

## CHAPTER 1

### STRUCTURAL MOLECULAR RECOGNITION: AN OVERVIEW

#### 1.1. Introduction

The concept of molecular recognition through non-bonded interactions between molecules is of vital significance in understanding various biological phenomena. Enzymatic reactions, for example, involve the formation of an enzyme-substrate complex prior to the catalytic process. Similar is the case with other processes like drug action, action of hormones, translation and transmission of the genetic code, transport of ions across cell membranes etc. These biological hosts recognize the guest molecules primarily by means of noncovalent interactions such as hydrophobic, electrostatic, hydrogen bonding, metal coordination etc. Organic chemists have been interested in imitating and generalizing these biochemical reactions of nature. The earliest model receptors capable of mimicking the function of selective complexation and transport associated with biological membranes were the cation binding antibiotics. But these receptors were too complex in structure to allow ready synthetic strategies for the recognition studies. At the beginning of 1950s, Cramer<sup>1</sup> carried out

successful studies on the complexing properties of natural cyclodextrins. During the same period Stetter and Roos<sup>2</sup> reported their work on cyclophanes which was the first approach to synthetic receptors. Despite all these studies the progression to synthetic host systems did not occur until late sixties. The developments in this area were triggered only with the accidental discovery of crown ethers by Pedersen<sup>3</sup>. His results demonstrated that molecular complexation can occur in synthetic systems also. The extreme simplicity of the structure and synthesis of crown ethers inspired chemists and formed the basis for building synthetic organic host molecules in a highly structured manner.

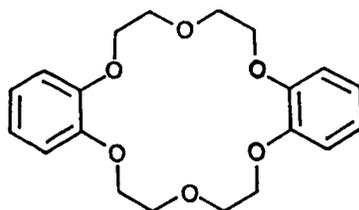
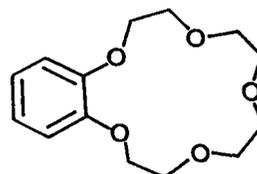
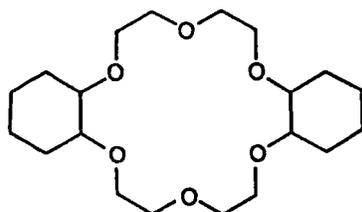
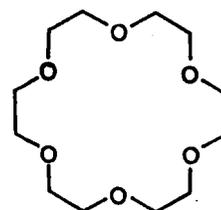
The design of host molecules capable of complexing with a guest species in high specificity has several implications. For example, receptors which can discriminate closely similar substrates such as enantiomers offer great potential in separation and purification techniques. Complexation can cause substantial modifications in the physical and chemical properties of substrates. Physical changes like change in viscosity, solubility, volatility, physical state etc are of great practical applications. Modifications in chemical reactivity of the substrate in the complexed stage offer scope for selective synthetic transformations. Finally, synthetic catalysts with high specificity resembling enzymes have important applications in many transformations. We have carried out some work in this fascinating area of molecular receptors. As a prelude to the discussion

of our experiments, the major historic developments in this area are briefly discussed in this chapter.

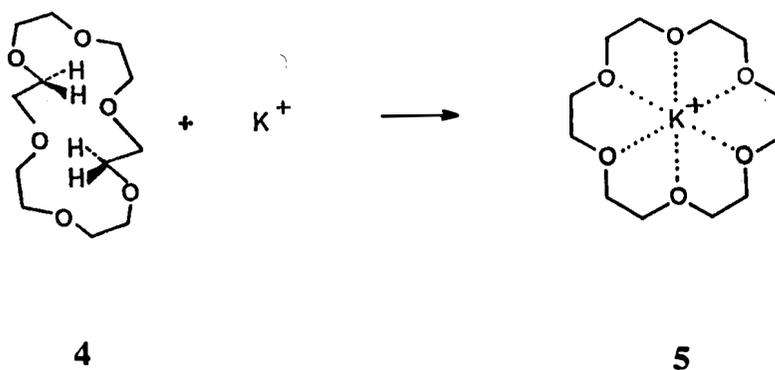
## 1.2. Models for Molecular Recognition

### 1.2.1. Crown-type Compounds

The first synthetic receptor, benzo-[18]-crown-6 (**1**) was reported by Pedersen<sup>3</sup> in 1967. This class of compounds called crown ethers are macrocyclic polyethers where the oxygen atoms are separated by ethano bridges.

**1****2****3****4**

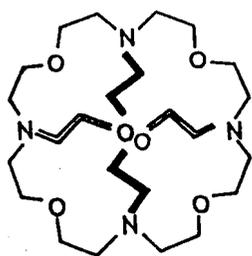
In the name, the number in square brackets refers to the number of ring atoms, which is followed by the class name and number of hetero atoms in the ring. Benzo-[15]-crown-5 (**2**), dicyclohexano-[18]-crown-6 (**3**) and 18-crown-6 (**4**) are some of the most common examples of crown ethers. Compound **1** formed stable complexes with a range of metal ions ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Rb}^+$ ,  $\text{Cs}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Ba}^{2+}$ ,  $\text{Cd}^{2+}$ , etc), ammonium and substituted ammonium salts. X-ray crystal structure of 18-crown-6 and other compounds have shown that they do not contain cavities in the uncomplexed state, since the methylene bridges are turned towards the center of the molecule to fill the intramolecular voids. But on complexation the molecule reorganizes to have a cavity to accommodate the guest atom and is held at the center at a specific interatomic distance by non-bonded interactions as shown in **5**.



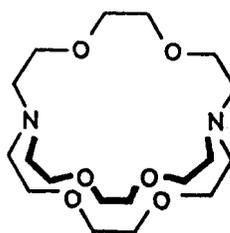
In the binding of substrates with  $-\text{NH}_3^+$  ions to 18-crown-6, Cram<sup>4</sup>

suggested a three point binding model, where the three triagonally disposed hydrogen atoms are held to the three alternate oxygen atoms on the ring by electrostatic attraction. In spite of the metal ion complexation studies, not much investigations were done on the receptor properties of the 3n-crown-n series of crown ethers.

Lehn<sup>5</sup> modified the monocyclic crown ethers by bridging them with additional oligoether chains with the purpose of creating better complexing agents. He reasoned that the bound cation will be entirely surrounded by the three dimensional cavity and hence the complex will be more stable than those derived from the monocyclic crown ethers. The new compounds were called cryptands and the conventional ones (eg. **6**) possess two bridgehead nitrogen atoms joined by three oligooxa chains of different length and number of donor atoms.



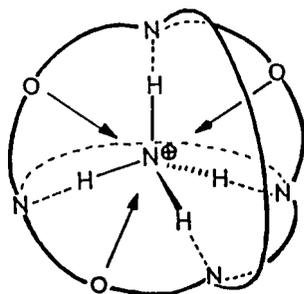
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Other variations involving replacement of donor sites by heteroaromatic rings as well as compounds with additional bridging and donor sites were also developed. Cryptands, though conformationally less mobile than the monocyclic analogues, also fill their own cavities in the uncomplexed state and are reorganized by the guest during complexation.

Spherical as well as tetrahedral recognition, where the receptor shows selectivity towards spherical and tetrahedral substrates respectively, was achieved with cryptands<sup>6</sup>. For example, compound **7** showed a preference for ammonium ion compared to similarly sized potassium ion which is having a spherical charge distribution. The stability of ammonium complex is attributed to the high degree of structural and energetical complementarity. In other words, the receptor possesses tetrahedral recognition sites, where the four nitrogen atoms are located at the corners of a tetrahedron and the ammonium ion has the proper size and shape for fitting into the cavity forming  ${}^+\text{NH} \dots \text{N}$  hydrogen bonds as shown in **8**.

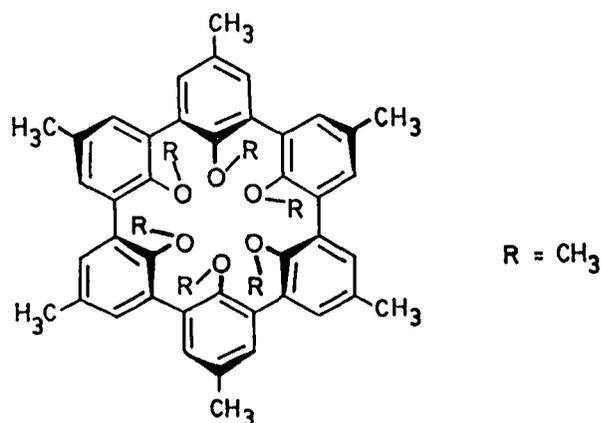


Hence it is obvious that the prerequisite for selectivity would be the largest number of substrate-receptor interactions arising as a result of complementarity in size, shape and binding sites and not limited to steric fit alone.

Various receptors were developed for the recognition of anionic substrates like halides, carboxylates, phosphates and complex anions of transition metals. Coreceptors bearing several binding subunits which can perform multiple recognition, heterotopic coreceptors with binding subunits of different nature that can bind substrates by interacting simultaneously with cationic and anionic sites, ditopic coreceptors with the subunits at the two poles of the structure and metalloreceptors which are able to bind both metal ions and organic molecules are few examples of the different modifications of cryptands<sup>7</sup>.

Unlike the monocyclic crown ethers and cryptands, another class of compounds called spherands<sup>8</sup> developed by Cram possess well defined cavities even in their uncomplexed stage. As the name implies spherands have a spherically complex arrangement and are rigidly organized during their synthesis rather than during the complexation. For example, in compound **9** the oxygen atoms are arranged octahedrally with their unshared electrons lining a cavity. These atoms are buried within the hydrocarbon shell and they remain unsolvated. The rigidity of the system inhibits all but small rotations around the aryl-aryl or aryl-oxygen bonds and the compound possesses only a single conformation ideal for binding  $\text{Li}^+$  or  $\text{Na}^+$ . Hence

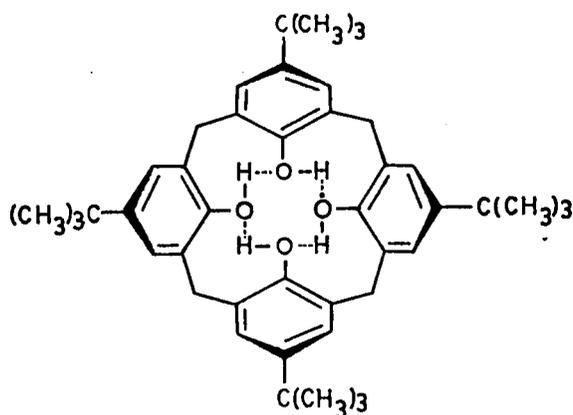
the compound is preorganized for binding.



Other modifications like 'cavitands' where the compounds have enforced cavities with the shape of bowls, vases or wells and 'carcerands', the synthetic molecular cells with the shape of pots where there is ample room for the guests to enter and escape, have also been investigated in detail<sup>9</sup>.

It is noteworthy that the spherands and the recently well-popularized 'calixarenes'<sup>10</sup> have close structural resemblances. Calixarenes are cyclic oligomers made of benzene units and one of the earliest compounds to be synthesized<sup>11</sup> was **10**. This was obtained by the treatment of 4-t-butylphenol with formaldehyde in the presence of a base.

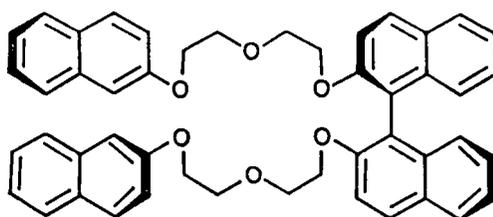
An essential difference between the molecular recognition abilities of the spherands and the calixarenes is that in the latter, the cavity is flexible due to the rotational freedom of the benzene rings.



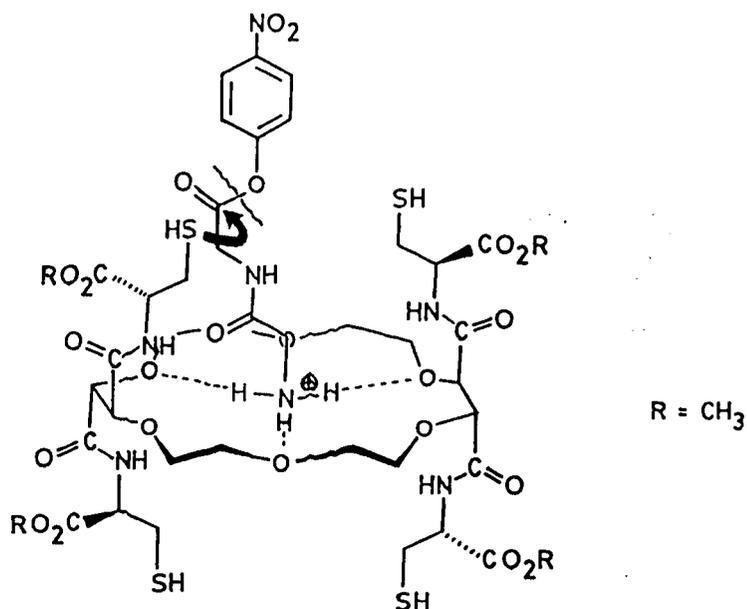
The class of compounds called podands<sup>12</sup> generally constitute open chain crown compounds and cryptands. The polyether chain is stiffened by donor terminal groups. Subsequently, multiarmed polyethers, where oligoether units or ion-terminated chains are attached to a basic framework like benzene or cyclotrimeratrylene (octopus and hexapus molecules) and other similar systems were synthesized. Murakami and co-workers<sup>13</sup> have carried out thorough investigations on these type of

compounds. The stereochemistry and conformational rigidity of the supporting framework play a crucial role in imparting the binding properties to these compounds. Still the catalysts based on multiarmed systems are not expected to show high specificity, as the flexible arms do not offer a precise fit for the guest molecule.

A landmark development in the area of crown ethers was the synthesis of chiral receptors and the evolution of chiral recognition. The 22-crown-6 derivative **11** synthesized by Cram<sup>14</sup> is the first compound to exhibit chiral recognition. It showed selectivity towards the (R)-enantiomer of racemic-phenylethylammonium hexafluorophosphate. Resolution of several amino acid salts were also carried out by chromatographic means<sup>15</sup>, where the receptors were immobilized by attachment to resins. All these studies led to an important development in the area of artificial enzymes.

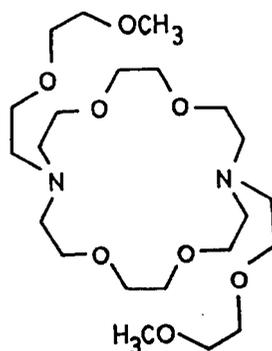


Most of the biochemical reactions of Nature are catalysed by enzymes. These are very specific in their action, show very high rate accelerations under extremely mild conditions and hence perform chemistry in a very attractive manner. With a view to understanding the mechanism of enzymatic reactions as well as using this knowledge to improve the efficiency of *in vitro* reactions, several artificial enzymes were prepared. Cram and co-workers have synthesized partial transacylase mimics<sup>9b</sup> (chymotrypsin models) which showed high rate accelerations. Lehn has developed several systems<sup>7</sup> for ester cleavage, ATP hydrolysis etc. As an example, macrocyclic polyether fitted with L-cysteinyl side arms binds *p*-nitrophenyl esters of peptides and reacts with the bound species releasing *p*-nitrophenol as shown in 12.



The reaction showed substrate selectivity, high chiral recognition between enantiomeric dipeptide esters and very high rate enhancement.

Before concluding the overview of crown-type compounds, a brief mention may be made of lariat ethers. These belong to a relatively new class of compounds, introduced by Gokel<sup>16</sup>. They possess a macrocyclic polyether ring and a flexible arm extending from the ring to which electron donor groups are attached as shown in **13** and possess structural features of monocyclic crown ethers, cryptands and podands.

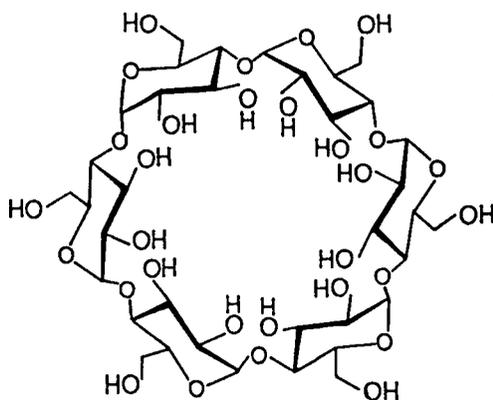


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### 1.2.2. Cycloamyloses

Cyclodextrins<sup>17</sup> are the most thoroughly studied of the naturally occurring receptors that possess rigid cavities. These cyclic oligosaccharides are obtained by the enzymatic hydrolysis of starch. They generally contain

6-8 glucose units linked by 1,4-glucosidic bonds and possess a comparatively hydrophobic interior cavity with 4-7 Å diameter. As a result of the pioneering work of Cramer, Bender, Breslow and others, it is now well established that in aqueous medium  $\alpha$ -cyclodextrin (14) readily forms inclusion complexes with a variety of organic guest molecules including aliphatic and aromatic hydrocarbons, alcohols, phenols, esters, ethers, carboxylic acids etc. These molecules are held inside the cavity by hydrophobic interactions. Due to their extensive complexing properties, cyclodextrins have been widely used for masking odours, stabilizing labile materials, increasing solubility and for changing oily compounds into microcrystalline solids.



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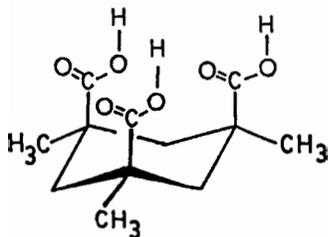
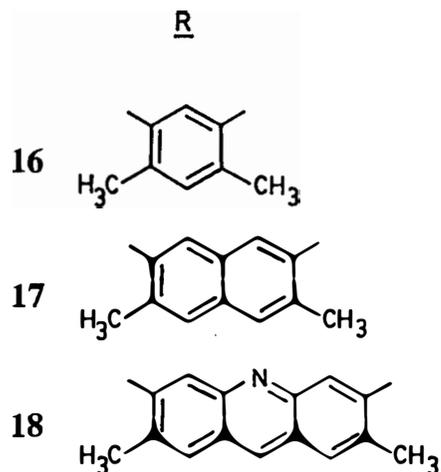
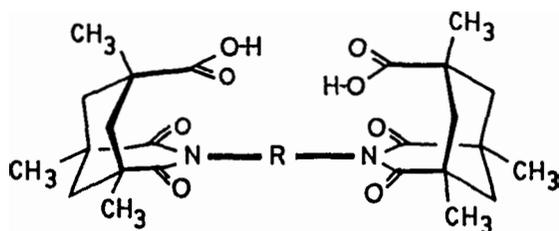
Breslow<sup>18</sup> has devoted considerable effort to investigate the potential of these compounds as enzyme models. In the presence of

$\alpha$ -cyclodextrin, high selectivity was observed for aromatic substitution and ester hydrolysis reactions. For example, chlorination of anisole in the presence of  $\alpha$ -cyclodextrin yielded the *para*-substituted product. But in its absence the reaction led to a mixture of *ortho* and *para*-substituted products. Similarly the rate of hydrolysis for *meta*-substituted esters were significantly greater than the *ortho* or *para* analogues.  $\alpha$ -Cyclodextrin has also been used as mimics for transaminase and ribonuclease with modest rate accelerations<sup>18a</sup>. In later studies derivatized cyclodextrins were used for accelerating the rate of acyl transfer reactions. But dramatic rate enhancements occurred only when the substrate geometry was optimized. Substrates based on ferrocene nucleus showed rate increases of the order of  $10^7$ , exceeding the acceleration achieved by the enzyme  $\alpha$ -chymotrypsin for the hydrolysis of *p*-nitrophenyl acetate.

### 1.2.3. Molecular Clefts

A striking feature of the structures that have already been discussed in the context of molecular recognition is their macrocyclic shape. In contrast to this, Rebek and co-workers<sup>19</sup> have developed a few molecular clefts by converging carboxylic acids and these compounds showed recognition towards a variety of organic guest molecules. In their experiments diamines derived from substituted benzene, naphthalene,

acridine etc were condensed with two molecules of Kemp's triacid (**15**) to get 'C' shaped molecules **16-18**. Since the carboxyl functions are buried in the cleft intermolecularly hydrogen bonded dimers were not observed.

**15**

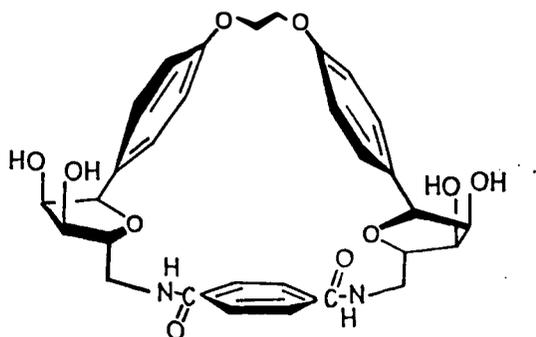
In the acridine derived cleft **18**, the distance between opposing carboxyl functions is 8-9 Å. This compound is a good complexing agent and

showed high selectivity towards pyrazine compared to the stronger base pyridine. It is proposed that the diamine is chelated between the carboxylic acid functions. Studies on quinoxaline and phenazine complexes showed that  $\pi$ -stacking interaction between aromatic units provided additional stability. Stoichiometric complexes were formed with carboxylic acids like oxalic, malonic and phthalic acids and 2:1 complexes with phenyl alanine. Fluorene derived diacids showed selective binding to glutaric and camphoric acids and specific stabilization was observed for substrates bearing aromatic functions. Chiral recognition properties were observed with naphthalene and acridine derived clefts. Apart from these systems, they have also developed some model compounds for the study of base pairing, and enzyme models that catalyse  $\alpha$ -hydrogen exchange of quinuclidinone in deuterated solvents.

#### *1.2.4. Glycophanes*

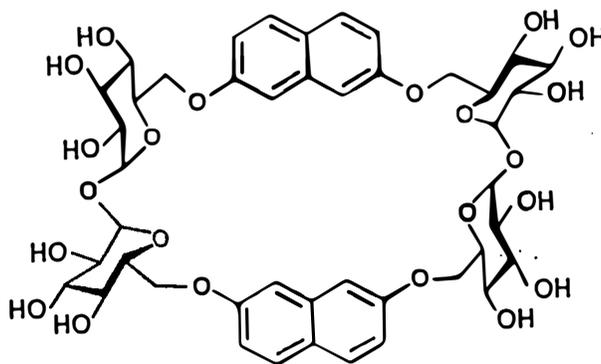
Among the molecular receptors, cyclodextrins have been widely used for the study of molecular interactions in aqueous medium. Apart from this, cyclophanes<sup>20</sup> also have provided models for the above studies. These are a class of macrocyclic compounds where the backbone is entirely made of carbon and hydrogen atoms and are among the versatile class of synthetic receptors. Although these compounds are much more hydrophobic than crown-type compounds, they can be rendered water soluble by attaching

ionic groups. But Wilcox and co-workers<sup>21</sup> adopted some new synthetic approaches towards enantiomerically pure water soluble cyclophanes with hydrophobic cavities, and receptor **19** is the first example of this type. This compound constituted of sugar units and aromatic units is endowed with the attributes of both cyclodextrins (chirality, water solubility and lipophilicity) and cyclophanes (aromatic interactions). Few analogous compounds were also synthesized by Wilcox<sup>22</sup>. These compounds were called 'glycophanes' and are among the more recent class of chiral receptors. Yet another system incorporating D-glucose and aromatic segments was synthesized by Barrett<sup>23</sup>. But no data were available on the complexing properties of these glycophanes.

**19**

Recently, Penades and co-workers<sup>24</sup> have described their elegant work on the synthesis and complexing properties of an interesting

group of glycophanes. They used  $\alpha,\alpha'$ -trehalose which is conformationally more restricted than monosaccharides, for linkage with aromatic spacers like 2,7-dihydroxy naphthalene and 4,4'-isopropylidene diphenol. Glycophane **20**, incorporating naphthalene units, showed donor-acceptor interactions with electron deficient aromatic guests in methanol-water mixture and exhibited chiral discrimination towards racemic amino acids. This receptor also served as a model for studying carbohydrate-carbohydrate interactions in water.



In conclusion, it is evident that the design and synthesis of molecular receptors and their use in the study of molecular interactions are of enormous topical interest. Recent reports have shown that carbohydrate

derivatives can play a significant role in this area. Our studies have been focussed on the synthesis of various macrocyclic molecules incorporating D-glucose and polyethylene glycol units as well as aromatic units. Such compounds can function as receptors with varying cavity sizes and hydrophobicity and a study of their complexing properties is of great interest. The results of our investigations in this area are embodied in this thesis.