ACD/Labs Application Note

Log*P*—Making Sense of the Value

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Introduction

The fact that water and many organic substances do not mix but form separate layers when combined together has far-reaching implications for chemistry, biology, and the environment. The partition coefficient (*P*) describes the propensity of a neutral (uncharged) compound to dissolve in an immiscible biphasic system of lipid (fats, oils, organic solvents) and water. In simple terms, it measures how much of a solute dissolves in the water portion versus an organic portion. Solutes that are predominantly dissolved in the water layer are called hydrophilic (water liking) and those predominantly dissolved in lipids are lipophilic (lipid liking). The partition coefficient is an important measurement of the physical nature of a substance and thereby a predictor of its behavior in different environments. The log*P* value provides indications on whether a substance will be absorbed by plants, animals, humans, or other living tissue; or be easily carried away and disseminated by water.[1]

As a result of its wide and varied applications, the partition coefficient is also referred to as Kow or Pow.

The log*P* value is a constant defined in the following manner:

Log*P* = log10 (Partition Coefficient)   Partition Coefficient, *P* = [organic]/[aqueous]

Where [ ] indicates the concentration of solute in the organic and aqueous partition.

A negative value for log*P* means the compound has a higher affinity for the aqueous phase (it is more hydrophilic); when log*P* = 0 the compound is equally partitioned between the lipid and aqueous phases; a positive value for log*P* denotes a higher concentration in the lipid phase (i.e., the compound is more lipophilic). Log*P* = 1 means there is a 10:1 partitioning in Organic : Aqueous phases.

Although log*P* is a constant, its value is dependent on the choice of the organic partitioning solvent and, to a lesser degree, on the conditions of measurement. ACD/Labs' log*P* algorithms specifically calculate partitioning between octan-1-ol and water—the most commonly used system.

In this application note, we will discuss specific applications of log*P* in order to offer a deeper understanding of this parameter and to demonstrate its wide-ranging impact in chemistry.

Applications of Log*P*

As a fundamental property of matter, lipophilicity is a descriptor that can help scientists predict and understand the transport and impact of chemicals in physiological and ecological systems. Log*P* values are important to many industries and areas of research in determining how to deliver chemical substances to specific sites, or eliminate chemicals from others, as well as limiting unwanted dispersal of chemicals through the environment.

Drug Discovery

Log*P* is used in the pharmaceutical/biotech industries to understand the behavior of drug molecules in the body. Drug candidates are often screened according to log*P*, among other criteria, to help guide drug selection and analog optimization. This is because lipophilicity is a major determining factor in a compound's absorption, distribution in the body, penetration across vital membranes and biological barriers, metabolism and excretion (ADME properties). According to 'Lipinski's Rule of 5' (developed at Pfizer) the log*P* of a compound intended for oral administration should be <5. A more lipophilic compound:

- Will have low aqueous solubility, compromising bioavailability. If an adequate concentration of a drug cannot be reached or maintained, even the most potent in-vitro substance cannot be an effective drug.
- May be sequestered by fatty tissue and therefore difficult to excrete; in turn leading to accumulation that will impact the systemic toxicity of the substance.
- May not be ideal for penetration through certain barriers. A drug targeting the central nervous system (CNS) should ideally have a logP value around 2;[2] for oral and intestinal absorption the idea value is 1.35–1.8, while a drug intended for sub-lingual absorption should have a log*P* value >5.

Not only does log*P* help predict the likely transport of a compound around the body. It also affects formulation, dosing, drug clearance, and toxicity. Though it is not the only determining factor in these issues, it plays a critical role in helping scientists limit the liabilities of new drug candidates.

Agrochemicals

Use of log*P* in insecticide, fungicide, and herbicide research is in many ways similar to that in drug discovery. It helps scientists to understand the transport and loss process of chemicals. In agrochemical discovery and development, scientists are charged with finding chemicals that are effective for a specific action while being relatively harmless to surrounding plants, insects, humans, and the environment (especially waterways).

Bioavailability in agrochemistry refers to uptake of a chemical by a plant through soil or foliage, or ingestion by a pest. 'Briggs Rule of 3' suggests that for an agrochemical to be bioavailable (among other parameters) it should have a log*P* value <3.

Other reasons to achieve an appropriate balance between hydrophilicity and lipophilicity by understanding and modifying log*P* are:

- While the best mode of application of a chemical may be spraying as an aqueous solution, the active compound must be lipophilic enough to resist leaching into waterways. For chemicals that end up in the water table, environmental impact must also be considered.
- Toxicity of agrochemicals must be understood and is also related to log*P*. Wildlife such as fish and birds are obviously open to more direct exposure, but since chemicals can carry over into food by being taken up by the plant, human toxicity must also be understood.

Environmental Chemistry

The environmental impact of chemicals has become a more visible issue over the years. Concerns include pharmaceutical and agrochemical residues, and waste chemicals generated by industry. Log*P* is one molecular property factor that can help in developing an environmental profile of the fate of chemicals from bioaccumulation in soil, exposure to wildlife, and the impact to human health.

Flavors and Fragrances

New flavors and fragrances are a powerful driving force behind food, beverages, cosmetics, and household products. We come into contact with (or ingest) many products from these categories on a daily basis and lipophilicity has some interesting implications.

Partitioning between lipid and aqueous media is said to influence flavor perception.[3] Achieving an acceptable log*P* value for the fragrance in fabric softener is important for deposition of perfume on the fabric after rinsing. As well as helping to predict the desired effect of a compound, understanding lipophilicity helps scientists determine their in-vivo fate (ADME properties and toxicity) in case of ingestion.

This handful of uses are not the only areas for which log*P* is important. For example, there is on-going research on log*P* as one important parameter in helping to classify the irritant and/or corrosive nature of chemicals in order to minimize the number of animals required in the testing of new substances.[4]

How Can I Obtain LogP Values?

The partition coefficient of a compound can be experimentally measured using a variety of widely accepted methods. The two most common methods are Shake Flask and HPLC. The Shake Flask Method, suitable for the broadest range of solutes, is rather time-consuming, though generally thought to be the most accurate. High performance liquid chromatography (HPLC) is a faster method that can be used when the chemical structure of the solute is known.

Prediction of log*P* is another method for obtaining this information. Software, such as ACD/Log*P*,[5] uses algorithms to calculate the log*P* of a compound by the sum of its fragments (logP values for individual fragments are obtained from experimental data and/or determined statistically). Prediction is a powerful resource because it can be done in the absence of a compound sample. It is used, even by groups that carry out measurements of log*P*, to plan experiments and verify results.

Conclusion

Log*P* is an important molecular physical property that impacts a wide range of systems. Used in conjunction with other critical parameters, it can help drive research forward in many industries and help determine the ultimate fate of chemical substances in our environment. Although there are well-established methods for measurement of the partition coefficient, these can be cumbersome and costly. Using prediction of log*P* before a substance is even synthesized offers a means to guide scientists toward more fruitful research and development.

References

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