Molecular Topographic Indices

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We have introduced geometry dependent invariants as novel topographic indices. We have outlined the approach on various benzenoid shapes, i.e., planar objects that can be embedded on a graphite lattice. This apparent restriction is not a limitation to the approach that can be extended to general curvilinear shapes and three-dimensional shapes. First we consider in some detail the topographic index D^2, which is based on squared distances between atoms on the molecular periphery. It is shown that D^2 is proportional to the moment of inertia of a molecule perpendicular to the molecular plane. The atomic components of D^2, which one obtains by adding the elements in a single row of the corresponding matrix, describe local environments along a shape periphery. Atomic components were used to estimate the degree of similarity of suitably oriented planar shapes. We end the outline by considering general shape descriptors constructed from considering various powers of interatomic distances. The derived sequence of descriptors D^1, D^2, D^3, D^4, D^5, ... suitably normalized defines the proposed shape profile of a molecule. In this way we succeeded to map a two-dimensional object (a contour of a shape), and even a three-dimensional object (a surface of a shape), onto a one-dimensional object (a sequence).

1. INTRODUCTION

The study of structure—property relationships has seen considerable progress with the rapid development of chemical graph theory[1] since early 1970s. The important step in the development of mathematical characterization of molecules has been the introduction of the so called topological indices. These are numerical quantities that one can derive from a known molecular skeletal form. In this way one can assign to an individual chemical structure a single number as a descriptor. Already in late 1940s Platt[2] suggested paths in molecular graphs as potentially useful descriptors. A path between two atoms is given by the number of consecutive bonds between the atoms considered. Wiener[3] at the same time introduced a molecular descriptor to be used in regression analysis of molecular properties. This molecular descriptor gives the number of all paths between all pairs of atoms in a molecule. It was later shown by Hosoya[4] that Wiener number can be obtained as the sum of all graph theoretical distances between atoms in a molecule. Topological indices (which should have been called graph theoretical indices since they represent graph theoretical invariants) represent mathematical properties of associated molecular graph. Topological indices have been widely used as molecular descriptors for multiple regression analysis in structure—property and structure—activity studies.[5] The traditional approach to structure-activity has been often based on use of selected molecular properties as descriptors.[6] Mathematical descriptors have an important advantage—they allow interpretation of the results in terms of structural concepts. This particularly became unambiguous with the recent advances in construction of mutually orthogonal descriptors.[7]

Apparent disadvantage of topological indices is that they are topological (i.e., graph theoretical) and not structural, based on a fixed molecular geometry. Thus such indices do not distinguish stereoisomers, such as *cis* and *trans*, etc. Because molecular graphs do not reflect stereospecificity of the molecular structure some critics of chemical graph theory rushed to dismiss graph theoretical approaches as too limited. However, objections to a "two-dimensional" model of molecular structure, as given by chemical graph theory, are often misplaced. [We have written "two-dimensional" with the quotation marks because a pictorial representation of a molecule on a sheet of paper is a two-dimensional object, whereas graphs (mathematically) viewed are one-dimensional objects.[8]] Chemical graph theory does not "insist" on a "two-dimensional" picture of molecules. The interest in the use of graphs in chemistry is to clarify to what extent selected molecular properties are dominated by the "through-bonds" rather than "through-space" interactions. Some molecular properties depend on direct interaction of atoms through space, but other of these properties can be successfully modeled by through-bond interactions. As an illustration of through-bond interaction we may mention various inductive effects. Ultimately, all those molecular properties that can be adequately represented by atom or bond additivities depend primarily on molecular connectivity and are not so sensitve to details of molecular geometry.

The success of graph theory in offering insights in structure—property relationships has inspired extension of the techniques and concepts of chemical graph theory to three-dimensional objects. Several recent papers reported extensions of selected graph theoretical approaches to molecules embedded in three-dimensional space.[9–11] It is hoped that so derived 3-D molecular descriptors, which have been already referred to as topographic indices,[9] will become as useful for discussion of through-space interactions just as topological indices have been useful for modeling of through-bond interactions.

2. NOVEL TOPOLOGICAL INDICES

Before we outline novel topographic indices we will briefly review a novel trend in the design of topological indices.

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Since the time of the first topological indices, those of Wiener,[3] of Hosoya[4] and the connectivity index,[12] the number of topological indices has proliferated. Several recent studies, however, have demonstrated that despite the relatively large number of descriptors reported in the literature only at most one dozen appear to have found wider application in structure—property—activity studies.[13] On the other hand, one cannot deny a need for additional or better descriptors. In recent years several contributions were made toward that goal. Kier has considered modifications of the connectivity indices that apparently better reflect shape attributes of a molecular graph.[14] Here "shape" refers to a differentiation between the extreme forms for graphs. In the case of small graphs one of the extreme forms is given by a path graph, while the other form is represented by the complete graph K_n. In another study using shape indices Kier extends such considerations to molecular flexibility.[15]

Another direction of extending topological descriptors was outlined by one of the present authors.[16] The basic idea is to construct a novel matrix for a graph. From such novel matrices one can extract novel mathematical invariants. For example, from a matrix the elements of which enumerate restricted random walks one can obtain a global molecular descriptor that gives yet the best simple correlation of calorimetric entropies for alkanes.[17] Novel matrices need not be restricted to "two-dimensional" graphs, as was illustrated by D/D matrices for graphs embedded in three-dimensional space.[18] The elements of D/D (distance/distance) matrices are given as the quotient of the geometrical distance and the graph theoretical distance between any pair of atoms. It was suggested that the first eigenvalue of D/D matrices indicate the degree of "folding" of a path graph. In the present work we will consider yet another route to structural invariants that one can extract from geometry-dependent information on a molecule.

3. NOVEL TOPOGRAPHIC INDEX

A way to arrive at novel topographic indices is to design matrices, the elements of which depend on the molecular geometry. The entries in such a matrix could be 3-D geometric distances between atoms or some even more general function of interatomic distances. Mathematical invariants of such matrices can be viewed as topographic indices should they be promising in applications to structure—property studies. Another source of invariants is enumeration of selected molecular substructures. In the case of molecular graphs many invariants are given by integers, since they resulted from enumeration of selected graph components. It is easy to see that integer topographic indices will be an exception rather then a rule, since interatomic distances are given by square root function. So even when the coordinates of atoms are given as integers (as a result of embedding of the molecule on a particular coordinate grid) the distances will not be necessarily integers.

We would like to report here first on an integer topographic index for planar polycyclic benzenoid molecules. Although polycyclic benzenoid structures need not be strictly planar we will assume here that carbon atoms forming the molecular skeletons of a benzenoid are in a plane, i.e., a benzenoid molecule can be embedded in a graphite lattice. It is not difficult to see that for any pair of sites on a graphite lattice, the squared distances between two points is integer.
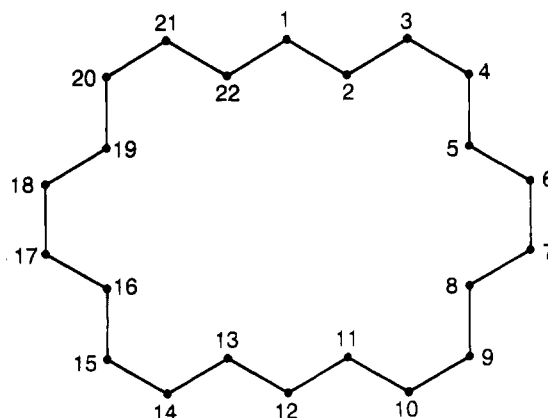

Figure 1. Numbering of carbon atoms on the periphery of ovalene.

Table 1. Squared Distances for Symmetry Nonequivalent Carbon Atoms of Ovalene Periphery

distance to	from 1	from 2	from 3	from 4	from 5	from 6
1	0	1	3	7	9	16
2	1	0	1	3	4	9
3	3	1	0	1	3	7
4	7	3	1	0	1	3
5	9	4	3	1	0	1
6	16	9	7	3	1	0
7	21	13	12	7	3	1
8	19	12	13	9	4	3
9	27	19	21	16	9	7
10	28	21	25	21	13	12
11	21	16	21	19	12	13
12	25	21	28	27	19	21
13	21	19	27	28	21	25
14	28	27	37	39	31	36
15	27	28	39	43	36	43
16	19	21	31	36	31	39
17	21	25	36	43	39	49
18	16	21	31	39	37	48
19	9	13	21	28	27	37
20	7	12	19	27	28	39
21	3	7	12	19	21	31
22	1	3	7	12	13	21
sum	329	296	395	428	362	461
overall sum						8426

In Table 1 we illustrated the squared distances for carbon atoms of the molecular periphery of ovalene (Figure 1). We have only shown the distances from the six symmetry nonequivalent carbon atoms to all the remaining atoms. The six columns of Table 1 are six columns of a 22 × 22 matrix of squared distances. When each of the entries in such a matrix is replaced by its square root, one obtains a geometry based distance matrix of a molecule. From such a matrix we can extract first quantities that characterize individual atoms and then atomic descriptors, and then using such atomic descriptors we can construct a molecular descriptor. For example, the last row in Table 1, which gives the sum of all the entries in the column (or a row of a full 22 × 22 matrix), gives one such atomic characterization. As we see the row sum (or the column sum) gives different values for different atoms. Later, we will see that this need not always be the case, but nevertheless the derived row sums appear fairly characteristic. It turns out that the row sums represents a measure of the centrality of an atom. Atoms that are close to the center of the molecule have smaller atomic sums, while those far from the center have large atomic sums.

From the listed atomic parameters we can construct a molecular structural invariant by summing (or averaging) the
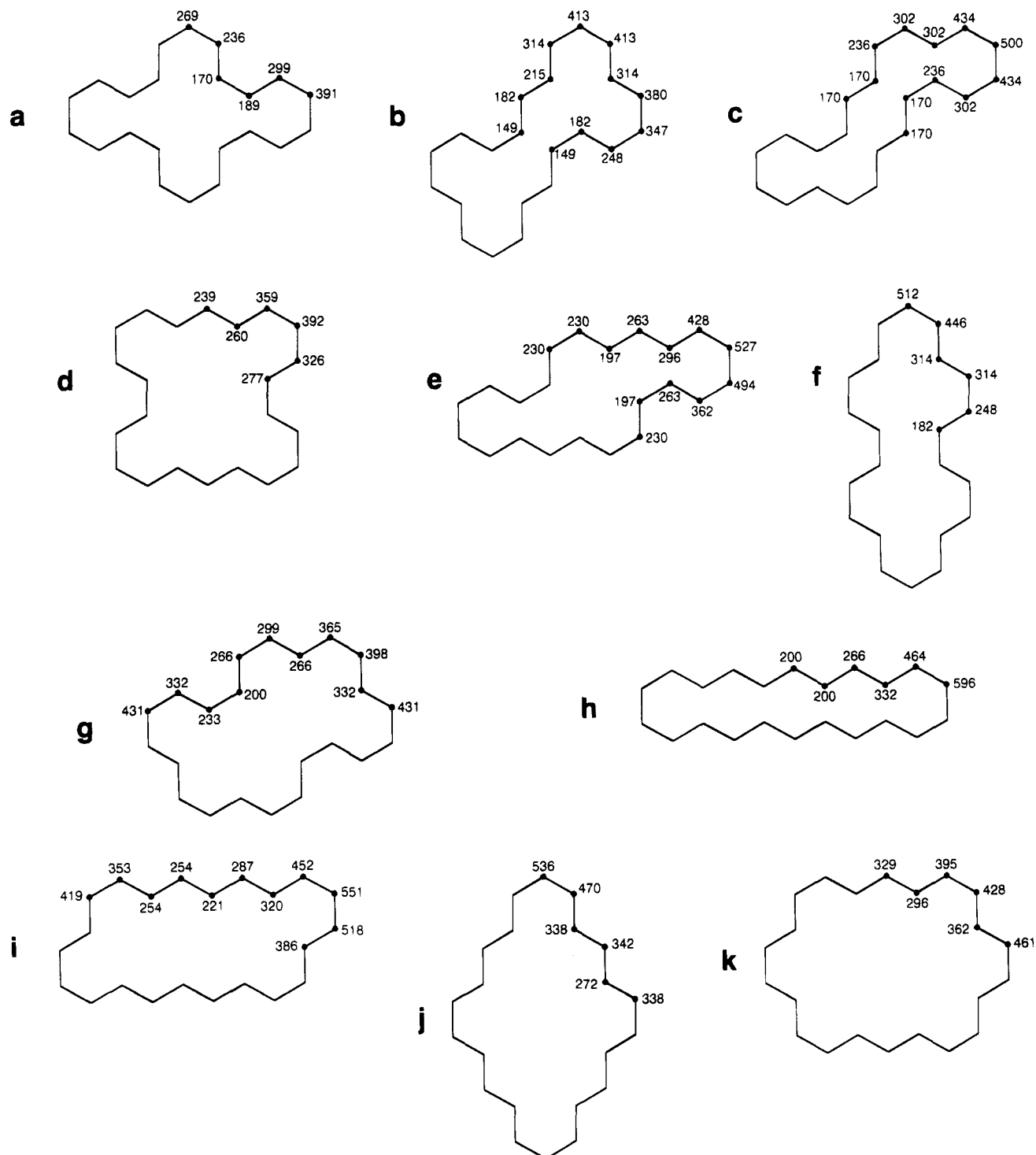
Figure 2. The atomic d^2 values for a selection of symmetrical benzenoid shapes.

atomic contributions. The overall sum, which is conceptually related to the Wiener index for ordinary graphs by being derived from summing elements of a distance matrix, represents a novel molecular topographic index. We will designate the novel index as D^2. In the case of ovalene D^2 has the value 8426.

The novel index differs from the so called "3-D Wiener number" (ref 1, pp 262—269) in two important respects. First, D^2 is based on the squared distances rather than on actual distances. Furthermore, we have considered only the contributions from atoms on the molecular periphery. The index can be viewed as a shape descriptor or a shape invariant since the interior of the molecule plays no role in

the construction of the index. Since in the case of polycyclic benzenoids carbon atom sites always coincide with the sites of the underlying idealized graphite network, the novel index will always be an integer.

4. SHAPE INVARIANTS FOR SMALLER BENZENOIDS

We will use symbol d^2 to represent atomic (squared) distance sums, while D^2 will represent the corresponding molecular index. In Figure 2 we illustrated d^2 for a selection of centrosymmetrical benzenoids all having the molecular periphery of a same length $P = 22$ (i.e., all having 22 carbon atoms or 22 CC bonds around the periphery). Nonequivalent
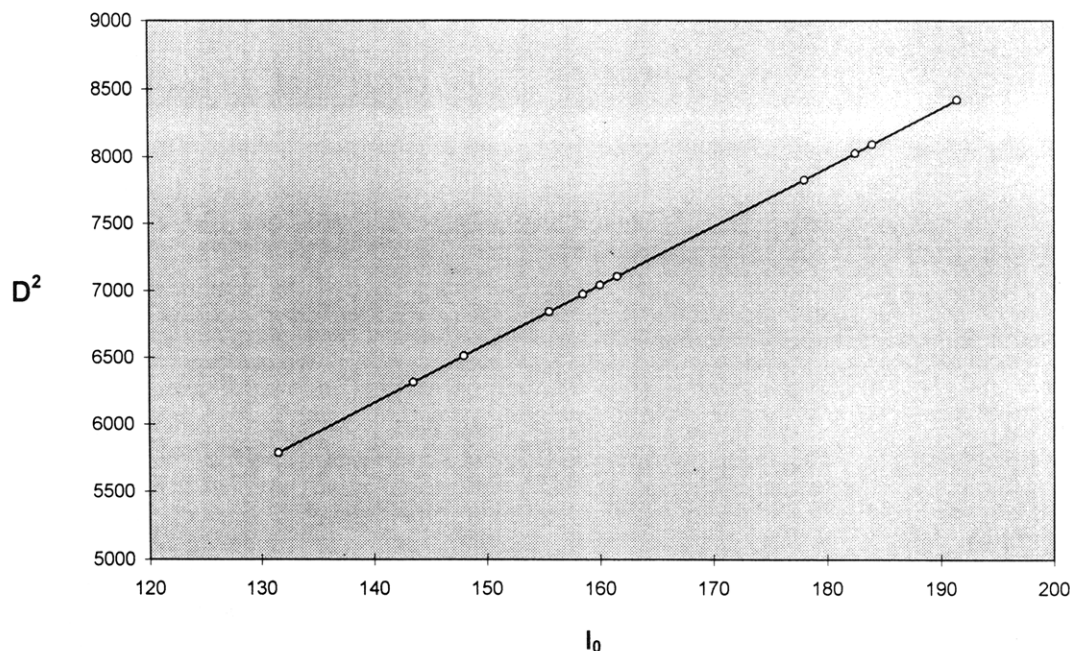
Figure 3. Strict proportionality between the topographic index D^2 and the moments of inertia perpendicular to the plane of the benzenoid shapes of Figure 2.
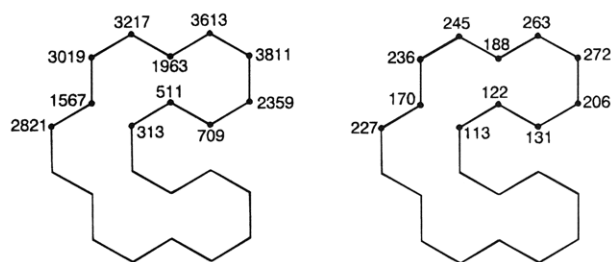
Table 2. Topographic Index D^2 for a Selection of Benzenoid Shapes Having Periphery of a Same Length $(P = 22)^a$

	molecule	topographic index	moment of inertia
a	dibenzo[d,k]pyrene	5786	131.50
b	zethrene	6314	143.50
c	dibenzanthracene	6512	148.00
d	bisanthene	6842	155.50
e	dibenzo[a,h]pyrene	6974	158.50
f	peropyrene	7040	160.00
g	dinaphtho[bcd,ijk]pyrene	7106	161.50
h	pentacene	7832	178.00
i	pyrenopyrene	8030	182.50
j	dibenzocoronene	8096	184.00
k	ovalene	8426	191.50

^{a} The directly calculated moments of inertia about the axis perpendicular to the plane of the molecule are shown in the last column.

All divided by 484,
i.e. 313/484, 511/484. etc.

$I_0 = 47806/484 =$
$= 98.77272727...$

$D^2 = 4346$

$D^2/2P = 4346/44 =$
$= 98.77272727...$

Figure 4. The proportionality of D^2 with the moment of inertia is illustrated on dibenzophenanthrene shape for which the center of mass is in a general position.

carbon atoms, as a rule, will have a different d^2, but occasionally the same d^2 appears for such atoms. This is the case with the central carbon atoms in pentacene and occurs as well in peropyrene, dibenzcoronene, and several other molecules. The corresponding D^2 values are listed in Table 2.

Topological or topographic descriptors serve a purpose if they describe some structural property or provide an insight into structure—property relationships. In order to test the new integer topographic index we have selected the moments of inertia perpendicular to the molecular plane as a shape dependent property. In Figure 3 we depicted the linear relationship found between D^2 and the moments of inertia based on d_i^2 contributions from carbon atoms forming the molecular periphery. Not unexpectedly we find the correlation coefficient $R = 1$ and the standard error $S = 0$. This means that the index is mathematically exactly related to the moments of inertia. In fact, the individual d_i^2 value represent the moment of inertia of the molecular periphery around the axis perpendicular to the molecular plane and passing through atom i. According to a theorem of classical mechanics of Steiner the moment of inertia around an axis

passing through the center of mass (I_0) and the moment of inertia around an axis parallel to it at a distance x away (I_x) are simply related

$$(I_x) = I_0 + x^2$$

The proportionality of D^2 and I_0 (Figure 3) allows one to find the moment of inertia of a benzenoid system by computing its topographic index. In this way one can obtain I_0 without a need to know the exact coordinates of the center of mass of the molecule. Although finding the center of mass is not difficult, the calculations become tedious if the center of mass is in a general position. For example, for the benzenoid shown in Figure 4 the x-coordinates for atoms at the right of the coordinate system are $3\sqrt{3}/22$, $7\sqrt{3}/11$, and $25\sqrt{3}/22$ while the x coordinates for points at the left side of the coordinate system are $4\sqrt{3}/11$, $19\sqrt{3}/22$, and $15\sqrt{3}/11$. At the left side of Figure 4 we show the contributions of the individual carbon atoms to the moment

Table 3. Computed Moments of Inertia for Selection of Benzenoid Shapes of a Lower Symmetry Based on the Formula $D^2/2P$, Where D^2 is the Topographic Index and P Is the Length of the Molecular Perimeter

molecule	topographic index	moment of inertia
A		4346	98.772 73
B		5498	124.954 54
C		6026	136.954 55
D		6062	137.772 73
E		6224	141.454 55
F		6314	143.5
G		6400	145.454 55
H		6656	151.272 73
I		6786	154.227 27
J		7082	160.954 55
K		7266	165.136 36

of inertia I_0, and on the right side we show the atomic contributions d^2 to the topological index D^2. By adding all the contributions at the left side we have $I_0 = 47806/484 = 98.77272727...$, while by adding all atomic contributions at the right side we obtain $D^2 = 4346$. The quotient $4346/98.77272727 ... = 44$, that is, twice the number of contributing atoms. Hence the quotient $D^2/2P$, where P is the length of the perimeter, allows one to calculate the moment of inertia I_0 of benzenoids without searching first for the coordinates of the center of the molecule. In Table 3 we report the computed moments of inertia using the topographic index D^2 for all benzenoids having perimeter $P = 22$ and a single reflection plane. For such molecules the center of symmetry cannot be determined from the symmetry considerations alone as was possible for the compounds of Table 2.

In deriving moments of inertia (listed in the last columns in Tables 2 and 3) we used only contributions from the carbon atoms on the molecular periphery. Hence, the observed correlation between the novel index defined by the molecular periphery and a shape-dependent property justifies one to refer to D^2 as a true shape index. In contrast, the κ shape indices of Kier[14] pertain to molecular graphs and, hence, are not true shape invariants. While legitimate and useful, they do not necessarily represent fully molecular shape but reflect the differences between a graph relative to extreme graphs to which a given structure belongs.
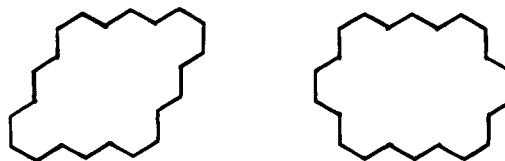
Figure 5. Different relative orientation of the last two shapes of Figure 2.
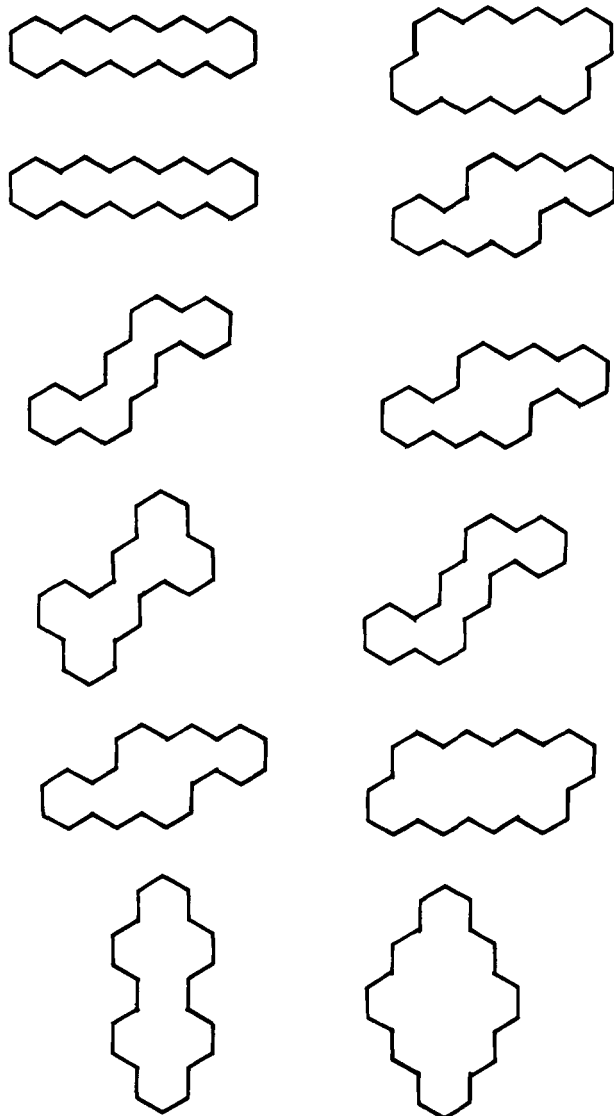
5. ORIENTED SIMILARITY

We can use the atomic entries d_i^2 as local indicators of molecular shape. We see from Figure 2 that the closer a carbon atom is to the molecular center, the smaller d_i^2; more distant carbon atoms are associated with larger d_i^2 values. Indeed, the largest d_i^2 value is to be found for carbon atoms of the terminal benzene ring of pentacene (Figure 2h), while the smallest value is that of the central carbon atoms in zethrene (Figure 2b) which are only half of CC distance away from the center of the molecule. Within a single molecule nonequivalent carbon atoms having the same d_i^2 are at the same distance from the center. The same value of d_i^2 in different molecules does not necessarily mean that the corresponding carbon atoms are necessarily at the same distance from the corresponding molecular centers. For example $d_i^2 = 170$ in dibenzo[d,k]pyrene (Figure 2a) and in dibenzanthracene (Figure 2c) belongs to atoms at different distance from the centers of corresponding molecules. The same occurs again with $d_i^2 = 200$ in benzenoids of Figure 2 (parts g and h) dinaphtho[bcd,ijk]pyrene and pentacene, respectively. This is because the d_i^2 values are derived from the distances along the molecular periphery and not, as happens in the calculations of the moment of inertia, from the center of the molecules. It is only when we average all d_i^2 values that the two quantities become equivalent. Hence, d_i^2 values are characteristic of individual carbon atoms. They represent local atomic descriptors for individual atoms in a molecule.

We will use d_i^2 to outline the idea of the oriented similarity. Usually, when one speaks of similarity and dissimilarity one considers objects that prior to the comparison are suitably oriented. For example, if we visually inspect shapes in Figure 2 (parts j and k), as they are displaced, they show limited similarity, if any. However, if we reorient one of them as shown in Figure 5, we can see a greater similarity. Thus our perception depends on the orientation of objects. For some applications objects can be freely oriented, but in other situations one may come across objects that are in relatively fixed orientation. We refer to such a study of similarity of objects that are in a fixed relative orientation as oriented similarity. Typically the issue of oriented similarity comes when one considers local similarity, such as is of interest in the "docking" problem in drug-receptor interactions. There, one has to select only a fraction of the molecular surface, or only a fraction of the molecule, the pharmacophore, and seeks its similarity with the corresponding elements on the receptor. If such "local" similarity extends to a molecule as a whole, one obtains a global oriented similarity of the two oriented molecules. For drug-receptor problems this is not relevant, but for objects forced in one particular orientation it will be. Such could be the case with doping of the solids and other problems of embedding structures in matrices of a known crystal structure.

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Table 4. Similarity/Dissimilarity Table for the 11 Shapes of Figure 2

	A	B	C	D	E	F	G	H	I	J	K
A	0	436	412	606	398	791	430	641	618	763	699
B		0	328	428	367	896	457	509	450	869	564
C			0	555	288	984	408	371	414	895	548
D				0	612	617	451	741	575	625	415
E					0	969	334	281	328	839	517
F						0	745	1149	976	329	774
G							0	522	477	630	410
H								0	270	976	537
I									0	801	341
J										0	585
K											0

Figure 6. The most similar "oriented" shapes among those of Figure 2.

Figure 7. The least similar "oriented" shapes among those of Figure 2.

We can use d_i^2 to assess the orientation similarity for the 11 shapes of Figure 2. We will leave molecules as they are drawn in Figure 2 and will superimpose their centers and both the horizontal and the vertical axes. We use atomic d_i^2 row (or column) sums as descriptors of the molecular peripheries. Thus the periphery of ovalene, the last shape in Figure 2, is represented by the vector (329, 296, 395, 428, 362, 461, 461, 362, 428, 395, 296, 329, 296, 395, 428, 362, 461, 461, 362, 428, 395, 296) in all 22 components, the 22 values of d_i^2. Using such vectors for all the compounds of
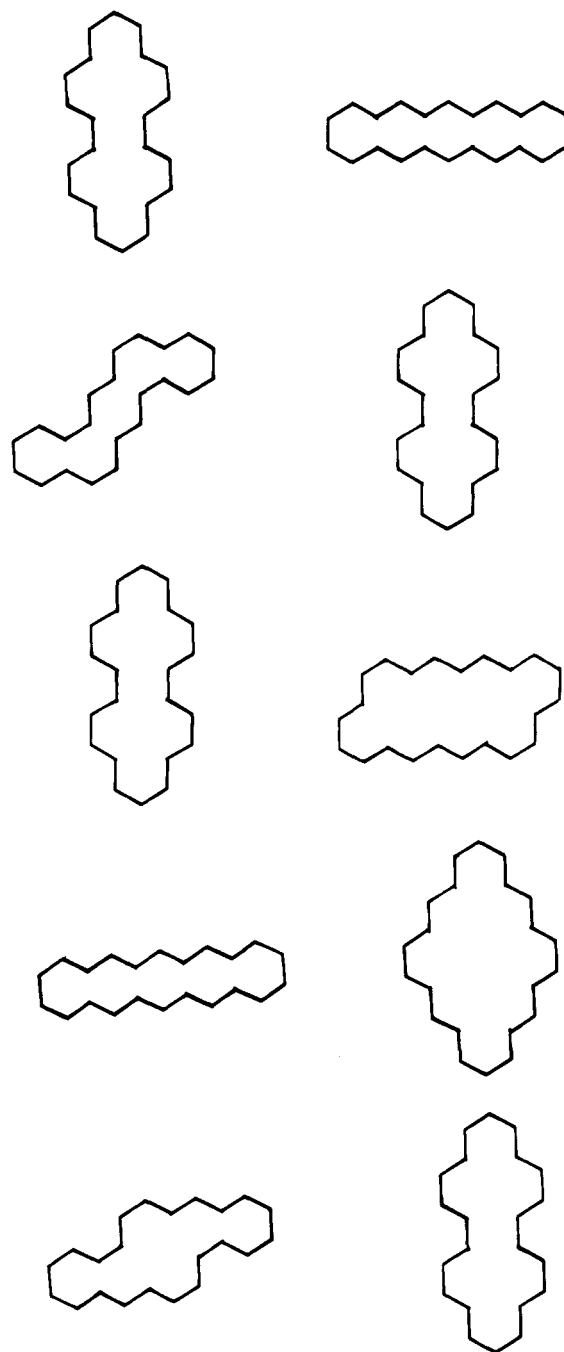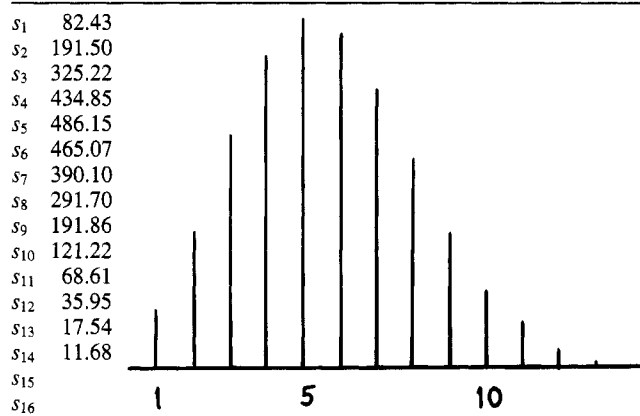
Figure 2 we obtain the similarity, or dissimilarity, values shown in Table 4. Here we assumed the Euclidean distance as the measure of the similarity: small values indicate more similar objects; large values correspond to the least similar pair of structures.

From Table 4 we can easily pick up the most similar oriented shapes and the least similar. The most similar are the following pairs: (H, I); (E, H); (C, E); (B, C); (E, I); and (F, J); all are shown in Figure 6. The least similar are as follows: (F, H); (C, F); (F, I); (H, J); and (E, F); all are shown in Figure 7. In order to see the difference between an "ordinary" similarity and the oriented similarity let us consider again the pair peropyrene (F) and pentacene (H), which were found to be the least similar. If we orient peropyrene "horizontally" so that it parallels tetracene as shown in Figure 8, we obtain a completely different answer:

Figure 8. "Horizontally" oriented peropyrene compared to pentacene.

Table 5. Shape Profile of Ovalene (S_i Values)

s_1	82.43
s_2	191.50
s_3	325.22
s_4	434.85
s_5	486.15
s_6	465.07
s_7	390.10
s_8	291.70
s_9	191.86
s_{10}	121.22
s_{11}	68.61
s_{12}	35.95
s_{13}	17.54
s_{14}	11.68
s_{15}	
s_{16}	

The similarity now becomes 194, which makes this the most similar of all the shapes shown in Figure 2.

6. TOPOGRAPHIC INDICES AND SHAPE PROFILES

We will end this introductory paper on characterization of molecular shapes by considering additional topographic descriptors. The index D^2 and its components d_i^2, the entries of the last row of Table 1, were only one possible index that can be "extracted" from the molecular periphery. D^2 can be viewed as a special case of general index D^k, with k = 2.[19] The entries of Table 1 represent elements of a distance-type matrix, with d^2 taken as the basis for measuring separations. If we had used d, the normal distance, Table 1 would represent the distance matrix. From the row sums of such matrix we would obtain the corresponding index D^1. However, we can consider other functions of d, the distance as well. In Table 5 we show suitably normalized powers of distance elements for the case of ovalene. One can formally consider a power expansion

$$S = 1 + D/1! + D^2/2! + D/3! + D^4/4 + D^5/5! + D^6/6! + D^7/7! + D^8/8! + ...$$

or the elements of the sequence

$$SP = (1, S, S^2, S^3, S^4, S^5, S^6, S^7, S^8, ...)$$

as novel topographic descriptors defining the shape profile.

Here D^k is the sum of all the elements in the distance matrix. In the case of ovalene D^2 is the topographic descriptor 8426 that is shown in Table 1 and was used in regression against the moment of inertia. Normalization is based on averaging this first by the number of contributing atoms, hence, the normalized value in our case would be 8426/22 or 383. The corresponding topographic index S_2 is then 383/2! = 191.5, which is shown in Table 5. The first coefficient in Table 5 is the corresponding value obtained from the distance matrix, while the other values are obtained using higher powers of the distance. We show the result of using the first 16 powers of the distance.

Table 6. Shape Profile of Adamantane and Adamantane Tetramer (S_i Values)

s_1	14.260	46.193	s_9	0.006	1.640
s_2	12.000	58.121	s_{10}	0.001	0.644
s_3	7.053	54.455	s_{11}		0.234
s_4	3.222	41.781	s_{12}		0.079
s_5	1.212	27.473	s_{13}		0.025
s_6	0.389	15.886	s_{14}		0.007
s_7	0.109	8.213	s_{15}		0.002
s_8	0.027	3.842	s_{16}		0.001

We refer to the sequence SP of Table 5 as the shape profile. In contrast to the sequence of components d_i^2, i.e., the sequence (329, 296, 395, 428, 362, 461, ...), the SP sequence is based on shape invariant and is independent of atomic labels, i.e., the origin of the sequence. Such label-independent quantities are true shape invariant, hence they deserve special attention. What we have succeeded in is to map a two-dimensional object, a shape, into a one-dimensional object, a sequence. Such a sequence contains information on the shape, is shape sensitive, and hence is referred to as a shape profile. In Table 5 we show the shape profile of ovalene graphically, using bars to indicate the magnitudes of the components.

CONCLUDING REMARKS

We started our characterizations of molecular shape by considering a very special case: the hexagonal planar "animals". So one can expect questions like the following: (1) How can this approach be generalized to planar curvilinear shapes and (2) how can this approach be extended to three-dimensional objects.

Let us briefly outline the extension of the proposed approach to the more general situation. First, observe that the entries in Table 1, from which all the other quantities considered here were derived, do not necessarily require that the underlying structure be built from fused hexagons. It assumes uniformly distributed n points along a planar shape. Moreover, even "uniform" is not essential, and one can space the number of points depending of the curvature of the contours considered. If one desires a higher resolution of shape forms the number of points on the periphery of a shape should be increased. A normalization procedure should take into account the increase in the number of entries. One could normalize the length of the molecular periphery to the standardized length of one unit.

Is it possible to extend the present approach to three-dimensional shapes? The answer is yes. One way is to represent a three-dimensional object by a contour map and then apply the outlined procedure to the individual contours. In this case instead of a sequence of descriptors, such as shown in Table 5, we will have an ordered set of sequences, i.e., a matrix. Thus the shape profile will become a shape matrix. The other way, a direct way, is simply to use n atoms (points) distributed over the surface of a shape. One then considers $n \times n$ distance matrix from which descriptors d_i^k, the row sums d_i, and finally the global indices D^k are constructed, just as they have been in the case of 2-dimensional shapes. For illustration in Table 6 we illustrate the shape profile of the carbon skeleton of adamantane and its "tetramer", a 22-atomic three-dimensional shape obtained by fusing four adamantane units.

While we are very enthusiastic and optimistic about our own approach to characterization of molecular shapes, we

do not wish to be misunderstood that we claim this to be the only road to the "fuzzy" notion of molecular shape. We see our approach as sufficiently elegant to merit further attention. Alternative normalization of the sequences of powers of distances are likely to emerge. There will be other schemes, based on other graph matrices and powers of their elements. Just as the number of topological indices spread widely since the introduction of the first such indices, so one can expect the number of topographic and shape indices to proliferate in the future. Only future applications will show and justify which of the alternatives have advantages over the others.

ACKNOWLEDGMENT

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