

Lowering the Intra- and Intermolecular Degeneracy of Topological Invariants*

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A review is presented of the recent progress in designing local vertex invariants with low intramolecular degeneracy and the derived topological indices with low intermolecular degeneracy; in other words, an attempt is made to assign to graph vertices real (*i.e.* non-integer) numerical invariants which are different for non-equivalent vertices and similarly to assign to non-isomorphic molecular graphs distinct real-number topological indices.

INTRODUCTION

One of the most rapidly developing chemical applications of the graph theory involves topological (TIs).¹⁻⁷ These are numbers associated with molecular chemical structures, and they serve for quantitative structure-activity or structure-property correlations (QSAR and QSPR, respectively). TIs do not depend on how one labels the atoms in a molecular (constitutional) graph and are, therefore, molecular invariants.

A molecular graph usually consists of vertices (points) symbolizing non-hydrogen atoms and of edges (lines) symbolizing covalent bonds.

At present, the TIs do not have a one-to-one correspondence with chemical structures, but are more or less degenerate: this means that more than one structure may correspond to the same value of a TI. Indeed, taking into account the fast increase of possible structures with increasing numbers of vertices, the designing of TIs with low intermolecular degeneracy is not an easy task.

When TIs are integer numbers formed on the basis of integer local vertex invariants (LOVIs), such as vertex degrees or topological distances, by simple (book-

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keeping) operations, the degeneracy of TIs is high. This is the case of the earlier TIs, such as Wiener's index W .⁸

When the TIs are formed by more sophisticated operations, their degeneracy is lower: this is the case of Randić's index⁹ or of Balaban's index J ,¹⁰ which are real numbers based on integer LOVIs.

The lowest degeneracy of TIs, however, is expected to be reached when they are formed by sophisticated operations from real-number LOVIs. During the last few years, our efforts have been directed towards finding new real-number LOVIs, and have developed such intramolecular invariants, which will be reviewed briefly in this paper. It should be noted, however, that we have so far limited our efforts to the simplest operations for assembling these new LOVIs into TIs; this was done only to check the suitability of the new LOVIs by intra- and intermolecular comparison. It is expected that, on the basis of these new LOVIs, the degeneracy of TIs will be substantially reduced. This reduction is not a goal *per se*, because it could go on indefinitely; diminishing rewards would have to mark a point when the search should stop. However, this point has not yet been reached to date, as it will be apparent from the treatment below.

INTRAMOLECULAR DEGENERACY OF LOVIs

When topologically non-equivalent vertices have the same LOVI values, they are said to be degenerate. Evidently, vertex degrees have a high intramolecular degeneracy, since they are normally four integers 1, 2, 3, or 4. The smallest alkane graphs with such degeneracy are isopentane (**1**) with non-equivalent primary carbon atoms (*i.e.* of vertex degree one), and pentane (**2**) with non-equivalent secondary carbon atoms.

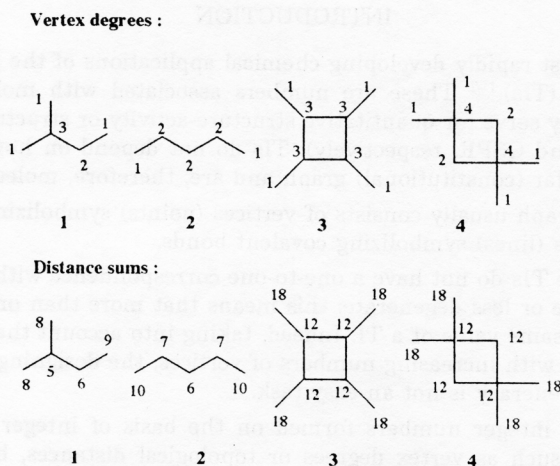


Figure 1. The simplest LOVIs: vertex degrees and distance sums. It can be observed that graphs **1** and **2** have intramolecular degeneracy of vertex degrees, and that graph **4** has intramolecular degeneracy of distance sums, for non-equivalent vertices.

Topological distance sums are integers without upper bounds, so they have lower degeneracy, as seen for graphs **1** and **2** where non-equivalent vertices have distinct distance sums (Figure 1).

The pair of graphs **3** and **4** illustrate both the intramolecular degeneracy of LOVIs (distance sums) and intermolecular degeneracy of the topological index J . This pair is actually an example of the smallest monocyclic graphs with degenerate J values (for acyclic graphs, the smallest such examples contain twelve vertices).¹¹

In graph **4**, non-equivalent vertices of degrees 2 and 4 have the same distance sums, **12**. It will be observed, however, that the distance sums s_i have different partitions:

$$18 = 1+(2+2+2)+3+(4+4) = 1+(2+2)+(3+3+3)+4;$$

$$12 = (1+1+1+1)+2+(3+3) = (1+1)+(2+2+2+2+2) = \\ = (1+1+1)+(2+2+2)+3.$$

For brevity, the above distance vectors are denoted, in the abbreviated form, as follows:

$$18 = 1^1 2^3 3^1 4^2 = 1^1 2^2 3^3 4^1$$

$$12 = 1^4 2^1 3^2 = 1^2 2^5 = 1^3 2^3 3^1$$

One can take the advantage of this fact and resolve intramolecular degeneracies of distance sums, when partitions differ, by applying intramolecularly the information theory using Shannon's formula. This was done earlier by Basak, Raychaudhury, Klopman and coworkers,¹²⁻¹⁶ and more recently, in a different manner, by Balaban and Balaban.¹⁷ (The first application of information theoretic formulas for TI molecular invariants was implemented by Bonchev and Trinajstić¹⁸). Four new LOVIs, denoted by u , v , x , and y are defined according to formulas (1) - (4).

$$u_i = - \sum_i (j g_j / S_i) \log_2(j/S_i) \quad (1)$$

$$v_i = S_i \log_2 S_i - u_i \quad (2)$$

$$y_i = \sum_j j g_j \log_2 j \quad (3)$$

$$x_i = S_i \log_2 S_i - y_i \quad (4)$$

In the above formulas, for any given vertex i , the distance vectors indicate how many times (g_j) any distance j occurs.

On summing up over all edges the products of LOVIs for the endpoints of each edge (Randić-type formulas), one obtains TIs denoted by U , V , X , and Y . For an infinitely long linear alkane, U tends towards infinity, while V , X , and Y tend towards zero. For comparison, index J tends towards a finite value, namely the number $\pi =$

3.14159. The informational indices U , V , X , and Y were tested in correlations with critical data of alkanes, with coefficients of Antoine's equation for vapor pressure of alkanes, with good results.¹⁹

There are cases when non-equivalent vertices have identical distance sums and distance vectors. One example is the graph corresponding to 1-ethyl-2-methylcyclopropane, **5**, for which two non-equivalent vertices of degree two have distance sums 9 resulting from the same distance vector ($1^2 2^2 3^1$), as seen in Figure 2.

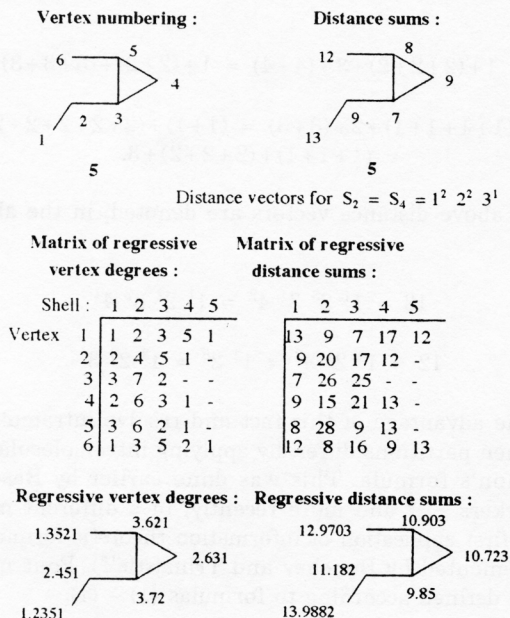


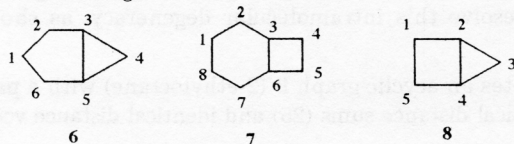
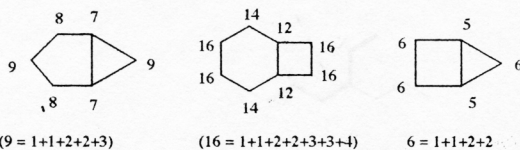
Figure 2. Intramolecular degeneracy of distance sums and distance vectors illustrated for graph **5**. It can be observed that both regressive vertex degrees and regressive distance sums resolve the degeneracy.

In this case, a second or third approach may be followed to resolve this intramolecular degeneracy, namely by means of regressive vertex degrees (RVDs),²⁰ or regressive distance sums (RDSs), respectively.²¹

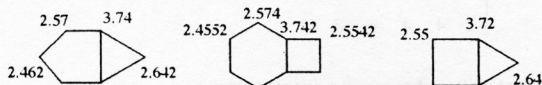
The idea in both cases is that vertex degrees indicate only the closest neighbors, whereas in distance sums the largest contributions arise from the most remote vertices. By introducing progressively attenuated contributions of the more remote vertices, it is possible to obtain real-number LOVIs, which are slightly augmented RVDs and RDSs, respectively. This is done by constructing non-symmetrical matrices for successive shells around each vertex, and summing up for all vertices, in each shell the vertex degrees or distance sums, respectively. The first shell is the vertex itself and, therefore, entries in the first column are the vertex degrees and distance sums, respec-

tively, as seen in Figure 2. For each row in the matrix for regressive vertex degrees, the sum of entries m_{ij} is twice the number of edges (like in the adjacency matrix) and, correspondingly, for the matrix of regressive distance sums the sum of entries over rows is twice the Wiener number. Attenuation with increasing distances may be *via* a reciprocal cubic formula (5) or *via* reciprocal powers of 10, as indicated by formula (6).

$$\text{LOVI}_j = \sum_i i^{-3} m_{ij} \quad (5)$$

Vertex numbering :

Distance sums (distance vectors) :

Matrices of regressive vertex degrees :

Shell :	1 2 3 4	1 2 3 4 5	1 2 3
Vertex 1	2 4 6 2	2 4 5 5 2	2 5 5
2	2 5 7 -	2 5 7 4 -	3 7 2
3	3 7 4 -	3 7 4 2 -	2 6 4
4	2 6 4 2	2 5 5 4 2	3 7 2


Matrices of regressive distance sums :

Shell :	1 2 3 4	1 2 3 4 5	1 2 3
Vertex 1	9 16 14 9	16 30 26 28 16	6 11 11
2	8 16 24 -	14 28 44 30 -	5 17 6
3	7 24 17 -	12 42 46 16 -	6 10 12
4	9 14 16 9	16 28 26 30 16	5 17 6

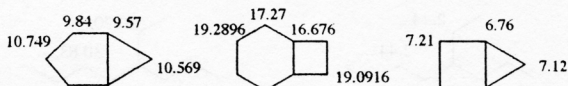


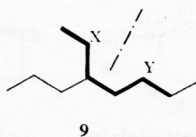
Figure 3. Intramolecular degeneracy of distance sums and distance vectors in condensed bicyclic systems 6 – 8 with unequal ring sizes. It can be observed that both regressive vertex degrees and regressive distance sums resolve the degeneracy.

$$\text{LOVI}_j = \sum_i 10^{1-i} m_{ij} \quad (6)$$

Figure 2 illustrates the application of the latter formula. It can be seen that both of these regressive LOVIs resolve the intramolecular degeneracy of distance sums and distance vectors for the two vertices labelled 2 and 4 in graph 5.

In Figure 3, three other general cases of intermolecular degeneracy of distance sums are presented; whenever two rings of different sizes are condensed, the highest distance sum belongs to the pair of nonequivalent vertices; moreover, the distance vectors are also the same and, therefore, information theoretic formulas cannot resolve this intramolecular degeneracy. However, both regressive vertex degrees and the regressive distance sums do resolve this intramolecular degeneracy, as shown in Figure 2 for graphs 6 - 8.

Figure 4 illustrates an acyclic graph 9 (2-ethyloctane) with a pair of nonequivalent vertices having identical distance sums (25) and identical distance vectors ($1^2 2^2 3^2 4^2 5^1$).

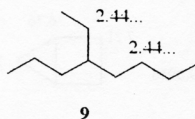


Partial matrix of regressive vertex degrees :

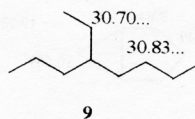
Shell :	1	2	3	4	5	6
Vertex						
X	2	4	4	4	3	1
Y	2	4	4	4	3	1

Partial matrix of regressive distance sums :

Shell :	1	2	3	4	5	6
Vertex						
X	25	52	58	48	62	37
Y	25	52	44	54	68	39



Regressive vertex degrees



Regressive distance sums

Figure 4. Graph 9 with the vertices X and Y having identical vertex degrees, distance sums, distance vectors, and regressive vertex degrees, but with distinct regressive distance sums.

It can be seen that the regressive vertex degrees for that pair do not resolve the intramolecular degeneracy while the regressive distance sums do.

On attaching to graph **9** pairwise paths of various lengths, symmetrically with respect to the middle of the thick line, one obtains graphs with 12 (e.g. graphs **10** – **12**), 14 (e.g. graphs **13** – **15**), or with $10 + 2k$ vertices (k being a natural integer). Again, in all these cases, the marked vertices have identical distance sums, distance vectors, and regressive vertex degrees, but the regressive distance sums resolve the intramolecular degeneracies (Figure 5).

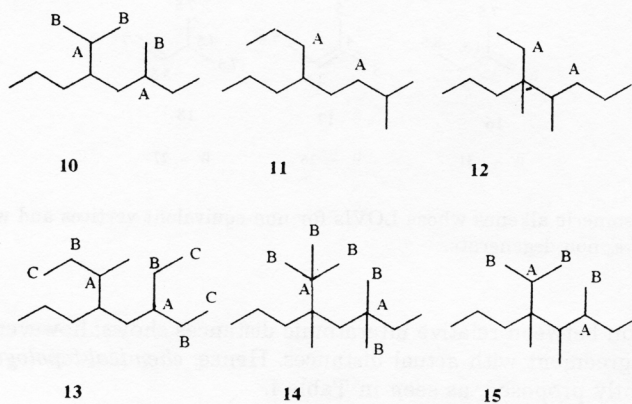


Figure 5. Graphs **10** – **12** with 12 vertices and **13** – **15** with 14 vertices resulting from graph **9** by symmetrical attachment (relative to vertices X and Y) of one or two pairs of vertices, respectively. Vertices marked by the same letters have identical vertex degrees, distance sums, distance vectors, and regressive vertex degrees, but distinct regressive distance sums.

PRESENCE OF HETEROATOMS AND/OR MULTIPLE BONDS

So far, molecular graphs were supposed to represent the carbon skeleton of hydrocarbons. One can include information on the presence of heteroatoms for index J , by means of a formula proposed by Trinajstić²² and coworkers, *via* the atomic number Z of the heteroatom. However, as chemical properties vary periodically with Z , another approach was proposed, making use of electronegativities or of covalent radii which also vary periodically with Z .²³ A coefficient is calculated relative to carbon, and this coefficient multiplies the LOVIs (for J , this is the distance sum). An additional weighting factor is sometimes necessary, as shown in correlations with the anti-cancer activity of retinoids.^{24,25} For correlations with normal boiling points of ethers, acetals, peroxides and their sulfur analogues, both the oxygen and sulfur heteroatoms could be put together into the index J with a single weighting factor.²⁶

One may simultaneously include information on heteroatoms and multiple bonds by making use of modified distances, as shown in the next section.

MODIFYING TOPOLOGICAL DISTANCES

For putting in information on the presence of multiple bonds, a simple approach is to consider the topological distance equal to the reverse bond order b_i^{-1} (this is 1, 2, 3, or 1.5 for single, double, triple, and aromatic bonds, respectively). One puts these entries into the distance matrix between multiple-bonded atoms, and one computes the resulting LOVIs. Then, the TIs are able to discriminate isomers of alkenes, as shown for 2-methylpentenes **16** – **18** in Figure 6.²⁷

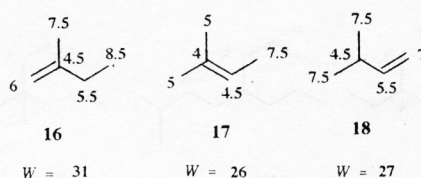


Figure 6. Three isomeric alkenes whose LOVIs for non-equivalent vertices and whose resulting TIs are distinct, *i.e.* non-degenerate.

A comparison between relative interatomic distances shows, however, that entries b_i^{-4} give close agreement with actual distances. Hence, *chemical-topological distances* have been recently proposed, as seen in Table I.

TABLE I
Topological distances RTD, and chemical-topological distances CD, for multiple bonds

Bond	R (Å) ^a	RED ^b	b	RTD ^c	CD ^d
C–C	1.54	1.00	1	1.00	1.00
C=C (Ar)	1.40	0.91	1.5	0.67	0.90
C=C	1.33	0.86	2	0.50	0.84
C≡C	1.20	0.78	3	0.33	0.76
C–N	1.47	1.00	1	1.00	1.00
C=N	1.29	0.88	2	0.50	0.84
C≡N	1.16	0.79	3	0.33	0.76
N–N	1.45	1.00	1	1.00	1.00
N=N	1.26	0.87	2	0.50	0.90
C–O	1.41	1.00	1	1.00	1.00
C=O	1.21	0.86	2	0.50	0.84
O–O	1.45	1.00	1	1.00	1.00
N–O	1.47	1.00	1	1.00	1.00
N=O	1.15	0.78	2	0.50	0.84
C–S	1.81	1.00	1	1.00	1.00
C=S	1.61	0.89	2	0.50	0.84

^aExperimental interatomic distance (in Ångströms).

^bRelative experimental distance (standard : single bonds).

^cRelative topological distance b^{-1} .

^dChemical-topological distance b^{-4}

A different approach consists of multiplying integer or real-number LOVIs (resulting from the application of any method) by factors f_i , determined from experimental covalent radii, as shown in Table II; the experimental radius r_i is divided by the value of 0.77 Å, corresponding to sp^3 -hybridized carbon, to obtain factor f_i . Thus, one accounts simultaneously for heteroatoms and bond multiplicity. This approach was used in combination with the exponential TIs, which will be described below.^{28,29}

TABLE II
Covalent radii r_i (in Ångströms) and factors f_i

Atom i	$s p^3$ -hybridized		$s p^2$ -hybridized		$s p$ -hybridized	
	r_i	f_i	r_i	f_i	r_i	f_i
C	0.77	1.000	0.665	0.864	0.60	0.779
Si	1.17	1.519	—	—	—	—
F	0.64	0.832	0.54	0.701	—	—
Cl	0.99	1.286	0.89	1.156	—	—
Br	1.14	1.480	1.04	1.350	—	—
I	1.33	1.727	1.23	1.397	—	—
O	0.65	0.844	0.55	0.714	0.50	0.649
S	1.04	1.350	0.94	1.220	0.88	1.143
N	0.70	0.909	0.60	0.779	0.55	0.714
P	1.10	1.428	1.00	1.299	—	—

Independently, the Zagreb³⁰ and the Bucharest groups³¹ proposed *reciprocals of topological distances* as entries in a new symmetrical matrix, whose sums over rows and columns are new rational-number LOVIs. The global sum is called the Harary number, H . In some cases this TI presents lower degeneracies than the Wiener index W ; thus, bicyclic condensed systems with two even-membered rings of sizes k and $k+2$ have the same W number as isomeric bicyclic condensed systems with ring sizes $k-1$ and $k+3$, but the H numbers differ. Otherwise, this TI parallels closely the Wiener index in intermolecular ordering of isomeric systems.

Klein and Randić³² used the *resistance distance* for cyclic graphs, defined as follows: let each edge in a graph be a one-ohm resistor. Then, the resistance between any two vertices is the resistance distance. In the corresponding symmetrical matrix, sums over rows and columns are new rational number LOVIs, and the global half-sum is a new TI, called the Kirchhoff number K of the graph. For acyclic graphs, the resistance distance equals the topological distance and, therefore, for such graphs $K = W$. On multiplying the LOVIs and TIs by the number of spanning trees in any cyclic graph, one obtains integers.³³ The degeneracy of Kirchhoff numbers is very low and resolves practically all cases of degeneracy for the Wiener and Harary numbers, such as those encountered with linearly condensed systems with 3 or more even-membered rings arranged in different orders of ring sizes. Only one pair of the six possible isomers (differing by permuting ring sizes in linearly condensed systems having ring size 4, 4, 6, and 8) was found to have degenerate K values namely graphs **19** and **20**, which have degenerate K , H , and W values (Figure 7).³⁴

However, even this exceptional degeneracy of K values is solvable, since all LOVIs of graphs **19** and **20** are different; any operation more sophisticated than the simple

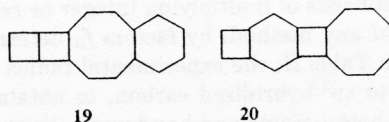


Figure 7. The single pair of isomeric polycyclic graphs with degenerate W and H indices, having also degenerate K values.

summation (*e.g.* information theoretic formulas) will therefore lead to different TIs for all polycyclic graphs known to date.

Three other types of real-number LOVIs and the corresponding TIs (mainly by simple summation) have been proposed in the last few years.

(i) Conversion of the adjacency or distance matrix into a system of linear equations, by including two column vectors conveying chemical (*e.g.* the atomic number Z or a periodically-varying property) or topological information (*e.g.* the vertex degrees, the distance sum), or even a constant. One of these two vectors provides the coefficient for the main diagonal and the other provides the free term. Simple summation affords a variety of TIs denoted by a triplet (matrix, main diagonal column vector, and free term column vector). Excellent correlations with the boiling points of alkanes were obtained with the AZV LOVIs. Intra- and intermolecular degeneracies of LOVIs and TIs, respectively, are quite low.^{35,36}

(ii) Eigenvectors corresponding to extreme eigenvalues can be used as LOVIs. In a systematic investigation of all alkanes, it was found that the eigenvectors of the adjacency matrix, but not of the distance matrix, presented intramolecular degeneracy.³⁷

By the simple summation or by more sophisticated operations, these LOVIs were then combined into several TIs, which were tested in correlations with normal boiling points of all alkanes with 2 to 8 carbon atoms.

(iii) In the search for real-number LOVIs and TIs with low degeneracy, exponential formulas were proposed, leading to LOVIs in the range 0 to 1. By simple summation, one can obtain the corresponding TIs, which were tested in correlations with physical properties with satisfactory results.^{28,29}

FRAGMENT TOPOLOGICAL INDEXES

In addition to LOVIs for atoms and to TIs for whole molecules, we also developed several approaches for TIs associated with molecular fragments (radicals or substituents) because, in designing new molecules, one often has to make correlations with structures in which only a part of the molecule is changed.

In cooperation with D. Bonchev and O. Mekenyan, integer number TIs were proposed for molecular fragments.³⁸

A different approach was used for index J , namely the distance sum of the root vertex (*i.e.* the atom of the substituents connecting it to the major moiety of the molecule) was multiplied by the factor 0.1; then, J was computed.³⁹

The exponential LOVIs, which range from 0 to 1, were used for fragment TIs by constructing the symmetrical dimer of the fragment, computing the exponential LOVIs, and discarding one half of the dimer.²⁹

CONCLUDING REMARKS

This paper has reviewed recent work in devising LOVIs with low intramolecular degeneracy and TIs with high discrimination ability in intermolecular comparisons and good properties for use in QSAR/QSPR. Both the recently devised LOVIs and TIs are real numbers, rather than integers and, therefore, these TIs are 3rd generation TIs.⁴⁰⁻⁴²

In addition to structural correlations with physico-chemical properties, TIs are frequently used for drug design,^{1,7,43-46} an area where mathematical modelling can spare much effort in synthesizing and testing new compounds.

We have focused this review on the efforts of our group in Bucharest,⁴²⁻⁴⁶ but, fortunately, during the last few years new cooperations became possible (in addition to those we had with the Technical University in Burgas, Bulgaria and the University of Trondheim, Norway), namely with universities in the USA: Virginia Commonwealth University in Richmond, Virginia, and the Texas A & M University in Galveston, Texas.

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SAŽETAK

Snižavanje intra- i intermolekulske degeneracije topologijskih invarijanti

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U ovom preglednom članku prikazan je suvremeni napredak u kreiranju lokalnih topologijskih invarijanti vezanih na čvorove molekulskog grafa s niskom intramolekulskom degeneracijom i u izvođenju topologijskih indeksa s niskom intermolekulskom degeneracijom.