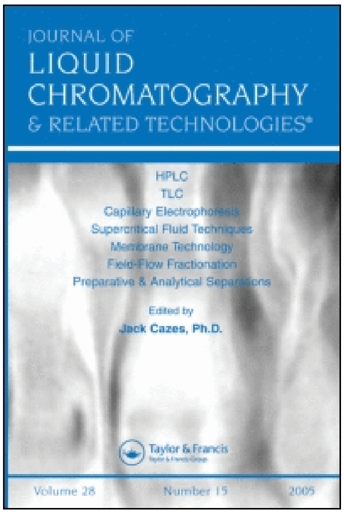

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RETENTION OF SUBSTITUTED INDOLE COMPOUNDS ON RP-HPLC: CORRELATION WITH MOLECULAR CONNECTIVITY INDICES AND QUANTUM CHEMICAL DESCRIPTORS

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ABSTRACT

The capacity factors (k') were determined by reversed phased high-performance liquid chromatography (RP-HPLC) on a C_{18} column for 18 substituted indoles. The linear relationship between the (k') values and the percentage of the methanol in the eluent was tested for each compound. The molecular connectivity indices and quantum chemical parameters were calculated for the tested chemicals and used to develop quantitative structure-retention relationships (QSRR).

Results demonstrated that the molecular connectivity indices and quantum chemical parameters could be used to predict the k' for all of the test compounds, and the molecular connectivity indices MCI method was more accurate.

INTRODUCTION

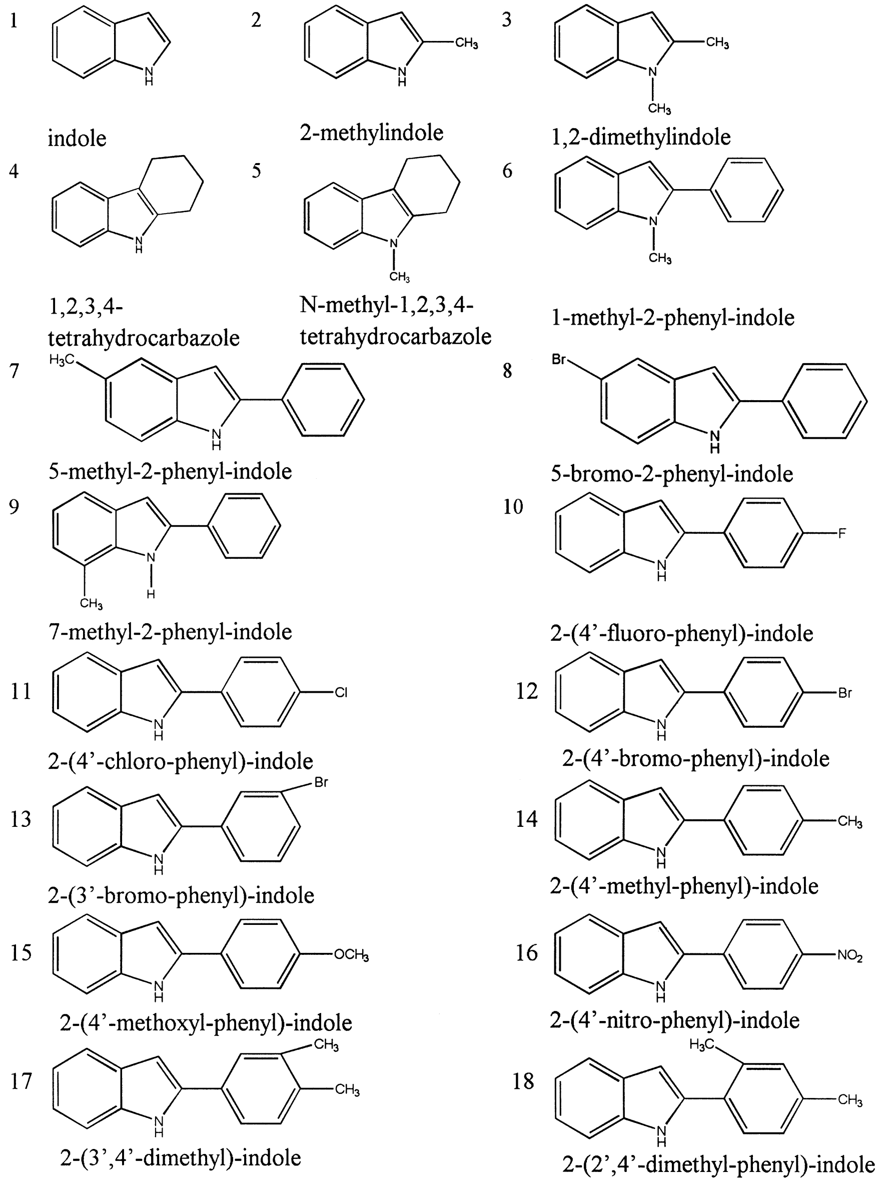
The study of the relationship between retention indices and parameters describing the structure of molecules of the solute is one of the most intensively investigated question in modern chromatography because it can (i) predict chromatographic retention behavior, (ii) measure physico-chemical parameters, and (iii) lead to an understanding of the retention mechanism. Various methods have been used to correlate, quantitatively, the logarithm of the capacity factor with the molecular structure parameters (empirical, semi-empirical, and non-empirical) such as hydrophobic parameter,[1] linear solvation energy parameters,[2] the molecular connectivity indices,[3] and quantum chemical parameters[4] in reversed phase HPLC.

Molecular connectivity is a method describing molecular structure based solely on bonding and branching patterns rather than physical or chemical characteristics. Based on earlier work by Randic,[5] Kier and Hall[6] have developed connectivity index. For a given molecular structure, several types and orders of molecular connectivity indices (MCIs) can be calculated. Information of the molecular size, branching, cyclization, unsaturation, and heteroatom content of a molecule is encoded in these various indices.

A large number of studies have demonstrated that many physicochemical and biological properties, such as water solubility, Kow, Koc, solute retention in HPLC,[7] and biological activity, correlate with the connectivity indices.[8]

Quantum chemical descriptor is a kind of non-empirical structural descriptor which can be obtained by the chemical structure and quantum chemical software. The obvious advantages of quantum structural descriptors are: they are not restricted to closely related compounds, they can be easily obtained, and describe clearly defined molecular properties. Because of their advantages, they are widely used in the QSRR studies.[9-11]

Indole and its derivatives are used extensively as intermediates to synthesize medicines, dyes and pesticides. For example, indoline is used to synthesize analgesics and anti-hypertensives, and 3-(2-aminoethyl)-indole for the synthesis of the vasodilator and antihypertensive. 2-Methylindole is a starting material for commercially important cationic diazo dyes. Cyanine dyes are synthesized from 2-methylindole, 1-methyl-2-phenylindole. In addition, indolyl-methane dyes are produces from 1-methyl-2-phenylindole. Fungicidal and bactericidal plant protectives are synthesized from indoline.[12] Indole and its derivatives are being introduced into the environment. Their environmental behavior and ecological effects should be estimated. However, few published data are available for their environmental behavior and physicochemical properties.



1 indole

2 2-methylindole

3 1,2-dimethylindole

4 1,2,3,4-tetrahydrocarbazole

5 N-methyl-1,2,3,4-tetrahydrocarbazole

6 1-methyl-2-phenyl-indole

7 5-methyl-2-phenyl-indole

8 5-bromo-2-phenyl-indole

9 7-methyl-2-phenyl-indole

10 2-(4'-fluoro-phenyl)-indole

11 2-(4'-chloro-phenyl)-indole

12 2-(4'-bromo-phenyl)-indole

13 2-(3'-bromo-phenyl)-indole

14 2-(4'-methyl-phenyl)-indole

15 2-(4'-methoxyl-phenyl)-indole

16 2-(4'-nitro-phenyl)-indole

17 2-(3',4'-dimethyl)-indole

18 2-(2',4'-dimethyl-phenyl)-indole

Figure 1. Structures and names for the indole series of compounds.

RP-HPLC capacity factors (k') were determined on C_{18} column for 18 substituted indoles. We have tried to use MCIs descriptors and semi-empirical quantum chemical descriptors to develop QSRR for the studied chemicals, and obtained the statistics significant equations which can be used to predict the retention index for structure-related compounds, and to elucidate the retention mechanism for these compounds on RP-HPLC. Furthermore, effectiveness of regression equations in predicting capacity factors (k') of the studied chemicals was compared.

EXPERIMENTAL

Instruments

The HPLC system (Shimazu Japan) consisted of a SCL-8A system monitor, a LC-8A pump, a C-R4A integrator, and a SPD-6AV ultraviolet spectrophotometer as the detector.

Reagents

Methanol (A.R. and redistilled); Doubly distilled water; Sodium nitrate (A. R.).

Samples

Indole was analytical reagent grade (A.R.). The others were synthesized by the College of Chemistry and Chemical Engineering of Nanjing University.

Purities were monitored by HPLC to assure purity.[13] The structures and names of the chemical are listed in Figure 1.

Determination of Capacity Factors

A Nucleusil7 C_{18} column, 15cm×4.6mm i.d.(made by Dalian Institute of Chemical Physics, Academia Sinica) was used. Chromatography was carried out using eluents with the following proportions (v/v) of methanol to water 100:0, 90:10, 85:15, 80:20, 75:25(v/v).

The flow rate was 0.8mL/min. Aqueous solution of sodium nitrate was used for the measurement of dead time. All measurements were made in at least duplicate. The average reproducibility of each determination was better than 1.0% relative.

Table 1

Selected Molecular Connectivity Indices for the Studied Compounds*

No.	$^0X_p^v$	$^1X_p^v$	$^2X_p^v$	$^3X_p^v$	$^4X_p^v$	$^3X_{pc}^v$	$^4X_{pc}^v$	$^5X_{pc}^v$	$^6X_{pc}^v$
1	4.964	2.988	2.065	1.463	0.995	0.156	0.353	0.452	0.348
2	5.887	3.404	2.540	1.665	1.219	0.300	0.485	0.688	0.626
3	6.834	3.799	2.904	2.192	1.427	0.389	0.939	1.171	1.029
4	7.638	5.035	3.835	3.006	2.358	0.321	0.840	1.364	1.602
5	8.585	5.429	4.209	3.434	2.716	0.416	1.191	1.975	2.342
6	9.221	5.460	4.013	3.021	2.175	0.408	1.001	1.475	1.489
7	9.196	5.476	4.140	2.861	2.025	0.478	0.855	1.124	1.225
8	10.157	5.957	4.695	3.160	2.255	0.638	1.028	1.343	1.514
9	9.196	5.482	4.088	2.949	2.081	0.446	0.944	1.270	1.302
10	8.574	4.998	3.777	2.623	1.795	0.374	0.748	0.959	0.924
11	9.328	5.376	4.213	2.875	1.951	0.500	0.894	1.074	1.080
12	10.157	5.790	4.691	3.151	2.059	0.638	1.053	1.200	1.252
13	10.157	5.957	4.695	3.158	2.283	0.638	1.028	1.360	1.463
14	9.196	5.309	4.136	2.831	1.899	0.478	0.868	1.054	1.053
15	9.604	5.588	3.999	2.931	2.000	0.379	0.829	1.050	1.086
16	9.460	5.565	4.074	2.919	1.992	0.423	0.872	1.072	1.100
17	10.119	5.893	4.569	3.348	2.138	0.600	1.287	1.388	1.464
18	10.119	5.893	4.589	3.202	2.334	0.612	1.131	1.564	1.536

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* $^tx_p^v$ represents *t*th order valence path index (t=0-4), $^tx_{pc}^v$ represents *t*th order valence path cluster index (*t*=3-6).

Calculation of MCIs

Valence connectivity parameters were calculated using a program developed by our laboratory (designed with FORTRAN language) according to the method described by Kier and Hall.[6] Values of −Cl, −F, −Br, −O−, −N<, =O were 0.78, 7, 0.26, 6, 5, and 6, respectively.[14] Values of MCIs were then calculated (Table 1).

Calculation of Quantum Structural Descriptors

Molecular geometry was optimized and parameters were calculated using the semi-empirical orbital MOPAC6.0 procedures according to methods PM3.[15]

MOPAC6.0 was used to determine the individual structural parameters influencing retention, including the average polarizablity (α), the dipole moment (μ), the energy of the highest occupied molecular orbital (E_{homo}), and

Table 2

Quantum Structure Descriptors for 18 Studied Chemicals Using the PM3 Method

No.	α [a.u.]	μ [a.u.]	$-E_{homo}$ [eV]	E_{lumo} [eV]	qH^+ [a.c.u.]	$-q^-$ [a.c.u.]	HOF [kcal/mol]	-TE $\times 10^3$[eV]	-EE $\times 10^3$[eV]	CCR $\times 10^3$[eV]
1	73.074	0.733	8.402	0.136	0.137	0.235	42.577	1.217	5.872	4.655
2	82.925	0.715	8.405	0.091	0.128	0.197	32.270	1.367	7.066	5.699
3	91.383	0.812	8.314	0.112	0.128	0.178	31.443	1.516	8.479	6.963
4	140.504	0.685	8.214	0.129	0.105	0.208	23.145	1.785	11.000	9.214
5	113.017	0.748	8.151	0.137	0.106	0.185	22.279	1.934	12.656	10.720
6	141.209	0.811	8.281	-0.268	0.130	0.149	65.912	2.139	13.929	11.790
7	144.502	0.645	8.281	-0.338	0.130	0.175	56.599	2.139	13.594	11.460
8	150.347	1.224	8.569	-0.588	0.132	0.163	72.713	2.327	13.623	11.300
9	142.845	0.660	8.322	-0.393	0.130	0.154	56.827	2.139	13.744	11.605
10	137.295	0.544	8.501	-0.614	0.129	0.161	22.217	2.414	13.803	11.389
11	148.481	0.458	8.452	-0.588	0.129	0.161	59.026	2.291	13.607	11.316
12	150.546	0.479	8.509	-0.608	0.130	0.166	73.490	2.327	13.599	11.271
13	148.880	0.752	8.503	-0.595	0.132	0.165	73.494	2.327	13.653	11.326
14	145.470	0.712	8.343	-0.391	0.129	0.160	56.283	2.139	13.567	11.428
15	152.440	0.694	8.295	-0.340	0.129	0.187	27.648	2.432	15.285	12.853
16	155.946	2.120	8.827	-1.438	0.134	0.602	56.884	2.721	16.587	13.866
17	153.840	0.753	8.322	-0.360	0.129	0.161	47.731	2.289	15.211	12.922
18	150.300	0.731	8.371	-0.216	0.131	0.163	48.940	2.289	15.392	13.104

the energy of the lowest unoccupied molecular orbital (E_{lumo}), the most positive net atomic charges on hydrogen (qH^+), the largest negative atomic charge on an atom (q^-), the heat of formation (HOF), the total energy (TE), electronic energy (EE), core-core repulsion (CCR) (Table 2).

The regression analysis was performed using the "Statgraphics" program (STSC, Inc, 1987).

RESULTS AND DISCUSSION

The capacity factors (logk′) at different mobile compositions are shown in Table 3. The relationship between logk′ and methanol concentration in mobile phase given by Snyder *et al.* [16] is as follows:

$$\log k' = \log k'_w - S\varphi_{CH3OH}$$

where $\log k'_w$ and S are, respectively, the intercept and slope value of the above equation, $\log k'_w$ represents the k′ value for a compound if pure water is used as

Table 3

Capacity Factors Obtained at Different Mobile Phase and Parameters of Linear Fit of Logk’ vs. φ_{CH3OH} in Mobile Phase

				Log k’			Intercept	-Slope		
No.	**φ:100%**	**φ:95%**	**φ90%**	**φ:85%**	**φ:80%**	**φ:75%**	**φ(Logk’$_w$)**	**(-S)**	**r[a]**	**SE[b]**
1	-0.2068	-0.1016	-0.0516	0.0291	0.1117	0.2043	1.385	1.586	0.997	0.013
2	-0.1699	-0.0464	0.0172	0.1165	0.2243	0.3249	1.770	1.934	0.998	0.014
3	-0.0195	0.1617	0.2350	0.3658	0.4995	0.6399	2.534	2.537	0.996	0.023
4	-0.0250	0.1643	0.2657	0.4162	0.5886	0.7466	2.990	3.017	0.998	0.021
5	0.2407	0.4579	0.6016	0.7815	0.9844	1.1711	3.911	3.663	0.999	0.018
6	0.1313	0.3506	0.5051	0.7341	0.9434	1.0931	4.034	3.894	0.998	0.023
7	-0.0003	0.2190	0.3477	0.5736	0.7965	0.9419	3.814	3.811	0.998	0.028
8	0.0531	0.3023	0.4563	0.7124	0.9515	1.1249	4.381	4.321	0.998	0.027
9	-0.0167	0.1914	0.3845	0.5383	0.7316	0.9023	3.633	3.634	0.999	0.017
10	-0.0647	0.1118	0.2585	0.4187	0.6207	0.7857	3.324	3.393	0.999	0.015
11	0.0419	0.2363	0.4161	0.5882	0.8350	1.0234	3.967	3.934	0.999	0.017
12	0.0693	0.2752	0.4749	0.6560	0.8914	1.1023	4.179	4,115	0.999	0.015
13	0.0672	0.2677	0.4752	0.6539	0.8894	1.1662	4.355	4.307	0.997	0.032
14	-0.0016	0.1786	0.3611	0.5211	0.7484	0.9784	3.849	3.868	0.998	0.027
15	-0.0783	0.0810	0.2418	0.3767	0.5593	0.7723	3.236	3.237	0.998	0.024
16	0.0501	0.1503	0.3214	0.4675	0.6509	0.8973	3.365	3.363	0.992	0.045
17	0.0619	0.2483	0.4550	0.6395	0.8521	1.1301	4.232	4.192	0.998	0.031
18	0.0399	0.2088	0.4066	0.6017	0.8098	1.0849	4.136	4.127	0.997	0.033

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[a] r = correlation coefficient, [b] SE = standard error of regression

eluent, S is the slope of the regression curve, and φ_{CH3OH} is the volume percentage of methanol in the eluent. The log k′ for each studied compound was plotted against the volume fraction of methanol in the eluent. The parameters derived from regression equation for the investigated chemicals are given in Table 3. Excellent linear relationships were obtained.

In order to describe the relationship between the retention indices of tested chemicals and the calculated structural parameters, a multiparameter regression analysis was performed. The obtained QSRR equations are presented below:

MICs:

$$\log k' = -0.949(\pm 0.26) + 1.13(\pm 0.07)\,{}^{2}x_{p}^{v}$$

$$R^2(adj)=0.9407,\ R=0.970,\ SE=0.209,\ n=18,\ F=270.9,\ p<0.0000 \quad (1)$$

$$S=0.591(\pm 0.23) - 1.034(\pm 0.06)\,{}^{2}x_{p}^{v}$$

$$R^2(adj)=0.9492,\ R=0.974,\ SE=0.177,\ n=18,\ F=318.35,\ p<0.0000 \quad (2)$$

Table 4

Comparison of Experimental Data for Logk'$_w$ and -S with Values Calculated from a Correlation Equation

No.	Logk'$_w$ Exp.	Pre. eqs(1)	Diff.	Slope (S) Exp.	Pre. eqs(2)	Diff.
1	1.3853	1.4562	-00709	-1.586	-1.6677	0.0817
2	1.7703	1.8877	-0.1174	-1.934	-2.015	0.0775
3	2.5339	2.2157	0.3182	-2.537	-2.3291	-0.2080
4	2.9994	3.2528	-0.2534	-3.017	-3.1427	0.1257
5	3.9111	3.6387	0.2724	-3.663	-3.5225	-0.1405
6	4.0338	4.1894	-0.1556	-3.894	-4.1585	0.2645
7	3.8140	3.8571	-0.0431	-3.811	-3.8472	0.0362
8	4.3806	4.1734	0.2072	-4.321	-4.0963	-0.2244
9	3.6328	3.9468	-0.3141	-3.634	-3.9353	03013
10	3.3239	3.1677	0.1562	-3.393	-3.1926	-0.2004
11	3.9671	3.9567	0.0104	-3.934	-3.9000	-0.0340
12	4.1788	4.2651	-0.0863	-4.115	-4.1594	0.0444
13	4.3553	4.1965	0.1589	-4.307	-4.1169	-0.1902
14	3.8485	3.8879	-0.0393	-3.868	-3.8740	0.0060
15	3.2363	3.5627	-0.3264	-3.327	-3.5910	0.2640
16	3.3651	3.3344	0.0307	-3.363	-3.3433	-0.0197
17	4.2322	4.0582	0.1740	-4.192	-4.0582	-0.1338
18	4.1361	4.0577	0.0784	-4.127	-4.0766	-0.0504

PM3:

$$\log k'_w = 4.32(\pm 0.97) - 33.059(\pm 7.91)qH^+ + 2.47(\pm 0.53)q^- + 0.02(\pm 0.004)HOF - 2.2\times 10^{-4}(\pm 2\times 10^{-5})EE$$

$$R^2(adj)=0.935,\ R=0.967,\ SE=0.22,\ n=18,\ F=61.8,\ p<0.0000 \qquad (3)$$

$$S = -3.42(\pm 0.84) + 22.91(\pm 6.88)qH^+ - 2.31(\pm 0.46)q^- - 0.02(\pm 0.003)HOF + 2.3\times 10^{-4}(\pm 2\times 10^{-5})CCR$$

$$R^2(adj)=0.941,\ R=0.970,\ SE=0.19,\ n=18,\ F=68.98,\ p<0.0000 \qquad (4)$$

Where the number in parentheses is the standard error associated with each coefficient, R is the correlation coefficient adjusted by degree of freedom, SE is the standard error of estimates, n is the number of chemicals, F is the *F*-test value, p is the significance level of the whole equation.

The F and p values of eqs. (1)-(4) show that the equations are significant. Eqs. (1)-(4) have large correlation coefficients and small SE values. This indicated that $\log k'_w$ and S can be predicted by model based on valence connectivity indices and quantum chemical descriptors. It can be seen from eqs. (1), (3) that $\log k'_w$ can be predicted by a model based on quantum chemical method, but the correlation was weak with large SE compared with the valence connectivity. This indicated that the valence connectivity method is more effective than the quantum chemical method in predicting retention indices for studied compounds. The predicted $\log k'_w$(using eq. (1)), S (using eq. (2))values and the residuals for the test chemicals are shown in Table 4. A plot of predicted $\log k'_w$ (using eq. (1)) and S(using eq. (2)) versus observed $\log k'_w$ and S are shown in Figures 2-3, respectively. The predicted $\log k'_w$ and S were well fitted with observed $\log k'_w$ and S.

Furthermore, the student *t* values for partial correlation coefficient are -10.7, 5.84, 4.6, -4.18 for EE, HOF, q^-, and qH^+ descriptors in equation 3, respectively. This indicated that electronic energy (EE) descriptor is the most significant factor for $\log k'_{w.}$ The EE provides information about the bulkiness of the solute. This size-related descriptor may be related to the interaction between the solute molecule and the stationary phase occurring in reversed-phase liquid chromatography. The larger the solute molecule, the stronger the solute-adsorbent interaction. The heat of formation (HOF) descriptor possibly determines the ability of the solute participate in electron-dipole interactions with mobile phase.

In addition, the most positive net atomic charges on hydrogen (qH^+) and the largest negative atomic charge on an atom (q^-) descriptors are related to the ability of the solutes to participate in hydrogen-bonding interactions with eluent molecules. Their participation in the correlation equations are even less than the HOF term; this indicates that this kind of interaction is rather less importance for retention. The parameters EE and qH^+ have a negative sign, which means that the larger EE and qH^+, the smaller is the $\log k'_w$ value. The parameters HOF and q^- have a positive sign, which means that the larger EE and q^-, the larger is the $\log k'_w$ value. On the contrary, it can be seen from eq.(4), except for the core-core repulsion (CCR) descriptor, the sign of qH^+, HOF and q^- are opposite to those in eq(3). The CCR descriptor provides information similar to EE descriptor.

In summary, the correlations obtained between the valence connectivity indices and quantum chemical descriptors and the retention indices for substituted indoles are very good and may be used to predict the retention properties of the structure-related molecules. Compared with the quantum chemical method, the valence connectivity method is more effective in predicting retention indices for studied compounds.

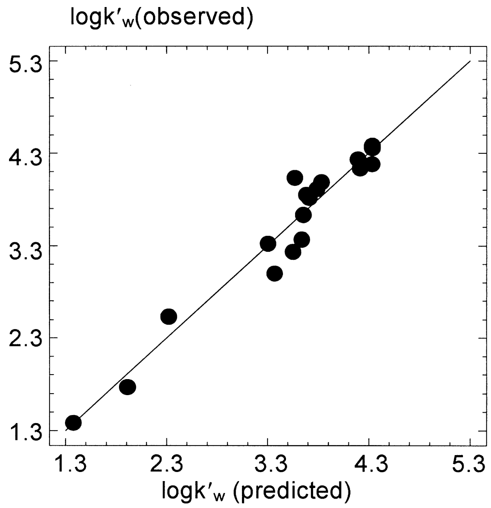

Figure 2. Plot of the predicted and the calculated logk′w values according to Eq.(1).

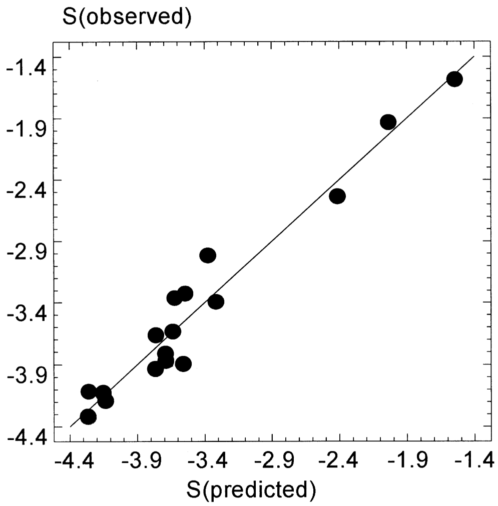

Figure 3. Plot of the predicted and the calculated S values according to Eq.(2).

Nevertheless, the quantum parameters have clear physicochemical interpretations. Retention in RP-HPLC is found to be the net effect of bulkiness-dependent interactions and electrostatic interaction involving solute molecules and molecules of both mobile and stationary phases. The electronic energy (EE) descriptor which is related to the interaction between the solute molecule and the stationary phase occurring in reversed-phase liquid chromatography seems to be dominant in retention mechanism.

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