Thermodynamics of the Complexation of *N*-(Pyridin-2-ylmethylene) Isonicotinohydrazide with Lighter Lanthanides

Sharmeli Yumnam and Lonibala Rajkumari*

Department of Chemistry, Manipur University, Manipur 795 003, India

N-(Pyridin-2-ylmethylene)isonicotinohydrazide, pmINH, has been synthesized and characterized on the basis of elemental and spectral data. The protonation constants of pmINH and the stability constants of the base with trivalent La, Pr, Nd, Sm, Eu, and Gd at constant ionic strength (I, mol·dm^{-3} = 0.05 M $NaClO_4$) and at different temperatures, T = (293, 303, and 313) K, were determined potentiometrically in water−dioxane (30 %) medium. The ligand forms only 1:1 complexes with the lanthanides. Both protonation and complexation reactions are found to be exothermic in nature. The trend in the formation constants follows the order: $La^{3+} < Pr^{3+} < Nd^{3+} < Gd^{3+} < Sm^{3+} < Eu^{3+}$ and shows a break at gadolinium. The thermodynamic parameters associated with the complexation reactions were also calculated. The values of ΔG, ΔH, and ΔS are negative for all the systems and suggest that all reactions are enthalpy driven. The thermodynamic parameters of the complexation are correlated with the reciprocal ionic radii of the metal ions. Raw and normalized isothermal calorimetric data for the titrations of Gd^{3+}−pmINH solutions at 303 K show that the reaction was exothermic and metal−ligand stoichiometry to be 1:1.

1. Introduction

The chemical properties of hydrazones having N,O-donor atoms have been intensively investigated in several research areas. The interest in the study of these compounds arose from their tendency to form chelates with transition metals, lanthanides, and main group metals, and their interactions have served as model systems for the study of many biomolecules and metalloproteins. There have been several reports on metal complexes of hydrazones having a variety of applications in medicine, analytical, industrial, and organic synthesis.[1−6] In recent years, there has been an increased interest in the study of the lanthanide complexes. Owing to the unique properties of the lanthanide ions, lanthanides have often been effectively employed as active Ca^{2+} and Mg^{2+} substitutes in many metalloproteins,[7] as chiral NMR shift reagents, MRI contrast agents,[8] and also luminescent probes of metal binding in biological systems.[9] Thus, keeping the above facts in mind and in continuation of our earlier work,[10,11] we have carried out a solution study on the complexation of a hydrazone derived from the condensation of isonicotinic acid hydrazide (INH) and 2-pyridine carbaldehyde with some trivalent lanthanides at various temperatures at a constant ionic strength because such a study may help to explain the nature and driving forces for the interactions of lanthanides with a ligand. We report herein the dissociation constant of the hydrazone (pmINH) (**1**), the stability constants of the complexes, and the thermodynamic parameters that have been calculated based on the formation constants.

2. Experimental Section

2.1. Materials and Solutions. Isonicotinic acid hydrazide, pyridine-2-carbaldehyde, NaOH, $HClO_4$, and $NaClO_4$ were obtained from E. Merck, and the metal salts $LnCl_3$ and $6H_2O$ (Ln = La, Pr, Nd, Sm, Eu, Gd) were purchased from Sigma-Aldrich. All solutions of NaOH, $HClO_4$, $NaClO_4$, and the metal salts were prepared in double distilled water. Sodium hydroxide solution was standardized[12] with standard oxalic acid solution (0.05 M), which was again used for the standardization of $HClO_4$. The metal salt solutions were standardized.[13] The ligand solution was prepared in 1,4-dioxane (E. Merck).

2.2. Apparatus and Procedure. Potentiometric Titration. Potentiometric titrations were carried out using a Systronic μ-362 pH meter with a glass calomel electrode at three different temperatures, (293, 303, and 313) K. All the titrations were thermostatted with a Circular D_8-G Haake Mess Techinik. In all the cases, the pH meter has been standardized with standard buffer solutions of pH 4.00, 7.00, and 9.00.

Three sets of reaction mixtures were prepared and titrated potentiometrically against standard 0.02 M NaOH solution: (a) 1.00 mL of $HClO_4$ (0.001 M) + 1.25 mL of $NaClO_4$ (0.05 M), (b) solution (a) + 1.00 mL of pmINH (0.0003 M), and (c) solution (b) + 2.5 mL of $LnCl_3 \cdot 6H_2O$ (0.00015 M). The volume of each set was made up to 25 mL with 30 % (v/v) aqueous−dioxane mixture. The ionic strength of each reaction mixture was maintained at 0.05 M using $NaClO_4$ solutions. The equations of Irving and Rossotti[14,15] were used to determine the protonation constant of the ligand and the formation constants of the complexes. The pH titrations were terminated when the pH readings became unstable. In all cases, no calculations have been performed beyond the precipitation point. Therefore, the hydroxyl species likely to be formed beyond this point could not be studied.

Calorimetric Titration. The isothermal calorimetric (ITC) titrations were performed with a 2-Drop Calorimeter (Calorimetric Science Corporation, Utah) at 303 K. This titration measures the heat released or absorbed by the stepwise addition of a ligand solution to a solution containing the metal ion. For measurements, the metal solution (0.5 mL of 0.003 M $GdCl_3$ solution) was loaded into the sample cell of the calorimeter. A stirrer-syringe designed for the calorimeter was then fitted with 0.1 mL of 0.03 M ligand solution. Temperature equilibration

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* Corresponding author. E-mail: lonirk@yahoo.co.uk. Fax No.: 0385 2435 145.

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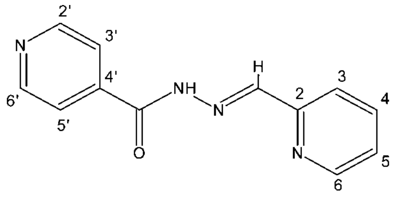


pmINH (1)

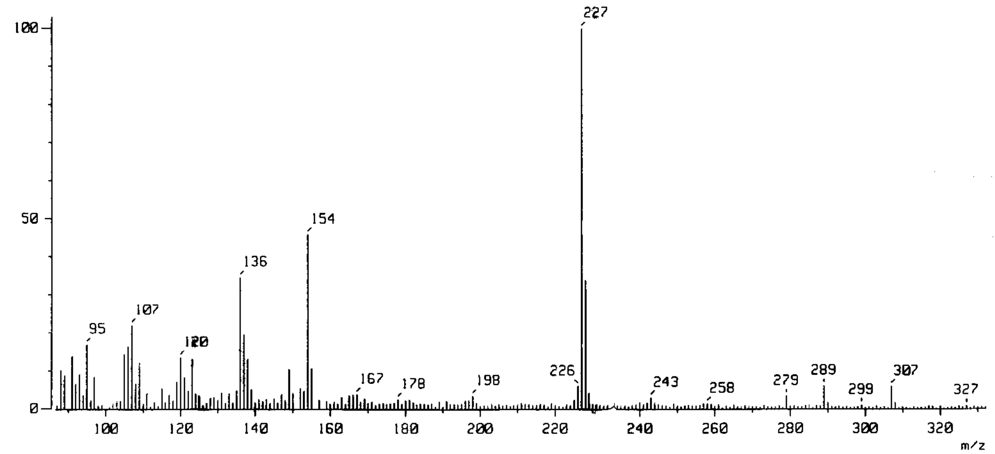


Figure 1. Mass spectrum of pmINH.

at 303 K (~2 h) was then allowed to occur. Once the stable baseline was recorded, the automated programmed injection sequence of the ligand solution into the metal salt solution was initiated. The heat change observed for each injection is displayed as a peak on a computer-output plot, and the area of each peak represents the amount of heat evolved accompanying binding of the ligand, for the amount of ligand added in the particular injection. The total heat evolved was then plotted against the total ligand concentration, employing the computer software (BindWork 3.0), and metal−ligand stoichiometry (*n*) was obtained by nonlinear least-squares fitting of the experimental data using a single-site binding model of the Origin software package (version 4.0) provided with the instrument.

2.3. Preparation and Characterization of the Ligand. *N*-(Pyridin-2-ylmethylene) isonicotinohydrazide, pmINH, was prepared by refluxing the ethanolic solutions of isonicotinic acid hydrazide (0.02 M, 2.747 g in 30 mL) and pyridine-2-carbaldehyde (0.02 M, 2.142 g in 5 mL) for 4 h. Solid crystals precipitated out on cooling the reaction mixture. The precipitate was filtered and washed with ethanol. It was then recrystallized from warm ethanol to give pale yellow crystals. % yield = 80 %; mp (162 to 4) °C; M^+ peak at 227 as the base peak in the mass spectrum of the ligand (Figure 1).

Elemental Analysis: Found % (calcd % for $C_{12}H_{10}N_4O$). C, 63.85(63.72); H, 4.25(4.42); N, 24.97(24.78); N_2H_4, 14.01(14.16).

IR (ν, cm^{-1}). 3294 (NH), 1666 (amide I), 1545 (amide II), 1587 (CN), 993 (NN), 951, 684, and 447 (pyridine ring vibrations).

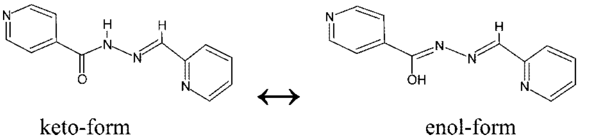
^1H NMR (δ). 12.25 (s, NHCO), 2.08 (s, CH), 8.82 − 8.49 (d, ring protons), 8.01 − 7.43 (m, ring protons).

^{13}C NMR (ppm). 162.36 (s, CO), 153.41 (s, NCH), 150.86 − 120.56 (8s, ring carbons).

2.4. Physical Measurements. C, H, and N were microanalyzed using a Perkin-Elmer model 240C, and the hydrazine content was estimated volumetrically, after subjecting the compound to acid hydrolysis for 4 h. The IR spectrum was recorded in a KBr medium on a Shimadzu FTIR-8400, and the mass spectrum was obtained on a JEOLSX102/DA.6000 mass spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on a Jeol AL 300 FT NMR spectrometer.

3. Results and Discussions

3.1. Titration Curves. The ligand, pmINH, was potentiometrically titrated with standard NaOH at $I = 0.05$ mol·dm^{-3} $NaClO_4$ and at three different temperatures, (293, 303, and 313) K. Figure 2 represents the potentiometric equilibrium curves at 303 K where (a) represents the acid titration curve, (b) the ligand curve, and (c−h) the metal−ligand titration curves for La^{3+}, Pr^{3+}, Nd^{3+}, Sm^{3+}, Eu^{3+}, and Gd^{3+}, respectively. Similar curves are obtained for the titrations at other temperatures. A single inflection point is observed at pH 5 to 11.5, which corresponds to the neutralization of one proton in the aqueous−dioxane solution. Addition of metal ion to the free ligand solution shifts the buffer region of the ligand to a lower pH value as observed in the curves (c−h). This shows that complex formation proceeds by releasing protons from the base. Hydrazones are reported[2,3,16] to bond to metal ions through the carboxylic oxygen and hydrazinic nitrogen/nitrogen of the imino group in the aqueous medium where there is a conjugate chelate ring formed by ligand enolization in the complexes. Thus, pmINH is also expected to exhibit keto−enol tautomerism, and the amido proton can be dissociated through enolization as shown in eq 1.



(1)

3.2. Protonation Constant. The proton dissociation constant (log K_1^H) of the ligand pmINH has been used for computation of

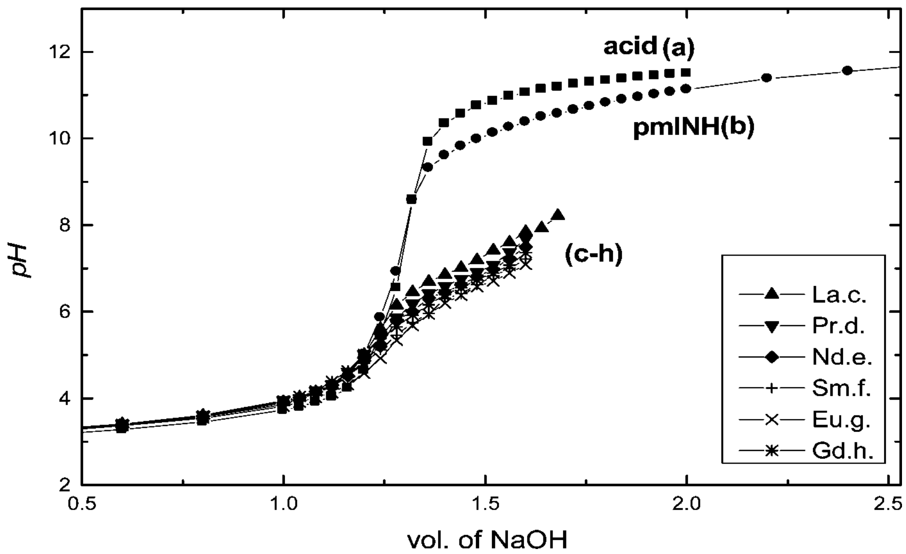


Figure 2. Potentiometric titration curves of Ln^{3+}−pmINH complexes at $I = 0.05\ \text{mol}\cdot\text{dm}^{-3}$ $NaClO_4$ at 303 K.

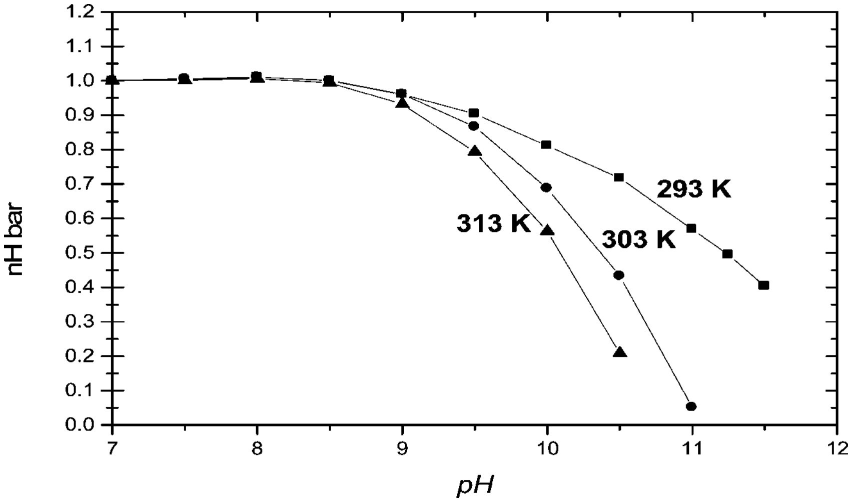


Figure 3. Proton−ligand formation curves at different temperatures and $I = 0.05\ \text{mol}\cdot\text{dm}^{-3}$ $NaClO_4$.

the stability constant of the metal−ligand complexes. Log $K_1{}^H$ was determined from the acid−ligand titration curves using the Irving−Rossotti technique.[15] The average number of protons, $\bar{n}_H$, associated with pmINH at various pH meter readings was calculated from acid and ligand titration curves using the relation (2)

$$\bar{n}_H = Y - \frac{(V_L - V_A)(N + E^0)}{(V_0 + V_A)T_L^0} \tag{2}$$

where Y is the number of dissociable protons present in the ligand. V_L and V_A are the volumes of NaOH of concentration N (0.02 M) consumed by solutions (b) and (a), respectively, for the same pH reading, and (V_L − V_A) measures the displacement of the ligand curve with respect to the acid curve. V_0 is the initial volume of the reaction mixture (25 cm^3), and E^0 and T_L^0 are the resultant concentrations of perchloric acid (0.001 M) and pmINH (0.0003 M) in the reaction mixture, respectively. The protonation curves for the proton−ligand systems at temperatures (293, 303, and 313) K (Figure 3) were obtained by plotting $\bar{n}_H$ vs pH. The curves do not extend beyond 1.0 on the $\bar{n}_H$ scale showing the presence of only one dissociable proton in the ligand. The protonation constants of the ligand at different temperatures were evaluated from the curves using Bjerrum's half-integral method[17] and are collected in Table 1.

Table 1. Protonation Constant (log $K_1{}^H$) of pmINH and Thermodynamic Parameters of the Dissociation Reaction of the Ligand at Different Temperatures and at $I = 0.05\ \text{mol}\cdot\text{dm}^{-3}$ $NaClO_4$ in 30 % (v/v) Aqueous−Dioxane Mixture

temperature (K)	log $K_1{}^H$	−ΔG (kJ·mol^{-1})	−ΔH^a (kJ·mol^{-1})	−ΔS^a (J·deg^{-1}·mol^{-1})
293	11.26 ± 0.00	63.18 ± 0.02	104.81 ± 0.04	147.19 ± 0.04
303	10.38 ± 0.01	60.21 ± 0.02		
313	10.10 ± 0.01	60.54 ± 0.03		

[a] ΔH and ΔS were computed using the linear-fit program.

The decrease in the protonation constant value of pmINH with an increase in temperature shows that dissociation of the ligand is favorable at lower temperature, and the values so obtained are in good agreement with the reported data.[18]

3.3. Metal Ligand Formation Constant. $\bar{n}$ is the average number of ligands attached per metal ion and is determined by the following expression

$$\bar{n} = \frac{(V_M - V_L)(N + E^0)}{(V_0 + V_A)T_M^0\bar{n}_H} \tag{3}$$

where N, E^0, V_L, V_0, and V_A have the same meaning as in eq 2. V_M is the volume of alkali added to solution (c) to attain the pH reading as that of V_L and T_M^0 is the metal ion concentration

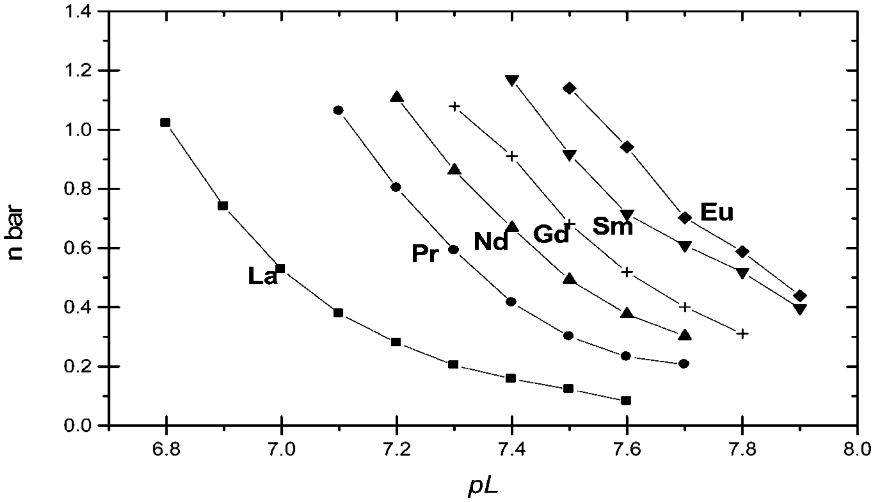


Figure 4. Metal−ligand formation curves of Ln^{3+}−pmINH chelates at $I = 0.05$ mol·dm^{-3} $NaClO_4$ at 303 K.

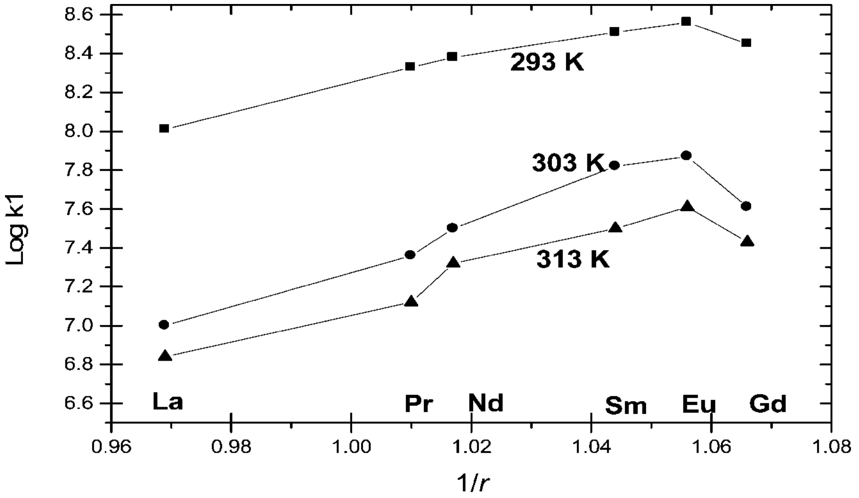


Figure 5. Plot of log K vs $1/r$.

Table 2. Stability Constants (log K) of Ln^{3+}−pmINH Chelates (1:1) at Different Temperatures and at $I = 0.05$ mol·dm^{-3} $NaClO_4$ in 30 % (v/v) Aqueous−Dioxane Mixture

temperature	lanthanides					
(K)	La^{3+}	Pr^{3+}	Nd^{3+}	Sm^{3+}	Eu^{3+}	Gd^{3+}
293	8.01 ± 0.01	8.33 ± 0.02	8.38 ± 0.01	8.51 ± 0.04	8.56 ± 0.02	8.45 ± 0.02
303	7.00 ± 0.00	7.36 ± 0.01	7.50 ± 0.03	7.82 ± 0.01	7.87 ± 0.04	7.61 ± 0.03
313	6.84 ± 0.03	7.12 ± 0.02	7.32 ± 0.05	7.50 ± 0.01	7.61 ± 0.02	7.43 ± 0.00

(0.00015 M) in the reaction mixture. The values of $\bar{n}$ ($0.2 < \bar{n} < 1.5$) indicate that the complexes formed are in the 1:1 metal−ligand stoichiometry. The free ligand exponent, pL, was calculated from relation (4)

$$pL = \log_{10}\left[\frac{\sum_{n=0}^{n=j}\beta_n H\left(\frac{1}{\text{anti log pH}}\right)^n}{T_L^0 - \bar{n}T_M^0}\cdot\frac{V_0 + V_M}{V_0}\right] \tag{4}$$

The metal−ligand formation curves for the Ln^{3+}−pmINH complexes at various temperatures (Figure 4) were obtained by plotting $\bar{n}$ vs pL. The stability constants (log K) of the complexes evaluated[17] from these curves are given in Table 2. At constant temperature, the stability of the metal chelates increases in the order: $La^{3+} < Pr^{3+} < Nd^{3+} < Gd^{3+} < Sm^{3+} < Eu^{3+}$. The steady increase in stability constants from La^{3+} to Eu^{3+} may be due to a decrease in size with subsequent increase in ionic potential of the Ln^{3+} along the series.[19] The decrease of the values of the stability constants with temperature (Table 2) shows that the complex formation process is exothermic in nature and more favorable at lower temperature. A plot of log K_1 vs $1/r$ (Figure 5) indicates that the stability constants of metal chelates increase with atomic number and there is a break at gadolinium, the half-filled shell ion which is in accordance with the results of earlier workers.[20−22] The abnormal behavior of Gd^{3+} known as the "Gd break" may be attributed to (i) zero-field stabilization energy, (ii) unavailability of the well-shielded 4f electron for bond formation,[23] and (iii) a structural change in the hydration sphere of lanthanide ions near the middle of the series.[20,24]

3.4. Effect of Temperature. The change in free energy (ΔG) was calculated from the formation constant values (log K) at various temperatures using the following equation

$$\Delta G = -2.303RT \log K \tag{5}$$

where R (ideal gas constant) = 8.314 J·K^{-1}·mol^{-1}; K = dissociation constant of pmINH or stability constant of the complexes; and T = absolute temperature.

Table 3. Thermodynamic Parameters of Ln^{3+}−pmINH (1:1) Complexes at Various Temperatures and $I = 0.05$ mol·dm^{-3} $NaClO_4$ in 30 % (v/v) Aqueous−Dioxane Mixture

	$-\Delta G$ (kJ·mol^{-1})			$-\Delta H^a$	$-\Delta S^a$
Ln^{3+}−pmINH chelates	293 K	303 K	313 K	(kJ·mol^{-1})	(J·deg^{-1}·mol^{-1})
La^{3+}	44.94 ± 0.04	40.75 ± 0.01	41.00 ± 0.04	105.44 ± 0.05	213.47 ± 0.05
Pr^{3+}	46.74 ± 0.03	42.68 ± 0.01	42.68 ± 0.02	109.16 ± 0.05	219.41 ± 0.05
Nd^{3+}	47.03 ± 0.03	43.51 ± 0.01	43.85 ± 0.02	99.75 ± 0.06	171.80 ± 0.04
Sm^{3+}	47.74 ± 0.01	45.35 ± 0.01	44.94 ± 0.03	91.76 ± 0.04	153.13 ± 0.04
Eu^{3+}	48.03 ± 0.02	45.65 ± 0.01	45.56 ± 0.03	86.32 ± 0.05	134.22 ± 0.03
Gd^{3+}	47.40 ± 0.03	44.14 ± 0.02	44.52 ± 0.04	91.96 ± 0.05	157.82 ± 0.06

[a] ΔH and ΔS were computed using the linear-fit program.

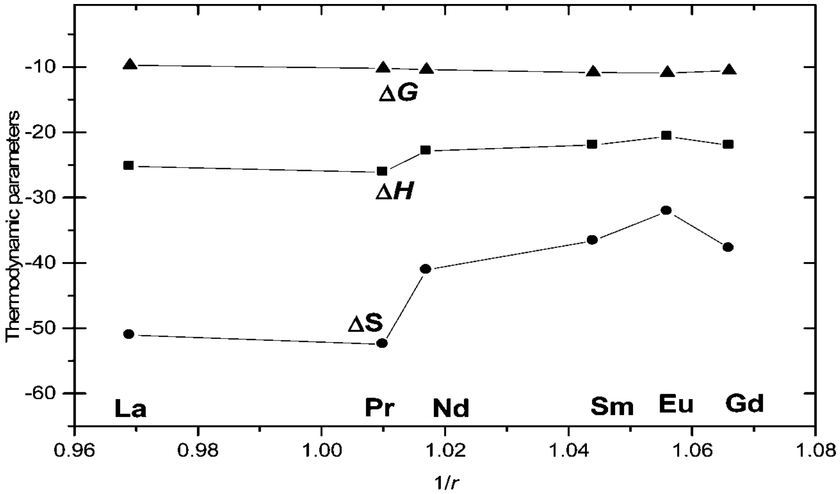


Figure 6. Thermodynamic parameters against $1/r$. ΔG plotted are the values at 303 K.

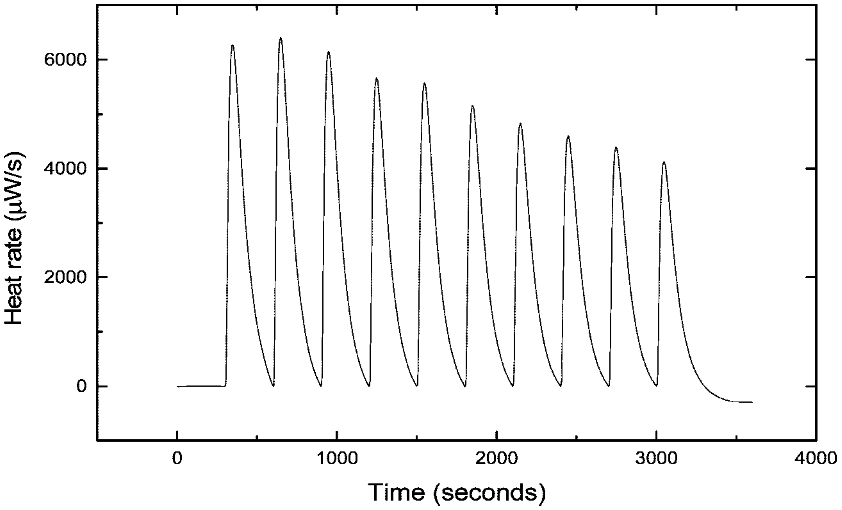


Figure 7. Raw isothermal titration calorimetry data demonstrating saturable exothermic evolution of heat upon sequential addition of pmINH to Gd^{3+} solution. Area is corrected after statistical fittings.

The enthalpy change (ΔH) for the dissociation of pmINH and complexation process was evaluated from the slope of the plot (log K_1^H or log K vs $1/T$) using the graphical representation of Van't Hoff's equation (6), and the change in entropy (ΔS) could then be calculated using relationship (7)

$$\Delta G = \Delta H - T\Delta S \tag{6}$$

$$\Delta S = (\Delta H - \Delta G)/T \tag{7}$$

The calculated thermodynamic parameters for the dissociation of pmINH are included in Table 1, and those for the complexation are collected in Table 3. It is observed from the tables that all the values of the thermodynamic parameters are negative. The negative ΔG values indicate that both dissociation of the ligand and the complexation process are spontaneous. These values have no sharp behavior with temperature showing the independent nature of the reactions with respect to temperature.[25]

A decrease in log K with an increase in temperature and the negative values of ΔH for the complexation show that all the complexation reactions are exothermic, and the metal−ligand binding process is enthalpy driven. However, the ΔS values are all negative, and the complexation has an unfavorable change of entropy. An extensive solvation of metal chelates in aqueous−organic medium[22] for all the Ln complexes may also be responsible for the negative ΔS values.

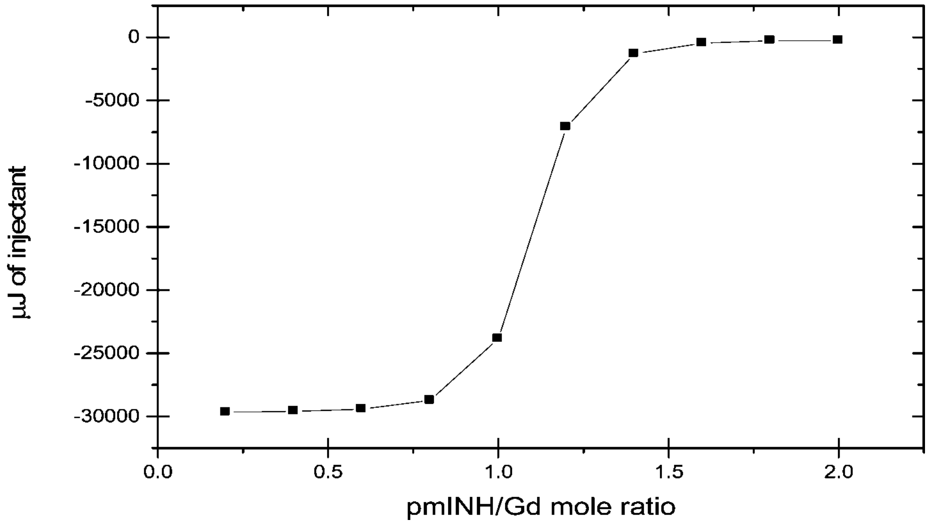


Figure 8. Normalized ITC data for titrations plotted vs the molar ratio of titrant/pmINH. Data analysis using Origin 4.0 Software indicates that the binding data fit well to a single binding-site model.

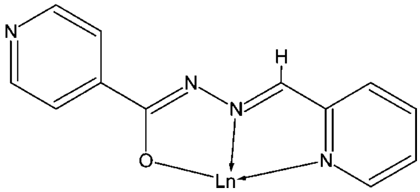


Figure 9. Proposed binding in pmINH−Ln^{3+} chelates.

3.5. Thermodynamic Parameters of Complexation as a Function of Ionic Radii of the Lanthanides. Figure 6 represents the correlation between the thermodynamic parameters of the complexation with the reciprocal ionic radii of the metal ions. It is important to see how the ionic size of the lanthanides affects the stability constants and the changes in free energy, enthalpy, and entropy. Both ΔH and ΔS values decrease, and the ΔG value increases with a decrease in the ionic size from lanthanum to europium with a break at gadolinium. A small break is also observed in the ΔH and ΔS values at praseodymium. Such patterns of the thermodynamic data against ionic size are generally true for complexes of the Ln series.[20]

3.6. Calorimetric Studies. ITC titrations have been carried out for the pmINH and Gd^{3+} solutions in 30 % (v/v) aqueous−dioxane medium at temperature 303 K. Figure 7 is the heat profile diagram of the pmINH−Gd^{3+} interaction for 10 injections of the ligand solution. The area of each peak was calculated employing BindWork 3.0 and gives the corresponding amount of heat evolved for the amount of ligand added and plotted against the metal−ligand molar ratio (Figure 8). Negative ΔH (change in enthalpy) given by the calorimetric titrations shows that the binding of pmINH with Gd is exothermic in nature. Stability constant, K, and metal−ligand stoichiometry, n, are obtained by nonlinear least-squares fitting of the isothermal calorimetric titration data using the software Bindwork 3.0. K for the Gd(III)−complex is $3.4 \cdot 10^6$. Metal−ligand stoichiometry, n, is 1 showing formation of only 1:1 metal−ligand complex. Detailed calorimetric studies of the interaction of pmINH with lanthanides are currently in progress.

On the basis of the foregoing discussion, the bonding sites of pmINH in the lanthanide complexes tentatively proposed are carbonyl oxygen, imino-nitrogen, and ring nitrogen of the aldehydic group where pmINH acts as a uninegative tridentate ligand as shown in Figure 9. Potentiometric and calorimetric studies of the complexes of pmINH show that only one molecule of ligand is bound to the Ln^{3+} ions forming 1:1 complexes. Since pmINH is a tridendate ligand, binding of only one molecule of pmINH would not satisfy the coordination number of the metal ions. Therefore, other ligands that would possibly bind to the lanthanides so as to satisfy the coordination number of the metal ions are the chloride ions and solvent molecules.

Acknowledgment

We acknowledge SAIF, Central Drug Research Institute, Lucknow, for mass spectrum and C, H, and N analysis of the ligand.

Supporting Information Available:

Normalized ITC data for titrations of 0.003 M $GdCl_3$ solution against pmINH and values of n bar and pL for the Ln(III)−pmINH systems at 303 K at different pH values are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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Received for review May 31, 2008. Accepted November 14, 2008.

JE8003904