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Confined molecules: experiment meets theory in small spaces

Yang Yu[1] and Julius Rebek Jr[1,2]

[1]Center for Supramolecular Chemistry & Catalysis and Department of Chemistry, College of Science, Shanghai University, 99 Shang-Da Road, Shanghai 200444, China and [2]Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037, USA

Short Review

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Authors for correspondence:
Yang Yu, E-mail: yangyu2017@shu.edu.cn;
Julius Rebek, E-mail: jrebek@scripps.edu

Abstract

The behavior of molecules confined to small spaces is fascinating chemistry and lies at the heart of signaling processes in biology. Our approach to confinement is through reversible encapsulation of small molecules in synthetic containers. We show that confinement leads to amplified reactivities in bimolecular reactions, stabilization of otherwise reactive species, and limitation in motions that create new stereochemical arrangements. The isolation of molecules from solvent makes for manageable computations and has stimulated theorist to examine reaction details in the limited space. Transition states for reactions and rearrangements can be calculated, the effects of (de)solvation can be evaluated and the magnetic properties of the containers can be compared with experimental observations. Finally, we outline several potential applications, including entanglement chemistry and the use of isomers in data storage.

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Introduction

It's now been 25 years since we prepared a spherical container compound – the 'softball'. It was not our first synthetic container, but it was the first large enough to confine *two* molecules inside and it triggered our study of chemistry – bond making and breaking – in isolation. Many enzymes were known that could fuse two molecules together as substrates, but synthetic vessels that promoted bimolecular reactions were rare (Mock *et al.*, 1983; Breslow and Guo, 1988), and incapable of completely surrounding and isolating reactants. By isolation we mean confinement by reversible encapsulation of molecules in small spaces, rather than, say, isolation through very low pressures in the gas phase. And by small spaces we mean container compounds which more or less completely surround a well-defined volume, rather than open-ended compounds. This is a review of our experimental probes of molecules confined in these containers enhanced by the computational observations of our collaborators. The results led to the notion that 55% represents an optimal filling of space in solution, about which more, later.

Reaction

The earliest container we prepared was the notional 'tennis ball', a dimeric capsule that could bind molecules no larger than ethane (Wyler *et al.*, 1993). But when we had in hand the proportionally larger softball (Fig. 1) (Meissner *et al.*, 1995) and found it accommodated one adamantane or two molecules of benzene inside, who could resist its use as a reaction vessel? A paradise for reacting species – what could be better for a cycloaddition reaction? The translational and rotational motions of the reactants are coupled by containment; entropic prices for bringing reactants together are paid for by the forces of encapsulation and the costs of solvent

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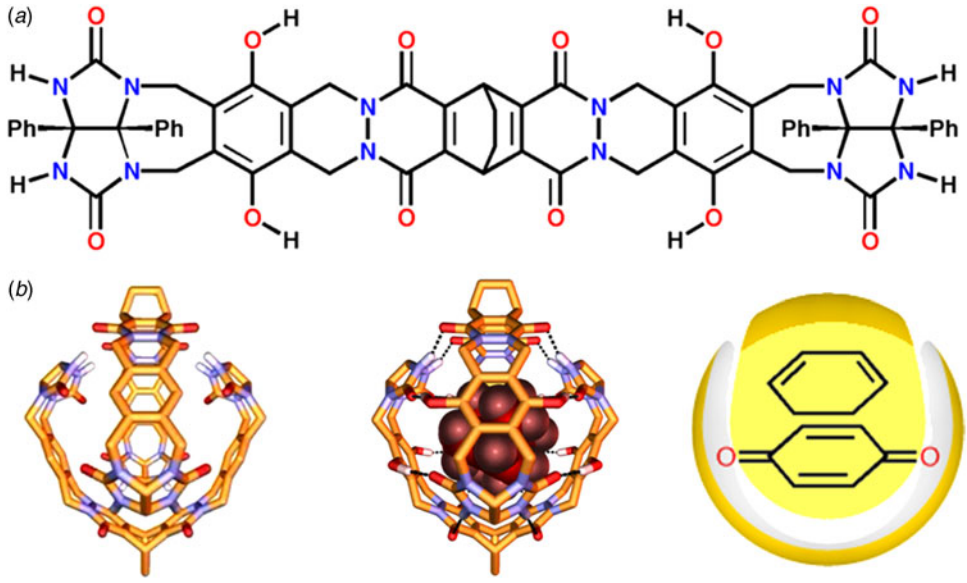

Fig. 1. (*a*) Chemical structure of the monomer of the softball. (*b*) Modeled structures of the softball dimer (left) and with adamantane guest (middle). Cartoon of co-encapsulated cyclohexadiene and *p*-benzoquinone (right). From Kang *et al*. (1998*a*, 1998*b*).

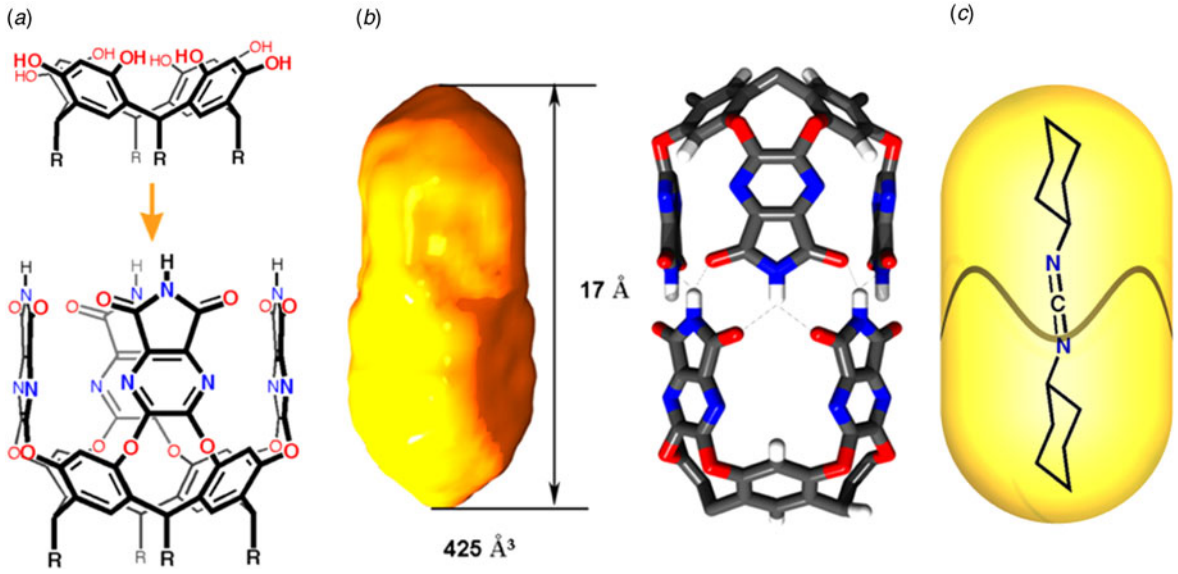

Fig. 2. (*a*) Chemical structure of a resorcinarene (top) and its vase-shaped, deep cavitand (bottom). (*b*) The shape and dimensions of the space inside the cylindrical capsule formed through hydrogen bonding. (*c*) Cartoon of dicyclohexylcarbodiimide in the capsule. Adapted from Heinz *et al*. (1998).

reorganization at the transition state are of no concern, since the container *is* the solvent cage, arranged carefully by synthesis. And it gets better. Concentrations? Great – the volume of the softball is 3.5×10^{-25} l so any molecule in this space enjoys a concentration of >4 M. Timing? Luxurious – the lifetime of the capsular assembly is >1 s compared to the nanosecond lifetime of a diffusion complex in a typical solvent cage. These benefits for the reaction of cyclohexadiene with *p*-benzoquinone are summarized in the cartoon of Fig. 1.

And the reaction did succeed (Kang and Rebek, 1997), with regiospecificity in several contexts (Kang *et al*., 1998*a*), and in one case even with (feeble) catalytic turnover (Kang *et al*., 1998*b*). Most cases showed classic product inhibition because two reactant molecules were unable to displace the single, well-fitting product (Kang and Rebek, 1996). Other peculiarities made this case difficult to study quantitatively. For example, the resting state of the capsule contained two molecules of the quinone inside and the 'Michaelis complex' shown in the cartoon was never actually observed. To be sure, the reaction inside was thousands of times faster than the reaction proceeding outside the container (reflecting molar *versus* millimolar concentrations) but there is an entire cottage industry for setting up systems to calculate, interpret, and exaggerate rate enhancements. We did not pursue these analyses with the softball. It was not until we had a container of the right shape and size to favor the Michaelis complex – one molecule of each reactant observed inside – that we had confidence in

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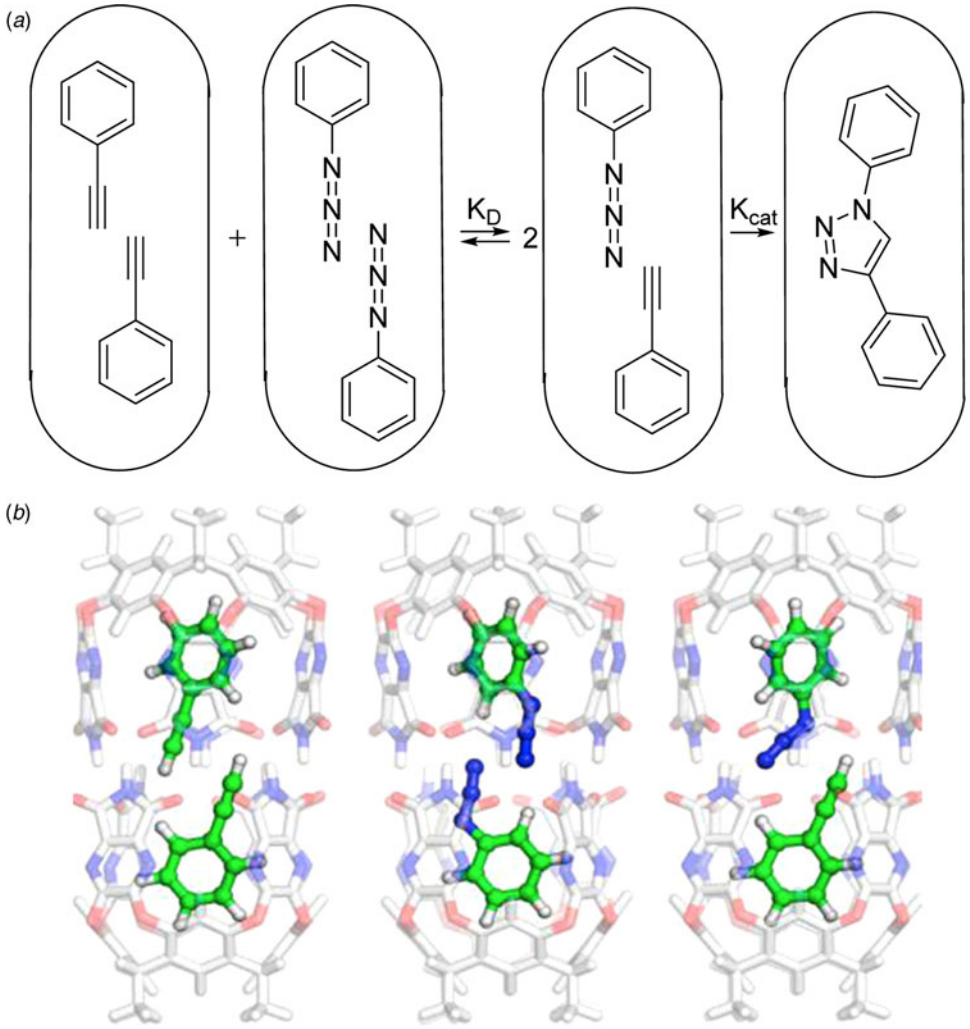

Fig. 3. (*a*) Cartoons of the encapsulated components of the click reaction. (*b*) Energy-minimized models for disproportionation of encapsulated acetylene (left) and azide (middle) to give the Michaelis complex. From Daver *et al*. (2017).

kinetic analyses. This was accomplished with a cylindrical capsule (Fig. 2) (Heinz *et al*., 1998).

The cylindrical capsule is prepared from a resorcinarene platform by building walls with hydrogen bonding functions on the periphery. The vase-shaped structure known as a cavitand can dimerize through a cyclic seam of hydrogen bonds. The space inside is tapered at the ends as shown in the figure and the shape controls the alignment of guests inside. For example, a long molecule such as dicyclohexylcarbodiimide is readily accommodated, but two (or even three) smaller molecules such as chloroform can be arranged inside – about which more later. For the moment, the cylinder takes in two phenyl acetylene or two phenyl azide guests aligned as shown in Fig. 3*a*. But, a mixture of the two symmetrically-filled capsules spontaneously disproportionate (K_D) favoring the Michaelis complex of the newly introduced, but not yet a famous 'click' reaction (Kolb *et al*., 2001).

The reaction proceeds inside to give a single regioisomer which eventually fills the capsule (Chen and Rebek, 2002). At the millimolar concentrations used in the experiment, the reaction inside the capsule is calculated to proceed at a rate 240 times faster than that outside the capsule. The acceleration (not catalysis) of the reaction in the capsule caught the attention of theoreticians Fahmi Himo, Jeremy Harvey and collaborators and triggered computational analysis in Fig. 3*b* (Daver *et al*., 2017). In particular, the question they raised was why – given the advantages listed above – was the reaction not faster? The answer emerged as follows.

Initially, the resting states of the capsule were calculated, and with guest solvents present, a previously unrecognized approximately *C*4-symmetric geometry for the capsule was identified as the most stable complex. In this complex, the walls of the capsule collapse to make better contacts with guests and the structure is maintained also when other guests bind inside.

Rearrangement

The second reaction studied inside was an intramolecular one, the rearrangement is shown in Fig. 4 (Sather *et al*., 2011). The reaction involves a 1,3 N → O acyl shift of a N-nitroso amide but in simpler, visually accessible terms the rearrangement makes the molecule thinner and longer. We had expected that substrates that fit snugly in the capsule would be less likely to undergo the step, although mere inhibition of the reaction was not our goal. The simple fact that the capsule alters the course of the reaction speaks volumes-reactions inside confined spaces are different

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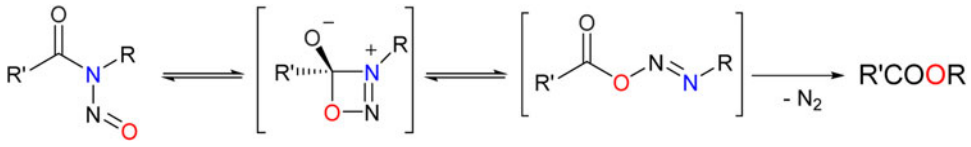

Fig. 4. The rearrangement involving a 1,3 N → O acyl shift of a N-nitroso amide.

whether enzymes or synthetic containers as shown capsules and deep cavitands – have emerged as the most realistic models of enzymes active sites. The use of small molecule compounds in dilute solutions to model enzyme reactions behavior is inadequate. Encapsulated compounds had been used with photochemistry as the trigger (Kaanumalle *et al.*, 2005), to show how confinement affects reaction pathways in a number of processes (Ramamurthy, 2015; Mohan Raj *et al.*, 2019). These features comprise high-binding selectivity, large rate enhancements, and stabilization of reactive intermediates.

The calculations nicely reproduced the inhibition of the decomposition inside the capsule (Brea *et al.*, 2019*a*, 2019*b*). They confirm that the inhibition is due to an increase in the energy barrier of the 1,3 N → O acyl transfer to form the diazoester intermediate, which is the rate-determining step of the reaction. A distortion–interaction energy breakdown was used to analyze the energy barrier increase. The calculations also predicted that ion pairs that are unstable in mesitylene solution can be stabilized in the capsule by nearby hydrogen bonds. That is, confinement favors (hypothetical) intermediates that might form inside the capsule but are unexpected in solution. The details of the reaction outside were thoroughly examined by density-functional theory (DFT) calculations (Brea *et al.*, 2019*a*, 2019*b*).

New stereochemistries

The cylindrical shape and volume of the capsule offered sustained arrangements of small molecules confined in its space. These arrays represent new forms of stereochemistry that are unknown in bulk solution – an emergent aspect of the behavior of confined molecules. First, molecules such as *p*-ethyl-toluene are taken in are too long to tumble in the capsule but leave enough space for a second guest, say, chloroform (Fig. 5*b*). Two arrangements can be observed in the NMR spectrum – one with the ethyl near the chloroform (80%) and one with the methyl near the chloroform (20%). The two occupants are too wide to slip past each other while in the container, so the isomeric arrangements are stable as long as they remain isolated, in the container. They can interconvert only by exiting the capsule and re-entering in the other arrangement, a process that occurs on the timescale of seconds. The ratio of the two isomers reaches equilibrium on mixing the components and allows calculation of small differences in energy between what we call 'social isomers'. We examined a series involving 15 pairs of co-encapsulated guests and measured their social isomers in the container. The energetics of their pairwise functional group interactions could be evaluated at the sub-kilocalorie level. Much of what we know of these guest–guest interactions is due to our computational collaborators Giannoula Theodorakopoulos and Ioannis Petsalakis in Athens who provided the theoretical underpinnings for forces acting in small spaces (Tzeli *et al.*, 2011).

Second, the cylindrical container's ability to accommodate three small molecules gave rise to yet another form of isomerism. For example, three chloroform molecules are taken up, and even though they are able to tumble freely in the space, they are too large to slip past each other while inside. The centrally-located guest stays there and shows a separate NMR signal from those guests at either end of the space. Now, suppose that a second guest is introduced to replace a resident chloroform molecule. We used isopropyl chloride since it is of comparable size and shape and polarity. Two new complexes were formed as there are two positions for the new guest: center or end. We called these constellational isomers as shown in Fig. 5*a*.

Third, co-encapsulation of the various picolines provided an opportunity to test another form of isomerism in the shape-space of the capsule. Aromatics fit each half of the container best when diagonally positioned (Fig. 5*c*). These guests are short enough to tumble freely inside, but the space of the container – two square prisms rotated by 45° does not allow the two aromatics to be coplanar (Tzeli *et al.*, 2012). Instead, the ground state arrangements of *β*-picoline can place the nitrogen atoms at proximal or distal positions, as shown. This introduces new stereochemistry, 'rotational isomerism' for guests with hindered rotation along the capsule's long axis. The computations of the Athens group showed the preferred arrangement of the complexes in agreement with experiment (Fig. 5*c*) but also revealed guest–guest interactions and even unexpected host–guest hydrogen bonding for *β*-picoline (Ajami *et al.*, 2013).

These emergent behaviors arise from the size and shape of the container's space operating on the confined guests. Why new names? In a formal view, the cases above are diastereomers, writ large, since they differ in 'connectedness'. But rather than covalent connectedness, which is the test in classical chemistry, it is container connectedness in the chemistry of capsules. Carceroisomerism (Timmerman *et al.*, 1994) has also been proposed to describe the different arrangements of molecules at such close range.

Solvent models

Incorporation of charged groups on the feet (periphery) of the containers and functions on the 'rim' that can hydrogen bond to water made water-soluble containers available. We used a rim featuring ureas (benzimidazolones) to form a formidable seam of hydrogen bonds (Ebbing *et al.*, 2002), a pattern introduced by De Mendoza. The expectation was that co-operativity and multivalency in rim-to-rim interactions of a dimeric capsule would overcome the hydrogen bonding to the ocean of water. In fact, millimolar water solubility resulted and an intact capsule persists with longer guests. In Gibb's cavitands and ours, hydrophobic processes drive the confinement and choices are made constantly between open-ended cavitand and more or less sealed capsules for quarantine. For our cases, shorter hydrocarbons form 1:1 cavitand complexes and longer alkanes 2:1 (capsular) complexes, but for *n*-decane, an equilibrium was observed between the 1:1 and 2:1 complexes, see Fig. 6*a*.

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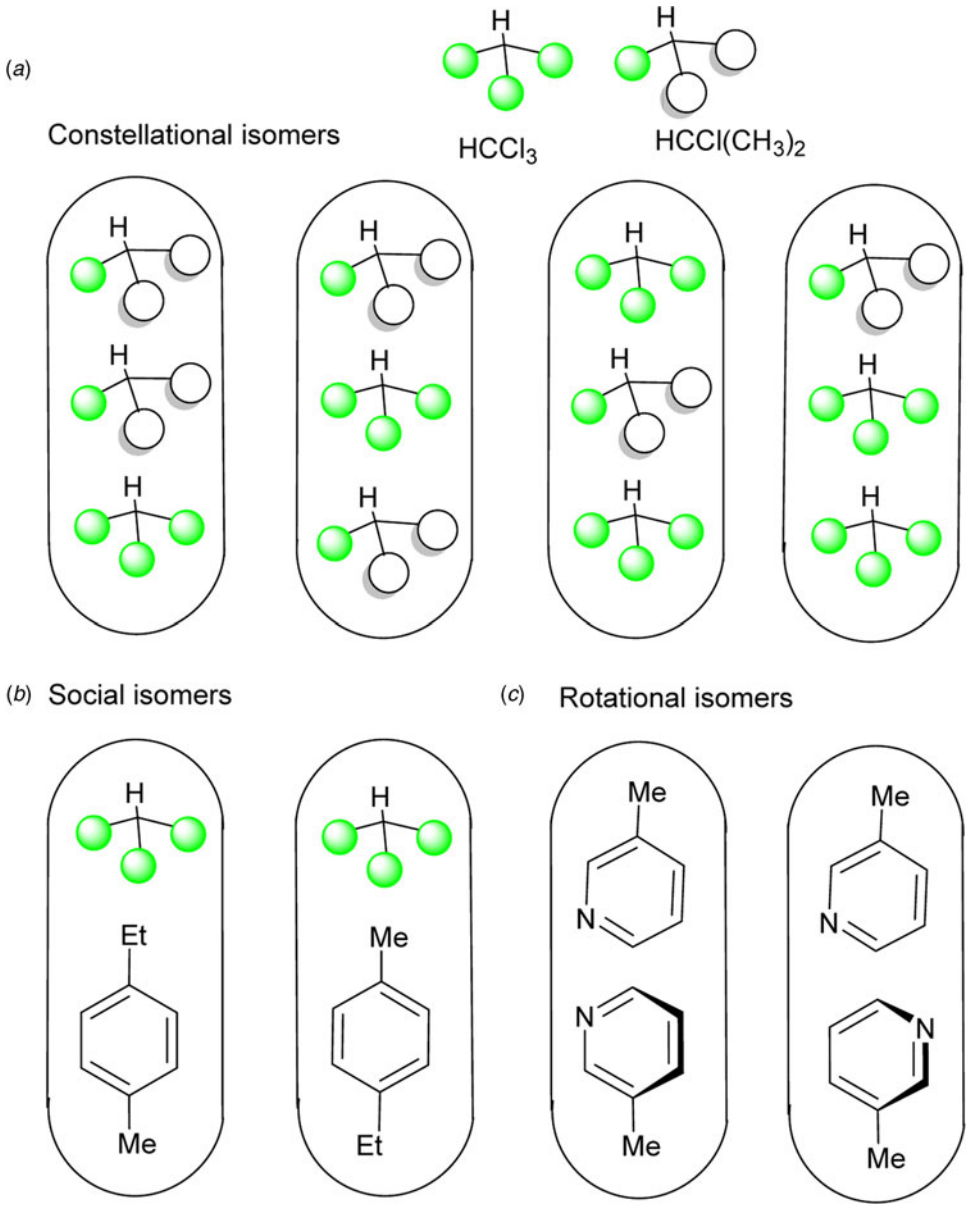

Fig. 5. (*a*) Cartoons of constellational isomers – chloroform with isopropyl chloride in cylindrical capsule. (*b*) Cartoons of social isomers – chloroform with *p*-ethyl-toluene in cylindrical capsule. (*c*) Cartoons of rotational isomers – two *β*-picoline in a cylindrical capsule.

Himo and collaborators realized that advanced computational protocols were prone to give very large errors arising from an implicit solvation model in water (Fig. 6*b*). Accordingly, a mixed explicit–implicit solvation protocol was developed. The explicit waters were placed around the rim in ways that were indicated to stabilize the vase conformation and observed in the X-ray structures of related cavitands. These waters bridge adjacent heterocyclic walls. The parameterization of the hydration free energy of water is set such that water cluster formation in water is predicted to be thermoneutral (Daver *et al.*, 2018).

Magnetic environments of containers

Of the many forces recruited to assemble container structures, none is more exotic than chalcogen bonding (CB). Closely related to halogen bonding, CB made desultory appearances in other supramolecular assemblies, before it was introduced into capsules by Diederich, who recognized the 2,1,3 Z-benzodiazole as just another *o*-disubstituted panel with self-complementary assembly potential (Riwar *et al.*, 2018) (Fig. 7*a*). Using Z = S and Te, he found weak and strong CB, respectively, of capsules organic media and the solid state. Our own efforts – in water – began with the synthesis of Z = Se and a curiosity about the compatibility of CB with the powerful forces of hydrogen bonding.

The CB capsules proved to be robust and 'leakproof' in water (D_2O); the CB donors and acceptors were orthogonal to those of hydrogen bonding. The magnetic environment within the CB capsule, however, showed a peculiarity: unlike in capsules with benzimidazolone or pyrazine imide walls depicted in Fig. 7*b*, guest nuclei in the center of the space (near the Se atoms) showed sizable upfield shifts in their ^{1}H NMR spectra. To understand the observed NMR chemical shifts, the Greek collaborators

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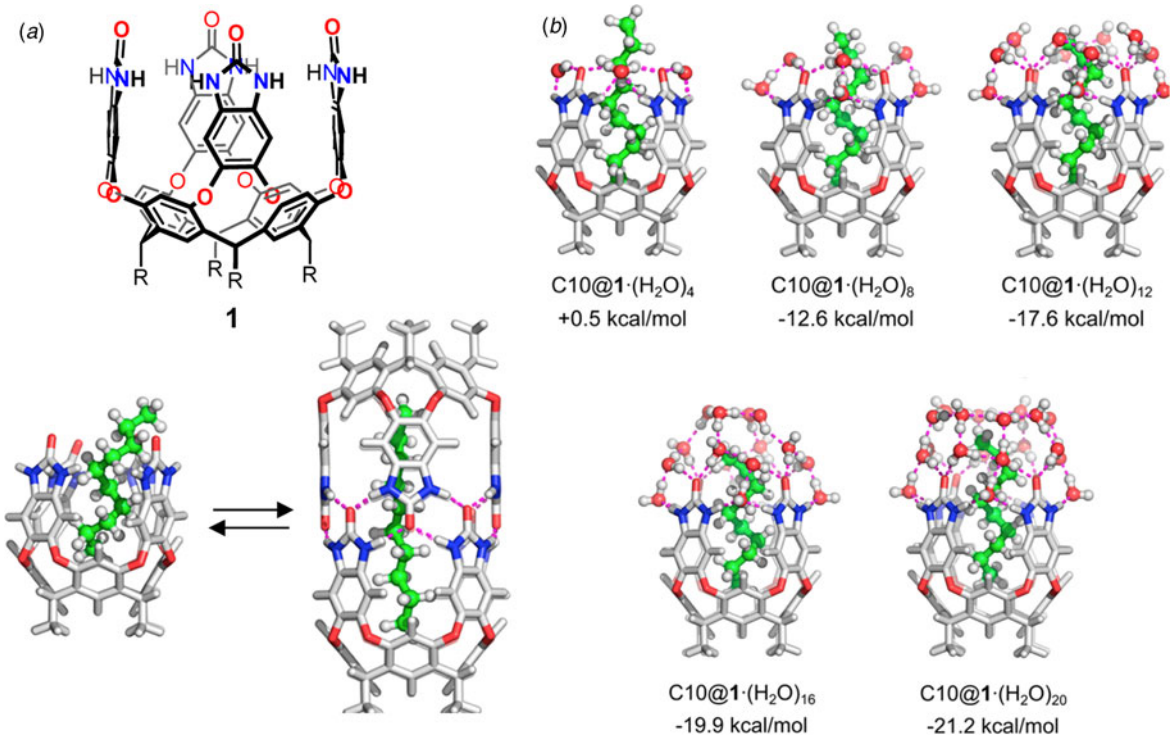

Fig. 6. (*a*) Chemical structures for benzimidazolone cavitand **1** (top); an equilibrium between the 1:1 and 2:1 complexes of *n*-decane and cavitand **1** (bottom). (*b*) Computational models for *n*-decane in cavitand **1** with different numbers of explicit water molecules. Adapted from Daver *et al.* (2018).

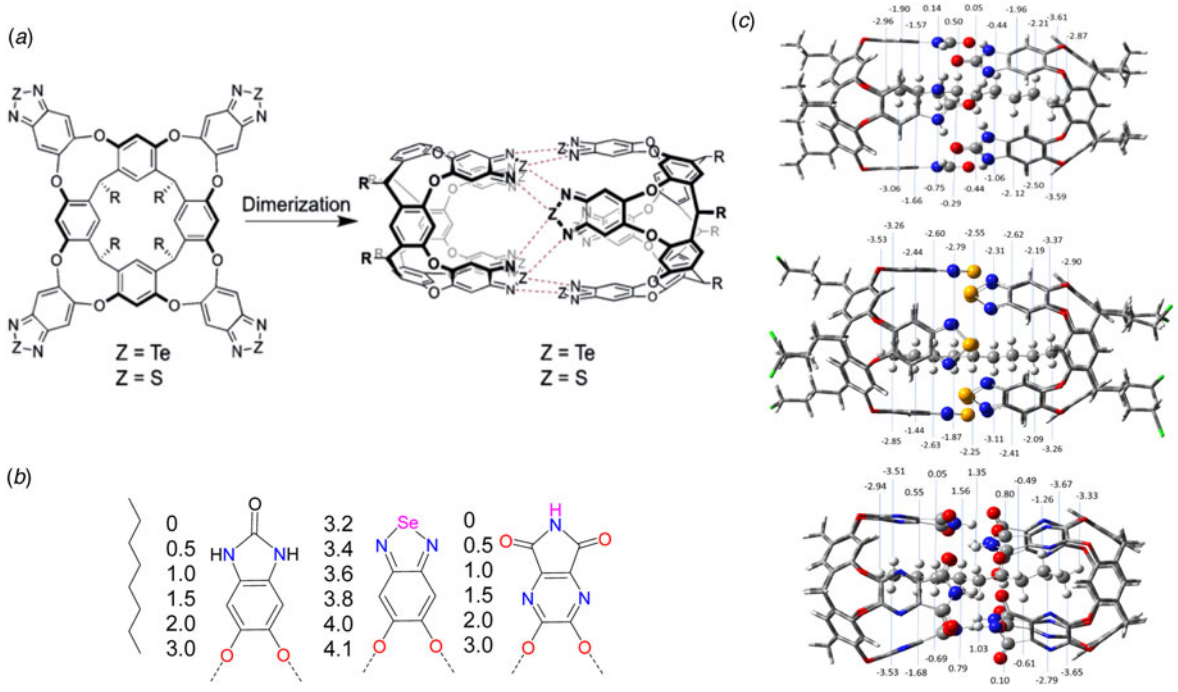

Fig. 7. (*a*) Dimerization of the 2,1,3-benzochalcogenadiazole motif to give a capsule. Adapted from Riwar *et al.* (2018). (*b*) Typical upfield chemical shifts ($-\Delta\delta$ ppm) experienced by nuclei different depths in cavitands with heterocyclic walls. (C) Upfield shifts of encapsulated *n*-nonane calculated with PBE0/6-31G(d,p): benzimidazolone (top), benzoselenadiazole (middle), and pyrazine imide (bottom). From Rahman *et al.* (2020).

performed DFT calculations of capsular complexes corresponding to the three aromatic panels. The dimeric capsules studied used one molecule of *n*-nonane (C_9H_{20}) in an extended conformation inside. The computational approach involved DFT calculations using two functionals, M062X and PBE0, in conjunction with the 6-31G(d,p) basis set. The calculated geometries of the

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complexes and the computed ^{1}H NMR chemical shifts of the guest are shown in Fig. 7*c* (Rahman *et al.*, 2020). The computations and experimental values are in excellent agreement.

Filling space

It has become increasingly clear that the behavior of molecules in dilute aqueous solution does not reflect their behavior in confined spaces. The synthetic receptors recognize and fold around their target guests, isolate them from the bulk solvent, provide a hydrophobic environment and present the guests with each other fixed in arrays set by the limited space. These features combine to show high-binding selectivity, large rate enhancements, and stabilization of reactive intermediates – resembling enzymes and receptors. The rules that govern capsule assembly are written in the hydrogen bonding patterns and the curvature of the modules, *but the final instruction is the proper filling of the space inside*. Recognition – size, shape, and chemical surface complementarity – lies at the heart of the confinement phenomena. It requires a good fit between guest and container, but what makes a good fit? For rigid guests, the size estimates are accurate; the dimensions are fixed and cannot exceed those of the cavity. For flexible guests, folding, bending, and other contortions are often encountered. The hosts are not rigid; they collapse on the guest to make whatever contacts are on offer at favorable van der Waals distances. Some time ago, we proposed 55% occupancy based on limited data and crude estimations of volumes (Mecozzi and Rebek, 1998). This figure corresponds to that encountered in typical organic liquids but the estimate has spread in the supramolecular community and even beyond academia to medicinal chemistry (Ehmke *et al.*, 2011). We would be happy to have theoretical community rescue us with a better formulation.

Conclusions and predictions

The water-soluble capsules discovered by Gibb (Jordan and Gibb, 2015), who mapped the contortions of guests in his capsules (Wang and Gibb, 2017) and applied them as protecting groups (Liu *et al.*, 2010). Atoms buried deep in the cavitand are hidden from reagents while atoms near the middle of capsules can be exposed to reagents in the solvent. The chemistry of folded molecules is a relatively new undertaking. Folding brings the guest's ends closer together, and sites that are remote in bulk solution are no longer so in the container. The two ends are subject to mutual neighboring group participation, a form of entanglement (Yu and Rebek, 2018). Product distributions that are statistically determined in solution are significantly altered in cavitands (Shi *et al.*, 2016) and chaperoned macrocyclization has given access to molecules that cannot be made by conventional means. Amplification and chain-reaction kinetic have also been encountered (Chen *et al.*, 2002). But any number of container compounds – MOFs, COFs, or capsules made of metals and ligands – can exhibit properties of confined molecules and expand the research beyond chemistry to materials science.

For speculation, we propose applications in data storage. The various forms of isomerism described above represent *information*. With three different guests in the cylindrical capsule, 18 constellations can be arranged. This is multiplied many times if social and rotational isomers are possible – all in a space of about 2 nm^3. This application requires that the isomers be 'written' rapidly and accurately, stored indefinitely and 'read' instantly. The speed of these processes (determined by the motion of molecules) is at a disadvantage compared to electronic motion, but the space involved represents an advantage. The challenges are monumental but the rewards may be momentous.

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