

# Graph Theoretical Descriptors of Two-Dimensional Chirality with Possible Extension to Three-Dimensional Chirality<sup>‡</sup>

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We report on construction of a graph theoretical descriptor of chirality for two-dimensional benzenoid hydrocarbons. For achiral molecules the index is zero, while for chiral molecules it takes a positive or negative value for a molecule and one for its mirror image. Hence, we also have obtained a descriptor that measures chirality on an absolute scale, i.e., it assigns to a molecule a positive (or a negative) value without ever requiring information on the enantiomer of the molecule considered or any other pair of standards. In addition, we have briefly outlined how this is the 2-D approach extended to characterization of chiral objects in 3-D space, at least in the case of *n*-alkane rotamers.

## INTRODUCTION

“Miracles we perform instantly, the impossible may take a leetle longer.” Lee Sallow<sup>1</sup>

The last 25 years have seen an impressive expansion of chemical graph theory, particularly in the area of the development of mathematical descriptors for characterization of chemical structures.<sup>2</sup> Hundreds of descriptors, usually referred to as topological indices,<sup>3</sup> have become available for use in regression analysis, pattern recognition, principal component analysis, similarity studies, neural networks, etc. For example, the computer package CODESSA<sup>4</sup> (Comprehensive Descriptors for Structural and Statistical Analysis) evaluates several hundred molecular descriptors (graph theoretical as well as quantum mechanical). Novel topological indices continue to be developed<sup>5–10</sup> and have been extended not only for a characterization of 3D molecular structures, for characterization of 3D molecular shape, but also for characterization of folded proteins,<sup>11</sup> DNA sequences,<sup>12</sup> and two-dimensional maps, including proteomics maps.<sup>13</sup> However, none of the hundreds of topological, topographic, or geometrical indices can discriminate between a molecule and its enantiomer when considered in isolation. In our approach chiral index should not only *differentiate* among a molecule and its enantiomer but should also assign such pairs of descriptors of *the same magnitudes but opposite signs*. No such chirality indices have hitherto been proposed.

## 2. ON 3-D CHIRALITY

3-D chirality, that is, the chirality of three-dimensional objects in three-dimensional space, are generally well understood to relate to molecular asymmetry that is reflected in differences between an object and its mirror image (enantiomer).<sup>14</sup> When two such objects are looked at in isolation they have identical physical, chemical, or math-

ematical properties. It is only when such objects are in the vicinity of other objects or in an environment that removes the isotropy of the space and can discriminate different molecular shapes that the differences between a compound and its mirror image may manifest.

Although chirality is an old concept and generally well understood it was only relatively recently that it was recognized that one can associate with chirality a metric.<sup>15–20</sup> Hence, not only that one can speak of “more chiral” and “less chiral” molecules but one can express their degree of chirality numerically. Different authors considered different “measures” of quantitative chirality, which include discrete as well as continuous measures of chirality. Hence “the degree of chirality” of a molecule may depend on which particular method of characterization of molecules is considered.

While there is no dispute in establishing whether a molecule is chiral or achiral, (regardless what type of quantitative measure of chirality was assumed), it is not so straightforward to classify all chiral molecules as left or right. Ruch<sup>21</sup> has pointed out that despite having reference objects (such as the left and the right-hand and rules associated with assignment of such labels to simple systems) one may come across chiral objects that one cannot assign such simple classifications (illustrated on case of chiral potatoes). Randić and Razinger<sup>22,23</sup> have even illustrated cases where though classification of pairs of structures of a set was possible, when the standards used for determining which molecule belongs to one class (say positive (+) or negative (–), to avoid labels “left” and “right” that imply adoption of anthropological standards) have changed and new classifications may alter the assignments so that two molecules that were in the same subclass (say +) now belong to different classes. Hence, the determination of the chirality subclassification is relative. It can lead to cases that cannot be determined and may change the classification character of a molecule (and its enantiomer), depending on the standards adopted and the procedure adopted to measure differences among structures considered and among molecules and their enantiomers.

Before we outline our approach to chirality let us state what constitutes chiral molecular index, at least from our

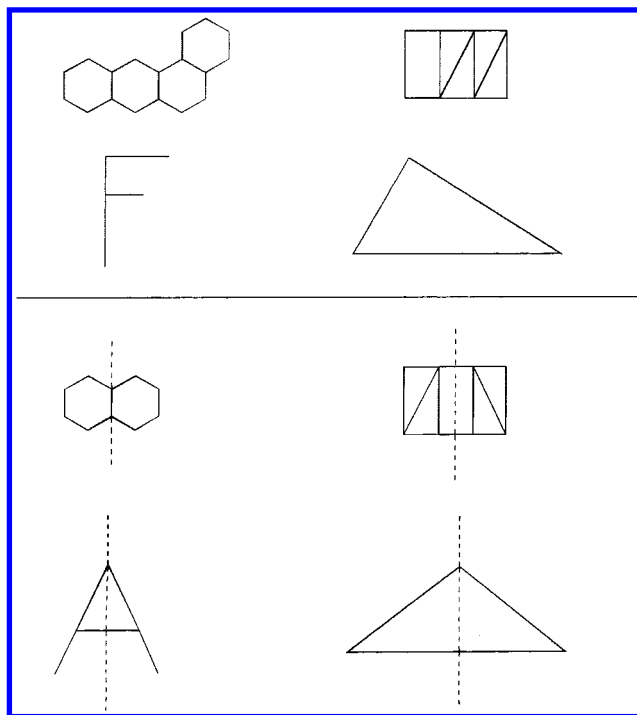
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<sup>‡</sup> Dedicated to Professor Ivar Ugi (München), a pioneer in Combinatorial Chemistry.

point of view. We consider that the essential quality that a chirality index has to satisfy are as follows: (1) enantiomers should have indices of the same magnitude but opposite sign and (2) the same procedure (algorithm) when applied to achiral systems should necessarily give zero chirality index.

In this respect we depart from the position taken recently by Golbraikh, Bonchev, and Tropsha<sup>24</sup> and also earlier considered by Schultz, Schultz, and Schultz.<sup>25</sup> These authors considered indices obtained by assigning to the diagonal entries of adjacency matrix values  $\pm c$  (called chirality correction). When such a procedure is applied to a selection of topological indices, it results in different numerical values for a compound and its enantiomer. Golbraikh et al. have illustrated this on the Zagreb group indices,<sup>26</sup> the molecular connectivity indices,<sup>27–29</sup> the extended connectivity indices,<sup>30</sup> the overall connectivity indices,<sup>31</sup> and the topological charge indices.<sup>32</sup> Invariants extracted from so modified adjacency matrices, in our view, do not qualify as chirality indices as they do not satisfy our first requirement that enantiomers have indices of the same magnitude but opposite signs. In fact about 10 years ago in this fashion, i.e., by altering the diagonal entry of the adjacency matrix of a molecular graph, the molecular connectivity indices have been generalized for heteroatomic systems.<sup>33–37</sup> More recently it was found that this approach need not be restricted to discrimination of heteroatoms in molecules but can be used also to differentiate the same kind of atoms if they are placed in a different local environment. For example, one can discriminate oxygen atoms in alcohols, ketones, ethers, esters, and fatty acids,<sup>38</sup> carbon atoms in rings from carbon atoms in acyclic parts of the same molecule,<sup>39</sup> and even when all atoms are of the same kind a “diagonal” correction of the graph theoretical valence of atoms can improve the statistics of regression analysis.<sup>40</sup> It is significant, for example, that in the case of oxygen atoms in different environments it was found that the optimal weights inserted as the diagonal entries of augmented adjacency matrices that reduce the standard error in a multivariate regression analysis (analogous to “the chirality correction” of Golbraikh et al.) correlated quite well with computed charges on oxygen atoms obtained by using traditional semiempirical quantum chemical calculations.<sup>38</sup> If this interpretation holds it would mean that atomic charges on chiral centers in chiral molecules are different, which in turn will contradict our perception of enantiomers. We should add, however, that this does not mean that the approach of Golbraikh et al. has no merits because, indeed, in an achiral environment, such as is typical in QSAR analysis, enantiomers may assume different atomic charges. The attempt to use chirality descriptors in QSAR was made several years ago by considering the predictive power for IC<sub>50</sub> values of the ligands for a series of dopamine and classification of barbiturates as sedatives or stimulants.<sup>41</sup>

It remains to be seen if the approach of Golbraikh, Bonchev, and Tropsha<sup>24</sup> and Schultz, Schultz, and Schultz,<sup>25</sup> mentioned earlier can lead to true chiral indices that will assign to enantiomers numerically the same magnitudes but opposite sites. A way to transform an index that does not satisfy this condition to one that does is to make appropriate linear combinations of “unsatisfactory” indices. Assume that a compound and its enantiomer have indices with numerical values  $X$  and  $Y$  ( $Y \neq -X$ ). If we subtract from these values the average  $(X + Y)/2$  we obtain modified indices  $X^*$  and



**Figure 1.** Top part: 2-D chiral objects embedded in a plane, which include the molecular skeleton of benzantracene and an asymmetrical triangle. Bottom part: 2-D achiral objects embedded in a plane, which include the molecular skeleton of naphthalene and an equilateral triangle.

$Y^*$  given as  $X^* = X - (X + Y)/2 = (X - Y)/2$  and  $Y^* = Y - (X + Y)/2 = (Y - X)/2$ , which are clearly of the same magnitude but opposite signs. So revised indices will satisfy our condition that enantiomers have indices of the same magnitude and opposite signs, but that does not make  $X^*$ ,  $Y^*$  automatically chiral descriptors. The situation is analogous to the requirement that shape indices do not depend on molecular size. If an index increases with size linearly (as many indices do) one could obtain size-independence by simply dividing such an index by  $n$ , the number of vertices in the molecular graph. This, as Rücker has pointed out,<sup>42</sup> does not necessarily make such indices shape descriptors, because shape involved besides branching, and cyclicity, which such indices may characterize additional qualities.

### 3. ON 2-D CHIRALITY

In view of the stated requirements for chirality descriptors we may conclude that no chiral descriptor has yet been found. The situation may be somewhat simpler when we restrict attention to the chirality in 2-D, rather than considering objects in 3-D space. Already at the beginning of this century the concept of chirality has been extended to  $n$ -dimensional spaces, including 2D plane, by Lord Kelvin.<sup>43</sup> Chirality in 2-D concerns planar objects embedded in a plane, such as those shown in the top part of Figure 1, which include an asymmetrical triangle as well as a molecular skeleton of benzantracene, which cannot be superimposed on themselves by sliding within the plane. If an object in 2-D has a plane of symmetry perpendicular to the 2D-plane it is achiral, shown in the lower part of Figure 1. The concept of quantitative chirality extends also to 2D chirality and in fact was considered for asymmetric triangles.<sup>17,20</sup> We will in this contribution consider a measure of chirality of planar

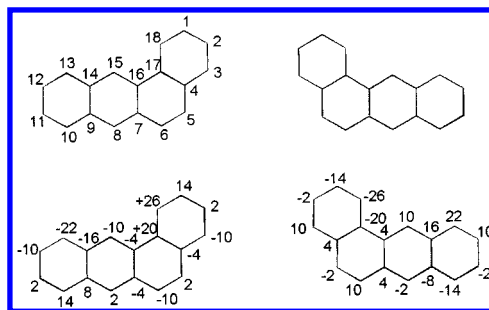
benzenoid hydrocarbons and will see that by focusing attention to pure graph theoretical aspects of such compounds we will obtain a descriptor that will differentiate a molecule and its enantiomer not merely by assigning to them *different* numerical values but numerical values of the *opposite* sign.

Although the chirality aspects of 2-D space are simpler it is not easy to see how one is to modify existing molecular descriptors, whether they relate to molecular graphs or embedded molecular skeletons in 2-D or 3-D space, so that enantiomers are described by descriptors of opposite sign, if we disregard indices obtained by earlier mentioned manipulation of adjacency matrix—for which it remains to be shown that they related to chirality and not to other molecular features, like charge, etc. If the “chirality correction” would point to a significant variation of charge on chiral atom, and such atoms are not found to change their charge in achiral environment, one should suspect that the “correction” is an artifact of the particular approach, rather than reflecting the actual difference between a chiral structure and its mirror image in the considered environment.

Can we arrive at chiral descriptors by a direct comparison of similarities and differences between an object and its mirror image? The apparent impossibility to construct a topological index that will discriminate among enantiomers is due to our considering individual chiral molecules in isolation! We will, nevertheless, show that for chiral molecules in 2D space one can design an index which discriminates enantiomers. We will illustrate the approach on planar benzenoid hydrocarbons embedded in 2D.

Some planar benzenoid hydrocarbons when confined to a plane are chiral and some are achiral. Excluding benzene, naphthalene is the smallest achiral benzenoid, and benzanthracene is the smallest 2-D chiral benzenoid hydrocarbon. Of course, all benzenoids are achiral in 3-D space. We will outline our approach to construction of graph theoretical chirality index on benzanthracene. Preliminary mention of this approach has been reported in ref 44. The essence of the approach is consideration of the molecular periphery. If molecular periphery is circumnavigating in a clockwise direction it shows different features then when it is circumnavigated in the anticlockwise direction. Observe that by considering circling around a molecule we have introduced an asymmetry, an element outside an isolated molecule, even when we consider but a single structure.

We start by focusing attention on the individual carbon atoms on the molecular periphery. For each atom selected we will examine the two alternative routes of circling around the periphery in the opposing directions. Clearly, in the case of chiral benzenoid hydrocarbons, such as benzantracene, the two directions of circumnavigating molecular periphery are not equivalent. Important, however, is to recognize that this is true whether we consider as a model rigid geometrical planar benzantracene model or whether we consider a molecular graph of benzantracene without any geometrical constraints imposed on bond lengths and bond angles. In the case of rigid benzenoid model which can be viewed as a section of regular hexagonal lattice as we walk around the molecular periphery we can construct two sequences that list the change of the direction at each carbon, as we go to the left (L) or to the right (R) at each vertex site. This convention was already outlined by Rouse Ball in his book on mathematical recreations<sup>45</sup> for labeling cyclic paths in



**Figure 2.** Molecular diagram of benzantracene and its mirror image (top) and the atomic sums obtained from the partial sums based on the binary codes.

cubic graphs. Alternatively, we can use binary labels, 1 for L, and zero for R, or *vice versa* or other pairs of typographical signs, like the left and the right parentheses.<sup>46</sup> If we choose 1 for L and zero for R we obtain binary sequences that were considered by Randić and Razinger in deriving their binary periphery code for planar (chiral and achiral) benzenoids.<sup>12,13</sup> If we choose to label the successive graph theoretical valences of each carbon atom as we walk around the molecular periphery, which are either 2-valent or 3-valent, we obtain a mathematically isomorphic sequence where R and L are replaced by 2 and 3, respectively.

We have labeled carbon atoms at the molecular periphery from 1 to 18 (Figure 2), hydrogens have been ignored, and their presence can be easily deduced. Then for carbon atom 1 the above-mentioned sequences which describe the two opposing walking around the molecular periphery are

clockwise	R	R	R	L	R	R	L	R	L	R	R	R	R	L	R	L	R	L
anticlockwise	L	L	R	R	L	R	L	L	L	R	L	R	L	R	L	R	L	L
clockwise	2	2	2	3	2	2	3	2	3	2	2	2	2	3	2	3	3	2
anticlockwise	2	2	3	3	2	3	2	2	2	2	3	2	3	2	2	3	2	2
clockwise	1	1	1	0	1	1	0	1	0	1	1	1	0	1	0	1	0	1
anticlockwise	1	1	0	0	1	0	1	1	1	1	0	1	0	1	1	0	1	1

Each sequence encodes local asymmetry of circumnavigating along the molecular periphery for each of the atom considered atom. Because all three sequences are isomorphic (mathematically equivalent) we will use the binary labels, being the simplest, rather than the numerical labels based on valences of atoms at the molecular periphery. However, we should not lose sight that the latter, which clearly indicates their graph theoretical origin are not based on assuming a regular hexagonal geometry for fused benzene rings, justifies our claim that derived invariants from such sequences will *also* be graph theoretical invariants rather than *solely* geometrical invariants.

The next task is to extract from the collection of such sequences for all atoms an invariant, a quantity that is independent of the atomic labels. Mathematical sequences whose magnitudes alternate, as is the case with the sequences of valences shown above, have some limitations. So instead of the sequences of valences we will consider the corresponding sequences of partial sums, which for atom #1 of benzantracene are

C: 1 2 3 3 4 5 5 6 6 7 8 9 10 10 11 11 12 12  
A: 1 2 2 2 3 3 4 5 6 7 7 8 8 9 10 10 11 12

This sequence is obtained from the corresponding binary sequence by adding at each site all entries preceding that site. In Table 1 we have listed the sequences of partial sums





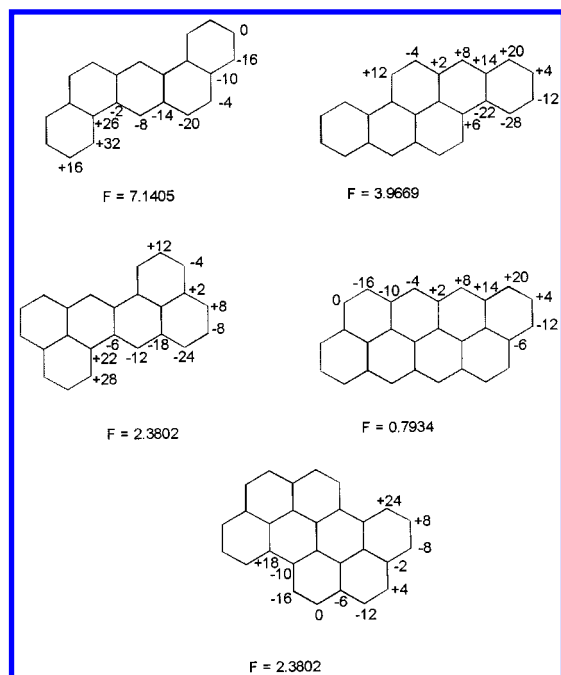
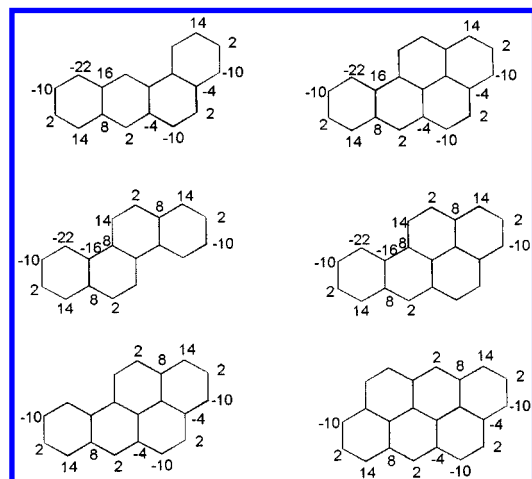


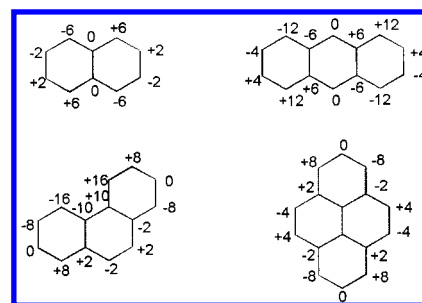
Figure 4.



**Figure 5.** The atomic sums obtained from the partial sums based on the binary codes for more symmetrical chiral benzenoids having  $n = 22$  carbon atoms on their periphery. Under each diagram the chirality index  $F$  is indicated.

cyclic hydrocarbon one obtains (positive, negative or zero) multiples of 24. This particular empirical property offers a convenient check on possible numerical errors of calculated atomic sums.

There are additional regularities for atomic sums for atoms in a similar local environment that become apparent when we compare atomic sums of corresponding carbon atoms in different molecules. For example, consider a section of neighboring atomic sums of benzantracene with benz[*a*]-pyrene and anthanthrene. When benzantracene is superimposed on benz[*a*]pyrene or anthanthrene so that it overlaps with the corresponding four benzene rings of these molecules, we find a long stretch of the periphery of both molecules to have the same atomic sums. This is illustrated in Figure 5 on a number of cases, including also the case of benzantracene and its overlap with benz[*a*]pyrene and anthanthrene. One can take advantage of this property and deduce the atomic sums in less symmetrical benzenoids from those of more symmetrical benzenoids. Thus from data on



**Figure 6.** Comparison of sections of molecular periphery having the same atomic sums for the corresponding carbon atoms which overlap when two benzenoids are superimposed.

chrysene and anthanthrene one can extract atomic sums for all carbon atoms in less symmetrical benzantracene and benz[*a*]pyrene.

It is clear from the definition of atomic sums in a molecule and in the corresponding atomic sums an enantiomer will be of the same magnitude but of the opposite sign. This is because the only difference in calculating the two quantities is the change of the sense of the clockwise to the anticlockwise circumnavigating the molecule. Because of that each atom in an achiral molecule (which will also show asymmetry) will necessarily have symmetry equivalent counterparts of the opposite sign. This point is illustrated in Figure 6 for several smaller achiral benzenoids. Although the sum of atomic asymmetry indices is always zero, whether we consider chiral or achiral molecules, the important difference when looking at atomic asymmetry indices between the chiral and achiral molecules is that in the former the zero sum occurs without matching individual contributions of different atoms, while in the latter the zero sum comes from the cancellations of the contributions of symmetry equivalent atoms.

#### 4. CHIRALITY INDEX $F$

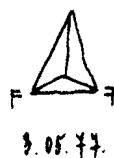
The next task is to extract a graph theoretical invariant from the set of atomic sum indices. A simple way to obtain a nonzero index from contributions that add to zero is to consider odd powers of the same quantities. Hence, we will define the chirality index  $F$  as a suitably normalized sum of third powers of atomic asymmetry contributions  $a_i$ , i.e.

$$F = \sum a_i^3 / n^3$$

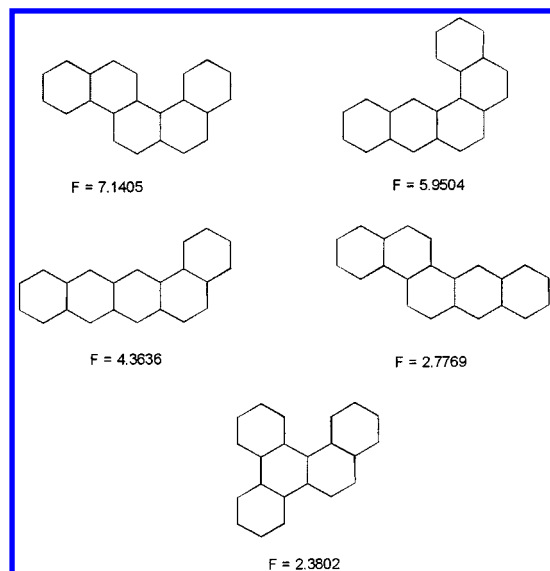
Here  $n$  is the number of (non-hydrogen) atoms in the molecule. We have selected letter  $F$  as a label for our index of chirality to avoid confusion with more obvious choices, like  $\chi$  and  $\kappa$ , in view that these labels have been already used for the connectivity index<sup>27</sup> and Kier's kappa shape indices, respectively.<sup>48</sup> The letter  $F$  is the first (capital) letter of the alphabet that is chiral in two-dimensional world and has been used to illustrate chiral centers by V. Prelog (Figure 7).<sup>49</sup>

In the case of benzantracene we have the following contributions coming from atomic asymmetry (positive and negative grouped separately):

$$14^3 + 2^3 + 2^3 + 2^3 + 8^3 + 14^3 + 2^3 + 20^3 + 26^3 - 10^3 - 4^3 - 4^3 - 10^3 - 22^3 - 16^3 - 10^3 - 4^3$$



**Figure 7.** Letter *F*, the first chiral latter of the alphabet, used by Prelog to label chiral centers.



**Figure 8.** The atomic sums obtained from the partial sums based on the binary codes for less symmetrical chiral benzenoids having  $n = 22$  carbon atoms on their periphery. Under each diagram the chirality index  $F$  is indicated.

The sum equals 12 672, hence it is different from zero! By normalizing the sum, using the above definition of  $F$ , we obtain for benzantracene  $F = 12\,672/18^3 = 2.17284$ . The negative value  $-2.17284$  belongs to the mirror image of benzantracene of Figure 2.

In Figure 3 we have shown the  $F$  values for smaller chiral benzenoids, having 18 carbon atoms on its periphery, while the  $F$  values for more symmetrical benzenoids having 22 carbon atoms on the periphery were shown in Figure 4. The  $F$  values of additional (less symmetric) benzenoids having 22 carbon atoms on the periphery are shown in Figure 8. Molecules have been ordered by increasing values of  $F$ . Let us first focus attention on the magnitude of  $F$  index for different benzenoids (Figures 3, 4, and 8). Do they support our intuitive feelings about the relative magnitudes for chirality? This appears to be the case for the extreme cases. It is to be expected that chrysene ( $F = 3.1605$ ) and dibenzo-[ah]anthracene ( $F = 7.1405$ ) are more chiral than the anthanthrene ( $F = 0.3951$ ) and a structurally analogous compound of Figure 4 ( $F = 0.7934$ ), respectively.

Observe the presence of degeneracy of  $F$  for several compounds having the same size periphery. Of 10 chiral benzenoids in Figures 4 and 8 two have  $F = 7.1405$  while three have  $F = 2.3802$ . These compounds have different shapes, and one should not conclude that because they have the same particular measure of asymmetry (with respect to circling around molecules in opposite directions) that they are necessarily of the same chiral characteristics. That topological indices often show degeneracy is well-known. Degeneracy reflects the fact that topological indices represent mathematical invariants of a structure, and it is inherent that

**Table 2.** The Higher Order Chirality Indices for Benzenoid Hydrocarbons Having  $n = 18$  Carbon Atoms on Their Periphery

	benzantracene	chrysene	benz[a]pyrene	anthanthrene
$F_1$	0	0	0	0
$F_2$	0.27778	0.48148	0.20988	0.06173
$F_3$	0.27160	0.19753	0.17284	0.04938
$F_4$	0.21279	0.13380	0.12068	0.02625
$F_5$	0.15851	0.08535	0.07926	0.01219
$F_6$	0.11672	0.05309	0.05044	0.00531
$F_7$	0.08578	0.03264	0.03152	0.00223
$F_8$	0.06303	0.01995	0.01949	0.00092
$F_9$	0.004631	0.01216	0.01198	0.00037
$F_{10}$	0.03399	0.00741	0.00734	0.00015

their construction usually accompanied some loss of structural information. The only remedy that is available in such a situation is to either introduce *additional* invariants or to *modify* the existing invariant so as to increase its discriminatory power. Both these approaches have been considered in the literature on application of graph theoretical descriptors in structure–property-activity studies.<sup>50</sup> Here we will consider the former alternative by generalizing the present approach to what we may refer to as “the higher order chirality indices”.

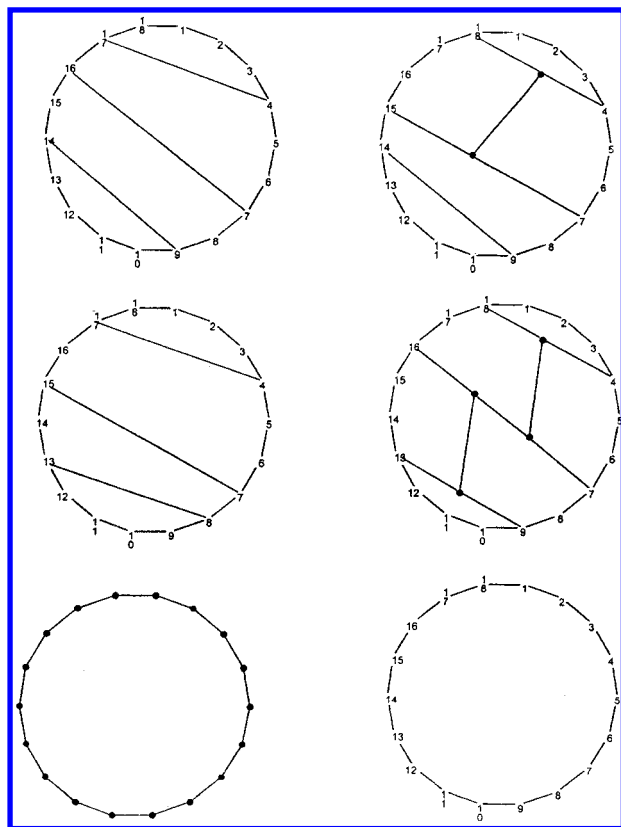
## 5. THE HIGHER ORDER CHIRALITY INDICES

There is a natural way to generalize chirality index  $F$  by considering other powers of the atomic sums, besides the third power used to obtain  $F$ . This generalization has already been hinted in the preliminary report of chirality index  $F$ .<sup>44</sup> If we apply this approach to the atomic sums of carbon atoms of benzantracene we obtain, using the successive odd powers, the following sequence: 3.7888, 6.7675, 33.5828, 95.5663, .... The first entry in the sequence is our  $F$  index of benzantracene. The sequence is divergent and needs some modification. The cause for the divergence is occurrence of atomic sums which are bigger than  $n$ , the number of carbon atoms in a molecule. Rather than introducing additional normalization factor, such as  $n!$ , we will reduce the magnitudes of the input atomic contributions by half. In this way no atomic sum exceeds the number of carbon atoms, and therefore all the numbers entering summation are less than 1, which ensures convergence. In addition we will consider all powers of atomic sums but will subtract the total of the positive partial contributions arising from the positive atomic sums from the total of the negative partial contributions arising from the negative atomic sums. In this way we do not need to skip the even powers, which would all be equal to zero if we would simply add the corresponding atomic sums raised to an even power.

We will refer to these generalized chirality indices as “the higher order” chirality indices and will use notation  $F_k$  for indices obtained by using atomic sums raised to the power  $k$ . In Table 2 we have listed generalized  $F_k$  indices for benzantracene and other planar benzenoid hydrocarbons having  $n = 18$  carbon atoms on the periphery. In Table 3 we have listed the higher order chirality indices only for those planar benzenoid hydrocarbons having  $n = 22$  carbon atoms on the periphery which have shown degenerate  $F$  values. As we see, the degeneracy of  $F$  can be considered “accidental”, because it is not present for other powers.

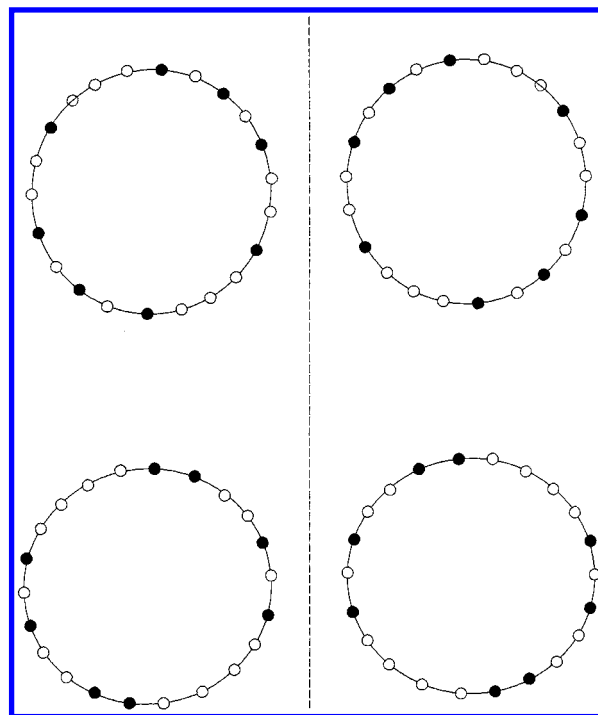
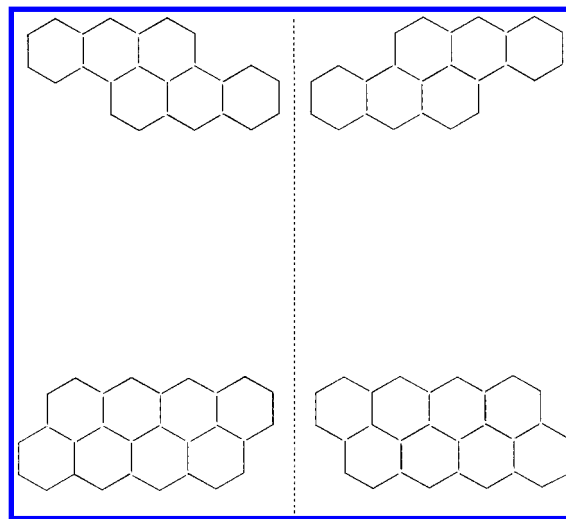
**Table 3.** The Higher Order Chirality Indices for Benzenoid Hydrocarbons Having  $n = 22$  Carbon Atoms on Their Periphery and Showing Degeneracy for the Chirality Index  $F$ 

$F_1$	0	0	0	0	0
$F_2$	0.73967	0.95041	0.33058	0.38843	0.24793
$F_3$	0.89256	0.89256	0.29752	0.29752	0.29752
$F_4$	0.87042	0.68983	0.21911	0.18112	0.28195
$F_5$	0.79913	0.50406	0.15163	0.10245	0.24998
$F_6$	0.71839	0.36103	0.10201	0.05631	0.21599
$F_7$	0.64086	0.25679	0.06758	0.03060	0.18422
$F_8$	0.57029	0.18239	0.04436	0.01655	0.15618
$F_9$	0.50740	0.12968	0.02894	0.00895	0.13115
$F_{10}$	0.45187	0.09240	0.01881	0.00484	0.10989

**Figure 9.** An alternative representation of benzantracene, chrysene, benz[a]pyrene, and anthanthrene displaying the same periphery codes when  $d = 3$  and  $d = 2$  valences are replaced by zero and one.

## 6. ON INTERPRETATION OF THE $F$ INDICES

The difficulty in attempting to interpret the  $F$  numbers for different benzenoid hydrocarbons is “hidden” in the fact that the approach outlined, although it has been applied to the periphery of various benzenoids, when stripped of irrelevant geometrical aspect of embedded benzenoids, becomes equivalent to the problem of characterization of the so-called (chiral) bracelets. Bracelets are combinatorial objects which can be represented by a graph depicted as circular arrangements of white and black beads. There is a one-to-one correspondence between any of the benzenoids considered and a bracelet in which vertices with valence 2 are represented as white circles and those with valence three as black circles. In Figure 9 we show the four cyclic forms corresponding to the four benzenoids of Figure 3 from which one can easily derive the corresponding bracelets by deleting the inscribed connecting edges. Hence, our mathematical approach equally holds for benzenoids and bracelets, but their

**Figure 10.** Chiral bracelets having  $n = 22$  beads, which are colored white or black, corresponding to chiral benzenoids of Figure 11.**Figure 11.** id hydrocarbons and their mirror images showing apparent opposite orientations yet having  $F$  index of the same sign.

pictorial forms are quite distinctive, which makes interpretation somewhat difficult. In Figure 10 we shows bracelets corresponding to two benzenoids of Figure 11, which one may expect to have  $F$  values of the opposite sign although they do not. Such an expectation, however, is not apparent from the corresponding diagrams of the bracelets and their mirror images, for which we have no such “apparent” indications as to the sign of  $F$ . The computed numbers  $\pm 3.9669$  and  $\pm 0.7934$  equally belong to bracelets in Figure 10 as to more familiar forms of the benzenoids in Figure 11. Hence, an interpretation of the chirality indices hang on the better understanding of the relationship of molecular forms of benzenoids and the underlying graph theoretical bracelets—a topic that has not yet received attention.

Finally, we should add that we anticipate further developments in construction of chiral indices. We have introduced here chirality index  $F$  and  $F_n$ , but clearly our approach also



has a number of “arbitrary” elements, that can be replaced by different choices. For example, we used valences of vertices, we used the partial sums, we simply added atomic asymmetries, and we used initially the third powers of atomic asymmetries and later other powers of atomic sums. Some of these steps can be altered, but an essential part of our approach is that of circumnavigating molecules in opposite direction, which results in recording different structural details, from which we extracted chirality indices.

We would like to point to another novel aspect of our approach, which apparently was not recognized earlier. Our procedure as defined leads to an *absolute* measure of chirality, which is not dependent on selected standards (like the left and the right-hand). We can classify chiral planar benzenoids as positive or as negative, depending on the outcome of the procedure. This has an important advantage because it does not call for a *comparison* between molecules, its mirror image, and the preselected standard objects for which chirality has been selected by convention. This is conceptual novelty, and it is remarkable that it is based on graph theoretical considerations, not on geometrical or topographic considerations, which require detailed (or less detailed) information on molecular distances, angles, etc.

There are a number of questions that the present article raises that we have not tried to answer. For example, is there some physicochemical significance of the calculated chirality indices? Do the relative magnitudes relate to some other shape characterizations of chiral molecules? What determines the sign of  $F$  values? Why do, for example, chrysene ( $F = 3.1605$ ) and dibenzo[ah]anthracene ( $F = 7.1405$ ) appear as having an opposite apparent orientation? There are several similar pairs of benzenoids, including those shown in Figure 11, that upon visual inspection one would expect  $F$  to be associated with  $F$  values of opposite sign. These are problems that need not be simply explained or fully understood. However, we should recall that until now it was not even suspected that a pure graph theoretical algorithm can not only discriminate among a planar structure and its mirror image but also attribute to such numerical values of the opposite sign.

## 7. LOOKING AHEAD

Now that we have offered a solution for 2-D chirality it is very important to consider the following questions: (1) how relevant for chemistry is 2-D chirality in general and (2) how useful for characterization of 3-D chirality are 2-D chirality approaches. Let try to answer these questions one at a time.

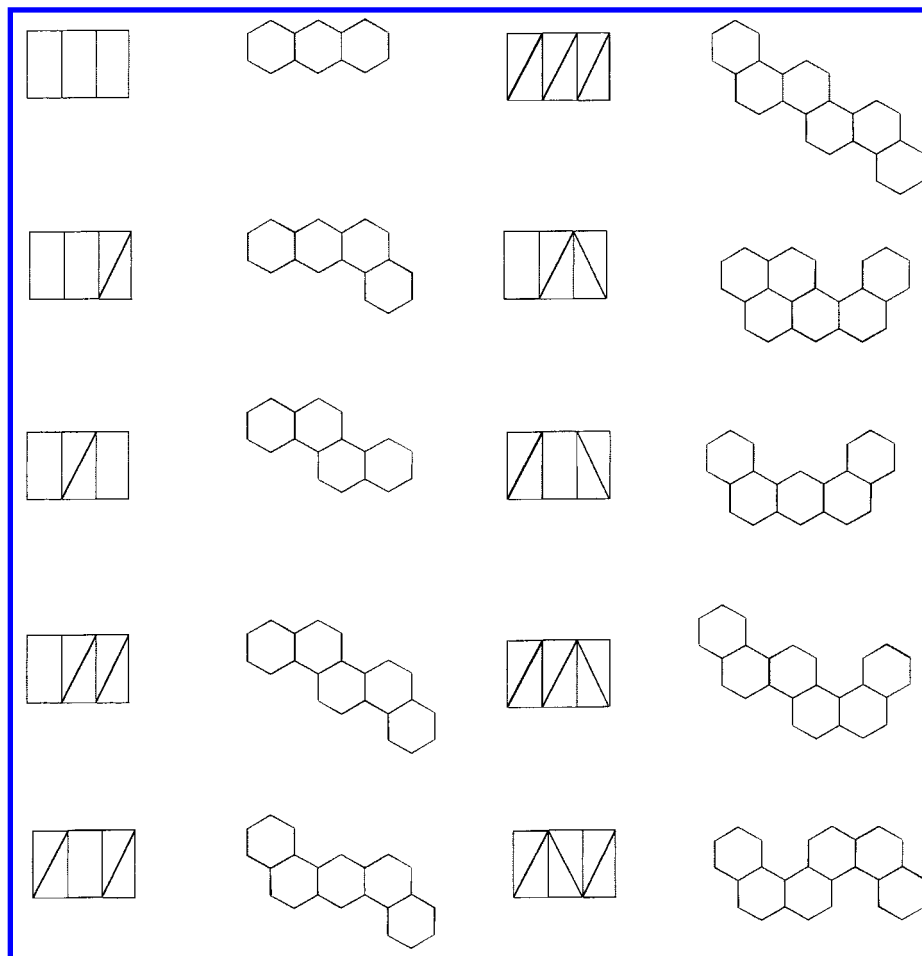
Planar benzenoids, of course, are part of chemistry in general. The relevance of 2-D chirality, therefore, depends on the relevance of models of embedded benzenoids in a 2-D space. One can think of paper and gel chromatographies as illustrations, but neither are we sure that under those experimental conditions molecules cannot flip over (hence escape from 2-D space), nor such experiments will discriminate among enantiomers because of the isotropy of the media. More relevant illustration would be to think of benzenoids being on a surface of a protein or other macroscopic system. Just as 3-D chiral molecules on a surface of a protein are discriminated the same can happen for a planar 2-D receptor on a molecular surface, if such can be identified.

Be as it may, most chemists may consider 2-D chirality an esoteric subject. But if we can tie 2-D chirality to 3-D chirality we would no doubt have full justification in considering 2-D chirality an essential theoretical model for chemistry. Indeed, there is a connection, as we will briefly here outline. It is generally not widely recognized, even within the chemical graph theory community not to mention chemistry as a whole, that apparently “planar” 2-D graphs can encode sometimes some aspect of molecular 3-D geometry! Klein and Zhu<sup>51,52</sup> have recently draw attention to this unexpected quality of graphs, but for our discussion here very important are the so-called augmented molecular graphs of  $n$ -alkanes.<sup>53</sup> They have been constructed as an alternative graph theoretical, in fact purely graphical, route to enumeration of rotational isomers, the enumeration of which has been reported earlier by Balaban.<sup>54</sup> The vertices in augmented graphs represent carbon and hydrogen atoms, while the lines in such graphs indicate, besides C–C connections and C–H connections, also as “connections” between hydrogen atoms at adjacent carbon atoms, but only if they are not in trans position. When the constant aspects of these augmented graphs are deleted, the graph reduces to simple block diagrams shown on the left side of Figure 12. These block diagrams are equivalent to simple ternary codes, which can be depicted as “empty” blocks or blocks with diagonal having positive or negative slope. Such codes are trivially transformed into numerical ternary codes using 0,  $\pm 1$ , if necessary (for computer manipulations).

We would like to emphasize an important aspect of this novel graphical representation of 3-D rotational isomers of  $n$ -alkanes, which has not been emphasized at the time when these graphs were introduced. The 2-D augmented graphs are in *one-to-one correspondence* with 3-D rotational isomers of  $n$ -hexane, which in fact can be viewed as an algorithm for transformation of a three-dimensional object to a unique two-dimensional graph. On the other hand, we have just seen that an index of chirality of graphs embedded in a plane can be obtained. The one-to-one correspondence of 3-D structures and 2-D graphs makes it possible to construct chiral indices for 3-D structures—at least such as considered here. However, even as this may appear a straightforward procedure to arrive at a characterization of chirality of 3-D objects, it is not.

The problem in deriving 3-D chiral indices from block diagrams is that the outlined procedure in this case apparently does not lead to nonzero  $F$  indices. When we use graph degrees of achiral block diagrams and consider clockwise and anticlockwise circulating around graph of Figure 12 we obtain complete cancellations of all atomic sums. This is just what happens in the case of achiral benzenoids, although here most of the block diagrams corresponding to  $n$ -alkane rotamers are chiral. For example, in the case of the third block diagram of Figure 12 for the eight vertices on the periphery we obtain the following valence sequences for the vertex at the left up corner: clockwise (C): 2, 3, 4, 2, 2, 3, 4, 2 and anticlockwise (A): 2, 2, 4, 3, 2, 2, 4, 3. From this one obtains the following partial sums: C: 2, 5, 9, 11, 13, 16, 20, 22 and A: 2, 4, 8, 11, 13, 1, 19, 22. By subtracting the corresponding entries we obtain for the (C–A) sequence: 0, 1, 1, 0, 0, 1, 1, 0, which gives for the vertex sum +4. When similar considerations are applied to the remaining vertices we obtain the sequence of atomic sums: +4, +8, -4, -8, +4, +8, -4, -8. That this should add to





**Figure 12.** The reduced block diagram derived from the augmented graphs of  $n$ -hexane rotational isomers and the corresponding benzenoids obtained by mapping each face of block diagrams into hexagonal rings following algorithm described in the text.

zero is to be expected, but in chiral structure the contributing atomic sums are in general different, while in achiral structures each positive contribution is fully canceled by a negative contribution of the symmetry equivalent atom. In the case above each contribution is fully canceled by symmetry nonequivalent atoms.

Hence, somewhat disappointingly, though most of the objects of the diagrams of  $n$ -hexane rotamers are chiral we cannot produce a nonzero contribution as was the case with benzenoids. The reason for this is not difficult to see: Although the augmented graphs and their reduced block diagrams may be chiral in 2-D space (and most are), their *periphery* is not chiral! So if we are to take advantage of the construction of chiral indices based on the periphery codes we have to transform our block diagrams into an object that results in *chiral periphery* for chiral cases. One way of obtaining such a transformation is illustrated in Figure 12 on the right-hand side where we assign to each face of block diagram a cata-condensed benzenoid obtained in the following way.

Replace each face of a block diagram by a hexagonal face in the following way: Start at the left and replace the first block by a benzene ring. Attach the next hexagon to one of the three right-hand side CC bonds of benzene depending on the slope of the boundary between adjacent faces in the block diagram. If the next cell is separated by a vertical line (no slope), attach the next benzene ring to the vertical CC bond line of the first benzene ring. If the next cell is separated

by a line with a positive slope, attach the next benzene ring to the CC bond line of the first benzene ring with positive slope. If the next cell is separated by a line with a negative slope, attach the next benzene ring to the CC bond line of the first benzene ring with a negative slope.

Because different block diagrams have a different number of faces (despite that they all represent isomers of  $n$ -hexane) we obtain cata-condensed benzenoids having a different number of fused rings. Observe also that for the cases illustrated in Figure 12 two block diagrams are achiral (in the sense of 2-D chirality), consequently, two of the 10 cata-condensed benzenoids of Figure 12 are achiral (i.e., anthracene and dibenzo[*a*]anthracene). These aspects of the ternary codes are a welcome bonus, because it is much easier to visualize if a molecule is chiral or achiral than to visualize the same for 3-D rotational models of  $n$ -hexane. Of course, since we already outlined the recipe for construction of 2-D chiral indices, we can calculate such indices for the benzenoids of Figure 12 and assign them to the corresponding rotamer of  $n$ -hexane.

## 8. CLOSING REMARKS

The epigraph heading in this article by Lee Sallow was composed to describe a solution to Martin Gardner's famous "Impossible Problem" in view of the monumental difficulty of Gardner's problem. Its use here should not suggest that the difficulties that we faced with "invention" of graph

theoretical chirality indices in some way commensurate with the “difficulty” of the original problem of Gardner. The epigraph was meant to impress on willing readers that Graph Theory is not merely limited to characterization of 2-D molecular skeletal forms, an obviousity—a misconception that endures despite reports on numerous graph theoretical invariants that hold specifically for 3-D molecular systems. One should not overlook the fact that before we embarked on this problem there were two major obstacles to overcome: (1) how to arrive at chirality index for 2-D structures and once we obtained 2-D indices (2) how to generalize the approach to 3-D chiral structures. The answer to the first problem, as we have seen, was found in taking the advantage of *circumnavigating* the molecular periphery in opposite directions, from which we were able to extract chirality indices. By viewing this first problem neither “miracle” nor “impossible” we then confronted the second obstacle of generalizing the approach yielding 2-D indices to construction of 3-D indices. Again, no apparent generalization appears in sight, because circling an object in 2-D space has no obvious counterpart in 3-D space. We face an “impossible” generalization, but as we have seen by “projecting” a 3-D structure onto a 2-D special diagram (augmented graphs and their reduced block diagrams) which preserve the chirality properties of 3-D objects and display 2-D chirality we “reduced” the “impossible” to “possible”. In the final step one additional transformation was required that “translates” an “inside” chirality of 2-D objects to the “perimeter” chirality, which allows computation of 2-D chirality indices for 3-D chiral objects.

In no way we would like to leave an impression that the 3-D chirality problem, and even the 2-D chirality problem, have been solved. All that we can say is that we have a solution for the 3-D case of *n*-alkane rotational isomers and the 2-D case of planar benzenoid hydrocarbons. One can expect for both, the 3-D and the 2-D cases, to see further development which may eventually bring solutions that may find use in various potential applications when analyzing chiral objects. If we have done nothing more than to show that the task of construction of graph theoretical chirality indices, that satisfy the crucial requirement for chirality indices that enantiomers be attributed indices of opposite sign, is practical we succeeded in showing that what until recently appeared impossible is in fact possible.

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