

Novel local (fragment-based) topological molecular descriptors for QSPR/QSAR and molecular design

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Dedicated to M. Randić, L.B. Kier and L.H. Hall for the development and application of the molecular connectivity index during its first 25 years.

Abstract

Novel molecular descriptors based on local spectral moments of the bond matrix are defined. Mathematical expressions relating bond moments to linear combinations of structural fragments are derived. The novel descriptors are used to describe boiling points of alcohols producing a good QSPR model accounting for more than 98% of variance. A quantitative structure–reactivity model is obtained to predict the specific rate constant ($\log k$) of the nucleophilic addition of mercaptoacetic acid to 2-furylethylene derivatives. The model accounts for more than 96% of the variance in $\log k$. Two other models were also obtained by using molecular connectivity indices and total spectral moments of the bond matrix that account for <84% of the variance in this reactivity index. A model based on quantum chemical descriptors accounts for the same variance than that obtained with bond moments. The model based on local moments permitted to compute the contribution of different structural fragments to the reactivity, and a good relationship ($r = 0.98$) was obtained with these group contributions with Hammett σ_p constants for 21 groups. © 2001 Elsevier Science Inc. All rights reserved.

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1. Introduction

Molecular descriptors play an important role in the quantitative description of molecular structure to find appropriate predictive models. Molecular descriptors are “terms that characterize a specific aspect of a molecule” [1] and can be classified as “global” and “local” according to the way in which they characterize the molecular structure. The so-called topological indices (TIs) are among the most useful molecular descriptors known nowadays [2–5]. These descriptors are “numerical values associated with chemical constitution for correlation of chemical structure with various physical properties, chemical reactivity or biological activity” [1]. The history of these molecular descriptors started more than 50 years ago with the introduction of the so-called Wiener index [6,7]. However, it was the definition and applications of the molecular connectivity indices 25 years ago that marked a step forward in the study of such descriptors [8–10]. Most of TIs known today can be considered as global molecular descriptors. It means that TIs characterize the molecule as a whole describing the branching

or shape of the entire structure. One exception in this sense is the index of electrotopological state (E-state) [11,12]. This index is computed for each atom in the molecule characterizing its electronic and topological environment. So, it can be considered as a local molecular descriptor. The great success of the E-state index in QSPR/QSAR and drug discovery stimulated us to propose here some novel local descriptors based on a topological characterization of the molecular structure.

The necessity of deriving novel molecular descriptors can be understood by considering the recent advances in drug discovery technologies that promise to accelerate the process of lead discovery and optimization. Pharmacogenomics [13], combinatorial chemistry [14,15] and high-throughput screening [16] permit to obtain and evaluate thousand of compounds in a short time. These technologies have produced new challenges for computational scientists, as they demand novel approaches to the computer-aided lead discovery and optimization in an accelerated way [17]. Consequently, molecular diversity and rational combinatorial library design [18], virtual screening [19] and computer-aided drug design [20] have emerged as important points of attention in drug discovery researches. The traditional quantitative structure–activity relationships (QSAR)

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[21,22] approaches as well as the novel 3D-QSAR techniques [23] have not only been applied for improving the biological activity of leads but also to improve their physicochemical, pharmacokinetic and toxicological properties [24–26].

The strategy that we will follow here is based on the calculation of local spectral moments of the bond matrix. Spectral moments of bond matrix have been used as the basis of our approach to molecular design named TOSS-MODE (topological sub-structural molecular design) [27–30]. This approach has been successfully applied to virtual screenings and rational designs of sedative/hypnotic [31], anticancer [32] and anticonvulsant [33] compounds, as well as to different QSPR and QSAR studies [34–37], including the modeling of 3D structure of small/medium sized molecules and proteins [38] and toxicological properties [39]. Here this approach will be extended to account for local structural characteristics of molecules in an explicit way and some examples of applications will be analyzed.

2. Theoretical approach

The current approach is based on the calculation of local spectral moments of the bond matrix. The bond matrix is a square and symmetric matrix whose elements e_{ij} are ones or zeros depending if the corresponding bonds i and j in the molecule are adjacent or not [40–42]. Two bonds are adjacent if they are incident to the same atom. When heteroatoms are explicitly considered, the diagonal entries of the bond matrix are values characterizing different properties of the chemical bonds. For instance, bond distances, standard bond dipole moments, standard bond polarizabilities and several other bond weights have been used in the context of the TOSS-MODE approach [27–39]. The total spectral moments of the bond matrix are defined as [27–30]

$$\mu_k = \text{Tr}(B^k) = \sum_{i=1}^s (e_{ii})^k \quad (1)$$

where Tr means the trace of the matrix, that is the sum of the diagonal entries of the matrix and the elements $(e_{ii})^k$ are the diagonal entries of the k th power of the bond matrix.

Local spectral moments are defined as the sum of diagonal entries of the different powers of the bond matrix corresponding to a given molecular fragment. In mathematical terms, local spectral moments of the bond matrix are defined as follows:

$$\mu_k(f) = \sum_{i=1}^f (e_{ii})^k \quad (2)$$

where f is the corresponding fragment for which the moments are defined and the sum is carried out over all bonds forming the fragment f . The simplest case is when f corresponds to a single bond, and in this case the k th local moment is defined as the diagonal entry corresponding to this bond in the matrix raised to the k th power.

In previous papers on the TOSS-MODE approach, we have shown that the spectral moments of the bond matrix can be expressed as linear combinations of the different fragments of the molecule [27–39]. Similarly, local moments of a fragment can be expressed in terms of substructures of different sizes containing the corresponding fragment. The simplest case is that of spectral moments defined for bonds in the molecule without considering heteroatoms in the molecule. In this case, the bond moments, $\mu_k(B)$, are expressed in terms of structural fragments through the following expressions:

$$\mu_2(B) = |F_2(B)| \quad (3)$$

$$\mu_3(B) = 2|F_3(B)| \quad (4)$$

$$\mu_4(B) = |F_2(B)| + 4|F_3(B)| + 6|F_4(B)| + |F_5^1(B)| + 2|F_5^2(B)| \quad (5)$$

$$\mu_5(B) = 10|F_3(B)| + 30|F_4(B)| + 2|F_6^1(B)| + 4|F_6^2(B)| + 2|F_6^3(B)| \quad (6)$$

$$\mu_6(i) = |F_2(i)| + 20|F_3(i)| + 120|F_4(i)| + 3|F_5^1(i)| + 6|F_5^2(i)| + 5|F_6^1(i)| + 10|F_6^2(i)| + 4|F_6^3(i)| + |F_7^1(i)| + 2|F_7^2(i)| + 6|F_8^1(i)| + 12|F_8^2(i)| + 6|F_8^3(i)| + 4|F_9^1(i)| + 8|F_9^2(i)| \quad (7)$$

$$\mu_7(B) = 42|F_3(B)| + 420|F_4(B)| + 18|F_6^1(B)| + 34|F_6^2(B)| + 14|F_6^3(B)| + 36|F_8^1(B)| + 72|F_8^2(B)| + 30|F_8^3(B)| + 18|F_9^1(B)| + 40|F_9^2(B)| + 2|F_{10}^1(B)| + 4|F_{10}^2(B)| + 4|F_{10}^3(B)| + 2|F_{10}^4(B)| + 2|F_{11}^1(B)| + 4|F_{11}^2(B)| + 2|F_{11}^3(B)| + 12|F_{12}^1(B)| + 24|F_{12}^2(B)| + 12|F_{12}^3(B)| \quad (8)$$

$$\mu_8(B) = |F_2(B)| + 84|F_3(B)| + 1386|F_4(B)| + 7|F_5^1(B)| + 14|F_5^2(B)| + 44|F_6^1(B)| + 82|F_6^2(B)| + 30|F_6^3(B)| + 5|F_7^1(B)| + 11|F_7^2(B)| + 178|F_8^1(B)| + 342|F_8^2(B)| + 132|F_8^3(B)| + 74|F_9^1(B)| + 168|F_9^2(B)| + 5|F_{10}^1(B)| + 10|F_{10}^2(B)| + 8|F_{10}^3(B)| + 4|F_{10}^4(B)| + 5|F_{11}^1(B)| + 12|F_{11}^2(B)| + 6|F_{11}^3(B)| + 96|F_{12}^1(B)| + 204|F_{12}^2(B)| + 90|F_{12}^3(B)| + |F_{13}^1(B)| + 2|F_{13}^2(B)| + 2|F_{13}^3(B)| + 6|F_{14}^1(B)| + 12|F_{14}^2(B)| + 12|F_{14}^3(B)| + 6|F_{14}^4(B)| + 6|F_{15}^1(B)| + 12|F_{15}^2(B)| + 6|F_{15}^3(B)| + 4|F_{16}^1(B)| + 8|F_{16}^2(B)| + 4|F_{16}^3(B)| + 8|F_{16}^4(B)| + 4|F_{16}^5(B)| + 4|F_{17}^1(B)| + 8|F_{17}^2(B)| + 36|F_{18}^1(B)| + 72|F_{18}^2(B)| \quad (9)$$

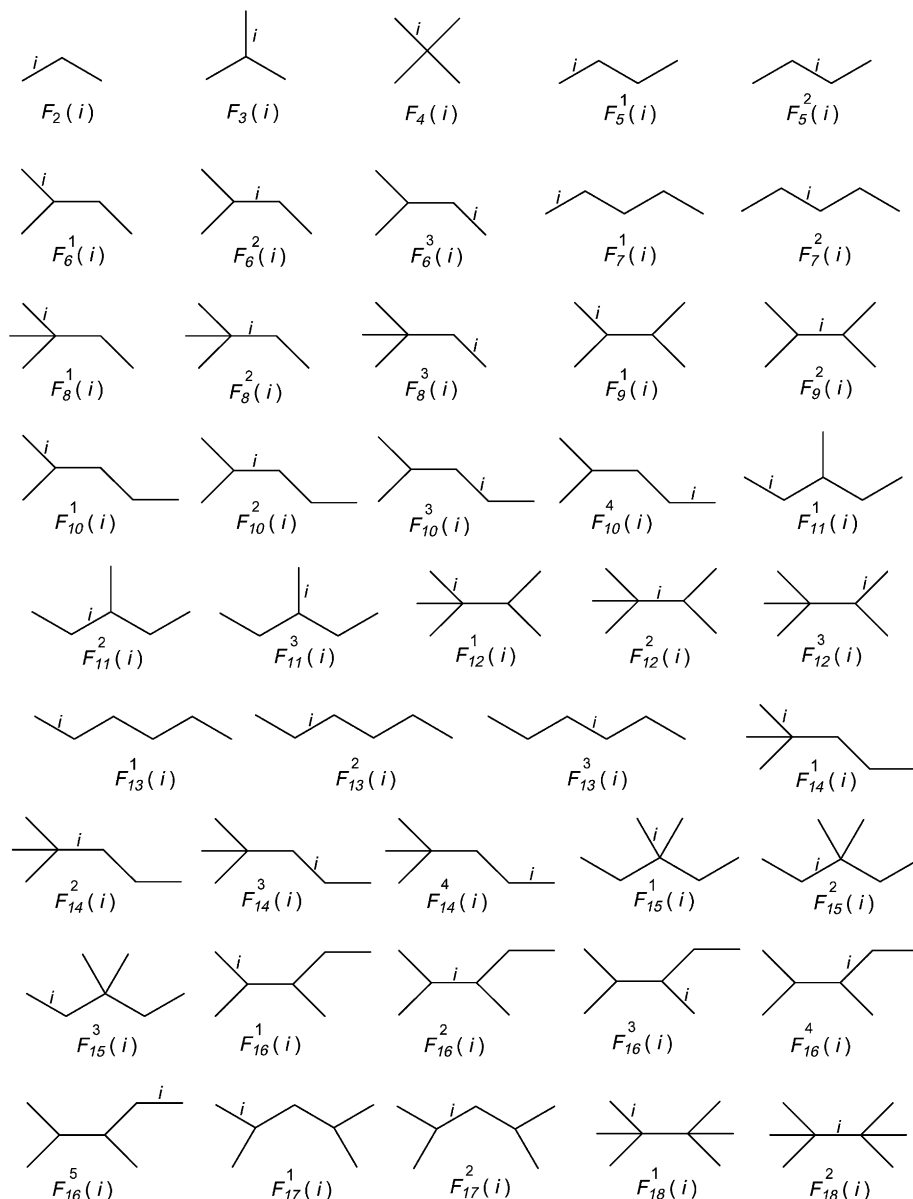


Fig. 1. Contributions of different structural fragments to bond local moments of molecules with no consideration of heteroatoms.

where the terms $F_p^q(f)$ represent subgraphs of type p , sub-type q , containing the fragment f (given in Fig. 1), and the vertical bars mean the number of such subgraphs.

When heteroatoms are explicitly considered by using weights in the diagonal entries of the bond matrix the derivation of similar expressions is more complicated. It is due to the combinatorial explosion in the number of fragments that appears with different heteroatoms in the molecule. For instance, the mathematical expressions relating the bond spectral moments up to order 3 to the weights used in the diagonal entries of the bond matrix are given as follows:

$$\mu_1(i) = d_i \quad (10)$$

$$\mu_2(i) = 2|F_2(i)| + d_i \quad (11)$$

$$\mu_3(i) = 2|F_3(i)| + (d_i)^3 + |F_2(i, j)|(2d_i + d_j) \quad (12)$$

where d_i is the weight used in the diagonal entry of the bond matrix corresponding to bond i . The term $|F_k(i)|$ represents the number of fragments of type F_k in which the bond i is included and the term $|F_2(i, j)|$ means the number of fragments F_2 containing bond i adjacent to a bond j . Instead of using these expressions, we have elaborated a computational strategy that permits to compute automatically the contribution of any structural fragment to the local spectral moments desired [43]. The application of this approach is as follows. Suppose that we are interested in calculating the contribution of a substructure s containing the fragment f in its structure for which local moments were computed. For instance, if we are computing bond moments of a given

bond in a molecule, f will be the corresponding bond and s will be any fragment of interest containing this bond, e.g. a $F_3(i)$ fragment. So, our computational strategy consists in calculating the local spectral moments of this substructure s as well as of all subgraphs contained in it. In the example analyzed we have to compute the local moments of $F_3(i)$ as well as those of $F_2(i)$ and $F_1(i)$, i.e. the corresponding bond. Now, the contribution of $F_3(i)$ to the local spectral moments is obtained as the difference of the moments of $F_3(i)$ less the moments of the subgraphs contained in it.

The magnitude of the local spectral moments increases as the order of the moment increases as a consequence of the greater amount of structural information contained in higher order moments. For instance, the local moment of order 7 contains information about 20 structural fragments (see Eq. (8)). However, the moment of order 8 contains information on 44 fragments, which will dramatically increase its numerical value respect to the previous one. This increment is exponential in the order of the moment not showing oscillations as the order of the moment increases. These values do not increase in a chaotic way but they have well-defined lower and upper bounds. If we consider a series of graphs having the same number of edges, the lower and upper bounds for the spectral moments will be given by the corresponding moments of the path and star, respectively. Thus, if we consider the local moments of C–O bond of alcohols having four bonds, we will observe an exponential increment of the indices as the order of the moment increases. However, the maximal value obtained for any higher order local moment will be for the *tert*-butyl alcohol (star graph) and the minimal one for the *n*-butyl alcohol (path graph). An illustration of this behavior of local moments is given in Fig. 2.

3. General approach to QSPR/QSAR

In applying the current approach to QSPR/QSAR studies, the following series of steps are carried out:

1. draw the hydrogen-depleted molecular graphs for each molecule in the data set;
2. use appropriated bond weights in order to differentiate the molecular bonds;
3. compute the local (bond or fragment) spectral moments of the bond matrix with the appropriated weights for each molecule in the training data set generating a table in which the rows correspond to molecules in the data set and columns correspond to the local spectral moments of the bond matrix;
4. find a QSPR/QSAR model by using linear regression analysis (LRA)

$$P = a_0\mu_0(i) + a_1\mu_1(i) + a_2\mu_2(i) + a_3\mu_3(i) + \dots + b$$

where P is the physicochemical or biological property, $\mu_k(i)$ the k th local spectral moment of fragment i , and the a_k 's are the coefficients obtained by the LRA;

5. test the predictive capacity of the QSPR/QSAR model by using cross-validation techniques;
6. compute the contribution to the local moments of the different fragments or groups of interest (expressions like Eqs. (3)–(12)) and substitute them in the QSPR/QSAR model obtained to generate quantitative contributions of these fragments to the property P under study.

4. Describing physical properties

As a starting point for analyzing the novel descriptors in QSPR/QSAR studies we will consider a data set of alcohols

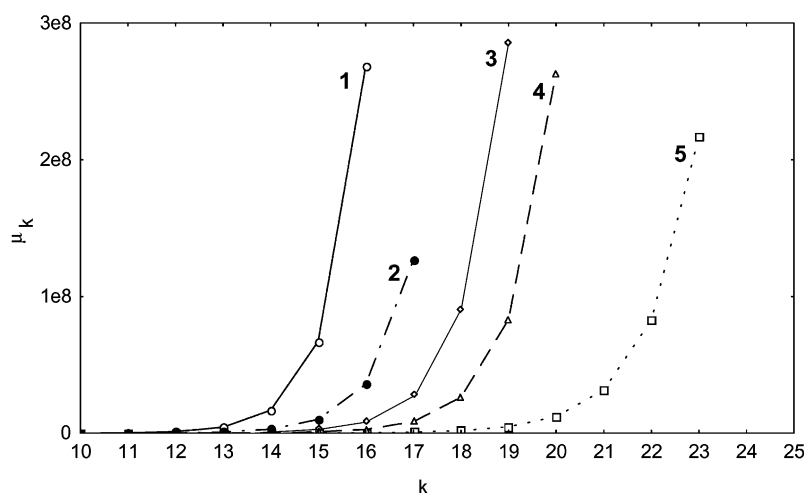


Fig. 2. Behavior of higher order local moments (order 10–25) of the bond C–O of five alcohols having four bonds: *tert*-butyl alcohol (1); cyclopropyl alcohol (2); *sec*-butyl alcohol (3); *iso*-butyl alcohol (4); *n*-butyl alcohol (5). Observe that lower and upper bounds correspond to path (*n*-butyl alcohol) and star (*tert*-butyl alcohol), respectively.

Table 1

Experimental and calculated values of the boiling points of alcohols used in this study

Alcohol–R	BP (°C)	Calculated BP (°C)	Residual
(CH ₃) ₂ CH–	82.3	82.9	–0.6
CH ₃ CH ₂ CH ₂ –	97.2	96.0	1.2
CH ₃ (CH ₂) ₃ –	117.7	115.2	2.5
CH ₃ CH(CH ₃)CH ₂ –	107.8	108.0	–0.2
CH ₃ CH ₂ C(CH ₃) ₂ –	102.4	105.4	–3.0
CH ₃ CH ₂ CH ₂ CH(CH ₃)–	119.3	114.4	4.9
CH ₃ CH(CH ₃)CH ₂ CH ₂ –	131.1	134.5	–3.4
CH ₃ CH ₂ CH(CH ₃)CH ₂ –	128.0	127.3	0.7
CH ₃ (CH ₂) ₄ –	137.9	134.3	3.6
CH ₃ C(CH ₃) ₂ CH(CH ₃)–	120.4	129.3	–8.9
CH ₃ (CH ₂) ₂ C(CH ₃) ₂ –	121.1	124.9	–3.8
(CH ₃ CH ₂) ₂ C(CH ₃)–	122.4	121.9	0.5
CH ₃ CH ₂ C(CH ₃) ₂ CH ₂ –	136.5	142.5	–6.0
CH ₃ CH(CH ₃)CH ₂ CH(CH ₃)–	131.6	133.9	–2.3
CH ₃ CH(CH ₃)CH(CH ₃)CH ₂ –	126.5	121.9	4.6
CH ₃ CH(CH ₃)CH(CH ₃)CH ₂ –	144.5	146.7	–2.2
CH ₃ CH ₂ CH ₂ CH(CH ₃)CH ₂ –	149.0	146.4	2.6
CH ₃ (CH ₂) ₅ –	157.6	153.4	4.2
(CH ₃ CH(CH ₃)) ₂ CH–	138.7	136.4	2.3
CH ₃ CH(CH ₃)CH ₂ CH(CH ₃)CH ₂ –	159.0	165.5	–6.5
(CH ₃ CH ₂) ₃ C–	142.0	138.6	3.4
CH ₃ (CH ₂) ₆ –	176.4	172.5	3.9
(CH ₃ CH ₂ CH ₂) ₂ (CH ₃)C–	161.0	160.9	0.1
(CH ₃ CH ₂) ₃ (CH ₃ CH ₂)(CH ₃)C–	163.0	160.5	2.5
CH ₃ CH(CH ₃)CH ₂ (CH ₂) ₄ –	188.0	191.6	–3.6
CH ₃ (CH ₂) ₇ –	195.1	191.6	3.5
CH ₃ (CH ₂) ₅ C(CH ₃)–	178.0	182.2	–4.2
(CH ₃ CH ₂ CH ₂) ₂ (CH ₃ CH ₂)C–	182.0	177.6	4.4

previously studied by Kier and Hall by using the E-state index [12]. This data set is composed by 28 alcohols, 14 of them are primary, 6 secondary, and 8 tertiary. These authors derived a QSPR model to describe the boiling point (BP) of such compounds by using E-state and bimolecular encounter parameters, which explains more than 92% of the variance in the experimental values of BP with a standard deviation of 5.8°C. The data set of compounds is given in Table 1. We detected some typographic errors for structures and BP values given in the table published in [12] that were corrected in Table 1.

We have computed the spectral moments of order 2–8 for the C–O bond of these alcohols, $\mu_k(\text{C–O})$, $k = 2$ –8, and use them to describe their BPs. The best QSPR model obtained by using these descriptors and the number of carbon atoms, N , in the molecule is given as follows:

$$\begin{aligned} \text{BP (}^\circ\text{C)} = & 19.093N - 42.428\mu_2(\text{C–O}) + 29.451\mu_3(\text{C–O}) \\ & - 7.755\mu_4(\text{C–O}) + 0.018\mu_8(\text{C–O}) + 96.555, \\ N = 28, \quad r^2 = 0.982, \quad s = 4.2, \quad F = 23.8 \end{aligned} \quad (13)$$

As can be seen, this model explains more than 98% of the variance in the experimental values of BP for these alcohols. However, the main advance of using this approach to

QSPR/QSAR studies is the possibility of calculating the contribution of all different fragments to the property studied. By using expressions (3)–(9) for local spectral moments in terms of fragments we can obtain an expression that directly relates BP with the molecular structure of alcohols. This expression is simply obtained by substituting Eqs. (3)–(9) into the QSPR model for BP. By using this expression we can analyze the influence that any substructure has on the property studied as well as to compute this property in terms of an additive function. The resulting model, which has the same statistical parameters as model (13), is given as follows:

$$\begin{aligned} \text{BP (}^\circ\text{C)} = & 19.093N - 50.165|F_2(\text{C–O})| \\ & + 29.394|F_3(\text{C–O})| - 21.582|F_4(\text{C–O})| \\ & - 7.629|F_5^1(\text{C–O})| - 15.258|F_5^2(\text{C–O})| \\ & + 0.792|F_6^1(\text{C–O})| + 1.476|F_6^2(\text{C–O})| \\ & + 0.54|F_6^3(\text{C–O})| + 0.09|F_7^1(\text{C–O})| \\ & + 0.198|F_7^2(\text{C–O})| + 3.204|F_8^1(\text{C–O})| \\ & + 6.156|F_8^2(\text{C–O})| + 2.367|F_8^3(\text{C–O})| \\ & + 1.332|F_9^1(\text{C–O})| + 3.024|F_9^2(\text{C–O})| \\ & + 0.09|F_{10}^1(\text{C–O})| + 0.18|F_{10}^2(\text{C–O})| \\ & + 0.144|F_{10}^3(\text{C–O})| + 0.072|F_{10}^4(\text{C–O})| \\ & + 0.09|F_{11}^1(\text{C–O})| + 0.216|F_{11}^2(\text{C–O})| \\ & + 0.108|F_{11}^3(\text{C–O})| + 1.728|F_{12}^1(\text{C–O})| \\ & + 3.672|F_{12}^2(\text{C–O})| + 1.62|F_{12}^3(\text{C–O})| \\ & + 0.018|F_{13}^1(\text{C–O})| + 0.036|F_{13}^2(\text{C–O})| \\ & + 0.036|F_{13}^3(\text{C–O})| + 0.108|F_{14}^1(\text{C–O})| \\ & + 0.216|F_{14}^2(\text{C–O})| + 0.216|F_{14}^3(\text{C–O})| \\ & + 0.108|F_{14}^4(\text{C–O})| + 0.108|F_{15}^1(\text{C–O})| \\ & + 0.216|F_{15}^2(\text{C–O})| + 0.108|F_{15}^3(\text{C–O})| \\ & + 0.072|F_{16}^1(\text{C–O})| + 0.144|F_{16}^2(\text{C–O})| \\ & + 0.072|F_{16}^3(\text{C–O})| + 0.144|F_{16}^4(\text{C–O})| \\ & + 0.072|F_{16}^5(\text{C–O})| + 0.072|F_{17}^1(\text{C–O})| \\ & + 0.144|F_{17}^2(\text{C–O})| + 0.648|F_{18}^1(\text{C–O})| \\ & + 1.296|F_{18}^2(\text{C–O})| + 96.555 \end{aligned}$$

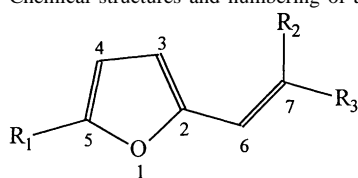
In the following section, we will provide another example of application of the novel molecular descriptors introduced here. In this case, we will consider explicitly the heteroatoms of the structure and we will compare these results to those obtained by using TIs and total spectral moments.

5. Predicting chemical reactivity

One of the main limitations of topological descriptors is their inability to describe chemical reactions. Although these descriptors are very useful in describing solvation

Table 2

Chemical structures and numbering of atoms in the furylethylene compounds used in this study



Number	R ₁	R ₂	R ₃	Number	R ₁	R ₂	R ₃
1	H	NO ₂	COOCH ₃	18	NO ₂	H	CONHCH(CH ₃)C ₂ H ₅
2	CH ₃	NO ₂	COOCH ₃	19	NO ₂	H	CONHC(CH ₃) ₃
3	Br	NO ₂	COOCH ₃	20	NO ₂	H	CONHCH ₂ C(CH ₃) ₃
4	I	NO ₂	COOCH ₃	21	NO ₂	H	COOCH ₃
5	COOCH ₃	NO ₂	COOCH ₃	22	NO ₂	H	COOC ₂ H ₅
6	NO ₂	NO ₂	COOCH ₃	23	NO ₂	H	COO(CH ₂) ₂ CH ₃
7	NO ₂	COOC ₂ H ₅	COOC ₂ H ₅	24	NO ₂	H	COOCH(CH ₃) ₂
8	NO ₂	H	NO ₂	25	NO ₂	H	COO(CH ₂) ₃ CH ₃
9	H	H	NO ₂	26	NO ₂	H	COOCH ₂ CH(CH ₃) ₂
10	NO ₂	H	CONH ₂	27	NO ₂	H	COOCH(CH ₃)C ₂ H ₅
11	NO ₂	H	CONHCH ₃	28	NO ₂	H	COOC(CH ₃) ₃
12	NO ₂	H	CON(CH ₃) ₂	29	NO ₂	H	COO(CH ₂) ₄ CH ₃
13	NO ₂	H	CONHC ₂ H ₅	30	NO ₂	H	Br
14	NO ₂	H	CONH(CH ₂) ₂ CH ₃	31	NO ₂	H	CN
15	NO ₂	H	CONHCH(CH ₃) ₂	32	NO ₂	H	OCH ₃
16	NO ₂	H	CONH(CH ₂) ₃ CH ₃	33	NO ₂	H	H
17	NO ₂	H	CONHCH ₂ CH(CH ₃) ₂	34	NO ₂	CN	COOCH ₃

and partition between phases, which can be understood as “global” chemical reactivity processes, they are unable to describe “local” chemical transformations, such as addition, substitution, elimination reactions, and so forth [44]. These difficulties arise due to the global nature of most TIs and the local nature of the processes to be modeled. Here we propose to describe the nucleophilic addition of mercaptoacetic acid to 2-furylethylenes with the novel local descriptors introduced here.

A data set of 34 2-furylethylenes with different substituents at position 5 of the furan ring as well as at the carbon β of the exocyclic double bond were used in this study. The values of the specific rate constant of the nucleophilic addition of mercaptoacetic acid to these compounds were taken from the literature [45]. The importance of these compounds is marked by their antimicrobial activity that has permitted the identification of several compounds with potential use in industry and veterinary as well as human clinics [46–50]. The role of the nucleophilic addition reaction in a possible detoxification mechanism has also been speculated recently [51]. In Table 2, we illustrate the structure of these compounds as well as the numbering of atoms in the furylethylene framework.

Here we want to compare the results obtained by using the local spectral moments of the bond matrix to those derived by using other types of molecular descriptors. Thus, we have selected a set of topological and quantum chemical descriptors to carry out this study. The TIs selected were a set of molecular connectivity indices, atom [9–11] and bond connectivities [43,44,52], and the total spectral moments of the bond matrix [27–29]. Quantum chemical descriptors

[53] were computed after full-geometry optimization of the molecular structures of furylethylenes with the semiempirical quantum chemical method AM1 [54]. In a previous paper, we proved that this method give the best results from three semiempirical methods as compared to experimental results from NMR and X-ray diffraction [55], in which AM1 was determined to be the best. The symbols and definitions of the descriptors used are provided in Table 3.

First, we derived quantitative structure–reactivity models to describe the specific rate constant of the nucleophilic ad-

Table 3

Symbols for topological and quantum chemical descriptors and their definitions

$^h\chi_p$	Path connectivity index of order $h = 0-6$
$^h\chi_c$	Cluster connectivity index of order $h = 3-6$
$^h\chi_{pc}$	Path-cluster connectivity index of order $h = 4-6$
$^h\chi_p^v$	Valence path connectivity index of order $h = 0-6$
$^h\chi_c^v$	Valence cluster connectivity index of order $h = 3-6$
$^h\chi_{pc}^v$	Valence path-cluster connectivity index of order $h = 4-6$
$^h\varepsilon_p$	Path bond connectivity index of order $h = 1-6$
$^h\varepsilon_c$	Cluster bond connectivity index of order $h = 3-6$
$^h\varepsilon_{pc}$	Path-cluster bond connectivity index of order $h = 4-6$
$Q(i)$	Electronic charge on atom i of the furylethylene framework
$ES_\sigma(i)$	σ -Electrophilic superdeslocalizability on atom i
$ES_\pi(i)$	π -Electrophilic superdeslocalizability on atom i
$ES_T(i)$	Total electrophilic superdeslocalizability on atom i
$NS_\sigma(i)$	σ -Nucleophilic superdeslocalizability on atom i
$NS_\pi(i)$	π -Nucleophilic superdeslocalizability on atom i
$NS_T(i)$	Total nucleophilic superdeslocalizability on atom i
E_{HOMO}	Energy of the highest occupied molecular orbital
E_{LUMO}	Energy of the lowest unoccupied molecular orbital
μ_i	Total spectral moment of order i
$\mu_i(p-q)$	Local spectral moment of order i for the bond $p-q$

dition of the thiol to 2-furylethylenes by using connectivity indices. The best QSPR models obtained by using these molecular descriptors is given as follows:

$$\begin{aligned} \log k = & 0.544 + 2.937(^6\chi_{\text{PC}}) - 5.647(^6\chi_{\text{P}}) - 3.954(^3\chi_{\text{C}}^{\text{v}}) \\ & + 2.778(^2\chi_{\text{P}}) - 9.742(^4\chi_{\text{P}}) + 7.996(^4\varepsilon_{\text{P}}) \\ & - 4.753(^5\varepsilon_{\text{P}}), \quad N = 34, \quad R = 0.906, \quad s = 0.681, \\ & s_{\text{CV}} = 0.737, \quad F(7, 26) = 17.1 \end{aligned} \quad (14)$$

This model explains <84% of the variance in the experimental values of $\log k$. The use of the global spectral moments produces similar results, which indicates that the question is not concerned with the graph invariant used in the definition of the molecular descriptors but with the global nature of them. The QSPR model with the global spectral moments is given as follows:

$$\begin{aligned} \log k = & -0.478 + 1.278(\mu_1) + 0.085(\mu_7) - 4.30 \\ & \times 10^{-6}(\mu_{13}) - 0.421(\mu_5) + 0.583(\mu_3) - 3.40 \\ & \times 10^{-3}(\mu_{10}) + 3.28 \times 10^{-4}(\mu_{12}), \quad N = 34, \\ & R = 0.918, \quad s = 0.655, \quad s_{\text{CV}} = 0.711, \\ & F(7, 26) = 18.8 \end{aligned} \quad (15)$$

The use of local molecular descriptors, such as quantum chemical ones defined for atoms in the molecule, produces a significant improvement in the statistical quality of the model describing this reactivity index. The model obtained by using these descriptors is illustrated as follows:

$$\begin{aligned} \log k = & 20.878 + 208.914[\text{ES}_{\sigma}(6)] + 66.122[\text{ES}_{\pi}(6)] \\ & + 235.54[\text{ES}_{\text{T}}(5)] + 0.540[\text{NS}_{\sigma}(5)] \\ & - 0.938[\text{NS}_{\pi}(2)] - 0.284[\text{NS}_{\text{T}}(7)] + 3.256[Q(7)], \\ & N = 34, \quad R = 0.984, \quad s = 0.288, \\ & s_{\text{CV}} = 0.305, \quad F(7, 26) = 112.2 \end{aligned} \quad (16)$$

It explains more than 96% of the variance in $\log k$ with a standard deviation that is less than a half of that obtained with the graph theoretical molecular descriptors. The molecular descriptors included in this equation clearly pointed to the identification of the reaction centers involved in the chemical interaction studied. The atoms 6 and 7 are those involved in the exocyclic double bond of the furylethylene that is attacked by the thiol group.

The final objective of this study is to show whether or not local spectral moments of the bond matrix are able to describe this local reactivity index. Thus, we computed the first 15 local moments for each of the bonds that forms the skeleton of the furylethylene framework, which give a total of 105 (15×7) local moments. By using these descriptors, we generated a quantitative model together with the statistical parameters as follows:

$$\begin{aligned} \log k = & 4.698 + 0.143[\mu_6(6-7)] + 0.0054[\mu_{13}(6-7)] \\ & - 0.504[\mu_6(2-6)] - 0.069[\mu_{11}(6-7)] \\ & - 0.044[\mu_7(6-7)] + 3.10 \times 10^{-4}[\mu_9(2-6)] \\ & + 4.729[\mu_3(6-7)], \quad N = 34, \quad R = 0.982, \\ & s = 0.320, \quad s_{\text{CV}} = 0.339, \quad F(7, 26) = 70.4 \end{aligned} \quad (17)$$

This model is comparable to that obtained by using quantum chemical descriptors. It explains more than 96% of the variance in the experimental values of $\log k$. We have taken into account in this comparison that the number of descriptors included in all four model is always the same, i.e. seven variables per model. As can be seen most of the local spectral moments included in this model are related to the bond 6–7, which is the bond directly implicated in the nucleophilic attack of the thiol groups. The other bond represented by the local moments included in this model is also involved in the chemical reaction under study because it represents the interaction of the carbon atom 6, the center attacked by

Table 4

Experimental and calculated values of the specific constant for the reaction of nucleophilic addition of thiols ($\log k$) to the exocyclic double bond of the furylethylenes studied

Number	Experimental	TIs	Total moments	QC	Local moments
1	6.591	7.532	6.281	6.780	6.679
2	6.518	6.983	5.583	6.646	6.563
3	6.914	6.352	6.893	7.021	6.979
4	6.982	6.997	6.554	6.935	7.069
5	7.176	6.750	7.390	7.137	7.291
6	7.602	6.685	7.410	7.466	7.572
7	5.255	5.533	5.002	5.212	4.934
8	6.763	4.965	5.962	6.737	6.662
9	5.623	4.997	4.839	5.454	5.599
10	3.813	4.831	4.455	3.695	4.318
11	3.840	3.636	4.876	3.616	4.034
12	3.874	4.162	2.911	3.537	3.448
13	3.825	3.916	4.255	3.562	3.875
14	3.623	3.798	4.032	3.550	3.841
15	3.751	3.528	3.255	3.522	3.721
16	3.784	3.114	3.437	3.566	3.842
17	3.697	4.175	3.468	3.570	3.826
18	3.705	3.934	3.157	3.541	3.711
19	3.697	3.264	3.686	3.482	3.798
20	3.650	3.526	4.269	3.581	3.851
21	4.000	3.693	5.184	3.985	3.735
22	3.920	3.974	4.202	3.920	3.617
23	3.790	3.856	4.409	3.926	3.596
24	3.763	3.869	3.438	3.849	3.552
25	3.623	3.172	3.893	3.921	3.600
26	3.650	4.233	4.178	3.917	3.610
27	3.592	4.193	3.613	3.873	3.566
28	3.584	4.0586	3.569	3.819	3.881
29	3.590	3.478	3.204	3.918	3.600
30	2.987	3.463	3.534	3.281	2.785
31	3.273	3.070	3.779	4.089	3.651
32	2.140	3.070	2.794	2.287	2.751
33	3.553	3.780	2.716	3.338	3.485
34	5.557	5.114	5.474	4.969	5.524

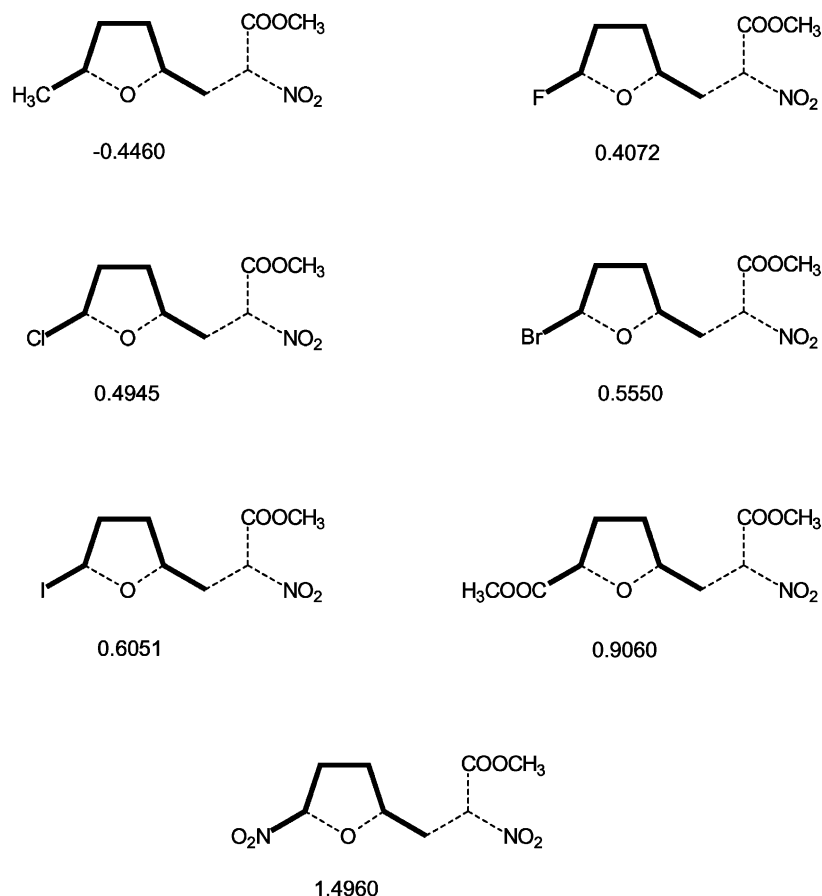


Fig. 3. Contribution of different structural fragments containing the exocyclic double bond of the furylethylene framework to the rate constant for the addition reaction of thiols.

the thiol group, with the carbon 2 which is in the furan ring. The values of $\log k$ calculated from connectivity, total and local moments as well as the experimental ones are given in Table 4.

On the other hand, model (17) permits to find the quantitative contribution of the different fragments containing bonds 6–7 and 2–6, which are those included in the spectral moments of the model found. For instance, an illustration of some six-bond fragments including bond 6–7 and several substituents at position 5 of the furan ring is given in Fig. 3, together with their contribution to $\log k$.

As can be seen from Fig. 3, the presence of the group CH_3 produces a negative contribution to $\log k$, while the greatest positive contribution are made by the groups COOCH_3 and NO_2 . This can be interpreted in terms of the electronic effects of these substituents in complete agreement with the experimental results. For instance, compound number 2 having a methyl group at position 5 of the furan ring (see Table 2) has a value of $\log k$ lower than that of the unsubstituted compound (no. 1 in Table 2). The reactivity increases in the order $\text{Br} < \text{I} < \text{COOCH}_3 < \text{NO}_2$. This is exactly the same order of the contributions of the different fragments illustrated in Fig. 3.

Table 5

Values of the group contributions calculated from local moments for different substituents in the position 5 of the furan ring of the furylethylene compounds

Group	GC(1) ^a	Group	GC(1)
H	0.00	<i>Cis</i> - C_3H_7	−0.32
CH_3	−0.12	<i>Is</i> o- C_3H_7	−0.12
F	0.11	C_2H_5	−0.13
Cl	0.25	C_6H_5	0.039
Br	0.30	COOH	0.59
I	0.39	COCH_3	0.63
COOCH_3	0.61	CF_3	0.70
NO_2	0.89	CN	0.74
$\text{N}(\text{CH}_3)_2$	−0.62	OH	−0.49
NH_2	−0.54	OCH_3	−0.38
$\text{C}(\text{CH}_3)_3$	−0.12		

^a Group contribution when substituents in the exocyclic double bond are NO_2 and COOCH_3 .

We know that the calculation of group contribution of substituents not included in the data set used to develop model (17) is risky. For instance, there is no experimental evidence for confirming if the order of reactivity of F and Cl corresponds to that predicted by their group contributions. In spite of this, we have computed the group contribution of

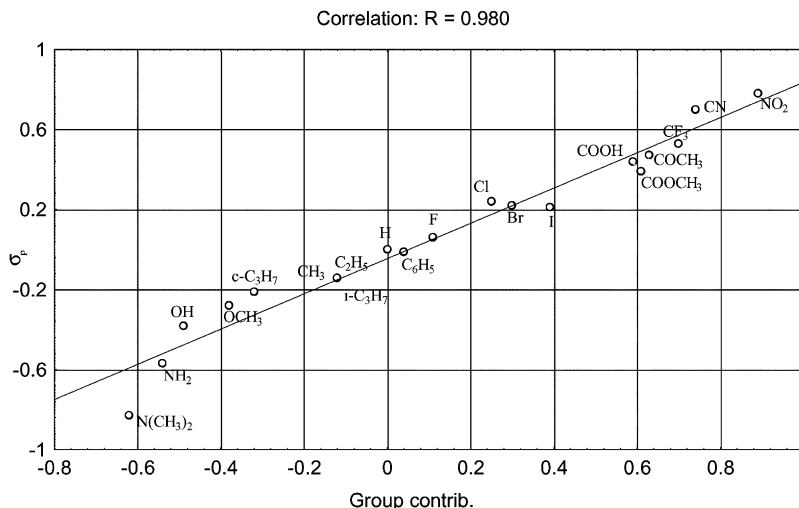


Fig. 4. Correlations between the group contribution of substituents at position 5 of the furan ring to $\log k$ and the Hammett σ_p constants when NO_2 and COOCH_3 are at position β of the exocyclic double bond.

a large number of substituents R_1 at position 5 of the furan ring in 1-(5- R_1 -fur-2-yl)-2-carboxymethyl-2-nitroethylene. These values are given in Table 5 for a set of 21 substituents. In order to test the validity of these group contributions obtained by extrapolation from model (17), we obtained a correlation with the Hammett σ_p constants [56]. In Fig. 4, we illustrate the linear correlation between these two factors. The high correlation coefficient ($r = 0.98$) shows that an excellent correlation exists between our group contributions derived from a theoretical model and the Hammett constants obtained experimentally.

These results illustrate how a graph-theoretical approach permits to find, even by extrapolation from a regression model, magnitudes that describe correctly the reactivity behavior of some chemicals.

6. Concluding remarks

The role of TIs for modeling physicochemical and biological properties has been in several cases misunderstood. Since most TIs are global molecular descriptors they are considered as appropriate to describe only "global" properties of molecules. This excludes the possibility of studying local properties, such as chemical reactivity, with the use of such descriptors. For instance, Mekenyan and Basak [57] have concluded that "Topological indices have a predominant role in determining molecular reactivity where metric and electronic aspects of molecular architecture plays a very minor role in the reaction process".

First Kier and Hall with the E-state index, and now we with the local bond moments, demonstrated that the definition of TIs is not circumscribed to the description of the molecule as a whole. The definition of molecular descriptors based on graph-theoretical invariants that contain important information on atoms or bonds in an explicit way

is not only possible but also necessary. Taking into account that total spectral moments have been successfully applied to the discovery of novel sedative/hypnotic [31], anticancer [32] and anticonvulsant [33] compounds from large pools of chemical databases we think that the new local molecular descriptors introduced here will increase the arsenal of molecular designers to discover novel lead compounds and to improve their properties through QSPR and QSAR modeling.

We have shown here that the local spectral moments of the bond matrix are useful molecular descriptors for modeling important physicochemical properties of organic compounds. This approach permits to find the quantitative contribution of different structural fragments or atomic groups to the property studied. The example provided here for modeling chemical reactivity of some molecules with biological interest shows the many possibilities of this method in QSPR/QSAR and molecular design. The use of local spectral moments is now being used intensively in our laboratory to describe biological properties of organic compounds. One of the main directions for the development of this approach is to define and apply "bond-type" moments in full analogy to the "atom-type" E-state indices. On the other hand, the use of these novel descriptors in a "autocorrelation" analysis is also of interest and it is under development.

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