Journal of Chromatography, 547 (1991) 247–257
Elsevier Science Publishers B.V., Amsterdam

CHROM. 23 298

Topological indices as structural parameters

Structure–retention relationships for oxyethylene derivatives of alcohols, thioalcohols and alkylamines

ADAM VOELKEL
Poznań Technical University, Institute of Chemical Technology and Engineering, Pl. M. Skłodowskiej-Curie 2, 60-965 Poznań (Poland)

(First received October 24th, 1990; revised manuscript received March 13th, 1991)

ABSTRACT

A quantitative structure–retention relationship analysis is presented for the retention indices and topological parameters of a set of oligooxyethylene derivatives. The usefulness of the topological indices as structural descriptors was examined.

INTRODUCTION

Oligooxyethylene derivatives of alcohols, thioalcohols and alkylamines have been examined as solutes on typical stationary phases of various polarities [1,2] and have also been characterized by inverse gas chromatography [3]. The properties of topological indices as structural parameters for oligooxyethylene derivatives have been discussed previously [4]. It was shown that the molecular connectivity and valence molecular connectivity indices, the Balaban index and the Wiener number are all sensitive to the presence and size of alkyl group(s), oligooxyethylene chains(s) and heteroatoms, as well as position in the molecule.

The structure of molecules can be translated into numerical descriptors using chemical graph theory [5]. Trinajstič *et al.* [6] placed all the structural parameters discussed in this paper into the group of structure-explicit quantitative structure–activity relationship models. These models offer a clear mathematical characterization of the fundamental chemical structure and are non-empirical in origin. The well defined structural parameters have a precise structural interpretation. It has been pointed out [6] that a good choice of structural descriptor can produce a simple and physically valid correlation. However, a poor choice may lead to bad correlations or may not recognize a regularity in the data. Kaliszan [5] cautioned against the overfitting of the structural data, which can make the quantitative structural–retention relationship (QSRR) dubious. Special attention should be paid to the possible intercorrelations among the structural descriptors used as independent variables in the same equation. Kaliszan [5]

0021-9673/91/$03.50

recommended the presentation of results of the correlation analysis, including statistics, as given in Tables IV and VII.

It was proved that the chromatographic retention parameter should be described by at least a two-parameter equation:

$$R = aP + bNP + c \tag{1}$$

where R is the retention parameter, P is the polar interactions parameter and NP is the apolar interactions parameter; a, b and c are constants.

Lamparczyk and co-workers [7,8] derived such an equation from the general relationship for Van der Waals forces acting between the solute and liquid stationary phase in chromatographic process:

$$RI = \frac{1}{P}\left[\frac{(A\mu_{\mathrm{ph}}^2 + \alpha_{\mathrm{ph}})\mu_{\mathrm{s}}^2 + (B_{\mathrm{s}}\alpha_{\mathrm{ph}} + \mu_{\mathrm{ph}}^2)\alpha_{\mathrm{s}}}{B_{\mathrm{N}}\alpha_{\mathrm{ph}} + \mu_{\mathrm{ph}}^2}\right] - C \tag{2}$$

where α_{ph} and α_{s} are the polarizability parameters for the stationary phase and the solute, respectively; μ_{ph} and μ_{s} are the dipole moments for the stationary phase and the solute, respectively; $A = (2/3)kT$, where k is Boltzmann's constant and T is the absolute temperature; $B_{\mathrm{s}}[(I_{\mathrm{ph}}I_{\mathrm{S}})/(I_{\mathrm{ph}} + I_{\mathrm{s}})$; $B_{\mathrm{N}} = [(I_{\mathrm{N}}I_{\mathrm{S}})/(I_{\mathrm{N}} + I_{\mathrm{s}})$; I_{s}, I_{N} and I_{ph} are the first ionization potential for the solute, reference *n*-alkane and stationary phase, respectively; and p and C are constants.

When the respective parameters for the stationary phase are not known, eqn. 2 converts to eqn. 1. Such relationships have been used by several workers [9–11]. However, dipole moments are often not available from the literature. The method of calculation of the so-called chromatographic dipole moments has been successfully used in the QSRR analysis of alkenes [11].

QSRR with the use of topological indices has not yet been presented for oxyethylated derivatives of alcohols, thioalcohols and alkylamines. Previously reported relationships correlated the retention parameters with only the number of carbon atoms or oxyethylene units in the molecules. In this paper the appropriate chromatographic dipole moments for the examined compounds will be evaluated. Their dependence on the topological parameters used in the calculation procedure and on the chemical nature of the stationary phase will be given. The advantages and limitations of the use of topological parameters in structure–retention relationships will be illustrated.

EXPERIMENTAL

Thirty pure model oligooxyethylene derivatives of alcohols, thioalcohols and alkylamines of the general formula $RX(CH_2CH_2O)_nR'$ (where $R = C_4H_9$, C_6H_{13}, C_8H_{17}; $R' = H$, CH_3; $X = O$, NH, S; $n = 0$–3) were used as solutes. These compounds have been characterized previously [1,2]. Retention indices and the thermodynamic solution parameters were taken from Voelkel [2]. All the retention parameters considered were estimated on four stationary phases, *i.e.* SE-30, Apiezon K, OV-17 and QF-1. The molecular connectivity indices $^n\chi$ and valence molecular indices of various orders $^n\chi^v$, the Balaban index (I_B) and the Wiener number [$W(G)$]

were used as structural parameters. The methods of their calculation have been presented by Voelkel [4].

RESULTS AND DISCUSSION

Voelkel [4] has indicated that the considered topological indices are sensitive to the presence of heteroatoms. The values of the calculated topological parameters and some structural data are summarized in Tables I and II. The increase of the number of carbon atoms in the alkyl group decreases I_B, whereas the other considered topological indices increase. An increase in the oligooxyethylene chain length increases all the structural parameters. The attachment of each oligooxyethylene group increases the molecular connectivity indices ${}^1\chi$, ${}^2\chi$ and ${}^3\chi$ by 1.5, 1.0606 and 0.75 I.U., respectively. The same increments for the valence molecular connectivity indices ${}^1\chi^v$, ${}^2\chi^v$ and ${}^3\chi^v$ are 1.0774, 0.6124 and 0.3720, respectively.

TABLE I

TOPOLOGICAL INDICES AND STRUCTURAL DATA FOR OLIGOOXYETHYLENE DERIVATIVES OF ALCOHOLS, THIOALCOHOLS AND ALKYLAMINES: $RX(CH_2CH_2O)_nR'$

No.	R	R′	X	*n*	Balaban index, I_B	Wiener number, $W(G)$	Rouvray index, $R(G)$
1	C_4H_9	H	O	0	2.2836	19.125	38.25
2	C_4H_9	H	O	2	3.1250	190.375	380.75
3	C_4H_9	H	O	3	3.2747	388.5	777
4	C_6H_{13}	H	S	0	2.5824	52.5625	105.125
5	C_6H_{13}	H	S	1	3.2625	135.0625	270.125
6	C_6H_{13}	H	S	2	3.4860	292.5625	585.125
7	C_6H_{13}	H	S	3	3.5535	547.5625	1095.125
8	C_6H_{13}	H	O	0	2.4996	54.625	109.25
9	C_6H_{13}	H	O	1	2.8809	151.75	303.5
10	C_6H_{13}	H	O	2	3.1116	323.871	647.75
11	C_6H_{13}	H	O	3	3.2550	593.5	1187
12	C_6H_{13}	H	NH	0	2.4748	55.2135	110.427
13	C_6H_{13}	H	NH	1	2.7882	156.5115	313.023
14	C_6H_{13}	H	NH	2	3.0192	332.8095	665.619
15	C_6H_{13}	H	NH	3	3.1785	606.6075	1213.215
16	C_8H_{17}	H	S	0	2.6792	115.3125	230.625
17	C_8H_{17}	H	S	1	3.1603	246.8125	493.625
18	C_8H_{17}	H	S	2	3.3922	468.3125	936.625
19	C_8H_{17}	H	S	3	3.4969	802.3125	1604.625
20	C_8H_{17}	H	O	0	2.6280	118.125	236.25
21	C_8H_{17}	H	O	1	2.8974	268.75	537.5
22	C_8H_{17}	H	O	2	3.0912	509.375	1018.75
23	C_8H_{17}	H	O	3	3.2266	862.5	1725
24	C_8H_{17}	H	NH	0	2.6136	118.9275	237.855
25	C_8H_{17}	H	NH	1	2.8303	275.0095	550.019
26	C_8H_{17}	H	NH	2	3.0156	521.0915	1042.183
27	C_8H_{17}	H	NH	3	3.1569	879.6735	1759.347
28	C_6H_{13}	CH_3	O	3	3.2960	707.5	1415
29	C_8H_{17}	CH_3	O	3	3.2652	1007.5	2015
30	$C_{10}H_{21}$	CH_3	O	3	3.2360	1383.5	2767

TABLE II

MOLECULAR CONNECTIVITY INDICES FOR COMPOUNDS STUDIED

No.	Molecular connectivity index			Valence molecular connectivity index		
	$^1\chi$	$^2\chi$	$^3\chi$	$^1\chi^v$	$^2\chi^v$	$^3\chi^v$
1	2.4142	1.3536	0.7071	2.0233	1.0772	0.5117
2	5.4142	3.4749	2.2071	4.1780	2.3019	1.2499
3	6.9142	4.5355	2.9571	5.2554	2.9143	1.6219
4	3.4142	2.0607	1.2071	3.5710	2.1715	1.2855
5	4.9142	3.1213	1.9571	5.2511	3.6168	2.4225
6	6.4142	4.1820	2.7071	6.3284	4.2292	2.7783
7	7.9142	5.2426	3.4571	7.4058	4.8416	3.1057
8	3.4142	2.0607	1.2071	3.0233	1.7843	1.0117
9	4.9142	3.1213	1.9571	4.1007	2.3936	1.3779
10	6.4142	4.1820	2.7071	5.1780	3.0090	1.7499
11	7.9142	5.2436	3.4571	6.2554	3.6214	2.1219
12	3.4142	2.0607	1.2071	3.1154	1.8493	1.0577
13	4.9142	3.1213	1.9571	4.2304	2.5343	1.4957
14	6.4142	4.1820	2.7071	5.3078	3.1466	1.8659
15	7.9142	5.2426	3.4571	6.3851	3.7590	2.2379
16	4.4142	2.7678	1.7071	4.5710	2.8786	1.7855
17	5.9142	3.8284	2.4571	6.2511	4.3239	2.9225
18	7.4142	4.8891	3.2071	7.3284	4.9363	3.2787
19	8.9142	5.9497	3.9571	8.4058	5.5487	3.6507
20	4.4142	2.7678	1.7071	4.0233	2.4914	1.5117
21	5.9142	3.8284	2.4571	5.1007	3.1037	1.8779
22	7.4142	4.8891	3.2071	6.1780	3.7161	2.2499
23	8.9142	5.9497	3.9571	7.2554	4.3285	2.6219
24	4.4142	2.7678	1.7071	4.1154	2.5564	1.5577
25	5.9142	3.8284	2.4571	5.2304	3.2414	1.9957
26	7.4142	4.8891	3.2071	6.3078	3.8537	2.3659
27	8.9142	5.9497	3.9571	7.3851	4.4661	2.7379
28	8.4142	5.5962	3.7071	6.6361	3.8906	2.3180
29	9.4142	6.3033	4.2071	7.6361	4.5977	2.8180
30	10.4142	7.0104	4.7071	8.6361	5.3048	3.3180

The main disadvantage of the first-order molecular connectivity indices introduced by Kier and Hall [12] is the impossibility of distinguishing between compounds containing different heteroatoms. For example, the second-order molecular connectivity index for $C_8H_{17}S(CH_2CH_2O)_2H$, $C_8H_{17}O(CH_2CH_2O)_2H$ and $C_8H_{17}NH(CH_2CH_2O)_2H$ is 4.8891 in each instance (see Tables I and II). The ability to discriminate between heteroatoms is much better for other topological parameters. Different values of parameters maybe assigned to derivatives of alcohol, thioalcohol and alkylamine. I_B arranges the examined compounds in the following order: derivatives of thioalcohols > derivatives of alcohols > derivatives of alkylamines. The value of W(G), Rouvray index and valence molecular topological indices are highest for the derivatives of thioalcohols and lowest for derivatives of alcohols. It can be stated that the considered structural parameters are generally sensitive (except $^1\chi$, $^2\chi$ and $^3\chi$) to changes in the molecule constituents.

TABLE III

RELATIONSHIPS BETWEEN RETENTION INDICES ON DIFFERENT STATIONARY PHASES AND TOPOLOGICAL PARAMETERS

L = linear, $I_R = a + bX$; M = multiplicative, $I_R = aX^b$

Topological parameter	Relationship	Liquid phase											
		Apiezon K			SE-30			OV-17			QF-1		
		a	*b*	*R*	*a*	*b*	*R*	*a*	*b*	*R*	*a*	*b*	*R*
$^1\chi^v$	L	185	222.3	0.992	129	234.5	0.991	166	258.7	0.987	226	274.6	0.977
	M	5.8	0.848	0.991	5.8	0.881	0.986	5.9	0.876	0.984	6.0	0.851	0.972
$^2\chi^v$	L	310	325.0	0.970	270	340.2	0.961	134	377.3	0.963	383	400.7	0.953
	M	6.3	0.757	0.972	6.3	0.781	0.960	6.4	0.778	0.961	6.5	0.752	0.947
$^9\chi^v$	L	471	452.4	0.938	443	471.0	0.925	503	524.2	0.931	583	556.9	0.921
	M	6.8	0.636	0.947	6.8	0.648	0.930	6.9	0.651	0.933	7.0	0.631	0.917
I_B	L	−1494	962.8	0.864	−1699	1034	0.878	−1945	1172	0.899	−1992	1237	0.884
	M	4.7	0.133	0.894	4.6	4.605	0.914	4.7	2.411	0.962	4.9	2.334	0.914
$W(G)$	L	1025	0.971	0.872	1006	1.048	0.891	1145	1.126	0.864	1267	1.190	0.852
	M	5.7	0.268	0.958	5.6	0.281	0.967	5.8	0.281	0.962	5.9	0.272	0.958

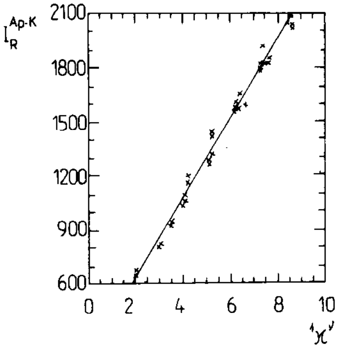

Fig. 1. Relationship between retention indices on Apiezon K and first-order valence molecular connectivity index $^1\chi^v$ for studied compounds.

The relationships between the retention indices of the examined compounds and their topological parameters are given in Table III. Both linear and multiplicative models were considered. The best results were obtained for $^1\chi^v$ used as a structural parameter (Fig. 1). All the relationships were statistically valid; the full statistical parameters for the two relationships are given in Table IV. In some instances better correlation coefficients were obtained for the multiplicative model. However, in this instance the physico-chemical interpretation of the relationship is not clear. The slopes of the linear relationships and regression coefficients *a* in the multiplicative model increase with an increase of the polar character of the stationary phase.

Gassiot-Mates and Firpo-Pamies [9] proposed the use of the chromatographic dipole moment, μ_{chr}, which characterizes the ability of a solute to undergo polar interactions under chromatographic conditions. Their procedure [9] was used in this work for the calculation of chromatographic dipole moments. The numerical values of such defined parameters will depend on the topological index used as structural

TABLE IV

STATISTICS FOR SELECTED QUANTITATIVE STRUCTURE–RETENTION RELATIONSHIPS BETWEEN RETENTION INDICES AND TOPOLOGICAL PARAMETERS

Statistic	Relationship			
	I_R^{Ap-K} *versus* $^1\chi^v$	I_R^{SE-90} *versus* $^2\chi^v$	I_R^{OV-17} *versus* I_B	I_R^{QF-1} *versus* $^3\chi^v$
Function	$185 + 222.3\,(^1\chi^v)$	$270 + 340.2\,(^2\chi^v)$	$4.7 I_B^{2.4}$	$583 + 556.7\,(^3\chi^v)$
Correlation coefficient (*R*)	0.992	0.961	0.962	0.921
Standard error of estimation	47.6	110.0	218.2	185.2
F-test value	1732.2	341.5	300.1	155.9
p Significance level	0.0000	0.0000	0.0000	0.0000
Confidence intervals for regression coefficients	$121.7 < a < 248.5$ $211.3 < b < 233.2$	$143.3 < a < 404.8$ $302.4 < b < 377.9$	$4.4 < a < 4.8$ $2.3 < b < 2.5$	$379.6 < a < 787.3$ $465.3 < b < 648.1$

TABLE V

CHROMATOGRAPHIC DIPOLE MOMENTS FOR EXAMINED COMPOUNDS

$^1\chi^v$ as structural parameter.

No.[a]	Stationary phase			
	Apiezon K	SE-30	OV-17	QF-1
1	1.6245	1.7517	1.6725	1.8107
2	2.2876	2.1145	1.8114	2.2962
3	3.4942	2.3503	1.8931	2.5699
4	2.3039	1.5473	1.5257	1.2734
5	1.8889	1.8504	1.7245	2.1054
6	0.9143	2.0375	1.7997	2.4087
7	2.2966	2.2235	1.8952	2.6545
8	2.3251	1.5819	1.6672	1.5575
9	1.9915	1.8223	1.6953	2.5050
10	1.0802	2.0505	1.7402	2.2642
11	1.9977	2.2412	1.8450	2.5242
12	2.7639	1.5379	1.5582	1.4381
13	2.7873	2.0160	1.7870	2.2834
14	3.0723	2.2192	1.8017	2.4444
15	3.1738	2.3747	1.8726	2.6963
16	1.2121	1.6749	1.5366	1.4677
17	2.6850	2.0334	1.7113	2.3614
18	1.6638	2.2257	1.7936	2.7005
19	2.4368	2.4694	1.8734	2.9346
20	1.8006	1.5256	1.6452	1.8861
21	1.6856	1.8279	1.6791	2.0420
22	1.7605	2.0963	1.7889	2.4261
23	2.8486	2.3367	1.7752	2.7233
24	1.2338	1.4215	1.4431	1.5709
25	3.0774	1.9193	1.7481	2.3667
26	3.2679	2.1432	1.8173	2.6867
27	3.9327	2.4385	1.8753	2.8489
28	1.8430	2.1110	1.7361	2.1007
29	1.7823	2.2003	1.7510	2.2905
30	1.2682	2.3453	1.6744	2.4355

[a] Numbers of compounds as in Table II.

parameter and the chemical nature of the stationary phase. The chromatographic dipole moments calculated for the examined compounds ($^1\chi^v$ as a structural parameter) are reported in Table V. The value of μ_{chr} usually increases with an increase in the oxyethylene units in the solvent molecule, although some perturbations are observed (Apiezon K, and, in some instances QF-1). Statistically significant relationships have been observed between μ_{chr} values and the polarity of the stationary phase. The μ_{chr} value obtained using various connectivity indices on the same liquid phase are similar, whereas those calculated using $W(G)$ or I_B differ significantly.

The chromatographic dipole moments were used in the modified form of eqn. 1:

$$I_R = a\mu_{chr}^2 + bTP + c \qquad (3)$$

TABLE VI

STATISTICS FOR RELATIONSHIPS OF TYPE $I_R = (a\mu^2_{chr}) + (bTP) + c$

Statistic	Stationary phase		
	Apiezon K	SE-30	OV-17
Function	$(8.29\mu^2_{chr}) + (220\,{}^1\chi^v) + 151.8$	$(72.44\mu^2_{chr}) + (266.4\,{}^2\chi^v) + 172.4$	$(217.1\mu^2_{chr}) + (229.6\,{}^1\chi^v) - 331.5$
Correlation coefficient (R)	0.991	0.998	0.999
Standard error of estimation	36.2	17.5	0.354
F-test value	1512.8	7249.5	2195904
p Significance level	0.0000	0.0000	0.0000
Confidence intervals for	$4.63 < a < 11.96$	$68.4 < a < 77.54$	$216.6 < a < 217.5$
regression coefficients	$211.7 < b < 228.4$	$258.8 < b < 274$	$229.5 < b < 229.7$

TABLE VII

PREDICTION OF RETENTION INDEX FOR STUDIED COMPOUNDS ON APIEZON K

$^{1}\chi^{v}$ as structural parameter.

Compound	Retention index		Error	
	Observed	Fitted	Absolute	Relative
1	675.0	619.3	55.7	8.3
2	1150.0	1114.5	35.5	3.0
3	1437.0	1409.4	27.6	1.9
4	931.0	981.5	−50.5	5.4
5	1318.0	1336.8	−18.8	1.4
6	1564.0	1551.2	12.8	0.8
7	1829.0	1825.1	3.9	0.2
8	815.0	861.8	−46.8	5.8
9	1054.0	1087.0	−33.0	3.1
10	1325.0	1300.8	24.2	1.8
11	1576.0	1561.3	14.7	0.9
12	815.0	900.6	−85.6	10.5
13	1183.0	1147.0	36.0	3.0
14	1424.0	1398.0	26.0	1.8
15	1656.0	1640.3	15.7	1.0
16	1200.0	1169.7	30.3	2.5
17	1603.0	1587.0	16.0	1.0
18	1791.0	1787.2	3.8	0.2
19	2045.0	2050.6	− 5.6	0.3
20	1044.0	1063.9	−19.9	1.9
21	1274.0	1297.7	−23.7	1.9
22	1552.0	1536.9	15.1	1.0
23	1822.0	1815.5	6.5	0.3
24	1091.0	1057.8	33.2	3.0
25	1408.0	1381.2	26.8	1.9
26	1645.0	1628.3	16.7	1.0
27	1913.0	1905.0	8.0	0.4
28	1592.0	1679.0	−87.0	5.5
29	1837.0	1837.1	− 0.1	0.0
30	2028.0	2065.4	−37.4	1.8

where *TP* is the topological parameter and *a, b* and *c* are regression coefficients.

In all instances statistically significant relationships were obtained. The relevant data are given in Table VI. With the use of the known structural parameter and chromatographic dipole moment it is possible to predict the retention data of a compound (Table VII).

The problem of over-fitting the data used as independent variables in the regression equation should be taken into consideration, as a high intercorrelation among variables could cause the QSRR to be suspect. As topological parameters are to some extent used in the procedure of the estimation of μ_{chr}, the statistical independence of both variables to be used in eqn. 2 should be checked. Intercorrelation matrices were constructed for the first-order connectivity index and respective μ_{chr} values (Table VIII) as well as for *W*(*G*) and the appropriate μ_{chr} values. It can be assumed that $^{1}\chi^{v}$,

TABLE VIII

INTERCORRELATION MATRIX FOR $^1\chi^v$, $^2\chi^v$ AND APPROPRIATE CHROMATOGRAPHIC DIPOLE MOMENTS

Independent variable	$^1\chi^v$	μ_{chr}^{ApK}	μ_{chr}^{SE-30}	μ_{chr}^{OV-17}	μ_{chr}^{QF-1}
$^1\chi^v$	1.0000	0.0795	0.3104	0.5707	0.4179
μ_{chr}^{ApK}		1.0000	0.3960	0.5039	0.3723
μ_{chr}^{SE-30}			1.0000	0.8655	0.8996
μ_{chr}^{OV-17}				1.0000	0.8826
μ_{chr}^{QF-1}					1.0000
	$^2\chi^v$	μ_{chr}^{ApK}	μ_{chr}^{SE-30}	μ_{chr}^{OV-17}	μ_{chr}^{QF-1}
$^2\chi^v$	1.0000	–	0.6101	0.4731	0.6568
μ_{chr}^{ApK}		–	–	–	–
μ_{chr}^{SE-30}			1.0000	0.9515	0.9015
μ_{chr}^{OV-17}				1.0000	0.9111
μ_{chr}^{QF-1}					1.0000

$^2\chi^v$ and the respective μ_{chr} values are uncorrelated whereas $W(G)$ strongly influences the values of the calculated chromatographic dipole moment with the use of this topological parameter. This will probably limit the application of $W(G)$ and I_B in QSRR analysis for gas chromatographic retention indices.

CONCLUSIONS

The best retention–structure correlations were obtained when the valence molecular connectivity indices were used as structural parameters. The Balaban index, I_B, and Wiener number, $W(G)$, are also useful as structural parameters as they are sensitive to any change in the molecule structure. However, the structure–retention relationships obtained using I_B and $W(G)$ are characterized by only moderate statistical characteristics. The chromatographic dipole moments, μ_{chr}, calculated using these topological indices are very high and their physico-chemical meaning is doubtful. In addition, μ_{chr} values are significantly influenced by I_B and $W(G)$.

The valence molecular connectivity indices of various orders can be used in the relationships of eqns. 1 and 3. Both types of relationship are statistically significant and allow the prediction of the retention index for a given oxyethylated derivative. Eqn. 3 expresses the complexity of retention in the column and is recommended for QSRR analysis. It should be also noted that the considered relationships are limited to a given group of homologues, *i.e.* herein the oxyethylene derivatives of alcohols, thioalcohols and alkylamines.

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