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Solvation Parameters and Solubility of N-Arylhydroxamic Acid

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Abstract: N-arylhydroxamic acid shows drug likeliness therefore, the hydrogen bond donor (HBD), hydrogen bond acceptor (HBA) and solubility ratio (So/Sw) of three such molecules N-phenylbenzohydroxamic acid, were measured in water and co-solvent system by shake-flask method following the measurement of the concentration by UV spectroscopy. 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. The salvation parameter gives comparable estimates to that of the group contribution method for estimating the lipophilicity of the molecules. The solubility and salvation parameter gives good estimate of the partition coefficient for the solutes used in the present study.

Index Terms **-** Hydroxamic acid, solubility and solvation parameters.

I. INTRODUCTION

Hydroxamic acids have been recognized as compound of pharmacological, toxicological and pathological importance [1]-[3]. 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" [4] 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. Hydroxamic acids are an important class of organic molecules playing a key role in many biologically relevant interactions [5]. They are known as constituents of antibiotics, growth factors, food additives, tumour inhibitors and cell division factors.

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 [6]-[9]. Solvation parameters represent the solutes influence on various solute/solvent phase interactions. The coefficients c, e, s, a, b, and υ, which are obtained via multiple linear regression against known log (Cs/Cw) values, correspond to the complimentary effect on the phases of these interactions [10]. 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 [11], [12]. 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 [13], [14].

The aim of present study is to examine the solubility of three biomolecules, N-phenylbezohydroxamic acid, in solvent and water, by shake-flask method using UV-visible Spectrophotometer. Solubility has a profound influence on the transport properties of molecules in human body.

II. MATERIAL AND METHODS

All the hydroxamic acids 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 methanol (Merck, HPLC, 99.7%), ethanol (Bengal chemical, absolute), 1-propanol (Aldrich, 99.9%), 1-octanol (Aldrich, 99.8%), chloroform (Merck, 99%) were purchased from sources.

1.1 SOLUBILITY MEASUREMENTS

Solubility of hydroxamic acids were directly determined 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 by UV spectrophotometer. The entire procedure was carried out at least twice for each compound and each analysis was also conducted in triplicate.

III. RESULTS AND DISCUSSION

Experimentally based methods are used to correlate and predict solubilities following the Linear Solvation Energy Relationships (LSER). The LSER method is based on Multilinear Regression (MLR) analysis of the solubilities of solutes in different solvents and has gained increasing attention during the past decades. The method was originally developed by Kamlet and Taft [17]-[20] and further refined and applied by Abraham and co-workers [21]-[23] who have applied it to numerous solutes. The LSER, MLR model. The solubility ratio gives good estimates of the partition coefficient for the solute in the present system. Partition coefficients for solvents that are partially or completely immiscible with water 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, the calculated partition coefficient is referred as the hypothetical (indirect) partition between the two pure solvents, such partitions data 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.

$$SR = P = SO/SW \quad (1)$$

or

$$\text{Log SR} = \log SO - \log SW \quad (2)$$

where, SR is solubility ratio, S_o and S_w are the molar solubility of the solute in solvent and water, respectively. The co-solvent (S_o) and water (S_w) solubility of the compound measured are listed in Table 1 along with the values of SR and partition data. It is observed that the solubility ratio dose not differ greatly from the observed partition coefficient. A plot of observed log *P* versus log SR for the data from Table 1 is presented in Fig 1. The strength of the approach depends on combining all these characteristics into a single model, thus providing a solid basis to know the solute-solvent interactions and also the ability to rank each type of interaction for each solute-solvent pair.

Table 1: Organic Solvent/ 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

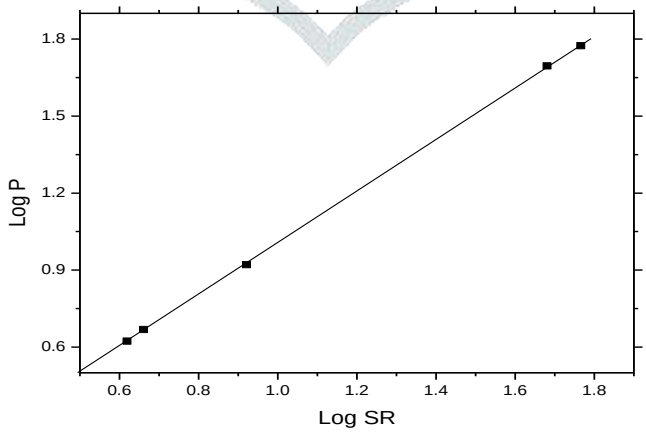

Fig 1: Plots of relationship between the partition coefficients and solubility ratio of N-phenylbezohydroxamic acid

2.1 Basic Mathematical form of the Abraham Model

The general solvation parameter model of Abraham [24], [25] is one of the most useful approaches for the analysis and prediction of free energies of partition in chemical and biochemical systems. Applying the LSER approach, the intermolecular forces governing the partition of neutral organic solutes can be studied using six structural parameters equation,

$$\log (C_S/C_W) = c + rRm_2 + s\pi^H + a\sum\alpha_2^H + b\sum\beta_2^H + \upsilon V_x \quad (3)$$

where,

C_S/C_W	=	The solute solubility in the organic solvent and water.
R_M	=	Excess molar refraction.
V_X	=	The McGowan volume of the solute.
$\Sigma\alpha_2^H$	=	Hydrogen-bonds acidity.
$\Sigma\beta_2^H$	=	Hydrogen-bonds basicity.
π_2^H	=	Dipolarity/polarizability descriptor.

In this equation, log(Cs/Cw) is the dependent variable while others are independent variables. Molar volume and excess molar refractivity of these molecules measured experimentally and all these data were used to generate the parameters by applying Abraham equation. In equation (3), capital letters represent the solutes properties and the small letters show the complementary properties. These parameters represent the solutes influence on various solute/solvent phase interactions. The coefficients c, e, s, a, b, and υ, which are obtained via multiple linear regression against known log (Cs/Cw) values, correspond to the complimentary effect on the phases of these interactions. The coefficients are regarded as system constants which characterize and contain chemical information of the phase in question and can be interpreted as follows, the r-coefficient indicates the tendency of the phase to interact with solutes through polarizability type interactions, mostly via electron pairs, the s-coefficient represents the tendency of the phase to interact with dipolarity/polarizability of solutes, the a-coefficient denotes the hydrogen bond basicity of the phase, because acidic solutes will interact with basic phases, the b-coefficient is a measure of the hydrogen bond acidity of the solvent phase, the υ-coefficient represents the work needed to create a solvent cavity where solute will reside and the general dispersion interaction energy between the solute and solvent phase, and in the case of partition coefficients, where two solvent phases are involved, coefficients the c, r, s, a, b, and υ represent differences in the solvent phase properties.

The solute descriptors, HBD, HBA and polarizability are based on the physically meaningful theoretical cavity model of solute- solvent interactions. The solute descriptors represent the solute's influences on various solute-solvent phase interactions and coefficients correspond to the complementary effect of solvent phases on these interactions. Equation (3) actually predicts partition coefficients.

The predictive applicability of the Abraham general salvation model is relatively straightforward. With the set of equations that we have been constructed for the partition of hydroxamic acids between water and a given solvent. Table 1,2 gives the coefficients in equation (3) for the water–solvent partitions. The actual numerical values differ slightly from values reported. Three specific conditions must be met in order to use the Abraham solvation parameter model to predict saturation solubility.

2.2 Multiple Regression and Selection of an Optimal Set of Solvents

The multiple regression analysis (MRA) was performed using ORIGIN 8 PROGRAM. An optimal set of 14 solvents–water systems is selected out of 22 systems. Due to some experimental limitations, the optimal sets are then reduced to 9 solvents that give the smallest value of standard deviation.

2.3 Multiple Linear Regression Models

Regression models are among the most useful and most used statistical method because they allow relatively simple analyses of complicated situations. Multiple linear regressions give the relationship between two or more independent variables and a dependent variable by fitting a linear equation to the observed data.

2.4 Standard Deviation

Standard deviation (SD) is a statistical measure of the spread or uncertainty around the mean. It is defined by the equation,

$$SD = \sqrt{\frac{\left(\sum y_i - \bar{y}\right)^2}{(n-p-1)}}$$

were,

yi	=	each individual data point.
$\bar{y}$	=	the mean of the dataset.
n	=	the number of data points.
p	=	the number of independent variables.

If many data points are clustered tightly around the mean, then the standard deviation is small. However, if data points are scattered widely around the mean, then the standard deviation is large. A useful property of standard deviation is that, unlike variance, it is expressed in the same units as the data.

Table 2 Coefficients of Solvent for Partition

ORGANIC SOLVENT	COEFFICIENTS					
	c	r	s	a	b	v
Chloroform	0.327	0.157	-0.391	-0.391	-3.437	4.191
1,2-Dichloroethane	0.227	0.278	-0.167	-2.816	-4.324	4.205
Benzene	0.142	0.464	-0.588	-3.099	-4.625	4.491
Dichloromethane	0.314	0.001	0.022	0.022	-4.137	4.259
Chlorobenzene	0.040	0.246	-0.462	-3.038	-4.769	4.640
Bromobenzene	-0.130	0.394	-0.280	-0.280	-4.640	4.583
Toluene	0.143	0.527	-0.720	-3.010	-4.824	4.545
Ethyl acetate	0.358	0.362	-0.449	-0.668	-5.016	4.155
Isooctane	0.288	0.382	-1.668	-3.639	-5.000	4.461
Heptane	0.325	0.670	-2.061	-3.317	-4.733	4.543
Cyclohexane	0.159	0.784	-1.678	-3.740	-4.929	4.577
Hexane	0.361	0.579	-1.723	-3.599	-4.764	4.344
1-Octanol	-0.034	0.490	-1.048	-0.028	-4.229	4.219
Heptanol	-0.026	0.491	-1.258	0.035	-4.155	4.415
Decanol	-0.062	0.754	-1.461	0.063	-4.053	4.293
Butanol	0.152	0.437	-1.175	0.098	-3.914	4.119
Propanol	0.147	0.494	-1.195	0.495	-3.907	4.048
Methanol	0.329	0.299	-0.671	0.080	-3.389	3.512
Ethanol	0.208	0.409	-5.959	0.186	-3.645	3.928
Dimethyl Sulfoxide	−2.390	0.230	0.880	1.310	-4.600	3.400
Octane	0.223	0.642	-1.647	-3.480	-5.067	4.526
2-propanol	0.063	0.320	-1.024	0.445	-3.824	4.067

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Table 3 Solvation Parameters of N-phenylbezohydroxamic acid

NO. OF SOLVENTS/WATER SYSTEMS (n)	π	α	β	SD
n = 15	1.0589	0.2079	1.1305	0.2051
n = 16	1.1459	0.3542	0.9926	0.2608
n = 17	0.9641	0.3240	1.1660	0.3138
n = 18	0.6550	0.3066	1.0050	0.5562

IV. CONCLUSIONS

Hydrogen-bonding and solute molecular volumes are the major properties that influence the partition of solute which is also considered as model blood/lipid partition and successfully used in QSAR relationship. Predictive QSPR model which is based on molecular descriptors is proposed in this study to correlate the aqueous solubility of drug compounds. Application of the developed model to a testing set of compounds demonstrates that the new model is reliable with good predictive accuracy and simple formulation. Since the QSPR was developed on the basis of theoretical molecular descriptors calculated exclusively from molecular structure, the proposed model could potentially provide useful information about the solubility of these drugs like molecules. Lipophilic character, log *P* is a physico-chemical property of solute. Knowledge of this plays an important role to decide the solutes ability to interface with biochemical systems. It is the measure of the ease with which drug penetrate membranes and bind to lipophilic surface.Comparatively smaller value for PBHA indicates the electron donating effect of methyl group. The values of basicity further confirm the above statement. The values of πH are appreciably smaller for both the solutes but comparatively difference is larger, hydroxamic acids behave as nonpolar compounds. 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.

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