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Cavitands as containers for *α,ω*-dienes and chaperones for olefin metathesis

Nai-Wei Wu, Ioannis D. Petsalakis, Giannoula Theodorakopoulos, Yang Yu* and Julius Rebek, Jr.*

Abstract: We describe here the behavior of *α,ω*-dienes sequestered in cavitands **1a** and **1b** in aqueous (D_2O) solution. Hydrophobic forces drive the dienes into the cavitands in conformations that best fill the space on offer. Shorter dienes (C9 and C10) bind in compressed conformations that tumble rapidly in the cavitands. Longer dienes induce capsule formation in cavitands with self-complementary hydrogen bonding sites, where the dienes exist in extended conformations. In cavitands unable to form capsules, longer dienes adopt folded structures. The wider open ends allow the synthesis of medium sized cycloalkenes by ring closing metathesis reactions with the Hoveyda−Grubbs-II catalyst. Yields of cycloheptene and cyclooctene were enhanced by the chaperones in water when compared with reactions of the free dienes in aqueous media or chloroform, and even cyclononene could be prepared in the cavitand.

Molecular container hosts have received much attention for their ability to confine guest molecules and affect their reactivity. The use of self-assembly has expanded the use of these containers for the promotion of reactions in small spaces.[1] We recently reported the synthesis and characterization of the deep cavitand **1a**[2] (Figure 1). The self-complementary pattern of hydrogen bond donors and acceptors on the upper rim was devised by de Mendoza,[3] who showed that dimerization to host capsules occurs with suitable guests in organic solvents. We found that pyridinium or methylimidazolium "feet" provided good solubility in water, and the formation of capsules occurs even in aqueous solutions when large hydrophobic guests are present.[4] To prevent such dimerization, we exhaustively *N*-methylated the benzimidazolones of the upper rim to form octamethyl urea **1b**. (See SI). Cavitand **1b** showed good solubility in water (D_2O), where it exists as a velcrand[5] dimer in the absence of guests. Here we report the complexation of symmetrical aliphatic *α,ω*-dienes (C9–C14) with cavitands **1a** and **1b**, and their applications for olefin metathesis in otherwise reluctant cyclizations.

Alkenes bound inside synthetic host structures are not often reported,[6] because the NMR signals of the olefinic protons are rarely observed because of overlap with the signals of the cavitands.[7] We used the commercially available *α,ω*-dienes: C9 1,8-nonadiene (**2a**), C10 1,9-decadiene (**2b**), C11 1,10-undecadiene (**2c**), C12 1,11-dodecadiene (**2d**) and C13 1,13-tetradecadiene (**2f**); the C14 1,12-tridecadiene (**2e**) was synthesized through reaction of 10-bromo-1-decene with allylmagnesium bromide.[8] Brief sonication of these *α,ω*-dienes (0.5 mM) with cavitand **1a** (0.5 mM) in water (D_2O) gave host-guest complexes with guest ^1H NMR signals characteristically upfield-shifted by the shielding of the aromatic panels of the host structure (Figure 2 and SI). The longer *α,ω*-dienes: **2c**, **2d**, **2e** and **2f** show signals which are spread out between 1.5 and -2.0 ppm (Figure 2). The terminal vinyl hydrogen signals of C11 appear at +0.05 ppm ($\Delta\delta$ = -4.70 ppm, H_{11a}) and -0.17 ppm ($\Delta\delta$ = -4.84 ppm, H_{11b}) (Figure S5 and Figure S6)**.** These olefinic protons experienced the maximum upfield shifts offered by the deepest part of the cavity in **1a**. This, and the wide spread of other signals are characteristic of an extended conformation, fixed in a symmetrical environment of the hydrogen-bonded capsule: **1a·1a**.

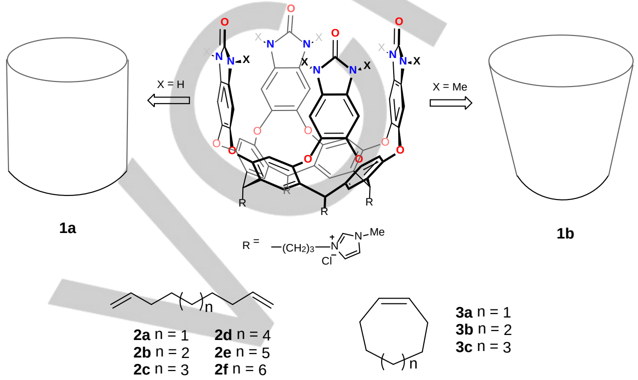

Figure 1. Chemical structures and cartoon abbreviations of cavitands **1a** and **1b**, the dienes **2a-2f** and the cycloalkenes **3a-3c**.

The spectra observed for encapsulated C12 and C13 also followed this pattern, but their terminal C-H signals unexpectedly moved downfield. Apparently, these longer dienes coil through *gauche* conformations along the chains that pull their two terminal olefinic hydrogens from the deepest parts of the capsule. The large separation between H_{11a} and H_{11b} for C11 termini means that H_{11b} is deeper than H_{11a}. In contrast, similar upfield shifts for C12 and C13 termini indicates their depths are comparable (Figure S13). Yet for the longest guest C14, the *penultimate* protons (H_2 = H_{13}) experience the furthest upfield shift (-$\Delta\delta$ of 4.44 ppm): they are, on average, the deepest in the cavitand. The terminal olefinic protons (H_{1a} = H_{14a} and H_{1b} = H_{14b}) show –$\Delta\delta$'s of only 4.26 and 4.21 ppm, respectively. A folded conformation of the diene at the tapered end of the cavity is proposed in Figure 2 and Figure S14 that place H_2 and H_{13} at the deepest positions. This is in accord with observations of longer *n*-alkanes (C14–C18) that are encapsulated in folded conformations.[9] These subtleties are depicted in the cartoons of Figure 2e, where the discontinuity occurs with the terminally

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folded C14. Complete COSY spectra and the assignments for **2c-2f** inside capsule **1a·1a** are available in Figures S5-S14.

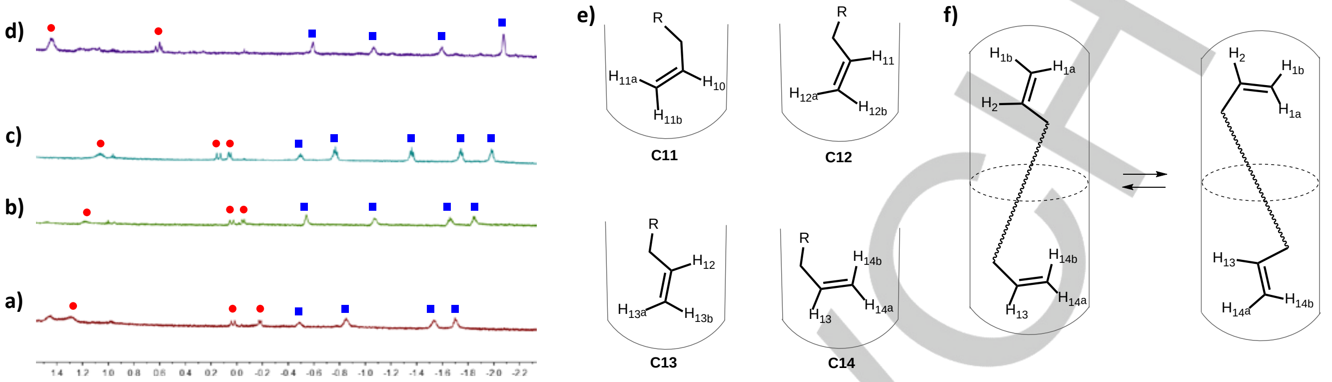

Figure 2. Left: partial ^1H NMR (600 MHz, D_2O, 298 K) spectra of the capsules formed between **1a·1a** and (a) 1,10-undecadiene; (b) 1,11-dodecadiene; (c) 1,12-tridecadiene; (d) 1,13-tetradecadiene. (The peaks labeled with red dots are from olefins, the peaks labeled with blue squares are from methylenes). Center: (e) positions of the vinyl hydrogens vary with diene length. Right: (f) folding at one end of tetradecadiene is rapidly transmitted to the other end.

The shorter *α,ω*-dienes: C9 and C10 showed simplified spectra in **1a** with the methylene signals appearing between 0 and -1.5 ppm. The olefinic signals of these dienes appear at around 3.0 ppm, which overlap with the signals of the cavitand **1a**. Apparently, these short guests are not long enough to fill the molecular capsule **1a·1a**, and instead they occupy the monomer **1a**. Their spectra are time-averaged by the exchange of magnetic environments of the two ends of the dienes. A rapid (on the NMR timescale) tumbling motion of a coiled guest is consistent with the observed signals (Figure S15). This tumbling is not an exclusive description: any rapid motion that exchanges the magnetic environment of the guest's ends would explain the spectra. The proposed coiling of the guest leads to better C-H/π contacts within the complex.[10]

The dimeric capsule **1a**·**1a** is stabilized by hydrogen bonding between two cavitand units and this makes for a narrower, somewhat rigid space. The vase conformation of cavitand **1a** is also reinforced by hydrogen bonds between the solvent D_2O and the ureas of the rim.[11] The N-Me groups at the upper rim of **1b** widen the "mouth", allow looser wall motions and affect its guests' conformations and mobilities. Sonication of **1b** with any of the *α,ω*-dienes also gave stoichiometric host-guest complexes. Unlike the complexes of **1a**, none of the olefinic protons of the dienes appeared in the upfield region below 1.0 ppm; the termini do not spend much time at the bottom of the cavitand. But there is reason to believe that the bottom of the cavitand is always occupied, since an unsolvated cavitand surface would create a vacuum. This leaves only methylenes to occupy the bottom of the cavity, and their signals do appear in the upfield region (Figure 3 and SI). For example, C9 **(2a)** showed three methylene signals at 1.09, -2.02 and -2.12 ppm, corresponding to upfield shifts (–Δδ) of 2.95, 3.23, 3.28 ppm calculated from the spectrum of free diene in water (D_2O). These assignments were established by 2D COSY spectra (Figure S17-S22). This NMR evidence indicates that the *central* CH_2 groups of these guests (**2a-2c**) show the furthest upfield shifts, and place them deepest in the cavity. Simply put, the chains are folded inside cavitand **1b**. Methylenes fixed at the bottom of such cavitands experience the largest upfield shifts (-Δδ of 4.0 to 4.5 ppm) while those near the rim show the smallest upfield shifts (-Δδ of 0 to 0.5 ppm). The NMR signals indicate folding of the guests in **1b**, and they are moving. We propose a rapid "*yo-yo"* motion[12] between J-shaped conformations which leads to a time-averaged environment for the signals; The binding energies of J and folded conformations for 1,9-decadiene were calculated using Gaussian 16[13] and only a 0.12 eV difference was found between them, supporting the "*yo-yo*" motion (Figure 4 and SI). Attempts to freeze out the motion of **2b** at lowered temperatures were unsuccessful (Figure S29). The longer guests C12-C14 (**2d**, **2e** and **2f**) protrude further outside cavitand **1b** than the shorter ones (**2a**-**2c**).

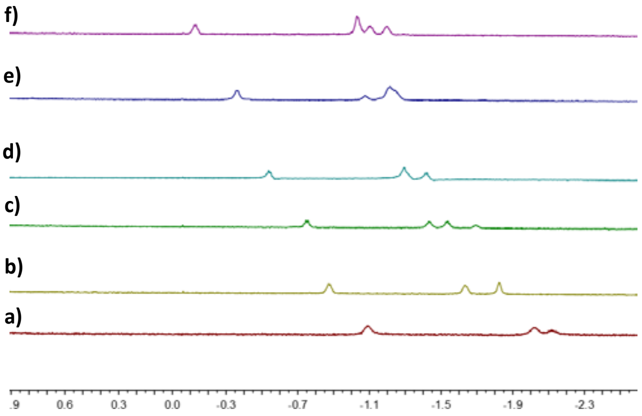

Figure 3. Partial ^1H NMR (600 MHz, D_2O, 298 K) spectra of the complexes formed between **1b** and (a) C9; (b) C10; (c) C11; (d) C12; (e) C13 (f) C14. (The signal assignments are in Figure S17-S28).

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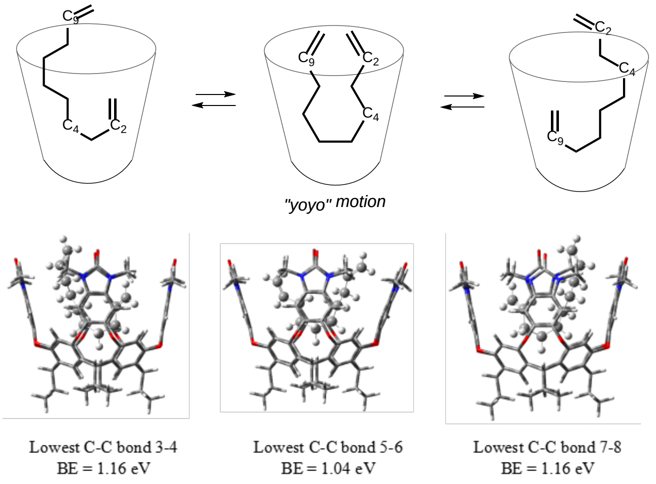

Figure 4. Top: Cartoon of the proposed "*yo-yo*" motion between J-shaped conformations of the complex of **1b** with C10; Bottom: Calculated structures of complexes of cavitand **1b** with 1,9-decadiene.

The folded conformations of these *α,ω*-dienes in **1b** bring the ends closer together and expose them to reagents in the bulk solution. These characteristics promote medium to large ring cyclizations in amide forming reactions,[2,14] and their application to ring-closing metathesis (RCM) reactions seemed possible. Olefin metathesis is widely used for ring formation,[15] but medium rings represent challenges,[16] as torsions and transannular strains arising during the reaction result in relatively inefficient cyclization.

We began by using **1b** as a chaperone to synthesize a 7-membered ring cycloheptene (**3a**) from C9 (**2a**). The complex was formed by sonication of the diene and cavitand for one hour in an NMR tube (2.0 mM). Then the commercially available Hoveyda−Grubbs-II catalyst (3%), which shows high activity under mild reaction conditions in water,[17] was added. As shown in Figure 5, the signals of **2a** disappeared while the product **3a** increased with time. The conversion of **3a** is nearly quantitative after a reaction time of 6 hrs. Reference spectra of authentic cycloheptene in the cavitand **1b** (top trace of Figure 5) indicated nearly no byproduct formation. The signals of cycloheptene in **1b** showed a –Δδ of 2.37 ppm for the olefin C-H's and -Δδ of 3.24, 3.93, 4.07 ppm for the methylenes. The cartoon of the product complex is consistent with these values, but doubtless some spinning motion of the guest takes place in the cavitand (Figure S30-S31). To the extent that the double bond is buried in the cavitand, it would be protected from further reversible reactions.

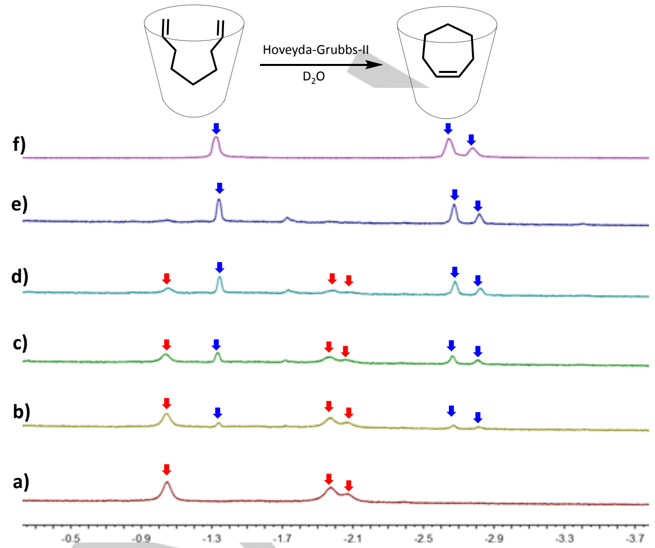

Figure 5. Partial ^{1}H NMR (600 MHz, D_2O, 298K) spectra of the RCM reaction of **2a** catalyzed by Hoveyda-Grubbs-II with cavitand **1b**. (a) **2a** (2.0 mM) in the cavitand **1b** (2.0 mM); (b) after treatment with Hoveyda-Grubbs-II for 1.5 h; (c) 3.0 h; (d) 4.0 h; (e) 6.0 h; (f) authentic cycloheptene in cavitand **1b**. The peaks labeled with red arrows are from substrate 2a; the peaks labeled with blue arrows are from product **3a**.

Closure of eight-membered rings is a difficult RCM process[18] and reactions that form *Z*-cyclooctene (**3b**) usually require either appropriate vicinal ring substitution or fusion to other ring systems[19]. For example, the case of Scheme S1 (compiled by Maier[20]) does not yield the 8-membered ring. The complex of C10 (**2b**) in **1b**, when treated as described above,

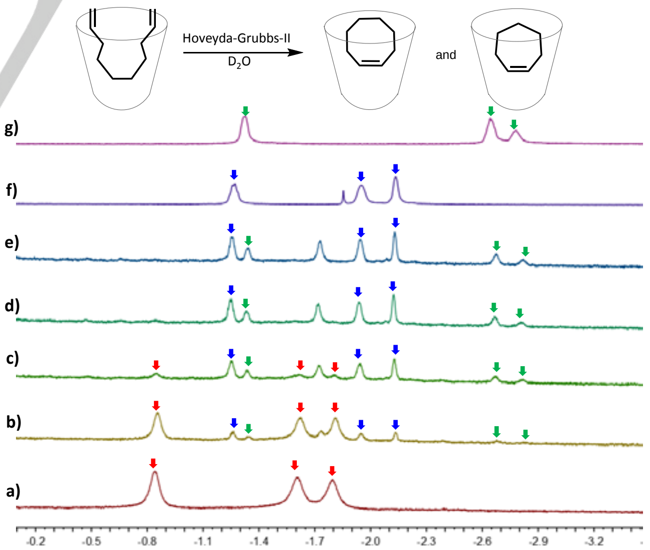

Figure 6. Partial ^{1}H NMR (600 MHz, D_2O, 298K) spectra of the RCM reaction of **2b** catalyzed by Hoveyda-Grubbs-II with cavitand **1b**. (a) **2b** (2.0 mM) in the cavitand **1b** (2.0 mM); (b) after treatment with Hoveyda-Grubbs-II catalyst for 0.5 h; (c) 2.0 h; (d) 4.0 h; (e) 6.0 h; (f) authentic cyclooctene in cavitand **1b**; (g) authentic cycloheptene in cavitand **1b**. The peaks labeled with red arrows are from substrate 2b, the peaks labeled with blue arrows are from product **3b** and green arrows are from **3a.** (For more details see SI).

gave rise to signals that matched the complex of authentic cyclo-octene *and* cycloheptene bound by **1b** (Figure 6). Diene isomerization by metathesis catalysts or ruthenium–alkylidenes is well established, and isomerization of terminal olefins is a versatile tactic of organic synthesis.[21] The appearance of cycloheptene likely derives from this process followed by cyclization. When C11 (**2c**) in cavitand **1b** at a more dilute concentration (1.0 mM), was exposed to the same conditions, *Z*-cyclononene (**3c**) was obtained, albeit in low yield. Oligomers and polymers were also formed (Figure S41).

The conversions of these chaperoned reactions were calculated by NMR integration using dimethyl sulfone as the water-soluble internal standard. The conversion of cycloheptene formed from **2a** was 98% in cavitand **1b**. The conversion of cyclo-octene from **2b** was 53%, along with 39% isomerization product cycloheptene. *Z*-cyclononene was produced in 9% from **2c**. No cycloalkene signals were found from the chaperoned reactions of longer dienes **2d-2f**. (SI) However, a recent report shows successful RCM of large rings by removal of the products through distillation as they are formed. [22] The isolated yield of **3a** with cavitand on a preparative scale was 79%, obtained by extraction followed by purification through chromatography.

Control reactions were performed in both an organic solvent ($CDCl_3$) and an aqueous medium (D_2O/DMSO-d_6) under the same conditions without added cavitand **1b**. Diene **2a** in $CDCl_3$ was found to produce **3a** with 78% yield (NMR) as a completely homogeneous phase in $CDCl_3$. The yield of **3b** formed from **2b** was only 13% in $CDCl_3$. The isolated yield of **3a** in $CHCl_3$ was 64%. We found no *Z*-cyclononene under these reaction conditions in $CDCl_3$ (Figure S47-S50). In control experiments in an aqueous phase (D_2O/DMSO-d_6 500µL/5µL), the α,ω-dienes **2a-c** were treated with Hoveyda−Grubbs-II catalyst (3%). After stirring for 6 hrs, excess cavitand **1b** was added to completely sequester any cycloalkene products. Neither cycloheptene nor cyclooctene were observed from the reaction of 1,8-nonadiene and 1,9-decadiene without cavitand **1b** (Table 1 and Figure S51). Stoichiometric amounts of cavitand were required for the olefin metathesis, pairwise competition experiments show cycloalkenes were better guests, but the cavitand could be reused by simple extraction (Figure S52-S54).

Table 1. Yields of cycloalkenes with or without cavitand 1b.[a]

cycloalkene	Conv,[a] % with **1b**	Conv,% without **1b** ($CDCl_3$)	Conv,% without **1b** (D_2O/DMSO)
3a	98 (79[b])	78 (64)	*N*[c]
3b	53	13	*N*
3c	9	*N*	*N*

[a] Calculated based on ^1H NMR integration. [b] Isolated yield. [c] *N* = too low to be determined. The concentrations of the substrate **2a** and **2b** are 2.0 mM, **2c** is 1.0 mM. The concentration of **1b** is 4.0 mM.

In summary, we have shown that cavitands **1a** and **1b** act as a supramolecular containers for α,ω-dienes in D_2O to give extended, coiled and folded guest complexes as homogeneous solutions. The cavitand **1b** not only dissolves the substrate but also plays a role as template for RCM reactions with a water compatible catalyst.[23] The host/guest interactions bring the reacting ends closer together in a precyclization conformation that overcomes some internal strains. The yield of 7, 8 and 9-membered cycloalkenes were significantly enhanced even compared with the reaction in homogeneous chloroform phase. The cavitand buries hydrophobic surfaces and the shape of the space on offer pushes the reactions along congruent pathway, even some that are not readily observed in bulk solution.

Experimental Section

Experimental Details are provided in the Supporting Information.

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Keywords: water-soluble cavitands •α,ω-dienes • olefin metathesis • cyclization • cycloalkenes

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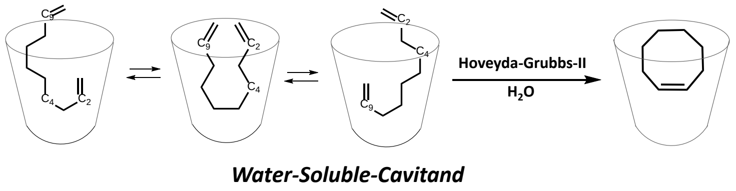

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Cavitands as containers for α,ω-dienes and chaperones for olefin metathesis