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Synthesis of Ester Group Based Macrocyclic Diacetylene

A Thesis Presented

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Abstract of the Thesis

Synthesis of Ester Group Based Macrocyclic Diacetylene

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Due to its interesting reactivity and structural characteristics, discovery of the effective methods to synthesize macrocyclic compounds has been a center of interest of many chemists. The fact that macrocyclic compounds contain large cavity at their center has led to the possibility that polymerization of macrocyclic compounds would result in a supramolecular tube, through which ion complexes or microscopic compounds may pass in and out. Such structural characteristic of a tubular structure has inspired many chemists to exploit and investigate potentials of the macrocyclic compounds, and to design variable derivatives of these compounds.

For the above reasons, we set out to synthesize a diacetylene macrocyclic compound which possesses an ester functional group substituted on both benzene rings located in the opposite sides of the macrocyclic ring (Figure 1). This project focuses on step by step reactions starting from tribromo benzene to the final product of interest. Due

to many technical difficulties, which added complication to our reaction, we were able to obtain only ^{1}H NMR data of the final product. Since ^{1}H NMR data is the only source with which we could analyze the structure of the final product, we could not confidently confirm a successful synthesis of an ester based macrocyclic diacetylene. Nevertheless, all peaks in the ^{1}H NMR spectrum of the final product are positioned at the reasonable chemical shifts, which correspond to what we would expect from the target product (See Figure 15-3 on the page 29).

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Chapter A. Introduction

A.1 Introduction to Supermolecules

One of the challenges that modern supermolecular chemistry research faces is the synthesis of macrocyclic or cage-like cavities up to a nanometer scale. Due to their capability to act as hosts for particular substrates, such molecules may play important roles such as storage devices or as reaction cavities.[1] Macrocyclic molecules, for instance, may encapsulate catalysts in order to optimize the selectivity of catalytic reactions by formulating specific reaction channels.[3] When these macrocyclic molecules stack up one after another, a nanometer-scale tube-like structure forms, or simply what is called nanotube. Generally speaking, a supermolecule, which is a broader term to include a nanotube, can be defined as a "molecule beyond a molecule" - a large and complex entity formed from other molecules.[1,2] According to Dr. Lehn, who invented this term, a supermolecule is an organized, complex entity that is created from the association of two or more chemical species held together by intermolecular forces.[5] Nanotubular structures are the result of not only additive but also cooperative interactions, including hydrogen bonding, hydrophobic interactions and coordination, and their properties are different (often better) than the sum of the properties of each individual component.[3] Accordingly, our effort to synthesize such individual component, carbonyl group - based diacetylene macrocycle has been driven by strong desire to observe potential capabilities of nanotubes built from our macrocyclic molecules.

The origin of "molecular recognition" is often said to be the "lock and key" principle proposed by Emil Fischer in 1894.[6,8] This concept proposed that the mechanism by which an enzyme recognizes and interacts with a substrate can be likened to a lock

and a key system. The presence of natural products that can recognize particular molecules was already known by the 1950s: for example, the recognition capabilities of the cyclic oligosaccharide cyclodextrin and those of the cyclic oligopeptide valinomycin.[6] In 1967, Pedersen observed that crown ether showed molecular recognition - the first artificial molecule found to do so.[7] Cram developed this concept to cover a wide range of molecular systems and established a new field of chemistry, host–guest chemistry, where the host molecule can accommodate another molecule, called the guest molecule.[4] The molecular recognition can be regarded in many ways as the most fundamental kind of supramolecular chemistry, because all supramolecular chemistry is based on how to recognize molecules, how to influence molecules, and how to express specific functions due to molecular interactions.[5] The importance of molecular recognition first came to light in the middle of the nineteenth century - considerably before the concept of supramolecules was established.[9] For example, Pasteur noticed during microscopic observations that crystals of tartaric acid occurred in two types, that were mirror images of each other, and found that mold and yeast recognize and utilize only one of these types.[6] In 1978, Lehn attempted to organize these novel chemistries, and first proposed the term "supramolecular chemistry".[5,27] This represented the moment that supramolecular chemistry was clearly established. Together, Pedersen, Cram and Lehn received the Nobel Prize for Chemistry in 1987.[4,5]

A.2 Design of Macrocyclic Supramolecules

As the functional capability of macrocyclic compound has been widely recognized and studied by many chemists since the Pederson's discovery of crown ether in 1967, understanding how the structure of an individual macrocyclic compound would affect the overall structure of macrocyclic supramolecule or macrocyclic nanotube was also considered as important in supramolecular chemistry.[10] In other words, a successful design of a macrocyclic nanotube comes from not only well understanding of noncovalent-intermolecular force which spontaneously binds individual macrocyclic compound with another,[13,21] but also covalent interaction within individual macrocyclic compound. First, let's see what types of intermolecular forces are available which are necessary to aggregate macrocyclic compounds to form a tube.[25,33,34]

> Electrostatic interactions occur between charged molecules. An attractive force is observed between oppositely charged molecules, and a repulsive force between molecules with the same type of charge (either negative or positive). The magnitude of this interaction is relatively large compared to other non-covalent interactions. The strength of this interaction changes in inverse proportion to the dielectric constant of the surrounding medium. Therefore, in a more hydrophobic environment with a smaller dielectric constant, the electrostatic interaction becomes stronger. If a functional group is in equilibrium between ionized and neutral forms, the population of the latter form decreases in a hydrophobic medium, resulting in a decreased contribution from the electrostatic interaction.

Dipole–dipole and dipole–ion interactions play important roles in neutral species instead of electrostatic interactions.

Hydrogen bonding often plays a crucial role in the design of macrocyclic supramolecules, although a hydrogen bonding interaction is weaker than an electrostatic interaction. Hydrogen bonding only occurs when the functional groups that are interacting are properly oriented. This is why hydrogen bonding is the key interaction during recognition between molecules in many cases. The importance of hydrogen bonding to molecular recognition is illustrated by the base-pairing that occurs in DNA strands, where nuclear bases recognize their correct partners in a highly specific way. Hydrogen bonding is one type of dipole–dipole interaction, where positively polarized hydrogen atoms in hydroxyl (OH) groups and amino groups (–NH–) contribute. Because the polarized hydrogen atom has a small radius, it strongly interacts with other electron-rich atoms (O in C=O, N in CN) located nearby. This results in relatively strong direction-specific hydrogen bonding between these functional groups.

Coordinate bonding is another type of direction-specific interaction. This type of interaction occurs between metal ions and electron-rich atoms and is of moderate strength. Such interactions have also been utilized in the formation of supramolecular assemblies.

The van der Waals interaction is weaker and less specific than those described above, but it is undoubtedly important because this interaction generally applies to all kinds of molecules. It is driven by the interactions of dipoles created by instantaneous unbalanced electronic distributions in neutral substances. Although individual interactions are negligible, the combined cooperative contributions from numerous van der Waals interactions make a significant contribution to molecular recognition. When the interacting molecules have surfaces with complementary shapes, as in the lock and key concept, the van der Waals interaction becomes more effective. This interaction is especially important when the host molecule recognizes the shape of the guest molecule. In an aqueous medium, the hydrophobic interaction plays a very important role. It is the major driving force for hydrophobic molecules to aggregate in an aqueous medium, as seen in the formation of a cell membrane from lipid-based components. The hydrophobic interaction is not, as its name may suggest, an interaction between hydrophobic molecules. This interaction is related to the hydration structure present around hydrophobic molecules. Water molecules form structured hydration layers that are not entropically advantageous. It is believed that hydrophobic substances aggregate to minimize the number of water molecules involved in hydration layers. However, the mechanism and nature of the hydrophobic interaction is not that clear. Unusual characteristics, such as incredible interaction distances, have been reported for the hydrophobic interaction, and the fundamentals of hydrophobic interaction are still under debate even today.

π–π interactions occur between aromatic rings, and these sometimes provide important contributions to molecular recognition. When the aromatic rings face each other, the overlap of π-electron orbitals results in an energetic gain. For example, the double-strand structure of DNA is partially stabilized through π–π interactions between neighboring base-pairs.

In considering the use of hydrogen bonds in organic crystal engineering, it is important to establish the applicability of different classes of hydrogen bonds.[44] This will depend upon hydrogen bond strength, the reliability of hydrogen bonded recognition motifs and how abundant or attainable the particular hydrogen bonds may be.[34,38] While many texts classify hydrogen bonds as 'strong' and 'weak', the borderline between these classes, usually delineated in terms of hydrogen bond energies, often varies depending on the context in which hydrogen bonding is being discussed.[34] The classifications provided by Desiraju and Steiner,[34e] which are assigned in the context of the utility of hydrogen bonds in supramolecular chemistry, are documented in **Table 1**. Hydrogen bond types that are widely used in organic crystal engineering, primarily D-H---A where D, A = O or N, will inevitably be important in organic systems since the same functional groups that form such hydrogen bonds, i.e. carboxyl, amide, oxime, alcohol, amine, etc., can be present as part of organic infrastructure used in supramolecular building blocks.[34b,35] These are strong hydrogen bonds (ca 4-15 kcal/mol) when formed between neutral ligands but can be stronger still when involving ionic species due to the additional electrostatic attraction between the ions, often referred to as 'charge-assistance'.[39,40] Strong hydrogen bonds can be effective at directing association of building blocks and are therefore very valuable in

crystal engineering.[22,36]

	Very Strong	Strong	Weak
Bond Energy (Kcal/mole)	15-40	4-15	<4
Examples	$[F\cdots H\cdots F]^-$ $[N\cdots H\cdots N]^+$ P-OH···O=P	O-H···O=C N-H···O=C O-H···O-H	C-H···O N-H···F-C O-H···π
Bond Lengths	D-H≈H···A	D-H<H···A	O-H<<H···A
Lengthening of D-H (Å)	0.05-0.2	0.01-0.05	≤0.01
D···A range (Å)	2.2-2.5	2.5-3.0	3.0-4.5
H···A range (Å)	1.2-1.5	1.5-2.2	2.2-3.5
D-H···A Angles range (^{O})	175-180	130-180	90-180
Effect on Crystal Packing	Strong	Distinctive	Variable
Utility in Crystal Engineering	Unknown	Useful	Partly useful
Covalency	Pronounced	Weak	Vanishing
Electrostatic Contribution	Significant	Dominant	Moderate

Table 1: Classification and properties of hydrogen bonds, D-H---A.[34e]

In the molecular recognition systems that appear in the following illustrations, selective and effective recognition is achieved through the above-mentioned molecular interactions. A successful intermolecular interaction between macrocyclic compounds leads to the synthesis of hollow nanotubular structures, the potential roles of which are widely applicable in biology, chemistry and material science.[11,19] In most of cases, designing such supramolecular architecture relies on self-assembly and self-organization.[28]

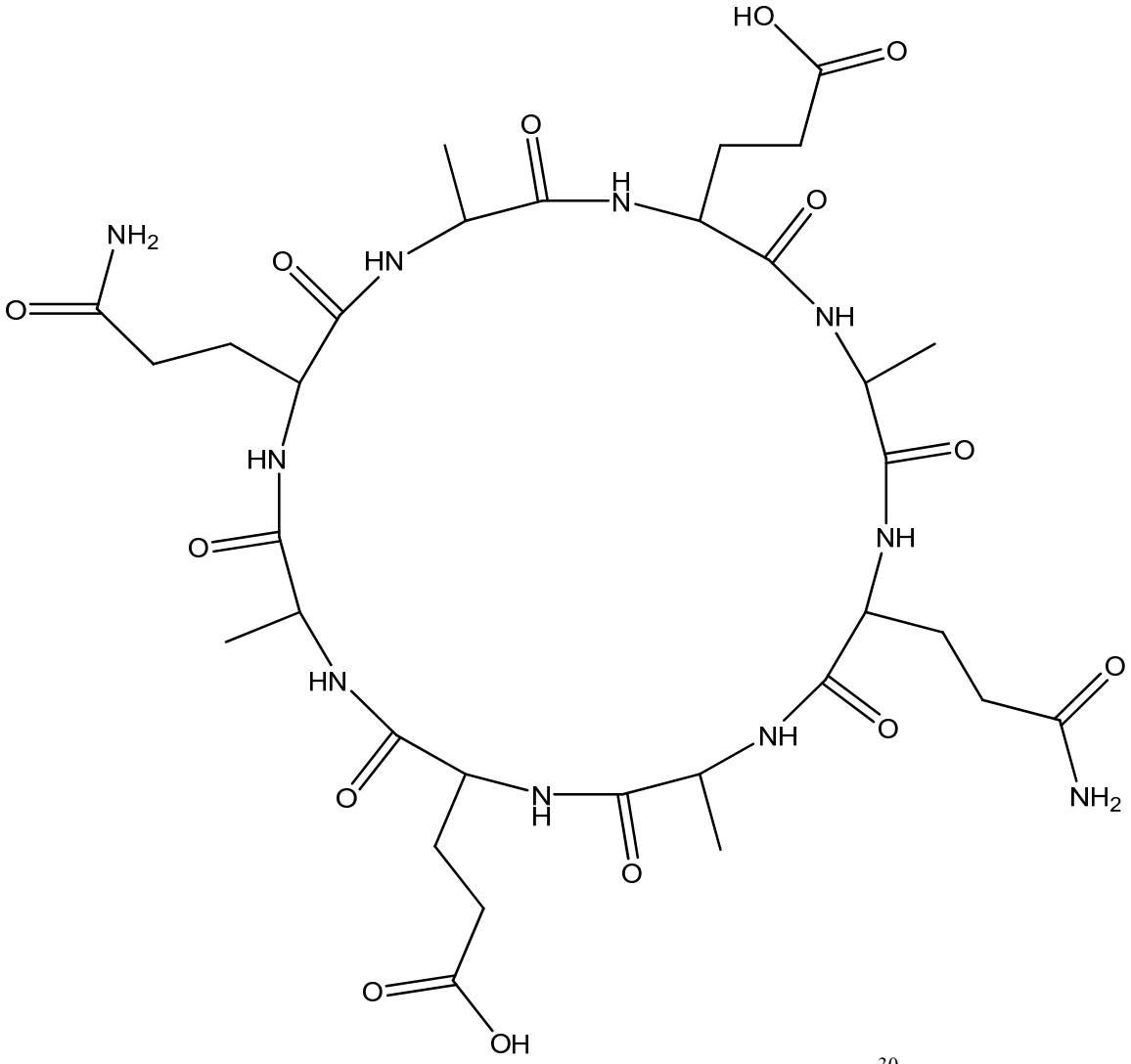
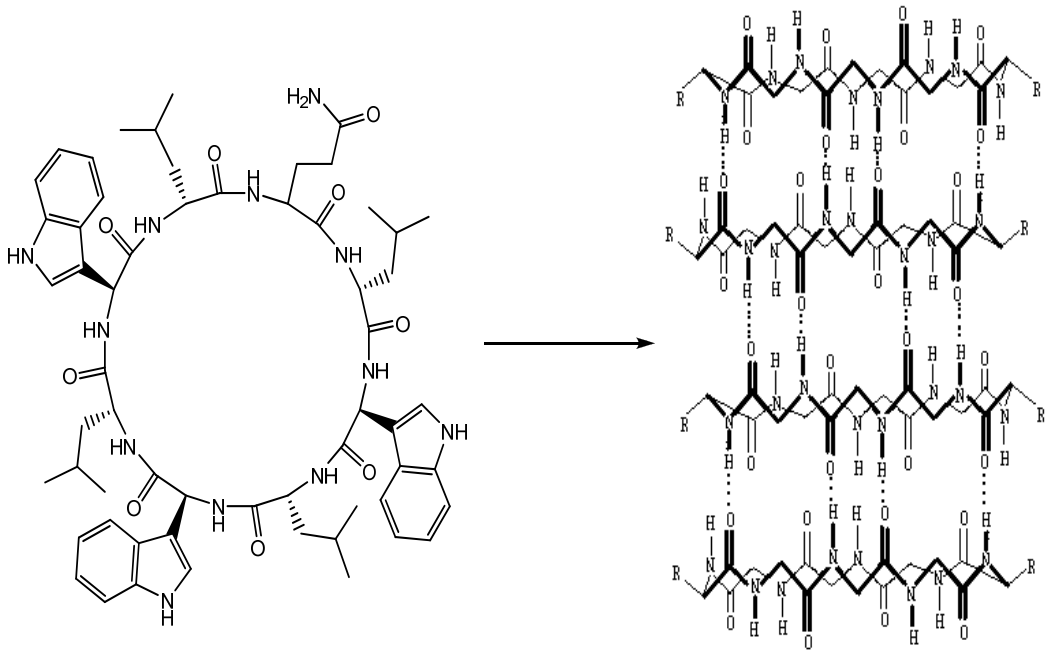


Figure 1: Octapeptide cyclo-[-(D-Ala-Glu-D-Ala-Gln)$_2$] [30]

It has been found that self-assembled nanotubes (**Figure 2**) are spontaneously built from cyclic peptides made up of alternating D- and L-amino acids.[30] As predicted by DeSantis group in the mid 1970s, the octapeptide cyclo-[-(D-Ala-Glu-D-Ala-Gln)$_2$] (**Figure 1**) is approximately planar with NH and C=O bonds orientated perpendicularly to the mean plane of the macro-ring thus favoring formation of hydrogen bond.



1

Figure 2: Self-assembled nanotube built from cyclic peptides[30]

Hydrophobic side chains in cyclo-[-(Trp-D-Leu)$_3$-Gln-D-Leu] **1** obtained by Ghadiri and coworkers enabled the incorporation of such nanotube into a membrane where **1** can play a role of trans-membrane channel capable of proton transport (**Figure 3**).[30] The channel pore diameter leading to a selective transport of ions depends on the macrocycle size. A modified peptide as a transmembrane channel was also reported by Meillon and Voyer.[31]

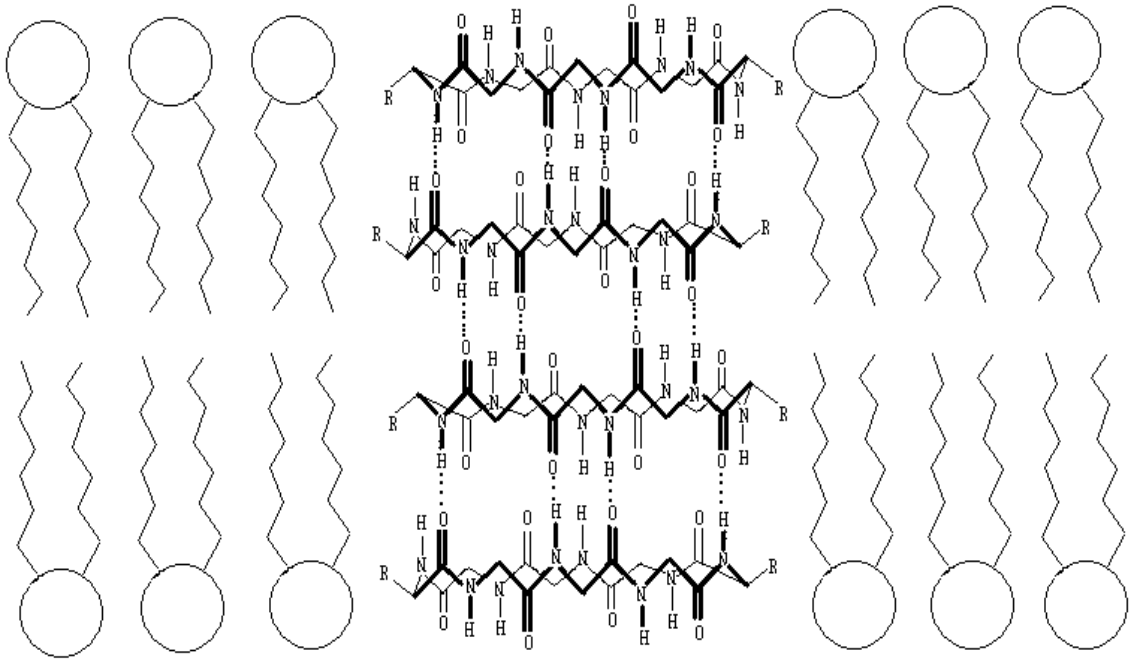
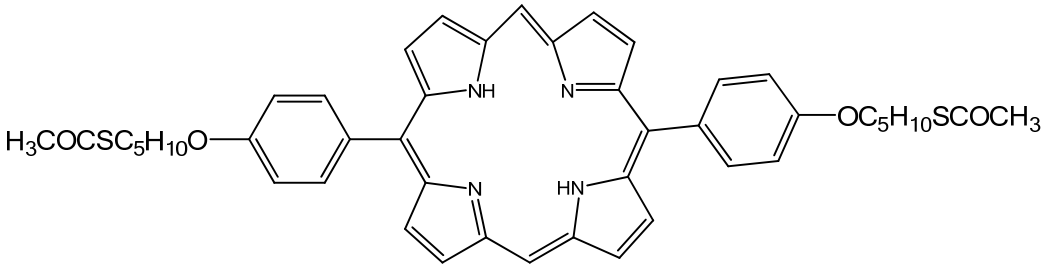


Figure 3: Self-assembled peptide nanotube incorporated into a membrane[30]

In 2008, Gao et al. designed metal-free 5,15-di[4-(5-acetylsulfanylpentyloxy) phenyl] porphyrin H_2[DP(CH3COS$C_5H_{10}O)_2$P] **1** and its zinc congener Zn[DP(CH_3COS$C_5H_{10}O)_2$P] **2** (**Figure 5**).[20] **Figure 5** shows the crystal packing diagrams for both porphyrin derivatives. As revealed in the crystal-packing diagram of metal-free porphyrin **1** (**Figure 5A**), the solvated chloroform molecules connect neighboring metal-free porphyrin molecules into a face-to-face stacking supramolecular structure depending on the C-H$\cdots\pi$ interaction in the crystal of **1**, leading to a relatively large separation between the neighboring metal-free porphyrin rings, 5.19 Å.[20] According to their report, this in turn will result in a relatively weak π-π interaction between neighboring stacking porphyrin ligands in the direction perpendicular to the porphyrin rings because of the relatively large intermolecular distance.[20]

The porphyrinato zinc analogue **2** is packed differently in the crystal structure. As

shown in **Figure 5B**, each porphyrinato zinc molecule is bound with two neighboring molecules, forming a head-to-tail porphyrin supramolecular chain via the Zn-O coordination bond between the central metal zinc of porphyrin molecule with the carbonyl oxygen in the aryloxy side chain of meso-attached phenyl groups in the neighboring porphyrin molecules.[20]



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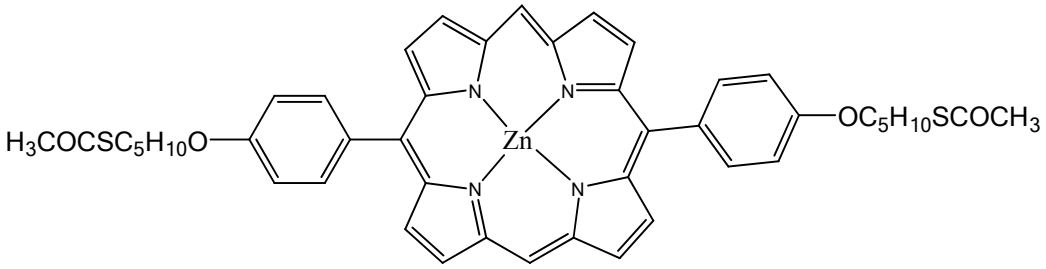

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Figure 4: Macrocycles synthesized by Gao and co-workers[20]

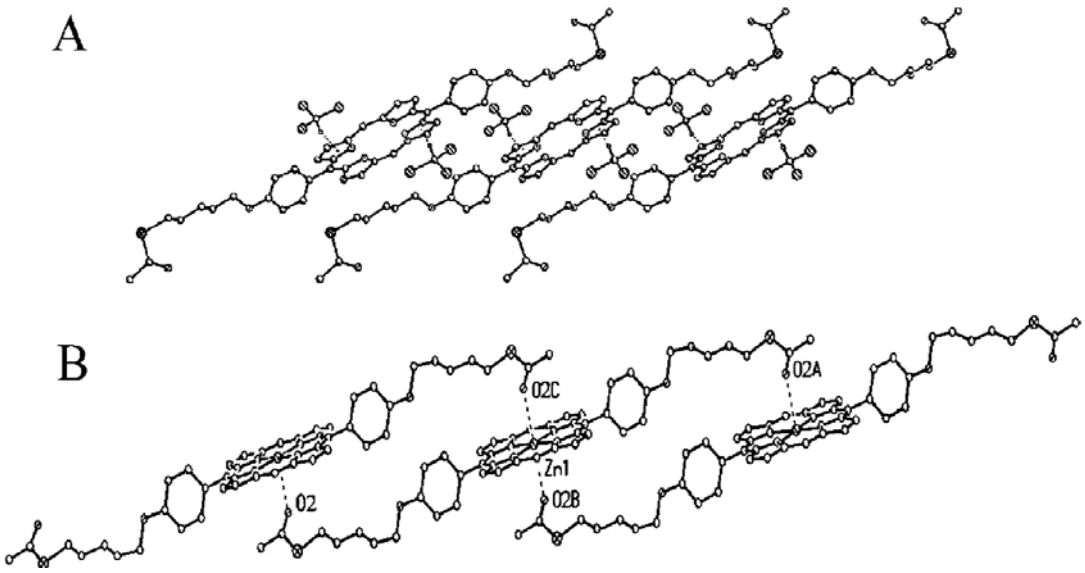


Figure 5: Crystal-packing diagrams for $H_2[DP(CH_3COSC_5H_{10}O)_2P]$ **1** (A) and $Zn[DP(CH_3COSC_5H_{10}O)_2P]$ **2** (B) in side view[20]

Depending mainly on the intermolecular π-π interaction in cooperation with the van der Waals interaction, molecules of metal-free porphyrin **1** self-assemble into nanostructures with hollow sphere morphology with a diameter of ca. 700 nm.[20]

For porphyrinato zinc complex **2**, self-assembly process in *n*-hexane leads to the formation of nanostructures with hollow sphere morphology with diameter of ca. 40 nm.[20]

In 2008 Ghosh et al. reported "the synthesis and self-assembly of a series of organogelators based on perylene bisimide (PBI) dyes" (**Figure 6**) containing amide groups at imide positions.[18] The intermolecular hydrogen bonding among the amide functionalities and π-π interaction between the PBI units directs the formation of the self-assembled structure in solution (**Figure 7**). PBI having linear alkyl substituents in R^1, R^2, and R^3 positions prefer to self-assemble as "more compact H-type aggregates," whereas PBI containing three branched alkyl substituents in R^1, R^2, and R^3 positions prefer to self-

assemble as "J-type aggregates" as shown in **Figure 7**.[18]

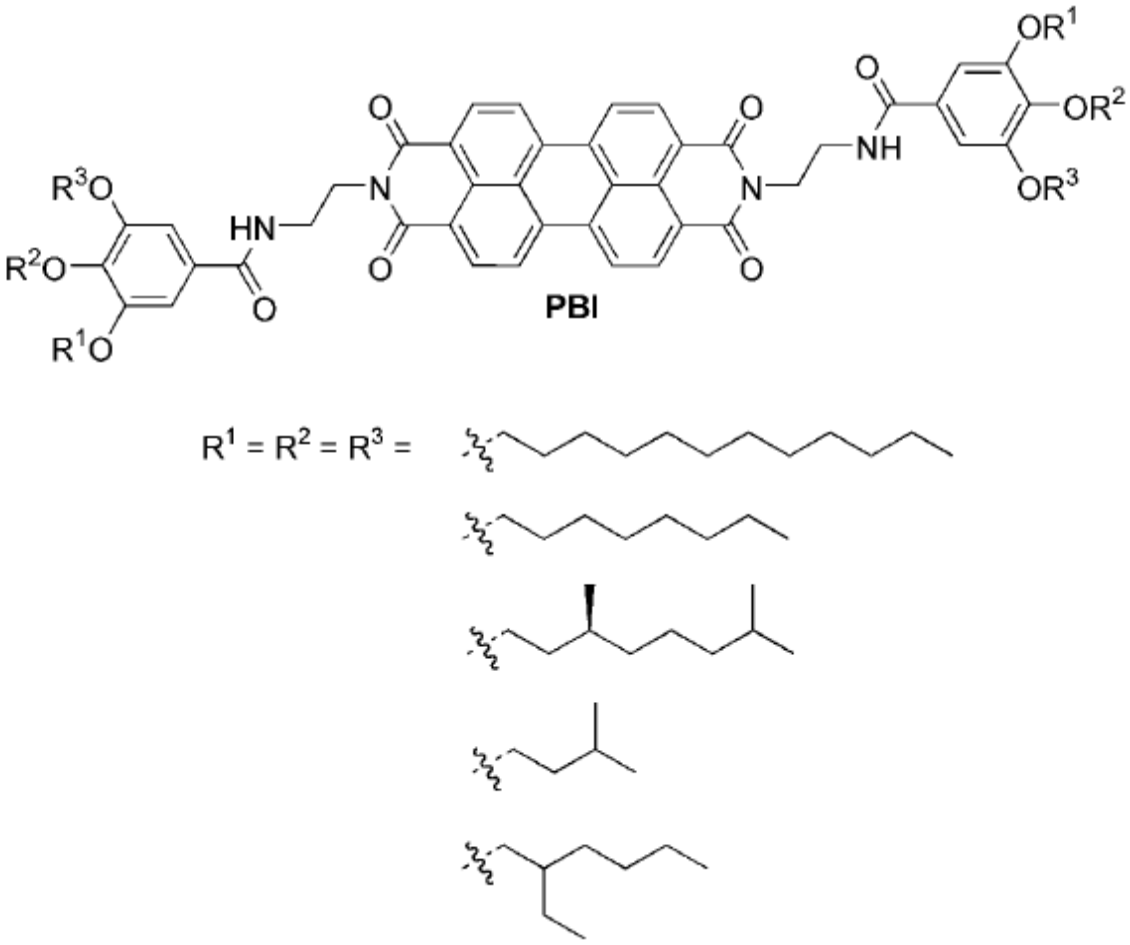


Figure 6: Structure of perylene bisimide (PBI)[18]

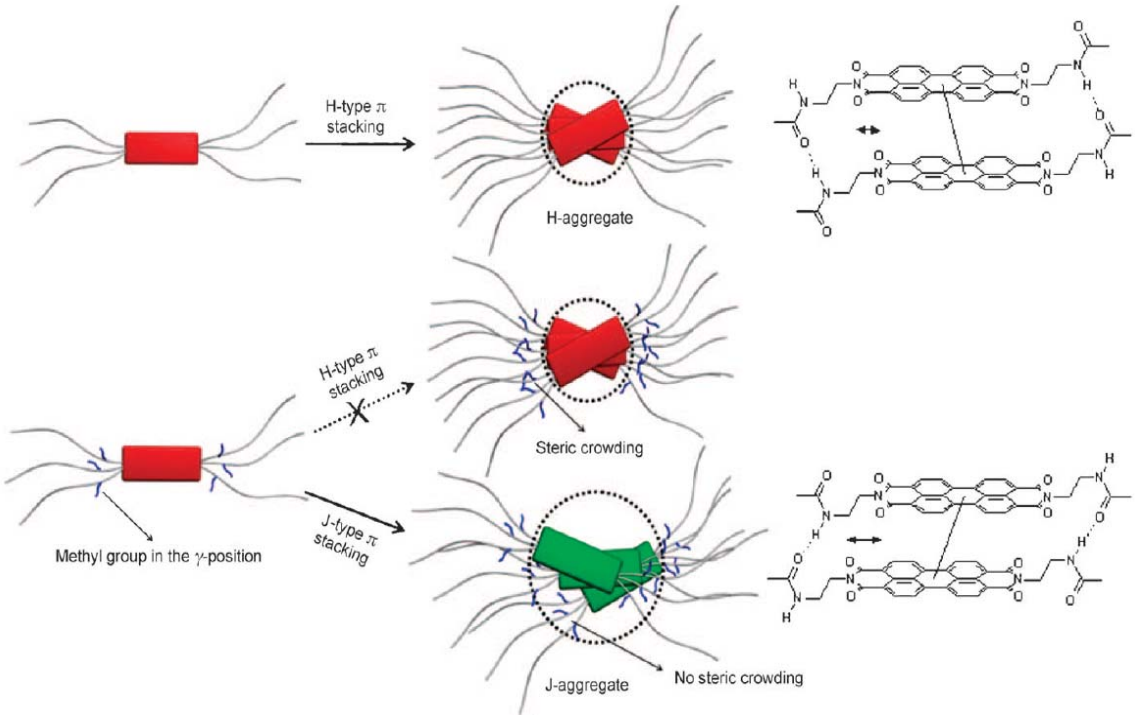


Figure 7: Schematic diagram of packing of PBI with linear (top) and branched (bottom) alkyl substituents[18]

The structural characteristics of macrocyclic compounds has led to the conclusion that polymerization of these compounds via intermolecular forces would make a hollow tubular structure through which target ions complexes or organic and inorganic compounds may pass in and out. Such a significant structural characteristic of macrocyclic supramolecules have inspired many chemists and material scientists to exploit and investigate potentialities of the macrocyclic compounds, and to design an effective strategy to synthesize these compounds. Because the intermolecular forces such as hydrogen bonding, van der Waals interaction, and π–π interactions play a pivotal role in determining stacking pattern of macrocyclic compounds, the variable application of these interactions links to the development and advancement of supramolecular chemistry.

In the next section, we will see how these intermolecular interaction influences the polymerization of diacetylene; and how they predict the outcome of our project goal.

A.3 Host-Guest Strategy to Design Macrocyclic Supramolecules

The exemplar cases of polymerization of macrocyclic compounds shown in the previous section can be recognized as "intrinsic reactivity" because the stacking arrangement of the macrocyclic compounds was not controlled under a condensed medium or highly ordered state which often induces high region-, chemo-, and stereo-selectivity; and which therefore put a limitation on atomic and molecular movement in crystal states.[14] If the stacking process took place in such an environment, we would call it a topochemical reaction, which was postulated by Kohlshutter in 1918.[15] He characterizes the topochemical reaction as "one in which both the nature and properties of the products are governed by such a constraining system."[14] Then, what is the benefit of using this kind of system to carry out stacking process of macrocyclic compounds? Due to high degree of selectivity, the solid state of topochemical reaction system enables one to produce a well defined and organized crystal tube in a highly controlled manner, so that one may easily explain the formation of a product.[28] Nevertheless, there are strict rules for a successful topochemical reaction.[23] First, the medium of the reaction must be in a highly ordered solid state, so that the movement of individual macrocyclic compound would be very minimal. The restrictive control over their movement is very important because the integrity of crystal structure shall not be disturbed. Second, in order to achieve a desired reaction, the specific distance between two macrocyclic compounds must be maintained. For this reason, this type of reaction requires a well controlled intermolecular spacing among all molecules in the system. Host-Guest reaction is a type

of topochemical reaction; and is the one by which we may be able to construct a well-defined supramolecular tube assembled from carboxyl-based macrocyclic diacetylenes.

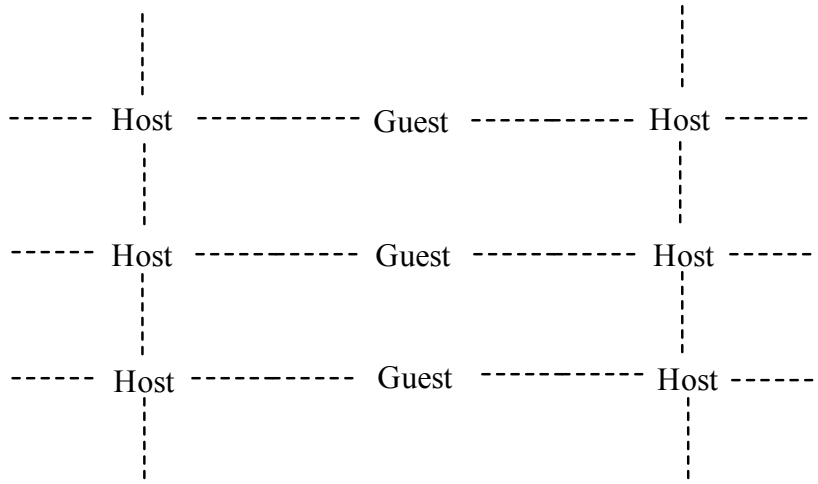


Figure 8: Host-Guest Strategy

Figure 8 shows the basic idea of the host-guest strategy. The host molecules are the compounds, which can self assemble into α-hydrogen bonding networks with a giving spacing and impose the same spacing onto the guest.[28] "The guest molecules are compounds that provide functionality."[28] Because this strategy is accomplished by the intermolecular interaction between host compounds and guest compounds, it is also called "co-crystal" strategy. To be more specific, guest molecules are our carbonyl based-macrocyclic diacetylenes, and host molecule is one of candidate molecules listed below (**Figure 9**).

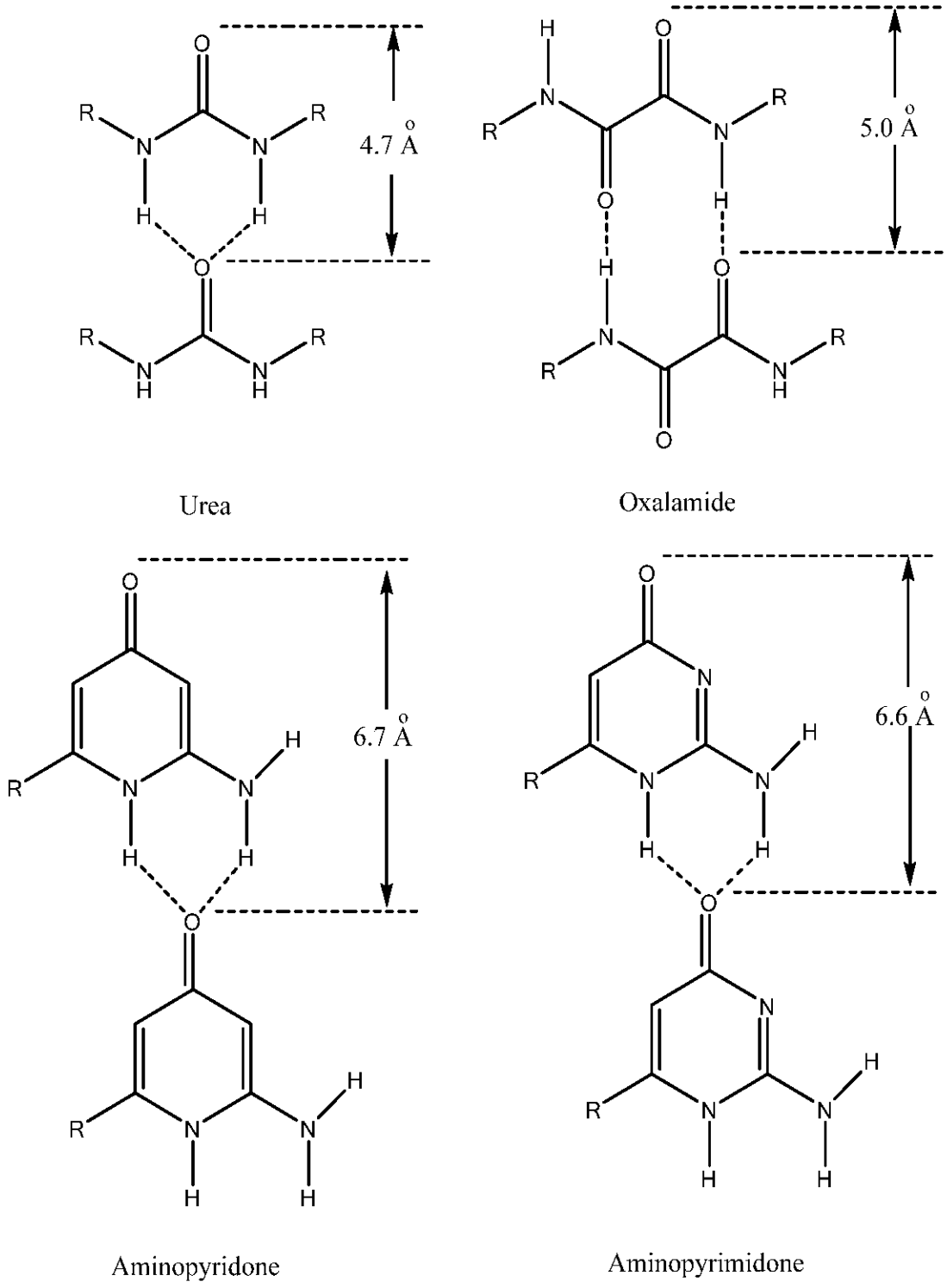


Figure 9: Examples of hydrogen bonding host molecules with variable repeating distances[28]

If we assume that the established scheme in **Figure 8** would be applicable to our reaction scheme; and hydrogen bonding interconnection would exist between our macrocyclic unit and a host molecule, a postulated structure in **Figure 10** (See below) might be deduced. Of course, this figure should be labeled as a model because it is presented here only to enhance our understanding of Host-Guest strategy.

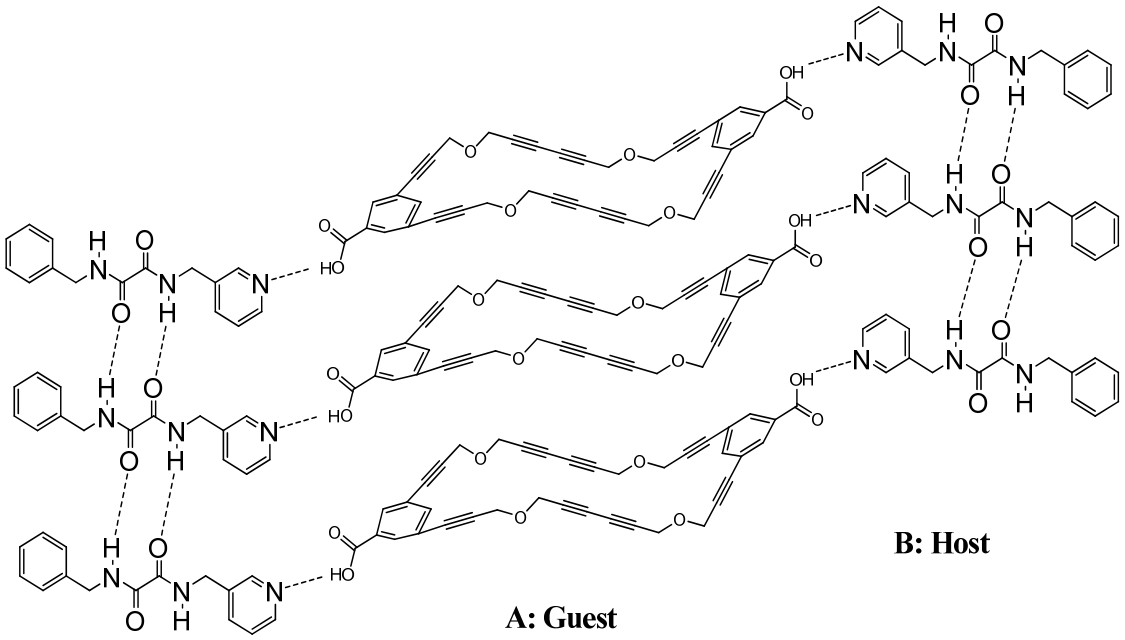


Figure 10: Postulated structure of Host-Guest Network of Carbonyl based-macrocyclic diacetylenes (**A: Guest**) and **Host** (**B**)

In **Figure 10**, Host molecules (**B**) are interconnected with each other by hydrogen bonds, and they are also held together with guest molecules (**A**), or carbonyl based-macrocyclic diacetylenes. As you can see, hydrogen bonding between host molecules provides a

spacing distance of a certain magnitude between guest molecules. In addition, this specific distance is so important to our reaction. We will see why this distance is important to us.

We now know the basic role of a host molecule, and choosing an appropriate one will provide a desired repeating distance between the macrocyclic diacetylenes. More importantly, in order to ensure the consistency of such repeating distances, we need a topochemical mechanism which would innervate between guest molecules and produce a covalent bond between them. Topochemical 1,4-polymerization (**Figure 12**) is so far most convincing source to explain this reaction.[33] Therefore, we will see how 1,4-polymerization would affect the diacetylene functional groups (See the area in the square in **Figure 11**) in our guest molecules (**Figure 11**).

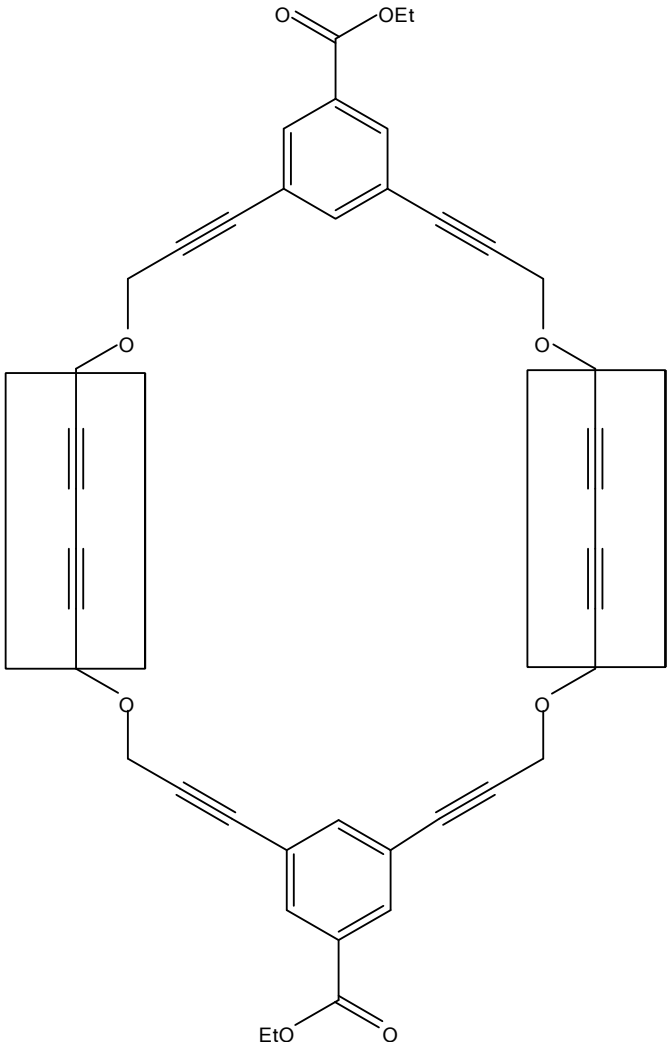


Figure 11: Structure of our macrocyclic compound (Diacetylene functional groups in squares undergoes 1,4-polymerization)

The 1,4-polymeriazation reaction, which was pioneered by G. Wegner in 1969, requires two conditions (See **Figure 12**):[24]

First, the spacing between two diacetylene monomers must be arranged with a repeating spacing distance (d) of about 4.9 Å, which will be slightly altered after polymerization. Second, the monomers must be tilted at an angle (ϕ) of about 45^{o}, which brings the contact distance ($C_{1,4}$) into 3.5 Å, which is the sum of the van

der walls radius of C_1 and C_4. The reaction can then take place with a minimum amount of atom motion and that of an in-place rotational movement of the diacetylene core unit.

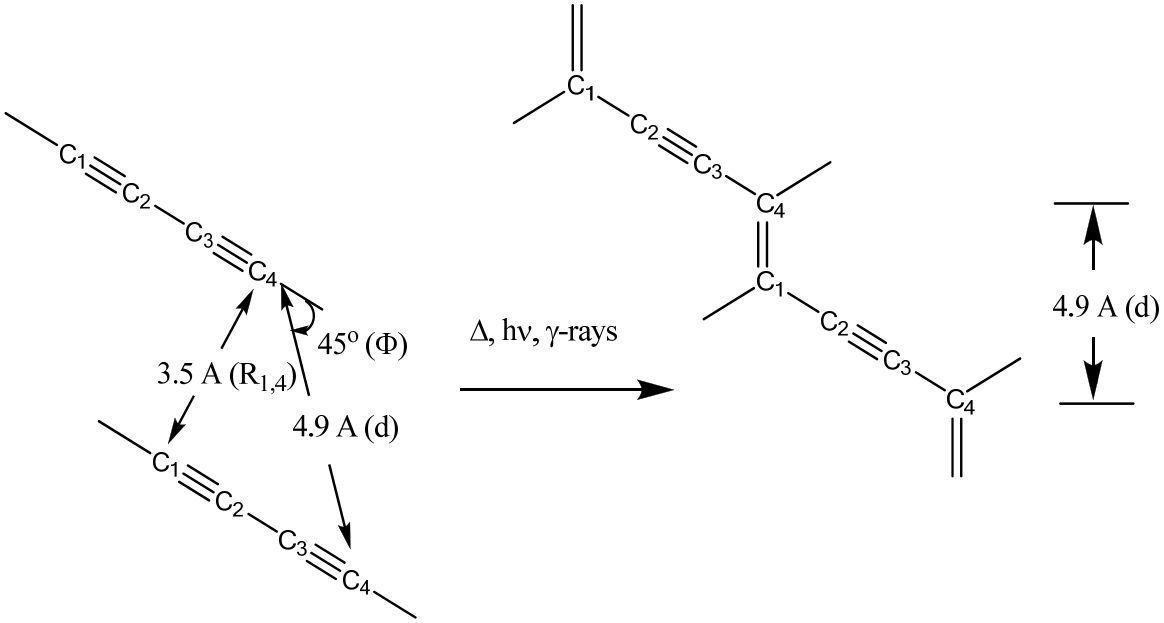
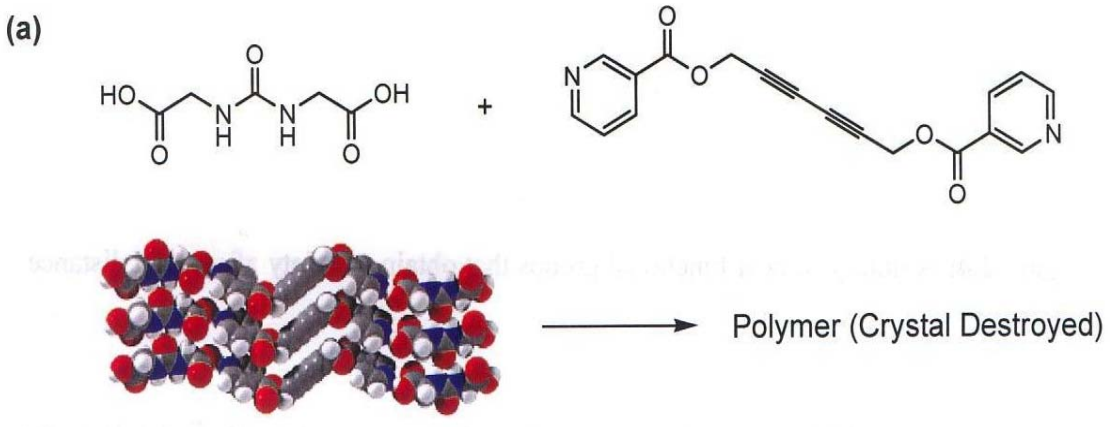


Figure 12: Illustration of 1,4-topochemical polymerization and required structure parameters

Therefore, in order to obtain required spacing between two diacetylenes, we need host molecules whose intermolecular repeating distance between themselves is the same as or close enough to such distance. In this case, urea and oxalamide seem suitable for our purpose. As you noticed in **Figure 12**, a covalent double bond between C_1 and C_4 has formed. In the past, in order to explain this bond formation between diacetylene units, our group established two mechanisms: The "Turn-Stile" and "Swinging-Gate" Mechanisms.[16, 17, 25, 26] The detailed information and definition of each mechanism are provided below:[33]

The "Turn-Stile" Mechanism: To prepare co-crystals with bispyridiyl-substituted diacetylene, our group applied urea of glycine (**Figure 13.1a**) and oxalamide of glycine (**Figure 13.1b)** as hosts. The resulted spacing distance of the bispyridiyl-substituted diacetylene with urea of glycine host is 4.70 Å, which is a bit too short. The C_1-C_4 distance, on the other hand, is 4.12 Å, which is a bit too long. Even though this spacing distances lead to the destruction of crystal structure after the 1,4-polymerization, the application of the oxalamide of glycine host improves the result. The spacing distance and the C_1-C_4 distance in this case are 4.97 Å and 3.38 Å respectively.[16] Our group observed the diacetylene guest molecules rotate after the 1,4-polymerization. The rotational axis is located between carbon 2 and carbon, which is in the middle of the diacetylene guest. This is a 1,4-polymerization that undergoes the "Turn-Stile" mechanism. This "Turn-Stile" mechanism had been observed frequently in non-terminal diacetylene guests (**Figure 13.1**).



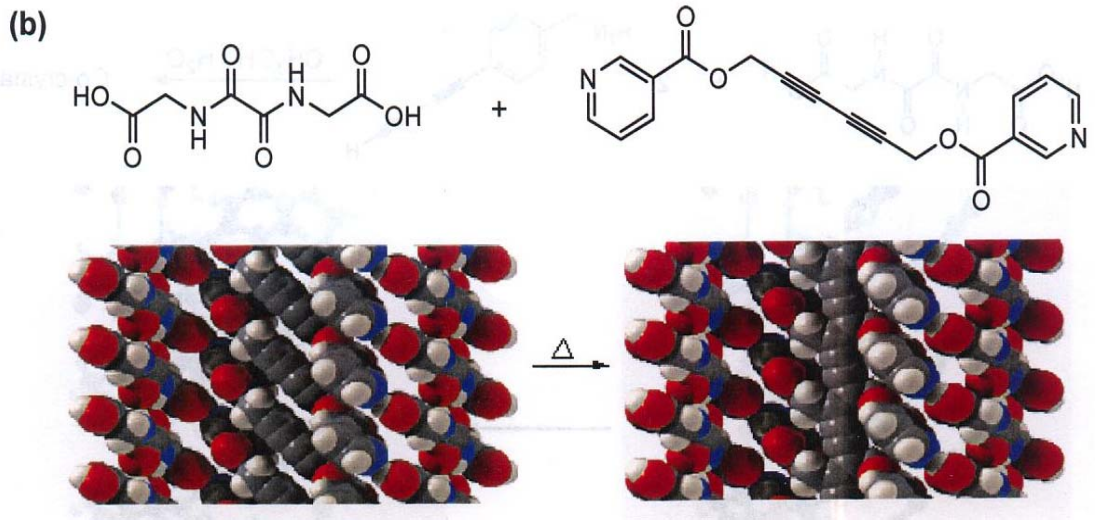


Figure 13.1: Illustration of "Turn-Stile" mechanism: (a) Reaction between the urea of glycine host (left) and the bispyridiyl-substituted diacetylene (right); (b) Reaction between the oxalamide of glycine host (left) and the bispyridiyl-substituted diacetylene (right)[16]

The "Swinging-Gate" Mechanism: Co-crystal of 4-butadiynylbenzyl ammonium salt with oxalamide of glycine in 2:1 ratio was prepared and red crystals was observed after recrystallization. The observed repeat distance between each diacetylene is 4.94Å. The tilted angle and the C_1-C_4 distance are 46.8^o and 3.57 Å respectively. With this approximately correct spacing distances and angle, the diacetylene undergoes 1,4-polymerization successfully and the movement of the aromatic ring in the guest molecules was also observed (**Figure 13.2**).[25] In contrast to the "Turn-Stile" mechanism, terminal diacetylene guest molecules undergo the "Swinging-Gate" mechanism, which the terminal acetylene guests "swing" downward in order to make the C_1-C_4 contact. The terminal carbon had moved for approximately 2.45 Å in this case (**Figure 13.2**)

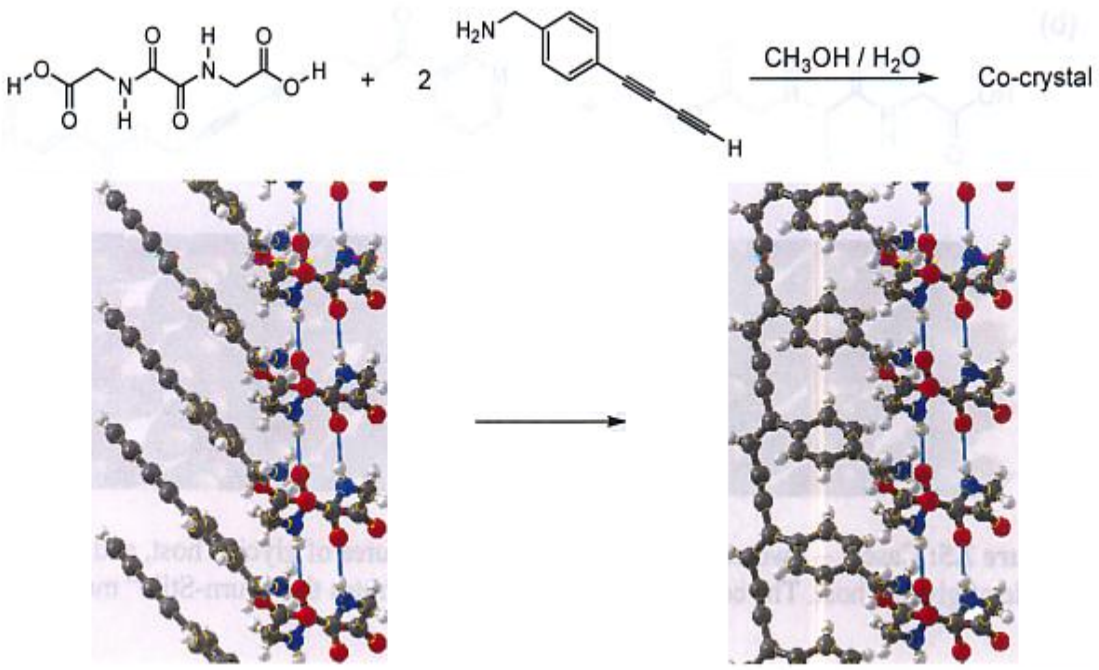


Figure 13.2: Illustration of "Swinging-Gate" mechanism: Reaction between the oxalamide of glycine host (left) and the 4-butadiynylbenzyl ammonium salt (right)[25]

Finally, **Figure 13.3** generalizes each of the two mechanisms in a pictorial way.

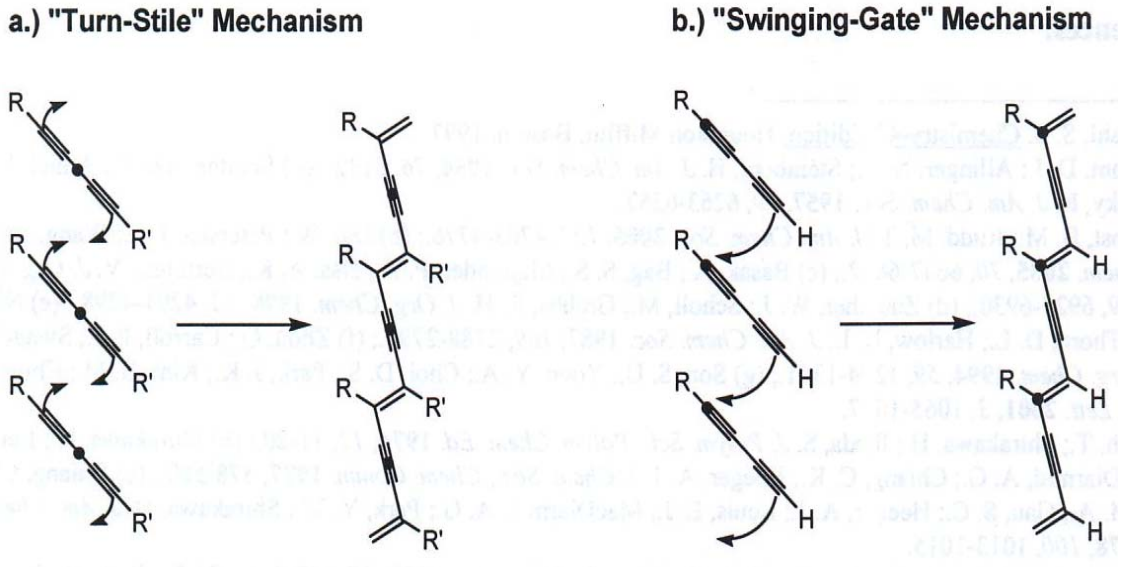
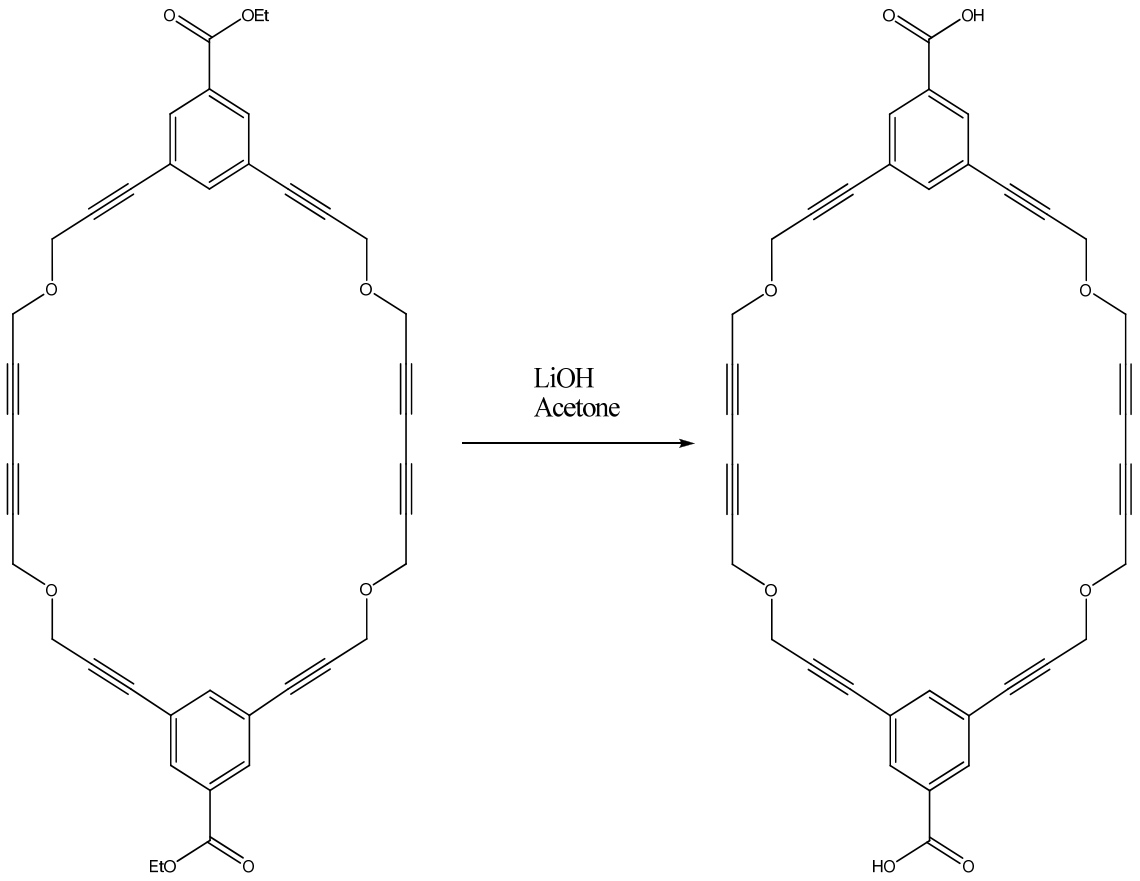


Figure 13.3: (a) "Turn-Stile" mechanism (b) "Swinging-Gate" mechanism[33]

The ester functional group of our macrocyclic compound (**Figure 11**) can be converted to a carboxylic acid functional group via base catalyzed hydrolysis (**Scheme A**). The electrons in the carbonyl group, C=O are not distributed evenly between the two component atoms.[37] Because oxygen is more electronegative than carbon, the carbon of a carbonyl group is partially positively charged, the oxygen partially negative.[37] This polarization can be represented by a charge-separated resonance form (**Figure 14**).



a **b**

Scheme A: Base Catalyzed Hydrolysis

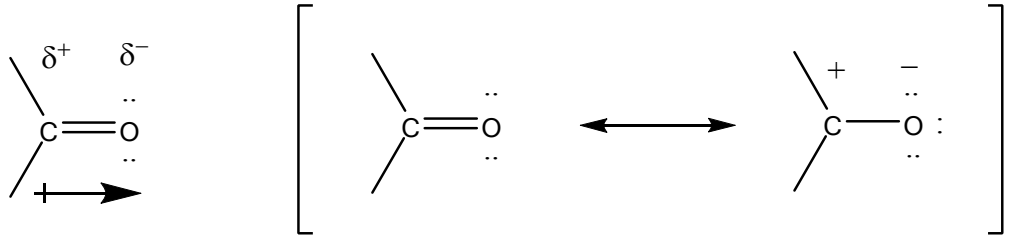


Figure 14: Polar Character of the Carbonyl Functional Group of Guest Molecule

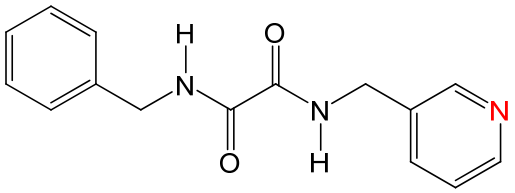


Figure 14-1: Host molecule – type 1

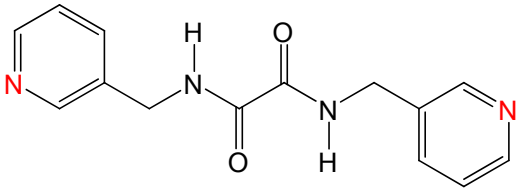


Figure 14-2: Host molecule – type 2

The polarity of this carbonyl group renders the adjacent hydroxyl group hydrogen-bonding capable, so that electron rich nitrogen atom (colored in red) of host molecule in **Figure 14-1** or **Figure 14-2** may accomplish hydrogen bonding connectivity to hydroxyl group of carboxylic acid moiety in the guest molecule. If we postulate that polymerization of our macrocyclic diacetylene **b** in **Scheme A** would be driven by the intermolecular hydrogen bonding between the hydroxyl group of the molecule **b** and electron rich nitrogen atom (colored in red) of a host molecule (**Figure 14-1 or 14-2**) through the host-guest design, the host compounds could well coordinate the discrete diacetylene macrocycles with desired parameters (See **Figure 10**). In addition, if the

topochemical 1,4-polymerization is assumed to be successfully applicable to our case, the construction of a macrocyclic tube built from the carboxyl based-macrocyclic diacetylene **b** would lead to the following significance:

1. Formation of organic tube from macrocyclic diacetylenes
2. Production of a covalent bonded tube

A.4 Synthesis of Macrocyclic Diacetylene

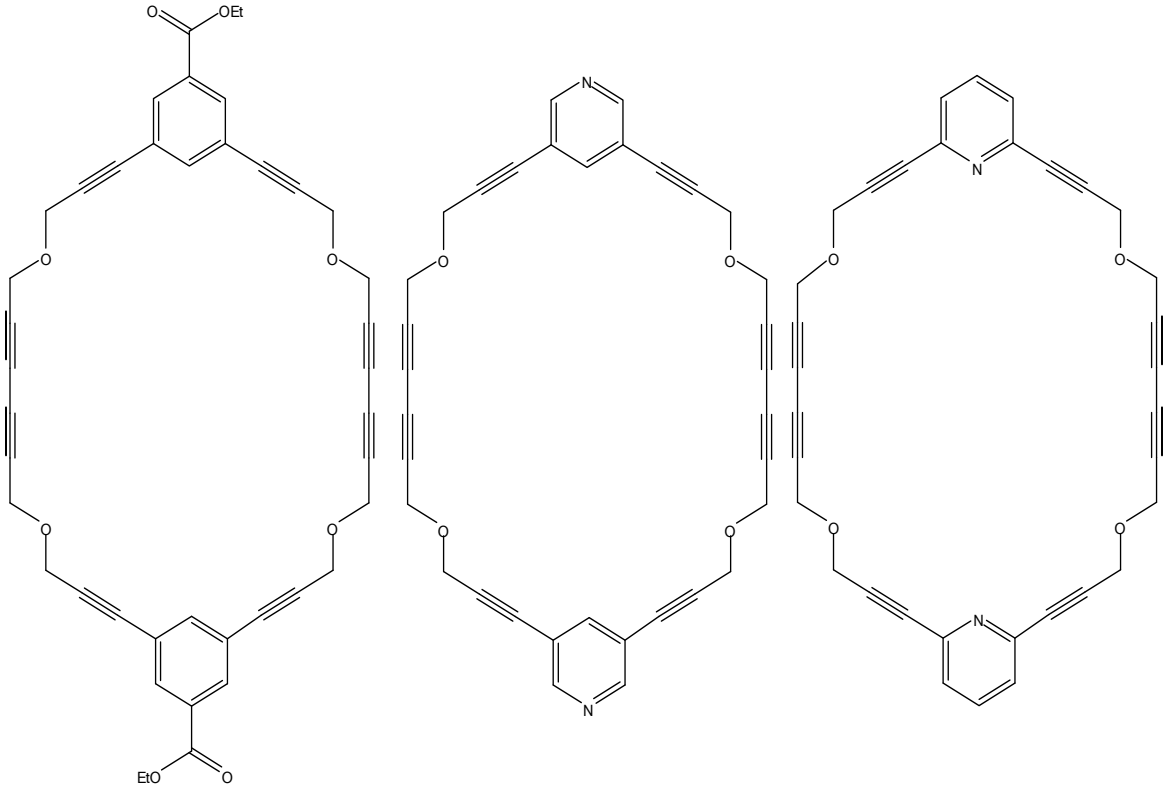
Wang and Chow have recently reported the successful synthesis of macrocyclic diacetylene **4** and **5** in which symmetrically alkynated pyridine building blocks were connected through diacetylenic bridges. Structural properties of these macrocyclic compounds have also been studied by crystallography.[28, 33] The primary goal of our project is to build **3** in which both pyridines are replaced by the benzene aromatic ring substituted with a carboxyl functional group, so that we could analyze its unique structural feature; and hypothesize function of a supramolecular tube built from **3**.

The last step of synthesis of our macrocyclic diacetylene involves Hay coupling reaction (See **Scheme 6**). That is, the coupling reaction between terminal acetylenes of molecule **3a** must be successfully accomplished through a mechanism predicted by Hay and his coworkers. For the purpose of understanding Hay coupling reaction, let's briefly review the basic concept of chemistry of acetylene.

The chemistry of acetylene has been widely studied by chemists in various fields because the physical and chemical properties of the carbon-carbon triple bond introduce a basis for understanding its industrial and technological usefulness.[32] In acetylene, the two carbons are sp hybridized. The two perpendicular p orbitals on each carbon contain one

electron each. These two sets overlap to form two perpendicular π bonds. Because π bonds are diffuse, the distribution of electrons in the triple bond resembles a cylindrical cloud. As a consequence of hybridization and the two π interactions, the strength of the triple bond is about 229 kcal mol^{-1}, considerably stronger than either the carbon-carbon double or single bonds.[37] As with alkenes, however, the alkyne π bonds are much weaker than the σ component of the triple bond, a feature that gives rise to much of its chemical reactivity.

As a simplest member of unsaturated hydrocarbons, acetylene is most important of all starting materials for organic synthesis.[37] Usefulness of acetylene is partly due to the variety of addition reactions which its triple bond undergoes and partly due to the fact that its weakly acidic hydrogen atoms are replaceable by reaction with strong bases to form acetylide salts.[37]



3 **4** **5**

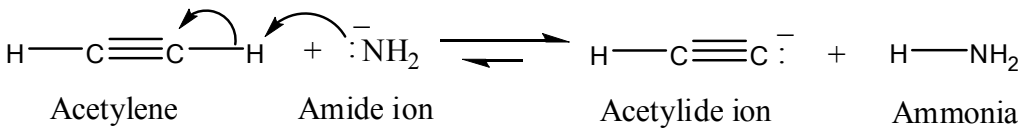
Figure 15: Structures of macrocyclic diacetylene rings

As briefly mentioned above, one important chemical property of alkynes, the acidity of acetylene and terminal alkynes, plays a useful role in the formation of bonds between sp^2 carbon and sp carbon; or between sp carbons.[28] Although acetylene and terminal alkynes are far stronger acids than other hydrocarbons, they are, nevertheless, very weak acids – much weaker than water and alcohols, for example. Hydroxide ion is too weak a base to convert acetylene to its anion in meaningful amounts. The position of the equilibrium described by the following equation lies overwhelmingly to the left:

Acetylene Hydroxide ion Acetylide ion Water

Because acetylene is a far weaker acid than water and alcohols, these substances are not suitable solvents for reactions involving acetylide ions. Acetylide is instantly converted to acetylene by proton transfer from compounds that contain – OH groups.[37]

Amide ion is a much stronger base than acetylide ion and converts acetylene to its conjugate base quantitatively.



Solutions of sodium acetylide ($HC{\equiv}CNa$) may be prepared by adding sodium amide ($NaNH_2$) to acetylene in liquid ammonia as the solvent. The terminal alkynes react similarly to give species of the type $RC{\equiv}CNa$.[37]

Anions of acetylene and terminal alkynes are nucleophilic and react with alkyl halides to form carbon-carbon bonds by nucleophilic substitution. Some useful applications of this reaction are discussed below.

The Sonogashira coupling reaction (**Figure 16**) typically requires two catalysts: a zerovalent palladium complex and a halide salt of copper (I). The palladium complex activates the organic halides by oxidative addition into the carbon-halogen bond while copper (I) halides react with the terminal alkyne and produce copper (I) acetylide, which acts as an activated species for the coupling reactions.[41]

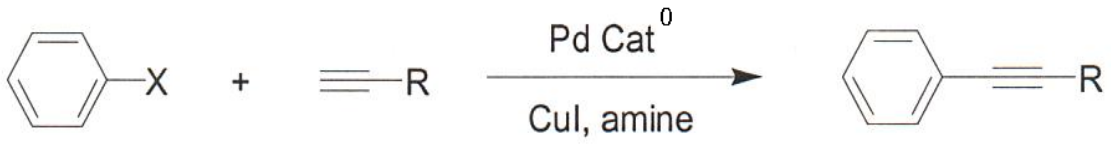
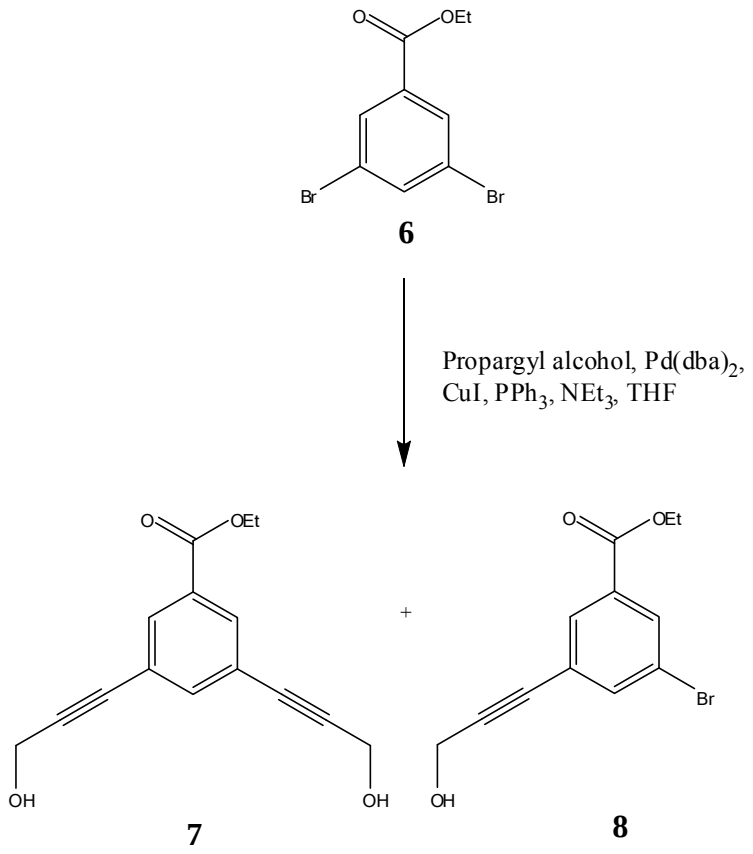


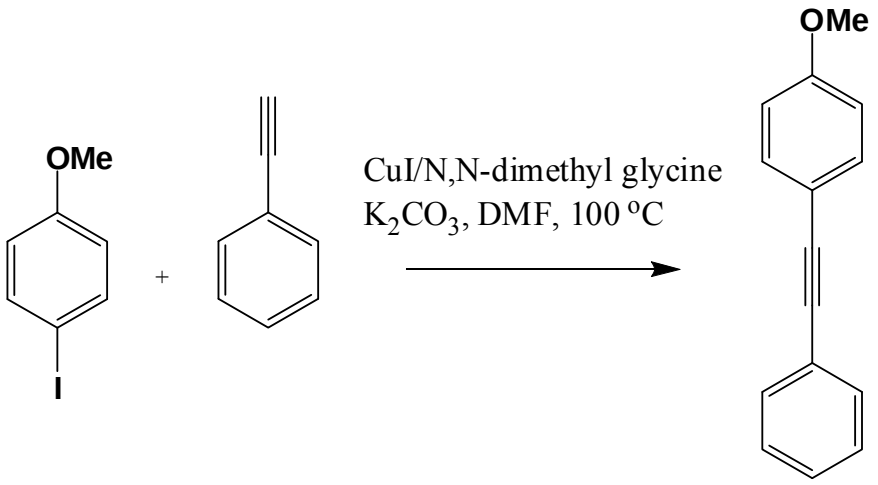
Figure 16: A generalized form of Sonogashira coupling reaction

In 2003, Blencowe et al. reported that use of the original coupling conditions employed by Sonogashira with the ethyl 3,5-dibromobenzoate **6** and propargyl alcohol only led to formation of the mono-substituted product **8** as a result of the deactivation of the aromatic ring by the ethyl ester functionality (**Scheme B**).[42] This effect was also observed by Thorland and Krause in the coupling of trimethylsilylacetylene to methyl bromobenzoate and higher catalyst loadings were employed in this case to increase the cross-coupling efficiencies.[43] However, when this approach was applied to the coupling of ethyl 3,5-dibromobenzoate **6** and propargyl alcohol, it proved ineffective. Consequently, Blencowe and co-workers looked for palladium catalysts and ligand combinations in order to optimize the production of the bis-acetylenic ethyl ester **7**. The result of their search for an appropriate catalyst afforded a modified Sonogashira cross-coupling procedure with a palladium catalyst system [triethylamine/bis(dibenzylideneacetone)palladium/triphenylphosphine/copper iodide/THF] that produced the bis-acetylenic ester **7** in an acceptable yield of 70%.[42] More details on the application of this scheme to our advantage is presented in the next chapter of this report.



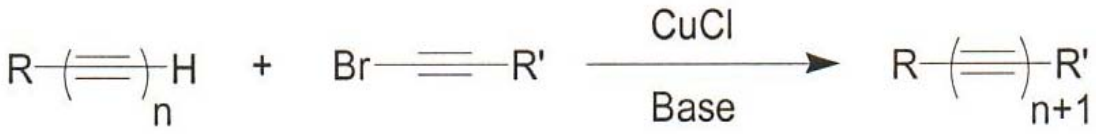
Scheme B: Synthesis of bis-acetylenic ester **7**

In 2004, in an attempt to improve the original catalytic condition of Sonogashira coupling reaction in which phosphine and high-cost palladium are employed as catalysts, Dawei and Feng made CuI/N,N-dimethylglycine-catalyzed coupling reaction of aryl halides with terminal alkynes to produce the desired coupling products in excellent yields (**Scheme B.1**).[45] We have attempted to apply this scheme to our coupling reaction of ethyl 3,5-dibromobenzoate **6** and propargyl alcohol, and the result will be presented in the next chapter.



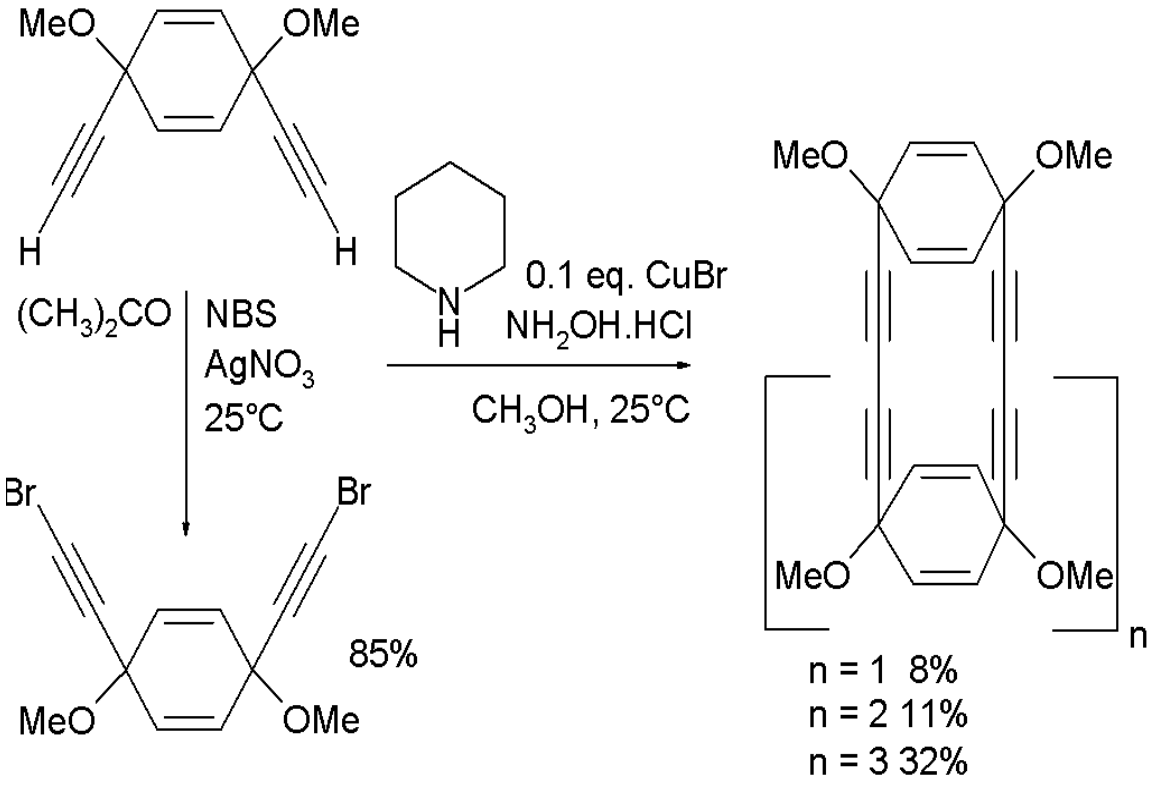
Scheme B.1: CuI/N,N-dimethylglycine-catalyzed coupling reaction

The Cadiot-Chodkiewicz coupling is a coupling reaction between a terminal alkyne and a haloalkyne catalyzed by a copper (I) salt such as copper (I) bromide and an amine base. The reaction product is a di-acetylene or di-alkyne (**Scheme B.2**).[46] Its reaction mechanism involves deprotonation by base of the acetylenic proton followed by formation of a copper (I) acetylide.[46]



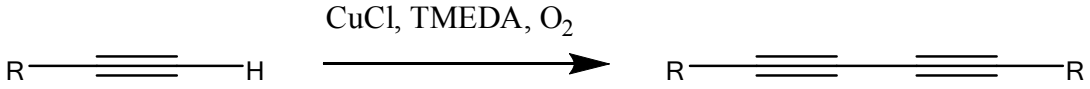
Scheme B.2: Cadiot-Chodkiewicz coupling reaction

Sethuraman et al. applied Cadiot-Chodkiewicz coupling in the synthesis of acetylene macrocycles starting from cis-1,4-diethynyl-1,4-dimethoxycyclohexa-2,5-diene (**Scheme B.3**).[48]



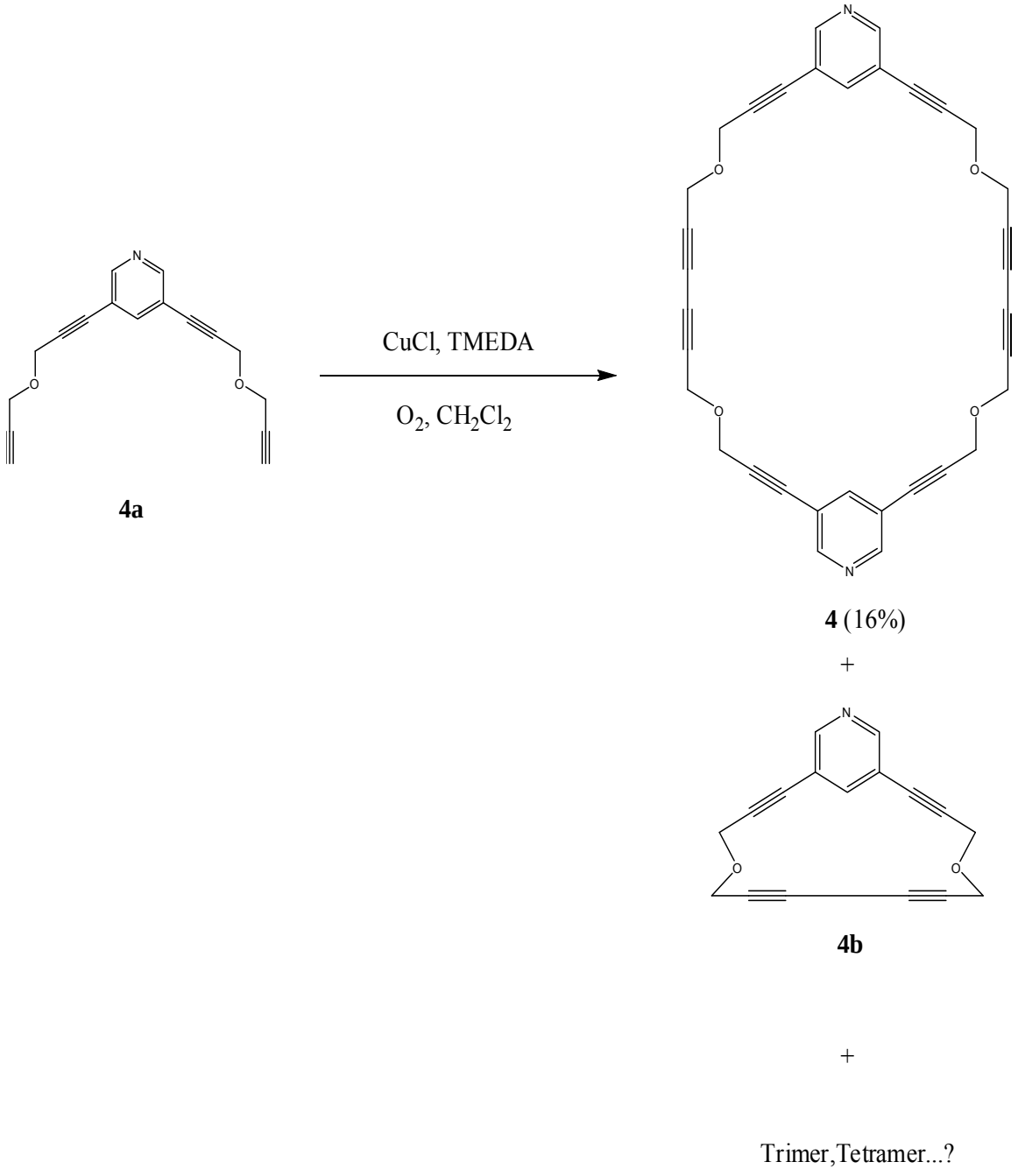
Scheme B.3: Application of Cadiot-Chodkiewicz coupling

Hay coupling reaction is a synthesis of symmetric or cyclic diacetylene via a coupling reaction of terminal alkynes (**Scheme B.4**).[47] The copper-TMEDA complex used is soluble in a wide range of solvents so that the reaction is more versatile.[47]



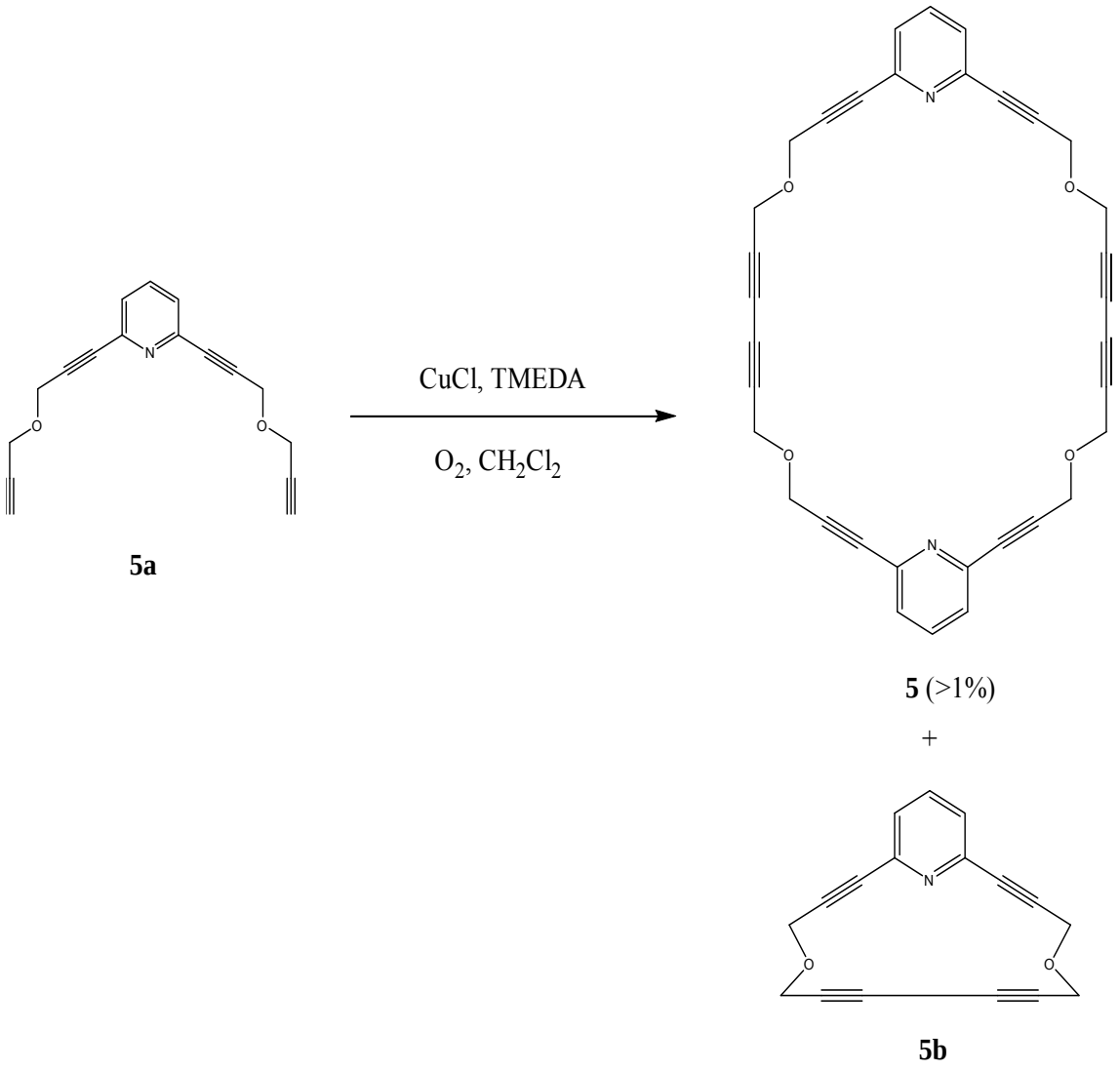
Scheme B.4: Hay Coupling Reaction

Curtis and Wang attempted to dimerize **4a** via Hay coupling in order to get **4** (**Scheme C**).[28] However, diether 4a underwent cyclization with itself and formed a monomer **4b**. It also formed trimers or tetramers. Nevertheless, the production of the desired product **4** was achieved in spite of its low yield (16%).[28]



Scheme C: Dimerization of Diether **4a** via Hay Couping

Steven also tried to synthesize **5** via Hay coupling to get monomers **5b** and approximately 1% yield of the desired product **5** (**Scheme D**).[33]



5a

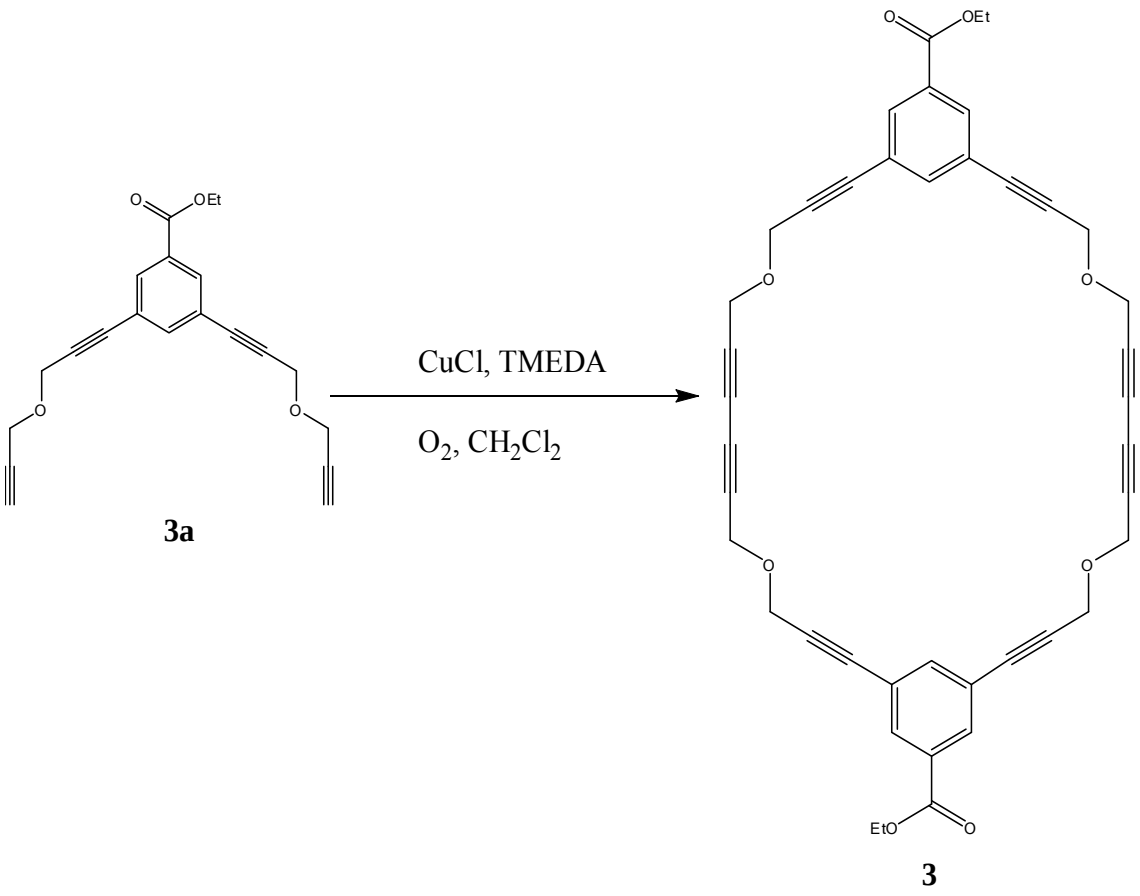
5 (>1%)

+

5b

Scheme D: Synthesis of 2,6-pyridine-based macrocycle **5**

It was our great pleasure to see how Hay coupling would affect the productivity of our reaction (**Scheme E**). The result of our case is presented in the next chapter.



3a **3**

Scheme E: Our plan to design product **3**

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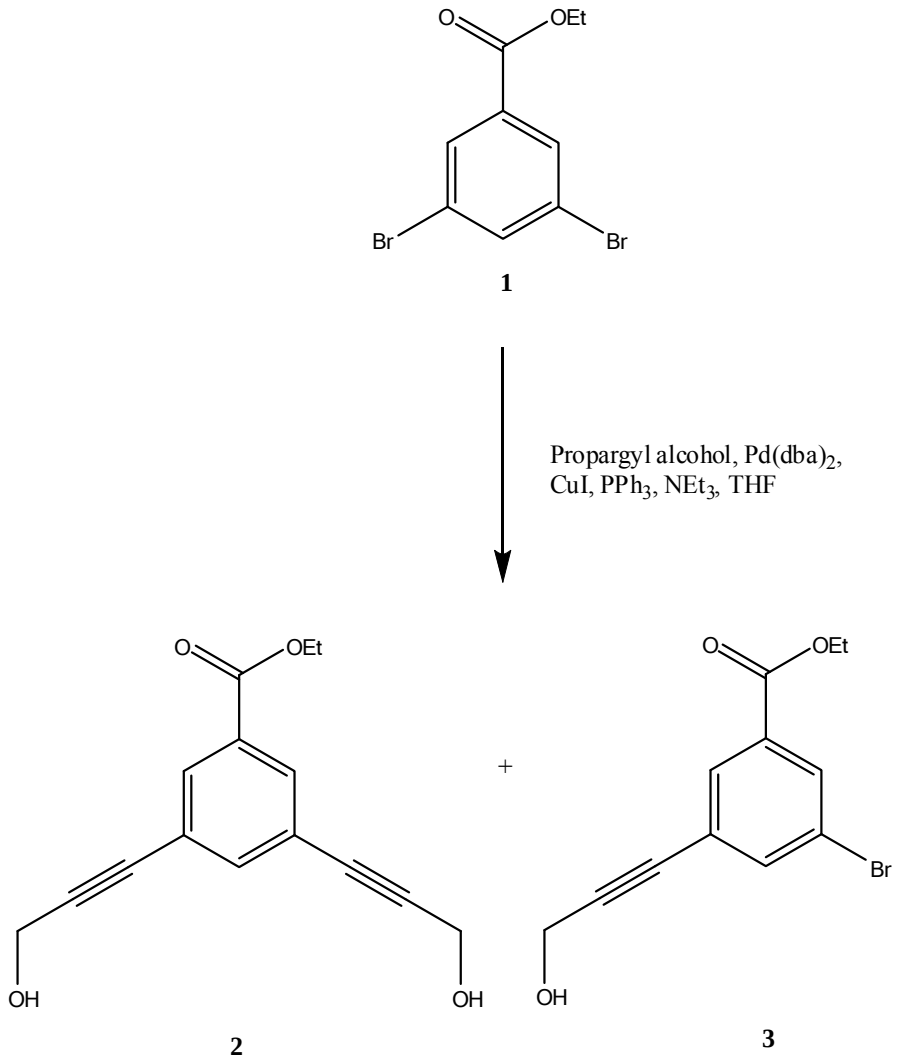
Chapter B. Strategy to synthesize Carbonyl Group Based Diacetylene Macrocycle (Part 1)

B.1 Modification to Sonogashira Coupling Reaction

The original condition employed by Sonogashira coupling reaction has been proven to be ineffective and impractical against the coupling of arylbromides and terminal alkynes according to Stephan T. and Norbert K., who also reported that the yield of arylakynes were substantially improved by replacing amine solvents with THF or DMF in Sonogashira coupling.[1] However, when Blencowe et al. performed coupling of ethyl 3,5-dibromobenzoate and propargyl alcohol in THF solvent, only mono-substituted product **3** (**Scheme 1**) was synthesized because the ethyl ester functional group deactivated the aromatic ring.[2] The problem with Stephan and Norbert's method was the choice of palladium catalyst, and we added palladium catalyst, bis-(dibenzylideneacetone) palladium, which Blencowe and his coworkers used in their synthesis of **2**, in a hope to achieve acceptable yield of the target product **2**. Then, after approximately two days of reflux, we could achieve 43% yield of the product **2**, which was lower than the reported yield of Blencowe's reaction (70%). According to the Blencowe's report, the mono-acetylenic ester **3** was also formed (10%).[2] Preliminary condition for this coupling reaction was to protect the carboxylic functional group of commercially available 3,5-dibromobenzoic acid. The protection reaction was achieved by adding ethanol and coupling reagents such as DCC and DMAP.[2] The resulted amount of **2** was acceptable enough to be used in our next scheme. We attributed this lower productivity to the reduction of the original volume of the THF used, which was due to the leakage of gaseous THF during the 2-day reflux. There was an occasion that the THF was almost dried off and remained only roughly 3 milliliters in the container even though

the whole system was deemed to be assembled tightly. The yield was only 5% at that time. The leakage seemed to occur in the narrow space around the conjunction between the water-cooling condenser and the round bottom flask containing THF, and when the condenser slightly bumped out of its position due to the pressure developed by the gaseous THF. In order to prevent this accident, we used Parafilm® sealing tape to wrap around every suspicious opening. However, this method still could not prevent leakage of THF gas, but increased the yield to 43%.



Scheme 1: Synthesis of 3,5-bis (3-hydroxylprop-1-ynyl) benzoic acid ethyl ester

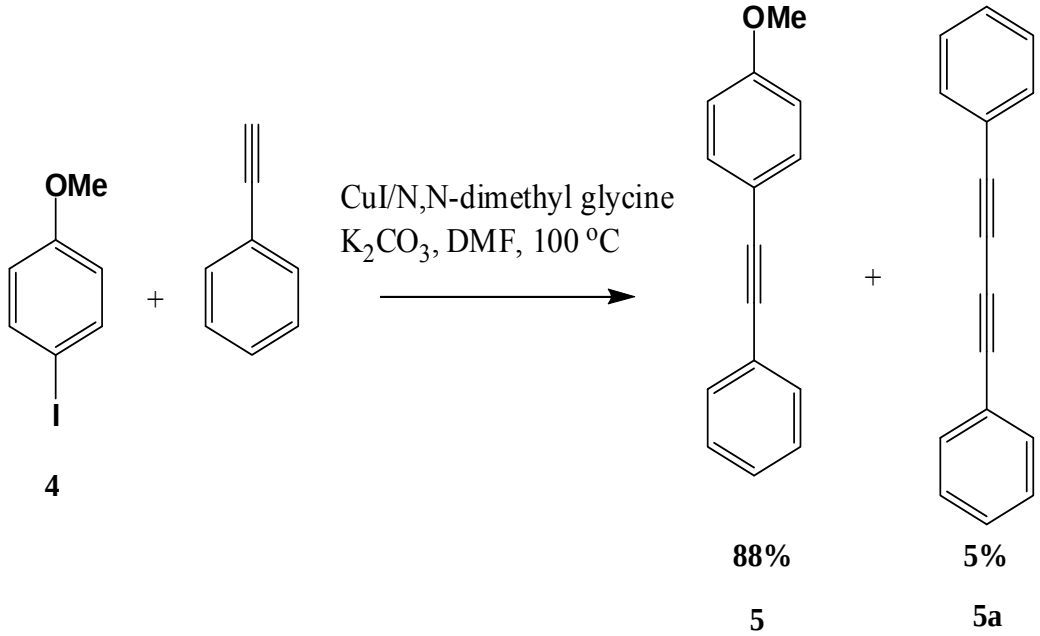
B.2 Application of CuI/N,N-dimethylglycine-catalyzed Coupling Reaction

Due to incompatibility with the coupling reaction of aryl bromides and terminal alkynes; and the high cost of palladium which denies the practical use for industry, Sonogashira's original catalytic system has been subject to improvement. As discussed in the previous section, the change made to the Sonogashira's palladium complex and solvent made our coupling reaction possible. However, our catalytic system still uses palladium as a reagent, and we decided to look for another catalytic condition which would hopefully meet the standard of industrial use. We learned from Dawei's report that coupling of 4-iodoanisole **4** and aryl terminal alkyne resulted in formation of **5** with excellent yield (88%) when catalyzed with the combination of N,N-dimethyl glycine and copper iodide as shown in **Scheme 2**.[3] It was important to keep 3:1 ratio of N,N-dimethyl glycine and copper iodide for an optimum result (**Table 2**).[3] Since primary and secondary amines such as L-proline or N-methyl glycine tend to couple with aryl halides to decrease the activity of the catalytic system, N,N-dimethyl glycine, which is unable to couple with aryl halides, was chosen as a best catalytic reagent.[3] However, this best candidate still could not prevent the undesirable impurities from being formed (**Scheme 2**, **5a**), yet in very minimal yield (5%).[3] Nevertheless, we wanted to see if this catalytic system, which is palladium free, would allow aryl dibromides to couple with two terminal alkynes. The mixture of 3,5-dibromobenzoic acid, propargyl alcohol, N,N-dimethyl glycine, CuI and K_2CO_3 in DMF and H_2O was heated at 100^{o}C for two days, after which time the crude solution was washed and filtered with flash column chromatography. Unfortunately, based on TLC check, melting point value and ^{1}H NMR analysis, the result showed that the final product perfectly matched with those of 3,5-dibromobenzoic acid, a starting

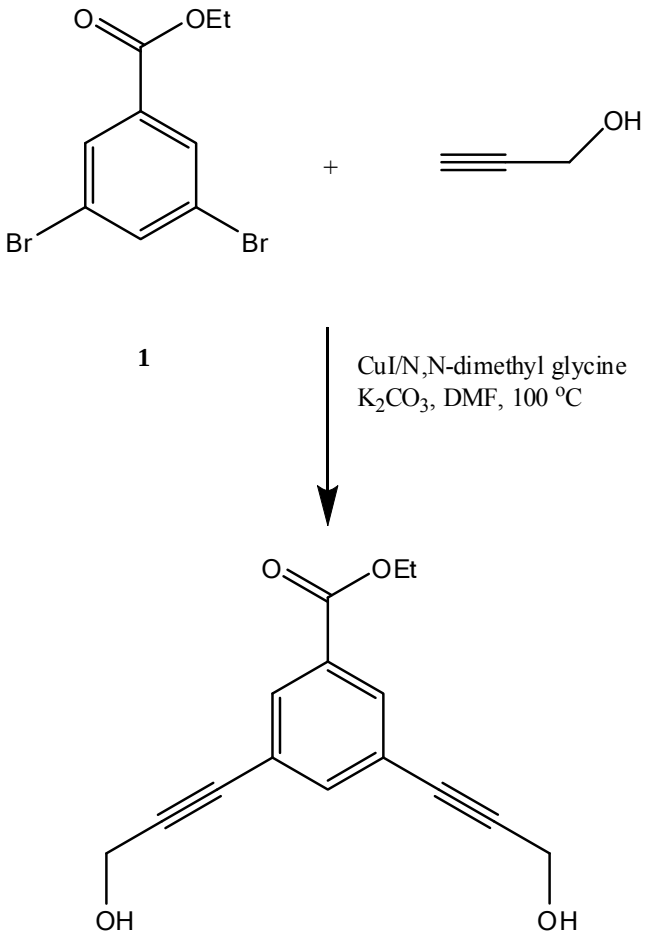
reactant of our reaction. Three more attempts did not give us a desired product, and we concluded that this strategy was not compatible with our new reaction scheme (**Scheme 2-1**).

Entry	**Condition (N,N-dimethylglycine:CuI)**	**% Yield**
1	1:1	37%
2	2:1	52%
3	3:1	88%

Table 2: Attempted reactions with various catalytic conditions[3]



Scheme 2: CuI/N,N-dimethylglycine catalyzed coupling reaction of 4-iodoanisole with aryl terminal alkyne



1

0 %

2

Scheme 2-1: CuI/N,N-dimethylglycine catalyzed coupling reaction of dibromo acid ethyl ester with propargyl alcohol

References:

[1] Thorland, S.; Krause, N. *J Org Chem*. **1998**, *63*, 8551

[2] Blencowe, A.; Davidson, L.; Hayes, W. *European Polymer Journal* **2003**, *39* 1955-1963,

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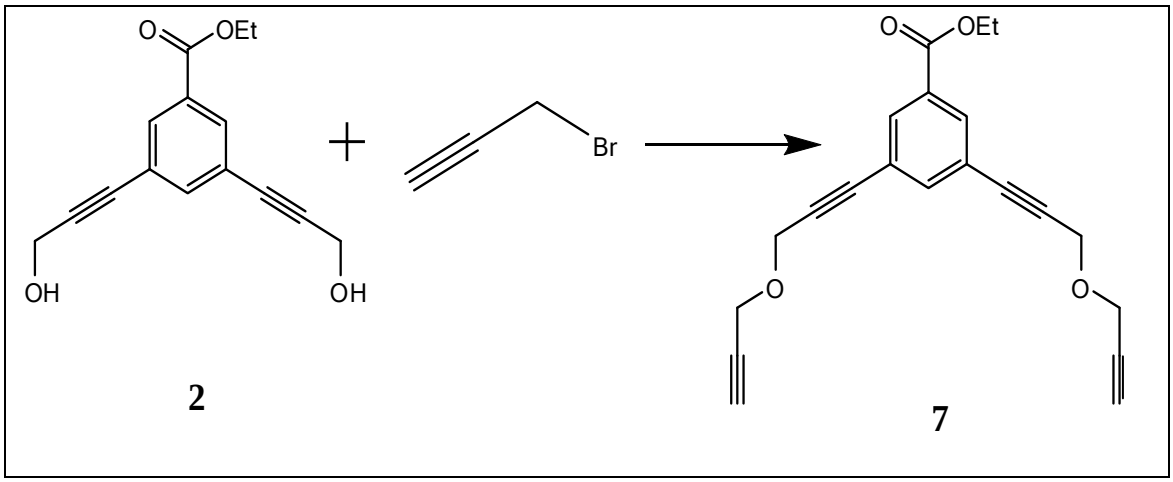
Chapter C. Strategy to synthesize Carbonyl Group Based Diacetylene Macrocycle (Part 2)

C.1 Synthesis of 3,5-bis (dipropynyl ether) benzoic acid ethyl ester

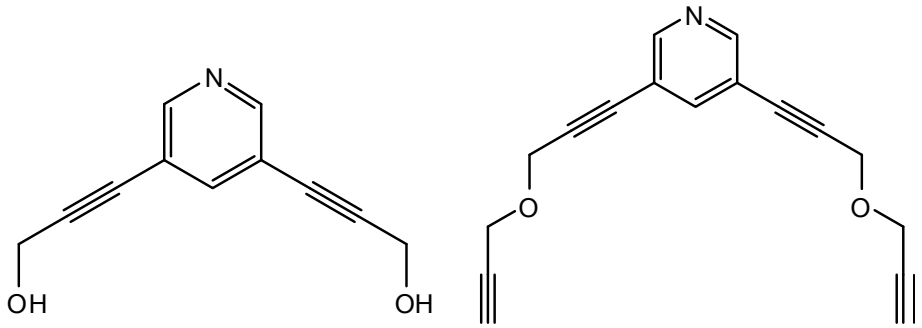
The synthetic route for this part of the reaction involves alkylation of diols **2** by propargyl bromide in the presence of sodium hydride and 18-crown-6 ether. 18-crown-6 ether accelerates our reaction by isolating sodium cations from nucleophilic dialkoxide intermediate forms of **2.** Previously, Wang, who also performed alkylation with 3,5-pyridine-based diols **1a** in the presence of the same chemical reagents as ours, reported that the reaction condition should be maintained at the temperature of ice bath formulated either by the combination of ice and water, or that of ice and acetone.[1] Nevertheless, our reaction appeared to prefer the combination of ice and water as to get a satisfactory result as indicated in **Table 3**. In order to answer what exactly cause this discrepancy between ice/water and ice/acetone, we compared ^{1}H NMR data of each product from a respective trial. As a result, we found that peaks characterizing aromatic ring were completely missing in the products from trial 2 and 3, while the data from trial 1 preserved them. However, the physical appearances of all products were the same; all were transparent and bright yellow oil. We reasoned that if some slight temperature difference between two ice bath systems caused this disagreement among the results, the trial 4 with ice/water should give us a right product with high yield like trial 1. However, the result again missed our expectation. Like those from trial 2 and 3, ^{1}H NMR data from trial 4 indicated that the aromatic ring was missing. Then, if the temperature was not the issue, something must have gone wrong with the starting material **2**. The ^{1}H NMR analysis on **2** showed unusually strong and broad multi peaks on the range over 1.8 ppm through 2.6 ppm while aromatic peaks were well preserved. This abnormal peak was never observed

in the first ^{1}H NMR analytic data on **2** which was conducted immediately after we obtained the product **2** from the previous reaction. Our assumption is that **2** must be either easily decomposable in the room temperature, or might possess reactivity very sensitive to water in the air. The validity of the existence of **7** was confirmed by ^{1}H-NMR analysis and its comparison with that of Wang's compound **1b**[1] in **Figure 17**. The spectrum of our sample describes that the two strong singlet peaks at 4.50 and 4.60 ppm are characteristic of 8 methylene groups (s, -CH_2-) in the diether components of **7**, while the quartet at 4.37 ppm indicates one methylene group in the ester moiety. The downfield signals at 7.67 and 8.05 ppm also confirm the presence of benzene rings. The singlet at 2.45 ppm indicates terminal alkyne groups. In addition, the triplet in the 1.39 ppm region indicates the presence of one methyl group (-CH_3) in the ester moiety. The comparison between our ^{1}H-NMR spectrum of the product **7** and that of **1b**[1] obtained by Curtis and Wang also supports the existence of our ring structure. The chemical shifts of the peaks characteristic of terminal alkynes, benzene and methylene groups in **1b**[1] are consistent with those of our spectrum of the compound **7**.



Trial	Condition	% Yield
1	NaH, 18-Crown-6 Ether, THF, Ice/Water	92 %
2	NaH, 18-Crown-6 Ether, THF, Ice/Acetone	33 %
3	NaH, 18-Crown-6 Ether, THF, Ice/Acetone	39 %

Table 3: Ice/Water vs. Ice/Acetone for the Optimum Reaction Condition



1a **1b**

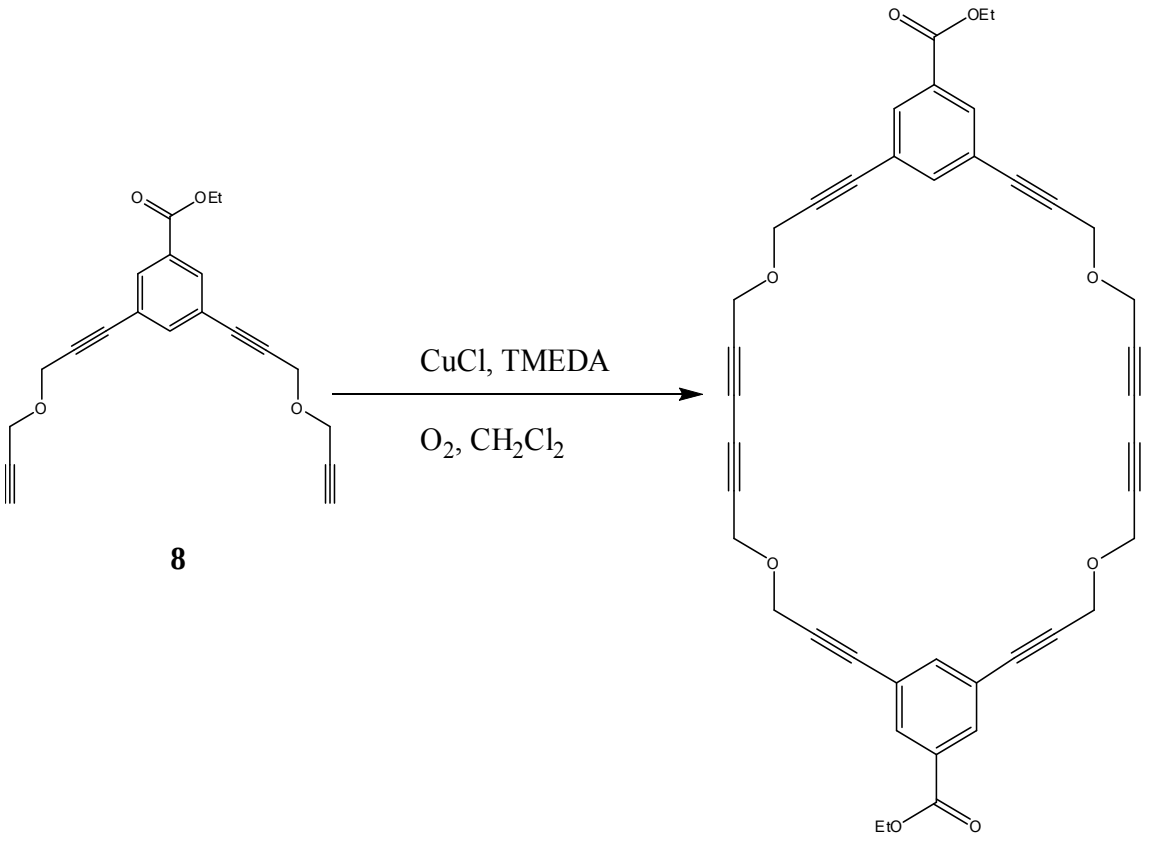
Figure 17: 3,5-pyridine-based diol and diether

C.2 Synthesis of Diacetylene Macrocycle

The synthetic strategy for constructing our target product, carbonyl group-bearing diacetylene macrocycle, employs Hay coupling reaction (**Scheme 3**). In 2005, taking advantage of Hay's coupling reaction, Wang has synthesized 3,5-pyridine-based macrocycle **9b**; and he has reported that due to 'the flexibility of methylene groups,' other isomers of his target product were formed (**Scheme 4**) as indicated in his TLC showing more than five spots.[1] In contrast, our TLC showed one spot. Even though the yield of this product **9**, which resembles white crystal, was relatively low (30%), the amount obtained was sufficient enough for ^{1}H NMR analysis. The spectrum of our sample describes that the signals at 4.50 and 4.51 ppm are characteristic of 8 methylene groups (s, -CH_2-) in the ring structure **9**, while quartet in the 4.37-4.39 ppm region indicates 2 methylene groups in the ester moiety. The downfield signals at 8.06 and 8.06 ppm also confirm the presence of benzene rings. In addition, the triplets in the 1.37-1.42 ppm region indicate the presence of 2 methyl groups in the ester moiety. The comparison between our ^{1}H-NMR spectrum of the product **9** and that of **9b**[1] obtained by Curtis and Wang also supports the existence of our ring structure. Even though the spectrum of **9b** does not contain triplets and quartet corresponding to methyl and methylene groups respectively in the ester moiety, the chemical shifts of other peaks characteristic of benzene and methylene groups in **9b**[1] are consistent with that of our spectrum of the compound **9**.

After 1 day of storage of our product **9** in chloroform-d at the room temperature, we observed the change in color of the solution. We analyzed this sample in ^{1}H-NMR spectrum, and obtained the existence of so many strong distracting peaks, which might be

attributable to an accidental contamination by impure chemicals, or the instability of **9** in chloroform D in the room temperature. We tried to recover our product **9** from chloroform D by vacuum evaporation. As a result, yellow and gum-like solids were obtained. Even though the physical appearance of the unknown product was very different from that of the product **9**, we attempted to purify the unknown with recrystallization. However, the purification was not successful with the common solvents such as a mixture of hexane and ethyl acetate due to its insolubility in them.

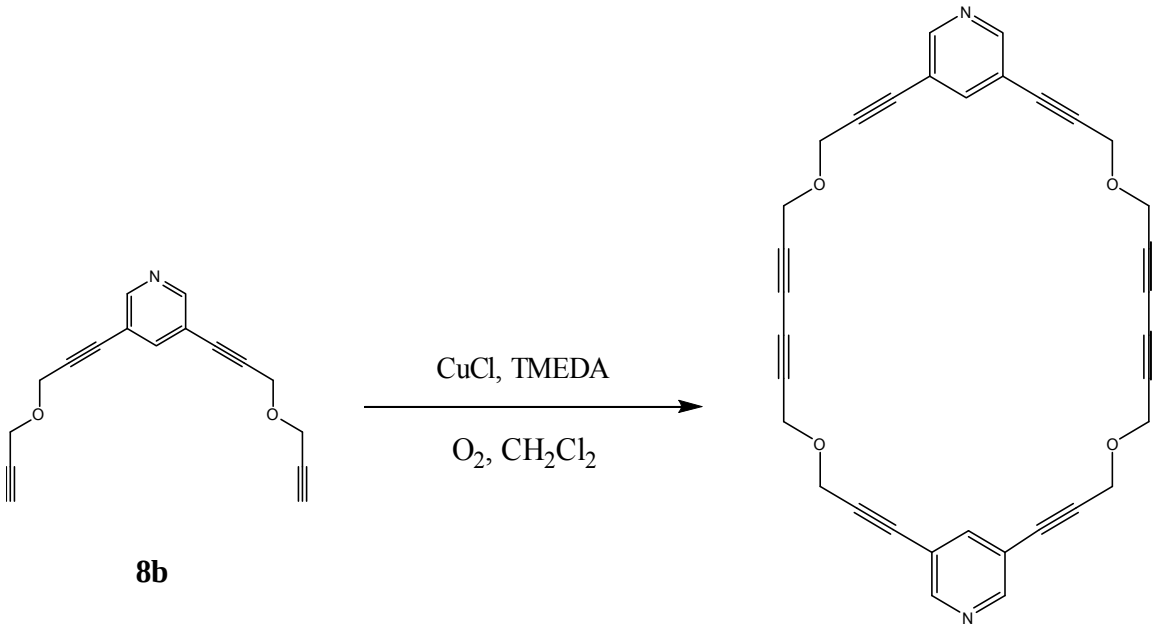


8

9

(30%)

Scheme 3: Synthesis of **9** with Hay's coupling reaction



8b

Dimer (16%)

9b

+

Monomer

9c

+

Trimer,Tetramer...?

Scheme 4: Synthesis of 3,5-pyridine-based macrocycle via Hay's Coupling Reaction[1]

C.3 Future Plan and Conclusion

Even though a pure sample of **9** was obtained, 40 hour reaction to synthesize product 3,5-bis (3-hydroxylprop-1-ynyl) benzoic acid ethyl ester **2** seem to affect the overall reaction time of our whole process. Besides, the high cost of palladium in the modified Sonogashira synthetic route to synthesize **2** does not seem to be appropriate for an ideal industrial use. If successful, the alternative synthetic route via N,N-dimethyl glycine and copper iodide catalysts could have been a nice solution to palladium dependent environment and relatively long time process. Therefore, an alternative method for this part may still have to be explored.

Due to the unexpected qualitative change of macrocycle **9** in chloroform D solvent prior to X-ray crystallographic analysis, we were unable to measure parameters of the structure of **9**. We may have to look for an explanation for this accidental problem. Nevertheless, considering the importance of the potential roles of a macrocycle **9**-based nanotube**,** it will still be necessary for us to define our final crystal's structure in a three dimension so that the significance of carbonyl groups in macrocycle **9** has to be evaluated in a practical fashion.

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Chapter D. Experimental Section

D.1 3,5-dibromobenzoic acid

Under a nitrogen atmosphere 1,3,5-tribromobenzene (3.16 g, 10.04 mmol) and anhydrous diethyl ether (100 ml) were placed in a 250 ml three-necked flask. The contents were cooled to -78°C and n-C_4H_9Li (42.54 ml of 0.236 M in hexane solution, 10.04 mmol) was added at an even rate over 30 min while maintaining the internal temperature at -78 °C. The solution was stirred at -78 °C for an additional 30 minutes. The diethyl ether solution of 3,5-dibromophenyllithium in the three-necked flask was bubbled with CO_2 gas while maintaining the internal temperature at -78°C. After 2 hours, the solvents were removed; the residue acidified with 2N HCl, extracted with diethyl ether and diethyl ether solution further extracted with dil. NaOH. On acidifying the aqueous NaOH solution with 2 N HCl, the 3,5-dibromobenzoic acid (2.110 g, 75 % yields) precipitated. The melting point at 208°-210°C was identical to that in literature.

D.2 3,5-dibromobenzoic acid ethyl ester

To a solution of 3,5-dibromobenzoic acid (2.073 g, 7.400 mmol) in diethyl ether (50 ml) was added absolute ethanol (0.5 ml), followed by DCC (1.680 g, 8.140 mmol) and DMAP (0.091g, 0.740 mmol). The reaction was stirred at room temperature for 24 hours. The precipitated dicyclohexylurea by-product was filtered off under suction and washed with diethyl ether. The combined filtrate and washing were washed with water (3 x 20 ml), 10% acetic acid (3 x 20 ml) and water (10 ml). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated to yield the 3,5-dibromobenzoic acid ethyl ester (1.3074 g, 63 % yield) as a cream solid; melting point 58°-59°C; ^{1}H NMR (300

MHz, $CDCl_3$, TMS) δ_H 1.400 (t, 3H, J = 6Hz, C*H*$_3$), 4.37 (q, 2H, J = 6Hz, C*H*$_2$), 7.84 (s, 1H, ArC*H*), 8.10 (d, 2H, 2ArC*H*).

D.3 3,5-bis (3-hydroxylprop-1-ynyl) benzoic acid ethyl ester

To a rapidly stirring solution of 3,5-dibromo benzoic acid ester (2.000 g, 6.500 mmol) and triethylamine (6 ml) in anhydrous THF (32.5 ml) under an inert N_2 atmosphere, was added, bis(dibenzylideneacetone) palladium (0.141 g, 0.245 mmol), triphenylphosphine (0.321 g, 1.225 mmol) and copper iodide (0.0524 g, 0.275 mmol). The mixture was stirred for 1 hour and then propargyl alcohol (1.11g, 1.17 ml, 19.8 mmol) was added continuously over a period of 3 hours, after which time the mixture was heated to and maintained under reflux for 40 hours. Upon cooling to room temperature, the mixture was filtered and the filtrate concentrated in vacuo. The resultant oil was dissolved in chloroform (30 ml), and then washed with 1 M HCl (15 ml) and water (2 x 25 ml). The organic phase was then dried ($MgSO_4$), filtered at the pump and the filtrate concentrated in vacuo. The resulting oil was purified by flash column chromatography (SiO_2; 4:1 v:v, CH_2Cl_2:EtOAc) to afford *3,5-bis (3-hydroxylprop-1-ynyl) benzoic acid ethyl ester* as a pale yellow solid (0.7174 g, 43%); melting point 90°-92°C; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ_H 1.39 (t, 3H, C*H*$_3$), 4.36 (q, 2H, C*H*$_2$), 4.50 (s, 4H, 2C*H*$_2$), 7.62 (s, 1H, ArC*H*), 8.03 (d, 2H, 2ArC*H*).

D.4 3,5-bis (dipropynyl ether) benzoic acid ethyl ester

To NaH (0.17 g, 7.02 mmol) in a 50 ml round bottom flask under an inert N_2 atmosphere was added THF (15 ml). The mixture was stirred for 5 minutes, and then cooled to 0°C. To the cooled mixture in an ice bath was added drop wise *3,5-bis (3-*

hydroxylprop-1-ynyl) benzoic acid ethyl ester (0.100 g, 0.390 mmol) dissolved in THF (3ml), then the mixture was stirred for 30 minutes, after which time the mixture was added 18-Crown-6 (0.210 g, 0.780 mmol), then stirred for another 30 minutes in the ice bath. To the cooled mixture was added drop wise propargyl bromide (0.140 g, 0.105 ml, 1.160 mmol), then the mixture was stirred for 15 hours under room

temperature. After the stirring was complete, cold water was added slowly to quench the reaction, and then the mixture was washed with diethyl ether (3 x 10 ml). The organic phase was then dried ($MgSO_4$), filtered at the pump and the filtrate concentrated in vacuo. The crude oil product was purified by flash column chromatography (SiO_2; 1:1 v:v, Hexane:EtOAc) to afford *3,5-bis (dipropynyl ether) benzoic acid ethyl ester* as a pale yellow oil (0.118 g, 92 %); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ_H 1.39 (t, 3H,C*H*$_3$), 2.45 (s, 2H, 2CH), 4.37 (q, 2H, C*H*$_2$), 4.50 (s, 4H, 2C*H*$_2$), 4.60 (s, 4H, 2C*H*$_2$), 7.67 (s, 1H, ArC*H*), 8.05 (d, 2H, 2ArC*H*).

D.5 Diacetylene Macrocycle

To a rapidly stirring solution of *3,5-bis (dipropynyl ether) benzoic acid ethyl ester* (0.050g, 0.150 mmol) in dry methylene chloride (50 ml) was added copper chloride (0.099 g, 1.000 mmol) and TMEDA (0.302g, 2.600 mmol). The mixture was bubbled with O_2 for 2 hours, after which time the reaction was quenched with water. The organic phase was extracted with methylene chloride (2 x 20 ml), and was washed with saturated ammonium chloride (3 x 20ml). The resulting solution was dried ($MgSO_4$), filtered at the pump, and the filtrate concentrated in vacuo. The resulting crude solid product was purified by flash column chromatography (SiO_2; 1:1 v:v, Hexane:EtOAc) to afford

diethylene macrocycle as a crystal like white solid (0.0141 g, 30 %); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ_H 1.39 (t, 6H, 2C*H*$_3$), 4.37 (q, 4H, 2C*H*$_2$), 4.50 (s, 8H, 4C*H*$_2$), 4.60 (s, 8H, 4C*H*$_2$), 7.68 (s, 2H, 2ArC*H*), 8.06 (d, 4H, 4ArC*H*).

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Chapter B

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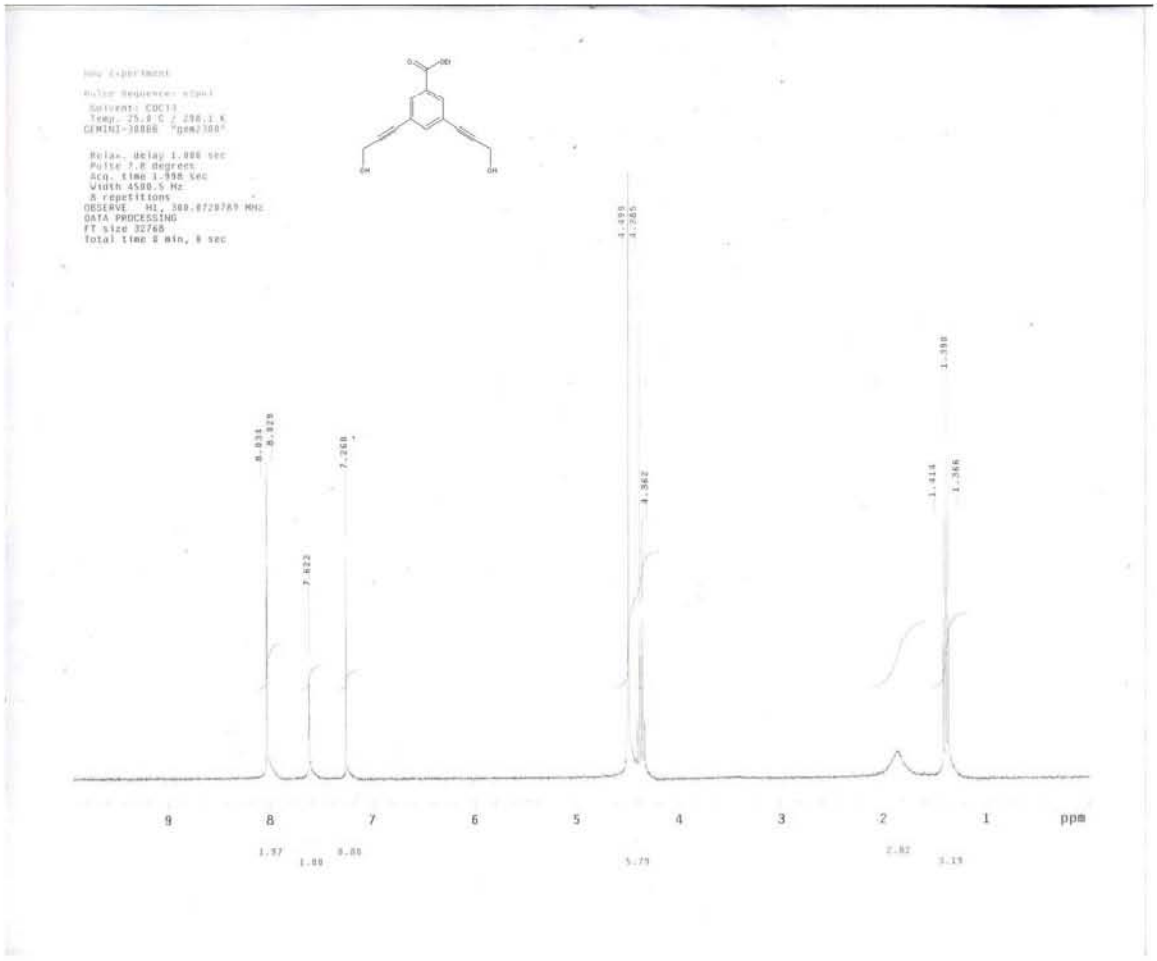
Chapter C

[1] Wang, T. M.S. Thesis (Chemistry), SUNY at Stony Brook, 2005

Appendix

^{1}H NMR Spectra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Pulse 7.8 degrees
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Width 4500.5 Hz
8 repetitions
OBSERVE H1, 300.0729769 MHz
DATA PROCESSING
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Total time 0 min, 8 sec
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8.029
7.822
7.268
4.399
4.385
4.362
1.398
1.414
1.366
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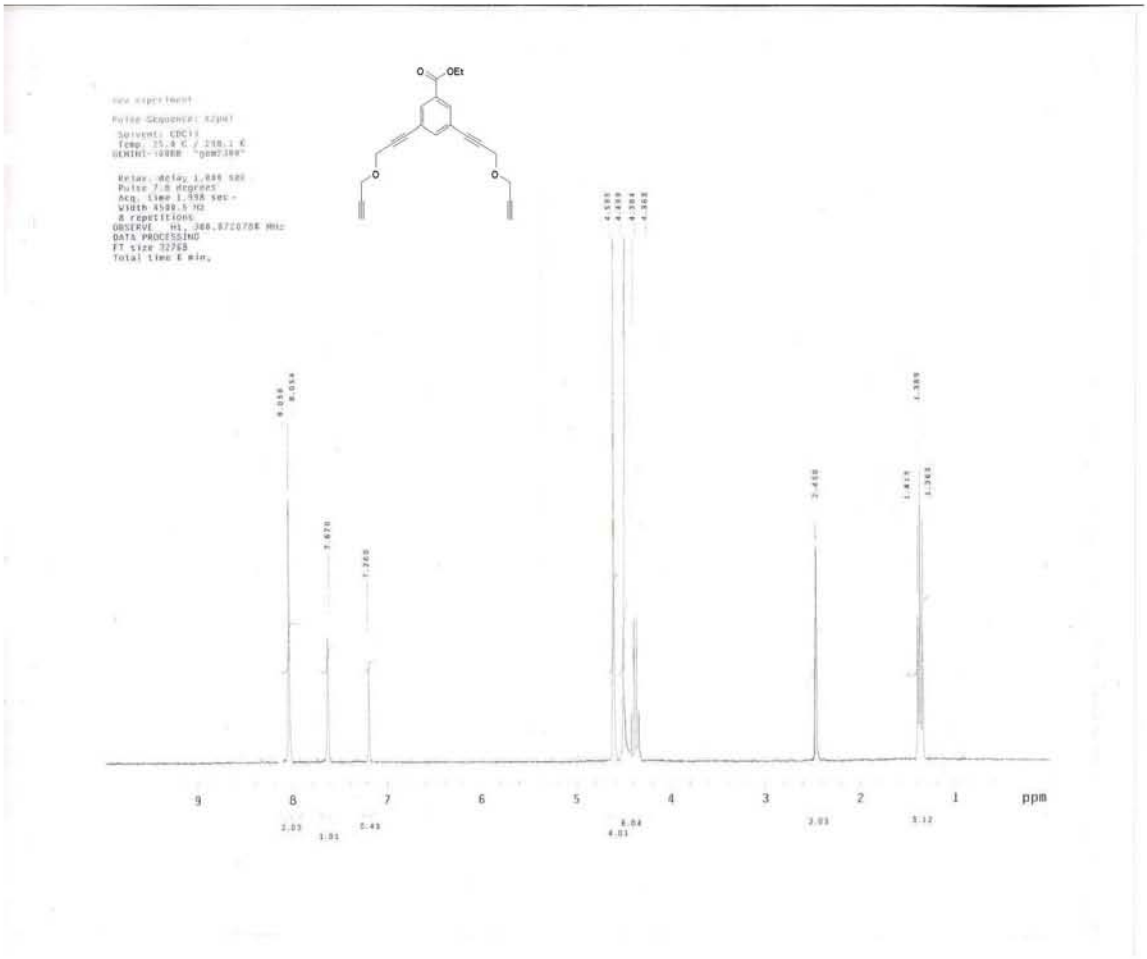
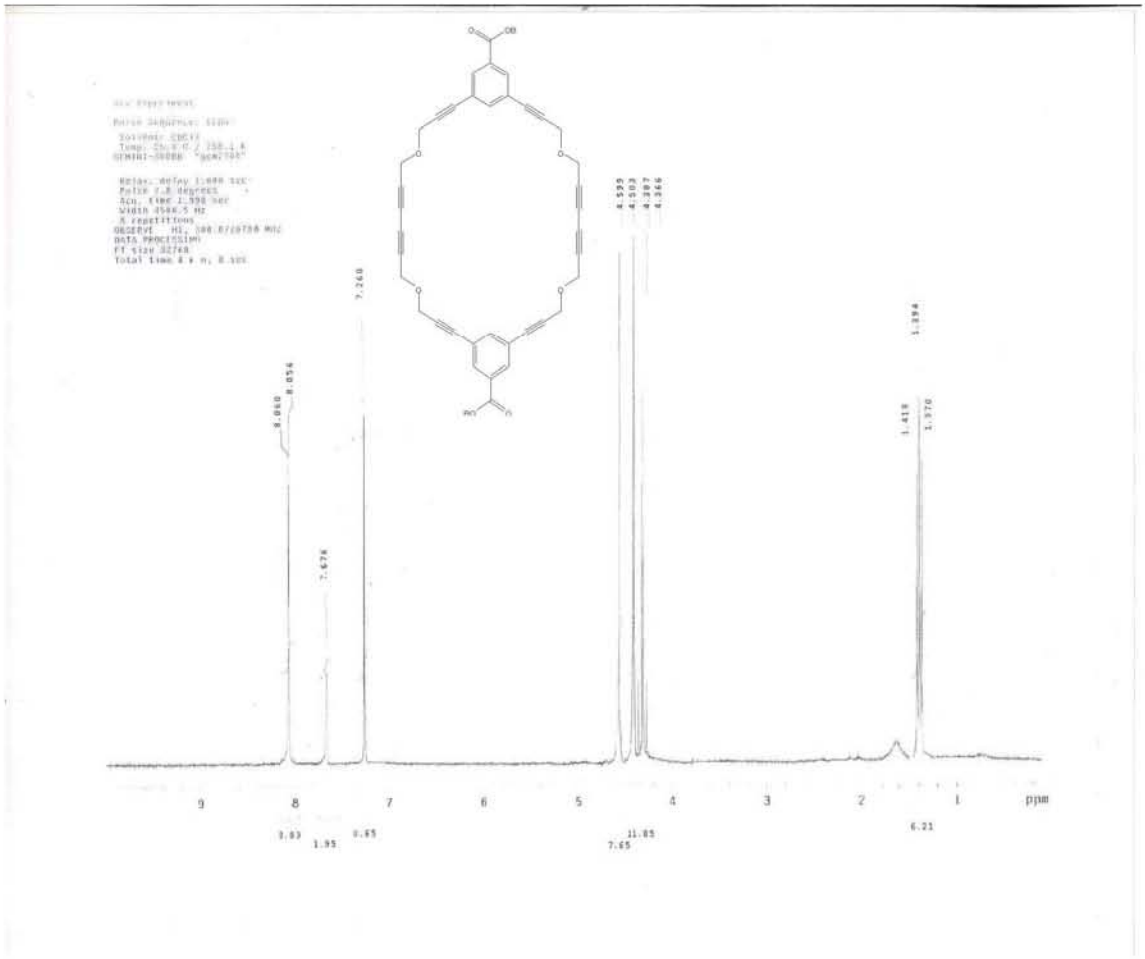

OEt
ppm


8.060
8.054
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9
8
7
6
5
4
3
2
1
ppm
3.83
1.95
4.65
7.65
11.85
6.21