Alkane/water partition coefficients and hydrogen bonding

Peter Kenny
(pwk.pub.2008@gmail.com)
Neglect of hydrogen bond strength: A recurring theme in medicinal chemistry

- Rule of 5
- Rule of 3
- Scoring functions for virtual screening
- Polar surface area (PSA)
- Relationships between thermodynamic properties and buried polar & non-polar surface area
Measuring hydrogen bond strength

**Acceptors**

\[
pK_{HB}^{*}
\]

![Structure of pK\textsubscript{HB}](image)

\[
\log K_{\beta}
\]

![Structure of logK\textsubscript{\beta}](image)

- Taft et al., *JACS* **1969**, 91, 4801-4808

**Donors**

\[
\log K_{\alpha}
\]

![Structure of logK\textsubscript{\alpha}](image)


logK_β: Heteroaromatic nitrogen

Azines

<table>
<thead>
<tr>
<th>Compound</th>
<th>pKa</th>
<th>logK_β</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.22</td>
<td>2.52</td>
</tr>
<tr>
<td></td>
<td>9.70</td>
<td>3.54</td>
</tr>
<tr>
<td></td>
<td>2.24</td>
<td>2.53</td>
</tr>
<tr>
<td></td>
<td>1.23</td>
<td>1.67</td>
</tr>
<tr>
<td></td>
<td>0.65</td>
<td>1.46</td>
</tr>
</tbody>
</table>

Azoles

<table>
<thead>
<tr>
<th>Compound</th>
<th>pKa</th>
<th>logK_β</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.25</td>
<td>3.68</td>
</tr>
<tr>
<td></td>
<td>2.09</td>
<td>2.22</td>
</tr>
<tr>
<td></td>
<td>0.80</td>
<td>1.67</td>
</tr>
<tr>
<td></td>
<td>-2.03</td>
<td>1.06</td>
</tr>
</tbody>
</table>

Modelling Hydrogen Bonding

Calculate energy of complex
- Need to know complexation partner
- Need to generate multiple 3D models of complex
- BSSE
- Relevance to physiological media?

Calculate molecular electrostatic properties
- No explicit reference to complexation partner
- More appropriate to general parameterisation
Minimised electrostatic potential has been shown to be an effective predictor of hydrogen bond basicity.

- Plot of $V/kJmol^{-1}$ against $r/Å$ for pyridine on lone pair axis showing electrostatic potential minimum 1.2Å from nitrogen.

**Electrostatic potential as function of position for acceptor**
Comparison of $V_{\text{min}}$ and $pK_a$ as predictors of $\log K_\beta$

Heteroaromatic nitrogen in five and six-membered rings

Kenny *JCS Perkin Trans 2* 1994, 199-202
Non-equivalent acceptors provide validation set

<table>
<thead>
<tr>
<th>Structure</th>
<th>Predicted logK&lt;sub&gt;β&lt;/sub&gt;</th>
<th>Measured logK&lt;sub&gt;β&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Structure 1]</td>
<td>2.64</td>
<td>2.38</td>
</tr>
<tr>
<td>![Structure 2]</td>
<td>1.68</td>
<td>1.98</td>
</tr>
<tr>
<td>![Structure 3]</td>
<td>2.51</td>
<td>2.36</td>
</tr>
<tr>
<td>![Structure 4]</td>
<td>1.90</td>
<td>2.17</td>
</tr>
<tr>
<td>![Structure 5]</td>
<td>2.50</td>
<td>1.99</td>
</tr>
</tbody>
</table>

Kenny *JCS Perkin Trans 2* 1994, 199-202
Donors: The $V_\alpha(r)$ descriptor

Calculate electrostatic potential ($V$) at this point
$V_\alpha(r)$ as predictor of $\log K_\alpha$

Sensitivity to distance from donor hydrogen

\begin{align*}
r &= 0.55 \text{ Å} \\
R^2 &= 0.93 \\
RMSE &= 0.20
\end{align*}

\begin{align*}
r &= 1.20 \text{ Å} \\
R^2 &= 0.65 \\
RMSE &= 0.43
\end{align*}

Kenny, *JCIM*, 2009, 49, 1234-1244
Fluorine: A weak hydrogen bond acceptor

-0.122

-0.113

-0.071

-0.038
Hydrogen bonding of esters

Quantifying the effect of complex formation

K\(_1\) + Ternary complex \(\rightleftharpoons\) K\(_2\)

Kenny, *JCIM*, 2009, 49, 1234-1244
Effect of complex formation on $V_{\text{min}}$

Effect of complex formation on predicted $\log K_\alpha$

1.2
(\sim Alcohol)

2.0
(\sim Phenol)

2.8
(\sim 4-CF_3 Phenol)

Kenny, *JCIM*, 2009, 49, 1234-1244
An alternative view of the Rule of 5

ClogP $\leq 5$

Acc $\leq 10$; Don $\leq 5$
Octanol/water is not the only partitioning system.
log$P_{\text{alk}}$: Experimental challenges

- Many polar solutes are poorly soluble in alkane solvents
- Self-association
  - Masks polarity
  - Limits concentration at which measurements can be made.
  - Need to vary concentration to demonstrate that it is not an issue
Differences in octanol/water and alkane/water logP values reflect hydrogen bonding between solute and octanol

\[ \log P_{\text{oct}} = 2.1 \]
\[ \log P_{\text{alk}} = 1.9 \]
\[ \Delta \log P = 0.2 \]

\[ \log P_{\text{oct}} = 1.5 \]
\[ \log P_{\text{alk}} = -0.8 \]
\[ \Delta \log P = 2.3 \]

\[ \log P_{\text{oct}} = 2.5 \]
\[ \log P_{\text{alk}} = -1.8 \]
\[ \Delta \log P = 4.3 \]

PSA is not predictive of hydrogen bond strength

\[ \Delta \log P = 0.5 \]
\[ \text{PSA} = 48 \, \text{Å}^2 \]

\[ \Delta \log P = 4.3 \]
\[ \text{PSA} = 22 \, \text{Å}^2 \]

Measured values of $\Delta \text{log}P$

Prediction of contribution of acceptors to $\Delta \log P$

$\Delta \log P = \Delta \log P_0 \times \exp(-kV_{\text{min}})$

Prediction of blood/brain partitioning

\[ \log(P_{\text{brain}}/P_{\text{blood}}) \]

- \( R^2 = 0.66 \)
- \( \text{RMSE} = 0.54 \)

- \( R^2 = 0.82 \)
- \( \text{RMSE} = 0.39 \)

- \( R^2 = 0.88 \)
- \( \text{RMSE} = 0.32 \)

Selected references