

Molecular Shapes and Chirality

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In this report we consider quantitative characterization of molecular chirality based on the binary code that describes the shape of the molecular periphery. We have limited our attention to chirality in two-dimensional space and consider benzenoid forms that are chiral and have constant perimeter P , i.e., we consider planar structures constructed from fused regular hexagons. The binary codes used assign either zero or one to CC bonds on the molecular periphery depending on whether we turn right or left, respectively, at each branching site of graphite lattice as we move around the molecular periphery. We have examined all benzenoid structures having molecular perimeter of 22 and fewer CC bonds (over 30 pairs of chiral structures). Since enantiomers have distinct codes, we based our quantitative measure of chirality on the degree of dissimilarity between the codes for a structure and its mirror image. As discussed in the text, the measure of dissimilarity depends on the length of the segments of the codes used in the comparison. Use of longer segments of the codes improve the “resolution” among different chiral pairs. By gradually changing the length of the segment of the code used for comparison we obtain a sequence of chirality values, rather than a single value chirality measure. Hence, our characterization of the chirality of two-dimensional chiral objects can be represented by a vector rather than by a single number. The comparisons of the codes were accomplished by a computer program.

INTRODUCTION

Many molecular properties depend on the details of the molecular shape, i.e., the precise geometry and the conformation of the molecular system. Yet, while the individual conformations of a molecule can often be studied in great detail, with quantum chemical methods the overall characterization of molecular shape, which is outside the domain of quantum chemistry, remains at best, qualitative, ambiguous, or unspecified. Recently we addressed the elusive characterization of molecular shape and proposed binary codes for a class of molecular shapes that are defined by the contours of planar benzenoid polycyclic aromatic hydrocarbons.¹ It should be stressed that we discuss in this paper binary codes of the periphery of molecular *model* and when speaking of the shapes we consider the geometrical outline of structures built from fused hexagons. We will continue, however, to refer to these as benzenoid shapes, although it is clear that there are many models for benzenoids, and simple geometrical models based on fused hexagons is not necessarily adequate in many applications. Benzenoids here are illustrations of geometrical shapes, a large family of structures which shows variations in shapes and diversity in structural features. Hence when we speak of the shape of naphthalene or the shape of benzantracene one should not take the labels literally. In order to emphasize the distinction between the more realistic model of a benzenoid and the simplified geometrical model based on fused hexagons we deliberately omitted drawing inner CC bonds. Most of our molecular diagrams show only the outline of fused hexagons, their periphery. On the other hand, although we consider only relatively simple shapes of smaller benzenoids our approach to characterize molecular periphery by the binary code is not limited only to smaller

benzenoids. As already described¹ arbitrary planar shapes can be approximated by hexagon-based shape. Moreover, it is possible to extend the concept of the periphery codes to arbitrary shapes, i.e., grid-free planar shapes.² Admittedly, benzenoids are but a rather narrow class of compounds, yet they include a diversity of shapes that have hitherto been at best only qualitatively described. To the best of our knowledge our approach represents the first systematic quantitative representation of molecular shapes though only for a well-defined class of compounds.

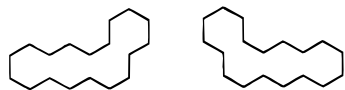
A need to study quantitatively molecular shapes as a separate topic, distinct and different from the studies concerned with molecular geometry and molecular electronic structure, is clear from the studies of drug–receptor interactions. It is well-known from the time of Emil Fischer and his model of “lock and key”³ that molecular shape is the critical factor that dominates biological activity. The interaction of small molecules with large proteins includes, for example, studies of smell and taste.

Molecular shape is critical for description of other molecular properties, e.g., crystal packing and melting temperatures. As we will see in this paper shape is also important when studying chirality, particularly when one is interested in quantitative measures of chirality.

By definition an object is chiral, if and only if, it and its mirror image can not be brought into the complete overlapping by continuous translations. The concept of chirality has been extended to n -dimensional spaces already by Lord Kelvin at the beginning of this century.⁴ Molecules embedded in a plane may therefore be chiral, even though when viewed in the three-dimensional space they are not chiral. Thus, for example, benzantracene, when embedded in a plane, i.e., allowed only to slide within the plane in which it is placed, is chiral, since it cannot be brought into coincidence with its mirror image:

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Transformation of one of the benzantracene forms into the other requires one to take the molecule *out of the plane* in which it is embedded. Thus the objects that are chiral in lower dimensional space will not remain chiral if placed into a space of higher dimension.

Early papers on chirality can be traced to Kitaigorodskii⁵ who was interested in correlation between chirality and chemical properties and Kauzmann and collaborators⁶ and Ugi⁷ who were interested in "chirality functions" and considered attachment of ligands to achiral molecular frame. In this paper we will consider the chirality of molecular shapes embedded in two-dimensional plane and will in particular consider how to measure the degree of chirality for the planar benzenoid systems considered. We will demonstrate that despite that we have limited our attention to smaller benzenoid shapes our approach can be extended to planar objects in general.

MOLECULAR SHAPE

There are very few studies considering characterization of the molecular shape. One way to characterize molecular shape was to examine their topological properties, to study mathematical properties of molecular surfaces, as their symmetry and similarity and including also an algorithmic computer analysis and detection of their chirality.⁸ We will consider a different route: Our efforts serve first to arrive at a molecular code that represents a shape and then study properties of such code, rather than directly considering molecular periphery or molecular surface (contours in two-dimensional case). We will thus endeavor to quantify and not just detect the chirality of the shapes in question. To this end we will use recently proposed binary codes for shapes derived by fusing regular hexagons.¹

By considering a relatively simple case of hexagonal shapes we hope to learn more not only about the difficulties and the limitations in characterization of molecular shapes but also about the equally evasive task of quantifying the differences among individual molecular shapes. The latter will directly lead to a measure of molecular chirality, a topic of recently increased interest in chemistry.^{9,10} Background information on chirality measures can be found in the recent paper of Zabrodsky and Avnir¹¹ who themselves proposed a novel continuous measure of chirality. Their continuous scale is based on the minimal distances that the vertices of a shape must move in order to attain the nearest achiral geometry. Quantitative chirality is a new area, rather unexplored until recently. It is not surprising therefore to see that different authors advocate different aspects of molecular shape as dominant. Consequently there are several definitions for "the degree of chirality".¹² Recently suggestions on unified approach to quantification of chirality have been initiated.^{13,14} Often people will agree that two molecules have a similar or dissimilar shape, but which pair of molecules is more similar or dissimilar is already a more difficult problem. In the case of chirality there are no disputes as whether a system is chiral or not, but deciding which pair of chiral objects is "more chiral" or "less chiral"

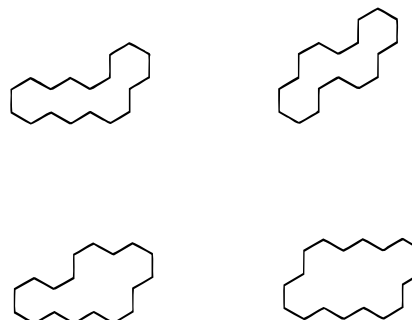


Figure 1. The smallest chiral shapes based on fused benzene rings.

Table 1. The Binary Periphery Codes for Chiral Benzenoids Having 18 CC Bonds on Their Boundary ($P = 18$)

benzantracene	001011110101101111
	001111011010111101
benz[a]pyrene	001101110110101111
	001111010110111011
chrysene	001101111001101111
	001111011001111011
anthrathene	010110111101011011
	010111011010111011

is very far from obvious. Our approach to such a problem is pragmatic: We will not dwell on the definition of molecular shape, we will rather derive codes to represent shapes and then use properties of such codes to quantify their degree of chirality.

PERIPHERY CODES

In Figure 1 we have illustrated the four smallest chiral shapes possible on a hexagonal map, those of benzantracene, chrysene, benzpyrene, and anthrathene. The length P of the periphery for all of them is the same: $P = 18$ (CC bonds). The periphery of such objects built from fused regular hexagons can be described by a binary code in the following way:¹ As one moves around the molecular periphery one either goes to the left or to the right after traversing each carbon atom, depending on the local situation. To keep the record of the movement, one needs only two symbols, 0 and 1. Since molecular periphery is a closed curve the so derived boundary code is a finite (cyclic) binary sequence of the length P . The precise form of the code will depend on the origin, the starting place when circumscribing the molecular periphery. Among different codes so constructed one can select the code that formally corresponds to the smallest number as canonical.

In Table 1 we illustrate the binary periphery code for the enantiomers of benzenoids of Figure 1. In Figure 2 we presented the binary codes for enantiomers of benzantracene. Only the canonical code for each enantiomer is shown. First observe that the code for the molecule and its enantiomer are not palindromes. This signifies that the object is chiral. Palindrome codes, i.e., the codes that are the same whether they are read from left to right or from right to left, characterize achiral structures.¹ Although the two codes for an enantiomer pair are different, they are nevertheless simply related: When the codes are viewed as cyclic, one code is obtained by reading the entries on the cycle clockwise and the other code is obtained when reading the same cyclic code anticlockwise as can be verified from Figure 2.

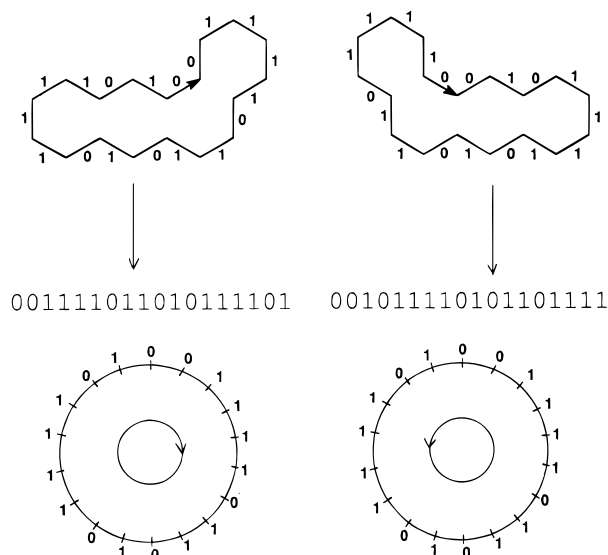
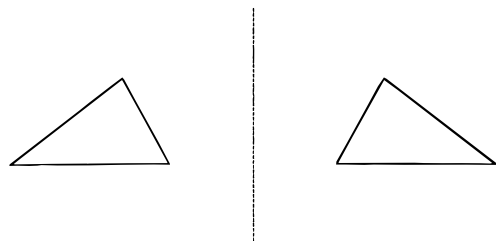


Figure 2. The binary codes for enantiomers of benzantracene. The starting CC bond is indicated by an arrow. The two codes can be derived from cyclic diagram by reading the entries in clockwise and anticlockwise sense.

TWO-DIMENSIONAL CHIRALITY

Recently, Buda and Mislow discussed the concept of chirality as it applies to two-dimensional objects.¹⁵ They considered asymmetrical triangles and convincingly argued that one can speak of a “more chiral” and “less chiral” triangle. One way to determine the degree of chirality of such triangles is to measure the departure of a triangle from its mirror image:



The maximal overlap of the two figures gives the degree of chirality of asymmetrical triangles.

Just as it would be arbitrary to label one triangle as the left and the other one as the right so it would be equally arbitrary also to label one form of a chiral benzenoid as the left and the other as the right. We can identify molecules in three-dimensional space as the left and the right enantiomers (their mixture being racemic). To arrive at such a classification one has to adopt a convention (i.e., the rules) of how to assign such labels. The labels “left” and “right” are based on analogy with the left and the right hand as a reference for comparison. Assignment of such labels to a general object is not necessarily straightforward. The left and the right labels may even be meaningless and impossible in some situations using the existing rules to determine whether a general chiral object, such as an asymmetrical potato, should be classified as left or right. Moreover, as we argue elsewhere,¹⁶ such classification is not necessarily absolute. That is, an object which has been classified in one class (say left) relative to another object as a standard upon a change of the reference structure may be found to switch the class.

The periphery code for chiral benzantracene does not show mirror symmetry, as was the case with the codes of anthracene, phenanthrene, and pyrene. Hence, one can by inspection of codes decide whether a shape is chiral or not. That it is quite arbitrary which of the two forms we label as the left or *l*-benzantracene and which we label as the right or *d*-benzantracene is apparent from Figure 3 in which distinct orientations of benzantracene enantiomers are shown. If we view the “benz” part of benzantracene as a thumb of a hand, then the top row parallels the “left” and the “right” shapes of a hand. If we consider the “anthracene” part as a thumb of a hand, then the opposite happens: The right becomes left and the left becomes right. Formally, we can use the moments of inertia as internal coordinate system. If we assign the *x* axis to coincide with the smallest moment of inertia and the *z* axis with the largest moment of inertia, the coordinate systems of enantiomers will correspond to the left and the right Cartesian coordinate system.

The form of a code, once the starting edge is selected, depends on the sense of “circulation” around an object. Hence, when considering shapes of planar structures embedded in a plane we could speak of “directional shapes”, rather than simply shapes. Some shapes will show different characteristics when the sense of circulation around is changed, others will not. Those which depend on the direction of circulation are chiral, while those that do not depend on the sense of circulation are achiral. A circle or a square will always appear to be the same shape regardless of the direction of circulation, but a nonsymmetrical triangle, just as the chiral benzantracene, will display two distinct oriented shapes corresponding to the two distinct images, the molecule and its mirror image.

We could say that two (chiral) triangles, just as two isomers of benzantracene, while having the same geometrical shape, have distinct “oriented” shapes. One can recognize the notion of “oriented” shapes in the ordinary life. The left and the right glove, or the left and the right shoe, have the same shape, but they are at the same time different. The difference is in the orientation. To climb a “triangular hill” represented by a profile of a chiral triangle is different when the hill is approached from opposite sides. The two directions of climbing such a hill are clearly not equivalent. Some may prefer to climb the gentle slope first and slide down the steep slope, other may prefer to do the opposite. When speaking of shapes, we do not differentiate normally between the left and the right forms, but when such objects are related to other objects (or embedded in space with directional properties) the directional property of shape will manifest itself and two geometrically equal shapes will be discriminated.

We could, in the case of planar chiral structures, assign enantiomers to a single class uniquely. For example, we could classify chiral benzenoids based on the relative magnitude of their canonical code. One class consists of the enantiomers with the smaller canonical label, and in the other class consists of enantiomers having larger canonical label. In Figure 4 this is illustrated on several smaller benzenoids. As we see such classification does not parallel geometrical appearance. Some of the benzenoids appear as “leaning” to the left (e.g., benzantracene and anthrathene), while others appear to be “leaning” toward the right (e.g., chrysene and benzo[*a*]pyrene). The same again happens for

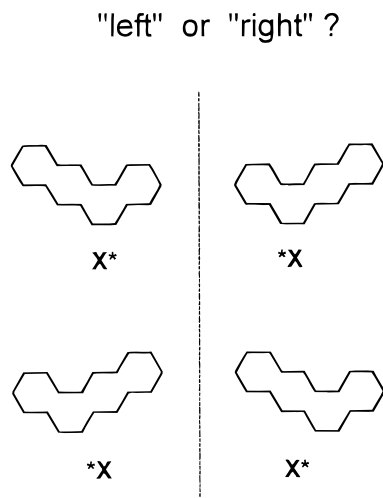


Figure 3. Ambiguities (and arbitrariness) of assignment of the "left" and the "right" labels to enantiomers.

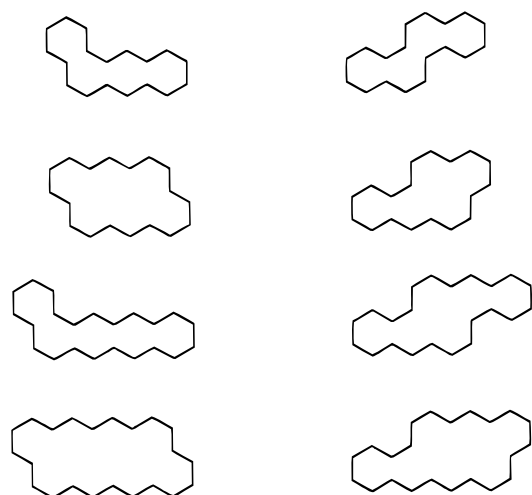


Figure 4. The enantiomers of selected benzenoids having the smaller canonical label. Half of the enantiomers appear to "lean to the left" and half appear to "lean to the right".

benzenoids with periphery $P = 22$ (the lower part of Figure 4). Hence, use of the canonical label does not agree with "natural" classification based on usual orientations of such figures.

LARGER CHIRAL BENZENOID SHAPES

When comparing the results of a quantitative measure of chirality we will consider only molecules having the perimeter P of the same length. It is therefore of interest to examine all smaller benzenoids having the same perimeter. However, even for smaller benzenoids it is not easy to find *all* structures. Once all structures of a given P are found it is not difficult to extract all chiral structures. Trial and error constructions are prone to errors. It is easy to omit some of structures even if detecting and eliminating duplicates need not be too difficult. With larger benzenoids the task to construct *all* possible (chiral or achiral) molecular shapes of a given perimeter will become quite tedious. An algorithmic approach is necessary in order to eliminate inefficient search for qualified structures. Construction of all benzenoid forms having the same perimeter P has apparently not yet been considered in the literature. Brak, Enting, and Guttman¹⁷ have considered a somewhat similar problem: Construction

of oriented shapes, i.e., counting as different the same shapes embedded on a grid differently.

In Figure 5 we depicted all two-dimensional chiral benzenoid shapes having perimeter $P = 22$. We have shown only one of the two chiral forms. In Table 2 we give the canonical (minimal) perimeter codes for all the chiral benzenoids of Figure 5. The benzenoid shapes were ordered so that the first shape has the smallest binary code, while the last shape has the largest canonical (minimal) code. Of the two possible chiral forms, one associated with the smaller binary code is used for ordering of structures (this being the form shown in Figure 5).

Figure 5 as well as Table 2 can be viewed as a shape catalogue (pictorial and binary, respectively) for chiral 2-D benzenoid shapes of perimeter $P = 22$. Clearly, the number of shapes increases exponentially when one considers structures of larger perimeter. This is apparent from the information on the total number of polyhex forms for a given number of fused rings. The earlier enumeration by Klarner¹⁸ reported that there are already 83 such hexagonal animals for $n = 6$ rings, of which 37 are cata-condensed. Hence the number of benzenoid shapes with perimeter $P = 26$ is greater than 37. Enumeration of hexagonal "animals" was extended by Knop and collaborators¹⁹ to benzenoid forms having up to 10 fused rings. The number of cata-condensed polyhexes having ten rings is already 6693 indicating the exponential growth of the lower bound on the number of hexagonal animals of constant perimeter as their perimeter increases. Therefore an extension of the periphery codes and the associated shape analysis to much larger benzenoids would become impractical unless fully automated. On the other hand, large benzenoids allow examination of finer details of individual shapes. With an increase in the resolution we can differentiate shapes that differ little from each other. Extension of the approach to structures built by fusing large number of hexagons is important as the increase is associated with the refinement of analysis which will eventually lead to better and better approximation of forms defined by smooth contours. Increase in n or relative decrease of the size of the graphite template grid will certainly reduce if not eliminate artefacts associated with the discrete hexagonal model of general shapes derived by fusion of regular hexagons.

CHIRALITY MEASURES BASED ON BINARY CODE

Let us first state the definition of chirality and then introduce the corresponding definition of chirality modified for chiral objects represented by binary codes.

Definition: An object X^* is chiral if and only if it is nonsuperimposable upon its mirror image $*X$.

In view that we work with molecular codes we can reformulate the above definition by replacing "physical superposition" or lack of superposition by superposition and nonsuperposition of the corresponding binary codes.

Definition: An object is chiral if and only if its code C is not a palindrome, i.e., C^* is not equal to its mirror image $*C$.

Clearly if a code is a palindrome when reconstructed it will give either X^* or $*X$, depending on the sense of circumscription. But since the code $C^* = *C$ necessarily $X^* = *X$, i.e., the object is achiral.

Chirality measures have been divided into²⁰

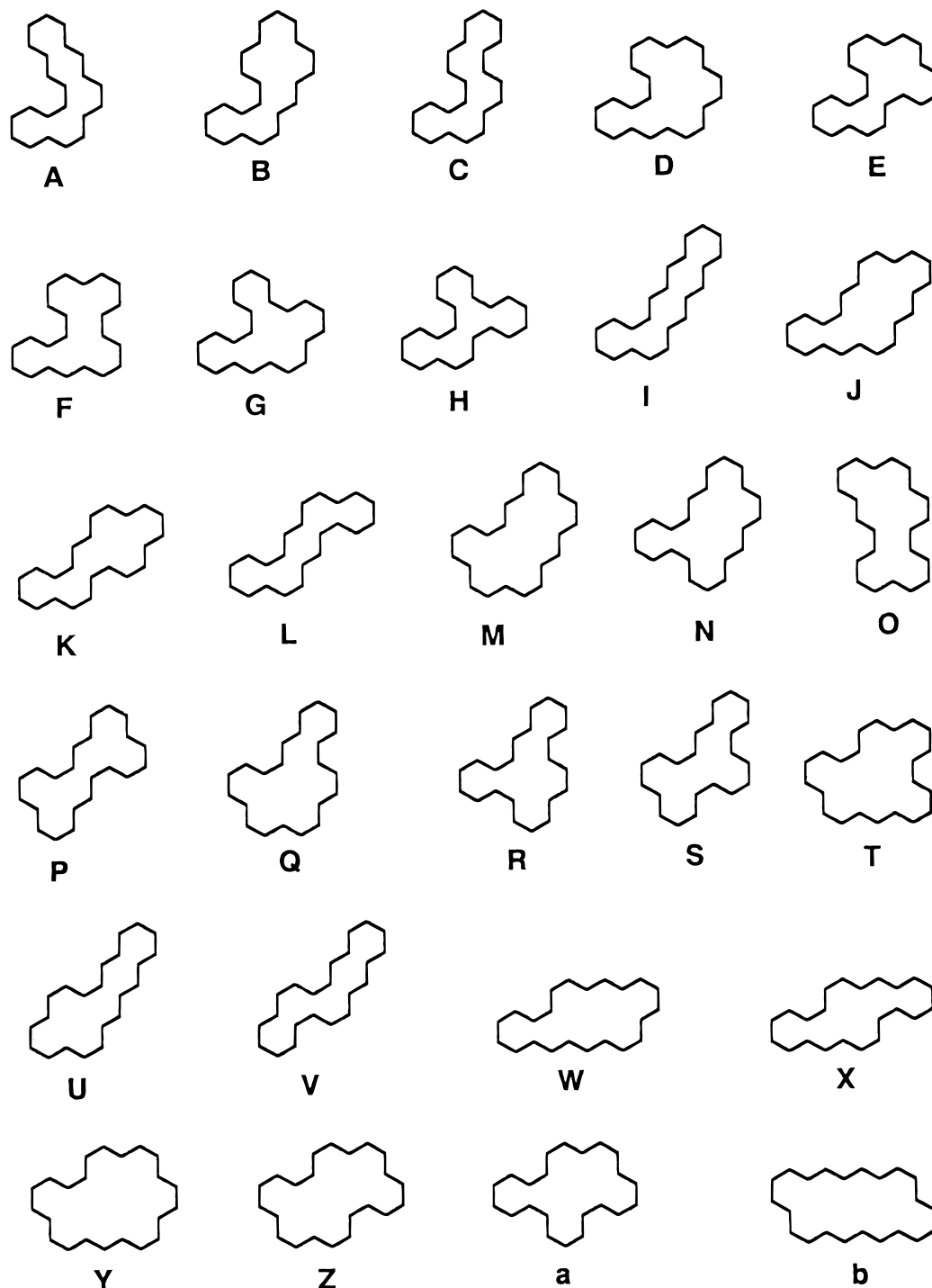


Figure 5. The 28 chiral benzenoids having the perimeter $P = 22$. The enantiomers shown have smaller canonical labels than their mirror images.

(1) Measures of the first kind: Those that gauge the extent to which a chiroid differs from an achiral object; and

(2) Measures of the second kind: Those that gauge the extent to which two enantiomers differ.

Here, we will consider the chirality measure of the second kind for the planar benzenoids. As the measure of chirality we will use the degree of similarity–dissimilarity between the pair of enantiomers. We will consider the 28 chiral shapes of Figure 5 having periphery $P = 22$. Apparently it is not easy by inspection of Figure 5, and its mirror image to decide which pair of chiral shapes is the “most chiral”. We will therefore use Hamming distance as the criterion for the similarity and dissimilarity between X^* and $*X$. Since

we work with codes this translates into similarity and dissimilarity of the corresponding codes C^* and $*C$. Hamming distance²¹ is the standard measure of coincidence between binary sequences (of equal length). It counts the number of noncoincidental sites in the code; the larger the number of places in which the two codes do not agree, the less similar are the codes, and the less similar are the corresponding shapes.

LIMITED COMPARISON—LIMITED DIFFERENTIATION

We have already outlined the procedure for a quantitative measure of molecular similarity on achiral structures.¹ Two codes that are to be compared, in order to find their Hamming

Table 2. The Binary Periphery Codes for Chiral Benzenoids Having 22 CC Bonds on Their Boundary ($P = 22$)

molecule	periphery code
A	0001011110101101101111
	0001111011011010111101
B	0001101110110101101111
	0001111011010110111011
C	0001101111001101101111
	0001111011011001111011
D	0001110110110110101111
	0001111010110110110111
E	0001110110111100110111
	0001111011001110110111
F	0001110111001110101111
	0001111010111100111011
G	0001111001110110101111
	0001111010110111001111
H	0001111001111001101111
	0001111011001111001111
I	0010101111010101101111
	0011110110101011110101
J	0010110111010110101111
	0011110101101011101101
K	0010110111011001101111
	0011011101101001111011
L	0010110111100101101111
	0011110110100111101101
M	0010111011010110110111
	0011101101101011011101
N	0010111011010111001111
	0011101011011101001111
O	0010111011011001110111
	0011011011101001110111
P	0010111011100101110111
	0011101110100111011101
Q	0010111100110110110111
	0011101101101100111101
R	0010111100110111001111
	0011101100111101001111
S	0010111100111001110111
	0011100111101001110111
T	0011011100111010110111
	0011101100111011010111
U	0010111101010110111011
	0011011101101010111101
V	0010111101011001111011
	0011101111010011011111
W	0011010111011010101111
	0011110101011011101011
X	0011010111100110101111
	0011110101100111101011
Y	0011011011011010101111
	0011101101101101101101
Z	0011011011100110110111
	0011101101100111011011
a	0011011011100111001111
	0011100111011011001111
b	0101011011101010110111
	0101011101101010111011

distance, are first aligned, and then one code is gradually shifted by one place and again the Hamming distance sought. The smallest Hamming distance is taken as the measure of the similarity/dissimilarity between the two structures. The same procedure applies also to evaluation of the similarity of X^* and its enantiomer $*X$.

When the code of a structure and its enantiomer are compared, entry by entry, we find that there is but a limited differentiation among different pairs of chiral shapes. In the first column of Table 3 we show the resulting similarities among the pairs of chiral components based on the Hamming distance between the corresponding codes. All the 28

structures can be grouped into two classes: Those having Hamming distance 4 (24 cases) and those having Hamming distance 6 (four structures). As we see using a single entry in a code for comparison does not produce much discrimination among the chiral shapes. The four structures, A, C, Q, and U, are to be viewed as more chiral than the rest.

In a way the outcome is a disappointment since such limited discrimination is of limited interest when searching for a quantitative measure of chirality. It is hard to imagine that so many molecules would have the same chirality measure. Clearly, we need to increase the resolution power of the approach. In order to increase the "resolution" and detect additional differences among the codes we should compare longer segments of the codes or longer "windows" of comparison. Comparison of longer segments of the molecular peripheries will increase the sensitivity of the approach. This appears particularly important for discussion of chirality, since when molecular fragments are viewed in isolation chirality is obscured. Chirality originates from the differences of a structure as a *whole*; hence, the longer the fragments of the code are that are compared, better representation for the differences among enantiomers will be obtained.

How long should the segments of the code be when used for the comparison of the codes? To obtain some insight we decided to gradually increase the length of the segment of the code and see what happens. The remaining columns of Table 3 show the Hamming distance between enantiomer pairs when longer "windows" of comparison are used. As the length of the segment, the "path" used for comparisons of the codes, is increased, greater differentiation among enantiomers occurs. The last row in Table 3 gives the number of different entries in each column. Indeed as expected the number of distinct chirality values increases as the length of the segment of the code is increased, reaching its maximum for paths of length six to eight. After that the "resolution" power of the comparison as a function of the length of the "path" decreases and when we reach segments of length 16 we see that saturation has been achieved. Further increase of the length of the segment does not lead to differentiation, the structures and their enantiomers have been maximally discriminated.

This is an interesting finding suggesting "natural" places to stop the comparison of the codes: (1) we can stop at the maximal differentiation of compounds, here at paths of length 7 (about 1/3 of the code length); or (2) we can go to and base our measures of chirality on the "final" values, here those given by paths of length 16 (about 2/3 of the code). There is no point in going beyond paths of length 16 in our example since each structure is equally affected resulting in constant increments for the derived totals.

To arrive at useful measure for chirality we should, once we have chosen the maximal length of the segment of comparison, consider "totals". In this way we avoid ambiguities that result when the results in different columns are compared. Consider, for example, the initial values for A and L, i.e., Hamming distances between A^* and $*A$, and L^* and $*L$:

difference	path 1	path 2	path 3	path 4
$A^* - *A$	6	10	12	14
$L^* - *L$	4	8	12	16

Table 3. Variations of the Hamming Distance between Enantiomers of Benzenoids with $P = 22$ as the Segment of the Comparison (Path) Increases^a

	path 1	path 2	path 3	path 4	path 5	path 6	path 7	path 8	path 9	path 10	path 11	path 12	path 13	path 14	path 15	path 16	total 1–16
A	6	10	12	14	16	17	18	19	20	21	22	22	22	22	22	22	285
B	4	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	229
C	6	11	14	16	18	19	20	21	22	22	22	22	22	22	22	22	301
D	4	6	8	10	12	14	16	17	18	19	20	21	22	22	22	22	253
E	4	8	10	11	12	13	14	15	16	17	18	19	20	21	22	22	242
F	4	8	12	13	14	15	16	17	18	19	20	21	22	22	22	22	265
G	4	6	8	10	12	14	15	16	17	18	19	20	21	22	22	22	246
H	4	8	10	11	12	13	14	15	16	17	18	19	20	21	22	22	242
I	4	8	10	11	12	13	14	15	16	17	18	19	20	21	22	22	242
J	4	8	10	11	12	13	14	15	16	17	18	19	20	21	22	22	242
K	4	8	10	11	12	13	14	15	16	17	18	19	20	21	22	22	242
L	4	8	12	16	18	20	22	22	22	22	22	22	22	22	22	22	298
M	4	6	8	10	12	14	15	16	17	18	19	20	21	22	22	22	246
N	4	8	10	12	14	16	18	19	20	21	22	22	22	22	22	22	274
O	4	6	8	10	12	14	15	16	17	18	19	20	21	22	22	22	246
P	4	6	8	10	12	14	16	18	20	22	22	22	22	22	22	22	262
Q	6	10	12	14	15	16	17	18	19	20	21	22	22	22	22	22	278
R	4	6	8	10	12	14	16	18	20	21	22	22	22	22	22	22	261
S	4	8	11	12	13	14	15	16	17	18	19	20	21	22	22	22	254
T	4	6	8	10	12	14	16	17	18	19	20	21	22	22	22	22	253
U	6	10	12	14	15	16	17	18	19	20	21	22	22	22	22	22	278
V	4	8	10	12	14	16	18	19	20	21	22	22	22	22	22	22	274
W	4	8	12	16	17	18	19	20	21	22	22	22	22	22	22	22	289
X	4	8	12	14	16	18	20	22	22	22	22	22	22	22	22	22	290
Y	4	6	8	10	12	14	15	16	17	18	19	20	21	22	22	22	246
Z	4	8	10	12	14	16	18	20	22	22	22	22	22	22	22	22	278
a	4	8	10	12	13	14	15	16	17	18	19	20	21	22	22	22	253
b	4	6	8	10	12	14	16	18	18	20	22	22	22	22	22	22	240
	2	4	6	6	8	9	9	9	8	7	6	5	4	3	2	1	

^a The last column is the sum of the preceding 16 columns. The last row indicates the number of different entries in each column, a measure of the resolution power of the length of the segment used.

Initially A is found to be more chiral than L, at “path” 3 the two are “equally chiral” and finally as the path length of the segment for comparison of codes increases we find L to be more chiral than A.

While some may be disturbed by ambiguities inherent to the introduced measure of chirality one should recognize that here we have an illustration of a typical “resolution based chirality measure”, a special case of which is Mezey’s approach using inner coverings of an object with subunits. As Mezey has outlined, the outcome of gradual refinement of the covering is a transformation of achiral cover to a chiral one. The scale at which this transition occurs gives a measure of chirality. Our approach can be viewed conceptually as an extension of this kind of analysis in that we continue to refine the scale of comparison (here given by the length of the segment of comparison of codes). Thus by increasing the resolution we arrive at different numerical values for chirality which describe the history of the progression in the comparison.

OPTIMAL COMPARISON—MAXIMAL DIFFERENTIATION

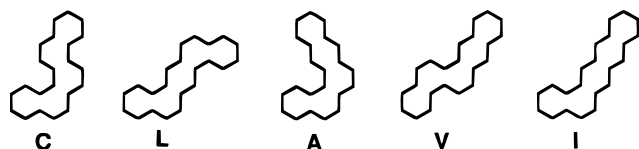
In Table 3 we give the Hamming distances for all 28 pairs of chiral benzenoids of Figure 5 using from 1 to 16 paths. The last column gives the total, the relative values of which will remain the same since no further differentiation between the codes are possible. We have achieved the maximal differentiation of the codes. In the final column we find values between 301 and 229, sums of 16 different chirality values for the 28 compounds. Several compounds are

represented by identical rows in Table 3, such as Q and U, N and V, and D and T. Similarly G, M, O, and Y, as well as E, H, I, J, and K have among their enantiomers the same Hamming distances. All these benzenoids generate the same sequences respectively and within the model cannot be differentiated. In the case of the benzenoids *a* the total is the same as that of the pair D, T, but the sequences from which the total is obtained are different.

We could not detect structural features that cause the above mentioned degeneracy. It is possible that by studying larger systems this particular aspect of the chirality measure based on the binary codes becomes visible. It is equally difficult to see how the final measure of chirality (the last column in Table 3) is related to structural components of individual benzenoids. Again we have too many variations in structural composition and too few benzenoids which have the same common characteristics to make the particular structure–chirality relationship apparent. In part this may be due to the relatively small number of structures considered ($N = 28$). They show considerable variability in various structural elements and lack of similar structural features that could allow one to look for trends. Observe that while all the structures have the same P (the length of the perimeter), some of them have different areas, i.e., they are built using different numbers of fused benzene rings. However, if we restrict attention only to the nonbranched cata-condensed benzenoids C, L, A, V, and I, then the order based on the chirality measure as given by the last column in Table 3 parallels fully the ordering based on the number of Kekulé structures K for each benzenoid:

Table 4. The Averages of Hamming Distances between Benzenoids with $P = 22$ and Their Mirror Images as the Segment of the Comparison (Path) Is Increased^a

	mean 1	mean 2	mean 3	mean 4	mean 5	mean 6	mean 7	mean 8	mean 9	mean 10	mean 11	mean 12	mean 13	mean 14	mean 15	mean 16	RANK
A	6	8	9.33	10.50	11.6	12.5	13.29	14	14.67	15.30	15.91	16.42	16.85	17.21	17.53	17.82	5
B	4	6	7	7.75	8.40	9	9.59	10.13	10.67	11.20	11.73	12.25	12.77	13.29	13.80	14.31	28
C	6	8.50	10.33	11.75	13	14	14.86	15.63	16.33	16.90	17.36	17.75	18.08	18.36	18.60	18.81	1
D	4	5	6	7	8	9	10	10.88	11.67	12.40	13.09	13.75	14.38	14.93	15.40	15.81	16–18
E	4	6	7.33	8.25	9	9.67	10.29	10.88	11.44	12	12.55	13.08	13.62	14.14	14.67	15.13	23–27
F	4	6	8	9.25	10.2	11	11.71	12.38	13	13.60	14.18	14.75	15.31	15.79	16.20	16.56	11
G	4	5	6	7	8	9	9.86	10.63	11.33	12	12.64	13.25	13.85	14.43	14.93	15.38	19–22
H	4	6	7.33	8.25	9	9.67	10.29	10.88	11.44	12	12.55	13.08	13.62	14.14	14.67	15.13	23–27
I	4	6	7.33	8.25	9	9.67	10.29	10.88	11.44	12	12.55	13.08	13.62	14.14	14.67	15.13	23–27
J	4	6	7.33	8.25	9	9.67	10.29	10.88	11.44	12	12.55	13.08	13.62	14.14	14.67	15.13	23–27
K	4	6	7.33	8.25	9	9.67	10.29	10.88	11.44	12	12.55	13.08	13.62	14.14	14.67	15.13	23–27
L	4	6	8	10	11.6	13	14.29	15.25	16	16.60	17.09	17.50	17.85	18.14	18.40	18.63	2
M	4	5	6	7	8	9	9.86	10.63	11.33	12	12.64	13.25	13.85	14.43	14.93	15.38	19–22
N	4	6	7.33	8.50	9.60	10.67	11.71	12.63	13.44	14.20	14.91	15.50	16	16.43	16.80	17.13	9–10
O	4	5	6	7	8	9	9.86	10.63	11.33	12	12.64	13.25	13.85	14.43	14.93	15.38	19–22
P	4	5	6	7	8	9	10	11	12	13	13.82	14.50	15.08	15.57	16	16.38	12–13
Q	6	8	9.33	10.5	11.40	12.17	12.86	13.5	14.11	14.70	15.27	15.83	16.31	16.71	17.07	17.38	6–8
R	4	5	6	7	8	9	10	11	12	12.90	13.73	14.42	15	15.50	15.93	16.31	14
S	4	6	7.67	8.75	9.60	10.33	11	11.63	12.22	12.80	13.36	13.92	14.46	15	15.47	15.88	15
T	4	5	6	7	8	9	10	10.88	11.67	12.40	13.09	13.75	14.38	14.93	15.40	15.81	16–18
U	6	8	9.33	10.5	11.40	12.17	12.86	13.50	14.11	14.70	15.27	15.83	16.31	16.71	17.07	17.38	6–8
V	4	6	7.33	8.50	9.60	10.67	11.71	12.63	13.44	14.20	14.91	15.50	16	16.43	16.80	17.13	9–10
W	4	6	8	10	11.4	12.5	13.43	14.25	15	15.70	16.27	16.75	17.15	17.50	17.80	18.06	4
X	4	6	8	9.50	10.80	12	13.14	14.25	15.11	15.80	16.36	16.83	17.23	17.57	17.87	18.13	3
Y	4	5	6	7	8	9	9.86	10.63	11.33	12	12.64	13.25	13.85	14.43	14.93	15.38	19–22
Z	4	6	7.33	8.50	9.60	10.67	11.71	12.75	13.78	14.60	15.27	15.83	16.31	16.71	17.07	17.38	6–8
a	4	6	7.33	8.50	9.40	10.17	10.86	11.5	12.11	12.70	13.27	13.83	14.38	14.93	15.40	15.81	16–18
b	4	5	6	7	8	9	10	11	12	13	13.82	14.50	15.08	15.57	16	16.38	12–13

^a The last column gives the ranking of the 28 benzenoids based on the value in the last column of Table 3.

Number of Kekule structures:

13 12 11 11 9

Total Hamming distances 1-16:

301 298 285 274 242

This is an interesting result though not quite unexpected. It is known that aromaticity in benzenoid hydrocarbons of the same size increases with the number of Kekulé valence structures K .²² In the case of linearly and angularly fused cata-condensed benzenoids K increases with the number of “kinks” in the structure.²³ On the other hand, the chirality apparently also increases with the increase of “kinks”. It will be of interest to see if this regularity will be confirmed by study of larger cata-condensed non branched polycyclic aromatic compounds.²⁴

ORDERING OF STRUCTURES

Stepwise resolution approach as described results in a characterization of chirality by a sequence or a vector, not a single number. Even the approach of Mezey, which constitutes a resolution-based measure, gives as the answer a single, threshold, value for chirality measure. We have seen that gradual sharpening of resolution results in what

we may call the chirality sequence. For example, in the case of A and L we have

A: 6, 10, 12, 14, ...

L: 4, 8, 12, 16, ...

If now we want to establish which of the two structures is more and which is less chiral we have to consider the corresponding sequences *in toto*, not the individual entries of the sequences. Comparison of compounds thus leads to comparison of sequences. The problem of comparison of sequences was considered by Muirhead at the beginning of the century.^{25,26} According to Muirhead, when making a comparison of two sequences, such as A and L shown above, one should first construct the corresponding sequences AA and LL, respectively, the elements of which are the partial sums. That is

$$aa_i = \sum a_k$$

$$ll_i = \sum l_k$$

where the summation index runs from $k = 0$ to $k = i$. Hence, one is not comparing the entries of the original sequences but entries that show accumulation, and thus include in a single entry the past history of the sequence. Hence, we have to consider the respective partial sums for A, L sequences:

AA: 6, 16, 28, 42, ...

LL: 4, 12, 24, 40, ...

If elements of one of the sequences of partial sums always

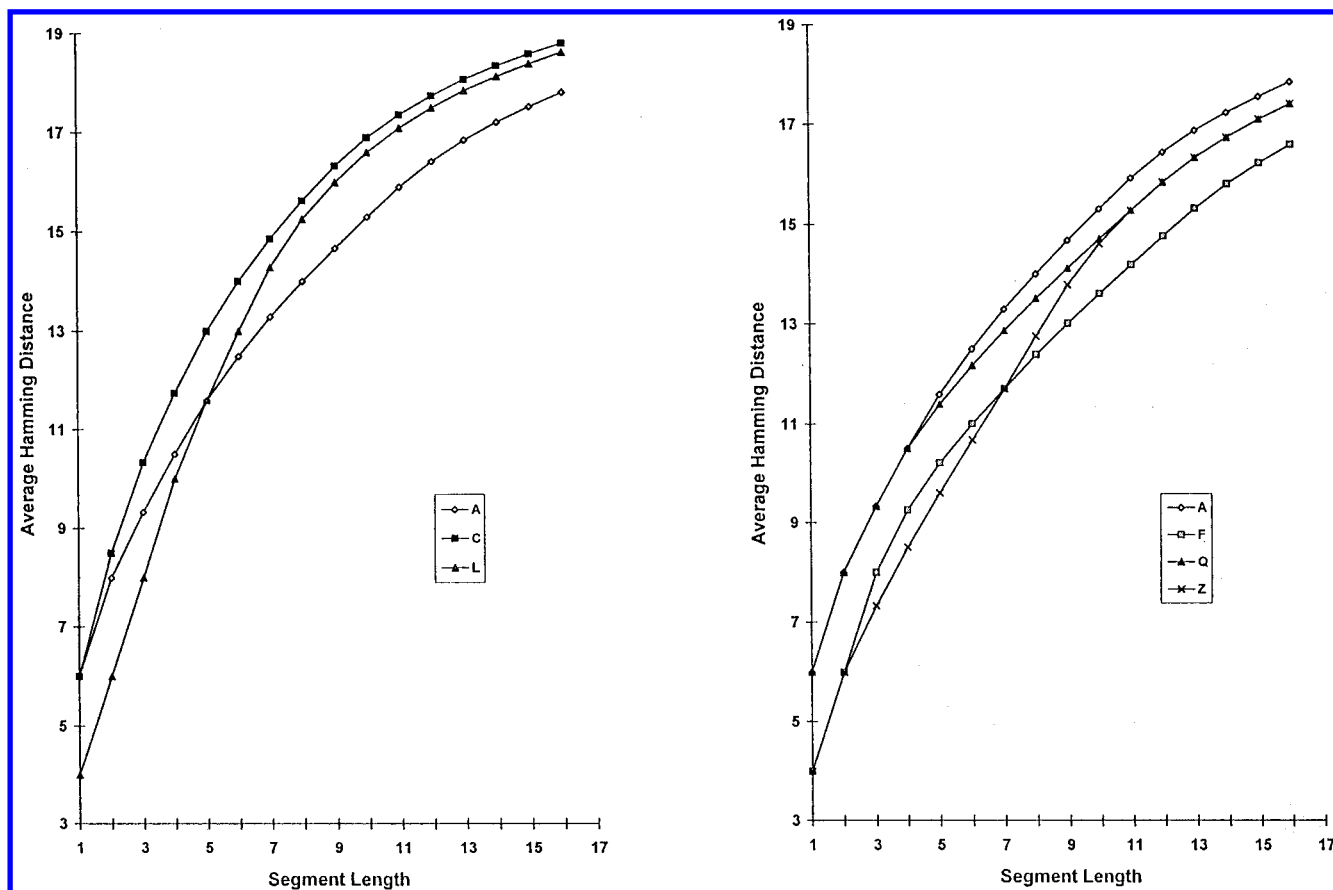


Figure 6. Variation of the average Hamming distance with the length of the segment of the code used in comparison for selected chiral benzenoids. Crossing of curves signifies noncomparability of the structures.

dominate (or at least are equal to) the corresponding elements of the other sequence, then we can say that the former structure dominates (in the particular property) the latter one. This approach to comparability immediately suggests that we should extend the comparison of the codes by including all elements in the sequences, or at least we should extend the sequences until we reach the maximal differentiation among the sequences. In our case this is achieved with path of length 16. From the entries of Table 3 we can easily construct the sequence of partial sums. Without the loss of generality we can normalize partial sums by dividing each sum by the number of entries used. In this way we obtain sequences of average values of the measured chirality, the process which will not change the relative values in any columns of Table 3. The average values for chirality as derived by stepwise increase of the segment of the code used for comparison are given in Table 4. The rows of Table 4 represent the history of accumulation of chirality measure for the benzenoids considered. Derived sequences can be formally viewed as "chirality vectors". Significance of this way of looking on chirality is in generalizing property that was hitherto viewed as scalar to a vector form.

Sequences A and B either satisfy or do not satisfy the conditions:

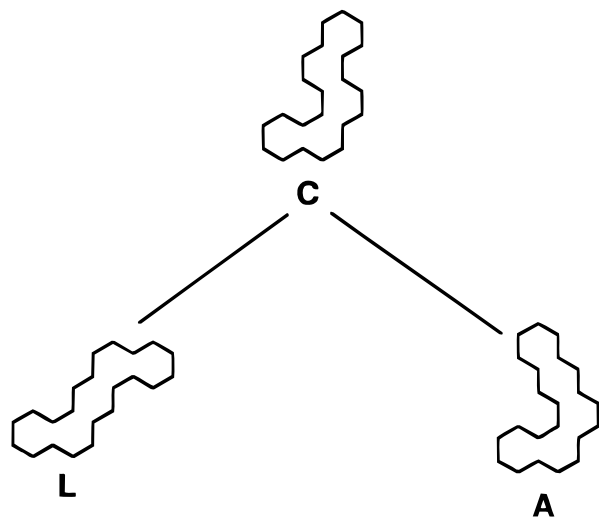
$$aa_i > bb_i \text{ or } aa_i = bb_i \text{ for all } i$$

If the above is true, then we say that the sequences (or objects that they represent) are comparable (with A dominating B in the above case). If the above is not true, we say that the two sequences are not comparable. However, even if two sequences are found not comparable, they both can

dominate the same sequence C or be dominated by another sequence. The result is the Partial Order, that can be represented by a hierarchical diagram in which objects which dominate others are placed above; those that are not comparable are placed side by side in different branches of the diagram, and those that are dominated by others are placed below them.

For sequences shown in Table 3, the entries of Table 4 correspond to sequences of (normalized) partial sums. Hence, we can use the entries of Table 4 directly to construct the hierarchical diagram representing partial order for the 28 chiral benzenoids of Figure 5.

In order to illustrate construction of the partial order for the 28 benzenoids consider first the sequences belonging to A, C, and L. Inspection of Table 4 shows that for all 16 columns C is always greater (or equal in the beginning) to the corresponding members of the sequence A and sequence L. Hence, C dominates A and L. On the other hand, A and L cannot be ordered since for initial segments of comparison A dominates L, up to path 4. At path 5 the two sequences have an equal magnitude (11.60), and after that L dominates A. In Figure 6 (left) we have illustrated the situation by plotting the average values of the accumulated chirality against the length of the segment of the code used in comparison. As we see the curve corresponding to C is above the curves representing both A and L. However the curves for A and L cross each other, which signifies that the corresponding objects cannot be ordered, i.e., neither A dominates L nor L dominates A. The outcome of such comparisons can be summarized briefly in a diagram:



This is the beginning of the partial order diagram shown in Figure 7. Next we consider separately each of the two branches. In the right hand side of Figure 6 we illustrated crossing of F and Z (hence, again a pair of objects that are not comparable) and dominance of A over Q and Q over both F and Z. Complete diagram of the partial order (Figure 7) is obtained when all sequences have been compared.

As we see from Figure 7 the most chiral benzenoid is C since it dominates all other structures. In several cases we find structures, like W and X, which are incompatible, i.e., cannot be directly compared, even though the final value for the chirality for W (18.25) is somewhat larger than the value for X (18.13). Sometimes the difference in the final chirality values for structures which are incompatible are even larger, like S (15.88) and P (16.38).

Perhaps the most interesting aspect of the above comparison of 28 benzenoid shapes is that, while there is the most chiral structure (C), apparently there is not a single, least chiral structure. The structure with the least value of chirality B (14.31) is not comparable with other structures of low chirality, the structures D and T (both having the chirality measure of 16.38), and structures dominated by D and T.

The potential importance of chirality sequences (vectors) and the partial ordering may arise when considering simultaneously several properties that quantitatively depend on chirality. Different properties need not follow exactly a single quantitative chirality value derived using one specific chirality measure. Alternatively the partial order may be of interest when comparing different congruity-based chirality measures. Since different procedures and different measures are based on different qualities of chiral systems, partial order can serve as a template diagram which can show to what degree such different methods agree.

Finally, if one would be interested in the application of multivariate analysis, the elements of the sequence a_i could serve as descriptors for statistical analysis.

ON THE RESOLUTION MEASURES OF CHIRALITY

Because our approach implies resolution-based measure, it is worthwhile to discuss in more details its relationship to the resolution-based chirality measure of Mezey.²⁷ Almost all the measures of chirality, according to Weinberg and Mislow,¹⁴ fall into the same class, one in which the degree of chirality of an object is defined with a reference to another

achiral object (measures of the first kind) or chiral object (measures of the second kind). The only approach that Weinberg and Mislow could not classify in such a manner "that does not fit into this (unification) picture and that opens up an entirely new dimension in discussion of chirality" is an approach of Mezey.²⁷ Mezey focuses his analysis of the properties of a system on properties of substructure obtained by covering of the system. He defines the degree of the chirality by the upper bound of the resolution at which the substructure becomes chiral.

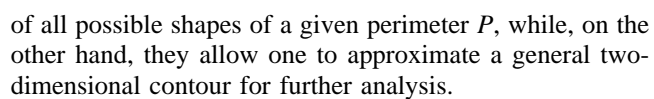
In its simplest form one can cover (or inscribe) within the contour of a two-dimensional object integral portion of a Cartesian coordinate grid (Figure 8, left). Alternatively one can use hexagonal graphite lattice and similarly inscribe inside the contour the maximal number of fused hexagons (Figure 8, middle). Finally, as we have shown, one can overlap the contours using hexagons along the periphery of the two-dimensional objects (Figure 8, right).

There are similarities and differences between the two "resolution-based" approaches. While Mezey's approach is referred to as resolution-based (which it is) from our point of view it could be also labeled as "threshold-based", since it is tied to the detection of a signal, rather than measuring variation in signals for different systems, which is what we have been considering. Nevertheless, it is worthwhile to observe elements of parallelism between the "resolution based chirality measure" of Mezey and our "resolution of chirality measure" based on the length of the fragment used for comparison of the codes for enantiomers. This parallelism particularly becomes apparent when one considers general shape of a two-dimensional contour. Clearly, chiral shapes under very low resolution could be approximated by achiral forms as illustrated in the top row of Figure 8. As the resolution increases the shape contour eventually is approximated by a chiral form (of square animals, fused hexagons or their periphery only) as illustrated by the bottom row in Figure 8.

Our interest, however, was not focused on the threshold achiral/chiral representation which underlay the approach of Mezey. Instead we start with an object as given and increase the differentiation among enantiomers by considering longer and longer fragments of the periphery codes. Although the focus here is different, one can nevertheless see that the two approaches can be related. All that one has to do is to start with achiral substructures (based on fused hexagons as illustrated in Figure 8) and increase the length of the code (by considering smaller and smaller hexagons) until one observes the first achiral substructure. The length of the code P then corresponds to the resolution measure χ_r . Moreover, in contrast to Mezey's approach, we could differentiate among two chiral objects having same P (or χ_r) since for each of them we can determine the degree of dissimilarity between the enantiomeric forms using various fragments of the codes in comparisons. We may say that our stepwise-resolution approach in a way unifies all chirality measures, those congruity-based as well as those threshold-based, since we place no restriction on how individual elements of the chirality vectors are derived.

CONCLUDING REMARKS

We considered the use of binary codes for benzenoid-like planar systems that represent molecular boundary for deriving



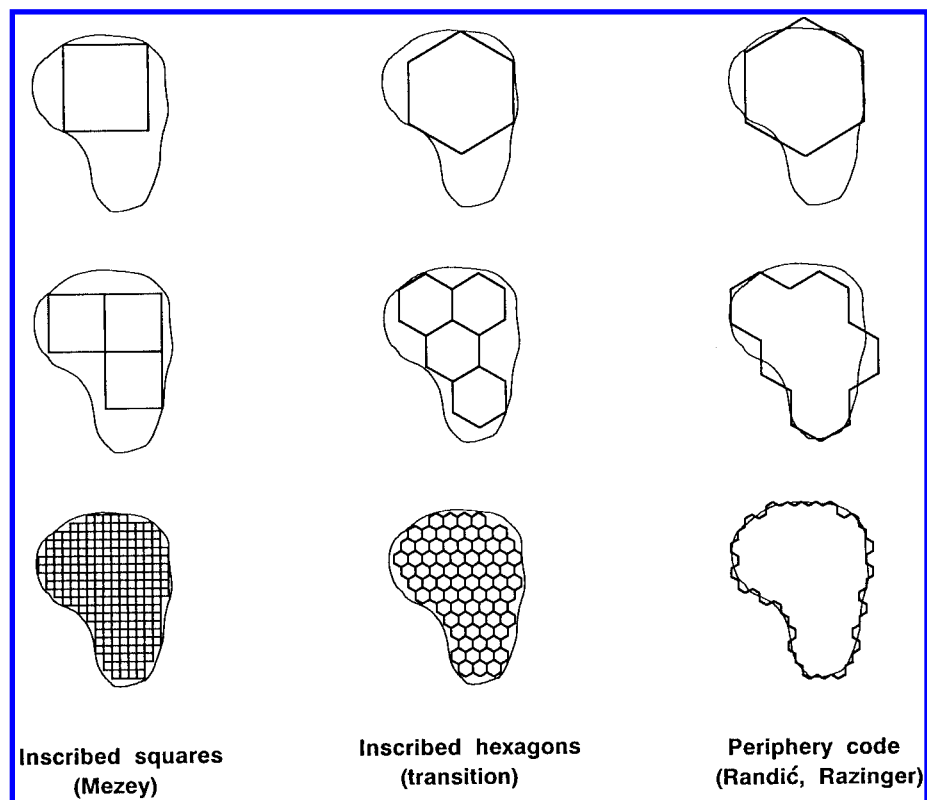


Figure 8. The similarities and differences between Mezey's approach of covering molecular shape with "square animals" and our approach on characterization of molecular periphery by binary code.

Similarity between enantiomers based on the shape codes has been examined. Dissimilarity among chiral components, which have different codes due to different circumscribing of the molecular periphery, can serve as a measure of the "degree of chirality". It was found that the relative value for the degree of chirality depends on the length of the fragment of the code used in comparison. By extending the length of the fragment of the code one achieves better and better resolution among the enantiomers of different benzenoid forms considered. Finally, it was argued that chirality sequences, based on an increased resolution of the chirality measure, may offer a better characterization of chirality than single-valued chirality indices.

The present work has demonstrated that molecular shapes can be tackled quantitatively using appropriate codes to describe the molecular periphery. The shapes considered represent a special case, nevertheless, hitherto even such relatively simple and regular shapes could not be quantitatively studied. Our approach to characterization of shapes and chirality is by no means the only route to quantitative chirality. We do, however, believe that our approach is conceptually sufficiently elegant and simple that it deserves further attention. At the same time we should be aware of the limitations of the model. Apparent limitation of the model is that while it is in principle simple and elegant, in practice when applied to very large systems it may prove tedious. The main apparent drawback is that it represents a straight line segment by a zigzag line, which implies use of very fine graphite lattice as template for increased accuracy of the model.

While limitation of grid points (hexagonal or Cartesian) are apparent we would like to remind the readers that we consider as the main result of our work not so much the use of the graphite grid to derive the binary code but use of codes

for quantitative characterization of molecular properties that are shape dependent, such as chirality. Hence the concept of the periphery code is more important than the particular realization of the concept. In fact, our preliminary work is directed toward construction of periphery codes that do not depend on selection of a template grid used to outline the contours of a shape. Grid-free codes are no longer binary, or even based on integers, but are represented by real numbers. While novel grid-free codes have important advantages, particularly when considered contours defined by closed smooth curves, the binary codes will remain of interest when considered objects build from regular geometrical units. It is difficult to anticipate future developments, but we have sufficient grounds to be optimistic that the elusive concept of shape, and molecular shape in particular, if not yet tamed is likely to be so in the near future. "When you can measure what you are speaking about, and express it in numbers, you know something about it"—stated Lord Kelvin about 100 years ago.²⁸ Today we can say therefore that chemists know something about the molecular shape, and soon they will know much more!

ACKNOWLEDGMENT

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