CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Hybrid molecular container based on glycoluril and triptycene: synthesis, binding properties, and triggered release

Authors: Wenjin Liu, Xiaoyong Lu, Weijian Xue, Soumen K Samanta, Peter Y Zavalij, Zihui Meng, and Lyle Isaacs

To be cited as: *Chem. Eur. J.* 10.1002/chem.201802981

Link to VoR: http://dx.doi.org/10.1002/chem.201802981

Supported by
ACES

WILEY-VCH

10.1002/chem.201802981

WILEY-VCH

Hybrid molecular container based on glycoluril and triptycene: synthesis, binding properties, and triggered release

Wenjin Liu,[a,b] Xiaoyong Lu,[b] Weijian Xue,[b] Soumen K. Samanta,[b] Peter Y. Zavalij,[b] Zihui Meng,*[a] and Lyle Isaacs*[b]

Dedication ((optional))

Abstract: We designed and synthesized a "hybrid" molecular container **1** which is structurally related to both cucurbit[n]uril (CB[n]) and pillar[n]arene type receptors. Receptor **1** was fully characterized by ^{1}H NMR, ^{13}C NMR, IR, MS and X-ray single crystal diffraction. The self-association behavior, host-guest recognition properties of **1**, and the [salt] dependence of K_a were investigated in detail by ^{1}H NMR and isothermal titration calorimetry (ITC). Optical transmittance and TEM measurements provide strong evidence that receptor **1** undergoes co-assemble with amphiphilic guest **C10** in water to form supramolecular bilayer vesicles (diameter 25.6 ± 2.7 nm, wall thickness ≈ 3.5 nm) that can encapsulate the hydrophilic anticancer drug doxorubicin (DOX) and the hydrophobic dye nile red (NR). The release of encapsulated DOX or NR from the vesicles can be triggered by hexamethonium (**8c**) or spermine (**10**) which leads to the disruption of the supramolecular vesicles.

Introduction

With the aim of developing novel supramolecular assembly systems with sophisticated architectures and functions, the field of supramolecular chemistry has been extensively studied since the pioneering work of Pedersen, Lehn, and Cram.[1] One of the focal points for supramolecular chemists is the design and synthesis of new macrocyclic compounds that function as molecular containers for complementary guests in aqueous.[2] Accordingly, several classes of macrocyclic receptors (e.g. cyclodextrins, calixarenes and cyclophanes) received intense investigation over the past half century since the discovery of crown ethers.[3] More recently, the supramolecular chemistry of cucurbit[n]urils (CB[n], n=5, 6, 7, 8, 10, 14, Figure 1) – a class of pumpkin-shaped molecular containers which are composed of *n* glycoluril units connected by *2n* methylene bridges – has become a focal point of research in supramolecular chemistry.[4] The high interest in CB[n] stems in part from the exceptionally high binding affinity (K_a up to 10^{17} M^{-1}) and selectivity displayed by CB[n] towards hydrophobic cationic guests in aqueous solution, as well as the stimuli responsiveness of CB[n]·guest complexes.[5] Accordingly, CB[n] have become popular components for the construction of a variety of functional systems including supramolecular polymers and materials, supramolecular catalysts, chemical sensing ensembles, molecular machines, and affinity capture materials.[6]

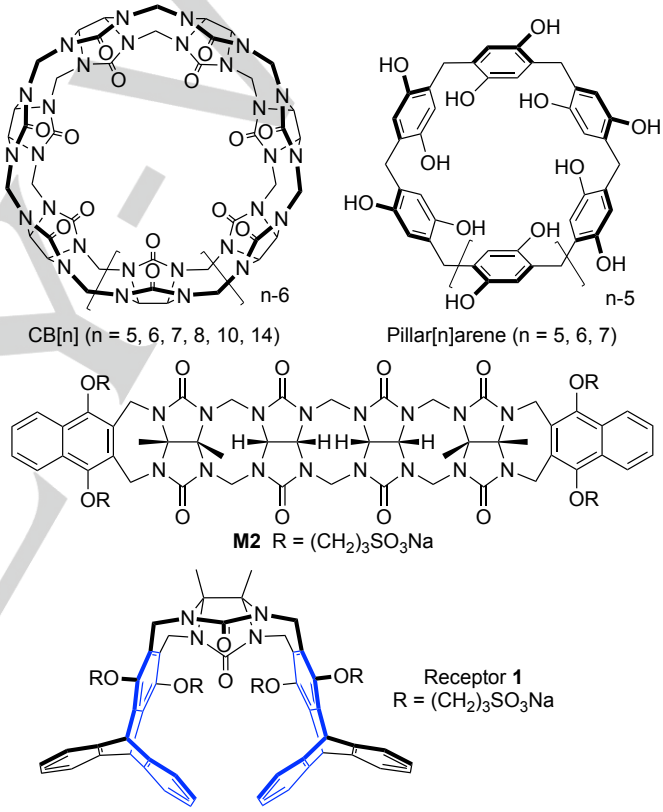


Figure 1. Chemical structures of CB[n], prototypical acyclic CB[n]-type molecular containers, Pillar[n]arenes and the pillar-shaped hybrid receptor **1**.

Several years ago, the Isaacs group designed and synthesized a class of acyclic CB[n]-type molecular containers (e.g. prototypical **M2**, Figure 1) which retained the essential binding properties of macrocyclic CB[n].[7] These acyclic CB[n]-type receptors feature a central C-shaped glycoluril tetramer which promotes binding to hydrophobic cations, two terminal substituted aromatic sidewalls (e.g. substituted benzenes, substituted napthalenes, and triptycene) to enable their recognition of aromatic guests by π-π interactions, and four sodium sulfonate groups that greatly enhance the aqueous solubility of this class of compounds.[8] The structural

[a] W. Liu, Prof. Dr. Z. Meng
School of Chemistry and Chemical Engineering
Beijing Institute of Technology
5 South Zhongguancun Street, Beijing 100081, P. R. China
E-mail: m_zihui@yahoo.com
[b] W. Liu, Dr. X. Lu, Dr. W. Xue, Dr. S. K. Samanta, Dr. P. Y. Zavalij, Prof. Dr. L. Isaacs
Department of Chemistry and Biochemistry
University of Maryland
College Park, Maryland 20742, USA
E-mail: lisaacs@umd.edu.
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://doi.org/xxxxxxxx

flexibility of these acyclic CB[n] receptors results in binding toward not only the common CB[n] guests but also toward unusual guests including carbon nanotubes, Stoddart's blue box and Fujita's squares, nitrosamines, insoluble drugs and neuromuscular blocking agents which are less complementary toward cyclic CB[n].[8-9] Moreover, acyclic CB[n]-type receptors exhibit good biocompatibility in both *vitro* and *vivo* tests, which makes them candidates for drug formulation, delivery, and even the *in vivo* reversal of neuromuscular blocking agents and drugs of abuse (e.g. methamphetamine).[7] Water soluble C-shaped receptors based on glycoluril, norbornene, and anthracene building blocks with striking chemical and biological functions have also been prepared by Nolte, Klärner, Schrader, Yoshizawa, and Schneebeli.[10]

Most recently, pillar[n]arenes (n = 5, 6, 7, Figure 1) have emerged as an exciting class of molecular containers for basic and applied supramolecular chemistry.[11] Unlike the basket-shaped calixarenes which feature aromatic rings bridged by methylene units in the *meta*-positions, pillar[n]arenes are based on aromatic rings bridged by methylene units at the *para*-positions, which gives rise to a rigid pillar architecture.[11a] Because of their unique physiochemical properties, facile preparation, and easy functionalization, pillar[n]arenes are receiving more and more attention in recent years. Pillar[n]arenes have been used to create functional systems like mechanically interlocked molecules, artificial transmembrane channels, chemosensors, and supramolecular amphiphiles and polymers.[11c, 12] Earlier this year, Feihe Huang's group reported the synthesis and recognition properties of an acyclic "clip[4]arene" based on triptycene in acetone solution.[13] We envisioned the possibility of creating a water soluble hybrid acyclic receptor (**1**, Figure 2) whose structure and properties would blend those of pillar[n]arenes, (acyclic) CB[n]-type receptors, and molecular clips. Receptor **1** contains a central glycoluril unit that is capped with two triptycene walls (doubly para-linked) that enforce a C-shaped curvature to the molecule similar to the para-linked pillar[n]arene macrocycles. Receptor **1** also contains four sulfonate groups which promote its aqueous solubility and enhance ion-ion interactions in complexes with cationic guests. In this paper, we report the synthesis and molecular structure of receptor **1**, its basic molecular recognition properties, and the formation of supramolecular vesicles for triggered release application.

Results and Discussion

This results and discussion section is organized as follows. First, we discuss the design and synthesis of receptor **1**, followed by the X-ray crystallographic determination of its solid state structure. Next, we describe its self-association behaviour and host-guest recognition properties. Finally, we present the use of receptor **1** as a building block to construct supramolecular vesicles and use these supramolecular vesicles for the encapsulation and triggered release of a hydrophilic drug and a hydrophobic dye.

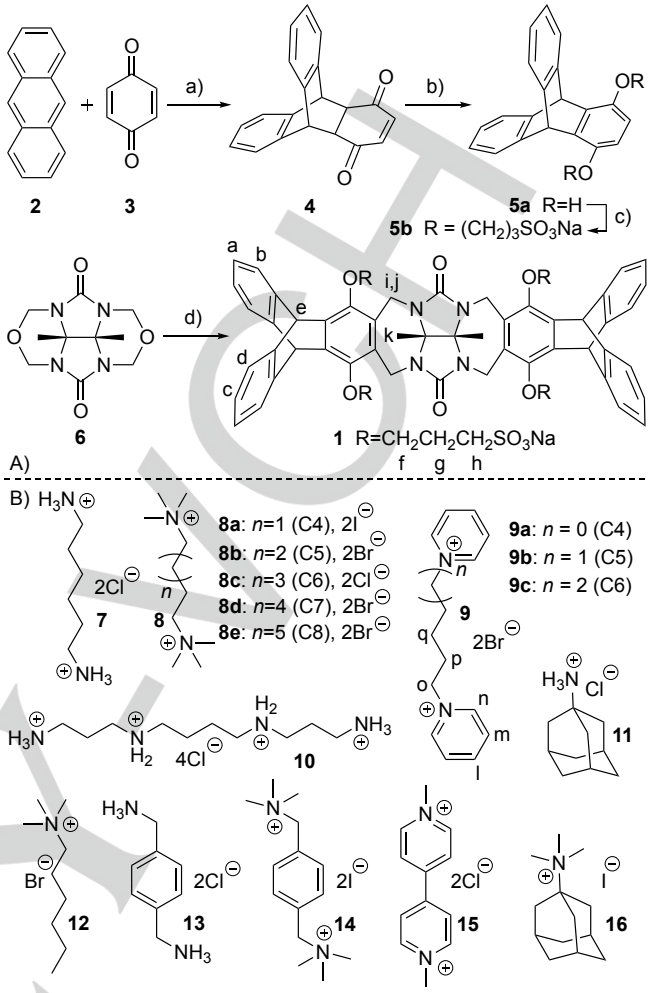


Figure 2. A) Synthesis of triptycene derived wall **5b** and receptor **1**. Conditions: a) xylene, reflux, 5.5 h, 75%; b) CH_3COOH/HBr, reflux, 1 h, 88%; c) propanesultone, 1,4-Dioxane/NaOH (1M), RT, overnight, 75%; d) TFA/Ac_2O, 90 °C, 3.5 h, 34%. B) Structures of cationic guests (**7** – **16**) used in this study.

Design and synthesis of acyclic CB[n]-type receptor 1

We have previously described our building block approach toward acyclic CB[n] receptors (e.g., **M2**) which is based on the double electrophilic aromatic substitution between a glycoluril oligomer bis(cyclic ether) and a sulfonate substituted aromatic building block to enable π-π interactions and aqueous solubility.[7-8] For the design of receptor **1** we employed a triptycene derivative as sidewall. Triptycene can be viewed as a benzo fused derivative of [2.2.2] bicyclooctane which imparts 120° bond angles between the aromatic blades and high structural rigidity; accordingly, triptycene and its derivatives have found wide applications in crystal engineering, materials science and molecular machines.[14] To connect these concave triptycene binding units, we choose dimethylglycoluril bis(cyclic ether) **6**[15] such that the cavity of the resulting receptor **1** is shaped by four aromatic rings and one glycoluril ring similar to the cavity of pillar[5]arene. The aromatic and glycoluril units result in an anisotropic shielding region inside the cavity which allows for straightforward monitoring of host•guest complexation by ^{1}H

NMR spectroscopy.

The preparation of triptycene wall **5b** followed a known procedure, involving the Diels-Alder reaction of anthracene (**2**) with 1,4-benzoquinone (**3**) to give **4** in 75% yield (Figure 2). Compound **4** was tautomerized to dihydroxy triptycene (**5a**) in 88% yield under acidic conditions (CH_3COOH, HBr, reflux). Treatment of **5a** with propanesultone under basic conditions (NaOH, H_2O, dioxane) gave the required wall **5b** bearing sodium sulfonate groups in 75% yield. Finally, double electrophilic aromatic substitution reaction of **5b** with glycoluril bis(cyclic ether) (**6**) delivered receptor **1** in 34% yield after purification by recrystallization from a mixture of water and ethanol. As expected for the depicted C_2v-symmetric structure, the ^{13}C NMR of **1** in water displayed the expected 17 resonances and the ^1H NMR displayed two pairs of resonances for the two different *o*-xylylene rings of receptor **1**. The solubility of **1** in 20 mM NaH_2PO_4 buffered D_2O (pD 7.4, RT) is greater than 40 mM.

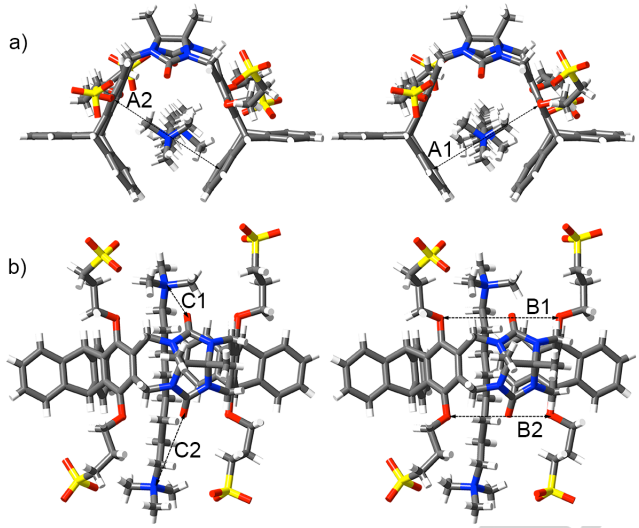


Figure 3. Cross-eyed stereoscopic representation of the geometry of one molecule of **1•8e** from the X-ray crystal structure: a) from top view; b) from side view. Color code: C, grey; H, white; N, blue; O, red; S, yellow.

X-ray crystal structure of receptor 1

We were fortunate to obtain single crystals of receptor **1** as its complex with hexamethyloctanediammonium ion (e.g. **1•8e**) by slow evaporation from a mixture of methanol/isopropanol and to solve its structure by X-ray crystallography (CCDC-1846604). Figure 3 shows a cross-eyed stereoview of one molecule of **1•8e** in the crystal. As expected, the unique three-dimensional rigid structure of triptycene is retained, which helps define the acyclic pillar-shaped cavity of receptor **1**. The distances between the centroids of the two opposite benzene rings are measured to be 7.842 Å (Ar···Ar distance A1) and 7.880 Å (Ar···Ar distance A2) (Figure 3a), smaller than the corresponding distances of pillar[6]arene (9.974 Å) but similar to those of pillar[5]arene (7.621 Å).[16] As observed in the crystal structures of acyclic-CB[n] receptors, the sodium sulfonate solubilizing groups of receptor **1** are oriented away from the hydrophobic cavity, thus leaving the cavity free for host-guest complexation. It is worth noting that the glycoluril unit in this molecule is slightly twisted and the distance between the ureidyl C=O O-atoms of the glycoluril unit of **1** within **1•8e** is 5.702 Å which is comparable to that observed for **M2** (5.645 - 6.184 Å)[8] but shorter than that observed for CB[n] (≈ 6.1 Å).[4g] Accordingly, the cavity of this molecule is also slightly twisted and asymmetric. For example, the distances betweenthe O-atoms of the $O(CH_2)_3R$ sidechains are 7.134 Å (O···O distance B1) and 6.416 Å (O···O distance B2), respectively (Fig 3b), which means the bottom part of the cavity is narrower than the top part. Due to this subtle asymmetry of the cavity, the guest molecule **8e** is asymmetrically accommodated within the cavity. For example, the distances between the ureidyl C=O O-atoms and the adjacent quaternary N-atom of the guest are 3.979 Å (N···O distance C1) and 5.909 Å (N···O distance C2), respectively. The wider portal complexes the bulkier quaternary ammonium region of the guest whereas the more narrow lower portal complexes the $(CH_2)_n$ region. The lower quaternary ammonium ion appears to benefit from electrostatic interactions with the SO_3^- solubilizing groups. The three dimensional packing of the molecules of **1** in the crystal does not show any unusual features.

Self-association behaviour and binding properties of receptor 1

A prerequisite for using receptor **1** as a molecular container to encapsulate guest molecules is that it does not undergo strong self-association which would compete with the host-guest complexation.[8] Accordingly, we first studied the self-association behaviour of receptor **1** by ^1H NMR dilution experiments in 20 mM NaH_2PO_4 buffered D_2O at pD 7.4 (Supporting information). Solutions of receptor **1** were diluted from 20 mM to 0.125 mM and the changes in chemical shift of H_e were monitored and fitted to a standard two-fold self-association model within Scientist™ as a function of concentration.[9d, 15b, 17] The self-association constant (K_s) of **1** is determined to be 186 ± 11 M^{-1}. This dilution experiment establishes that **1** undergoes only weak self-association which will not interfere with the encapsulation of guest molecules at lower concentrations (e.g. ≤ 1 mM) where **1** remains largely monomeric.

Subsequently, we studied the binding ability of **1** toward guests **7** – **16**. Initially, the binding properties of **1** towards **7** – **16** were qualitatively screened by measuring ^1H NMR spectra for 1:1 and 1:2 mixtures of **1** (1 mM) with guests **7-16** (Supporting Information). Figure 4 shows the ^1H NMR spectra recorded for **1** (1 mM) alone and in the presence of bis(pyridinium)hexane guest **9c** (1 mM and 2 mM). Protons H_p and H_q of guest **9c** undergo substantial upfield shifts upon the formation of the **1•9c** complex which indicates they are located in the magnetic shielding region of the cavity of **1**.[9d, 18] The presence of only a single set of broadened resonances for the 1:2 mixture of **1** and **9c** indicates that guest exchange is in the intermeditate to fast regime on the ^1H NMR chemical shift timescale which is commonly observed for complexes of modest affinity.[19] Proton H_o adjacent to the N-atoms also undergoes upfield shifts but not as large as H_p and H_q, which suggests that H_o is located within the cavity of **1** but closer to the C=O portals.[18] As expected, H_l – H_n on the aromatic rings of **9c**

undergo very small shifts because they are not included in the cavity of receptor **1**. Analogous experiments were performed for the remainder of guests **7** – **16** and are reported in the Supporting Information. We did not observe any significant changes in chemical shift for solutions of **1** and two of the bulkier guests (Adamantaneammonium **11** or *p*-xylenediammonium **13**) which can be rationalized based on the small and relatively rigid cavity of **1** which is analogous to a pillar[5]arene which is known to prefer n-alkane derived guests.[11d] When solutions of **1** are treated with solutions of guests **10** (spermine) or **14** we observe the formation of a precipitate containing both components. We suspect that complexation between tetraanionic **1** and tetracationic **10** gives a poorly soluble neutral zwitterionic complex. The stoichiometry of the **1•8c** complex is confirmed to be 1:1 by Job plots (Supporting Information); this 1:1 binding mode is common for the smaller (e.g. n = 5 – 7) pillar[n]arene and CB[n]-type receptors.[4g, 11d]

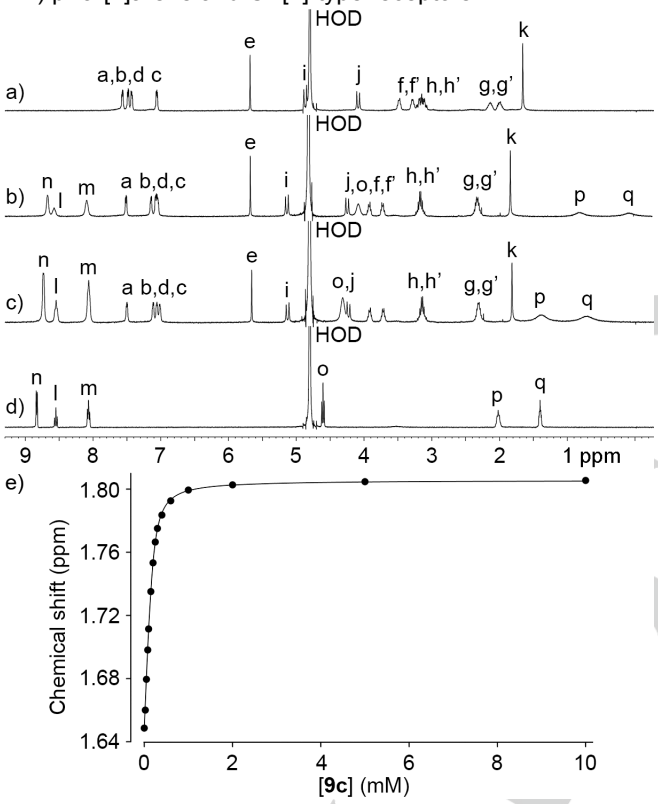


Figure 4. ^{1}H NMR spectra recorded (400 MHz, D_2O) for: a) **1** (1 mM), b) **1** and **9c** (1:1), c) **1** and **9c** (1:2), d) **9c** (2 mM); e) Plot of the change in chemical shift of H_k as a function of [**9c**] during the ^{1}H NMR titration of **1** (0.25 mM) with **9c** (0-10 mM). The solid line is the best non-linear fit of the data to a 1:1 binding model with K_a = (3.03 ± 0.29) × 10^4 M^{-1}.

After having performed the qualitative binding study, we performed quantitative ^{1}H NMR binding titrations in 20 mM NaH_2PO_4 buffered D_2O (pD 7.4) to determine the binding constants for these complexes. Figure 4e shows the changes in the ^{1}H NMR chemical shift of proton H_k of receptor **1** as a function of [**9c**] monitored during the titration of receptor **1** (0.25 mM) with **9c** (0–10 mM). By fitting the changes in chemical shift versus [**9c**] to a standard 1:1 binding model implemented within Scientist™ we determined the binding constant for the **1•9c** complex (K_a = (3.03 ± 0.29) × 10^4 M^{-1}). The binding constants for the complexes with other guests were determined in an analogous manner (Table 1, Supporting Information).

Table 1. Binding constants (K_a, M^{-1}) measured for receptor **1** toward various guests in 20 mM NaH_2PO_4 buffered D_2O at pD 7.4 by ^{1}H NMR titration.

Guest		K_a with **1** (M^{-1})
7	hexanediammonium	(1.93 ± 0.11) × 10^3
8a	hexamethylbutanediammonium	(4.78 ± 0.18) × 10^3
8b	hexamethylpentanediammonium	(1.55 ± 0.12) × 10^4
8c	hexamethonium	(4.05 ± 0.25) × 10^4
8d	hexamethylheptanediammonium	(1.35 ± 0.19) × 10^4
8e	hexamethyloctanediammonium	(1.19 ± 0.13) × 10^4
9a	butanebis(pyridinium)	(4.54 ± 0.11) × 10^3
9b	pentanebis(pyridinium)	(3.38 ± 0.04) × 10^4
9c	hexanebis(pyridinium)	(3.03 ± 0.29) × 10^4
10	spermine	ppt
11	adamantaneammonium	n.b.
12	trimethylhexaneammonium	(4.72 ± 0.05) × 10^2
13	*p*-xylenediammonium	n.b.
14	hexamethyl-*p*-xylenediammonium	ppt
15	methyl viologen	(3.50 ± 2.22) × 10^3
16	trimethyladamantaneammonium	(3.17 ± 0.44) × 10^2

n.b. = no binding detected. ppt = precipitation occurred.

The binding constants for **1** toward the guests **7** – **16** range from no binding up to 4.05 x 10^4 M^{-1} for hexamethonium **8c**. Given the fact that receptor **1** has only one glycoluril unit in its molecule, it is not surprising that the binding constants measured for **1** are relatively low compared to those for other CB[n]-type receptors.[15b] Below, we comment on some of the trends (e.g. nature (1° versus 4°) of ammonium ion, chain length) seen in the K_a versus guest structure data. Receptor **1** binds to primary hexanediammonium (**7**) weakly with a K_a value of (1.93 ± 0.11) × 10^3 M^{-1} but 20-fold more tightly to the quaternary diammonium **8c** K_a = (4.05 ± 0.25) × 10^4 M^{-1} with the same chain length. A similar result was obtained for the interaction between **1** and **9c** with a K_a value of (3.03 ± 0.29) × 10^4 M^{-1}, which suggests that receptor **1** has a preference for quaternary ammonium guests to primary ammonium guests. The influence of chain length on the binding of CB[n]-type receptors toward alkanediammonium ions is well known and seeks to optimize ion-dipole interactions at both portals while maintaining a maximal hydrophobic effect.[4f] For the rigid CB[6], the maximum binding constants are observed for pentanediammonium and hexanediammonium (**7**) and they are greatly reduced for longer and shorter primary diammonium ion guests.[4a, e] Less rigid acyclic CB[n] type receptors (e.g. **M2**) are less selective toward the chain lengths of guests but usually show a preference to longer guests such as heptanediammonium (C7) and octanediammonium (C8) because the structural flexibility of the acyclic CB[n] type receptors allows guests with longer hydrophobic chains to fold inside their cavities.[20] In contrast, pillar[5]arene shows a preference for cationic

guests with a shorter butane chain.[11d] Accordingly, the chain length preferences of **1** toward guests **8a** – **8e** and **9a** – **9c** were examined (Table 1). Similar to macrocyclic CB[n], receptor **1** forms the tightest complex with hexane derived guest **8c** (K_a = (4.05 ± 0.25) × 10^4 M^{-1}) although the selectivities are modest with values of only 8.5 and 3.4, respectively over **8a** and **8e**. The lower selectivity of **1** compared to CB[6] is probably due to the fact that **1** does not contain a fully formed C=O portal and that electrostatic interactions at the portals are less of a driving force than in the case of CB[n]. A similar trend was observed for **9a** – **9c** where **9a** binds 8.4 and 6.7-fold weaker than the longer guests **9b** and **9c**. We also measured the binding constants of **1** towards alkanebis(pyridinium) guests **9a**-**9c** which are commonly used as guests in pillar[n]arene studies. Unsurprisingly, K_a values of receptor **1** towards **9b** (C5) and **9c** (C6) are 8.4 and 6.7-fold larger than with shorter guest **9a** (C4). It is noteworthy that for guests **8a** and **9a**, both with four-carbon chains, the K_a values are decreased almost 10-fold to (4.78 ± 0.18) × 10^3 M^{-1} and (4.54 ± 0.11) × 10^3 M^{-1} respectively compared to the K_a values of guests **8c** and **9c** with six-carbon chains. The host-guest recognition properties of **1** are distinct from CB[n] and pillar[n]arenes from which it is conceptually derived.

Next, we explored the binding capacity of receptor **1** by studies of guests **11**, **13**-**16** which are larger and more voluminous. For example, receptor **1** shows no binding towards *p*-xylenediammonium (**13**) which has a similar chain length to that of hexanediammonium (**7**). Apparently, the wider *p*-phenylene ring of guest **13** greatly reduces the binding affinity toward **1**. Compound **14** with a similar *p*-phenylene linker, but more complementary quaternary ammonium ions does appear to form an insoluble complex with **1** which precluded measurement of its K_a. Methyl viologen **15** which has a similar *p*-arylene geometry and a six carbon spacing between N-atoms forms the **1•15** complex with K_a = 3.50 × 10^3 M^{-1}. As expected, receptor **1** does not bind to the even more voluminous adamantaneammonium guest (**11**) according to ^{1}H NMR. Since receptor **1** has a preference for quaternary ammonium guests to primary ammonium guest, we also checked the binding ability of **1** towards the corresponding quaternary ammonium guest **16**. The binding constant for the **1•16** complex was determined to be (3.02 ± 0.46) × 10^2 M^{-1}. However, analysis of ^{1}H NMR chemical shifts gives no evidence of cavity inclusion of the adamantane moiety, but rather binding of the Me_3N^+ group near the portal in an exclusion complexation type geometry.[4i] Accordingly, It appears that **1** – similar to pillar[5]arene – prefers guests derived from n-alkanes. Receptor **1** is capable of accommodating slightly larger guests in the form of *p*-arylene derived guests **14** and **15**.

Ion-ion electrostatic interactions also appear to play an important role in the complexation behavior of **1**. For example, quaternary monoammonium ion **12** binds to **1** (K_a = 4.72 × 10^2 M^{-1}) 86-fold weaker than quaternary diammonium **8c** does. To further confirm the importance of electrostatic ion-ion and ion dipole interactions in the complexation behavior of **1**, the binding affinity of **1** toward **8c** in water containing different concentrations of NaCl (0, 5, 10, 20, 40, 60, 80, 100 mM) were measured by isothermal titration calorimetry (Supporting Information, Table S1, Figure S41 and S42). In pure water, the K_a for **1•8c** is 9.27 x 10^4 M^{-1} whereas at 100 mM NaCl it is reduced 22-fold to 4.13 x 10^3 M^{-1}. We attribute this reduction in binding affinity – which is also commonly seen for CB[n]-type receptors[21] – to the screening of ion-ion interactions between sulfonate anion and ammonium cation and perhaps also to competitive coordination of the Na^+ ions to the glycoluril C=O groups. Overall, the binding properties of **1** can be seen as a blend of the preferences of the CB[n] and pillararene receptors from which it is derived augmented by the presence of the sulfonate solubilizing groups which allows it to engage in direct ion-ion interactions.

The ability of receptor 1 to form supramolecular vesicles with amphiphilic guest through self-assembly

Liposomes and vesicles are playing significant roles in the field of drug delivery and have been widely studied during the past decades. Moreover, the United States Food and Drug Administration has approved the use of liposomes to formulate some antitumor drugs used clinically.[22] Compared to traditional liposomes and vesicles, supramolecular vesicles are more stimuli responsive because they are formed by discrete recognition processes of their constituent supramolecular amphiphiles.[23] The stimuli responsiveness of supramolecular vesicles makes it easier to control the release of drugs encapsulated within the vesicles, with the potential to improve the therapeutic efficacy and mitigate the side effects of the drugs. The use of pillar[n]arenes and their host•guest complexes with amphiphilic guests to create supramolecular vesicles that encapsulate drugs and undergo triggered release of guest (drugs) has been extensively investigated in recent years.[11c, 12a, h, i, 22c, 23b, 24] Based on the structural similarities between receptor **1** and pillar[n]arenes, we next explored its potential in the construction of supramolecular vesicles when combined with an amphiphilic guest. Accordingly, we modified hexamethonium **8c** with a hydrophobic n-decyl chain to obtain the amphiphilic guest **C10** (Figure 5). Hexamethonium (**8c**) was chosen in this study because it is biocompatible and the K_a for **1•8c** (K_a= 4.05 × 10^4 M^{-1}) is of comparable stability to host•guest assemblies used to construct pillar[n]arene-based supramolecular vesicles.[23b, 24d, e]

Guest **C10** itself is an amphiphile with a long alkyl chain as the hydrophobic tail and a hexamethonium moiety as the hydrophilic head and therefore has the potential to aggregate on its own to form micelles. Accordingly, we first measured the critical aggregation concentration (CAC) of guest **C10** in the absence of receptor **1** by monitoring the optical transmittance at 450 nm of an aqueous solution of **C10** (Supporting Information). No significant change of the optical transmittance occurred as the concentration of guest **C10** was changed from 10 μM to 1.2 mM, which indicates that guest **C10** does not aggregate by itself over this wide concentration range. We next performed the optical transmittance measurements for 1:1 ratio of **1** and **C10** but did not observe a clear CAC which suggested aggregation would occur at a different host:guest stoichiometry.

10.1002/chem.201802981

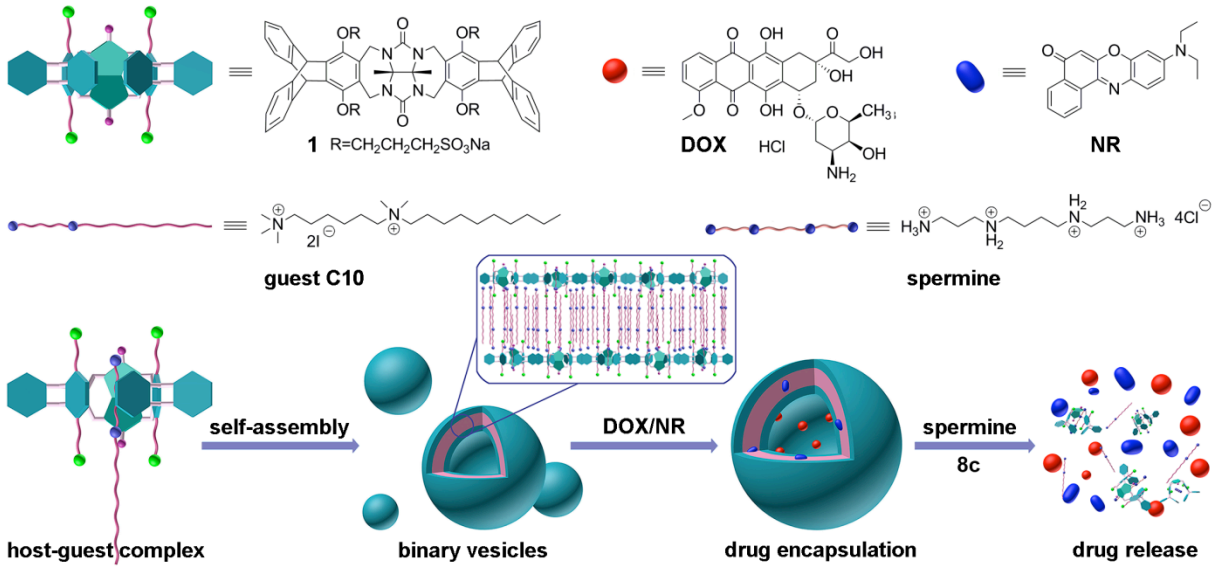


Figure 5 Chemical structures of amphiphilic guest **C10**, doxorubicin (DOX) and nile red (NR) and schematic illustration of the formation of the bilayer vesicles and the process of stimuli responsive release of doxorubicin (DOX) and nile red (NR).

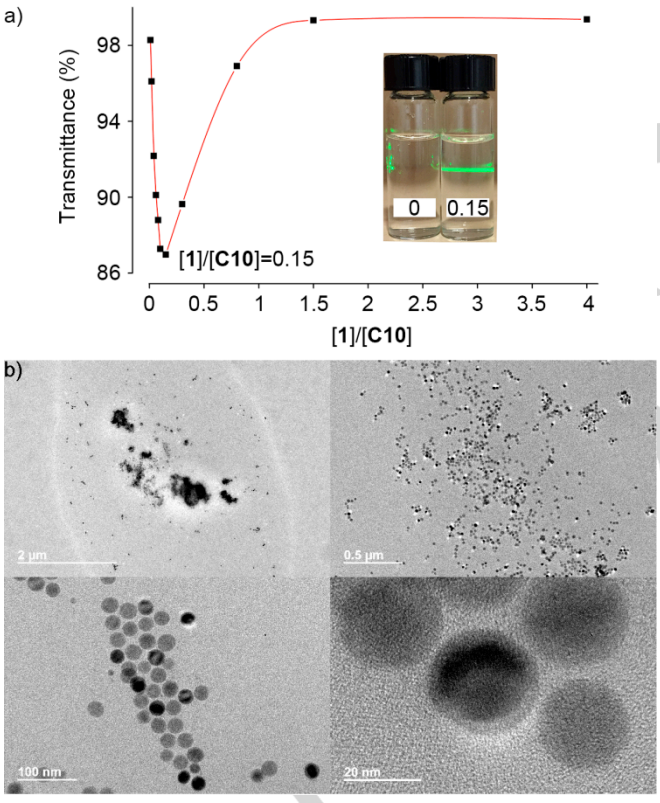


Figure 6 a) Dependence of the optical transmittance at 500 nm on receptor **1** concentration with a fixed guest **C10** concentration (200 μM) at 25 °C. Insert: Tyndall effect of free guest **C10** ([**C10**] = 200 μM, left) and **1•C10** complex ([**C10**] = 200 μM, [**1**] = 30 μM right). b) TEM images of **1•C10** assembly with different scale bar.

In contrast, when a solution of **1** is titrated with a solution of guest **C10** the transmittance decreases, suggesting that aggregation occurs under these conditions. By plotting the transmittance at 450 nm versus the concentration of guest **C10**, we are able to determine the complexation-induced CAC of guest **C10**. At different concentrations of receptor **1** (20 μM, 50 μM, 100 μM) the corresponding CACs are determined to be 28 μM, 72 μM, 150 μM, respectively (Supporting Information). These results demonstrate that the CAC of guest **C10** as its **1•C10** complex in the presence of excess **C10** is significantly lower than uncomplexed **C10**. This complexation induced decrease in CAC is a key design criteria for the preparation of supramolecular vesicles.[25] Next, we determined the best molar ratio between receptor **1** and guest **C10** that leads to the most abundant and robust amphiphilic assembly using the method described by Liu and co-workers for a related system employing sulfonated calix[4]arene and myristoylcholine.[23a] For this purpose, we measured the change in the optical transmittance upon adding **1** into an aqueous solution of **C10** ([**C10**] = 200 μM). To eliminate the influence of self-association of receptor **1**, the changes in the optical transmittance caused by the self-association of receptor **1** alone was subtracted. Figure 6a shows the plot of transmittance at 500 nm as a function of the molar ratio of receptor **1** and guest **C10**. Upon the gradual addition of **1**, the transmittance decreases sharply until a minimum appears at a [**1**]/[**C10**] ratio of 0.15 followed by an increase with further addition of receptor **1** which eventually reaches a plateau. The rapid decrease before the minimum point indicates the formation of a higher-order complex of receptor **1** and **C10** to give a supra-amphiphilic assembly. However, excess amount of receptor **1** in the solution leads to the disassembly of the higher-order complex to afford a simple 1:1 inclusion complex, which therefore results in the recovery of the transmittance after the inflection point. So for the receptor **1** and guest **C10** system, the best molar ratio for the amphiphilic assembly is 0.15 ([**1**]/[**C10**]). The clear Tyndall effect (Figure 6a inset) exhibited by receptor **1** (30 μM) and guest **C10** (200 μM) solution with a molar ratio

0.15 provides strong evidence for the presence of vesicles in solution. In contrast, the Tyndall effect is not observed for a solution of free **C10** (200 μM), further confirming that free **C10** does not form vesicular aggregates at this concentration, which is in accord with the optical transmittance studies. Further evidence of the amphiphilic assembly of receptor **1** and guest **C10** is provided by transmission electron microscopy (TEM, Figure 6b) which shows a relatively homogenous population of spherical nanoparticles (See the Supporting Information for additional and enlarged TEM images). We measured the diameter of 100 particles to determine the average diameter of the vesicles as 25.6 ± 2.69 nm; the thickness of the walls of the hollow vesicles is measured from the TEM images as ≈ 3.5 nm which is comparable to the length of two **1•C10** complexes with antiparallel packing, suggesting that the vesicles have a bilayer wall. We also performed dynamic light scattering (DLS) measurements of solutions of vesicles formed from receptor **1** (30 μM) and guest **C10** (200 μM) which showed an average diameter of ≈ 200 nm which is larger than that determined by TEM. We attribute this discrepancy to the further agglomeration of the vesicles which is apparent in the TEM image (Figure 6b, top left). We find that a 10-fold dilution of the solution of vesicles ([**1**] = 3 μM; [**C10**] = 20 μM) results in a decrease in the average diameter measured by DLS to 140 nm (Supporting Information) which lends further support to this interpretation. Next, we performed optical transmittance measurements as a function of time to monitor the stability of the vesicles. The optical transmittance of **1•C10** aggregation does not change significantly within 48 hours at 25 °C, indicating that the vesicles are stable in water and the vesicular structure can be maintained at least for 48 hours at room temperature (Supporting information).

Encapsulation and Chemical-responsive Release

Bilayer vesicles are able to encapsulate hydrophilic guest molecules within their interior aqueous phase as well as hydrophobic molecules inside the bilayer wall. Therefore, the vesicles formed from receptor **1** and guest **C10** were utilized to encapsulate the hydrophilic drug doxorubicin (DOX) hydrochloride and the hydrophobic dye nile red (NR). Addition of an excess amount of DOX or solid NR to an aqueous solution of vesicles ([**1**] = 30 μM; [**C10**] = 200 μM) results in the encapsulation of DOX or NR, respectively (Supporting information) as evidenced by UV/Vis or fluorescence spectroscopy. For hydrophilic DOX encapsulation, the excess free DOX was removed by dialyzing the DOX@vesicles solution against water and excess hydrophobic NR was simply removed by filtering the NR@vesicles suspension through a 0.45 μM microfilter to obtain a clear solution of NR@vesicles. The encapsulation of NR can be visually observed by the intense color of the solution (Figure 7d). As a control, we attempted to solubilize NR under the same conditions in plain water, but the solution remained nearly colorless.[26] These visual observations were confirmed by UV/vis spectroscopy (Figure 7c). The NR@vesicles solution displays an intense UV/Vis absorbance while NR in water shows a weak absorbance, indicating that only a small amount of NR can be dissolved in water in the absence of vesicles formed by receptor **1** and guest **C10**. The encapsulation of both hydrophilic (DOX) and hydrophobic (NR) molecules within the vesicles provides further evidence of their bilayer structure.

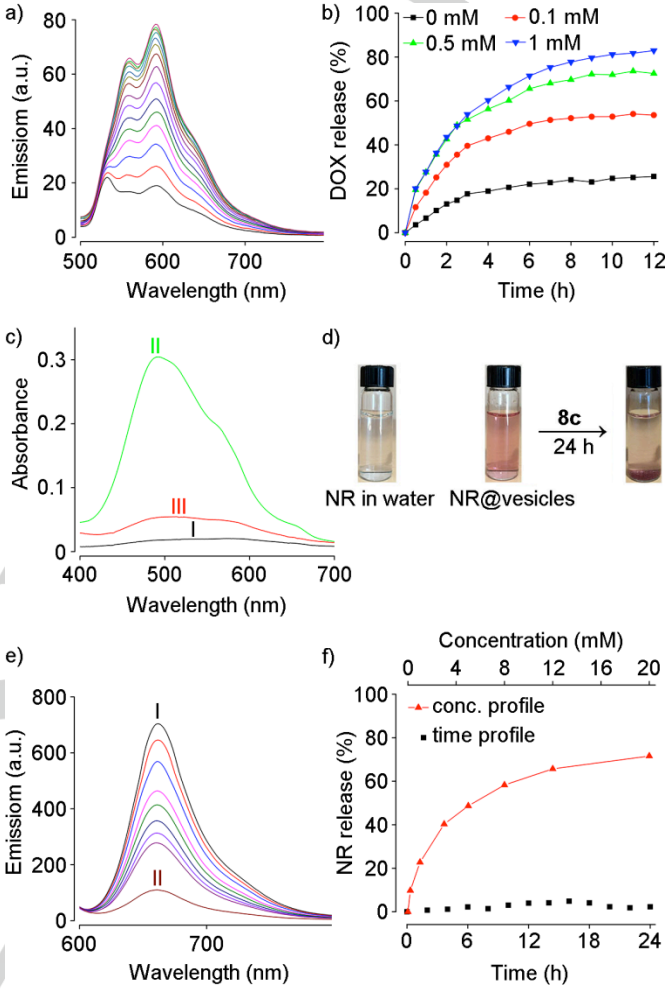


Figure 7 a) Increase of fluorescence of DOX outside the dialysis bag during the release process triggered by hexamethonium **8c** from DOX@vesicles (λ_{ex} = 450 nm) inside the dialysis bag. b) Plot of release percentage of DOX based on emission intensity at 590 nm versus time. c) UV/vis spectrum of (I) free NR in water, (II) NR@vesicles in water, and (III) NR@vesicles in water after treating with hexamethonium **8c** (1 mM) for 24 h. d) Naked eye detection of hydrophobic NR encapsulation and chemical-responsive release. e) Fluorescence titration of NR@vesicles with **8c** (λ_{ex} = 580 nm) in water. f) Plot of release percentage of NR based on emission intensity at 660 nm for NR@vesicles in the absence of **8c** versus time and separately with increasing concentration of **8c**.

We next sought to demonstrate the triggered release of the encapsulated cargo DOX and NR. For this purpose, we employed guest hexamethonium (**8c**) as a chemical stimulus because **8c** should have the same binding affinity towards receptor **1** as the amphiphilic guest **C10** does, which can compete with guest **C10** to form the **1•8c** complex and thereby trigger the disruption of the vesicles. Figure 7a shows the fluorescence emission spectra outside the dialysis bag of the systems comprising DOX@vesicles in the dialysis bag in the presence of **8c** (1 mM) outside the dialysis bag over a period of 12 h. The increase of the

fluorescence intensity signals that DOX is released from the vesicles and accumulated outside the dialysis bag. The normalized release of DOX (%) triggered by **8c** at a series of concentrations is plotted versus time in Figure 7b. Prior to the use of the trigger, the supramolecular vesicles show a premature leakage of ≈ 25% encapsulated DOX. In the presence of guest **8c**, the majority of the cargo is released as a result of the competitive binding of guest **8c** towards receptor **1** and the subsequent disruption of the supramolecular vesicles. The cumulative release efficiency is 54% with 0.1 mM guest **8c** which increases to 73% with 0.5 mM **8c** and 83% with 1 mM **8c**, respectively. For the release of hydrophobic NR we simply added different amounts of guest **8c** into the NR@vesicles solutions and kept them standing still for 24 h. Figure 7d shows the pictures of the solution of NR@vesicles and precipitated NR observed 24h later after the addition of guest **8c**. The UV/vis spectrum (Figure 7c) shows a dramatic drop of absorption intensity after the addition of 20 mM guest **8c** into the NR@vesicles solution. These results further establish that guest **8c** displaces the amphiphilic guest **C10** from the cavity of receptor **1** and triggers the disassembly cascade that releases encapsulated NR. Similarly, the fluorescence emission intensity at 660 nm of solutions of NR@vesicles decreases substantially during the titration with guest **8c** (0 – 20 mM) (Figure 7e), reflecting the chemical responsive release of NR from the hydrophobic wall of bilayer vesicles constructed by receptor **1** and guest **C10.** We calculate that 72% of NR is released due to the addition of 20 mM guest **8c** into the solution of NR@vesicles (Figure 7f). We also measured the fluorescence intensity of freshly prepared samples of NR@vesicles without **8c** over 12 h to test the premature leakage and we did not observe significant changes in fluorescence intensity over this period time (≤10% leakage observed) for NR loaded vesicles (Supporting information), which suggests the premature leakage of hydrophobic drugs from vesicles constructed by receptor **1** and guest **C10** will not be problematic (Figure 7f).

Finally, we tried to improve the release efficiency of DOX and NR by employing spermine (**10**) which causes the precipitation of receptor **1** from **1•8c** complex (Supporting information). Unfortunately, the release efficiency of DOX and NR is not improved when spermine (1 mM) is used as trigger giving only 73% release of DOX over the period of 24 h. Similarly, the addition of spermine (20 mM) gave only 56% release of encapsulated NR (Supporting information). In spite of its ability to precipitate receptor **1**, spermine is a relatively poor trigger for the disassembly of DOX@vesicles or NR@vesicles. We attribute the relatively poor triggering ability of spermine (**10**) to an inability to outcompete **8c** as a binder for **1** as might be expected based on the binding properties of the other primary ammonium guests measured above.

Conclusions

In summary, we have synthesized water soluble tetrasulfonated C-shaped molecular container **1** that comprises glycoluril and triptycene building blocks and that can be viewed as a hybrid of CB[n] and pillar[n]arene type receptors. X-ray crystallography confirms the expected molecular conformation of the receptor with pillar[5]arene sized cavity that is defined by four aromatic rings and one glycoluril unit. Receptor **1** does not undergo significant self-association in dilute aqueous solution (K_s = 186 M^{-1}). Receptor **1** binds to hydrophobic cations (e.g. hexamethonium) in aqueous solution and displays guest length, guest functional group (e.g. 1˚ versus 4˚ ammonium), and [salt] dependent binding affinities that are reminiscent of CB[n]-type hosts but is selective for narrow $(CH_2)_n$ derived guests as is commonly observed for pillar[5]arenes. Receptor **1** and amphiphilic guest **C10** co-assemble to form supramolecular bilayer vesicles in water with an average diameter of 25.6 ± 2.69 nm. The hydrophilic interior cavity and the hydrophobic bilayer regions of the vesicles can be utilized to encapsulate water soluble drug DOX and hydrophobic dye NR, respectively, and their release can be triggered by chemical stimulus in the form of **8c** and **10** due to competitive host•guest binding which induces disruption of the vesicles. The work sets the stage for the use of **1** and related compounds in the variety of chemical and biological applications now envisioned for pillararenes and CB[n] including drug solubilization and delivery, optical sensing, molecular machines, and polymer stabilization and processing. In these latter areas, the acyclic nature of **1** may be particularly advantageous since it allows complexation directly at the center of a chain rather than translocation along the chain. Work along these directions will be reported in due course.

Acknowledgements

We thank the National Science Foundation (CHE-1404911 and CHE-1807486) and the International Graduate Exchange Program of Beijing Institute of Technology for financial support.

Conflicts of interest

The authors declare no conflict of interest.

Keywords: cucurbituril • pillararene • hybrid• triptycene • triggered release

[1] a) C. J. Pedersen, *J. Am. Chem. Soc.* **1967**, *89*, 7017–7036; b) J.-M. Lehn, J. P. Sauvage and B. Dietrich, *J. Am. Chem. Soc.* **1970**, *92*, 2916-2918; c) D. J. Cram, *Science* **1983**, *219*, 1177-1183; d) M. M. Boyle, R. A. Smaldone, A. C. Whalley, M. W. Ambrogio, Y. Y. Botros and J. F. Stoddart, *Chem. Sci.* **2011**, *2*, 204-210; e) E. R. Kay and D. A. Leigh, *Angew. Chem. Int. Ed.* **2015**, *54*, 10080-10088; f) M. D. Pluth and K. N. Raymond, *Chem. Soc. Rev.* **2007**, *36*, 161-171; g) D.-H. Qu and H. Tian, *Chem. Sci.* **2011**, *2*, 1011-1015; h) J.-P. Sauvage, *Acc. Chem. Res.* **1998**, *31*, 611-619; i) M. Yoshizawa, J. K. Klosterman and M. Fujita, *Angew. Chem. Int. Ed.* **2009**, *48*, 3418-3438; j) J. Zhou, G. Yu and F. Huang, *Chem. Soc. Rev.* **2017**, *46*, 7021-7053; k) I. V. Kolesnichenko and E. V. Anslyn, *Chem. Soc. Rev.* **2017**, *46*, 2385-2390.

[2] a) D. J. Cram, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1009-1020; b) D. J. Cram and J. M. Cram, *Container molecules and their guests*, Royal Society of Chemistry, **1997**.

[3] a) F. Bellia, D. La Mendola, C. Pedone, E. Rizzarelli, M. Saviano and G. Vecchio, *Chem. Soc. Rev.* **2009**, *38*, 2756-2781; b) M. V. Rekharsky and Y. Inoue, *Chem. Rev.* **1998**, *98*, 1875-1917; c) M. Ortiz, C., J. M. Garcia Fernandez and J. M. Benito, *Chem. Soc. Rev.* **2011**, *40*, 1586-1608; d) V. Böhmer, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 713-745; e) D. S. Guo and Y. Liu, *Chem. Soc. Rev.* **2012**, *41*, 5907-5921; f) C. D. Gutsche, *Acc. Chem. Res.* **1982**, *16*, 161-170; g) S. B. Nimse and T. Kim, *Chem. Soc. Rev.* **2013**, *42*, 366-386; h) F. Diederich, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 362-386; i) S. Misumi and T. Otsubo, *Acc. Chem. Res.* **1978**, *11*, 251-256; j) D. Fiedler, D. H. Leung, R. G. Bergman and K. N. Raymond, *Acc. Chem. Res.* **2005**, *38*, 351-360; k) J. Rebek, *Acc. Chem. Res.* **2009**, *42*, 1660-1668; l) Z. Laughrey and B. C. Gibb, *Chem. Soc. Rev.* **2011**, *40*, 363-386.

[4] a) W. L. Mock and N.-Y. Shih, *J. Org. Chem.* **1986**, *51*, 4440-4446; b) J. Kim, I.-S. Jung, S.-Y. Kim, E. Lee, J.-K. Kang, S. Sakamoto, K. Yamaguchi and K. Kim, *J. Am. Chem. Soc.* **2000**, *122*, 540-541; c) A. Day, A. P. Arnold, R. J. Blanch and B. Snushall, *J. Org. Chem.* **2001**, *66*, 8094-8100; d) J. W. Lee, S. Samal, N. Selvapalam, H. J. Kim and K. Kim, *Acc. Chem. Res.* **2003**, *36*, 621-630; e) J. Lagona, P. Mukhopadhyay, S. Chakrabarti and L. Isaacs, *Angew. Chem. Int. Ed.* **2005**, *44*, 4844-4870; f) K. I. Assaf and W. M. Nau, *Chem. Soc. Rev.* **2015**, *44*, 394-418; g) S. J. Barrow, S. Kasera, M. J. Rowland, J. del Barrio and O. A. Scherman, *Chem. Rev.* **2015**, *115*, 12320-12406; h) A. E. Kaifer, *Acc. Chem. Res* **2014**, *47*, 2160-2167; i) E. Masson, X. Ling, R. Joseph, L. Kyeremeh-Mensah and X. Lu, *RSC Adv.* **2012**, *2*, 1213-1247; j) X.-J. Cheng, L.-L. Liang, K. Chen, N.-N. Ji, X. Xiao, J.-X. Zhang, Y.-Q. Zhang, S.-F. Xue, Q.-J. Zhu, X.-L. Ni and Z. Tao, *Angew. Chem. Int. Ed.* **2013**, *52*, 7252-7255.

[5] L. Cao, M. Sekutor, P. Y. Zavalij, K. Mlinaric-Majerski, R. Glaser and L. Isaacs, *Angew. Chem. Int. Ed.* **2014**, *53*, 988-993.

[6] a) Y. H. Ko, E. Kim, I. Hwang and K. Kim, *Chem. Commun.* **2007**, 1305-1315; b) H. Yang, B. Yuan, X. Zhang and O. A. Scherman, *Acc. Chem. Res.* **2014**, *47*, 2106-2115; c) J. del Barrio, P. N. Horton, D. Lairez, G. O. Lloyd, C. Toprakcioglu and O. A. Scherman, *J. Am. Chem. Soc.* **2013**, *135*, 11760-11763; d) B. C. Pemberton, R. Raghunathan, S. Volla and J. Sivaguru, *Chem. Eur. J.* **2012**, *18*, 12178-12190; e) R. N. Dsouza, A. Hennig and W. M. Nau, *Chem. Eur. J.* **2012**, *18*, 3444-3459; f) L. Isaacs, *Acc. Chem. Res.* **2014**, *47*, 2052-2062; g) Y. Ahn, Y. Jang, N. Selvapalam, G. Yun and K. Kim, *Angew. Chem. Int. Ed.* **2013**, *52*, 3140-3144; h) D. W. Lee, K. M. Park, M. Banerjee, S. H. Ha, T. Lee, K. Suh, S. Paul, H. Jung, J. Kim, N. Selvapalam, S. H. Ryu and K. Kim, *Nat. Chem.* **2011**, *3*, 154-159.

[7] S. Ganapati and L. Isaacs, *Isr. J. Chem.* **2018**, *58*, 250-263.

[8] D. Ma, G. Hettiarachchi, D. Nguyen, B. Zhang, J. B. Wittenberg, P. Y. Zavalij, V. Briken and L. Isaacs, *Nat. Chem.* **2012**, *4*, 503-510.

[9] a) T. Minami, N. A. Esipenko, B. Zhang, M. E. Kozelkova, L. Isaacs, R. Nishiyabu, Y. Kubo and P. Anzenbacher, Jr., *J. Am. Chem. Soc.* **2012**, *134*, 20021-20024; b) C. Shen, D. Ma, B. Meany, L. Isaacs and Y. Wang, *J. Am. Chem. Soc.* **2012**, *134*, 7254-7257; c) D. Ma, B. Zhang, U. Hoffmann, M. G. Sundrup, M. Eikermann and L. Isaacs, *Angew. Chem. Int. Ed.* **2012**, *51*, 11358-11362; d) B. Zhang and L. Isaacs, *J. Med. Chem.* **2014**, *57*, 9554-9563; e) X. Lu, S. K. Samanta, P. Y. Zavalij and L. Isaacs, *Angew. Chem. Int. Ed.* **2018**, ASAP.

[10] a) X. Liu, Z. J. Weinert, M. Sharafi, M. Liao, J. Li and S. T. Schneebeli, *Angew. Chem. Int. Ed.* **2015**, *54*, 12772-12776; b) F.-G. Klaerner and T. Schrader, *Acc. Chem. Res.* **2013**, *46*, 967-978; c) K. Jono, A. Suzuki, M. Akita, K. Albrecht, K. Yamamoto and M. Yoshizawa, *Angew. Chem. Int. Ed.* **2017**, *56*, 3570-3574; d) P. Talbiersky, F. Bastkowski, F.-G. Klärner and T. Schrader, *J. Am. Chem. Soc.* **2008**, *130*, 9824-9828; e) D. Bier, R. Rose, K. Bravo-Rodriguez, M. Bartel, J. M. Ramirez-Anguita, S. Dutt, C. Wilch, F.-G. Klärner, E. Sanchez-Garcia, T. Schrader and C. Ottman, *Nat. Chem.* **2013**, *5*, 234-239; f) A. E. Rowan, J. A. A. W. Elemans and R. J. M. Nolte, *Acc. Chem. Res.* **1999**, *32*, 995-1006.

[11] a) T. Ogoshi, S. Kanai, S. Fujinami, T. A. Yamagishi and T. Nakamoto, *J. Am. Chem. Soc.* **2008**, *130*, 5022-5023; b) M. Xue, Y. Yang, X. Chi, Z. Zhang and F. Huang, *Acc. Chem. Res* **2012**, *45*, 1294–1308; c) X. Chi, X. Ji, D. Xia and F. Huang, *J. Am. Chem. Soc.* **2015**, *137*, 1440-1443; d) T. Ogoshi, T. A. Yamagishi and Y. Nakamoto, *Chem. Rev.* **2016**, *116*, 7937-8002.

[12] a) G. Yu, X. Zhou, Z. Zhang, C. Han, Z. Mao, C. Gao and F. Huang, *J. Am. Chem. Soc.* **2012**, *134*, 19489-19497; b) S. H. Li, H. Y. Zhang, X. Xu and Y. Liu, *Nat. Commun.* **2015**, *6*, 7590; c) T. Ogoshi, T. Akutsu, D. Yamafuji, T. Aoki and T. A. Yamagishi, *Angew. Chem. Int. Ed.* **2013**, *52*, 8111-8115; d) X. B. Hu, Z. Chen, G. Tang, J. L. Hou and Z. T. Li, *J. Am. Chem. Soc.* **2012**, *134*, 8384-8387; e) W. Si, Z. T. Li and J. L. Hou, *Angew. Chem. Int. Ed.* **2014**, *53*, 4578-4581; f) P. Wang, Z. Li and X. Ji, *Chem. Commun.* **2014**, *50*, 13114-13116; g) G. Yu, Z. Zhang, C. Han, M. Xue, Q. Zhou and F. Huang, *Chem. Commun.* **2012**, *48*, 2958-2960; h) X. Chi, G. Yu, L. Shao, J. Chen and F. Huang, *J. Am. Chem. Soc.* **2016**, *138*, 3168-3174; i) Q. Duan, Y. Cao, Y. Li, X. Hu, T. Xiao, C. Lin, Y. Pan and L. Wang, *J. Am. Chem. Soc.* **2013**, *135*, 10542-10549; j) Z. Zhang, Y. Luo, J. Chen, S. Dong, Y. Yu, Z. Ma and F. Huang, *Angew. Chem. Int. Ed.* **2011**, *50*, 1397-1401.

[13] R. Zhao, K. Jie, Y. Zhou, E. Li, J. Liu and F. Huang, *Tetrahedron Lett.* **2018**, *59*, 1204-1207.

[14] a) J. H. Chong and M. J. MacLachlan, *Chem. Soc. Rev.* **2009**, *38*, 3301-3315; b) Y. Han, Z. Meng, Y. X. Ma and C. F. Chen, *Acc. Chem. Res.* **2014**, *47*, 2026-2040; c) T. M. Swager, *Acc. Chem. Res.* **2008**, *41*, 1181-1189.

[15] a) W.-H. Huang, P. Y. Zavalij and L. Isaacs, *J. Am. Chem. Soc.* **2008**, *130*, 8446-8454; b) L. Gilberg, B. Zhang, P. Y. Zavalij, V. Sindelar and L. Isaacs, *Org. Biomol. Chem.* **2015**, *13*, 4041-4050.

[16] a) Y. X. Ma, X. Chi, X. Yan, J. Liu, Y. Yao, W. Chen, F. Huang and J.-L. Hou, *Org. Lett.* **2012**, *14*, 1532-1535; b) C. Han, F. Ma, Z. Zhang, B. Xia, Y. Yu and F. Huang, *Org. Lett.* **2010**, *12*, 4360-4363.

[17] D. Sigwalt, D. Moncelet, S. Falcinelli, V. Mandadapu, P. Y. Zavalij, A. Day, V. Briken and L. Isaacs, *Chem. Med. Chem.* **2016**, *11*, 980-989.

[18] N. She, D. Moncelet, L. Gilberg, X. Lu, V. Sindelar, V. Briken and L. Isaacs, *Chem. Eur. J.* **2016**, *22*, 15270-15279.

[19] a) C. Li, L. Zhao, J. Li, X. Ding, S. Chen, Q. Zhang, Y. Yu and X. Jia, *Chem. Commun.* **2010**, *46*, 9016-9018; b) G. Yu, C. Han, Z. Zhang, J. Chen, X. Yan, B. Zheng, S. Liu and F. Huang, *J. Am. Chem. Soc.* **2012**, *134*, 8711-8717.

[20] D. Ma, P. Y. Zavalij and L. Isaacs, *J. Org. Chem.* **2010**, *75*, 4786-4795.

[21] a) H. J. Buschmann, E. Cleve and E. Schollmeyer, *Inorganica Chimica Acta* **1992**, *193*, 93-97; b) C. Marquez, R. R. Hudgins and W. M. Nau, *J. Am. Chem. Soc.* **2004**, *126*, 5806-5816; c) C. A. Burnett, D. Witt, J. C. Fettinger and L. Isaacs, *J. Org. Chem.* **2003**, *68*, 6184-6191; d) Y. M. Jeon, J. Kim, D. Whang and K. Kim, *J. Am. Chem. Soc.* **1996**, *118*, 9790-9791.

[22] a) H. I. Chang and M. K. Yeh, *Int. J. Nanomedicine* **2012**, *7*, 49-60; b) K. M. Giacomini, S. M. Huang, D. J. Tweedie, L. Z. Benet, K. L. Brouwer, X. Chu, A. Dahlin, R. Evers, V. Fischer, K. M. Hillgren, K. A. Hoffmaster, T. Ishikawa, D. Keppler, R. B. Kim, C. A. Lee, M. Niemi, J. W. Polli, Y. Sugiyama, P. W. Swaan, J. A. Ware, S. H. Wright, S. W. Yee, M. J. Zamek-Gliszczynski and L. Zhang, *Nat. Rev. Drug Discov.* **2010**, *9*, 215-236; c) L. Jiang, X. Huang, D. Chen, H. Yan, X. Li and X. Du, *Angew. Chem. Int. Ed.* **2017**, *56*, 2655-2659; d) R. Langer, *Science* **1990**, *249*, 1527-1533.

[23] a) D. S. Guo, K. Wang, Y. X. Wang and Y. Liu, *J. Am. Chem. Soc.* **2012**, *134*, 10244-10250; b) D. Xia, P. Wang and B. Shi, *Org. Lett.* **2017**, *19*, 202-205.

[24] a) X. Liu, K. Jia, Y. Wang, W. Shao, C. Yao, L. Peng, D. Zhang, X. Y. Hu and L. Wang, *ACS Appl. Mater. Interfaces* **2017**, *9*, 4843-4850; b) L. Rui, L. Liu, Y. Wang, Y. Gao and W. Zhang, *ACS Macro Letters* **2015**, *5*, 112-117; c) L. Shao, J. Zhou, B. Hua and G. Yu, *Chem. Commun.* **2015**, *51*, 7215-7218; d) G. Yu, W. Yu, L. Shao, Z. Zhang, X. Chi, Z. Mao, C. Gao and F. Huang, *Adv. Funct. Mat.* **2016**, *26*, 8999-9008; e) G. Yu, R. Zhao, D. Wu, F. Zhang, L. Shao, J. Zhou, J. Yang, G. Tang, X. Chen and F. Huang, *Polym. Chem.* **2016**, *7*, 6178-6188.

[25] C. Wang, Z. Wang and X. Zhang, *Acc. Chem. Res.* **2012**, *45*, 608-618.

[26] S. K. Samanta, J. Quigley, B. Vinciguerra, V. Briken and L. Isaacs, *J. Am. Chem. Soc.* **2017**, *139*, 9066-9074.

10.1002/chem.201802981

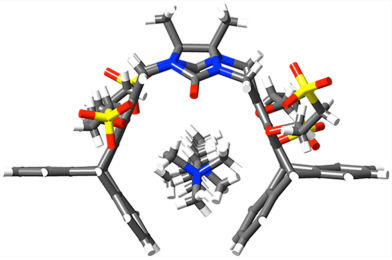
WILEY-VCH

10.1002/chem.201802981

WILEY-VCH

FULL PAPER

Cucurbituril-pillararene hybrid molecular container: we report the synthesis, x-ray crystal structure, molecular recognition properties and triggered release application of a hybrid receptor **1**.



Wenjin Liu,[a,b] Xiaoyong Lu,[b] Weijian Xue,[b] Soumen K. Samanta,[b] Peter Y. Zavalij,[b] Zihui Meng,[a] and Lyle Isaacs*[b]*

Page No. – Page No.

Hybrid molecular container based on glycoluril and triptycene: synthesis, binding properties, and triggered release