CHAPTER I

General Introduction

Modern coordination compounds and transition metals play the pivotal role in catalysis, biological and other applications. Over the years, synthesis and application of transition metal complexes have attracted the researchers worldwide for their synthetic and operational flexibility and interesting structural features. Though most of the coordination compounds formed by the organic ligands containing more than fifty percent of carbon, they are included under inorganic chemistry due to involvement of the central metal ion that is accountable for their reactivities. In the biological processes, traces of metals are essential. For the proper folding into an active three dimensional (3-D) structure, 30 - 40 % of all known proteins including metalloenzymes need metal cofactors (e.g., Fe, Cu, Zn, Ni, Mn).[1,2] The reactivity of transition metal complexes can easily be modulated by simply changing the metal ions and their oxidation states as well as the ligand system. Research has shown that the transition metal complexes utilized as drugs to treat several human diseases, *viz.* cisplatin, carboplatin and oxaplatin (Platinum, Pt) as anticancer agents, arsenic trioxide (Arsenic, As) as anticancer agent, auranofin (gold, Au) as anti-rheumatoid agent, ebselen (selenium, Se) as anti-inflammatory agent, scralfate and polaprezincdiabetes (aluminum, Al and zinc, Zn) as anti-ulcer agents.[3,4] Development of transition metal complexes as drugs is not a simple task. Accumulation of free metal ion inside the cell may cause severe side effects.[5] For example, cisplatin is a successful chemotherapeutic drug but its clinical application is limited by its severe side effects such as dose-dependent nephrotoxicity, nausea, vomiting, ototoxicity and neurotoxicity. Another important limitation of the transition metal complexes is that most of them are sparingly soluble in water or they have very limited aqueous solubility. Solubility is one of the main parameters to achieve desired concentration of a drug for obtaining its required pharmacological response.[6] Such sparingly water soluble drugs required high doses to obtain optimal therapeutic plasma concentrations after administration. The low solubility and poor dissolution rate of such drugs in the aqueous gastrointestinal fluids often results inadequate bioavailability. At the site of absorption any drug must be present in the form of an aqueous solution.[7] Despite of this limitation, the use of transition metal complexes as therapeutic agents/drugs has

become more pronounced. Problem of aqueous solubility is a main challenge for the formulation scientist.[8]

Transition metals and their coordination compounds play an important role in catalyzing numerous chemical reactions. In such reactions mixture of water and water-miscible organic solvents such as THF, t-BuOH and DMSO are generally used as solvents.[9] Since most organic solvents like VOCs (volatile organic compounds) are toxic, carcinogenic, flammable, or explosive.[10,11] Their use is associated with safety, health and environmental issues. For example many Palladium-catalyzed C–C coupling reactions have been reported and major drawbacks associated with them are the use of toxic solvents, high temperature and long reaction time, *etc*.[11] From the standpoint of green chemistry, water is the best replacement for organic solvents.[12-14] The major advantages associated with water are its abundance, low cost, no toxicity and non-flammability.[15] In addition, water offers exceptional chemical reactivity and selectivity through its ability to solvate salts and polar compounds.[16] In catalytic reactions, the use of water as a solvent with hydrophilic metal catalysts results into easy separation and recycling of the catalyst from the products. Recently, interest in the exploration of catalytic reactions in neat water is increasing dramatically owing to the advantages such as work-up procedure simplification, reaction rate acceleration. *etc.*, offered by this eco-friendly and naturally available solvent.[17] Hence it is clear that water is the most favorable solvent for its versatile properties regarding catalytic, biological and other applications and hence it is desirable to prepare the water soluble transition metal complexes. The water-solubility of transition-metal complexes can be enhanced by suitable ligand design/ligand modification and thus widening the scope of applicability.[18] Solubility of metal complexes in water can be gained by incorporation of polar substituents such as ammonium or sulfonate side groups.[18] There have been several examples of water-soluble transition-metal complexes based on monodentate alkanesulfonated NHC ligands,[19-22] and the complexes have found applications in (transfer) hydrogenation and regioselective deuteration of aromatic compounds[23] and cross couplings.[24] Along with this type of ligand modification, cyclodextrins (CDs) have also drawn much attention due to their high water-solubility and special hydrophobic cavity. Indeed, CDs, their derivatives and their metal complexes have shown excellent performances in aqueous organic reactions (oxidation, reduction, hydrolysis, hydroformylation, and so on[25], enzyme mimicking, molecular recognition and drug delivery in aqueous medium.[26,27] The necessity of

preparing water soluble metal complexes has motivated the researcher to do further work towards the improvement of novel *β*-cyclodextrin based metal complexes with superior properties. However, the application of *β*-cyclodextrin based metal complexes in catalysis has not been fully explored, especially in aqueous medium and their application in the field of DNA interactions is very rare. Also the studies on their antioxidant property and antibacterial activity are less common. Metal complexes with changeable coordination environments and versatile spectral, electrochemical properties offer a great extent for design of water soluble *β*-cyclodextrin based species that are suitable for catalytic, antibacterial, antioxidant, DNA binding and cleavage activities.

Chemistry of coordination complexes with organic molecules has gained extensive attention throughout the world. Alfred Werner (1866-1919), the Nobel Prize winner was the first scientist who majorly contributed to the discovery of this branch of chemistry by his 'Coordination Theory' in 1913.[28] His coordination theory became one of the greatest milestones in chemistry and influenced other chemists to explore coordination chemistry of metal complexes. The contribution of other pioneers like Lewis, Sidgwick, Linus Pauling, Bethe, Orgel, Jorgenson, Ballhausen and Pearson *etc*, in the structure and bonding are landmarks in the history of coordination compounds. Coordination chemistry is described as the study of the bonding in compounds formed between metal ions (lewis acid) and neutral or negatively charged ligands (lewis base) that donate electrons to the metal. The ligands generally contain oxygen, nitrogen, and sulphur, *etc*, donor sites and they readly form chelates with metal(II) ions through a stable coordinate bond (M → L). Chelation causes dramaic changes in the biological properties of ligands as well as of the metal moiety and in many cases it causes synergistic effects for both metal ion and ligand.[29,30] In coordination chemistry, the modified *β*-cyclodextrin based ligands with several transition metals have found important roles in catalysis, molecular recognition, food and pharmaceutical industries, *etc*.[31] Different synthetic modifications of CD can be accomplished for better complexing ligand molecule. But modification of CD as a ligand has been explored far less in the field of organometallic catalysis for various transformations in aqueous media. Recently, some authors have published articles on the coordination chemistry of *β*-cyclodextin based ligands and their metal complexes.[32,33] Metal ions complexes with cyclodextrins have potentialilty to act as metallo-enzyme models.[34] Because of their many potential applications,[35-40] they

inspired the chemists to choose this field for research particularly for biological and catalytical interests. Metal ion dependent processes are abundant in bioscience and vary tremendously in their function and complexity. It is well known that metal ions control a vast range of processes in biology. There is an increasing interest towards the use of metal complexes with organic chelating molecules as therapeutic agents. Catalysts are highly specific compounds. The specificity of the metal catalysts especially depends on their associated metal ions. In view of all the above facts studies on the coordination chemistry of transition metal complexes with modified *β*-cyclodextrin based ligand systems are very important.

1.1.Biological and Catalytic importance of some transition metals

Catalysis lies at the core of modern synthetic chemistry. 90 % of all commercial chemicals are produced by preparative methods involving at least one catalytic step. Accordingly, the worldwide catalyst market has grown steadily over the past several decades. Transition metal and their complexes have played an important role as catalysts in modern organic[41] and organometallic[42] chemistry, because of their inherent properties like variable oxidation number, ease of complex ion formation and catalytic activities. Metal ions play key roles in about one third of enzymes.[43] The electron flow in a substrate or enzyme can be modified by these ions, thus effectively controlling an enzyme catalyzed reaction. The role of some transition metal ions in biological and catalytic field are therefore given below:

1.1.1. Iron

Iron is one of the common elements in earth crust. Iron plays a main role in forming complexes with molecular oxygen in myoglobin and hemoglobin. Also many important redox enzymes dealing with oxidation, reduction and cellular respiration in plants and animals contain iron at their active sites. Inorganic iron involves in redox reactions in the iron-sulfur clusters of many enzymes, *viz*, nitrogenase and hydrogenase. Non-heme iron proteins include the enzymes ribonucleotide reductase (reduces ribose to deoxyribose; DNA biosynthesis), methane monooxygenase (oxidizes methane to methanol) and hemerythrins (oxygen transport and fixation in marine invertebrates).

Because of low toxicity and low cost of the iron salts, it is attractive as a stoichiometric reagent. In the Haber process of ammonia preparation iron plays the role of catalyst. Iron compounds such as $Fe(acac)_3$ catalyze a wide range of cross-coupling reactions similar to Kumada coupling (the catalysts are based

on palladium and nickel). Fe-Complexes derived from Schiff bases are active catalysts for olefin polymerization.[44] Fenton's reagent (solution of H_2O_2 with typically $FeSO_4$) acts as a catalyst that is used for oxidizing the contaminants of waste waters.

1.1.2. Cobalt

Cobalt is also one of the important trace elements in the world of living systems. Cobalt is an important part of the Corrine ring of vitamin B_{12} and a fundamental coenzyme of cell mitosis. Cobalamin is very much crucial for normaly of the nervous system, formation of red blood cells, DNA synthesis and development of children. Another non-corrin cobalt enzyme is nitrile hydratase, an enzyme in bacteria that is able to metabolize nitriles.[45] Moreover, cobalt is extremely important for forming amino acids and some proteins to create myelin sheath in nerve cells. However, ingestion of higher doses of cobalt over a period of days may affect hemoglobin content and produce polycythaemia and hyperlipaemia. Many cobalt compounds exhibit useful catalytic properties. Pauson-Khand reaction is catalysed by cobalt complex in which [2+2+1] cycloaddition occurs between an alkyne, an alkene and carbon monoxide to form a α,β-cyclopentenone. Cobalt is also acts as catalyst in the Fischer-Tropsch process for the hydrogenation of carbon monoxide into liquid fuels.[46] In hydroformylation of alkenes generally uses cobalt octacarbonyl as a catalyst.

1.1.3. Copper

Copper plays a vital role in human metabolism, because it allows many critical enzymes to function properly, for example, superoxide dismutase (SOD) is one of the example of Copper containing enzyme.[47] Copper is vital for maintaining the strength of the skin, blood vessels, epithelial and connective tissue throughout the body and also for skin pigmentation, brain function and iron metabolism. Copper plays a crucial role in the production of melanin, hemoglobin, myelin and it keeps thyroid gland healthy.[48] Copper can act as antioxidant as well as pro-oxidant. As an antioxidant, Copper scavenges or neutralize free radicals and it may help to prevent the damage triggered by free radicals.[49-52] Maintaining the right dietary balance of Copper, along with other minerals such as zinc and manganese is vital.[49] There are various blue proteins like plastocyanine and azurine containing copper liable for electron transfer in plants and in bacteria respectively. Wilson’s disease occurs as result of copper accumulation in the liver. Copper is relatively economical and efficient metal compared to other transition metals utilized in catalysis in many industrially important

reactions.[53] Several known reactions, such as Click applications, C–N and C-C cross-coupling, C–H functionalization, trifluoromethylations, asymmetric Ullmann and Goldberg couplings, asymmetric acetylide additions to carbonyl groups, radical alkylations and asymmetric conjugate additions, heterocycle synthesis, amide bond formation are cupper catalyzed reactions.[53] Recently, copper based nanoparticles have been found to be the most useful catalysts for various organic transformations.[53]

1.1.4. Zinc

Zinc is known as an essential trace element in biological system. It is involved in numerous stages of cellular metabolism.[54] Zinc is liable for the catalytic activity of more than 200 enzymes.[55,56] It plays a serious role in immune function,[56,57] cellular division,[58] protein synthesis, wound healing,[66] respiration, energy release, sugar metabolism and in alcohol metabolism, DNA synthesis. Zinc is important for correct sensing of taste and smell,[59,60] normal growth and development during pregnancy, childhood, and adolescence.[61-64] Zinc possess antioxidant properties and thus can protect against accelerated aging.[62] Carboxypeptidase and Carbonic-anhydrase are the example of zinc-containing enzymes and they are important to the processes of digestion of proteins and carbon dioxide regulation, respectively. Trace amount of Zinc ions can acts as potent antimicrobial agents. Cells within the exocrine gland, prostate, immune system and intestine communicate with other cells through Zn signaling.[65] Within the brain, glutamatergic neurons store zinc in specific synaptic vesicles and may modulate brain excitability.[66] However, excess intake of zinc often causes nausea, vomiting, colic, diarrhoea, lethargy, loss of appetite, stomach cramps, headache and peripheral neuritis resulting to paralysis.[47]

Organozinc compounds are widely utilized in different types of reactions in organic chemistry, *e.g,* Reformatskii reaction, Negishi reaction, Frankland–Duppa reaction, Fukuyama reaction, *etc*.[67] Additionally, the merits of zinc catalysts for the reactions,viz, aldol reaction, Mannich reaction and Henry reaction have been proved by extreme literature.[68] Zinc catalyzed C-N bond and C-O bond formation was also reported in the literature.[69]

1.1.5. Palladium

Palladium has no well known biological roles. Recently, several Pd(II) complexes with promising anticancer activity against tumor cell lines are reported.[70]As acrucial feature of metal-containing anticancer agents, Pd complexes are expected to have less nephrotoxicity than cisplatin.[70,71] As many new Pd

complexes containing amine ligands may have promising anticancer activities with lower side effects, they will find potential applicability in medicinal field.[70-71]

Palladium-catalysed reactions have had a huge impact on organic synthesis and have several applications in target-oriented synthesis. Their extensive use in organic synthesis is because of the mild conditions related to the reactions together with their tolerance to a good range of functional groups. Several reactions, such as Suzuki–Miyaura, Sonogashira, Mizoroki–Heck cross-coupling reactions and glaser reaction, which are catalyzed by palladium in routine organic syntheses.[72]

1.2. Cyclodextrin

Cyclodextrins are obtained from the enzymatic degradation of starch by glycosyltransferase enzyme. They are also known as Schardinger dextrins, cycloamyloses and belong to the family of cyclic oligosaccharides possessing of α-1,4-linked glucopyranose units. Depending on the number of glucopyranose units present in cyclodextrin (CD) structures, they are named as *α*-CD (containing 6 glucopyranose units), *β*-CD (containing 7 glucopyranose units) and *γ*-CD (containing 8 glucopyranose units) (as shown in Fig 1.1). The study of the crystal structure of cyclodextrins has indicated that all glucose moieties in the ring possess the thermodynamically favoured $^4C_1$ chair conformation and all substitutions in the equatorial position. The cyclodextrins are not proper cylindrical molecules but are toroidal or cone shaped because of the absence of free rotation about the bonds connecting the glucopyranose units.

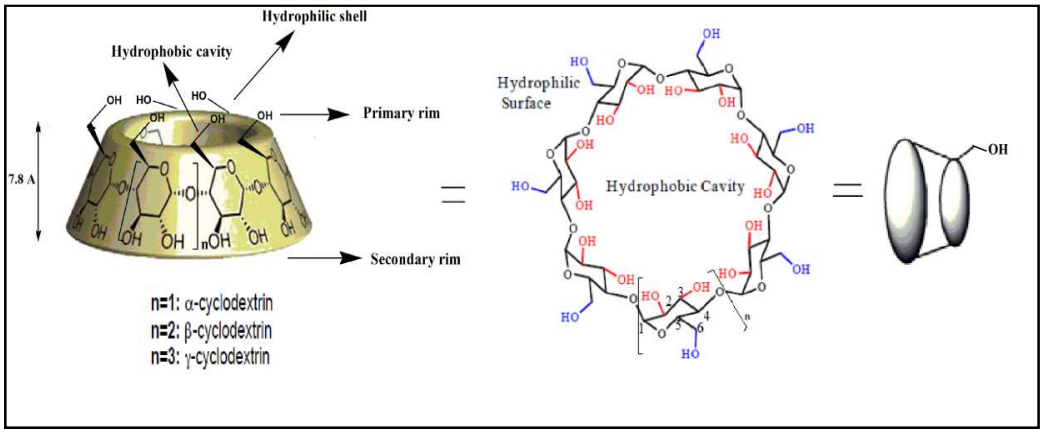

Fig 1.1. Schematic representation of the structural characteristic of cyclodextrins.

In the structure of cyclodextrins, the primary hydroxyl groups (6-OH) are sited on the narrow side of the torus while the secondary hydroxyl groups (2-OH and 3-OH) are sited on the wider edge. Due to the presence of hydroxyl groups the outer surface of a

cyclodextrin is hydrophilic in nature; where as its inner cavity lined with ether-like anomeric oxygen atoms is hydrophobic. Such property makes the cyclodextrins cavity a useful tool, for the inclusion of guest molecules of various types generally with non-polar groups. The cavity diameters (maximum values based on the Van der Waals radii) are 5.0, 6.2, and 8.0 Å for α-CD, β-CD and γ-CD, respectively. The conformations of cyclodextrin in solution and in crystalline state are almost identical.[73] Cyclodextrins are stable under alkaline conditions and cleaved by acid hydrolysis. Glucose is produced in the acid hydrolysis of the cyclodextrins. Cyclodextrins are chiral due to the existence of asymmetric carbon atoms on the glucose units and glycosidic bridges between the glucose units. The hydroxyl groups on the primary side and secondary sides of cyclodextrin are nucleophilic in nature and these group can be modified with different functional groups like aldehyde, alkanedioates, disulfides, amino, dipyridines and imidazole, *etc.*[74-81]

Owing to the relatively apolar cavity compared to the polar exterior, cyclodextrins can form inclusion compounds with hydrophobic guest molecules in aqueous solutions because of hydrophobic interactions.[82,83] To form the inclusion complexes the 1st requirement is hydrophobic interactions and 2nd requirement is that the guest molecule must be able to fit in the cavity of the cyclodextrin. It must be highlighted that the formation of inclusion compound is an intricate process and various factors also take decisive roles.[84] This is demonstrated by the fact that not only apolar compounds but also acids, amides, small ions and even rare gases can be included.[85,86] Small molecules generally form 1:1 inclusion compounds with one cyclodextrin ring. Partial inclusion of a guest with the cyclodextrin ring is also possible. This occurs when size of the guest molecules is larger than the cavity of inclusion. Depending upon the size and nature of guest molecules different types of inclusion compounds can be formed as shown in (Figure 1.2).

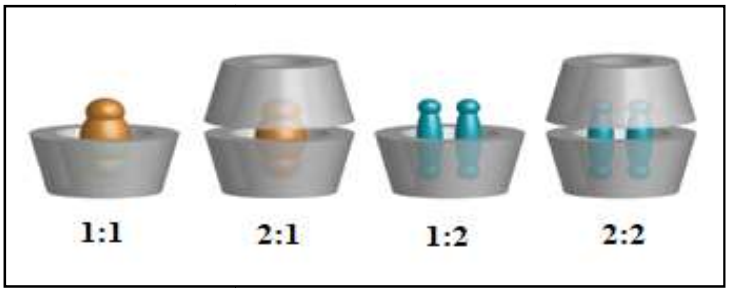

Fig 1.2. Schematic illustration of different types of inclusion complexes between cyclodextrin (Host) and substrate (guest).

Cyclodextrin may change some of the physical and chemical properties (such as solubility, stability, taste, smell) of the guest molecule through the formation of inclusion complexes and thus leads to a large number of applications related to analytical chemistry, food technology, pharmaceutical chemistry, chemical synthesis, catalysis, *etc*.[87]

1.2.1. Functionalization

A hydrophilic exterior is formed by two rims of hydroxyl groups surrounding the hydrophobic molecular cavity. Various functional groups can be covalently bonded to the hydroxyl groups.[88,89] When the hydroxyl groups are modified, the complexation behavior of cyclodextrins are altered and thus it is possible to create cyclodextrin based polydanted ligands and on reaction with transition metals they can form water soluble metal complexes. Selective modification of cyclodextrins with catalytic and biologically active groups can initiate activities in aqueous phase organic synthesis and in biological systems. That's why several functional groups were placed on the periphery of cyclodextrins for specific purpose.[90,91]Functionalization of cyclodextrins can be performed with complete sets of hydroxyl group or this partial functionalization *e.g*, monofunctionalization, functionalization of one particular –OH group. Monofunctionalization of β-CD is discussed below:

1.2.1.1. Approaches to selective modification of cyclodextrins

Modifications of CDs are performed by modifying the hydroxyl groups and since these are nucleophilic in nature, the initial reaction involves an electrophilic attack on these groups. However, due to their abundance and similarity, these hydroxyl groups compete for the reagent and make selective modification tough. Of the three types of hydroxyl groups (hydroxyl group at C2-, C3- and C6), hydroxyl groups at the 6-position are the most basic and often most nucleophilic, those at the 2-position are the most acidic (p*Ka* ~ 12.1) and those at the 3-position are the most inaccessible shown in (Figure 1.3).[92]

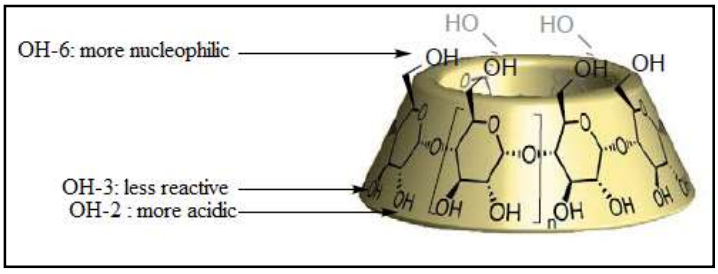

Fig 1.3. Schematic illustration of different –OH groups of cyclodextrins.

1.2.1.1.1. Primary face monomodification

Primary hydroxyl groups are more nucleophilic than their secondary counterparts; they are easily modified into other functional groups. There are some paths by which mono modification of CD occurs (shown in Figure 1.4).

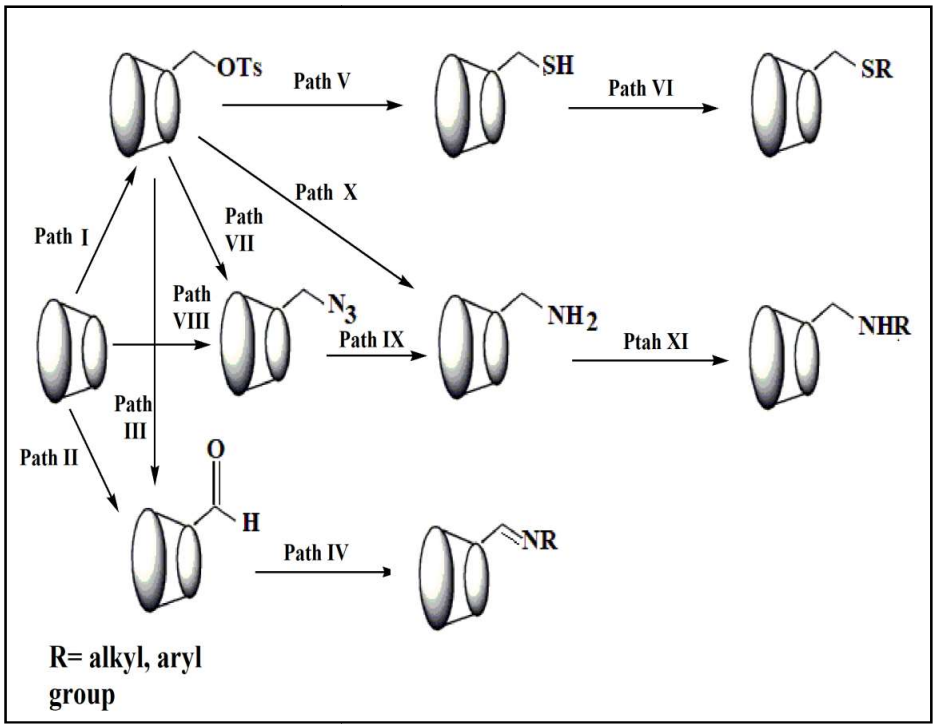

Fig 1.4. Different pathways for the mono-modification at the C6-position of *β*-CD.

Mono-6-Tosyl-*β*-CDs are important precursors for a variety of modified CDs. Monosubstitution at the 6-position is most commonly achieved by nucleophilic attack on mono-6-Tosyl -CDs. The most popular path for mono-6-CD tosylation (notably β-CD) is through the reaction of the CDs with *p*-toluenesulfonyl chloride in alkaline solution,(Path I in Fig 1.4)[92] with reasonable yield and purity. Starting from mono-6-Tosyl-*β*-CDs, the subsequent nucleophilic displacement of the tosyl group by suitable nucleophiles results into monoiodo-, azido-, thio-, hydroxyamino- or alkylamino-CDs.[92] Modifications of C6 of CD other than by tosylation are very rare. However, a single-step synthesis of CD monoaldehydes has been published. Dess–Martin perodinane was added to the solution of CD (dissolved in an organic solvent) and stirred for 1 h at ambient temperature. Addition of acetone and cooling allowed isolation of the crude product by filtration (Path II in Fig 1.4).[92,93,94] The monoaldehyde has been synthesized by oxidizing mono-6-Tosyl-*β*-CD using DMSO (Path III in Fig 1.4).[95,96] Hydroxylamine or hydrazine on reaction with mono-6-

aldehyde-CD produce a monooxime or a monohydrazone derivatives (Path IV in Fig 1.4).[96] Mono-6-mercapt-*β*-CD has been synthesized from mono-Tosyl-*β*-CD (Path V in Fig 1.4).[97] This compound was then combined with tri- or tetravalent carbosilane bromide and any alkyl or aryl bromide in liquid ammonia to obtain different CD derivatives as a new core substance for the construction of a variety of functional materials (Path VI in Fig 1.4).[97,98] Monoazides of CD are indirectly obtained by heating the monotosylate with sodium or lithium azide salt in DMF (VII in Figure 3).[99] A direct azidation of CDs with sodium azide by reduction with triphenylphosphine–carbon tetrabromide in aqueous ammonium medium has also been reported (Path VIII in Fig 1.4).[100] Monoamino derivatives of CDs are also obtained from monoazides of cyclodextrin (Path IX in Fig 1.4).[100] The monoamino derivative of CD is also obtained from mono-Tosyl-*β*-CD with reaction of different amines in presence of Dimethylformamaide (DMF), Dimethylaminopyridine (DMAP) and Pottasium iodide (KI) (Path X in Fig 1.4).[101] Monoamines are invaluable in attaching desired groups to the primary side of CDs via N, N′-dicyclohexylcarbodiimide (DCC) coupling technology (XI in Fig 1.4).[102] This strategy has been used to connect various sugar units such as *α*-D-glucose, *α*-D-galactose, R-D-mannose, and *α*-D- and L-fructose to cyclodextrins through alkyl chains. Solution of D- or D-*N*-dansylleucine in DMF containing 1-hydroxybenzotriazole and DCC on reaction with monoamines at ambient temperature form D- or L-mono-6-(*N*-dansylleucylamino)-6-deoxy-*α*-cyclodextrin with 50% yield.[103]

1.2.1.1.2. Secondary face modification

Presence of twice the number of hydroxyl groups in secondary side of CDs makes this side more crowded than that of the primary side. The hydroxyl groups at the 2- and 3-positions are more rigid and less flexible than hydroxyl groups at the 6-position due to hydrogen bonding between them. All these factors make the secondary side less reactive and harder to selective functionalization than the primary face. Modification at the wide rim by *p*-toluenesulfonyl chloride in DMF with dibutyltin oxide and triethylamine as catalysts often involves sulfonation at the 2-position. The elimination of the tosyl group at the 2-position affords the 2,3- manno-epoxide CDs, and this is its turn can affort to further nucleophilic attack to yield 3-substituted CDs. Methods to achieve selective mono- and poly-substitutions of CDs at either 2-, 3-, or 6-position are also reported.[92]

1.3. Functionalized *β*-cyclodextrin as ligand and their metal complexes

Functionalization of the hydroxyl groups of CD with various functional groups can bring proper coordination sites into action and thus CDs can acts as polydanted ligands. Most of CD derivatives with different binding sites reported in literature have been obtained by modifying the primary sites, mainly involved with the modification on the *β*-CD.[104] The mono-6-tosyl-CD is generally synthesized as precursor in order to obtain monofunctionalized CDs. A nucleophilic displacement of the tosyl group of mono-6-tosyl-CD by suitable nucleophiles (such as iodide, azide, thioles, hydroxylamine, carboxylate, amines and polyamines) is the next reaction step to obtained monofunctionalized CDs. The general synthetic route of the formation of monofunctionalized CDs is shown in Figure 1.5.

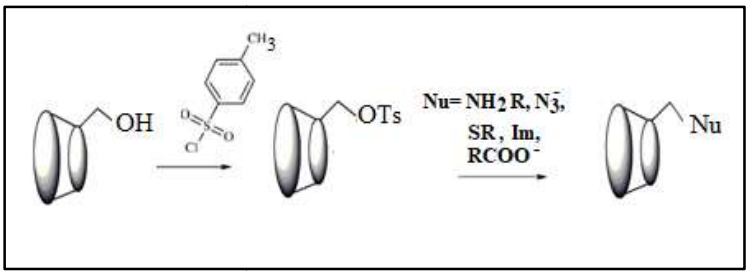

Fig 1.5. Tosylaton of CD and subsequent nucleophilic displacement of the tosyl group.

For example, amino cyclodextrins are known to be efficient ligands for first-sphere coordination of metal ions. The presence of lone pair of electrons in nitrogen atoms of $-NH_2$ or –NH- group can make these groups doner sites. But only the presence of such groups in cyclodextrins is not sufficient for being good chelting ligand but when amino group is connected with aromatic aldehydes having effective conjugated systems or when in combination with one or more donor atoms close to the amine groups cyclodextrins become excellent chelating agent. In general, the donor nature of the ligand depends on both the type of amines employed and the compound (generally carbonyl compound) that reacts with the amine group of amino functionalized CDs for increasing number of donor sites. Such modified cyclodextrins may act as bi-, tri-, tetra- or polydentate ligands depending on the number of donor sites present in their structure. Some illustrations examples are given below in Figure 1.6. A number of these selectively functionalized CDs possesses N, S, O donor sites and have a variety

of applications such as enzyme mimics, miniature devices, sensors, catalysis and drug delivery systems.

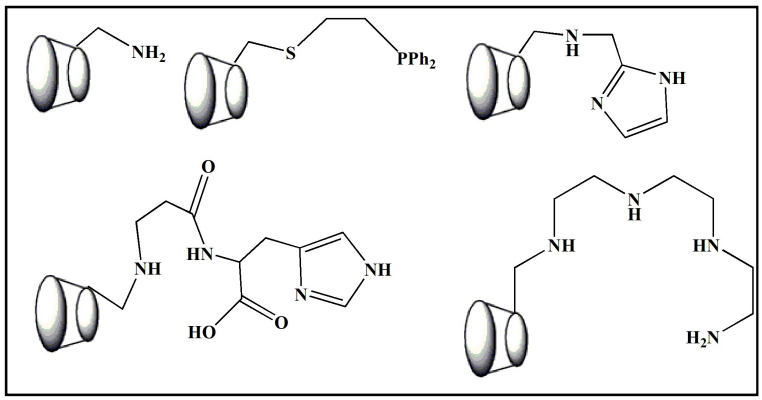

Fig1.6. Some modified CDs used as chellating agents.

Salen functionalized CD which derived from diamino-CD family also acts as ligands. When the $–NH_2$ group of amino cyclodextrin is condensed with different types of aldehyde salen functionalized β-CDs results. Some examples of salen functionalized β-CDs used as ligands are depicted in Figure 1.7.

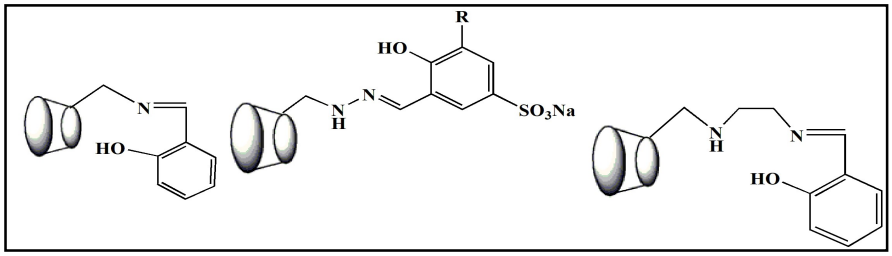

Fig 1.7. Some Salen functionalized CDs used as chelating ligands.

In addition to these, a large number of *β*-CD dimer with linker containing dimethyl amino pyridine, 1,10 phenanthroline 2,9-aminomethyl, ethelynediamine, bypyridyl, terephthalate group, *etc.*, were prepared and they find wide range of applications in the development of supramolecular chemistry.[105] A few examples of *β*-CD dimer are depicted in Figure 1.8.

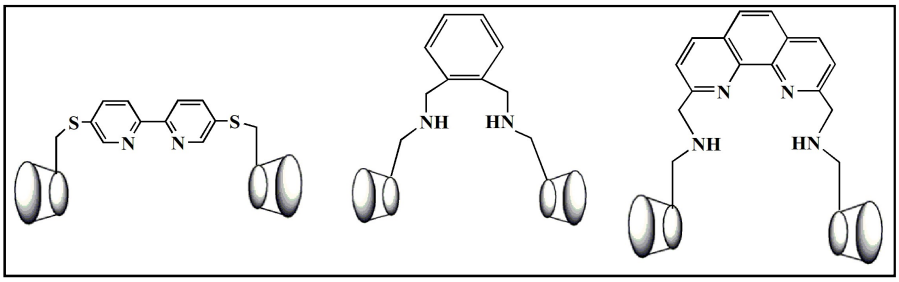

Fig 1.8. Some *β*-CD dimer linked with different functional group used as chelating ligands.

Functionalized *β*-CD have a number of applications, *viz.*, enzyme mimics, miniature devices, sensors, supramolecular and drug delivery systems, abiotic receptors, fluorescence indicators and molecular actuators and catalysis, *etc*. In salen functionalized *β*-CD derivatives, the (-HC=N-) linkage is essential for biological activity and several azomethine compunds were reported to possess remarkable antibacterial, antimalerial activities.[106] If a cyclodextrin dimer has a catalytic group in the linker, one might observe strong catalytic activity. Attachment of a simple catalytically active group to a cyclodextrin can afford interesting enzyme mimics. Amino- and polyamino-cyclodextrins have significant catalytic activities. Amino-cyclodextrins can catalyze or inhibit catechol autoxidation,[107] they can act as catalysts for decarboxylation,[108] and aldol condensations.[109,110]

Normally CDs are inefficient first sphere ligands, but there ligating properties can be improved by deprotonation of the hydroxyl groups at high pH. The metal binding ability of modified CDs also depends on the conformation of a pendant group and its interaction with the hydrophobic cavity.[111] In addition, appropriate functionalization permits the complexation of a metal ion to further improve their potential applications especially in the field of chiral recognition and of metalloenzyme mimicking.[112] On the contrary, the requirements of a particular geometry for the metal complex can be a driving force for the inclusion of guest into the CD cavity.[113] The nature of the metal is another parameter that controls the stability of modified CD complexes. Usually, experimental data on the characterization of functionalized CD complexes with several metals[114,115] are consistent with the Irving–Williams series.[116] An exception is showed by CDs modified at the primary rim with imidodiacetate (CDida).[117] In this case, the steric hindrance of the cavity and the coordination of a primary hydroxy group may be the cause of its unusual metal binding behaviour.[117]

Matsui *et al.* were the first to report the formation of a metal-CD complex with the metal ion coordinated directly to the cyclodextrin.[118] Figure 1.9 shows the proposed binuclear hydroxyl-bridged structure for this complex.

Nair and Dismukes[119] prepared a complex of *β*-CD with Mn(III) with a Mn:CD ratio of 2:1. The electronic and vibrational spectroscopy results suggested a bridged structure similar to that proposed by Matsui *et al*.[118]

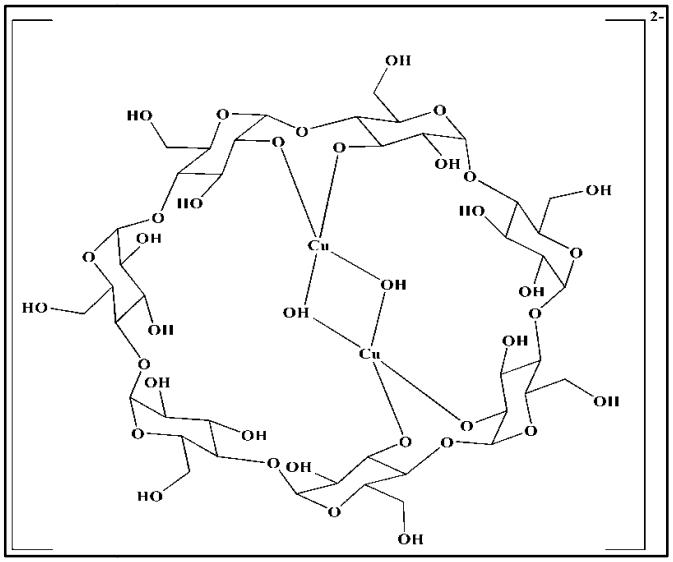

Fig 1.9. First reported metal-CD complex in which metal ion is directly coordinated to the cyclodextrin.

Modifying cyclodextrins can also allow themself to act as first sphere ligands for metal coordination. These derivatised CDs have been used as metallo-enzyme mimics and as catalysts. Breslow and Overman prepared the nickel(II) chelate of an *α*-CD ester of pyridine-2,5-dicarboxylic acid (Figure 1.10; 1).[120] The electron donating nitrogen and oxygen atoms allow for the coordination of the metal ion. This derivative was further developed by Szejtli and Pagington resulting in "Breslow's Enzyme" (shown in Figure 1.10; 2) that can increase the rate of hydrolysis of *p*-nitrophenylacetate over 1000-fold.[121]

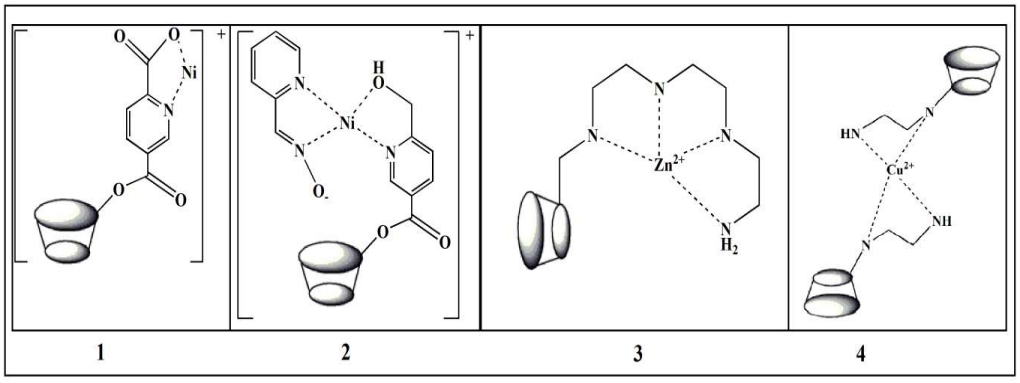

Fig 1.10. Metal complexes of cyclodextrin based polydantate ligands:1, Ni^{2+}-complex of an *α*-CD ester of pyridine-2,5-dicarboxylic acid; 2, Breslow's Enzyme; 3, Zn^{2+}complex of polyamine functionalized *β*-CD; 4, Cu^{2+}complex of 6-deoxy-6-[1-(2-amino)ethylamino]-*β*-cyclodextrin (CDEn).

Almost at the same time, Pioneer work was also reported by Tabushi's group, including *β*-CD complex functionalized by polyamines with $Cu^{2+,}$ Zn^{2+} or Mg^{2+} as

metal ions (Zn Complex is shown in Figure 1.10; 3).[122] Nitrogen-modified cyclodextrins have been reported to be particularly efficient ligands for first sphere coordination of various metal ions. Matsui *et al.* reported the synthesis of the Cu(II) complex with 6-deoxy-6-[1-(2-amino)ethylamino]-*β*-cyclodextrin (CDEn) derivative at pH of 10.5 (shown in Figure 1.10; 4).[123] Bonomo *et al.* showed the formation of 1:1 complex of CDEn and Cu(II) at pH 7.8 and this complex showed some enantiomeric stereo-selectivity towards amino acids.[124] Brown *et al.* reported same type of selectivity using a range of metal centres (Co(II), Ni(II), Cu(II) and Zn(II)) with a diaminopropane derivative of *β*-CD (CDPn).[125]

Metal complexes of functinalized cyclodextrins are generally prepared by treating metal salts with modified ligands under suitable experimental conditions. An elaborate discussion on the synthesis and characterization of functinalized cyclodextrn based metal complex are available in numerous literature.[120-127] Guofu Zhang *et al.* synthesized triazolyl β-cyclodextrin supported palladium complex (PdLn@β-CD) by treating the obtained ligand with $Pd(OAc)_2$ in anhydroustoluene for 12 h (Figure 1.11).[126]

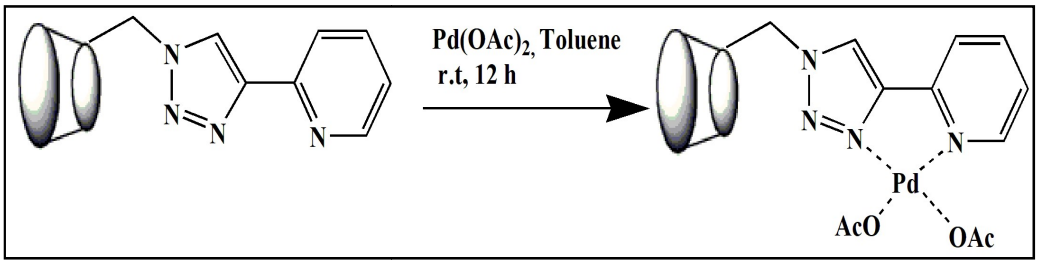

Fig 1.11. Metallation process of triazolyl β-cyclodextrin supported ligand with $Pd(OAc)_2$.

Liu *et al.* reported Cu(II) complex of novel triethylenetetraamine-tethered bis(*β*-cyclodextrin) by reaction with aqueous solution of a slight excess of copper(II) perchlorate (Figure 1.12).[127]

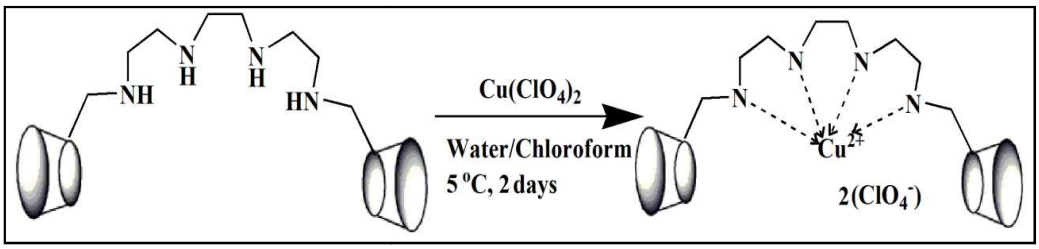

Fig 1.12. Metallation process of novel triethylenetetraamine-tethered bis(*β*-cyclodextrin) ligand with $Cu(ClO_4)_2$.

1.4. Catalysis

The production of most industrially important chemicals involves catalysis. Most of our liquid fuels and about 80% of the chemical products are manufactured with the aid of catalytic conversions. The continuing increase of the quality of the chemical products and the steadily decreasing production costs of bulk and fine chemicals can be ascribed to a great extent to improvements in catalytic systems. Chemical reactions with a half-lifetime as long as centuries can be accomplished in minutes or hours by the use of a catalyst. The general feature of a catalyst is that it provides a reaction pathway with lower free energy change to the rate-limiting transition state than the corresponding non-catalyzed reaction, thus increasing the rate of a reaction. The term '*catalysis'* was first proposed by Berzelius in 1836 when he had noticed changes in substances when they were brought in contact with small amounts of certain substances later termed as 'catalysts'.[128] The definition that nowadays is used to reads: "A catalyst is a substance that increases the rate of a chemical reaction without being consumed in the process". It can open a precise route to the desired product using fewer resources and generating less waste. Depending on the nature of reactants and catalysts used the catalytic process can be divided into two types: 1) Homogeneous catalysis and 2) Heterogeneous catalysis.

1.4.1. Homogeneous catalysis *vs.* heterogeneous catalysis

In homogeneous catalysis the reactants and the catalysts are in the same phase such as liquid or gaseous phase and are together with the reactants in the reaction medium. In heterogeneous catalysis, the catalyst is in a different phase from the reactants and products. Homogeneous catalysts have numerous advantages with respect to the heterogeneous counterparts.[129,130] They generally display very high activities, very high selectivity and the reaction is not limited by mass transfer. Despite all these advantages the basic problem with homogeneously catalyzed processes is the separation of the catalyst from the products. The processes necessary to achieve this usually include thermal operations such as distillation, decomposition, transformation and rectification, and may lead to thermal stresses on the catalyst. These can cause decomposition reactions and progressive deactivation during the lifetime of the catalyst. But in heterogeneous catalysis the separation of catalyst from product is easy as they are in different phase.

1.4.2. Heterogeneous catalysis of water soluble metal complexes

Since catalyst-product separation is a major problem with the homogeneous reactions, heterogenization of the catalyst is in vogue for the last couple of decades. Various ways have been attempted for heterogenization. The homogeneous metal complex catalysts are heterogenized on to a solid support, by binding on modified silica, polymer (polyethylene glycol) and other functionalized supports (sulfonate salt or quaternary ammonium salt), *etc*.[131] The catalysts are also heterogenized into a second immiscible in aqueous liquid phase as in biphasic catalysts using water, ionic liquids, and perfluorinated solvents *etc*.[132] This concept involves selection of two liquid phases, such that the catalyst is soluble in only one phase, while the product present in other phase. The substrate should have finte solubility in the catalyst phase, so that obtain reasonable reaction rate while being immiscible with catalyst phase. The recent development of water soluble metal complexes has made it feasible to conduct reactions in the biphasic mode to gain easy separation of the catalyst and products. Product separation is simpler for two-phase systems incorporating water-soluble catalysts.[133]

Generally the hydrophilic catalyst, which is insoluble in the organic product phase, is an (organometallic) coordination complex and as such is molecularly well defined like conventional homogeneous catalysts.[133] It brings about the catalytic reactions (*e.g.*, *C*-*C* coupling) in the aqueous phase or at the phase boundary and is removed from the desired product at the end of the reaction by a simple phase separation.[133] Thermal separation processes can have a detrimental effect on the active life of the catalyst and are thereby avoided. Because of the high polarity of the water-soluble catalyst and its consequent insolubility in the organic phase, the loss rate is often below the limit of detection. Recently, interest in the exploration of catalytic reactions of water-soluble ligands and their metal complexes in neat water is increasing dramatically due to advantages such as reaction rate acceleration, easy work-up procedure and catalyst separation *etc.*, offered by this green and naturally available solvent.[134] So, it is a challenge for the researchers to prepare water soluble metal complexes with catalytic potentiality. For example Nehra *et. al* synthesized a novel palladium complex of imidazolium ionic liquid-tagged Schiff base complex and explored its catalytic activity for the Heck and Suzuki reactions in aqueous media.[135] Wei *et al.* reported SiO_2-supported imidazolium ionic liquid-immobilized Pd-EDTA as an efficient and reusable catalyst for the Suzuki reaction in water.[136]

Furthermore, native β-CD has been widely used as a host and catalyst for various transformations in aqueous medium.[137] Selectively modified cyclodextrins are currently used as sensors as well as catalysts.[31,138]Aminomodified β-CD compounds are employed as biomimetic catalysts for Kemp elimination,[139]deprotonation,[140] and chiral-recognition processes.[141] Amino modified cyclodextrins and their metal complexes are known to be efficient ligands for first-sphere coordination of metal ions and their complexes are used in aqueous organometallic catalysis.[31,142] Aminocyclodextrin/$Pd(OAc)_2$ complex as an efficient catalyst for the Mizoroki–Heck cross-coupling reaction.[143] These types of newly developed systems represent an efficient and environmentally benign coupling protocol and are inspiration for the design of water-soluble catalysts to mediate aqueous organic reactions. However, the application of hydrophilic CD derivatives as ligands in organometallic catalysis has not been fully explored, especially for aqueous phase coupling reactions.

1.5. DNA

The determination of the structure of DNA by Watson and Crick in 1953[144] is often said to mark the birth of modern molecular biology and is of high importance since it provides the foundation for the central molecule of life. The strands of DNA are composed of an alternating sugar-phosphate backbone consisting of deoxyribose sugar groups and phosphodiester groups. A series of heteroaromatic bases project from the sugar molecules in this backbone. There are two types of bases that occur in DNA –a) the purine bases, guanine (G) and adenine (A) and b) the pyrimidine bases, cytosine (C) and thymine (T). The two anti-parallel strands of nucleic acid that form DNA can assume several distinct conformations.[145] The two strands are held together primarily *via* Watson Crick hydrogen bonds where adenine (A) forms two hydrogen bonds with thymine (T) and cytosine (C) forms three hydrogen bonds with guanine (G). The DNA double helix is further stabilised by π-π stacking interactions between the aromatic rings of the base pairs.[146] The asymmetry of the bases gives rise to minor and major grooves along the DNA helix.

1.5.1. Modes of DNA interactions with of transition metal complexes

DNA is the main intracellular target of anticancer drugs, so interaction of small molecules with DNA has gained much attention.[147,148] Many small molecules that bind to DNA have been clinically proven to be therapeutic agents which inhibit the proliferation of cancer cells by causing DNA damage and blocking their division.[147] Two common modes of covalent interaction between small molecules and

DNA have been found: 1) Irreversible covalent binding between the different nucleophilic sites in DNA either phosphate back bone or ring nitrogen bases which is known as Mono adduct (base or phosphate binding) and 2) covalently crosslinked with the nucleotide residues of the same DNA strand (intrastrand cross link) or from opposite strands (interstrand crosslink). Sometimes inter helical DNA cross linking may happen.[149] Along with the above two common modes of covalent interaction there are three common modes of noncovalent interactions between DNA and small molecules: (1) interactions (electrostatic) with the negatively charged phosphate backbone, (2) binding interactions with the minor and major grooves of DNA double helix, and (3) intercalation between the stacked base pairs of double-stranded DNA resulting to perturbation in DNA structure.[148] According to strength of the interaction, the binding of these molecules with DNA can be categorized into strong interactions and weak electrostatic attractions. The intercalation into adjacent base pairs in DNA strands, hydrogen bonding and reciprocal association of hydrophobic region between the ligands and DNA strands are typical examples of strong interaction.[150.] The major grooves and minor grooves in the DNA structure are generally binding sites for groove binders that fit into grooves causing little perturbation of DNA structure. The selective binding and damaging capabilities of DNA by transition metal complexes were investigated by various number of experiments, owing to their possible applications as cancer therapeutic agents and their photochemical properties make them potential probes of DNA structure and conformation.[151,152] Metal complexes can cleave the DNA through hydrolytic, oxidative and photolytic cleavages types of mechanisms.[153-155] In recent years, the study of interactions between transition metal complexes and DNA have gained much attention due to their possible applications in cancer therapy and molecular biology.[156-159]

DNA is the primary target molecule of many anticancer agents and the binding between DNA and metal complexes can be used in understanding the interaction between the drugs and DNA. In general, the tumour cells can be destroyed by stopping the replication of the unnatural DNA. The degree of variability of transition metal complexes imparted by the metal, its oxidation state, coordinated ligands, overall size and shape of the complex allows for a high degree of selectivity towards numerous biological targets.[160-163] Dwyer realized that the diversity of coordination metal complexes could be used to provide insight into the structure of biomolecules.[164,165] The coordination geometry of the metal and the orientation of the

ligands on the binding site show the influence on metal complex-DNA interactions. For example, the most widely used anticancer drug planner *cisplatin* obtains its cytotoxicity by forming both coordinate covalent DNA intrastrand and interstrand cross-links as well as protein-DNA cross links in the cellular genome.[166-167] Again, square planar complexes allow deeper insertion of an intercalator compared to octahedral or tetrahedral geometries.[168] Metal complexes like $[Pt(phen)(en)]^{2+}$ (where, phen=1,10-phenanthroline, en=1,2-diaminoethane) can intercalate between the base pairs of DNA[169] and depending on the choice of the ancillary ligand, may insert beyond the platinum(II) centre, effectively offsetting the size of small intercalating ligands such as phen.[170,171] However, when incorporated octahedral complexes such as $[Co(phen)_3]^{2+}$ or $[Ru(phen)_3]^{2+}$, the geometric arrangement of the ligands can hinder full insertion.[168,172] For complexes like $[Ru(phen)_2Cl_2]$, they can inhibit covalent binding because of steric crowding by the DNA phosphate backbone.[173] Further, a study that compared cobalt (octahedral) and zinc (tetrahedral) complexes incorporating a porphyrin ligand revailed that the cobalt complex bound to DNA via intercalation but the zinc complex was inhibited by the presence of an axial water ligand.[174] It is clear that different transition metal complexes can undergo different binding interactions with DNA. Now-a-days the DNA interaction with water soluble metal complex obtained much attention because of the bioavailability of a metal ion in body. Arunadevi *et al.* synthesized the water soluble Cu(II), Co(II), Ni(II) and Zn(II) complexes of tryptophan-derived Schiff base ligand and there complexes were found to efficiently bind to CT-DNA through intercalation mode.[175] Again most of the functionalized β-cyclodextrin and their metal complexes are water soluble and biologically potent and they may have probability to cleave DNA and may act as potential drugs with moderate to high bioavailability. But their capability and nature of interaction with DNA have not been explored sufficiently till date.

1.5.2. DNA Cleavage

Gel electrophoresis was used to study cleavage of supercoiled DNA by the different compounds. When circular plasmid DNA is put through electrophoresis, comparatively fast migration will be noticed for the intact supercoil form (Form I). If scission happens only on one strand (nicking), the supercoil will generate a slower moving open circular form (Form II). If both strands are cleaved, a linear form (Form III) will be generated and that migrates between Form-I and Form-II. Above said three forms of DNA are shown in Figure 1.13.[175]

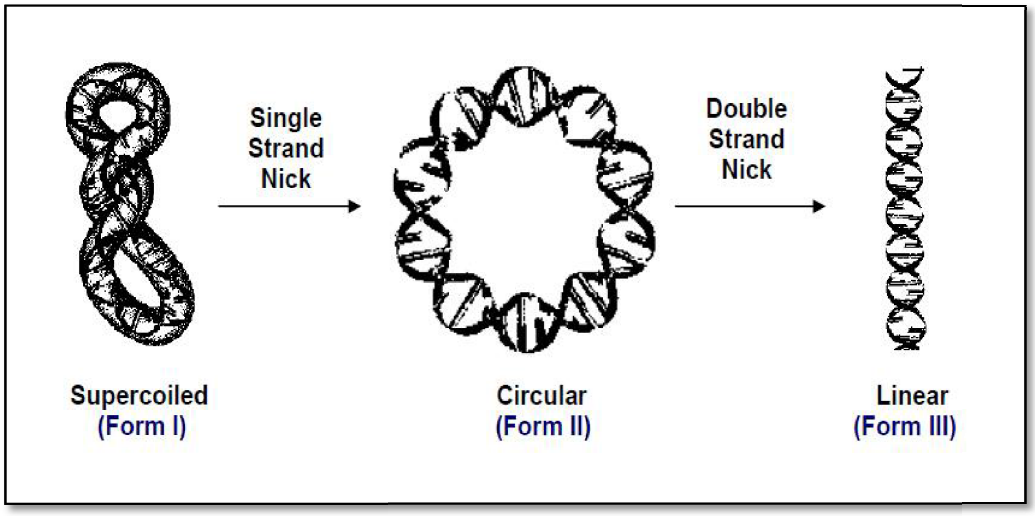

Fig 1.13. Schematic representation of DNA cleavage process.

1.6. Antioxidant Activity

It was found that generation of reactive oxygen and nitrogen species (ROS and RNS) play a crucial role in the pathogenesis and development of the disease. ROS are produced mainly in the biological system during the cellular metabolism and by the influence of environmental resources. Although ROS are produced during normal aerobic cell metabolism but its excessive production causes oxidative stress. Oxidative stress is a situation where in there is an imbalance between the generation of ROS and the capacity to neutralize them, leading to the oxidation of several intracellular components such as lipids, proteins and nucleic acids as well as extracellular matrix components like proteoglycans and collagens. This may result in the alteration of structure and biological functions of those molecules that are recognized as antigens by the immune system and autoantibodies formed against these modified molecules and create life limiting chronic diseases such as cardiac infection, hypertension, cancer, arteriosclerosis, rheumatism and cataracts, *etc*.[176] Antioxidant can control this autoxidation by interrupting the propagation or inhibiting the generation of free radicals and subsequently decrease the oxidative stress, improve immunity and increase longevity. Most organisms are protected to some extent by free radical (peroxide, hydro-peroxide or lipid peroxyl) damage by enzymes like super-oxide dismutase and catalase or compounds such as ascorbic acid, phenolic acids, tocopherols, polyphenols, glutathione and flavonoids. However, antioxidant supplements or dietary antioxidants may protect the body from the damaging effects created by free radicals. Antioxidants are considered as important nutraceuticals

because of their many health benefits and are extensively used in the food industry.[177,178] The combination of certain foods, natural and synthetic rubbers, and gasolines with oxygen in air at room temperature cause to undesirable status such as rancidity in foods, loss of elasticity in rubbers and production of gums in gasolines. Currently, synthetic antioxidants are widely used because they are cheaper and effective than natural antioxidants. Antioxidant activity of a synthesized compound can be measured by using its scavenging potential for trapping of the free radicals. The finding for metal-derived antioxidants has received much attention. Recently, variety of Schiff-base metal complexes has been investigated as potential scavengers of ROS or as antioxidants.[101,177] It is highly expected that the water soluble metal complexes of *β*-CD based Schiff bases may show some potential antioxidant activity.

1.7. Antimicrobial studies

Antibacterial activity of a compound is associated with its preferential ability to provincially kill bacteria or slow down their rate of growth without being extensively toxic to nearby tissues.[179] Antibacterial agents are the most important in fighting infectious diseases. The antibacterial properties of metals have been recognized for centuries and have been represented by some of the most fundamental breakthroughs in medicinal history. Probably the first antibacterial experiment involved a metal compound in laboratory was done by Koch in 1890. The investigation involving the activity of mercuric chloride on anthrax spores and the introduction of the organoarsenical compound Salvarsan™ (in 1912) for the treatment of syphilis is considered to be the first synthetic therapeutic agent. The major hindrance associated with the chemical substances as antimicrobes is their toxicity to the host cell as well as microbial cells. Hence, the chemical substances used should have selective toxicity towards the harmful microbes but not much to the host tissues. Certain chemicals of synthetic and plant origin are toxic to the bacteria and fungi, but not to the host animal and their wide use as well as abuse, the appearance of bacterial resistance toward antibacterial agents has become a major problem for today's pharmaceutical industry.[180-184] The above problems motivates the scientists to synthesize and study the new agents for antimicrobial activities.

1.7.1. Antimicrobial activity of metal complexes

Transition metal complexes with various ligands have been shown to exhibit antimicrobial activities against a spectrum of microbes and also they have been shown to possess toxicity against a number of cell lines of rodents and human in cell culture.

Various organic ligands possess strong antibacterial, herbicidal, insecticidal and fungicidal properties.[185] Metal complexes or coordination complexes have been widely used in medicine[186] and pharmaceutical fields,[187] because of their broad bioactivities against bacteria and fungi.[188,189] Metal chelates play an important role in biological systems where in enzymes are known to be activated by metal ions. The enzyme containing metal ions acts as a cofactor for enzyme activity.[190,191] Literature review suggests that the inclusion complexes of CDs and modified-CD have potential antibacterial activities[192] and metal associated fictionalized *β*-cyclodextrin have vast application in medicinal field. Metals serve two functions; 1) to provide proper stereochemical orientation and 2) to bring the reacting molecules closer to the reacting sites of the enzyme so that reaction may occur. The activity of the metal chelates depends upon the steric, electronic and pharmokinetic factors.[193] Such bio-activities depend upon the interactive forces that bind the compound to the organisms. These forces may vary from the rigid covalent bonding to the weak Van der Waals forces.

Christian Grams (Danish Physician) discovered the differential staining technique called as Gram staining. This technique differentiates the bacteria into two groups "Gram positive" and "Gram negative". Gram positive bacteria retain the crystal violet and resist decolorization with acetone or alcohol and hence appear deep violet in colour; while Gram negative bacteria, loose the crystal violet and counter-stained by saffranin and hence appear red in colour. The details regarding some bacteria are given below:

1.7.1.1. *Escherichia coli*

E. coli (*Escherichia coli*) is a Gram-negative, facultative anaerobic, rod-shaped bacterium. This microorganism was first described by Theodor Escherich in 1885. Most *E. coli* strains harmlessly colonize the gastrointestinal tract of humans and animals as a normal flora but some strains causing diarrhea, intestinal and urinary tract infections. One strain can lead to kidney failure to mortality if not properly managed. Eating contaminated food and water is the most common way to get an E. coli infection. They grow best at 37 $^{\circ}$C.[194]

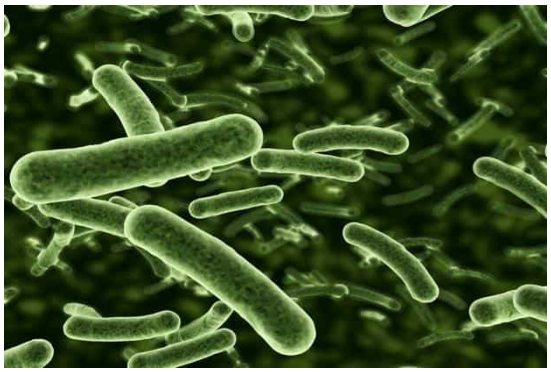

Fig 1.14. *E. coli* bacteria.[194]

1.7.1.2. *Staphylococcus aureus*

S. aureus is a gram-positive, round-shaped, facultative anaerobic bacterium that is frequently found in the nose, respiratory tract, and on the skin. It is often positive for catalase and nitrate reduction. The cell wall of *S. aureus* is made up of peptidoglycan interspersed with teichoic acid and protein. Enzymes also contribute to the virulence of this organism. *S. aureus* is approximately 1μm diameter and it divides to form the cluster characteristic of the genes. In liquid media, it is present in different forms such as singles, pairs and short chains. It grows on nutrient agar medium, incubated in air for 18-24 h at the optimal growth temperature of 37 °C. Although *S. aureus* is not always pathogenic *S. aureus* causes skin infections like skin abscess, respiratory infections like sinusitis, and food poisoning. These bacteria are spread by direct contact with an infected person, by using a contaminated object, or by infected droplets dispersed by sneezing or coughing. The bacteria can also spread through the bloodstream and infect distant organs. Pathogenic strains often promote infections producing virulence factors such as potent protein toxins, and the expression of cell surface proteins that bind and inactivate antibodies.[194]

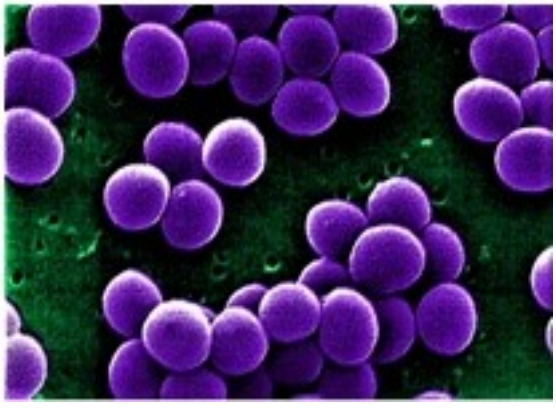

Fig 1.15. *Staphylococcus aureus* bacteria.[194]

1.7.1.3. *Klebsiella pneumoniae*

K. pneumoniae is a gram-negative, encapsulated, rod-shaped, lactose-fermenting, facultative anaerobic bacteria. Generally it is found in the normal flora of the mouth, intestines and skin. It can cause destructive changes to human and animal lungs, specifically to the alveoli leading to bloody sputum. In recent years, *Klebsiella* species became important pathogens in nosocomial infections. It naturally occurs within the soil, and near about 30% of strains can fix nitrogen in anaerobic conditions. Its nitrogen-fixation system has been much-studied due to agricultural interest as *K. pneumoniae* has been illustrated to increase crop yields in agricultural conditions.[194]

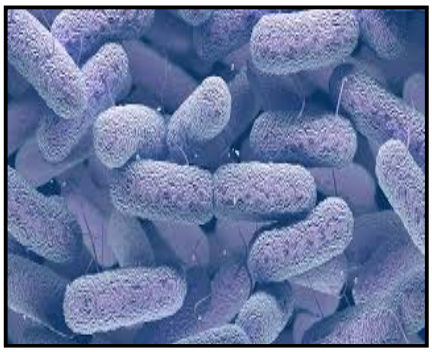

Fig 1.16. *K. pneumoniae* bacteria.[194]

1.7.1.4. *Bacillus subtilis*

B. subtilis is a gram-positive, catalase-positive bacterium, generally found in the gastrointestinal tract of ruminants and humans and in soil. *B. subtilis* is rod-shaped, and can form a tough, protective endospore that allowing it to bear extreme environmental conditions.[194]

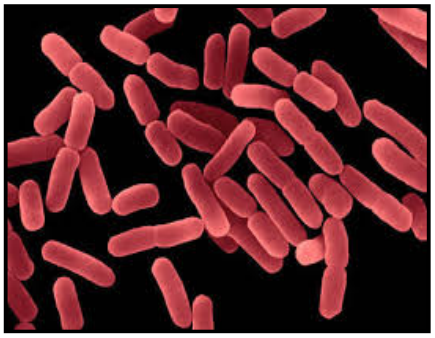

Fig 1.17. *B. subtilis* bacteria.[194]

1.8. Review of literature

In 1977 Tabushi *et al.* reported the first coordination complex based on aminomodified CDs as charged system with two cooperative recognition sites.[195]

After this example, various complexes have been synthesized and investigated as chiral selectors of coordinating substrates.[196,197] In particular, the copper(II) complex of 6-deoxy-6-[2-(imidazol-4-yl)ethyl]amino-*β*-cyclodextrin (CDhm) represents the first example of this class of chiral selectors which is capable of resolving a racemic mixture of amino acids.[197,198] The chromatographic enantioselectivity has also been examined using $[Cu(CDhm)]^{2+}$ as chiral additive to the eluent in ligand exchange chromatography (LEC). Later, copper(II) complexes of fluorescent functionalized CDs have been investigated as sensors of enantiomers of unmodified amino acids.[199] The nickel(II), zinc(II), copper(II) and cobalt(II) complexes of 6-deoxy-6-(3-aminopropylamino)-*β*-cyclodextrin (CDpn) have been investigated by potentiometry. as chiral selectors. On the basis of the stability constant values of binary and ternary complexes, the authors suggested a recognition mechanism of the L/D-Trp (Tryptophane) in which the side chain of the amino acid is included in the cavity in both the two diastereoisomer ternary complexes.[200,201] Furthermore, the largest enantioselectivity has been reported for the nickel(II) complexes, while no enantioselectivity was found when zinc(II) had been used. The Co(II) and Cu(II) complexes showed enantioselectivity lower than that of the nickel(II) complexes. A similar trend was observed also for the recognition of the phenylalanine using metal complexes of CDpn.[202] The Co(II), Ni(II), Cu(II) and Zn(II) complexes of 6-deoxy-6-(hydroxyethylamino)-*β*-cyclodextrin (CDea) have also been studied and enantioselectivity had been found except for zinc(II) complexes with Tryptophane, Phenylalanine and Histidine.[203] Schlatter *et al.* suggested the application of ruthenium complexes of the amino alcohol β-CDs as catalysts in enantioselective reduction of aromatic and aliphatic ketones.[204] The hydrophobic and hydrophilic features make the CDs extremely attractive components to mimic enzyme systems. Zinc(II) complexes with CDs monofunctionalized with different macrocyclopolyamines, 1,5,9-triazacyclododecane, 1,4,7,10-tetraazacyclododecane and 1,4,8,11-tetrazacyclododecane, have been synthesized as models of carboxypeptidase enzyme (CPA).[205] This enzyme is a zinc exopeptidase, that catalyzes the hydrolysis of C-terminal amino acids from polypeptide with a preference for substrates with aromatic side chains. Zinc(II) complexes with CD-monoamine bound to the monooxime of 1,10-phenanthroline-2,9-dicarbaldehyde displayed a catalytic activity for the p-nitrophenylacetate hydrolysis more effectively than analogous complexes with Cu(II) and Ni(II).[206] The metal ions after complexation with modified CDs act as the

catalytic center. Many artificial enzymes based on CDs have been synthesized, *e.g.*, Zn(II) complex of a CD-difunctionalized with two histamins acts as artificial carbonic anhydrase.[26] Cu(II) complex of 6-deoxy-6-(2-aminoethylamino)-*β*-cyclodextrin resembles redox enzyme capable to oxidize furoin 20 times faster than either the uncatalysed reaction or CD alone.[123] Cu(II) complexes of functionalized CDs with amines have also been proposed as supoeroxidedismutaste models and the O_2^- scavenging activity was also determined.[207] Mn(II) porhyrin complexes attached to two or four *β*-CDs were investigated as catalysts for the epoxidation of some stilbene derivatives.[208] Functionalization of CD with proper coordination sites may form the polydanted ligand and their metal complexes. Amino cyclodextrins are known to be efficient ligands for first-sphere coordination of metal ions, and their complexes are used in aqueous organometallic catalysis. Indeed, CDs and their derivatives have shown excellent performances in aqueous organic reactions including oxidation, reduction, hydrolysis, hydroformylation, and so on.[209] Sakuraba *et al.* proposed Mo(V) and Cu(II) complexes with *β*-CD derivatives having a catechol-type ligands. Their chiral catalytic activity was examined in the asymmetric oxidation of aromatic sulfides with hydrogen peroxide in water (pH 6.0).[210]

Recently imidazolium β-cyclodextrin and per-6-amino-β-cyclodextrin are used in Pd-catalyzed C-C coupling reactions.[143,211] Patrigeon *et al.* synthesized new water-soluble Pt(II) and Rh(II) complexes of bidentate ligands through noncovalent complementary interactions and metal coordination*, i.e*, by inclusion of sodium salt of the bis- (3 sodiosulfonatophenyl)(4-tert-butylphenyl)phosphane in the hydrophobic cavity of CD moiety of mono-N,N-diethylamino-β-CD and monopyrrolidino-β-CD. They have possibility to acts as mimic Rh(II) and Pt(II) catalysts.[212]

Legrand *et al.* were first to report the synthesis of an NHC-appended methylated CD as a catalyst in dioxane and studied its solubility, aggregation and recognition properties of its imidazolium precursor as well as its coordination and catalytic behaviors. Furthermore, a Suzuki cross-coupling reaction was performed using this compounds generating catalytically active species with a palladium precursor but unfortunately, the catalytic experiments performed in water failed probably due to the unstability of this carbene in the presence of labile protons.[213] Zhang *et al.* (2013) reported a triazolyl β-cyclodextrin supported palladium complex and it exhibited extremely high efficiency for Suzuki–Miyaura coupling reactions in water. This newly developed system represents an efficient and environmentally benign coupling

protocol and could provide a valuable approach for the design of water-soluble catalysts to mediate aqueous organic reactions.[126] Kairouz *et al.* (2014) reported novel dodecyl imidazolium modified *β*-CD and successfully studied the catalytic properties of a compound in presence of palladium source in neat water as a catalyst for the Suzuki–Miyaura coupling reaction. The introduction of a dodecyl chain on the imidazolium moiety attached to the primary face of a native *β*-cyclodextrin allows the formation of a highly stable self-assembled catalytic reactor for the Suzuki– Miyaura cross coupling reaction in water.[214]

Dindulkar *et al.* (2016) synthesized 2-aminopyridine modified β-cyclodextrin supported palladium complex which is effective for Mizoroki–Heck cross-coupling reactions in aqueous medium under aerobic conditions and gave excellent yield with easy recovery process.[215] Khan *et al.* (2016) synthesized an ionic Pd(II) complex of water soluble pyridinium modified β-cyclodextrin. The resulting complex showed very good catalytic activity in Suzuki- Miyaura and Heck C-C coupling reactions in aqueous phase.[216] Recently, Shinde *et al* (2019) reported an ethylene-*β*-cyclodextrin supported palladium complex and showed its catalytic pathway in Suzuki–Miyaura coupling reactions in water.[217]

1.9. Object and application of the research work

A detailed survey of the literature showed that of formation of inclusion complexes and the modification of the hydroxyl group of *β*-cyclodextrin with different functional groups have fascinating properties and applications in synthetic chemistry and chemical applications. Therefore in view of the above facts the dissertation was undertaken to address the following objectives:

1. To design and synthesize new water-soluble *β*-cyclodextrin based polydentate ligands and their transition metal complexes.
2. To characterize the synthesized ligands and metal complexes by various physico-chemical methods like elemental analysis, ESI-MS, UV-Visible, FTIR, NMR spectroscopy and magnetic moment measurements, *etc*.
3. To study their potential applications such as catalytic activities, antioxidative proprieties, antimicrobial and cytotoxic effect, DNA interaction and antibacterial activity, *etc*.

Therefore, some funtionalized *β*-cyclodextrin based polydanted ligand systems and their transition metal complexes were synthesized and their catalytic and biological activities were thoroughly studied.

This present dissertation includes a total of seven chapters including this introductory one. The experimental section is discussed under Chapter II wherein details of chemicals and the various physico-chemical techniques used to study the synthesized compounds were described. The synthesis, structural characterization, physico-chemical properties and potential applications of the synthesized compounds are discussed in Chapters III to VI, followed by concluding remarks in chapter VII.

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