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Short communication

Hydroxamic acids: proton donor and acceptor strength for use in drug design

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Abstract

Hydroxamic acids, the naturally occurring and synthetic products, generally have low toxicities and are of interest for many therapeutic applications. The present investigation describes the measurement of hydrogen bond donor (HBD) strength of ten hydroxamic acids by measuring their log P(O/W) values. Hydroxamic acid functional group contains two oxygen and one nitrogen atom as the acceptor sites. Thus, HBA strength of these reagents is also computed. A knowledge of these parameters is valuable in the field of toxicology, pharmacology and environmental sciences.

Keywords: Hydroxamic acids; Proton donor and acceptor strength

1. Introduction

Hydroxamic acids ($R_1NOH{\cdot}R_2C{=}O$, where R_1 and R_2 are phenyl or substituted phenyl groups) have been the source of much biochemical interest in recent years due to the fact that they show a wide range of biological activities and have low toxicities. Much of the activities of these compounds are due to their chelating properties with metal ions. The occurrence of hydroxamic acids in nature was first reported in 1967 [1], their presence in micro-organism is also mentioned. The function of naturally occurring hydroxamic acid is to transport the iron present outside through the cell wall, by chelation through metabolism [2]. At present, a number of hydroxamic acids and their derivatives are reported as effective antibacterial and antifungal agents [3]. Their ability to coordinate to metal ions is responsible for their antimicrobial action. Some of these are potential antimalarials [4]. Commercially available ''Desferal'' is used for the removal of iron from the body [5]. Derivatives of 3,4,5-trimethoxybenzohydroxamic acid act as mental tonic. ''Bufexmac'' is used as an antiinflammatory agent [6] in humans. These reagents are of interest for other possible therapeutic applications as anticancer [7], antibiotics [8] and antitumor agents [9]. They also serve as collagenase inhibitors [10], antiinfectives [11] and influenza virus polymerase inhibitors. These have been reported to inhibit stone formation in the urinary tract [12], for the treatment of disease

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related to connective tissue degradation, in HIV-1-infected Hg cells and to inhibit reterovirus replication. Their use as agonists [13], antagonists [14] and pesticides [15] are also important.

In past, several reports have been published [16,17] describing the measurement of hydrogen bonding capacity of various solutes involved in medicinal fields. Such parameters are important for medicinal chemist in the context of potential drug–receptor interactions. The present investigation describes the measurement of partition coefficient P, of ten hydroxamic acids in 1-octanol–water system. The logarithm of P is treated as lipophilicity of solute, which measures its relative affinity for two phases. This parameter is important to understand the solvation mechanisms responsible for their partition and to evaluate the hydrogen bonding capacity. They also provide structural information and establish its relation with biological activity [18]. The solute parameters derived are the molecular volume V_x, the hydrogen bond donor (HBD) strength α, the hydrogen bond acceptor (HBA) strength β, molecular dipole moment μ, and the values of Hanch pai, for these neutral compounds. In life sciences, the hydrogen bond is an important kind of specific molecular interaction. A knowledge of these parameters will help in designing the better drug delivery system and more accurately marked pharmaceuticals and pesticides.

2. Experimental

2.1. Synthesis

Hydroxamic acids were synthesised in this laboratory following the procedure reported in literature [19]. These were purified by recrystallisations from benzene thrice and dried in vacuum over phosphorous pentoxide for 24 h prior to use.

1-Octanol and other chemicals used were of analytical grade.

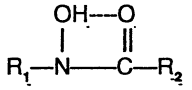
2.2. Measurement of partition coefficient

An aliquot of solution of desired hydroxamic acids (20–30 mg) in 1-octanol/chloroform was shaken with 100 ml of water at 303.65 K. The volumes of the two phases to be taken were dependent on the magnitude of distribution ratio. After separation, the two phases were analysed spectrophotometrically following the vanadium(V) method [20].

3. Results and discussion

3.1. 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 [19] 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 [21].

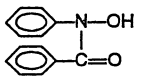
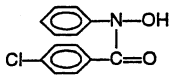
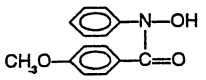
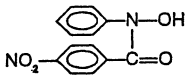
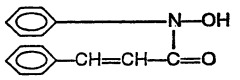
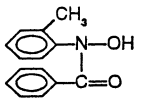
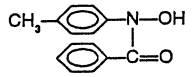
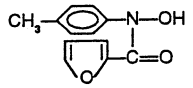
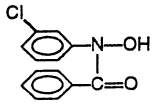
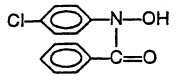


(I)

3.2. Hydrogen bond donor behaviour of hydroxamic acids

Hydrophobicity parameter as HBD acidity of ten hydroxamic acids is determined. Hydrophobic character or lipophilicity is a physico-chemical

Table 1
HBD parameters of hydroxamic acids

No.	Hydroxamic acids	Structure	log*P* (Cl/W)	log*P* (O/W)	log*P* (O/Cl)	V_x	εα	log*P* eq (4)
I	N–phenylbenzo–		2.47	2.50	0.03	172.25	0.56	2.26
II	N–phenyl–p–chlorobenzo–		2.41	2.52	0.11	200.65	0.67	2.81
III	N–phenyl–p–methoxybenzo–		2.39	2.54	0.15	225.00	0.76	2.15
IV	N–phenyl–p–nitrobenzo–		2.36	2.52	0.16	255.32	0.85	2.15
V	N–phenylcinnamo–		2.35	2.54	0.19	228.88	0.78	2.99
VI	N–o–tolylbenzo–		2.35	2.46	0.12	198.64	0.66	2.71
VII	N–p–tolylbenzo–		2.31	2.47	0.16	211.73	0.72	2.71
VIII	N–p–tolyl–2–furo–		2.00	2.41	0.41	160.46	0.64	1.57
IX	N–m–chlorophenylbenzo–		2.96	2.73	–0.23	225.99	0.64	2.81
X	N–p–chlorophenylbenzo–		2.47	2.49	0.02	174.02	0.56	2.81

property of solute denoted by log P (logarithm of partition coefficients).

Hydroxamic acids are extremely low soluble in water. Their partition coefficient between 1-octanol and water, log P(O/W) provides an accurate measure of their lipophilic character. Log P(O/W) is the ratio of concentration of a singular molecular species in two phases, water and 1-octanol, which are in equilibrium with each other. Values of log P(O/Cl) are calculated [21] following the expression,

$$\log P(\mathrm{O/Cl}) = \log P(\mathrm{O/W}) - \log P(\mathrm{Cl/W}) \quad (1)$$

where, log P(O/Cl) and log P(Cl/W) are the 1-octanol/chloroform and chloroform/water partition coefficients of the solute, respectively. In this system, solute acts as HBD acid and solvent as HBA base. It is assumed that there is no significant solute–solute as well as no strong solute–solvent interactions. Then, HBD strength is calculated [21] following the equation,

$$\log P(\mathrm{O/Cl}) = -1.0(0.01\mathrm{V_x}) + 3.20\varepsilon\alpha - 0.03 \quad (2)$$

where, $\varepsilon\alpha$ is the HBD strength and $\mathrm{V_x}$ is the molecular volume of solute ($\mathrm{V_x}$ = mol. wt./density).

The values of log P(Cl/W), log P(O/W) and log P(O/Cl) along with $\mathrm{V_x}$ and $\varepsilon\alpha$ of ten hydroxamic acids at 303.65 K are reported in Table 1. A log P(O/W) value of 2.50 for N-phenylbenzohydroxamic acid means that this hydrophobic compound is preferably found in 1-octanol phase. A knowledge of this hydrophobic character plays an important role to decide the solute's ability to interface with the biochemical systems.

3.3. Substitution constant, π

π is analogous to the Hammett σ constant and is obtained by the relation [22],

$$\pi_x = \log \mathrm{P_x} - \log \mathrm{P_H} \quad (3)$$

where, π is the logarithm of the partition coefficient of the function x, $\mathrm{P_H}$ is the parent or unsubstituted molecule and $\mathrm{P_x}$ is the derivative of $\mathrm{P_H}$. The following system shows the evaluation of π values.

$$\pi_{p\mathrm{Cl}} = \log P_{N\mathrm{phenyl}p\mathrm{Clbenzo}} - \log P_{N\mathrm{phenylbenzo}} = 0.019$$

$$\pi_{p\mathrm{OCH_3}} = \log P_{N\mathrm{phenyl}p\mathrm{methoxybenzo}} - \log P_{N\mathrm{phenylbenzo}} = 0.038$$

$$\pi_{p\mathrm{NO_2}} = \log P_{N\mathrm{phenyl}p\mathrm{nitrobenzo}} - \log P_{N\mathrm{phenylbenzo}} = 0.021$$

$$\pi_{\mathrm{-CH{=}CH-}} = \log P_{N\mathrm{phenylcinnamo}} - \log P_{N\mathrm{phenylbenzo}} = 0.037$$

$$\pi_{m\mathrm{Cl\ \ phenyl}} = \log P_{Nm\mathrm{Clphenylbenzo}} - \log P_{N\mathrm{phenylbenzo}} = 0.229$$

$$\pi_{p\mathrm{Cl\ \ phenyl}} = \log P_{Np\mathrm{Clphenylbenzo}} - \log P_{N\mathrm{phenylbenzo}} = -0.010$$

$$\pi_{\mathrm{OCH_3}} = \log P_{NO\mathrm{tolylbenzo}} - \log P_{N\mathrm{phenylbenzo}} = -0.044$$

$$\pi_{p\mathrm{CH_3}} = \log P_{Np\mathrm{tolylbenzo}} - \log P_{N\mathrm{phenylbenzo}} = -0.032$$

The π values calculated for variously substituted hydroxamic acids are presented here. Positive value for electron withdrawing group and negative value for electron donating group is obtained. When chlorine is present in the lower ring, the effect is minimised with a negative sign due to distance.

3.4. Calculation of log P from molecular volume

Bodor and Buchwald [23] have proposed a two parameter equation for calculating the logarithm of the partition coefficient (log P) 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,

$$\log P = 0.032\upsilon_{\mathrm{BB}} - 0.723N \quad (4)$$

where, log P is H-bond acceptor strength of the solute and υ_{BB} is the van der Waals volume. This equation is based on the partition process. The transfer of an organic molecule from water to 1-

octanol is favoured by greater energy required to create a cavity for the molecule in water. This energy is proportional to the size of the solute molecule and represented by first term on RHS of equation. On the other hand, the polar hydrophilic groups in the solute molecule will be compensated by its stronger H-bonding to water than 1-octanol, which favour the transfer of the solute from 1-octanol to water and this is represented by the second term on RHS of equation. Bodor and Buchwald found that, the energy required to form a cavity in solvent is proportional to the volume of the solute molecule.

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

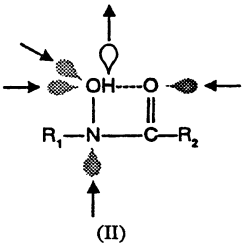
$$\upsilon_{BB} = 0.838\upsilon_W \quad (5)$$

in which υ_{BB} is related to υ_w linearly. υ_w is obtained by the addition of the volume increments of the constituent atoms. The increment values for different groups are taken from the literature [25]. These are 76.1 for $-C_6H_5$, 7.2 for >N–, 70.6 for $-C_6H_4$, 25.8 for –Cl, 6.2 for –O–, 8.1 for >C=, 5.5 for H(C), 28.1 for $-NO_2$, 22.1 for $-CH_3$, 11.1 for >CH–, 13.4 for –OH, 19.4 for >C=O groups. It is the measure of the cavity term in linear solvation energy relationships.

The second parameter, N, is obtained by summation of the integral N values associated with the different polar groups present in the molecule. The N parameter is a measure of total number of H-bonds between the hydrogen of water and hydrogen acceptor bonding sites of the various polar groups of solute molecules, as shown in structure II. According to Bodor and Buchwald [23], the –OH and –CO–, each have the value of $N = 2$, but in case of hydroxamic acids the value of N for –CO– is 1, due to the presence of intramolecular hydrogen bonding. For nitrogen also $N = 1$ and therefore, the total value of N for the general structure of hydroxamic acid is 4. For functional groups, $-OCH_3$ and $-NO_2$, the value of $N = 1$ in the corresponding compounds. The values of log P calculated from the equations (4) is presented in Table 1.

Table 2
HBA parameters of hydroxamic acids

Number	μ	εβ
I	0.020	1.35
II	0.018	1.70
III	0.033	1.99
IV	0.036	2.36
V	0.020	2.03
VI	0.023	1.69
VII	0.027	1.85
VIII	0.026	1.24
IX	0.013	1.94
X	0.018	1.38



(II)

3.5. Hydrogen bond acceptor behaviour of hydroxamic acids

A molecule is said to be HBA, when it contained an atom, which is capable of accepting a positive hydrogen atom, a reverse phenomenon of HBD system. Following the method of Leo and Hoekman [26], the HBA strength is calculated following the equation,

$$\log P(\mathrm{O/W}) = 3.67(0.01\mathrm{V_x}) - 0.40(0.1\mu^2) - 0.0\varepsilon\alpha - 3.00\varepsilon\beta + 0.24 \quad (6)$$

where, β is HBA strength and ε represents the effective sum of interactions of multifunctional groups in hydroxamic acids. The important parameter, μ, is the molecular dipole moment. It is obtained following the expression,

$$\mathrm{P_t} = \mathrm{R_M} + \frac{4\pi \mathrm{N_o}}{9kT}\,\mu^2 \quad (7)$$

where, $\mathrm{P_t}$ is total polarisation, $\mathrm{R_M}$ is molecular

refraction, N_o is Avogadro number ($=6.023\times10^{23}$ g atom), k is Boltzmann constant (1.38×10^{-16} ergs/° per mol) and T is absolute temperature (303.65 K). The calculated values of μ and εβ are presented in Table 2.

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. Hydroxamic acids serve as antagonists [14] and their drug–receptor interaction can be explained on the basis of H-bonding, such information is useful for medicinal chemists.

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