

CHAPTER I

INTRODUCTION

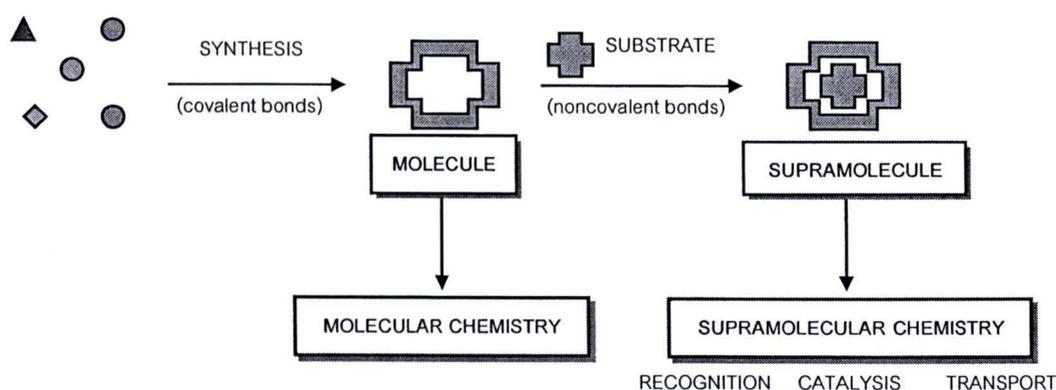
1.1 The Importance of Anions

The ubiquity of inorganic anions in nature, biological system, their importance as food additives, agricultural fertilizers and industrial raw materials, commands considerable attention of the scientific community. For example, chloride is a chemical the human body needs for metabolism and also helps keep the body's acid-base balance. Also, in the central nervous system, the inhibitory action of glycine and some of the action of gamma-aminobutyric acid (GABA) relies on the entry of chloride ion into specific neurons [1]. In the petroleum industry, the chlorides are a closely monitored constituent of the mud system. The increase of the chlorides in the mud system could indicate the possibility of drilling into a high-pressure saltwater formation. Its increase can also indicate the poor quality of target sand. The bromide ion is antiepileptic, and bromide salts are used, particularly in veterinary medicine [2]. Bromide compounds, especially potassium bromide, were frequently used as sedatives in the 19th and early 20th century. Sodium benzoate is a preservative. It is bacteriostatic (antibiotic limit the growth of bacteria) and fungistatic (chemical agent that stop fungi from reproducing) under acidic conditions. It is used most prevalently in acidic foods such as salad dressings, carbonated drinks, jams and fruit juices and condiments.

As these results, the industrial and agricultural utilization of anions raises a number of environmental concerns. The existence of some anions in high level can cause harmful pollution. For instance, nitrate anions from fertilizers run off agricultural land into the water supply leading to disrupts aquatic life cycles [3]. Therefore, these issues necessitate the development of highly sensitive sensor materials for anions of environmental, biological and medical importance based on the supramolecular chemistry involving molecular recognition of anionic species.

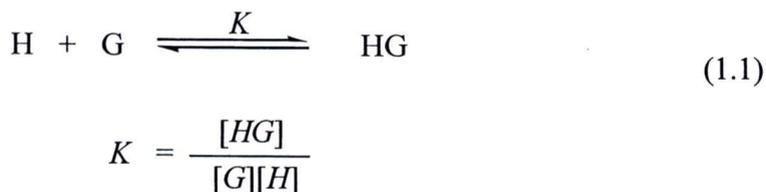
1.2 Concept of Supramolecular Chemistry

Supramolecular chemistry [4] refers to the area of chemistry that focuses on the noncovalent bonding interactions of molecules. While traditional chemistry focuses on the covalent bond, supramolecular chemistry examines the weaker and reversible non-covalent interactions between molecules such as hydrogen bonding interactions, ion-dipole interactions, dipole-dipole interactions, van der Waals interactions, pi-pi interactions and electrostatic interactions as shown in Scheme 1.1. Construction of any supermolecule leads to the three important functions: molecular recognition, translocation and transformation [5]. Molecular recognition plays an important role in biological systems such as antigen-antibody, DNA-protein, sugar-lectin, or RNA-ribosome. A good example of molecular recognition is the antibiotic vancomycin that selectively binds with the peptides with terminal D-alanyl-D-alanine in bacterial cells through five hydrogen bonds. In supramolecular chemistry, such interactions between two or more molecules or ions in a unique structure arrangement are known as host-guest chemistry [6]. The host component is defined as an organic molecule or ion whose binding sites converge in the complex and the guest component is defined as any molecule or ion whose binding sites diverge in the complex. An advanced and challenging target in host-guest chemistry is the construction of a host molecule having the ability of specific recognition with a guest molecule.



Scheme 1.1 The scope of supramolecular chemistry

In host-guest chemistry, the stability constant K of a host/guest (1:1) complex is defined by the equilibrium:



Where H, G and HG represent the host, guest and complex species.

1.3 Molecular Recognition to Chemical Receptors for Anions

In the field of supramolecular chemistry, the progress in synthetic receptors for anions has attracted considerable attention due to their biological, environmental and medical importance as mentioned before. However, sensing of anions is a particularly challenging area of research. Anions are larger than isoelectric cations, therefore anion require receptors of considerably greater size and electrostatic binding of anions to the receptors are less effective because of lower charge-to-radius ratio than cations. Moreover, anions have a wide range of geometries which results in higher design complexity of receptors and sensors required for successful recognition and binding [1].

There have been a number of researches devoted to the development of synthetic molecular receptors for anions using molecular recognition properties. Several types of interactions are available in designing an anion-binding host. Some of the fundamental characteristics of anions have been considered. For example, the vast majority of anions are Lewis bases. This property suggests that hosts containing Lewis acidic atoms might make the basis of a suitable host by formation of coordinate bonds or hydrogen bonds [7]. The negative charge of anion suggests that both neutral, and especially positively charged hosts will bind anions [8]. Moreover, anions are highly polarisable and so van der Waals or hydrophobic interaction will be significant. While nondirectional, these are related to the contact surface area of host and anion, and so three-dimensional encapsulation of the anion should enhance binding of all anions capable of fitting within the host [9]. Therefore, chemical receptors for anions are frequently incorporate of functional groups that provide the hydrogen bonding interactions, while the framework usually provides the metal

coordination and or hydrophobic effects. The functional groups for hydrogen bonding such as amides, sulphonamides, ureas, thioureas and pyrroles are shown in Figure 1.1.

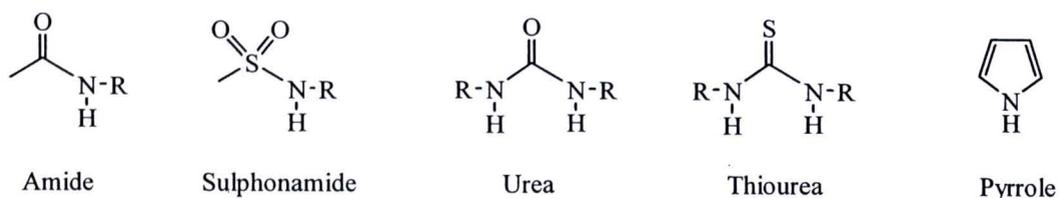


Figure 1.1 Functional groups providing hydrogen bonding interactions.

1.4 Anion Receptors Based on Calix[4]arene

A calix[4]arene is a macrocycle based on a hydroxyalkylation product of a phenol and an aldehyde and has 4 repeating units in the ring. They are characterized by a three-dimensional basket, cup or bucket shape. Calix[4]arene exists in different chemical conformations because rotation around the methylene bridge is not difficult. There are 4 up-down conformations: cone, partial cone, 1,2 alternate and 1,3 alternate, Figure 1.2. The four hydroxyl groups interact by hydrogen bonding and stabilize the cone conformation. In many researches, calix[4]arene was used as a building block for anion receptors because the narrow rim and the wide rim can be placed with any substituents. As a result, conformation of calix[4]arene can be locked in place with proper substituents replacing the hydroxyl groups on the narrow rim or a bulky substituent on the wide rim. Therefore, the calix[4]arene can be used as a building block to obtain desired structures for anion receptors.

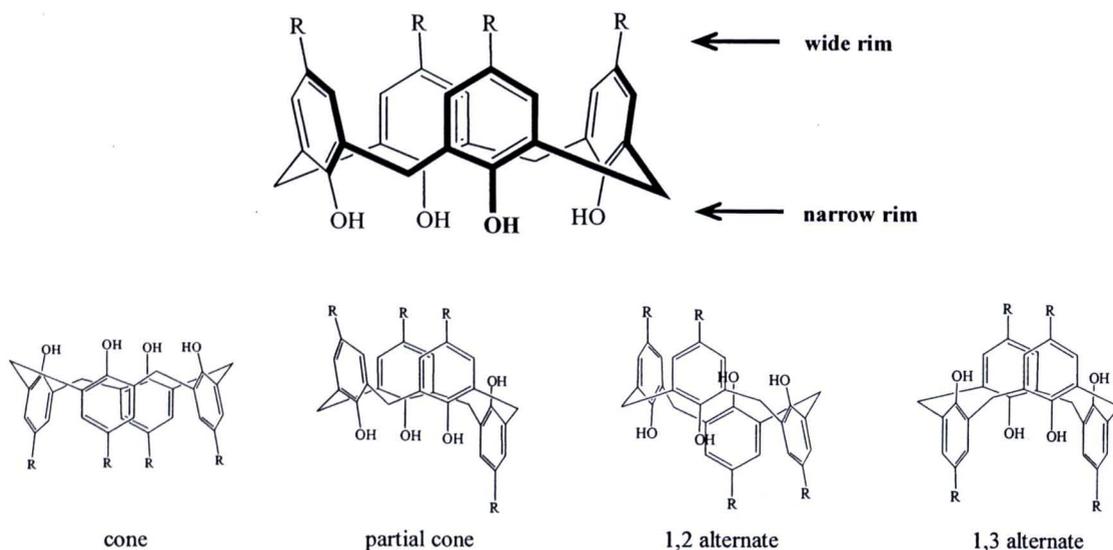
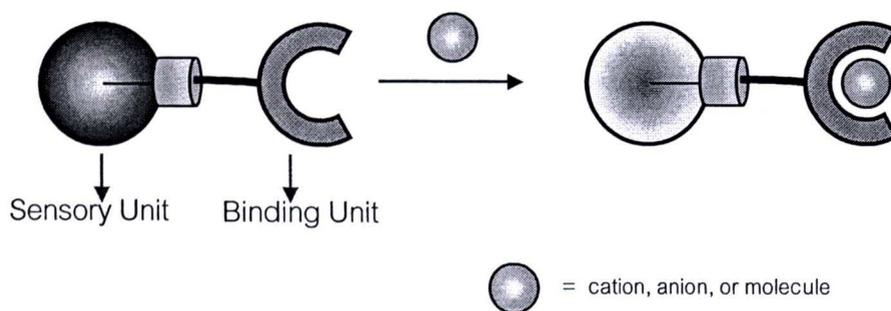


Figure 1.2 Conformations of calix[4]arene

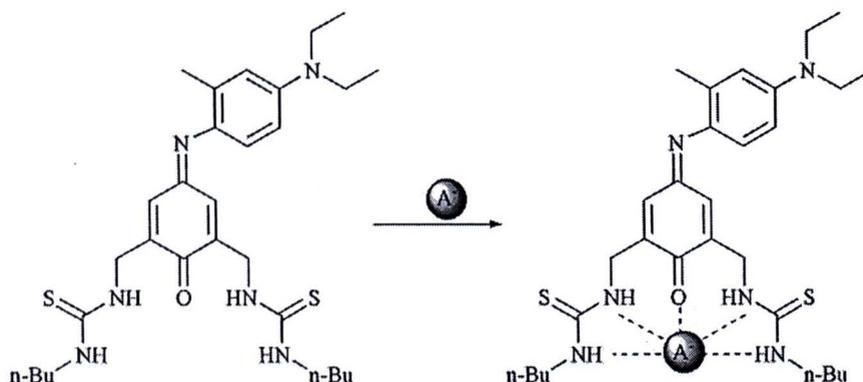
1.5 Anion Sensors

Receptors specifically designed for sensing proposed are called sensors. The basic concept of a molecular sensor illustrated in Scheme 1.2. A sensor consists of two parts: the binding subunit and the signalling subunit. The guest must be coordinated to a binding subunit of the sensor which is communication with a signalling unit that can change some characteristics upon guest coordination. Therefore, in the guest binding event, the signalling unit generates a signal in the form of an emission of electromagnetic radiation (photochemical sensing) [10], a change of redox potential (electrochemical sensing) [11] or an otherwise externally measurable change (e.g. in color or pH) [12, 13].



Scheme 1.2 the concept of chemical sensors

For example, Hong and co-workers have reported anion coordination with a new chromogenic indoaniline-thiourea based sensor, compound **1.1**, Scheme 1.3 [14]. This sensor showed significant color and UV-Vis spectral changes upon binding anions. Upon the addition of H_2PO_4^- or HSO_4^- , the color of the CHCl_3 solution changed from blue-green to deep blue. In addition, in the case of AcO^- , F^- , Cl^- , Br^- and I^- , no or less intense color change were observed. This sensor, thus, allows the selective colorimetric detection of tetrahedral oxoanions such as HSO_4^- and H_2PO_4^- .



Scheme 1.3 Sensor **1.1** and its anion coordination

1.6 Electrochemical Anion Sensors

The study of the electrochemical properties of supramolecular systems is an area of intense interest. A subset of this field of study is the production of redox-active molecular sensors capable of sensing charge or neutral guests and reporting their presence by means of an electrochemical response. A variety of redox-active centers have been incorporated into various host frameworks and been shown to electrochemically detect guests as shown in Figure 1.3. Normally, the electrochemical sensors contain two components: an electroactive group and binding site. As a consequence of the electrochemical shift effect, molecular redox sensors are able to transform chemical information into electronic signals, which can be applied as molecular devices for converting molecular recognition processes in molecular level into macroscopically measurable electronic signals.

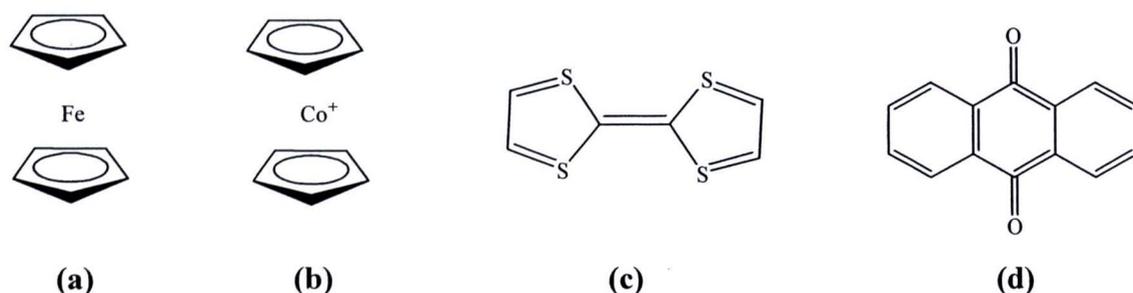
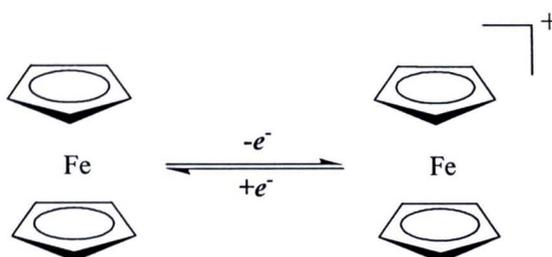


Figure 1.3 Redox-active molecules for electrochemical sensing (a) ferrocene, (b) cobaltocenium, (c) tetrathiafulvalene and (d) anthraquinone.

The use of ferrocene modified receptors as redox-active sensors for guests has been explored by a number of researchers. Ferrocene has been employed in the electrochemical sensing of cations, anions and neutral molecules in both organic and aqueous media [14]. Moreover, ferrocene exhibits good reversibly electrochemical signals and cyclopentadiene ring is easy to functionalize. Basically, ferrocene can be oxidized to ferrocenium ion involving one electron transfer process as shown in Scheme 1.4. The magnitudes of oxidation potential shifts depend on the interaction between the ferrocenium ion and incoming guest species.



Scheme 1.4 The oxidation process of ferrocene to ferrocenium ion

Ferrocene units appended with secondary amides have been used for anion recognition as shown in Figure 1.4. Being neutral, these receptors have no inherent electrostatic attraction. However, electrostatic interactions can be switched on by oxidation of ferrocene to ferrocenium and consequently these molecules exhibits interesting electrochemical anion recognition effects. For example, sensors **1.2-1.5** are capable of detection H_2PO_4^- via large cathodic shifts of up to 240 mV because the ferrocene moiety is easy to oxidize. These behaviors will significantly enhance the binding strength towards anions and also exhibit the interesting electrochemical anion recognition.

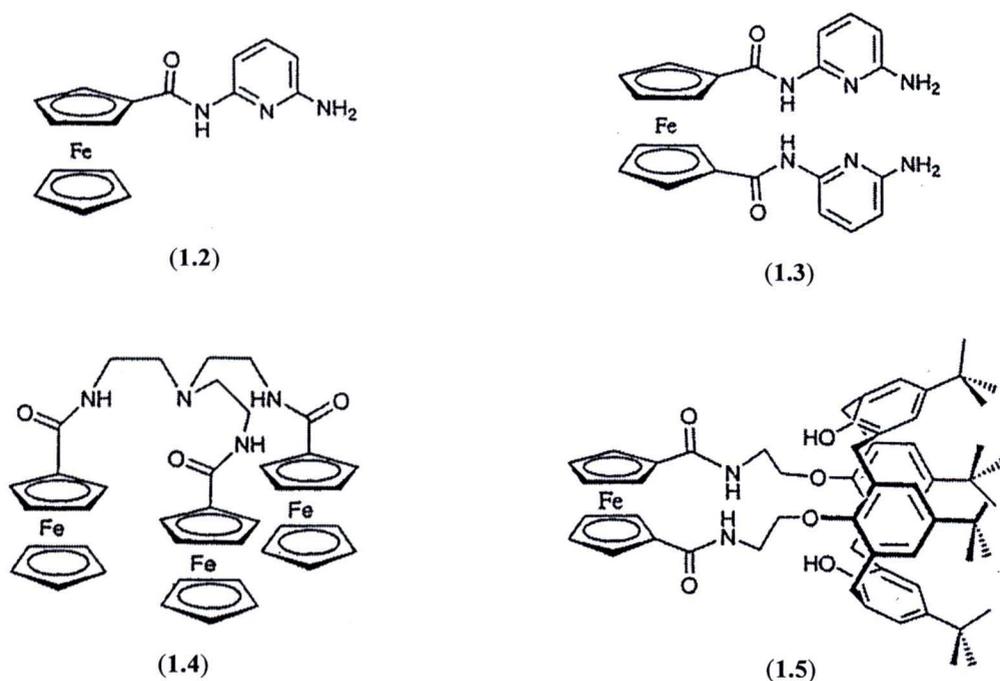
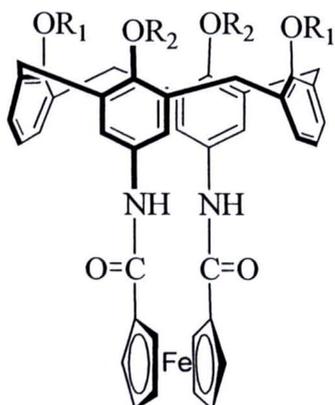


Figure 1.4 Ferrocene-amide based receptors

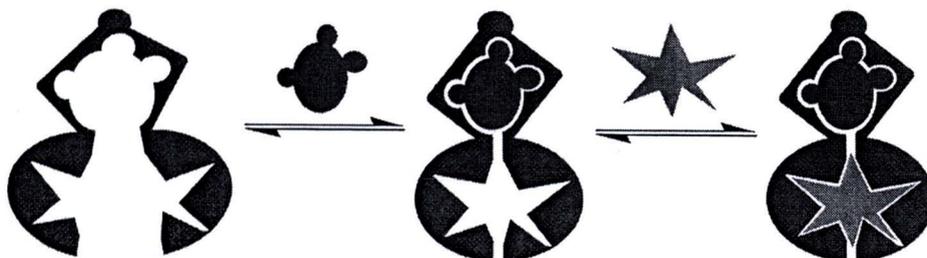
In 2001, Tomapatanaget and co-worker synthesized anion sensors **1.6-1.8**, calix[4]arene derivative containing ferrocene amide at the lower rim and ethyl ester groups at the upper rim [15]. Anion-binding studies by $^1\text{H-NMR}$ titration showed that compounds **1.6-1.8** were able to bind selectively with carboxylate anions. Moreover, cyclic voltammetry and square wave voltammetry illustrated that these receptors can act as electrochemical sensors for carboxylate anions as well.



- 1.6:** R₁, R₂ = CH₃
- 1.7:** R₁, R₂ = CH₂CO₂Et
- 1.8:** R₁ = CH₃, R₂ = CH₂CO₂Et

1.7 Heteroditopic Receptors and Sensors

The ditopic receptor is a compound that has conformation coupling between two binding sites. Binding at one site produces a conformational change that influences the binding ability of the second site. System such as this is called allosteric system which is known as one of the elegant strategies for precisely regulating and controlling the function in biological systems. This concept is exemplified in Scheme 1.5, where one part of the molecule is coordinated to a first guest results in the allosteric organization of a second distant binding site.

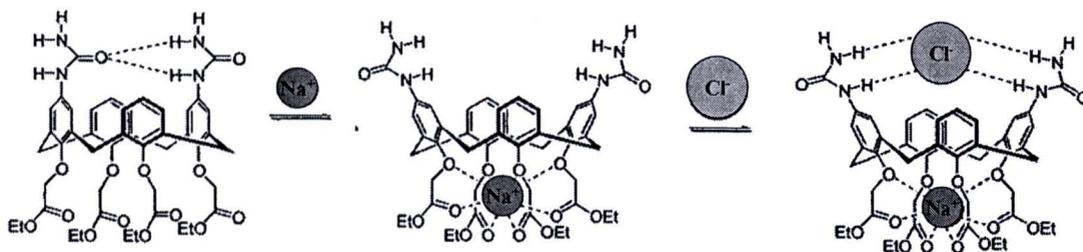


Scheme 1.5 Schematic illustration of allosteric effect of ditopic receptor

Most of the early examples of this concept were homoditopic receptors and sensors that contained two identical binding sites connected by linker [16, 17]. More recently, attention has turned to heteroditopic receptors and sensors that contain two quite different sites [18, 19]. The binding of one charged species may facilitate the coordination of the other ion. Thus, the binding constants are higher than that of one species alone. The cooperative behavior which is the association of one ion influences the binding affinity of the other being either enhanced or reduced. The cooperative behavior can result from several factors, such as through-space or through bond electrostatic interactions between bound guest molecules or conformation changes induced by binding.

For example, in 1996, the Reinhoudt group synthesized a calixarene ditopic receptor **1.9** [20]. This receptor adopts a pinched conformation due to intramolecular hydrogen bonding between the trans-like urea groups, thus preventing anion binding. However, when sodium ions are added, cation complexation at the lower rim alters the calix conformation, thereby breaking the hydrogen bonds between the urea groups. As a result, chloride ion can be recognized at the upper rim, as evidenced by

downfield shifts in the $^1\text{H-NMR}$ signals of the urea hydrogens. This chemistry is summarized in Scheme 1.6.

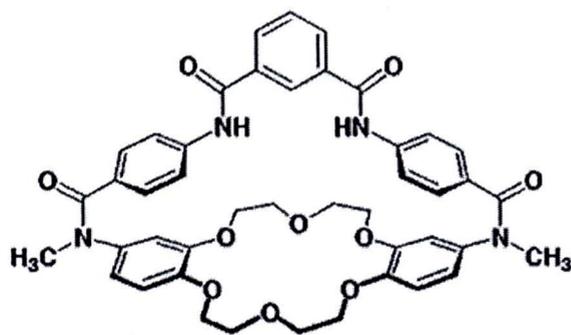


Scheme 1.6 Proposed sequential binding of NaCl by calixarene ditopic receptor **1.9**

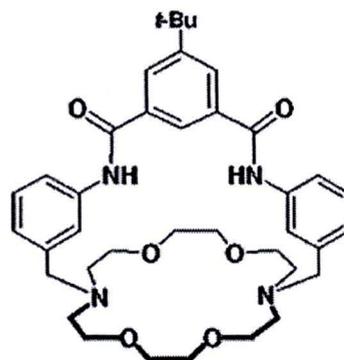
1.8 Literature Review of Heteroditopic Anion Receptors and Sensors

There have been a number of researches devoted to the development of synthetic heteroditopic sensors for anions of environmental, biological and medical concerns. Most of these heteroditopic sensors are designed based on ion-pair recognition, in which host simultaneously bind both cationic and anionic guests, to exhibit cooperative or allosteric behavior. The binding of one guest ion can induce electrostatic and conformational changes in the host, thereby enhancing the complexation of the counter ion. These receptors combine, for example, crown ethers and calixarenes for cation complexation with Lewis acid centers, pyrroles, amides or urea groups for anion recognition. Some examples of heteroditopic receptors and sensors are described below.

Smith and co-workers synthesized the macrobicyclic receptors **1.10** [21]. The complexation studies revealed that the chloride anion affinities normally displayed by receptor **1.10** were increased in the presence of Na^+ or K^+ ion. It was shown that the binding cooperativity would be improved if the salt were bound to the receptor as a contact ion-pair. Thus, macrobicycle receptor **1.11** was designed as a salt-binding analogue of **1.10** but with a smaller distance between the anion and cation binding sites [22]. They found that receptor **1.11** bound a contact ion-pair in solution more strongly than either of the free ions. The binding studies showed that the **1.11**/ Cl^- binding constant was hardly affected by the presence of Na^+ , but it increased more than 10-fold by the presence of K^+ . An explanation of why K^+ enhances **1.11**/ Cl^- binding better than Na^+ is provided by the X-ray diffraction technique.



1.10



1.11

Single crystal X-ray diffraction structures obtained for the NaCl and KCl complexes of receptor **1.11** are shown in Figure 1.5. In the case of the **1.11**/NaCl complex, the average distance from the four diazacrown oxygens to the Cl⁻ is 4.20 Å, which is significantly closer than 4.71 Å observed in the **1.11**/KCl complex. The implication is that once K⁺ cation is bound, receptor **1.11** forms a contact ion-pair with Cl⁻ more favourably than **1.11**/NaCl complex.

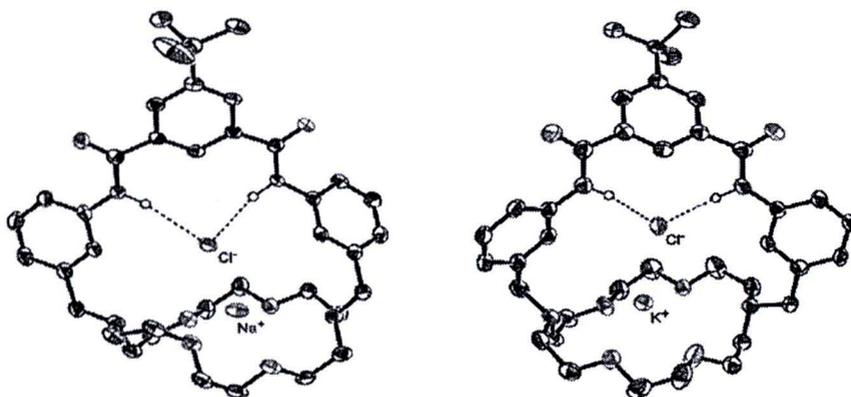


Figure 1.5 X-ray crystal structure of [1.11/NaCl] and [1.11/KCl] complexes

In 2001, the Beer groups has reported the calix[4]arene esters linked to ruthenium(II)- or rhenium(I)-bipyridyl metal site (receptor **1.12**) [23]. In the presence of one equivalent of the alkali metal cations, the complexation studies showed significant increases in the binding constants for both Br⁻ and I⁻. The enhanced affinities for these anions in the presence of the co-bound cation was believed to arise from cation-anion attraction, preorganizational effects and increased strength in hydrogen bonding to the bound anion owing to cation complexation disrupting an

intramolecular hydrogen bond between the amide NH proton and a calixarene ester moiety.

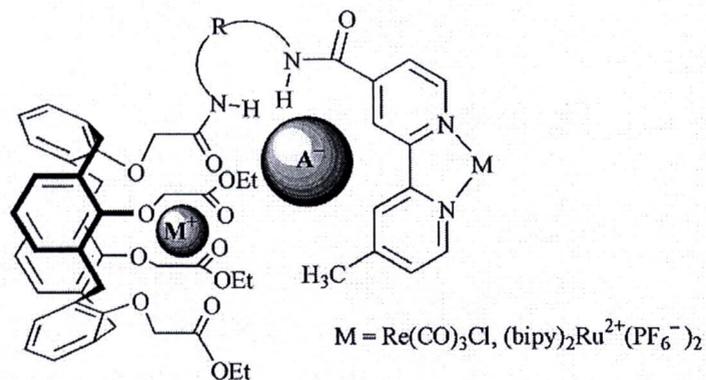
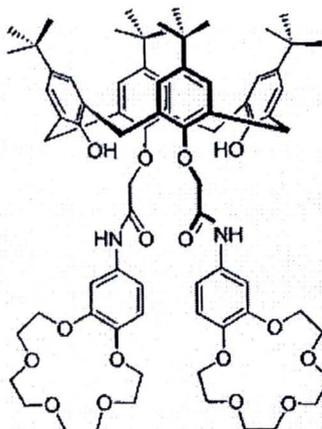


Figure 1.6 Proposed binding of receptor **1.12**

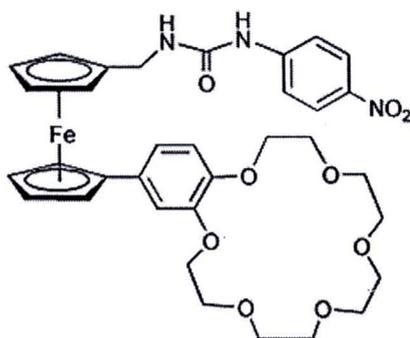
One further example of a calix[4]arene based heteroditopic receptor has been reported. Receptor **1.13**, consists of two benzo[15]crown-5 groups attached to a calixarene through amide linker [24]. Receptor **1.13** alone showed very little affinity for anions. In the presence of K^+ or NH_4^+ ions, however, a sandwich complex is formed between the two benzocrown units, which in turn bring the amide groups into closer mutual proximity. These conformational changes, couple with the increased electrostatic attraction provided by the co-bound cation, led to a particular strong binding of dihydrogen phosphate.



1.13

In 2002, Miyaji and co-workers reported a ferrocene-based heteroditopic receptor, compound **1.14**, that contains a urea and a benzocrown ether unit for anion and cation binding sites [25]. Compound **1.14** can function as a molecular switch by using appropriate combinations of anions and cations in solution to control its color.

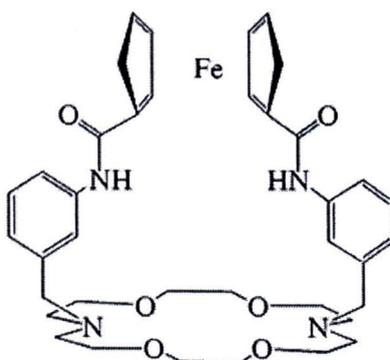
Upon addition of F^- to **1.14** in acetonitrile, the color was changed in the appearance of the solution from colorless to yellow. Interestingly, in the addition of K^+ to the solution of **1.14**/ F^- , the yellow color induced by the presence of F^- turned to colorless. This implied that the color change was controlled by F^- 'switches on' and K^+ 'switches off'. Thus, this system may provide a useful addition to the range of optical devices that can operate at the molecular level.



1.14

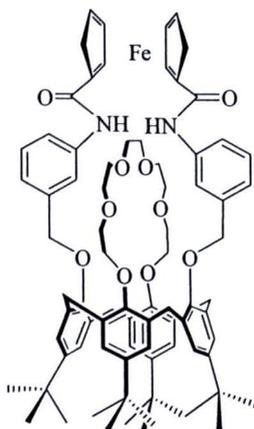
The heteroditopic receptor **1.15** containing a crown ether and amidoferrocene groups was reported by Suksai and co-workers [26]. The anion binding and sensing properties were investigated by NMR spectroscopy and electrochemistry. In 1H -NMR titration experiments, the addition of Cl^- , Br^- and I^- ions to the solution of receptor **1.15** resulted in slightly downfield shifts of the NH amide protons in the absence of alkali metal ions. However, in the presence of alkali metal ions, the results can be categorized into two groups: negative and positive effects. The system of **1.15**/ $NaCl$, **1.15**/ KCl and **1.15**/ KBr show the negative binding behavior due to ion-pair formation between bound metal cations and unbound anions. In contrast, the systems of **1.15**/ $NaBr$, **1.15**/ NaI and **1.15**/ KI were found to have the positive binding behavior. The binding constants of anion in such systems were markedly enhanced in the presence of metal cations. Therefore, the presence of alkali metal ions in receptor **1.15** switches on Br^- and I^- binding. In the electrochemical studies, the presence of metal ions leads to increase of cathodic shift of the redox potential of **1.15** upon binding Cl^- and Br^- anions. Thus, compound **1.15** showed the ability to sense Cl^- and Br^- electrochemically.





1.15

Moreover, Suksai and co-workers synthesized the receptor **1.16**, the amidoferrocene on *p-tert*-butylcalix[4]arene containing pseudo crown ether. They expected that preorganization of molecular binding site are easier due to the flexible structure of calix[4]arene. In the presence of Na^+ , they found that receptor **1.16** showed high selectivity towards Br^- and AcO^- . Electrochemical studies have showed that in the presence of metal cations, the interactions of heteroditopic receptor **1.16** towards Cl^- and AcO^- were higher than its free form.



1.16

1.9 Objectives of This Research

This project has been focused on the synthesis of heteroditopic electrochemical anion sensors containing ferrocene as the sensory unit. Recognition sites of cations and anions were considered firstly. As outlined, according to the previous reports on electrochemical anions sensors based on calix[4]arene, compound **1.16**, containing pseudo crown ether as a cation binding site and amidoferrocene as a anion binding site in the same site of the receptor. The compound **1.16** presented a

