ORIGINAL PAPER

Matías Tueros · Eduardo A. Castro
Andrey A. Toropov

Maximum topological distance-based indices as molecular descriptors for QSPR. 3 – Calculation of the hydrophobicity of polyaromatic hydrocarbons

Abstract Maximum topological distance-based indices are used together with standard ones to compute the hydrophobicity of polyaromatic hydrocarbons. Several variables and higher-order regression equations are computed and shown to be excellent predictors for the chosen physical-chemistry property. This new alternative offers advantages the usual manner of deriving global topological indices for QSPR. Some possible future extensions are pointed out.

Keywords Detour matrix · Hydrophobicity · Topological indices · Polyaromatic hydrocarbons · QSAR/QSPR theory

Introduction

The topological geometry of molecules should pertain to either the weak polar–polar interactions or the geometric requirements for substrate–receptor complex formation in which the whole molecule takes part. The first sort of interactions, however, are relevant to such primary effects as substrate partitioning between phases of different polarity, soil sorption, association coefficients, etc. These primary effects and/or geometric demands for fitting into a receptor cavity (thus facilitating either hydrophobic or electronic interactions) can determine secondary biological effects such as acute toxicity, carcinogenecity, etc. [1]

M. Tueros · E.A. Castro (✉)
CEQUINOR, Departamento de Química,
Facultad de Ciencias Exactas, Universidad Nacional de La Plata,
C.C. 962, La Plata 1900, Argentina
e-mail: castro@dalton.quimica.unlp.edu.ar

A.A. Toropov
Vostok Innovation Company, S. Azim street 4,
Tashkent 700047, Uzbekistan

Hydrophobic solutes [2] (also known as "structure-making" solutes) are sparingly soluble in water, since the intermolecular forces between water and solute molecules are weaker than the hydrogen-bond interactions between the water molecules. [3, 4] The IR spectra of their solutions resemble that of water at higher temperatures and hence indicate a corresponding structural rearrangement as "structure makers". The dissolution of such molecules causes a positive change (loss) in entropy. The solute molecules or ions are placed in holes in the water structure, which are adaptable to the need of the solute molecule for free rotation. [5]

It is also worth mentioning that hydrophobic bonds play a key role in association and in conformational changes in biological systems, for example in stabilizing the helical structure by incorporation between two neighboring residues of the α-helix. The helical form of DNA is stabilized by the addition of electrolytes, [6] and the effects are greatly influenced by the concentration.

On the other hand, the stereospecificity of the reduction of acetaldehyde by DPNH and ADH, leading to the formation of only one enantiomer of ethanol-1-D when a deuterium atom is transferred, is explicable in terms of a "hydrophobic region" at the active site that can distinguish the small alkyl group (hydrogen) from the large alkyl group (ethyl). [7] Good experimental evidence for a hydrophobic region in the active site is given by the discovery that long-chain fatty acid amides complex with DPNH and ADH. [8]

It is well known that tertiary structure of the protein arises from a tendency for many long chains to fold back on themselves with stabilization arising from interhelical hydrogen bonds, disulfide linkages, hydrophobic bonds, and ionic interactions. [9, 10, 11, 12] "Hydrophobic bond" is a loose term useful for describing the juxtaposition of nonpolar portions of the protein molecule produced by removing these nonpolar portions from the structure-forming water regions. [13] From a macroscopical point of view and from thermodynamic studies it would seem that the stability of these hydrophobic bonds is primarily due to a favorable entropy effect. [14] If it

were to occur, the direct interaction of a nonpolar group would cause the formation of a highly ordered frozen array of water molecules around the nonpolar groups. [15]

Thus, several significant biological phenomena such as protein folding, membrane formation, drug binding to proteins, and the formation of amyloid plaques in Alzheimer's disease tissues are largely driven by hydrophobic interactions. In an extremely simplified view, water squeezes out nonpolar molecules or groups, resulting in attractive interactions between hydrophobic solutes. [16] From this simple and na picture, one can expect there could be a close relationship with the usual topological indices employed in QSAR/QSPR theory and primary and secondary reactivity effects.

Hydrophobic effects have been studied with numerous theoretical models and computer simulations. [17]

The hydrophobicity (log P, octanol–water) of different sets of molecules has been predicted from their topological indices very effectively. [18, 19] Global topological indices were also found to correlate with biological data. In general, structure–activity/property models include parameters responsible for both main steps of the biological process: the penetration and the stereoelectronic interaction. In these cases the topological indices can be included in the models because of their relationship either with the penetration parameter (reflecting polar-polar interactions with the biological phases) or with the stereoelectronic one (representing substrate–receptor geometric correspondence). Some recent reviews on these issues that bring new ideas into focus in this area can be found in [20].

The aim of this paper is to present the results of several models to predict the hydrophobicity of polyaromatic hydrocarbons (i.e. polycyclic aromatic hydrocarbons). These models are based on maximum topological distance-based indices as molecular descriptors for QSPR/QSAR and they complement two previous studies on this issue [21, 22] about alkyl-benzenes and alcohols.

This paper in organized as follows: the next section deals with the explanation in detail of the particular choice of maximum topological distance-based indices making suitable comparisons with other similar ones. Then, we describe the calculation method and give the results, paying special attention to the analysis, in a comparative fashion, of the predicted results with alternative global topological descriptors. The degree of accuracy of the regression equations is discussed from the relevant statistical parameters as well as their predictive capabilities. Finally, we present the conclusions in order to show the advantages of the present choice of descriptors and pointing out some possible further extensions to study other physical-chemistry properties and biological activities.

Maximum topological distance-based indices

The term "topological index" was first proposed by Hosoya [23] for characterizing the topological nature of a graph. It is an integer quite easily obtained from a graph by a specified recipe. Since then, more than one hundred different topological indices for chemical graphs have been proposed. [24]

A graph is a mathematical object and can be represented either in a geometrical or algebraic way, i.e. via a matrix. Define a N×N adjacency matrix, A, for a graph, of the order N=V (where V is the number of vertices), with elements such that $A_{ij}=\{1$ for an adjacent pair v_i and v_j, and 0 otherwise}. If G is given, then A is uniquely determined, and vice versa. The distance matrix D can be defined for G with elements $D_{ij}=d(ij)$, the distance, or the *least* number of steps from v_i to v_j. If a graph G is given, the matrix D can be reproduced uniquely, while by wiping out all the elements in D except for unity, one obtains A. Thus one can assert that matrices A and D, for G are mathematically equivalent

$$G \quad \begin{array}{ccccc} 1 & 2 & 3 & 4 & 5 \\ o\!-\!\!-\!\!-\!o\!-\!\!-\!\!-\!o\!-\!\!-\!\!-\!o\!-\!\!-\!\!-\!o \end{array}$$

$$A = \begin{bmatrix} 0 & 1 & 0 & 0 & 0 \\ 1 & 0 & 1 & 0 & 0 \\ 0 & 1 & 0 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 \\ 0 & 0 & 0 & 1 & 0 \end{bmatrix} \qquad D = \begin{bmatrix} 0 & 1 & 2 & 3 & 4 \\ 1 & 0 & 1 & 2 & 3 \\ 2 & 1 & 0 & 1 & 2 \\ 3 & 2 & 1 & 0 & 1 \\ 4 & 3 & 2 & 1 & 0 \end{bmatrix}$$

$$A \leftrightarrow G \leftrightarrow D$$

Distance matrix D has been particularly useful and fruitful for defining several distance-based indices as molecular descriptors for QSPR/QSAR. [1] Later on, an interesting change was suggested in the definition of D; to resort to the concept of non-redundant maximum distance instead of least steps from v_i to v_j. [25, 26] This new D_{max} matrix (detour matrix) opened the possibility of redefining all indices associated with the distance concept and gave rise to a new set of "maximum topological distance-based indices". Several initial numerical tests on the basis of these new indices have proven to be quite promising since in many cases they yield better results than those developed from the standard definition of distance. [21, 22, 25, 26]

Here our purpose is to extend the set of chemical properties and biological activities to be tested in order to obtain more definitive conclusions about the usefulness of this new set of topological indices. Thus, we have chosen the hydrophobicity of a group of 44 polyaromatic hydrocarbons and have selected several well-known indices based upon the topological distance matrix to compute the corresponding regression equations. These indices are the Wiener index (W), the Harary index (H), the Balaban index (J), the molecular topological index of Schultz (MTI), zero-, first-, and second-order molecular connectivity indices ($^{0}\chi$, $^{1}\chi$, and $^{2}\chi$, respectively), and Zagreb group indices (M_1 and M_2).

Since all these are well-known global topological indices and their definitions have been published elsewhere, [1, 21, 22, 25, 26] we do not include their formulae here.

Calculation method

We have selected the set of 44 polyaromatic hydrocarbons chosen by Basak et al. [18] and made a thorough search of the best one-, two-, three-, four-, and five-variable correlations up to third-order equations for hydrophobicity. Although the number of compounds chosen (44) is rather small, numerical results do not change significantly with a larger set. The fitting equations have the general form

$$P = \sum_{i=1}^{m} a_i q_i + b \tag{1}$$

$$P = \sum_{i=1}^{m} a_i q^i p^i + b_i q^i + c_i p^i + d \tag{2}$$

$$P = \sum_{i=1}^{m} a_i q^i p^i + b_i q^i + c_i p^i + d_i q^i + e_i r^i + f_i p^i + g \tag{3}$$

$$P = \sum_{i=1}^{m} a_i q^i p^i + b_i q^i r^i + c_i p^i r^i + d_i q^i s^i + e_i p^i s^i + f_i r^i s^i + g_i q^i + h_i p^i + j_i s^i + k \tag{4}$$

$$P = \sum_{i=1}^{m} a_i q^i p^i + b_i q^i r^i + c_i p^i r^i + d_i q^i s^i + e_i p^i t^i + f_i p^i t^i + g_i r^i t^i + h_i s^i t^i + j_i p^i s^i + k_i r^i s^i + l_i p^i + m_i q^i + n_i r^i + o_i s^i + u_i t^i + v \tag{5}$$

where $m=1, 2, 3$; a_i, b_i, c_i, d_i, e_i, f_i, g_i, h_i, j_i, k_i, l_i, m_i, n_i, o_i, u_i, b, d, g, k, and v are real numbers arising from the fitting procedure, P is the property (i.e. hydrophobicity) and p, q, r, s, and t are the topological descriptors (i.e. $^0\chi$, $^1\chi$, $^2\chi$, M_1, M_2, W, H, J, MTI, W_{max}, H_{max}, J_{max}, and MTI_{max}). No pair of these variables is not closely correlated, so they can be used as (nearly) independent variables in the polynomial regression equations.

We have previously verified the need to resort to several variables and higher-order equations to attain meaningful predictive models within the realm of QSAR/QSPR and that it is not necessary to go beyond third-order equations. [27, 28, 29, 30]

We have employed the standard software included in the MATHEMATICA package [31] to perform the multilinear regression analysis of hydrophobicity versus global topological indices. The whole set of descriptors was used in two steps: first we made a complete search among the standard indices based on the normal definition of D, and then we performed a total search among the whole set of the topological indices. This particular partition was selected just for comparative purposes.

Results

In Table 1 we display the topological descriptors for the molecular set. The first choice consisted of the usual indices while the second choice added to the first set those computed on the basis of the maximum distance matrix.
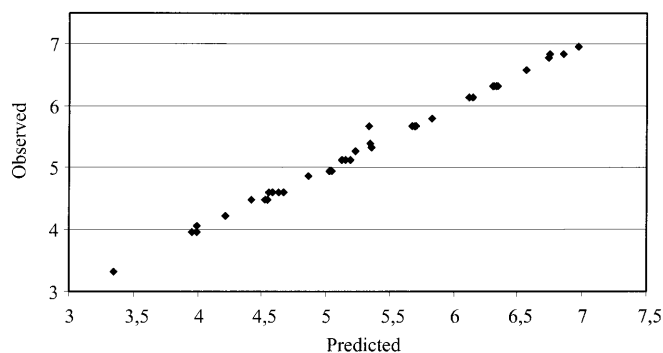

Fig. 1 Observed versus predicted hydrophobicity of polyaromatic hydrocarbons via the best one-variable linear regression (i.e. hydrophobicity=$a^0\chi$+b where a, b$\subset\Re$)
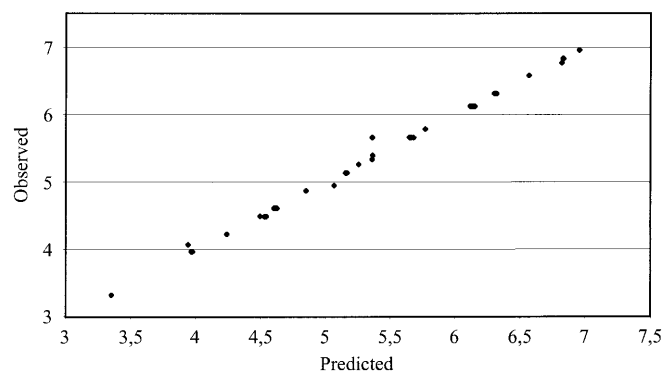

Fig. 2 Observed versus predicted hydrophobicity of polyaromatic hydrocarbons via the best one-variable second-order regression (*i.e* hydrophobicity = $A^0\chi$+$B(^0\chi)^2$+C where A, B, C $\subset\Re$)

For the first choice of descriptors, the best one-, two-,..., five-variable correlations are (shown in Tables 2 and 3): $^0\chi$, $^1\chi$, $^2\chi$, M_1, M_2, W, H, J, MTI.

Similar results hold for third-order equations.

The best one-, two-,..., five-variable correlations among the complete set of topological indices are shown in Tables 4 and 5): $^0\chi$, $^1\chi$, $^2\chi$, M_1, M_2, W, H, J. MTI, W_{max}, H_{max}, J_{max}, MTI_{max}.

Once again, similar results hold for third-order equations, so that we do not include them here. Complete results are available as supplementary material.

A comparison of the results for the first restricted molecular descriptors set (i.e. $^0\chi$, $^1\chi$, $^2\chi$, M_1, M_2, W, H, J, and MTI) with those derived from the second more complete molecular descriptors set (i.e. $^0\chi$, $^1\chi$, $^2\chi$, M_1, M_2, W, H, J, MTI, W_{max}, H_{max}, J_{max}, and MTI_{max}) clearly shows that those descriptors based on the detour matrix perform better.

In Figs. 1 and 2 we show two relationships (best one-variable linear regression and best one-variable second-order regression, respectively) between theoretical and experimental hydrophobicity data for polyaromatic

Table 1 Experimental hydrophobicity and topological indices of polyaromatic hydrocarbons

Molecule	Hydr	$^0\chi$	$^1\chi$	$^2\chi$	M1	M2	W	H	J	MTI	W_{max}	H_{max}	J_{max}	MTI_{max}
1-ethylnaphthalene	4.494	8.389	11.830	9.615	60	140	182	31.533	1.987	816	518	10.444	0.662	2280
1-methylbenz[a]anthracene	6.313	12.820	18.653	17.046	108	264	632	65.708	1.541	2952	2542	12.561	0.364	11818
5,6-dimethylchrysene	6.962	13.690	19.508	17.865	114	282	734	70.942	1.537	3376	2854	14.595	0.374	13150
5-methylchrysene	6.313	12.820	18.653	17.066	108	264	644	65.479	1.518	3002	2550	12.520	0.363	11848
6-methylbenzo[e]pyrene	6.773	13.974	20.653	19.399	126	318	748	79.985	1.551	3567	3532	13.480	0.312	16851
9,10-dimethylanthracene	5.788	11.121	15.575	13.885	88	216	378	50.952	1.831	1724	1342	12.665	0.488	6076
9-methylanthracene	5.139	10.251	14.720	13.023	82	198	326	45.769	1.760	1515	1174	10.447	0.465	5367
Acenaphthene	4.070	7.966	11.899	10.593	68	166	166	33.400	1.845	824	627	7.043	0.474	2970
Anthracene	4.490	9.380	13.865	12.161	76	180	279	40.786	1.682	1324	1015	8.339	0.444	4692
Benzo[a]fluorene	5.339	11.242	16.865	15.115	98	242	461	56.057	1.560	2211	1914	9.821	0.357	9060
Benzo[a]pyrene	6.124	13.104	19.832	18.257	120	302	680	73.680	1.487	3302	3166	11.523	0.305	15242
Benzo[b]fluoranthene	6.124	13.104	19.865	18.112	120	304	676	73.668	1.504	3271	3201	11.414	0.302	15406
Benzo[b]fluorene	5.399	11.242	16.865	15.288	98	240	471	55.658	1.522	2262	1906	9.865	0.359	9028
Benzo[e]pyrene	6.124	13.104	19.865	18.108	120	304	652	74.548	1.553	3160	3190	11.418	0.303	15356
Benzo[ghi]perylene	6.584	14.259	21.832	20.543	138	356	815	88.043	1.475	4032	4433	12.093	0.259	21832
Benzo[j]fluoranthene	6.124	13.104	19.865	18.108	120	304	678	73.611	1.500	3282	3188	11.489	0.303	15338
Chrysene	5.664	11.949	17.865	15.798	102	250	545	60.721	1.538	2584	2275	10.460	0.351	10664
Dibenz[a,h]anthracene	6.838	14.518	21.798	19.782	128	316	971	81.742	1.346	4620	4261	12.724	0.292	20192
Dibenz[a,j]anthracene	6.838	14.518	21.798	19.782	128	316	955	81.974	1.367	4540	4265	12.712	0.292	20208
Fluoranthene	4.950	10.535	15.899	14.278	94	236	364	52.467	1.677	1772	1581	9.234	0.368	7556
Fluorene	4.225	8.673	12.899	11.305	72	174	219	36.893	1.762	1056	815	7.603	0.452	3812
Naphthalene	3.316	6.812	9.933	8.178	50	114	109	23.900	1.925	520	345	5.998	0.588	1560
Phenanthrene	4.490	9.380	13.899	11.988	76	182	271	41.143	1.740	1284	1019	8.294	0.443	4708
Pyrene	4.950	10.535	15.865	14.423	94	234	362	52.610	1.671	1770	1564	9.293	0.373	7474
Triphenylene	5.664	11.949	17.899	15.673	102	252	513	61.729	1.642	2424	2229	10.749	0.359	10428
2-methylnaphthalene	3.965	7.682	10.720	9.446	56	128	144	27.633	1.932	664	424	8.049	0.629	1890
12-methylbenz[a]anthracene	6.313	12.820	18.687	16.853	108	266	620	66.163	1.573	2898	2538	12.593	0.365	11798
1,4-dimethylnaphthalene	4.614	8.552	11.575	10.288	62	146	176	32.000	2.055	790	516	10.161	0.664	2270
Perylene	6.124	13.104	19.865	18.108	120	304	654	74.490	1.545	3172	3190	11.642	0.308	15116
Benzo[k]fluoranthene	6.124	13.104	19.832	18.261	120	302	698	72.931	1.453	3384	3178	11.527	0.304	15296
Benz[a]anthracene	5.664	11.949	17.832	15.971	102	248	553	60.363	1.512	2624	2265	10.509	0.352	10624
Benz[b]anthracene	5.664	11.242	16.865	15.135	98	242	440	56.862	1.626	2114	1894	9.910	0.362	8956
6-methylchrysene	6.313	12.820	18.687	16.853	108	266	632	65.851	1.544	2948	2560	12.482	0.362	11892
7-ethylbenz[a]anthracene	6.842	13.257	19.763	17.259	112	276	714	71.100	1.580	3288	2834	15.098	0.376	13068
7-mehtylbenz[a]anthracene	6.313	12.820	18.687	16.833	108	266	624	66.023	1.562	2916	2540	12.856	0.364	11806
2-methylphenanthrene	5.139	10.251	14.687	13.256	82	196	334	45.454	1.722	1547	1180	10.359	0.463	5393
2-methylanthracene	5.139	10.251	14.653	13.429	82	194	342	45.096	1.673	1587	1174	10.419	0.465	5369
2,6-dimethylnaphthalene	4.614	8.552	11.508	10.713	62	142	186	31.150	1.936	834	512	10.211	0.669	2254
2,3-dimethylnaphthalene	4.614	8.552	11.542	10.461	62	144	182	31.700	1.976	818	514	10.191	0.667	2262
1-methylfluorene	4.874	9.544	13.720	12.360	78	190	267	41.467	1.786	1255	959	9.617	0.471	4429
1-methylnaphthalene	3.965	7.682	10.754	9.233	56	130	140	27.850	1.993	646	426	8.024	0.626	1898
1,5-dimethylnaphthalene	4.614	8.552	11.575	10.288	62	146	176	32.000	2.053	790	518	10.141	0.662	2278
1,3-dimethylnaphthalene	4.614	8.552	11.542	10.525	62	144	179	31.833	2.015	804	515	10.175	0.665	2266
1,4,5-trimethylnaphthalene	5.263	9.422	12.397	11.363	68	162	216	36.400	2.123	948	618	12.378	0.699	2688

Table 2 Best linear one-, two-,...., five-variable correlations

Variables	Regression coefficient	Final loss	Variance Explained
$^0\chi$	0.9749	1.8688	95.04%
$^0\chi$, $^1\chi$	0.9964	0.2687	99.29%
$^0\chi$, $^1\chi$, J	0.9966	0.2534	99.66%
$^0\chi$, $^1\chi$, $^2\chi$, M_1	0.9970	0.2269	99.70%
$^0\chi$, $^1\chi$, $^2\chi$, M_1, M_2	0.9972	0.2078	99.72%

Table 3 Best quadratic one-, two-,..., five-variable correlations

Variables	Regression coefficient	Final loss	Variance explained
$^0\chi$	0.9751	1.4452	96.43%
$^0\chi$, $^1\chi$	0.9966	0.2588	99.31%
$^0\chi$, $^1\chi$, J	0.9972	0.2140	99.43%
$^0\chi$, $^1\chi$, $^2\chi$, M_1	0.9973	0.2032	99.46%
$^0\chi$, $^1\chi$, $^2\chi$, M_1, M_2	0.9977	0.1767	99.53%

hydrocarbons. Complete results (i.e. best one-variable third-order, best two-variables first-order, etc. regressions) are available as supplementary material.

The analysis of above results reveals the excellent predictive power of the present regression for computing hydrophobicity. A comparative examination of previous equations allows us to verify the better performance of topological indices based on maximum distance matrix with respect to the others. In this regard, especially important are Balaban and Harary maximum indices. We can also see that higher-order equations improve on linear ones, although the differences are not spectacular. A similar comment applies on going from one- to several-variable equations.

Table 4 Best linear one-, two-,..., five-variable correlations

Variables	Regression coefficient	Final loss	Variance explained
$^0\chi$	0.9749	1.8688	95.04%
$^0\chi$, H_{max}	0.9972	0.2143	99.43%
$^0\chi$, $^1\chi$, H_{max}	0.9976	0.1833	99.51%
$^0\chi$, $^1\chi$, H_{max}, J_{max}	0.9977	0.1706	99.55%
$^0\chi$, $^1\chi$, MTI, H_{max}, J_{max}	0.9978	0.1684	99.55%

Table 5 Best quadratic one-, two-,..., five-variable correlations

Variables	Correlation coefficient	Final loss	Variance explained
$^0\chi$	0.9751	1.4452	96.43%
$^0\chi$, H_{max}	0.9972	0.2112	99.44%
$^0\chi$, $^1\chi$, H_{max}	0.9977	0.1711	99.55%
$^0\chi$, $^1\chi$, H_{max}, J_{max}	0.9979	0.1612	99.57%
$^0\chi$, $^1\chi$, MTI, H_{max}, J_{max}	0.9980	0.1513	99.60%

Conclusions

The inclusion of maximum distance-based topological indices gives significant improvements in the calculations of regression equations for prediction the hydrophobicity of polyaromatic hydrocarbons compared to the standard descriptors derived from the usual distance matrix. It is especially important to resort to several variables and higher-order equations to attain very good predictive models. All these conclusions agree with those derived in previous studies on this issue.

Since we have up to now analyzed just two physical-chemistry properties (boiling points and hydrophobicity) for a very specialized set of molecules (hydrocarbons and alcohols), we consider there is not yet enough room to give definitive conclusions about the real merits of the proposed alternative set of maximum distance based indices as molecular descriptors for QSPR. However, the present results are sufficient to encourage new efforts to look for new application areas and different molecules in order to test these new topological descriptors.

Research along these lines is being carried out in our laboratories and results will be published elsewhere.

Supplementary material Complete results are available as supplementary material or upon request to the corresponding author.

References

1. Mekenyan, O.; Basak, S. C. Topological indices and chemical reactivity. In *Graph Theoretical Approaches to Chemical Reactivity*; Bonchev, D; Mekenyan, O., Eds.; Kluwer: Dordrecht, 1994, p. 232.

2. Bene, J. D.; Pople, J. A. *J. Chem. Phys.* **1970**, *52*, 4858.

3. Luck, W. P. A. *Top. Curr. Chem.* **1976**, *64*, 115.

4. Luck, W. P. A. The hydrogen bond recent developments. In *Theory and Experiment*, Schuster P. et al., Eds.; North-Holland: Amsterdam, 1976, Chapter 28.

5. Gutman, V. *The Donor–Acceptor Approach to Molecular Interactions*; Plenum Press: New York, 1978, p. 95.

6. Eagland, D. A comprehensive treatise. In *Water*, vol. 5, Franks F. Ed.; Plenum Press: New York, 1975, p. 1.

7. Kosower, E. M. *Molecular Biochemistry*; McGraw-Hill: New York, 1962, p. 218.

8. Winer, A. D.; Theorell, H. *Acta Chem. Scand.* **1960**, *14*, 1729.

9. Lindestrom-Lang, K. V.; Schellman, J. A. *The Enzymes*, vol. 1; Academic Press: New York, 1959, chapter 10.

10. Boyer, P. D. *Protein Structure and Function Brookhaven Symposia in Biology*, 1960, 13, BNL 608 (C-30), p. 1.

11. Klotz, I. M. *Protein Structure and Function Brookhaven Symposia in Biology*, 1960, 13 BNL 608 (C-30), p. 25.

12. Scheraga, H. A. *Protein Structure and Function Brookhaven Symposia in Biology*, 1960, 13, BNL 608 (C-30), p. 71.

13. Kosower, E. M. *Molecular Biochemistry*; McGraw-Hill: New York, 1962, p. 275.

14. Kauzmann, W. *Adv. Protein Chem.* **1959**, *14*, 1.

15. Salem, L. Intermolecular forces in biological systems. In *Electronic Aspects of Biochemistry*; Pullman B. Ed.; Academic Press: New York, 1967, p. 297.

16. Richards, F. M. *Sci. Am.* **1991**, *264*, 54.

17. (a) Oobatake, M.; Ooi, T. *Prog. Biophys. Mol. Biol.* **1993**, *59*, 237. (b) Giesen, D. J.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem.* **1994**, *98*, 4141. (c) Tuñón, I.; Silla, E.; Pascual-Ahuir, J. L *J. Phys. Chem.* **1994**, *98*, 377. (d) Fukunishi, Y.; Suzuki, M. *J. Phys. Chem.* **1996**, *100*, 5634. (e) Ashbaugh, H. S.; Kaler, E. W.; Paulaitis, M. E. *Biophys. J.* **1998**, *75*, 755. (f) Rank, J. A.; Baker, D. *Protein Sci.* **1997**, *6*, 347. (g) Besseling, N. A. M.; Lyklema, J. *J. Phys. Chem. B* **1997**, *101*, 7604. (h) Madan, B.; Sharp, K. *J. Phys. Chem. B* **1997**, *101*, 11237. (i) Matubayasi, N.; Reed, L. H.; Levy, R. M. *J. Phys. Chem.* **1994**, *98*, 10640. (j) Kinoshita, M.; Hirata, F. *J. Chem. Phys.* **1997**, *106*, 5202. (k) Hummer, G.; Garde, S. *Phys. Rev. Lett.* **1998**, *80*, 4193. (l) Wallqvist, A.; Berne, B. J. *J. Phys. Chem.* **1995**, *99*, 2893. (m) Head-Gordon, T, *J. Am. Chem. Soc.* **1995**, *117*, 501. (n) Garde, S.; Hummer, G.; Paulaitis. M. E. *Faraday Discuss.* **1996**, *103*, 125. (o) Lüdemann, S.; Abseher. R.; Schreiber, H.; Steinhauser, O. *J. Am. Chem. Soc.* **1997**, *119*, 4296. (p) Forsman, J.; Jönsson, J. *J. Chem. Phys.* **1994**, *101*, 5116. (q) Beutler, T. C.; Béguelin, D. R.; Van Gunsteren, W. F. *J. Chem. Phys.* **1995**, *102*, 3787. (r) Beglov, D.; Roux, B. *J. Chem. Phys.* **1994**, *100*, 9050. (s) Silverstein, K. A. T.; Haytmet, A. D. J.; Dill, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 3166. (t) Arthur, J. W.; Haymet, A. D. *J. Chem. Phys.* **1998**, *109*, 7991. (u) Cheng, Y. K.; Rossky, P. J. *Nature* **1998**, *392*, 696. (v) Lum, K.; Luzar, A. *Phys. Rev. E* **1997**, *56*, R6283. (w) Hummer, G.; Garde, S.; García, A. E.; Pohorille, A.; Pratt, L. R. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 8951. (x) Berne, B. J. *Proc. Natl. Acad. Sci. USA* **1996**, *93*, 8800. (y) Lum, K.; Chandler, D.; Weeks, J. D. *J. Phys. Chem. B* **1999**, *103*, 4570. (z) Hummer, G. *J. Am. Chem. Soc.* **1999**, *121*, 6299.

18. (a) Basak, S. C.; Niemi, G. J.; Veith, G. D. *J. Math. Chem.* **1990**, *4*, 185. (b) Murray, W. J.; Hall, L. H.; Kier, L. B. *J. Pharm. Sci.* **1975**, *64*, 1978.

19. Mekenyan, O.; Weith, G.; Bradburry, S.; Russom, C. *Quant. Str.–Act. Relat.* **1993**, 12.

20. Lipkowitz, K. B.; Boyd, D. B. (Eds.) *Reviews in Computational Chemistry*, vol. 11; Wiley–VCH: New York, 1997, chapters 3–5.

21. Firpo, M.; Gavernet, L.; Castro, E. A.; Toropov, A. A. *J. Mol. Struct. (Theochem)* **2000**, *501*, 419.

22. Tueros, M.; Castro, E. A.; Toropov, A. A. *Comput. Chem.* **2000**, *24*, 571.

23. Hosoya, H. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2332.

24. Rouvray, D. The origins of chemical graph theory. In *Chemical Graph Theory*; Bonchev, D.; Rouvray, D. H. Eds.; Abacus Press/Gordon and Breach: New York, 1991.
25. (a) Toropov, A. A.; Toropova, A. P. *Russ. J. Coord. Chem.* **1997**, *23*, 789. (b) Toropov, A. A.; Toropova, A. P. *Russ. J. Coord. Chem.* **1998**, *24*, 89.
26. Harary, F. *Graph Theory*; Addison-Wesley: Reading, MA, 1969, p. 203.
27. Romanelli. G.; Cafferata. L. F. R.; Castro, E. A. *J. Mol. Struct. (Theochem)* **2000**, *504*, 261.
28. Firpo, M.; Gavernet, L.; Castro, E. A. *Rom. J. Phys.* **1999**, *44*(1,2), 181.
29. Firpo, M.; Gavernet, L.; Castro, E. A. *Polish J. Chem.* **1999**, *73*, 1041.
30. Castro, E. A. *Comput. Chem.* **1997**, *21*, 305.
31. Adamchik, V. *Guide to Standard Mathematica Package Version 222*, Technical Report, Wolfram Research, 1999.