

PRF# 57223-ND4
The Activation of Strong C-H Bonds with Catalytic Molecular Baskets
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We started the proposed work by examining the conjugation of *tris*(2-pyridylmethyl)amine (TPA) ligand **2** to concave scaffold **3** (Figure 1). The reaction conditions were optimized for obtaining capsule **1** in satisfactory 65% yield. ¹H NMR spectroscopic measurements along with molecular mechanics and density functional theory calculations showed that *C*₃ symmetric **1** was poorly preorganized with three pyridines at the rim adopting a propeller-like orientation and undergoing a rapid *P*-to-*M* (or vice versa) stereoisomerization ($\Delta G^\ddagger < 8$ kcal/mol). Moreover, the tertiary nitrogen group undergoes a low barrier inversion of configuration ($E_a \sim 10$ kcal/mol).

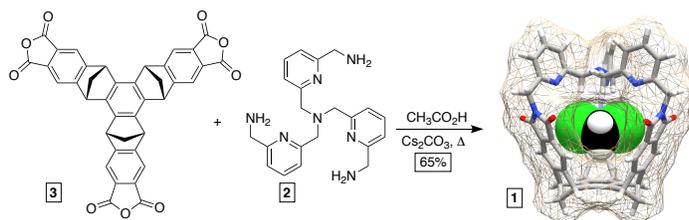


Figure 1. The synthesis of molecular capsule **1**, holding a molecule of methane in its cavity.

As a result of such poor preorganization, capsule **1** was found to be a poor host for trapping CH₄, CH₃Cl, CH₂Cl₂, CHCl₃ and CCl₄ guests ($K_a < 7$ M⁻¹; Figure 1). Note that trapping small hydrocarbons in the cavities of molecular capsules is essential for their activation. Accordingly, protonation of **1** with HCl gave [**1**·H]⁺-Cl⁻, with the solid-state structure showing the TPA lid being “flattened” at the top of the host and ⁺N-H---Cl hydrogen bonded group residing outside (Figure 2). Importantly, the *P*-to-*M* stereoisomerization for [**1**·H]⁺-Cl⁻ was found to be slower ($\Delta G^\ddagger = 11$ kcal/mol, VT ¹H NMR), with the quaternary center unable to invert its configuration. More preorganized [**1**·H]⁺-Cl⁻ acted as a good host of CH₄ but could also complex CH₃Cl, CH₂Cl₂, CHCl₃ and CCl₄ guests ($K_a = 100$ – 400 M⁻¹, ¹H NMR spectroscopy). The results of both theory (DFT) and experiments (¹H/¹³C NMR spectroscopy) suggested that the complexation of increasingly larger guests took place in an induced-fit fashion, with the capsule (a) elongating along its vertical axis by moving the TPA “lid” by 1 Å and concurrently (b) twisting pyridines from *P* into *M* (or vice versa) chiral orientation. Capsule **1** is an allosteric host that, after being prompted with a chemical input, changes the conformational dynamics of its TPA lid, while predominantly preserving the shape of its cavity, to affect the encapsulation thermodynamics. Moreover, the entrapment of differently sized achiral guests switches the capsule’s helical chirality. These results were published as an article in *J. Am. Chem. Soc.* **2018**, *140*, 11091-11100

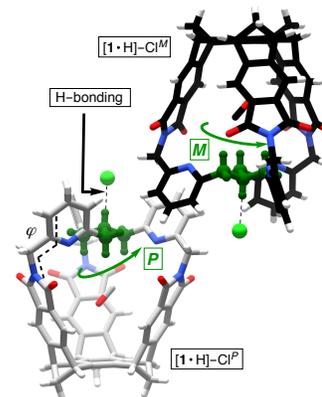


Figure 2. X-Ray structure of protonated capsule **1**, holding a molecule of methanol in its cavity.

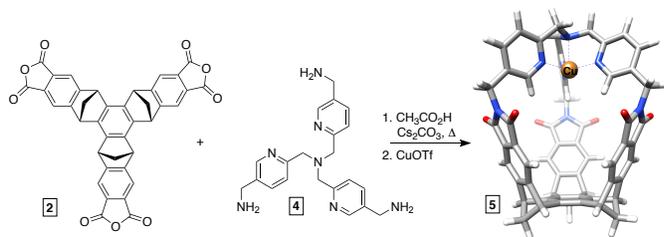


Figure 3. Preparation of molecular capsule **5**, holding a Cu(I) at top of its cavity.

and we have acknowledged the financial support from ACS PRF. Three students working on the projected (supported by PRF) benefited from this work by learning about (a) synthetic methodologies for the preparation of complex molecules, (b) physical organic methods for characterizing encapsulation complexes and (c) computational methods for guiding design and characterization of molecules.

To examine the activation of methane with capsule **1**, we added CuOTf to its solution in acetone and obtained desired **1** • Cu(I) complex. This coordination compound was, however, labile with intriguing dynamic characteristics. Using ^1H NMR spectroscopy, we observed the coordination of acetonitrile to Cu(I) with this ligand occupying the capsule's inner space. The molecule was not active in the conversion of NO to NO_2 (see below). In an attempt to obtain a more stable Cu(I) containing capsule, we worked on conjugating TPA **4** to basket scaffold **2** (Figure 3). The synthesis was optimized with, importantly, **5** being able to coordinate Cu(I) and give stable **5** • Cu(I) complex (fully characterized with NMR spectroscopy and mass spectrometry). Indeed, x-ray structure of **5** (Figure 4) showed its preorganization with four nitrogen atoms poised to complex Cu(I) and position it on top of the cavity (where the oxidation should take place). Following, we used UV-Vis spectroscopy to examine the complexation of oxygen to **5** • Cu(I). To our surprise O_2 could not form a complex (even at a higher pressure and lower temperatures) from which we hypothesized that this molecule was a poor ligand unable to shed solvents away from the cavity of **5** • Cu(I). Next, we turned to study the complexation of NO ligand using variable temperature UV-Vis spectroscopy. To our delight, we found that NO would bind to **5**-Cu(I) and then change into another molecule (Figure 5). The formation of **5**-Cu(I)NO was found to be transient with the complex turning into **5**-Cu(II)NO₂. We hypothesize, that the transformation occurs by a mechanism shown in Figure 5 in which the elusive Cu(III)O forms! At present, we are completing VT-IR and EPR measurements to test our mechanistic hypothesis. If the formation of Cu(III)O indeed precedes the product formation (Figure 5), we should be able to intercept it with CH_4 or another more reactive molecule (ethylene, isopropane, ethane etc.) and have the insertion of oxygen into C-H taking place. This work is now completed in collaboration with two research groups here at the OSU . Prof. Shiyu Zhang is completing EPR and IR measurements of the reaction while Prof. Hannah Shafat is doing kinetic measurements. This is the main reason for postponed publication of this work. Students are learning a variety of spectroscopic methods for characterizing coordination complexes and completing catalytic reactions in confined environments. We are also collaborating with Prof. Shiyu (OSU) on spectroscopic measurements in which students correspond with researchers from other (inorganic chemistry) areas of science. Finally, students presented this work at several local symposia and tremendously benefited from discussing their progress with other scientists. We believe that the progress we have made, in the first year of the project, is exceptional and should help us develop important knowledge pertaining the activation of hydrocarbons in confined spaces.

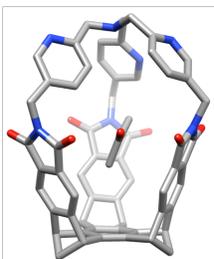


Figure 4. X-Ray structure of molecular capsule **5**, holding a molecule of acetone in its cavity.



Figure 5. Coordination complex **5** • Cu(I) is able to activate NO (excess) in CH_2Cl_2 and turn it into **5** • Cu(II)NO₂.

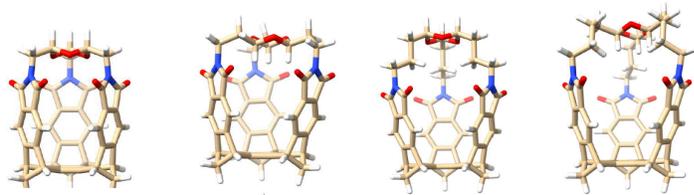


Figure 6. A series of molecular capsules obtained in our lab possess a small, yet increasingly larger, inner space for safely storing gas in the solid state and then releasing it with an external stimulus (acid).

(Figure 6). Importantly, these labile hosts pack as tubes in the solid state. Due to the trioxane lid, they are likely to be labile which, we posit, could lend themselves for storing gas molecules, methane, helium, hydrogen etc. We are currently examining these options and a paper will be written with the acknowledgement to the ACS-PRF.

At last, we also developed a synthetic methodology to “close” the basket concave scaffold at its rim using trioxane platform