

Complex Formation of N'-[4-(dimethylamino)phenyl]methylene Isonicotinohydrazide with Lanthanide Ions in Water-Dioxane Medium and the Associated Thermodynamics

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Interaction of N'-[4-(dimethylamino)phenyl]methylene isonicotinohydrazide (damINH) with La^{3+} , Pr^{3+} , Nd^{3+} , Sm^{3+} , Eu^{3+} and Gd^{3+} ions in 30 % water-dioxane medium has been studied potentiometrically at ionic strength 0.05 M NaClO_4 at 20, 30 and 40 °C. The pH-metric titration curve of the ligand shows only one inflection point indicating the presence of only one dissociable proton and the dissociation constant of damINH, $\log K_1^{\text{H}}$ has been determined from the pH-metric titration data. Formation of only 1:1 metal-ligand complexes is inferred from the metal-ligand formation curves and the formation constants ($\log K$) evaluated for the Ln(III) complexes, follows the trend: $\text{La}^{3+} < \text{Pr}^{3+} < \text{Nd}^{3+} < \text{Sm}^{3+} < \text{Eu}^{3+} > \text{Gd}^{3+}$, showing a break at Gd. Calorimetric studies are carried out for the Gd^{3+} complex at 30 °C in 30 % water-dioxane medium and change in enthalpy (ΔH), n (metal-ligand stoichiometry) and K (stability constant) are obtained by nonlinear least-squares fitting of the calorimetric data. Calorimetric studies also suggest formation of 1:1 Gd(III)-damINH complex. Thermodynamic parameters associated with both the protonation and complexation reactions have been calculated and the values suggest spontaneity and exothermic nature of all the reactions. ΔS values indicate that the deprotonation of damINH is both enthalpy and entropy-driven process while the complexation reactions are entropically unfavourable.

Key Words: Potentiometry, Calorimetry, Protonation and stability constants, N'-[4-(Dimethylamino)phenyl]methylene isonicotinohydrazide, Lanthanides.

INTRODUCTION

Aroylhydrazones derived from pyridine carboxylic acid hydrazides have attracted much attention from chemists in recent years due to their biological activities and strong tendency to form chelates with transition, lanthanide and main group metals in which these ligands act as neutral or mononegative bidentate ligands or even as dianionic ligands depending on the aroyl substituents and the reaction conditions¹. These ligands containing N and O-donor atoms are considered to be very important in the studies of various analytical and biological reactions because their interactions have served as model systems for the study of many biomolecules and metalloproteins^{2,4}. Of the pyridine carboxylic acid hydrazides, isonicotinic acid

hydrazide (INH) is a drug of proven therapeutic importance and has been used against a wide spectrum of bacterial ailments such as tuberculosis^{5,6} and in many cases, an increase of such therapeutic effect was observed when the hydrazide was complexed with a metal ion⁷. Isonicotinohydrazide have attracted the attention of several investigators since the report that there was a ten-fold increase in its anti-tubercular activity upon complexation with Cu(II) ion⁸. Further, it has also been reported⁹⁻¹¹ that hydrazones derived from the condensation of isonicotinic acid hydrazide with aromatic aldehydes or ketones showed better antitubercular/anti-tumor activity than INH. The remarkable biological activity of these acid hydrazides R-CO-NH-NH₂, their corresponding aroylhydrazones R-CO-NH-N=CH-R' and dependence of their mode of chelation have been of significant importance^{12,13}. Pyridoxal isonicotinoyl hydrazone, an orally available iron chelator for excretion of the excess iron acquired by chronic blood transfusion, was found to be effective at mobilizing iron *in vivo* at doses that are not toxic^{4,14}. However, to understand the activities of the hydrazones and their complexes, it is necessary to have detailed knowledge about the thermodynamic and solution equilibria involved in the reactions. The extent to which a ligand binds to a metal ion is normally expressed in terms of the stability constant and information about the concentration of a metal complex in an equilibrium mixture can be predicted on the basis of the formation constants in solution. Thus, keeping the above facts in mind and in continuation of our earlier work¹⁵⁻¹⁷, we have synthesized a novel Schiff base, N'-[4-(dimethylamino)phenyl]-methylene isonicotinohydrazide, damINH (Fig. 1) and carried out a systematic study on its interactions with the Ln³⁺ ions at ionic strength 0.05 M NaClO₄ at temperatures 20, 30 and 40 °C in water-dioxane media employing potentiometric and calorimetric titration techniques. We report herein the dissociation constant of the hydrazone, the stability constants of the complexes and the thermodynamic parameters associated with the reactions under study.

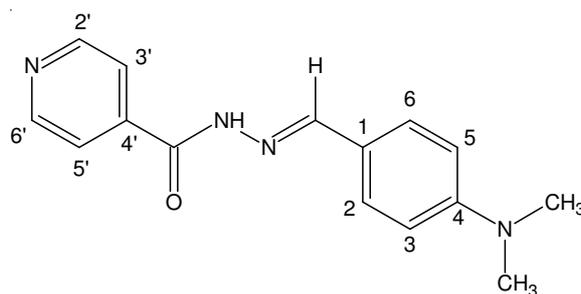


Fig. 1. Structure of the ligand

EXPERIMENTAL

Isonicotinic acid hydrazide, *p*-dimethylamino benzaldehyde, 1,4-dioxane, NaOH, HClO₄ and NaClO₄ were obtained from E. Merck and metal salts,

$\text{LnCl}_3 \cdot 6\text{H}_2\text{O}$ (Ln = La, Pr, Nd, Sm, Eu, Gd) were purchased from Sigma-Aldrich. All the other chemicals used in this study were of AnalaR grade. All the solutions were prepared in double distilled water. Sodium hydroxide solution was standardized¹⁸ with standard oxalic acid solution (0.05 M), which was again used for the standardization of HClO_4 . The metal salt solutions were standardized¹⁹. The ligand was insoluble in water and hence 30 % water-dioxane (v/v) solution was used to prepare the ligand solution.

Potentiometric titrations were carried out using a Systronic μ -362 pH meter with a glass calomel electrode (± 0.01) which was thermostated with a Circular D₈-G Haake Mess Technik. In all the cases, the pH-meter has been standardized with standard buffer solutions of pH 4, 7 and 9. C, H and N were microanalyzed using a Perkin-Elmer model 240C and hydrazine content was estimated volumetrically¹⁸. The IR spectrum was recorded in KBr medium on a Shimadzu FTIR-8400 and the mass spectrum was obtained on a JEOL SX102/DA.6000 mass spectrophotometer. The ¹H and ¹³C NMR spectra were recorded on a Jeol AL 300 FT NMR spectrometer. The calorimetric measurements were carried out in a CSC-2200 two drop titration calorimeter. The minimum detectable heat effect of the calorimeter was about 3 mcal with an accuracy of ± 0.25 mcal or 1 % of measured heat. The calorimeter has been calibrated using tris[hydroxymethyl] aminomethane following the standard procedure.

Preparation and analysis of ligand: N'-[4-(Dimethylamino)phenyl]methylene isonicotinohydrazide, damINH was prepared by refluxing the ethanolic solutions of isonicotinic acid hydrazide (0.02 M, 2.75 g in 30 mL) and *p*-dimethylamino-benzaldehyde (0.02 M, 2.98 g in 15 mL) for 4 h. Solid bright yellow crystals precipitated out on cooling the reaction mixture was filtered, washed repeatedly with ethanol and recrystallized from warm ethanol. The recrystallized crystals was dried in air and characterized. Yield 85 %; m.p. 202-4 °C; M⁺ at m/e 269 as base peak in the mass spectrum of the ligand (Fig. 2).

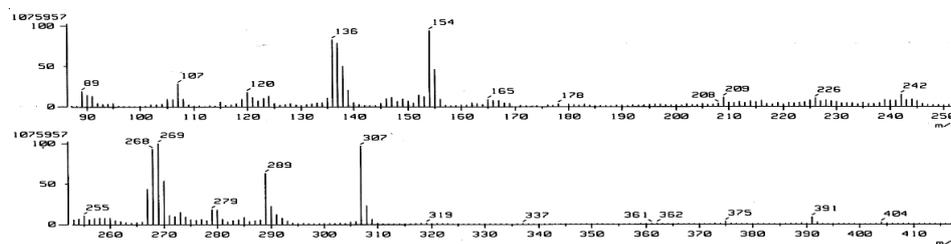


Fig. 2. Mass spectrum of damINH

Elemental analysis: Found. (%) (calcd. (%) for $\text{C}_{15}\text{H}_{16}\text{N}_4\text{O}$). C, 67.84 (67.16); H, 6.54 (5.97); N, 20.66 (20.89); N_2H_4 , 11.61 (11.94). IR (KBr, ν_{max} , cm^{-1}): 1666 (amide I), 1525 (amide II), 1591 (CN), 1057 (NN), 1007, 591 and 440 (pyridine ring vibrations). ¹H NMR (δ): 11.75 (s, NHCO), 8.31 (s, CH), 2.98-2.93 (s, CH_3)

8.77-7.79 (d, pyridine ring protons), 7.57-6.75 (d, phenyl ring protons). ^{13}C NMR (ppm): 161.03 (s, CO), 151.69 (s, NCH), 39.78, 39.72 (d, CH_3) 150.24 -111.76 (7s, ring carbons).

Procedure

Potentiometric titrations: For evaluation of stability constant, three different reaction mixtures were prepared and titrated potentiometrically against standard 0.02 M NaOH solution: (a) 1 mL HClO_4 (0.001 M) + 1.25 mL NaClO_4 (0.05 M), (b) solution (a) + 1 mL damINH (0.0003 M) and (c) solution (b) + 2.5 mL $\text{LnCl}_3 \cdot 6\text{H}_2\text{O}$ (0.00015 M). The volume of each set was made up to 25 mL with 30 % (v/v) water-dioxane solution. The ionic strength of each reaction mixture was maintained at 0.05 M using NaClO_4 solution. The metal to ligand ratio was kept as 1:2 in all the reaction mixtures. The titrations were carried out at three different temperatures 20, 30 and 40 °C.

Calorimetric titrations: The calorimetric 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 at 30 °C (*ca.* 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 the 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)²⁰ 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 6.0).

RESULTS AND DISCUSSION

Potentiometric studies: The ligand was potentiometrically titrated with standard NaOH at ionic strength 0.05 M NaClO_4 and at 20, 30 and 40 °C. Fig. 3 represents the potentiometric titration curves at 30 °C where (a) represents 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. The figure shows that the ligand curve (b) was shifted to the left of the acid curve (a) in the initial stage of the titration at pH 3.08-3.88. It was due to the basic properties of the ligand that can accept a proton from the acidic solution. The ligand curve then coincided with the acid curve and started diverging from the acid curve at pH 4.40 and extended to pH 11.13. Divergence of the ligand from the acid curve was caused by the liberation of proton from the ligand. A single inflection point was observed at pH 4.00-11.50 corresponding to the dissociation of one proton from the ligand at these pH ranges. Similar curves

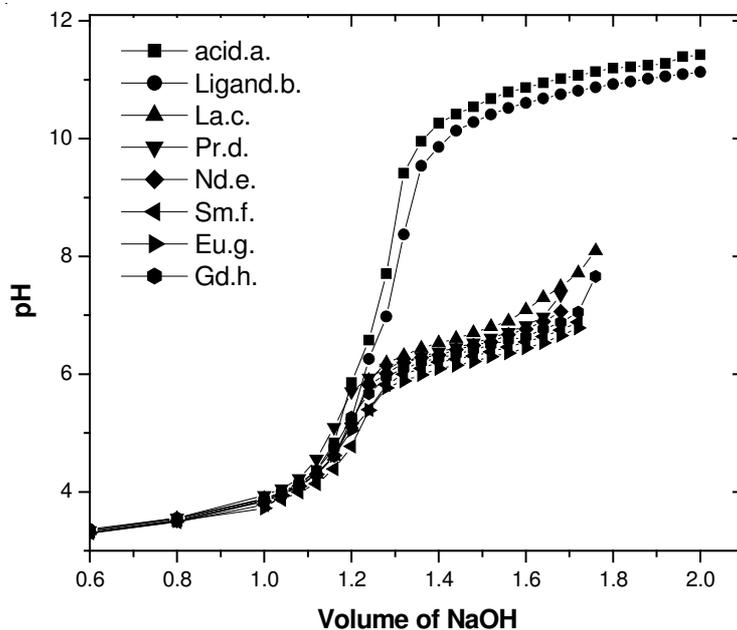


Fig. 3. Potentiometric titration curves of Ln^{3+} -damINH complexes at ionic strength $I = 0.05 \text{ M NaClO}_4$ at 30°C

are obtained for the titrations at other temperatures. Addition of metal ion to the free ligand solution caused a shift in the buffer region of the ligand to a lower pH value as observed in the curves (c-h). The curves (c-h) containing the trivalent La, Pr, Nd, Sm, Eu and Gd ions, respectively almost coincided with the ligand curve (b) in the initial stage. However, these curves diverged at pH ranges 3.08-5.93 showing that the complex formation proceeds by releasing proton from the base. Titration was terminated when precipitation due to formation of hydroxo complexes occurred.

The proton dissociation constant ($\log K_1^{\text{H}}$) of the ligand has been used for the computation of the stability constant of the metal-ligand complexes. The average number of protons associated with damINH at various pH-meter readings (\bar{n}_{H}) were calculated from acid and ligand titration curves following Irving and Rossotti's pH metric titration technique²¹ and the proton-ligand formation curves for the dissociation of proton at temperatures 20, 30 and 40°C (Fig. 4) were obtained by plotting \bar{n}_{H} versus pH. The curves extended upto 1 on the \bar{n}_{H} scale showing the presence of only one dissociable proton in the ligand. $\log K_1^{\text{H}}$ at different temperatures were determined from the proton-ligand formation curves using Bjerrum's half integral method²² modified by Irving and Rossotti²¹ and are collected in Table-1. The decrease in the protonation constant value of damINH with increase in temperature shows that dissociation of the ligand is more favourable at low temperature²³.

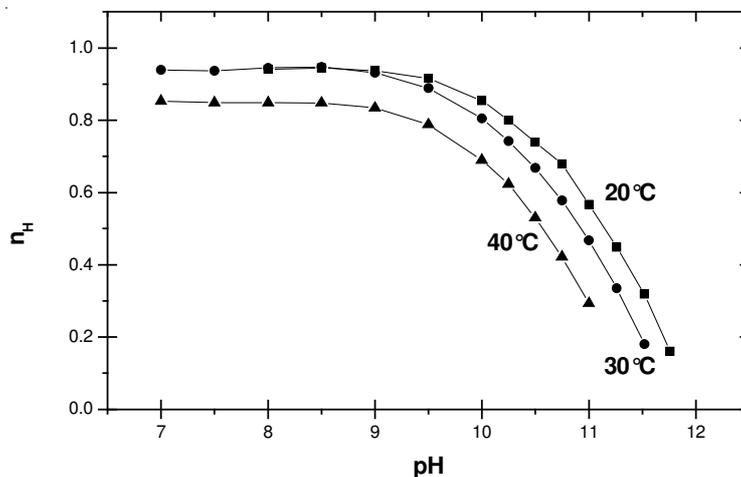


Fig. 4. Proton-ligand formation curves of damINH at ionic strength, $I = 0.05 \text{ M NaClO}_4$ at different temperatures

TABLE-1
PROTONATION CONSTANTS OF THE LIGAND ($\log K_1^H$) AND STABILITY
CONSTANT OF THE COMPLEXES ($\log K$) AT IONIC STRENGTH $0.05 \text{ M (NaClO}_4)$
AND AT DIFFERENT TEMPERATURES IN WATER-DIOXANE MEDIUM

Temperature (°C)	$\log K_1^H$	$\log K$					
		La	Pr	Nd	Sm	Eu	Gd
20	11.16 ± 0.01	8.46 ± 0.04	8.65 ± 0.02	8.69 ± 0.03	8.83 ± 0.06	8.99 ± 0.03	8.77 ± 0.03
30	10.92 ± 0.01	8.24 ± 0.02	8.36 ± 0.02	8.37 ± 0.02	8.60 ± 0.01	8.71 ± 0.02	8.48 ± 0.03
40	10.58 ± 0.01	7.67 ± 0.06	7.86 ± 0.04	7.98 ± 0.05	8.08 ± 0.02	8.17 ± 0.03	8.01 ± 0.02

The average number of ligands attached per metal ion (\bar{n}) and the free ligand exponent (pL) were calculated from the pH-metric titration data using Irving and Rossotti's technique²¹. The values of \bar{n} ($0.20 < \bar{n} < 1.00$) indicate that the complexes formed were in the 1:1 metal-ligand stoichiometry. The metal-ligand formation curves for the Ln(III) complexes at various temperatures were obtained by plotting \bar{n} versus pL and Fig. 5 exhibits the metal-ligand formation curves for the complexes at 30 °C. The stability constants ($\log K$) of the complexes evaluated from these curves employing Bjerrum's half integral method²² are also included in Table-1. There is a gradual decrease in the values of the stability constants with increase in temperature suggesting that the complex formation process was exothermic and more favourable at lower temperature. At constant temperature, the trend in the stability constants of Ln(III) complexes is: $\text{La}^{3+} < \text{Pr}^{3+} < \text{Nd}^{3+} < \text{Sm}^{3+} < \text{Eu}^{3+} > \text{Gd}^{3+}$, where the complexes showed a steady increase in the stability from La^{3+} - Eu^{3+} and a decrease at Gd^{3+} . A plot of $\log K$ versus $1/r$ (Fig. 6) also indicates that the stability constants of metal chelates showed an increase with increasing atomic number with a break at gadolinium, the half-filled shell ion which is in accordance with the results of the earlier workers²⁴⁻²⁶. The abnormal behaviour of Gd^{3+} may be attributed

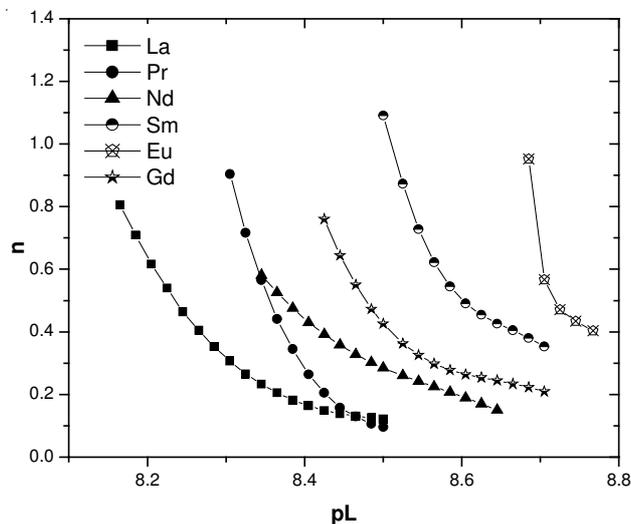


Fig. 5. Metal-ligand formation curves of Ln^{3+} -damINH complexes at $I = 0.05 \text{ M NaClO}_4$ at 30°C

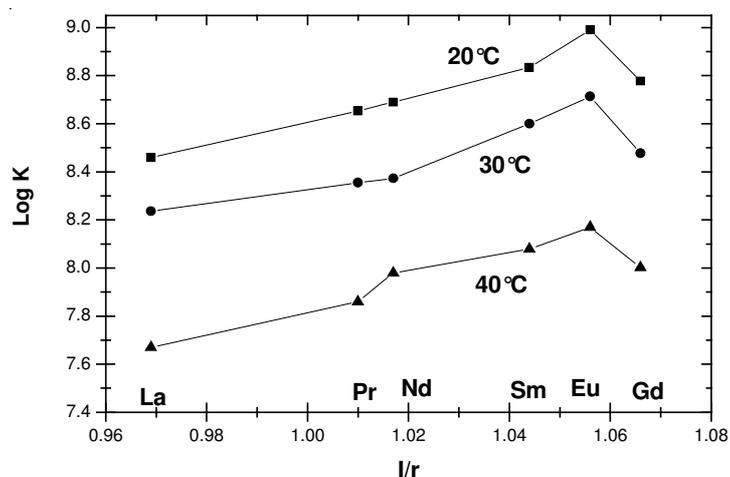


Fig. 6. A plot of $\log K$ of Ln^{3+} -damINH chelates *versus* $1/r$. r is the ionic radii of the Ln^{3+} ions

to (i) zero field stabilization energy, (ii) unavailability of the well shielded $4f$ electron for bond formation²⁷ and (iii) a structural change in the hydration sphere of lanthanide ions near the middle of series^{24,28}.

Change in free energy (ΔG), entropy (ΔS) and enthalpy (ΔH) associated with the dissociation and complexation reactions of damINH were calculated and collected in Table-2. It is observed from the table that all the parameters except ΔS for the dissociation of the ligand were negative. Negative ΔG values indicate that both dissociation of the ligand and the complexation process were spontaneous. These

TABLE-2
THERMODYNAMIC PARAMETERS OF THE LIGAND AND COMPLEXES
AT IONIC STRENGTH 0.05 M (NaClO₄) AND AT DIFFERENT
TEMPERATURES IN WATER-DIOXANE MEDIUM

Metal ions	-ΔG (kcal mol ⁻¹)			-ΔH* (kcal mol ⁻¹)	-ΔS* (Cal deg ⁻¹ mol ⁻¹)
	20 °C	30 °C	40 °C		
H ⁺	14.96 ± 0.01	15.14 ± 0.02	15.15 ± 0.03	12.66 ± 0.05	8.18 ± 0.05
La	11.34 ± 0.04	11.42 ± 0.02	10.99 ± 0.03	17.30 ± 0.06	19.40 ± 0.05
Pr	11.60 ± 0.04	11.58 ± 0.01	11.26 ± 0.04	17.34 ± 0.05	18.98 ± 0.06
Nd	11.65 ± 0.03	11.61 ± 0.01	11.43 ± 0.02	15.49 ± 0.05	12.80 ± 0.03
Sm	11.84 ± 0.01	11.92 ± 0.01	11.57 ± 0.02	16.54 ± 0.04	15.23 ± 0.04
Eu	12.05 ± 0.02	12.08 ± 0.03	11.70 ± 0.03	17.95 ± 0.04	19.36 ± 0.04
Gd	11.77 ± 0.02	11.75 ± 0.03	11.46 ± 0.03	16.94 ± 0.05	17.10 ± 0.05

*ΔH and ΔS were computed using linear-fit programme at 30 °C. Temperature used for calculation is in the absolute scale.

values have no sharp behaviour with temperature showing the independent nature of the reactions with respect to temperature²⁹. Negative ΔH and positive ΔS values indicate that the deprotonation of damINH was both enthalpy and entropy-driven process. Decrease in log K with increase in temperature and negative values of ΔH for the complexation reactions show that all the reactions were exothermic and the metal-ligand binding process was enthalpy driven. However, negative ΔS for the complexation reactions suggest that the reactions had an unfavourable change of entropy. An extensive solvation of metal chelates in aqueous-organic medium²⁶ for all the Ln complexes might also be responsible for the negative ΔS values.

Calorimetric studies: The calorimetric titrations had been carried out for damINH and Gd(III)-damINH complex in 30 % water-dioxane medium at 30 °C. The heat profile diagram of the Gd(III)-damINH complexation reaction for 10 injections of the ligand solution into the metal solution along with the plot of the area of each peak calculated *versus* the metal-ligand molar ratio are shown in Fig. 7(a-b). The metal heat of dilution for Gd(III) was obtained experimentally and then subtracted from the overall reaction heat. The heat of enthalpy for the complexation of damINH obtained from calorimetric studies is negative and shows the exothermic nature of reaction. The value of stability constant, K for the Gd(III)-complex was 1.04×10^6 . Metal-ligand stoichiometry, n is 1 showing that damINH formed 1:1 complexes with Ln³⁺ ions.

Both potentiometric and calorimetric studies of the complexes of damINH indicate that only one molecule of ligand is bound to the Ln³⁺ ions forming 1:1 complexes. In water-dioxane medium, the ligand shows keto-enol tautomerism^{11,30} (**1**), deprotonating the amido proton through enolization and behaves as a uninegative bidentate ligand coordinating through enolic oxygen and azomethine nitrogen.

Since the ligand is a bidentate ligand, binding of only one molecule of damINH would not satisfy the charge and coordination number of Ln ions. Therefore, other ligands that would possibly bind to the lanthanides so as to satisfy both the charge

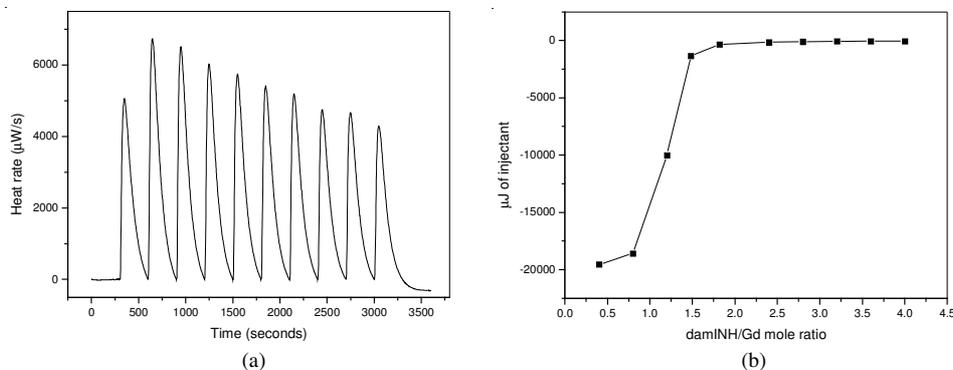


Fig. 7. (a) Raw isothermal titration calorimetry data demonstrating saturable exothermic evolution of heat upon sequential addition of damINH to Gd^{3+} solution. Area is corrected after statistical fittings. (b) Normalized ITC data for titrations plotted *versus* the molar ratio of titrant/damINH. Data analysis indicates that the binding data fit well to a single binding-site model

and the coordination number of the metal ions would be the chloride ions and solvent molecules. However, in absence of the isolated complexes, only the bonding sites of damINH in the Ln(III) complexes are tentatively proposed as shown in Fig. 8.

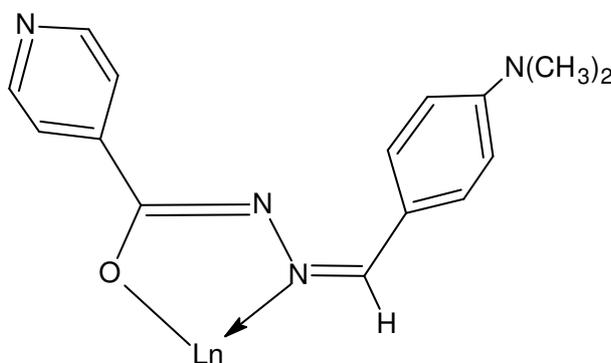
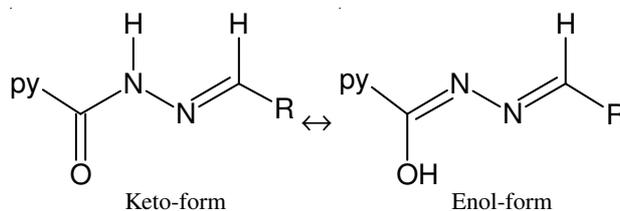


Fig. 8. Proposed binding of damINH in Ln(III) complexes



(1)

where py = pyridine ring; R = $C_8H_{10}N$

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