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A mitochondria-targeting supramolecular photosensitizer based on pillar[5]arene for photodynamic therapy

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A mitochondria-targeting supramolecular photosensitizer system TPP-QASs/WP5/DTAB was constructed based on host-guest inclusion complex. The supramolecular system could efficiently release and activate TPP-QASs in an acidic environment, which demonstrated to preferentially accumulate in mitochondria. The singlet oxygen (¹O₂) could be *in situ* generated in mitochondria under light irradiation, and then further enhance the PDT efficacy.

Supramolecular chemistry based on modularized and specific noncovalent interactions have been widely studied with the aim of developing sophisticated self-assembly systems, such as molecular machines, supramolecular polymers, and supramolecular gels.¹ Among these noncovalent interactions, host-guest recognition has been extensively applied in supramolecular chemistry.³ To date, a variety of macrocyclic hosts have been explored to construct supramolecular amphiphilic *via* host-guest recognition.⁴ Pillar[n]arenes, as a new type of synthetic macrocyclic hosts, also have attracted great interests due to their symmetrical pillar architecture, facile and high-yield synthesis, and accessible derivatizations.⁵ Nowadays, pillar[n]arene-based host-guest chemistry has been used in the construction of supramolecular amphiphiles, which could provide a useful platform for the applications of supramolecular amphiphiles such as explosive detectors, transmembrane channels, and drug delivery systems (DDS).⁶ Water-soluble pillar[n]arenes (n = 5, 6) have demonstrated to be pH-responsive and significantly biocompatible in aqueous media.²² Some nascent studies based on host-guest chemistry of water-soluble pillar[n]arenes have been presented in the fabrication of stimuli-responsive supramolecular systems. Recently, Huang, Wang, and Pei have developed a series of supramolecular amphiphiles based on water-soluble pillar[n]arenes, which can further assemble to form higher-

ordered aggregates to achieve controllable delivery of anticancer drugs.⁷

Targeted drug delivery systems have received increasing attention due to their advantages of precise tumor targeting, enhanced antitumor efficacy and reduced systemic toxicity.⁸ In recent years, precise delivery of therapeutic agents to subcellular organelles has been exhibited to hold great promise to further minimize side effects and combat multi-drug resistance. Mitochondria as vital subcellular organelles in eukaryotic cells play a critical role in human metabolism, which determine the apoptotic cell death.⁹ Hence, mitochondria have been recognized as the subcellular targeting sites for cancer treatment, since the damage of mitochondria could induce the mitochondrial dysfunctions and the mitochondria-mediated apoptosis.¹⁰ In particular, as mitochondria are susceptible to excessive reactive oxygen species (ROS),¹¹ the modulation of intrinsic apoptosis by mitochondria-targeting antitumor agents associated with the generation of ROS is a potential therapeutic approach to eradicate cancer cells. Recently, Zhang, Wu, Liu, Kim and their co-workers have done a lot of works on mitochondria-targeting antitumor agents.¹²

As a noninvasive and reliable cancer-therapy modality with high spatiotemporal precision, PDT has been received great attention.¹³ PDT involves the administration of tumor-localizing photosensitizers (PSs) followed by the activation with a specific wavelength of light to generate ROS (for example, singlet oxygen, ¹O₂), which ultimately cause irreversible tissue damage. Unfortunately, most of ROSs have a short half-life (< 40 ns) and exhibit severely small radius of action (< 20 nm).^{12a,14} Thus, the damage of ROS to biomolecules is strongly restricted to the immediate vicinity of ROS generation.¹⁵ Obviously, transporting the PSs to the mitochondria for *in situ* generation of ROS can perturb ROS homeostasis and further induce cell apoptosis. Additionally, activatable PSs that can be activated by tumor-associated stimuli have been developed to further minimize the side effect of PDT.¹⁵ Therefore, it is highly desirable to develop pH-activatable supramolecular photosensitizers nanosystems based on the host-guest interaction of **WP5** and a PS that possess the ability of mitochondria-targeting, simultaneously, exhibit enhanced fluorescence and phototoxicity.

Herein, we designed a supramolecular photosensitizer system using supramolecular amphiphiles based on host-guest

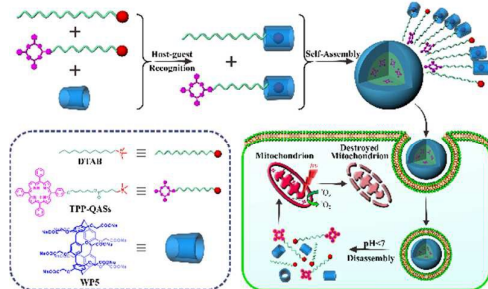
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COMMUNICATION

interaction between **WP5** and tetraphenylporphyrin-containing quaternary ammonium salts (**TPP-QASs**) as photosensitizer to realize PDT (**Scheme 1**). The supramolecular system displayed silenced fluorescence and photoactivity in physiological environments, whereas in acid conditions, it could rapidly release the **TPP-QASs** and efficiently switch to an active state to dramatically increase the fluorescence signal of **TPP**. Interestingly, the released **TPP-QASs** could selectively accumulate in mitochondria because of its lipophilic cationic property. More importantly, the *in situ* generation of $^1\text{O}_2$ in mitochondria further enhanced the PDT efficacy under light irradiation, leading to substantial cell death due to the decrease of the mitochondrial membrane potential.



Scheme 1. Assembly of **TPP-QASs**/**WP5**/**DTAB** in aqueous media, and schematic representation of intracellular tracking and the therapeutic effect of **TPP-QASs**/**WP5**/**DTAB** supramolecular system in cancer cells.

WP5 was synthesized according to established procedures,¹⁶ and the preparation of **TPP-QAS** was given in Supporting Information (**Scheme S1**, **Fig. S1-S4**). Since **TPP-QAS** exhibits poor water solubility, a model guest G_M was used to investigate the host-guest complexations of **WP5** and **TPP-QAS** by ^1H NMR (**Fig. S5**). It could be seen that the proton signals of phenyl protons (H_1) and methylene protons (H_2 , H_3 and H_4) on **WP5** shifted downfield slightly. On the other hand, the peaks related to protons H_a , H_b , H_c , H_d , and H_e from G_M clearly shifted upfield. Whereas, the signals H_a on G_M shifted upfield slightly and butyl protons (H_b , H_c , H_d , and H_e) shifted upfield remarkably due to the shielding effect of the electron-rich cavities of **WP5**. These phenomena suggested that the complexation between **WP5** and G_M occurred in aqueous solution.¹⁷

The stoichiometry of complexation between **WP5** and **TPP-QASs** in water was studied by Job's plot method using the fluorescence spectroscopy, which demonstrated the 1:1 binding stoichiometry between **WP5** and **TPP-QASs** (**Fig. S6**).^{6c} As shown in **Fig. 1A**, upon gradual addition of **TPP-QASs** into **WP5**, the fluorescence intensity of **WP5** was gradually quenched, revealing the occurrence of host-guest interaction. The association constant (K_a) was determined to be $(1.42 \pm 0.36) \times 10^5 \text{ M}^{-1}$ by using a nonlinear curve-fitting method (**Fig. 1B**), indicating a strong binding affinity between **WP5** and **QASs** moieties.¹⁸ Furthermore, as shown in **Fig. S7**, a red-shift was observed from UV-vis absorption spectroscopy due to electronic interactions between **WP5** and **TPP-QASs**, further revealing the formation of a stable host-guest complex.^{6c, 18}

After the establishment of **WP5**→**TPP-QASs** recognition motif in water, the supramolecular amphiphiles were utilized to construct stable supramolecular nanoparticles in water. Firstly, the self-assembly behavior of **TPP-QAS** itself was studied. Interestingly, there was no aggregate formed from **TPP-QASs**

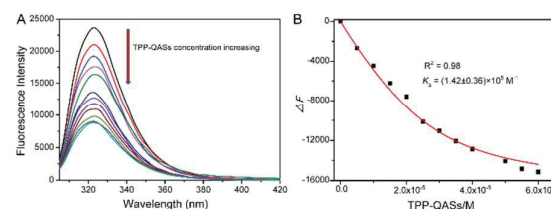


Fig. 1 (A) Fluorescence spectra of **WP5** ($2.50 \times 10^{-5} \text{ M}$, excitation spectrum: 290 nm) in aqueous solution at room temperature with different concentrations of **TPP-QASs**: 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5, 5.5, and $6 \times 10^{-5} \text{ M}$ in aqueous solution at room temperature. (B) The fluorescence intensity changes upon addition of **TPP-QASs**. The red solid line was obtained **WP5** from the non-linear curve-fitting using the above equation.

solution. However, with adding different amounts of **WP5** into **TPP-QASs** solution, the solution became opalescent, which means the formation of the supramolecular aggregates. Moreover, from the fluorescence spectra in **Fig. S8**, the emission intensity of **TPP** sharply decreased with addition of **WP5** content. These phenomena suggested that the host-guest complexation occurred to form supramolecular amphiphiles and **WP5** has a unique tendency to induce the aggregation behavior of **TPP-QASs** by decreasing the CAC (**Fig. S9**), enhancing aggregate compactness.¹⁹ Therefore, it was necessary to determine the molar ratio between **WP5** and **TPP-QASs** for constructing stable supramolecular aggregates. The best molar ratio of 10.5:1 (**TPP-QASs**/**WP5**) was obtained for the formation of supramolecular amphiphilic nanoparticles according to the inflection point based on the results of UV-vis absorption (**Fig. S10**). Subsequently, as shown in **Fig. S11A**, the ζ potentials of the nanoparticles gradually changed from positive to negative upon the addition of **WP5** in the titration experiments. In particular, the ζ -potential of the nanoparticles constructed at the molar ratio (**TPP-QASs**/**WP5** = 10.5:1) was close to 0 mV, which means that the nanoparticles obtained at the molar ratio were not stable, and easily formed the larger aggregates.^{6c} Therefore, considering the repulsive-force-induced increasing stability of nanoparticles, the molar ratio of 5:1 **TPP-QASs**/**WP5** (ζ potential = -26.80 mV , **Fig. S11B**) was chosen for further investigation of its stimuli-responsive property. Unfortunately, the micellar solution of **TPP-QASs**/**WP5** (molar ratio, 5/1) generated precipitation when it was dialyzed against deionized water for removing DMF. For solving the problem, **DTAB** was introduced into the **WP5**→**TPP-QASs** amphiphilic system with keeping the molar ratio of 5:1 **QASs**/**WP5** to increase stabilization of the supramolecular nanoparticles. We speculated that the addition of **DTAB** into the **WP5**→**TPP-QASs** amphiphilic system to slightly reduce the electrostatic repulsion between hydrophilic **WP5** and the π - π stack between **TPPs**, thus leading to stable nanostructures and extensive applications.

Reprecipitation technique is often utilized to fabricate stable supramolecular micelles. Here, **TPP-QASs**/**DTAB** (molar ratio, 7/4) DMF solution was added dropwise into **WP5** aqueous solution with stirring, and then the mixture solution was dialyzed against deionized water for removing DMF. According to the best molar ratio, the fluorescence spectra of **TPP-QASs**/**WP5**/**DTAB** based on supramolecular nanoparticles was measured. As shown in **Fig. S12**, nearly no fluorescence of the **TPP-QASs**/**WP5**/**DTAB** solution was detected, compared to the strong fluorescence intensity of the **TPP-QASs** solution.¹⁹ The

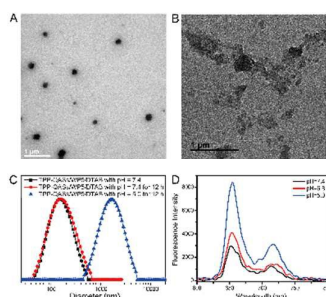


Fig. 2 TEM images: (A) **TPP-QASs/WP5/DTAB** supramolecular nanoparticles; (B) **TPP-QASs/WP5/DTAB** supramolecular nanoparticles after the solution of pH was adjusted to 5.0. (C) Size distribution of **TPP-QASs/WP5/DTAB** supramolecular nanoparticles determined by DLS. Blank line: pH = 7.4 for 0 h, red line: pH = 7.4 for 12 h, blue line: pH = 5.0 for 12 h. (D) Fluorescence spectra of TPP in **TPP-QASs/WP5/DTAB** supramolecular micellar solution with the different pH at 25 °C after standing for 3 h.

CAC of **TPP-QASs/WP5/DTAB** solution was about 4.7×10^{-3} mg mL⁻¹ measured by the fluorescence absorbance with pyrene as a probe (Fig. S13). Moreover, the assembled morphology and size of **TPP-QASs/WP5/DTAB** aggregates were characterized by TEM and DLS, respectively. The TEM images exhibited a spherical nanoparticle with average diameter of around 150 nm (Fig. 2A), which is agreeable with the hydrodynamic diameter (D_h) of approximately 150 nm calculated by DLS (Fig. 2C). Then, the stimuli-responsive behavior of the obtained supramolecular nanoparticles was further studied. Compared to the micellar solution with pH = 7.4, irregular larger aggregates could be observed in the TEM image (Fig. 2B) after adjusting pH = 5.0 accompanied by a dramatic increase of scattering intensity determined by DLS (Fig. 2C), and meanwhile the fluorescence intensity at 660 nm corresponding to the characteristic peak for TPP was significantly increased (Fig. 2D). All these results suggested the disassembly of the supramolecular nanoparticles by adjusting the solution pH to 5.0.

The pH-responsive **TPP-QASs/WP5/DTAB** supramolecular nanoparticles could be smart for controllable release of **TPP-QASs** (Fig. S14). The results indicated that a gradual release of **TPP-QASs** was determined under acidic conditions (pH = 6.8 or 5.0), with the cumulative release amount of 40% at pH = 6.8 and 62% at pH = 5.0 within 12 h, respectively. However, under the physiological condition (pH = 7.4), the cumulative leakage of **TPP-QASs** was less than 20% within 12 h. The results suggested that the decrease of pH led to the destruction of the supramolecular nanoparticles with concomitant release of the **TPP-QASs** molecules.

The cellular uptake of **TPP-QASs/WP5/DTAB** supramolecular nanoparticles was investigated by confocal laser scanning microscope (CLSM). Firstly, co-localization imaging experiments were performed in A549 cells simultaneously loaded with molecular TPPs (**TPP-QASs** or free porphyrin) and rhodamine 123 (Rh123, a commercial mitochondrial dye) to demonstrate the subcellular localization of **TPP-QASs**. As shown in Fig. S15, the fluorescence of Rh123 and **TPP-QASs** overlapped well, and an obvious orange signal was observed in the merged image, while the nontargeting free porphyrin exhibited poor colocalization with Rh123. Moreover, Fig. 3 showed the confocal microscopic images for A549 cells costained with **TPP-QASs/WP5/DTAB** supramolecular nanoparticles and Rh123. It could be found that dotted red fluorescence in the edge of the A549 cells at 1 h of incubation,

indicating **TPP-QASs/WP5/DTAB** supramolecular nanoparticles had been internalized by the cells. With the increase of incubation time, red fluorescence intensity increased inside cells. Upon 24 h of incubation, the strong red fluorescence could be found in cells, which may suggest the **TPP-QASs** molecules had been released from the supramolecular nanoparticles. More importantly, the fluorescence signals from Rh123 and **TPP-QASs** matched well and obvious orange fluorescence could be found in the mitochondria, revealing the mitochondria-targeting ability of molecular **TPP-QASs** upon being released from supramolecular nanoparticles.^{12b,12e}

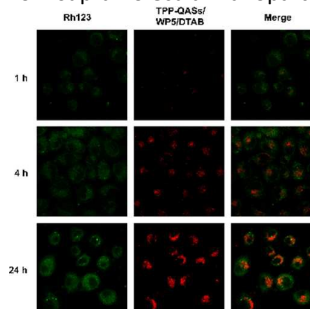


Fig. 3 (A) Confocal laser scanning microscopic images for A549 cells costained with **TPP-QASs/WP5/DTAB** nanoparticles and Rh123 at varied time periods.

The PDT effect can lead to mitochondria damage and the subsequent apoptosis of cells. For obtaining direct insight into the toxic mechanism of **TPP-QASs/WP5/DTAB** supramolecular nanoparticles, the mitochondrial membrane potential was monitored using JC-1 dye as the sensor. The results of JC-1 experiments against A549 cells were shown in Fig. 4A. It can be seen that the clear fluorescence change of JC-1 for the cells treated with **TPP-QASs/WP5/DTAB** supramolecular nanoparticles under different light irradiation time, where the green fluorescence increased with the increasing irradiation time while the red fluorescence decreased.^{12a,12b,12e} The fluorescent changes of JC-1 revealed that the generation of ROS could destroy the mitochondria and result in the loss of the mitochondrial membrane potential. In addition, flow cytometry also showed a decrease in red fluorescence (FL2 channel) with the increasing time of irradiation after the cells were treated by supramolecular nanoparticles (Fig. S16), further proving the mitochondria damage resulted from the ¹O₂.

To verify the therapeutic efficiency of the mitochondrial targeted supramolecular nanoparticles system, MTT assays were performed for A549 cell lines after treatment with different PDT systems. As shown in Fig. 4B, after 24 h incubation, no obvious cytotoxicity is observed in dark condition even at a porphyrin concentration of 10 mg mL⁻¹ whenever for free porphyrin or **TPP-QASs/WP5/DTAB** supramolecular nanoparticles. This is because there was no ¹O₂ generated in the dark. Here, only **TPP-QASs** exhibited a slight dark cytotoxicity for A549 cells compared with the supramolecular nanoparticles. This may be because positively charged ammonium ions of **TPP-QASs** produced the cytotoxicity, which could be reduced by **WP5** coverage in supramolecular nanoparticles by forming a stable host-guest complex.¹⁸ The phototoxicity was further evaluated after the cells were incubated for 24 h with the different PDT systems followed by 10 min of light irradiation with visible light LED

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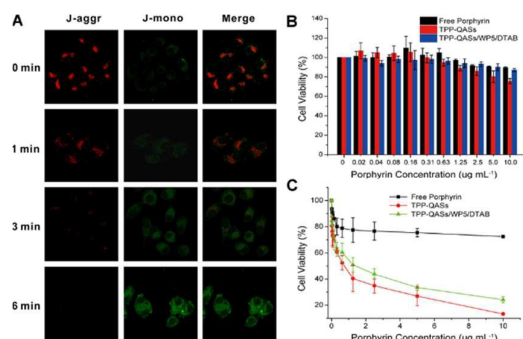


Fig. 4 (A) Confocal microscopic images for A549 cells incubated with $10 \mu\text{g mL}^{-1}$ of TPP-QASs/WP5/DTAB for 24 h at porphyrin concentrations and then exposed to light emitting diode (LED) lamp light irradiation for 0, 1, 3, and 6 min respectively, and then stained with $2.5 \mu\text{g mL}^{-1}$ JC-1. "J-aggr" and "J-mono" are the abbreviations for "aggregation state of JC-1 dye" and "monomer state of JC-1 dye", respectively. In vitro cytotoxicity of free porphyrin, TPP-QASs, and TPP-QASs/WP5/DTAB supramolecular micelles against A549 cells: dark cytotoxicity (B) and phototoxicity (C) at different porphyrin concentrations.

lamps (400 mW cm^{-2}). The results showed that free porphyrin has low phototoxicity, perhaps due to its low internalization efficiency (Fig. 4C). The phototoxicity of the supramolecular nanoparticles increased with the increasing concentration of porphyrin in the supramolecular nanoparticles, which is much higher than that of free porphyrin. However, the phototoxicity of the supramolecular nanoparticles was weaker than that of TPP-QASs. This is probably because the TPP-QASs contains a quaternary ammonium cationic ion and the cationic ion has slight cytotoxicity for cells, further suggesting that WP5 could decrease the cytotoxicity of TPP-QASs based on host-guest complex.^{18,20} As a consequence, the supramolecular nanoparticles systems could serve as a good PS delivery system since its low dark cytotoxicity, high phototoxicity and selective targeting ability towards mitochondria.

In conclusion, we developed a mitochondria-targeted and pH-activatable PSs self-delivery system constructed by host-guest inclusion complex of TPP-QASs, DTAB, and WP5 in water for highly efficient of PDT. The supramolecular nanoparticles system exhibited silent fluorescence and PDT activity at physiological environment, which subsequently could efficiently release and activate TPP-QASs in an acidic environment. More importantly, the released TPP-QASs could quickly and selectively accumulate in mitochondria in cancer cells. Upon light irradiation, the PS generated $^1\text{O}_2$ and induced oxidant damage to the mitochondria, as evidenced by the loss of the mitochondrial membrane potential, and eventually led to the death of cancer cells.

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