1.1 Semicarbazones: An introduction

Semicarbazones are usually obtained by the condensation of semicarbazide with suitable aldehydes and ketones (Scheme 1.1).

According to IUPAC recommendations, semicarbazones may be named by adding the class name ‘semicarbazone’ after the name of the condensed aldehyde or ketone. It also includes derivatives with substituents on the amide nitrogen in this class. The IUPAC numbering scheme is shown in the Fig. 1.1.
An interesting fact is that the semicarbazones exist predominantly in the amido form in the solid state, whereas due to the interaction of the solvent molecules they can exhibit a amido-iminol tautomerism (Fig. 1.2) in solution state. Amido form acts as a neutral ligand and the iminol form can deprotonate and serve as anionic ligand in metal complexes. Thus semicarbazones are versatile ligands in both neutral and anionic forms.

Both tautomeric forms have an efficient electron delocalization along the semicarbazone moiety. Aromatic substituents on the semicarbazone skeleton can further enhance the delocalization of electron charge density. These classes of compounds usually react with metallic cations giving complexes in which the semicarbazones behave as chelating ligands. Upon coordination to a metal center, the delocalization is further increased through the metal chelate rings. The coordination possibilities are further increased if the substituent has additional donor atoms.
1.2. Binding modes of semicarbazones

A review of semicarbazones shows that the C=N–NH–CO–NH₂ backbone of unsubstituted semicarbazones in the solid state is usually planar, with O atom trans to the azomethine N atom. However, few semicarbazones are exceptions to this rule [1]. Although there are several electronic and steric factors that may contribute to the adoption of this rearrangement, the most important is probably that the trans arrangement places the amine and azomethine nitrogen atoms in relative positions (Fig. 1.3) suitable for intramolecular hydrogen bonding [2].

![Diagram of semicarbazone structure]

**Fig. 1.3** O atom is trans to the azomethine N atom

An interesting aspect is that the semicarbazones show a variety of coordination modes with transition metals. The coordination mode is influenced by the number and type of substituents. This is because the active donor sites of the ligand vary depending upon the substituents. According to the reports, the coordination mode of the semicarbazone is very sensitive towards minor variations in the experimental conditions, the nature of the substituents on the carbonyl compound and the metal salt [3]. The presence of di-2-pyridyl ketone at the carbonyl part attributes many interesting coordinating possibilities for the ligand systems under study. In most of the metal complexes we synthesized...
semicarbazones act as tridentate ligand and in some other cases, semicarbazones exhibit as potential quadridentate ones when the second pyridyl nitrogen of di-2-pyridyl ketone involves in coordination process. The ONO tridentate coordination mode of the semicarbazones is given below [4].

\[O, N, O-tricoordination.\]

The different coordination modes of benzaldehyde semicarbazone are given below [5].

\[C,N,O-tricoordination.\]

\[N,O-coordination forming a stable five membered chelate ring.\]
1.3. Applications of semicarbazones and their complexes

The metal complexes of semicarbazones play an essential role in agriculture, pharmaceutical and industrial chemistry and they are used as catalysts, in various biological systems, polymers and dyes, besides some uses antifertility and enzymatic agents. The biological properties of semicarbazones are often related to metal ion coordination. Firstly, lipophilicity, which controls the rate of entry into the cell, is modified by coordination [6]. Also, the metal complex can be more active than the free ligand. The mechanism of action can involve binding to a metal \textit{in vivo} or the metal complex may be a vehicle for activation of the ligand as the cytotoxic agent. Recently it has been shown that semicarbazones of aromatic and unsaturated carbonyl compounds have anticonvulsant properties [7]. Moreover, coordination may lead to significant reduction of drug-resistance [8]. They are also used as spectrophotometric agents as well for the analysis of metal ions [9] and are frequently used in the qualitative organic analysis of carbonyl compounds [10].

Recently, thiosemicarbazones have been synthesized and screened against the three parasitic cysteine proteases cruzain, falcipain-2, and rhodesain and against their respective parasite sources, \textit{Trypanosoma cruzi}, \textit{Plasmodium falciparum}, and \textit{Trypanosoma brucei} [11]. The results obtained suggested that
thiosemicarbazones represent validated leads that kill several species of protozoan parasites through the inhibition of cysteine proteases as well as through action against other targets. Furthermore, semicarbazones, which can also be regarded as urea derivatives, have gained considerable importance [12] in recent years in the design of enzyme inhibitors [13], as replacement for the amide (–CO–NH–) bond in peptidomimetics [14] and as sources of self-complementary bidirectional hydrogen bonding motif in supramolecular chemistry [15]. Since peptides have poor metabolic stability and limited oral absorption, they are rarely useful drug candidates.

Epilepsies are common and frequently devastating and affect around 1–2% of the world population. The convulsions of approximately 25% of epileptics are inadequately controlled by the standard drug therapy [16,17]. The number of drugs useful for the treatment of epilepsy is remarkably small. Fewer than 20 drugs are currently marketed in the United States, and of these, only five or six are widely used [17]. Semicarbazones are a class of compounds which shows anticonvulsant activity [18]. Arylsemicarbazones can be orally administered and are more active as anticonvulsants than mephenytoin or phenobarbital, besides the fact that they generally exhibit low or absent neurotoxicity [19].

In the development of new metal-based therapeutics, detailed studies on the interactions between biomolecular targets such as DNA and structurally defined transition metal complexes can provide invaluable information [20]. Among the non-platinum compounds exhibiting anticancer properties, those of ruthenium are very promising, showing activity on even such tumors which developed resistance to cisplatin or in which cisplatin is totally inactive. Furthermore, it possesses mutagenic properties [21], exhibits good
A brief survey on semicarbazones and their transition metal complexes

Department of Applied Chemistry, Cochin University of Science and Technology

antineoplastic activity against several murine metastasizing tumors [22] and interacts in vitro with DNA to form covalent bonds with the nucleobases [23].

A variety of 5-nitrofuryl semicarbazone derivatives have been developed for the therapy of Chagas disease, a major problem in the Central and the South America [24]. 4-Bromobenzaldehyde semicarbazone has been used as anticonvulsant. Recently, a review reported on the anticonvulsant activity of thiosemicarbazones, semicarbazones and hydrazones derived from aromatic and unsaturated carbonyl compounds as well as from other precursors [25]. In contrast to thiosemicarbazones, literature records fewer examples of semicarbazones presenting significant anticancer and cytotoxic activity but some nitroso, naphtopyran, and fluorine derivatives showed anti-leukemia effect in mice [26]. Several $N^4$-substituted semicarbazone derivatives of o- and p- chlorobenzaldehyde and 2,6-dichlorobenzaldehyde exhibit potent anti-hypertensive effects [27]. The orally administered drug naftazone (1,2-naphtoquinone semicarbazone) protects the vascular system through an inhibitory effect on nitric oxide synthesis [28].

1.4. Objectives of the work

The unusual coordination modes of semicarbazones when bound to metals, the wide applications and structural diversity of metal complexes of semicarbazones provoked us to synthesize and characterize the tridentate ONO and NNO-donor semicarbazones and their transition metal complexes. This work is focused on the studies on complexes of three $N^4$-phenylsemicarbazones synthesized by changing the carbonyl compounds.

This work is concerned with the studies of two new semicarbazones, 2-formylpyridine-$N^4$-phenylsemicarbazone (HL$_1^1$) and 3-ethoxysalicylaldehyde-$N^4$-phenylsemicarbazone (H$_2$L$_2^1$) and a reported semicarbazone,
2-benzoylpyridine-$N^4$-phenylsemicarbazone (HL$_3$) [29]. The compositions of these semicarbazones were determined by the CHN analyses and IR, UV and NMR spectral studies were used for the characterization of these compounds. The molecular structure of 3-ethoxysalicylaldehyde-$N^4$-phenylsemicarbazone (H$_2$L$_2$) was obtained by single crystal X-ray diffraction studies. Also, we have synthesized Cu(II), Cd(II), Zn(II) and Ni(II) complexes of these three semicarbazones. The complexes were characterized by various spectroscopic techniques, magnetic and conductivity studies. We could isolate single crystals of some complexes of all metals suitable for X-ray diffraction studies. This thesis is divided into six chapters.

Chapter 1 gives an introduction of semicarbazones and their metal complexes with an extensive literature survey relating the applications and recent developments. This includes a detailed idea about coordination modes and stereochemistry of the semicarbazones.

Chapter 2 explains syntheses and characterization of two NNO donor semicarbazones and an ONO donor semicarbazone.

Chapters 3, 4, 5 and 6 describe the syntheses and characterization of Cu(II), Cd(II), Zn(II) and Ni(II) complexes of these semicarbazones.

References


A brief survey on semicarbazones and their transition metal complexes


..............................