

## Potentiometric Studies on the Complexation Equilibria Between Some Trivalent Lanthanide Metal Ions and Biologically Active 2-Hydroxy-1-Naphthaldehyde Thiosemicarbazone (*HNATS*)

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**Summary.** The chelation behaviour of some trivalent lanthanide and yttrium metal ion with biologically active 2-hydroxy-1-naphthaldehyde thiosemicarbazone (*HNATS*) has been investigated by potentiometric measurements at  $20 \pm 0.5^\circ\text{C}$  in 75% (*v/v*) dioxane-water medium at various ionic strengths of sodium perchlorate. The method of Bjerrum and Calvin, as modified by Irving and Rossotti has been used to find out the values of  $\bar{n}$  (average number of ligand bound per metal ion) and  $pL$  (free ligand exponent). The formation constants of metal chelates have been computed on a PC-XT computer, using a program patterned after that of Sullivan et al. to give  $\beta_n$  values using weighted least squares method. The  $S_{min}$  values ( $S_{min} = \chi^2$ ) have been calculated. The order of formation constants of chelates was found to be:  $\text{La}^{3+} < \text{Ce}^{3+} < \text{Pr}^{3+} < \text{Nd}^{3+} < \text{Sm}^{3+} < \text{Eu}^{3+} < \text{Gd}^{3+} < \text{Y}^{3+} < \text{Tb}^{3+} < \text{Dy}^{3+}$ . The formation constants of the chelates formed have been correlated to size and ionization potentials of the metal ions.

**Keywords.** Lanthanide metal ion; 2-Hydroxy-1-naphthaldehyde thiosemicarbazone (*HNATS*); Formation constant; Potentiometry.

### Potentiometrische Untersuchungen der Komplexbildungsgleichgewichte zwischen einigen trivalenten Metallionen und biologisch aktivem 2-Hydroxy-1-naphthaldehyd-thiosemicarbazon (*HNATS*)

**Zusammenfassung.** Es wurde das Chelierungsverhalten einiger trivalenter Lanthanidenionen mit biologisch aktivem 2-Hydroxy-1-naphthaldehyd-thiosemicarbazon (*HNATS*) mittels potentiometrischer Messungen bei  $20 \pm 0.5^\circ\text{C}$  in 75% (*v/v*) Dioxan-Wasser bei verschiedener Ionenstärke an Natriumperchlorat untersucht. Die Methode nach Bjerrum und Calvin in der Modifikation nach Irving und Rossotti wurde zur Ermittlung der Werte  $\bar{n}$  (mittlere Anzahl an Liganden pro Metallion) und  $pL$  (Exponent an freiem Liganden) verwendet. Die Komplexbildungskonstanten wurden in Anlehnung an Sullivan et al. an einem PC-XT Computer errechnet. Die  $S_{min}$ -Werte ( $S_{min} = \chi^2$ ) wurden ebenfalls bestimmt. Die Reihung der Chelatbildungskonstanten war:  $\text{La}^{3+} < \text{Ce}^{3+} < \text{Pr}^{3+} < \text{Nd}^{3+} < \text{Sm}^{3+} < \text{Eu}^{3+} < \text{Gd}^{3+} < \text{Y}^{3+} < \text{Tb}^{3+} < \text{Dy}^{3+}$ . Die Bildungskonstanten sind mit der Größe und dem Ionisierungspotential der Metallionen zu korrelieren.

### Introduction

Thiosemicarbazones are compounds which act as complexing agents for various metal ions. They have many analytical applications [1–4] and they are also of

interest in various biological systems. The thiosemicarbazones and semicarbazones of certain aldehydes and ketones have significant antimicrobial activities [5–10]. Domagk et al. [11] reported for the first time the antitubercular activities of metal thiosemicarbazones and semicarbazones. Since then a number of papers have appeared on the pharmacology of these compounds. The activity of thiosemicarbazones is thought to be due to their power of chelation with traces of metal ions present in biological systems.

2-Hydroxy-1-naphthaldehyde thiosemicarbazone (*HNATS*) has been used earlier as a potential anticancer and antiviral agent [12]. Benjamin et al. [13] proved through their investigation that thiosemicarbazone of O-hydroxy naphthaldehyde showed promise in Sarcoma 190, Adenocarcinoma 755 and Leukemia 1 210 mouse screening program. Recently antimicrobial activity of thiosemicarbazone of this aldehyde has been reported by Hyozo et al. [14].

As part of an intensive study undertaken in our laboratory of the complexation behaviour of metal complexes of biologically active O-hydroxy naphthaldehyde and its derivatives [15, 16], we describe here potentiometric studies on the chelation behaviour of *HNATS* with some lanthanide metal ions, viz.  $\text{La}^{3+}$ ,  $\text{Ce}^{3+}$ ,  $\text{Pr}^{3+}$ ,  $\text{Nd}^{3+}$ ,  $\text{Sm}^{3+}$ ,  $\text{Eu}^{3+}$ ,  $\text{Gd}^{3+}$ ,  $\text{Y}^{3+}$ ,  $\text{Tb}^{3+}$ ,  $\text{Dy}^{3+}$  in 75% (*v/v*) dioxane-water medium at various ionic strengths.

## Experimental Part

2-Hydroxy-1-naphthaldehyde thiosemicarbazone (*HNATS*) was prepared by reacting requisite amounts of thiosemicarbazide hydrochloride (Fluka A. R.) dissolved in ethanol and equimolar amounts of 2-hydroxy-1-naphthaldehyde (*HNA*) (Aldrich Chemical Company, Inc., U.S.A.). A small amount of acetic acid was also added in the reaction mixture. The reaction mixture was refluxed for 4 h on a water bath, filtered (if necessary) and cooled overnight in a freezer. The thiosemicarbazone was precipitated by adding dilute hydrochloric acid and recrystallised in ethanol. The purity of newly prepared compounds was checked by m.p., TLC, NMR, IR and elemental analysis. Solution of *HNATS* was prepared in 75% (*v/v*) dioxane-water medium.  $\text{Me}_4\text{NOH}$  (*TMAH*) (E. Merck, A.G. Darmstadt) in 75% (*v/v*) dioxane was used as titrant.  $\text{HClO}_4$  was standardised and diluted to the required molarity (0.05 *M*) with doubly distilled water.  $\text{NaClO}_4$  (E. Merck) was used to maintain the ionic strength constant. Dioxane (E. Merck) was freed from peroxide by refluxing with sodium metal for 24 h and it was freshly distilled over sodium before use.

The solutions of lanthanide metal ions, viz.  $\text{La}^{3+}$ ,  $\text{Ce}^{3+}$ ,  $\text{Pr}^{3+}$ ,  $\text{Nd}^{3+}$ ,  $\text{Sm}^{3+}$ ,  $\text{Eu}^{3+}$ ,  $\text{Gd}^{3+}$ ,  $\text{Y}^{3+}$ ,  $\text{Tb}^{3+}$ , and  $\text{Dy}^{3+}$  were prepared and standardised by conventional methods [17].

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 measurements were made at a definite temperature maintained constant by using a MLW (West Germany) (NBE type) thermostat. A PC-XT computer was used for computation of equilibrium constants.

Investigations have been carried out at four different ionic strengths, viz. 0.100 *M*, 0.050 *M*, 0.025 *M*, and 0.010 *M*  $\text{NaClO}_4$  at 20°C. For each set of experiments, the final volume was made up to 20  $\text{cm}^3$  maintaining the 75% (*v/v*) dioxane medium.

The concentration of  $\text{HClO}_4$ , *HNATS* and metal ions in the volumes were 0.002 *M*, 0.00515 *M* and 0.00051 *M*, respectively. Each set was titrated against 0.05 *M* *TMAH* in 75% (*v/v*) dioxane-water medium.

The titrations were carried out in a covered double walled glass cell in an atmosphere of nitrogen which was presaturated with the solvent 75% (*v/v*) dioxane-water, before being passed into the reaction solution. The following sets of solutions have been titrated:

(i) 0.8 cm<sup>3</sup> HClO<sub>4</sub> (0.05 M) + 1.0 cm<sup>3</sup> NaClO<sub>4</sub> (2.0 M) + 3.2 cm<sup>3</sup> double distilled water + 15.0 cm<sup>3</sup> dioxane.

(ii) 0.8 cm<sup>3</sup> HClO<sub>4</sub> (0.05 M) + 1.0 cm<sup>3</sup> NaClO<sub>4</sub> (2.0 M) + 0.7 cm<sup>3</sup> double distilled water + 10.0 cm<sup>3</sup> ligand (0.01 M) + 7.5 cm<sup>3</sup> dioxane.

(iii) 0.8 cm<sup>3</sup> HClO<sub>4</sub> (0.05 M) + 1.0 cm<sup>3</sup> NaClO<sub>4</sub> (2.0 M) + 0.2 cm<sup>3</sup> double distilled water + 0.5 cm<sup>3</sup> metal ion solution (0.02 M) + 10.0 cm<sup>3</sup> ligand (0.01 M) + 7.5 cm<sup>3</sup> dioxane.

During complexation the phenolic proton of *HNATS* is replaced by an equivalent amount of metal.

From the titration curves of solutions (i), (ii), and (iii) the values of  $\bar{n}$  (average number of ligand bound per metal ion) and  $pL$  (free ligand exponent) have been calculated using a PC-XT computer. The corresponding values of stability constants have been calculated using the weighted least squares method of Sullivan et al. [18]. The weighted least squares treatment determines that set of  $\beta_n$  values which makes the function:

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

nearest to zero, by minimizing

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

with respect to the variation in  $\beta_n$ .

We report the  $S_{min}$  values for different metal complexes.  $S_{min}$  has the same statistical distribution as  $\chi^2$  with  $K$  degrees of freedom and with weights defined in accordance with Sullivan et al. [19].  $S_{min}$  can be equated to  $\chi^2$ . The stability constants thus calculated are given in Table 1.

## Results and Discussion

For calculation of  $\bar{n}$  and  $pL$  values we have taken the volume 19.67 cm<sup>3</sup> instead of 20 cm<sup>3</sup> due to volume contraction in dioxane-water medium. The  $pH$  values in aquo-organic mixtures were corrected using the method of Van Uitert and Hass [20] and volume corrections were also applied according to the method of Rao

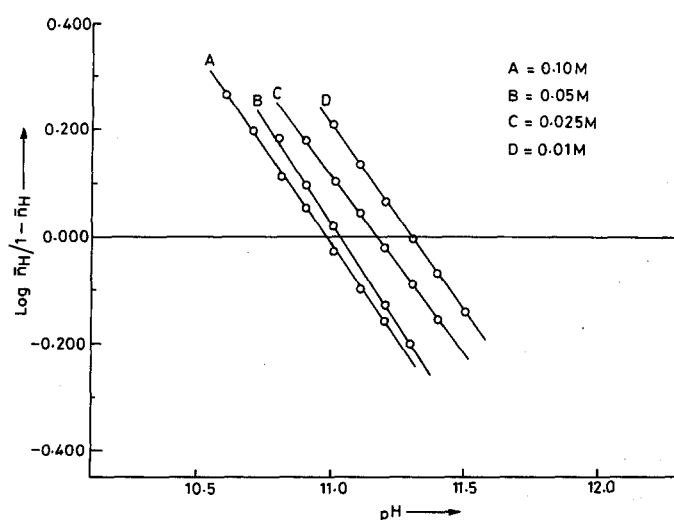


Fig. 1. Determination of proton ligand stability constants ( $pK_a$ ) of *HNATS* at  $\mu = 0.10$ , 0.05, 0.025, and 0.01 M NaClO<sub>4</sub> in 75% (v/v) dioxane-water medium at  $20 \pm 0.5^\circ\text{C}$

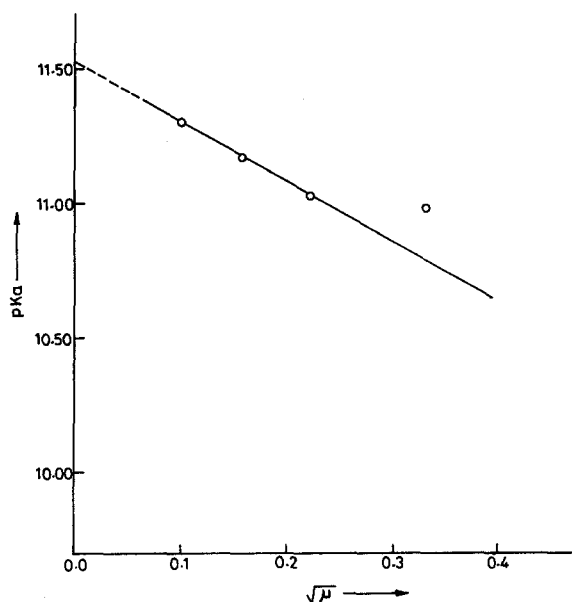


Fig. 2. Plot of ligand dissociation constants ( $pK_a$ ) of *HNATS* vs. ionic strength ( $\sqrt{\mu}$ )

and Mathur [21]. The values of  $\bar{n}_H$ , the average number of protons bound to each ligand molecule (which is not bound to the metal), were calculated at various  $pH$  values from the titration curves (i) and (ii). The  $pK_a$  (acid dissociation constant) of the ligand (*HNATS*) was obtained by plotting  $\log(\bar{n}_H/1-\bar{n}_H)$  vs.  $pH$  and the values thus obtained were 10.98, 11.03, 11.17, and 11.30 at  $\mu = 0.100 M$ ,  $0.050 M$ ,  $0.025 M$ , and  $0.010 M$   $\text{NaClO}_4$ , respectively, at  $20^\circ\text{C}$  (Fig. 1).

In these studies the values of ligand dissociation constants were found to decrease with increasing ionic strength of the medium (Fig. 2), in agreement with the Debye-Hückel equation [22].

$$pK_a^0 - [A\sqrt{\mu}/(1 + \alpha\sqrt{\mu})] + C\mu = pK_a$$

It has been observed that the stabilities from  $\text{La}^{3+}$  to  $\text{Dy}^{3+}$  follow the same order as the increasing acidity. The order of  $\log K_1$  values for *HNATS* complexes is found to be  $\text{La}^{3+} < \text{Ce}^{3+} < \text{Pr}^{3+} < \text{Nd}^{3+} < \text{Sm}^{3+} < \text{Eu}^{3+} < \text{Gd}^{3+} < \text{Y}^{3+} < \text{Tb}^{3+} < \text{Dy}^{3+}$ .

The same trend has also been reported by several workers [23–24]. The  $\log K_1$ ,  $\log K_2$ ,  $\log \beta_2$ ,  $\log K_1/K_2$  and  $S_{min}$  values at  $20 \pm 0.5^\circ\text{C}$  for the trivalent metal ion chelates at different ionic strengths are summarised in Table 1. Formation curves (plot  $\bar{n}$  and  $pL$ ) of metal complexes are shown in Fig. 3. For these chelates,  $\bar{n}$  values greater than 2.0 have not been obtained. We have, therefore, concluded that not more than two chelates of metal ( $M$ ) and ligand ( $L$ ) ratio, i. e. 1 : 1 and 1 : 2 ( $M:L$ ) are formed in each system.

As the tendency of a metal ion to take up a ligand is proportional to the number of vacant sites, the ratio between consecutive stability constants ( $\log K_1/\log K_2$ ), is to a certain extent statistically determined [25]. For anionic ligands the coulombic attraction is more for  $M^{3+}$  as compared to  $ML^{2+}$ . Therefore  $\log K_1 - \log K_2$  is usually positive [26]. Table 1 shows that for all systems studied here,  $\log K_1 - \log K_2$  is positive and lies within 0.51–1.78 log units.

**Table 1.** Formation constants of some lanthanide and yttrium metal ion chelates of *HNATS* at different ionic strength ( $\mu$ ) ( $M$  NaClO<sub>4</sub>) at a temperature of  $20 \pm 0.5^\circ\text{C}$ 

System	Stability constants and $S_{min}$ values	Weighted least squares method			
		Ionic strength ( $\mu$ )			
		0.100 $M$	0.050 $M$	0.025 $M$	0.001 $M$
<i>HNATS</i>	$pK_a$	10.98	11.03	11.17	11.30
$\text{La}^{3+}$ - <i>HNATS</i>	$\log K_1$	6.60	6.67	6.97	7.22
	$\log K_2$	5.12	4.97	5.33	5.98
	$\log (K_1/K_2)$	1.48	1.70	1.64	1.24
	$\log \beta_2$	11.72	11.64	12.30	13.20
	$S_{min}$	0.0040	0.0687	0.0267	0.0215
$\text{Ce}^{3+}$ - <i>HNATS</i>	$\log K_1$	7.10	7.22	7.47	7.53
	$\log K_2$	5.35	5.50	6.12	6.36
	$\log (K_1/K_2)$	1.75	1.72	1.35	1.17
	$\log \beta_2$	12.45	12.72	13.59	13.89
	$S_{min}$	0.0699	0.0020	0.0060	0.0317
$\text{Pr}^{3+}$ - <i>HNATS</i>	$\log K_1$	7.36	7.41	7.88	8.18
	$\log K_2$	5.58	6.22	6.77	6.88
	$\log (K_1/K_2)$	1.78	1.19	1.11	1.30
	$\log \beta_2$	12.94	13.63	14.65	15.06
	$S_{min}$	0.0063	0.0031	0.0111	0.0014
$\text{Nd}^{3+}$ - <i>HNATS</i>	$\log K_1$	7.40	7.48	8.00	8.21
	$\log K_2$	6.10	6.35	6.98	7.09
	$\log (K_1/K_2)$	1.30	1.13	1.02	1.12
	$\log \beta_2$	13.50	13.83	14.98	15.30
	$S_{min}$	0.0087	0.0296	0.0098	0.0149
$\text{Sm}^{3+}$ - <i>HNATS</i>	$\log K_1$	7.43	7.65	8.16	8.25
	$\log K_2$	6.37	6.46	6.82	7.33
	$\log (K_1/K_2)$	1.06	1.19	1.34	0.92
	$\log \beta_2$	13.80	14.11	14.98	15.58
	$S_{min}$	0.0105	0.0107	0.0095	0.0189
$\text{Eu}^{3+}$ - <i>HNATS</i>	$\log K_1$	7.45	7.69	8.22	8.38
	$\log K_2$	6.76	6.60	6.63	7.05
	$\log (K_1/K_2)$	0.69	1.09	1.59	1.33
	$\log \beta_2$	14.21	14.29	14.85	15.43
	$S_{min}$	0.0206	0.0166	0.0170	0.0061
$\text{Gd}^{3+}$ - <i>HNATS</i>	$\log K_1$	7.58	7.74	8.25	8.42
	$\log K_2$	6.95	6.64	6.73	7.13
	$\log (K_1/K_2)$	0.63	1.10	1.52	1.29
	$\log \beta_2$	14.53	14.38	14.98	15.55
	$S_{min}$	0.0363	0.0132	0.0292	0.0157
$\text{Y}^{3+}$ - <i>HNATS</i>	$\log K_1$	7.64	7.87	8.31	8.44
	$\log K_2$	7.13	6.48	6.85	7.26
	$\log (K_1/K_2)$	0.51	1.39	1.46	1.18
	$\log \beta_2$	14.77	14.35	15.16	15.70
	$S_{min}$	0.0413	0.0174	0.0139	0.0258

Table 1 (continued)

System	Stability constants and $S_{min}$ values	Weighted least squares method			
		Ionic strength ( $\mu$ )			
		0.100 M	0.050 M	0.025 M	0.001 M
$Tb^{3+}$ -HNATS	$\log K_1$	7.79	7.89	8.36	8.51
	$\log K_2$	7.04	6.77	7.00	7.46
	$\log (K_1/K_2)$	0.75	1.12	1.36	1.05
	$\log \beta_2$	14.83	14.66	15.36	15.97
	$S_{min}$	0.0174	0.0346	0.0298	0.0234
$Dy^{3+}$ -HNATS	$\log K_1$	7.90	7.95	8.43	8.71
	$\log K_2$	7.09	7.00	6.87	7.70
	$\log (K_1/K_2)$	0.81	0.95	1.56	1.01
	$\log \beta_2$	14.99	14.95	15.30	16.41
	$S_{min}$	0.0240	0.0524	0.0502	0.0155

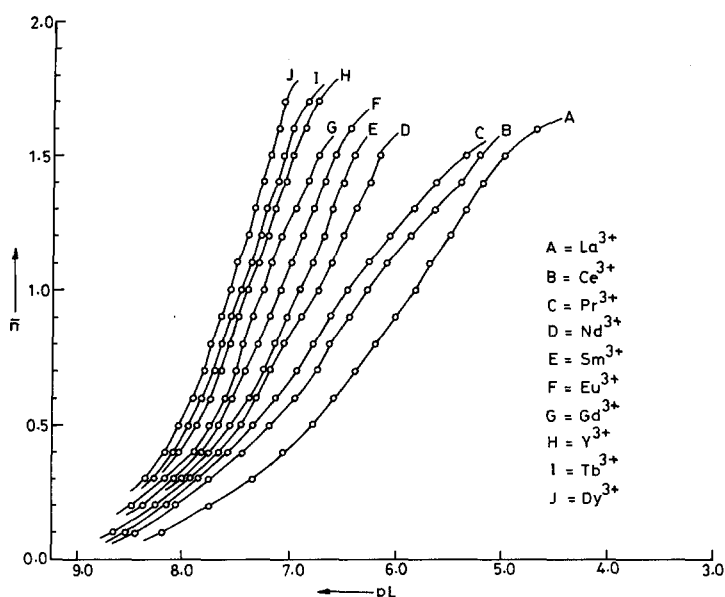


Fig. 3. Formation curves of lanthanide complexes of HNATS at  $\mu = 0.1 M NaClO_4$  in 75% (v/v) dioxane-water medium at  $20 \pm 0.5^\circ C$

The values of stability constants of lanthanon(III) complexes increase as the ionic radius of the metal ion decreases and the ionization potential increases, and only 2-hydroxy-1-naphthaldehyde thiosemicarbazone (HNATS) molecules enter into the coordination sphere of lanthanon(III) ions. The  $\log K_1$  value of yttrium lies between terbium and gadolinium because of the lack of ligand field stabilization.

In view of the fact that a very low concentration of metal ions ( $5.0 \times 10^{-4} M$ ) has been used in the titration, it has been assumed that the possibility of polynuclear complex formation is negligible.

On the basis of spectral studies of Varshney et al. [27], the tentative structures shown in the formulas can be assigned to the two forms of *HNATS* (**1** = thioamide form, **2** = thiolimine form) and its metal chelates (**3**). The structure of metal chelates of *HNATS* shows a tridentate nature with three binding sites.

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