Introduction: Metal Directed Self-assembly of Dithiocarbamate and Xanthate Ligands

Abstract

An introduction to self-assembly, its importance in biological system and the great assistance of coordination chemistry in the development of diverse self-assembled molecular architectures has been comprised in this chapter. The exploitation of unique stereoelectronic properties of metal ions and dithiocarbamate/ xanthate ligands in metal directed self-assembly process leads to discrete supramolecular structures with fascinating physico-chemical properties and broad spectrum of applicability is highlighted in this section. The main objectives of the present work along with materials and general instrumentation methods are also included at the end of this chapter.

1.1. Self-Assembly

Self-assembly is one of the most dynamic and interdisciplinary areas of science, with great potential for applications in a range of fields including medicine, energy, materials engineering, and devices. It refers to a process in which a number of components leads to an organized structure or pattern due to the specific, local interactions amongst the components themselves, without external guidance. It can take place at the macroascopic level, *viz*. the self-assembly of magnets, or at the microscopic level, *viz*. crystal formation. Extensive numbers of self assemblies are known to date and the mechanism of the self-assembly process has been well studied and elucidated over the years. It can be broadly classified in two types as static and dynamic. In the ***static*** self-assembly, the ordered state is reached when the system approaches equilibrium with a reduction of its free energy, whereas in the ***dynamic*** self-assembly, components are organized through the direction of the specific local interactions. Directing factors involved in the process are mainly non-covalent interactions (e.g. Hydrogen bonding, hydrophobic forces, Van der Waals forces, π-π interactions, and/or electrostatic interactions) and electromagnetic interactions.

The structures formed through self assembling process are well known as *self-organized structures*. When the constitutive components are molecules, that adopt a defined arrangement without guidance from an outside source, the process is known as *molecular self-assembly*. Molecules can be directed to self-assemble spontaneously into multi-component complex structures with specific size and shapes. The directive instructions for self-assembly are conveyed to the molecule during its synthesis. The process is accomplished with reversible and dynamic steps, resulting in the continuous formation and breakdown of the complex product and this feature ensures a significant defect free assembly.[1] In conventional covalent synthesis, atoms are connected together in any conformation of interest, that may or may not be energetically favourable. The weak interactions present in a self-assembly make the system sensitive to external perturbations, which might lead to marked changes in the structure and even compromise it, either during or after self-assembly. The weak nature of interactions is responsible for the flexibility of the architecture that permits rearrangements of the structure in the direction determined by thermodynamic factors. Elegant choice of precursor molecules allows a fine control over the formation of highly complex structures. The process also helps researchers to carry out the most

difficult synthetic steps, including atomic level modification in the structures using highly developed techniques of synthetic chemistry.[2] Molecular self-assembly can be broadly classified into two types: *intra-molecular* and *inter-molecular* self-assemblies. The folding of polypeptide chains in proteins and that of nucleic acids into their functional forms are examples of *intra-molecular* self-assembled biological structures. The double helical DNA through hydrogen bonding of the individual strands is an excellent example of *inter-molecular* self-assembly depicting its importance in nature. Various interesting examples of supramolecular assemblies presenting their potential applicability are reported by J.-M Lehn *et.al*.[3] and Atwood *et.al.*[4]. (Figure 1 and 2)

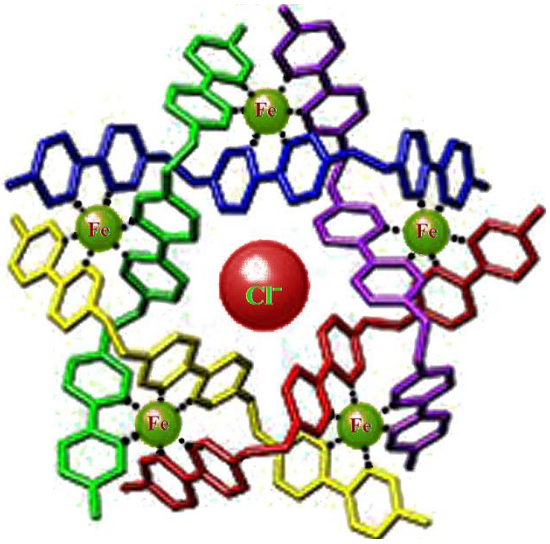


Figure 1. Representation of the formation of 1-D networks of through noncovalent interactions.

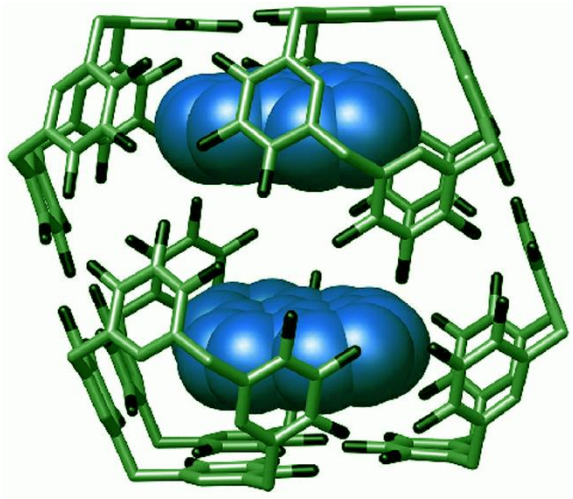


Figure 2. Graphical representation of the formation of 1-, 2-, and 3-D networks in crystalline solids directed by the noncovalent interactions.

Molecular self-assembly is an essential concept of supramolecular chemistry as it provides a scope for constructing numerous aggregates of diverse shapes such as spherical, helical, ladder, macrocyclic, rod-like or sheetlike architectures. [5] Some examples are displayed in figures 3-4.[6]

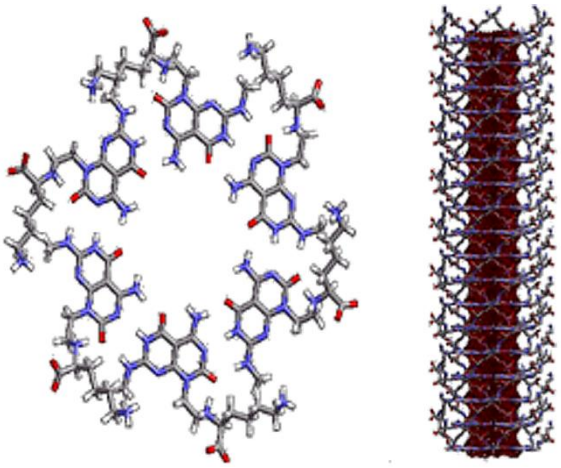


Figure 3. Representation of the formation of 1-D networks of through non-covalent interactions

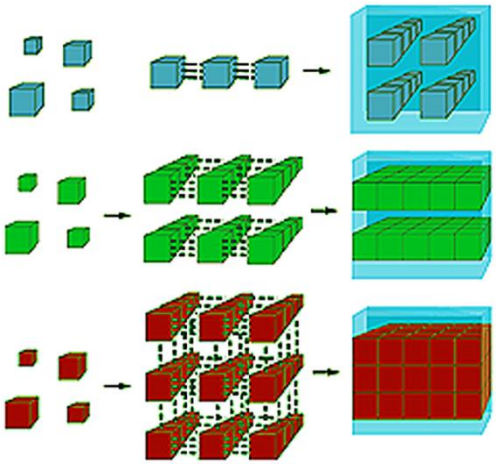


Figure 4. Graphical representation of the formation of 1-, 2-, and 3-D networks in crystalline solids directed by the non-covalent interactions

Hence, self-assembly has greatly widened the scope of the chemistry intending synthesis of diverse products with higher order and functions, extending chemical bonds to non-covalent interactions.[7]

A tremendous number of molecular self-assemblies are present in nature, especially biological systems[8] which are so crucial for the function of a cell. Self-assembly forms the basis for many natural processes, including protein folding, DNA transcribing and hybridization, and the formation of cell membranes. The process of self-assembly in nature is governed by inter- and intra-molecular forces that drive the molecules into a stable, low energy state. These forces primarily include hydrogen bonding, electrostatic interactions, hydrophobic interactions, and Van der Waals forces. For instance, self-assembly of lipid forms the cellular membrane, whereas, that of proteins form quaternary structures responsible for enzyme activity. A number of biochemical processes and double helical DNA are formed through the well defined hydrogen bonding of the individual strands. (Figure 5-6)

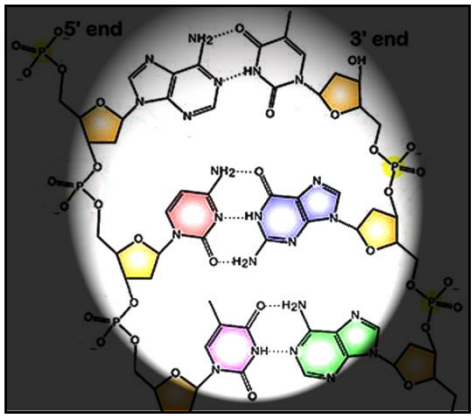


Figure 5. Formation of 1-D networks of through non-covalent interactions.

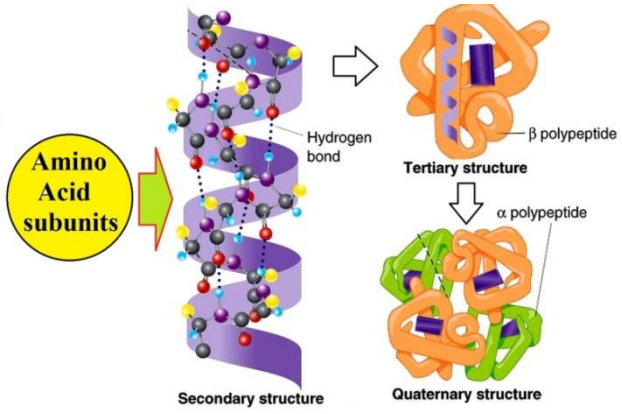


Figure 6. Representation of the protein folding through involvement of exhaustive non-covalent interactions.

Since an incorrect molecular self-assembly could lead to serious problems, viz. genetic mutations in living organisms, or neurodegenerative diseases caused by incorrectly folded proteins, it is therefore essential to understand the accuracy in the self-assembly process. The beauty and complexity of self-assembly processes occurring in the nature have inspired synthetic chemists to impersonate such structures at a molecular level. Hence, construction of biological architectures imitating naturally occurring assemblies has received much attention, since Lehn introduced the concept of supramolecular chemistry.[5c]

Metal-directed self-assembly has emerged as one of the most efficient approaches towards the design and synthesis of diversified supramolecular architectures like one-, two-, and three-dimensional infinite organic /inorganic hybrid frameworks such as filament, rod, ladder, rack, cylinder, brick wall, box, square grid, honeycomb, parquet, helical, diamondoid, etc. Thus, ***coordination chemistry*** has been successfully used to construct discrete structures with fascinating physicochemical properties.[9] (Figure 7)

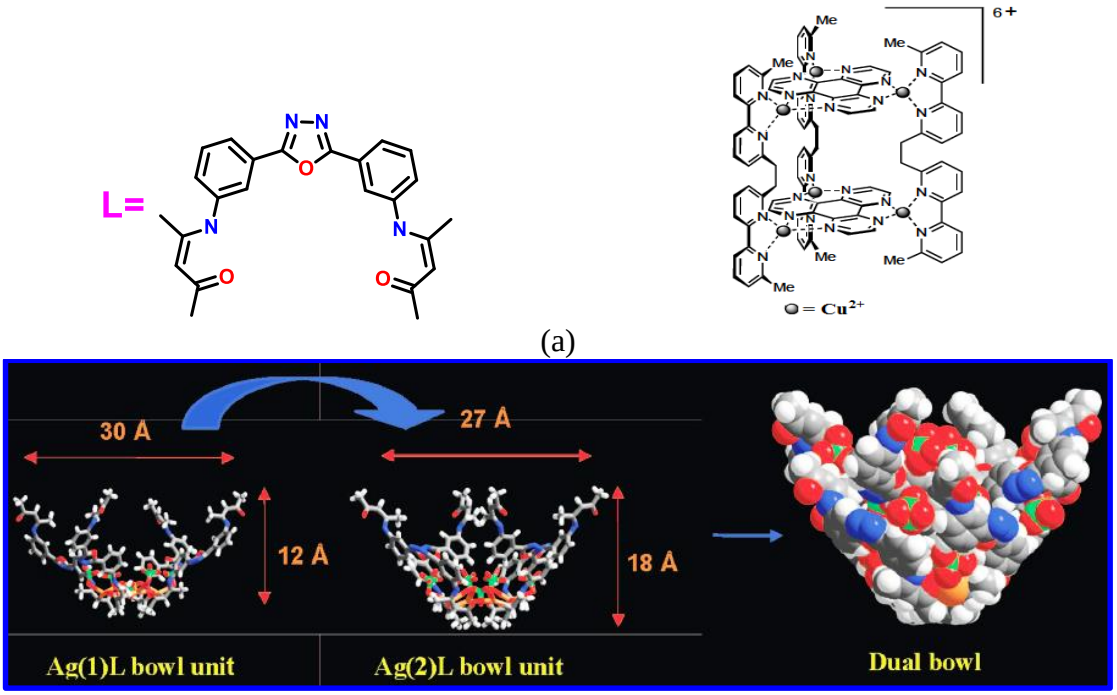


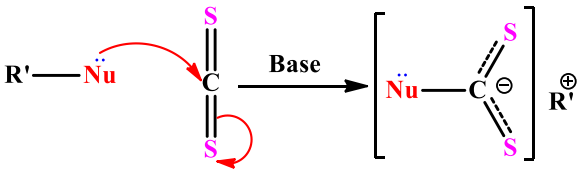
Figure 7. Coordination chemistry used in construction of diverse molecular architectures.

This has lead to coordination-driven self-assembly emerging as an active research area of chemistry in recent years.[10] It offers an additional scope for fine tuning of the electronic and structural properties of such architectures through imaginative modification in ligand system and judicious choice of metal ions.[6a]

Among diverse supramolecular architectures, macrocyclic structures with varied cavity size[11] are of great interest due to their potential applications in diverse fields such as catalysis,[12] host-guest chemistry,[6a,13] molecular and ion sensing,[14] separation, transport, and storage.[15] The insights of changes induced by external perturbations on self-assembly can facilitate the design and development of macrocyclic compounds with potential applicability in drug delivery, two-phase transport, biosensing.[16]

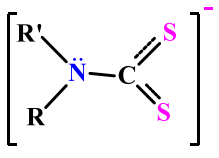
1.2. 1,1-Dithio Ligands

The 1,1-dithio ligand class primarily comprises of the different structural moieties: dithiocarbamates (dtc), dithiocarboxylates (xanthate) and dithiophosphonates. Owing to the fascinating stereoelectronic features of 1,1-dithio ligands, especially their strong binding ability and varied binding modes towards various transition/ non-transition metal ions present in different oxidation states, this class of ligands are highly promising for the development of novel coordination-driven self-assembled molecular architectures.[12f,13f,17] Transition metal dithiocarbamate and xanthate complexes have received immense attention as they exhibit diverse biological, agriculture and industrial applications.[18] Thus, this class of ligands have become an essential factor for the design of diversified self-assembled novel supramolecular structures. A large number of 1,1-dithio ligands are efficiently synthesized by the general reaction of carbon disulfide with various nucleophiles under diverse experimental conditions. (Scheme 1)

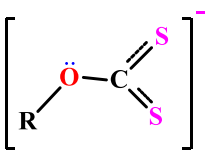


Scheme 1. General synthetic strategy for 1,1-dithio ligands.

Among the different 1,1-dithio ligands, dithiocarbamate and xanthates are largely studied, as they are readily synthesized by the nucleophilic addition of amines or alcohols to the CS_2 carbon. Thus, a broad spectrum of ligands can be efficiently synthesized by merely varying the nucleophilic species.



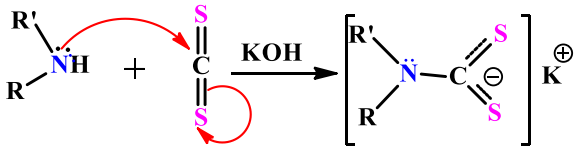
Dithiocarbamate (DTC)



Dithiocarboxylate (Xanthate)

1.2.1. Dithiocarbamate (DTC)

Dithiocarbamate is the analogue of a carbamate in which both oxygen atoms are replaced by sulfur atoms and are prepared by the reaction of aliphatic/aromatic, primary or secondary amines with carbon disulfide in the presence of base[19] as illustrated in scheme 2.

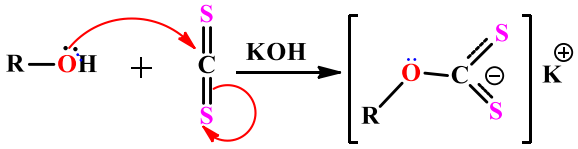


Scheme 2. General synthetic strategy for dithiocarbamate ligands.

Reportedly, dithiocarbamic acid (H_2NCS_2H) is unstable but yields stable salts; hence the alkali metal dithiocarbamate salts with various degrees of hydration are obtained by using an alkali metal hydroxide *in situ* as a base.[20] Generally, the dithiocarbamates derived from primary amines are unstable, as they readily convert into isothiocyanates under basic conditions.[21] The dithiocarbamates derived from secondary amines are more stable, but they tend to decompose under acidic conditions.[22] Hence dithiocarbamates generated from secondary amines are widely explored due to their higher stability than those of primary amines.[23] Beer and co-workers have contributed much in preparing a range of exciting new supramolecular architectures based on multifunctional dithiocarbamate ligands, many of them show interesting structural, redox properties.[13,17c,23b,24]

1.2.2. Dithiolate (Xanthate)

Dithiolate is a carbonate analogue in which both oxygen atoms are replaced by sulfur atoms are known as xanthates, also referred to, as esters of xanthic acid. The $HOCS_2H$, free acid is unknown as it is highly unstable and hence O-alkyl derivatives of dithiocarbonic acid are usually prepared by the reaction of alcohol and carbon disulfide under basic condition[19a,25] as illustrated below (scheme 3).



Scheme 3. General synthetic strategy for xanthate ligands.

Acidification of the alkali metal salts of xanthates produce unstable carbonodithioic acids (Xanthic acids).[26] Both dithiocarbamate/ xanthate ligands are mono-anionic in nature and exhibit high stability due to resonating forms as shown below.

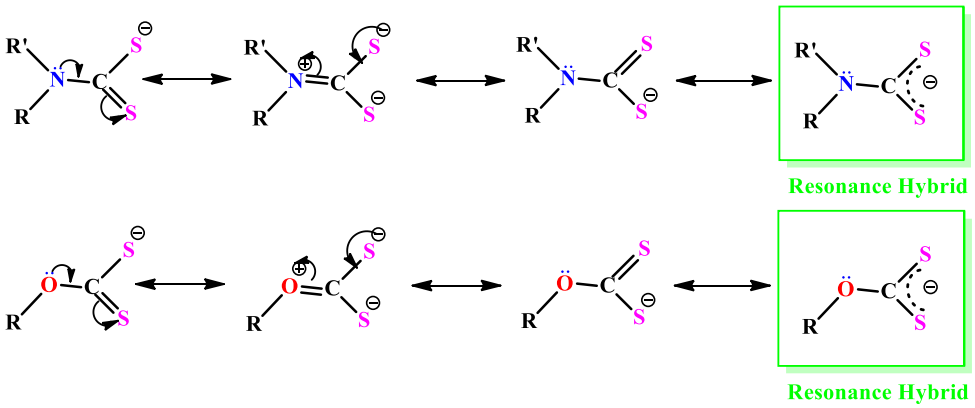
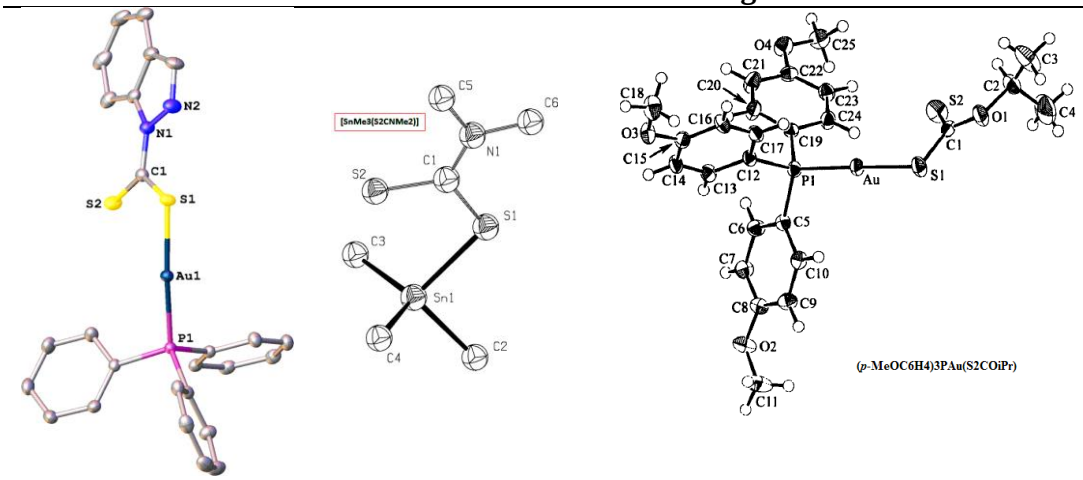
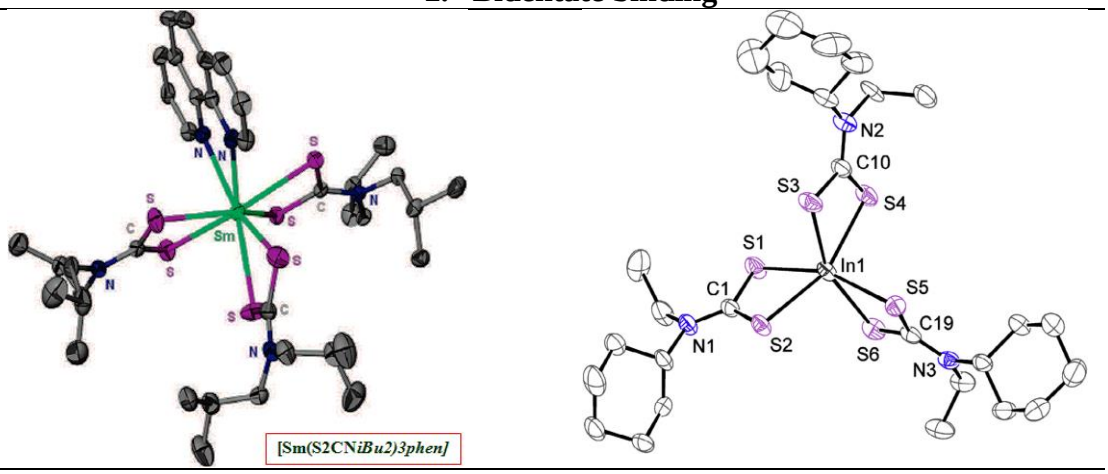
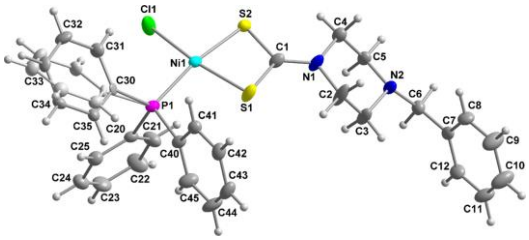
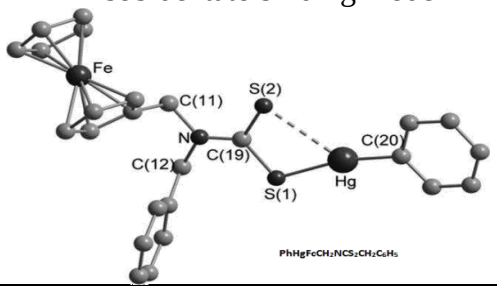


Figure 8. Resonating forms of dithiocarbamate/ xanthate ligands.

As per the stereoelectronic requirements, dithocarbamate/xanthate ligands can adopt diverse binding modes viz. mono or bidentate, however, bidentate binding could be isobidentate or anisobidentate binding. Few examples illustrating diverse binding modes of are summarized in table 1.[19a,27]

Table 1. Examples illustrating diverse binding modes of dtc/xan ligands.

1. Monodentate binding

2. Bidentate binding


Isobidentate binding mode	Anisobidentate binding mode
	

1.2.3. Classification of dtc/xan self-assembled complexes

Depending upon the number of metal centres in the molecular framework, dithiocarbamate/xanthate complexes can be classified as, monometallic, bimetallic and polymetallic dtc/xan complexes. In the formation of monometallic dithiocarbamate/xanthate self-assemblies, a single metal centre is coordinated to the ligand molecule(s), where metal:ligand stoichiometry is dependent on the oxidation state and coordination number of metal ion, as illustrated below.[28]

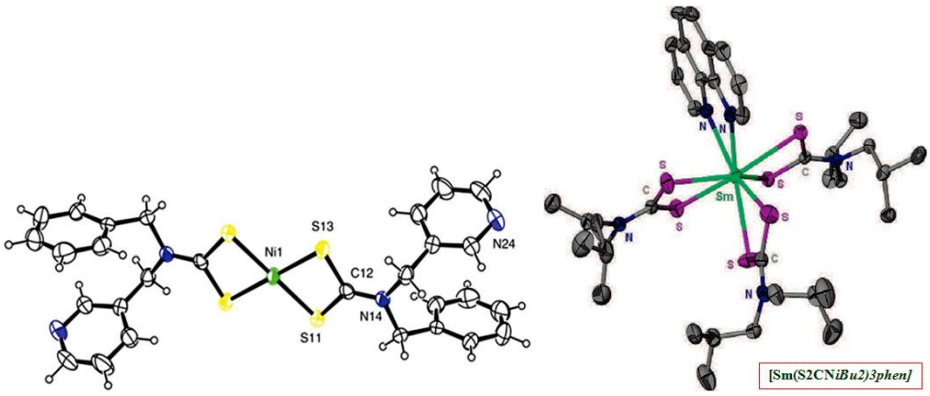


Figure 9. Monometallic dithiocarbamate/xanthate self-assembled structures.

However, metals like Cu, Cd are known to assemble two monometallic complexes through M…S bonding leading to the formation of dimeric species (illustrated below).[29]

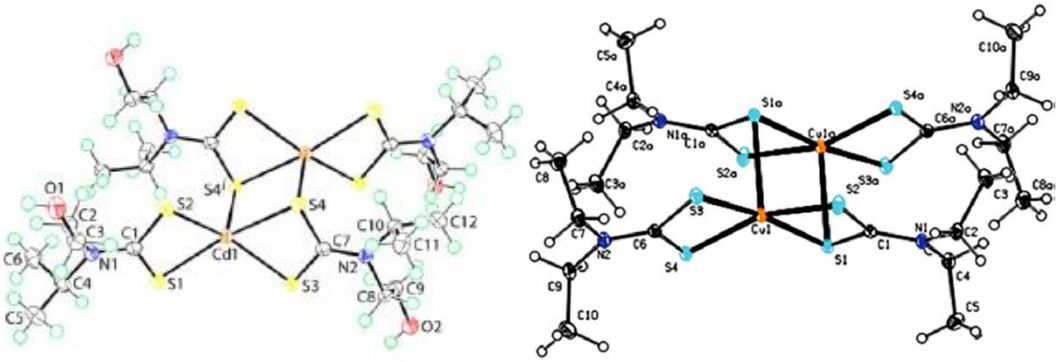


Figure 10. Dimeric species formed through M...S linking in dithiocarbamate complexes.

In case of bimetallic dtc/xan complexes, two metal centres are bridged by linker moiety and shape of the molecular assembly is predominantly dependent upon conformational rigidity/flexibility of ligand framework. For instance, rigid linear ditopic linker can hold two metal centres at opposite end, wherein self-assembly can limit to two metal centres by use of blocking ligands and hence avoids the possibility of polymerization. Ditopic linkers with flexible or arc shaped molecular framework may efficiently lead to the binuclear macrocyclic self assembly.[27a,30]

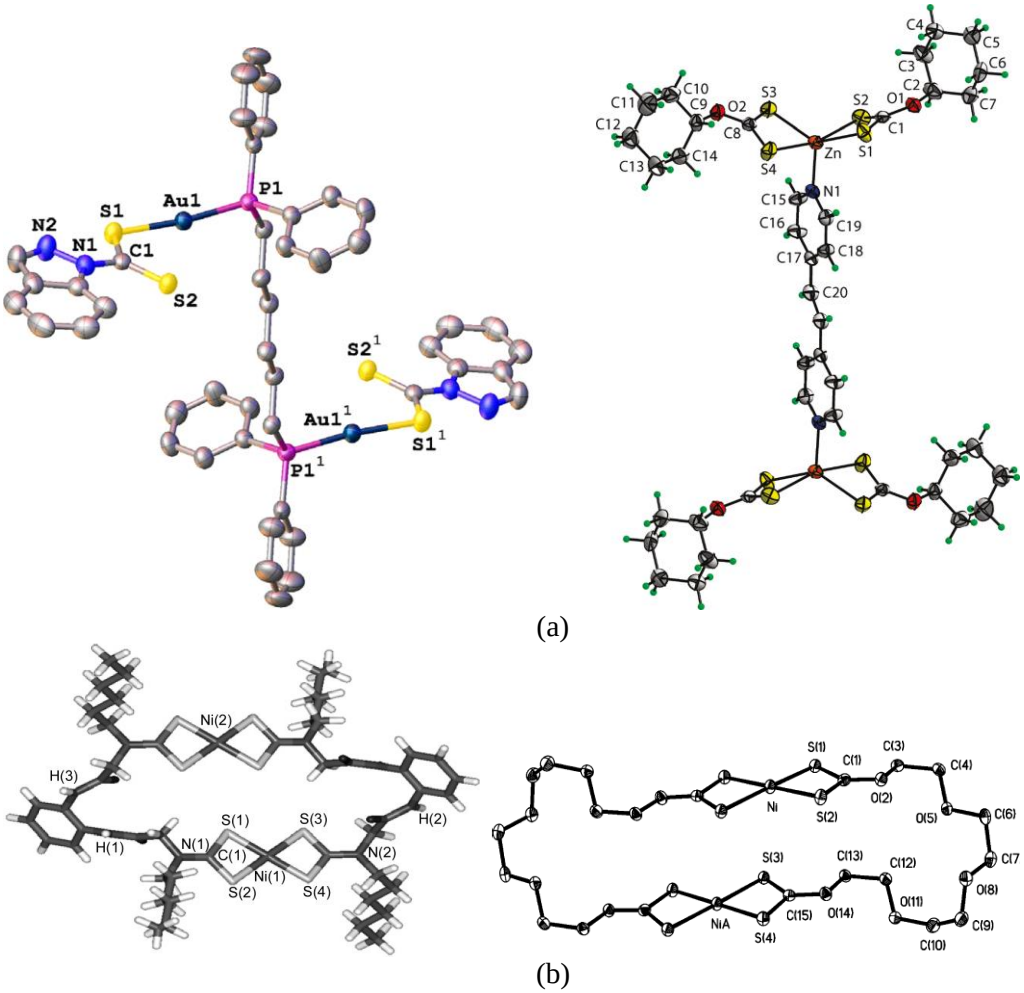
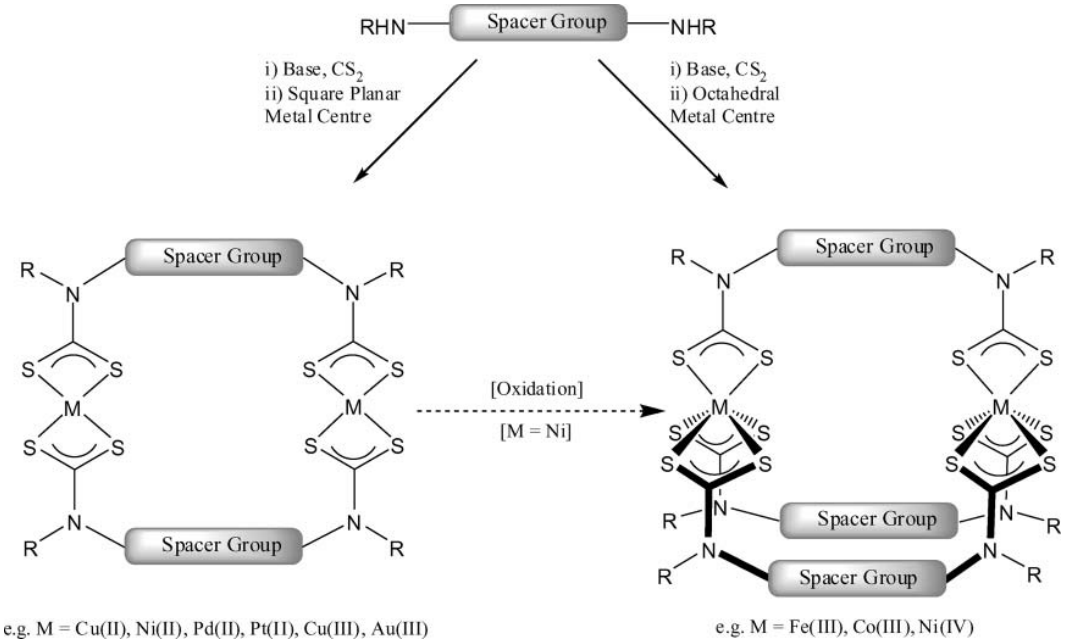


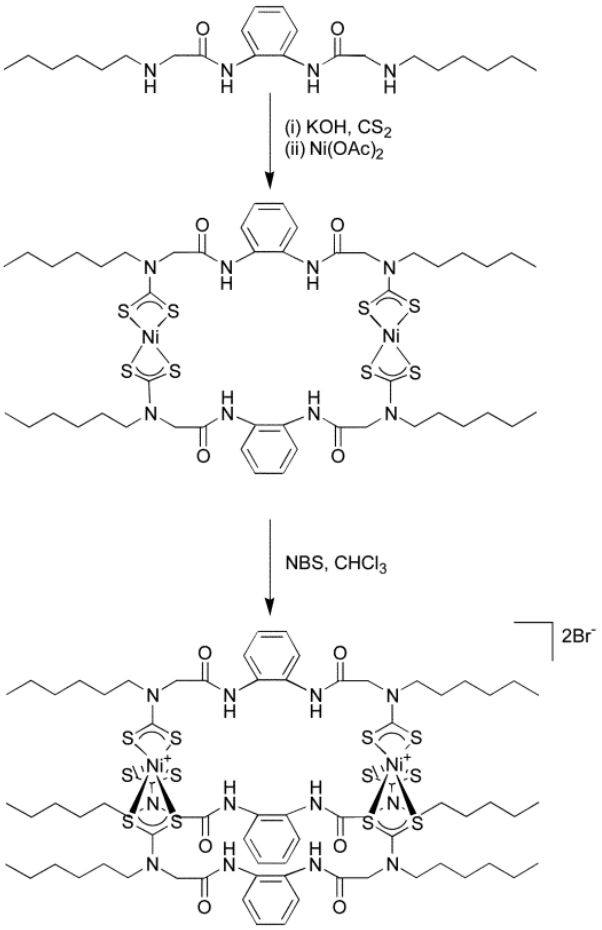
Figure 11. Binuclear dithiocarbamate/xanthate self-assembled structures; (a) acyclic (b) macrocyclic.

The synthesis of two- and three-dimensional macrocyclic and cage-like host molecules using metal-directed self-assembly is a current area of intense research activity.[11c,31] Through judicious selection of ligand and the stereochemical requirement of the mediating metal ion, the resulting unusual self-assembled polymetallic molecular architecture may be designed to exhibit unique redox, magnetic and photochemical properties, and have the potential to bind, sense or react with guest substrates.[32] Reportedly, the 1,1-dithio (dtc or xan) ligand has proven to be an attractive structural class for metal-directed self-assembly because it offers plenty

of opportunities for introducing different metals into the supramolecular array like catenanes, assorted macrocycles and trinuclear cages.[13g,30c] In addition, the incorporation of redox-active functionalities into the molecular framework, a macrocyclic system gains the possibility of being used as a host for various guests as well as an electrochemical sensor. Interestingly, oxidation of metal ions present in bimetallic macrocyclic structures generates a scope to accommodate one additional ligand molecules and this may lead to the development of macro-bi-cyclic self-assembly i.e. bimetallic dithiocarbamate transition metal cryptands.[23,30c] (Scheme 4 and 5) Control over the arrangement and shape of the self-assembly to obtain a selective product is still a challenge in supramolecular chemistry.[33]

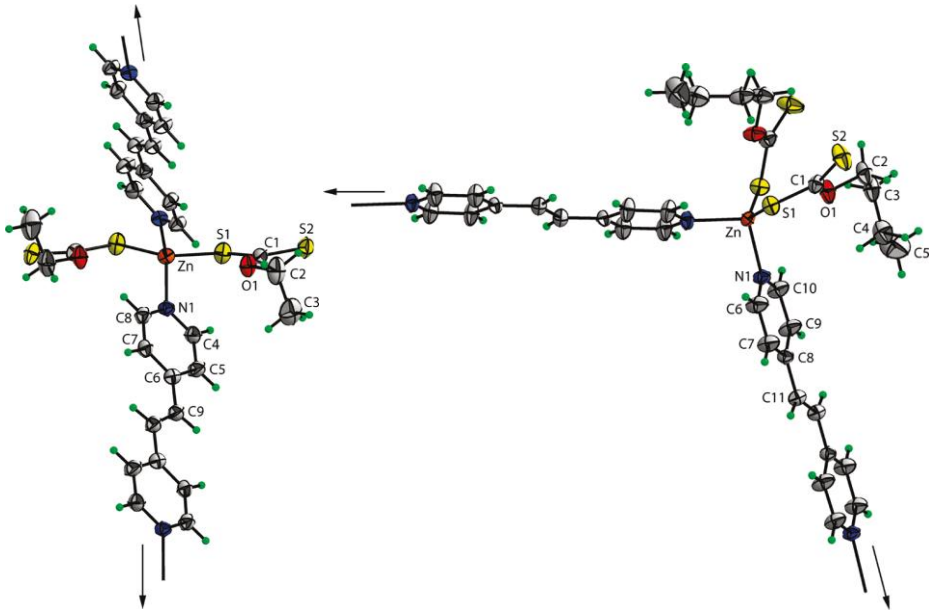


Scheme 4. General synthetic methodology for dinuclear macrocyclic and bimacrocyclic complexes.



Scheme 5. Synthetic methodology of nickel (IV) dtc based cryptand.

In the absence of blocking ligands, ditopic ligands with a rigid molecular framework may lead to polymerization yielding diverse coordination polymers[30b,34] with fascinating physicochemical properties. (Figure 12)



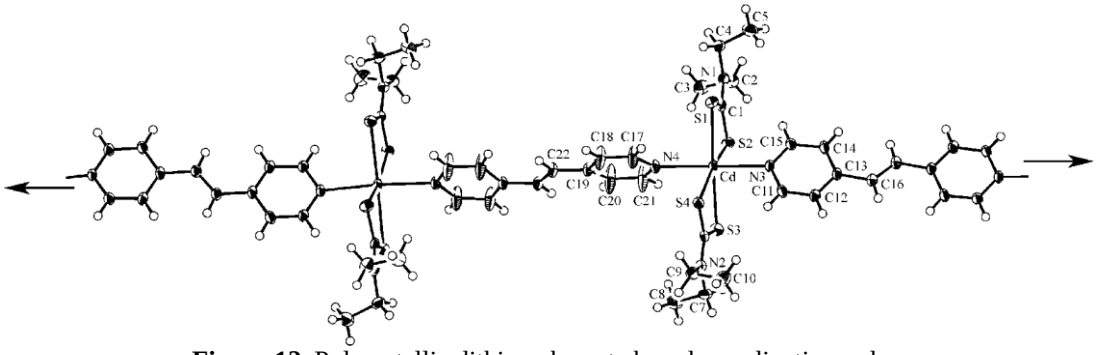


Figure 12. Polymetallic dithiocarbamate based coordination polymers.

The coordination polymers are promising candidates as new molecular materials with applications in fields as diverse as electronic devices, magnetic materials, separation science, gas storage, and catalysis. In this context, mono-, di-, tetra-, and polynuclear zinc complexes[30b] attracted significant attention[35] towards photoluminescence, in particular the generation of blue-emitting materials.

Beside these aspects, metal directed self-assembly of dithiocarbamates/ xanthates are found to be advantageous[36] over traditional covalent syntheses as,

i. Only a few basic subunits are required to generate complex architectures, in one or few convergent steps.
ii. Exhibits less solvent and p_H dependence than H-bonded structures.
iii. The product's stability and bonding properties of macrocyclic bis-dithiocarbamate or bis-xanthates can be controlled by the choice of metal ion.
iv. The incorporation of transition metal centre confers potential new properties to the hosts such as charge, magnetism, color, chemical and redox activity.
v. Can generate internal cavities which may be used as a receptor to bind several guest species.

1.2.4. Applications

Depending on the stereoelectronic features of ligand part and metal centre the transition metal complexes derived from 1,1-dithio ligands possesses fascinating physico-chemical properties and exhibit a broad spectrum applicability in various fields of synthetic chemistry, supramolecular chemistry, catalysis, biological, agriculture and industrial applications.[37] This class of compounds is widely being used in vulcanisation of rubber analytical reagent and as fungicides. Pictorial representation and some examples are summarized below. (Figure 13 and 14)

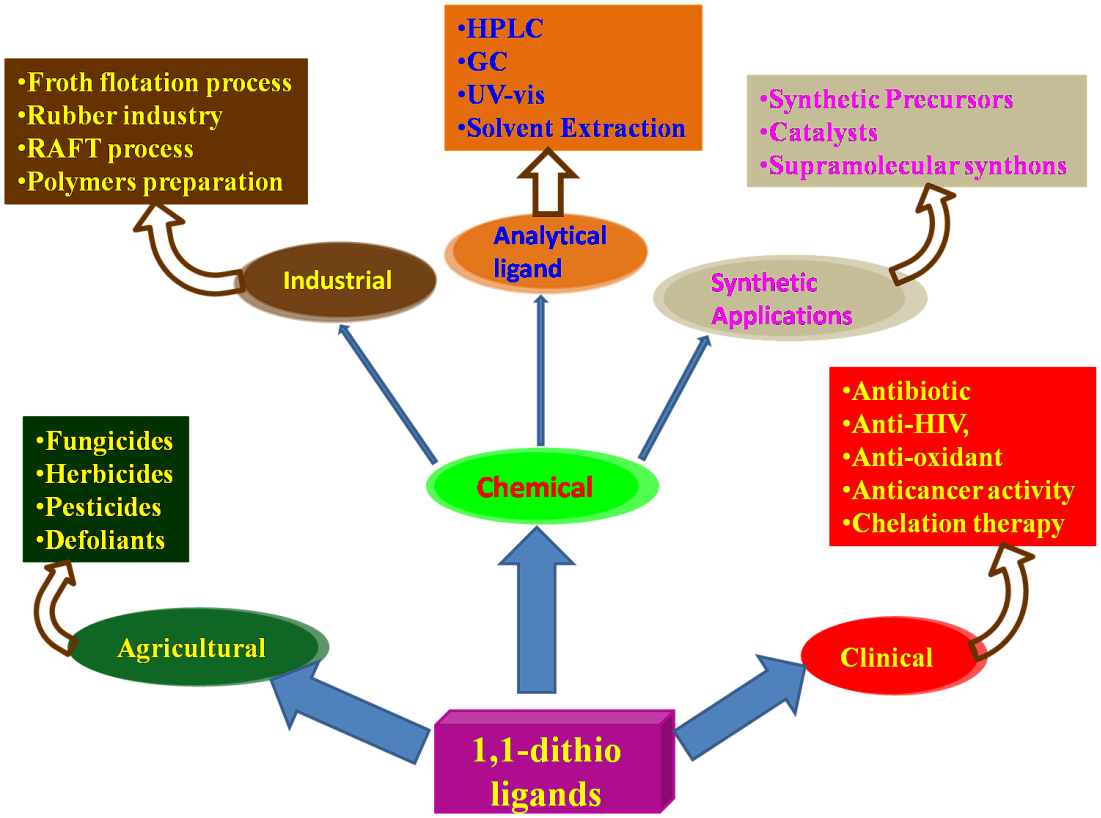


Figure 13: Pictorial representation for a broad spectrum applicability of compounds complexes derived from 1,1-dithio ligands.

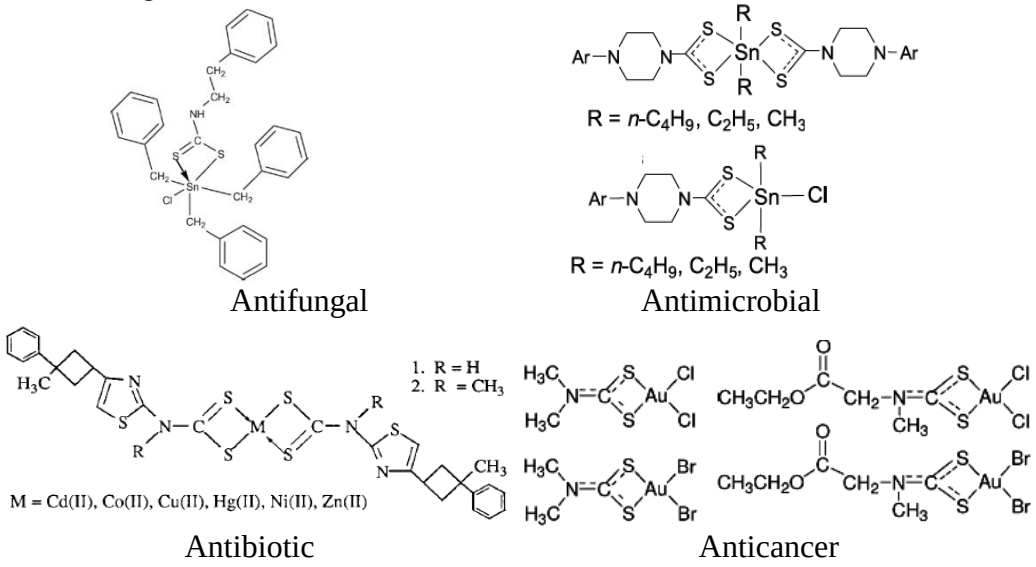


Figure 14: Examples of complexes derived from 1,1-dithio ligands depicting medicinal significance.

The flexibility of the architecture and exhaustive weak interactions present in the macrocyclic self-assembly make the system sensitive to external perturbations, which add merit to their potential applicability in supramolecular chemistry, especially 'host-guest reactivity' study towards variety of guests species like cationic, anionic, neutral guests and ion-pair recognition. In host-guest reactivity, host–guest binding stoichiometry (1 : 1 or 2 : 1) are predominantly dependent upon the size

compatibility of the hosts-guests (Figure 15) and electronic aspects. For instance, due to the small macrocyclic cavity size, receptor only forms 2 : 1 host–guest complexes, whereas larger for macrocycles leads to 1 : 1 indicating the formation of intramolecular inclusion complexes. (Figure 15) However, if macrocyclic cavity is compatible ditopic hosts prefers formation of intramolecular inclusion complexes with ditopic guests.[24a] Due to the presence of voids such material can be used as purifier in ppm level and trapping wide variety of molecules.[38]

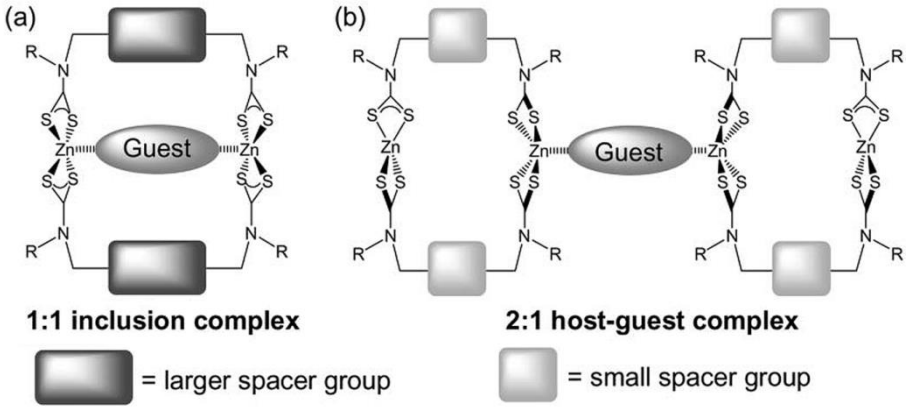


Figure 15: Formation of host-guest complexes (1 : 1 or 2 : 1) based on the size compatibility of the hosts-guests.

With the other hand, the molecules bearing sulfur atom plays a vital role in biological processes and interacts efficiently with biomolecules.[39] Organic compounds bearing 1,1-dithio moieties exhibit valuable biological effects, including antibacterial, antifungal, antioxidant activity,[40] inhibition of cardiac hypertrophy,[41] etc.

Despite major breakthroughs in many areas of medicinal chemistry over a period of time, the successful treatment of cancer remains a significant challenge in the 21st century. Discovery of novel agents having an ability to inhibit proliferation of tumor cells selectively without causing toxicity is difficult, which limits the use of traditional cancer chemotherapy. Hence, pharmaceutical development is one of the prime concerns of current research in the battle against cancer wherein large-scale synthesis for lower cost of production of generic and proprietary products is a big challenge. In this field, medicinal inorganic chemistry offers additional opportunities for the design of therapeutic agents not accessible to organic compounds.[42] The diverse coordination numbers, geometries, redox states, thermodynamic-kinetic characteristics, and intrinsic properties of the metal ion and ligand itself offer the medicinal chemist a large variety of reactivities to be exploited. Moreover, the

widespread success of cisplatin in the clinical treatment of various types of neoplasias has placed coordination chemistry of metal-based drugs in the frontline in the fight against cancer.[42,43] Although highly effective in treating a variety of cancers, the cure with cisplatin is still limited by dose-limiting side effects[44] and inherited or acquired resistance phenomena, only partially amended by employment of new platinum drugs.[45] Hence, the efforts in the evaluation of anticancer drugs have been shifted to non-platinum metal-based agents who do not only depend on direct DNA damage but also may engage proteins and enzymes for their activity to avoid significant side effects and the emergence of drug resistance associated with platinum chemotherapeutics.[46] In fact, the sulfur donor ligand plays a vital role in transporting and addressing the molecule to the targets as well as in the protection of pharmacophore against untimely exchanges with biomolecules.[39] For instance, the diethyldithiocarbamate anion, has been extensively used in Wilson's disease to overcome copper poisoning[47] and for better nephrotoxicity in platinum-based chemotherapy.[48] Even though dithiocarbamates demonstrated neurotoxic effect in animal models as well as in human,[49] only gold and copper dithiocarbamate complexes were studied over past few decades for their anti-cancer activity[27a,50] while other transition metal dithiocarbamate complexes were relatively underexplored.

Moreover, a wide range of natural products bearing macrocyclic motif and their synthetic derivatives have long been clinically used as they enable high degree of structural pre-organization with sufficient flexibility towards better binding interactions with the target molecules without a major entropic loss on binding leading to high degree of potency as well as selectivity.[51] Hence, the wider use of macrocyclic scaffolds in medicinal chemistry is one of the current thrust in the search for new drugs for increasingly challenging targets. Despite these valuable characteristics and a great success of dithiocarbamate based macrocyclic complexes in supramolecular chemistry, especially host-guest reactivity study,[13] this structural class (binuclear M^{II}dithiocarbamate/xanthate macrocyclic complexes) is surprisingly not yet exploited in medicinal chemistry especially for anticancer activity.

Besides, the use of binuclear transition metal dtc/xan complexes can be further extrapolated to the effective synthesis of macrocycles via synthetic transformations. In spite of, a very large number of syntheses for a wide variety of compounds reported over the years, macrocycles are often (and rightly so) perceived as difficult to

synthesize. The macrocyclization step suffers from low yields and often requires high dilution conditions to counterbalance entropic loss[52]; also lack of suitable sythons is major issue to be addressed. Hence, it is essential to explore the newer dimensions of metal complexes towards synthesis of macrocyclic scaffolds (organic and coordination complex), those are enormously difficult to synthesize by conventional methodologies.

1.3. Objectives

In the light of all these aspects of self-assembly, efforts have been put into the development of a number of metal-directed self-assembled structures using dithiocarbamate/xanthate ligands. The objectives of the current study are briefly stated below.

- To design and synthesize novel organic diamine/diol precursors suitable for the development of macrocyclic bimetallic bis-dithiocarbamate/ bis-xanthate self-assemblies.
- To synthesize bis-dithiocarbamate/ and bis-xanthate ligands from secondary diamines / and diol precursors, carbon disulphide and the presence of a base.
- To investigate the possible reactivity of 1,1-dithio ligands towards transition metal ions as well as organometallic building blocks such as diphenyltin(IV) in the development of novel binuclear dithiocarbamate/ and xanthate macrocyclic complexes.
- To characterize newly synthesized compounds by micro-, thermogravimetric analysis and relevant spectroscopic techniques such as mass, IR, NMR, UV visible.
- To determine the unambiguous structure of compounds by single crystal XRD studies and to evaluate the crystal packing patterns.
- To perform DFT calculations to optimize the geometry and to get an insight of the experimental outcomes.
- To investigate the binding affinities of newly synthesized macrocyclic hosts towards a number of neutral and cationic guest species.
- To investigate the impact of structural modifications upon the cytotoxic activity of the relevant compounds against human cancer cell lines, HEP 3B and IMR 32 cells.

1.4. General Instrumentation and Methods

1.4.1. Material and physical measurements

The reagents such as 4,4'-diaminodiphenyl ether (99%), sodium borohydride (95%) and 1-naphthaldehyde (95%) were purchased from National Chemicals, Merck and Chemlabs, respectively. 9-formyl anthracene and 9-formyl phenanthrene were synthesized as per the literature procedure. [23] Primary amines were purchased from Loba Chemie or Sigma Aldrich. Metal acetates (Co^{II}, Ni^{II}, Cu^{II}, Zn^{II}) and diphenyltin dichloride (96 %) were purchased from Merck and Sigma Aldrich, respectively. All the other chemicals and solvents used in this work were of laboratory grade available at various commercial sources and used without further purification. The reactions and manipulations were performed under an inert atmosphere. Melting points were recorded in open capillaries and uncorrected. Thin layer chromatography was performed on Merck 60 F254 aluminium coated plates to monitor the progress of a reaction. Elemental analyses (C, H, N) were performed on a Perkin-Elmer 2400 analyzer. Mass spectra were obtained on Water's QTOF, Thermo Scientific DSQ-II GCMS or AB SCIEX 3200 Q TRAP LCMS instrument. FT-IR (KBr pellets) spectra were recorded in the 4000-400 cm^{-1} range using a Perkin-Elmer FT-IR spectrometer. The NMR spectra were obtained on a Bruker AV-III 400 MHz or Bruker AV-III 500 MHz spectrometer in $CDCl_3$/d^6-DMSO solvents as per the solubility and chemical shifts are reported in parts per million (ppm). For relevant compounds, the assignments of NMR signals were supported by gCOSY and DEPT-135 and HSQC experiments for the relevant compounds. UV-visible spectra were recorded on a Perkin Elmer Lambda 35 UV-visible spectrophotometer and the optical characterization of solid samples was performed by using the UV-visible transmittance measurements. Fluorescence was recorded on JASCO make spectrofluorometer model FP-6300. TGA/DTA plots were obtained using SII TG/DTA 6300 in flowing N_2 with a heating rate of 10 °C min^{-1}. All the geometry optimizations were performed with the Gaussian 03 program suite and molecular orbitals were generated using GaussView 3.0 program.[53]

1.4.2. In vitro cytotoxic study

1.4.2.1. Cell line and culture

The human cancer cell lines **HEP 3B** (Hepatoma) and **IMR 32** (Neuroblastoma) were acquire from the National Centre for Cell Science, Pune

whereas Dubecoos Modified Essential Medium (DMEM) and Foetus Bovine Serum (FBS) were obtained from HiMedia. Cisplatin is procured from Sigma–Aldrich. The cancer cell lines **HEP 3B** and **IMR 32** were established in DMEM with 10% FBS in humidified atmosphere supplied with 5% CO_2 at 37 °C. The **IMR 32** cell line was allowed to differentiate as a neuron by using sodium butyrate for 9 days of incubation in 5% CO_2 atmosphere at 37°C. Both these human cancer cell lines were utilized to screen all the newly synthesized compounds for their potential antitumor activity at various concentrations.

1.4.2.2. Statistical analysis for determination of IC_{50}

Each sample was screened in six duplicates subsequent data was analyzed in Prism/OriginPro 8 for standard error and probit analysis. The percent cytotoxicity index (% CI) was calculated as:

$$\% CI = [1 - (OD \text{ of treated cells}/OD \text{ of control cells})] \times 100\ \%$$

where, CI= cytotoxicity index, OD= optical density.

The % CI versus concentration obtained from the experimental data for each set of experiments was plotted and the IC_{50} values (50% growth inhibition of cell) were obtained from the graph. Each test was repeated at least three times and the results were expressed as mean $IC_{50} \pm SD$.

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