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Perspective

Molecules in Confined Spaces: Reactivities and Possibilities in Cavitands

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Template effects are at the origin of supramolecular chemistry, but the behavior of folded molecules is a relatively new undertaking. Water-soluble cavitand hosts bind hydrocarbons through hydrophobic effects and force long-chain guests into folded conformations. This brings their ends closer together, and sites that were remote in solution become neighbors in the confined space and affect each other's reactivity. Amphiphilic guests fold in the cavitand to bury hydrophobic surfaces and expose the hydrophilic surfaces to the bulk solution. This arrangement leads to product distributions in monofunctionalization reactions that are significantly altered from the statistically determined outcomes in solution. The cavitand also acts as a template for macrocyclic processes involving direct reaction of the guests' ends. We propose applying the effects of folding in cavitands to truly remote functionalization reactions and provide access to molecules that cannot be made by conventional means.

The Bigger Picture

Challenges and opportunities:

- An effective protocol for macrocyclization without high dilution is developed.
- Water-soluble cavitands as dynamic systems are used in monofunctionalization.
- Applications for remote C–H activation in the confined space are proposed.

INTRODUCTION

Long before we thought about isolating molecules in containers, biochemists and biophysicists had been looking for the consequences of confinement for some time: enzymes and receptors confined single molecules, separated from their cohorts and the aqueous medium, in small spaces carefully sculpted by evolution. The biological phenomena that resulted—catalysis, signaling, metabolism, and replication—were so spectacle filled that it was easy to overlook the role of confinement in these processes. But now, some 25 years later, we write about chemical behavior as it takes place in confinement with an eye on what isolation means for the molecule inside the container. The filling of space—a fundamental driving force of nature—lies at the heart of the forces involved. It can impose distortions on the molecule inside and results in reaction outcomes that are unlikely for free molecules in bulk solution. Even species unknown in solution can be observed in the protective space of a container.

There are many number of containers to be had. Most concave structures—clefts,[1] armatures,[2] tweezers,[3] and the like—have been used as synthetic receptors, but macrocyclic shapes, probably inspired by the naturally occurring cyclodextrins,[4] dominate. Cucurbiturils,[5] cyclophanes,[6] bowls,[7] and other open-ended vehicles were devised and synthesized before the idea of more-or-less completely surrounding a target—reversible encapsulation—took hold. The tennis ball was one of the first of these dynamic containers, but the capsules of Raymond, Fujita, and Gibb[8] have been hugely successful and popular given that they operate in water (Figure 1A). These highly charged systems have isolated and stabilized reactive intermediates: phosphine carbonyl adducts, labile siloxanes, organometallics, and white phosphorus.[9] Many types of capsules are now available: covalent bonding,[10]

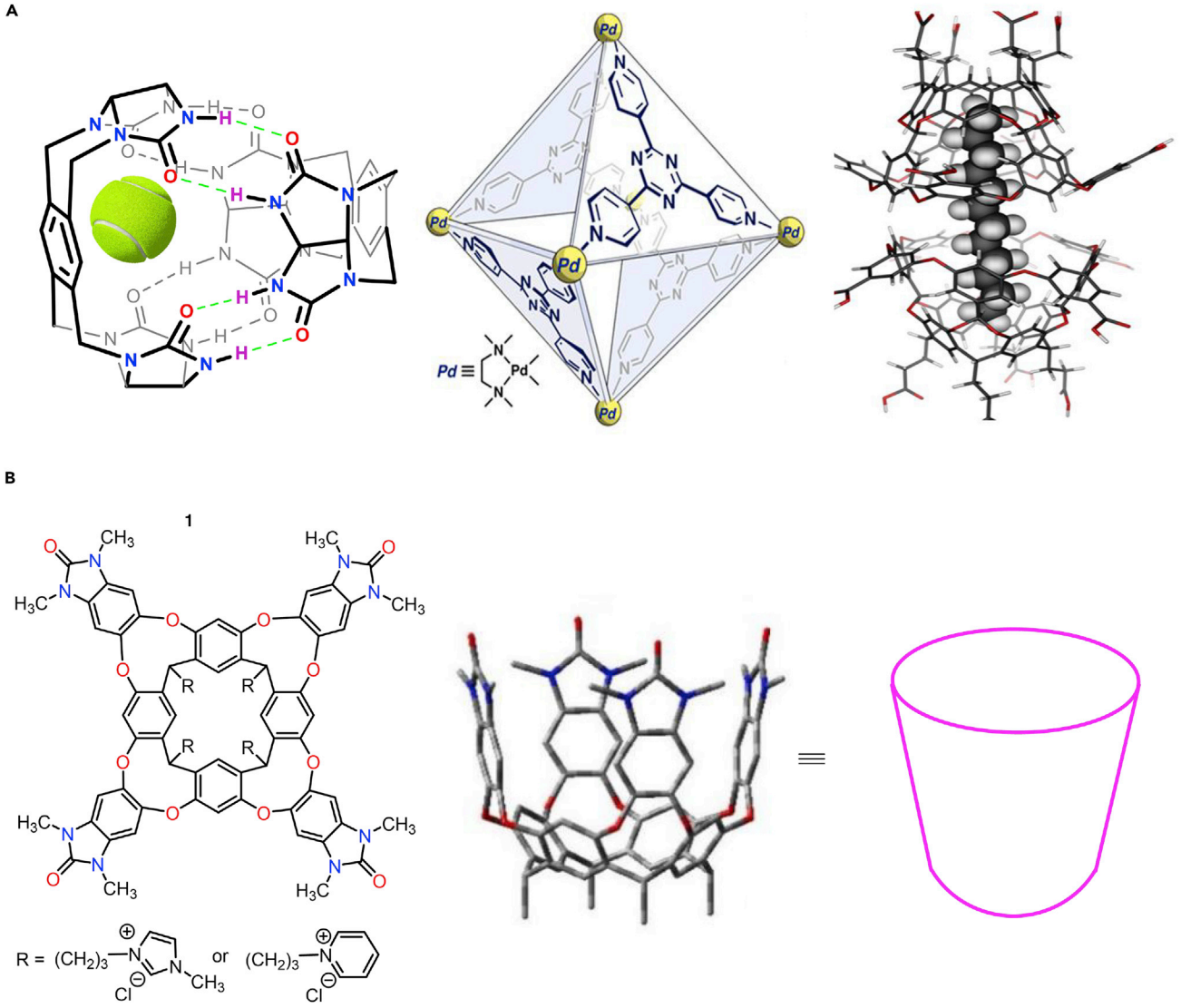

Figure 1. Dynamic Containers

(A) Left: a model of the hydrogen-bonded notional tennis ball (left). Middle: line drawing of Fujita's metal-ligand capsule (adapted with permission from Fujita et al.,[16] copyright 2019 American Chemical Society). Right: graphic of Gibb's hydrophobic capsule with an alkane inside.

(B) Chemical structures and cartoon of the water-soluble cavitands **1**.

self-assembly with hydrogen bonding,[11] metal-ligand interactions,[12] ionic interactions,[13] halogen bonding,[14] chalcogen bonding,[15] and even purely hydrophobic effects.[8c]

To manage the topic of confinement, we limit our review to containers known as cavitands (Figure 1B)—container molecules with one open end. They lie somewhere between covalent networks (such as fullerenes) that have essentially no openings and tubular container compounds (such as cyclodextrins, cucurbiturils, or pillararenes) that have two open ends—something like a vase is, shape-wise, somewhere between a sphere and a doughnut. And to keep the discussion somewhat current, we restrict the scope of this Perspective to our recent results and aspirations to water-soluble cavitands—we will blend what has been done with what might be done.

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General Features of the Cavitands and Their Complexes

The cavitands were introduced as platforms for covalent cage compounds—the carcerands[17]—and subsequently used for complexation of small molecules in their own right.[18] Deeper cavitands **1** are built up from a resorcinarene[19] core by adding aromatic panels as walls and refining the groups at the rim and the feet for special functions and solubility. Long alkyl or aryl feet impart solubility in organic solvents, and cavitand behavior in organic media has been known for decades.[20] Water-soluble cavitands have a shorter history. For recent examples, see Badjić's work,[21] and for reviews, see Gibb's work.[22] They typically have ionizable groups on the feet or rim and operate at limited pH ranges.[23] Although neutral water-soluble cavitands exist,[24] their molecular properties tend to be unwieldy. Simple benzimidazolone functions on the rim[25] are strong hydrogen-bond donors and acceptors, and two such cavitands can dimerize and form capsules, even in water.[26] Exhaustive methylation of the rim, as in **1**, prevents dimerization and imparts a wider open end to the cavitand.[27] The cavitands with either pyridinium or imidazolium feet show mM solubility in water independently of pH. We will use the generic cartoon (Figure 1B) to represent these cavitands in their complexes.

Simple sonication of cavitands **1** with lipophilic compounds as potential guests in D_2O gives complexes[28] readily characterized by NMR methods. Suitable guests must fit into and solvate the cavitand's hydrophobic interior. As the cavity is surrounded by aromatic panels, the guests experience a special magnetic environment; their NMR signals are shifted far upfield in the spectra. A good correlation exists between the size of the shifts and the depths of the nuclei in the cavitand: the deeper the position, the larger the upfield shift. For example, nonenal, the compound responsible for some human odors, is readily taken up by sonication with **1**, and the NMR spectrum shows well-resolved signals for the bound methyl and methylene groups.[29] The methyl group shows the greatest shift as expected for its position at the cavity's bottom.

The exchange of guests in and out of the cavitands is relatively slow on the NMR chemical shift timescale, and separate signals are generally seen for the bound guest and its counterpart, free in bulk solution. This facilitates the evaluation of association constants when solubilities are appropriate and also permits the energy barriers to exchange to be determined through exchange spectroscopy experiments. Frequently, diffusion ordered spectroscopy can be used to support assignments of stoichiometries for cavitands and their complexes.

Forces Involved in Cavitand Complexation

Given the aqueous medium and the structure of the cavitands, it is reasonable that hydrophobic forces are the principal drivers of complex formation. Small molecules with good solubility in water are unlikely to confine themselves in cavitands since they are perfectly happy to be free—in the translational and rotational senses—outside in bulk solution. But for those small molecules driven in by hydrophobic tendencies, there are several ways to be accommodated. The simplest complexes to understand are the cycloalkanes. These compounds have preorganized conformations complementary to the interior; the U-turns of their chains have been paid for during their syntheses and are "built in." Bound cyclohexane shows a single sharp resonance (Figure 2, middle), and the signals for the cavitand are simple indicating a time-averaged C_{4v} symmetry. These features indicate rapid motion of the guest inside the cavitand—rotations on all three axes that exchange every H's environment to give averaged signals. Simple, short alkanes also undergo rapid movement in the cavitand, and signals reflect their symmetries.

Long-chain amphiphiles, bola-amphiphiles, and hydrocarbons such as *n*-dodecane undoubtedly assume folded conformations inside the cavitand. The shortest (narrowest)

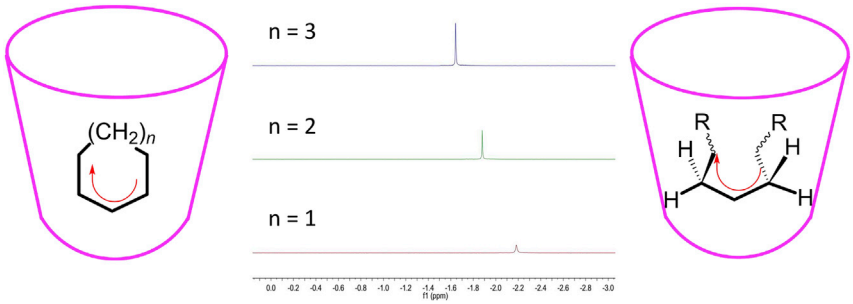


Figure 2. Cartoons of Confined Hydrocarbons in the Cavitand
(Left) Cartoon of the cycloalkanes in **1** indicates the U-turns of their carbon chains.
(Middle) Their partial ^{1}H-NMR spectra indicate rapid motion inside the cavitands.
(Right) Cartoon of a long open-chain compound, folded (*gauche*$^{+}$/*gauche*$^{+}$) within the cavitand.

U-turn possible is the *gauche*$^{+}$/*gauche*$^{-}$ conformation in pentane, some ~3.7 kcal/mol above the energy of the lowest-energy extended state.[30] Figure 2 (right) shows an open-chain compound folded through a *gauche*$^{+}$/*gauche*$^{+}$ conformation at a price of some 1.8 kcal/mol. (This is assumed to interconvert rapidly with the corresponding *gauche*$^{-}$/*gauche*$^{-}$ conformation.) The folding corresponds to the "excluded volume" in polymer chains but is an essential requirement for fitting into the cavitand.

What Has Been Done

Macrocyclic Processes

Others have observed folded, long-chain hydrocarbons in water-soluble container compounds; Kim[31] induced folded bola-amphiphiles in cucurbiturils, and Gibb has described unconventional alkane shapes with his capsules in solution.[32] Chemical reactions performed on these contorted guests are scarce, and we have moved to take advantage of this situation. Folding brings the molecule's ends closer together, and inevitably, cyclization processes are more likely. Termini previously remote are now in a position to interact and can do so by direct reaction or by more subtle means. Initially, we reported lactamization of α,ω-amino acids[33] in cavitands, followed by macrocyclization of folded diamines with active diesters. The yields were enhanced up to 10-fold yield in the cavitand chaperone (Figure 3A).[34]

More recently, the cavitand was applied to ring-closing olefin metathesis (RCM).[35] The RCM cyclization to eight-membered rings is normally a difficult reaction[36] and usually requires preorganization or fusion to other ring systems for success.[37] For example, neither cycloheptene nor cyclooctene was observed from the reaction of 1,8-nonadiene or 1,9-decadiene, respectively, in solution using the Hoveyda-Grubbs-II catalyst. But the folding supplied by the use of the cavitand as a chaperone gave good yields for these ring sizes (Figure 3B).

Cavitands for Desymmetrization

Binding in the water-soluble cavitands follows a simple rule: polar groups are exposed, and hydrophobic groups are buried. For symmetrical guests without polar ends (such as the diene of Figure 3B), the tendency to escape from water induces a yo-yo motion of the compound in which the ends take turns in the shelter of the cavitands. The rapid motion on the NMR chemical shift timescale leads to simplified spectra. But amphiphilic guests assume a biased arrangement in the cavitand, which leads to complicated spectra. Accordingly, even subtle differences in the polarity of guest termini can be sensed by their cavitand complexes. Take the diformamides of α,ω-diamines (Figure 4A). At first glance, these molecules are perfectly symmetrical, but secondary amide groups exist

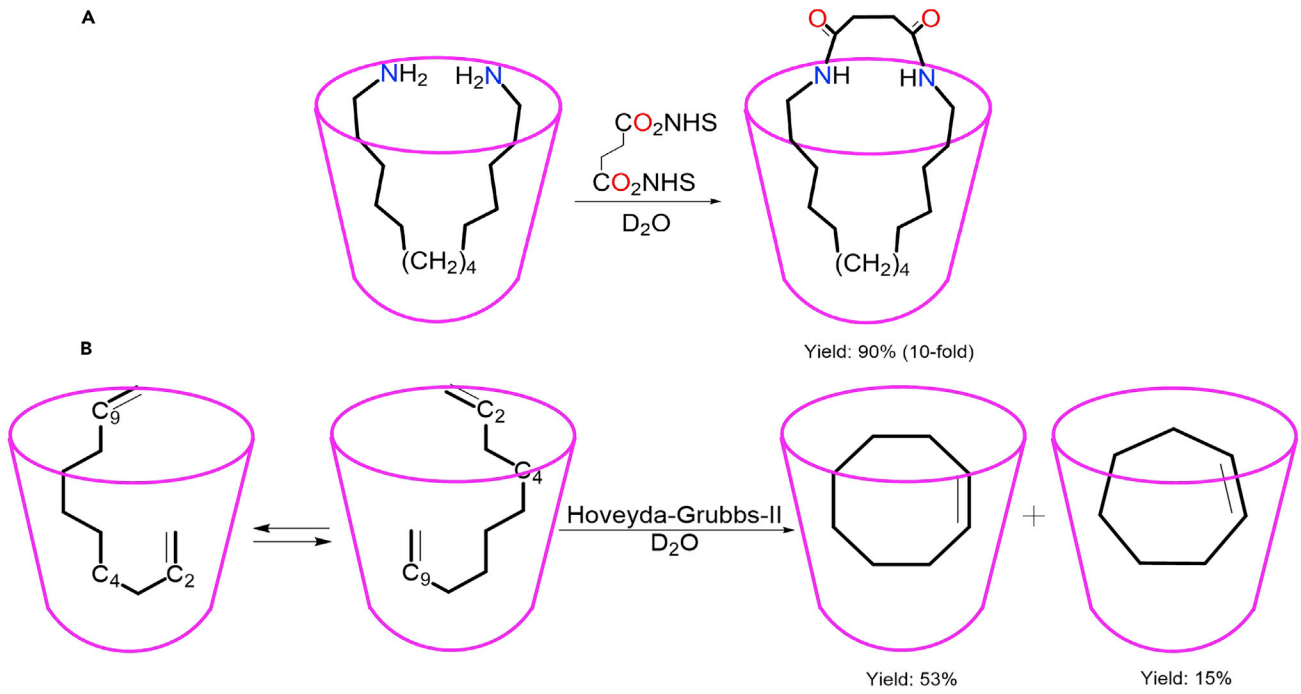


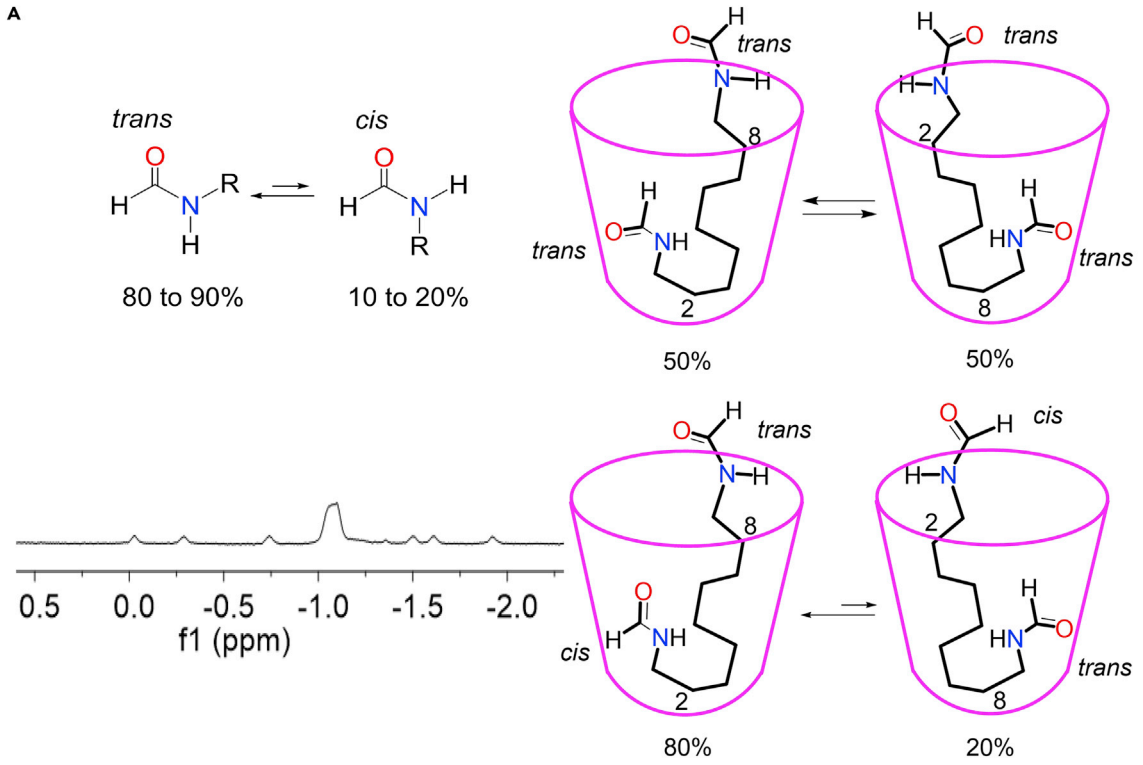
Figure 3. Cartoons of Cyclization Reactions in Confined Spaces

Cartoons for cyclization processes enhanced in cavitands: (A) macrodilactam formation and (B) ring-closing metathesis.

in both *trans* and *cis* conformations. Formamides show appreciable amounts of *cis*, typically 10%–20%. These cannot be separated under ordinary conditions because they interconvert rapidly on the human timescale. The cavitand complex shows two sets of NMR signals—a cluster of methylene peaks for the symmetrical *trans,trans*-diformamide and a spread of peaks for the *trans,cis*-diformamide (Figure 4A). The assignments indicate that the *cis* end of the guest is more hydrophobic than the *trans*.[38]

An application for the preference of the hydrophobic end for the interior is to use this bias as a means of protection from solvent-borne reagents. That is, using the cavitand as a protecting group. The water-soluble capsules introduced by Gibb[40] had already been applied as such,[41] and we have used cavitands to manipulate difunctional compounds. This situation is often encountered in chemistry and can present a pesky problem: when the two sites are identical and truly remote, the first and second reaction rate constants are identical ($k_1 = k_2$). A purely statistical yield (only about 37%) of the monofunctional product is expected, as shown graphically in Figure 4B. At the same time in the course of the reaction, both unreacted and doubly reacted compounds are present in comparable amounts, leading to troublesome separations. The situation is shown for long-chain diester hydrolysis. In the presence of the cavitand, the esters showed a faster rate of initial hydrolysis under acidic conditions (the cavitand helps dissolve the diester) due to their increased solubility. But the rate of the second hydrolysis decreased given that the ester end of the desired product remained protected in the cavitand.[39] The asymmetric binding translated into $k_1 = 4k_2$ and allowed the yield of desired product (the monoester monoacid) to exceed 60%.

In principle, any α,ω-bifunctional long-chain guest can be desymmetrized if the reaction alters the polarity (hydrophobicity or hydrophilicity) of the termini. In practice, this has been accomplished with several symmetrical compounds. For example, the reduction of diazides[42] proceeded quite cleanly to the monoamine (Figure 4C). The starting


A
trans
cis
80 to 90%
10 to 20%
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trans
trans
50%
50%
0.5
0.0
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-2.0
f1 (ppm)
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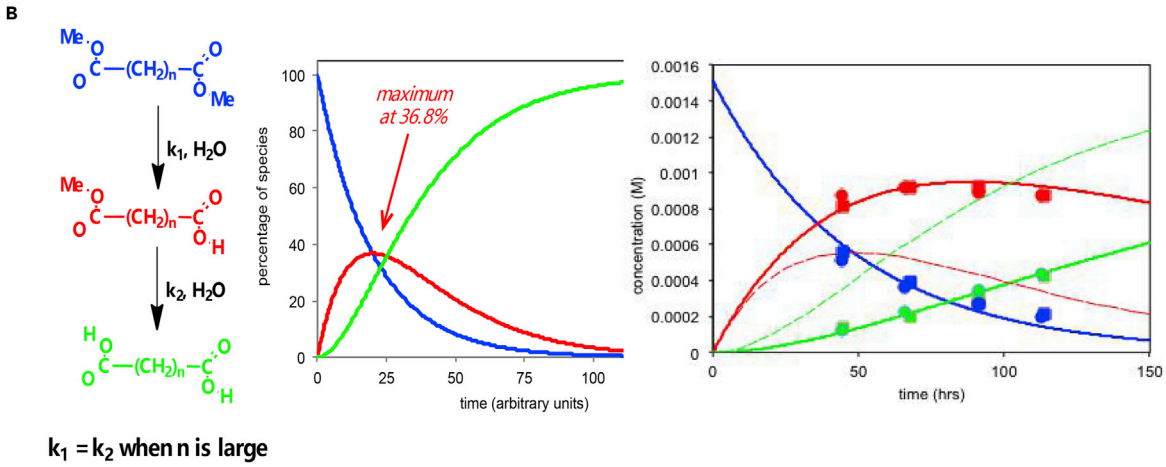
trans
cis
trans
80%
20%


B
k1, H2O
k2, H2O
maximum at 36.8%
percentage of species
time (arbitrary units)
concentration (M)
time (hrs)
k1 = k2 when n is large

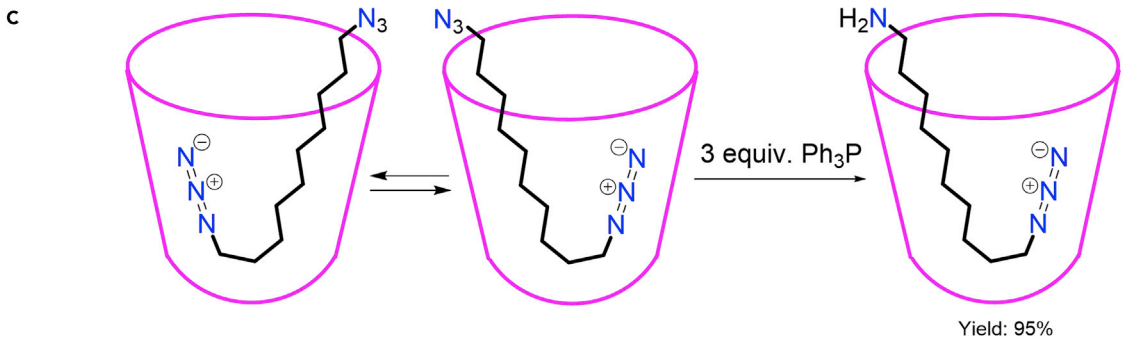

C
3 equiv. Ph3P
Yield: 95%

Figure 4. Cartoons of Desymmetrizations in Cavitands

(A) Conformations of formamides and the partial ^{1}H-NMR spectrum for a diformamide in the cavitand. Left: the cluster of methylene peaks at −1.1 ppm represents the symmetrical *trans*,*trans*-isomer, and the smaller, separated peaks are the unsymmetrical *trans*,*cis*-isomer. Right: cartoons of the diformamide copmlexes; the *cis* formamide terminus is more hydrophobic.

(B) Sequential hydrolysis (diester to monoester to diacid) of a long-chain diester (left). Product distributions (blue, diester; red, monoester; green, diacid) expected for $k_1 = k_2$ (center). Observed product distributions (dots) for the acid-catalyzed hydrolysis of the C14 dimethylester chaperoned by the cavitand. Solid lines represent the best fit for the data and indicate $k_1 = 4.6$ and $k_2 = 1.1$. Dashed red and green lines show the monoester and diacid concentrations expected for $k_1 = k_2$ (right). Adapted with permission from Rebek et al.[39] Copyright 2016 National Academy of Sciences.

(C) Cartoon of the desymmetrization of a diazide; the cavitand protects the remaining azide while the amine is exposed.

(nonpolar) diazide undergoes the yo-yo motion in a symmetrical sense, but once the reduction takes place, the preferred arrangement is biased: the polar amine end remains exposed to the reagents in the aqueous solvent while the remaining azide groups are buried deep in the cavitand and protected from reagents. The competition between termini is strictly predictable: polar atoms outside and nonpolar atoms inside. The mono-epoxidation[43] of dienes works just as described above. The intermediate bromohydrin fixes the guest, and then cyclization to the epoxide completes the monofunctionalization process. Further examples include hydrolysis of dihalides.[44]

What Might Be Done

Cavitand Applications in C–H Activation

Truly remote C–H activation is an unmet need. More than 40 years ago, Breslow[45] recognized the limitations of the conventional, nearby functionalization offered by Hofmann-Loeffler-Freitag (HLF) reactions, Barton oxidation, or related reactions. He developed departures that depended on folded structures. Even supramolecular approaches using cyclodextrins[46] were reported in a desultory way, but they had limited success. However, recently real progress has been made,[47] again with a U-shaped reagent. The cavitands should achieve C–H activation on folded guests at distances considerably greater than conventional methods allow.

The HLF reaction and its milder variants due to Suarez[48] and Ban[49] involve hydrogen abstractions or amination cyclizations[50] proceeding through six-membered transition states. Barton oxidation[51] follows the same rules; exceptions are rare and occur only with highly rigid substrates.[52] Long amphiphilic compounds, such as 1-tetradecanol, fold in the cavitand that places the methyl near the rim. This positioning has implications for remote functionalization anchored by the alcohol group or any other polar function: the nearby CH_2 units are buried and inaccessible for H abstraction. Instead, the reaction should be channeled along unprecedented (and presently unpredictable) pathways, as proposed in Figure 5A. The challenge is to find conditions compatible with the cavitand complexes and their aqueous environments.

For example, Yu has found that even simple nitriles can be activated by Pd^{II} with the use of auxiliary ligands such as (Ac-Gly-OH) with acrylate coupling partners.[53] The Pd is anchored to the amino acid C terminus (Figure 5B), and this binding tolerates 20% water in hexafluoro isopropanol (HFIP).[54] Tight metal binding to the substrate is the key to these processes and is one reason why they are usually incompatible with water. Such C–H activation of folded substrates chaperoned by cavitands is also expected to reach beyond the usual ring sizes, as proposed in Figure 5B. The binding of long-chain alkyls in the cavitands is commonly observed in HFIP.[55] The inspired work of Yu also applies U-shaped ligands to span increased distances.[56] Our suggestion is to force a U-turn on the *substrate* rather than the reagent[57] or ligand. Hydrophobic binding provides the force for bending the hydrocarbon chains. Accordingly, the need is to develop reaction processes and catalysts that are compatible with the greenest of solvents: water.

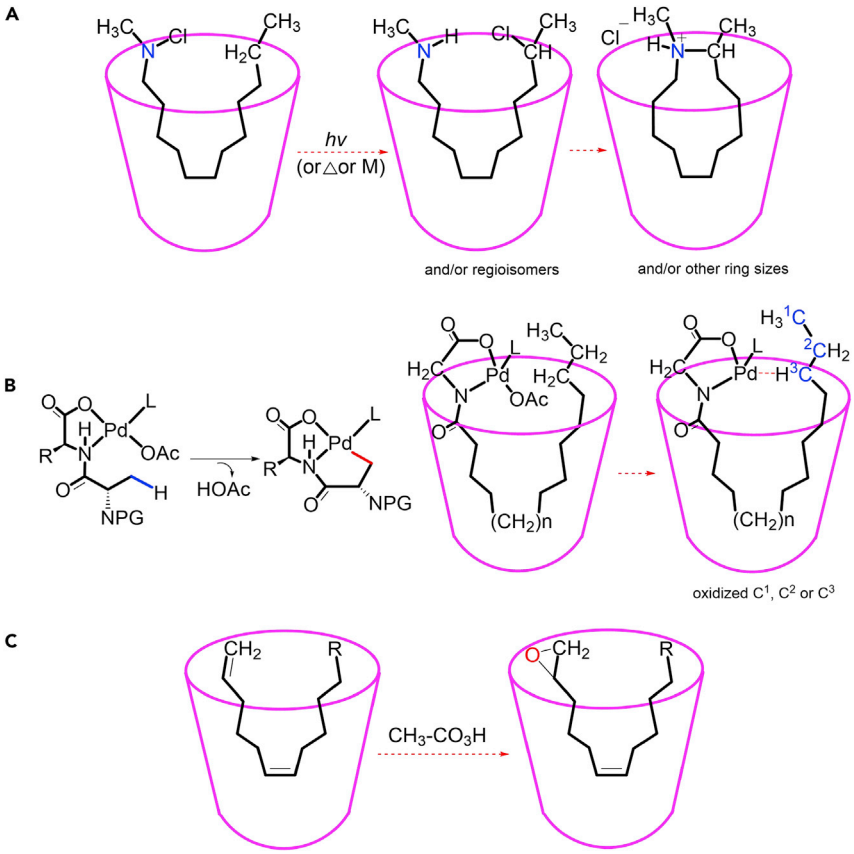


Figure 5. Cartoons of Proposed Remote Functionalization or Regioselective Expoxidation in Cavitands

(A) Proposed cavitand-templated version of the HLF reaction; a 12-carbon chain length is shown, but any length from 10 to 15 carbons could be used reliably for complex formation in water.
(B) Pd-mediated C–H activation (left); acylated glycine as substrate in the cavitand (right).
(C) Proposed regioselective epoxidation in the cavitand that overcomes intrinsic reactivities by protection of the internal double bond.

Cavitands Overcoming Reactivity

We intend to take advantage of unsymmetrical binding induced by cavitands to manipulate reactivity. For example, peracids react an order of magnitude faster with disubstituted alkenes than with terminal ones—an intrinsic property of electrophiles. But the protection of cavitand (Figure 5C) could reverse the reactivity: the exposed terminal double bond has the advantage in reactions with electrophiles if the internal double bond remains inaccessible. Reaction with peracids, OsO_4, and other compatible electrophiles should serve to demonstrate the concept. Although site-selective methods for epoxidation do exist,[58] they do not overcome the intrinsic reactivity differences of variously substituted alkenes. Mapping the contortions of guests in cavitands has excellent precedent,[59] but the application of containers as supramolecular blocking groups has scarcely been demonstrated.[16]

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AUTHOR CONTRIBUTIONS

J.Y. designed the figures; Y.Y. and J.R., Jr. designed the research and wrote the manuscript.

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