CHAPTER I

NECESSITY OF THE RESEARCH WORK

I.1 Object, Scope And Application Of The Research Work

"Supramolecular chemistry" is often named as "chemistry beyond the molecule'' and most commonly called as "Host Guest Chemistry". The concept of host-guest chemistry has paved the way to the continuous development of supramolecular (inclusion) complexes with physicochemical properties superior to those of the guest molecule. The 'Host' molecule is considered as an organic molecule containing convergent binding sites and large cavities, which allow them to incorporate the other compounds (i.e. guest molecules).On the other hand, 'Guest' molecule can be regarded as synthetic counterpart, which contains divergent binding sites to the receptor sites in enzymes, genes, antibodies and ionophores.

Host-guest chemistry involves the idea of complementary binding between two or more molecules through non- covalent interactions, hydrogen bonding, π-π stacking interactions, dispersion and inductive forces, and hydrophobic or solvatophobic effects [1] [2] **(Fig. I.1)**. Organic host molecules usually bind anions, cations, and neutral molecules such as proteins and enzymes, and have a widespread application as optical sensors, electrochemical sensors, supramolecular catalysts, and in the pharmaceutical industry as anti-cancer agents [3]. The stability of the inclusion complexes depends on the sizes and designs of the guest molecules, along with the dimensions of the empty cavities of the host molecules.

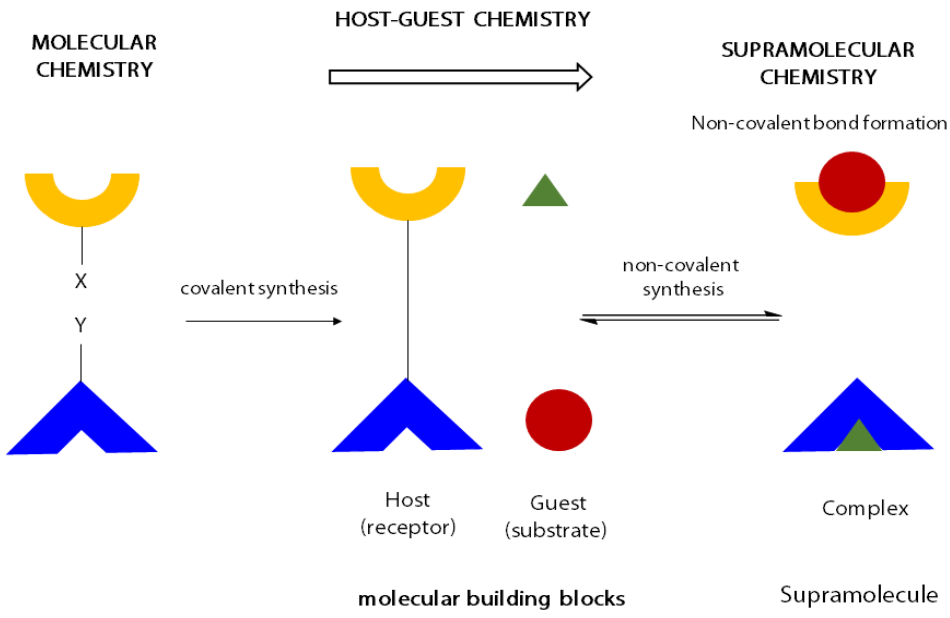


Fig. I.1. Host-Guest Chemistry

Chapter I

In this thesis, I have studied the inclusion phenomenon of cyclodextrins and crown ethers with different biologically and industrially potent molecules in aqueous and non- aqueous medium. Native and modified cyclodextrins (CDs) dramatically affect the properties of guest molecules solubilized within the relatively hydrophobic interior [4].Cyclodextrins are chemically stable., water-soluble oligosaccharide hosts derived partial enzymatic starch degradation. As their interiors are relatively lipophilic and their exteriors hydrophilic, cyclodextrins can bind hydrophobic guests to form inclusion complexes in aqueous solution [1] [5]. Crown ethers were the first artificial host molecules discovered accidentally by Pedersen in early 1937.This was found as a byproduct during the synthesis of bisphenol [6]. Among the potential advantages of using host-guest inclusion complexes in oral drug delivery are enhanced rate and greater extent of drug (guest) dissolution, and thus improved bioavailability, of poorly soluble drugs. The future looks likely to bring many more opportunities for host-guest chemistry to play a part in our everyday lives.

I.2. Importance Of Chemicals Used

I.2.1 Macrocyclic Host Molecules

In a typical host-guest inclusion complex, a host molecule offers a cavity to encapsulate a guest molecule through noncovalent interactions. Crown ethers, Macrocyclic polyamine, Calixarene, Cyclophane, Cucurbiturils and Cyclodextrins (CDs) are the well-accepted host molecules on account of their wide applications in the biomedical field [7]

I.2.1.1 Cyclodextrin-Naturally occuring Host molecule

Among the many host molecules discovered and utilized for building up supramolecular systems, CDs are a popular class of macrocyclic rings that have attracted a lot of attention of researchers, especially for their biological applications. CDs refer to a series of macrocyclic molecules composed of α-1,4 glycosidic bond linked oligosaccharides, which can be produced from enzyme triggered starch degradation. They were discovered by Villiers in 1891 [8] and ever since CDs have undergone extensive studies in a variety of fields, such as analytical chemistry [9] enzyme technology [10], catalytic reactions [11] and pharmaceutics [12] [13].Within the CD family, the ones consisting of 6, 7, and 8 glucose units are named as α-, β-, and γ-CD (**Fig. I.2.**), respectively. The CDs have a truncated cone-resembled shape with a hollow cavity. The sizes of the primary and secondary sides of the CDs depend on the unit number of glucose (**Table. 1**). The depth of the hollow cavity is 0.78 nm for all three types of CDs. The hydroxyl groups of the glucose units are directed toward the outside at the orifice of the two ends, while methinic protons are located inside the cavity, the structure of which enables CDs

with a hydrophilic external surface and hydrophobic hollow cavity. Thus, a variety of guests can easily be encapsulated into the hollow cavities via the host-guest interaction in aqueous conditions and even in the solid state. The formation and dissociation of the host-guest complexes are closely associated with the kinetic and thermodynamic properties of the complexes, the sizes of the host and guest, as well as the environmental conditions (pH and temperature), contributing all possibilities for the responsiveness of the host-guest systems [14] [15].Because of the natural availability from starch, CDs have good water solubility, good biocompatibility, and nontoxicity toward biological systems [16]. By the formation of the host-guest complexes between drugs and CDs or CD derivatives, the water solubility of hydrophobic drugs can be increased to a greater extent, thereby enhancing the drug availability in biological systems. This is the direct application of CDs for drug delivery [17]. For better pharmaceutical uses, chemical modifications on CDs were carried out in order improve their solubility, ability of drug encapsulation, and drug release capability while minimizing the toxicity of the CDs. In this aspect, a large variety of functional groups were directly modified onto CDs. Cationic CDs were synthesized by introducing amino-containing groups onto the primary side of the CDs [18]. Native and modified Cyclodextrin and their crown ethers are selected as host molecules. Encapsulation in cyclodextrins provides an intimate effect on the physicochemical properties of guest molecules as they are temporarily encapsulated within the host cavity which gives rise to beneficial modifications of guest molecules, which are not achievable otherwise. The advantages of these characteristics are solubility improvement of highly insoluble guests, stabilization of labile guests against the degradative effects of environment (oxidation, light and heat), control of volatility and sublimation, physical isolation of incompatible compounds (via chromatography), taste modification by masking off flavours, odour elimination and controlling of drug and flavour release.

Table.1. Physical properties of Cyclodextrins

Properties	**Cyclodextrins**		
	α-CD	β-CD	γ-CD
Number of glucose units	6	7	8
Molecular weight(g/mol)	972	1135	1297
Solubility in water at 25°C (%,w/v)	14.5	18.5	23.2
Outer diameter (Å)	14.6	15.3	17.5
Cavity diameter (Å)	4.7-5.3	6.0-6.5	7.5-8.3
The height of torus (Å)	7.8	7.8	7.8
Cavity volume (Å)	174	262	427

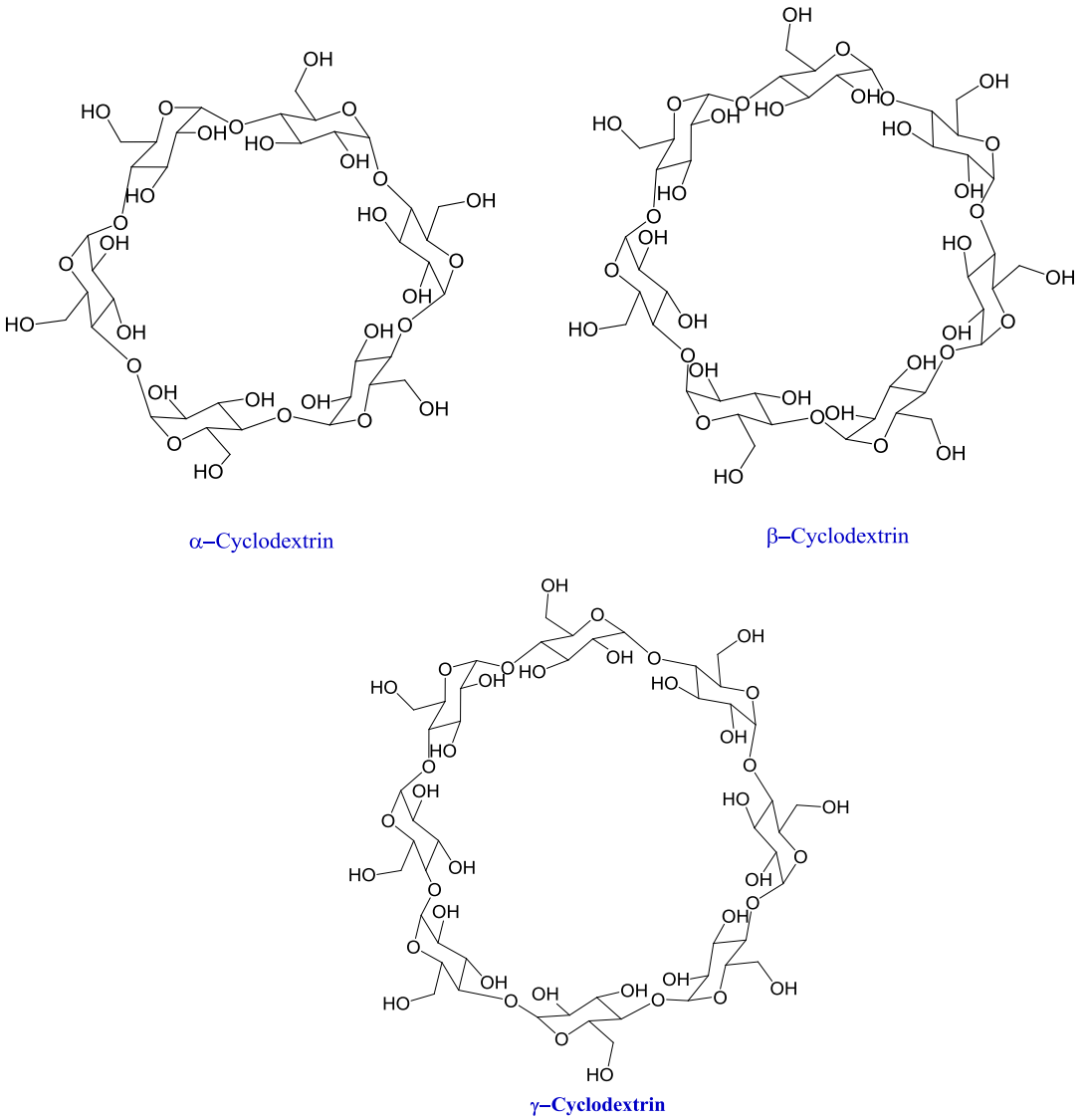
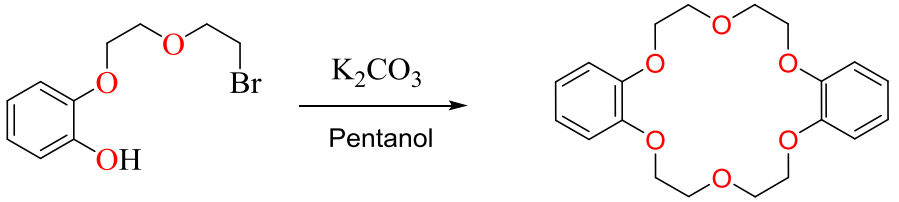


Fig. I.2. Cyclodextrin molecules

I.2.1.2 Crown Ethers- The First Class of Artificial Host

Crown ethers are heterocyclic compounds which contains cyclic polyethers. Necessarily, there is a repeating ethyleneoxy [–CH_2CH_2-O-] unit. In case of dioxane two such units are present there, whereas in case of 18-crown-6, six ethyleneoxy units are observed. These macrocycles are well known as crown because of their specific property of binding with selected cations. In earlier 1937 Luttringhaus [19]reported synthesis of a twenty member ring compound (**Scheme I.1.**).



Scheme I.1. Synthesis of a twenty member ring compound Dibenzo18-C-6

Stewart [20] noticed that minute quantity of potassium got soluble in a cyclic compound **(Fig. I.3.)**.

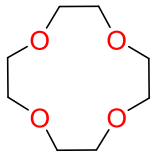
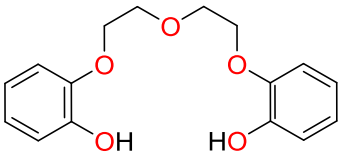


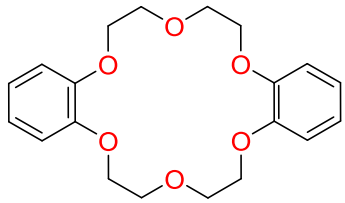
Fig. I.3. 12-Crown-4

In mid 1960s Pedersen [21] started with catechol moiety and the motive of that work was to link two catechol molecules through their hydroxyl groups. This system could wrap up the metal cation and the other -OH groups will neutralize the cation. During preparation of one of the ligand, he found an impurity of white crystalline substance, which was insoluble in methanol as such.

Later he came to know that a small addition of NaOH to the compound increased its solubility in methanol. He observed that this change in solubility was due to presence of cations. This anomalous behavior of the compound led to the discovery of dibenzo-18-crown-6 **(Fig. I.4.)**.



Pedersen's target molecule



Dibenzo-18-crown-6(impurity)

Fig. I.4. Pedersen's target molecule and Dibenzo-18-crown-6

This accidental discovery of crown ether created path breaking revolutions in the areas of supramolecular chemistry, phase transfer catalysis, anionic catalysts, ion transport mechanism in biological systems, host-guest chemistry and in most recent applications to the solar cell systems. The molecular modeling of dibenzo-18-crown-6 showed that the crown ether is enveloping the guest cation as if it is crown of that cation. This observation made Pedersen to introduce the term crown ether. The hetero atoms present in the ring provide ability to coordinate wide range of cations inside vacant space of the molecule4. The basic crown ethers are prepared by using modified Williamson ether synthesis procedure. Some of the recently reported crown ethers are depicted in below (**Fig. I.5.**)-

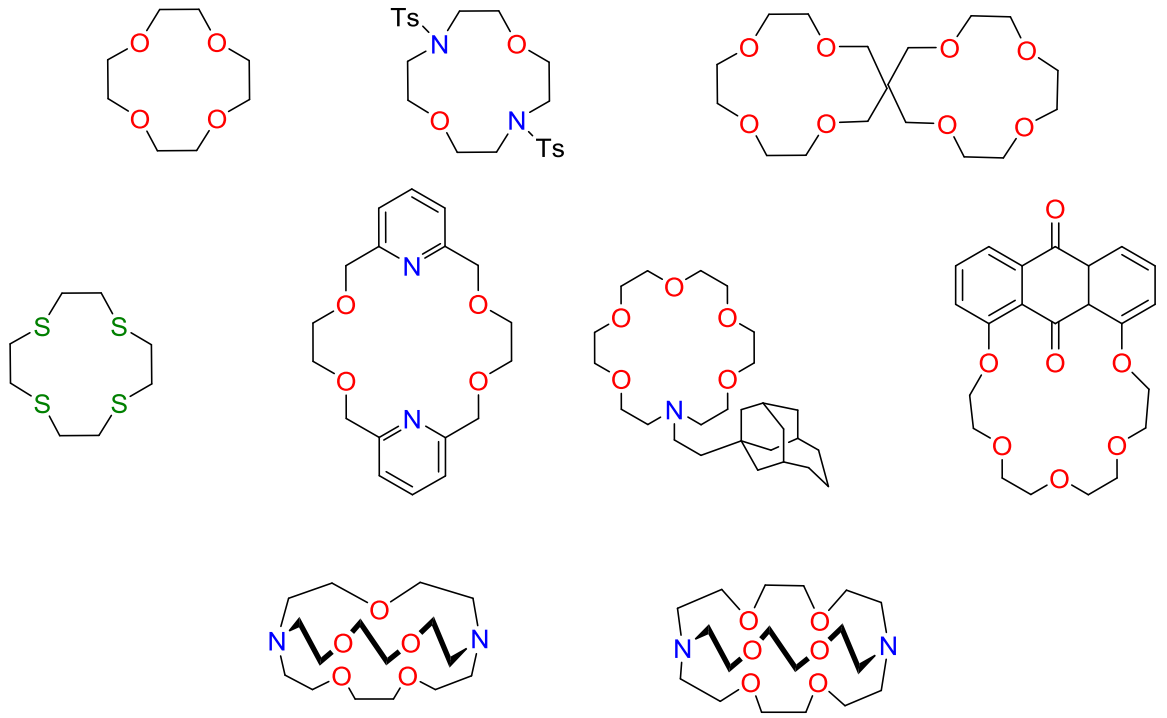


Fig. I.5. Different Crown Ethers

The compounds are named on the basis of the number of repeating ethylene oxy units present in certain compounds, for instance 18-crown-6 contains 6 repeating ethylene oxy units. Due to high versatility in selectivity binding wide variety of metal ions and neutral and ionic organic species [22]. crown ethers are playing key role in the area of host-guest chemistry and in building of variety of supramolecular assemblies [23] [24] [25].

I.2.1.3 Chemistry of Crown Ethers

The chemical structure of crown ether consists hydrophilic cavity of ether oxygen atoms surrounded by hydrophobic ethylenic groups. The number before "crown" implies the total number of atoms in the cycle, and the number after "crown" gives the number of oxygen atoms in the cyclic structure. For example, 18-crown-6 is a cyclic crown ether having twelve carbon atoms and six oxygen atoms. The oxygen atom because of having high electronegativity, can act as a binding site for metal ions and ammonium ions through dipole–ion interactions. Thus, stable complex formation takes place, which in turn enhances solubility of metals in non-aqueous media.

Complex formation capacity of crown ether is dependent upon sizes of cavity and sizes of cation. For instance, 18-crown-6 coordinates well with potassium while sodium ion fits well in cavity of 15-crown-5 [26] **(Fig. I.6.)**. For small crown ethers the stability of coordination complexes

depends upon penetration of cation into the cavity. The extent of complexation also depends on charge density, nucleophilicity of counter ion and nature of solvent. The larger crown ethers exhibit high conformational mobility and can accommodate a wide variety of cations into its cavity, which leads to the possibility of formation of sandwich compounds. The cation might get sandwiched between two crown ether molecules [27]. Such distinct arrangement of these binding sites is preferable to ion recognition via cooperative interaction. Therefore, matching the sizes of the ion and crowns is prior to efficient binding behavior.

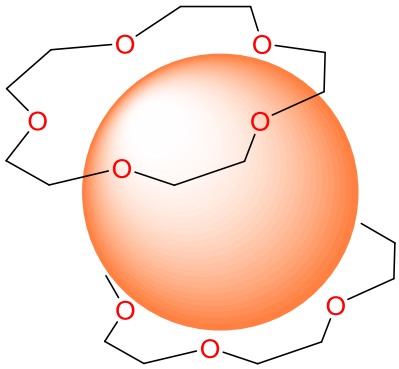


Fig. I.6. Sandwich Arrangement of 15-crown-5

Interaction of such crown ethers with cation deals with the proton transfer process. The proton transfer is a fundamental process in most of the basic chemical transformations such as acid base reaction [28].

I.2.1.4 Solutes used

I have chosen α and β-Cyclodextrin molecules and Crown ethers like 18-Crown-6, Dibenzo-18-Crown-6, Dicyclohexano-18-Crown-6 as host molecules. Some bioactive guest molecules i.e. Azelaic acid, Dopamine hydrochloride, L-Glutamic Acid, L-Aspartic acid, N-Benzoylthiourea and industrially important Alizarin complexone (dye) have been used during the work.

Water has been used as a solvent in most of the cases. In a few cases, Methanol (99.9%) has also been used due to solubility issue.

The detailed descriptions of the compounds used have been given in **CHAPTER III**.

I.3 Physicochemical Parameters & Methods Of Investigation

The following physicochemical methods have been applied to study the inclusion phenomenon and diverse interactions occuring in the medium-

- Densitometry

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- Viscometric study
- Surface tension study
- Conductometric study
- Refractometry
- FTIR Spectroscopy
- UV-Visible Spectroscopy
- NMR Spectroscopic Study ($^{1H\ NMR}$ and 2D ROESY study)
- Raman Spectroscopic study
- HRMS Study
- Scanning Electron Microscope (SEM) Study

Thermodynamic properties, like partial molar volumes obtained from density measurements, are generally convenient parameters for interpreting solute-solvent/ion-solvent ad solute-solute/ion-ion interactions in solution. The sign and magnitude of partial molar volume (ϕ_V^0) also provides information about the nature and magnitude of ion-solvent interaction while the experimental slope (S_v^*) provides information about ion-ion interactions. Viscosity B-coefficient obtained from the viscosity values indicates the extent of ion-solvent interaction in a solution.