

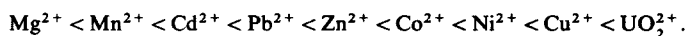
Chelation behaviour of biologically active *o*-hydroxy naphthaldehyde derivatives with bivalent metal ions in different solvents: A potentiometric study

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Abstract. Equilibria between the derivatives of *o*-hydroxy naphthaldehyde and protons or bivalent metal ions have been investigated potentiometrically at constant ionic strength while varying the solvents in definite ratios (solvent:water). The method of Bjerrum and Calvin as modified by Irving and Rossotti (1954) has been used to find the values of \bar{n} and pL . The formation constants of metal chelates have been calculated using a weighted least squares method. The values of $S_{\min} = \chi^2$ have also been calculated. The order of stability constants is determined as



Solvent effects on stability constants and comparative studies of both the derivatives of *o*-hydroxy naphthaldehyde have been reported.

Keywords. Stability constants; *o*-hydroxy naphthaldehyde derivatives; bivalent metal ions; weighted least squares method.

1. Introduction

o-Hydroxy naphthaldehyde derivatives are potential analytical reagents because these form special coloured complexes with various metal ions. The semicarbazones and thiosemicarbazones of certain aldehydes and ketones have significant antimicrobial activities (Bauer *et al* 1963; Petering *et al* 1964; Bareet 1965; West *et al* 1990). The antitubercular activities of metal semicarbazones and thiosemicarbazones have been reported by Domagk *et al* (1946) for the first time. Since then a number of research papers have appeared on the pharmacology of these compounds. The semicarbazone and thiosemicarbazone activities could be due to their power of chelation with traces of metal ions present in biological systems.

The semicarbazone of *o*-hydroxy naphthaldehyde (HNAS) is a potential analytical reagent for determining gallium fluorometrically (Deguchi *et al* 1983). The thiosemicarbazone of 2-hydroxy naphthaldehyde (HNAS) has been reported for its antimicrobial and anticancerous activities (Rusay 1980).

As part of our studies on the chelation behaviour of metal complexes of biologically active *o*-hydroxy naphthaldehyde and its derivatives (Sahadev *et al* 1988), we report here potentiometric studies on the chelation behaviour of bivalent metal complexes

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of 2-hydroxy-1-naphthaldehyde semicarbazone (HNAS) and 2-hydroxy-1-naphthaldehyde thiosemicarbazone (HNATS) under the effect of constant solvent composition while varying the nature of the solvents in mixed aqueous solvent media.

2. Experimental

2.1 Preparation of the ligand

2-Hydroxy-1-naphthaldehyde semicarbazone (HNAS) or 2-hydroxy-1-naphthaldehyde thiosemicarbazone (HNATS) was prepared by reacting the requisite amount of 2-hydroxy-1-naphthaldehyde (Aldrich Chemical Company, USA) dissolved in the minimum amount of absolute ethanol with semicarbazide or thiosemicarbazide hydrochloride (Fluka AR) in water containing glacial acetic acid. The whole reaction mixture was refluxed for 2 h (semicarbazone derivative) or 4 h (thiosemicarbazone derivatives), filtered (if required) and cooled in ice. HNAS or HNATS was precipitated by adding dilute hydrochloric acid and recrystallized from absolute ethanol.

2.2 Characterization of the ligands (HNAS and HNATS)

The purity of the product (HNAS and HNATS) was checked by IR, $^1\text{H NMR}$ spectroscopy, elemental analysis, thin layer chromatography and decomposition temperature.

2.2a Elemental analysis and decomposition temperature: Elemental analyses and decomposition temperatures of the derivatives of *o*-hydroxy naphthaldehyde (HNAS and HNATS) are shown in table 1.

2.2b IR spectra: IR spectra of ligands were taken in potassium bromide pellets. The data are given in table 2.

2.2c $^1\text{H NMR}$ spectra: Proton magnetic resonance spectra of ligands taken in dimethyl sulphoxide (DMSO) chemical shifts for proton (δ scale) as observed are $^1\text{H NMR}$ (δ ppm)

11.5[s, 1H, -OH (phenolic)]; 9.3[(s, 1H, -NH)]; 7.8(s, 1H, -CH), 5.3(s, 2H, -C-NH₂); 7.25(d, 2H, B-H) (orthocoupling of ring B in naphthalene); 6.2-6.6(m, A-H coupling of ring A in naphthalene)

Table 1. Elemental analysis and decomposition temperature.

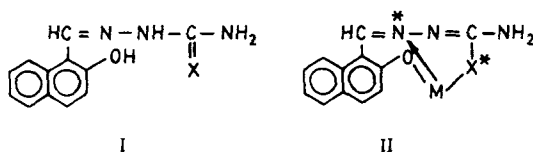
Ligand	Decomp. temp. (°C)	Found (calc.) (%)		
		C	H	N
HNAS	214	62.35 (62.88)	4.85 (4.80)	15.35 (18.34)
HNATS	280	58.10 (58.77)	4.71 (4.49)	16.46 (17.14)

Table 2. IR data of ligands.

Ligand	Bands	IR frequency $\nu(\text{cm}^{-1})$
HNAS and HNATS	Aromatic (C-H) stretch	3030
	Aromatic (C-O)	1240
	Aromatic (C=N)	1630
	NH and NH ₂ stretch	3440
	Phenolic (OH)	3240
HNAS	Aliphatic (C=O) stretch	1720
	Aliphatic (C=S) stretch	1180

2.2d Thin layer chromatography: The solvent system used was methanol-chloroform (1:9), the spots were applied using the solution of the compound 2-hydroxy-1-naphthaldehyde (starting material) and the product (HNAS and HNATS) in ethanol on a TLC plate ($20 \times 5 \text{ cm}^2$). The spots were detected by exposure to iodine vapour. A single spot for the product showed the purity of the ligand.

On the basis of the above analysis the results of Varshney *et al* (1986), structure (I) may be assigned to *o*-hydroxy naphthaldehyde derivative (HNAS or HNATS) and structure (II) to the metal chelate of *o*-hydroxy naphthaldehyde derivative (HNAS or HNATS)



where $X = \text{O}$ (HNAS); $X = \text{S}$ (HNATS).

The sites of coordination are shown by asterisks on nitrogen, oxygen (phenolic group) and X atom ($X = \text{O}$ for HNAS and $X = \text{S}$ for HNATS).

2.3 Instrumentation

A digital pH meter (ECIL, model pH 5651) in conjunction with a glass electrode (0–14 pH range) was used for pH measurements. The pH meter was standardized with potassium hydrogen phthalate and phosphate buffers before titration. All measurements were made at a definite temperature maintained constant by using an MLW (F.R.G.) (NBE type) thermostat. A PC–XT computer was used for calculations.

2.4 Reagents

The derivative of *o*-hydroxy naphthaldehyde (HNAS or HNATS) solution was prepared in freshly distilled 75% (v/v) organic solvent. The bivalent metal ions solution was standardized by conventional methods. Me_4NOH (tetramethyl ammonium hydroxide—TMAH) (E Merck, A G Darmstadt) in 75% (v/v) organic solvent (aqueous) was used as a titrant. Its solution was standardized using oxalic acid. HClO_4 (E Merck) was standardized using standard Na_2CO_3 and diluted to the required molarity (0.05 M)

with double distilled water. NaClO_4 (E Merck) was used to maintain the ionic strength. Dioxane A. R. (B.D.H.) was purified by the method given by Vogel (1956). All other solvents and chemicals used were of reagent grade.

2.5 Potentiometric titration technique

The titration procedure adopted here were the same as given earlier (Sahadev *et al* 1988). Investigations were carried out at constant ionic strength (0.100 M NaClO_4) and solvent composition (75%, v/v) but by varying the nature of solvents (dioxane, acetone and methanol). For each set of experiments, the final volume was made up to 20 cm^3 . Each set was titrated against 0.05 M TMAH. The titrations were carried out in a covered double-walled glass cell in an oxygen-free atmosphere (nitrogen atmosphere), which was presaturated with the solvent (dioxane, acetone and methanol, all in water), before being passed into the reaction solution.

The pH values in aquo-organic solvent mixture were corrected using the method of Van Uitert and Hase (1953) and the volume corrections by using the method of Rao and Mathur (1969).

2.6 Calculations

The derivative of *o*-hydroxy naphthaldehyde (HNAS and HNATS) is a monobasic acid. The acid dissociation constant pK_a of the ligand was obtained earlier (Sahadev *et al* 1988). The formation constant values of metal chelates were finally obtained by weighted least squares method using a computer program. The weighted least squares treatment developed by Sullivan *et al* (1959) determined the set of stability constants β_n values which make the function U ,

$$\left[U = \sum_{n=0}^N (y - x - nz) \beta_n x^n \right]$$

nearest to zero, by minimizing S ,

$$\left[S = \sum_{i=1}^I W_i U(x_i, y_i, z_i) \right]$$

with respect to variation in β_n . S_{\min} has the same statistical distribution as χ^2 with K degrees of freedom and the weight defined in accordance with Sullivan *et al* (1959). S_{\min} can be equated to χ^2 .

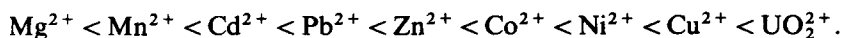
3. Results and discussion

Dissociation and stability constants were calculated at constant ionic strength (0.1 M NaClO_4) at 20°C varying the different nature of solvent in definite solvent composition (solvent: water).

3.1 Order of stability constants

The order of the stability constants of the metal chelates with *o*-hydroxy naphthaldehyde

derivative (HNAS or HNATS) is as follows:



The order of formation constants of the metal complexes is in good agreement with that reported by Mellor and Maley (1947) and Irving and Williams (1948). All the complexes appear to be high-spin. In all the systems, the value of $\log K_1$ is greater than $\log K_2$. As the tendency of a metal ion to take up ligand is proportional to the number of vacant sites, the ratio between consecutive stability constants $\log(K_1/K_2)$ to a certain extent is statistically determined (Bjerrum 1941). For anionic ligands the coulombic attraction is greater for M^{2+} as compared to ML^+ . As such $\log K_1 - \log K_2$ is usually positive stability constants of metal ion complexes (Chemical Society,

Table 3. Stability constants of some bivalent metal complexes with derivatives of *o*-hydroxy naphthaldehyde (HNAS and HNATS) varying nature of solvents having definite solvent composition (75% v/v), solvent-water mixture media at 0.1M NaClO_4 ionic strength (Temp. = $20 \pm 0.5^\circ\text{C}$).

System	Stability constant (S_{\min}^+)	Weighted least squares method				
		HNAS			HNATS	
		Dioxane-water	Acetone-water	Methanol-water	Dioxane-water	Acetone-water
1	2	3	4	5	6	7
H^+	pK_a	10.45	10.40	10.31	10.98	10.50
Mg^{2+}	$\log K_1$	3.22	3.05	3.15	3.39	3.29
	$\log K_2$	3.03	2.77	2.87	3.31	3.21
	$\log(K_1/K_2)$	0.19	0.28	0.28	0.08	0.08
	$\log \beta_2$	6.25	5.82	6.02	6.70	6.50
	S_{\min}	0.0051	0.0022	0.0032	0.0024	0.0018
Mn^{2+}	$\log K_1$	5.03	3.98	4.94	5.67	4.78
	$\log K_2$	4.17	2.87	4.42	4.25	2.96
	$\log(K_1/K_2)$	0.86	1.11	0.52	1.42	1.82
	$\log \beta_2$	9.20	6.85	9.36	9.92	7.74
	S_{\min}	0.0341	0.0060	0.0104	0.0019	0.0044
Cd^{2+}	$\log K_1$	5.65	4.79	5.41	6.55	6.01
	$\log K_2$	4.23	3.16	4.63	4.87	4.12
	$\log(K_1/K_2)$	1.42	1.63	0.78	1.68	1.89
	$\log \beta_2$	9.88	7.95	10.04	11.42	10.13
	S_{\min}	0.0302	0.0006	0.0274	0.0769	0.0044
Pb^{2+}	$\log K_1$	6.05	5.49	5.99	7.64	7.17
	$\log K_2$	5.80	3.70	4.86	5.81	5.26
	$\log(K_1/K_2)$	0.25	1.79	1.13	1.83	1.91
	$\log \beta_2$	11.85	9.19	10.86	13.45	12.43
	S_{\min}	0.0548	0.0044	0.0450	0.0049	0.0078
Zn^{2+}	$\log K_1$	7.82	6.39	7.15	8.35	7.87
	$\log K_2$	6.43	4.28	5.48	6.59	5.83
	$\log(K_1/K_2)$	1.39	2.11	1.67	1.76	2.04
	$\log \beta_2$	14.25	10.67	12.63	14.94	13.70
	S_{\min}	0.0196	0.0033	0.0107	0.0370	0.0181

(Continued)

Table 3. (Continued)

1	2	3	4	5	6	7
Co ²⁺	log K_1	8.59	7.22	8.14	9.00	8.61
	log K_2	7.59	5.65	6.71	7.08	6.67
	log(K_1/K_2)	1.00	1.57	1.43	1.92	1.94
	log β_2	16.18	12.87	14.85	16.08	15.28
	S_{\min}	0.0097	0.0808	0.0867	0.0149	0.0051
Ni ²⁺	log K_1	8.93	7.84	8.59	9.60	8.75
	log K_2	7.99	5.89	6.95	8.22	7.24
	log(K_1/K_2)	0.94	1.95	1.64	1.38	1.51
	log β_2	16.92	13.73	15.54	17.82	15.99
	S_{\min}	0.2232	0.0209	0.0010	0.0580	0.0212
Cu ²⁺	log K_1	9.10	8.16	9.06	9.78	9.08
	log K_2	8.25	6.17	7.38	8.89	7.62
	log(K_1/K_2)	0.85	1.99	1.68	0.89	1.46
	log β_2	17.35	14.33	16.44	18.67	16.70
	S_{\min}	0.2512	0.0094	0.0007	0.0558	0.0000
UO ₂ ²⁺	log K_1	9.97	8.93	9.30	10.08	9.34
	log K_2	9.36	7.20	7.98	8.38	8.01
	log(K_1/K_2)	0.61	1.73	1.32	1.70	1.33
	log β_2	19.33	16.13	17.28	18.46	17.35
	S_{\min}	0.1163	0.0218	0.0572	0.0217	0.0547

London 1957). Table 3 shows that all systems studied here, $\log K_1 - \log K_2$ is positive and lies within 0.08–2.11 unit. The $\log K_1$, K_2 , $\log(K_1/K_2)$, $\log \beta_2$ and S_{\min} values at $20 \pm 0.5^\circ\text{C}$ for bivalent metal ion chelates at constant ionic strength (0.100 M NaClO₄), in constant solvent composition 75% (v/v), solvent-water mixture varying the nature of solvents (dioxane, acetone and water), for *o*-hydroxy naphthaldehyde derivative (HNAS and HNATS) are summarized in table 1. For these chelates \bar{n} values greater than 2.0 have not been obtained. We therefore conclude that not more than two chelates, i.e. 1:1 and 1:2 (metal:ligand) are formed in each system. In view of the very low (5.0×10^{-4} M) concentration of metal ions used in titration, it has been assumed that the possibility of polynuclear complex formation is negligible.

The results show that the stability of the metal chelates increases regularly from Mn²⁺ to Cu²⁺ and falls again at Zn²⁺. Furthermore, the stability order is independent of the ligand. Minor deviation can be predicted on theoretical grounds. The regularity of this stability sequence can be correlated with a monotonic decrease in the ionic radii, and a monotonic increase in the second ionization potential which, in passing from Mn²⁺ to Cu²⁺, may be taken to indicate that either the coordination has not altered the electronic ground state of the metal ions or that any modification are of secondary importance.

3.2 Solvent effects on the formation constants

The proton-ligand stability constant pK_a and formation constants of the metal complexes in 75% (v/v) solvent composition varying the nature of organic solvents, are reported in table 3. For stability constants in definite solvent composition, the sequence of $1/\epsilon$ (ϵ = dielectric constant of solvent) is as follows: Dioxane-water > acetone-water > methanol-water. But for the same (v/v) solvent composition, pK_a in

different nature of solvent-water mixtures follows the sequence: Acetone-water > dioxane-water > methanol-water. This indicates that the above sequence does not follow the order of dielectric constants of the media. In mixed aqueous organic solvent, pK_a of ligand (HNAS and HNATS) may be influenced by different solvent characteristics. These effects are (I) dielectric constants of the mixed solvents, (II) change in hydrogen-bonding in water in presence of organic solvents and (III) proton solvation or protonation of organic solvents.

(I) Franks and Ives (1966) reviewed the relationship between the stability of the complexes and different solvent characteristics. Bates *et al* (1966) and Rorabacher *et al* (1971) have stressed upon the effect of both electrostatic and non-electrostatic phenomenon on pK_a and β_n of metal chelates, characterizing the latter effect as the solvent basicity effect. They have concluded that the non-electrostatic phenomenon becomes increasingly important in solvents containing organic solvent in more than 50% (v/v) solvent composition.

It also appears that the non-electrostatic part of the interaction is related to the proton acceptance property of the medium and protonation of the organic solvent.

(II) According to Braude (1948), the tetrahedral lattice structure of water gradually breaks down, when an organic solvent is added and owing to the denser packing and smaller extent of hydrogen bonding between the molecules, the stability of hydroxonium (H_3O^+) increases and the proton donating property of the medium falls. This may imply that the proton accepting property of the solvent increases. It is also believed that hydrogen-bonded structure is less prevalent in pure acetone and pure dioxane. Gergley and Kiss (1977) indicated that the dioxane molecule progressively breaks down the hydrogen-bonded structure of water whereas methanol can form hydrogen-bonded association with water. It is therefore expected that the extent of the hydrogen bonding in methanol-water is greater than that in dioxane-water or acetone-water.

(III) When the amount of organic solvent becomes sufficiently large in a water-organic solvent mixture, proton solvation or protonation of the organic solvent takes place. Brause (1948) reported that the basicities of the pure solvent molecule decreases in the following order: water > dioxane > methanol > acetone. Thus the proton solvation of pure acetone is minimum.

The effects of (II) and (III) depend upon the concentration of mixed aqueous media and they may be contracting with respect to proton acceptance property of the media. The more a solvent accepts proton the more the ligand acid is dissociated and so the proton ligand dissociation constant (pK_a) tends to decrease.

The foregoing solvent effects influence the pK_a of ligand conjugate acid in the following manner: (i) with decrease of solvent dielectric constant, the pK_a of ligand increases and *vice versa*. (ii) On decreasing the extent of hydrogen bonding in water by organic solvent, proton-accepting property of water increases. So, pK_a of ligand decreases. (iii) Increasing proton solvation by the organic solvent decreases the pK_a of ligand and *vice versa*.

The sequence of pK_a values in different solvents is almost the same as that of the dielectric constant of the solvents except acetone which is in top place (slightly higher than dioxane). Dioxane comes second because of its lowest dielectric constant but greater capacity to decrease hydrogen bonding in water. Methanol follows the sequence as expected from its dielectric property. Moreover, methanol has higher proton solvation than acetone.

3.3 Comparative study on the chelation behaviour of HNAS and HNATS

Experimental results reveal that pK_a of both the ligands (HNAS and HNATS) and stability constants of their metal chelates are in the order, HNATS > HNAS. The variation in pK_a of ligands and stability constants of their chelates is due to a combination of the following factors (Hammett 1940), (i) steric effects, (ii) electronic effect and (iii) size and electronegativity of the coordinated atoms.

The increase in electron density on the coordinating atoms enhances the basicity, i.e. nucleophilic character of the donor atom, thus favouring the formation of coordinate σ -bond and giving it greater stability.

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