

RESEARCH ARTICLE

The pK_a values of ligands and stability constants of the complexes of Fe(III), Cu(II) and Ni(II) with some hydroxamic acids: a comparative study of three different potentiometric methods

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Abstract: The determination of ionization constants and the chelating properties exhibited by a series of derivatives of N-phenylbenzohydroxamic acid, N-phenyllaurohydroxamic acid and 1-naphthalenemethyliminodiacetohydroxamic acid type ligands toward Fe(III), Cu(II) and Ni(II) ions were studied by pH-metric method. The data obtained by pH-metric method were analyzed by three standard methods namely, Bjerrum's method, Irving and Rossotti method, and Sarkar and Kruck method. The ionization constants of hydroxamic acids and the stability constants of metal-ligand complexes were calculated using the above three methods and it was found that the values obtained closely agreed with each other. The evaluation of the calculated stability constants shows that the substituent effect on the N-phenyl ring leads to more basic character at the carbonyl oxygen and it influences significantly the stability of the complex species formed by the hydroxamate moieties. The stability constant and the species distribution of Fe(III) - 1-naphthalenemethyliminodiacetohydroxamic acid system at physiological pH range (6.8 - 7.2) suggest that 1-naphthalenemethyliminodiacetohydroxamic acid is an effective source for the iron overload.

Keywords: Bjerrum method, hydroxamic acid, Irving and Rossotti method, Sarkar and Kruck method, stability constant

INTRODUCTION

Hydroxamic acids are a group of naturally occurring or synthetic weak organic acids having the general formula $RC(=O)N(R')OH$. They are weaker proton donors than the structurally related carboxylic acids $RC(=O)OH$. These acids are widespread in the tissues of plants, in metabolites of bacteria and fungi, including complex compounds. With regard to the significant complex-forming ability of hydroxamic acid, the biological activity of the ligands must be closely correlated with the formation of their

metal complexes^{1,2}. In this study, potentiometric data were analyzed by three standard analytical procedures namely, Bjerrum method³, Irving and Rossotti method⁴, and Sarkar and Kruck method⁵ and the values obtained for the ionization constants and the stability constants of the complexes of Fe(III), Cu(II) and Ni(II) formed with some hydroxamic acids were compared.

METHODS AND MATERIALS

Calculation of ionization constant: Bjerrum³ used Expression (1) to calculate the \bar{n}_H values (average number of hydrogen ions bound to the ligand) at different pH values and plotted a graph \bar{n}_H Vs pH and equated the value of pK_a to the value of pH at which the value of $\bar{n}_H = 0.5$.

$$\bar{n}_H = j + \frac{[HClO_4] - [NaOH] + [OH^-] - [H^+]}{[H_jA]} \quad \dots\dots(1)$$

j is the total number of ionizable hydrogen in the ligand, $[H_jA]$ is calculated amount of H_jA added, $[NaOH]$ is calculated amount of NaOH added, $[HClO_4]$ is calculated amount of $HClO_4$ added, $[H^+] = \text{antilog}(-pH)$ and $[OH^-] = K_w / [H^+]$.

H. M. Irving and H. S. Rossotti⁴ used Expression (2) to calculate the \bar{n}_H values at different pH values and used Expression(3) to calculate the ionization constant of a ligand.

$$\bar{n}_H = j + \frac{(\psi' - \psi'') ([HClO_4] + [NaOH])}{(V^0 + \psi') [H_jA]} \quad \dots\dots (2)$$

$$\log \left(\frac{(\bar{n}_H - j + i)}{(j - i + 1 - \bar{n}_H)} \right) + pH = pK_{a_i} \quad \dots\dots (3)$$

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where V^0 is the initial volume of the solution, V^I and V^{II} are the volumes of the base used to bring the solutions (i) mineral acid alone and (ii) a mixture of same amount of mineral acid and the ligand to the same pH value.

Theo P. A. Kruck and Bibudhendra Sarkar⁵ performed a series of titrations of weak acid, each differing in C_A where C_A is the total concentration of ligand in all forms and used Expression (4) to calculate the values of \bar{n}_H at different pH values.

$$\bar{n}_H = j - \left(\frac{\partial C_{NaOH}}{\partial C_A} \right)_H \quad \text{..... (4)}$$

Calculation of stability constants: Bjerrum³ used Expression (5) and (6) to calculate the stability constants values.

$$\bar{n}_A = \frac{T_A^0 - (T_H - [H]) / \bar{n}_H}{T_M^0} \quad \text{..... (5)}$$

$$\sum_{i=0}^n (i - \bar{n}_A) \beta_i [A]^i = 0 \quad \text{..... (6)}$$

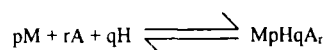
where; \bar{A} is the total concentration of ligand; A, M is the total concentration of metal; M, T_H is the total concentration of proton (bound + unbound) present in the solution and \bar{n}_A is the average number of ligands bound per metal.

Irving and Rossotti⁴ used Expression (2), (7), (8) and (9) to calculate the stability constants values.

$$pA = -\log [A] = \log \left\{ \frac{\sum_{i=0}^j \beta_i [H]^i}{T_A^0 - \bar{n}_A T_M^0} \left(\frac{V^0 + V^{III}}{V^0} \right) \right\} \quad \text{..... (7)}$$

$$\log K_i = pA - \log \left(\frac{i - \bar{n}_A}{\bar{n}_A - i + 1} \right) \quad \text{..... (8)}$$

$$\bar{n}_A = \frac{(V^{III} - V^{II}) ([HClO_4] + [NaOH])}{(V^0 + V^{II}) \bar{n}_H T_M^0} \quad \text{..... (9)}$$



$$pA_r = pA_0 - j pH + \sum_{i=1}^j pK_i + \int_{pH_0}^{pH} \left(\frac{\partial C_{NaOH}}{\partial C_A} \right)_H dpH \quad \text{..... (10)}$$

$$pM_r = pM_0 + \int_{pH_0}^{pH} \left(\frac{\partial C_M}{\partial C_M} \right)_H dpH \quad \text{..... (11)}$$

$$\beta_{pqr} = \frac{[MpHqA_r]}{[M]^p [H]^q [A]^r} \quad \text{..... (12)}$$

$$(C_M - [M_r]) = \sum p \beta_{pqr} [M_r]^p [H]^q [A]^r \quad \text{..... (13)}$$

where V^{III} is the volume of base used to bring the mixture of solution mineral acid, ligand and metal ion to a same pH value, K_i is the stepwise stability constant and β_i is the overall stability constant.

Sarkar and Kruck⁵ used Expression (10), (11), (12) and (13) to calculate the stability constants and species distribution of the complexes formed in the following equilibrium.

Experimental: Potentiometric titrations were performed using a Metrohm 702 SM Titrino Auto Titrator and all titrations were thermostated to 25 °C using a water circulating pump. Metrohm 6.0203.100 combined pH glass electrode was used to collect the experimental data. GBC 932 plus atomic absorption spectrometer was used to measure the concentration of the metal ions in the stock solutions. Absorption spectra were obtained using Jasco V-500 and Helios thermo spectronic spectrophotometer. ¹H NMR spectra were obtained on a Bruker 200 MHz and Varian Mercury-300 MHz instrument. Infrared spectra were recorded on a Thermo Nicolet AVATAR-320 FT/IR spectrophotometer.

All chemicals were of analytical reagent grade from Aldrich or Merck of highest purity available and used without any further purification, except for vacuum drying. HPLC grade methanol solvent was used in all spectroscopic measurements. The solutions were prepared with double distilled water. All glassware were soaked overnight in a 5% nitric acid solution and carefully cleaned with doubly distilled water and dried in a dust-free environment prior to use. The standard stock solutions of iron(III), copper(II) and nickel(II) were prepared from their corresponding sulphate salts. All measurements were carried out at a constant ionic strength using 0.2 mol dm⁻³ NaClO₄. Carbonate free NaOH solution of known concentration (about 0.25 mol dm⁻³) was used as the titrant. The pH-metric titrations were performed throughout the pH range of 2.0-12.5 or below the precipitation on samples of

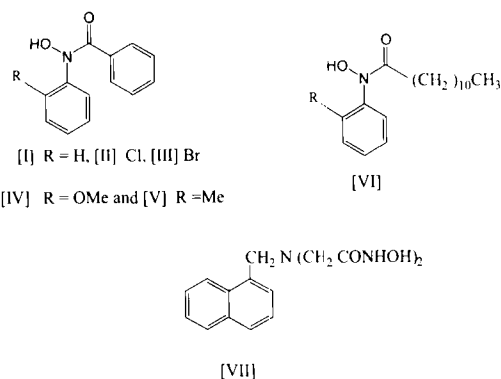


Figure 1: Structures of compounds synthesized in this study

100 cm³. The ligand concentrations were varied in the range of 1.0×10^{-3} mol dm⁻³ to 5.0×10^{-3} mol dm⁻³. In all cases, the metal to ligand ratio was maintained greater than 1:5 to avoid hydrolysis and possible polymerization. Since the ligands and also the metal complexes are insoluble in water as well as in water-methanol medium (above pH = 7), 1:1 water-ethanol solvent system was maintained throughout the experiment except for N-phenyllauroylhydroxamic acid for which 1:3 water-ethanol solvent system was employed.

Synthesis of compounds [I]-[VI]: N-phenyllauroylhydroxamic acid [VI], N-phenylbenzohydroxamic acid [I] and its phenyl derivatives such as (o-chloro)phenyl-[II], (o-bromo)phenyl-[III], (o-methoxy)phenyl-[IV] and (o-methyl)phenyl-[V], benzohydroxamic acids were synthesized by the general procedure as described in the literature⁶ (reduction of appropriate nitro compound and then coupled with benzoyl chloride for compounds [I]-[V] and with lauroyl chloride for compound [VI]).

Synthesis of compound [VII]: Solutions of 1-naphthalenemethylamine (2.8 cm³, 0.019 mol) in 50 cm³ dry acetonitrile and ethylbromoacetate (4.40 cm³, 0.04 mol) in 25 cm³ dry acetonitrile were added simultaneously and dropwise over a period of 4 h to a warm magnetically stirred suspension of potassium carbonate (25 g) in 50 cm³ dry acetonitrile. The resulting mixture was refluxed for 16 h on a water bath, cooled to room temperature, concentrated, filtered, and the filtrate was evaporated to dryness under reduced pressure to give 1-naphthalenemethyliminodiethylacetate as an off white product (yield 80%).

A solution of diethyl-1-naphthalenemethyliminodiacetate (3.0 g, 0.01 mol) in absolute ethanol (25 cm³) was added dropwise while stirring into a solution of hydroxylamine (0.02 mol) in absolute ethanol (30 cm³) at pH 8 cooled in an ice-water bath. The resulting solution was stirred for further sixteen hours at ice-water temperature, and filtered. The filtrate was concentrated and cooled in ice-water bath to obtain 1-naphthalenemethyliminodiacetohydroxamic acid [VII], as a white product (yield 88%).

RESULTS AND DISCUSSION

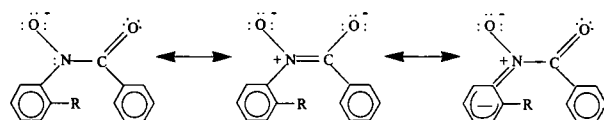


Figure 2: Resonance structures of phenyl derivatives of N-phenylbenzohydroxamic acid anion

The electron accepting nature of the phenyl group, the substituents of phenyl ring derivatives on the N atom (R_N substituents) reflect a greater effect due to both resonance and inductive effects⁷. Therefore, it can be expected that the superposition of the substituent effects can modify the ionization constant of the chelate and the stability constant of the metal chelates. In this study, the ionization constants for compounds [I]-[VII] (Table 1) fall in the normal range ($pK_a = 8 - 10$) for all hydroxamic

Table 1: The comparison of pK_a values obtained for compounds [I]-[VII]

Compound	Bjerrum method	Irving and Rossotti method	Sarkar and Kruck method
[I]	9.80	9.80	9.81
[II]	9.64	9.64	9.64
[III]	9.73	9.72	9.72
[IV]	9.97	9.96	9.97
[V]	9.90	9.92	9.90
[VI]	11.21	11.16	11.21
[VII] pK_{a_1}	9.60	9.64	9.62
pK_{a_2}	10.74	10.54	10.57

acids. It has been found that the pK_a values obtained by the three methods are in good agreement with each other after the least square refinement. In least square refinement a fixed value 10^{-8} was used as error fit in all cases.

The relative order of pK_a values obtained for the phenyl derivatives of N-phenylbenzohydroxamic acid by Sarkar and Kruck method for the systems studied is as follows:

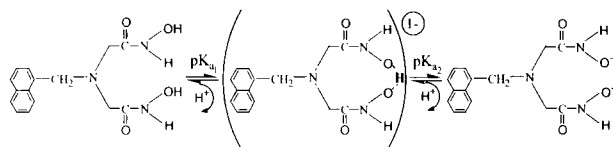
N-(o-methoxy)phenylbenzohydroxamic > N-(o-methyl)phenylbenzohydroxamic acid > N-phenylbenzohydroxamic acid > N-(o-bromo)phenylbenzohydroxamic acid > N-(o-chloro)phenylbenzohydroxamic acid.

Due to the inductive effect of the long chain attached to the carbonyl group (R_C substituent) and the solvent system used the pK_a value obtained for N-phenyllauroylhydroxamic acid [VI] is greater than that of N-phenylbenzohydroxamic acid.

There is an expectation that $pK_{a_1} < pK_{a_2}$ and that for statistical reasons $pK_{a_1} - pK_{a_2} \sim 0.6$ for a diprotic acid with two equivalent acid sites⁸. Table 1 shows that in compound [VII], $pK_{a_1} < pK_{a_2}$ slightly greater than that expected (0.6), suggesting some degree of intramolecular interaction between the two hydroxamic acid units. The

enhanced difference in pK_{a1} and $< pK_{a2}$ is due to a lower value for pK_{a1} .

This is in agreement with deduction of Crumbliss *et al.*⁸ where the stability of the conjugate base HA^- occurs



due to the interaction through H bonding between the hydroxamic acid functional groups associated with long

chain or a big chromophore. The ab-initio calculations⁹ carried out by our research group also confirm this. This intramolecular H-bonding formed in between the two hydroxamic acid groups is illustrated above:

In general, the stability constants calculated (Table 2-8) for all metal-ligand complexes of compounds [I]-[VII] by Bjerrum method, Irving and Rossotti method and Sarkar and Kruck method are in reasonably good agreement with each other after the least square refinement. For all metal ions [Fe(III), Cu(II) and Ni(II)] studied the distribution of species of the compounds [I]-[VI] in the physiological pH range (6.7 – 7.2) is almost

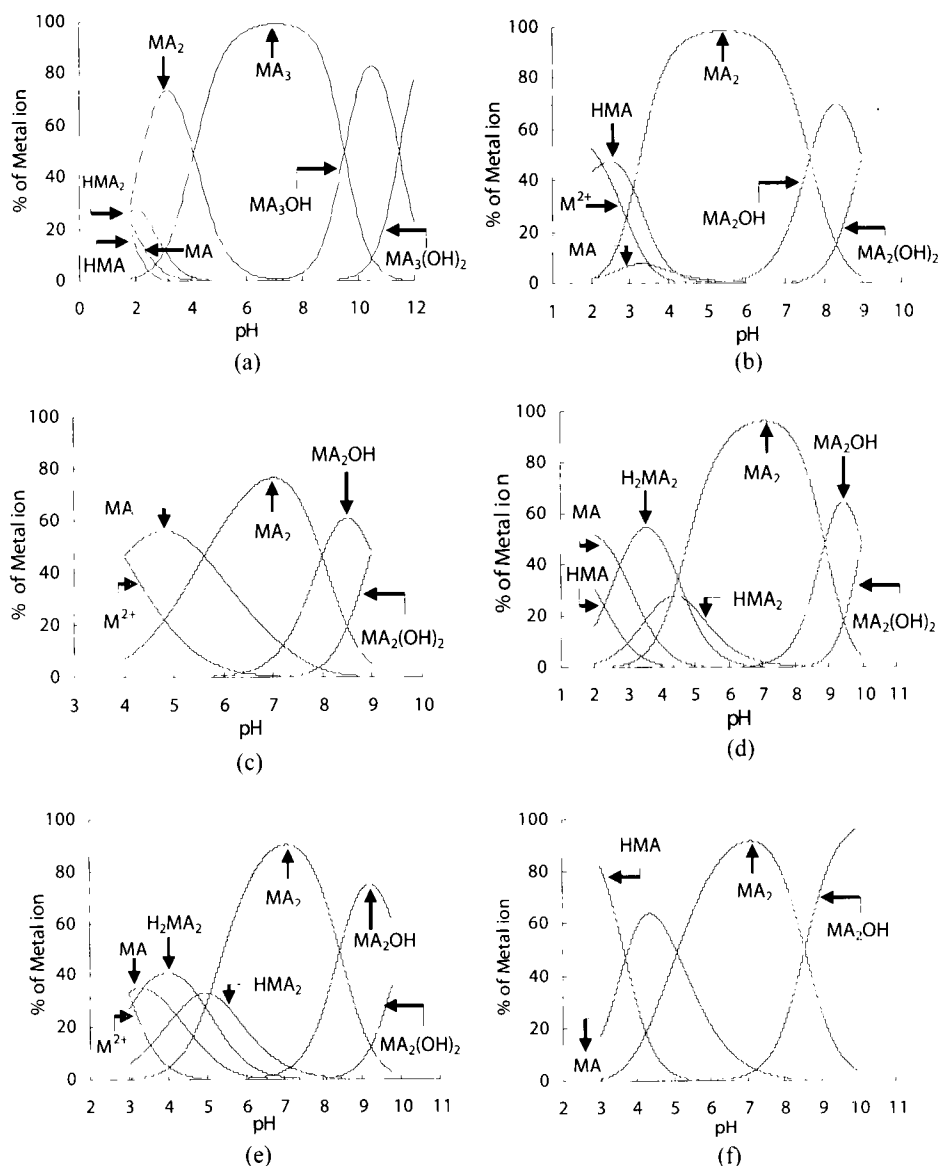


Figure 3: Species distribution of (a) Fe(III)-compound (I), (b) Cu(II)-compound (I), (c) Ni(II)-compound (I), (d) Fe(III)-compound (VII), (e) Cu(II)-compound (VII), and (f) Ni(II)-compound (VII) using Sarkar and Kruck method as representative sets

identical, but in acidic and basic region the relative amount of species formed and the pH values of maxima are slightly different. The species distribution curves of

Fe(III), Cu(II) and Ni(II) of N-phenylbenzohydroxamic acid are shown in Figure 3 (a)-(c) as a representative set and that of 1-naphthalenemethyliminodiacetohydroxamic

Table 2: The stability constant values ($\log \beta$) for Fe(III), Cu(II) and Ni(II) complexes of N-phenylbenzohydroxamic acid (I) system

Metal ion	Species			Bjerrum method	Irving and Rossotti method	Sarkar and Kruck method	pH Range
	M _p	L _q	H _r				
Fe(III)	1	3	-2			36.24	> 10
	1	3	-1			33.70	> 7.8
	1	3	0	29.22	29.51	29.20	2-12
	1	2	1			21.87	2-4.5
	1	2	0	19.35	19.63	20.17	2-6.8
	1	1	1			11.25	< 3.5
	1	1	0	9.58	9.72	9.55	< 4
Cu(II)	1	2	-2			25.54	> 7.5
	1	2	-1			21.28	> 6
	1	0	3	15.72	15.60	-	-
	1	0	2	12.65	12.62	12.89	2-9
	1	1	1			10.14	2-5
	1	1	0	7.20	7.29	7.17	2-5.5
Ni(II)	1	2	-2			14.34	> 7.5
	1	2	-1			11.44	> 6
	1	3	0	12.72	12.78	-	-
	1	2	0	8.01	7.80	7.96	4-9
	1	1	0	4.25	4.33	4.11	4-8.5

Table 3: The stability constant values ($\log \beta$) for Fe(III), Cu(II) and Ni(II) complexes of N-(o-chloro)phenylbenzohydroxamic acid (II) system

Metal ion	Species			Bjerrum method	Irving and Rossotti method	Sarkar and Kruck method	pH Range
	M _p	L _q	H _r				
Fe(III)	1	3	-2			34.25	> 10
	1	3	-1			31.88	> 7.7
	1	3	0	28.21	28.51	27.36	2-12
	1	2	0	18.78	18.87	18.49	2-6
	1	1	0	9.35	9.15	8.63	< 4
Cu(II)	1	2	-2			25.31	> 7.5
	1	1	-2			21.06	> 5.8
	1	3	0	15.07	15.14	-	-
	1	2	0	12.48	12.16	12.21	2-9
	1	1	1			9.74	< 5
	1	1	0	6.88	6.73	6.84	2-5
Ni(II)	1	2	-2			12.73	> 7.3
	1	2	-1			10.32	> 6
	1	3	0	12.17	12.18	-	-
	1	2	0	7.48	7.53	7.28	4-9
	1	1	0	3.83	3.83	3.83	4-8.5

Table 4: The stability constant values ($\log \beta$) for Fe(III), Cu(II) and Ni(II) complexes of N-(o-bromo)phenyl benzohydroxamic acid (III) system

Metal ion	Species			Bjerrum method	Irving and Rossotti method	Sarkar and Kruck method	pH Range
	M_p	L_q	H_r				
Fe(III)	1	3	-2			35.58	> 10
	1	3	-1			33.23	> 8
	1	3	0	28.71	28.99	28.80	2 – 12
	1	2	1			21.23	< 4.5
	1	2	0	19.06	19.19	19.53	2 – 6.5
	1	1	0	9.46	9.47	8.81	< 4
Cu(II)	1	2	-2			25.42	> 7
	1	2	-1			21.17	> 5.5
	1	3	0	15.19	15.18	–	–
	1	2	0	12.41	12.41	12.48	2 – 9
	1	1	1			9.83	2 – 5
	1	1	0	6.95	6.90	6.91	2 – 6
Ni(II)	1	2	-2			13.03	> 7.5
	1	2	-1			10.51	> 6.2
	1	3	0	12.35	12.46	–	–
	1	2	0	7.71	7.66	7.51	4 – 9
	1	1	1			4.03	4 – 8
	1	1	0	4.00	4.09	4.03	4 – 8

Table 5: The stability constant values ($\log \beta$) for Fe(III), Cu(II) and Ni(II) complexes of N-(o-methoxy)phenyl benzohydroxamic acid (IV) system

Metal ion	Species			Bjerrum method	Irving and Rossotti method	Sarkar and Kruck method	pH Range
	M_p	L_q	H_r				
Fe(III)	1	3	-2			36.90	> 10
	1	3	-1			34.37	> 7.8
	1	3	0	30.41	30.42	29.87	2 – 12
	1	2	0	20.12	20.24	21.30	2 – 7.5
	1	1	1			12.28	< 3
	1	1	0	10.41	10.16	10.58	< 4.5
Cu(II)	1	2	-2			26.52	> 7
	1	2	-1			22.26	> 5.5
	1	3	0	15.94	15.93	–	–
	1	2	0	13.21	13.25	13.02	2 – 9
	1	1	1			10.78	2 – 5
	1	1	0	7.60	7.56	7.59	2 – 6.5
Ni(II)	1	2	-2			15.04	> 7.5
	1	2	-1			12.04	> 6.5
	1	3	0	15.62	15.75	–	–
	1	2	0	8.91	8.95	8.51	4 – 9
	1	1	1			7.10	< 6
	1	1	0	4.60	4.59	4.70	4 – 8.5

Table 6: The stability constant values ($\log \beta$) for Fe(III), Cu(II) and Ni(II) complexes of N-(o-methyl)phenylbenzo hydroxamic acid (V) system

Metal ion	Species			Bjerrum method	Irving and Rossotti method	Sarkar and Kruck method	pH Range
	M_p	L_q	H_r				
Fe(III)	1	3	-1			34.19	> 7.8
	1	3	0	29.86	30.00	29.66	2 - 12
	1	2	1			22.19	2 - 4.5
	1	2	0	19.75	19.91	20.49	2 - 7
	1	1	1			11.47	< 3
	1	1	0	9.96	10.00	9.77	< 4
Cu(II)	1	2	-2			25.87	> 7
	1	2	-1			21.61	> 5.5
	1	3	0	15.88	15.76	-	-
	1	2	0	13.01	13.07	12.97	2 - 9
	1	1	1			10.43	2 - 5
	1	1	0	7.32	7.31	7.38	2 - 6
Ni(II)	1	2	-2			14.45	> 7.5
	1	2	-1			11.65	> 6
	1	3	0	14.27	14.17	-	-
	1	2	0	8.80	8.64	8.30	4 - 9
	1	1	1			6.62	< 6.4
	1	1	0	4.47	4.49	4.38	4 - 8

Table 7: The stability constant values ($\log \beta$) for Fe(III), Cu(II) and Ni(II) complexes of N-phenyllauroylhydroxamic acid (VI) system.

Metal ion	Species			Bjerrum method	Irving and Rossotti method	Sarkar and Kruck method	pH Range
	M_p	L_q	H_r				
Fe(III)	1	3	-1			34.03	> 11
	1	3	0	33.47	33.75	32.88	3 - 12
	1	2	0	23.17	23.50	23.43	2 - 8
	1	1	1			13.36	< 3
	1	1	0	11.99	11.93	11.92	2 - 5.5
Cu(II)	1	2	-2			26.44	> 7.2
	1	2	-1			22.33	> 5.6
	1	3	0	16.06	16.19	-	-
	1	2	0	13.39	13.55	13.32	2 - 9
	1	1	1			10.69	< 5
	1	1	0	8.01	8.02	7.99	2 - 6.5
Ni(II)	1	2	-2			17.35	> 7.2
	1	2	-1			13.23	> 6.7
	1	3	0	17.22	17.23	-	-
	1	2	0	9.77	9.82	9.76	4 - 9
	1	1	1			7.56	< 6
	1	1	0	4.94	4.88	4.99	4 - 8

Table 8: The stability constant values (log β) for Fe(III), Cu(II) and Ni(II) complexes of 1-naphthalenemethyliminodiaceto hydroxamic acid (VII) system.

Metal ion	Species			Bjerrum method	Irving and Rossotti method	Sarkar and Kruck method	pH Range
	M _p	L _q	H _r				
Fe(III)	1	2	-2			34.58	> 8.5
	1	2	2			32.25	2 – 6.8
	1	2	-1			30.58	> 7
	1	3	0	30.96	30.99	–	
	1	2	1			29.96	2 – 8
	1	2	0	25.51	25.44	25.46	3 – 10
	1	1	1			20.09	< 4
	1	1	0	16.59	16.77	16.56	< 5
Cu(II)	1	2	-2			25.24	> 8.5
	1	2	2			23.72	3 – 7
	1	2	-1			21.24	> 6.7
	1	3	0	25.16	25.04	–	–
	1	2	1			20.63	3 – 8
	1	2	0	15.51	15.46	15.67	3 – 10
	1	1	0	12.79	12.82	12.84	< 6
Ni(II)	1	2	-1			15.53	> 6.8
	1	3	0	15.29	15.49	–	–
	1	2	0	10.31	10.24	10.09	3 – 10
	1	1	1			8.98	3 – 5.5
	1	1	0	7.44	7.35	7.28	3 – 8

acid is shown in Figure 3 (d)-(f). The results obtained for Fe(III) complexes of the compounds [I]-[VI] indicate that the MA₃ complex is the major complex species formed in the physiological pH range. The relative order of the stability constants obtained is the same as that the order of pK_a values of the hydroxamic acids obtained in this study.

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