ORGANIC LETTERS

2009
Vol. 11, No. 15
3163−3165

Cavitands with Mobile Walls

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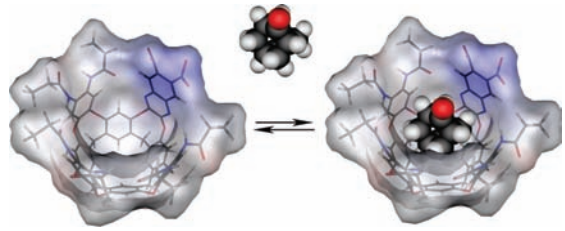
Received May 21, 2009

ABSTRACT



Deep cavitands having three fixed walls and one mobile wall were prepared. The longer wall, built from a quinoxaline spacer, showed enhanced NMR spectra of guests, but the shorter wall based on a benzene spacer showed tighter binding and slower exchange of guests.

Deep cavitands are receptors that more or less surround their targets but feature one open end. They form host−guest complexes by folding around their targets and temporarily isolating them from the bulk solvent. When properly derivatized, the cavitands present functional groups to guests[1] and impose interactions otherwise found only at the active sites of enzymes.[2] This arrangement of groups on host and guest can result in large rate accelerations,[3,4] organocatalysis,[5,6] and even the stabilization of otherwise labile reaction intermediates.[7,8] Access to greater volumes of space requires the incorporation of larger aromatic panels in the synthesis, and we report here our experiences with a quinoxaline "wall".

Cavitands are inevitably obtained from resorcinarenes using the synthesis devised by Högberg. The octol **1** (Figure 1) was condensed with 3 equiv of the benzene panels as previously described,[9] reduced, and then acylated to give the hexamide **2**, a molecule with recognition properties of its own.[10,11] Condensation with the 2,3-dichloro-6,7-dinitroquinoxaline gave the target dinitro compound **3** in 65%.

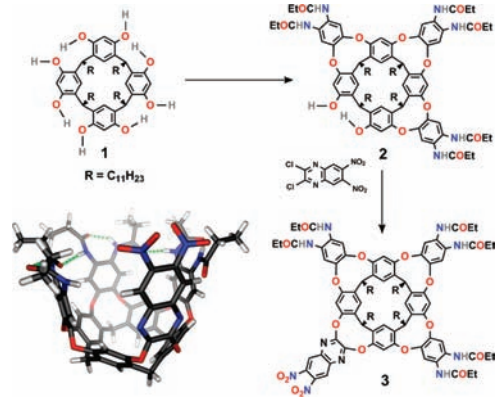


Figure 1. Synthesis of cavitand **3** and an energy minimized structure in the vase conformation.

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10.1021/ol9011037 CCC: $40.75
Published on Web 07/02/2009

Because of two intramolecular hydrogen bonds between amides on neighboring panels, the vase-like structure is stabilized as reported by the characteristic downfield shifts of the methine protons.[9] The overall arrangement of the six secondary amides can be clockwise or anticlockwise, and they interconvert at approximately the NMR time scale. Accordingly, the cavitands are chiral at any given instant but racemize rapidly on the human time scale. The racemization is fast enough to show only three types of methines and amide N−H resonances, although the latter signals are broadened in the NMR spectra (Figure 2).

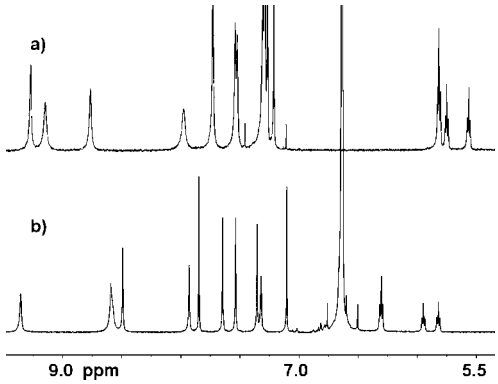

Figure 2. Downfield region of the ^{1}H NMR spectra (600 MHz): (a) **3** in $CDCl_3$ and (b) **3** in mesitylene-d_{12} at 300 K.

A series of guests were examined using deuterated mesitylene as the solvent (Figure 3). Trimethyl ammonium

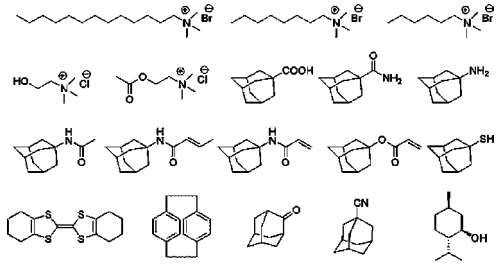

Figure 3. Line drawing of the guests that bind to the cavitand **3**.

ions provide an appropriate anchor for the cavitand through cation/π attractions, and their derivatives including choline and acetyl choline salts were readily bound. Even though they do not provide the polar interactions, adamantanes fill the cavitand's space properly and were good guests. Menthol gave a single complex in which the lone methyl group is directed deep into the tapered end of the cavitand, and the hydroxyl functionality can make contact with the secondary amides. The menthol hydrogens are also seen as a first order spectrum; the longer wall exposes most of the hydrogens of the guest to the anisotropy of the π surface and spreads out the signals (Supporting Information).

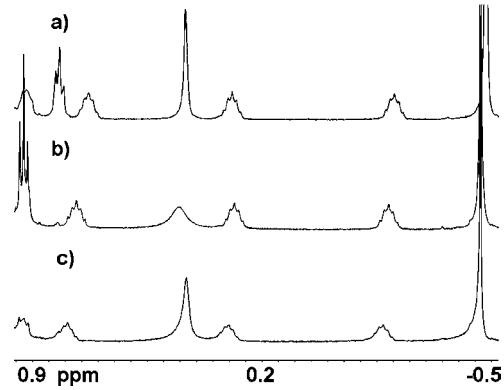

Figure 4. Upfield region of the ^{1}H NMR spectra of the cavitand **3** in mesitylene-d_{12} at 300 K with (a) *n*-tridecyl-trimethylammonium bromide, (b) *n*-octyltrimethylammonium bromide, and (c) *n*-hexyltrimethylammonium bromide.

The superior depth of the fourth wall is apparent in the upfield shifts of the methylene groups for the ammonium salts. Four methylenes of these guests can be found influenced by the anisotropy of this cavitand.[12]

One of the largest guests for resorcinarene-based cavitands is 2,2′-paracyclophane, and it was also taken up by **3**. While models show it was packed very tightly (Figure 5), the 2D NMR spectrum showed that motions were quite rapid inside. The paracyclophane spins along its long axis and tumbles[13]

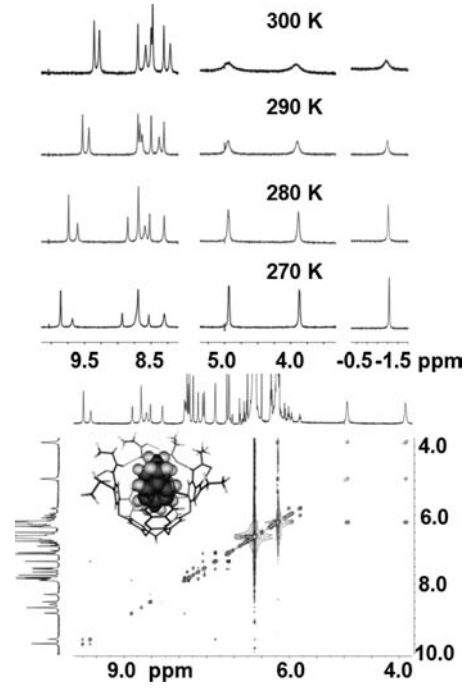

Figure 5. (Top) ^{1}H NMR (600 MHz) spectra of the cavitand **3** complex with paracyclophane in mesitylene-d_{12} at different temperatures. (Bottom) 2D ROSEY spectrum (600 MHz mesitylene-d_{12}) indicates that paracyclophane tumbles and also exchanges with free guest in the solution at the NMR time scale at 280 K.

while inside the cavity as shown by the appropriate cross peaks (Figure 5). Also, it was observed that it moves in and out of the cavitand. An activation barrier of 16.4 kcal/mol was found for the exchange process[14] at 280 K, and tumbling of the paracyclophane at the same temperature has an activation barrier of 15.2 kcal/mol. This is considerably less than the 17 kcal/mol[15] found earlier for the exchange of adamantane in and out of the related octamide cavitands which feature a complete seam of hydrogen bonds. For **3** only two such bonds need to be broken as the walls flip outward to expose the resident guest to the substitution reaction that constitutes exchange.

The "looseness" of the fourth (benzoquinoxaline) wall is also revealed by a 2D ROSEY spectrum showing that bound 2-adamantanone in **3** exchanges with free guest in solution at room temperature (Supporting Information) The activation barrier for this exchange measured to be 17.2 kcal/mol. The 2-adamantanone exhibits the same behavior with cavitand **4**, and 2D ROSEY spectroscopy revealed a slightly higher activation barrier (17.5 kcal/mol) for replacement of the guest.

We performed direct competition experiments between **3** and the cavitand with a shorter fourth wall, **4**, for a number of typical guests (Table 1). Unexpectedly, **4** proved to be by far the superior host. NMR titration experiments gave the association constants shown in Table 2 and confirmed the competition results.

Table 1. Guest Partitions in Competition Experiments with (1:1:1) Ratio of (Cavitand **3**:Cavitand **4**:Guest) in Mesitylene-d_{12} at 300 K

guest molecule	free guest (%)	in **4** (%)	in **3** (%)
1-adamantanecarbonitrile	50	50	0
N-(1-adamantyl)acetamide	10	90	0
2-adamantanone	20	65	15
menthol	8	92	0

Table 2. Binding Constants of Guests with **3** and **4** in Mesitylene-d_{12} at 300 K

guest molecule	binding in **4** (M^{-1})	binding in **3** (M^{-1})
N-(1-adamantyl)acetamide	8,300 ± 350	330 ± 15
2-adamantanone	2,200 ± 80	640 ± 25
menthol	>10,000 ± 450	80 ± 4

What causes the differences in binding and guest exchange rates? One possibility is a hydrogen bond between an anilide N−H donor and one of the nitro groups in **4**. This source of stabilization is precluded in **3** by distance. Another is the richer π electron surface of **4** vs **3** to complement the C−H bonds of the guests. Whatever the reason might be, the mobility of this fourth wall, apparently unattached to the other three walls, is reflected in the looser binding and more rapid in/out exchange of the guests. These dynamics should be advantageous for turnover in potential catalytic applications, which we are currently pursuing.

Acknowledgment. We are grateful to the Skaggs Institute for Research, and the National Institutes of Health (GM 27932) for financial support. S.X. is a Skaggs Post-Doctoral Fellow.

Supporting Information Available: Synthesis of cavitand **3** and ^{1}H NMR spectra of binding experiments of cavitand **3** and **4** with different guests. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9011037

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