Copper (I) Mediated Folding of a Molecular Basket

A Senior Honors Thesis

Presented in Partial Fulfillment of the Requirements for Graduation with Distinction in Chemistry in the Undergraduate College of Mathematical and Physical Sciences of The Ohio State University

By

Wanji Seo

The Ohio State University
August 2007

Project Advisor: Professor Jovica D. Badjić
Abstract

This thesis describes a new synthetic pathway for the preparation of molecular basket 1. Earlier synthetic difficulties comprising harsh experimental conditions (high pressure) and low diastereoselectivities were resolved in herein described procedures. That is, molecular basket 1 is now obtained in a diastereoselective Cu (II) promoted cyclotrimerization of stannylated norborene 7 (syn/anti =1:1.4) in a good yield (41%). The folding of 1 was examined with 1H NMR spectroscopy. An incremental addition of Cu (I) to its solution caused considerable changes in its 1H NMR spectrum and ascribed to the folding of its pyridine arms about the Cu (I) cation.

Chapter I. Introduction

1. Host-Guest Complex in Supramolecular Chemistry

Since Jean-Marie Lehn introduced the term Supramolecular Chemistry in 1978, a large number of the synthetic host-guest molecular systems have been rigorously studied. Initially, the concept of host-guest complexation was adopted from self-assembly and molecular recognition present in biological world. Nowadays, the synthetic supramolecular chemistry, explores a range of self-assembling molecules beyond naturally occurring systems. Furthermore, it has paved the way for designing large and complex artificial machines and molecular devices using original synthetic approaches.

The interaction of molecular assembly is regulated by dynamic, non-covalent bonding such as hydrogen bonding, electrostatic, π-π, and van der Waals forces, etc. Earlier, many recognition studies focused on the hydrogen bonding because it was widely encountered in
biological world. In the 1980s, an increasing number of metallo-supramolecular structures employing the metal-ligand coordination were investigated.2

Generally, metallo-supramolecular systems employ the metal ion as a mediator to incorporate another guest, mostly organic molecules. As different metal ions take on various coordination geometries, the modification of molecular structures become more flexible. In this type of molecular system, the coordination geometries and suitable ligands, both the host-guest, plays a pivotal role in the self-assembly process.3 The particular conformational preference provides the driving force for the formation of predicted structures.

Due to different transition metal ions of coordinative bonds, the binding affinities of metal toward ligands are worth being discussed. The lability and stability are important factors to achieve a desired binding dynamics. d10 transition metals such as Ag (I) and Cu (I) have good binding affinities with the macrocyclic host.4 The d-orbitals are completely filled with electrons, and the bonding to any ligands surrounding the metal ion is labile. As the transition metal-ligand coordination has a certain degree of covalency, the rich electron density of d10 metal ions also promotes the synergic effect. The d orbitals undergo the σ and π bonding with certain ligands, resulting in the metal- to- ligand charge transfer complexation.

The acid-base theory explains the compatibility of metal-ligand coordinations. The selective affinity of a host to a particular guest is based on the hard/soft acid - base theory; for example, hard acids (e.g. Na+, K+) have better affinities with hard bases (e.g. O, Cl). Softer acids (e.g. Ag+, Cu+ and other transition metal ions) favor softer bases characterized by high polarizability (e.g. N, S).5 For this reason, the host containing bipyridyl or terpyridyl moieties are commonly used as ligands, because the pyridyl group is a good σ- and π- donor as well as a π-acceptor.
In addition to initial reactivity between the metal ion and the ligand, the study of the molecular recognition phenomena has focused on the thermodynamics of binding interactions. The formation of a host-guest complex through noncovalent interactions involves enthalpy and entropy changes as well as Gibbs free energy.\(^6\)

Prior to the formation of self-assembled supramolecular complex, the preorganization of the host is important for the effective host-guest assembly. This motion requires complementary steric and electrostatic interactions in the host and guest, making the molecular assembly more favorable.\(^7\) The inclusion of the guest requires that the host have a certain degree of rigidity to contain a guest, while still being capable of folding.

As the host-guest complex is formed in a liquid, the solvent effect is also an important parameter contributing to the thermodynamic stability of the system. The solvation/desorvation process of the metal ion is an important issue to be examined. The more closely the binding sites of the host molecule are arranged for binding to a guest, the more favorable it is to the association of host-guest. If the metal-ligand system tends to form aggregates separately, the probability for the desired complexation will be low. Therefore, finding a solvent system that solubilizes both the host and the guest is mandatory.

Analytical techniques that allow for the quantification of thermodynamics of the host-guest complex provide a deeper understanding of the non-covalent intermolecular interactions and mechanisms. The most common analysis of the binding thermodynamics is the titration experiment using \(^1\)H NMR and UV-vis spectroscopic methods.

In the titration experiment, the known initial concentration of the host is titrated with the known concentration of the guest. From a spectrometric measurement, the relationship between the concentration of the added guest and the physical response of the host is established. Finally,
the fitting curve is constructed, providing a quantitative measure of the binding affinity of the
host-guest under a given condition. This binding isotherm gives a value for $K_B$, also known as
the equilibrium constant of the association. Furthermore, the value of binding constant provides
the standard state Gibbs free energy ($\Delta G^\circ$).

$$\Delta G^\circ = -RT \ln K_B$$

Another common method for examining binding phenomena is isothermal titration
calorimetry (ITC). This analysis will provide a thermodynamic parameter, enthalpy ($\Delta H^\circ$)
characterizing the binding strength of the host-guest. From the calculation of standard Gibbs
free energy ($\Delta G^\circ$) found from the value of $K_B$, entropy ($\Delta S^\circ$) is calculated based on the
following equation, $\Delta G^\circ = \Delta H^\circ - T \Delta S^\circ$. Entropy ($\Delta S^\circ$) indicates the change in the host-guest
molecular arrangement in a given solution matrix. Thereby, these parameters will predict the
relative thermodynamic stability of a supramolecular complex.

The present analytical study of the host-guest complex is not fully completed; and only
$^1$H NMR spectroscopy has been used. The kinetic study of the host-guest binding event is in a
preliminary state: only the relative ratio of the association to dissociation rate is obtained from
the binding constant. Developing suitable kinetic analyses is another subject that we need to in
for out system.

2. Molecular Basket Design

Molecular baskets of our interest were designed in our laboratory. A guest is chosen to
be fully encapsulated in the host. The host is a macrocyclic receptor with aromatic or cyclic
rings that can create space to include a guest, akin to hydrophobic pocket in biological systems.
The upper rim of the host is functionalized, capable of enclosing the space via folding mediated hydrogen bonding or metal-ligand coordination.

The polydentate molecular basket 1 was synthesized in 2007 (Figure 1). It has several features. The upper rim of the basket is functionalized with pyridine. The nitrogen atoms of the pyridyl groups can coordinate with a metal cation. They can also be protonated due to their basic character, and the resulting charge can create a strong ionic bonding with an anionic guest. Another characteristic is the stereochemical effect resulting from the coordination between nitrogen and a metal cation. During folding upon binding to a metal cation, the proximity of gates in the upper rim is close enough, and based on a calculation, they adopt a propeller shape dynamic. The presence of chiral center can be examined in the context of the polydentate 1 preferring binding to chiral guests.

In order to study the conformational dynamics and recognition properties of polydentate 1, titration experiments with several guests are in progress. Before the metal ion was employed in the host-guest complex, organic guests such as the tri-methylammonium hexafluorophosphate ((CH$_3$)$_3$NH$_3^+$ PF$_6^-$) were experimented first. Based on the $^1$H NMR titration experiments,
polydentate 1 did not successfully bind to the organic guest. Due to the poor binding affinity between the basket 1 and (CH₃)₃NH⁺, different binding modes of the host-guest complex had to be examined.

The next system studied was the coordination complex. In this case, the complexation was designed using a silver (I) cation (AgOTf) (Figure 2). An organic guest was indirectly bound to the host through the metal ion.

As the formation of the host-metal ion complex was indicated in ¹H NMR titration experiments, further investigation of the dynamics in the polydentate 1 - silver (I) (AgOTf) interaction were continued. The experiments result suggested that polydentate 1 bound with the silver (I) in a 1:1 ratio. As silver (I) tends to form tetrahedral conformation, it was assumed that three nitrogen atoms of the pyridine moieties of 1 were bound to the silver (I) and a solvent molecule was positioned at the fourth ligand site. This binding affinity with 1 was examined by means of ¹H NMR and the isothermal titration calorimetry (ITC). Although the thermodynamic parameters obtained from ITC showed that the assembly of Ag (I) was an endothermic process (ΔH° = 3.0 ± 0.1 kcal/mol), the positive value of entropy (ΔS° = 34 eu) suggested that the binding event with silver (I) compound was entropy driven.

Furthermore, the complexation of Ag (I) folded basket was observed. All of them were bound to Ag (I) ion outside the basket. In order to include the organic guest molecule inside the basket, the binding between the fourth ligand and the metal mediator had to be stronger than that
of the host-metal. Therefore, the affinity of the fourth ligand demanded a different metal mediator.

A metal ion similar to Ag (I) was sought out to improve the binding affinity with the fourth ligand—an organic guest, which would be inserted inside the cavity. Cu (I) is another potential d^{10} metal ion. The advantage of using Cu (I) over Ag (I) is its high geometric selectivity in forming the tetrahedral coordination. The geometric preference of Cu (I) was also thought as possible to induce a stronger binding with ligands. Recently, a related concept was examined in the experiments with carlix[6]arenes. The success of positioning acetonitrile (CH$_3$CN) inside the calix[6]arene molecule also supported our assumption that the binding strength of the Cu (I) - organic guest (or the fourth ligand) would improve.

The experiment with Cu (I) was expected to allow the chelation of metal with three pyridine groups of 1 and an organic guest. The Cu (I) was in the perching state: the metal cation sits over the host ligand—pyridyl group—rather than positioned inside the cavity. The final stage of the Cu (I) mediated host-guest complexation was to examine if the guest bound to the Cu (I) also enclosed inside the host (Figure 3).

![Figure 3. Complexation of Host-Cu(I)-Guest](image)

a) Host-Cu (I) Complexation (b) Guest Bound to Host-Cu (I) (c) Encapsulation of Guest
Chapter II. Results and Discussions

1. Synthesis

The preliminary step of the molecular design constituted computer modeling calculating the theoretical optimal potential energy of the polydentate 1 and its binding behavior with guests. Semi-empirical calculation (PM5) was used for the calculation of the potential energy of molecules.

In this thesis, the preparation of 1 of polydentate 1 was examined first (Scheme 1). As shown in the originally developed procedure (Scheme 2), hexaester 7 was obtained from the trimer 6. However, some difficulties in applying a Diels-Alder reaction under high pressure challenged the procedure in Scheme 2.10 Overall, a low yield was encountered. We wanted to develop a more effective synthetic pathway for the preparation of our basket.

The first two steps, the Diels-Alder cyclo-addition and the addition of bromine via a radical process were reproduced successfully. Then, instead of synthesizing the bromo(trimethylstannyl)triene, the halogen elimination of 3 with t-BuOK yielded 4 (84%). The resulting product, a bromodiene, was reacted with dimethyl acetylenedicarboxylate (DMAD), a dienophile, via a Diels-Alder reaction. This new synthetic procedure was similar to the previous method using a Diels-Alder reaction, but high pressure was not applied. Compound 5 was subsequently aromatized with DDQ. The bromo hexaester 6 was reacted with lithium diisopropylamide (LDA), a highly regioselective strong base for the substitution of trimethyl tin group. The stannylation step promoted a coupling reaction of cyclotrimerization with three equivalents of the compound 6. The trimerization reaction yielded a 1:1.4 mixture of syn- and anti-trimer, and yielded 11% of pure syn-trimer 8. Although the combined yield of syn- and anti-trimer was lower than the previous result, the yield of pure syn-trimer was similar.
Scheme 1. New Synthesis of Polydentate 1

1. LDA, THF, HCl (aq)
2. Me3SnCl

150 °C

47 %

Cl
C10H18

Br

64 %

3

4

Br

Br

Cl

7

84 %

DMAD
CCl4 / ∆

CO2Me

CO2Me

5

6

8

DDQ
CH2Cl2

Br

Br

Br

78 %

CO2Me

CO2Me

1. LDA
2. Me3SnCl

64 %

CO2Me

CO2Me

Me3Sn

7

11 % (syn)

1. (aminomethyl)-pyridine, Toluene, 120 °C / Reflux
2. pyridine

Polydentate 1

1. LiOH, THF, HCl (aq)
2. Ac2O / ∆

61 %

1. Cu(NO3)2, acetone, <50 °C

87 %
Scheme 2. Previous Synthesis of Polydentate 1

1. LDA
2. Me3SnCl

1. LiOH, THF, HCl (aq)
2. Ac2O / Δ

1. 3-(aminomethyl)-pyridine,
   Toluene, 120 °C / Reflux
2. pyridine
In the course of the cyclotrimerization, some intriguing ideas were postulated. Because the cyclotrimerization process requires three equivalents of the precursor, the use of acetone as a reaction solvent was found essential. In the previous experiment of silver (I), a single crystal X-ray analysis showed that an ordered acetone molecule was positioned inside the polydentate 1 (Figure 4).

The parallel arrangement of the $C_{2v}$ - acetone and the $C_{3v}$ - folded polydentate 1 axes suggested that a C-H---π interaction between those molecules may have caused them to be arrayed in a particular fashion. This assumption hinted that acetone could have been organized the precursor molecules more efficiently in the cyclotrimerization process than other reaction solvents such as THF.

A similar mechanistic characteristic is applied in the template effect seen in the synthesis of crown ether and other inorganic syntheses. Because acetone contributed to the $C_{2v}$ - $C_{3v}$ parallel arrangement, the new ratio of syn- and anti-trimer may have been much closer than the 1:4 ratio of the previous experiment. The incompatibility of anti- trimer and acetone symmetries may have precluded the formation of anti-trimer.

The synthesis of Tris(anhydride) followed the conventional way. A carboxylic acid was made via a base-catalyzed hydrolysis of the ester group of the syn-trimer 8. The reaction with acetic anhydride and the carboxylic acid gave a high yield of Tris(anhydride). The final step of
amidation prepared with a primary amine (3-(aminomethyl)-pyridine) and an acidic anhydride (Tris(anhydride)) was also commonly encountered. However, the published methodology using only those compounds gave low yields\textsuperscript{12}. Therefore, some modifications were made in the silver (I) mediated molecular basket experiment. In order to bring about the competing effect of a co-reactant, a catalytic amount of pyridine was added. This step was successful only when the heat and the sequence of addition of pure pyridine were applied correctly.

2. Solubility

Polydentate 1 was not greatly soluble in chloroform or dichloromethane. This compound was, however, solubilized in chloroform with methanol. More experiments confirmed that 1 can be solubilized more effectively in a more polar solvent such as acetonitrile.

3. \textsuperscript{1}H NMR Titration

3-1. Complexation of Host-Cu (I)

A sample of polydentate 1 was dissolved in a solution of and deuteroacetonitrile (CD\textsubscript{3}CN) and deuteroacetone (CD\textsubscript{3}COCD\textsubscript{3}). The concentration of sample was 43.05 (mM). The same concentration of the host was used for dissolving a sample of Cu(CH\textsubscript{3}CN)\textsubscript{4}PF\textsubscript{6} in CD\textsubscript{3}CN throughout the titration. Successive aliquots of the metal cation solution were added to the host NMR sample.
The $^1$H NMR titration spectra are illustrated in Figure 5-1. After each addition of 0.45 equivalents Cu (I) to the host solution in CD$_3$CN, a $^1$H NMR spectra was measured. The proton positions of 1 and the corresponding $^1$H peak were identified in the illustrations (Figure 5-2). Some of the proton peaks shifted clearly as the amount of Cu (I) added to the solution of 1 increased. This result corroborated that there were molecular interactions in the host-guest. In the spectra of Cu (I), the overall peak change was greatest after the addition of 0.45 equivalents. Then, the shift was reduced slowly from 0.90 to 1.35 equivalents. The change was almost indiscernible after 1.35 equivalents. It is highly possible that polydentate 1 was bound to Cu (I) in a 1:1 ratio.

The qualitative analysis of titration results is also useful to understand the behavior of folding and unfolding of the host molecule. The spectra polydentate 1 indicated that the chemical shift change ($\Delta\delta$: ppm) in the downfield were more apparent than in the upfield (Figure 5-1). The protons of the downfield were assigned to the pyridine protons. It was obvious that the peaks of $H_a$, $H_c$, $H_d$, but not $H_b$, changed greatly as the amount of the addition of Cu (I) increased (Figure 5-2). This result suggests that $H_a$, $H_c$, and $H_d$ protons change their renvironment during the complexation of pyridines with Cu (I). On the contrary, the chemical shift of $H_b$ was not as dramatic as three other protons, indicating that the $H_b$ was the rotational center of folding-unfolding of 1 along the $C_3v$ symmetry. The peaks of $H_a$, $H_c$, and $H_d$ in the upfield were not critically shifted. While the pyridine moiety folded, the lower part of the basket remained rigid without undergoing the same degree of the conformational change. The pyridine flaps were likely organized into the propeller-like conformer, also observed in the previous experiment of silver (I).
The pattern of chemical shift changes also accounted for the location of Cu (I). If Cu (I) was positioned inside the basket, the H₆ peak of the pyridine moiety would have been shifted differently: it could have shifted more downfield. Rather than being enclosed deeper in the cavity, the perching state of Cu (I) seemed highly plausible. This hypothesis became more convincing when the host-metal complex was tested with organic guests.

**Figure 5-1. **¹H NMR Titration of Cu(CH₃CN)₄PF₆ in CD₃CN

**Figure 5-2 Corresponding proton position for NMR**
3-2. Complexation of Host- Cu (I) – Organic Guest

Titrations of the host-Cu (I) complex were performed with pyridine, acetonitrile, (methyleneophenyl)nitrile, aziridine, and imidazole. Pyridine did not cause substantial changes in the $^1$H NMR spectra. This is perhaps because the molecular size is large compared to the cavity of the host 1.

**Figure 6-1. Titration of host-Cu (I) complex with CH$_3$CN in CD$_3$COCD$_3$**

The titration experiment of acetonitrile showed most significant result. The NMR spectra of room and low temperature were compared (**Figure 6-1**). Generally, low-temperature NMR is useful to capture the slow molecular movement. At room temperature, the NMR chemical shift of the guest exchange is recorded as an average value of in/out. Thereby, the in/out exchange of guest is measured more effectively at the low temperature, allowing for the characterization of the host - Cu (I) - guest complexation.$^{13}$

The 69 equivalents of CH$_3$CN (10 µL) was added to the host-Cu (I) complex in CD$_3$COCD$_3$. At room temperature, the CH$_3$CN peak was about 1.96, the same value of the free CH$_3$CN molecule. As the NMR temperature was lowered from room temperature down to -
60 °C, the peak of CH$_3$CN became shifted to the upfield, showing the value of about -1.8 (ppm). This increased shielding effect of CH$_3$CN was due to the CH - π bond interaction with the surrounding benzene rings of the host. This shifted value down to the -1.8 (ppm) suggests that a CH$_3$CN molecule was encapsulated inside the basket via a binding with the Cu (I) (Figure 6-2). The peak ratio of polydentate 1 and CH$_3$CN was 1:0.46, suggesting that 46 % of CH$_3$CN molecule occupied inside the cavity. In addition, the increased shielding is also indicative of its parallel alignment to the C$_{3v}$ axis.

Figure 6-2. Encapsulation of CH$_3$CN
Chapter IV. Conclusions and Future Work

In the series of the molecular baskets our research program has developed, polydentate 1 presented interesting aspects of synthesis and a notable progress in the host-guest assembly.

The new synthetic route for the preparation of polydentate 1 included the trimerization 8 using template effect and the hexa ester 5 via Diels-Alder reaction without the application of high pressure. Few low-yielding reactions still need to be improved. In the case of bromination compound 3, each trial of the reaction showed inconsistent yields. The reaction is re-examined to promote bromine radicalization in relation to photochemical condition and different reaction solvent.

\(^1\)H NMR studies suggested that Cu (I) was bound to the polydentate 1 in a 1:1 ratio. This binding stoichiometry was the same as that of Ag (I), corroborating that both metal ions form the same geometric coordination—tetrahedral—with the polydentate 1. The titration result provided a possible folding behavior of the polydentate 1 upon the binding to the Cu (I) ion. It also showed that the folding pattern of polydentate 1 was similar to the experiment with Ag (I).

The most substantial progress in this experiment was the encapsulation of CH\(_3\)CN inside the host-Cu (I) complex. Previously, organic guests were bound to Ag (I) positioned only outside the host. The quantification of binding isotherm with the CH\(_3\)CN is in progress. A preliminary analysis of UV-visible absorption spectrometric titration experiments was performed as a complementary \(^1\)H NMR technique. From these analyses, a more accurate understanding of the binding affinity is expected. In addition, ITC experiments will be performed to gain thermodynamic parameters. Then, the parameters of two different metal mediators, Ag (I) and Cu (I) will be compared. After all experiments are performed, a set of data regarding the
potential polydentate 1-metal mediator-organic guest reactions will be recorded, enriching the study of the synthetic molecular recognition and supramolecular chemistry.
Chapter V. Experimental

General Procedures. All solvents were purified based on standard literature protocols. Chromatography separations and purifications were performed using silica gel 60 (Sorbent technologies 40 – 75 µm, 200 x 400 mesh). Thin-layer chromatography (TLC) was performed on silica-gel plate w/ UV254 (200 µm). $^1$H NMR spectra were obtained from Bruker DRX 500 MHz and DPX 250 spectrometers. The changes in $^1$H NMR chemical shift of the sample were recorded manually. The sample preparation for all of the titration experiments were executed in a glovebox because Cu (I) was found susceptible to oxidation. All chemical shifts were measured relative to residual solvent peaks. Samples were prepared using CDCl$_3$, CD$_3$CN, and CD$_3$COCD$_3$ were purchased from Cambridge Isotope Laboratories. The chemical shift values are expressed as δ values and the coupling constant values (J) are in Hertz (Hz). The following abbreviations were used for signal multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; and br, broad.

Compound 2

\[
\text{Cl}\quad \text{Cl}\quad \text{Cl}
\]
\[
\text{hexane}
\]
\[
200 \degree C
\]
\[
71 \%
\]
\[
(MW: 190.97 \text{ g/mol})
\]

In order to isolate pure cyclopentadiene (2.65, 0.04 mol), solidified cyclopentadiene (4.16, 0.033 mol) was heated in a hot water bath at 160 °C for 2 hours. A Diels-Alder reaction proceeded
with pentadiene and 1,4-dichloro-2-butene for 4.5 hours. The reaction mixture was distilled, and the compound 1 was collected at 100 °C. The compound 2 (4.5 g, 71 %) was obtained. \( ^1H \) NMR (250 MHz, CDCl₃, 25 °C): \( \delta = 6.25 \) (dd, 2H, \( J_1 = J_2 = 1.8 \) Hz), 3.31 (dd, 2H, \( J_1 = 5.7 \) Hz, \( J_2 = 10.7 \) Hz), 3.14-3.09 (m, 4H), 2.63-2.60 (m, 2H), 1.55 (m, 1H), and 1.37 ppm (d, 1H, \( J = 8.6 \) Hz)

**Compound 3**

\[
\begin{align*}
\text{Cl} & \quad \text{Br}_2 \quad \text{C}_{10}H_{18} \quad 150 ^\circ C \\
2 & \quad \text{Cl} & \quad \text{Br} & \quad \text{Cl}
\end{align*}
\]

(MW: 190.97 g/mol) 47 % (MW: 350.88 g/mol)

A bromine solution was prepared in cis-decaline (350 mL). The compound 2 (23.6 g, 67.2 mmol) was mixed with 200 mL of cis-decaline, and the bromine (Br₂) (14.2 mL, 0.13 mol) was added using a syringe. The reaction mixture was heated at 150 – 160 °C for 15 minutes. Residual bromine was removed through a weak vacuum suction. Distillation was performed to isolate cis-decaline at about 50 °C from the crude product via a high vacuum suction. A creamy whitish yellow solid compound 3 was collected, purified by column chromatography (hexane : dichloromethane = 4 : 1). A solution of pure 3 in dichloromethane was yellow. \( ^1H \) NMR (250 MHz, CDCl₃, 25 °C): \( \delta = 4.34 \) (d, 2H, \( J = 2H \)z), 3.54 (dd, 2H, \( J_1 = 5 \) Hz, \( J_2 = 11 \) Hz), 3.29 (dd, 2H, \( J_1 = 13 \) Hz, \( J_2 = 9 \)Hz), 2.76 (d, 2H, \( J = 1.5 \) Hz), 2.47 – 2.30 (m, 2H), 2.43 (d, 1H, \( J = 11.0 \) Hz), and 1.43 ppm (t, 1H, \( J_1 = 10 \) Hz).
The compound 3 (8.7 g, 24.8 mmol) was dissolved in THF (100 mL). Potassium t-OBu (53.1 g, 0.47 mol) was added to the solution. The reaction mixture was maintained at 0 °C for 2.5 hours. After the reaction was completed, the compound 4 was filtered through hexane using a silica gel to remove excessive potassium t-BuOK. The reaction yielded the compound 4 (3.12 g, 63.6 %)

$^1$H NMR (250 MHz, CDCl$_3$, 25 ºC): $\delta = 6.20$ (dd, 1H, $J = 2$ Hz), 5.31 (s 1H), 5.25 (s, 1H), 5.14 (s, 1H), 5.00 (s, 1H), 3.37 (s, 1H), 3.30 (s, 1H), 2.05 (dd, 1H, $J = 2$Hz), and 1.64 ppm (dd, 1H $J = 10$ Hz).

The compound 5 (MW: 197.01 g/mol) was synthesized by reacting compound 4 with DMAD in CCl$_4$. The reaction yielded the compound 5 (MW: 339.18 g/mol)
A solution of compound 4 (0.177 mg, 0.089 mmol) and dimethyl acetylenedicarboxylate (DMAD) (0.1 mL, 0.083 mmol) were prepared in dissolved in CCl₄ (15 mL). The reaction yielded compound 5a via Diels-Alder reaction. The compound 5a was separated using column chromatography (toluene : acetone = 3 : 1). The product was a crude oil (0.25 g, 84%). ¹H NMR (250 MHz, CDCl₃, 25 ºC): δ = 6.71(s, 1H), 3.85(s, 2H), 3.46 (t, 1H), 3.33(t, 1H), 3.01 – 3.29 (m, 4H), and 2.43 ppm (s, 2H).

**Compound 6**

![Chemical structure of 5 and 6]

(MW: 339.18 g/mol)  78 %  (MW: 337.17 g/mol)

The compound 5 (3.816 g, 11.2 mmol) was dissolved in dichloromethane, followed by the addition of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (2.928 g, 12.9 mmol) at room temperature. The color changes from dark to light brown. The entire aromatization requires completely dried condition without any residual water. A vacuum and argon were applied alternatively. The product 6 was collected via column chromatography (toluene : acetone = 9 : 1). A crude oil of the product was produced (8.76 g, 78 %) ¹H NMR (250 MHz, CDCl₃, 25 ºC): δ = 7.26 (d, 1H, J₁ = 8.6 Hz), 7.22(d, 1H, J = 3Hz), 6.75 (d, 1H, J = 3.3 Hz), 4.02(s, 1H), 3.92 (s, 6H), and 2.38 ppm (s, 1H).
Lithium diisopropylamide (LDA) was prepared with diisopropyl amine (1.3 mL, 9.3 mmol) and n-butyl lithium (1.6 M in hexane, 5.6 mL, 59.4 mmol) at 0 °C under an atmosphere of argon. The mixture was cooled down to -78 °C for 20 minutes. A solution of LDA was prepared with THF (20 mL). A solution of Me₃SnCl (1.2 g, 6.0 mmol) was added to compound 6 (1.87 g, 5.5 mmol) in THF (20 mL) was added to LDA over 10 minutes. After 30 minutes, the mixture was warmed to room temperature. Then, the mixture was left stirred overnight. The crude product was quenched using water and extracted with diethyl ether. The separated organic phase was dried with MgSO₄ and the liquid was vacuum suctioned. The yellow residue was purified with column chromatography (hexane: ethyl acetate = 8:1). A crude product was collected (1.75 g, 63.6 %) $^1$H NMR (250 MHz, CDCl₃, 25 °C): $\delta = 7.64$ (s, 1H), 7.45 (s, 1H), 4.07 (s, 1H), 3.89 (s, 6H), 2.40 (dd, 2H, $J_1 = 7.5$ Hz, $J_2 = 7.5$ Hz), and 2.39 ppm (s, 9H).
Compound 7 (179.8 mg, 0.4 mmol) was dissolved in five equivalents of acetone (10 mL). Copper (II) nitrate (Cu(NO₃)₂·2.5 H₂O) (471.4 mg, 2.0 mmol) was used as a catalyst. The reaction was heated at 50 °C about 18 hours. The syn-trimer was separated via column chromatography. Two different eluents were used. The several initial impurities were isolated with a solution of ethyl acetate and hexane (1:1), and the anti- and syn- compounds were separated using column chromatography (dichloromethane : acetone = 9:1). The crude syn-trimer 7 was a yellow liquid. The reaction yielded 40.6 % of the syn-trimer and anti-trimer: a white syn-trimer (11 mg, 11%). ¹H NMR (250 MHz, CDCl₃, 25 °C): δ (ppm) = 7.43 (s, 6H), 4.41 (s 6H), 3.78 (s, 18H), and 2.52 ppm (s, 6H).
**Compound 9**

(MW: 768.76 g/mol) 61% (MW: 658.084 g/mol)

*syn*-trimer 8 (50.6 mg, 0.066 mmol) in THF (4 mL) and a solution of LiOH (101.0 mg, 4.21 mmol) in water (4 mL) and were reacted in a reflux for 3.5 hours. A solution of HCl (10 mL) in water (20 mL) was added to the mixture to neutralize the reactants. A slightly yellow solid were precipitated out. The yellow aqueous layer was removed via centrifuge. Then, the collected pale yellow solid 9 was dissolved in acetic anhydride (5 mL) at 130 °C for 2 hours. The reaction yielded a yellowish white solid (26.7 mg, 61.2 %). ¹H NMR (250 MHz, CD₃SOCD₃, 25 °C): δ = 7.99 (s, 6H), 4.77 (s, 6H), and 2.56 ppm (s, 6H).
Tris-anhydride (2.5 mg, 0.004 mmol) was dissolved in toluene (1.0 mL). A solution of 3-(aminomethyl)-pyridine (2.6 mg, 0.024 mmol) was prepared in toluene (0.5 mL) and mixed with the tris-anhydride solution. After the mixture was heated up to 120 °C, dried pyridine (150 μL) was added to the mixture using a syringe. The catalytic amount of pyridine should be about 1% of toluene. The reaction continued 24 hours at the same temperature setting. The mixture was separated using a column chromatography (toluene: acetone = 2:1 with 1 (vol %) of pyridine). The reaction yielded a white solid compound, the polydentate molecular basket 1 (3.6 mg, 87 %). $^1$H NMR (250 MHz, CD$_3$CN, 25 °C): $\delta$ (ppm) = 8.26 (s, 6H), 7.49 (s, 6H), 7.35 (d, 3H, $J = 7.5$ Hz), 4.46 (d, 6H, $J = 8.8$ Hz), 2.47 – 2.30 ppm (dd, 6H, $J_1 = 14.3$ Hz, $J_2 = 8.5$ Hz).
**Bibliography**

11. Ibid., 5888.