Prediction of liquid chromatography retention factors for \( \alpha \)-branched phenylsulfonyl acetates using quantum chemical descriptors

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Abstract: The logarithms of retention factors normalized to a hypothetical pure water eluent (log \( k_w \)) were determined on a reversed-phase high-performance liquid chromatography (RP-HPLC) column (Li Chrosorb RP-18 column) for 20 new \( \alpha \)-branched phenylsulfonyl acetates. The atomic charge method was applied to develop quantitative structure-retention relationships (QSRRs). Among the available geometric and electronic descriptors, surface area (S), ovality (O), and the charge of carboxyl group (Qa) are significant. In the model, the contribution of surface area (S) is the greatest. The molecular mechanism of retention was demonstrated through the model. With the correlation coefficient (\( r^2 \) adj, adjusted for degrees of freedom) of 0.964, the standard error of 0.164 and the F-value of 170.39, the model has good predictive capacity.

Keywords: phenylsulfonyl acetates; quantum chemical descriptor; quantitative structure-retention relationships (QSRRs); retention factor

Introduction

The hydrophobicity of a compound plays an important role in phenomena of physico-chemical, biological and environmental interest. Due to its advantages (Thur, 1985), 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, 1993). Quantitative structure-retention relationships (QSRRs; Kaliszyn, 1992) have been widely applied in predicting retention for a new solute, evaluating physicochemical properties of chemicals, predicting relative biological activities.

Many types of QSRRs have been employed on the basis of various variables such as the logarithms of octanol/water partition coefficients (log \( K_{ow} \); Kaliszyn, 1999), the molecular connectivity indices (Hong, 1995), ISER-based descriptors (Carr, 1986; Kaliszyn, 1999; Sadek, 1985; Sandi, 1998a; 1998b; Tan, 1996), quantum chemical descriptors from calculational chemistry (Buszewski, 1997; Cupid, 1993; Kaliszyn, 1997; Nord, 1998). In general, it is more useful to use descriptors derived mathematically from either two-dimensional or three-dimensional molecular structure. Especially, the approaches based on the three-dimensional molecular structure are more significant since flexible compounds can adopt different conformations in different situation.

Aromatic sulfones, used extensively in the manufacture of pesticides, herbicides and anthelmintics, and also in the petrochemical and metallurgical industries (Han, 1992), are being introduced into the environment. Their environmental behavior and ecological effects should be anticipated. Recently, we synthesized 20 new \( \alpha \)-substituted phenylsulfonyl acetates. In this paper, logarithms of retention factors normalized to a hypothetical pure water eluent (log \( k_w \)) are reported. To predict potential behavior of chemicals, atomic charge method (Bordor, 1989; 1992; Liu, 2001) is applied to correlate the retention factors of \( \alpha \)-substituted phenylsulfonyl acetates.

1 Materials and methods

1.1 Apparatus

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.

1.2 Reagents and chemicals

Spectrophotometric-grade methanol was obtained from Tedia Company, Inc. (Fairfield, Ohio, USA). Sodium nitrate was analytical grade. Water was doubly distilled in quartz. 20 α-substituted phenylsulfonyl acetates were synthesized in the laboratory (Table 1).

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>1</td>
<td>4-NO₂-Ph-SO₂-C(Ph)-CO₂-Me</td>
<td>0.648</td>
<td>0.666</td>
<td>-0.018</td>
<td>226.092</td>
<td>1.101</td>
<td>1.351</td>
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<td>2</td>
<td>4-NO₂-Ph-SO₂-C(Me)-CO₂-Me</td>
<td>0.941</td>
<td>0.985</td>
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<td>4-NO₂-Ph-SO₂-C(Ph)-CO₂-Me</td>
<td>1.637</td>
<td>1.591</td>
<td>0.046</td>
<td>258.769</td>
<td>1.050</td>
<td>1.342</td>
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<tr>
<td>4</td>
<td>4-NO₂-Ph-SO₂-C(α-Bu₂)-CO₂-Me</td>
<td>3.125</td>
<td>2.918</td>
<td>0.207</td>
<td>363.108</td>
<td>1.158</td>
<td>1.590</td>
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<tr>
<td>5</td>
<td>4-NO₂-Ph-SO₂-C(CH₃Ph₂)-CO₂-Me</td>
<td>3.377</td>
<td>3.409</td>
<td>-0.032</td>
<td>357.718</td>
<td>0.971</td>
<td>1.494</td>
</tr>
<tr>
<td>6</td>
<td>4-NO₂-Ph-SO₂-C(α-Bu₂)-CO₂-Et</td>
<td>3.469</td>
<td>3.167</td>
<td>0.302</td>
<td>336.017</td>
<td>1.069</td>
<td>1.421</td>
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<tr>
<td>7</td>
<td>4-NO₂-Ph-SO₂-C(Me)(CH₃Ph)-CO₂-Et</td>
<td>2.335</td>
<td>2.545</td>
<td>-0.210</td>
<td>314.355</td>
<td>1.035</td>
<td>1.437</td>
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<td>8</td>
<td>4-NO₂-Ph-SO₂-C(Me)(CH₃CH = CH₂)-CO₂-Et</td>
<td>1.710</td>
<td>1.794</td>
<td>-0.084</td>
<td>275.951</td>
<td>1.077</td>
<td>1.385</td>
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<tr>
<td>9</td>
<td>4-NO₂-Ph-SO₂-C(Ph)(CH₂ = CH₆Ph)-CO₂-Et</td>
<td>3.176</td>
<td>3.249</td>
<td>-0.073</td>
<td>356.387</td>
<td>1.028</td>
<td>1.511</td>
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<td>10</td>
<td>4-NO₂-Ph-SO₂-C(α-Bu₂)-CO₂-i-Pr</td>
<td>3.621</td>
<td>3.494</td>
<td>0.127</td>
<td>350.728</td>
<td>1.102</td>
<td>1.427</td>
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<td>11</td>
<td>4-NO₂-Ph-SO₂-C(CH₃)-CO₂-C(CH₃)₃</td>
<td>2.105</td>
<td>2.196</td>
<td>-0.091</td>
<td>297.405</td>
<td>0.939</td>
<td>1.432</td>
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<td>12</td>
<td>4-NO₂-Ph-SO₂-C(CH₂CO₂Et)-CO₂-Me</td>
<td>1.026</td>
<td>0.853</td>
<td>0.173</td>
<td>291.180</td>
<td>2.202</td>
<td>1.495</td>
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<td>4-NO₂-Ph-SO₂-C(CH₂CO₂-i-Pr)-CO₂-i-Pr</td>
<td>1.974</td>
<td>2.139</td>
<td>-0.165</td>
<td>338.012</td>
<td>1.934</td>
<td>1.516</td>
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<td>14</td>
<td>4-NO₂-Ph-SO₂-C(CH₂CO₂-i-Pr)-CO₂-i-Pr</td>
<td>3.061</td>
<td>3.172</td>
<td>-0.111</td>
<td>393.662</td>
<td>2.337</td>
<td>1.542</td>
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<td>15</td>
<td>4-NO₂-Ph-SO₂-C( = CHPh)-CO₂-Me</td>
<td>1.553</td>
<td>1.530</td>
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<td>291.816</td>
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<td>16</td>
<td>4-NO₂-Ph-SO₂-C( = CHPh)-CO₂-Et</td>
<td>1.946</td>
<td>1.912</td>
<td>0.034</td>
<td>308.964</td>
<td>1.124</td>
<td>1.519</td>
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<tr>
<td>17</td>
<td>4-NO₂-Ph-SO₂-C( = CHPh)-CO₂-i-Pr</td>
<td>2.259</td>
<td>2.361</td>
<td>-0.102</td>
<td>322.292</td>
<td>1.006</td>
<td>1.541</td>
</tr>
<tr>
<td>18</td>
<td>4-NO₂-Ph-SO₂-C( = CHPh)-CO₂-i-Pr</td>
<td>2.423</td>
<td>2.688</td>
<td>-0.265</td>
<td>338.798</td>
<td>1.003</td>
<td>1.534</td>
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<tr>
<td>19</td>
<td>4-Me-Ph-SO₂-C( = CHPh)-CO₂-i-Pr</td>
<td>2.283</td>
<td>2.233</td>
<td>0.050</td>
<td>320.230</td>
<td>1.127</td>
<td>1.513</td>
</tr>
<tr>
<td>20</td>
<td>4-CI-Ph-SO₂-C( = CHPh)-CO₂-i-Pr</td>
<td>2.414</td>
<td>2.182</td>
<td>0.232</td>
<td>315.903</td>
<td>1.125</td>
<td>1.502</td>
</tr>
</tbody>
</table>

Notes: Extr. is the extrapolated value; Pred. is the predicted value by Equation (3); Res. is the residual between the extrapolated and predicted value; S is in Å²; QOC is in Å²

1.3 Chromatographic procedures

An analytical RP-HPLC column was used: 150 mm × 4.6 mm id Li Chorsorb RP-18 (5 μm) column (Shanghai Institute of Pharmaceutical Science, Chinese Academy of Sciences), with the flow rate of 1.0 ml/min, at ambient temperature of 20 ± 2 °C. The detector was set at a certain wavelength according to each compound. The mobile phases were 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 (tₙ) (Horváth, 1977). All measurements were made in triplicate. The average reproducibility of each determination was better than 1.0% relative. The retention factor (k') was determined using Equation (1):

\[ k' = \frac{(t_R - t_n)}{t_o}, \]  

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

\[ \log k' = \log k_\infty - S \phi, \]  

where k_∞ represents the k' value for a hypothetical pure water eluent (φ = 0).
1.4 Geometric and electronic descriptors

The molecule was drawn using the CS CHEMOFFICE 5.0 (CambridgeSoft Corp., 1999) software package 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 surface area (S in Å²), and ovality (O) were calculated by Connolly method. The electronic descriptors such as dipole moment (μ in D), polarizability (α in au), atomic charge (in au), were achieved. Based on the elementary descriptors, the derived parameters were generated. The available descriptors are listed in Table 2.

1.5 Statistics

The stepwise regression analysis with a confidence limit of 95% was performed using SPSS 8.0 software package (SPSS Inc., 1989 – 1997). The linear least-squares method was performed to give the best fit of the predicted log kₐ values to the extrapolated data.

2 Results and discussion

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, 1976; KaliszAN, 1999).

For the atomic charge approach model, sufficient geometric and electronic descriptors were used to correlate log kₐ. The essential geometric parameters include surface area(S), ovality(O), molecular weight (MW), and indirectly the volume(V). The molecular size and shape are important factors of solvation properties, since they contain cavity formation energy in solvent (Pearlman, 1986) and solute-solvent dispersion interactions (Hermann, 1972; Schützmann, 1994; 1995).

All the remaining parameters are quantum chemical electronic ones, which characterize the electrostatic interactions of the solute and solvent molecules. Hydrogen-bonding effect has been shown to be mainly electrostatic interactions in nature (Dinur, 1991; Scheiner, 1991).

By using the stepwise linear regression, a great number of different models were tested and the following regression equation was found the best:

$$\log k_a = 2.660 + 0.026S - 0.670Q_{OC} - 5.267O,$$

$$\left( n = 20, r^2 = 0.964, SD = 0.164, F = 170.39, P < 0.001 \right)$$
where \( n \) represents the number of compounds, \( r_{adj}^2 \) is the correction coefficient (adjusted for degrees of freedom), \( SD \) is the standard deviation, \( F \) is the \( F \)-test value, and \( p \) is the significance level of \( F \)-value. All other variables were found statistically insignificant, so they were omitted. The applied parameters are listed in Table 1.

For \( \log k_w \) (between 0.648 and 3.621), Equation (3) give a correlation coefficient of 0.964, a standard error of 0.164, and a \( F \) of 170.39. Fig. 1 shows the excellent fits between the predicted and observed values. Table 1 reveals that the bias is at a range from \(-0.018\) to \(0.302\) log unit for \( \log k_w \). The model is very successful. \( T \)-test (Table 3) reveals the parameters significant. It is clear that for solute retention, molecular size, shape (ovality), and the charge of carboxyl group play dominant roles. Within electronic descriptors, the contribution of \( Q_{oc} \) is great.

The geometric parameter, surface area, and indirectly the volume is the most significant in the model. It means that the important influencing factor of solute retention is the creation of a cavity and dispersive interactions. The positive coefficient with \( S \) term suggests that the hydrophobic effect increases with increasing surface area of the solute. 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. Ovality (\( O \)) is also a volume-related parameter. The negative sign at ovality term shows that the hydrocarbon ligand of the stationary phase is sensitive to the shape of the solute molecule. These parameters, however, cannot fully describe the wide variation of the solute retention. The electronic parameters are the overall descriptors of the electrostatic interactions, involving dipolarity/polarizability and the capability of hydrogen-bonding formation. The negative sign at \( Q_{oc} \) term reflects that the higher strength of attractive interactions between the polar group of the solute and the polar molecules of the eluent in comparison with the same type of interactions between the solute and the non-polar stationary phase. The function of geometric and electronic parameters can be seen to fit well with the extrapolated data for 20 \( \alpha \)-substituted phenylsulfonyl acetates.

**Table 3** Model fitting results for \( \log k_w \)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coefficient</th>
<th>( SD )</th>
<th>( t )-statistics</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>2.660</td>
<td>0.094</td>
<td>2.943</td>
<td>0.010</td>
</tr>
<tr>
<td>( S )</td>
<td>0.026</td>
<td>0.001</td>
<td>19.172</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( Q_{oc} )</td>
<td>-0.670</td>
<td>0.096</td>
<td>-6.950</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( O )</td>
<td>-5.267</td>
<td>0.815</td>
<td>-6.464</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

3 Conclusions

Generally, the theoretical predictive model based on quantum chemical calculations for retention factors has good predictive capability and general applicability. The atomic charge approach is successful because of consideration of more complete factors influencing retention mechanism. The geometric and electronic descriptors account for dispersive interactions, electrostatic interactions. The obtained model can reveal the molecular mechanism of solute retention in reversed-phase high-performance liquid chromatography.

References:


Braumann T, 1986. Determination of hydrophobic parameters by reversed-phase liquid chromatography: theory, experimental techniques and
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