

Local versus Global (i.e. Atomic versus Molecular) Numerical Modeling of Molecular Graphs

Alexandru T. Balaban

Organic Chemistry Department, Polytechnic University of Bucharest, Bucharest, Roumania, and
Marine Sciences, Texas A&M University, Galveston, Texas 77553-1675

Received May 18, 1993*

We developed new local vertex invariants (LOVIs) which are real (i.e. non-integer) numbers in order to reduce the intramolecular degeneracy of LOVIs and the intermolecular degeneracy of topological indices (TIs), which are created from these LOVIs and which are also real numbers.

1. INTRODUCTION

For the purpose QSAR/QSPR studies, global numerical modeling of molecular graphs has been carried out by means of various molecular descriptors; from them we shall discuss here topological indices (TIs).^{1–7} So far, most TIs have been based on two types of local vertex (i.e. atomic) invariants (LOVIs): (i) vertex degrees and (ii) distance sums. The former ones result by summing over rows or columns the entries in the adjacency matrix of the hydrogen-depleted molecular graph. Analogously, the latter LOVIs result by summing over rows or columns the entries in the topological distance matrix of the corresponding graph. The topological distance is defined as the number of edges on the shortest path between two vertices. In chemical graphs, vertex degrees are usually integers ranging from 1 to 4, whereas distance sums are integers whose upper bound for a graph with N vertices is $(N - 1)^2$.

When two or more different chemical structures (corresponding to non-isomorphic molecular graphs) have the same TI, such a case is known as degenerate. Topological indices have a high degeneracy when they are integers (such as Wiener's index)⁸ and a lower degeneracy when they are real (i.e. non-integer) numbers (e.g. molecular connectivities of Randić,⁹ valence connectivity indices of Kier and Hall,^{5,6} or the average distance sum connectivity, denoted as the topological index $J^{2,10}$).

If one wishes to use TIs not only for QSAR but also for helping to enumerate isomers, or for structure coding and retrieval, the degeneracy must be drastically reduced. For this purpose, we first tried various approaches based on the above two LOVIs with limited success, but then went on to develop new LOVIs which are themselves real numbers, rather than integers. On the basis of such new LOVIs, TIs which were designated as "third-generation TIs"^{11,12} (which of course are also real numbers) can be assembled in various ways. Such new TIs are expected to have very low degeneracy and, at the same time, to enable QSAR/QSPR studies.

The aim of our efforts was to develop new tools for people interested in QSAR, i.e. to provide new methodology rather than new correlations. Therefore we checked our new LOVIs using precisely measured properties such as normal boiling points of simple systems (hydrocarbons or their derivatives with only one category of heteroatoms). The validation of LOVIs was based on both intramolecular and intermolecular comparisons of LOVIs in sets of isomers differing in their branching degree.

In addition to using the new LOVIs for constructing from them global molecular models (TIs), we also developed approaches for devising TIs for molecular fragments (substituents), because in many studies carried out for drug design

the molecular core is kept constant, and only one or a few substituents are varied.^{5,6,13–16}

2. MODIFIED DISTANCES AND DERIVED LOVIS

2.1. Modified Topological Distances. It was shown above that topological distances (d_i) are integer numbers indicating how many edges one has to cross from vertex i to vertex j on the shortest path. Distances, unlike vertex degrees, allow an easy incorporation of chemical information concerning the presence of multiple bonds and/or heteroatoms. Thus, for two vertices joined by a multiple bond, the topological distance may be considered to be shorter. One possibility is to have just four types of bonds with bond orders $b = 1, 2, 3$ for single, double, or triple bonds, respectively, and 1.5 for aromatic bonds, and then the *topological distance* for such bonds will be b^{-1} . For the presence of heteroatoms, Trinajstić et al.¹⁷ advocated the use of the atomic number Z in a coefficient multiplying the distance sum. A second alternative is to use an atomic property which varies in accordance with the periodic system of elements. We employed either *relative covalent radii*, or *relative electronegativities* (with carbon atoms taken as standard).¹⁸

A third possibility,¹⁹ accounting simultaneously for heteroatoms and/or multiple bonds, is to consider both the nature of the heteroatom and its hybridization state, introducing parameters modeled according to covalent radii (Table 1) which multiply the distance sum to obtain the LOVI. A fourth and last possibility is to introduce *chemical distances*,²⁰ defined (again relative to the C–C bond distances taken as standard) as $b^{-1/4}$. In this case, the entries in the distance matrix approximate well the actual geometry of molecules, but stereochemistry is ignored, as in all previous cases.

Table 1. Covalent Radii r_i (Angstroms) and Factors f_i

atom i	sp ³ -hybridized		sp ² -hybridized		sp-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		

2.2. Reciprocal Distances. Independently, both our group in Bucharest²¹ and Trinajstić's group in Zagreb²² explored the implication of constructing a reciprocal distance symmetrical matrix whose entries are $r_{ij} = r_{ji} = d_{ij}^{-1}$. Then the sum of entries over rows or columns gives LOVIs, which are

* Abstract published in *Advance ACS Abstracts*, February 15, 1994.

reciprocal distance sums, r_i :

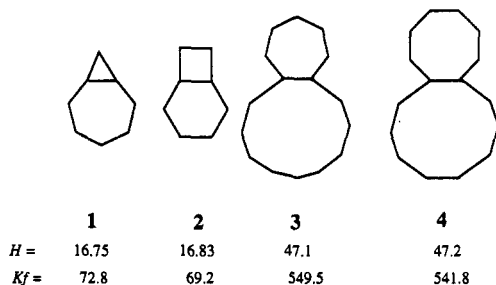
$$r_i = \sum_j r_{ij}$$

Summation of all r_i values in the upper triangle of the reciprocal distance matrix yields a TI which we agreed to call the Harary number, H . As will be shown in section 2.3, this TI is slightly less degenerate than the Wiener index W (which is its analog resulted from the distance matrix and distance sums S_i), but essentially H and W present the same intermolecular ordering of isomeric molecules. In other words, the metrics introduced intermolecularly by topological distances (d_i) and by reciprocal distances (r_i) are practically identical.

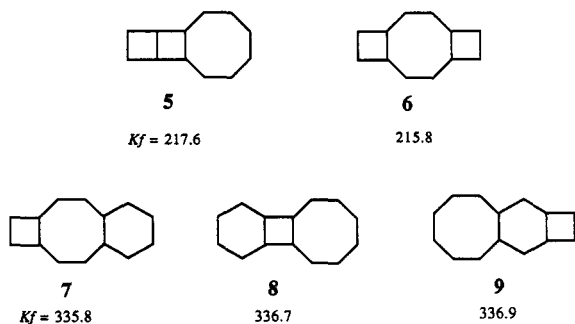
2.3. Resistance Distances. Kirchhoff's laws for electrical circuits prompted Klein and Randić²³ to introduce a new type of distance, called *resistance distance*: if one assimilates each edge of graph G with a $1-\Omega$ resistor, then the resistance of G between vertices i and j is called the resistance distance. This is a rational number which, if multiplied by the number T of spanning trees of G , yields an integer representing the number of spanning forests with two components, one containing vertex i and the other one containing vertex j .²⁴

The resistance distances of acyclic graphs are identical to topological distances. For cyclic graphs, one may sum all the resistance distances emanating from one vertex, arriving thereby at a LOVI of that vertex. The sum of all such graph LOVIs affords a TI which is called the Kirchhoff number Kf of the graph. This TI is much less degenerate than W or H . With Bonchev, Klein, and Liu, we explored a variety of polycyclic systems comparing the three TIs denoted by W , H , and Kf .²⁵

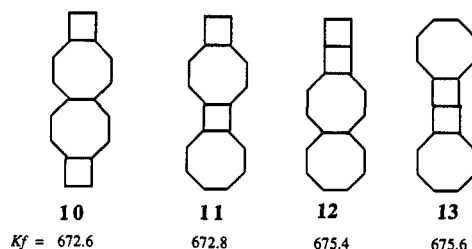
An interesting conclusion was that for some systems with two condensed rings, H discriminates better than W . This is illustrated by pairs of graphs 1 and 2 (both with $W = 58$) or 3 and 4 (both with $W = 428$).



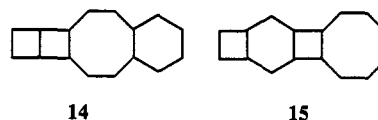
With very few exceptions, linearly-condensed ribbons of even-membered rings have degeneracy both for W and H , but not for Kf . This is illustrated by the tricyclic isomeric pair 5 and 6 (with $W = 184$ and $H = 31.9$) and triplet 7–9 (with $W = 283$ and $H = 40.3$).



Practically all tetracyclic systems with degenerate W and H are discriminated by Kf , as illustrated by the quadruplet 10–13 (all having $W = 557$ and $H = 58.8$).



The only exception we found was one pair of the sextuplet of isomeric systems with ring sizes 4, 4, 6, and 8. All six systems have $W = 410$ and $H = 49.9$, and different Kf values except for pair 14 and 15 both with $Kf = 427.7$.

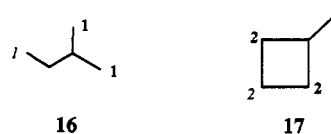


We do not yet know if there are other isomeric polycyclic systems which have the same values for their Kirchhoff numbers.

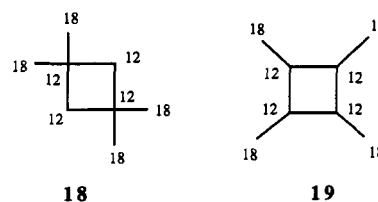
3. INTRAMOLECULAR DEGENERACY OF LOCAL VERTEX INVARIANTS AND ITS REDUCTION BY MEANS OF INFORMATION THEORY

Intermolecular Degeneracy of integer LOVIs needs not worry us because it is inevitable and because molecular properties can also show "near-degeneracies". However, we wish to reduce intramolecular degeneracy, which exists whenever two non-equivalent vertices in the same molecular graph (*i.e.* vertices belonging to different orbits, in graph-theoretical parlance) have identical LOVIs.

Intramolecular Degeneracy is also practically inevitable when the LOVIs are vertex degrees ν_i . For example, the smallest acyclic graph illustrating this case corresponds to the hydrocarbon isopentane 16 (2-methylbutane) which has non-equivalent vertices with the same degree, namely, 1. The smallest cyclic graph illustrating this case also has five vertices and corresponds to methylcyclobutane 17 which has non-equivalent vertices of degree 2 (vertex degrees for distinct orbit vertices are written with different fonts).



When the LOVI is the distance sum s_i , intramolecular degeneracy occurs less often. One set of new LOVIs reducing the intramolecular degeneracy of distance sums is obtained on dividing distance sums s_i by vertex degrees ν_i : $t_i = s_i/\nu_i$. The idea behind the new LOVI t_i is that usually vertices with the highest distance sums have the lowest vertex degrees; therefore the above new LOVI enhances the intramolecular differences. This new LOVI solves some of the intermolecular degeneracies encountered with the topological index J . Thus, the smallest pair of monocyclic graphs 18 and 19



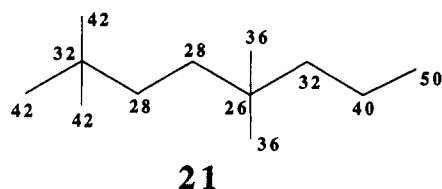
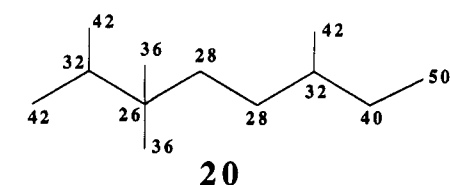
with degenerate J values no longer presents degeneracy for the modified J_t index when the distance sum s_i is replaced by t_i :

$$J_t = \frac{q}{\mu + 1} \sum_{\text{edges } ij} t_i t_j$$

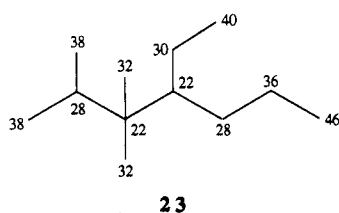
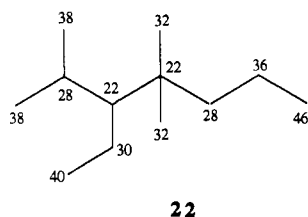
Here, q is the number of edges, and μ is the cyclomatic number of the graph.

The distance sums 12 originate in the following distance vectors: $1^4, 2^1, 3^2; 1^3, 2^3, 3^1; 1^2, 2^5$. The distance sums 18 originate in the vectors: $1^1, 2^3, 3^1, 4^2; 1^1, 2^2, 3^3, 4^1$. We indicated in abbreviated form the *distance vector*; thus, 1^3 indicates that distance 1 occurs three times, i.e. that the vertex has degree 3, and so on.

Among the smallest acyclic graphs with degenerate J values, some of them like the pair **20** and **21**,²⁶ having two vertices

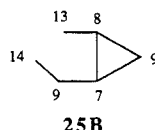
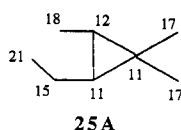
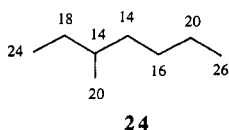


with distance sums 32 either of degrees 3 and 3, or 2 and 4, will no longer have degenerate J_t values; other ones like the pair **22** and **23** have degeneracy for both J and J_t indices



because there is no difference between the two graphs in the vertex degrees for vertices with identical distance sums.

The unique identity tree **24** with eight vertices (3-methylheptane) exemplifies an acyclic graph, and 1-ethyl-2,2,3-trimethyl-cyclopropane **25A** illustrates a monocyclic

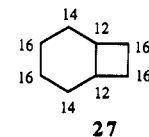
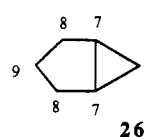


graph with intramolecular degeneracy of distance sums. The former has two pairs of non-equivalent vertices with the same distance sums, 14 ($1^3, 2^2, 3^1, 4^1$ and $1^2, 2^3, 3^2$); and 20 ($1^1,$

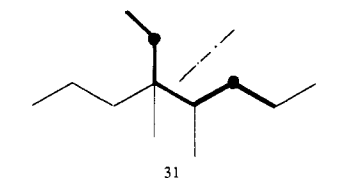
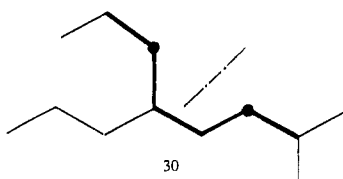
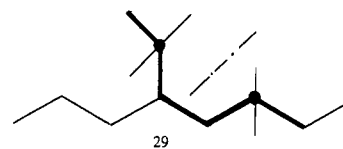
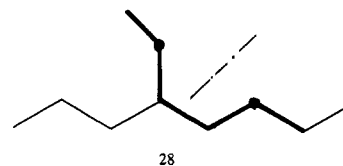
$2^2, 3^2, 4^1, 5^1$ and $1^2, 2^1, 3^1, 4^2, 5^1$); the latter has one such pair with distance sum 11 ($1^3, 2^4$ and $1^4, 2^2, 3^1$).

When the distance vectors are different but the distance sum is the same, the degeneracy of TIs may be resolved by applying locally information theory via Shannon's formula. Information theory was applied globally by Bonchev and Trinajstić²⁷ and locally by Basak, Raychaudhury, Klopman and et al.,²⁸⁻³² and our group;³³ in the following, we present our approach (which differs from that of the preceding authors).

However, when the distance vector is the same (hence of course also the distance sum), information theory cannot resolve the degeneracy. This is the case of the monocyclic graph **25B** with the distance vector 9 ($1^2, 2^2, 3^1$). For bicyclic graphs, one can generalize such examples to all condensed systems having two rings of unequal sizes; the smallest systems with two odd-membered or two even-membered rings are illustrated by graphs **26** and **27**. In all similar cases, non-equivalent vertices will have degenerate LOVIs with identical distance vectors.



For acyclic graphs, a search of 4-trees (whose vertices have degrees of 4 or less) has revealed cases with intramolecular degeneracy of LOVIs associated with degeneracy of distance vectors. One such example³³ is provided by graph **28** where the marked vertices possess identical distance vectors $1^2, 2^2, 3^2, 4^2, 5^1$. By adding pairwise to these two vertices, or to another pair of vertices on the heavy line at equal distance from the indicated axis, paths of various lengths, one can obtain larger graphs having pairs of vertices with identical distance vectors; examples are provided by graphs **29-31**.



As mentioned earlier, information-theoretical formulas can be applied. One such approach converts the distance vectors into real-number LOVIs (u, v, x, y) whose global sums over the whole graph afford new information-based TIs $U, V, X,$

and Y , respectively.^{33,34}

$$u_i = -\sum_j (jb_j/S_i) \log_2(j/S_i)$$

$$v_i = S_i \log_2 S_i - u_i$$

$$y_i = \sum_j jb_j \log_2 j$$

$$x_i = S_i \log_2 S_i - y_i$$

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

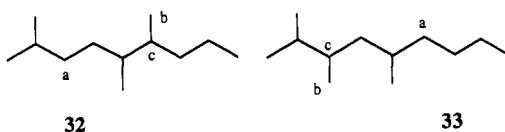
The corresponding TIs V , X , and Y increase with molecular branching and decrease slightly with increasing number N of non-hydrogen atoms, whereas index U increases with branching and increases fast with increasing N .

4. OTHER REAL-NUMBER LOCAL VERTEX INVARIANTS AND DERIVED TOPOLOGICAL INDICES

Since most of the following items have already been published, only a brief overview of our own contributions with relevant literature quotations will be given.

4.1. Solutions of Linear Equation Systems. The adjacency matrix A or the distance matrix D can be converted into linear equation systems by inscribing on the main diagonal a column vector providing chemical information on the respective atom (e.g. its atomic number Z), topological information (e.g. vertex degree v_i or the number N of non-hydrogen atoms), or even a numerical constant. Then another similar column vector identical to, or different from, the previous one provides the free terms for the system of linear equations whose solutions are the LOVIs for the given graph. The triplet notation (formed by the matrix, main diagonal column vector, and free term column vector) serves to designate the type of LOVI.³⁵

In the case of the LOVIs obtained with the AZV triplet, the dodecane isomers 32 and 33 present intermolecular degeneracy for the pairs of marked vertices with vertex degrees 1, 2, and 3.



Summation of all LOVIs for the given graph provides topological indices with very low degeneracy and (in some cases such as AZV triplets) excellent correlation ability.³⁵ The wide choice for components of the triplet, the possibility to input information on heteroatoms, and the different resulting trends in intramolecular variation of such LOVIs makes them extremely interesting for future development.³⁶

4.2. Eigenvectors of Adjacency and Distance Matrices Corresponding to Extremal Eigenvalues. The eigenvectors corresponding to the largest negative eigenvalue of the adjacency matrix D or the distance matrix A can serve as LOVIs. Intramolecular degeneracy is observed in the case of alkanes for such LOVIs obtained from A , but not from D .³⁷

From these LOVIs, by various types of operations (simple summation, or application of Randić-type formulas), various TIs can be obtained. They were tested in correlations against boiling points of alkanes with satisfactory results for some of them.³⁷

4.3. Regressive Vertex Degrees. Starting from the idea that vertex degrees reflect only the immediate vicinity, we

introduced new³⁸ nonsymmetrical matrices and resulting LOVIs, where the contribution of more remote vertices is taken into account with progressively attenuated weight as the distance increases. The resulting LOVIs are slightly augmented vertex degrees. Two types of attenuation were considered: inverse cubic attenuation and exponential attenuation by powers of 10. The two corresponding formulas are

$$\text{LOVI}_i^{(1)} = \sum_j r^{-3} j_{ij}$$

$$\text{LOVI}_j^{(2)} = \sum_i 10^{-i} j_{ij}$$

Each entry in the matrix indicates how many vertices are in successive shells around each vertex i . Thus shell j is the summation of vertex degrees at distance $j-1$ from vertex i . Therefore the first column is the vertex degree, and what follows reflects the progressively decreasing contributions of vertices in the more remote shells. In the case of the second formula, rows in the corresponding matrix are read sequentially from entries j_{ij} converted into decimal numbers, as exemplified by isopentane (Figure 1).

4.4. Regressive Topological Distance Sums. Analogously to the preceding LOVIs, nonsymmetrical matrices containing sums of topological distances for vertices in successive shells afford by means of similar formulas augmented distance sums which are real (non-integer) numbers.^{3,9} Again, the result for the isopentane graph shown in Figure 1 constitutes a good intramolecular validation. The new LOVIs were used for devising from them new TIs, which were tested in QSAR studies.

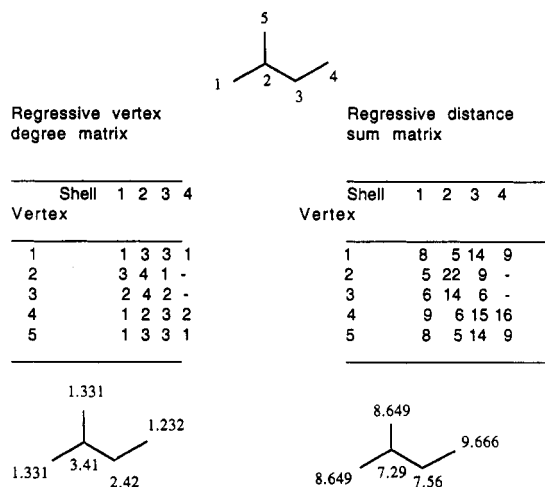


Figure 1.

4.5. Exponential Distance Sum Connectivities. In order to obtain real-number LOVIs c_i in the range from zero to one, the following formulas were proposed:⁴⁰

$$g_i = v_i^{-1/2} \left(\sum_{j=1}^{v_i} v_j \right)^{-1} \quad (1)$$

$$\log G_i = \left(\prod_{j=1}^{v_i} g_j \right) \log g_j \quad (2)$$

$$\log c_i = \left(\sum_{k=1}^{k_{i,m}} k \prod_{k=1}^{k_{i,m}} G_{i,k} \right) \log G_i \quad (3)$$

where ν_i is the degree of vertex i , and the sum in formula 1 extends to all immediate neighbors of vertex i , while the sum and product in formula 3 extend to topological distances k from vertex i to all other vertices, including the maximum distance $k_{i,m}$; $G_{i,k}$ denotes the G_i value for each vertex situated at distance k from vertex i .

In addition to LOVIs c_i , another set of LOVIs (denoted by c'_i) was based on three similar formulas, the only difference being the inclusion of a product into formula (1'), yielding the

$$g'_i = \nu_i^{-1/2} \left(\sum_{j=1}^{\nu_i} \nu_j \prod_{j=1}^{\nu_j} \nu_j \right)^{-1} \quad (1')$$

G'_i values by substituting g'_j for g_j in (2), and LOVIs c'_i by substituting in (3) G'_i for G_i and $G_{i,k}'$ for $G_{i,k}$.

The resulting LOVIs have very low degeneracy and by summation yield TIs with satisfactory correlating ability.⁴⁰

In addition to these TIs for molecules, we have proposed TIs for substituents (molecular fragments) by constructing symmetrical dimers of these substituents and calculating their LOVIs c_i . Then half of this molecule is discarded, leaving a substituent with reasonable LOVIs which can be used for QSAR/QSPR studies.¹⁹

4.6. Steric Vertex Topological Index. A different approach for obtaining a topological parameter (SVTI) reflecting the steric effect of alkyl substituents consists in summing⁴¹ the distances not greater than three between the attachment site and the carbon atoms of the alkyl group. Though the SVTI values for the four alkyls with four carbon atoms result in an unusual order (*n*-butyl, 6; *tert*-butyl, 7; *sec*-butyl, 8; and isobutyl, 9), one obtains good correlations with experimental kinetic data and with other steric parameters such as Taft's E_s and Kier's parameter Ξ .

For substituents which include heteratoms and/or multiple bonds, SVTI values (which are no longer integers as for alkyl or cycloalkyl groups) may be computed by means of parameters based on covalent bond lengths for each atom in its hybridization state, as shown in Table 1.

5. CONCLUSION

Until a few years ago, practically all available LOVIs were integers, which led to considerable degeneracy of TIs. The new LOVIs and TIs which function as atomic and molecular descriptors, respectively, are real (non-integer) numbers, and they provide the basis for devising such descriptors with very low degeneracy.

In the preceding sections, the discussion was concentrated on our own efforts in this area. Recent papers by other authors,⁴² in which other types of atomic and molecular descriptors are introduced, prove that this is a field of considerable interest for QSAR/QSPR as well as for molecular modeling and drug design.

ACKNOWLEDGMENT

The assistance of the co-authors from Roumania and abroad indicated in the bibliography is gratefully acknowledged. Thanks are expressed to Professor J. R. Dias for the invitation

to take part in the Kansas City Symposium. Acknowledgement is made for support of part of this research by the R. E. Welch Foundation of Houston, and by Professors D. J. Klein, T. G. Schmalz, and W. A. Seitz from the Texas A&M University at Galveston, Texas.

REFERENCES AND NOTES

- (1) Balaban, A. T.; Motoc, I.; Bonchev, D.; Mekenyan, Q. Topological Indices for Structure-Activity Correlations. In *Steric Effects in Drug Design*; Charton, M., Motoc, I., Eds.; Topics in Current Chemistry; Springer: Berlin, 1983; Vol. 114, p 21.
- (2) Balaban, A. T. *Pure Appl. Chem.* **1983**, *55*, 199.
- (3) Bonchev, D. *Information Theoretic Indices for Characterization of Chemical Structures*; Research Studies Press: Chichester, U.K., 1983.
- (4) Trinajstić, N. *Chemical Graph Theory*, 2nd ed.; CRC Press: Boca Raton, FL, 1983.
- (5) Kier, L. B.; Hall, L. H. *Molecular Connectivity in Chemistry and Drug Research*; Academic Press: New York, 1976. Kier, L. B.; Hall, L. H. *Molecular Connectivity in Structure-Activity Analysis*; Wiley: New York, 1986.
- (6) Rouvray, D. H., *J. Comput. Chem.* **1987**, *8*, 470.
- (7) Stankevich, M. I.; Stankevich, I. V.; Zefirov, N. S. *Russ. Chem. Rev.* **1988**, *59*, 191 (translation of: *Usp. Khim.* **1988**, *59*, 337).
- (8) Wiener, H. *J. Am. Chem. Soc.* **1947**, *69*, 17, 2636.
- (9) Randić, M. *J. Am. Chem. Soc.* **1975**, *97*, 6609.
- (10) Balaban, A. T. *Chem. Phys. Lett.* **1982**, *80*, 399.
- (11) Balaban, A. T. *J. Chem. Inf. Comput. Sci.* **1992**, *32*, 23.
- (12) Balaban, A. T.; Balaban, T. S. *J. Chim. Phys.* **1992**, *89*, 1735.
- (13) Balaban, A. T.; Niculescu-Duvaz, I.; Simon, Z. *Acta Pharm. Jugosl.* **1987**, *37*, 7.
- (14) Sabljic, A.; Trinajstić, N. *Acta Pharm. Jugosl.* **1982**, *31*, 189.
- (15) Balaban, A. T.; Chiriac, A.; Motoc, I.; Simon, Z. *Steric Fit in Quantitative Structure Activity Relations: Lecture Notes in Chemistry No. 15*; Springer: Berlin, 1980.
- (16) Voiculescu, N.; Balaban, A. T.; Niculescu-Duvaz, I.; Simon, Z. *Modeling of Cancer Genesis and Prevention*; CRC Press: Boca Raton, FL, 1990.
- (17) Barysz, M.; Jashari, G.; Lall, R. S.; Srivastava, V. K.; Trinajstić, N. in *Chemical Applications of Graph Theory and Topology*; King, R. B., Ed.; Elsevier: Amsterdam, 1983, p 222.
- (18) Balaban, A. T. *Math. Chem.* **1986**, *21*, 115.
- (19) Balaban, A. T.; Catana, C. *SAR QSAR Environ. Res.* in press.
- (20) Balaban, A. T.; Bonchev, D.; Seitz, W. A. *J. Mol. Struct. (THEOCHEM)* **1993**, *280*, 253.
- (21) Ivanciuc, O.; Balaban, T. S.; Balaban, A. T. *Math. Chem.* **1993**, *12*, 309.
- (22) Playsić, D.; Nikolić, S.; Trinajstić, N.; Mihalić, Z. *J. Math. Chem.* **1993**, *12*, 235.
- (23) Klein, D. J.; Randić, M. *J. Math. Chem.* **1993**, *12*, 85.
- (24) Shapiro, L. W. *Math. Mag.* **1987**, *60*, 36.
- (25) Bonchev, D.; Balaban, A. T.; Liu, X.; Klein, D. J. *Int. J. Quantum Chem.*, in press.
- (26) Balaban, A. T.; Quintas, L. V. *Math. Chem.* **1983**, *14*, 213.
- (27) Bonchev, D.; Trinajstić, N. *J. Chem. Phys.* **1977**, *67*, 4517.
- (28) Ray, S. K.; Basak, S. C.; Raychaudhury, C.; Roy, A. B.; Ghosh, A. *Arzneimitt.-Forsch.* **1982**, *32*, 322; **1983**, *33*, 352.
- (29) Roy, A. B.; Raychaudhury, C.; Ghosh, J. J.; Ray, S. K.; Basak, S. C. In *Quantitative Approaches to Drug Design*; Dearden, J. C., Ed.; Elsevier: Amsterdam, 1983; p 75.
- (30) Klopman, G.; Raychaudhury, C.; Hendersen, R. V. *Math. Comput. Model.* **1988**, *11*, 635.
- (31) Klopman, G.; Raychaudhury, C. *J. Chem. Inf. Comput. Sci.* **1990**, *30*, 12.
- (32) Raychaudhury, C.; Ray, S. K.; Ghosh, J. J.; Roy, A. B.; Basak, S. C. *J. Comput. Chem.* **1984**, *5*, 581.
- (33) Balaban, A. T.; Balaban, T. S. *J. Math. Chem.* **1991**, *8*, 383.
- (34) Ivanciuc, O.; Balaban, T. S.; Balaban, A. T. *J. Math. Chem.* **1993**, *14*, 21.
- (35) Filip, P. A.; Balaban, S.; Balaban, A. T. *J. Math. Chem.* **1987**, *1*, 61.
- (36) Ivanciuc, O.; Balaban, T. S.; Filip, P.; Balaban, A. T. *Math. Chem.* **1992**, *28*, 151.
- (37) Balaban, A. T.; Ciubotariu, D.; Medeleanu, M. *J. Chem. Inf. Comput. Sci.* **1991**, *31*, 517.
- (38) Diudea, M. V.; Minailiuc, O.; Balaban, A. T. *J. Comput. Chem.* **1991**, *12*, 527.
- (39) Balaban, A. T.; Diudea, M. V. *J. Chem. Inf. Comput. Sci.* **1993**, *33*, 421.
- (40) Balaban, A. T.; Catana, C. *J. Comput. Chem.* **1993**, *14*, 155.
- (41) Ivanciuc, O.; Balaban, A. T. *J. Math. Chem.*, in press.
- (42) Rücker, G.; Rücker, C. *J. Chem. Inf. Comput. Sci.* **1993**, *33*, 683. Figueras, J. *Ibid.* **1993**, *33*, 717.