

CHAPTER I

INTRODUCTION



1.1 Macrocyclic compounds

Macrocyclic compounds or macrocyclic ligands are polydentate ligands which can bind metal ions [1]. They contain at least three donor atoms and the macrocyclic rings should consist of a minimum of nine atoms. These ligands have specificity to bind metal ions or other guests depend on some important properties of the ligand [2] such as

1. The relative cation and ligand cavity sizes
2. The binding sites within the macrocyclic compounds such as nitrogen (-aza compounds), oxygen (-oxa compounds) and sulfur (-thia compounds)
3. The oxidation number and the size of cations or other guests
4. Steric hindrance in the rings
5. Solvent effect

The stability constant of complexation depends on interactions such as ion-dipole between ion or guest with ligand which is a host [3].

1.2 Calixarenes

Calixarenes, which are metacyclophanes comprising phenolic linked together by methylene bridges [4] and forming basket-shape cavities, are becoming an important class of compounds in supramolecular chemistry [5,6]. The name “calixarene” has been given by Gutsche [5]. The word “calix” comes from chalice (in Greek : calix) and arene represents of aryl rings in the molecular framework. The functionalization of calixarenes can be performed by changing at the *para* position or “upper rim” and at the OH groups or lower rim of calixarenes, thus they are excellent platforms/building blocks in supramolecular chemistry [7]. Esters, amides, carboxylic acids, crown ethers, etc. at the lower rim of derivative of calixarenes can bind to metal cations. Because of

their unique molecular architecture, easy derivatization, and well-preorganized cavity, appropriately modified calixarenes can act as receptors for cations, anions and neutral guest molecules [8]. Calixarenes can be prepared by base-catalyzed condensation of *p*-substituted phenol with formaldehyde [9] as shown in Figure 1.1.

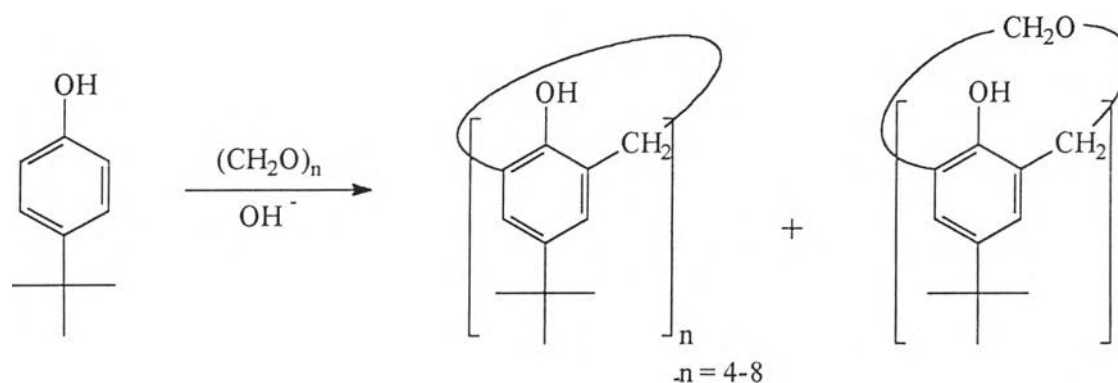


Figure 1.1 Preparation of calix[*n*]arene by condensation of *p*-substituted phenol with formaldehyde.

1.3 Calix[4]arenes

The smallest macrocycle of known calixarenes is calix[4]arene which have 4 phenolic units. Calix[4]arene is useful building blocks for host molecules with different properties [5] which are strongly influenced by the conformation of calix[4]arene derivatives [11]. *p*-*tert*-Butylcalix[4]arene has been shown to be the most important starting building block because (a) it can be prepared in large quantities from cheap commercial starting materials [12], (b) it can easily be chemically modified at the lower rim and at the upper rim and (c) the chemically modifications associated with the conformational properties lead to a large variety of tailor made receptors [5,6].

Functionalization at lower rim of calix[4]arene with bulky substituents prevents the interconversion among the four conformations : cone, partial cone, 1,2-alternate and 1,3-alternate (Figure 1.2) [13]. The most stable conformation of calix[4]arenes is, however, cone conformation because of intramolecular hydrogen bonding.

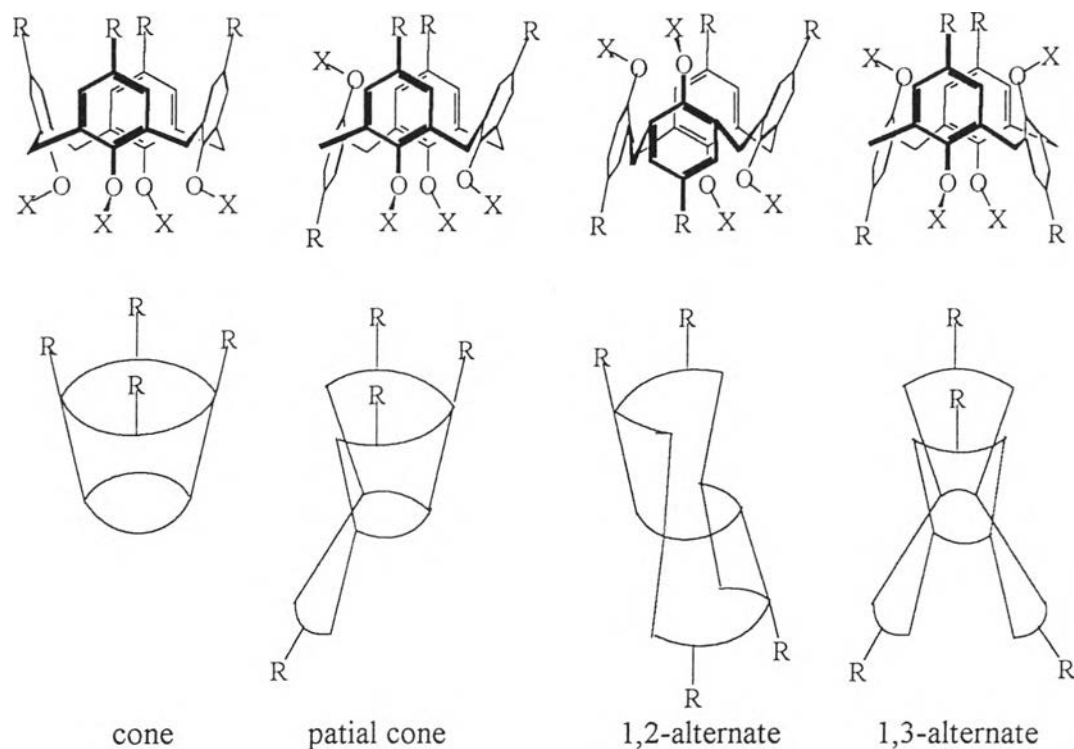


Figure 1.2 Four conformations of the calix[4]arenes.

Temperature, solvent, and counter cation of the used base influence the conformations of the products [14-18]. For instance, ethylation with EtI in the presence of *t*-BuOK in THF is used to prepared tetraethyl ester as shown in Figure 1.3 (a). The obtained tetraethoxy calix[4]arenes were predominant in partial cone conformation. The tetramethoxy derivative (b) also showed interesting conformational behaviors. Reinhoudt and coworkers used variable temperature ^1H NMR and EXSY NMR experiments to show that b (at $-30\text{ }^\circ\text{C}$) possessed all four possible conformations of the calix[4]arene unit : cone, partial cone, 1,2- and 1,3-alternate [19]. The same group also demonstrated by quantum calculations that hydrogen bonding and solvent inclusion could affect the conformational changes [20].

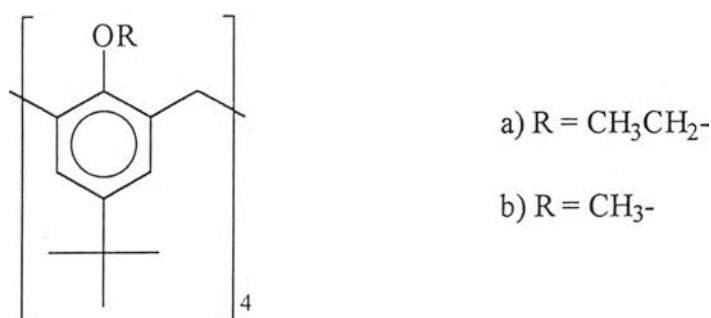


Figure 1.3 Tetraalkoxy calix[4]arene derivatives.

1.4 Chemical functionalization of calix[4]arene for host-guest chemistry

The lower rim of calix[4]arene has been modified in many types such as ether, ester [21-26], amide [27,28], ketone [29], thioamide [30], pyridine [31-33], carboxylic acid, hydroxamate [34], alkyl ether and phosphinite donor pendant group which can bind to different metals. The calix[4]arene derivatives with ester, ketone and amide groups at the lower rim can strongly bind alkali cations [8, 35-38] and alkaline earth cations preferably for Ca^{2+} and Sr^{2+} to Ba^{2+} and Mg^{2+} [39] in methanol. Calix[4]arene tetrathioamide **1a** (Figure 1.4) is a good complexing agent for heavy and transition metal cations but its selectivity has not been observed [29]. Later, Ungaro et al.[40] prepared calix[4]arene trihydroxamate **1b**, which has selectivity for Fe^{3+} .

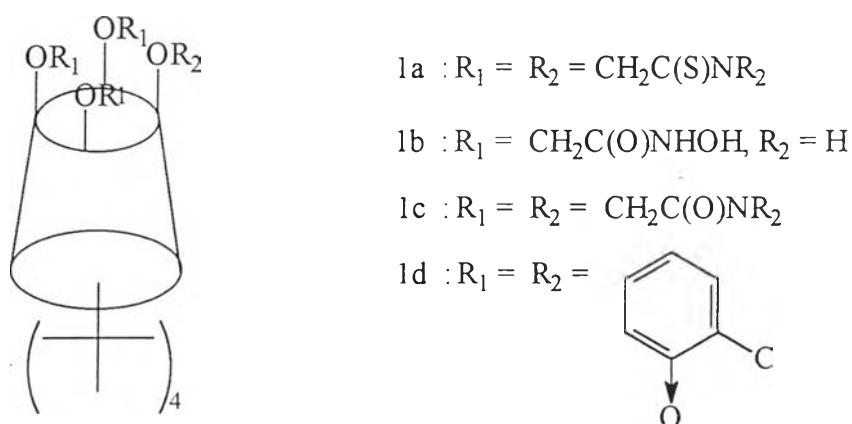


Figure 1.4 Calix[4]arene derivatives.

For another derivatives such as **1c** [41] which possesses thioamide and **1d** which has methylpyridine N-oxide moieties [42] can bind lanthanide ions. Alfieri et al. [43] reported the synthesis of the first member of a new class of macropolycyclic crown compounds with diametrically OH groups of *p-tert*-butylcalix[4]arene which was bridged by a pentaethylene glycol chain. Later, 1,3-distal capping of calix[4]arene at the lower rim has been made by poly(oxyethylene) chains e.g calix-crown ethers [44,45], calix-doubly-crowned [10], double-calix-crown [46,47], by terphenyl units (calixspherands) [48,49], by salophene group [50], by a metallocene unit (metallocene calix[4]arene) [51], by disulfonyl and diacetyl dichlorides [52], by diaza-crown units (calixcryptand) [53] and by phosphorus atoms (phosphorus polybridged calixarenes) [54].

Most of mentioned ligands can form complex with alkali and alkaline earth cations. Investigation of poly-(azaethylene)-bridge, calix[4]arene which presents nitrogen atom in the chain, can bind soft metal ions [54] and Schiff base of *p-tert*-butylcalix[4]arene derivatives have complexation abilities with soft metal ions, heavy metal ions, transition and lanthanide ions. [55].

In 1991, Ostaszewski et al. [56] synthesized calix-aza-crown as shown in Figure 1.5. Complexation study of these compounds with trivalent metal ions by fast atom bombardment mass spectrometry (FAB-MS) was carried out. The studied cations are Sc^{3+} , Y^{3+} , In^{3+} , Gd^{3+} and Bi^{3+} . From the results, the calix-crown-aza compound (Figure 1.5a) can bind Sc^{3+} with the highest stability among the cations studied, but it cannot form complex with In^{3+} and Bi^{3+} . The methyl derivative (Figure 1.5b) of calix[4]arene can complex with Y^{3+} with the highest stability among the mentioned ions. However, the methyl derivative can form complexes with trivalent transition metal ions which are less stable than the non-methyl derivative (Figure 1.5a), except for Bi^{3+} .

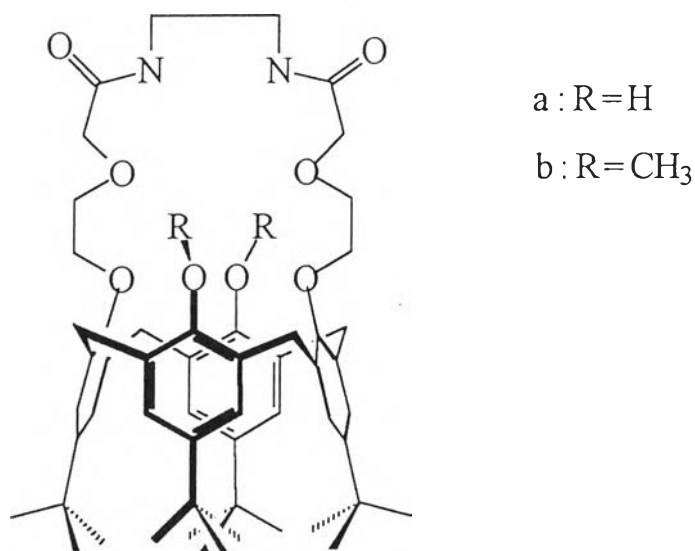


Figure 1.5 Aza-crown-calix[4]arene derivatives.

In 1992-1994, diaza benzo crown ether-*p-tert*-butylcalix[4]arene [57] as shown in Figure 1.6 were prepared and investigated its complexation with Zn^{2+} , where the counter anions are Cl^- , Br^- , I^- , ClO_4^- and NO_3^- by 1H -NMR spectroscopy. It was concluded that the stabilities of the Zn^{2+} complexes varied with different counter anions : $NO_3^- > ClO_4^- > I^- > Br^- > Cl^-$. Later, the protonation of this ligand [57,58] and its complexation with Zn(II)perchlorate were investigated by potentiometric and ultraviolet spectroscopic titrations [57]. Extensive works were devoted to the stability constants of this ligand and Zn^{2+} which was also studied by 1H NMR spectroscopy [59].

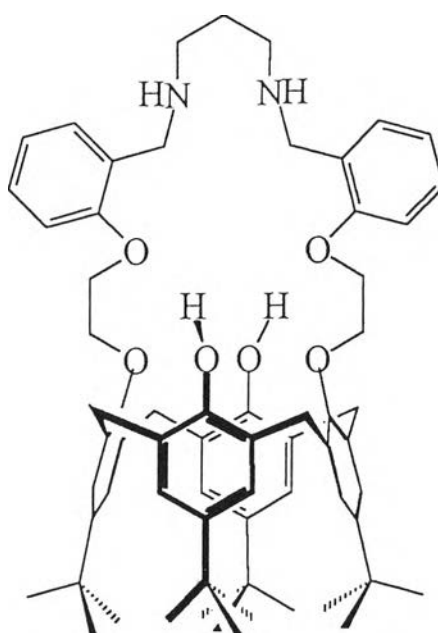


Figure 1.6 Diaza benzo crown ether-*p-tert*-butylcalix[4]arene.

In 1994, Schiff base calix[4]arenes [55] in Figure 1.7 were synthesized and studied their complexation by extraction. The extraction of alkali and alkaline earth cations are very poor for ligands a-c. The better extraction of Li^+ and Na^+ ions with c may be explained by the greater flexibility of the longer carbon chain. Fe^{2+} and Cu^{2+} were extracted more efficiently among transition metal ions, and among heavy metal ions, and Pb^{2+} were better extracted by ligands b and c. In the lanthanide series, b had high selectivity for Nd^{3+} and Eu^{3+} , but c was selective for Eu^{2+} . Ligand d had high selectivity towards Cu^{2+} .

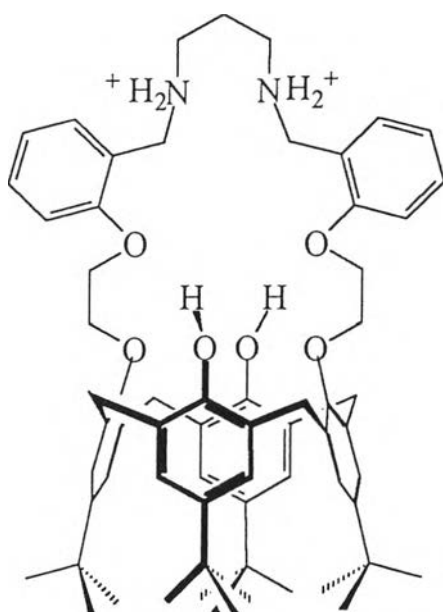


Figure 1.8 25,27-[*N,N'*-di-((2-ethoxy)benzyl)propylenediamine]-*p-tert*-butylcalix[4] arene dihydrochloride (9).

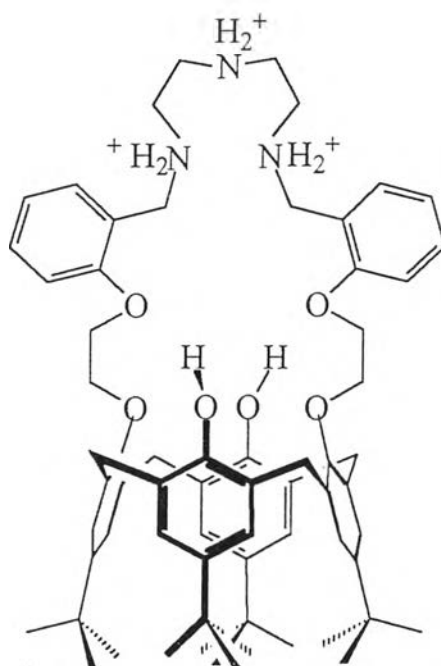


Figure 1.9 Ammonium derivative of triaza-benzo-crown ether-*p-tert*-butylcalix[4] arene.

Two years later, the protonation constants of triaza benzo-crown ether *p-tert*-butylcalix[4]arene (Figure 1.10) and stability constants of this ligand with divalent transition metal ions (M^{2+}) were investigated at 25 °C by potentiometric titration [62]. It was found that three protonation constants in CH_3OH using of $5.0 \times 10^{-2} M$ Et_4NClO_4 as inert background electrolyte were larger than those using $Bu_4NCF_3SO_3$. The order of complexation constants of the ligand toward Co^{2+} , Ni^{2+} , Cu^{2+} and Zn^{2+} ions are as follows : $CuL^{2+} > NiL^{2+} > CoL^{2+} > ZnL^{2+}$.

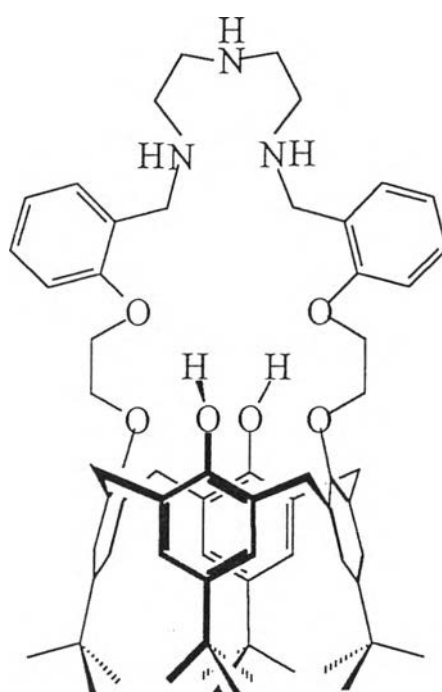


Figure 1.10 Triaza-benzo-crown ether-*p-tert*-butylcalix[4]arene.

In 1996, the tripodal-amine capped benzo-crown-*p-tert*-butylcalix[4]arene was synthesized [63] as shown in Figure 1.11 and its protonation constants were determined by potentiometric titration. By 1H NMR spectroscopy method, it was found that the synthesized ligand could bind with $ZnBr_2$ in ratio of ligand: $ZnBr_2$ of 1:1 in which Zn^{2+} might locate in the cavity of the N donors while Br^- maybe in the cavity of phenolic oxygen. The complex with $Zn(NO_3)_2$ in ratio of ligand: $Zn(NO_3)_2$ of 1:2 was also observed where one Zn^{2+} maybe in the nitrogen cavity while the other was in the phenolic oxygen cavity. One year latter, the protonation constants of this ligand

in methanolic solution of 0.01 M $\text{Bu}_4\text{NCF}_3\text{SO}_3$ and the complexation of this ligand with Zn^{2+} were investigated by potentiometric titration which found that ZnL^{2-} , Zn_2L^{4+} and $\text{ZnH}_2\text{L}^{4+}$ were presented in the solution [64].

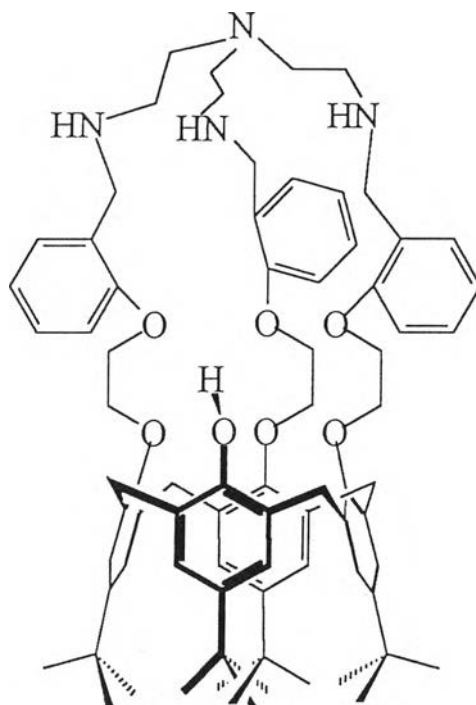


Figure 1.11 Tripodal-amine capped benzo crown-*p-tert*-butylcalix[4]arene.

1.5 Objective and scope of the research

In the past, our research group encountered problems when performing potentiometric titration of 1,3-disubstituted calix[4]arene derivatives. One of them is the fact that the (unsubstituted) phenolic protons may be deprotonated by a basic titrant in a basic pH region. This leads to an uncertainty in calculating protonation constants. The goal of this research is thus to synthesize 25,27-[*N,N'*-di-((2-ethoxy)benzyl)propylenediamine]-26,28-dimethoxy-*p*-*tert*-butylcalix[4]arene dihydrochloride (**L.2HCl**), a tetra substituted calix[4]arene (Figure 1.12a), to avoid deprotonation at the calix[4]arene framework. Studies of basicity of 25,27-[*N,N'*-di-((2-ethoxy)benzyl)propylenediamine]-26,28-dimethoxy-*p*-*tert*-butylcalix[4]arene (**L**) and complexation ability toward Zn^{2+} and Cu^{2+} ions will then be pursued. In addition, the intriguing conformational isomerism of the ligand (which is lack of intermolecular hydrogen bonding interactions) in various solvents and temperature will be investigated by NMR experiments.

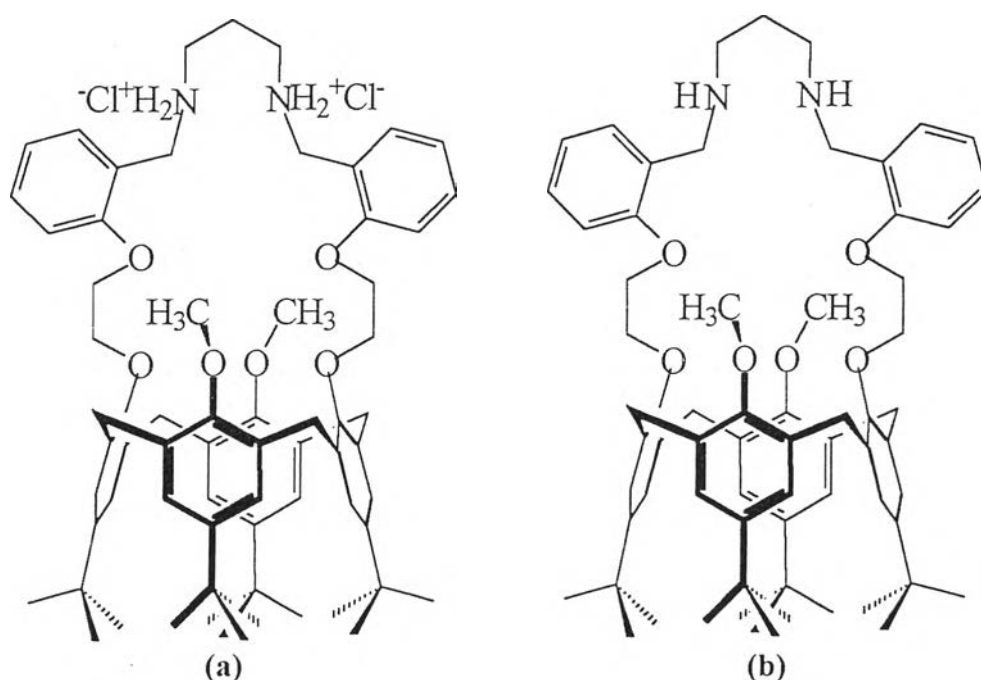


Figure 1.12 Structure of a) 25,27-[*N,N'*-di-((2-ethoxy)benzyl)propylenediamine]-26,28-dimethoxy-*p*-*tert*-butylcalix[4]arene dihydrochloride (**7**, **L.2HCl**) and b) 25,27-[*N,N'*-di-((2-ethoxy)benzyl)propylenediamine]-26,28-dimethoxy-*p*-*tert*-butylcalix[4]arene (**L**).