

Three-Dimensional Molecular Descriptors Based on Electron Charge Density Weighted Graphs

Ernesto Estrada

Centro de Bioactivos Químicos, Universidad Central de Las Villas, Santa Clara 54830, Villa Clara, Cuba

Received May 15, 1994[®]

Electron charge density calculated from quantum-chemical methods is used as vertex weight in molecular graphs. One graph theoretical index is obtained by using the Randić-type invariant in the present approach. The new index contains information on 3D features of molecules, and it is discriminative between geometrical isomers, such as *cis-trans* alkenes and between conformers. This index is used in quantitative structure–property relationships with boiling points of alkenes, and its performance is compared to the valence molecular connectivity index of Kier and Hall. Another index considering a correction to include the influences of different hydrogen atoms in the molecule is also proposed. Both novel indexes are more isomer sensitive than 2D molecular connectivity indexes, and the statistical analysis shows that correlations obtained with the 3D molecular descriptors are better than with the 2D ones.

INTRODUCTION

The study of topological features of molecules has become of major interest in the last years,^{1–3} and a great number of derived indices have been published in the chemical literature.^{4–7} These indices are based on graph-theoretical representations of molecules and the use of several invariants from mathematical properties of a structure.⁸

One of the principal areas of research in chemical graph theory is the development and application of topological indices in quantitative structure–property (QSPR) and quantitative structure–activity relationships (QSAR) studies.^{9–12} The importance of this type of approach in the reduction of analysis of molecules to property–property or property–activity comparisons, where mathematical properties are compared to physicochemical or biological properties, have been emphasized by Randić.^{13–15}

There are many topological indices described in the literature¹⁰ (more than 120), among the most important ones are the Wiener number,¹⁶ Hosoya index,¹⁷ Randić index of molecular connectivity,¹⁸ valence molecular connectivity of Kier and Hall,¹⁹ Balaban index,²⁰ molecular ID number,²¹ and so forth. The proliferation of new topological indices continues,^{22–27} and some attempt to the systematization and generalization of them has been proposed in the literature.^{28–31}

There are two main limitations of topological indices in order to describe the chemical structure of molecules: they are the nonconsideration of multiple bonds and heteroatoms in calculations and the lack of information about molecular spatial properties, such as conformation.

The first limitation has been considered in several works, and different approaches can be found in the literature to resolve this problem.^{1,15,32–34}

The second question is related to the nature of graph-theoretical descriptors, because they are derived from a molecular graph, that is a two-dimensional representation of a molecule rather than the molecular structure.

It is clear that three-dimensional properties of molecules are of profound importance, specially when one considers

stereospecific interactions and bioactivity, which are abundant in the information of drug–receptor complexes.³⁵ This appears to be a serious drawback and generate criticism from users of this type of approach.³⁶

Only three approaches, to our knowledge, have been proposed to solve this limitation of topological indices. Randić^{37–39} proposes an extension of graph theoretical methodology to structures embedded in three-dimensional space; Bogdanov et al. suggests the use of geometric distance matrix to calculate three-dimensional Wiener number,⁴⁰ and Estrada and Montero use the bond orders, calculated from different quantum-chemical methods, as edge weights in calculation of three-dimensional molecular connectivity.⁴¹

Our purpose in the present work is to use the electron charge density, calculated from quantum chemical semiempirical methods, as vertex weights in molecular graphs in order to generate a three-dimensional valence molecular connectivity index that permits differentiation molecules with multiple bonds and heteroatoms as well as molecules with different spatial properties, such as configuration and conformation. The influence of different hydrogen atoms in molecules will be considered as a correction to the proposed index.

THE MOLECULAR CONNECTIVITY INDEXES

In the context of chemical graph theory, molecules are considered as simple graphs $G = \{V, E\}$, where $V = \{v_i/i = 1, 2, \dots, n\}$ is the vertex set representing atoms and $E = \{e_i/i = 1, 2, \dots, m\}$ is the edge set, which elements represent bonds in the molecule.

The molecular connectivity index was introduced by Randić¹⁸ as a good measurement of branching in molecules, and it is calculated as

$$\chi = \sum_k [(\delta_i \delta_j)^{-1/2}]_k$$

where the summation is over all pairs of adjacent atoms (bonds) in the molecule, and δ_i is the degree of atom i calculated as the sum of all elements of the i th row or column in the adjacency matrix A of graph G representing the molecule.

[®] Abstract published in *Advance ACS Abstracts*, June 15, 1995.

Further development of this index was performed by the treatment of unsaturation and a rational way of quantifying heteroatom content^{11,42} introduced by Kier and Hall and called valence molecular connectivity index (χ^V). The calculation of χ^V proceeds exactly as for the simple molecular connectivity index but using a modified value for δ_i parameter. The new value for δ parameter is assigned to an atom based on the number of valence electrons (Z^V) not involved in bonds to hydrogen. Thus, $\delta_i^V = Z_i^V - h_i$, where h_i is the number of hydrogen bonded on atom i .

A great number of applications published in the literature use molecular connectivity indexes to correlate several physico-chemical properties^{9,11,42} as well as biological activities of different types of compounds.^{11,12}

Among the principal disadvantage of molecular connectivity indexes we can find the nonhighly discriminative power of isomeric compounds and the inability to reflect fine stereochemical alternatives, i.e., it does not register any difference between *cis* and *trans* isomers or between conformers.³⁶

THREE-DIMENSIONAL DESCRIPTORS

In the present approach the electron charge densities on atoms are used as weights for vertices in the hydrogen suppressed graph representing molecules.

The electron charge density on atom i (q_i) is calculated from quantum chemical methods using the expression

$$q_i = Z_i - \sum_{\mu \in i} (PS)_{\mu\mu}$$

where Z_i is the nuclear charge, P is the density matrix, S is the overlap matrix, and the term $\sum_{\mu \in i} (PS)_{\mu\mu}$ is the Mulliken population⁴³ (the number of electrons in each atomic orbital μ).

Now we calculate the electron charge density connectivity, $\delta(q_i)$ of the atom i , subtracting from q_i the number of hydrogen atoms bonded to i (h_i)

$$\delta_i(q) = q_i - h_i$$

and the three-dimensional valence connectivity index $\Omega(q)$ is calculated using the Randić-type invariant as

$$\Omega(q) = \sum_k [\delta_i(q)\delta_j(q)]_k^{-1/2}$$

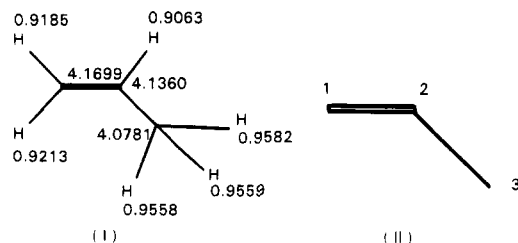
where the summation is taken into account for all pairs of bonded atoms in the hydrogen depleted graph.

In order to consider the influence of the different hydrogen atoms in the molecule we calculate a corrected electron charge density connectivity as follows

$$\delta^c(q_i) = q_i - \sum_j q_{hj}$$

where q_{hj} is the electron charge density of the j th hydrogen atom bound to the atom i . A corrected 3-D valence connectivity index $\Omega^c(q)$ is calculated in the same way as $\Omega(q)$ but using values of $\delta^c(q_i)$ instead of $\delta(q_i)$.

Calculations of Ω indexes were performed by using the electron charge density calculated from quantum chemical semiempirical method PM3⁴⁴. Full geometry optimizations



b) Calculations of electron charge density connectivities for each atom of propene:

$$\delta_1(q) = 4.1699 - 2 = 2.1699$$

$$\delta_2(q) = 4.1360 - 1 = 3.1360$$

$$\delta_3(q) = 4.0781 - 3 = 1.0781$$

$$\delta_1^c(q) = 4.1699 - 1.8398 = 2.3301$$

$$\delta_2^c(q) = 4.1360 - 0.9063 = 3.2297$$

$$\delta_3^c(q) = 4.0781 - 2.8697 = 1.2084$$

c) Calculation of Ω indices.

$$\Omega(q) = 0.9272$$

$$\Omega^c(q) = 0.8708$$

Figure 1. The computation of Ω indices for propene: (a) values of electron charge density on each atom of the molecule (I) and molecular graph representing the carbon skeleton of propene with labeled vertices (II). (b) calculations of electron charge density connectivities for each atom of propene, and (c) calculation of Ω indices.

with the Broyden-Fletcher-Goldfarb-Shanno algorithm⁴⁵ were carried out using the package MOPAC version 6.0⁴⁶ and computation of Ω indexes was made with the system MODEST version 1.0⁴⁷. As an example, the computation of both indices for propene is shown in Figure 1.

APPLICATIONS IN QSPR STUDIES

The valence molecular connectivity index and three-dimensional descriptors $\Omega(q)$ and $\Omega^c(q)$ were used in QSPR models for predicting the boiling points of a series of 53 C₄–C₈ alkenes. The experimental boiling points and topological indexes are given in Table 1.

In order to describe the boiling points of alkenes as a function of topological indexes we use linear least-squares fit of the form

$$\text{bp } (^\circ\text{C}) = a + b \text{ TI}$$

The statistical parameters of these correlations are depicted in Table 2 for the three descriptors, where r is the linear correlation coefficient, s is the standard deviation of regression and F is the Fisher ratio. As expressed by these parameters, equations using the three-dimensional descriptors $\Omega(q)$ and $\Omega^c(q)$ represent better QSPR models than the equation with two-dimensional valence connectivity index χ^V .

With the objective to obtain good QSPR models to describe the boiling points of alkenes according to the recently proposed methodology of Mihalic and Trinajstić,¹⁰ we introduce the number of methyl groups directly bonded to double bonds as a new variable in the regression equations, obtaining the following models

$$\text{bp } (^\circ\text{C}) = a + b \text{ TI} + C \# \text{CH}_3$$

The statistical characteristics of the above correlations are given in Table 3. The best agreement with experimental

Table 1. Boiling Points (in °C) and Topological Indexes $\Omega(q)$, $\Omega^c(q)$, and χ^V for a Series of 53 Alkanes

	alkene	bp (°C) ^a	χ^V	$\Omega(q)$	$\Omega^c(q)$
1	<i>cis</i> -butene-2	0.88	1.4881	1.4045	1.3197
2	<i>trans</i> -butene-2	3.72	1.4881	1.4051	1.3209
3	3-Me-butene-1	20.10	1.8963	1.7959	1.7024
4	pentene-1	29.90	2.0235	1.9123	1.8096
5	2-Me-butene-1	31.20	1.9143	1.8173	1.7417
6	<i>cis</i> -pentene-2	36.90	2.0260	1.9150	1.8045
7	<i>trans</i> -pentene-2	36.40	2.0260	1.9156	1.8054
8	3,3-diMe-butene-1	41.20	2.1969	2.0858	1.9862
9	2-Me-butene-2	38.50	1.8661	1.7735	1.6776
10	4-Me-pentene-1	53.90	2.3794	2.2511	2.1352
11	3-Me-pentene-1	54.10	2.4342	2.3016	2.1808
12	<i>cis</i> -4-Me-pentene-2	56.30	2.3988	2.2715	2.1487
13	<i>trans</i> -4-Me-pentene-2	58.60	2.3988	2.2737	2.1514
14	2,3-diMe-butene-1	55.70	2.2971	2.1829	2.0735
15	2-Me-pentene-1	60.70	2.4143	2.2874	2.1677
16	hexene-1	63.30	2.5235	2.3876	2.2627
17	2-Et-butene-1	64.70	2.4750	2.3471	2.2216
18	<i>trans</i> -hexene-3	67.10	2.5639	2.4259	2.2894
19	<i>cis</i> -hexene-3	66.40	2.5639	2.4240	2.2864
20	2-Me-pentene-2	67.30	2.4040	2.2845	2.1627
21	<i>cis</i> -3-Me-pentene-2	70.40	2.4268	2.3042	2.1789
22	<i>trans</i> -3-Me-pentene-2	67.60	2.4268	2.3040	2.1787
23	<i>trans</i> -hexene-2	67.90	2.5260	2.3893	2.2575
24	<i>cis</i> -hexene-2	68.80	2.5260	2.3895	2.2582
25	4,4-diMe-pentene-1	72.50	2.6700	2.5344	2.4138
26	2,3-diMe-butene-2	73.20	2.2500	2.1483	2.0405
27	3,3-diMe-pentene-1	77.50	2.7576	2.6119	2.4814
28	2,4-diMe-pentene-1	81.60	2.7702	2.6293	2.4989
29	2,4-diMe-pentene-2	83.40	2.7768	2.6406	2.5072
30	3-Et-pentene-1	85.00	2.9721	2.8080	2.6596
31	2,3-diMe-pentene-1	84.30	2.8350	2.6895	2.5530
32	4-Me-hexene-1	87.50	2.9173	2.7601	2.6180
33	3-Me-2-Et-butene-1	89.00	2.8578	2.7135	2.5753
34	2-Me-hexene-1	91.10	2.9143	2.7668	2.6281
35	2-Et-pentene-1	94.00	2.9750	2.8195	2.6712
36	<i>trans</i> -heptene-3	96.00	3.0639	2.9009	2.7452
37	<i>cis</i> -heptene-3	95.70	3.0639	2.8984	2.7394
38	2-Me-hexene-2	95.80	2.9004	2.7557	2.6113
39	2-Et-pentene-2	94.00	2.9268	2.8285	2.6688
40	2,3-diMe-pentene-2	97.50	2.8107	2.6757	2.5363
41	<i>cis</i> -heptene-2	98.50	3.0260	2.8641	2.7098
42	<i>trans</i> -heptene-2	98.00	3.0260	2.8645	2.7108
43	2,4,4-triMe-pentene-1	101.40	3.0608	2.9081	2.7703
44	2,4,4-triMe-pentene-2	101.90	3.0774	2.9300	2.7897
45	2,5-diMe-hexene-2	112.60	3.2599	3.1010	2.9489
46	2,3,4-triMe-pentene-2	116.50	3.1935	3.0356	2.8793
47	octene-1	121.30	3.5235	3.3390	3.1700
48	<i>cis</i> -octene-3	122.90	3.5639	3.3743	3.1946
49	<i>trans</i> -octene-3	123.30	3.5639	3.3753	3.1953
50	<i>cis</i> -octene-4	122.50	3.5639	3.3730	3.1935
51	<i>trans</i> -octene-4	121.90	3.5639	3.3734	3.1939
52	<i>cis</i> -octene-2	125.60	3.5260	3.3409	3.1657
53	<i>trans</i> -octene-2	125.00	3.5260	3.3408	3.1653

^a Experimental boiling points were taken from ref 48.**Table 2.** Statistical Parameters for the Linear Correlation between Boiling Points and Topological Indexes of Alkenes

model	index	<i>a</i>	<i>b</i>	<i>r</i>	<i>s</i>	<i>F</i> ratio
1	χ^V	-79.905	58.238	0.9824	5.90	1411
2	$\Omega(q)$	-79.967	61.437	0.9841	5.62	1561
3	$\Omega^c(q)$	-79.534	64.658	0.9842	5.59	1576

boiling temperatures obtained with these models can be explained by the fact that methyl groups increase the electron density in double bond (by inductive and hyperconjugative effects) which must be causing variations in van der Waals molecular interactions not included in topological indexes. Boiling temperatures calculated by the six equations considered here are shown in Table 4.

Table 3. Statistical Parameters for the Linear Correlation between Boiling Points vs Topological Indexes and Number of Methyl Groups Bonded to Double Bond of Alkene

model	index	<i>a</i>	<i>b</i>	<i>c</i>	<i>r</i>	<i>s</i>	<i>F</i> ratio
4	χ^V	-91.794	60.862	5.335	0.9951	3.14	2558
5	$\Omega(q)$	-90.986	63.966	5.041	0.9955	3.03	2743
6	$\Omega^c(q)$	-90.400	67.282	4.994	0.9954	3.04	2715

Table 4. Calculated Boiling Points (in °C) of the Studied Series of Alkenes

alkene	calculated boiling point					
	model 1	model 2	model 3	model 4	model 5	model 6
1	6.76	6.32	5.80	9.44	8.94	8.38
2	6.76	6.36	5.87	9.44	8.97	8.46
3	30.53	30.37	30.54	23.62	23.89	24.14
4	37.94	37.52	37.47	31.36	31.34	31.35
5	31.58	31.68	33.08	30.05	30.30	31.78
6	38.09	37.68	37.14	36.85	36.55	36.00
7	38.09	37.72	37.20	36.85	36.59	36.06
8	48.04	48.18	48.89	41.91	42.44	43.23
9	28.77	28.99	28.94	37.78	37.58	37.45
10	58.67	58.33	58.52	53.02	53.01	53.26
11	61.86	61.44	61.47	56.36	56.24	56.33
12	59.80	59.59	59.40	59.54	59.35	59.16
13	59.80	59.72	59.57	59.54	59.49	59.34
14	53.88	54.14	54.54	53.35	53.69	54.10
15	60.70	60.56	60.63	60.48	60.37	60.44
16	67.06	66.72	66.77	61.79	61.74	61.84
17	64.24	64.23	64.11	58.84	59.15	59.07
18	69.41	69.07	68.50	64.25	64.19	63.63
19	69.41	68.96	68.30	64.25	64.07	63.43
20	60.10	60.39	60.30	65.19	65.23	65.10
21	61.43	61.60	61.35	66.57	66.49	66.19
22	61.43	61.58	61.34	66.57	66.47	66.17
23	67.21	66.82	66.43	67.28	66.89	66.48
24	67.21	66.84	66.48	67.28	66.90	66.53
25	75.59	75.74	76.54	70.71	71.13	72.00
26	51.13	52.02	52.40	66.48	66.60	66.86
27	80.69	80.50	80.91	76.04	76.09	76.55
28	81.43	81.57	82.04	82.14	82.24	82.72
29	81.81	82.26	82.58	87.88	88.00	88.28
30	93.19	92.55	92.43	89.09	88.63	88.54
31	85.20	85.27	85.54	86.08	86.09	86.36
32	90.00	89.60	89.74	85.76	85.57	85.74
33	86.53	86.74	86.98	82.14	82.58	82.87
34	89.82	90.02	90.39	90.91	91.04	91.42
35	93.36	93.25	93.18	89.27	89.37	89.32
36	98.53	98.25	97.97	94.68	94.57	94.30
37	98.53	98.10	97.59	94.68	94.41	93.91
38	89.01	89.33	89.31	95.40	95.37	95.28
39	90.55	93.81	93.03	91.67	94.98	94.16
40	83.79	84.42	84.46	95.27	95.29	95.23
41	96.33	95.99	95.68	97.71	97.26	96.91
42	96.33	96.02	95.74	97.71	97.28	96.98
43	98.35	98.70	99.59	99.83	100.07	100.98
44	99.32	100.04	100.84	106.17	106.52	107.28
45	109.95	110.55	111.14	117.28	117.45	118.00
46	106.08	106.53	106.64	113.24	113.27	113.31
47	125.30	125.17	125.43	122.65	122.60	122.88
48	127.65	127.34	127.02	125.11	124.85	124.54
49	127.65	127.40	127.07	125.11	124.92	124.59
50	127.65	127.26	126.95	125.11	124.77	124.46
51	127.65	127.28	126.98	125.11	124.80	124.49
52	125.45	125.29	125.16	128.14	127.76	127.59
53	125.45	125.28	125.13	128.14	127.75	127.56

CHARACTERISTIC FEATURES OF Ω INDEXES

The general features of Ω indices depends on the sensitivity of δ_i values, which its calculations are based on. The use of electron charge density in the calculation of δ_i values represents an improvement in its sensitivity in order to differentiate dissimilar atoms or atomic groups in molecules.

Table 5. Values of 2D- δi and 3D- δi Parameters for Different Atomic Groups

group	δ^v	$\delta(q)$	$\delta^c(q)$
CH ₃ ^a	1	1.0750	1.2034
CH ₃ ^b	1	1.1102	1.2208
-CH ₂ -	2	2.1006	2.2015
=CH ₂	2	2.1611	2.3250
-NH ₂ ^a	3	2.9438	3.0028
-NH ₂ ^b	3	3.0374	3.0817
-CH<	3	3.0759	3.1349
=CH ^c	3	3.1475	3.2848
=CH ^d	3	3.1532	3.2861
=NH ^c	4	4.1098	4.1684
=NH ^d	4	4.0988	4.1576
-NH ^a	4	3.8913	3.9454
-NH ^b	4	4.0636	4.1082
=C<	4	4.1154	4.1154
>C<	4	4.0413	4.0413
-OH ^a	5	5.2418	5.4335
-OH ^b	5	5.3089	5.4900
>NH-	5	5.0794	5.0794
=O	6	6.3146	6.3146
-O ^a	6	6.1385	6.1385
-O ^b	6	6.2776	6.2776

^a α,β -Unsaturated. ^b Saturated. ^c *Cis* isomer. ^d *Trans* isomer.

Table 6. Isomeric Octenes with Degenerated Values of χ^v Index That Can Be Differentiated by Ω Indexes

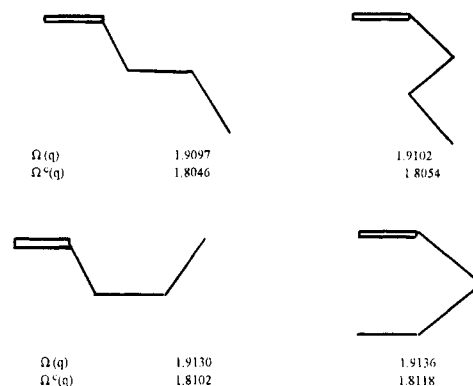
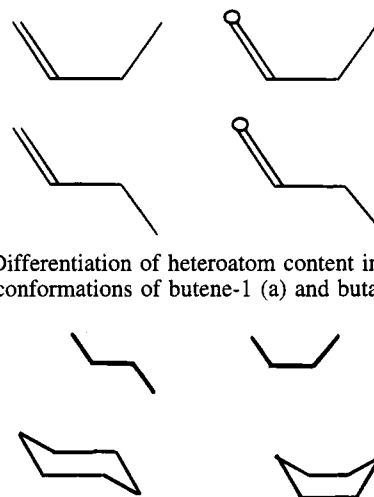
compound	χ^v	$\Omega(q)$	$\Omega^c(q)$
<i>cis</i> -octene-4	3.5639	3.3730	3.1935
<i>trans</i> -octene-4	3.5639	3.3734	3.1939
<i>cis</i> -octene-3	3.5639	3.3743	3.1946
<i>trans</i> -octene-3	3.5639	3.3753	3.1953

In Table 5 we can observe that 3D- δi values have the same features of 2D- δi values of Kier and Hall for the differentiation of groups with a distinct number of valence electrons (not bonding to hydrogen). The 3D- δi values are also able to discriminate among groups having the same number of valence electrons but that have (i) different hybridization ($-\text{CH}_2-$ and $=\text{CH}_2$), (ii) different substituents in α -position (C_{sp3} $-\text{OH}$ and C_{sp2} $-\text{OH}$), and (iii) different spatial distribution of atoms in the group (*cis* $=\text{CH}-$ and *trans* $=\text{CH}-$). All of these features are not present in the 2D- δi values.

The 3D molecular descriptors $\Omega(q)$ and $\Omega^c(q)$ appear to be more isomer-sensitive than the 2D index χ^v . For instance, there are no pairs of isomers for the studied series of alkenes with the same values of Ω indexes; this discrimination includes geometrical isomers, i.e., *cis-trans* isomers, too. The 2D valence connectivity index is unable to discriminate not only geometrical isomers but also some positional isomers; as an example in Table 6 we illustrate four isomeric octenes, including geometrical and positional isomers, with degenerated values of χ^v index; this degeneracy is well resolved when the 3D indexes are used.

Another two desired features for the molecular descriptors are also included into Ω indexes; they are the ability to differentiate conformations of alkyl chains and the quantification of heteroatoms content into the structures. In Figure 2 we illustrate the four conformational isomers (rotamers) of pentene-1 and the values of Ω indexes. In Figure 3 an example of the heteroatoms differentiation is given for the two conformers of butene-1 and butenal.

In both examples, the values of Ω indexes change regularly with the variations in the conformations of chains, i.e., where

**Figure 2.** Differentiation of conformational isomers of pentene-1 using Ω indexes.**Figure 3.** Differentiation of heteroatom content in the structures for distinct conformations of butene-1 (a) and butenal (b).**Figure 4.** The *gauche* and *anti* conformers of *n*-butane and *chair* and *boat* conformers of cyclohexane.**Table 7.** Values of the 3D Molecular Descriptors for the Conformational Isomers Depicted in Figure 4

conformer	$\Omega(q)$	$\Omega^c(q)$	3D-ID ^a
A	1.7861	1.6754	7.6804
B	1.7867	1.6766	7.7219
C	2.3852	2.2805	13.4521
D	2.3880	2.2854	13.4569

^a Values of 3D-ID were taken from ref 39.

the structure is more bent ("compact"), the indexes have greater values.

It is interesting to compare Ω indexes with other 3D descriptors based on atom connectivity in molecules, such as the 3D molecular identification number introduced by Randić.³⁹

In order to illustrate the variations in 3D molecular descriptors (Ω indexes and 3D-ID number) we consider two molecules in their different conformations, depicted in Figure 4. The conformations A (*anti*-butane) and C (*chair*-cyclohexane) can be considered as "extended" structures, while conformations B (*gauche*-butane) and D (*boat*-cyclohexane) represent "compact" conformers.

In Table 7 we give the values of 3D molecular descriptors for all conformers illustrated in Figure 4. Similar variations are observed for the 3D-molecular identification number compared to the Ω indexes.

The fact that the "extended" conformations, such as all *trans* isomers have the smallest ID number and the most

"compact" isomers have the largest ID numbers, was determined by Randić for the four *n*-pentane rotamers and the 10 *n*-hexane rotamers.³⁹ The same is observed too for the Ω indexes of all conformational isomers illustrated in Figures 2, 3, and 4.

These similarities between Ω indexes and ID numbers illustrate well that two very different approaches can contain similar information about important structural features of molecules that can be useful in QSPR and QSAR studies now in progress.

CONCLUDING REMARKS

The use of weighted graphs to generate structural invariants appears to be a very useful approach in theoretical chemistry. Randić³³ has stressed the importance of considering any matrix as a weighted graph in order to further the development of chemical combinatorics and topology.

In the present study we use the electron charge density on atoms in the molecule as vertex weights in molecular graphs. This approach introduces two very desired properties in the graph-theoretical invariant: heteroatoms differentiation and spatial properties of molecules.

We want to make some remarks about the further possibilities of the present approach. The Ω indexes, generated using the electron charge density weighted graph, represent only an example of the applications of this type of weighted graphs in chemistry, because other more discriminative indexes such as the ID numbers can be easily obtained as 3D descriptors using this type of weighted graphs.

In this work we used the electron charge density generated from PM3 Hamiltonian using a full geometry optimization technique, but the use of any other quantum chemical approach (semiempirical or *ab initio*) is valid too. For instance, the use of the AM1 approach in the calculation of Ω indexes produces no significant change in the correlation with boiling temperatures of alkenes. Another important question is referred to the use of geometry optimization that is not a necessary condition to generate the Ω indexes, as was recently proved,⁴¹ and we can use a frozen geometry model for the sake of simplicity to be used in non-time-consuming calculations by simple computers.

On the other hand, if we consider in the same model, the use of bond orders, and electron charge density as edge and vertex weights in molecular graphs, respectively, then we are using the quantum chemical bond order and charge matrix as a weighted graph in order to generate structural invariants that encode important chemical information about the "chemical structure".

Several applications of the present approach are now in progress in order to determine the range of its usability in QSPR⁴⁹ and QSAR⁵⁰ studies.

REFERENCES AND NOTES

- (1) Balaban, A. T. *Chemical Application of Graph Theory*; Academic: London, 1976.
- (2) Balaban, A. T. Application of Graph Theory in Chemistry. *J. Chem. Inf. Comput. Sci.* **1985**, 25, 334–343.
- (3) Trinajstić, N. *Chemical Graph Theory*, 2nd revised ed.; CRC: Boca Raton, FL, 1992.
- (4) Hansen, P. J.; Jurs, P. C. Chemical Application of Graph Theory. Part I. *J. Chem. Educ.* **1988**, 65, 574–580.
- (5) Balaban, A. Topological Indices and Their Uses: A New Approach for the Coding of Alkanes. *THEOCHEM*. **1988**, 42, 243–253.
- (6) Trinajstić, N.; Nikolić, S.; Horvat, D. Mathematical Models of Molecular Structure. *Kem. Ind.* **1987**, 36, 493–502.
- (7) Hladka, E. Topological Indexes. *Chem. List.* **1988**, 82, 1009–1029.
- (8) Trinajstić, N.; Klein, D.; Randić, M. On Some Solved and Unsolved Problems of Chemical Graph Theory. *Int. J. Quantum Chem.: Quantum Chem. Symp.* **1986**, 20, 699–742.
- (9) Sabljic, A.; Trinajstić, N. Quantitative Structure–Activity Relationships: The Role of Topological Indices. *Acta Pharm. Jugosl.* **1981**, 31, 189–194.
- (10) Mihalic, Z.; Trinajstić, N. A Graph-Theoretical Approach to Structure–Property Relationships. *J. Chem. Educ.* **1992**, 69, 701–711.
- (11) Kier, L. B.; Hall, L. H. *Molecular Connectivity in Chemistry and Drug Research*; Academic Press: New York, 1976.
- (12) Kier, L. B.; Hall, L. H. *Molecular Connectivity in Structure–Activity Analysis*; Research Studies Press: Letchworth, Herts, 1986.
- (13) Randić, M.; Hansen, P. J.; Jurs, P. C. Search for Useful Graph Theoretical Invariants of Molecular Structure. *J. Chem. Inf. Comput. Sci.* **1988**, 28, 60–68.
- (14) Randić, M. Resolution of Ambiguities in Structure–Property Studies by Use of Orthogonal Descriptors. *J. Chem. Inf. Comput. Sci.* **1991**, 31, 311–320.
- (15) Randić, M. On Computation of Optimal Parameters for Multivariate Analysis of Structure–Property Relationships. *J. Comput. Chem.* **1991**, 12, 970–980.
- (16) Wiener, H. J. Structural Determination of Paraffin Boiling Points. *J. Am. Chem. Soc.* **1947**, 69, 17–20.
- (17) Hosoya, H. Topological Index. A Newly Proposed Quantity Characterizing the Topological Nature of Structural Isomers of Hydrocarbons. *Bull. Chem. Soc. Jpn.* **1971**, 44, 2332–2339.
- (18) Randić, M. On Characterization of Molecular Branching. *J. Am. Chem. Soc.* **1975**, 69, 6609–6615.
- (19) Kier, L. B.; Hall, L. L. Derivation and Significance of Valence Molecular Connectivity. *J. Pharm. Sci.* **1981**, 70, 583–589.
- (20) Balaban, A. T. High Discriminating Distance-Based Topological Index. *Chem. Phys. Lett.* **1982**, 89, 399–404.
- (21) Randić, M. On Molecular Identification Numbers. *J. Chem. Inf. Comput. Sci.* **1984**, 24, 164–175.
- (22) Diudea, M. V.; Minailuc, O.; Balaban, A. T. Molecular Topology. IV. Regressive Vertex Degree (New Graph Invariants) and Derived Topological Indices. *J. Comput. Chem.* **1991**, 12, 527–535.
- (23) Shultz, H. P.; Shultz, E. B.; Shultz, T. P. Topological Organic Chemistry. 2. Graph Theory, Matrix Determinant and Eigenvalues, and Topological Indices of Alkanes. *J. Chem. Inf. Comp. Sci.* **1990**, 30, 27–29.
- (24) Shultz, H. P.; Shultz, T. P. Topological Organic Chemistry. 3. Graph Theory, Binary and Decimal Adjacency Matrices, and Topological Indices of Alkanes. *J. Chem. Inf. Comp. Sci.* **1991**, 31, 144–147.
- (25) Shultz, H. P.; Shultz, E. P.; Shultz, T. P. Topological Organic Chemistry. 4. Graph Theory, Matrix Permanents, and Topological Indices of Alkanes. *J. Chem. Inf. Comp. Sci.* **1992**, 32, 70–72.
- (26) Randić, M.; Guo, X. F.; Oxley, T.; Krishnapriyan, H. Wiener Matrix-Source of Novel Graph Invariants. *J. Chem. Inf. Comput. Sci.* **1993**, 33, 709–716.
- (27) Yao, Y. Y.; Xu, L.; Yang, Y. Q.; Yuan, X. S. Study on Structure–Activity Relationships of Organic Compounds. 3. New Topological Indices and Their Applications. *J. Chem. Inf. Comput. Sci.* **1993**, 211, 478–483.
- (28) Razinger, M.; Chrétien, J. R.; Dubois, J. E. Structural Selectivity of Topological Indexes in Alkane Series. *J. Chem. Inf. Comput. Sci.* **1985**, 25, 23–27.
- (29) Basak, S. C.; Magnuson, V. R.; Niemi, G. J.; Regal, R. R.; Veith, G. D. Topological Indices: Their Nature, Mutual Relatedness, and Applications. *Math. Modeling* **1987**, 8, 300–305.
- (30) Mihalic, Z.; Nikolic, S.; Trinajstić, N. Comparative Study of Molecular Descriptors from the Distance Matrix. *J. Chem. Inf. Comput. Sci.* **1992**, 32, 28–37.
- (31) Randić, M. Generalized Molecular Descriptors. *J. Math. Chem.* **1991**, 7, 155–168.
- (32) Grossman, S. C.; Jerman-Blazic, B.; Randić, M. A Graph Theoretical Approach to Quantitative Structure–Activity Relationships. *Int. J. Quantum Chem.: Quantum Biol. Symp.* **1986**, 12, 123–139.
- (33) Randić, M. The Nature of Chemical Structure. *J. Math. Chem.* **1990**, 4, 157–184.
- (34) Randić, M. Novel Graph Theoretical Approach to Heteroatoms in Quantitative Structure–Activity Relationships. *Chemometrics and Intell. Lab. Sys.* **1991**, 10, 213–227.
- (35) Ariens, E. J. Stereoselectivity of Bioactive Agents: General Aspects. In *Stereochemical and Biological Activity of Drugs*; Ariens, E. J., Ed.; Blackwell Sci. Pub.: Oxford, 1983; p 11.
- (36) Albert, A. *Selective Toxicity. The Physico-Chemical Basis of Therapy*; Chapman and Hall: London, 1984.
- (37) Randić, M. Molecular Topographic Descriptors. IN *MATH/CHEM/COMP 1987*; Lacher, R. C., Ed.; Elsevier: Amsterdam, 1988; p 101.

- (38) Randić, M. On Characterization of Three-Dimensional Structures. *Int. J. Quantum Chem.: Quantum Biol. Symp.* **1988**, 15, 201–208.
- (39) Randić, M.; Jerman-Blazic, B.; Trinajstić, N. Development of 3-Dimensional Molecular Descriptors. *Computers Chem.* **1990**, 14, 237–246.
- (40) Bogdanov, B.; Nikolic, S.; Trinajstić, N. On the Three-Dimensional Wiener Number. *J. Math. Chem.* **1989**, 3, 299–309.
- (41) Estrada, E.; Montero, L. A. Bond Order Weighted Graphs in Molecules as Structure-Property Indices. *Mol. Eng.* **1993**, 2, 363–373.
- (42) Hall, L. H.; Kier, L. B. The Molecular Connectivity Chi Indexes and Kappa Shape Indexes in Structure-Property Modeling. In *Reviews Computational Chemistry*; Lipkowitz, K. B., Boyd, D. B., Eds.; VCH Publishers: New York, 1991; p 367.
- (43) Sadlej, J. *Semiempirical Methods of Quantum Chemistry*; Ellis Horwood Ltd.: West Sussex, 1985; p 152.
- (44) Stewart, J. J. P. Optimization of Parameters for Semi-Empirical Methods. I. Method. *J. Comput. Chem.* **1989**, 10, 209–220.
- (45) Shanno, D. F. *J. Optim. Theor. Appl.* **1985**, 46, 87–94.
- (46) Stewart, J. J. P. *Quantum Chemistry Program Exchange No. 581*.
- (47) Rodríguez, L.; Estrada, E.; Gutiérrez, Y.; Muñoz, I. *MODEST (MOlecular DESing Tools)* version 1.0 Central University of Las Villas, Santa Clara, Cuba, 1993.
- (48) Weast, R. C. *CRC Handbook of Chemistry and Physics*, 67th ed.; 3rd printing; CRC: Boca Raton, FL, 1987.
- (49) Estrada, E.; Morales, S. Topographic Indices and the Prediction of Chromatographic Properties of Alkenes. Submitted for publication.
- (50) Estrada, E. Work in progress.

CI9400526