CAPSULES AND CAVITANDS: CONCAVE MOLECULES BUILT ON THE CYCLOTRIBENZYLENE (CTB) SCAFFOLD

A Thesis
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By

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Molecules possessing large, enforced concave surfaces are fairly prevalent in naturally occurring systems, but there are relatively few synthetic molecules that share these characteristics. Cyclotribenzylenes (CTBs) and cryptophanes are examples of synthetic molecules that meet these criteria and are also lend themselves to facile functionalization to create new platforms with which to explore recognition and supramolecular chemistry.

A series of $C_3$-symmetric, pyridyl-substituted, extended cavity CTBs have been synthesized with the intent of exploring larger self-assembled molecular moieties and cavitand-containing coordination polymers through the exploitation of labile metal-pyridine bonds, with the strategic interest of incorporating an inherently chiral CTB ligand to explore the effect of the shape and chirality on the potential self-assembled aggregates. Reaction of these molecules with organic carboxylic acids has also provided nearly isostructural materials from acetone and MeOH, two solvents having opposite hydrogen bonding characteristics.

Additionally using the CTB scaffold, cyclotrianisidines ((+/−)-CTAs), an amine functionalized CTB, have been synthesized—both $C_3$ symmetric and $C_1$ symmetric—using a novel one-step method, avoiding the previously reported tedious and expensive
synthetic route to the useful CTA supramolecular scaffold. The synthesis and characterization of CTAs of various symmetry and numbers of amino functional groups for future use as ligands is also explored and discussed.

Cryptophanes, molecules consisting of two bridged CTBs, have also been synthesized bearing endohedral and exohedral functional groups through the use of \( m \)-xylyl bridges and their derivatives. The introduction of interior pyridine functionalization—using bridges derived from 2,6-lutidine—have led to the observation of a stable, ‘imploded’ conformation of a cryptophane—the first reported in organic solvent at room temperature. These studies shed light on the conformational properties of cryptophanes in the context of other CTB containing molecules, and the ability of cryptophanes to selectively encapsulate substrates. Other approaches to incorporate nitrogen heteroatoms into cryptophane molecules are also highlighted within this thesis.

Lastly, the utility of \( m \)-xylyl bridges has also been exploited to functionalize the exterior of cryptophanes through the synthesis and characterization of a water soluble cryptophane bearing six exohedral carboxylic acid moieties. The synthesis and isolation of the \( \text{syn} \) and \( \text{anti} \) diastereomers of has been achieved and is described herein.
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$$ (+/-)-3.3 \subset \text{EtOAc} \cdot \text{EtOAc} \text{ all result in a mixture of } CC \text{ and } CS$$


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<td>1D</td>
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</tr>
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<td>2D</td>
<td>Two dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>Three dimensional</td>
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<tr>
<td>BTC</td>
<td>1,2,4,5-Benzene Tetracarboxylic Acid</td>
</tr>
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<td>Coordination Polymer</td>
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<td>Pentamethylocyclopentadienyl cation</td>
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<td>Cyclotrianisidine</td>
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<td>K⁺</td>
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CHAPTER 1: Introduction

1.1. Molecular Containers in Supramolecular Chemistry

Supramolecular chemistry, or the ‘chemistry beyond the molecule’\(^1\), studies the structures and functions of molecules based on intermolecular interactions—the non-covalent interaction of two or more chemical entities. Non-covalent interactions are the basis by which nature performs highly specific tasks such as protein folding, enzyme substrate binding, the assembly of protein complexes, genetic transcription, and cell recognition, to name a few. The manipulation of chemical structural features to take advantage of non-covalent interactions—hydrogen bonding, \(\pi-\pi\) stacking, hydrophobic effects, and metal ligand interactions, for example—within a chemical architecture can allow for artificially made receptor molecules to bind substrates strongly and selectively. To accomplish this task, size, shape, and binding site complementarity must be considered. This concept is an extension of Emil Fisher’s ‘lock and key’ theory which describes the specific interaction of an enzyme and a substrate based upon the complementary structures of the two components.\(^2\) Embracing the inspiration provided by nature, Donald J. Cram,\(^3\) Jean-Marie Lehn,\(^1\) and Charles J. Pedersen\(^4\) developed molecular host molecules with “structure-specific interactions of high-selectivity” and were jointly awarded the Nobel Prize in Chemistry in 1987 for their pioneering work.
Designing and synthesizing molecular compounds to mimic and study the principles of molecular recognition phenomena has led to the development of synthetic ‘molecular containers,’\(^5\) a class of molecules that have had a sizeable impact in the supramolecular chemistry community. As the name implies, molecular containers are designed to contain and/or store guests based on attributes such as charge,\(^5\) size and shape,\(^7,8,9\) and chirality.\(^10,11\) The ability of container-like hosts to discriminate between guests with a high degree of selectivity suggests possible uses as micro-reaction vessels or catalysts,\(^12\) molecular (drug) delivery/transport-type systems,\(^13\) molecular storage or separation agents,\(^14\) and as environments within which to study weak intermolecular interactions. Nature exquisitely employs molecular containers in a similar capacity; examples such as viral capsids,\(^15\) Ferritin,\(^16\) and the tobacco mosaic virus (TMV),\(^17\) provide inspiration to the synthetic chemist (Figure 1.1). These complex, nanometer-

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**Figure 1.1.** Nature provides us with inspiration for the design of useful molecular containers, including a) the tobacco mosaic virus\(^17\) (300 nm x 15 nm), b) Ferritin\(^16\) (12 nm diameter), and c) a viral capsid\(^15\) (66 nm diameter). (All figures reproduced from citations with permission)
scale assemblies are sustained by weak non-covalent interactions and/or “mechanical bonds,” and non-natural molecular containers should be capable of performing related functions. The evolution of the chemical complexity and internal volumes of non-natural molecular containers can be seen through the work of Collet’s elegant cryptophanes (1981), Cram’s (hemi)carcerands (1985), Rebek’s (1993), Fujita’s (1995), Raymond’s (1998), and Atwood’s (1997) size and shape selective self-assembling capsules and species assembled via dynamic covalent chemistry, among the now many, many examples (Figure 1.2).

Cryptophanes and (hemi)carcerands are examples of molecular containers constructed of covalent chemical bonds. The synthesis of these types of containers typically involves the stepwise formation of covalent chemical bonds, and, like all

![Figure 1.2. Molecular capsules can be covalently synthesized as portrayed by a) Collet’s cryptophanes and b) Cram’s (hemi)carcerands, or through non-covalent self-assembly, as shown by c) Rebek’s, d) Raymond’s, and e) Atwood’s self-assembled containers. All of these species demonstrate molecular encapsulation, as shown in the ball and stick or space filling illustrations.](image)
traditional chemical syntheses, there lies the inherent limitation in that the more complex the molecule, the more synthetic steps that are required, and the lower the overall yield of the synthesis, limiting the yield of product and directly impacting their practical or commercial utility. Self-assembled capsules, however, are sustained by individually weak, but collectively strong, intermolecular interactions guided by the principles of self-assembly.\textsuperscript{26,27} Self-assembly concerns the ability of a molecule to recognize itself, or complimentary partners, via non-covalent interactions, and allows for the aggregation and organization of multiple species into larger, more complex structures of some stability. Self-assembled systems require the synthesis of only the smaller, simpler components of the desired final architecture. The components possess a molecular, shape, size, and binding site pattern—a blueprint, of sorts—to direct the formation of the aggregate, which can exhibit behavior that none of the individual components possesses, behaviors such as molecular recognition.

The formation of a molecular capsule results in what Cram calls the ‘inner phase’\textsuperscript{3} reaction environment. The advantage of a molecule residing in the ‘inner phase’ of a molecular container is that the molecular properties can be different from that displayed in the bulk phase. To take advantage of the inside of the container, potential guests must travel through some sort of molecular portal or ‘window.’ Many container molecules are essentially, though not always, closed surface spheroidal entities; there often exists a significant kinetic barrier to entering and exiting the cavity, which is largely governed by the portals. This property, shared to some degree by all molecular
containers was described by Cram as constrictive binding. Constrictive binding (Figure 1.3c) is defined as the activation free energy for guest complexation ($\Delta G_c^\ddagger$). $\Delta G_c^\ddagger$ is equal to the activation free energy of host-guest decomplexation ($\Delta G_d^\ddagger$) less the intrinsic thermodynamic driving force for guest complexation ($\Delta G_i^\circ$). Constrictive binding provides a means by which complexes of even relatively low intrinsic thermodynamic stability ($\Delta G_i^\circ$) can be kinetically stabilized and exhibit long lifetimes.

Constrictive binding has important ramifications on the kinetics of supramolecular complex association and dissociation. Most individual non-covalent interactions are typically characterized by a rather low intrinsic thermodynamic stability (Figure 1.3b). For example, an individual O-H···O hydrogen bond typically measures < 25 kJ/mol. Typically, intermolecular complexes with a low thermodynamic stability will exhibit short lifetimes, associating and dissociating rapidly. Some host-guest complexes,
however, exhibit a large intrinsic free energy for complexation (\(-\Delta G_i > 35\ \text{kJ/mol}\)) due to the contribution of multiple host-guest interactions. The most extreme example is perhaps the non-covalent avidin-biotin complex with an association constant of \(\sim 10^{15}\ \text{M}^{-1}\).\(^{28}\) In terms of artificial host-guest complexes, crown ether-metal ion complexes are a familiar example, where 18-crown-6 complexes \(\text{K}^+\) in methanol at 25°C with a \(\Delta G = 35\ \text{kcal/mol}\).\(^{29}\) Consequently, host-guest complexes with high thermodynamic stability will also show an appreciable kinetic stability (Figure 1.3a).

The large kinetic barrier to complexation (\(\Delta G^\ddagger_c\)) introduced by constrictive binding results in intermolecular complexes with long lifetimes, even if the thermodynamic stability of the complex is low. This is the case with many host-guest container molecular complexes. The constrictive binding effect provides the opportunity to study subtle intermolecular interactions and forms of supramolecular isomerism. In an example in 2004 by Rebek and coworkers, the constrictive binding effect of self-assembled capsule 1.1 is significant enough that the lifetime of the host-guest species in solution allows the observation and study of a type of stereochemistry that the authors refer to as ‘constellational isomerism,’ where the arrangement of multiple guest molecules within a molecular container give rise to different stereochemical isomers (Figure 1.4).\(^{30}\) The existence of these isomers results from the translation of the guests within the molecular cavity being restricted by the container effect, and by the container’s selectivity for different guests (\(\text{CHCl}_3\) and 1,2-dichloroethane). The complexes are sufficiently stable that the different constellational isomers can be
observed on the NMR timescale. The guests remain in the capsules even after the complex is heated en vacuo.

**Figure 1.4.** Rebek’s self-assembled capsule 1.1 encapsulates 3 guests constrictively, resulting in a distribution of guests within the capsule giving rise to and allowing the study of so-called constellational isomers. *Reproduced with permission Proc. Natl. Acad. Sci.*
1.2. Concave Molecules and CTBs

Molecules of a concave shape are especially suited to construct effective recognition sites, taking advantage of the convergent arrangement of binding sites the curvature provides. Relatively few synthetic molecules possess large, enforced concave surfaces, however this scaffold is fairly prevalent in nature’s macromolecules. Some examples of small molecules possessing concavity include the naturally occurring cyclodextrins\(^3\) and the artificial crown ethers\(^2\), spherands\(^3\), cryptands\(^4\) and cucubiturils\(^5\) seen in Figure 1.5. These molecules are well studied platforms in supramolecular chemistry.

![Figure 1.5. Examples of some concave molecules.](image)

Because of their more or less rigid\(^6\), bowl-shaped—*i.e.* cavitation\(^5\)—structures, there has been tremendous interest in calix[n]arenes\(^7\), resorcin[n]arenes\(^8\), and
cyclotribenzylenes (CTBs)\textsuperscript{30} (Figure 1.6). These three classes of hosts lend themselves to chemical modification at the R, R’, and R” groups, and all contain a preorganized, cyclic, arene-based scaffold that provides the concave structural integrity. These concave hosts can be exploited as scaffolds for the construction of molecules that may complex various guests.

Calix[n]arenes (Figure 1.6a) are the condensation product of para-substituted phenols and formaldehyde. The similarly derived resorcinol based macrocycles are called resorcin[n]arenes (Figure 1.6b). Several books and reviews have been published on these molecules.\textsuperscript{40,5a} Calix[n]arenes and resorcin[n]arenes have two distinct areas of variable synthetic interest, the ‘lower rim’ (R) and the ‘upper rim’ (R’ and R”).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1_6.png}
\caption{(a) Calix[n]arenes, (b) resorcin[n]arenes, and (c) cyclotribenzylenes are all concave molecules whose scaffold is based off of methylene bridged arenes.}
\end{figure}

The work described herein deals with molecules based on the CTB scaffold (Figure 1.6c). CTB-based macrocycles have been studied for more than 150 years.\textsuperscript{41} Present-day interest is commonly associated with the rigid,\textsuperscript{34} cup-shaped structure of the CTB scaffold in the context of tuning the host through R’ and R” to exploit supramolecular
chemistry. CTBs are among the most studied macrocycles in the field. There have been multiple reviews on the synthesis and properties of CTBs,\textsuperscript{42} the most recent being that in 2010 by Hardie.\textsuperscript{43} The shallow cavities of CTBs can be easily modified and have been developed over the years for the complexation of neutral molecules—e.g. fullerenes,\textsuperscript{44} cations,\textsuperscript{45} and anions.\textsuperscript{46,47} CTB derivatives have also been used as liquid crystal mesogens,\textsuperscript{48} to construct monolayers on surfaces\textsuperscript{49} or at the air-solution interface,\textsuperscript{50} in dendrimers,\textsuperscript{51} in organic/metallogels,\textsuperscript{52} and in other organic materials.\textsuperscript{53}

CTBs can be synthesized through the acid catalyzed condensation of appropriate arenes with formaldehyde or a formaldehyde equivalent such as paraformaldehyde (Figure 1.7). This method works best for 1,2-disubstituted arenes containing two ortho-positioned electron donating groups (R’, R”), such as alkyl ethers. If the two R’ R” groups are identical, then the CTB is achiral and \( C_3 \) symmetric. If, however, R’ \( \neq \) R” then chiral \( C_3 \) symmetric or \( C_1 \) symmetric isomers are possible. Chapter 5 of this dissertation concerns the condensation of formaldehyde with amido anisole to give amido and ultimately amino CTBs.

\[
\begin{align*}
R' & \quad R'' \\
+ & \quad \text{HCHO} \\
\text{H}^+ & \quad \rightarrow \\
\text{C}_3 & \quad \begin{array}{c}
R' = R'' \\
R' \neq R''
\end{array}
\end{align*}
\]

**Figure 1.7.** The acid catalyzed condensation of formaldehyde with 1,2-disubstituted arenes yields CTBs as \( C_3 \) or \( C_1 \) isomers.
Probably the most common synthesis of CTBs is based on the reaction in Figure 1.8, which involves the acid catalyzed condensation of an appropriate precursory benzyl alcohol. The use of a benzyl alcohol results in the formation of only the (+/-)-$C_3$ symmetric product (under kinetic control) for unsymmetrically substituted benzyl alcohols. This synthesis traditionally uses harsh conditions, such as perchloric acid in methanol, acetic acid, or formic acid. The condensation of benzyl alcohols to CTBs has also been reported using milder Lewis acids such as Sc(OTf)$_3$ in acetonitrile.$^{54}$

![Figure 1.8. Condensation of the appropriate precursory benzyl alcohol will result in a variety of $C_3$ symmetric CTBs.](image)

The $R''$ substituents in this reaction are limited to strongly donating, para-directing groups–usually methoxy–to achieve reasonable yields. The $R'$ groups are less important, but the choices are limited (e.g. –OR, -SR, -NHCOR). Synthetic limitations usually dictate that functionalization of $R'$ and $R''$ occur after the CTB forming step.

A handful of CTBs have been well explored as scaffolds for further chemical functionalization, and can readily be produced in reasonable quantities. The most notable of these are: $C_{3v}$ symmetric, cyclotriveratrylene (CTV, $R' = R'' = OCH_3$) and its demethylated derivative cyclotricatechylene (CTC, $R' = R'' = OH$), and the chiral, $C_3$ symmetric, cyclotrianisidine ((+/−)-CTA, $R' = NH_2$, $R'' = OCH_3$) and
cyclotriguaiacylenes (\((+/-)-\text{CTG,} \ R' = \text{OH,} \ R'' = \text{OCH}_3\)) cavitands (Figure 1.9). The synthesis of \((+/-)-\text{CTA}\) is expensive, however, discussed in detail in Chapter 5.

\[
\begin{array}{cccc}
\text{Cyclotriveratrylene} & \text{(CTV)} & R' = \text{OMe} & R'' = \text{OMe} \\
\text{Cyclotricatechylene} & \text{(CTC)} & R' = \text{OH} & R'' = \text{OH} \\
(+/-) \text{Cyclotrianiisidine} & (+/-) \text{CTA} & R' = \text{NH}_2 & R'' = \text{OMe} \\
(+/-) \text{Cyclotriguaiacylene} & (+/-) \text{CTG} & R' = \text{OH} & R'' = \text{OMe}
\end{array}
\]

*Figure 1.9* Some useful CTB scaffolds for further chemical functionalization include CTB, CTC, \((+/-)-\text{CTA}\), and \((+/-)-\text{CTG}\).

The rigid crown shape adopted by CTB molecules creates a shallow, electron rich cavity in which guest molecules can be non-covalently bound and a large variety of molecules based on the CTB scaffold have been reported, including extended-cavity CTBs with large side arms to increase the depth and volume of the cavity. For example, Holman and coworkers have prepared aryl-extended CTBs by substitution of \([\eta^5-\text{C}_5\text{H}_5]\text{Fe}^{II} (\eta^6-\text{chloro}-\text{arenes})]^+\) at the OH positions of \text{CTG}. These cationic cavitands bind anions in solution and in the solid state.\(^{56}\)

CTBs almost exclusively exist in the *crown* conformation, as evidenced by NMR spectra and crystal structures.\(^7\) It is also known, however, that the crown conformation can invert, as demonstrated by the slow racemization of optically pure CTBs. As an intermediate between the two *crown* enantiomers, the molecule exists in a saddle-twist
This process involves the inversion of a single methylene bridge through the annular macrocyclic ring, and is illustrated in Figure 1.10. The conformational properties of CTBs are discussed in greater detail in Chapter 3. This process has an inversion barrier ($\Delta G^\ddagger \approx 26-28 \text{ kcal mol}^{-1}$) that is large enough to allow for the isolation of enantiopure CTBs. $(+/\text{-})$-CTG, for example, can be resolved by chromatographic separation of diastereomeric esters. Another example is the $C_3$ symmetric nonmethoxy $(+/\text{-})$-CTV (right) that was resolved using preparative scale chiral HPLC. These studies are addressed in Chapter 2.
1.3. Cryptophanes

1.3.1. Structure

One of the first reported and most studied classes of container molecules, cryptophanes,\textsuperscript{60} were originally reported by Collet \textit{et al.} in 1981.\textsuperscript{61} Their influence on the supramolecular chemistry community can be illustrated by the various reviews on the subject in 1987,\textsuperscript{62} 1993,\textsuperscript{19,59c} 1996,\textsuperscript{7} 2004,\textsuperscript{59c} and most recently 2009.\textsuperscript{63} Cryptophanes are small, tunable, and sometimes chiral molecular containers consisting of two cup-shaped CTBs connected to one another by (usually) three bridges (Y in Figure 1.11). Due to the typical $C_3$ symmetry of CTBs, cryptophanes can exhibit two diastereomeric structures. The \textit{syn} diastereomer (Figure 1.11a) has the X and X' groups on the same side of the bridges and results from connecting two CTBs of opposite chirality. The (+/-)-\textit{anti} diastereomer (Figure 1.11b) is inherently chiral, arising from

![Figure 1.11](https://example.com/figure1.11.png)

\textbf{Figure 1.11.} Cryptophanes are composed of two CTB moieties connected by usually three bridges. The CTBs are chiral and give rise to two diastereomers, the $C_{3h}$ \textit{syn} (meso) isomer ($X = X'$), and the $D_3$ (+/-)-\textit{anti} isomer.
the joining of two CTB moieties of the same chirality, resulting in the \( X \) and \( X' \) groups being positioned on the opposite sides of each bridge. Should the bridge be symmetric, and the top and bottom CTBs of the cryptophane molecule be the same \( (X = X') \), the \textit{syn} diastereomer will be achiral, possessing \( C_{3h} \) point group symmetry, and the \((+/-)-anti\) isomer will be chiral, with \( D_3 \) point group symmetry.

The identification of cryptophanes by IUPAC names is challenging and results in long, inconvenient names. For this reason, Collet has named the cryptophanes using letters from the alphabet chosen in chronological order, the first cryptophane being named cryptophane-A \((+/-)-anti; X = X' = \text{OMe}, Y = (\text{CH}_2)_2\), and so on. More recently, a nomenclature depicted in Figure 1.11c has appeared in the literature, which provides the advantage that the names at least allude to the number of carbons in the bridges. There are now over 100 known cryptophanes, but a cohesive nomenclature is still lacking.

1.3.2. Synthesis

Cryptophanes can be prepared by three general routes; the so-called ‘template’ method, the ‘two-step’ or direct method, and the ‘capping’ method (Figure 1.12). All cryptophane syntheses, regardless of the route chosen, rely upon the acid catalyzed cyclization of the two CTB moieties. The three approaches differ in terms of how they approach the step of CTB formation. The cyclization step is typically performed under moderate to high dilution to avoid the likelihood of producing polymeric material versus the desired cryptophanes.
For symmetric \((X = X')\) cryptophanes, the direct, or ‘two-step’ method (Figure 1.12b) is the most convenient because it is simple and fast, however the yields of this synthesis are typically less than 20%. The reaction also tends to be diastereoselective, favoring the \textit{anti} diastereomer. The first step of the synthesis involves appending the desired bridge unit \((Y)\) with two equivalents of vanillyl alcohol to yield effectively one-third of the cryptophane structure. The second step then cyclizes 3 of these molecules to form the two CTBs simultaneously. The benefit to this synthesis is that, due to the ease of making the bis-vanillyl alcohol unit, the cryptophanes can often be made in gram scale quantities.

\textbf{Figure 1.12.} There are three methods to synthesizing cryptophanes: a) the template method, b) the direct, or ‘two-step’ method, and c) the capping method.
The template method (Figure 1.12a), the first employed by Collet, starts with a preformed CTB, e.g. cyclotriguaiacylene (CTG, X = OMe). The molecule is then appended at the phenolic positions with the desired linking unit (Y) containing a pendant vanillyl alcohol. The formation of the second CTB is now an intramolecular reaction that is templated by the first CTB. Consequently, the yields from this method tend to be the highest (>60%), though the syntheses are multi-step.

The capping method (Figure 1.12c) is the third route of cryptophane synthesis. The synthesis involves the joining of two preformed CTB moieties through some variation of a covalent bond forming reaction. The first reported example by Cram involved the Cu-catalyzed coupling of terminal alkyne functionalized CTBs to give rigid, bis-alkyne bridged syn and anti cryptophanes. A relatively unexplored area concerning the capping method is the use of a guest to template the reactions. Only very recently has guest templation been successful in the syntheses of cryptophane containers.

Optically pure CTBs have also been used as a starting point to prepare chiral cryptophanes (see Section 1.3). Cryptophanes can be sustained by covalent bonds, H-bonds, and metal-ligand interactions, and have received much attention in recent years.

1.3.3. Cryptophane Complexes

NMR is the principal and most powerful tool for the characterization of cryptophanes and their complexes with guests. When studying the complexation behavior of these small molecule containers, interpretation must always be described in the context of the
solvent used, since solvent molecules—usually small—may compete with potential guests for encapsulation. As a consequence of this competition, a majority of recognition studies involving cryptophanes and other container molecules are done in non-conventional solvent systems; that is, with solvent molecules that are large enough to be completely excluded from the cavity and thereby do not compete for encapsulation. Examples of such solvents include hexachloroacetone, 1,1,2,2-tetrachloroethane, and, due to the hydrophobic effect, water.

Resulting from the relatively large ΔG‡ (constrictive binding energy) of guest encapsulation, guests bound within the smaller cryptophanes (e.g. cryptophane-333 and smaller) typically exchange slowly on the NMR timescale. Thus, when monitoring the guest complexation equilibrium via NMR spectroscopy, guest molecules will simultaneously display two distinguishable sets of signals, one for the free dissolved species and one for the encapsulated (bound) species. Notably, guests bound within the cavity invariably exhibit large upfield chemical shifts due to the chemical shielding provided by the arene rings of the cryptophane host. For example, the room temperature ¹H NMR spectrum of cryptophane-333 (Y = (CH₂)₃, X = X' = OMe) dissolved in (CDCl₂)₂, with added CHCl₃, shows a signal for the free guest chloroform molecule at 7.24 ppm, and a signal for the encapsulated CHCl₃ at 2.82 ppm (Figure 1.13)—a 4.42 ppm upfield shift. Linewidth analysis (or other NMR experiments) can provide information on the exchange rate of guests. When the guest molecules are in fast exchange relative to the NMR time scale the two guest signal sets will appear as a
broadened signal located at the weighted chemical shift average of the molar ratio of the bound and free guest species. By cooling the sample, it is sometimes possible to slow the exchange and deconvolute the signal into the two separate peaks, providing information about the exchange rate.

Figure 1.13. The 'H NMR spectrum of the slow exchange binding of CHCl₃ is exhibited by cryptophane-333 in (CDCl₂)₂ at room temperature.

The constrictive binding properties of cryptophanes are tunable by variations in the bridges (Y), and the X and X’ groups, affecting the gating mechanism. An elegant example by Dutasta and coworkers⁶⁸ in 2003 investigated the change in recognition behavior between hexa-methoxy (X = X’ = OMe) and hexa-thiomethoxy (X = X’ = SMe) cryptophane-333 derivatives. Sulfur substitution did not significantly change the effective cavity size or the equilibrium binding affinity of the host for CHCl₃, but the energy barriers of association (ΔG⁺) and dissociation (ΔG⁻) were increased for the hexa-thiomethoxy structure (ΔΔG⁺ = 4.6 kcal mol⁻¹; ΔΔG⁻ = 5.1 kcal mol⁻¹ @ 298 K) relative to the hexamethoxy structure due to greater obstruction of the portals by the
larger sulfur atoms. Thus the half life of the CHCl₃ complex is dramatically influenced by a small change in the portal diameter (OMe, t₁/₂ = 0.55 s; SMe, t₁/₂ = 24 min.).

The size of the molecular cavity is, of course, also tunable by changing Y. Varying the bridge length, size, or chemical composition, are the most frequent and facile methods used to change the size, shape, and/or electronic nature of the cavity. Figure 1.14 shows our analysis of cryptophanes-111, -222, -333, and -555 and their respective cavity volumes (as determined from the published single crystal structures of host-guest complexes), illustrating the differences that simple alkane bridge variations have on the cavity volume, which can be as small as 30-70 Å³ for cryptophane-111 and >133 Å³ for cryptophane-555. Of course longer bridges are also possible, but the portals become large.

![Diagram of cryptophanes](image)

**Figure 1.14.** Simple variations in the length of alkyl bridges of cryptophanes result in differently sized and shaped molecular cavities. (*Acknowledgement: Akil Joseph*)

The cavity volume has a dramatic effect on the selective binding properties of the cryptophanes. Figure 1.15 represents our compilation of a great deal of data spanning several published works regarding the binding behavior of cryptophanes-333, -222 (in
(CDCl$_2$)$_2$) and cryptophane-111 (in CDCl$_3$) at room temperature. Experiments with the three structurally similar cryptophanes, namely cryptophane-111, cryptophane-222 and cryptophane-333, binding a neutral guest in a common solvent system, show that the thermodynamic intrinsic driving forces ($\Delta G^\circ_i$) for the complexation of neutral guests by

Figure 1.15. Cryptophanes can encapsulate neutral and cationic guests and exhibit guest selectivities based on size, shape and functional group characteristics. (Reproduced with permission from K. Travis Holman)
these neutral lipophilic hosts, in lipophilic solvents can be as high as 15-24 kJ/mol (3.5-5.7 kcal/mol) for the optimal guest. These values are comparable to a strong H-bond under similar conditions. Clearly, cryptophanes tend to be highly volume and shape selective in their complexation of neutral molecules. The volume selectivity profiles for similarly shaped guests tend to resemble skewed Gaussian functions. Guests smaller or larger than some optimal volume are bound less effectively, and molecules too large to enter the cavity are not bound at all. Remarkably, there is an effective discrimination between guests of subtle volume differences (< 10 %). Cryptophane-333 (X = X’ = OMe) for example, discriminates between CHCl₃ (72 Å³) and CHCl₂Br (77 Å³) by ~1.5 kJ mol⁻¹. Notably, fluorinated compounds tend to show a low binding affinity, even if the size and shape of the guest suggest that they should be bound strongly. For example, Cryptophane-222 has little affinity for CHF₂Cl (V = 52 Å), but a high affinity for both Xe (V = 42 Å³) and CH₂Cl₂ (V = 57 Å³). Not surprisingly, the cryptophanes are also rather shape selective, as can be seen by comparing the affinity of cryptophane-333 for iso-butane over n-butane.

Cryptophane guests are not limited to only neutral molecules. In organic solvents, they have been shown to recognize and bind suitable organic cations. The free energies of association at 300K in (CD₂Cl₂)₂ between cryptophane-333 and a series of alkyl ammonium cations are plotted in Figure 1.15, along with the data for neutral molecule complexation under the same conditions. The host displays a sharp size selectivity profile for cation encapsulation, but the binding energies of these complexes are
significantly larger (orders of magnitude difference in $K_a$) than those for neutral guests under identical conditions. This is attributed to the affinity of the electron-rich, arene lined cavities for cations—the so-called cation···π interaction. Notably, much larger cations can be bound compared to uncharged guests, highlighting the challenge of accurately defining the volumes of nanospaces.

Recently, the electron rich cryptophanes have been rendered more electron deficient by the appendage of cationic, electron withdrawing transition metal fragments to the outer faces of the arene rings, taking advantage of electrostatics and ostensible anion-π interactions to encapsulate anions (Figure 1.16).\textsuperscript{69} Fairchild and Holman appended six $[\text{Cp}^*\text{Ru}]^+$ moieties to cryptophane-333 and the resulting cation $((+/\sim)-1.2^{6+})$ was shown to encapsulate $[\text{CF}_3\text{SO}_3]^{-}$, $[\text{SbF}_6]^{-}$ and $[\text{PF}_6]^{-}$ anions in solution and in the solid state.

![Figure 1.16](image)

**Figure 1.16.** (a) The metallation of cryptophane-333 results in a π-acidic cryptophane that encapsulates (b) $[\text{CF}_3\text{SO}_3]^{-}$ and (c) $[\text{SbF}_6]^{-}$ (images are ‘sliced’ to illustrate the guest)

Notably, these anions are larger than species that would normally be accommodated by cryptophane-333, suggesting that the interior arenes are acting as π-acids and facilitating anion-π interactions. Notably, also, the chloride salts of the metallated cryptophane-333 and cryptophane-111 are water soluble.\textsuperscript{73} The latter is the first reported water soluble derivative of cryptophane-111 and exhibits the highest binding
constant ever reported for the complexation of Xe \( (K_a = 29(2) \times 10^4 \text{ M}^{-1} \) in D$_2$O @ 298 K).

Other cryptophanes have also been designed to be water soluble, both through variations at the X and X’ positions, and through functionalization of the bridges. These capsules bind small molecules, noble gases, and cations in aqueous media by taking advantage of the hydrophobic effect, which is discussed in detail in Chapter 4.

The study of cryptophanes has led many advances in the understanding of molecular recognition chemistry and the ability and manner by which small molecules occupy nanospaces. The ability of cryptophanes to discriminate between small molecule guests based on their size, shape, and electronic character is exceptional, and the ability to tailor these molecules through various, relatively simple means lends them to further developments in molecular recognition chemistry, among other fields.

1.4. Thesis Overview

The CTB scaffold has proved useful in exploring supramolecular chemistry and molecular recognition as briefly highlighted above. This thesis is broadly concerned with the synthesis and study of new concave molecules based on the 1.1.1-orthocyclophane (CTB) scaffold, including cryptophanes and substituted CTBs.

Chapter 2 describes the synthesis and characterization of a series of $C_3$-symmetric, pyridyl-substituted, extended cavity CTGs. Many examples of self-assembly have been reported that exploit labile metal-pyridine bonds, however the ligands tend to be rigid,
achiral molecules of a linear or bent geometry. The pyridyl extended CTBs in Chapter 2 were synthesized with the intent of exploring larger self-assembled molecular moieties and cavitand-containing coordination polymers, with the strategic interest of incorporating an inherently chiral CTB ligand to explore the effect of the shape and chirality on the potential self-assembled aggregates.

Chapter 3 discusses the synthesis, inclusion behavior, and conformational properties of the first endohedral pyridyl-functionalized cryptophane. There have been few reports of cryptophane functionalization in the literature, however, it has been found that $m$-xylyl bridges and their derivatives—such as bridges derived from 2,6-lutidine—provide the opportunity to specifically introduce functionality to the interior and/or exterior of the molecular cavity. Our introduction of interior pyridine functionalization had led to the observation of a stable, ‘imploded’ conformation of a cryptophane in organic solvent at room temperature. These studies shed light on the conformational properties of cryptophanes in the context of other CTB containing molecules, and the ability of cryptophanes to selectively encapsulate substrates. Other approaches to incorporate nitrogen heteroatoms into cryptophane molecules are also highlighted.

Chapter 4 explores the utility of $m$-xylyl bridges to functionalize the exterior of the capsule through discussion of the synthesis and characterization of a water soluble cryptophane bearing six exohedral carboxylic acid moieties. Synthesis and isolation of the syn and anti diastereomers is described.
In Chapter 5, a novel synthetic route to cyclotrianisidines \((+/L)L\text{-CTAs} \), both \(C_3\) symmetric and \(C_1\) symmetric, is explored. An efficient, one-step synthetic route is described for the known, but tedious to synthesize amido precursor to the \(C_3\) symmetric \((+/L)L\text{-CTA} \), as well as to the \(C_1\text{ CTA}\) isomer. The synthesis of a \(C_2\) symmetric cyclodanisidine (CTA), a substituted CTB with two amine groups on adjacent arenes, for future use as a ligand is also explored.

1.5. References


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Chapter 2: Toward Self-Assembled Capsules through Pyridyl Substituted Cyclotriguaiacylenes (CTGs)

2.1. Introduction

2.1.1. Self-Assembly

Self-assembly, according to Whitesides, is “the spontaneous assembly of molecules into structured, stable, non-covalently joined aggregates,”¹ and by Hamilton as, “the non-covalent interaction of two or more molecular subunits to form an aggregate whose novel structure and properties are determined by the nature and positioning of the compounds.”² The key to the self-assembly approach to chemical synthesis is that the non-covalent interactions of importance are typically weaker than covalent bonds and therefore lend themselves to reversibility. The most common of these tools, hydrogen bonds and coordinate covalent bonds, are highly directional, but reversible, making them ideal motifs for controlling the intermolecular arrangements of molecules in space. The inherent reversibility of weaker, non-covalent interactions allows for ‘error correction’ within a self-organized chemical system, allowing the assembly of molecules under thermodynamic control into the lowest energy supramolecular structure(s).³ In this sense, the components sustained by covalent chemical bonds in a self-assembled system contain all of the information necessary for the ‘correct’ assembly to occur.⁴ Many important chemical structures in the natural world are governed by, and owe properties to, the principles of self-assembly—e.g. cell
membranes, surfactants, peptides/proteins, viruses, polymers, crystals/materials, and coordination compounds to name a few. Since the 1990’s, and perhaps before, there has been a push by research chemists to master the art of self-assembly and non-covalent chemical synthesis in much the same way that chemists control the covalent bond.

Molecules created through classical synthetic chemistry rely on the stepwise and strategic formation of covalent bonds. This method, although powerful, is limited when applied to the construction of extremely large and complex molecules—e.g. at the multiple nanometer scale. Stepwise syntheses of such species would take an excessive amount of time, and each step would have to proceed with absolute reliability, or in quantitative yield, in order to ensure even reasonable overall yields. Indeed, even solid phase peptide synthesis is limited by yields and purity issues, and peptides in the range of 70-amino acids (equivalent in length to only the smallest of naturally occurring proteins) push the limits of synthetic accessibility. At the point of these limitations, self-assembly provides a useful alternative to classic molecular synthesis in accessing the multi-nanometer length scale. Even nature exploits the assembly of smaller molecules into larger nano aggregates and assemblies.

2.1.2. Self-Assembled Capsules

A large variety of systems exhibiting self-assembly have been designed by Whitesides,\textsuperscript{5} Stoddart,\textsuperscript{6} Reinhoudt,\textsuperscript{7} Lehn,\textsuperscript{8} Fujita,\textsuperscript{21} Stang,\textsuperscript{9} and many others. The high-
impact of self-assembly on modern chemistry provoked *Science Magazine* to release a special issue in March of 2002 dedicated to “Supramolecular Chemistry and Self-Assembly.” Among the many studied chemical systems of self-assembly, self-assembled capsules have received a great deal of attention for their potential applications as contained chemical environments. Self-assembled capsules are, as defined by Rebek, “receptors with enclosed cavities that are formed by the reversible noncovalent interaction of two or more, not necessarily identical, subunits.” The aggregate of molecular subunits will typically exhibit binding behavior that none of the individual components possesses alone, behavior such as size and/or shape selective complexation. Examples of metal-ligand self-assembled systems that exhibit molecular recognition properties include discrete squares, helices, grids, cylinders, and cages, providing the ability to mimic chemical environments such as viruses, cells, organelles, vesicles, and storage proteins for example.

An example of a simple, but illustrative self-assembled complex is Fujita’s well-known molecular square, first reported in 1990, comprised of four Pd (II) metal ions chelated by ethylenediamine ligands and coordinated to four 4,4’-bipyridine ligands in a cisoid fashion (Figure 2.1a). The ~90° bond angle between the available palladium coordination sites prevents larger ring systems, which would necessarily be more strained, from forming such that, the quantitative self-assembly of the square is observed upon simple mixing of equimolar amounts of metal complex and ligand in an aqueous solution.
The lability of certain metal ligand interactions coupled with derivatized sidearm design of concave molecules, as opposed to linear or bent molecules, has provided many examples of metallo-supramolecular assemblies as well. Notably, related to our work, Shinkai and coworkers created self-assembled cryptophanes and (+/−)−2.26+ (Figure 2.1c) by reacting a rigid pyridyl CTB with a chelated palladium (II) species in a 2:3 ratio. The cryptophane species are presumed to interconvert readily between the racemic (+/−)-anti ((+/−)-2.26+) and the (meso)-syn (2.16+) diastereomers. Shinkai and coworkers have also reported using square-planar metal complexes to couple pyridyl calixarenes (CTB analogues) into molecular capsules with predictable structures.

CTBs have also been modified to assemble around both anions and cations. Recently, Robson and coworkers reported that cyclotricatechylene (CTC, R₁ = R₂ = OH; Figure 2.2) has shown selectivity for Rb⁺, Cs⁺, and N(Et)₄⁺ upon its deprotonation,
forming a capsular clam-like structure with two cavitands hydrogen bonding at varying distances to accommodate the cation.\(^{21}\) 2-quinolinemethyl derived CTB \((+/−)-2.4\) has shown a fluorescence response to Cu(II) binding,\(^{22}\) and a phosphinous amino acid derived CTB \((+/−)-2.5\) has shown selectivity for actinides, specifically Americium, which is a radioactive byproduct in nuclear waste.\(^{23}\) Anion binding host-guest chemistry is historically difficult, because the sizes, shapes, pH dependence, and solvation effects of anions are quite variable. There have been two approaches taken to binding anions using CTBs: i) metallation of the arene rings, or arenes of extended side arms, discussed in Chapter 1, and ii) the introduction of functional groups with hydrogen bond donating capabilities. For example, amide derivatized CTB \((+/−)-2.6\)

\[
(+/-)-2.4 \quad R_1 = \text{OMe}; \quad R_2 = \quad \text{structure image}
\]

\[
(+/-)-2.5 \quad R_1 = \text{OMe}; \quad R_2 = \quad \text{structure image}
\]

\[
(+/-)-2.6 \quad R_1 = \text{OMe}; \quad R_2 = \quad \text{structure image}
\]

\[
(+/-)-2.7 \quad R_1 = \text{OMe}; \quad R_2 = \quad \text{structure image}
\]

\[
X = \text{C}_{11}\text{H}_{23}
\]

**Figure 2.2.** Examples of extended CTGs that exhibit interesting properties such as fluorescence sensing \((+/−)-2.4\), anion \((+/−)-2.5\) and cation \((+/−)-2.6\) binding.
strongly binds OAc$^-$, and weakly binds H$_2$PO$_4^-$, through hydrogen bonding, and the thiol
group can also be assembled onto a gold surface as a SAM (Self-Assembled
Monolayer) and retain the selectivity and binding.$^{24}$

Extended CTB (+/−)-2.7, containing 4-ureidopyrimidinone moieties, has been
reported by de Mendoza and coworkers to dimerize and selectively encapsulate C$_{70}$ over
C$_{60}$. (+/−)-2.7 was subsequently used to isolate C$_{70}$ from a mixture of fullerenes and
fullerites through a solid-liquid single extraction in THF, requiring no chromatography
or tedious separations.$^{25}$ The same ligand was then later calculated (Figure 2.3) to have
a more favorable energy of interaction with C$_{84}$ (the third most abundant member of the
fullerene family) and it was found that at lower concentrations of (+/−)-2.7, C$_{84}$
encapsulation was raised relative to C$_{70}$, which is favored at high concentrations of (+/−-)
-2.7.$^{26}$

**Figure 2.3.** Optimized model of 2.7$^\cdot$C$_{84}$ complex reported by de Mendoza and coworkers.
(Reproduced with permission)
Atwood, and later Stang, have proposed using the principles of solid geometry to approach the rational synthesis and design of molecular subunits to guide the design of molecules that will assemble into container or cage-like structures akin to the Platonic and Archimedean solids (Figure 2.4). Platonic solids are comprised of different numbers of the same regular polygons so that each of the vertices and edges are equivalent. There are five possible platonic solids; tetrahedron (P1), icosahedron (P2), dodecahedron (P3), octahedron (P4) and cube (P5) and possess cubic symmetry. The

**Figure 2.4.** The five Platonic solids are the tetrahedron (P1), icosahedron (P2), dodecahedron (P3), octahedron (P4) and cube (P5). The 13 Archimedean solids are the truncated tetrahedron (A1), truncated icosahedron (A2), snub cube (A3), snub dodecahedron (A4), rhombicosidodecahedron (A5), truncated icosidodecahedron (A6), truncated cuboctahedron (A7), icosidodecahedron (A8), rhombicuboctahedron (A9), truncated dodecahedron (A10), cuboctahedron (A11), truncated cube (A12), and truncated octahedron (A13). *(Figure reproduced with permission)*
Archimedean solids, comprised of at least two different regular polygons, can be derived from the Platonic solids by truncation of the vertices or the twisting of faces of the Platonic solids. Two of the Archimedean solids are chiral—the snub cube (A3) and snub dodecahedron (A4)—with the remaining 11 being achiral. Both families of solids represent the ways in which you can assemble regular polygons, or a molecule of appropriate symmetry, to approximate the surface of a sphere, and in effect create a container or molecular host. In metal-ligand self-assembly, for example, treatment of ligands and/or metals (or metal complexes) as being equivalent to the regular polygons provides a means of predicting whether self assembly can potentially create a desired molecular container.\textsuperscript{28}

Illustrative of this concept, Fujita has reported a 36-component coordination sphere (Figure 2.1b), constructed from bent bipyridyl ligands coordinating to palladium (II) ions.\textsuperscript{29} The 36-component sphere has a diameter of 5.2 nm and is an elegant example of nano-scale molecule synthesis using self-assembly. Upon close inspection, the structure can be described as a cuboctahedron (A11), with the square-planar Pd (II) ions serving the role as the squares, and the windows to the interior of the capsule as the triangles, giving just one example of the Archimedean and Platonic solids approach.

\textbf{2.1.3. CTB-Derived Inclusion Materials}

Many crystalline inclusion compounds and coordination polymers have also been constructed using CTB-based ligands.\textsuperscript{30} The synthesis of coordination polymers
(CPs),\textsuperscript{31} has received much attention recently and the CP field is being guideded towards the incorporation of functional ligands into the design of new materials. Many elegant examples of interesting and elaborate structures have been reported. The incorporation of molecular hosts as ligands may provide a way of integrating chemical attributes intrinsic to this class of molecule into the solid state. Some such properties include host-guest recognition and unusual ligand topologies not available with conventional ligands.

It is clear that self-assembly is a lucrative tool for the preparation of large and complex molecules from simple molecular building blocks and can address the main shortcoming of conventional multi-step synthesis (i.e. low yields). Appropriate design of the building blocks allows one to effectively give the molecules a set of directions to follow for assembling, as opposed to typical covalent chemical synthesis. It is not difficult to see how this approach toward precise nano-sized structures can be extrapolated and exploited to go where traditional synthetic chemistry has met its limitations.

2.2. Synthesis and Structures of Pyridyl Functionalized CTBs: Toward Self-Assembled Capsules

With the ultimate goal of synthesizing discrete cryptophane-like molecules and higher-order assemblies via metal-ligand self-assembly, pyridyl-extended cyclotriguaiacylenes (CTGs) were targeted. The metal-pyridine bond is one of the most
exploited reversible interactions in self-assembly, as briefly illustrated by the examples in Figure 2.2 and many, many others. Introduction of the pyridine moiety onto a CTG scaffold provides the ability to use these concave molecules as ligands that provide curvature to promote the formation of self-assembled capsules. Due to their $C_3$ symmetry, pyridyl substituted CTGs can be thought of as a regular triangle in the formation of Platonic and Archimedean solids. Reaction of the appropriate ligand with a square-planar metal (Pd(II) or Pt(II) for example) ought to form an Archimedean snub cube (A3), a rhombicuboctahedron (A9), or a cuboctahedron (A11)(as seen in Figure 2.5) via the complimentary assembly of the $C_3$-symmetric ligand and the $C_4$-symmetric metal ion subunits. The yellow squares in Figure 2.5 represent openings into the cavity of the molecular assembly. It is interesting to note that both the cuboctahedron and
rhombicuboctahedron have $O_h$ symmetry, which would not be possible with chiral CTBs, and the snub cube has chiral $O$ symmetry.

We initially focused on the synthesis and isolation of novel $C_3$-symmetric pyridyl ligands (+/-)-2.8, (+/-)-2.9, and (+/-)-2.10 because of their simplicity (Figure 2.6). Pyridyl nitrogens can be readily located at the 2-, 3-, or 4- positions according to Figure 2.6a, and one can also see that, in fact, 2-, 3-, and 4- substituted pyridines can be attached in any combination desired to yield interesting asymmetric ligands (Figure 2.6). Most pyridyl ligands already exploited for self assembly have been rigid, as illustrated by the self-assembled cryptophane reported by Shinkai and coworkers.

**Figure 2.6.** The synthesis of pyridyl extended CTBs are accomplished through simple $S_N2$ substitution of CTG with the appropriately halogenated picoline.
discussed earlier. The palladium source for Shinkai’s cryptophane has two of the coordination sites of the palladium occupied and the CTB ligand is rigid, idealizing the geometry of both the ligand and the metal to form cryptophanes. It was hypothesized by our group that a more flexible, benzyl-type pyridyl substituent would allow conformations of the ligand that would be more conducive to one of the \( \text{M}_6\text{L}_8 \) polygonal topologies when reacted with a naked square-planar metal ion (e.g. \( \text{Pd}^{2+} \))—exhibiting ‘error correction’ features. Another interesting attribute of the use of CTBs (+/-)-2.8, (+/-)-2.9 and (+/-)-2.10 is that they are chiral. This statistically dictates that of the possible Archimedean solids, there are conceivably up to \( 2^8 \) possible stereoisomers of each \( \text{M}_6\text{L}_8 \) polygon. It was of interest to us to examine the effect of stereochemistry in such a complicated system.

Starting with (+/-)-cyclotriguaiacylene (CTG), readily made in 3 steps from vanillyl alcohol (4-hydroxy-3-methoxy benzyl alcohol), three \( \text{S}_2\text{N}_2 \) reactions were carried out using the appropriate halogenated picoline to yield (+/-)-2.8, (+/-)-2.9 and (+/-)-2.10. The reaction of (+/-)-CTG with bromopicoline 2.11 gave (+/-)-2.8 in 25 % yield, however the reaction of (+/-)-CTG with bromopicolines 2.12 and 2.13 resulted in less than 3 % yield of (+/-)-2.9 and (+/-)-2.10, respectively, returning mostly the starting CTG material. This is thought to be attributable to polymerization of the bromopicolines 2.12 and 2.13 by way of the nitrogen attacking the benzylic carbon of another picoline before the reaction of (+/-)-CTG could occur with the appropriately halogenated picoline. To hinder this reaction, chlorinated HCl salts 2.14 and 2.15 were
used, blocking the nucleophilic nitrogens, to yield 11% and 26% of (+/-)-2.9 and (+/-)-2.10 respectively.

Figure 2.7. The crystal structure of (P)-2.8•4½EtOH concomerate, illustrating a) a thermal ellipsoid plot (50 %) of (P)-2.8, b) the chiral eclipsed columns of (P)-2.8, and c) the packing of the unit cell and the 9 Å channels between the columns that are filled with molecules of ethanol.
X-ray single crystal structures of ligands (+/-)-2-8 and (+/-)-2-10 were obtained as solvates with EtOH and i-PrOH, respectively. (+/-)-2-8 crystallizes as a (M)-2.8•4\(\frac{2}{3}\)EtOH and (P)-2.8•4\(\frac{2}{3}\)EtOH conglomerate from EtOH, packing in the highly symmetric R3 space group. The molecules assemble as eclipsed homo-chiral columns.

Figure 2.8. The isopropanol solvate crystal structure of (+/-)-2.10 (a) crystallizes in chiral staggered columns (b) with enantiomers of 2.10 alternating within the column (b). The columns are close packed (c) with one isopropanol and one water per molecule of 2.10.
(Figure 2.7b). SQUEEZE analysis of the disordered solvent regions estimates that 4⅔ ethanol per molecule of 2.8 reside within in the 9 Å diameter channels created by the chiral columns (Figure 2.7c). The crystals are therefore both homochiral and polar, which may be important because crystal polarity is a requirement for many physical properties, including Second-Harmonic Generation (SHG).33 (+/-)-2.10 (Figure 2.8) crystallizes from i-PrOH as [(+/−)-2.10•(i-PrOH)2•(H2O)] in the P21 space group. The CTB portion of the molecule stacks in a staggered column comprised of alternating enantiomers of 2.10. Like 2.8, the columns of (+/-)-2.10 also face the same direction, again resulting in a polar crystal, but the crystals are a racemate. The pyridyl nitrogen is hydrogen bonded to solvent, isopropanol and water, filling the small voids between the columns, and connecting stacked pyridines along a column.

Initial experiments, borrowing from the likes of Fujita, Shinkai and others, were conducted by reacting (+/-)-2.8, (+/-)-2.9 and (+/-)-2.10 with PdCl2 or Pd(NO3)2 in DMSO in a 3:4 metal to ligand ratio and left to equilibrate. The formation of discrete molecular assemblies in solution can be monitored by 1H NMR, and is typically indicated by the observation of sharp signals in the spectrum, corresponding to a homogeneous species as opposed to oligomers. When (+/-)-2.8, (+/-)-2.9 and (+/-)-2.10 were reacted with either PdCl2 and Pd(NO3)2 in solution, the 1H NMR spectra showed significantly broadened, and sometimes indiscernible peaks, indicative of the formation of oligomeric or polymeric species, even after heating and/or long equilibration times. This behavior was seen in all spectra with these molecules, regardless of the ligand to
metal ratio or solvent choice. So, unfortunately, it was concluded that (+/-)-2.8, (+/-)-2.9 and (+/-)-2.10 do not spontaneously assemble into any of the desired Archimedean structures.

In attempts to synthesize other Platonic and Archimedean structures through self-assembly, (+/-)-2.8, (+/-)-2.9 and (+/-)-2.10 were also reacted with the metal ions Cu’, Cu’, Fe’, Ni’, Co’ and Zn’ with various counter anions. Crystalline products have been recovered from several of these reactions, including Co’ and Fe’ species isolated as [NO₃]’ and [Cl]’ salts from acetone, MeOH and EtOH – but a single crystal structure determination has not yet been possible due to insufficient crystal quality and/or size. A majority of the reactions attempted with (+/-)-2.8, (+/-)-2.9 and (+/-)-2.10 and metal salts in various solvents resulted in fibrous, gel-like materials that have not yet been studied in detail.

During the course of this project, Hardie and coworkers were apparently successful in achieving our initial goals of assembling an M₆L₈ Archimedean solid with Pd’ ions and pyridyl substituted CTG ligands by working with a similar family of pyridyl CTBs. Specifically, they synthesized (+/-)-2.16 and in a reaction with Pd(NO₃)₂ in a 4:3 ligand/metal ratio and excess o-carborane in DMSO yielded [Pd₆{(M)-2.7}₈]¹²⁺, a cuboctahedron equivalent to the A11 schematic illustrated in Figure 2.5. The complex, homochiral capsule was characterized by single crystal X-ray diffraction (Figure 2.9) and was shown to be essentially the only product in solution as determined by Diffusion Ordered Spectroscopy (DOSY). Remarkably, and this was not part of the discussion
of the paper, the species self-assembles with eight ligands of identical chirality. This is remarkable because, as discussed earlier, there are $2^8$ possible diastereomers resulting from a CTB of either chirality residing at each site in a $[\text{Pd}_6(2.16)_8]^{12+}$ species. So, the $M$ and $P$ $[\text{Pd}_6(2.16)_8]^{12+}$ species isolated in crystalline form are exactly two of the $2^8$ possible steroisomeric products. This illustrates the astonishing stereoselectivity of the

Figure 2.9. a) Reaction of $(+/-)-2.16$ with Pd(NO$_3$)$_2$ in DMSO in a 3:4 metal to ligand ratio results in a $M_6L_8$ ‘starburst’ assembly $[\text{Pd}_6((M)-2.16)_8]^{12+}$ and $[\text{Pd}_6((P)-2.16)_8]^{12+}$ as reported by Hardie and coworkers.$^{35}$ The structure resembles a rhombicuboctahedron as depicted in b) ball and stick form and c) space-fill models.
self-assembly process. The assembly is 3.1 nm in diameter with disordered solvent and anions residing within the cavity, which was described as a ‘star-burst’ metallo-supramolecular assembly. It seems evident through this work and subsequent publications,\textsuperscript{35} that the presence of the carbonyl moiety proximity to the sidearm of the derivatized CTG proves important in the assembly of this family of molecules. The reason for this is not understood, but likely stems from limiting the conformational degrees of freedom.

In 2005, during the course of this work, Hardie and coworkers reported\textsuperscript{36} their own synthesis of (+/-)-2.8, and their reaction of (+/-)-2.8 with AgPF\textsubscript{6} to give a 3D coordination polymer of the structure Ag\textsubscript{3}[(+/-)-2.8\textsubscript{2}](PF\textsubscript{6}). The pyridyl groups of Ag\textsubscript{3}[(+/-)-2.8\textsubscript{2}](PF\textsubscript{6}) are highly disordered and the silver centers are of only 50%...
occupancy, but the data were of sufficient quality to perform a structural analysis. Four molecules of (+/-)-2.8 ligands are arranged in a back-to-back fashion (Figure 2.10a) creating a tetrahedron, with π-stacking interactions between the arenes of the CTBs. The tetrahedra are connected through almost linear N···Ag⁺···N bonds to give the 3D coordination network shown in Figure 2.10b. The network, although highly disordered, can be described as a 4-fold interpenetrating (10,3)-a net (Figure 2.10c). This network is ascribed by the authors as the first example of a 3D coordination network formed from a CTB based ligand.

2.3. Co-crystals of Carboxylic Acids and Pyridyl Functionalized CTBs

Another approach to the synthesis of large self-assembled cavities exhibiting an Archimedean-solid structure could be to exploit the pyridyl moieties via H-bonding. (+/-)-2.8, (+/-)-2.9 and (+/-)-2.10 were then explored with respect to their interaction with H-bond donors, e.g. particularly those of a square shape. One pseudo-square shaped molecule explored was 1,2,4,5-benzene tetracarboxylic acid (BTC). Equimolar solutions of BTC and (+/-)-2.8 in methanol were mixed resulting in colorless needles crystallizing from solution within 20 minutes. Characterization of the crystals by single crystal X-ray diffraction revealed a material composition of [(+/-)-2.8•BTC•4MeOH•H₂O] that packs in the P-1 space group. The structure consists of corrugated 2D sheets of hydrogen bonded pyridyl-CTBs and BTC molecules. The sheets run parallel to the (201) plane. The structure is a racemate, with the cavities of
the enantiomers of 2.8 facing opposite directions within the unit cell. The methanol molecules are H-bonded in a 1D chain filling the remaining void space within the crystal (Figure 2.9a).

Figure 2.11. Reaction of (+/-)-2.8 with BTC gives nearly isostructural crystalline materials a) [(+/-)-2.8•BTC•4MeOH•H2O] from MeOH and b) [(+/-)-2.8•BTC•3(acetone)] from acetone. The stacked 2D hydrogen bonded sheets are illustrated with solvent molecules colored yellow and BTC green for clarity.
When the same procedure is followed using acetone as opposed to methanol, colorless needles of \([(+/—)-2.8\text{BTC}\text{-}3\text{(acetone)}]\) precipitate within 20 minutes, as determined by single crystal X-ray diffraction. Analysis of the structure reveals a corrugated 2D sheet of pyridyl-CTBs and BTC molecules with an acid-base H-bonding pattern that is isostructural to that observed in \([(+/—)-2.8\text{BTC}\text{-}4\text{MeOH}\text{-}\text{H}_2\text{O}].\) In \([(+/—)-2.8\text{BTC}\text{-}3\text{(acetone)}]\) however, the solvent accessible space is occupied by 3 acetone molecules (Figure 2.11b). The observation of identical motifs from the two different solvents is peculiar, considering that these solvents have opposite hydrogen bonding characteristics, MeOH being an H-bond donor (and acceptor) and acetone being an H-bond acceptor. Nonetheless, the \((+/—)\text{-}2.8\text{BTC}\) H-bonded structures are essentially isostructural in \([(+/—)-2.8\text{BTC}\text{-}4\text{MeOH}\text{-}\text{H}_2\text{O}]\) and \([(+/—)-2.8\text{BTC}\text{-}3\text{(acetone)}]\).

The hydrogen bonding pattern of the sheets in \([(+/—)-2.8\text{BTC}\text{-}4\text{MeOH}\text{-}\text{H}_2\text{O}]\) and \([(+/—)-2.8\text{BTC}\text{-}3\text{(acetone)}]\) is illustrated in Figure 2.12. Each of the three pyridyl nitrogens of 2.8 is H-bonded to an acid group of one of the two symmetry-unique BTC molecules that lies on an inversion center. Thus, apart from solvents, the ASU contains one molecule of 2.8, and two symmetry-unique half molecules of BTC (BTC-1 and BTC-2), each hydrogen bonding to cavities of the opposite chirality. The cavities of adjacent CTBs face in opposite directions and are related by an inversion center. The binding chain \(A_{\text{pyr1}}\cdots A_{\text{1}}\cdots B_{\text{1}}\cdots C_{\text{pyr2}}\) (see Figure 2.12) connects two cups that are stacked in a back-to-back fashion, interacting through \(\pi-\pi\) stacking. This ‘dimer’ propagates through BTC-1 in one direction of the (2 0 1) plane. The second direction of the plane
Figure 2.12. The hydrogen bonding pattern along the [2|0|1] plane in the isostructural
[(+/−)-2.8•BTC•4MeOH•H₂O] and [(+/−)-2.8•BTC•3(acetone)].

is propagated through BTC-2 via the Bₚyr1···C₂·C₂···Bₚyr2 H-bonding pattern to another
‘dimer’ following the inversion symmetry. The space between the ‘dimer’ units is filled
by, disordered in [(+/−)-2.8•BTC•4MeOH•H₂O], solvent molecules. The D₂ of BTC-2
donates and H-bond to one of the included MeOHs. The pattern creates a 2D H-bonded
sheet that stacks with others such that the Bₚyr arms of the one cavitand sit in the cavity
of the adjacent layer.
2.4. Conclusions

Although the project was abbreviated due to the appearance in the literature of competing work by another group, it is apparent that the philosophy behind the use of functionalized CTBs—specifically pyridyl functionalized CTBs—is sound. Clearly, certain examples of these molecules can be influenced to assemble into very interesting homochiral capsules and the approach is valid for the self-assembly of discrete molecular assemblies, and for the synthesis of coordination polymers. The synthesis and characterization of new molecules (+/-)-2.9, and (+/-)-2.10 has been accomplished, along with the report of the crystal structures of the (M)-2.8•4½EtOH / (P)-2.8•4½EtOH racemate, assembling in a high symmetry space group (R3) as eclipsed homo-chiral columns with solvent filled 9 Å channels, and [(+/—)-2.10•(i-PrOH)2•(H2O)] as staggered columns comprised of alternating enantiomers of 2.10, both resulting in polar crystals.

The reaction of (+/-)-2.8 with the pseudo square-planar BTC has also been reported to form H-bonded, essentially isostructural [(+/—)-2.8•BTC•4MeOH•H2O] and [(+/—)-2.8•BTC•3(acetone)] from solvents have opposite hydrogen bonding characteristics. At the outset of this document, the molecules (+/-)-2.9 and (+/-)-2.10 have not yet been reported in the literature.
2.5. Experimental

2.5.1. Materials and Methods

All solvents were used as received from Fisher (Pittsburg, PA). Reagents were obtained from Acros (Pittsburgh, PA) or Aldrich (Milwaukee, WI) and were used without further purification. All reactions were carried out under nitrogen atmosphere. Chromatography was carried out on silica gel (32-64µm). NMR spectra were recorded on either a Mercury Varian 300 MHz or an Inova 400 MHz Spectrometer operating at 300 or 400 MHz (\(^1\)H), or 75.5 or 100.5 MHz (\(^{13}\)C), respectively. All NMR spectra were collected at room temperature (298(2) K) unless otherwise noted and chemical shifts were indirectly referenced to TMS using residual solvent signals as internal standards. Elemental analyses were carried out on a Perkin-Elmer PE2400 microanalyzer.

2-({[6,13,20-trimethoxy-12,19-bis(pyridin-2-ylmethoxy) tetracyclo [15.4.0.0\(^{3,8}\).0\(^{10,15}\)]henicosa-1(17),3(8),4,6,10(15),11,13,18,20-nonaen-5-yl]oxy}methyl)pyridine (\((+/−)-2.8\)). To a stirring solution of \((+/−)-\)-cyclotriguaiacylene (0.50 g, 1.0 mmol) and potassium carbonate (2.0 g, 14 mmol) in 40 mL of acetone was added dropwise a solution of 2-bromomethyl pyridine (0.93 g, 3.0 mmol) dissolved in 10 mL of acetone. After 24 hours, the solution was poured into methylene chloride (100 mL) and water was added (100 mL). The aqueous layer was extracted with methylene chloride (3 x 100 mL) and the organic layers collected, dried over magnesium sulfate, and evaporated under vacuum. The resultant solid was recrystallized from 2-propanol to yield a colorless crystalline solid. Yield (0.83 g, 25 %); \(^1\)H NMR (acetone-\(d_6\)); \(\delta\) 8.52
(d, $J = 1.8$ Hz, 3H, pyr-H); δ 7.73 (t, $J = 8.1$ Hz, 3H, pyr-H); δ 7.51 (d, $J = 7.8$ Hz, 3H, pyr-H); δ 7.24 (t, $J = 6.0$ Hz, 3H, pyr-H); δ 7.17 (s, 3H, aryl-H); δ 7.05 (s, 3H, aryl-H); δ 5.12 (s, 6H, O-CH$_2$-pyr); δ 4.76 (d, $J = 13.9$ Hz, 3H, H$_a$); δ 3.74 (s, 9H, OCH$_3$); δ 3.55 (d, $J = 13.9$ Hz, 3H, H$_e$). Anal. calcd. for C$_{42}$H$_{39}$O$_6$N$_3$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.36; H, 5.79; N, 6.25.

3-({[6,13,20-trimethoxy-12,19-bis(pyridin-3-ylmethoxy)tetracyclo [15.4.0.0$^3,8$.0$^{10,15}$]henicosa-1(17),3(8),4,6,10(15),11,13,18,20-nonaen-5-yl]oxy}methyl)pyridine (+/-)-2.9. To a stirring 100 mL DMF solution of cyclotriguaiacylene (1.00 g, 2.0 mmol) and K$_2$CO$_3$ (2.5 g, 15.0 mmol) was added dropwise 3-chloromethylpyridine HCl dissolved in a minimal amount of DMF. The solution was then heated to 60°C and stirred for 24 hours. The solution was cooled, poured into methylene chloride (100 mL) and water was added (100 mL). The aqueous layer was extracted with methylene chloride (3 x 100 mL) and the organic layers collected, dried over magnesium sulfate, and evaporated under vacuum. The resultant solid was recrystallized from 2-propanol to yield a colorless crystalline solid. Yield (0.18 g, 11%); mp = 158-161 °C; $^1$H NMR (CDCl$_3$): δ 8.57 (s, 3H, pyr-H); δ 7.64 (d, $J = 5.2$ Hz, 3H, pyr-H); δ 7.49 (d, $J = 7.6$ Hz, 3H, pyr-H); δ 7.19 (d of d, $J = 7.6$ Hz, $J = 5.2$ Hz, 3H, pyr-H); δ 6.79 (s, 3H, aryl-H); δ 6.63 (s, 3H, aryl-H); δ 5.23 (s, 6H, O-CH$_2$-pyr); δ 4.65 (d, $J = 13.9$ Hz, 3H, H$_a$); δ 3.70 (s, 9H, OCH$_3$); δ 3.40 (d, $J = 13.9$ Hz, 3H, H$_e$). $^{13}$C NMR (CDCl$_3$): Aromatic Region: δ 157.9, δ 149.3, δ 148.4, δ 146.8, δ 137.2, δ 132.8, δ 131.9, δ 122.9, δ 121.5, δ 115.4, δ 113.8. Aliphatic Region: δ 72.0, δ
4-\left(\left[6,13,20\text{-trimethoxy}-12,19\text{-bis(pyridin-4-ylmethoxy)}\right]\text{tetracyclo} 
\left[15.4.0.0^{3,8}.0^{10,15}\right]\text{henicosa-1(17),3(8),4,6,10(15),11,13,18,20-nonaen-5-yl}]\text{oxy}\right)\text{methyl)} \text{pyridine} \ (\pm/-)\text{-2.10).}

To a stirring 100 mL DMF solution of cyclotriguaicylene (1.00 g, 2.45 mmol) and K$_2$CO$_3$ (20.5 g, 15.0 mmol) was added dropwise 4-chloromethylpyridine HCl (2.11 g, 7.35 mmol) dissolved in a minimal amount of DMF. The solution was then heated to 60°C and stirred for 24 hours, poured into H$_2$O (100 mL), and extracted with CH$_2$Cl$_2$ (3 x 100 mL). The organic layers were collected, dried over MgSO$_4$, and evaporated under vacuum resulting in a dark crystalline solid. The solid was chromatographed with 10:1 CHCl$_3$/MeOH ($R_f = 0.2$) and evaporated under vacuum leaving an off-white solid, which was recrystallized from 2-propanol (~50 mL) to give a colorless solid. Yield (430 mg, 26%); mp = 160-164 °C; $^1$H NMR (CDCl$_3$): $\delta$ 8.58 (d, $J^3 = 5.4$ Hz, 6H, pyr-H); $\delta$ 7.36 (d, $J^3 = 5.4$ Hz, 6H, pyr-H); $\delta$ 6.77 (s, 3H, aryl-H); $\delta$ 6.65 (s, 3H, aryl-H); $\delta$ 5.10 (s, 6H, O-CH$_2$-pyr); $\delta$ 4.69 (d, $J^2 = 13.9$ Hz, 3H, H$_a$); $\delta$ 3.70 (s, 9H, OCH$_3$); $\delta$ 3.45 (d, $J^2 = 13.9$ Hz, 3H, H$_b$). $^{13}$C NMR (CDCl$_3$): Aromatic Region: $\delta$ 150.3, $\delta$ 148.8, $\delta$ 146.8, $\delta$ 133.5, $\delta$ 131.9, $\delta$ 121.5, $\delta$ 116.6, $\delta$ 113.9, $\delta$ 100.2. Aliphatic Region: $\delta$ 70.3, $\delta$ 56.4, $\delta$ 36.7. Anal. calcd. for C$_{42}$H$_{39}$O$_6$N$_3$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.37; H, 6.35; N, 3.89.
2.5.2. Crystal Growth

\((P)-2.8\cdot4\frac{2}{3}\text{EtOH}.\)  \textit{ca.} 5 mg of (+/-)-2.8 was placed in ~2 mL ethanol in a sealed vial. The vial was heated until the material dissolved. Upon cooling at room temperature, colorless needles formed.

\((+/-)-2.10\cdot(\text{-PrOH})_2\cdot(H_2O).\)  \textit{ca.} 5 mg of (+/-)-2.10 was placed in ~2 mL isopropanol in a sealed vial. The vial was heated until the material dissolved. Upon cooling at room temperature, colorless needles formed.

\((+/-)-2.8\cdot\text{BTC}\cdot4\text{MeOH}\cdot\text{H}_2\text{O}.)\)  A minimal amount of methanol was used to dissolve both \textit{ca.} 5 mg of (+/-)-2.8 and BTC separately. The solutions were layered in a vial precipitating prismatic crystals.

\((+/-)-2.8\cdot\text{BTC}\cdot3\text{acetone}.\)  A minimal amount of acetone was used to dissolve both \textit{ca.} 5 mg of (+/-)-2.8 and BTC separately. The solutions were layered in a vial precipitating prismatic crystals.

2.5.3. X-Ray Crystallography

Single crystal diffraction data were collected using a Siemens SMART 1k CCD X-ray diffractometer with Mo Kα radiation (0.71073 Å) at 173(2) K. The crystal structures were solved by direct methods using SHELXS, and all structure refinements were conducted using SHELXL-97-2.\textsuperscript{37} All non-hydrogen atoms were modeled with anisotropic displacement parameters, with the exception of some included solvents and/or disordered moieties. In \((P)-2.8\cdot4\frac{2}{3}\text{EtOH} the SQUEEZE subroutine in
PLATON\textsuperscript{38} was used to model the electron density associated with the highly disordered EtOH molecules to confirm the stoichiometry of the included solvent. Summary of crystallographic data are given in Table 2.1. The program X-Seed was used as a graphical interface for the SHELXL software suite and for the generation of figures.\textsuperscript{39}
### Table 2.1. Summary Crystallographic Data

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<th>(+)-2.8* (CH₃CH₂OH)₄⁺</th>
<th>(+/-)-2.10* (i-PrOH)₂•(H₂O)</th>
<th>(+/-)-2.8* BTC•(MeOH)₄•H₂O</th>
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<td>0.71073</td>
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<td>triclinic</td>
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<td>space group</td>
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<td>P₂₁</td>
<td>P-1</td>
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<td>colorless</td>
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<td>15.392(6)</td>
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<td>173(2)</td>
<td>173(2)</td>
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**Table 2.1. Summary Crystallographic Data (cont’d)**

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2.6. References


Chapter 3: Endohedrally Functionalized Cryptophanes and Insights into the
Conformational Isomerism of Cryptophanes

3.1. Introduction

The rational design of catalysts for asymmetric synthesis has developed into a prominent and diverse area of investigation. Successful catalyst development has required synthetic expertise, mechanistic understanding and chemical intuition. The importance of the latter factor stems from the fact that asymmetric induction is inherently a supramolecular process. The chirality determining step of any asymmetric reaction essentially involves the supramolecular (i.e. noncovalent) interaction of reacting partners; steric is a manifestation of supramolecular chemistry.

Selective substrate recognition and binding is a feature of catalysis displayed in nature by enzymes and other naturally occurring species. Once one or more target molecules are bound to an active catalytic site, they can react with dramatic rate increases and high selectivities for reasons such as induced proximity or transition state stabilization—provided by multiple or specifically oriented functional groups—or changes in solvation—active sites in enzyme are typically hydrophobic. Traditional catalyst development provides a means to deconvolute the overall catalytic activity of these systems by providing simpler synthetic hosts designed to explore components of the overall interaction displayed by the complicated natural systems.
There are numerous known or conceptual molecular scaffolds upon which one might attempt to construct chiral, concave (or capsular) reagents or catalysts. There are also several features that optimal candidates will exhibit: i) an appropriately sized cavity, large enough to allow certain reagents access to the active site, but small enough to still discriminate between potential reactive partners; ii) sufficient rigidity, to prohibit active functionality from turning to the outside of the molecule, away from the cavity; iii) sufficiently fast rates of substrate (i.e. reagent) complexation/decomplexation so as to allow reasonable turnover; and iv) a sufficiently chiral environment at the active site so as to induce asymmetry.

Synthetic molecular containers show exceptional promise in acting as novel reaction microchambers. Much work has clearly demonstrated the ability of container-like molecules to act as discriminatory hosts for appropriate guests, commonly altering guest conformational dynamics and organizing co-encapsulated molecular species into well-defined arrangements. Moreover, reaction kinetics and product outcomes of organic transformations involving encapsulated reagents are dramatically influenced by the supramolecular effects of encapsulation. Remarkably, there remain few examples of molecular capsules, or cavitands, with inwardly directed functional groups capable of directly participating in bond making or bond breaking processes.
As discussed in Chapter 1, simple alkyl bridged cryptophanes have shown remarkable size and shape selectivity for neutral, cationic, and even anionic guests. In principle, utilization of \( m \)-xylyl bridges (and their derivatives) provide an opportunity to specifically functionalize the interior and/or exterior of cryptophanes (Figure 3.1.1a).\(^2,3\) \( m \)-Xylyl bridged cryptophanes can be expected to exhibit an internal volume similar to that of cryptophane-555 (Figure 1.14). However, the larger steric bulk of the xylyl linkers have fewer degrees of freedom, and suggest that the kinetic barriers to guest ingress and egress may differ from that of cryptophane-555.

![Figure 3.1.1.](image)

**Figure 3.1.1.** (a) Functionalizing the positions \( exo \) and \( endo \) of an \( m \)-xylyl bridged cryptophane molecule can provide useful chemical characteristics. (b) \( Exo \)-acid \((+/F)_{anti}H_3\text{3.1}\) and (c) \( endo \)-acid functionalized \((+/)-anti-3.2\) cryptophanes illustrate these characteristics, respectively.

Functionalization of the cavity exteriors (\( exo \)-functionalization) can be expected to be useful for affecting capsule solubility or in providing opportunities to direct the assembly of these molecules in solution, in the solid state, or onto surfaces. For example, Mough and Holman have reported an \( exo \)-acid functionalized cryptophane \((+/-/anti-H_3\text{3.1})\)\(^2\) based on a 5-carboxyl substituted \( m \)-xylyl bridge (Figure 3.1.1b). This capsule was assembled into a 1D crystalline coordination polymer, namely 

\[ [Cu_{1.5}((+/)-anti-3.1\supset DMF)(C_6H_5N)_3(MeOH)]_x DMF_yMeOH, \]

the first coordination
polymer derived from cryptophane container molecules. The material was synthesized by reacting (+/-)-anti-H₃3.1 with Cu(NO₃)₂•2.5H₂O in the presence of pyridine (Chapter 2). This ‘flexible’ crystalline material is an illustration of coordination polymers derived from container molecules, the binding and storage properties of which may be largely governed by the container-like ligand.

Clearly, functionalization of the cavity interiors (endo) has the potential to affect the recognition properties of the host and certain functional groups may provide opportunities for the host molecules to directly participate in chemical reactions. Additionally, in solution, guest exchange in and out of these cryptophanes is typically on the sub-microsecond timescale, suggesting that reasonable substrate turnover rates should be possible. Past work in our group has additionally shown that the volumes of said cavities are on the order of 150 Å³, sufficiently large for arene-sized substrates, or simple portions of larger molecules. Inner phase functionality may also provide the opportunity to use these molecules in sensing applications, and it has been shown that chiral cryptophanes are able to discriminate between enantiomers of even the simplest of chiral guests, e.g. CHFClBr. Weber has also reported endo-ester and endo-acid ((+/-)-anti-3.2) functionalized cryptophanes based on a 2,5-substituted m-xylyl bridge (Figure 3.1.1c). The acid substituents of this endo-functionalized cryptophane, however, occupy a majority of the ellipsoidal cavity volume, limiting guests to small metal cations.
Based upon these considerations we have initiated a project motivated by two frontiers of modern chemistry, namely asymmetric organocatalysis\(^8\) and supramolecular encapsulation\(^9\) through the synthesis of endohedral pyridine functionalized cryptophane molecular containers. Pyridines make attractive functionalization targets because: 1) they are basic, 2) they can act as hydrogen bond acceptors, 3) when protonated, they

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**Figure 3.1.2.** Pyridine functional groups make attractive targets due to their versatility in the fields of catalysis and supramolecular chemistry.
may bind anions, 4) they can coordinate metals, 5) they may function as catalysts, for example as organocatalysts for acyl-transfer reactions, 6) they can be converted to their N-oxides, which may act as chiral Lewis bases, and 7) they are small and won’t fill the cavity. Considering the chirality of the anti cryptophanes, these molecules further promise to be reasonable candidates for asymmetric catalysis. The versatility of pyridine based on these properties is illustrated in Figure 3.1.2.

3.2. Synthesis and Implosion Behavior of an Endohedral Pyridyl Cryptophane

3.2.1. Introduction: The Conformational Isomers of CTBs and Cryptophanes

Central to the ability of cryptophanes to encapsulate and discriminate between molecule-sized substrates is the notion that these hosts exist in a conformation that offers a definite cavity for the encapsulation of appropriate guests. Although the smaller cryptophanes are indeed somewhat rigid, the CTB subunits from which they are constructed are well known to be conformationally dynamic, interconverting slowly—but readily at room temperature—between rigid crown (C) and equivalent (or enantiomeric) inverted-crown (Ci) forms via the flexible intermediate saddle-twist (S, hereafter simply ‘saddle’) conformer (Figure 3.2.1). Moreover, the crown and

![Figure 3.2.1. CTBs are conformationally dynamic and interconvert readily between the crown (C) and saddle (S) conformations.](image-url)
corresponding saddle conformers of even simply substituted CTBs (e.g. cyclotriveratrylene) can be as close in energy as 1.37 kcal/mol,\textsuperscript{10} coexisting in equilibrium at room temperature.

The $C$ to $S$ inversion barrier ($\Delta G_{C \rightarrow S}^{\ddagger}$) has been reported for a number of CTBs and is sufficiently large enough (26.5-31.5 kcal/mol; Table 3.2.1)\textsuperscript{11} to allow monitoring of the crown to crown inversion. The inversion is most easily studied with CTBs that are chiral, where the crown-to-crown conversion, monitored by the optical rotation, converts a chiral solution of CTB molecules to a racemic, optically inactive mixture on the order of days. The $\Delta G_{C \rightarrow S}^{\ddagger}$ has a surprisingly narrow range of values, even for

\textbf{Figure 3.2.2.} CTBs maintain a conformational flexibility that allows a crown-to-crown inversion that occurs through a saddle-twist intermediate (S).
large-group substituted CTBs (e.g. DOBOB) and CTBs bearing a Y’ substituent, and the C→S conformation process is ΔH favored.

The $K_{eq}$ for this process is however not well studied, with only two reports of CTBs that include a discussion of thermodynamic parameters. The $C_1$-symmetric saddle-twist intermediate conformational isomer is between 1.3 and 2.9 kcal/mol higher in energy than the crown conformation (c in Figure 3.2.2) and interconverts quickly on the $^1$H NMR time scale between six equivalent conformers where either one or two methylenes are inverted (‘down’, d or ‘up’, u) relative to the crown conformer. Therefore the $^1$H NMR spectrum of the $C_1$-symmetric saddle-twist form appears as a time averaged

Table 3.2.1. The kinetics and thermodynamics of numerous CTBs have been reported in the literature, including large group substituted CTBs.

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[a] 4-Hydroxymethyl-2-methoxybenzoxymethyloxoy. [b] 3,4,5-tris(p-n-dodecylbenzoxymethyloxoy (DOBOB). [c] Calculated from reported $\Delta G^\circ$ and $\Delta G^\circ$. [d] Calculated from reported $E_{eq}$. [e] 418 K. [f] Calculated from reported $\Delta H$ and $\Delta S$ using $\Delta G=\Delta H-T\Delta S$ @ 298K

76
pseudo-$C_3$ symmetric species, even at low temperatures. The high positive equilibrium entropy, $\Delta S^°_{\text{C-S}}$, appears to be reliant on the conformational dynamics of the saddle form, which allow many more degrees of conformational freedom than the non-flexible crown-form. The $K_{eq}$ also seems to be solvent dependent, favoring the saddle conformation in non-polar solvents, and the crown conformation in more polar solvents. For example,\textsuperscript{11b} CTV (Table 3.2.1; $X = Y = \text{OCH}_3$, $Y' = \text{H}$) in DMF ($K_{eq}(300K) \approx 0.008$) has a considerably lower $K_{eq}$ versus CHCl$_3$ ($K_{eq}(300K) \approx 0.1$), likely because the saddle-form—averaged over the conformational cycle—is non-polar, and the crown-form has a permanent dipole.

Considering that cryptophanes are essentially connected CTBs, it is therefore necessary to consider the existence of up to six possible minimum energy cryptophane conformational isomers that can conceivably result from all possible combinations of crown ($C$), inverted-crown ($C_i$), and saddle-twist ($S$) CTB forms—the crown/crown ($CC$), the crown/saddle ($CS$), crown/inverted-crown ($CC_i$), saddle/saddle ($SS$), saddle/inverted-crown ($SC_i$), and, finally, inverted-crown/inverted-crown ($C_iC_i$) conformational isomers (Figure 3.2.3). It is important to recognize that, while the cryptophanes are often considered to be rigid, hollow structures, it is generally only the crown-crown ($CC$) conformation of these hosts that offers a cavity amenable for the complexation of guests. The remaining conformers can be considered to be ‘imploded’\textsuperscript{2a} or ‘deflated’\textsuperscript{14} relative to the $CC$ form. These imploded species have been treated much as a curiosity in the literature and have not been well studied. The
conformational isomers of guest free cavitands and capsules, however, have been of recent interest because they have been shown to exhibit remarkable gas storage properties. For cryptophanes, the evacuation of guests from the host cavity can also result in an empty rigid cage (CC).

Collet and co-workers were the first to observe cryptophanes to adopt imploded conformations. The $^1$H NMR spectra of as-synthesized *syn* and *anti* diastereomeric mixtures of cryptophanes with long bridges (Figure 3.2.4b, $R = R' = OCH_3$, $Y = O(CH_2)_nO$, $n = 6-10$) showed imploded cryptophanes species that slowly, but
completely, converted to their \( CC \) forms at room temperature. The \( CC \) forms were observed to partially revert to their imploded forms upon warming, implying that the imploded forms of these cryptophanes are entropically favored. Similarly, cryptophane-\( 555 \) \( (3.7; \) Figure 3.2.4b, \( R = R' = OCH_3, Y = O(CH_2)_3O \) implodes upon heating (and emptying) to 523 K in the solid state, but reverts completely to its \( CC \) form upon standing in \( CHCl_3 \).\(^{15} \) Understandably, each of the aforementioned imploded cryptophanes was originally ascribed to be the \( CC_i \) conformational isomer on the basis of \(^1H\) NMR spectra that are consistent with a \( C_3 \) symmetric species.

![Diagram of cryptophanes](image)

**Figure 3.2.4.** The general structures of \( m \)-xylyl and aliphatic bridged cryptophanes.

In 2004, however, our group was the first to propose and demonstrate the existence of a \( CS \) cryptophane as an isolable conformational isomer with our report of the \( m \)-xylyl bridged, exo-ester functionalized cryptophane (+/-)-3.4.\(^{2a} \) The \( CC \) form of (+/-)-3.4 was partially converted to its imploded \( CS \) form by thermal liberation of tetrahydrofuran (THF) from its \( CC-(+/-)-3.4@THF \cdot 3THF \) clathrate. The single crystal structure of the
purified imploded form of (+/-)-3.4 unequivocally demonstrated it to be the CS conformational isomer, data that was further supported by complete (2D ROESY, COSY and variable temperature) $^1$H NMR spectroscopic characterization and kinetics following the explosion process. Notably, the $^1$H NMR spectrum of purified CS-(+//-)-3.4 exhibits a time-averaged $C_3$ symmetry and is remarkably similar to the reported spectra of the aforementioned imploded cryptophanes, suggesting to us that the earlier reported species may have in fact been CS, and not $C_{C_i}$ forms. Since 2004, there have been two other reports of imploded cryptophane species, each demonstrating CS forms of the much smaller cryptophane-222 scaffold. Specifically, Berthault and coworkers reported in 2006 the CS form of the 222-acid (3.8, Figure 3.2.4, $R = R' = OCH_2COOH$, $Y = O(CH_2)_2O$) in basic $D_2O$, the $^1$H NMR of which is $C_1$ symmetric, with the short bridges dramatically slowing the interconversion of the $C_1$ forms with an activation barrier of CS to CS of $E_a = 79.1 \pm 0.4$ kJ/mol. Dmochowski and co-workers have also serendipitously obtained and reported (in 2010) the crystal structure of the CS form of a tris-allyl functionalized cryptophane-222 derivative (Figure 3.2.4, $R = OCH_3$, $R' = OCH_2CH=CH_2$, $Y = O(CH_2)_2O$).

3.2.2. An Endo-Pyridine Functionalized Cryptophane

The synthesis and study of (+/-)-3.4 was part of our ongoing efforts to selectively functionalize the exteriors or interiors of cryptophanes. As discussed earlier, interior functionalization will affect the recognition properties of the cryptophanes and may
allow the use of their interiors as substrate-selective (organo)catalysts.\(^{19}\) As part of our continuing efforts in this area, we have synthesized an endo-pyridyl functionalized cryptophane, (+/-)-3.3. The synthetic route to (+/-)-3.3 can be seen in Figure 3.2.5, and follows the well-known ‘two-step’ method.\(^{20}\) Two diastereomers typically arise from the two-step method, the (+/-)-anti form (\(D_3\)), and the syn (meso) diastereomer (\(C_{3h}\)) but the synthesis of (+/-)-3.3 seems to give exclusively the anti form. (+/-)-3.3 has been characterized crystallographically (Figure 3.2.6) as a number of different clathrates, namely (+/-)-3.3⊂EtO•½Et₂O, (+/-)-3.3⊂(CH₂Cl₂•EtOH), (+/-)-3.3⊂MTBE•NO₂Me, (+/-)-3.3⊂iPr₂O•iPr₂O and (+/-)-3.3⊂EtOAc, unequivocally establishing the reaction product as the (+/-)-anti diastereomer. Thermal ellipsoid plots of the (+/-)-3.3 encapsulation complexes are shown in Figure 3.2.6. Single crystal structures from
acetone/H$_2$O, n-butanol, 3-heptanol, and THF were also collected, but the data was of insufficient quality for complete modeling. The crystal grown from THF evaporation did however show that a disordered THF molecule resided within the cavity of (+/-)-3.3.

In all but one of these structures, the guest is not a strong H-bond donating molecule, and no interactions are seen with the pyridyl nitrogen. Instead, the bridges adopt conformations that allow the pyridyl arene rings to occupy the remaining available space in the cavity of the molecule. Upon inspection of the crystal structures, the pyridine bridges can qualitatively be considered to adopt one of three general

**Figure 3.2.6.** The encapsulated solvent complexes of a) (+/-)-3.3⊂Et$_2$O • ½Et$_2$O b) (+/-)-3.3⊂(CH$_2$Cl$_2$ + EtOH)•CH$_2$Cl$_2$ c) (+/-)-3.3⊂EtOAc d) (+/-)-3.3⊂iPr$_2$O•iPr$_2$O e) (+/-)-3.3⊂MTBE•NO$_2$Me as determined by single crystal X-ray diffraction. TEPs are shown at 70% probability along with spacefill models of each complex.

In all but one of these structures, the guest is not a strong H-bond donating molecule, and no interactions are seen with the pyridyl nitrogen. Instead, the bridges adopt conformations that allow the pyridyl arene rings to occupy the remaining available space in the cavity of the molecule. Upon inspection of the crystal structures, the pyridine bridges can qualitatively be considered to adopt one of three general
orientations (Figure 3.2.7). If the angle of the pyridyl arene relative to the tangent of the CTB is from -45° (315° in the figure) to 45°, the bridge can be considered to be in a sideways position (135-225° is also sideways), or from 45-135° an outside position, and from 225-315° an inside position. The terms ‘inside’ facing, ‘outside’ facing, and ‘sideways’ facing refer to the direction that the pyridyl nitrogen is facing.

Figure 3.2.7. The orientation of the pyridyl arenes in the solid state can be considered a) ‘outside’, ‘inside’, and ‘sideways’ facing, and refer to the direction of the pyridyl nitrogen. b) The angle of the arene plane in relation to the tangent of the curve of the CTB portion of the molecule was used to determine which orientation the bridge was classified.

The packing of (+/-)-3.3 tends to be either a triclinic or a monoclinic space group. (+/-)-3.3⊂(CH₂Cl₂•EtOH)•CH₂Cl₂, (+/-)-3.3⊂MTBE•NO₂Me, and (+/-)-3.3⊂EtOAc are nearly isostructural with respect to the conformation of (+/-)-3.3, and all pack in the triclinic P-1 space group with the bridges oriented in a sideways, sideways, outside fashion. (+/-)-3.3⊂Et₂O•½Et₂O packs in a monoclinic space group (P2₁/n) with the bridges oriented sideways, sideways, outside, and the Et₂O guest is disordered about 2 positions.
The bridges in the (+/-)-3.3⊂iPr₂O•iPr₂O structure adopt a sideways, sideways, inside conformation with the inside facing pyridyl nitrogen directed at the C-H bonds of the closest methyl of the encapsulated isopropanol. In the (+/-)-3.3⊂(CH₂Cl₂•EtOH)•CH₂Cl₂ coencapsulated structure the EtOH molecule is held in the ‘window’ of the capsule by an O-H···N interaction (O···N is 2.80 Å), which provides a sideways facing pyridyl bridge by, and the CH₂Cl₂ molecule resides (disordered) in the remaining volume of the cavity. In cases where the guest molecules are small ((+/−)-3.3⊂(CH₂Cl₂•EtOH)•CH₂Cl₂, (+/-)-3.3⊂MTBE•NO₂Me, and (+/-)-3.3⊂EtOAc•EtOAc, more of the bridges are aligned outside facing, which allows the hydrocarbon portion of the pyridyl bridge to fill the extra cavity space instead of encapsulating a second guest, whereas larger guests force the bridges into a sideways or interior facing position. The only exception to this is in the coencapsulated CH₂Cl₂ + EtOH, where the second guest (EtOH) occupies the free space.

The cyclization of cryptophanes via the 2-step method is proposed to be a kinetically controlled reaction, and results in the formation of various polymers and polymeric materials. The formation of these side products is the reason for the typically low yield when performing these reactions. To minimize polymerization, the cyclization reactions are performed under moderate to high dilution conditions. Isolation of an intermediate cyclic dimer 3.12 when cyclizing 3.11 to synthesize (+/-)-3.3 (Figure 3.2.8) has been accomplished and a crystal structure has been determined. This molecule is only observed on occasion when working up the cyclization reaction. As a
logical reaction intermediate, it is assumed that 3.12 can undergo further reaction to form a cryptophane, or be incorporated into a polymeric side product. The workup of this reaction involves using basic methanol. It is anticipated that this step is responsible for the methanol substitution at the benzylic positions of the dimer.

3.2.3. Crystal Structure of a Protonated Endohedral Pyridyl Cryptophane

Receptor development for anion complexation has become a valuable field in supramolecular chemistry, driven in part by the biological and environmental importance of anionic species (e.g. TeO₄⁻, SO₄²⁻, F⁻). Developing highly selective anion receptors, however, is significantly more difficult than designing cation binding
due to variations in anion size, geometry, charge localization, and solvation properties. Design approaches to address these variations have included rigid and flexible receptors

utilizing neutral or cationic hydrogen bond donors, Lewis acid metal centers, and anion-π interactions to name a few.

Protonation of (+/-)-3.3 provides the opportunity to explore potential uses of these molecules as cationic, hydrogen bond donating, anion receptors. A crystal structure of the $\text{H}_3(+/-)-\text{3.3}[\text{HSO}_4]_3\subset\subset\subset 2\text{DMSO}\cdot2(\text{CH}_3)_2\text{CO}$ was obtained by protonating (+/-)-3.3 with excess $\text{H}_2\text{SO}_4$ in a 3:1 DMSO/H$_2$O solution (Figure 3.2.9a) followed by diffusion of acetone vapor into the reaction flask. The resultant structure, surprisingly, did not encapsulate any anions, but two DMSO molecules (Figure 3.2.9e), with three $[\text{HSO}_4]$ anions associating to the outside of the capsule (Figure 3.2.9c). The two DMSO
molecules residing in the cavity induce the pyridyl bridges into a sideways, inside, inside conformation.

As can be seen in Figure 3.2.9b, the cavity of H₃-(+/-)-3.3 possesses hydrophilic pyridinium cations within an otherwise hydrophobic pocket. This may also explain the absence of encapsulated [HSO₄]⁻ anions in the X-ray structure as the protonated capsule may prefer small molecule amphiphiles, supported by the alignment of the somewhat amphiphilic DMSO molecules in such an orientation to match the capsule profile. Investigation of protonated (+/-)-3.3 as an anion binder in solution has yet to be explored.

3.2.4. Conformational (Implosion) Behavior of (+/-)-3.3.

The ¹H NMR spectrum of the bulk (+/-)-3.3⊂(CH₂Cl₂+EtOH)•CH₂Cl₂ crystals dissolved in CDCl₃ initially gives a D₃-symmetric spectra with a residual ethanol and CH₂Cl₂ signals, as would be anticipated (Figure 3.2.10b), and contains the characteristic doublet of doublets at 4.58 ppm and 3.36 ppm arising from the axial and equatorial diastereotopic methylenic protons (Hₐ and Hₑ; Figure 3.2.12) on the lower rim of the CTB portion of the molecule. When left in solution at ambient conditions, however, the spectra begins develop new peaks that indicate the appearance of a species of seemingly C₃ symmetry. The same C₃-looking species is present when crystals of (+/-)-3.3⊂(CH₂Cl₂+EtOH)•CH₂Cl₂ are first treated by thermally by thermogravimetric analysis (TGA) to thermally liberate the CH₂Cl₂ and EtOH guests. The resulting
Figure 3.2.10. a) The previously reported spectrum of CS-(+/-)-3.4. b) The $^1$H NMR spectrum of crystals of CC-(+/-)-3.3⊂(CH$_2$Cl$_2$+EtOH)•CH$_2$Cl$_2$, immediately after dissolving. c) (+/-)-3.3 after heating crystals of CC-(+/-)-3.3⊂(CH$_2$Cl$_2$+EtOH)•CH$_2$Cl$_2$ to 413 K, resulting in the thermal liberation of EtOH and CH$_2$Cl$_2$. d) The nearly pure CS-(+/-)-3.3 conformational isomer that closely resembles that of CS-(+/-)-3.4. All spectra taken at room temperature in CDCl$_3$. Residual CC isomer is indicated by (*).

spectrum shows a pure mixture of CC and forms of the pseudo-C$_3$-symmetric CS (+/-)-3.3, the molecule responsible for the new proton peaks. Though almost all thermal experiments resulted in removal of EtOH and CH$_2$Cl$_2$ from (+/-)-
3.3⊂(CH₂Cl₂+EtOH)•CH₂Cl₂, leading to a solid mixture of CC and CS (+/-)-3.3, in one case of thermal guest loss, a pure sample of the CS-(+/-)-3.3 species was serendipitously obtained (Figure 3.2.10c). The thermal liberation of the guests can also be achieved using (+/-)-3.3⊂Et₂O•½Et₂O, and (+/-)-3.3⊂EtOAc•EtOAc (Figure 3.2.11), and the spectra of the resulting materials exhibit behavior identical to that obtained from (+/-)-3.3⊂(CH₂Cl₂+EtOH)•CH₂Cl₂. Extensive experiments were performed to determine the thermodynamics of the solid state equilibrium of the conformational change, but problems with reproducibility of the results yielded only the conclusion that the equilibrium favors the imploded species at higher temperatures, indicating a positive value for ΔS°_{CC→SC}.

Figure 3.2.11. The thermal liberation of guests from the clathrate crystals (+/-)-3.3⊂(CH₂Cl₂+EtOH) • CH₂Cl₂, (+/-)-3.3⊂Et₂O•½Et₂O, and (+/-)-3.3⊂EtOAc•EtOAc all result in a mixture of CC and CS (+/-)-3.3.
When the CDCl₃ was removed from this sample and the solid redissolved in acetonitrile, the spectrum eventually returned completely to the D₃ symmetric CC-(+/-)-3.3 spectrum, indicating that the new peaks were resultant of conformational isomers whose interchange is slow on the NMR timescale. Although the spectrum of CS-(+/-)-3.3 appears to correspond to a C₁-symmetric species (as drawn in Figure 3.2.12)—perhaps more fitting for a CC₈ isomer—there are several features that suggest that the spectrum of (+/-)-3.3 in Figure 3.2.11d does in fact correspond to a C₁-symmetric CS-(+/-)-3.3 species that displays time-averaged C₃-symmetry. Most notably, the spectrum of CS-(+/-)-3.3 closely resembles that of CS-(+/-)-3.4 (compare to Figure 3.2.11a).

![Diagram of CC and CS isomers](image)

**Figure 3.2.12.** The implosion of (+/-)-3.3 results in an equilibrium between D₃-symmetric CC and C₁ (pseudo C₃) symmetric CS-(+/-)-3.3 conformational isomers, which was unequivocally characterized to be the CS form by single crystal X-ray diffraction, and complete peak assignments (2D ROESY, COSY, and variable temperature) that showed extreme broadening at low temperature due to the slowing of the C₁→C₁ conformational dynamics.
The following observations are important in making this assignment. First, all of the signals corresponding to the assigned saddle CTB experience significant broadening, indicating a dynamic process. Specifically, Proton 2s, and to a lesser extent 1s, of the saddle CTB is upfield shifted and highly broadened relative to the crown-form CTB. Similarly, the OMe₃ (the OCH₃ protons of the saddle form CTB) is highly broadened and appears Δδ = 0.9 ppm upfield from OMe₃, the OCH₃ protons of the crown-form CTB. The crystal structure of isosteric CS-(+/−)-3.4 finds one of the three OMe₃ groups residing within the cavity/bowl of the crown-form CTB. The signals of a putative CCI isomer of (+/−)-3.3 would not be expected to exhibit this behavior.

It is well known that the protons of the guests within cryptophane cavities experience significant shielding due to their proximity to the arene carbons of the crown-form CTBs. For example, the Δδ for CHCl₃ bound by cryptophane-333 is ~4.3 ppm (Figure 1.3) upfield shifted from its free value. Similarly, at any given time, one-third of the OMe₃ protons find themselves within the crown-form CTB, and are correspondingly upfield shifted by ~1.2 ppm.

Another important feature in the assignment of the CS conformation comes from the behavior of the (formerly) ‘axial’ protons of the saddle-form CTBs. With all known crown-form CTBs, the more notable characteristic feature in the ¹H spectrum is the ~1.2 ppm downfield shift of the axial, Hₐ, methylenic protons relative to the equatorial, Hₑ, protons that arises from the extreme crowding of the intra-annular Hₐ protons in the crown-form. The Hₐ···Hₐ distance in (+/−)-3.3 is only around 2.0 Å on average. This
extreme chemical shift difference is all but lost in the assigned saddle-form CTB of CS(-/-)-3.3. H$_{as}$ and H$_{es}$ of the saddle-form are sterically less congested, and separated by only 0.16 ppm, whereas H$_{ac}$ and H$_{ec}$—the axial and equatorial protons of the crown-form of CTB—remain separated by 1.22 ppm. This observation strongly supports the contention that the assigned saddle-form CTB cannot be in the crown conformation.

3.2.5. The $CC \leftrightarrow CS$(-/-)-3.3 Equilibrium

Interestingly, and unlike other cryptophanes which appear to exist exclusively as their $CC$ forms at room temperature in organic solvents, (+/-)-3.3 gives rise to appreciable quantities of its $CS$ form in CDCl$_3$ under similar conditions, but this is not true for all solvents. A guest free mixture of $CC$ and $CS$ isomers was dissolved in various solvents to determine the room temperature $K_{eq}$ ($K_{CC \leftrightarrow CS}$) by integrating the aromatic $^1$H NMR signals for the $CS$ species (H$_{1c}$, H$_{2c}$, H$_{1s}$, and H$_{2s}$) versus the aromatic

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Table 3.2.2. The $K_{eq}$ of $CC \leftrightarrow CS$ was determined in various solvents and compared to the bulk solvent properties to seek some correlation.
signals for the $CC$ species ($H_1$ and $H_2$). The material was surprisingly insoluble in alcohols and various other solvents, limiting the number of solvents used to determine the concentration independent $K_{eq}$ values in Table 3.2.2.

When attempting to correlate the $K_{eq}$ values to solvent parameters such as the Gutmann donor (alpha) and acceptor (beta) number, the volume, dipole moment, or dielectric constant, no clear correlation can be drawn. The equilibrium seems to be molecule dependent and does not correlate to any one bulk solvent parameter. We hypothesize that the $CC \rightleftharpoons CS$ equilibrium depends on the ability of a specific molecule to occupy, or solvate, the interior of the capsule. We feel that careful study of the equilibrium will provide insight into the conformational properties of cryptophanes, so we sought to measure the thermodynamic components of the $K_{eq}$ in CHCl$_3$.

The ability to differentiate between the $CC$ and $CS$ species by solution $^1$H NMR—specifically the arene region—provided the ability to spectroscopically investigate the $CC \rightleftharpoons CS$ conformational equilibrium by directly determining the equilibrium constant ($K_{CC \rightleftharpoons CS}$) and interconversion rates ($k_1$ and $k_{-1}$) as a function of temperature in CD$_3$CN and CDCl$_3$. Solvent-free pure mixtures of $CS$-$(+/\cdot)$-$\textbf{3.3}$ and $CC$-$(+/\cdot)$-$\textbf{3.3}$ were prepared by heating crystals of $CC$-$(+/\cdot)$-$\textbf{3.3}$⊂(CH$_2$Cl$_2$•EtOH)•EtOH via TGA to 140°C, typically yielding a solid material that had been converted to ~75-80 % imploded species. For all samples, this preconditioned mixture of solvent-free $CS$-$(+/\cdot)$-$\textbf{3.3}$ and $CC$-$(+/\cdot)$-$\textbf{3.3}$ (~2 mg) was dissolved in 1.00 mL of the appropriate deuterated solvent and placed in an NMR tube. For the kinetics measurements, the solution was prepared immediately
before the spectra acquisition to observe as much of the \( CS \) form as possible at the beginning of the experiment. The equilibrium of interest and the rate expression for the process are:

\[
CC-(+/)-3.3 \quad \frac{k_\text{f}}{k_\text{i}} \quad CS-(+/)-3.3 \quad K_{CC \leftrightarrow CS} = \frac{k_\text{f}}{k_\text{i}} = \frac{[CS-(+/)-3.3]}{[CC-(+/)-3.3]}
\]

For determination of the equilibrium constants, \( K_{CC \leftrightarrow CS} \), solutions were made in CDCl\(_3\) (1.00 mL) using the solvent free \( CS-(+/)-3.3/CC-(+/)-3.3 \) mixture from the TGA (~2 mg) and placed in a thermostated bath for hours to days until the \(^1\)H NMR spectrum reached equilibrium, showing no changes to the integrated peak areas. Equilibrated spectra were taken at 10 °C intervals from 30-70 °C. The equilibrium constant was taken as the integrated areas of the aromatic peaks of the two isomers. These results are plotted as the van’t Hoff plot in Figure 3.2.13.

**Figure 3.2.13.** Van’t Hoff plot of \( K_{CC \leftrightarrow CS} = [CS-(+/)-3.3]/[CC-(+/)-3.3] \) as measured from the \(^1\)H NMR spectra in chloroform solutions as a function of the inverse absolute temperature.
Analysis of the plot and its results using the equation:

$$K_{CC\rightarrow CS} = \exp\left[\frac{-(\Delta H - T \Delta S)}{RT}\right]$$

where $T$ is temperature in Kelvin and $R$ is the real gas constant, gives the thermodynamic parameters of the equilibrium to be $\Delta G^{\circ}_{298} = 0.35(6)$ kcal/mol ($\Delta H^{\circ}_{298} = 0.81(4)$ kcal/mol and $\Delta S^{\circ}_{298} = 1.52(13)$ cal/mol·K). To our knowledge, this is the first measurement of an equilibrium constant between imploded (i.e. $CS$) and exploded (i.e. $CC$) cryptophane conformers. Of course, the small positive value of $\Delta G^{\circ}_{298}$ indicates that, in CHCl$_3$ solution at room temperature, $CC$-$(+/\text{-})$-3.3 is slightly more stable than the $CS$-$(+/\text{-})$-3.3. The positive values of $\Delta H^{\circ}$ and $\Delta S^{\circ}$ indicate that $CC$-$(+/\text{-})$-3.3 is the enthalpically favored form in CHCl$_3$ and that $CS$-$(+/\text{-})$-3.3 is entropically favored. These trends of $\Delta H^{\circ}$ and $\Delta S^{\circ}$ for the $CC\rightleftharpoons CS$ equilibrium are consistent with those measured for CTV and tris-methoxy-CTV (Table 3.2.1), providing further evidence that the formation of the saddle $CS$-$(+/\text{-})$-3.3 is entirely entropically driven.

Indeed, the $C_1$-symmetric $CS$-$(+/\text{-})$-3.3 appears to be much more conformationally dynamic than $CC$-$(+/\text{-})$-3.3, the conformational dynamics of the saddle portion of the former giving rise to a time-averaged $C_3$-symmetric spectrum. Interestingly, the $\Delta S^{\circ}$ of the $CC \rightarrow CS$ process for $(+/\text{-})$-3.3 (1.52 cal/mol·K) is less than those measured for other CTBs (3.3-8.27 cal/mol·K; see Table 3.2.1). This suggests that the tethered saddle macrocycle in $CS$-$(+/\text{-})$-3.3 has fewer conformational degrees of freedom than a free saddle macrocycle. Notably, in the $CS$ form of acid-cryptophane-222, the conformational degrees of freedom of the tethered saddle macrocycle are significantly
restricted as compared to a free saddle macrocycle as the interconversion between the equivalent $C_1$ conformations of acid-cryptophane-222 is slow on the NMR timescale at room temperature.\textsuperscript{16} This contrasts to Luz’s $C_1 \rightarrow C_1$ kinetics for nonamethoxy-CTV where the upper limit of $\Delta H^\ddagger = 13$-15 kJ/mol.\textsuperscript{11d} Additionally, $\Delta H^\circ$ is less positive for the $CC \rightleftharpoons CS$ equilibrium of (+/-)-3.3 than in related CTBs. This may be related to enthalpy-entropy compensation issues.

Overall, then, it may seem surprising that the $CS$ form of (+/-)-3.3 is so close in energy to the $CC$ form in CHCl$_3$ over the entire temperature range of the solvent ($\Delta G_{298} = 0.81$ and $\Delta G_{334} = 0.30$). For example, the 2-pyridyl CTG (+/-)-2.8 reported in Chapter 2 can be considered a non-capsular analogue of (+/-)-3.3. In CDCl$_3$ solution at room temperature at equilibrium, no amount of the saddle form of (+/-)-2.8 is observed by $^1$H NMR spectroscopy. Assuming a lower limit of detection of about 1% ($K_{eq} < 0.01$), the $\Delta G^\circ_{298}$ between the crown and saddle forms of (+/-)-2.8 is therefore at least 2.7 kcal/mol. Considering that the $\Delta S$ for the crown (+/-)-2.8 to saddle (+/-)-2.8 conversion would be expected to be more positive than for the $CC$ to $CS$ conversion of (+/-)-3.3, it is therefore clear that the 2-pyridyl substituted cavitand is not predisposed to adopt the saddle form.

An important difference between (+/-)-2.8 and (+/-)-3.3, however, is that the crown form of (+/-)-2.8 possesses a permanent dipole, whereas the $CC$ form of (+/-)-3.3 has no net dipole. Thus, bulk solvent polarity is expected to favor the crown form of (+/-)-2.8 relative to the saddle form. Luz et. al. have noted that the crown conformation of CTV
is more favored in polar solvents. So, the observation of a relatively stable CS form of (+/-)-3.3 (versus what would be expected based upon consideration of the CTB components) might be due to the lack of a solvent polarity effect—e.g. (CD₂Cl₂)₂ results in all CC-(+/-)-3.3, but CHCl₃ and CH₂Cl₂, having similar dipole moments result in significant amounts of CS-(+/-)-3.3—but \( K_{\text{eq}} \) does not seem to correlate with bulk solvent polarity.

Another important consideration governing the \( CC \Leftrightarrow CS \) equilibrium concerns the ability of the solvent to occupy, or solvate, the interior of the cryptophane nanocavity. Effective cavity solvation would be expected to more stabilize the \( CC \) form relative to the \( CS \) form in solution. Conversely, if the solvent is unable to access, solvate, the cryptophane molecular cavity, one might expect the \( CS \) and \( CC \) forms to be closer in energy. Indeed, Berthault and coworkers observed considerable formation of the \( CS \) form of acid-cryptophane-{222} in D₂O. We attribute this observation to the hydrophobic effect, where the inability of H₂O to effectively solvate the organic cryptophane interior leads to collapse of the capsule into the \( CS \) form.

To gain insight into the solvent dependent factors that govern the \( CC \Leftrightarrow CS \) equilibrium in cryptophanes, we sought to study the \( CS \Leftrightarrow CC \) interconversion kinetics in different solvents. Two solvents were chosen for this study: i) CDCl₃, because appreciable quantities of \( CS-(+/-)-3.3 \) are found to remain at equilibrium in this solvent; and ii) CD₃CN, because no \( CS-(+/-)-3.3 \) can be observed at room temperature at
equilibrium by $^1$H NMR, implying that, in this solvent, the $\Delta G_{298}^\circ$ between $CC$ and $CS$ ($\pm$)-3.3 in $\geq 2.3 \text{ kcal/mol}$ (assuming a 2% detection limit).

The $CS$-($\pm$)-3.3 to $CC$-($\pm$)-3.3 interconversion kinetics were studied by following the changes with time of the $^1$H NMR signals at different temperatures. A freshly prepared, solvent-free pure mix of $CS$-($\pm$)-3.3/$CC$-($\pm$)-3.3 (~2 mg) in preheated

\[ \text{Figure 3.2.14. Plots of the approach-to-equilibrium-parameter, } \ln\left(\frac{(R-R_e)}{(R+1)}\right), \text{ as a function of equilibrium time, } t. \text{ The different plots correspond to different temperatures, as indicated. The peak intensities were derived from spectra of the type shown in Figure 3.2.10.} \]

CDCl$_3$ (1 mL) in an NMR tube was immediately placed in a preheated NMR probe at the desired temperature (range from 35-65 °C), and spectra were recorded at regular time intervals until equilibrium was reached. At least 3 half-lives of data are plotted (Figure 3.2.14) using the expression$^{11b}$ (3.1) for a first order, reversible equilibrium:

\[
\ln \left( \frac{(R-R_e)}{(R+1)} \right) = (k_{CC \rightarrow CS} + k_{CS \rightarrow CC})t \quad (k_{CC \rightarrow CS} + k_{CS \rightarrow CC}) = k_{obs} \tag{3.1}
\]
where \( R \) is the ratio of \([CS- (+/-)-3.3]/[CC- (+/-)-3.3]\) at time \( t \) and \( R_e \) is the ratio of \( CS/CC \) at equilibrium at a certain temperature. Analysis of these results using the Eyring expression (3.2):

\[
k_{obs} = A \exp \left[ \frac{-E_a}{RT} \right] = \left[ \frac{k_B T}{h} \right] \exp \left[ \frac{-\left( \Delta H - T \Delta S \right)}{RT} \right]
\]  

(3.2)

yields \( k_{obs} \), which can be deconvoluted into the plot for \( k_{CC \rightarrow CS} \) and \( k_{CS \rightarrow CC} \) shown in Figure 3.2.15

\[
k_{CS \rightarrow CC} = \frac{k_{obs}}{(K_{eq} - 1)}
\]  

(3.3)

\[
k_{CC \rightarrow CS} = k_{CS \rightarrow CC} - k_{obs}
\]  

(3.4)

by using equations (3.3) and (3.4), where \( K_{eq} \) is the equilibrium constant at that temperature calculated from the van’t Hoff plot in Figure 3.2.13.

**Figure 3.2.15.** Eyring plots of the \( CS \leftrightarrow CC \) interconversion rates, \( k_{CC \rightarrow CS} \) and \( k_{CS \rightarrow CC} \), as measured from \(^1\)H NMR spectra of the type shown in Figure 3.2.10.
For CD₂CN, the equilibrium is pseudo first order for the conversion of CS-(+/−)-3.3 to CC-(+/−)-3.3 (equation 3.5). Since the ΔG between CC-(+/−)-3.3 and CS-(+/−)-3.3 is at

![Graph](image)

**Figure 3.2.16.** a) Plots of the approach-to-equilibrium-parameter, ln([CS]/[CC]), as a function of equilibrium time, t. The different plots correspond to different temperatures, as indicated. The room temperature data is not shown on this plot due to the length of time needed for the data collection. b) Eyring plot of the CS-(+/−)-3.3 to CC-(+/−)-3.3 conversion in acetonitrile.
least 2.7 kcal/mol in this solvent, the \( \text{CS} \rightarrow \text{CC} \) conversion process is effectively irreversible under the conditions of the experiment.

\[
\text{CS}- (+/-)-3.3 \rightarrow \text{CC}- (+/-)-3.3 \quad \ln[\text{CS}/\text{CC}] = -kt + \ln[\text{CS}/\text{CC}]
\] (3.5)

This \( \text{CS} \rightarrow \text{CC} (+/F)-3.3 \) conversion was studied with CD$_3$CN in the temperature range of 25-75 °C and the data are shown in Figure 3.2.16a. The results were used to generate an Eyring plot following Equation (3.2) and are shown in Figure 3.2.16b.

The reversion of \( \text{CS}-(+/F)-3.3 \) to \( \text{CC}-(+/F)-3.3 \) follows pseudo first order kinetics in acetonitrile with an energy barrier of \( \Delta G^\ddagger_{\text{CS} \rightarrow \text{CC}(298K)} = 25.9(7) \) kcal/mol (\( \Delta H^\ddagger_{\text{CS} \rightarrow \text{CC}(298K)} = 26.2(3) \) kcal/mol and \( \Delta S^\ddagger_{\text{CS} \rightarrow \text{CC}(298K)} = 0.94(8) \) cal/mol·K). In CDCl$_3$, the conversion follows first order reversible kinetics with an energy barrier of \( \Delta G^\ddagger_{\text{CS} \rightarrow \text{CC}(298K)} = 24.9(5) \)

![Figure 3.2.17. A schematic of the potential energy profile resulting from the kinetic and thermodynamic data collected for (+/F)-3.3.](image)
kcal/mol ($\Delta H_{CS \rightarrow CC(298K)} = 20.7(5)$ kcal/mol and $\Delta S_{CS \rightarrow CC(298K)} = -14.1(9)$ cal/mol·K) and $\Delta G_{CS \rightarrow CC(298K)} = 25.3(2)$ kcal/mol ($\Delta H_{CC \rightarrow CS(298K)} = 20.4(5)$ kcal/mol and $\Delta S_{CC \rightarrow CS(298K)} = -14.2(9)$ cal/mol·K). In chloroform, the $\Delta G^{\circ}_{298} = 0.35(6)$ kcal/mol ($\Delta H^{\circ} = 0.81(4)$ kcal/mol and $\Delta S^{\circ} = 1.52(13)$ cal/mol·K). These results, paired with the fact that the conformational changes associated with this equilibrium are the same as in CTBs, allow one to summarize the equilibrium in terms of the energy diagram in Figure 3.2.17.

A limited amount of thermodynamic and kinetics data for the imploded⇌exploded (CS⇌CC, in our view) equilibrium for other cryptophanes exists in the literature. What is known is summarized in Table 3.2.3 along with our data accumulated for (+/-)-3.3. Specifically, Collet and coworkers measured the barrier of the explosion (inflation) process for cryptophane-555. The process was originally ascribed to the inflation of the cup-in-cup $CC\_F$ to $CC\_F$ in CDCl$_3$, but, our analysis suggests the process is, in fact, a $CS\_F$ to $CC\_F$ conversion. Holman and Mough measured the kinetics of $CS$-

<table>
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<th>Molecule</th>
<th>X</th>
<th>Y</th>
<th>Solvent</th>
<th>$\Delta G^{\circ}_{CS \rightarrow CC}$ kcal/mol$^a$</th>
<th>$\Delta H^{\circ}_{CS \rightarrow CC}$ kcal/mol$^a$</th>
<th>$\Delta S^{\circ}_{CS \rightarrow CC}$ cal/mol·K$^a$</th>
<th>$\Delta G^{\circ}_{CC \rightarrow CS}$ kcal/mol$^a$</th>
<th>$\Delta H^{\circ}_{CC \rightarrow CS}$ kcal/mol$^a$</th>
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<td>nr</td>
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<td>-(CH$_2$)$_2$-</td>
<td>CHCl$_3$</td>
<td>nr</td>
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<td>-8.59</td>
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<td>nr</td>
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<tr>
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<td>-(CH$_2$)$_2$-</td>
<td>D$_2$O/NaO$_D$</td>
<td>25.1</td>
<td>$\geq 2.7^b$</td>
<td>nr</td>
<td>nr</td>
<td>(negative)</td>
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<td>nr</td>
</tr>
<tr>
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<td>-</td>
<td>CHCl$_3$</td>
<td>$\geq 26.7^a$</td>
<td>23.7</td>
<td>16.75</td>
<td>-23.45</td>
<td>$\geq 2.7^b$</td>
<td>nr</td>
<td>nr</td>
</tr>
<tr>
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<td>-</td>
<td>AcN</td>
<td>$\geq 28.6^b$</td>
<td>25.9(7)</td>
<td>26.2(3)</td>
<td>0.94(8)</td>
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<td>nr</td>
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<td>CHCl$_3$</td>
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<td>24.9(5)</td>
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<td>0.35(6)</td>
<td>0.80(4)</td>
<td>1.52(13)</td>
</tr>
</tbody>
</table>

$^a$ calculated from $\Delta G^\circ$ and $\Delta H^\circ$

$^b$ A detection limit of 1% is determined by $^1$H NMR and calculates to $^\circ$ kcal/mol difference in energy

$^c$ 298K
(+/-)-3.4 converting to CC-(+/-)-3.4 in CDCl₃ and Berthault and coworkers measured the rate of collapse of CC-acid-222 to CS-acid-222 in D₂O. The first feature worth noting in the data shown in Table 3.2.3 is that the barriers for conversion of imploded cryptophane species to exploded species (in our view the CS→CC process) are all below 26 kcal/mol, ranging form 20.5 kcal/mol for 555 in CDCl₃ to 26.0 kcal/mol for (+/-)-3.3 in CD₃CN. These values are lower than all of the known barriers for crown to crown conversions in CTBs, a process that proceeds via the saddle CTB form. This in itself is strong evidence for the contention that the imploded cryptophane species are in the CS form as opposed to the CC form as reported for 555. A CC<formula>→</formula>CC conversion would be expected to exhibit a higher barrier, similar to the barriers observed for the C<formula>→</formula>Cᵢ conversion of CTBs.

It is useful to compare the CC<formula>↔</formula>CS conversion kinetics of (+/-)-3.3 in CDCl₃ versus CD₃CN. In CDCl₃, the ΔG (+0.35(6) kcal/mol) and ΔH (0.81(4) kcal/mol) between CS and CC conformational isomers is small, whereas in CD₃CN, the ΔG ≥ 2.7 kcal/mol. It was of interest to determine, via the kinetics measurements, whether the greater stability of the CC form relative to the CS form in CD₃CN versus CDCl₃ could be attributed to a better solvation of the cavity interior by CD₃CN. Notably, in CD₃CN, (+/-)-3.3, behaves as most all other cryptophanes reported in the literature, with the implosion equilibrium favoring the CC isomer. In CDCl₃, however, the two species are similar in energy.
The two situations that can potentially give rise to the observation of the $CS-(+/-)-3.3$ isomer in CDCl$_3$ at room temperature are: i) the free energy of $CS-(+/-)-3.3$ ($\Delta G^0_{CS}$) is lowered compared to that of the $CS-(+/-)-3.3$ species in CD$_3$CN, or ii) the free energy ($\Delta G^0_{CC}$) of $CC-(+/-)-3.3$ is raised related to the $CC-(+/-)-3.3$ species in CD$_3$CN. Either of these effects would cause the difference in energy between the two species to (e in Figure 3.2.17) to decrease, providing the existence of the $CS$ form in observable equilibrium. An alternative model is the case in which, if in the gas, or amorphous solid phase, the intrinsic energies of the two species ($CS$ and $CC$ ($+/-)-3.3$) fall into two

![Figure 3.2.18](image)

**Figure 3.2.18.** a) Solvation of the interior of $CC$ when the stability of $CS \approx CC$ will result in a more favorable energy for $CC$, where b) if $CC$ is intrinsically more stable, the solvation of the capsule interior by implosion will result in lowering the energy of $CS$
regimes. In the first the energies are roughly equivalent in stability. In this case, a solvent such as CD$_3$CN, which has been found experimentally to prefer the CC conformation exclusively, will solvate the interior of the cryptophane, stabilizing the CC conformation via the CC⊂solvent complex. This leaves the S→C barrier unaffected, but raises the barrier of C→S. In the second case, the CC conformation is intrinsically more stable than the CS form, but the CS conformation is stabilized by the solvation of the interior of the cavity by implosion, effectively solubulizing itself.

To determine which scenario is more likely—either the free energy of CS-(+)/-3.3 (ΔG°$_{CS}$) is lowered or the free energy (ΔG°$_{CC}$) of CC-(+)/-3.3 is raised—relative to the equilibrium in CD$_3$CN, we can consider the kinetic data for CC-(+)/-3.3. The CS→CC barrier for the two systems (ΔG‡$_{CS→CC}$) is ~1 kcal/mol different (b in Figure 3.2.15), where the CC→CS barriers (a in Figure 3.2.15; ΔG‡$_{CC→CS}$), are different by 3.3 kcal/mol, (+/-)-3.3 showing a larger CC→CS barrier in CD$_3$CN. These differences support the conclusion that CC-(+)/-3.3 in CDCl$_3$ is becoming higher in energy relative to CC-(+)/-3.3 in CD$_3$CN, and is the primary contributor to the change in e in Figure 3.2.17.

Inspection of the kinetic and thermodynamic data leads to the conclusion that the energy preference of cryptophanes to adopt the CC conformation can be attributed to the stabilization that arises from the solvation of the interior of the capsule. Solvents (or guests) that are complimentary to the cryptophane cavity will result in a strong preference for the cryptophane to adopt the CC form, whereas the relative amount of the
CS form observed would be expected to be more significant when the solvent is not complimentary to the cavity. For certain solvents, those that poorly solvate the interior, the enthalpic benefits of the interior solvation (typically a few kcal/mol) is lost. This loss is also the main driving force behind implosion as a result of the hydrophobic effect. This difference appears to derive from the nitrogen heteroatoms into the $m$-xylyl bridges—the only difference between (+/-)-3.3 and other $m$-xylyl bridged cryptophanes that do not display implosion at room temperature. The exact nature of the effect is, however, unclear. These results provide insight into the conformational implosion properties of cryptophanes and, specifically, how the conformational equilibrium is largely affected by the unique complementarity between the cavity interior and the solvent/guest molecule.
3.3. Other interesting Endohedral Pyridine Functionalized Cryptophanes

3.3.1. An exohedral-chloro-endohedral-pyridyl Cryptophane

The most common application of pyridine containing molecules as catalysts is in their direct nucleophilic addition to electrophiles, such as in acyl transfer reactions, or the addition of alcohols to ketenes, as highlighted in Figure 3.3.1. Incorporation of pyridines into the bridges of cryptophanes might express similar activity, and may also catalyze organic transformations by i) enhancing the nucleophilicity of encapsulated reagents (alcohols, for example) through hydrogen bonding, or, ii) via complete deprotonation, acting as a chiral Brønsted acid.

![Chemical Structures](image)

**Figure 3.3.1.** Concave bases have been used by Lüning to catalyze a) the addition of alcohols to ketenes and b) by Fu in the enantioselective acylation of alcohols.

Lüning and coworkers\(^2\) have been successful in using concave bases to activate alcohols toward their addition to ketenes with remarkable size/shape selectivity. Fu and coworkers\(^3\) have shown that the chirality determining step in the enantioselective
addition of pyrroles to ketenes (catalyzed by the chiral DMAP-N derivative in Figure 3.3.1b) involves the protonation of an achiral enolate by the protonated form of the chiral catalyst. Furthermore, the DMAP catalyzed acylation of alcohols is highly accelerated by the presence of auxiliary pyridine general bases, which, by enhancing the nucleophilicity of the alcohol, accelerate the rate determining nucleophilic addition of the alcohol to the acyl group of the N-acylated intermediate. It is anticipated that the “extra” pyridyl nitrogens present on the interiors may allow I to function in an unprecedented dual role capacity; one interior nitrogen could act a nucleophilic catalyst, by being acylated, and another may act as a general auxiliary base to activate the approaching alcohol.

For acyl transfer reactions, substitution alpha to the pyridyl nitrogen atom is known to dramatically attenuate the activity of the catalyst by inhibiting planarity and π-conjugation within the N-acylated intermediate. For instance, relative to the background reaction, the rates of catalysis by DMAP, pyridine, 2-methylpyridine, and 2,6-dimethyl pyridine for the benzoylation of benzyl alcohol using BzCl in benzene are: 3.45×10^8, 9.29×10^3, 435, and 115. It is important to note that 2,6-substitution decreases the rate, relative to pyridine, by a factor of ~80, but 4-N-dimethylation increases the rate by a factor of almost 4×10^4.31 Tuning of the nucleophilicity/basicity of the interior nitrogen can be accomplished by introducing electron donating groups (e.g. N(alkyl)₂) at the 4- positions (R, in Figure 3.1.2) potentially compensating for this loss in activity.32
A synthetic pathway devised for incorporating substitution at the 4-position on a pyridyl bridge can be seen in Figure 3.3.2. Starting with 2,6-lutidine, peroxide is used to make N-oxide 3.14, which is then nitrated to afford 3.15. Concentrated HCl is then used at high pressure under reflux to replace the nitro group with a chloro functionality resulting in 3.16. Phosphorous tribromide is then used to remove the N-oxide resulting in 3.17 which is then halogenated via NBS to give 3.18. The bis-halogenated 3.18 is then reacted with vanillyl alcohol to give 3.19, the molecule needed for the two-step method approach to the synthesis of (+/-)-3.12 and 3.13.

Figure 3.3.2. The two-step method synthetic pathway to (+/-)-3.12 and 3.13.
All of the intermediates up to 3.19 have been synthesized in good yield (> 63 %) with the exception of 3.18 (25 %). The bromination reaction is known to produce many different products as a consequence of proceeding through a radical mechanism. The cyclization of 3.19 has been attempted, providing $^1$H NMR evidence of the cryptophane through the appearance of doublets for the $H_a$ and $H_e$ protons, which will only be present if the cup portion of the molecule is formed. Unfortunately, isolation of either the syn or the anti diastereomer has not been achieved. Other synthetic routes – i.e. the template or capping methods – may prove to be more effective at synthesizing this molecule and are being considered as future work towards a DMAP cryptophane. An additional area for future work is determination of the optimal step at which to add the $N$(alkyl)$_2$ group. This is an important consideration since the value of the cryptophane is high, and unless the reaction proceeds quantitatively with an easy recovery, it is not advised to perform chemistry on cryptophanes (+/-)-3.12 and 3.13.

The exo-chloro route to DMAP type cryptophanes also provides the opportunity to couple other useful groups exo to the capsule and potentially induce interesting properties. From the chloro derivative, it is conceivable to i) couple a fluorophore, such as anthracene, for sensing purposes, ii) introduce amine groups for potential imine chemistry, iii) introduce a hydrogen bond donor/acceptor (i.e. carboxylate/carboxylic acid) to provide water solubility or potentially build metal organic frameworks, and iv) introduce sulfonate groups to provide water solubility, and when the pyridine is protonated, be zwitterionic.
3.3.2. A Phenanthroline Bridged Cryptophane

Chelating agents such as 2,2'-bipyridine and 1,10-phenanthroline have been extensively used as ligands in coordination chemistry. Interest in these molecules stems from their catalytic, redox, and photoredox properties, and their versatility in complexation of a wide variety of various metals. Incorporating these types of pyridine-based chelating ligands as bridges in a cryptophane would provide the ability to explore already established reactions using these metal chelating moieties as they occur in the ‘inner phase’ of the molecular container.

The first reaction pathway used to incorporate these ligands into a cryptophane molecular container can be seen in Figure 3.3.3. Adapting literature procedures, neocuproine was converted to the aldehyde 3.22 with SeO₂, and successively reduced to the benzyl alcohol 3.23. Halogenation of this species gave 3.24, and subsequent

![Chemical structures and reactions](image)

**Figure 3.3.3.** The two-step method synthetic route to phenanthroline bridges cryptophanes 3.20 and (+/-)-3.21.
reaction with 2 equivalents of vanillyl alcohol provides the precursor 3.25 for the two step method for forming the phenanthroline cryptophanes 3.20 and (+/-)-3.21.

Initial cyclization attempts of 3.25 in both formic acid and HCl gave only polymeric material as determined by \(^1\)H NMR. It is hypothesized that the cyclization, which proceeds through an electrophilic aromatic substitution mechanism, must compete with the reaction between the benzylic alcohol and arenes in the phenanthroline, forming undesired polymeric materials. This further decreases the already low expected yield of cyclization. Current plans for synthesizing 3.20 and (+/-)-3.21 are being directed toward use of the capping method, where the reaction of 3.25 with CTG should provide a greater yield of the cryptophane. It is recognized that the windows to the cavity of both 3.20 and (+/-)-3.21 are large and that the constrictive binding effect of the molecule will be attenuated if not absent completely. The environment inside the capsule, however, is still size selective, and in the case of (+/-)-3.21, chiral.

3.4. Experimental

3.4.1. Materials and Methods

All solvents were used as received from Fisher (Pittsburgh, PA). Reagents were obtained from Acros (Pittsburgh, PA) or Aldrich (Milwaukee, WI) and were used without further purification. All reactions were carried out under nitrogen atmosphere. Chromatography was carried out on silica gel (32-64µm). NMR spectra were recorded on either a Mercury Varian 300 MHz or an Inova 400 MHz Spectrometer operating at
300 or 400 MHz ($^{1}$H), or 75.5 or 100.5 MHz ($^{13}$C), respectively. All NMR spectra were collected at room temperature (298(2) K) unless otherwise noted and were indirectly referenced to TMS using residual solvent signals as internal standards. Elemental analyses were carried out on a Perkin-Elmer PE2400 microanalyzer.

2,6-bis-Bromomethyl Pyridine (3.10). To a suspension of 2,6-bis(hydroxymethyl)pyridine (1.00 g, 7.19 mmol) in chloroform (20 mL) was added phosphorous tribromide (5.8 mL, 2.2 mmol) drop wise at –10 °C. The solution was then heated under reflux for 2 hours, cooled to room temperature and was added to 50 mL water. The organic layer was separated and the aqueous layer washed with chloroform (3 x 50 mL). The combined organic layers were dried over magnesium sulfate and evaporated under vacuum to give a colorless crystalline solid. Yield (1.3 g, 4.9 mmol, 69 %); $^{1}$H NMR (CDCl$_3$): δ 7.65 (dd, $^{3}$J = 7.8 Hz, $^{3}$J = 7.8 Hz, 1H, p-H); δ 7.36 (d, $^{3}$J = 7.8 Hz, 2H, m-H); δ 4.52 (s, 4H, CH$_2$).

2,6-Bis-(4-hydroxymethyl-2-methoxy-phenoxymethyl)-pyridine (3.11). 3-methoxy-4-hydroxy benzyl alcohol (2.33 g, 15.1 mmol), 2,6-bromomethyl pyridine (3.10) (2.00 g, 7.54 mmol), and K$_2$CO$_3$ (8.35 g, 60.4 mmol), were stirred in 300 mL acetone under nitrogen at room temperature for 24 hours. 500 mL of water was added and the solution was extracted with CH$_2$Cl$_2$ (3 x 100 mL). The organic fractions were collected, dried over MgSO$_4$ and evaporated en vacuo. The resulting solid was recrystallized from NO$_2$CH$_3$ to yield a colorless solid. Yield (2.50 g, 80.6%); mp = 128-130°C; $^{1}$H NMR (acetone-d$_6$): δ 7.83 (dd, $^{3}$J = 7.8 Hz, $^{3}$J = 7.8 Hz, 1H, Ar); δ
7.51 (d, \(^3J = 10.4\) Hz, 2H, Ar); \(\delta\) 7.00 (d, \(^3J = 2.4\) Hz, 2H, Ar); \(\delta\) 6.95 (d, \(^3J = 10.8\) Hz, 2H, Ar); \(\delta\) 6.81 (d of d, \(^3J = 10.8\) Hz, \(^3J = 2.4\) Hz, 2H, Ar); \(\delta\) 5.13 (s, 4H, ArCH\(_2\)O); \(\delta\) 4.51 (s, 4H, ArCH\(_2\)OH); \(\delta\) 3.82 (s, 6H, OCH\(_3\)). \(^13\)C NMR (acetone-d\(_6\)):

Aromatic Region: \(\delta\) 158.24, 150.90, 148.18, 138.37, 137.19, 121.12, 119.74, 115.17, 112.17. Aliphatic Region: \(\delta\) 72.62, 64.66, 56.27. Anal. calcd. for C\(_{22}\)H\(_{25}\)O\(_6\)N: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.37; H, 6.35; N, 3.89.

(+/−)-3.3. To stirring 6 M HCl (4.5 L) was added 3.05 g (8.2 mmol) of 2,6-bis(4-hydroxymethyl-2-methoxy-phenoxymethyl)pyridine (3.11). The reaction was stirred at room temperature for 24 hours and the solvent was then removed under vacuum. The residue was dissolved in hot methanol (150 mL) and poured into H\(_2\)O (~50 mL). Concentrated methanolic NaOH was added until the solution was basic by litmus paper. The aqueous solution was extracted with CH\(_2\)Cl\(_2\) (3 x 200 mL) and the organic layers were collected, dried over MgSO\(_4\) and evaporated under vacuum. The resulting solid was chromatographed with 5% triethylamine in ethyl acetate (R\(_f\) = 0.62) and recrystallized by diffusion of diethyl ether into a CH\(_2\)Cl\(_2\) solution of the compound to yield colorless crystals. Yield (425 mg, 15.3 %); mp = 210-212 °C; \(^1\)H NMR (CDCl\(_3\); labeled according to Figure 3.2.12): \(\delta\) 7.49 (dd, \(^3J = 7.8\) Hz, \(^3J = 7.8\) Hz, 3H, H\(_4\)); \(\delta\) 7.27 (d, \(^3J = 7.8\) Hz, 6H, H\(_3\)); \(\delta\) 6.73 (s, 6H, H\(_1\)); \(\delta\) 6.52 (s, 6H, H\(_2\)); \(\delta\) 5.18 (d, \(^2J = 14.0\) Hz, 6H, H\(_b\)); \(\delta\) 5.01 (d, \(^2J = 14.0\) Hz, 6H, H\(_c\)); \(\delta\) 4.58 (d, \(^2J = 13.7\) Hz, 6H, H\(_d\)); \(\delta\) 3.64 (s, 18H, OCH\(_3\)); \(\delta\) 3.36 (d, \(^2J = 13.7\) Hz, 6H, H\(_e\)). \(^13\)C NMR (CDCl\(_3\)): Aromatic Region: \(\delta\) 157.4; \(\delta\) 148.6; \(\delta\) 146.7; \(\delta\) 137.0; \(\delta\) 133.3; \(\delta\) 131.8; \(\delta\) 120.1; \(\delta\) 117.4; \(\delta\) 113.9. Aliphatic
Region: $\delta$ 72.4; $\delta$ 56.6; $\delta$ 36.6. Anal. calcd. for C$_{69}$H$_{63}$O$_{12}$N$_3$ $\cdot$ (CH$_3$CH$_2$)$_2$O $\cdot$ 0.75 CH$_2$Cl$_2$: C, 70.07; H, 5.94; N, 3.33. Found: C, 69.91; H, 6.01; N, 3.35.

$[\text{H}_3(+/-)-3.3][\text{HSO}_4]_3$. 10 mg of (+/-)-3.3 was dissolved in 1 mL 3:1 DMSO:H$_2$O and 0.5 mL of H$_2$SO$_4$ conc. was added dropwise. The solution was evaporated under vacuum to yield a yellow solid. Yield (12.3 mg, 98.4 %). $^1$H NMR (3:1 DMSO-$d_6$: D$_2$O): $\delta$ 8.40 (dd, $J^3 = 7.8$ Hz, 3H, pyr-H); $\delta$ 8.01 (d, $J^3 = 7.8$ Hz, 6H, pyr-H); $\delta$ 7.20 (s, 6H, aryl-H); $\delta$ 7.07 (s, 6H, aryl-H); $\delta$ 5.25 (d, $J^2 = 14.0$ Hz, 6H, O-CH$_2$-pyr); $\delta$ 4.99 (d, $J^2 = 14.0$ Hz, 6H, O-CH$_2$-pyr); $\delta$ 4.73 (d, $J^2 = 13.7$ Hz, 6H, H$_a$); $\delta$ 3.97 (s, 18H, OCH$_3$); $\delta$ 3.54 (d, $J^2 = 13.7$ Hz, 6H, H$_c$).

2,6-dimethylpyridine-N-oxide (3.14).$^{35}$ 30 mL (0.27 mol) of 2,6-lutidine was added to 300 mL of acetic acid and treated with 40 mL 35 % H$_2$O$_2$ at room temperature. The reaction mixture was then heated to 80 °C. After 3 hours, 10 mL of 35 % H$_2$O$_2$ was added and the solution heated for another 9 hours. The solution was then concentrated under vacuum to ~75 mL and diluted with 100 mL H$_2$O. The solution was then evaporated under vacuum to near dryness and anhydrous Na$_2$CO$_3$ was added slowly until the solution was strongly alkaline. 250 mL CHCl$_3$ was then added and the solids were filtered off. The organic layer was dried over MgSO$_4$ and evaporated under vacuum to yield an orange-yellow liquid. Yield (26.0 g, 76.3 %). Proton spectra were consistent with those previously reported.$^1$H NMR (CDCl$_3$): $\delta$ 7.12 (d, $J^3 = 7.8$ Hz, 2H, Ar); $\delta$ 7.07 (t, $J^3 = 6$ Hz, 1H, Ar); $\delta$ 2.52 (s, 6H, CH$_3$).
4-nitro-2,6-lutidine N-oxide (3.15).\(^{35}\) 26.0 g (mol) of 2,6-lutidine N-oxide was added to 78 mL conc. \(\text{H}_2\text{SO}_4\) and 30 mL conc. \(\text{HNO}_3\) and refluxed for 12 hours. The solution was cooled to room temperature, poured into excess ice, and extracted with \(\text{CHCl}_3\) (5 x 100 mL). The organic layers were collected, dried over \(\text{MgSO}_4\) and evaporated under vacuum to yield a yellow-green solid. The solid was recrystallized twice from EtOH (200 mL) to give a white fluffy solid. Yield (22.4 g, 63 %). Proton spectra were consistent with those previously reported. \(^1\text{H NMR (CDCl}_3\): \(\delta 8.00\) (s, 2H, Ar); \(\delta 2.56\) (s, 6H, Me).

4-chloro-2,6-lutidine N-oxide (3.16).\(^{35}\) 7.00 g (0.04 mol) of 4-nitro-2,6-lutidine N-oxide was dissolved in 100 mL conc. \(\text{HCl}_\text{aq}\) and heated at 200 °C for 24 hours in a pressure flask. The solution was then evaporated to dryness and dissolved in a minimal amount of \(\text{H}_2\text{O}\). The solution was extracted with \(\text{CHCl}_3\) (3 x 100 mL), the organic layers collected and dried over \(\text{MgSO}_4\) and evaporated to yield a yellow-white solid. Yield (5.34 g, 82 %). Proton spectra were consistent with those previously reported. \(^1\text{H NMR (CDCl}_3\): \(\delta 7.13\) (s, 2H, Ar); \(\delta 2.48\) (s, 6H, Me).

4-chloro-2,6-lutidine (3.17).\(^{35}\) 5.0 g (0.03 mol) 4-chloro-2,6-lutidine-N-oxide was dissolved in cold \(\text{CHCl}_3\) (150 mL) and treated with 20 mL (0.14 mol) \(\text{PCl}_3\) and heated to reflux for 2 hours. The solution was cooled and slowly quenched with ice. Basic water (sat. \(\text{NaOH}_\text{aq}\)) was added until the solution was basic by \(\text{pH}\) paper and extracted with \(\text{CHCl}_3\) (3 x 50 mL). The organic layers were collected, dried over \(\text{MgSO}_4\) and evaporated to dryness. The resulting solid was dissolved in a minimal amount of
nitromethane and the product was precipitated with diethyl ether and collected by filtration. Yield (4.3 g, 96 %). Proton spectra were consistent with those previously reported.

2,6-Bis-bromomethyl-4-chloro pyridine (3.18). 4.0 g (0.03 mol) 4-chloro-2,6-lutidine was dissolved in 150 mL CHCl$_3$ and treated with 2.5 equivalents NBS (12.6 g, 0.07 mol) and the solution was irradiated with $h\nu$ and followed by TLC (~3 hours). The reaction was washed with NaHCO$_3$ (3 x 50 mL), dried over MgSO$_4$ and evaporated. The resulting solid was chromatographed with CH$_2$Cl$_2$ ($R_f$ = 0.6) yielding a white solid. Yield (8.4 g, 25 %). Proton spectra were consistent with those previously reported.

(4,4′-(4-chloropyridine-2,6-diyl)bis(methylene)bis(oxy)bis(3-methoxy-4,1-phenylene))dimethanol (3.19). 3-methoxy-4-hydroxy benzyl alcohol (2.33 g, 15.1 mmol), 2,6-bromomethyl-4-chloro pyridine (3.10) (2.00 g, 7.54 mmol), and K$_2$CO$_3$ (8.35 g, 60.4 mmol), were stirred in 300 mL acetone under nitrogen at room temperature for 48 hours. 500 mL of water was added and the solution was extracted with CH$_2$Cl$_2$ (3 x 100 mL). The organic fractions were collected, dried over MgSO$_4$ and evaporated en vacuo. The resulting solid was recrystallized from NO$_2$CH$_3$ to yield a colorless solid. Yield (1.51 g, 45 %); mp = 119-123°C; $^1$H NMR (CDCl$_3$): $\delta$ 7.49 (s, 2H, Pyr-Ar); $\delta$ 6.96 (d, $^3J$ = 2.4 Hz, 2H, Ar); $\delta$ 6.86 (d, $^3J$ = 11.2 Hz, 2H, Ar); $\delta$ 6.82 (d of d, $^3J$ = 11.2 Hz, $^3J$ = 2.4 Hz, 2H, Ar); $\delta$ 5.22 (s, 4H, ArCH$_2$O); $\delta$ 4.62 (s, 4H, ArCH$_2$OH); $\delta$ 3.92 (s, 6H, OCH$_3$). $^{13}$C NMR (CDCl$_3$): Aromatic Region: $\delta$ 169.30, 157.33, 150.71, 149.23, 139.24, 129.37, 128.92, 122.73, 118.52. Aliphatic Region: $\delta$

1,10-phenanthroline-2,9-dicarbaldehyde (3.22).\textsuperscript{36} 1.38 g SeO\textsubscript{2} (0.0126 mol) was added to a stirring solution of neocuproine (1.00 g, 0.0050 mol) in 75 mL 1,4-dioxane. The solution was refluxed for 3 hours and filtered hot through a Celite plug. The filtrate was evaporated to dryness and the residue dissolved in DMF and cooled to 0 °C. Any precipitate was removed by filtration and water was added to the DMF solution until precipitation was complete. The solid precipitate was collected on a glass frit. Yield (0.97 g, 86 %). Proton spectra were consistent with those previously reported.

(1,10-phenanthroline-2,9-diyl)dimethanol (3.23).\textsuperscript{36} 1.36 g NaBH\textsubscript{4} (0.036 mol) was added to a stirring solution of 3.22 (3.0 g, 0.013 mol) in 150 mL EtOH. The solution was refluxed for 2 hours and evaporated to dryness en vacuo. The residue was recrystallized from water to yield clear needles. Yield (2.35 g, 79 %).

2,9-bis(bromomethyl)-1,10-phenanthroline (3.24).\textsuperscript{36} 2.3 g (0.009 mol) was refluxed in 100 mL 48 % HBr for 2 hours. The solution was cooled to 0 °C and slowly treated with solid Na\textsubscript{2}CO\textsubscript{3} until precipitation was complete. The solid precipitate was collected on a glass frit and recrystallized from EtOH to yield red crystalline needles. Yield (2.3 g, 66 %). Proton spectra were consistent with those previously reported.

(4,4'-(1,10-phenanthroline-2,9-diyl)bis(methylene)bis(oxy)bis(3-methoxy-4,1-phenylene))dimethanol (3.25). To 150 mL acetone was added 3.24 (2.3 g, 0.0063 mol), 3-methoxy-4-hydroxy benzyl alcohol (2.48 g, 0.016 mol), and K\textsubscript{2}CO\textsubscript{3} (5.25 g,
0.038 mol). The solution was stirred at room temperature for 48 hours. 500 mL of water was added and the solution extracted with CHCl₃ (3 x 100mL). The organic fraction was dried over MgSO₄ and evaporated en vacuo. Yield (1.92 g, 60 %); mp (decomp.) = 208-211°C; ¹H NMR (CDCl₃): δ 7.83 (t, 1H, Ar); δ 7.51 (d, 2H, Ar); δ 7.00 (d, 2H, Ar); δ 6.95 (d, 2H, Ar); δ 6.81 (d of d, 2H, Ar); δ 5.13 (s, 4H, ArCH₂O); δ 4.51 (s, 4H, ArCH₂OH); δ 3.82 (s, 6H, OCH₃). ¹³C NMR (acetone-d₆): Aromatic Region: δ 158.24, 150.90, 148.18, 138.37, 137.19, 121.12, 119.74, 115.17, 112.17. Aliphatic Region: δ 72.62, 64.66, 56.27. Anal. calcd. for C₂₂H₂₅O₆N: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.37; H, 6.35; N, 3.89

3.4.2. Crystal Growth.

(+-)-3.3⊂Et₂O•½Et₂O. ca. 5 mg of crude (+-)-3.3 was dissolved in a minimal amount of CH₂Cl₂. In a sealed vial, diethyl ether vapor was allowed to diffuse into the solution giving colorless prismatic crystals.

(+-)-3.3⊂EtOAc. A minimal amount of EtOAc was used to dissolve ca. 5 mg of (+-)-3.3⊂Et₂O•½Et₂O in a sealed vial. Diethyl ether vapor was allowed to diffuse into the solution giving colorless prismatic crystals.

(+-)-3.3⊂(CH₂Cl₂•EtOH)•CH₂Cl₂. A minimal amount of CH₂Cl₂ was used to dissolve ca. 5 mg of (+-)-3.3⊂Et₂O•½Et₂O. EtOH was carefully layered on top of the solution in a sealed vial. Slow liquid-liquid diffusion generated colorless prismatic crystals.
(+/-)-3.3⊂MTBE•NO₂Me. A minimal amount of nitromethane was used to dissolve ca. 5 mg of (+/-)-3.3⊂Et₂O•½Et₂O in a sealed vial. Methyl-t-butyl ether (MTBE) vapor was allowed to diffuse into the solution giving colorless prismatic crystals.

(+/-)-3.3⊂iPr₂O•iPr₂O. A minimal amount of CH₂Cl₂ was used to dissolve ca. 5 mg of (+/-)-3.3⊂Et₂O•½Et₂O in a sealed vial. iPr₂O vapor was allowed to diffuse into the solution giving colorless prismatic crystals.

[H₃(+/-)-3.3][HSO₄]₃⊂2DMSO•2(CH₃)₂CO. A minimal amount of 3:1 DMSO/H₂O was used to dissolve ca. 2 mg (+/-)-3.3 and 5 drops of conc. H₂SO₄ were added. Acetone vapor was allowed to diffuse into the solution giving yellow prismatic crystals.

3.12. During the workup of a reaction of 3.11 to make (+/-)-3.3, crystals precipitated out of a CHCl₃ solution of mostly pure (+/-)-3.3. The clear prismatic crystals gave 3.12.

3.4.3. Kinetic Experiments

Imploded (+/-)-3.3 was preconditioned by heating via TGA the (+/-)-3.3⊂ (CH₂Cl₂ • EtOH)•CH₂Cl₂ clathrate to 140 °C via TGA yielding a solid material that was converted to ~75 % of the imploded species. A small amount of the preconditioned material (ca. 2 mg) was accurately weighed and dissolved in a known volume of either acetonitrile or CDCl₃ (1.00 mL) and monitored by ¹H NMR. Four peaks identified as CS-(+/-)-3.3 (1s, 2s, 1c, and 2c), and two peaks as CC-(+/-)-3.3 (1 and 2) were monitored over time via integration. Under these conditions, arene peaks from both the imploded and exploded species were integrated and plotted as a ratio (CS-(+/-)-3.3/CC-(+/-)-3.3) using the
appropriate rate equation. Experiments were monitored for at least 3 half lives. The corresponding rate constant values were calculated from the slope, and used to derive Eyring plots. The Eyring plots for both acetonitrile and chloroform were used to derive the activation parameters for both the reversible (chloroform) and irreversible (acetonitrile) CS-(+/-)-3.3 to CC-(+/-)-3.3 process.

3.4.4. X-Ray Crystallography

Single crystal diffraction data were collected using a Siemens SMART 1k CCD X-ray diffractometer with Mo Kα radiation (0.71073 Å) at 173(2) K. The crystal structures were solved by direct methods using SHELXS, and all structure refinements were conducted using SHELXL-97-2. All non-hydrogen atoms were modeled with anisotropic displacement parameters, with the exception of some included solvents and/or disordered moieties. Summary of crystallographic data are given in Table 3.3. The program X-Seed was used as a graphical interface for the SHELXL software suite and for the generation of figures.
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<th>(+/-)-3.3⊂ (CH₂Cl₂ • EtOH)•CH₂Cl₂</th>
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<td>0.71073</td>
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Table 3.3. Summary of Crystallographic Data (cont’d)

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<td>R1, wR2 (all data)</td>
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3.5. References


   **2007**, *36*, 236.  


9. a) Cram, D. J.; Cram, J. M *Container molecules and their guests*; Royal Society  
   **2002**, *41*, 1488-1508.  
   g) MacGillivray, L. R.; Atwood, J. L. *Angew. Chem. Int. Ed.* **1999**, *38,*


Chapter 4: Exohedral Hexa-acid Functionalized Cryptophanes

4.1. Introduction

4.1.1. Water Soluble Cryptophanes

One goal in supramolecular chemistry is creating molecules that have a high affinity for selectively binding guests in water. Naturally occurring biological systems provide inspiration for the design of aqueous receptors and provide insight into the intricate supramolecular workings of nature. Although natural processes take place in an aqueous medium, the vast majority of the artificial receptors designed thus far have been studied in organic solvents. Working in water with organic molecules presents many issues, the most common being solubility. Additionally, achieving various states of protonation of pH dependent functional groups often requires buffers, which, depending on the buffer, can affect the binding properties of the host, or even compete as a guest.

Cryptophanes—known for their affinity for small, neutral molecules—are large hydrophobic molecules and require functionalization to induce water solubility, yet there are limited structural variations available for the introduction of water solubilizing functional groups. The first water soluble cryptophanes were reported by Collet and coworkers in the 1980’s through conversion of the methoxy groups into water soluble carboxylates. Following the sequence of reactions shown in Figure 4.1, demethylation of cryptophane-222 was accomplished using PPh$_2$Li, which has been shown to be
selective for methyl groups, leaving the alkoxy bridges unaffected.\textsuperscript{1} Since this report, several other cryptophanes have been converted from their hexa-alkoxy to their hexaphenol analogues ((+/−)-4.7 through (+/−)-4.10) in good yields,\textsuperscript{2} including the

![Chemical Structures](image)

**Figure 4.1.** Water soluble cryptophanes have been synthesized through introduction of carboxylic acid functionalities at the OMe groups. This has been reported for alkyl bridged cryptophanes-222 through -555 (4.19-4.22), and asymmetric cryptophanes-223 and -332 (4.23, 4.24).
asymmetric cryptophanes-223 ((+/-)-4.11) and -233 ((+/-)-4.12). Further modification of the phenolic groups with methyl bromoacetate led to hexa-ester derivatives (+/-)-4.13 through (+/-)-4.18. Hydrolysis of the ester groups in basic conditions produced the sparingly water soluble hexa-acid cryptophanes (+/-)-4.19 through (+/-)-4.24. Cryptophane (+/-)-4.22, with six carboxylic acid groups, was shown to bind aminoxyl radicals,\(^3\) and tetra-alkyl derivatives M(alk)\(_4\) (alk = CH\(_3\), C\(_2\)H\(_5\); M = Si, Ge, Sn, Pb) in water.\(^4\) Water soluble (+/-)-4.20 and (+/-)-4.22 have also been reported to encapsulate choline and acetylcholine, with 4.22 exhibiting higher binding constants.\(^5\)

There has been a recent surge of interest in using molecular capsules as biosensors, aiming to exploit the specificity and strength of biological ligand-target interactions to selectively signal the presence of molecular or macromolecular targets. Specifically,

![Figure 4.2. The structure of the biosensor molecule designed by Pines as a 129Xe NMR based biosensor.](image)
cryptophane biosensor systems have extensively exploited the affinity of the 222 core for Xe binding in water, the $^{129}\text{Xe}$ nucleus being an NMR reporter. Pines and coworkers$^6$ illustrate the Xe encapsulation approach to biosensing by tethering cryptophane-222—a high affinity xenon receptor—through one of the phenolic groups with a peptide based solublizing chain to a biotin ligand. The cryptophane demonstrated a $^{129}\text{Xe}$ NMR signal response to the binding of the sensor by avidin in aqueous solution (Figure 4.2).

The large chemical shift difference reported between the free and bound $^{129}\text{Xe}$ signals (~123 ppm) presents a unique opportunity for multiplexing,$^7$ due to the variations in chemical shift of $^{129}\text{Xe}$ based upon the volume of the encapsulating cryptophane cavity. Berthault and coworkers$^8$ illustrated the NMR chemical shift sensitivity of the $^{129}\text{Xe}$ nucleus through the water soluble cryptophanes (+/-)-4.19, (+/-)-4.20, (+/-)-4.23, and (+/-)-4.24. Even the small difference of one carbon between (+/-)-

\[
\text{Figure 4.3. a) Hexaphenol cryptophane (+/-)-4.25 and b) metallated cryptophane-111 (4.26) are water soluble cryptophanes.}
\]
4.19 ($n = m = 2$) and (+/-)-4.23 ($n = 3, m = 2$) results in a chemical shift difference of ~13 ppm for the $^{129}$Xe signal. More recently, Berthault and coworkers have reported a water-soluble hexa-phenol cryptophane ((+/-)-4.25) and explored the effect of pH and counterions on its Xe encapsulation properties. There are now a plethora of water soluble cryptophanes that exhibit some affinity for Xe. The field has recently been reviewed by Berthault$^9$ and Dmochowski.$^{10}$

Our group has recently reported that cryptophanes can be rendered water soluble by metallation of the six arene faces with [Cp*Ru]$^+$ moieties. The chloride (and certain

![Figure 4.4](image)

**Figure 4.4.** a) Synthesis of metallated cryptophane [(+/-)-4.27][X]$^6$ (i): [Cp*Ru(CH$_3$CN)$_3$][X] ($X = [[CF_3SO_2]]^-, [SbF_6]^-$), CH$_2$Cl$_2$, 55°C, 24 h). b) Ball and stick and spacefill representations of [(+/-)-4.27 $⊂$ SbF$_6$]$^{5+}$ (reproduced with permission from K. Travis Holman)
other) salts of these species are highly water soluble over a wide pH range, unlike the many known carboxylate functionalized cryptophanes.\textsuperscript{11} The hexametallated chloride salt of cryptophane-111 (namely (+/-)-4.26\textsuperscript{6+}) has the highest known affinity of any molecular host for xenon in pure water ($K_a = 2.9(2) \times 10^4$ M\textsuperscript{-1}). The metallated cryptophanes are also able to encapsulate anions in organic solvent, showing that the interiors are apparently somewhat π-acidic (Figure 4.4).\textsuperscript{12} This type of chemistry has been explored prior to this report by Atwood and co-workers who explored several metallated cavitands that bind anions within their cup-shaped, arene based cavities.\textsuperscript{13} The metallation of cryptophane-333 (\textit{i.e.} (+/-)-4.2) by Holman and coworkers resulted in cryptophane (+/-)-4.27\textsuperscript{6+} that has exhibited encapsulation of anions PF$_6^-$, CF$_3$SO$_3^-$, and SbF$_6^-$. The kinetics for complexation of [CF$_3$SO$_3^-$] by (+/-)-4.27\textsuperscript{6+} were determined in CD$_3$NO$_2$ to be $\Delta H^\ddagger = 73.2$ kJ mol$^{-1}$ and $\Delta S^\ddagger = 8.4$ J K$^{-1}$ mol$^{-1}$ ($\Delta G^\ddagger_{298} = 75.2$ kJ mol$^{-1}$), illustrating a considerable constrictive binding effect. It has also been determined that metallation also apparently increases the cavity volume.\textsuperscript{11,14}

\textbf{4.1.2. Container Molecule Coordination Polymers (CPs)}

In the design and synthesis of functional materials, one goal is to develop materials with functional and useful cavities or pores. These types of materials incorporate permanent, readily accessible cavities that extend through the structure and have proven advantageous for various uses. Zeolites—aluminosilicate materials that possess channels or pores of variable size (4-13 Å) and shape—are well-known porous
materials that can selectively absorb molecules. Upon inclusion, the guest molecules may be stored and/or separated from the bulk, or potentially partake in chemical transformations. These characteristics have been well exploited, and have greatly impacted the chemical industry since their discovery in 1862.

It remains difficult to incorporate chemical functionality within zeolites during their synthesis. It has been shown that crystalline polymers sustained by coordinate-covalent bonds can provide novel materials with properties akin to, and in some senses far superior to, zeolites. Using metals or metal clusters as nodes and organic moieties as bridges, polymeric crystalline structures having different 3D topologies can be constructed, often with an element of design. These coordination polymers (CPs), also known as metal-organic frameworks (MOFs), initially incorporate solvent molecules upon synthesis that may be easily removed, sometimes leaving empty pores as opposed to collapsing.

Of the numerous CPs that have been developed, metal carboxylates have emerged as a very important class. Metal-carboxylate CPs are typically more robust than those built on other metal-ligand coordinating groups as a corollary of the strength of the metal oxygen bonds. Yaghi and coworkers (and now many others) have been successful in designing metal carboxylate materials that exhibit permanent porosity. Some of these materials have been shown to have among the highest surface area and lowest density known for crystalline materials. Porous materials of this genre have also been designed by Rosseinsky, Long, Kitigawa, and others that have shown
to reversibly adsorb gases such as H$_2$, O$_2$, CO$_2$, and C$_2$H$_2$, to name a few. The CP with the largest surface area, 5900 m$^2$/g, has been reported by Férey and coworkers and is a metal carboxylate CP. The field of porous CP materials has been extensively reviewed by multiple authors over the past decade.

The modular nature of CPs allows for the exchange of ligands and/or nodes to allow for the incorporation of functionality. Functionality has been displayed through the synthesis of a variety of CPs illustrating storage, catalytic, sensing, magnetic, biomedical (imaging and drug delivery), separation, and optical properties. This has been accomplished through the introduction of coordinating groups including but not limited to amines, cyano, sulphonates, nitrogen-containing heterocycles (such as pyridine), phosphines, and carboxylates. This has also been achieved in our own group by Kumalah-Robinson through the use of metallated aryl carboxylates. Through the success of these syntheses, organic ligand spacers have proven to be versatile, modular, and easily functionalized to incorporate well understood chemistry into materials.

Along with the trend of incorporating more functional ligands, with well defined properties (e.g. catalysts, optical switches, etc.), into CPs, ligands that possess inherent molecular recognition properties would be an interesting advance. In this sense, cryptophanes are interesting ligand candidates as they are selective binders, and furthermore, functionalizing molecular capsules with functional groups that typically participate in forming coordination frameworks should result in microcavity-within-micropore materials.
Our own group has used $m$-xylyl bridges, namely (+/-)-4.28 to exo-functionalize a cryptophane with three carboxylic acid moieties (Figure 4.5a). This molecular container is water soluble in basic solutions, but, perhaps more interestingly, been

**Figure 4.5.a** Cryptophane (+/-)-4.28 possesses exo-positioned carboxylic acids moieties and reacts with metals to make CPs. b) The 1D polymeric structure of [Cu$_{1.5}$((+)/4.28 ⊂ DMF)(C$_6$H$_3$N)$_3$(MeOH)]·x solvent. c) A closer look at the two independent Cu(II) coordination sites. (*some images reproduced with permission from K. Travis Holman*)
reported to implode\textsuperscript{39} (see Chapter 3), and has also been reported to react with Cu(NO\textsubscript{3})\textsubscript{2}•2.5H\textsubscript{2}O in DMF-MeOH with pyridine to give a one-dimensional soft coordination polymer [Cu\textsubscript{1.5}((+/−)-\textsuperscript{4.28}⊂DMF)(C\textsubscript{6}H\textsubscript{5}N)\textsubscript{3}(MeOH)]\textbullet solvent (Figure 4.5b).\textsuperscript{40} The coordination polymer packs inefficiently, producing 1D ladder-shaped tunnels along the [001] direction of the crystal and can be reversibly partially desolvated while retaining single crystallinity, with a 23% contraction in channel volume upon desolvation.

This work shows that the appendage of ligating functionalities exterior (exo) to cryptophane cavities should provide opportunities for the crystal engineering of coordination polymers through reactions of acid functional groups with transition metal ions. Such compounds could be described as microcavity-within-micropore materials, with the expectation that the remarkable binding and recognition properties of the cryptophanes may convey to these materials.

The work described in this Chapter is concerned with the synthesis of exohedral hexa-carboxylic acid functionalized m-xyllyl bridged cryptophanes \textsuperscript{4.29} and (+/−)-\textsuperscript{4.30}, analogues of cryptophane (+/−)-\textsuperscript{4.28}. With the addition of more acid groups, the solubility of the molecule in water should be enhanced, and, as a consequence of the different functional group arrangement, incorporation into coordination polymers will differ greatly based on the molecules’ bonding geometry with respect to metal ions.
4.2. Synthesis of Exohedral Hexa-acid Functionalized Cryptophanes

With the ultimate goal of synthesizing water soluble cryptophanes and container molecules capable of being incorporated into MOFs by reaction with metal ions, molecules 4.29 and (+/-)-4.30 were targeted. These molecules were synthesized by the two-step method of cryptophane synthesis (Chapter 1) following Figure 4.6. Starting with \( m \)-xylene, and following literature procedures, chloromethyl groups were added at the 4- and 6- positions to give 4.31 and were converted \textit{in situ} to afford carboxylic acid substituted 4.32. The acid was then converted to its ethyl ester via the acyl chloride.

![Synthetic route to cryptophanes 4.29 and (+/-)-4.30.](image)

\textbf{Figure 4.6.} The synthetic route to cryptophanes 4.29 and (+/-)-4.30.
Halogenation of 4.33 with N-bromosuccinimide (NBS) gave a good yield (54%) of 4.34. The bis halogenated 4.34 was reacted with two equivalents of vanillyl alcohol to give the cyclization precursor 4.35, a new molecule. Cyclization of 4.35 in formic acid afforded a mixture of 4.36 and (+/-)-4.37, the syn and anti diastereomers of the hexa ethyl ester cryptophanes in 8.4% and 7.3% yield, respectively. The cryptophanes 4.36 and (+/-)-4.37 were separated chromatographically and subsequently hydrolyzed in near quantitative yields to afford the syn (4.29) and anti ((+/-)-4.30) hexa-exo-acid target molecules.

Although not reported here due to the low quality of the data, an X-ray crystal structure of 4.29 was isolated from the diffusion of (i-Pr)$_2$O into a nitromethane solution of the compound (triclinic, P-1, $a = 14.33$ Å, $b = 18.28$ Å, $c = 19.09$ Å; $a = 65.75^\circ$, $\beta = 84.88^\circ$, $\gamma = 81.14^\circ$) was obtained, and unequivocally establishes the identities of the syn and anti diastereomers.

4.3. Experimental

All solvents were used as received from Fisher (Pittsburg, PA). Reagents were obtained from Acros (Pittsburgh, PA) or Aldrich (Milwaukee, WI) and were used without further purification. All reactions were carried out under nitrogen atmosphere. Chromatography was carried out on silica gel (32-64µm). $^1$H (300.1 MHz) and $^{13}$C (75.5 MHz) NMR were carried out on a Varian Unity Inova Spectrometer. All NMR spectra were collected at 25°C unless otherwise noted and were indirectly referenced to
TMS using residual solvent signals as internal standards. Elemental analyses were carried out on a Perkin-Elmer PE2400 microanalyzer at Georgetown University. The syntheses presented in this Chapter were all performed by the author, with contributions to the project made earlier by Farnoush Ghaderi and Mark Russo, undergraduate students in our research lab.

1,5-Bis(chloromethyl)-2,4-dimethylbenzene (4.31). To a solution of 11.6 g (0.387 mol) paraformaldehyde in 160 mL concentrated HCl and 40 mL glacial acetic acid was added 20 mL (0.16 mol) \( m \)-xylene. The reaction was stirred at 100°C for two days. The solution was extracted with \( \text{CH}_2\text{Cl}_2 \) (3 x 100mL). The organic layers were combined and washed with dilute NaHCO\(_3\) (aq) (3 x 50mL) and water (3 x 50mL). The organic layer was dried over magnesium sulfate, filtered, and evaporated under vacuum to give a white solid. Recrystallization from hexane yielded 19.63 g (51.50 %) of 4.31. The spectral characteristics were identical with those reported previously.

4,6-Dimethylisophthalic acid (4.32). To a solution of 11.83 g KOH in 1 L of water, 11.13 g of 4.31 was added. The solution was refluxed until all the solid dissolved. The solution was then cooled to 50°C and 20.2 g of KMnO\(_4\) was added slowly. After 12 hours, stirring at 50°C the solution was filtered through Celite© and acidified to pH = 1 with concentrated HCl. The white precipitate was collected and recrystallized from methanol to yield 2.9 g (32%) of compound 4.32. The spectral characteristics were identical with those reported previously.

Diethyl 4,6-dimethylisophthalate (4.33). To a stirring solution of 20.00 mL
thionyl chloride, 3.6 g of 4.32 was added and heated to reflux until all solid dissolved. The solution was removed under vacuum and 10 mL of ethanol (200 proof) was added over ice. The solution was stirred until only 4.32 was present via thin layer chromatography \([R_f(CH_2Cl_2) = 0.68]\). The solvent was removed under vacuum. Recrystallization from methanol yielded 3.38 g (73 %) of 4.33. The spectral characteristics were identical with those reported previously.

**Diethyl 4,6-bis(bromomethyl)isophthalate (4.34).** To 25 mL CHCl₃ was added 2.7 g of 4.33 and 0.5 g N-bromosuccinimide. The solution was irradiated under \(h\nu\) for approximately 3 hours. The solution was poured into 100 mL CH₂Cl₂ then washed with NaHCO₃(\(aq\)) (2 x 100 mL) and H₂O (2 x 100 mL). The organic layers were collected, dried over MgSO₄ and solvent removed under vacuum. Flash chromatography on silica was performed using CH₂Cl₂ and 2.40 g of 4.34 (54 %) was collected \([R_f = 0.75]\). The spectral characteristics were identical with those reported previously.

**Diethyl 4,6-bis((4-(hydroxymethyl)-2-methoxyphenoxy)methyl) isophthalate (4.35).** In 250 mL acetone, 3.2 g (20.8 mmol) of 4-hydroxy-3-methoxybenzyl alcohol and 11.1 g (80.0 mmol) of potassium carbonate were stirred at room temperature for 30 minutes. To the solution was added dropwise 3.4 g (8.0 mmol) of 4.34 dissolved in a minimal amount of acetone. The reaction stirred for 48 hours at room temperature. The solution was poured into 150 mL water and extracted with CH₂Cl₂ (3 x 150 mL). The collected organic layers were washed with NaHCO₃(\(aq\)) (2 x 100 mL). The organic layers were dried over MgSO₄ and evaporated to dryness. The resulting solid was
recrystallized from NO$_2$Me yielding colorless 4.35. Yield (4.10 g, 93 %); mp = 128-131°C. $^1$H NMR (chloroform-d): δ 8.63 (s, 1H, Ar); δ 8.07 (s, 1H, Ar); δ 6.86 (s, 2H, Ar); δ 6.60 (m, 4H, Ar); δ 5.85 (s, 4H, ArCH$_2$O); δ 4.59 (s, 4H, ArCH$_2$OH); δ 4.39 (q, $J^3 = 7.2$ Hz, 4H, OEt CH$_2$); δ 3.86 (s, 6H, OCH$_3$); δ 1.42 (t, $J^3 = 7.2$ Hz, 6H, Ar). $^{13}$C NMR (CDCl$_3$): Aromatic Region: δ 166.1; δ 149.6; δ 147.4; δ 144.2; δ 134.0; δ 133.4; δ 126.9; δ 126.4; δ 119.1; δ 113.6; δ 111.0. Aliphatic Region: δ 69.2; δ 65.1; δ 61.4; δ 55.9; δ 14.2.

Cryptophanes $\textit{syn}$-4.36 and (+/-)-$\textit{anti}$-4.37. Diol 4.35 (2.0 g, 3.8 mmol) was dissolved in 25 mL CHCl$_3$. The solution was added drop-wise to 3.0 L stirring HCOOH. The solution was stirred at room temperature for 4 days. The solvent was removed en vacuo and the resulting solid was redissolved in 200 mL CHCl$_3$. Solid Na$_2$CO$_3$ was added until the solution was neutral via pH paper. The solution was washed with H$_2$O (3 x 50 mL). The organic layer was dried over MgSO$_4$, and evaporated under vacuum. The crude product was chromatographed on silica gel with 25:1 CH$_2$Cl$_2$/acetone and recrystallized by dissolving in CH$_2$Cl$_2$ and precipitating with MeOH and collected by vacuum filtration on a glass frit. Cryptophane diastereomers appear as white solids.

$\textit{Syn}$-4.36. Yield (0.14 g, 8.4 %); T > 325-327°C (decomp.); $R_f = 0.65$ (25:1 CH$_2$Cl$_2$/acetone). $^1$H NMR (CDCl$_3$): δ 8.62 (s, 3H, Ar-bridge); δ 8.34 (s, 3H, Ar-bridge); δ 6.57 (s, 6H, aryl-H); δ 6.42 (s, 6H, aryl-H); δ 5.57 (d, $J^2 = 14.0$ Hz, 6H, O-CH$_2$-bridge); δ 5.32 (d, $J^2 = 14.0$ Hz, 6H, O-CH$_2$-bridge); δ 4.57 (d, $J^2 = 13.7$ Hz, 6H,
H\textsubscript{a}); \(\delta 4.43\) (q, \(J^3 = 7.2\) Hz, 12H, ethyl-CH\textsubscript{2}); \(\delta 3.44\) (s, 18H, OCH\textsubscript{3}); \(\delta 3.34\) (d, \(J^2 = 13.7\) Hz, 6H, H\textsubscript{a}); \(\delta 1.45\) (t, \(J^3 = 7.2\) Hz, 18H, ethyl-CH\textsubscript{3}). \(^{13}\text{C}\) NMR (CDCl\textsubscript{3}): Aromatic Region: \(\delta 165.9\); \(\delta 147.8\); \(\delta 146.9\); \(\delta 145.3\); \(\delta 132.7\); \(\delta 131.9\); \(\delta 131.5\); \(\delta 125.8\); \(\delta 114.2\); \(\delta 113.4\). Aliphatic Region: \(\delta 69.0\); \(\delta 61.5\); \(\delta 55.8\); \(\delta 46.7\); \(\delta 36.2\); \(\delta 14.4\). Anal. calcd. for: C, 69.49; H, 5.83; N, 24.68. Found: C, 69.45; H, 5.87; N, 24.66.

\((\pm)-\text{Anti-4.37}\). Yield (0.13 g, 7.3 %); \(T > 322-325^\circ\text{C}\) (decomp.); \(R_f = 0.57\) (25:1 CH\textsubscript{2}Cl\textsubscript{2}/acetone). \(^1\text{H}\) NMR (CDCl\textsubscript{3}): \(\delta 8.50\) (s, 3H, Ar-bridge); \(\delta 7.48\) (s, 3H, Ar-bridge); \(\delta 6.56\) (s, 6H, aryl-H); \(\delta 6.42\) (s, 6H, aryl-H); \(\delta 5.50\) (d, \(J^2 = 14.4\) Hz, 6H, O-CH\textsubscript{2}-bridge); \(\delta 5.25\) (d, \(J^2 = 14.4\) Hz, 6H, O-CH\textsubscript{2}-bridge); \(\delta 4.59\) (d, \(J^2 = 13.6\) Hz, 6H, H\textsubscript{a}); \(\delta 4.39\) (q, \(J^3 = 6.0\) Hz, 12H, ethyl-CH\textsubscript{2}); \(\delta 3.45\) (s, 18H, OCH\textsubscript{3}); \(\delta 3.36\) (d, \(J^2 = 13.6\) Hz, 6H, H\textsubscript{a}); \(\delta 1.37\) (t, \(J^3 = 7.2\) Hz, 18H, ethyl-CH\textsubscript{3}). \(^{13}\text{C}\) NMR (CDCl\textsubscript{3}): Aromatic Region: \(\delta 166.4\); \(\delta 160.7\); \(\delta 148.1\); \(\delta 146.3\); \(\delta 143.2\); \(\delta 132.3\); \(\delta 131.3\); \(\delta 128.4\); \(\delta 114.1\); \(\delta 113.3\). Aliphatic Region: \(\delta 69.1\); \(\delta 61.5\); \(\delta 55.9\); \(\delta 47.2\); \(\delta 36.2\); \(\delta 14.2\). Anal. calcd. for: C, 69.49; H, 5.83; N, 24.68. Found: C, 69.41; H, 5.88; N, 24.62.

\textbf{Syn-4.29}. In 80 mL of 2:1 EtOH/H\textsubscript{2}O was refluxed 100 mg (0.065 mmol) of \textbf{4.36} and 156 mg (4.0 mmol) NaOH for 36 hours. The solution was cooled and acidified using concentrated HCl until acidic. The cryptophane was collected as a white solid. Yield (0.088 g, 99 %). \(^1\text{H}\) NMR (CDCl\textsubscript{3}): \(\delta 8.51\) (s, 3H, Ar-bridge); \(\delta 8.08\) (s, 3H, Ar-bridge); \(\delta 6.69\) (s, 6H, aryl-H); \(\delta 6.52\) (s, 6H, aryl-H); \(\delta 5.48\) (d, \(J^2 = 16.0\) Hz, 6H, O-CH\textsubscript{2}-bridge); \(\delta 5.23\) (d, \(J^2 = 16.0\) Hz, 6H, O-CH\textsubscript{2}-bridge); \(\delta 4.54\) (d, \(J^2 = 13.6\) Hz, 6H, H\textsubscript{a}); \(\delta 3.42\) (d, \(J^2 = 13.6\) Hz, 6H, H\textsubscript{a}); \(\delta 3.31\) (s, 18H, OCH\textsubscript{3}). \(^{13}\text{C}\) NMR (CDCl\textsubscript{3}):
Aromatic Region: δ 187.1; δ 171.6; δ 167.7; δ 147.5; δ 146.8; δ 144.6; δ 132.3; δ 126.9; δ 114.7; δ 114.3. Aliphatic Region: δ 69.1; δ 55.9; δ 51.5; δ 35.4.

(+/-)-Anti-4.30. In 80 mL of 2:1 EtOH/H$_2$O was refluxed 100 mg (0.065 mmol) 4.37 and 156 mg (4.0 mmol) NaOH for 36 hours. The solution was cooled and acidified using conc. HCl until acidic by pH paper. The cryptophane was collected as a white solid. Yield (0.087 g, 98 %). $^1$H NMR (DMSO-$d_6$): δ (s, 3H, Ar-bridge); δ (s, 3H, Ar-bridge); δ (s, 6H, aryl-H); δ (s, 6H, aryl-H); δ (d, $J^2$ = Hz, 6H, O-CH$_2$-bridge); δ (d, $J^2$ = Hz, 6H, O-CH$_2$-bridge); δ (d, $J^2$ = Hz, 6H, H$_a$); δ (s, 18H, OCH$_3$); δ (d, $J^2$ = 13.7 Hz, 6H, H$_c$). $^{13}$C NMR (CDCl$_3$): Aromatic Region: δ 167.9; δ 165.7; δ 147.8; δ 146.5; δ 143.1; δ 133.1; δ 131.7; δ 129.3; δ 127.7; δ 114.6. Aliphatic Region: δ 67.7; δ 55.9; δ 35.4; δ 11.3.

4.4. References


4180-4181.

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Chapter 5: Amine Functionalized Cyclotribenzylenes

5.1. Introduction

5.1.1. Synthetic Mechanisms and Important Considerations in CTB Synthesis

Cyclotribenzylenes (CTBs) are rigid, concave molecules that have been derivatized to perform specific functions (Chapter 2), and are also the defining component of cryptophane molecular containers (Chapters 3 and 4). CTBs are the trimeric, major condensation product of a benzyl cation—generated from a variety of precursors—under acidic conditions and their synthesis has been reviewed in detail by Collet.\(^1\) Cyclotriveratrylene (CTV, 5.2), the first characterized CTB\(^2\) is the major condensation product of the veratryl cation, 5.1\(^+\), under acidic conditions. Many procedures have been reported for the synthesis of CTV, as can be seen in Table 5.1, and the formation

![Diagram of chemical structures](image)

**Figure 5.1.** The condensation product of the veratryl cation (5.1) under acidic conditions is CTV (5.2). Under some conditions, CTTV (5.3) is formed. Veratrole (5.4) and veratryl alcohol (5.5) are both precursors to the benzyl cation 5.1.
of 5.2 is often accompanied by at least a small amount of the corresponding tetrameric
cyclophane 5.3 (cycdotetrameratrylene – CTTV) and very likely other higher order cyclic
oligomers in very low yields. Molecule 5.3 is not a very well studied species because it
is not cavitand shaped, and its formation appears to be more favored in organic solvents
rather than aqueous mineral acids. The formation of the benzyl cation has come from a
variety of starting materials, most commonly veratrole (5.4) or veratryl alcohol (5.5).

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Acid</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>CTV (5.2)</th>
<th>CTTV (5.3)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.4 + ‘HCHO’²</td>
<td>70 % H₂SO₄</td>
<td>none</td>
<td>25</td>
<td>70</td>
<td>-</td>
<td>3a</td>
</tr>
<tr>
<td>5.4 + ‘HCHO’²</td>
<td>70 % H₂SO₄</td>
<td>none</td>
<td>0</td>
<td>21</td>
<td>-</td>
<td>3b</td>
</tr>
<tr>
<td>5.4 + ‘HCHO’²</td>
<td>70 % H₂SO₄</td>
<td>none</td>
<td>0</td>
<td>68</td>
<td>16</td>
<td>3c</td>
</tr>
<tr>
<td>5.4 + ‘HCHO’²</td>
<td>60 % HClO₄</td>
<td>none</td>
<td>25</td>
<td>70</td>
<td>-</td>
<td>3d</td>
</tr>
<tr>
<td>5.4 + ‘HCHO’²</td>
<td>Conc. HCl</td>
<td>none</td>
<td>25</td>
<td>45</td>
<td>-</td>
<td>3e</td>
</tr>
<tr>
<td>5.5</td>
<td>H₂SO₄</td>
<td>Acetic acid</td>
<td>90</td>
<td>68</td>
<td>16</td>
<td>3c</td>
</tr>
<tr>
<td>5.5</td>
<td>H₂SO₄</td>
<td>Acetic acid</td>
<td>warm</td>
<td>87</td>
<td>-</td>
<td>3b</td>
</tr>
<tr>
<td>5.5</td>
<td>60 % HClO₄</td>
<td>none</td>
<td>25</td>
<td>35</td>
<td>-</td>
<td>3d</td>
</tr>
</tbody>
</table>

Table 5.1. Selected synthesis procedures for 5.2 and 5.3

When X ≠ Y, it becomes important to consider whether the mechanisms are
kinetically or thermodynamically controlled. The CTB trimer is more often the kinetic
product of the cyclization reaction and usually precipitates. Most CTB syntheses are
under kinetic control, but molecule 5.6 (Figure 5.1), synthesized independently, can
undergo self-condensation to give small amounts of CTV, which illustrates some level
of reversibility in the electrophilic aromatic substitution reactions, at least under some
conditions."
To address the functional group dependence of the mechanism, it is important to look at the products of each reaction path. CTB formation via benzyl alcohols such as 5.5 (Figure 5.2a), involves treating an appropriately 3,4-substituted benzyl alcohol with a strong acid, e.g. H₂SO₄, HCl, HClO₄, CF₃CO₂H, or HCOOH, for example, and, under kinetic control, results in only the C₃ symmetric CTB. When X ≠ Y, the CTB becomes chiral, and is formed as a racemic mixture. This reaction is useful, but, for certain X and Y substituents requires the potentially tedious synthesis of the appropriate benzyl alcohol. The functional group tolerance of the condensation reaction dictates that Y must be electron donating (e.g. alkoxy) while X can simply be a place holding group, and ultimately results in low yields. These restrictions limit the range of practical availability of the as-synthesized CTBs, often resulting in modifying the X or Y groups after the cyclization step to introduce desired chemical functionality. This method only yields C₃ symmetric CTBs.

![Figure 5.2](image.png)

**Figure 5.2.** Synthesizing CTBs can be approached through the benzyl alcohol route (a), or through the arene/carbon source route (b).
Some notable functional groups that have been explored in the literature following the benzylic alcohol route can be seen in Table 5.2.\textsuperscript{5} Experimentally it has been found by others that the Y group must be activating, facilitating electrophilic attack at the para-position. The X group also plays a role in the reaction, by either activating the ring, or by protecting the position toward undesired electrophilic attacks.

![Diagram of benzylic alcohol reaction](image)

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCH$_3$</td>
<td>OCH$_3$</td>
<td>70</td>
<td>2</td>
</tr>
<tr>
<td>OH</td>
<td>OCH$_3$</td>
<td>0</td>
<td>4a</td>
</tr>
<tr>
<td>OC$_2$H$_5$</td>
<td>OCH$_3$</td>
<td>51</td>
<td>4b</td>
</tr>
<tr>
<td>OCH$_2$CO$_2$H</td>
<td>OCH$_3$</td>
<td>45</td>
<td>4c</td>
</tr>
<tr>
<td>OCH$_3$</td>
<td>OCH$_3$CH$_3$</td>
<td>42</td>
<td>1</td>
</tr>
<tr>
<td>OCH$_2$CH$_2$OCH$_2$CO$_2$H</td>
<td>OCH$_3$</td>
<td>40</td>
<td>4d</td>
</tr>
<tr>
<td>OCH$_2$CH=CH$_2$</td>
<td>OCH$_3$</td>
<td>55</td>
<td>4a</td>
</tr>
<tr>
<td>OCH$_2$CH=CH$_2$</td>
<td>OC$_2$H$_5$</td>
<td>15</td>
<td>4b</td>
</tr>
<tr>
<td>Br</td>
<td>OCH$_3$</td>
<td>25-40</td>
<td>4e</td>
</tr>
<tr>
<td>OCH$_3$</td>
<td>Br</td>
<td>0</td>
<td>4e</td>
</tr>
<tr>
<td>H</td>
<td>OCH$_3$</td>
<td>6.5</td>
<td>4f</td>
</tr>
<tr>
<td>NHCOCH$_3$</td>
<td>OCH$_3$</td>
<td>97</td>
<td>9a</td>
</tr>
</tbody>
</table>

Table 5.2. Some reported functional groups for CTB synthesis via the benzylic alcohol

The ‘direct’ approach (Figure 5.2b) treats an appropriately 1,2-disubstituted arene, such as 5.4, with a ‘carbon source’—formaldehyde or paraformaldehyde—and a strong acid. This mechanism can result in the $C_3$ symmetric CTB as produced by the first mechanism, but can also produce the $C_1$ symmetric CTB when $X \neq Y$, where one of the arenes is reversed relative to the $C_3$ CTB.
Depending on the starting material used to produce CTV—formaldehyde and veratrole, or veratryl alcohol—different mechanisms can play a role in the formation of CTV. When starting with benzyl alcohols (e.g. 5.5; Figure 5.1; X = Y = OMe), CTB synthesis mechanistically proceeds stepwise, starting with 5.5 through the mono- (a), di- (b), and trimeric (c) cationic species, which then quickly cyclizes to the CTB, or further react to give linear oligomers such as d, which can then cyclize to form cyclotetrabenzylene (e.g. CTTV, 5.3) and other cyclic oligomers and polymeric materials (Figure 5.3).

The alternative direct method—e.g. reacting a carbon source directly with a substituted (usually disubstituted; X and Y) arene (e.g. veratrole)—can potentially proceed through a different mechanism (Figure 5.4). This approach can also produce the same mono-, di-, and trimeric species (a, b, and c, respectively) as in the cyclization

\[ \text{CTB} \]

**Figure 5.3.** The benzyl alcohol route to CTBs proceeds through the monomeric (a), dimeric (b), trimeric (c) intermediates. The trimer c can then react further to produce tetrameric d, a precursor to CTTBs.
of benzylic alcohols, but one would also expect the possible additional formation of molecules e through t as a result of various combinations of the formaldehyde with 5.4.

![Diagram](image_url)

**Figure 5.4.** The direct method to CTB synthesis produces numerous intermediates, some of which can only produce only $C_1$ or $C_3$ CTBs.

This mechanism still relies on the step-wise addition of arene rings to form trimers before an intramolecular cyclization reaction can take place. Therefore, if $X = Y$, there is a statistical distribution of 3:1 $C_1/C_3$ products—$(j + l + n)/(c)$—when performing this reaction. The relative ability of $X$ and $Y$ to activate their para-positions for electrophilic aromatic substitution is expected to dramatically affect the $C_1/C_3$ ratio. If, for example, $X$ is significantly more activating than $Y$, the reaction would be expected to proceed preferentially through an intermediate such as e or o in Figure 5.3, thus leading to the
evolution of more $C_1$ product. This is evidenced later in this Chapter by the isolation of a dimeric molecule resembling the structure of e, resultant from one of the groups being significantly more donating then the other. The larger the donating ability of one group versus the other, the larger the ratio of $C_1/C_3$ because more intermediates like e or f are formed first, resulting in strictly the formation of $C_1$ CTBs.

The cationic species formed during this reaction are short lived, reacting quickly with other molecules of 5.4. The formation of bis-cations (g, h, p, and q) is unlikely based on work by Weinelt and Schneider, who studied the mechanism of forming macrocycles between arenes—specifically resorcinol—and aldehydes through electrophilic aromatic substitution; the formation of intermediates during the direct method can be anticipated to follow a similar pathway.

5.1.2 Amino CTBs and Related Molecules

Many functional groups have been reported as useful appendages to CTBs (see Chapter 2). Amino-functionalized CTBs have been of significant interest in supramolecular chemistry for their use as precursors for nitrogen containing ligands and for the formation of interesting supramolecular cages and coordination polymers. Specifically, cyclotrianisidine (+/-)-5.7 has been a starting point for other functionalized CTB ligands. For example, (+/-)-5.7 has been used by Hardie and coworkers to synthesize CTB ligands bearing tris(pyridylmethylamino) functionalities (Figure 5.5). These ligands have been shown to react with AgPF$_6$ to form a dimeric capsule.
[Ag$_2$(5.8)$_2$(CH$_3$CN)$_2$]$^{2+}$ and with AgBF$_4$ to form tetrahedral metallo-supramolecular prism [Ag$_4$(5.9)$_4$(CH$_3$CN)$_4$]⊂4CH$_3$CN.$^8b$

The original reported synthesis of (+/-)-5.7 was reported by Collet in 1993, and was synthesized through the intermediate amide (+/-)-5.13 via the multistep synthesis seen in Figure 5.6. This process, although it results in high yields for in the cyclization step (97 %), involves multiple steps and is quite expensive. The starting material 5.10 is ~$62/1$ g (Aldrich, 2010), with the added cost of Pd/C (~$24/1$ g) and perchloric acid (~$76/50$ mL).
Amino functionalized molecules hold an increasingly important role in supramolecular chemistry. In particular, the reaction of amines with aldehydes can provide the thermodynamic imine bond in water, potentially forming large scale container molecules through powerful dynamic covalent chemistry (DCC) methods. Dynamic covalent chemistry, and particularly imine bond formation, is an increasingly popular supramolecular strategy that aims to synthesizing complex macromolecules. Imine chemistry possesses the advantage that the normal acid sensitive imine bonds can subsequently be reduced to provide more stable amines and the desired macrocycle is formed. Some examples of this powerful chemistry in the context of CTBs have been illustrated by Warmuth and coworkers. In one elegant example, DCC was utilized to synthesize a nanometer sized covalently linked homochiral cube (Figure 5.7). By exploiting the reversible imine reaction, this work resulted in not only the construction...
of the cube, but also the dynamic kinetic resolution of the aldehyde functionalized CTB. Enantiopure (+)-5.14 was isolated by reaction of the (+/-)-5.14 racemate with (R,R)-diaminocyclohexane, eventually converting all of the CTBs into an enantiopure cryptophane, which is then subsequently hydrolyzed to give a single enantiomer of (+)-5.14. Reaction of (+)-5.14 with dianiline 5.15 in a 8:12 ratio under DCC conditions then provides the homochiral nanocube 5.16 in ~90 % yield. The molecular diameter as determined by DOSY NMR is 3.7 nm, similar to that of globular proteins. Other linear diamines were also shown to link the aldehyde CTBs into similar cubes.

In closely related work reported in 2011, Warmuth and coworkers described the

![Image](image_url)

**Figure 5.7.** The synthesis of homochiral cube 5.16 exploits dynamic covalent chemistry with an amino functionalized CTB. *(parts of this figure reproduced with permission)*
templated formation of cryptophane complexes via DCC in water (Figure 5.8). The reaction of tris-aldehyde (+)-5.14 (R = O(CH₂)₃CH₃) with diamino linker 5.18 resulted in the spontaneous assembly of molecule 5.19, joined by six reversible imine bonds. This is also the first example of a guest-templated capping method synthesis of a cryptophane.

![Figure 5.8. The formation of a cryptophane through the use of imine chemistry using a guest as a template has been illustrated by Warmuth and coworkers in 2011. (Reproduced with permission)]
5.2. Single Step $C_1$ and $C_3$ Amino-CTB Synthesis

The aforementioned work by Hardie, Warmuth, and other work within our own group prompted the investigation for a simpler and cheaper synthesis that would yield amino CTBs as readily available and useful building blocks for the chemical community. Due to the availability and ultra-low cost, N-(2-Methoxyphenyl)acetamide (5.20; $24/100$ g) and paraformaldehyde ($68.30/\text{kg}$) were explored as starting materials that could/should lead to amino CTBs and perhaps provide a more efficient and cost effective synthesis (Figure 5.9). The original synthesis of $(+/-)$-5.7 reported by Collet utilized the benzyl alcohol method, and strictly relies on the electrophilic aromatic substitution para to the OMe group, which is strongly donating. It is not obvious that the position para to the amido group would undergo the same reaction and that the reaction of 5.20 with any amount of paraformaldehyde would result in anything but a dimeric product such as $e$ in Figure 5.4. However, the reaction of amido methoxy substituted 5.20 with paraformaldehyde at room temperature in acidic solution (10 % HClO$_4$ in acetic acid) provided a 63 % total yield of a $C_1$-symmetric $(+/-)$-5.21 and $C_3$-

\[
\begin{align*}
\text{O} & \quad \text{NH} & \quad \text{O}^- \\
\text{5.20} & \quad \Big[\text{O}_\text{n}\Big] & \quad \text{CH}_2\text{COOH} \\
& \quad \text{HClO}_4 & \quad \rightarrow \\
& \quad \text{MeO} & \quad \text{MeO} \\
& \quad \text{OMe} & \quad \text{OMe} \\
& \quad \text{MeO} & \quad \text{MeO} \\
& \quad \text{MeO} & \quad \text{OMe} \\
& \quad \text{R} & \quad \text{R} \\
& \quad \text{R} & \quad \text{R} \\
(+)\text{-5.21} & \quad R = \text{NHCOCH}_3 & \quad (+)\text{-5.13} & \quad R = \text{NHCOCH}_3 \\
(+)\text{-5.22} & \quad R = \text{NH}_2 & \quad (+)\text{-5.23} & \quad R = \text{NH}_2 \\
(+)\text{-5.24} & \quad R = \text{Na}^- & \quad (+)\text{-5.24} & \quad R = \text{Na}^- \\
(+)\text{-5.24} & \quad R = \text{H} & \quad (+)\text{-5.24} & \quad R = \text{H} \\
\end{align*}
\]

**Figure 5.9.** The one step synthesis of a $C_3$ $(+/-)$-5.7 and $C_1$ $(+/-)$-5.24 mixture proceeds through the reduction of amido CTBs $(+/-)$-5.21 and $(+/-)$-5.13, respectively.
symmetric (+/-)-5.13 mixture in just 12 hours at room temperature. The mixture was then quantitatively hydrated to the ammonium chloride salt using HCl in EtOH giving a mixture of (+/-)-5.22 and (+/-)-5.23, respectively, and was subsequently basified to isolate a mixture of tris-amine CTBs (+/-)-5.24 and (+/-)-5.7.

Recrystallization of the C₁/C₃ amine mixture from EtOH gave pure C₁-symmetric

Figure 5.10. (a) The 70 % probability thermal ellipsoid plot (with isotropically refined atoms labeled) and spacefill models of one enantiomer of 5.24. Arene C is disordered about the positions of the anime and methoxy groups. (b) TGA of (+/-)-5.24•EtOH crystals freshly recrystallized from EtOH. The expected percent mass loss is 10.3 %.
(+/-)-5.24 in a 70 % isolated yield from the mixture (44 % overall yield from 5.20), implying the mixture is predominantly the $C_1$ isomer. A single crystal X-ray structure was determined (Figure 5.10a). The ASU of the crystal structure of (+/-)-5.24 contains one half of a molecule of 5.24, residing on a mirror plane. Therefore, both enantiomers of 5.24 are disordered about the same position, each at 50 % occupancy. Aromatic rings A and B are well behaved, with the disorder occurring between the amine and methoxy group only on arene C. The disorder required that the nitrogen and oxygen atoms be refined with isotropic thermal parameters. The crystal also includes one disordered EtOH molecule per molecule of 5.24. The 1:1 EtOH:5.24 stoichiometry was verified by modeling the disordered EtOH using the Squeeze$^{10}$ subroutine of PLATON, which estimates 78e$^-$ to be associated with disordered solvent (EtOH has 26 e$^-$). The stoichiometry calculated for the mass loss of one EtOH molecule (10.3 %) also matches well with the experimental thermogravimetric analysis (TGA) data (10.25 %) on crystalline (+/-)-5.24•EtOH.

It was initially difficult to determine the $C_1$/$C_3$ ratio of products (+/-)-5.21/(+/-)-5.13 from the reaction of 5.20 with paraformaldehyde (Figure 5.11). The diastereomeric

![Figure 5.11](image)

**Figure 5.11.** The 1H NMR spectrum of (+/-)-5.21/(+/-)-5.13 is broad with significant peak overlap, making it unfeasible determination of the ratio.
products could not be separated, moreover, the $^1$H NMR spectrum of the amido mixture was broad and could not be used to determine the $C_1/C_3$ ratio due to significant peak overlap.

The $^1$H NMR spectrum of the pure amino CTB mixture of $C_1$ symmetric (+/-)-5.24 and $C_3$ symmetric (+/-)-5.7, however, showed that the peaks corresponding to the arene ring protons could be almost fully resolved (Figure 5.12). Comparing the pure $C_3$ $^1$H NMR spectrum of (+/-)-5.7, previously reported, to the $C_1/C_3$ mixture allows the

![Image of NMR spectra and molecular structures]

**Figure 5.12.** (a) The (+/-)-5.7 ($C_3$) and (+/-)-5.24 ($C_1$) isomers can be separated by recrystallization from EtOH. (b) The pure $C_1$ spectrum of (+/-)-5.24 and (c) the mixture of $C_3$ and $C_1$ are shown to illustrate the peaks resultant from the $C_3$ isomer in the mixture.
assignment of protons H\textsubscript{1} and H\textsubscript{2} as the C\textsubscript{3} isomer. Furthermore, the integrated area for the arene proton signals estimates a ratio of \textasciitilde85:15 C\textsubscript{1}/C\textsubscript{3} and thereby it is concluded that the same ratio is present in the (+/-)-5.21/ (+/-)-5.13 amide mixture. Pure C\textsubscript{3}-symmetric (+/-)-5.7 has not yet been isolated from the 5.7/5.24 mixture due to some decomposition (oxidation) upon recrystallization. Figure 5.11b illustrates the pure (+/-)-5.24 spectrum isolated from recrystallization of the amine mixture. The aromatic peaks for C\textsubscript{3} symmetric (+/-)-5.7 (H\textsubscript{1} and H\textsubscript{2}) were used to determine the mixture ratio by integrating versus H\textsubscript{3}-H\textsubscript{8}. There are three characteristic doublets for both the axial and equatorial protons (H\textsubscript{a1}-H\textsubscript{a3} and H\textsubscript{e1}-H\textsubscript{e3}) of the methylene bridges in the spectra for the (+/-)-5.24, and in the mixture, the signals for H\textsubscript{a} and H\textsubscript{e} from (+/-)-5.7 can be seen overlapping these peaks. As can be seen in 5.12b, the peaks corresponding to (+/-)-5.7 disappear upon recrystallization of the (+/-)-5.24/ (+/-)-5.7 mixture from EtOH.

The separation and synthesis of the C\textsubscript{1} and C\textsubscript{3} amino-CTBs illustrates a cost-effective and powerful single step method of synthesis, and also provides an opportunity to make various cryptophanes and/or capsules asymmetric by joining (+/-)-C\textsubscript{1} and/or (+/-)-C\textsubscript{3} cups in various ways, with dialdehydes for example.

5.3. Direct method Mono-amide and Bis-amide CTBs

Using the ‘one-step’ approach to CTB synthesis also allows for the mixing of arene precursors to produce asymmetric CTBs having varying degrees of substitution.\textsuperscript{14} Only having one or two amine substituents will provide the opportunity to couple CTBs in a
tunable and efficient manner using DCC or a variety of other methods. The amino groups provide opportunity for both reversible imine bond formation, and the ability to coordinate to metals, providing a potentially catalytic site. Amino-functionalized CTBs present the opportunity to combine the molecular recognition properties of concave molecules with the catalytic properties of certain metal-imine complexes by using the CTB ligands to shape the three-dimensional space around a catalytically active metal center.

One possible ligand that should be available from an amino functionalized CTB is the $\beta$-diketiminate scaffold that is well studied in the Warren group at Georgetown University. Using amino CTBs as the ancillary ligands with the $\beta$-diketiminate backbone, one can conceive of at least two potential approaches (Figure 5.13). The first would include a monoamino functionalized CTB, which would be chiral (denoted by *).

\[ \text{(mixture of achiral (syn) and chiral (anti) diastereomers)} \]

**Figure 5.13.** Using the $\beta$-diketiminate backbone, it is conceivable to use amino CTBs as ancillary ligands to define the space around a coordinated metal center.
to form a single metal-coordinating bridge. Introducing two amino groups in to a CTB ligand would provide the ability to coordinate multiple metals within the space defined by the CTBs (Figure 5.13).

In pursuing the first approach, the monoamide CTB (+/-)-5.26 was initially targeted (Figure 5.14). The synthesis of (+/-)-5.25 was attempted via the co-reaction of veratrole and amido anisole 5.20 with paraformaldehyde in acidic solution. The ratio of veratrole to 5.20 greatly affects the product distribution of this reaction, with the most prominent product seen in most cases being CTV (Figure 5.1; X = Y = OMe). To avoid the synthesis of CTV, a series of reactions were performed where the ratio of veratrole to 5.20 was lowered until no evidence of CTV formation was seen by thin layer chromatography. The ratio of 1:5:6 veratrole: 5.20: paraformaldehyde gives molecules (+/-)-5.25, dimeric 5.27, a small amount of polymeric material, and virtually no CTV. The methoxy groups are more strongly directing/donating than the amido groups,

![Synthetic Route](image)

*Figure 5.14. The synthetic route to (+/-)-5.26 also produces 5.27 that was analyzed by single crystal XRD.*
causing formaldehyde to react highly preferentially at positions para to the methoxy group. This difference of reactivity results in the formation of the $C_s$ symmetric 5.27, and once the paraformaldehyde has been depleted, the resultant main products are 5.27 and (+/-)-5.25.

The isolation of 5.27 was verified via $^1$H NMR and single crystal X-ray diffraction (Figure 5.14). Evidence of molecule (+/-)-5.25 has been acquired via $^1$H NMR, however, this reaction was carried out on a qualitative scale, thus providing no accurate yields, and the subsequent reaction to synthesize (+/-)-5.26 through the hydrolysis of (+/-)-5.25 has not yet been attempted. The $^1$H NMR evidencing the synthesis of (+/-)-5.25 (Figure 5.15) has a small amount of impurity, but the major peaks share some spectral features with the $C_1$ symmetric (+/-)-5-24, as would be anticipated giving the $C_1$ symmetry of (+/-)-5.25. The $H_a$ protons centered around 4.75 ppm share the pattern seen in (+/-)-5.24 ($H_{a1}$-$H_{a3}$), showing a well defined set of three doublets from the

![Figure 5.15. The labeled $^1$H NMR spectrum of slightly impure (+/-)-5.25.](image)

174
inequivalent protons. The aromatic region of the spectra displays 6 singlets for the aromatic protons, and a broadened singlet at 7.5 ppm correlating to the NH proton. Four of the arene peaks are close to each other in chemical shift (H_{3}-H_{6}; 6.77-6.81 ppm), one is shifted by 0.15 ppm, and the last one is shifted by 1.6 ppm, located at 8.4 ppm. The shifted protons are assigned to the protons on the amide bearing arene. The H_e region of the spectra overlaps with some impurity and also the OMe peaks (3.4 - 4.0 ppm). The integration for the amide methyl peak at 2.1 ppm calculates to one amide methyl group, also supporting the assignment of the molecule as (+/−)-5.25.

The isolation of 5.27 in the above described reaction led to the investigation of the synthesis of 5.33, an achiral bis amino substituted CTB (Figure 5.16). This molecule piques interest because it is C_s symmetric and achiral and its dimerization by reaction with acac (acetylacetone) would lead to a similarly achiral bis-CTB pre-capsule as shown in Figure 5.12. Such a species may provide the opportunity to put two metal centers into a confined space with limited access to the metals. The synthesis of 5.27 was improved by reaction of paraformaldehyde with 5.20 in a 1:2 ratio yielding 5.27 in ~85% yield. Two methods were then envisaged to potentially synthesize 5.33. The first route explored the addition of excess formaldehyde to the dimer 5.27 in an attempt to make the bis benzyl alcohol 5.31 (Figure 5.16b). Subsequent reaction with veratrole would be expected to provide diacetamido-CTB 5.32, which could then be hydrolyzed to 5.33. Oddly, this method proved unsuccessful, with no evidence of 5.31 being formed. The \textsuperscript{1}H NMR spectrum of the reaction of paraformaldehyde with 5.27 under
acidic conditions showed no indication of substitution at the arene position to form 5.31, even under the same conditions used to make the C₁/C₃ mixture of (+/-)-5.24 and (+/-)-5.7 discussed in Chapter 5.2. This is surprising since these conditions are known to allow reaction to occur at the less activated positions para to the amido group, as supported by the formation of (+/-)-5.21 and (+/-)-5.13 as described earlier.

The second synthetic route envisaged to 5.33 (Figure 5.16a) involves essentially introducing benzyl alcohol moieties to veratrole at the 4 and 5 positions, giving 5.30 from 5.28 via a bicyclic intermediate 5.29. Subsequent reaction of 5.29 with 5.27 could then provide the bis-amido CTB 5.32. A literature preparation for molecule 5.30 following this route has been reported, however, upon the first attempt in our lab, has provided no evidence of 5.30.
5.4. Experimental

5.4.1. Materials and Methods

All solvents were used as received from Fisher (Pittsburgh, PA). Reagents were obtained from Acros (Pittsburgh, PA) or Aldrich (Milwaukee, WI) and were used without further purification. All reactions were carried out under nitrogen atmosphere. Chromatography was carried out on silica gel (32-64µm). NMR spectra were recorded on either a Mercury Varian 300 MHz or an Inova 400 MHz Spectrometer operating at 300 or 400 MHz (\textsuperscript{1}H), or 75.5 or 100.5 MHz (\textsuperscript{13}C), respectively. All NMR spectra were collected at room temperature (298(2) K) unless otherwise noted and were indirectly referenced to TMS using residual solvent signals as internal standards. Elemental analyses were carried out on a Perkin-Elmer PE2400 microanalyzer. The syntheses presented in this Chapter were all performed by the author, with contributions to the project made by Scott Mough in our research lab.

(+/-)-5.21 and (+/-)-5.13. To a 50 mL, stirring, room temperature, acetic acid suspension of 10.0 g (60.0 mmol) 5.20 and 1.83 g (60.0 mmol) paraformaldehyde was added dropwise 100 mL HClO\textsubscript{4}. After addition, the solution was stirred for 24 hours at room temperature. The solution was then poured into 1 L water and filtered. The solid filtrate was washed successively with EtOH (100 mL) and diethyl ether (100 mL) resulting in an off-white solid of the mixed $C_1$ (+/-)-5.21 and $C_3$ (+/-)-5.13 cyclic amide products, later determined to be present in an 85:15 ratio. Throughout the filtering and washing, care was taken to keep the solid wet with the rinsing solvents to avoid the
material becoming dry, which results in a brown, insoluble material. Yield (6.7 g, 13 mmol, 63%). $^1$H NMR (DMSO-$d_6$): see Figure 5.10.

(+/-)-5.22 and (+/-)-5.23. 6.7 g (0.013 mol) of the (+/-)-5.21/(+/-)-5.13 mixture was suspended in 75 mL EtOH. To the stirring suspension was added dropwise 300 mL conc. HCl$_{(aq)}$. The solution was then refluxed for 4 hours and formed a precipitate. The precipitate was filtered and washed with minimal amounts of EtOH, diethyl ether, and CH$_2$Cl$_2$ in succession. The resultant white solid is a mixture of the $C_1$ (+/-)-5.22 and $C_3$ (+/-)-5.23 ammonium chloride salts (later determined to be an 85:15 ratio). Yield (3.62 g, 8.0 mmol, 62%).

(+/-)-5.24 and (+/-)-5.7. To a 10 mL aqueous solution of 100 mg of the (+/-)-5.22/(+/-)-5.23 mixture was added 2M NaOH, forming a precipitate. The precipitate was filtered and washed with water to yield a white solid. The mixture was determined to consist of ~85:15 (+/-)-5.24/(+/-)-5.7 by $^1$H NMR. On this basis, the ratios of (+/-)-5.22/(+/-)-5.23 and (+/-)-5.21/(+/-)-5.13 were similarly estimated as given above. Yield (75.6 mg, 0.212 mmol, 99%). Separation of the (+/-)-5.24 and (+/-)-5.7: The mixture (~85 % (+/-)-5.24) was recrystallized 3 times from ethanol at a concentration of ~1.0 g/100 mL. The resulting needles gave a $^1$H NMR spectrum consistent with pure $C_1$ (+/-)-5.24. The collected solid after 3 recrystallizations was filtered to give light yellow crystalline needles. Yield (37 mg, 44 % based on 5.20); mp (+/-)-5.24 = 144-147°C; $^1$H NMR (CDCl$_3$): δ 6.73 (s, 1H, Aryl-H); δ 6.72 (s, 1H, Aryl-H); δ 6.69 (s, 1H, Aryl-H); δ 6.68 (s, 1H, Aryl-H); δ 6.66 (s, 1H, Aryl-H); δ 6.65 (s, 1H, Aryl-H); δ 4.70 (d, $^2J = 13.6$
Hz, 1H, \text{H}_a); \delta 4.66 (d, ^2J = 13.6 \text{ Hz}, 1H, \text{H}_a); \delta 4.63 (d, ^2J = 13.6 \text{ Hz}, 1H, \text{H}_a); \delta (s, 9H, OCH_3); \delta (s, 9H, OCH_3); \delta (s, 9H, OCH_3); \delta 3.59 (s, 6H, NH_2); \delta 3.46 (d, J^2 = 13.6 \text{ Hz}, 1H, \text{H}_a); \delta 3.42 (d, J^2 = 13.6 \text{ Hz}, 1H, \text{H}_a); \delta 3.38 (d, J^2 = 13.6 \text{ Hz}, 1H, \text{H}_a). ^{13}\text{C} \text{NMR (CDCl}_3\text{): Aromatic Region:} \delta 157.4; \delta 148.6; \delta 146.7; \delta 137.0; \delta 133.3; \delta 131.8; \delta 120.1; \delta 117.4; \delta 113.9. \text{ Aliphatic Region:} \delta 72.4; \delta 56.6; \delta 36.6.

(+/-)-5.25. To 50 mL of acetic acid was added 0.69 g (0.005 mol) veratrole, 4.13 g (0.025 mol) 5.20, and 0.9 g (0.03 mol) paraformaldehyde. To the stirring solution was added 5 mL HClO_4 dropwise. After addition, the solution was stirred for 24 hours at room temperature. The solution was then poured into 1 L water and extracted with CHCl_3 (3 X 50 mL). The organic layer was dried over MgSO_4, and evaporated under vacuum. Crude product was chromatographed on silica gel with 1:1 CHCl_3/acetone to yield a yellow-brown solid. R_f = 0.66 (1:1 CHCl_3/acetone). ^1\text{H} \text{NMR (CDCl}_3\text{): see Figure 5.14.}

5.27. To 50 mL of acetic acid was added 5.00 g (0.03 mol) 5.20, and 0.45 g (0.015 mol) paraformaldehyde. To the stirring solution was added 5 mL HClO_4 dropwise. After addition, the solution was stirred for 24 hours at room temperature. The solution was then poured into 1 L water and extracted with CHCl_3 (3 x 50 mL). The organic layer was dried over MgSO_4, and evaporated under vacuum. Crude product was chromatographed on silica gel with 2:1 acetone/CHCl_3. 5.27 appears as a yellow-brown solid. Yield (4.14 g, 80.3 %); R_f = 0.69 (1:1 CHCl_3/acetone). ^1\text{H} \text{NMR (CDCl}_3\text{):} \delta 8.23 (d, ^4J = 1.2 \text{ Hz}, 2H, Arvl-H); \delta 7.70 (br s, 2H, NH); \delta 6.85 (dd, ^3J = 7.6 \text{ Hz}, ^4J =
1.2 Hz, 2H, Aryl-H); δ 6.75 (d, \(J = 7.6\) Hz, 2H, Aryl-H); δ 3.87 (s, 2H, Ar-CH\(_2\)-Ar); δ
3.83 (s, 6H, OCH\(_3\)); δ 2.17 (s, 9H, NHCOCH\(_3\)). \(^{13}\)C NMR (CDCl\(_3\)): Aromatic Region:
δ 167.9; δ 145.9; δ 134.4; δ 123.7; δ 120.2; δ 109.8. Aliphatic Region: δ 55.7; δ 40.9; δ
37.9; δ 24.9.

5.4.2. Crystal Growth.

(+/-)-\(\text{5.24}\). \(ca.\) 5 mg of \(\text{5.24}\) was placed in ~5 mL ethanol in a sealed vial. The vial
was heated until the material dissolved. Upon cooling at room temperature, colorless
needle single crystals formed.

\(\text{5.27}\). Single crystals of \(\text{5.27}\) were grown by slow evaporation from a concentrated
solution of \(\text{5.27}\) in 1:1 CHCl\(_3\)/acetone.

5.4.3. X-Ray Crystallography

Single crystal diffraction data were collected using a Siemens SMART 1k CCD X-
ray diffractometer with Mo K\(\alpha\) radiation (0.71073 Å) at 100(2) K. The crystal
structures were solved by direct methods using SHELXS, and all structure refinements
were conducted using SHELXL-97-2.\(^1\)\(^7\) Summary of crystallographic data are given in
Table 5.1. The program X-Seed was used as a graphical interface for the SHELXL
software suite and for the generation of figures.\(^1\)\(^8\) In the refinement model of (+/-)-\(\text{5.24}\),
the methoxy and amine groups on arene C in Figure 5.6a were found to be disordered
over two positions in an estimated 50:50 ratio. The relative site occupancies of the atom
positions were estimated by refining their site occupancy factors (s.o.f’s) and constraining the sum of their occupancies to be unity. The disordered atoms were refined with isotropic thermal parameters. The SQUEEZE routine of PLATON\textsuperscript{19} was employed to model the electron density associated with the disordered solvent molecules present in the structure. SQUEEZE estimates a total void volume per unit cell of 332.9 Å\textsuperscript{3}. The total electron density of 78 e- per unit cell outputted by PLATON calculates to 19.5 e- per molecule of (+/-)-5.24. The electron density can be attributed to the EtOH solvent species, and the electron count loosely agrees with that calculated for one ethanol molecule (26 e-). The output from the SQUEEZE calculation is included in the CIF file.
Table 5.3. Summary of Crystallographic Data

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R1, wR2[I > 2σ(I)] 0.0751, 0.1928; 0.0743³, 0.1983³ 0.0258, 0.0643
R1, wR2 (all data) 0.0893, 0.1998; 0.0853³, 0.2060³ 0.0272, 0.0651
G.O.F. 1.079; 1.041³ 1.057

³ Values are reported after running SQUEEZE routine.
5.5. References


