



## A [2]catenane containing an upper-rim functionalized calix[4]arene for anion recognition

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### ABSTRACT

A novel [2]catenane is synthesized in good yield from an upper-rim functionalized calix[4]arene macrobicycle and a nitro-substituted isophthalamide threading component in the presence of a chloride anion template via a ring-closing metathesis (RCM) reaction. After halide anion template removal the resulting catenane host exhibits a high degree of selectivity for chloride in competitive organic solvent mixtures.

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Interlocked structures, in particular rotaxanes and catenanes, have long held the interest of the supramolecular community.<sup>1,2</sup> While originally thought of as just a curiosity due to their aesthetically pleasing and topologically interesting nature, the construction of interlocked systems of increasing complexity and functionality has become, in itself, a leading area of research. Although there is currently much interest in the incorporation of rotaxanes and catenanes into molecular switches and machines,<sup>3–6</sup> the potential of these molecules to function as selective host systems in molecular recognition applications has been largely overlooked. This is somewhat surprising given their unique three-dimensional topological binding cavities. Indeed, using anion templation we have recently synthesized a variety of interlocked host structures which exhibit high degrees of selectivity toward chloride<sup>7–9</sup> and sulfate<sup>10,11</sup> guest species.

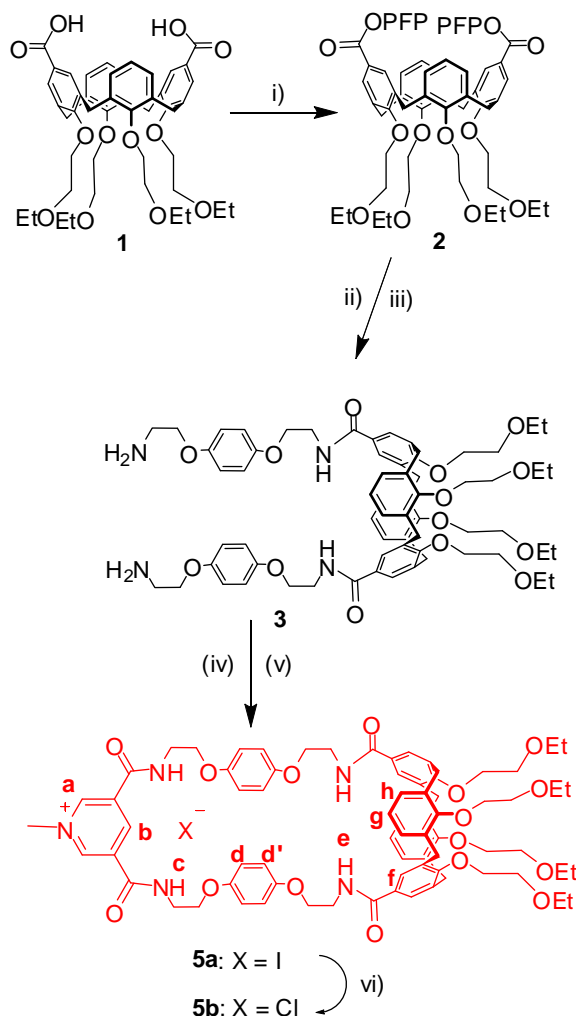
Calixarenes are well-defined molecular scaffolds that are renowned for their versatility and ease of functionalization at both the lower and upper rims.<sup>12</sup> As such, the use of these structures in interlocked assemblies has attracted much interest over the years. For example, these versatile molecules have been used as both molecular wheels<sup>13–16</sup> and stoppers<sup>17</sup> in the formation of rotaxanes. Meanwhile their pre-organized nature and ability to encapsulate guests<sup>18</sup> have led to the development of tetraurea hydrogen-bonded dimers that have been subsequently used in the synthesis of a series of multicyclic catenanes<sup>19–21</sup> and rotaxanes.<sup>22,23</sup> Furthermore, incorporation of both electron-rich<sup>24,25</sup>

and electron-poor<sup>26,27</sup> aromatic systems into the calixarene framework has led to a number of catenanes utilizing  $\pi$ - $\pi$  stacking interactions.

With the longer term aim of fabricating interlocked host systems onto surfaces for anion sensory device applications<sup>28</sup> we have begun to incorporate the calix[4]arene framework into catenane molecular structures. In our first example, a lower-rim functionalized calix[4]arene [2]catenane was prepared.<sup>29</sup> Herein we describe the synthesis of a novel [2]catenane containing an upper-rim functionalized calix[4]arene via exploitation of a strategic anion templation methodology.<sup>30,31</sup>

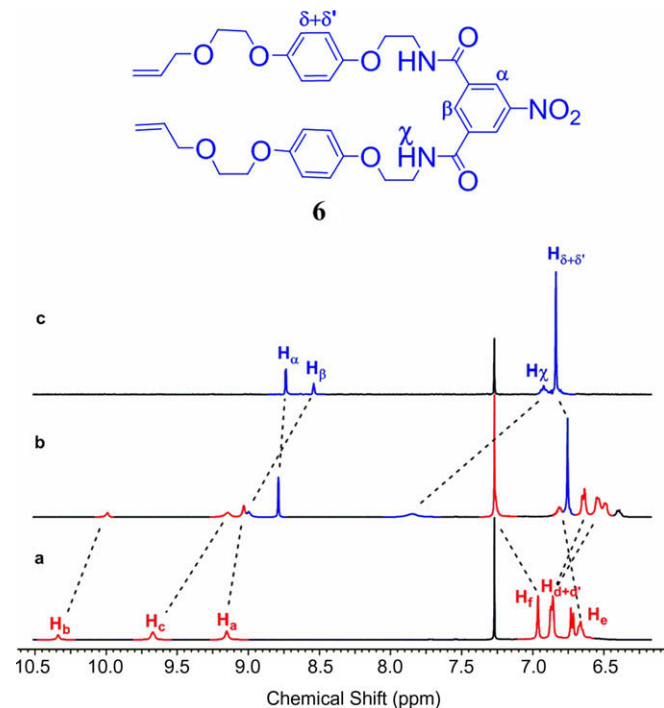
Synthesis of the new upper-rim calix[4]arene macrobicyclic component of the catenane **5b** is depicted in **Scheme 1**. Starting from calix[4]arene,<sup>32</sup> the upper-rim bis acid-functionalized calix[4]arene **1** was prepared, using the literature procedures.<sup>33–35</sup> Conversion of **1** into the activated pentafluorophenol (PFP) ester derivative **2** was achieved utilizing dicyclocarbodiimide (DCC) as a coupling reagent in dichloromethane. Treatment of **2** with 2-(4-(2-azidoethoxy)phenoxy)ethanamine (see **Supplementary data**) in the presence of triethylamine resulted in the formation of a bis-azide which, upon reduction with hydrogen, gave the bis-amine **3**. Reaction of this species under high dilution conditions with pyridine-3,5-dicarbonyl dichloride gave upper-rim functionalized calix[4]arene macrobicycle **4** in 50% yield (see **Supplementary data**) which was subsequently alkylated with methyl iodide to give the pyridinium-derivatized macrocycle **5a**. Anion exchange using saturated aqueous ammonium chloride solution afforded the calix macrobicycle as the desired chloride salt **5b**, as confirmed by the respective downfield shifts of protons  $H_b$  and  $H_c$  due to stronger hydrogen-bonding interactions with chloride.

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**Scheme 1.** Reagents and conditions: (i) PFP, DCC,  $\text{CH}_2\text{Cl}_2$ , 85%; (ii) 2-(4-(2-azidoethoxy)phenoxy)ethanamine,  $\text{CH}_2\text{Cl}_2$ ,  $\text{NEt}_3$ , 50%; (iii) Pd/C,  $\text{H}_2$ , 100%; (iv) pyridine-3,5-dicarbonyl dichloride,  $\text{NEt}_3$ ,  $\text{CH}_2\text{Cl}_2$ , 50%; (v) MeI,  $\text{CH}_3\text{COCH}_3$ , 95%; (vi) sat  $\text{NH}_4\text{Cl}(\text{aq})$ , 95%.

To ascertain the ability of calix[4]arene macrobicyclic **5b** to form pseudorotaxanes as precursors to the desired catenane,  $^1\text{H}$  NMR studies were undertaken with a previously synthesized nitro-substituted isophthalamide thread **6** (Fig. 1).<sup>8</sup> Addition of an increasing concentration of thread **6** to macrobicyclic **5b** in  $\text{CDCl}_3$  produced a number of shifts in the  $^1\text{H}$  NMR spectra which indicated pseudorotaxane formation. Firstly, significant upfield shifts of the respective hydroquinone protons of both the thread and macrocycle were observed. These can be attributed to  $\pi$ – $\pi$  stacking interactions between the electron-rich hydroquinones and the complementary electron-deficient pyridinium and nitro-isophthalamide groups of the macrocycle and thread. In addition to these observations, marked upfield shifts of the protons of the macrocycle involved in hydrogen bonding to the chloride counterion ( $H_b$  and  $H_c$ ) were evident. These changes are consistent with the introduction of a competing binding site for chloride, and as such, protons  $H_b$  and  $H_c$  of the thread were seen to move downfield concurrently. Further evidence for pseudorotaxane formation and the relative orientation of the two components to each other could be obtained from the comparative downfield shifts of protons located at the upper rim of the calixarene. Both the amide protons,  $H_e$ , and those of the aromatic ring involved in the macrobicyclic,  $H_f$ , are observed to move downfield, which in conjunction with the other changes seen can be attributed to



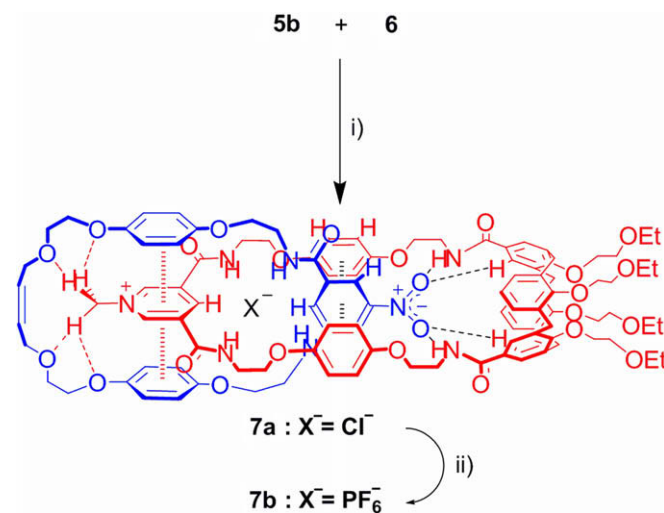
**Figure 1.** Partial  $^1\text{H}$  NMR spectra (500 MHz,  $\text{CDCl}_3$ , 293 K) of (a) macrocycle **5b**, (b) **5b** and 1 equiv of **6** and (c) free thread **6**.

additional hydrogen-bonding interactions to the nitro group of the thread.

Encouraged by this evidence of anion-templated pseudorotaxane assembly, attempts were made to ring-close the thread to form the target catenane. The catenation reaction was undertaken by the addition of Grubbs' second generation ring-closing metathesis (RCM) catalyst to a stirring solution of **5b** and **6** in dichloromethane at room temperature (Scheme 2).

The target [2]catenane **7a** was obtained in 60% yield following purification by preparative silica thin layer chromatography and characterized by  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, and ESI-MS. The partial  $^1\text{H}$  NMR spectrum of **7a** in chloroform is displayed in Figure 2.

As was observed in the pseudorotaxane assembly studies, the protons of the calix macrocycle component of the catenane in-



**Scheme 2.** Reagents and conditions: (i) Grubbs' second generation catalyst,  $\text{CH}_2\text{Cl}_2$ , 60%; (ii)  $\text{AgPF}_6$ ,  $\text{CH}_2\text{Cl}_2$ , 90%.

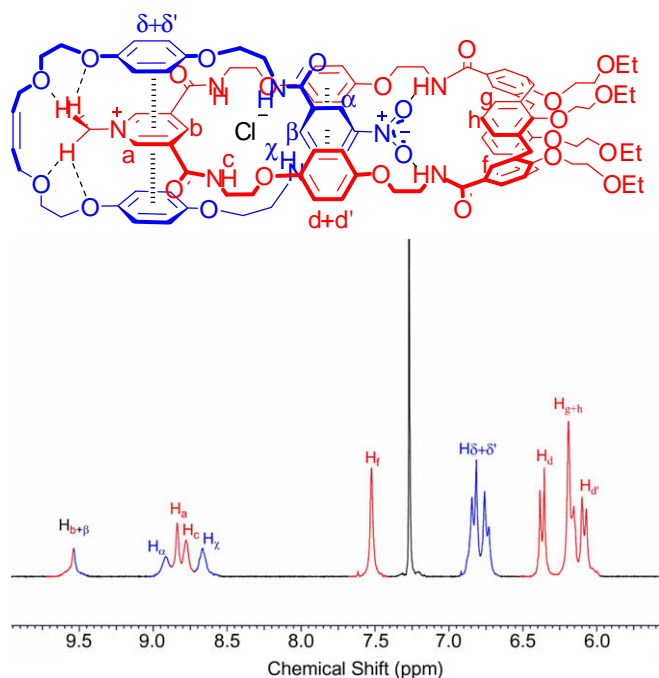


Figure 2. Partial  $^1\text{H}$  NMR spectrum (500 MHz,  $\text{CDCl}_3$ , 293 K) of **7a**.

involved in hydrogen bonding to the chloride template are significantly moved upfield ( $\Delta\delta = 0.79$  ppm  $H_b$ ,  $0.88$  ppm  $H_c$ ) relative to the macrocycle **5b**. Simultaneously, the hydroquinone protons ( $H_{d+d'}$ ) are observed to move upfield and split ( $\Delta\delta = 0.5$  and  $0.78$  ppm) indicating substantial  $\pi$ - $\pi$  stacking interactions with the nitro-substituted isophthalamide group. In addition, significant downfield shifts of the upper-rim calixarene protons ( $\Delta\delta = 0.56$  ppm  $H_f$ ) are consistent with hydrogen-bonding interactions to the nitro group of the thread.

Similar but opposing shifts of the thread protons downfield ( $\Delta\delta = 1$  ppm  $H_b$ ,  $1.74$  ppm  $H_x$ ) accompanied by an upfield shift and split of the hydroquinone protons ( $H_{\delta+\delta'}$ ) further corroborate the changes seen in the pseudorotaxane studies.

ESI-MS evidence for the formation of the catenane was obtained via observation of a single molecular ion peak at  $m/z = 1924.7$ .

Removal of the chloride anion template from the [2]catenane cavity was achieved via exchange with hexafluorophosphate upon the addition of  $\text{AgPF}_6$  to **7a**. Confirmation of successful anion exchange was obtained via  $^1\text{H}$  NMR and elemental analysis.

$^1\text{H}$  NMR anion titration studies of the catenane **7b** were undertaken in a 1:1  $\text{CDCl}_3/\text{CD}_3\text{OD}$  solvent mixture. Both the *para*-pyridinium ( $H_b$ ) and *para*-nitro ( $H_\beta$ ) protons of the catenane were observed to shift significantly downfield upon addition of chloride (Fig. 3) while by way of contrast, bromide, fluoride, acetate, and dihydrogen phosphate anions produced only modest perturbations, suggesting weaker binding.

Job plot and WinEQNMR<sup>36</sup> analysis of the titration data (see Supplementary data) enabled association constants for 1:1 complexes to be determined.

Table 1 shows that the catenane strongly and selectively binds chloride in preference to the other anions tested. This observation suggests that the unique interlocked host cavity of catenane **7b** is of complementary size and shape for the chloride template. Presumably the larger bromide and basic oxoanions are unable to be completely encapsulated by the catenane binding pocket.

In conclusion, a new upper-rim functionalized calix[4]arene macrobicycle has been synthesized and used in the chloride anion-templated preparation of a novel [2]catenane. After halide anion template removal, the resulting catenane host exhibits a

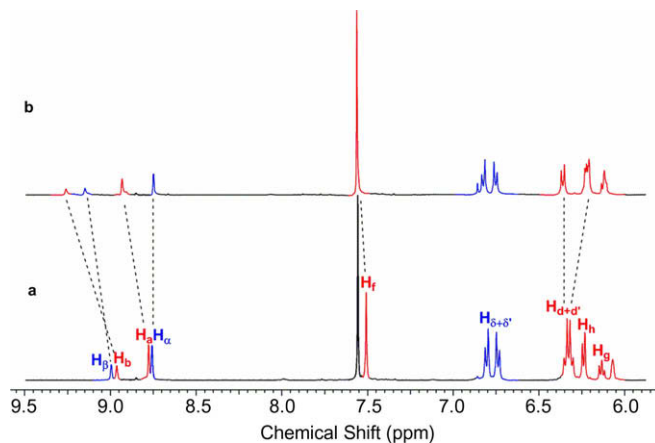


Figure 3. Partial  $^1\text{H}$  NMR spectra (500 MHz, 1:1  $\text{CDCl}_3/\text{CD}_3\text{OD}$ , 293 K) of (a) catenane **7b**, and (b) **7b** and 1 equiv of TBACl.

Table 1

Association constants ( $K_{11}$ ,  $\text{M}^{-1}$ ) of **7b** with various anions

| Anion <sup>a</sup>        | $K_{11}$ |
|---------------------------|----------|
| $\text{Cl}^-$             | 2050     |
| $\text{Br}^-$             | 840      |
| $\text{H}_2\text{PO}_4^-$ | 290      |
| $\text{AcO}^-$            | 160      |
| $\text{F}^-$              | 120      |

Solvent 1:1  $\text{CDCl}_3/\text{CD}_3\text{OD}$ , 293 K, errors <10%.

<sup>a</sup> Anions introduced as tetrabutylammonium salts.

high degree of selectivity for chloride in competitive organic solvent mixtures.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.212.

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