

**NJC****Binding of alkyl halides in water-soluble cavitands with urea rims**

| | |
|-------------------------------|--|
| Journal: | <i>New Journal of Chemistry</i> |
| Manuscript ID | NJ-ART-03-2018-001567.R1 |
| Article Type: | Paper |
| Date Submitted by the Author: | 02-May-2018 |
| Complete List of Authors: | Yu, Yang; Shanghai University, Li, Yong-Sheng; Shanghai University Rebek, Julius; The Scripps Research Institute, The Skaggs Institute for Chem. Biol |
| | |

SCHOLARONE™
Manuscripts

Binding of alkyl halides in water-soluble cavitands with urea rims

 Yang Yu,^{*a} Yong-Sheng Li^a and Julius Rebek, Jr.^{*a,b}

 Received 00th January 20xx,
Accepted 00th January 20xx

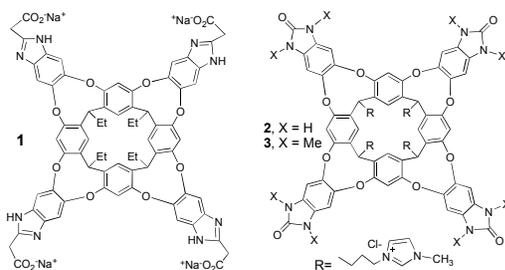
DOI: 10.1039/x0xx00000x

www.rsc.org/

The complexation of primary alkyl halides C_n-X ($n = 5, 6$ and 9 ; $X = Cl, Br$ and I) in a new, water-soluble cavitand is evaluated. The complexes are dynamic; the host and guest adapt their shapes to accommodate each other and the guest undergoes tumbling or yo-yo like motions in the space. Evidence for halogen bonding of the halides to the aryl surfaces of the cavitand is presented.

Introduction

Earlier¹ we described a water-soluble cavitand host **1** (Fig. 1) and its binding of hydrophobic² and amphiphilic guests. The solubility of the cavitand results from its carboxylates, and it functions at basic pH, binding simple alkyl halides and other primary aliphatic derivatives.³ The halide complexes showed unexpected positioning of the Br and I guests: the halide ends were often found at the bottom of the cavitands in a manner that correlated with halogen bonding to the resorcinarenes. Problems with hydrolysis of the halides – apparently accelerated by the carboxylates – and guest aggregation events made conclusions concerning the role of halogen bonding in the complexation difficult to draw. We have devised new cavitands that mitigate these problems and we report our findings here.



^a Center for Supramolecular and Catalytic Chemistry and Department of Chemistry, Shanghai University, 99 Shang-Da Road, Shanghai 200444, China.

^b Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, CA 92037.

Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x

Figure 1. Chemical structures of water-soluble cavitands.

Cavitand binding in water

We prepared the imidazolium salts **2** and **3**, both of which showed good (>1 mM) solubility in water (D_2O)⁴. The benzimidazolones of the “rim” were introduced earlier by de Mendoza⁵ and Choi⁶ as self-complementary features for dimerization to capsules, but the strong hydrogen bonding donors and acceptors are also effective for solubility in water. The charged groups on the “feet” of the cavitands further impart solubility over a wide pH range but, unlike **1**, cannot make direct contact with the guests inside. The resting state of **2** or **3** in water without a suitable guest present is a dimeric structure known as a “velcrand” (Fig. 1).⁷ In this state, the aromatic panels of one cavitand are extensively stacked on those of the other and no cavity is present to receive guests.

Complexation of alkyl guests

Exposure of aqueous solutions of **2** or **3** to hydrophilic molecules causes no changes in the cavitand’s disposition as the potential guests prefer solvation by water. However, brief sonication with *hydrophobic* guests breaks up the unreceptive velcrand dimers and results in the formation of complexes.

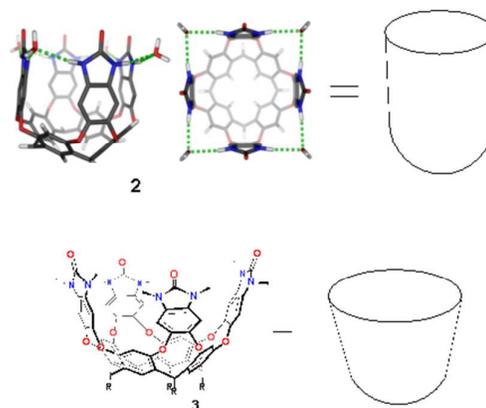


Figure 2. Shapes and cartoon representations of the cavitands. The unsubstituted benzimidazolone units **2** are bridged by hydrogen

bonds to solvent water, while the methylated **3** features a wider mouth.

The hydrophobic guests escape water to solvate the interior of the cavitands. In the case of **2**, water molecules can bridge the urea functions of the rim and complete the seam of hydrogen bonds that stabilize the vase-like conformation for guest reception (Fig. 2). In the case of **3**, the N-Me groups prevent such hydrogen bonds and the receptive shape of the cavitand has a wider "mouth".

Spectroscopy of complexes

NMR spectroscopy is the most useful method to characterize these complexes, as the spectra report stoichiometry and offer structural information on the disposition of both host and guest. For the host, the characteristic resonance of the methine protons of the "feet" at ~ 5.6 ppm signals the presence of the vase shape while the complexity (or simplicity) of the aromatic signals reflects the overall symmetry of the complex – at least on the NMR timescale. For the guest, there are well-established correlations of changes in chemical shift ($\Delta\delta$) for the guest nuclei and their positions within the cavitands. The 8 aromatic panels create a magnetic anisotropy that shields the guests and moves their signals far upfield. The effects can be calculated for a given fixed host structure, using the method of Schleyer.⁸ Nuclei near the bottom of the cavity can be shifted by nearly -5 ppm with the effect decreasing gradually as nuclei approach the "rim". There, the changes in shifts are much smaller (-0.5 ppm or less). Typically, the cylindrical cavitand shows larger upfield shifts since, on average, its aromatic panels are closer to the guest than those of the cone-like methylated cavitand. But these cavitands have flexibility in the walls that can alter the magnetic environment of the cavity. Gibb⁹ has devised related cavitands that have covalently fixed walls. They feature wider "bores"¹⁰ that can accommodate folded and other alkyl shapes which show different magnetic environments that can be accurately mapped.¹¹

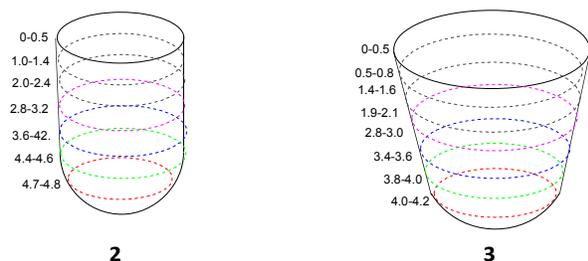


Figure 3. Approximate upfield shifts ($-\Delta\delta$) experienced by nuclei in the two cavitands.

A number of binding studies with long-chain alkyl derivatives are summarized in the cartoons of Figure 3.¹² The levels indicated correspond to the positions of alkyl carbons when the methyl group occupies the bottom. A terminal methyl signal typically appears at -4.0 ppm in the NMR spectra of **2** ($\Delta\delta$ -4.8 ppm) and at -3.3 ppm in **3** ($\Delta\delta$ -4.1 ppm).

Binding of organic halides

Figure 4 shows the upfield regions of the spectra with *n*-hexyl halide guests in **2**. The obvious conclusion drawn from the terminal methyl resonances at -3.0, -2.6 and -1.8 ppm for the alkyl Cl, Br and I, respectively, is that their methyl groups spend only part of their time at the bottom of the cavitand. One interpretation involves a system where the guest tumbles rapidly on the NMR timescale between two ground states (Fig. 5). In one state the methyl is in the down position (at the bottom of the cavitand) and experiences a $\Delta\delta$ of -4.8 ppm; in the other state the methyl group is in the up position (near the rim) where it experiences a $\Delta\delta$ of -0.4 ppm, and the halide is in the down position. Using these values for the hexyl derivatives, the chloride is down 20% of the time; the bromide is down 30% of the time and the iodide is down 52% of the time. The *n*-pentyl derivatives showed parallel behavior with the Cl 17% down; Br 25% down and I 50% down. We note that the addition of *n*-pentyl or *n*-hexyl halides into aqueous solutions of the cavitand led to clear solutions. In contrast, injection of *n*-hexyl bromide into pillar[5]arene aqueous solutions produced faint opacities in the mixture.¹³

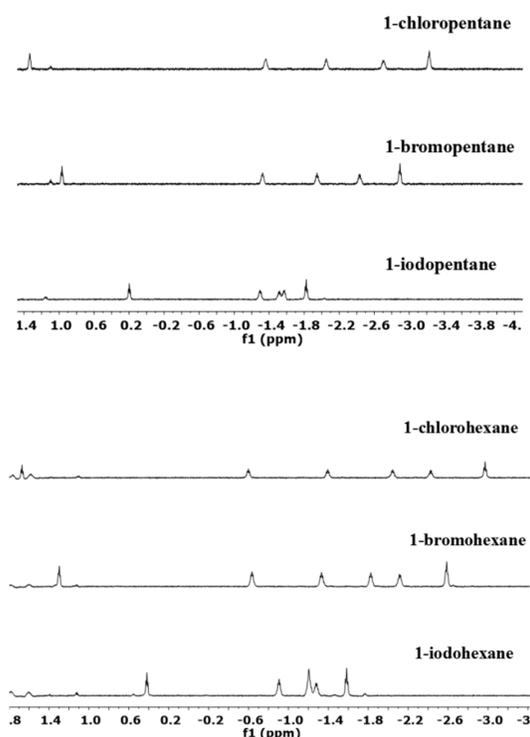


Figure 4. Upfield regions of the NMR spectra (600MHz, D₂O, 298K) of alkyl halides in cavitand **2**.

The increased fraction of the iodide in the down position is consistent with halogen bonding: the Iodo atom shows a higher affinity to the aromatic floor of the resorcinarene.¹⁴

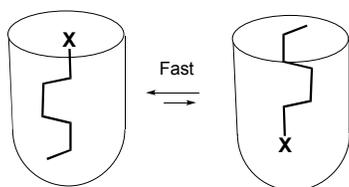


Figure 5. Cartoon of tumbling motion of hexyl halides between two ground states.

The results with the cone-shaped **3** were similar but a much closer clustering of the signals between -1.2 and -2.0 ppm was observed (SI). That is, the nondescript CH₂ groups and the CH₃ enjoy nearly the same depths - on average - in the cavitand. Again, the results in the cone were harder to interpret in a 2-state system due to broadening of the signals (SI).

The qualitative difference in binding of the two cavitands came with the longer nonyl derivatives (Fig. 6). These halides induced capsule formation with **2** (for example **2**: 1-chlorononane = 2:1 in their complexes, see SI) as this arrangement shields the entire hydrophobic surface of the guest from the aqueous environment. A fully extended chain is readily accommodated in the dimer of **2**, and the chemical shifts of the methyl signals indicate an anchoring effect; that is, the methyls remain near the end of the capsule (-3.6 to -3.8 ppm).¹⁵ The iodide showed a second complex is present. The clustering of the signals does not allow deconvolution and unambiguous assignments but are consistent with a folded conformation of the guest in **2**.

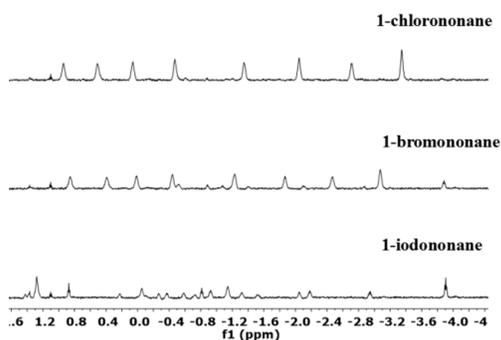


Figure 6. Upfield regions of the NMR spectra (600 MHz, D₂O, 298K) of nonyl halides in cavitand **2**.

The dimerization to a capsule is not available to **3** and this is reflected in its complexes with the nonyl halides. The spectra are shown in Fig. 7. The signals for the alkyl groups of the chloride and bromide are tightly clustered, further downfield and consistent with guests that are folded and dynamic. Unlike the shorter halides, there is no preference for the methyl group to be at the bottom of the cavitand as there are no far-upfield signals. Yet the signals for the halide-bearing methylenes are similar to those of the shorter C₅ and C₆ analogs. That is, the longer halides and the shorter ones spend comparable amounts of time near the cavitand's bottom. A rolling motion, allowed by the flexibility of the walls, is consistent with the NMR spectra as shown in Figure 7. Again,

this allows for - but does not guarantee - the involvement of halogen bonding.

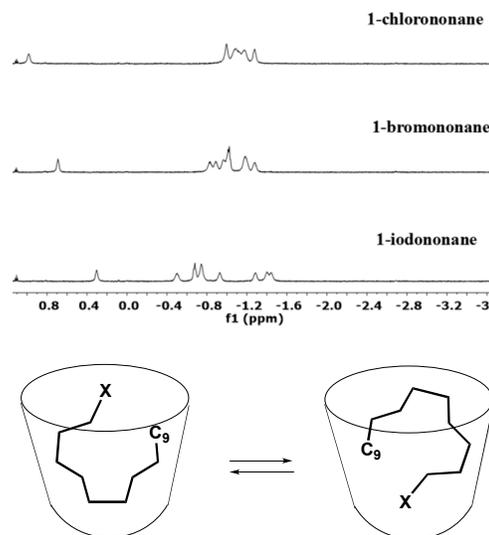


Figure 7. Upfield regions of the NMR spectra (600 MHz, D₂O, 298K) of alkyl halides in cavitand **3** (top); Proposed rolling motion of nonyl halides in **3** (bottom).

Competition between halide guests and cavitands

For the hexyl and pentyl derivatives comparable binding was observed in competition experiments with all three halides using cavitand **2** (SI). The iodo compound consistently showed highest affinity and the bromides showed slightly higher affinity than the chlorides. In competition for the cavitands, hexyl bromide preferred cavitand **2** to **3** by about a factor of three (Fig. 8).

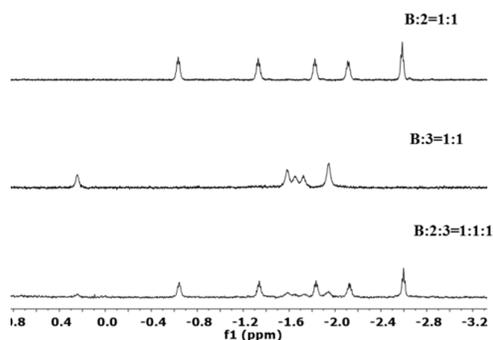


Figure 8. Upfield regions of the NMR spectra (600MHz, D₂O, 298K) of *n*-hexyl bromide in cavitand **2**, **3** and a mixture.

Conclusions

The binding of alkyl halides in water-soluble cavitands follows trends consistent with bonding of the halogen to the resorcinarene floor. However, the preferred orientation of the halides within the cavitands also consistent with

considerations of hydrophobicity: the most hydrophobic iodide avoids contact with the aqueous medium more than do the bromide and chloride. The combined forces – hydrophobic and halogen bonding – cannot yet be deconvoluted and are the subject of our ongoing studies.

We are grateful for financial support from the US National Science Foundation (CHE 1506266) and Shanghai University (N.13-0101-17-202), Shanghai, China. We thank Mrs. Yan-hong Song for NMR spectroscopic assistance.

Conflicts of interest

There are no conflicts to declare.

References

- 1 L. Trembleau and J. Rebek, Jr., *Science*, 2003, **301**, 1219.
- 2 R. J. Hooley, S.M. Birois and J. Rebek, Jr., *Chem. Comm.*, 2006, **5**, 509.
- 3 R. J. Hooley, J. V. Gavette, M. Mettry, D. Ajami and Julius Rebek, Jr., *Chem. Sci.*, 2014, **5**, 4382.
- 4 a) S. Mosca, Y. Yu and J. Rebek, Jr., *Nat. Protoc.* 2016, **11**, 1371; b) S. Mosca, Y. Yu, J. V. Gavette, K.-D. Zhang and J. Rebek, Jr., *J. Am. Chem. Soc.* 2015, **137**, 14582.
- 5 M. H. K. Ebbing, M. J. Villa, J. M. Valpuesta, P. Prados and J. de Mendoza, *Proc. Nat. Acad. Sci. U.S.A.*, 2002, **99**, 4962.
- 6 H. J. Choi, Y. S. Park, C.S. Cho, K. Koh, S. H. Kim and K. Paek, *Org. Lett.*, 2004, **6**, 4431.
- 7 D. J. Cram, H. J. Choi, J. A. Bryant and C. B. Knobler, *J. Am. Chem. Soc.*, 1992, **114**, 7748.
- 8 P. v. R. Schleyer, C. Maerker, A. Dransfeld, H. Jiao and N. J. R. v. E. Hommes, *J. Am. Chem. Soc.*, 1996, **118**, 6317.
- 9 H. P. Xi, C. L. D. Gibb, E. D. Stevens and B. C. Gibb, *Chem. Commun.*, 1998, 1743.
- 10 S. Liu, D. H. Russell, N. F. Zinnel and B. C. Gibb, *J. Am. Chem. Soc.*, 2013, **135**, 4314.
- 11 a) K. Wang and B. C. Gibb, *J. Org. Chem.* 2017, **82**, 4279; b) J. W. Barnett, B. C. Gibb and H. S. Ashbaugh, *J. Phys. Chem. B*, 2016, **120**, 10394; c) J. H. Jordan and B. C. Gibb, *Chem. Soc. Rev.*, 2015, **44**, 547; (d) R. Kulasekharan, M. V. S. N. Maddipatla, A. Parthasarathy and V. Ramamurthy, *J. Org. Chem.*, 2013, **78**, 942.
- 12 a) K. Zhang, D. Ajami and J. Rebek, Jr., *J. Am. Chem. Soc.* 2013, **135**, 18064; b) K. Zhang, D. Ajami, J. V. Gavette and J. Rebek, Jr., *J. Am. Chem. Soc.* 2014, **136**, 5264; c) Q. Shi, D. Masseroni and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2016, **138**, 10846; d) N. Wu and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2016, **138**, 7512.
- 13 W. Cheng, H. Tang, R. Wang, L. Wang, H. Meierc and D. Cao, *Chem. Commun.*, 2016, **52**, 8075.
- 14 D. Hauchecorne, B. J. van der Veken, W. A. Herrebout and P. E. A. Hansen, *Chem. Phys.*, 2011, **381**, 5.
- 15 K. d. Zhang, D. Ajami, J. V. Gavette and Julius Rebek, Jr., *Chem. Commun.*, 2014, **50**, 4895.