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Thermal studies on the chelation behaviour of biologically active 2-hydroxy-1-naphthaldehyde thiosemicarbazone (HNATS) towards bivalent metal ions: a potentiometric study

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Abstract

Potentiometric investigation on complexes of various bivalent metal ions, namely, Mg^{2+}, Mn^{2+}, Cd^{2+}, Pb^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+} and UO_2^{2+}, with 2-hydroxyl-1-naphthaldehyde thiosemicarbazone (HNATS) have been carried out at different temperatures, i.e. 20 ± 0.5°C, 30 ± 0.5°C, 40 ± 0.5°C and 50 ± 0.5°C, in 75% (v/v) dioxan–water medium in order to determine the stability constants of the complexes at constant ionic strength I 0.1 mol dm^{-3} $NaClO_4$. The stability constants and value of $S_{min} = \chi^2$ have been calculated on a PC-XT/AT computer using a weighted least-squares method. The order of stability constants was found to be $Mg^{2+} < Mn^{2+} < Cd^{2+} < Pb^{2+} < Zn^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+} < UO_2^{2+}$. The thermodynamic parameters $\Delta G°$, $\Delta H_f°$ and $\Delta S°$ have also been evaluated from the stability constants obtained for different temperatures at constant ionic strength.

INTRODUCTION

Recently it has been found that the metal chelates of *o*-hydroxynaphthaldehyde and derivatives have numerous applications, i.e. as fungicides [1–3], as neoplasm inhibitors [4], and as antibacterial agents [5,6], and possess anticancerous properties [7] or constitute physiologically active compounds [8–10] in our biological system.

Thiosemicarbazones of 2-hydroxy-1-naphthaldehyde may act as potential antimicrobial agents [11] or as analytical reagents [12] and have wide applications in the treatment of several diseases such as sarcoma 190, adenocarcinoma 755 and leukaemia 1210 mouse screening programme [13].

It has been assumed that the microbial activity of thiosemicarbazones is due to their ability to chelate with traces of metals, the metal complexes themselves being active components. Considering the biological and analyt-

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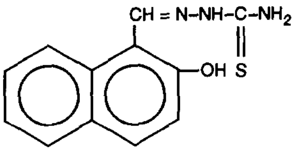
ical applicability of 2-hydroxy-1-naphthaldehyde thiosemicarbazone and its metal chelates, the present study was undertaken to assess the stability and other thermodynamic properties of some bivalent metal chelates which could be applicable in improved form for biological systems.

EXPERIMENTAL

Chemicals

2-Hydroxy-1-naphthaldehyde thiosemicarbazone (HNATS) was prepared by reacting the requisite amounts of thiosemicarbazide hydrochloride (BDH, A.R.) (0.85 g) dissolved in water and 2-hydroxyl-1-naphthaldehyde (Aldrich Chemical Co., USA) (0.1 g) dissolved in the minimum amount of ethanol. A small amount of acetic acid was also added to the reaction mixtures. The whole mixture was refluxed for 3.5 h on a water bath, filtered (if necessary) and then cooled overnight in a freezer. The thiosemicarbazone was precipitated by adding dilute hydrochloric acid, and was recrystallized from ethanol. The purity of the product (HNATS) was checked by its melting point (280°; decomposition point), IR and proton NMR spectroscopy, thin layer chromatography and elemental analysis.

On the basis of the above analysis, and the spectral study of Varshney et al. [14], structures **I** and **II** may be assigned to HNATS and its metal chelates.



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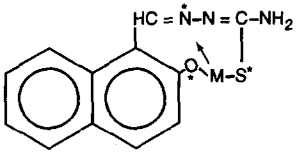

II

2-Hydroxy-1-naphthaldehyde thiosemicarbazone (HNATS)

The sites of coordination are shown by the asterisks on the nitrogen, oxygen and sulphur atoms, demonstrating that HNATS acts as a tridentate ligand.

The solution of HNATS was prepared in dioxan diluted with water to contain 75% (v/v) of dioxan. Dioxan (Merck) was freed from peroxide by refluxing it with sodium metal for 24 h and was freshly distilled over sodium before use. Sodium perchlorate (Merck) was used to keep the ionic strength constant. A solution of tetramethylammonium hydroxide (TMAH) (Merck) in 75% (v/v) dioxan–water was used as the titrant, which was standardised with oxalic acid. All other chemicals used were of reagent grade. All the metal ion solutions were prepared and standardised by conventional methods. Perchloric acid was standardised against pre-standardised sodium carbonate and diluted to the required molarity (0.05 mol dm^{-3}) with doubly distilled water.

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 standardised with potassium hydrogen phthalate and phosphate buffers before performing the titration. All the measurements were made at various temperatures maintained constant by using an MLW (FRG) NBE type thermostat accurate to ± 0.5°C. A PC-XT/AT computer was used for most of the calculations.

Potentiometric titration technique

The method of Bjerrum and Calvin as modified by Irving and Rossotti [15] was used to calculate the values of $\bar{n}$ (the average number of ligand molecules bound per metal ion) and pL (the free ligand exponent). The following solutions (total volume equal to 19.67 cm^3 instead of 20 cm^3 owing to the contraction in volume on mixing dioxan and water) were titrated potentiometrically against standard 0.05 mol dm^{-3} TMAH in 75% (v/v) dioxan–water medium to determine $\bar{n}$ and pL values of the bivalent metal complexes.

(a) 0.8 cm^3 $HClO_4$ (0.05 mol dm^{-3}) + 1.0 cm^3 $NaClO_4$ (2.0 mol dm^{-3}) + 2.7 cm^3 doubly distilled H_2O + 15.0 cm^3 dioxan + 0.5 cm^3 KNO_3 or K_2SO_4 (0.02 mol dm^{-3}).

(b) 0.8 cm^3 $HClO_4$ (0.05 mol dm^{-3}) + 1.0 cm^3 $NaClO_4$ (2.0 mol dm^{-3}) + 0.2 cm^3 doubly distilled H_2O + 0.5 cm^3 K_2SO_4 or KNO_3 (0.02 mol dm^{-3}) + 10.0 cm^3 ligand (HNATS) (0.01 mol dm^{-3}) + 7.5 cm^3 dioxan.

(c) 0.8 cm^3 $HClO_4$ (0.05 mol dm^{-3}) + 1.0 cm^3 $NaClO_4$ (2.0 mol dm^{-3}) + 0.2 cm^3 doubly distilled H_2O + 0.5 cm^3 metal ion solution (0.02 mol dm^{-3}) + 10.0 ml HNATS (0.01 mol dm^{-3}) + 7.5 cm^3 dioxan.

Investigations were carried out at different temperatures, namely 20, 30, 40 and 50 $\pm$ 0.5°C at an ionic strength of 0.1 mol dm^{-3} ($NaClO_4$). The potentiometric titrations of the above mixtures were carried out in a covered double-walled glass cell in an atmosphere of N_2 which was presaturated with the solvent (dioxan in water) before being passed into the reaction solution.

During complexation, the phenolic proton of the ligand (HNATS) dissociates first and the pK_a value of the ligand corresponds to the dissociation of this proton.

From the titration curves of solutions (a) and (b), the values of $\bar{n}_H$ (average number of protons bound per ligand molecule) were calculated at various pH values. From a plot of log $\bar{n}_H/(1-\bar{n}_H)$ vs. pH, the pK_a value of HNATS was obtained; the plot was a straight line of intercept equal to pK_a (Fig. 1) and the slope was equal to unity. From the titration curves of

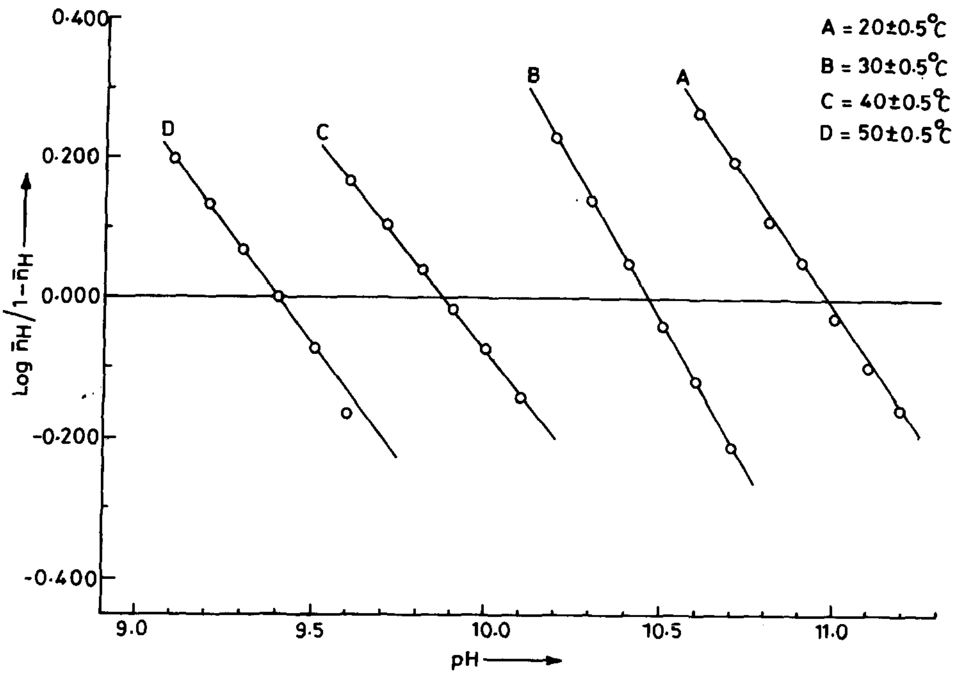

Fig. 1. Determination of ligand dissociation constant (pK_a) value of HNATS at $I = 0.1$ M $NaClO_4$ in 75% (v/v) dioxan–water medium at 20±0.5°C, 30±0.5°C, 40±0.5°C and 50±0.5°C.

solutions (a), (b) and (c), $\bar{n}$ and pL values were calculated by making use of the equations

$$\bar{n} = \frac{(V''' - V'')[N_B + E_0 + T_L(y - \bar{n}_H)]}{(V^0 + V'')\bar{n}_H T_M} \tag{1}$$

$$\mathrm{pL} = \log\left[\left(\frac{1 + 10^{(\mathrm{p}K_a - \mathrm{pH})}}{T_L - \bar{n}T_M}\right) \times \left(\frac{V_0 + V'''}{V^0}\right)\right] \tag{2}$$

where V', V'' and V''' are the volumes of alkali required to reach the same pH in the curves for solutions (a), (b) and (c) respectively, $\bar{n}_H$ is the average number of protons associated with the ligand molecules, and T_M is the total initial concentration of metal ion–ligand complex, which is equivalent to the initial metal ion concentration taken in mixture (c). The symbol T_L is the total concentration of ligand, N_B and E_0 are the normality of TMAH and the initial concentration of the free acid ($HClO_4$) respectively, β is the metal–ligand complex formation constant and all the other symbols have their usual meanings. From these data, the values of the metal–ligand formation constants are obtained. The formation curves ($\bar{n}$ vs. pL) are shown in Fig. 2 and the results are recorded in Table 1.

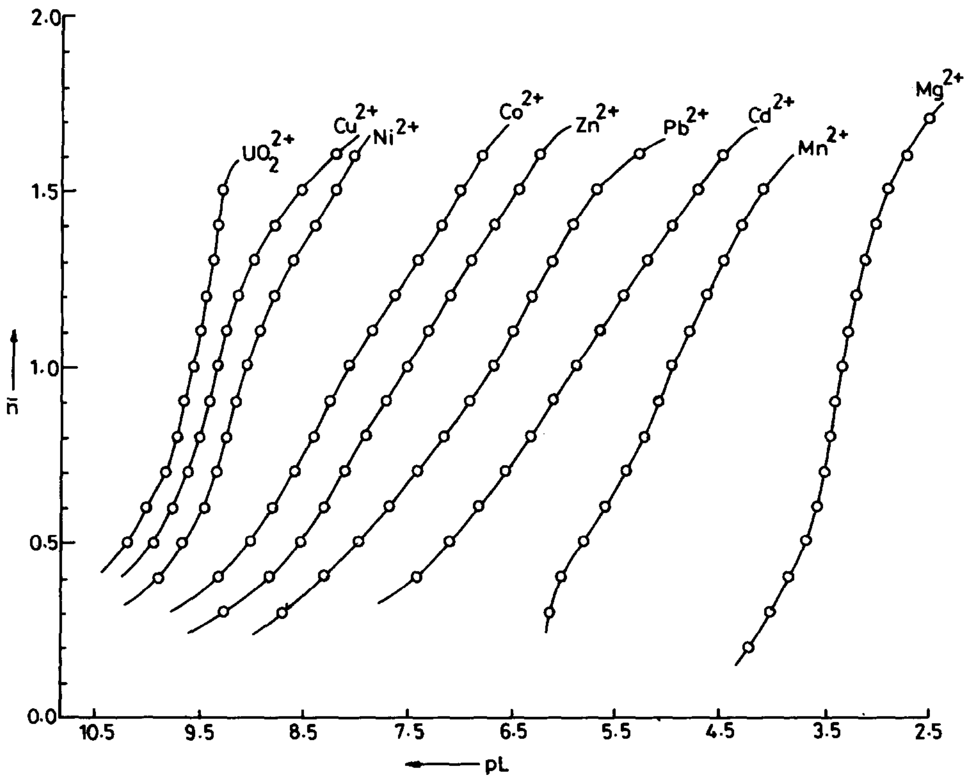

Fig. 2. Formation curves of bivalent metal complexes of HNATS at $I = 0.1$ M $NaClO_4$ in 75% (v/v) dioxan-water medium and at 20 ± 0.5°C.

A rapid attainment of equilibrium and no change in pH value are observed during titration. This indicates that HNATS does not undergo hydrolysis under the experimental conditions. Moreover, there is no precipitation observed during the titration, which rules out the possibility of the hydrolysis of the metal ions.

Examination of the titration curves of solutions (a), (b) and (c) indicates that the addition of metal ion to the ligand solution causes a decrease in the pH value. This suggests that the complexation reaction proceeds by the replacement of a proton from the ligand. On plotting the $\bar{n}$ values against the pL values for the systems under investigation (Fig. 2), it is evident that the degree of metal–ligand formation $\bar{n}$ extends between 0.1 and 2.0, confirming the formation of complex species with metal-to-ligand ratios of 1 : 1 and 1 : 2 in solution. The stoichiometric ratios obtained are in accordance with those obtained from potentiometric titrations.

Data treatment

From the titration curves of solutions (a), (b) and (c), the values of $\bar{n}$ and pL were calculated using a PC-XT/AT computer. The corresponding values of the stability constants were calculated using a weighted least-squares treatment that determines the set of β_n values which makes up the function U, where

$$U = \sum_{n=0}^{N} (y - x - nz)\beta_n \chi^n$$

nearest to zero by minimising S.

$$S = \sum_{i=1}^{I} W_i U^2(x_i, y_i, z_i)$$

with respect to the variation in β_n.

We report the $S_{\min}$ values for the different bivalent metal complexes. $S_{\min}$ has the same statistical distribution as χ^2 with K degrees of freedom and the weightings defined in accordance with Sullivan et al. [16]; $S_{\min}$ can be equated to χ^2. The stability constants thus calculated are given in Table 1.

RESULTS AND DISCUSSION

The order of stability constants of the bivalent metal complexes of HNATS was found to follow the order $Mg^{2+} < Mn^{2+} < Cd^{2+} < Pb^{2+} < Zn^{2+} < Co^{2+} < Ni^{2+} < Cu^{2+} < UO_2^{2+}$.

This is in good agreement with the order found by Mellor and Maley [17] and by Irving and Williams [18,19]. The order is in agreement with the increasing acidity and decreasing ionic radius of the metal ion.

In all the systems, the values of log K_1 are greater than the log K_2 values. The values of log K_1, log K_2, log K_1/K_2 and log β_2 at different temperatures are given in Table 1. Values of $S_{\min}$ ($S_{\min} = \chi^2$) at various temperatures are reported in Table 2. All the complexes appear to be of high spin type. The values of the stability constants in Table 1 decrease in almost all cases with increasing temperature; similarly the pK_a values decrease with increase in temperature. These results are in good agreement with those of Pitzer [20].

Thermodynamic functions, i.e. the enthalpy of complex formation ΔH_f°, the free energy change ΔG° and the entropy change ΔS°, are determined from the following equations

$$\Delta G^\circ = -RT \ln K$$

$$\frac{\mathrm{d} \log K}{\mathrm{d}/(1/T)} = \frac{\Delta H_f^\circ}{2.303R}$$

$$\Delta S^\circ = (\Delta H_f^\circ - \Delta G^\circ)/T$$

On plotting the relationship between R ln K and $1/T$, straight lines are obtained for the systems under investigation. The values of ΔH_f° and ΔS°

TABLE 1

Stability constants of bivalent metal complexes of 2-hydroxy-1-naphthaldehyde thiosemicarbazone (HNATS) in 75% (v/v) dioxan–water medium at 0.1 mol dm^{-3} $NaClO_4$ and at various temperatures

System	Constant	Weighted least-squares method			
		Temperature			
		20 ± 0.5°C	30 ± 0.5°C	40 ± 0.5°C	50 ± 0.5°C
HNATS	pK_a	10.98	10.46	9.87	9.40
Mg^{2+}–HNATS	$\log K_1$	3.40	3.34	3.31	3.25
	$\log K_2$	3.30	3.18	2.90	2.33
	$\log (K_1/K_2)$	0.10	0.16	0.41	0.92
	$\log \beta_2$	6.70	6.52	6.21	5.58
Mn^{2+}–HNATS	$\log K_1$	5.67	5.36	5.20	4.66
	$\log K_2$	4.25	3.53	3.54	3.07
	$\log (K_1/K_2)$	1.42	1.83	1.66	1.59
	$\log \beta_2$	9.92	8.89	8.74	7.73
Cd^{2+}–HNATS	$\log K_1$	6.56	6.47	6.12	5.93
	$\log K_2$	4.86	4.73	4.06	3.99
	$\log (K_1/K_2)$	1.70	1.74	2.06	1.94
	$\log \beta_2$	11.42	11.20	10.17	9.92
Pb^{2+}–HNATS	$\log K_1$	7.64	7.23	6.68	6.57
	$\log K_2$	5.81	5.51	4.90	4.80
	$\log (K_1/K_2)$	1.83	1.72	1.79	1.77
	$\log \beta_2$	13.45	12.74	11.58	11.37
Zn^{2+}–HNATS	$\log K_1$	8.35	8.11	7.70	7.17
	$\log K_2$	6.59	6.26	5.78	5.53
	$\log (K_1/K_2)$	1.76	1.85	1.92	1.64
	$\log \beta_2$	14.94	14.37	13.48	12.70
Co^{2+}–HNATS	$\log K_1$	9.00	8.43	8.13	7.89
	$\log K_2$	7.08	6.78	7.48	5.67
	$\log (K_1/K_2)$	1.92	1.65	0.65	2.22
	$\log \beta_2$	16.08	15.21	15.61	13.65
Ni^{2+}–HNATS	$\log K_1$	9.60	9.13	9.07	8.37
	$\log K_2$	8.22	7.31	7.29	6.00
	$\log (K_1/K_2)$	1.48	1.82	1.78	2.37
	$\log \beta_2$	17.82	16.44	16.36	14.37
Cu^{2+}–HNATS	$\log K_1$	9.78	9.34	9.29	8.68
	$\log K_2$	8.89	7.95	7.65	6.63
	$\log (K_1/K_2)$	0.89	1.39	1.64	2.05
	$\log \beta_2$	18.67	17.28	16.94	15.31
UO_2^{2+}–HNATS	$\log K_1$	10.09	9.64	9.48	9.26
	$\log K_2$	8.38	8.53	8.75	7.46
	$\log (K_1/K_2)$	1.71	1.11	0.73	1.80
	$\log \beta_2$	18.47	18.17	18.23	16.72

are obtained from the slopes and the intercepts with the abscissa respectively. The overall free energy change, enthalpy change and entropy change at 20 ± 0.5°C are reported in Table 3.

TABLE 2

Values of S_{min} ($S_{min} = \chi^2$) for bivalent metal complexes of 2-hydroxy-1-naphthaldehyde thiosemicarbazone (HNATS) at ionic strength 0.1 mol dm^{-3} $NaClO_4$ and at various temperatures [a]

System	Temperature			
	20 ± 0.5°C	30 ± 0.5°C	40 ± 0.5°C	50 ± 0.5°C
Mg^{2+}-HNATS	0.0024	0.0138	0.0020	0.0000
Mn^{2+}-HNATS	0.0019	0.0014	0.0097	0.0081
Cd^{2+}-HNATS	0.0769	0.0216	0.0371	0.0059
Pb^{2+}-HNATS	0.0049	0.0133	0.0512	0.0580
Zn^{2+}-HNATS	0.0370	0.0150	0.0074	0.0781
Co^{2+}-HNATS	0.0149	0.0476	0.0286	0.0164
Ni^{2+}-HNATS	0.0580	0.0101	0.0169	0.0009
Cu^{2+}-HNATS	0.5580	0.0461	0.0535	0.0450
UO_2^{2+}-HNATS	0.0217	0.0308	0.0949	0.0591

[a] Constant is S_{min}.

The decrease in log K_1 values with increasing temperature indicates that the complex formation reactions for all metal ion–ligand systems are exothermic. This is in agreement with the negative values of ΔH_f°. The negative values of ΔG° indicate that all complexes under study are formed spontaneously in solution. Furthermore, the values of ΔS° are positive for some systems indicating that entropy is favourable for complexation, whereas for other systems the negative values of ΔS° show the unfavourable nature of complex formation. The change in entropy is probably due to the displacement of water molecules from the hydration shell of the metal ion, which accompanies the electrostatic interaction between the positively charged metal ion and the negatively charged oxygen atom of the

TABLE 3

Thermodynamic parameters of the bivalent metal complexes of HNATS at $I = 0.100$ mol dm^{-3} $NaClO_4$ and at a temperature of 20 ± 0.5°C

Complexing ion	Ligand (HNATS)		
	$-\Delta G^\circ$ (kJ mol^{-1})	$-\Delta H_f^\circ$ (kJ mol^{-1})	ΔS° (kJ mol^{-1} K^{-1})
Mg^{2+}	19.08	8.96	+0.0345
Mn^{2+}	31.81	60.42	−0.0976
Cd^{2+}	36.81	37.67	−0.0029
Pb^{2+}	42.87	63.86	−0.0716
Zn^{2+}	46.85	56.40	−0.0326
Co^{2+}	48.91	49.14	−0.0008
Ni^{2+}	53.86	73.42	−0.0667
Cu^{2+}	54.87	65.77	−0.0372
UO_2^{2+}	56.61	49.52	+0.0242

phenolic group of the ligand. This can be explained with the help of the following reaction:

$$M(H_2O)_6(aq)^{2+} + 6L(aq) \rightleftharpoons ML(aq) + 6H_2O$$

The change in entropy upon complexation of a bivalent metal ion is related to the change in the number of particles in the system, and to changes in modes of vibration of these particles. In aqueous systems, complexation by chelation is favoured by the release of bound water molecules [21]. As a consequence, the major contribution to the change in free energy is the change in entropy, and the chelates are said to be entropy stabilised.

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