A new water-soluble cavitand with deeper guest binding properties

Journal:	*Organic Chemistry Frontiers*
Manuscript ID	QO-RES-01-2019-000049.R1
Article Type:	Research Article
Date Submitted by the Author:	14-Feb-2019
Complete List of Authors:	Rahman, Faiz-Ur; Shanghai University Feng, Hai-Na; Shanghai University Yu, Yang; Shanghai University,

Journal Name

COMMUNICATION

A new water-soluble cavitand with deeper guest binding properties†

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

Faiz-Ur Rahman[a], Hai-Na Feng[a,b], Yang Yu[a*]

A new water-soluble cavitand was synthesized that showed isomeric conformations in different solvents. The cavitand displayed multiple conformations - vase, kite, velcrand and intermediate shapes - in CD_3OD. Binding properties with hydrophobic (cycloalkanes) and amphiphilic (cycloalkyl carboxylic acids) guests in D_2O indicated a deep aromatic pocket.

Cavitands are synthetic containers that display dynamic shapes between vase and kite conformations. The stability of these conformations depends on experimental conditions and the presence or absence of a suitable guest[1-3]. The complexation of a guest requires and stabilizes the vase form of the cavitand[4]. Cavitands are important entities in molecular recognition and self-assembly processes. With water-soluble cavitands, the hydrophobic effect is the essential driving force that isolates the guest from water and drives it into the confined space of the cavitand[5-7]. The aromatic panels of the cavitand provide the features that define its binding of the guest in a water-free environment. In short, the structure of the host and guest determine the complementarity and stability of the host-guest complex. For a particular cavitand the ideal binding guest should have congruent shape and size and should occupy ~ 55% of the volume of the cavity[8]. Cavitand research has shown promising applications for reactions in aqueous medium[9-11]; cavitands can control the conformation of particular intermediate or product and promote alternative reaction pathways[12-15].

Water is an ideal green solvent but many organic reactions do not proceed in water[16] due to solubility problems of reactants or catalysts and the intermediacy of water reactive species. Water-soluble cavitands can provide a good platform for avoiding these problems during organic reactions in water medium. Binding of a substrate in water-soluble cavitand not only aids in the solubility of certain substrates but also helps in the stabilization or protection of a reactive substrate, reaction intermediate or product[10, 11, 17, 18].

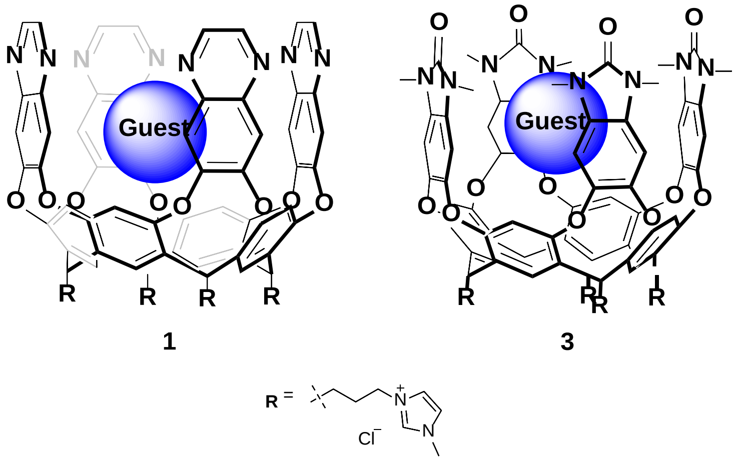

Fig. 1 Depictions of guests in the new cavitand **1** and Rebek's previous cavitand **3**.

There are relatively few water-soluble cavitands reported. They belong to two main classes: Gibb's rigid cavitands and Rebek's dynamic cavitands (Fig. 1 **3**)[19-22]. Cram and co-workers[3, 23, 24] reported the quinoxaline (benzopyrazine) deep cavitands in which quinoxaline was attached to resorcin[4]arene ring through pyrazine ring. Many of these and related cavitands were rigid and adopted vase conformations in organic media under normal conditions [25-27]. Due to the rigid vase structure of these cavitands, the guest binding in the solution state of such hosts was scarcely reported, showing the structural dynamic properties of a cavitand in solution state increase the chances for capturing of a particular guest in the cavity. To our knowledge, no related cavitands were reported or studied for the binding of molecular guests in aqueous media.

Here we describe a new, isomeric form of the quinoxaline-walled cavitand that showed dynamic behaviour and displayed good binding of small organic molecules. This modified cavitand **1** showed better solubility in water and showed a deeper aromatic cavity for small organic guests compared to cavitand **3**. The octaamino cavitand hydrochloric acid salt (**Cav-8NH$_3$Cl**) was prepared as reported previously by Mosca[28]. This salt was treated with K_2CO_3 and glyoxal then stirred at ambient conditions overnight, giving **2** in excellent isolated yield (Fig. 2). Compound **2** was refluxed in N-methyl

[a] *Center for Supramolecular Chemistry & Catalysis and Department of Chemistry, College of Science, Shanghai University, 99 Shang-Da Road, Shanghai 200444, China;*
[b] *School of Chemical and Enviromental Engineering, Shanghai Institute of Technology, 100 Hai-Quan Road, Shanghai 201418, China.*
**Corresponding Authors E-mail: yangyu2017@shu.edu.cn; +86 21 66136512*

*Dedication to Professor Julius Rebek, Jr.'s 75th birthday

†Electronic Supplementary Information (ESI) available: Characterization data, ^{1}H, ^{13}C, NMR, ESI-MS spectra, guest binding ^{1}H NMR spectra or other information in electronic format See DOI: 10.1039/x0xx00000x

imidazole at 90 °C and the water-soluble cavitand **1** was isolated in quantitative yield. Cavitand **1** was highly soluble (>25 mM) in water and showed a well-resolved ^{1}H NMR spectrum at 25 mM in D_2O. The cavitands **2** and **1** were obtained in pure forms from the reaction mixture without chromatography. All precursors and the water-soluble cavitand were characterized by ^{1}H, ^{13}C NMR spectroscopy and high-resolution electrospray mass (HR ESI-MS) spectrometry (ESI Fig. S1-8).

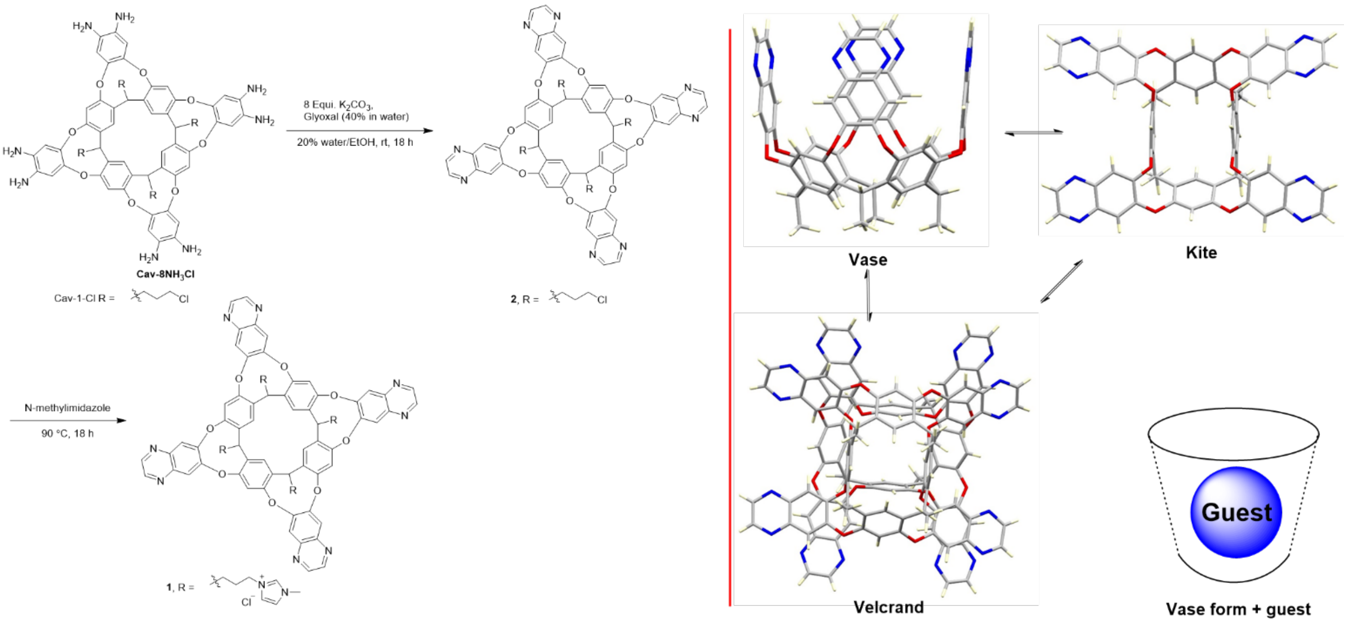

Fig. 2 Route for the synthesis (left) and structural conformations (right) of **1**, and a cartoon showing cavitand/guest complex, velcrand is formed by dimerization of the two molecules in kite form

The vase/kite/velcrand conformations of cavitands can be determined by ^{1}H NMR spectroscopy. The vase form has its characteristic methine protons chemical shift observed around 5.5 ppm, while the kite form the methine is reported to be below 4 ppm[20, 29, 30]. The new water-soluble cavitand **1** showed characteristic vase and kite conformation in different solvents as revealed by the ^{1}H NMR spectra in various solvents such as DMSO, methanol and water (Fig. 3 and ESI Fig. S9-12). In DMSO the characteristic methine proton chemical shift was observed at 5.51 ppm showing only the vase conformation while the other protons showed single sets of chemical shifts. In D_2O the characteristic chemical shift was observed at 3.91 ppm showing exclusively the kite conformation of this cavitand. The other protons showed multiple sets of chemical shifts showing the presence of this conformation in water. In deuterated methanol **1** showed a complex mixture of different conformations where the methine protons chemical shifts could be observed around 5.5, 5.2, 4.4, 4.2 and 3.9 ppm. This showed the existence of multiple conformations (vase, vase intermediate, velcrand and kite) in methanol.

Cavitand **1** was found exclusively in the kite or dimeric kite conformation (velcrand) in water. The most fascinating property of this cavitand was its complexation with a number of various cyclic guests. Upon binding with the guest, the kite form of this cavitand is converted to vase form while forming a cavity in which the hydrophobic guest (cyclic alkane guests) or hydrophobic part of the guest (cyclic acid guests) is captured. As mentioned earlier, upon binding with the guest the characteristic vase conformation methine protons chemical shift of **1** appeared downfield around 5.5 ppm and that is observed at 3.91 ppm for kite conformation. We found that cyclic alkanes could bind to **1** resulting in the vase form of the cavitand that was studied by ^{1}H NMR spectroscopy. The binding of the guest is achieved by folding and unfolding of the walls of the cavitand. This uptake and release of the guest is influenced by several factors that are well documented in previous studies with other related cavitands (e.g. **3**) including the hydrophobicity of the guest, solvent size and polarity. The sparingly or non-soluble cyclic alkane guests showed good occupation of the small cavity formed by **1**. The protons

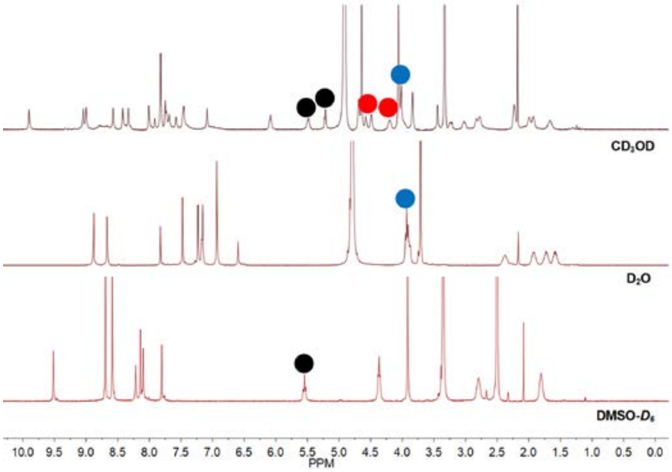

Fig. 3 Effect of solvents on the vase kite form of **1**; 1 mg of **1** was dissolved in 0.5 mL of particular deuterated solvent (from bottom to top, DMSO-d_6, D_2O, CD_3OD) and analysed by ^{1}H NMR spectroscopy. Black dots represent methine protons of vase form or vase intermediate form, red dots represent methine protons of velcrand form and blue dots represent methine protons of kite form.

chemical shifts for all these bound guests were observed upfield in the negative region of the spectrum caused by the shielding of the aromatic panels of the walls of **1**. Each guest acquired a specific position in the cavity depending on its size. A single chemical shift was observed for all protons of these guests indicating fast rotation of each cyclic compound in the cavity. This also showed that the guest is not fixed in the cavity but remains in constant motion. Bound cyclohexane signals were observed at - 3.34 ppm. Free cyclohexane's chemical shift in the absence of cavitand is assigned at 1.40 ppm while upon binding in **1** it is shifted up field $\triangle\delta$ = - 4.74 ppm. This is a larger value as compared to binding with **3**[31] (i.e. $\triangle\delta$ = - 3.58 ppm) (ESI Fig. S21-22). This larger upfield shift in **1** is possibly due to the deeper binding of the guest or the higher aromatic walls of the host. With an increase in the size of the cycloalkane, the chemical shifts were shifted upfield. In the case of cyclodecane, it was observed at - 2.24 ppm, showing a higher average position of the guest methylenes in **1** as compared to cyclohexane. The integration of the host methine protons and the guest methylene protons showed a 1:1 complex stoichiometry (Fig. 4 and ESI Fig. S11-14).

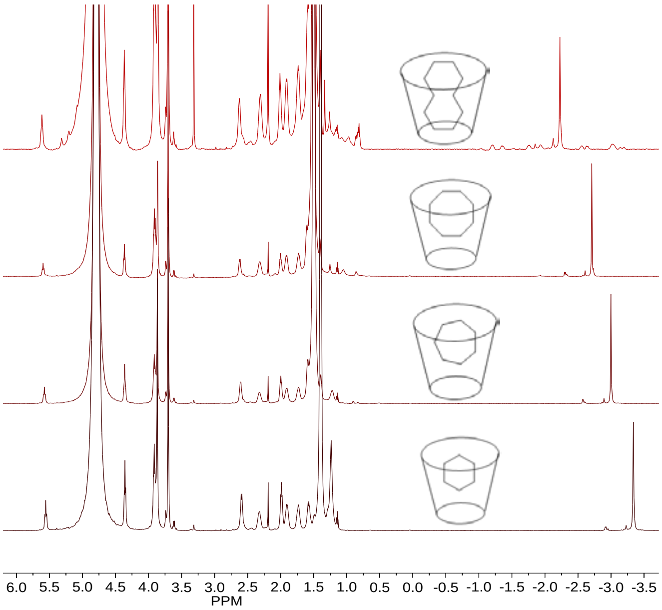

Fig. 4 Spectra of cavitand **1** in D_2O with bound guests. From bottom to top; **1** + cyclohexane, **1** + cycloheptane, **1** + cyclooctane, **1** + cyclodecane, excess of pure guest was added to 0.5 mL, 1 mM solution of **1** in D_2O, sonicated for 1 h and analyzed by ^{1}H NMR spectroscopy at rt.

We also tested the binding of various carboxylic acid guests and found that even water-soluble acids would be taken up by **1**. The proton signals for these bound guests were observed in the upfield region due to the anisotropic shielding provided by the aromatic walls. Each guest bound in a similar fashion with alkyl part inside the cavity at a depth corresponding to its size, while keeping the most hydrophilic function (COOH) exposed to the water solvent. This was also observed previously with the cavitand **3**[31]. The terminal methyl groups of 3-methylbutanoic acid showed a chemical shift at - 4.12 ppm showing their averaged position deep in the cavity, while for other acid guests the deepest methylene chemical shift was found above - 4.0 ppm. Accordingly, the methylenes are unable to reach as deep as the methyls of 3-methylbutanoic acid. The integration of the host methine proton and the guest protons showed a strict 1:1 complex formation (Fig. 5 and ESI Fig. S15-20).

Cavitand **3** was extensively studied in capturing different small organic molecule guests in D_2O and formed 1:1 host guest complexes. The size and hydrophobicity of the guest determined the depth of binding of the guest in the cavity of **3** (ESI Fig. S21-31). Interestingly, we found the binding of these organic small molecule guests showed further upfield shifts in the cavity of **1** when compared to those observed for **3**. In addition, water-soluble cyclopentyl carboxylic acid bound to **1** but not to **3** (ESI Fig. S26), indicating a somewhat stronger affinity of **1**. This property of **1** will be explored for other related guests and may bring applications in selective recognition of such small molecules.

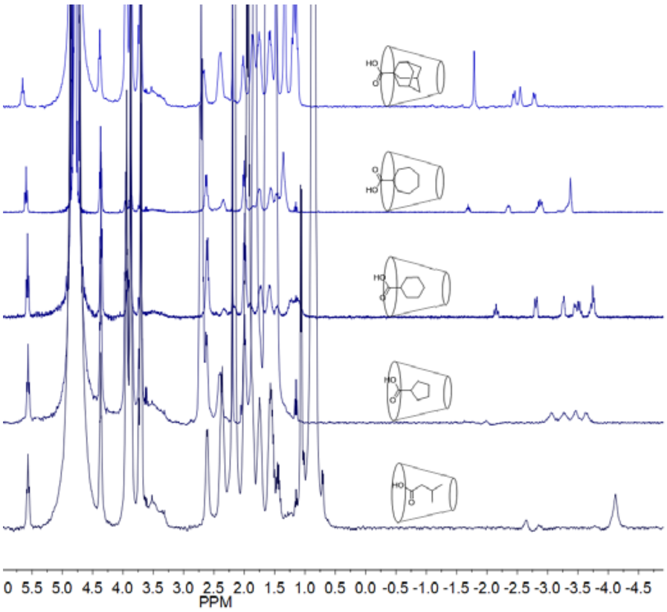

Fig. 5 Spectra of complexes of **1** in D_2O and guests from bottom to top; **1** + 3-methylbutanoic acid, **1** + cyclopentylcarboxylic acid, **1** + cyclohexylcarboxylic acid, **1** + cycloheptylcarboxylic acid, **1** + adamantanecarboxylic acid, excess of pure guest was added to 1 mM solution of **1** in D_2O, sonicated for 1 h and analyzed by ^{1}H NMR spectroscopy at rt.

In summary, a new and deeper cavitand that showed good solubility in water was prepared and characterized. Depending on the solvent, this cavitand existed in vase, kite or multiple forms. This water-soluble cavitand showed binding properties for small organic molecule guests such as cyclic alkanes and carboxylic acids. The easy synthesis, purification and good water solubility make it an improved platform for catalysis, sensing and molecular recognition in aqueous environments. The presence of N-donor atoms near the top of the quinoxaline rim may further be used for the coordination of metals for catalysis reactions of bound guest.

This work was supported by Chinese NSF (No. 21801164), US National Science Foundation (CHE 1506266 and CHE1213415) and by Shanghai University (N.13-0101-17-202), Shanghai, China. Dr. Yang Yu thanks the Program for Professor of Special Appointment (Dongfang Scholarship) of the Shanghai Education Committee.

Conflicts of interest

The authors declare no conflict of interest.

Notes and references

1. E. Dalcanale, P. Soncini, G. Bacchilega and F. Ugozzoli, *J Chem Soc, Chem Commun*, 1989, 500-502.
2. J. R. Moran, S. Karbach and D. J. Cram, *J Am Chem Soc*, 1982, **104**, 5826-5828.

3. J. M. C. Donald J Cram, *Container Molecules and Their Guests*, The Royal Society of Chemistry, 1997.
4. F. Durola and J. Rebek, Jr., *Angew Chem Int Ed Engl*, 2010, **49**, 3189-3191.
5. R. Pinalli, A. Pedrini and E. Dalcanale, in *Comprehensive Supramolecular Chemistry II*, ed. J. L. Atwood, Elsevier, Oxford, 2017, pp. 87-115.
6. F. D. A. Azov Vladimir, *Switching Processes in Cavitands, Containers and Capsules* Molecular Switches, Volume 1, Second Edition, Volume Editors, Prof. Dr. Ben L. Feringa Dr. Wesley R. Browne, 2011 Wiley-VCH Verlag & Co. KGaA, Boschstr. 12, 69469 Weinheim, Germany .
7. Y. Yu, Y.-S. Li and J. Rebek, *New J Chem*, 2018, **42**, 9945-9948.
8. S. Mecozzi and J. J. Rebek, *Chem Eur J*, 1998, **4**, 1016-1022.
9. S. Mosca, Y. Yu, J. V. Gavette, K. D. Zhang and J. Rebek, Jr., *J Am Chem Soc*, 2015, **137**, 14582-14585.
10. Q. Shi, D. Masseroni and J. Rebek, Jr., *J Am Chem Soc*, 2016, **138**, 10846-10848.
11. N. W. Wu and J. Rebek, Jr., *J Am Chem Soc*, 2016, **138**, 7512-7515.
12. L. S. Kaanumalle, C. L. Gibb, B. C. Gibb and V. Ramamurthy, *J Am Chem Soc*, 2004, **126**, 14366-14367.
13. R. J. Hooley, S. M. Biros and J. Rebek, Jr., *Angew Chem Int Ed Engl*, 2006, **45**, 3517-3519.
14. J. L. Hou, D. Ajami and J. Rebek, Jr., *J Am Chem Soc*, 2008, **130**, 7810-7811.
15. P. Restorp and J. Rebek, Jr., *J Am Chem Soc*, 2008, **130**, 11850-11851.
16. G. V. Oshovsky, D. N. Reinhoudt and W. Verboom, *Angew Chem Int Ed Engl*, 2007, **46**, 2366-2393.
17. Y. Yu and J. Rebek, Jr., *Acc Chem Res*, 2018, **51**, 3031-3040.
18. D. Masseroni, S. Mosca, M. P. Mower, D. G. Blackmond and J. Rebek, Jr., *Angew Chem Int Ed Engl*, 2016, **55**, 8290-8293.
19. J. J. Perry IV, J. A. Perman and M. J. Zaworotko, *Chem Soc Rev*, 2009, **38**, 1400-1417.
20. K. D. Zhang, D. Ajami and J. Rebek, *J Am Chem Soc*, 2013, **135**, 18064-18066.
21. J. H. Jordan and B. C. Gibb, *Chem Soc Rev*, 2015, **44**, 547-585.
22. K. D. Zhang, D. Ajami, J. V. Gavette and J. Rebek, Jr., *J Am Chem Soc*, 2014, **136**, 5264-5266.
23. J. R. Moran, J. L. Ericson, E. Dalcanale, J. A. Bryant, C. B. Knobler and D. J. Cram, *J Am Chem Soc*, 1991, **113**, 5707-5714.
24. D. J. Cram, H. J. Choi, J. A. Bryant and C. B. Knobler, *J Am Chem Soc*, 1992, **114**, 7748-7765.
25. F. Lagugne-Labarthet, Y. Q. An, T. Yu, Y. R. Shen, E. Dalcanale and D. K. Shenoy, *Langmuir*, 2005, **21**, 7066-7070.
26. L. D. Shirtcliff, H. Xu and F. Diederich, *Eur J of Org Chem*, 2010, **2010**, 846-855.
27. P. J. Skinner, A. G. Cheetham, A. Beeby, V. Gramlich and F. Diederich, *Helvetica Chimica Acta*, 2001, **84**, 2146-2153.
28. S. Mosca, Y. Yu and J. Rebek, Jr., *Nat Protoc*, 2016, **11**, 1371-1387.
29. P. Roncucci, L. Pirondini, G. Paderni, C. Massera, E. Dalcanale, V. A. Azov and F. Diederich, *Chem Eur J*, 2006, **12**, 4775-4784.
30. J. A. Bryant, C. B. Knobler and D. J. Cram, *J Am Chem Soc*, 1990, **112**, 1254-1255.
31. H.-N. Feng, M. Petroselli, X.-H. Zhang, J. Rebek Jr. and Y. Yu, *Supramol Chem*, 2019, 10.1080/10610278.10612018.11564830.