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Complete List of Authors:	Angamuthu, Venkatachalam; Shanghai University, Center for Supramolecular Chemistry and Catalysis and Department of Chemistry, College of Science Petroselli, Manuel; Shanghai University, Center for Supramolecular Chemistry and Catalysis and Department of Chemistry, College of Science Rahman, Faiz-Ur; Shanghai University, Center for Supramolecular Chemistry and Catalysis and Department of Chemistry, College of Science Yu, Yang; Shanghai University, Center for Supramolecular Chemistry and Catalysis and Department of Chemistry, College of Science Rebek, Julius; Scripps Research Institute, Skaggs Institute and Department of Chemistry

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Binding orientation and reactivity of alkyl α,ω-dibromides in water-soluble cavitands

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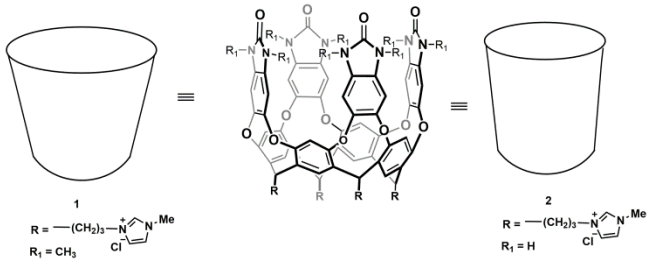
Venkatachalam Angamuthu,[a] Manuel Petroselli,[a] Faiz-Ur Rahman,[a] Yang Yu*[a] and Julius Jr. Rebek.*[ab]

Host-guest complexation of long chain α,ω-dibromides was evaluated in deep water-soluble cavitands 1 and 2. The bound dibromides (C_7–C_{12}) tumble rapidly on the NMR timescale and averaged signals were observed. The complexation allows mono hydrolysis of dibromides in aqueous solution. The arrangement of the products in the host-guest complex was fixed in an unsymmetrical manner that protects the guest from further reaction. Up to 93% yields of the mono-alcohols were obtained. The α,ω-dibromides formed an capsule with cavitand 2 and remained unreactive to hydrolysis.

Mono functionalization is generally hard to achieve for symmetrical compounds in bulk solution. The common problem is the formation of product mixtures due to identical functional groups on the substrate. In a long chain substrate, terminal sites are truly remote and act independently, leading to mono-, di- and unfunctionalized products. Molecules in confined spaces behave differently with respect to those in bulk solution and confinement can create special circumstances. In this regard, a number of container molecules have been developed to exploit these differences, and the use of these containers for the promotion of reactions in small spaces has expanded.[1-17]

Cavitands are open-ended containers used as hosts for complementary organic and biological guests. They are readily accessible through chemical synthesis[18] and generally display a dynamic equilibrium between two different structural conformations – the vase and kite – depending on experimental conditions.[19,20] Suitable guests are always required to stabilize the vase form of the cavitand.[21, 22] The driving-force for the formation of the host-guest complex in water is principally due to the hydrophobic effect, which drives the guest molecule into the confined space of the cavitand.[23] Many organic reactions do not proceed in aqueous medium due to low solubility of reagents or catalysts.[24] Water-soluble cavitands can help the dissolution of insoluble guests by the formation of stable host-guest complexes.[25-29] Application of molecular containers in aqueous media has shown much promise development in organic transformations.[30-33] Previously, we have applied deep, water-soluble cavitands to the mono hydrolysis of long-chain diesters,[25] the synthesis of macrocyclic ureas[34] and the Staudinger reactions of diazides.[29] The successes arise from the unusual orientations of linear and cyclic alkyl halides reported[27,35,36] in cavitands **1** and **2** (Figure. 1). Here we report the binding and reactivity of α,ω-dibromides in these cavitands that promote mono hydrolysis.

The synthesis of cavitands **1** and **2** has been recently reported by our group.[26,37] These cavitands have good solubility in water (> 2 mM) and are stable over a wide range of pH in water.[30,37] In the vase form of **1** and **2** the characteristic methine protons appear at 5.6 ppm in the ^{1}H NMR spectrum, while in the kite form the signal is observed near 4 ppm.[38-40] The presence of *N*-Me groups on the upper rim of **1** prevents the formation of a hydrogen bonded capsule, but either cavitand is a dimeric velcrand form in solution when suitable guests are not present. Guests in the vase forms experience upfield shifts in their NMR spectra and the approximate upfield shifts (–Δδ) of guest nuclei are given in the supporting information. (Figure S1).



[a]*Center for Supramolecular Chemistry and Catalysis and Department of Chemistry, Shanghai University, 99 Shang-Da Road, Shanghai 200444, P. R. of China.*
[b]*The Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States*
** Corresponding author: Email: yangyu2017@shu.edu.cn; jrebek@scripps.edu*
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Figure 1. Chemical structures and schematic cartoons of the deep, water-soluble cavitands **1** and **2**.

The binding and reactivity of alkyl α,ω-dibromides (C_7-C_{12}) were investigated in **1**. Compounds **3a-f** were sonicated with cavitand 1 in D_2O (1.4 mM) and formed (1:1) host-guest complexes. The ^{1}H NMR signals of the guest shifted to the upfield region (Figure 2a). Guests **3a-f** show proton signals clustered from 1.6 to −1.5 ppm (i.e., –Δδ of about 1.7 to 2.3 ppm). The spectra are consistent with the rapid tumbling of the guests inside the cavity.[35] The upfield shifts (–Δδ) for bound guests varied with different lengths of the carbon chain: In longer α,ω-dibromides, portions of the guest spend more time outside the vase and the averaged signals move downfield and are closer to those of the free guest. The assignments of the signals were made by 2D COSY experiments (Figure S3-5)

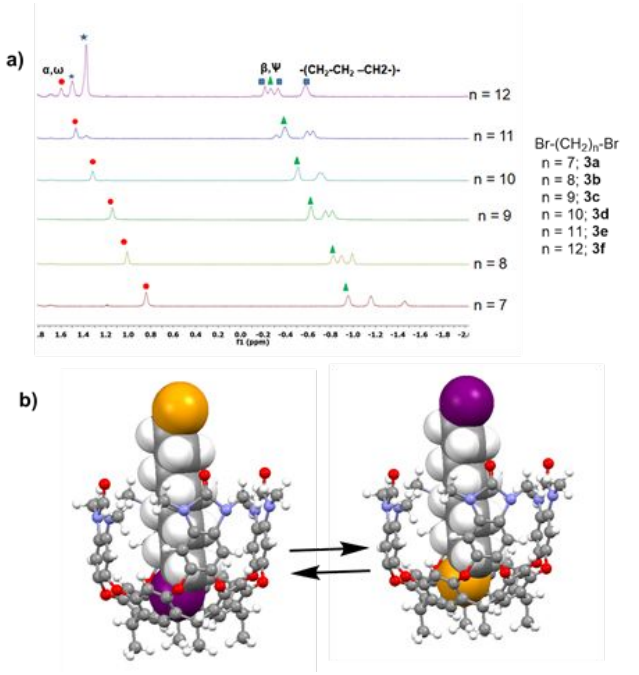

Figure 2. a) Partial ^{1}H NMR (600 MHz, D_2O, 298 K) spectra of the complexes formed between host **1** (1.4 mM) and α,ω-dibromides (**3a-f**). Red circles indicate α,ω methylenes, green triangles indicate β,ψ methylenes and blue squares indicate middle methylenes; stars indicates free guest. b) Model of the rapid tumbling inside the cavitand that leads to simplified signal patterns.

The reactivity of bound guests was studied using DMSO as a co-solvent because of its promotion of S_N2 type reactions.[41, 42] Other co-solvents such as DMF, 1,4-dioxane, acetone, acetonitrile or acetic acid were also investigated (Figure S7). As shown in Figure 3a, the signals of the complexed α,ω-dibromide (C_{10}) (**3d**) decrease in intensity as a new set of peaks appear in the upfield region after several hours of stirring at 50 ºC. These are signals of mono hydroxyl bromide in the cavitand and range from +1.34 to −2.45 ppm. The signal pattern is consistent with a fixed arrangement in the cavitand with the OH exposed and the remaining Br buried. Parallel results were obtained with other dibromides (Figure S8-11).

The assignments of mono hydroxyl product signals are summarized in Figure 3b, with -Δδ values calculated from the 2D COSY experiments (Figure S12). Methylene protons in the α and *β* positions from the Br in the monobromides are shifted furthest upfield. This is apparently because the Br group allows a nearby sharp bend in its attached chain.

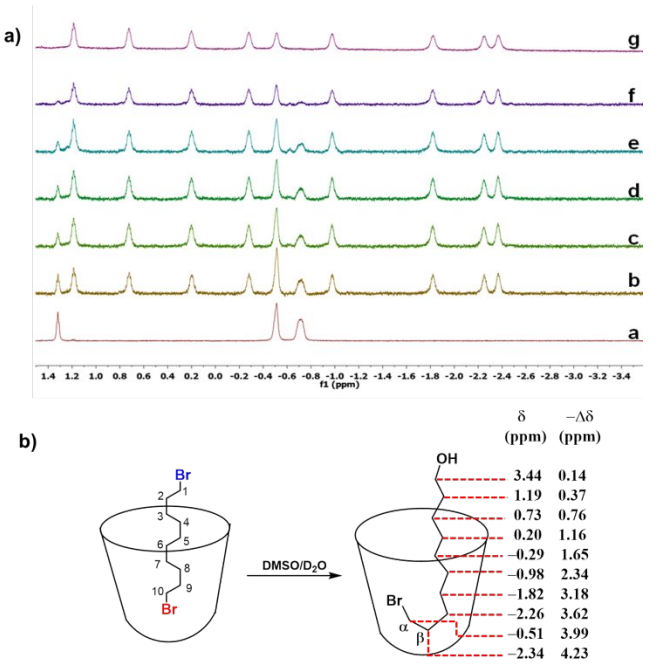

Figure 3. Top (a): Partial ^{1}H NMR (600 MHz, D_2O, 298K) spectra of α,ω-dibromide (C_{10}) **3d** in **1** recorded after sequential additions of DMSO-d_6 (4 µL). (a) after 6 h of sonication at 25 ºC without DMSO-d_6; (b) 4 µL, 24 h, 50 ºC; (c) 8 µL, 56 h, 50 ºC; (d) 12 µL, 112 h, 50 ºC; (e) 136 h, 50 ºC; (f) 172 h, 50 ºC; (g) authentic 10-bromodecan-1-ol in cavitand **1**. Bottom (b): Cartoons of reaction in the complex of (C_{10}) dibromide **3d** with assignments of the product methylene signals.

The fixed conformation of the complex in Figure 3, with the bromide end buried in the cavity, prevents further hydrolysis reactions. Addition of another 10 equivalents of DMSO to the reaction mixture after 2 days did not change the ^{1}H NMR spectra and confirmed that the Br group is protected by cavitand and inaccessible. Even after one month no changes in the spectra were observed. Only compounds with longer lipophilic chains such as compounds **3e** and **3f** showed small amounts (10%) of dihydroxy products in this reaction (Figure S16). The NMR yields of products were calculated using dimethyl sulfone as an internal standard and were 69, 93, 69, and 76% for **4c**, **4d**, **4e** and **4f**, respectively (Figure S17 to Figure S20).

Stringent control experiments are difficult to perform without the cavitand because most of the long chain dibromides are practically insoluble in water. Instead, control experiments were performed using a mixture of acetone-d_6 in D_2O (25% v/v) and with DMSO-d_6 (3.6%) as co-solvent. In these

experiments, the hydrolysis reactions were slower and gave mixtures of products (Figure S21). After prolonged times or increased DMSO-d_6 concentrations (D_2O/Acetone-d_6/DMSO-d_6 (5:2:1), the dibromides were converted quantitatively into the dihydroxyl products without any mono hydroxyl products detected. This result highlights the striking ability of the cavitand to suppress the second hydrolysis step.

The binding results with cavitand **2** were different from **1**, with the NMR signals between -0.3 and -2.1 ppm. As shown in Figure 4, all dibromides were readily encapsulated by **2**, and the chemical shifts of the α,ω-methylene signals indicated that the Br groups remain near the ends of the capsule (-Δδ = 4.51). The assignments were made by 2D-COSY experiments (Figure S29 and Figure S30).

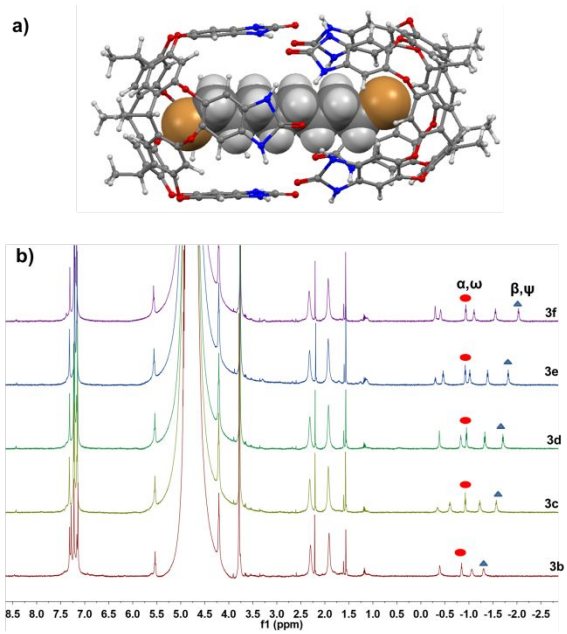

Figure 4. a) Model of extended (C_{10}) dibromide in the capsule formed by cavitand **2**; b) NMR spectra of encapsulated dibromides C_8-C_{12} (**3b-f**). Red circles indicates α,ω methylene signals and blue triangles are β,Ψ methylene signals.

The encapuslated dibromides (**3b-3f**) showed signals between –1.30 to –2.03 ppm, consistent with completely surrounded guests.[43] The upfield shifts for protons increased with length from C_7-C_{12} (Figure 4). Longer alkyl groups are known to adopt gauche conformations to compress and fit into the capsule.[44] This effect consequently pushes C-H groups toward the walls of the capsule and moves the signal upfield. Both bromines are deep inside the ends of the capsule and inaccessible to water. The hydrolysis does not proceed under the standard conditions above.

In summary, we reported the binding orientations of α,ω-dibromides in water-soluble cavitands **1** and **2**. These dibromides show exchange of the two ends in **1** but the details of the rapid motion are unknown. Mono hydroxyl bromides were obtained as major products by the hydrolysis of the α,ω-dibromides in the water soluble cavitand **1**. The products were protected from further hydrolysis in **1**. Cavitand **2** forms a capsule with α,ω-dibromides which protects the guests from hydrolysis.

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Conflicts of interest

There are no conflicts to declare.

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