การสังเคราะห์คาลิกซ์[4]เอรีนที่มีคราวน์อีเทอร์และยูเรียเป็นองค์ประกอบสำหรับการจดจำแอนไอออน

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วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต

สาขาวิชาเคมี ภาควิชาเคมี

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SYNTHESIS OF CALIX[4]ARENE CONTAINING CROWN ETHER AND UREA FOR ANION RECOGNITION

Mr. Pan Tongraung

A Dissertation Submitted in Partial Fulfillment of the Requirements
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By	Mr. Pan Tongraung
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Thesis Advisor	Assistant Professor Thawatchai Tuntulani, Ph.D.
Thesis Co-Advisor	Associate Professor Nuanphun Chantarasiri, Ph.D.

Accepted by the Faculty of Science, Chulalongkorn University in Partial Fulfillment of the Requirements for the Doctor's Degree

…….Dean of Faculty of Science
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(Assistant Professor Thawatchai Tuntulani, Ph.D.)

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(Oravan Sanguanruang, Ph.D.)

…….Member
(Assistant Professor Warinthorn Chavasiri, Ph.D.)

…….Member
(Associate Professor Sunit Suksamrarn, Ph.D.)

แพน ทองเรือง : การสังเคราะห์คาลิกซ์[4]เอรีนที่มีคราวน์อีเทอร์และยูเรียเป็นองค์ประกอบสำหรับการจดจำแอนไอออน (SYNTHESIS OF CALIX[4]ARENE CONTAINING CROWN ETHER AND UREA FOR ANION RECOGNITION) อาจารย์ที่ปรึกษา:ผศ.ดร. ธวัชชัย ตันฑุลานิ; อาจารย์ที่ปรึกษาร่วม:รศ.ดร. นวลพรรณ จันทรศิริ; 106 หน้า. ISBN 974-17-4474-9

ได้ทำการสังเคราะห์อนุพันธ์ของคาลิกซ์[4]เอรีนชนิดใหม่คือ 5,17-diphenylurea-25,27-dihydroxy-26,28-dimethoxycalix[4]arene (**13**) จากการคัปปลิง 5,17-diamino-25,27-dihydroxy-26,28-dimethoxycalix[4]arene (**12**) กับ ฟีนีลไอโซไซยาเนต และสังเคราะห์สาร 5,17-diphenylurea-25,27-tetraethylene glycoloxy-26,28-dimethoxycalix[4]arene (**17**) และ 5,17-dihexylurea-25,27-tetraethylene glycoloxy-26,28-dimethoxycalix[4]arene (**19**) จากการคัปปลิง 5,17-diamino-25,27-tetraethylene glycoloxy-26,28-dimethoxycalix[4]arene (**16**) กับ ฟีนีลไอโซไซยาเนตและเฮกซีลไอโซไซยาเนตตามลำดับ เมื่อทำการศึกษาคุณสมบัติการเกิดสารประกอบเชิงซ้อนกับแอนไอออนของลิแกนด์ **13** **17** และ **19** ในตัวทำละลาย DMSO-d_6 ด้วยเทคนิกโปรตอนเอ็นเอ็มอาร์สเปกโทรสโกปี พบว่าลิแกนด์ **13** **17** และ **19** สามารถเกิดสารประกอบเชิงซ้อนแบบ 1 : 1 กับแอนไอออน และเกิดสารประกอบเชิงซ้อนกับ Cl^-, Br^-, NO_3^- และ $H_2PO_4^-$ ได้แตกต่างกัน ค่าคงที่การเกิดสารประกอบเชิงซ้อนของ **13** และ **17** กับแอนไอออนเรียงตามลำดับดังนี้ $H_2PO_4^- > Cl^- > Br^- > NO_3^-$ แต่สำหรับลิแกนด์ **19** เรียงลำดับได้ดังนี้ $H_2PO_4^- > Br^- > NO_3^- > Cl^-$ สำหรับ I^- ไม่เกิดสารประกอบเชิงซ้อนกับลิแกนด์ทั้งสาม อย่างไรก็ตาม เมื่อเปรียบเทียบลิแกนด์ **13** กับ **17** และ **19** ซึ่งมีคราวอีเทอร์ พบว่าการมีคราวน์อีเทอร์จะทำให้การจับกับ $H_2PO_4^-$ ลดลง การเติม Na^+ และ K^+ ลงไปในลิแกนด์ **17** ช่วยเพิ่มความสามารถในการจับกับ $H_2PO_4^-$ เป็นผลของการเกิด cooperative ion-pair binding ส่งผลให้ค่าคงที่การเกิดสารประกอบเชิงซ้อนของลิแกนด์กับ $H_2PO_4^-$ เพิ่มขึ้น แต่สำหรับลิแกนด์ **19** ไม่ปรากฏว่ามี cooperative ion-pair binding เกิดขึ้น

ภาควิชา…….. ลายมือชื่อนิสิต…….

สาขาวิชา……. ลายมือชื่ออาจารย์ที่ปรึกษา…….……

ปีการศึกษา…….. ลายมือชื่ออาจารย์ที่ปรึกษาร่วม……. ……

4273819023 : MAJOR CHEMISTRY.

KEY WORDS: CALIX[4]ARENE, ANION BINDING, ^{1}H-NMR TITRATION, ION-PAIR ENHANCEMENT

PAN TONGRAUNG: SYNTHESIS OF CALIX[4]ARENE CONTAINING CROWN ETHER AND UREA FOR ANION RECOGNITION. THESIS ADVISOR: ASSISTANT PROF. THAWATCHAI TUNTULANI, Ph.D. THESIS CO-ADVISOR: ASSOCIATE PROF. NUANPHAN CHANTARASIRI, 106 pp ISBN 974-17-4474-9

A calix[4]urea compound, 5,17-diphenylurea-25,27-dihydroxy-26,28-dimethoxycalix[4]arene (**13**) was synthesized from a coupling reaction between 5,17-diamino-25,27-dihydroxy-26,28-dimethoxycalix[4]arene (**12**) and phenyl isocyanate. Two calix[4]crown urea compounds, 5,17-diphenylurea-25,27-tetraethylene glycoloxy-26,28-dimethoxycalix[4]arene (**17**) and 5,17-dihexylurea-25,27-tetraethylene glycoloxy-26,28-dimethoxycalix[4]arene (**19**) were synthesized from coupling reactions between 5,17-diamino-25,27-tetraethylene glycoloxy-26,28-dimethoxycalix[4]arene (**16**) with phenyl isocyanate and hexyl isocyanate, respectively. ^{1}H-NMR titrations of **13**, **17** and **19** with anions in DMSO-d_6 showed that 1:1 complex and formed complexes with Cl^-, Br^-, NO_3^- and $H_2PO_4^-$ to a different extent. The association constants of **13** and **17** towards anions were calculated and found to vary as $H_2PO_4^- > Cl^- > Br^- > NO_3^-$ but those of compound **19** were found to vary as $H_2PO_4^- > Br^- > NO_3^- > Cl^-$. The three compounds cannot bind with I^-. However, compared to **13** the presence of the crown unit in **17** and **19** resulted in a lower affinity to bind $H_2PO_4^-$. Upon addition of Na^+ and K^+, the binding ability of **17** towards $H_2PO_4^-$ was increased due to the cooperative ion-pair enhancement. However, compound **19** did not show the cooperative ion-pair binding effect.

Department…… student's signature……..

Field of study……. Advisor's signature…….

Academic year……... Co-advisor's signature..……..

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LIST OF ABBREVIATIONS AND SYMBOLS

DMAP	4-(*N*,*N'*-dimethyl amino)pyridine
δ	Chemical shift
J	Coupling constant
^{o}C	Degree Celsius
Equiv.	Equivalent
g	Gram
Hz	Hertz
mp	Melting point
Ms	Methane sulfonyl group
mmol	Millimol
mL	Milliliter
M	Molar
M^{-1}	Per molar
ppm	Part per million
^{1}H-NMR	Proton nuclear magnetic resonance
s, d, t, m	Splitting patterns of ^{1}H-NMR (singlet, doublet, triplet, multiplet)
THF	Tetrahydrofuran
DMSO	Dimethyl sulfoxide
HBD	Hydrogen bond donor
EPD	Electron pair donor
EPA	Electron pair acceptor
DN	Donor number
AN	Acceptor number

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CHAPTER I

INTRODUCTION

1.1 Molecular Recognition

Molecular recognition is one of the corner stones of supramolecular chemistry.[1] An appropriate receptor, possessing structural and chemical features suitable for substrate recognition, can be designed. The key word is shape. This concept is illustrated in Figure 1.

Molecular recognition is central to many areas of chemistry and biochemistry, including catalysis, cell adhesion, signal transduction, and enzyme inhibition.[2-4] Synthetic hosts and guests have been developed to mimic such activities and to elucidate the underlying intermolecular interactions. Synthetic chemists have addressed the challenge of designing and building concave receptors having shapes and dimensions suitable for hosting any kind of substrate and the ability of establishing with the substrate interactions of a sufficient energy (e.g. hydrogen bonds or π- interactions for a molecule; coordinative interactions for a metal ion and electrostatic interactions for an anion).

Figure 1.1 The basic principle of *molecular recognition* : for any given substrate a receptor possessing geometrical and bonding features for specific interaction can be designed.

1.1 Calix[4]arene

One of important building blocks in supramolecular chemistry is calixarene. Condensations of *p*-substituted phenols with formaldehyde under base-catalyzed condition 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.[5-7] 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.[8] Since synthetic methods were reported by Gutsche,[9-10] 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 atoms (that called “lower rim or narrow rim” , methylene bridge carbon or *para* position of aromatic rings which named “upper rim or wide rim”).[6,11-12] Among the calixarene family, calix[4]arene is the smallest member and served as the most popular building block in syntheses of new compound 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 intra molecular hydrogen bonding. However, chemically modified calix[4]arene can adopt other conformations as ‘partial cone’, ‘1,2-alternate’ and ‘1,3-alternate’(Figure 1.2). All four conformation 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}H-NMR spectra because each isomer has its unique methylene proton signals pattern.[14,15]

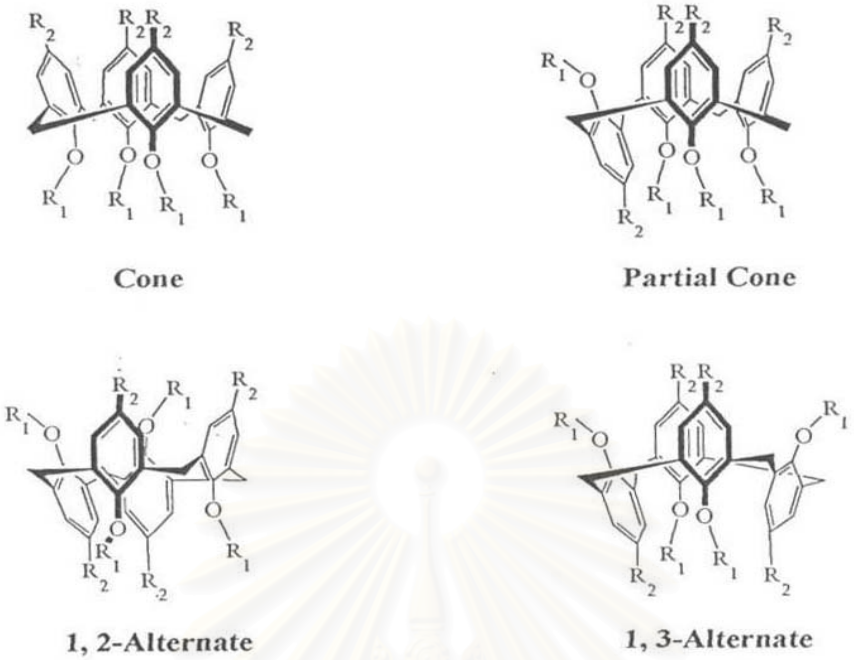


Figure 1.2 : Conformational isomers of calix[4]arene

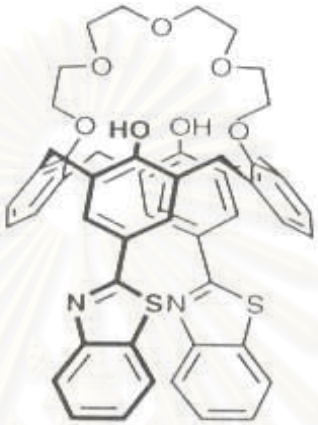
1.2 Cation Recognition

Cation recognition is undoubtedly the most studied and best developed application of calixenes in sensing devices. Molecules such as derivatives of calix[4]arene in its *cone* conformation with, for example, ester,[16] ether,[17] ketone,[18] carboxylic acid,[19] amide,[20] crown ether,[21] and hemispherand [22] substituents, have been extensively studied over the years.

In 2002, a new benzothiazolyl functionalized ionophore based upon the calix[4]arene-crow-5 ether[23](Figure 1.3) was prepared and its fluoroionophoric properties toward Ca^{2+} ions were investigated. The compound exhibited a pronouncedly selective fluoroionophoric behavior toward Ca^{2+} ions among the surveyed physiologically important metal ions of Na^{+}, K^{+}, and Mg^{2+}. Detection limit for Ca^{2+} ions was found to be $9x10^{-5}$ M in dioxane - water (80:20 v/v) solution.

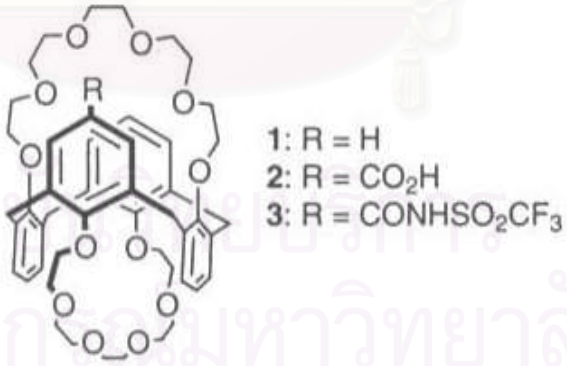
In the same year, two 1,3 – alternate calix[4]arene-biscrowns with one proton-ionizable group and two dibenzocrown-6-ether units were synthesized (Figure1.4).[24]

The compounds exhibit high Cs^+ extraction efficiency and selectivity. Cs^+/Na^+ and Cs^+/K^+ selectivities for the new *N*-(trifluoromethylsulfonyl) carbamoyl-substituted calix[4]arene-bis (dibenzocrown-6) were found to be higher than an analog with no benzo group substituents in the crown ether units.



1

Figure 1.3 Calix[4]arene-crown-thiazole



2: R=H, **3**: R=CO_2H, **4**: R=$CONHSO_2CF_3$

Figure 1.4 1,3-Alternate calix[4]arene-crown-6-ether

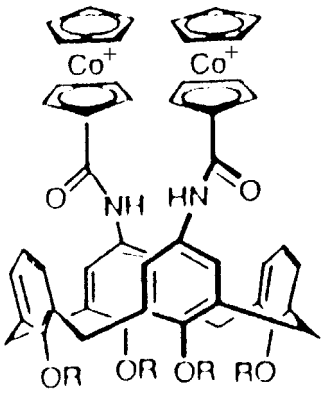
1.3 Calixarene-based anion receptors

Anions play a number of fundamental roles in biology and chemistry. The development of selective synthetic anion receptors is an area of current importance. The use of anions as nucleophiles, bases, redox-active agents and phase transfer catalysts has led to the desire for receptors which enable stabilization and separation through coordination. The increasing problem of environmental anion pollutants such as phosphate and nitrate, which lead to eutrophication, and radioactive pertechnecate, a product of the nuclear fuel cycle, is also an area of concern. Biochemically, anions are essential to normal metabolic function, both ATP and DNA being anionic, thus the development of anion binding mimetics would enable investigation of basic biological processes. A number of disease stales including cystic fibrosis, cancer and Alzheimur′s invole misregulation of anion function, offering the long term goal of a medical role for anion receptors.

The development of synthetic anion receptors has been slow in comparison to cation receptors. This is due, in the main, to a number of unique properties of anions that need to be addressed in the design of receptors. There include the negative charge, which is often delocalised over a number of atoms, and the size and shape of anions. In contrast to cations, anions are larger and have diverse biology, being spherical, linear, planar, tetrahedral or octahedral. Binding of anions is also affected by their pH dependence and solvation. For a given anion and cation of comparable size, for example fluoride and potassium, the anion is more strongly hydrated and thus more difficult to disolvate a pre-requisite for binding.

In 1968, the first reported synthetic anion receptor was the poly ammonium cryptand of Simmons and Park.[25] This compound bound halide anions by directional hydrogen bonding.

In 1993, Beer and coworkers[26,27] demonstrated that 1,3 upper-rim-difunctionalised calix[4]arene-based receptor (Figure1.5) was an effective receptor of halides, nitrate and hydrogen sulphates as well as series of dicarboxylates. The dicaboxylates form very strong (K_{ass} = 11510 M^{-1} for adipate in $(CD_3)_2(O)$) 1:1 host : guest complex in which the anion was bound between the cobaltoceniums.

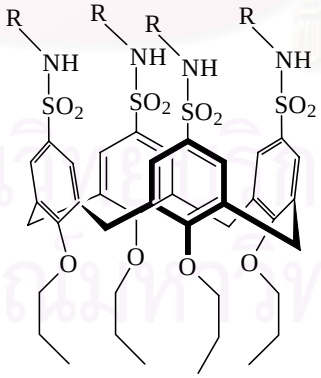


$(PF_6^-)_2$

5

Figure 1.5 Cobaltocenium based receptors.

The receptor for organic-based systems such as amide based receptors and thioureas based receptors can bind anion using hydrogen bonding unit. In 1993, Morzherin and coworkers[28] have synthesized molecule shown in Figure 1.6. In this case, selectivity for the tetrahedral hydrogensulphate anion over both planar and spherical anions was seen in $CDCl_3$, a second amide unit is included in the side chain. This selectivity is particularly marked (K_{ass} HSO_4^- = 103,400 M^{-1}, Cl^- = 1250 M^{-1} , NO_3^- = 513 M^{-1}).



a : R=H, **b** : R=t-butyl, **c** : R=$CH_2CH_2NHC(O)Me$

6

Figure 1.6 Calix[4]arene based anion receptor incorporated a sulfonamide hydrogen bonding unit

A bis calix[4]arene receptor in Figure 1.7 has been prepared two amide linkage.[29] ^{1}H NMR titrations in CD_2Cl_2 showed a pronouced selectivity for binding of fluoride over chloride, hydrogen sulphate and dihydrogen phosphate in an order of magnitude. This selectivity can be considered to depend on anion size and the cavity size of the ligand.

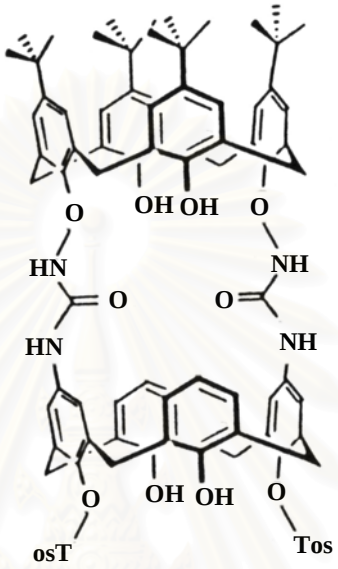


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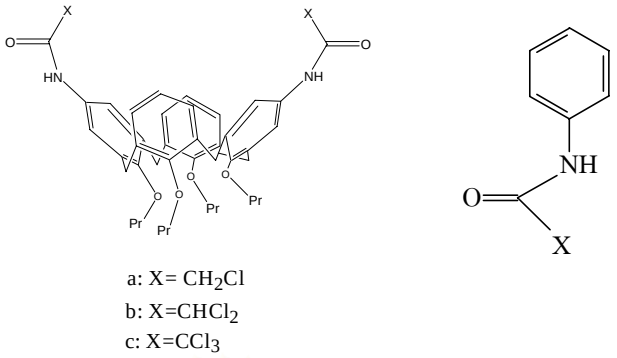
Figure 1.7 A Bis Calix[4]arene receptor

Synthesis of possibly tunable anion receptor in Figure 1.8 is based upon 1,3-functionalisation of the upper rim of a calix[4]arene.[30] Introduction of electron withdrawing groups, in the terminal portion of the amide, increases the acidity of the amide proton and thus is effective in increasing anion binding strength e.g., K_{ass} benzoate 5610 M^{-1} (x = $CHCl_2$), 107 M^{-1} (x = CH_2Cl) in $CDCl_3$. Introduction of more electron withdrawing groups as in Figure1.8, x = CCl_3 results in a loss of anion binding ability, proposed to be due to steric crowding.



a: X= CH_2Cl
b: X=$CHCl_2$
c: X=CCl_3

a: X=CH_2Cl, **b**: X=$CHCl_2$, **c**: X=CCl_3

8

Figure 1.8 Amide based receptor

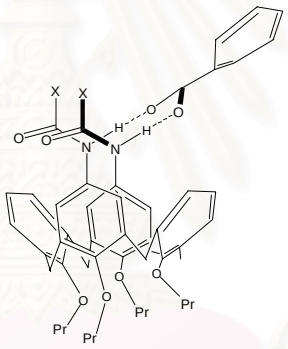


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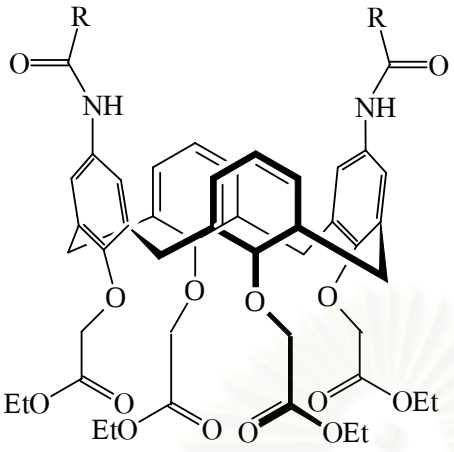
Figure 1.9 Interactions between an amide based receptor and benzoate anion.

In 1997, Stiber and coworkers[31] have synthesized bidentate receptors and quadridentate receptors shown in Figure 1.10 and 1.11 respectively. The bidentate receptor (**10a**) illustrated in Figure 1.10 showed pronounced selectively based on the length of the dianion, binding adipate and terephthalate over glutarate and isophthalate in $(CD_3)CO$. For quadridentate ligand (Figure 1.11) selective binding of squarate is observed, although this selectivity is solvent dependent, being more pronounced in CD_3CN than $(CD_3)_2CO$. Binding of anions by the receptor(**11b**) shown in Figure 1.11 was not evaluated due to association in solution.



a : R = C_6F_5

b : R = C_5H_4N

10

Figure 1.10 Bidentate amide

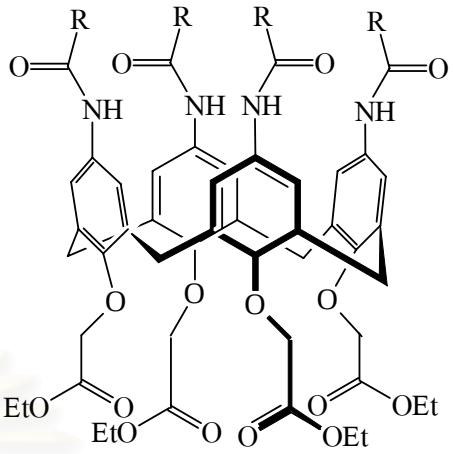


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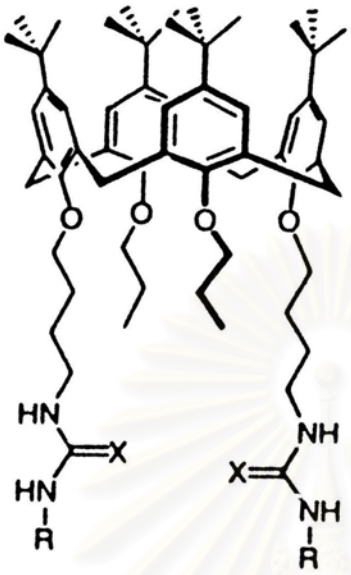
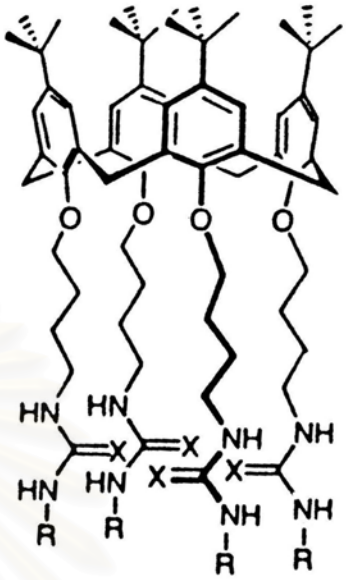
Figure 1.11 Quadridentate amide

A number of receptors have structures based on urea units attached to calix[4]arene. For example, in 1994, Scheerder and coworkers[32] have synthesized urea based receptors through four carbon spacers on the lower rim. Anion binding abilities of both bidentate (Figure 1.12) and quadridentate receptors (Figure 1.13) were evaluated by ^{1}H NMR and mass spectral studies. In general, higher association constants were obtained for bidentate receptors with a selectivity for chloride > bromide > cyanide in $CDCl_3$ for all receptors . The higher association constants with these anions were considered to be due to their stronger hydrogen bonding receptors properties and better steric complementarity. No binding of fluoride was observed. In separate study,[33] the anion binding capabilities of this system were investigated using Monte Carlo simulations. Here, the general selectivity through the halide group was confirmed, fluoride was shown to bind effectively and it was proposed that the lack of experimental binding was due to the presence of adventitions water molecules. Despite the higher acidity of the NH protons in thioureas, the ligand (**12d**) in Figure 1.12 showed less binding of all anions. This is

possibly due to the formation of very strong host intra-and intermolecular hydrogen bonds.





a : X = O , R = phenyl

b : X = O , R = propyl

c : X = O , R = *t*-butyl

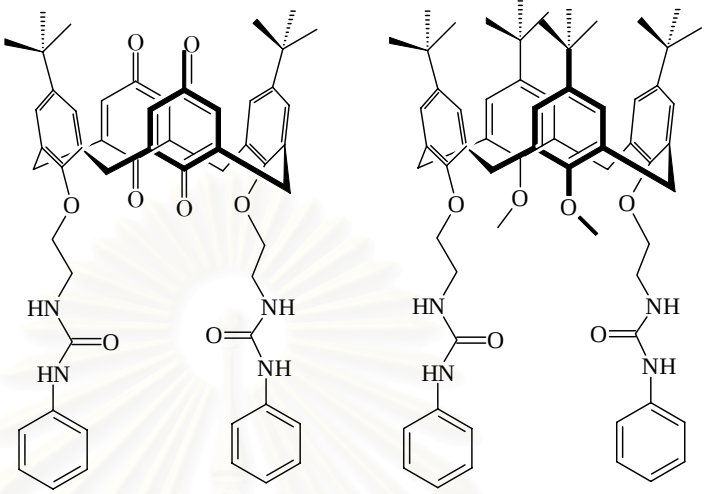
d : X = S , R = phenyl

12 **13**

Figure 1.12 Bidentate urea **Figure 1.13** Quadridentate urea

In 1999, anion binding by the lower rim urea groups of a calix[4]diquinone (Figure 1.14) was reported.[34] The combination of the receptor capabilities of the urea moieties with electron accepting quinones enables analysis of binding capabilities by both electrochemical and ^{1}H-NMR techniques. This is particularly pronounced with hydrogen sulphate which is thought to be due to hydrogen bonding interactions of the

anion with the quinone. This is confirmed by electrochemical studies where large cathodic shift is observed in the presence of hydrogen sulphate.



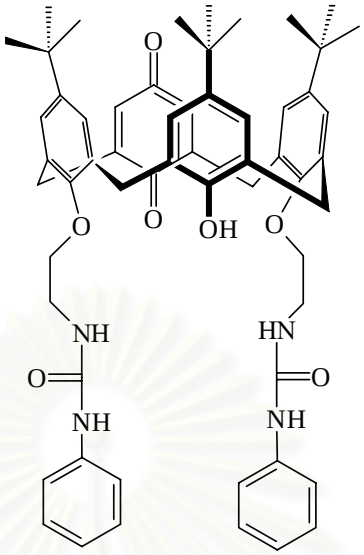
14

Figure 1.14 Calixdiquinone

15

Figure 1.15 Calixurea

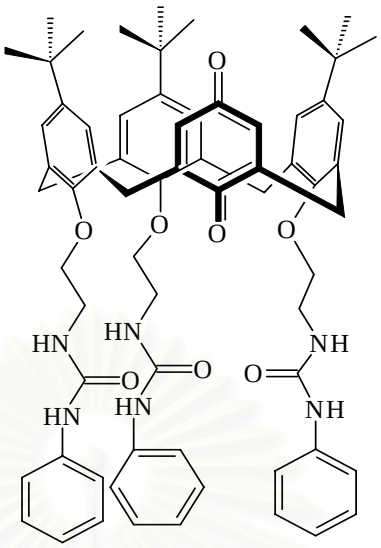
Calix[4]monoquinone (Figure 1.16) was synthesized in the same year by Nam and coworkers.[35] The presence of one equivalent HSO_4^- caused a cathodic shift (64 mV) of the first potential of calix[4]monoquinone. This result indicates that hydrogen sulfate coordinates to the amide moieties of calix[4]monoquinone with greater binding constants than with other anions because of the powerful hydrogen bonding between the quinone and hydrogen sulfate bound to the calix[4]monoquinone.



16

Figure 1.16 Calix[4]monoquinone.

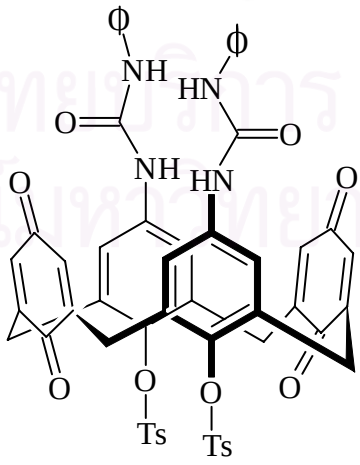
Redox switchable receptors which have anion binding urea units as well as quinone moieties were also developed.[35] A bisurea derivative of calix[4]diquinone showed a selective binding property toward hydrogen sulfate ion. In a series of work of anion binding urea derivaties of calixarene, Nam and coworkers[36] synthesized a trisurea derivative of calix[4]monoquinone (Figure 1.17) and studied its complexation behavior with anions. From previously report a bisurea derivative of calix[4]diquinone showed a selectivity of HSO_4^- due to the additional hydrogen bonding between quinone and OH proton of HSO_4^-. The trisurea derivative of calix[4]arene showed the high binding stability of Cl^-, HSO_4^-, $H_2PO_4^-$ (K_{ass} Cl^-=17200 M^{-1}, HSO_4^- = 15700 M^{-1}, $H_2PO_4^-$ = 13000 M^{-1}) without much selectivity and complexed 1:1 solution stoichiometry with anions.



17

Figure 1.17 Trisureacalix[4]monoquinone.

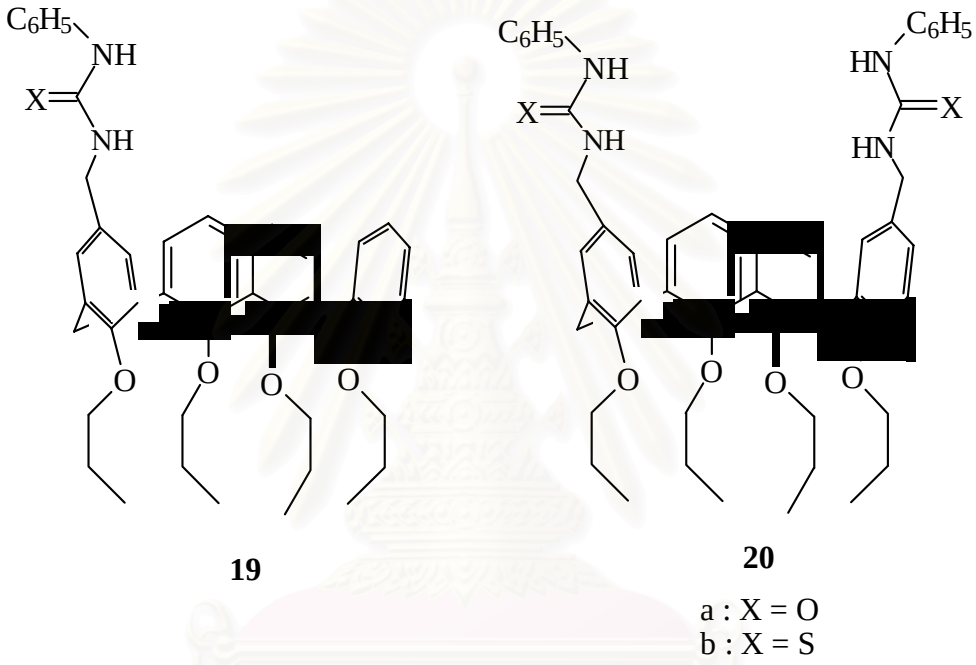
In 2001, Nam and coworkers[37] have reported the second urea derivative of calix[4]diquinone (Figure 1.18) which utilized at the upper rim of calixarene for the introduction of urea groups. This novel neutral anion receptor bound anions through hydrogen bonding and showed a high selectivity with $H_2PO_4^-$. The addition of dihydrogen phosphate anion caused a 94 mV cathodic shift in the quinone/semiquinone redox couple.



18

Figure 1.18 A urea derivative of calix[4]diquinone.

Both uni- and bidentate upper rim receptors have been prepared and their interactions with monocarboxylates evaluated.[38] The monofuctional receptors showed good binding in $(CD_3)_2SO$ with preference for butyrate and benzoate. For butyrate and benzoate, which have higher association constants, they propose that binding occurs within the cavity of calixarene enabling further stabilization by CH_3/π and π/π interactions. The bidentate receptor gives the highest association constant with acetate, possibly through interactions with all four NH groups of the urea moieties.



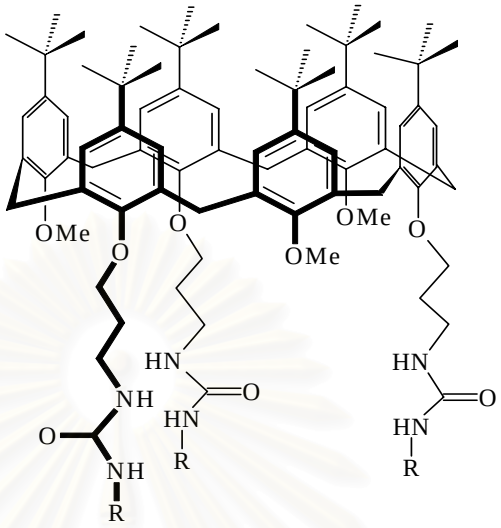
19 **20**

a : X = O
b : X = S

Figure 1.19 Unidentate and bidentate upper rim receptors.

Thiourea and urea derivatives of calix[6]arene (Figure 1.20) have been prepared which show remarkable anion binding selectivity.[39] The incorporation of three urea units at the lower rim of a calix[6]arene combined with three methyl substituents gives a flattened cone conformation. Binding of small spherical anions was demonstrated by FAB mass spectrometry and ^1H NMR studies in $CDCl_3$. Surprisingly, bromide is bound more effectively than chloride, despite its lower acidity, possibly because the cavity size is more complementary. With tricarboxylate anions it was proposed that larger association constants would be observed through

secondary electrostatic interactions between the slightly positively charged NH and the partially negatively chared oxygen of the carboxylate.

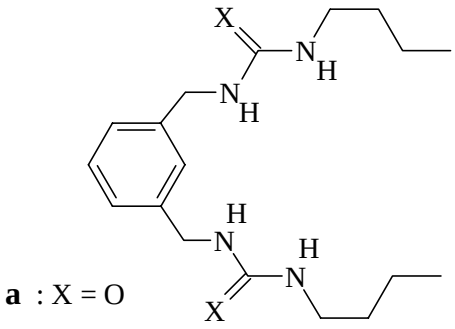


a : X = O, R = phenyl
b : X = S, R = phenyl

21

Figure 1.20 Urea derivative of calix[6]arene.

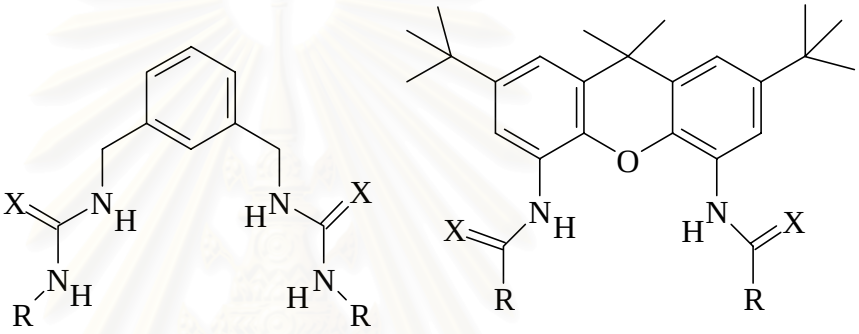
A bis-urea and a bis-thiourea have been synthesized by Umezawa and coworkers,[40,41] both are shown to bind dihydrogen phosphate selectively over various other anions ($H_2PO_4^-$ > CH_3COO^- > Cl^- > HSO_4^- > ClO_4^-). Much stronger binding of $H_2PO_4^-$ by the bis-thiourea is rationalized by stronger H-bond donor strength of the thiourea groups and the binding selectivity is explained in terms of the complex geometry and basicity of the guest anions.



a : X = O

b : X = S

22



a :X = O, R = Bu; **b** :X = S, R = Bu
c :X = S, R = Ph
d :X = S, R = 1-naphthyl

e :X = S, R = NHBu
f :X = S, R = NHPh
g :X = O, R = OCH_2Ph

23

Figure 1.21 A bis urea and a bis thiourea.

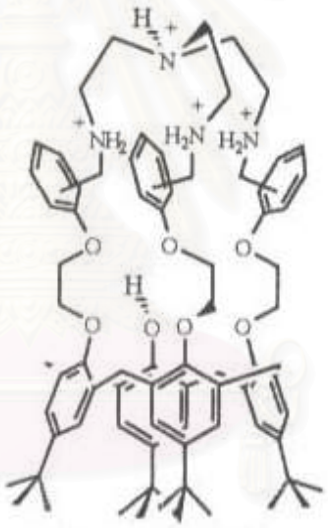
1.5 Ditopic Receptors

The design of receptors for cations and more recently anions is a continuing challenge to supramolecular chemists. A ditopic receptor contains two binding cavities for either the same or different ions. In the case that ditopic receptors are designed for two alkali cations,[42] two transition metal cations,[43-45] or one organic salt with the same ends,[46-48] they are defined as "*homoditopic receptors*". On the other hand, the receptors for alkaline earth cation-transition metal cation,[49] alkali cation-

anion,[50-52] transition metal cation-anion[53,54] or organic ion pairs[55] are categorized as *"heteroditopic receptors"*.[56]

The simultanneous complexation of cationic and anionic guest species by heteroditopic multisite receptors named *"ion pair recognition"* is a new field of supramolecular chemistry which is the interface of cation and anion coordination.[57] The basic approach to develop receptors that recognize the salt as an associated ion pair is to reduce the interference of anions during cation binding study or *vice versa*.

Tripodal aza crown ether calix[4]arenes containing both cation and anion binding sites (a and b) have been synthesized.[58] ^{1}H NMR titrations of the two ligands with various halide anions indicate that **24a** and **24b** can form complexes with Br^-, I^- and NO_3^-. The presence of K^+ enhances the binding of **24a** towards Br^-.



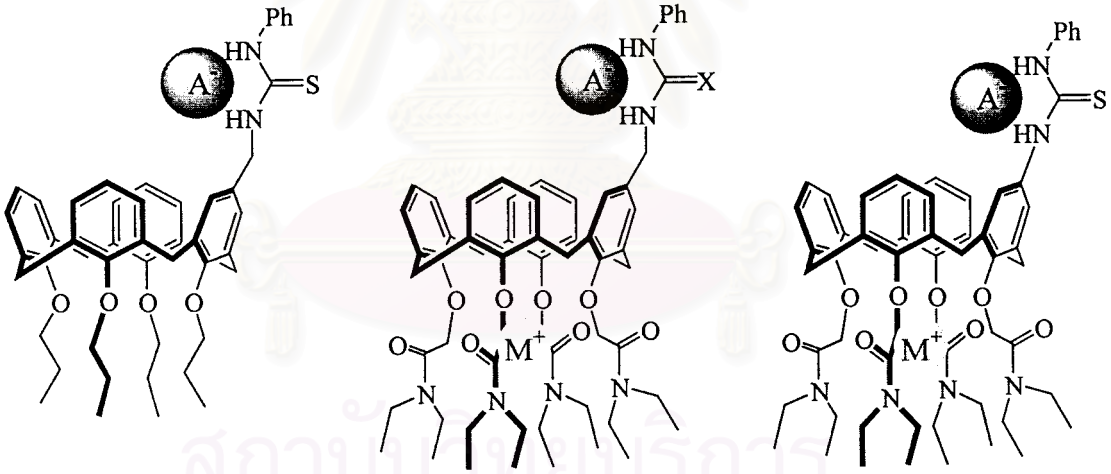
a : *ortho* (86%), **b** : *para* (95%)

24

Figure 1.22 Aza crown ether calix[4]arenes containing cation and anion binding sites

Beer and colleague have synthesized hetero ditopic ferrocene receptors containing two ethyl estercalix[4]arene units bridged by a ferrocene amide moiety.[59] It was found that the binding ability of this ligand toward halide anions increased in the presence of Na^+.

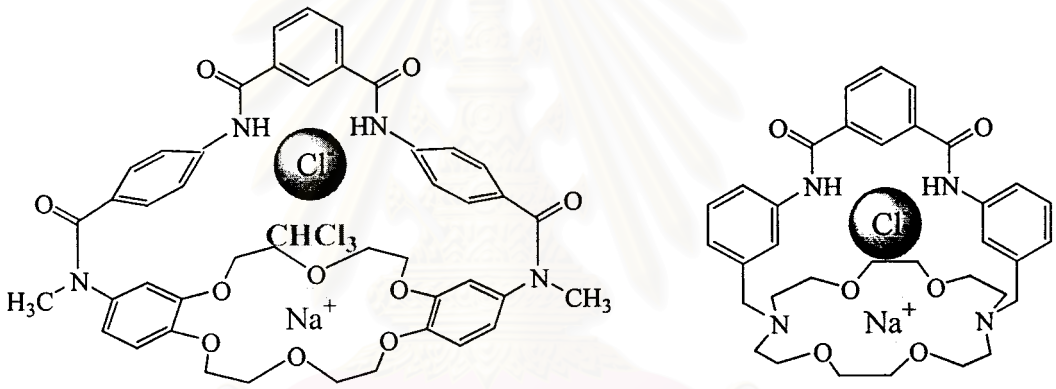
Calix[4]arene tetraamide mono(thio)urea derivatives (Figure 1.23) were synthesized to reduce the effect of intramolecular hydrogen bonding by Pelizzi and coworker.[60] Sodium ion was encapsulated at the narrow rim of the free ligand. Co-bound sodium ion in **26a** enhanced binding ability of anions toward receptor **25** due to intermolecular hydrogen bonding and electrostatic interactions. Moreover, apolar cavity of the calix[4]arene building block is rigidfied by encapsulation of alkali ions. In addition, they have found that the anion coordination ability of the moleccule that contains methylene linkage between the calixarene scaffold and the thiourea moiety has been affected by addition of sodium ion in the solution of the host. Receptor **27** containing thiourea group directly connected to the aromatic units is more efficient than **26a**, which has methylene spacer, because of electron-delocalization effect. Nevertheless, this coopeative binding decreases the selectivity. These receptors were found to selectively bind Y-shape carboxylate anions over spherical anions. Receptors **26** and **27** bound acetate stronger than benzoate and formate.



25 **26a :** X = S **27**
26b : X = O

Figure 1.23 Calix[4]arene tetramide mono(thio)urea derivatives.

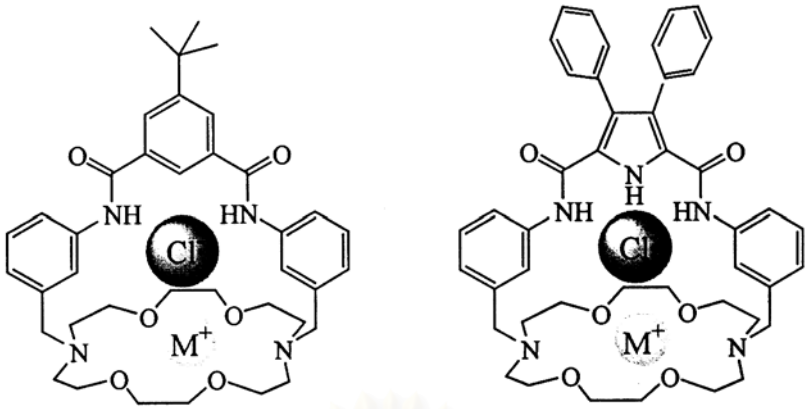
Deetz and coworker reported an X-ray crystal structure of heteroditopic receptor **28** binding NaCl as a solvent separated ion pair.[61] However, the binding cooperativity would be improved if the salt were bound to the receptor as a contact ion pair. Later, they designed host **29** as a salt binding analogous of **28** but with a shorter distance between the anion and cation binding site.[62] These results suggested that macrocycle **29** is the first unambiguous example of a ditopic receptor that binds alkali halide as their contact ion pair in solution more strongly than free ions (sodium or potassium were used as cation while chloride was served as anion). The solvent separated ion pair of **28** and contact ion pair of **29** are displayed in Figure 1.24.



28 **29**

Figure 1.24 Effect of the chain length towards the formation of solvent separate or contact ion pairing.

Analogous receptors have reported by Mahoney et al. (Figure 1.25).[63] Compared to heteroditopic **30**, bicyclic **31** was found to be a better host towards chloride anion either in the absence or the presence of an alkali cation (sodium or potassium). The crystal structure of **30.**NaCl was obtained. The contact ion pair affect was found as expected.



30 **31**

Figure 1.25 Contact ion pair recognitions.

1.6 Objective of research

To gain a basic understanding of molecular recognition, synthesis of receptor molecules with a high selectivity for a particular guest molecule has been of interest to supramolecular chemists. This has been one of the driving forces for design of synthetic receptors. In the last few years evidence has been accumulated showing that preorganization plays a fundmental role in molecular recognition by synthetic receptors. Preorganization and rigidity of host molecules are usually obtained by covalently linking binding groups or rigid spacers to suitable templates.

However, these seems to be no report, to our knowledge, on calixarene based receptors having urea groups as a part of macrocyclic framework, despite the fact that preorganization of the binding sites is excepted which would improve the binding ability and selectivity. Our approach utilizes cyclic framework to control molecular architecture and consequently to preorganize the host molecules. Moreover, the rigid molecular components have been used to hold hydrogen bonding groups at a fixed distance. The urea units lead to receptors that form strong, multi hydrogen bonded complexes with dihydrogen phosphate. In this research, we are interested in synthesizing neutral anion receptors using calix[4]arene as the building block and attaching urea units as receptors for anions at the wider rim. In addition, in one of target molecules, a crown ether group is attached to a calix[4]arene urea of the narrow

rim. Anion binding studies of the hosts synthesized with various anions have been performed to investigate the effect of the crown ether unit and different cations towards anion binding ability. Therefore, calix[4]arene containing urea units and calix[4]arene containing crown ether unit and urea units have been synthesized. The target molecules are shown in Figure 1.26. The binding ability of these compounds has been investigated by ^{1}H-NMR titrations.

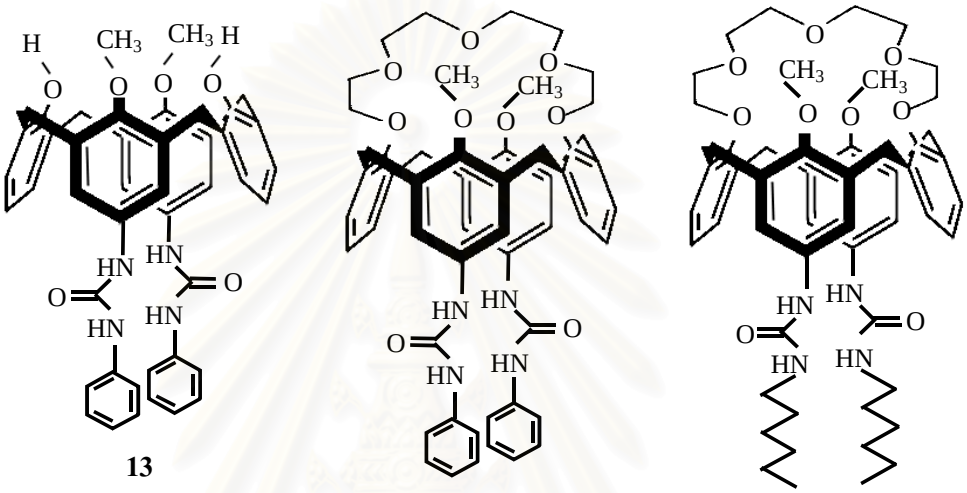


Figure 1.26 A bisurea calix[4]arene and crown 5 bisureacalix[4]arene

CHAPTER II

EXPERIMENTAL

2.1 Materials

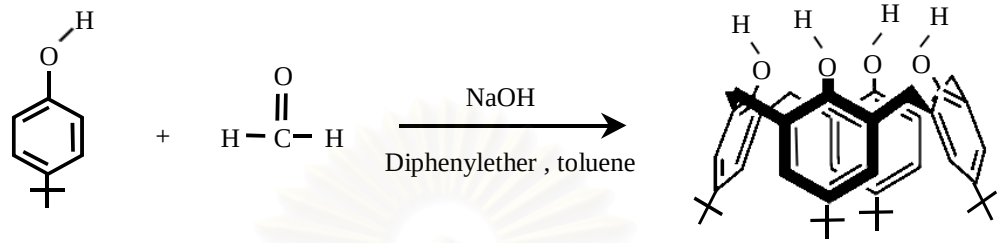
Unless otherwise noted, all materials and solvents were standard analytical grade, purchased form Fluka, BDH, Aldrich, Carlo Erba, Merck or J.T Baker. They were used without further purification. Commercial grade solvents such as acetone, dichloromethane, hexane, methanol and ethyl acetate were purified by distillation. Acetonitrile, toluene and dichloromethane were dried over CaH_2 and freshly distilled under nitrogen atmosphere prior to use. Column chromatography was carried out on silica gel (Kiesel gel 60, 0.063 - 0.200 mm, Merck). All eluents for column chromatography were stored over molecular sieves 3 Aº or 4 A° prior to use. Thin – layer chromatography (TLC) were performed on silica gel plates (Kieselgel 60 F_{254}, 1mm, Merck). Compounds on TLC plates were detected by the UV – light. All manipulations were carried out under nitrogen atmosphere. Starting material such as *p–tert*butylcalix [4]arene, **1** was prepared according to literature procedure[64] and calix [4] arene was prepared using the previously described procedure.[65]

2.2 Analytical Procedures

Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker ACF 200 MHz and a Bruker AVANCE 300 MHz. All chemical shifts were reported in part per million (ppm) using the residual proton. Elemental analyses were carried out on a Perkin – Elmer CHON/S analyzer (PE 2400 series). All melting points were obtained on an Electrothermal 9100 apparatus.

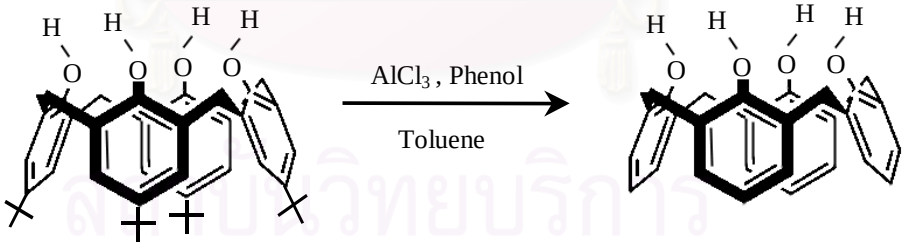
2.3 Synthetic Procedures

2.3.1 Preparation of *p-tert*-butylcalix[4]arene.



p-tert-Butylcalix[4]arene was synthesized as described previously[10,65] and obtained as colorless plate-like crystals after recrystallization from toluene : m.p. 344-346 ^{o}C.

2.3.2 Preparation of 25,26,27,28-tetrahydroxycalix[4]arene (**1**).



1

Into a 250 mL two-necked round bottom flask equipped with a magnetic bar, p-tert-Butylcalix[4]arene (13.3 g, 200 mmol), $AlCl_3$ (14 g, 105 mmol), phenol (9.02 g, 96.0 mmol) and toluene (125 mL) were stirred under nitrogen atmosphere at room temperature for 1 hours. The reaction was poured into 100 mL of 3 M hydrochloric and stirred for 30 miniutes. The mixture was extracted with dichloromethane. The

organic layer was dried over anhydrous sodium sulfate, filtered and concentrated on a rotary evaporator. The methanol was subsequently added to precipitate a white powder **1** (6.77 g, 78 %).

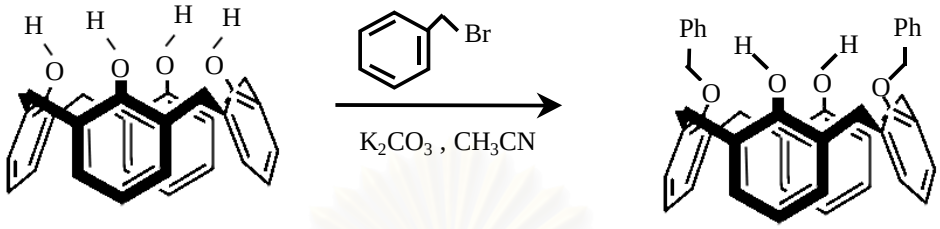
Charaterization data for 1

^{1}H NMR spectrum (200 MHz, $CDCl_3$) : δ (in ppm)

δ 8.36 (d, *J* = 8 Hz, 4H, Ar***H*** $_{benzoyl}$), 7.07 (t, *J* = 8 Hz, 2H Ar***H*** $_{benzoyl}$), 7.53 (t, *J* = 8 Hz, 4H, Ar***H*** $_{benzoyl}$), 7.07 (d, *J* = 4H, Ar***H***), 6.66- 6.94 (m, 8H, Ar***H***), 5.50 (s, 2H, Ar***OH***), 3.98 (d, *J* = 14Hz, 4H, Ar***CH***$_2$Ar).

Melting Point : 313 – 315 ^{o}C

2.3.3 Preparation of 25,27–dibenzyloxy–26,28–dihydroxycalix[4]arene (**2**).



1 **2**

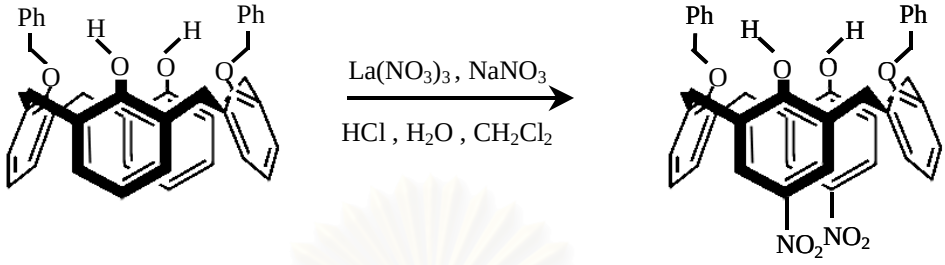
Into a 250 mL two-necked round bottom flask equipped with a magnetic bar, **1** (4.24 g, 10 mmol), anhydrous potassium carbonate (10.90 g, 100 mmol) and acetonitrile (125 mL) were mixed and stirred for 30 minutes. Benzyl bromide (2.61 mL, 22 mmol) was added into the mixture. The mixture was heated at reflux under nitrogen for 2 hours. The mixture was allowed to cool to room temperature and evaporated to dryness under reduced pressure. The residue was dissolved in dichloromethane and the aqueous solution of 3 M hydrochloric acid was subsequently added until the pH of the solution reached 1. The organic layer was dried over anhydrous sodium sulpate and filtered. The volume of the organic layer was reduced. Methanol was added to precipitate a white powder **2** (5.44 g, 90%). The compound was kept in a desiccator and dried in *vaccuo*.

Characterization data for 2

^{1}H NMR spectrum ($CDCl_3$, MHz) : δ (in ppm)

δ 7.81(s, 2H, ArO***H***), 7.66-7.61(m, 4H, Ar***H***), 7.31(m, 6H, Ar***H***), 7.04(d, *J* = 7Hz, 4H, Ar***H***), 6.88(d, *J* = 7Hz, 4H, Ar***H***), 6.76-6.60(m, 4H, Ar***H***), 5.05(s, 4H, -OC***H*****$_2$**Ar), 4.30(d, *J* = 12Hz, 4H, ArC***H*****$_2$**Ar), 3.33(d, *J* = 12Hz, 4H, ArC***H*****$_2$**Ar).

2.3.4 Preparation of 5,17–dinitro–25,27–dibenzyloxy–26,28-dihydroxycalix[4] arene (**3)**



2 **3**

Into a 500 mL two-necked round bottom flask equipped with a magnetic bar, 25,27–dibenzyloxy–26,28–dihydroxycalix[4]arene (6.04 g, 10 mmol)and dichloromethane (200 mL) was stirred under nitrogen atmosphere. Sodium nitrate (2.55 g, 30 mmol) and a catalytic amount of $La(NO_3)_3.6H_2O$ in a mixture of aqueous (150 mL) and concentrated hydrochloric (20 mL) were added into the reaction. The mixture was stirred overnight at room temperature. The color of the mixture turned yellow. The aqueous layers were then separated and extracted with dichloromethane (100x2). The organic layer was combined and washed with saturated aqueous ammonium chloride (100x2) and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporator. Hexane was added to precipitate a yellow powder **3** (4.52 g, 65%). The compound was kept in a dessicator and dried in *vaccuo*.

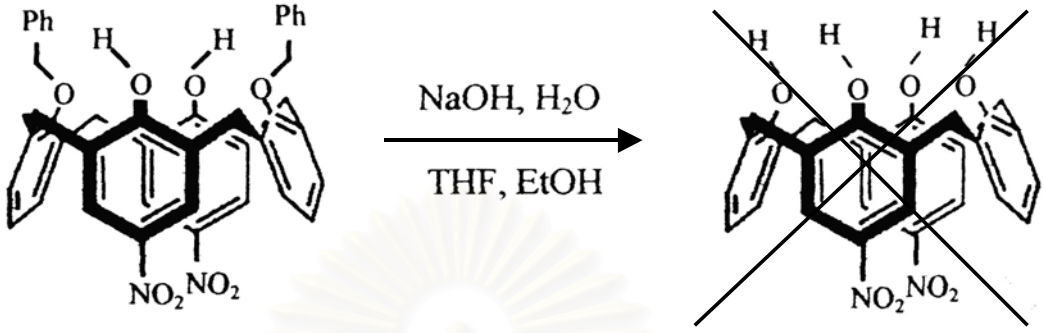
Characterization data for 3

^{1}H NMR spectrum (200 MHz, $CDCl_3$) : δ (in ppm)

δ 8.98 (s, 2H, ArO***H***), 8.02 (s, 4H NO_2Ar***H***), 7.60-7.55 (m, 4H, Ar***H***), 7.41-7.36 (m, 6H, Ar***H***), 6.99- 6.85 (m, 6H, Ar***H***), 5.07(s, 4H, -OC***H*****$_2$**Ar), 4.24 (d, *J* = 13Hz, 4H, Ar***CH***$_2$Ar), 3.45 (d, *J* = 13Hz, 4H, Ar***CH***$_2$Ar).

.

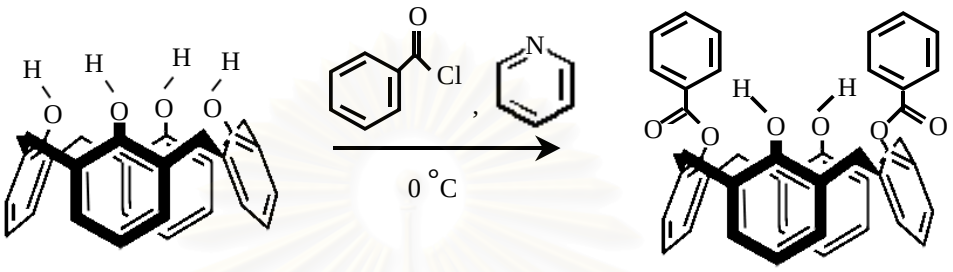
2.3.5 Preparation of 5,17–dinitro–25,26,27,28-tetrahydroxycalix[4] arene (**4)**



3 **4**

Into a 250 mL two-necked round bottom flask containing a **3** (2.0 g, 2.88 mmol) in the THF (75 mL) and EtOH (40 mL) was treated with sodium hydroxide in aqueous solution (7.7 g, 192 mmol). The mixture was stirred and heated at refluxed with stirring under nitrogen atmosphere for 15 hours. The mixture was allowed to cool to room temperature and evaporated under reduced pressure. 3 M hydrochloric acid was added into the residue until the pH of the solution reached 1. The mixture was filtered and washed with methanol. The filtrate was dissolved in a minimum amount of dichloromethane, mixed with silica gel and placed on a silica-gel column. The desired product was characterized by ^{1}H-NMR spectroscopy. The signal of ArC***H*****$_2$**O- at about 5.05 ppm on the ^{1}H-NMR spectrum indicated that the desired product was not obtained.

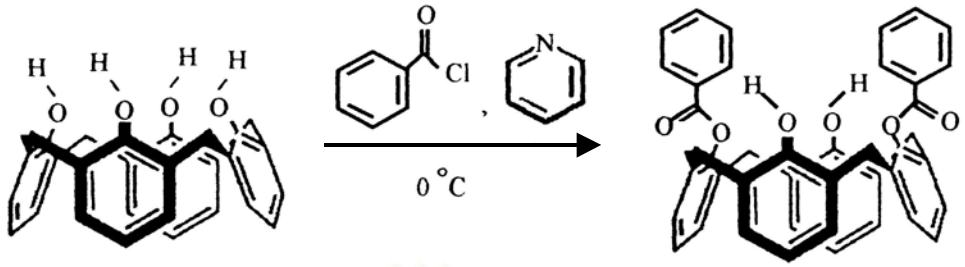
2.3.6 Preparation of 25,27–dibenzoyloxy–26,28–dihydroxycalix[4]arene (**5**).



1 **5**

Into a 100 mL two-necked round bottom flask equipped with a magnetic bar, **1** (4.24 g, 10 mmol), pyridine (50 mL) was stirred at ice bath temperature. Benzoyl chloride (2.55 mL, 22 mmol) was added into the mixture. The mixture was stirred at 0 ^{o}C for 1 hour and allowed to slowly warm to room temperature for another hour. The volume of the mixture was reduced under reduced pressure. Methanol was added to precipitate white crystals **5** (4.43 g, 70%). The compound was kept in a dessicator and dried in *vaccuo*.

2.3.6 Preparation of 25,27–dibenzoyloxy–26,28–dihydroxycalix[4]arene (**5**).



1 **5**

Into a 250 mL two-necked round bottom flask equipped with a magnetic bar and a reflux condenser, **1** (4.24 g, 10 mmol), anhydrous sodium carbonate (10.60 g, 100 mmol) and acetonitrile (125 mL) were mixed and stirred for 30 minutes. Benzoyl chloride (2.55 mL, 22 mmol) was added into the mixture. The mixture was heated at reflux under nitrogen for 2 hours. The mixture was allowed to cool to room temperature and evaporated to dryness under reduced pressure. The residue was dissolved in dichloromethane and the aqueous solution of 3 M hydrochloric acid was subsequently added until the pH of the solution reached 1. The organic layer was dried over anhydrous sodium sulfate and filtered. The volume of the organic layer was reduced to a quater. Methanol was added to precipitate a white crystals **5** (5.69 g, 90%). The compound was kept in a desiccator and dried in *vaccuo*.

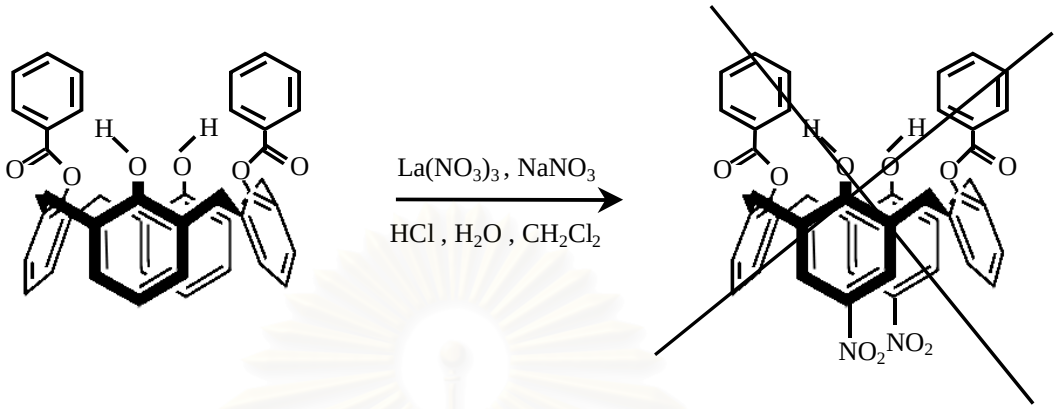
Characterization data for 5 :

^{1}H NMR spectrum (200 MHz, $CDCl_3$) : δ (in ppm)

δ 8.36 (d, *J* = 8 Hz, 4H, Ar***H*** $_{benzoyl}$), 7.07 (t, *J* = 8 Hz, 2H Ar***H*** $_{benzoyl}$), 7.53 (t, *J* = 8 Hz, 4H, Ar***H*** $_{benzoyl}$), 7.07 (d, *J* = 4H, Ar***H***), 6.66- 6.94 (m, 8H, Ar***H***), 5.50 (s, 2H, Ar***OH***), 3.98 (d, *J* = 14Hz, 4H, Ar***CH***$_2$Ar).

Melting Point : 269 – 271 ^{o}C

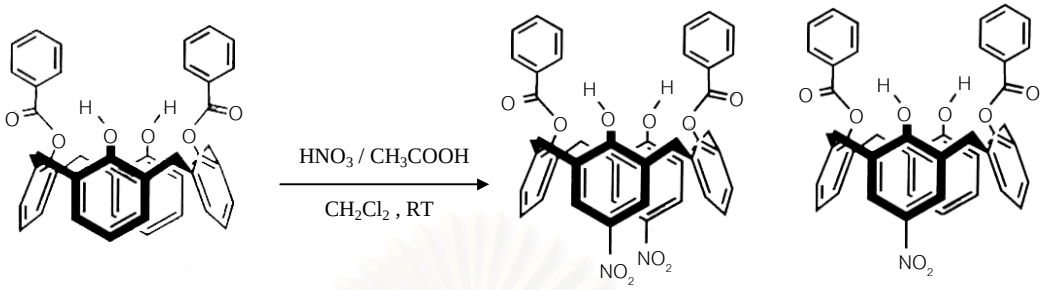
2.3.7 Preparation of 5,17–dinitro–25,27–dibenzoyloxy–26,28-dihydroxycalix[4] arene (**6)**



5 **6**

Into a 250 mL two-necked round bottom flask equipped with a magnetic bar, **5** (3.6 g, 5.69 mmol) and dichloromethane (100 mL) were stirred under nitrogen atmosphere. Sodium nitrate (1.45 g, 17.07 mmol) and a catalytic amount of $La(NO_3)_3.6H_2O$ in a mixture of aqueous (50 mL) and concentrated hydrochloric (10 mL) were added into the reaction. The mixture was stirred overnight at room temperature. The color of the mixture was not turned yellow. The aqueous layers were then separated and extracted with dichloromethane (50 mLx2). The organic layer was combined and dichloromethane (50 mLx2) and dried over anhydrous sodium sulfate. The solvent was removed by a rotary evaporator. Hexane was added to precipitate white powder. It was characterized by ^{1}H-NMR spectroscopy but the signal of ArO***H*** proton which was substituted by nitro groups at about 6.3 ppm was not observed on the ^{1}H-NMR spectrum indicated that the desired product was not obtained.

2.3.7 Preparation of 5,17–dinitro–25,27–dibenzoyloxy–26,28-dihydroxycalix[4] arene (**6)**



5 **6**

Into a 250 mL two-necked round bottom flask equipped with a magnetic bar, **5** (3.6 g, 5.69 mmol), acetic acid (20 mL) and dichloromethane (40 mL) were stirred. Nitric acid (65%, 1.08 mL) was added into the mixture. The reaction mixture was stirred under nitrogen atmosphere for 4 hours at room temperature and washed with Sodium hydrogencarbonate solution. The mixture was extracted with dichloromethane. The organic layer was dried over sodium sulfate anhydrous, filtered and concentrated on a rotary evaporator. The methanol was subsequently added to precipitate. The precipitation was dissolved in a minimum amount of dichloromethane, mixed with silica gel and placed on a silica gel column using the ratio of the precipitation and silica gel of 1 : 30. Both of the desired product, 5,17–dinitro–25,27–dibenzoyloxy–26,28–dihydroxycalix[4]arene (**3**) and 5–mononitro–25,27–dibenzoloxy–26,28–dihydroxycalix[4]arene were eluted with dichloromethane. The mononitro calix[4]arene was eluted from the column after its dinitroanalogue. The collected fraction of dinitro compound was slowly evaporated and added methanol to precipitate a yellowish green crystals (1.85 g, 45%). The compound was kept in a desiccator and dried in *vacuo*.

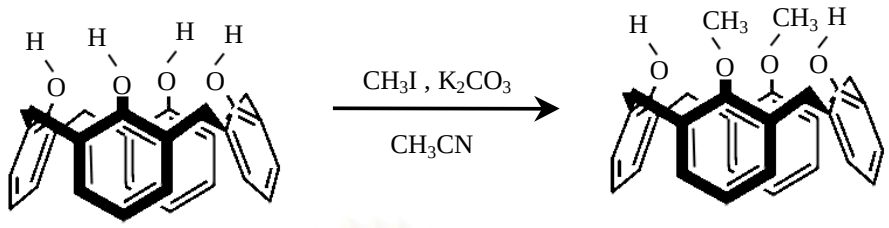
Characterization data for 6

^{1}H NMR spectrum ($CDCl_3$, MHz) : δ (in ppm)

δ 8.21 (d, J = 8 Hz, 4H, Ar***H***), 7.97 (S, 4H, Ar***H***), 7.76 (t, *J* = 7Hz, 2H Ar***H***), 7.53 (t, *J* = 7 Hz, 4H, Ar***H***), 7.01 (m, 6H, Ar***H***, 6.33 (S, 2H, Ar***OH***), 3.99 (d, *J* = 14 Hz, 4H, Ar***CH$_2$***Ar), 3.66 (d, *J* = 14 Hz, Ar***CH$_2$***Ar).

Melting point : 288 – 289 ^{o}C

2.3.8 Preparation of 25,27–dimethoxy–26,28–dihydroxycalix [4]arene (**7**)



1 **7**

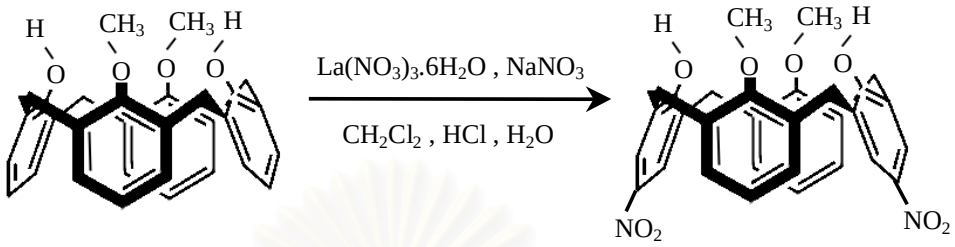
Into a 250 mL two-necked round bottom flask equipped with a magnetic bar, **1** (4.25 g, 10 mmol) and potassium carbonate (1.51 g, 10.9 mmol) and acetonitrile (100 mL) was stirred under nitrogen atmosphere for 1 hour. Iodomethane (1.313 g, 22 mmol) was then added and the mixture was heated at reflux overnight. The mixture was cooled to room temperature. The reaction was filtered and the filtrate was then concentrated by a rotary evaporator. The residue was dissolved in dichloromethane and washed with 3 M hydrochloric acid 3 times. The organic layer was dried over anhydrous sodium sulfate. The volume of the solvent was reduced by using a rotary evaporator. Upon adding methanol, a white solid of compound **7** was precipitated (3.97 g, 88%).

Characterization data for 7

^{1}H NMR spectrum ($CDCl_3$, 200 MHz) : δ (in ppm)

δ 7.72 (s, 2H, ArO***H***), 7.09-6.63(m, 12H, Ar***H***), 4.33 (d, *J* = 3 Hz, 4H Ar***CH$_2$***Ar), 3.97 (s, 6H, ArO***CH$_3$***), 3.42 (d, *J* = 13 Hz, 4H, Ar***CH$_2$***Ar).

2.3.9 Preparation of 5,17-dinitro-25,27-dimethoxy-26,28-dihydroxycalix[4]arene (**8**)



7 **8**

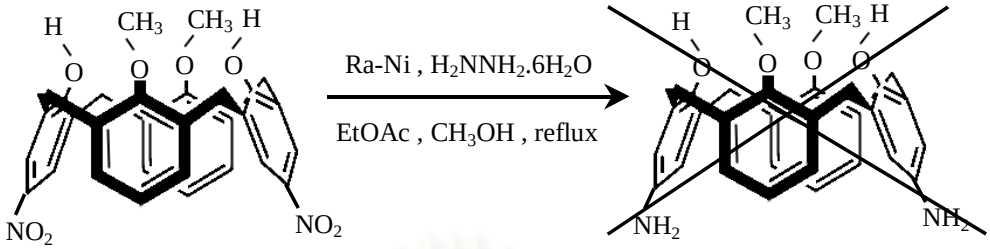
Into a 500 mL two-necked round bottom flask equipped with a magnetic bar, **7** (5 g, 11.05 mmol) and dichloromethane (250 mL) were stirred under nitrogen atmosphere. Sodium nitrate (2.82 g, 33.15 mmol) and a catalytic amount of $La(NO_3)_3.6H_2O$ in a mixture of aqueous (150 mL) and concentrated hydrochloric acid (25 mL). The mixture was stirred overnight at room temperature. The color of the mixture turned yellow. The aqueous layers were then separated and extracted with dichloromethane (100x2). The organic layer was combined and washed with saturated aqueous ammonium chloride (100x2) and dried over anhydrous sodium sulfate. The solvent was removed by a rotary evaporator and the product was crystallized by adding hexane to give a yellow powder (4.26 g, 70%).

Characterization data for 8

^{1}H NMR spectrum ($CDCl_3$, 200 MHz) : δ (in ppm)

δ 8.93 (s, 2H, ArO***H***), 8.04 (s, 4H, ***H***Ar-NO_2), 6.94 (d, *J* = 7.2 Hz, 4H, *m*-***H***Ar-OCH_3), 6.81 (t, 2H, *J* = 7.4 Hz, *p*-***H***Ar-OCH_3), 4.28 (d, *J* = 13.3 Hz, 4H, Ar***CH$_2$***Ar), 4.02 (s, 6H, ArOC***H$_3$***), 3.57 (d, *J* = 13.3 Hz, ArC***H$_2$***Ar).

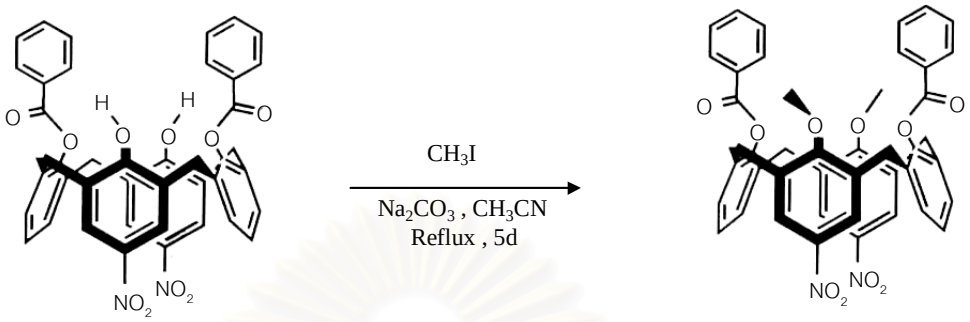
2.3.10 Preparation of 5,17-diamino-25,27-dimethoxy-26,28-dihydroxycalix[4]arene (**9**)



8 **9**

5,17-Dinitro-25,27-dihydroxy-26,28-dimethoxycalix[4]arene(**8**) (1.06 g, 1.95 mmol) and Raney Ni (2.095 g) were suspended in the mixture of ethyl acetate (80 mL) and methanol (40 mL). Hydrazine (4 mL) was then added into the mixture. The mixture was refluxed for 2 hours and allowed to cool to room temperature. The solvent was subsequently removed under reduced pressure. The residue was dissolved in dichloromethane and extracted and washed with several portions of aqueous. The organic layer was removed. The residue was characterized by ^{1}H-NMR spectroscopy. The signal of amino proton was not observed on the ^{1}H-NMR spectrum indicated that the desired product was not obtained.

2.3.11 Preparation of 5,17-dinitro-25,27-dibenzoyloxy-26,28-dimethoxycalix[4]arene (**10**)



6 **10**

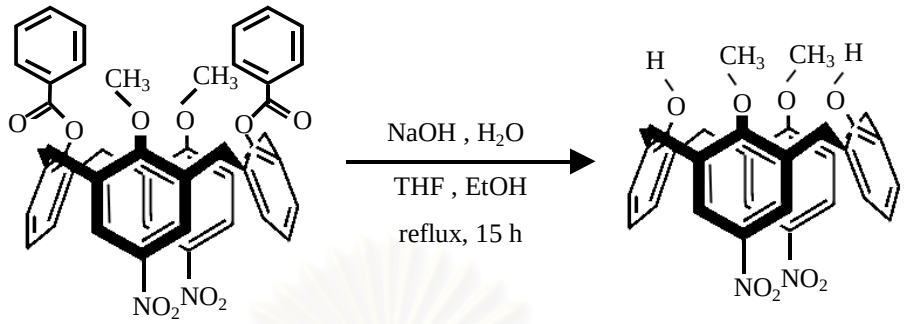
Into a 250 mL two–necked round bottom flask equipped with a magnetic bar and a reflux condenser, **6** (3.00 g, 4.150 mmol), anhydrous sodium carbonate (4.40 g, 41.50 mmol) and acetonitrile (125 mL) were mixed and stirred for 30 minutes. Methyl iodide (1.30 mL, 20.750 mmol) was added into the mixture. The mixture was heated at reflux under nitrogen for 5 days. The mixture was allowed to cool to room temperature and evaporated to dryness under reduced pressure. The residue was dissolved in dichloromethane and the aqueous solution of 3 M hydrochloric acid was subsequently added until the pH of the solution reached 1. The organic layer was dried over anhydrous sodium sulfate and filtered. The volume of the organic layer was reduced to a quater. Methanol was added to precipitate a yellow powder **10** (2.65 g, 85%). The compound was kept in a desiccator and dried in *vaccuo*.

Characterization data for 10

^{1}H – NMR spectrum (200 MHz, $CDCl_3$) : δ (in ppm)

δ = 6.75–8.19 (m, 20H, Ar***H***), 3.35–3.82 (m, ArO***CH₃***, Ar***CH₂***Ar)

2.3.12 Preparation of 5,17–dinitro–25,27–dihydroxy–26,28–dimethoxycalix[4]arene (**11**)



10 **11**

Into a 250 mL two – necked round bottom flask contraining a **10** (3.00 g, 4.00 mmol) in the THF (75 mL) and EtOH (40 mL) was treated with sodium hydroxide in aqueous solution (9.92 g, 248 mmol). The mixture was stirred and heated at refluxed with stirring under nitrogen atmosphere for 15 hours. The mixture was allowed to cool to room temperature and evaporated under reduced pressure. 3 M Hydrochloric acid was added into the residue until the pH of the solution reached 1. The mixture was filtered and washed with methanol. The filtrate was dissolved in a minimum amount of dichloromethane, mixed with silica gel and placed on a silica-gel column. The desired product, 5,17-dinitro–25,27–dihydroxy–26,28–dimethoxycalix[4]arene **11** was eluted with a mixture of dichloromethane and ethyl acetate (95:5). The collected fraction of **11** was slowly evaporated, methanol was then added to precipitate a yellowish green powder (1.08 g, 50%). The compound was kept in a desiccator and dried in *vacuo*.

Characterization data for 11

^{1}H NMR spectrum ($CDCl_3$, 200 MHz) : δ (in ppm)

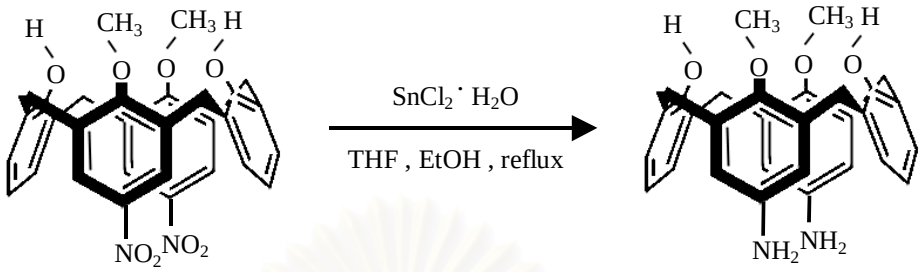
δ 7.80 (S, 4H, Ar***H***), 7.52 (S, 2H, Ar***OH***), 7.14 (d, *J* = 7 Hz, 4H, Ar***H***), 6.75 (t, *J* = 6 Hz, 2H, Ar***H***), 4.33 (d, *J* = 3 Hz, 4H Ar***CH$_2$***Ar), 4.05 (S, 6H, ArO***CH$_3$***), 3.51 (d, *J* = 13 Hz, 4H, Ar***CH$_2$***Ar)

FAB mass spectrum ; 542.84 (M^+) m / z

Elemental Analysis: Calculated result for $C_{28}H_{26}O_8N_2$: C = 66.41; H = 4.77; N = 5.16

Found : C = 66.41; H = 4.83; N = 5.16

2.3.13 Preparation of 5,17–diamino-25,27–dihydroxy–26,28–dimethoxycalix[4] arene (**12**) .



11 **12**

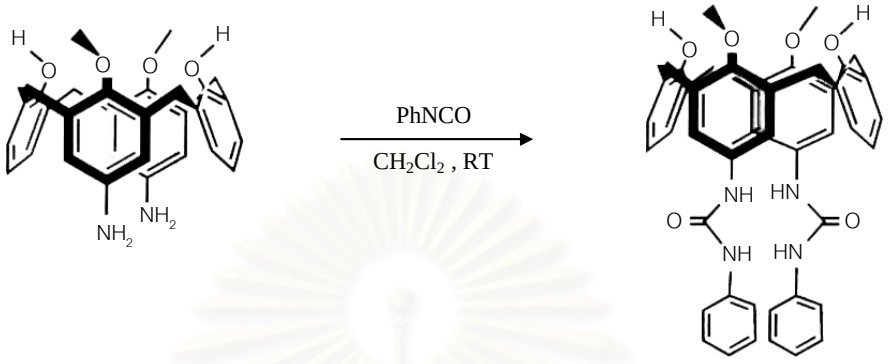
Into a 250 mL two–necked round bottom flask equipped with a magnetic bar and a reflux condenser, **11** (0.20 g, 0.368 mmol), $SnCl_2 \cdot 2H_2O$ (1.25 g, 5.53 mmol), THF and EtOH were mixed. The mixture was heated at reflux under nitrogen for 12 hours and then allowed to cool to room temperature. The reaction mixture was poured into ice and stirred. The aqueous solution of sodium hydrogencarbonate was added until the pH of the solution reached 8. The mixture was extracted with dichloromethane (3x30 mL) and stirred with water for 12 hours. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness to obtain a yellowish orange powder of **12** (70%). The compound was kept in a desiccator and dried in *vacuo*.

Characterization data for 12

^{1}H NMR spectrum ($CDCl_3$, 200 MHz) : δ (in ppm)

δ 7.88 (S, 2H, Ar***OH***), 7.02 (d, *J* = 7 Hz, 4H, Ar***H***), 6.64 (t, *J* = 7 Hz, 2H, Ar***H***), 6.18 (S, 4H, Ar***H***), 4.21 (d, *J* = 14 Hz, Ar***CH$_2$***Ar), 3.89 (S, 6H, ArO***CH$_3$***), 3.27 (d, *J* = 14 Hz, 4H, Ar***CH$_2$***Ar), 1.78 (br, 4H, -***NH$_2$***).

2.3.14 Preparation of 5,17–diphenylurea–25,27–dihydroxy–26,28–dimethoxycalix[4] arene (**13**).



12 **13**

Compound **12** (0.20 g, 0.414 mmol) was dissolved in dry dichloromrthane (10 mL) and reacted with phenylisocyanate (0.10 mL, 0.911 mmol) in 25 mL round bottom flask. The solution was stirred under nitrogen for 24 hours. A white solid was precipitated from the solution. The product **13** (0.18 g, 60%) was filtered and washed with dichloromethane. The compound was kept in a desiccator and dried in *vacuo*.

Characterization data for 13

^{1}H NMR spectrum (DMSO-d_6, 200 MHz) : δ (in ppm)

δ 8.42 (S, 2H, Ar***H***), 8.30 (S, 2H, Ar*H*), 8.17 (S, 2H Ar***OH***), 7.08 – 7.33 (m, 16H, Ar***H***), 6.89 (t, *J* = 7Hz, 2H, Ar***H***), 6.60 (t, *J* = 7Hz, 2H, Ar***H***) , 4.15 (d, *J* = 13Hz, 4H Ar***CH$_2$***Ar), 3.89 (S, 6H, ArO***CH$_3$***), 3.46 (d, *J* = 13 Hz, 4H, Ar***CH$_2$***Ar).

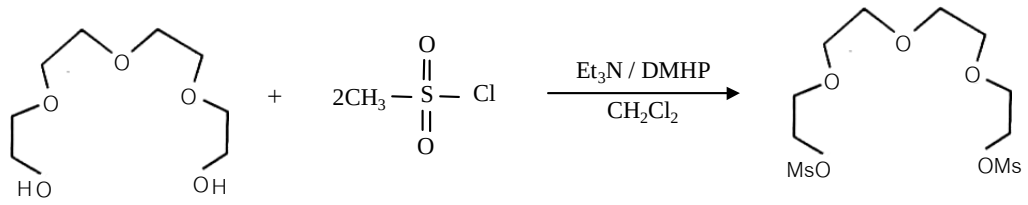
Melting point = 220-224 ^{o}C

ESI mass spectrum : 720.99 [M^+] m/z

Elemental Analysis: Calculated result for $C_{44}H_{40}N_4O_6$: C = 73.32; H = 5.59; N = 7.77

Found : C = 73.16; H = 5.63; N = 7.74

2.3.15 Preparation of tetraethylene glycol dimetylsulfonate



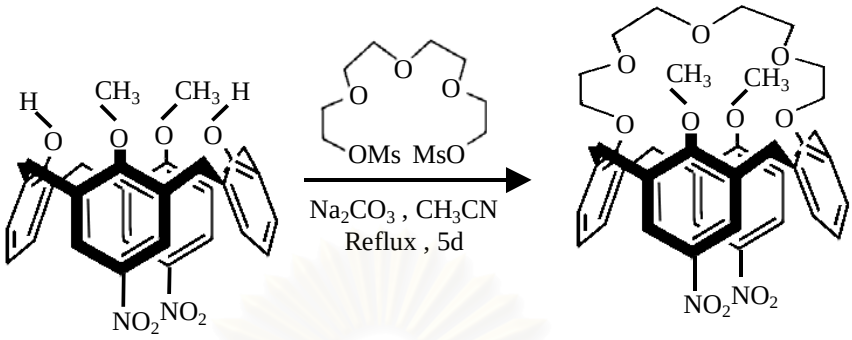
Into a 250 mL round bottom flask, a dichloromethane solution (150 mL) of tetraethylene glycol (7.38 mL, 50 mmol), triethylamine (7.25 mL, 100 mmol) and a catalytic amount of DMAP was chilled 10 °C with an ice bath and stirred under nitrogen. Methane sulfonyl chloride (7.35 mL, 95 mmol) in dichloromethane (50 mL) was then added dropwise over 30 minutes into the solution. The reaction mixture was allowed to stir at room temperature under nitrogen atmosphere for 4 hours. After the reaction was complete, the mixture was then poured into an aqueous solution of 3 M hydrechloric acid (100 mL) and stirred for 30 minutes and then extracted with dichloromethane (2x50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness to obtain a yellow oil of tetraethylene glycol dimethanesulfonale (70%). The product was dried in *vacuo* and kept in a desiccator.

Characterization

^{1}H NMR Spectrum (400 MHz , $CDCI_3$) : δ (in ppm)

δ 4.313–4.357 (m, 4H, - O***CH₂CH₂***O-), 3.580–3.746 (m, 12H, -O***CH₂CH₂***O-), 3.03 (S, 6H, ***CH₃***)

2.3.16 Preparation of 5,17–dinitro–25,27–tetraethyleneglycoloxy-26,28–dimethoxycalix[4]arene (**14**).



11 **14**

Into a 250 mL round bottom flask equipped with a magnetic bar and a reflux condenser, **11** (0.50 g, 0.921 mmol), anhydrous sodium carbonate (0.98 g, 9.21 mmol) and acetronitrile (100 mL) were mixed and stirred for 30 minutes. Tetraethylene glycol dimethanesulfonate (0.698 g, 2.030 mmol) in acetronitile (50 mL) was added dropwise to the mixture. The reaction mixture was heated at reflux with stirring under nitrogen for 5 days. The solution was allowed to cool to room temperature and evaporated to dryness under reduced pressure. The residue was dissolved in dichloromethane (100 mL) and the aqueous solution of 3 M hydrochloric acid was subsequently added and stirred for 30 minutes. The solution was extracted with dichloromethane (2x50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness to obtain a yellowish orange residue. The residue was dissolved in a minimum amount of dichloromethane and placed on a silica gel column. 5,17–dinitro–25,27–tetraethyleneglycoloxy–26,28–dimethoxy calix[4]arene (**14**) was eluted with a mixture of dichloromethane and ethyl acetate (95:5). The volume of the solution of **14** were reduced to a quater and methanol was added to precipitate a yellowish green powder (0.29 g, 45%). The compound was kept in a desiccator and dried in *vacuo*.

Characterization data for 14

^{1}H NMR spectrum ($CDCl_3$, 200 MHz) : δ (in ppm)

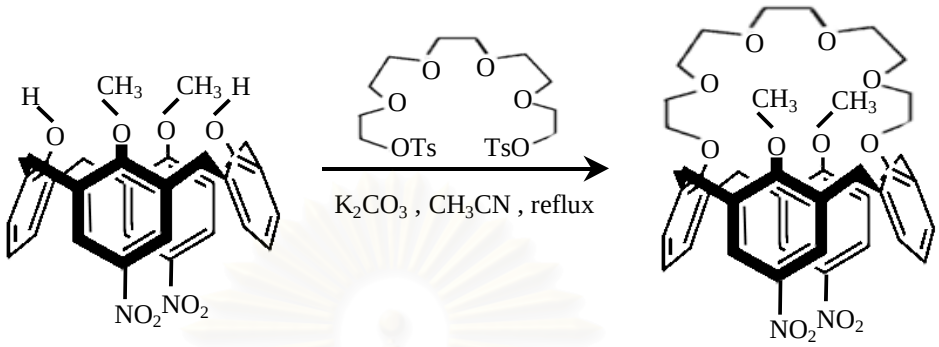
δ 8.04–8.28 (m, 4H, Ar***H***), 6.50–6.94 (m, 6H, Ar***H***), 4.42 (d, *J* = 3Hz, 4H, Ar***CH$_2$***Ar), 3.24–21.20 (m, 26H, ArO***CH$_3$***, -OC***H$_2$CH$_2$***O- and Ar***CH$_2$***Ar)

ESI massspectrum : 723.40 ($M^+ + Na^+$) m/z

Elemental Analysis: Calculated result for $C_{38}H_{40}N_2O_{11}$: C = 65.13; H = 5.75; N = 4.00

Found : C = 65.13; H = 5.78; N = 4.03

2.3.17 Preparation of 5,17-dinitro-25,27-pentaethyleneglycoloxy-26,28-dimethyloxycalix [4] arene (**15**).



11 **15**

Into a 250 mL round bottom flask equipped with a magnetic bar and a reflux condenser, **11** (0.50 g, 0.921 mmol), anhydrous potassium carbonate (1.27 g, 9.21 mmol) and acetronitrile (100 mL) were mixed and stirred for 30 minutes. Pentaethylene glycol ditosylate (0.98 g, 2.030 mmol) in acetronitile (50 mL) was added dropwise to the mixture. The reaction mixture was heated at reflux with stirring under nitrogen for 5 days. The solution was allowed to cool to room temperature and evaporated to dryness under reduced pressure. The residue was dissolved in dichloromethane (100 mL) and the aqueous solution of 3 M hydrochloric acid was subsequently added and stirred for 30 minutes. The solution was extracted with dichloromethane (2 x 50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness to obtain a yellowish orange residue. The residue was dissolved in a minimum amount of dichloromethane and placed on a silica gel column. 5,17–dinitro–25,27–pentaethyleneglycoloxy–26,28–dimethoxy calix[4]arene (**15**) was eluted with a mixture of dichloromethane and ethyl acetate (95:5). The volume of the solution of **15** was reduced to a quarter and methanol was added to precipitate a yellowish green powder (0.14 g, 20%). The compound was kept in a desiccator and dried in *vacuo*.

Characterization data for 15

^{1}H NMR spectrum ($CDCl_3$, 200 MHz) : δ (in ppm)

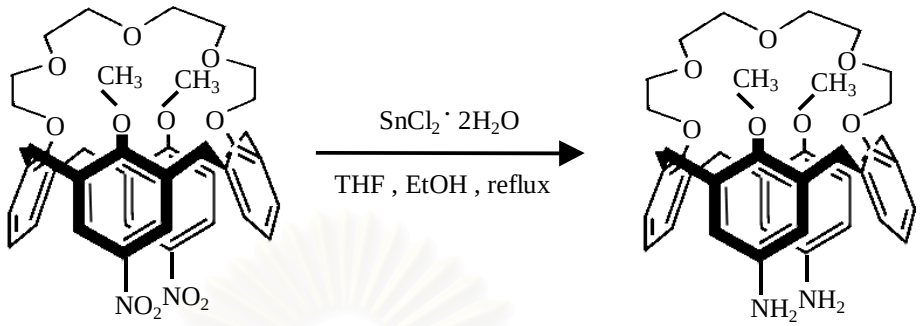
δ 8.04–8.28 (m, 4H, Ar***H***), 6.50–6.94 (m, 6H, Ar***H***), 4.42 (d, *J* = 3Hz, 4H, Ar***CH$_2$***Ar), 3.24–21.20 (m, 26H, ArO***CH$_3$***, -OC***H$_2$CH$_2$***O- and Ar***CH$_2$***Ar)

ESI massspectrum : 723.40 ($M^+ + Na^+$) m/z

Elemental Analysis: Calculated result for $C_{38}H_{40}N_2O_{11}$: C = 65.13; H = 5.75; N = 4.00

Found : C = 65.13; H = 5.78; N = 4.03

2.3.18 Preparation of 5,17-diamino-25-27-tetraethyleneglycoloxy-26,28-dimethoxycalix[4]arene (**16**)



14 **16**

Into a 250 mL two–necked round bottom flask equipped with a magnetic bar and a reflux condenser, **14** (0.29 g, 0.414 mmol), $SnCl_2 \cdot 2H_2O$ (1.40 g, 6.210 mmol), THF (50 mL) and EtOH (30 mL) were mixed. The mixture was heated at reflux with stirring under nitrogen for 12 hours and then allowed to room temperature. The reaction mixture was poured into ice and stirred. The aqueous solution of sodium hydrogencarbonate was subsequently added until the pH of the solution reached 8. The mixture was extracted with dichloromethane (3x30 mL) and stirred with water for 12 hours. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness to obtain a yellowish orange of **16** (0.21 g, 80%). The compound was kept in a desiccator and dried in *vacuo*.

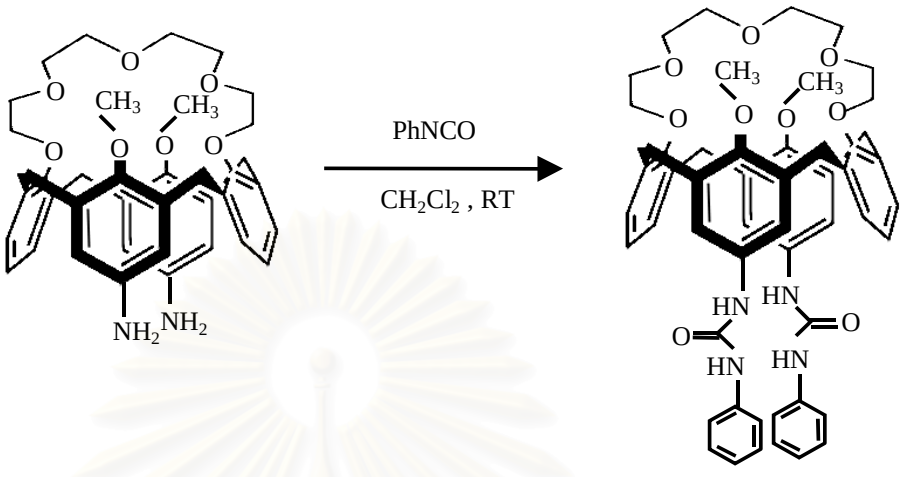
Characterization data for 16

^{1}H NMR spectrum ($CDCl_3$, 200 MHz) : δ (in ppm)

δ 6.47–6.97 (m, 10 H, Ar***H***), 4.33 (d, *J* = 12 Hz, 4 H, Ar***CH$_2$***Ar), 4.01 (s, 6H, ArO***CH$_3$***), 3.28–3.92 (m, 16 H, -O***CH$_2$CH$_2$***O-), 2.99 (d, *J* =12 Hz, 4H, Ar***CH$_2$***Ar), 2.74 (br, 4H, Ar***NH$_2$***).

Melting point : 153-155 °C

2.3.19 Preparation of 5,17–diphenylurea–25,27–tetraethyleneglycoloxy-26,28-dimethoxycalix[4]arene (**17**).



16 **17**

5,17–diamino–25,27–tetraethyleneglycoloxy–26,28–dimethoxycalix[4]arene (**16**) (0.21 g, 0.33 mmol) was dissolved in dry dichloromethane (10 mL) reacted with phenylisocyanate (0.08 mL, 0.726 mmol) in 25 mL round bottom flask. The solution was stirred under nitrogen for 24 hours. Yellow solid of **17** was precipitated from the solution (0.058 g, 20%). The product was filtered and washed with dichloromethane. Compound **17** was kept in a desiccator and dried in *vacuo*.

Characterization data for 17

^{1}H NMR spectrum (DMSO-d_6, 200 MHz) : δ (in ppm)

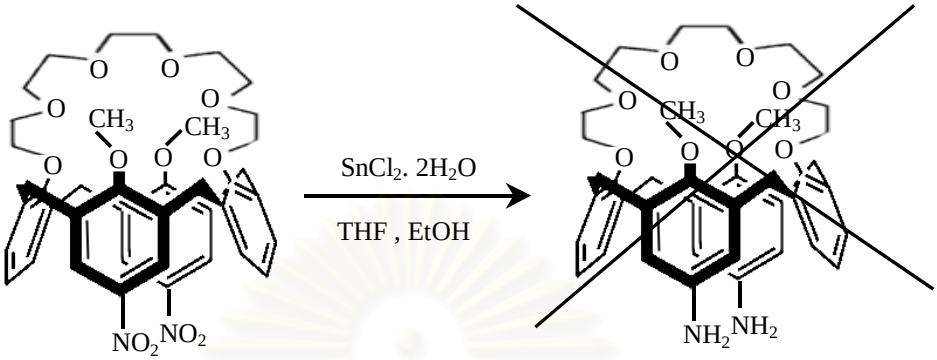
δ 8.59 (s, 2H, Ar***NH***-), 8.37 (s, 2H, Ar***NH***-), 7.44 (d, *J* = 8 Hz, 4H,Ar$\boldsymbol{H_{ph}}$), 7.26 (t, *J* = 8 Hz, 6H, Ar$\boldsymbol{H_{ph}}$), 6.94 (t, *J* = 7 Hz, 2H, Ar***H***), 6.45–6.59 (m, 8H, Ar***H***), 4.30 (d, *J* = 12 Hz, 4H, Ar$\boldsymbol{CH_2}$Ar), 4.03 (s, 6H, ArO$\boldsymbol{CH_3}$), 3.34–3.84 (m, 16H, -O$\boldsymbol{CH_2CH_2}$O-), 3.13 (d, *J* = 13 Hz, 4H, Ar$\boldsymbol{CH_2}$Ar).

ESI mass spectrum : 901.69 [$M^+ + Na^+$] m/z

Elemental Analysis :Calculated result for $C_{52}H_{54}O_9N_4$: C = 68.26; H = 6.39; N = 6.12

Found : C = 68.05; H = 5.96; N = 6.65

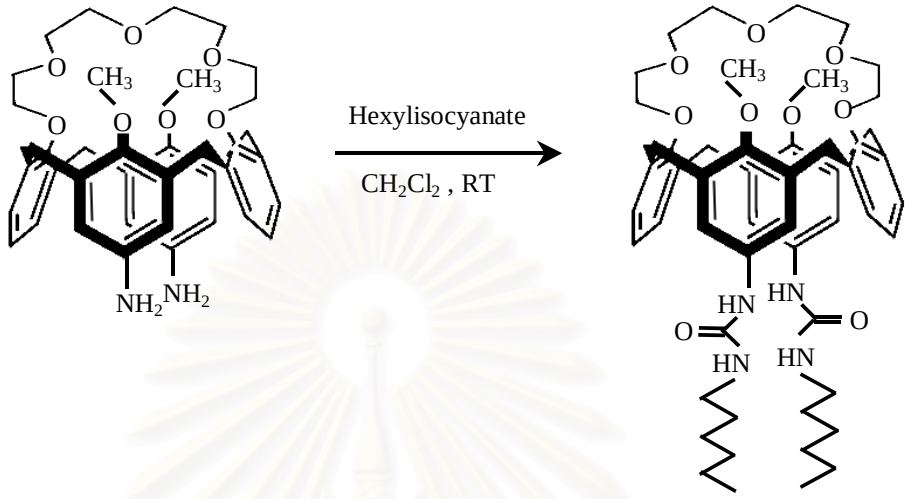
2.3.20 Preparation of 5,17–diamino–25,27–pentaethyleneglycoxy–26,28–dimethoxycalix [4] arene (**18**)



15 **18**

Into a 250 mL two–necked round bottom flask equipped with a magnetic bar and a reflux condenser, **15** (0.31 g, 0.414 mmol), $SnCl_2 \cdot 2H_2O$ (1.40 g, 6.210 mmol), THF (50 mL) and EtOH (30 mL) were mixed. The mixture was heated at reflux with stirring under nitrogen for 12 hours and then allowed to room temperature. The reaction mixture was poured into ice and stirred. The aqueous solution of sodium hydrogencarbonate was subsequently added until the pH of the solution reached 8. The mixture was extracted with dichloromethane (3x30 mL) and stirred with water for 12 hours. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated to dryness to obtain a yellowish orange. The compound was characterized by ^{1}H-NMR spectroscopy. The signal of amino proton (Ar-N***H*****$_2$**) was not observed on the ^{1}H-NMR spectrum indicated that the desired product was not obtained.

2.3.21 Preparation of 5,17–dihexylurea–25,27–tetraethyleneglycoxy–26,28–dimethoxycalix [4] arene (**19**).



16 **19**

5,17–diamine–25,27–tetraethyleneglycoloxy–26,28–dimethoxycalix[4]arene (**16)** (0.21 g, 0.330 mmol) was dissolved in dry dichloromethane (10 mL) and reacted with hexyl isocyanate (0.065 mL, 0.726 mmol) in 25 mL round bottom flask. The solution was stirred under nitrogen for 2 days and were then added the mixture of hexane and methanol to result in the pink precipitation of **19** (0.12 g, 40%). The compound was filtered and washed with a minimum amount of dichloromethane. Compound **19** was kept in desiccator and drird in *vacuo*.

Characterization data for 19

^{1}H NMR spectrum (DMSO-d_6, 300 MHz) : δ (in ppm)

δ 8.04 (s, 2H, Ar***NH***-), 7.08 (s, 4H, Ar***H***), 6.55 (d, *J* = 16Hz, 4H, Ar***H***), 6.41 (t, *J* = 7 Hz, 2H, Ar***H***), 5.97 (s, 2H , -$\boldsymbol{NH_{hexyl}}$), 4.23 (d, *J* = 12Hz, 4H, Ar$\boldsymbol{CH_2}$Ar), 3.97 (s, 6H, ArOCH_3), 3.32–3.80 (m, 20H, -O$\boldsymbol{CH_2CH_2}$O-, Ar$\boldsymbol{CH_2}$Ar), 3.04 (m, 8H, $\boldsymbol{H_{hexyl}}$), 1.24–1.38 (m, 18H, $\boldsymbol{H_{hexyl}}$).

ESI mass spectrum : 933.70 ($M^+ + K^+$)

Elemantal Analysis :Calculated result for $C_{52}H_{70}O_9N_4$: C = 69.77; H = 7.88; N = 6.26

Found : C = 69.78; H = 7.95; N = 6.36

2.4 Complexation studies

2.4.1 Complexation studies of ligands **13**, **17** and **19** with anions (Cl^-, Br^-, I^-, NO_3^- and $H_2PO_4^-$)

A solution of 0.01 M of ligands **13**, **17** and **19** (5×10^{-6} mol) in DMSO-d_6 (0.5 mL) was prepared in NMR tubes. A solution of 0.10 M of tetrabutylammonium salts ($5x10^{-5}$ mol, Bu_4NCl, Bu_4NBr, Bu_4NI, Bu_4NNO_3 and $Bu_4NH_2PO_4$) in DMSO-d_6 (0.50 mL) was prepared in a vial. The solution of anion was added directly to the NMR tube by micro syringe to give anion : ligand ratios as shown in table 2.1 ^1H NMR spectra were recorded after each addition.

2.4.2 Complexation sutdies of ligands **17** and **19** with cations (Na^+ and K^+) and $H_2PO_4^-$ ion.

A solution of 0.01 M of ligands **17** and **19** (5×10^{-6} mol) in DMSO-d_6 (0.5 mL) was prepared in NMR tubes. The solution of cations (6×10^{-6} mol, Na^+ and K^+) was added to the NMR tube. A solution of 0.10 M of $(Bu)_4NH_2PO_4$ ($5x10^{-5}$ mol) in DMSO-d_6 (0.50 mL) was prepared in a vial. The solution of $(Bu)_4NH_2PO_4$ was added directly to the NMR tube by a micro syringe to obtain anion : ligand ratios as shown in Table 2.3 . ^1H NMR spectra were recorded after each addition.

Table 2.1 Ratios of anion : ligand in DMSO-d_6

Ratios of anion : ligand	Volume anion added (mL)	Mole anion in NMR tube (mol)	Total volume in NMR tube (mL)
0.0 : 1.0	0.000	0.0	0.500
0.2 : 1.0	0.010	1.0×10^{-6}	0.510
0.4 : 1.0	0.010	2.0×10^{-6}	0.520
0.6 : 1.0	0.010	3.0×10^{-6}	0.530
0.8 : 1.0	0.010	4.0×10^{-6}	0.540
1.0 : 1.0	0.010	5.0×10^{-6}	0.550
1.2 : 1.0	0.010	6.0×10^{-6}	0.560
1.4 : 1.0	0.010	7.0×10^{-6}	0.570
1.6 : 1.0	0.010	8.0×10^{-6}	0.580
1.8 : 1.0	0.010	9.0×10^{-6}	0.590
2 : 1.0	0.010	10.0×10^{-6}	0.600
2.5 : 1.0	0.025	12.5×10^{-6}	0.625
3.0 : 1.0	0.025	15.0×10^{-6}	0.650
3.5 : 1.0	0.025	17.5×10^{-6}	0.675
4.0 : 1.0	0.025	20.0×10^{-6}	0.700

Table 2.3 Ratios of anion : ligand : cation in DMSO-d_6 : DMSO-d_6 : CD_3CN

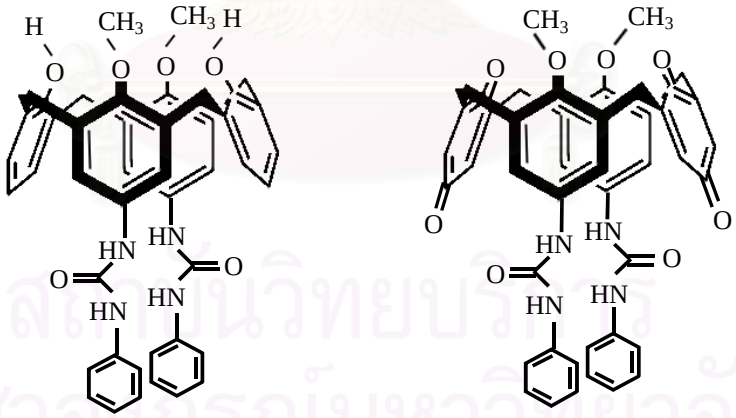
Mole of cation (mol)	Mole of ligand (mol)	Mole anion in NMR tube (mol)	Volume anion added (mL)	Ratios of anion : ligands	Total volume in NMR tube (mL)
6.0×10^{-6}	5.0×10^{-6}	0.0	0.000	0.0 : 1.0	0.500
6.0×10^{-6}	5.0×10^{-6}	1.0×10^{-6}	0.010	0.2 : 1.0	0.510
6.0×10^{-6}	5.0×10^{-6}	2.0×10^{-6}	0.010	0.4 : 1.0	0.520
6.0×10^{-6}	5.0×10^{-6}	3.0×10^{-6}	0.010	0.6 : 1.0	0.530
6.0×10^{-6}	5.0×10^{-6}	4.0×10^{-6}	0.010	0.8 : 1.0	0.540
6.0×10^{-6}	5.0×10^{-6}	5.0×10^{-6}	0.010	1.0 : 1.0	0.550
6.0×10^{-6}	5.0×10^{-6}	6.0×10^{-6}	0.010	1.2 : 1.0	0.560
6.0×10^{-6}	5.0×10^{-6}	7.0×10^{-6}	0.010	1.4 : 1.0	0.570
6.0×10^{-6}	5.0×10^{-6}	8.0×10^{-6}	0.010	1.6 : 1.0	0.580
6.0×10^{-6}	5.0×10^{-6}	9.0×10^{-6}	0.010	1.8 : 1.0	0.590
6.0×10^{-6}	5.0×10^{-6}	10.0×10^{-6}	0.010	2.0 : 1.0	0.600
6.0×10^{-6}	5.0×10^{-6}	12.5×10^{-6}	0.025	2.5 : 1.0	0.625
6.0×10^{-6}	5.0×10^{-6}	15.0×10^{-6}	0.025	3.0 : 1.0	0.650
6.0×10^{-6}	5.0×10^{-6}	17.5×10^{-6}	0.025	3.5 : 1.0	0.675
6.0×10^{-6}	5.0×10^{-6}	20.0×10^{-6}	0.025	4.0 : 1.0	0.700

CHAPTER III

RESULTS AND DISCUSSION

3.1 Design of receptor molecules

The first two target molecules in this work are shown in Figure 3.1. The two compounds were chosen because they contain urea units (**13)** and urea as well as diquinone units (**a**). Anion binding studies of these hosts can be investigated by electrochemical methods and NMR spectroscopy. Quinones play a key role in photosynthetic energy conversion.[66] They are ultimate electron acceptors in the cascade of electron-transfer reactions initiated when photosynthetic reaction centers are excited. Incorporation of anion binding urea and electron accepting quinone moieties into the calix[4]arene frame work was described previously.[33-35, 67,68] Target molecules in this work were synthesized and characterized as shown in Scheme 3.1-3.4.



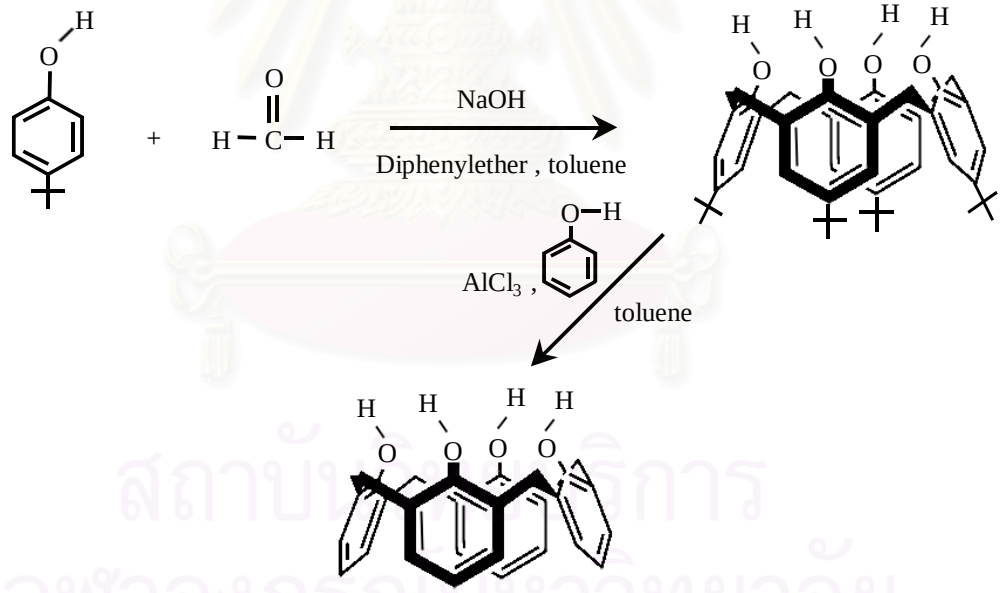
13 **a**

Figure 3.1 Calix urea and calix diquinone urea

3.2 Synthesis and characterization of calix[4] arene derivatives

3.2.1 Synthesis and characterization of 25,26,27,28-tetrahydroxycalix[4]arene (1)

Calix[4]arene was synthesized from *p-tert*-butylcalix[4]arene by 2 steps, as shown in scheme 3.1. In the first step, *p-tert*-butylcalix[4]arene was synthesized as described previously.[10,69] It can be easily prepared in good yield by the base-induced "one-step" condensation of *p-tert*-butylphenol and formaldehyde. The last step, aluminum chloride catalyzed removal of the *p-tert*-butyl groups proceeds in excellent yield, making calix[4]arene **1** a readily available starting material for the introduction of functional groups onto the calixarene molecule. The yield of calix[4]arene was 70 %.



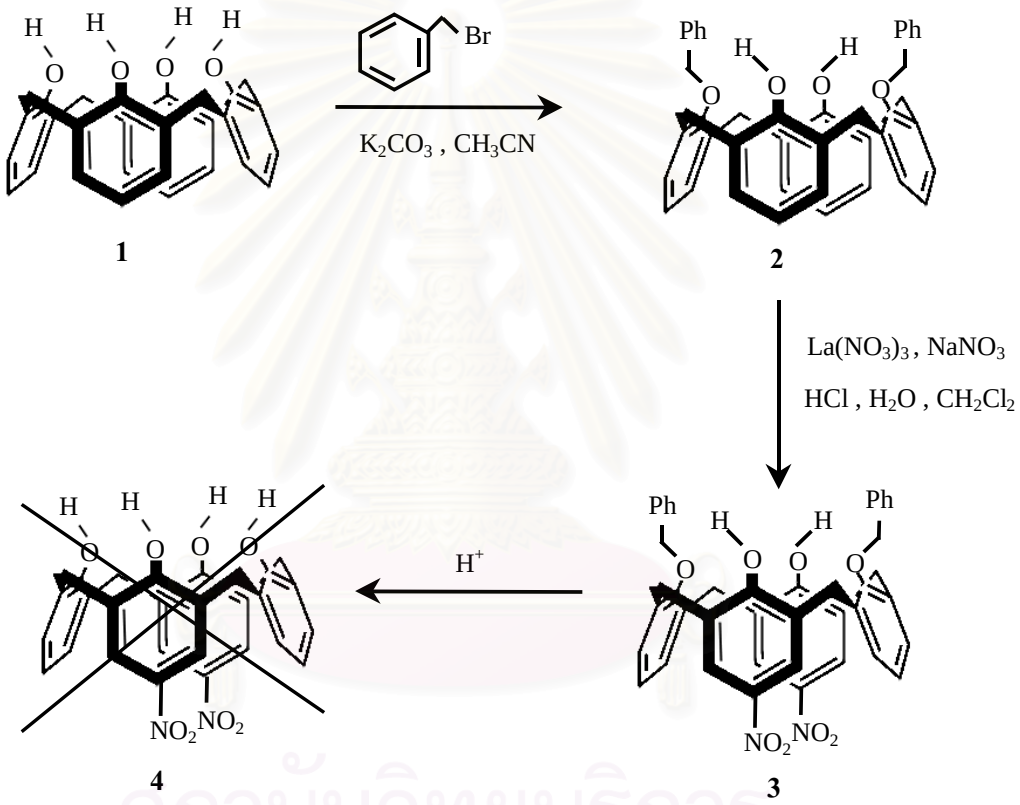
1

Scheme 3.1 Synthesis of 25,26,27,28-tetrahydroxycalix[4]arene (**1**)

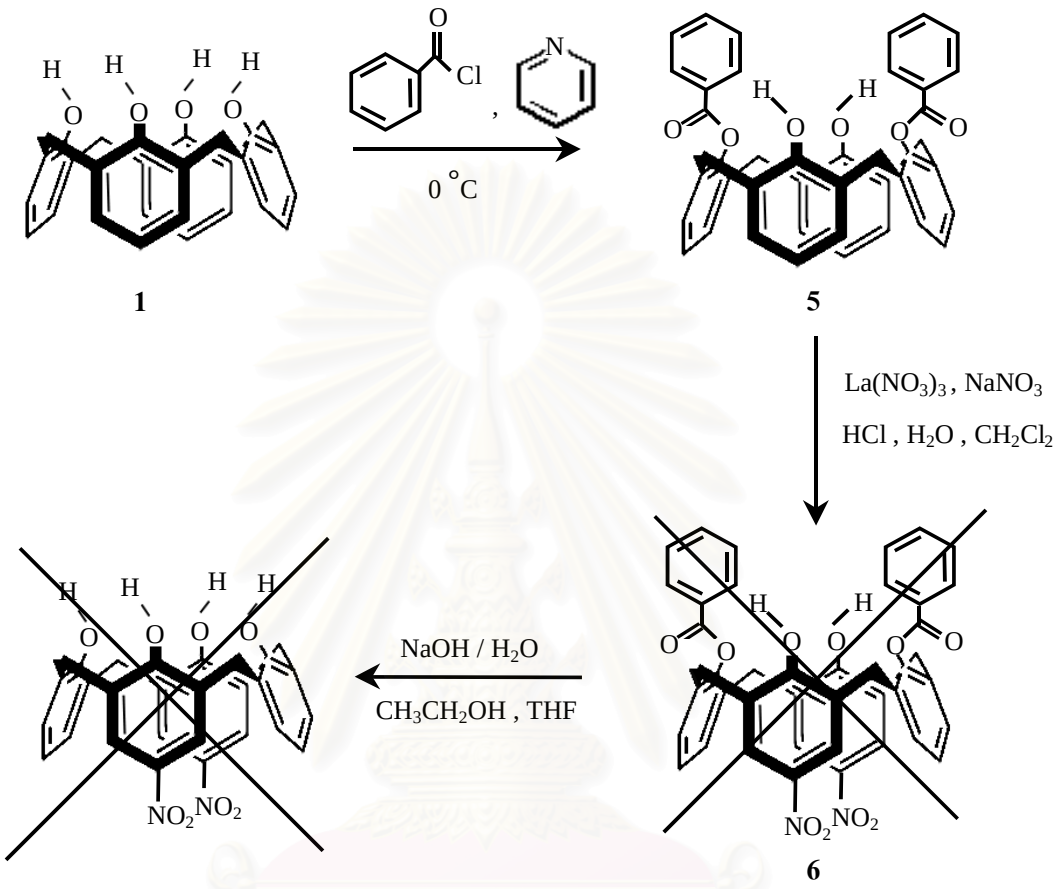
3.2.2 Synthesis and characterization of 5,17-dinitro-25,26,27,28-tetrahydoxycalix[4]arene (**4**)

The synthesis of 5,17-dinitro-25,26,27,28-tetrahydroxycalix[4]arene (**4**) can possibly be carried out in two pathways as shown in Scheme 3.2.

Pathway I



Pathway II



Scheme 3.2 Possible synthetic pathways of 5,17-dinitro-25,26,27,28 tetrahydroxycalix[4]arene (**4**)

Pathway I

We planed to synthesize 5,17-dinitro-25,26,27,28-tetrahydroxycalix[4]arene (**4**) from calix[4]arene (**1**). This synthetic pathway was started with the protection of calix[4]arene by benzyl bromide in the presence of anhydrous potassium carbonate in acetonitrile heating at reflux under nitrogen for 2 hours. After the reaction was cooled to room temperature, a white powder of compound **2** was obtained in 90% yield by precipitating with methanol. From ^{1}H-NMR, the hydroxy phenol protons (ArO***H***) appeared at 7.81 ppm. The multiplets of aromatic protons (Ar***H***) showed 7.36-7.31 ppm and 6.76-6.60 ppm. The two doublets of aromatic protons (Ar***H***) showed up at 7.04 ppm and 6.88 ppm. The characteristic peaks of benzyl singlet of ArC***H*****$_2$**O- appeared at 5.05 ppm. The methylene bridge protons of (ArC***H*****$_2$**Ar) calix[4]arene gave two doublets at 4.30 ppm and 3.33 ppm.

The next step, nitration of **2** with sodium nitrate, a mixture of a catalytic amount of $La(NO_3)_3.6H_2O$ and concentrated hydrochloric acid in an aqueous and dichloromethane solution was stirred over night. A yellow solid of compound **3** was obtained in 65% yield. From ^{1}H-NMR spectrum, compound **3** is in cone conformation due to the presence of ArC***H*****$_2$**Ar protons as two doublets at 4.24 ppm and 3.45 ppm. The hydroxy phenol on the benzene rings which possessed nitro group substituents appeared at 8.98 ppm. The three multiplets of aromatic protons (Ar***H***) appeared at 7.60-7.55, 7.36 and 6.99-6.88 ppm. The charateristic peak of benzyl, singlets of (ArC***H*****$_2$**O-) showed up at 5.07 ppm.

Removal of benzyl groups from **3** was performed by adding excess NaOH in the mixture of ethanol and THF. The product was obtained, which was then characterized by ^{1}H-NMR spectroscopy. The NMR spectrum indicated that the desired product was not obtained.

Pathway II

There are two recations for benzoylation of calix[4]arene. Benzoyltion of calix[4]arene with 2 equiv. of benzoyl chloride was carried out in pyridine at 0 ^{o}C as described by Nam and coworker.[70] The product were dibenzolate calix[4]arene (**5**) (70% yield) and the trace amount of mono- and tribenzolate calix[4]arene. Later, Nam group developed the benzoylation of calix[4]arene using 2 equiv. of benzoyl chloride in acetronitrile in the presence of anhydrous sodium carbonate as base under N_2. The reaction was heated at reflux for 2 h to give **5** in 90% yield. From ^{1}H-NMR spectrum, this compound was in cone conformation due to the presence of Ar***H*$_{benzoyl}$**, protons as two triplets and doublets at 7.72, 7.53 and 8.36 ppm, respectively. The hydroxy phenol (ArO***H***) appeared at 5.50 ppm. The two doublets of methylene bridge protons (ArC***H*$_2$**Ar) appeared at 3.98 and 3.52 ppm.

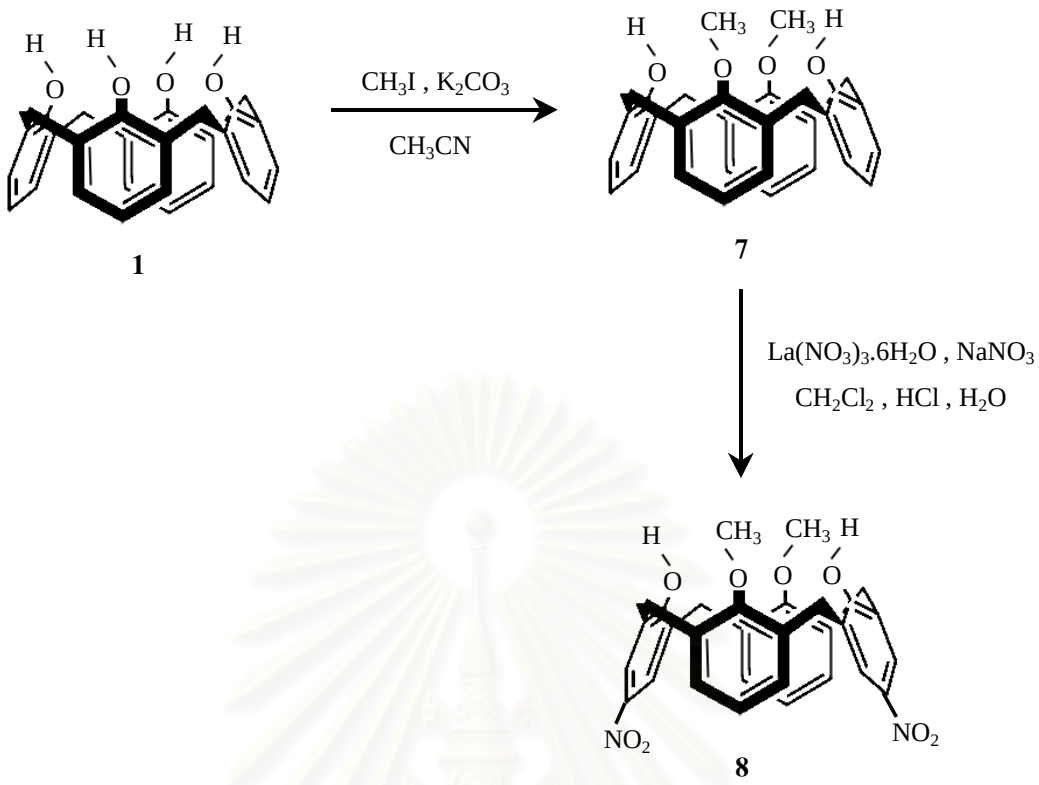
The second step, nitration of **5** with sodium nitrate, a catalytic amount of $La(NO_3)_3.6H_2O$ and concentrated hydrochloric acid in a mixture of aqueous and dichloromethane was stirred overnight to give a white solid. From ^{1}H-NMR spectrum, the signal of hydroxy phenol was not observed, indicated that the desired product was not obtained. The compound **6** cannot be synthesized because the reagents ($NaNO_3$, $La(NO_3)_3.6H_2O$) was possibly not strong enough for inducing the nitration reaction.

We then changed our plan to synthesize 5,17-dinitro-25,27-dimethoxycalix[4] arene, compound **8**, instead of compound **4**.

3.2.3 Synthesis and Characterization of 5,17-dinitro-25,27-dimethoxycalix[4]arene (**8**)

Synthesis of 5,17-dinitro-25,27-dimethoxycalix[4]arene **8** was showed in Scheme 3.3. The first step, methylation of **1** with CH_3I in acetonitrile using anhydrous sodium carbonate as base and refluxing the reaction for overnight. A white solid of 25,27-dimethoxycalix[4]arene **7** was obtained in 88% yield by precipitating with methanol. The ^{1}H-NMR spectrum of **7** showed the characteristic peaks of the methoxy proton (ArOC***H*****$_3$**) as a singlet signal at 3.97 ppm. The singlet of hydroxy of phenol (ArO***H***) appeared at 7.72 ppm. The two doublets of methylene bridge protons (ArC***H*****$_2$**Ar) appeared at 4.33 ppm and 3.42 ppm.

The next step, nitration of **7** with sodium nitrate, a catalytic amount of $La(NO_3)_3.6H_2O$ and concentration hydrochloric acid in a mixture of aqueous and dichloromethane was stirred over night. A yellow solid of compound **8** was obtained in 70% yield. The ^{1}H-NMR spectrum of **8** showed the characteristic peak of hydroxy phenol on benzene rings which possessed nitro groups (O_2NArO***H***) appeared at 8.04 ppm. The doublet of *meta* aromatic protons (m-***H***ArOCH$_3$) appeared at 6.94 ppm. The triplet of *para* aromatic protons (*p*-***H***ArOCH$_3$) appeared at 6.86 ppm. The singlet of methoxy protons (ArOC***H*****$_3$**) appeared at 4.02 ppm. The two doublets of methylene bridge protons (ArC***H*****$_2$**Ar) appeared at 4.28 ppm and 3.52 ppm.



1 **7** **8**

Scheme 3.3 Synthesis of 5,17-dinitro-25,27-dimethoxycalix[4]arene

Although we changed the starting compound for the synthesis of the final products from compound **4** to compound **8**, the final product could not be synthesized. Compound **8** has phenol rings which possessed nitro groups. Therefore, the product obtained by reduction of **8** was not stable in air.

We then changed the starting compound for synthesizing the final product from compound **8** to 5,17-dinitro-26,28-dimethoxycalix[4]arene, compound **11**.

3.2.4 Synthesis and characterization of 5,17-dinitro-26,28-dimethoxycalix [4]arene (**11**)

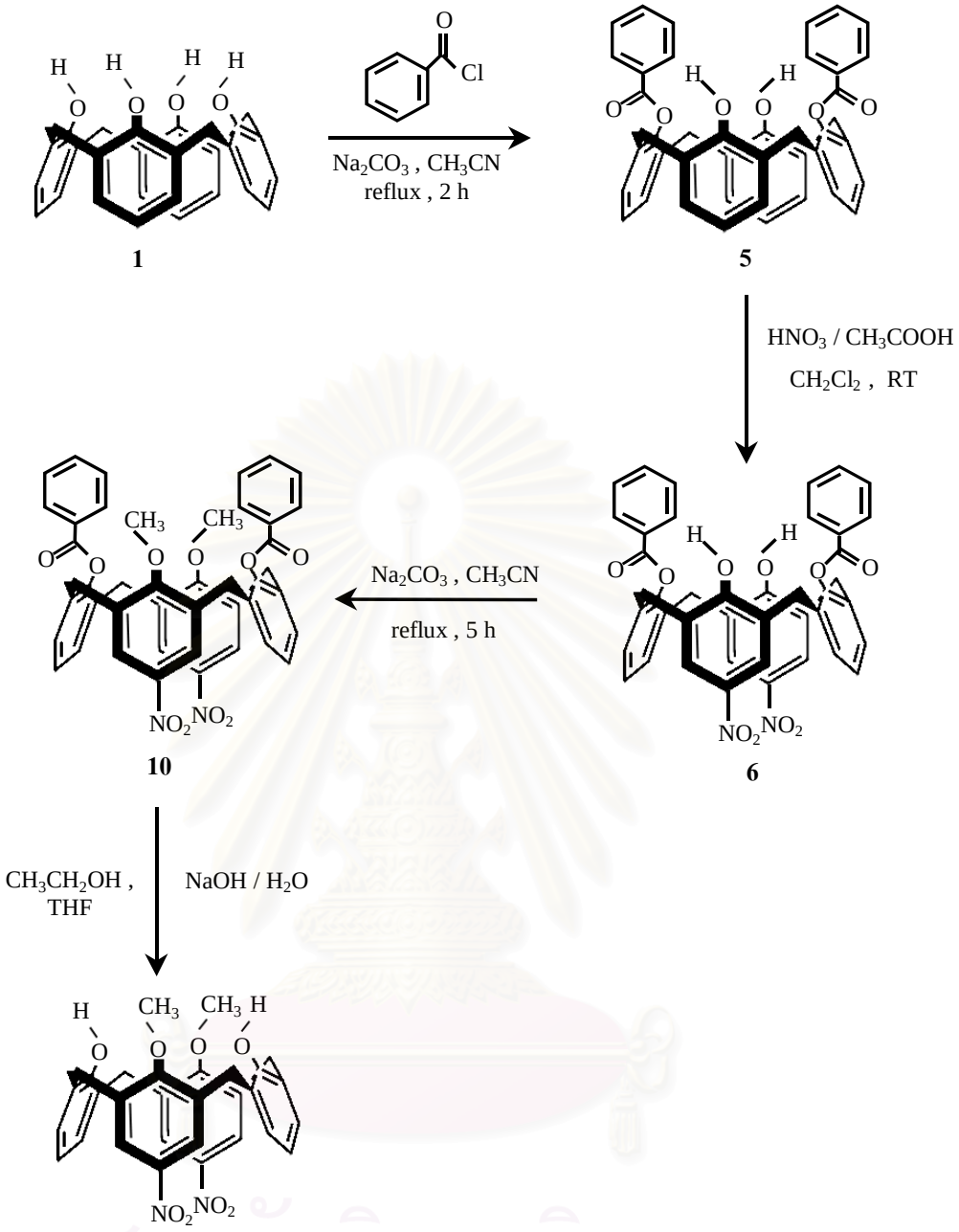
5,17-Dinitro-26,28-dimethoxycalix[4]arene **11** was successfully synthesized from calix[4]arene through 4 steps as shown in Scheme 3.4. In the first step, protection of calix[4]arene with benzoyl chloride using anhydrous sodium carbonate as base was carried out. This method provides the best way to synthesize a specific nitro substituent calix[4]arene.

The next step, specific nitration of calixarene was reported by Bohmer[71], Reinhoudt[72] and Nam[73] groups. Bohmer's group synthesized mononitrocalix[4]arene via step-wise methods. Reinhoudt group reported the synthesized 1,3-dinitrocalix[4]arene. Nam group reported the synthesis of two nitro-calix[4]arenes including mononitrocalix[4]arene and 1,3-dinitrocalix[4]arene with concentrated nitric acid. Direct nitration of calix[4]arene with nitric acid failed to introduce the specific nitro groups to the *para* position of calix[4]arene. To introduce the nitro groups to the calix[4]arene specifically, one must use the difference reactivity of the substituted- and non-substituted phenol OH's groups. Nitration of **5** with 65% HNO_3 and CH_3COOH in CH_2Cl_2 at room temperature gave mononitro and dinitro compound **6**. Dinitro compound **6** was a major product of this nitration reaction. Both mononitro and dinitro compound **6** were obtained and purified by silica gel column chromatography using dichloromethane as an eluant. The yield of compound **6** was 45%. From ^{1}H-NMR spectrum, this compound is in cone conformation due to the presence of ArC***H*****$_2$**Ar protons as two doublets at 3.99 and 3.66 ppm. The hydroxy phenol protons appeared at 6.33 ppm.

Methylation of **6** was the third step. The easier way to introduce the methyl groups to the dinitro compound was by a nucleophilic substitution reaction. When nitro groups were reduced by $SnCl_2.2H_2O$ to amines, the product will be air stable.

Methylation of **6** with CH_3I in CH_3CN using Na_2CO_3 as base and refluxing the reaction for 5 days resulted in dimethyldinitro calix[4]arene **10** in a good yield (85%). From the ^{1}H-NMR spectrum, compound **10** showed very complicated signals in the aromatic proton regions. This behavior stems from the lack of intramolecular hydrogen bonding in **10**. The aromatic protons as multiplets appeared around 6.75-8.19 ppm. The aromatic methoxy and methylene bridge (ArC***H*****$_2$**Ar) protons appeared at 3.35-3.82 ppm as multiplets.

The fourth step was the hydrolysis of benzoyl groups of compound **10**. Removal of the benzoyl groups from **10** by excess NaOH resulted in a dimethyldinitro calix[4]arene building block **11** in 50% yield. This compound is in cone conformation due to the presence of ArC***H*****$_2$**Ar protons as two doublets at 4.33 and 3.51 ppm. The ArO***H*** protons and ArOC***H*****$_3$** protons appeared at 7.25 and 4.05 ppm, respectively. FAB mass spectra also supported the structure of compound **11** showing an intense line at m/z 542.84 due to the $[M^+]$ and the elemental analysis result was in good agreement with the structure.

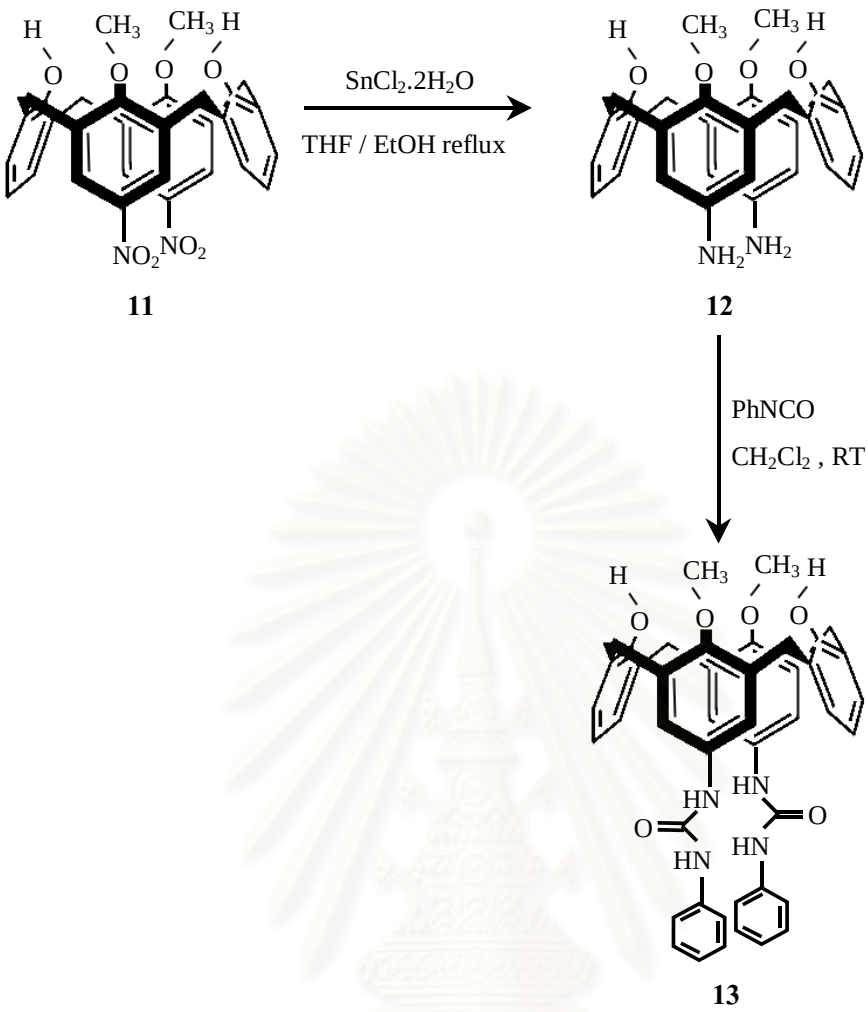


1 **5** **6** **10** **11**

Scheme 3.4 Synthesis of 5,17-dinitro-26,28-dimethoxycalix[4]arene

3.2.5 Synthesis and characterization of 5,17-diphenylurea-26,28-dimethoxycalix[4]arene (**13**)

The synthesis of the control compound calix urea **13** is shown in Scheme 3.5. Reduction of the nitro groups of **11** with $SnCl_2 \cdot 2H_2O$ gave the dimethyldiamino calix [4] arene **12** in 70% yield. The presence of the methyl groups at the *para* position to the amine groups aids in stabilizing compound **12**. Nevertheless, compound **12** was immediately coupled with phenyl isocyanate in CH_2Cl_2 at room temperature. The white solid **13** precipitated out of the reaction in 60% yield. The dimethoxydiurea calix[4]arene **13** is highly polar and dissolves only in polar solvents such as DMF and DMSO. The ^{1}H-NMR spectrum of compound **13** showed the characteristic peaks of urea (ArN***H***-) at 8.42 and 8.30 ppm. The ArO***H*** protons appeared at 8.17 ppm and the ArOC***H₃*** protons appeared at 3.89 ppm. Two doublets of the methylene bridge protons (ArC***H₂***Ar) appeared at 4.15 and 3.46 ppm. ESI mass spectra also supported the structure of this compound showing an intense line at m/z 720.99 [M^+] and the elemental analysis result was in good agreement with the structure.



11 **12** **13**

Scheme 3.5 Synthesis of 5,17-diphenylurea-26,28-dimethoxycalix[4]arene

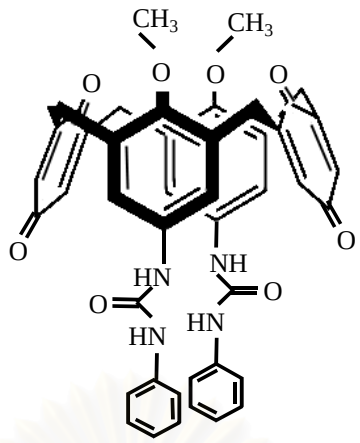


Figure 3.2 Calix[4]diquinone urea

Calix[4]diquinone urea in Figure 3.2 which is another final product of this work, synthesized by oxidation of the final product **13** using $NaBO_3$ in tetrafluoroacetic acid for study of electrochemical and complexation behavior with anions. Unfortunately, this compound have already been synthesized by Nam and coworkers.[37]

We then change our target molecules from calix[4]diquinone urea to calix crown urea for investigation anion binding properties of hosts and the effect of the crown ether unit towards anion binding ability. Target molecules are shown in Figure 3.3.

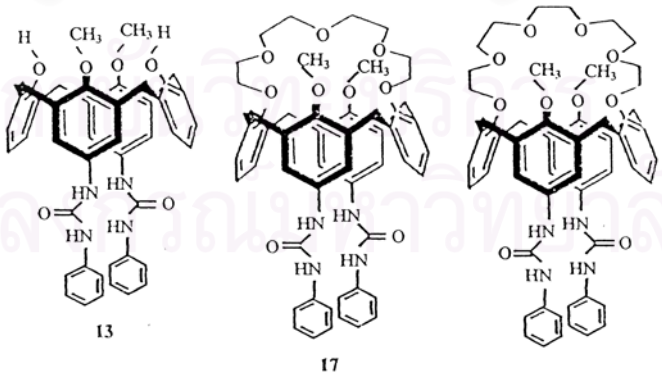


Figure 3.3 Calix urea and Calix crown urea

3.2.6 Synthesis and characterization of 5,17-diphenylurea-25,27-tetraethyleneglycoloxy-26,28-dimethoxycalix[4]arene (**17**)

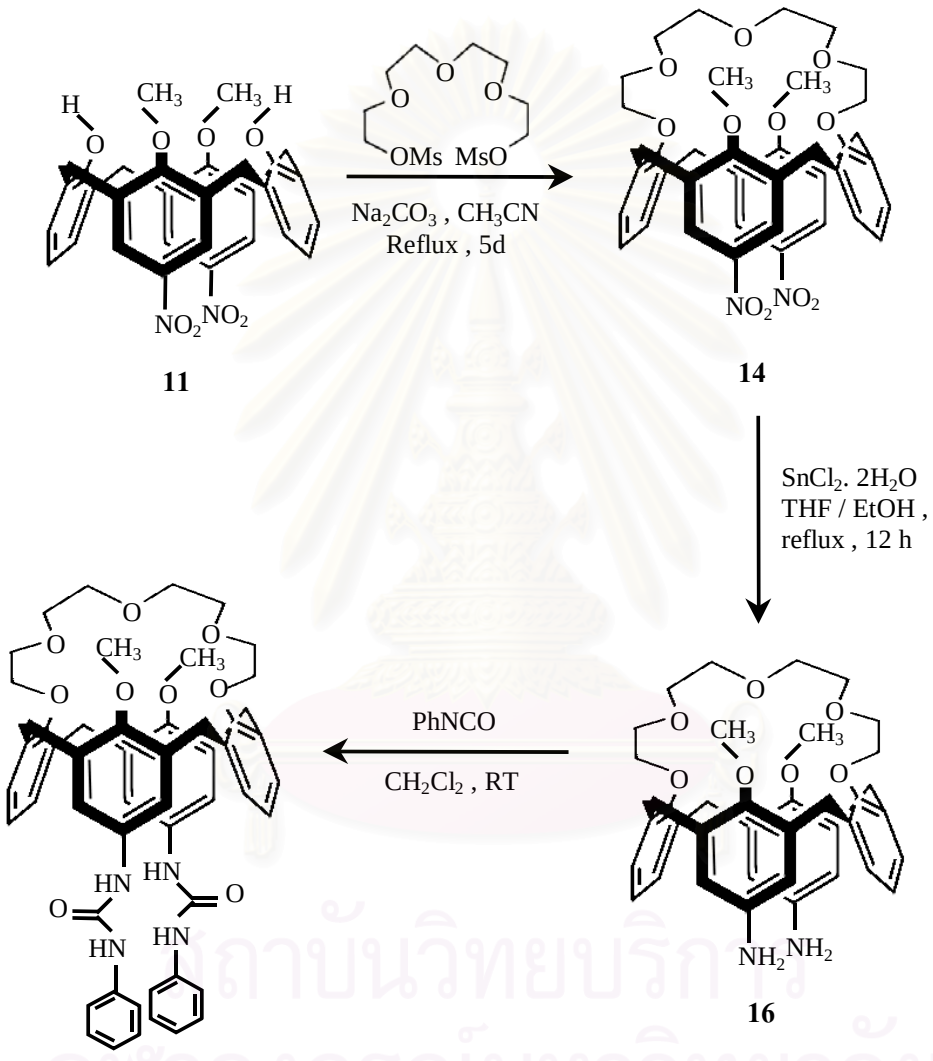
Tetraethylene glycol dimethanesulfonate, the starting material for compound **14**, was prepared by mesylation of tetraethylene glycol in the presence of 2 equivalents of triethylamine and a catalytic amount of DMAP in dichloromethane at room temperature for 4 hours. A yellow compound was obtained in 70% yield. ^{1}H-NMR spectrum of the compound showed the characteristic peak of mesyl groups:singlet of C***H***$_3$ at 3.03 ppm and two multiplets of –OC***H₂***C***H₂***O– at 4.31-4.36 ppm and 3.58-3.75 ppm. This agrees with the structure of tetraethylene glycol dimethanesulfonate.

Calix[4] crown urea **17** was synthesized from compound **11** in 3-steps, as shown in Scheme 3.6. In the first step, a nucleophilic substitution reaction of **11** with tetraethylene glycol dimethanesulfonate in CH_3CN using Na_2CO_3 as base and heating at reflux for 5 days yielded the dimethyldinitro crown calix[4]arene **14** in 45% yield. The ^{1}H-NMR spectrum of dimethyldinitro crown calix[4]arene **14** showed two multiplets of Ar***H*** protons at 8.04–8.28 ppm and 6.50–6.94 ppm. The ArC***H₂***Ar protons showed up as doublets at 4.42 ppm. The multiplets of ArOC***H₃***, -OC***H₂***C***H₂***O- and ArC***H₂***Ar appeared at 3.24-4.20 ppm. ESI mass spectra also supported the structure of the compound showing an intense line at m/z 723.40 due to the $[M^+ + Na^+]$.

Reduction of the nitro groups of **14** with $SnCl_2$ $2H_2O$ gave the crown dimethyldiaminocalix[4]arene **16** in 80% yield. The ^{1}H-NMR spectrum of compound **16** showed the ArC***H₂***Ar protons at 4.33 and 2.99 ppm. The bridging glycolic protons (-OC***H₂***C***H₂***O-) appeared at 4.28–3.92 ppm. The broad signal of ArN***H₂*** appeared at 2.74 ppm. ^{1}H-NMR spectra of compounds **14** and **16** showed very complicated signals in the aromatic and alkyl proton regions that signified aryl ring inversion in the calix[4]arene unit due to the lack of intramolecular hydrogen bonding.[74]

The final step was a coupling reaction between **16** and phenylisocyanate at room temperature resulted in the precipitation of calix[4]arene crown urea **17** in 20% yield. Although **17** lacks intramolecular hydrogen bonding, the substituents on the urea nitrogen prohibit the ring inversion. Compound **17** is hardly soluble in common organic solvents such as CH_2Cl_2 and $CHCl_3$. It dissolves in highly polar solvents such as DMSO. The ^{1}H-NMR spectrum of the calix[4]arene crown urea **17** showed the charecteristic peaks of urea (Ar***NH***) at 8.37 and 8.59 ppm. The two doublets of

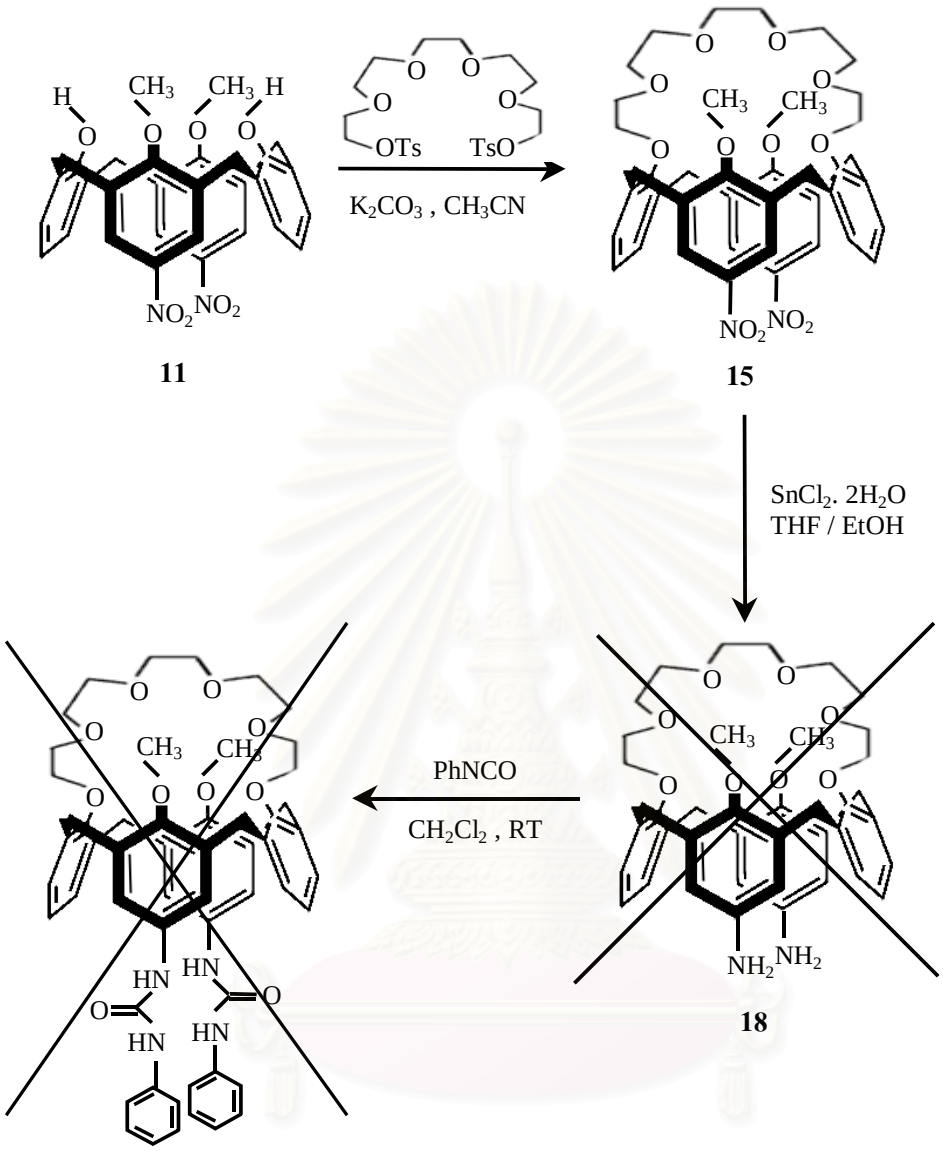
methylene bridge protons (Ar***CH₂***Ar) appeared at 4.30 and 3.13 ppm and the ArO***CH₃*** protons appeared at 4.01 ppm. The bridging glycolic protons (-O***CH₂CH₂***O-) appeared at 3.34–3.84 ppm. ESI mass spectra also supported the structure of this compound showing an intense line at m/z 901.69 due to the [M^+ + Na^+]. Elemental analysis was in good agreement with the structure.



Scheme 3.6 Synthesis of 5,17-diphenylurea-25,27-tetraethyleneglycoloxy-26,28-dimethoxycalix[4]arene

3.2.7 Synthesis and characterization of 5,17-diphenylurea-25,27-pentaethyleneglycoloxy –26,28-dimethoxycalix[4]arene

We attempts to synthesize 5,17-diphenylurea-25,27-pentaethyleneglycoloxy-26,28-dimethoxycalix[4]arene by the procedure shown in Scheme 3.7. The first step, a nucleophilic substitution reaction of **11** with pentaehylene glycol ditosylate in acetronitrile using anhydrous potassium carbonate as a base and heating at reflux for 5 days yielded the dimethyldinitrocrown 6 calix[4]arene **15** in 20% yield. ^{1}H-NMR spectrum of compound **15** showed the multiplets of ArOC***H*****$_3$**, -OC***H*****$_2$**C***H*****$_2$**O- and ArC***H*****$_2$**Ar at 3.12-4.51 ppm. The multiplets of Ar***H*** protons showed up at 6.37-6.59 ppm and the two doublets of Ar***H*** protons showed up at 6.91 and 8.03 ppm. The singlet of Ar***H*** protons appeared at 8.24 ppm. ESI mass spectra also supported the structure of the compound showing an intense line at m/z 767.3 and m/z 783.3 due to the $[M^+ + Na^+]$ and $[M^+ + K^+]$, respectively. Reduction of the nitro groups of **15** with $SnCl_2.2H_2O$ was not given the crown dimethyldiaminocalix[4]arene **18**. Therefore, 5,17-diphenylurea-25,27-pentaethyleneglycoloxy–26,28-dimethoxycalix[4]arene cannot be synthesized.



Scheme 3.7 The procedure for synthesizing 5,17-diphenylurea-25,27-pentaethyleneglycoloxy –26,28-dimethoxycalix[4]arene.

We then change our target molecules and they are shown in Figure 3.4.

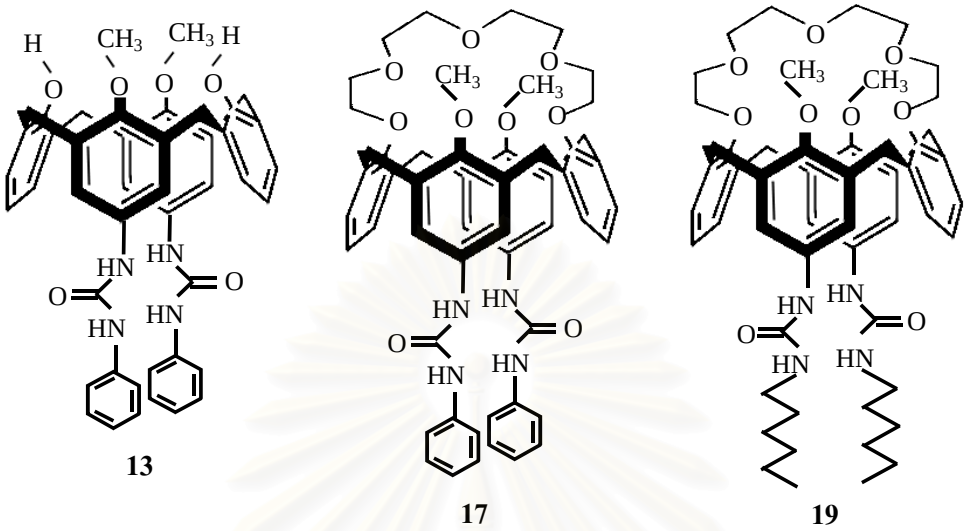
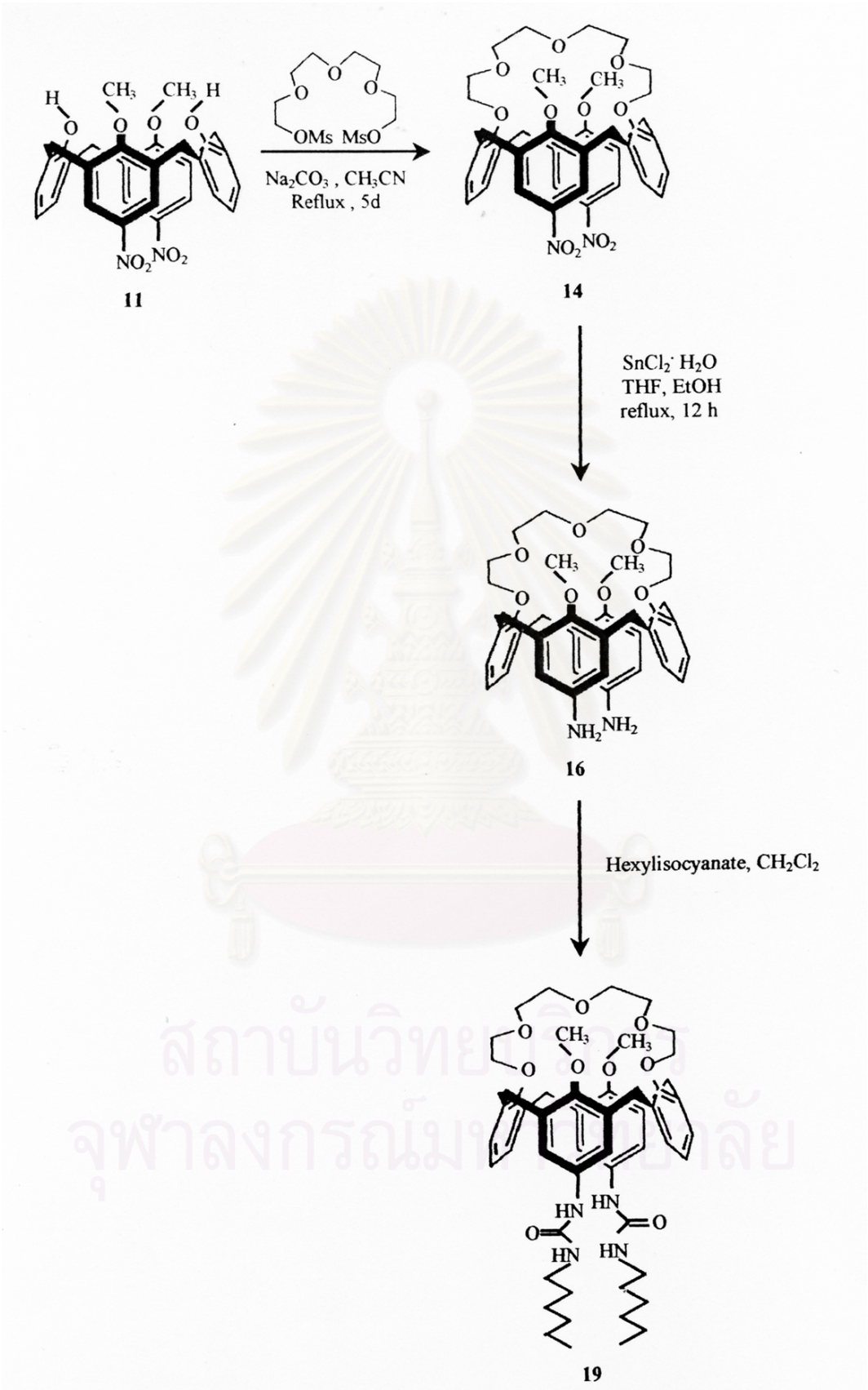


Figure 3.4 Target molecules in this work

3.2.8 Synthesis and characterization of 5,17-dihexylurea-25,27-tetraethyleneglycoloxy-26,28-dimethoxycalix[4] arene (**19**)

The synthesis of calix[4] crown urea **19** is similar to that of compound **17** except the last step. Compound **16** reacted with hexy isocyanate at room temperature resulting in a pink precipitation of calix[4] arene urea **19** in 40% yield as shown in Scheme 3.8. Compound **19** is hardly soluble in CH_3CN. It dissolves in CH_2Cl_2, $CHCl_3$ and highly polar solvents such as DMSO. Although **19** lacks intramolecular hydrogen bonding, the substituents on the urea nitrogen prohibit the ring inversion. The ^{1}H-NMR spectrum ofcompound **19** showed the characteristic peaks of urea (hexyl N***H*** -) at 8.04 and 5.97 ppm. The doublets of methylene bridge protons (ArC***H*****$_2$**Ar) appeared at 3.32 –3.80 ppm. The hexyl protons appeared at 3.04 and 7.24-1.38 ppm. ESI mass spectra also supported the structure of this compound showing an intense line at m/z 933.7 due to the $[M^+ + K^+]$ and the elemental analysis was in good agreement with the structure.



Scheme 3.8 The synthetic procedure for 5,17-dihexylurea-25,27-tetraethyleneglycoloxy-26,28-dimethoxycalix[4]arene

The starting compound **11** for syntheses of compounds **13**, **14**, **15, 17** and **19** were characterized by mass spectrometry and elemental analysis as shown in Tables 3.1 and 3.2.

Table 3.1 Mass spectrometry results of **11**, **13**, **14**, **15, 17** and **19**

Compounds	Molecular weight	$[M^+]$	$[M^+ + Na^+]$	$[M^+ + K^+]$
11	542.0	542.84		
13	720.82	720.99		
14	700.74		723.40	
17	879.03		901.69	
15	744.80		767.30	783.30
19	895.15			933.70

Table 3.2 Elemental analysis results of compounds **11**, **13**, **14**, **17** and **19**

Compounds	%C Found (cald)	%H Found (cald)	%N Found (cald)
11	66.41 (66.41)	4.77 (4.83)	5.16 (5.16)
13	73.16 (73.32)	5.63 (5.59)	7.74 (7.77)
14	65.14 (65.13)	5.78 (5.75)	4.03 (4.00)
17	68.05 (68.26)	5.96 (6.39)	6.65 (6.12)
19	69.78 (69.77)	7.95 (7.88)	6.36 (6.26)

3.3 Complexation studies

Compounds **13**, **17** and **19** contain urea units for binding anions. This research aimed to compare the binding ability of compounds **13**, **17** and **19** towards anions. Because of their importance in environmental and biological systems, anions such as $H_2PO_4^-$, NO_3^-, Cl^-, Br^- and I^- were chosen for studies. Anion binding studies of compounds **13**, **17** and **19** were carried out by ^1H NMR titrations. Compounds **17** and **19** contain crown ether unit which have oxygen donors for binding alkaline cations such as Na^+ and K^+. We aim to investigate the effect of the crown ether unit towards anion binding ability.

3.3.1 Investigation of binding ability

Compound **13** is expected to bind anions. Synthetic compounds **17** and **19** are expected to encapsulate both cations and anions simultaneously. The binding ability of this kind of receptors toward anions should be enhanced by electrostatic forces between cations and anions. Thus the binding efficacy of receptors **17** and **19** will be investigated toward cations, anions as well as ion pairs.

The stability of the host-guest adducts is strongly dependent on the polarity of the media. In fact, salts are present as ion pairs or more likely as aggregates of ion pairs in apolar media. Comparison to a $CDCl_3$ solution which show strongly ion-pair effect, the free species which release from the ion pairs are determined to be more in the other more polar deuterated solvents such as CD_3OD, CD_3CN or DMSO-d_6.

Methanol is a typical protic or a hydrogen bond donor (HBD) solvent. On the contrary, dimethylsulfoxide and acetonitrile are solvents that commonly referred to as aprotic solvents, but they are in fact not aprotic (solvent without proton donor groups). In reactions where strong bases are employed, their protic character can be recognized. Hence, the term aprotic solvents should be replaced by nonhydroxylic or better by non-HBD solvents.[75]

The electron pair donor and acceptor are one of the main criteria for complexation in supramolecular chemistry area. In principle, a donor is able to form a complex with a receptor. Hereby, an electron pair donor (EPD) and an electron pair

acceptor (EPA) solvent should form a complex. Some solvents act as donors (nucleophiles) while some solvents serve as acceptors (electrophiles).

In principle, all solvents are amphoteric in this respect. EPD solvents are particularly important for cation complexation. The high EPD-properties make the solvent to be excellent cation solvators which is known as coordinating solvents. An empirical semiquantitative measure of the nucleophilic properties of EPD solvents is provided by the donor number *DN* (or donicity) of Gutmann.

Table 3.3 exhibits the donor numbers of some solvents. The higher of the donor number reflect to the stronger of the interaction between the solvent and the acceptor. The donor number has proven very useful in coordination chemistry, since it can be correlated with other physical properties for such reactions, e.g. thermodynamic (ΔG or K), kinetic (rates), electrochemistry (polarographic half-wave and redox potentials), and spectroscopy (chemical shifts of NMR signals).

Table 3.3 Donor numbers determined calorimetrically in dilute 1,2-dichloroethane solution at room temperature

Solvents	DN/kcalmol^{-1}
Acetone	14.1
Acetonitrile	17.0
Dimethyl sulfoxide	29.8

Reciprocally, EPA solvents play a particular important role for anion complexation. An analogous empirical quantity for characterizing the electrophilic properties has been named acceptor number *AN* (acceptivity). Some organic solvents in the order of increasing acceptor numbers are given in Table 3.4.

Table 3.4 Acceptor numbers which are determined ^{31}P –NMR spectroscopically at 25 °C

Solvents	AN
Acetone	12.5
Acetonitrile	18.9
Dimethyl sulfoxide	19.3
Dichloromethane	20.4
Chloroform	23.1
Methanol	41.5
Water	54.8

In our preliminary experiments, we found that ligands **13, 17** and **19** were able to dissolve in DMSO-d_6. Moreover, either tetrabutylammonium anions or cation hexafluorophosphate salt that used in this thesis hardly dissolved in DMSO-d_6 and CD_3CN. Therefore, CD_3CN and DMSO-d_6 were perfect solvents for the whole experiments. The competitive interaction between the anion and the solvent from using DMSO-d_6 and CD_3CN were also effected. However, this effect is less than that from water.

^{1}H-NMR spectroscopy has been widely used to investigate receptor-substrate interactions and it allows access to the detail of the interaction between host and guest molecules. Therefore the anion binding ability of the novel urea receptors based on calix[4]arene building block in DMSO-d_6 was investigated by ^{1}H-NMR titrations.

Unsurprisingly, the three receptors exist in cone conformation in DMSO-d_6 ; likein $CDCl_3$, which could be observed from a pair of doublet[76,77] at 4.49 and 3.30 ppm for **17** (J = 12.51 Hz) and a pair of doublet at 3.44 and 4.35 ppm for **19** (J = 12.38 Hz). Compared to other conformation of calix[4]arene, cone is the most steric conformation but it is stabilized in more polar solvent due to the higher dipole moment. To reduce the interference arising from ion-pair formation as well as hydrogen bonded aggregation, the dilute solution of hosts (about 0.01 mol/L) in DMSO-d_6 were used in titration experiments. Furthermore, no effort was made to

maintain a constant ionic strength, but care was taken to avoid water absorption from the atmosphere. Additionally, calculated association constants were always within 10% of the error.

3.3.2 Complexation studies of compound 13, 17 and 19 with $H_2PO_4^-$, NO_3^-, Cl^-, Br^- and I^- ions.

^{1}H-NMR spectra of compounds **13**, **17** and **19** with or without anions in DMSO-d_6 at room temperature were recorded. The ^{1}H-NMR spectrum of compound **13** showed signals at 8.30 ppm and 8.42 ppm due to the NH urea protons. The NH signals of compound **17** appeared at 8.37 ppm and 8.59 ppm while the NH signals of compound **19** appeared at 5.97 ppm and 8.04 ppm. Upon addition of anions, both signals of the NH protons were shifted markedly downfield as shown in Tables 3.5, 3.6 and 3.7. The data in Tables 3.5, 3.6 and 3.7 indicated that all the anions (except I^- ion) from complexes with compounds **13**, **17** and **19** via hydrogen-bonding interactions between the ureas and anions.

Table 3.5 ^{1}H-NMR chemical shifts (ppm) for compound **13** (in DMSO) in the absence or the presence of anions.

Anions	-NH_A (ppm)	-NH_B (ppm)
None	8.30	8.42
Cl^-	8.39	8.54
Br^-	8.31	8.44
I^-	no shift	no shift
NO_3^-	8.31	8.43
$H_2PO_4^-$	8.95	9.21

Table 3.6 ^{1}H-NMR chemical shifts (ppm) for compound **17** (in DMSO) in the absence or the presence of anions.

Anions	-NH_A (ppm)	-NH_B (ppm)
None	8.37	8.59
Cl^-	8.53	8.77
Br^-	8.40	8.63
I^-	no shift	no shift
NO_3^-	8.38	8.60
$H_2PO_4^-$	9.25	9.54

Table 3.7 ^{1}H-NMR chemical shifts (ppm) for compound **19** (in DMSO) in the absence or the presence of anions.

Anions	-NH_A (ppm)	-NH_B (ppm)
None	5.97	8.04
Cl^-	6.05	8.13
Br^-	5.99	8.06
I^-	no shift	no shift
NO_3^-	5.98	8.05
$H_2PO_4^-$	6.44	8.45

Binding abilities of compounds **13** and **17** toward anions were compared. Addition of the tetrabutylammonium salt of a guest anion such as $H_2PO_4^-$, Cl^-, Br^- and NO_3^- to a DMSO-d_6 solution of receptors **13**, **17** and **19** resulted in significant dowfield shifts of the NH resonances, which is consistent with the formation of hydrogen-bonded complexes. Addition of more than 1.0 equiv. of anions showed slightly shift of the NH protons, indicated that **13**, **17** and **19** formed complexes with anions in a 1:1 stoichiometry. The plots between the mole ratios of anion : **13** and the NH chemical shift of compound **13** are illustrated in Figure 3.2. Association constants of **13**, **17** and **19** towards $H_2PO_4^-$, Cl^-, Br^- and NO_3^- calculated by the program EQNMR[78] are collected in Table 3.15.

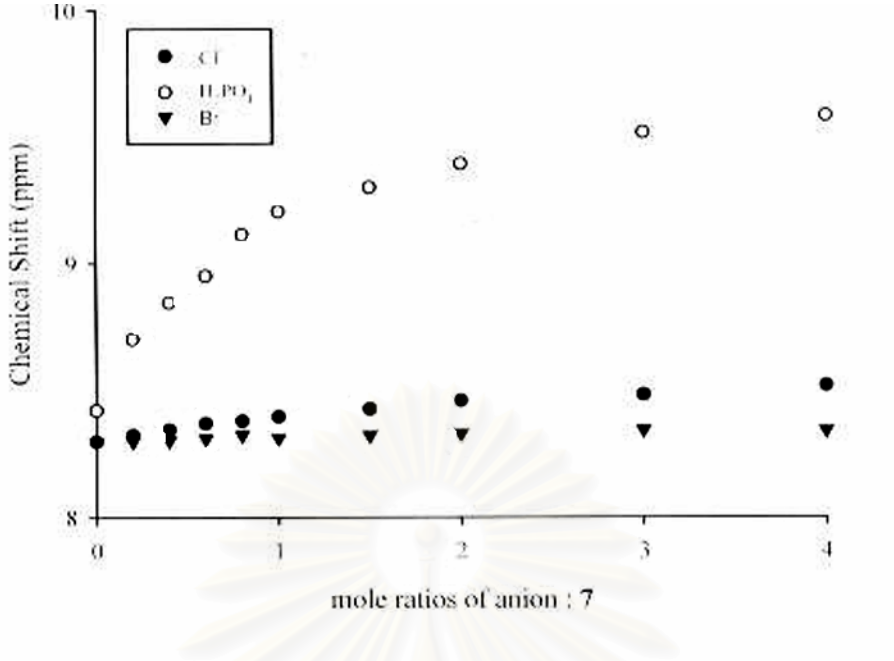


Figure 3.5 Plots between mole ratios of anions **13** and the NH chemical shifts.

Compound **19** was selected to compare the binding ability of compound **13** and **17** towards anions, because both **13** and **17** were hardly soluble in common organic solvents such as CH_2Cl_2 and $CHCl_3$. They dissolve only in highly polar solvents such as DMSO. This solvents has effected the binding ability towards anions and association constants. Compound **19** dissolves in $CHCl_3$, CH_2Cl_2 and DMSO but hardly dissolved in CH_3CN. The ^1H NMR spectrum of compound **19** in $CDCl_3$ is showed in Figure 3.3.

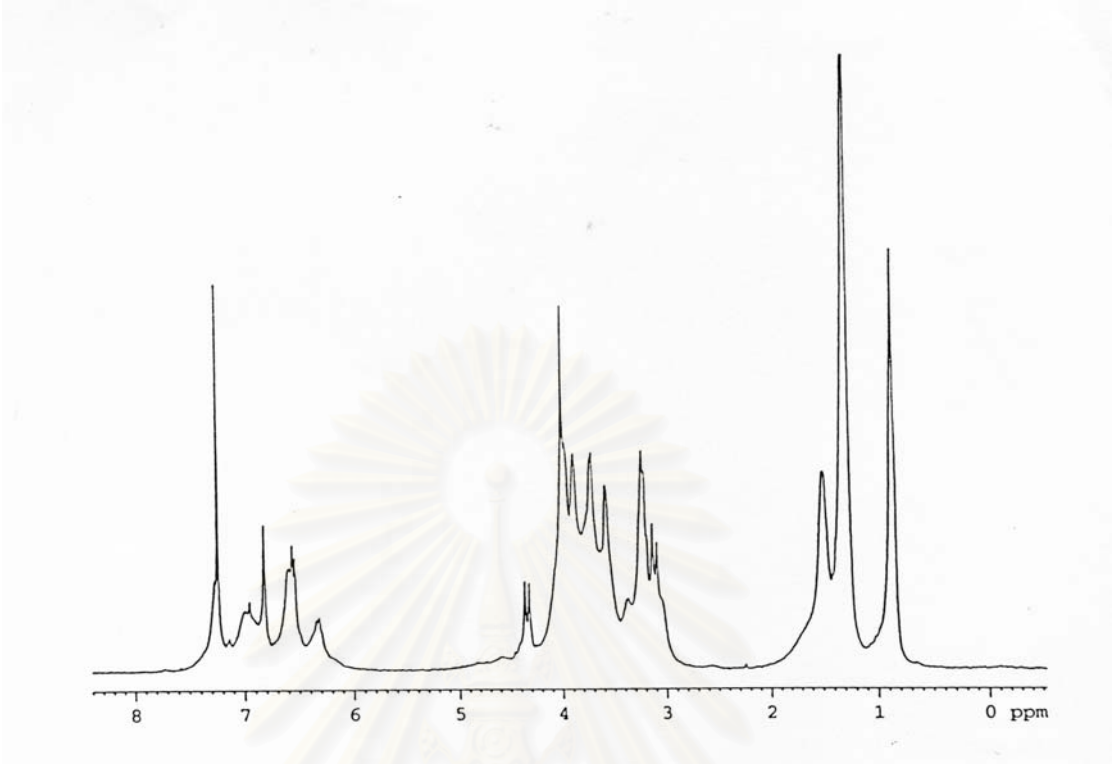


Figure 3.6 ^{1}H-NMR of Compound **19** in $CDCl_3$

From ^{1}H-NMR spectra the signal of $CDCl_3$ interferes with signals of the NH protons, thus $CDCl_3$ cannot be used for investigating the binding ability of **19** towards anions. Therefore, the binding ability of **19** towards anions was investigated in DMSO.

Table 3.8 Association constants of ligands **13**, **17** and **19** towards $H_2PO_4^-$, Cl^-, Br^- and NO_3^- using nBu_4N^+ as countercation

Anion	Association constants (M^{-1})		
	13	**17**	**19**
$H_2PO_4^-$	250	200	53
Cl^-	43	60	11
Br^-	30	31	19
I^-	No binding	No binding	No binding
NO_3^-	13	11	15

Results in Table 3.6 indicate that compounds **13**, **17** and **19** bind Cl^-, Br^-, NO_3^-, and $H_2PO_4^-$ to a different extent. Both compounds **13** and **17** form the most stable complexes with $H_2PO_4^-$ and the least stable complexes with NO_3^-. Compound **19** forms the most stable complexes with $H_2PO_4^-$ and the least stable complexes with Cl^-. Compound **17** binds Cl^- more strongly than **13**. However, **13** forms a more stable complex with $H_2PO_4^-$ than compound **17**. Compound **13** binds Br^- within the same extent as compound **17**. These results indicate that the presence of the crown bridging group in compound **17** has increased the binding ability towards Cl^- and Br^-. Both compounds **13** and **17** are found to bind $H_2PO_4^-$ selectively over various other anions ($H_2PO_4^- > Cl^- > Br^- > NO_3^-$) and bind $H_2PO_4^-$, Cl^- and Br^- more strongly than compound **19**. These results indicate that the presence of the hyxyl group in compound **19** has decreased the binding ability towards $H_2PO_4^-$, Cl^- and Br^- because of the decreasing of the acidity of hexyl NH protons. Moreover, all compounds do not bind I^-.

3.3.3 Complexation studies of compounds 17 and 19 towards $H_2PO_4^-$ in the presence of alkali cations

Ion-pair recognition has attracted chemists' attention. Beer and colleagues have discovered that the presence of a suitable cation increases the binding ability of anion receptors containing cation binding units.[59,79,80] Compounds **17** and **19** includes a crown-5 unit which is well known to form stable complexes with Na^+ or K^+. We are also interested to investigate the effect of the ion-pair enhancement in the binding ability of compounds **17** and **19**. Upon adding 1.2 equiv. of $NaPF_6$ or KPF_6 to DMSO-d_6 solutions of receptors **17** and **19**. Large chemical shifts in the region of the proton resonance of the crown ether unit were observed suggesting complex formation between Na^+ or K^+ and the crown ether unit. Addition of $nBu_4NH_2PO_4$ to the solution caused the NH peak to shift downfield. The association constant were then calculated by the program EQNMR and shown in Table 3.7.

Table 3.9 **A**ssociation constants of compounds **17** and **19** with $H_2PO_4^-$

Compounds	Association constant (M^{-1})		
	No Na^+ or K^+	Na^+	K^+
17	200	1028	280
19	51	59	58

From Table 3.7 the presence of Na^+ and K^+ thus increases the binding ability of **17** towards $H_2PO_4^-$. However, the presence of Na^+ and K^+ does not seem to effect the binding ability of **19** towards $H_2PO_4^-$. The presence of Na^+ increases the binding ability of **17** towards $H_2PO_4^-$ more than the presence of K^+. Na^+ ion can bind compound **17** better than K^+ ion. Thus **17** can bind $H_2PO_4^-$ strongly in the presence of Na^+.

CHAPTER IV

CONCLUSION

A calix[4]urea compound, 5,17-diphenylurea-25,27-dihydroxy-26,28-dimethoxycalix[4]arene (**13**) and two calix[4]crown urea compounds, 5,17-diphenylurea-25,27-tetraethylene glycoloxy-26,28-dimethoxycalix[4]arene (**17**) and 5,17-dihexylurea-25,27-tetraethylene glycoloxy-26,28-dimethoxycalix[4]arene (**19**) have been synthesized by coupling reactions between 5,17-diamine-25,27-dihydroxy-26,28-dimethoxycalix[4]arene (**12**) and 5,17-diamine-25,27-tetraethylene glycoloxy-26,28-dimethoxycalix[4]arene (**16**) with phenyl isocyanate and hexyl isocyanate in 60%, 20%, 40% yields, respectively.

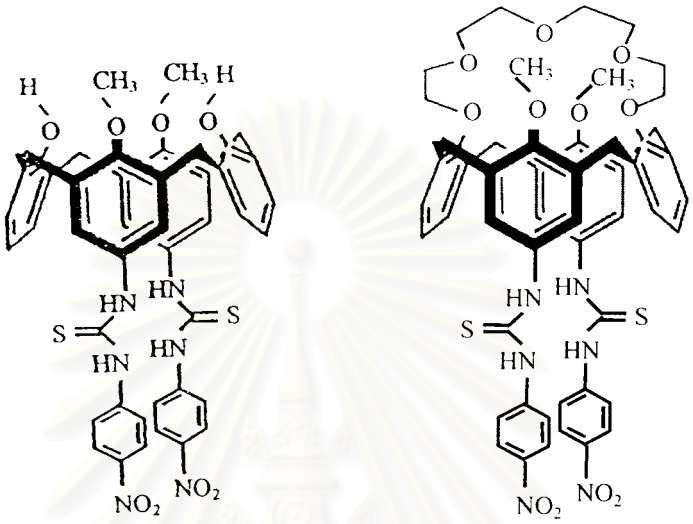
^{1}H-NMR titrations show that **13**, **17** and **19** can bind anions $H_2PO_4^-$, Cl^-, Br^- and NO_3^-. Compounds **13**, **17** and **19** are shown to bind $H_2PO_4^-$ selectively. Association constants of **13** with $H_2PO_4^-$ is the highest because both **17** and **19** are rigid, which decreased the binding ability (**13**, 250 M^{-1}, **17**, 200 M^{-1}, **19**, 53 M^{-1}). The incorporation of the crown ether unit in the calix[4]urea rusults in a slightly higher affinity of **17** for Cl^- and Br^-, but a lower affinity for $H_2PO_4^-$.

Both compounds **17** and **19** can form complexes with Na^+ and K^+. The presence of Na^+ and K^+ is found to enhance the affinity of **17** for $H_2PO_4^-$.

Future works

The compounds in this work were only soluble in DMSO, which has effected the binding ability towards anions and association constants and they contained urea units, it can bind anions weaker than thiourea units. It was reported by Umezawa and coworker.[40] The compounds **13**, **17** and **19** cannot be used for anions sensors because they have not chromophore. Thus, we are currently synthesizing other derivatives of calix[4]arene containing crown/thioureas and studying their anion binding and sensing ability. They

contain thiourea units, which has effected increasing of association constants and contain nitro benzene. The compounds will be anion sensors.



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APPENDIX

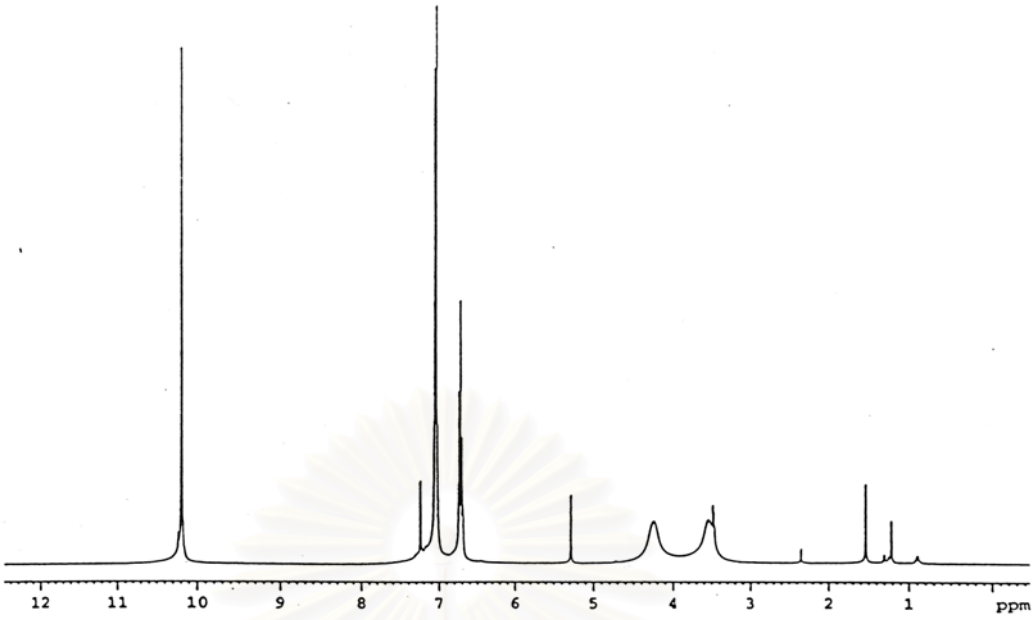

Figure A. 1: ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum of 25,26,27,28-tetrahydroxycalix[4]arene (**1**)

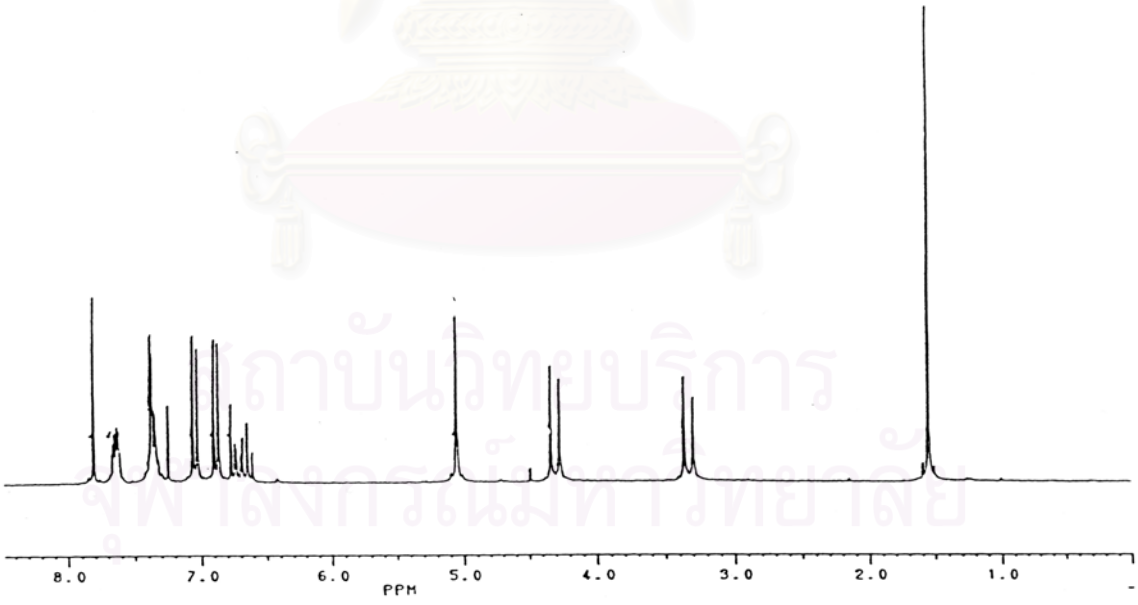

Figure A. 2: ^{1}H-NMR (200 MHz, $CDCl_3$) spectrum of 25,27-dibenzyloxy-26,28-dihydroxycalix[4]arene (**2**)

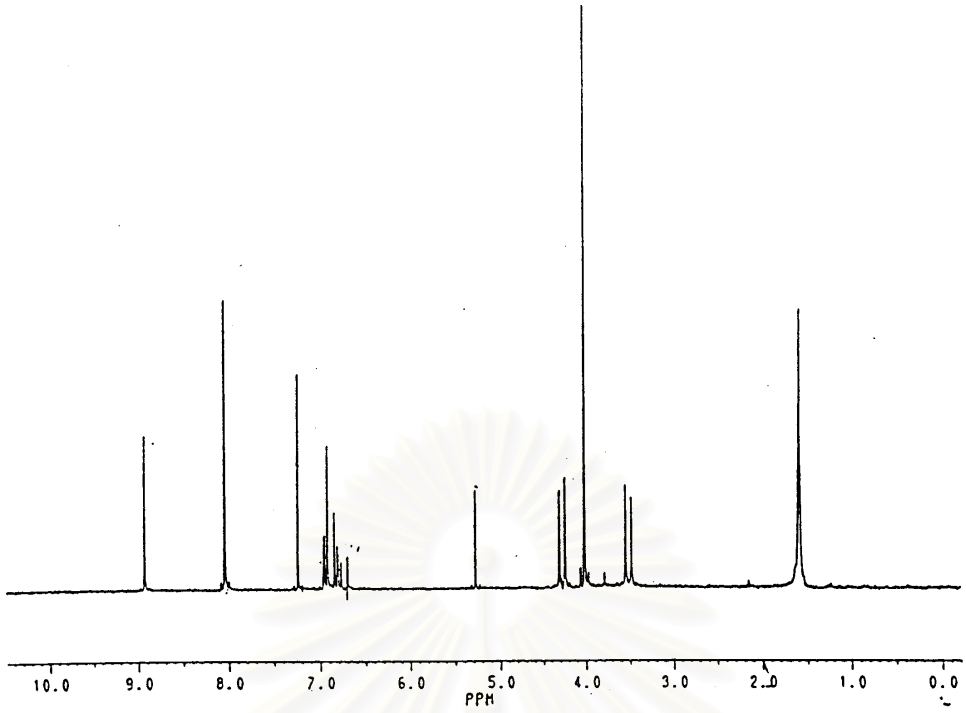

Figure A. 3: ^{1}H-NMR (200 MHz, $CDCl_3$) spectrum of 5,17-dinitro-25,27-dibenzyloxy-26,28-dihydroxycalix[4]arene (**3**)

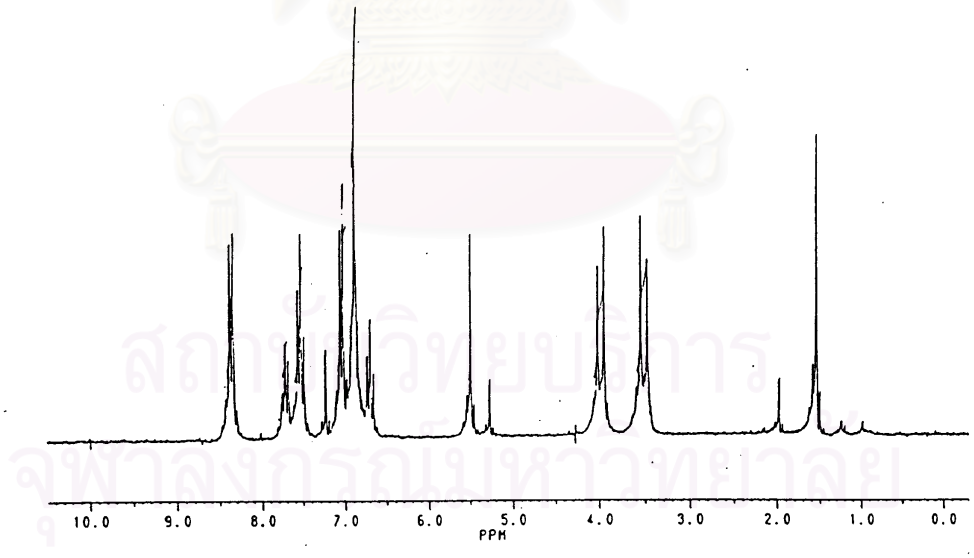

Figure A. 4: ^{1}H-NMR (200 MHz, $CDCl_3$) spectrum of 25,27-dibenzoyloxy-26,28-dihydroxycalix[4]arene (**5**)

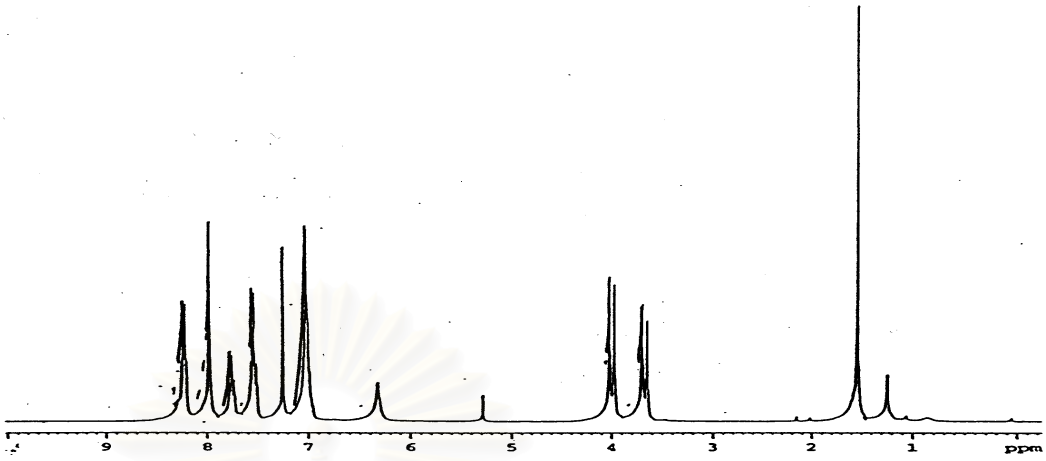

Figure A. 5: ^{1}H-NMR (200 MHz, $CDCl_3$) spectrum of 5,17-dinitro-25,27-dibenzoyloxy-26,28-dihydroxycalix[4]arene (**6**)

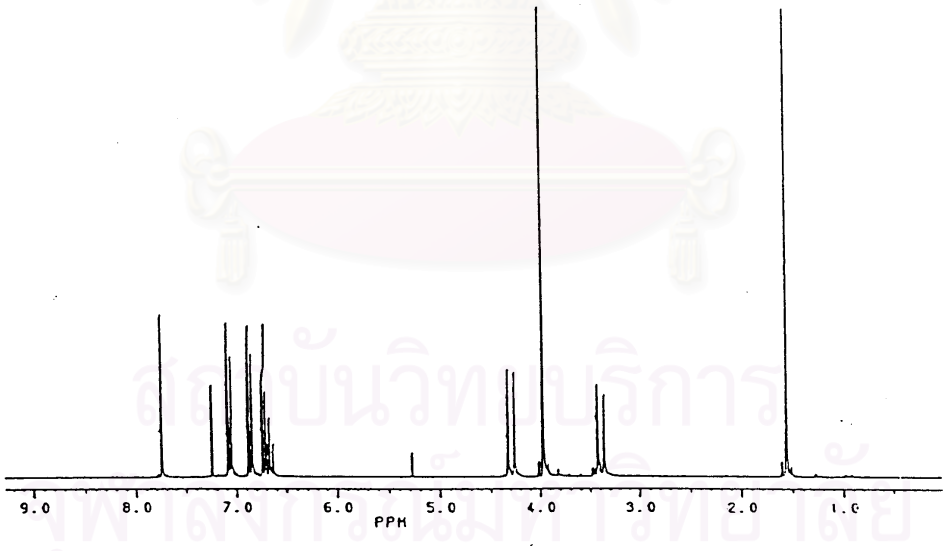

Figure A. 6: ^{1}H-NMR (200 MHz, $CDCl_3$) spectrum of 25,27-dimethoxy-26,28-dihydroxycalix[4]arene (**7**)

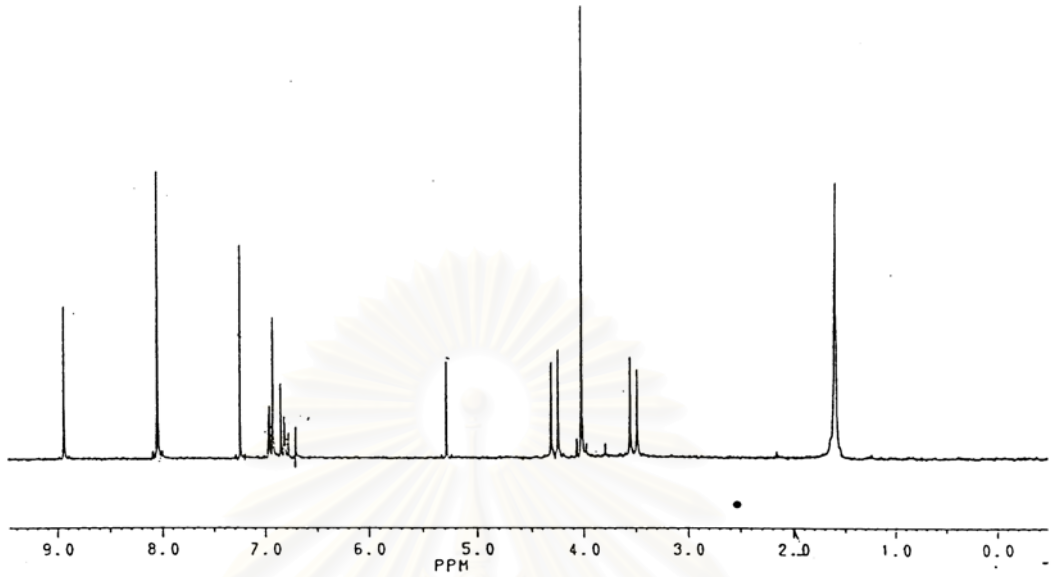

Figure A. 7: ^{1}H-NMR (200 MHz, $CDCl_3$) spectrum of 5,17-dinitro-25,27-dimethoxy-26,28-dihydroxycalix[4]arene (**8**)

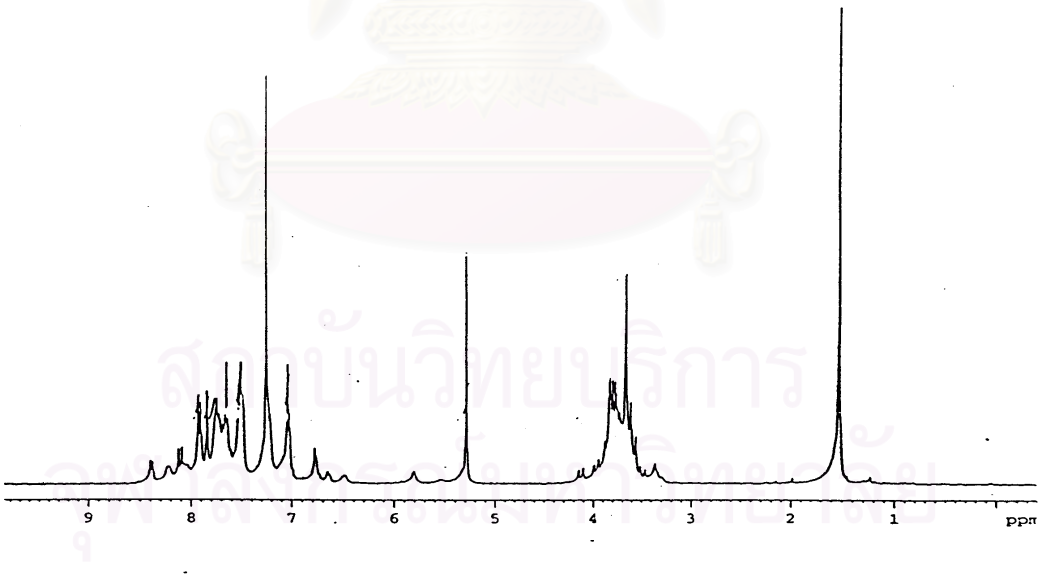

Figure A. 8: ^{1}H-NMR (200 MHz, $CDCl_3$) spectrum of 5,17-dinitro-25,27-dibenzoyloxy-26,28-dimethoxycalix[4]arene (**10**)

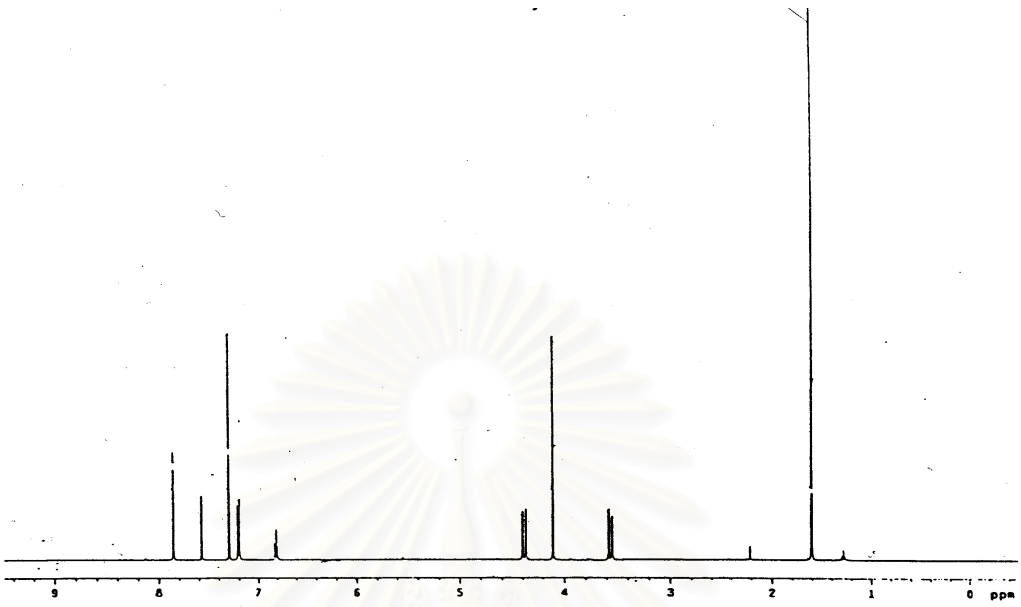

Figure A. 9: ^{1}H-NMR (400 MHz, $CDCl_3$) spectrum of 5,17-dinitro-25,27-dihydroxy-26,28-dimethoxycalix[4]arene (**11**)

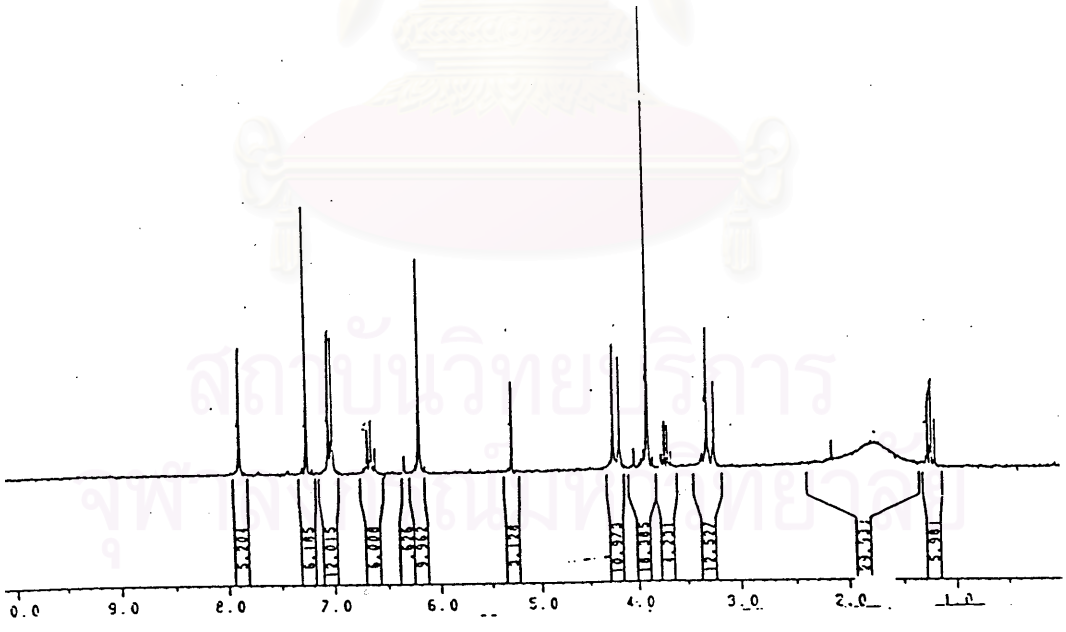

Figure A. 10: ^{1}H-NMR (200 MHz, $CDCl_3$) spectrum of 5,17-diamino-25,27-dihydroxy-26,28-dimethoxycalix[4]arene (**12**)

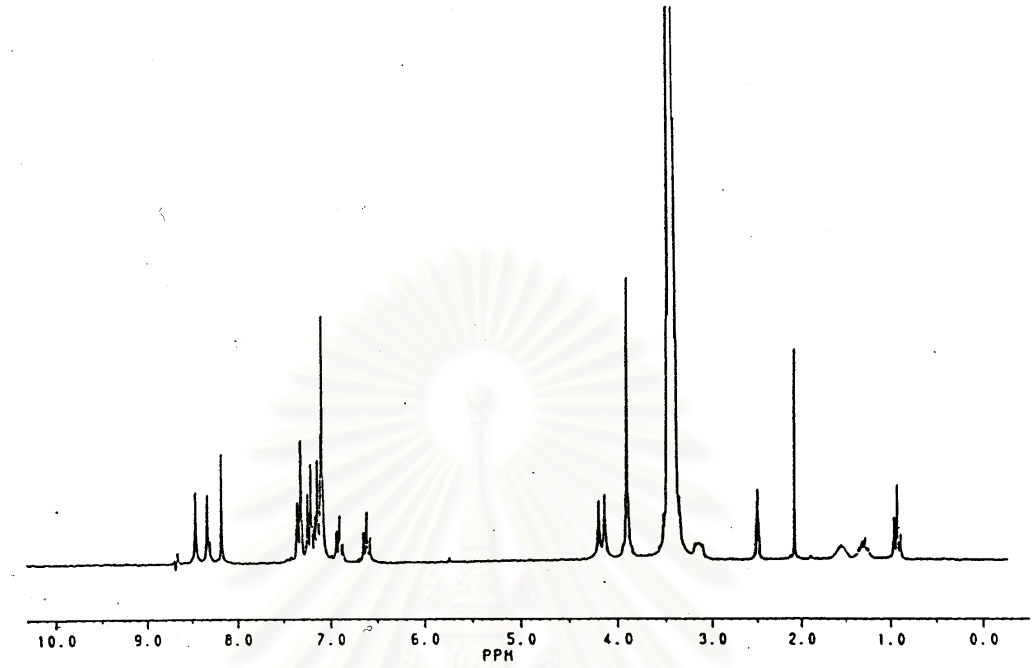

Figure A. 11: ^{1}H-NMR (200 MHz, DMSO) spectrum of 5,17-diphenylurea-25,27-dihydroxy-26,28-dimethoxycalix[4]arene (**13**)

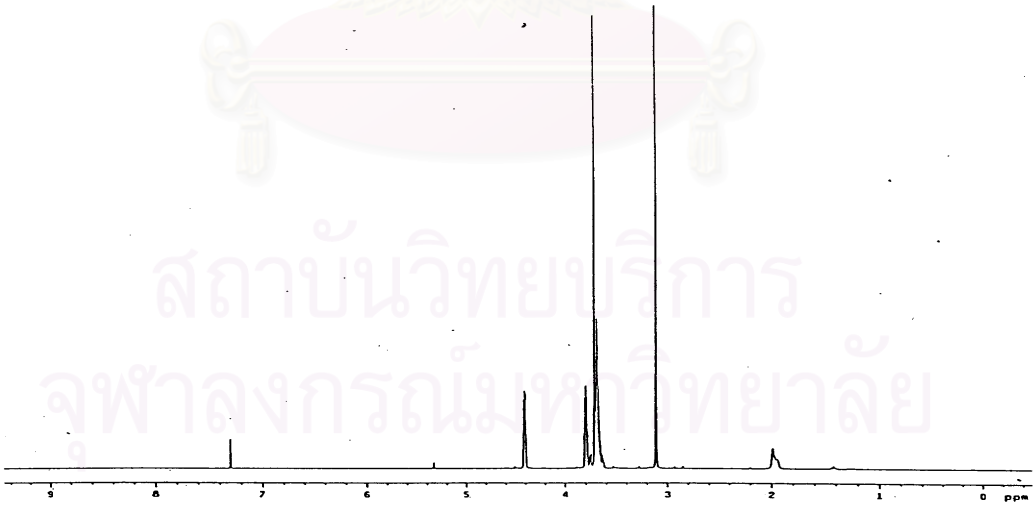

Figure A. 12: ^{1}H-NMR (400 MHz, DMSO) spectrum of tetraethylene glycol dimethylsulfonate

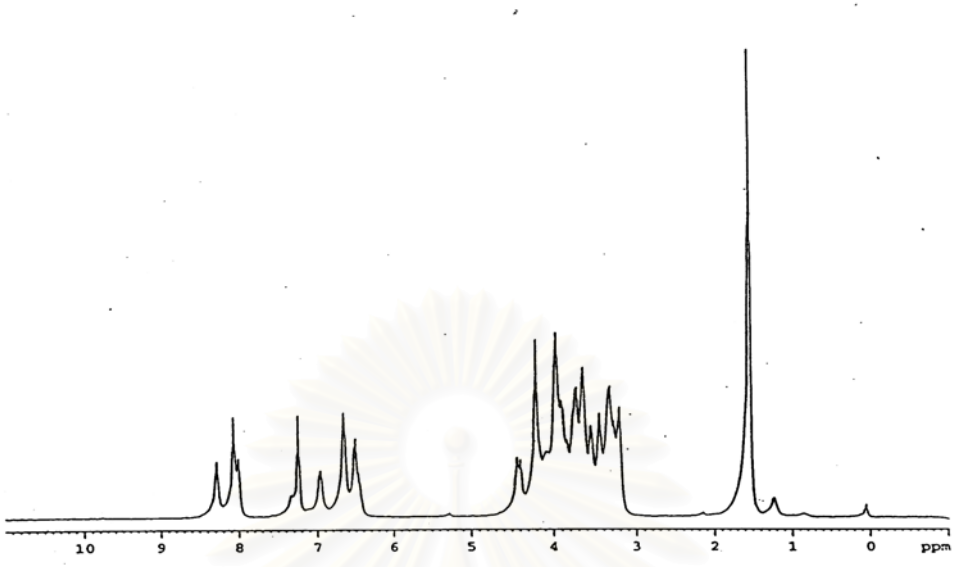

Figure A. 13: ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum of 5,17-dinitro-25,27-tetraethylene glycoloxy-26,28-dimethoxycalix[4]arene (**14**)

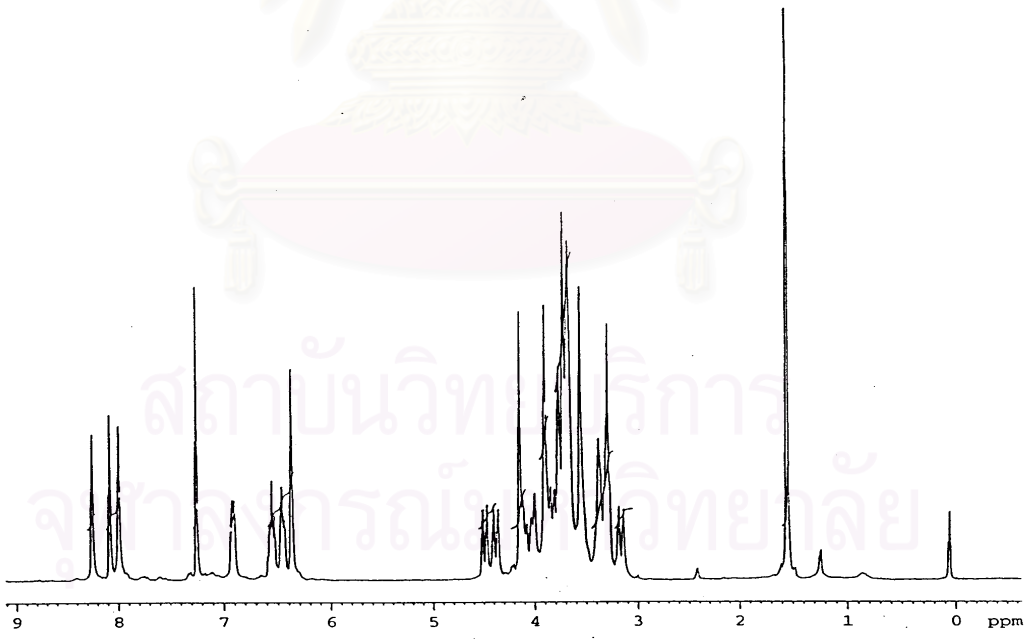

Figure A. 14: ^{1}H-NMR (300 MHz, $CDCl_3$) spectrum of 5,17-dinitro-25,27-pentaethyleneglycoloxy-26,28-dimethoxycalix[4]arene (**15**)

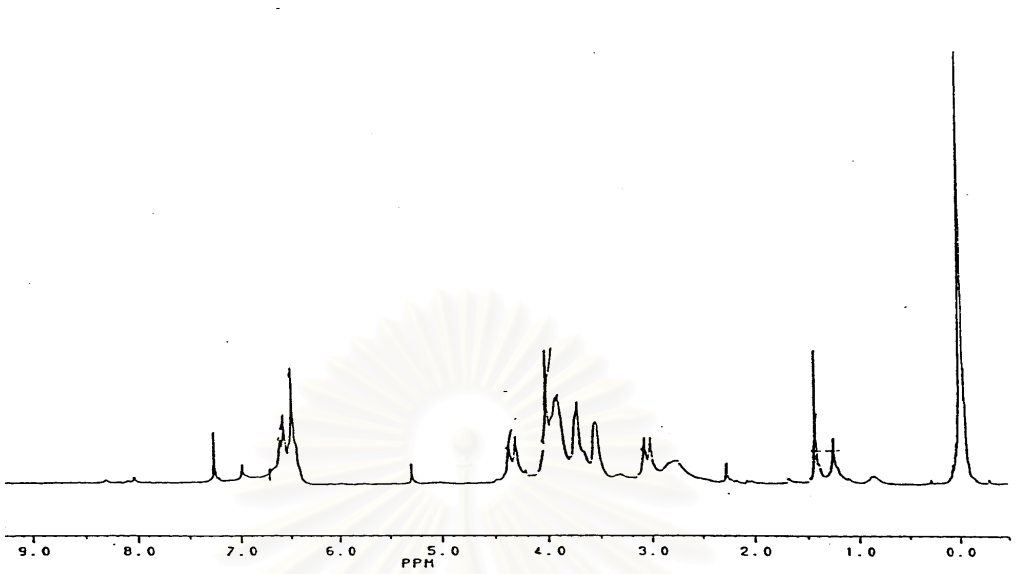

Figure A. 15: ^{1}H-NMR (200 MHz, $CDCl_3$) spectrum of 5,17-diamino-25,27-tetraethylene glycoloxy-26,28-dimethoxycalix[4]arene (**16**)

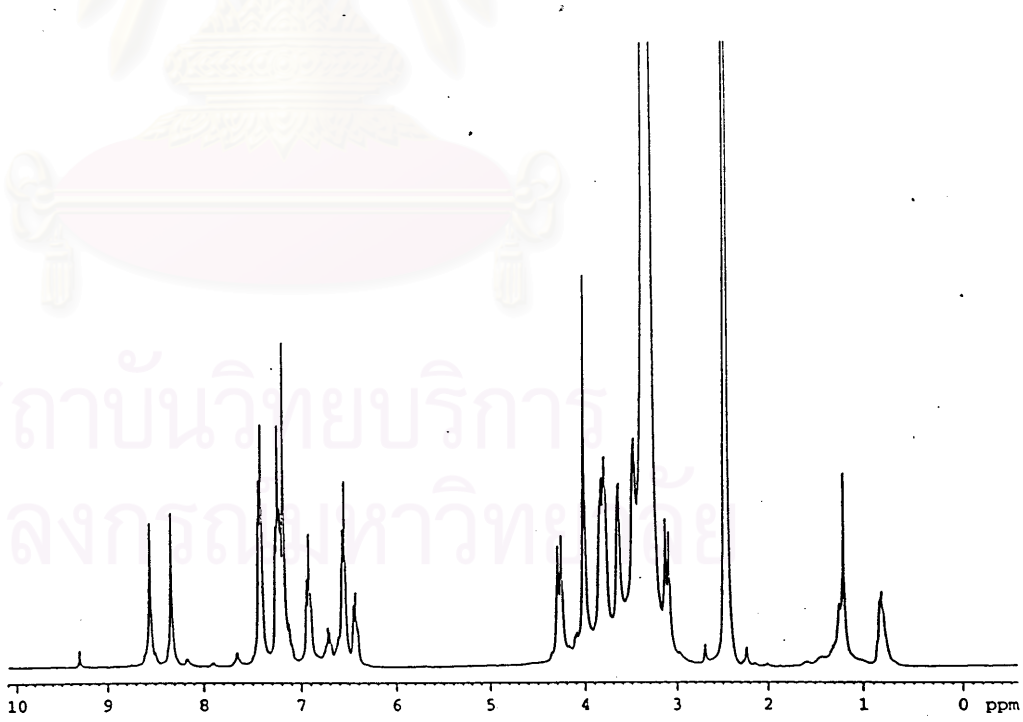

Figure A. 16: ^{1}H-NMR (200 MHz, DMSO) spectrum of 5,17-diphenylurea-25,27-tetraethylene glycoloxy-26,28-dimethoxycalix[4]arene (**17**)

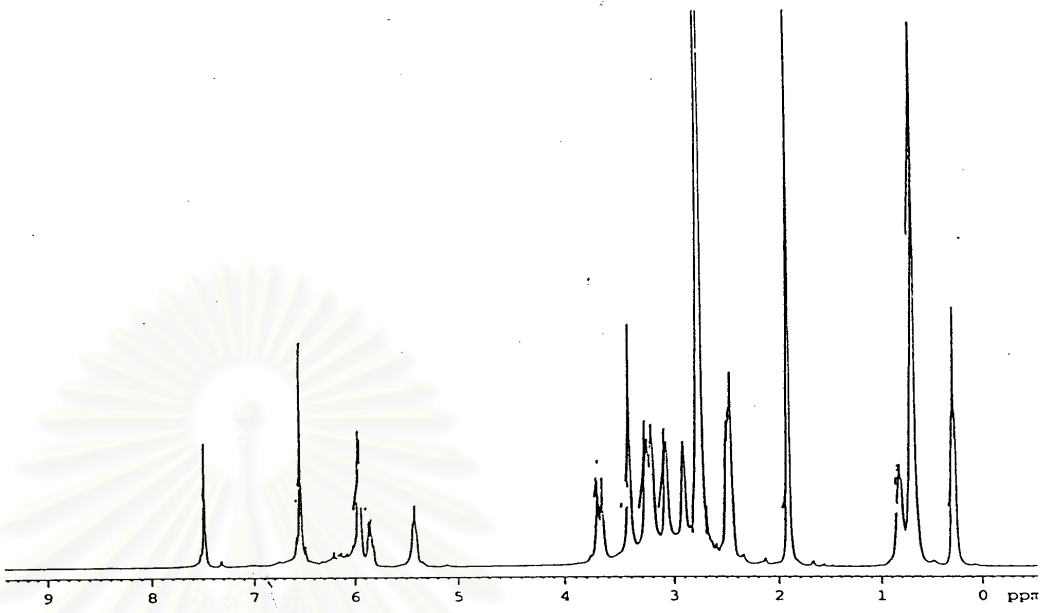

Figure A. 17: ^{1}H-NMR (300 MHz, DMSO) spectrum of 5,17-dihexylurea-25,27-tetraethylene glycoloxy-26,28-dimethoxycalix[4]arene (**19**)

VITA

Mr. Pan Tongraung was born on April 15, 1971 in Ubonratchatani, Thailand. He graduated with a high school diploma from Patoompitayakom School, Ubonratchatani in 1989. He received his Bachelor degree of Science in Chemistry from Khonkaen University in 1993 and Master degree of Science in Chemistry from Chulalongkorn University in 1997. Since 1999, He has been a graduate student at the Department of Chemistry, Chulalongkorn University and become a member of the Supramolecular Chemistry Research Laboratory under the supervision of Assistant Professor Dr. Thawatchai Tuntulani. He finished his Doctor of Philosophy degree in the academic year 2004.