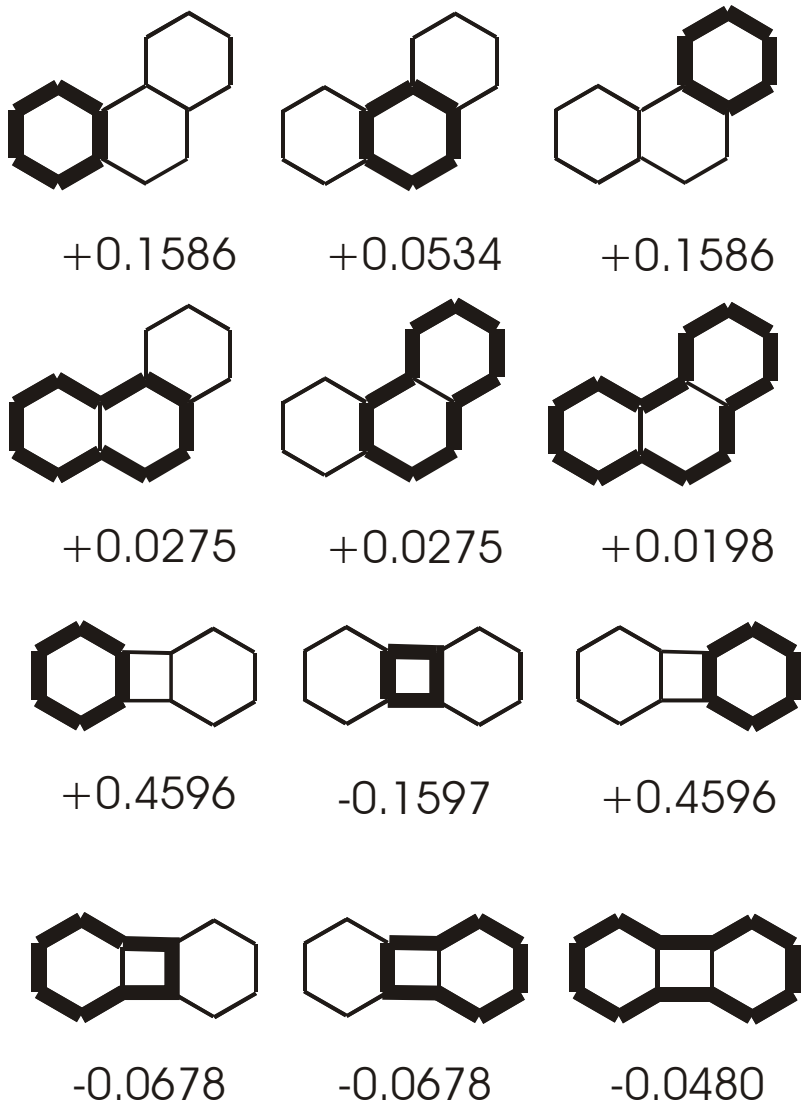

Figure 5. The energy-effects of the cycles of phenanthrene and biphenylene, expressed in the units of the HMO resonance integral β.

The examples shown in Fig. 5 illustrate some basic properties of cyclic conjugation, which - again - would not be recognized without use of mathematics.

(a) Not only rings, but also larger cycles (often ignored by chemists) have their energy contributions.

(b) The energy-effect usually decreases with increasing size of the cycle, but has a non-negligible value also for cycles of larger size.

(c) Cycles of the same size may have significantly different energy-effects.

(d) In the examples shown in Fig. 5, the 6-, 10- and 14-membered cycles have a stabilizing effect, and the 4-, 8- and 12-membered cycles a destabilizing effect. This is in full agreement with the Hückel *4m+2* rule.

(e) However, contrary to what chemists may expect based on their "intuition", the Hückel *4m+2* is not generally obeyed. Surprisingly, only the following result could be rigorously proven (Gutman, 1979):

(f) In all alternant polycyclic conjugated hydrocarbons, cycles of size 4, 8, 12, 16, ... always have a negative *ef*-value and thus always destabilize the respective molecule. (This is just one half of the Hückel *4m+2* rule.)

(g) In the majority of cases, cycles of size 6, 10, 14, 18, ... have a stabilizing effect. However, there exist exceptions, namely alternant polycyclic conjugated hydrocarbons in which some of the (*4m+2*)-membered cycles have a destabilizing energy-effect and thus violate the Hückel *4m+2* rule (Gutman and Stanković, 1994).

* * *

Although the results (f) and (g) can be stated and made understandable without any mathematical formalism, they hardly could have been deduced without use of mathematical reasoning. These results could be viewed as examples of what chemistry may gain from mathematics:

Over half a century, chemists believed that a certain regularity holds and is generally valid. Only a couple of years after a couple of mathematical chemists started to apply graph theory, it could be shown that one half of the regularity is generally valid (and is thus a law on Nature), whereas the other half is not.

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