ORGANIC LETTERS

2008
Vol. 10, No. 17
3669−3671

Recognition of Guests by Water-Stabilized Cavitand Hosts

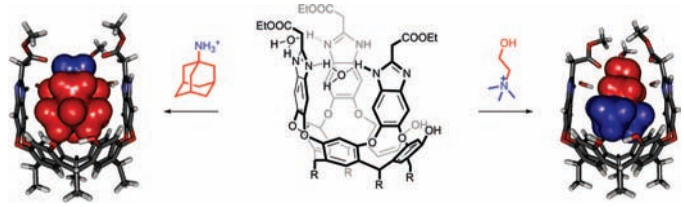
Agustí Lledó, Richard J. Hooley, and Julius Rebek, Jr.*

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

jrebek@scripps.edu

Received June 5, 2008

ABSTRACT



Water stabilized, deep cavitands with three walls and an open side are shown to be receptors for amines and ammonium cations bearing bulky aliphatic groups. The missing wall allows the binding of guests not accommodated by the four-walled counterparts.

Resorcinarenes are versatile modules for modern studies of molecular recognition.[1] The monomeric resorcinarene (e.g., **1**, Figure 1) and its simple derivatives show recognition properties, but their shallow curvatures cannot provide sufficient surface contacts for selecting between targets. Nonetheless, they bind ammonium ions, choline, acetylcholine, and carnitine in protic solvents.[2] Ideally, a synthetic receptor should provide a congruent surface and chemical complementarity to the target molecule: a large fraction of the target should be surrounded, but how much? Deepened cavitands are prepared by fusing four aromatic "walls" to the resorcinarene.[3] This increases the curvature of the cavitand's space. Cavitands with only three walls have been known since 1992,[4] but their recognition properties were discovered by Ballester only in 2006.[5] We describe here additional resorcinarene-derived cavitands with three walls and characterize their behavior in aqueous and organic media.

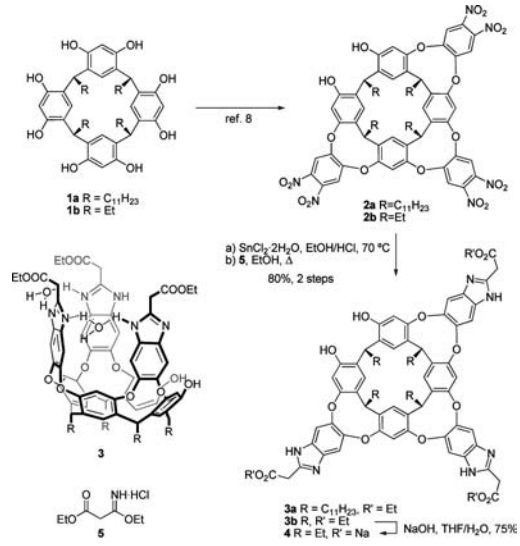


Figure 1. Synthesis of cavitands **3** and **4** and representation of **3** in the vase conformation.

(1) (a) Szumna, A. *Org. Biomol. Chem.* **2007**, *5*, 1358–1368. (b) Hayashida, O.; Ito, J.; Matsumoto, S.; Hamachi, I. *Org. Biomol. Chem.* **2005**, *3*, 654–660. (c) Saito, S.; Nuckolls, C.; Rebek, J, Jr. *J. Am. Chem. Soc.* **2000**, *122*, 9628–9630.

(2) (a) Lehn, J.-M.; Meric, R.; Vingeron, J. P.; Cesario, M.; Guilheim, J.; Pascard, C.; Asfari, Z.; Vicens, J. *Supramol. Chem.* **1995**, *5*, 97. (b) Atwood, J. L.; Barbour, L. J.; Junk, P. C.; Orr, W. *Supramol. Chem.* **1995**, *5*, 105. (c) Schneider, H.-J.; Schneider, U. *J. Org. Chem.* **1987**, *52*, 1613. (d) Murayama, K.; Aoki, K. *Chem. Commun.* **1997**, 119.

(3) (a) Dalcanale, E.; Soncini, P.; Bacchilega, G.; Ugozzoli, F. *J. Chem. Soc., Chem. Commun.* **1989**, 500–502. (b) Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1989**, *54*, 1305–1312. (c) Biros, S. M.; Rebek, J., Jr. *Chem. Soc. Rev* **2007**, *36*, 93–104. (d) Rudkevich, D. M.; Rebek, J., Jr. *Eur. J. Org. Chem.* **1999**, *9*, 1991–2005.

10.1021/ol801228b CCC: $40.75
Published on Web 07/26/2008

Deep cavitands with benzimidazoles on their upper rims allow the study of molecular recognition events in protic solvents.[6] Their vase-like conformations are stabilized (rather than disrupted) by water or alcohols because hydroxyl functions complete the hydrogen bond seam that helps maintain the shape of the receptor. The synthesis of two- and three-walled cavitands is low-yielding but has led to a number of intriguing applications.[7] We used the known hexanitroderivative[8] **2** to prepare the cavitand **3**. Reduction with tin(II) chloride then condensation with **5** gave the cavitand with **3** benzimidazole walls, each bearing an ester function. In addition, synthesis of the ethyl-footed analog **3a** and subsequent saponification gave a water-soluble cavitand **4**.

Although **3a** dissolves well in $CDCl_3$, its ^1H NMR spectrum shows broad and unassignable signals that sharpen upon addition of MeOH-d_4 (Figure 2).[9] The two methine

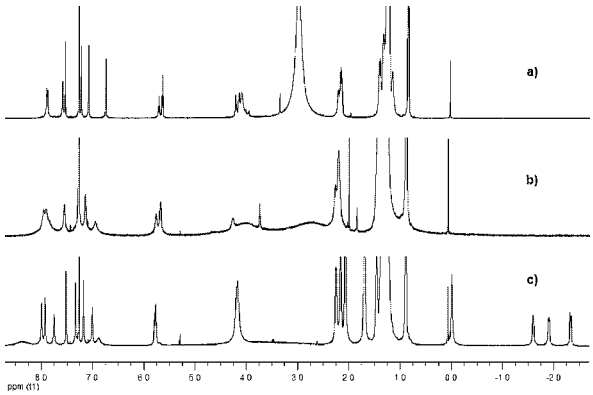


Figure 2. ^1H NMR spectra (600 MHz) of (a) **3a** in $CDCl_3$/5% CD_3OD, (b) **3a** in $CDCl_3/D_2O$ saturated, and (c) **3a** + **6a** in $CDCl_3/D_2O$ saturated.

resonances at 5.69 (H_a) and 5.62 (H_b) ppm indicate a vase conformation[10] that is occupied by solvent. The fourth methine proton at the site of the missing wall appears at 4.20 ppm.[11] Folding is less pronounced when using D_2O-saturated chloroform, but the presence of a suitable guest again brings well-resolved signals. Cavitand **3b** is only partially soluble in CD_2Cl_2/CD_3OD. It dissolves and forms a folded structure in THF-d_8/D_2O, but the organic solvent outcompetes potential guests in binding.

The large π-surfaces of the cavity are known to bind ammonium cations through cation-π and CH-π interactions.[3,5] Accordingly, we examined various amines, ammonium cations and adamantanes (**6**−**13**, Figure 3) as potential guests.

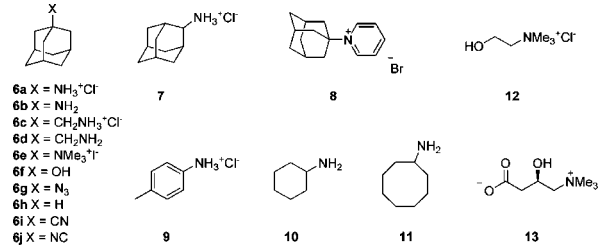


Figure 3. Structures of guests **6**−**13**.

Typically, the anisotropy imparted by eight aromatic walls induces upfield shifts of up to 5 ppm in the NMR signals of guests. Alkanes, for example, appear in the region 0 to −4 ppm. We found that both an amine/ammonium group and a bulky aliphatic region which properly fills the inner space appear necessary for binding (Table 1).

Table 1. Binding Constants for Guests **6**−**11**, Determined by ^1H NMR[a]

guest	K_a [100 M^{-1}]	guest	K_a [100 M^{-1}]
6a	2.4	**6e**	3.4[b]
6b	9.8	**6f**	
6c	1.6	**6g**	
6d	1.5	**6h**	
7	3.0	**6i**	
8	2.0	**6j**	0.04
9		**11**	0.49
10	0.37	**12**	4.2
		13	20.5

[a] In D_2O saturated $CDCl_3$ at 300 K, [**3a**] = 4−6 mM. [b] At 285 K.

An additional feature of **3a** is its selectivity in binding naturally occurring ammonium cations.[12] Both choline and carnitine, which are poorly soluble in water-saturated chloroform, were taken up, but acetylcholine was not.

The NMR signatures[13] of the encapsulated guests in the upfield region and molecular modeling studies[14] reveal that

(4) Soncini, P.; Bonsignore, S.; Dalcanale, E.; Ugozzoli, F. *J. Org. Chem.* **1992**, *57*, 4608–4612.

(5) Ballester, P.; Sarmentero, M. A. *Org. Lett.* **2006**, *8*, 3477–3480. (b) Sarmentero, M. A.; Ballester, P. *Org. Biomol. Chem.* **2007**, *5*, 3046–3054.

(6) (a) Far, A. R.; Shivanyuk, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 2854–2855. (b) Biros, S. M.; Ullrich, E. C.; Hof, F.; Trembleau, L.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 2870–2876. (c) Hooley, R. J.; Van Anda, H. J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 13464–13473. (d) Hooley, R. J.; Van Anda, H. J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 3894–3895. (e) Choi, H.-J.; Park, Y. S.; Song, J.; Youn, S. J.; Kim, H.-S.; Kim, S.-H.; Koh, K.; Paek, K. *J. Org. Chem.* **2005**, *70*, 5974–5981.

(7) (a) Azov, V. A.; Schlegel, A.; Diederich, F. *Angew. Chem., Int. Ed.* **2005**, *44*, 4635–4638. (b) Castro, P. P.; Zhao, G.; Masangkay, G. A.; Hernandez, C.; Gutierrez-Tunstad, L. M. *Org. Lett.* **2004**, *6*, 333–336. (c) Renslo, A. R.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2000**, *39*, 3281–3283.

(8) (a) Renslo, A. R.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 7459–7460. (b) Iwasawa, T.; Wash, P.; Gibson, C.; Rebek, J., Jr. *Tetrahedron* **2007**, *63*, 6506–6511.

(9) The broad methine resonances observed around 4 ppm suggest that the cavitand is in an open (kite-like) conformation and forms dynamic aggregates.

(10) Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826–5828.

(11) This is in good agreement with ref 2a.

(12) Ballester, P.; Shivanyuk, A.; Far, A. R.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 14014–14016.

(13) In the cases herein described, multiplicity and integration of bound guest peaks in the downfield region unequivocally allow one to determine which are the less shielded protons and, thus, the ones posed deep in the cavity.

different binding modes operate depending on the guest (Figure 4). Primary ammonium cations or amines are

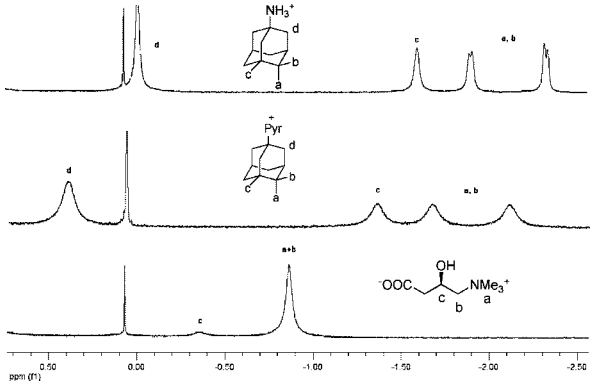


Figure 4. Upfield region in the ^{1}H NMR spectra of **6a**, **8**, and **13** and their assignments.

positioned appropriately to hydrogen bond with the groups on the cavitand's rim. Bulkier groups such as a trimethylammonium or a pyridinium can maintain an electrostatic interaction with the ester groups on the rim only if they protrude from the cavity.

Trimethylammonium guests with small hydrophobic regions such as choline or carnitine are accommodated with the trimethylammonium group positioned deep inside the cavity. For these guests, the hydroxyl and carboxylate functions can provide hydrogen bonding interactions with the groups at the rim. The ester group of acetylcholine appears unable to reach such binding sites.

The water-soluble cavitand **4** displays different host behavior. Saponification of **3b** gave **4**, as shown by ESI-HRMS (see Supporting Information), but when **4** was dissolved in D_2O, only broad signals were observed in the ^{1}H NMR spectrum. Four-walled cavitands of this type display broad signals in the presence of salts; most likely, the cavitands exist as velcrand dimers[6c,15] or larger, kinetically unstable aggregates (Figure 5).

Upon addition of excess 1-adamantanol **6f**, the ^{1}H NMR spectrum sharpened and peaks for folded cavitand binding 1-adamantanol were seen. The presence of a guest that correctly fills the hydrophobic cavity stabilizes the folded conformation of **4**, breaking up the aggregates and providing a sharp spectrum of a 1:1 complex. Attempts to extend the range of guests were unsuccessful; cavitand **4** is not a sufficiently strong host to extract hydrophobics such as hexane, cyclohexane, isooctane, or adamantane into solution, as its four-walled counterpart can.[6c] Other adamantane-based guests such as **6b**, **6d**, and **6e** did not fold the cavitand, presumably due to their higher water-solubility. Choline and

(14) Minimized structures for the complexes of a C1 analog of **3a** and different guests were obtained at semiempirical level (PM3) using Spartan 04 software.

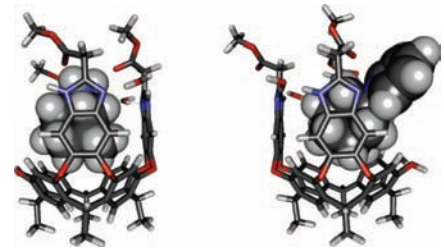


Figure 5. Side views of a simplified model for the complex **3**·2H_2O and **6a** (left) and **8** (right) showing different orientations of the adamantyl group.

acetylcholine also failed to break up the aggregates, although broad guest peaks were observed at δ −1 ppm, indicating some dynamic association of the guest and a folded host.

In conclusion, new water-stabilized, deep cavitand recognizes various amines and ammonium guests of different shapes. The synthesis of a water-soluble derivative was also achieved and shown to bind suitably-sized hydrophobic molecules in aqueous medium. The absence of a fourth wall allows the binding of bulky ammonium groups and appears as a promising template for more flexible receptors with improved selectivity for biologically relevant ammonium guests. These and the cavitands reported earlier[5] provide a bridge between more open-sided receptors[16] and the capsules that more or less completely surround their guests.[17]

Acknowledgment. We are grateful to the Skaggs Institute and the NIH (GM 50174) for support. A.L. thanks Fundación Ramón Areces (Spain) for a fellowship.

Supporting Information Available: Preparation and characterization data for compounds **3** and **4** and general procedures used for the binding experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801228B

(15) Moran, J. R.; Ericson, J. L.; Dalcanale, E.; Bryant, J. A.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 5707–5714.

(16) (a) Jeong, K. S.; Muehldorf, A. V.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 6144–6145. (b) Galán, A.; de Mendoza, J.; Toiron, C.; Bruix, M.; Deslongchamps, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 9424–9425. (c) Park, T. K.; Schroeder, J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 5125–5127.

(17) (a) Dong, V. M.; Fiedler, D.; Carl, B.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 14464–14465. (b) Ziegler, M.; Brumaghim, J. L.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 4119–4121. (c) Yoshizawa, M.; Kusukawa, T.; Fujita, M.; Yamaguchi, K. *J. Am. Chem. Soc.* **2000**, *129*, 6311–6312. (d) Iwasawa, T.; Mann, E.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 9308–9309. (e) Kawano, M.; Kobayashi, Y.; Ozeki, T.; Fujita, M. *J. Am. Chem. Soc.* **2006**, *128*, 6558–6559. (f) Fiedler, D.; Bergman, R. G.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6748–6751. (g) Sato, S.; Iida, J.; Suzuki, K.; Ozeki, T.; Fujita, M. *Science* **2007**, *313*, 1273–1276. (h) Murase, T.; Sato, S.; Fujita, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1083–1085. (i) Chen, J.; Rebek, J., Jr. *Org. Lett.* **2002**, *4*, 327–329. (j) Valdés, C.; Spitz, U. P.; Kubik, S. W.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1995**, 1885–1887. (k) Brody, M. S.; Schalley, C. A.; Rudkevich, D. M.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **1999**, *38*, 1640–1644. (l) Shivanyuk, A.; Rebek, J., Jr. *Chem. Commun.* **2001**, *237*, 4–2375. (m) Shivanyuk, A.; Rebek, J., Jr. *Chem. Commun.* **2001**, *242*, 4–2425.