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## A supramolecular host with a cavitand core and four cholate side arms

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Copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) was employed to synthesize a new cavitand (**1**) having four cholate groups covalently connected to the cavitand core. CuAAC between a tetrapropargyl cavitand **2** and 3 $\alpha$ -azido-cholic acid **3** led to the isolation of pure cavitand **1**, which was fully characterized by the usual complement of spectroscopic techniques. While its solubility was limited in pure aqueous media, the complexation of three 4,4'-bipyridinium (viologen) guests could be investigated, using square wave voltammetric (SWV) techniques, in a mixture of H<sub>2</sub>O/DMSO (5 : 2 v/v) also containing 40 mM sodium tetraborate as the supporting electrolyte and further experimental evidence supporting the formation of a complex between cavitand **1** and V<sup>2+</sup> (viologen) with a 1 : 1 stoichiometry was obtained using ITC and electrospray ionization mass spectrometry (ESI-MS). Computational studies at the GFN2-xTB/ALPB(water) semiempirical level of theory revealed that the cavitand adopts a compact globular structure in solution, while docking effectively with methylviologen as a guest without forming an inclusion complex.

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### Introduction

Cavitands are bowl-shaped compounds that constitute an important class of supramolecular hosts. Initially prepared and termed by Cram,<sup>1,2</sup> they offer a number of possibilities for functionalization. Cram's definition of cavitands<sup>1</sup> as 'synthetic organic molecules with enforced cavities large enough to complex complementary organic compounds or ions' is general enough to include many classes of hosts. However, most supramolecular chemists use the term 'cavitands' specifically to designate host compounds derived from the acid-catalyzed condensation of aldehydes and resorcinols, as pioneered by Cram's group. This reaction initially produces a group of macrocycles termed 'resorcinarenes', whose phenolic OH groups can be further interconnected by suitable bifunctional reagents, such as CH<sub>2</sub>BrCl or CH<sub>2</sub>Br<sub>2</sub>, to yield the bowl-shaped cavitands.<sup>3</sup> Most cavitands are built from the initial condensation of four aromatic (resorcinol) groups, although larger cavitands have also been reported.<sup>4</sup> Since the internal cavity

afforded by simple cavitands is rather small, elongation of the cavity *via* functionalization of its upper rim is a common method to synthetically access host compounds with the ability to complex larger molecules.<sup>5,6</sup> Numerous carcerands, hemicarcerands and other hosts based on cavitands have been prepared.<sup>7</sup> The Gibbs group<sup>8,9</sup> has reported extensively on a cavitand derivative functionalized with eight carboxylate units and its interesting dimerization and binding properties in aqueous media. Our own group has explored the functionalization of cavitands with redox-active 4,4'-bipyridinium (viologen) groups<sup>10</sup> and Fréchet-type dendrons.<sup>11</sup>

As a result of its facial amphiphilic nature, anionic cholate molecules aggregate in aqueous solution to form small micellar assemblies with hydrophobic cavities.<sup>12–14</sup> Previously, we investigated the electrochemistry of a series of viologen derivatives with varying amphiphilic character in cholate micellar media.<sup>15</sup> Our experimental data were consistent with the interaction of all surveyed viologens with cholate assemblies. Out of the three oxidation states presented by viologens [dication (V<sup>2+</sup>), cation radical (V<sup>•+</sup>) and neutral species (V)] cholate micellar assemblies preferentially stabilized the cation radical form.<sup>15</sup> Therefore, we decided to prepare a cavitand functionalized with four identical cholate groups connected to its upper rim (see Fig. 1) and investigate its binding interactions with several viologen derivatives. Our main goal was to compare these results with those obtained in cholate micellar media in an attempt to shed some light on the types of dynamic cavities existing in these media, since we initially thought that, given

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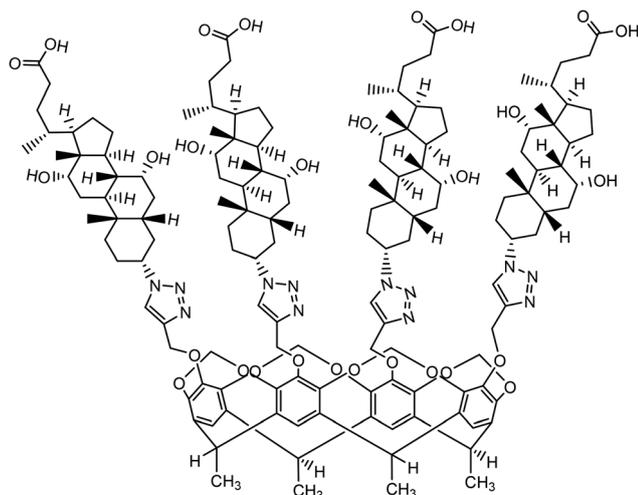
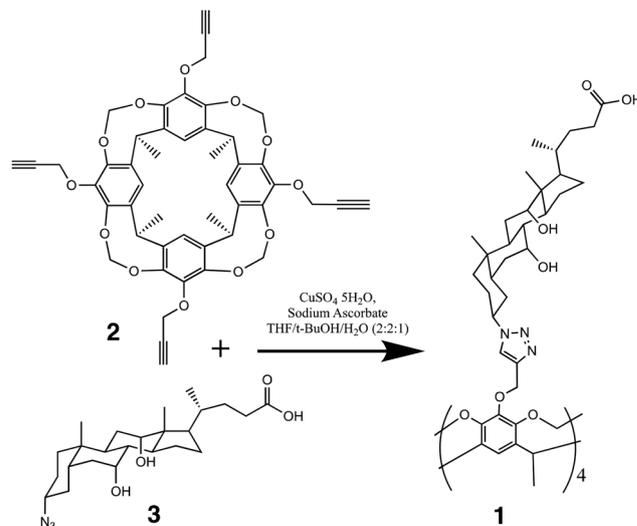


Fig. 1 Structure of the target tetracholate cavitanol (1).



Scheme 1 Synthesis of tetracholate cavitanol 1 from precursors 2 and 3.

its structure, the new tetracholate cavitanol would exhibit a better defined and more stable cavity, forced by the attachment of the four cholate groups to the upper cavitanol rim.

As guests in this preliminary investigation we selected three viologen derivatives, namely methylviologen ( $MV^{2+}$ ), butylviologen ( $BV^{2+}$ ) and ethyl-heptylviologen ( $EHV^{2+}$ ). The first guest is the least hydrophobic on account of the two simple methyl substituents on the dicationic 4,4'-bipyridinium nucleus. The other two viologen guests are both more hydrophobic but possess different distributions of the hydrophobic groups (alkyl chain substituents) around the viologen nucleus (Fig. 2).

## Results and discussion

### Synthesis

The synthesis of the target tetracholate cavitanol was carried out using click chemistry, that is, copper(i)-catalyzed azide-alkyne cycloaddition<sup>16,17</sup> (CuAAC) between the tetrapropargyl cavitanol 2<sup>18–22</sup> and 3 $\alpha$ -azido-cholic acid 3<sup>23–26</sup> (Scheme 1). Very briefly, 2 was prepared by hydroxylation of the known tetrabromo cavitanol followed by treatment in refluxing acetone

with propargyl bromide in the presence of  $K_2CO_3$  to yield cavitanol 2. Synthesis of the azide derivative 3 started by esterification of cholic acid with methanol, followed by mesitylation of the alcohol group on position 3, treatment with  $NaN_3$  to give the azide derivative of the methyl ester and, finally, hydrolysis of the ester to yield the 3 $\alpha$ -azido-cholic acid 3. The CuAAC reaction between 2 and five equivalents of 3 was carried out in a THF/*t*-BuOH/ $H_2O$  (2 : 2 : 1) solvent mixture in the presence of  $CuSO_4$  and sodium ascorbate. After purification, the isolated tetracholate cavitanol (61% yield) was fully characterized using spectroscopic methods (see Experimental section). The viologen guests were prepared as iodide or bromide salts using the same methods already reported by our group.<sup>15</sup>

### Preliminary binding studies in solution

Not unexpectedly, cavitanol 1 had limited solubility in aqueous media, even when solutions with  $pH > 7$  were used to foster aqueous solubility through the deprotonation of the cholic acid groups ( $1^{4-}$ ). After assessing the solubility of 1 in various solvent mixtures, we settled on a 5 : 2 (v/v) mixture of  $H_2O$  and DMSO (containing 40 mM sodium borate for pH control) for our guest–host binding solution studies. Because of their redox properties and our previous experience with these compounds we chose a series of representative bipyridinium (viologen) derivatives as potential guests for binding interactions with cavitanol  $1^{4-}$ . The electrochemical behavior of viologen dications ( $V^{2+}$ ) consists of two fast one-electron reduction steps, which lead successively to the radical cation ( $V^{\cdot+}$ ) and the neutral species ( $V$ ). Since these two reduction steps diminish the initial positive charge on the dication, the resulting viologen species are less water-soluble, typically leading to stronger interactions with hydrophobic cavities that might be present in the media or possible precipitation on the working electrode surface in electrochemical experiments.<sup>15</sup>

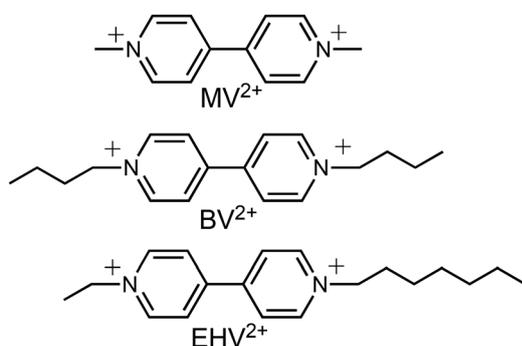


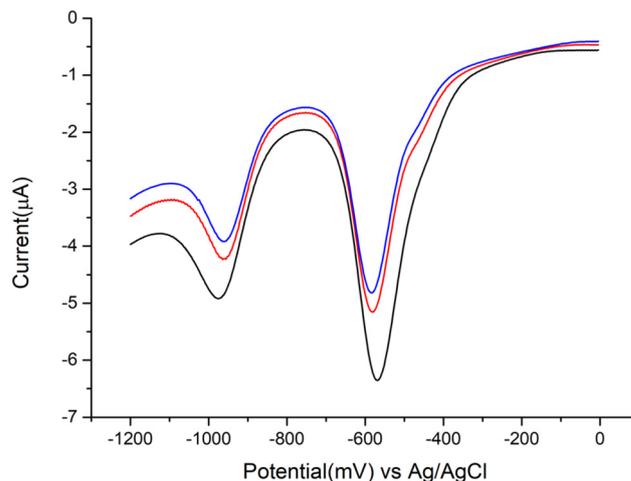
Fig. 2 Structures of the viologen guest dications.



Unfortunately, the limited solubility of cavitand  $1^{4-}$  in aqueous media made impossible the use of  $^1\text{H}$  NMR experiments to investigate its possible host binding interactions with any of the viologen dications; and the UV-vis absorption region of cavitand  $1^{4-}$  overlaps with those of  $\text{MV}^{2+}$ ,  $\text{BV}^{2+}$  and  $\text{EHV}^{2+}$ . Therefore, we jumped directly into Square Wave Voltammetric (SWV) experiments which allow the assessment of electrochemical behavior changes experienced by the viologen dications, at concentrations as low as 0.1 mM, in the presence of similar concentrations of tetracholate cavitand. These changes offer insight on the host-guest binding interactions taking place in the solution phase. To see if any aggregates form, we measured the UV-vis dilution experiments and the absorbance of the host is perfectly linear and only starts showing some curvature at concentrations of 0.15 mM or higher (Fig. S19). Of course, at these concentrations the absorbance is already so high ( $A > 1.0$ ) that errors caused by stray light and other photometric factors affect the measured values. In any instance, we did not find any evidence of aggregation at host concentrations of 0.1 mM or lower, as indicated by the linearity of the absorbance vs. concentration plot in this concentration range.

The SWV behavior of  $\text{MV}^{2+}$  in  $\text{H}_2\text{O}:\text{DMSO}$  (5 : 2, v/v, containing 40 mM sodium borate) consists of two cathodic peaks centered at potentials of  $-0.568$  V and  $-0.976$  V vs. Ag/AgCl. The first peak corresponds to the one-electron reduction of  $\text{MV}^{2+}$  to its radical cation ( $\text{MV}^{\cdot+}$ ) and the second to the one-electron reduction of the radical cation to the neutral species ( $\text{MV}$ ). Addition of 1.0 equiv. of cavitand  $1^{4-}$  leads to decreased current levels for both SWV peaks, which is consistent with the association of  $\text{MV}^{2+}$  with  $1^{4-}$ , as the increased molecular weight of the supramolecular complex will result in slower diffusion rates to the electrode surface and, thus, lower currents. The presence of 1.0 equiv. of cavitand also shifts the first reduction peak to a more negative potential value ( $-0.580$  V) while the second reduction peak shifts in the opposite direction to  $-0.964$  V. These potential changes are small but perfectly measurable, considering that our potential values are affected by a typical error margin of  $\pm 0.003$  V. Similar, although less pronounced, changes take place upon addition of an additional equiv. of cavitand. The SWV behavior of  $\text{MV}^{2+}$  in the absence and presence of cavitand  $1^{4-}$  is shown in Fig. 3 and the peak potential values compiled for all three viologens are given in Table 1.

SWV peak potentials are equal to half-potential values ( $E_{1/2}$ ), which are considered an excellent approximation to the corresponding formal potentials ( $E^\circ$ ).<sup>27</sup> Therefore, the shifts on the measured peak potentials contain information on the relative thermodynamic stability of the three redox states of the viologen guest. For instance, with  $\text{MV}^{2+}$  the difference between the first and the second peak potentials decreases as the cavitand concentration increases, reflecting the decreased thermodynamic stability of the radical cation ( $\text{MV}^{\cdot+}$ ) compared to the dication and neutral states in the presence of the cavitand. Interestingly, this effect on the relative stability of the radical cation is the opposite to what was observed in the pres-



**Fig. 3** SWV response of  $\text{MV}^{2+}$  (0.1 mM) on a glassy carbon electrode ( $0.071 \text{ cm}^2$ ) in the absence (black) and in the presence of 1.0 equiv. (red) and 2.0 equiv. (blue) of tetracholate cavitand  $1^{4-}$ . Supporting electrolyte: 40 mM sodium tetraborate. Scan rate:  $80 \text{ mV s}^{-1}$ .

**Table 1** SWV peak potentials (V vs. Ag/AgCl) measured for the viologen guests in the presence of variable concentrations of cavitand  $1^{4-}$ . The guest concentration was constant at 0.1 mM. Supporting electrolyte: 40 mM sodium tetraborate. Scan rate:  $80 \text{ mV s}^{-1}$

Guest	+ 0 equiv. cavitand $1^{4-}$	+ 1 equiv. cavitand $1^{4-}$	+ 2 equiv. cavitand $1^{4-}$
$\text{MV}^{2+}$	$-0.568/-0.976$	$-0.580/-0.964$	$-0.584/-0.960$
$\text{BV}^{2+}$	$-0.520/-0.904$	$-0.544/-0.920$	$-0.548/-0.940$
$\text{EHV}^{2+}$	$-0.512/-0.900$	$-0.536/-0.960$	$-0.528/-0.952$

ence of cholate micelles.<sup>15</sup> The more hydrophobic viologen guest  $\text{BV}^{2+}$  shows different SWV peak potential behavior (Fig. S20), with both peaks shifting to more negative values as the cavitand concentration increases. Finally, in the case of  $\text{EHV}^{2+}$  (Fig. S21), both peak potentials shift to more negative values in the presence of 1 equiv. of cavitand, but this trend partially reverses itself upon addition of an extra equiv. of cavitand host. These cavitand-induced peak potential shifts indicate that all redox states are relatively stabilized by the presence of cavitand  $1^{4-}$ . In all cases, the addition of cavitand leads to decreased current levels, reflecting the formation of more slowly diffusing supramolecular complexes.

While the detailed interpretation of the observed peak potential shifts for the three viologen guests is complicated at this time, we notice that the shifts elicited by 1 equiv. of cavitand are much larger than those resulting from the addition of one additional equivalent. This suggests that the equilibrium concentration of complex is close to saturation when mixing viologen guest and cavitand  $1^{4-}$  both at equal concentrations of 0.1 mM.

In order to obtain the corresponding association equilibrium constant ( $K$ ), we carried out isothermal titration calorimetry (ITC) experiments. The  $K$  value obtained was  $1.28 \times 10^5$



$M^{-1}$  for tetracholate cavitant complexation with  $MV^{2+}$ . Thermodynamic parameters obtained by ITC: (1)  $\Delta H^\circ = -36.91 \text{ kJ mol}^{-1}$ , (2)  $-T\Delta S^\circ = 7.77 \text{ kJ mol}^{-1}$  and (3)  $\Delta G^\circ = -29.14 \text{ kJ mol}^{-1}$ . These parameters indicate that the binding process was primarily driven by enthalpy.

Further experimental evidence supporting the formation of a complex between cavitant **1** and  $V^{2+}$  was obtained using electrospray ionization mass spectrometry. We detected signals for complexes of  $[1 \cdot MV^{2+}]^{2+}$ ,  $[1 \cdot BV^{2+}]^{2+}$  and  $[1 \cdot EHV^{2+}]^{2+}$  (Fig. S22, S24 and Fig. 5), which confirm the formation of stable  $[1 \cdot V^{2+}]^{2+}$  complexes with 1:1 stoichiometry. The major peak in the spectrum (Fig. 4) of a solution containing cavitant **1** and  $EHV^{2+}$  appears at the  $m/z$  ratio of 1413.3253, which can be assigned to the 1:1 complex of  $[1 \cdot EHV^{2+}]^{2+}$  and the simulated isotopic distribution of the complex matches well with the experimental isotopic distribution. The same consistent isotopic distributions between the simulated one and the observed one were observed for  $[1 \cdot MV^{2+}]^{2+}$  (Fig. S23) and  $[1 \cdot BV^{2+}]^{2+}$  (Fig. S25).

### Computational studies

To better understand the structure of the tetracholate cavitant in aqueous solution, we employed the well-established Conformer-Rotamer Ensemble Sampling Tool (CREST), which

explores the conformational space through metadynamics-based sampling in combination with genetic algorithms.<sup>28</sup> Conformational searches were performed using standard settings together with the generic force field GFF-xTB,<sup>29</sup> and the resulting structural ensembles were subsequently re-optimized and ranked at the efficient GFN2-xTB semiempirical level of theory (2nd generation Geometry, Frequency, Noncovalent, eXtended Tight-Binding method).<sup>30</sup> In all cases, solvation effects in water were included using the analytically linearized Poisson-Boltzmann (ALPB) model, an implicit solvation approach parametrized for the xTB methods.<sup>31</sup>

Conformational analysis of the tetracholate cavitant  $1^{4-}$  led to the preferred, energy-minimized conformation represented in Fig. 6, which shows a globular structure with two of the cholate units blocking the cavity of the cavitant core and the other two wrapped around the macrocycle. This conformation ( $1_p^{4-}$ ) can be rationalized by the inability of the cholate units to expose their hydrophilic hydroxyl-containing faces to the aqueous environment, an orientation imposed by their connection to the macrocycle through the  $\alpha$  position of the C3 atom. Therefore, the compact, globular structure is adopted to minimize the solvation of hydrophobic surfaces by decreasing as much as possible the solvent-accessible surface area, allowing as well for the establishment of multiple stabilizing intramolecular hydrogen bonds.

In order to assess the preferred structure of the potential supramolecular species formed by the interaction of  $1_p^{4-}$  and  $MV^{2+}$ , docking studies were carried out at the GFN2-xTB/ALPB (water) level, using the recently-developed automated Interaction Site Screening (aISS) algorithm.<sup>32</sup> This approach systematically explores possible binding geometries through an initial grid-based scan and force-field screening, followed by refinement and final optimization at the GFN2-xTB level. The structure proposed by the aISS workflow for the lowest-lying aggregate was found to position the guest on a lateral surface of the cavitant core, with one of the carboxylate cholate groups near enough to develop electrostatic interaction with the cationic guest, and without a significant distortion of the initial preferred conformation  $1_p^{4-}$  for the host (Fig. 7).

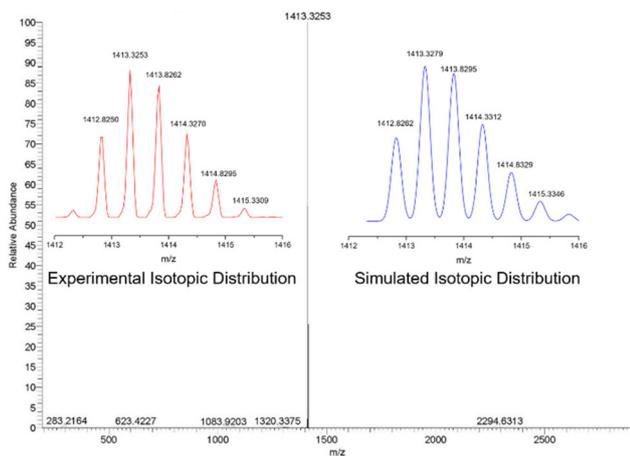


Fig. 5 ESI-MS spectrum of  $[1 \cdot EHV^{2+}]^{2+}$ .

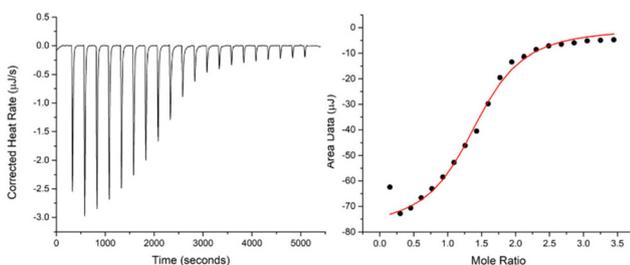


Fig. 4 ITC profiles for the tetracholate cavitant complexation with  $MV^{2+}$  at 298.15 K in  $H_2O$ :DMSO (5:2 v/v) containing 40 mM sodium tetraborate.

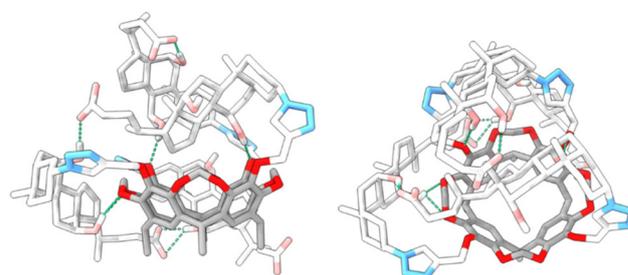
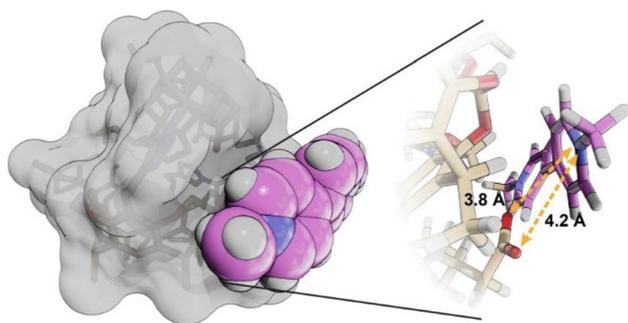


Fig. 6 Side and top views of a stick representation found for the preferred conformation  $1_p^{4-}$  of the targeted cavitant at the GFN2-xTB/ALPB(water) level of theory. For clarity, non-polar hydrogen atoms are omitted, C: dark grey (macrocycle) and light grey (cholate), N: light blue, O: red (macrocycle) and light red (cholate). Hydrogen bonds shown as dashed green lines.





**Fig. 7** Energy-minimized structure for the most favored complex formed by cavitand  $1_p^{4-}$  (van der Waals surface) and guest  $MV^{2+}$  (van der Waals spheres, C: violet, N: blue, H: white) found using the aISS docking protocol. The magnified image on the right shows the spatial proximity between one of the carboxylate groups on the host and the cationic guest.

Finally, the free energy of association was computed at the GFN2-xTB/ALPB(water) level of theory using the preferred conformation  $1_p^{4-}$  as reference for the host. The obtained value for the association reveals that this process is clearly exergonic, with  $\Delta G^\circ = -10.00$  kcal mol $^{-1}$ , and does not require the formation of an inclusion complex to achieve remarkable thermodynamic stability in the final adduct. In this case, the calculated  $K$  value is  $2.16 \times 10^7$  M $^{-1}$ , which is around two orders of magnitude higher than the  $K$  value determined from our ITC measurements. The computational work was carried out in pure water, which may explain the difference in thermodynamic stability with the experimentally obtained values in H $_2$ O : DMSO (5 : 2 v/v). In any instance, the considerable stability of the complex is well established both by our experimental and computational results, which constitutes an interesting and rare finding for an external, non-inclusion host-guest complex.

## Experimental

### Materials

All solvents and chemicals were commercially available and used as received, except *N*-bromosuccinimide, which was freshly recrystallized before use. Water was purified using an Ulupure water purification system (Chengdu, Sichuan). Cavitand **2** and azido derivative **3** were prepared according to published procedures. The viologens were prepared by treatment of 4,4'-bipyridine with the appropriate iodo- or bromoalkanes, as reported previously by our group. Synthetic schemes and other details are provided in the SI.  $^1\text{H}$  NMR (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) spectra were recorded on a JEOL JNM-ECZL400S Spectrometer. HRMS (ESI) was obtained on a Thermo Scientific Q Exactive Focus Orbitrap LC-MS/MS System.

### Synthesis of tetracholate cavitand (**1**)

Cavitand **2** (80.0 mg, 0.1 mmol) and azido derivative **3** (217.0 mg, 0.5 mmol) were dissolved in 8.0 mL of a

2 : 2 : 1 mixture of THF/*t*-BuOH/H $_2$ O (v/v), followed by the addition of CuSO $_4$ ·5H $_2$ O (12.48 mg, 0.05 mmol) and sodium ascorbate (50.49 mg, 0.255 mmol). The solution was stirred in an oil bath at 60 °C for 24 h. The solvent was removed under vacuum. The crude product was dissolved in THF (10 mL), followed by the addition of H $_2$ O (3 mL). The solution was extracted by EtOAc (10 mL). The extracted organic layer was washed with H $_2$ O (3 mL  $\times$  2) and dried over MgSO $_4$ . The solvent was removed under vacuum, then the solid material was washed with EtOAc to afford 156.2 mg (61.4%) of the final product as a white solid.

$^1\text{H}$  NMR (400 MHz, (CD $_3$ ) $_2$ SO):  $\delta$  11.92 (s, 4H, COOH), 8.09 (s, 4H, H-triazole), 7.46 (s, 4H, ArH), 5.96 (d, 4H, outer of OCH $_2$ O), 4.94 (d, 8, OCH $_2$ -triazole), 4.80 (q, 4H, CH $_3$ CH), 4.29 (bs, 8H, H-3 $\beta$  and inner of OCH $_2$ O), 4.16 (d, 4H, OH-12 $\alpha$ ), 4.11 (d, 4H, OH-7 $\alpha$ ), 3.80 (s, 4H, H-12 $\beta$ ), 3.63 (s, 4H, H-7 $\beta$ ), 2.86–0.96 (m, 96H), 1.82 (d, 12H, CH $_3$ CH), 0.93 (d, 12H, H-21), 0.91 (s, 12H, H-19), 0.60 (s, 3H, H-18).  $^{13}\text{C}$  NMR (100 MHz, (CD $_3$ ) $_2$ SO):  $\delta$  174.94, 147.19, 143.72, 142.78, 139.83, 122.80, 115.70, 99.40, 71.10, 66., 66.68, 66.15, 60.43, 46.19, 45.83, 41.90, 41.42, 36.98, 35.48, 35.04, 34.51, 31.34, 30.87, 30.82, 28.53, 27.25, 26.28, 22.77, 22.58, 16.98, 15.82, 12.33.

HRMS (ESI/Q-TOF)  $m/z$ : [M + H] $^+$  calcd for C $_{144}$ H $_{197}$ N $_{12}$ O $_{28}$  2542.4360; found 2543.4460.

### Methods

The electrochemical experiments were recorded in a single-compartment glass cell, using a CH Instruments potentiostat (Austin, TX). Typically, the cell was fitted with a glassy carbon disk working electrode (0.071 cm $^2$ ), platinum auxiliary electrode, a Ag/AgCl reference electrode, and a nitrogen inlet Teflon tubing. Nitrogen gas was bubbled through the solution to remove dissolved oxygen gas. During the voltametric scans, nitrogen gas was maintained above the solution to prevent the redissolution of atmospheric oxygen. The working electrode was polished on a soft felt surface covered with an aqueous slurry of alumina (0.05  $\mu\text{m}$ ), and rinsed extensively with purified water.

## Conclusions

We have prepared a new cavitand-based molecule (**1**), having four cholate groups covalently attached to the cavitand core *via* triazole units. The final molecule was synthesized using the copper(i)-catalyzed azide-alkyne cycloaddition (CuAAC) between the tetrapropargyl cavitand **2** and 3 $\alpha$ -azido-cholic acid **3** (Scheme 1). The new cavitand showed limited solubility in aqueous media. However, SWV electrochemical measurements showed that the tetracholate cavitand  $1^{4-}$  effectively binds three viologen guests in a 5 : 2 (v/v) mixture of H $_2$ O and DMSO (containing 40 mM sodium borate for pH control). And ESI-MS shows direct evidence for the complexes between the cavitand **1** and the viologen guests. ITC experiments yielded a  $K$  value of  $1.28 \times 10^5$  M $^{-1}$  for the formation of the 1·MV $^{2+}$  complex. Computational studies showed that the cavi-



tand host adopts a globular conformation in aqueous media to minimize the exposure and solvation of hydrophobic surfaces. Docking studies with the methylviologen guest reveal the formation of a very stable complex (calculated  $\Delta G^\circ = -10$  kcal mol<sup>-1</sup> in water and experimental  $\Delta G^\circ = -7.0$  kcal mol<sup>-1</sup> in H<sub>2</sub>O : DMSO, 5 : 2 v/v) in which the guest attaches itself to one the external surfaces of the cavitand core. Therefore, formation of an inclusion complex is not necessary to achieve considerable stabilization of the final supramolecular adduct, which is likely to be further stabilized by the globular conformation adopted by the host.

A recent publication has reported the preparation of a related compound containing three cholate groups.<sup>33</sup> These results combine well with our findings on the conformational complexity of cavitand **1**<sup>4-</sup> as well as the relatively surprising structure of its highly stable adduct with methylviologen, and fuel our interest to continue the exploration of more aqueous soluble related host compounds with multiple cholate groups. Potential strategies to improve water solubility by introducing hydrophilic groups (e.g., sulfonate, carboxylate) on the feet of the cavitand core are under consideration.

## Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: synthetic details, <sup>1</sup>H, <sup>13</sup>C NMR spectra and mass spectra of relevant compounds. SWV behavior of butylviologen and ethyl-heptylviologen. ESI-MS spectra of [1·MV<sup>2+</sup>]<sup>2+</sup> and [1·BV<sup>2+</sup>]<sup>2+</sup>. Computational study details. See DOI: <https://doi.org/10.1039/d6ob00175k>.

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## References

- 1 D. J. Cram and J. M. Cram, *Container Molecules and Their Guests*, The Royal Society of Chemistry, Cambridge, 1994.
- 2 D. J. Cram, Cavitands: Organic Hosts with Enforced Cavities, *Science*, 1983, **219**, 1177.
- 3 P. Timmerman, W. Verboom and D. N. Reinhoudt, Resorcinarenes, *Tetrahedron*, 1996, **52**, 2663.
- 4 C. Naumann, E. Román, C. Peinador, T. Ren, B. O. Patrick, A. E. Kaifer and J. C. Sherman, Expanding Cavitand Chemistry: The Preparation and Characterization of [n] Cavitands with n ≥ 4, *Chem. – Eur. J.*, 2001, **7**, 1637.
- 5 R. Hooley and J. Rebek, Deep Cavitands Provide Organized Solvation Reactions, *J. Am. Chem. Soc.*, 2005, **127**, 11904.
- 6 S. Mosca, Y. Yu, J. Gavette, K.-D. Zhang and J. Rebek, A Deep Cavitand Templates Lactam Formation in Water, *J. Am. Chem. Soc.*, 2015, **137**, 14582.
- 7 A. Jasat and J. C. Sherman, Carceplexes and Hemicarceplexes, *Chem. Rev.*, 1999, **99**, 93.
- 8 C. L. D. Gibb and B. C. Gibb, Well-Defined, Organic Nanoenvironments in Water: The Hydrophobic Effect Drives a Capsular Assembly, *J. Am. Chem. Soc.*, 2004, **126**, 11408.
- 9 C. L. D. Gibb and B. C. Gibb, Templated Assembly of Water-Soluble Nano-Capsules: Inter-Phase Sequestration, Storage, and Separation of Hydrogen Gases, *J. Am. Chem. Soc.*, 2006, **128**, 16498.
- 10 C. Peinador, E. Roman, K. Abboud and A. E. Kaifer, Novel Cavitands Containing Electrochemically Active 4,4'-bipyridinium Subunits, *Chem. Commun.*, 1999, 1887.
- 11 R. Toba, J. M. Quintela, C. Peinador, E. Roman and A. E. Kaifer, Dendritic Cavitands: Preparation and Electrochemical Properties, *Chem. Commun.*, 2002, 1768.
- 12 A. Roda, A. F. Hofmann and K. J. Mysels, The Influence of Bile-Salt Structure on Self-Association in Aqueous Solutions, *J. Biol. Chem.*, 1983, **258**, 6362.
- 13 O. Rinco, M. H. Kleinman and C. Bohne, Reactivity of Benzophenones in the Different Binding Sites of Sodium Cholate Aggregates, *Langmuir*, 2001, **17**, 578.
- 14 C. Yihwa, F. H. Quina and C. Bohne, Modulation with Acetonitrile of the Dynamics of Guest Binding to the Two Distinct Binding Sites of Cholate Aggregates, *Langmuir*, 2004, **20**, 9983.
- 15 B. Cheng and A. E. Kaifer, Electrochemistry of Viologen Dications in Cholate Media and Competition between the Cholates Assemblies and the Cucurbit[7]uril Host, *Langmuir*, 2015, **31**, 2997.
- 16 V. Rostovtsev, L. Green, V. Fokin and K. B. Sharpless, A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective “Ligation” of Azides and Terminal Alkynes, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596.
- 17 C. W. Tornøe, C. Christensen and M. Meldal, Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides, *J. Org. Chem.*, 2002, **67**, 3057.
- 18 D. J. Cram, S. Karbach, H.-E. Kim, C. B. Knobler, E. F. Maverick, J. L. Ericson and R. C. Helgeson, Host-Guest



- Complexation., 46. Cavitands as Open Molecular Vessels Form Solvates, *J. Am. Chem. Soc.*, 1988, **110**, 2229.
- 19 E. Roman, C. Peinador, S. Mendoza and A. E. Kaifer, Improved Synthesis of Cavitands, *J. Org. Chem.*, 1999, **64**, 2577.
- 20 J. R. Fraser, B. Borecka, J. Trotter and J. C. Sherman, An Asymmetric Carceplex and New Crystal Structure Yield Information Regarding a 1 Million-Fold Template Effect, *J. Org. Chem.*, 1995, **60**, 1207.
- 21 P. Timmerman, K. G. A. Nierop, E. A. Brinks, W. Verboom, F. C. J. M. van Veggel, W. P. van Hoorn and D. N. Reinhoudt, Hydrophobic Concave Surfaces and Cavities by Combination of Calix[4]arenes and Resorcin[4]arenes, *Chem. – Eur. J.*, 1995, **1**, 132.
- 22 D. J. Cram, R. Jaeger and K. Deshayes, Host-Guest Complexation., 65. Hemicarcerands that Encapsulate Hydrocarbons with Molecular Weights Greater than Two Hundred, *J. Am. Chem. Soc.*, 1993, **115**, 10111.
- 23 B. Dayal, J. Speck, E. Bagan, G. S. Tint and G. Salen, p-Toluenesulfonic Acid/Methanol: Mild Reagent for the Preparation of Bile Acid Methyl Esters, *Steroids*, 1981, **37**, 239.
- 24 B. N. S. Thota, A. J. Savyasachi, N. Lukashev, I. Beletskaya and U. Maitra, Tripodal Bile Acid Architectures Based on a Triarylphosphine Oxide Core Obtained by Copper-Catalysed [1,3]-Dipolar Cycloaddition: Synthesis and Preliminary Aggregation Studies, *Eur. J. Org. Chem.*, 2014, 1406.
- 25 Y. Zhao and Z. Zhong, Oligomeric Cholates: Amphiphilic Foldamers with Large Internal Hydrophobic Cavities, *J. Am. Chem. Soc.*, 2005, **127**, 17894.
- 26 C. Massarenti, O. Bortolini, G. Fantin, D. Cristofaro, D. Ragno, D. Perrone, E. Marchesi, G. Toniolo and A. Massi, Fluorous-tag Assisted Synthesis of Bile Acid-bisphosphonate Conjugates via Orthogonal Click Reactions: an Access to Potential Anti-resorption Bone Drugs, *Org. Biomol. Chem.*, 2017, **15**, 4907.
- 27 A. E. Kaifer and M. Gómez-Kaifer, *Supramolecular Electrochemistry*, Wiley-VCH, Weinheim, 1999.
- 28 P. Pracht, F. Bohle and S. Grimme, Automated Exploration of the Low-Energy Chemical Space with Fast Quantum Chemical Methods, *Phys. Chem. Chem. Phys.*, 2020, **22**, 7169.
- 29 S. Spicher and S. Grimme, Robust Atomistic Modeling of Materials, Organometallic and Biochemical Systems, *Angew. Chem., Int. Ed.*, 2020, **59**, 15665.
- 30 C. Bannwarth, S. Ehlert and S. Grimme, S. GFN2-xTB—An Accurate and Broadly Parametrized Self-Consistent Tight-Binding Quantum Chemical Method with Multipole Electrostatics and Density-Dependent Dispersion Contributions, *J. Chem. Theory Comput.*, 2019, **15**, 1652.
- 31 S. Ehlert, M. Stahn, S. Spicher and S. Grimme, Robust and Efficient Implicit Solvation Model for Fast Semiempirical Methods, *J. Chem. Theory Comput.*, 2021, **17**, 4250.
- 32 C. Plett and S. Grimme, Automated and Efficient Generation of General Molecular Aggregate Structures, *Angew. Chem., Int. Ed.*, 2023, **62**, e202214477.
- 33 A. Kawka, H. Koenig, D. Nowak and T. Pospieszny, Quasi-Podands with 1,2,3-Triazoles Rings from Bile Acid Derivatives: Synthesis, and Spectroscopic and Theoretical Studies, *J. Org. Chem.*, 2024, **89**, 7561.

