STEREO-SELECTIVE SYNTHESIS OF BIS-BRIDGED CALIX[6]ARENES

THESIS

Presented to the Graduate Council of
Southwest Texas State University
In Partial Fulfillment of the Requirements

For the Degree

Master of Science

By

Sara J. Staggs, B.S.

San Marcos, Texas
May 2003

ACKNOWLEDGEMENTS

I would like to thank my family and friends for supporting me through the past two years of this eventful learning experience.

I am blessed to have the opportunity to have Dr. Blanda as a mentor and teacher. I have been challenged to be the best I can be and I am forever grateful.

I treasure the time spent with the close-knit group of the SWT Chemistry and Biochemistry graduate students. We have definitely been there for each other.

I would also like to thank the department as a whole for the rewarding experience I have received throughout my graduate career.

This manuscript was submitted May 2003.

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ABSTRACT

Stereo-Selective Synthesis of Bis-bridged Calix[6]arenes

Thesis Supervisor: Dr. Michael T. Blanda, Associate Professor

In recent years, there has been a growing interest in the rational design of synthetic catalysts capable of achieving significant enhancement of reaction rates and stereo-selectivities. Ideally, a new catalyst would mimic highly efficient biological catalysts such as enzymes. In order to achieve this goal, the synthetic catalyst system would need to be constructed so to as complement the size, shape and charge of the specific substrate and/or metal ion that would be required in a particular reaction. This can be accomplished primarily through supramolecular interactions that involve hydrogen bonding, Van der Waals forces, electrostatic interactions, and ion-dipole to interact with the substrate and metal ion to form a complex. Calixarenes have certain structural features analogous to enzymes, which include a well-defined cavity for host-guest complex interactions, and potential for structural variation.

Research conducted in the Blanda group has focused on the synthesis of new, rigid calix[6]arenes that have the potential to function as

enzyme mimics. The synthetic protocol generally calls for the rigidification of the calix[6]arene via synthesis of a bis-bridged calix[6]arene. The development of a stereo-selective synthetic strategy has allowed the synthesis of two distinct conformational isomers of the bis-bridged calix[6]arene. Structural characterization of each isomer was derived by NMR spectroscopy and X-ray crystallography. During the NMR characterization the discovery of a ^{13}C rule emerged which allowed for rapid and reliable structural assignment in solution.

1.0 INTRODUCTION

1.1 Calix[6]arenes

Calix[6]arenes are macromolecules which are synthesized by a base-catalyzed condensation reaction between *tert*-butyl-phenol and formaldehyde using a Rb^+ ion as a template for the cyclization.[1]

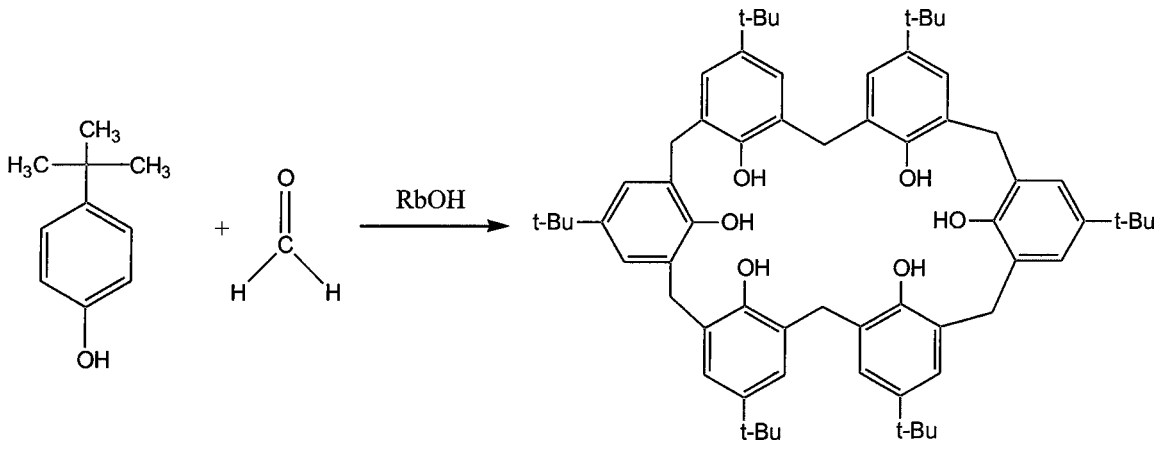


Figure 1.1 Synthesis of Calix[6]arene.

The name calixarene was coined by Dr. David Gustche meaning vase or chalice composed of aryl rings.[2] The cavity developed by the macrocycle is a potential binding site for either cations, anions or neutral guests. The cavity of a calix[6]arene is larger than that of the smaller calix[4]arene, which can house larger guest molecules in the cavity.[3-5] The guest that complexes with the calix[6]arene host would have to have

complementary shape, size and polarity with the cavity. The cavity can be selectively tailored for a specific design using the upper and lower rim of the calix[6]arene. Calix[6]arenes have a characteristic upper ring and lower ring on the chalice that can be functionalized for selective host/guest interactions. The upper ring of the calix[6]arene usually has t-butyl groups residing, but these groups can be removed and new groups can be added or left as hydrogen depending on the type of functionalization desired. The lower rim is composed of hydroxyl groups from each phenol residue which can be functionalized via bridging linkers (across the annulus), monofunctional groups, or capping moieties. There are numerous possibilities with the functionalization of the rims of the calix[6]arene.

1.2 Conformation Mobilility

The parent calix[6]arenes are conformationaly mobile which is characterized by the phenolic residues rotation through the annulus.[6] A result of this flexibility is that the binding affinity of a host to a guest is decreased, due to the rearrangement of the calix[6]arene in solution. This movement does not allow for selective binding to the calix[6]arene. The phenolic residue is composed of an aromatic ring with a t-butyl group *para* to a hydroxyl group. These two substituents can rotate through the annulus of the calix[6]arene. The sister compound, calix[4]arene is composed of 4 phenolic residues which only allows the hydroxyl group to rotate through the annulus and can be rigidified by functionalization of the

lower rim.[2] The lack of rotation and aromatic residues of the calix[4]arene offer less conformations of the molecule to be formed. The calix[6]arene is larger and has more potential conformations that can be tailored via selected synthetic strategies.

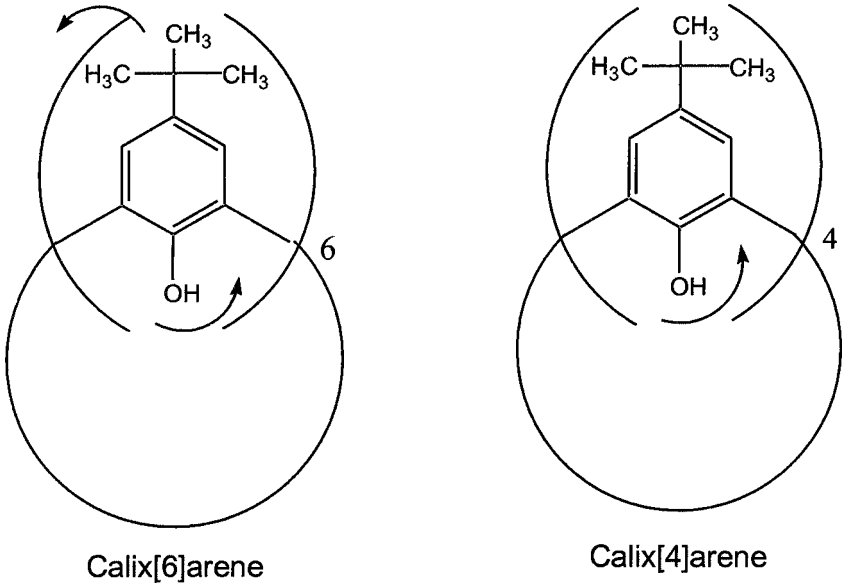


Figure 1.2 Ring mobility of Calixarene.

The more flexible larger calix[6]arene molecule is an incentive for the discovery of selective synthesis of individual conformations. There are 12 different conformations of the calix[6]arene. The placement of the hydroxyl groups in relation to the upper and lower rim of the molecule constitutes a different conformation. The mobility of the molecule allows for the formation of each of the isomers although some are seen more than others.

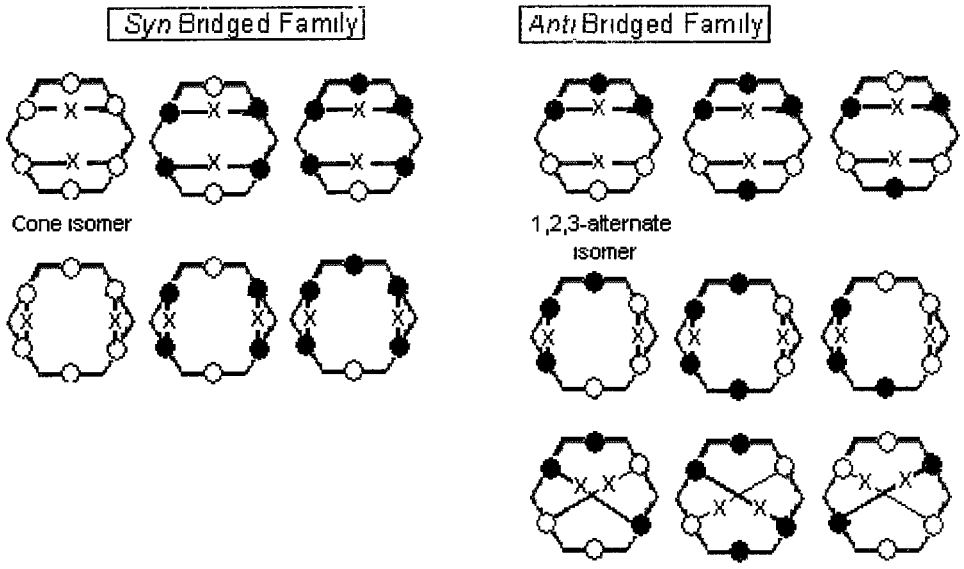


Figure1.3 Conformations of Calix[6]arene.

The 15 isomeric conformations shown above are the *syn* and the *anti* family which contain the most studied conformations; cone and 1,2,3-alternate, respectively. There are different 15 orientations that these isomers can have although the structure of each is very similar. The syn isomer has all four of the internal hydroxyl groups facing in the same direction and the outer hydroxyl groups can alternate. The *anti* isomer has the two bridges on opposite sides of the calix[6]arene, unlike the *syn* family. The two major isomers synthesized are the cone and the 1,2,3-alternate with are illustrated in figure 1.5.

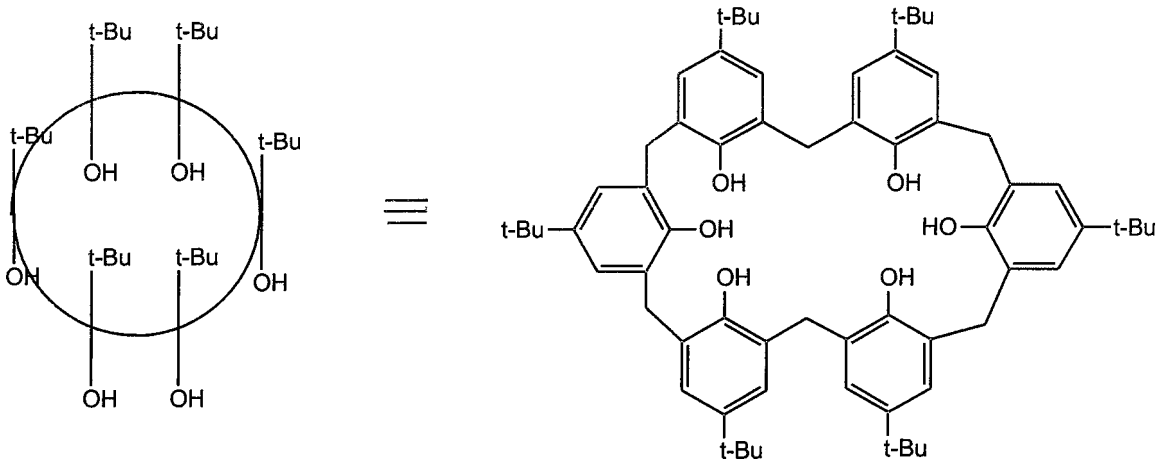
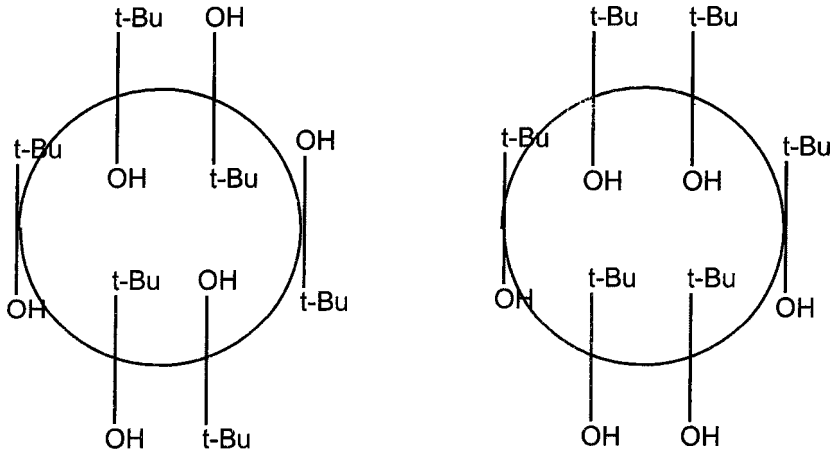


Figure 1.4 Calix[6]arene is represented as a cartoon.

The cartoon representation of the calix[6]arene can be for the cone or 1,2,3,-alternate configuration. Figure 1.5 demonstrates the use of the cartoon representation.



1,2,3-Alternate Conformation Cone Conformation

Figure 1.5 Conformational Isomers.

The other potential conformations shown in figure 1.3 are rarely synthesized. The cone and 1,2,3-alternate are usually the conformations

that are found in synthesis. Synthesizing the desired isomer is a hurdle that could become less significant with a selective synthesis of the calix[6]arene. Choosing the specific isomer would be regulated on the type of interaction with the guest that the host will be seeking. The syntheses of specific conformations are due to the specific experimental conditions that are modified such as temperature, solvent polarity, or alkylation of the hydroxyl groups.[7]

1.3 Conformationally Immobile Calix[6]arenes

To construct a conformationally immobile or rigid calix[6]arene the hydroxyl groups need to be functionalized with bulky groups large enough to hinder C-C rotations. When the calix[6]arene is rigidified there is a higher affinity for the guest as a result of preorganization of the binding site. Achieving an immobile calix[6]arene is difficult so chemists have looked at the sister molecule calix[4]arenes.[8] Calix[4]arenes are not as flexible as calix[6]arenes because of the smaller annulus. The knowledge gained from calix[4]arene has given the research a starting place to begin the laborious task of rigidifying the calix[6]arene. The interconversions of the calix[4]arene are due to only the hydroxyl groups. The annulus of the calix[4]arene is too small for the bulky t-butyl groups to rotate through. To rigidify the calix[4]arenes large bulky groups are added onto the hydroxyl groups hindering the rotation through the annulus.[2,9] Unlike the calix[4]arene, the calix[6]arene has a larger annulus due to the two more

phenolic residues. This structural difference causes the calix[6]arene to have an increased amount of flexibility than observed by the calix[4]arene. This causes it to be more difficult to rigidify calix[6]arene in a certain conformation by functionalizing the lower rim, because of the upper rim rotation through the annulus.[10] Although the process is more difficult than the smaller calix[4]arene where the upper rim does not rotate through the annulus, chemists have found good techniques for rigidifying the lower rim of calix[6]arene. Many years of research has been put into the calix[4]arene molecule and the techniques work. The calix[6]arene is a sister molecule to the calix[4]arene, as a result some of the same concepts hold true with the rigidification of the molecule. There are different intramolecular methods to rigidify the macrocycle such as incorporating a single-strap, the use of capping groups, or bis-bridging across the annulus of the calix[6]arene.

1.3.1 Monostrapping of Calix[6]arene

The use of monostrapping across the calix[6]arene annulus rigidifies the flexible macrocycle and allows for a complementary binding site for selected guest. The technique of monostrapping utilizes two phenolic residues from the calix[6]arene in the mono-bridging across the annulus via a tethering moiety.

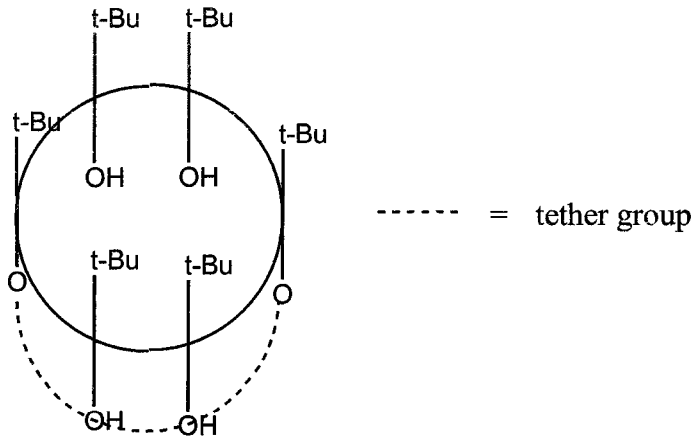


Figure1.6 Monostrapping across the annulus.

The other four phenolic residues could be left as hydroxyl groups or altered in some other way to help with the immobilization. Different research groups have developed or discovered unique techniques. The results of Okazaki *et al.* indicated that the parent calix[6]arene can be bridged by a *m*-xylenyl unit without altering its cone conformation which is stabilized by a network of hydrogen bonds between the hydroxyl groups.[11] This demonstrates that the monostrap across the annulus helped to rigidify the macrocylce, but did not disturb the hydrogen bonding characteristic. The use of a single poly-ether bridge along with alkylating the remaining phenol hydroxyl groups with large bulky moieties is used as an alternative strategy aimed at reducing the conformational flexibility of a calix[6]arene.[5] Monostrapping is also a mode for conducting polymeric self-assembly. A phthaloyl residue links two adjacent hydroxyl groups of a calix[6]arene. The phthaloyl hydrogen atoms interact with the aromatic π

clouds of an adjacent calix[6]arene basket and the hydrogen atoms of the methyl groups of the adjacent calix[6]arene interact with the π electrons from the phthaloyl group.[12] With these interactions of the calix[6]arene align themselves. The technique of linking across the annulus was also researched by Luning *et al.* The group conducted experiments synthesizing rigid monostrapped calix[6]arenes with a functional linker such as a pyridine moiety.[13] The tether was held in a cone, 1,2,3-alternate, and partial cone positions where the strap could link the upper rim to the lower rim.

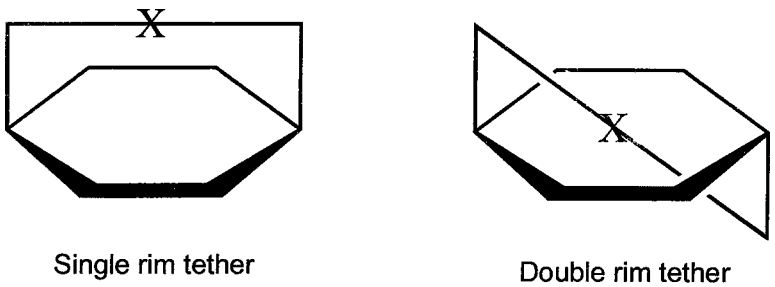


Figure 1.7 The conformational tether positions for Luning *et al.*

Despite the fact that the pyridine tether was held in different isomeric configurations the molecule was more conformationally immobile with the preorganization of the monostrap. These experiments illustrate the apparent need for a selective synthesis of a rigid calix[6]arene in order to synthesize one isomer. The monostrapping technique donates less

flexibility to the calix[6]arene, but not full structural rigidity which led to other studies.

1.3.2 Capping the Calix[6]arene

The technique of capping incorporates a link between more than two of the phenolic residues. The linker is called a cap because it can resemble a hat on the calix[6]arene. The research of calix[4]arene usually has some impact on the recent studies of calix[6]arene. The capping of the calix[4]arene via the upper and lower rim with simple aromatic moieties, polyoxyethylene glycol, or alkyl chains result in an increase of immobilization of the molecule.[14] This knowledge leads to the potential of the calix[6]arene to be capped with larger capping moieties thus becoming more rigid.

The capping of the calix[6]arene causes complete rigidification which results in no interconversions of the phenolic residues via rotation through the annulus. The moieties chosen to be the capping agent are usually multi-functional. This allows the molecule to have multiple points of reaction with the calix[6]arene thus forming a true bowl shape for the cone conformation. The 1,2,3,-alternate isomer causes the capping compound to lay within the annulus to reach the opposite rims hydroxyl groups for connection as shown in figure 1.7. Either isomeric configuration the calix[6]arene offers rigidification of the ring.

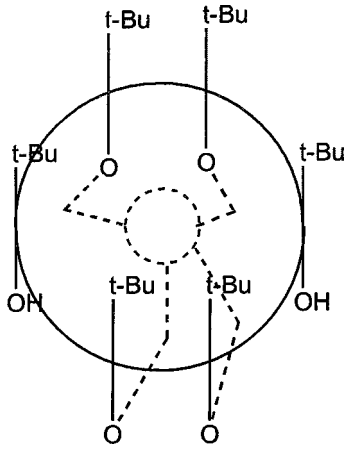


Figure 1.8 Schematic example of a moiety capping the calix[6]arene.

Otsuka *et al.* stopped the rotation of the rings via capping a calix[6]arene with a tri-alkylating xylene unit. The capping incorporated itself with the upper and lower rim of the macrocycle via esterification.[15] When the calix[6]arene is rigid it proves to make a good binding site. Through NMR and extraction studies Otsuka's group found their capped calix[6]arene to be a good binding site for Cs^+ and Ag^+. Kim *et al.* has synthesized a quadruple attachment at the lower rim which immobilizes the calix[6]arene to an even greater extent than the tri-alkylated attachment.[6] Capping across the annulus has proven to be a good tool for complete immobility of the flimsy calix[6]arene. Although having a range immobilization offers many advantages such as a more specific binding site for a particular guest, which led to the studies of bis-bridged calix[6]arenes.

1.3.3 Bis-Bridging Calix[6]arenes

The monostrap offered a degree of flexibility when in place while the capping tether offered no mobility to the once flexible calix[6]arene. The calix[4]arenes have utilized bis-bridging for a state of less conformational mobility and the logical experiments to follow were the calix[6]arenes using the same techniques. Bis-bridging of the calix[6]arenes is an effective way of immobilizing the macrocycle.[16-18] Bis-bridging calix[6]arenes is a technique that involves the connection of four phenolic residues via a bridging linker. The bridging of the macrocycle can result in two main families with twelve possible isomers. The most common conformations are cone and 1,2,3,-alternate shown below. The specific isomers are shown in figure 1.3.

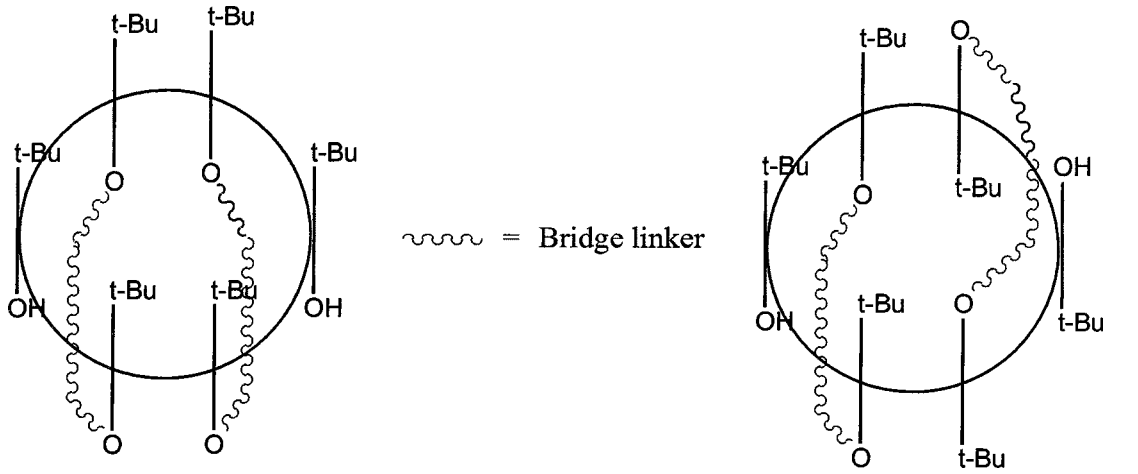


Figure1.9 General bis-bridged calix[6]arene.

The calix[6]arene has increased rigidity and has less flexibility as a result of bridging due to restricted ring interconversions. The macrocycle is still flexible enough to allow a guest molecule to be exchanged from the cavity. The bridging linkers may be composed of different types such as flexible crown ethers, and rigid aromatic moieties. Calixcrowns posses a well defined preorganized structure and rigid binding sites; they exhibit superior recognition ability toward alkali metal ions and other ions by the co-operation effect of calixarene and crown moieties.[19] Blanda *et al.* surveyed two bis-crown stereoisomers with cone and 1,2,3-alternate conformations. Binding studies were conducted with the alkali metal cations and it was found that the cavity had the highest affinity for Cs^+. [20]

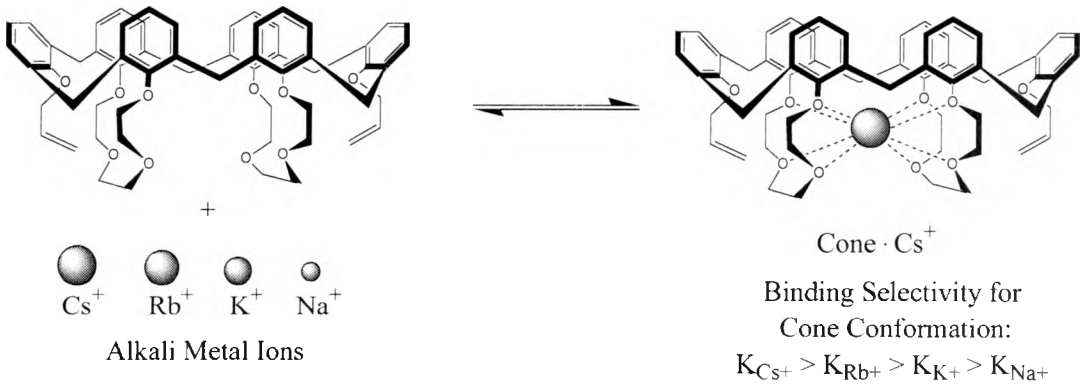


Figure 1.10 Metal binding study for bis-bridged calix[6]arene crowns.

Bis-bridging to a flexible calix[6]arene adds structural stability and functionalization to the molecule. The synthesis of the bis-bridged structure is crucial to forming the desired the final product. The

calix[4]arene family has been extensively studied to achieve the selective synthesis of the final product.[2] The tailoring of the molecules allows for more planned preorganization. The calix[4]arene has been functionalized via bis-bridging with crown ether resulting in the four possible conformational isomers; cone, partial cone, 1,2-alternate, and 1,3-alternate.[21-24] The resemblance of the four available groups in the two molecules (A, B, C, D calix[4]arene and B, C, E, F calix[6]arene) demonstrate the that similar methodology can be used in bis-bridging. These linking techniques can be used to functionalize the four empty hydroxyl groups rings B, C, E, and F.

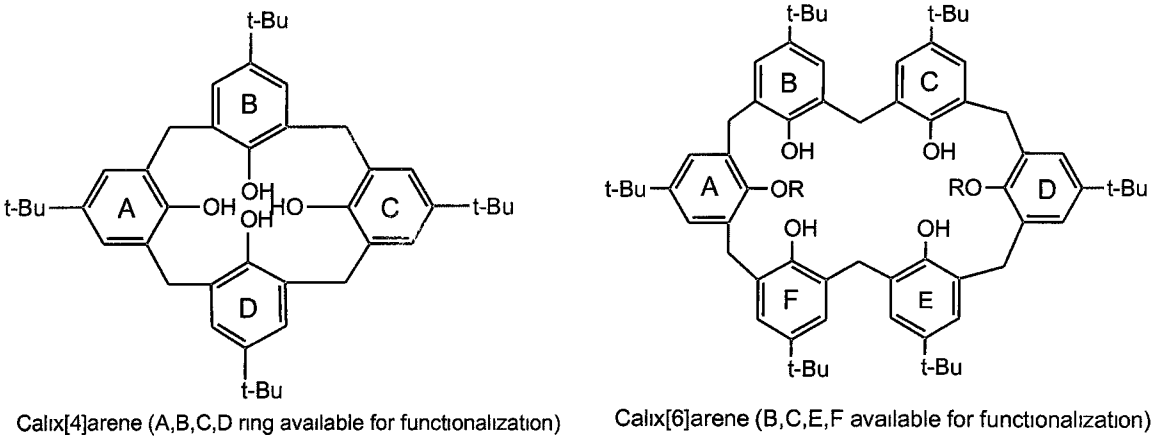


Figure 1.11 Similar positions of functionalization for calix[4]arene and calix[6]arene.

Most of the research conducted on the calix[6]arene has been focused on the rigidification of the molecule. Much less research has been conducted on the selective synthesis design to achieve rigidification of the flexible structures. The incorporation of the two ideals would result

in selectively rigidifying the calix[6]arene with potential functionality of the final product. Recent studies in the Blanda group have resulted in selectively synthesis of the cone or the 1,2,3,-alternate conformations by modifying the base and solvent conditions in the bridging reactions. The crown ether bridging units were replaced by aromatic species as the linking moiety in the bridging of the calix[6]arene. The addition of the aryl rings allows for numerous avenues of functionality. The aromatic rings can be preorganized to have a charge, a desired shape, or influence the size of the cavity by functionalization as a better binding site for a specific guest. Below are the designs of the cone and the 1,2,3-alternate isomers which can be selectively synthesized.

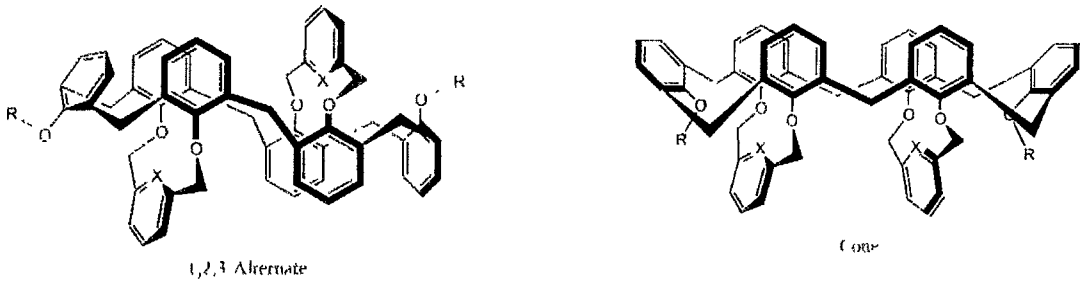


Figure 1.12 Aromatic Bis-bridged Calix[6]arenes.

Each bridging species would cause a different interaction with selected guest molecules. The limited flexibility of aromatic bis-bridges allow for a breathable cavity, which can complex or release a complementary guest in certain conditions. The methodology of using bis-bridging units to

functionally rigidify the calix[6]arene had provided comparable results to the monostrap and capping techniques. The choice of technique used for conformational immobility in the flexible calix[6]arene is dependant on the specific planned function of the compound.

2.0 SYNTHETIC STRATEGY

The synthesis of a *para*-t-butyl-calix[6]arene is well known and documented from Gutsche's research.[1] The large macrocycle of *para*-t-butyl-calix[6]arene is formed through a condensation reaction with t-butyl-phenol, paraformaldehyde and RbOH in specific molar ratio (.45 molar equivalents) via a metal template effect. The metal ion is thought to aid in the cyclization of the t-butyl phenol residues by bringing together the podands reactive sites in close proximity for the promotion of the base catalyzed condensation. The kinetic template effect synthesizes the product that is formed at the most rapid rate. This strategy minimizes polymerization, and maximizes cyclization because of the organization given to the reactants around the metal ion due to the attraction of partial charge. Generally the smaller the macrocyclic annulus the smaller the metal ion used for the template effect. The synthesis of calix[4]arene utilizes the Na^+ to form the annulus while the calix[6]arene utilizes the Rb^+, (See figure 2.1 for detailed reaction) and the larger calix[8]arene forms a hourglass shape around two K^+ metal cations.

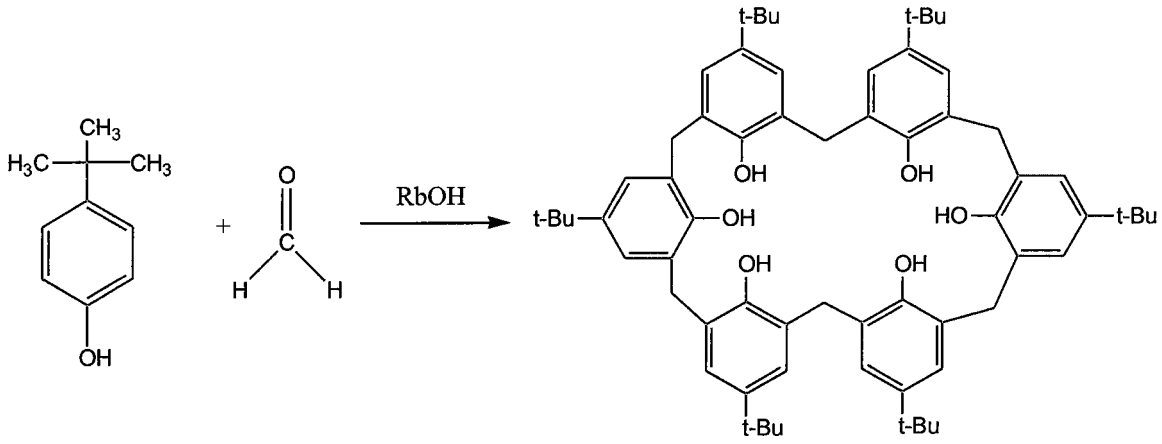
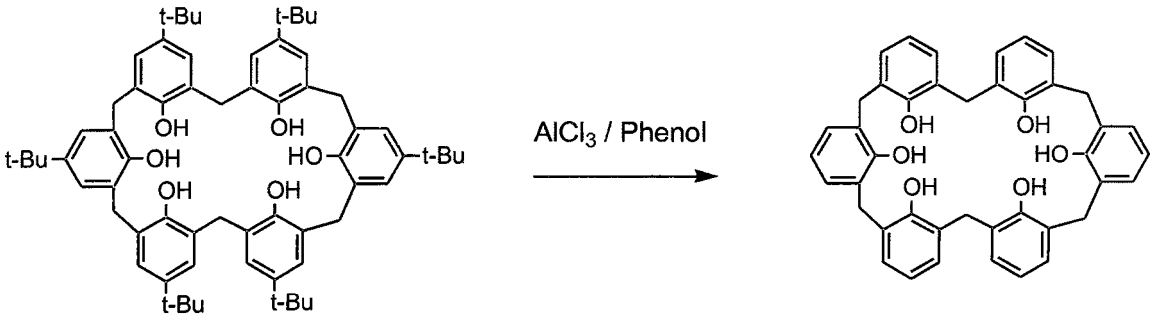


Figure 2.1 Synthesis of para-t-butyl-calix[6]arene.

The t-butyl groups are removed before further functionalization of the macrocycle through a reverse Friedels-Crafts alkylation using $AlCl_3$. The reaction conditions for dealkylating the t-butyl groups from calix[6]arenes are well researched and the structural properties have been documented. [1] The removal of the tert-butyl groups allow for an increase in the rate of rotation of the rings through the annulus, thus giving the dealkylated calix[6]arene more structural flexibility. Although this may seem to be a disadvantage, the scaffold is now available for functionalization on either the upper or lower rim of the phenolic residues which give the molecule more versatility.



Alkylated Calix[6]arene

Dealkylated Calix[6]arene

Figure 2.2 The dealkylation of t-butyl-calix[6]arene.

The methodology for selective functionalization is crucial to the outcome of the final compound. The six aromatic residues are designated as A-F rings. Figure 2.3 demonstrates the lettering scheme. Potentially each ring can be functionalized via the hydroxyl groups to form either an ester or ether linkage.

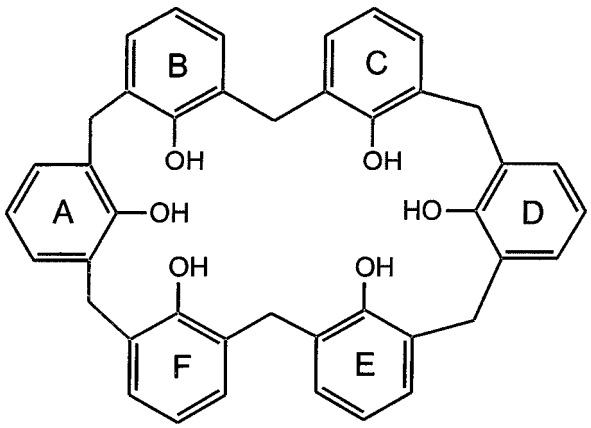


Figure 2.3 Relative position of the calix[6]arene A-F rings.

The calix[6]arene structure can be studied with more certainty when the compound is rigid. Rigidification also allows for better complexation of a guest base on the principle, preorganization. The strategy to synthesize rigidified calix[6]arenes is shown in the diagram below.

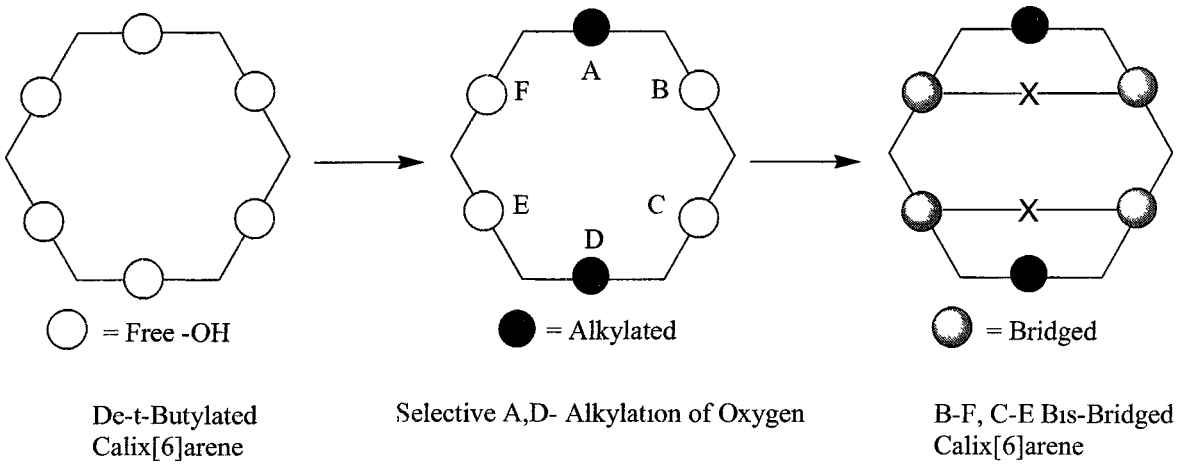


Figure 2.4 Strategy of calix[6]arene functionalization.

The A and the D rings are selectively functionalized with a diallyl group from the reaction with allylbromide and $K^+(CH_3)_3SiO^-$ resulting in a dialkylated calix[6]arene.[20] The A and D ring are selectively alkylated because of the need for stabilization of hydrogen bonds between the phenolate ion formed and the two flanking hydroxyl groups from the phenols. The first position of alkylation then becomes the A ring and the D ring alkylates in the same method.

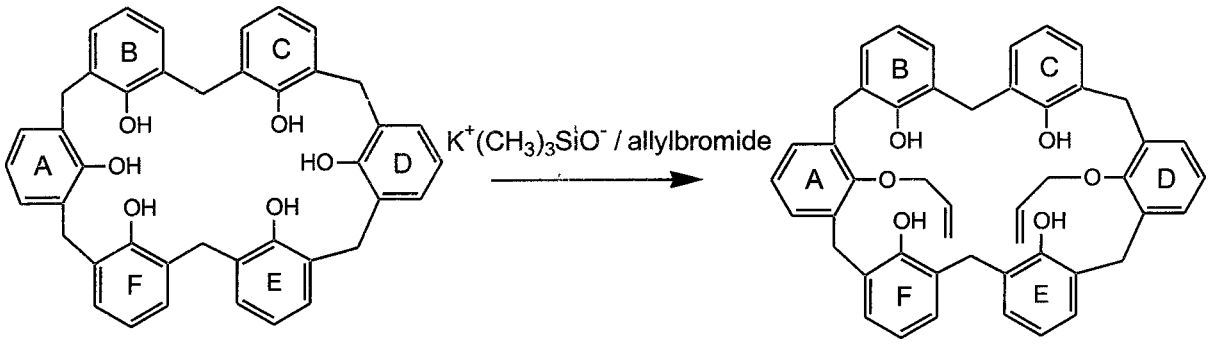


Figure 2.5 The synthesis of diallyl calix[6]arene.

The next step of the synthesis is to rigidify the ring through bridging the remaining four rings. The potential for bis-bridging at the B, C, E, and F aromatic residues on the scaffold gives rise to two distinct families; *syn* bridged and the *anti* bridged calix[6]arenes that contain a total of 18 isomers. The structure of the *syn* bis-bridged family has all four central (B,C,E, & F) rings facing in the same direction while the A and D rings can alternate facing the upper and lower rim. The *syn* family contains nine isomeric configurations of which three criss-cross isomers are negligible because of steric hinderance in the bis-bridged compounds. The *anti* bis-bridged family contains nine isomeric configurations which have the characteristic of one bridge facing toward the lower rim while the other bridge faces the upper rim so that the bridges are opposite or anti from each other. The A and D rings are also variable in the *anti* family just as they are in the *syn* family. Once the calix[6]arene is tethered via bis-bridged moieties the structure is locked into place and the rotation is restricted around the annulus which keeps the families separate. The

major isomers usually synthesized when bis-bridged are the 123-alternate (*anti* family) and the cone (*syn* family) calix[6]arenes. In figure 2.6 the hydroxyl groups are shown in the up position (white) or the down position (black) in relation to the macrocyclic annulus of the calix[6]arene which represent the two families.

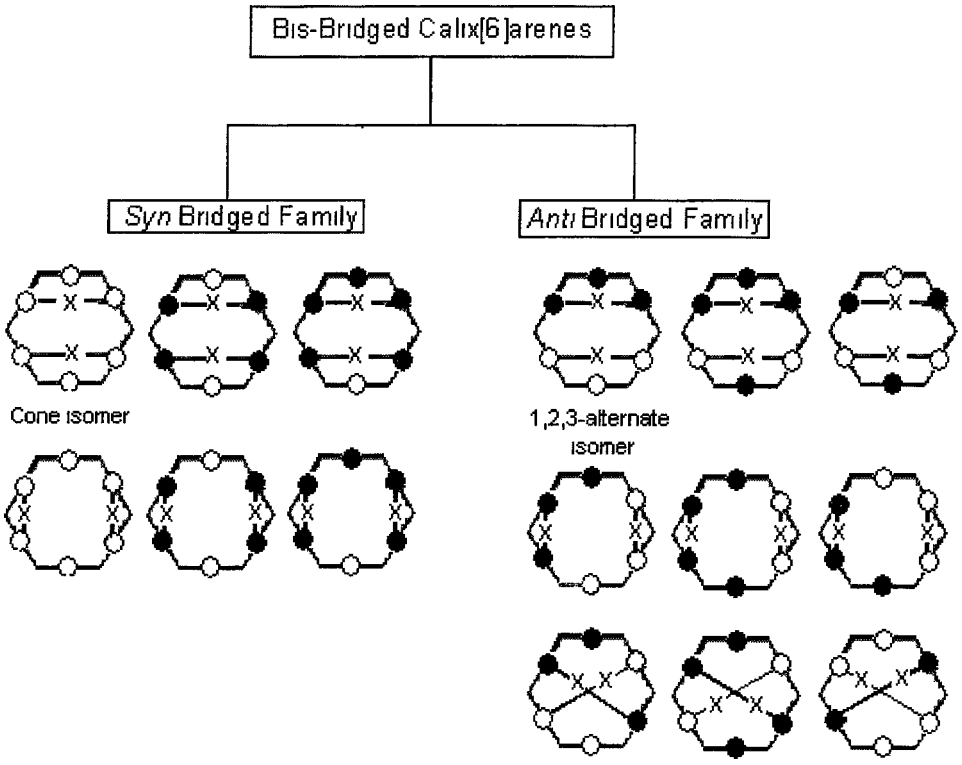


Figure 2.6 Potential conformational isomers of bis-bridged calix[6]arene.

The annulus can be bridged with two bis-electrophiles (bis-strapped) for a more rigid compound; one electrophile (mono-strapped) for a semi-rigid structure, or for a very rigid structure a multi-functional capping moiety can be used. There are a few different options for bridge

formations that are dependant on length of linker, molar quantities of linker, and reactivity of the linker.

The reaction conditions and type of bridge depict which isomeric structure will be formed. Bis-bridging is most common when the bridge crosses the full diameter of the annulus by A to F ring and the B to E ring. The other bridging units are possible which are dependent on the size of bridging unit and the molar equivalents used in the reaction. The strategy used in this research is directed toward the selective synthesis of the most common bis-bridge design.

3.0 STEREO-SELECTIVE SYNTHESIS OF BIS-BRIDGED CALIX[6]ARENE CONFORMATIONS

The formation of bis-bridge calix[6]arene required specific reaction conditions. Several reactions were closely studied to find the best conditions for two different isomers of the calix[6]arene (cone and 1,2,3-alternate conformations). Of the 18 possible isomers the selective synthesis provides a strategy for synthesizing the most prevalent and studied isomers, one from each family of isomeric conformations. Previous results have demonstrated that the both the cone and the 1,2,3-alternate calix[6]arene isomers can be synthesized using a crown ether as the bridging unit across the annulus in a B/C – E/F fashion.[20]

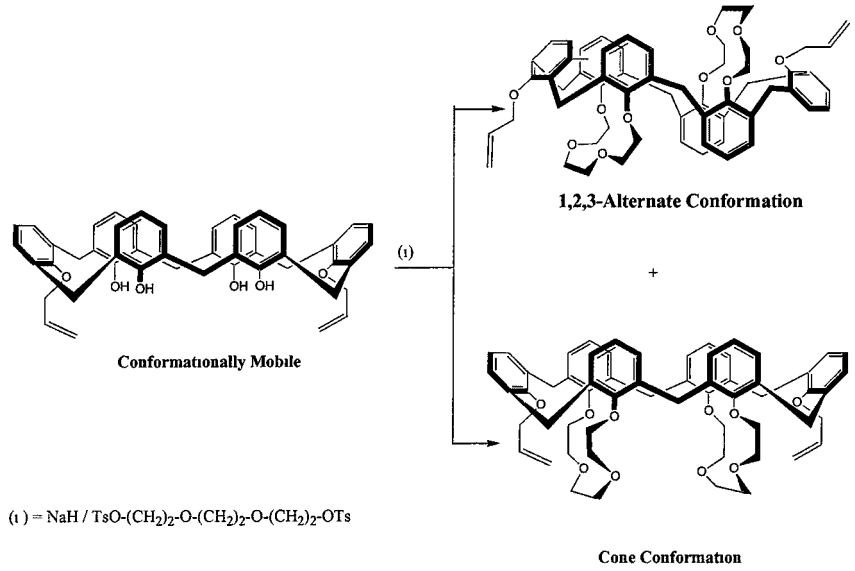
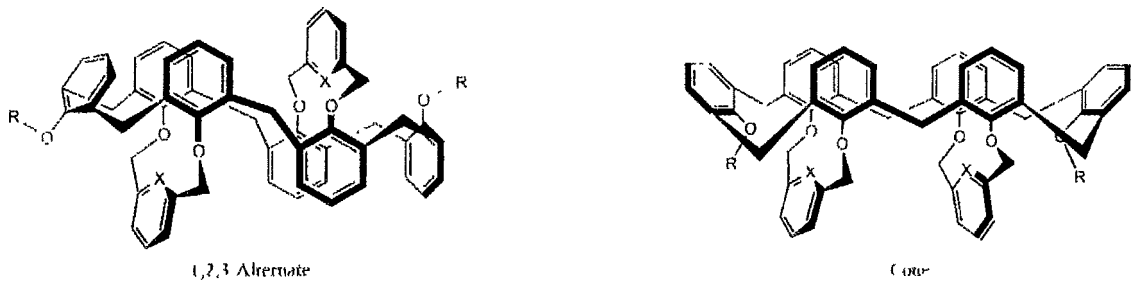


Figure 3.1 Synthesis of Diallyl-bis-4-crown-calix[6]arene.

The synthesis of the diallyl-bis-4-crown-calix[6]arene was successful and paved the synthetic pathway for studies using new linkers for bis-bridged calix[6]arene. The linking moieties can and should be varied so that the calix[6]arene can have the most potential supramolecular interactions with the guest analytes. Using an aromatic linker would allow the bowl shape of the cone isomer to be bulky on the lower rim restricting the exit of the guest molecule. The aromatic linkers have the opportunity to be multi-functionalized thereby allowing the host molecule to be more versatile. The bridging reagents chosen were α,α-dibromo-m-xylene and 2,6-bis(bromomethyl)pyridine groups. Each linker was reacted with the dially-calix[6]arene to give a different product shown in figure 3.2.



X= CH, N

Figure 3.2 The structural representation of the bis-aromatic-bridged calix[6]arenes.

During analysis of the bis-aromatic-bridging reactions a surprising result occurred when the solvent and base conditions were altered from the conditions shown in figure 3.1. Only the cone isomer was isolated when the reaction conditions were Cs_2CO_3 / CH_3CN. Only the 1,2,3-alternate isomer was isolated when the reaction conditions were NaH / THF-DMF.

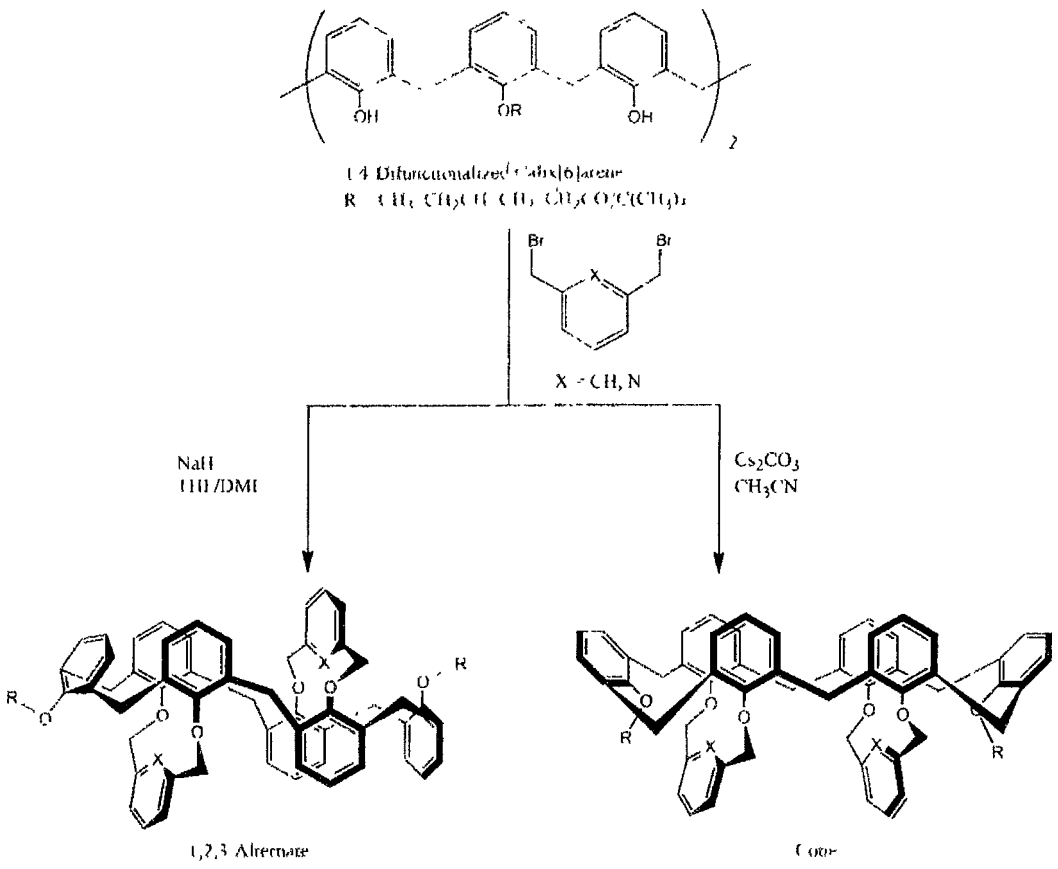


Figure 3.3 The stereo-selective synthesis of bis-bridged diallylcalix[6]arene.

These results prompted the question of what is causing the selectivity in the synthesis of the specific isomers. The formation of the parent calix[6]arene utilized the template effect in the synthesis of the macrocycle. A similar template effect could also be influencing the stereochemistry that occurs during the bridging reaction. Further studies were conducted to verify this hypothesis.

The reaction conditions were varied to determine if the metal ion, the base, the solvent effect, or all three were acting as a guide to the diallyl-calix[6]arene in the formation of the bis-bridge. The α,α-dibromo-m-xylene was chosen to bridge the annulus of the calix[6]arene in the test experiments. The xylenyl tether would provide less complications of the synthesis because of the location of a carbon in the place of where a nitrogen would be on a 2,6-bis(bromomethyl)pyridine bridging unit on the aromatic ring. The four different bases that were chosen to be varied were NaH, KH, Na_2CO_3, K_2CO_3, Cs_2CO_3 which were used to catalyze the formation of a bis-bridged isomer of calix[6]arene. The base variation was decided on by the previous knowledge of the selective synthesis of calix[4]arene.[2] The four phenolic hydroxyl groups available in the calix[6]arene after the A and D ring alkylation are in a similar form as a calix[4]arene as discussed in the the synthetic strategy. The hydride bases were reacted in a 90:10 ratio of THF/DMF, while the carbonate bases were reacted in acetonitrile as the solvent. The experimental details are in chapter 5. After the each reaction was complete the product was characterized by TLC to determine the conformation of the calix[6]arene, by comparing the rf values to known TLC rf values for the cone and the 1,2,3-alternate isomers of bis-bridged diallyl-calix[6]arene.

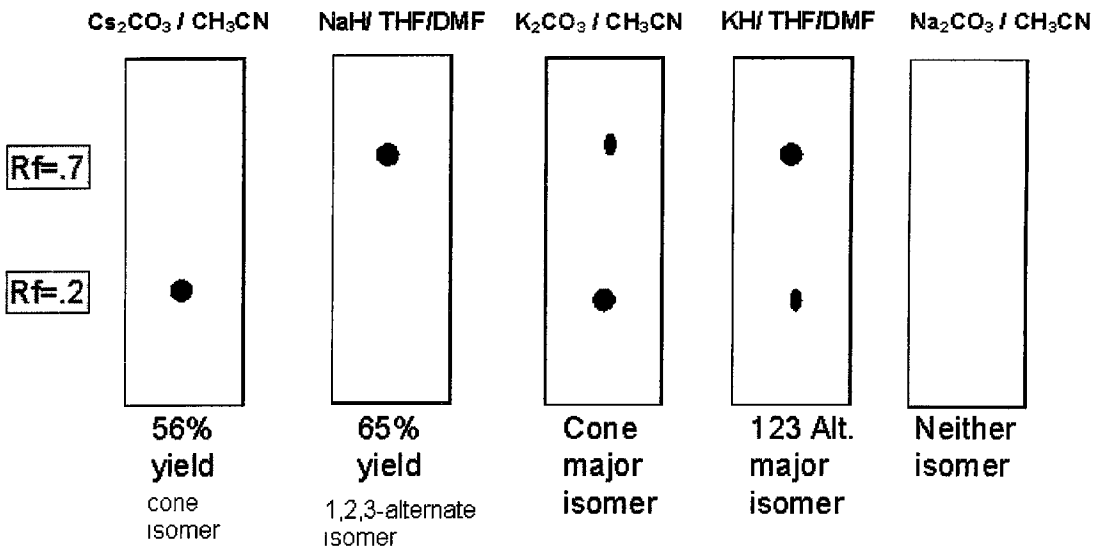


Figure 3.4 The TLC results from varied base and solvent conditions.

The results indicated that the Cs_2CO_3 / CH_3CN reaction synthesized only the cone isomer. The K_2CO_3 / CH_3CN formed a mixture of products including both the cone and the 1,2,3-alternate isomers with the cone isomer as the majority of the product. The Na_2CO_3 / CH_3CN demonstrated no indication of bridged calix[6]arene in the reaction. This could be due to the hard Na^+ ion and the hard CO_3^- ion which do not disassociate well in solvents, unlike the soft/hard ion pair with the $CsCO_3$. The carbonates seemed to give rise to the cone isomer as the majority product more than the hydrides, which demonstrated majority of product for 1,2,3-alternate isomer. The smaller potassium hydride synthesized the 1,2,3-alternate as the majority of the product with traces of cone formation. The NaH / THF/ DMF reaction conditions did select for the synthesis of 1,2,3-alternate isomer with no cone product. The selective synthesis

reactions were repeated for the 2,6-bis(bromomethyl)pyridine bridging reagent with success. These experiments show that with the specific base and solvent combination there is a selection for one conformational isomer of the calix[6]arene. This could be from the metal effect were the Na^+ ion is smaller so the ability for the bis-bridged tethers to be on opposite sides is an option, while the Cs^+ ion is larger and offers more of a restricted structural design, and K^+ was not able to discriminate between the different isomers in either reaction conditions. The solvents used in the reactions also had the potential to stabilize the product. CH_3CN stabilized the formation of the cone isomer better than the 1,2,3-alternate isomer; while the mixture of THF/DMF was a better solvent to promote the formation of the 1,2,3 alternate configuration.

To confirm the results, ^1H, ^{13}C, variable temperature, COSY, NMR and X-ray crystallography were conducted on the pure isomers synthesized in the respective conditions. The NMR spectra can be viewed in the appendix.

4.0 STRUCTURAL CHARACTERIZATION

The X-ray crystal structures for the diallyl-bis-xylenyl-calix[6]arene was solved for both the cone and the 1,2,3-alternate isomers. The crystal structure confirmed the selective synthesis strategy produced the two individual specific isomeric configurations in the solid state.

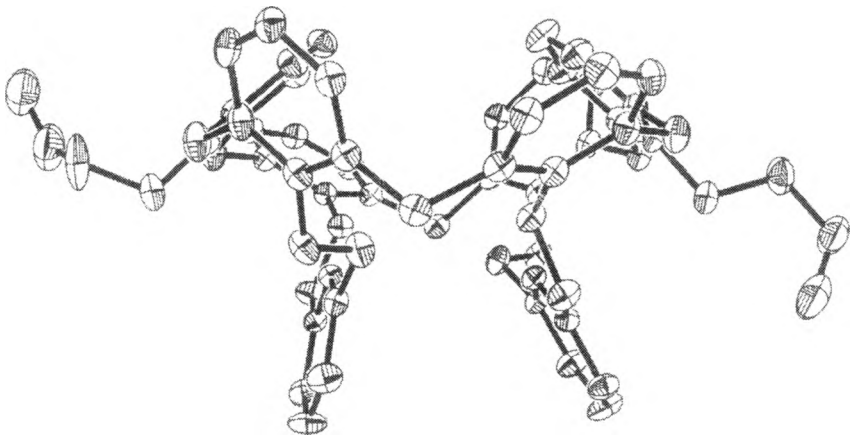


Figure 4.1 X-ray crystal structure of cone diallyl-bis-m-xylenyl-calix[6]arene.

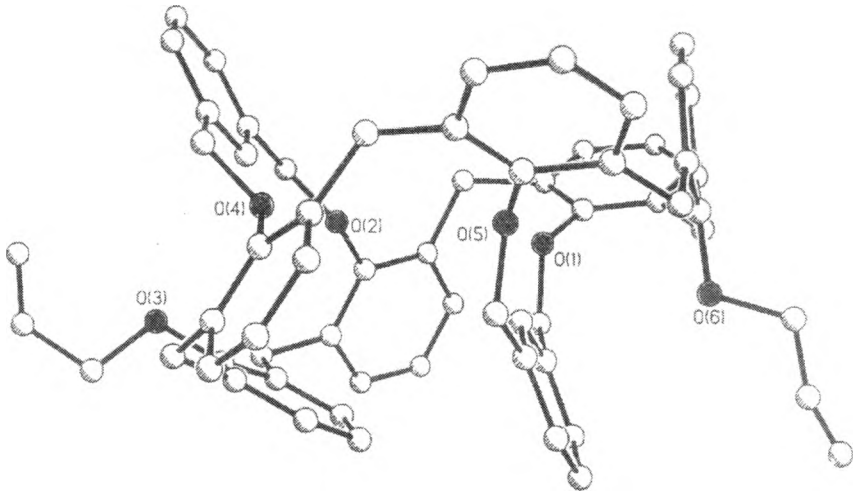


Figure 4.2 X-ray crystal structure of 1,2,3- alternate diallyl-bis-m-xylenyl-calix[6]arene.

To confirm the stereo-chemical outcome of the bridging reactions, NMR studies were conducted. Variable temperature NMR studies showed that the 1,2,3-alternate bis-bridged xylenyl calix[6]arene had a coalescence point at 12.6 Kcal at 251K. This related the solid and liquid state characterization due to the doubling of the proton NMR at low temperatures indicating that the molecule was not equilateral. That was illustrated in the crystal structure in figure 4.2 above. The cone bis-bridged xylenyl did not reach coalescence point. Studies were also run on the bis-bridged pyridinyl calix[6]arene. The cone isomer coalescence point was 11.2 Kcal at 238 K. The 1,2,3-alternate isomer demonstrated no coalescence point. Studies were conducted withCOSY and hetcor to

understand the coupling of the signals which can be viewed in the appendix.

Review of the ^{13}C NMR spectra revealed that certain signal sets correlated with a specific isomeric conformation. The signals represented the $ArCH_2AR$ in the macrocycle between the joined phenolic resides of the calix[6]arenes. The signals indicate weather there is a *syn* or *anti* configuration about the $ArCH_2Ar$ bonds, which are shown below.

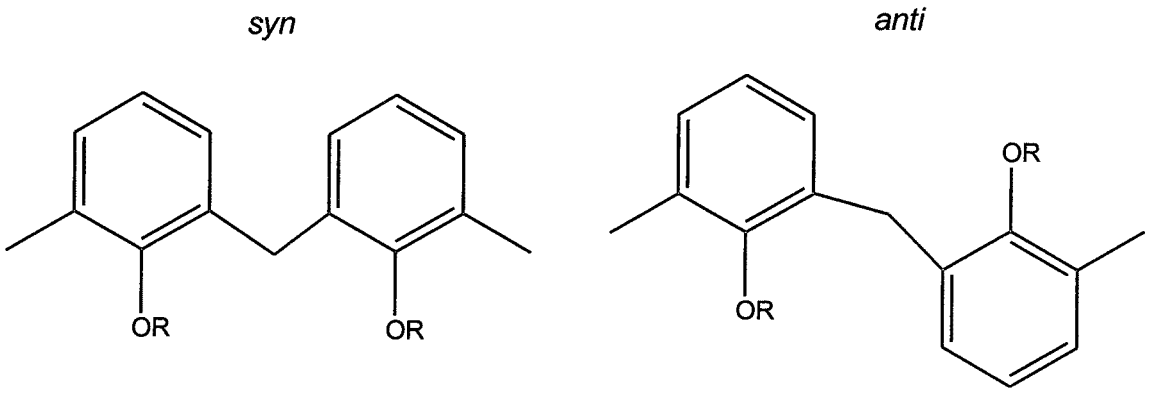


Figure 4.3 The *syn* and *anti* arrangement

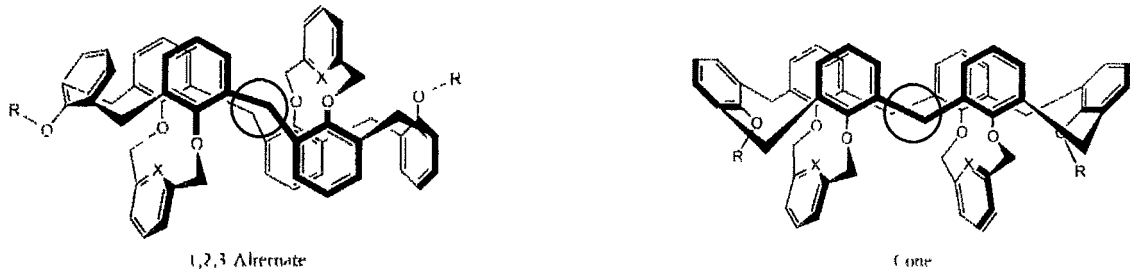


Figure 4.4 The location of syn and anti signals.

Each isomeric configuration has a combination of *syn* and *anti* signal patterns indicated in the NMR spectra for the $ArCH_2Ar$. Of the 15 viable isomeric configurations that can potentially form, the cone and the 1,2,3-alternate isomers were selectively synthesized and the spectra can distinguish the two isomers from different families by the difference of the ppm shift for the $ArCH_2Ar$ signals. The *syn* signals are observed when the aryl rings have the substituent groups on the same side of the marcrocyclic plane (i.e. cone) while the anti signal is observed when the aryl rings have the substituent located on opposite sides of the plane (i.e. 1,2,3-alternate). The ^{13}C NMR spectrum for BC/EF bridged calix[6]arenes had two signals in within the range of 28-32 ppm which represent these configurations. The cone isomer was identified when the signals were separated by ~2-3ppm, while the 1,2,3-alternate isomers signals were separated by <1ppm. There is currently a rule for the ^{1}H of a calix[6]arene that states, the methylene group connecting two neighboring aryl groups which appear to be a pair a AB doublets if the aryl groups are *syn* to each other.[25-27] A similar rule has been published by de Mendoza for the calix[4]arene determination between isomers.[27] The discovery of this ^{13}C empirical rule could be thought of as a sub-set of the rules that exist for the bis-functional dialkylated calix[6]arene. The ^{13}C rule is only relevant when there are tethering groups attached to the B, C, E, F rings that cause the aliphatic carbon to experience different shifts in the spectrum. The applicable groups include bifunctional-bridging units,

capping moieties, or any substituent that locks the calix[6]arene into a rigid structure. The ^{13}C spectra shown below illustrate the ease and clarity the new rule has discerning isomers of calix[6]arene.

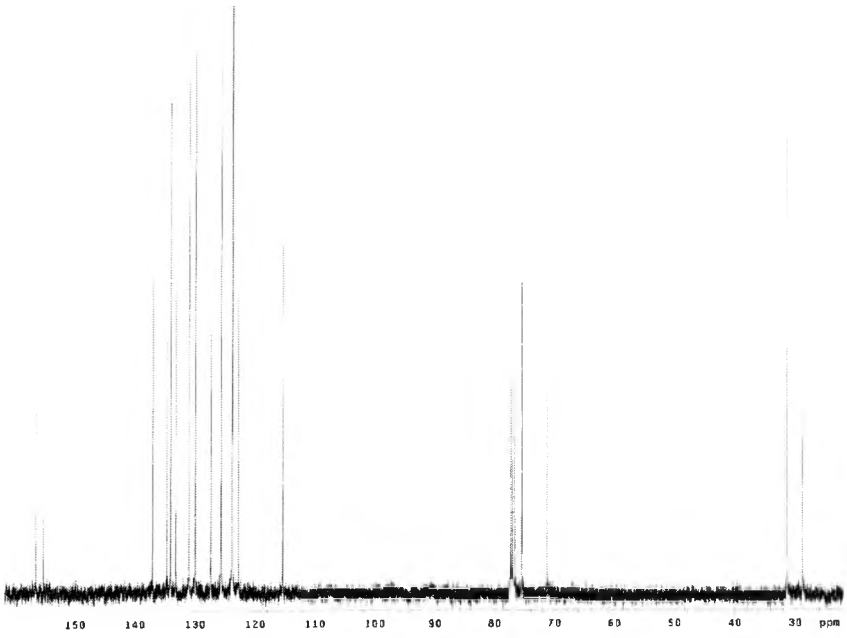


Figure 4.5 The ^{13}C NMR spectrum for bis-bridged xylenyl-cone calix[6]arene.

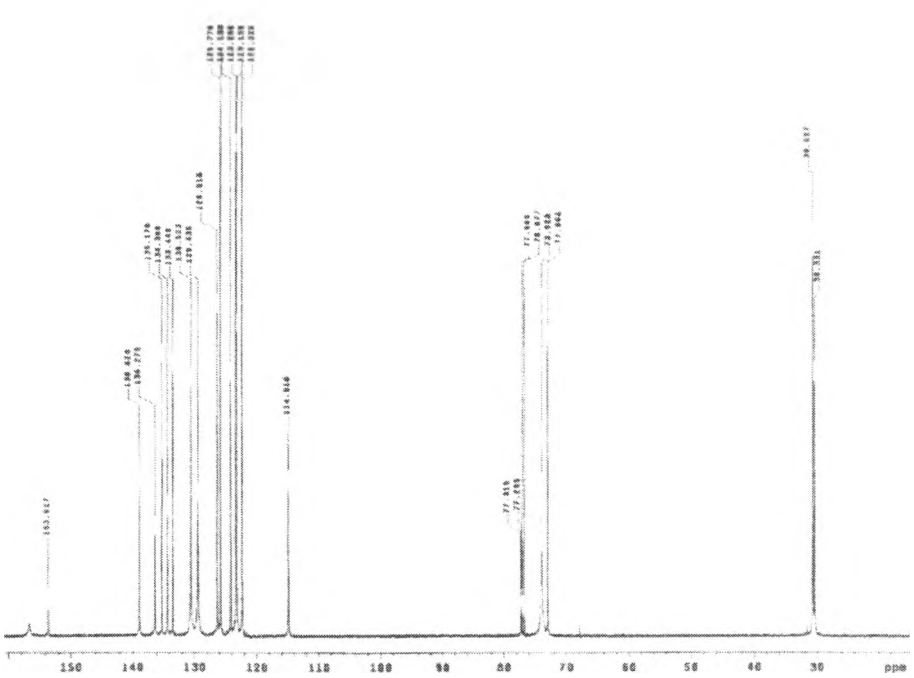


Figure 4.6 The ^{13}C NMR spectrum for bis-bridged xylenyl-1,2,3-alternate calix[6]arene.

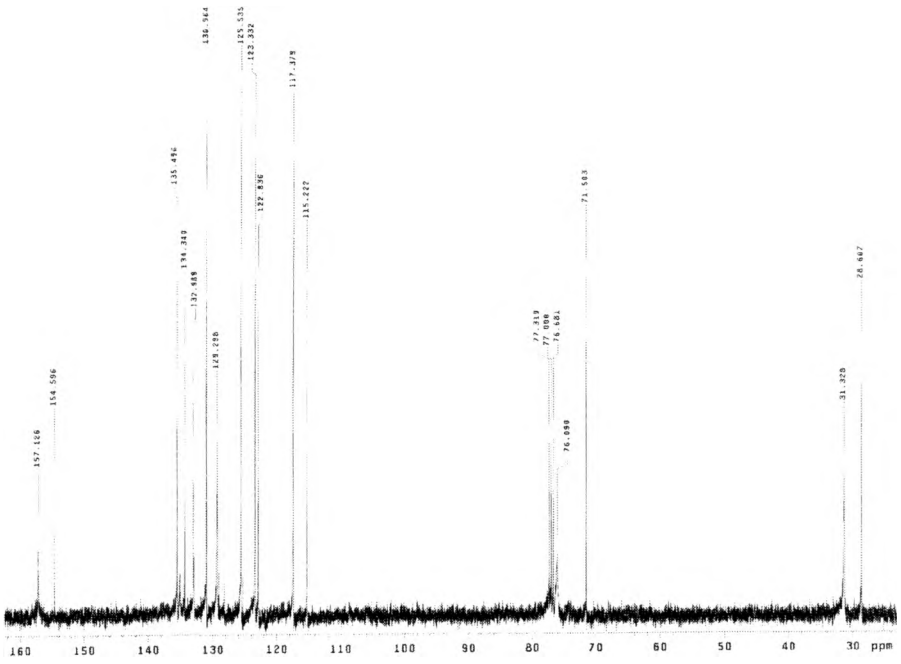


Figure 4.7 The ^{13}C NMR spectrum for bis-bridged pyridinyl cone calix[6]arene.

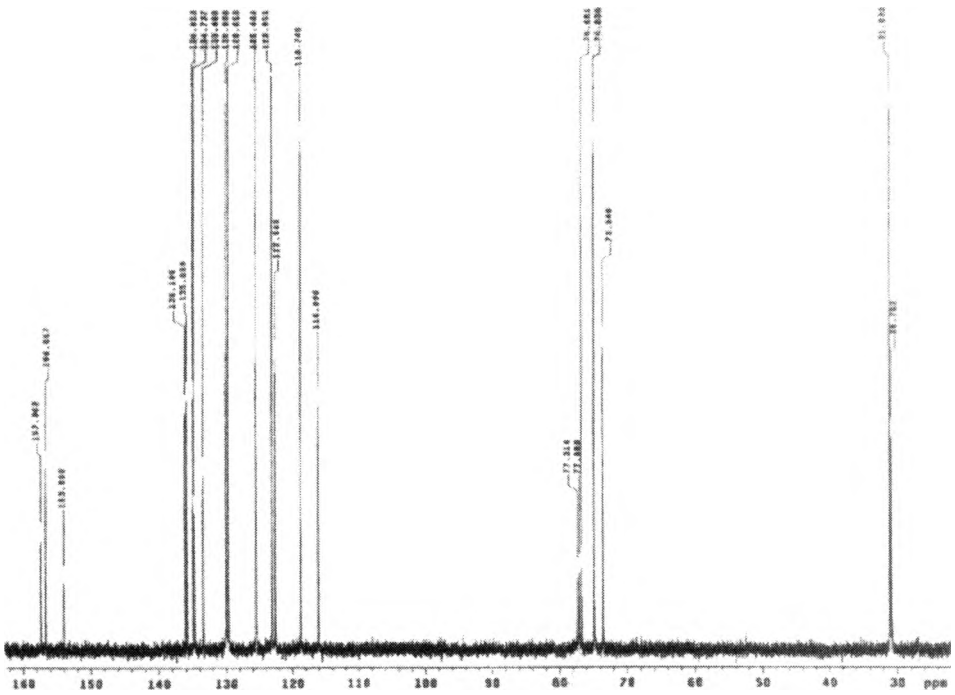


Figure 4.8 The ^{13}C NMR spectrum for the bis-bridged pyridinyl 1,2,3-alternate calix[6]arene.

Through the solving of the crystal structures and interpreting the ^{13}C NMR data the rule emerged and indicated that the two isomeric configurations can be distinguished via the $\Delta\delta$ shift in the ^{13}C NMR spectra.

The rule was applied to the cone and the 1,2,3-alternate conformations of diallyl-bis-pyridinal-calix[6]arene and was confirmed. The ^{13}C rule should hold firm in the literature experiments as well. Okazaki *et al.* synthesized a compound trimethylammino calix[6]arene which demonstrates the determined range of ppm for the cone (^{13}C NMR δ= 27.89, 31.62)

and 1,2,3-alternate (^{13}C NMR δ= 30.09, 30.53) configurations.[28] Another literature confirmation is a compound that incorporated a capping a dialkylcalix[6]arene at the location of the four phenolic hydroxyl groups resembling a bis-bridge locking formation. The ^{13}C NMR spectra had a signal at δ= 29.65, 33.72 which indicated a cone configuration.[29]

Compound	δ up field	δ down field	$\Delta\delta$
Cone bis-m-xylenyl-calix[6]arene	31.41	28.77	2.64
1,2,3-alternate bis-m-xylenyl-calix[6]arene	31.28	30.87	0.41
Cone bis-pyridinyl-calix[6]arene	31.33	28.61	2.72
1,2,3-alternate bis-pyridinyl-calix[6]arene	31.03	30.78	0.25
Cone bis-4-crown-calix[6]arene[20]	30.88	27.09	3.79
1,2,3-alternate bis-4-crown calix[6]arene[20]	31.55	30.13	0.42
Cone trimethylammino calix[6]arene[28]	31.62	27.89	3.73
1,2,3-alternate trimethylammino calix[6]arene[28]	30.53	30.09	0.44
Capped dialkylated calix[6]arene[29]	33.72	29.65	4.07

Table 4.1 Table of ^{13}C NMR shifts.

An empirical rule referring to the ^{13}C NMR spectra was emerging with the knowledge of the solid and liquid state of the cone and the 1,2,3-alternate isomeric configurations. This indicated that the empirical rule was successfully distinguishing between the cone and the 1,2,3-alternate configurations. The technique became a regular protocol within the research conducted in the lab. This gave a consistent ability to verify the particular conformation even when a crystal structure could not be solved.

5.0 EXPERIMENTAL

See appendix for NMR spectra.

5.1 Materials

All chemical reactions were conducted under inert argon atmosphere. All solvents were used as received from the suppliers providers without further purification. ^{1}H and ^{13}C NMR spectra were obtained on a Varian NMR 400 MHz in $CDCl_3$ and were referenced to the residual proton signal in $CDCl_3$. Melting points were obtained in an unsealed capillary tube and were uncorrected. Elemental analysis was performed at the Desert Analytics Laboratory in Tuson, Arizona. Analytical thin layer chromatography (TLC) was performed on precoated silica gel plates (Silica Gel IB2-F) and column chromatography was performed with Silica Gel IB2-F 150, 60-200 Mesh (75-250 micron). The parent compound para-*tert*-butyl-calix[6]arene **1** was prepared according to known procedures as well as the dealkylated-calix[6]arene **2** which was obtained by treatment of the parent compound with $AlCl_3$ and phenol.[30-31] The diallyloxy-calix[6]arene **3** was prepared according to know procedures by treating **2** with allyl bromide and potassium trimethyl-silanolate.[20]

5.2 Preparation of para-*tert*-butylated Calix[6]arene (1)[30]

A 3 liter three necked round-bottom flask equipped with a mechanical overhead stirrer, Dean-Stark trap, and condenser was set up under argon atmosphere. The reagents were added to the round-bottom in the following protocol; 100.0 g, (0.666 mol) of p-tert-butyl-phenol and 40.0 g (1.33 mol) of paraformaldehyde were suspended in the 1.5 L of xylene. Rubidium hydroxide (50% wt. aqueous solution) was added in the amount of 26.65 mL (exactly 0.34 molar equivalents 0.2363 mol) to the reaction. The Dean-Stark trap was filled with xylene and the reaction was heated to reflux for 20 h. The solution was cooled and precipitate was filtered via vacuum filtration. The filter cake was then dissolved in $CHCl_3$ (2 L) and washed 3 X 1.5L of 1M HCl. To compensate for the emulsion back extractions were needed. All of the $CHCl_3$ layers where collected and dried over $MgSO_4$ and the solution was gravity filtered. The volume of the solvent was reduced to 200 mL and then poured into 800mL CH_3OH. The off-white precipitate was filtered yielding 82 g, 76% of compound **1**. mp. 380-381°C; Rf=.63 in $CHCl_3$ (3parts)/ hexane (4 parts); ^1H NMR (400 MHz, CD_2Cl_2) δ=10.2 (s, ArOH, 12H) 7.10 (s, ArH, 12H), 3.88 (s, $ArCH_2Ar$, 12H), 1.25 (s, $C(CH_3)_3$, 54H). ^{13}C NMR (400 MHz, $CDCl_3$) δ=147.2, 144.2, 126.9, 126.1, 34.0, 33.1, 31.4.

5.3 Preparation of de-*tert*-butylated Calix[6]arene (2)[31]

A three neck round-bottom was flame dried and then fitted with an overhead stirrer, 70.0g (0.072mol) of compound **1** along with 60 g (0.65 mol) of phenol and 115 g (0.863 mol) of $AlCl_3$ were dissolved in 1.5 L of

toluene. The reaction was allowed to stir for 72 h at room temperature under an argon atmosphere. When the reaction was complete the toluene was reduced to dryness and the residue was redissolved in ~1 L of $CHCl_3$. The solution was then washed 3 X 200 mL of 1M HCl, the organic layer was collected and dried over $MgSO_4$. The $MgSO_4$ solution was filtered with a gravity filter. The dried organic solution was reduced to 100 mL and then recrystallized in 600 mL methanol. The dealkylated calix[6]arene, compound (**2**), precipitated out of solution and was filtered and washed to provide a white powder yielding 39.1 g (85%). mp. 417-418 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ= 10.4(s, ArOH, 6H), 6.7-7.4 (m, ArH, 16H), 4.0 (s, $ArCH_2Ar$, 12H).

5.4 Preparation of Diallyloxy-Calix[6]arene (3)[20]

To a two neck 2 liter round-bottom flask equipped with a magnetic stirrer 20.0 g (32.7 mmol) of compound **2** and 27.1 g (190 mmol) of potassium trimethyl-silanolate ($K^+(CH_3)_3SiO^-$) was placed into 1.20 L of dry THF and 120 mL of DMF. The reaction mixture was cooled for 15 minutes in a 0 °C ice bath. The allylbromide was added in the amount of 7.75 mL (88.7 mmol) and the reaction was allowed to stir under an argon atmosphere 24h. The solvent was reduced and the residue was redissolved in $CHCl_3$ (1L) and then washed 3 X 100 mL of 1M HCl. The organic layer was collected and dried over $MgSO_4$. The solution was filtered with a gravity filter and then the dried solvent was reduced to 100 mL. The solution was poured into approximately 600mL of hexane and a

white precipitate formed. The precipitate was collected via filtration resulting in 21.8 g, 96% of compound **3**. mp = 188-190 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ= 8.03 (s, -OH, 4H), 7.09-6.89 (m, ArH, 14H), 6.76 (t, Arh, 4H, J= 6.0 Hz), 5.95 (m, -CH=, 2H), 5.40 (d, $=CH^2$, 2H, J= 20.0 Hz), 5.08 (d, $=CH_2$, 2H, J= 12.0 Hz), 4.46 (d, $-OCH_2-$, 4H, J= 6.0 Hz), 3.94 and 3.78 (two s, $ArCH_2Ar$, 12H). ^{13}C NMR (100 MHz, $CHCl_3$) δ= 162.5, 152.4, 151.8, 133.2, 131.8, 129.1, 128.9, 128.7, 127.5, 127.1, 125.5, 120.2 and 118.5 (Ar and $-CH=CH_2$), 75.9 ($-OCH_2-$), 36.4 and 31.5 ($ArCH_2Ar$).

5.5 Preparation of Diallyloxy-bis-*m*-xylenyl-calix[6]arene 1,2,3-alternate isomer(4)

In a 500 mL single neck round-bottom flask 2.0 g (2.8mmol) of compound **3** dissolved in 200 mL of dry THF along with 20 mL of DMF. A 60% sodium hydride (NaH) dispersion in mineral oil was added in the amount of 0.68g (17 mmol) and allowed to stir at room temperature for 30 minutes before 3.8 g (14 mmol) of α,α-di-bromomethyl-m-xylene was added. The solution was refluxed for 24h under an argon atmosphere. The solvent was then removed under reduced pressure. The residue was redissolved in $CHCl_3$ (1L) and washed 3 X 100 mL of 1M HCl and then dried over $MgSO_4$. The solution was filtered and the solvent volume was reduced. The crude material was then purified by gravity column chromatography on silica gel 70% CH_2Cl_2 30% Hex with the Rf=.85. The reaction yielded 65% of compound **4** (1.6 g). mp. 261-263°C (dec) ^{1}H NMR (400 MHz $C_2D_2Cl_4$, +140 °C) δ= 7.39 (s, 2H), 7.19 (d of d, 8H), 7.13

(t, J= 7.6 Hz), 7.06 (t, 4H, J= 7.6 Hz), 6.80 (d, 4H, J= 7.6Hz), 6.06 (d, 4H, J= 7.6 Hz), 5.76 (t, 2H, J= 6.4 Hz), 5.73 (m, 2H), 4.45 (m, 4H), 4.39 (d, 4H, J= 12.8 Hz), 4.33 (d, 4H, J= 12.8 Hz), 4.25 (d, 4H, J= 15.2 Hz), 4.01 (s, 4H), 3.99 (d, 4H, J= 2 Hz), 3.21 (d, 4H, J= 15.2 Hz). ^{13}C NMR (100 MHz, $C_2D_2Cl_4$, +140 °C) δ= 157.22, 153.62, 139.21, 136.32, 135.44, 134.30, 133.52, 130.74, 129.62, 126.46, 126.00, 124.69, 123.39, 123.19, 122.59, 115.54, 74.34, 73.49,31.38, 30.86. Anal. Calcd. for $C_{64}H_{56}O_6$: C, 83.5%; H, 6.1%;O, 10.4%.

5.6 Preparation of Diallyloxy-bis-m-xylenyl-calix[6]arene cone isomer (5)

In a 1liter single-neck round-bottom flask 3.0 g (4.2 mmol) of compound **3** dissolved in 500 mL of CH_3CN. The strapping agent α,α-dibromo-m-xylene was added to the solution in the amount of 2.65 g (10.0 mmol) along with 8.17 g (25 mmol) of Cs_2CO_3. The solution was heated to reflux for 12 h under an argon atmosphere. The completed reaction was cooled and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (100mL) and washed 3 X 50 mL of 1M HCl then dried over $MgSO_4$. The solution was filtered and the solvent was evaporated under reduced pressure to yield a crude product. The crude product was purified via column chromatography using silica gel. (80% CH_2Cl_2 and 20% Hexane) (Rf=.25) Compound **5** yielded 56% (2.16 g). ^1H

NMR (400 MHz, $CDCL_3$, 25 °C) δ= 7.401 (d of d, 2H, J= 8.8 Hz), 7.396 (d of d, 2H, J= 8.8 Hz), 7.184 (M, 8H), 7.050 (t, 2H, J= 14.8 Hz), 6.948 (d, 4H, J= 7.2 Hz), 6.555 (t, 2H, J= 15.6 Hz), 6.226 (d, 4H, J= 8.0 Hz), 5.853 (M, 2H), 5.465 (s, 2H), 5.139 (d of d, 2 H, J= 14 Hz), 4.215 (d, 8H, J=16 Hz), 4.063 (d of d, 4H, J= 1.2 Hz), 3.566 (d, 2H, J=14.4Hz), 3.443 (d, 4H, J=14.2 Hz). ^{13}C NMR (100MHz, CDCl3, 25 °C) δ= 156.4, 155.2, 137.0, 134.6, 134.0, 133.2, 130.2, 130.9, 129.9, 127.4, 125.7, 123.8, 115.5, 75.5, 71.3, 31.4, 28.8. Anal. Calcd. for $C_{64}H_{56}O_6$: C, 83.5 % H, 6.1%. Found C:80%, H:6%.

5.7 Preparation of Diallyloxy-bis-pyridinyl-calix[6]arene 1,2,3-alternate isomer (6)

Into a 500 mL single-necked round-bottom flask were placed 2.0 g (2.8 mmol) of Compound **3** dissolved in a 200 mL of THF containing 20 mL of DMF (THF/DMF 90:10 mixture). A 60% sodium hydride, NaH dispersion in mineral oil in the amount of 0.68 g (17 mmol) was added and allowed to stir at room temperature for 30 minutes. 2,6-bis(bromomethyl) pyridine in the amount of 1.68 g (6.3 mmol) was added and the solution was allowed to stir at room temperature under argon atmosphere for seven days. The completed reaction solvent was reduced under pressure and the residue was redissolved in 500 mL $CHCl_3$. The solution was washed 3 X 100 mL of 1M HCl. All the organic layers were collected and the dried over $MgSO_4$. The solution was filtered off via gravity filtration. The solvent was reduced to the crude material. The

crude material was purified by column chromatography on aluminum oxide 60% EtOAc and 40% $CHCl_3$ (Rf= .65) Compound **6** yielded 55% (1.4g). mp. 248-250 C ^{1}H NMR (400MHz, $C_2D_2Cl_4$, + 140 °C) δ= 7.48 (t, 2H, J= 7.6 Hz), 7.23 (d, 4H, J= 8 Hz), 7.15 (d, 4H, J= 7.6 Hz), 7.04 (t, 4H, J= 7.2 Hz), 6.86 (d, 4H, J= 7.2 Hz), 6.03 (d, 4H, J= 8 Hz,), 5.72 (m, 2H), 5.57 (d,2H, J=7.2 Hz), 5.04 (s,2H), 5.01 (d, 2H, J= 7.6 Hz), 4.56 (d, 4H, J= 12.4 Hz), 4.24 (s, 4H), 4.16 (d, 6H, J= 12.4 Hz), 4.11 (d, 4H, J= 15.2 Hz), 3.87 (d, 4H, J= 5.6 Hz), 3.16 (d, 4H, J= 14.8 Hz), 2.85 (s, 4H). ^{13}C NMR (100 MHz, $C_2D_2Cl_4$, +140 °C) δ= 157.36, 156.67, 124.00, 136.11, 135.83, 134.92, 134.74, 133.41, 130.00, 129.65, 125.48, 123.06, 122.54, 118.74, 116.10, 76.68, 74.84, 73.55, 31.032, 30.782. Anal. Calcd. for $C_{62}H_{54}O_6N_2$: C, 79.8%; H, 5.8%; O, 10.3%; N, 4.1%. Found C, 79.6% H, 5.9%.

5.8 Preparation of Diallyloxy-bis-pyridinyl-calix[6]arene cone (7)

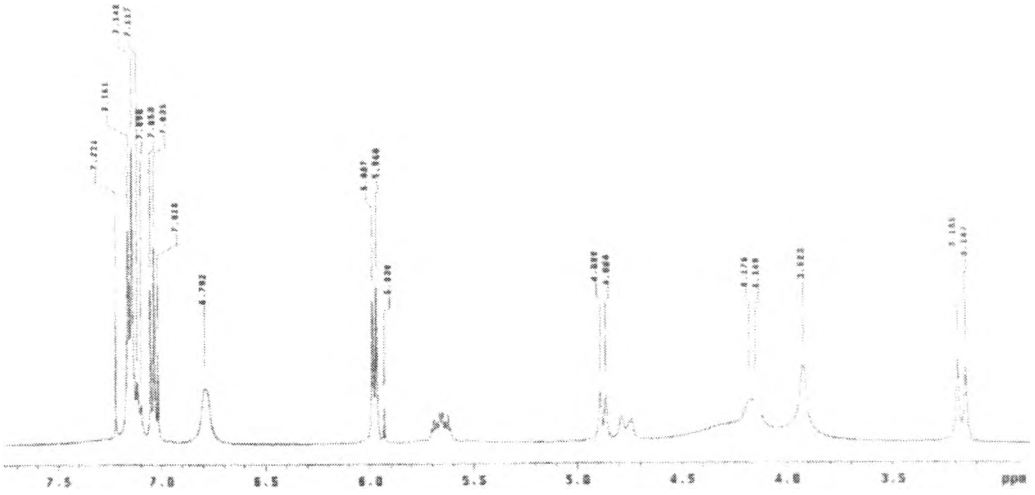
In a single-necked 1 L round-bottom flask 5.0 g (6.9 mmol) of compound **3** was dissolved in 500 mL of CH_3CN. The strapping reagent 2,6-bis(bromomethyl) pyridine in the amount of 4.43 g (17 mmol) was added to the flask along with 13.48 g (41 mmol) of Cs_2CO_3. The mixture was allowed to stir at room temperature for seven days under argon atmosphere. The CH_3CN solvent was then reduced to dryness under pressure. The residue was redissolved in 500 mL of CH_2Cl_2 and washed 1 X 100mL of 1 M HCl and washed again 2 X 100 mL of 6M NaOH. The organic layer was collected and dried over $MgSO_4$. The solution was filtered and the solvent was reduced to approximately 50 mL. The 50 mL

solution was poured into 500 mL of CH_3OH creating a white precipitate which was filtered. The crude material was recrystallized in 250mL $(C_6H_5)CH_3$ and ~200 mL CH_3OH for 5 days. This resulted in a pure product that yielded 2.6% (0.150 g). 90% TLC conditions: alumina oxide plates (CH_2Cl_2 / 10% CH_3OH) Rf= .60 (streak) ^1H (400MHz, CD_3Cl_2, 25 °C) δ= 7.402 (t, 4H, J = 15.6Hz), 7.295 (d, 4H, J= 6.8Hz), 7.180 (t, 2H, J= 14.8Hz), 7.067 (M, 8H), 6.346 (t, 2H, J=15.6Hz), 6.118 (d, 4H, J= 7.6Hz), 5.769 (M, 2H), 5.115 (d of d, 2H, J= 17.2), 5.021 (d of d, 2H, J= 10.4Hz), 4.960 (s, 4H), 4.806 (d, 2H, J = 13.6Hz), 4.821 (s,4H), 4.070 (d, 4H, J= 16.8Hz), 3.967 (d, 4H, J= 4.8Hz), 3.370 (d, 2H, J= 13.6Hz), 3.271 (d, 4H, J= 16.8Hz). ^{13}C-NMR (100MHz, CD_3Cl_2, 25°C) (δ = 157.1, 154.6, 135.5, 134.3, 132.9, 130.9, 129.3, 125.5, 123.3, 122.8, 117.4, 115.2, 76.1, 71.5, 31.3, 28.607) Anal. Calcd. $C_{62}H_{54}O_6N_2$: %C 80.6, %H 5.8, %N 3.0. Found for $C_{62}H_{54}O_6N_2$: %C 79.4, %H 5.8.

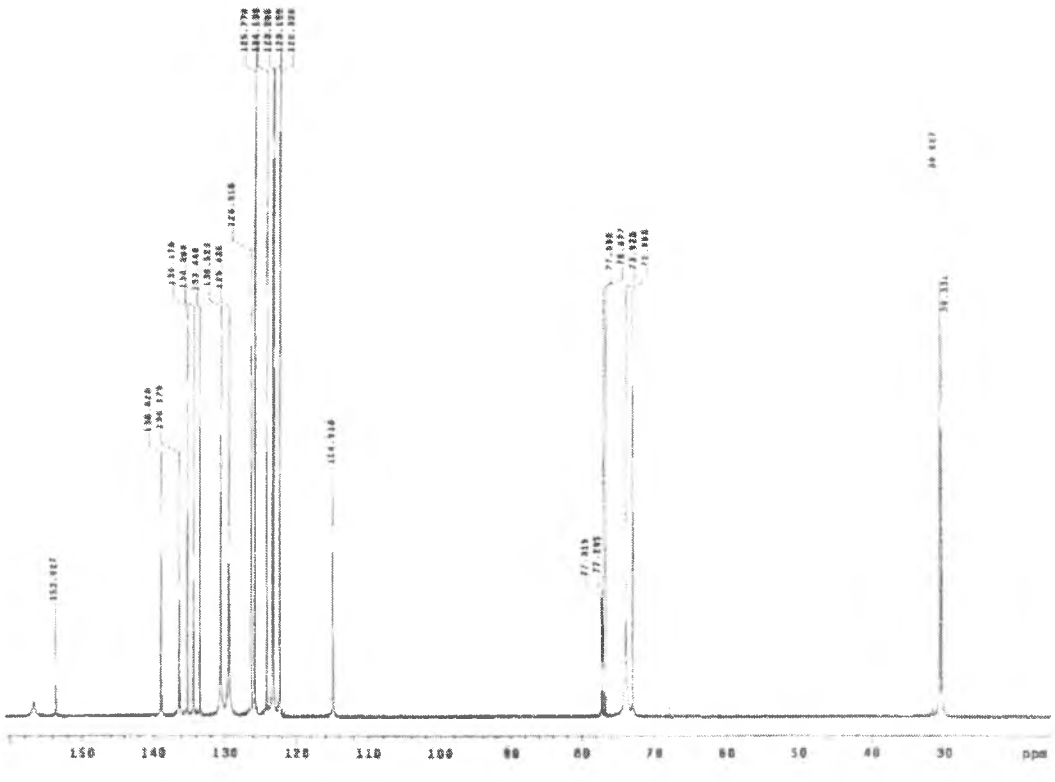
6.0 CONCLUSION

A stereo-selective synthesis of bis-bridged calix[6]arene was discovered by altering the base and solvent conditions. This enabled the synthesis of two of the most studied isomeric configurations from the *syn* and *anti* families; cone and the 1,2,3-alternate calix[6]arene. Through the synthesis process a subset to the NMR rule for calix[6]arene was formulated which can distinguish between each of the two bis-bridged isomers by specific signals on the ^{13}C NMR spectrum. Crystal structures and literature studies verified that the rule was accurate and reliable in distinguishing between the two isomers.

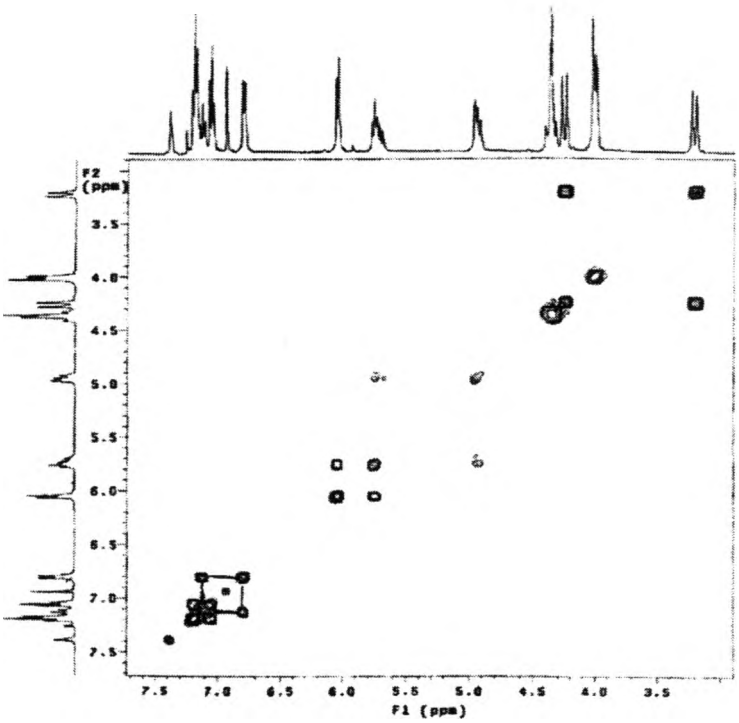
APPENDIX: Spectra



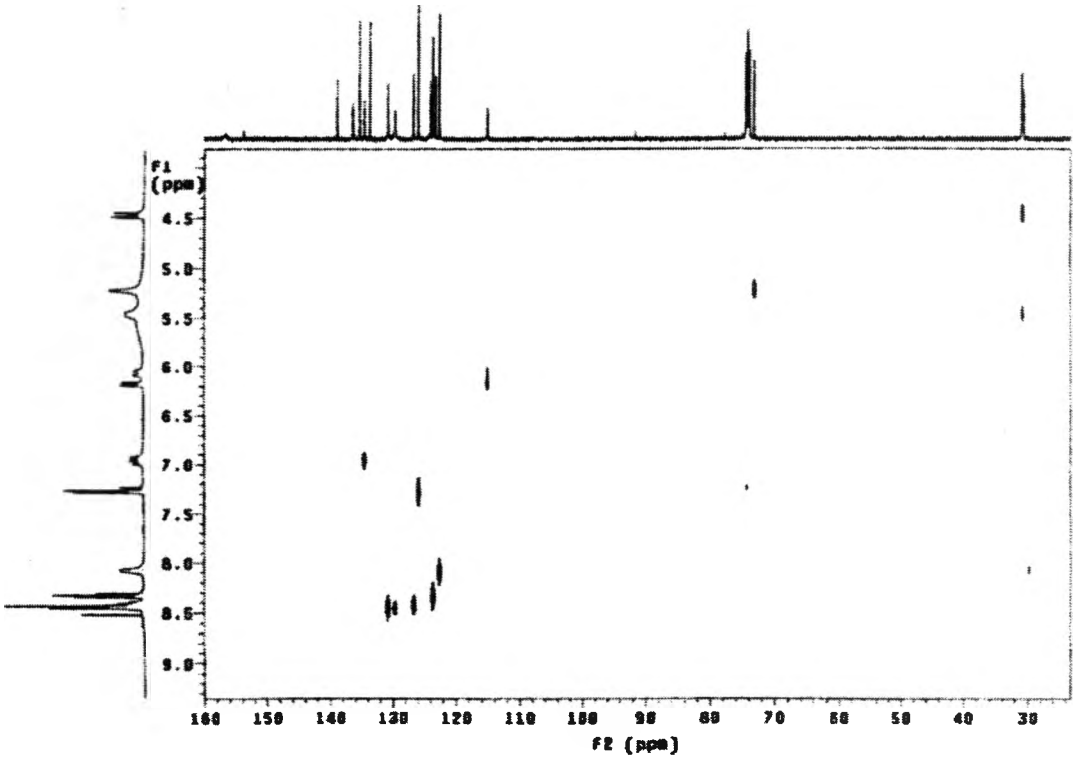
Spectrum 1 ^{1}H NMR of compound **4**.



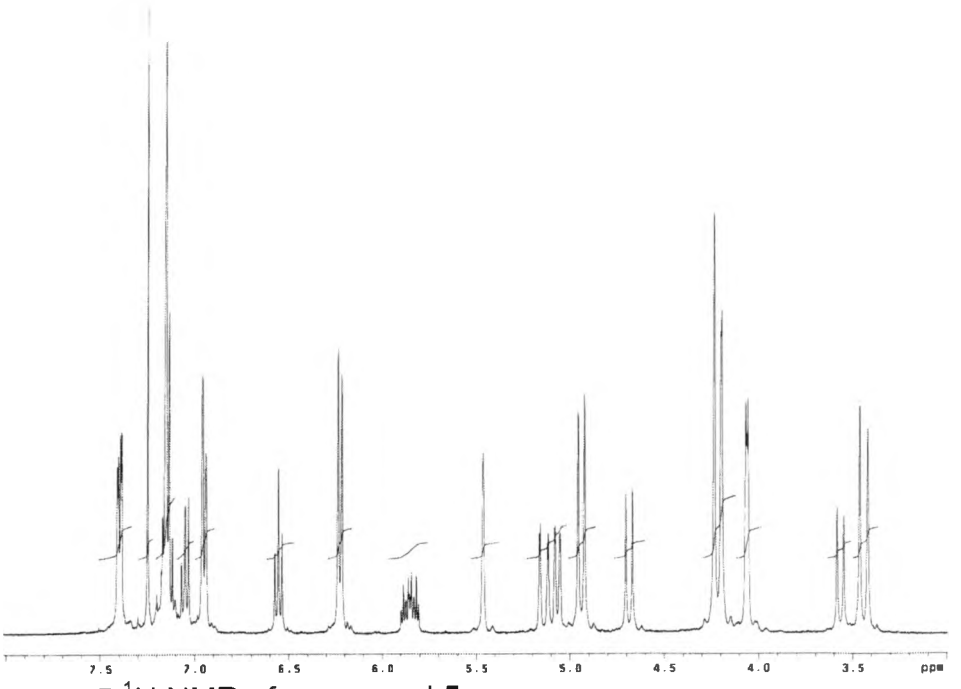
Spectrum 2 ^{13}C NMR of compound **4**.



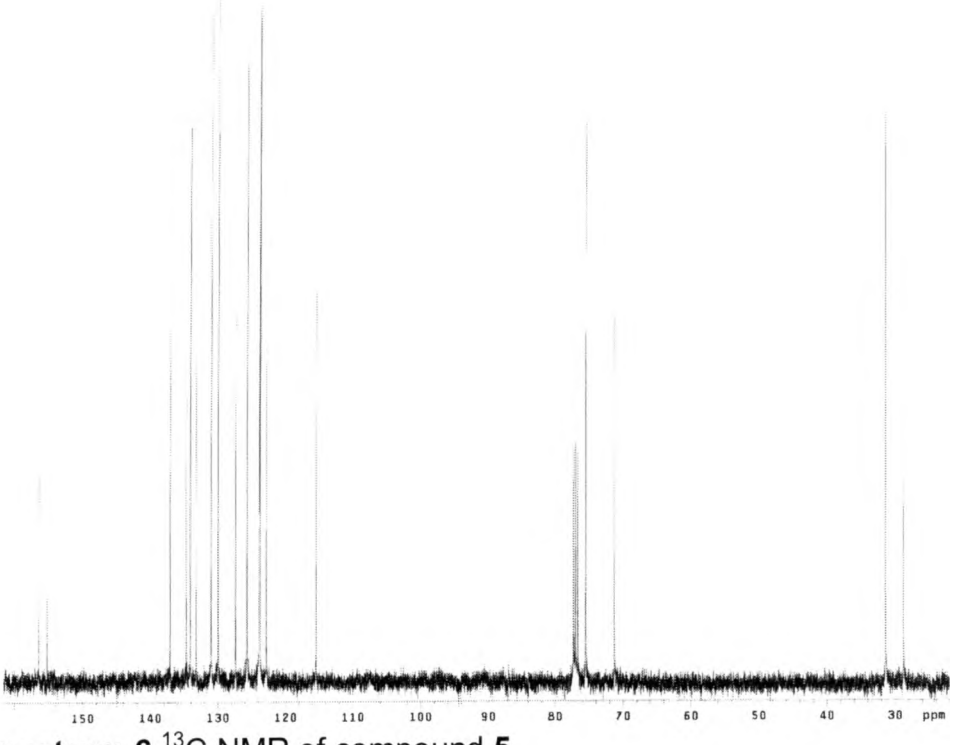
Spectrum 3 NMR COSY of compound **4**.



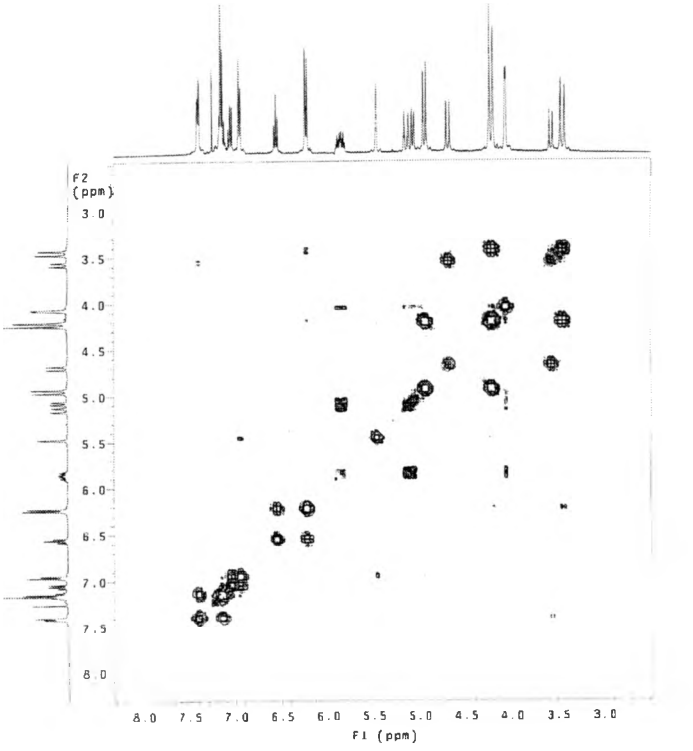
Spectrum 4 NMR hetcor of compound **4**.



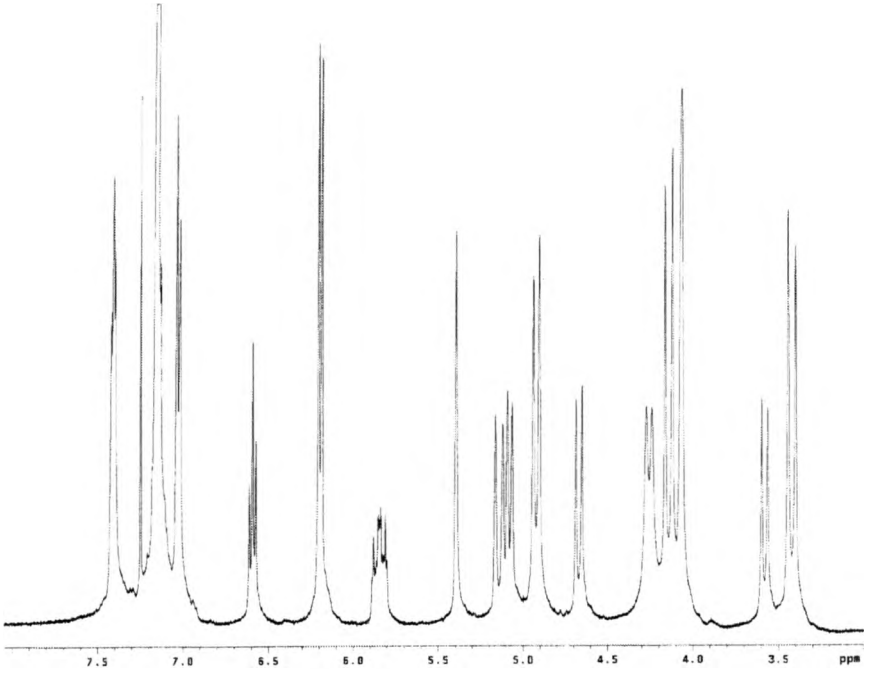
Spectrum 5 ^{1}H NMR of compound **5**.



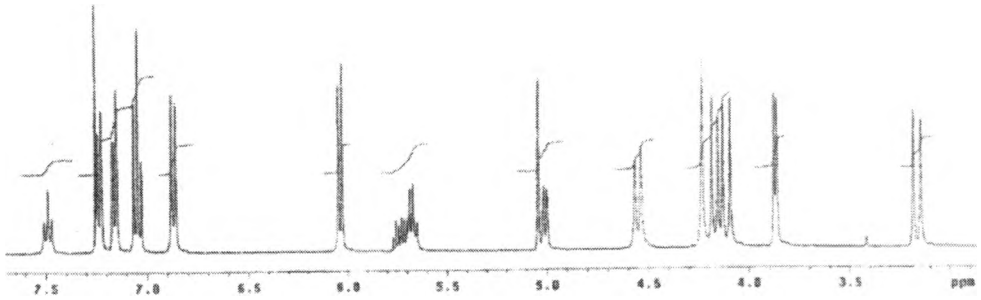
Spectrum 6 ^{13}C NMR of compound **5**.



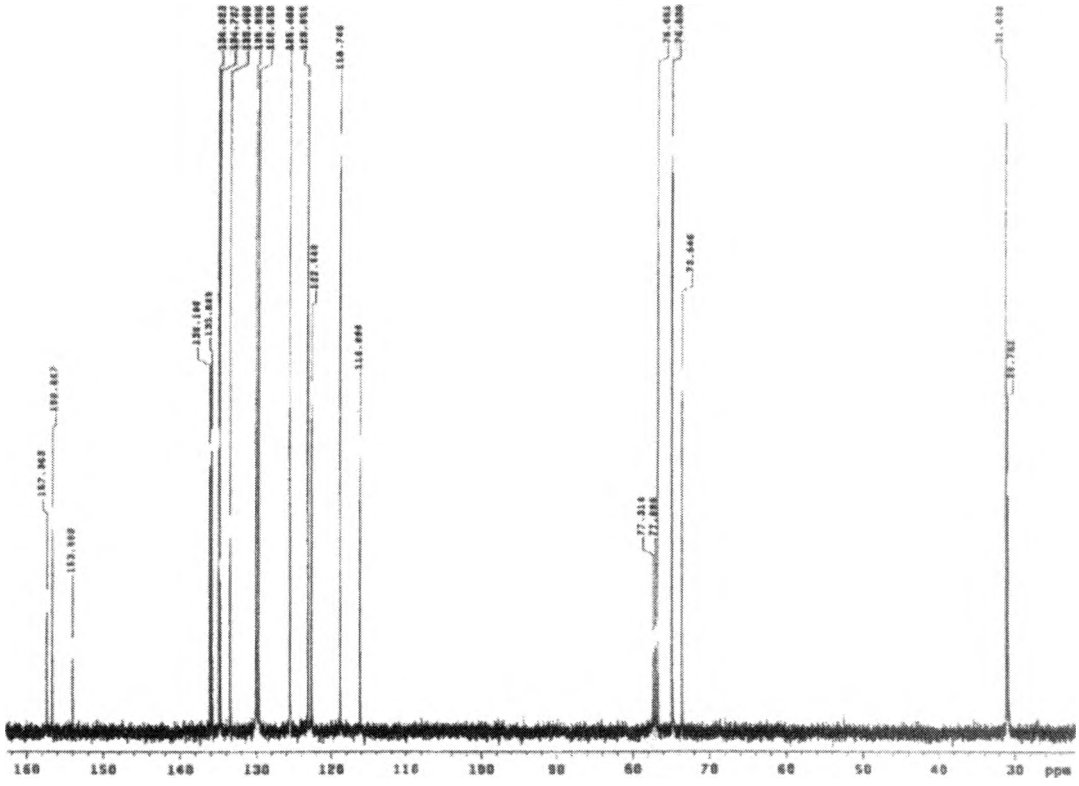
Spectrum 7 NMR COSY of compound **5**.



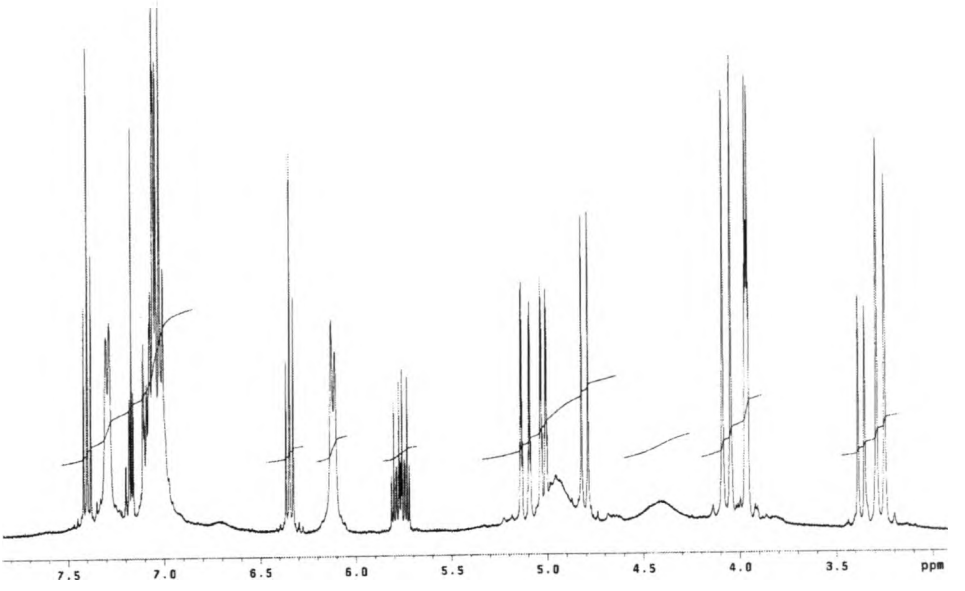
Spectrum 8 Variable temperature at 50 ^{o}C for compound **5**.



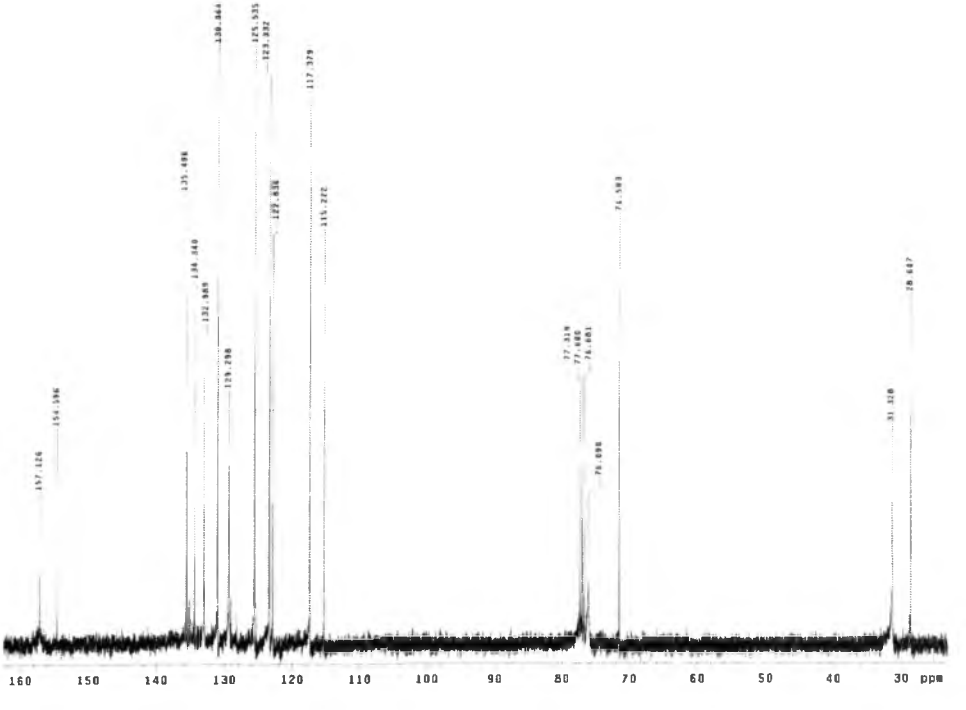
Spectrum 9 ^{1}H NMR of compound **6**.



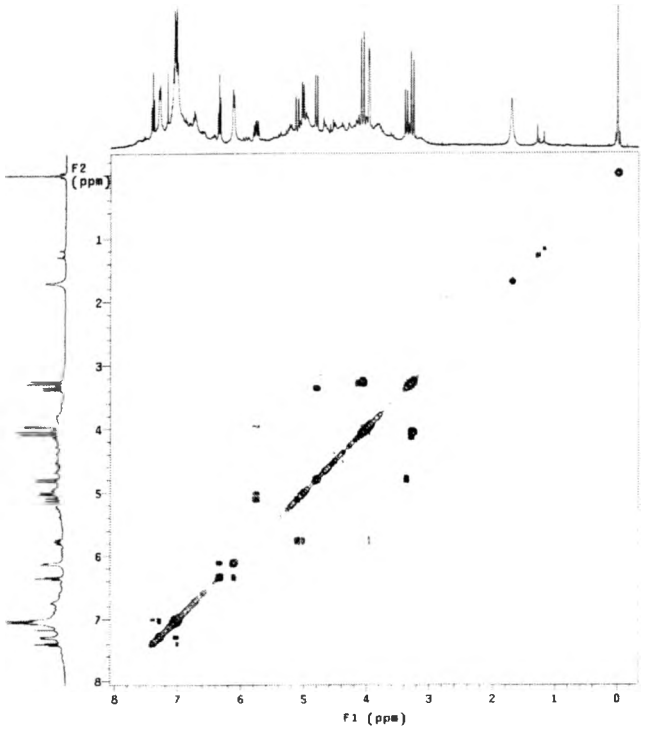
Spectrum 10 ^{13}C NMR of compound **6**.



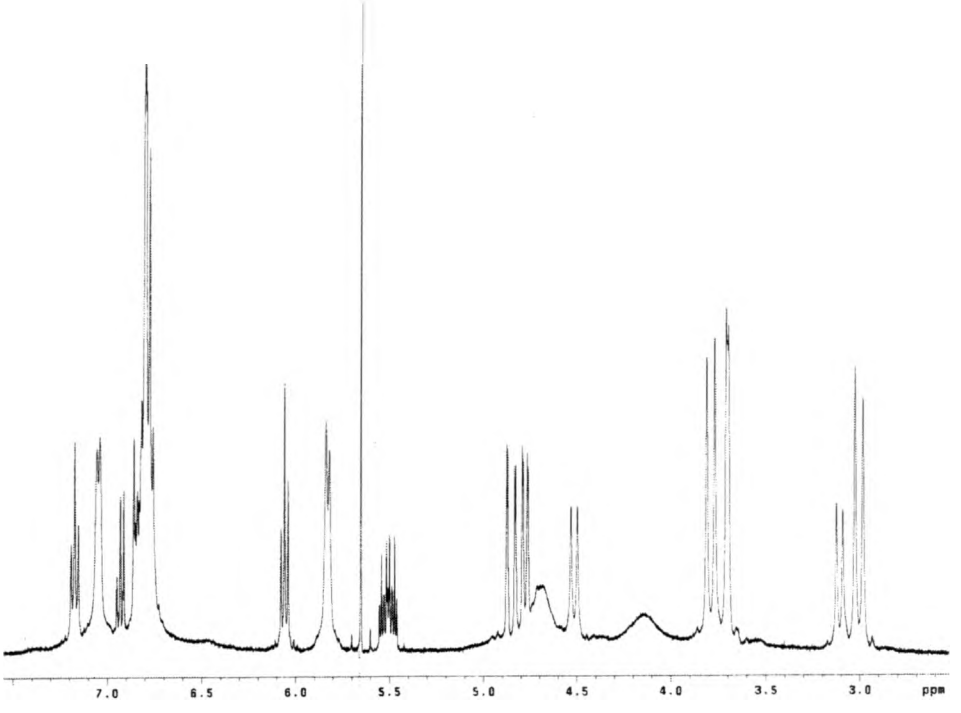
Spectrum 11 ^{1}H of compound **7**.



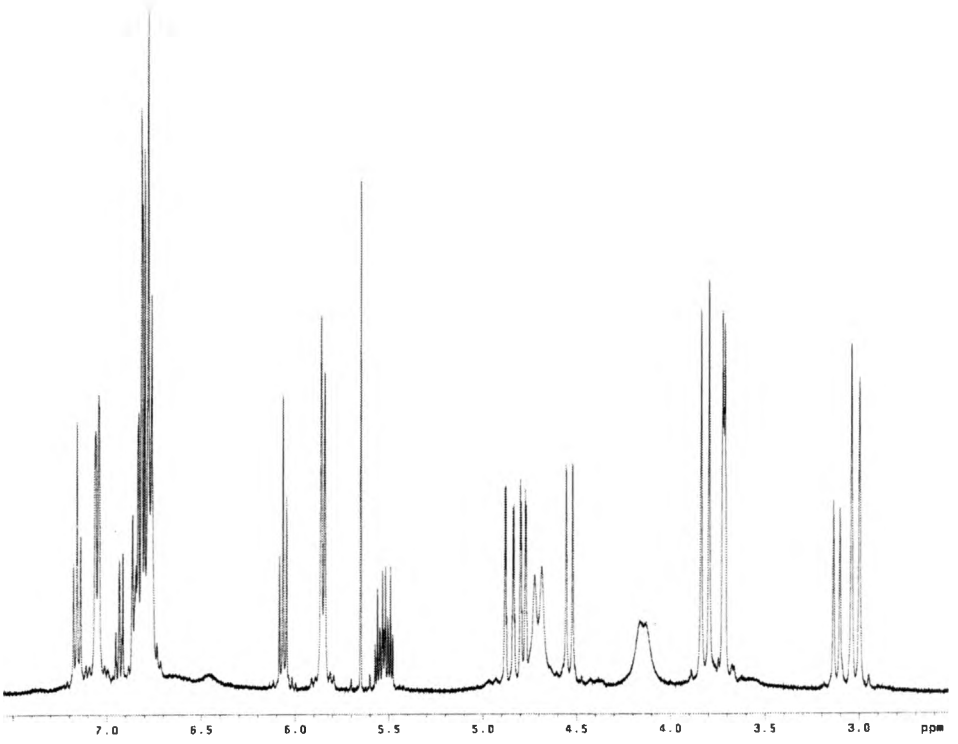
Spectrum 12 ^{13}C of compound **7**.



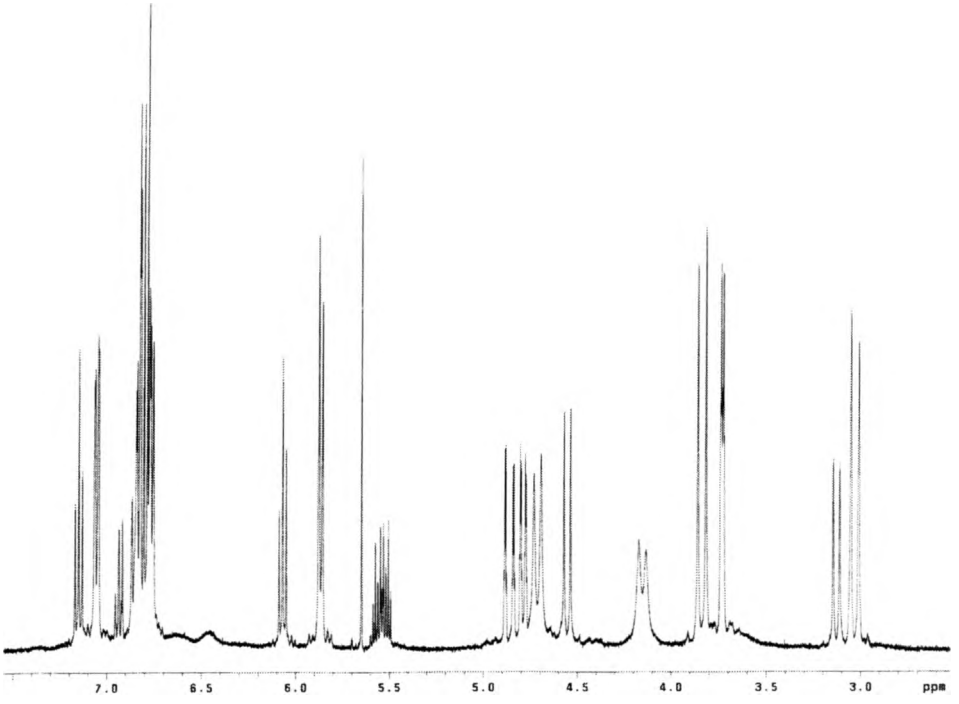
Spectrum 13 NMR COSY of compound **7**.



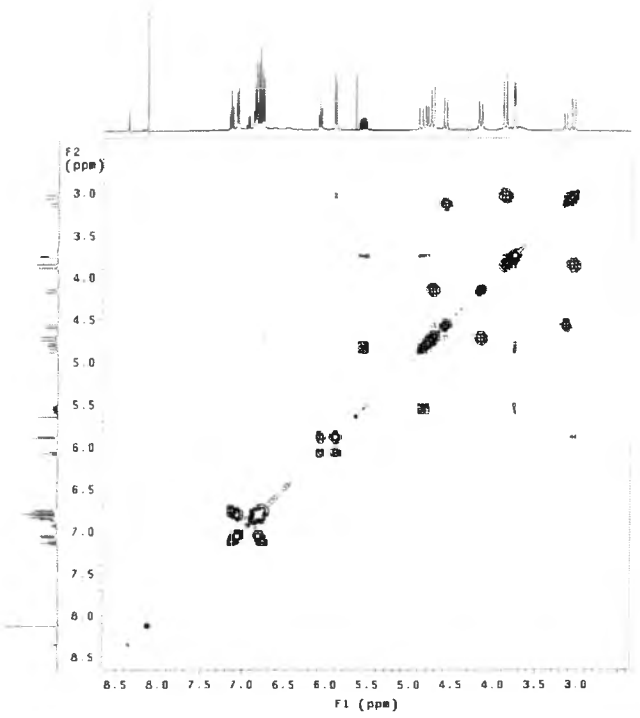
Spectrum 14 Variable temperature at 22 ^{o}C of compound **7**



Spectrum 15 Variable temperature at 50 °C of compound **7**.



Spectrum 16 Variable temperature at 70 °C of compound **7**.



Spectrum 17 NMR COSY at 100 ^{o}C of compound **7**.

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VITA

Sara Jean Staggs was born in Fort Worth, Texas, on October 5, 1978, the daughter of Nancylee Whitfield Staggs and Michael Jon Staggs. After completing her work at Richland High School, North Richland Hills, Texas, in 1997, she entered Southwest Texas State University in San Marcos, Texas, during which time she studied biology and was involved in many volunteer activities. She started undergraduate research in the Chemistry and Biochemistry department her senior year. She received the degree of Bachelor of Science in Biology from Southwest Texas State University in May 2001. She entered graduate school at Southwest Texas State University in the Chemistry and Biochemistry department in August 2001 to obtain a Master of Science in Biochemistry.

Permanent Address: 1409 N. Bishop St. #5
San Marcos, TX 78666

Sara J. Staggs typed this Thesis.