Topological Substituent Descriptors

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Abstract

Motivation. Substituted 1,3,5-triazines are known as useful herbicidal substances. In view of reducing the cost of biological screening, computational methods are carried out for evaluating the biological activity of organic compounds. Often a class of bioactives differs only in the substituent attached to a basic skeleton. In such cases substituent descriptors will give the same prospecting results as in case of using the whole molecule description, but with significantly reduced computational time. Such descriptors are useful in describing steric effects involved in chemical reactions.

Method. Molecular topology is the method used for substituent description and multi linear regression analysis as a statistical tool.

Results. Novel topological descriptors, X_{LDS} and W_s, based on the layer matrix of distance sums and walks in molecular graphs, respectively, are proposed for describing the topology of substituents linked on a chemical skeleton. They are tested for modeling the esterification reaction in the class of benzoic acids and herbicidal activity of 2-difluoromethylthio-4,6-bis(monoalkylamino)-1,3,5-triazines.

Conclusions. Ws substituent descriptor, based on walks in graph, satisfactorily describes the steric effect of alkyl substituents behaving in esterification reaction, with good correlations to the Taft and Charton steric parameters, respectively. Modeling the herbicidal activity of the seo of 1,3,5-triazines exceeded the models reported in literature, so far.

Keywords

Steric effect, Substituent descriptors, Molecular topology, Herbicidal activity.

Abbreviations and notations

MLR, multi linear regression; SVTI, substituent volume topological index; E_S, Taft's steric parameter; n, Charton's steric parameter.

1. Introduction

In the field of chemical reactivity, the first proposal of a substituent steric parameter is due to Taft [1, 2]. He tried to quantify the steric influence of a substituent located on the hydrocarbon part of organic esters in the acid-catalysed hydrolysis of aliphatic carboxylic esters, RCOOR'. His E_s steric parameter is defined as:

$$E_s = \log(k_R / k_{Me})_A \qquad (1)$$

where $\log(k_R / k_{Me})_A$ is the ratio of acid-catalysed hydrolysis rate constant of RCOOR' to that of MeCOOR'. By definition, $E_s(Me) = 0$.

The E_S parameter has been defined empirically [3]. Taft himself pointed out that E_S varies parallel to the atom group radius. Charton also found that E_S is linearly dependent on the van der Waals radius of the substituent, thus defining a new steric parameter, n [4-8].

Murray [9] found correlations between the Taft parameter and the Randić [10] topological index, for a series of substituted alkyls. In this respect, Ivanciuc and Balaban [3] have proposed a topological descriptor, *SVTI*, which encodes the topological distances (i.e., the number of bonds/edges, D_{ij}, joining the atoms/vertices *i* and *j* on the shortest path) in a molecular graph, G.

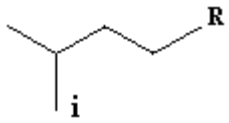
It is defined on the fragment F (i.e. an alkyl group) attached to the vertex i of G, as:

$$SVTI(F) = \sum_{j=1}^{N_F} D_{ij}; \quad D_{ij} \le 3 \qquad (2)$$

The summation runs over all N_F vertices of *F* and the distance D_{ij} is limited to 3, in agreement to the Charton's

conclusion about the limit of the influence of the steric effect beyond the gamma carbon [5-8].

The calculation of SVTI is exemplified for the *sec*-butyl group (R = H) or higher homologues (R ¹ H):



SVTI (s-Bu) = 1+ 2 + 2 + 3 = 8

The above authors have tested their descriptors in describing the reaction rates of acid-catalysed hydrolysis of RCOOR' (the Taft's set).

In the present work, two novel descriptors for substituents are proposed. They are now tested in modeling the effector-receptor interaction in the herbicidal activity of 2-difluoromethylthio-4,6-bis(monoalkylamino)-1,3,5-triazines.

2. Substituent Topological Descriptors, X_{LDS} AND W_S

The substituent descriptors X_{LDS} and W_s herein proposed are constructed with the aid of layer matrices.

Before defining our descriptors, let's recall some knowledges about the layer matrices [11-17].

A partition G(i) with respect to the vertex i, in a graph, is defined [11, 14, 15] as:

$$G(i) = \{G(u)_j, j \in [0, ecc_i] \quad \text{and} \quad u \in G(u)_j\} \tag{3}$$

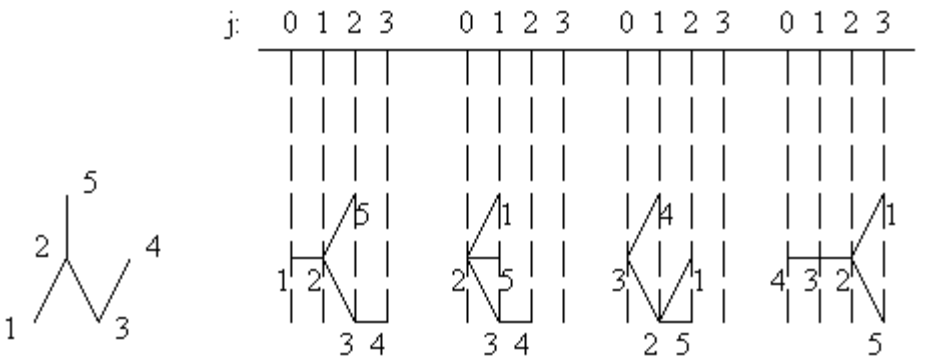
where D_{iu} is the topological distance (see above) and ecc_i is the eccentricity of *i* (i.e. the largest distance between i and any vertex in *G*). Figure 1 illustrates the relative partitions for the graph G_1.

Let $G(u)_j$ be the layer *j* of the vertices u located at distance j, in the relative partition G(i):

$$G(u)_j = \{u : D_{iu} = j\} \tag{4}$$

The entries in a layer matrix, **LM,** collect the topological property P_u for all vertices u belonging to the layer $G(u)_j$:

$$[\mathbf{LM}]_{ij} = \sum_{u \in G(u)_j} P_u \qquad (5)$$



G_1 $G_1(1,5)$ $G_1(2)$ $G_1(3)$ $G_1(4)$

$G_1(1) = \{\{1\},\{2\},\{3,5\},\{4\}\};$ $G_1(2) = \{\{2\},\{1,3,5\},\{4\}\};$

$G_1(3) = \{\{3\},\{2,4\},\{1,5\}\};$ $G_1(4) = \{\{4\},\{3\},\{2\},\{1,5\}\};$

$G_1(5) = \{\{5\},\{2\},\{1,3\},\{4\}\}.$

Figure 1. Partitions of G_1 with respect to each of its vertices

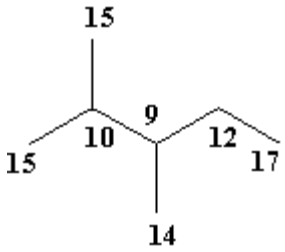
The matrix **LM** can be written as:

$$\mathbf{LM(G)} = \left\{ [\mathrm{LM}]_{ij}; i \in V(G); j \in [0, d(G)] \right\} \qquad (6)$$

where $V(G)$ is the set of vertices in graph and $d(G)$ is the diameter (i.e., the largest distance) of G. The dimensions of such a matrix are $N' (d(G)+1)$.

Figure 2 illustrates the *layer matrix of distance sums*, **LDS** [13], the topological property **M** which collects being the sum of distances joining a vertex i with all the remainder vertices in G. Note that the first column contains just the vertex topological property.

(in this case, $DS_i = \sum_j D_{ij}$, marked in the weighted graph, $G_2\{DS_i\}$).



G_2

$i \setminus j$:	0	1	2	3	4
(1)	15	10	24	26	17
(2)	10	39	26	17	0
(3)	9	36	47	0	0
(4)	12	26	24	30	0
(5)	17	12	9	24	30
(6)	15	10	24	26	17
(7)	14	9	22	47	0

LDS(G_2)

*Figure 2. Matrix **LDS** for the graph G_2*

This matrix and the invariants calculated on (*e.g.*, the well-known Wiener index [18], counting all distances in *G*) are useful tools in topological description of molecular graphs [13, 14].

Another interesting matrix is the *layer matrix of walk degrees* [15], $\mathbf{L}^e\mathbf{W}$. A walk, *W*, is defined [19] as a continuous sequence of vertices, $v_1, v_2, ..., v_m$; it is allowed edges and vertices to be revisited.

If the two terminal vertices coincide ($v_1 = v_m$), the walk is called a closed (or self returning) walk, otherwise it is an open walk.

If its vertices are distinct, the walk is called a path. The number e of edges traversed is called the length of walk.

Walks of length e**,** starting at the vertex *i***,** ${}^eW(i)$, can be counted by summing the entries in the row *i* of the e^{th} power of the adjacency matrix **A** (whose nondiagonal entries are 1 if two atoms are adjacent and zero otherwise):

$$ {}^{e}W(i) = \sum_{j \in V(G)} [A^e]_{ij} \qquad (7) $$

where ${}^eW(i)$ is called the walk degree (of rank *e*) of vertex *i* (or atomic walk count [15, 20]).

Walk degrees, ${}^eW(i)$, can be also calculated by summing the first neighbours degrees of lower rank, according to

an additive algorithm[11] illustrated in figures 3 and 4.

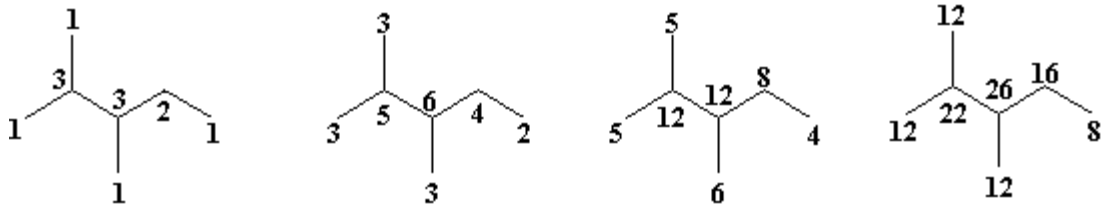
Local and global invariants based on walks in graph were considered for correlating with physico-chemical properties [15, 20].

Figure 3 illustrates the *layer matrix of walk degrees*, $\mathbf{L}^{e}\mathbf{W}$, e = 1-4, for G_2. Note that the first column in $\mathbf{L}^{1}\mathbf{W}$ is just the vertex degree or the vertex valency. Note that the matrix $\mathbf{L}^{e}\mathbf{W}$ was re-invented by Randic in 2001, for e = 1, under the name "valence shells" [21].

The substituent descriptor X_{LDS} is the local "centrocomplexity index", X_{LM} [14], defined on the **LDS** matrix:

$$X_{LDS}(i) = \sum_{j=0}^{ecc_i} [LDS]_{ij} \cdot 10^{-zj} \qquad (8)$$

where i is the attachment point of the substituent to a given chemical structure (see figure 4) and z denotes the number of bits of max[**LDS**]$_{ij}$ in G. Calculation of X_{LDS} is exemplified in figure 4.



$G_2\{^1W_i\}$ $G_2\{^2W_i\}$ $G_2\{^3W_i\}$ $G_2\{^4W_i\}$

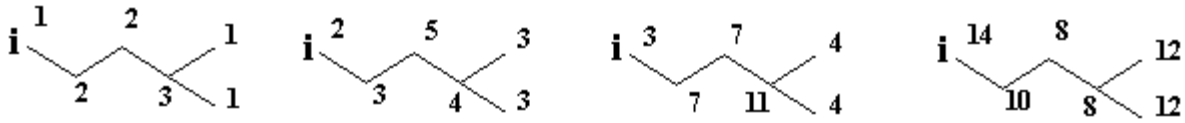
$\mathbf{L}^{1}\mathbf{W}$ **$\mathbf{L}^{2}\mathbf{W}$** **$\mathbf{L}^{3}\mathbf{W}$** **$\mathbf{L}^{4}\mathbf{W}$**

i \ j	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
1	1	3	4	3	1	3	5	9	7	2	5	12	17	14	4	12	22	38	28	8
2	3	5	3	1	0	5	12	7	2	0	12	22	14	4	0	22	50	28	8	0
3	3	6	3	0	0	6	12	8	0	0	12	26	14	0	0	26	50	32	0	0
4	2	4	4	2	0	4	8	8	6	2	8	16	18	10	0	16	34	34	24	0
5	1	2	3	4	2	2	4	6	8	6	4	8	12	18	10	8	16	26	34	24

6	1	3	4	3	1		3	5	9	7	2		5	12	17	14	4		12	22	38	28	8
7	1	3	5	3	0		3	6	9	8	0		6	12	20	14	0		12	26	38	32	0

Figure 3. Layer matrix of walk degrees, $\boldsymbol{L^eW}$ for the graph G_2

(calculated by summing the first neighbor degrees of lower rank)



{^1W} {^2W} {^3W} {*DS*} (a)

W_s (*i*) = 7+7/2+11/3+8/4 ≈ 16.167;

$X_{\mathrm{LDS}}(i) = 14\cdot10^{0}+10\cdot10^{-2}+8\cdot10^{-4}+8\cdot10^{-6}+12\cdot10^{-8}+12\cdot10^{-10} = 14.1008081212 \approx 14.101$; (b)

Figure 4. (a) Walk degrees, ^eW, (calculated by summing the first neighbors degrees of lower rank) and distance sums, DS; (b) Evaluation of W_s and X_{LDS} descriptors

W_S is based on the walks in a connected molecular graph. It is calculated from the layer matrix $\mathbf{L^3W}$ by:

$$W_s(i) = \sum_{j=1}^{ecc_i} ([\mathbf{L}^3\mathbf{W}]_{ij} / j) \qquad (9)$$

where ^3W is the walk number, of length 3.

We limited here to elongation 3 by following the Charton's suggestion about the limit of the influence of steric effect (see above). The calculation of the parameter W_s is exemplified in figure 4.

The *X* descriptor is similar to the *SVTI* parameter, both of them counting distances in the substituent.

LDS

W_s describes the branching in the vicinity of the attachment point *i*.

All these parameters suggest the steric influence of a substituent in the interaction of the skeleton (or a situs of it) with a partner (*e.g.*, a reactant [3, 22] or a biological receptor). They are free of electronic contributions, at least in the variant in which the heteroatom is not considered.

3. Correlating Test

The utility of the substituent descriptors, X_{LDS} and W_s, was proven on a set of thirty aminoalkyl fragments (table 1) involved in the inhibition of Hill reaction of triazines [23] (figure 5).

In this respect, the fragmental volumes, V, (in cm^3/mol) for the considered substituents have been calculated as described below. Other parameter herein considered was the number of atoms different from hydrogen, N.

All these descriptors have been calculated separately for the two sites, A and B (see figure 5).

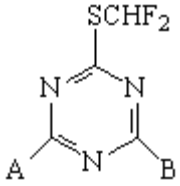


Figure 5. Herbicidal bioactive triazines

Table 1. Topological descriptors and biological activity pI_{50} for the triazines in figure 5

No	A	B	N_A	N_B	$W_{s,A}$	$W_{s,B}$	X_A *	X_B	V_A **	V_B	pI_{50}
1	NH_2	NH_2	1	1	1	1	1.1	1.1	18.763	18.763	3.82
2	NH_2	$NHCH_3$	1	2	1	5	1.1	3.23	18.763	32.636	5.20
3	NH_2	NHC_2H_5	1	3	1	8.5	1.1	6.446	18.763	47.908	5.34
4	NH_2	NH-i-C_3H_7	1	4	1	13.66	1.1	9.061	18.763	60.766	5.83
5	$NHCH_3$	$NHCH_3$	2	2	5	5	3.23	3.23	32.636	32.636	6.01
6	NHCH	NHC H	2	3	5	8.5	3.23	6.446	32.636	47.908	6.39

	$NHCH_3$	NHC_2H_5	2	3	5	8.5	3.23	6.446	32.636	47.908	6.82
7	$NHCH_3$	NHC_3H_7	2	4	5	11.75	3.23	10.071	32.636	62.393	6.75
8	$NHCH_3$	NH-i-C_3H_7	2	4	5	13.66	3.23	9.061	32.636	60.766	6.76
9	$NHCH_3$	NHC_4H_9	2	5	5	13.93	3.23	15.111	32.636	76.638	6.74
10	$NHCH_3$	NH-s-C_4H_9	2	5	5	15.16	3.23	13.091	32.636	75.039	6.76
11	$NHCH_3$	NH-t-C_4H_9	2	5	5	20.50	3.23	12.081	32.636	74.106	6.78
12	$NHCH_3$	NHC_5H_{11}	2	6	5	15.62	3.23	21.161	32.636	88.241	7.12
13	NHC_2H_5	NHC_2H_5	3	3	8.5	8.5	6.446	6.446	47.908	47.908	6.82
14	NHC_2H_5	NHC_3H_7	3	4	8.5	11.75	6.446	10.071	47.908	62.393	6.74
15	NHC_2H_5	NH-i-C_3H_7	3	4	8.5	13.66	6.446	9.061	47.908	60.766	6.89
16	NHC_2H_5	NHC_4H_9	3	5	8.5	13.93	6.446	15.111	47.908	76.638	6.95
17	NHC_2H_5	NH-i-C_4H_9	3	5	8.5	16.16	6.446	14.101	47.908	74.497	7.01
18	NHC_2H_5	NH-s-C_4H_9	3	5	8.5	15.16	6.446	13.091	47.908	75.039	6.87
19	NHC_2H_5	NH-t-C_4H_9	3	5	8.5	20.50	6.446	12.081	47.908	74.106	6.97
20	NHC_2H_5	NHC_5H_{11}	3	6	8.5	15.62	6.446	21.161	47.908	88.241	6.94
21	NHC_2H_5	NHC_6H_{13}	3	7	8.5	17.00	6.446	28.222	47.908	102.032	7.21
22	NHC_2H_5	NHC_7H_{15}	3	8	8.5	18.17	6.446	36.292	47.908	116.672	7.01
23	NHC_2H_5	NHC_8H_{17}	3	9	8.5	19.18	6.446	45.373	47.908	128.770	6.81
24	NHC_3H_7	NHC_3H_7	4	4	11.75	11.75	10.071	10.071	62.393	62.393	6.45
25	NH-i-C_3H_7	NHC_3H_7	4	4	13.66	11.75	9.061	10.071	60.766	62.393	6.75
26	NH-i-C_3H_7	NH-i-C_3H_7	4	4	13.66	13.66	9.061	9.061	60.766	60.766	6.75
27	NH-i-C_3H_7	NHC_4H_9	4	5	13.66	13.93	9.061	15.111	60.766	76.638	6.71
28	NH-i-C_3H_7	NH-s-C_4H_9	4	5	13.66	15.16	9.061	13.091	60.766	75.039	6.88
29	NH-i-C_3H_7	NH-t-C_4H_9	4	5	13.66	20.50	9.061	12.081	60.766	74.106	6.70
30	NH-i-C_3H_7	NHC_5H_{11}	4	6	13.66	15.62	9.061	21.161	60.766	88.241	6.69

* The symbol X stands for X_{LDS} (see text);

** Volume, [cm^3/mol].

Table 2. Statistics of multivariable regression (distinct variables on branches A and B)

No.	X_I	b_i	A	r	s	v(%)	F
1	$1/N_{,B}$	-3.786	7.549	0.8987	0.311	4.752	117.587
2	$1/W_{s,B}$	-3.372	6.933	0.8298	0.396	6.047	61.899
3	$1/X_B$	-3.806	7.038	0.8835	0.333	5.076	99.598
4	$1/V_B$	-72.276	7.760	0.8975	0.313	4.779	115.936
5	$1/N_A$	-1.234	7.810	0.9577	0.208	3.175	149.557
	$1/N_B$	-2.678					
6	$1/W_{s,A}$	-1.335	7.118	0.9615	0.199	3.030	165.554
	$1/W_{s,B}$	-2.077					
7	$1/X_A$	-1.317	7.252	0.9662	0.186	2.844	189.755
	$1/X_B$	-2.526					
8	$1/V_A$	-22.999	8.048	0.9478	0.231	3.519	119.237
	$1/V_B$	-52.514					
9	$1/W_{s,A}$	-1.114	7.618	0.9714	0.172	2.619	226.162
	$1/V_B$	-47.194					
10	$1/W_{s,A}$	-1.180	7.159	0.9729	0.167	2.550	239.280
	$1/X_B$	-2.458					
11	$1/W_{s,A}$	-1.120	7.484	0.9746	0.162	2.472	255.491
	$1/N_B$	-2.484					
12	N_A	-0.385	9.477	0.9834	0.134	2.039	254.937
	$1/N_A$	-2.777					
	$1/N_B$	-2.444					
13	$W_{s,A}$	-0.025	7.372	0.9661	0.190	2.903	121.327
	$1/W_{s,A}$	-1.594					
	$1/W_{s,B}$	-2.056					
14	X_A	-0.078	7.876	0.9818	0.140	2.132	232.401
	$1/X_A$	-2.047					
	$1/X_B$	-2.413					
15	V_A	-0.036	10.649	0.9808	0.144	2.193	219.227
	$1/V_A$	-65.998					

	$1/V_B$	-45.367					
16	X_A	-0.155	9.762	0.9815	0.141	2.152	228.039
	$1/V_A$	-59.011					
	$1/V_B$	-46.244					
17	X_A	-0.154	9.337	0.9836	0.133	2.029	257.426
	$1/V_A$	-60.818					
	$1/X_B$	-2.399					
18	X_A	-0.153	9.614	0.9846	0.129	1.968	274.318
	$1/V_A$	-58.888					
	$1/N_B$	-2.430					

In table 2 A and b_i values are the coefficients of:

$$Y_{calc} = \mathbf{a} + \sum_i \mathbf{b}_i X_i \qquad (10)$$

and leave one out procedure (loo) has the results:

loo(12): r = 0.9768; s = 0.153; v(%) = 2.332;

loo(18): r = 0.9778; s = 0.149; v(%) = 2.271. (11)

The inhibitory activities of triazines on *Chlorella* have been taken from the study of Morita *et al* [24]. They are expressed as pI50, which represents the negative logarithm of concentration required for 50% inhibition of Hill reaction. The correlating results are listed in table 2.

4. Results and Discussion

In *single variable regression*, the descriptors for the substituents in branch B (table 2) are not satisfactory to model the inhibitory activity of triazines; the correlation coefficient, r, is lower than 0.9 (for those in A, r is still lower) and the coefficient of variance, v, is about 5 %. Note that all these "steric" descriptors are taken as reciprocal values, suggesting that the triazine ring fits at the biological receptor as better as the substituent is less sterically involved.

In *two variables regression*, by adding the descriptors for the branch A the correlation is improved, as indicates the higher values for r and F (the Fisher ratio) and the drop in the dispersion, s, and v(%) values (entries 5-8, table 2). When the descriptors for the two branches are heterogeneous, the result is still better (entries 9-11).

In *three variables regression*, the correlation is once more improved. Again the heterogeneous descriptors model the inhibition reaction better that the homogeneous ones (compare entries 16-18 with 12-15, Table 2).

The best model found (see also entry 18) was:

$$pI_{50} = 9.614 - 0.153 \cdot X_A - 58.888 \cdot 1/V_A - 2.430 \cdot 1/N_B;$$

$$n = 30;\ r^2 = 0.9694;\ s = 0.129;\ v(\%) = 1.968;\ F = 274.3; \qquad (10)$$

The cross validation (leave-one-out, "*loo*", procedure) test for the equations in entries 12 and 18 are given in the bottom of table 2.

Despite the excellent model offered by equation (10), a brief inspection on the general structure of these triazines showed a rather surprising error: the molecule is symmetric, so that the two branches A and B are interchangeable! In consequence, the two columns of descriptors have no meaning if they are taken as distinct descriptors. Thus, the contribution of the substituents in A and B in modeling the global biological activity must somehow be mixed!

The simple summation (or simple arithmetic mean) of contributions of the two branches, A and B, did not provide satisfactory results. More reliable appeared in other kinds of average: geometric ("geo") and harmonic ("har"). The best correlating results are included in table 3. The cross validation test, loo, is given for each entry.

From table 3 it appears that, in *single variable* regression, the descriptor $1/X_{(LDS)geo}$ provides a rather good ($r > 0.95$) description of the activity, both in estimation and prediction, "*loo*" (entry 2).

The best prediction is offered by the *three variables* equation, in entry 6 ($r > 0.975$), all of them as harmonic average of the descriptors of A and B branches:

$$pI_{50} = 10.292 - 119.503 \cdot 1/V_{har} - 0.097 \cdot X_{har} - 0.047 \cdot W_{s,har};$$

$$n = 30;\ r = 0.9807;\ s = 0.144;\ v(\%) = 2.198;\ F = 218.158; \qquad (11)$$

The corresponding arithmetic averaged descriptors used in (11) supplied a correlation of r = 0.955 which is, of course, unsatisfactory.

This equation was chosen for a tempting *prediction in the past.* The experimental data for the compounds no. 3, 12, 21 and 24 (showing residuals, y_{calc}-y_{exp}, about two times or larger than the value of standard error of estimate:

s = +0.144; -0.254; +0.236; +0.301 and -0.398, respectively

were changed by the values:

5.6209; 6.8778; 6.9073 and 6.8471, respectively

calculated by equations:

$$pI_{50} = 10.292 - 119.503\ 1/V_{har} - 0.097\ X_{har} - 0.047\ W_{s,har}$$

n = 26; r = 0.9932; s = 0.086; v(%) = 1.309; F = 530.484 (12)

The correlating data, obtained by using the new column of activities, y_{cor}, are included in table 3 as the rows "y_{cor}". The improvement in the statistical parameters of the regression equations is obvious for all data of table 3 (where * means "leave one out" cross validation procedure; and ** are y_i corrected for i = 3, 12, 21 and 24):

Table 3. Statistics of multivariable regression, $Y_{calc} = a + \sum_i b_i X_i$ (averaged variables)

No.	X_i	b_i	a	r	s	v(%)	F
1	$1/W_{s,har}$	-3.151	7.121	0.9553	0.210	3.204	292.215
	*loo**			0.9467	0.229	3.489	
	y_{cor}**			0.9666	0.175	2.669	398.721
2	$1/X_{geo}$	-3.891	7.253	0.9621	0.194	2.956	348.097
	loo			0.9558	0.209	3.183	
	y_{cor}			0.9793	0.138	2.108	655.776
3	$1/V_{har}$	-126.800	11.091	0.9763	0.156	2.387	275.063
	N_{har}	-0.541					
	loo			0.9721	0.167	2.543	
	y_{cor}			0.9924	0.086	1.307	875.466

4	$1/V_{har}$	-113.340	10.010	0.9777	0.152	2.318	292.278
	X_{har}	-0.137					
	loo			0.9735	0.163	2.480	
	y_{cor}			0.9907	0.095	1.446	713.286
5	$1/N_{har}$	-5.614	9.491	0.9798	0.147	2.247	208.342
	X_{har}	-0.056					
	$W_{s,har}$	-0.057					
	loo			0.9742	0.160	2.446	
	y_{cor}			0.9918	0.091	1.380	523.336
6	**$1/V_{har}$**	-119.503	10.292	**0.9807**	**0.144**	**2.198**	218.158
	X_{har}	-0.097					
	$W_{s,har}$	-0.047					
	loo			**0.9752**	**0.157**	**2.397**	
	y_{cor}			**0.9938**	**0.079**	**1.204**	690.328
7	$1/V_{har}$	-105.131	9.058	0.9824	0.141	2.144	172.608
	X_{har}	-0.232					
	$W_{s,har}$	-0.081					
	N_{har}	0.673					
	loo			0.9742	0.160	2.444	
	y_{cor}			0.9938	0.080	1.226	499.253
8	$1/N_{har}$	-4.724	7.858	0.9825	0.140	2.139	173.400
	X_{har}	-0.228					
	$W_{s,har}$	-0.070					
	V_{har}	0.052					
	loo			0.9751	0.157	2.401	
	y_{cor}			0.9924	0.089	1.358	405.773

More over, among the 24 descriptors (N, V, W_s, X_{LDS} , $1/N$, $1/V$, $1/W_s$, $1/X_{LDS}$, taken as "ari", "har" and "geo" average) used in single variable regression, in 20 of them an improvement of the statistics was recorded. Again the equation in entry 6 was the best model. This test suggested that the experimental data for the compounds, above mentioned, are "in error".

From eq 11 and table 3, it comes out that the inhibitory activity of triazines is controlled by the possibility of the triazine ring (i.e., the pharmacophor) to accommodate at the receptor situs.

This opinion is supported by the reciprocal values and the negative regression coefficient, and negative partial correlation index of these "steric" descriptors involved in an eq. of type 11. It suggests that the triazine ring fits at the biological receptor as better as the substituent is less sterically involved.

A plot of the observed vs. calculated (by eq 11) pI_{50} values is given in figure 6. For comparison, the plot for the same descriptors and "y_{cor}" is given in Figure 7.

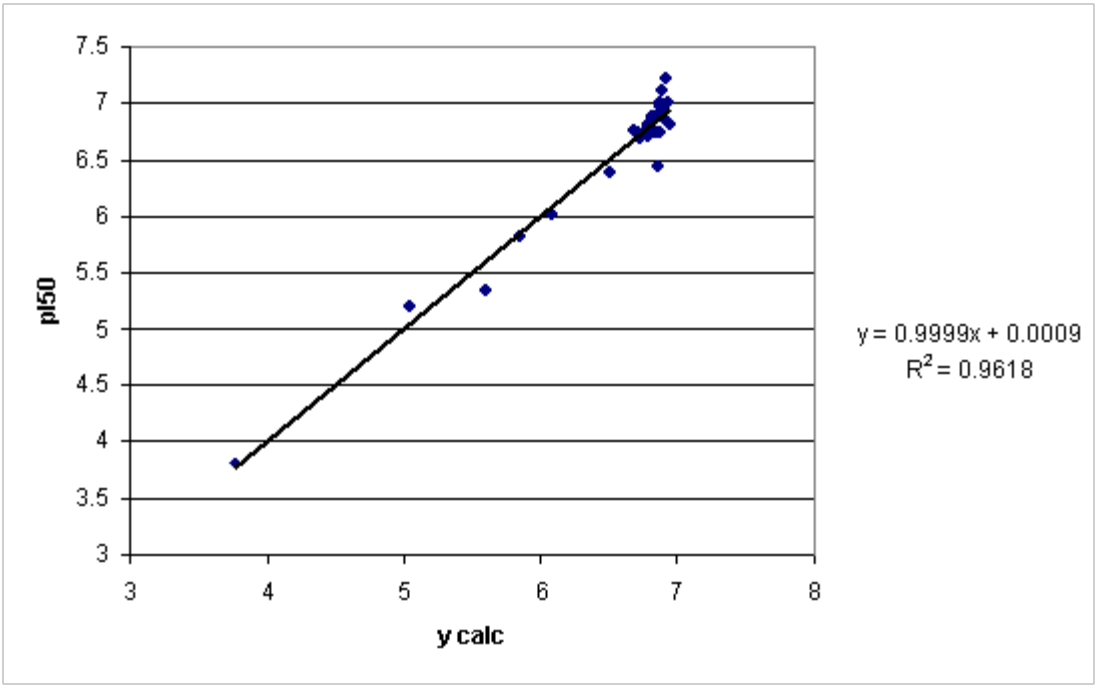


Figure 6. Plot of experimental biological activity (VAR1) vs. y_{calc}. (cf. eq 11) values

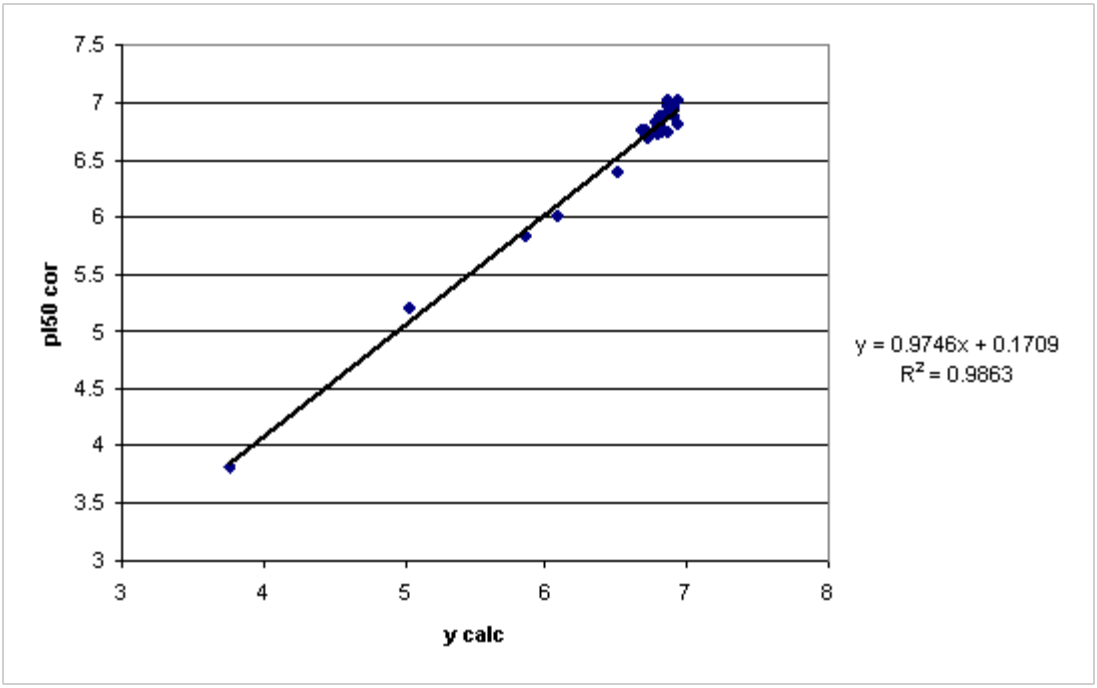


Figure 7. Plot of experimental biological activity (VAR1) vs. y_{cor} values

4. Computation of Fragmental Volumes

The geometries of the hydrocarbon fragments (in fact, the corresponding radicals) were fully optimized at the Unrestricted Hartree-Fock (UHF) level of theory, using the 6-31G** basis set (of DZP quality), which contains a single set of *d* polarization functions on carbons, and a single set of *p* polarization functions on hydrogens for better description of the radical wavefunctions.

The Berny's optimization algorithm was used (the energy derivatives with respect to nuclear coordinates were computed analytically [25]), along with the initial guess of the second derivative matrix.

Standard harmonic vibrational analysis was applied to test the character of the optimized geometries (stationary points at the potential energy hypersurfaces - PES). All stationary points corresponded to real minima on the explored PES.

Molecular volume calculations were performed for the optimized structures, by the Monte-Carlo method. Since Monte-Carlo method for calculating molecular volume (defined as the volume inside a contour of 0.001 electrons/Bohr^3 density) is stochastically based algorithm, it often leads to results accurate up to several percents.

Therefore, 11 volume calculations per fragment were performed for each fragment, and the arithmetic average

value was taken as the closest approximation to the real one (at the level of theory employed).

In order to increase the density of points for a more accurate integration, the "Tight" option of the Gaussian "Volume" keyword was used. All calculations were performed with Gaussian 94 suite of programs [26].

5. Conclusions

The W_S descriptor, based on the walks in graph, satisfactorily describes the steric effect of alkyl substituents in the esterification reaction.

It is a pure steric parameter, not affected by the electronic effects. W_S correlate well to the fragmental volumes (over 0.92) and show a lower degeneracy in comparison to the *SVTI*, n and N_C parameters.

It is also well correlated[18] to the Taft, E_S, (0.9637), and Charton, n, (0.9587), parameters, which makes from W_S a promising alternative in describing the steric effect of alkyl substituents.

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