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## A light controlled cavitand wall regulates guest binding†

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### Abstract

Here we report a cavitand with a photochemical switch as one of the container walls. The azo-arene switch undergoes photoisomerization when subjected to UV light producing a self-fulfilled cavitand. This process is thermally and photochemically reversible. The reported cavitand binds small molecules and these guests can be ejected from the cavitand through this photochemical process.

Molecular devices on the nanoscale continue to attract attention,<sup>1</sup> and a variety of stimuli to drive the machinery are available. Changes in redox,<sup>2</sup> pH,<sup>3</sup> metal ion presence,<sup>4</sup> and other chemical inputs<sup>5</sup> have been used to cycle between well-defined molecular states, but perhaps the oldest—and one of the most frequently used stimuli—is light. In supramolecular devices the *trans/cis* photoisomerism of the azo benzene module provided the first switching mechanism applied to the binding behavior of cyclodextrins<sup>6</sup> and crown ethers.<sup>7</sup> Its ease of introduction, reliable shape and distance changes and broad applicability, even to foldamers<sup>8</sup> and biological molecules such as proteins comprising ion channels,<sup>9</sup> have insured the popularity of the photoisomerization process. Surprisingly, the azobenzene module has not appeared in deep cavitands and we correct that omission here.<sup>10</sup>

In contrast to most photo-switchable devices—where the photo-responsive unit is appended on the structure's periphery to impart function—we integrated it into the cavitand's structure. We devised two light-responsive cavitands that exhibit very different guest binding behavior when exposed to light. Control of guest uptake and release is achieved through an unusual conformational preference, but only when a *tert*-butyl group is present on the azo-arene substituent. The switching is dictated by weak attractive forces and not through typical covalent bonds or steric constraints.

We prepared azo cavitands **1** and **2** in one step from the known mono-amine cavitand **3**<sup>11</sup> (Scheme 1). Mixing nitrosoarenes<sup>12</sup> at room temperature in glacial acetic acid with cavitand **3** resulted in the precipitation of pure azo-arene cavitands as orange solids (see ESI<sup>†</sup> for <sup>1</sup>H, <sup>13</sup>C NMR and mass spectrometry characterization data).

In the resting configuration azo-arene cavitands *trans*-**1** and *trans*-**2** present deep cavities for guest binding. Upon irradiation with UV light, the azo substituent undergoes photoisomerization to produce *cis*-**1** and *cis*-**2**. The *tert*-butyl substituent of **1** was expected to fold into and occupy the cavitand void where it can enjoy stabilizing CH– $\pi$  interactions.

†Electronic supplementary information (ESI) available: Characterization details, equilibrium studies, computations and kinetics of photoisomerization. See DOI: 10.1039/c0cc03865b

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In contrast, the unsubstituted azo cavitand *cis-2* can neither reach the same CH- $\pi$  distances nor adequately fill the space.

The switching capabilities of **1** and **2** were investigated in *d*<sub>12</sub>-mesitylene. Both cavitands present only *trans* configuration by <sup>1</sup>H NMR after heating to reflux and cooling to room temperature in the dark. Under ambient conditions a small percentage of *cis* cavitand is observed, 8% for **1** and 5% for **2**.<sup>13</sup>

Computational and crystallographic studies reveal that *cis*-azobenzene derivatives adopt a non-planar conformation with a CCNN dihedral angle of ~53°. <sup>14</sup> Photoisomerization converts both cavitands to their respective *cis* configurations but with different consequences. Irradiating cavitand **2** with 365 nm light for 15 minutes converts it to *cis-2* where it can adopt numerous *cis* conformations. In contrast, the photoisomerization of cavitand **1** places the *tert*-butyl substituent *inside* the cavitand in a contorted conformational preference.

This isomerization can be monitored by <sup>1</sup>H NMR. Exposing *trans-1* (Fig. 1, bottom) to 365 nm light for 15 minutes converts it to the self-contained *cis-1* (Fig. 1, top); the shielded magnetic environment of the cavitand's interior causes the characteristic upfield shift of the *tert*-butyl group to -2.2 ppm (see ESI<sup>†</sup> for NOE analysis). *Cis-1* and *cis-2* revert to their *trans* configurations by heating to 164 °C for 5 minutes or irradiating with 450+ nm light for 20 minutes. This switching cycle can be repeated 5 times without detectable degradation of the system.

Cavitands **1** and **2** feature a cavity defined by 8 aromatic panels. This concave surface is suited to complement neutral or cationic small molecules of appropriate shape and size. Adamantane derivatives, for example, are taken up by *trans-1* in *d*<sub>12</sub>-mesitylene with binding constants ranging from 5 to >600 M<sup>-1</sup> (Table 1). The exchange rates of these guests in and out of the cavity are slow on the NMR time scale and separate (upfield) signals are seen for the bound adamantane guests. The largest association constants are observed for adamantanes **7** and **8** which are stabilized by hydrogen bonding and polar interactions with the upper rim of the cavitand. Cavitand **2** binds the same adamantane guests with similar trends in affinity and magnitude as those observed for **1** with association constants ranging from 6 to >700 M<sup>-1</sup>.

The effect of UV radiation on guest binding was different for the two types of cavitands. When cavitand **2** adamantane complexes were subjected to UV light, there was no change in the concentrations of bound guest.<sup>15</sup> Only the magnetic environment of the guest was altered. Fig. 2 shows the relevant spectra of cavitand **2** containing 2-adamantanone (**8**) in both the *trans* (top) and *cis* (bottom) configuration. The broadened <sup>1</sup>H NMR spectrum observed for *cis-2* is due to the multiple *cis* conformations that cavitand **2** adopts when a guest molecule is present. The rate of the switching process in the presence of guest molecules is slightly retarded and can be achieved by heating or application of light (ESI<sup>†</sup>). However, bound adamantane signals are present in either cavitand configuration confirming that light cannot be used to control guest uptake and release in **2**.

In contrast, light does control the uptake and release of adamantane guests in cavitand **1**. Exposing its host/guest complexes to UV light for 15 minutes forces out the resident guests and replaces them with the inwardly-directed *tert*-butyl group. For instance, the bound guest 2-adamantanone (**8**) exhibits 5 upfield signals (Fig. 3, red squares, bottom); after UV irradiation, these signals disappear as 2-adamantanone is released into solution (Fig. 3 middle). The process is reversed by heating the system to 164 °C for 5 minutes (Fig. 3, top) or by application of visible light for 20 minutes where it reaches a photostationary state of 71% *trans-1*. The process was cycled 5 times without noticeable degradation. Light can be

used to completely control the uptake and release of all adamantane guests (**4–8**) in cavitand **1**.

The well-defined molecular environments of cavitands have afforded numerous applications.<sup>16</sup> Although the conformations of these molecules can be manipulated by temperature,<sup>17</sup> pH<sup>18</sup> or metal ions,<sup>19</sup> there are few methods that reversibly control guest binding. Diederich and co-workers used acid/base chemistry to control the uptake and release of cycloalkanes,<sup>20</sup> and we have used metal ions to manipulate a self-included “ouroborand” cavitand.<sup>21</sup> These systems function well, but less invasive switching processes are also desirable.<sup>22</sup> The two new cavitands presented here respond to light and heat by changing their conformations, but only the *tert*-butyl substituted **1** forces guests out upon irradiation. The process is reversible and can be cycled numerous times. The control of guest binding underscores the subtle influence of appropriate filling of space in recognition processes.<sup>23</sup>

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

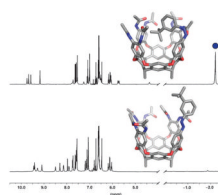
## Acknowledgments

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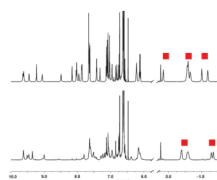
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10. Two examples of azo-arenes attached to resorcin[4]arenes have been reported. However, these molecules are not deep cavitands and their guest binding function was not investigated, see: (a)

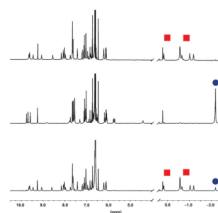
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  12. The synthesis of 3-tert-butyl nitrosobenzene is adapted from the literature procedure: Defoin A. *Synthesis* 2004:706–710. Experimental details can be found in the ESI<sup>†</sup>.
  13. The photostationary state is dependent on the conditions employed. For instance, after heating in the dark, nearly all of **1** persists in the *trans* conformation for extended periods of time (Fig. 1, bottom). Under ambient conditions a small amount of *cis*-**1** is present. The quartz metal halide light employed in later experiments produces even more *cis*-**1** at that photostationary state.
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  15. Only in experiments where a minimal amount of the weakest guests are present did we observe a slight decrease in the amount of bound guest.
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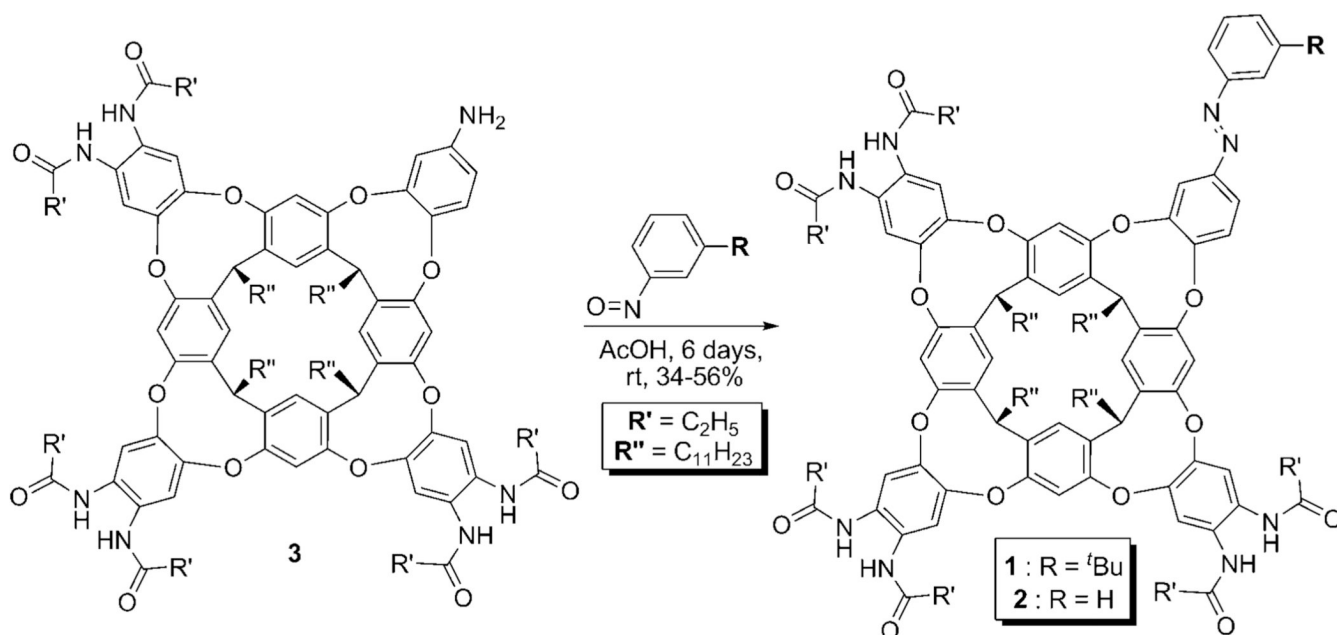
**Fig. 1.**  $^1\text{H}$  NMR spectra in  $d_{12}$ -mesitylene showing *trans*-**1** (bottom) and self-contained *cis*-**1** (top). The inverted *tert*-butyl signal is marked by a blue circle.



**Fig. 2.**  $^1\text{H}$  NMR spectra in  $d_{12}$ -mesitylene showing cavitant **2** binding 2-adamantanone (**8**, 9.3 eq.) both in the *trans* configuration (top) and *cis* configuration (bottom). The guest remains bound when cavitant **2** is in either configuration and the bound guest signals are marked with red squares.



**Fig. 3.** Select regions of the  $^1\text{H}$  NMR spectra in  $d_{12}$ -mesitylene illustrate how UV light affects guest binding in **1**. Complex with **8** (7.8 eq.) before UV irradiation (bottom), after UV irradiation (middle) and after heating to 164 °C for 5 minutes (top). Signals for bound 2-adamantanone (**8**) are marked by red squares; the introverted *tert*-butyl is marked by a circle.



**Scheme 1.**  
Synthesis of azo cavitands **1** and **2**.



**Table 1**Association constants of **1** and **2** with adamantane guests **4–8**<sup>a,b</sup>

Guests	<b>1</b>	<b>2</b> $K_a/M^{-1}$
1-Adamantanemethanol ( <b>4</b> )	5	6
1-Chloroadamantane ( <b>5</b> )	37	45
1-Adamantaneamine ( <b>6</b> )	166	145
1-Adamantanecarbonitrile ( <b>7</b> )	311	226
2-Adamantanone ( <b>8</b> )	653	703

<sup>a</sup>The  $K_a$  ( $M^{-1}$ ) values are the average of 3–6 experiments with errors estimated at 20% (see ESI†).

<sup>b</sup>All experiments were performed in *d*<sub>12</sub>-mesitylene at 300 K, with initial [**1**] or [**2**] = 2.3 to 5.8 mM.