CHAPTER-I

INTRODUCTION

1.1 INTRODUCTION OF SEMICARBAZONE AND THIOSEMICARBAZONE,

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CHAPTER-I

1.1 INTRODUCTION:
Thiosemicarbazones, semicarbazones and their derivatives as well as transition metal complexes have aroused considerable interest in the area of chemistry. Thiosemicarbazones and semicarbazones have a wide range of biological applications. Thiosemicarbazone derivatives were found to wide applications in the medicine. Semicarbazide and thiosemicarbazide are characteristics reagents whose chemical formulas are (NH₂NH.CO.NH₂) and (H₂N NH.CS.NH₂).

Thiosemicarbazide has been prepared by Kozokov and Vostovskii. The initial amine was treated successively with carbon disulphide sodium chloroacetate and hydrazine hydrate to get thiosemicarbazide on cooling. The thiosemicarbazide was condensed with different aromatic aldehyde to furnish thiosemicarbazone.

\[
\begin{align*}
1. & R-NH₂ + CS₂ \xrightarrow{NH₂OH} R-N-C \\
   & \quad \leftarrow SH \\
   & \quad \leftarrow \text{CLICH₂COONa} \\
   & \quad \leftarrow \text{-HCl} \\
2. & R-NH-C-S-CH₂COONa \xrightarrow{N₂H₄, H₂O} R-NH-C-NH-NH₂ + \\
   & \quad \text{Semicarbazide} \xrightarrow{\text{Aldehyde Semicarbazone}} \quad \text{Semicarbazide} \\
   & \quad \leftarrow \text{S} \leftarrow \text{H₂O} \leftarrow \text{S}
\end{align*}
\]
Thus, thiosemicarbazide on condensation with various aldehydes or ketones gave a new product, thiosemicarbazone. Thiosemicarbazone can also be cyclised by alkaline $K_3[Fe(CN)_6]$ in alcohol.

\[
\begin{align*}
R-NH-C-NH-N & = CH - R' \\
\rightleftharpoons & \\
S & \\
K_3[Fe(CN)_6] & \\
\rightarrow & \\
R-N = C & \\
\rightleftharpoons & \\
C-R' & \\
S & \\
\text{(1, 3, 4 thiadiazolines)}
\end{align*}
\]

(I). **SEMICARBAZONES:**

The product of the reaction between an aldehyde or ketone with semicarbazide ($H_2N\text{ NH CO NH}_2$) are called semicarbazones.

\[
\begin{align*}
R & \\
C = O + H_2N.COHNH.NH_2 & \rightarrow & \\
H & \\
\text{(Aldehyde)} & \rightarrow & \\
C = N.COHNH.NH_2 + H_2O & \rightarrow & \\
H & \\
(\text{Aldehyde Semicarbazone})
\end{align*}
\]
(II). THIOSEMICARBAZONES:

Similarly, the products of the reaction between an aldehyde or ketone with thiosemicarbazide (NH2.NH.CS.NH2) are termed thiosemicarbazones.

As it is clear from all the above reactions that the condensation reaction takes places to form all types of concern carbazones viz., semicarbazones and thiosemicarbazones.

As we know, that ligand is the fundamental tool of the co-ordination chemistry, it is necessary to mention that semicarbazones and thiosemicarbazones behave as
ligands. It is because

I. they have better co-ordination tendency.

II. they form more stable complexes.

III. they may form macrocyclic ligand.

IV. they have better selectivity.

V. they have ability to produce some new and unique complexes which enhanced biological/analytical properties.

Semicarbazones and thiosemicarbazones have gained special attention in the field of co-ordination chemistry due to their complexation behavior. When semicarbazones and thiosemicarbazones present in their ligational form, they becomes more important.

The biological and medicinal properties of these ligands and their derivatives have gained much interest. Thiosemicarbazones and their 3d- metal complexes have found to show antifungal, anti-bacterial, anti-viral, anti-tubercular and anti-carcinogenic activity. The antifungal activity of these compounds is due to the presence of toxophorically important >N - C = S moiety. Thiosemicarbazide and their Schiff bases also display anti-tumours activity. It is expected that this thio-ligand will also show variability in structure and bonding in its transition metal complexes and will also exhibit significant anti-tumour activity.

It has been reported that thiosemicarbazide and its complexes with 3d- metal ions show in vitro and vivo anti-tumour activity. Thiosemicarbazones are also interesting analytical reagent. Thiosemicarbazones also used for spectrophotometer determination of the metal ions. Further the metal complexes
formed with these reagents are of great medicinal value in the treatment of disease like influenza, protozoa, smallpox and certain kinds of tumours.

Metal complexes of thiosemicarbazones possess significant biological activities and are now a days widely used as potential drugs. However, the corresponding semicarbazones appear to be inactive. The bacterial and fungicidal activity of transition metal due to their ability to form chelates with the essential metal ions bond through nitrogen as well as sulphur donor atom of ligand. However, we know that structural factors which hinder the semicarbazide ability to function as a chelating agent diminish its biological activity. Electrochemical studies have been performed on their metal complexes because their biological activities may be related to their redox behavior.

Although thiosemicarbazones and semicarbazones have been known to form stable complexes with transition metal ions, it is only known recently that the detailed stereochemistry and reactions of these complexes have been investigated.

1.2. OBJECT AND SCOPE:

Thiosemicarbazone and semicarbazone act as a chelating agent for metal ions by bonding through sulphur or oxygen.

There has been a continued interest in ever increasing domain of pharmacological properties of the different thiosemicarbazones and semicarbazones. They have been found to be active against influenza, smallpox, tuberculosis, herpes, protozoa, fungi, pets, and a variety of microbes and are also useful as coccidiostatic compounds. Reports on their anti-viral, anti-tumour,
anti-bacterial\textsuperscript{27}, anti-fungal activities\textsuperscript{28-30} and anti-inflammatory\textsuperscript{31} and tumour blood flow tracer\textsuperscript{32,33} have led to a heightening of interest in the chemistry of these compounds particularly in relation to transition metal.

Domagk et al.\textsuperscript{7} reported for the first time the anti-tubercular activities of metal thiosemicarbazones and semicarbazones.

It has been shown that 3-ethoxy-2-oxobutyraldehyde bis(thiosemicarbazone) has a marked carcinostatic\textsuperscript{19,34-37} action and the cytotoxicity of this compound enhanced by the presence of Cu ions\textsuperscript{8}. It has also been shown that Cu(II) ions enhanced the anti-tubercular activity of p-acetaamide benzaldehydethiosemicarbazone. 3-acetyl lumbelliferone\textsuperscript{38} thiosemicarbazone also showed antitumour activity. Their metal complexes like Cu, Ni and Co also show effects on human breast, ovarian, HL-60 human leukemia and colon cancer cells\textsuperscript{40-42}. The antiviral activity of 2-acetyl pyridine thiosemicarbazone observed in an assay of influenza, virus and R.N.A. dependent R.N.A. polymerase activity might be due to chelation of Zn ion in the enzyme. The anti-tumour activity, anti-cancer activity of thiosemicarbazone is enhanced by the presence of some metallic ions due to their ability to form chelates.

West et al.\textsuperscript{43-45} carried out a lot of work on the complexation behaviour and biological activity of nitrogen and sulphur donor ligands thiosemicarbazide/thiosemicarbazone. The 2-formylpyridine thiosemicarbazone has received much attention because of its anti-tumour activity. Some reports\textsuperscript{46} are there in which they are tested for their antitumour and anti HIV activity\textsuperscript{47}. 2-formyl, 2-acetyl and 2-benzoyl pyridine –(N)-4 – Substituted thiosemicarbazone have shown to possess
substituted in vitro activity against various tumours\textsuperscript{48,49}. Their Cu(II) complexes also exhibit activity against various tumors strains. Thiosemicarbazone of 2-acetyl pyridine have been evaluated for the chemotherapeutic properties. A study of the cytotoxic activity of the copper complexes characterized recently as well as Cu(II) complexes exhibit activity against animal and human strains\textsuperscript{50}. Phosphorus analogs of 2- formylpyridine thiosemicarbazone has anti tumour activity when combined with Cu(II).

Cu(II) complexes of pyrualdehyde and kethoxal bis (thiosemicarbazone) have carcinostatic\textsuperscript{51} activity which enhance the anticancer activity of parentally administered drug. Thiosemicarbazone usually acts as chelating ligands with transition metal ions bonding through the sulphur and hydrazine nitrogen atom. Metal complexes of semicarbazone and thiosemicarbazone were found to have pronounced carcinostatic\textsuperscript{52} properties against a wide range of transplanted neoplasia. While the oxygen derivative of (semicarbazone) was found to be inactive carcinogenetic agents\textsuperscript{53}.

Investigations on anti-tumour cytotoxicity of thiosemicarbazones and their complexes like Co, Cu, Ni and Zn revealed that anti-tumour cytotoxicity is correlated better with electronic parameter than with structural parameter. Further studies on coordination compounds as anti-tumour agents have been shown that thiosemicarbazones are more toxic than semicarbazones when structural aspects are considered\textsuperscript{54}.

Metal complexes of thiosemicarbazone and thiosemicarbazide have been investigated extensively but less information is available on semicarbazone and
semicarbazide complexes. The study of thiosemicarbazones and semicarbazones compounds has received great impetus due to their remarkable potential in inhibiting ribonucleotide reductase, an inhibiting ribonucleotide reductase an obligatory enzyme in D.N.A. Synthesis, beside the anti-tumor properties, these compounds have also been shown to possess anti-tubercular, anti-malarial antifungal and anti-leishmenial activities\textsuperscript{55,56}.

The Fe(III) complexes of 2-hydroxy-1,4- napthoquinone-1- thiosemicarbazone and its 3- methyl derivatives have shown to be active against P-388 leukemia as well as MCF-7 breast cancer cells. [Cu(Hsb)Cl]H$_2$O was first found to be a potent inhibitor of D.N.A. synthesis and cell growth in a number of human and rodent cell lines\textsuperscript{57-62}. The compounds not only have wide inhibitory activity against inomyona\textsuperscript{63}, smallpox, and several kinds of tumours, but also can be used as pesticides, fungicides. There are also some reports on the anti-cancer activity of some transition metal complexes of thiosemicarbazone\textsuperscript{64}. Semicarbazones of various ketones are known to act as insecticides. Some thiosemicarbazones also show bacteriostatic action\textsuperscript{65,66}.

Semicarbazones and thiosemicarbazones were also found uses in industry\textsuperscript{67,68} as stabilizer of polyurethane moulding and brightening agents in electrolytic coating. Thiosemicarbazones or their derivatives as well as their transition metal complexes have aroused\textsuperscript{69} considerable interests in the areas of chemistry and biology. They have been used for metal analysis, for device applications related to telecommunication, optical computing storage and information processing\textsuperscript{70}. Some
derivatives of thiosemicarbazones show anti-parasitic and anti-neoplastic activities. The biological activities of thiosemicarbazones are related to their chelating properties to metal ions in vivo.

Kurup et al. recently reported that Cu(II) complexes of 2-benzoypyridine-N-(4) phenyl thiosemicarbazones show anti-microbial activity. The antimicrobial activity was assayed by using the cup-plate agar diffusion method by measuring the zone of inhibition.

All the compounds were screened in vitro for their anti-microbial activity against varieties of bacterial strains such as E.coli, B.magaterium, S.cureus and fungi A.Niger.

The interest to study coordination behaviour of thiosemicarbazone in chemistry on account of the following reasons.

(I). Thiosemicarbazones are biodegradable.

(II). Metal derivatives of thiosemicarbazones display better pharmacological properties over thiosemicarbazones.

(III). Metal–thiosemicarbazones interactions offer a variety of bonding properties and structural novelties.

Various transition metal (Cu, Ni, Fe and Co) complexes with a variety of thiosemicarbazones show antifungal activity. Apart from the biological importance, semicarbazones and thiosemicarbazones and their metal complexes have been widely used as analytical reagents for the determination of the metal ions. The chemistry of concern ligands and their complexes continues to attract
many researchers because of its wide applications in food industry, dyes industry, catalysis and agrochemical industry.

Thiosemicarbazide derived from 1-formyl isoquinoline and 2-formyl pyridine are related heterocyclic bases inhibit the growth of D.N.A. viruses of the herps family and ROUSE SACROMA virus. They were also active against canine lymphoma. It has been shown that N-heterocyclic thiosemicarbazones have inhibitory activities. However, in the presence of Fe^{3+} ions the inhibitory activity of these ligands is enhanced.

O-hydroxy substituted thiosemicarbazones have been frequently used for the spectrophotometric determination of the metal ions but metal substituted thiosemicarbazones are not. Only a few semicarbazones and thiosemicarbazones are used in the gravimetric determination of the metal ions. Some semicarbazone derivatives have been synthesized and they also show activity against the causative agent of “chagas” disease. A variety of 5-nitrofuryl semicarbazone derivatives have been developed for the therapy of chagas disease.

Semicarbazones and thiosemicarbazones present a wide range of bioactivities. Their chemistry and pharmacological applications have been extensively investigated. The biological properties of semicarbazones and thiosemicarbazones are often related to the metal ion coordination. Firstly, lipophilicity, which controls the rate of entry into cell, is modified by the coordination. Semicarbazones have been screened for their anti-fungal, anti-bacterial, biocidal and anti-convulsant activities.
Cu(II) complexes of furan oxime semicarbazone and thiosemicarbazone were found to be potent cytotoxic agent in both murine and human tissue cultured cell lines, as well as in solid tumors. Embelinsemicarbazone and thiosemicarbazone were screened for their antilepral, anti-tubercular, anti-viral, anti-malarial, anticancer, and anti-bacterial drugs. Mn(II) and Cu(II) complexes of semicarbazone were screened for their anti-microbial activity by agar disc diffusion method against the bacteria X. citri and the fungi A. solini.C. Cu(II), Ni(II) and Co(II) complexes of vitamin K3 thiosemicarbazone possess strong inhibitory action against G(+) Staphylococcus aureus G(-) Hay bacillus. Salicyaldehyde thiosemicarbazone has been used in the determination of Cu in blood using adsorptive stripping voltammetry.

2-benzoyl pyridine N-(4)- phenyl thiosemicarbazone was found to be active against Staphylococcus aureus, and its Cu(II) complexes were screened against Vibrio cholerae 01 and Salmonella paratyphi. Cis-3,7 dimethyl-2, 6- octadiene semicarbazone and its complexes were screened for their antibacterial activity. Their complexes exhibit strong inhibitory action against G(+) bacteria Staphylococcus aureus and G(-) bacteria Escheria Coli.

Cu(II) complexes of bis (thiosemicarbazones) show high activity for hypoxic cells, and this has led to their radiolabeled analogues being used for the positron emission agents for blood perfusion. Electrochemical studies have been performed on their metal complexes because their biological activities may be related to their redox behaviour. Thiosemicarbazones and semicarbazones were also used for the spectrophotometric agents. In view of the above studies on
transition metal complexes, it may be concluded that these ligands are biological active and this activity is enhanced in the presence of transition metal complexes.

1.3. MODE OF COORDINATION:

(A). BONDING IN SEMICARBAZONE:

The semicarbazide may act as a monodentate or bidentate chelating agent.

Crystal structure studies by Nardelli et al., of some semicarbazide complexes viz, [Cu(Sc)₃]Cl₂, [Zn(Sc)₂]Cl₂ show that semicarbazide is bidentate. According to these authors, in both the compounds each metal atom is surrounded by a trans planar arrangement of two O and two N atoms lying at the corners of a square.

The axial position completed by two chloride atoms so that the whole geometry can be described as a distorted octahedron. The semicarbazide molecule is planar and there is no significant difference in the bond distances between metal coordinated semicarbazide and semicarbazide hydrochloride (structure-III).

![Structure-III]
Semicarbazide and substituted semicarbazide are also expected to use one oxygen atom of the carbonyl group and or the hydrazine nitrogen atom to coordinate as a bidentate or mono-dentate ligands.

In the resent study cf, both semicarbazone (p-vanillin and p-tolualdehyde) act as bidentate ligands with all the metal ions which is confirmed by the IR spectrum of the ligands and the complexes.

**B) BONDING IN THIOSEMICARBAZONE:**

It has been shown that the thiosemicarbazone molecule itself exists in the trans configuration (structure IV-a) and while complexing in this configuration, behaves as a monodentate ligand, bonding only through the sulphur atom. Gerbeleu et. al\textsuperscript{99} have been shown that the bonding may also occur through the hydrazine nitrogen and the amide nitrogen (structure IV-b), if the sulphur centre is substituted.

In most of the complexes the thiosemicarbazone function co-ordinates to the bonding the metal ion in the cis-configuration (structure IV-a), as a bidentate ligand bonding through the thione/ thiol sulphur atom and the hydrazine nitrogen atom. When an additional coordinating functionally is present in the proximity of the SN donating centres, the ligands are found to act as tridentate species (structure IV-d) yielding, a polymeric compound in some cases.

Gerbeleu and co-workers\textsuperscript{100} also showed that alkylaition of the thiocarbonyl sulphur of thiosemicarbazone derivatives induces not only complexation through the terminal amino group but also enough acidic character for it to function as a monoacidic ligands. In the presences of various metals salts e.g. Cu(II),
These ligands are capable of condensing at the terminal amino nitrogen atom through another aldehydes or the ketones to yield quaternary-
ligands of the type (vanilline-H). By using such templates reaction shown, in
schematically illustrated and the present structures are complexed with
thiosemicarbazides of (p-vanilline and thiocarbamates) have act as didebate
ligands with all metal ions. They coordinated through either O=S and the nitrogen
of the σ(C=N) group, which is confirmed by the IR spectra.

**SYNTHESIS OF LIGANDS**

Preparation of L-type and L′-type chemically semicarbazone

A hot ethanolic solution of 1.64 gm (3.84 ml) and a

A hot ethanolic solution of 20 ml. of semicarbazide thiocarbamido

A hot ethanolic solution of 20 ml. of semicarbazide thiocarbamido

**SCHEME -1**

\[(M=\text{VO}^{2+}, \text{Ni}^{2+}, \text{Cu}^{2+})\]

\[R=\text{H}^+, \text{NH}_4^+, \text{Na}^+ \text{ or K}^+\]
Ni(II), VO(IV), these ligands are capable of condensing at the terminal amino nitrogen atom through another aldehydes or the ketones to yield quadri dentate ligands of the type (structure-V). By using such templates reactions as shown in the scheme (I), Gerbeleu and Zhovmir claimed to have isolated thiosemicarbazone complexes without coordination. In the present study semicarbazones and thiosemicarbazones of (p-vanillin and p-tolualdehyde) both act as bidentate ligands with all metal ions. They coordinated through either O/S and the nitrogen of the u(C=N) group, which is confirmed by the IR spectra.

SYNTHESIS OF LIGANDS

Preparation of Ligands L^1 and L^2: (p-vanillin semicarbazone)

thiosemicarbazone

A hot ethanolic solution of (20 mL) solution of p-vanillin (3.04 gm) and a hot/aqua ethanolic solution (20 mL) of semicarbazide/thiosemicarbazide (1.82 gm), were mixed slowly with constant stirring. The white colour crystals are precipitated out. It was filtered, washed with 50% ethanol and dried in the electric oven at 70°C. (Yield 65-80%).

Preparation of Ligands L^3 and L^4: (p-tolualdehyde semicarbazone)

thiosemicarbazone

A hot ethanolic solution of (20 mL) solution of p-tolualdehyde (3.04 gm) and hot aqua/ethanolic solution (20 mL) of semi/thiosemicarbazide (1.82 gm), were mixed slowly with constant stirring. This mixture was refluxed at ~80°C for 6-7 h. On cooling cream coloured precipitate was separated out. It was filtered, washed with 50% ethanol and dried in the electric oven at 70°C. (Yield 65-80%).
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