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Original Research

Solution Equilibrium Study of the Complexation of Co(II) and Zn(II) with Nicotinaldehyde Thiosemicarbazone

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Abstract

The interaction of nicotinaldehyde thiosemicarbazone with Co(II) and Zn(II) was investigated in SDS-water(1.15%w/v) at 303K and ionic strength of 0.1 mol dm^{-3}. The speciation and stability constants of the metal complexes formed were determined by pH-metric method. Protonated and simple mononuclear species in different protonation and deprotonation states were identified. The corresponding formation constants calculated using MINIQUAD-75 computer program, and species distribution diagrams produced using the HYSS computer program. Selection of the best-fit chemical models was based on statistical parameters. The results obtained from the study revealed that, the NTSC on interaction with metal ions in solution, a series of mononuclear $[M(LH_h)]$ (h = 1, 0), and bis-mononuclear $[M(L_2H_h)]$ (h = 2, 1, 0,) species were identified.

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INTRODUCTION

Thiosemicarbazones and their metal complexes are compounds that possess antitumor, antibacterial, antifungal and antiviral properties. For example, Triapine® (3-aminopyridine-2-carboxaldehyde thiosemicarbazone) has been developed as an anticancer drug and has reached clinical phase II on several cancer types (Nutting *et al*., 2009; Ma *et al*., 2008). At large the activity of the ligand is greatly enhanced by the presence of a metal ion. Thiosemicarbazones are receiving more attention largely in areas of antitumor, antiaprotozoal, antibacterial or antiviral activities and in all cases their action has been shown to involve interaction with metal ions (Finch *et al*., 1999; Antholine *et al*., 1977; Beraldo and Gambino, 2004).

The arrays of compounds of thiosemicarbazones are very interesting in their use against cancer because of their topology which is important in selectivity. The presence of a metal ion almost systematically increases the activity or contributes to mitigate the side effects of the organic parent compounds (French and Blanz, 1965). The coupling of thiosemicarbazones with metals, gives good biological activity due to the synergistic effect. The main identified effects related to their anticancer activity are ribonucleotide reductase (RR) inhibition (Brockman *et al*., 1970), reactive oxygen species (ROS) production (Shao *et al*., 2006), topoisomerase II inhibition (Hall *et al*., 2000), mitochondria disruption (Yuan *et al*., 2004), and a multidrug resistance protein (MDR1) inhibition (Ludwig *et al*., 2006 and Wu, 2007). The metal complexes of thiosemicarbazone are also widely studied for their chemical and analytical purposes (Akinchan *et al*., 1996; Offiong, 1994; Sushil and Srivastava, 1985; Belicchi *et al*., 1986; Belicchi *et al*., 1992; Hingorani and Agarawala, 1990; Tempereni *et al*., 1995; Revathy and Palaniappan, 1990).

In solution thiosemicarbazones are known to exist in thiol form tautomerizing from the thione form. Complexation usually takes place via dissociation of the acidic proton, resulting in the formation of usually four-membered or depending on the alkyl/aryl group a five-membered chelate ring (Pal *et al*., 2002).

To understand the way thiosemicarabzones and their metal complexes are acting as anticancer agents, it is imperative to understand the solution equilibria of these compounds. With this interest the protonation constant and the stability constants of Co(II) and Zn(II) complexes of nicotinaldehyde thiosemicarbazone were studied and reported here under.

MATERIALS AND METHODS

Material, Solutions and Apparatus

All the chemicals used were of AnalaR or equivalent grade. Chlorides of Co (II) and Zn (II), EDTA disodium dehydrate, sodium hydroxide pellets, potassium hydrogen phthalate (KHP) and oxalic acid were purchased from E. Merck. Pro. analysis. All other solutions, including hydrochloric acid, sodium hydroxide, and sodium chloride, were prepared using doubly glass distilled water through which nitrogen gas was purged to expel any dissolved oxygen or carbon dioxide. Nicotinaldehyde thiosemicarbazone (NTSC) was supplied by Fluka, AR and Sodium chloride was obtained from BDH AnalaR.

The way the stock solution of metal chlorides, ligand (NTSC) solution, standardization of acid-base solutions were prepared following the standard procedures explained else were (Kenie and Satyanarayana, 2015).

A Control Dynamics pH-meter model APX 175 E/C in conjunction with a combination electrode (0–14 pH range) was used for pH measurements. The pH correction factor was calculated before each set of experimental titrations by Gran method (Gran, 1952**;** Gran, 1950; Giuseppe *et al.*, 1979).

Titration Procedure and Data Analysis

Calvin-Wilson titration technique modified by Rossotti (Irving and Rossotti, 1953, 1954) was employed for the study of protonation and complex equilibria of the ligand (NTSC) in the same condition of the metal-ligand complexation. Titrations were carried out at 1:1 and 1:2 ratios of initial concentrations of metal to ligand in SDS (1.15% w/v)-water mixture. The ligand is poorly soluble in water, and various SDS/H_2O solvent mixtures were tested as suitable media for aqueous solution equilibrium studies; 1.15 % (w/v) SDS/H_2O was found to be sufficient for dissolution of the ligand at the concentration levels necessary for pH potentiometric titrations (i.e., ≥1–2mM). In the titrations the upper pH limit of rejecting data was determined by the appearance of opalescence leading to precipitation indicated by a downward drift of the pH-meter dial readings.

For a system containing a metal ion and a ligand forming N complexes, the formation constant of a complex can be represented as,

$$m.\mathrm{M} + l.\mathrm{L} + h\,\mathrm{H} \rightleftharpoons \mathrm{M}_m\mathrm{L}_l\mathrm{H}_h$$

and the overall formation constant is given by,

$$\beta_{mlh} = [\mathrm{M}_m\mathrm{L}_l\mathrm{H}_h]_i \,/\, [\mathrm{M}]_i^{\,m}.[\mathrm{L}]_i^{\,l}.[\mathrm{H}]_i^{\,h}$$

Where $[M]_i$, $[L]_i$ and $[H]_i$ are the free concentrations of metal, ligand and hydrogen ion respectively at i^{th} experimental point. Different species in solution possess different values of stoichiometric coefficients *m, l* and *h.* Positive value of h indicates protonated species and negative value indicates either deprotonated or hydroxylated species. The potentiometric titration data obtained was subjected to analysis by Miniquad-75 program (Gans, 1976).

The stoichiometry and stability constants of the species formed in solutionwere determined by examining various chemically possible composition models for the systems studied. Thebest-fit models were selected on the basis of U (sum of the squares of residuals in mass balance equations), standard deviations in formation constants and other statistics like χ^2 test which tests the distribution of errors against a normal one. Species distribution diagrams for all the systems under study were generated using HYSS (Alderighi, 1999) program.

RESULTS AND DISCUSSION

Protonation of Nicotinaldehyde Thiosemicarbazone (NTSC)

The protonation and deprotonation equilibria of NTSC are shown in Figure 1. The best-fit model obtained using Miniquad-75 program for NTSC was reported in our previous work (Kenie and Satyanarayana, 2015).

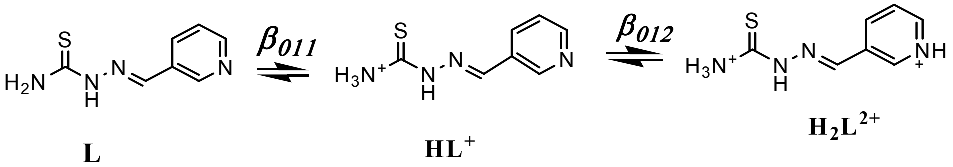


Figure 1: Protonation and deprotonation equilibria of NTSC

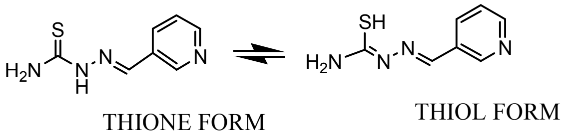
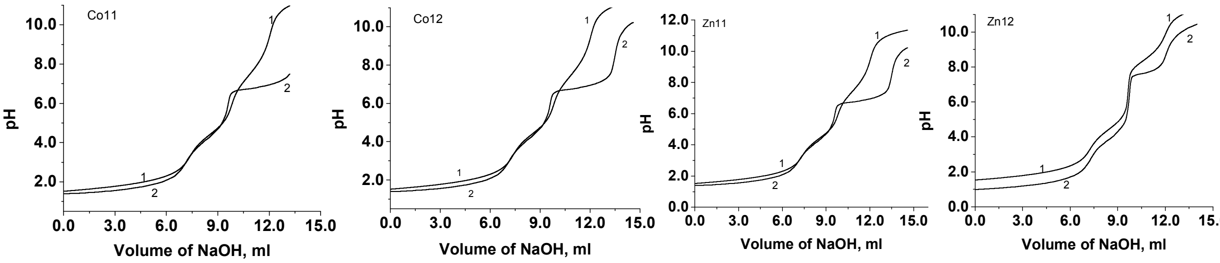


Figure 2: Thione- thiol Tautomerisation of NTSC .

Complex Formation of NTSC with Divalent Metal Ions

The potentiometric titration data for 1:1 and 1:2 metal to ligand concentration ratios for different metal ions was used to calculate the formation constants of mononuclear complexes. The acquired data was first subjected to analysis by classical procedures (Irving and Rossotti, 1953) to get the formation constants of simple mono-nuclear complexes like ML, ML_2 etc. Simulated titration curves were then generated using a computer program SOPHD (Rao *et al.*, 1984) to see whether these species satisfy the experimental data. The simulated titration curves thus obtained were plotted along with the experimental ones to identify the regions of pH where they differ. Titration curves for the systems for all the compositions are shown in Figure 3. The wide difference between the simulated and experimental curves reveals the presence of other major species in addition to simple mono-nuclear complexes. Different chemical models containing chemically plausible species depending on the nature of the ligand, metal and the pH region of difference in the curves were tested using the Miniquad-75 program. The required initial estimates of the formation constants were calculated basing on the formation constants of simple complexes and protonation/ deprotonation constants of the ligand.

The experimental titration data indicated that the ligand was efficient metal-ion chelator in a wide pH range for both metal ions. It should be noted, however, that the ligands were not able to keep the metal ions in solution at a metal to-ligand ratio of 1:1 and 1:2 at highly basic pH, and precipitation occurred. The complex formation processes with the ligand start at low pH (pH ≈2.3) in the case of both metal ions. The stoichiometries of the metal complexes and the stability constants furnishing the best fits to the pH-potentiometric experimental data together with equilibrium constants are given in Table 1.The data reveal the formation of mono-ligand complexes and bis-ligand complexes.



(a) **(b)**

Figure 3: Simulated and experimental titration curves for (a) cobalt (II)-NTSC and (b) zinc (II)-NTSC systems for 1:1, and 1:2 compositions in 1.15% w/v SDS-water mixture. (1. Simulated titration curve 2. Experimental titration curve)

The results of the analysis i.e., the stoichiometry and the overall formation constants of various species giving the best fit to the experimental data for all the systems are given in Table 1. The best-fit models contain protonated, and unprotonated mononuclear species. The investigation revealed that the best-fit models ML and MLH for 1:1 ratio ; ML_2, ML_2H, and ML_2H_2 for 1:2 ratio species between the ligand and Co(II) and Zn(II) ions are formed depending on pH. The formation constants are in good agreement with Irving-Williams order (Irving and Williams,1948 *and* 1953) i.e. $Mn^{II} < Co^{II} < Ni^{II} < Cu^{II} > Zn^{II}$.

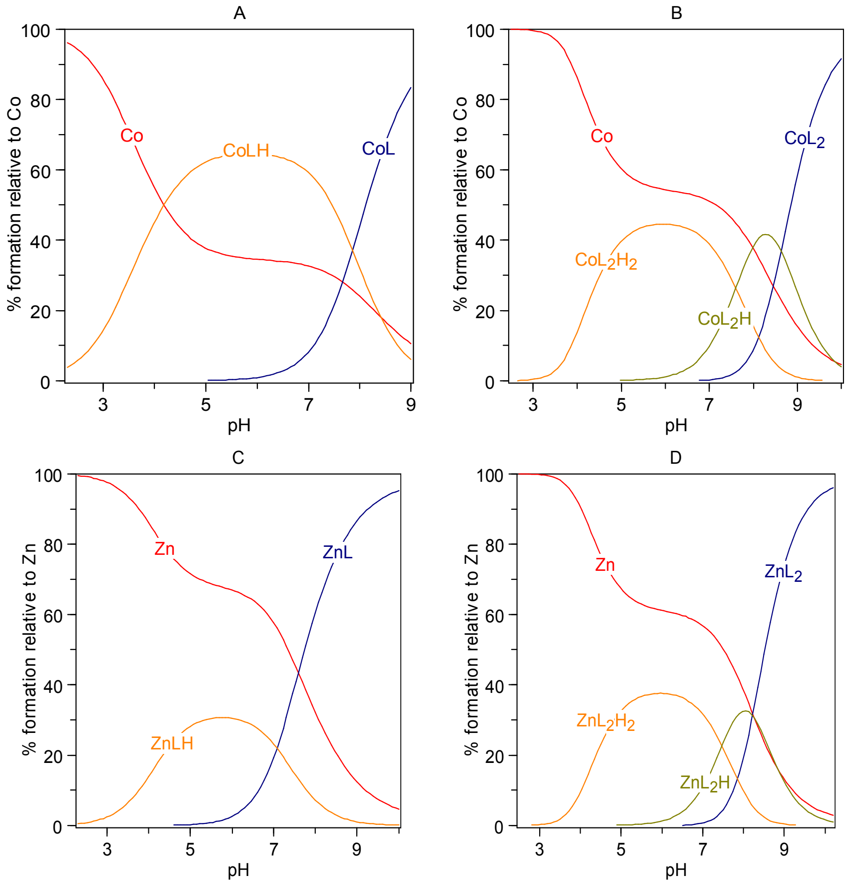


Figure 4: Species distribution diagrams of M^{II}-NTSC systems for 1:1, and 1:2 (M:L) concentration ratios compositions in 1.15% w/v SDS-water mixture. ((A). Co^{II}-NTSC(1:1), (B). Co^{II}-NTSC(1:2), and (C). Zn^{II}-NTSC(1:1) and (D). Zn^{II}-NTSC(1:2)

Table 1: Best-Fit models for NTSC- metal ion systems (Temp. =30 ± 1°C and ionic strength, *I* = 0.1 mol dm^{-3}) in SDS-water mixture 1.15%(w/v)

Metal	Log β_{mlh} (SD)			Np	U_{corr}	χ^2	Skewness	Kurtosis	R-Factor	pH-Range
						1:1				
	110	**111**								
Co(II)	05.36(6)	13.21(5)		62	3.8	14.20	-0.35	4.41	0.0041	2.5-9.0
Zn(II)	05.24(3)	12.31(2)		36	0.9	16.07	-0.48	6.68	0.0017	2.5-10.0
						1:2				
	120	**121**	**122**							
Co(II)	08.58(7)	17.21(6)	24.81(8)	42	2.5	12.30	-0.50	5.26	0.0054	2.5-10.2
Zn(II)	08.89(7)	17.11(8)	24.58(4)	66	0.8	9.45	0.09	6.55	0.0025	2.5-10.10

Ucorr=Ux10^{-8}/NP-m; NP= number of points; m= number of species; SD=standard deviation

The species distribution diagrams for metal-ligand systems (Figure 4) give the percentage of formation of various species as a function of pH. For 1:1 and 1:2 compositions at pH below ~6.0, the protonated species MLH, and ML_2H_2 are prevalent for the metal ions under study and the species ML_2H appear in between pH 6.0 and 8.0 for both metal ions. In the protonated species MLH, ML_2H and ML_2H_2 probably the protons can presumably be attributed to the non-coordinating pridinic nitrogen and the NTSC is invoved in bonding as a bidentate with the metal ions through the sulfur, in thione form and iminic nitrogen atom. The species ML_2H_2 with increase in pH loses a proton on non-bonding side and forms ML_2H. Beyond pH 4.0 simple complexes like ML and ML_2 appear in solutions of compositions 1:1 *and* 1:2 (M: L), in which neutral form of NTSC participates in complexation as a bidentate bonding through thiol form of sulfur via deprotonation of the –SH group and iminic nitrogen atom. This is the typical coordination for the pyridinecarbaldehyde thiosemicarbazones (West *et al*., 1993).

The percentage of formation of the diprotonated complexes is 35% and 45% for Zn(II) and Co(II) respectively. The formation of the simple system is dominant beyond pH 7 reaching 80-97% for different metal ions. The formation of these species may be due to the tautomerisation of the thione to thiol form (Fig.2) of the ligand in bonding.

CONCLUSION

The results obtained clearly indicate that nicotialdehyde thiosemicarbazone(L) possesses a number of potential donor atoms. Depending on pH, the ligand exists in various protonated and deprotonated forms, LH_2^{2+}, LH^+, and L. The protonation is at the pyridine nitrogen atom and deprotonation is from the thiol forms at higher pH. On interaction with metal ions in solution, a series of mononuclear [M(LH$_h$)] (*h* = 1, 0), and bis-mononuclear [M(L$_2$H$_h$)] (*h* = 2, 1, 0,) species were identified. The formation constants and species distribution indicate strong complexation in most of the cases. It was also concluded that the formation of mono and bis-ligand protonated complexes is favourable with both metal ions in the physiological pH range.

Conflict of Interest

Conflict of interest none declared.

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