# Edge Adjacency Relationships and Molecular Topographic Descriptors. Definition and QSAR Applications

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Edge adjacency relationships in molecular graphs have been used to define a new topographic index. The novel index is calculated considering molecules as weighted graphs, where the elements of edges set are substituted by the bond orders between connected atoms in the molecule. Good linear correlations were found between molar refractivity of alkanes and the proposed $\epsilon$ ($\rho$) index. The applicability of the novel index in QSAR studies was evaluated by using a data of pharmacokinetic properties for a series of amphetamine derivatives. The results obtained were statistical and pharmacologically significant. Special interest is dedicated to discrimination of isomers, including heteroatom's differentiation and conformational isomerism.

## I. INTRODUCTION

One of the most prolific applications of graph theory to chemistry is in the generation of molecular descriptors. This kind of descriptor is based on invariants obtained from the representation of molecular structures as graphs. Most of these invariants are generated from the adjacency or distance matrices of the graphs.[1] Important classes of these descriptors are the so called topological indices, which are simple numbers obtained by mathematical manipulation of graphs associated to molecules. There are more than 120 topological indices described in the literature,[2] but only at most a dozen have been widely applied in structure−property and structure−activity studies.[3] Topological indices such as the molecular connectivity of Randić,[4] based on vertex adjacency matrix, and the Wiener number,[5] based on the distance matrix,[6] have received great attention due to their applications in chemistry and drug research.[7−11] These indices have also shown interesting mathematical features.[12−15] A new source of graph theoretical invariants was recently proposed by one of the present authors.[16] The main idea is to represent the edge adjacency relationships in a matrix form. Some topological indices related to molecular volume of alkanes[16] and other series of organic compounds[17] have been derived from this graph theoretical matrix.

The main drawback of simple topological indices is its lack of information about the three-dimensional features of molecules, which generates some criticism to QSAR applications of these descriptors.[18] This criticism is in part justified by the fact that specific drug actions strongly depend of spatial features of molecules such as configuration and conformation. Clearly, global three-dimensional properties of molecules are of profound importance in QSAR, where stereospecific interactions are abundant in the formation of drug−receptor complexes.[19]

Recent attention of graph theoretical chemists has been focused to resolve this problem. The inclusion of spatial molecular features into graph theoretical descriptors seems to be first introduced by Randić[20] in 1987, who named it topographic descriptors. Randić's approach is based on the consideration of real distance matrices as the adjacency matrix of the weighted complete graph $K_n$. Distance matrix is obtained by embedding the molecular graph into a graphite-like lattice[20,21] or any other three-dimensional lattice.[22] Another important step in the search of three-dimensional descriptors was given by Bogdanov *et al.*,[23] who calculated a three-dimensional Wiener number. This topographic index is based on a 3D-distance matrix in which the nondiagonal entries of the matrix are geometric distances rather than topological ones. The 3D-Wiener number has been successfully applied in quantitative structure−property relationship studies of thermodynamic[23] and chromatographic properties.[24]

Recent approaches to topographic descriptors have appeared in this journal that are also defined by considering three-dimensional distance matrices. In one of these papers, Diudea et al.[25] proposed two types of topographic indices of centricity and centrocomplexity on the basis of 3D-Metric distances supplied by molecular mechanic calculations. The other approach was introduced by Randić and Razinger.[26] They calculated a topographic index $D^2$ for benzenoid shapes, which is based on squared distances between atoms on the molecular periphery. Both sets of indices appears to be prominent in QSPR and QSAR studies.

All the afore-mentioned topographic descriptors have been defined by using some kind of geometric distances between atoms in the molecule. A different approach to topographic descriptors was given by Estrada and Montero in 1993.[27] In this approach the authors considered a three-dimensional adjacency matrix based on graphs weighted with bond orders or valency indices between bonded atoms, calculated from semiempirical quantum chemical methods. The topographic $\Omega$ index defined in that work was well correlated with thermodynamic properties of alkenes[27,28] and biological properties of alcohols,[28] permits one to differentiate among geometrical isomers, and has been used in QSAR studies in combination with quantum chemical descriptors.[29] The use of charge densities as diagonal entries in topographic adjacency matrices for molecular graphs was recently introduced by Estrada.[30] Topographic indices derived from this approach have been used to describe boiling points[30] and chromatographic[31] properties of alkenes as well as in

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the differentiation of geometrical and conformational isomers.[30]

In the present work, we extend the edge adjacency matrix **E** in molecular graphs in a 3D-**E** matrix in order to generate topographic indices which can be useful in QSPR and QSAR studies of molecules with spatial diversity.

## 2. THEORETICAL APPROACH

The edge adjacency matrix in simple molecular graphs was defined as a square and symmetric matrix **E**, the rows and columns of which correspond to the edges (bonds) of the graph. The nondiagonal entries of the matrix are either ones or zeroes depending on whether the corresponding bonds are adjacent or not, respectively.[16]

In the present approach we will use molecular graphs with edges weighted by bond orders calculated from quantum chemical methods. Bond orders defined by Armstrong et al.[32] will be used as edge weights. These bond orders are more appropriately called valence indexes and their calculation is as follows

$$\rho_{AB} = \sum_{\lambda}^{A} 2p_{\lambda\lambda} - \sum_{\lambda}^{A}\sum_{\sigma}^{B} p_{\lambda\sigma}^2$$

where

$$p_{\lambda\sigma} = 2\sum_{i}^{occ} C_{i\lambda}C_{i\sigma}$$

are the elements of density matrix and eigenvectors $C_{i\lambda}$ sum is over all occupied orbitals.

Elements of the edge adjacency matrix for the weighted molecular graph are now defined in a more complex way. For instance, let $e_i$ and $e_j$ be two adjacent edges in $G$. If $e_i$ is incident with vertices $v_A$ and $v_B$, and $e_j$ is incident with $v_B$ and $v_C$, then the elements $e_{i,j}$ and $e_{j,i}$ of the **E** matrix are $\rho_{BC}$ and $\rho_{AB}$, respectively. As can be appreciated the **E** matrix for bond orders weighted molecular graphs is nonsymmetric. Thence, edge degrees, $\delta(e_i)$, are defined as the sum of elements of $i$th row in **E** matrix

$$\delta(e_i) = \sum_{j} e_{ij}$$

In other words $\delta(e_i)$ is the sum of bond orders associated to all bonds adjacent with $e_i$. The topographic edge connectivity index $\epsilon(\rho)$ is introduced here using the Randić-type invariant as follows

$$\epsilon(\rho) = \sum_{s} [\delta(e_i)\delta(e_j)]_s^{-1/2}$$

where summation is over all adjacent bonds in the molecule. In Figure 1 we illustrate the calculation of $\epsilon(\rho)$ index for a molecule of 2-methylbutane.

## 3. APPLICATION OF THE NOVEL INDEX IN QSPR STUDIES

The topographic descritor $\epsilon(\rho)$ was used in QSPR models for predicting the molar refractivity (MR) of a series of 69 $C_5$−$C_9$ alkanes. Molar refractivity was calculated as follows

$$MR = \frac{\eta_0^2 - 1}{\eta_0^2 + 2}\frac{MW}{d}$$

where $\eta_0$ is the index of refraction, MW is the molecular weight, and $d$ is the density (g/cm$^3$) at 20 °C; all values were taken from ref 33. Calculation of $\epsilon(\rho)$ was performed by using the bond orders calculated from quantum chemical semiempirical method PM3.[34] Full geometry optimization with the Broyden−Fletcher−Goldfarb−Shanno algorithm[35] was carried out using the package MOPAC version 6.0,[36,37] and computation of the index was implemented in the system MODEST version 1.0.[38]

Molar refractivity was selected as a property to prove the possibilities of $\epsilon(\rho)$ in QSPR studies because it was successfully correlated with the topological $\epsilon$ index in a previous paper.[16] On the other hand, MR is an important bulkiness parameter used in QSAR studies to model the steric and hydrophobic[39] interactions between drugs and biological receptors.

Regression equation and statistical parameters obtained for the correlation are shown below

$$MR = 7.7314 + 9.2009\epsilon(\rho) \quad (1)$$

$$n = 69 \quad r = 0.9936 \quad s = 0.598 \quad F = 5169$$

where $r$ is the correlation coefficient, $s$ is the standard deviation, and $F$ is the Fisher ratio. Analysis of the model showed that 3,3-diethylpentane was a statistical outlier. This compound was identified as outlier because it exceeded the diagostic cut-off values of several standard statistical tests known as residuals, standardized residuals, studentized residuals, leverage, DFITS statistics, and Cook's distance.[40] Residuals are the difference between observed and calculated MR. A standardized residual is a residual divided by the standard deviation of the regression equation. The studentized residual is the residual for one observation divided by its own standardized deviation. The leverage is Mahalanobis' distance divided by $N - 1$. It is a measure of the influence that one observation has on the regression's fit. The DFITS statistic is used to describe the difference in the fit of the equation caused by the removal of an observation. Finally, the Cook's distance is a measure of how much omission of a case from the computation of the regression equation will change the residuals of all the cases. It serves as a measure of a case's influence on the regression rsults. Since the outlier significantly influenced the model in a way not accounted for by the $\epsilon(\rho)$ index, it was eliminated from consideration in subsequent work, leaving a revised series of 68 alkanes.

The regression model was rebuilt using the revised series of 68 alkanes yielding the following equation

$$MR = 7.7471 + 9.1860\epsilon(\rho) \quad (2)$$

$$n = 68 \quad r = 0.9951 \quad s = 0.523 \quad F = 6726$$

In this model no compounds were identified as outliers using the criteria previously discussed.

In order to test the advantage of $\epsilon(\rho)$ index, we contrast the correlations obtained to describe MR with other topological and topographic indices. These correlations were obtained by using the topographic $\Omega$ index[27] and the topological $\epsilon$ index[16]

$$MR = 5.4121 + 9.0743\Omega \quad (3)$$

$$n = 68 \quad r = 0.9680 \quad s = 1.333 \quad F = 981$$

and

$$MR = 7.6513 + 9.3624\epsilon \quad (4)$$

$$n = 68 \quad r = 0.9932 \quad s = 0.621 \quad F = 4768$$

Values of the three descriptors as well as the experimental molar refractivity are depicted in Table 1. The predicted values of MR and the residuals calculated by the three different models are illustrated in Table 2.

The $\Omega$ index can be considered as a topographic Randić's branching index, which is defined by using bond order weighted graphs. The use of this index to describe MR of alkanes is not successful, as can be appreciated in statistical parameters of eq 3. On the other hand, the comparison of eqs 2 and 4 demonstrate that the use of bond orders in the definitions of $\epsilon(\rho)$ index introduce some features that are important for the description of MR in alkanes. The improvement in the description of MR by $\epsilon(\rho)$ compared to topological $\epsilon$ index can be understood considering the fact that molar refractivity has the units of molar volumes, but it is considered to possess a polarizability component.[41]

The quality of QSPR models can be conveniently evaluated by the correlation coefficient $r$ and the standard deviation. A good model must have, as suggested by Mihalić and Trinajstić[2] in a recent strategy to design QSPR models, $r > 0.99$ and standard deviation dependent on the property under study. According to this statement, eq 2 represents a good model to describe the molar refractivity of alkanes.

The good correlation between $\epsilon(\rho)$ index and molar refractivity, considered as a molecular bulkiness parameter, permits us to interpret the novel index as a good measurement of molecular volume. This index contains also information about polarizability or polarity of molecules present in the pure liquid. These interactions are important in processes such as partition of solutes between two phases and aqueous solubility,[42] giving to $\epsilon(\rho)$ index possibilities to be used in several types of QSAR studies.

There are several useful properties fulfilled by the $\epsilon(\rho)$ index that are important for molecular descriptors in order to have a practical use in QSPR and QSAR studies. A list of attributes for topological indices has been proposed by Randić[1] that represents the very high level of sophistication that is desirable for topological indices. Among these attributes we can find the direct structural interpretation, to have a good correlation with at least one property, good discrimination of isomers, to be simple, and so forth.

Considering that several topological indexes are interrelated with each other, it is desirable that the new descriptors contain structural information not contained in other indices previously defined. The $\epsilon(\rho)$ index satisfies this demand, which can be proved by the fact that molar refractivity is a property not successfully described with the existing topological indexes.[16]

## 4. APPLICATION IN QSAR STUDIES

Quantitative structure−activity analysis is one of the main applications of molecular descriptors. In order to prove the applicability of the novel topographic index in QSAR studies, we select a series of 15 N-alkyl-substituted amphetamine derivatives for which pharmacokinetic properties in humans have been used in QSAR studies with physico-chemical parameters.[43] The cumulative urinary excretion of unchanged drug expressed as the percent of the administered dose (percent excreted unchanged, PEU) will be correlated with the topographic $\epsilon(\rho)$ index. Three subjects were used in the study of Testa and Salvesen.[43] The first two subjects were kept under acidic urinary control by ingestion of ammonium chloride (pH values of 5.0−5.2 and 4.9−5.1, respectively), while urinary pH of the third subject was not controlled. The values of log PEU for the subjects 1−3 are depicted in Table 3.

Stepwise regression was used to correlate the $\epsilon(\rho)$ index against the experimental values of log PEU. Other three graph-theoretical descriptors were regressed with log PEU in order to compare the models found. These descriptors were the topological indices of edge connectivity[16] $\epsilon$ and valence connectivity[9] ${}^1\chi^v$ as well as the topographic $\Omega$ index.[27] Values of all molecular descriptors are reported in Table 4.

In the previous QSAR study for the same series of amphetamine derivatives, Testa and Salvesen[43] reported good quadratic models with the apparent *n*-heptane−water partition coefficient (log $P_H$) in order to describe the values of log PEU. In Table 5 we give the best models obtained by using the graph theoretical descriptors and the best models found by Testa and Salvesen to describe the percent of amphetamine derivative excreted unchanged for subjects 1−3.

The best models found for subjects 1 and 2 by using graph theoretical descriptors are those obtained with the topographic $\epsilon(\rho)$ index, while the subject 3 the best model is obtained with the topological $\epsilon$ index. There are some resemblances in the statistical features of equations obtained with $\epsilon(\rho)$ and log $P_H$ for subjects 1 and 2, for instance they are quadratic models with similar correlation coefficients and standard deviations of regressions. However, there are significant differences in the physical interpretation of the results obtained with physico-chemical parameters and with graph theoretical ones. The differences obtained with topological and topographic edge adjacency indices to describe the values of log PEU in dependence of whether the subjects have urinary pH control or not are very important. Urinary pH has an important influence on the passive tubular reabsorption of drugs with moderated acid−base character. As a consequence, acids will be more reabsorbed (less excreted) at acid urinary pH, and bases will be preferably reabsorbed at alkaline urinary pH. The excretion process for subjects 1 and 2 is controlled by the dissociation of amphetamines at the acidic pH used. Thence, the values of log PEU will be dependent of the bulkiness (topological) and electronic properties of molecules, two features that appear to be contained in the topographic index. For subject 3, where urinary pH was not controlled, the excretion process is not dependent of the electronic features of amphetamines and the best model found is by using the topological $\epsilon$ index. This index does not discriminates among heteroatoms in molecules. This fact can be understood as a noninfluence of heteroatom differentiation in the excretion of amphetamines when no pH control is kept. Of course, this differentiation of heteroatom can be related with the protonation of nitrogen in such molecules, because nitrogen is the only heteroatom in amphetamines and is the protonation

**Table 1.** Values for the Molecular Descriptors (Topographic and Topological Indices) and Observed Molar Refractivities for a Series of Alkanes

| no. | alkane | MR obsd | Ω | $\epsilon$ | $\epsilon(\varrho)$ |
|---|---|---|---|---|---|
| 1 | pentane | 25.2656 | 2.4297 | 1.9142 | 1.9316 |
| 2 | 2-methylbutane | 25.2923 | 2.2962 | 1.8937 | 1.9227 |
| 3 | 2,2-dimethylpropane | 25.7243 | 2.0425 | 1.9998 | 2.0425 |
| 4 | hexane | 29.9066 | 2.9359 | 2.4142 | 2.4378 |
| 5 | 2-methylpentane | 29.9459 | 2.8019 | 2.4317 | 2.4669 |
| 6 | 3-methylpentane | 29.8016 | 2.392 | 2.3043 | 2.3442 |
| 7 | 2,2-dimethylbutane | 29.9347 | 2.6081 | 2.3660 | 2.4219 |
| 8 | 2,3-dimethylbutane | 29.8104 | 2.8842 | 2.4142 | 2.4622 |
| 9 | heptane | 34.5503 | 3.4422 | 2.9142 | 2.9441 |
| 10 | 2-methylhexane | 34.5908 | 3.3082 | 2.9317 | 2.9722 |
| 11 | 3-methylhexane | 34.4597 | 3.3451 | 2.8423 | 2.8878 |
| 12 | 3-ethylhexane | 34.2827 | 3.3823 | 2.7318 | 2.7836 |
| 13 | 2,2-dimethylpentane | 34.6166 | 3.1135 | 2.9267 | 2.9880 |
| 14 | 2,3-dimethylpentane | 34.3237 | 3.2265 | 2.8350 | 2.8919 |
| 15 | 2,4-dimethylpentane | 34.6192 | 3.1736 | 2.9661 | 3.0163 |
| 16 | 3,3-dimethylpentane | 34.3323 | 3.1733 | 2.7381 | 2.8081 |
| 17 | 2,2,3-trimethylbutane | 34.3736 | 3.0059 | 2.9069 | 2.9828 |
| 18 | octane | 39.1922 | 3.9484 | 3.4142 | 3.4503 |
| 19 | 2-methylheptane | 39.2316 | 3.8143 | 3.4317 | 3.4784 |
| 20 | 3-methylheptane | 39.1001 | 3.8515 | 3.3423 | 3.3935 |
| 21 | 4-methylheptane | 39.1174 | 3.8508 | 3.3803 | 3.4313 |
| 22 | 3-ethylhexane | 38.9441 | 3.8879 | 3.2698 | 3.3265 |
| 23 | 2,2-dimethylhexane | 39.2525 | 3.6197 | 3.4267 | 3.4931 |
| 24 | 2,3-dimethylhexane | 38.9808 | 3.7337 | 3.3730 | 3.4368 |
| 25 | 2,4-dimethylhexane | 39.1300 | 3.7171 | 3.3767 | 3.4382 |
| 26 | 2,5-dimethylhexane | 39.2596 | 3.6803 | 3.4492 | 3.5063 |
| 27 | 3,3-dimethylhexane | 39.0087 | 3.6789 | 3.2988 | 3.3741 |
| 28 | 3,4-dimethylhexane | 43.6780 | 3.7712 | 3.2556 | 3.3241 |
| 29 | 2-methyl-3-ethylpentane | 38.8362 | 3.7707 | 3.2725 | 3.3427 |
| 30 | 3-methyl-3-ethylpentane | 38.7171 | 3.7390 | 3.3154 | 3.3929 |
| 31 | 2,2,3-trimethylpentane | 38.9449 | 3.5490 | 3.3344 | 3.4198 |
| 32 | 2,2,4-trimethylpentane | 39.2617 | 3.4858 | 3.4711 | 3.5476 |
| 33 | 2,3,3-trimethylpentane | 38.7617 | 3.5710 | 3.2116 | 3.3719 |
| 34 | 2,3,4-trimethylpentane | 38.8681 | 3.6153 | 3.3716 | 3.4469 |
| 35 | nonane | 43.8423 | 4.4547 | 3.9142 | 3.9566 |
| 36 | 2-methyloctane | 43.8795 | 4.3205 | 3.9317 | 3.9846 |
| 37 | 3-methyloctane | 43.7296 | 4.3574 | 3.8423 | 3.8995 |
| 38 | 4-methyloctane | 43.7687 | 4.3570 | 3.8803 | 3.9369 |
| 39 | 3-ethylheptane | 43.6420 | 4.3943 | 3.7698 | 3.8221 |
| 40 | 4-ethylheptane | 43.4907 | 4.3938 | 3.8078 | 3.8697 |
| 41 | 2,2-dimethylheptane | 43.9138 | 4.1260 | 3.9267 | 3.9994 |
| 42 | 2,3-dimethylheptane | 43.6269 | 4.2397 | 3.8730 | 3.9422 |
| 43 | 2,4-dimethylheptane | 43.7393 | 4.2229 | 3.9147 | 3.9817 |
| 44 | 2,5-dimethylheptane | 43.8484 | 4.2233 | 3.8598 | 3.9272 |
| 45 | 2,6-dimethylheptane | 43.9258 | 4.1865 | 3.9492 | 4.0128 |
| 46 | 3,3-dimethylheptane | 43.6870 | 4.1851 | 3.7988 | 3.8792 |
| 47 | 3,4-dimethylheptane | 43.5473 | 4.2769 | 3.7936 | 3.8676 |
| 48 | 3,5-dimethylheptane | 43.6378 | 4.2599 | 3.7873 | 3.8586 |
| 49 | 4,4-dimethylheptane | 43.6022 | 4.1844 | 3.8595 | 3.9400 |
| 50 | 2-methyl-3-ethylhexane | 43.6550 | 4.2761 | 3.8105 | 3.8848 |
| 51 | 2-methyl-4-ethylhexane | 43.6472 | 4.2595 | 3.8042 | 3.8758 |
| 52 | 3-methyl-3-ethylhexane | 43.2680 | 4.2445 | 3.8761 | 3.7665 |
| 53 | 3-methyl-4-ethylhexane | 43.3746 | 4.3136 | 3.6931 | 3.7729 |
| 54 | 2,2,3-trimethylhexane | 43.6226 | 4.0547 | 3.8724 | 3.9630 |
| 55 | 2,2,4-trimethylhexane | 43.7638 | 4.0289 | 3.8817 | 3.9688 |
| 56 | 2,2,5-trimethylhexane | 43.9356 | 3.9917 | 3.9442 | 4.0268 |
| 57 | 2,3,3-trimethylhexane | 43.4347 | 4.0769 | 3.8438 | 3.9389 |
| 58 | 2,3,4-trimethylhexane | 43.3917 | 4.1595 | 3.6231 | 3.8786 |
| 59 | 2,3,5-trimethylhexane | 43.6474 | 4.1058 | 3.9074 | 3.9868 |
| 60 | 2,4,4-trimethylhexane | 43.6598 | 4.0505 | 3.7695 | 3.9330 |
| 61 | 3,3,4-trimethylhexane | 43.3407 | 4.1144 | 3.6231 | 3.8097 |
| 62 | 3,3-diethylpentane | 43.1134 | 4.3049 | 3.5000 | 3.6007 |
| 63 | 2,2-dimethyl-3-ethylpentane | 43.4571 | 4.0932 | 3.7788 | 3.8768 |
| 64 | 2,3-dimethyl-3-ethylpentane | 42.9542 | 4.1368 | 3.6652 | 3.7693 |
| 65 | 2,4-dimethyl-3-ethylpentane | 43.4037 | 4.1576 | 3.8191 | 3.9054 |
| 66 | 2,2,3,3-tetramethylpentane | 43.2147 | 3.8993 | 3.7932 | 3.9109 |
| 67 | 2,2,3,4-tetramethylpentane | 43.4359 | 3.9373 | 3.8751 | 3.9782 |
| 68 | 2,2,4,4-tetramethylpentane | 43.8747 | 3.7980 | 3.9820 | 4.0844 |
| 69 | 2,3,3,4-tetramethylpentane | 43.2016 | 3.9693 | 3.8309 | 3.9399 |

**Table 2.** Calculated Values of Molar Refractivities of Alkanes by Using the Three Different Models Found in This Paper

| | eq 3 | | eq 4 | | eq 2 | |
|---|---|---|---|---|---|---|
| no. | MR | residual | MR | residual | MR | residual |
| 1 | 27.4598 | −2.1942 | 25.5728 | −0.3072 | 25.4300 | −0.1644 |
| 2 | 26.2484 | −0.9561 | 25.3808 | −0.0885 | 25.3400 | −0.0477 |
| 3 | 23.9462 | 1.7781 | 26.3742 | −0.6499 | 26.4203 | −0.6960 |
| 4 | 32.0532 | −2.1466 | 30.2542 | −0.3474 | 30.0599 | −0.1533 |
| 5 | 30.8372 | −0.8913 | 30.4179 | −0.4720 | 30.3143 | −0.3684 |
| 6 | 31.1757 | −1.3741 | 29.2532 | 0.5484 | 29.1881 | 0.6135 |
| 7 | 29.0786 | 0.8561 | 29.8027 | 0.1320 | 29.8890 | 0.0457 |
| 8 | 29.7692 | 0.041 | 30.2540 | −0.4436 | 30.2730 | −0.4626 |
| 9 | 36.6475 | −2.0971 | 34.9353 | −0.3849 | 34.6888 | −0.1384 |
| 10 | 35.4315 | −0.8407 | 35.0991 | −0.5083 | 34.9405 | −0.3497 |
| 11 | 35.7663 | −1.3066 | 34.2621 | 0.1976 | 34.1596 | 0.3001 |
| 12 | 36.1039 | −1.8212 | 33.2275 | 1.0552 | 33.1969 | 1.0858 |
| 13 | 33.6648 | 0.9518 | 35.0523 | −0.4347 | 35.0663 | −0.4497 |
| 14 | 34.6901 | −0.3664 | 34.1938 | 0.1299 | 34.2092 | 0.1145 |
| 15 | 34.2101 | 0.4091 | 35.4212 | −0.8020 | 35.3391 | −0.7199 |
| 16 | 34.2074 | 0.1249 | 33.2865 | 1.0458 | 33.4082 | 0.9241 |
| 17 | 32.6884 | 1.6852 | 34.8669 | −0.4933 | 35.0094 | −0.6358 |
| 18 | 41.2408 | −2.0486 | 39.6165 | −0.4243 | 39.3204 | −0.1282 |
| 19 | 40.0240 | −0.7924 | 39.7804 | −0.5488 | 39.5694 | −0.3378 |
| 20 | 40.3615 | −1.2614 | 38.9434 | 0.1567 | 38.7839 | 0.3162 |
| 21 | 40.3552 | −1.2378 | 39.2991 | −0.1817 | 19.1312 | −0.0138 |
| 22 | 40.6918 | −1.7477 | 38.2646 | 0.6795 | 38.1703 | 0.7738 |
| 23 | 38.2581 | 0.9944 | 39.7335 | −0.4810 | 39.6860 | −0.4335 |
| 24 | 39.2926 | −0.3118 | 39.2308 | −0.2500 | 39.1642 | −0.1834 |
| 25 | 39.1420 | −0.0120 | 39.2654 | −0.1354 | 39.1835 | −0.0553 |
| 26 | 38.8080 | 0.4516 | 39.9442 | −0.6846 | 39.8128 | −0.5532 |
| 27 | 38.7953 | 0.2134 | 38.5361 | 0.4726 | 38.5782 | 0.4305 |
| 28 | 39.6329 | −0.7876 | 38.1316 | 0.7137 | 38.1336 | 0.7117 |
| 29 | 39.6283 | −0.7921 | 38.2898 | 0.5464 | 38.3099 | 0.5263 |
| 30 | 39.3407 | −0.6236 | 38.6915 | 0.0256 | 38.9144 | −0.1973 |
| 31 | 37.6166 | 1.3083 | 38.8694 | 0.0555 | 39.0062 | −0.0813 |
| 32 | 37.0431 | 2.2186 | 40.1492 | −0.8875 | 40.1848 | −0.9231 |
| 33 | 37.8162 | 0.9455 | 37.7197 | 1.0420 | 38.5671 | 0.1946 |
| 34 | 38.2182 | 0.6499 | 39.2177 | −0.3496 | 39.2680 | −0.3999 |
| 35 | 45.8351 | −1.9928 | 44.2978 | −0.4555 | 43.9511 | −0.1088 |
| 36 | 44.6173 | −0.7378 | 44.4616 | −0.5821 | 44.2001 | −0.3206 |
| 37 | 44.9522 | −1.2226 | 43.6246 | 0.1050 | 43.4156 | 0.3140 |
| 38 | 44.9486 | −1.1799 | 43.9804 | −0.2117 | 43.7546 | 0.0141 |
| 39 | 45.2870 | −1.6450 | 42.9458 | 0.6962 | 42.7946 | 0.8474 |
| 40 | 45.2825 | −1.7918 | 43.3016 | 0.1891 | 43.1290 | 0.3617 |
| 41 | 42.8433 | 1.0705 | 44.4148 | −0.5010 | 44.3177 | −0.4039 |
| 42 | 43.8842 | −0.2573 | 43.9120 | −0.2851 | 43.7849 | −0.1580 |
| 43 | 43.7317 | 0.0076 | 44.3024 | −0.5631 | 44.1532 | −0.4139 |
| 44 | 43.7353 | 0.1131 | 43.7884 | 0.6000 | 43.6618 | 0.1866 |
| 45 | 43.4014 | 0.5244 | 44.6254 | −0.6996 | 44.4481 | −0.5223 |
| 46 | 43.3887 | 0.2983 | 43.2173 | 0.4697 | 43.1988 | 0.4882 |
| 47 | 44.2217 | −0.6744 | 43.1686 | 0.3787 | 43.1014 | 0.4459 |
| 48 | 44.0675 | −0.4296 | 43.1097 | 0.5282 | 43.0151 | 0.6228 |
| 49 | 43.3823 | 0.2199 | 43.7856 | −0.1834 | 43.7555 | −0.1533 |
| 50 | 44.2145 | −0.5592 | 43.3269 | 0.3281 | 43.2649 | 0.3901 |
| 51 | 44.0638 | −0.4166 | 43.2669 | 0.3793 | 43.1960 | 0.4512 |
| 52 | 43.9277 | −0.6596 | 43.9411 | −0.6731 | 42.1699 | 1.0981 |
| 53 | 44.5547 | −1.1801 | 42.2277 | 1.1469 | 42.2223 | 1.1523 |
| 54 | 42.2054 | 1.4172 | 43.9064 | −0.2838 | 43.9723 | −0.3497 |
| 55 | 41.9713 | 1.7925 | 43.9935 | −0.2297 | 44.0191 | −0.2553 |
| 56 | 41.6337 | 2.3019 | 44.5786 | −0.6430 | 44.5602 | −0.6246 |
| 57 | 42.4069 | 1.0278 | 43.6386 | −0.2039 | 43.7417 | −0.3070 |
| 58 | 43.1564 | 0.2353 | 41.5723 | 1.8194 | 43.2015 | 0.1902 |
| 59 | 42.6691 | 0.9783 | 44.2341 | −0.5867 | 44.1918 | −0.5444 |
| 60 | 42.1673 | 1.4929 | 42.9430 | 0.7168 | 43.6912 | −0.0314 |
| 61 | 42.7472 | 0.5935 | 41.5723 | 1.7698 | 42.5613 | 0.7794 |
| 63 | 42.5548 | 0.9032 | 43.0301 | 0.4270 | 43.1795 | 0.2776 |
| 64 | 42.9504 | 0.0039 | 41.9665 | 0.9877 | 42.1911 | 0.7631 |
| 65 | 43.1392 | 0.2645 | 43.4074 | 0.0037 | 43.4597 | −0.0560 |
| 66 | 40.7953 | 2.4194 | 43.1649 | 0.0498 | 43.4918 | −0.2771 |
| 67 | 41.1401 | 2.2958 | 43.9317 | −0.4958 | 44.1055 | −0.6696 |
| 68 | 39.8761 | 3.9986 | 44.9325 | −1.0578 | 45.0774 | −1.2027 |
| 69 | 41.4305 | 1.7711 | 43.5179 | −0.3163 | 43.7316 | −0.5300 |

**Table 3.** Percent of Amphetamine Derivative Excreted Unchanged (PEU) for Three Subjects

| | | log PEU | | | | | |
|---|---|---|---|---|---|---|---|
| | | subject 1 | | subject 2 | | subject 3 | |
| no. | compd | obsd | calcd | obsd | calcd | obsd | calcd |
| I | amphetamine | 1.78 | 1.77 | 1.76 | 1.79 | 1.79 | 1.95 |
| II | *N*-methyl | 1.83 | 1.79 | 1.79 | 1.78 | 1.69 | 1.72 |
| III | *N*-ethyl | 1.68 | 1.72 | 1.66 | 1.68 | 1.16 | 1.40 |
| IV | *N*-*n*-propyl | 1.51 | 1.52 | 1.49 | 1.48 | 1.08 | 1.07 |
| V | *N*-2-propyl | 1.59 | 1.50 | 1.60 | 1.47 | 1.35 | 1.04 |
| VI | *N*-*n*-butyl | 0.87 | 1.20 | 0.76 | 1.19 | 0.29 | 0.71 |
| VII | *N*-2-butyl | 1.28 | 1.24 | 1.34 | 1.22 | 1.10 | 0.75 |
| VIII | *N*-benzyl | −0.23 | −0.30 | −0.27 | −0.28 | −0.78 | −1.00 |
| IX | *N*,*N*-dimethyl | 1.59 | 1.72 | 1.61 | 1.69 | 1.33 | 1.40 |
| X | *N*,*N*-diethyl | 1.60 | 1.31 | 1.44 | 1.28 | 1.29 | 0.82 |
| XI | *N*,*N*-di-*n*-propyl | 0.25 | 0.29 | 0.17 | 0.36 | −0.28 | −0.02 |
| XII | *N*,*N*-di-*n*-butyl | −1.16 | −1.16 | −0.82 | −0.90 | −1.12 | −0.92 |
| XIII | *N*-ethyl-*N*-methyl | 1.54 | 1.56 | 1.58 | 1.53 | 1.18 | 1.13 |
| XIV | *N*-methyl-*N*-*n*-propyl | 1.38 | 1.24 | 1.40 | 1.22 | 0.87 | 0.75 |
| XV | *N*-*n*-butyl-*N*-methyl | 0.47 | 0.58 | 0.57 | 0.57 | −0.21 | −0.06 |

**Table 4.** Values of Topological and Topographic Descriptors for the Series of Amphetamine Derivatives

| no. | $^1\chi^V$ | Ω | $\epsilon$ | $\epsilon(\varrho)$ |
|---|---|---|---|---|
| I | 3.583 | 3.961 | 4.966 | 4.117 |
| II | 4.038 | 4.487 | 5.377 | 4.522 |
| III | 4.599 | 4.997 | 5.915 | 5.062 |
| IV | 5.099 | 5.502 | 6.415 | 5.569 |
| V | 4.982 | 5.376 | 6.449 | 5.617 |
| VI | 5.599 | 6.007 | 6.915 | 6.074 |
| VII | 5.520 | 5.918 | 6.860 | 6.040 |
| VIII | 6.156 | 6.674 | 8.933 | 7.173 |
| IX | 4.402 | 4.875 | 5.907 | 5.065 |
| X | 5.554 | 5.973 | 6.766 | 5.943 |
| XI | 6.554 | 6.981 | 7.842 | 7.032 |
| XII | 7.554 | 7.991 | 8.842 | 8.041 |
| XIII | 4.978 | 5.422 | 6.328 | 5.494 |
| XIV | 5.478 | 5.927 | 6.866 | 6.039 |
| XV | 5.978 | 6.432 | 7.884 | 6.544 |

**Table 5.** Statistical Characteristics of the Models Found to Describe the log PEU of Amphetamines with Single Topological or Topographic Indices[a]

| | index | *a* | *b* | *c* | $r^2$ | *s* | *F* |
|---|---|---|---|---|---|---|---|
| log $PEU_1$ | $^1\chi^V$ | −0.843 | 1.490 | −0.205 | 0.893 | 0.306 | 50.2 |
| | Ω | −1.595 | 1.691 | −0.207 | 0.908 | 0.284 | 59.4 |
| | $\epsilon$ | −2.385 | 1.684 | −0.168 | 0.920 | 0.266 | 68.4 |
| | $\epsilon(\varrho)$ | −2.626 | 2.033 | −0.232 | 0.959 | 0.189 | 141.3 |
| | log ($P_H$) | 1.43 | −0.345 | −0.077 | 0.947 | 0.220 | 88.7 |
| log $PEU_2$ | $^1\chi^V$ | 0.170 | 1.061 | −0.162 | 0.868 | 0.318 | 39.3 |
| | Ω | −0.429 | 1.239 | −0.165 | 0.883 | 0.299 | 45.4 |
| | $\epsilon$ | −1.605 | 1.422 | −0.147 | 0.931 | 0.230 | 80.9 |
| | $\epsilon(\varrho)$ | −1.457 | 1.588 | −0.191 | 0.940 | 0.214 | 94.2 |
| | log ($P_H$) | 1.48 | −0.341 | −0.064 | 0.949 | 0.201 | 92.5 |
| log $PEU_3$ | $^1\chi^V$ | 2.903 | | $-7.42 \times 10^{-2}$ | 0.828 | 0.391 | 62.8 |
| | Ω | 3.073 | | $-6.88 \times 10^{-2}$ | 0.843 | 0.374 | 69.8 |
| | $\epsilon$ | 3.274 | | $-5.36 \times 10^{-2}$ | 0.922 | 0.263 | 153.9 |
| | $\epsilon(\varrho)$ | 3.162 | | $-6.86 \times 10^{-2}$ | 0.888 | 0.315 | 103.5 |
| | log ($P_H$) | 0.943 | −0.517 | | 0.896 | 0.307 | 94.4 |

[a] Equations are of the form log PEU = $a + bI + cI^2$.

in the main chemical process that can occur with these molecules in the studied conditions.

The normal urinary pH has a mean value of 6.3; however, it has big oscillations during the day producing a wide range of urinary pH values among 4.5−8.5, which can alter the dissociation process of amphetamine derivatives.

The validity of the stated hypothesis can be tested extracting the electronic information contained in the topographic $\epsilon(\rho)$ index and using it as an independent variable in novel QSAR models. Both graph theoretical descriptors, the topological $\epsilon$ index and the topographic $\epsilon(\rho)$ index, are based on the same invariant, and their main difference is in the use of bond orders (an electronic feature) as edge weights in the definition of $\epsilon(\rho)$. Thence, we can consider the topographic index as a corrected $\epsilon$ index, where the correction factor is *C*. Mathematically, this definition of $\epsilon(\rho)$ can be expressed as follows

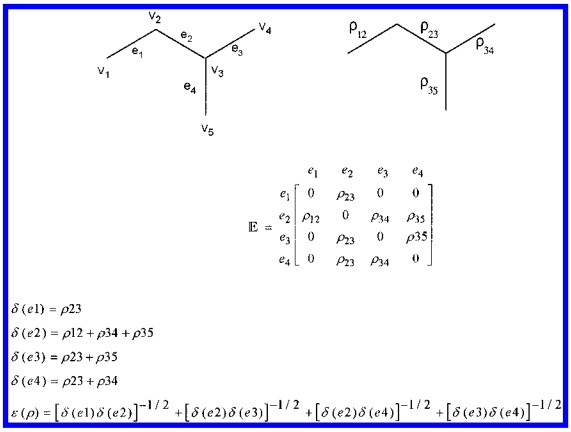



**Figure 1.** Computation of the $\epsilon(\rho)$ for a graph representing skeleton of 2-methylbutane.

$$\epsilon(\rho) = \epsilon + C$$

We have no analytical expression for the correction factor *C*, but we can obtain it from the calculated values of $\epsilon(\rho)$ and $\epsilon$ indices. Using *C* as a novel descriptor, the following models for log PEU of subjects 1 and 2 were obtained

$$\log PEU_1 = 2.104\epsilon(\rho) - 0.235[\epsilon(\rho)]^2 - 0.435C - 2.547 \quad (5)$$

$$r^2 = 0.975 \quad s = 0.156 \quad F = 141.0$$

$$\log PEU_2 = 1.672\epsilon(\rho) - 0.194[\epsilon(\rho)]^2 - 0.511C - 1.364 \quad (6)$$

$$r^2 = 0.964 \quad s = 0.172 \quad F = 99.7$$

As can be appreciated from the statistical parameters of the eqs 5 and 6, both models are very significant. No analogue model can be found for log $PEU_3$. Values of log PEU for subjects 1−3 calculated with the best models found here are depicted in Table 3. The *C* index can be associated in some way with the electronic characteristics responsible of the dissociation of amphetamine derivatives. Indices analogous to *C*, obtained from the differences between other topographic and topological indices based on the same graph-theoretical invariantk, have been successfully applied in QSPR and QSAR studies by one of the present authors.[28] The results obtained here shown the power of using topographic descriptors in QSAR analysis.

## 5. CHARACTERISTIC FEATURES OF E(ρ) INDEX

The differentiation of a heteroatom's positions in organic compounds is one of the desirable properties of topographic indices. In Figure 2 we can appreciate that the $\epsilon(\rho)$ index shows a regular variation with the position of the heteroatom in a series of aliphatic ethers. The greater values of $\epsilon(\rho)$

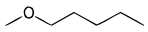
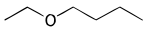
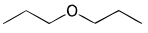
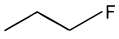
| Ether | $^1\chi$ | $^1\chi^v$ | $\epsilon(\rho)$ |
|---|---|---|---|
|  | 3.414 | 2.905 | 2.963 |
|  | 3.414 | 2.992 | 2.971 |
|  | 3.414 | 2.992 | 2.976 |

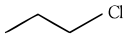
**Figure 2.** Numerical values of $\epsilon(\rho)$ index for isomeric ethers with degenerated values of connectivity indexes.

| | *anti* | *gauche* |
|---|---|---|
| |  |  |
| $\epsilon(\rho)$ | 1.4122 | 1.4132 |
| $\chi\chi$ | 1.9814 | 1.9918 |
| | *chair* | *boat* |
| |  |  |
| $\epsilon(\rho)$ | 3.0264 | 3.0298 |
| $\chi\chi$ | 3.0000 | 2.9997 |

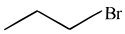
**Figure 3.** Values of topographic $\epsilon(\rho)$ and $\chi\chi$ indexes for *anti* and *gauche* conformers of *n*-butane as well as *chair* and *boat* conformers of cyclohexane.



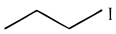

1.4266




1.4311




1.4532




1.4573

**Figure 4.** Values of $\epsilon(\rho)$ index for *n*-propyl halides.

are obtained when a heteroatom is positioned at the center of the molecule.

In Figure 3 we illustrate the *anti* and *gauche* conformations of *n*-butane and the *chair* and *boat* conformations of cyclohexane. In both cases we also give the values of the topographic index $\chi\chi$ introduced by Randić,[20−22] which is based on graphs embedded into three-dimensional grids. As can be appreciated both indices produce discrete differentiation of conformational isomers, showing regular variation of the indices' values according to the "compactness" of the chemical structure.

In Figure 4 we depicted another characteristic of the topographic edge connectivity index $\epsilon(\rho)$: differentiation of heteroatoms in chemical structures. In this example we can appreciate that $\epsilon(\rho)$ index changes regularly with the volume variation of heteroatom from fluorine to iodine. The importance of heteroatom differentiation by molecular descriptors to be used in QSPR and QSAR studies is evident and has been mentioned elsewhere.[44,45]

## 6. CONCLUDING REMARKS

A new topographic index based on edge adjacency relationships in molecular graphs is defined considering molecules as weighted graphs. Elements of edge set are substituted by the bond orders between the connected atoms in the molecule. The importance of using weighted graphs to generate structural invariants has been emphasized by Randić. This author remarked the importance of considering any matrix as a weighted graph in order for the further development of chemical combinatorics and topology.[44]

When we are concerned with the generation of one descriptor to be used in QSAR studies, the consideration of global spatial features of molecules is a desirable condition. As a consequence, the use of topographic rather than topological indices is necessary.

Among the most important features of the topographic $\epsilon(\rho)$ index we can mention the isomer differentiation that includes compounds with different branching, position of heteroatoms, and chain conformations. The novel index permits differentiation among compounds with different heteroatoms and has been proven to be useful in QSPR and QSAR studies.

The $\epsilon(\rho)$ index has been obtained in this work by using the semiempirical quantum chemical method PM3, but the use of any other quantum chemical approach (semiempirical or *ab initio*) is valid too. On the other hand, the use of geometry optimization is not a necessary condition to generate the new index. We can use a frozen geometry or molecular mechanics models in the sake of simplicity to be used in non-time-consuming calculations of larger molecules of biological interest, by simple computers.

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