

CHAPTER I

INTRODUCTION

1.1 The Importance of Transition Metals and Their Compounds

Among over 115 elements that found on the earth, transition metals, as it well known, cover more than 50 percent of all elements in the modern periodic table. Members of this interesting group encompass various elements from scandium (group III) to precious metals such as silver and gold. The chemistry of transition metals has fascinated many inorganic chemists for many years. They exhibit various oxidation states and some of their compounds are colored in one if not all oxidation states. Moreover, because of partially filled d-shells, they can form some paramagnetic complexes, which show interesting magnetic properties.¹ Complexes of transition metals also play important roles in many fields, which can be categorized as follows:

1.1.1 Industrially, many transition metal complexes, in particular, organometallic complexes of these elements, are utilized as potential catalysts in many industrial processes. For example, $\text{Rh}(\text{PPh}_3)_3\text{Cl}$ or Wilkinson's catalyst, is a good catalytic reagents for the hydrogenation process.²⁻³ Some water-soluble ruthenium complexes containing sulfonated arylphosphines, such as $\text{Ph}_2\text{P}(m\text{-C}_6\text{H}_4\text{SO}_3\text{Na})$ and $\text{P}(m\text{-C}_6\text{H}_4\text{SO}_3\text{Na})_3$, or triaza phosphadmantane are reasonable choices for regioselective hydrogenation of aldehydes in two phases catalytic system.⁴

1.1.2 Environmentally, existence of some transition metal ions in high level can cause harmful pollution. Clearly, chromium ion, especially in oxidation state VI as in CrO_4^{2-} or $\text{Cr}_2\text{O}_7^{2-}$ from many dyes industries, is mentioned as a severe carcinogenic substance. High quantity of Ni^{2+} ion in natural resources is also fatal to human beings.

1.1.3 Biologically, although transition metal ions occur in trace scale in living bodies, they are indispensable components in oxygen transporters and metalloenzymes that control and regulate biological functions. Iron, the most abundant heavy metallic element in organisms, is a center core of two well-known oxygen carriers, hemoglobin and myoglobin, in warm-blooded animals. In contrast, arthropods and mollusks use copper containing proteins like hemerythrin and hemocyanin to uptake and transport dioxygen molecules. Some important enzymes such as carbonic anhydrase and carboxypeptidase A have zinc ion as their essential constituents. Cobalt, which found in vitamin B-12 and coenzyme vitamin B-12, acts as a metal core center of reductase and methyl transfer metalloenzymes.⁵⁻⁶

1.1.4 Medically, no one will contradict that more than 85-90% of drugs, which used in this period of time, are organic compounds. Nevertheless, some research groups are concentrated on studies and developments of inorganic medicinal compounds that can be other candidates for treatments of some diseases.⁷ The most important members of medically employed inorganic compounds are radiopharmaceutical, drugs containing radionuclides. Technetium-based radiopharmaceuticals, which emit gamma ray, are known as imaging agents for diagnostic of multifunction organs.⁸⁻¹⁰ The examples of these drugs are ^{99m}Tc-*d,l* HMPAO, which approved as a cerebral perfusion imaging agent,¹¹ and ^{99m}Tc-MAG₃ that provide suitable biological characteristics for renal imaging observation.¹² Water-soluble vanadium complexes like *bis(maltolato)* oxovanadium ([VO(malto)₂])¹³ and VO-Salen¹⁴ were found to be effective insulin mimics. Auranofin, [Au(PEt₃)(ttag)] (ttag = tetra-O-acetylthioglucose), and its related gold(I) thiolate compounds have been the primary drugs which used for rheumatoid arthritis treatments.¹⁵ Cisplatin, [*cis*-Pt(NH₃)₂Cl₂], and its platinum-based derivatives are considered to be drugs against human malicious cancers and for protein repair.¹⁶⁻¹⁷

1.2 Concepts of Supramolecular Chemistry

Supramolecular chemistry becomes one of the most rapidly expanded fields in modern chemistry.¹⁸ The knowledge from this enchanting topic can be applied to enormous diversities of chemical systems especially the production of molecular devices and artificial biological systems. The definition of supramolecular chemistry may be expressed in many terms as 'chemistry of molecular assemblies and of the intermolecular bond' or 'chemistry of the non-covalent bond'.¹⁹ Supermolecules consist of two or more species held together by weak intermolecular forces (non-covalent intermolecular bond) such as hydrogen bonding, van der Waals interaction, electrostatic interaction or π - π interaction.²⁰ Constructions of any supermolecule are lead to the three important functions: molecular recognition, translocation and transformation.²¹ Indeed, molecular recognition has become characteristics of the language of supramolecular chemistry and has been studied more widely than the others.

1.3 Molecular Recognition and Molecular Receptors

As mentioned above, molecular recognition is defined by the energy and the information involved in the binding and selection of many substrates by a given receptor molecule. It can be implied as the (molecular) storage and (supramolecular) read out of molecular information. High recognition between receptors and substrates was affected by several factors as follows:

- a.) steric complementarity: it depends on shapes and sizes of receptors and substrates;
- b.) interactional complementarities, i.e. presence of complementarity binding sites in the suitable disposition on a substrate and a receptor;
- c.) large contact area between molecules of a receptor and a substrate;
- d.) multiple interaction sites due to weak intermolecular interactions;
- e.) strong overall bindings.¹⁸

Studies of molecular recognition require suitable molecular receptors to specifically interact with many substrates. Molecular receptors are clearly defined as organic structures held by covalent bonds, that are able to bind ionic or molecular substrates by means of intermolecular interactions, leading to an assembly of two or more species. Excellent molecular receptor is one that can bind a particular substrate with high selectivity, high stability and high flexibility.²⁰ Receptors are divided in two types according to the binding position of substrate, **endoreceptors**, which the substrate comprises into the cavity of the receptor, and **exoreceptors** that bearing external binding site. Molecular receptors in supramolecular chemistry are based on the chemistry of crown ethers and cryptands.²²⁻²³ Nevertheless; it is no doubt that highly considerable expansion of this field is based on the establishment of calixarenes chemistry.

1.4 Calixarenes

Condensations of *p*-substituted phenols with formaldehyde under base-catalyzed conditions afford a new class of oligophenolic macrocyclic compounds called calixarenes (in Greek, calix means *chalice* or Eucharistic cup). Calixarenes are defined as [1_n]metacyclophanes comprising phenol units linked by methylene bridges.²²⁻²⁴ Most common calixarenes have a number of phenol groups either 4, 6 or 8 while odd-number ring calixarenes are less studied due to the difficulty of their syntheses. Rotation of phenol units around methylene carbons causes many conformational isomers that give a great number of cavities with different size and shape.²⁵ Since synthetic methods were reported by Gutsche²⁶⁻²⁷, Calixarenes have become one of the most attractive building blocks in supramolecular chemistry. They can be modified to gain numerous types of molecular receptors by many chemical reactions. The modification can be introduced at oxygen atom (that called 'lower rim'), methylene bridge carbon or *para* position of aromatic ring (which named 'upper rim').^{23,28-30} Among the calixarene family, calix[4]arene is the smallest member and served as the most popular building block in syntheses of new compounds which have high selectivity towards ionic and neutral molecules. It is

known that unmodified calix[4]arene exists in 'cone' conformation due to its strong intramolecular hydrogen bonding. However, chemically modified calix[4]arene can adopt other conformations as 'partial cone', '1,2-alternate' and '1,3-alternate'. All four conformations of calix[4]arene can be immobilized in only one of them by different reaction condition. Determination of conformational differences should be deduced from $^1\text{H-NMR}$ spectra because each isomer has its unique methylene proton signals pattern.³¹⁻³²

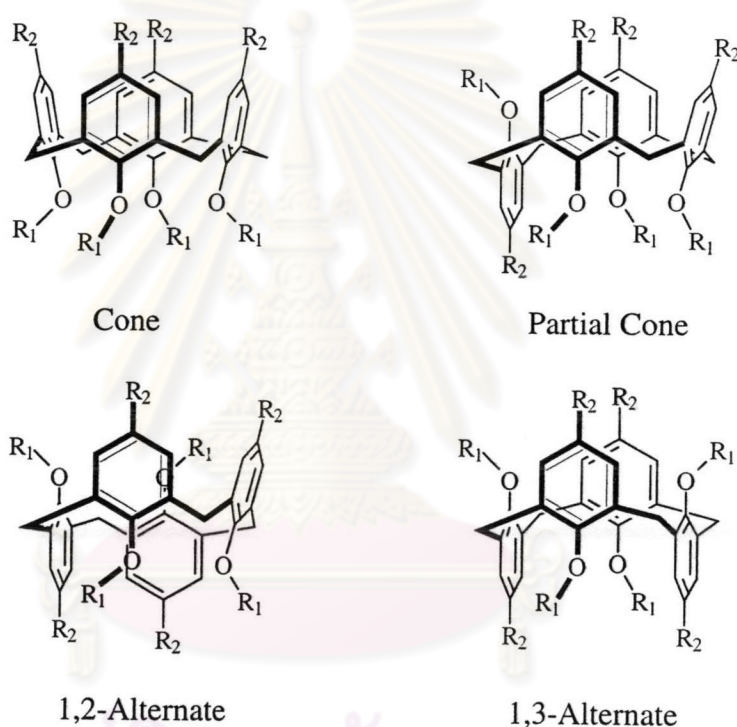


Figure 1.1 Conformational isomers of calix[4]arene

1.5 Calixarene-based Molecular Receptors for Transition Metal Ions³⁴

Modified calixarenes that play, as highly selective host molecules for transition metal ions have been less studied in comparison with the others for binding with alkali and alkaline earth metal ions. The major reason may be less importance in biological functions. Main purposes of metal ions complexations are as follows:

- a) to afford, both electrochemical and photochemical, chemosensors that have high sensitivity towards ions.
- b) to develop new classes of extractants for treatment of toxic and radioactive metal ions.
- c) to obtain new potential catalysts in homogeneous or heterogeneous systems.

High selectivity and high stability of the complexes of transition metals are depend on several factors; size of the binding site, stable geometry of the complex and the most important criterion: the hard-soft complementary of metal ions and donor atoms on receptors. Calixarene receptors for transition metal ions are divided in two types due to the position of metal ions on the molecule of calixarene.

1.5.1 Calixarene ligands possessing transition metal on phenolic oxygen atoms

These types of receptor are obtained from the reaction between compounds of transition metal group V such as titanium (Ti), zirconium (Zr) or tungsten (W) and calixarene derivatives in which the former was treated with strong base like BuLi.³⁵⁻³⁶ These metals are electron deficient and require harder donors like phenoxide ions in calixarenes to form stable complexes. The main propose for a construction of this complex type is a production of novel catalysts for oxidation reaction such as epoxidation reaction that converts unsaturated alkenes to epoxides, which are more valuable industrial materials.

1.5.2 Calixarene ligands possessing transition metal ions on pendant binding sites

These ligands are categorized by types of donor atoms:

1.5.2.1 Calixarenes containing phosphorous donors

Phosphorous(III) is a versatile donor atom in both coordination chemistry and organometallic chemistry. It can bind both moderately hard and soft transition metals, especially ones on second and third rows. Moreover, complexes containing phosphorous ligands are easily studied by ^{31}P -NMR spectroscopy that shows significant shifts of the position of P-signals. Almost phosphorous donor calixarene derivatives are prepared in order to provide novel catalysts where the catalytic center operates inside a spatially confined environment.³⁷ Types of metal complex that have been widely studied are of highly potential metals in catalytic processes such as Ru, Rh, Pd and Pt.

Multidentate phosphorous(III) calixarenes have been well investigated by Dominique Matt and his coworkers.³⁸⁻⁴⁵ Many donor groups such as phosphinite (phosphorous atom directly attached at oxygen atom), phosphine and phosphine oxide (phosphorous form double bond with oxygen) were introduced to calixarene platform and the coordination chemistry of some transition metals were carefully observed. Monophosphino and 1,3-diphosphino diester calix[4]arenes (Figure 1.2) showed different coordination properties towards Pt^{2+} and Pd^{2+} ions.⁴¹ Monophosphino calix [4]arene formed stable complexes with both metal ions in the ratio of metal to ligand as 1:2. Surprisingly, all complexes are in *trans*-isomer while diphosphino diester calix [4]arene reacted with Pt(II) compounds yielded tetrameric complex which can be confirmed by large chemical shift of P atom from 123.0 to 101.8 ppm in ^{31}P -NMR spectra. Vapor-phased osmometry of a Pt-tetramer complex showed the molecular mass at 5445 due to four calix[4]arene units accompanied with 4 Pt^{2+} ions and 8 chloride ions which bound near the metal centers.

In 1999, tetraphenylphosphine calix[4]arene was synthesized and its binding ability with Au^+ ion was investigated.⁴⁵ Among the addition of $[\text{AuCl}(\text{THT})]$ (THT = tetrahydrothiophene), this ligand can form mononuclear, binuclear and tetranuclear species of AuCl-complexes depended on concentration of added Au(I) compounds. Each Au^+ ion bound directly to phosphorous atom cooperated with chloride ion as another ligand and the geometry around Au^+ center in the complex is

distorted linear. In order to determine the stability constant of each complex. UV-spectrophotometric titration was employed to calculate the formation constant for each step at 25 °C. In the first step, the stability constant for monogold complexes was $\log \beta_1 = 4.4 \pm 0.2$ while the addition of the second AuCl fragment gave $\log \beta_2 = 7.0 \pm 0.7$. The tetranuclear species which dominated the equilibrium mixture at high molar ratios of [AuCl(THT)] was formed with $\log \beta_4 = 14.5 \pm 2.0$.

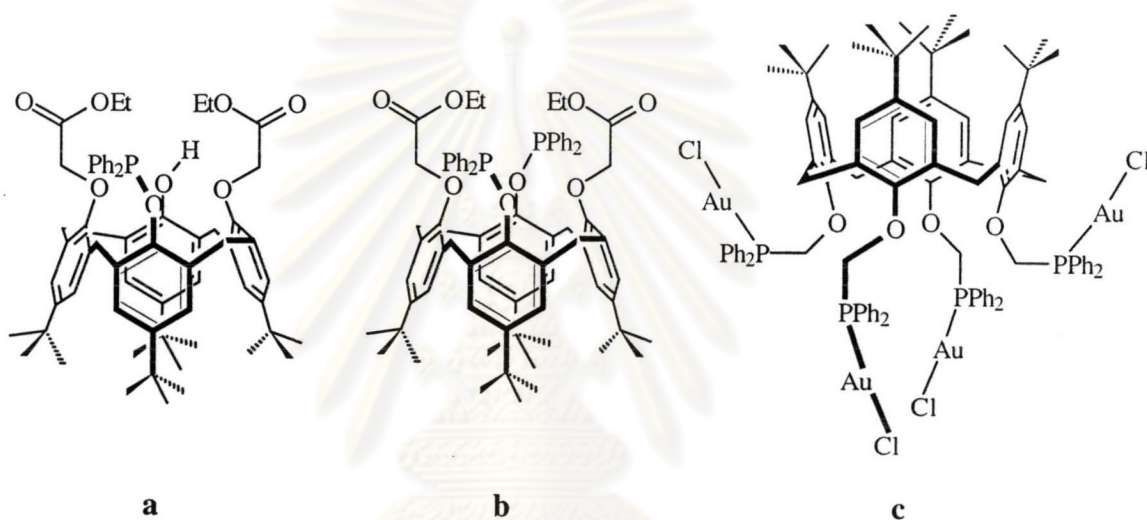


Figure 1.2 a) A monophosphino diester *p*-*tert*-butylcalix[4]arene
 b) A diposphino diester *p*-*tert*-butylcalix[4]arene
 c) A gold(I) complex of tetraphosphine calix[4]arene

Upper rim functionalized P(III) calix[4]arenes were less studied than its lower rim analogues. Tetraether diphenylphosphine calix[4]arene (Figure 1.3a) was synthesized *via* reaction between diphenylphosphino lithium with its alkyl chloride derivative.⁴⁶ This phosphine bearing calix[4]arene formed organometallic compounds with Ru and Rh that containing π ligands as *p*-cymene and norbornadiene, respectively. The rhodium complex of this compound (Figure 1.3b) catalyzed the styrene hydroformylation in the presence of NEt₃ and gave a high regioselectivity for the branched aldehyde to the linear chain aldehyde at ratio of 91:9 with the turnover frequency of 31 mol of alkene/mol of Rh/hour. This high selectivity and activity that

observed in the rhodium complex suggested that the *tert*-butyl group inhibited the substrate from entering through the cavity.

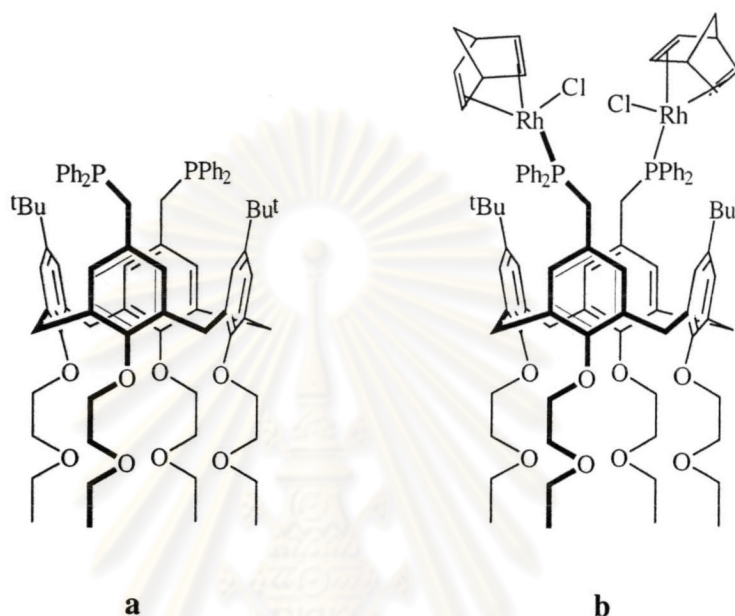


Figure 1.3 a) Structure of an upper rim diphosphine derivatized-calix[4]arene
b) Structure of a rhodium-norbornadine complex of diphosphine calix[4]arene

1.5.2.2 Calixarene ligands with O and S donor atoms

Calixarene-derived receptor containing oxygen donor atoms have found as complexing agents for oxophilic cations such as alkali, alkaline earth and lanthanide ions. Nevertheless, some oxygen bearing functional groups have been attached to calixarenes and exhibit binding ability towards some transition metal ions. Tetrasubstituted hydroxamic acid-derived calix[4]arene (Figure 1.4a) was chosen as extractant for some metal ions such as Cu^{2+} , Co^{2+} , Fe^{3+} , Zn^{2+} and Ni^{2+} .⁴⁷ It was functionalized with triethoxysilane groups and immobilized on silica and XAD-4 resin to prepare compact cartridges. These materials were employed for extraction of metal ions from aqueous phase to chloroform. Calix[4]arene-modified materials showed high percentage of Fe^{3+} , Pb^{2+} and Cu^{2+} uptakes at pH lower than 5.0. At pH

higher than 8.0, other cations such as Co^{2+} , Ni^{2+} and Zn^{2+} were quantitatively extracted to the chloroform phase. These materials may be useful for the preconcentration of cations from an aqueous sample.

Attachment of fluorescent chromophores such as anthracene and pyrene to hydroxamate group leading to a metal ion sensory system.⁴⁸⁻⁵⁰ Frédéric Fages and his coworkers reported the synthetic procedure of a fluorescent biperynyl bishydroxamate calix[4]arene (Figure 1.4b).⁵¹ In the presence of Cu^{2+} and Ni^{2+} at $\text{pH} = 7.4$, the dramatically quenching of fluorescence was observed from the fluorometric titration method while Fe^{3+} and Co^{2+} did not lead to any effect on the photophysical properties of the pyrene group.

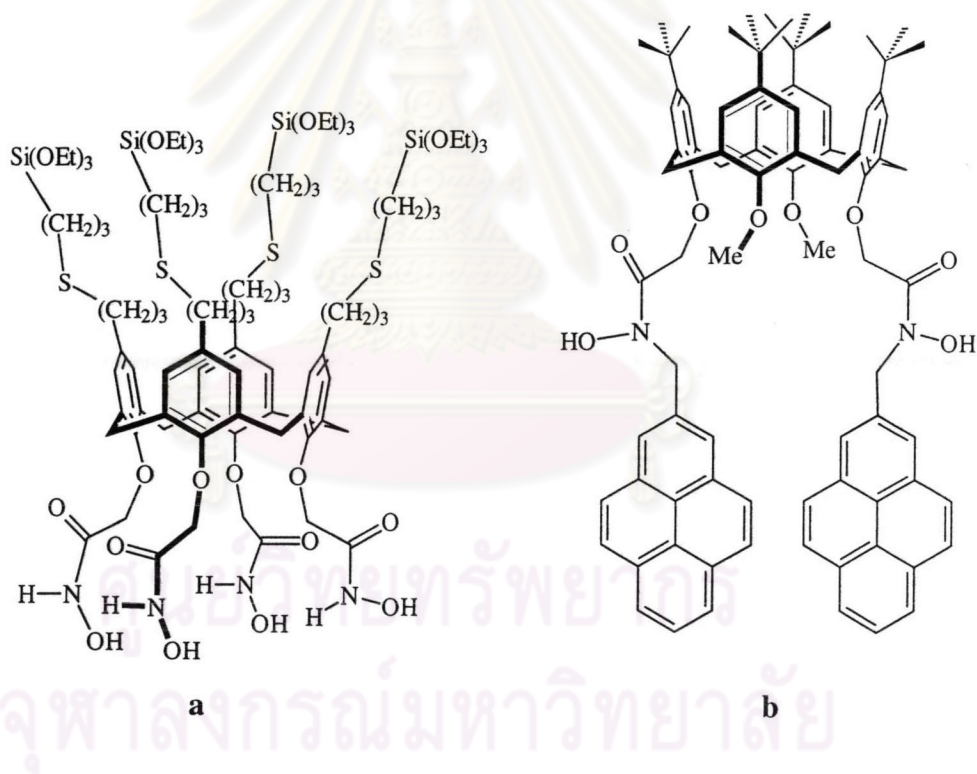


Figure 1.4 a) Structure of a triethoxysilane derivative of tetrahydroxamic calix[4]arene
 b) Structure of a dipyrenyl hydroxamate calix[4]arene fluorescent sensor

On the other hand, soft donor atoms such as sulfur are more suitable for heavy metals and precious metals bindings than oxygen. Several lower rim sulfur functionalized calix[4]arenes have been designed by Roundhill and his colleagues.⁵²⁻⁵⁷ The goal of these studies is to obtain novel high selective extractors for toxic heavy metal separation. Studies of extractability of tetrathiocarbamoyl *p-tert*-butylcalix[4]arene and tetramethylthioethoxy *p-tert*-butylcalix[4]arene (Figure 1.5) using an ICP-AES technique showed that the tetrathiocarbamoyl derivative was an effective extractant for Au^{3+} and Pd^{2+} but not for Ni^{2+} or Pt^{2+} or Pt^{4+} while the tetramercaptoethoxy-*p-tert*-butylcalix[4]arene was moderately effective for Pd^{2+} but could quantitatively extract Au^{3+} from aqueous phase to the chloroform phase. If *tert*-butyl groups were removed, the effective extractability for Au^{3+} was not changed but Pd^{2+} selectivity was decreased. Factors that controlled the heavy metal selectivity were expected to be ionic size of metal ions, polarizability effect and kinetic inertness of each ion.⁵⁷

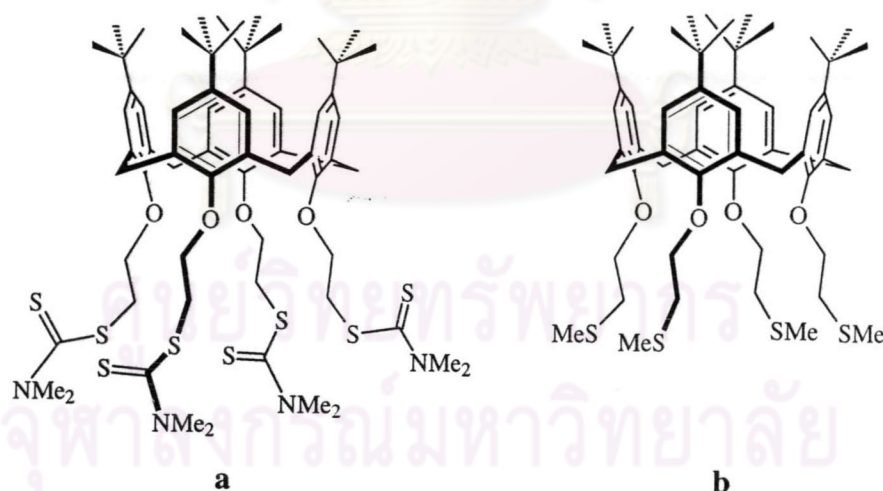


Figure 1.5 Structures of lower rim sulfur-derivatized *p-tert*-butylcalix[4]arenes
 a) A tetrathiocarbamoyl *p-tert*-butylcalix[4]arene
 b) A tetramethylthioethoxy *p-tert*-butylcalix[4]arene

1.5.2.3 Calixarene derivatives bearing nitrogen donors

Due to the principle of Hard-Soft Acids –Bases,⁵⁸ nitrogen containing functional groups are classified as borderline bases. So, these donor groups prefer to bind borderline metal ions such as the first row divalent transition metal ions, Pb^{2+} , Sn^{2+} and Sb^{3+} . Functionalizations of calixarenes for binding borderline ions are able to operate both at upper rim and lower rim. Main functional groups are both aliphatic and aromatic amines.

In 1995, Paul Beer described the synthetic method of *bis*(triazanonane) calix[4]arene. After the addition of $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ and recrystallization, X-ray crystallographic data showed the binuclear nickel complex with three 1,1 end-on-bonded azide bridges (Figure 1.6 (1)). The conformation of calix[4]arene framework was cone and two nickel ions possessed distorted octahedral geometry. In addition, this complex displayed an anti-ferromagnetic behaviour. This result was quite strange because 1,1-bridge nickel complexes usually have ferromagnetic properties.⁵⁹

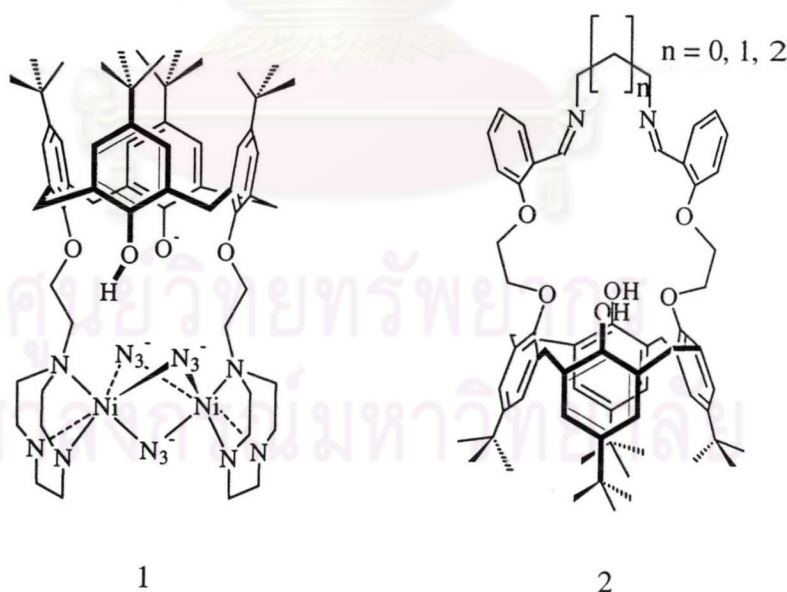


Figure 1.6 1) A dinuclear Ni(II) complex of *bis*(triazanonane) calix[4]arene
2) Structure of Schiff base *p-tert*-butylcalix[4]arenes

In order to combine good characteristic of crown ethers to nitrogen donor calix[4]arene, three 1,3-Schiff base *p-tert*-butylcalix[4]arenes (Figure 1.6(2)) were synthesized from condensation between 1,3-dialdehyde derivative with primary diamines.⁶⁰⁻⁶¹ Preliminary binding properties of these Schiff base calix[4]arenes were tested by solvent extraction of numerous picrate salts into dichloromethane in neutral condition. Alkali and alkaline earth metal cations were absolutely poorly extracted. However, Fe^{2+} , Cu^{2+} and some lanthanide ions such as Nd^{3+} and Eu^{3+} were extracted more efficiently. Furthermore, the reduced form of diaza crown calix[4]arene bearing three carbons bridge was used for zinc complexation study by $^1\text{H-NMR}$ spectroscopy. The titration curve indicated a 1:1 and 1:2 ligand to metal ratio until complete addition of 6 equivalents of Zn^{2+} . The reaction solution reached equilibrium after 26 days with a total formation of 2:1 complex with first and second formation constants as $\log K_1 = 3.6$ and $\log K_2 = 3.0$, respectively.⁶²

Nitrogen heterocycles such as 2,2'-bipyridine and 2,2'-bithiazole have also been attached to calixarene at the lower rim in order to afford fluorescent sensors (Figure 1.7). All mono(2,2'-bipyridine) and di(2,2'-bipyridine) functionalized calix[4]arenes were able to form stable 1:1 or 1:2 metal to ligand ratio complexes with Cu^+ ion.⁶³⁻⁶⁷ The familiar results were also observed in case of 2,2'-bipyridine was replaced by 2,2'-bithiazole group.⁶⁸⁻⁷⁰ These results can be suggested that both bipyridine and bithiazole podand arms were available to rearrange their molecules to provide tetrahedral geometry that matched with Cu^+ ion.

Upper rim position can also be anchored nitrogen donors fragments to obtain other kinds of transition metal receptor. Introduction of one or two bipyridine units at calix[4]arenes platform was performed by means of the Wittig reaction to give novel bipyridyl-based calix[4]arene podands.⁷¹ These derivatives were studied as ligand for Co^{2+} complexation. $^1\text{H-NMR}$ and X-ray crystallographic data indicated that Co^{2+} complexes were in tetrahedral geometry and coordinating to the bipyridine podands and two chloride ions. The ORTEP diagram of a Co^{2+} monobipyridine calix[4]arene complex were shown in Figure 1.8.

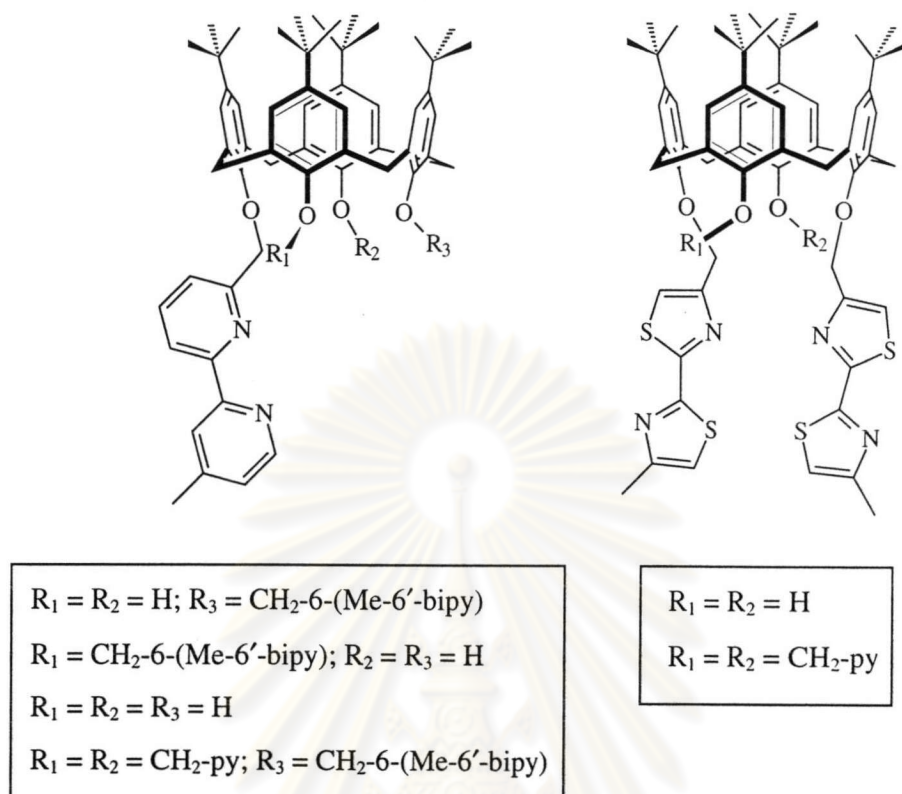


Figure 1.7 Structures of some 2,2'-bipyridine and 2,2'-bithiazole functionalized calix[4]arenes

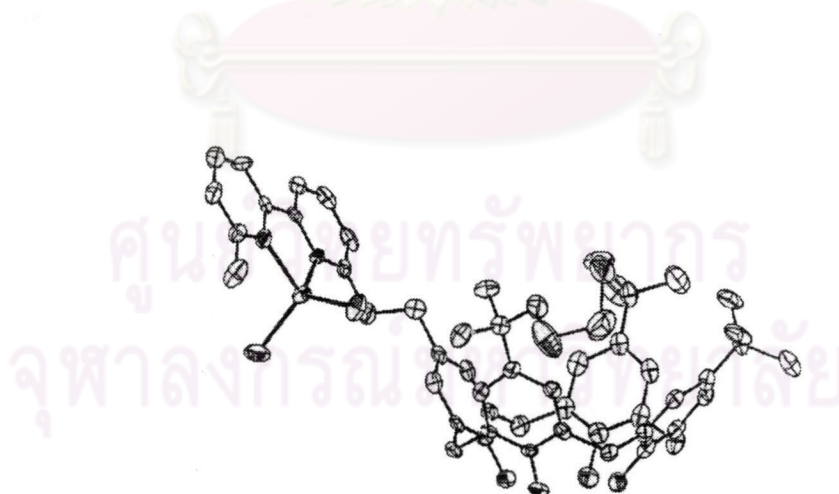
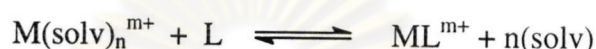


Figure 1.8 The ORTEP diagram of a Co^{2+} monobipyridine calix[4]arene complex

1.6 Measurement of Binding Constant: Potentiometric Titration^{72,73}

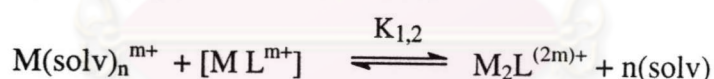
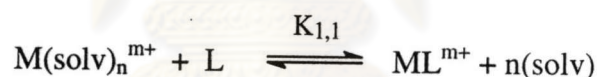
The thermodynamic stability of a metal-macrocycle complex in a given solvent is gauged by measurement of the binding constant, K . Consider the equilibrium constant for the reaction between a metal, M , and a ligand, L , in a solvent, solv (ignoring activity effect):



$$K = \frac{[ML^{m+}]}{[M(\text{solv})_n^{m+}][L]} \quad (\text{unit: dm}^3 \text{ mol}^{-1} \text{ or, M}^{-1})$$

Thus a large binding constant corresponds to a high equilibrium concentration of bound metal, and hence a more stable metal-macrocycle complex.

If a sequential process involving the binding of more than one metal ion is involved, the two K values may be measured: K_{11} and K_{12}



$$K_{1,2} = \frac{[M_2L^{(2m)+}]}{[M(\text{solv})_n^{m+}][ML^{m+}]}$$

In these circumstances, a stepwise binding constant, β_{12} may be defined for the overall process:

$$\beta_{12} = K_{11} \times K_{12}$$

or more generally,
$$\beta_{m,n} = \frac{[M_m L_n]}{[M]^m [L]^n}$$

Magnitudes of binding constants can vary widely, so they are often reported as $\log K$, hence:

$$\log \beta_{12} = \log (K_{11} \times K_{12}) = \log K_{11} + \log K_{12}$$

The subscript numbers in stepwise binding constant notation refer to the ratio of one complexing partner to another. Thus in a multistep process, the association of the host with the first guest might be denoted as K_{11} , while the association of the resulting 1:1 complex with a further guest to produce a 1:2 complex has an equilibrium constant K_{12} etc. Furthermore, because binding constants are thermodynamic parameters, they are related to the free energy of the association process according to the Gibbs equation: $\Delta G^\circ = -RT \ln K$. Therefore, the general affinity of a host for a guest under specific conditions (solvent, temperature, pressure etc.) may be given either in terms of K or $-\Delta G^\circ$ values.

In principle, binding constants may be assessed by any experiment technique that can afford information about the concentration of a complex as a function of changing concentration of the host. There are many methods used for this purpose. The main techniques are NMR spectroscopy, UV-visible spectrophotometry, fluorescent titration and solvent extraction. Nonetheless, potentiometric titration is the most convenient and widely employed in order to determine the binding constants.

The main criterion of potentiometric titration is the host molecule must be susceptible to protonation. This implies that all host ligands, which can be studied by potentiometric method, have to provide proton-acceptable functional groups like amines or carboxylic acids. The protonation constants (and hence pK_a values) may be determined readily using highly accurate pH-electrodes to follow an acid-base titration. Addition of a metal cation will perturb the host molecule basicity by competition with proton for the donor lone pair and therefore will affect the shape of the titration curves. Stability constants for the metal complexation reactions are evaluated from an analysis of the various equilibria by a curve fitting computer program (e.g. program such as MINQUAD⁷⁴ or SUPERQUAD⁷⁵).

1.7 Objectives and Scope of this research

The main goals of this research are to develop the new synthetic procedure for preparation of cryptand-like tetraaza crown calix[4]arene derivatives, **6a** and **6b** (Figure 1.8) and investigate their binding properties towards some transition metal ions. In addition, we have tried to find the possible way that may lead to the application of these receptors as fluorescent sensors for metal ions when there is a suitable chromophore attached to the ligand frameworks. Both **6a** and **6b** are in cone conformation and provided four nitrogen donor atoms that served to bind cations *via* ion-dipole interaction. The protonation and complexation studies of these compounds with Co^{2+} , Cu^{2+} and Zn^{2+} ions are also studied by means of potentiometric titration. The results of this research should give valuable information about their binding abilities towards first-row divalent transition metal cations. The effect of size and shape of host molecules towards metal ion recognition will also be obtained.

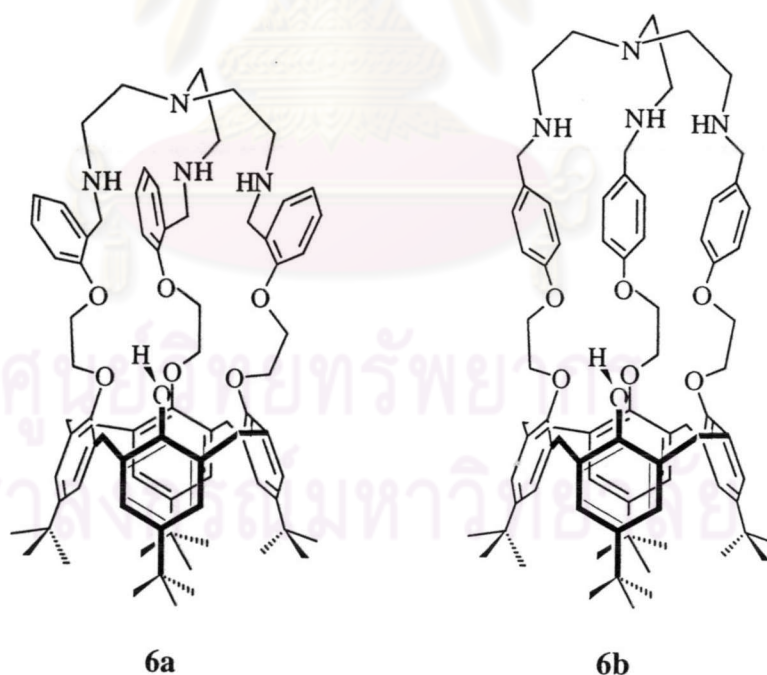


Figure 1.9 Structures of cryptand-like tetraaza crown *p*-*tert*-butylcalix[4]arenes **6a** and **6b**