

CHAPTER I

Introduction

1.1 Supramolecular Chemistry

One of the most actively pursued fields of science is supramolecular chemistry. Its implications reach from molecular recognition in synthetic and natural complexes to exciting new applications in chemical technologies, materials, biological and medical science. Principles and Methods in Supramolecular Chemistry gives a systematic and concise overview of this diverse subject. Particular emphasis is given to the physical principles and methods which are important in the design, characterization, and applications of supramolecular systems. Supramolecular chemistry is concerned with entities of higher complexity than molecules themselves. The supramolecular species and assemblies are held together and organized by means of intermolecular binding interactions. It is a highly interdisciplinary field of science and technology, bridging chemistry to biology and physics. Examples of supramolecules are complexes using non-covalent bonds such as hydrogen bonding interactions, electrostatic interactions, cation- π interactions and π - π interactions. The modification by association is a general phenomenon, and a major field of supramolecular chemistry. Alternately, supramolecular chemistry is known as **Host-Guest Chemistry**. The definition of supramolecular chemistry is depicted in the **Figure 1.XX**.

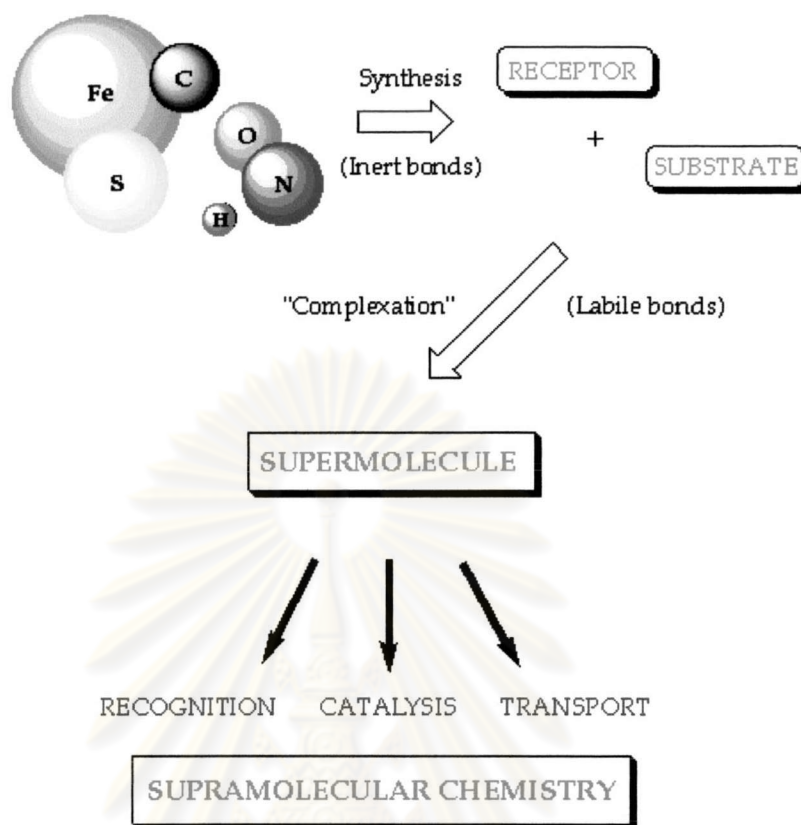


Figure 1.1 Definition of supramolecular chemistry ¹

In early years, the meaning of 'supramolecular' described the interaction between macromolecules²⁻³ and the organization of enzyme and membrane systems.⁴ Currently, supramolecular can mean either 'extramolecular' or 'intermolecular'. Occasionally, although rarely, 'supramolecular' is applied to both intra- and extra- molecular aspects of one chemical system.⁵

Therefore 'supramolecular chemistry' currently has three different meanings:

- (a) intermolecular interaction;
- (b) applied coordination chemistry;
- (c) a strategy of controlled organization of multiple separate compounds.

1.2 Hydrogen bonding interaction

Hydrogen bonding is particularly a kind of dipole-dipole interaction and is ubiquitous in supramolecular chemistry. It consists of interactions between hydrogen bond acceptors

and hydrogen bond donors. A hydrogen atom attaches to an electronegative atom (or an electron withdrawing group). Typically this occurs where a partially positively charged hydrogen atom lies between partially negatively charged oxygen and nitrogen atoms, but is also found elsewhere, such as between fluorine atoms in HF_2^- and between water and the smaller halide ions F^- , Cl^- and Br^- (e.g. $\text{HO-H}\cdots\text{Br}^-$)⁶, and to a much smaller extent to I^- .⁷ In theoretical studies, strong hydrogen bonds even occur to the hydrogen atoms in metal hydrides (e.g. $\text{LiH}\cdots\text{HF}^8$). Hydrogen bond interactions can be divided into three different types: strong, moderate and weak. This depends on the functional groups of donors and acceptors. (Table 1.1) resulting in different properties of hydrogen bonding interactions. (Table 1.2). Hydrogen bonds come in a bewildering range of lengths, strength and geometries. Typically, hydrogen bonded $\text{O}\cdots\text{O}$ distances are 2.5-2.8 Å in lengths.⁹ Hydrogen bonds to larger atoms such as chloride are generally longer, and may be weaker as a consequence of the reduced electronegativity of the larger halide acceptor. In addition, the hydrogen bond donor is encountered depending on the environment, not only hydrogen on the electronegativity atoms but also that on carbon atoms in close distance such as $-\text{C-H}\cdots\text{O-C}-$.¹⁰



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Table 1.1 Functional groups that form hydrogen bonds¹⁰

Strong hydrogen bonds	
Donors and acceptors	
$[F\cdots H\cdots F]^-$	Symmetrical hydrogen bifluoride ion
$[H\cdots F\cdots H]_n^-$	Anions in fluoride HF adducts
$[O\cdots H\cdots O]$	Organic hydrogen anions, hydrogen phosphates and sulfates, hydrogen carboxylate ions
$[O^+\cdots H\cdots O]$	Hydroxonium ions, pseudo hydrates
$[N^+\cdots H\cdots N]$	Proton sponges
$[N\cdots H\cdots N]$	
Moderate hydrogen bonds	
<i>Donors and acceptors</i>	
$O\cdots H, P\cdots O\cdots H,$ $H\cdots O_w\cdots H$	Water, hydrates, alcohols, carboxylic acids, phenols, carbohydrates, oligo- and polysaccharides, nucleosides, nucleotides, nucleic acid
$\begin{array}{c} C & & N \\ & \diagdown & / \\ & N-H & N-H \\ & / & \diagdown \\ C & & C \end{array}$	Secondary amines, amides, carbamates, hydrazides, purines, pyrimidines, barbiturates, nucleosides, nucleotides, peptides, proteins (main chain and side chain)
<i>Donors only</i>	
$N^+(H_3)H$	Ammonium salts
$\text{---}N^+(H_2)H$	Zwitterion amino acids
$\text{---}N^+(H)H$	
$S\cdots H$	Cysteine
$\begin{array}{c} C \\ // \\ C-N^+-H \\ \\ C \end{array}$	Proteins (side chain, nucleic acids (low pH))
$C=N(H)H$	Primary amines, pyrimidines, purines, barbiturates

<i>Acceptor only</i>	
	Ethers, carbohydrates, oligo- and polysaccharides
	(ring and glycosidic oxygens)
	Carboxylates, zwitterion amino acids
	Carboxylic acids, ketones, esters, N-oxides, pyrimidines, purines, nucleosides, nucleotides, nucleic acids, peptides, proteins (main chain)
	Oxyanions, nitrates, chlorates, sulfates, phosphates
	Tertiary amines
	Purines, pyrimidines, barbiturates, nucleosides, nucleotides, nucleic acid
	Aromatic nitro compounds
	Methionin
<i>Weak hydrogen bonds</i>	
<i>Donors</i>	
$C-H, Si-H$	
<i>Acceptors</i>	
$C\equiv H, F-C,$	aromatic ring

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Table 1.2 Properties of hydrogen bonded interactions.¹⁰

	Strong	Moderate	Weak
A-H...B interaction	Mainly covalent	Mainly electrostatic	Electrostatic
Bond energy (kJ mol ⁻¹)	60-120	16-60	<12
Bond lengths (Å)			
H...B	1.2-1.5	1.5-2.2	2.2-3.2
A...B	2.2-2.5	2.5-3.2	3.2-4.0
Bond angles (°)	175-180	130-180	90-150
Relative IR vibration shift (stretching symmetrical mode, cm ⁻¹)	25%	10-25%	<10%
¹ H-NMR chemical shift downfield (ppm)	14-22	<14	-
Examples	Gas phase dimers with strong acids/base Proton sponge HF complexes	Acids Alcohols Biological molecules	Minor components of bifurcated bonds C-H hydrogen bonds and O-H...π hydrogens

Many techniques are powerful to investigate the hydrogen bonding properties such as spectroscopy, x-ray diffraction, theoretical and thermochemical methods. ¹H-NMR spectroscopy is a well-known technique to monitor hydrogen bonds. It is a consequence of the extremely sensitive proton magnetic resonance toward the electron environment around the proton.

1.3 Molecular Receptors- Design Principles

Chemistry of artificial receptor molecules is worthwhile not only limited to transition-metal ions but also extended to all types of substrates: cationic, anionic, or neutral species of

organic, inorganic, or biological natures. Purpose to achieve high recognition, it possibly occurs with macromolecular receptors in which the guest molecules are wrapped and the complex is a consequence of establishing numerous noncovalent binding interactions corresponding to its molecular size, shape, and architecture. Furthermore, the behaviors between rigidity and flexibility are of particular importance for the dynamic properties of hosts and of guests. Molecules may be designed with rigidly organized receptors. Processes of exchange, regulation, co-operativity, and allostery require a built-in flexibility. In recent years, biological receptor-substrate interactions were found to be the great importance of flexibility. Receptor design thus covers both static and dynamic features of macropolycyclic structures. The stability and selectivity of guest binding result from the set of interaction sites in receptor and may be structurally translated into *accumulation* (or collection) and *organization* (or orientation), i.e., bringing together binding sites and arranging them in a suitable pattern. It is reasonable to design the binding site attached on the building block or framework in which the functional groups can be modified, namely calixarenes¹¹ resorcarenes¹², porphyrin¹³, calixpyrole¹⁴ and cyclodextrin.¹⁵ Typically, the receptor can be classified into cation receptors, anion receptors and neutral molecule receptors depending on types of substrates.

1.3.1 Cation receptors

Recognition of cationic guest species by synthetic receptors containing the cationic binding site, namely uncharged donor electron atom of nitrogen and oxygen atoms and negative charged site, is a rapidly interesting subject in recent years. One application of cationic receptors is to get rid of metallic pollutants in the environment and to study a metal ion playing an important role in living systems. In the past decades, the principle of cation recognition has been used in cation sensory molecules. Designed receptors containing the sensory unit have a capacity of displaying the signal changes between absence and presence of metal ions. Echegoyen et al. have synthesized dithia-crowntetrathiafulvalene derivatives in order to be a cation receptor and give electrochemical signals. Additionally, series of these receptors contain disulfide groups can be a self-assembled monolayers (SAMs) on

gold.¹⁶ Effects of preorganizing structure to cation binding ability were studied by varying the cation binding site. (**Figure 1.2**)

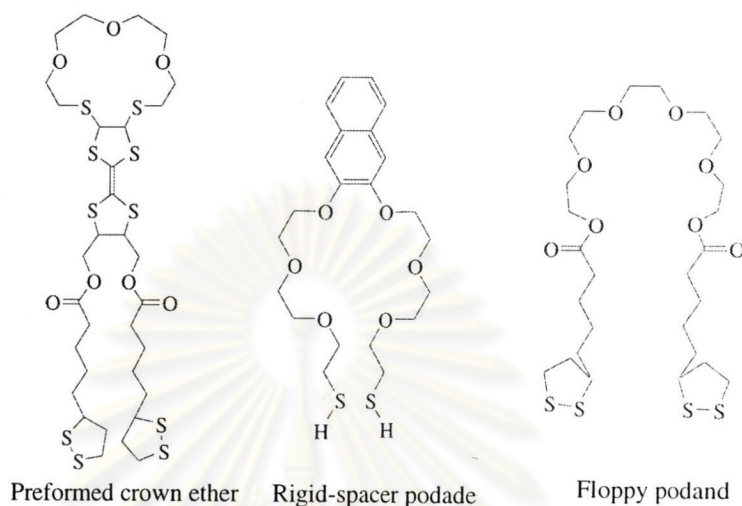


Figure 1.2 Structure representing different degrees of preorganizing of ion binding.

Kim and coworkers prepared the 1,3-calix[4]-bis-crowns receptors containing a crown ether unit for hard acid and an azacrown ether unit for soft acid using electrostatic interactions as shown in **Figure 1.3**. It was found that the crown ether unit preferentially binds K^+ and the azacrown ether unit binds Ag^+ selectively.¹⁷

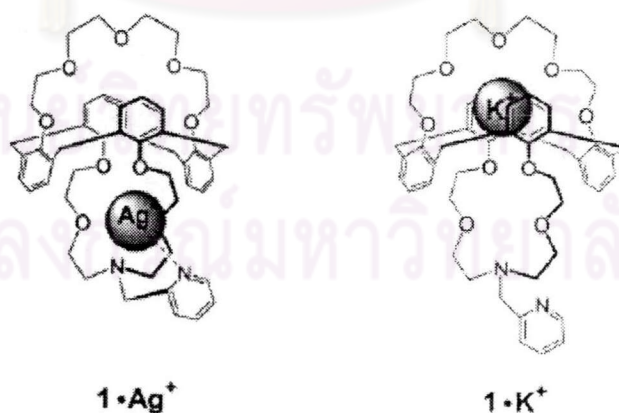


Figure 1.3 1,3-calix[4]-bis-crown receptor with metal ions

1.3.2 Anion receptor

Compared to relatively well-developed cation receptors¹⁸, development of anion receptors is only emerging as a research area of significant importance.¹⁹ The slow development of anion recognition can be related to some inherent differences between anions and cations:²⁰

- i) Anions are relatively large and therefore require (macrocyclic) receptors with a much larger binding site. The smallest anion, F^- , has the same ionic radius (1.33 Å) as a moderately size cation (K^+)
- ii) Anions have many different shapes, e.g., spherical halides, linear SCN^- , trigonal planar NO_3^- , and tetrahedral $H_2PO_4^-$.
- iii) Anions are more strongly hydrated than cations of equal size, whereas the solvation by organic solvents is generally less favorable.²¹
- iv) Several anions are presented only in a narrow pH window, e.g. $H_2PO_4^-$ and CO_3^{2-} anions in an acidic and basic environment, respectively.

Researchers have realized that anion species play important roles in biological and environmental systems. Developing artificial anion receptors is extensively growing in supramolecular fields. A neutral macrocyclic anion receptor (**Figure 1.4**) was prepared by functionalization of two L-alanine units and a 2,6-diacetylpyridine bridge on a calix[4]arene framework on the upper rim. Enantioselective recognition of chiral carboxylates is important because several pharmaceutical compounds possess this functional group. The binding abilities of acetate and benzoate anions as well as chiral carboxylate anions were studied. The ligand binds aromatic carboxylate, namely benzoate, *p*-methoxybenzoate and *N*-acetylphenylalanine carboxylate, employing both hydrogen bonding interactions at NH groups and π - π stacking interactions with pyridine bridge and has the enantioselective binding to D-phenylalanine.²²

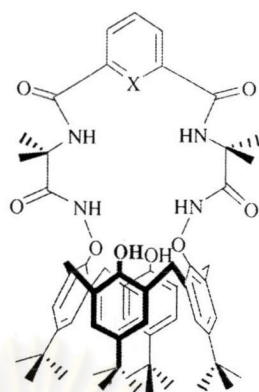


Figure 1.4 The anion receptor containing amide units

Stibor and coworkers²³ synthesized anion receptors based on bis-calix[4]arenes with an appropriate spacer in order to enhance rigidity. (**Figure 1.5**) They can bind anions at urea or amide functional groups using hydrogen bonding interaction. Ligand **B** was expected to bind anions in a stoichiometry of 1:2 host guest ratio; however job's plot procedure unambiguously confirmed the exclusive formation of only 1: 1 complexes with halides or benzoate. The possible explanation may lie in the repulsive interactions between two negative charged sites in close proximity in a non-polar solvent.

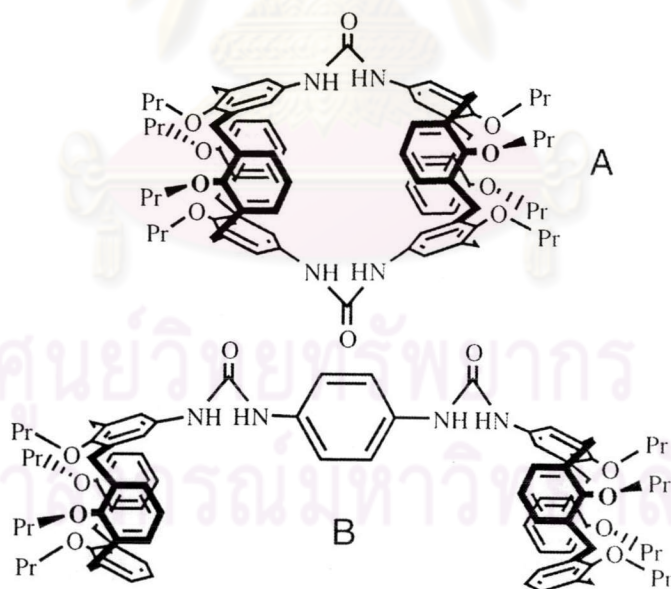


Figure 1.5 Bis-calix[4]arene derivatives containing urea for anion recognition

1.3.3 Neutral receptor

A neutral receptor can bind neutral guest molecules using hydrogen bonding interactions. Reinhoudt and coworkers synthesized calix[4]arene derivatives of dimelamines (**Figure 1.6**) to study the dynamic assemblies between host and guest molecules (barbiturate derivatives) undertaken 30 noncovalent hydrogen-bonded assemblies. The results of assemblies present in three isomerism forms: D_3 , C_{3h} and C_s symmetries. (**Figure 1.7**)

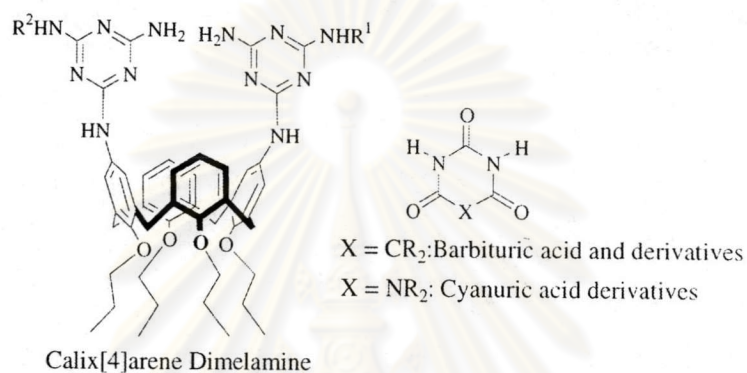


Figure 1.6 Calix[4]arene derivatives and guest molecules

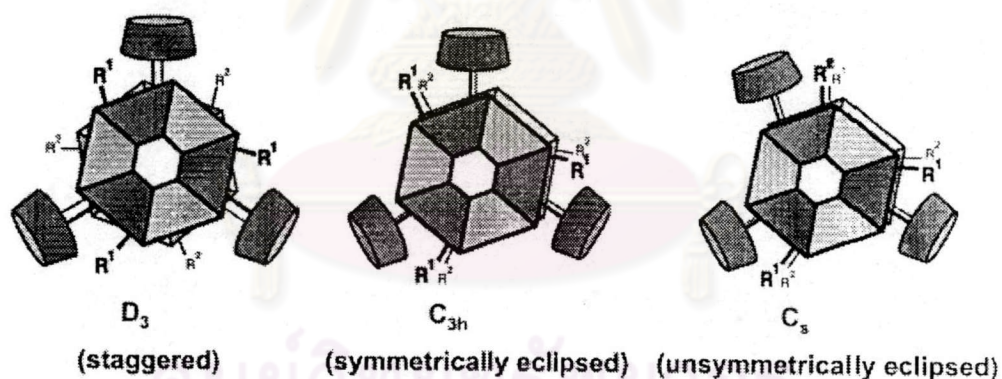


Figure 1.7 The three structural isomers of self-assembly between host and cyanuric acid derivatives

The chiral substituents can have a strong directing effect on the isomeric distribution of hydrogen-bonded assemblies. The handedness of chiral groups, namely (*R*) or (*S*), can generate an energetic difference between the staggered and eclipsed isomers, resulting in preferential formation of the D_3 isomer in the case of dimelamine bearing R_1 and R_2 as (*R*) and preferential formation of C_{3h} and C_s isomer in the case of dimelamine having R_1 and R_2 as (*R*) and (*S*), respectively.²⁴⁻²⁵

1.3.4 Bifunctional receptors.

Ligands simultaneously binding cations and anions²⁶ have been a topic of current interest in supramolecular chemistry.²⁷⁻³⁰ Ditopic receptors have been prepared by attaching both cation and anion binding sites on a core molecule, either a rigidified framework or a non-rigidified one. A ditopic ferrocene receptor consisting of a crown ether unit for binding alkali metals and a urea unit for binding anion has been synthesized as **figure 1.8**. Interestingly, this receptor not only binds cation and anion species but shows a remarkable colour switching (ON- and -OFF) properties induced by anion and cation recognition. A calix[4]arene based Lewis acid UO_2 -center and amido $C(O)NH$ units as additional binding sites is excellent receptor for anions with a high selectivity for dihydrogen phosphate $H_2PO_4^-$. (**Figure 1.8b**) This receptor can bind simultaneously both anionic and cationic species particularly $NaH_2PO_4^-$. Recently, calix[4]arene-based bifunctional receptors³¹ which have selective separation properties for alkali metal phosphate were applied in terms of anion transport through supported liquid membranes.³²⁻³³

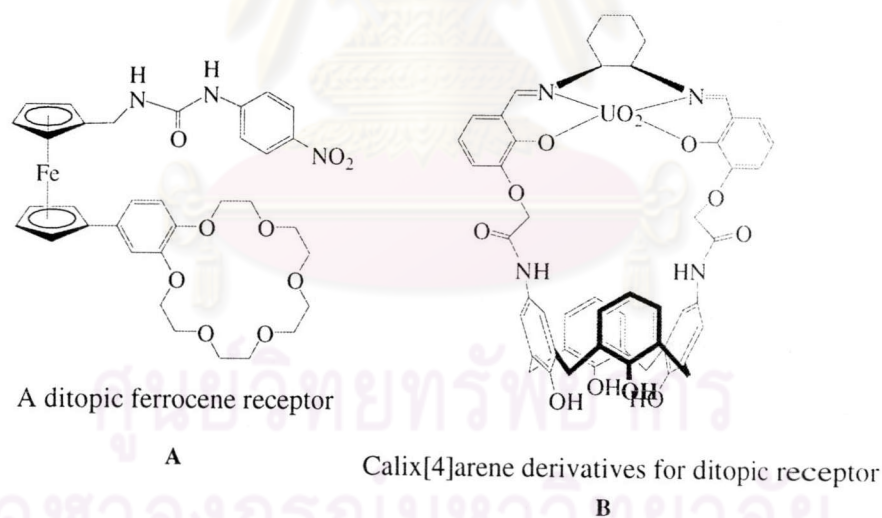


Figure 1.8 The example of ditopic receptors

1.4. Molecular Template

Template is used widely in chemistry, biochemistry, and materials science. Its use has spread dramatically since the 1960s. A general definition of template can be described as:³⁴

- i) a template organizes an assembly of atoms in a specific spatial arrangement.
- ii) a template favors the formation of a single product where the possibility of forming more than one exists.
- iii) a template is more than just a platform onto which a structure is built.

In general, after a template has directed the formation of a product, it is removed to yield the template-free product,³⁵ although sometimes the template becomes inextricably locked into the structure it helps to create.³⁶ Moreover, all intermolecular forces that play a role in host-guest complex effect a stabilization of necessary binary or tertiary complexes. The principle of template effect in figure 1.9 exhibits the guest acting as the template species in order to achieve the desired macromolecules.

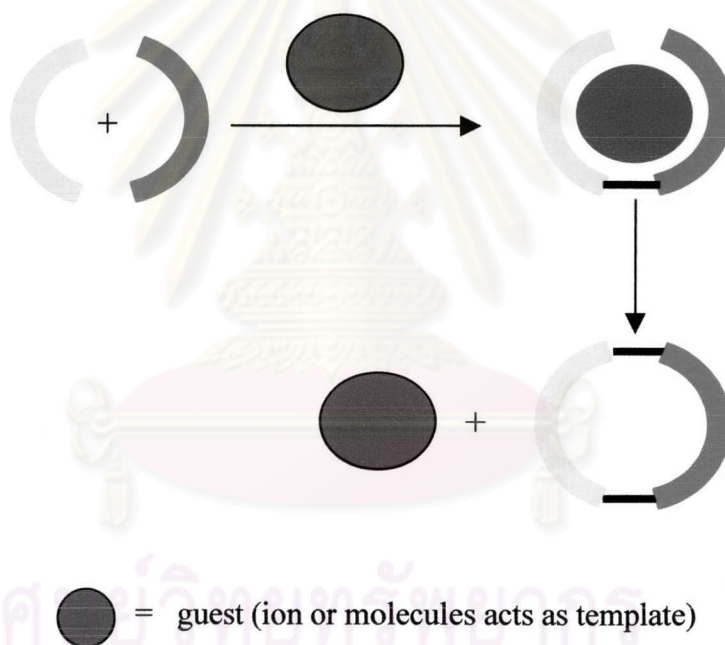


Figure 1.9 Principle of the template effect: The guest (ion or molecule, indicated by shading) acts as a template, favoring connection of decisive bond³⁷

1.5 Objective of research

In this research, we aim to synthesize receptors and sensors for anions. Therefore, diaza dioxo dithia calix[4]arenes and calix[4]arene containing ferrocene amide have been synthesized. This dissertation described two main topics:

- (i) synthesize of diaza dioxo dithia calix[4]arene by metal template method
- (ii) synthesize of calix[4]arene containing ferrocene amide as anion receptors and sensors.

The binding and sensing abilities of these compounds were investigated by $^1\text{H-NMR}$ titrations and electrochemical methods, respectively. The target molecules were shown below.

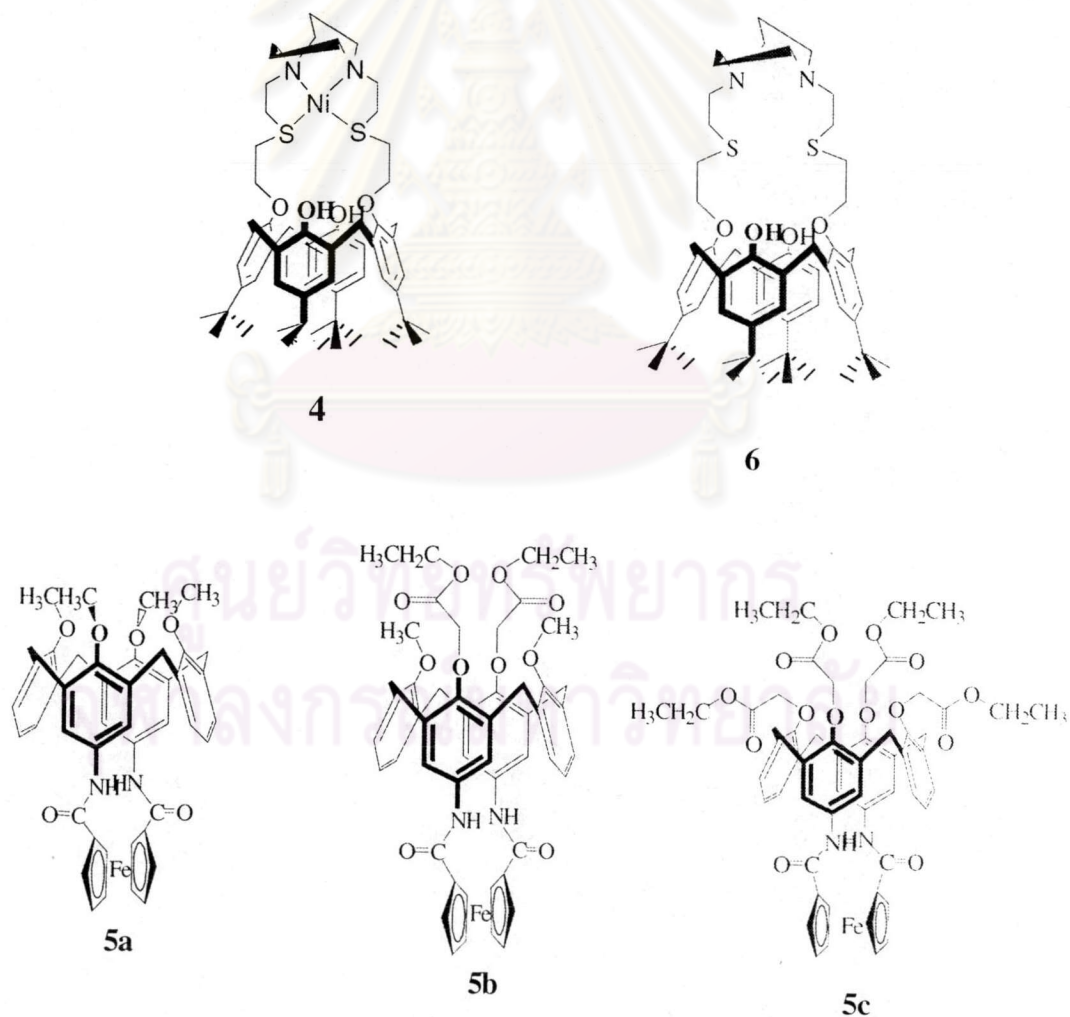


Figure 1.10 Target molecules