

Study of Protonation Behaviour and Distribution Ratios of Hydroxamic Acids in Hydrochloric and Perchloric Acid Solutions-Through Hammett Acidity Function, Bunnett-Olsen and Excess Acidity Method

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Abstract – The protonation parameters, dissociation constants (pK_{BH^+}) of conjugate acid, slope values (m , ϕ and m^*) and correlation coefficients (r) of hydroxamic acids were determined by Hammett acidity function method, Bunnett-Olsen method and excess acidity method in hydrochloric and perchloric acid solutions. Effect of acid concentration on partition and percentage protonation was also studied. pK_{BH^+} values show that hydroxamic acids do not behave as Hammett bases, but hydroxamic acids behave as weak bases in strong acidic solutions. The values of pK_{BH^+} obtained through Bunnett-Olsen method and excess acidity method were compared with the Hammett acidity function. ChemAxon's MarvinSketch 6.1.5 software was also used for determining pK_a , pI and microspecies distribution (%) of hydroxamic acids with pH. Hydrogen donor and acceptor values and $\log D$ were also obtained. The results show that N-p-chlorophenyl-4-bromobenzohydroxamic acid has the highest pK_a and lowest $\log D$ values. On the contrary, N-phenyl-3,5-dinitrobenzohydroxamic acid has lowest the pK_a and highest $\log D$ values.

Key words: Dissociation constant, hydroxamic acid, $\log D$ and protonation parameters

1. Introduction

The protonation constant is a quantitative measure of the strength of an acid/base in solution that allows the calculation of the ratio of neutral and charged species at any pH, in addition to the basic or acidic properties of the compound. The acid-base dissociation constant has an ample effect on the biopharmaceutical properties of drugs and chemicals. It helps in understanding the ionic form in which a molecule exists at different pH [1]. Kostianen *et al.* (2003) reported that the protonation constant influences lipophilicity, solubility and permeability of a drug, which has a direct effect on its pharmacokinetic characteristics, absorption, distribution, metabolism and excretion (ADME) [2]. Several biochemical reactions occurring inside living organisms are also affected by pH.

Early investigators have already reported that hydroxamic acids are a remarkable class of compounds as they have a broad spectrum of applicability [3-5]. They are used as analytical reagents for organic and inorganic analyses and find medical applications as well. Vernon and Eccles (1976) and Sharma *et al.* (2013) reported that poly(hydroxamic acid) chelating resin can be used for extraction of iron from various salts [6-7]. Hassan *et al.* (2011) reported that poly-hydroxamic acids are useful for separation of Zr (IV) from Y (III)

and Sr (II) and purification of Zr [8]. Gidwani *et al.* (2009) reported that a new chromogenic calixarene with hydroxamic acid acts as chelating agent for sequential separation of Ti (IV) and Zr (IV) [9]. Farkas *et al.* (2001) reported that complexes formed between iron (II) and different siderophore model hydroxamic acids may contribute to a better understanding of the different biological processes [10]. Jiao *et al.* (2017) reported the role of poly(amidoxime-hydroxamic acid) cellulose derivative in heavy metal ion removal [11]. Therefore, the present investigation was undertaken to study the protonation behaviour and distribution ratios of hydroxamic acids.

2. Materials and Methods

N-phenyl-2-nitrobenzohydroxamic acid, N-phenyl-3,5-dinitrobenzohydroxamic acid, N-m-chlorophenylbenzohydroxamic acid, N-m-chlorophenyl-2-methoxybenzohydroxamic acid and N-p-chlorophenyl-4-bromobenzohydroxamic acid were prepared according to the reported literature [12,13]. Their purity was ascertained by determining their melting points, UV and IR analyses. Analytical grade chemicals were purchased from Merck (Japan).

The protonation equilibria of hydroxamic acids were evaluated as a function of pH in hydrochloric acid and perchloric acid. Analytical grade carbon tetrachloride and hydrochloric acid were used for distribution ratio determination. Hydrochloric acid was standardized with sodium hydroxide solution, which was titrated against potassium hydrogen phthalate using phenolphthalein as indicator [14,15]. Acidic solutions of different concentrations were prepared by dilu-

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tion with distilled water. The protonation constant and distribution ratio were calculated from Equations (1) and (2), respectively.

$$pK_b = H_0 + \frac{(K_D + D)}{D} \quad (1)$$

$$K_D = D + \frac{Dh_0}{K_{BH^+}} \quad (2)$$

where, H_0 is Hammett acidity function, K_D is thermodynamic distribution constant of hydroxamic acid, D is the distribution ratio and K_{BH^+} is the acid dissociation constant. A saturated solution of ammonium metavanadate was prepared in distilled water. Chloroform was distilled after shaking five times with equal volume of water to remove ethanol and was stored in a cool place. HCl was used to maintain the acidity during extraction. The hydroxamic acid concentration was determined in both the phases spectrophotometrically through the vanadium (V) method. Hydroxamic acids form water insoluble coloured complexes with pentavalent ions, in presence of hydrochloric acid. Extraction of the colored complex with chloroform forms the basis of its spectrophotometric estimation.

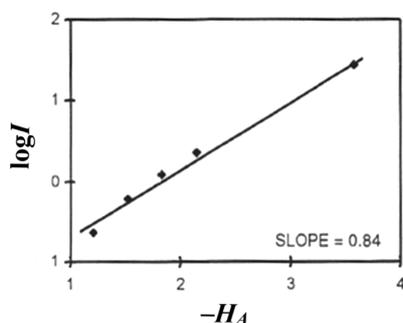
An aliquot of the solution was transferred to a separating funnel containing 10 ml of chloroform for the analysis of organic phase. 5 ml of aqueous saturated solution of ammonium metavanadate and hydrochloric acid was added. The pH of the solution was maintained between 3.5-7 for maximum color development. The two phases were vigorously shaken for 2 minutes and were allowed to separate. The colored organic layer was transferred to a beaker containing 1 to

2 grams of anhydrous sodium sulfate. The aqueous phase was washed with chloroform. The washings and extract were transferred to a volumetric flask after drying over sodium sulfate. The absorbance was measured against chloroform as blank. Batch extraction with chloroform was applied for the analysis of aqueous phase. This chloroform layer was used to develop the colored complex. Hydroxamic acid concentration was obtained in each phase by calibration curve. Solvent extraction method was used for determining total concentration of molecular and protonated species. Several water immiscible solvents were tried for the extraction of coloured complex from aqueous phase.

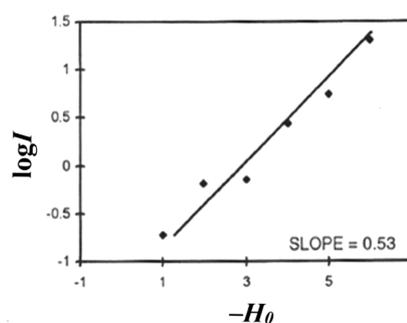
Hydroxamic acids behave as weak organic bases in the presence of strong mineral acid. But these concentrated solutions are non-ideal as they become much more acidic than their concentrations below a pH of about 1.5. Therefore, the pH scale cannot be used in such cases. Acidity scales known as acidity functions or excess acidities have to be used in such non-ideal media. Acidity constants outside the accessible range in water can also be estimated, which provides help in understanding the mechanisms of acid- and base-catalyzed reactions [16]. The protonation studies of N-arylsubstituted hydroxamic acids were done through Hammett Acidity Function Method (HAFM), Bunnett-Olsen method (BOM) and excess acidity method (EAM).

2-1. Excess acidity method (EAM)

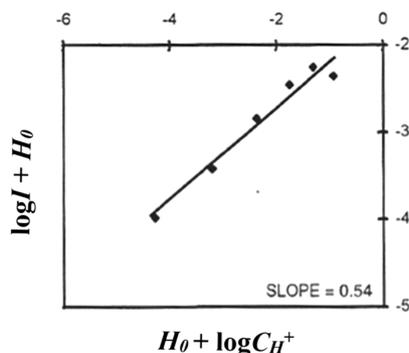
Excess acidity, also known as X-function, is used for the determination of acidity constant or acid dissociation constant of weak



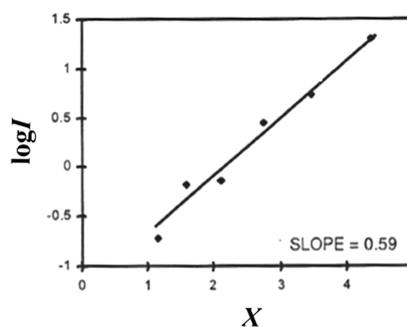
Plot of $\log I$ vs. $-H_A$ for HAFM



Plot of $\log I$ vs. $-H_0$ for HAFM



Plot of $\log I + H_0$ vs. $H_0 + \log C_{H^+}$ for BOM



Plot of $\log I$ vs. X for EAM

Fig. 1. Slopes m , ϕ and m^* for N-p-chlorophenyl-4-bromobenzo hydroxamic acid.

bases. The extrapolation to the aqueous standard state is used. This method for obtaining acidity constants, in spite of medium effects, is based on excess medium acidity, X , which represents the excess acidity [17,18]. Buglass *et al.* (1971) and Bunnett and Olsen (1966) reported that excess acidity is the difference between the observed acidity and the acidity in case of ideal solution [19,20]. Equation (3) shows the general thermodynamic equation for the definition of

$$\log(C_{BH^+}/C_B) - \log C_{H^+} = \log(f_B f_{BH^+} / f_{BH^+}) + pK_{BH^+} \quad (3)$$

where, BH^+ is protonated hydroxamic acid and pK_{BH^+} is protonation constant, C is the molar concentration and f is the molar activity coefficient. On assuming the activity coefficient term as a linear function of a similar term for a standard base, B , slope, in this equation m^* and the X -function (Fig. 1), Equation (4) is obtained

$$\log(f_B f_{BH^+} / f_{BH^+}) = m^* \log(f_B f_{H^+} / f_{BH^+}) = m^* X \quad (4)$$

The concept of excess medium acidity involves proton concentration and is summarized as Equation (5)

$$\log I - \log C_{H^+} = m^* X + pK_{BH^+} \quad (5)$$

where, C_{H^+} is the proton concentration and m^* is the slope.

2-2. Hammett acidity function method (HAFM)

The Hammett acidity function (H_0) is a thermodynamic quantitative measure of the acidic strength of nonaqueous or concentrated Bronsted acids. Lower Hammett values show stronger ability of the acid to transfer a proton [21]. Evaluation of pK_{BH^+} requires ionization ratio (I) measurement at various acid concentration obtained from Equation (6).

$$I = \frac{C_{BH^+}}{C_B} \quad (6)$$

where, C_{BH^+} and C_B are the molar concentration of protonated and unprotonated hydroxamic acid, respectively. Thus ionization ratio, I , is measured by Equation (7),

$$I = (K_D - D) / D \quad (7)$$

where, K_D and D are the thermodynamic distribution constant and distribution ratio of hydroxamic acids between the organic layer and aqueous acid, respectively. K_D is estimated from Equation (8),

$$a \Sigma X + b \Sigma X^2 = \Sigma XY$$

$$a \Sigma X + b \Sigma X^2 = \Sigma XY \quad (8)$$

where, n is the number of observations, i.e., range of percentage of sulfuric acid, X is D/h_0 , where, D is the distribution ratio and h_0 is Hammett activity coefficient which is obtained by Equation (9),

$$H_0 = -\log h_0 \quad (9)$$

where, H_0 is the Hammett acidity function. Distribution ratio, D , of hydroxamic acids was measured between an organic solvent and aqueous hydrochloric acid and aqueous perchloric acid, respectively.

2-3. Bunnett-olsen method (BOM)

The linear free energy approach of Bunnett and Olsen can be used for determining [22] using Equation (10), provided the plot of $\log I + H_0$ vs. ($H_0 + \log C_{H^+}$) is linear.

$$\log I + H_0 = \phi(H_0 + \log C_{H^+}) + pK_{BH^+} \quad (10)$$

The slope is a measure of susceptibility of the equilibrium to changing acid concentration and $(1-\phi)$ is the slope of free energy relationship.

ChemAxon's MarvinSketch 6.1.5 software was used to study the hydrogen donor and acceptor strength along with protonation behaviour of hydroxamic acids. The variation of $\log D$ of hydroxamic acids with pH was also studied [23].

3. Results and discussion

In the presence of a strong mineral acid, hydroxamic acids behave as weak organic bases. Therefore, their protonation behaviour was studied in aqueous solution of hydrochloric acid and perchloric acid. Hydroxamic acid (B) is protonated in presence of aqueous hydrochloric acid solution as depicted by Equation (11),



The distribution ratio, D of a base between the organic solvent and aqueous acidic solution is a function of their respective concentration. It was calculated between organic solvent and aqueous perchloric acid and hydrochloric acid solutions. The values obtained are reported in Tables 1 and 2.

X -values for the aqueous hydrochloric acid and perchloric acid

Table 1. Distribution ratios, D of N-arylhydroxamic acids between organic solvent and aqueous perchloric acid solutions

S. No.	Hydroxamic acids	Molarity of perchloric acid									
		1	2	3	4	5	6	7	8	9	10
	N-phenyl-2-nitrobenzo-	10.00	7.51	5.73	4.41	3.81	2.75	2.25	2.00	1.83	0.11
	N-phenyl-3,5-dinitrobenzo-	40.52	32.00	27.01	23.10	18.51	13.49	12.11	7.51	5.00	3.00
	N-m-chlorophenylbenzo-	40.40	30.21	21.00	15.61	12.01	8.60	4.95	3.50	1.40	0.20
	N-m-chlorophenyl-2-methoxybenzo-	34.44	28.01	21.21	15.01	10.31	7.22	4.61	2.62	1.21	0.21
	N-p-chlorophenyl-4-bromobenzo-	106.01	87.51	72.50	58.00	44.51	32.00	22.21	14.01	8.20	2.50

Table 2. Distribution ratios, D of N-arylhydroxamic acids between organic solvent and aqueous hydrochloric acid solutions

S. No.	Hydroxamic acid	Molarity of hydrochloric acid									
		1	2	3	4	5	6	7	8	9	10
1	N-phenyl-2-nitrobenzo-	11.80	11.00	9.91	8.48	6.91	5.95	4.21	3.90	3.25	3.00
2	N-phenyl-3,5-dinitrobenzo-	53.50	51.30	48.51	47.20	45.00	35.61	32.40	24.51	15.65	7.50
3	N-m-chlorophenylbenzo-	69.01	72.21	65.11	53.03	45.04	32.00	25.01	16.10	10.00	6.21
4	N-m-chlorophenyl-2-methoxybenzo-	60.55	64.21	60.10	54.01	45.03	35.00	26.01	16.02	8.00	5.21
5	N-p-chlorophenyl-4-bromobenzo-	655.23	640.40	615.50	565.10	490.01	405.02	325.00	235.13	135.14	80.00

Table 3. Values of H_A , H_0 and X as a function of acid concentrations

S. No.	Molarity, M	Hydrochloric acid			Perchloric acid		
		$-H_A$	$-H_0$	X	$-H_A$	$-H_0$	X
1	1	0.50	0.20	0.500	0.06	0.02	0.120
2	2	0.78	0.69	0.479	0.50	0.49	0.280
3	3	1.04	1.05	0.563	0.86	0.87	0.490
4	4	1.43	1.40	0.828	1.20	1.23	0.725
5	5	1.73	1.76	1.031	1.51	1.62	1.145
6	6	2.02	2.12	1.242	1.83	2.07	1.585
7	7	2.33	2.53	1.485	2.15	2.60	2.100
8	8	2.60	2.93	1.697	2.60	3.29	2.730
9	9	2.88	3.31	1.926	3.09	4.17	3.470
10	10	3.18	3.60	2.180	3.56	5.28	4.365

system are given in Table 3 along with corresponding H_A and H_0 values. The slopes, m , are the plots of $\log I$ vs. H_0/H_A , ϕ are the plots of $(H_0 + \log C_{H^+})$ vs. $(\log I + H_0)$ and m^* are the plots of $\log I$ vs. X for HAFM, BOM and EAM methods, respectively. If slope = 1, then B is a Hammett base. But the slopes are lower than 1.0 in case of N-arylhydroxamic acids. Typical protonation slope values for the carbonyl group are nearly 0.6 [20], and that of amides is between 0.51-0.57 [18]. Similar values have been obtained in the present investigation as well. Its value ranges between 0.42 to 0.58 in HAFM, 0.42 to 0.64 in BOM and 0.48 to 0.59 in EAM. Therefore, it can be concluded that hydroxamic acids do not behave as Hammett bases. The pK_{BH^+} is not thermodynamic quantity in such cases, but it represents the H_0 values of the acids, in which the base is half-protonated.

The values of D as a function of aqueous perchloric acid and aqueous hydrochloric acid concentrations are presented in Tables 1 and 2, respectively. Table 3 presents the data for H_A , H_0 and X as a function of acid concentrations. Table 4 reports the protonation parameters of N-arylsubstituted hydroxamic acids in perchloric acid based on HAFM, BOM and EAM methods. The correlation coefficients for these plots are good enough and the ϕ values are in the expected range. N-arylhydroxamic acids are weak bases and are protonated only in the presence of strong acid. Therefore, 4–10 M acidic solu-

tions are used. The effect of substituents on acidity constants derived from HAFM, BOM and EAM are similar. The substituent position produces base strengthening and weakening effects. Generally, the introduction of alkyl and alkoxy group increases basicity due to +I effect, whereas halogen group decreases basicity due to -I effect. Hydroxamic acids containing nitro groups are less basic than unsubstituted products due to electron withdrawing nature of nitro groups. The introduction of two nitro groups is even more effective. N-phenyl-3,5-dinitrobenzohydroxamic acid has pK_{BH^+} value -3.19, which is less than that of N-phenyl-2-nitrobenzohydroxamic acid with pK_{BH^+} value -2.92.

ChemAxon's MarvinSketch 6.1.5 software [23] was used to obtain the pKa , pI and microspecies distribution (%) of hydroxamic acids with pH. The Microspecies distribution (%) curve of hydroxamic acids (Fig. 2) shows that the concentration of protonated species decreases with increase in pH value, whereas the concentration of unprotonated species increases with pH value. The variation of Hydrogen acceptor and donor values along with $\log D$ of hydroxamic acids with pH was also obtained by using ChemAxon's MarvinSketch 6.1.5 software. The H acceptor and donor values (Fig. 3A and 3B) show that all these compounds have similar hydrogen donor values, but the hydrogen acceptor values vary. N-phenyl-3,5-dinitro-

Table 4. Protonation parameters of N-arylsubstituted hydroxamic acids in perchloric acid based on HAFM, BOM and EAM methods

S. No.	Hydroxamic acids	K_D	pKa	pI	HAFM				BOM			EAM				
					pK_{BH^+}	m	r	σ	pK_{BH^+}	ϕ	r	σ	pK_{BH^+}	m^*	r	σ
1	N-phenyl-2-nitrobenzo-	4.92	8.11	-	-2.92	0.53	0.935	0.31	-1.70	0.52	0.920	0.32	-2.07	0.58	0.931	0.33
2	N-phenyl-3,5-dinitrobenzo-	20.24	8.01	-	-3.19	0.42	0.919	0.27	-1.41	0.64	0.964	0.25	-2.09	0.48	0.932	0.25
3	N-m-chlorophenylbenzo-	18.13	8.27	1.71	-2.46	0.58	0.992	0.11	-1.59	0.42	0.974	0.14	-2.30	0.57	0.991	0.09
4	N-m-chlorophenyl-2-methoxybenzo-	15.84	8.13	-	-2.37	0.50	0.994	0.13	-1.04	0.56	0.989	0.14	-1.58	0.59	0.992	0.12
5	N-p-chlorophenyl-4-bromobenzo-	52.88	8.28	1.72	-2.92	0.53	0.986	0.14	-1.64	0.54	0.984	0.14	-2.14	0.59	0.989	0.12

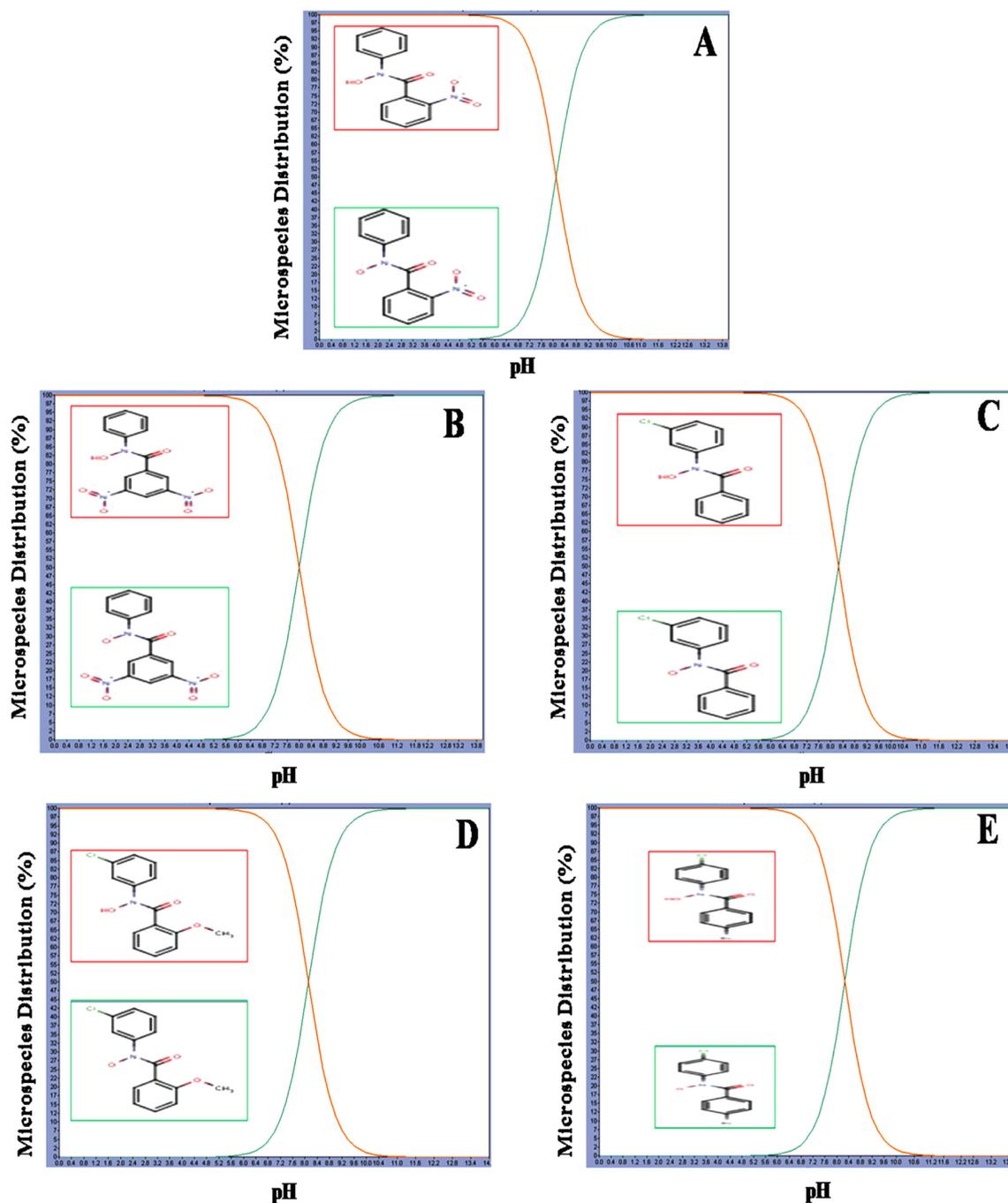


Fig. 2. Microspecies distribution (%) of (A) N-phenyl-2-nitrobenzohydroxamic acid (B) N-phenyl-3,5-dinitrobenzohydroxamic acid (C) N-m-chlorophenylbenzohydroxamic acid (D) N-m-chlorophenyl-2-methoxybenzohydroxamic acid and (E) N-p-chlorophenyl-4-bromobenzohydroxamic acid with pH.

benzohydroxamic acid has the highest hydrogen acceptor value; however, N-p-chlorophenyl-4-bromobenzohydroxamic acid has the lowest value. Fig. 3C shows the variation of $\log D$ of hydroxamic acids with pH. N-p-chlorophenyl-4-bromobenzohydroxamic acid shows highest $\log D$ value between the pH range considered for this theoretical study, whereas N-phenyl-3,5-dinitrobenzohydroxamic acid shows the lowest $\log D$ value. These findings are consistent with the fact that the compound N-p-chlorophenyl-4-bromobenzohydroxamic acid having the lowest hydrogen acceptor value and the

highest pK_a value has low ionizing ability compared to other hydroxamic acids; therefore it has higher $\log D$ value as well. Similarly, the highest hydrogen acceptor value and the lowest pK_a value in case of N-phenyl-3,5-dinitrobenzohydroxamic acid can be correlated to its lower $\log D$ value.

Vernon and Khorassani (1978) reported caprylohydroxamic acid as a suitable extractant for the removal of titanium (IV), vanadium (V), chromium (VI) molybdenum (VI) and uranium (VI) from 6M hydrochloric acid [24]. Pande and Tandon (1991) studied the rela-

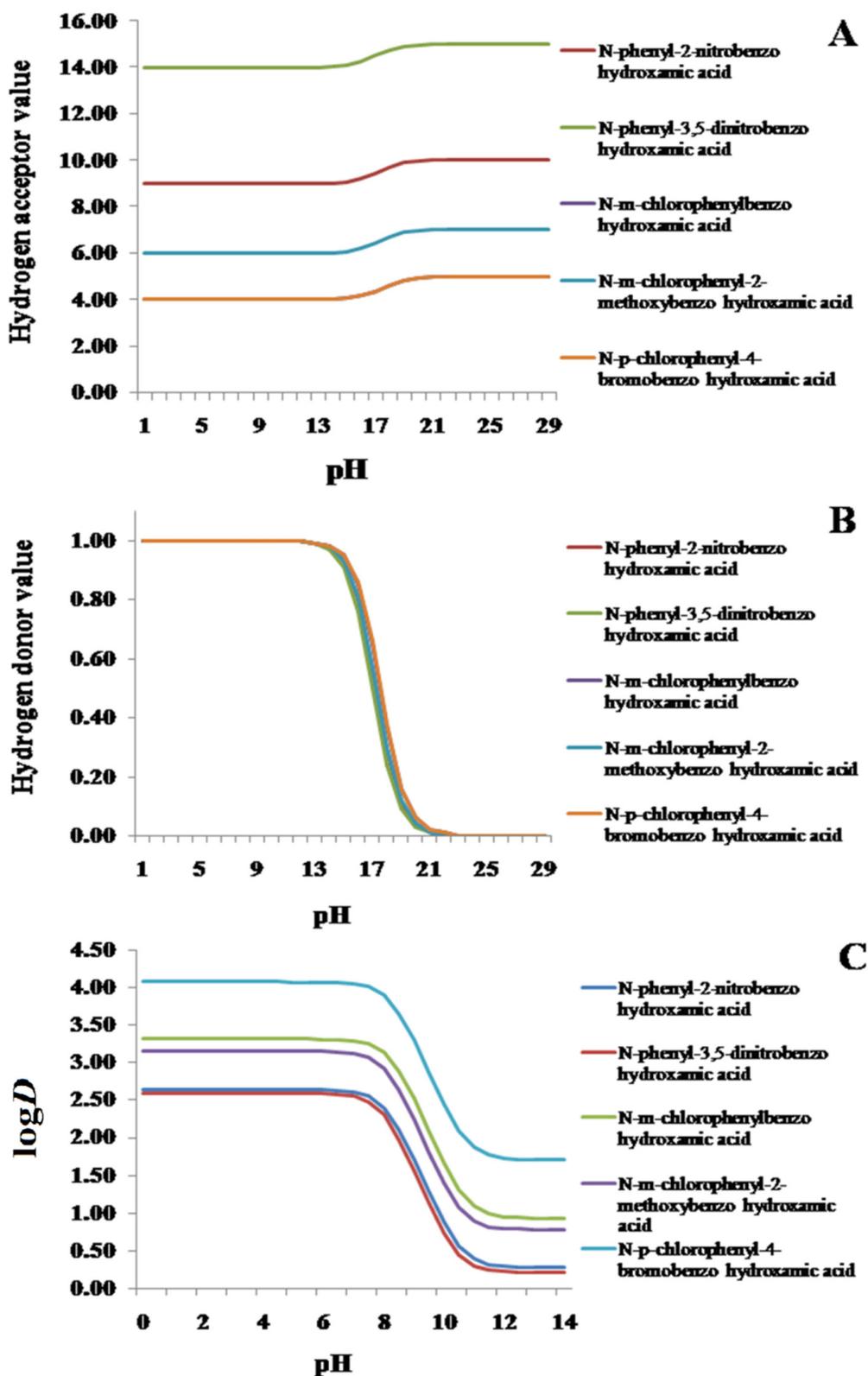


Fig. 3. Variation of (A) Hydrogen acceptor, (B) Hydrogen donor values and (C) $\log D$ of hydroxamic acids with pH.

tion between protonation and solvent extraction of N-p-tolylbenzo-hydroxamic acid in hydrochloric acid medium [25]. They reported that the solubility and distribution ratio as well as the metal-extracting properties of these reagents in acid solutions depends on the for-

mation of a protonated species. Knowledge of protonation constant is essential for the determination of extraction coefficients of their metal chelates. Monzyk (1992) reported that N-ethyl hydroxamic acids act as useful metal chelants [26]. Cheng *et al.* (2012) also reported

the extraction and separation of nickel and cobalt with hydroxamic acids [27]. Ghosh (2000) reported that an accurate knowledge of the protonation and the deprotonation behaviour is required both for structure-reactivity correlations and detailed analysis of acid-base catalyzed reactions [28]. Venturini *et al.* (2001) reported hydroxamic acids as weak base indicators and studied protonation in strong acid media [29]. Beccia (2012) discussed the hydroxamic acids interactions with metals in aqueous and micellar media along with their protonation behaviour [30]. Therefore, the protonation behaviour and distribution ratios of the hydroxamic acids calculated in the present investigation will form a basis for the determination of their metal extractant ability.

4. Conclusions

The present investigation shows the protonation behaviour and distribution ratios of hydroxamic acids, which behave as weak organic bases in hydrochloric and perchloric acid solutions. N-arylhydroxamic acids are weak bases and are protonated only in the presence of strong acid. Three different approaches, Hammett acidity function method, Bunnett-Olsen method and excess acidity method were used to study protonation parameters. The substituent position affects base strength, and introduction of alkyl and alkoxy group increases basicity, whereas halogen group decreases basicity. Nitro groups substituted hydroxamic acids are less basic than unsubstituted products. The physico-chemical parameters of these compounds can be used further for QSAR study.

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