Chapter 1

A BRIEF PROLOGUE TO THIOSEMICARBAZONES AND THEIR METAL COMPLEXES

Contents

1.1. Introduction

Inorganic chemistry has considerable impact on our everyday lives and on other scientific disciplines. It is essential to the formulation and improvement of modern materials such as catalysts, semiconductors, optical devices, superconductors and advanced ceramic materials. The environmental and biological impact of inorganic chemistry is also huge. Coordination compounds are the backbone of modern inorganic and bio-inorganic chemistry and chemical industry. The chemistry of coordination compounds is an important and challenging area of modern inorganic chemistry. During the last fifty years, advances in this area have provided development of new concepts and models of bonding and molecular structure and novel breakthroughs in chemical industry. Coordination compounds are of great importance since they provide critical insights into the functioning and structures of vital components of biological systems.

They also find extensive applications in metallurgical processes, analytical and medicinal chemistry.

Coordination compounds are of importance in medical diagnosis and therapy. They act as contrast agents for magnetic resonance imaging (MRI) and are the active compounds in chemotherapy and photodynamic therapy for the treatment of cancer. Coordination compounds include such substances as vitamin B_{12}, hemoglobin, chlorophyll, dyes, pigments and catalysts used in preparing organic substances. The origin of coordination chemistry as a distinct branch of chemistry dates back to the beginning of the 20^{th} century and is marked by the award of a Nobel Prize to Alfred Werner in 1913 [1]. Among other achievements, Werner established the structure of the compound now known as cisplatin which is used in cancer therapy.

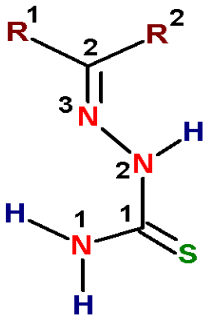
The architectural beauty of coordination compounds is due to the interesting ligand systems containing different donor sites say ONO, NNO, NO and NNS. It provides many new directions in research such as, in molecular magnetism, supramolecular chemistry, non-silicon-based devices, precursors for vapor phase deposition and single molecule-based photonic devices and sensors [2].

The thiosemicarbazones of aromatic aldehydes and ketones form stable chelates with transition metal cations by utilizing both their sulfur and azomethine nitrogen as donor atoms. They have been shown to possess a diverse range of biological activities including anticancer [3], antitumor [4], antibacterial [5,6], antiviral [7,8], antimalarial [9] and

antifungal [10] properties owing to their ability to diffuse through the semipermeable membrane of the cell lines. The enhanced effect may be attributed to the increased lipophilicity of the metal complexes compared to the ligand alone. The presence of coordination sites in the complexes enhances their activity. The inhibitory effect occurs by action of the complexes on the proliferation and differentiation of the cell lines. These complexes can further find their use in the treatment of other incurable diseases such as hepatitis, AIDS etc. [11] and catalytic activity [12]. Hence the structural and chemical properties of thiosemicarbazones and their metal complexes have attained considerable attention. They have been investigated intensively since they hold good promises in various fields of medicine. The pharmacological activity of thiosemicarbazones of *o*-hydroxy aromatic aldehydes is correlated to their ability to form chelates with biologically important metal ions by bonding through O, N and S atoms [13-17] and reductive capacity. It is observed that biological activity depends on the parent aldehyde or ketone [18-20] and increases remarkably when bulky groups are present at N^4 position [21]. Metal complexes of thiosemicarbazones often display enhanced activities when compared to the uncomplexed thiosemicarbazones.

1.2. Thiosemicarbazones

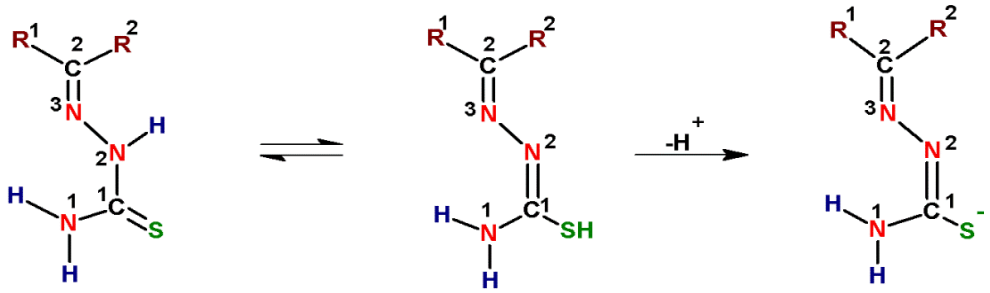
Thiosemicarbazones are thiourea derivatives and are prepared by the condenzation of thiosemicarbazides with aldehydes or ketones in acidic medium [22]. They are represented by the general formula given below.



They are extensively delocalized systems, especially when aromatic radicals are bound to the azomethine carbon atom. Thiosemicarbazones with additional donor groups at the substituent R^1 or R^2 are of special interest since they can coordinate in a tridentate fashion which results in significant increase of the stability of the complexes.

1.3. Bonding and coordination strategy of thiosemicarbazones

Thiosemicarbazones generally exist in the thioamido form in the solid state but in solution, they tend to exist as an equilibrium mixture of thioamido and thioiminol forms. The thioamido-thioiminol equilibrium depends on the pH of the medium used for reaction. Thiosemicarbazones can bind to a metal center in the neutral or the anionic forms. The anionic form is generated after loss of $-N^2H$ or –SH hydrogen ions.

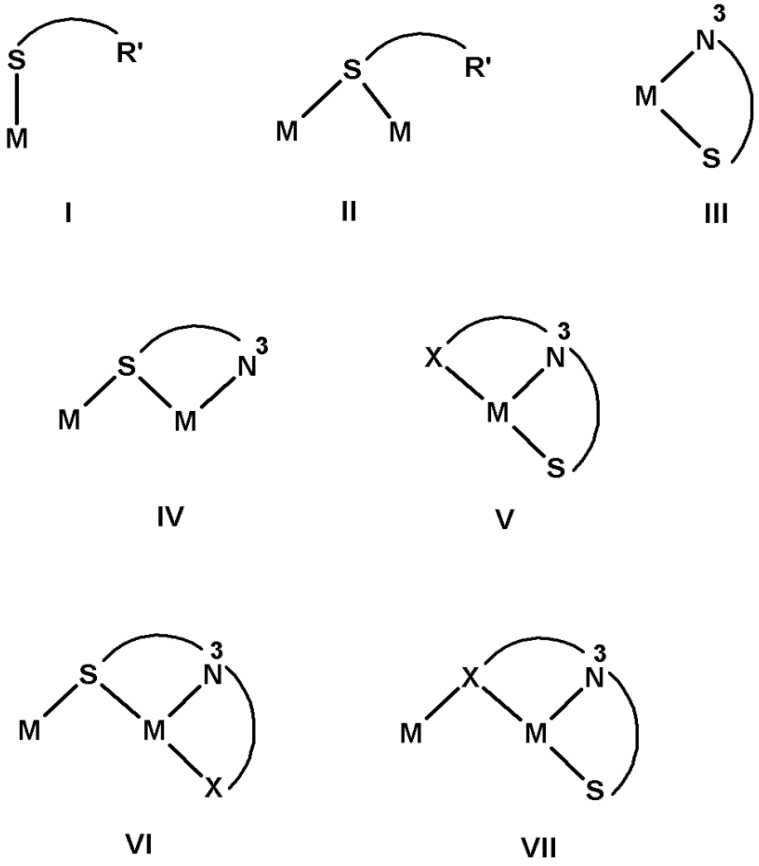


thioamido **thioiminol** **anionic**

A number of bonding modes have been observed for the thiosemicarbazones in their neutral or anionic forms.

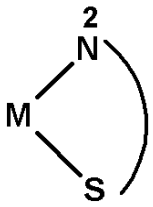
1.3.1. Bonding modes in neutral form

In neutral form, the binding occurs *via* only S atom in η^1-S (I), μ^2-S (II), η^2-N^3, S-chelation (III), η^2-N^3, S-chelation and S-bridging (IV) modes. However, if the substituent at C^2 has a donor atom, and engages in bonding, the additional bonding modes observed are, η^3-X, N^3, S-chelation (V), η^3-X, N^3, S-chelation and S-bridging (VI) and η^3-X, N^3, S-chelation and X-bridging (VII) (eg. X = N, O) [23-32].

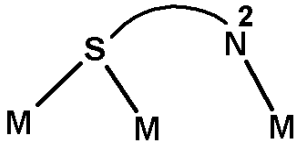


1.3.2. Bonding modes in anionic form

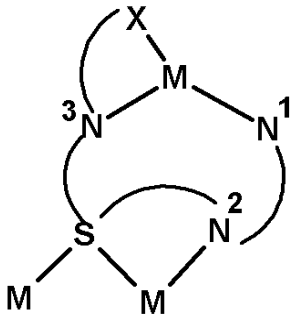
The modes (I-VII) shown by the neutral ligands are also exhibited by the anionic ligands, *viz*. η^1-S, μ^2-S, η^2-N^3, S-chelation, η^2-N^3, S-chelation and S-bridging, η^3-X, N^3, S-chelation, η^3-X, N^3, S-chelation-cum-S-bridging and η^3-X, N^3, S-chelation and X-bridging [33-39]. In addition, η^2-N^2, S (VIII) and η^2-N^2, S-bridging (IX) modes are identified [40,41]. A rare example of pentacoordination (X) by a thiosemicarbazone ligand has also been reported [42].



VIII



IX



X

The potential of thiosemicarbazones as ligands for a wide range of metals was realised and Jensen established the basis of their coordination chemistry in seminal papers in the 1930s [43,44]. He proposed that

coordination occurred *via* the sulfur and the azomethine nitrogen with the formation of a five membered ring (Fig. 1A). In the presence of base, loss of one of the ligand protons occurred, giving the ligand a uninegative charge. Without the advantage of X-ray structures he suggested that it was the exocyclic nitrogen that was deprotonated (Fig. 1B) whereas we now know that it is in fact a hydrazinic proton that is lost (Fig. 1C). These ligands can therefore provide a non-reducing source of anionic sulfur and also due to residual multiple bonding between C and S, the tendency for sulfur atom to bridge metal ions is substantially less compared to thiolate. The ability of this class of ligands to act as a source of 'masked thiolate' is one of the contributing factors to their ability to act as highly versatile donors towards a range of metal ions.

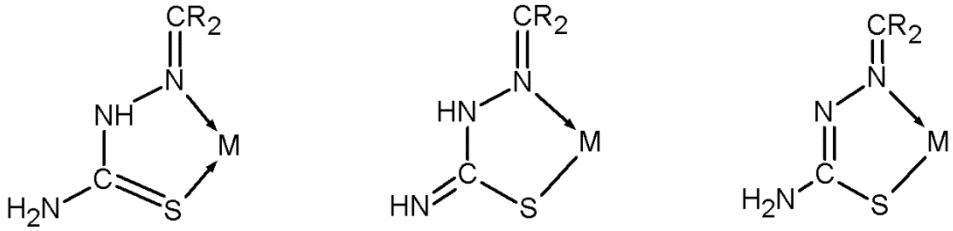


Fig. 1. Jensen models for the coordination of thiosemicarbazones in neutral (A) and anionic (B) forms. Currently accepted structure representation for anionic binding (C).

1.4. Importance of thiosemicarbazones

Thiosemicarbazones and their metal complexes show significant biological activity, suggesting accessibility of coordination site which is a fundamental requirement for biological activity by the complexes [45].

1.4.1. Biological applications

1.4.1a. Antifungal and antibacterial properties

2-Benzoylpyridine thiosemicarbazone and its copper(II) complexes show antifungal activity against various strains of the pathogenic fungi. The activity varied with the nature of the substituent at the amino nitrogen of thiosemicarbazone. 2-Benzoylpyridine-N(4)-isopropyl thiosemicarbazone as well as its square pyramidal complex, $[Cu(HL)Cl_2]$ [46] were fungitoxic against the human pathogenic fungi, *A. niger* and *P. variotti*. 2-Benzoylpyridine thiosemicarbazone with N(4) phenyl substituent was most active against *S. aureus* while its dimeric complex $[Cu_2L_2X_2]$ (X=Cl, NCS) [47] was inactive against this strain. They, however, exhibited activity against other strains, *S. paratyphi* and *V. cholerae*, while thiosemicarbazones with bulkier hexamethyleneiminyl group at the amino nitrogen were more active both as free ligand as well as in the form of a copper(II) complex [CuLCl] [46]. Owing to the lower solubility of complexes in the non-aqueous solvents compared with the free ligand, $[CuL(NO_3)(H_2O)]\cdot H_2O$ showed a lower fungitoxic activity against phytopathogenic fungi, *A. alternata*, *F. phaseoline* and *F. equisetti* [48]. Square pyramidal Zn(II) complexes of N(4) substituted 2-acetylpyridine thiosemicarbazones *viz*. $[Zn(HL)Cl_2]$ and $[Zn(HL)(H_2O)SO_4]$ display activities against four strains of bacteria (*B. subtilis*, *S. aureus*, *E. coli*, *P. aeruginosa*), two yeasts (*C. albicans*, *S. cerevisae*) and two molds (*A. niger, P. citrinum*) [49].

1.4.1b. Anticancer properties

Thiosemicarbazones as well as their complexes are well known for their anticancer properties. They act by inducing apoptosis in the cancerous cell lines. Some anticancer drugs act by inducing apoptosis by activating the endonucleotidase leading to the DNA fragmentation [50]. The presence of a metal ion almost systematically increases the activity or contributes to mitigate the side effects of the organic parent compounds. The anti-leukemic effect of 2-formylpyridine thiosemicarbazone was first reported by Brockman *et al*. [51] in 1956. Sartorelli *et al*. [52] observed that these compounds repressed the incorporation of ^{3}H thymidine into the DNA and first proposed the inhibition of ribonucleotide reductase as the mechanism through which these molecules work [53,54]. Ribonucleotide reductase is an iron-dependent enzyme that promotes the reduction of ribose to deoxyribose through a free radical mechanism that is triggered by a tyrosyl radical. Inhibition of this enzyme leads to a block in the synthesis phase of the cell cycle and eventually to cell death by apoptosis. They also indirectly demonstrated that the active species was the iron(II) complex of 1-formylisoquinoline thiosemicarbazone. In fact, it was later discovered that iron and copper complexes are by far more active than the free ligands [55].

1.4.2. Analytical applications

Due to the tendency of thiosemicarbazones to form complexes with metals, analytical applications have also been observed. Thiosemicarbazones are used in the determination of the trace metals in the biological and the pharmaceutical samples, in the extraction of metals, for the inhibition of corrosion etc. Basic mode of action is the formation of colored chelates with the metal ions which can be extracted into suitable solvents [10].

Trace amounts of Cu^{II} were determined with cyclopentanone thiosemicarbazone by using stripping voltammetry (detection limits, 1.57×10^{-9} M) [56]. N-Ethyl-3-carbazolecarboxaldehyde thiosemicarbazone was used for spectrophotometric determination of Cu^{II} in the environmental and pharmaceutical samples, by forming a green complex (pH 3.0), which can be extracted into *n*-butanol [57]. The low cost of thiosemicarbazones as well as their easy preparative methods could provide a major attraction for the development of analytical reagents for a range of applications in future.

1.5. Objectives of the present work

Thiosemicarbazones have emerged as an important class of ligands over a period of time, for a variety of reasons, such as variable donor properties, structural diversity and biological applications. Interesting as the coordination chemistry may be, the driving force for the study of these ligands has undoubtedly been their biological properties and the majority of the 3000 or so publications on thiosemicarbazones since 2000 have alluded to this feature. Some valuable reviews have appeared in this period on the structural features, biological activities and analytical applications of thiosemicarbazone complexes [10], the chemistry of copper complexes of thiosemicarbazones [58], structure activity relationships of metal complexes of thiosemicarbazones [59] and applications of metal complexes of thiosemicarbazones for imaging and therapy [60]. The potent biological activity of tridentate thiosemicarbazones and their metal complexes has been recognised for over 50 years [51,61]. Thiosemicarbazones have been investigated for their Topoisomerase II inhibition by a number of groups. An intriguing recent application of copper bis(thiosemicarbazone)

complexes has been in the potential clinical treatment of Alzheimer's Disease (AD) reported by Donnelly *et al*. This is based on the fact that increased intracellular concentrations of copper can activate Akt (protein kinase B) signalling and thereby inhibit glycogen synthase kinase 3β (GSK3β) which regulates the accumulation of amyloid-β aggregates [62].

In order to pursue the interesting coordinating properties of thiosemicarbazones, complexes with different types of ligand environments are essential. So in the present work we chose two different ONS donor thiosemicarbazones as principal ligands. Introduction of heterocyclic bases like 1,10-phenanthroline, 2,2′-bipyridine, 4,4′-dimethyl-2,2′-bipyridine and 5,5′-dimethyl-2,2′-bipyridine, the classical N,N donor ligands leads to the syntheses of mixed ligand complexes which can cause different bonding, spectral properties and geometries in coordination compounds. All the above said facts stimulated our interest in the study of transition metal complexes with ONS donor thiosemicarbazones and we undertook the present work with the following objectives.

- To synthesize some ONS donor thiosemicarbazones by the condenzation of 5-bromo-3-methoxysalicylaldehyde with N(4)-phenylthiosemicarbazide and N(4)-cyclohexylthiosemicarbazide.
- To characterize the synthesized thiosemicarbazones by different physicochemical techniques.
- To synthesize different transition metal complexes using the synthesized thiosemicarbazones as principal ligands and some heterocyclic bases as coligands.

- To study the coordination modes of different thiosemicarbazones in metal complexes by using different physicochemical methods like partial elemental analysis and by different spectroscopic techniques.
- To establish the structure of the compounds by isolating single crystals of the compounds and by collecting and refining single crystal X-ray diffraction data.

In the present work two different thiosemicarbazones were synthesized and characterized. The molecular structures of these thiosemicarbazones were established by single crystal X-ray diffraction studies. The metals selected for the preparation of the complexes are vanadium, nickel, copper, zinc, cadmium and molybdenum. The crystal structures of four of the complexes were studied through single crystal XRD.

1.6. Physical measurements

The physicochemical methods adopted during the present study are discussed below.

1.6.1. Elemental analyses

Elemental analysis is a process where a sample of a chemical compound is analyzed for its elemental and sometimes isotopic composition. Elemental analysis can be qualitative (determining what elements are present) and it can be quantitative (determining how much of each is present). This information is important to help to determine the purity of a synthesized compound. Elemental analyses of C, H, N and S present in all the compounds were done on a Vario EL III CHNS elemental

analyzer at the Sophisticated Analytical Instrument Facility, Cochin University of Science and Technology, Kochi-22, Kerala, India.

1.6.2. Conductivity measurements

The conductivity (or specific conductance) of an electrolyte solution is a measure of its ability to conduct electricity. The SI unit of conductivity is siemens per meter (S/m). Conductivity measurements are used as a fast, inexpensive and reliable way of measuring the ionic content in a solution. The molar conductivities of the complexes in DMF solutions (10^{-3} M) at room temperature were measured using a Systronic model 303 direct reading conductivity meter at the Department of Applied Chemistry, CUSAT, Kochi, India.

1.6.3. Magnetic susceptibility measurements

In electromagnetism, the magnetic susceptibility is a dimensionless proportionality constant that indicates the degree of magnetization of a material in response to an applied magnetic field. Magnetic susceptibility measurements of the complexes were carried out on a Vibrating Sample Magnetometer using $Hg[Co(SCN)_4]$ as a calibrant at the SAIF, Indian Institute of Technology, Madras.

1.6.4. Infrared spectroscopy

Infrared (IR) spectroscopy is one of the most common spectroscopic techniques used by inorganic chemists. The main goal of IR spectroscopic analysis is to determine the chemical functional groups in the sample. Different functional groups absorb characteristic frequencies of IR radiation. Thus, IR spectroscopy is an important and popular tool for

structural elucidation and compound identification. Infrared spectra of some of the complexes were recorded on a JASCO FT-IR-5300 Spectrometer in the range 4000-400 cm^{-1} using KBr pellets at the Department of Applied Chemistry, CUSAT, Kochi, India.

1.6.5. Ultraviolet-visible spectroscopy

Ultraviolet-visible spectroscopy is a technique in which intensity of light passing through a sample (I) is measured and is compared to the intensity of light before it passes through the sample (I_0). The ratio (I/I_0) is called the transmittance and is usually expressed as a percentage (%T). The electronic spectra of the compounds were taken on a Spectro UV-vis Double Beam UVD-3500 spectrometer in the 200-900 nm range at the Department of Applied Chemistry, CUSAT, Kochi, India.

1.6.6. Mass spectroscopy

Mass spectrometry (MS) is an analytical technique that measures the mass-to-charge ratio of charged particles. It is used for determining masses of particles, for determining the elemental composition of a sample or molecule and for elucidating the chemical structures of molecules. MS works by ionizing chemical compounds to generate charged molecules or molecular fragments and measuring their mass-to-charge ratios. Mass spectra of the thiosemicarbazones were recorded by direct injection on WATERS 3100 Mass Detector using Electron Spray Ionization (ESI) technique designed for routine HPLC-MS analyses at the Department of Applied Chemistry, CUSAT, Kochi, India.

1.6.7. NMR spectroscopy

Nuclear magnetic resonance spectroscopy, most commonly known as NMR spectroscopy, is a research technique that exploits the magnetic properties of certain atomic nuclei to determine physical and chemical properties of atoms or the molecules in which they are contained. It relies on the phenomenon of nuclear magnetic resonance and can provide detailed information about the structure, dynamics, reaction state and chemical environment of molecules. ^{1}H NMR spectra of thiosemicarbazones were recorded using Bruker AMX 400 FT-NMR Spectrometer with deuterated DMSO as the solvent and TMS as internal standard at the Sophisticated Analytical Instrument Facility, CUSAT, Kochi, India.

1.6.8. EPR spectroscopy

Electron paramagnetic resonance (EPR) or electron spin resonance (ESR) spectroscopy is a technique for studying materials with unpaired electrons. The basic concepts of EPR are analogous to those of nuclear magnetic resonance (NMR), but it is electron spins that are excited instead of the spins of atomic nuclei. Because most stable molecules have all their electrons paired, the EPR technique is less widely used than NMR. The EPR spectra of the complexes in the solid state at 298 K and in DMF/DMSO at 77 K were recorded on a Varian E-112 spectrometer using TCNE as the standard, with 100 kHz modulation frequency, 2 G modulation amplitude and 9.1 GHz microwave frequency at SAIF, IIT Bombay, India.

1.6.9. Single crystal X-ray diffraction studies

Single crystal X-ray diffraction is a non-destructive analytical technique which provides detailed information about the internal lattice of

crystalline substances, including unit cell dimensions, bond lengths, bond angles and details of site-ordering. Ideal crystals should be between 150-250 microns in size. Samples are mounted on the tip of a thin glass fiber using an epoxy or cement. This fiber is attached to a brass mounting pin, usually by the use of modeling clay and the pin is then inserted into the goniometer head. The goniometer head and sample are then affixed to the diffractometer. Then data is collected and phase problem is solved to find the unique set of phases that can be combined with the structure factors to determine the electron density and therefore, the crystal structure. The trial structure is then solved and refined.

Single crystal X-ray diffraction studies of the compounds were carried out using a Bruker SMART APEXII CCD diffractometer at SAIF, Cochin University of Science and Technology, Kochi-22, Kerala, India. Bruker SMART software was used for data acquisition and Bruker SAINT software for data integration [63]. Absorption corrections were carried out using SADABS based on Laue symmetry using equivalent reflections [64]. The structure was solved by direct methods using SHELXS97 [65] and refined by full-matrix least-squares refinement on F^2 using SHELXL97 [66]. The graphics tool used was DIAMOND version 3.2g [67].

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