Physicochemical Property Modules Overview

Chemical properties related to biological activity are receiving increased attention for designing out the inherent hazards of a chemical. Of the physicochemical properties, there are several that are especially important to estimating hazards and risks. They each have significant roles in exposure or hazard estimations. They are being explored in models and new tools for predicting the toxicity of chemicals. It is important to note that the importance of understanding the physiochemical properties of a chemical is due to the fact that these chemicals must interact with living systems in order to be considered toxic, and so recalling some basic physiology and biochemistry principles are important to putting together these chemical properties with *why* they impact living systems.

Can chemical properties predict the inherent nature of the molecules and can they serve as a guideline to reduce hazard? To address this question, a group of researchers from Yale University performed an analysis to see if toxic compounds share similar physiochemical properties. They were motivated to explore if compounds with established toxicity would have similar property distribution. The study analyzed over 550 commercial chemicals classified as toxic by the EPA, including chemicals from various industry sectors including manufacturing, metal and coal mining, hazardous waste treatment, and electric utilities. After applying mathematical algorithms, the distribution of physiochemical properties of these toxic compounds was different than control group made of chemicals listed as benign by the EPA. This study provides missing link that connects physiochemical properties with toxicity, and confirms that classification of highly toxic compounds is indeed possible by only couple of quantifiable parameters. This breakthrough became a stepping stone in the research which was proposed by Molecular Design Research Network (MoDRN) to develop property based toxicity prediction tools. Computational sciences can serve as a starting point, and rests on three pillars including chemical structure, dynamics, and reactivity for building predictive models.

If you are trying to make a decision without testing every possible endpoint and therefore without full knowledge, there are a variety of tools that you can use to fill data gaps. EPA has developed a number of “screening-level” tools that allow estimations in the absence of measured data. These tools generally use chemical structure and structure-activity relationships (SARs) to estimate the properties of the substance. These are not the only tools and, are not necessarily the best tools, but they are quite effective, they are free, and are certainly sufficient for beginning your process for designing safer chemicals.

Module 1: Aqueous and Lipid Solubility

Introduction: The relative solubility of a chemical in water (aqueous) or lipids is a major factor of the toxicity, environmental mobility, and persistence of a chemical; how likely is it to contact living systems, whether it can enter into living systems, whether it can be metabolized, and whether it can be excreted. Chemical designers are starting to use solubility as an important factor when creating chemicals that have potential exposure to living systems. Solubility may be essential for chemical function, but it may increase hazard for chemicals with significant toxicity.

Learning Outcomes: By the end of this module, the student will be able to:

- Define Kow and logP.
- Associate related chemical properties with solubility.
- Use ExpoBox and external websites and data to learn more about physicochemical properties that determine solubility and chemical transport.

Background and Information: Solubility of a chemical is determined by its structure and solution conditions. Aqueous solubility is important because, except for gases, chemical agents in the environment are transported and made available to living systems as aqueous solutions. Chemicals are either hydrophilic (water-soluble) or hydrophobic (water-insoluble). Aqueous solubility is measured by Kow (also denoted by "P" in some references). Kow is a shorthand term for the octanol-water partition coefficient. It measures relative solubility of a chemical with water (a polar molecule) and compared with octanol (a non-polar molecule similar to biological phospholipids found in cell walls/membranes). Kow provides information on how the chemical is likely to partition in biological organisms. For this module, we are focusing on the toxicology applications of Kow for purposes of chemical design; other resources exist for understanding Kow as it relates to other uses such as environmental fate, chemical behavior and hazard. A lower Kow indicates a preference for water over oily solvents; a higher Kow means it is more lipid-loving than water loving ("lipophilic"). Kow is useful because it predicts the preference a chemical has for lipids and for other organic media such as soil organic matter. In regard to lipid solubility, it is an important measure of the relative safety of chemicals because cells have lipid membrane/cell wall barriers, and so movement of chemicals across membranes and into organs and cells is dependent on its lipophilicity (lipid-solubility). The lipophilicity of a chemical is measured by log P (or log Kow- both expressed as a base -10 exponent. A P value of 1000 or 10^3 has a log P value of 3). In general, liquids with a log P between 2-4 tend to absorb well through skin. Likewise, a value that exceeds 5 to 6 does not absorb well, and tends to bioconcentrate in the lipid portion of the membrane.

Chemical designers rely on many factors when determining appropriate chemical design choices that result in low toxicity products including polarity, molecular size, surface area, and other descriptors of solute-solvent interactions. Aqueous and lipid solubility are just a few of several physiochemical properties that can help us understand how likely a chemical will be absorbed through biological membranes. Solubility data is available for many commonly used chemicals through reliable sources in the literature, such as Merck Index and Beilstein. The Interstate Chemicals Clearinghouse (IC2) framework, guiding development and use of safer chemicals and products, describes additional chemical properties that must be considered for reaching Green Chemistry Principle #4: Chemical products should be designed to preserve efficacy of function while reducing toxicity. In addition, several screening tools, such as EPA's EPI SuiteTM are available to assist in estimating physical/chemical and environmental fate properties when data is not available or when one is designing a new chemical.

Assignment:

Visit the following webpage: http://www2.epa.gov/expobox

Under the "Media" Column, click "Aquatic Biota" and then select the "Fate & Transport" Tab.

Click on the link for "Physicochemical/Environmental Factors" and look over the physicochemical properties in addition to the *Kow* or *log*P that can determine the solubility and transport of chemicals.
Many of these properties that help predict and determine the fate and transport a chemical has in the environment are also used in determining the biological activity (ADME - Adsorption, Distribution, Metabolism, Excretion) of chemicals in living organisms including us. In addition to *Kow* are factors such as the half-life which can be an index of persistence, Henry's law constant (K_H) which is an index of air/water partitioning. Consideration of all physicochemical properties is important, however the *Kow* of a chemical is very useful for environmental assessments. If the *Kow* of a compound is known, it can serve as a reliable predictor to estimate the *Kow* value for other chemicals within that class of compounds.

Consider the following data provided by the EPA investigating "Basic Concepts of Contaminant Sorption at Hazardous Waste Sites" (see References):

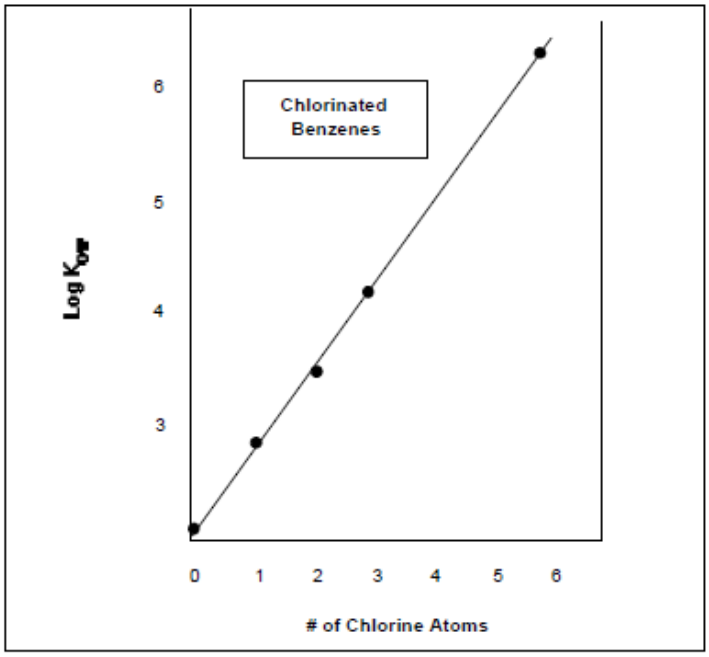


Figure A. Relationship of Molecular Structure to Hydrophobicity

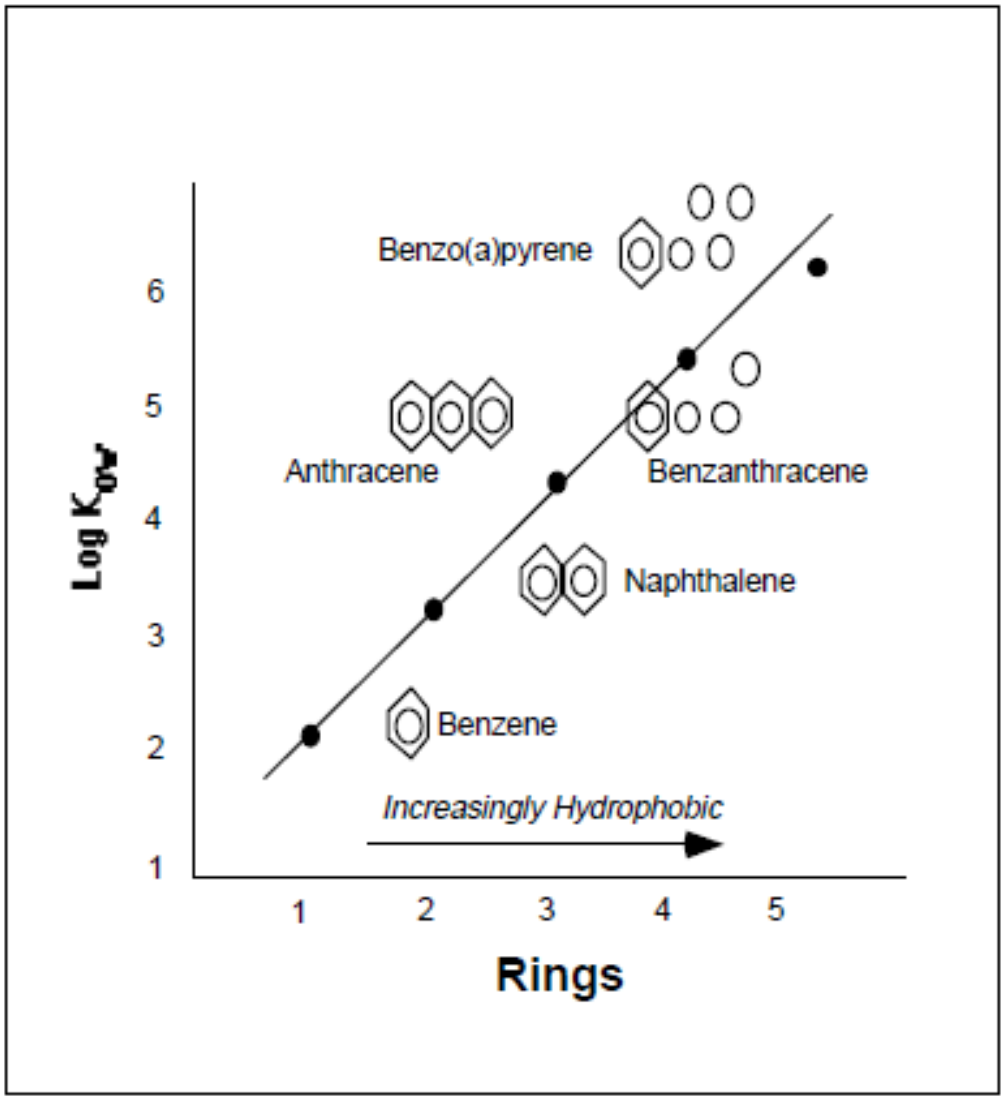
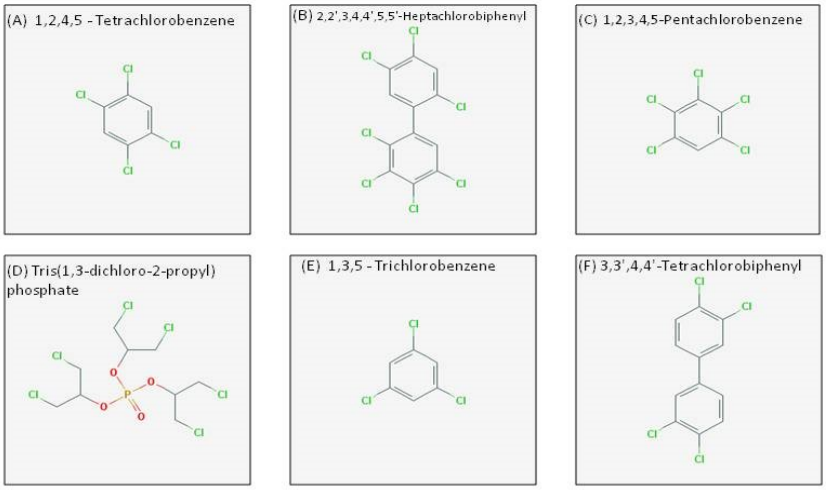


Figure B. Relationship of Molecular Structure to *Kow*

In these two examples, the *Kow* can be reliably predicted from the molecular structures. In the first graph it is correlated with the number of chlorine atoms, while in the second it is correlated with the number aromatic rings associated with the chemical. Now let us consider these concepts looking at some examples of a chemical class called Polychlorinated biphenyl's (PCB's) that were manufactured and used mainly as flame-retardant lubricants in the U.S. until they were banned by Congress in 1979.

Visit https://pubchem.ncbi.nlm.nih.gov/search/ and perform a search on each of the six chemicals to determine their respective K*ow*. How would you rank these chemicals from lowest to highest *Kow*?



Assignment answer found HERE: Aqueous and Lipid Solubility Answer Sheet

Additional Assignments:

- Read this National Toxicology Program report for chlorinated paraffins found here: http://ntp.niehs.nih.gov/ntp/roc/content/profiles/chlorinatedparaffins.pdf - summarize the role of lipid or aqueous solubility in the designation of its carcinogenicity in animal studies. How do these properties impact how the molecule can enter into humans and how it may impact the health of living animals?

- Describe what a safe chemical would "look" like or what properties it would have using the following physicochemical properties: *logP*, molecular weight, molecular size, surface area, and membrane permeability.

Resources:

- American Chemical Society. (2015) Green Chemistry Principle #4. Retrieved from http://www.acs.org/content/acs/en/greenchemistry/what-is-green-chemistry/principles/gc-principle-of-the-month-4.html#articleContent_headingtext_2
- Mergel, M. (2001). Chlorinated Parrafins. Retrieved from http://www.toxipedia.org/display/toxipedia/Chlorinated+Paraffins
- Piwoni, M. D., & Keeley, J. W. (1990). Basic concepts of contaminant sorption at hazardous waste sites. Retrieved from http://www2.epa.gov/sites/production/files/2015-06/documents/basic_concepts_sorption_haz_site.pdf
- Price, D. A., Blagg, J., Greene, N., & Wager, T. (2009). Physicochemical drug properties associated with in vivo toxicological outcomes: a review. *Expert Opinion on Drug Metabolism & Toxicology 5*(8), 921-931.

• PubChem. (2016). Retrieved from https://pubchem.ncbi.nlm.nih.gov/
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Module 2: REDOX Reactions

Introduction: Redox reaction is a short name for oxidation-reduction reactions. As the name implies, it involves two interdependent half reactions, oxidation and reduction. This type of reactions occurs naturally as part of the necessary processes in all biological systems. If they're intervened by harmful chemicals, undesired consequences may follow. Therefore, it is necessary to understand the fundamental chemistry of redox reactions for the purpose of designing safer chemicals.

Learning Outcomes: By the end of this module, the student will be able to:

- Define reduction and oxidation
- Recognize the role of reduction potential in the flow of electrons
- Describe the Nernst equation
- Identify REDOX reactions in biological systems

Background and Information: There are two key players, oxidants and reductants, in a redox reaction, connected by two indispensable processes, gaining and losing electrons. Oxidation refers to when the reductant loses electrons to the oxidant and itself gets oxidized. Reduction refers to when the oxidant gains electrons from the reductant and itself gets reduced. Clearly, oxidation and reduction need to take place at the same time.

*HINT: One can use a simple mnemonic "**OILRIG**" to memorize the redox reactions. **O**xidation **I**s **L**oss (of electrons). **R**eduction **I**s **G**ain (of electrons).*

It is important to recognize that electron transfer process is directional. A natural question to ask is, what factors determine the flow direction of the electrons? To answer this question, we need to introduce the concept of reduction potential. Reduction potential is a measure of the tendency of a chemical species to gain electrons and therefore be reduced (reduced by its charge, not the number of electrons it has!). The higher the reduction potential, the stronger the power a chemical gaining electrons. Quantitatively, it can described by the Nernst equation.

$$E_{red} = E^{\theta}_{red} - \frac{RT}{nF}\ln Q$$

where

E_{red} is the reduction potential under the specific condition

E^{θ}_{red} is the standard reduction potential

Q is the reaction quotient

One can view E^{θ}_{red} as an intrinsic property of a chemical.

Note that E^{θ}_{red} is modulated by its environment to assume a specific value. A typical example of redox reaction is the Zn/Cu displacement reaction. In this case, metal Zn has lower reduction potential (-0.76 V) and thus gives up two electrons to a Cu cation. The Cu+ cation with higher reduction potential (0.34 V) thus acquires the electrons from Zn and thereby gets reduced. The reduction potential for Cu in the form of Nernst equation can be expressed as below.

$$E^{Cu}_{red} = E^{Cu,\theta}_{red} + \frac{RT}{nF}\ln([Cu^{2+}])$$

Redox reactions are involved in numerous metabolic processes in living organisms. The life dependent energy production process is essentially a chain of oxidation reactions. Take glucose as an example. It is first oxidized into a pyruvate ion during glycolysis. Afterwards, pyruvate enters the citric acid cycle to complete its combustion reaction and produce 38 units of ATP. Another example of step-wise enzymatic oxidation reactions is alcohol metabolism, which leads to the final acid production throughout the chemical reactions it undergoes toward the final product. Importantly, it is critical to maintain interacellular redox homeostasis, which is the balanced state between reductants and oxidants, for the sake of cell survival. Excessive amount of redox active chemicals, such as reactive oxygen species, can overthrow this balance and lead to cellular disease conditions or death. In this way, then, chemical reduction potential is an informative parameter to consider when designing safer chemicals.

Assignments:

1. Using Nernst equation to calculate the reduction potential of hydrogen peroxide at pH 2, 4, and 6. Explain why the results differ between each other or not.

$$H_2O_2 + 2H^+ + 2e \rightarrow 2H_2O(E^{\theta} = 1.776V)$$

2. Find an example in biological system in which redox reactions are involved and identify the reductants/ oxidants for each step.

Assignment answer found HERE: REDOX Reactions Answer Key

Resources:

- UC Davis ChemWiki. (2015). Oxidative-Reduction Reactions. Retrieved from http://chemwiki.ucdavis.edu/Analytical_Chemistry/Electrochemistry/Redox_Chemistry/Oxidation-Reduction_Reactions
- Interactive Concepts in Biochemistry. (2002). REDOX Reactions. Retrieved from http://www.wiley.com/college/boyer/0470003790/reviews/redox/redox.htm
- Timberlake, K. C. (2014). An Introduction to General, Organic and Biological Chemistry. 12th ed. Prentice Hall Publishers.
- Atkins, P. & de Paula, J. (2014). Physical Chemistry. 10th ed. W.H. Freeman Publishers.

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