Chemical Speciation Studies on Complexation of Ditopic Ligands: Interaction of Adipic Acid Dihydrazide with Pb^{2+}, Hg^{2+} and Cd^{2+} Metal Ions in Aqueous Medium

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Authors' contributions

*This work resulted from the collaboration between all the authors. Author URB performed the
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prepared the final manuscript for communication. All authors read and approved the final manuscript.*

Original Research Article

ABSTRACT

Chemical modelling study of the ligational behaviour of adipic acid dihydrazide (AADH) towards the
toxic metal ions Pb^{2+}, Hg^{2+} and Cd^{2+} has been carried out potentiometrically in aqueous medium.
AADH possesses two coordinating units on either side of the molecule making it a ditopic ligand.
Speciation analysis of the metal ion-AADH systems of different molar ratios using the Miniquad-75
program indicated the formation of mono and binuclear species in different states of protonation.

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1. INTRODUCTION

Biochemically, there is a need of non-toxic polytopic ligands that are efficient at sequestering toxic metal ions with high atom efficiency. The safest and simplest way to excrete toxic metal ions is in the form of simple or mixed ligand metal complexes using non-toxic ligands. Dihydrazides and their derivatives [1] are found to act as ditopic ligands that can accommodate two metal ions in different coordination pockets. These ligands are of recent interest as they allow the creation of well-ordered extended complexes containing different cations. Dihydrazides are capable of forming symmetric and asymmetric bimetallic complexes in addition to mono-nuclear species. The presence of two metal ions in the same species separated by a flexible part of the molecule leads to several interesting applications like creation of supramolecular structures to mimic metalloproteins [2] and to understand their structure-reactivity relationship, DNA binding, specific and selective catalysis, [3,4] sequestering of metal ions and other biological and industrial applications. *In vitro* and *in vivo* tests [5] proved dihydrazides to be non-genotoxic. Food and Drug Administration approved [6] the use of dihydrazides as cross linkers for coatings on plastics used for food package not in direct food contact. The role of dihydrazides as ditopic ligands in sequestering heavy metal ions is therefore, worth investigating. This involves a chemical speciation study of dihydrazide-metal ion systems in solution. Therefore, in continuation of our studies on the ligational behaviour of dihydrazides [7-9] we present here, a chemical modelling study on the complexation of AADH with toxic heavy metal ions Pb^{2+}, Hg^{2+} and Cd^{2+}.

Several reports were found in the literature on the metal complexes of dihydrazides. Most of these studies [10-21] involve synthesis and structural elucidation of the complexes by elemental analyses, magnetic moments, molar conductance, and electronic, ESR, IR, and X-ray diffraction studies. Characterization of the complexes is often specific to an isolated/ precipitated single species and may not be relevant to the solution behaviour of the compound wherein a number of species coexist. Only a few reports [22-27] on the metal-ligand equilibria of AADH in solution phase were found in the literature. No reports were found on its complexing tendencies in solution towards Pb^{2+}, Hg^{2+} and Cd^{2+}. Lead is a well known insidious poison. Mercury is poisonous even at very low

levels and is deceptive. Often the symptoms are misleading and attributed to other causes. Cadmium replaces metal ions in essential biological reactions and is therefore toxic. However, by complexing with appropriate non-toxic ligands, these toxic metals can be excreted out of the body. Speciation study is a well-known tool for the solution chemists to determine the nature of species formed by the toxic metal ions with exogenous or biological ligands to access their toxic effects on the biological systems.

2. MATERIALS AND METHODS

2.1 Reagents

Adipic acid dihydrazide obtained from Fluka Chemie, Buchs, Switzerland, was recrystallized from water and dried at 100℃. All other chemicals used were of analytical grade. Solutions were prepared in distilled and deionized water. Stock solutions (~0.1 mol dm^{-3}) of the metal ions, Pb(II), Hg(II) and Cd(II) were prepared by dissolving respective metal chlorides (BDH, Merck) in ~0.01 mol dm^{-3} hydrochloric acid solution [28] to prevent possible hydrolysis. The metal ion solutions were standardized [29] volumetrically using standard procedures. Sodium hydroxide stock solution (~0.2 mol dm^{-3}) was stored under a nitrogen atmosphere and its carbonate content was checked regularly by Gran method [30,31].

2.2 Equipment

The potentiometric titrations were carried out with a Control Dynamics pH-meter (model APX 175 E/C) in conjunction with a combination electrode of 0-14 pH range. The calibration of electrode system in − log [H$^+$] units at I= 0.1 mol dm^{-3} (NaCl) was carried out before each set of titrations by titrating hydrochloric acid with sodium hydroxide solution and analysing the data by Gran method. A tip less double walled Pyrex glass vessel of 100 ml capacity was used for carrying out the potentiometric titrations. The temperature of the solution (30.0±0.1℃) was maintained by passing thermostated water through the annular space between the walls of the titration cell. Carbon dioxide was excluded from the experimental solutions by nitrogen gas bubbling.

2.3 Data Acquisition and Analysis

The primary aim of the speciation study is to calculate the concentrations of all the species present in solution including the free metal ion and free ligand at any given experimental point

or pH under the specified experimental conditions. Consider a system containing a metal ion (M) and a ligand (L) involved in the formation of a generalized species, represented by the equilibrium (equation 1),
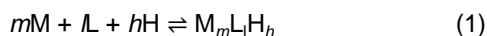
$$m\text{M} + l\text{L} + h\text{H} \rightleftharpoons \text{M}_m\text{L}_l\text{H}_h \qquad (1)$$

and the overall formation constant is given by equation (2),

$$\beta_{mlh} = \frac{[\text{M}_m\text{L}_l\text{H}_h]}{[\text{M}]^m[\text{L}]^l[\text{H}]^h} \qquad (2)$$

Stoichiometric coefficients m, l and h specify the composition of the formed species. Positive, zero and negative values of 'h' indicate, respectively, the formation of protonated, unprotonated and deprotonated (or hydroxylated) species. [M], [L] and [H] represent the free concentrations of the metal ion, ligand and proton respectively.

Data acquisition [32,33] involves the titrations of solutions (total volume, 50.0 cm^3) containing a mixture of hydrochloric acid (4.0-5.0×10^{-2} mol dm^{-3}), AADH (0.005 to 0.015 mol dm^{-3}) and metal ion (0.005 to 0.02 mol dm^{-3}) with carbonate free sodium hydroxide (~0.2 mol dm^{-3}). The ionic strength was maintained at 0.1 mol dm^{-3} with sodium chloride as the background electrolyte. The C_M: C_L molar concentration ratio in different experiments was maintained at 1:1, 1:2 and 2:1. Titrations were conducted until the appearance of turbidity due to precipitation leading to a downward drift in pH of the solution. The data from different experiments with different metal to ligand ratios were analysed using the Miniquad-75 program [34] and species distribution diagrams were generated using Hyss2009 program [35]. The best-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.

3. RESULTS AND DISCUSSION

Adipic acid dihydrazide (AADH) is a symmetrical molecule with a C4 backbone between two -CONHNH$_2$ complexing groups (Fig. 1) on either side of the molecule.
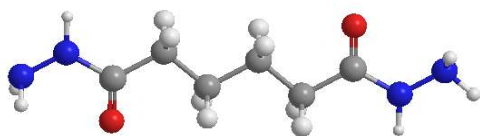

Fig. 1. Adipic acid dihydrazide

It offers amino and carbonyl group functionality at both the ends which makes it a ditopic ligand and excellent cross-linking agent for water-based emulsions. In solution at low pH AADH (L) exists as a biprotonated species, the protonation being at the two amino groups. Hydrazides are prone to lose enolic protons in basic medium. In the case of AADH as there are two hydrazide groups, there is a chance of formation of LH$_{-1}$ and LH$_{-2}$ type of species in basic medium. As reported elsewhere, [9] the best-fit model obtained by the Miniquad-75 program, for the proton-ligand equilibria of AADH contains three formation constants, β_{011}, β_{012} and β_{01-1} with log β values 3.67, 6.24 and -12.03 respectively, corresponding to the formation of mono-protonated, biprotonated and mono-deprotonated forms of AADH. The formation constant, β_{01-2}, corresponding to the formation of LH$_{-2}$ in which AADH loses both the enolic protons was not converged as its equilibrium may not be accessible pH metrically. But in the presence of a metal ion this dissociation may take place leading to the formation MLH$_{-2}$ type of species. Therefore, depending on the pH, AADH exists in solution as LH$_2^{2+}$, LH$^+$, L and LH$_{-1}$ (Fig. 2) that may interact with a metal ion.

In the case of binary metal-AADH systems, the acquired data for different concentration ratios was first subjected to analysis by classical procedures [32,33] to get the formation constants of simple mono-nuclear complexes. Simulated titration curves were then generated using a computer program SOPHD [36] developed in our laboratory to see whether these species satisfy the experimental data. The simulated titration curves thus obtained were plotted together with the experimental ones to identify the regions of pH where they differ. Titration curves for metal ion-AADH systems for all the compositions are shown in Figs. 3 to 5.

Differences between the simulated and experimental curves reveal the presence of other major species in addition to simple mono-nuclear complexes. Different chemical models containing chemically plausible species, based 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 best-fit models along with the statistical parameters are depicted in Table 1.
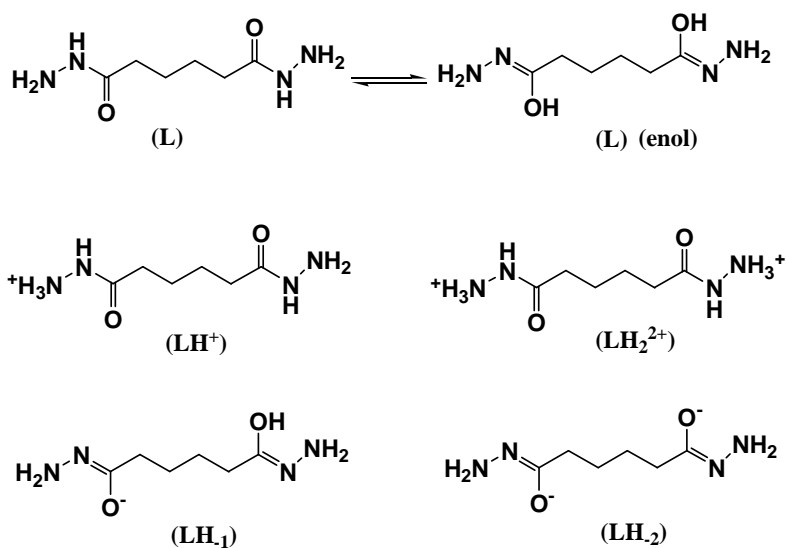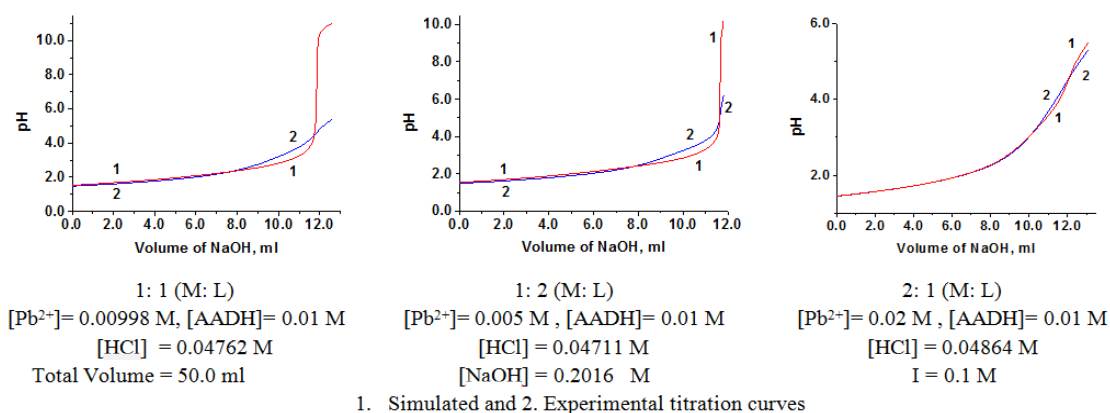
Fig. 2. Proton-ligand species of AADH

1: 1 (M: L)	1: 2 (M: L)	2: 1 (M: L)
[Pb²⁺]= 0.00998 M, [AADH]= 0.01 M	[Pb²⁺]= 0.005 M , [AADH]= 0.01 M	[Pb²⁺]= 0.02 M , [AADH]= 0.01 M
[HCl] = 0.04762 M	[HCl] = 0.04711 M	[HCl] = 0.04864 M
Total Volume = 50.0 ml	[NaOH] = 0.2016 M	I = 0.1 M

1. Simulated and 2. Experimental titration curves

Fig. 3. Simulated and experimental titration curves of Pb²⁺-AADH systems

1: 1 (M: L)	1: 2 (M: L)	2: 1 (M: L)
[Hg²⁺]= 0.01 M, [AADH]= 0.01 M	[Hg²⁺]= 0.00498M , [AADH]= 0.01 M	[Hg²⁺]= 0.02 M , [AADH]= 0.01 M
[HCl] = 0.04768 M	[HCl] = 0.04714 M	[HCl] = 0.04877 M
Total Volume = 50.0 ml	[NaOH] = 0.2016 M	I = 0.1 M

1. Simulated and 2. Experimental titration curves
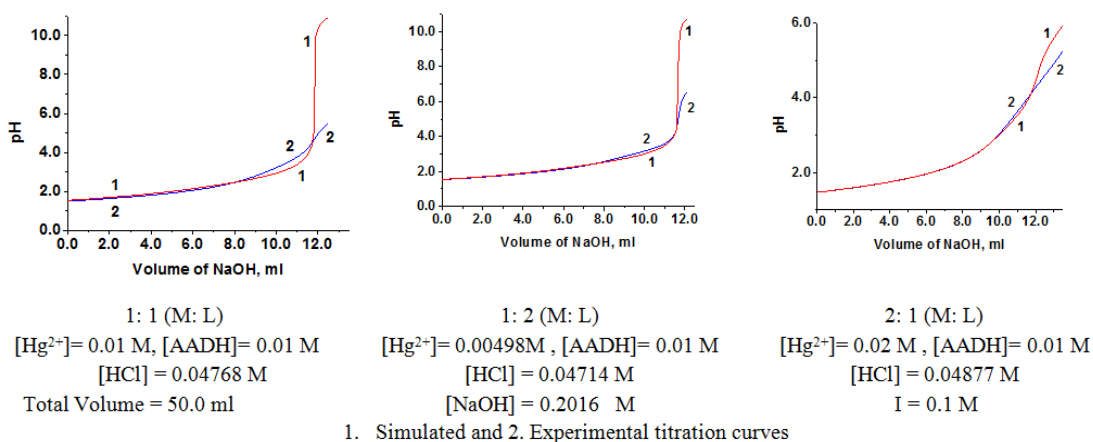
Fig. 4. Simulated and experimental titration curves of Hg²⁺-AADH systems

1: 1 (M: L)
$[Cd^{2+}]$= 0.01 M, [AADH]= 0.01 M
[HCl] = 0.04743 M
Total Volume = 50.0 ml

1: 2 (M: L)
$[Cd^{2+}]$= 0.00504 M , [AADH]= 0.01 M
[HCl] = 0.04681 M
[NaOH] = 0.2016 M

2: 1 (M: L)
$[Cd^{2+}]$= 0.02 M , [AADH]= 0.01 M
[HCl] = 0.04868 M
I = 0.1 M

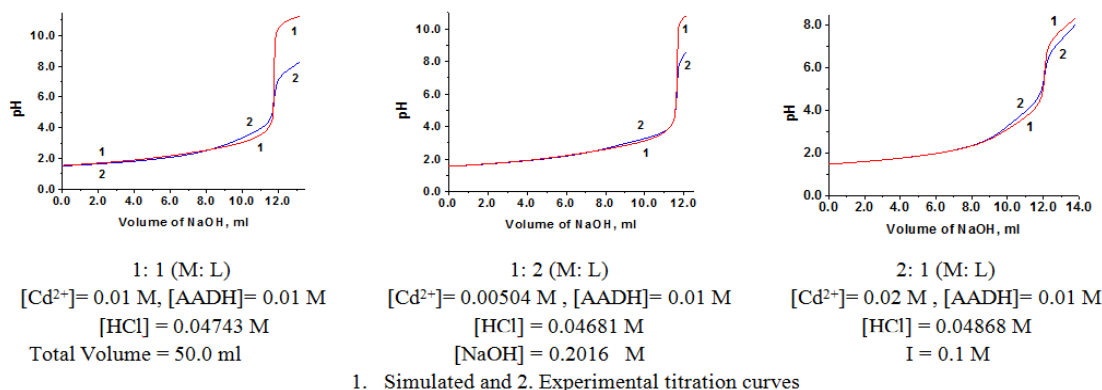1. Simulated and 2. Experimental titration curves

Fig. 5. Simulated and experimental titration curves of Cd^{2+}-AADH systems

Table 1. Best-Fit models for AADH- metal ion systems

Concentration ratio (M: L)	Species mlh	Log β_{mlh} (SD[*])		
		Pb^{2+}	Hg^{2+}	Cd^{2+}
1:1	111	6.99 (4)	6.60 (2)	6.52 (4)
	110	3.62 (4)	3.28 (2)	3.02 (4)
	11-1	-2.00 (5)	-2.51 (7)	-4.91 (10)
	U/NP	3.374×10^{-7}	1.425×10^{-8}	3.305×10^{-7}
	χ^2	32.02	30.01	62.85
	R	0.0204	0.0132	0.020
1:2	111	6.99	-	-
	110	3.62	-	-
	122	13.82 (6)	12.58(2)	12.17 (4)
	121	10.57 (6)	9.04 (6)	-
	120	7.18 (2)	6.45 (1)	5.94 (2)
	12-1	0.13 (5)	-0.30 (8)	-2.66 (6)
	U/NP	9.940×10^{-9}	8.025×10^{-8}	2.809×10^{-8}
	χ^2	27.88	25.69	76.24
	R	0.0068	0.0055	0.0117
2:1	111	6.99	6.60	6.52
	210	5.84 (5)	5.38 (7)	4.88 (7)
	21-1	0.54 (7)	0.49 (6)	-2.40 (10)
	U/NP	3.528×10^{-7}	4.945×10^{-8}	6.458×10^{-7}
	χ^2	13.76	5.11	27.47
	R	0.0305	0.0375	0.0425

SD= Standard Deviation in the least significant digit

The species converged for 1:1 (C_M: C_L) metal ion-AADH systems were MLH, ML and MLH$_{-1}$ (M= Pb^{2+}, Hg^{2+} and Cd^{2+}). The formation of MLH species indicates that one of the hydrazide groups of AADH is bonded to the metal ion while the other is free and protonated. [37,38] With an increase in the pH of the solution, MLH species loses its proton on the non-bonding side leading to the formation of ML. The formation of MLH$_{-1}$ species may be due to the loss of enolic proton or hydroxylation. The species distribution diagrams generated using HYSS2009 program

are shown in Figs. 6-8. The extent of formation of MLH species varies between 55 to 63% of total metal ion with a maximum around ~2.5 pH. The formation of ML is above 70% of the total metal in all the cases.

The best-fit model for 1:2 metal to ligand molar concentration ratio indicates the formation of ML$_2$H$_2$, ML$_2$H, ML$_2$ and ML$_2$H$_{-1}$ species. In all these species probably, only one of the hydrazide groups of the ligand is attached to the metal ion. Bimetallic species of the type M$_2$L and

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M_2LH_{-1} were found to exist in 2:1 (C_M: C_L) solution for all the metal ions under study. In homo-binuclear type of species (M_2L), AADH acts as a ditopic ligand bonding through amino and carbonyl groups on both the sides. These species are predominant in 2:1 systems and represent 60 to 70% of the total metal concentration. With an increase in the pH, M_2L species are converted to M_2LH_{-1} by losing an enolic proton. Further deprotonation or hydroxylation could not be observed due to precipitation. Bakir Jeragh et al. [21] in their studies on solid state metal complexes of AADH with various metal ions including Hg^{2+} and Cd^{2+}, reported the behaviour of the ligand as a neutral bidentate in mononuclear complexes and neutral or binegative tetradentate in binuclear species. In neutral state the ligand bonds through carbonyl oxygen and amino group nitrogen of one (bidentate) or both (tetradentate) of the hydrazide moieties. In binegative tetradentate state the ligand bonds through enolic oxygen and amino groups of both the hydrazide moieties. This supports our speciation results of identification of mono and binuclear species in protonated, unprotonated and deprotonated forms in solution. The probable bonding nature of AADH in some of the observed species supported by solid state structural elucidation [19-21,39-40] is shown in Fig. 9.

The relative stabilities of metal ion-AADH complexes were found to be in the order Pb^{2+} > Hg^{2+} > Cd^{2+}. The stability of a complex formed between a ligand and a metal ion depends on several factors like; 1. Chelating behaviour of the ligand, 2. Type of the bond between a metal ion and a coordinating atom, which may vary from purely electrostatic to nearly covalent, 3. Ionic size and coordination number of the metal
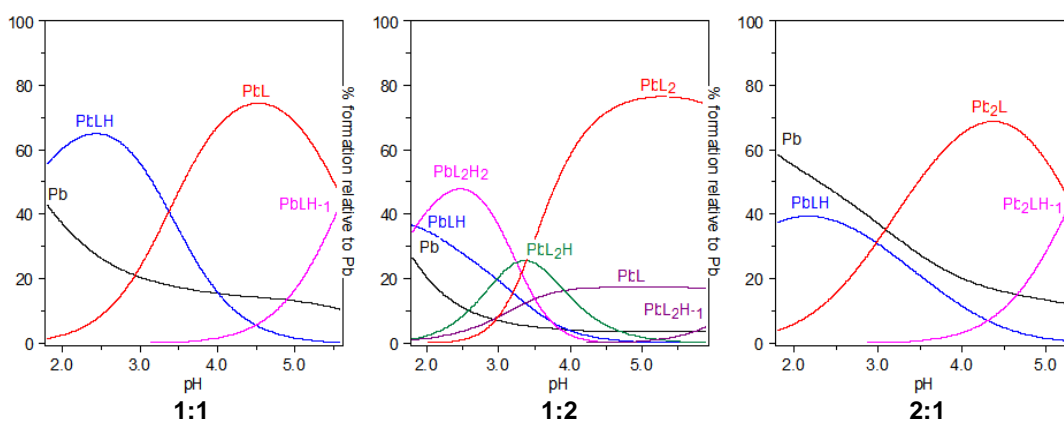

Fig. 6. Species distribution diagrams for 1:1, 1:2 and 2:1 (C_M : C_L) compositions of Pb^{2+}- AADH system
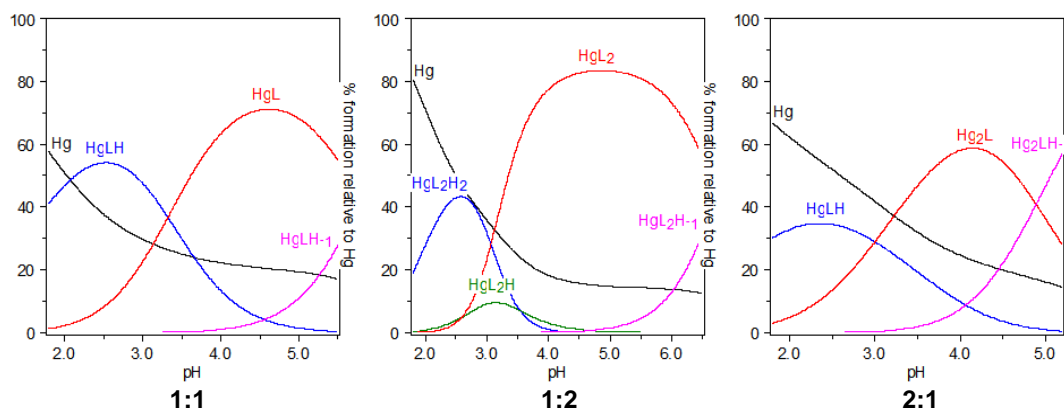

Fig. 7. Species distribution diagrams for 1:1, 1:2 and 2:1 (C_M : C_L) compositions of Hg^{2+}- AADH system
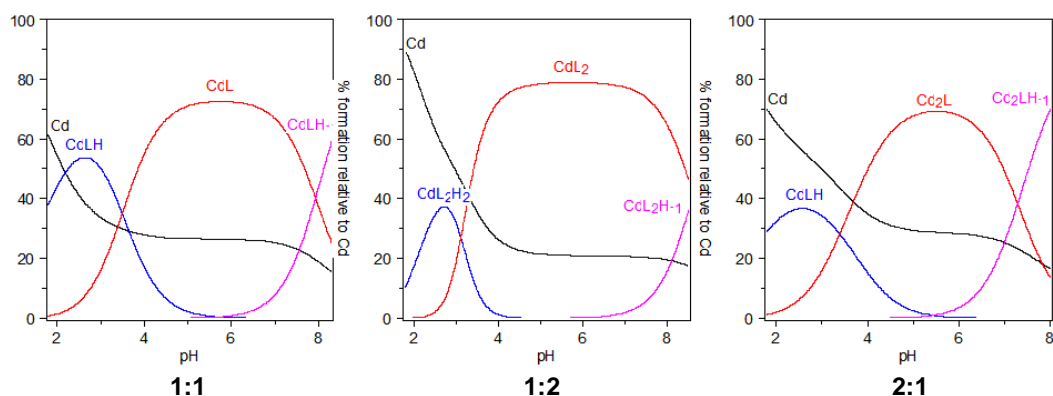
Fig. 8. Species distribution diagrams for 1:1, 1:2 and 2:1 ($C_M : C_L$) compositions of Cd^{2+}- AADH system
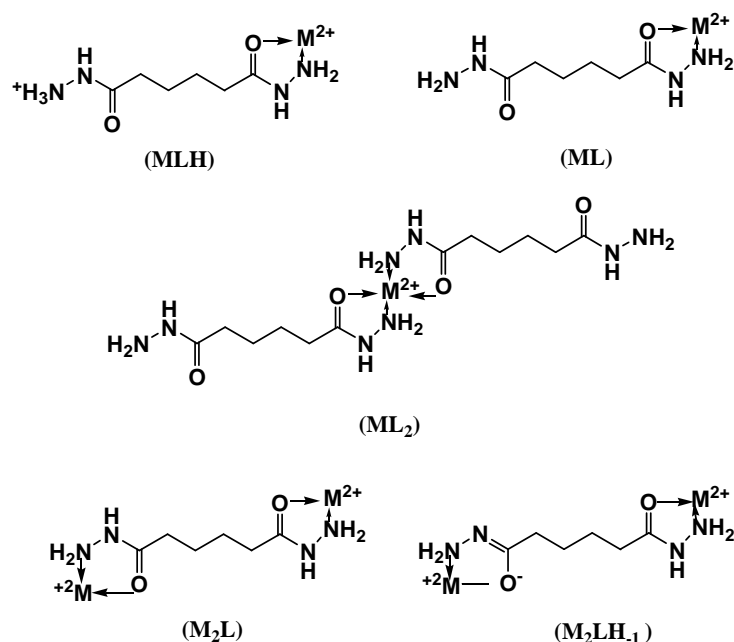

Fig. 9. Bonding nature in some species of metal ion-AADH systems

ion, 4. Hard & soft acid-base nature of both metal ion and donor atom and 5. Chelate ring size and other geometric factors.

- According to Pearson's HSAB theory, Hg^{2+} and Cd^{2+} are soft Lewis acids while Pb^{2+} belongs to borderline category. On the other hand AADH provides hard oxygen and borderline $-NH_2$ donors. Hard acids prefer binding to the hard bases to give ionic complexes, whereas the soft acids prefer binding to soft bases to give covalent complexes. Metal ions of borderline category can behave as either

hard or soft acid, depending on solvent, stereochemical and electronic structural factors. Therefore, the HSAB principle accounts well for the decreased affinity of AADH towards metal ions, from Pb^{2+} to Hg^{2+} and Cd^{2+}.

- Another factor to be considered is the size of the chelate ring relative to the size of the metal ion. [41,42] Ligands that form 5-membered chelate rings are better pre-organized for coordinating with large metal ions, [43] while those that form 6-membered chelate rings are better pre-organized for coordinating with small metal

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ions. Solid state studies using spectral, thermal and magnetic measurements indicated that each hydrazide group of AADH acts as a bidentate bonding through terminal -NH_2 group and amide oxygen forming a five membered ring. The ionic sizes of Pb^{2+} (0.118 nm) > Hg^{2+} (0.102 nm) > Cd^{2+} (0.095 nm) which is also the order of the decreasing stabilities of the complexes.

- Oxygen atoms of amide group donors are of great importance in biological reactions. It has been showed many times that the use of neutral oxygen donors increases the affinity of ligands towards larger metal ions [44]. This leads to an increase in the stabilities of complexes with large metal ions relative to small ions. A contributing factor to this observation lies in the geometry of chelate rings. Literature reports on Infrared spectral studies of AADH metal complexes [10,19,21] clearly indicate the involvement of amido oxygen in bonding. The increase in stability of metal complexes from Cd^{2+} to Hg^{2+} to Pb^{2+}, which is also the order of increasing ionic size, is therefore explicable.

All the above factors contribute to the observed relative stabilities of the complexes.

4. CONCLUSIONS

Adipic acid dihydrazide is a ditopic ligand with two hydrazide groups on either side of the molecule. Solid state studies indicate [21] that the ligand is capable of bonding to the metal ions as a i) neutral bidentate (ON donor) bonding through carbonyl oxygen and –NH_2 group, ii) neutral tetradentate (ditopic) bonding through two carbonyl and two –NH_2 groups and iii) mono or binegative tetradentate bonding in enolic form. The ligational behaviour of the ligand in aqueous solution, towards toxic metal ions, Pb^{2+}, Hg^{2+} and Cd^{2+} was examined using pH-potentiometric technique. The data were analyzed using the Miniquad-75 program. Several species depending on the metal to ligand concentration ratio were found to exist in solution with overlapping equilibria. The best-fit models obtained were found to include both mono and symmetric binuclear species in protonated, unprotonated and deprotonated forms. The relative order of stability of various species was found to be Pb^{2+} > Hg^{2+} > Cd^{2+}, which was explained on the basis of HSAB theory, ionic size and stereochemistry.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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