

Interaction of 1-Pyrrolidine Carbodithioic Acid with Cu(II), Ni(II) and Co(II) ions

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Abstract

The interaction of 1-pyrrolidine carbodithioic acid with Cu(II), Ni(II) and Co(II) ions in mixed solvent has been studied to investigate the molar ratios of interaction, stability constants and the energy profiles for the formation of complexes. Electroanalytical and spectrophotometric methods were used for the analysis. It has been found that 1-pyrrolidine carbodithioic acid forms stable 1:1 and 1:2 complexes with Ni(II), whereas only 1:1 stable complexes are formed with Cu(II) and Co(II) at different pHs, temperature and ionic strengths. The stability constants of the complexes have been determined from Ardon plots while the heat and free energies of the complexation process were calculated using the Vant Hoff's equation.

Key words: metal complex, pyrrolidine carbodithioic, copper, nickel, cobalt

Introduction

The study of interaction of biological important medicinal agents with metal ions is gradually becoming more interesting particularly in the areas of drug design and development. Complexation of drug molecules with metal ions play a vital role in different biological processes and markedly influences the bioavailability of drugs since a large number of metals are taken into the body system either with drugs or in the form of diet. Metals can form stable complexes in the body which might be toxic to the body. Similarly, toxic metals can be quantitatively eliminated using suitable ligands. Drug molecules combine with metal ions according to the availability of lone pair electrons in these compounds and the capability of the metal ions to utilize these electrons to form donor-acceptor bonds.

There has been no report about the complexation of 1-pyrrolidine carbodithioic acid (Figure 1) with Cu(II), Ni(II) and Co(II) ions. It should be mentioned that esters of carbodithioic acid showed spermicidal, antifungal and anti-*Trichomonas* activities. This study also revealed that the incorporation of carbodithioic acid residue directly into fluoxetine structure leads to compounds with better antifungal and anti-*Trichomonas* activities (Kumar *et al.*, 2008). It is worthwhile to investigate the interaction of this molecule with the above mentioned metal ions since they have biological importance. It is well known that copper is

essential for the human metabolic processes. All other animals as well as human possess a homeostatic mechanism for absorption, transport, utilization and excretion of copper and in man at least two lethals, hereditary disorders of copper metabolism, Wilson's diseases and Menke's kinky hair syndrome are known. Nickel has some toxic effects on human beings and animals. On the other hand, it is a useful trace element for the body. If nickel is injected in the body, blood pressure is lowered. Nickel is also toxic to bacteria and no doubt some of the bacterial inhibition is due to this property. The best known biological function of cobalt is its intimate involvement in the coenzyme related to vitamin B₁₂. Certain porphyrin complexes of Co(II) in presence of bases show reversible oxygen binding capacity and these complexes can be introduced into globin to form a cobalt substituted hemoglobin that has the same type of cooperative oxygen uptake as hemoglobin itself.

Several authors including Martel and Smith (1982) have summarized the stability constants of metal ligand complexes. Trivedi (1985) studied Cu(II), Ni(II), Co(II), Fe(II), Mn(II) complexes of N-salicylaldeno-actyl hydrazine pyridinium chloride potentiometrically at 27°C and ionic strength 0.1M and found the stability constants in the order of Mn<Ni<Cu<U<Fe<Co. Electron spin resonance of the Cu(II) complex of L-dopa and related systems was studied by Smith *et al.* (1971). Complexes of

Os, U, Mo and W with catecholamine, adrenaline, noradrenaline, dopamine, dopa, and isoproterenol were studied by El-Hendawy (1988). Rabindra and Pani (1961) also studied the citrate complexes of Zn(II) and Mn(II) by pH and conductometric titration methods.

Since metals play some important role in physiological processes on human and animals, their complexation with drugs like 1-pyrrolidine carbodithioic acid may have important biological implications.

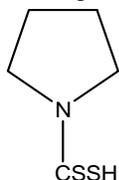


Figure 1. Structure of 1-pyrrolidine carbodithioic acid

This paper reports the process of complexation, nature and strength of the complexes arising due to the interaction of 1-pyrrolidine carbodithioic acid with Cu(II), Ni(II) and Co(II) at different pH and ionic strengths.

Materials and Methods

Chemicals and reagents: The chemicals and reagents used in this work were analar grade. Copper, Nickel and Cobalt were used as their nitrate salts, $\text{Cu}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$, $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ and $\text{Co}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (BDH) respectively and 1-pyrrolidine carbodithioic acid was in the form of ammonium salt (Aldrich). Stock solutions were freshly prepared and the solutions were buffered at the desired pH. Anhydrous potassium chloride (BDH) was used to adjust the ionic strength of the experimental solutions and to prepare KCl/HCl buffer of pH 2.5. Acetate buffers (pH 4.5, 7.4 and 9.4) were obtained using requisites of glacial acetic acid (E. Merck) and anhydrous sodium acetate (BDH). EDTA solution was prepared in de-ionized water to standardize the metal salt solutions.

Potentiometric titrations: For the potentiometric titrations (Alam *et al.*, 1995), solutions ($5.0 \times 10^{-3}\text{M}$) of pure 1-pyrrolidine carbodithioic acid and metal salts and their 1:1 and 1:2 molar mixtures were titrated with a standard sodium hydroxide ($2.0 \times 10^{-2}\text{M}$) solution. The titration curves of the mixtures were compared with the summation curve of free 1-pyrrolidine carbodithioic and metal solutions.

Conductometric titration: The conductometric titrations (Niebergall *et al.*, 1966) were done by using

absolute alcohol-water (80:20v/v) as solvent. 1-pyrrolidine carbodithioic solution was titrated with the metal salt solution followed by a reverse titration. The plots of conductance versus molar ratios were prepared after volume correction as $\Lambda = \Lambda_0(v+u)/v$ where v is the original volume of the solution, u is the reagent added, Λ_0 is the observed conductance and Λ is the corrected conductance.

Job's spectrophotometric method of continuous variation: For Job's spectrophotometric method (Nabi *et al.*, 1974), absorbance of a series of 1-pyrrolidine carbodithioic-metal mixtures were measured at 211 nm (absorbance maximum of 1-pyrrolidine carbodithioic) by keeping the total moles constant. The absorbance differences were plotted against the mole fractions of 1-pyrrolidine carbodithioic in the mixtures.

The Ardon's spectrophotometric method: In the Ardon's spectrophotometric method (Ardon, 1957) the absorbances of free metal solutions (C) and those of different mixtures (D) were measured at 211 nm where the concentrations of 1-pyrrolidine carbodithioic were varied but the metal concentration was kept constant ($2.5 \times 10^{-4}\text{M}$). Values of $1/(D - \epsilon_A C)$ were plotted against $1/PLC$ using the Ardon equation.

$$1/(D - \epsilon_A C) = 1/Kc(\epsilon_{\text{com}} - \epsilon_A)[B]^n + 1/C(\epsilon_{\text{com}} - \epsilon_A)$$

Where D is the absorbance of a complex mixture, C is the molar concentration of metal, ϵ_A is the molar extinction co-efficient of metal, ϵ_{com} the molar extinction coefficient of the complex and K is the stability constant. The method is valid only when $n=1$. From these plots, the values of stability constants K were obtained; since it is seen the $K = \text{intercept/slope}$ of the straight lines so obtained.

Apparatus: A TOA pH Meter HM-26S was used to adjust pH and for the potentiometric titrations. A TOA CM conductivity meter of CM-5S was used for the conductometric titrations. The spectrophotometric measurements were carried out with a UV-160A, and UV-visible recording spectrophotometer (Shimadzu) with XY plotter.

Results and Discussion

1-Pyrrolidine carbodithioic acid has an absorption maximum at 211 nm, but Cu(II), Ni(II) and Co(II) ions have zero absorbance at this wavelength under all the pH and ionic strengths studied. This is due to the fact that Cu(II), Ni(II) and Co(II) do not undergo any electronic transitions in the UV range. It has been observed that the

absorbance of 1-pyrrolidine carbodithioic acid-metal mixtures were higher than those of 1-pyrrolidine carbodithioic acid alone even though the absorption maxima do not shift in most cases. Appreciable change in absorption maxima occurred for Co(II)-1-pyrrolidine carbodithioic acid at lower pH values (acidic medium) for 1:1 molar mixtures. For Ni(II)-1-pyrrolidine carbodithioic acid, the changes occurred at higher pH values (alkaline medium) for 1:1 molar mixtures. The changes in the spectral patterns of the pyrrolidine carbodithioic acid-metal mixtures from those of the pure 1-pyrrolidine indicated the possibility of complex formation (Figure 2), though the change in spectral behaviour of the compound in presence of metals vary with pH of the medium. This change has been found to be increasing with increasing acidity (Figure 3). A similar phenomenon was observed by Gur Yanova et al., (1975) who reported that a change in intensities of absorbance is a common phenomenon in the case of donor acceptor complexes.

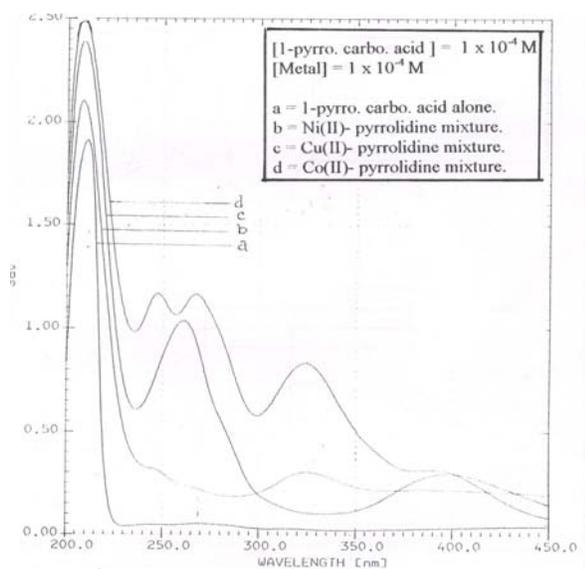


Figure 2. UV-spectra of 1-pyrrolidine carbodithioic acid and mixtures (1:1) Cu(II), Ni(II) and Co(II) nitrate at pH 3.4

The plots of conductance versus molar ratios of the species showed breaks at points where possible interaction occurred. A sharp break corresponding to a 1:1 molar ratio was obtained for the Cu-1-pyrrolidine carbodithioic acid. Breaks at 1:1 and 1:2 molar ratios were obtained for Ni-1-pyrrolidine carbodithioic acid interaction (Figure 4). Co(II) forms stable complex with ligand 1-pyrrolidine carbodithioic acid at 1:1 molar ratio and unstable

complexes are formed at ratio 1:2 in absolute alcohol water (80:20,v/v).

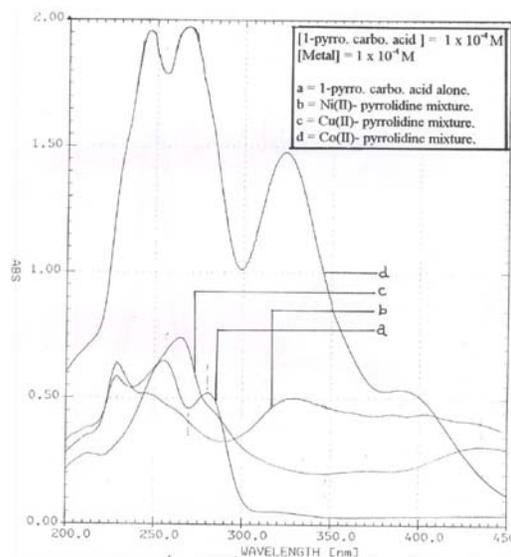


Figure 3. UV-spectra of 1-pyrrolidine carbodithioic acid and mixtures (1:1) Cu(II), Ni(II) and Co(II) nitrate at pH 6.4

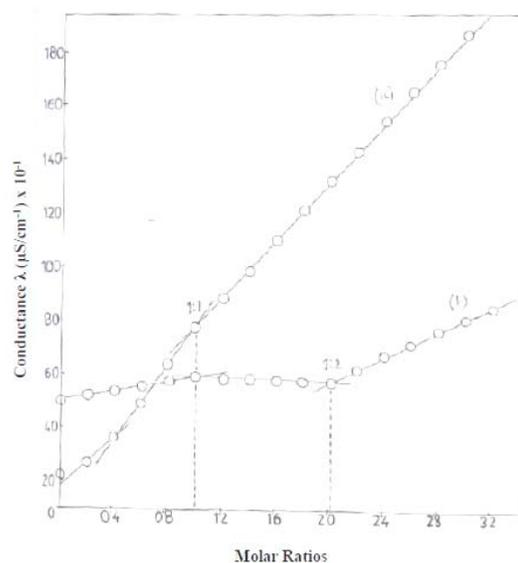


Figure 4. Conductometric titration, (a). 1-pyrrolidine carbodithioic acid with Ni(II) and (b) Ni(II) 1-pyrrolidine carbodithioic acid in absolute alcohol-water (80:20, v/v)

From the Ardon plots the stability constant values were obtained ($k = \text{intercept/slope}$), which varied with pH but did not differ with ionic strength. The values of K (Tables 1 & 2) indicate that stable complexes are formed between 1-pyrrolidine carbodithioic acid and the three metal ions under the given pH and ionic strengths.

Table 1. Values for stability constants of 1-pyrrolodine carbodithioic acid–Cu(II), Ni(II), and Co(II) system at different temperature under various pHs.

pH	Temperature °C	Stability constant		
		1-prrro.carbo. acid- Cu(II) system $K \times 10^{-3}$	1-prrro.carbo.acid-Ni(II) system $K \times 10^{-3}$	1-prrro.carbo.acid-Co(II) system $K \times 10^{-3}$
1.4	28	0.628	0.420	0.800
	38	0.600	0.392	0.590
	48	0.533	0.373	0.440
2.4	28	0.825	3.157	0.257
	38	0.720	2.571	0.255
	48	0.514	2.319	0.245
3.4	28	7.719	19.00	1.333
	38	6.933	11.20	0.560
	48	6.750	7.700	0.400
4.4	28	3.150	2.600	1.400
	38	2.112	2.437	1.200
	48	1.870	2.275	1.050
6.4	28	1.800	2.800	0.444
	38	1.680	2.599	0.400
	48	1.440	2.399	0.375
7.4	28	1.633	8.100	1.560
	38	1.597	6.60	1.400
	48	1.000	5.850	1.357

Table 2. Values for stability constants of 1-pyrrolodine carbodithioic acid–Cu(II), Ni(II), and Co(II) system at different ionic strength under various pHs.

pH	Ionic strength ^(M)	Stability constant		
		1-prrro.carbo. acid- Cu(II) system $K \times 10^{-3}$	1-prrro.carbo.acid-Ni(II) system $K \times 10^{-3}$	1-prrro.carbo.acid-Co(II) system $K \times 10^{-3}$
2.4	0.14	0.133	1.600	2.430
	0.42	0.200	1.666	3.240
	0.72	0.240	2.000	3.780
3.4	0.14	0.733	1.400	24.00
	0.42	0.800	1.540	27.20
	0.72	1.800	1.600	34.20
4.4	0.14	1.860	2.700	11.70
	0.42	1.000	2.399	11.20
	0.72	0.428	1.800	10.36
6.4	0.14	2.100	10.36	0.109
	0.42	0.914	10.24	0.080
	0.72	0.625	10.15	0.050
7.4	0.14	9.600	14.95	0.800
	0.42	6.400	12.60	0.560
	0.72	4.800	12.00	0.450

Table 3. Values for logarithm of stability constants and reciprocal of absolute temperature for Cu(II)-1-pyrrolidine carbodithioic acid at pH 3.4 and 6.4.

pH	Temperature °K	Stability constant Kx10 ⁻³	logK	(1/T) x10 ³
3.4	301	7.719	3.887	3.322
	311	6.933	3.840	3.215
	321	6.750	3.829	3.115
6.4	301	1.800	3.255	3.322
	311	1.680	3.255	3.215
	321	1.440	3.158	3.115

Table 4. Values for logarithm of stability constants and reciprocal of absolute temperature for Ni(II)-1-pyrrolidine carbodithioic acid at pH 3.4 and 6.4.

pH	Temperature °K	Stability constant Kx10 ⁻³	logK	(1/T) x10 ³
3.4	301	19.00	4.278	3.322
	311	11.20	4.049	3.215
	321	7.700	3.886	3.115
6.4	301	2.800	3.447	3.322
	311	2.599	3.414	3.215
	321	2.399	3.380	3.115

Table 5. Values for logarithm of stability constants and reciprocal of absolute temperature for Ni(II)-1-pyrrolidine carbodithioic acid at pH 3.4 and 6.4.

pH	Temperature °K	Stability constant Kx10 ⁻³	logK	(1/T) x10 ³
3.4	301	1.300	3.113	3.322
	311	0.560	2.748	3.215
	321	0.400	2.602	3.115
6.4	301	0.444	2.647	3.322
	311	0.400	2.602	3.215
	321	0.375	2.574	3.115

The highest value of K was obtained at pH 3.4 under ionic strength 0.70M for the 1-pyrrolidine carbodithioic acid-Co(II) system. Thus 1-pyrrolidine seems to retain lowest stability in presence of Co(II) giving rise to appreciably stable complexes with this metal ion. The stability constants of the complexes with the other ions (Cu²⁺ and Ni²⁺) are also high under the conditions studied. The present case therefore, is indicative of a common feature of stable complexes between divalent transition metal ions and ligands.

The values of stability constants K for the interaction of 1-pyrrolidine carbodithioic acid with Cu(II), Ni(II) and Co(II) ions at different pH, ionic strengths and

temperatures were determined. From Table 1 and 2, it is seen that the reactions of the ligands with metal ions show a significant influence of temperature, ionic strength and pH on the stability constants. The values of stability constants are quite high at pH 3.4 both for 1-pyrrolidine carbodithioic acid-Cu(II) and Ni(II) system. Whereas, for 1-pyrrolidine carbodithioic acid-Co(II) system, the stability constants are higher at pH 7.4. For 1-pyrrolidine carbodithioic acid-Cu(II), Ni(II) and Co(II) systems, there is gradual increase in the stability constants with increase of ionic strengths at pH 2.4 and 3.4.

But the situation was reverse at pH 4.4, 6.4 and 7.4, where the values of stability constants decreased with the

increase of ionic strength in each cases. This is a phenomenon of primary salt effect, where the values of rate constants or stability constants are responsive to the addition of inert salts in the reaction mixtures that contain ionic species.

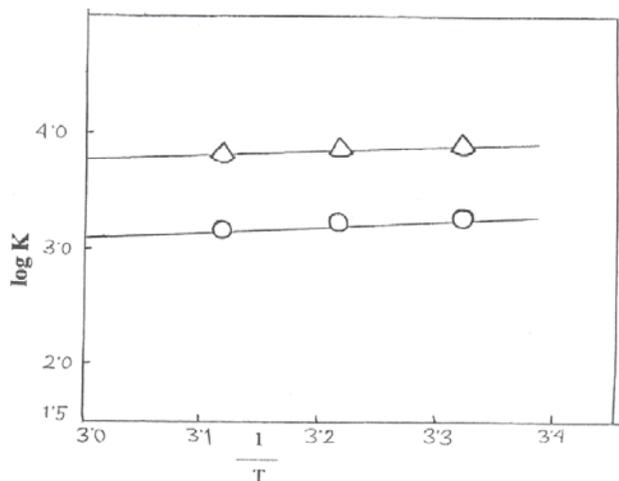


Figure 5. Plot of $\log K$ vs $1/T$ for Cu(II)-1-pyrrolidine carbodithioic acid system at pH (Δ) and 6.4 (○).

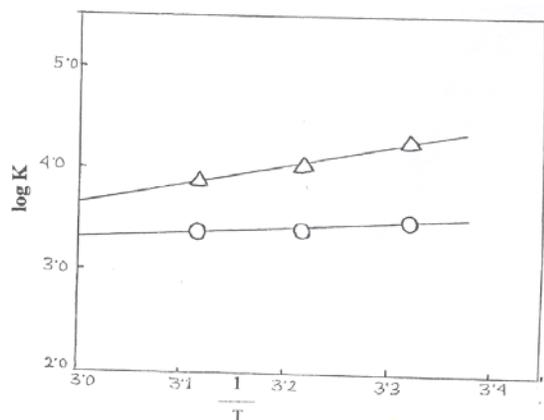


Figure 6. Plot of $\log K$ vs $1/T$ for Ni(II)-1-pyrrolidine carbodithioic acid system at pH 3.4 (Δ) and 6.4 (○).

The values of the heat formation of the complex have been obtained by using the Van't Hoff equation in a series of plots (Figures 5-7) of $\log K$ vs $1/T$, whereas the values of standard free energy changes have been calculated from the relation $\Delta G^\circ = -2.303RT \log K$. The $\log K$ values are 3.88 for Cu(II)-1-pyrrolidine carbodithioic acid, 4.27 for Ni(II)-1-pyrrolidine carbodithioic acid and 3.11 for Co(II)-1-pyrrolidine carbodithioic acid at pH 3.4. The values of heat of reactions have been found large negative values as

-40.96×10^2 kcal/mole for Cu(II)-1-pyrrolidine carbodithioic acid, -27.00×10^2 kcal/mole for Ni(II)-1-pyrrolidine carbodithioic acid and -30.40×10^2 kcal/mole for Co(II)-1-pyrrolidine carbodithioic acid at pH 1.4, whereas, the values for standard free energies have been found comparatively more negative as -3.85×10^3 kcal/mole for Cu(II)-1-pyrrolidine carbodithioic acid and -4.48×10^3 kcal/mole for Co(II)-1-pyrrolidine carbodithioic acid system at 1.4 and 301°K . This significant property demonstrates the uniform phenomenon for the complexes due to the formation of smooth donor-acceptor bonds without any molecular degradation. It may therefore be remarked here that in such cases of interaction the ligand and the metal centers probably retain a favourable distance from each other so that the donor-acceptor bond can assume the most stable character.

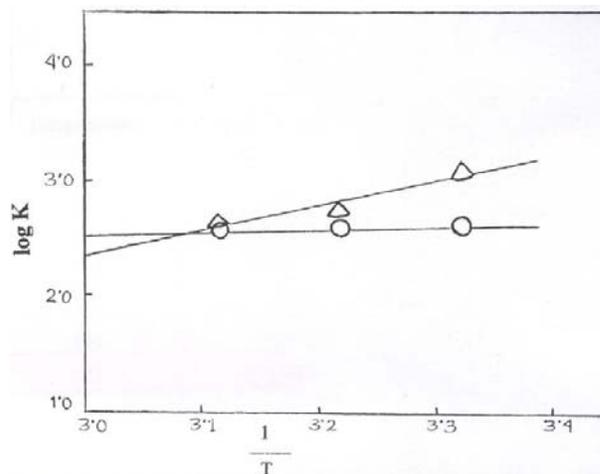


Figure 7. Plot of $\log K$ vs $1/T$ for Co(II)-1-pyrrolidine carbodithioic acid system at pH 3.4 (Δ) and 6.4 (○).

Conclusion

It can be concluded that copper and cobalt can form only 1:1 complexes with 1-pyrrolidine carbodithioic acid, whereas nickel can form both 1:1 and 1:2 complexes. Thus these metal ions can reduce the concentration of drug in the body.

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