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π-Electron Currents in Polycyclic Conjugated Hydrocarbons of Decreasing Aromatic Character and a Novel Structural Definition of Aromaticity[#]

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Abstract: We consider a set of nine polycyclic conjugated hydrocarbons, which includes at one extreme benzene, the prototype of aromatic compounds, and at the other extreme cyclooctatetraene, a well-known nonaromatic compound, while the remaining seven compounds illustrate molecules of decreasing degree of aromaticity. Using the model of conjugated circuits for calculations of ring currents, we report on variations in the π-electron ring currents in these molecules with the decrease of their degree of aromaticity. This contribution is a hybrid of original scientific paper and a review, and if viewed as provocative, it is so by design.

Keywords: Aromaticity, conjugated circuits, CC bond currents, ring currents.

[#]Dedicated to colleage and friend Professor Alexandru T. Balaban on the occasion of approaching 80th anniversary.

So the ultimate judgment on whether a novelty is desirable or not will be decided by those who tried such models, not by those who read about them! [1].

INTRODUCTION

Aromaticity is one of the central concepts of organic chemistry, which despite its lack of formal structural definition and multitude of competing pseduo-definitions, remians one of the basic notion in chemistry. The subject of aromaticity is so broad that it is impossible to give it justice by citing all articles that discuss the «problem» of aromaticity. Instead we have collected a selection of articles, reviews, and books, including papers that relate to aromaticity in general, and to aromaticity of some of the compounds considered in this article [2- 33].

The «problem» of aromaticity started from the beginning, the time when Kekulé introduced his famous ring structural formula for benzene [34, 35], the prototype of aromaticity. While Kekulé argued that the concept of aromaticity should be tied to molecular structure, already next year Erlenmayer proposed that the concept of aromaticity be characterized by molecular properties. But that was easy to state and difficult to implement, because as is well-known, molecular properties may vary gradually obscuring the distinction between aromatic and not-aromatic molecular features for many borderline molecules. Consider, for example, the nine compounds illustrated in Fig. (**1**), mentioned in a review article on the aromaticity of polycyclic conjugated hydrocarbons by this author [7]. There are no disputes that benzene [34, 35] and naphthalene [36], at the top of the list, illustrate aromatic compounds and that planar octalene [37] and cyclooctatetraene [38], at the bottom of the list, are not aromatic. Here both the structural approach and criteria based on most molecular propreties, would agree – but what can be stated for the compounds in between?

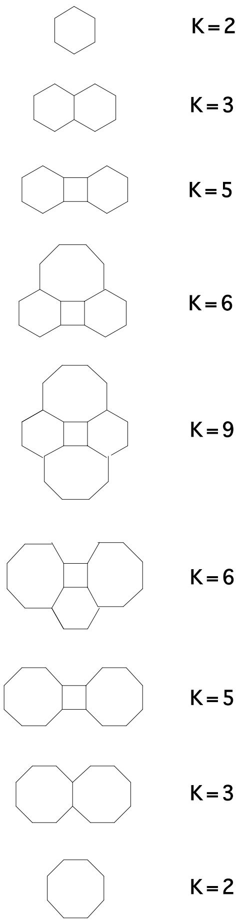

Fig. (1). Set of compounds starting with benzene and ending with cyclooctatetrene ordered in decreasing degree of aromaticity.

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We should add that there appears a consensus on what are typical «aromatic» properties. This is, for example, how aromatic character of molecules was summarized by Minkin *et al.* [5]:

Aromaticity is one of the most widely recognized concepts of organic chemistry. To chemists, the term implies special thermodynamic stability, lack of characteristic alkene reactivity, absence of (or diminished) bond length alternation, and diamagnetic anisotropy ("aromatic ring current").

If one is to follow August Kekulé, who proposed structure of benzene [34, 35], rather then Emil Erlenmayer, who proposed structures of naphthalene as two fused benzene rings [36], one has to come with some *structural* definition of aromaticity. One of the greatest successes of young quantum chemistry is due to the theoretical physicist Erich Hückel [39-42] and consist of a *mathematical* solution to the characterization of aromaticity in *monocyclic* conjugated compound, known today as the famous Hückel *4n+2* Rule: Monocyclic system having *4n+2* π-electrons are aromatic. This results was one of the consequences of the HMO theoretical model of E. Hückel [42-45], and follows from the filling of available low-energy orbitals by π-electrons, the result which was made easy to visualize by the graphical representation of orbital energies of monocyclic systems by Frost and Musulin [46], who depicted geometrically the eigenvalues of simplified hamiltonian matrices.

In the following decades, as is well known, numerous attempts to extend the Hückel Rule to polycyclic systems failed. Apparently many people have given up any hope that *simple structrual* characterization of aromaticity is possible, till finally in mid 1970s, more than 40 years after Hückel, a general *structural* rule for aromaticity valid for polycyclic aromatic hydrocarbons has been proposed. By this time, it appears, few people have recognized the importance of this result, if one is to judge by continuous efforts for use of various pseudo-defintions of aromaticity, including those based on NMR [47], NICS [48-51] and ring currents [22, 52, 53], currently being the leading pretenders for the the vacant throne of aromaticity. The proposed structural definition of aromaticity, formulated for polycyclic conjugated hydrocarbons, is as follows [7, 54]:

Polycyclic conjugated hydrocarbons, the Kekulé valence structures of which have only 4n+2 conjugated circuits, are fully aromatic.

Polycyclic conjugated hydrocarbons, the Kekulé valence structures of which have only 4n conjugated circuits, are non aromatic (anti-aromatic).

Conjugated circuits are those circuits in individual Kekulé valence structures in which there is a regular alternation of CC single and CC double bonds. Alternatively one can define the concept of conjugated circuit, as pointed out by Schaad and Hess [55], as follows: imagine a particular Kekulé structure of some conjugated hydrocarbon. Start with any carbon atom, and traverse any path through bonds, returning finally to the original atom. If the path consists of alternating single and double bonds, the path is defined to be a conjugated circuit; otherwise it is not.

Similarly an alternative form of the above structural defintion of aromaticity is as follows [56]:

Aromatic systems are those systems none of whose conjugated circuits appearing in any Kekulé structure are divisible by 4.

Late Professor E. Bright Wilson, in his book: Introduction to Scientific Research, has stated [57]: "*The most rewarding work is usually to explore a hitherto untouched field. These are not easy to find today. However, every once in a while some new theory or new experimental method or apparatus makes it possible to enter a new domain. Sometimes it is obvious to all that this opportunity has arisen, but in other cases recognition of the opportunity requires more imagination*".

This seems to be the case with the structural defintion of aromaticity stated above. Although this extension of the famous Hückel *4n+2* Rule was published in highly visible journal, few scientists have immediately recognized its paramount significance [58, 59, see Appendix A for more], the fact that in fourty years the paper in which it was presented is hardly approaching 500 citation, clearly tells that novel approaches based on novel tools requires more imagination to be recognized and accepted for what they are worth!

The new tool, *conjugated circuits* [60], are the novel structural components, which could have been discerned even in the time of Hückel, but were not. Gutman and Cyvin [61, 62] pointed out that the structural concept named *conjugated circuits* has been known in graph theory as *alternating cycles* [63]. Hence, conjugated circuits have been known in mathematics (graph theory) and now for the first time have been found of interest in chemistry. Conjugated circuits are the cycles contained in a "symmetric difference" of two Kekulé structures (= two perfect matchings). This is a term of Set Theory that was adopted in Graph Theory. The symmetric difference of two sets is the set of elements which are in either of the sets and not in their intersection. In the case of Kekulé valence structures, the intersection of any pair of Kekulé valence structures (with C=C bonds considered as elements) will result in a conjugated circuit. A complete set of conjugated circuits (or symmetric difference) of Kekulé valence structures was illustrated already in 1979 on coronene by Gutman and Randić [64].

CONJUGATED CIRCUITS REVISITED

In Fig. (**2**) we have illustrated all conjugated circuits for cycloocta[*def*]biphenylene, one of the compounds of Fig. (**1**), which has six Kekulé valence structures, which are shown at the top row of Fig. (**2**). Conjugated circuits are necessarily even, having *4n+2* or *4n* carbon atoms (π-electrons) and come in pairs, because each conjugated circuit has two Kekulé valence structures. An important theorem of Gutman [64] tells that the total number of conjugated circuits in a molecle having *K* Kekulé valence structures is *K(K-1)*, which is equal to 30 in the case of compound **4** of Fig. (**2**), having *K*=6. In Fig. (**2**) under each Kekulé valence structure are shown all its conjugated circuits, which are arranged so that they appear as a (graphical) matrix with blanks on the main diagonal. The order in which conjugated circuits are listed in the matrix is such that for the first Kekulé valence structure conjugated circuits appear also as the first conjugated circuit in the first row of the graphical matrix under the remaining five Kekulé valence structures. The conjugated circuits under the second Kekulé valence structure, which represent the second column of the graphical matrix are arranged in the second row of the graphical matrix, again in the order that they appear in the column of the corresponding Kekulé valence structure, which superimposed produce the same conjugated circuit, and so on. Clealry, in this way the matrix of conjugated circuits is symmetric, and its form depends only on the initial ordering of the Kekulé valence structures. When conjugated circuits are arranged in this way it is easy to see that a *single* Kekulé valence structure contains information on *all the remaining* Kekulé valence structures, which follows as corollary of the theorem of Gutman and was illustrated in [64]. This is easy to see by simply exchanging all CC double bonds with CC single bonds and *vice versa* in each conjugated circuit of a single Kekulé valence structure. The graphical matrix of Fig. (**2**) also illustrates an algorithm for the systematic construction of conjugated circuits of a molecule: All that is needed is to consider pairwise superpositions of all Kekulé valence structures, because this is an alternative interpretation of the graphical matrix of Fig. (**2**). There are computer programs for enumeration of conjugated circuits [65, 66].

Graphical matrices have been introduced in chemical graph theory almost 15 years ago [67]. They offer an additional representation of polycyclic conjugated hydrocarbons. Traditionally, polycyclic conjugated hydrocarbons have been represented by a set of Kekulé valence structures, but now with each polycyclic conjugated hydrocarbon one can associate a *single* graphical matrix. In Fig. (**3**) we illustrate the graphical matrix for naphthalene, which leads to an alphanumeric matrix, when conjugated circuits having six π-electrons are represented as R_1 and conjugated circuit with ten π-electrons are represented by R_2. Although matrices are not unique (their form depends on the ordering of elements) the invariants of matrices are however unique. One such invariant is the characteristic polynomial of a matrix. For example, the characteristic polynomial of naphthalene alphanumeric matrix is:

$$\mathrm{Ch}(x) = x^3 + (2\,R_1^{\,2} + R_2^{\,2})x - 2\,R_1^{\,2}R_2.$$

Alphanumeric matrices are not a novelty in chemistry. Almost 50 years ago Spialter [68-70] introduced atom connectivity matrix (ACM), which is constructed by modifying the adjacency matrix of molecular graph by inserting on the main diagonal of the adjacency matrix atomic labels. The characteristic polynomial of ACM was of interest for new computer-oriented chemical nomenclature of that time. A more recent type of alphanumeric matrices of interest in chemistry are the augmented connectivity matrices in which zeros on the main diagonal of the matrix are replaced by variables x_i for atoms of different type [71, 72],

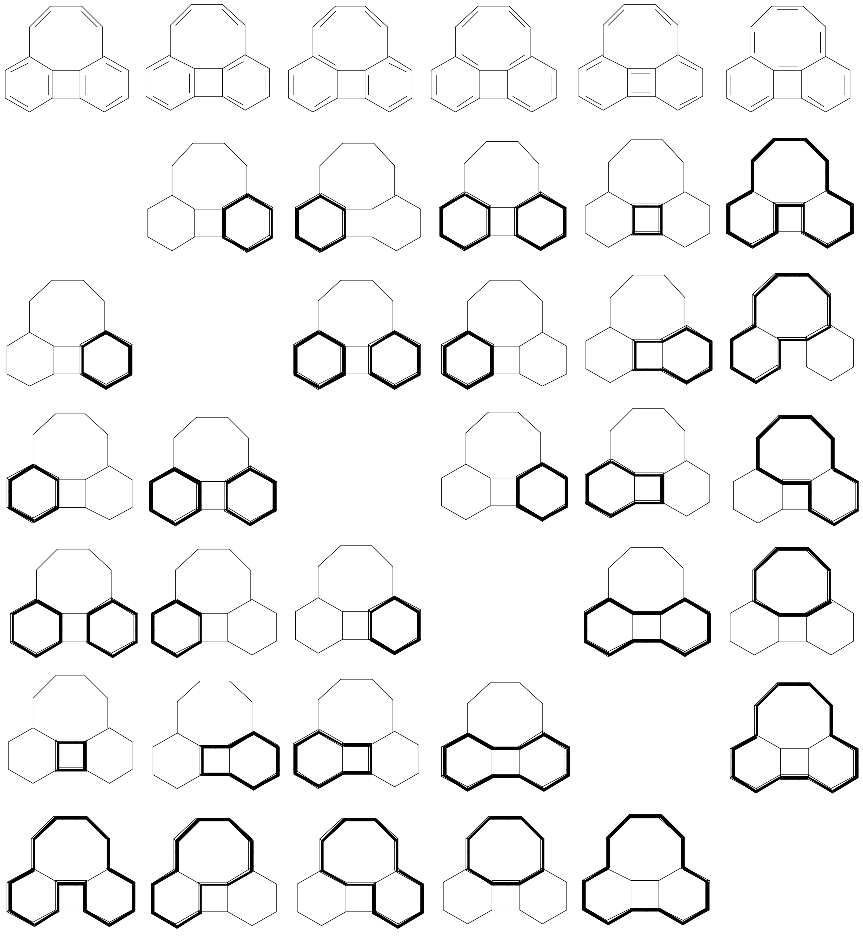
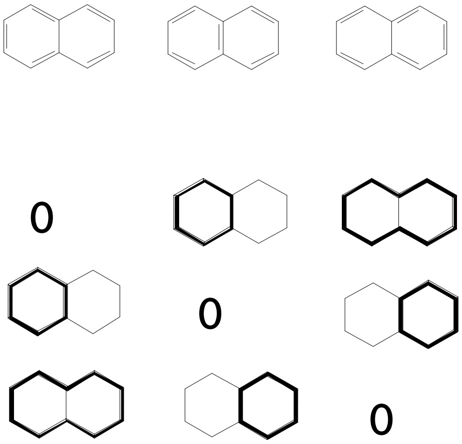


Fig. (2). Conjugated circuits for cycloocta[*def*]biphenylene, one of the structures of Fig. (**1**).

and even for atoms of the same kind, but in significantly different local environment [73]. From such matrices one can obtain expressions for the variable connectivity index, an important novelty in the traditional QSAR studies. The variable connectivity indices have demonstrated their great potential in structure-property / activity relationship (QSPRs and QSAP, respectively), yielding regressions of very high quality as compared to the use of the same number of traditional topological indices instead [74-80]. The same is true for other variable indices which incorporate variable parameters [81-83]. Unfortunately, as is not uncommon for novelties, apparently only few scientists have initially recognized their significance. Meanwhile this novelty has been not only overlooked, at least for a while, by most scientists involved in structure-property studies, but also misrepresented [84, 85], see Appendix B].



$$\begin{matrix} 0 & R_1 & R_2 \\ R_1 & 0 & R_1 \\ R_2 & R_1 & 0 \end{matrix}$$

Fig. (3). Conjugated circuits graphical matrix and alphanumeric matrix for naphthalene.

Until relatively recently, that is during the past 40 years, the main use of conjugated circuits was for (1) *classification* of polycyclic conjugated hydrocarbons as aromatic, partially aromatic or non-aromatic, and for (2) deriving *formulas* for molecular resonance energies (RE) [86-99]. We have to emphasize «formulas» rather than saying «for calculations of moleculer RE», because in order that one obtains numerical values of RE for these molecules one has to know numerical values of the relative contributions to the molecular resonance energy of conjugated circuits of different size [86], and possibly of different shape [100]. Numerical values have to be determined either empirically, based on avaialble known RE values, or computed by alternative quantum chemical models. For more on this, interested readers should consult the giant review article «Aromaticity of Polycyclic Conjugated Hydrocarbons» [7].

Few years back, in 2003, an additional important use of conjugated circuits was described, that of use of conjugated circuits for calculation of ring current in planar polycyclic conjugated hydrocarbons when exposed to external homogenous magnetic field [101]. We will outline in the next section this graph theoretical approach to calculation of ring currents in benzenoid and nonbenzenoid hydrocarbons.

Let us end this section by stating that conjugated circuits, a structural concept which may be mystery to most organic chemists and many theoretical chemists, may well be more important and computationally more useful structural concept than are Kekulé valence structures, or oherwise stated, the importance of Kekulé valence structures in chemistry undoubtedly has increased visibly because of the relevance of the underlying conjugated circuits contained therein for the quantiative discussion of aromaticity.

GRAPH THEORETICAL APPROACH TO π-ELECTRON RING CURRENTS

As has already been mentioned, CC bond currents are calculated by assigning counter-clockwise direction to currents induced in conjugated circuits of size $4n+2$ and clockwise direction to currents induces in conjugated circuits of size $4n$. The first such graph theoretical calculation of ring currents was described on three smaller non-benzenoid compounds: azulenopentalene $C_{14}H_8$, azupyrene $C_{16}H_{10}$ and one of its isomer [101]. The first structure has three 5-membered rings and one 7-membered ring, whereas the other two have each two such rings.

In Fig. (**4**) we illustrate CC bond currents for the conjugated circuits of cycloocta[*def*]biphenylene, $C_{16}H_{10}$, the fourth compound in Fig. (**1**), also an isomer of azupyrene. Again we have arranged individual conjugated circuits in a form of a matrix. We would like to draw attention of readers to different views on this important results of early chemical graph theory as applied to benzenoid hydrocarbons by sharing comments of annonymous referees to the same manuscript (ref. [64]) coming from two different journals, one evaluation being highly negative and the other highly positive [see Appendix A]. On the basis of the first two referee reports, the manuscript has been rejected when initially submitted to the *Journal of Chemical Physics*. The second evaluation came from a referee of *Chemical Physics* (European counterpart to the *Journal of Chemical Physics*) where the manuscripts was sent afterwords, and where it has been accepted in unchanged form and published. This incident nicely illustrates not only the observation of late Professor E. Bright Wilson, quoted in the introduction of this article about *imagination* and *lack of imagiantion* among scientists, but also of *competence* and *lack of competence* among scientist who are passing views on topics outside areas of their formal training.

At the bottom of Fig. (**4**) I have summarized CC bond current for all six Kekulé valence structures of cyclooocta[*def*]biphenylene separately. Observe that Kirchhoff's currents laws are fully satisfied at each junction for all Kekulé valence structures. When all CC bonds for the six Kekulé valence structures are superimposed, one obtains the results shown in Fig. (**5**), which ends the calculation of bond currents in the molecule.

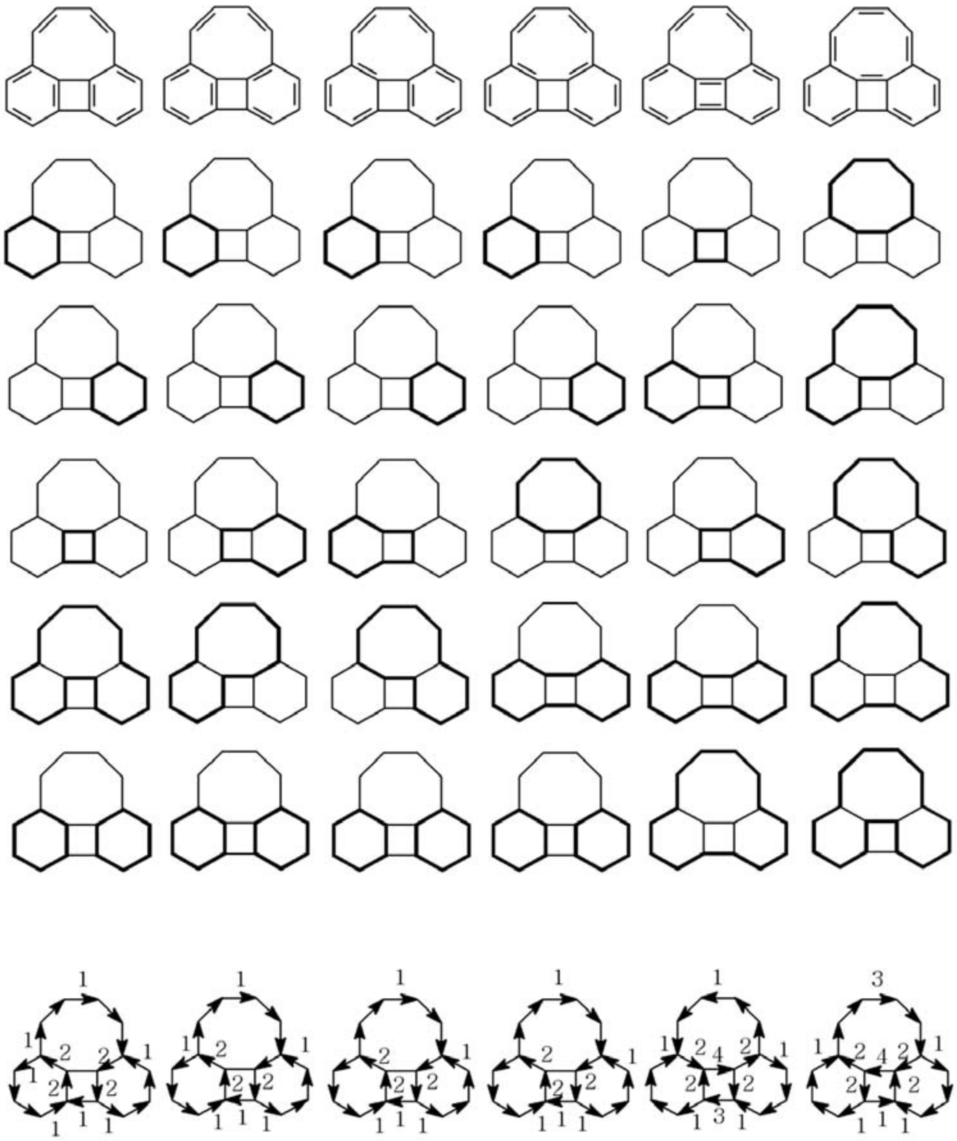


Fig. (4). Conjugated circuits currents for cycloocta[*def*]biphenylene, one of the structures of Fig. (**1**).

It has been known for some time that compounds of similar geometries can have significantly different properties, as is illustrated, for example, by the set of coronene isomers (having five- and seven-membered rings on their periphery instead of benzenoid rings), the ring currents of which have been recently investigated [102-105]. Such studies of ring currents in apparently similar structures revealed that calculated ring currents in 18 molecules that were studied have shown that they form two classes of compounds, one group having only *4n+2* conjugated circuits and only local diamagnetic currents, while the other has an admixture of *4n* conjugated circuits adding local paramagenetic contributions.

Our approach to calculating the magnetic properties of polycyclic conjugated hydrocarbons, which can be viewed as a graph theoretical analysis, is based on calculations of ring currents induced in individual conjugated circuits. The calculation of ring currents in polycyclic conjugated compounds has attracted attention in the early days of quantum chemistry, which were based on HMO calculations (Hückel molecular orbital method [42-45]). It was only more recently that the problem of π-electron currents induced in polycyclic conjugated hydrocarbons when placed in homogenous external magnetic field was considered using *ab initio* computations [102, 106-109], and using the graph-theoretical approach based on conjugated circuits [103-105, 110-112]. We should point, however, that in ref. [111], instead of speaking of *conjugated circuits* the authors choose to speak of *symmetric difference*, as if conjugated circuits and *alternating cycles* of graph theory (which lead to symmetric difference) are something different. Intentionally or unintentionally these authors failed to give reference to earlier work on conjugated circuits! Moreover, in ref. [111] authors also failed to cite the first paper on graph theoretical approach to ring currents, outlined six years earlier, in 2003 [105]. Symmetric difference, in graph-theoretical terminology, is the superposition graph of two *complete covers* of graphs, which in the case of polycyclic conjugated hydrocarbons is the superposition of two *Kekulé valence structures* of a molecule [61-63].

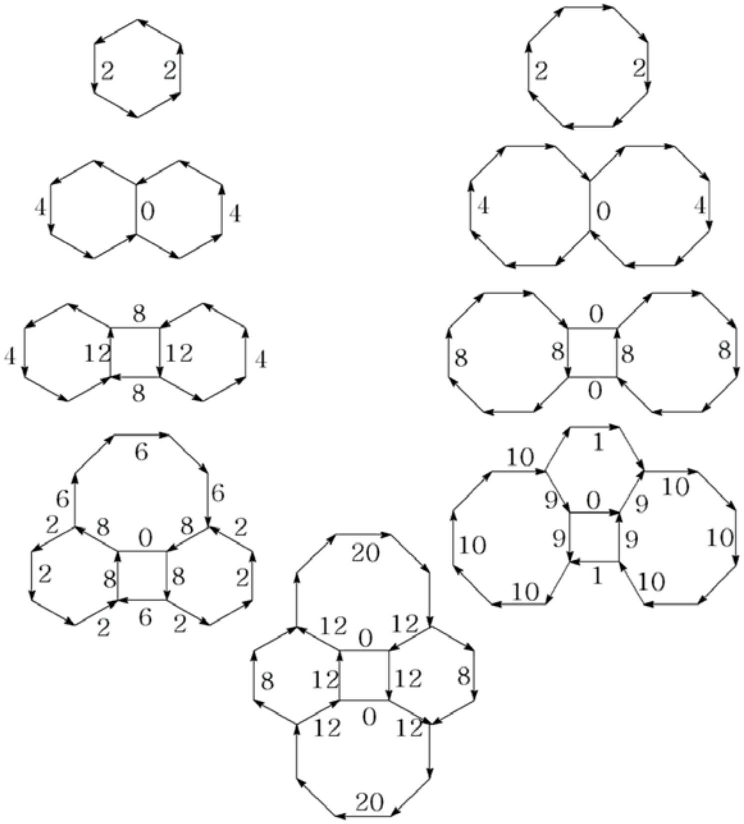


Fig. (5). CC bond currents for compounds of Fig. (**1**).

RESULTS

The CC bond currents in benzene (**1**) and in 1,3,5,7-cyclooctatetraene (**9**, synthetized already in 1905 by Richard Willstätter [32]), are trivially equal to 2, there being two Kekulé structures for a single ring. Neither is it difficult to see that in case of naphthalene (**2**) and octalene (**3**) there are no CC currents for the central CC bond, resulting in an un-normalized ring current of 4. For other structures of Fig. (**1**), one should depict all Kekulé valence structures and analyze them as was shown on cycloocta[*def*]biphenylene in the previous section. In Fig. (**6**) we show CC bond currents for the individual Kekulé valence structures of compounds **3** and **7**, while in Fig. (**7**) we show CC bond currents for the individual Kekulé valence structures of compounds **5** and **6**.

Although the final results of graph theoretical calculations are the bond currents for a molecule as a *whole* and not the results for individual Kekulé valence structures, it is of interest to examine Figs. (**6** and **7**) more closely. Observe for

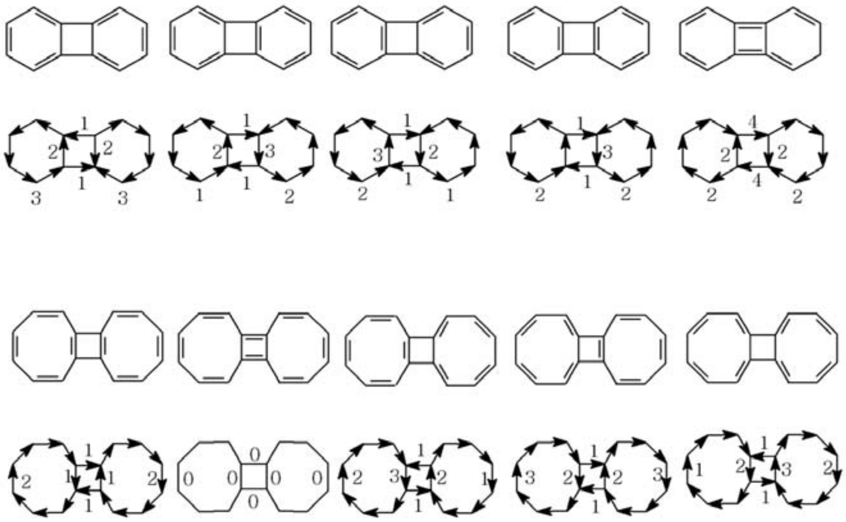


Fig. (6). CC bond currents in compounds **3** and **7** of Fig. (**1**).

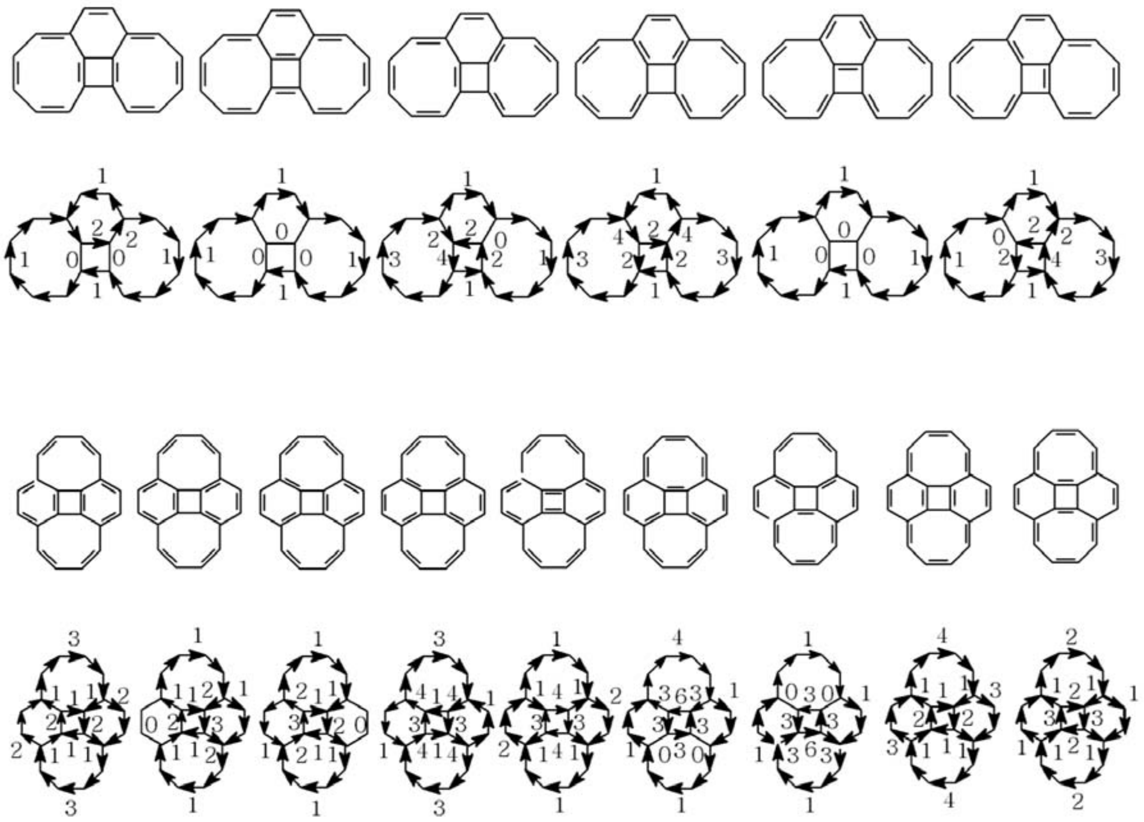


Fig. (7). CC bond currents in compounds **5** and **6** of Fig. (**1**).

instance that for compound **7** (in Fig. **6**) one Kekulé valence structure has no CC bond currents, while in the case of structure **6** (in Fig. **7**) one Kekulé valence structure has CC bond current along molecular periphery. Of more interest, of course, are the results shown in Fig. (**5**) with all CC bond currents and the results shown in Fig. (**8**) in which CC bond currents have been partitioned to individual molecular rings. The partitioning of CC bond currents to individual rings is unique, and allows results of this graph theoretical approach to be compared with other theoretical models which give ring currents. We should add that the currents shown in Fig. (**8**) have not been normalized, so if one is to compare currents between molecule having different number of Kekulé valence structures, then one should normalize the π-electron currents by dividing the magnitudes shown in Figs. (**5** and **8**) by $K(K-1)$, where K is the number of Kekulé valence structures of a molecule. For the molecules of Fig. (**8**) the normalizing factors are: 1, 1/6, 1/20, 1/30, and 1/72, respectively, for each row of structures of Fig. (**8**). If one want to have an idea of the magnitudes of induced magnetic flux the normalized ring currents should be further multiplied by the relative areas of different rings, which if one ignores minor distortions of bond lengths and bond angles within rings, are 1, $3\sqrt{3}/2$ and 5 for the square, the hexagon, and the octagon rings, respectively.

A close look at Fig. (**8**) shows that the aromaticity of benzene (**1**) and naphthalene (**2**) has been diminished in benzene rings of biphenylene (**3**), from 1 and 4/3 (in **1** and **2**, respectively) to 4/20, and in the case of cycloocta[*def*]biphenylene (**4**) to 2/30. In addition both biphenylene and cycloocta-[*def*]biphenylene have paramagnetic currents in their four-member ring that will affect the magnitude of magnetic shielding. Observe that in the next compound of Fig. (**8**), which has been listed in anticipation of showing decreasing aromatic characteristics, the ring current even in benzene rings is clockwise or paramagnetic current! The same is true also for all the remaining structures that follow: in these structures in all rings only paramagnetic ring currents (or no ring current) appear. Thus all these structures are devoid of diamagnetic ring currents.

Fig. (**8**) thus leads to:

NOVEL STRUCTURAL DEFINITION OF AROMATICITY

(1) Compounds which have only diamagnetic (counterclockwise) ring currents are *fully aromatic*. They necessarily have only $4n+2$ conjugated circuits;

(2) Compounds which have both, diamagnetic (counterclockwise) ring currents and paramagnetic (clockwise) ring currents are *partially* aromatic;

(3) Compounds which have only paramagnetic (clockwise) ring currents are *non-aromatic*;

(4) Compounds which have only paramagnetic (clockwise) ring currents and only $4n$ conjugated circuits are *anti-aromatic*.

Observe the two important aspects of this novel *structural* definition of aromaticity:

(i) To answer the question whether a structure is aromatic, partially aromatic, non-aromatic or anti-

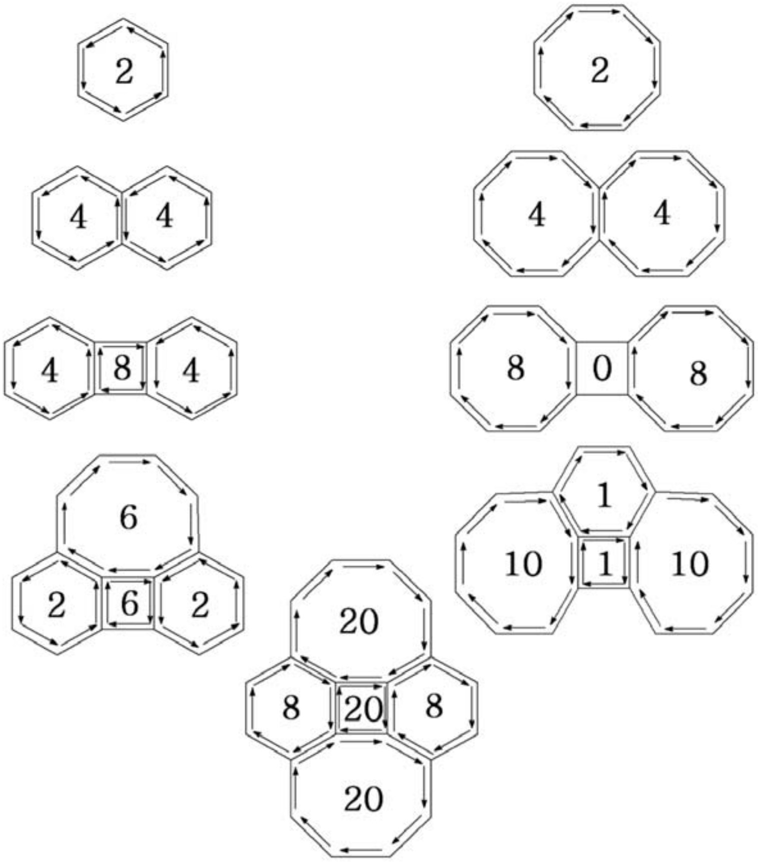


Fig. (8). Ring currents calculated using graph theoretical approach based on enumeration of contributions of bond currents induced in individual conjugated circuits of a molecule.

aromatic it suffice only to know *structural formula of the molecule*;

(ii) Novel definition characterizes aromaticity on the basis of *local* structural molecular features.

The underlying structural components which determine if a compound is fully aromatic, partially aromatic, non-aromatic or anti-aromatic are obviously conjugated circuits. This approach *parallels* the classification of polycyclic conjugated hydrocarbons with that based on conjugated circuits, but in addition it divides compounds which have both, *4n+2* and *4n* conjugated circuits, the partially aromatic compounds, into two subclasses. One subclass qualifies as *partially aromatic*, and the other as *non-aromatic*. In order to implement a similar discrimination of structures, again based on the presence of having both, *4n+2* and *4n* conjugated circuits, if ring currents are not used, it was necessary to determine the relative weights of conjugated circuits of different size in order to find out which conjugated circuits play a dominant role. This requires an *outside* selection of parameters for characterization of the relative role of conjugated circuits of different size, which could be based on the experimentally deduced molecular RE (resonance energy) or obtained from a quantum chemical computational model. Observe that above approach based on graph theoretical evaluation of ring currents from contributing conjugated circuits strictly depends only on molecular structure, without the need for outside computations or use of experimental data.

The proposed novel *definition* of local aromaticity, as one can expect, parallels to other local criteria for aromaticity, such as NICS values, and in this respect there may not be much novelty. But important distinction is that in order to find the result using our novel approach one essentially has only to *enumerate* qualified structural components, whereas approaches using resonance energy contributions and approaches based on MO calculations involve *computing*, and/or use of empirical schemes, and as such do not qualify as *structural* but rather as *metric* or *geometrical*. That is, they involve information on molecular geometry, interactions of electrons and such, and even though that information may be obtained as a result of *ab initio* computations, the results are *computational*, not structural in the spirit of molecular model of graph theory. In practical terms the novel approach may not in many cases give new conclusions, but has returned the discussion of aromaticity "back to square 1", where it belonged in the time and mind of August Kekulé.

AROMATICITY IS DEAD. LONG LIVE AROMATICITY

Let us end this article on aromaticity by pointing to three essential steps in defining and clarifying the concept of aromaticity, one of the central concepts of organic chemistry:

(1) Hückel *4n+2* Rule and *4n* Rule for monocyclic conjugated hydrocarbons;

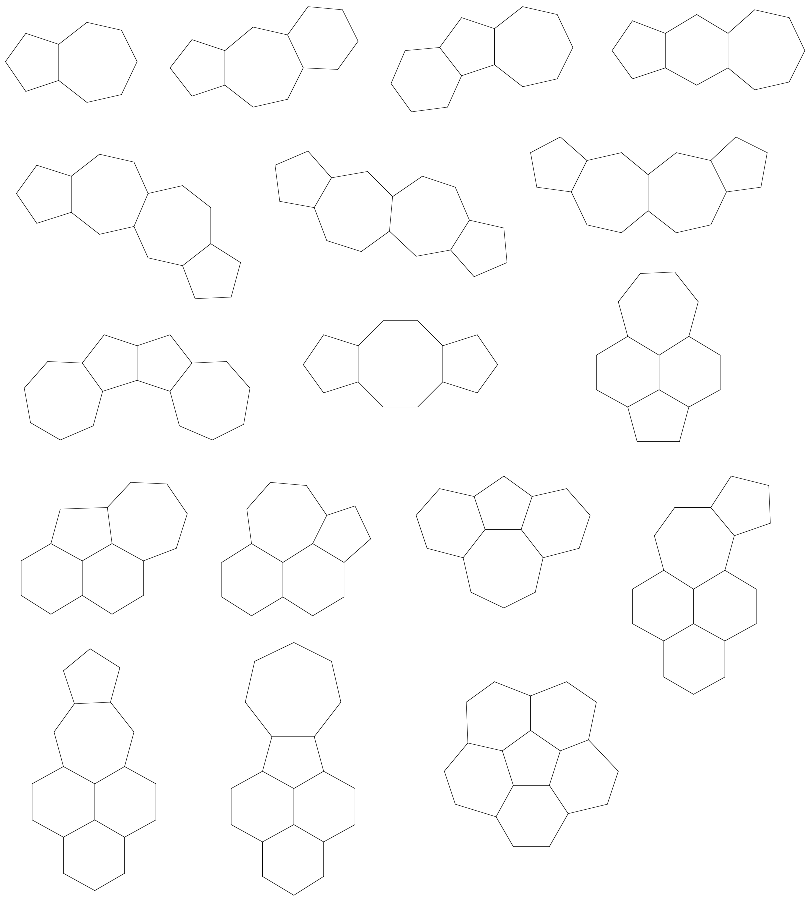


Fig. (9). Non-benzenoid polycyclic conjugated hydrocarbons having only *4n+2* conjugated circuits.

(2) Conjugated Circuits *4n+2* Rule and *4n* Rule for polycyclic conjugated hydrocarbons;

(3) Aromaticity is *local* and not *global* molecular property.

In view of these insights one may argue that questions like «is compound A or B aromatic or not» is a misdirected question. Instead the question should be: «Does compound A or B have local aromatic domains (rings) or not?» Because benzenoid hydrocarbons have only *4n+2* conjugated circuits, all their local domains are aromatic and for this class of compounds one can speak of them as aromatic compounds, meaning that *all their local domains are aromatic.* There is still another class of polycyclic conjugated hydrocarbons, illustrated in Fig. (**9**), the smallest member of which is azulene, which can eaqually be refered to as aromatic compounds, meaning, as already said, that *all their local domains are aromatic.* These are molecules that have only *4n+2* conjugated circuits. For all other molecules, which have both conjugated circuits of *4n+2* size and *4n* size, one can only speak of *local* aromatic characteristrics and *local* aromatic properties, and one may refer *qualitatively* to these compounds as partially aromatic. If one wants to characterize quantitatively the degree of their local aromaticity, then models based on ring currents and NICS appear as promising tool of the trade.

Hence, the final word on aromaticity, one of the central concepts in chemistry, can be summerized in: *Aromaticity is dead. Long live Aromaticity*!

The meaning of the above is that, aromaticity is dead as *global* molecular characterization, except for benzene and benzenoid hydrocarbons, azulene and azulenoid hydrocarbons, and other non-benzenoid compounds not having azulene substructure but having only *4n+2* conjugated circuits, like corannulene [113], compounds that can be referred to as non-benzenoid aromatics, molecules to which one can still refer as fully aromatic compounds. For other molecules aromaticity is dead! Howeveer, aromaticity is very much alive as *local* molecular feature (property), compounds which will show some properties of fully aromatic compounds as defined above, which may to a degree be diminished, depending on the degree of departure of these compounds from pure aromatic structures.

An extension of this views on aromaticty to heterocyclic compounds is possible, because the key ingrediant to local aromaticity are the number of π-electrons in molecular cycles, not the number of atomic centers (or the geometry or the size of conjugated circuits), and hopefully heterocyclic chemists should not have difficulties in recognizing local aromaticity in heterocyclic compounds.

In my review article on aromaticity [7] I have summarized the difficulties that accompany discussions of aromaticity by stating: *There is no Royal road to Aromaticity*,” paraphrasing the well known statment of Euclid: *There is no Royal road to Geometry.* This is said to have been reply of Euclid to King Ptolemy's request for an easier way of learning mathematics. Indeed, if one looks at the three crucial steps for clarification of aromaticity, namely: (1) The Hückel Rule (1931); (2) The generalization of the Hückel Rule to polycyclic conjugated systems (1977); and (3) Local *versus* global nature of aromaticity (2011), one sees a span of 80 years! So the road to Aromaticity has been long and tracheres, but hopefully, finally, we may be at its end. Looking in retrospect, it appears now that there were no obvious unsolved difficulties that could prevent us of arriving at this final stage in much shorter time, except for an apparent inertia of visible part of scientific community to accept novelty without undue scepticism and prejudice.

Whom should we thank that finally we came to the end of a tunnel, for facilitating the resolution of thorny and long dilemma about aromaticity? The answer is graph theory, the novelty of application of discrete mathematics in chemistry. It is interesting to mention that few knew at the time of the widespread use of HMO in quantum chemistry that the hamiltonian matrix of HMO, which can be reduced to a binary matrix, has been all the time «masked graph theory». Hückel never mentioned graph theory, and most quantum chemists who did many HMO calculations apparently also did not know of the close ties between HMO and graph theory. This came to light only relatively late, in early 1970s, mostly through the work of I. Gutman, N. Trinajstić and their collaborators [108-123] as well as through D. Rouvray's reviews [124-127]. Unfortunately, this came to be at the time when popularity of HMO gradually faded out, and uninformed quantum chemists identified graph theory with «simple» HMO calculations! Of course, there were always exceptions, such as J. Dunitz, M. E. Fisher, H. Günthard, E. Heibronner, J. Lederberg, V. Prelog, H. Primas, K. Ruedenberg, H. H. Schmidtke, and like, people who knew better [128-133]. The main tool of graph theory is *enumeration*. The early attention to importance of *enumerations* to chemistry was drawn by G. N. Lewis, who wrote in 1923 (almost 90 years ago), before the arrival of quantum chemistry [134]:

> *"Two quantitative methods have been available to scientists. One consists in counting and the other consists in measuring. The former has been the basis of the theory of numbers; the latter has lead to the development of geometry. The first of these sciences has been the mere plaything of abstruse mathematicians; the second has become the working tool of the scientist and engineer. Geometry is based on the theory of the continuum, and so also is the closely related science of calculus. We have been taught that an integration of the infinitesimal elements of a continuum may be approximately replaced by a summation of finite terms, but that the former method is exact and absolute while the second gives but an approximation. Are we not now going to be obliged to reverse this decision and to recognize that the branch of mathematics which will come nearest to meeting the needs of science will be the theory of numbers, rather than a theory of extension, and that measuring must be replaced by counting?"*

There is no doubt that G. N. Lewis, who died at the age of 70, in 1946, could have seen vindication of his views on the role of *enumerations* versus *computations* in chemistry, were his word taken at the time, and time after, more seriously by theoretical chemists. Judging on the past, one should not be surprised if theoretical and quantum chemists continue to stay clear of discussing aromaticity, as otherwise they would have to acknowledge importance of Graph Theory in chemistry, for what most of them may not be ready. This would clearly imply that they have been on the wrong track for so long time, with respect to use of Graph Theory in chemistry. However, experimental chemists do not carry such a burden, and I am convinced that experimental chemists will find the novel view on aromaticity practical and useful and may lead the way to a wider acceptance of this and other theoretical novelties in Chemistry.

CONCLUDING REMARKS

When I decided to examine and calculate ring currents for the nine compounds of Fig. (**1**) with stepwise decreasing aromaticity I have not expected that this project would eventually offer a *novel* structural definition of aromaticity, which is not only simple but it also agrees with much of what has been known for a long time, that all benzenoid hydrocarbons are aromatic compounds, and that there are non-benzenoid hydrocarbons such as azulene that are also aromatic. In addition, the novel definition of *local* aromaticity is likely to parallel most, if not all, findings based on *computational* approach to magnetic properties of polycyclic conjugated hydrocarbons using Schleyer's NICS approach. By having results for several hundred ring currents in some hundred molecules obtained during the past year, it did not take much imagination to realize that aromaticity is a *local* molecular feature and not *global* one. This conclusion parallels and illustrates Hegel's hypothesis on "Transition from Quantity to Quality." Accumulation of data on ring currents (quantity), intended to facilitate characterization of aromaticity as *global* molecular distinguished quality, supplied enough of illustration that pointed out to aromaticity not being a molecular *global* feature but rather a molecular *local* feature! The outcome of this *novel* viewing of aromaticity is that only molecules in which all *local* segments have aromatic characteristics can be referred to as *aromatic* compounds, and those which fail this test can be *partially aromatic*, *non-aromatic* or *anti-aromatic*. Superficially not much has been changed and not much will be changed, but this novel view on aromaticity will redirect question on aromaticity of molecules to question of aromatic fragments in molecules, and in this way may bring closer the historic opposing views of Kekulé and Erlenmayer on characterization of aromaticity.

So if one wishes to know whether this novel definiton of aromaticity is a promising novelty or irrelevant one, the answer will be known by those who try to use it and find out if they were better off with such novelties or without them. Everything else, would be mere speculation, undocumented opinon, misrepresentation or wishful thinking!

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APPENDIX A

Early Positive Views on Conjugated Circuits

This is how one of my papers on Graph Theoretical Approach to Conjugation was evaluated by an anonymous reviewer of *Tetrahedron*:

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

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

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

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

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

"Dear Professor Randic:

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

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

(1936). . . .

Again let me thank you for writing to me.

Sincerely,

Linus Pauling"

Let continue with a report on the paper by I. Gutman and myself "A correlation between Kekulé valence structures and conjugated circuits," which appeared in *Chemical Physics* after the following evaluation (dated January 5, 1979):

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

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

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

Finally an invitation

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

"Aromaticity and Conjugation"

Dear Dr. Randić,

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

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

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

Hoping for your soon and favorable reply,

I am with kind regards

Yours Sincerely,

Dr. F. Boschke

Early Negative Views on Conjugated Circuits

REFEREES REPORT File: 1363A8 (Journal of Chemical Physics, JCP)

Title: A correlation between Kekulé valence structures and conjugated circuits

Authors: Ivan Gutman and Milan Randić

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

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

Second report on the same manuscript (dated Nov. 14, 1978):

Comments on “A Correlation Between Kekulé Valence Structures and Conjugated Circuits” by I. Gutman and M. Randić

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

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

The above two reports are about the paper which was characterized in *Chemical Physics* as: *“that few would have thought contained such plums.”*

My Comment

To recognize the significance of «plums» one needs a few prerequisits, such as to develop a taste, to appreciate, and to have imagination; arrogance and ignorance, not so uncommon, are not an advantage in a search for the truth.

Allow me, instead of trying *“to convince the rest of the error of their judgment”* state that there are numerous publication in which *conjugated circuits* (“the plums”) have been used, considered, and related to other models. Here I am listing just a small fraction of such publication. I selected only publications that mentioned *conjugated circuits* in the *title* of the publication. This should suffice to illustrate that even if “*most of the scientists interested in chemical bonding in aromatic polycyclic molecules do <u>not</u> find this approach very fruitful*” some do. It has always been my conviction that it is better to have approval of a *single* scientist who understands what one is doing that bother with opinions of 100 who do not. The titles of 15 papers which appeared after my paper in *Chem. Phys. Lett.* that announced the concept of conjugated circuits listed below show some diversity of problems and uses of conjugated circuits. There may be few more papers having *conjugated circuits* as a part of their title, but this should suffice to illustrate serious limitations of the peer review system, which can be characterized by the motto “*The same judge sues you, and judge sentences you*,” which was the hallmark of the Ottoman (Turkish empire) “justice” system during 400 years of occupation of most of Balkan penisula in late medieval times.

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APPENDIX B

On Misrepresentation of the Variable Connectivity Index

Let me start by listing various branches of science of interest in chemistry that did not have an easy start, that is, have not been appreciated at the time of their inception:

Stereochemistry (tetrahedral carbon of Van't Hoff ,1874)

Quantum Theory (Max Planck, 1900)

Relativity (Albert Einstein, 1905)

Quantum Chemistry (Harold Urey, Joe Mayer, John Kirkwood, Robert Mulliken and others early 1930s)

Density Functional Theory (Walter Kohn during 1990s)

Chemical Graph Theory (Alexandru T. Balaban, Ivan Gutman, Nenad Trinajstić and others, since 1970s)

Mathematical Descriptors in QSAR (Lemont B. Kier and L. H. Hall, late 1970s)

Novelty comes in big and small packages, but regardless of size, more often than not it is not welcome by the Establishment. Significantly, Establishments change with time and views of Physical Chemistry in the early 1930s on Quantum Chemistry were hostile, but by 1980 Quantum Chemistry became an established part of Chemistry, which was hostile to DFT, the Density Functional Theory of W. Kohn, hostility which dissipated when W. Kohn shared Nobel Prize in Chemistry with J. A. Pople in 1998, but the Establishment may still harbor hostility towards Chemical Graph Theory.

The same antagonism can be detected toward many “small packages” of novelty, which one may say relate to “details” rather than to major direction in science. There are several formats of this hostility, often hidden behind anonymity, which can be in a form of:

(1) Ignoring seminal contributions to new direction in a field;

(2) Misrepresenting a novelty as if its claims are invalid;

(3) Claiming misconduct when the opposite is the case;

(4) Exporting bias and misjudgments by the Establishment

The good news is that many novelties have been intiated by younger scientists, who are likely to survive their critics, the bad news is that there are much novelty also that comes from senior scientists whose views are unprofessionally criticized by younger scientists. In such cases, only the genaration after the next one may settle the problem. Be it as it may, one should not be timid and passively wait for time to settle the matter. There is a cuirous paradox regarding misunderstandings in science, in that often those who are outside a particular research area can better judge which side is right. The problems is that contenders are often entrenched in their own positions and lose ability to be objective. Outsiders may have a lesser technical knowledge on the subject but are likely to be open to opposite views.

That is the reason for mentioning the misunderstanding of the varaible connectivity index here, as it appears more promising to explain misunderstandings to laymen than to a professional people who are not listening. In the same venue, this is why it may appear to some people as revolutionary to advertise aromaticity as a *local* concept and not of global one, as has been beleived for over hundred years. Old views and opinions tend sometimes to continue for some time having paramount qualities that hardly need revision. Aromaticity may well be one of such historical concept.

To return to MRA (Multivariate Regression Analysis), the oldest statistical methodology still widely used in QSAR and QSPR there are here two *separate* and distinct but highly important computational features when considering and comparing different regression results: (1) What is the *number* of descriptors used in a regression; and (2) How big is the *pool* of descriptors used for selection of the best subset of descriptors. Regressions having similar statistical parameters (e. g., standard errors) but using *fewer* descriptors are better. Regressions having similar statistical parameters (e. g., standard errors) but using *smaller* pool of descriptors are less likely to be spurious. These two factors important for MRA are separate issues and should not be mixed. In addition it need to be said that the *number of descriptors* are determined by the *number of variables in the regression equation* and this has nothing to do with how and when the molecular descriptors have been evaluated.

Confusion in publication of N. S. Zefirov and V. A. Palyulin [63] and ten years later repeated by W. C. Herndon [64], arose from their misconception of the variable connectivity index, which instead of being counted as a single index is vieved as multiple (having some kind of «hidden» multiplicity). Thus they attribute its higher peformance as being due to «additional» hidden descriptors. Nonsense. To see this imagine that prior to starting your regression with the variable connectivity index you in advance calculate say 400 numerical values by changing the variable parts of the index. Then you search for optimal descriptor (in a pool of 400) and you find the best single connectivity index. This would be an imitation what is offered for instance in CODESSA, one of the widely used statistical software in QSAR and QSPR. The resulting regression, all would agree, would involve a single descriptor. Suppose we have connectivity index with two variables x, y, the optimal values of which have to be determined. Rather than calculating in advance some 400 connectivity indices, from which to chose one, in practice I start assuming x = y = 0 (which reduces the variable connectivity index to an ordinary connectivity index), record the standard error of this simple regression, and consider a simple regression for a set of numerical values (0.5, 0), (-0.5,), (0, 0.5) and (0, -0.5) for variable (x, y). The smallest corresponding standard error indicates the direction for the search for optimal parameters (x, y), which typically I was able to find in some 40 steps, when calculating x, and y on accuracy of ±0.05 (as can be seen for example from ref. [49-56]. The outcome of this strategy is more efficient, because instead of calculating 400 indices for each molecule, one calculates only about 40, but the outcome is the same, single, connectivity index. As one can see nothing has been here «hidden», and if a question is to be raised about this *novel* approach to MRA (in which descriptors are optimized during the process of search for optimal regression) it should be about the possibility of chance correlation – but such a question has not yet been raised, and it is not difficult to answer and verify the results by randomization of input data. Apparently the *novelty* is discomforting for old ways of doing things, which may be one of the reasons for not being greeted with the enthusiasm that it deserves. If one is to go forward the *novelty* cannot be drawback but only an asset, if useful and offering better insights, or irrelevant, if not found not useful or not offering sound results. So if one wishes to know whether the variable connectivity index or the novel definiton of aromaticity are promising novelties or irrelevant, then the answer will be known by those who try to use them and find out if they were better off with such novely or without them. Everything else, like criticisms of Zefirov, Palyulin, and Herndon about the variable connectivity index, are mere speculations, undocumented opinons or wishful thinking!

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