

LogP and logD calculations

This background material explains the theory behind the $\log P$ and $\log D$ calculation:

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Introduction

The mass flux of a molecule at the interface of two immiscible solvents is governed by its lipophilicity. The more lipophilic a molecule is, the more soluble it is in lipophilic organic phase. For the same reason drug penetration into a biological membrane is also influenced by the lipophilicity of the drug. When a molecule is ionizable at a given pH, it forms a hydrophilic anion or cation and subsequently fails to dissolve in organic phase. Ionization of a molecule leads to the accumulation of the hydrophilic form in the aqueous phase. In contrast, its lipophilic form decreases in both aqueous and organic phase due to the law of conservation of mass.

The partition coefficient of a molecule observed in a water-*n*-octanol system has been adopted as the standard measure of lipophilicity. The observed partition coefficient depends on the support electrolyte concentration of the bulk phase the compound is dissolved in. Extra ion-pair forming chemical agents added to the aqueous/organic phase may have a significant effect on the partitioning behaviour of a molecule.

It is often meaningful to obtain the partition coefficients of molecules by calculation. The molecular structure and extent of ionization are the primary factors in calculating the partition coefficient. The standard partition coefficient of ionized and unionized species calculated from the molecular structure is based largely on the atomic $\log P$ increments given in [Viswanadhan et al.](#) The extent of ionization at a given pH is obtained from the predicted pK_a of the molecule. Our calculation method takes into account the effect of the counterion concentration on $\log D$ and $\log P$.

Symbols used

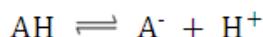
Throughout the document we use the following symbols:

- P_i (upper case) is the macro partition coefficient, where subscript i refers to the ionization state of species included in P_i , e.g. $i = -2, -1, 0, +1, +2$
- p_i (lower case) is the micro partition coefficient, where subscript i refers to the microspecies, e.g. $i = 1, 2, 3, 4, \dots$
- D is the distribution coefficient
- $[]$ means concentration of microspecies
- $\log P$ is the logarithm of the partition coefficient
- $\log D$ is the logarithm of the distribution coefficient

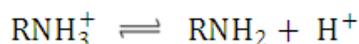
Definition of $\log P$ and $\log D$

The partition coefficient is the ratio of the concentration of the compound in octanol to its concentration in water. The distribution coefficient is the ratio of the sum of the concentrations of all species of the compound in octanol to the sum of the concentrations of all species of the compound in water. Based on acidic/basic dissociation reactions, we can introduce the concept of a partition coefficient for cationic and anionic species and for neutral species.

The following figure gives the definition of partition and distribution coefficients for ionized and unionized species.



$$P_0 = \frac{[AH]_{\text{octanol}}}{[AH]_{\text{water}}} \quad P_{-1} = \frac{[A^-]_{\text{octanol}}}{[A^-]_{\text{water}}} \quad D = \frac{[AH]_{\text{octanol}} + [A^-]_{\text{octanol}}}{[AH]_{\text{water}} + [A^-]_{\text{water}}}$$



$$P_0 = \frac{[RNH_2]_{\text{octanol}}}{[RNH_2]_{\text{water}}} \quad P_{+1} = \frac{[RNH_3^+]_{\text{octanol}}}{[RNH_3^+]_{\text{water}}} \quad D = \frac{[RNH_2]_{\text{octanol}} + [RNH_3^+]_{\text{octanol}}}{[RNH_2]_{\text{water}} + [RNH_3^+]_{\text{water}}}$$

Fig. 1 Partition and distribution coefficients for ionized and unionized species

The partition and distribution coefficients for multiprotic compounds are defined in much the same way as for monoprotic compounds using the following formulae.

$$P_0 = \frac{[\text{sum of the concentrations of the neutral species}]_{\text{octanol}}}{[\text{sum of the concentrations of the neutral species}]_{\text{water}}}$$

$$P_i = \frac{[\text{sum of the concentrations of the microspecies with gross charge } i]_{\text{octanol}}}{[\text{sum of the concentrations of the microspecies with gross charge } i]_{\text{water}}}$$

$$D = \frac{[\text{sum of the concentrations of all microspecies}]_{\text{octanol}}}{[\text{sum of the concentrations of all microspecies}]_{\text{water}}}$$

Fig. 2 Partition and distribution coefficients for multiprotic compounds

Example

In this example we suppose that a compound $A_1A_2B_1B_2$ contains two acidic and two basic ionization sites. This compound has 16 protonation states in aqueous solution. The microspecies which are assigned to the protonation states are summarized in the following table.

Microspecies	charge
$A_1A_2B_1B_2$	0
$A_1^-A_2B_1B_2$	-1
$A_1A_2^-B_1B_2$	-1
$A_1A_2B_1^+B_2$	+1
$A_1A_2B_1B_2^+$	+1
$A_1^-A_2^-B_1B_2$	-2

$A_1^-A_2B_1^+B_2$	0
$A_1^-A_2B_1B_2^+$	0
$A_1A_2^-B_1^+B_2$	0
$A_1A_2^-B_1B_2^+$	0
$A_1A_2B_1^+B_2^+$	+2
$A_1^-A_2^-B_1^+B_2$	-1
$A_1^-A_2^-B_1B_2^+$	-1
$A_1^-A_2B_1^+B_2^+$	+1
$A_1A_2^-B_1^+B_2^+$	+1
$A_1^-A_2^-B_1^+B_2^+$	0

Fig. 3 All microspecies with their charge values generated from the initial compound

Partition and distribution coefficients

Partition and distribution coefficients then can be expressed as follows:

- Partition coefficient of the neutral species is

$$P_0 = \frac{[A_1A_2B_1B_2 + A_1^-A_2B_1^+B_2 + A_1A_2^-B_1B_2^+ + A_1A_2B_1^+B_2 + A_1A_2^-B_1B_2^+ + A_1A_2B_1^+B_2^+]}{[A_1A_2B_1B_2 + A_1^-A_2B_1^+B_2 + A_1A_2^-B_1B_2^+ + A_1A_2B_1^+B_2 + A_1A_2^-B_1B_2^+ + A_1A_2B_1^+B_2^+]_{\text{water}}}$$

- Partition coefficients of the anionic and the cationic species are

$$P_{-1} = \frac{[A_1^- A_2^- B_1 B_2 + A_1 A_2^- B_1 B_2 + A_1^- A_2^- B_1^+ B_2 + A_1^- A_2^- B_1 B_2^+]_{\text{octanol}}}{[A_1^- A_2^- B_1 B_2 + A_1 A_2^- B_1 B_2 + A_1^- A_2^- B_1^+ B_2 + A_1^- A_2^- B_1 B_2^+]_{\text{water}}}$$

$$P_{+1} = \frac{[A_1 A_2 B_1^+ B_2 + A_1 A_2 B_1 B_2^+ + A_1^- A_2 B_1^+ B_2^+ + A_1 A_2^- B_1 B_2^+]_{\text{octanol}}}{[A_1 A_2 B_1^+ B_2 + A_1 A_2 B_1 B_2^+ + A_1^- A_2 B_1^+ B_2^+ + A_1 A_2^- B_1 B_2^+]_{\text{water}}}$$

and

$$P_{-2} = \frac{[A_1^- A_2^- B_1 B_2]_{\text{octanol}}}{[A_1^- A_2^- B_1 B_2]_{\text{water}}}$$

$$P_{+2} = \frac{[A_1 A_2 B_1^+ B_2^+]_{\text{octanol}}}{[A_1 A_2 B_1^+ B_2^+]_{\text{water}}}$$

- Distribution coefficient of the original molecule is

$$D = \frac{\sum_{i=1}^{i=16} [\text{microspecies}]_{i,\text{octanol}}}{\sum_{i=1}^{i=16} [\text{microspecies}]_{i,\text{water}}}$$

The micro partition coefficient is the ratio of the concentration of two microspecies defined with ρ_i as expressed with the next relation:

$$\rho_i = \frac{[\text{microspecies}]_{i,\text{octanol}}}{[\text{microspecies}]_{i,\text{water}}}$$

Relation between macro and micro partition coefficients

Macro partition coefficients $P_0 \dots P_i$ can also be expressed as a function of micro partition coefficients $\rho_0 \dots \rho_i$. From the definition of micro partition coefficients we obtain the following formula for the concentration of microspecies in octanol:

$$[\text{microspecies}]_{i,\text{octanol}} = \rho_i [\text{microspecies}]_{i,\text{water}}$$

where ρ_i is the micro partition coefficient of microspecies i .

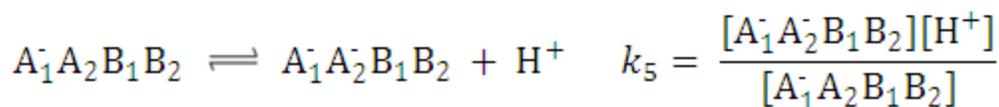
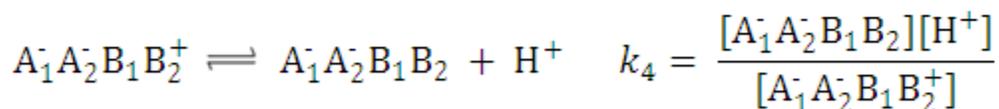
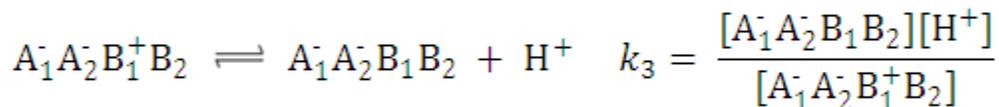
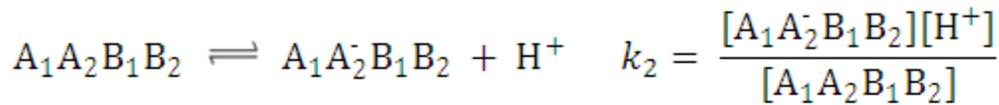
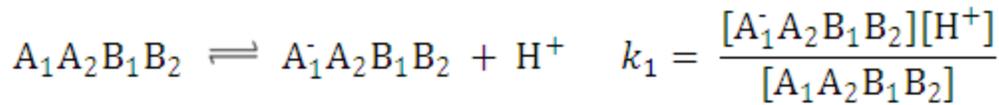
For example, P_{-1} includes four micro partition coefficients ($\rho_1, \rho_2, \rho_3, \rho_4$). They are given by the following formulae:

$$\begin{aligned}
 \rho_1 &= \frac{[A_1^- A_2 B_1 B_2]_{\text{octanol}}}{[A_1^- A_2 B_1 B_2]_{\text{water}}} & \rho_2 &= \frac{[A_1 A_2^- B_1 B_2]_{\text{octanol}}}{[A_1 A_2^- B_1 B_2]_{\text{water}}} \\
 \rho_3 &= \frac{[A_1^- A_2 B_1^+ B_2]_{\text{octanol}}}{[A_1^- A_2 B_1^+ B_2]_{\text{water}}} & \rho_4 &= \frac{[A_1^- A_2 B_1 B_2^+]_{\text{octanol}}}{[A_1^- A_2 B_1 B_2^+]_{\text{water}}}
 \end{aligned}$$

After substituting the ρ_i s into the original formula for P_{-1} we get the following simpler formula which includes only aqueous concentration of the appropriate microspecies:

$$P_{-1} = \frac{\rho_1 \times [A_1^- A_2 B_1 B_2]_{\text{water}} + \rho_2 \times [A_1 A_2^- B_1 B_2]_{\text{water}} + \rho_3 \times [A_1^- A_2 B_1^+ B_2]_{\text{water}} + \rho_4 \times [A_1^- A_2 B_1 B_2^+]_{\text{water}}}{[A_1^- A_2 B_1 B_2]_{\text{water}} + [A_1 A_2^- B_1 B_2]_{\text{water}} + [A_1^- A_2 B_1^+ B_2]_{\text{water}} + [A_1^- A_2 B_1 B_2^+]_{\text{water}}}$$

This can be further simplified if we introduce the acid dissociation constants of the $A_1 A_2 B_1 B_2$ molecule. The next five ionization reactions of the $A_1 A_2 B_1 B_2$ molecule are used to rearrange P_{-1} into a concentration free form:



So we can further simplify the formula for P_{-1} to the following. This expression reveals that P_{-1} does not depend on the pH of the solution:

$$P_{-1} = \frac{p_1 + p_2 \times \frac{k_2}{k_1} + p_3 \times \frac{k_5}{k_3} + p_4 \times \frac{k_5}{k_4}}{1 + \frac{k_2}{k_1} + \frac{k_5}{k_3} + \frac{k_5}{k_4}}$$

Similarly, one could show that P_0 , P_{+1} , P_{-2} and P_{+2} are also pH-independent.

In contrast to this, the distribution coefficient D does depend on the solution pH (see Klopman et al.):

$$D = \frac{\sum_{i=1}^{i=16} p_i \times [\text{microspecies}]_{i,\text{water}}}{\sum_{i=1}^{i=16} [\text{microspecies}]_{i,\text{water}}}$$

Log P calculation methods

Log P calculations are based on a pool of fragments predefined in the log P calculator. This set is based on the data set in [Viswanadhan et al.](#) Every fragment is assigned a unique name and a value. The log P value of a molecule is the sum of the fragment values that are present in the molecule.

i log P plugin handled only one fragment set until version 5.1.2, but then it was extended with two additional sets. The sets are based on a published data set (see [Klopman et al.](#)) and the [PhysProp[®] database](#). These methods however are *not* available separately in the newer versions of the log P calculator.

The trainable log P calculation (available from version 5.1.3) offers the user to define his own log P database and calculate log P values based on experimental data. New fragment value extensions make a more precise calculation possible.

To have more information on the currently available log P calculation methods see [this page](#).

Examples for log P and log D calculations

The following examples show log P /log D results for special molecules types. The calculations were performed with the default settings of the log P plugin.

Example #1

The compound below is zwitterionic that has the form of a $A_1A_2B_1B_2$ molecule mentioned in the theoretical section above. Lipophilicity of this compound [reaches its maximum](#) near to the isoelectric point. (pI is 4.43 in this case, while the global maximum of the log D function is 5.25. The calculated log D value at the pI point is 5.24.)

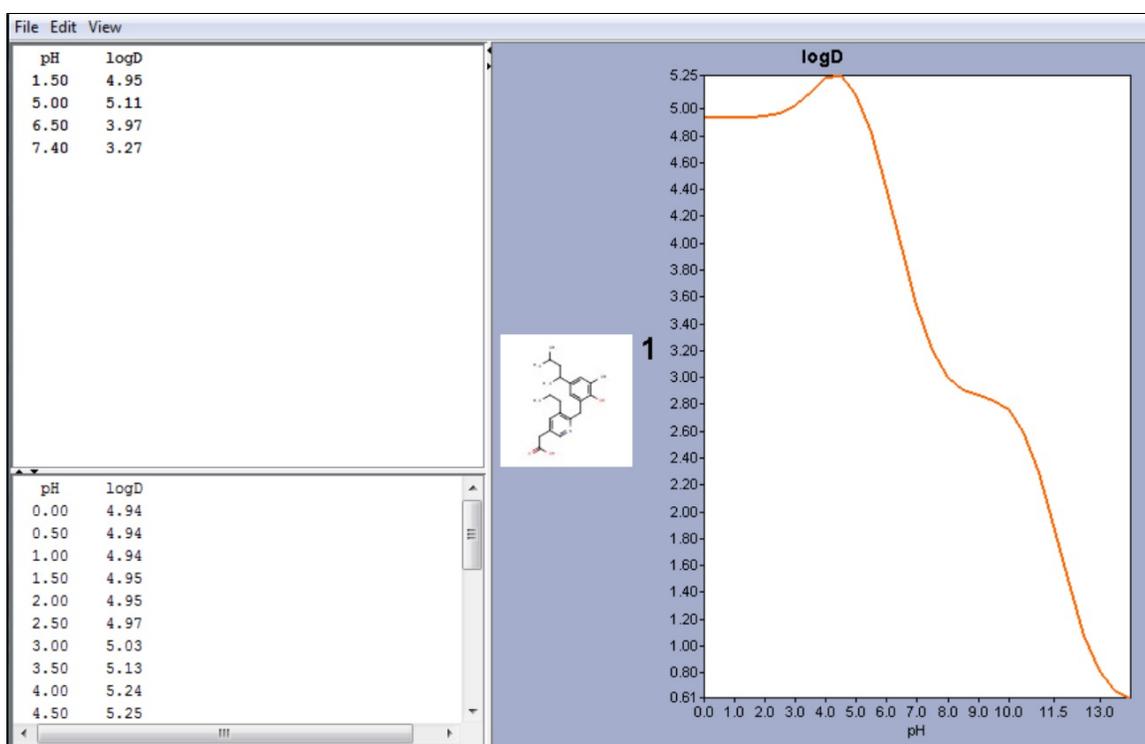
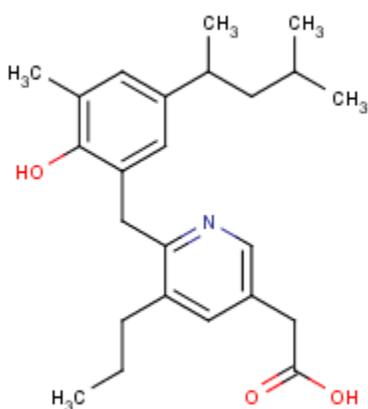


Fig. 3 Zwitterionic molecule and its lipophilicity plot

Example #2

Homidium is a quaternary ammonium ion with strong hydrophilic character. Its $\log P$ is calculated with the use of the ionic fragment of the N^+ ion. The calculated and **measured** $\log P$ values are -0.91 and -1.10, respectively.

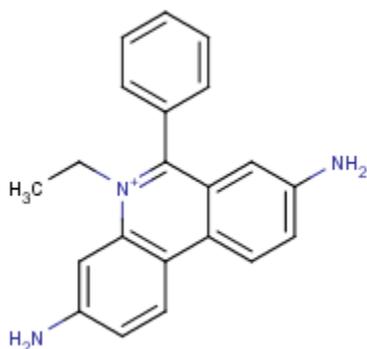


Fig. 4 Homidium molecule

Example #3

Ibuprofen has the typical $\log D$ vs. pH profile that is characteristic of acidic compounds. Lipophilic behavior of ibuprofen will be dominant when its carboxylic group is unionized (at low pH). At higher pH values the carboxylic group reaches the fully ionized state and hydrophilicity becomes more enhanced.

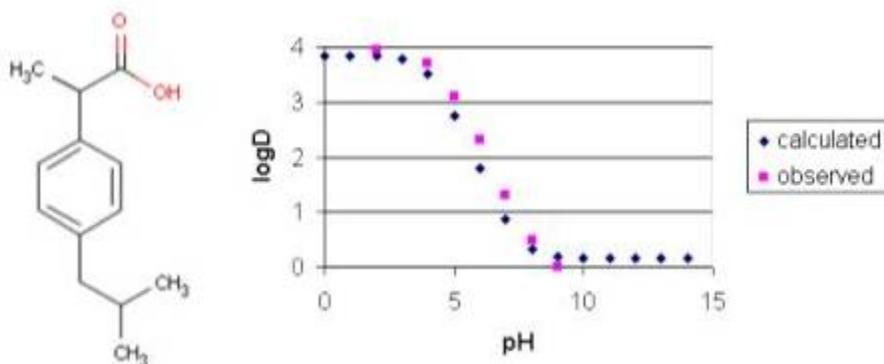


Fig. 6 Ibuprofen and its $\log D$ -pH plot

Example #4

The measured distribution coefficients also depends on the measurement method. The shake flask and the pH-metric methods are the most popular in practice. The figure below shows the calculated and measured $\log D$ of lignocaine as function of pH.

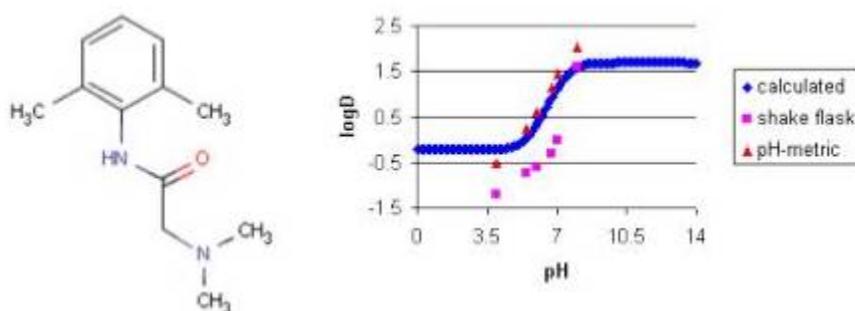


Fig. 7 Lignocaine and its $\log D$ -pH plot

References

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