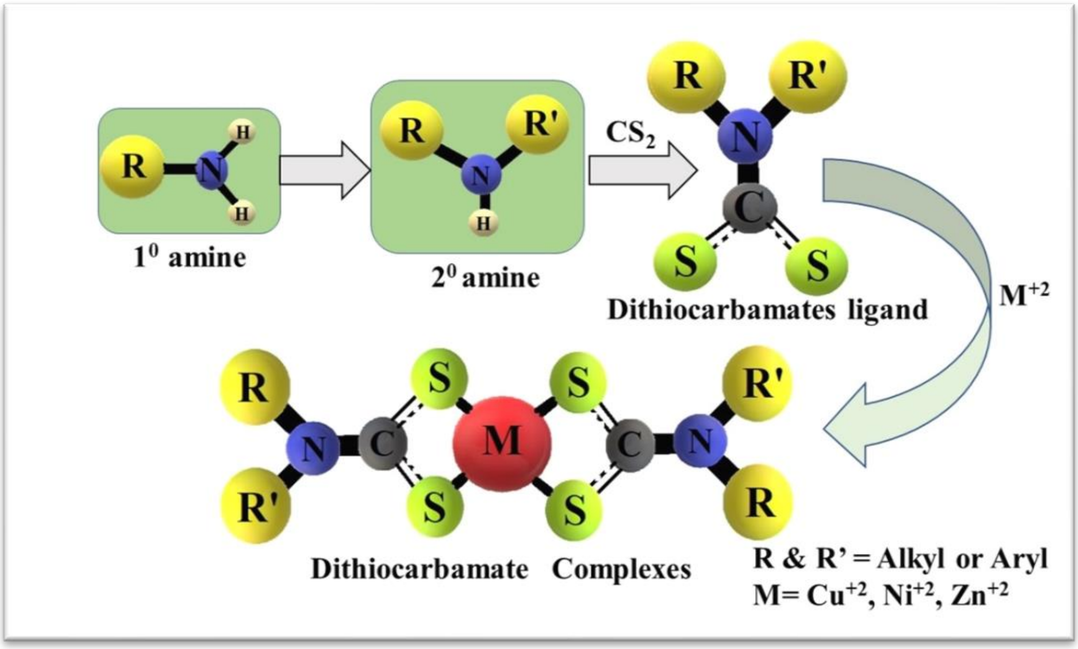
Introduction: Synthesis, Characterization and Biological Property of Amine Functionalized Ligand Precursors and Their Metal Dithiocarbamate Derivatives

Abstract



A systematic thorough literature survey on chiral 1,1-dithiocarbamate base ligand systems containing ferrocene or benzyl moiety and they are useful in coordination chemistry with transition and non-transition metals in a variety of stoichiometries and properties has been comprised in this chapter. The exploitation of unique stereoelectronic properties of metal ions and dithiocarbamate ligands in metal directed self-assembly process leads to distinct supramolecular structures with fascinating physico-chemical properties and broad spectrum of applicability is highlighted in this section. Supramolecular frameworks with interesting physico-chemical properties and their application in the biological system has also been highlighted in this section. The objectives of the present work are also mentioned at the end of this chapter.

1.1 Self- Assembly

Self-assembly is one of the most effective tools in science, with great potential for application in a wide range of field including materials, engineering, medicine, energy and devices. Self-assembling processes have been used by self-organized structures. Self-assembly is a process in which a disordered system of pre-existing components forms an organized structure or pattern as a consequence of specific, local interactions among the components themselves without external direction.

Self-assembly can be classified into two types: static and dynamic. In static self-assembly, the ordered state forms as a system approaches equilibrium, reducing its free energy. Dynamic self-assembly comes into existence when the formation of an ordered state of equilibrium requires the dissipation of energy. In other words, the weak interactions like Hydrophobic, π-π stacking, hydrogen bond, coordination bond are responsible for the formation of structures or patterns between components occur only if the system dissipates energy.[1] However, in dynamic self-assembly, designs of pre-existing components planned by specific local interactions are not commonly described as "self-assembled" by scientists in the associated disciplines. These structures are better defined as "self-organized", although these terms are often used interchangeably. Some examples of "self-organised" structures are shown in Figure 1.[2]

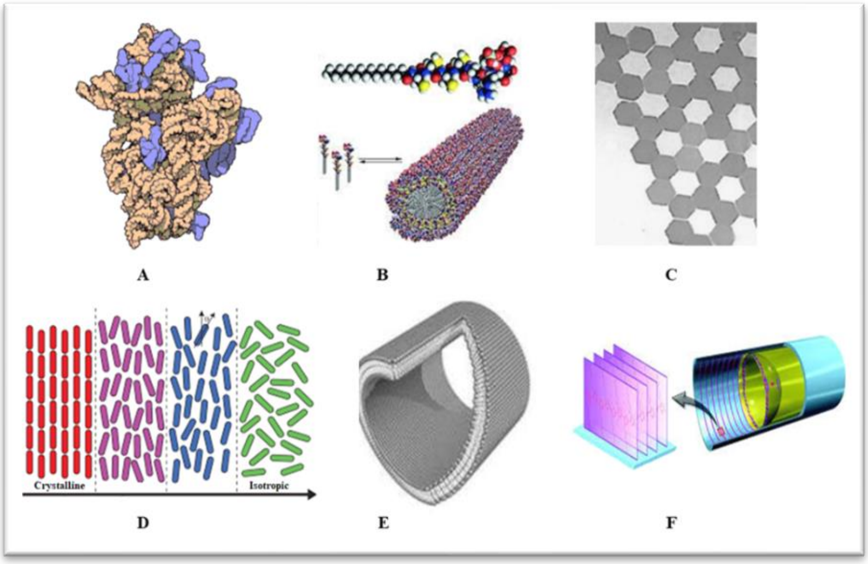


Figure 1. Examples of static self-assembly (A) Crystal structure of a ribosome. (B) Self-assembled peptide–amphiphile nanofibers. (C) An array of millimeter-sized polymeric plates assembled at a water–perfluorodecalin interface by capillary interactions. (D) Thin film of a nematic liquid crystal on an isotropic substrate. (E) Micrometer-sized metallic polyhedra folded from planar substrates. (F) A 3D aggregate of micrometer plates assembled by capillary forces.

Self-assembly is the essential ability of various numbers in biological structures to assemble from their module parts through random movements of molecules and the formation of weak chemical bonds between surfaces with corresponding shapes. A few examples of self-assembled structures that can be found in biological systems are the phospholipid bilayer of human cell membranes [3], RNA [4], and DNA complexes.[5] The molecular building mechanisms fundamental the formation of bacteriophage and viral particles are all based on self-assembly. A number of biochemical progressions and double helical DNA are formed through the well-defined hydrogen bonding of the individual strands. (Figure 2)

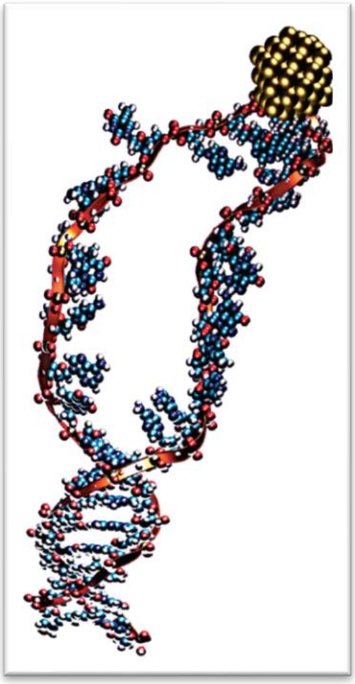


Figure 2. Metal nanocrystal–coupled biomolecule DNA.

Molecular self-assembly is a powerful phenomenon taken from nature by scientists for fabricating novel supramolecular architectures. Molecular self-assembly is the assembly of molecules without guidance from an outside source. Molecular self-assembly is to design molecular building blocks that can undergo spontaneous organization into a well-defined and stable macroscopic structure using non-covalent bonds.[6] This is mainly governed by weak non-covalent bonds like electrostatic interactions (ionic bonds), hydrogen bonds, hydrophobic and hydrophilic interactions, water-mediated hydrogen bonds and van der Waals interactions. [6,7] (Figure 3)

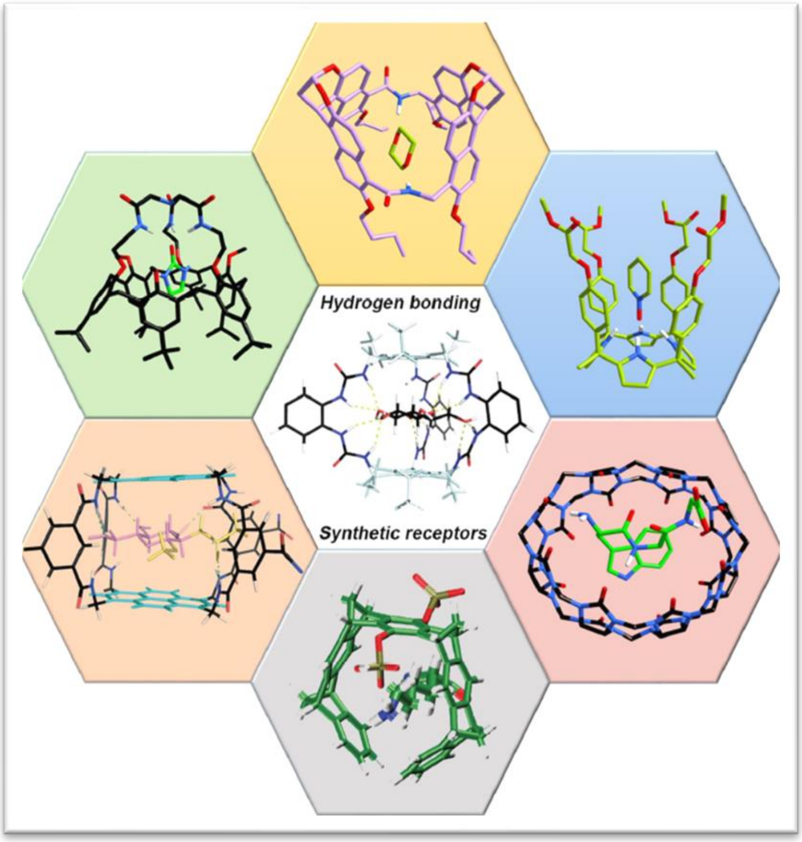


Figure 3. Molecular self-assembly via weak interactions.

Although these forces are weak, their collective interactions can produce chemically and structurally stable molecular self-assembly. Commonly, molecular self-assembly depend on chemical complementarity and structural compatibility.[6,8] The molecular components need complementary properties such as specific surface characteristics, surface charge, polarizability, mass, and surface functionalities to self-assemble into different physiological forms.[8] Biological molecules like peptides, proteins, lipids, nucleic acids, and other cellular components with complementary properties self-assemble to form the basic biological unit, the cell. Cellular events like amyloid fibril formation, antigen–antibody recognition, chromatin assembly, and phospholipid membrane self-assembly are excellent examples of molecular self-assembly.

1.2 1,1-Dithio Ligands

Dithiocarbamates (DTCs) were probably first prepared over 155 years ago, although at this time they were not formulated correctly. In the dominant century a puzzling array of different dithiocarbamates have been prepared. Dithiocarbamates are in wide range which stems simply from the ability to alter the substituent on nitrogen, that has been brought this specialty of Dithiocarbamates ligand to in the front of transition metal Chemistry.[9] (Chart 1) Still today, there is a scope of modification on the substituent on Nitrogen atom and synthesized new dithiocarbamate ligand and their transition and non-transition metal complexes.

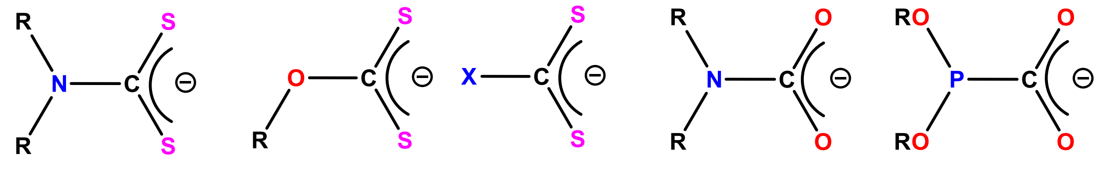
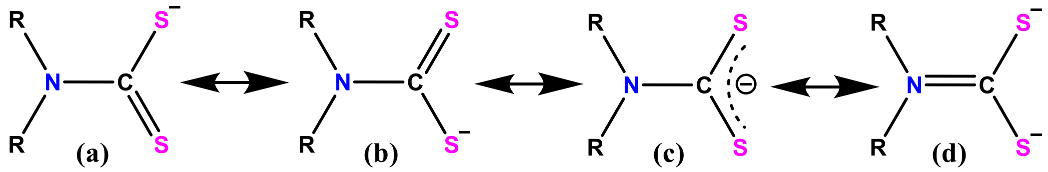


Chart 1: Group of compounds comprises 1,1-dithio ligands.

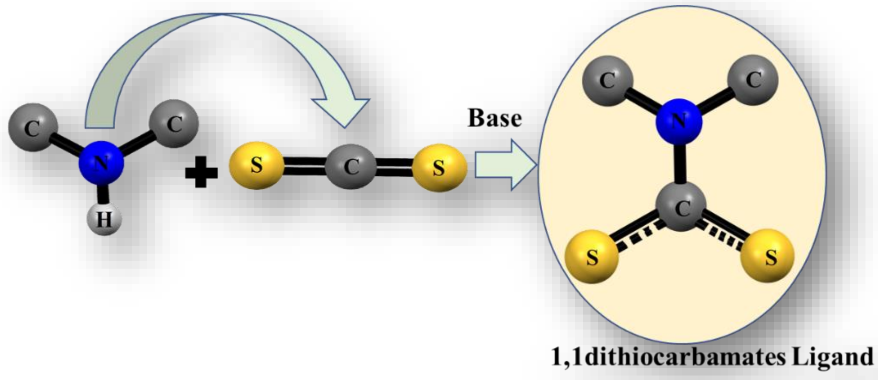
The structure of these monoanionic 1,1-dithio ligands[10] can be defined by four resonance structures. (Scheme 1) The role of structure (d) is important in the report of the overall structure of dithiocarbamates based on the IR band in the region 1450-1550 cm^{-1} give out to the υ bonds. [11-12]



Scheme 1. Resonance forms of the 1,1 dithiocarbamate ligand.

1.2.1 Preparation of the 1,1-dithiocarbamate ligand

1,1-dithiocarbamate ligands are easily formed from a wide range of easy and cheap available secondary and primary amine are reacted with carbon disulphide (CS_2) in basic condition, normally acetonitrile, methanol, water and some other simple organic solvents are also applicable.[13] (Scheme 2)While alkali-metal salts use as base (MOH), (M = Li, Na, K), has good water solubility, use of organic bases such as $[R_4N][OH]$ affords ammonium salts, $[NR_4][S_2CNR_2]$, which are insoluble in water but have good solubility in common organic solvents. Thus, the physical properties of 1,1-dithiocarbamate ligands (DTC) salts can easily be changed.[14] We also highlight here, as it is often incorrectly represented in the literature, that free dithiocarbamic acids, R_2NCS_2H and $RHNCS_2H$, are unstable [15,16] and addition of CS_2 to primary or secondary amines in the absence of added base affords salts, $[RNH_3][RHNCS_2]$ and $[R_2NH_2][R_2NCS_2]$ respectively, in which one equivalent of amine acts as a base and the second a nucleophile.[17,18]



Scheme 2. General synthesis of 1,1-dithiocarbamate Ligand.

As previously discussed, a tremendous range of dithiocarbamate ligands, different in their substituents, have been prepared for the drives of this evaluation, we will subdivide these into three types: (**A**) symmetrically disubstituted, (**B**) unsymmetrically disubstituted, and (**C**) monosubstituted. In symmetrically disubstituted 1,1-dithiocarbamate ligand both substituents which are attached to nitrogen atom are same. In case of unsymmetrically disubstituted 1,1-dithiocarbamate ligand both substituents which are attached to nitrogen atom are different and monosubstituted 1,1-dithiocarbamate ligand only one alkyl/aryl group is attached to nitrogen atom as well.[19]

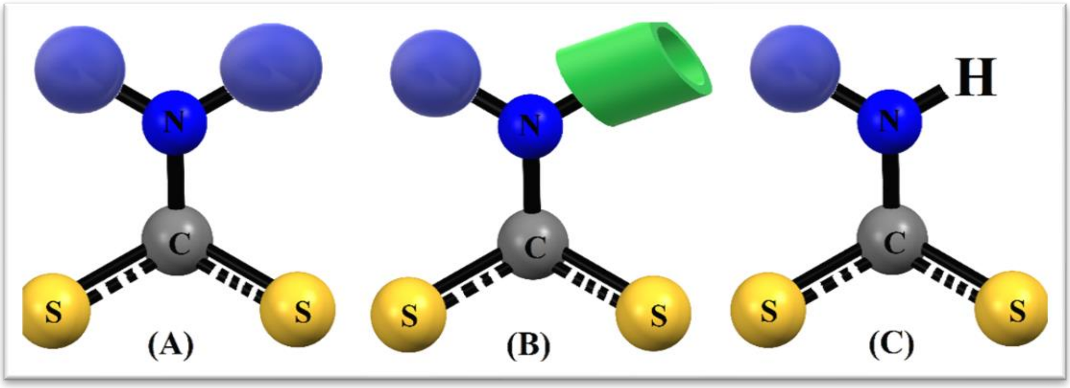


Figure 4. Illustrations of some different types of 1,1 dithiocarbamate ligands (**A**) symmetrically disubstituted, (**B**) unsymmetrically disubstituted, and (**C**) monosubstituted

1.2.2 Binding Mode of Dithiocarbamates

Dithiocarbamate ligands are known as to coordinate the metal ions in a variation binding modes. One to four metal ions can be attached by the ligand in different ways. The 1,1-dithiocarbamate ligands moiety can form complexes where both Sulphur atoms are coordinated to the same metal atom forming a four coordinated chelating ring. (Figure 5)

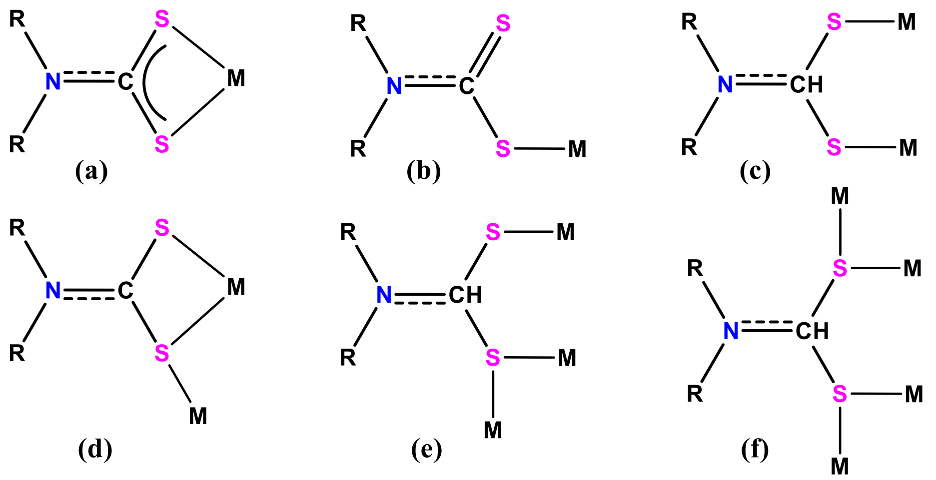


Figure 5. Different binding modes of 1,1- dithiocarbamate ligand

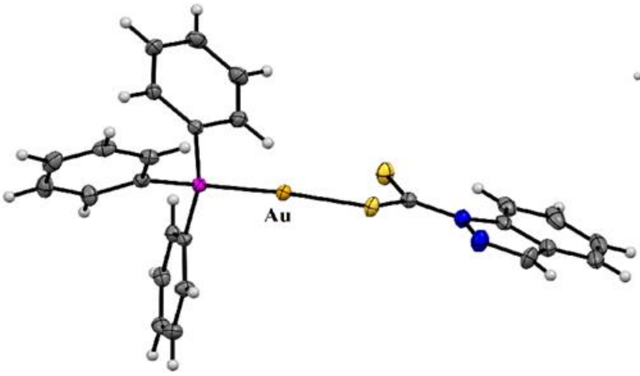
However, there are examples of metal dithiocarbamate complexes with unequal metal-sulphur bonds. The NCS_2 moiety of 1,1-dithiocarbamate ligands are known to bind with various metal ions which are present in their high oxidation state as well as in low oxidation states. Although, variety of transition or non-transition metal dithiocarbamate complexes bearing simple alkyl/aryl N-substituents is known, however, functionalization of 1,1-dithiocarmate ligand backbone is still in the early stage of investigations. Because of ready availability, primary and secondary amines as starting materials can be designed and synthesized which can be subsequently utilized in the development of corresponding dithiocarbamate ligands. Still today, there are no many reports on the chiral amine use as 1,1- dithiocarbamate ligand. So, there are scope of use chiral secondary amine use as initial material and synthesized their chiral dithiocarbamate complexes and explore their physical and chemical property.

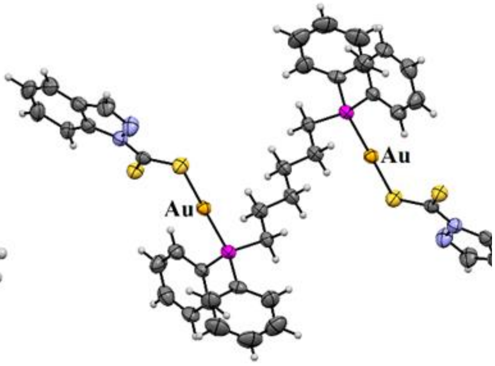
1.2.3 Self-assembly of 1,1-Dithiocarbamates complexes

According to the published research data, the stereoelectronic requirements, 1,1-dithocarbamate/xanthate ligands can adopt various binding modes viz. monodentate or bidentate. However, bidentate binding could be monomettalic dithiocarbamate, monomettalic Bis-dithiocarbamate, monomettalic Tris-dithiocarbamate and isobidentate binding. Few examples demonstrating in various binding modes are summarized in Table 1. [20-28]

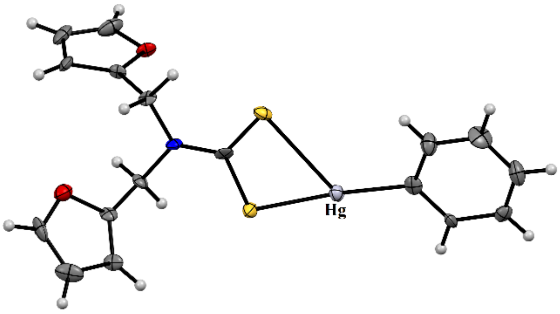
Table 1. Examples demonstrating various binding modes of dithiocarbamate ligands.

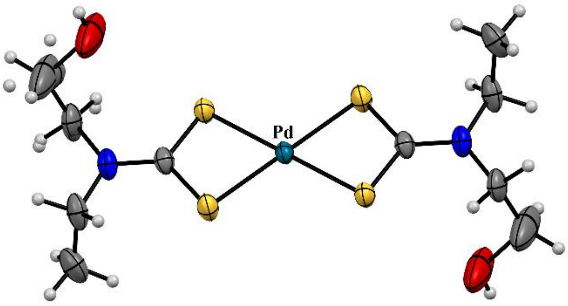
Monodentate mode of dithiocarbamate complexes

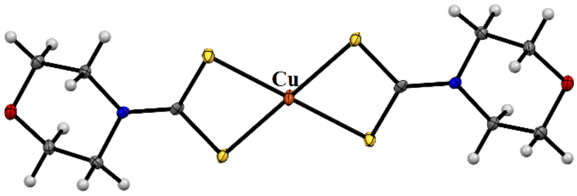


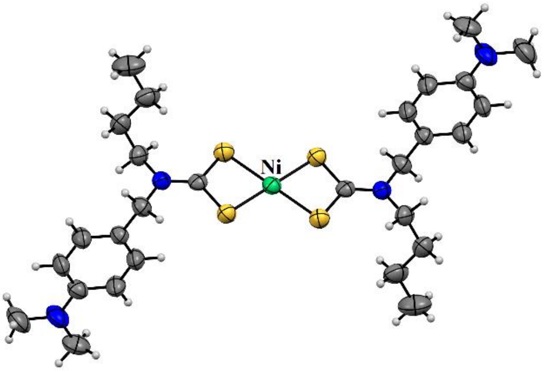


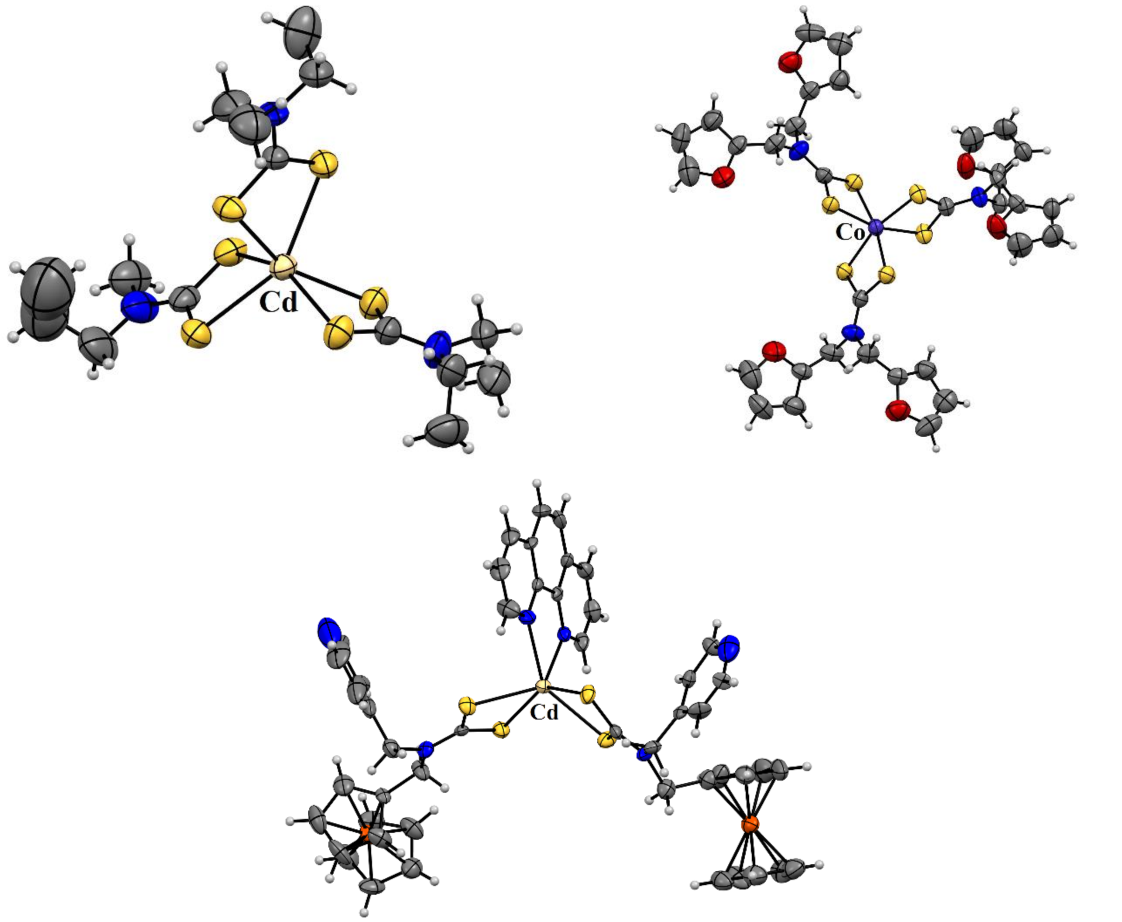
Bidentate mode of dithiocarbamate complexes



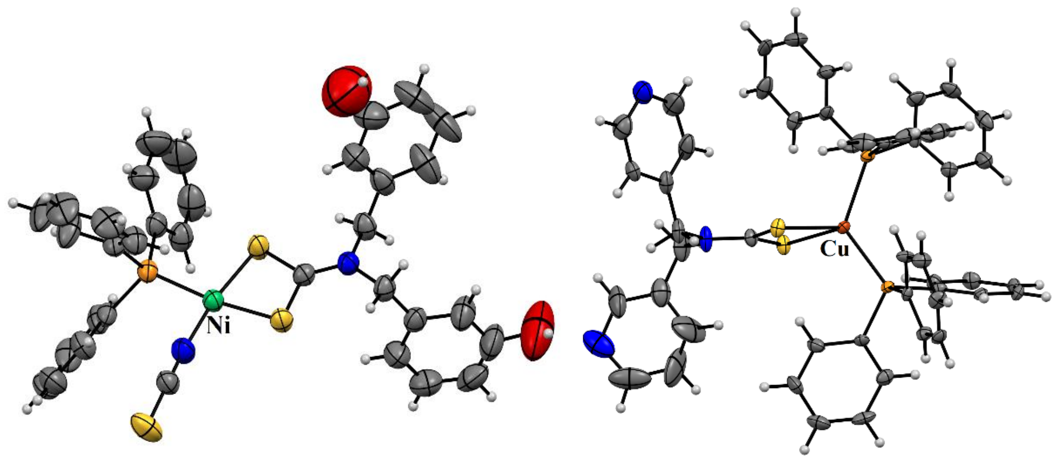






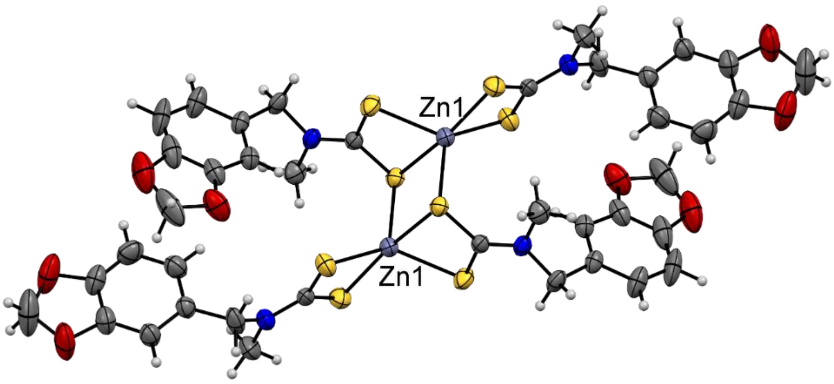


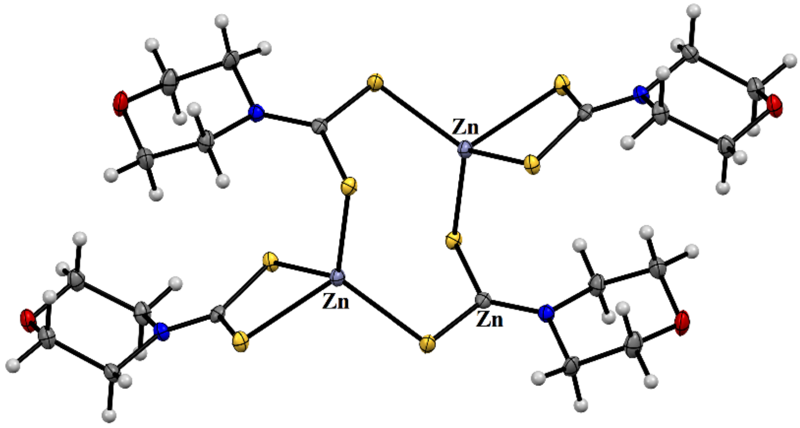
Isobidentate binding mode



It is very interesting to note here that of molecular framework of dithiocarbamate complexes can be bind with different number of metal centres. On this basis, dithiocarbamate complexes can be classified as monometallic, bimetallic and polymetallic dithiocarbamate complexes. Self-assemblies of monometallic dithiocarbamate complexes, ligands are coordinated with single metal centre while monometallic bis dithiocarbamate complexes two ligands are coordinated with single metal centre. In the case of monometallic tris dithiocarbamate complexes three ligands are coordinated with single metal centre. Which are illustrated above. (Table 1)

However, metals like Cu, Zn and Cd are well known to gather two monometallic dithiocarbamate complexes through M…S bonding important to the formation of dimeric species (illustrated below). [27-28]





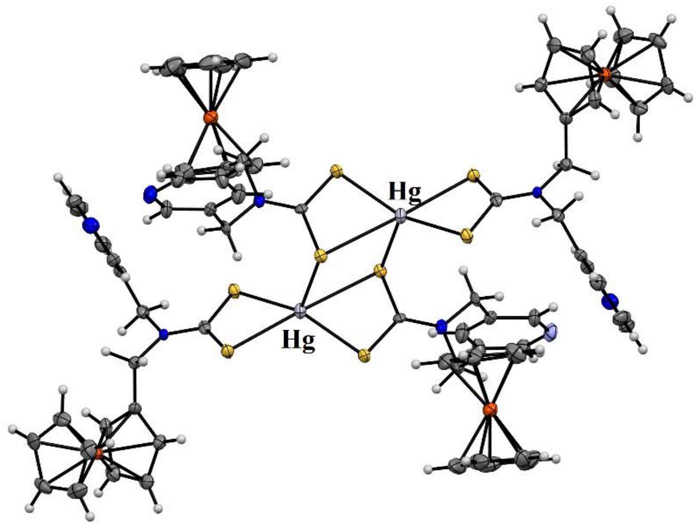


Figure 6. Dimeric species formed through M....S connecting in dithiocarbamate complexes

If ligands are binuclear with flexible spacer, it forms monomettalic macrocyclic dithiocarbamate complexes. Examples of macrocyclic complexes are demonstrated in Figure 7. [29-30]

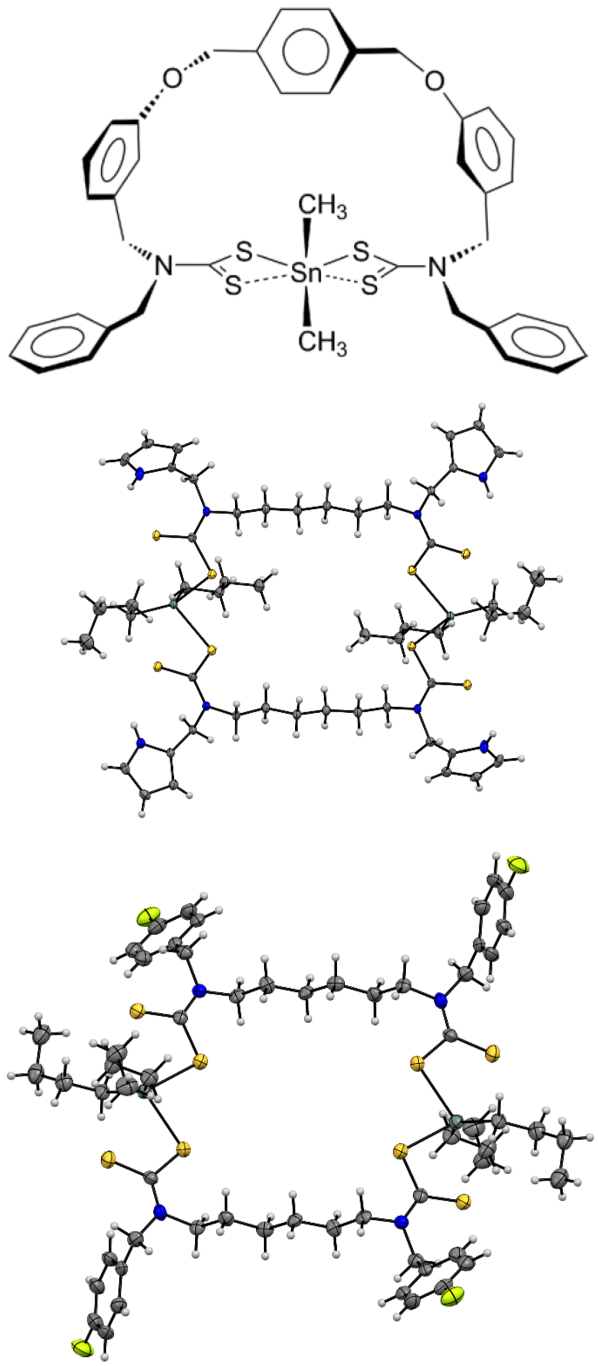


Figure 7. Macrocyclic dithiocarbamate complexes assembly obtained by metal-directed dithiocarbamate ligands.

1.2.4 Application of Dithiocarbamates

Dithiocarbamate ligands have found plenty of uses in coordination chemistry.[31] Dithiocarbamate ligands are more complex compounds consisting of organic sulfur. This may be due to the CSS group's low bite angle, which can interact with most of the transition and non-transition metals in the periodic table and it has the sulfur atoms that can add a single pair of electrons to the central metal atom to form complexes.[32]

Commercial application of dithiocarbamate complexes were used as a fungicide for the first-time during World War II.[33] Other various applications can see that range over a variety of fields such as flotation agents, agriculture (pesticide), biology, materials science, medicine, [34-36] vulcanization accelerators [37-39] and catalysis, [39-41] organic synthesis, photo-stabilizing polymers and protecting radiators.[42, 43] In addition, they are suitable single source precursors for the preparation of corresponding metal sulfides [44-46] which form semiconductor nanocrystals, [47] nanotubes, [48] nanofibers [48] and thin films.[49-50]

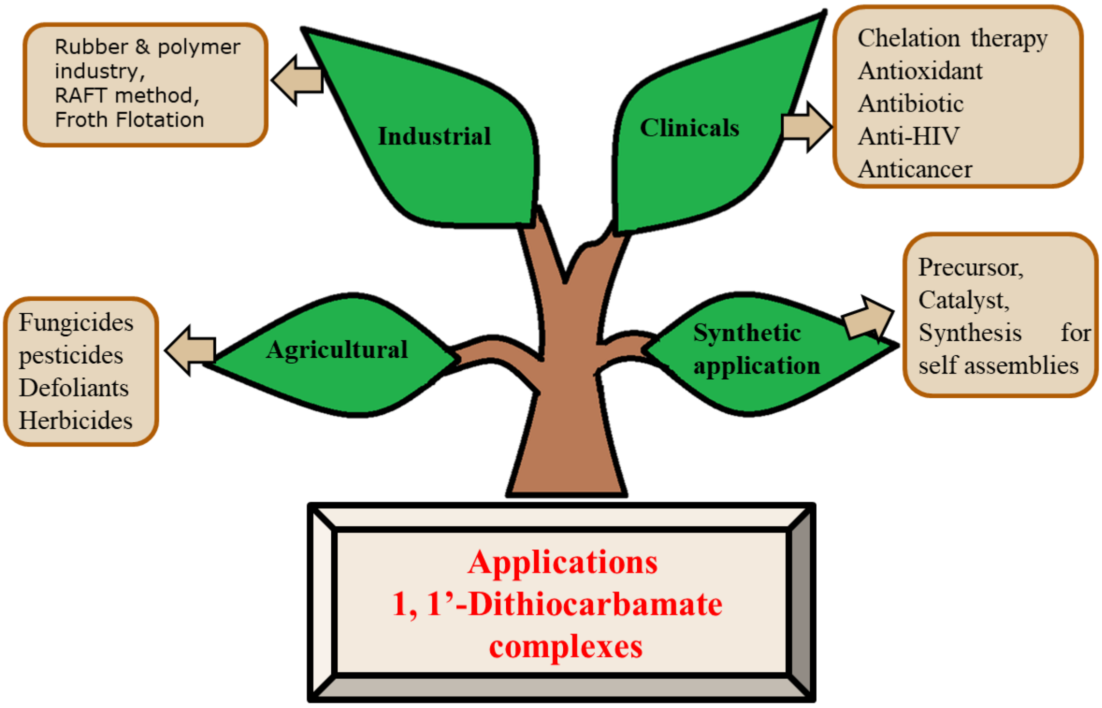


Figure 8. Pictorial representation for applicability of 1,1-dithiocarbamate complexes derived from 1,1-dithio ligands.

1.3 Objectives of the present work

In the light of all these features of self-assembly, efforts have been put into the development of chiral amide functionalized secondary amines and their metal-directed self-assembled dithiocarbamate complexes. The objectives of the current study are briefly specified below:

- To design and synthesize novel chiral amide functionalised secondary amines or diol precursors suitable for the development of chiral bimetallic bis-dithiocarbamate/ macrocyclic bis-xanthate self-assemblies.
- To synthesize bis-dithiocarbamate/bis-xanthate ligands from secondary diamines/diol precursors, carbon disulphide and the presence of a base.
- To investigate the possible reactivity of 1,1-dithio ligands towards transition metal ions.
- To characterize newly synthesized chiral amide functionalized secondary amines and a number of dithiocarbamate complexes from chiral amines, by micro- thermogravimetric analysis and relevant spectroscopic techniques such as mass, IR, ^{1}H, ^{13}C NMR, UV visible.
- To determine of molecular structure of the compounds by means of Single Crystal X-ray Diffraction studies and 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 impact of structural modifications upon the cytotoxic activity of the chiral amines and their dithiocarbamates complexes against human cancer cell lines, MCF 7, IMR 32, HepG2, and immortal L132 cell lines.

1.4 References

[1] Emerging Nanotechnologies in Dentistry Processes, *Materials and Applications Micro and Nano Technologies*, **2012**, 209.

[2] G. M. Whitesides, B. Grzybowski, *Science*, **2002**, 295, 2418.

[3] C. C. Ng, Y. L. Cheng, P. S. Pennefather, *Biophys. J.*, **2004**, 87, 323.

[4] L. Nasalean, S. Baudrey, N. B. Leontis, L. Jaeger, *Nucleic Acids Res.*, **2006**, 34, 1381.

[5] J. Won, S. K. Chae, J. H. Kim, H. H. Park, Y. S. Kang, H. S. Kim, *J. Membr. Sci.*, **2005**, 249, 113.

[6] S. Zhang, Molecular *Elsevier Science, Oxford, UK*, **2001**, 5822.

[7] J. A. Pelesko, Chapman & Hall/CRC, London, **2007**, 5.

[8] S. Zhang, *Nat. Biotechnol*., **2003**, 21, 1171.

[9] G. Hogarth. *Mini-Reviews in Medicinal Chemistry,* **2012***, 12*, 1202.

[10] K. D. Karlin, *Prog. Inorg. Chem*., **2005**, 53, 71.

[11] B. B. Kaul, A. B Pandeya, *Transition Met. Chem*., **1979**, *4*, 112.

[12] M. Sarwar, S. Ahmad, S. Ali, S. A. Awan, *Transition Met. Chem*., **2007**, *32*, 199.

[13] S. Kanchi, P. Singh, K. Bisetty, *Arabian J. Chem*., **2014**, *7*, 11.

[14] J. C. Sarker, G. Hogarth, *Chem. Rev*., **2021**, 121, 10, 6057.

[15] E. Humeres, N. A. Debacher, S. M. Sierra, J. D. Franco, A. Schutz, *J. Org. Chem*., **1998**, 63, 1598.

[16] E. Humeres, N. A. Debacher, M. M. D. S. Sierra, *J. Org. Chem*., **1999**, 64, 1807.

[17] G. Hogarth, *Prog. Inorg. Chem*., **2005**, 53, 71.

[18] W. D. Rudorf, *J. Sulfur Chem.*, **2007**, 28, 295.

[19] J. C. Sarker, G. Hogarth, *Chem. Rev.*, **2021**, 121, 10, 6057.

[20] F. K. Keter, I. A. Guzei, M. Nell, W. E. van Zyl, J. Darkwa, *Inorg. Chem*., **2014**, 53, 2058.

[21] P. Selvaganapathia, S. Thirumarana, S. Ciattini, *J.Mol. Stru*., **2017**, 1148, 547.

[22] L. K. Macreadiea, C. M. Forsythb, D. R. Turnerb, A. S. R. Chesman, *Chem. Commun.*, **2018**, 54, 8925.

[23] G. Gurumoorthya, P. J. Rania, S. Thirumarana, S. Ciattinib, *Inorganica Chimica Acta*, **2017**, 445, 132.

[24] E. Sathiyaraj, S. Thirumaran, S. Selvanayagam, B. Sridhar, S. Ciattini, *J. Mol. Stru.*, **2018**, 1159, 156.

[25] F. F. Bobinihi, D. C. Onwudiwe, E. C. Hosten, *J. Mol. Stru*., **2018**, 1164, 475.

[26] P. Lakshmanana, R. ArulmozhibS.ThirumaranaS.Ciattinic, *Polyhedron,* **2022**, 218,1157.

[27] P. A. Ajibade, F. P. Andrew, N. L. Botha, N. Solomane, *Molecules,* **2020**, 25, 3584.

[28] (a) K. K. Manar, C. L. Yadav, N. Tiwari, R. K. Singh, A. Yadav, M. G. B. Drewd, N. Singh, *CrystEngComm*, **2017**, 19, 2660; (b) A. K. Singha, C. L. Yadava, K. B. Mishrab, S. K. Singhc, A. N. Guptaa, V. K. Tiwaria, M. G. B. Drewd, N. Singha, *Molecular Catalysis*, **2019**, 470,152; (c) V. Kumar. K. K. Manar, A. N. Gupta, V. Singh, M. G. B. Drew, N. Singh *Journal of Organometallic Chemistry*, **2016**, 820, 62e69

[29] M. G. Vasquez-Ríos, V. Reyes-Márquez, H. Höpfl, A. Torres-Huerta, J. Guerrero-Álvarez, M. Sánchez, I. F. Hernández-Ahuactzi, K. Ochoa- Lara, A. Jiménez-Sánchez, R. Santillán, *Eur. J. Inorg. Chem.*, **2016**, 3429.

[30] P. Selvaganapathi, S. Thirumaran, S. Ciattini, *Appl Organometal Chem.*, **2019**, e5089.

[31] (a) P. J, Prog. *Inorg. Chem.* **2005**, 53, 1; (b) G. Hogarth, *Prog. Inorg. Chem.*, **2005**, 53, 71.

[32] Nami S. A., Ullah I., Alam M., Lee D-U., Sarikavakli N., *J. of Photochemistry and Photobiology B: Biology*, **2016**,160, 392.

[33] N. C. Rath, K. S. Rasaputra, R. Liyanage, G. R. Huff, M. E. Huff, Ed., Intech, Rijeka, Croatia, **2011**.

[34] S. D. Oladipo, B. Omondi, C. Mocktar, *Polyhedron.*, **2019**, 170, 712.

[35] F. P Andrew, P. A. Ajibade, *J. Mol. Struct.*, **2018**, 1170, 4.

[36] L. Ronconi, L. Giovagnini, C. Marzano, F. Bettìo, R. Graziani, G.Pilloni, D. Fregona, *Inorg. Chem.*, **2005**, 44, 1867.

[37] L. M. G. Cunha, M. M. M. Rubinger, J. R. Sabino, L. L. Y. Visconte, M. R. L. Oliveira, *Polyhedron*, **2010**, 29, 2278.

[38] P. J. Nieuwenhuizen, A. W. Ehlers, J. G. Haasnoot, S. R. Janse, J. Reedijk, E. J. Baerends, *J. Am. Chem. Soc.*, **1999**, 121, 163.

[39] Z. Trávníček, R. Pastorek, V. Slovák, *Polyhedron*, **2008**, 27, 411.

[40] J. A. Vale, W. M. Faustino, P. H. Menezes, G. F. de Sa, *Chem. Commun.*, **2006**, 31 3340.

[41] P. Pitchaimani, K. M. Lo, K. P. Elango, *Polyhedron*, **2015**, 93, 8.

[42] A. Jayaraju, K. Rameshbabu, J. Sreeramulu, *Ijppr. Human*, **2015**, 4, 241.

[43] X. Hou, X. Li, H. Hemit et al., *J. Coordination Chem.*, **2014**, 67, 461.

[44] D. C. Onwudiwe, P. A. Ajibade, *Mater. Lett.*, **2011**, 65, 3258.

[45] A. M. Paca, P. A. Ajibade, *Mater.Chem. Phys.*, **2017**, 202, 143.

[46] E. Sathiyaraj, G. Gurumoorthy, S. Thirumaran, *New J. Chem*., **2015**, 39, 5336.

[47] F. P. Andrew, P. A. Ajibade, *J. Mol. Struct*., **2018**, 1155, 843.

[48] N. Thammakan, E. Somsook, *Mater. Lett*., **2006**, 60, 1161.

[49] M. D. Khan, M. Akhtar, M. A. Malik, N. Revaprasadu, P. O'Brien, *ChemistrySelect*, **2018**, 3, 2943.

[50] U. Farwa, K. S. Ahmad, Z. Hussain, S. Majid, *Surf. Interfaces*., **2018**, 12, 190.