Octanol-Water Partition

• Another phase change

\[ A_{\text{water}} \leftrightarrow A_{\text{octanol}} \]

\[ K_{ow} = \frac{[A_{\text{octanol}}]}{[A_{\text{water}}]} \]
Octanol-Water Partition

• Why octanol?
  • drug uptake
    • animal testing
    • mortality related to $K_{ow}$
  • oral absorption (two needs)
    • drug must first pass through lipid bilayers in the intestinal epithelium
    • drug must be hydrophobic enough to partition into the lipid bilayer
    • drug must be hydrophilic enough to avoid retention, non-selective effects
Octanol-Water Partition

- Why octanol?
  - environmental transport
    - sorption to organic matter
    - uptake by organisms
  - organic matter and organisms are octanol-like

Model structure of humic acid (Stevenson 1982)
Octanol-Water Partition

- Wide range of $K_{ow} \quad 10^{-0.24}$

\[
\begin{array}{|c|c|}
\hline
\text{compound} & K_{ow} \\
\hline
\text{benzene} & 10^{2.13} \\
\text{phenol} & 10^{1.45} \\
\text{trichloroethene} & 10^{2.42} \\
\text{phenanthrene} & 10^{4.57} \\
\text{2,2',5,5'-tetrachlorobiphenyl} & 10^{6.18} \\
\hline
\end{array}
\]
Octanol-Water Partition

\[ \gamma_{iw} = 3.7 \times 10^3 \]

\[ 1/\gamma_{iw} = x_{iw} = 2.7 \times 10^{-4} \]

1 water for \( \sim 4 \) octanol (Octanol)
8 octanol for \( \sim 100000 \) waters (Water)

\[ K_{iow} = \frac{C_{io}}{C_{iw}} = \frac{\bar{V}_w}{\bar{V}_o} \times \frac{\gamma_{iw}}{\gamma_{io}} \]

pure n-octanol = 0.16 L/mol (at 25°C)

Use approximation or calculate

\[ V_{mix} = (0.75)(0.16) + (0.25)(0.018) = 0.12 \text{ L mol}^{-1} \]
Octanol-Water Partition

- At equilibrium:

\[ K_{ow} = \frac{[A_{oct}]}{[A_w]} \]

\[ K_{ow} = \frac{x_{oct}}{x_w} \frac{V_{oct}}{V_w} = \frac{x_{oct} V_w}{x_w V_{oct}} = \left( \frac{1}{\gamma_{oct}} \right) \frac{V_w}{V_{oct}} \]

\[ K_{ow} = \frac{\gamma_w V_w}{\gamma_{oct} V_{oct}} \]
Octanol-Water Partition

At equilibrium:

- molar volume of octanol
  - pure octanol, $V_{oct} = 0.16 \text{ L mol}^{-1}$
  - water in octanol: $1:4$
  - $V_{oct} = 0.12 \text{ L mol}^{-1}$
- molar volume of water
  - 1 octanol per 12,500 H$_2$Os
  - $V_w \sim 0.018 \text{ L mol}^{-1}$
Octanol-Water Partition

• Assumptions

  • $\gamma_w^{sat} \approx \gamma_w^{\infty}$
  - even at saturation, solute molecules will not be near each other

  • octanol present in water does not affect $\gamma_w$

  • $\gamma_{oct} \approx 1$ to 10 for most compounds

\[ K_{ow} = \frac{[A_{oct}]}{[A_w]} = \frac{\gamma_w \bar{V}_w}{\gamma_{oct} \bar{V}_{oct}} \]
Octanol-Water Partition

• Is $K_{ow}$ related to aqueous solubility?
  • $\log K_{ow}$ vs. $\log C_w^{sat}(L)$

$$
K_{ow} = \frac{[A_{oct}]}{[A_w]}
$$

$$
K_{ow} = \frac{C_{oct}^{sat}(L)}{C_w^{sat}(L)} = \frac{1}{C_w^{sat}(L)} \frac{1}{\gamma_{oct} V_{oct}}
$$

$$
\log K_{ow} = -\log C_w^{sat}(L) - \log \gamma_{oct} - \log V_{oct}
$$
Octanol-Water Partition

• Experimental determination of $K_{ow}$
  • “shake flask”
  • measure solute distribution in octanol and water phases
  • (should be) limited to $K_{ow} < 10^5$
• poor reproducibility among researchers
  • e.g., DDT, log $K_{ow}$ range of 4.89 to 6.91; over 60 different papers
    (Pontolillo and Eganhouse, 2001)
  • need for reliable estimation method
Octanol-Water Partition

Pontolillo and Eganhouse (2001)

- original data correctly cited
- “erroneous data” (incorrectly cited)
Octanol-Water Partition

• Example: lindane
  • $10^{-6}$ mole of lindane is added to 100 mL separatory funnel containing 10 mL of octanol and 90 mL of water.

At equilibrium and 25°C, what concentration (M) of lindane will be found in the water?
Octanol-Water Partition

17 oz. multi-dose bottle
O.T.C.* lindane from Canadian sources

2 oz. single-dose bottle
Prescription lindane in U.S.

by Sean Delonas
New York Post - Jan. 18, 1995
Octanol-Water Partition

- Lindane
  - $K_{ow} = 10^{3.78}$

$\gamma$-hexachlorocyclohexane

\[ f_w = \frac{\text{total moles in water}}{\text{total moles in octanol and water}} \]

\[ f_w = \frac{[\text{lin}]_w V_w}{[\text{lin}]_o V_o + [\text{lin}]_w V_w} \]

$K_{ow} = \frac{[\text{lin}]_o}{[\text{lin}]_w}$

$[\text{lin}]_o = K_{ow}[\text{lin}]_w$

\[ f_w = \frac{[\text{lin}]_w V_w}{K_{ow}[\text{lin}]_w V_o + [\text{lin}]_w V_w} \]

\[ f_w = \frac{V_w}{K_{ow} V_o + V_w} \]
Octanol-Water Partition

- Lindane
  - $K_{ow} = 10^{3.78}$

$$f_w = \frac{V_w}{K_{ow}V_o + V_w}$$

$$f_w = \frac{90 \text{ mL}}{(10^{3.78} \times 10 \text{ mL}) + 90 \text{ mL}} = 0.0015$$

$$n_{lin,w} = f_w n_{lin,T} = (0.0015)(10^{-6} \text{ mol}) = 1.5 \times 10^{-9} \text{ mol}$$

$$[lin]_w = \frac{n_{lin,w}}{V_w} = \frac{1.5 \times 10^{-9} \text{ mol}}{0.090 \text{ L}} = 1.7 \times 10^{-8} \text{ M}$$
Octanol-Water Partition

• Estimation of $K_{ow}$
  • related to partitioning in other solvents
    • butanol, hexane
    • not much data
  • related to aqueous solubility and activity coefficients (Table 7.3, book)
    \[
    \log K_{ow} = -a \log C_w^{sat} + b'
    \]
    \[
    \log K_{ow} = a \log \gamma_w + b
    \]
  • related to retention time in chromatography (Figure 7.7 next slide)
Octanol-Water Partition

Figure 7.7  Relation between log octanol–water partition constants and log retention times on a reversed-phase liquid chromatography system for a series of nonpolar organic compounds (data from Veith et al., 1979).

C-18 column, MeOH: Water system, use reference compounds
Octanol-Water Partition

- Example
  - estimate the $K_{ow}$ of lindane using its aqueous solubility and $T_m = 112 \degree C$

<table>
<thead>
<tr>
<th>Set of Compounds</th>
<th>n</th>
<th>$R^2$</th>
<th>$a(\pm \sigma)$</th>
<th>$b(\pm \sigma)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkanes</td>
<td>16</td>
<td>0.91</td>
<td>0.81</td>
<td>-0.20</td>
</tr>
<tr>
<td>Polycyclic aromatic hydrocarbons</td>
<td>8</td>
<td>0.99</td>
<td>0.87(±0.03)</td>
<td>0.68(±0.16)</td>
</tr>
<tr>
<td>Substituted benzenes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only nonpolar substituents</td>
<td>23</td>
<td>0.98</td>
<td>0.86(±0.03)</td>
<td>0.75(±0.09)</td>
</tr>
<tr>
<td>Including polar substituents</td>
<td>32</td>
<td>0.86</td>
<td>0.72(±0.05)</td>
<td>1.18(±0.16)</td>
</tr>
<tr>
<td>Phthalates</td>
<td>5</td>
<td>1.00</td>
<td>1.06(±0.03)</td>
<td>-0.22(±0.09)</td>
</tr>
<tr>
<td>PCBs</td>
<td>14</td>
<td>0.92</td>
<td>0.85(±0.07)</td>
<td>0.78(±0.47)</td>
</tr>
<tr>
<td>Alcohols</td>
<td>41</td>
<td>0.94</td>
<td>0.90</td>
<td>0.83</td>
</tr>
<tr>
<td>Miscellaneous pesticides</td>
<td>14</td>
<td>0.81</td>
<td>0.84(±0.12)</td>
<td>0.12(±0.49)</td>
</tr>
</tbody>
</table>
Octanol-Water Partition

• Lindane
  • alkane? PCB?

\[
\log K_{ow} = -0.85 \log C_{w}^{sat} (L) + 0.78
\]

• \( C_{w}^{sat}(L) \)
  • solubility of liquid or subcooled liquid
  • no melting for octanol-water partition

\[
C_{w}^{sat} (L) = C_{w}^{sat} (s) \frac{p_{L}^{*}}{p_{s}^{*}}
\]
Octanol-Water Partition

- Lindane
  - \( C_{w}^{\text{sat}}(s) = 10^{-4.60} \text{ M} \)
  - \( p_{s}^{\ast}/p_{L}^{\ast} \) ?
    - \( \tau = ? \)
    - \( \sigma = ? \)

\[
\ln \frac{p_{s}^{\ast}}{p_{L}^{\ast}} = -(6.8 + 1.1\tau - 2.3 \log \sigma) \left( \frac{T_{m}}{T} - 1 \right)
\]
Octanol-Water Partition

• Lindane
  • What is the torsional bond number $\tau$ for lindane?

  A. 0
  B. 5
  C. 5.5

$$\tau = \sum (SP3 + 0.5SP2 + 0.5RING) - 1$$
$$\tau = \sum (0 + 0.5(0) + 0.5(1)) - 1$$
$$\tau = 0$$
Octanol-Water Partition

• Lindane
  • What is the rotational symmetry number $\sigma$ for lindane?

A. 1
B. 2
C. 4
D. 12
Octanol-Water Partition

• Lindane
  • \( C_w^{sat}(s) = 10^{-4.60} \text{ M} \)
  • \( \frac{p_s^*}{p_L^*} \)
    • \( \tau = 0; \quad \sigma = 1 \)

\[
\ln \frac{p_s^*}{p_L^*} = -\left(6.8 + 1.1(0) - 2.3\log(1)\right)\left(\frac{385.2}{298.2} - 1\right)
\]

\[\ln \frac{p_s^*}{p_L^*} = -1.98\]

\[
\frac{p_s^*}{p_L^*} = 0.14 \quad \frac{p_L^*}{p_s^*} = 7.2
\]
Octanol-Water Partition

- Lindane

\[ C_{w}^{\text{sat}}(L) = C_{w}^{\text{sat}} \frac{P_L^*}{P_s} = 10^{-4.60} \quad (7.2) \]

\[ C_{w}^{\text{sat}}(L) = 10^{-3.74} \text{ M} \]

\[ \log K_{ow} = -0.85 \log C_{w}^{\text{sat}}(L) + 0.78 \]

\[ \log K_{ow} = -0.85(-3.74) + 0.78 \]

\[ \log K_{ow} = 3.96 \quad \text{measured } \log K_{ow} = 3.78 \]