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Cucurbit[7]uril-Based Vesicles Formed by Self-assembly of Supramolecular Amphiphiles†

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Cucurbituril (CB), a well-known macrocyclic cavitand, has been used extensively to construct supramolecular aggregates. Based on host-guest intertactions, an adamantanyl derivative guest molecule was designed and synthesized to prepare a supramolecular amphiphile with cucurbit[7]uril. In aqueous solution, the cucurbit[7]uril based supramolecular amphiphiles self-assemble into well-defined vesicles, and their disassembly can be achieved by addition of excess competitive agent 1-adamantanamine hydrochloride. This vesicle functions as a new nanocapsule to encapsulate molecules within its hollow cavity. Through competitive disassembly of supramolecular amphiphiles, the vesicles behave as a novel drug delivery carrier.

Keywords self-assembly, cucurbituril, vesicles, supramolecular amphiphiles, drug delivery

Introduction

Self-assembled vesicles have been a subject of intense research for the last three decades[1-4] because of their potential applications in various areas such as the development of biomimetic systems,[5] drug/gene delivery systems[6-9] and nanostructured materials.[10-12] Among a number of designed vesicles, vesicles formed by self-assembled supramolecular amphiphilic molecules have attracted much attention.[13-17] In recent years, supramolecular amphiphiles formed through noncovalent driving forces have been developed as a new type of building block for future fabrication of supramolecular architectures through multilevel self-assembly.[18-27] Among them, the host-guest interactions, such as cucurbit[*n*]uril and cyclodextrin systems, have been proven to be important in the construction of supramolecular amphiphiles. The self-assembly of host-guest superamphiphiles can provide opportunities not only for structural versatility but also for functional modulation of nanomaterials.[24,28-38] For example, the easily controlled assembly and disassembly can be used to realize drug delivery.

Cucurbit[*n*]uril (CB[*n*] $n=5$—8), a family of macrocyclic compounds comprising *n* glycoluril units, has a hydrophobic cavity that is accessible through two identical carbony-fringed portals.[39,40] These homologues have much larger internal cavities and portals and thus can be expected to have much improved host abilities as compared to cucurbituril itself, especially CB[7] and CB[8]. CB[7] has an internal cavity with a diameter of 7.3 Å and a portal diameter of 5.4 Å.[41] The size of the cavity is similar to that of β-cyclodextrin (β-CD), which is a typical host-guest pair with adamantane. The previous complex experiments demonstrated that the cavity inside CB[7] is ideally suitable for the encapsulation of adamantane.

Supramolecular chemistry of CB[*n*], including their host-guest chemistry, has been studied extensively by Mock,[39,42] Kim,[41,43-49] and others.[50-61] As known, however, the supramolecular architectures through multilevel self-assembly based on CB[7] have rarely been reported before.[62] Herein, we report a novel way to construct vesicles triggered by direct self-assembly of CB[7]-based host-guest superamphiphiles (Scheme 1). The disassembly of vesicles can be controlled by adding a guest analogue to compete with the guest molecule within the CB[7] cavity. Using fluorescent rhodamine B (RB) as a drug model, the controlled release experiments have been performed. The results demonstrated that this new kind of supramolecular assembly has great potential to function as drug-loaded nanocapsules for controlled drug release.

Experimental

Materials

Glycoluril was purchased from Yinghua Co. (Tai-

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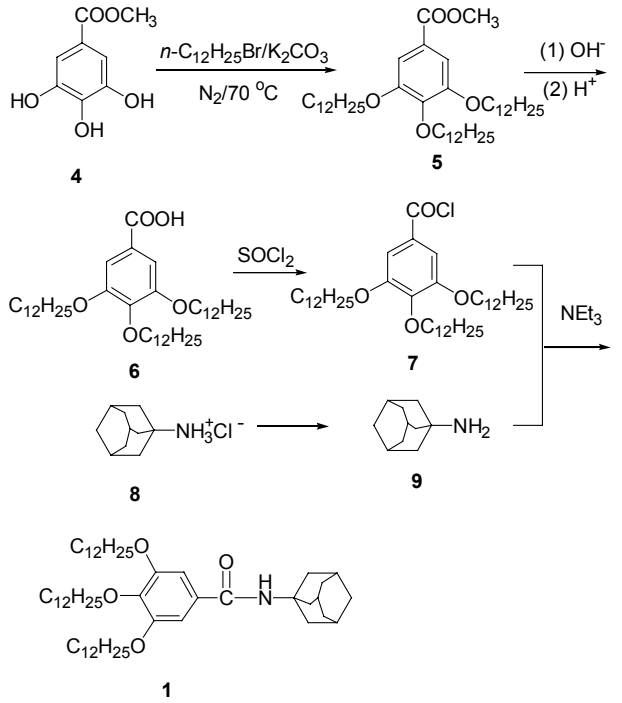
Scheme 1 Synthetic routes of the guest molecule **1**



yuan, China) and further purified by recrystallization for three times in water. Methyl 3,4,5-trihydroxybenzoate (methyl gallate) of 98% was obtained from Alladdin Co. (Shanghai, China). 1-Bromododecane of 98% and 1-adamantanamine hydrochloride of 99% were purchased from Alfa Aesar. Dialysis membrane (MWCO: 2000) was obtained from Sangon Biotech Co., Ltd (Shanghai, China). In all the experiments, organic solvents were reagent or high-performance liquid chromatography (HPLC) grade, and doubly distilled water was used.

Synthesis of cucurbit[7]uril (host)

The host molecule (cucurbit[7]uril) was synthesized according to the method reported by Kim.[63] Glycoluril (5.68 g, 40 mmol) was reacted with formaldehyde (w= 37%, 7.0 mL) in 9 mol•L^{-1} sulfuric acid (20 mL) at 75 ℃ for 24 h and then at 100 ℃ for 12 h. After the reaction mixture was poured into water (200 mL), acetone (1.0 L) was added to produce precipitate. The precipitate was separated by decantation, washed with water/acetone (V∶V=1∶4), and filtered. 300 mL of water/acetone (V∶V=1∶2) was added to the resulting solid and stirred for a few minutes. The precipitate is the major product CB[6] that was separated by filtration. Acetone (800 mL) was added to the filtrate to produce precipitate which was filtered, washed with acetone and dried under vacuum to produce a mixture of most CB[5] and CB[7]. The mixture of CB[5] and CB[7] was dissolved in water (75 mL). Methanol (75 mL) was added to the solution to produce precipitate which was filtered, washed with methanol (10 mL) and dried under vacuum to yield a white power containing most CB[7] (600 mg). The further purification of CB[7] can be achieved by recrystallization. ^{1}H NMR (D_2O, 500 MHz) δ: 5.75 (d, 14H, $CH_2\times14$), 5.50 (s, 14H, $CH\times14$), 4.21 (d, 14H, $CH_2\times14$).

Synthesis of adamantanol-1-3,4,5-trihydroxy-benzoicamide (guest)

The guest molecule was synthesized according to the method reported previously (Scheme 1).[64] Methyl 3,4,5-trihydroxybenzoate (**4**, 1 g, 5.43 mmol) and roasted K_2CO_3 (5 g) were added to a deoxygenated mixture of DMF (15 mL) and 1-bromododecane (6 mL, 25.03 mmol) under nitrogen for 1 h. Then the mixture was heated at 70 ℃ for 12 h. Plentiful water was added when the reaction mixture was cooled to room temperature. The crude product was filtrated and recrystallized for three times in acetone to get **5** as a yellow solid (3.31 g, 89% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.25 (s, 2H, ArH), 4.03—3.99 (m, 6H, $OCH_2\times3$), 3.89 (s, 3H, OCH_3), 1.84—1.78 (m, 4H, $CH_2\times2$), 1.77—1.72 (m, 2H, CH_2), 1.50—1.44 (m, 6H, $CH_2\times3$), 1.34—1.26 (m, 48H, $CH_2\times24$), 0.88 (t, J=7.1 Hz, 9H, $CH_3\times3$).

A solution of **5** (1.0 g, 1.45 mmol) and excess potassium hydroxide (5.6 g, 0.1 mol) in ethanol (100 mL, 95%) was kept refluxing for 2 h. Hydrochloric acid (15%) was added to make the solution acidic. A large amount of water was added and the resulting precipitate was collected by filtration. After recrystallization from acetone for 3 times, 3,4,5-trihydroxybenzoic acid (**6**) was obtained as a white solid (0.78 g, 76% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.32 (s, 2H, Ar), 4.06—4.01 (m, 6H, $OCH_2\times3$), 1.85—1.79 (m, 4H, $CH_2\times2$), 1.78—1.72 (m, 2H, CH_2), 1.51—1.45 (m, 6H, $CH_2\times3$), 1.35—1.27 (m, 48H, $CH_2\times24$), 0.88 (t, J=7.1 Hz, 9H, $CH_3\times3$).

An aqueous solution of sodium hydroxide was added slowly to a stirred solution of amantadine hydrochloride (310 mg, 1.65 mmol) in deionized water (20 mL). The solution was extracted by dichloromethane for three times and the solvent was removed by rotary evaporator. The residue was dried under vacuum to yield a white solid **9**, which was used for the next step without further purification.

3,4,5-Trihydroxybenzoic acid (**6**, 1.0 g, 1.48 mmol) was dissolved in some thionyl chloride (about 1 mL) and stirred for 3 h at room temperature to get **7**. The volatiles were evaporated and the residue was redissolved together with dry triethylamine (3 mL) in anhydrous dichloromethane. The solution of **9** in 20 mL anhydrous dichloromethane was added into the above mixture solution and stirred overnight with ice bath. The volatiles were removed and the residue was purified by column chromatography (silica gel, dichloromethane as eluent) to give an orange solid **1** (0.82 g, 69% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.90 (s, 2H, ArH), 5.68 (s, 1H, CONH), 4.01—3.95 (m, 6H, $OCH_2\times3$), 2.12 (s, 9H, $CH_2\times3$ & $CH\times3$ in adamantane), 1.82—1.70 (m, 12H), 1.49—1.43 (m, 6H, $CH_2\times3$), 1.35—1.26 (m,

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48H, $CH_2\times24$), 0.88 (t, $J=7.1$ Hz, 9H, $CH_3\times3$). MALDI-MS calcd for $C_{53}H_{93}NO_4$ $[M+H]^+$ 807.7, found 808.8.

Preparation of vesicles

In a general preparation procedure, the purified guest molecules **1** (8.08 mg) were dispersed in DMF (1 mL) by ultrasonic till a clear solution was obtained at 40 ℃. Then DMF solution (100 μL) was slowly injected into a cuvette with 9.9 mL CB[7] solution (100 μmol/L) in it at 40 ℃ with ultrasonication. Opalescence appeared immediately, which indicated the formation of aggregates. The fine dispersion was cooled to room temperature at ambient conditions overnight for further study.

Disassembly of vesicles

Disassembly of the vesicles can be achieved easily by adding a competitive molecule of guest. After the vesicles were formed, excess 1-adamantanamine hydrochloride, an analogue of the guest molecule that can compete with the guest molecule within the CB[7] cavity, was added. The vesicles can be disassembled in 10 min with ultrasonication.

Scanning electron microscopy (SEM)

Samples for scanning electron microscopy were prepared by transferring a drop of sample solution onto a silicon wafer. The samples were freeze-dried before measurement. All SEM measurements were carried out on a JEOL JSM 6700F electron microscopy, and operated at an acceleration voltage of 3.0 kV.

Transmission electron microscope (TEM)

Samples for transmission electron microscopy were prepared by placing a drop of sample solution on a 300-mesh, carbon-coated copper grid on filter paper and air-dried before measurement. TEM experiments were performed with a JEOL1011 transmission electron microscope and operated at an acceleration voltage of 100 kV.

Dynamic light scattering (DLS)

The mean size distribution of the vesicles was measured by Malvern-ZetaSizer Nano ZS dynamic light scattering instrument at 25 ℃. Each experiment was repeated 3 times. The average diameter given by this instrument is number weighed.

In vitro drug release studies

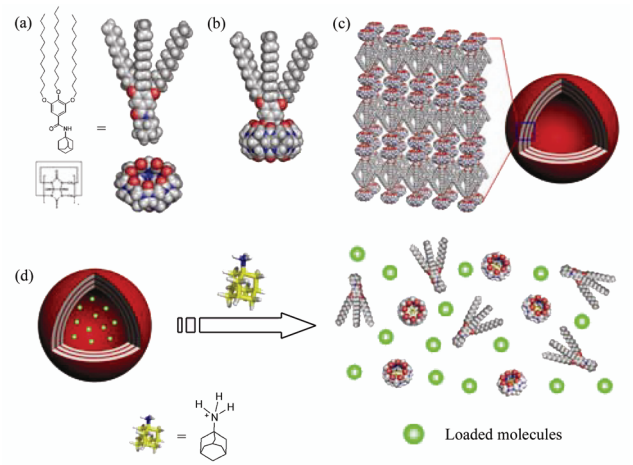
Fluorescent rhodamine B (RB) was used as the drug model compound. The release of RB from vesicle solution and disassembled vesicle solution was examined using the dialysis method at room temperature and was compared with free RB dissolved in water. Before the *in vitro* release experiments, the concentrations of RB were adjusted to 10^{-5} mol/L. An aliquot of each solution (10 mL) was placed in a dialysis membrane (DWCO: 2000 Da) and tightly sealed. The dialysis bag was immersed in 500 mL deionized water. A magnetic stirrer was used to slowly stir the release medium. Samples (1 mL) were taken out from the deionized water outside the dialysis bag and replaced with the same amount of deionized water at given time intervals. The release experiment was analyzed over a time period of 12 h and the amount of released RB was determined using fluorometry.

Results and Discussion

Formation and self-assembly of supramolecular amphiphiles

β-CD, which has seven glucose units, can recognize adamantane well, and this typical host-guest pair has been widely utilized to build up supramolecular materials and devices[28-32] because it can form stable 1∶1 complex in water.[28-31] CB[7], which has an similar cavity with *β*-CD, also has this property. As reported, adamantane and its derivant can strongly bind to CB[7].[65,66] Thus we designed and synthesized an adamantane derivative **1** as guest molecule to prepare supramolecular amphiphile with CB[7] (Schemes 2a, 2b). The formation of the stable host-guest complex **3** can be driven by hydrophobic interactions between the adamantanyl moiety of guest molecule **1** and the hydrophobic cavity of CB[7]. Because of the amphiphilic nature of amphiphiles, supramolecular amphiphile **3** was found to self-assemble into vesicles (Scheme 2c).

Scheme 2 Structures of (a) guest (**1**) and host molecule CB[7] (**2**), (b) supramolecular amphiphile **3**, (c) supramolecular vesicles and possible self-assembled multilayers, and (d) schematic of the controlled disassembly of CB[7] based supramolecular vesicles



The morphology of the self-assembled supra-molecular amphiphiles was investigated by SEM. The SEM analysis shows that a typical vesicle aggregate was obtained with a diameter ranging from 150 to 200 nm (Figure 1a). Indeed, the CB[7] and guest molecule **1** can not form this morphology. When the guest molecule dispersed in DMF was slowly injected into water, it can self-assemble into a fiber-like aggregate with a diameter of about 1 μm and a length of more than 20 μm (Figure

1c). Moreover, the vesicles can also be obtained by an alternative approach that CB[7] was added under ultrasonic after the fiber like aggregate formed. Dynamic light scattering (DLS) was then used to measure the vesicle size. DLS analysis shows that the average diameter of the vesicles is about 190 nm with a width of 53.5 nm (Figure 1d), which was identical with SEM analysis.

The image of transmission electron microscopy (TEM) provided more detailed structural information for the vesicles (Figure 1b). The results demonstrated that the hollow feature, as it shows a strong contrast between the center and the periphery, was vital for vesicle structure with a diameters of about 200 nm and a wall thickness of about 20 nm.

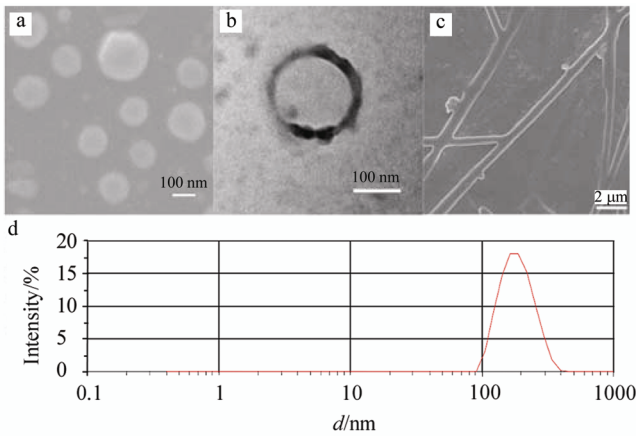


Figure 1 (a) SEM image of the aggregates formed by self-assembly of supramolecule amphiphile **3**. (b) TEM image of the aggregates formed by self-assembly of supramolecule amphiphile **3**. (c) SEM image of the aggregates formed by self-assembly of **1** alone. (d) DLS analysis of the vesicles.

Disassembly of vesicles

As supramolecular amphiphiles **3** was formed by host-guest chemistry, this supramolecular complex can be affected by the competitive recognition of guest analogue. By this means, the disassembly of the vesicles can be realized. SEM was used to observe the disassembly of the vesicles. When a small amount of 1-adamantanamine hydrochloride (1∶1 with the guest molecule) was added, the vesicles were partly disassembled, and a few fibers formed by direct assembly of guest molecules in water (Figure 2a) were obtained. With the continuous addition of 1-adamantanamine hydrochloride (10∶1 with the guest molecule), the vesicles were completely disassembled and a lot of fibers were obtained (Figure 2b). Dynamic light scattering (DLS) analysis provided effective evidence for the disassembly of the vesicles. As demonstrated by the DLS analysis (Figure 2c), the average size of the aggregate changed from 200 to 2000 nm with the disassembly of vesicles, revealing the formation of new aggregates.

In vitro release of Rhodamine B

The controlled release of vesicle-encapsulated com-

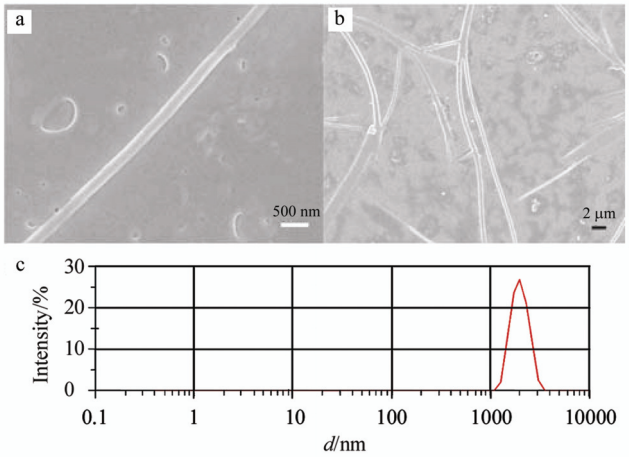


Figure 2 SEM image of the disassembly of the vesicles when 1-adamantanamine hydrochloride was added at the amounts of 1∶1 (a) and 10∶1 (b) with the guest molecule. (c) DNS analysis of the disassembly of the vesicles (1-adamantanamine hydrochloride was added at the amount of 10∶1 with the guest molecule).

pounds is important and promising for drug delivery system. At present, the controlled-release system generally contains two patterns. One is that the delivery carriers can release the drug automatically and selectively under the triggered physical and chemical conditions, such as pH, ionic strength, and temperature, *etc*. The other is that the drug release can be modulated by alteration of the structure of drug carriers *in vitro*.[67] We take an easy way to change the structure of the vesicles so as to realize the drug release (Scheme 2d). RB-loaded assembly solution was separated into two equal parts. One part was directly dialyzed against the deionized water. The other part was added 1-adamantanamine hydrochloride, at the amount of 10∶1 with the guest molecule, to disassemble the vesicles and then dialyzed against the deionized water. RB solution which has the same concentration was used as control to dialyze against the deionized water. From the data in Figure 3, it was observed that the speed of RB release in the solution of RB-loaded vesicles was much slower than that in the RB solution. After 1-adamantanamine hydrochloride was added to disassemble the vesicles, the speed of RB release increased significantly, that is in accordance with the RB solution.

Through investigating the release time of the RB (Figure 4), we found that the RB solution had a release time of about 7 h. After the RB-loaded vesicles were disassembled, the release time became to be about 8 h, which is as same as that of the RB solution. This means that the RB loaded in the vesicles was almost totally released to the solution once the vesicles were disassembled. These results demonstrated that a controlled release system can be obtained through the control of the disassembly of the CB[7] based vesicles. Therefore, the controllable CB[7] based vesicles can serve as new nanocapsules to release a variety of functional molecules or drugs.

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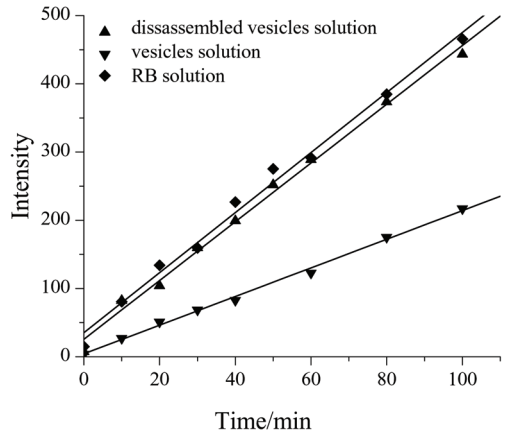

Figure 3 Speed of *in vitro* release of rhodamine B in RB solution, vesicle solution and disassembled vesicle solution.

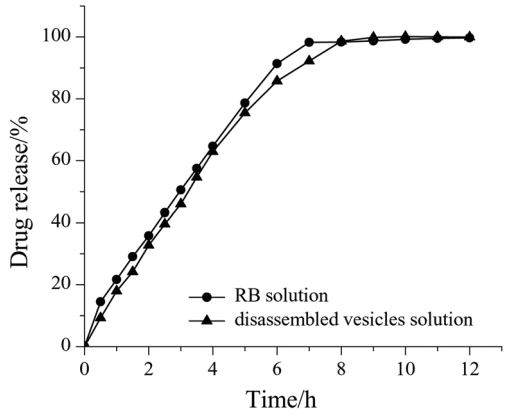

Figure 4 Release time of RB in RB solution and disassembled vesicle solution.

Conclusions

In this study, we have developed an effective strategy for the facile preparation of vesicles via multilevel self-assembly of CB[7] and guest molecules based on host-guest interactions and superamphiphile self-assembly. The disassembly of vesicles can be realized by addition of excess 1-adamantanamine hydrochloride. The vesicles can act as nanocapsules to encapsulate molecules within their hollow cavities and used as controlled drug delivery carriers due to their disassembly caused by the competitive guest molecule. It is anticipated that this supramolecular self-assembly system provides a nice approach to design the drug delivery carrier with controlled release ability.

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