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A Thesis Presented to the Department of Chemistry,
Colby College, Waterville ME
In Partial fulfillment of the Requirements for Graduation
With Honors in Chemistry

Submitted May, 2008
Using Azahetercyclic Electrophiles to Synthesize Novel Bicyclooxa
calixarennes and Oxacalix[2]N-hexyl
aphthalimide[2]naphthyridines

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Vita

Douglas Alexander Rooke, son of Alec and Donna Rooke, was born on August 1, 1985, in Seattle, WA. He was raised in Shoreline, WA.

Since a young age, Doug has always been interested in how things work, which is why he loves the sciences. His love for chemistry was instilled in the lab of his senior organic chemistry class at The Lakeside School in Seattle.

Upon his matriculation at Colby College in Waterville, ME, Doug realized that chemistry research would be something worth trying. In the fall of 2006 he began research for Professor Jeffrey Katz (Colby College) while he pursued the rigorous Chemistry-A.C.S major. In May 2008, Doug received his Bachelor’s of Arts Degree in Chemistry.

While not in lab, Doug can be found at the hiking in the mountains, working out in the gym or cooking.

In August, 2008, Doug entered the Colorado State University in Fort Collins, CO to pursue a PhD. in Organic Chemistry.
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good food, an appreciation for the outdoors, and a worldly view on life. My mother has given me the will to be the best and get stuff done. My father has given me the passion for science and how things work. That combination has proven to be very useful, and hopefully will render me successful in life.
# Table of Contents

Title page ........................................................................................................... 1
Signature Page ...................................................................................................... 2
Vita ....................................................................................................................... 3
Acknowledgements ............................................................................................... 4
Table of Contents .................................................................................................. 6
List of Figures ........................................................................................................ 7
List of Schemes ...................................................................................................... 8
Abstract ............................................................................................................... 9
Introduction ......................................................................................................... 10
Discussion .......................................................................................................... 20
Experimental ....................................................................................................... 33
List of Figures

Figure 1: General reaction diagram for a carbon bridged calixarene..................11

Figure 2: Fluoride ion complexation with bicycles 15 and 6..........................15

Figure 3: 1,3-alternate conformations of oxacalixarenes with approximate centroid-centroid distances.................................................................17

Figure 4: X-Ray crystal structures of previously synthesized macrocycles........18

Figure 5: Thermal ellipsoid and space filling models from the X-ray crystal structure of m,p,m,p-oxacyclophane 7......................................................20

Figure 6: Space filling and thermal ellipsoid X-ray crystal structures of bicycle 5.................................................................21

Figure 7: X-ray structure of tricyclooxacalixarene 16......................................23

Figure 8: X-ray structure of salicylic acid bound to 25.................................25

Figure 9: Oxacalix[2]N-hexynapthalimide[2]napthryidine 22 titrated with quantitative amounts of salicylic acid.......................................................25

Figure 10: MOE models of 1,8-diaminonaphthalene 24 bound to Oxacalix[2]N-hexynapthalimide[2]napthryidine 22.................................................26

Figure 11: Oxacalix[2]N-hexynapthalimide[2]napthryidine 22 titrated with 1,8-diaminonaphthalene 24.................................................................27

Figure 12: Guest, 24, titrated with TFA..........................................................28

Figure 13: TFA titrated into a solution of 22....................................................29

Figure 14: Equimolar solution of oxacalix[2]N-hexynapthalimide[2]napthryidine 22 and 1,8-diaminonaphthalene 24 titrated with TFA.............................30

Figure 15: Vials showing the different solutions of 24, 22, and TFA..............30
List of Schemes

**Scheme 1:** General reaction scheme for the synthesis of an n-oxacalix[4]arene

**Scheme 2:** General synthetic pathways toward oxacalixarenes containing azaheterocyclic electrophiles

**Scheme 3:** Formation of bicyclooxacalixarenes 5 and 6

**Scheme 4:** Formation of m,p,m,p-oxacyclophanes 7 and 8

**Scheme 5:** Crystallization induced synthesis of tricyclooxacalixarene, 16

**Scheme 6:** The synthesis of 17


**Scheme 8:** Reaction diagram for the formation of 16
Abstract:

Various bicyclooxacalixarenes, tricyclooxacalixarenes and oxacalix[2]N-hexynaphthalimide[2]naphthyridines are synthesized via SNAr condensation. This research has involved synthesis optimization. The oxacalix[2]N-hexynaphthalimide[2]naphthyridines have exhibited host-guest binding in fluorescence experiments. These compounds have been characterized by NMR spectroscopy as well as single crystal X-ray diffraction.
Introduction:

Intensive research of carbon bridged calixarenes over the past half century has allowed these fascinating cyclophanes to carve out their own niche in modern supramolecular chemistry.\(^1\) The word calixarene is derived from the Greek calix, which means "vase" or "chalice"\(^2\). Though he was never able to isolate a pure product, calixarenes were believed to be first synthesized by Adolf von Bayer in the 1870's by reacting phenols with formaldehyde. Leo H. Baekeland and his Bakelite Company brought phenol-formaldehyde resins into commercial use at the turn of the 20th century\(^3\). It was not until about one hundred years after Bayer when David Gutsche's group at Washington University decided to reinvestigate phenol-formaldehyde chemistry and was the first to correctly determine the structures and characterizations of calixarenes. The Gutsche group worked for years to optimize reaction conditions for calixarene synthesis\(^4\) (Figure 1). They found that any slight delineation from their prescribed reaction conditions would result in poor yields of the desired calixarene.

Calixarenes have been proven to be useful due to their unique conformational and cavity structures. Today calixarenes have uses in the fields of chiral catalysis, nuclear waste extraction, and molecular recognition\(^5\).

Figure 1: General reaction diagram for a carbon bridged calixarene

Oxygen bridged calixarenes (oxacalixarenes) were first reported in 1966 in low yield\(^6\). Later, other groups reported increased but still modest yields (28%) of the same tetranitrooxacalix[4]arene\(^7\). The Katz group has been focusing on the study of this type of macrocycle using nucleophilic aromatic substitution, and is able to synthesize a number of oxacalixarenes in high yields (Scheme 1). Unlike their carbon bridged counterparts, the reaction conditions for the synthesis of oxacalixarenes are operationally simple. These reactions involve condensing di- or triphenols with dichloro-aromatic electrophiles bearing electron stabilizing groups in the presence of base.

Scheme 1: General reaction scheme for the synthesis of an oxacalix[4]arene

In their first paper on oxacalixarenes, the Katz group reported the use of both $K_2CO_3$ and $Cs_2CO_3$ to promote the reactions for the formation of tetranitrooxacalix[4]arenes with near quantitative yields in as fast as 10 minutes at room temperature. These $S_NAr$ condensation reactions for oxacalixarenes are thermodynamically controlled allowing them to run the reactions at high concentration. The flexibility of this $S_NAr$ based route has allowed the Katz group to synthesize a variety of highly functionalized oxacalixarenes.\(^1\)

The Katz group also reported equally high yields with potassium fluoride and sodium carbonate.\(^1\) Later, $Cs_2CO_3$ was used exclusively because, as a counter ion, cesium does not interact with the oxy-anion as much as the smaller sodium or potassium would, effectively increasing the rate of the $S_NAr$. This choice of cesium cation proved to be essential as less electrophilic heterocycles were used (Scheme 2). Promotion by fluoride base was later revisited when anhydrous conditions were required and also in attempts to alter product selectivity.

**Scheme 2:** General synthetic pathways toward oxacalixarenes containing azaheterocyclic electrophiles
One of my first projects was the synthesis of different oxacalixarenes by condensing azaheterocyclic electrophiles such as 4,6-dichloropyrimidine (1) or 2,6-dichloropyrazine (2) with phloroglucinol (3) or hydroquinone (4). The reactions involving phloroglucinol lead to pyrazine bicyclooxacalixarene 5 or pyrimidine bicyclooxacalixarene 6 (Scheme 3).

Scheme 3: Formation of bicyclooxacalixarenes 5 and 6

The reactions involving hydroquinone afforded m,p,m,p-oxacycloclophanes 7 or 8 (Scheme 4). Low to modest yields of the aforementioned compounds were obtained with cesium carbonate. I then attempted the reaction for the formation of 5 in the presence of CsF and found a significant increase in yield. This led me to continue using CsF as a base in subsequent reactions. Yields of several other oxacalixarenes and oxygen-bridged cyclophanes, originally synthesized with cesium carbonate, have shown increased yields with cesium fluoride.
Scheme 4: Formation of m,p,m,p-oxacyclophanes 7 and 8

In July 2007, the Wu group published a calculational study\(^8\) showing that hexanitrobicyclooxacalixarene 15, previously synthesized and published by the Katz group\(^9\), was capable of complexing fluoride ion in the gas phase. The calculation showed that fluoride should favorably interact with the three hydrogens pointing to the inside of the cage. These findings led us to revisit the synthesis of bicycle 6, due to its three inward pointing hydrogens. The pyrimidine nitrogens should make the rest of the ring electron deficient making each hydrogen pointing to the center of the cyclophane relatively acidic. We were very excited about the possibility of fluoride complexation because CsF could be used as a base for this synthesis. Possibly, the fluoride could act to help template the formation of the

\(^{8}\) Chun-shan Zuo; Jun-Min Quan; Yun-Dong Wu  *Organic Letters*. **2007**, *4219*-4222.

cage. Hypothetically, fluoride templated formation of 6 would mean that the fluoride ion would interact with the hydrogen atoms of the 3 pyrimidine molecules facilitating the ultimate closing of the bicyclic structure.

Figure 2: Fluoride ion complexation with bicycles 15 and 6

As a result of the studies and synthesis optimization of 6, a novel tricyclooxacalixarene was inadvertently synthesized. An unpurified reaction mixture for the formation of 6 was allowed to stand in acetone-\(d_6\) for approximately one month. We were pleasantly surprised to see that crystals had formed in the NMR tube. X-ray diffraction data showed that the structure of the crystal was of a compound that we could have never imagined forming selectively, tricycle 16 (Scheme 5).

Scheme 5: Crystallization induced synthesis of tricyclooxacalixarene 16
The main challenge of my final semester of research at Colby has been to selectively synthesize and purify 16. Although I was unable to synthesize 16 directly from 1 and 3, I have developed a two step method involving the condensation of oxacalix[2]phloroglucinol[2]pyrimidine 17 with another equivalent of 1 (Scheme 6).

![Scheme 6: The synthesis of 17](image)

**Oxacalixarene Guest-Host Chemistry**

Guest-host chemistry of oxacalixarenes is another area that I have explored extensively during my tenure in the Katz group. It has been observed previously, with X-ray crystal structures, that oxacalix[4]arenes adopt a 1,3-alternate conformation. The bridging oxygen atoms' lone pairs donate into the pi system of the electrophile, forcing the nucleophilic component aromatic rings into a coparallel position. Crystal structures show that oxacalix[4]arenes and derivatives, with one benzene ring as a spacer, have a 4.5 Å spacing between aromatic walls, which is far too small to contain a guest molecule. In fact, with that distance of
separation, the pi-clouds of both nucleophilic components almost overlap. To render oxacalix[4]arenes as potential host molecules, larger electrophilic components can be used such as naphthalenes and naphthyridines. Molecular modeling revealed that the use of these electrophiles would result in a cavity 7 Å in size\(^{10}\) (Figure 3). By using 2,7-dichloro-1,8-naphthyridine as an electrophile, the nitrogens would face the inside of the cavity giving four possible hydrogen bonding sites for guests (Figure 4).

![Figure 3: 1,3-Alternate conformations of oxacalixarenes with approximate centroid-centroid distances](image)

Another possible interaction between the guest and the host that can affect complexation is \(\pi-\pi\) stacking. It has been documented in the literature by Hunter and Sanders\(^{11}\) that aromatic groups can be stacked to afford energy maxima and minima. The interactions likely to be observed between guests and our oxacalixarene hosts are the direct overlap and offset overlap conformations of \(\pi\) orbital stacking. The direct overlap aromatic \(\pi\) orbitals leads to an unfavorable interaction and would decrease the possibility of host guest binding in that situation. However, if the guest was to adopt an offset \(\pi\) stacking conformation, 

\(^{10}\) Katz, J.L.; Geller, B.J.; Foster, P.D. Chem. Commun., 2007, 1026-1028

we would likely observe an increase in binding. Previous oxacalixarenes synthesized by the Katz group incorporating naphthyridines have been crystallized with solvent molecules inside the cavity, showing that small molecules can indeed fit inside the cavity.

Figure 4: X-Ray crystal structures of previously synthesized macrocycles, note that methylene chloride is in the cavity of “a” and acetonitrile is in the cavity of “b”.

With the knowledge that small molecules can fit inside the cavity of oxacalix[4]arenes bearing naphthyridine spacers, the door was opened to synthesize bigger and better hosts. The Katz Group has successfully synthesized oxacalix[2]N-hexylnaphthalimide[2]naphthyridine 22, and this macrocycle exhibits strong fluorescence properties. With this knowledge I was then able to explore the ability of 22 to bind to various small molecules using fluorescence spectroscopy.

Host-guest complexes often exhibit static fluorescence quenching. Fluorescence quenching refers to any process where the fluorescence intensity (quantum yield) decreases due to any of the following: static quenching, collisional quenching, or energy transfer. Static quenching occurs when the excited fluorophore (host) is allowed to relax through interactions with the ligand (guest). We can use this method to calculate binding constants so long as there is no collisional quenching or non-radiative energy transfer.
Results and Discussion:

m,p,m,p-oxacyclophanes

I first investigated the aforementioned m,p,m,p-oxacyclophanes. Although the reaction for the formation of 7 was quite clean, 7 proved to be exceedingly difficult to purify using a silica flash column. Fortunately, enough pure compound was isolated to perform crystallization experiments, and several large single crystals were obtained within twenty-four hours of setting up the vapor diffusion chambers. This allowed Mike Abers to obtain an X-ray crystal structure (Figure 5). Unexpectedly the two benzene rings do not adopt a coparallel arrangement but instead tilt at an angle. This conformation could be a consequence of the molecules packing together to form the crystal or it could be a result of the unfavorable direct aromatic π orbital overlap.

Figure 5: Thermal ellipsoid and space filling models from the X-ray crystal structure of 7
The preparation of 7 originally used cesium carbonate as a base. Upon running this reaction for the formation of 7 instead in the presence of CsF, we have found a much cleaner reaction, with a much larger mass recovery. However, due to the poor solubility of 7, we were unable to purify it using silica, consequently, no pure yields were obtained.

**Bicyclo Oxacalixarenes**

Another compound that undergoes a more facile synthesis under fluoride mediated conditions is bicycle 5 (Figure 6). Compound 5 behaves well on silica and is easy to purify allowing a facile comparison of fluoride and carbonate as reaction promoters. With ten equivalents of CsF, 5 has been synthesized in yields up to 77% whereas the same reaction catalyzed with five to seven equivalents of Cs₂CO₃ only afforded a yield of 25%. Crystallization of 5 from methylene chloride occurred within 24 hours and afforded large hexagonal crystals that were stable outside of the solvent, which allowed us to obtain an X-ray crystal structure.

![Space filling and thermal ellipsoid X-ray crystal structures of 5](image)

**Figure 6:** Space filling and thermal ellipsoid X-ray crystal structures of 5

The comparison of the two bases, Cs₂CO₃ and CsF became much more interesting when I began to focus on the synthesis of 6. To this day I have been
unsuccessful in synthesizing $\textit{6}$ using Cs$_2$CO$_3$ as a base, and I initially had quite a lot of trouble using CsF as a reaction promoter. At first I conducted this reaction under the same conditions as for the synthesis of $\textit{5}$. Interestingly enough, these conditions did not form $\textit{6}$ as hoped. Instead, $\textit{17}$ was found to be the major product, but was produced in low yield. One logical explanation for this would be that $\textit{2}$ was either polymerizing or decomposing over time at $120^\circ\text{C}$. This failure led me to screen milder conditions to attempt to synthesize $\textit{6}$. Reactivity was found as low as $50^\circ\text{C}$, yet the reactions run at $70^\circ\text{C}$ for approximately 9 hours were the highest yielding for the formation of $\textit{6}$. One unusual aspect of the $^1\text{H}$ NMR spectrum of $\textit{6}$ is the one of the pyrimidine hydrogen shifts is extremely upfield (5.85 ppm) for an aromatic hydrogen. This upfield shift is because the three hydrogens, one from each pyrimidine, point into the center of the cage. Due to the aromatic rings above and below, the hydrogens experience a smaller magnetic field than that of a normal aromatic proton.

One exciting discovery happened in early January 2008. A reaction mixture for the formation of $\textit{6}$ was subjected to an aqueous workup, dried in vacuo, and then placed in acetone-$d_6$ for an NMR experiment. The $^1\text{H}$ NMR spectrum of the contents in the tube identified $\textit{6}$ as the major product. The solution of $\textit{6}$ in acetone-$d_6$ was left in the NMR tube during the winter break (approximately 4 weeks). After a few days back Professor Katz peered into the tube and found several large single crystals suitable for an X-ray diffraction experiment. However, what the X-ray diffraction pattern elucidated was not a structure of $\textit{6}$ but of $\textit{16}$.
instead (Figure 7). During our time away, 6 had dimerized and crystallized into 16.

Figure 7: Chemdraw and X-ray structure of 16

Once the structure was determined, I turned my efforts toward selectively synthesizing 16. The crystals were dissolved in DMSO-d<sub>6</sub> and a clean <sup>1</sup>H NMR spectrum was obtained. Future reactions run at 70°C and 9 hours showed competitive formation of 6 and 16, but yields for both were very poor.

While trying to optimize the syntheses of 6 and 16, I also was able to synthesize 17. This condensation occurred at 70°C for 90 minutes in relatively high yield (85%).

I next attempted to synthesize 16 by condensing 17 with one equivalent of 2. Selective formation of 16 was observed after 15 minutes at 90°C in DMSO with ten equivalents of CsF with respect to the electrophile (Scheme 8). I was able to find the aforementioned conditions to selectively synthesize 16. I have obtained 16 in yields as high as 20%, even when using 17 as an unpurified reaction mixture. Compound 16 separates well on silica, is relatively soluble in methylene chloride, and can be purified using flash column chromatography.
**Scheme 8:** Reaction diagram for the formation of 16


The condensation of 20 and 21 readily forms oxacalix[2]N-hexylnapthalimide[2]naphthyridine. Originally, Cs₂CO₃ was used as a base to catalyze the nucleophilic aromatic substitution. Like many aforementioned reactions, it was found that CsF acts as a much better promoter, and gave greatly increased yields. For the formation of 22, it was found that adding approximately 10 equivalents of CsF led to the highest product yields.

Upon amassing a significant amount of 22 I began fluorescence studies. Due to the poor solubility of 5 we were limited in our choice of solvents. Since 5 is fairly soluble in methylene chloride, we decided to use it for our initial fluorescence studies and then branch out to different solvents at lower concentrations of 22 (Figure 8). It was previously shown by the Katz Group that

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12 Rooke, D.A.; Spring research paper 2007
oxacalix[2]naphthalene[2]naphyridine 25 weakly binds to salicylic acid (23)$^{13}$ (Figure 8).

**Figure 8:** X-ray structure of salicylic acid bound to 25

The weak binding is most likely due to the fact that salicylic acid has only one hydrogen bonding site that can interact with the naphthyridine nitrogens in oxacalixarenes 22 and 25. The Katz group has shown that 25 binds 22 in the solid state$^{13}$.

**Figure 9:** 22 titrated with quantitative amounts of 23

Another guest studied was 1,8-diaminonaphthalene (24). The number of possible hydrogen bond donating sites led us to believe that it would be an ideal guest for binding to 22. Molecular modeling of 24 bound to 22 using MOE showed two potential hydrogen bonds, leading us to hypothesize that 24 would readily bind to 22 (Figure 9).

![Diagram of molecules]

**Figure 10:** MOE models of 24 bound to 22 in a) and protinated 24 bound to 22 in b)

The molecular model of protonated 24 shows that 24 internally hydrogen bonds to itself, forcing four amino hydrogens to point towards the four nitrogens on 22 and leading to more guest-host hydrogen bonds. This would suggest that binding to 24 would be more favorable in the protonated state than in the
unprotonated state. By observing emission spectra of a solution containing a fixed concentration of 22 and varying concentrations of 24 with excitation at 375 nm, we were able to qualitatively conclude that there relatively weak binding of 24 to 22 when 24 is unprotonated.

Figure 11: 22 titrated with 24 (excitation at 375 nm)

Figure 10 shows a slight red shift in λ-max as the concentration of 24 increases relative to 22. This red-shift can be accounted for because the emission λ-max of 24 is 415 nm. Since 24 can be slightly excited at the excitation maximum for 22, there will be some emitted light as a result of the guest. The overall fluorescence intensity shown in Figure 10 is not actually increasing as one would expect with the addition 24 due to its fluorescence properties, in fact, it is decreasing slightly. A possible explanation for both the decrease in fluorescence and the red-shift would be because of a simultaneous
occurrence of weak binding of 24 to 22 resulting in the quenching of 22, and the increase in fluorescence at a higher wavelength due to the increase in concentration of unbound 24.

For the next experiment, we needed to find out whether or not the addition of acid would change the ability of 24 to bind to 22. A cuvette of 24 and 22 in a 5:1 (guest:host) concentration ratio was prepared and trifluoracetic acid (TFA) was titrated in (Figure 11). The emission was observed to decline substantially with each addition of acid. This is significant since the fluorescence of 22 is only weakly affected by the addition of acid (Figure 12).

![Graph showing fluorescence changes](image)

**Figure 12**: Guest, 24, titrated with TFA

As previously stated, 24 does absorb and emit light at 375 nm and will emit light at around 400 nm which is the λ-max for 22. Also, the fluorescence of 24 is quenched with the addition of TFA. However, the intensity of this signal is small relative to that of 22.
Figure 13: TFA titrated into a solution of 22.

The fluorescence quenching observed upon addition of TFA was significant compared to the quenching exhibited without TFA (Figure 10). Since the 5:1 host:guest plus acid exhibited strong fluorescence quenching, a 1:1 host:guest solution was prepared for the acid titration (Figure 13). Again, the fluorescence quenching was quite substantial. With the addition of two equivalents of TFA to the cuvette, the fluorescence intensity was less than half of the intensity when there was no TFA in the solution.
Figure 14: Equimolar solution of 22 and 24 titrated with TFA

Figure 15: Vials showing the different solutions of 24, 22, and TFA

In the future we would like to calculate binding constants for the complexation of guests 23 and 24 with 22. Although 24 can be excited at 375 nm and can be quenched by the addition of acid, the intensity of emission due to
24 is very insignificant at the studied wavelengths. We need to study the possibilities of energy transfer as well as collisional quenching that could account for decrease in fluorescence intensity. With the elucidation of all fluorescence quenching interactions, the Katz group will be able to calculate binding constants using fluorescence spectroscopy.
Conclusion:

Utilizing the $S_n$Ar reaction pathway has proven to be an effective method for the synthesis of novel bicyclooxacalixarenes and oxacalix[2]N-hexynaphthalimide[2]naphthyridines. The Katz group is making progress toward the synthesis and applications of oxacalixarene-based host molecules. We have evidence that guest molecules bind to some of our oxacalixarenes. The success of 22 as well as other oxacalixarenes as a host for various guests may pave the way for oxacalixarene use for many modern day applications. Research will continue with 22 as well as other oxacalixarenes to study binding ability to various guests. As more data is compiled and we learn more about the host-guest interactions, we can calculate binding constants for our oxacalixarene hosts with a variety of guests.

Bicycle- and tricyclooxacalixarenes are fascinating compounds that demand more research. Future directions will include further optimization of reaction conditions for 6 as well as 16. We also hope to continue to study the possibility of fluoride ion binding to 6. With the knowledge that cesium fluoride is a superior base for the $S_n$Ar condensation the Katz group can move on to synthesize even more novel oxacalixarenes. This work has led us to explore the use of different bases that may produce different oxacalixarene product distributions.
Experimental:

\textbf{m,p,m,p-Pyrazine-cyclophane (7).} 2,6-Dichloropyrazine (1) (0.061 g, 0.41 mmol), hydroquinone (4) (0.054 g, 0.49 mmol) and cesium carbonate (0.79 g, 2.4 mmol) were combined and placed under an atmosphere of argon. Anhydrous DMSO (6.5 ml) was added and the mixture turned a light yellow. The reaction flask was placed in a 120°C oil bath and allowed to stir for 16 hours. Upon heating, the mixture turned a dark brown. The mixture was worked up by precipitating the compound out of solution upon addition of de-ionized water and 1M HCl. No yield was obtained due to poor solubility.

\textbf{m,p,m,p-Pyrazine-cyclophane (7).} 2,6-Dichloropyrazine (1) (0.058 g, 0.42 mmol), hydroquinone (4) (0.046 g, 0.39 mmol) and cesium fluoride (0.79 g, 2.4 mmol) were combined and placed under an atmosphere of argon. Anhydrous DMSO (6.5 ml) was added and the mixture turned a light yellow. The reaction flask was placed in a 120°C oil bath and allowed to stir for 15 minutes. The final reaction solution was light translucent brown. The mixture was worked up by precipitating a white solid out of solution upon addition of de-ionized water and 1M HCl. The compound was eluted with 5% methanol/methylene chloride through a silica flash column with poor separation. No yield was obtained due to poor solubility.
Crystalization\textsuperscript{14} of 7:

Crystalization yielded colorless crystals using the vapor diffusion method with methylene chloride in the inner vial (diameter: 1 cm, height: 3.5 cm) and toluene in the outer vial (diameter: 3 cm, height: 5 cm). Hexagonal crystals were also grown using methylene chloride in the inner vial and either acetone, ethyl acetate, or acetonitrile in the outer vial. Crystal formation occurred within 48 hours in each case. The unit cell was solved to monoclinic and a data set was taken overnight.

**Pyrazine-bicycloxacalixarene 5.** 2,6-Dichloro pyrazine (1) (0.0943 g, 0.63 mmol), phloroglucinol (3) (0.056 g, 0.44 mmol) and cesium carbonate (0.89 g, 2.7 mmol) were combined and placed under an atmosphere of argon. Anhydrous DMSO (6.5 ml) was added and the mixture turned a light yellow. The reaction flask was placed in a 120°C oil bath and allowed to stir for 18 hours. Upon adding heat, the mixture turns a dark brown. The mixture was worked up by precipitating the compound out of solution upon addition of de-ionized water and 1M HCl. The product was eluted with 30% ethyl acetate/hexanes through a silica flash column. (0.0278 g, 26%).

**Pyrazine-bicycloxacalixarene 5.** 2,6-Dichloropyrazine (1) (0.266 g, 1.78 mmol), phloroglucinol (3) (0.150 g, 1.19 mmol) and cesium fluoride (2.00 g, 13.2 mmol) were combined and placed under an atmosphere of argon. Anhydrous DMSO (6.5

\textsuperscript{14} Courtesy of Mike Abers '10
ml) was added and the mixture turned a light yellow. The reaction flask was placed in a 120°C oil bath and allowed to stir for 20 hours. Upon adding heat, the mixture turns a dark brown. The mixture was worked up by precipitating the compound out of solution upon addition of de-ionized water and 1M HCl. The product was eluted with 30% ethyl acetate/hexanes through a silica flash column. (0.187 g, 77.1%).

**Crystallization of 5:**

Crystallization yielded hexagonal crystals using the vapor diffusion method with methylene chloride in the inner vial (diameter: 1 cm, height: 3.5 cm) and acetone in the outer vial (diameter: 3cm height: 5 cm). Crystal formation occurred within 24 hours, producing 8-10 colorless crystals. The crystal was stable outside of methylene chloride environment and mounted on X-ray diffractometer. The diffraction was strong, producing intense, random spots in each frame. The unit cell was solved to monoclinic and a data set was taken overnight.

**m,p,m,p-Naphthyridine-cyclophane 8.** 1,8-dichloronaphthyridine (0.440 g, 2.2 mmol), hydroquinone (0.244 g, 2.2 mmol) and cesium carbonate (3.0 g, 9.2 mmol) were added to a 25-ml roundbottom flask. A coldfinger with a rubber septum was connected to the reaction flask and the reaction was placed under argon. Anhydrous DMSO (6.5 ml) was added and the mixture turned a light brown. The reaction flask was placed in a 120°C oil bath and allowed to stir for 24 hours. Upon adding heat, the mixture slowly turned a dark brown. The mixture was worked up by precipitating the compound out of solution upon
addition of de-ionized water. The compound has yet to be purified due to solubility issues.

**pyrimidine bicyclooxacalixarene 6** 4,6-Dichloropyrimidine (0.102 g, 0.68 mmol), phloroglucinol (0.057 g, 0.45 mmol) and cesium carbonate (0.55 g, 1.7 mmol) were added to a 10-ml roundbottom flask. A coldfinger with a rubber septum was connected to the reaction flask and the reaction was placed under argon. Anhydrous DMSO (3 ml) was added and the mixture turned a light yellow. The reaction flask was placed in a 120°C oil bath and allowed to stir for 20 hours. Upon adding heat, the mixture slowly turned to a brownish orange over the course of 5 minutes. The mixture was worked up by adding 1M hydrochloric acid until the mixture was acidic and then extracted with brine, water and methylene chloride. The compound was eluted on a silica flash chromatography column with a gradient of 3-6% methanol/ methylene chloride. No isolable amount of 6 was obtained under these reaction conditions.

**Oxacallix[2]phloroglucinol[2]pyrimidine 17.** Phloroglucinol (118 mg, 0.94 mmol), 4,6-dichloropyrimidine (139 mg, 0.93 mmol), and cesium fluoride (1.388 g, 9.1 mmol) were suspended in 4 mL of anhydrous DMSO. The reaction mixture was heated to 70°C for 1 hour. The product was precipitated from the DMSO with about 2 mL of 1M HCl and 10 mL de-ionized water. (163 mg, 0.403 mmol, 85.8% yield)
Pyrimidine bicyclo-bicyclooxacalixarene **16.** A crude reaction mixture of oxacalix[2]phloroglucinol[2]pyrimidine **17** (99 mg, 0.24 mmol), 4,6-dichloropyrimidine (36 mg, 0.24 mmol), and cesium fluoride (317 mg, 2.1 mmol) were suspended in 2.5 mL of anhydrous DMSO. The reaction mixture was heated to 90° C for 10 minutes. The product was precipitated from the DMSO with ~2 mL 1M HCl and 10 mL de-ionized water. The product was eluted through a silica flash column with 2% methanol/methylene chloride affording 18 mg (0.019 mmol, 15% yield) of pyrimidine bicyclo-bicyclooxacalixarene **16**.

**Crystalization of Pyrimidine-bicyclo-bicyclooxacalixarene 16** A crude reaction mixture for pyrimidine bicyclooxacalixarene **6** underwent an aqueous/ethyl acetate separatory funnel workup and dried in vacuo. The resulting solids were dissolved in acetone-d$_6$ and let stand for approximately 4 weeks. Large, colorless crystals of **16** were afforded and were stable outside of the solvent. The crystal was mounted on the X-ray diffractometer. The structure was solved to 8%.

5,8-dihydroxy-N-hexynaphthalimide **20.** 5,8-Dihydroxynaphthalene anhydride (734 mg, 3.2 mmol) and n-hexylamine (0.46 mL, 3.5 mmol) were suspended in 16 mL of anhydrous toluene. A Dean-Stark trap was filled with toluene and was attached to the reaction flask. After 7 hours of stirring at 130° C the reaction mixture was cooled and the toluene was removed under reduced pressure.
Oxacalix[2]N-hexynaphthalimide[2]naphthyridine 22. 5,8-Dihydroxy-N-hexynaphthalimide 20 (102 mg, 0.32 mmol), 2,7-dichloronaphthyridine (21) (67 mg, 0.34 mmol), and cesium fluoride (399 mg, 2.6 mmol) were suspended in 3 ml of DMSO. The reaction mixture was heated to 120°C for 14 hours. The product was precipitated out of solution with approximately 20 ml of H2O. The resulting precipitate was vacuum filtered and dried. The dry precipitate was stirred in 75 ml of methylene chloride. That mixture was filtered and the methylene chloride was removed under reduced pressure. The crude product was purified on a 12 g “Single Step” silica MPLC column. The crude product was eluted with methylene chloride. The reaction afforded 27 mg of white powder 22.

Crystalization of 22:

Crystalization yielded prism shaped crystals using the vapor diffusion method with methylene chloride in the inner vial and toluene in the outer vial. Hexagonal crystals were also grown using methylene chloride in the inner vial and either acetone, ethyl acetate, or acetonitrile in the outer vial. Crystal formation occurred within 48 hours in each case. The unit cell was solved to monoclinic and a data set was taken overnight.

Oxacalix[2]N-hexynaphthalimide[2]naphthyridine 22 Fluorescence Studies: 1.6 mM 22 in methylene chloride was prepared. A Perkin-Elmer 650-10S fluorescence spectrophotometer was used to examine the fluorescence; exitation slit at: 5 nm, emission slit at: 5 nm, and the sensitivity at: 0.3. The exitation

15 Courtesy of Mike Abers '10
monochromator was set at 355 nm and emission wavelengths were scanned from 480 to 375 nm at a scan rate of 20 nm/min. The resulting potentials were recorded and the emission max was found to be 405 nm. Then the emission monochromator was set at 405 nm and excitation wavelengths were scanned from 350 to 390 nm at a scan rate of 20 nm/sec. The excitation max was found to be 375 nm.

Host:Guest + Acid Titrations:

22 titrated with 23
A 1.6 mM solution of 22 in methylene chloride was prepared. Nine solutions of varying equivalents of 23 per ml, also in methylene chloride, were prepared. Emission spectra were taken of 1 ml of the solution of 22 and 1 ml of one of the solutions of 23. The titration was performed using a Perkin-Elmer 650-10S fluorescence spectrophotometer. Excitation was set at 375 nm.

22 titrated with 24
A 0.50 mM solution of 22 in methylene chloride was prepared. 9 solutions of varying equivalents of 24 per ml also in methylene chloride were prepared. Emission spectra were taken of 1 ml of the solution of 22 and 1 ml of one of the solutions of 24. The titration was performed using a PTI Xenon-Flash Spectrofluorometer. Excitation was set at 375 nm.
5:1 mixture of 24 and 22 titrated with TFA

One ml of 0.50 mM 22 and 1 ml 2.5 mM 24 (both in methylene chloride) were added to a fluorescence cuvette. A 50 mM solution of TFA in methylene chloride was prepared so that 10 uL of this solution would be equal to one equivalent of 22. Successive equivalents of TFA were titrated into the cuvette containing 22 and 24, and an emission spectrum was obtained after each equivalent of TFA was added using a PTI Xenon-Flash Spectrofluorometer.

1:1 mixture of 24 and 22 titrated with TFA

1 ml of 0.50 mM 22 and 1 ml 0.50 mM 24 (both in methylene chloride) were added to a fluorescence cuvette. A 50 mM solution of TFA in methylene chloride was prepared so that 10 uL of this solution would be equal to one equivalent of 22. Successive equivalents of TFA were titrated into the cuvette containing 22 and 24, and an emission spectrum was obtained after each equivalent of TFA was added using a PTI Xenon-Flash Spectrofluorometer.

24 titrated with TFA

1 ml 0.50 mM 24 in methylene chloride and 1 ml methylene chloride were added to a fluorescence cuvette so that the concentration of 24 would be equal to what it was in the 1:1 host:guest titration that was previously mentioned. A 50 mM solution of TFA in methylene chloride was prepared so that 10 uL of this solution would be equal to one equivalent of 24. Successive equivalents of TFA were titrated into the cuvette containing 24, and an emission spectrum was obtained.
after each equivalent of TFA was added using a PTI Xenon-Flash Spectrofluorometer exciting at 375 nm.

**22 titrated with TFA**

1 ml 0.50 mM 22 in methylene chloride and 1 ml methylene chloride were added to a fluorescence cuvette so that the concentration of 22 would be equal to what it was in the 1:1 host:guest titration that was previously mentioned. A 50 mM solution of TFA in methylene chloride was prepared so that 10 μL of this solution would be equal to one equivalent of 22. Successive equivalents of TFA were titrated into the cuvette containing 22, and an emission spectrum was obtained after each equivalent of TFA was added using a PTI Xenon-Flash Spectrofluorometer exiting at 375 nm.
NMR Spectroscopy:

[Diagram of molecular structure]

[Data parameters]

42
Sample: 67% high
Model: 67% high
Melts sequence: 67% high
Sample: 67% low
Model: 67% low
Melts sequence: 67% low
Sample: 50% high
Model: 50% high
Melts sequence: 50% high
Sample: 50% low
Model: 50% low
Melts sequence: 50% low
Sample: 45% high
Model: 45% high
Melts sequence: 45% high
Sample: 45% low
Model: 45% low
Melts sequence: 45% low