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A Deep Cavitand with a Fluorescent Wall Functions as an Ion Sensor

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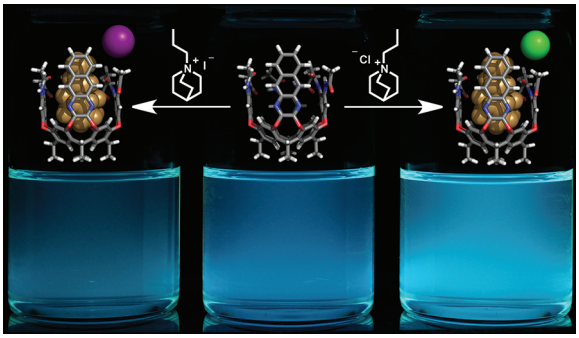
ABSTRACT



The synthesis and characterization of a deep cavitand bearing a fluorescent benzoquinoxaline wall is reported. Noncovalent host–guest recognition events are exploited to sense small charged molecules including acetylcholine. The cavitand also exhibits an anion dependent change in fluorescence that is used to differentiate halide ions in solution.

Developing sensors for biologically relevant ions and small molecules is a timely topic of research.[1] The versatility and sensitivity of photoluminescence have made it a favorite readout of sensor systems. Photophysical properties of luminescent molecules can be fine-tuned through a number of different interactions such as heavy atom effects; electron-, proton-, and energy-transfer processes; destabilization of excited states; and changes in electron density.[2] These interactions can quench ("turn-off") or enhance ("turn-on") the intensity of the fluorescent emission; these processes have been studied in many cavitands and capsules.[3] Numerous fluorescent sensors have been reported, and different analytes are targeted through covalent bonding or noncovalent interactions.[4] The controlled microenvironments of host molecules makes them appealing choices to sense analytes through noncovalent interactions. In particular, fluorescence spectroscopy and cavitand molecules offer unique opportunities to study noncovalent recognition processes. One approach has been to use the displacement indicator method[5] with nonfluorescent cavitands in combination with fluorescent guests.[6] Another method showed that calix[4]arenes with pyrene substituents appended to the lower rim exhibited changes in excimer emission upon guest binding.[7] Other calixarenes and resorcinarenes with fluorophores appended to the periphery have been shown to function as

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sensors.[8] Recently, a resorcin[4]arene with four organoboron "walls" was reported to exhibit a hypsochromic shift upon guest binding.[9] Here we detail an approach where the fluorescent functionality is one of the walls of a deep cavitand host, in which the guest analyte is placed in direct contact with the fluorophore. Upon guest binding the cavitand displays a bathochromic shift and an anion dependent change in fluorescence.

Cavitand **1** was synthesized in one step from known hexa-amide cavitand **3**.[10] The fourth wall is attached to the cavitand by two nucleophilic aromatic substitution reactions between 2,3-dichlorobenzoquinoxaline and the free phenols on **3** (Figure 1). Cavitand **1** features six amides positioned on the upper rim of the cavitand which form intramolecular hydrogen bonds, stabilizing the vase conformation. The fluorescent benzoquinoxaline completes the cavitand's concave structure and functions as the spectroscopic signal for host–guest studies. A control molecule (**2**), featuring the benzoquinoxaline functionality without the well-defined molecular space of cavitand **1**, was also synthesized (Figure 1).

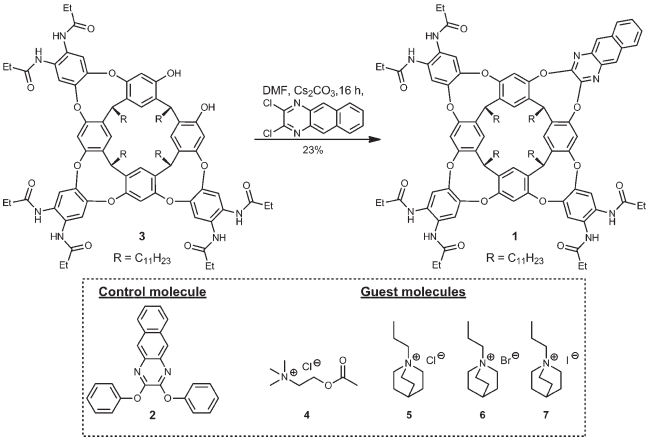

Figure 1. Synthesis of cavitand **1** (top). Control and guest molecules (bottom).

^{1}H NMR spectra in $CDCl_3$ reveal that cavitand **1** adopts a folded vase conformation but with broadened signals (Figure 2, bottom). This suggests a dynamic behavior different from that of the parent octa-amide system.[11] The fluxional behavior of cavitand **1** is a result of the extended benzoquinoxaline wall and the absence of two amide substituents. Interestingly, the addition of a guest molecule such as acetylcholine chloride (**4**) results in sharper signals characteristic of a kinetically stable complex (Figure 2, top).

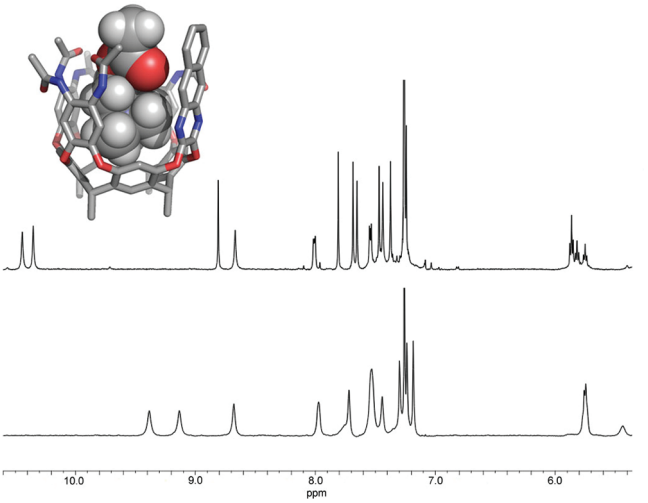

Figure 2. Select portions of the ^{1}H NMR spectrum of cavitand **1** in $CDCl_3$ at 300 K (bottom) and in the presence of acetylcholine chloride (**4**) (top). A CAChe MM3 minimized model of **1** and acetylcholine is provided in the upper left inset.

Cavitand **1** and control **2** display similar spectroscopic properties dictated by the benzoquinoxaline fluorophore. Both molecules are characterized by a broad absorbance centered at 365 nm that tails into the visible region resulting in yellow compounds. The green fluorescence of the 2,3-dichlorobenzoquinoxaline starting material is shifted to a blue fluorescence once integrated into compounds **1** and **2**. When excited at 365 nm these molecules emit a broad emission centered at 460 nm with quantum yields of $\Phi_F = 0.24$ for cavitand **1** and $\Phi_F = 0.19$ for control **2**. The structured microenvironment of the cavitand improves the quantum yield of this fluorophore. The characteristic blue fluorescence of these molecules is used to probe host–guest interactions in this system.

Cavitand **1** functions as a sensor for alkyl ammonium salts that are small enough to complement the receptor cavity. The addition of 5 equiv of acetylcholine chloride (**4**) to a $CHCl_3$ solution of cavitand **1** produces a bathochromic shift and an increase in fluorescence. The change in emission is attributed to the proximity of the cation and anion to the fluorophore (see below). A titration with this analyte results in isosbestic conversion (Supporting Information (SI)). The fluorescence of control molecule **2** is not altered by the same addition of guest, highlighting the necessity of the host–guest interaction (Figure 3). Tetra-*N*-butylammonium bromide—which

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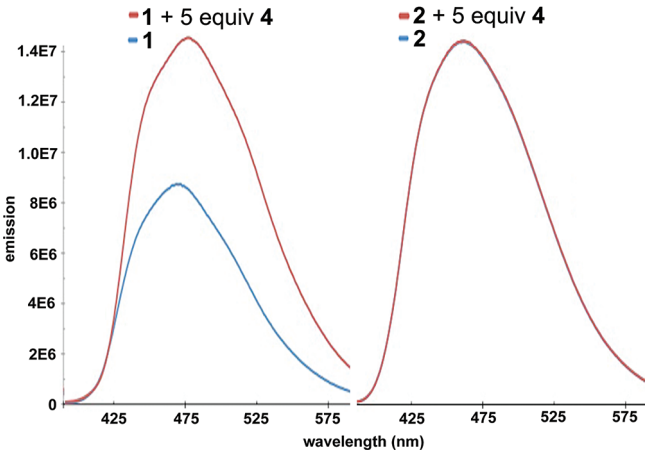

Figure 3. Acetylcholine chloride (**4**) induced fluorescence enhancement of cavitand **1** (left) and static fluorescene of control **2** (right, red and blue lines overlap completely) in $CHCl_3$ at 298 K.

does not fit into **1**—had minimal effect on the fluorescence spectrum (see SI).

Fluorescent sensors for anions are increasingly studied.[12] The guest binding and emission of **1** are dependent on the guest counteranion. To study this dependence we turned to *N*-propylquinuclidinium halide guests. ^{1}H NMR and NOESY spectra reveal that *N*-propylquinuclidinium binds to **1** with the propyl group directed toward the open end of the cavitand. The association constants of *N*-propylquinuclidinium guests **5**–**7** are 8.0×10^3 M^{-1} for **5**, 4.9×10^3 M^{-1} for **6**, and 2.3×10^3 M^{-1} for **7**. This trend is in accord with the most basic chloride forming the strongest hydrogen bonds with the amide protons on the upper rim of **1**. The ^{1}H NMR of these complexes corroborate this assertion with the greatest downfield shifts of the amide protons observed for the complex with **5** (Figure 4, bottom).

The fluorescence spectrum of **1** also showed a strong dependence on the counteranion of the guest.[13] Emission spectra were obtained for cavitand **1** with guests **5**–**7** (Figure 5). The chloride guest (**5**) produced an increase in fluorescence, while the bromide guest (**6**) led only to a small increase. Iodide is well-known for its fluorescence quenching capability,[14] and the iodide guest (**7**) resulted in a significant decrease in fluorescence which is likely due to a collisional quenching process of the excited state. The addition of other iodide salts to the cavitand (*N*-methylquinuclidinium iodide or *N*-propyl-*N*-methylpiperidinium iodide) also resulted in a decrease in fluorescence. The changes in emission are likely due to subtle effects from both the cation and anion. The cation binds to the host which rigidifies the structure and reduces the nonradiative energy transfer. Additionally, the close proximity of the

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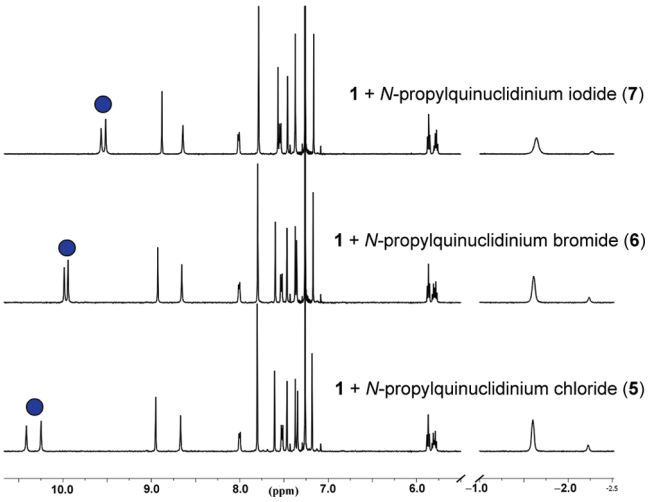

Figure 4. Select regions of the ^{1}H NMR spectra of cavitand **1** in $CDCl_3$ with 2 equiv each of *N*-propylquinuclidinium iodide (top), bromide (middle), and chloride (bottom). The shifted hydrogen bonding amide protons are noted by blue circles.

cationic charge polarizes the environment around the fluorophore resulting in altered emission. The anions collisionally quench fluorescence to varying degrees depending on their location and association with the upper rim of the cavitand. This interplay results in a balance between emission enhancement and quenching ultimately dictated by the anion.

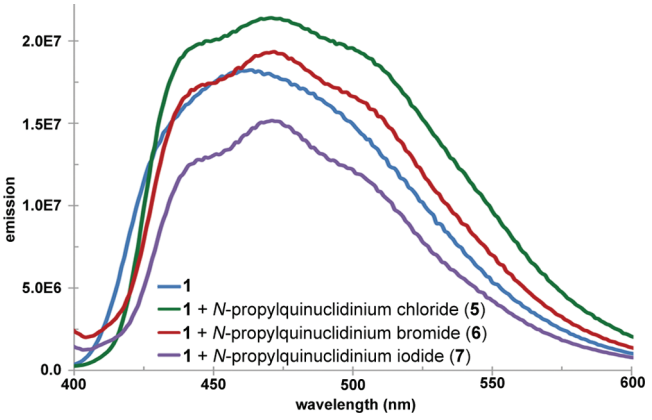

Figure 5. Anion dependent fluorescence of cavitand **1** in $CHCl_3$. *N*-Propylquinuclidinium chloride (**5**, green line) and bromide (**6**, red line) both produce fluorescence enhancement while *N*-propylquinuclidinium iodide (**7**, purple line) quenches fluorescence.

In conclusion, we report a deep cavitand containing a fluorescent benzoquinoxaline as one of the walls. The cavitand displays fluxional behavior in chloroform, but complexes kinetically stable on the NMR time scale are formed when good guests are introduced. The end result is

a deep cavitand that functions as a fluorescent sensor for ions. Future studies will explore other guest molecules for selective recognition.

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Supporting Information Available. Experimental procedures, UV−vis, fluorescence studies, and NMR data. This material is available free of charge via the Internet at http://pubs.acs.org