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Physico-Chemical Studies on the Chelation Behaviour of Biologically Active 2-Hydroxy-1-Naphthaldehyde Semicarbazone (*HNAS*) with Some Lanthanons

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Summary. The chelation behaviour of the complexes of La^{3+}, Ce^{3+}, Pr^{3+}, Nd^{3+}, Sm^{3+}, Eu^{3+}, Gd^{3+}, Y^{3+}, Tb^{3+}, Dy^{3+}, Ho^{3+} with biologically active 2-Hydroxy-1-naphthaldehyde semicarbazone (*HNAS*) has been studied potentiometrically in 75% (*v*/*v*) dioxane-water medium at various ionic strengths. The method of Bjerrum and Calvin, as modified by Irving and Rossotti has been used to find out the values of $\bar{n}$ and pL. The formation constants of metal chelates and the values of S_{min} have been calculated. The order of formation constants of chelates was found to be: $La^{3+} < Ce^{3+} < Pr^{3+} < Nd^{3+} < Sm^{3+} < Eu^{3+} < Gd^{3+} < Y^{3+} < Tb^{3+} < Dy^{3+} < Ho^{3+}$.

Keywords. Potentiometry; Formation constant; 2-Hydroxy-1-naphthaldehyde semicarbazone (*HNAS*); Lanthanons.

Physikochemische Untersuchungen zur Komplexierung von biologisch aktivem 2-Hydroxy-1-naphthaldehyd-Semicarbazon (*HNAS*) mit Lanthanoiden

Zusammenfassung. Das Chelierungsverhalten von La^{3+}, Ce^{3+}, Pr^{3+}, Nd^{3+}, Sm^{3+}, Eu^{3+}, Gd^{3+}, Y^{3+}, Tb^{3+}, Dy^{3+} und Ho^{3+} mit 2-Hydroxy-1-naphthaldehydsemicarbazon (*HNAS*) wurde potentiometrisch in 75% (*v*/*v*) Dioxan-Wasser bei verschiedenen Ionenstärken untersucht. Die Werte für $\bar{n}$ und pL wurden nach der Methode von Bjerrum und Calvin in der Modifikation von Irving und Rossotti bestimmt. Die Komplexbildungskonstanten der Metallchelate und die Werte S_{min} wurden ermittelt. Die Reihung der Komplexbildungskonstanten war $La^{3+} < Ce^{3+} < Pr^{3+} < Nd^{3+} < Sm^{3+} < Eu^{3+} < Gd^{3+} < Y^{3+} < Tb^{3+} < Dy^{3+} < Ho^{3+}$.

Introduction

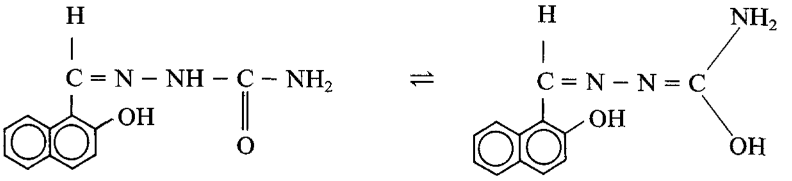
In comparison with d-block metal ions, the lanthanon ions as a whole form far fewer complexes and yield complexes with significantly different properties [1–3]. Metal chelates of 2-hydroxy-1-naphthaldehyde (*HNAS*) are well known for their analytical [4–5] and biological [6–7] activities. Domagk et al. [8] reported for the first time the antitubercular activities of metal semicarbazone. Since then a number of papers have appeared on the pharmacology of these compounds. The activity of semicarbazone is thought to be due to their power of chelation with traces of metal ions present in biological systems. The semicarbazones and thiosemicarbazones of certain ketones and aldehydes have significant antimicrobial activities [9–10]. A survey of literature reveals that some work has been done on the bivalent metal chelates of 2-hydroxy-1-naphthaldehyde semicarbazone (*HNAS*) [11–12] but no work on lanthanon complexes of this biologically active ligand has been reported till now. So, considering the wide applicability of *HNAS*, the present study was undertaken to investigate the chelation behaviour of lanthanons with this chelating agent at various ionic strengths in 75% (*v*/*v*) dioxane – water medium.

Materials and Methods

A digital pH-meter (ECIL model pH 5651) with a glass electrode (0–14 *pH* range) was used for *pH* measurements. The *pH* meter was standardized with potassium hydrogen phthalate and phosphate buffer before performing the titration.

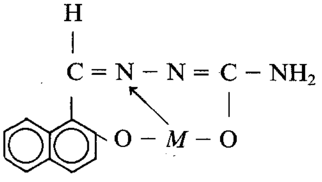
The preparation of 2-hydrody-1-naphthaldehyde semicarbazone (*HNAS*) has been reported in our earlier papers [11–12]. According to these papers 2-hydroxy-1-napthaldehyde (*HNA*) (Aldrich Chemical Co. U.S.A.) was dissolved in the minimum amount of ethanol and an aqueous solution having equal amounts of semicarbazide hydrochloride and anhydrous sodium acetate was added to it. The whole mixture was refluxed for 2 h, filtered and cooled in ice. The semicarbazone was precipitated by adding dilute hydrochloric acid and recrystallized from ethanol. The purity of this chelating agent was checked by m.p., TLC, elemental analysis, and IR, ^1H NMR spectra.

On the basis of these spectral data and using the results of Varshney et al. [13], the tentative structures of *HNAS* (amide form in solid and hydroxylamine form in solution) and the metal chelate of *HNAS* are as following:



(Amide form)
I

(Hydroxylamine form)
II



III

The structure of metal chelates of *HNAS* shows therefore three binding sites in the chelation process.

The solution of HNAS was prepared in freshly distilled dioxane. All the metal ion solutions were prepared and standardized by conventional procedures. Sodium perchlorate (E. Merck) was used to keep the ionic strength constant for differerent sets. A solution of tetramethyl ammonium hydroxide (*TMAH*) (E. Merck) in 75% (*v*/*v*) dioxane – water was used as a titrant. It was standardized with oxalic acid.

Dioxane (E. Merck) was freed from peroxide by refluxing it with sodium metal for 24 h and was freshly distilled over sodium before use. All other chemicals used were of reagent grade. The titrations were carried out in an atmosphere of nitrogen, which was presaturated with 75% (*v*/*v*)dioxane – water.

All measurements were made at a definite temperature which was kept constant by using a M.L.W. (Federal Republic of Germany) (NBE type) thermostat. A PC-XT computer was used for the calculation of stability constants of metal chelates. The method of Bjerrum and Calvin as modified by Irving and Rossotti [14], was used to determine $\bar{n}$ (average number of ligand molecule bound to per metal ion) and *pL* (free ligand exponent during the complexation process). The following solutions (total volume = 19.67 ml instead of 20 ml, due to contraction in volume on mixing dioxane and water) were titrated potentiometrically against 0.05 *M TMAH* in 75% (*v*/*v*) dioxane – water medium to determine $\bar{n}$ and *pL* values of the complexes.

(i) 0.8 ml $HClO_4$ (0.05*M*) + 1.0 ml $NaClO_4$ (2*M*) + 3.2 ml of double distilled H_2O + 15.0 ml of dioxane.

(ii) 0.8 ml $HClO_4$ (0.05*M*) + 1.0 ml $NaClO_4$ (2*M*) + 3.2 ml of double distilled H_2O + 10.0 ml of ligand (*HNAS*) + 5.0 ml of dioxane.

(iii) 0.8 ml $HClO_4$ (0.05*M*) + 1.0 ml $NaClO_4$ (2*M*) + 2.7 ml double distilled H_2O + 0.5 ml metal solution (0.02*M*) + 10.0 ml of ligand (*HNAS*) + 5.0 ml of dioxane.

In other sets a requisite amount of $NaClO_4$ was added to maintain the ionic strenght at 0.05, 0.025, and 0.010*M*.

From the corresponding titration curves of solutions (i) and (ii), the parameter $\bar{n}_H$, the average number of proton bound per free ligand ion, was determined by the expressions described by Irving and Rossotti [14] in order to evaluate the pK_a value (acid dissociation constant) of the ligand. The values of log ($\bar{n}_H/1 - \bar{n}_H$) versus *pH* gave linear plots with intercepts equal to the pK_a values and slopes equal to unit (shown in Fig. 1). During complexation, the phenolic group of *HNAS* dissociates first and the pK_a values of the ligand (*HNAS*) correspond to the dissociation of this group. Thus, *HNAS* acts as a monobasic acid.

From the above titration curves of solutions (i), (ii) and (iii) the values of $\bar{n}$ and *pL* have been calculated. The corresponding values of stability constants have been calculated using the weighted least squares method of Sullivan et al. [15]. The

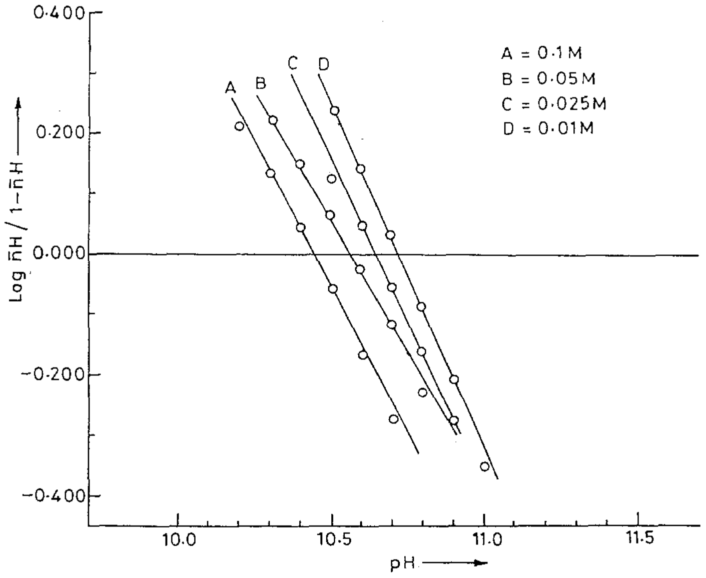


Fig. 1. Determination of the ligand dissociation constant value (pK_a) of *HNAS* at $\mu = 0.1\,M$, 0.05 *M*, 0.025 *M* and 0.01 *M* $NaClO_4$ in 75% (*v*/*v*) dioxan – water at 20 ± 0.5°C

Table 1. Stability constants of lanthanon metal ion complexes with 2-hydroxy-1-naphthaldehyde semicarbazone (*HNAS*) at varying ionic strengths (μ) (M $NaClO_4$) at a constant temperature (20 ± 0.5°C) in 75% (v/v) dioxane – water

System	Stability constants and S_{min}	Weighted least squares method			
		Ionic strength (μ)			
		0.100 M	0.050 M	0.025 M	0.010 M
HNAS	pK_a	10.4500	10.5600	10.6500	10.7200
La^{3+}-*HNAS*	log K_1	7.0962	7.9144	8.0474	9.1815
	log K_2	5.5438	5.9501	6.2145	7.2106
	log (K_1/K_2)	1.5524	1.9643	1.8329	1.9711
	log β_2	12.6400	13.8645	14.2619	16.3921
	S_{min}	0.0074	0.0076	0.0029	0.0101
Ce^{3+}-*HNAS*	log K_1	7.9140	8.2896	8.4927	9.2690
	log K_2	6.4806	6.3123	7.0032	7.2246
	log(K_1/K_2)	1.4334	1.9773	1.4895	1.8444
	log β_2	14.3946	14.6019	15.4959	16.4936
	S_{min}	0.0115	0.0200	0.0020	0.0082
Pr^{3+}-*HNAS*	log K_1	8.2921	8.6201	8.8459	9.5912
	log K_2	6.8996	6.7442	7.2345	7.6952
	log ($K1/K_2$)	1.3925	1.8759	1.6114	1.8960
	log β_2	15.1917	15.3643	16.0804	17.2864
	S_{min}	0.0293	0.0302	0.0217	0.0557
Nd^{3+}-*HNAS*	log K_1	8.6697	9.0422	9.1694	9.8223
	log K_2	6.9749	7.2919	7.2868	7.7290
	log (K_1/K_2)	1.6948	1.7503	1.8826	2.0933
	log β_2	15.6446	16.3341	16.4562	17.5513
	S_{min}	0.0053	0.0060	0.0158	0.0067
Sm^{3+}-*HNAS*	log K_1	8.9595	9.1492	9.2716	9.9142
	logK_2	7.1883	7.3802	7.6043	7.9854
	log (K_1K_2)	1.7712	1.7690	1.6673	1.9288
	log β_2	16.1478	16.5294	16.8759	17.8996
	S_{min}	0.0036	0.0484	0.0180	0.0268
Eu^{3+}-*HNAS*	log K_1	9.0479	9.5759	9.8153	10.0380
	log K_2	7.2366	7.6134	7.6900	8.0099
	log (K_1/K_2)	1.8113	1.9625	2.1253	2.0281
	log β_2	16.2845	17.1893	17.5053	18.0479
	S_{min}	0.0013	0.0440	0.0028	0.0141
Gd^{3+}-*HNAS*	log K_1	9.1218	9.8437	10.0277	10.2801
	log K_2	7.4193	7.8871	7.9679	8.2168
	log (K_1/K_2)	1.7025	1.9566	2.0598	2.0633
	log β_2	16.5411	17.7308	17.9956	18.4969
	S_{min}	0.0023	0.0090	0.0396	0.0053
Y^{3+}-*HNAS*	log K_1	9.2153	9.9297	10.1910	10.3538
	log K_2	7.5994	8.2031	8.0674	8.4311
	log (K_1/K_2)	1.6159	1.7266	2.1236	1.9227

Table 1 (continued)

System	Stability constants and S_{min}	Weighted least squares method			
		Ionic strength (μ)			
		0.100 *M*	0.050 *M*	0.025 *M*	0.010 *M*
	log β_2	16.7147	18.1328	18.2584	18.7839
	S_{min}	0.0025	0.0499	0.0242	0.0159
Tb^{3+}-*HNAS*	log K_1	9.3153	10.3316	10.4929	10.5559
	log K_2	7.5994	8.4097	8.5142	8.5925
	log (K_1/K_2)	1.7159	1.9219	1.9787	1.9627
	log β_2	16.9147	18.7413	19.0071	19.1477
	S_{min}	0.0025	0.0134	0.0061	0.0033
Dy^{3+}-*HNAS*	log K_1	9.5515	10.5206	10.5479	10.7624
	log K_2	7.7929	8.8390	8.6611	8.7340
	log (K_1/K_2)	1.7586	1.6216	1.8868	2.0284
	log β_2	17.3444	18.3596	19.2090	19.4964
	S_{min}	0.0049	0.0105	0.0696	0.0108
Ho^{3+}-HNAS	log K_1	9.5807	10.6314	10.7748	10.8653
	log K_2	7.9766	9.4309	9.6172	9.3196
	log (K_1/K_2)	1.6041	1.2005	1.1576	1.5457
	log β_2	17.5573	20.0623	20.3920	20.1849
	S_{min}	0.0196	0.1224	0.0717	0.0908

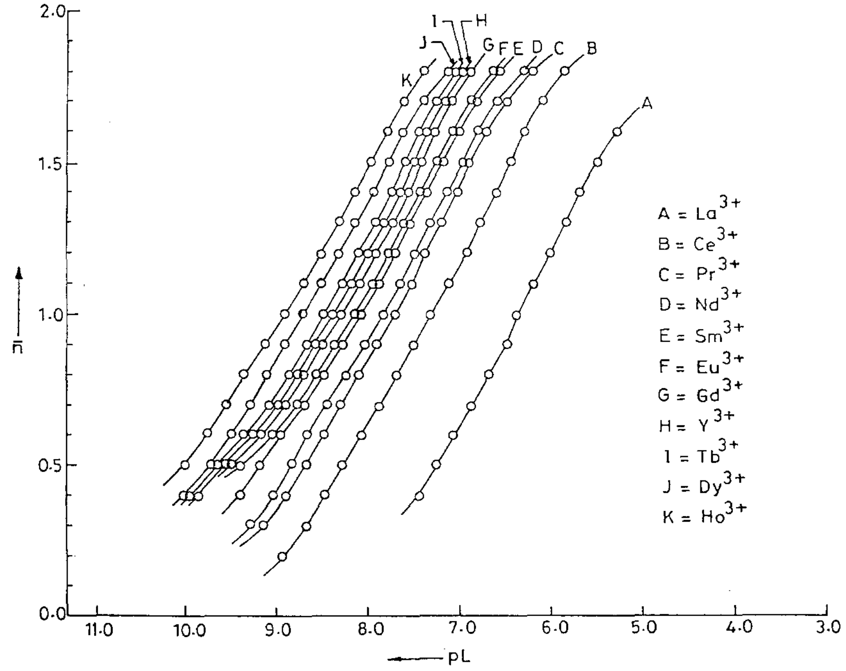


Fig. 2. Formation curves of lanthanon complexes of *HNAS* at $\mu = 0.10\,M$ $NaClO_4$ in 75% (*v*/*v*) dioxan – water and at 20 ± 0.5°C

weighted least squares treatemnt determines the set of β_n values which give the function U,

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

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 β_n.

S_{min} has the same statistical distribution as χ^2 with K degrees of freedom and with weight defined in accordance with Sullivan et al. [16]. S_{min} can be equated to χ^2. The stability constants and S_{min} values calculated are given in Table 1. The formation curves ($\bar{n}$ vs pL) for the metal chelates are shown in Figs. 2–5.

Results and Discussion

Chelates of lanthanon ions with *HNAS* show an increase in stability from La^{3+} to Ho^{3+} in agreement with the increasing acidity of the metal ion. The order of stability constants for the first and second steps in the formation of lanthanide complexes with *HNAS* is found to be: $La^{3+} < Ce^{3+} < Pr^{3+} < Nd^{3+} < Sm^{3+} < Eu^{3+} < Gd^{3+} < Y^{3+} < Tb^{3+} < Dy^{3+} < Ho^{3+}$. The same trend has also been noticed in the chelates of α-iminodiacetic acid, α-hydroxy isobutyric acid, nitrilotriacetic acid (*NTA*), ethylenediamine N,N,N′,N′-tetraacetic acid (*EDTA*),

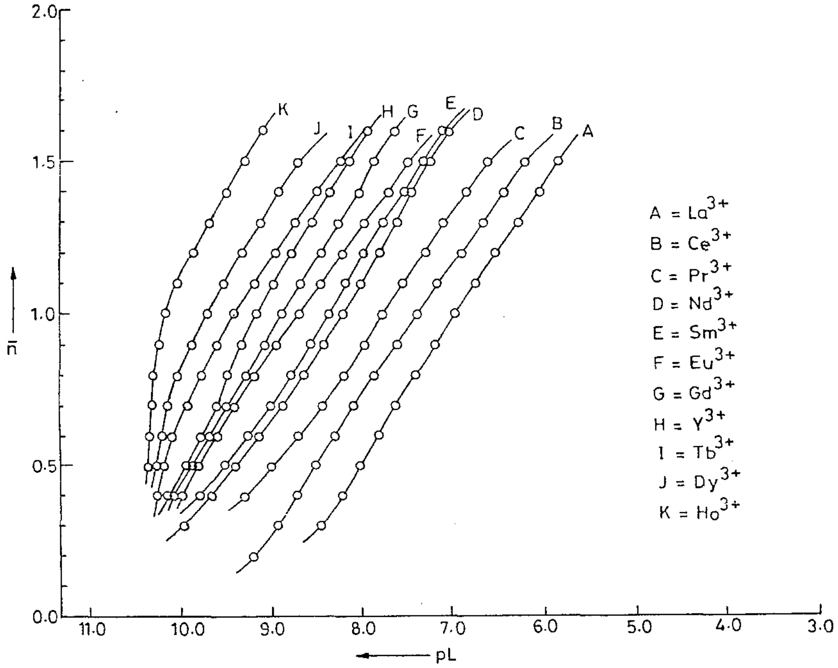


Fig. 3. Formation curves of lanthanon complexes of *HNAS* at $\mu = 0.05\,M$ $NaClO_4$ in 75% (*v*/*v*) dioxan–water and at 20±0.5°C

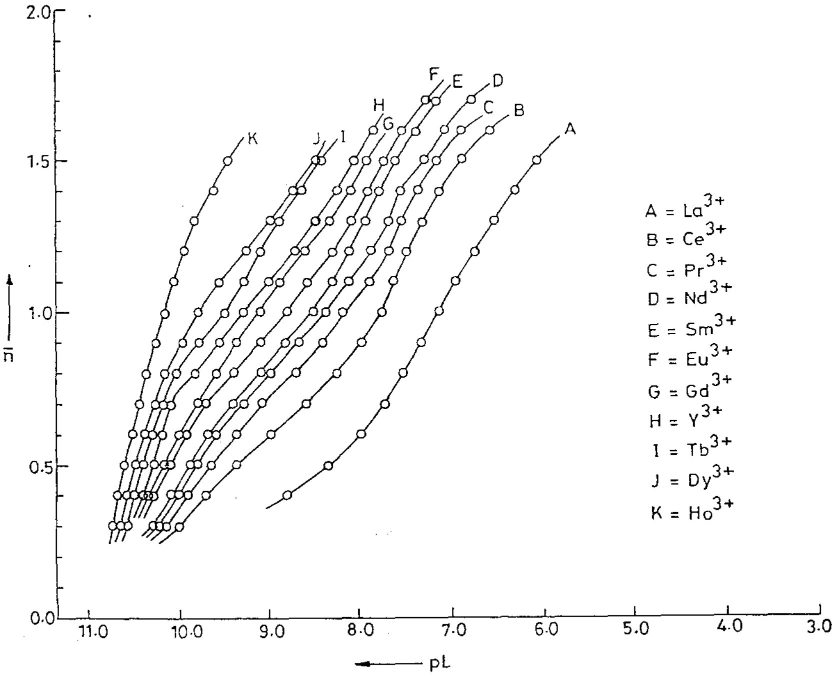


Fig. 4. Formation curves of lanthanon complexes of *HNAS* at $\mu = 0.025\,M$ $NaClO_4$ in 75% (*v*/*v*) dioxan – water and at 20 ± 0.5°C

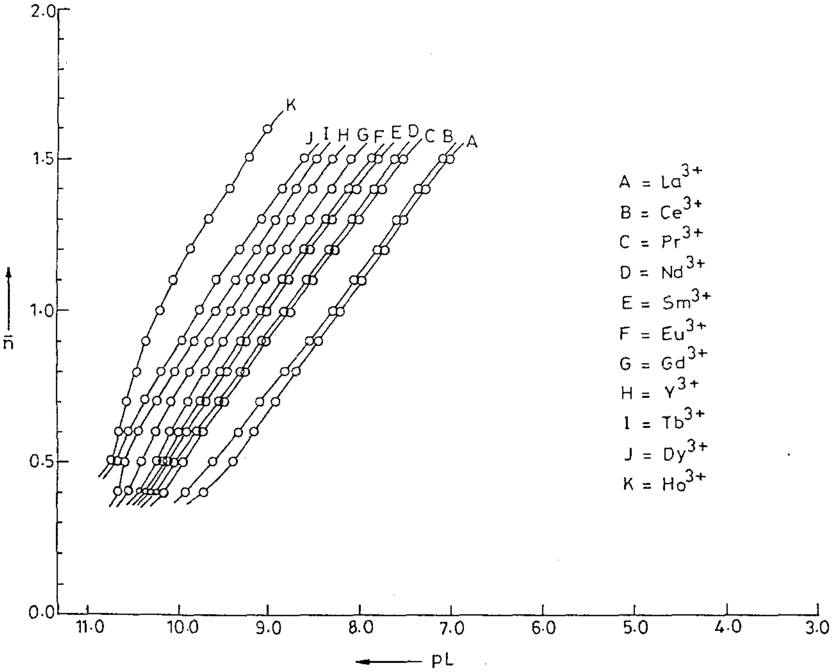


Fig. 5. Formation curves of lanthanon complexes of *HNAS* at $\mu = 0.01\,M$ $NaClO_4$ in 75% (*v*/*v*) dioxan – water and at 20 ± 0.5°C

tropolone, β-isopropyl tropolone [17] and *cis*-1,2,3,4-cyclopentane-tetracarboxylic acid [18].

The log K_1, log K_2, log (K_1/K_2), log β_2 and S_{min} value at 20 ± 0.5°C for lanthanon metal ion chelates at different ionic strength for *HNAS* are summarized in Table 1. 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 [19]. For anionic ligands the coloumbic attraction is more for M^{3+} as compared to $(ML)^+$; log K_1–log K_2 is usually positive [20]. Table 1 shows that for all systems studied here, log K_1–log K_2 is positive and lies within 1.1576–2.1253 log units.

The log K_1 values for yttrium lie between terbium and gadolinium due to the lack of ligand field stabilization. For these metal chelates no $\bar{n}$ values greater than 2.0 have been obtained. We have therefore concluded that not more than two chelates, i.e. 1 : 1 and 1 : 2 (M : L), are formed in each system. Due to the very low concentration of metal ion ($5.0 \cdot 10^{-4} M$) which was used in the titration, it may be assumed that the possibility of polynuclear complex formation is negligible.

In these studies the stability constants of the metal chelates are found to decrease with increasing ionic strengths of the medium which is in agreement with the Debye-Hückel equation [19]. Similar to the stability constants, the values of the proton dissociation constants (pK_a) of *HNAS* were also found to decrease with the increase of ionic strength of the medium (shown in Fig. 6).

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

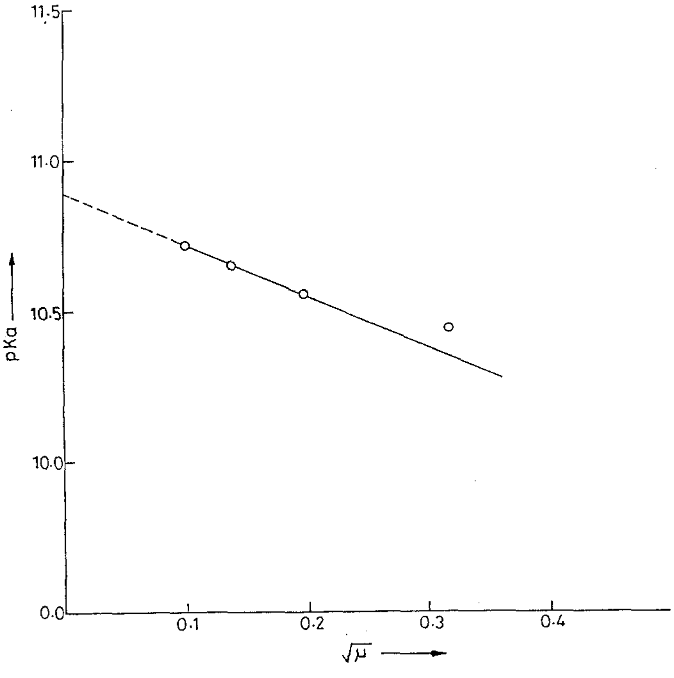


Fig. 6. Plot of ligand dissociation constants (pK_a) of *HNAS* vs. ionic strength ($\sqrt{\mu}$)

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