Hydroscopicity Parameters Determined by Reversed-Phase Liquid Chromatography. XVI: A New Hydrogen-Accepting Parameter for Monosubstituted Thiophenes and Furans for Correlating Retention Factors and Octanol–Water Partition Coefficients1)

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We recently proposed a new hydrogen-accepting parameter, $S_{HA}$, for monosubstituted (di)azines on the basis of the heat of formation calculated by the conductor-like screening model (COSMO) method. In this work, $S_{HA}$ values for monosubstituted thiophenes and furans were calculated and the results were applied to the analysis of relationships between log $P$ ($P$: 1-octanol/water partition coefficient) and log $k$ ($k$: retention factor obtained by reversed-phase HPLC). The $S_{HA}$ parameter was found to work effectively as a hydrogen-bonding parameter in a range of heteroaromatic compounds.

Key words partition coefficient; retention factor; hydrogen-accepting parameter; thiophene; furan; conductor-like screening model (COSMO)

In connection with recently developed methodologies for rational drug design, rapid prediction of the hydrophobicity of candidate-compounds before synthesis has increasingly become important.2,3) In particular, much attention has been devoted to predicting the hydrophobicity for heterocyclic compounds. Hydrophobicity, which is generally expressed by the logarithm of 1-octanol/water partition coefficient, log $P$, is often predicted by calculations or estimated from the retention factor, log $k$, obtained experimentally by reversed-phase high performance liquid chromatography (RP-HPLC), and extensive studies have been reported on this subject.4)–12)

Despite this, no universal method has been established yet to predict reliable values of log $P$ for heterocyclic compounds. This is largely due to the fact that parameters like log $P$ and log $k$ for heterocyclic compounds involve H-bonding effects, of which contributions are difficult to evaluate. With the RP-HPLC approach, such H-bonding effects often give non-linearity between log $P$ and log $k$, leading us to erroneous estimations. Accordingly, a major problem for providing accurate predictions lies in estimating the contributions of H-bonding effects. One widely used procedure for expressing H-bonding effects is to adopt indicator variables, $HB_A$ and $HB_B$, which take the value of 1 for H-acceptors and H-donors, respectively, and 0 for others.13)

Although the physical meaning of using such discrete-type parameters is well discussed,13) their applications are limited to a group of compounds whose H-bonding abilities are constrained within a defined range. We have used the $HB_A$ parameter to analyze the relationship between log $k$ and log $P$ for monosubstituted heteroaromatic compounds,14)–19) such as (di)azines, furans and thiophenes, and also to correlate log $P$ values for (di)azines obtained in different partitioning systems,20) but in some cases, somewhat arbitrary classification of the substituents into highly and weakly H-accepting ones was needed.18,20) Therefore, in order to deal with a variety of substituents covering a wide range of H-bonding abilities, we have recently proposed21) a new H-accepting parameter $S_{HA}$ for (di)azines (pyridines, pyrazines and pyrimidines). Values of $S_{HA}$ are accessible by semi-empirical MO calculations using the conductor-like screening model (COSMO) method.22)

By using this pre-determined parameter, we formulated Eq. 1 as a general equation for log $k$ values for monosubstituted (di)azines, AR-X, where X-substituents are non-H-bonding or H-accepting, eluted by various compositions of aqueous methanol solutions.23)

$$\log k = \log P + s S_{HA} + \rho \sigma + \text{const.} \tag{1}$$

In Eq. (1), $S_{HA}$ represents the H-accepting parameter of the X-substituent; and $\sigma$, the inductive electronic constant,23) expresses the electronic effect of X on H-bonding of the ring N atom(s). By examining the coefficients of these correction terms, we concluded that H-bonding effects are minimal in eluents of about 50% aqueous methanol.

The H-bond acidity and basicity scales of Abraham and coworkers24)–26) provide one of the most comprehensive H-bonding parameters, applicable to quantitative structure–activity studies, currently available. Unfortunately, the data for heterocyclic compounds are not extensive, probably due to a lack of the experimental data necessary for their calculation. Accordingly, we wished to examine whether our $S_{HA}$ parameter, readily accessible by calculation, would be applicable to estimation of H-bonding effects for other heteroaromatic series. To this end, we determined $S_{HA}$ values for monosubstituted thiophenes (TH-X) and furans (FR-X) for which log $k$ values had previously been analyzed by using the HBA parameter,26,19) and reanalyzed the log $k$ values by Eq. 1 in order to verify the validity of our parameter. Applications were further extended to analyses of log $k$ measured in eluents containing acetonitrile as an organic modifier.

Experimental

Chemicals Compounds, TH-X, and FR-X, with the non-H-bonding and H-bonding substituents shown in Table 1 were used. These substituents are similar to those used in the previous studies,16,19) but some strongly H-accepting substituents, including disubstituted derivatives, 32–34, were added in this work to examine more clearly the applicability of the $S_{HA}$ parameter.

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work. As shown in ref. 16, those for most of the furan derivatives were measured at 25 °C where 

\[ t_0 \] and \[ t_e \] express elution times of methanol and sample, respectively.

Table 2. \( \log k \) Values for Monosubstituted Thiophenes (TH-X) in Various Compositions of Acetonitrile-buffer (pH 7.4) Mobile Phases

<table>
<thead>
<tr>
<th>No.</th>
<th>Substituent</th>
<th>A10 (^{a})</th>
<th>A20</th>
<th>A30</th>
<th>A40</th>
<th>A50</th>
<th>A60</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>1.244</td>
<td>1.053</td>
<td>0.821</td>
<td>0.587</td>
<td>0.375</td>
<td>0.088</td>
</tr>
<tr>
<td>2</td>
<td>2-Me</td>
<td>1.769</td>
<td>1.506</td>
<td>1.179</td>
<td>0.871</td>
<td>0.679</td>
<td>0.289</td>
</tr>
<tr>
<td>3</td>
<td>3-Me</td>
<td>1.766</td>
<td>1.488</td>
<td>1.166</td>
<td>0.860</td>
<td>0.586</td>
<td>0.275</td>
</tr>
<tr>
<td>4</td>
<td>2-Et</td>
<td>—</td>
<td>1.933</td>
<td>1.521</td>
<td>1.142</td>
<td>0.814</td>
<td>0.474</td>
</tr>
<tr>
<td>5</td>
<td>2-Cl</td>
<td>1.947</td>
<td>1.642</td>
<td>1.283</td>
<td>0.951</td>
<td>0.661</td>
<td>0.347</td>
</tr>
<tr>
<td>6</td>
<td>3-Cl</td>
<td>1.814</td>
<td>1.523</td>
<td>1.177</td>
<td>0.860</td>
<td>0.578</td>
<td>0.264</td>
</tr>
<tr>
<td>7</td>
<td>2-Br</td>
<td>2.071</td>
<td>1.739</td>
<td>1.352</td>
<td>1.001</td>
<td>0.697</td>
<td>0.377</td>
</tr>
<tr>
<td>8</td>
<td>3-Br</td>
<td>1.954</td>
<td>1.638</td>
<td>1.268</td>
<td>0.930</td>
<td>0.632</td>
<td>0.313</td>
</tr>
<tr>
<td>9</td>
<td>2-OMe</td>
<td>1.567</td>
<td>1.274</td>
<td>0.958</td>
<td>0.672</td>
<td>0.417</td>
<td>0.115</td>
</tr>
<tr>
<td>10</td>
<td>2-CN</td>
<td>1.025</td>
<td>0.778</td>
<td>0.530</td>
<td>0.321</td>
<td>0.127</td>
<td>0.059</td>
</tr>
<tr>
<td>11</td>
<td>2-Ac</td>
<td>1.016</td>
<td>0.766</td>
<td>0.536</td>
<td>0.366</td>
<td>0.167</td>
<td>0.000</td>
</tr>
<tr>
<td>12</td>
<td>3-Ac</td>
<td>0.995</td>
<td>0.618</td>
<td>0.337</td>
<td>0.140</td>
<td>0.019</td>
<td>0.024</td>
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<tr>
<td>13</td>
<td>2-CO2Me</td>
<td>1.496</td>
<td>1.088</td>
<td>0.735</td>
<td>0.466</td>
<td>0.241</td>
<td>0.050</td>
</tr>
<tr>
<td>14</td>
<td>2-CO2Et</td>
<td>1.975</td>
<td>1.487</td>
<td>1.060</td>
<td>0.726</td>
<td>0.449</td>
<td>0.139</td>
</tr>
<tr>
<td>15</td>
<td>2-CO2Pr</td>
<td>—</td>
<td>1.931</td>
<td>1.416</td>
<td>1.009</td>
<td>0.675</td>
<td>0.337</td>
</tr>
<tr>
<td>16</td>
<td>3-CO2Me</td>
<td>1.446</td>
<td>1.038</td>
<td>0.692</td>
<td>0.434</td>
<td>0.218</td>
<td>0.065</td>
</tr>
<tr>
<td>17</td>
<td>3-CO2Et</td>
<td>1.913</td>
<td>1.435</td>
<td>1.018</td>
<td>0.695</td>
<td>0.429</td>
<td>0.125</td>
</tr>
<tr>
<td>18</td>
<td>2-CNMe2</td>
<td>—</td>
<td>1.874</td>
<td>1.375</td>
<td>0.978</td>
<td>0.654</td>
<td>0.322</td>
</tr>
<tr>
<td>19</td>
<td>2-CNMe2</td>
<td>0.883</td>
<td>0.366</td>
<td>0.016</td>
<td>0.177</td>
<td>0.030</td>
<td>0.061</td>
</tr>
<tr>
<td>20</td>
<td>3-CNMe2</td>
<td>0.779</td>
<td>0.271</td>
<td>0.077</td>
<td>0.268</td>
<td>0.034</td>
<td>0.071</td>
</tr>
</tbody>
</table>

\( a \) The figures after A represent volume % of acetonitrile in eluents. \( b \) Not measured due to long retention times.

Data for \( \log k \) Retention factors, \( \log k \), obtained in eluents containing different concentrations of methanol were taken from our previous work.\(^{16,19}\) Those for additional compounds were measured under the same conditions as those used previously. For thiophenes, \( \log k \) values were also obtained in eluents with acetonitrile as an organic modifier according to the method described for methanolic solutions.\(^{19}\) Retention times were measured at 25 °C with acetonitrile as an organic modifier according to the method described for methanolic solutions.\(^{19}\) Retention times were measured at 25 °C with acetonitrile as an organic modifier according to the method described for methanolic solutions.\(^{19}\) Retention factors, \( k \), were calculated by \( k = (t_e - t_0)/t_0 \) where \( t_e \) and \( t_0 \) express elution times of methanol and sample, respectively.

Data for \( \log P \) Octanol-water partition coefficients, \( P \), were taken from our previous work.\(^{16,19}\) As shown in ref. 16, those for most of the furan derivatives are literature values. The \( \log P \) values for compounds newly added in this study were measured by the conventional shake-flask method.\(^{20}\) The data are given in Table 1.

\( S_{\text{IA}} \) Parameters The procedure for calculating the \( S_{\text{IA}} \) parameter was previously described in detail.\(^{21}\) First, the minimum energy conformation of each compound (Ar-X) in the gaseous state was established using the AM1 method\(^{29}\) in the MOPAC 93 program package incorporated in an ANCHOR II modeling system.\(^{30}\) By using this conformation as the initial geometry, heats of formation, \( \Delta H_F \) in various solvents were calculated by the COSMO method\(^{21}\) which approximates the effects of solvent molecules surrounding the molecule in question with the eps (\( \epsilon \)) values for the unsubstituted compound (Ar-H), providing a linear relationship between the minimum energy conformation of each Ar-X molecule were plotted against the corresponding \( \Delta H_F / \epsilon \) values in the following five dielectric media were calculated: \( \epsilon = 1 \) (gas), \( \epsilon = 4.8 \) (chloroform), \( \epsilon = 10.3 \) (octanol), \( \epsilon = 32.7 \) (methanol), and \( \epsilon = 78.4 \) (water). The \( \Delta H_F / \epsilon \) values calculated for the five dielectric environments for an Ar-X molecule were plotted against the corresponding \( \Delta H_F / \epsilon \) values for the unsubstituted compound (Ar-H), providing a linear relationship with a positive slope; the higher the dielectric constant of the medium, the lower the \( \Delta H_F / \epsilon \) value indicating the greater stabilization induced by solvation with the more polar solvent molecules. The slope of this straight line is defined as \( S_{\text{IA}} \) for the Ar-X compound. As the X-substituents do not contain an H-donating site and the solvents examined are amphiprotic, the \( S_{\text{IA}} \) parameter is expected to reflect the H-accepting ability of the X-substituent. The Table 1. Physicochemical Parameters for Substituted Thiophenes (TH-X) and Furans (FR-X)

<table>
<thead>
<tr>
<th>No.</th>
<th>Substituent</th>
<th>( \log P^{a} )</th>
<th>( S_{\text{IA}} )</th>
<th>( \log P^{a} )</th>
<th>( S_{\text{IA}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>1.90</td>
<td>1.00</td>
<td>1.34</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>2-Me</td>
<td>2.47</td>
<td>0.94</td>
<td>1.85</td>
<td>0.96</td>
</tr>
<tr>
<td>3</td>
<td>3-Me</td>
<td>2.45</td>
<td>0.98</td>
<td>2.40</td>
<td>0.92</td>
</tr>
<tr>
<td>4</td>
<td>2-Et</td>
<td>3.15</td>
<td>0.88</td>
<td>1.44</td>
<td>1.34</td>
</tr>
<tr>
<td>5</td>
<td>2-Cl</td>
<td>2.69</td>
<td>1.06</td>
<td>0.52</td>
<td>1.94</td>
</tr>
<tr>
<td>6</td>
<td>3-Cl</td>
<td>2.55</td>
<td>1.24</td>
<td>1.00</td>
<td>2.35</td>
</tr>
<tr>
<td>7</td>
<td>2-Br</td>
<td>2.84</td>
<td>1.25</td>
<td>1.52</td>
<td>2.32</td>
</tr>
<tr>
<td>8</td>
<td>3-Br</td>
<td>2.73</td>
<td>1.44</td>
<td>1.28</td>
<td>2.38</td>
</tr>
<tr>
<td>9</td>
<td>2-OMe</td>
<td>2.13</td>
<td>1.59</td>
<td>1.78</td>
<td>2.34</td>
</tr>
<tr>
<td>10</td>
<td>2-CN</td>
<td>1.34</td>
<td>1.94</td>
<td>0.41</td>
<td>2.38</td>
</tr>
<tr>
<td>11</td>
<td>2-Ac</td>
<td>1.27</td>
<td>2.72</td>
<td>0.24</td>
<td>2.58</td>
</tr>
<tr>
<td>12</td>
<td>3-Ac</td>
<td>1.26</td>
<td>2.87</td>
<td>1.84</td>
<td>2.20</td>
</tr>
<tr>
<td>13</td>
<td>2-CO2Me</td>
<td>1.83</td>
<td>2.93</td>
<td>0.94</td>
<td>1.88</td>
</tr>
<tr>
<td>14</td>
<td>2-CO2Et</td>
<td>2.39</td>
<td>2.87</td>
<td>0.79</td>
<td>3.73</td>
</tr>
</tbody>
</table>

\( a \) Taken from our previous work (ref. 19) unless otherwise noted. \( b \) Taken from ref. 27 unless otherwise noted. \( c \) Taken from our previous work (ref. 16). \( d \) This work.
standard deviations.

emanner: the slope of the straight line in the plot of
the fact that the ring
smaller than the corresponding values for TH-X, reflecting
ning abilities of 2-substituents to a greater extent than the 3-
property of the ring hetero atom (\textsuperscript{18}). This finding conforms to the expectation that hetero-
atom effects of the ring
atom is more electron-withdrawing
water-rich eluents as shown in Table 3 and Fig. 2. The
meter worked effectively in improving the correlations in
sure that the reliability of some log
term was again statistically insignificant in all eluents. We
improved the fit to the extent of providing precise corre-
ments given in Table 1, we performed regression analyses of
log \( k \) for thiophenes with methanolic eluents by using Eq. 1

\[ \text{HA value should be close to } 1.0 \text{ for non-H-bonders and increase with increasing the H-ac-
significant for eluents of all methanol concentrations, con-
form to the results previously derived from analyses by
using } HB_p \text{ in place of } S_{\text{HA}} \text{ in Eq. 1.19) }

\text{Relationship between Retention Factors and}
\text{Octanol/Water Partition Coefficients} \quad \text{By using the parameters}
given in Table 1, we performed regression analyses of
log \( k \) for thiophenes with methanolic eluents by using Eq. 1
and obtained excellent correlations. Table 3 summarizes the
most statistically significant regression coefficients and inter-
cepts at each eluent composition. Although a direct plot of
log \( k \) against log \( P \) (Fig. 1A) showed that, in water-rich elu-
ents, strong H-accepting substituents, such as CO$_2$R and
CONMe$_2$, deviate significantly from the linear relationship
yielded by non-H-bonders (H and alkyls), addition of the $S_{\text{HA}}$ term improved the fit to the extent of providing precise corre-
lations (Fig. 1B, Table 3). The \( \sigma_I \) term was statistically in-
significant for eluents of all methanol concentrations, con-
forming to the results previously derived from analyses by

\[ \text{Results and Discussion} \]

\textbf{Comparison of } $S_{\text{HA}}$ \textbf{in Different Heteroaromatic Series} \quad \text{According to its definition, the } S_{\text{HA}} \text{ value should be close to}
1.0 for non-H-bonders and increase with increasing the H-ac-
cepting ability. This parameter should constitute a substituent
constant specific to each skeletal system. In accord with this,
the } S_{\text{HA}} \text{ values in Table 1 demonstrate the following charac-
teristics. (1) } S_{\text{HA}} \text{ values for all alkyl substituents (non-H bon-
ders) are close to unity. (2) } S_{\text{HA}} \text{ values for 2-substituted deriv-
atives are smaller than those for the corresponding 3-sub-
stituted derivatives, indicating that the electron-withdrawing
property of the ring hetero atom (} S \text{ or } O \text{) reduces H-accepting
abilities of 2-substituents to a greater extent than the 3-
substituents. (3) Except for alkyls, } S_{\text{HA}} \text{ values for FR-X are
smaller than the corresponding values for TH-X, reflecting
the fact that the ring } O \text{ atom is more electron-withdrawing
than the ring } S \text{ atom. In fact the } S_{\text{HA}} \text{ values for TH-X are
close to those for Ph-X\textsuperscript{21)} (monosubstituted benzenes, data
not shown) as shown by } S_{\text{HA}} \text{ values for disubstituted furans,
were calculated in the same manner: the slope of the straight line in the plot of } \Delta H_l \text{ for a disubstituted furan against } \Delta H_l \text{ for furan being defined as } S_{\text{HA}}.\]

\[ S_{\text{HA}} \text{ values for } 32-34, \text{ were calculated in the same manner: the slope of the straight line in the plot of } \Delta H_l \text{ for a disubstituted furan against } \Delta H_l \text{ for furan being defined as } S_{\text{HA}}. \]

\[ \text{Results and Discussion} \]

\textbf{Comparison of } $S_{\text{HA}}$ \textbf{in Different Heteroaromatic Series} \quad \text{According to its definition, the } S_{\text{HA}} \text{ value should be close to}
1.0 for non-H-bonders and increase with increasing the H-ac-
cepting ability. This parameter should constitute a substituent
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property of the ring hetero atom (} S \text{ or } O \text{) reduces H-accepting
abilities of 2-substituents to a greater extent than the 3-
substituents. (3) Except for alkyls, } S_{\text{HA}} \text{ values for FR-X are
smaller than the corresponding values for TH-X, reflecting
the fact that the ring } O \text{ atom is more electron-withdrawing
than the ring } S \text{ atom. In fact the } S_{\text{HA}} \text{ values for TH-X are
close to those for Ph-X\textsuperscript{21)} (monosubstituted benzenes, data
not shown) as shown by } S_{\text{HA}} \text{ values for disubstituted furans,
were calculated in the same manner: the slope of the straight line in the plot of } \Delta H_l \text{ for a disubstituted furan against } \Delta H_l \text{ for furan being defined as } S_{\text{HA}}.\]

\[ S_{\text{HA}} \text{ values for } 32-34, \text{ were calculated in the same manner: the slope of the straight line in the plot of } \Delta H_l \text{ for a disubstituted furan against } \Delta H_l \text{ for furan being defined as } S_{\text{HA}}. \]
it were possible to obtain more accurate log \(P\) values, this could even improve the correlations.

By comparing the resultant correlations, we can estimate the contributions of H-bonding effects and so obtain specific information about optimal HPLC conditions for linearity between log \(P\) and log \(k\). Inspection of the correlations given in Table 3 and those so far formulated by Eq. 1 for various (di)azine series\(^{21}\) shows that the contributions of the \(S_{HA}\) and \(\sigma_i\) (if required) terms, are minimal at 50% MeOH concentration but increase with decreasing methanol concentration in all the series. These additional examples extend our earlier conclusion that the use of eluents containing around 50% MeOH provides the most practical method for predicting log \(P\).\(^{14–21}\)

In both series, the \(S_{HA}\) term was found to make a greater contribution to log \(k_w\) than to log \(k_{M50}\), confirming the superiority of the log \(k_{M50}\) parameter over log \(k_w\).

It is of interest to note that, in the case of thiophenes and furans, not only was the \(\sigma_i\) term insignificant but also the contribution of the \(S_{HA}\) term was much smaller than in (di)azines (e.g., \(s=0.809\) and \(r=−0.494\) with M15 for pyrazine series).\(^{21}\) This can be rationalized in terms of the stronger electronic interactions between the substituent X and the ring hetero atom(s) that should produce more significant changes in H-bonding abilities on both the sites in (di)azines than in furans and thiophenes.

Attempts were also made to apply Eq. 1 to analyzing log \(k\) for thiophenes measured in acetonitrile solutions. As shown in Table 3, use of the \(S_{HA}\) parameter improved the correlations. In both solvent systems, the coefficient of \(S_{HA}\) varied from more positive to more negative as the content of organic solvent increased. This means that elution of derivatives with substituents of higher \(S_{HA}\) tend to be accelerated relative to the unsubstituted compound (Ar-H) with highly water-rich eluents but to be retarded with eluents of high organic solvent content, suggesting the possibility of reversion of the elution order with the mobile phase composition. Accordingly, for accurate predictions of log \(P\), it is very important to
select an optimal eluent composition at which the coefficients of $S_{\text{HA}}$ and $\sigma_1$ terms are minimal. Since acetonitrile has no H-donating site, it is only the water in aqueous acetonitrile eluents that bonds to H-accepting sites of the solutes; this would be expected to shift the optimal concentration for aqueous acetonitriles to one more water-rich than that which is optimal for aqueous methanols (50% water). In the present case, such a situation was achieved at around 20% CH$_3$CN (80% water). It would be possible to establish the most suitable acetonitrile content in eluents if similar analyses of log $k$ were performed for a range of solute systems.

The present work has demonstrated that the $S_{\text{HA}}$ parameter effectively works to correlate log $P$ with log $k$ for various heteroaromatic systems and for different mobile phase systems. By quantifying the H-accepting effects, we have been able systematically to establish optimal HPLC conditions for predicting log $P$ with high reliability. In methanolic eluents, we found that intervention of H-accepting effects was minimum at around 50% MeOH regardless of heteroaromatic nucleus. The $S_{\text{HA}}$ parameter is also expected to be utilized for describing the characteristics (particularly silanol effects) of different stationary phases, so that an appropriate column free from H-accepting effects can be selected. The definition of a similar H-donor parameter is still to be established. Analyses for compounds containing H-donors are now underway.

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References and Notes
1) A part of this work was based on a lecture presented at LogP2000-The Second Lipophilicity Symposium, University of Lausanne, Lausanne, on 8 March 2000.