Revue Roumaine de Chimie, **1999**, *44* (6), 539–547

DESIGN OF TOPOLOGICAL INDICES. PART 21.[1]

MOLECULAR GRAPH OPERATORS FOR THE COMPUTATION OF GEOMETRIC STRUCTURAL DESCRIPTORS

Ovidiu IVANCIUC and Alexandru T. BALABAN

Department of Organic Chemisty, Faculty of Chemical Technology,
"Politehnica" University of Bucharest, Oficiul 12 CP 243,
78100 Bucharest, Romania
E-mail: o_ivanciuc@chim.upb.ro

Received May 5, 1999

Topological indices represent an important class of structural descriptors, widely used in modeling physical, chemical, or biological properties, in similarity and diversity assessment, database mining, and in the virtual screening of combinatorial libraries. Recently, the distance matrix computed from the molecular geometry was used as the source of a new series of structural descriptors, the topographic indices. Topographic indices are structural invariants computed from three-dimensional molecular geometry with the formulas defined for topological indices. Using molecular matrices derived from three-dimensional molecular geometry, denoted **3M**, we define new families of structural descriptors, the information-theory operators **U(3M)**, **V(3M)**, **X(3M)**, and **Y(3M)**. These operators are computed from atomic invariants that measure the information content of the matrix elements associated with the respective atom. Structural descriptors computed with the operators **U(3M)**, **V(3M)**, **X(3M)**, and **Y(3M)** are used in a quantitative structure-retention relationship model for alkylphenols in gas-liquid chromatography.

INTRODUCTION

The computation of molecular properties from the molecular structure represents an important problem in theoretical chemistry. The molecular structure is considered at various levels of complexity: the molecular graph level, the geometrical level, and the quantum level. The first level of molecular structure description uses the connectivity of atoms, and does not consider the information regarding the three-dimensional structure of the molecule. The structure of the molecular graph determines a large number of molecular properties ranging from physico-chemical and thermodynamic properties to chemical reactivity and biological activity. Among the large class of molecular graph invariants used to describe the chemical structure, we mention here graph theoretic polynomials, spectra, spectral moments, topological indices, distances, walks, and paths. The most used molecular graph descriptors in establishing Quantitative Structure-Property Relationships (QSPRs), Quantitative Structure-Activity Relationships (QSARs), and structural similarity models are topological indices (TIs).[2-15] A topological index is a numerical descriptor of the molecular structure derived from the corresponding molecular graph. The topological description of a molecule contains information on the atom-atom connectivity in the molecule, and encodes the size, shape, and branching features that determine the molecular properties. This graph description of molecules neglects information on bond lengths, bond angles, and torsion angles.

With the development of chemical databases containing the three-dimensional structure of a large number of compounds, and with the possibility to compute the gemetrical structure of (almost) any chemical compound with various molecular mechanics or quantum mechanics software, it is now

feasible to generate structural descriptors directly from the molecular geometry. Such structural invariants, that are computed from three-dimensional molecular geometry with the formulas defined for topological indices, are called topographic indices.[16-26] The structural descriptors computed from the molecular geometry offer a simple and efficient way for treating molecules with heteroatoms and/or with multiple bonds. Using only the constitutional (connectivity) information contained in the molecular graph it is not possible to discriminate between *cis/trans (E/Z)* or other types of stereoisomers. The descriptors computed from the molecular three-dimensional structure discriminate such diastereoisomers, and this is a clear advantage of this kind of descriptors. On the other hand, they are not unique; the three-dimensional structure can be experimentally determined or computed with various methods, all giving different results. Therefore, the value of geometrical descriptors depends on the method used to compute the molecular geometry. Also, a flexible compound exists as a mixture of conformers that are dynamically interconverted; such a compound is not rigid, and usually it is difficult to identify all important conformers and their proportion in the whole population of conformers. It is clear that the numerical value of a geometrical descriptor will be different for different conformers of a specific chemical compound, and this makes difficult to characterize the molecular structure with a single number. In this paper we propose new families of structural descriptors derived from three-dimensional molecular geometry, the information-theory operators **U(3M), V(3M), X(3M),** and **Y(3M).** These operators are computed from atomic invariants that measure the information content of the matrix elements associated with the respective atom.

NEW DESCRIPTORS FROM GEOMETRIC MOLECULAR MATRICES

Using information theory applied to graph distances, the highly discriminating topological indices *U, V, X,* and *Y* were introduced.[27,28] These four information indices were used with good results in QSPR models to estimate the critical volumes, temperatures, and pressures of 49 alkanes, as well as for the coefficients of the Antoine equation that give the saturation pressure versus the absolute temperatures.[29] Recently, the information indiced were extended for any symmetric molecular matrix and for vertex- and edge-weighted molecular graphs, giving the operators **U(M), V(M), X(M),** and **Y(M)** that are a measure of the information on matrix elements.[1] Although by design the information on distances indices *U, V, X,* and *Y* are very selective, it was found that certain acyclic[30] and cyclic[31] graphs that have non-equivalent vertices with identical distance degree sequences can generate pairs of graphs with degenerate *U, V, X,* and *Y* indices.

Formerly, the *U, V, X,* and *Y* indices were computed from the graph distance matrix. In this section we extend their definitions for molecular matrices **3M** derived from three-dimensional molecular geometry, giving the information-theory operators **U(3M), V(3M), X(3M),** and **Y(3M).** These operators are computed from atomic invariants that measure the information content of the matrix elements associated with the respective atom. Three-dimensional descriptors can be computed for the hydrogen-depleted molecular structure, i.e. the heavy-atom molecular structure, denoted with *G,* or for the whole molecule, denoted with *H.* These four operators can be computed from any molecular matrix **3M** derived from three-dimensional molecular geometry, such as the geometric distance matrix or the reciprocal geometric distance matrix.

The three-dimensional distance matrix, **3D** = **3D**(*G*), of a molecular structure *G* with *N* atoms is a real symmetric $N \times N$ matrix with the element $[\mathbf{3D}]_{ij} = [\mathbf{3D}]_{ji}$ representing the shortest Cartesian distance between atoms *i* and *j* in *G;* all geometric distances from the present paper are in Å. The reciprocal geometrical distance matrix of a molecular structure *G* with *N* atoms, **3RD** = **3RD**(*G*), is the square $N \times N$ symmetric matrix whose entries $[\mathbf{3RD}]_{ij}$ are equal to the reciprocal of the geometric distance between atoms *i* and *j,* i.e. $1/[\mathbf{3D}]_{ij}$, for non-diagonal elements, and is equal to zero for the diagonal elements:

$$[\mathbf{3RD}]_{ij} = \begin{cases} 1/[\mathbf{3D}]_{ij} & \text{if } i \neq j \\ 0 & \text{if } i = j \end{cases} \tag{1}$$

As mentioned above, these molecular matrices can be computed both for the heavy atom molecular structure *G*, or for the whole molecule *H*.

The graph vertex operators **VUinf(3M, *G*)**, **VVinf(3M, *G*)**, **VXinf(3M, *G*)**, and **VYinf(3M, *G*)** apply the information theory equations to the non-zero elements of the molecular matrix **3M** that correspond to an atom *i*:

$$\mathbf{VUinf(3M)}_i = -\sum_{\substack{j=1 \\ j \neq i}}^{N} \frac{[\mathbf{3M}]_{ij}}{\mathbf{AS(3M)}_i} \log_2 \frac{[\mathbf{3M}]_{ij}}{\mathbf{AS(3M)}_i} \tag{2}$$

$$\mathbf{VVinf(3M)}_i = \mathbf{AS(3M)}_i \log_2 \mathbf{AS(3M)}_i - \mathbf{VUinf(3M)}_i \tag{3}$$

$$\mathbf{VXinf(3M)}_i = \mathbf{AS(3M)}_i \log_2 \mathbf{AS(3M)}_i - \mathbf{VYinf(3M)}_i \tag{4}$$

$$\mathbf{VYinf(3M)}_i = \sum_{\substack{j=1 \\ j \neq i}}^{N} [\mathbf{3M}]_{ij} \log_2 [\mathbf{3M}]_{ij} \tag{5}$$

where $\mathbf{AS(M)}_i$ represents the atom sum of the atom *i*, and the summations in equations (2) and (5) are done for the non-zero elements of the molecular matrix **3M**, $[\mathbf{3M}]_{ij} \neq 0$. The atom sum operator of the atom *i*, $\mathbf{AS(3M)}_i$, of a molecular structure *G* or *H* with *N* atoms, is defined as the sum of the elements in the column *i*, or row *i*, of the molecular matrix **3M**:

$$\mathbf{AS(3M)}_i = \sum_{j=1}^{N} [\mathbf{3M}]_{ij} = \sum_{j=1}^{N} [\mathbf{3M}]_{ji} \tag{6}$$

For a general molecular matrix **3M** derived from three-dimensional molecular geometry, the matrix elements $[\mathbf{3M}]_{ij}$ may have values lower than 1, giving negative terms for certain vertes structural descriptors computed with the graph vertex operators **VUinf(3M)**, **VVinf(3M)**, **VXinf(3M)**, and **VYinf(3M)**. The Randić-like formula[32] used in the case of the indices *U*, *V*, *X*, and *Y* is therefore replaced by the following equation:

$$f(x,y) = \begin{cases} (xy)^{-1/2} & \text{if } xy > 0 \\ -(|xy|)^{-1/2} & \text{if } xy < 0 \end{cases} \tag{7}$$

The operators **U(3M)**, **V(3M)**, **X(3M)**, and **Y(3M)**, representing information on matrix elements, are computed with the equations:

$$\mathbf{U(3M)} = \frac{M}{\mu + 1} \sum_{\text{bonds}} f(\mathbf{VUinf(3M)}_i, \mathbf{VUinf(3M)}_j) \tag{8}$$

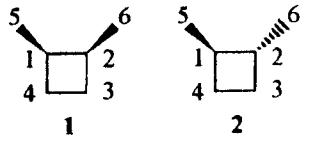
$$\mathbf{V(3M)} = \frac{M}{\mu + 1} \sum_{\text{bonds}} f(\mathbf{VVinf(3M)}_i, \mathbf{VVinf(3M)}_j) \tag{9}$$

$$\mathbf{X(3M)} = \frac{M}{\mu + 1} \sum_{\text{bonds}} f(\mathbf{VXinf(3M)}_i, \mathbf{VXinf(3M)}_j) \tag{10}$$

$$\mathbf{Y(3M)} = \frac{M}{\mu + 1} \sum_{\text{bonds}} f(\mathbf{VYinf(3M)}_i, \mathbf{VYinf(3M)}_j) \tag{11}$$

where *M* is the number of covalent bonds in the molecular structure *G* or *H*, μ is the cyclomatic number of *G* or *H*, i.e. the number of cycles in the graph, $\mu = M - N + 1$, and the summation goes over all bonds.

An example for the computation of the information operators **U(3M)**, **V(3M)**, **X(3M)**, and **Y(3M)** is presented for the molecular graph of *cis*-1,2-dimethylcyclobutane **1** and *trans*-1,2-dimethylcyclobutane **2**:



The geometry of the two isomers was optimized with the molecular mechanics method MM+ implemented in HyperChem.[33] The geometrical distance matrix of the carbon skeleton of *cis*-1,2-dimethylcyclobutane **1**,**3D**(**1**,*G*), is:

3D(1,*G*)

	1	2	3	4	5	6
1	0.000	1.563	2.205	1.559	1.543	2.648
2	1.563	0.000	1.559	2.205	2.648	1.543
3	2.205	1.559	0.000	1.556	3.370	2.598
4	1.559	2.205	1.556	0.000	2.598	3.370
5	1.543	2.648	3.370	2.598	0.000	2.962
6	2.648	1.543	2.598	3.370	2.962	0.000

The atom sum vector **AS** is computed with formula (6) as the sum of the elements in the column *i*, or row *i*, of the matrix **3D**:

$$\mathbf{AS(3D, 1)} = \{9.517, 9.517, 11.287, 11.287, 13.122, 13.122\}$$

The information-theory operators **VUinf(3D**,*G*), **VVinf(3D**,*G*), **VXinf(3D**,*G*), and **VYinf(3D**,*G*) are applied to the geometric distance matrix **3D** to compute with formulas (2–5) new atom invariants:

$$\mathbf{VUinf(3D,1)} = \{2.283, 2.283, 2.257, 2.257, 2.280, 2.280\}$$

$$\mathbf{VVinf(3D, 1)} = \{28.651, 28.651, 37.210, 37.210, 46.453, 46.453\}$$

$$\mathbf{VXinf(3D, 1)} = \{21.730, 21.730, 25.477, 25.477, 29.919, 29.919\}$$

$$\mathbf{VYinf(3D, 1)} = \{9.204, 9.204, 13.991, 13.991, 18.813, 18.813\}$$

The information on geometric distance matrix operators **U(3D)**, **V(3D)**, **X(3D)**, and **Y(3D)** are computed with equations (8–11) from the above vectors:

$$\mathbf{U(3D, 1)} = 7.916 \qquad \mathbf{V(3D, 1)} = 0.534$$

$$\mathbf{X(3D, 1)} = 0.746 \qquad \mathbf{Y(3D, 1)} = 1.525$$

The reciprocal geometric distance matrix **3RD** is computed with equation (1) to give for *cis*-1,2-dimethylcyclobutane **1** the matrix **3RD(1,*G*)**:

3RD(1,*G*)

	1	2	3	4	5	6
1	0.000	0.640	0.454	0.642	0.648	0.378
2	0.640	0.000	0.642	0.454	0.378	0.648
3	0.454	0.642	0.000	0.643	0.297	0.385
4	0.642	0.454	0.643	0.000	0.385	0.297
5	0.648	0.378	0.297	0.385	0.000	0.338
6	0.378	0.648	0.385	0.297	0.338	0.000

The reciprocal geometric distance matrix **3RD** is the basis for the computation of the information-theory atom operators **VUinf(3RD,*G*)**, **VVinf(3RD,*G*)**, **VXinf(3RD,*G*)** and **VYinf(3RD,*G*)** using the corresponding **AS** vector:

AS(3RD, 1) = {2.761, 2.761, 2.420, 2.420, 2.045, 2.045}

VUinf(3RD, 1) = {2.290, 2.290, 2.262, 2.262, 2.262, 2.262}

VVinf(3RD, 1) = {1.755, 1,755, 0.823, 0.823, –0.152, –0.152}

VXinf(3RD, 1) = {6.321, 6.321, 5.473, 5.473, 4.626, 4.626}

VYinf(3RD, 1) = {–2.276, –2.276, –2.388, –2.388, –2.515, –2.515}

The above vectors of atom invariants are utilized to compute the indices **U(3RD)**, **V(3RD)**, **X(3RD)**, and **Y(3RD)**:

U(3RD, 1) = 7.910 **V(3RD, 1)** = – 1.276

X(3RD, 1) = 3.152 **Y(3RD, 1)** = 7.655

The geometrical distance matrix of the carbon skeleton of *trans*-1,2-dimethylcyclobutane **2**, **3D(2,*G*)**, is:

3D(2,*G*)

	1	2	3	4	5	6
1	0.000	1.566	2.211	1.563	1.547	2.613
2	1.566	0.000	1.563	2.211	2.613	1.547
3	2.211	1.563	0.000	1.561	3.352	2.612
4	1.563	2.211	1.561	0.000	2.612	3.352
5	1.547	2.613	3.352	2.612	0.000	3.792
6	2.613	1.547	2.612	3.352	3.792	0.000

The information-theory operators **VUinf(3D,2)**, **VVinf(3D,2)**, **VXinf(3D,2)**, and **VYinf(3D,2)** are computed from the **AS(3D,2)** vector:

AS(3D, 2) = {9.500, 9.500, 11.300, 11.300, 13.916, 13.916}

VUinf(3D, 2) = {2.285, 2.285, 2.258, 2.258, 2.264, 2.264}

VVinf(3D, 2) = {28.568, 28.568, 37.272, 37.272, 50.596, 50.596}

VXinf(3D,2) = {21.708, 21.708, 25.520, 25.520, 31.507, 31.507}

VYinf(3D, 2) = {9.145, 9.145, 14.010, 14.010, 21.353, 21.353}

The information on geometric distance matrix operators **U(3D)**, **V(3D)**, **X(3D)**, and **Y(3D)** computed with the above vectors are:

U(3D, 2) = 7.920 **V(3D, 2)** = 0.527

X(3D, 2) = 0.740 **Y(3D, 2)** = 1.502

Using equation (1) one obtains the reciprocal geometric distance matrix **3RD** for *trans*-1,2-dimethylcyclobutane **2**:

3RD(2,*G*)

	1	2	3	4	5	6
1	0.000	0.639	0.452	0.640	0.647	0.383
2	0.639	0.000	0.640	0.452	0.383	0.647
3	0.452	0.640	0.000	0.640	0.298	0.383
4	0.640	0.452	0.640	0.000	0.383	0.298
5	0.647	0.383	0.298	0.383	0.000	0.264
6	0.383	0.647	0.383	0.298	0.264	0.000

The above reciprocal geometric distance matrix **3RD** gives the vectors **AS(3RD, 2)**, **VUinf(3RD, 2)**, **VVinf(3RD, 2)**, **VXinf(3RD, 2)**, and **VYinf(3RD, 2)**:

AS(3RD, 2) = {2.760, 2.760, 2.413, 2.413, 1.974, 1.974}

VUinf(3RD, 2) = {2.291, 2.291, 2.263, 2.263, 2.245, 2.245}

VVinf(3RD, 2) = {1.751, 1.751, 0.805, –0.308, –0.308}

VXinf(3RD, 2) = {6.322, 6.322, 5.461, 5.461, 4.432, 4.432}

VYinf(3RD, 2) = {–2.280, –2.280, –2.393, –2.393, –2.495, –2.495}

The above vectors of atom invariants are utilized to compute the indices **U(3RD)**, **V(3RD)**, **X(3RD)**, and **Y(3RD)**:

U(3RD, 2) = 7.917 **V(3RD, 2)** = 2.320

X(3RD, 2) = 3.178 **Y(3RD, 2)** = 7.653

On comparing the above results it can be seen that:

(1) With the exception of index **V(3R)** and **V(3RD)**, the topographic indices are surprisingly similar for one and the same compound when based either on the **D** or on the **RD** matrix.

(2) Whereas index **U(3R)** or **U(3RD)** does not discriminate markedly pairs of diastereoisomers, the three remaining topographic indices are quite different for diastereomeric pairs.

The extension of the **U**, **V**, **X**, and **Y** operators to molecular matrices derived from three-dimensional molecular geometry offers four new families of structural descriptors for QSPR and QSAR models. In the following section we present an application of the **U(3M)**, **V(3M)**, **X(3M)**, and **Y(3M)** descriptors to a quantitative structure-retention relationship model for alkylphenols in gas-liquid chromatography.

MODELING THE ALKYLPHENOLS RETENTION INDICES

The identification of organic compounds from a mixture can be made with the method of chromatographic peak comparison with a standard sample of each compound. Because samples of pure compounds are not always available it is important to develop quantitative structure-retention relationships (QSRR) that can efficiently predict retention parameters by using theoretical descriptors computed from the chemical structure. Chromatographic retention is a physical phenomenon that is primarily dependent on the interactions between the solute and the stationary phase. With the aid of QSRR the interactions associated with this phenomenon can be related to the constitutional, molecular graph (topological), geometric, electrostatic, and quantum descriptors of the molecules. In the present study we will develop QSRR models for alkylphenols in gas-liquid chromatography with the aid of topological indices. The retention indices of 50 alkylphenols were determined on a column packed with 5% hexaphenyl ether on Chromatone N AW HMDS (0.16–0.20 mm) at 160°C.[34] In a previous QSRR study of this set of 50 phenols we have obtained the following biparametric model:[35]

$$RI = 1132.209 + 169.274\,{}^{3}\chi_{p}^{v} + 0.9137\,Sz(P) \qquad (12)$$

$$n = 50\ r = 0.9528\ s = 38.08\ F = 231.68$$

where ${}^{3}\chi_{p}^{v}$ is a Kier and Hall connectivity index[2,3] and $Sz(P)$ is the Szeged index computed with the weighting scheme P.[36]

The list of the 14 structural description used in the QSRR study is presented below:

(1) the molecular weight, **MW;**

(2) the Kier and Hall connectivity indices: ${}^{0}\chi^{v}$, ${}^{1}\chi^{v}$, ${}^{2}\chi^{v}$, ${}^{3}\chi_{p}^{v}$, ${}^{3}\chi_{c}^{v}$;[2,3]

(3) the information indices derived from the geometrical distance matrix: **U(3D)**, **V(3D)**, **X(3D)**, and **Y(3D)**;

(4) the information indices derived from the reciprocal geometrical distance matrix: **U(3RD)**, **V(3RD)**, **X(3RD)**, and **Y(3RD)**.

In Table 1 we present the statistical indices (r, correlation coefficient, s, standard deviation, and F, Fisher test) for all monoparametric regression equations for the 14 structural descriptors. The best

Table 1

Structural descriptor (**SD**) and statistical indices for the MLR equations with one independent variable established for the computation of the retention indices of the 50 alkylphenols from ref. 34

SD	r	s	F
MW	0.9322	44.93	318.59
${}^{0}\chi^{v}$	0.9442	40.89	394.51
${}^{1}\chi^{v}$	0.8996	54.22	203.71
${}^{2}\chi^{v}$	0.9189	48.98	260.48
${}^{3}\chi_{p}^{v}$	0.9065	52.42	221.27
${}^{3}\chi_{c}^{v}$	0.2429	120.44	3.01
U(3D)	0.9253	47.08	285.77
V(3D)	-0.6857	90.37	42.61
X(3D)	-0.6958	89.18	45.04
Y(3D)	-0.6291	96.51	31.44
U(3RD)	0.9249	47.19	284.23
V(3RD)	-0.1407	122.92	0.97
X(3RD)	0.8569	64.00	132.68
Y(3RD)	0.9218	48.13	271.46

results are obtained with the connectivity index $^0\chi^v$, followed by the molecular weight: $^0\chi^v$, $r = 0.9442$, $s = 40.89$, F = 394.51; **MW**, $r = 0.9322$, $s = 44.93$, F = 318.59. The QSRR model can be improved by using biparametric multilinear regression (MLR) equations. The best five such equations are presented in Table 2.

Table 2

Coefficients, structural descriptors, and statistical indices for the best MLR equations with two independent variables that model the retention indices of the 50 alkylphenols from ref. 34. The MLR equations have the general form:

$$RI = a_0 + a_1\mathbf{SD}_1 + a_2\mathbf{SD}_2$$

a_0	a_1	$\mathbf{SD}_1$	a_2	$\mathbf{SD}_2$	r	s	F
1662.97	233.946	$^3\chi_p^v$	-767.255	**X(3D)**	0.9566	36.55	253.46
1517.99	235.799	$^3\chi_p^v$	-806.444	**V(3D)**	0.9561	36.77	250.15
1401.95	245.301	$^3\chi_p^v$	-200.000	**Y(3D)**	0.9560	36.82	249.34
923.32	189.056	$^3\chi_p^v$	71.603	**X(3RD)**	0.9551	37.16	244.38
840.67	117.660	$^0\chi^v$	-2.3560	**V(3RD)**	0.9522	38.31	228.57

The best equation from Table 2, with $r = 0.9566$, $s = 36.55$, and F = 253.46, contains the connectivity index $^3\chi_p^v$ and the information index **X(3D)**; this QSRR model is slightly better than that obtained with the Szeged index, in the MLR presented in Eq. (12). The connectivity index $^3\chi_p^v$ is a measure of molecular branching and is a weighted sum of the linear subgraphs containing four atoms. It is obvious that this index is important in biparametric models, because it appears in the first four equations from Table 2. All equations in Table 2 contain a connectivity index and an information index computed from geometrical matrices. The results obtained here show that the **U(3M)**, **V(3M)**, **X(3M)**, and **Y(3M)** descriptors offer good QSRR models for the phenols retention indices. The QSRR models with three independent parameters do not show a significant increase in r, indicating that new descriptors would be needed in order to improve the structure-retention model for alkylphenols.

CONCLUSIONS

Initially, the *U*, *V*, *X*, and indices were computed from the graph distance matrix; in this paper we have used their mathematical formulas to define new structural descriptors computed with molecular matrices derived from three-dimensional molecular geometry. The new information-theory operators **U(3M)**, **V(3M)**, **X(3M)**, and **Y(3M)** can be used to generate families of structural descriptors directly from the molecular geometry. Using only the constitutional (connectivity) information contained in the molecular graph, topological indices are not able to discriminate between *cis/trans* (*E/Z*) or other types of stereoisomers. The descriptors computed from the molecular three-dimensional structure discriminate such diastereoisomers, and this is a clear advantage of the descriptors defined in this paper. Structural descriptors computed with the operators **U(3M)**, **V(3M)**, **X(3M)**, and **Y(3M)** were used with success in a quantitative structure-retention relationship model for 50 alkylphenols in gas-liquid chromatography.

ACKNOWLEDGMENT. We acknowledge the partial financial support of this research by the Roumanian Ministry of National Education under Grant 7001 T34.

REFERENCES

1. Part 20: O. Ivanciuc and A. T. Balaban, *Rev. Roum. Chim.*, **1999**, *44*, 479–489.
2. L. B. Kier and L. H. Hall, "Molecular Connectivity in Chemistry and Drug Research", Academic Press, New York, **1976**.
3. L. B. Kier and L. H. Hall, "Molecular Connectivity in Structure-Activity Analysis", Research Studies Press, Letchworth, **1986**.
4. M. V. Diudea and O. Ivanciuc, "Molecular Topology", Comprex, Cluj, Romania, **1995**.

5. O. Ivanciuc and A. T. Balaban, Graph Theory in Chemistry. In: "The Encyclopedia of Computational Chemistry", Eds.: P. v. R. Schleyer, N. L. Allinger, T. Clark, J. Gasteiger, P. A. Kollman, H. F. Schaefer III, and P. R. Schreiner. John Wiley & Sons, Chichester, **1998**, pp. 1169–1190.
6. A. T. Balaban and O. Ivanciuc, Historical Development of Topological Indices. In: "Topological Indices and Related Descriptors in QSAR and QSPR", Eds.: J. Devillers and A. T. Balaban. Gordon and Breach Science Publishers, The Netherlands, **1999**, pp. 21–57.
7. O. Ivanciuc and A. T. Balaban, The Graph Description of Chemical Structures. In: "Topological Indices and Related Descriptors in QSAR and QSPR", Eds.: J. Devillers and A. T. Balaban. Gordon and Breach Science Publishers, The Netherlands, **1999**, pp. 59–167.
8. O. Ivanciuc, T. Ivanciuc, and A. T. Balaban, Vertex- and Edge-Weighted Molecular Graphs and Derived Structural Descriptors. In: "Topological Indices and Related Descriptors in QSAR and QSPR", Eds.: J. Devillers and A. T. Balaban. Gordon and Breach Science Publishers, The Netherlands, **1999**, pp. 169–220.
9. O. Ivanciuc and T. Ivanciuc, Matrices and Structural Descriptors Computed from Molecular Graph Distances. In: "Topological Indices and Related Descriptors in QSAR and QSPR", Eds.: J. Devillers and A. T. Balaban. Gordon and Breach Science Publishers, The Netherlands, **1999**, pp. 221–277.
10. A. T. Balaban, I. Moţoc, D. Bonchev, and O. Mekenyan, *Top. Curr. Chem.*, **1983,** *114*, 21–55.
11. A. T. Balaban, *J. Chem. Inf. Comput. Sci.*, **1992,** *32*, 23–28.
12. A. T. Balaban, *J. Chem. Inf. Comput. Sci.*, **1994,** *34*, 398–402.
13. A. T. Balaban, *Rev. Roum. Chim.*, **1994,** *39*, 245–257.
14. A. T. Balaban, *SAR QSAR Environ. Res.*, **1995,** *3*, 81–95.
15. O. Ivanciuc, T. Ivanciuc, and M. V. Diudea, *SAR QSAR Environ. Res.*, **1997,** *7*, 63–87.
16. A. T. Balaban (Ed.), "From Chemical Topology to Three-Dimensional Geometry", Plenum, New York, **1997**.
17. M. Randić, *Int. J. Quantum Chem.: Quantum Biol. Symp.*, **1988,** *15*, 201–208; M. Randić, Molecular topographic descriptors, in "MATH/CHEM/COMP 1987", Proceedings of an International Course and Conference on the Interfaces between Mathematics, Chemistry and Computer Science, Dubrovnik, Yugoslavia, 22–26 June 1987 (R. C. Lacher, Ed.). Elsevier, Amsterdam, 1988, pp. 101–108.
18. B. Bogdanov, S. Nikolić, and N. Trinajstić, *J. Math. Chem.*, **1989,** *3*, 299–309.
19. M. Randić, B. Jerman-Blazić, and N. Trinajstić, *Comput. Chem.*, **1990,** *14*, 237–246.
20. B. Bogdanov, S. Nikolić, and N. Trinajstić, *J. Math. Chem.*, **1990,** *5*, 305–306.
21. S. Nikolić, N. Trinajstić, Z. Mihalić, and A. Carter, *Chem. Phys. Lett.*, **1991,** *179*, 21–28.
22. Z. Mihalić, and N. Trinajstić, *J. Mol. Struct. (Theochem)*, **1991,** *232*, 65–78.
23. P. Tvaruzek, and J. Komenda, *Coll. Czech. Chem. Commun.*, **1991,** *56*, 253–257.
24. M. V. Diudea, D. Horvath, and A. Graovac, *J. Chem. Inf. Comput. Sci.*, **1995,** *35*, 129–135.
25. M. Randić, and M. Razinger, *J. Chem. Inf. Comput. Sci.*, **1995,** *35*, 140–147.
26. M. Randić, *New J. Chem.*, **1995,** *19*, 781–791.
27. A. T. Balaban and T. S. Balaban, *J. Math. Chem.*, **1991,** *8*, 383–397.
28. A. T. Balaban and T. S. Balaban, *J. Chim. Phys.*, **1992,** *89*, 1735–1745.
29. A. T. Balaban and V. Feroiu, *Rep. Mol. Theor.*, **1990,** *1*, 133–139.
30. O. Ivanciuc, T. S. Balaban, and A. T. Balaban, *J. Math. Chem.*, **1993,** *14*, 21–33.
31. O. Ivanciuc, T. Laidboeur, and D. Cabrol-Bass, *J. Chem. Inf. Comput. Sci.*, **1997,** *37*, 485–488.
32. M. Randić, *J. Am. Chem. Soc.*, **1975,** *97*, 6609–6615.
33. HyperChem 5.1, Hypercube, Inc., Florida Science and Technology Park, 1115 N.W. 4th Sreet Gainesville, Florida 32601, U.S.A., Voice: 352–371–7744, Fax: 352–371–3662, Email info@hyper.com, www http://www.hyper.com.
34. P. Buryan, V. M. Nabivach, and V. P. Dimitrikov, *J. Chromatogr.*, **1990,** *509*, 3–14.
35. Part. 15: O. Ivanciuc, *Rev. Roum. Chim.*, **2000,** *45*, 000–000.
36. Part 12: O. Ivanciuc, *Rev. Roum. Chim.*, **2000,** *45*,000–000.