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Physico-Chemical Parameters of Hydroxamic Acids

Sandhya Patre [1] and Rama Pande [1+]

School of Studies in Chemistry,
Pt. Ravishankar Shukla University, Raipur (C.G.) 492010, India

Abstract. Solubility, partition phenomena and lipophilicity are the three important physico-chemical parameters to be screened at early stage of the drug development process. Solubility of solid compound in solvent is governed by interactions between molecules in the crystal lattice, intermolecular interactions in the solution and the entropy changes accompying fusion and dissolution. N-arylhydroxamic acids shows drug likeliness therefore, solubility ratio (S_O/S_W) of three such molecules N-phenylbenzohydroxamic acid, N-phenyl-4-nitrobenzohydroxamic acid, and N-phenyl-4-methyl-3-nitrobenzohydroxamic acid, were measured in water and co-solvent system by shake-flask method following the measurement of the concentration by UV spectroscopy. The co-solvents are methanol, ethanol, 1-propanol, 1-octanol and chloroform. The solubility ratio gives comparable estimates to that of the group contribution method for estimating the lipophilicity of the molecules. The values obtained after regression analysis are in the range from 0.996 to 0.999, which shows that the solubility ratio gives good estimate of the partition coefficient for the solutes used in the present study.

Keywords: solubility, partition coefficient, solubility ratio, hydroxamic acid.

1. Introduction

Solubility is a parameter of prime importance in the drug discovery process. Indeed, solute must be soluble in order to reach their targets. Solubility of solute in liquid solvent, play an important role in the design of pharmaceuticals compound as well as in the development and optimization of drug manufacturing process.[1-4] The thermodynamic ideal solubility of solute depends only on the thermophysical data of solute and can be used as a first approximation of the solubility. In recent years, the solubility of drug like molecule is measured in many laboratories with different methods. When the solubility of solute is very low the classical saturation shake-flask method is more reliable and commonly used.[5,6] Molecular interactions between dissolved solute and surrounding solvent molecules can be used to calculate numerical values of partition coefficient that describe the equilibrium of a solute between two immiscible liquid phases. The partitioning process plays an impotent role in determining whether a given chemical is able to cross biological membranes or not.[7,8]

Hydroxamic acids have been recognized as compound of pharmacological, toxicological and pathological importance.[9-11] N-arylhydroxamic acids of general formula $R_1NOH.R_2C{=}O$ show drug likeness for which two factors are important, (i) they follow the "Lipinski Rule of 5" [12] and (ii) hydroxamic acid functionality serves as pharmacopheore with one HBD site of hydroxyl hydrogen and three HBA sites which are two oxygens and one nitrogen atoms. This HBD and HBA capability is responsible for solute-solvent interactions in case of neutral molecules. Hydrogen bonds also provide the binding interaction with receptors and these are weak bonds rapidly form and break Lipophilicity is also one of the important parameters which measure the ease with which drug penetrate the membranes and bind to lipophilic surface therefore, it is a fundamental physico-chemical property in drug discovery.[13,14]

+ Corresponding author. Tel.: (+91-9827198370); fax: + (491-771-226268).
E-mail address: (rama.pande11@gmail.com.).

The aim of present study is to examine the solubility of three hydroxamic acids N-phenylbezohydroxamic acid, N-phenyl-4-nitrobenzohydroxamic acid, and N-phenyl-4-methyl-3-nitrobenzohydroxamic acid in methanol, ethanol, 1-propanol, 1-octanol, chloroform and water, by shake-flask method using UV-visible Spectrophotometer. Solubility has a profound influence on the transport properties of molecules in human body.

2. Material and Method

Three hydroxamic acids namely N-phenylbenzohydroxamic acid (PBHA), N-phenyl-4-nitrobenzohydroxamic acid (PNHA) and N-phenyl-4-methyl-3-nitrobenzohydroxamic acid (PMNHA), were prepared by the procedure reported in literature[15] and purified by crystallizing thrice with benzene and dried over phosphorus pentoxide in vacuum for several hours. The purity of the compounds were ascertained by determining their melting points, UV and IR spectra. The data were tally with the literature[16]. Solvents were purchased from sources methanol (Merck, HPLC, 99.7%), ethanol (Bengal chemical, absolute), 1-propanol (Aldrich, 99.9%), 1-octanol (Aldrich, 99.8%), chloroform (Merck, 99%).

2.1. Water and Co-solvent Solubility Measurements

solubility of hydroxamic acids were directly determined in this laboratory by equilibrating an excess of solute with co-solvent in a sealed regent bottle for 24 h. Mixing was performed by electronic shaker and more solute was added if crystals were not observed. Saturation was assumed when crystals were observed in solvent and the solution was rotated for additional 5 hours to assure that the equilibrium was obtained. Then the samples were centrifuged and their observances were measured using a UV-visible Spectrophotometer. The entire procedure was carried out at least twice for each compound and each analysis was also conducted in triplicate.

3. Results and Discussion

Partition coefficients for solvents that are partially or completely immiscible with water such as, 1-octanol and chloroform were calculated as the ratio of the molar solutes solubility in the organic solvent and water obtained from direct partition between water (saturated with the organic solvent) and organic solvent (saturated with the water). In the case of solvents that are fully miscible with water, such as methanol, ethanol, 1-propanol, the calculated partition coefficient must refer to the hypothetical (indirect) partition between the two pure solvents, Although “hypothetical”, these partitions are very useful, they can be used to predict solubilities in the pure solvent. The partition coefficient of a solid between water and solvent phase, P, is related as in equations 1, 2.

$$SR = P = S_O/S_W \quad (1)$$

or

$$\text{Log } SR = \log S_O - \log S_W \quad (2)$$

where, SR is solubility ratio, So and Sw is the molar solubility of the solute in solvent and water, respectively. The co-solvent (So) and water (Sw) solubility of the compound studied are listed in Table 1 from these values the solubility ratio, (SR) of solute in water and co-solvent are calculated. The values of SR are also listed in Table 1 along with observed partition coefficient and the difference between these two parameters for all three compounds. It is observed that the solubility ratio dose not differ greatly from the observed partition coefficient. A plot of observed logP versus logSR for the data from Table 1 is presented in Figure 1. The regression analysis values are in the range from 0.996 to 0.999 and the average absolute error is less than 0.3 log unit show that the solubility ratio gives good estimates of the partition coefficient for the solute in the present system.

On the basis of the investigated data the following trend is noticed, (a) all solute molecules reveal very low solubility in water and in alcohols, (b) the solubility of all measured solutes in alcohol is higher than

water, (c) the solubility in water is detectable only by the UV method. The solubility of all the hdyroxamic acids is higher in 1-octanol and chloroform as compare to other solvents.

4. Conclusions

The water and co-solvent solubility ratio can be used as the estimate of the partition coefficient for the solutes. This approach assumes that P is equal to the SR of the solute in organic solvent and water. The SR method has been shown to be simple and easy to use by measuring the solubilities in water and organic solvents while the group contribution method requires all the fragmentation or structure parameters of the molecules. All three hdyroxamic acids are more soluble in 1-octanol and chloroform as compare to other solvents. We believe that our new systematic solubility data will improve Pk/PD prediction- method development and precision.

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6. References

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Table 1. Organic Solvents/Water Solubility, Solubility Ratio and Partition Coefficients, Lipophilicity of Hydroxamic Acids.

Solvents	**Log S_o**	**Log S_w**	**Log SR**	**P**	**Log P**	**log P − log SR**
N-phenylbenzohydroxamic acid						
Methanol	-0.698	-1.619	0.921	8.337	0.921	0.000
Ethanol	-1.000	-1.619	0.619	4.197	0.623	0.004
1-Propenol	-0.958	-1.619	0.661	4.655	0.668	0.007
1-Octanol	0.062	-1.619	1.681	49.545	1.695	0.014
Chloroform	0.146	-1.619	1.766	59.429	1.774	0.008
N-phenyl-4-nitrobenzo hydroxamic acid						
Methanol	-0.523	-1.569	1.046	11.376	1.056	0.010
Ethanol	-0.824	-1.569	0.745	6.067	0.783	0.038
1-Propenol	-0.886	-1.569	0.683	5.035	0.702	0.019
1-Octanol	0.049	-1.569	1.618	46.026	1.663	0.045
Chloroform	0.139	-1.569	1.708	52.844	1.723	0.015
N-phenyl-4-methyl-3-nitrobenzohydroxamic acid						
Methanol	-1.000	-1.678	0.678	5.236	0.719	0.041
Ethanol	-1.301	-1.678	0.377	3.775	0.577	0.200
1-Propenol	-1.301	-1.678	0.377	4.083	0.611	0.234
1-Octanol	0.068	-1.678	1.746	60.67	1.783	0.037
Chloroform	0.149	-1.678	1.827	67.143	1.839	0.012

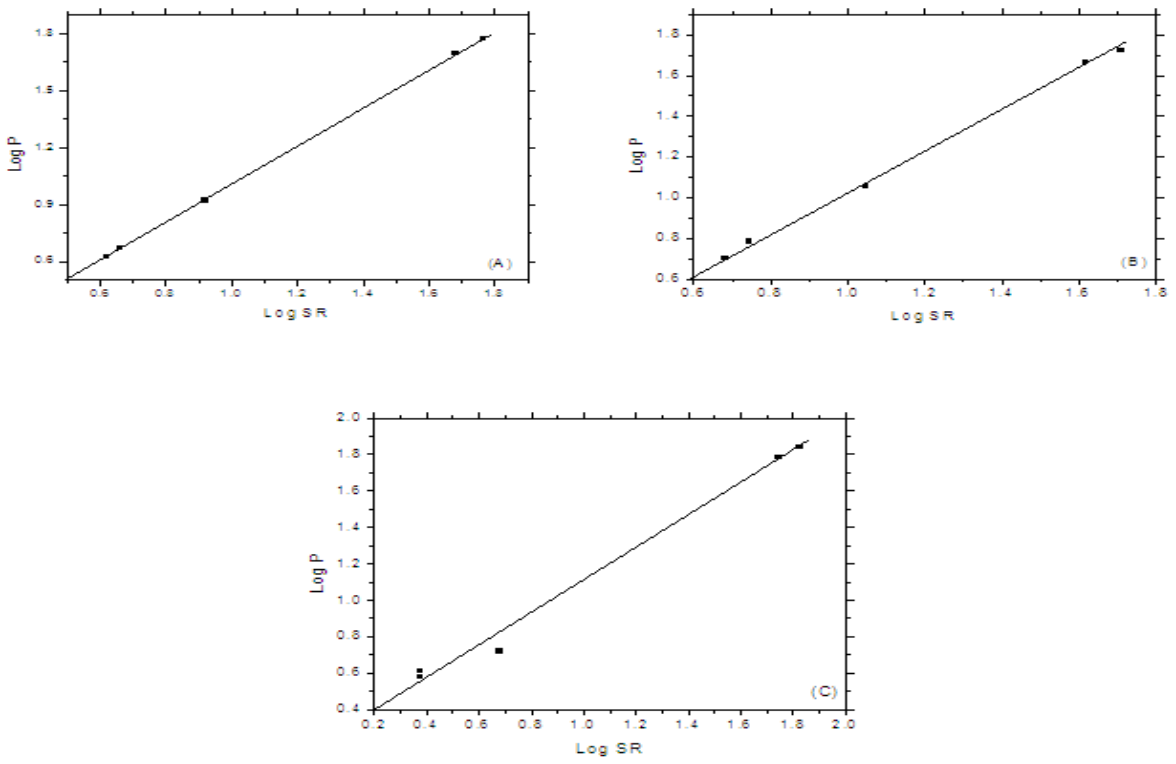

Figure 1. Plots of relationship between the partition coefficients and solubility ratio of (A) PBHA, (B) PNHA, (C) PMNHA.