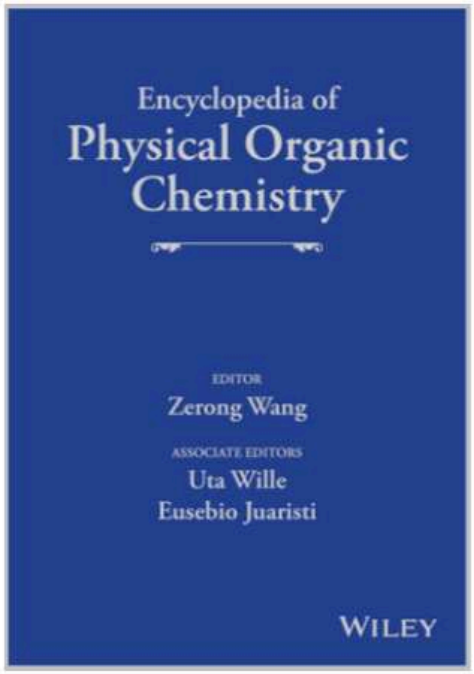
Encyclopedia of Physical Organic Chemistry

EDITOR
Zerong Wang

ASSOCIATE EDITORS
Uta Wille
Eusebio Juaristi

WILEY



Encyclopedia of Physical Organic Chemistry, 6 Volume Set

Zerong Wang (Editor), Uta Wille (Associate Editor), Eusebio Juaristi (Associate Editor)

ISBN: 978-1-118-47045-9 | January 2017 |

4464 Pages

TABLE OF CONTENTS

TABLE OF CONTENTS

Volume 1

LOG *P*

SUPRIYO SAHA

Department of Pharmaceutical Sciences, Sardar Bhagwan Singh Post Graduate Institute of Biomedical Sciences and Research, Dehradun, Uttarakhand, India

DILIPKUMAR PAL

Department of Pharmaceutical Sciences, Guru Ghasidash Vishwavidyalaya, (A Central University), Bilaspur, Chhattisgarh, India

1 INTRODUCTION

1.1 *log P*

Lipophilicity represents the affinity of a molecule or a moiety of molecule for a lipophilic environment. It is commonly measured by a ratio of distribution constants in an immiscible biphasic system. log *P* is the logarithmic form of partition coefficient for a chemical between octanol and water, which gives a measure of the lipophilicity of a compound. Lipophilicity is an important property of a drug molecule as it influences a number of physiological properties including transport through cell membranes, rate of metabolism, and interaction with receptor binding sites [1]. It should be pointed out that the log *P* value refers to the lipophilicity of unionized species. Lipophilicity changes as a function of pH for ionizable compounds. A similar term known as log *D* value denotes the lipophilicity of a chemical at a given pH. The log *D* and log *P* values are equal at the pH where the compound is neutral, that is, completely unionized [2]. If one of the solvents is a gas and the other is a liquid, the "gas/liquid partition coefficient" is the same as the dimensionless form of Henry's law constant. Partition coefficient is useful to estimate the distribution of drugs within the body. Hydrophobic drugs with high octanol/water partition coefficients are preferentially distributed to hydrophobic compartments such as the lipid bilayers of cells while hydrophilic drugs (low octanol/water partition coefficient) preferentially are found in aqueous compartments such as blood serum [3, 4]. For example, the blood/gas partition coefficient of a general anesthetic measures how easily the anesthetic passes from gas to

Encyclopedia of Physical Organic Chemistry, First Edition. Edited by Zerong Wang.
 ISBN 978-1-118-46858-6.

blood. Partition coefficients can also be used when one or both solvents are solids. The term *partition coefficient* is now considered obsolete by IUPAC, whereas "partition constant," "partition ratio," or "distribution ratio" is more appropriate term to be used. Different ionic species of a molecule differs in physical, chemical, and biological properties and so it is important to predict which ionic form of the molecule is present at the site of action [5]. The partition coefficient is a very useful parameter that may be used in combination with pK_a to predict the distribution of a drug compound in a biological system. Factors such as absorption, excretion, and penetration of central nervous system (CNS) may be related to the log P value of a drug [6, 7]. Partition coefficient is the preferred descriptor of molecular lipophilicity or hydrophobicity and thus of relationships between a solute (e.g., a drug), a polar medium (e.g., an aqueous buffer), and a nonpolar organic medium or a drug carrier. The partition coefficient is commonly identified as a ratio of solute quantities in two media, as represented in Equation 1, which has even been used to characterize solute association with or binding to a surface (e.g., of an HPLC column or a drug carrier) [8].

$$P = \frac{[S]_{\text{organic}}}{[S]_{\text{water}}} \tag{1}$$

1.2 Basic Features of log P

The log P value is the logarithm of its partition coefficient between n-octanol and water and is a well-established measurement of a compound's hydrophilicity. A large value of log P often indicates low hydrophilicity, which associates with poor absorption or permeation. In case of a drug to be absorbed across intestinal epithelium, it must be able to partition into lipid bilayer. pK_a and log P values are useful parameters for understanding the behavior of drug molecules. Different ionic species of a molecule may differ in physical, chemical, and biological properties, hence it is important to predict which ionic form of the molecule is present at the site of action to correlate with partition coefficient. Partition coefficient is used with dissociation constant value for the prediction of drug distribution inside a biological system. Partition coefficients are influenced by not only solvent system but also other process conditions, such as concentration, temperature, and pH. Basic molecule exists as a neutral species when the pH of solution is about 2 pH units greater than the pK_a of the conjugated acid of the molecule, whereas for an acidic molecule such as acetic acid, it will exist in neutral when the pH of solution is about 2 pH units less than the pK_a of the acid. As a result, the log P will vary according to the conditions under which it is measured and the choice of partitioning solvent [9]. When octanol and water are chosen as the two partitioning solvents, the log P value of a compound is used to measure a compound's lipophilicity, as shown in Equation 2 [10].

$$\log P_{\text{oct/water}} = \log \frac{[\text{solute}]^{\text{unionized}}_{\text{octanol}}}{[\text{solute}]^{\text{unionized}}_{\text{water}}} \tag{2}$$

1.2.1 Generalization to Ionized Forms of Solute In cases where the strong dominance of unionized form in the nonpolar phase is no longer ensured, or where greater precision is required, one must also consider the partition of all ionized forms between the two phases. If M indicates the number of ionized forms, for the Ith ionized form ($I = 1, \ldots, M$) of a chemical species, the logarithm of its corresponding partition coefficient log P is defined