Lipophilicity Descriptors: Understanding When to Use Log*P* & Log*D*

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Introduction

Molecular physical properties play an important role in aiding our understanding of the behavior of compounds in the real world. The values of molecular physical properties such as log*P*, log*D*, solubility, and pK_a can help us evaluate and predict the likely behavior of a compound prior to synthesis. Lipophilicity is represented by the descriptors log*P* (also known as Kow or Pow) and log*D*, and is used, for example, to help predict in-vivo permeability of active compounds in drug discovery; to anticipate the impact of insecticides, herbicides, and fertilizers on various species in agrochemicals research; to develop environmental profiles of waste chemicals and help understand bioaccumulation, exposure to wildlife, and the impact on human health; and to understand flavor perception in the food industry and the behavior of compounds in many other areas of chemical research.

Definition of Log*P* and Log*D*

The partition coefficient, P, is a measure of the differential solubility of a compound in two immiscible solvents. The most commonly used solvent system is octan-1-ol/water. The partition coefficient is the descriptor of lipophilicity for neutral compounds, or where the compound exists in a single form.

$$\text{Log}P = \log_{10}(\text{Partition Coefficient}) \qquad \text{Partition Coefficient, } P = \frac{[\text{Compound}]_{\text{octanol}}}{[\text{Compound}]_{\text{water}}}$$

> **Note** Log*P* = 1 means there is a 10:1 ratio Organic:Aqueous

For ionizable solutes, the compound may exist as a variety of different species in each phase at any given pH. D, the distribution coefficient, is the appropriate descriptor for ionizable compounds since it is a measure of the pH-dependant differential solubility of all species in the octanol/water system (typically used in the logarithmic form log*D*).

Distribution coefficient,

$$\text{Distribution coefficient, } D = \frac{\sum[\text{Microspecies}]_{\text{octanol}}}{\sum[\text{Microspecies}]_{\text{water}}}$$

Partitioning of methylamine illustrates the difference between these two descriptors:

$$MeNH_3^+ \rightleftharpoons MeNH_2 + H^+$$

$$P_{MeNH_2} = \frac{[MeNH_2]_{\text{octanol}}}{[MeNH_2]_{\text{water}}} \qquad \text{and/or} \qquad P_{MeNH_3^+} = \frac{[MeNH_3^+]_{\text{octanol}}}{[MeNH_3^+]_{\text{water}}}$$

$$D = \frac{[MeNH_2]_{\text{octanol}} + [MeNH_3^+]_{\text{octanol}}}{[MeNH_2]_{\text{water}} + [MeNH_3^+]_{\text{water}}}$$

Application of Lipophilicity Descriptors in Drug Discovery

To accurately predict a compound's lipophilicity based on predicted molecular physical properties it is imperative that the correct descriptor be applied in an appropriate manner. In the 1980's and 90's few software companies offered accurate prediction of the distribution coefficient log*D*. As a result, use of the partition coefficient, log*P*, became widespread. Even today there is only modest adoption of log*D*. To address lipophilicity concerns many companies have deployed computational alerts based on Log*P* which can lead to incorrect conclusions for ionizable compounds.

In this application note we will discuss the significance of applying log*D* instead of log*P* using drug discovery as an example where lipophilicity is correlated with in vivo permeability.

Prevalent Ionic Forms Under Changing pH in Physiological Conditions

Figure 1 illustrates the changing pH environments that an orally administered compound is likely to encounter in the gastrointestinal (GI) tract. There is no constant pH in the body and it is therefore essential that we consider an appropriate pH when predicting the *in vivo* behavior of a drug candidate.

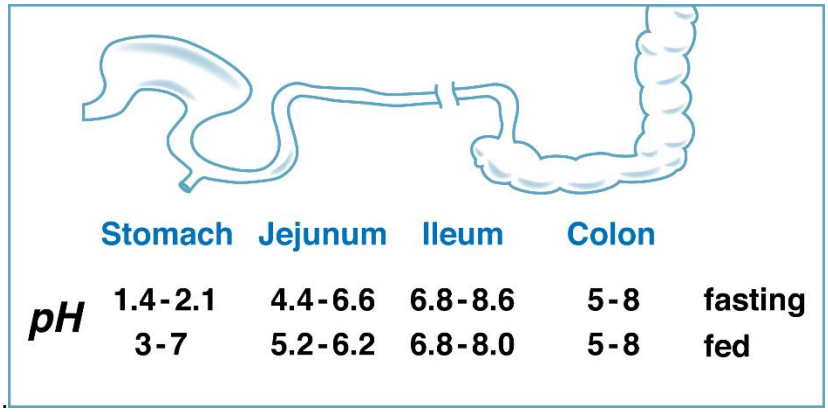
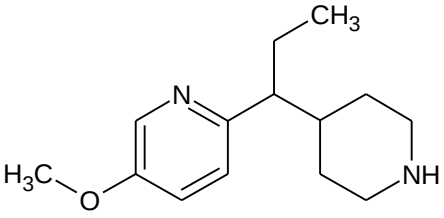


Figure 1: The pH environment of the human gastrointestinal tract.[1]

Let us use 5-Methoxy-2-(1-piperidin-4-ylpropyl)pyridine to study the difference between judging lipophilicity based on predicted log*P* and pH-dependant log*D*.



5-Methoxy-2-(1-piperidin-4-ylpropyl)pyridine

Table1: pK_a values of 5-Methoxy-2-(1-piperidin-4-ylpropyl)pyridine.[2]

pK_a	Ionization centre
4.8	Pyridine
10.9	Piperidine

From the graph in Figure 2 it is evident that the neutral form of 5-Methoxy-2-(1-piperidin-4-ylpropyl)pyridine is almost non-existent at physiologically relevant pH (1–8). The neutral form only dominates at ~pH 13. For the sake of comparison of the two lipophilicity descriptors, however, we can disregard this fact and see what conclusions we can make about the lipophilicity of this compound from

log*P* alone. Predicted log*P* is 2.7 ± 0.3. The conclusion we draw from this is that the compound shows a preference to be associated with the lipid phase (>30 fold affinity for octanol over water), and by extension will likely permeate biological membranes spontaneously.

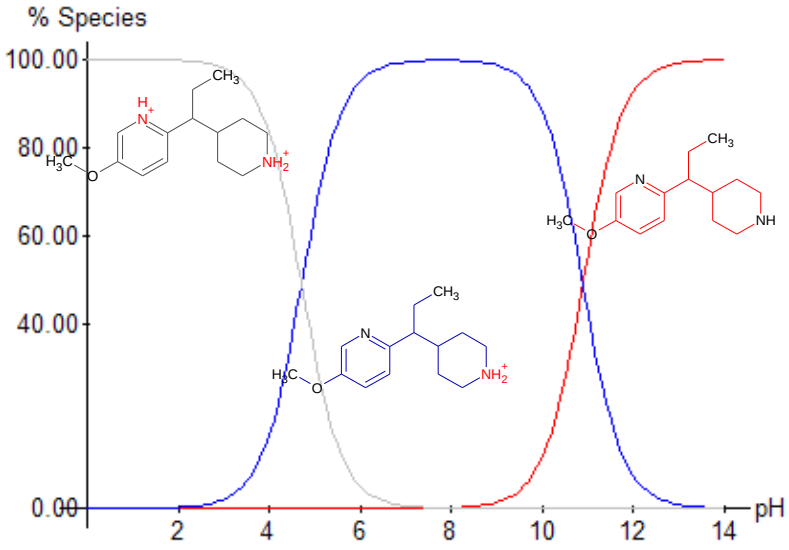


Figure 2: A graph illustrating the changing ionic forms of 5-Methoxy-2-(1-piperidin-4-ylpropyl)pyridine with pH.[2]

Partitioning of Physiologically Relevant Forms

The pH dependence of log*D* for 5-Methoxy-2-(1-piperidin-4-ylpropyl)pyridine is shown in Figure 3. It is obvious from this plot of log*D* versus pH, that ionization of the compound greatly affects octanol-water partitioning and that lipophilicity cannot be simplified to a constant. Lipophilicity of the compound is low below pH 12 when the majority of the compound exists in an ionized form. In fact, the conclusion we draw from predicting the log*D* profile of 5-methoxy-2-(1-piperidin-4-ylpropyl)pyridine is contradictory to that derived from examination of log*P* alone. Negative values of log*D* (-1.44 to 0) in the physiologically relevant pH range (pH 1–8) lead us to conclude that this compound would be more susceptible to higher aqueous solubility and of lower lipophilicity in the body. As a result we would expect membrane permeability to be poor.

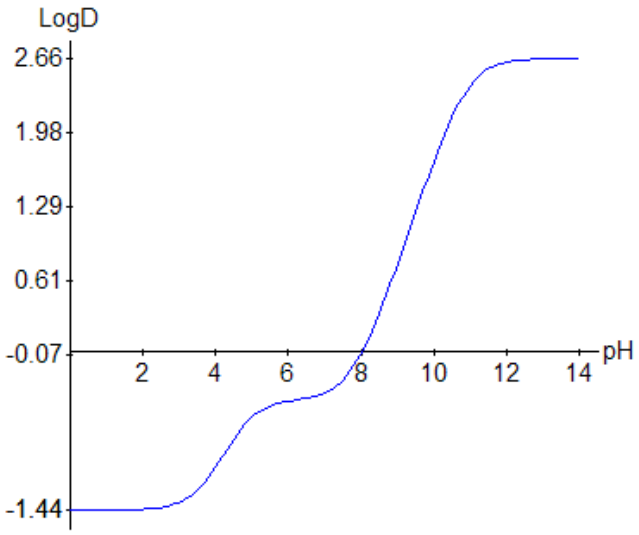


Figure 3: The logD curve of 5-Methoxy-2-(1-piperidin-4-ylpropyl)pyridine.[2]

Although we have only given an example of discriminating between log*P* and log*D* in a drug discovery setting, this reasoning is equally relevant for other areas of research. In environmental chemistry, for example, the presence of different ionic species of a compound is relevant when studying the behavior of chemicals affected by the pH of different soil, or acid rain.

Experimental Measurement of Lipophilicity

While it is important to understand the implications of pH when predicting the behavior of compounds based on descriptors, it is equally critical that the difference between log*P* and log*D* is understood for experimental measurement of lipophilicity. In order to accurately measure and report lipophilicity, the scientist must take great care in measurement of log*P* at a pH where the compound exists in its neutral form (>pH 12 in the case of 5-Methoxy-2-(1-piperidin-4-ylpropyl)pyridine), and/or report log*D* at a specific pH.

Conclusion

While log*P* and log*D* both describe the same physical property (lipophilicity) it is critical that we understand the differences between them and apply them accordingly. Log*D* is the appropriate descriptor for lipophilicity of ionizable compounds because it accounts for the pH dependence of a molecule in aqueous solution. Log*P* describes lipophilicity for neutral compounds only, and while it can be a very useful reference point for the comparison of overall trends it should be applied with caution, especially when working with ionizable compounds.

References

1. Dressman, Amidon, Reppas, and Shah, Pharm. Res., 1998, 15, 11.
2. ACD/Log*D*, www.acdlabs.com/logd/, Advanced Chemistry Development, Inc., Toronto, ON, Canada, 2019.