A Comparative QSAR Study Using Wiener, Szeged, and Molecular Connectivity Indices†

Manorama Mandloi

Department of Chemistry, Model Autonomous Holkar College, A. B. Road, Indore 452001, India

Arun Sikarwar and Nitin S. Sapre

Institute of Chemical Sciences, D. A. University, Vigyan Bhawan, Khandwa Road, Indore 452001, India

Sneha Karmarkar and Padmakar V. Khadikar*

Research Division, Laxmi Fumigation and Pest Control Pvt. Ltd., 3, Khatipura Road, Indore, India

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In this study we have investigated the relative correlation potential of Wiener (W), Szeged (Sz), and molecular connectivity indices ($^0\chi_R$, $^1\chi_R$ and $^2\chi_R$) in developing quantitative structure−activity relationships, QSAR; log *P* values of benzoic acid and its nuclear-substituted derivatives were used for this purpose. The statistical analyses for univariate and multivariate correlations had indicated that both W and Sz are closely related to the connectivity indices ($^m\chi_R$) and that the W, the Sz, and the $^1\chi_R$ indices have similar modeling potentials. $^1\chi_R$ gives slightly better results than both W and Sz. Other connectivity indices $^0\chi_R$ and $^2\chi_R$ correlate poorly with log *P*.

INTRODUCTION

"Problems don't hang on trees. Formulating a good problem is often the most important part of a theoretical research. New problems usually arise when you try to solve old ones."—Ivan Gutman.

The quantitative structure−property relationships (QSPR) as well as quantitative structure−activity relationships (QSAR), based on topological indices, are increasingly being used in several areas of chemistry, biochemistry, pharmacology, and environmental research.[1,2] An interesting achievement of these studies[3] was the effort to numerically encode molecules according to their structural features. The conversion of the structural formula into a numerical value, often called topological or graph theoretical index,[4,5] can be achieved in many ways.[6−9] The rules were even set to search for topological indices [8] of biochemical interest.[10,11]

It appears that among many topological indices[12] that have been proposed since the Wiener index in 1947,[13−23] the connectivity index[19] (χ-index) introduced by Randic 24 years ago in 1975 is the most often used index in QSAR and QSPR. Randic has also initiated two important advances in this field, that is, he introduced the connectivity basis[17−21] and the orthogonalized descriptors.[19−21]

Mihalic and co-workers[22] have observed that the connectivity index and its variants provide the most accurate models; this is a rather general observation whenever the connectivity index is compared to topological or topographic indices. The reasons for this unexpected success of the χ-index and its variants are many. Randic,[19] the originator of the connectivity index, emphasized that the index is a solution to the bond-ordering problem for physical properties. Seybold et al.[9] attributed the success of the connectivity index to its ability to represent the shape of a molecule, which in turn influences the packing ability of a molecule. Therefore, the connectivity index is expected to be especially effective in modeling the shape-dependent properties of molecules. However, since some of the distance indices, particularly three-dimensional distance indices,[23] also possess the above properties, there might be certain additional not-yet-designated factors responsible for the effectiveness of the connectivity index in representing properties as well as activities of various classes of molecules.

Very recently a new molecular graph distance based topological index was introduced by Gutman,[24,25] which was named "Szeged index" because it was conceived and its basic properties were established in Szeged, Hungary.[26]

The Szeged index (Sz) is designed so that for alkanes it coincides with the Wiener index (W), Sz = W. For cyclic molecular graphs, however, Sz and W have different numerical values. A few basic mathematical properties of Sz were established,[24−28] and its certain chemical, biochemical, and environmental applications were reported.[29,40,41]

In our earlier work[36] we have reported a comparative study of the Wiener and Szeged and Schultz (MTI) indices of cycloalkanes and demonstrated that these indices are closely related, being equally capable of predicting the physicochemical properties of cycloalkanes, while W yields slightly better results than both MTI and Sz in developing quantitative structure−property relationship. However, quantitative structure−activity relationships were not treated in this work. Moreover, up to this date no comparison among W, Sz, and $^m\chi_R$ has been made.

In view of the above, we have undertaken the present investigation wherein we have investigated the relative correlation potential of the newly introduced Szeged index, 24 years old (1975) connectivity index ($^m\chi_R$), and 52 years

† Dedicated to Professor Ivan Gutman, teacher, inspirer, friend, and proprietor of graph theory and topology.

* To whom correspondence should be addressed. Telephone: +91 731 531906. E-mail: pvkhadikar@yahoo.com.

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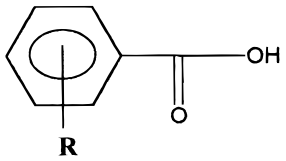

Figure 1. Structure of benzoic acids used in the present investigation.

old (1947) Wiener index. In this work an emphasis is given on the recent Szeged index for a sample of 32 derivatives of benzoic acids. Our results have shown that these indices are all highly linearly related; in particular, W and Sz are proportional.

Another emphasis of the present work is to justify the aforementioned findings by considering the real activities of the benzoic acids used. Therefore, log *P* of benzoic acids are correlated with the said topological indices. The univariate as well as the multivariate correlations have demonstrated that W, Sz, and $^{1}\chi_{R}$ have similar correlative potential in developing QSAR, $^{1}\chi_{R}$ being slightly better than both W and Sz. In monoparametric correlation $^{0}\chi_{R}$ and $^{2}\chi_{R}$ correlate poorly with log *P*. It is worthwhile to mention that the introduction of a dummy parameter (indicator parameter IP) has improved the correlation potential and the best results are obtained using W, Sz, $^{1}\chi_{R}$, $^{2}\chi_{R}$, and IP. The results are discussed below.

MOLECULAR MODELING

Five molecular modeling techniques for the group of 32 benzoic acids (Table 1) were considered. Transformation of the chemical structure of these acids into a mathematical graph makes it possible to express the chemical structure of benzoic acids by a single number. As is well-known, such a numerical index characterizing a molecule (or a corresponding molecular graph) is called a topological index.[3,4,8,12] Therefore, a topological index expresses topological information for a given chemical structure. A standard approach is to use the hydrogen-suppressed graphs, defined as the graphs corresponding to the bare molecular skeleton. In the present study we have used carbon−hydrogen suppressed molecular graphs. Note that in the set of 32 benzoic acids used, both the substituents and their positions are systematically chosen.

It is worthwhile to mention that the graphs here are all consist of one and the same cycle; they differ in the acyclic part only. Thus, they are monocyclic graphs of ring size six carrying zero, one, or two single treelike attachments. This has provided an opportunity to use eqs 6 and 7 of our earlier work[34] for calculating W and Sz for the benzoic acids used.

The advantage of topological indices is that they may be used directly as single molecular descriptors in QSPR as well as QSAR studies. These relationships are mathematical models that enable the prediction of properties and/or activities from structural parameters.

In the present study we have chosen benzoic acids (Figure 1) because they are the starting material for the synthesis of several drugs and they exhibit interesting biological and chemical properties and may eventually lead to useful applications.

Several molecular modeling using uni- as well as multivariate analyses were made using MSTAT software. First, a correlation matrix is derived from the program, and then regression parameters are obtained for several correlations. The results are summarized for comparison.

TOPOLOGICAL INDICES USED

All the three topological indices, namely, Wiener index (W), connectivity index ($^{m}\chi_{R}$), and Szeged index (Sz), as described above, are well presented in the literature.[8,12] Therefore, they will be described here rather briefly.

THE WIENER INDEX (W)

The Wiener index, W = W(G), of graph G is defined as the half-sum of the element of the distance matrix

$$W = {}^{1}/_{2} \sum_{i=1} \sum_{j=1} (D)_{ij} \tag{1}$$

where $(D)_{ij}$ is the *ij*th element of the distance matrix, which denotes the shortest graph-theoretical distance between vertices *i* and *j* in G. All graphs are hydrogen-suppressed.

THE CONNECTIVITY INDEX ($^{M}X_{R}$)

The connectivity index, $\chi = \chi(G)$, of G is defined[19] as

$$\chi = \Sigma[d(_i)d(_j)]^{-0.5} \tag{2}$$

where $d(_i)$ and $d(_j)$ are the valences of the vertices *i* and *j*, equal to the number of bonds connected to the atoms *i* and *j* in G, representing the graph of a compound.

The variants[12,14] of χ, namely, $^{0}\chi_{R}$, $^{1}\chi_{R}$, and $^{2}\chi_{R}$, used in the present investigation are defined as

$$^{0}\chi_{R} = \Sigma[d(_i)]^{-0.5} \tag{3}$$

$$^{1}\chi_{R} = \Sigma[d(_i)d(_j)]^{-0.5} \tag{4}$$

$$\chi_{R} = \Sigma[d(_i)d(_j)d(_z)]^{-0.5} \tag{5}$$

Note that $^{1}\chi_{R}$ is the same as the original χ connectivity index (see eq 2) proposed by Randic.[19]

THE SZEGED INDEX (SZ)

The Szeged index, Sz = Sz(g), of G is defined[27,31] as

$$Sz = Sz(G) = \sum_{u,v} n_u n_v \tag{6}$$

where summation goes over all edges (u, v) in a cyclic graph G. Here, in eq 6, n_u stands for the number of vertices nearer to the vertex v than u, and n_v stands for the number of vertices nearer to the vertex u than v.

The distance $d(u, v)$ is the number of edges in a shortest path connecting vertices v and u in G. Recall that in the case of cyclic graphs, there are vertices equidistant to both the ends of an edge. By definition of Sz, such vertices are not taken into account.

RESULTS

The structural descriptors (W, Sz, $^{0}\chi_{R}$,$^{1}\chi_{R}$, $^{2}\chi_{R}$, and IP) of benzoic acid and its nuclear-substituted derivatives are given in Table 1. The Table 1 also records the log *P* values of the benzoic acids used.

Table 1. The Five Molecular Modeling Techniques and Biological Properties of Benzoic and Substituted Benzoic Acids

S. no.	compound	log *P*	W	Sz	$^0\chi_R$	$^1\chi_R$	$^2\chi_R$	IP
1	benzoic acid	2.04	121	184	6.8115	4.8424	7.4992	0
2	2-Cl-benzoic acid	0.51	238	360	9.8449	6.1638	10.4833	1
3	2-Br-benzoic acid	2.14	152	228	8.2675	5.2510	8.6221	1
4	2-Cl-benzoic acid	2.02	152	228	8.2675	5.2510	8.6221	1
5	2-F-benzoic acid	1.52	152	228	8.2675	5.2510	8.6221	1
6	2-I-benzoic acid	2.45	152	228	8.2675	5.2510	8.6221	0
7	2-CH_3-benzoic acid	2.27	152	288	8.2675	5.2510	8.6221	1
8	2-NO_2-benzoic acid	1.20	238	360	9.8449	6.1638	10.4833	1
9	3-NH_2-benzoic acid	−0.79	250	380	9.8449	6.1469	10.6325	0
10	3-Br-benzoic acid	2.86	156	236	8.2675	5.2363	8.8346	1
11	3-Cl-benzoic acid	2.72	156	236	8.2675	5.2363	8.8346	1
12	3-I-benzoic acid	3.13	156	236	8.2675	5.2363	8.8346	1
13	3-CN-benzoic acid	1.65	202	299	8.9746	5.7738	9.1728	1
14	3-OH-benzoic acid	1.55	202	299	8.9746	5.7738	9.1728	1
15	3-CH_3-benzoic acid	2.38	156	236	8.2675	5.2363	8.8346	0
16	3-OCH_3-benzoic acid	1.98	202	299	8.9746	5.7738	9.1728	0
17	3-NO_2-benzoic acid	1.69	250	380	9.8449	6.1469	10.6325	1
18	3-N$(CH_3)_2$-benzoic acid	0.22	250	380	9.8449	6.1469	10.6325	0
19	4-NH_2-benzoic acid	0.76	262	404	9.8449	6.1469	10.6087	0
20	4-br-benzoic acid	2.81	160	244	8.2675	5.2363	8.8108	1
21	4-Cl-benzoic acid	2.62	160	244	8.2675	5.2363	8.8108	1
22	4-F-benzoic acid	2.05	160	244	8.2675	5.2363	8.8108	1
23	4-I-benzoic acid	3.05	160	244	8.2675	5.2363	8.8108	1
24	4-CN-benzoic acid	1.63	210	315	8.9746	5.6052	9.1490	1
25	4-OH-benzoic acid	1.41	210	315	8.9746	5.6052	9.1490	1
26	4-CH_3-benzoic acid	2.26	160	244	8.2675	5.2363	8.8108	0
27	4-OCH_3-benzoic acid	1.95	210	315	8.9746	5.6052	9.1490	0
28	4-NO_2-benzoic acid	1.84	262	404	9.8449	6.1469	10.6087	1
29	4-N$(CH_3)_2$-benzoic acid	1.28	262	404	9.8449	6.1469	10.6087	1
30	4-CHO-benzoic Acid	1.76	210	315	8.9746	5.6052	9.1490	0
31	2,5-di I-benzoic acid	2.82	192	288	9.1378	5.6469	9.8896	1
32	2,5di Cl-benzoic acid	1.80	192	288	9.1378	5.6469	9.8896	1

Table 2. Correlation Matrix for the Correlation log *P* of Benzoic Acid and Its Nuclear-Substituted Derivatives with Structural Descriptors W, Sz, $^0\chi_R$, $^1\chi_R$, $^2\chi_R$, and IP

	log *P*	W	Sz	$^0\chi_R$	$^1\chi_R$	$^2\chi_R$	IP
log *P*	1.0000						
W	−0.7151	1.000					
Sz	−0.7088	0.9851	1.000				
$^0\chi_R$	−0.6736	0.9613	0.9476	1.0000			
$^1\chi_R$	0.7316	0.9761	0.9598	0.9783	1.0000		
$^2\chi_R$	0.6532	0.9354	0.9286	0.9694	0.9547	1.0000	
IP	0.4044	−0.1597	−0.1598	−0.0755	−0.1347	−0.0820	1.0000

Recall that better results are obtained by introducing a dummy parameter (IP) for the substituents on the aromatic skeleton of benzoic acids. This indicator parameter (IP) is taken as unity for π-electron-withdrawing (nitro- and halogens) substituents; otherwise, it is zero. These IP's are also shown in Table 1.

At this stage it is worth mentioning that the halogens exhibit a negative inductive effect, i.e., are electron withdrawing via the σ bond. The halogen p−π interaction with the aromatic ring, however, is electron donating—a positive resonance effect. Halogens are rather a typical in this respect. Thus, in this respect, of the two groups mentioned above only the nitro group is completely electron withdrawing. Furthermore, it is also worth noting that all the various halogen acids of the same position have the same indices, but the log *P*(obsd) values show them with markedly different properties, emphasizing the markedly different influences Cl, Br, and I have on the parent acid as one runs up the vertical halogen family in the periodic chart. This could be solved by dealing only with those substituents that lie in the first horizontal row of the periodic chart, thus dropping the Cl, Br, and I benzoic acid derivative and comparing the F-substituted compounds with the O-, N-, and C-substituted compounds.

The correlation matrix for the correlation of log *P* with the former mentioned structural descriptors (topological indices) of benzoic acids is shown in Table 2.

The regression parameters as well as the quality of various uni- and multivariate correlations are summarized in Table 3.

The log *P* values for the benzoic acids used were estimated using the best multivariant correlation. Such estimated log *P* values are recorded in Table 4. The observed (experimental) log *P* values are also given in Table 4. The quality of correlations is demonstrated by the residue, i.e., the difference between observed and estimated log *P* values. These residues are also given in Table 4.

DISCUSSION

A perusal of the correlation matrix (Table 2) and the regression parameters recorded in Table 3 shows that in univariate correlations W, Sz, and $^1\chi_R$ are equally capable of predicting physicochemical properties as well as the biological activity of the benzoic acids used. $^1\chi_R$ gives slightly better results than both W and Sz.

The correlation matrix in Table 2 also indicates that all the five indices considered in the study are all highly linearly

Table 3. Regression Parameters and Quality of Correlation of log *P* with the Structural Descriptors (W, Sz, $^0\chi_R$, $^1\chi_R$, $^2\chi_R$, and IP) for Benzoic Acid and Its Nuclear Substituted Derivatives

S. no.	correlation parameter	A*i* $i = 1-5$	*B*	standard deviation SD	correlation coefficient R	*F*-ratio
1	W	−0.0131	4.4756	0.4808	−0.7527	36.602
2	Sz	−0.0084	4.3969	0.4876	−0.7445	34.817
3	$^1\chi_R$	−1.3988	9.7525	0.4714	−0.7638	39.198
4	W−IP	A1 = −0.0127 A2 = 0.4321	4.1072	0.4404	0.8058	24.997
5	Sz-IP	A1 = −0.0081 A2 = 0.4334	4.0292	0.4478	0.7984	23.743
6	$^1\chi_R$-Ip	A1 = −1.3667 A2 = 0.4591	9.2674	0.4226	0.8229	28.308
7	W, $^1\chi_R$, and IP	A1 = −0.9702E-5 A2 = −1.3565 A3 = 0.4589	9.2300	0.4307	0.8229	18.173
8	Sz, $^1\chi_R$, and IP	A1 = −4.5866E-4 A2 = −1.4384 A3 = 0.4608	9.5330	0.4306	0.8229	18.182
9	$^0\chi_R$, $^1\chi_R$, and IP	A1 = 0.7995 A2 = −2.8388 A3 = 0.3869	10.4710	0.4109	0.8403	20.817
10	$^1\chi_R$, $^2\chi_R$, and IP	A1 = −2.4235 A2 = 0.5324 A3 = 0.4030	10.2367	0.4073	0.8433	21.338
11	W, Sz, and $^1\chi_R$	A1 = −0.0224 A2 = 0.0131 A3 = −1.1257	8.4322	0.4369	0.8249	13.310
12	$^0\chi_R$, $^1\chi_R$, $^2\chi_R$, and IP	A1 = 0.4560 A2 = −2.9504 A3 = 0.3749 A4 = 0.3784	10.6363	0.4107	0.8471	15.881
13	$^0\chi_R$, $^1\chi_R$, W, and IP	A1 = 0.8312 A2 = −2.6180 A3 = −0.0027 A4 = 0.3775	9.4918	0.4182	0.8410	15.099
14	Sz, $^0\chi_R$, $^1\chi_R$, and IP	A1 = −9.4603E-04 A2 = 0.8175 A3 = −2.724 A4 = 0.3818	9.9504	0.4187	0.8405	15.044
15	W, Sz, $^1\chi_R$, $^2\chi_R$, and IP	A1 = 0.0524 A2 = −0.0318 A3 = −3.3748 A4 = 0.8226 A5 = 0.3796	12.0214	0.4163	0.8494	12.438
16	W, Sz, $^0\chi_R$, $^1\chi_R$, and IP	A1 = −0.0275 A2 = 0.0145 A3 = 0.8426 A4 = −2.3788 A5 = 0.3711	8.6083	0.4238	0.8434	11.832
17	W, Sz, $^0\chi_R$, $^2\chi_R$, and IP	A1 = −0.0835 A2 = 0.0426 A3 = 0.5869 A4 = −0.2731 A5 = 0.3961	2.7126	0.4523	0.8193	9.799
18	W, $^0\chi_R$, $^1\chi_R$, $^2\chi_R$, and IP	A1 = −0.0024 A2 = 0.4877 A3 = −2.7535 A4 = 0.3710 A5 = 0.3702	9.7667	0.4185	0.8477	12.253
19	Sz, $^0\chi_R$, $^1\chi_R$, and IP	A1−0.0017 A2 = 0.4712 A3 = −2.7544 A4 = 0.3927 A5 = 0.3690	9.731	0.4182	0.8479	12.776
20	W, Sz,$^1\chi_R$, $^2\chi_R$, and IP (deleting 5, 9, 16, and 18)	A1 = 0.0611 A2 = −0.0349 A3 = −4.5372 A4 = 1.2453 A5 = 0.3573	13.8132	0.3389	0.8864	16.139

related; in particular, W and Sz are proportional. The data shows that the correlation of all the three connectivity indices with W is slightly better than with Sz.

The correlation of biological activity (log *P*) of benzoic acids with W, Sz, and $^1\chi_R$ is also similar. Here also $^1\chi_R$ gives slightly better results than W and Sz. Note that the correlation

Table 4. Estimated and Observed log *P* Values of Benzoic Acid and Its Nuclear-Substituted Derivatives from the Regression Expression Eq 9

$$\log P = (0.0611)\mathrm{W} - (0.0349)\mathrm{Sz} - (4.5372)^{1}\chi_{\mathrm{R}} + (1.2453)^{2}\chi_{\mathrm{R}} + (0.3573)\mathrm{IP} + 13.8131$$

benzoic acids	log *P* (obsd)	log *P* (estd)	residue = log *P*(obsd) − log *P*(estd)
1	2.04	2.15	−0.11
2	0.51	0.87	−0.36
3	2.14	2.41	−0.27
4	2.02	2.41	−0.39
5			
6	2.45	2.41	0.04
7	2.27	2.05	0.22
8	1.20	1.23	−0.03
9			
10	2.86	2.70	0.16
11	2.72	2.70	0.02
12	3.13	2.70	0.43
13	1.65	1.30	0.35
14	1.55	1.30	0.25
15	2.38	2.35	0.03
16			
17	1.69	1.52	0.17
18			
19	0.76	1.03	−0.27
20	2.81	2.64	0.17
21	2.64	2.64	−0.02
22	2.05	2.64	−0.59
23	3.05	2.64	0.41
24	1.63	1.96	−0.33
25	1.41	1.96	−0.55
26	2.26	2.28	−0.02
27	1.95	1.60	0.35
28	1.84	1.39	0.45
29	1.28	1.39	−0.11
30	1.76	1.60	0.16
31	2.82	2.54	0.28
32	1.80	2.64	−0.47

of log *P* with remaining topological indices is rather poor.

The parameters recorded in Table 3 indicate that the correlation of the log *P* values of benzoic acids is improved by introducing indicator parameter IP as well as by using multiple regression analysis.

We tried several multiple correlations, and the best results are given in Table 3.

In all the possible bivariate correlations, best results are obtained when $^{1}\chi_{\mathrm{R}}$ and IP are used as the correlating parameters. This supports our earlier findings that $^{1}\chi_{\mathrm{R}}$ gives better results than W and Sz.

Note that by introducing IP in the bivariate correlation the quality of the correlation is considerably improved. The use of IP had resulted in the lowering of standard deviation as well as in an appreciable increase in the correlation coefficient.

The perusal of Table 3 shows that the quality of higher correlations is improved compared to both uni- and bivariate correlations. However, the correlation coefficient in all these higher multiple correlations is found to be close to 0.84.

The data presented in Table 3 indicate that use of five parameters, viz., W, Sz, $^{1}\chi_{\mathrm{R}}$, $^{2}\chi_{\mathrm{R}}$, and IP, gives the best results. This correlation had compounds 5, 9, 16, and 18 as outliers. Neglecting these four compounds gave the best correlation with correlation coefficient of the magnitude of 0.8864. Therefore, using the corresponding regression parameters from Table 3, the following regression expression can be proposed, which can be subsequently used to estimate log *P* of benzoic acids:

$$\log P = (0.0611)\mathrm{W} - (0.0349)\mathrm{Sz} - (4.5372)^{1}\chi_{\mathrm{R}} + (1.2453)^{2}\chi_{\mathrm{R}} + (0.3573)\mathrm{IP} + 13.8132 \quad (7)$$

Note that the low standard derivation (0.3389) and high correlation coefficient (0.8864) and *F*-ratio (16.139) indicate that out of all the correlations we tried (Table 3) the aforementioned correlation (eq 7) gives the best estimated value for log *P*.

To confirm our findings we have estimated log *P* values for benzoic acids using eq 7. These values are shown in Table 4. A comparison of these estimated values of log *P* with the observed ones as well as the magnitude of the residue between observed and estimated log *P* confirms the above findings.

The aforementioned results and discussion indicate that the recently developed Sz index and 24 years old (1975) connectivity index $^{1}\chi_{\mathrm{R}}$ as well as 52 years old (1947) Wiener index W in monoparameteric correlation have similar correlation potentials. In monoparametric correlation, $^{0}\chi_{\mathrm{R}}$ and $^{2}\chi_{\mathrm{R}}$ correlate poorly with log *P*. Thus, both W and Sz are better indices than $^{0}\chi_{\mathrm{R}}$ and $^{2}\chi_{\mathrm{R}}$ in QSAR studies; however, $^{1}\chi_{\mathrm{R}}$ gives better results than both W and Sz.

CONCLUDING REMARKS

The present study related to benzoic acid derivatives leads us to make the following conclusions:

(1) The indices W, Sz, and $^{\mathrm{m}}\chi_{\mathrm{R}}$ for benzoic acids are all highly linearly related; in particular, W and Sz are proportional.

(2) The correlation of W with $^{\mathrm{m}}\chi_{\mathrm{R}}$ is better than the corresponding correlation related to the Szeged index.

(3) In monoparametric correlations log *P* values of benzoic acids correlate equally well with W, Sz, and $^{1}\chi_{\mathrm{R}}$. $^{1}\chi_{\mathrm{R}}$ gives slightly better results than both W and Sz.

(4) The topological indices $^{0}\chi_{\mathrm{R}}$ and $^{2}\chi_{\mathrm{R}}$ in monoparametric correlations correlate poorly with log *P*. Hence, both W and Sz are the better topological indices than $^{0}\chi_{\mathrm{R}}$ and $^{2}\chi_{\mathrm{R}}$ in developing QSAR.

(5) The recently developed Szeged index can also be successfully used in developing QSPR as well as QSAR.

(6) Best results are obtained by adding the indicator parameter and by employing multiple regression analysis.

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