CHAPTER I

INTRODUCTION

A fundamental design principle in the construction of supramolecular assemblies is the alignment of functional groups on a respective molecular platform to achieve complementarity binding interactions towards a targeted structure. In regard to host-guest chemistry, the chemical and steric features given by a guest molecule have to be matched by a sufficiently predisposed host. In receptor molecules, binding groups are commonly arranged with a distinct conformation controlled by the covalent architecture of the receptor. The most common approach is the use of macrocycles and polyfused rings. In particular, structures that possess a special desired topology, such as calixarenes, fused aromatic rings, steroids and *cis,cis*-1,3,5-substituted cyclohexanes of the Kemp's acid type, are frequently applied as platforms for supramolecular system. In host molecules based on coordination compounds, the conformational control is achieved only upon complexation of an additional component, usually a metal cation.[1]

In order to avoid extensive synthetic effort, that is more or less required for the examples cited above, it would be favorable to exploit "steric gearing". Here, certain subunits within a molecule obtain and retain a preorganized geometry due to adoption of the thermodynamically favored conformation where steric interactions are minimized.[2] Hexasubstituted benzene has attracted much recent attention as efficient building blocks for the development of functional molecules such as molecular receptors and metal ligands in the fields of molecular recognition chemistry and supramolecular chemistry. It adopts a fully alternated "up-down" arrangement of the arms with all substituents oriented perpendicularly to aryl ring plane. In this arrangement, the substituents attached at the 1,3 and 5 positions of the central ring all pointing to the same face while the rest of substituents point in the opposite direction.

The major limitation for a wider use of these persubstituted benzene systems was the difficulty to synthesize receptors with different functionalities on one phenyl ring, that is the fact that all six substituents had to be the same. Traditionally, hexasubstitued benzene derivatives were restricted to study and development because

the limited substrates: hexafluorobenzene, hexa(bromomethyl)benzene and tris-aminomethyl triethylbenzene derivatives which are inturn, need to be synthesized in several steps and futher functionalized with many reagents to increase efficiency and specificity for binding targeted molecules.

1.1 Hexasubstituted Benzene

In 1976, MacNicol and coworkers were among the first group to design the preorganization of the functional groups in hexasubstituted benzene derivatives and determined the molecular structures by X-ray analysis.[3-5] In these systems, six identical substituents are adopt a fully alternated "up-down" arrangement of the arms with all substituents oriented perpendicularly to aryl ring plane (**Figure 1.1**). In this arrangement, the substituents attached at the 1,3 and 5 positions of the central ring all point to the same face while the rest of substituents are pointed toward the opposite direction, so as to impart approximate D_{3d} or S_6 symmetry. The unique steric features of hexasubstituted benzenes are the design principle for host molecules and supramolecular system. Due to the unavoidable steric repulsion between 2 adjacent substituents, the 1,3,5-substituted benzene spacer play an important role in controlling the steric configuration of the functional groups introduced into its 2,4,6-positions. The functional groups attached at the 2,4,6-positions are forced to lie at the opposite side of aryl ring of the spacer, so the "*ababab*" configuration (*a* denotes "above" and *b* denotes "below") as the most thermodynamically stable configuration.

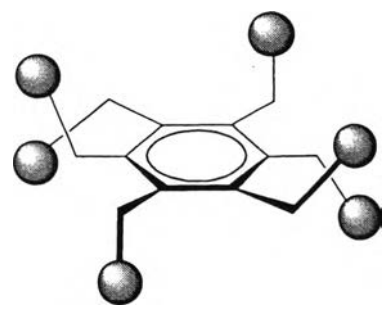


Figure 1.1 *ababab*-Hexasubstituted benzene scaffold

1.2 Stereochemistry of Hexasubstituted Benzene

1.2.1 The Ethyl Group

The ethyl substituent is the simplest alkyl group of non-conical symmetry. An ethyl group attached to a central ring can be depicted schematically as an "arm" consisting of a CH_3 group protruding from the axis connecting the ethyl group to the central ring (**Figure 1.2**). Polyethylated aromatic compounds can be viewed as multiarmed hydrocarbon (sometimes referred as "octopus molecules")[6] in which several arms radiated from a central polyatomic core. They are of interest as sterically crowded compounds. The analysis of their preferred conformations is particularly challenging because of the inherent stereochemical complexity of these conformationally flexible systems. The polyethylated derivatives are capable of existing in a large number of conformations, the relative energies of which are dictated by numerous nonbonded interactions (repulsive and attractive van der Waals interactions) between the ethyl groups. Usually the lowest energy conformation results from the need to avoid repulsive steric interactions between the groups.[7]

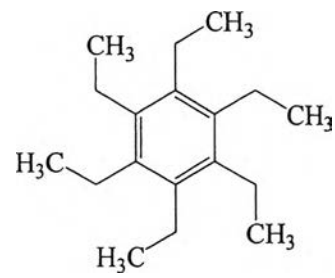


Figure 1.2 Hexaethylbenzene **1**

1.2.2 Conformation of Hexaethylbenzene

The static and dynamic stereochemistry of hexaethylbenzene **1** was analyzed in great detail by Iverson and coworkers.[8] Molecular mechanics calculation have indicated that the fully alternated conformation is ca. 3.46 kcal mol^{-1} lower in energy than a nonalternated conformation possessing two pairs of *ortho*-substituents oriented toward the same face of the benzene ring, usually designated as a *syn* arrangement, where its associated steric interaction (a *syn* interaction) is repulsive. All ethyl groups are perpendicular to the cental ring, giving eight possible different diastereomeric forms. Calculated has shown that relative steric energies of the form increased

roughly with the number of *syn* interactions present (none, two, four or six; **Figure 1.3**).

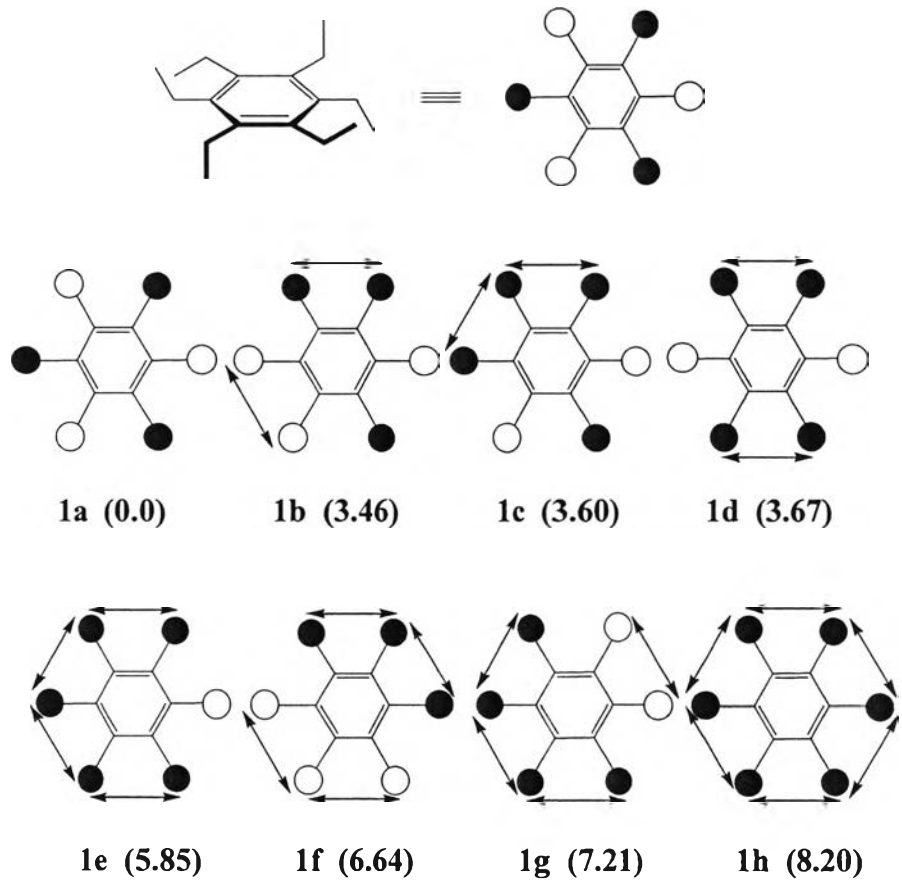


Figure 1.3 The eight ideal up-down forms of hexaethylbenzene and their calculated EFF (BIGSTRN-2) relative steric energies (kcal mol^{-1}) (filled and empty circles represent ethyl groups pointing to or away from the observer; a double arrow denotes a *syn* arrangement of two *ortho* ethyl groups)

As a further test of stereochemistry of **1**, relative energy levels for the eight structures were computed by the extended Hückel method: such hybrid EFF (BIGSTRN-2)[9] and EFF-EHMO[10] calculations showed the fully alternated form remains the ground state conformer (**Figure 1.4**). Both methods of calculations therefore predicted the same ground state conformation as found from the X-ray structure[8] and indicated that the solution of **1** contain more than 99% of this conformer at equilibrium under normal conditions. Higher energy conformers could be implicated as intermediates in the degenerate conformational rearrangement (topomerization) of the fully alternated conformer.

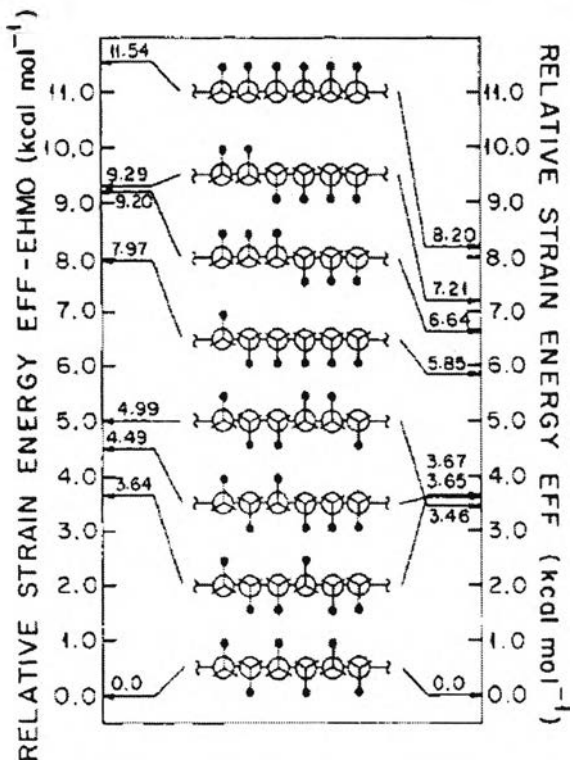
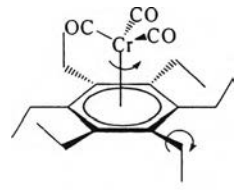


Figure 1.4 The eight up-down isomers of **1**. Each schematic projection represents a view around the perimeter of the benzene ring. The heavy dots stand for methyl groups. The scales on the right and left of the diagram indicate relative energies calculated by the EFF (BIGSTRN-2) and EFF-EHMO methods, respectively.

Transition metal complexation was used for the study the stereodynamics of alkylbenzene. The center of symmetry in D_{3d} and S_6, as well as the C_2 axes in D_{3h}, may be removed upon complexation of the aromatic ring with transition metals. As a result, the two faces of the benzene ring become nonequivalent and differentiable and site-exchange phenomena resulted from rotations of the side chains could be monitored by dynamic NMR (DNMR) techniques. Iverson and co-workers[8] were investigaeted the stereochemical features of such system in which hexaethylbenzene functioned as the η^6-arene in tricarbonylchromium, tricarbonyl-molybdenum and dicarbonyl(triphenylphosphine)chromium complexes (**Figure 1.5**). They provided information about the steric complimentarity between the metal fragment and the arene. The methyl groups in tricarbonylchromium **2** and tricarbonylmolybdenum complexes project alternately above and below the benzene plane. Three of ethyl groups are eclipsed by the carbonyl groups and their corresponding methyl groups project toward the uncomplexes side of the ring. But the structure of dicarbonyl(triphenylphosphine)chromium complex **3** differs markedly, in that all six

methyl groups project toward the uncomplexed side of the ring, and the molecule assumes a staggered rather than eclipsed conformation. This information in turn applied to the design of transition complexes where control of the steric environment around the metal modifies the reactivity of the complex. The utility of the method is limited by the degree to which the presence of the metal disturbs the stereodynamics of the parent compound. These limits can be probed through systems where the symmetry allows one to observe the stereodynamics of both free and metal-complexed arenes.[10]



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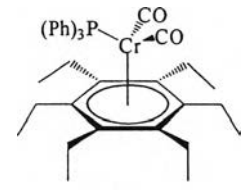

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Figure 1.5 Stereochemical regions in the tricarbonylchromium **2**, and dicabonyl (triphenylphosphine)chromium **3** complexes with **1**.

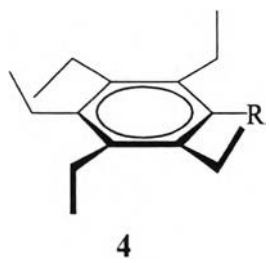
1.2.3 Rotational Barriers

The rotational barrier of polyethylated arene does not usually refer to the rotation of a single ethyl group but rather to the overall topomerization barrier determined by NMR spectroscopic methods. This observation is due to the fact that if a single conformation is detected, usually the energy of barrier is determined by monitoring the line sharp changes of diastereotopic groups that are rendered equivalent the dynamic process. This topomerization process may involve one or several consecutive ethyl group rotations and/or several intermediate conformers along the pathway but undetected in the NMR spectrum because of their low populations.

Molecular mechanics calculations indicated that the site exchange of the methylene proton of **1** proceeded through a stepwise process. The favored rearrangement pathway was found to be have calculated barrier height of 11.8 kcal mol^{-1}.[8] This result was supported by an analysis of ^{13}C-NMR lineshapes of the tricarbonylchromium and tricabonylmolybdenum complexes in CD_2Cl_2 at below -30 °C. The barriers of site exchange were 11.5 and 11.6 kcal mol^{-1} for tricarbonyl-chromium and tricarbonylmolybdenum complexes, respectively.

1.2.4 Polyethylated Benzene

In contrast to compound **1**, in the polysubstituted derivatives **4** (**Figure 1.6**) pair of the methylene protons on ethyl groups located *ortho* or *para* to the substituent (R) are diastereotopic under the conditions of slow side chain rotation on the NMR spectroscopic timescale, and their topomerization barrier can be determined readily by DNMR spectroscopy.[11-14] As showed in **Figure 1.6**, the rotational barrier of pentaethylbenzene **4a** is lower than the calculated barrier of **1**. During the 180° rotation of an ethyl group, a conformation is reached in which the CH_2-CH_3 bond is coplanar with the benzene ring. If the two *ortho*-substituents flanking the rotating ethyl group are different, two diastereoisomeric transition states are possible (**Scheme 1.1**). In the case when R = H, the *syn* transition state should be favored on steric grounds.



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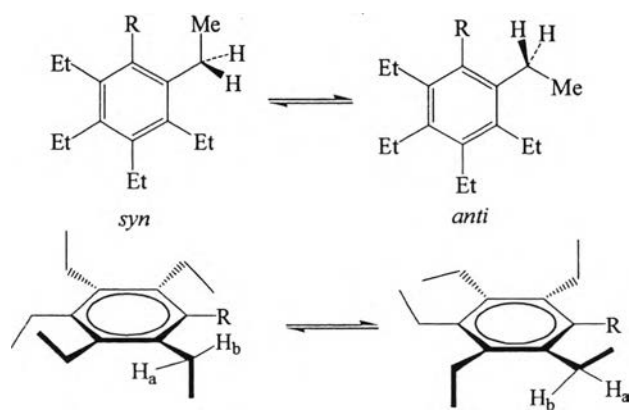
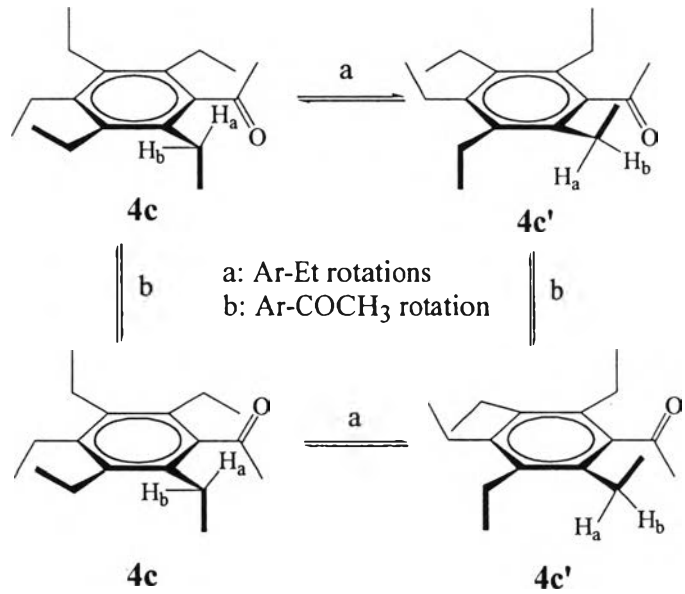
	topomerization barrier (kcal mol^{-1})
4a R = H	9.2
4b R = Br	10.2
4c R = $COCH_3$	13.7
4d R = $OCOCH_3$	14.6
4e R = OCOPh	16.7

Figure 1.6 Experimentally measured topomerization barriers of pentaethylphenyl derivatives **4**



Scheme 1.1 Diastereoisomeric transition states and diastereotopic protons in penta-ethylphenyl derivatives.

Ketone **4c** and esters **4d,e** displayed topomerization barriers substantially higher (13.7-16.7 kcal mol^{-1}) than the barrier calculated for **1**.[11] In **4c** the carbonyl group is nearly perpendicular to the aryl plane and two diastereomeric conformations are possible (**4c** and **4c'**, **Scheme 1.2**). These two conformers may interconvert either by 180° rotation of the five ethyl groups, or by single 180° rotation along the Ar-COR bond. To achieve topomerization of a given form, however, not only must the five ethyl groups rotate, but also the COR group must rotate by 180° and the high barrier of the latter process is the one that determines the overall topomerization barrier. Low-temperature NMR spectroscopic data were in agreement with this analysis and, for example, two sets of signals were observed in ^{13}C-NMR spectra of **4d** and **4e**.



Scheme 1.2 Diastereotopic protons in pentaethylphenyl acetone **4c** and **4c'**

Kilway and Siegel presented the experimental evidence to quantify the effect of tricarbonylchromium complexation on the stereodynamic of compounds related to **1**.[12-13] The molecular models are 1,4-dimethoxy-2,3,5,6-tetraethylbenzene **5**, 1,4-bis(methoxymethyl)-2,3,5,6-tetraethylbenzene **6**, and 1,4-dineohexyl-2,3,5,6-tetra-ethylbenzene **7** (**Figure 1.7**). The ground states of **5**, **6** and **7** are calculated by EFF methods to be the alternating up-down conformer analogous to **1**. In all three systems, they found only a minor perturbation of the barrier to ethyl group rotation when the metal tripod was introduced onto the arene. These results would indicate that for these systems the use of transition metals as desymmetrizing units for the study of such stereodynamics provides data that is a relatively accurate assessment of the parent-

ligand dynamics. This lock-and-key fit is also of importance to the design of arene ligands which modify the steric environment around a transition metal; 1,3,5-substituted hexaalkylbenzenes should be capable of enshrouding the metal without strongly altering the strength of the metal-arene bond.

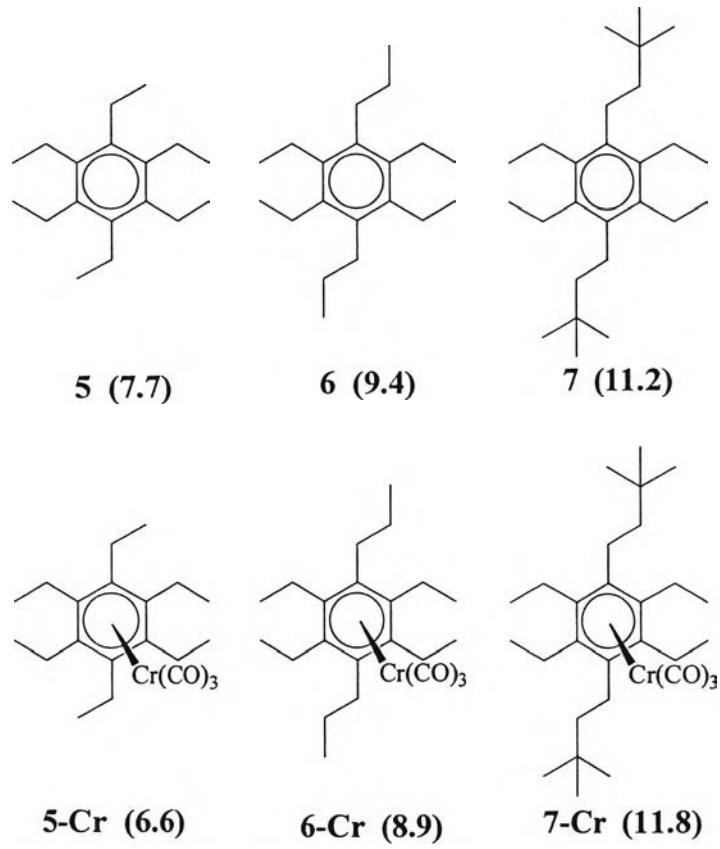


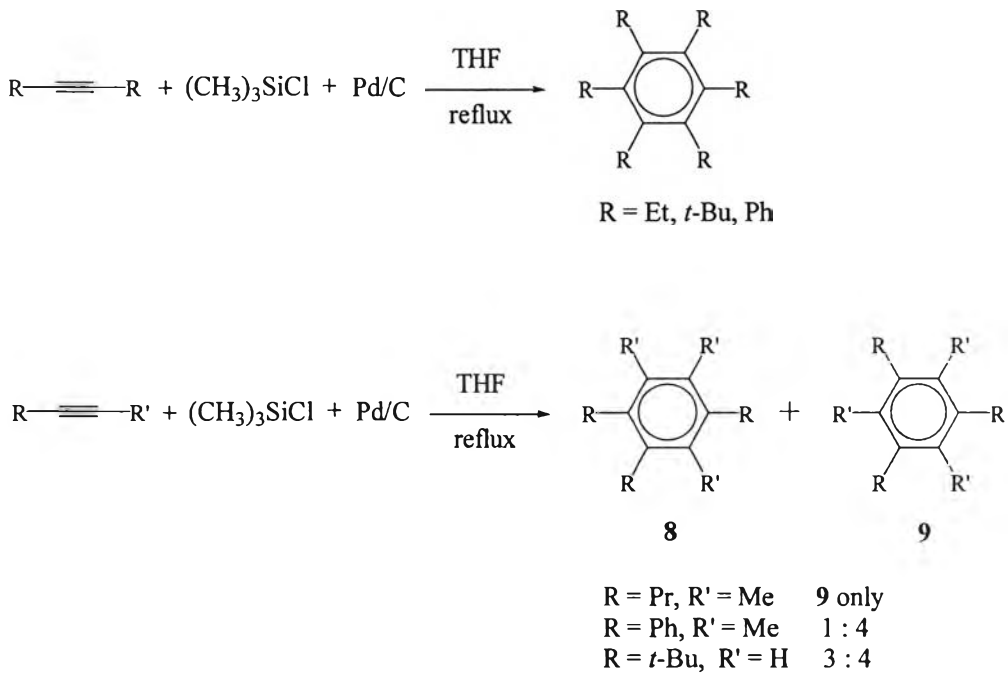
Figure 1.7 The barriers to rotation (kcal mol^{-1}) about the sp^2-sp^3 bond for 1,4-dimethoxy-2,3,5,6-tetraethylbenzene **5**, 1,4-bis(methoxymethyl)-2,3,5,6-tetraethyl-benzene **6**, and 1,4-dineohexyl-2,3,5,6-tetraethylbenzene **7** and their tricarbonyl-chromium complexes, **5-Cr**, **6-Cr** and **7-Cr**

1.3 Synthesis of Hexasubstituted Benzene

1.3.1 Cyclotrimerization[15]

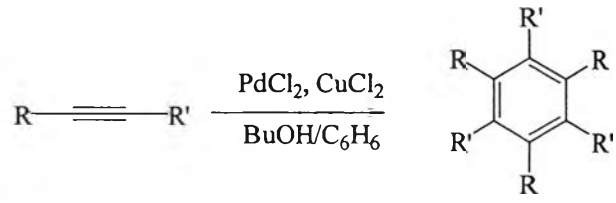
A variety of homogeneous transition metal carbonyl complexes could be employed for the preparative cyclotrimerization of alkynes to hexasubstituted benzene derivatives. Examples of these complexes were Ziegler catalyst (*i*-Bu_3Al and $TiCl_4$), Bis(benzonitrile)palladium chloride, $NaBH_4$ with $NiCl_2$, Ta_2Cl_6(tetrahydro-thiophene)$_3$ and Nb_2Cl_6(tetrahydrothiophene)$_3$. Many of these methods produced complex reaction mixtures which afforded low yields of the desired trimers while all

required very stringent reaction conditions. In 1987, during an attempted addition of trimethylsilyl chloride to alkynes in the presence of Pd/C, Jhingan and Maier[16] observed the formation of hexasubstituted benzene derivatives from symmetrical alkynes in high yields (**Scheme 1.3**). Furthermore, trimerization of the unsymmetrical alkynes produced the asymmetric trimer and the trimerization of terminal alkyne was selected to probe the sensitivity of the reaction to steric effects. The unsymmetrical 1,2,4-trimer was obtained as a minor product.



Scheme 1.3 Cyclotrimerization of alkynes with Pd catalyst

In 2001, Jiang and coworkers[17] presented a regioselective and highly chemoselective method for preparing hexasubstituted benzene derivatives via $PdCl_2$ catalyzed cyclotrimerization of alkynes in the presence of $CuCl_2$. They found that a symmetrically internal alkyne except diphenylacetylene was cyclotrimerized in high yield in the presence of $PdCl_2$-$CuCl_2$ in BuOH/benzene at room temperature. The cyclotrimerization did not yield benzene derivatives without adding $CuCl_2$ as the oxidant.

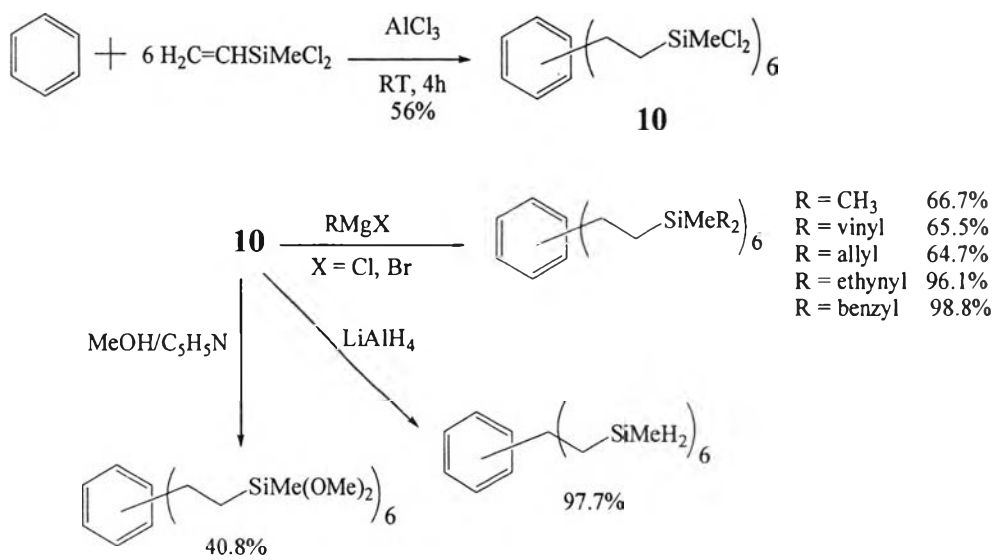


R = R' = C_3H_7	98%
R = R' = Ph	0%
R = C_5H_{11}, R' = H	78%
R = C_6H_{13}, R' = H	70%
R = *t*-Bu, R' = H	100%
R = *p*-MePh, R = H	95%
R = *p*-ClPh, R = H	90%

Scheme 1.4 $CuCl_2$-induced regiospecifical cyclotrimerization of alkynes

1.3.2 Benzene Substitution

Friedel-Crafts alkylation of vinyldichloromethylsilane to benzene in the presence of aluminum chloride catalyst at room temperature gave hexakis((dichloro-methylsilyl)ethyl)benzene **10** in 56% yield.[18] The chlorosilyl group can easily react with organometallic reagents, alcohols and amines to afford useful new organosilicon compounds which could be served as possible precursors for new silicon-containing materials. Compound **10** was treated with a variety of reagents such as methyl, vinyl, allyl, ethynyl, and benzyl Grignard reagents, methanol, and $LiAlH_4$ to give the corresponding derivatives (**Scheme 1.5**) in good to excellent yield.

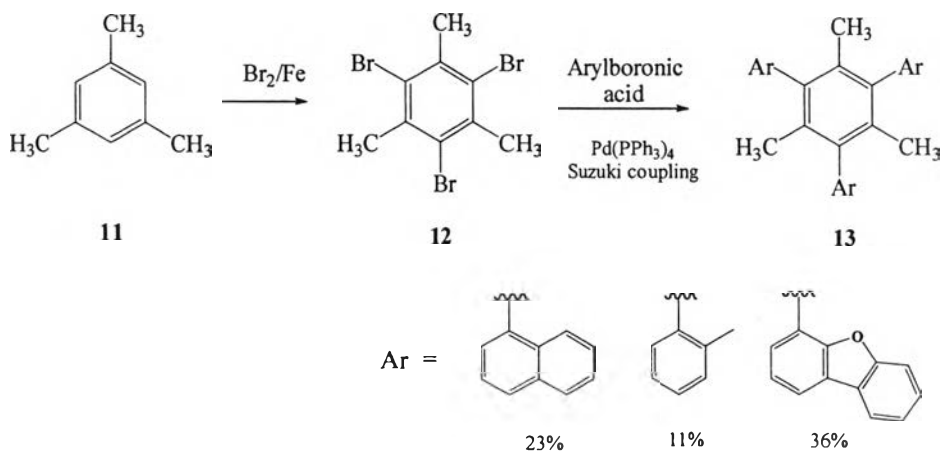


R = CH_3	66.7%
R = vinyl	65.5%
R = allyl	64.7%
R = ethynyl	96.1%
R = benzyl	98.8%

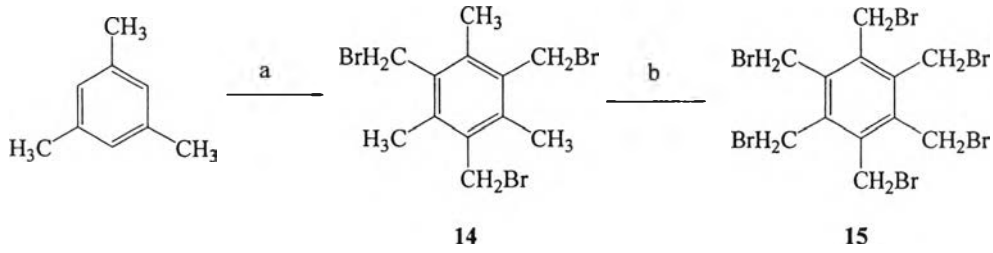
Scheme 1.5 Syntheses and structures of the hexa(methylsilylated)benzenes

1.3.3 1,3,5-Trialkylbenzene Substitution

Mesitylene **11** was used to synthesize triarylmesitylenes **13** using the Pd-catalyzed Suzuki coupling via tribromomesitylene **12** with arylboronic acid obtaining in low yield (**Scheme 1.6**).[19] Compound **13** was isolated all-syn (minor isomer) and by analytical HPLC. All-syn isomer was studied kinetics of interconversion and found that the methyl groups on compound **13** did provide a sufficient barrier to aryl-aryl bond rotation to prevent rapid isomer interconversion at room temperature. In 1993, van der Made and coworkers[20] discovered an easy synthetic route to threefold bromomethylation of mesitylene that led straightforward to the 1,3,5-tris(bromomethyl)-2,4,6-trimethylbenzene **14** by using paraformaldehyde in acid. In 1994, Závada and coworkers[21] presented the methodology to prepare an important intermediate, hexabromomethylbenzene **15**, for further modification to various hexasubstituted benzene derivatives (**Scheme 1.7**). Although this procedure afforded the desired product in good yield, it suffered from poor accessibility of the parent hydrocarbon, rendering a large scale exploitation difficult. In 1997, Anslyn and coworkers[22] improved the synthesis of hexasubstituted benzene derivatives through 1,3,5-tribromomethyl-2,4,6-triethylbenzene **17** form 1,3,5-triethylbenzene **16**. Compound **17** can be synthesized in one step following a different approach outlined in **Scheme 1.7**, but due to purification problems they choose to use this route shown in scheme **1.8** was developed that bromomethylation of compound **16** yielded **17** in greater than 53% yield over two steps. This product could be used as the main precursor to be synthesized another starting material for various ligand systems through functionalizations on bromomethyl groups.



Scheme 1.6 Synthesis of triarylmesitylenes derivatives

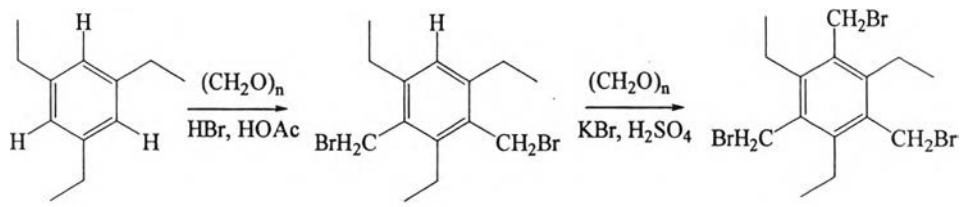


14 15

a $(CH_2O)_n$, KBr, $AcOH/H_2SO_4$, 95 °C, 6 h 97%

b $Br_2/BrCH_2CH_2Br$, reflux, 20 h 97%

Scheme 1.7 Synthesis of hexabromomethylbenzene



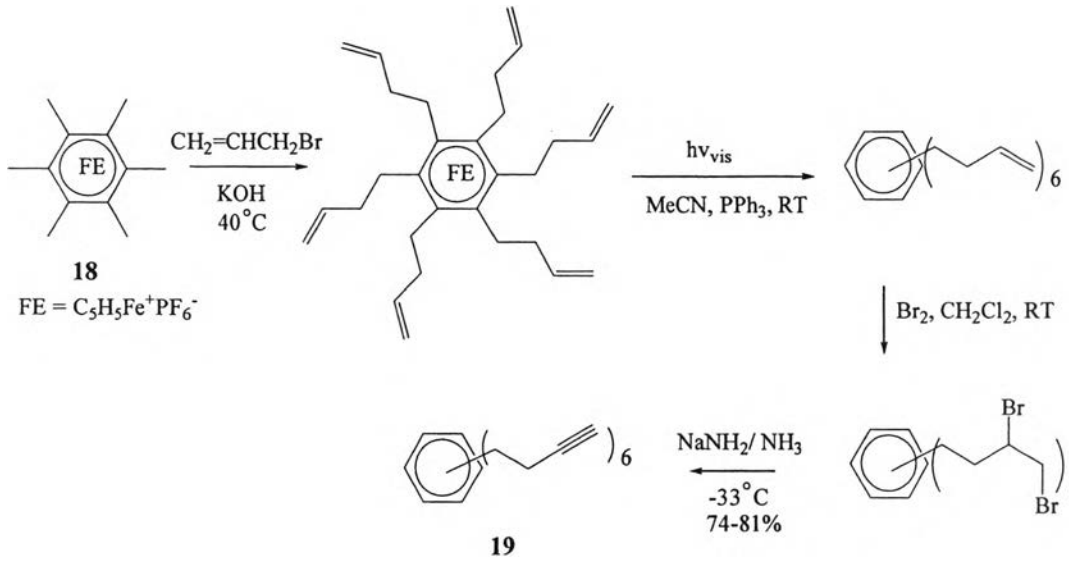
16 17

Scheme 1.8 Synthesis of 1,3,5-tribromomethyl-2,4,6-triethylbenzene

1.3.4 Hexasubstituted Benzene Functionalization

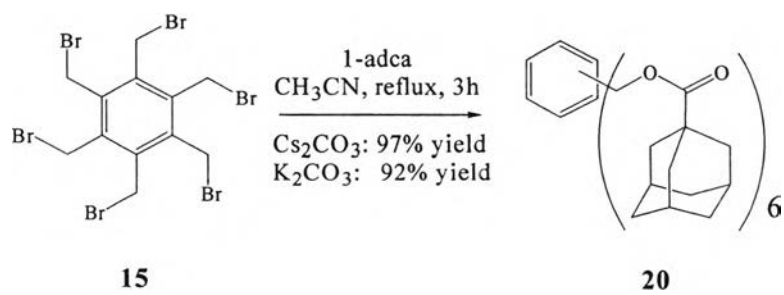
1.3.4.1 Homohexasubstituted Benzene

Homohexasubstituted benzene is a starting material that all substituents on the benzene ring are the same groups. For example, hexa(but-3-ynyl)benzene **19** was synthesized from hexasubstitution of $[FeCp(C_6Me_6)]^+PF_6^-$ **18** (**Scheme 1.9**).[23] The $FeCp^+$-induced formation of multiple C-C bonds proceeded readily with alkyl, allyl and benzyl halides. The polyalkyne compounds could be used as building blocks for the construction of extended molecular frameworks needed in supramolecular assemblies and molecular electronic devices.

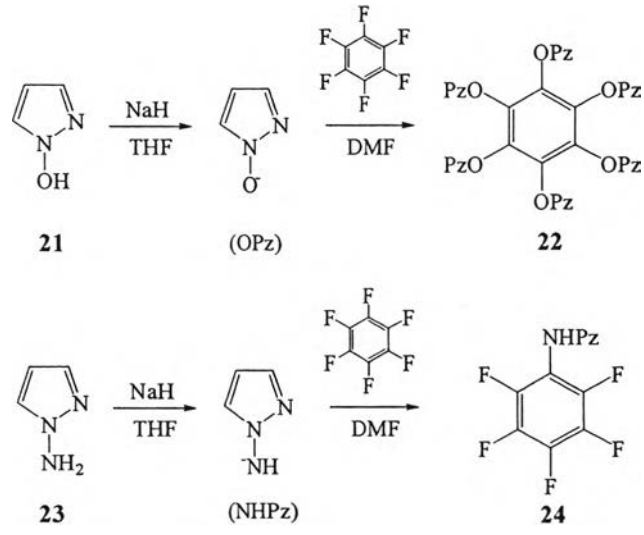


Scheme 1.9 Synthetic pathway to hexa(but-3-ynyl)benzene **19**

In 2001, Anslyn and coworkers presented the substitution of the halogen atoms of hexabromomethylbenzene **15** in order to cerate molecules with alternating groups on the phenyl ring. The reaction of 1-adamantylcarboxylic acid (1-adca) with **15** in 1:1 stoichiometry, they expected to obtain monosubstituted pentabromomethyl benzene. Surprisingly, the reaction gave the hexa(alkylcarboxy)benzene **20** in an almost quantitative yield, along with the recovery of **15** (**Scheme 1.10**).[24] In 2004, Sanz and coworkers obtained the hexasubstituted benzene derivatives as a major product with hexafluorobenzene substitution.[25] The reaction was carried out with ratios of *N*-hydroxypyrazole **21** per hexafluorobenzene to be 12/1 for 93 hours giving the product **22** in 64% yield (**Scheme 1.11**). The same reaction with *N*-aminopyrazole **23** afforded the product of monosubstitution **24**. When compound **24** was made to react with **23** no reaction was observed.



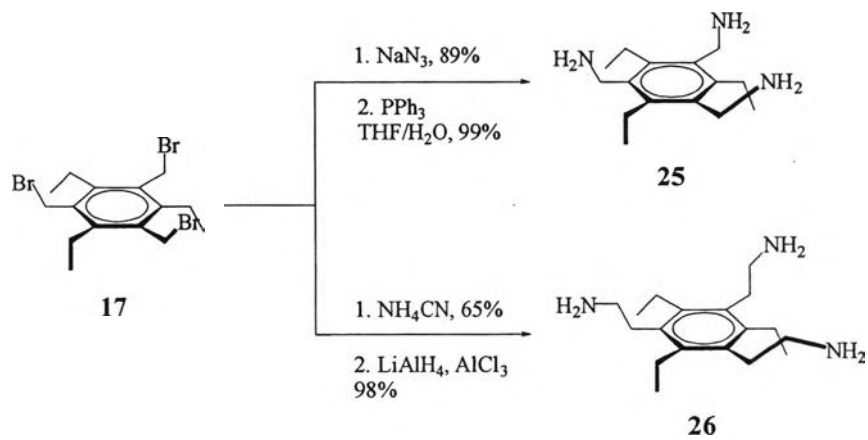
Scheme 1.10 Synthesis of hexasubstituted benzene form hexabromomethylbenzene



Scheme 1.11 Synthetic of hexasubstituted benzene from hexafluorobenzene

1.3.4.2 1,3,5-trisubstituted triethylbenzene

1,3,5-tribromomethyl-2,4,6-triethylbenzene **17** was the main precursor to be converted into the tris-amines **25** and **26** (**Scheme 1.12**).[22,26] These amines could be used as the starting materials for various ligand systems through functionalizations of amino group. Examples will be included in **Section 1.4**.

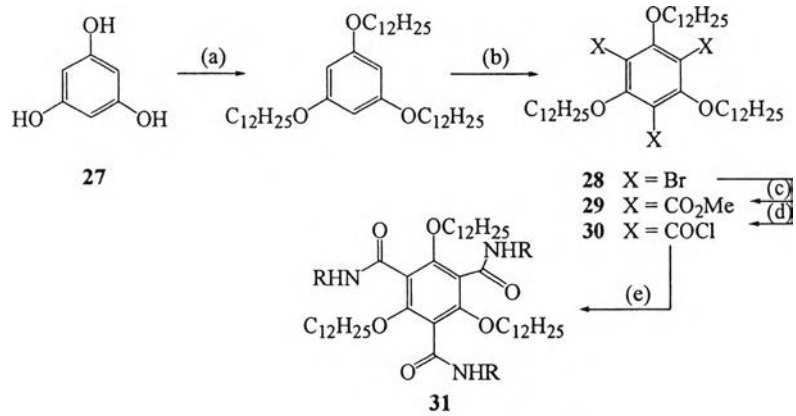


Scheme 1.12 Synthetic pathways to tris(aminoalkyl)triethylbenzenes **25** and **26**

1.3.5 Phloroglucinol

In 2001, Nuckolls and coworkers synthesized hexasubstituted benzene derivatives using phloroglucinol **27** as a starting material which was proceeded by triple O-alkylation and bromination to compound **28** then performed a triple lithium/halogen exchange at -78 °C and quenching the reaction with methyl

chloroformate to compound **29** obtained in 30% yield (**Scheme 1.13**).[27] The target structures **31a-d** are then synthesized in three steps: saponification, conversion to **30** and reaction with primary amines (75-81%). These products were studied self-assemble into column and their physical properties.

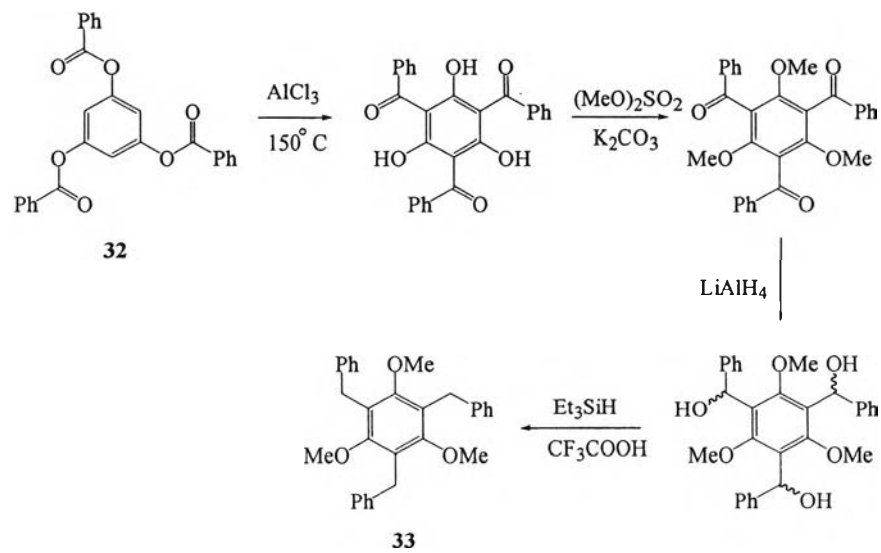


R = $C_{12}H_{25}$, CH_2CH_2Ph, Gly*Ot*-Bu

(a) K_2CO_3, $C_{12}H_{25}I$, reflux; (b) $Br_2/FeCl_3$; (c) *i*.*t*-BuLi; *ii*.$ClCO_2Me$; (d) *i*.NaOH, reflux; *ii*.$SOCl_2$, reflux; (e) RNH_2/Et_3N

Scheme 1.13 Synthetic pathway to hexasubstituted benzenes from phloroglucinol

In 2003, Biali and coworkers used 1,3,5-tribenzoyloxybenzene **32** as a starting material to synthesize compound **33** as shown in **Scheme 1.14**.[28] The triester **32** was rearranged and protected the phenolic hydroxyl by methylation. The three carbonyls were then reduced to methylenes in two-step sequence.



Scheme 1.14 Synthetic pathways to hexasubstituted benzene from 1,3,5-tribenzoyloxybenzene **32**

1.4 Applications

The applications of the 1,3,5-trisubstituted-2,4,6-triethylbenzene scaffold in supramolecular chemistry has emerged rapidly. Several receptor molecules for cationic, anionic and other guests have been designed by placing various binding groups around the benzene ring. The detail of each category is presented as follow:

1.4.1 Cationic Receptors

Raymond's group took advantage of the structural feature of this scaffold to predispose three catechol units around the benzene core to create a tripodal ligand **34** for the Fe(III) cation (**Figure 1.8**).[29] After having synthesized the respective 1,3,5-tris(catechol)benzene and mesitylene, the perfectly preoganized receptor **34** exhibited superior complexation properties compared to the previously studied receptors. The binding constant of **34** for Fe(III) even exceeded that of the natural compound enderobactin **35**, a siderophore with a uniquely strong binding affinity towards Fe(III). Other inorganic complexes have been explored using this benzene motif. By using 1,3,5-tris(pyrazol-1-ylmethyl)-2,4,6-triethylbenzene **36** as ligand for Pd(II), Hartshorn and Steel reported the spontaneous formation of the highly symmetric, ten-component metallosupramolecular cage.[30] It consists of six trans-dichloropalladium units that are arranged in psudo-octahedral array and are bridged by four pyrazol ligands. Kim and Ahn's group applied the cation coordination properties of these benzene-based ligands for selectively sensing NH_4^+ and alkylammonium cations. Ion selective electrodes (ISE) using the immobilized tris(pyrazole)benzene **37** responded to NH_4^+ over Na^+ and K^+ by a selectivity factor of nearly 5, working in a concentration range between 10^{-4} and 10^{-1} M.[31] Ahn and co-workers also studied the complexation of different alkylammonium caions by tris-oxazoline benzene in chloroform. The ligand **38** and **39** displayed a high selectivity for *n*-$BuNH_3^+$ with association constants of $10^{2.7}$ and 10^4, respectively.[32]

As a model compound for bio-inorganic systems,[33] Saak and coworkers prepared complex from **40** with Fe_4S_4 clusters. The tris-thiol ligand proved to be perfectly preorganized and rigid enough to create isolated 3:1 subsite-differentiated clusters.[34] The tridentate ligand **41** forms trinuclear complexes with Cu(I) in which the Cu center are kept on the same side of the central benzene plane. Electrochemical studies showed the separate transfer of three electrons from each Cu cation.[35]

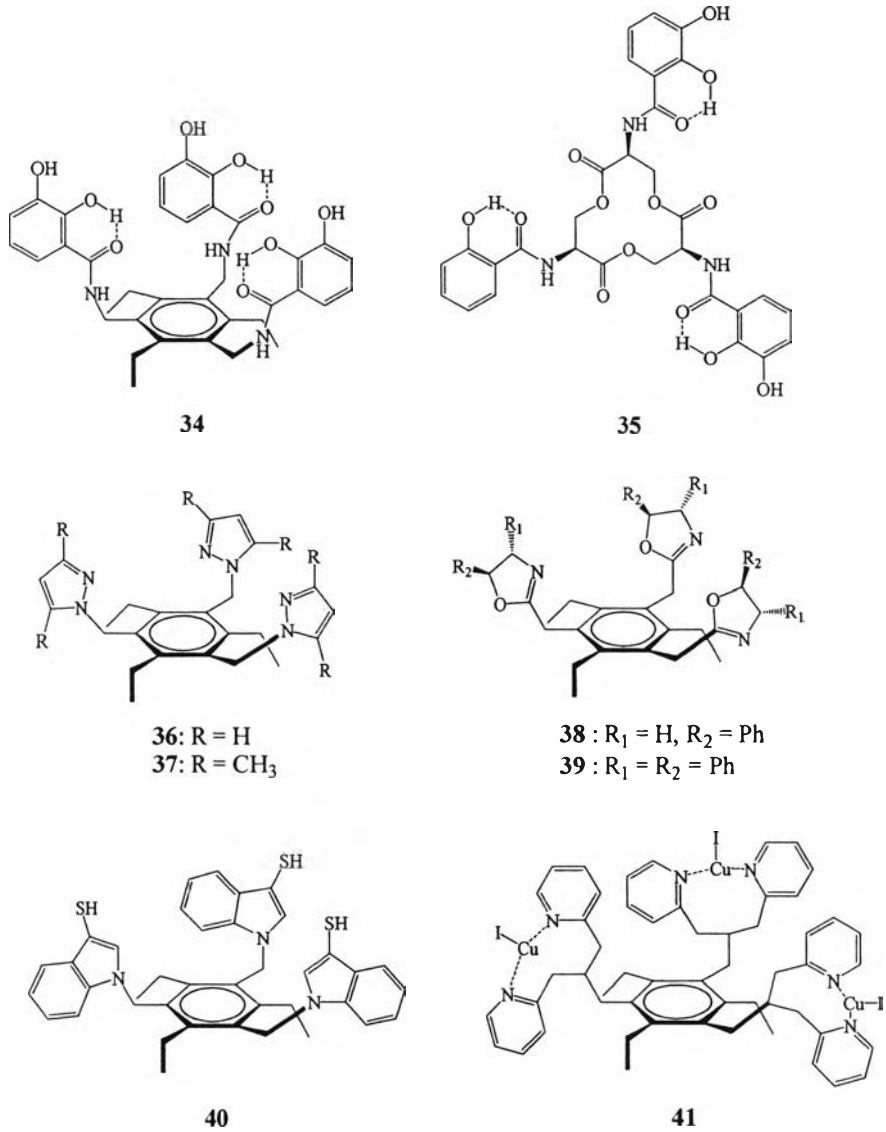


Figure 1.8 1,3,5-Trisubstitued-2,4,6-triethylbenzene **34, 36-41** for the complexation of cationic species

1.4.2 Anionic Receptors

In Anslyn's group, 1,3,5-trisubstituted triethylbenzene derivatives have been extensively explored as receptors for polyfunctional, biorelevent, anionic guest molecules. Different functional groups are predisposed around the benzene core to match with the functionalities and geometries given by the targeted guest. Receptor **42** has been prepare to bind citrate ion selectively over other similar carboxylate ion in D_2O with a binding constant of $6.9x10^3$ M^{-1} (**Figure 1.9**).[22] By employing a colorimetric competition essay method, a chemosensor was established using **42**, that was able to quantify the amount of citrate in various commercially available beverages.[36] In their competition essay, an indicator dye bind to the receptor and is

displaced by a stronger binding guest molecule. As a consequence, the indicator's microenvironment is changed as it is release from the host into the solution, which affects its UV/Vis or fluorescence spectroscopic properties. The same competition assay method proved that the bowl shaped host **43** bound inositol triphosphate in buffered water with a binding constant of $2.2x10^4$ M^{-1}, while conceivable competing substances showed significantly lower binding affinities. In this case, the binding of the different guests was monitored by fluorescence spectroscopy.[37] Addressing the same type of guests, they synthesized aza-calixarene **44** that forms a large cavity. Again, in a fluorimetric competition assay, selective binding of inositol triphosphate ($K_a = 2.4x10^5$ M^{-1}) and fructose-1,6-diphosphate ($K_a = 25.0x10^4$ M^{-1}) was obtained in aqueous solution.[38] Similarly, the use of a dye displacement assay with the tris-boronic acid receptor **45** revealed selective binding of glucose-6-phosphate over glucose and phosphate in 30% water/methanol.[39]

The mono-Boc protection of 1,3,5-tris(aminomethyl)2,4,6-triethylbenzene **25** has been used as a starting material for several receptors. This gives access to triethylbenzene with different functional groups in the 1,3-versus 5-positions. Tartate and malate bound to the imidazolinium portions of receptor **46** through their carboxyl groups and additionally to the boronic acid side with the hydroxyl functions. Receptor **46** was used in a chemosensor ensemble to measure the amount of tartaric acid and malic acid in wine at high accuracy.[40] The metalloreceptor **47** functioned as a fluorescent sensor for citrate which coordinated to both imidazolinium groups and the Cu(II) center.[41]

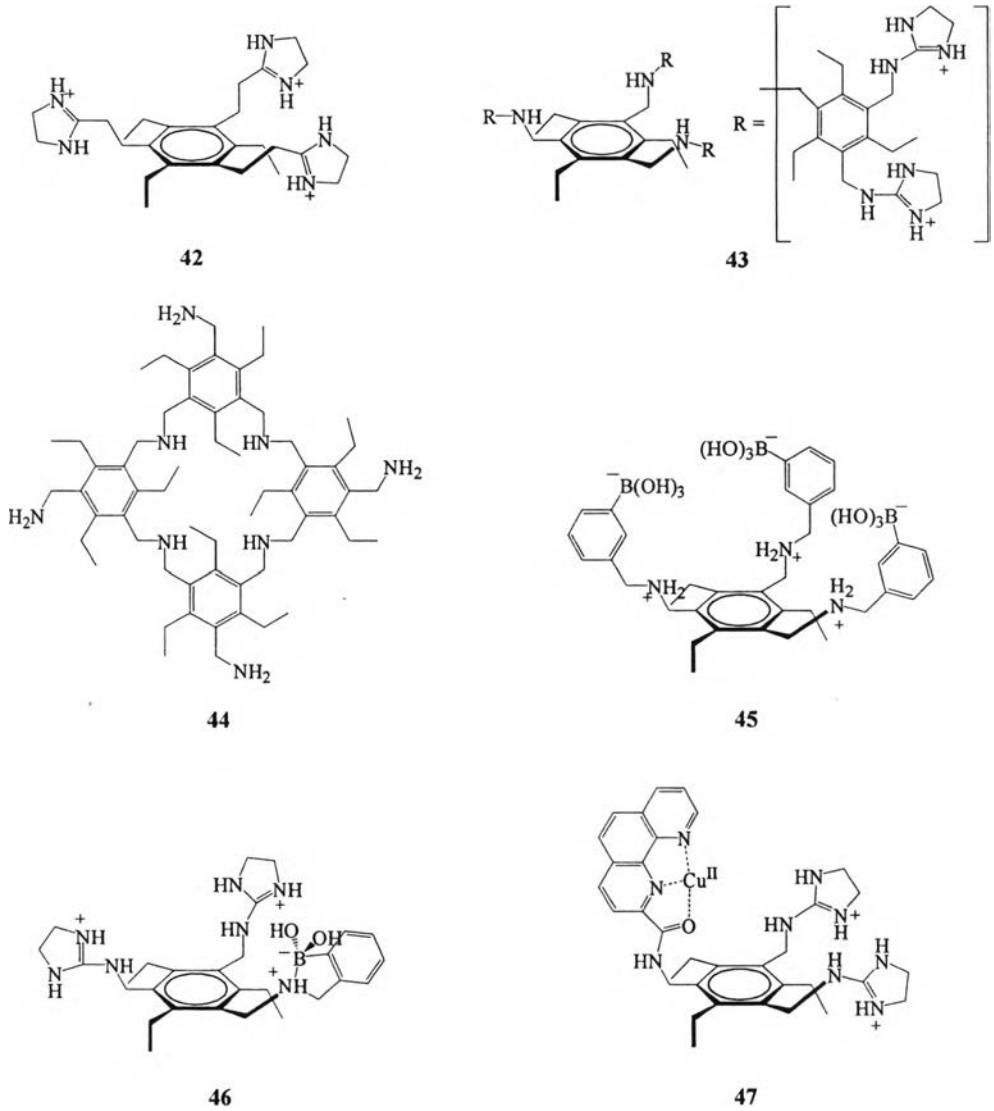
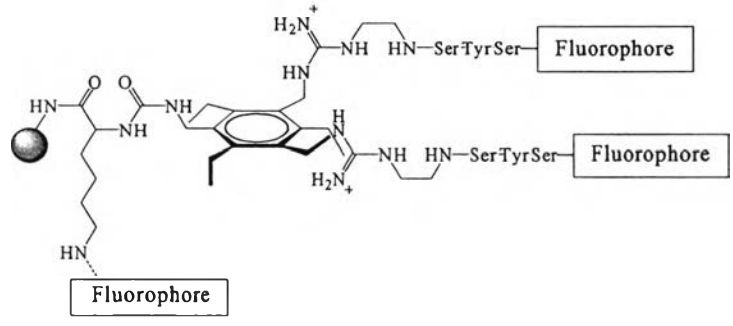


Figure 1.9 1,3,5-Trisubstituted-2,4,6-triethylbenzene based receptors **42-47** for biorelevant anionic guests

A different approach to analyte sensing was taken by attaching two tripeptide side arms onto the benzene scaffold bound to a resin (**Figure 1.10**). On the solid support, a library of approximately 3600 receptors with different peptide side arms was scanned by looking for a fluorescence respond in the presence of fluorophore-labeled ATP (adenosine triphosphate). The ATP was found to bind cooperatively to Ser-Tyr-Ser peptide arms and the guanidinium functions of **48**. The fluorescence receptor system **48** was synthesized by attaching fluorescent and end groups to the Ser-Tyr-Ser peptide arms, which displayed the best selectivity and sensitivity among all tripeptides. Hence, a sensor ensemble was obtained that could distinguished

between ATP, AMP, and GTP, with only ATP inducing a 1.5-fold fluorescence enhancement upon binding.[42]



48

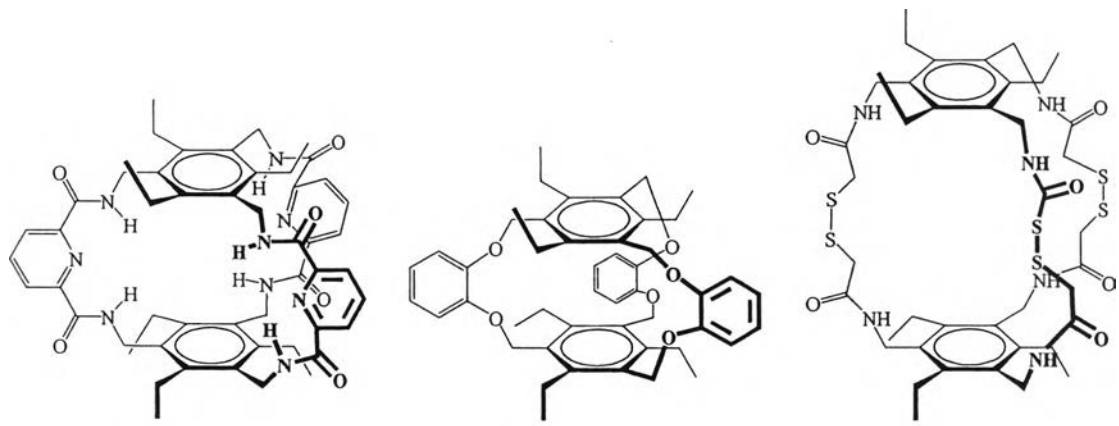
Figure 1.10 ATP-selective resin bound chemosensor ensemble

1.4.3 Cage Molecules

The preorganization of functional groups around the benzene ring makes the 1,3,5-substituted triethylbenzene scaffold a valuable building block in the synthesis of macrocycles. The known difficulties in the syntheses of such compounds can be overcome by arranging the reactive centers in a way that forces the closure of the desired ring system. Taking advantage of the predisposed NH_2 functionalities in the tris-amine **25**, compound **49** was obtained in 40% yield under mild conditions in a one-step reaction using **25** and pyridine-2,6-dicarbonyl dichloride (**Figure 1.11**).[43] Anslyn and coworkers reported the synthesis of the bicyclic cyclophane **49** and its abilities of forming defined inclusion complexes with nitrate and acetate anion. In a dye displacement assay, **49** has been employed in the optical sensing of inorganic anions.[44] Further, by encapsulstion of various enolates into the cavity of **49**, they were able to estimate the contribution of NH-π bonding versus hydrogen bonding to the nitrogen lone pair electron in the deprotonation of CH-acidic compounds.[45]

Kim and coworkers investigated the binding properties of **50** for NH_4^+, Na^+ and K^+ (**Figure 1.11**).[46] The selective ammonium binding turned out to be partially the result of a cooperative cation-π interaction within the receptor's cavity. Moreover, **50** was incorporated into ISE membrane to build a cation sensing device. The steric gearing induced by the benzene scaffold also lead to the macrocycle **51** in good yields.[47] Eventhough the formation of three disulfide bridges in the molecular assembly is disfavored in term of enthalpy due to the torsion angle strain, the dimeric compound **51** self-assembled from two equal monomers carrying terminal thiol

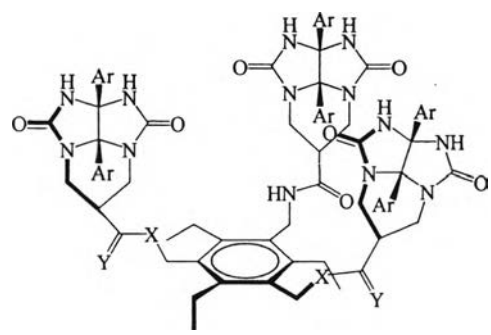
functions. Under equilibrium conditions, **51** was present in solution together with the monomeric tris-thiols and an oligomeric adduct.



49 **50** **51**

Figure 1.11 Macrobicyclic compounds for anion **49**, cation sensing **50** and from self-assembled formation into **51**.

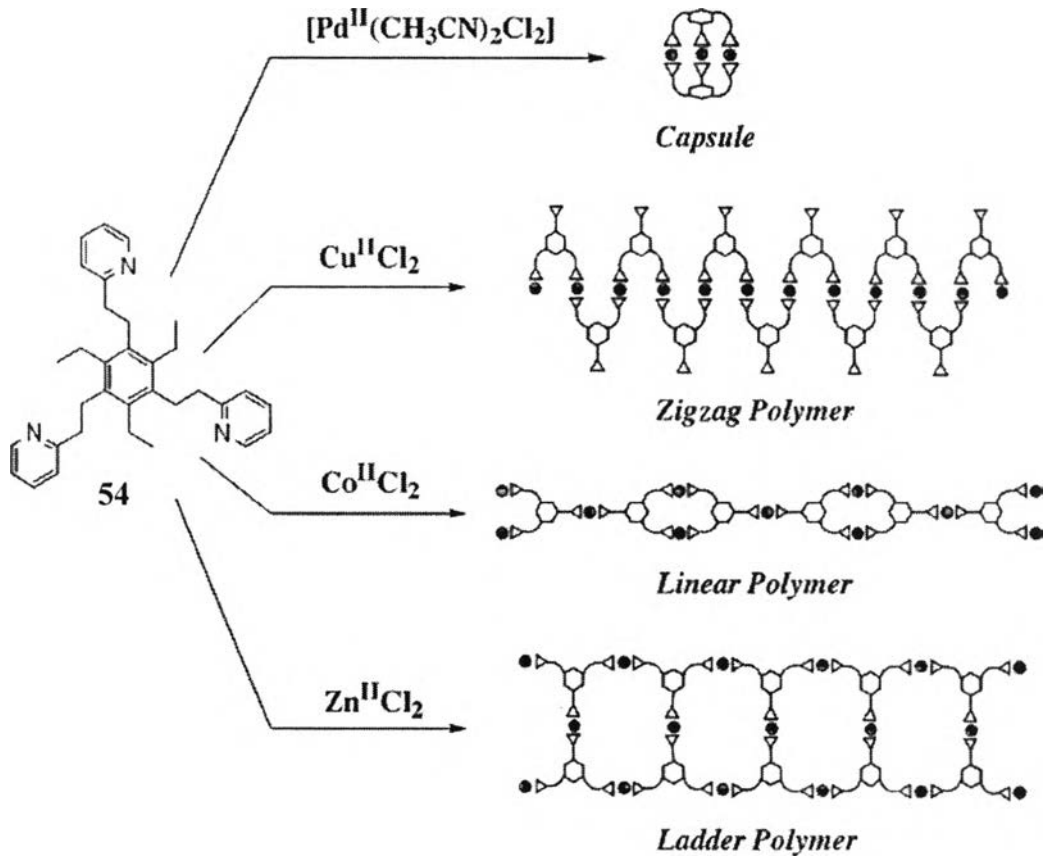
Rebek and coworkers took adventage of the predisposition of three glycoluril groups around 1,3,5-trisubstituted triethylbenzenes to achieve the formation of dimeric, hydrogen-bonded capsules.[48,49] The supramolecular assemblies formed by the two complementary "half-bowl" monomers **52** and **53** are capable, according to the size of the cavities and the guest molecules, of encapsulating and re-release the guest reversibly (**Figure 1.12**).



52 : X = NH, Y = C(O)
53 : X = C(O), Y = NH

Figure 1.12 Monomers **52** and **53** that self-assembled into dimeric capsules

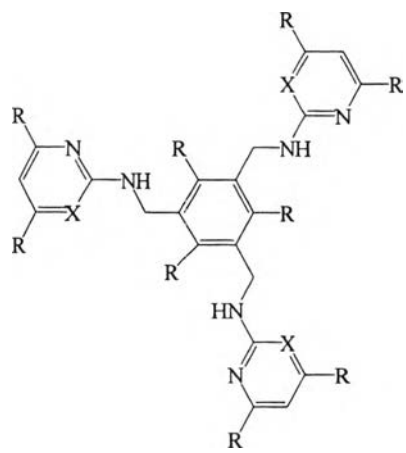
In 2004, Itoh and coworkers combined a tripodal tripyridine ligand containing a 1,3,5-triethylbenzene spacer **54** with several divalent transition metal chlorides, to obtain a variety of complexes exhibiting totally different structures. They have prepared capsule-type supramolecular complexes with zigzag polymer chain, linear polymer chain and ladder polymer chain structures (**Scheme 1.15**).[50] All structures were established in detail by single crystal X-ray diffraction analysis. The factors inducing the structural differences among the complexes are discussed by taking account of the differences in coordination geometry (square planar versus tetrahedral) as well as metal ligand binding strength in the complexes.

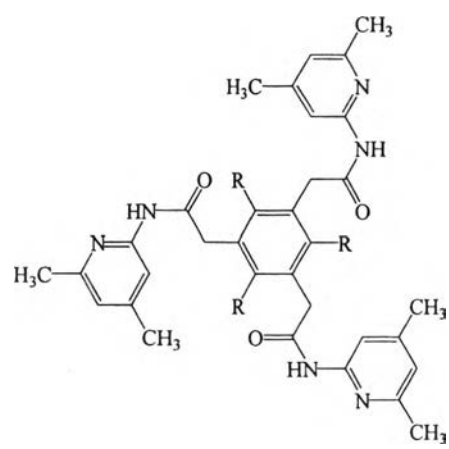


Scheme 1.15 The one-dimension (1D) coordination polymer complexes from tripodal tripyridine ligands containing a 1,3,5-triethylbenzene spacer **54**

1.4.4 Molecular Receptors

The tripodal receptor for molecular recognition of carbohydrates, especially monosaccharide, is an actively investigated topic in bioorganic chemistry. The prototypical host features a 1,3,5-trisubstituted triethylbenzene scaffold bearing three convergent H-bonding units. Mazik and coworkers, systematic studies toward recognition motifs for carbohydrates showed that aminopyridines, aminopyrimidine and amidopyridines provided an excellent structural motif for binding carbohydrates, associated with the ability to form cooperative and bidentate hydrogen bonds with the sugar OH groups. Aminopyridine receptors based on a trimethylbenzene **55**, triethylbenzene frame **56** and trimethylaminopyrimidine **57** showed high β versus α-anomer binding selectivity in the recognition of glucopyranosides (**Figure 1.13**).[51] Amidopyridine receptors **58** and **59** displayed high efficiency and an inverse selectivity in favor of α-anomer. The possible binding modes between the acyclic receptors and monosaccharides were analyzed on the basis of chemical shift changes in ^{1}H-NMR spectra and molecular modeling calculations.





55 : X = CH, R = CH_3

56 : X = CH, R = CH_2CH_3

57 : X = N, R = CH_3

58 : R = CH_3

59 : R = CH_2CH_3

Figure 1.13 The tripodal receptors for molecular recognition of monosaccharides

1.5 Objectives

The goal of this research is to improve the synthetic method of hexasubstituted benzene and functionalize the products to ligands. More specifically, the research is concentrated on functionalization of phloroglucinol (1,3,5-trihydroxybenzene) platform. The approach is based upon the assumption that the easily accessible triple O-substituted intermediates could rearrange to yield the desired hexasubstituted benzene scaffold, ready to be functionalized to tridentate ligands. Objectives of this research can be summarized as follows:

1. To synthesize hexasubstituted benzene derivatives from phloroglucinol with various electrophiles such as acid chlorides, alkyl halides.
2. To functionalize the synthesized hexasubstituted benzene by adding the binding sites to tridentate ligands.