



# Synthesis of elongated cavitands via click reactions and their use as chemosensors



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## ARTICLE INFO

### Article history:

Received 14 April 2013

Received in revised form 17 June 2013

Accepted 11 July 2013

Available online 18 July 2013

### Keywords:

Cavitand

Azide–alkyne cycloaddition

Copper

Iron

Palladium

## ABSTRACT

A very efficient modular reaction protocol was developed to attach various functionalities to a rigid cavitand scaffold. In this way, aryl, iodoaryl, benzyl, pyrrolidylmethyl groups, as well as a polyethylene-glycol chain were attached to the ‘triazol-level’ of the cavitand. The palladium-catalyzed ethynylation of the iodoarene moieties, followed by the copper(I)-catalyzed azide–alkyne cycloaddition produced novel cavitands with significantly elongated binding pockets. The dimensions of these molecules are calculated to be at least  $9 \text{ \AA} \times 18 \text{ \AA}$ , which place them amongst the largest *unimolecular* hosts obtained by pure covalent synthesis. A cavitand-based click conjugate is used for selective complexation of  $\text{Cu}^{2+}$  and  $\text{Fe}^{3+}$ , providing significant fluorescent quenching.

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## 1. Introduction

Cavitands are a class of molecular hosts containing sizeable internal cavities suitable for reversible molecular inclusion.<sup>1</sup> Cavitands and related cage-like structures show promise with potential applications as gas sensors, fluorescent probes, nano-reactors and drug delivery systems.<sup>2,3</sup> In our current research program, we aim to extend the inner cavity of such molecular containers through a modular strategy.<sup>4,5</sup> Click reactions, both minimizing the generation of hazardous substances and maximizing the reaction efficiency, are excellent representatives of the ‘green chemistry’ approach, an important contribution to sustainable development. The synthetic utility and simplicity of the very efficient copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC),<sup>6–8</sup> coupled with a wide variety of readily available azide derivatives, opens up the avenue to the facile synthesis of highly extended macrocycles. The click coupling has recently been applied to cavitands for attaching guanosine<sup>9</sup> or uridine<sup>10</sup> moieties as well as macromolecular side chains<sup>11</sup> via triazole linkers, or

alternatively, for covalently linking two macrocycle units.<sup>12,13</sup> Herein, we expand further the applicability of this versatile methodology by the synthesis of a novel series of elongated cavitands.

Click-derived triazoles have recently emerged as potential chemosensors due to their ability to bind both cations and anions. Sensitive reporting signals may arise from a binding event, a chemical reaction, a redox process or a conformational change.<sup>14</sup> Calixarenes are known to provide a convenient platform for positioning two<sup>15–18</sup> or four<sup>19</sup> triazole units in close proximity. These conjugates obtained by click chemistry were used to detect various metal ions including  $\text{Hg}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Cr}^{3+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Zn}^{2+}$  and  $\text{Cd}^{2+}$  through a photophysical change upon a binding event. The selectivity of the designed chemosensors greatly depended on the specific structural motifs that were incorporated into the macrocycle.

Here we report the first cavitand-based click conjugate that is used for selective complexation of  $\text{Cu}^{2+}$  and  $\text{Fe}^{3+}$ . These redox active metals undergo redox cycling reactions producing highly reactive radicals, which may eventually lead to oxidative stress in humans.<sup>20</sup> Therefore, it is very important to be able to monitor the presence of such metals. In contrast to the calixarene-based fluorescent probes that contained *pendant* functionalities for metal detection,<sup>15–19</sup> in our design the four triazole binding sites are attached on a more rigid cavitand framework, which

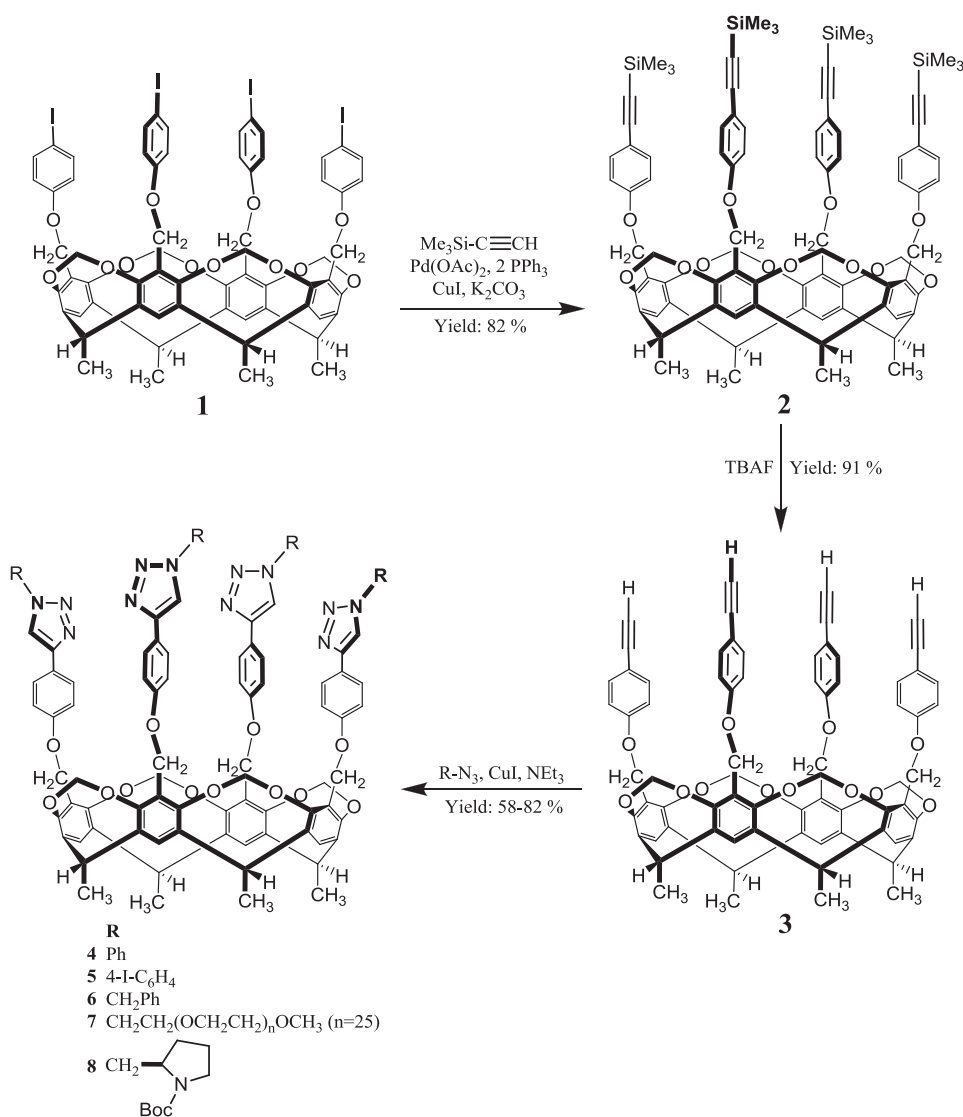
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may create a more rigid, pre-organized, electron-rich binding pocket.

## 2. Results and discussion

Tetraiodocavitand (**1**), bearing four excellent leaving groups, was synthesized in four consecutive steps according to our well-established protocol.<sup>5</sup> Trimethylsilyl-ethynyl functionalities were placed on the upper rim of the cavitand scaffold under typical Sonogashira-coupling conditions (**2**, Scheme 1). Deprotection of **2** with TBAF·3H<sub>2</sub>O in tetrahydrofuran afforded the corresponding tetra(ethynyl)cavitand (**3**) that was subsequently used as a coupling partner in fourfold CuAAC reactions. In this study, the commercially available azidobenzene, 1-azido-4-iodobenzene, benzyl azide, poly(ethylene glycol) methyl ether azide (PEG average  $M_n$  1000) and (*R*)-2-(azidomethyl)-1-Boc-pyrrolidine were used in the click coupling procedure in the presence of CuI at rt. In all cases, the <sup>1</sup>H NMR resonance corresponding to the terminal alkyne (3.01 ppm) was completely lost and replaced by the resonances of the aromatic protons of the triazole rings in the range of 7.70–9.14 ppm. All derivatives were fully characterized by IR, <sup>1</sup>H and <sup>13</sup>C NMR as well as by MS techniques (see Experimental section). The GPC characterization

of **7** revealed an average molecular weight of  $M_n=5800$  along with a narrow polydispersity (1.11), and the average number of repeat units was calculated to be  $n=25$ . Both the GPC and NMR analysis confirmed the quantitative coupling between cavitand **3** and the linear PEG chains. It is important to note that all reactions afforded the expected cavitand-based conjugates in good yields (58–82%), and in the course of this multistep synthesis starting from the condensation reaction of 2-methylresorcinol and acetaldehyde, no time-consuming chromatography was needed. Simple trituration of the products with MeOH usually afforded sufficiently pure materials. The developed procedure allowed us to extend significantly the inner cavity of these cavitands, and furthermore, incorporate various functionalities, such as additional aromatic walls (**4**, **5**, **6**), long PEG chains (**7**) and stereogenic centres (**8**). This study proved very well the high versatility and functional group tolerance of the CuAAC reaction on our macrocyclic platform. Moreover, it was expected that the addition of PEG side chains to the cavitand core could cause a change in its solubility in water. Indeed, unlike the other novel cavitand derivatives, the PEGylated cavitand (**7**) exhibited enhanced solubility in water ( $>25 \text{ mg mL}^{-1}$ ). On the other hand, the synthesis of a cavitand–aryl iodide conjugate (**5**) offers promise for further extension of this cavitand skeleton.



Scheme 1. Synthetic route to the novel click-based cavitands (**4**–**8**).

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