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## Communication

# pH-Responsive Supramolecular Vesicles Assembled by Water-Soluble Pillar[5]arene and BODIPY Photosensitizer for Chemo-Photodynamic Dual Therapy

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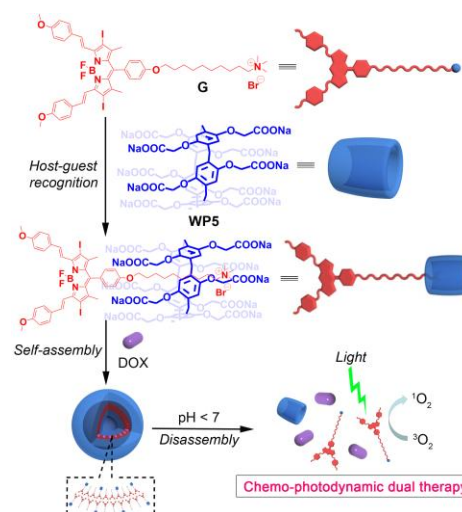
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Supramolecular vesicles which can successfully encapsulate DOX and exhibit rapid drug release in low-pH environment are constructed based on the host-guest interaction of water-soluble pillar[5]arene and a BODIPY derivative. They show remarkable combination of chemo- and photodynamic activities, suggesting a promising drug nanocarrier.

With the rapid development of nanotechnology, nano-sized aggregates are well-designed and applied as a versatile nanoparticle platform for anti-cancer drug delivery over the past three decades.<sup>1</sup> These “smart” nanocarriers can enhance the delivery and accumulation of small molecule drugs to tumor tissue *via* the enhanced permeability and retention (EPR) effect, reduce side-effect and even drug resistance compared with free drugs.<sup>2</sup> As the ideal drug delivery systems (DDSs), nanocarriers should be able to encapsulate drugs efficiently, maintain steady structure before reaching the tumor sites, and also can achieve the flexible and controlled release of drugs in response to environmental stimuli.<sup>3</sup> So far, a variety of molecular building blocks have been used to construct nanocarriers, among which supramolecular amphiphiles<sup>4</sup> based on the reversible and weak non-covalent interactions including hydrogen bonds, charge-transfer, hydrophilic/hydrophobic interaction, and  $\pi \cdots \pi$  interaction<sup>5</sup> are highly promising building blocks since the formed nanocarriers exhibit excellent dynamic properties, which can be controllably assembled as well as disassembled in response to numerous stimuli. Pillararenes,<sup>6</sup> as a new generation of macrocyclic hosts with unique symmetric pillar frameworks and  $\pi$ -rich cavities, have excited great interest in fabricating many interesting supramolecular assemblies which can be further applied as multifarious functional materials<sup>6a, 7</sup> such as chemosensors,<sup>8</sup> transmembrane channels,<sup>9</sup> fluorescent probes,<sup>10</sup> and especially DDSs.<sup>11</sup> Water-soluble pillar[6]arene (WP6) and pillar[5]arene (WP5) are the most commonly used building blocks for their pH-responsiveness and biocompatibility, which have great potential and competitiveness in constructing DDSs.

Up to now, although chemotherapy is still the leading cancer treatment, considerable side-effect and drug resistance greatly limit the therapeutic effect.<sup>12</sup> Therefore, it is highly desirable to develop new therapeutic strategies. Recently, combination of multiple therapies, especially chemotherapy and photodynamic therapy (PDT, a non-invasive and promising therapeutic modality

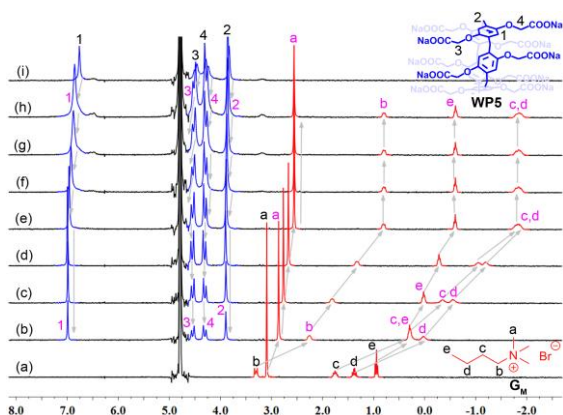
for cancer treatment), has become a research hotspot, since it can potentially overcome the disadvantages of individual chemotherapy through different mechanisms of actions to achieve enhanced anti-cancer efficacy.<sup>13</sup> For example, chemotherapeutic agents including doxorubicin (DOX),<sup>14</sup> cisplatin,<sup>15</sup> oxaliplatin derivative,<sup>16</sup> paclitaxel,<sup>14, 17</sup> and camptothecin<sup>18</sup> have been evaluated in combination with PDT. Remarkably, relatively enhanced anti-cancer efficacy with reduced drug dose could be observed, which revealed that chemo-photodynamic dual therapy provided a convenient and high efficient modality for cancer treatment. Moreover, PDT has particular advantages<sup>19</sup> in terms of minimally invasive nature, tolerance of repeated doses, and high specificity. In PDT, reactive oxygen species (ROS) are generated by the combined action of photosensitizer, light and tissue oxygen, namely photosensitizing effect, to kill tumor cells.<sup>20</sup> Therefore, the core component of PDT is photosensitizer, and lately boron-dipyrromethene (BODIPY) dyes which possess strong absorption coefficient, high ROS yield and significant photostability, are widely employed as ideal photosensitizers for PDT.<sup>21</sup>



**Scheme 1** Schematic illustration of the formation of WP5-G supramolecular vesicles and their pH-responsive drug release for chemo-photodynamic dual therapy.

Recently, we have pioneered the development of stimuli-responsive supramolecular nanocarriers and reported a series of WP6/WP5-based pH/Ca<sup>2+</sup>/UV/GSH-responsive nanoparticles for

controlled drug delivery.<sup>22</sup> However, these DDSs were involved only single chemotherapy, in order to take advantages of combined therapy, herein we designed a BODIPY-functionalized quaternary ammonium derivative **G** which acted as a guest and also a photosensitizer. Supramolecular vesicles were then fabricated by the amphiphile formed from **WP5** and **G**.<sup>22c</sup> They had good DOX encapsulation efficiency and the formed DOX-loaded vesicles showed rapid DOX release in low-pH environment. Such DOX-loaded vesicles could well localize in lysosomes and exhibited remarkable combination of chemo- and photodynamic activities against A549 cancer cells, suggesting a potential DDS for chemo-photodynamic dual therapy (Scheme 1).



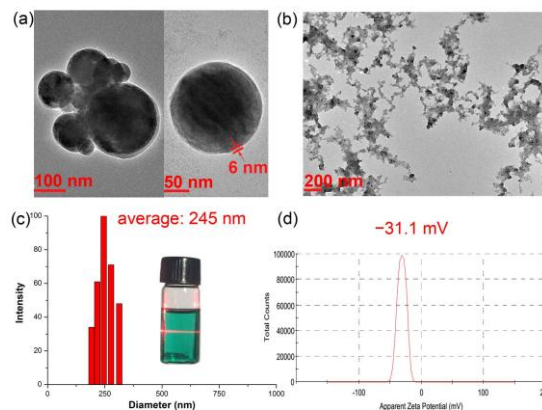
**Fig. 1**  $^1\text{H}$  NMR spectra (300 MHz,  $\text{D}_2\text{O}$ , 298 K) of  $\text{G}_\text{M}$  at a constant concentration of 2.00 mM with different concentrations of **WP5** (mM): (a) 0.00, (b) 0.50, (c) 0.75, (d) 1.00, (e) 1.50, (f) 2.00, (g) 3.00, (h) 4.00, and (i) individual **WP5** (2.00 mM). Purple characters represent the complexed host and guest proton signals.

**WP5** was synthesized according to the published procedure,<sup>23</sup> while **G** and  $\text{G}_\text{M}$  were prepared through quaternization reaction (Scheme S1, ESI $^\dagger$ ). Since **G** was inclined to self-aggregate in water, model guest  $\text{G}_\text{M}$  was used to investigate the host-guest complexation between **WP5** and **G** via  $^1\text{H}$  NMR and 2D ROESY spectroscopy in  $\text{D}_2\text{O}$ .<sup>22b</sup> As shown in Fig. 1, after complexation the signals of phenyl protons ( $\text{H}_1$ ) and methylene protons ( $\text{H}_2$ ,  $\text{H}_3$  and  $\text{H}_4$ ) from **WP5** shifted downfield slightly. Whereas, the signals derived from N-methyl protons ( $\text{H}_\text{a}$ ) of  $\text{G}_\text{M}$  shifted upfield slightly and butyl protons ( $\text{H}_\text{b}$ ,  $\text{H}_\text{c}$ ,  $\text{H}_\text{d}$ , and  $\text{H}_\text{e}$ ) shifted upfield remarkably due to the shielding effect of the electron-rich cavities of pillar[5]arene, which clearly demonstrated the inclusion of the alkyl chain of  $\text{G}_\text{M}$  into the hydrophobic **WP5** cavity. Moreover, the spatial conformation of such inclusion was further examined by 2D ROESY spectrum (Fig. S9, ESI $^\dagger$ ), from which intermolecular correlation signals could be clearly observed between protons  $\text{H}_1$ ,  $\text{H}_2$ ,  $\text{H}_3$ ,  $\text{H}_4$  of **WP5** and  $\text{H}_\text{b}$ ,  $\text{H}_\text{c}$ ,  $\text{H}_\text{d}$ ,  $\text{H}_\text{e}$  of  $\text{G}_\text{M}$ , respectively, confirming that the linear guest  $\text{G}_\text{M}$  was fully threaded through the hydrophobic **WP5** cavity to form a [2]pseudorotaxane.

The stoichiometry of **WP5** $\supset$  $\text{G}_\text{M}$  complex was further investigated by the Job's plot method and the results showed a 1:1 binding stoichiometry (Fig. S10, ESI $^\dagger$ ). And the association constant ( $K_\text{a}$ ) was further determined to be  $(5.46 \pm 1.27) \times 10^3 \text{ M}^{-1}$  by using  $^1\text{H}$  NMR titration (Fig. S11, ESI $^\dagger$ ). The binding affinity for such host-guest inclusion might be mainly driven by the cooperative electrostatic and hydrophobic interactions.

Similarly, we deduced that **WP5** and BODIPY derivative **G** could form a "tadpole-like" 1:1 inclusion as shown in Scheme 1. In addition, the formation of **WP5** $\supset$ **G** complex was also supported by experimental observations on the enhanced solubility of **G** in water upon adding the **WP5** solution.<sup>11a</sup>

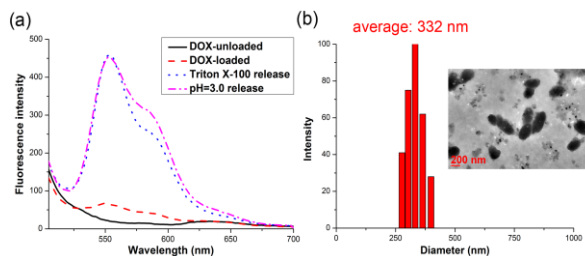
The ability of such amphiphile to form higher-order aggregates in water was further investigated. When a **WP5** solution ( $2.5 \times 10^{-5} \text{ M}$ ) was added to the transparent **G** solution ( $5 \times 10^{-5} \text{ M}$ ), a light opalescence and clear Tyndall effect (Fig. 2c Inset) could be observed, indicating the formation of microaggregates. The driving forces should be attributed to the amphiphilic property of **WP5** $\supset$ **G** complex as well as the  $\pi \cdots \pi$  stacking interactions of BODIPY.<sup>24</sup> The morphology and size of these aggregates were further investigated by TEM and DLS. TEM images indicated the hollow spherical morphology with a diameter about 250 nm (Fig. 2a), which was in good agreement with the DLS result (average diameter of 245 nm, Fig. 2c), indicating the formation of vesicular structure and the thickness of the hollow vesicles was calculated to be  $\sim 6$  nm. Subsequently, the best molar ratio between **WP5** and **G** for constructing these aggregates was determined to be  $[\text{WP5}]/[\text{G}] = 1/8$  (Fig. S12, ESI $^\dagger$ ). Furthermore,  $\zeta$ -potential measurements were carried out to examine the stability of the obtained vesicles with different **WP5**/**G** molar ratios, and finally, the molar ratio of  $[\text{WP5}]/[\text{G}] = 1/2$  ( $\zeta$ -potential =  $-31.1$  mV, Fig. 2d) was chosen for the subsequent drug encapsulation investigation, since the obtained vesicles under this condition might not further assemble into agglomeration due to the repulsive forces-induced increasing stability.<sup>25</sup> In addition, when the solution pH was adjusted to acidity, these vesicles disassembled into disordered structures as indicated from the TEM image (Fig. 2b), suggesting a good pH-responsiveness similar as our previous work.<sup>11a, 22a, 22b</sup>



**Fig. 2** TEM images of: (a) **WP5** $\supset$ **G** aggregates and (b) **WP5** $\supset$ **G** aggregates after the solution pH was adjusted to acidity; (c) DLS result of **WP5** $\supset$ **G** aggregates. Inset: photo showing the Tyndall effect of **WP5** $\supset$ **G** aggregates; (d) The  $\zeta$ -potential of **WP5** $\supset$ **G** aggregates at 25  $^\circ\text{C}$ .  $[\text{WP5}] = 2.5 \times 10^{-5} \text{ M}$  and  $[\text{G}] = 5 \times 10^{-5} \text{ M}$ ,  $[\text{WP5}]/[\text{G}] = 1/2$ .

DOX was chosen as a model drug to further investigate the encapsulation efficiency of **WP5** $\supset$ **G** vesicles as well as their pH-responsive drug release behavior. As shown in Fig. 3a, the unloaded vesicular solution has hardly any fluorescence intensity while the intensity of DOX-loaded vesicular solution in the range of 520-650 nm, which belongs to the characteristic emission of DOX, suddenly appears and becomes much stronger after treated

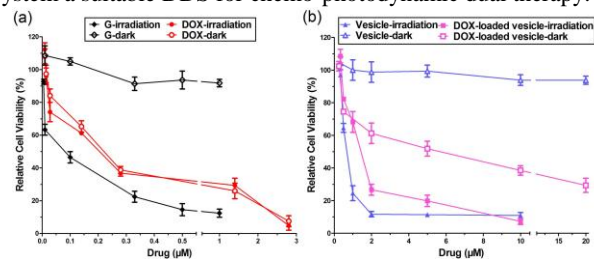
with Triton X-100 or HCl solution (pH = 3.0) to achieve the complete release of DOX. Moreover, the morphology of DOX-loaded vesicles turned to be ellipse shape in TEM observations (Fig. 3b Inset), and the DLS results showed that the size (average diameter of 332 nm, Fig. 3b) was a little larger than that of the unloaded vesicles (average diameter of 245 nm), confirming that DOX molecules were successfully loaded into the interior of **WP5** vesicles.<sup>11a</sup> According to the dependence of fluorescence emission intensity on concentration (Fig. S13, ESI<sup>†</sup>), the DOX encapsulation efficiency was calculated to be 14%. The release behavior of DOX from such vesicles could be controlled by changing the solution pH. The results showed that they were stable under physiological condition but exhibited effective and rapid release of DOX in acid environment, making such system promising candidate for controlled drug release (Fig. S14, ESI<sup>†</sup>).



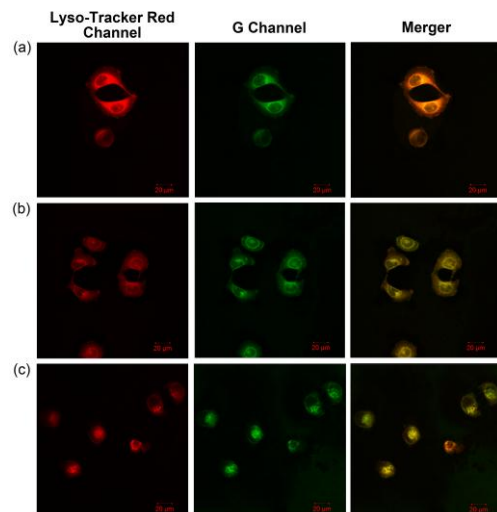
**Fig. 3** (a) Fluorescence emission spectra of unloaded vesicles (pH = 7.4), DOX-loaded vesicles at pH 7.4, pH 3.0, and treated with Triton X-100, respectively ( $\lambda_{ex}$  = 484 nm, in water, 25 °C); (b) DLS result of DOX-loaded vesicles. Inset: TEM image of DOX-loaded vesicles in water.

Considering the biocompatibility of DDSs is a significant index for biomedical applications<sup>22b</sup> and **WP5** has been proved to be biocompatible in aqueous media, the cytotoxicities of **G** and **WP5** vesicles were then investigated against NIH3T3 normal cells (a mouse embryonic fibroblast cell line). Obviously, the cell viability remains above 85% even up to the maximum measured dose, implying good biocompatibility (Fig. S15, ESI<sup>†</sup>). The cytotoxicities of **WP5** vesicles and DOX-loaded vesicles against A549 cancer cells (a lung adenocarcinoma cell line) upon irradiation with red light ( $\lambda$  = 690 nm, chosen based on the Q band of **G**, Fig. S16, ESI<sup>†</sup>) and in the dark were further investigated, and the cytotoxicities of **G** and DOX were also examined as controls. As shown in Fig. 4a, DOX exhibits equal cytotoxicity whether upon irradiation or in the dark ( $IC_{50}$  = 0.20  $\mu$ M, Table S1, ESI<sup>†</sup>). It is interesting to note that **G** shows no cytotoxicity in the dark, while the cytotoxicity enhances remarkably upon irradiation ( $IC_{50}$  = 0.08  $\mu$ M, Table S1, ESI<sup>†</sup>) because of the PDT effect (mainly due to the singlet oxygen photosensitized by **G**, Fig. S17, ESI<sup>†</sup>). Similarly, Fig. 4b shows that **WP5** vesicles also exhibit similar difference in cytotoxicity as that of free **G** upon irradiation ( $IC_{50}$  = 0.70  $\mu$ M, Table S1, ESI<sup>†</sup>) and in the dark, suggesting that the **WP5** vesicles were disassembled triggered by the acidic condition in cancer cells,<sup>26</sup> thus **G** escaped from these aggregates and generated PDT effect. Moreover, the light cytotoxicity of the DOX-loaded vesicles was also significant ( $IC_{50}$  = 1.40  $\mu$ M, which was comparable to that of unloaded vesicles, Fig. 4b, Table S1, ESI<sup>†</sup>). However, compared with non-cytotoxicity of unloaded vesicles, the DOX-loaded vesicles exhibited remarkable dark cytotoxicity ( $IC_{50}$  = 5.50  $\mu$ M), indicating the successful release of

DOX. According to the above results, these unloaded vesicles can be applied as a novel DDS for efficient PDT. Furthermore, it is believed that the DOX-loaded vesicles show a cooperative manner of chemo- and photodynamic activities, making this system a suitable DDS for chemo-photodynamic dual therapy.



**Fig. 4** The cytotoxicities of (a) **G**, DOX and (b) vesicles, DOX-loaded vesicles against A549 cancer cells upon irradiation ( $\lambda$  = 690 nm, 1.5 J cm<sup>-2</sup>) and in the dark, respectively. Data were treated as mean values  $\pm$  S.E.M. of three independent experiments, each performed in quadruplicate.



**Fig. 5** Cellular uptake and intracellular localization of: (a) **G**, (b) unloaded vesicles, and (c) DOX-loaded vesicles in A549 cancer cells examined by confocal laser scanning microscopy. Red and green fluorescence correspond to Lyso-Tracker Red and **G**, respectively.

Since the cellular internalization of DOX has been detailedly studied in our previous work,<sup>27</sup> thus we mainly focused on the cellular internalization of **WP5** vesicles, DOX-loaded vesicles, and **G** in A549 cancer cells, which was evaluated by confocal laser scanning microscopy. Lyso-Tracker Red (excited at 543 nm, monitored at 550-620 nm) was employed for the fluorescent-labeling of lysosomes (shown in red). Since **G** has inherent red fluorescence (excited at 633 nm, monitored at 650-750 nm, shown in green to distinguish from Lyso-Tracker Red), it can be clearly observed to reflect the cellular internalization of both unloaded vesicles and DOX-loaded vesicles. After incubated with **G** at 37 °C for 5 h and excited at 633 nm, the A549 cells showed intracellular intense green fluorescence (Fig. 5a), suggesting the essentially cellular uptake of **G**. When excited at 543 nm, the cells showed strong red fluorescence and it overlapped very well with the green fluorescence (Fig. 5a), indicating the co-localization of **G** and lysosomes, which was in accord with the results of literatures.<sup>28</sup> As shown in Fig. 5b-c, similar green fluorescence of both unloaded and DOX-loaded



vesicles demonstrated the good cellular uptake of these nanoparticles. Furthermore, the similar overlapped fluorescence images revealed that such nanocarriers entered cancer cells mainly *via* endocytosis and could well localize in lysosomes, where low-pH microenvironment triggered the disassembly of these vesicles to release DOX and **G** for combined cancer therapy.

In summary, we have synthesized a BODIPY derivative **G** which acts as a guest and also a photosensitizer, and then supramolecular vesicles were successfully constructed by the amphiphile formed from **WP5** and **G**. Chemotherapy drug DOX was successfully encapsulated into such supramolecular vesicles and the resulting DOX-loaded vesicles were stable under physiological condition but exhibited effective and rapid release of DOX in acid environment. Such vesicles had good biocompatibility and the DOX-loaded vesicles could well localize in lysosomes and showed remarkable combination of chemo- and photodynamic activities. To the best of our knowledge, this is the first example of pillararene-based supramolecular nanocarrier for effective chemo-photodynamic dual therapy, which extends the applications of pillararenes-based materials in the field of biomedical engineering.

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## Notes and references

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