Reactions of Zn^{2+}, Cd^{2+} and Hg^{2+} with Free Adenine

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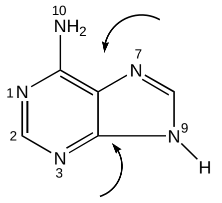
Abstract: We are reporting the fluorescence quenching, IR, Raman, ^{1}H-NMR, and potentiometric studies for the Zn^{2+}:adenine and the Cd^{2+}:adenine systems under ambient conditions. IR and Raman spectra suggest that Zn^{2+} and Cd^{2+} interact with adenine but the modes of interaction differ. Fluorescence spectra indicate that the interaction involving Zn^{2+} is more favorable than that of Cd^{2+}, and this effect is due to the difference in ionic radii. ^{1}H-NMR, potentiometry, and speciation diagrams indicate the formation of strong metal ion adenine complexes. Potentiometric titrations of the heavier member of group 12 metals (Hg^{2+}) show similar results to that of Zn^{2+} and Cd^{2+}. Some differences in the ^{1}H-NMR experiments appeared between both (Zn^{2+} and Cd^{2+}) compared to that of Hg^{2+}. Due to the fluorescence quenching of adenine, adenine can be used as a sensor of Zn^{2+} and Cd^{2+}.

Keywords: Adenine, Group 12, Fluorescence, IR, Raman, NMR, Potentiometry, Speciation.

1. INTRODUCTION

A relatively recent detailed paper on adenine in *Acc. of Chem. Res.*, presented the many facets of adenine including coordination chemistry, crystal patterns, and catalysis [1]. In this detailed paper the authors focused on the coordination of adenine to the mono-valent silver. The same paper also showed the possible coordination sites of this heterocyclic nucleo-base [1]. Previous studies on metal complexation with adenine have suggested that adenine is coordinated to metal ions through the N(1), N(3), N(7), and N(10) nitrogen atoms [2, 3]. Recently, we have investigated the effects of some trivalent metal ions (Cr^{3+}, Fe^{3+}, and Al^{3+}) on free adenine, and we demonstrated that N-9-H of the free adenine is also involved in the metal ion binding (Scheme **1**) [4]. Scheme **1** shows the atomic numbering system and all possible centers of attachments on adenine as well as the possible centers for forming a metal chelate.



Scheme 1: Possible centers of attachment between N(7) and N(10) for the small Zn^{2+}. The binding between N(3) and N(9) will fit better with the larger Cd^{2+} and Hg^{2+}.

From our ongoing efforts to study the role of metal ions on the versatile coordination ability of adenine, we focus our attention on the effect of some divalent metal ions on the structure of free adenine. Literature review indicated that many studies have been devoted to the interactions of Zn^{2+} and Cd^{2+} (among other di-valent metal ions) with a variety of biomolecules, such as tethered nucleo-bases, or ATP, or adenosine chloro-derivatives, or DNA itself [5-12]. Yet, very few papers investigated the interaction of free adenine with metal ions [2,4]. We have chosen to investigate the interaction of Zn^{2+} and Cd^{2+} with adenine partially because zinc was found to induce a tolerance to the cytotoxicity of cadmium in cultured vascular endothelial cells. The toxicity was evaluated by the [^{3}H] adenine release assay. Kaji *et al.* speculated that zinc would mimic cadmium in endothelial cells [5, 7]. A detailed survey of the coordination chemistry literature indicated that many papers were published related to the current topic presented here, but, not for the reaction of free adenine with metal ions [13-24]. In the current work, we investigate the interactions of Zn^{2+} and Cd^{2+} with free adenine using emission fluorescence, IR, Raman, ^{1}H-NMR, and potentiometric techniques.

2. EXPERIMENTAL SECTION

2.1. Materials and Methods

Adenine $C_5H_5N_5$ 99%, commonly known as vitamin B_4, Formula Weight 135.13 g/mol was purchased from Aldrich. $ZnCl_2•6H_2O$ and $CdCl_2•5H_2O$ were obtained from Fisher Scientific and used as received. All

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solutions including adenine were dissolved in doubly de-ionized (DI) water. The complexes were obtained by mixing aqueous solutions of the metal and adenine in various molar ratios (such as 5:1, 9:1) at pH 2, 7, and 9. Zinc nitrate nonahydrate, $Zn(NO_3)_2 \bullet 9H_2O$, cadmium nitrate nonahydrate, $Cd(NO_3)_2 \bullet 9H_2O$, and mercury nitrate monohydrate, $Hg(NO_3)_2 \bullet H_2O$ were purchased from Fisher Scientific (99+%) and used in collecting the potentiometric titrations. The pH-values of all solutions were adjusted using standard NaOH solution which was usually in the concentration range of ~ 0.1 M. The pH values were measured using Orion pH electrode model 720A+ connected to an Orion pH-meter. The ionic strength of all solutions was adjusted to 0.10 M by using 1.0 M $NaNO_3$ solution.

2.2. Apparatus of Spectroscopic Studies (IR and Raman)

A series of solutions was prepared with a constant adenine concentration and increasing metal ion concentrations. The change in vibration modes of adenine with metal ion concentration was then monitored using IR and Raman spectroscopes. FTIR measurements were carried out at room temperature on a Perkin Elmer Spectrum One equipped with a Diamond attenuated total reflectance (ATR) DuraVision accessory, a DTGS KBr detector and a KBr beam splitter. The infrared spectra were recorded between 4000 and 600 cm^{-1} at 4 cm^{-1} resolution and 64 scans were accumulated. All the infrared spectra were normalized. Confocal Raman spectra were acquired with a Horiba Jobin-Yvon HR800 spectrometer using an excitation wavelength of 632.81 nm, a 600 groove grating, and a 10X microscope objective. Spectra were collected by placing the resultant precipitant on a glass microscope slide and collecting spectra from the top portion of the sample. The spectra presented here represent an average of 8 individual spectra, with each spectrum collected over the course of 1 second. The detector was an open electrode CCD and the diameter of the pinhole immediately preceding the detector was 100 microns. All the Raman spectra were normalized [25].

2.3. Electronic Spectra

Absorption spectra were performed in a 1.00 cm quartz cuvette using a CARY BIO 300 spectrometer from Varian. Fluorescence emission spectra were similarly collected on an Eclipse spectrometer from Varian. The wavelength of excitation was 265 nm. DI water was used as blank [26]. Samples used to collect the Fluorescence spectra had the following concentrations: Adenine = 0.740 mM, Zn^{2+} = 3.68 mM, and Cd^{2+} = 6.66 mM. These concentrations gave the molar ratios of adenine: Zn^{2+} and adenine: Cd^{2+} of 1:5 and 1:9 respectively.

2.4. System Standardization and Adenine pKa Values

A standard phosphoric acid solution (H_3PO_4) was titrated to calibrate the whole potentiometric titration system before gathering the actual potentiometric titrations for either the free adenine, or the free metal ions titrations, or the metal ion-adenine reaction system in different molar ratios. It appeared that when the free adenine was titrated without any metal ion, it behaved as an H_2L ligand in which two protons were titrated. These protons came from one of the aromatic nitrogen(s) and the free aliphatic amino group. The corresponding pKa values of these groups are 4.26 and 9.69 respectively [27].

Standardizations of all metal ion solutions used in the potentiometric titrations were done by eluting a known volume of the metal ion. For example, 1.0 mL of Zn^{2+} solution was allowed to pass through Dowex 50X8-100 resin packed in a 7×1 inch glass column and titrating the eluant with a standard NaOH solution. The stock metal ion concentrations were in the range of 0.05 M. Typically seven to nine runs were averaged. These procedures are well documented in the literature [28-31].

2.5. Potentiometric Titrations

In all metal-ligand potentiometric titrations, the NaOH solution was the titrant. The methods used to prepare, standardize and prevent the contamination of the titrant with atmospheric CO_2 have been described elsewhere [4, 28-31]. In a typical titration, 2.0 mL of 0.050 M Adenine solution was added to a 100.0 mL volumetric flask. Then 2.0 mL of stock 0.05 M Zn^{2+} or Cd^{2+} solutions (separately) and 10.0 mL of 1.0 M $NaNO_3$ solution were added before dilution to the mark with D. I. water. Before each titration, the metal-adenine mixtures were allowed to stir for 20 minutes to reach a state of equilibrium. The NaOH solution was added in 100 μL increments using an Eppendorf micropipette with continuous stirring. The time intervals between the additions of the NaOH solution were set to 3 minutes, which was sufficient to get each of the pH values stabilized and reach a state of equilibrium. Typical titration experiment took about 5-6 hours to be completed. Each potentiometric titration was performed at least in triplicate.

2.6. ^{1}H-NMR Experiment

All ^{1}H-NMR spectra were acquired at room temperature using 5 mm OD NMR sample tubes and deuterium oxide to lock and shim the sample on a JEOL 270 MHz NMR spectrometer housed at the University of Memphis.

3. RESULTS AND DISCUSSION

3.1. Zn^{2+}- and Cd^{2+}-Adenine Systems Using FTIR

The IR and Raman spectra of free adenine and some tri-valent metal ions-adenine complexes have been documented [4]. In the current study, we focus on the main IR/Raman bands of free adenine and Zn^{2+} and Cd^{2+}-adenine systems at pH 2 (Table **1** in the supplemental materials), using the assignments proposed by Mathlouthi *et al*. [32] and Hamada *et al*. [4]. The spectral changes (intensity and shifting) of the IR peaks associated with the possible binding sites of adenine were monitored. In the 3500-2800 cm^{-1} region, the IR spectrum includes the peaks associated with the asymmetric and symmetric vNH_2 modes at 3282 and 3101 cm^{-1}, respectively, and the peak at 2970 cm^{-1} associated with v N-9-H. In the 1800-600 cm^{-1} region, the IR spectrum of free adenine includes bands at 1669 (δNH_2), 1598 cm^{-1} (δ C-N-9-H), 1502 cm^{-1} (υ C=N or υ C=C), 1449 cm^{-1} (δ imidazole ring), 1250 cm^{-1} (C-NH_2), 910 cm^{-1} (NH_2), and 866 cm^{-1} (ω N-9-H) [4].

At a Zn^{2+}:adenine molar ratio less than 5:1 (Cd^{2+}: adenine less than 9:1), the intensities of the bands cited above exhibit no major intensity change or shifting upon Zn^{2+} or (Cd^{2+}) complexation respectively. We conclude that there is no significant interaction between Zn^{2+} (or Cd^{2+}) and adenine at these low concentration ratios.

At a Zn^{2+}:adenine molar ratio 5:1, major spectral changes occurred for adenine vibrations at all the possible binding sites (Figure **1**). The interaction of adenine with Zn^{2+} is evident by the shift of the peaks associated with the asymmetric and symmetric NH_2 modes at 3282 and 3101 cm^{-1} to the higher wavenumbers of 3370 and 3165 cm^{-1}, respectively (Supplementary Table **1**). The shift to higher wavenumbers is explained by the weakening of the H-bonds between adenine molecules upon metal binding. This shift also suggests that the N(10) of the amino group is involved in the metal coordination. In the low wavenumber region, the peak at 1669 cm^{-1} assigned to δ(NH_2) has shifted to lower wavenumbers at 1662 cm^{-1}. The shifting to lower wavenumbers is explained as a weakening of the N-H bonds resulting from the electron drainage from the nitrogen atom due to its coordination to the Zn ion through the lone pair [33].

Another major observation is the splitting of the band at 1598 cm^{-1} assigned to N-9-H group into two different bands of similar intensities at 1602 and 1617 cm^{-1} (Δv = 15 cm^{-1}). The splitting into two bands suggests a strong interaction between adenine and

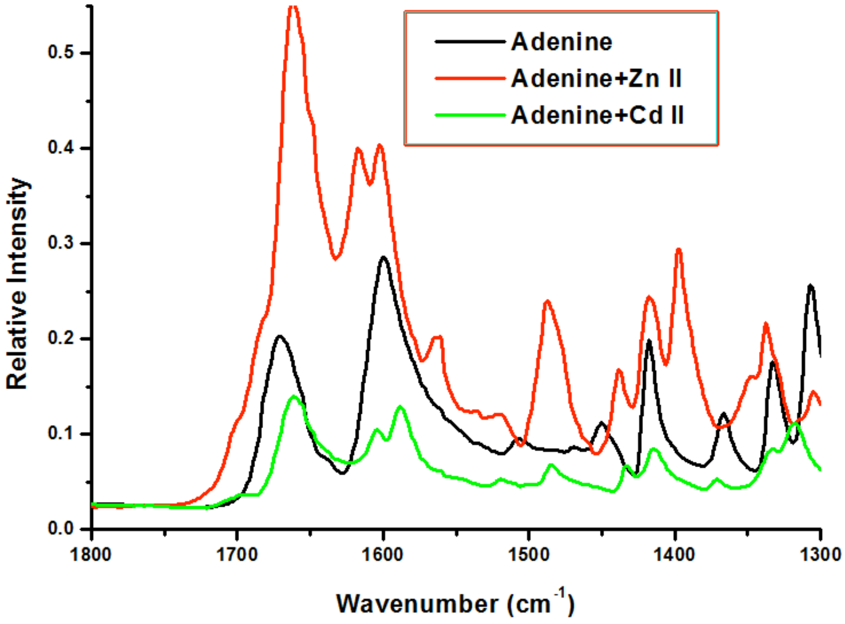

Figure 1: IR spectra of adenine with its complexes of Cd^{2+} and Zn^{2+} at pH 2.

zinc ion and the shift towards higher wavenumbers suggests the formation of a weak bond between Zn ion and the N-9-H group. The shift and intensity change of the peak at 1449 cm^{-1} (to 1488 cm-1) assigned to the imidazole ring also indicates the involvement of this group in the Zn^{2+} coordination process. We do not have an explanation of the strong peak that appeared at 1563 cm^{-1} in the spectrum of adenine-Zn.

At a Cd^{2+}:adenine molar ratio 9:1, the involvement of the amino group is evident by the shift of the peaks associated with the asymmetric and symmetric NH_2 modes at 3282 and 3101 cm^{-1} shifted to the higher wavenumbers 3432 and 3334 cm^{-1}, respectively. The peak at 2970 cm^{-1} associated with vN-9-H has almost disappeared, which suggests that N-9-H is mostly de-protonated. In addition, the splitting of the band at 1598 cm^{-1} assigned to δN-9-H group in metal-free adenine gives rise to a dissymmetric doublet at 1604 cm^{-1} (weak intensity) and 1588 cm^{-1} (high intensity) ($\Delta v = 16$ cm^{-1}) as seen in Figure **1**. The splitting into two peaks suggests a strong interaction between adenine and cadmium ion through the N atom of N-9-H group; in other terms, cadmium ion has replaced most of the H atoms of the N-9-H groups. The binding of Cd (with a large ionic radius and large electron density) to N-9 makes the bond N-9-Cd strong, which can explain the weakening of the peak of N-9-H and the shift of that peak to lower wavenumber at 1588 cm^{-1}. The peak at 1669 cm^{-1} has shifted to lower wavenumbers at 1661 cm^{-1}, as a result of the weakening of the N-H bond upon metal complexation. The shift and intensity change of the peak at 1449 cm^{-1} (to 1487 cm^{-1}) assigned to the imidazole ring also indicates the involvement of this group in the Cd^{2+} coordination process. According to these observations, Zn ion is transferring electrons to adenine, while cadmium is withdrawing electrons from adenine. This observation is confirmed by the Raman spectra.

At a Zn^{2+}:adenine molar ratio higher than 5:1 (Cd^{2+}:adenine higher than 9:1), the interaction is evident by the similar features compared to those at a Zn^{2+}:adenine molar ratio 5:1 (Cd^{2+}:adenine molar ratio 9:1), suggesting a similar mode of coordination of Zn^{2+} (Cd^{2+}) to adenine. The splitting of the band associated with N-9-H is observed at pH 2, 7 and 9 for Zn^{2+} while that of Cd^{2+} occurred at pH 2 and 7.

3.2. Zn^{2+}- and Cd^{2+}-Adenine Systems Using Raman Spectroscopy

In the low wavenumber region, especially below 500 cm^{-1}, the metal-ligand vibrations occur [25]. Assignment of the v (M-N) vibrations has been given carefully by comparing with data reported in the literature [4, 25, 33]. The additional bands observed in the spectra of the complexes of Figure **1** of supplementary material in the 600-200 cm^{-1} region are attributed to the coordination of adenine to Zn^{2+} (Cd^{2+}). There is one new band at 349 cm^{-1} in the Raman spectrum of the Zn^{2+}-adenine complex. This new bands at 349 cm^{-1} may be attributed to v (Zn-N-10), in agreement with the values reported in the literature [10, 34]. There are two new bands in the Raman spectrum of the Cd^{2+}-adenine complex (Figure **2** of supplementary). The new bands appeared at 449 cm^{-1} and 426 cm^{-1}. The peak at 449 cm^{-1} can be attributed to v (Cd-N-10), in agreement with the values reported in the literature [10, 34]. Also, the peak at 426 cm^{-1} can be attributed to v ($Cd-N_{ring}$), in agreement with data in the literature [10, 34].

3.3. Zn^{2+}- and Cd^{2+}-Adenine Systems Using Fluorescence

Figure **2** is the Fluorescence emission spectra of adenine with its complexes of Cd^{2+} and Zn^{2+} in aqueous solutions at pH 2. To the best of our knowledge, the fluorescence emission spectra presented here are the first fluorescence spectra of free adenine in aqueous solutions. In fact, the nucleic acids have been found to have very weak fluorescence at room temperature [35]. The fluorescence spectra of adenine with Zn^{2+} (Zn^{2+}:adenine molar ratio 5:1) and Cd^{2+} (Cd^{2+}: adenine molar ratio 9:1), are presented in Figure **2**. The fluorescence spectrum of adenine shows a maximum at 375 nm on excitation at 265 nm. The addition of Zn^{2+} and Cd^{2+} independently has a quenching effect on adenine. There is a decrease of ~ 78% and ~ 36% of the emission intensity of adenine after interaction with Zn^{2+} and Cd^{2+}, respectively. The addition of Zn^{2+} resulted also in a slight red shift of adenine spectrum (from 375 to 378 nm) and the appearance of a new peak at 423 nm. In contrast to Zn^{2+}, the addition of Cd^{2+} resulted in a slight blue shift of adenine spectrum (from 375 to 370 nm), and the appearance of two new peaks at 299 and 421 nm. These new bands correspond to new species [36-38]. This observation is in agreement with the existence of Zn^{2+} and Cd^{2+} complexes with different stoichiometries [6]. Because the decrease in the emission intensity upon Zn^{2+} addition was twice that obtained upon Cd^{2+} addition, we concluded that the interaction of Zn^{2+} with adenine is twice stronger than that of Cd^{2+}. Martell's Critical Stability Constants Database indicated that Zn^{2+} binds stronger to adenine compared to Cd^{2+} [27].

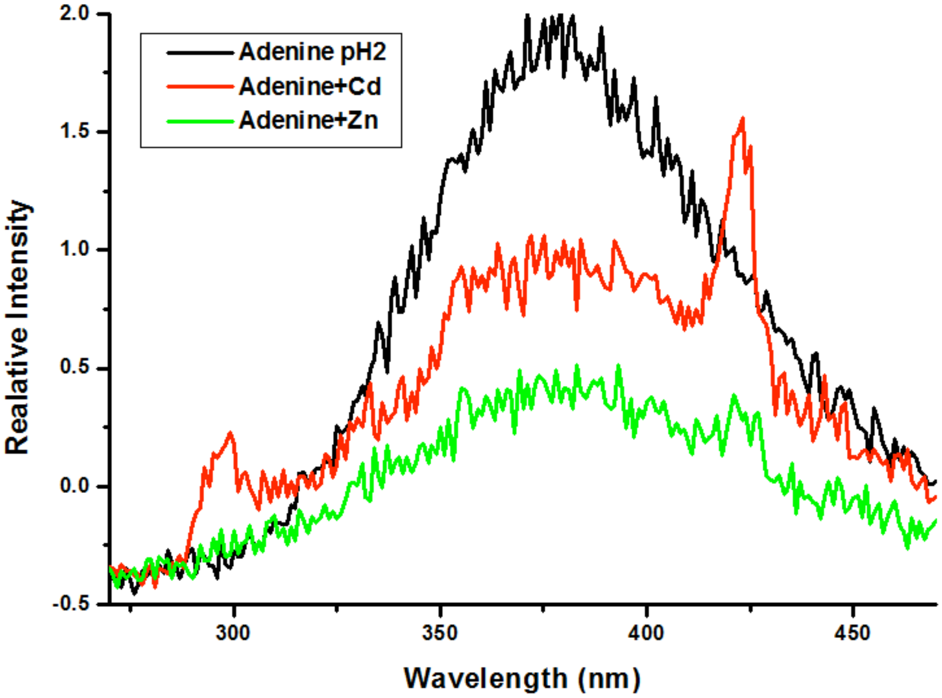

Figure 2: Fluorescence emission spectra of aqueous solutions of adenine with its complexes of Cd^{2+} and Zn^{2+} at pH 2.

3.4. Zn^{2+}-, Cd^{2+}-, and Hg^{2+}-Adenine Systems Using Potentiometry

Tables **2-4** of the supplementary material contain all of the runs conducted for the reactions of free adenine, free Zn^{2+}, free Cd^{2+}, free Hg^{2+}, Zn^{2+}:adenine, Cd^{2+}:adenine, and Hg^{2+}:adenine in various ratios (Typically 1:1, 1:2, and 1:3 metal : adenine ratio) . It appeared that no more than two protons were titrated with all of the above mentioned titration systems. It is clear that adenine had two titratable protons. Also, these divalent metal ions release two protons upon their titrations which one might expect for these divalent metal ions. Figure **3** is a sample titration graph for the reaction of Zn^{2+} with adenine in 1:1 molar ratio. Supplementary Figures **3** and 4 are titration graphs for group 12 metals with adenine. We have added minimum amount of standard HCl solution to the metal solutions to prevent the metal from hydrolyzing [39]. Figure **4** is the speciation diagram of the Zn^{2+}:adenine reaction in 1:1 molar ratio using Hyper quad Simulation and Speciation program [40]. This program was used successfully in similar reaction systems [29-31].

It is clear that the simple one-to-one metal-adenine chelate had been formed due to the fact that when one or two or three moles of adenine were added to the mole of metal ion (zinc, or cadmium, or mercury independently) only two protons were found as the location of the inflection points showed. We would expect the formation of three or four protons to be released into the titration solution if the metal hydroxo-complex were to form. This was not the case at all. We can report here with confidence that the reaction of free adenine with these group 12 divalent metal ions individually formed the simple one-to-one complex.

3.5. Zn^{2+}-, Cd^{2+}-, and Hg^{2+}-Adenine Systems Using ^{1}H-NMR

Figures **5** through **8** of supplementary material contain all ^{1}H-NMR of the free adenine in D_2O at pH ~ 3.5 as well as Zn^{2+}:adenine, Cd^{2+}:adenine, and Hg^{2+}:adenine in 1:1 ratios at the same pH value 3.5. Upon metal reaction with free adenine, there were shifts due to the binding of the three divalent metal ions to adenine in solutions at ambient temperature. For the free adenine, the two protons on the N(10) of the NH_2 group appeared at 7.01 ppm, the proton on the five-membered ring appeared at 8.13 ppm, and the proton on the six-membered ring appeared at 8.18 ppm. All showed up field shifts of at least 0.02 ppm when bound to Zn^{2+}, Cd^{2+}, and Hg^{2+} for the aliphatic-amine-protons. On contrast, the Hg^{2+} showed the large value of 0.19 ppm downfield shift for the aromatic protons when bound to adenine.

4. CONCLUSION

In the current paper we have used many quantitative as well as qualitative analytical tools for the

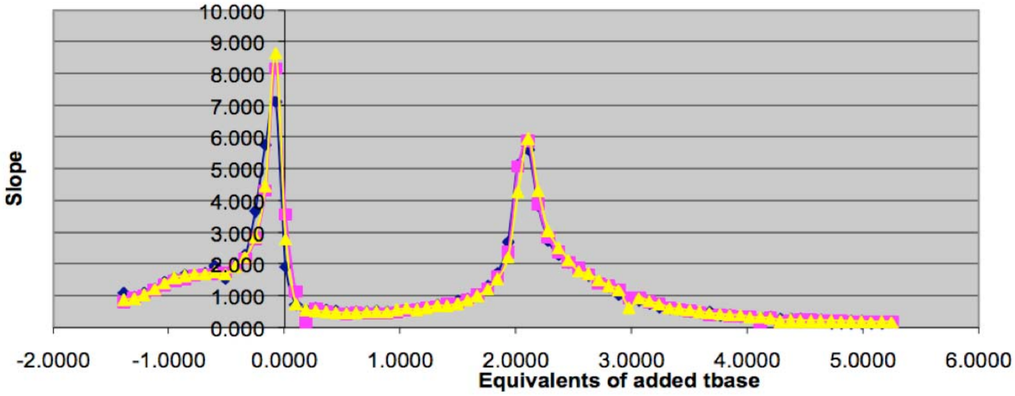

Figure 3: Three super imposed potentiometric titration graphs of Zn^{2+}:adenine in 1:1 ratio. See figure 4 for the speciation of the formation of the one-to-one metal complex.

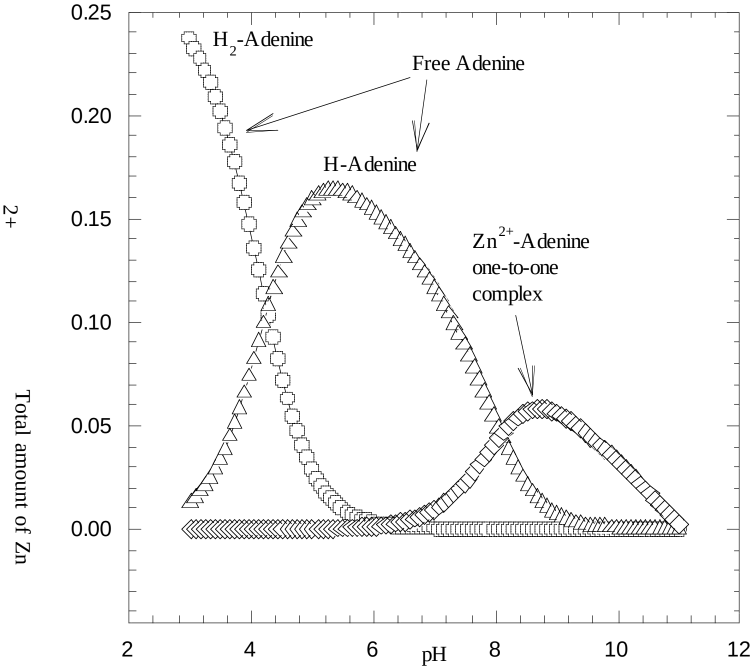

Figure 4: Speciation of Zn^{2+}: Adenine in 1:1 molar ratio.

reaction of free adenine with group 12 metal ions in solutions at room temperature. IR, Raman, ^{1}H-NMR, and potentiometric techniques were among the main tools used. We also presented novel fluorescence emission spectra of free adenine and with its complexes of Zn^{2+} and Cd^{2+} in aqueous solutions at acidic pH-value. All data indicated formation of strong metal ion adenine complexes. There is void in the literature on the reactions of free adenine with metal ions; this is perhaps due to many researchers reacted many metal ions with the more well known adenosine mono-, di-, tri- phosphates, or related bio-molecules such as, adenosine chloro-derivatives, or DNA itself.

From Scheme **1**, one might expect that the larger metal ion (such as Cd^{2+} or Hg^{2+}) will coordinate in a chelate fashion between the N(3) and N(9) while the smaller metal ion (Zn^{2+}) will fit better in the smaller chelate ring size between N(7) and N(10). The presented fluorescence emission spectra and their quenching effect due to metal ion binding are novel. We explicitly can conclude that there were no metal hydroxo complexes formed in any of the reaction systems studied in this paper due to the following two facts: 1- a maximum of two protons have been titrated from all runs using potentiometry regardless of the metal to adenine ratio, 2- the IR characteristic band of the metal hydroxide was absent.

Comparing our data with Martell's and Smith's most comprehensive compilation of critically selected stability constants of metal complexes with adenine

[27], we noticed that there only a few metal ions that have been reacted with adenine (Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}). There remains an enormous amount of theoretical and experimental work needed to be conducted in this area. Due to the apparent observed fluorescence quenching of adenine upon reaction with Zn^{2+} and Cd^{2+}, adenine can be used as a sensor of Zn^{2+} and Cd^{2+} [41-43].

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SUPPLEMENTAL MATERIALS

The supplemental figures and tables can be downloaded from the journal website along with the article.

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