Design of Topological Indices. Part 6.[1,2]
A New Topological Parameter for the Steric Effect of Alkyl Substituents

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The steric effect of alkyl groups is characterized by the Steric Vertex Topological Index (SVTI). SVTI is equal to the sum of the distances not greater than three between the attachment site and the carbon atoms of the alkly group. The correlations presented, either with reaction rates of acid-catalyzed esterification of carboxylic acids or with various steric parameters, *i.e.* E_s, E'_s, v, and $\varXi$, indicated that SVTI can serve as a useful steric parameter in reactivity studies.

INTRODUCTION

Establishment of relationships, as well as the possiblity of prediction, usually constitute the first step in the comprehension of a phenomenon.

Quantitative Structure-Activity Relationships (QSAR) for the chemical reactivity of classes of organic compounds were examined by using free-energy-related physico-chemical parameters. A major method of modeling the effect of structure variation on chemical reactivity, physical properties or biological activity of a set of substrates is the use of correlational analysis. In this method, it is assumed that the effect of structural variation of a substituent upon some chemical, physical or biological property of interest is a linear function of the parameters that constitute a measure of electrical, steric, and transport effects.[3–6]

The first and for many years the only successful method for parametrization of steric effects were the E_s constants introduced by Taft. The variation in the acid-catalyzed hydrolysis of aliphatic carboxylic esters RCOOR'

is mostly subject to the steric effect exerted intramolecularly by the substituent R on the formation of the tetrahedral reaction intermediate. Taft defined the steric parameter E_s[7,8] as

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

where $(k_R/k_{Me})_A$ refers to the ratio of acid-catalyzed hydrolysis rate constant of RCOOR' to that of MeCOOR'. By definition, $E_s(Me) = 0$. A number of research efforts were concentrated on the dissection of the E_s parameters, and on the prediction of E_s values from the molecular structure, using an additive model.[9-11] In an attmept to improve the E_s parameter, Dubois and coworkers defined the »revised« Taft steric parameter E'_s using the acid-catalyzed esterification of carboxylic acids (at 40 °C) as the reference reaction.[12,13]

From the definition of the E_s parameters it is not apparent how any structural feature determines the steric effect. Taft recognized that E_s varies parallel to the group radius. Charton examined the relationship between them quantitatively, and showed that the steric effect for selected series of substituent is linearly dependent on the van der Waals radius, defining a new type of steric parameter, v.[14-16]

A topological model of steric strain was defined by Brown[17,18] in the theory of homomorphs. In recent years, many different graph invariants have been propopsed for characterization of the structural features of chemical species. These are usually referred to in the chemical literature as topological indices (TI).[19-26] Such indices reflect, in different ways, the size and shape of the molecules they characterize and also provide some measure for the degree of molecular branching.

By removing all hydrogen atoms from the constitutional formula of a chemical compound containing covalent bonds, we obtain the hydrogen-depleted graph (or molecular graph) of that compound, whose vertices correspond to non-hydrogen atoms. In the particular case of hydrocarbons, the vertices of the molecular graph denote carbon atoms.

The link between the connectivity index χ (defined by Randić[26]) and E_s has been made evident by Murray,[27] who succeeded in finding correlations between the Taft parameter and χ for a series of substituted alkyls.

Schug and coworkers[28] revealed that, for sterically controlled reactions, the relative rates of series of substrates can be correlated either with the connectivity index of the substrates themselves or with the changes in the indices that accompany the formation of transition states.

The TI Ξ, reflecting the steric effect, was recently defined as a sum of three shape descriptors.[29] Index Ξ correlates well both with reactivity data and with a set of previously defined steric parameters.

In the present investigation, we will define a new Vertex Topological Index (VTI)[30] encoding the steric effect of an alkyl group.

THE STERIC TOPOLOGICAL PARAMETER SVTI

In defining the new steric topological parameter, we will use selected distances in the molecular graph as graph descriptors. The distance between vertices v_i and v_j in graph G is denoted by d_{ij} and is equal to the number of bonds on the shortest path between vertices v_i and v_j.

The Steric Vertex Topological Index (SVTI) of an alkyl group (A), attached to vertex v_i in the molecular graph, is equal to the sum of distances not exceeding length 3 between vertex v_i and every vertex of the alkyl group:

$$\text{SVTI (A)} = \sum_{\substack{j=1 \\ d_{ij} \leq 3}}^{N} d_{ij} . \qquad (1)$$

This limit is in accordance within Charton's conclusion about the limit of influence on the steric effect beyond the gamma carbon.[14,31]

Computation of the SVTI parameter is exemplified for the *sec*-butyl group (R = H) or higher homologues (R ≠ H):

$$\text{SVTI } (s\text{-Bu}) = 1 + 2 + 2 + 3 = 8 .$$
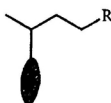
Block 1

We have to mention that all eighteen types of VTI's defined in Ref. 30 were investigated as possible candidates for a steric index, using different cutoff distances. As a validation criterion, we have used correlations with experimental reaction rates. The best results were obtained with the simple index defined in equation (1), with a cutoff distance of three. Linear and parabolic correlations were computed, with the latter performing best in terms of statistical indicators. Since in the parabolic correlations the coefficient of the linear term was nearly zero, we have used only correlations with quadratic terms.

Monoparametric correlations with rates of esterification of alkyl substituted carboxylic acids with methanol[32] were tested for SVTI with the following results, where n is the number of experimental data in the correlation, r the correlation coefficient and s the standard deviation. Depending on the particular conditions for determination of the reaction rates, the set of Eqs. (2–5) was computed.

TABLE I

Steric parameters SVTI and esterification rates catalyzed by $4\text{-}CH_3\text{-}C_6H_4SO_3H$

Alkyl group	SVTI	$-\log k_1$		Residual	$-\log k_2$		Residual
		obs.[a]	Eq.(2)		obs.[b]	Eq.(3)	
Me	1	1.58	1.33	0.25	1.35	1.13	0.22
Et	3	1.61	1.47	0.14	1.39	1.26	0.13
Pr	6	1.86	1.94	−0.08	1.63	1.71	−0.08
i-Pr	5	1.94	1.75	0.19	1.71	1.53	0.18
i-Bu	9	2.49	2.72	−0.23	2.25	2.47	−0.22
s-Bu	8	2.54	2.43	0.11	2.30	2.18	0.12
CH_2Bu	6	1.91	1.94	−0.03	1.68	1.71	−0.03
$CHEt_2$	11	3.55	3.42	0.13	3.26	3.14	0.12
$CH_2CH_2i\text{-}Bu$	6	1.81	1.94	−0.13	1.58	1.71	−0.13
CHMeHex	8	2.42	2.43	−0.01	2.19	2.18	0.01
CHEtAm	11	2.72	3.42	−0.70	2.47	3.14	−0.67
$CH_2CH_2CHEtBu$	6	1.82	1.94	−0.12	1.60	1.71	−0.11
$CH_2CHMeHex$	9	2.53	2.72	−0.19	2.28	2.47	−0.19
CHMeOct	8	2.44	2.43	0.01	2.21	2.18	0.03
$C_{11}H_{23}$	6	1.87	1.94	−0.07	1.63	1.71	−0.08
$(CH_2)_4CHEtBu$	6	1.83	1.94	−0.11	1.61	1.71	−0.10
CHMeNon	8	2.50	2.43	0.07	2.26	2.18	0.08
$CH_2[CH(Me)(CH_2)_3]_2CHMe_2$	9	2.53	2.72	−0.19	2.29	2.47	−0.18
$CHMeC_{12}H_{25}$	8	2.55	2.43	0.12	2.31	2.18	0.13
$C_{15}H_{31}$	6	1.89	1.94	−0.05	1.65	1.71	−0.06
$CHMeC_{14}H_{29}$	8	2.44	2.43	0.01	2.20	2.18	0.02
$C_{17}H_{35}$	6	1.89	1.94	−0.05	1.66	1.71	−0.05
$CHMeC_{16}H_{33}$	8	2.43	2.43	0.00	2.20	2.18	0.02
$CH_2[CH(Me)(CH_2)_3]_3CHMe_2$	9	2.65	2.72	−0.07	2.40	2.47	−0.07
$CHEtC_{16}H_{33}$	11	3.49	3.42	0.07	3.20	3.14	0.06
$CHPrC_{16}H_{33}$	11	3.55	3.42	0.13	3.26	3.14	0.12
$CHBuC_{16}H_{33}$	11	3.61	3.42	0.19	3.32	3.14	0.18
$CHHexC_{16}H_{33}$	11	3.68	3.42	0.26	3.37	3.14	0.23
$CHNonC_{16}H_{33}$	11	3.51	3.42	0.09	3.21	3.14	0.07
$CH(C_{10}H_{21})(C_{16}H_{33})$	11	3.49	3.42	0.07	3.20	3.14	0.06
$CH(C_{11}H_{23})(C_{16}H_{33})$	11	3.51	3.42	0.09	3.22	3.14	0.08
$CH(C_{16}H_{33})_2$	11	3.51	3.42	0.09	3.21	3.14	0.07

[a] t=30 °C, C_{AH} = 0.01, from Ref. 32.
[b] t=40 °C, C_{AH} = 0.01, from Ref. 32.

The experimental and computed esterification rates from Eqs. (2) and (3) are presented in Table I. The rates in Eqs. (2) and (3) were determined at a temperature of 30 °C, and 40 °C, respectively.

$$-\log k_1 = 1.1096 \ (\pm 0.1808) + 0.0167 \ (\pm 0.0022).\text{SVTI}^2 \qquad (2)$$
$$n = 32, \ r = 0.967, \ s = 0.174$$

$$-\log k_2 = 1.3142 \ (\pm 0.1908) + 0.0174 \ (\pm 0.0023).\text{SVTI}^2 \qquad (3)$$
$$n = 32, \ r = 0.966, \ s = 0.183$$

The experimental reaction rates in Table II were determined at the same two temperatures, but $C_{AH} = 0.05$ (C_{AH} represents the acid catalyst concentration).[33-36]

TABLE II

Steric parameter SVTI and esterification rates, catalyzed by HCl

Alkyl group	SVTI	$-\log k_3$		Residual	$-\log k_4$		Residual
		obs.[a]	Eq.(4)		obs.[b]	Eq.(5)	
Me	1	1.05	1.04	0.01	0.82	0.82	0.00
Et	3	1.12	1.18	−0.06	0.88	0.96	−0.08
Pr	6	1.43	1.67	−0.24	1.19	1.44	−0.25
i-Pr	5	1.58	1.47	0.11	1.35	1.24	0.11
Bu	6	1.38	1.67	−0.29	1.15	1.44	−0.29
i-Bu	9	2.06	2.50	−0.44	1.87	2.24	−0.37
s-Bu	8	2.14	2.19	−0.05	1.88	1.94	−0.06
t-Bu	7	2.57	1.91	0.66	2.31	1.67	0.64
CH_2Bu	6	1.37	1.67	−0.30	1.14	1.44	−0.30
CH_2i-Bu	6	1.42	1.67	−0.25	1.20	1.44	−0.24
CH_2s-Bu	9	2.03	2.50	−0.47	1.84	2.24	−0.40
CH_2t-Bu	12	2.80	3.64	−0.84	2.51	3.35	−0.84
$CHEt_2$	11	3.15	3.23	−0.08	2.88	2.95	−0.07
CH_2CH_2t-Bu	6	1.45	1.67	−0.22	1.21	1.44	−0.23
CHt-BuMe	14	4.40	4.59	−0.19	4.09	4.28	−0.19
CHEti-Pr	14	4.42	4.59	−0.17	4.11	4.28	−0.17
$CHPr_2$	11	3.20	3.23	−0.03	2.91	2.95	−0.04
$CHMeCH_2t$-Bu	8	2.95	2.19	0.76	2.69	1.94	0.75
Oct	6	1.42	1.67	−0.25	1.19	1.44	−0.25
CMe_2CH_2t-Bu	10	3.66	2.84	0.82	3.36	2.57	0.79
CH_2CH_2CHt-BuEt	6	2.11	1.67	0.44	1.87	1.44	0.43
$CHBu_2$	11	3.26	3.23	0.03	2.96	2.95	0.01
CHi-Bu$_2$	11	3.55	3.23	0.32	3.26	2.95	0.31
$C_{11}H_{23}$	6	1.39	1.67	−0.28	1.16	1.44	−0.28
$CH(CH_2t$-Bu$)_2$	11	4.25	3.23	1.02	3.94	2.95	0.99

[a]t=30 °C, $C_{AH} = 0.05$, from Refs. 33–36.
[b]t=40 °C, $C_{AH} = 0.05$, from Refs. 33–36.

$$-\log k_3 = 1.0179 \ (\pm 0.4421) + 0.0182 \ (\pm 0.0048).SVTI^2 \qquad (4)$$

$$n = 25, \ r = 0.912, \ s = 0.454$$

$$-\log k_4 = 0.8005 \ (\pm 0.4279) + 0.0177 \ (\pm 0.0046).SVTI^2 \qquad (5)$$

$$n = 25, \ r = 0.913, \ s = 0.439$$

From Eqs. (2–5) it is apparent that a high percentage of structural influence on the reaction rates is encoded by the SVTI parameter.

The success in predicting the esterification rate, interpreted as a measure of steric influence of a group, encouraged us to compare this model with

TABLE III

Steric parameters SVTI, E_s, E'_s, v, and Ξ used in obtaining equations (6–9)

Alkyl group	SVTI	E_s[a]	E'_s[b]	v[c]	Ξ[d]
Me	1	0.00	0.00	0.52	1.78
Et	3	0.07	0.08	0.56	1.71
Pr	6	0.36	0.31	0.68	1.90
i-Pr	5	0.47	0.48	0.76	3.67
Bu	6	0.39	0.31	0.68	1.99
s-Bu	8	1.13	1.00	1.02	4.19
i-Bu	9	0.93	0.93	0.98	2.59
t-Bu	7	1.54	1.43	1.24	5.91
CH_2Bu	6	0.40	0.31	0.68	1.93
CH_2i-Bu	6	–	–	0.68	–
CH_2s-Bu	9	–	0.97	1.00	–
CH_2t-Bu	12	1.74	1.63	1.34	–
$CHEt_2$	11	1.98	2.00	1.51	6.15
$CEtMe_2$	10	–	2.28	1.63	–
CHEti-Pr	14	–	3.23	2.11	–
CHt-BuMe	14	3.33	3.21	2.11	–
$CHPr_2$	11	2.11	2.03	1.54	6.80
$CHBu_2$	11	–	2.08	1.56	–
CHi-Bu_2	11	2.47	2.38	1.70	8.22
CH_2CH_2i-Pr	6	0.35	0.32	0.68	2.53
CH_2CH_2t-Bu	6	0.34	0.33	0.70	3.20
$CHMeCH_2t$-Bu	8	1.85	1.81	1.41	5.47
CMe_2CH_2t-Bu	10	2.57	2.48	1.74	7.63
$CH(CH_2t$-$Bu)_2$	11	3.18	3.06	2.03	9.82

[a]From Refs. 7,8,12
[b]From Refs. 12,13
[c]From Refs. 14–16
[d]From Ref. 29

other steric parameters. The values reported in literature for the steric parameters E_s, E'_s, v, and Ξ were correlated with SVTI values, with the results given in Eqs. (6–9). All data used in correlations are presented in Table III.

$$-E_s = -0.0222\ (\pm 0.5650) + 0.0183\ (\pm 0.0063).\text{SVTI}^2 \qquad (6)$$
$$n = 19,\ r = 0.896,\ s = 0.490$$

$$-E'_s = -0.0294\ (\pm 0.4938) + 0.0176\ (\pm 0.0050).\text{SVTI}^2 \qquad (7)$$
$$n = 23,\ r = 0.906,\ s = 0.459$$

$$v = 0.4968\ (\pm 0.2281) + 0.00877\ (\pm 0.00023).\text{SVTI}^2 \qquad (8)$$
$$n = 24,\ r = 0.911,\ s = 0.219$$

$$\Xi = 0.9986\ (\pm 1.7966) + 0.0549\ (\pm 0.0243).\text{SVTI}^2 \qquad (9)$$
$$n = 17,\ r = 0.861,\ s = 1.383$$

The correlations are significant, but not high, leading to the conclusion that the SVTI parameter does not closely parallel the values of steric constants defined earlier.

The SVTI descriptor meets several criteria for a successful steric parameter:

 (i)   it is free of all electrical and solvent effects.
 (ii) the values of the SVTI descriptor can be calculated for all types of alkyl groups
 (iii) it is a measure of the spatially directed steric effect of a group operating through the attached atom.

Obviously, the new steric index SVTI is highly degenerated, because the simple summation of the graph distances not longer than three loses a part of the structural information contained in the molecular graph. Despite its simplicity, SVTI reflects a major part of the steric effect of an alkyl substituent. Based on the results obtained with SVTI, we intend to elaborate topological steric indices with a better correlational ability.

We are encouraged to see that a structure-based index for substituents can encode sufficient information in order to correlate fairly well with the rate data. The SVTI parameter correlates well with the esterification reaction rates, and satisfactorily with a number of well-established steric constants, leading us to believe that this new theoretical descriptor of the steric effect may be useful in QSAR analyses where the role of shape parameters is significant.

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SAŽETAK

Nacrtba topoloških indeksa. 6. dio.
Novi topološki parametar za sterički učinak alkilnih supstituenata

Ovidiu Ivanciuc i Alexandru T. Balaban

Sterički učinak alkilnih skupina karakteriziran je steričkim čvornim topološkim indeksom (SVTI). SVTI jednak je sumi udaljenosti ne većih od 3 između ugljikovih atoma alkilne skupine i atoma na koji je grupa vezana. Prikazane korelacije s reakcijskim brzinama kiselinski katalizirane esterifikacije karboksilnih kiselina i s raznim steričkim parametrima (E_s, E'_s, ν i Ξ) pokazuju da SVTI može poslužiti kao sterički parametar u istraživanju reaktivnosti.