

Hydrogen-Bond Parameters and Lipophilicity of Hydroxamic Acids: Use in Drug Design

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Abstract: *Hydroxamic acid provides central functionality in a number of metalloproteinase inhibitors because of its ability to strongly coordinate with metal ions and as such has high relevance for the development of new pharmaceuticals. Hydroxamic acids, the naturally occurring and synthetic products, generally have low toxicities and are of interest for many therapeutic applications. The lipophilicity of a series of hydroxamic acids have been measured experimentally between chloroform-water, octanol-water and chloroform-octanol systems, by the shake-flask method. Measured lipophilicities of compounds obtained are in the range 2.516 to 2.358. The measured Hydrogen Bond Donor (HBD) and Hydrogen Bond Acceptor (HBA) strengths are in the range 0.6239 to 0.7098 and 1.9288 to 2.8292, respectively. This study is designed to assess the correlation between the lipophilicity of the compounds and their biological activity. The results show that these molecules have better chances to arrive at receptor sites. In QSAR where physico-chemical parameters of drugs are correlated with biological activities, lipophilicity plays a major role. A knowledge of these parameters will help in designing the better drug delivery system and more accurately marked pharmaceuticals and pesticides.*

Keywords: Hydroxamic acid, partition coefficient, hydrogen-bonds, lipophilicity.

1. Introduction

Hydroxamic acids represented by the general formula, $R_2\text{-CO-NR}_1\text{-OH}$, where R_1 and R_2 are phenyl or substituted phenyl groups. These are versatile metal extractants and behave as non-electrolyte. The hydroxamic acid functionality, $-\text{C}(=\text{O})\text{N.OH}$, is a key structural constituent of many biomolecules, some of which, are naturally occurring [1] and others, such as peroxidase, matrix metalloproteinase and urease inhibitors [2,3] are of synthetic origin. Hydroxamic acids, both naturally occurring and synthetic show a wide spectrum of applicability in various fields [4–14] and the structural part $-\text{NOH.C}=\text{O}$, is an important feature responsible for this versatility and serves as pharmacophore 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. The knowledge Lipophilicity for a series of drug-like molecules is a fundamental step for the optimization of their design, synthesis and biological applications. Hydrogen-bond is the most important kind of molecular interaction and is major force of recognition in biochemistry and molecular pharmacology. Hydrogen-bond capability deeply influences the transport and ADME (adsorption, distribution, metabolism and excretion) properties of a molecule as well as the specific interaction with biological receptors. Many QSAR studies have been reported in which hydrogen bonding interactions play a key role in modeling a particular target activity [15].

The remarkable feature of N-Arylhydroxamic acids is that they show drug likeness by following the “Lipinski Rule of 5”. This rule states that most drug like molecules have value of Mol. Wt ≤ 500 , Lipophilicity ≤ 5 , HBD sites ≤ 5 and HBA ≤ 10 . These molecules also show anti-tumor activity when tested in-vitro. Therefore, present investigation is to examine the Hydrogen-Bond Parameters and Lipophilicity

of five hydroxamic acids have been measured experimentally by determining the partition data between chloroform-water, octanol-water and chloroform-octanol systems following the simplest and most widely used shake flask method. Octanol has a structure similar to biological membrane. The knowledge of partitioning between two immiscible solvents is important to correlate biological activity for drug design, to predict the drug delivery system and fitting of a drug to receptor site. HBD and HBA strength were then calculated and found within the range. Lipophilicity is measured as logarithm of partition coefficient of a compound between octanol and water phases. The values obtained are less than 5.0 and positive. This is advantageous as the compounds with lower value of lipophilicity do not bioaccumulate into fat tissues because of their lower affinity for lipids. The rate of movement of organic molecule through cellular material also depends on lipophilicity. Based on lipophilicity data, hydrophobic parameter, π , have been calculated Biological activity is highly dependent on this character. These parameters will be of further used in quantitative-structure activity relationship (QSAR) analysis of these molecules. Knowledge of these parameters is valuable in the field of toxicology, pharmacology and environmental sciences.

2. Material and Methods

2.1 Synthesis

All the hydroxamic acids were prepared by the procedure reported in literature [16] and purified by crystallizing thrice with benzene and dried over phosphorus pentoxide in vacuum for several hours. The purity of the compounds was ascertained by determining their melting points, UV and IR spectra. The data were tally with the literature [17]. 1-Octanol, chloroform and other chemicals used were of analytical grade.

2.2 Measurement of QSAR Parameters

Hydrophobic Parameters, this includes the measurement of partition coefficients, P , in Octanol/Water and Chloroform/Water systems and lipophilicity. Hydrogen-Bond Parameters, HBD strength (α) and HBA strength (β), were evaluated.

3. Results and Discussion

The partition coefficient, P , has been known to be one of the quantitative physical properties that correlate with biological activity. The partition coefficient, between 1-octanol and water, $P(O/W)$, chloroform and water of five hydroxamic acids is calculated from the following equation (1).

$$P_{(O/W)} = A_f / A_i - A_f \times V_o / V_w \quad (1)$$

$$P_{(Cl/W)} = A_f / A_i - A_f \times V_{Cl} / V_w \quad (2)$$

where, A_i is Absorbance of hydroxamic acid in organic phase before partitioning, A_f is Absorbance of hydroxamic acid in organic phase after partitioning, V_{org} is Volume of organic phase, V_w is Volume of water phase.

3.1 Hydrophobic Descriptors

The most important solute-solvent interactions for neutral molecules are hydrogen bonds, where the solute may act as a donor/ acceptor, and dipole interactions. Dipolar interactions are represented by the dipolarity/polarizability term. The hydrogen bonding properties are represented by the effective hydrogen bonding acidity $\epsilon\alpha$ and basicity $\epsilon\beta$. The HBD strength of these compounds is calculated from $\log P_{(O/Cl)}$ which is expressed as,

$$\log P_{(O/Cl)} = \log P_{(O/W)} - \log P_{(Cl/W)} \quad (3)$$

where, $\log P_{(O/Cl)}$ is partition between octanol/chloroform system, $P_{(O/W)}$ is partition between octanol/water and $P_{(Cl/W)}$ is the chloroform-water partition coefficient of the solute. It is assumed that there is no significant solute-solvent and solute-solute interaction in this system.

3.2 Hydrogen bonds in hydroxamic acids

According to Jeffrey, "When a covalently bound hydrogen atom forms a second bond to another atom, the second bond is referred as hydrogen bond". In hydroxamic acids, the O-H stretching vibrations appear at lower frequencies, indicating the presence of intramolecular hydrogen bonding in these molecules as shown in structure I. At the same time, these reagents serve as HBD in the presence of HBA solvents and as HBA, when uses their atoms, oxygen and nitrogen, with a pair of electrons to bind with HBD system. Hydrogen bonds are rapidly formed and broken. When both the functions HBD and HBA are present in molecular structure then, solute-solute H-bonds compete with solute-solvent H-bonds and this phenomenon is observed in the equilibrium partitioning ($\log P$) of very low concentrations of solute between two immiscible solvents. Both of these functions, when present simultaneously are independent of

each other, at the same time $\log P$ values remain unaffected by the strength of intramolecular H-bonding.

3.3 Hydrogen Bond Donor Strength, $\epsilon\alpha$

HBD strength is an inherent atomic property. 1-Octanol-chloroform system acts as a HBA base whereas hydroxamic acid in it, acts as HBD solutes. Using the values of $\log P_{(O/Cl)}$ obtained from equation 3, the HBD strength, $\epsilon\alpha$, of hydroxamic acids are calculated by the equation 4 proposed by Taft and Leo [18].

$$\log P_{(O/Cl)} = -1.0(0.01V_x) + 3.20\epsilon\alpha - 0.03 \quad (4)$$

where, V_x is Molar volume of solute, ϵ is Represents the effective sum of interactions of multifunctional groups, α is HBD strength/capacity.

3.4 Hydrogen Bond Acceptor Strength, $\epsilon\beta$

Analysis of hydrogen-bond acceptor strength reveals two main contributions to this property, (i) the specific basicity of electronegative heteroatom, bearing lone pair of electrons, and (ii) the non-specific basicity of unsaturated species due to different H- π interaction. Accordingly, either the lone pairs or the π system of molecule, or both of them can act as hydrogen atom attracting sites in processes of proton transfer or hydrogen bonding.

Following the equation proposed by Leo and Hoekman, the HBA strength of hydroxamic acids are calculated by the expression (5),

$$\log P_{(O/W)} = 3.67(0.01V_x) - 0.040(0.1\mu^2) - 0.0\epsilon\alpha - 3.00\epsilon\beta + 0.24 \quad (5)$$

where, ϵ represents the effective sum of interaction of polyfunctional groups in hydroxamic acids.

3.5 Dipole Moment, μ

μ is the molecular dipole moment obtained by equation (6) [19],

$$P_t = M_R + 4\pi N_0 \mu^2 / 9KT \quad (6)$$

where, P_t is the total polarization, N_0 is Avogadro's number 6.023×10^{23} g-atom, k is Boltzmann's 1.38×10^{-16} erg/k/mole and T is the absolute temperature. The values of $\epsilon\alpha$, $\epsilon\beta$ and μ are given in Table 1.

3.6 Calculation of $\log P$ from molecular volume

Lipophilicity is an affinity of drug molecule, for a lipophilic environment and is often considered as a key property in transport process of drugs in a body. This include intestinal absorption, membrane permeability, protein binding and distribution among different tissues. For the drug to reach the site of action, it must be able to interact with two different environments, (i) Lipophilic, (membrane), (ii) Aqueous (cytoplasm). All living cells are surrounded by membrane, which is amphipathic in nature containing both hydrophobic and lipophilic sites. As hydroxamic acids are very sparingly soluble in water their logarithm of partition of 1-octanol/water system give lipophilicity. It is denoted by $\log P(o/w)$. The values of lipophilicities are given in Table 1.

3.7 Hydrophobic Substituent Constant, π_x

The difference of $\log P$ values between the parent compound and derivatives also gives a lipophilicity descriptor called hydrophobic substituent constant, π_x , which characterizes the influence of the substituent X [20].

$$\pi_x = \log P_X - \log P_H \quad (7)$$

where, P_H is the partition coefficient of parent molecule and P_X is the partition coefficient of derivative of P_H . The values of $\log P_H$ are taken from the literature. The value of π_x are reported in Table 1.

4. Conclusion

Hydroxamic acids show a wide spectrum of medicinal utility, therefore, the knowledge of their H-bond strength is useful to design a better drug and to gain the structural information. These are neutral and multifunctional compounds and such parameters are important to evaluate the physical forces which govern the partition between two phases and also applicable to QSAR studies. 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. Hydroxamic acids serve as antagonists and their drug/receptor interaction can be explained on the basis of H-bonding, such information is useful for medicinal chemists.

Table 1: Values of P(O/W), P(CL/W), P(O/CL), LOGP(O/W) and HBD strength, $\epsilon\alpha$, HBA strength, $\epsilon\beta$, DPOLE moment, μ , Substitution Constant, π_x , of Hydroxamic Acids.

S. No.	Hydroxamic Acids	P _(O/W)	P _(CL/W)	P _(O/CL)	LogP _(O/W)
1.	N-p-Tolyl-2-methylbenzo-	328.334	634.833	-306.499	2.516
2.	N-o-Tolyl-4-methylbenzo-	233.277	483.250	-249.973	2.367
3.	N-o-Tolyl-2-nitrobenzo-	205.834	420.900	-215.066	2.314
4.	N-o-Tolyl-4-nitrobenzo-	357.834	636.333	-278.499	2.553
5.	N-p-Tolyl-3,5-dinitrobenzo-	228.250	309.087	-80.837	2.358

S.No.	Hydroxamic Acids	$\epsilon\alpha$	$\epsilon\beta$	μ	π_x
1.	N-p-Tolyl-2-methylbenzo-	0.6239	1.9288	0.1805	0.3860
2.	N-o-Tolyl-4-methylbenzo-	0.6149	1.9762	0.1404	0.2370
3.	N-o-Tolyl-2-nitrobenzo-	0.6170	2.3400	0.1558	0.1840
4.	N-o-Tolyl-4-nitrobenzo-	0.6358	2.2597	0.2049	0.4230
5.	N-p-Tolyl-3,5-dinitrobenzo-	0.7098	2.8292	0.1646	0.2280

4.1 Lipophilicity By Bodor And Buchwald Method

A number of methods have been developed [21, 22] for calculating $\log P$. In these methods the molecules is broken in atom fragments. The fragment constants value of the component fragments present in the molecular structure, is determined. Then the values of $\log P$ are obtained by summation of these fragmental constants.

Bodor and Buchwald [23] have also proposed a two parameter equation for calculating the logarithm of the partition coefficient of an organic solute between 1-octanol and water. The first parameter is Van der Waals volume of the solute molecule and the second parameter is an integer, N, as in the following equation,

$$\log P = 0.032v_{BB} - 0.723N \quad (7)$$

where, v_{BB} is the Bodor-Buchwald version of Van der Waals volume and N is A positive integer

4.2 Computation of v_{BB}

Bondi [24] proposed a simpler method for calculating v_{BB} , as in the following expression,

$$v_{BB} = 0.838v_w \quad (8)$$

where, v_w is Van der Waals volume, The increment values for different groups taken from the literature [25], the values of v_{BB} , v_w of hydroxamic acids are presented in Table II. v_w is obtained by the addition of the volume increments of the constituent atoms. Van der Waals volume is a measure of the cavity term in linear solvation energy relationships. Bodor-Buchwald version of Van der Waals volume, v_{BB} , is linearly related to volume increments of the constituent atoms.

Table 2: Values of Van Der Waals Bodor-Buchwald parameter and lipophilicity of Hydroxamic Acid.

S. No.	Hydroxamic Acids	v_w	v_{BB}	$\log P$
1.	N-p-Tolyl-2-methylbenzo-	225.4	188.89	2.4293
2.	N-o-Tolyl-4-methylbenzo-	225.4	188.89	2.4293
3.	N-o-Tolyl-2-nitrobenzo-	231.4	193.91	2.5902
4.	N-o-Tolyl-4-nitrobenzo-	231.4	193.91	2.5902
5.	N-p-Tolyl-3,5-dinitrobenzo-	254	212.85	3.1963

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