Molecular Encapsulation in Kinetically Trapped, Hydrogen-bonded Pyrogallolarene Hexamers

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MOLECULAR ENCAPSULATION IN KINETICALLY TRAPPED, HYDROGEN-BONDED PYROGALLOLARENE HEXAMERS

A Dissertation

Presented to

the Faculty of Natural Sciences and Mathematics

University of Denver

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

by

Jennifer Christine Chapin Lake

June 2014

Advisor: Byron W. Purse
Pyrogallolarene and resorcinarene hexamers are hydrogen-bonded capsules that self-assemble in the solid state and can be studied in gaseous and solution phases. Guest loading within pyrogallolarene hexamers in solution has primarily been comprised of solvent molecules with some tertiary amines. A novel solvent-free method for loading guests into the interior of the hexamer has been shown to be effective for encapsulation of a variety of molecules. Aromatic and aliphatic compounds have particularly high guest loading within the hexamers and often result in kinetically stable guest-filled capsules in solution.

Kinetic studies of the encapsulation complexes of anthracene, biphenyl, fluoranthene, fluorene, naphthalene, norbornene and pyrene were performed in multiple solvents using $^1$H NMR. In all but one case the kinetically stable complexes completely exchanged the encapsulated guest for solvent resulting in guest release processes that were determined to be first order in capsule. Guest release requires the breakage of multiple hydrogen bonds simultaneously to create an opening in the hexamer for the guest to exit and solvent to enter. Small structural changes in both the solvent and the guest resulted in large differences in exchange rates. Those guests and solvents that were larger or had greater deviations from planarity had longer exchange rates due to the larger openings required for guest release.
Purification of the kinetically trapped species was successfully performed using size exclusion gel permeation chromatography. Chemical compartmentalization experiments were performed to determine the ability of the hexamer to sequester encapsulated guests from bulk solution and thereby isolate them from potential reactants. Both bromination and hydrogenation of the alkene functionality of norbornene resulted in no addition to the double bond for encapsulated norbornene. These results illustrate the high kinetic stability of the guest encapsulated pyrogallolarene hexamers in solution.

Monofunctionalization of the lower rim of pyrogallolarene was also attempted. A mixture of pyrogallolarenes was successfully synthesized with 0-3 terminal double bonds. Olefin metathesis with benzyl acrylate followed by hydrogenolysis successfully resulted in pyrogallolarenes with carboxylic acids on the lower rim. Peptide coupling to create an amide linkage has also been studied for use in attachment to polymers.
Acknowledgements

I would first like to thank my advisor Dr. Byron Purse for his support and guidance over the past five years. His positive attitude and declarations of the “awesome” results of experiments have been instrumental in getting me to this day.

I would also like to thank the many members of the Purse Group who I have had the pleasure of working with these past five years. Special thanks go to Mirek Kvasnica who taught me everything I know and Brittney Rodgers who helped me navigate the twists and turns of graduate school including a lab move halfway across the country.

The work presented in this dissertation was financially supported by the University of Denver, San Diego State University, and the ACS Petroleum Research Fund 52339-ND7 for which I am very grateful.

To all of the friends I have made at DU and SDSU who have supported, entertained, and commiserated with me, thank you. This experience would not have been the same without you.

To my parents, thank you for all of your support, the many phone calls, and for listening to me talk even when you had no idea what I was saying. To my brothers, thank you for always making me laugh and keeping my spirits up. And finally to my husband, Jeremy, thank you for your unconditional love and support. Your strength and compassion have gotten me through these last five years and none of this would have been possible without you.
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<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>∆G‡</td>
<td>standard Gibbs energy of activation</td>
</tr>
<tr>
<td>∆H‡</td>
<td>standard enthalpy of activation</td>
</tr>
<tr>
<td>∆S‡</td>
<td>standard entropy of activation</td>
</tr>
<tr>
<td>¹H NMR</td>
<td>proton nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>¹³C NMR</td>
<td>carbon nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>Å</td>
<td>angstrom</td>
</tr>
<tr>
<td>AFM</td>
<td>atomic force microscopy</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobisisobuyronitrile</td>
</tr>
<tr>
<td>BCB</td>
<td>benzocyclobutene</td>
</tr>
<tr>
<td>BOC</td>
<td>tert-butylxocarbonyl protecting group</td>
</tr>
<tr>
<td>C₆D₆</td>
<td>deuterated benzene</td>
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</tr>
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<td>CCl₄</td>
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<td>CD₂Cl₂</td>
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<td>CHCl₃</td>
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<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>DCC</td>
<td>dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCl</td>
<td>deuterated hydrochloric acid</td>
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DCM  dichloromethane
DIBAL-H  diisobutylaluminum hydride
DMF  dimethylformamide
DMPA  2,2-dimethoxy-2-phenylacetophenone
DMSO  dimethylsulfoxide
DOSY  diffusion ordered spectroscopy
$E_a$  activation energy
ESI  electron spray ionization mass spectrometry
EtOAc  ethyl acetate
FRET  fluorescence resonance energy transfer
GPC  gel permeation chromatography
GSD  global standard deconvolution
$h$  Planck’s constant
HCl  hydrochloric acid
HMBC  heteronuclear multiple-bond correlation spectroscopy
HSQC  heteronuclear single-quantum correlation spectroscopy
$k$  rate constant
$k_B$  Boltzman’s constant
MeOD  deuterated methanol
MeOH  methanol
MgSO$_4$  magnesium sulfate
MS  mass spectroscopy
$N_2$  nitrogen gas
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>Na₂SO₄</td>
<td>sodium sulfate</td>
</tr>
<tr>
<td>NaOH</td>
<td>sodium hydroxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>Pd/C</td>
<td>palladium on carbon</td>
</tr>
<tr>
<td>pyBOP</td>
<td>benzotriazol-1-yl-oxytriryrrolidinophosphonium hexafluorophosphate</td>
</tr>
<tr>
<td>pyBrOP</td>
<td>bromo-tris-pyrrolidinophosphonium hexafluorophosphate</td>
</tr>
<tr>
<td>r</td>
<td>rate</td>
</tr>
<tr>
<td>R</td>
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</tr>
<tr>
<td>VdW</td>
<td>van der Waals volume</td>
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Chapter 1: Resorcinarene and Pyrogallolarene

1.1 Introduction

The noncovalent interaction of two or more molecules is the primary interest of molecular recognition chemistry. Examples of molecular recognition are prevalent in biological systems such as enzymes, proteins, and even viruses, and without this capability life as we know it would not exist. Molecular recognition chemistry centers around synthetic molecules that mimic the remarkable ability of biological systems to discern and interact in beneficial ways with different molecules with which they come into contact. Naturally occurring host receptor sites are most commonly concave surfaces with high selectivity due to the compatibility of the receptor binding site for the substrate molecule. Complexation products are primarily the result of noncovalent interactions such as hydrogen bonding, ion pairing, pi stacking, metal ligand-binding, and van der Waals interactions, although the hydrophobic effect and entropic factors can also play a large role.

The genesis of molecular recognition chemistry can be traced to the 1967 publications known as the “Pedersen Papers” which presented the complexation of cations with cyclic polyethers. Pedersen’s crown ethers could almost completely surround various cations due to the size complementarity as well as the charge affinity of host and guest. In the case of polyethers there is no preorganized binding site. It is only in the complexed state that the “binding pocket” is established. This ability of self-
assembly between host and guest is a recurring theme throughout molecular recognition chemistry. The polyether host is also essentially planar in its complexed state causing a one dimensional encapsulation of a three dimensional molecule, though research has been done to modify polyethers with various appendages to create a more fully encapsulated complex.\textsuperscript{4-6} The discovery of polyether complexes sparked interest in the development of various other synthetic receptor molecules which could uptake or bind small molecules.

Calixarenes 1.1,\textsuperscript{7-10} and their subset resorcinarenes 1.2\textsuperscript{11-14} and pyrogallolarenes 1.3,\textsuperscript{15-18} are molecules that are well studied in the field of molecular recognition chemistry (Figure 1.1). All three are comprised of a tetrameric circular structure of alternating benzene rings and methine carbons.

Figure 1.1. Structures of calixarene 1.1, resorcinarene 1.2, and pyrogallolarene 1.3.

Calixarenes are most easily synthesized by base catalyzed condensation reactions of substituted phenols with formaldehyde.\textsuperscript{19,20} Resorcinarenes and pyrogallolarenes are most commonly produced by acid catalyzed condensation of resorcinol and pyrogallol, respectively, with an aldehyde.\textsuperscript{21-23} These molecules all form a shallow, bowl-type structure and symmetric specimens can easily be synthesized on kilogram scales. The resorcinarenes and pyrogallolarenes have a polar upper rim comprised of eight or twelve
hydroxyl groups and a lower rim, often referred to as the feet of the molecule, made up of the aldehyde chains. The base structures of resorcinarenes and pyrogallolarenes have been used as a scaffold for a variety of container molecules. Modifications have been made to the upper rim using phenolic hydroxyl chemistry to increase the depth of the cavity by building larger walls to form cavitands.\(^{24}\) The lower rim, or feet, of the molecule has also been modified to increase or decrease solubility, for labeling purposes, or for use in attachment of these molecules to substrates.\(^{25–27}\) Resorcinarenes and pyrogallolarenes have also been found to form hexameric capsules in solution as well as in solid state and gaseous phase.\(^{28–30}\) These large capsules enclose a volume of roughly 1300 Å\(^3\) and are held together by hydrogen bonds. Since their discovery they have been of great interest due to the large size of the interior which can fully sequester larger molecules or coencapsulate multiple small molecules with reversible guest loading and release.

### 1.2 History

Adolf Baeyer was the first to publish a paper on the synthesis of pyrogallolarene and resorcinarene in 1872.\(^{15}\) Baeyer had a long and distinguished career in chemistry. The Baeyer-Villiger reaction is in part named after him, he was the first to synthesize indigo, and he discovered phthalein dyes.\(^{31}\) In 1905, as Adolf von Baeyer, he was awarded the fifth ever Nobel Prize in Chemistry "in recognition of his services in the advancement of organic chemistry and the chemical industry, through his work on organic dyes and hydroaromatic compounds."\(^{32}\) Baeyer’s work on phthaleins, which are synthesized via a condensation reaction of phthalic anhydride and phenol, led him to
explore other condensation reactions. In his first 1872 paper, he described the condensation reaction of benzaldehyde with pyrogallol and resorcinol using hydrochloric or sulfuric acid, which formed a resinous product. In his following paper he refined the procedure and found that gradually adding the acid to the aldehyde and pyrogallol in a boiling alcohol solution formed a crystalline solid. The product formed was stated to have a chemical formula of $C_{26}H_{22}O_7$, indicating a reaction between two molecules of the aldehyde and two molecules of the pyrogallol but no structure was proposed. Baeyer published many other papers on the condensation reactions of aldehydes and phenols but his 1872 papers were the first published synthesis of resorcinarene and pyrogallolarene. The proposed chemical formula was incorrect but the acid catalyzed condensation method is still used in the synthesis of these molecules today.

Baeyer was not the only one interested in reactions of aldehydes with phenols. In 1883 Arthur Michael, best known for the Michael Reaction, published two papers on the acid catalyzed condensation of aldehydes with resorcinol. The first was a detailed paper on the reaction of benzaldehyde and resorcinol and the characterization of the resulting products, both the resinous and crystalline solids reported by Baeyer, while the second expanded the reaction to include orcinol and other aldehydes. In his first paper Michael detailed the difficulties involved in the analysis of the product due to problems with drying and solubility. He did propose a structure, 1.4, based on the same ratio of two molecules of aldehyde and two molecules of phenol that was put forth by Baeyer (Figure 1.2). Michael himself stated that the structure “cannot be considered other than that as a suggestion” based on the work that had been done to date. We now know that the
structure was indeed incorrect, however, he did correctly identify the base molecular formula of resorcinarenes to be \((C_{22}H_{20}O_4)_n\).

The correct tetrameric structure of resorcinarenes, and by extension pyrogallolarenes, was not determined until 1940 when Joseph B. Niederl and Heinz J. Vogel published a paper on the reaction of acetaldehyde with resorcinol.\(^{11}\) The year before Niederl and Victor Niederl published a paper on the multiple alkylation of resorcinol by ketones resulting in product 1.5, which illustrated the correct product for an electrophilic addition to the aromatic ring by two ketones, each one alpha to a carbon containing a hydroxyl group\(^{36}\) (Figure 1.2).

**Figure 1.2.** Michaels proposed structure 1.4, multiple alkylation of resorcinarene using ketones 1.5, and the correctly determined tetrameric structure of resorcinarene 1.2.

Niederl and Vogel used the concept of multiple alkylation of an aromatic ring as a basis for the structural determination of resorcinarene. Molecular weight determination yielded a molecular ratio of 4:4 for the aldehyde and phenol in the product rather than the 2:2 ratio that had previously been determined by Baeyer and Michael. This discrepancy was addressed by the ability of the product to “retain various amounts of water of crystallization very tenaciously, which may explain the difference in the analytical results obtained by the previous investigators”\(^{11}\) which was also stated to be a problem by
Michael in his investigations. Further tests proved the presence of eight free hydroxyls which supported the theory of multiple alkylations of the aromatic ring. Long chain polymerization was discarded as a possibility in part due to the high melting point and crystalline form of the product and the unlikely event of polymerization halting after the formation of the tetramer regardless of the reaction conditions or identity of the aldehyde. A ring comprised of a fourfold replicate structure, similar to that of chlorophyll and hemin, was therefore proposed 1.2 (Figure 1.2). Nearly 70 years after the original publication of the synthesis of resorcinarene and pyrogallolarene, the structure was determined.

1.3 Isomers

Once the tetrameric structure of the resorcinarene and, by extension pyrogallolarene, was determined the three dimensional structure was investigated. There are four possible stereoisomers of these molecules which are designated all-cis (rccc), cis-cis-trans (rcct), cis-trans-trans (rctt), and trans-cis-trans (rtct). These designations assume the ring of alternating aromatic moieties and methine carbons to be planar and the cis and trans designations refer to the orientation of the aldehyde chains with regard to the reference chain (Figure 1.3).
The first isomer to be isolated was the \textit{rcce} isomer for which a crystal structure was obtained in 1968.\textsuperscript{12} In 1980 Högberg published two papers in which he investigated various isomers of resorcinarene, both configurational and conformational.\textsuperscript{21,38} In these papers he was able to isolate both the \textit{rcce} and \textit{rctt} isomers. He found that in the reaction of acetaldehyde with resorcinol the initial product formed was the \textit{rctt} isomer, however, as the reaction progressed the amount of \textit{rctt} isomer decreased and was replaced with the \textit{rcce} isomer indicating that the formation of these molecules must be reversible. This finding may also explain the two products seen by Baeyer, one resinous and one crystalline. When the pure \textit{rcce} form was heated there was no \textit{rctt} isomer formed indicating that the \textit{rctt} isomer is a kinetic product while the \textit{rcce} isomer is the thermodynamic product.\textsuperscript{38,39} The \textit{rcct} and \textit{rtct} isomers have also been isolated but they comprise very minor percentages of the final product mixture.\textsuperscript{22,37,40}

Within each stereoisomer there are a variety of conformational isomers that are possible. In his 1980 papers Högberg discussed some of the possible conformational isomers of the isolated \textit{rcce} and \textit{rctt} forms. By \textsuperscript{1}H NMR he found that both isomers showed the side chains from the aldehyde to be equivalent while there were two signals
for the aromatic rings from the resorcinol indicating a loss of symmetry. The proposed structure for the \textit{rectt} isomer is a chair conformation of $C_{2h}$ symmetry, 1.6, with all of the alkyl side chains in axial positions (Figure 1.4). The three possible structures proposed for the \textit{rccc} isomer were that of a boat, with the aldehyde side chains either axial or equatorial, or that of a saddle. The boat structures have a large number of possible conformers depending on the angle of the aromatic ring of the resorcinol moiety with respect to the horizontal plane. The saddle conformer is a derivative of the boat conformer with two of the aromatic rings tilted downwards perpendicular to the horizontal plane. All these conformers have $C_{2v}$ symmetry which is consistent with the signals found on the NMR corresponding to equivalent alkyl side chains and two types of hydrogens for the aromatic resorcinol moiety. The boat conformer, 1.7, (Figure 1.4) with the aldehyde side chains in the axial position has the least steric crowding and corresponds with the x-ray structure of the \textit{rccc} isomer that was determined previously in 1968.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{structures.png}
\caption{Structures of the conformations of resorcinarene. Chair conformer with $C_{2h}$ symmetry, 1.6, boat conformer with $C_{2v}$ symmetry, 1.7, bowl conformer with $C_{4v}$ symmetry, 1.8.}
\end{figure}

Due to the low solubility of the resorcinarene products with short aldehyde side chains, the phenolic hydroxyl groups of the resorcinol moiety were esterified for these studies. The preference for the \textit{rccc} isomer in the boat conformation is commonly found
with resorcinarene molecules which have esterified phenolic hydroxyl groups due to the added bulkiness and the loss of the ability of the phenolic hydroxyl groups to hydrogen bond. Högberg did postulate that at high temperatures the boat conformation could undergo a type of pseudorotation through a bowl (sometimes called crown or cone) conformation, 1.8. For the unfunctionalized resorcinarene molecule with eight free hydroxyl groups, and the pyrogallolarene molecule with twelve hydroxyls, the preferred conformation is the bowl which has $C_{4v}$ symmetry (Figure 1.4) as demonstrated by numerous crystal structures.13,23,24,29 The many studies done on the formation of the different isomers has led to the current procedure that is used to synthesize the resorcinarene and pyrogallolarene molecules today. For solution phase studies long carbon chains are most often used to increase the solubility of the molecules in nonpolar solvents, which has the added benefit of causing selective precipitation of the tetrameric product from the solvent during synthesis. The increased time and heat that is used ensures that the $rccc$ isomer is the primary product, though it is possible that some of the other isomers may be left in the filtrate after isolation of the product.

The bowl conformer of resorcinarene and pyrogallolarene is the preferred product for chemists due to the enclosed guest-binding pocket. In order to further rigidify the upper rim of the resorcinarene methods were investigated to connect the oxygens using covalent bonds. Donald J. Cram was the first to link the hydroxyl groups of the upper rim together. Using bromo-chloro-methane he attached a methylene group between the oxygens of neighboring aromatic rings causing a rigid upper rim which restricts the cavitand into the bowl conformer, 1.9, (Figure 1.5).24 Silanes have also been used to
bridge the oxygens along the upper rim. These two methods force the cavitand into the bowl conformer, however, they have relatively small binding pockets which limits the size and therefore number of guests which can complex with these cavitands. A weak affinity of these cavitands for solvent molecules and a few ammonium compounds was determined from NMR measurements. A desire for a larger guest-binding pocket which would increase the size and number of guest molecules able to complex with the cavitands led to a study of deep cavitands.

1.4 Deep Cavitands and Dimers

The first deep cavitands were synthesized by Cram in 1982. Resorcinarene molecules were treated with 2,3-dichloroquinoxaline under basic conditions in DMF to form a nine-membered ring with bridging oxygens from the resorcinarene. The addition of the naphthalene unit to the upper rim of the resorcinarene yielded a bowl with much longer walls and a deeper binding pocket, 1.10, (Figure 1.5). Solvent was cocrystallized within these new cavitands. Unfortunately the nine-membered ring of this compound allowed for flexibility of the extended walls of the cavitand which permitted two different conformations. One was a vase-like form, suitable for binding guest molecules, and the other was a flat kite-like form which was unable to uptake guests. Further modifications of the upper rim of resorcinarene were attempted in order to make a cavitand that was more structurally sound in the vase-like form. The resorcinarene compound was treated with difluorodinitrobenzene which again took advantage of the phenolic hydroxyls to form a nine-membered ring. The nitro groups were then reduced to
Figure 1.5. Structures and molecular models of the rigidified cavitand, 1.9, and deep cavitands, 1.10-1.12. R groups have been removed for clarity.
amines and acylated to give a compound with eight amide functionalities on the upper rim or reacted with other molecules to build larger walls, $\textbf{1.11}$, (Figure 1.5).$^{44,45}$

The amides can undergo intraannular hydrogen bonding to bridge neighboring aromatic rings and increase the stability of the vase-like conformation.$^{46}$ These deep cavitands have been shown to uptake solvent as well as additional guest molecules such as adamantane.$^{46,47}$ In one case a deep cavitand was formed with a single bipyridyl linker on the upper rim attached to a carbon chain terminating in a cyclohexane ring. The cavitand could fold in on itself placing the cyclohexane ring in the interior of the cavitand acting as both host and guest. This unique cavitand was termed an ouroborand coined from the Greek “ouroborous” meaning tail eater, $\textbf{1.12}$, (Figure 1.5).$^{45}$ Deep cavitands have been a subject of significant research in their own right but the ability of these cavitands to undergo dimerization opened a new area of study for fully encapsulated host guest complexes. These dimers can be covalently bonded or they can be coordinated through hydrogen bonds.

Short hydrocarbon chains have been attached to the aryl groups of pyrogallolarene to link two molecules together forming cacerands, $\textbf{1.13}$, (Figure 1.6), closed-shell molecules which completely surround their guest molecules. By their nature the guest molecules must be encapsulated during formation as no opening exists through which they could enter once the cacerand has been created.$^{14,48}$ In this manner the guest molecules template the formation of the cacerand. The templating property of guest molecules to cause the formation of hydrogen-bonded dimers has also been studied with modified resorcinarenes.$^{49,50}$
Figure 1.6. Molecular models of the covalently linked cacerand, 1.13, and deep cavitand dimers, 1.14-1.15.

The ability of deep cavitands to form hydrogen-bonded dimeric assemblies, 1.14, (Figure 1.6), has been of great interest in the field of molecular recognition. Various solvents and guests have been encapsulated within these assemblies.\textsuperscript{51,52} The size of the guest molecule is of great importance and, with smaller guests, coencapsulation of different molecules has been observed.\textsuperscript{51} The affinity of specific guest molecules for the interior of the capsule and the rates of guest uptake and release have been the subject of
many studies. Azobenzenes are one type of guest molecule that has been shown to fit well within the dimeric capsules of modified resorcinarenes when in the \textit{trans} form. The photoisomerization of azobenzene to the \textit{cis} form causes the guest to be released from the capsule resulting in a controllable method to discharge guests from dimeric capsules. Additional spacer molecules such as glycouril can even be added in between the two halves of dimers while still maintaining the hydrogen-bonded integrity of the capsule increasing the size of the cavity and allowing for larger guests to be encapsulated, \textbf{1.15}, \textsuperscript{53,54} The size of these cavities is the main factor in guest encapsulation. A larger cavity can encapsulate a greater variety of guests or can coencapsulate a larger number of guests. The size of dimeric cavities is a few hundred cubic angstroms which allows for the encapsulation of many different guest molecules but larger complexes of resorcinarene and pyrogallolarene have also been studied.

\textbf{1.5 Hexamers}

In 1997 Jerry L. Atwood published a paper in which he described a unique property of resorcinarenes. He discovered an ordered crystal structure of six molecules of the unfunctionalized resorcinarenes in a hydrogen-bonded molecular assembly.\textsuperscript{29} Two years later Jochen Mattay published a similar crystal structure of pyrogallolarene in the same hexameric hydrogen-bonded assembly.\textsuperscript{16} These capsules were larger than the previously studied dimers of deep cavitands and could completely sequester guests from the bulk solution. Numerous studies on these hexameric assemblies have been done in solid, solution, and gaseous phases and newly discovered unique aspects of their stability are the focus of this dissertation.
1.5.1 Solid State and Gaseous Phase

The seminal paper by Atwood on the crystal structure of methylresorcinarene, (Figure 1.7), is a detailed study of the structure of the hexamer. The initial experiment attempted to cocrystallize the methylresorcinarene with hydrogen bond acceptors in nitrobenzene. Instead of the expected product, a spherical assembly of six molecules of resorcinarene and eight molecules of water was found. The exact pattern of the hydrogen bonds could not be determined from the crystal structure because the hydroxyl hydrogen atoms were not definitively located but it was possible to deduce the most likely pattern due to distance measurements and orientation of the molecules. The octahedral snub cube with a resorcinarene on each face has the hydroxyl groups of the upper rim pointed along the edges in order to hydrogen bond both with the neighboring resorcinarennes in an intermolecular fashion as well as intramolecularly with the nearby hydroxyls on adjacent benzene rings. The eight water molecules are arranged at the vertices of the cube and participate in hydrogen bonding with each of the three adjacent resorcinarennes. All together there are 60 hydrogen bonds which hold this assembly together. The interior cavity was reported to be over 1300 Å³, which was four times larger than biggest cavity previously reported at the time of publication. The interior of the hexamer was not able to be resolved due to disorder which has been a recurring problem in crystal structures of the resorcinarene and pyrogallolarene hexamers.

Two years later Mattay published his crystal structure of a hexameric form of isobutylpyrogallolarene which was crystallized from acetonitrile. A crystal structure for isobutylpyrogallolarene crystallized from ethanol was also reported. In ethanol the
molecules form a bilayer structure in which each layer is comprised of alternate orientations of the bowl. The polar ends essentially cup each other in a zig-zag pattern while the feet dangle off the front and the back and interact with the neighboring layer, 1.17 (Figure 1.7). Bilayer or dimeric crystal structures are typically seen in crystals grown in polar media.\cite{56-58} In acetonitrile the isobutylpyrogallolarene crystallized into a
hexamer similar to the one determined by Atwood. In the case of the pyrogallolarene hexamer there were no water molecules found crystallized in the structure. Instead the twelve hydroxyls appear to hydrogen bond both intermolecularly as well as intramolecularly between the pyrogallolarene units without any assistance from additional molecules. The pyrogallolarene hexamer has 72 hydrogen bonds holding it together making it more structurally sound than that of the resorcinarene hexamer, though once again the specific pattern cannot be directly determined from the crystal structure. The study of pyrogallolarene hexamers in the solid state is well documented with crystal structures for lower rim chains with one to eleven carbons, and almost everything in between, being reported.\textsuperscript{58–64} Solid state resorcinarene and pyrogallolarene hexamers have even been synthesized by solvent-free conditions using an acid catalyst with a mortar and pestle grinding method.\textsuperscript{65,66} Longer alkyl chains make the crystal structures harder to refine due to the conformational mobility of the chain and have been shown to encapsulate solvent molecules on the exterior of the hexamer.\textsuperscript{63}

In his 1999 paper, Mattay attempted to use mass spectrometry (MS) to further characterize the hexamers, but this proved to be unsuccessful. Two years later he was able to use MS to study dimers\textsuperscript{67} but resorcinarene and pyrogallolarene hexamers were not successfully characterized by MS until electrospray ionization MS was used.\textsuperscript{68,69} In 2006 Rissanen and Schalley published their first paper on gas phase analysis of hexamers. In order to overcome the difficulty of providing the charge necessary for MS experiments they used a charged ruthenium complex as the encapsulated guest molecule, $\text{[Ru}^\text{II}(\text{bpy})_3\text{]}^{2+}$, which is a metal complex with a pseudoctahedral shape that is
complementary to the spherical interior of the hexameric capsule. The guest encapsulated hexamer was the strongly dominating signal in MS experiments for both resorcinarene and pyrogallolarene. Further experiments were done with pyrogallolarene hexamers in which the fragmentation of the complex was studied. Since the metal guest is fully encapsulated within the hexamer it was assumed that a large number of the pyrogallolarene units would have to be removed before the signal for free guest would be seen. Exchange mechanisms for fully encapsulated complexes require an opening in the host that is large enough for the guest to pass through in order to exit the capsule. This can be achieved by complete dissociation of one or more of the subunits or by the rupture of multiple hydrogen bonds to create an opening while still maintaining association of all six pyrogallolarenes in the hexameric structure.\textsuperscript{70} In the MS experiment, fragmentation of one, two, and three consecutive pyrogallolarene monomers was seen before any signals corresponding to the free metal guest complex indicating a dissociative mechanism. This experiment illustrates the necessity for an opening of a large enough size for the guest molecule to exit. In this case since the metal complex is so big, half of the subunits of the hexamer dissociated before the encapsulated guest could be released. Guest exchange in solution phase studies also requires the presence of an opening through which the guest can exit which can be achieved through dissociation or simultaneous rupture of multiple hydrogen bonds.

1.5.2 Solution Phase Studies

In Atwood’s 1997 paper it was also stated that such a complex was formed in solution. \textsuperscript{1}H NMR peaks were identified in deuterated benzene which corresponded to a
symmetrical assembly. Further studies were performed to confirm this statement. In 2001 Rebek published two papers on guest encapsulated hexamers in solution. Quaternary ammonium salts were added to a solution of resorcinarene in wet deuterated chloroform resulting in broadening of the hydroxyl and aryl hydrogen peaks of the resorcinarene as well as the peak corresponding to water in the NMR. This indicated that water does participate in the molecular assembly which corroborated the findings by Atwood. There was also the appearance of new signals corresponding to encapsulated guests. Integration confirmed that there was one encapsulated guest molecule per six resorcinarenes which demonstrated the presence of a hexameric assembly. The proton peaks for encapsulated guest molecules are shifted upfield due to shielding making them easy to identify. Quaternary ammonium salts with propyl, butyl, pentyl, and hexyl alkyl chains were all shown to be encapsulated within the hexamer. The longer chains on the ammonium salt showed a greater shift in the NMR, likely due to the proximity of the farthest carbons from the nitrogen to the concave surface of the resorcinarenes. Tests were also done to determine if the entire ammonium salt was bound within the hexamer or just the cation. Two fluorine peaks were found corresponding to both free and encapsulated fluorine when BF$_4^-$ was the anion for tetrabutylammonium. Larger anion pairs showed no encapsulation of the tetrabutylammonium which indicated that both are encapsulated. Phosphonium salts and antimony bromides were also shown to be encapsulated within the hexamer. Encapsulation in the liquid state is usually optimal when ~55% of the interior cavity is filled, based on van der Waals volume, meaning that additional molecules can be encapsulated within the hexamer if the guest molecule
does not optimally fill the cavity. In the case of tetrabutylantimony bromide additional encapsulated guests included, ethylbenzene, *p*-xylene, propylbenzene, nitrobenzene, biphenyl, naphthalene, and anthracene, among others. The ability of additional molecules to be encapsulated was limited by their size.

**Figure 1.8.** Molecular models of resorcinarene encapsulation complexes of tetrahexylammonium tetrafluoroborate, A, and CHCl₃, B. Hydrogens were removed for clarity.

Guest encapsulation is a strong indication of the presence of the hexamer due to integration yielding one guest molecule per six molecules of resorcinarene. Diffusion NMR also corroborates the presence of hexamers in solution. The diffusion coefficients measured by NMR reflect the molecular weight of the compound or complex being measured therefore monomers or dimers of resorcinarene would have very different diffusion coefficients from hexamers. In 2002, Cohen used diffusion NMR to measure the diffusion coefficient of guest encapsulated hexamers of resorcinarene and resorcinarene in solution without additional guest molecules present, which were found to be the same.²⁸ Up until this point it was thought that when there was not a suitable guest to fill the interior of the hexamer in solution that the hexamer may not form. The finding
that the diffusion coefficient of both samples was identical proved that they must both represent hexamers, one guest encapsulated and one solvent encapsulated. Diffusion NMR was also used to support the presence of water molecules in the hydrogen bonding network of hexameric resorcinarene, though it has been shown that alcohols can also take the place of water as a hydrogen bonding partner, and to show that previously assigned complexes thought to correspond to dimers or 1:1 complexes with resorcinarene were in fact hexamers.

The elucidation of resorcinarene hexamers in solution led to the study of pyrogallolarene hexamers. Resorcinarene and pyrogallolarene are very similar molecules and as such behave in similar fashion. Both form hexamers in the solid state. Hexameric assemblies of both can also be studied in gaseous and solution phases. Using diffusion NMR, Cohen determined that the diffusion coefficient for pyrogallolarene hexamers was very similar to that of resorcinarene hexamers (0.26 ± 0.01 x 10⁻⁵ cm² s⁻¹ and 0.28 ± 0.02 x 10⁻⁵ cm² s⁻¹ respectively) and he showed that both encapsulated CHCl₃ and spontaneously formed hexamers in solution without the need for an additional guest. However, the presence of four additional hydroxyls on pyrogallolarene does cause some significant differences in the properties and abilities of the two related hexamers. The water molecules that are required for hexameric formation of resorcinarenes in solution are not needed for the pyrogallolarene hexamers. The additional hydroxyls of pyrogallolarene make outside hydrogen bonding partners unnecessary. Polar solvents have been shown to disrupt the hexameric assemblies. Due to the increased number of hydrogen bonds holding the pyrogallolarene hexamers together (72 vs. 60 for
resorcinarene) the amount of polar solvents needed to disrupt the assembly is much higher than that of resorcinarene hexamers.\textsuperscript{79–81,83} When mixed in solution, resorcinarenes and pyrogallololarenes self-sort into homohexamers and do not comingle. This interesting property was studied by both diffusion NMR\textsuperscript{80,81} and by FRET (fluorescence resonance energy transfer).\textsuperscript{83} Rebek monofunctionalized the lower rim of resorcinarene and then attached two separate fluorophores, pyrene and perylene, which make a FRET pair. The intent was to monitor the exchange of monomers in the solution. When monomers containing each of the two fluorophores were involved in the same hexamer the proximity yielded FRET fluorescence. The experiment was successfully repeated with pyrogallololaren hexamers.\textsuperscript{84} FRET was also used when pyrene appended pyrogallolarene and perylene appended resorcinarene were mixed in solution with the intent of measuring heterohexamers.\textsuperscript{83} No FRET emission was seen corresponding to a heterohexamer of resorcinarene and pyrogallolarene confirming the results of Cohen’s diffusion NMR experiments.

1.5.3 Guest Affinity

Resorcinarenes have been shown to encapsulate tetraalkylammonium salts as described in the previous section. When Cohen attempted to encapsulate the same tetraammonium salts in pyrogallololarene hexamers none were found to be captured within the hexamer.\textsuperscript{85} Trialkylamines were tested to determine if they could be encapsulated. In both resorcinarene and pyrogallolarene hexamers the addition of trihexylamine, and others, to a solution of hexamers in chloroform gave rise to encapsulated guest peaks upfield in the NMR. Deuterated hydrochloric acid, DCl, was added to each solution to
protonate the tertiary amine. The protonated amine was still encapsulated in the resorcinarene hexamer, which is expected, but it was ejected from the pyrogallolarene hexamer leaving only encapsulated chloroform. Resorcinarene hexamers can encapsulate both tertiary amines and ammonium salts but pyrogallolarene was only shown to encapsulate tertiary amines.\textsuperscript{85} This would suggest that charged species are not compatible with pyrogallolarene hexamers in solution. However, in 2005 Kaifer published a paper on the encapsulation of cobaltocenium within pyrogallolarene hexamers.\textsuperscript{86} The encapsulation of cobaltocenium within resorcinarene hexamers had been previously published\textsuperscript{87} which was consistent with the affinity of charged species for the interior of that hexamer. The pyrogallolarene encapsulation complex was found to have a lower relative stability compared to the resorcinarene complex due to the reduced affinity of the cobaltocenium for the inner space of the capsule.\textsuperscript{86}

Rebek’s early experiments with ammonium salts in resorcinarene\textsuperscript{71} showed greater shift for longer alkyl chains but in the case of tetraheptylammonium bromide there was an unusual arrangement of peaks in which the methyl hydrogen signal was found downfield of the neighboring CH\textsubscript{2} hydrogen peaks. This indicated that the carbon chains were likely folded within the hexamer to make the guest molecule fit inside.\textsuperscript{71} Since pyrogallolarene has no need of water molecules in order to form the hexamer it was thought that the capsule might form in the presence of aliphatic hydrocarbons.\textsuperscript{88} Pyrogallolarene was found to be soluble, after some heating, in n-octane and NMR spectra showed upfield peaks indicative of encapsulated hydrocarbons. n-Alkanes with five to twelve carbons were tested and the hexamer was determined to have been formed
in each case. Integration allowed for determination of the number of molecules bound within the hexamer. The packing coefficients were lower than the ideal 55%\textsuperscript{73} (0.40-0.54) but folding or coiling of the hydrocarbon chains could allow for the molecules to occupy a larger portion of the interior.\textsuperscript{88} Branched and cyclic alkanes were also found to be encapsulated. Because pyrogallolarene can form hexamers without the help of additional hydrogen bonding partner’s, nonpolar molecules in which water is not miscible can be used as solvents for solution phase study.

Solvents are often guest molecules in supramolecular chemistry, but there is a lot to be learned from simple solvent encapsulation. Cohen performed an experiment with CHCl\textsubscript{3} in which he observed that the encapsulated chloroform peak appeared to be a multiplet.\textsuperscript{17} A series of NMR experiments at varying magnetic field strengths determined that this peak corresponded to several singlets rather than one multiplet. The conclusion was that there are slightly different molecular capsules in the solution which could be explained by different orientations of the monomers within the capsule. Dissolution in benzene yielded the same variety of signals corresponding to differing capsules indicating that the symmetry of the hexamers may be in a lower point group than initially thought. In fact, \textsuperscript{13}C NMR of the pyrogallololarene hexamer shows that six aromatic carbons peaks are present instead of the expected four which would correspond to a strictly symmetric molecule.\textsuperscript{79}

Guest affinity and encapsulation within resorcinarene and pyrogallolarene hexamers in solution are still being investigated. Resorcinarene hexamers can encapsulate a variety of guest molecules including tertiary amines, ammonium salts and other charged
species. It has even been shown to encapsulate metal complexes\textsuperscript{89} and radical species.\textsuperscript{90,91} Pyrogallolarene has a much lower affinity for charged species and has been shown to encapsulate tertiary amines, aliphatic hydrocarbons, and in one case hydrogen gas,\textsuperscript{92} but no ammonium salts which are a staple in guest exchange experiments for related molecules. While they are close cousins, resorcinarene and pyrogallolarene hexamers have as many differences as they do similarities.

1.6 Conclusions

Resorcinarenes and pyrogallolarenes have been molecules of interest for over a century. They have been well characterized and methods for preparation are now optimized and standardized. The concave shape of the structure is particularly useful for molecular recognition and guest encapsulation studies. These shallow bowl shaped molecules can be modified to create larger, open-ended cavities which can reversibly bind various different guests. The ability of these deep cavitands to dimerize utilizing covalent bonds or weak interactions, such as hydrogen bonding, allows for more complete encapsulation of guests. Methods to control guest encapsulation within these cavitands and dimers are a subject of ongoing research.

The discovery of large hexameric assemblies opened a new area of interest within supramolecular chemistry and allowed for guests of increased size to be encapsulated. These hexamers have been studied in the solid state and in the gaseous phase as well as in solution. Solution phase research has yielded many studies of different encapsulated guests which are typically solvents or other liquids. These studies have also revealed large differences in the resorcinarene and pyrogallolarene hexamers, primarily their guest
affinities and capsule stabilities. The molecules are very similar in structure yet have significantly different properties. The large number of hydrogen bonds stabilizing the structure make pyrogallolarene hexamers more stable to disruptive polar media, more difficult to load with guest molecules, and makes guest exchange studies more challenging than those performed for resorcinarene hexamers.

The research presented in this dissertation focuses on pyrogallolarene hexamers. A new method for loading guests within the interior of the hexamer is presented which results in highly stable, kinetically trapped encapsulation complexes. The remarkable stability of these complexes in solution has the potential for various applications in molecular recognition chemistry, some of which have been explored.

The kinetics of guest exchange with solvent for these encapsulation complexes under nonequilibrium conditions was studied with an emphasis on the effect of structural differences of both the guest and solvent on capsule stability. Minor structural differences in guest and solvent resulted in a large influence on the kinetic stability of the capsules. In some cases the guest encapsulated hexamers are sufficiently stable in solution to allow for purification of the hydrogen-bonded capsule using gel permeation chromatography. The ability of these complexes to sequester guests from reactants in bulk solution and thereby affect the course of reactions has also been explored. Finally, methods to monofunctionalize the lower rim of pyrogallolarene with the intent appending pyrogallolarene subunits to polymers for study of mechanical control of hexamer formation and dissolution will be presented.
Chapter 2: Kinetics

2.1 Introduction

Chemical kinetics is the study of the rates of reactions and processes. While typically considered an aspect of physical chemistry, the use of chemical kinetics is widespread throughout all areas of chemistry as well as biochemistry and biology. The kinetics of a reaction is directly tied to the mechanism of the reaction making chemical kinetics of particular interest for organic chemists. Kinetic analysis of experimental data yields quantitative information about reactivity allowing for classification and comparison of similar reactions.

Chemical kinetics has been of interest for over 150 years. In the late 1880’s Arrhenius was the first to suggest that not all molecules could react; only those that had a minimum activation energy could undergo a chemical reaction. This hypothesis became the cornerstone of modern chemical kinetics. The methods by which this minimum activation energy could be acquired were proposed to be through absorption of radiative energy, as in photochemical reactions, or through collision transfer. These assumptions led to the development of collision theory which was proposed in the early 1900’s and stated that only a limited portion of collisions would result in a chemical reaction because a minimum transfer energy was needed to achieve the activation energy required for the reaction to progress. Collision theory accurately explained a large number of chemical reactions; however, it was not all encompassing, particularly in the case of unimolecular
reactions. In the 1930’s transition state theory was developed which assumes an equilibrium between the reactants and activated complexes in a reaction. In this theory a specific configuration of the molecules is required for a reaction to occur and this critical arrangement, which has the highest potential energy in the reaction path, is called the transition state. Both collision theory and transition state theory are still used today as each yield information about different aspects of rates of reactions.

Various factors can affect the rate of a reaction. Two of the most profound influences are the temperature at which the reaction is measured and the concentrations of the reactants. The rate of a reaction will change with increasing or decreasing temperature. This fact can be used to measure the rate of reaction at various different temperatures which can then be used to ascertain more information about the reaction of study such as enthalpic and entropic contributions to the rate. Since the rate of a reaction is different at different temperatures, the rate constants, $k$, and other quantitative information determined from rate constants, are not directly comparable when measured at different temperatures.

The concentration dependence of the rate is illustrated by the rate law and is what classifies the order of a reaction. For a reaction in which $A + B \rightarrow \text{C} + \text{D}$ the rate law is defined by the general equation: $r = k[A]^n[B]^m$ where $k$ is the rate constant and $[A]$ and $[B]$ are the concentrations of the reactants. If a reaction rate is independent of the concentration of reactants it is considered a zero-order reaction where $r = k$. If the reaction is dependent on the concentration of only one reactant, the reaction is first-order where $r = k[A]$. If the reaction is dependent on the concentration of two reactants, or
dependent on one second-order reactant, it is a second-order reaction and \( r = k[A][B] \) or \( r = k[A]^2 \). Higher order reactions are not common but they do exist as do fractional order reactions e.g. \( r = k[A]^{1.5} \). The order of a reaction allows for the experimental determination of the rate constant, \( k \), using the integrated rate law. For first-order reactions the linear form of the integrated rate law is shown in Equation 2.1 which can be rearranged to give the exponential decay equation, 2.2. Measurement of the concentration of the different species in the reaction over time allows for the rate constant to be calculated. The rate constant can be used to determine the half-life, \( t_{1/2} \), of a reaction (see Equation 2.3 for a first-order reaction). The rate constant can also be used to calculate the activation energy, \( E_a \), of a reaction using the Arrhenius equation, 2.4, or to determine the standard Gibbs energy of activation, \( \Delta G^\ddagger \), standard enthalpy of activation, \( \Delta H^\ddagger \), and standard entropy of activation, \( \Delta S^\ddagger \), using the Eyring-Polanyi equation, 2.5.\(^{93,95}\) The Eyring-Polanyi equation will be used for the research presented in this dissertation.

\[
t_{1/2} = \frac{\ln(2)}{k} \quad 2.3
\]

\[
k = Ae^{-E_a/(RT)} \quad 2.4
\]

\[
k = \frac{k_B T}{h} e^{-\Delta G^\ddagger/RT} \quad 2.5
\]

Kinetics calculations based on experimental data require accurate measurement of the concentrations of the components as the reaction is progressing. For reactions that are classified as fast, or those with half-lives of less than one second, special equipment and
techniques are required for kinetics measurements. Reactions with half-lives of minutes, hours, days, or even weeks are much easier to monitor throughout the course of the reaction. Various methods are available for observing these reactions as they progress. Chromatography, MS, and spectroscopic methods such as fluorescence, NMR, or photoelectron spectroscopy are used to monitor reactions for kinetics measurements. The experiments presented in this dissertation use NMR spectroscopy to monitor molecular recognition reactions that are slow on the NMR time scale with half-lives on the order of hours or longer.

2.2 Molecular Recognition Kinetics

Chemical kinetics is of particular interest in the field of molecular recognition chemistry. The determination of the rates of encapsulation of guest molecules within a host or guest exchange processes with other small molecules, including solvent, is important because each yield information about the complementarity of the guest and host. One overarching goal within molecular recognition is to tailor host molecules for the uptake of specific guests and the information gathered through guest complexation studies can influence further capsule design and modification. Chemical kinetics has been used throughout molecular recognition chemistry to measure association and dissociation constants, half-lives of guest encapsulated complexes, and even to do mechanistic studies on the method of guest exchange for various capsules. A diverse set of molecules have been studied using kinetics for molecular recognition chemistry. Some are based on the calixarene platform, such as the pyrogallolarene capsules presented in this dissertation, but there are many others, including cyclodextrins, xanthenol
clathrates, \(^{102}\) and nanocavities based on fullerenes that can uptake water molecules \(^{103}\). Most commonly kinetics measurements on these solution-phase systems are done using NMR spectroscopy. For reactions that are slow on the NMR timescale, such as the ones presented here, NMR gives a unique fingerprint for the different species involved in encapsulation chemistry such as a guest encapsulated complex, a solvent encapsulated complex or a molecule free in solution. Identifying these peaks allows for tracking the different species in solution which makes determination of the ratio of individual species and from there an accurate measurement of concentration possible.

In 2001 Christoph A. Schalley and coworkers published a study on the kinetics of rotaxanes. \(^{104}\) Rotaxanes are complexed molecules comprised of three parts, an axle, end stoppers, and a wheel. The end stoppers are covalently bonded to the axle while the wheel is noncovalently threaded onto the axle and as such is free to move along the axle and even dissociate completely (Figure 2.1). The end stoppers play a large role in the reaction kinetics because when they are small they allow the wheel to easily slide off the axle and decomplex the rotaxane and when they are very large the wheel cannot dissociate and remains trapped on the axle. The most interesting scenario is when the end stoppers are of a medium size which can allow for decomplexation of the wheel under the proper circumstances. Schalley studied this intermediate state using a variety of axle lengths with differing rigidity, stoppers of different shapes and sizes, and wheels with different heteroatoms. \(^1\)H NMR spectroscopy was used to track axle protons which showed a distinctly different chemical shift when the wheel was complexed on the axle and when it was not.
In this study it was shown that the shape of the stoppers was a major factor affecting the rate of the decomplexation reaction. Axles with end stoppers comprised of two $t$-butyl branches off of the end phenyl rings, 2.1, were compared to axles with additional phenyl rings as end stoppers, 2.2. The phenyl rings have larger van der Waals volumes making them bigger than the $t$-butyl end stoppers; however, the decomplexation of the wheel, 2.3, with the phenyl functionality stopper was faster than the dissociation with the $t$-butyl end stoppers (Figure 2.1). Schalley proposed that the planar phenyl groups may allow for the wheel to slip by the stopper more easily than the spherical $t$-butyl groups which would require a wider interior diameter of the wheel. The phenyl groups also have slightly more flexibility for bending than the $t$-butyl groups which may allow for a more favorable geometry for decomplexation.\textsuperscript{104} This result showed that shape and size of the stoppers are both important factors for the rate of decomplexation or unthreading. The largest difference in kinetics was seen when modifications were made to the wheel. In most cases the aromatic rings that made up the structure of the wheel were simply benzene rings, however, when one of the interior C-H groups was replaced with an isoelectric nitrogen yielding a pyridine ring, 2.4 (Figure 2.2), the half-life for the decomplexation increased by a more than a factor of $10^4$. This effect was postulated to be

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{rotaxane_axle}
\caption{Rotaxane axle with stoppers. Complexed with wheel on left, not complexed on right.}
\end{figure}
due to the intramolecular hydrogen bonding of the nitrogen with the amide protons causing a narrower inner diameter of the ring which would slow decomplexation.\textsuperscript{104} This study exemplifies the large differences that can be seen with very small changes in the identity of one of the molecules being studied as well as the great impact of the shape of molecules on the stability of complexes.

\textbf{Figure 2.2.} Structures of rotaxane components. Axle with \textit{t}-butyl end stoppers, 2.1, axle with phenyl end stoppers, 2.2, and wheel with phenyl substituents, 2.3, and substitution of \textit{CH} for nitrogen, 2.4.

Metal ligand hosts have also been used to encapsulate solvent molecules similar to that of pyrogallolarene and resorcinarene hexamers. Jonathan R. Nitschke is well known in the field of molecular recognition chemistry for his work on metal ligand capsules.\textsuperscript{105} A recent paper from the Nitschke group focused on the ability of guanidinium to modulate the guest uptake and exchange of a known metal ligand capsule.\textsuperscript{106} The \([\text{M}_4\text{L}_6]\) capsule with \textit{Fe}^{II} metal cations at the corners of the capsule has
twelve sulfonate moieties on the ligands which are aligned along the edges of the capsule. These sulfonate moieties are favorably oriented along the faces of the capsule to hydrogen bond with guanidinium (Figure 2.3).

![Figure 2.3](image)

**Figure 2.3.** Metal ligand capsule structure, left, and molecular model with guanidinium hydrogen-bonded at the face, right. A crystal structure was the basis for the model.\(^{100}\)

The addition of guanidinium to the complex effectively blocks one face of the capsule. It was determined that only one molecule of guanidinium was hydrogen-bonded to the face of the capsule; all other interactions are intermolecular with neighboring capsules. Studies showed that the blockage of this face caused a decrease in the guest uptake for the capsule and slowed guest exchange.\(^{100}\) There are a variety of mechanisms which are possible for guest encapsulation and release. Conformational changes can allow for openings through which guests can enter and exit, guest molecules themselves can force the expansion of opening in the host, and partial or complete dissociation of the host can occur to allow for guest exchange.\(^{70,107}\) This study showed that additional
molecules that complex with the system can change the ability of the capsule to uptake guests. Because the intermolecular interactions with guanidinium dramatically affected the exchange rate, the mechanism for guest encapsulation and release must be through-face rather than a dissociative mechanism.\textsuperscript{100}

\textsuperscript{1}H NMR studies were also performed to monitor the shift of the imine proton of the guest encapsulated and empty host metal capsules. These peaks were integrated to determine the fractional ratio of the different species in solution which gave the concentration of the individual capsules over time. The concentrations were used in pseudo-first order rate equations to determine the rate constants which give a quantitative measurement of the attenuation of the capsules ability to uptake and exchange guests due to the presence of guanidinium.

Kinetic measurements have also been performed with many different molecules based on the resorcinarene and pyrogallolarene platform. Guest exchange rates and half-lives for deep cavitands based on the resorcinarene platform,\textsuperscript{97,108} dimers,\textsuperscript{98,109} and hexamers of pyrogallolarene and resorcinarene\textsuperscript{83,99} have all been studied under various scenarios. The kinetics of guest→solvent exchange of pyrogallolarene hexamers is one focus of this dissertation. The following section presents the methods for analysis and kinetics calculations used for these exchange measurements.

\textbf{2.3 Pyrogallolarene Hexamer Kinetic Measurements}

In 2010 the Purse lab discovered a unique method of loading guest molecules, which are solid at room temperature, into the interior of pyrogallolarene hexamers. Dubbed the “melting method” it requires equal amounts of pyrogallolarene and guest
(w/w) which are then melted together until they are liquefied. The liquid mixture is allowed to cool and the resulting solid is simply dissolved in an NMR solvent and encapsulation complexes are seen.\textsuperscript{110} These encapsulation complexes are kinetically trapped and, in all but one case, guest molecules are completely exchanged for solvent within the interior of the hexamer yielding solvent-filled capsules as the preferred product. A variety of guests have been encapsulated using this method which will be discussed in chapter 3.\textsuperscript{110} In some cases the guest encapsulated within the hexamer underwent a slow exchange with solvent allowing for kinetic measurements which give quantitative data for comparison of the stability of these guest-filled hexamers.\textsuperscript{111} NMR measurements were taken for each guest encapsulated complex. Kinetic measurements were performed for biphenyl, fluoranthene, fluorene, naphthalene, norbornene, and pyrene guests in multiple solvents. These results will be discussed in section 3.5. Peaks corresponding to guest-filled and solvent-filled capsules were identified, integrated, and normalized to determine the percentage of the individual capsules at each time point. Two representative samples, the pyrene encapsulated complex measured in deuterated chloroform (CDCl\textsubscript{3}) and the fluorene encapsulated complex measured in carbon tetrachloride (CCl\textsubscript{4}) using a coaxial insert with an external benzene lock, will be used to explain the methods of analysis and determination of the rate constant, $k$, half-life, $t_{1/2}$, and standard Gibbs free energy of activation, $\Delta G^\ddagger$.

\textit{2.3.1 Monitoring by NMR and Integration}

Upon dissolution in an NMR solvent, a $^1$H NMR spectrum was taken for each complex using a 500 MHz NMR. The initial spectrum was considered to be the $t = 0$
point. Additional NMR spectra were taken over time and the frequency was determined by the rate of exchange of solvent with guest. NMR spectra were referenced to the deuterated solvent and normalized using MestReNova software. The normalization was in reference to either the methine hydrogens of the hexamer found at ~4.5 ppm, for which there are 24 hydrogens per capsule, or to the CH₂ neighboring the methine proton found at ~2.2 ppm, for which there are 48 hydrogens per capsule. The determination of which peak was used for normalization was based on the presence of additional peaks from host, guest, or solvent, which often overlapped with one or the other causing interference in the integration. In most cases the integration of the peaks of interest for guest-filled and solvent-filled capsules was straightforward as there were no additional peaks overlapping with them. Also in most cases the exchange mechanism followed a simple A→B direct exchange process in which there were only two capsules, guest-filled and solvent-filled, which required identification. Exceptions to these two cases will be discussed. An example of the A→B process is pyrene in CDCl₃. While there is an intermediate state present for this system the intermediate state is stable at room temperature and requires additional heating to undergo guest exchange with solvent. As such, two separate experiments can be performed, one at room temperature to measure the kinetics of the change from one pyrene-filled configuration to the other, and one at elevated temperature to measure the exchange of pyrene with solvent. The spectrum for the second configuration of pyrene in CDCl₃ at t = 0 (before heating) is shown in Figure 2.4. In this case there is a peak which overlaps with the methine hydrogen signal at 4.5 ppm (peak k) so the normalization was in reference to the CH₂ at 2.3 ppm (peak l).
In some cases there were overlapping peaks of interest and a more complicated mechanism for guest→solvent exchange. For cases involving overlapping peaks of interest global spectral deconvolution (GSD) algorithms were performed using the MestReNova software to determine the integrated values for each peak. An example of this is the fluorene complex in CCl₄. The identifiable peaks corresponding to the capsules overlap significantly with both each other and the peaks for free fluorene in solution making standard integration next to impossible. A set of overlapping peaks which corresponded to each of the different hexamers present during guest exchange with solvent located at 9.0 ppm was identified. GSD algorithms were performed on each spectrum taken during the experiment to identify the integrated value for each of the peaks which were then normalized to the methine hydrogen peak at 4.5 ppm. As with pyrene there is an intermediate state the fluorene→solvent exchange system. In this case the intermediate is not stable at room temperature and the three forms occur
simultaneously yielding an exchange process of the form of $A \rightarrow B \rightarrow C$. Figure 2.5 shows a spectrum with the three overlapping peaks.

![NMR spectrum](image)

**Figure 2.5.** $^1$H NMR spectrum for fluorene-filled hexamer. Peaks a-c were integrated using global spectral deconvolution algorithms and normalized with respect to peak d for kinetics experiments. (1 mM, CCl$_4$, 500 MHz)

### 2.3.2 Order Determination

As the dissociation of the guest molecule with reference to the capsule is a unimolecular reaction it was assumed that it would follow first-order kinetics as seen in other publications with similar systems involving guest release.$^{100,107}$ The data were fitted to zero-order, first-order, and second-order kinetics to verify this assumption. The first kinetics measurements performed were on pyrene in CDCl$_3$ and this system was utilized to determine the order of the reaction in capsule. The NMR peaks were normalized as described previously and converted to concentration. The concentrations were then plotted according to the linear form of the integrated rate laws. As seen in Figure 2.6 a linear fit is observed for the first-order approximation while the plots for zero-order and second-order do not show a linear relationship which confirms that the guest release does indeed follow first-order kinetics.
Figure 2.6. Pyrene→CDCl₃ exchange data plotted for A. zero-order kinetics ([A] vs. time) B. first-order kinetics (ln[A] vs. time) and C. second-order kinetics (1/[A] vs. time). The linear form of the rate laws are given next to plot.

[A] = −kt + [A]₀

ln[A] = −kt + ln[A]₀

1/[A] = kt + 1/[A]₀
2.3.3 Determination of Rate Constants and Half-Lives

Since the data was shown to be first-order in capsule the standard kinetics experiments of type $A \rightarrow B$ were easily plotted using the integrated peak values from the NMR spectra. Peaks corresponding to both host and guest were identified and integrated. Over time the value of these peaks decrease as the guest is exchanged for solvent (Figure 2.7). The exponential form of the first order rate law (Equation 2.2) was used to determine $k$ values for each system. As the data is first-order in capsule the integrated peak values were divided by the initial value to enable the plotting of concentration ($[A]/[A]_0$) vs. time as allowed when the exponential form of the rate law is rearranged to

$$\frac{[A]}{[A]_0} = e^{-kt}$$  \hspace{1cm} (2.6)

form Equation 2.6. Because the units of $k$ are s$^{-1}$ the integrated peak values do not need to be converted to concentrations as both the initial value and the time constrained value would be multiplied by the same initial concentration cancelling each other out. The initial measured point is taken to be $t = 0$ therefore the first point always has a value of 1.
Figure 2.7. Stacked $^1$H NMR spectra for pyrene exchange with CDCl$_3$. Peaks corresponding to the host and guest of the pyrene-filled hexamer decrease over time. Host and guest peaks are shown in boxes and time in hours is on the right of each spectrum.
The data was then plotted in Origin 8.1 according to Equation 2.7 where $y = \frac{[A]}{[A]_0}$, $x =$ time, and $a$ was set to equal 1. The rate constant, $k$, then equaled $b$. Each individual peak corresponding to the guest-filled capsule was plotted and the resulting $k$ values were averaged to give the average $k$ value for the system. Sample plots are shown in Figure 2.8 for the pyrene-filled capsule in CDCl$_3$. The half-lives for each system were determined individually for each peak using Equation 2.3 and then averaged.

$$y = a \cdot e^{-bx}$$

**Figure 2.8.** First-order plots for pyrene→CDCl$_3$ exchange for peak c corresponding to host capsule (left) and peak g corresponding to encapsulated guest (right) plotted using first-order exponential fit (see Figure 2.4).

For those systems which followed the A→B→C mechanism (see Figure 2.9) a different method for determining $k$ was used. In these cases the integrated peak values were converted to concentrations representing one of each of the species in solution. The initial concentration of the sample was 1mM (specific concentrations were determined based on individual samples) and the ratio of the peaks for each species gave the concentration at each time point.
Figure 2.9. Stacked $^1$H NMR spectra for fluorene exchange with CCl$_4$. Peaks corresponding to the two configurations of the fluorene-filled hexamer and the solvent filled hexamer were integrated using GSD algorithms, converted to concentration and plotted in KinTekSim.
These data were then plotted in KinTekSim\textsuperscript{112} and regression analysis was used to determine the $k$ values for each process concurrently. The mechanism used in KinTekSim was $A \rightarrow B \rightarrow C$ where $k_1$ represents $A \rightarrow B$, $k_2$ represents $B \rightarrow C$, and $k_{-1}$ and $k_{-2}$ were set to zero as no reverse guest encapsulation from solvent-filled hexamers was observed in the systems plotted.\textsuperscript{111} A sample KinTekSim plot for guest exchange of fluorene in CCl$_4$ is given in Figure 2.10. The half-lives for these systems were determined using Equation 2.3 from the calculated $k$ values.

![KinTekSim plot of fluorene guest exchange with solvent in CCl$_4$. Using mechanism $A \rightarrow B \rightarrow C$. Blue is $A$ configuration, green is $B$ configuration cyan is $C$ configuration which is the solvent-filled capsule. Rate constants $k_1$ ($A \rightarrow B$) and $k_2$ ($B \rightarrow C$) were fit, $k_{-1}$ and $k_{-2}$ were set to zero.](image)

**Figure 2.10.** KinTekSim plot of fluorene guest exchange with solvent in CCl$_4$. Using mechanism $A \rightarrow B \rightarrow C$. Blue is $A$ configuration, green is $B$ configuration cyan is $C$ configuration which is the solvent-filled capsule. Rate constants $k_1$ ($A \rightarrow B$) and $k_2$ ($B \rightarrow C$) were fit, $k_{-1}$ and $k_{-2}$ were set to zero.

KinTekSim was also used to fit the system of pyrene-filled capsules in CCl$_4$, the only case in which the guest does not completely exchange with solvent. For this system
~10% pyrene encapsulated hexamers are present at equilibrium. KinTekSim was used with regression analysis to simultaneously fit the rate constants for the guest release and encapsulation processes and, implicitly, the equilibrium position.

### 2.3.4 Eyring Analysis

From the rate constants, \( k \), the Gibbs energy of activation, \( \Delta G^\ddagger \), can be determined using the Eyring-Polanyi equation, 2.5, where \( k_B \) is Boltzman’s constant, \( h \) is Planck’s constant and \( R \) is the molar gas constant. The energy of activation is a measure of the stability of the complexes based on the amount of energy needed to release the guest. The Eyring-Polanyi equation can be rewritten to yield Equation 2.8 based on the definition of \( \Delta G^\ddagger \) where \( \Delta G^\ddagger = \Delta H^\ddagger - T \Delta S^\ddagger \). Using this equation a plot of \( \ln (k/T) \) vs. \( 1/T \) can be used to determine \( \Delta H^\ddagger \) and \( \Delta S^\ddagger \) where the slope is equal to \( \frac{-\Delta H^\ddagger}{R} \) and the intercept is equal to \( \ln \frac{k_B}{h} + \frac{\Delta S^\ddagger}{R} \). The exchange of norbornene in \( \text{CCl}_4 \) was chosen for this experiment due to the direct exchange mechanism of \( A \rightarrow B \) and the long exchange rates at low temperatures indicating that at higher temperatures the exchange kinetics would still be able to be accurately monitored over time. The exchange rates were measured at \( T = 296K, 310K, 323K, 343K, \) and \( 363K \). The \( k \) values at each temperature were determined as described previously. Then \( \ln (k/T) \) was plotted vs. \( 1/T \) in Origin to give the graph shown in Figure 2.11.
Figure 2.11. Norbornene→CCl\textsubscript{4} kinetics at T = 296K, 310K, 323K, 343K, and 363K plotted using the Eyring-Polanyi equation. The linear trendline equation is given on the plot.

The linear fit for this data has a slope of $-12830.6$ and an intercept of $22.37$ yielding a $\Delta H^\ddagger$ value of $25.5 \pm 1.5$ kcal mol$^{-1}$ and $\Delta S^\ddagger$ value of $-2.9 \pm 4.5$ cal mol$^{-1}$ K$^{-1}$. The entropic term was not calculated with enough accuracy to determine if the value is positive or negative as the error was greater than the value itself. What is quite clear is that the entropic term is a minor contributor to the value of $\Delta G^\ddagger$ in comparison to the enthalpic term.$^{111}$

2.4 Conclusions

Chemical kinetics is a powerful tool that allows for quantitative measurements of rates of reaction, half-lives for processes, and determination of activation energies. Widely used throughout the field of molecular recognition chemistry, kinetics can provide information about association or dissociation of self-assembled complexes, e.g.
rotaxanes. Kinetics are also used frequently in guest affinity experiments and to
determine mechanisms of exchange for fully encapsulated complexes, e.g. metal ligand
capsules and resorcinarene and pyrogallolarene hexamers.

The research presented in this dissertation has a large kinetic measurement
component. The methods of measurement using NMR spectroscopy for the different
systems studied have been described. Analysis of the NMR data and determination of the
first-order rate of reaction has been presented as have the methods for determination of
rate constant, \( k \), half-life, \( t_{1/2} \), and standard Gibbs energy of activation, \( \Delta G^\ddagger \). For systems
which did not follow the simple \( A \rightarrow B \) exchange mechanism regression analysis was
performed using KinTekSim to determine rate constants. Complete Eyring analysis was
performed on the norbornene system in \( \text{CCl}_4 \) to further study the enthalpic and entropic
contributors to the energy of activation which was found to greatly favor the enthalpic
term. For a full list of peak designations as well as example kinetics plots for each system
see Appendix A or the Supporting Information for the 2012 *Journal of the American
Chemical Society* publication\(^{111}\) and 2014 *Supramolecular Chemistry* publication\(^{113}\) from
the Purse lab.

The following chapter will analyze the results from the kinetic analysis of the
guest release of pyrogallolarene hexamers in numerous solvents. Many factors affect the
stability of the guest encapsulated hexamers including the identity of the guest and the
solvent.
Chapter 3: Guest Exchange

3.1 Introduction

Hydrogen-bonded pyrogallolarene hexamers, which form in nonpolar solvents, have been well characterized in solution\textsuperscript{17,114} as well as in solid form\textsuperscript{16,64} and gaseous phase.\textsuperscript{68} The hexameric assembly forms a roughly spherical capsule with an interior cavity of approximately 1300 Å\textsuperscript{3}. Molecules which can occupy the interior of this cavity are of great interest for molecular recognition studies. In solution the primary guest molecules previously found to be encapsulated within pyrogallolarene hexamers have been solvent molecules, with a few tertiary amines reported.\textsuperscript{85} Larger aromatic hydrocarbons have been proposed to be encapsulated in the solid state based on fluorescence data,\textsuperscript{115,116} however, NMR studies of these guest-filled hexamers yield very small peaks corresponding to encapsulated guest molecules which likely indicate a low occupancy of the guest on the interior of the hexamer. A method for more efficient loading of the interior of the hexamer with guest molecules was desired. It was proposed that solvent competition during hexamer formation may have been the cause for the poor guest loading of previous methods so solvent-free processes were investigated.

The technique discovered in the Purse lab in 2010 was named the “melting method” and has proven to be the most effective method to date of loading non-solvent molecules that are solid at room temperature into the interior of the hexamer.\textsuperscript{110} A wide variety of molecules have been shown to be encapsulated using this method. $^1$H NMR
was used to characterize these encapsulation complexes in solution due to the fact that
guest molecules on the interior of the hexamer yield peaks shifted upfield 1-3 ppm giving
a clear indication of encapsulation complexes. Some molecules tested showed small
encapsulation peaks indicating a low occupancy of the hexamer while others showed
strong guest encapsulation peaks corresponding to near complete loading of the guest
within the hexamer.

Seven of the molecules tested, anthracene, biphenyl, fluoranthene, fluorene,
naphthalene, norbornene, and pyrene, resulted in strong peaks on the $^1$H NMR
corresponding to encapsulation complexes with near complete occupancy and were
subsequently chosen for further kinetic analysis. In all but one case, solvent-filled
hexamers predominated at equilibrium and the guest encapsulated peaks decreased in
intensity over time indicating that the encapsulated guest exited the hexamer and was
replaced by solvent. The guest-encapsulated hexamers are therefore kinetically trapped
species which exist only prior to the establishment of equilibrium in solution. In many
cases they show great stability under nonequilibrium conditions with lifetimes of hours,
days, and even weeks. The lifetimes of the guest encapsulated complexes varied based on
the identity of the guest, the identity of the solvent, and temperature. Kinetic analysis was
performed as described in Chapter 2 to determine the rate constant, $k$, the half-life, $t_{1/2}$, and the activation energy, $\Delta G^\ddagger$, for each guest encapsulated complex.

A series of experiments was performed to determine the effect of solvent on the
stability of the hexamers using nonpolar chlorinated and aromatic solvents commonly
used for cavitand and hexamer characterization. The effect of structural differences of the
guest molecules was also examined. From these experiments information about the symmetry of the hexameric complexes as well as the mechanism of guest exchange with solvent were identified. In some cases a direct exchange mechanism occurred while in others intermediate states were seen which likely correspond to different configurations of the guest encapsulated hexamer or situations of coencapsulation with solvent. Complete kinetic characterization was not possible with all of these molecules due to the presence of multiple intermediate states which were prohibitively difficult to differentiate. However, even in these cases information about the stability of the capsules can be gleaned from the overall time required for the guest to exchange with solvent. No single factor appeared to be responsible for the kinetic stability of these capsules but general trends could be identified.

3.2 Guest Loading

Several methods were attempted to load molecules that are solid at room temperature into the interior of the pyrogallolarene hexamer. First a simple heating of the pyrogallolarene and guest in solution was performed. Unfortunately, this method was not successful in causing guest encapsulation in pyrogallolarene capsules as only solvent-filled hexamers were seen in the $^1$H NMR using deuterated chloroform (CDCl$_3$) as a solvent. Solvent competition was postulated to be interfering with guest loading so solvent-free methods were examined. A grinding method using equal amounts (w/w) of the pyrogallolarene and guest which were pulverized with a mortar and pestle, similar to the grinding method published by Atwood to form the pyrogallolarene hexamers in a solvent-free environment,$^{65}$ also proved to be unsuccessful in loading guest molecules
into the interior of the hexamer.\textsuperscript{110} Dr. Miroslav Kvasnica, a postdoc in the Purse lab, suggested melting together the pyrogallolarene with the guest under solvent-free conditions. In this method the guest molecule would liquefy causing the formation of a pseudo-solvent. Hexamers of the pyrogallolarene would then form in the nonpolar liquid. Since the “solvent” would be the guest molecule itself, formation of the hexamers would trap the guest inside resulting in guest encapsulated hexamers. This melting method proved to be a successful procedure for loading molecules that are solid at room temperature into the interior of the hexamer.

Initially an equal amount of pyrogallolarene and pyrene (w/w) were melted together using a heat gun, under an inert nitrogen atmosphere, until the mixture was completely liquefied. The molten mixture was then allowed to cool and resolidify. The resulting solid was dissolved in CDCl$_3$ and NMR measurements were taken (Scheme 3.1). Peaks corresponding to encapsulated pyrene were seen shifted between 2-3 ppm upfield due to the increased shielding of the hexamer. To illustrate that the additional peaks were not due chemical changes during heating, deuterated methanol (MeOD), which disrupts the hydrogen bonding of the hexamer causing disassembly, was added to the sample. After the addition of MeOD the shifted peaks disappeared and only peaks for the pyrogallolarene and free pyrene were seen in the NMR illustrating that the upfield-shifted peaks did in fact correspond to pyrene encapsulated within the hexamer. Further tests showed that the same encapsulation complexes were seen when the mixture was melted under atmospheric conditions and additional experiments were not performed under an inert atmosphere. Pyrene was chosen for the initial test because it is an aromatic,
nonpolar molecule with a melting point range of 145-148 °C. The nonpolar nature of pyrene made it an ideal choice as a guest because there are no polar functionalities which would interfere with the hydrogen-bonding interactions that hold the capsule together. The melting point range of 145-148 °C made it possible to melt the pyrene with a heat gun. It was determined that the melting point of the guest molecule needed to be below 260°C for the heat gun to successfully liquefy the guest in question.

Scheme 3.1. Melting method for loading guest molecules into the interior of the pyrogallololarene hexamer. Hydrogens and R groups of pyrogallololarene were removed for clarity.

Once a method was identified which could efficiently load guest molecules into the interior of the hexamer the scope of the method was tested. A wide variety of potential guest molecules were individually melted together with the pyrogallololarene in an attempt to determine which were best suited for the interior. After melting, the resulting solid was dissolved in CDCl₃ for NMR measurement. The guest molecules that were tested using the melting method are listed in Table 3.1. In each case, guest
molecules encapsulated within the hexamer yielded new peaks on $^1$H NMR spectra which were shifted 1-3 ppm upfield.

Aromatic and aliphatic molecules proved to be suitable guests for the interior of the hexamer and stable guest-filled capsules were seen in solution with a number of the molecules tested. In some cases sharp and clearly defined peaks were seen which correspond to a single hexameric capsule (entries 23, 27, 29, Table 3.1). In others there were a variety of peaks which correspond to multiple intermediate states (entries 8, 9, 13, 26, Table 3.1). These intermediate states likely involve coencapsulation of both guest and solvent molecules within the hexameric assembly. Potential guest molecules which contained polar functional groups including alcohols, aromatic amines, amides, carboxylic acid, esters, and ketones as well as some tetrabutyl ammonium compounds were also tested using this method. Expectedly some of these molecules were not encapsulated, e.g. tetrabutyl ammonium compounds which have previously been shown not to be encapsulated within pyrogallolarene hexamers \(^{85}\) (entries 31, 32, 33, Table 3.1). Some of the molecules with polar functionalities did show an assortment of small peaks corresponding to encapsulated guest molecules in the NMR spectra. The poor definition and small size of the encapsulated peaks indicate that these molecules had low guest loading and therefore were not well suited for the interior of the hexamer or that the exchange with solvent was mostly completed in the time it took to measure the sample by NMR (entries 15, 16, 19, 25, Table 3.1). Some liquid guests were also tested using this method. All liquid molecules were found to be encapsulated within the hexamer although some also had low guest loading (entries 1, 10, 12, 14, 17, 20, Table 3.1).
<table>
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<td>--</td>
</tr>
<tr>
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<td>no</td>
<td>yes</td>
</tr>
<tr>
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<td>2-ethylanthracene</td>
<td>yes(^b)</td>
<td>no</td>
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<td>--</td>
</tr>
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**Table 3.1.** Guest molecules tested using the melting method. Those listed as bound were encapsulated under direct heating with a heat gun. Those bound in wax were found to be encapsulated using wax as a solvent. d = decomposed during heating \(^a\) liquid guest \(^b\) low guest loading.
In some cases the guest molecules decomposed during the process of heating (entries 4, 18, 28, Table 3.1). A related method was designed for these compounds that decomposed under the harsh heating conditions of the heat gun in which the pyrogallolarene and guest were melted in paraffin wax. The large wax molecule is too big to fit inside of the hexamer, as proven by NMR, however, the low melting point of the wax (less than 100ºC) allowed for a liquid mixture to form below the melting point of the guest.\textsuperscript{110} Using this method the hexamer would form in the liquid wax “solvent” but instead of encapsulating the liquefied wax molecules the guest molecule must be encapsulated instead. The wax method was attempted with most of the guest molecules that had previously been tested using the heat gun method, however, no guests were found to be encapsulated using this method that were not previously encapsulated with the melting method. Disordered aggregates of the pyrogallolarene were presumed to form in experiments which did not encapsulate guest molecules.

Anthracene, biphenyl, fluoranthene, fluorene, naphthalene, norbornene, and pyrene were the seven molecules that all showed strong peaks on the NMR which correspond to near complete guest encapsulation within the hexamer and additional kinetic experiments were performed on these systems.

3.3 Stability and Symmetry of the Pyrene Encapsulated Hexamer

Pyrene was the first guest molecule to be tested using the melting method. The pyrene complex also proved to be the most interesting case in terms of stability and symmetry. When the melted mixture of pyrene and pyrogallolarene was allowed to solidify and then dissolved in CDCl\textsubscript{3} there were three distinct peaks seen in the range of
5.3-6.3 ppm on the NMR spectrum. (A in Figure 3.1) These peaks were moderately broadened and integration indicated that three pyrene molecules were encapsulated within the pyrogallolarene hexamer. Using a van der Waals (VdW) volume of 198 Å³ for pyrene and an interior cavity volume of 1300 Å³ the packing coefficient (which is a measurement of the percent of space the guest molecule takes up in the cavity) for pyrene was determined to be 0.46 which is close to the ideal packing of 55% for molecules in solution. The initial pyrene-filled hexamer was not stable in solution. Over the course of six hours at room temperature the peaks corresponding to the encapsulated pyrene decreased and were replaced by new peaks in the same region. The new peaks corresponding to the encapsulated guest were shifted slightly downfield and presented additional splitting that was not previously seen in the first configuration. The peaks corresponding to the aromatic and hydroxyl hydrogens of the pyrogallolarene also showed additional splitting (E in Figure 3.1). By integration it was determined that three molecules of pyrene were still encapsulated within the hexamer indicating a configuration change with no release of guest pyrene (Scheme 3.2). A DOSY NMR experiment was performed using a pyrene sample in CCl₄ in which the two different configurations of the pyrene encapsulated hexamer were present, to prove that both were in fact hexameric assemblies. Diffusion coefficients determined using DOSY are related to the size and shape of the molecules in solution. DOSY is very useful for measuring encapsulation complexes as both host and guest will have the same diffusion constant despite the smaller size of the guest molecule because they will diffuse together in solution. Both configurations yielded diffusion coefficients of $1.4 \pm 0.3 \times 10^{-6} \text{ cm}^2 \text{ s}^{-1}$
indicating that the capsules were the same size and must both have been hexamers. The much smaller pyrene that was free in solution had a diffusion coefficient of $9.5 \pm 4 \times 10^{-6}$ cm$^2$ s$^{-1}$.\footnote{111}

Figure 3.1. Stacked NMR spectra of the pyrene encapsulated hexamer in CDCl$_3$. A. $t = 5$ min at 23°C. B. $t = 20$ min at 23°C. C. $t = 30$ min at 23°C. D. $t = 70$ min at 23°C. E. $t = 6$ hours at 23°C. F. $t = 3$ hours at 70°C. G. $t = 20$ hours at 70°C. H. $t = 45$ hours at 70°C. For the $O_h$ configuration: ◊ = aryl hydrogen peak, ○ = encapsulated pyrene peaks. For the $D_3$ configuration: ■ = hydroxyl hydrogens, ▲ = aryl hydrogens, ● = encapsulated pyrene. For the solvent-filled hexamer: □ = hydroxyl hydrogens, ∆ = aryl hydrogens.
The second configuration of the pyrene-filled hexamer was much more stable than the initial configuration, in fact no change was seen in the NMR spectra over a period of nine weeks when the NMR tube was flame sealed. This kinetically stable conformation was puzzling as no encapsulated pyrene had been seen when heating of the two individual components in solution had been performed indicating that it was likely not the thermodynamic minimum of the system. In order to determine the thermodynamic minimum of the encapsulated pyrene system in CDCl$_3$ two samples were tested in tandem; one contained the melted mixture of pyrene-filled hexamers and one contained pyrene and pyrogallolarene which had been dissolved in CDCl$_3$ without first melting them together. Both samples in NMR tubes were initially heated in an oil bath at 50°C but after no measurable change in the NMR spectrum over a period of 20 hours the temperature was increased to 70°C. At 70°C the peaks corresponding to the encapsulated pyrene began to decrease and after 45 hours the encapsulated pyrene was completely exchanged for solvent (H in Figure 3.1). No change was seen in the NMR spectra for the sample containing the pyrene and pyrogallolarene free in solution indicating that the solvent-filled hexamer was the thermodynamic minimum of the system (Scheme 3.2). This finding supported the hypothesis of a reconfiguration of the hexamer without release of encapsulated pyrene as the solvent-filled hexamer was not shown to uptake any pyrene in solution.
Scheme 3.2. Depiction of the pyrene encapsulated hexamer configurations in CDCl$_3$. Initial melting, cooling and dissolution in CDCl$_3$ yields the $O_h$ configuration, A, which undergoes a configuration change to the $D_3$ configuration, B, in 6 hours at 23°C. Upon heating at 70°C encapsulated pyrene is exchanged for CDCl$_3$ in 45 hours resulting in CDCl$_3$-filled hexamers, C. When pyrene and pyrogallolarene are heated in solution without first melting them together only solvent-filled capsules, C, are seen. Hydrogens and R groups of pyrogallolarene were removed for clarity.
The unique splitting of both the host and guest peaks in the pyrene-filled hexamers was cause for additional investigation. The majority of guest-filled hexamers and all solvent-filled hexamers appear to be members of the point group $O$, based on the four peaks seen in the region of 6.3-9.5 ppm which correspond to the aryl and hydroxyl hydrogens of the pyrogallolarene. These four peaks indicate a chiral arrangement of the hydroxyl hydrogens which hydrogen bond to form the capsule. These hydrogens have a slow exchange on the NMR time scale and as such differentiate the hydroxyl hydrogens ortho to the methine carbons causing the four separate peaks (Figure 3.2). The $^{13}$C NMR of these $O$ symmetric hexamers show each of the six carbons in the benzene ring of the pyrogallolarene to be separate peaks as well which is a further support for the chiral arrangement of the hexamer. Guests encapsulated within these hexamers, including solvent, are presumed to tumble rapidly within the interior. Pyrene-filled hexamers are an exception to this trend.

*Figure 3.2.* Chiral arrangement of the hydroxyl groups found in $O$ symmetric capsules. R groups were removed for clarity.
The initial configuration of the pyrene encapsulated hexamers appeared to be of the point group $O_h$ (Figure 3.3). The hydroxyl hydrogens of this configuration are broadened along the baseline as determined by an H-D exchange experiment. This indicated a disordered arrangement of hydrogen bonds which undergo rapid shuffling on the NMR time scale making differentiation of the hydroxyl hydrogens impossible. The encapsulated pyrene is also thought to tumble rapidly within the interior in this configuration as evidenced by the broadened guest peaks on the $^1$H NMR. The point group of the pyrene-filled capsule changed after reconfiguration to the more stable, kinetically trapped hexamer. The increased splitting of the hydrogen signals for both the pyrogallolarene and the encapsulated pyrene indicates a loss of symmetry which corresponds to point group $D_3$ (Figure 3.3). In this case the encapsulated guest does not tumble rapidly within the interior. The pyrene is thought to spin on an axis perpendicular to the plane but the confined interior of the hexamer does not allow for a rearrangement of the stacked pyrene within the cavity. The lack of fast tumbling of the pyrene causes additional splitting for both host and guest (E in Figure 3.1).

A COSY NMR experiment performed on the $D_3$ configuration showed that the triplet and doublets of the pyrene at 5.67, 5.75 and 5.83 ppm respectively are coupled together meaning they must represent the hydrogens at positions a, b, and c. The additional splitting of the doublets means that b and c are distereotopic (Scheme 3.2). The remaining hydrogen signals for the encapsulated pyrene correspond to positions d and e (Scheme 3.2) and the overlapping complexity is likely due to the stacking of the
pyrene within the interior which may differentiate the inner and outer molecules. The additional splitting of the peaks corresponding to the host pyrogallolarene are a result of the inability of the pyrene to tumble rapidly within the interior. In this case the chiral arrangement of the hydroxyl hydrogens is the same as seen in the $O$ symmetric capsules but the proximity and arrangement of the pyrene on the interior causes the additional splitting. The pyrene-filled hexamer is the only complex tested with the unique symmetry described. All other capsules appear to belong to the point group $O$.

Figure 3.3. Structural models for point group $O_h$, A, and $D_3$ symmetry, B, for the pyrene encapsulated hexamer.

3.4 Solvent Effects on Kinetics

CDCl$_3$ is a common NMR solvent used in the study of pyrogallolarene and resorcinarene hexamers and as such was the chosen solvent for the initial studies of the melted mixture of pyrogallolarene and pyrene. The two separate configurations, one stable at room temperature, were a surprising finding during this initial study of pyrene-filled hexamers. To determine if there was a solvent effect on the stability of the guest
encapsulated hexamer, NMR studies were performed using other nonpolar solvents in which the hexamer would form. A coaxial insert containing deuterated benzene (C\textsubscript{6}D\textsubscript{6}) was used as an external lock for all non-deuterated solvents which will be discussed.

3.4.1 Chlorinated Solvents

Deuterated dichloromethane (CD\textsubscript{2}Cl\textsubscript{2}) and carbon tetrachloride (CCl\textsubscript{4}) were both tested as solvents for NMR kinetics measurements of pyrene encapsulated pyrogallolarene hexamers. Stacked spectra are shown in Appendix B.

When the melted mixture of pyrogallolarene and pyrene was dissolved in CD\textsubscript{2}Cl\textsubscript{2} and measured by NMR the same initial configuration of three broadened guest peaks with the hydroxyl hydrogens broadened along the baseline was seen. This initial configuration also spontaneously underwent a configuration change at room temperature. In the case of CD\textsubscript{2}Cl\textsubscript{2} this configuration change was complete within 20 minutes, much less time than the six hours that were required in CDCl\textsubscript{3}. The second configuration was analogous to that in CDCl\textsubscript{3} in that it had the same number of peaks for the guest pyrene and the host pyrogallolarene and it was also stable at room temperature. As with CDCl\textsubscript{3} two samples, one containing the melted mixture and one containing the components free in solution, were heated to determine the thermodynamic minimum of the system. When the second configuration in CD\textsubscript{2}Cl\textsubscript{2} was heated at 50°C the guest underwent exchange with solvent in nine hours. These experiments show that the pyrene-filled hexamer is more stable in CDCl\textsubscript{3} than it is in CD\textsubscript{2}Cl\textsubscript{2} as both the configuration change and the exchange with solvent occur in less time and with less heating.
The initial configuration with three broadened guest peaks was also seen when the melted mixture was dissolved in CCl$_4$, however, in this case the initial configuration was stable at room temperature. As with the previous samples, in order to determine the thermodynamic minimum of the system, two samples were heated side by side, one containing the melted mixture and one containing the individual components of pyrogallolarene and pyrene dissolved in CCl$_4$. Upon heating the CCl$_4$ samples at 70°C the second configuration was induced in eight hours. In CCl$_4$ there was additional splitting of the peaks corresponding to the pyrogallolarene in the $D_3$ configuration. Increased signal overlap in CD$_2$Cl$_2$ and CDCl$_3$ are the likely cause of the difference in the splitting of the pyrogallolarene peaks which could be attributed to small structural differences based on capsule solvation. As a temperature of 70°C was needed to induce the configuration change of the hexamer, the samples were heated in sealed pressure tubes at 120°C in an attempt to cause guest exchange with solvent. In the smaller chlorinated solvents the guest exchanged completely with the solvent at higher temperatures and this was expected to occur with CCl$_4$ as well. However, complete exchange with solvent at 120°C did not occur. While the peaks of the encapsulated pyrene did decrease in the sample containing the melted mixture, they did not completely vanish. The sample containing the pyrene and pyrogallolarene free in solution showed encapsulated pyrene peaks corresponding to the $D_3$ configuration which appeared after heating at 120°C. In both samples the guest-filled capsule composed about 10% of the hexamers at equilibrium as determined by integration. This was the only case studied in
which the solvent-filled hexamer was not the sole species at equilibrium and guest encapsulated hexamers were also present. Full kinetics data is given in Table 3.2.

3.4.2 Aromatic Solvents

To delve further into the question of solvent effect on the stability of the pyrene encapsulated hexamer, aromatic solvents, which are also commonly used in hexamer research, were examined. The aromatic solvents tested were benzene, toluene, xylenes, and mesitylene. Stacked spectra are shown in Appendix B.

In benzene (C₆D₆) the same three broad peaks that correspond to the initial $O_h$ configuration seen in the chlorinated solvents were again found. As in CDCl₃ and CD₂Cl₂ there was a configuration change that occurred at room temperature. In benzene the second configuration did not show the same distinct splitting pattern that was seen in all the chlorinated solvents; instead there was a broadening of the second configuration peaks. Also unlike the chlorinated solvents previously tested, the second configuration was not stable at room temperature and the encapsulated guests spontaneously exchanged with solvent in 80 hours. Since neither configuration was stable at room temperature all three hexameric assemblies ($O_h$ configuration, $D_3$ configuration, and solvent-filled) were present at once making kinetics calculations more difficult (see section 2.3.3 for data analysis methods).

When the melted mixture was dissolved in deuterated toluene (C₆D₅CD₃) the three broad guest peaks, characteristic of the initial configuration observed in all previous solvents, was again seen. This configuration was not stable at room temperature. However, instead of undergoing a configuration change prior to guest exchange with
solvent as seen in all previous experiments, the peaks for the $O_h$ configuration simply decreased indicative of a direct exchange with solvent which was completed in 80 hours. The time needed for the complete guest exchange for solvent is comparable for both benzene and toluene but the lack of a configuration change in toluene is a distinct difference that was not seen in any of the previous experiments.

When the melted mixture was tested in xylenes ($C_6H_4(CH_3)_2$ 1:1:1 ratio of ortho, meta, and para) it was found that, as in toluene, there was a single $O_h$ configuration, which underwent a direct exchange with solvent in six days at room temperature. Additional experiments were performed with o-xylene, m-xylene, and p-xylene individually but no significant difference in the exchange rate was determined.

The final aromatic solvent tested was mesitylene ($C_6H_3(CH_3)_3$), which is the largest of the aromatic solvent series. In mesitylene the same three broad guest peaks that are indicative of the $O_h$ configuration were seen but unlike the rest of the aromatic solvents this configuration was stable at room temperature. When heated at 50°C no configuration change was induced, but the guest pyrene was exchanged for solvent in 30 hours. Interestingly, benzene was the only aromatic solvent which showed the configuration change from $O_h$ to $D_3$ that was present in all of the chlorinated solvent experiments. All larger aromatic solvents showed a direct exchange with encapsulated pyrene. Full kinetics data is given in Table 3.2.

3.4.3 Cyclohexane

Kinetics measurements were also performed in cyclohexane ($C_6H_{12}$) using an external $C_6D_6$ lock. Stacked spectra are shown in Appendix B. The initial $O_h$
The configuration was found to be stable at room temperature so heating was required to induce guest-solvent exchange. The configuration change from $O_h$ to $D_3$ did occur in cyclohexane and was induced at 70ºC, however, the $D_3$ configuration was not stable at this increased temperature. Therefore, as with benzene, the $O_h$, $D_3$, and solvent-filled hexamers were all present in solution at the same time. The peaks corresponding to both configurations were also broadened similar to those seen in benzene. Upon heating at 70ºC the exchange of pyrene for cyclohexane was completed in 74 hours. Full kinetics data is given in Table 3.2.

### 3.4.4 Solvent Trends

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<th>$\Delta G^\ddagger$ (kcal/mol)</th>
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**Table 3.2.** Kinetics data for guest→solvent exchange of pyrene encapsulated hexamers in different solvents. Complete exchange was not achieved in CCl$_4$ rather an equilibrium was established after heating for 10 hours at 120ºC. The activation energy for the reverse process of solvent→pyrene exchange was determined to be 32 ± 0.7 kcal/mol.

It was quite obvious from the data for the pyrene encapsulated hexamer stability in chlorinated solvents that there was a distinct solvent effect on the stability of pyrene-filled capsules. The pyrene complex underwent the configuration change fastest in CD$_2$Cl$_2$, the solvent which was the smallest in size, and required heating to induce the configuration change in CCl$_4$, the largest of the chlorinated solvents. In order to cause the
guest to exchange with solvent the capsules needed to be heated and greater temperatures were required as the size of the solvent molecule increased. This size effect is a logical result for the guest exchange with solvent as the hexameric capsule must simultaneously break multiple hydrogen bonds in order to create an opening in the hexamer which is large enough for the guest molecule to escape and the solvent molecule to enter (Figure 3.4). The replacement of the small hydrogen atoms with much larger chlorine atoms would require a larger opening for the solvent molecule to enter. The experimental activation energies can reasonably be explained by the energetic requirement of breaking hydrogen bonds as well as the loss of multiple weak interactions (van der Waals, CH-π, π-π) which occur in the opened hexamer needed for guest exchange with solvent. A difference in ΔG‡ of 1.3 kcal/mol (approximately equal to one hydrogen bond or the van der Waals interaction of one methyl group) would account for a 10-fold difference in the rate for a first-order process. Therefore, a molecule which required a larger opening, even if the difference in size is only attributed to the breaking of a single hydrogen bond, could be expected to exchange 10 times more slowly than a molecule which could fit through a smaller opening. Sterically larger solvents, or guests as will be discussed in the following section, therefore cause a significant increase in the exchange rate as illustrated by the experiments involving chlorinated solvents.
If size were the only criteria that affected the rate of guest exchange with solvent it would be assumed that the aromatic solvents, all of which have larger VdW volumes than the chlorinated solvents, would cause greater stability of the pyrene-filled capsule and result in longer exchange rates. This assumption was proven untrue as the pyrene-filled hexamer was less stable in all four aromatic solvents than in CDCl$_3$ and CCl$_4$, and only mesitylene provided an environment for a more stable guest bound capsule than CD$_2$Cl$_2$. However, when looking at the aromatic solvents by themselves the size effect on the stability of the pyrene encapsulated hexamer once again can been seen since the guest bound capsule is more stable in larger aromatic solvents. The total time for guest exchange in benzene and toluene is 80 hours but the configuration change in benzene causes the half-life of the exchange between the guest pyrene of the second configuration and benzene to be less than that of toluene (16 and 23 hours, respectively). Therefore,
benzene, the smallest aromatic solvent, has the fastest exchange rate while mesitylene, the largest aromatic solvent, creates the most stable pyrene-filled hexamers and requires heating to cause exchange with solvent. Taken individually, the chlorinated solvents and the aromatic solvents show a correlation between solvent size and capsule stability. The reason for the discrepancy between the two solvent types is likely due to the shape of the solvent molecules. In order to exchange encapsulated pyrene with the solvent the hexamer must break hydrogen bonds and create an opening large enough for the solvent to enter. Since the aromatic molecules are primarily planar while the chlorinated solvents are tetrahedral in geometry, it is possible that the aromatic solvents can more easily slide into the interior cavity when the hexamer opens. This ability may explain the faster guest exchange with solvent in aromatic solvents than in chlorinated solvents. The tetrahedral carbons of the aromatic solvents contain only hydrogen which is a smaller atom than chlorine which may also explain why the chlorinated solvents cause more stable guest-filled capsules than toluene, xylenes, and mesitylene which all contain methyl branches. Cyclohexane which is a non-planar bulky solvent molecule required heating to induce the change in configuration as well as exchange with solvent. The chair conformation of cyclohexane is preferred but there is flexibility in the three-dimensional structure which could cause distortion of the solvent molecule as it enters the hexamer. Despite this fact, a planar geometry is not possible, making the cyclohexane more similar to the chlorinated solvents than the aromatic. Both the configuration change and guest release were completed at 70°C and the ΔG‡ values show that the stability of the pyrene-filled
hexamers in cyclohexane is the same as in CDCl$_3$ (27.5 ± 0.2 kcal/mol and 27.3 ± 0.4 kcal/mol respectively).\textsuperscript{111,113}

While size alone cannot account for the solvent effects on the hexamer stability it appears to be a definite factor as larger molecules of similar type have longer exchange rates with guests. The shape of the solvent molecule is also important due to the fact that planar molecules can slide through a narrow opening more easily than non-planar tetrahedral molecules.

3.4.5 Polar Additives

The final solvent test performed, was used to determine the resistance of the hexamer to the addition of polar solvents. Polar solvents cause the disassembly of the hexamer as they compete with the hydrogen-bonding network used to hold the hexamer together. Experiments have shown that addition of 50% MeOD to the sample causes complete disassembly of the capsule and only peaks for pyrene free in solution are seen.\textsuperscript{111} Methanol (MeOH) was titrated into a sample containing the pyrene-filled hexamer in CCl$_4$ which was chosen due to the stable $O_h$ configuration at room temperature. With the addition of 1% methanol the peaks corresponding to encapsulated pyrene of the $O_h$ configuration almost completely disappeared and were replaced with broadened signals in the same region. At 5% methanol addition, distinct peaks corresponding to the $D_3$ configuration were seen although they had a much lower intensity than the initial peaks which was caused by some guest release. The guest peaks of the $D_3$ configuration persisted with methanol addition up to 20% after which the guest peaks disappeared and only peaks corresponding to free pyrene were seen (Figure 3.5).
Figure 3.5. $^1$H NMR spectra for titration of MeOH into pyrene capsules in CCl$_4$. ○ represent peaks for encapsulated pyrene in the $O_h$ configuration, ● represent peaks for encapsulated pyrene in the $D_3$ configuration.

Ethyl acetate was also titrated into a sample of pyrene capsules in CCl$_4$. The pyrene-filled hexamer was more resistant to ethyl acetate addition than it was to methanol as peaks corresponding to the $O_h$ configuration were still seen upon addition of 10% ethyl acetate. No peaks clearly identifiable with the $D_3$ configuration were seen throughout the experiment. Additional peaks in the region of 5.4-6.5 ppm did appear but they likely correspond to mixed occupancy capsules formed due to partial substitution of pyrene for solvent. 40% ethyl acetate was needed for complete disruption of the hexamers.$^{111}$

The small amount of methanol (1%) that causes the disappearance of the peaks corresponding to the $O_h$ configuration can be explained by the participation of the polar methanol in the hydrogen bonding of the pyrogallolarene. As the $O_h$ configuration is thought to have a disordered seam of hydrogen bonds it is logical that it is more sensitive to disruption by a small amount of methanol which is a good hydrogen bond donor and

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acceptor. Addition of a larger amount of both methanol and ethyl acetate cause some
guest exchange as the peaks for encapsulated pyrene steadily decreased until complete
disassembly was achieved. The acceleration of guest exchange by polar additives is
expected as these solvents can both participate in hydrogen bonding and assist in
stabilization of a partially opened hexamer which is required for guest exchange.
Relatively large amounts of both methanol and ethyl acetate were required to completely
disrupt the hexamer, 20% methanol and 40% ethyl acetate. This is a rare tolerance of a
hydrogen-bonded capsule and likely results from the highly cooperative nature of the
capsule seams.

3.5 Kinetics Results for Encapsulated Guests

Kinetics measurements were performed using anthracene, biphenyl, fluoranthene,
fluorene, naphthalene, and norbornene to determine what effect the structure of the guest
molecule had on the stability of the capsule. All six of these guest encapsulated hexamers
were tested in CDCl$_3$ and CCl$_4$ which were the two solvents which yielded the most
stable pyrene-filled hexamers. With the exception of biphenyl and naphthalene, which
proved to be too unstable in the chlorinated solvents for complete kinetic measurement,
all were also tested in cyclohexane. As with pyrene, all capsules were more stable in CCl$_4$
than in CDCl$_3$. Stacked spectra are shown in Appendix B.

3.5.1 Anthracene

When the anthracene-filled hexamer was dissolved in CDCl$_3$ the initial peaks
corresponding to encapsulated anthracene, found between 5.0-6.5 ppm, decreased and
were replaced with multiple sets of encapsulated guest peaks in the same region which
may correspond to different configurations or mixed occupancy capsules (Figure 3.6). Identification of individual configurations was exceedingly difficult and as such complete kinetics measurements could not be performed. The exchange of anthracene with CDCl₃ was completed in 50 hours at room temperature. When the anthracene complex was dissolved in CCl₄ there was only one set of encapsulated guest peaks seen in the NMR spectrum. By integration it was determined that three molecules were encapsulated within the hexamer which yields a packing coefficient of 0.43 (188 Å³ VdW volume). In CCl₄, a direct exchange with solvent occurred as no additional peaks appeared on the NMR. Exchange of anthracene for solvent in CCl₄ took 300 hours at room temperature and resulted in a half-life of 140 hours with an activation energy of 25.3 kcal/mol. Direct exchange of anthracene with solvent was also seen in cyclohexane. At room temperature the completion of guest release took 840 hours with a half-life of 240 hours and activation energy of 25.6 kcal/mol.

Figure 3.6. ¹H NMR spectra for anthracene in CDCl₃ measured at 23ºC. Spectra from t = 0 to t = 50 have been overlayed to illustrate the multiple peaks corresponding to different intermediate capsules. t = 0 is red followed by yellow, green, blue and purple. ● = initial guest encapsulated peaks, ○ = multiple intermediate peaks.
3.5.2 Fluoranthene

When fluoranthene was loaded into the hexamer and measured in CDCl$_3$ five distinct, broadened peaks in the upfield region of 4.2-5.8 ppm which correspond to encapsulated guest molecules were seen. Integration showed three fluoranthene molecules were encapsulated within the hexamer which yields a packing coefficient of 0.47 (202 Å$^3$ VdW volume). The encapsulated guest peaks decreased as fluoranthene exchanged with CDCl$_3$ over the course of 150 hours at room temperature resulting in a half-life of 55 hours and activation energy of 24.7 kcal/mol. A few small peaks appeared during the guest release which likely correspond to a mixed occupancy hexamer of both guest and solvent but there was no significant population of these peaks which did not allow for integrated measurements. When the fluoranthene hexamer was dissolved in CCl$_4$ and cyclohexane the same five broad upfield shifted peaks were seen that were found in CDCl$_3$. The fluoranthene-filled hexamer was stable in both solvents at room temperature and required heating to induce exchange with solvent. When heated to 50°C the encapsulated fluoranthene peaks decreased and exchange with CCl$_4$ was complete in 50 hours (Figure 3.7), with $t_{1/2} = 10$ hours and $\Delta G^\ddagger = 27.6$ kcal/mol while exchange with cyclohexane took 74 hours at 70°C with $t_{1/2} = 18$ hours and $\Delta G^\ddagger = 28$ kcal/mol. The additional small peaks that were seen in CDCl$_3$ were not seen in CCl$_4$ or cyclohexane indicating a direct exchange mechanism.
Figure 3.7. $^1$H NMR spectra for fluoranthene from $t = 0$ to $t = 50$ h in CCl$_4$ heated at 50ºC. Spectra from $t = 0$ to $t = 50$ have been overlayed to illustrate the direct exchange mechanism. $t = 0$ is red followed by yellow, green, blue and purple. ● = encapsulated guest peaks.

3.5.3 Fluorene

When the melted mixture of fluorene and pyrogallolarene was dissolved in CDCl$_3$ the fluorene encapsulated hexamer sample yielded a number of peaks in the upfield region of 4.2-6.0 ppm indicative of the aromatic hydrogens for encapsulated fluorene. Fluorene also had a peak corresponding to the encapsulated bridging CH$_2$ found near 2 ppm however this peak was not used in calculations due to additional overlapping peaks. By integration it was determined that there were four fluorene molecules encapsulated within the hexamer giving a packing coefficient of 0.55 ($180$ Å$^3$ VdW volume). The initial NMR measurement had additional peaks corresponding to encapsulated fluorene and it was determined that there was an intermediate configuration which is almost completely populated prior to exchange with solvent. Over 50% of the initial configuration had already converted to the intermediate in the initial measurement and complete conversion to the second configuration was finished in 2 hours. The half-life was determined to be 30 minutes and the calculated activation energy for this
configuration change was 21.9 ± 0.6 kcal/mol. The second configuration was not stable at room temperature and exchanged with solvent in 60 hours resulting in a half-life of 10 hours and activation energy of 23.7 kcal/mol. When the sample was measured in CCl₄ there were four peaks corresponding to the bound aromatic hydrogens which again underwent a configuration change (Figure 3.8). The initial configuration of the encapsulated fluorene was much more stable in CCl₄ than in CDCl₃ and the reconfiguration required roughly 800 hours to complete and had a half-life of 150 hours and activation energy of 25.4 kcal/mol. The second configuration of the fluorene was also not stable in CCl₄ and exchanged with solvent in 1450 hours at room temperature yielding a half-life of 1010 hours and ∆G‡ of 26.5 kcal/mol. There was no additional splitting of the host peaks in either solvent which indicates that the second configuration of fluorene likely corresponds to a capsule of mixed occupancy that still shows fast tumbling within the interior of the cavity. When the fluorene complex was dissolved in cyclohexane a single configuration was seen. No intermediate state as seen in the chlorinated solvents was present during the experiment and direct replacement with solvent was completed in 70 hours upon heating at 50ºC. The half-life was 24 hours and the activation energy was 26.3 kcal/mol
Figure 3.8. $^1$H NMR spectra for fluorene from $t = 0$ to $t = 1440$h in CCl$_4$ taken at 23ºC. Spectra from $t = 0$ to $t = 1440$ have been overlayed to illustrate the single intermediate state during guest release. $t = 0$ is red followed by yellow, green, blue and purple. ● = initial configuration peaks, ○ = intermediate configuration peaks.

3.5.4 Norbornene

Unlike the previously discussed guest molecules, norbornene has no aromatic hydrogens. The encapsulated guest peak corresponding to the hydrogens of the double bond appears between 4.0-4.4 ppm while the other five encapsulated guest peaks are shifted upfield between −1.5-1.0 ppm. Two of the encapsulated guest peaks overlap, however, by integration it was determined that there were four guest molecules on the interior of the hexamer resulting in a packing coefficient of 0.35 (115 Å$^3$ VdW volume). A direct exchange of norbornene with solvent was seen in all experiments. In CDCl$_3$ the guest encapsulated complex was not stable at room temperature and exchange with solvent was complete in 80 hours resulting in a half-life of 17 hours and activation energy of 24.1 kcal/mol (Figure 3.9). When dissolved in CCl$_4$ the same distinct guest encapsulated peaks were seen, however, it took 1500 hours to exchange norbornene with CCl$_4$ which is over 15 times greater than the time needed in CDCl$_3$. The half-life in CCl$_4$ was 850 hours and the activation energy was 26.3 kcal/mol. When the norbornene
capsule was dissolved in cyclohexane the guest-filled hexamer was stable at room temperature. Upon heating at 50°C the exchange with solvent was complete in 70 hours with a half-life of 4 hours and activation energy of 26.5 kcal/mol.

**Figure 3.9.** $^1$H NMR spectra for norbornene from $t = 0$ to $t = 130$h in CDCl$_3$ measured at 23°C. Spectra from $t = 0$ to $t = 130$ have been overlayed to illustrate the single intermediate state during guest release. $t = 0$ is red followed by yellow, green, blue and purple. ● = guest encapsulated peaks.

### 3.5.5 Biphenyl and Naphthalene

Both biphenyl and naphthalene had many encapsulated guest peaks in both CDCl$_3$ and in CCl$_4$ likely corresponding to mixed occupancies within the capsule or different configurations. In both cases determining the number of configurations and which bound guest peaks corresponded to which configuration proved to be complex and imprecise. It was estimated that four molecules of biphenyl were encapsulated which yields a packing coefficient of 0.53 (173 Å$^3$ VdW volume) and six molecules of naphthalene were encapsulated resulting in a packing coefficient of 0.67 (145 Å$^3$ VdW volume). In the case of biphenyl guest release was complete within 20 hours in CDCl$_3$ and 100 hours in CCl$_4$ (Figure 3.10). For naphthalene the guest solvent exchange was complete in 8 hours in
CDCl$_3$ and in 300 hours in CCl$_4$ (Figure 3.11). Neither biphenyl nor naphthalene were tested in cyclohexane.

**Figure 3.10.** $^1$H NMR for biphenyl from $t = 0$ to $t = 200$ h in CCl$_4$ measured at 23ºC. Spectra from $t = 0$ to $t = 200$ have been overlayed to illustrate the multiple intermediate states during guest release. $t = 0$ is red followed by yellow, green, blue and purple. ● = initial peaks, ○ = intermediate peaks.

**Figure 3.11.** $^1$H NMR for naphthalene from $t = 0$ to $t = 430$ h in CCl$_4$ measured at 23ºC. Spectra from $t = 0$ to $t = 200$ have been overlayed to illustrate the multiple intermediate states during guest release. $t = 0$ is red followed by yellow, green, blue and purple. ● = initial peaks, ○ = intermediate peaks.
3.5.6 Data Tables

<table>
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<tr>
<th>Guest</th>
<th>$k$ (s$^{-1}$)</th>
<th>$t_{1/2}$ (h)</th>
<th>Time (h)</th>
<th>$\Delta G^\dagger$ (kcal/mol)</th>
<th>Temp (ºC)</th>
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**Table 3.3.** Kinetics data for guest→solvent exchange of guest encapsulated hexamers in CDCl$_3$. Data listed is for solvent exchange of the second configuration of fluorene. The first configuration has a half-life of 0.5 hours and activation energy of 21.9 ± 0.6 kcal/mol.

<table>
<thead>
<tr>
<th>Guest</th>
<th>$k$ (s$^{-1}$)</th>
<th>$t_{1/2}$ (h)</th>
<th>Time (h)</th>
<th>$\Delta G^\dagger$ (kcal/mol)</th>
<th>Temp (ºC)</th>
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<td>Fluoranthene</td>
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**Table 3.4.** Kinetics data for guest→solvent exchange of guest encapsulated hexamers in CCl$_4$ using an external lock. Data listed is for solvent exchange of the second configuration of fluorene. The first configuration has a half-life of 150 hours and activation energy of 25.4 ± 0.4 kcal/mol.

<table>
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<tr>
<th>Guest</th>
<th>$k$ (s$^{-1}$)</th>
<th>$t_{1/2}$ (h)</th>
<th>Time (h)</th>
<th>$\Delta G^\dagger$ (kcal/mol)</th>
<th>Temp (ºC)</th>
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</thead>
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<td>70</td>
<td>26.3</td>
<td>50</td>
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<tr>
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<td>26.5</td>
<td>50</td>
</tr>
<tr>
<td>Pyrene</td>
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<td>20</td>
<td>74</td>
<td>27.3</td>
<td>70</td>
</tr>
</tbody>
</table>

**Table 3.5.** Kinetics data for guest→solvent exchange of guest encapsulated hexamers in cyclohexane using an external lock. Data listed is for solvent exchange of the second configuration of pyrene. The first configuration has a half-life of 4 hours and activation energy of 27.0 kcal/mol.
3.6 Guest Comparisons and Trends

Pyrene and fluoranthene are structural isomers with calculated VdW volumes of 198 Å³ and 202 Å³ respectively. They are both flat, aromatic molecules with the main difference between them being geometry. Pyrene has the widest part of the molecule in the middle which has great shape complementarity with the interior of the hexamer. In contrast fluoranthene has the largest part of the molecule at one end which does not fit as well within the roughly spherical interior of the hexamer. While three molecules of each are encapsulated within the hexamer there is a large difference in the stability of the guest encapsulated hexamers in the chlorinated solvents. The additional splitting of the host and guest peaks of the pyrene $D_3$ configuration indicates that the pyrene does not tumble rapidly within the interior of the hexamer and corresponds to the tightest fit between the host and guest. The fluoranthene guest does tumble rapidly within the interior of the host and exchanges more quickly with solvent than pyrene in both CDCl$_3$ and CCl$_4$. Interestingly, the stability of the fluoranthene-filled hexamer in cyclohexane was slightly greater than that of pyrene which was unexpected and cannot be readily rationalized.

Fluoranthene and pyrene are the most stable guest-filled capsules in all solvents tested and the system of pyrene in CCl$_4$ creates the most stable guest-filled capsules to date which are even seen at equilibrium. The large size of both molecules is responsible for the increased stability of the guest-filled hexamers as a larger opening is needed for the guests to exit the capsule which means a greater number of hydrogen bonds must be broken to complete guest exchange with solvent.
Anthracene, biphenyl and fluorene are all of similar size; they have 14, 12, and 13 carbons respectively and VdV volumes of $188\,\text{Å}^3$, $173\,\text{Å}^3$, and $180\,\text{Å}^3$, however, their geometries are distinctly different. Anthracene is a rigid, planar, aromatic molecule, biphenyl is also aromatic but has freedom of rotation about the single bond which can allow for non-planar geometry, while fluorene has an sp$^3$-hybridized carbon bridge between the two aromatic rings causing a very rigid but non-planar geometry. As seen previously with solvent studies, geometry can have a large effect on capsule stability.

In CDCl$_3$ all three guest molecules have multiple guest encapsulation peaks which may correspond to different capsule occupancies or coencapsulation with solvent. The fluorene capsule has two specific sets of encapsulated peaks which indicate a single intermediate configuration while both anthracene and biphenyl have multiple guest peaks that are difficult to assign to specific individual species. In CCl$_4$ the fluorene complex again has a single intermediate configuration and biphenyl exhibits the same multitude of encapsulated guest peaks that was seen in CDCl$_3$. Anthracene on the other hand has only one set of encapsulated peaks, indicating a direct exchange mechanism. In cyclohexane both anthracene and fluorene undergo direct exchange with solvent and no peaks corresponding to intermediate states are seen. The change in exchange mechanism from intermediate states to direct guest exchange with solvent was also seen with pyrene in the aromatic solvent experiments. In all three cases in which a change in the exchange mechanism occurs the intermediate states are seen with the solvents of smaller size but not with the larger solvents. It is possible that the intermediate states involve some
coencapsulation with solvent molecules which is not possible with solvent molecules of a larger size.

Biphenyl, which is the smallest of the three guests of intermediate size, has the shortest exchange time in both CDCl$_3$ and CCl$_4$ which signifies that the rotation about the single bond does not greatly hinder the rate by which the biphenyl exits the capsule. When dissolved in CDCl$_3$ anthracene and fluorene have similar exchange times, however in CCl$_4$ and cyclohexane there is a larger disparity in the exchange rates between them. In both of these solvents the fluorene is significantly more stable than anthracene, taking more than three times as long to complete exchange in CCl$_4$ and requiring heating to induce guest release in cyclohexane.

Figure 3.12. Molecular models of the pyrogallolarene hexamer with encapsulated anthracene and encapsulated anthracene with CHCl$_3$. Hydrogens and R groups were removed for clarity.

To further probe the identity of the intermediate configurations a sample of the anthracene complex was dissolved in proteo chloroform (CHCl$_3$) and kinetic measurements were performed that mirrored those done in CDCl$_3$. The coencapsulation
of solvent with guest molecules could account for the low packing coefficients calculated for some of the guests, including anthracene (Figure 3.12). Comparison of the NMR spectra for the CHCl₃ sample with those of the CDCl₃ sample showed a peak at 4.2 ppm which was seen only on the CHCl₃ trial that was identified as encapsulated CHCl₃. This peak slowly grew in and later disappeared during the course of the experiment. The increase and decrease of this peak matched another peak found at 6.2 ppm which was attributed to encapsulated anthracene indicating a capsule of mixed occupancy which contains both anthracene and CHCl₃ (Figure 3.13). There is a high likelihood that encapsulated solvent peaks exist in other guest-filled NMR spectra but due to the close proximity of the encapsulated CHCl₃ peak found for the anthracene complex with the methine peak of the pyrogallolarene and guest encapsulated peaks for other aromatic molecules it is quite possible that they are obscured.

Figure 3.13. $^1$H NMR for anthracene in CHCl₃ measured at 23°C. ● = initial guest encapsulated peaks, ○ = intermediate guest peaks, □ = intermediate encapsulation of CHCl₃, ■ = encapsulation of CHCl₃ in solvent-filled hexamer, * = solvent impurity.
The smallest guest molecules that were tested were naphthalene (145Å³ VdW volume) and norbornene (115Å³ VdW volume). Naphthalene is a flat, aromatic molecule while norbornene is a small, compact, bridged molecule. While norbornene is smaller than naphthalene by 20%, it creates a much more stable guest encapsulated hexamer than naphthalene. When dissolved in both CDCl₃ and CCl₄ the naphthalene sample exhibited multiple guest peaks which increased and decreased indicative of multiple configurations or capsules of mixed occupancy. Norbornene showed only a single configuration which underwent direct exchange with solvent in both chlorinated solvents as well as cyclohexane.

As discussed when comparing the effect of aromatic vs. chlorinated solvents on the stability of the pyrene-filled capsule, it is possible that the planar aromatic molecules can move more easily in and out of the hexamer when it opens which can account for the large difference in stability. Naphthalene, being a planar aromatic molecule, requires a narrower opening through which it can exit meaning that it can likely slide out of the hinged aperture more easily than the bridged norbornene. This geometry difference is also a likely explanation for the difference in number of molecules bound as naphthalene appears to have six molecules encapsulated within the hexamer while norbornene only appears to have four. The naphthalene molecules can more easily stack on top of each other while norbornene cannot.

In CDCl₃ both guest-filled hexamers underwent exchange with solvent at room temperature; however, the norbornene complex was ten times more stable than that of naphthalene. The difference was not quite as large in CCl₄ but the norbornene complex
still took seven times longer to complete guest release. In cyclohexane the norbornene complex was stable at room temperature and required heating to induce exchange with solvent. Interestingly, with the exception of the pyrene and fluoranthene guests, norbornene is the most stable guest molecule studied despite being the smallest in size, while naphthalene is one of the least stable.

Another interesting comparison is that of azulene and naphthalene. These molecules are structural isomers, just like pyrene and fluoranthene. Both are fully aromatic compounds, but the naphthalene structure is composed of two fused six membered rings while the structure of azulene is that of a seven membered ring fused to a five membered ring which makes it slightly wider than naphthalene. It was assumed that the azulene would have a longer exchange rate with solvent than naphthalene due to the wider structure but this was proven to be incorrect. Azulene was completely replaced with solvent in CDCl₃ in one hour which was significantly shorter than the eight hours required for naphthalene. In CCl₄ the exchange with solvent took 120 hours for azulene but 200 hours for naphthalene, again contradicting the initial hypothesis. The reasoning for this apparent reversal in stability is not clear. Some guest exchange in host molecules is based on the ability of the guest to force an opening in the host which is large enough to allow the guest to exit. Perhaps the smaller end of azulene can more easily enter a narrow opening thereby forcing the pyrogallololarene hexamer to open further. One thing is clear, while size and shape are significant factors in predicting the stability of guest encapsulated hexamers there are still other influences which are not fully understood.
Selective encapsulation of guest molecules from a mixture was attempted, however, all experiments showed mixtures encapsulated within the hexamer. In no case was a single species present within the interior meaning that there is no selectivity in encapsulation using the melting method.

3.7 Conclusions

The melting method proved to be an effective procedure for loading a variety of guest molecules into the interior of the pyrogallolarene hexamer. Aromatic and aliphatic molecules were found to be exceptional guests with efficient loading corresponding to a high capsule occupancy in many cases. Even some guests with polar functionalities on larger hydrocarbon frameworks were shown to be encapsulated, although these typically had low capsule occupancy or fast exchange rates with solvent as determined by small indistinct peaks on the NMR.

The pyrene-filled capsule showed unique stability and unusual structural factors not seen in experiments with other guest molecules. The pyrene-filled hexamer underwent a configuration change in the chlorinated solvents to a guest encapsulated structure that was so stable there was no change seen in the NMR over a period of nine weeks in solution. The second configuration corresponds to a lower symmetry capsule which is defined by the high complementary fit of the guest pyrene with the interior of the pyrogallolarene hexamer. The lower symmetry configuration was also seen in benzene and cyclohexane.

Multiple solvents were examined using the pyrene-filled hexamer to determine the effect of solvent of the rate of guest release from the capsule. A general trend was
seen in which larger or more bulky solvents resulted in slower exchange rate with the pyrene indicative of more kinetically stable guest encapsulated hexamers. This concept was exemplified in the case of the pyrene complex in CCl$_4$ in which the guest did not completely exchange with solvent even after heating at 150ºC. In this special case the pyrene could be loaded into the hexamer by heating the individual components in solution resulting in 10% guest-filled capsule at equilibrium. In no other system studied were guest-filled capsules seen at the thermodynamic minimum, instead solvent-filled capsules predominated. Steric factors are expectedly important due to the fact that the exchange of guest for solvent on the interior of the hexamer requires the assembly to break multiple hydrogen bonds in order to create an opening large enough for the guest to exit and solvent to enter.

Additional aromatic and aliphatic molecules which showed high capsule occupancy were also tested to determine the kinetic stability of the capsules based on the structure of the guest. It was expected that larger and more sterically bulky molecules would have more stable guest-filled capsules. This hypothesis was true in a majority of cases. The most stable guest-filled capsules corresponded to pyrene, fluoranthene, and norbornene. Pyrene and fluoranthene are the largest molecules tested and norbornene has a bridging carbon which causes the greatest deviation from planarity of all the guest molecules examined. Fluorene and anthracene also showed good stability. Biphenyl and naphthalene were the smallest guest molecules tested and both showed multiple peaks corresponding to intermediate capsules which did not allow for full kinetic characterization.
Intermediate states were seen in many of the experiments indicating that there is not always a direct exchange of guest for solvent. A test using anthracene in proteo chloroform resulted in an encapsulated peak corresponding to chloroform which grew in and then disappeared indicating that the intermediate capsules can include capsules of mixed occupancy with solvent which would also account for the low packing coefficient calculated in some cases. There were, however, some specific exceptions to the trend of larger sizes corresponding to longer exchange times. Azulene had a faster exchange rate than naphthalene despite its wider structure and fluoranthene in cyclohexane was slightly more stable than pyrene which is the only case in which the pyrene-filled capsule did not have the highest kinetic stability.

The studies of guest-filled hexamers in solution have shown that guest encapsulated, hydrogen-bonded pyrogallolarene capsules have high kinetic stability. The information determined about the mechanism of guest exchange as well as steric factors attributed to both the solvent and guest structures is extensive. The melting method allows for guests to be loaded into the capsule under one set of conditions and then studied under another in which the guest-filled capsules would not otherwise have been formed. The kinetically trapped, guest encapsulated hexamers may lead to new applications in molecular recognition chemistry.

3.8 Experimental

3.8.1 General

All reagents and solvents were obtained from commercial sources and used without further purification. $^1$H NMR spectra were recorded using a 500 MHz Bruker
Avance spectrometer and referenced to solvent. An external lock was used for proteo solvents using a coaxial insert filled with deuterated benzene. Molecular modeling was performed using HyperChem 8.0.6 and Spartan ’04 and visualized using PyMol 1.2r1. Geometry optimizations were performed in HyperChem by fixing the atoms of the hexamer as determined from an X-ray crystal structure\textsuperscript{58} and minimizing the encapsulated guests at the AM1 level of theory. Kinetics calculations were performed using Origin 8.1 and KinTekSim. Cavity and VdW volumes were calculated using SwissPdbViewer. Data for $^1$H NMR are recorded as follows: chemical shift ($\delta$, ppm), multiplicity (s = singlet, t = triplet, m = multiplet, integration). MS analysis was performed at the Mass Spectrometry facility at the University of Colorado, Boulder.

3.8.2 Pyrogallolarene Synthesis

\begin{center}
\includegraphics{pyrogallolarene.png}
\end{center}

A solution of pyrogallol (10 g, 79.4 mmol) in ethanol (40 mL) and concentrated HCl (15 mL) was cooled to 0°C under a N$_2$ atmosphere. Undecanal (13.5 g, 79.4 mmol) in ethanol (20 mL) was added drop wise to the solution over a period of two hours. The solution was then refluxed for 24 hours at 80°C. After cooling the precipitate was filtered, washed with methanol, and recrystallized from boiling methanol to give
decylpyrogallolarene (17g, 77%): off-white solid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 8.78 (s, 4H, OH), 7.47 (s, 4H, OH), 6.88 (s, 4H, OH), 6.83 (s, 4H, H$_{arom}$), 4.37 (t, 4H, CH), 2.29-2.14 (m, 8H, CH-CH$_2$), 1.57-1.27 (m, 72H, (CH$_2$)$_9$), 0.88 (t, 12H, CH$_3$). $^{13}$C NMR (500 MHz, CDCl$_3$) $\delta$ = 138.53, 137.39, 131.41, 125.41, 124.10, 113.83, 34.13, 33.21, 31.97, 29.92, 29.80, 29.73, 29.69, 29.42, 28.28, 22.70, 14.08. MS (ESI+) calculated: 1111.75, found: 1111.75

3.8.3 Encapsulation Studies

A 1:1 (by weight) mixture of decylpyrogallolarene and guest was placed in a vial, heated to melting with a heat gun under ambient air and allowed to cool. The resulting solid was dissolved in solvent (proteo or deuterio) and measured by NMR. All spectra were measured at 23°C. Samples that were monitored at 23°C were kept at that temperature throughout the course of the exchange experiment and were measured periodically. The frequency of measurement was determined by the rate of exchange. Samples that were stable at room temperature were measured initially at 23°C and then heated in the NMR tube in a constant temperature oil bath for a specific amount of time unless otherwise stated. Samples were removed, cleaned, and measured by NMR periodically throughout heating.
Chapter 4: Purification and Compartmentalization

4.1 Introduction

The encapsulation of guest molecules within the pyrogallolarene hexamer under solvent-free conditions was a significant discovery in the Purse lab. The high stability of these kinetically trapped species allows for experimentation under nonequilibrium conditions which opens many other potential avenues of study. Simple procedures such as purification have not previously been attempted with hydrogen-bonded complexes such as these and this chapter details the purification method discovered by the Purse lab.

The initial desire for purified hexamers was based on the intrinsic fluorescent properties of many of the aromatic guest molecules which were found to have high guest loading within the pyrogallolarene hexamers. Some of these molecules have well characterized fluorescence spectra for excimeric and dimeric structures. The presence of these structures within the interior of the hexamer would allow for monitoring of the reactivity and guest release of encapsulated species using fluorescence spectroscopy. The accuracy of fluorescence measurements and other applications such as compartmentalization would likely be increased if the guest-filled hexamers were pure in solution. In the previous kinetics measurements there was an excess of guest molecules present in solution, which is a natural consequence of the melting method. Purification methods, which would remove excess guest molecules while still maintaining the integrity of the hydrogen-bonded capsule, were researched. It was determined that size
exclusion gel permeation chromatography, which is a method of separating molecules based on their size, would be a good candidate for purification because of its ability to separate the large hexamer from the small unencapsulated guest molecules. This method proved to be a successful process for obtaining the pure guest-filled capsule, without any guest release, which is the first example of the purification of a hydrogen-bonded capsule by chromatography.

Another aspect that was of interest in regards to the guest-filled hexamers was that of chemical compartmentalization. Chemical compartmentalization can be used in two ways. The first involves separating prospective reactants from each other in solution by the presence of a physical barrier, often a molecular capsule similar to the pyrogallolarene hexamers. The second involves encapsulating reactants together in a confined space thereby restricting the area in which the molecules can react. Chemical compartmentalization has already been shown to modify the outcome of reactions which occur within the interior of a capsule by restricting the spatial mobility of the transition state. The high kinetic stability of the encapsulation complexes formed with pyrogallolarene has the potential to control reactivity by isolating the guest molecules from potential reagents in the external bulk solution. The release of guest molecules in response to external factors allows for a method of controlling reactivity. Guest molecules can be released from the hexamer by heating or upon the addition of polar additives.

Two experiments were performed to study the ability of pyrogallolarene hexamers to sequester guests from reactive species. The system of encapsulated norbornene was
chosen for these experiments due to the reactive, non-aromatic double bond. The pyrogallolarene hexamers were shown to protect the sensitive alkene from external reagents under exposure to bromine, which adds to the double bond, and hydrogenation, which saturates the double bond. These initial experiments illustrate the potential for reaction control using the capability of the hexamer to sequester guests from solution.

4.2 Purification

Complete loading of the pyrogallolarene hexameric capsules using the melting method required an equal amount, by weight, of pyrogallolarene and guest. The premise of the melting method is that the guest liquefies and the pyrogallolarene dissolves in the newly formed “solvent.” As a result a large excess of guest molecules are required for the pyrogallolarene to fully dissolve and yield guest-filled hexamers with complete loading of the interior. When the resulting solid is dissolved in solution the excess guest molecules are free in solution resulting in large unencapsulated guest peaks in the NMR spectrum (Figure 4.1). A method for removing this excess guest while maintaining the integrity of the hydrogen-bonded capsule was investigated.
Purification using standard silica gel chromatography was not possible because pyrogalloporene adsorbs strongly to the silica due to the twelve hydroxyl groups on the upper rim. As a result, significant percentages of polar solvents are needed to elute pyrogalloporene, which causes disruption of the assembly and release of encapsulated guests. Size exclusion gel permeation chromatography (GPC) was analyzed as a possibility for purification of the guest-filled capsules due to the large size difference between the hexameric assembly and the excess guest molecules free in solution. GPC resin can be comprised of many different materials but one of the most common is polystyrene polymers. Polystyrene was ideal for testing the purification ability of GPC due to the nonpolar nature of the polymer which would not interfere with the hydrogen bonding network that holds the hexamer together. GPC media composed of a polystyrene polymer with a 3% crosslinking of divinylbenzene was purchased. The resin had a molecular weight limit of less than 2000 meaning that larger molecules should flow
through the column without getting caught in the pores of the polymer. As the hexamer has a molecular weight of over 6000 g/mol it was expected that it would pass through the column with a short retention time while the smaller guest molecules would be trapped in the pores of the resin resulting in a longer retention time through the column.

The choice of mobile phase was very important as the guest-filled hexamers would be dissolved in solvent for the duration of the purification process. As a result, the guest-filled hexamers needed to have a high stability in the chosen solvent otherwise the guest molecules would be released through simple guest exchange for solvent before the purification process could be completed. GPC purification was performed manually by loading the resin onto a column and using gravity to pull the mobile phase through the GPC media. Carbon tetrachloride was initially chosen as the mobile phase for chromatography due to the high stability of guest-filled capsules in this solvent. Unfortunately, carbon tetrachloride has a greater density than the GPC media which caused the resin to float to the top of the column. This combined with the high cost and large amount that was needed for purification chromatography made carbon tetrachloride a poor choice for GPC purification.

Cyclohexane is a common solvent used for GPC chromatography and was the next candidate assessed for the mobile phase. Kinetics measurements were performed in cyclohexane for anthracene, fluoranthene, fluorene, norbornene, and pyrene encapsulated hexamers to determine the stability of the guest-filled capsules in cyclohexane (see chapter 3) and all guest-filled capsules had high stability in cyclohexane. Only the anthracene-filled hexamer showed appreciable exchange with solvent at room
temperature. The half-life of the exchange of encapsulated anthracene for cyclohexane was calculated to be 240 hours, much longer than the time required for purification.\textsuperscript{113} Samples of other guest-filled capsules left for extended periods did show very slow exchange with cyclohexane at room temperature which indicated that the complexes could not be left dissolved in cyclohexane indefinitely prior to purification. The high stability of guest-filled capsules in cyclohexane, along with the low density of the solvent and the moderate cost, made it an ideal choice for the mobile phase of GPC chromatography.

GPC purification was performed manually. Initially, 50 g (unswelled) of the polystyrene GPC media was swelled in cyclohexane and the resulting slurry was loaded onto a column. Then, 32 mg samples of the melted mixture for each guest-filled hexamer was prepared (16 mg each of guest and pyrogallolarene) and dissolved in 3 mL of cyclohexane (Scheme 4.1). The solubility of the samples in cyclohexane was poor and an ultrasonic bath was used to fully dissolve the hexamer. Norbornene was an exception to the general sample preparation procedure. As stated earlier, the melting method takes advantage of the ability of the guest molecule to completely liquefy followed by dissolution of the pyrogallolarene in this newly formed “solvent” which causes the formation of the guest encapsulated hexamer. Norbornene has a melting point range of 42-46°C and a boiling point of 96°C. As a result the excess norbornene evaporates during the high temperatures caused by heating with a heat gun. In fact, not all norbornene samples prepared showed full encapsulation within the hexamer. In some cases the norbornene evaporated before the pyrogallolarene was completely dissolved resulting in
Scheme 4.1. Depiction of the purification process for guest encapsulated hexamers. Pyrogallolarene and fluorene were melted together and allowed to cool prior to dissolution in cyclohexane. The sample was then loaded onto the GPC column and the guest-filled hexamer eluted before the unencapsulated fluorene. Upon heating the encapsulated fluorene is released resulting in the cyclohexane-filled capsule. R groups were removed for clarity.
low guest loading. Methods were tested using an oil bath to heat the samples with no greater success of guest loading than seen with the melting method. Consequently, the melting method was preferentially used due to the speed of sample preparation. It was found that adding the pyrogallolarene to the norbornene sample, i.e. having the pyrogallolarene solid on top of the norbornene prior to melting, and even heating of the sample vial as opposed to one directional heating, was more successful in loading the norbornene into the interior of the hexamer. All norbornene samples were checked by NMR to ensure complete loading prior to use in experiments. However, due to the evaporation of the excess norbornene during heating, the guest encapsulated hexamers were the only species in solution. Consequently, all norbornene samples used for purification were doped after melting with excess free norbornene. This intrinsic purification of the guest-filled hexamers was not seen with any other guest molecules, even after extended heating with the heat gun, due to the high boiling points of the aromatic compounds.

An NMR was taken of each sample in proteo cyclohexane (using an external lock of deuterated benzene) prior to purification. The sample was then loaded onto the column and gravity filtration was used to run the column. Fractions were collected every two minutes. On average, the hexamer began to elute after 58 minutes and took 14 minutes to completely come off the column. The length of time required was increased if the sample was not fully dissolved in the cyclohexane. The pure fractions were individually measured by NMR to determine the effectiveness of the removal of the excess guest
molecules. Each sample showed peaks corresponding only to the pyrogallolarene and encapsulated guest with no excess guest free in solution (Scheme 4.1, Figure 4.2).

The purified guest-filled hexamers could be made to release the encapsulated guest molecules by heating as seen in previous encapsulation experiments (Figure 4.2). A large volume of cyclohexane was needed (> 200 mL) to cause elution of the unencapsulated guest molecules (Scheme 4.1). GPC purification proved to be an effective method of purifying the guest encapsulated hexamers while maintaining the integrity of the hydrogen-bonded capsule.

Figure 4.2. $^1$H NMR for fluorene in cyclohexane measured at 23°C prior to purification, A, after purification, B, and after guest release induced by heating, C. ● = guest encapsulated peaks, ▲ = unencapsulated guest peaks.

The percent recovery of this method was determined by transferring each individual fraction to a clean pre-weighed vial. The cyclohexane was then allowed to evaporate. The vials were weighed again after the solvent had evaporated and the total recovered mass was calculated. The percent recovery was based on the initial amount of
pyrogallolarene that was used in each experiment because the mass of the encapsulated guest was determined to be negligible in comparison. Percent recoveries were over 90% for all samples (Table 4.1). The resulting purified solid could also be dissolved in a different solvent and encapsulated hexamers were seen with little to no guest release.

<table>
<thead>
<tr>
<th>Guest</th>
<th>Percent Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracene</td>
<td>97</td>
</tr>
<tr>
<td>Fluoranthe</td>
<td>95</td>
</tr>
<tr>
<td>Fluorene</td>
<td>96</td>
</tr>
<tr>
<td>Norbornene</td>
<td>98</td>
</tr>
<tr>
<td>Pyrene</td>
<td>91</td>
</tr>
</tbody>
</table>

Table 4.1. Percent recovery of guest encapsulated hexamers after purification based on initial mass of pyrogallolarene.

4.3 Compartmentalization

Kinetically trapped encapsulation complexes have the potential to control the reactivity of guests in the interior of the hexamer. The act of encapsulation, by nature, sequesters the guest molecules from bulk solution and any reactants found therein. As a result the ability of the encapsulated molecules to react is severely decreased or eliminated while isolated from solution. In the case of guest-filled pyrogallolarene hexamers the reaction process could be controlled by timed release of the encapsulated guest molecule into solution. The guest release can be accomplished by two orthogonal methods previously discussed: heating, which has been shown to cause guest exchange for solvent, or addition of polar additives which completely disrupt the hydrogen-bonded assembly of the hexamer. Two experiments were performed with norbornene to evaluate the ability of the pyrogallolarene to completely segregate encapsulated guests from solution and thereby control the reactivity of the interior occupant. Norbornene is unique
among the guest molecules that have been tested in that it is a non-aromatic compound with an alkene functionality. The norbornene capsules have very high stability in solution making them ideal for compartmentalization experiments. The two experiments performed were addition of bromine to the alkene and hydrogenation of the alkene.

4.3.1. Bromine

Bromine addition to alkenes is a well-known and common reaction that is often performed in undergraduate organic chemistry labs. This experiment results in a colorimetric, qualitative measurement of the saturation of hydrocarbons in solution. The orange color of the bromine solution will only persist after full saturation of the reactant. The addition of bromine to a solution of encapsulated norbornene and free norbornene would allow for a qualitative measurement of the reactivity of norbornene in solution.

The norbornene encapsulated hexamer was formed using the melting method as previously described and then doped with additional norbornene because the free norbornene evaporated upon sample formation. This mixture was first tested in CDCl₃ for monitoring using NMR. A ~2M bromine solution was made and added drop wise to the sample in the NMR tube. An NMR spectrum was taken after each addition of bromine. Upon addition of the first drop of bromine solution, multiple peaks were seen on the NMR corresponding to reacted norbornene. The CDCl₃ was not dried prior to the experiment and as a result there were likely competing reactions which occurred in solution involving bromohydrin formation. Attempts to dry the CDCl₃ resulted in no additional distinction of peaks for the reacted norbornene. Complete reaction of the free norbornene with bromine, as determined by both the orange color of the sample and the
disappearance of the NMR peak at 6.25 ppm corresponding to the alkene, was achieved upon addition of three to five drops of bromine on average. The NMR spectra of the initial sample prior to bromine addition and the final sample after complete reaction of the free norbornene were compared and the peaks corresponding to the encapsulated norbornene were integrated. It appeared as though the bromine in solution interacted with the hexameric assembly causing some guest release. However, the majority (70%) of encapsulated norbornene was still present and unreacted with the bromine as determined by integration. Deuterated methanol was then added to the sample to disrupt the hexamer and the encapsulated norbornene was released and immediately reacted with the excess bromine in solution. Integration of the guest encapsulated peaks showed that no norbornene underwent bromine addition while still inside the hexamer.

The experiment was repeated in deuterated cyclohexane. In cyclohexane there was again 70% retention of the encapsulated norbornene after complete reaction of the free norbornene in solution with bromine as determined by NMR integration (Figure 4.3). Unfortunately MeOD is not miscible with cyclohexane and proteo ethyl acetate was used in an attempt to disrupt the hexamer. The high percentage of ethyl acetate needed to fully disrupt the sample interfered with the peaks of interest on the NMR and complete disassembly was not measured.

The stability of the guest encapsulated hexamer after addition of bromine was also tested in deuterated cyclohexane. It was determined that the encapsulated norbornene was completely released from the capsule in five hours at room temperature indicating that the bromine in solution interferes with the hydrogen-bonded assembly and catalyzes
guest release. Previous kinetics measurements of the norbornene complex in cyclohexane had no measurable guest release at room temperature.\textsuperscript{113} A timed NMR kinetics measurement was performed at 30ºC to determine the stability of the hexamer after addition of bromine. An NMR measurement was taken every 10 minutes over the course of 5 hours to monitor the presence of the guest encapsulated peaks. The increased temperature within the NMR does accelerate the guest exchange with solvent but even at 30ºC the guest-filled hexamers persisted up to 3 hours. As the reaction of bromine with alkenes is fast on the NMR timescale, taking about 1 second to complete, this result shows that the encapsulation of norbornene can slow the reaction rate by over 10,000 times. This experiment showed that even under conditions in which the hexamer is not indefinitely stable the encapsulation of guest molecules can allow for reaction control.

Figure 4.3. \textsuperscript{1}H NMR for norbornene capsules in cyclohexane measured at 23ºC with free norbornene in solution prior to bromine addition, A, after partial reaction of free norbornene with bromine, B, and after complete reaction of free norbornene with bromine, C. ● = guest encapsulated peaks, ○ = unencapsulated guest peaks.
4.3.2 Hydrogenation

The second experiment which tested the ability of the hexamer to sequester guests from reactants in solution was hydrogenation of the alkene functionality of norbornene. Hydrogenation of alkenes can be performed in many ways. One robust method uses palladium on carbon in conjunction with exposure to hydrogen gas. As chlorinated solvents are not commonly used for hydrogenation reactions, deuterated cyclohexane was chosen as the solvent instead. A sample of norbornene encapsulated pyrogallolarene was prepared using the melting method and doped with additional norbornene. An NMR was taken to provide an initial encapsulation spectrum. Palladium on carbon (20%) was added to the NMR sample in a Schlenk tube, the atmospheric gases were evacuated, and a hydrogen balloon was added to the reaction flask. After one hour the reaction was stopped and the solution was filtered through celite to remove the carbon. The resulting solution was measured by NMR and the peak at 6.25 ppm corresponding to the alkene of the free norbornene had completely disappeared indicating a complete reaction with hydrogen. The alkene peak for the encapsulated norbornene at 4.5 ppm was unchanged as determined by integration (Figure 4.4) which meant that the encapsulated norbornene was still present on the interior of the hexamer and did not react under the hydrogenation conditions. The sample was measured after three days and no additional guest release was seen. The hydrogenation experiment differs from the bromination test because additional reactants are removed after the completion of the reaction. As a result the spectrum for the encapsulated complex from the hydrogenation experiment did not exhibit any
additional changes to the encapsulation complex other than typical guest exchange with cyclohexane which occurs over time.

![Figure 4.4](image)

**Figure 4.4.** $^1$H NMR for norbornene in cyclohexane measured at 23°C with free norbornene in solution prior to hydrogenation, A, and after hydrogenation, B. ● = guest encapsulated peaks, ○ = unencapsulated guest peaks.

### 4.3.3 Additional Encapsulation Studies

Two studies were performed with the aim of utilizing the intrinsic fluorescent properties of guest molecules encapsulated within the hexamer. The first was based on the well characterized excimer formation of pyrene and the second was based on the photochemical dimerization of anthracene. Neither was successful.

Initial studies of guest encapsulation were performed with pyrene which has a well characterized fluorescence spectrum with a collection of monomeric peaks between 375-405 nm.$^{120}$ Pyrene has often been used for fluorescence studies, in fact it was previously used in a FRET pair with perylene to measure hexamer formation.$^{83,84,121}$ Pyrene also forms an excited dimer or excimer, which has a broad emission peak at ~460
nm, when two pyrene molecules are aligned in close proximity. The excimer formation has been commonly used in biophysics studies to measure distances between biomolecules.\textsuperscript{120,122,123} It was theorized that fluorescence spectra of the pyrene-filled hexamer would show characteristics of the excimeric state due to the close proximity of the three molecules of encapsulated pyrene. If this hypothesis was accurate, it would then be possible to monitor guest encapsulation and release using fluorescence spectroscopy by measuring the decrease in the excimer absorbance peak. Initial experiments proved that this hypothesis was incorrect and no fluorescence emissions corresponding to the excimer of pyrene were seen. This is likely due to the constrained interior of the hexamer which forces a stacked formation of the three pyrene molecules. Formation of the pyrene excimer requires a slightly staggered arrangement of pyrene molecules\textsuperscript{124} which is not possible while they are encapsulated.

The dimerization of anthracene is a well-studied photochemical reaction.\textsuperscript{125–127} It was theorized that the presence of three molecules of anthracene within the hexamer, and their close proximity in the constrained interior, would be an ideal environment for dimerization. The hope was that the dimerization would occur within capsule while still maintaining the encapsulation of the anthracene. A sample of the anthracene encapsulated hexamer was made using the melting method and dissolved in cyclohexane. The sample was measured by NMR and then irradiated in a Rayonet reactor for twenty minutes. The resulting NMR spectrum showed that the dimerization of anthracene did occur, however, no guest encapsulated peaks were seen indicating that the irradiation and subsequent dimerization of anthracene caused the encapsulated molecules to be expelled from the
hexamer (Figure 4.5). The result was not what was hoped for but was similar to the photodimerization of azobenzenes which was used to force guest release from dimeric capsules.\textsuperscript{128}

**Figure 4.5.** Anthracene encapsulated within the hexamer exits the capsule upon dimerization due to photochemical irradiation resulting in the cyclohexane-filled hexamer.

### 4.4. Conclusions

A natural consequence of the melting method is a large excess of unencapsulated guest molecules free in solution. A method for purifying the guest-filled capsules from the unencapsulated guest was desired for additional studies of the encapsulated complexes in solution. Size exclusion gel permeation chromatography takes advantage of the large size difference between the hexamers and the unencapsulated guests to isolate the guest-filled capsules. The nonpolar polystyrene polymer media does not interfere with the hydrogen bonding of the assembly and cyclohexane can be used as a mobile phase because the encapsulation complexes do not undergo guest exchange with solvent at appreciable rates at room temperature. Purified complexes were isolated with high recovery and upon evaporation of the cyclohexane these capsules could be dissolved in
other solvents for additional measurements. Heating of the purified capsules resulted in guest release as seen in prior experiments.

Compartmentalization experiments were also performed with the guest encapsulated hexamers. Bromine addition resulted in accelerated guest release in both cyclohexane and chloroform for the norbornene capsule but the guests that were still encapsulated showed no reaction with the bromine in solution. The hydrogenation experiment showed no guest release or reaction of the encapsulated norbornene during the course of the reaction. Both of these experiments are examples of the compartmentalization potential of the hexamer to isolate guests from possible reactants. Not all compartmentalization experiments were successful as illustrated by the fluorescence monitoring of the excimer of pyrene and the photochemical dimerization of encapsulated anthracene.

4.5 Experimental

4.5.1 General

Decylpyrogallolarene was synthesized as previously reported (section 3.8.2). GPC media was purchased from Bio-Rad. Cyclohexane was purchased from Fisher Scientific and used without further purification. All additional reagents and solvents were obtained from commercial sources and used without further purification. $^1$H NMR spectra for purification samples were recorded using a 500 MHz Brucker Avance spectrometer at 23°C and referenced to solvent. $^1$H NMR spectra for compartmentalization studies were recorded using a 400 MHz Varian spectrometer at 30°C unless otherwise stated. An
external lock was used for proteo cyclohexane samples in GPC purification experiments using a coaxial insert filled with deuterated benzene.

4.5.2 Purification

Bio-Rad Bio-Beads S-X3 was used for purification experiments. The beads are composed of a styrene divinylbenzene polymer with a 3% cross linkage and are 40-80 µm in size with a MW ≤ 2000. 50 g of the unswelled beads were initially swelled in carbon tetrachloride. When carbon tetrachloride proved to be unsuitable for the purification experiments the solvent was removed and the beads were then swelled in 200 mL of cyclohexane. The slurry of Bio-Beads in cyclohexane was loaded onto a column 31 cm in length and 2 cm in diameter. GPC samples were prepared by melting 16 mg of decylpyrogallolarene with 16 mg of guest with a heat gun until fully liquefied. The sample was allowed to cool and then dissolved in 3 mL of solvent. An ultrasonic bath at room temperature was used to dissolve the samples. The only exception to this procedure was that of norbornene in which the excess norbornene evaporated during heating with the heat gun. In this case 15 mg of norbornene was added to the sample prior to purification. Once dissolved in cyclohexane the sample was loaded onto the column containing the GPC media. Gravity filtration was used with cyclohexane as the solvent. Fractions were taken every two minutes and were, on average, 1.2 mL. The guest-filled capsules began to elute, on average, 58 minutes (34 mL) after loading and took 14 minutes (seven fractions or 8.4 mL) to completely elute from the column. Elution profiles were significantly broadened if the solubility of the capsule was low. A large volume of cyclohexane (> 200 mL) was flushed through the column after each purification run to
elute the guest molecule. NMR spectra were taken of the pure fractions in cyclohexane using a coaxial insert with a deuterated benzene lock. After NMR the samples were transferred to clean pre-weighed vials and the cyclohexane was allowed to evaporate yielding the pure guest-filled capsules.

4.5.3 Bromine Compartmentalization

16 mg of norbornene and 16 mg of decylpyrogallolarene were melted together using a heat gun. The sample was dissolved in 1 mL of deuterated chloroform or deuterated cyclohexane. An NMR spectrum was taken. 8 mg of norbornene was added to the sample and an additional NMR spectrum was taken. For samples measured in chloroform, 0.1 mL of bromine was diluted with 1 mL of deuterated chloroform. The bromine solution was added drop wise and NMR spectra were taken after each addition. After the unencapsulated norbornene was completely reacted deuterated methanol was added drop wise to disrupt the capsule and NMR spectra were taken after each addition. For samples measured in cyclohexane, 0.05 mL of bromine was dissolved in 0.5 mL deuterated cyclohexane. The bromine solution was added drop wise and NMR spectra were taken after each addition. After the unencapsulated norbornene was completely reacted ethyl acetate was added drop wise to disrupt the capsule. For the timed study of capsule stability after bromine addition an NMR measurement was recorded of the initial doped sample using a 600 MHz Varian spectrometer at 30ºC. Four drops of the bromine solution was added to the sample to completely react with the excess norbornene. NMR measurements were then taken every 10 minutes using a 600 MHz Varian spectrometer at 30ºC.
4.3.4 Hydrogenation

16 mg of norbornene and 16 mg of pyrogallolarene were melted together using a heat gun and allowed to cool. 8 mg of norbornene was added to the sample and then dissolved in 1 mL of deuterated cyclohexane. An NMR spectrum was taken. The sample was placed in a Schlenk tube and 4.5 mg of palladium on carbon (20%) was added. The Schlenk tube was sealed and evacuated and backfilled with nitrogen three times. The Schlenk tube was evacuated and a hydrogen balloon was inserted. After one hour the hydrogen balloon was removed and the sample was filtered through celite. An NMR spectrum was taken after filtration. An additional NMR spectrum was taken days later.

4.3.5 Pyrene Fluorescence Measurement

A pyrene encapsulated hexamer sample was made and then purified as specified above. The purified sample was diluted to 50 µM in cyclohexane. Two additional samples, one of pyrene in cyclohexane and one of decylpyrogallolarene in cyclohexane with no pyrene present, were made at the same concentration. Samples were measured using a Varian Cary Eclipse Fluorescence Spectrophotometer with an excitation wavelength of 317 nm.

4.3.6 Anthracene Photodimerization

An anthracene encapsulated hexamer sample was made and 8 mg was dissolved in 0.5 mL proteo cyclohexane. An NMR spectrum was taken using an external deuterated benzene lock. The NMR sample was then irradiated in a Rayonet reactor at 350 nm for twenty minutes. The sample was again measured by NMR.
Chapter 5: Lower Rim Functionalization

5.1 Introduction

The research presented in this dissertation thus far has focused on the ability of the pyrogallolarene hexamers to encapsulate guest molecules and the remarkable stability of these guest-filled capsules in solution. Disruption of the hydrogen-bonded assembly has been achieved both by heating, which causes guest exchange with solvent, and by addition of polar additives, which causes complete disassembly of the hexamer. An additional method for causing guest release was proposed which would use mechanical forces to pull apart the hexamer thereby breaking the hydrogen bonds that hold it together and releasing the encapsulated guests. Most chemical reactions are activated using thermal, photochemical, or electrochemical means but a fourth method, that of mechanochemistry, or the use of mechanical forces to affect chemical changes in molecules, is also possible. The use of mechanical forces to perform a chemical reaction has been mentioned previously in the case of the solvent-free grinding method published by Atwood which was shown to successfully synthesize pyrogallolarene hexamers. Mechanical forces can be used to form products or they can be used to break molecules apart.

Mechanochemistry is a burgeoning field, a large component of which is focused on polymer studies and applications for materials science. Today’s society is heavily reliant on polymers for everything from household items to military applications.
Creating new and better polymers is a constant challenge. A large area of research is focused on indicator polymers and self-healing polymers. Indicator polymers give an indication, e.g. a change in color or fluorescence, of increased stress prior to failure. Self-healing polymers can repair themselves after degradation on the molecular level has occurred. For these and other applications scientists are looking for ways in which to target bond breakage of polymers.

The use of mechanical force is a common method for testing the strength and resilience of polymeric materials and many studies focus on degradation at the molecular level. In fact the study of covalent bond breakage due to mechanical forces has been of interest for over 80 years. Mechanical forces cause homolytic cleavage of covalent bonds in polymers which typically results in chain scission of carbon-carbon bonds along the backbone of the polymer. Bond breakage has been shown to occur in the central region of the polymer because this is where the molecule experiences the greatest mechanically induced stress. The methods by which mechanical forces can be applied to the polymer are varied but one commonly used procedure is ultrasonication. Ultrasonication creates cavitation bubbles which collapse in on themselves creating areas of high pressure and temperature. Significant strain is experienced by polymers near collapsing cavitation bubbles because the end closest to the bubble is pulled towards the cavitation site at a faster velocity than the rest of the polymer. At a minimum molecular weight this strain can cause sufficient elongation along the polymer chain to result in bond breakage. Small polymers do not undergo chain scission, therefore, cleavage of polymers using ultrasonication sheer forces requires
that the polymers are above a certain molecular weight which is individually determined based on a variety of factors.\textsuperscript{133,134}

A new method for designing polymers which include mechanophores, small mechanically active molecules that are incorporated into polymers often as a target for bond breakage, have been a subject of interest.\textsuperscript{138} These molecules are considered weak links in the polymer backbone and are often comprised of small strained cyclic moieties.\textsuperscript{139–141} These strained structures preferentially undergo bond breakage often without complete scission of the polymer chain which gives the polymer more flexibility and increases resistance to stress. A few examples are described in the following section.

Most of these mechanophores result in covalent bond breakage which is a nonreversible process. The pyrogallololarene hexamer is held together by hydrogen bonds which are weak interactions and less force should be required to break hydrogen bonds than covalent bonds. If mechanical forces could be used to pull apart the hexamer by breaking the hydrogen-bonded network, while maintaining the covalently bonded structure, pyrogallololarene units would be able to reform hydrogen bonds with other units located elsewhere in the polymer allowing for a reversible bonding method which could have applications for self-healing polymers. Reversible cross-linking using hydrogen bonding in polymers has been shown to be effective in previous studies which support this hypothesis.\textsuperscript{142–144} Disruption of the capsule would also cause guest release and methods for monitoring encapsulation of guest molecules could be used for indication of polymer degradation. Pyrogallololarene hexamers form both in liquid and solid phases allowing for both solution phase studies, using ultrasonication, and solid phase studies.
The hexameric pyrogallolarene assembly was shown to be too small for sonication forces to have any effect on the structure by itself.\textsuperscript{113} Incorporation into a polymer would be necessary for mechanochemical studies. The polymer would need to be attached to the pyrogallolarene at the lower rim as the upper rim is involved in the hydrogen-bonded assembly of the hexamer. To this end, monofunctionalization of pyrogallolarene at the lower rim and subsequent modifications were attempted to append the molecules to a polymer.

\textbf{5.2 Mechanochemistry}

The design of polymers which will react in predictable ways to mechanical stress is the basis for the use of mechanophores. One unique example is that of benzocyclobutene (BCB). BCB undergoes an electrocyclic ring opening under both thermal and photochemical conditions. Under thermal or photochemical conditions \textit{cis}-BCB and \textit{trans}-BCB result in different products (\textit{E,E} or \textit{E,Z}-isomers) as expected by Woodward-Hoffman rules\textsuperscript{145} (Figure 5.1). However, when a single molecule of BCB was incorporated into the center of a polymer, targeted where the highest mechanical forces occur, and exposed to mechanical sheer forces both the \textit{cis} and \textit{trans} isomers resulted in the same \textit{E,E} isomeric product (Figure 5.1).\textsuperscript{146} This unique result illustrates the power of mechanical forces to break bonds in unexpected ways. The ring-opened product also allows for extension of the polymer chain by breaking the four-membered ring while maintaining the integrity of the polymer chain which adds additional flexibility to the polymer.
Another example of molecules targeted for bond breakage within polymers are gem-dihalocyclopropanes. These molecules are comprised of very strained cyclopropane rings with two halogen atoms bonded at the apex (Figure 5.2). These molecules break preferentially when exposed to stress forming allylic halides while maintaining the covalently bonded structure of the backbone of the polymer. Unlike the BCB polymers in which a single mechanophore was incorporated into the polymer, many cyclopropane units are found throughout the polymer in these studies. This results in many weak bonds that can be broken as the polymer is stressed allowing for increased flexibility without any chain scission. A recent publication regarding these polymers focused on a self-healing capability of these polymers. Dibromocyclopropanes were polymerized with polybutadiene as in previous reports. The allylic bromides that are
formed due to mechanically induced stress are able to undergo nucleophilic substitution to form crosslinks *in situ* with carboxylates present in the material. This crosslinking results in a material that is much stronger than the original polymer.\textsuperscript{148} In this case the consequence of mechanical stress on the polymer is actually a stronger material, not a degraded material (Figure 5.2).

![Diagram of crosslinking process](image)

**Figure 5.2.** *gem*-dibromocyclopropane functionalized polymers form allylic bromides under mechanical stress which can be crosslinked with carboxylates to form stronger crosslinked polymers.

Indicator polymers can also use mechanophores. These molecules have targeted bonds which result in a change in color or fluorescence when broken. One example of an indicating mechanophore is spiropyran, a well-studied molecular switch which undergoes electrocyclic ring opening to the merocyanine structure\textsuperscript{149} (Figure 5.3). Spiropyran is a colorless compound while merocyanine is brightly colored which allows for a colorimetric indicator of polymer stress. The force induced ring opening of spiropyran gives rise to a brightly colored material prior to the actual rupture of the backbone of the mechanophore containing polymer. The two forms of this molecular switch also have
distinctly different fluorescence spectra which allows for another method of monitoring distress in the material.\textsuperscript{150}

\textbf{Figure 5.3.} Colorless spiropyran (left) undergoes electrocyclic ring opening to the brightly colored merocyanine structure (right) upon activation with mechanical forces.

Another fluorescence study of material degradation involves tricinnamate polymers. Cinnamate monomers are fluorescent molecules which can undergo photochemically induced [2+2] cycloaddition to form cyclobutane rings. Cyclobutanes, as discussed previously, are good mechanophores because they will preferentially break when incorporated into polymers to relieve ring strain. In this case the cyclobutanes undergo an electrocyclic ring opening to reform the fluorescent cinnamate molecules (Figure 5.4) when mechanical forces are applied. This allows for fluorescent monitoring of the distressed regions of the polymer.\textsuperscript{141}

\textbf{Figure 5.4.} Electrocyclic ring opening of the cyclobutane ring upon activation with mechanical forces results in fluorescent cinnamate monomers.
These are just a few examples of self-healing polymers which actually become stronger upon exposure to mechanical stress and polymeric materials that have been synthesized with the purpose of indicating distress prior to complete cleavage of the material. Appending the pyrogallolarene to a polymer could allow for applications of indicator polymers as well as self-healing polymers by causing the breakage of the hydrogen-bonded hexamer upon exposure to mechanical forces. A related study was performed using atomic force microscopy (AFM) in which mechanical forces were used to pull apart hydrogen-bonded dimeric cavitands.\textsuperscript{27} Of course, there is the possibility that the hydrogen-bonding network of the pyrogallolarene would be strong enough to hold the hexamer together under stress resulting in bond breakage along the long chain foot instead. In some cases the combination of multiple weak interactions has been shown to break carbon-carbon bonds as illustrated by a study of brush-like polymers with high steric density. When these molecules were adsorbed onto a surface the steric repulsion caused extension of the backbone of the polymer and resulted in carbon-carbon bond cleavage.\textsuperscript{151,152} The pyrogallolarene hexamer is held together by 72 hydrogen bonds\textsuperscript{16} making a strong network of weak forces which hold the capsules together, but not all would have to break concurrently in order for a single pyrogallolarene molecule to be removed. As seen with the MS studies of hexameric pyrogallolarene in which the individual pyrogallolarene units dissociate one at a time,\textsuperscript{68} mechanically induced disassembly would also be most likely to fragment the hexamer by removal of individual subunits. The relatively low number of hydrogen bonds that would need to break for the
detachment of one molecule would likely be energetically more favorable than the breakage of a covalent bond. But testing the pyrogallolarene functionality within a polymer would be the only way to verify this hypothesis as mechanical forces have been shown to cause unexpected reaction products.

For these experiments each pyrogallolarene must have a single attachment point to the polymer to prevent crosslinking effects which could place undue stress on a single pyrogallolarene molecule in the hexamer (Figure 5.5). This single point attachment also allows for the pyrogallolarene hexamer to be centrally located in the polymer which is where the mechanical stress is the strongest. Therefore, methods for monofunctionalizing the lower rim of the pyrogallolarene molecule were investigated.

![Mechanical force induced disassembly of the pyrogallolarene hexamer.](image)

**Figure 5.5.** Mechanical force induced disassembly of the pyrogallolarene hexamer.

### 5.3 Lower-rim Functionalization

Extensive studies have been published on the modification of the resorcinarene base molecule. Using phenolic hydroxyl chemistry, modifications can be made to the upper rim of resorcinarene which allows for the formation of rigidified and deep cavitands. Upper rim chemistry is more difficult for pyrogallolarene due to the four
additional hydroxyl groups which is why deep cavitands are synthesized using resorcinarene instead of pyrogallolarene. Modifications to the lower rim of these molecules can be used to attach the cavitands to surfaces\textsuperscript{153,154} and to change the solubility of pyrogallolarene and resorcinarene. Shorter chain lengths are commonly used for crystallization while longer chain lengths are used for solution phase studies and cavitands soluble in water\textsuperscript{97,155,156} or fluorous solvents\textsuperscript{25} have been reported. In most cases the lower rim modifications are made to all four of the feet, because monofunctionalization of a single foot is very difficult, but a few cases of monofunctionalization have been reported.

\textbf{Scheme 5.1.} Methods for asymmetrical resorcinarene synthesis. Formation of a symmetric cavitand followed by selective reaction at a single foot, \textbf{A}. Formation of an asymmetrical cavitand during the initial synthesis using different aldehydes, \textbf{B}.

Functionalization of a single foot on the lower rim has been used to attach cavitands to a solid substrate for atomic force microscopy measurements\textsuperscript{27} and for
labeling purposes. There are two methods which have been used to monofunctionalize the lower rim. The first involves synthesis of the symmetrical tetrameric subunit followed by selective reaction of a single foot (Scheme 5.1, route A). The second involves synthesis of an asymmetrical subunit in which the identity of one foot is different than the other three. The first method was used with a resorcinarene with alkene terminated feet which was selectively epoxidized using *m*-chloroperoxybenzoic acid. The second method is more commonly found in literature in which three equivalents of a single aldehyde and one equivalent of a second aldehyde are added during the formation of the resorcinarene (Scheme 5.1, route B). This procedure results in a mixture of products including the desired monofunctionalized structure. Resorcinarenes with a single alcohol or double bond foot have been reported. Purification and further modification of the monofunctionalized product is performed with the hydroxyl groups of the resorcinarene protected, most often by pivylate protecting groups.

The only reported case of monofunctionalization of pyrogallolarene was by Rebek in 2007. He monofunctionalized the pyrogallolarene base molecule with pyrene and perylene molecules for FRET studies of the hexamer formation. The initial procedure that was attempted tried to use the same method for pyrogallolarenes as was used for resorcinarenes to yield a single alcohol on the foot of the pyrogallolarene. Unfortunately, due to the increased steric hindrance of the 12 hydroxyls on the upper rim of pyrogallolarene, as opposed to the eight hydroxyls of resorcinarene, a method to protect all 12 phenolic hydroxyls while leaving the lower rim hydroxyl intact proved to be difficult. Consequently a different method was used in which the pyrene and perylene
functionalities were appended to an aldehyde and used in direct synthesis of the pyrogallolarene. Purification by column chromatography of the protected pyrogallolarene afforded the monofunctionalized product. A monofunctional alcohol footed pyrogallolarene was synthesized in the Purse lab in an attempt to improve upon the synthesis reported by Rebek, however, purification of the single alcohol foot was prohibitively difficult as was differentiating the aliphatic and aryl OH groups based on reactivity. As a result other avenues for monofunctionalizing the lower rim of pyrogallolarene were investigated. The synthesis of an ester footed cavitand was also attempted but the identity of the product could not be confirmed either by NMR or MS.

5.4. Nitro-Footed Cavitands

The first method investigated for monofunctionalization involved the manufacture of a nitro-footed cavitand. This procedure followed the symmetric pyrogallolarene formation method with the intent of preferentially reducing a single nitro-foot to an amine. No aldehydes with an end terminated nitro functionality were found to be commercially available so various aldehydes with a terminal nitro group were synthesized.

Scheme 5.2. Synthetic route for formation of (4-nitro-phenyl)-propionaldehyde, 5.2.
(4-nitro-phenyl)-propionaldehyde, 5.2, was successfully synthesized by first nitrating 3-phenylpropanol, using nitric and sulfuric acids which form a nitronium ion that then undergoes electrophilic addition to the phenyl ring to form 5.1 (Scheme 5.2). The nitration is followed by a Swern oxidation of the alcohol to form the aldehyde needed for pyrogallolarene synthesis. In this mechanism oxalyl chloride and dimethylsulfoxide (DMSO) are reacted first to form the dimethylchlorosulphonium ion. Addition of the alcohol results in an alkoxy sulphonium ion. Upon addition of a base this intermediate is deprotonated resulting in a sulphonyl ylide. Intramolecular deprotonation of the α-carbon and elimination of dimethylsulfide resulted in the aldehyde product, 5.2 (Scheme 5.2). The nitro aldehyde was synthesized with 19% yield over two steps.

Scheme 5.3. Synthetic route for formation of pyrogallolarene, 5.3, using (4-nitro-phenyl)-propionaldehyde, 5.2.

The nitro aldehyde was used in pyrogallolarene synthesis (Scheme 5.3). The resulting product, 5.3, was a yellow solid that was not soluble in either MeOH or nonpolar chlorinated solvents. MS analysis determined that the product was successfully synthesized but the lack of solubility in nonpolar solvents made it unsuitable for the intended purpose and a new avenue was investigated.
Scheme 5.4. Synthetic route for formation of 6-nitrohexanal, \textit{5.5}.

The fact that the nitrated phenyl pyrogallolarene was insoluble in nonpolar solvents required for hexamer formation was likely due to the short rigid aldehyde chain. Therefore, a longer chain aliphatic molecule was investigated for nitration purposes. The synthesis of a nitrated aldehyde with a six carbon chain was attempted. This molecule was successfully produced by nucleophilic substitution of ethyl 6-bromohexanoate using sodium nitrite, which replaces the bromine with the nitro group resulting in product \textit{5.4}. In this case the nitration was followed by reduction of the ester to an aldehyde using diisobutylaluminum hydride (DIBAL-H) (Scheme 5.4).\textsuperscript{160} This nitrated aldehyde, \textit{5.5}, was synthesized with 6% yield over two steps. Pyrogallolarene synthesis was also attempted with this aldehyde. The resulting pyrogallolarene product was again not soluble in nonpolar solvents. As a result the desired solution phase hexameric studies were not possible. MS analysis could not confirm the identity of the product, likely due to a high salt concentration. This method was discarded in favor of a longer chain nitro-terminated aldehyde.
Scheme 5.5. Synthetic route for formation of 11-nitroundecanal, 5.7, and subsequent synthesis of nitro-footed pyrogallolarene, 5.8.

The synthesis of an eleven carbon chain aldehyde with a terminal nitro group was attempted. The synthesis of this molecule was initially attempted in the same manner as the hexanoate, using methyl 11-bromoundecanoate. Nucleophilic addition to 11-bromoundecanoate was successful; however, reduction with DIBAL-H yielded only the alcohol product and none of the desired aldehyde. A different method was attempted using 11-bromoundecanol. Initially a benzoyl protecting group was used so that the alcohol would not interfere with the nucleophilic addition of the sodium nitrite. Unfortunately the yield of the final product upon removal of the protecting group was very low which led to an attempt to nitrate the unprotected alcohol. This nitration using sodium nitrite was achieved with great success forming product 5.6. The alcohol was then oxidized to the aldehyde using a Swern oxidation. This product, 5.7, was
successfully synthesized with 18% yield over two steps (Scheme 5.5). The pyrogallolarene synthesis was performed with this aldehyde but the product, 5.8, (Scheme 5.5) proved to be difficult to isolate and purify. Column chromatography was used in an attempt to purify the product but this was deemed unsuccessful as determined by NMR. At this point the method for monofunctionalizing the pyrogallolarenes for polymer attachment using nitro footed cavitands was abandoned due to the poor solubility in nonpolar solvents and difficulty of isolation.

5.5 Thiol-ene reactivity

The next avenue investigated involved the “click-chemistry” thiol-ene reaction.\cite{161} Thiol-ene chemistry can be performed either thermally or photochemically\cite{162} and involves the addition of a thiol to a double bond by either a radical or an ionic mechanism. Thiol end-terminated polystyrene polymers are commercially available and could be directly coupled to the pyrogallolarene using a thiol-ene reaction. The possibility of an alkyne terminated pyrogallolarene was briefly considered for a thiol-yne reaction, however, it was determined that the alkyne would not survive the acidic reaction conditions needed to synthesize the pyrogallolarene. A symmetrical alkene footed pyrogallolarene, 5.9 (Scheme 5.6), was synthesized according to published procedures.\cite{110} The isolation of this product was more difficult than the alkane footed pyrogallolarene and required cooling overnight for crystals to form. Once the alkene footed pyrogallolarene had been synthesized thiol-ene reactions were tried with one equivalent of the thiol in an attempt to preferentially react a single alkene on the feet of pyrogallolarene.
Scheme 5.6. Thermal and radical thiol-ene reaction schemes using symmetric pyrogallolarene, 5.9.

The first attempt at a thiol-ene reaction used 2-aminoethanethiol hydrochloride under thermal conditions. AIBN was used as a catalyst and the reaction was heated to 80°C overnight (Scheme 5.6). The resulting product was not very soluble in CDCl$_3$ and what was soluble was determined to be unreacted starting material. Due to the solubility problems that had already been encountered with the nitro-footed pyrogallolarenes a different thiol was chosen, benzyl mercaptan, in an attempt to increase the solubility of the product. The $^1$H NMR of this product was promising and showed a decrease in the peaks of the terminal double bond indicating a reaction, however, the peaks corresponding to the hydroxyl hydrogens of the upper rim also decreased indicative of a side reaction. A third attempt using BOC-protected 2-aminoethanethiol under thermal conditions resulted in no definitive reaction with the double bond. Lastly, photochemical irradiation was attempted using DMPA as a radical initiator$^{162}$ with the BOC-protected 2-aminoethanethiol (Scheme 5.6). Incomplete reaction with the double bond was seen on the $^1$H NMR along with a decrease in the signal for the hydroxyl hydrogens. It is hypothesized that the twelve hydroxyl groups of the pyrogallolarene along the upper rim
interfere with the radical addition of the thiol to the double bond. A separate method for monofunctionalizing the lower rim of pyrogallolarene using olefin metathesis was being investigated at the same time as the thiol-ene chemistry. As the olefin metathesis method showed greater promise the thiol-ene reactions were abandoned.

5.6 Monofunctional foot

A third method was investigated for creating monofunctionalized pyrogallolarenes, this time using the method in which an asymmetrical pyrogallolarene is initially synthesized using two different aldehydes. In this case a single terminal double bond was desired and a reaction using three equivalents of undecylaldehyde and one equivalent of undecylenic aldehyde was performed according to published procedures.\(^\text{26}\)

The \(^1\)H NMR spectrum for the product, **5.10**, exhibited a 3:1 ratio of alkane to alkene feet but analysis by MS revealed that the resulting pyrogallolarene was the expected mixture of products with 0-3 double bonds on the lower rim (Scheme 5.7). Purification was not attempted at this point.

**Scheme 5.7.** Synthetic route for formation of pyrogallolarene with a single terminal double bond, **5.10**.
The single terminal alkene was needed for olefin metathesis. Olefin metathesis is a well characterized reaction using metal catalysts to exchange substituents of two olefins by breaking and then reforming the double bonds. The yield of the desired product is based on various factors including the characteristics of the alkenes and the identity of the catalyst. Primary alkenes result in good yields when reacted with acrylates using the Hoveyda-Grubbs catalyst (Scheme 5.8). Because of this characterization olefin metathesis was attempted using methyl acrylate and the pyrogallolarene 5.10. This reaction was successful resulting in a 57% yield of the metathesis product, 5.11 (Scheme 5.8).

Scheme 5.8. Synthetic route for olefin metathesis with methyl acrylate, 5.11.

Further reaction of the methyl acrylate-footed cavitand proved to be quite difficult. A reaction using nucleophilic thiol-ene chemistry was attempted with 2-BOC-aminoethanethiol, however, the base required for the reaction deprotonated the
hydroxyl and formed a purple precipitate. Heating without a base catalyst was also tried to no avail. Saponification was attempted using sodium hydroxide (NaOH) in water but the pyrogallolarene was not soluble. At this point the methyl acrylate footed compound was discarded in favor of a benzyl acrylate footed pyrogallolarene.

Benzyl acrylate was reacted with 5.10 using the Hoveyda-Grubbs catalyst for olefin metathesis as previously reported resulting in a 40% yield of the metathesis product, 5.12 (Scheme 5.9). This compound underwent hydrogenolysis with 20% palladium on carbon to remove the benzyl ether protecting group resulting in a carboxy footed pyrogallolarene, 5.13. This reaction also had the added benefit of hydrogenating the double bond remaining from the olefin metathesis reaction (Scheme 5.9). The carboxy footed pyrogallolarene was isolated with 89% yield though it was found to be insoluble in CDCl$_3$. Purification was attempted at this point with a diol column (see experimental) to separate the single carboxy-footed pyrogallolarene from the mixture, however, this proved to be unsuccessful as MS analysis showed the mixture of the 0-3 carboxy groups was still present.
Scheme 5.9. Synthetic route for olefin metathesis with benzyl acrylate, 5.12, and hydrogenolysis of the benzyl protecting group resulting in the carboxy-footed pyrogallolarene, 5.13.

Reaction of the carboxylic acid was attempted. Amine terminated polystyrene polymers are commercially available therefore peptide coupling reactions to form an amide bond were investigated. Peptide coupling using dicyclohexylcarbodiimide (DCC) was unsuccessful likely due to the poor solubility of the carboxy-footed
pyrogallolarene. Coupling with both pyBrOP and pyBOP were then attempted.\textsuperscript{167} The initial procedure called for Hunig’s base to be used, however, this strong base deprotonated the hydroxyls of the upper rim turning the solution a deep red color. The reaction was expectedly unsuccessful. Different possible bases with pKa’s below 9 were investigated. 2,6-lutidine (pKa 6.75) showed a slight color change when added to a solution of the carboxy-footed pyrogallolarene in MeOH indicating some deprotonation of the hydroxyls but addition of pyridine (pKa 5.25) did not result in a color change. This indicated that it did not deprotonate the phenolic hydroxyls and therefore most likely selectively deprotonated the carboxylic acid. Coupling with cyclohexylamine was not successful so the less sterically hindered benzylamine was used, which is also a better model for the amine terminated polymer (Scheme 5.10).

Scheme 5.10. Synthetic route for peptide coupling of 5.13 with benzylamine, using pyBOP.

This reaction appeared to be successful; however, standard silica gel purification methods did not isolate the product. As a result the analysis was done on a crude mixture.
When this reaction is performed with the amine terminated polymer, GPC purification can be used not only to separate the byproducts of the reaction from the product but to isolate the monofunctionalized pyrogallolarene from the mixture of pyrogallolarenes (zero, di, and tri substituted) which is still present. $^1$H, $^{13}$C, COSY, HSQC, and HMBC NMR studies were performed on the starting material, 5.13, and the product mixture. The carboxy-footed pyrogallolarene was not soluble in CDCl$_3$ so all measurements were made in MeOD. In the $^1$H NMR spectrum the benzylic CH$_2$ of the amide-footed pyrogallolarene overlapped with the methine CH at 4.3 ppm but HSQC NMR was used to show coupling of the protons to the two different carbons, the benzylic carbon at 44.2 ppm and the methine carbon at 35.3 ppm (Figure 5.6).

![Figure 5.6](image-url)

**Figure 5.6.** HSQC NMR for the product mixture showing the coupling of the methine hydrogen triplet at 4.3 ppm with the carbon at 35 ppm and the overlapping benzylic hydrogen with the benzylic carbon at 44 ppm.

HMBC NMR was used to show coupling of the benzylic CH$_2$ at 4.3 ppm to the amide carbon at 175.9 ppm. The amide carbon also showed coupling to hydrogens at 2.3 ppm which represent the CH$_2$ neighboring the carbonyl of the amide. There was also
coupling of protons at 2.3 ppm to a carbon at 177.8 ppm which corresponds to the carboxylic acid carbon and additional hydrogen coupling with a carbon at 175.5 ppm indicating that the desired amide compound is likely a minor product in the reaction (Figure 5.7).

![Figure 5.7. HMBC NMR for the product mixture showing the coupling of the benzylic hydrogens at 4.3 ppm with the amide carbon at 175.9 ppm. Additional coupling with the CH₂ hydrogens at 2.3 ppm is also seen. The CH₂ coupling with the carboxylic acid carbon at 177.8 ppm and additional coupling with a carbon at 175.5 ppm is also present.](image)

The benzyl group of the amide was not definitively identified using 2D spectroscopy but the protons of the phenyl group appear to be overlapping at 7.4-7.5 ppm in the ¹H NMR spectrum. Coupling with the benzylic carbon at 44 ppm on the HMBC supports this assertion. IR spectroscopy was used to differentiate the carboxylic acid and amide carbonyl stretches. The carboxy-footed pyrogallolarene had a peak at 1707.7 cm⁻¹ indicative of a carboxylic acid while the product mixture had an additional peak at 1634.2 cm⁻¹ indicative of an amide. All of these data suggest that the product was successfully synthesized, however, it is likely a minor product in the reaction mixture.
5.7 Conclusions

Mechanical activation of polymers and the resulting degradation is currently an area of extensive study. Modification of polymers which would be able to show increased flexibility and strength when exposed to mechanical stress are highly sought after for self-healing applications. Indicator polymers, which allow for spectroscopic measurement of increased stress prior to material failure, are also an important field of study. Pyrogallolarene hexamers could be useful mechanophores for both of these applications if they could be incorporated into polymers. For this to be possible, pyrogallolarenes must be attached to polymers at the lower rim because the upper rim is involved in the hydrogen bonding network which holds the hexamer together. A single point attachment is desired to most effectively translate mechanical forces to the hexamer.

Not many studies have been published on monofunctionalization of the lower rim of pyrogallolarene due to the many difficulties associated with this synthesis. Three different methods for monofunctionalizing the lower rim of pyrogallolarene were attempted. The first involved a symmetric nitro-footed cavitand. Problems with solubility for the pyrogallolarenes made from shorter chain aldehydes led to the synthesis of an eleven carbon chain aldehyde with a terminal nitro group. This molecule was difficult to purify and resulted in a low yield leading to the exploration of other methods for monofunctionalizing pyrogallolarene. These molecules were able to be synthesized but were not useful for the intended purpose. Other applications may be found to employ these molecules.
The second method used thiol-ene chemistry in an attempt to react a symmetric decylene-footed pyrogallolarene with thiols. These reactions were partially successful and could warrant further investigation. This line of research was suspended due to the more promising results of the third method, synthesis of an asymmetric pyrogallolarene with a single terminal double bond and reactions involving olefin metathesis which was shown to be successful with both methyl and benzyl acrylates. Further reactions with the methyl acrylate product proved unsuccessful but hydrogenolysis of the benzyl acrylate product successfully formed a carboxy-footed pyrogallolarene. Unfortunately, peptide coupling with this carboxy group has proven to be difficult due to the twelve hydroxyls of the upper rim. The pyBOP coupling procedure with benzylamine appeared to be successful in synthesizing the product but resulted in a small yield and poor purification. There are many additional peptide coupling reagents that could be used and one will likely result in a better yield than those tested so far. If a superior method for amide bond formation at the foot of the pyrogallolarene can be identified then polymers can be attached to the foot of the pyrogallolarene. Upon attachment to a polymer, GPC purification can be used to isolate the monofunctionalized pyrogallolarene. The monofunctionalized polymer attached pyrogallolarene can then be used for ultrasonication experiments to test the viability of mechanically induced disassembly of the capsule.
5.8 Experimental

5.8.1 General

All reagents and solvents were obtained from commercial sources and used without further purification. Diol columns contain covalently linked glycerol ester functionalized silica with terminal 1,2-diols that were purchased from Teledyne Isco. $^1$H NMR were recorded using a 500 MHz Brucker Avance spectrometer or a 400 MHz Varian spectrometer unless otherwise stated. Data for $^1$H NMR are recorded as follows: chemical shift ($\delta$, ppm), multiplicity (s = singlet, t = triplet, d = doublet, d of d = doublet of doublets, q = quartet, quint = quintet, m = multiplet, broad = broad, integration). $^{13}$C NMR were recorded using a 500 MHz Varian Spectrometer. 2D NMR were recorded using a 600 MHz Varian spectrometer. IR was performed using a Nicolet iS10 Thermo Scientific Spectrometer. MS was performed at the UC Riverside High Resolution Mass Spectrometry Facility.

5.8.2 Pyrogallolarene synthesis

General procedure: A solution of pyrogallol (10 g, 79.4 mmol) in ethanol (40 mL) and concentrated HCl (15 mL) was cooled to 0ºC under a N$_2$ atmosphere. The appropriate aldehyde (79.4 mmol) in ethanol (20 mL) was added drop wise to the solution over a period of two hours. The solution was then refluxed for 24 hours at 80ºC. After cooling the precipitate was filtered, washed with methanol, and recrystallized from boiling methanol to give pyrogallolarene.
(4-nitro-phenyl)-propylpyrogallolarene 5.3: Synthesized on a small scale, pyrogallol (0.7 g, 5.6 mmol), in 4 mL ethanol with 1.5 mL HCl, and (4-nitro-phenyl)propionaldehyde (1 g, 5.6 mmol) in 2 mL ethanol used. (0.4 g, 25%): yellow solid. MS (ESI+) calculated: 1149.07, found: 1149.3

11-nitroundecylpyrogallolarene 5.8: Synthesized on a small scale, pyrogallol (70 mg, 0.56 mmol), in 2 mL ethanol with 0.75 mL HCl, 6-nitrohexanal (120 mg, 0.56 mmol) in 1 mL ethanol used. Filtration and crystallization did not work instead a column was run in cyclohexane:ethyl acetate, product still contained impurities (15 mg, 8%): dirty yellow solid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta = 8.81$ (s, 4H, OH), 7.49 (s, 4H, OH), 6.90 (s, 4H, OH), 6.85 (s, 4H, H$_{arom}$), 4.39 (t, 12H, CH and CH$_2$-NO$_2$), 2.32-2.15 (m, 8H, CH-
\( \text{CH}_2 \), 2.06 (quint, \text{CH}_2-\text{CH}_2-\text{NO}_2), 1.65 (broad, \text{CH}_2-\text{CH}_2-\text{CH}_2-\text{NO}_2) \ 1.48-1.27 (m, 48\text{H}, (\text{CH}_2)_6).

Decylenepyrogallolarene 5.9: Undecylenic aldehyde (13.34g, 79.4 mmol) used. Cooling overnight was required for successful filtration of the product. (12.3g, 56%): off-white solid. \( ^1\text{H} \) NMR (500 MHz, CDCl\(_3\)) \( \delta = 8.81 \) (s, 4\text{H}, OH), 7.49 (s, 4\text{H}, OH), 6.91 (s, 4\text{H}, OH), 6.85 (s, 4\text{H}, H_{\text{arom}}), 5.85 (m, 4\text{H}, \text{CH}_2-\text{CH}=\text{CH}), 4.99 (d of d, 8\text{H}, \text{CH}=\text{CH}), 4.39 (t, 4\text{H}, \text{CH}), 2.32-2.15 (m, 8\text{H}, \text{CH}-\text{CH}_2), 2.06 (q, \text{CH}_2-\text{CH}=\text{CH}), \ 1.48-1.27 (m, 48\text{H}, (\text{CH}_2)_6).

Asymmetric decylene and decylpyrogallolarene 5.10: Undecanal (10.13 g, 59.5 mmol) and undecylenic aldehyde (3.34 g, 19.8 mmol) used. Cooling overnight was required for successful filtration of the product. (17.4g, 79%, mixture): off-white solid.
$^1$H NMR (500 MHz Varian, CDCl$_3$) δ = 8.78 (s, 4H, OH), 7.46 (s, 4H, OH), 6.89 (s, 4H, OH), 6.85 (s, 4H, H$_{arom}$), 5.85 (m, 1H, CH$_2$-CH=CH), 4.99 (d of d, 2H, CH=CH), 4.39 (t, 4H, CH), 2.32-2.15 (m, 8H, CH$_2$-CH$_2$), 2.06 (q, CH$_2$-CH=CH), 1.48-1.27 (m, 60H, (CH$_2$)$_6$ and (CH$_2$)$_9$), 0.89 (t, 9H, CH$_3$). MS (ESI+) calculated: 1111.53, found: 1114, 1112, 1110, 1108.

5.8.3 Nitrated aldehydes

Nitration to form 3-(4-nitro-phenyl)propanol 5.1. Alcohol (2 g, 14.7 mmol) was cooled to 0ºC. Nitric acid (HNO$_3$, 0.6 mL, 14.7 mmol) was added to sulfuric acid (H$_2$SO$_4$, 6 mL) and added drop wise to the alcohol. Mixture was stirred at 0ºC for one hour and then poured over ice. Product was extracted three times with DCM, washed with brine, and dried with MgSO$_4$. Solvent was evaporated and a column was run with DCM:MeOH. (0.53 g, 20%): yellow liquid. $^1$H NMR (500 MHz, CDCl$_3$) δ = 8.09 (d, 2H, H$_{arom}$), 7.35 (d, 2H, H$_{arom}$), 3.65 (t, 2H, CH$_2$-OH), 2.79 (t, 2H, CH$_2$-Ph), 2.55 (broad, 1H, OH), 1.87 (m, 1H, CH$_2$-CH$_2$-CH$_2$).

Oxidation to form 3-(4-nitro-phenyl)propionaldehyde 5.2. Oxalyl chloride (1.05 mL, 12.3 mmol) in 30 mL anhydrous DCM was cooled to -78ºC under a nitrogen atmosphere. DMSO (1.74 mL, 24.6 mmol) was added drop wise. After five minutes the
nitrated alcohol (2 g, 11.16 mmol) was added drop wise. The reaction was stirred for one hour after which triethylamine (Et$_3$N, 12 mL) was added. Reaction was allowed to warm to room temperature overnight. Reaction was quenched by pouring into water followed by extraction with DCM. The DCM layer was washed four times with water and dried with Na$_2$SO$_4$. Solvent was evaporated yielding the product. (1.9 g, 96%): yellow solid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta = 9.85$ (s, 1H, CHO), 8.09 (d, 2H, H$_{arom}$), 7.35 (d, 2H, H$_{arom}$), 3.05 (t, 2H, CH$_2$-CHO), 2.82 (t, 2H, CH$_2$-Ph).

\[
\text{O}_2\text{N} - \text{CH}_2 - \text{CH}_2 - \text{CHO} - \text{O}
\]

Nitration to form ethyl 6-nitrohexanoate 5.4. A 0.1 M solution of ester (1 g, 4.4 mmol) in anhydrous DMF (45 mL) was made under a N$_2$ atmosphere. Sodium nitrite (NaNO$_2$, 0.47 g 6.7 mmol) was added. Reaction was stirred at room temperature for four hours then quenched by pouring over ice. The product was extracted three times with diethyl ether and dried with MgSO$_4$. Solvent was evaporated and a column was run in hexanes:EtOAc to yield the pure product. (0.225 g, 27%): yellow solid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta = 4.40$ (t, 2H, CH$_2$-NO$_2$), 4.15 (q, 2H, CO-CH$_2$-CH$_3$), 2.35 (t, 2H, CH$_2$-CH$_2$-CO), 1.90 (quint, 2H, CH$_2$), 1.68 (quint, 2H, CH$_2$), 1.50 (m, 2H, CH$_2$), 1.29 (t, 3H, CH$_2$-CH$_3$),

\[
\text{O}_2\text{N} - \text{CH}_2 - \text{CH}_2 - \text{CH}_2 - \text{CHO}
\]

Reduction to form 6-nitrohexanal 5.5. A solution of ester (223 mg, 1.2 mmol) in 9 mL anhydrous DCM was cooled to -78ºC under a N$_2$ atmosphere. Diisobutylammonium
hydride (DIBAL-H, 1.5 mL) was added. After one hour the reaction was quenched with HCl (10 mL, 0.2 M). The product was extracted twice with DCM, washed with water, and dried with MgSO₄. Solvent was evaporated and a column was run in hexanes:EtOAc to yield the pure product. (40 mg, 23%): yellow solid. ¹H NMR (500 MHz, CDCl₃) δ = 9.80 (s, 1H, CHO), 4.40 (t, 2H, CH₂-NO₂), 2.50 (t, 2H, CH₂-CHO), 1.90 (quint, 2H, CH₂), 1.68 (quint, 2H, CH₂), 1.50 (m, 2H, CH₂).

Nitration to form 11-nitroundecanol 5.6. A 0.1 M solution of alcohol (0.5 g, 1.2 mmol) in anhydrous DMF (20 mL) was made under a N₂ atmosphere. Sodium nitrite (NaNO₂, 0.21 g 3 mmol) was added. Reaction was stirred at room temperature for four hours then quenched by pouring over ice. The product was extracted three times with diethyl ether and dried with MgSO₄. Solvent was evaporated and a column was run in hexanes:EtOAc to yield the pure product. (0.19 g, 45%): yellow solid. ¹H NMR (500 MHz, CDCl₃) δ = 4.40 (t, 2H, CH₂-NO₂), 3.67 (t, 2H, CH₂-OH), 2.05 (quint, 2H, CH₂-CH₂-NO₂), 1.57 (quint, 2H, CH₂-CH₂-OH), 1.44-1.27 (m, 14H, (CH₂)₇), 1.25 (broad, 1H, OH).

Oxidation to form 11-nitoundecanal 5.7. Oxalyl chloride (0.22 mL, 2.6 mmol) in 8 mL anhydrous DCM was cooled to -78°C under a nitrogen atmosphere. DMSO (0.36 mL, 5.1 mmol) was added drop wise. After five minutes the nitrated alcohol (0.5 g, 2.3 mmol) was added drop wise. The reaction was stirred for one hour after which
triethylamine (Et$_3$N, 3 mL) was added. Reaction was allowed to warm to room temperature overnight. Reaction was quenched by pouring into water followed by extraction with DCM. The DCM layer was washed four times with water and dried with Na$_2$SO$_4$. Solvent was evaporated and a column was run in hexanes:EtOAc yielding the product. (0.11 g, 23%): yellow solid. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ = 9.76 (s, 1H, CHO), 4.40 (t, 2H, CH$_2$-NO$_2$), 2.45 (t, 2H, CH$_2$-CHO), 2.05 (quint, 2H, CH$_2$-CH$_2$-NO$_2$), 1.65 (quint, 2H, CH$_2$-CH$_2$-CHO), 1.44-1.27 (m, 12H, (CH$_2$)$_6$).

5.8.4 Thiol-Ene reactions

General procedure for thermal thiol-ene reactions: Solvent was degassed by bubbling nitrogen gas through it for one hour. 1.2 equivalents of the chosen thiol (0.54 mmol) was added to a solution of decylenepyrogallolarene (5.9, 0.5 g 0.45 mmol) and AIBN (37 mg, 0.23 mmol) in 3.5 mL chlorobenzene (degassed). The solution was heated at 80ºC for 24 hours and then cooled. Solvent was evaporated and crude $^1$H NMR was taken.

Procedure for photochemical thiol-ene reactions: A 0.5 M solution of decylenepyrogallolarene (5.9, 0.5 g, 0.45 mmol) in CHCl$_3$ was made in a quartz round bottom flask. 1.2 equivalents of BOC-protected aminoethanethiol (61 µL, 0.54 mmol) was added along with 10 mg DMPA. The solution was then irradiated in a Rayonet reactor at 350 nm for three hours. Solvent was evaporated and crude $^1$H NMR was taken.

5.8.5 Lower-rim monofunctionalization

General procedure for olefin metathesis: Solvent was degassed by bubbling nitrogen gas through it for one hour. A solution of pyrogallolarene (1 g, 0.899 mmol) was
dissolved in 10 mL degassed DCM. 5 molar equivalents of the specified acrylate was dissolved in 5 mL degassed DCM and added to the pyrogallolarene solution. 2.5 mol % (14 mg) Hovedya-Grubbs catalyst was added to the solution and stirred at 35°C for five hours. Reaction was stopped after five hours and solvent was evaporated. A column was run in DCM:MeOH.

Methyl acrylate olefin metathesis 5.11: Methyl acrylate (0.39, 4.5 mmol) was used. (0.6 g, 57%, mixture): brown solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.75\) (s, 4H, OH), 7.45 (s, 4H, OH), 6.95 (m, 1H, CH=CH), 6.86 (s, 4H, OH), 6.82 (s, 4H, H\(_{arom}\)), 5.8 (d, 1H, CH=CH), 4.35 (t, 4H, CH), 3.70 (s, 3H, CO-CH\(_3\)), 2.32-2.15 (m, 8H, CH-CH\(_2\)), 1.57 (broad, CH\(_2\)-CH=CH), 1.48-1.27 (m, 60H, (CH\(_2\))\(_6\) and (CH\(_2\))\(_9\)), 0.85 (t, 9H, CH\(_3\)).
Benzyl acrylate olefin metathesis 5.12: Benzyl acrylate (0.73, 4.5 mmol) was used. (0.44 g, 40%, mixture): brown solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 8.75\) (s, 4H, OH), 7.45 (s, 4H, OH), 7.4-7.3 (m, 5H, Ph), 7.0 (m, 1H, CH=CH), 6.86 (s, 4H, OH), 6.82 (s, 4H, H\(_{\text{arom}}\)), 5.85 (d, 1H, CH=CH), 5.15 (s, 2H, CH\(_2\)-Ph), 4.35 (t, 4H, CH), 2.29-2.15 (m, 8H, CH-C\(_2\)H), 1.57 (broad, CH\(_2\)-CH=CH), 1.48-1.27 (m, 60H, (CH\(_2\))\(_6\) and (CH\(_2\))\(_9\)), 0.86 (t, 9H, CH\(_3\)).

Hydrogenolysis reaction 5.13: Benzyl protected pyrogallolarene (5.12, 0.4755g, 0.38 mmol) was dissolved in 10 mL MeOH. Palladium on carbon (20%, 96 mg) was added to the solution. The flask was evacuated and a balloon containing hydrogen gas was added. After one hour the balloon was removed and the solution was filtered through celite. The solvent was evaporated to yield the product. (0.39 g, 89%, mixture): brown
solid. $^1$H NMR (400 MHz, MeOD) $\delta = 6.76$ (s, 4H, H$_{arom}$), 4.31 (t, 4H, CH), 2.26 (t, 2H, CH$_2$-COOH), 2.14 (q, 8H, CH-CH$_2$), 1.59 (m, CH$_2$-CH$_2$-COOH), 1.45-1.22 (m, 60H, (CH$_2$)$_6$ and (CH$_2$)$_9$), 0.91 (t, 9H, CH$_3$). $^{13}$C NMR (500 MHz Varian, CDCl$_3$) $\delta = 177.801, 140.95, 134.39, 126.20, 114.01, 35.37, 35.15, 34.79, 33.17, 30.93, 30.83, 30.69, 30.59, 30.38, 29.31, 26.22, 23.83, 14.64. IR (cm$^{-1}$): 3300.7, 2920.8, 2851.4, 1707.7, 1614.2, 1465.7, 1297.9, 1115.7, 1089.6. MS (ESI+) calculated: 1157.75, found: 1114, 1158, 1202, 1246.

Peptide Coupling Procedure: Carboxy-footed pyrogallolarene (5.13, 0.1g, 0.086 mmol) was dissolved in 0.5 mL DCM using 10 drops (enough to solubilize 5.13) of EtOAc under a nitrogen atmosphere. pyBOP (54.1 mg, 0.1 mmol) was added followed by pyridine (13.9 $\mu$L, 0.17 mmol). Benzyamine (10.4 $\mu$L, 0.095 mmol) was added after 10 minutes and reaction was left at room temperature for two hours. Reaction mixture was acidified with HCl and the solvent was evaporated. Silica gel column chromatography was performed using DCM:MeOH. Purification did not successfully isolate the product.
Chapter 6: Conclusions and Future Work

The discovery of hexameric assemblies of resorcinarene and pyrogallolarene allowed for the encapsulation of larger and more numerous guests than had previously been possible in cavitands based on the resorcinarene platform. These hexameric assemblies are the subject of continuing research in solid state and in gaseous phase as well as in solution due to their ability to self-assemble and fully encapsulate small molecules.

The solvent-free melting method developed by the Purse lab has been shown to be a robust technique for loading guests into the interior of the pyrogallolarene hexamers. A large variety of guests have been shown to be encapsulated including some that have polar functionalities. Aromatic and aliphatic molecules are particularly good guests and result in high occupancy and kinetic stability in many cases. The melting method allows for loading of guests under one set of conditions and measurement of the resulting complexes under a different set of conditions. The kinetically trapped, guest-filled hexamers were studied using NMR to determine the effect of both guest and solvent on the exchange rates of the capsules.

The pyrene-filled hexamer showed unique stability in many solvents which corresponded to a loss in symmetry due to the complementary fit of the guest within the interior of the host as shown by additional splitting of the $^1$H NMR peaks for both host and guest. In all other cases studied the encapsulated molecules, be it guest or solvent,
tumbled rapidly within the interior. Pyrene was also the only guest molecule that could be loaded into the interior of the hexamer by heating in CCl$_4$ which is the only case studied in which guest-filled hexamers are present at equilibrium. In all other cases solvent-filled hexamers predominate. The effect of solvent on the stability of the hexamers was investigated using pyrene encapsulated hexamers. Expectedly, larger and more bulky solvents resulted in longer exchange with encapsulated guest molecules as a larger opening was required for the exchange of guest for solvent.

The effect of structural differences of the guest molecules themselves was also studied. Larger guests and those with the greatest deviations from planarity required the longest exchange times with solvent, again due to the larger openings in the hexamer which would be required for guest exchange with solvent. Small structural changes had large effects on the stability of the guest as evidenced by fluoranthene and pyrene which are structural isomers yet have significantly different exchange rates in both CDCl$_3$ and CCl$_4$. Many of the cases studied showed peaks on the $^1$H NMR corresponding to capsules of mixed occupancy containing both guest and solvent molecules that formed as intermediates during the exchange process. In some cases, e.g. anthracene, mixed occupancy capsules are no longer seen in larger solvents indicating that larger, bulkier solvents are not as easily coencapsulated with guests.

For those guest-filed hexamers that were sufficiently kinetically stable in cyclohexane, purification was performed using size-exclusion GPC to separate the hexamers from the excess guest free in solution. The polystyrene polymer of the GPC media and the nonpolar cyclohexane mobile phase did not interfere with the hydrogen-
bonding network which holds the hexamers together allowing for the isolation of the guest-filled hexamers while maintain the integrity of the capsules.

The ability of the hexameric assembly to sequester encapsulated guests from reagents in the bulk solution was examined for chemical compartmentalization applications. Bromination and hydrogenation of norbornene was performed on samples in which both encapsulated and unencapsulated norbornene were present. The unencapsulated norbornene reacted in both experiments but no reaction occurred when norbornene was encapsulated within the hexamer. The bromine in solution did cause increased guest release of encapsulated norbornene but there was no addition to the double bond while still encapsulated. Dimerization of anthracene was attempted within the hexamer; however, this caused the guests to be released from the capsule. Further studies of the chemical compartmentalization ability of the pyrogallolarene hexamer would be valuable. It has already been shown to sequester guest molecules from reagents in solution but the usefulness as a mini reaction chamber is so far unknown. The potential for use in reaction control is an aspect that should be studied further.

Lastly monofunctionalization of the pyrogallolarene host molecule was attempted. The symmetric nitro-footed pyrogallolarenes were successfully synthesized; however, the poor solubility of these compounds in nonpolar solvents made them unsuitable for the solution phase hexameric studies which were the ultimate goal of this project. The pyrogallolarene with terminal nitro groups on an eleven carbon chain foot had better solubility than the shorter chain nitro pyrogallolarenes and could be useful for further functionalization if a method for purification could be identified. The thiol-ene chemistry
with the symmetric double bond terminated pyrogallolarenes showed promise but was
discarded in favor of the olefin metathesis chemistry. Further study of the thiol-ene
chemistry would be beneficial as modifications to the feet of pyrogallolarene are quite
difficult and this may be a method for adding different functionalities to the lower rim.
The olefin metathesis of the mono-ene footed pyrogallolarene was very successful as was
the hydrogenolysis of the benzyl ether. The peptide coupling appears to have been
marginally successful, however, purification and isolation of the product would need to
be perfected. Additional peptide coupling reagents should be attempted to increase the
yield of the desired product. When using polymers for the peptide coupling the
purification can be used with GPC to isolate the mono-polymer attached pyrogallolarene.
Upon isolation of this product the melting method can be performed with the polymer
appended pyrogallolarene to form guest encapsulated hexamers. Purification of these
capsules can be performed using GPC and then solution phase mechanochemical studies
can be executed using sonication to determine if mechanical forces can be used to cause
guest release in pyrogallolarene hexamers.
References


(32) The Nobel Prize in Chemistry 1905


Appendix A

Spectra with labeled peaks used for kinetics measurements and sample kinetics plots

Anthracene in cyclohexane

Anthracene in carbon tetrachloride
Fluoranthene in cyclohexane
Fluoranthene in chloroform

Fluoranthene in carbon tetrachloride

172
Fluorene in cyclohexane
Fluorene in chloroform

Fluorene in carbon tetrachloride
Norbornene in cyclohexane
Norbornene in chloroform

Norbornene in carbon tetrachloride

176
23°C

37°C

50°C

70°C
90°C

Pyrene in cyclohexane
Pyrene in dichloromethane $D_3$ to solvent filled exchange

Pyrene in chloroform $O_h$ to $D_3$ configuration
Pyrene in chloroform $D_3$ to solvent filled exchange
Pyrene in carbon tetrachloride $O_h$ to $D_3$ configuration

Pyrene in carbon tetrachloride $D_3$ to solvent filled exchange
Pyrene in benzene
Pyrene in toluene

Pyrene in xylenes

183
Pyrene in mesitylene
Appendix B

Stacked NMR spectra for bound guests showing time dependent configuration changes and guest exchange with solvent.

Anthracene in cyclohexane (23°C)

Anthracene in CDCl₃ (23°C)
Anthracene in CCl$_4$ (23°C)

Biphenyl in CDCl$_3$ (23°C)

Biphenyl in CCl$_4$ (23°C)
Fluoranthene in cyclohexane (70°C)

Fluoranthene in CDCl₃ (23°C)

Fluoranthene in CCl₄ (50°C)
Fluorene in cyclohexane (50°C)

Fluorene in CDCl₃ (23°C)

Fluorene in CCl₄ (23°C)
Naphthalene in CDCl$_3$ (23°C)

Naphthalene in CCl$_4$ (23°C)

Norbornene in cyclohexane (50°C)
Norbornene in CDCl$_3$ (23°C)

- $t = 130\text{h}$
- $t = 81\text{h}$
- $t = 32\text{h}$
- $t = 7\text{h}$
- $t = 0$

Norbornene in CCl$_4$ (23°C)

- $t = 1440\text{h}$
- $t = 1200\text{h}$
- $t = 700\text{h}$
- $t = 338\text{h}$
- $t = 72\text{h}$
- $t = 0$

Pyrene in cyclohexane (70°C)

- $t = 74\text{h}$
- $t = 36\text{h}$
- $t = 15\text{h}$
- $t = 8\text{h}$
- $t = 4\text{h}$
- $t = 2\text{h}$
- $t = 0$
Pyrene in \( \text{CD}_2\text{Cl}_2 \) (50˚C)

Pyrene in \( \text{CDCl}_3 \) (\(a = 23˚C\), \(b = 70˚C\))

Pyrene in \( \text{CCl}_4 \) (\(a = 70˚C\), \(b = 150˚C\))

191
Pyrene in C₆D₆ (23°C)

Pyrene in toluene-d₈ (23°C)

Pyrene in xylenes (23°C)
Pyrene in mesitylene (50°C)