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Correlation of Reversed-Phase Retention Factors for α-Branched Phenylsulfonyl Acetates with Octanol/Water Partition Coefficients and Quantum Chemical Descriptors

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Aromatic sulfones, used extensively in the manufacture of pesticides, herbicides and anthelmintics, and also in the petrochemical and metallurgical industries (Han et al. 1992), are being introduced into the environment. Their environmental behavior and ecological effects should be anticipated.

It is widely recognized that the hydrophobicity of a compound plays an important role in phenomena of physical-chemical, biological and environmental interest. Reversed-phase high-performance liquid chromatography (RP-HPLC) using octadecyl silica as a stationary phase has been extensively used for rapidly measuring the hydrophobicity (Braumann 1986; Dorsey and Khaledi 1993).

Quantitative structure-retention relationships (QSRRs) (Kaliszan 1992) have been widely applied in predicting retention factor for a new solute, evaluating physicochemical properties of chemicals, predicting relative biological activities. Many types of QSRRs have been employed, based on various variables such as the logarithms of octanol/water partition coefficients (lg K_{OW}) (Kaliszan et al. 1999), the molecular connectivity indices (Hong et al. 1995), the LSER-based descriptors (Carr et al. 1986; Kaliszan et al. 1999; Sadek et al. 1985), the quantum chemical descriptors (Buszewski et al. 1997; Cupid et al. 1993; Nord et al. 1998). Generally, it is more useful to use descriptors derived mathematically from either two-dimensional or three-dimensional molecular topology. Especially, the approaches based on the three-dimensional molecular structure are more significant since flexible compounds can adopt different conformations in different situation.

In this work, logarithms of retention factors normalized to a hypothetical pure water eluent (lg k_w) are reported for 20 new α-substituted phenylsulfonyl acetates. Relationships between lg k_w, lg K_{OW} and TLSER (the theoretical linear solvation energy relationships) descriptors (Famini 1989; Wilson and Famini 1991), were discussed.

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MATERIALS AND METHODS

The HPLC system (Shimadzu, 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.

Spectrophotometric-grade methanol was obtained from Tedia Company, Inc. (Fairfield, Ohio, USA). Sodium nitrate was analytical grade. Water was doubly distilled in quartz. Twenty α-substituted phenylsulfonyl acetates (listed in Table 1) were synthesized in the laboratory.

Table 1. List of compounds and experimental lg K_{OW} and lg k_w values

No.	Compound	lg K_{OW} [a]	lg k_w [b]	S [c]
1	4-NO$_2$-Ph-SO$_2$-CH(Me)-CO$_2$-Me	1.06	0.648	1.156
2	4-NO$_2$-Ph-SO$_2$-C(Me)$_2$-CO$_2$-Me	1.38	0.941	1.419
3	4-NO$_2$-Ph-SO$_2$-C(Et)$_2$-CO$_2$-Me	2.24	1.637	2.045
4	4-NO$_2$-Ph-SO$_2$-C(n-Bu)$_2$-CO$_2$-Me	3.38	3.125	3.404
5	4-NO$_2$-Ph-SO$_2$-C(CH$_2$Ph)$_2$-CO$_2$-Me	4.46	3.377	3.716
6	4-NO$_2$-Ph-SO$_2$-C(n-Bu)$_2$-CO$_2$-Et	3.81	3.469	3.774
7	4-NO$_2$-Ph-SO$_2$-C(Me)(CH$_2$Ph)-CO$_2$-Et	3.40	2.335	2.697
8	4-NO$_2$-Ph-SO$_2$-C(Me)(CH$_2$CH=CH$_2$)-CO$_2$-Et	2.30	1.710	2.119
9	4-NO$_2$-Ph-SO$_2$-C(Me)(CH$_2$-α-Naph)-CO$_2$-Et	4.40	3.176	3.453
10	4-NO$_2$-Ph-SO$_2$-C(n-Bu)$_2$-CO$_2$-*i*-Pr	4.06	3.621	3.912
11	4-NO$_2$-Ph-SO$_2$-CH(Me)-CO$_2$-CH(CH$_2$)$_5$	2.82	2.105	2.501
12	4-NO$_2$-Ph-SO$_2$-CH(CH$_2$CO$_2$Et)-CO$_2$-Me	1.40	1.026	1.526
13	4-NO$_2$-Ph-SO$_2$-CH(CH$_2$CO$_2$-*i*-Pr)-CO$_2$-*i*-Pr	2.18	1.974	2.421
14	4-NO$_2$-Ph-SO$_2$-C(CH$_2$CO$_2$Et)$_2$-CO$_2$-*i*-Pr	3.56	3.061	3.374
15	4-NO$_2$-Ph-SO$_2$-C(=CHPh)-CO$_2$-Me	2.90	1.553	2.056
16	4-NO$_2$-Ph-SO$_2$-C(=CHPh)-CO$_2$-Et	3.20	1.946	2.399
17	4-NO$_2$-Ph-SO$_2$-C(=CHPh)-CO$_2$-*i*-Pr	3.62	2.259	2.687
18	4-NO$_2$-Ph-SO$_2$-C(=CHPh)-CO$_2$-*i*-Bu	3.68	2.423	2.650
19	4-Me-Ph-SO$_2$-C(=CHPh)-CO$_2$-*i*-Pr	3.92	2.283	2.660
20	4-Cl-Ph-SO$_2$-C(=CHPh)-CO$_2$-*i*-Pr	4.18	2.414	2.747

[a] lg K_{OW} data are from the literature (Liu et al. 2001); [b] lg k_w data are the extrapolated values from Equation 2; [c] S is slope, and the squared correction coefficient (r^2) from Equation 2 is more than 0.980.

A HPLC column was used: 150mm×4.6mm *id* Li Chrosorb RP-18 (5μm) column (Shanghai Institute of Pharmaceutical Science, Academic Sinica), with the flow rate of 1.0ml/min, at ambient temperature of 20±2℃. The detector was set at a certain wavelength according to each compound. The mobile phases consisted of different volume fractions of methanol in water (95:5, 90:10, 85:15, 80:20, 75:25 and 70:30). An aqueous solution containing sodium nitrate was used for the measurement of dead time (t_0) (Horváth et al. 1977). All measurements were made in triplicate. The retention factors (k') were determined using Equation 1,

$$k' = (t_R - t_0)/t_0 \qquad (1)$$

where t_R is the retention time of the compound. For the dependence of lg k' on the volume fraction (φ) of methanol in the aqueous eluent, Snyder et al. (1979) showed that a linear version of Equation 2 can be used,

$$\lg k' = \lg k_W - S\varphi \qquad (2)$$

where k_w represents the k' value for a hypothetical pure water eluent ($\varphi = 0$).

The molecule was drawn using the CS Chem3D 5.0 (CambridgeSoft Corp 1999) software to generate the starting geometry. Then geometric optimization was performed; geometric and electronic properties were determined by the AM1 method of the MOPAC 97 program. Using the optimum geometry, the molecular volume (V_m in Å^3) was calculated by Connolly method. The electronic descriptors such as dipole moment (μ in D), polarizability (α in au), energy of the highest occupied molecular orbital (E_{HOMO} in eV), energy of the lowest unoccupied molecular orbital (E_{LUMO} in eV), were achieved.

The stepwise regression analysis with a confidence limit of 95% was performed using SPSS 8.0 software package (SPSS Inc. 1989-1997). To obtain the best fit of the lg k_w values to the extrapolated ones, the linear least-squares method was performed.

RESULTS AND DISCUSSION

The lg k_w was linearly regressed against lg K_{OW} as follows:

$$\lg k_w = -0.026 + 0.736 \lg K_{OW} \qquad (3)$$

$$(n=20,\ r^2_{adj}=0.762,\ SE=0.421,\ F= 61.72,\ p<0.001)$$

where n represents the number of compounds, r^2_{adj} is the squared correction coefficient (adjusted for degrees of freedom), SE is the standard error, F is the F-test value, p is the significance level of F-value. The result illustrates the unsatisfactory correlation of lg K_{OW} with lg k_w values (lower r^2 and F, together with higher SE). The coefficient with lg K_{OW} reflects the degree to which the solute is surrounded by the stationary phase (Dill 1987; Knox and Ross 1997). For a bonded stationary phase this should be less than for liquid octanol. The difference of mechanisms (Braumann 1986) between solute retention in RP-HPLC and partitioning in octanol/water system may give a good explanation. In contrast with isotropic octanol, the stationary phase in RP-HPLC is highly anisotropic. The chemically bonded phase does not behave as a true liquid owing to the restricted mobility of the bonded ligands. Solute retention in RP-HPLC is a dynamic equilibrium process, and the octanol/water system is a static liquid-liquid partitioning.

Based on TLSER model (theoretical linear solvation energy relationships), six descriptors (listed in Table 2): V_{mc}; π^*; ε_a, ε_b, qH^+, q^-, which represent cavity, dipolarity/polarizability, and hydrogen bonding terms, are calculated by using AM1 procedure.

Table 2. Descriptors of TLSER model

No.	V_{mc}	π^*	ε_a	ε_b	qH^+	q^-
1	2.036	0.611	0.106	0.150	0.223	1.017
2	2.193	0.605	0.106	0.150	0.202	1.007
3	2.517	0.599	0.106	0.149	0.201	1.016
4	3.245	0.584	0.105	0.133	0.187	0.951
5	3.484	0.680	0.106	0.140	0.182	0.923
6	3.421	0.555	0.106	0.150	0.202	1.001
7	3.044	0.637	0.106	0.142	0.201	1.013
8	2.645	0.605	0.106	0.148	0.202	1.007
9	3.408	0.691	0.106	0.134	0.202	1.005
10	3.624	0.547	0.107	0.150	0.199	1.007
11	2.815	0.592	0.104	0.155	0.182	0.908
12	2.555	0.622	0.106	0.149	0.229	1.007
13	3.134	0.582	0.105	0.154	0.199	0.911
14	3.836	0.597	0.106	0.140	0.201	1.009
15	2.531	0.730	0.108	0.144	0.198	1.030
16	2.728	0.710	0.108	0.144	0.199	1.029
17	2.920	0.689	0.107	0.146	0.178	0.930
18	3.087	0.680	0.107	0.146	0.180	0.931
19	2.875	0.673	0.113	0.144	0.173	1.041
20	2.869	0.668	0.112	0.144	0.186	1.037

V_{mc} is $V_m/100$. π^* is equal to α/V_m. ε_b is the covalent contribution to Lewis basicity, q^- is the most negative atomic charge in the solute molecule. ε_a is the covalent contribution to Lewis acidity, qH^+ is the most positive charge of a hydrogen atom in the solute molecule.

With the six parameters, the model for lg k_w data was founded through stepwise regression analysis as follows:

$$\lg k_w = -2.805 + 1.716 V_{mc} \qquad (4)$$

$$(n=20,\ r^2_{adj}=0.871,\ SE=0.310,\ F=129.16,\ p<0.001)$$

Of six parameters, V_{mc} is significant. From the equation, the lower correction coefficient of 0.871, together with the greater standard error of 0.310 is obtained. Figure 2 shows that the fits are not good. Table 3 shows that the deviations are at a range from –0.716 to 0.404. This suggests that the model is not more successful.

Table 3. Predicted values and residuals for lg k_w

No.	Eqn.3		Eqn.4		Eqn.5	
	Pred.	Res.	Pred.	Res.	Pred.	Res.
1	0.755	-0.107	0.689	-0.041	0.640	0.008
2	0.990	-0.049	0.958	-0.017	1.092	-0.151
3	1.623	0.014	1.514	0.123	1.747	-0.110
4	2.462	0.663	2.764	0.361	2.805	0.320
5	3.257	0.120	3.173	0.204	3.420	-0.043
6	2.779	0.690	3.065	0.404	3.184	0.285
7	2.477	-0.142	2.418	-0.083	2.522	-0.187
8	1.667	0.043	1.734	-0.024	1.867	-0.157
9	3.213	-0.037	3.043	0.133	3.116	0.060
10	2.963	0.658	3.414	0.207	3.572	0.049
11	2.050	0.055	2.026	0.079	2.181	-0.076
12	1.005	0.021	1.580	-0.554	1.002	0.024
13	1.579	0.395	2.569	-0.595	2.197	-0.223
14	2.595	0.466	3.777	-0.716	3.434	-0.373
15	2.109	-0.556	1.539	0.014	1.321	0.232
16	2.330	-0.384	1.876	0.070	1.879	0.067
17	2.639	-0.380	2.205	0.054	2.109	0.150
18	2.683	-0.260	2.492	-0.069	2.212	0.211
19	2.860	-0.577	2.129	0.154	2.394	-0.111
20	3.051	-0.637	2.119	0.295	2.391	0.023

Pred. is the predicted value by Eqations3-5, Res. is residual between the extrapolated and predicted value.

The structures of compounds are significantly different, and result in the different retention mechanism. To avoid the influence of strikingly different structures on the regression model, the indicator variable for structure, *I*, is put forward. For No.12-14 compounds with several carboxyl groups and No.15-20 compounds with conjugate system, *I* is 0; and others (No.1-11), *I* is 1. With six TLSER parameters and the structural indicator variable, Equation 5 is obtained by stepwise regression analysis:

$$\lg k_w = -8.841 + 1.709 V_{mc} + 70.371 \varepsilon_a - 8.718 qH^+ + 0.461 I \qquad (5)$$

$$(n=20,\ r^2_{adj}=0.944,\ SE=0.203,\ F=81.593,\ p<0.001)$$

Comparison of Equation 4 with Equation 5 shows that the indicator variable is significant. The correction coefficient increases to 0.944, standard error decreases by approximate 0.11 log unit. The lower deviations (from Table 3), and the better

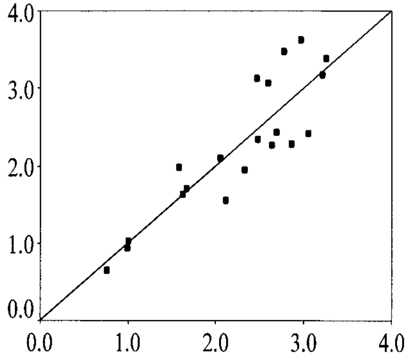

Figure 1

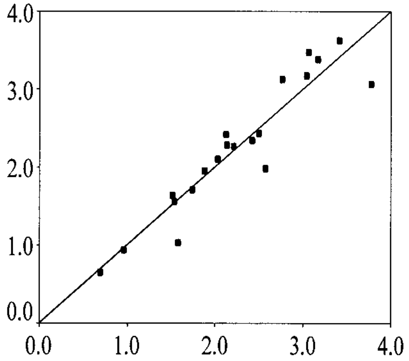

Figure 2

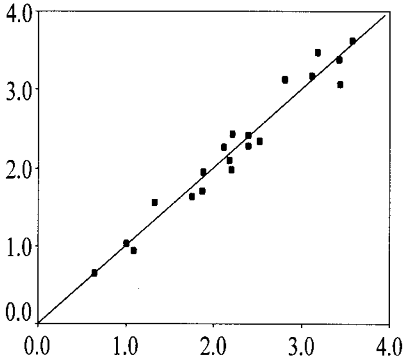

Figure 3

Figures 1–3. Plot of extrapolated versus predicted lg k_w data calculated from Equation 3 to 5, respectively. The Y axis represents the extrapolated values, and X axis represents the predicted values.

fits (from Figure 3) reflect the indicator much valuable. The indicator *I* may describe some of the electrostatic interactions, involving dipolarity/polarizability and the capability of hydrogen-bonding formation. The modified TLSER model using the structural indicator is satisfactory.

For RP-HPLC using chemically bonded hydrocarbonaceous phase, hydrophobicity is a complex net effect of various competing intermolecular interactions between the solute, the eluent and the stationary phase. Two basic kinds of attractive intermolecular interactions must be taken into consideration: the non-specific, molecular-sized, dispersive interactions and the polar interactions dependent on chemical constitution (inductive, orientation, hydrogen-bonding and charge-transfer interactions) (Horváth et al. 1976; Kaliszan et al. 1999).

In the models, the volume (V_{mc}) is the most significant descriptor. It means that the important factor of solute retention is the creation of a cavity and dispersive interactions. The positive sign at the volume term reflects that the attractive dispersive interactions between the solute and the hydrocarbon ligand of the stationary phase are stronger than the same non-specific attractive interactions between the solute and the small molecules of the eluent.

Because of the difference of mechanisms between solute retention in RP-HPLC and partitioning in octanol/water system, the regression of lg k_w with lg K_{OW} is not successful. TLSER is applied to model the retention factors of α-substituted phenylsulfonyl acetates. By introduction of the structural indicator variable, the modified TLSER model improves the regression effect.

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