

Photo and pH Dual-Responsive Supramolecular Vesicles Based on a Water-Soluble Tribenzotriquinacene and an Azobenzene-Containing Amphiphile in Water

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Abstract: We synthesized a new water-soluble tribenzotriquinacene-based hexacarboxylate (TBTQ-C₆, or H) which can associate with an azobenzene-containing amphiphile (*trans*-AZO) to form the H ⊃ *trans*-AZO supra-amphiphile by host-guest interactions in water. This supra-amphiphile further self-assembles into photo and pH dual-responsive vesicles. The reversible conversion between the vesicles and micelles can be easily controlled by both UV or visible light irradiation and pH adjustment. This work represents the first study of stimuli-responsive TBTQ-based supramolecular vesicles, which may have potential applications in various fields such as controlled drug delivery systems.

Stimuli-responsive supramolecular materials constructed in aqueous media by the self-assembly of host-guest supra-amphiphiles have attracted great attention due to their potential applications in fields like drug or gene delivery, cell imaging and tissue regeneration.^[1] Supra-amphiphiles^[2] that connect the hydrophilic and hydrophobic segments through noncovalent interactions can spontaneously assemble to a wide variety of well-defined nanostructures, such as vesicles, micelles, nanotubes and nanoribbons. These processes can be readily controlled by external stimuli including light, pH, temperature, enzymes, redox conditions and their combinations.^[3] Among these stimuli, light is particularly attractive because of its cleanness, low cost, controllability and highly sensitivity.^[4] Furthermore, pH stimulation is of interest due to the pH gradient between healthy cells and tumor cells, which can be applied in controlled cancer drug delivery systems.^[5]

Tribenzotriquinacene (TBTQ) derivatives are a class of versatile host molecules that can effectively encapsulate guest molecules due to their rigid bowl-shaped C_{3v}-symmetric skeleton.^[6] This could therefore open up potential applications similar to those of macrocyclic acceptors, such as crown ethers, cyclodextrins, calixarenes, cucurbiturils, pillararenes and cyclo-triveratrylenes, that bind donor species through host-guest interactions to form supra-amphiphiles.^[7] Host-guest interactions and self-assembly based on TBTQ derivatives in organic media have been well developed, whereas studies of TBTQ congeners in aqueous media have been reported only scarcely.^[8] Therefore, we believe TBTQ-based host-guest recognition systems in water to be of great potential as supra-amphiphiles.

In our previous report, a multiply sugar-functionalized water-soluble TBTQ derivative was synthesized and its host-guest chemistry with fullerenes in water was studied.^[9] In the present work, we have designed and synthesized a new water-soluble TBTQ-based hexacarboxylate (TBTQ-C₆, or "H") as a host and an azobenzene-containing amphiphile (*trans*-AZO) as a guest to form the corresponding H ⊃ *trans*-AZO supra-amphiphile by host-guest interactions in water. This supra-amphiphile was further self-assembled to construct photo and pH dual-responsive supramolecular vesicles (Figure 1). In essence, this represents the first example of stimuli-responsive TBTQ-based supramolecular vesicles.

The syntheses of TBTQ-C₆ and *trans*-AZO are shown in the Supporting Information. Before studying their mutual self-assembly processes, ¹H NMR spectroscopy was used to investigate the host-guest binding properties between TBTQ-C₆ and *trans*-AZO. Due to the poor water solubility of *trans*-AZO, a related model compound, 3-ethyl-1-methyl-1*H*-imidazol-3-ium bromide ("G", Figure 1), was used for these tests. As shown in Figure 2, the proton resonances of H_a, H_b, H_c, H_d, H_e and H_f of G were significantly shifted upfield (Δδ = -0.48, -0.84, -0.42, -0.45, -0.51 and -0.54 ppm, respectively) in the presence of equimolar amounts of TBTQ-C₆, which can be attributed to the shielding effect caused by the electron-rich cavity of the tribenzotriquinacene core,^[10] indicating that the G molecule was located deeply within the cavity of TBTQ-C₆. Moreover, these peaks became broadened due to the complexation dynamics. In addition, the signals of the sets of protons H¹, H², H³ and H⁴ of TBTQ-C₆ were also slightly shifted upfield (Δδ = -0.04, -0.06, -0.04 and -0.04 ppm, respectively), also suggesting the successful complexation of TBTQ-C₆ and G.

The H ⊃ *trans*-AZO complex formed in water was examined by fluorescence spectroscopy. Its stoichiometry was found to be 1:1, as elucidated from the Job's plot (Figure S10), and the

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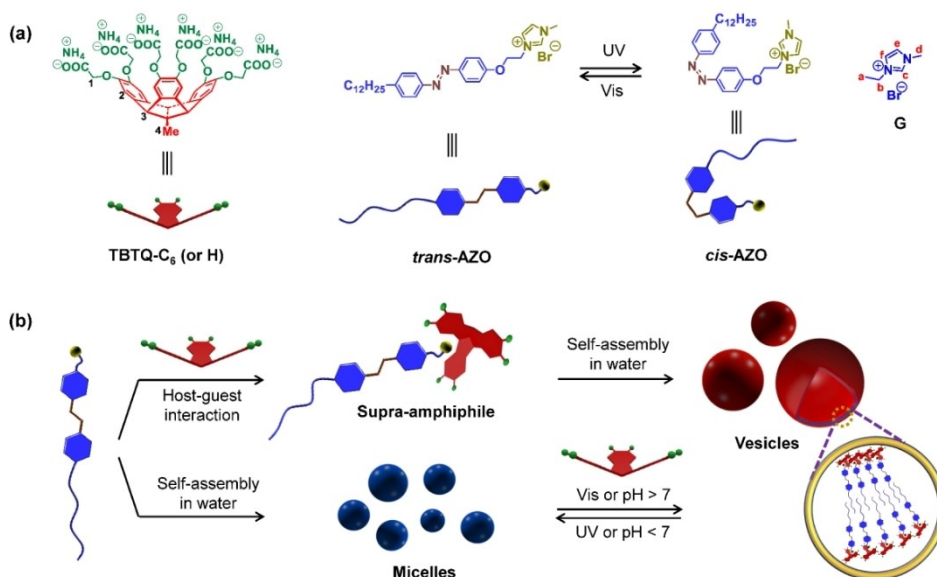


Figure 1. (a) Structures of TBQTQ-C₆ (or H), *trans*- and *cis*-AZO and G; (b) Schematic representation of the photo and pH dual-responsive self-assembly of H and *trans*-AZO in water.

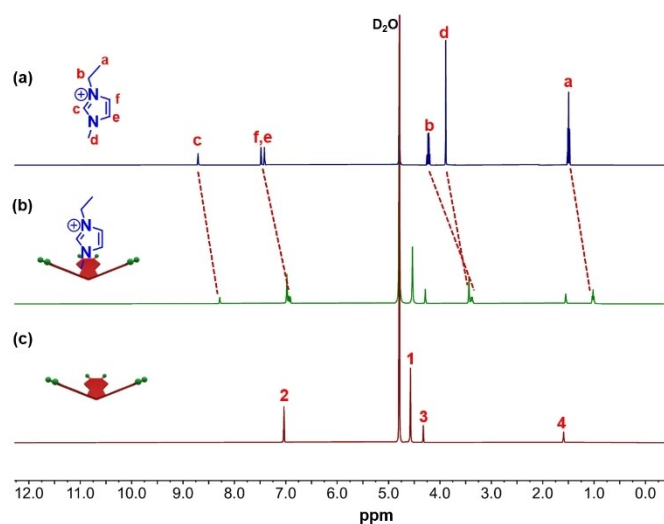


Figure 2. ¹H NMR spectra (400 MHz, D₂O, 25 °C) of (a) G alone; (b) TBQTQ-C₆ and G; (c) TBQTQ-C₆ alone ([TBQTQ-C₆] = [G] = 10 mM).

association constant was determined to be $K_a = (1.68 \pm 0.27) \times 10^5 \text{ M}^{-1}$ based on fluorescence titration and nonlinear curve fitting (Figure S11). As the concentration of *trans*-AZO increases, the emission is significantly quenched, indicating charge transfer from the electron rich host to the electron-deficient guest. These results demonstrate the successful formation of the H ⊃ *trans*-AZO inclusion complex in water. We supposed that it forms supra-amphiphiles where the TBQTQ-C₆ residue displays hydrophilicity and the alkylated azobenzene residue of *trans*-AZO displays hydrophobicity, as illustrated by the model shown in Figure 1b. In the next step, the further self-assembly behaviour of H ⊃ *trans*-AZO supra-amphiphiles in water was explored. Firstly, the critical aggregation concentrations (CACs) of *trans*-AZO alone and of the H ⊃ *trans*-AZO

complex were determined to be $4.3 \times 10^{-5} \text{ M}$ and $5.7 \times 10^{-5} \text{ M}$ (Figure S12), respectively, by means of concentration-dependent conductivity measurements. The aggregation behaviour was investigated by transmission electron microscopy (TEM) and dynamic light scattering (DLS) experiments. As depicted in Figure 3a, *trans*-AZO formed micelles with an average diameter of ~37 nm. Upon addition of TBQTQ-C₆, the H ⊃ *trans*-AZO complex formed vesicles with an average diameter of 172 nm (Figure 3b), corresponding to approximately two extended lengths of the supra-amphiphile and suggesting that the vesicles may occupy a bilayer structure with two hydrophilic carboxylate shell layers and one hydrophobic alkyl chain core

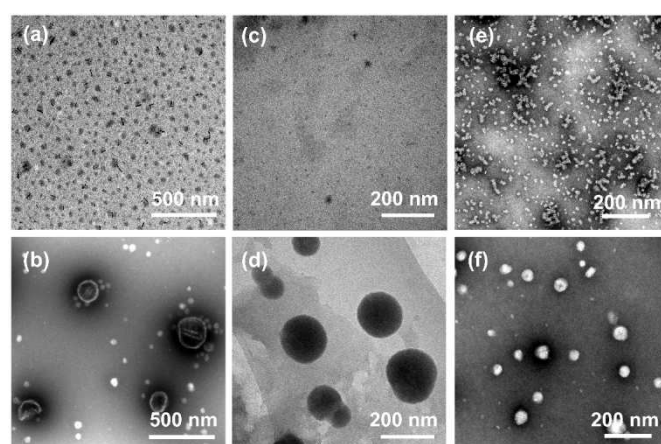


Figure 3. TEM images of (a) *trans*-AZO ($1.0 \times 10^{-4} \text{ M}$) aggregates in water; (b) H ⊃ *trans*-AZO aggregates in water ($1.0 \times 10^{-4} \text{ M}$ for both components); (c) after irradiation of solution (b) with UV light (365 nm); (d) after further irradiation of solution (c) with visible light; (e) after adjustment of solution (b) to pH 5.5; (f) after readjustment of solution (e) to 7.4.

layer, as illustrated in Figure 1b. The DLS measurements revealed that the average sizes of the *trans*-AZO aggregates and H \supset *trans*-AZO aggregates were 37 nm and 192 nm (Figure 4a), respectively, which is in agreement with the TEM results. Furthermore, the ζ -potential of the H \supset *trans*-AZO vesicles was measured to be -42.5 mV (Figure 4b), indicating that the good stability of the vesicles is induced by repulsive forces between them.

Interestingly, when the solution of the vesicles was irradiated with UV light (365 nm), the vesicles disassembled back into micelles (Figure 3c) and when it was subsequently irradiated with visible light, the micelles re-assembled back into vesicles (Figure 3d). Moreover, when the pH of the solution of the vesicles was adjusted to 5.5, the vesicles disassembled forming micelles (Figure 3e) and when the pH was adjusted back to 7.4, the vesicles were regenerated (Figure 3f). Thus, the TEM results clearly proved the photo and pH dual-responsivity of the H \supset *trans*-AZO vesicles.

UV-vis measurements were performed to examine the photo-responsive properties of azobenzene-containing *trans*-AZO and H \supset *trans*-AZO in water in detail. As shown in Figure S13a, *trans*-AZO exhibited a strong absorption at 331 nm and a very weak absorption at 440 nm, which are ascribed to the π - π^* and n - π^* transitions, respectively. Upon irradiation with UV light (365 nm), the absorption at 331 nm gradually decreased, whereas the absorption at 440 nm slightly increased, indicating photo-isomerization of *trans*-AZO to *cis*-AZO.^[1] In turn, when the solution was irradiated with visible light, the opposite changes were observed in the UV-Vis spectra (Figure S13b), which implies back-conversion from the *cis*- to the *trans*-form. In the UV-vis spectra of H \supset *trans*-AZO (Figure S13c-d), the absorption at 331 nm was red-shifted to 351 nm and its intensity clearly decreased, as compared with that of *trans*-AZO alone, due to the host-guest interactions. Upon sequential irradiation with UV light (365 nm) and visible light, the absorption of H \supset *trans*-AZO at 351 nm showed similar reversible changes as those found with *trans*-AZO, suggesting that the *trans*-*cis* photo-isomerization of the guest AZO takes place within the complex with TBTQ-C₆.

Furthermore, a first-order kinetic study on the *trans*-*cis* photo-isomerization of *trans*-AZO and H \supset *trans*-AZO was performed. The UV-vis spectra of *trans*-AZO and H \supset *trans*-AZO recorded after different time intervals are shown in Figure S14. The *trans*-*cis* isomerization rate constants (k_i) of *trans*-AZO and H \supset *trans*-AZO were determined to be $4.65 \times 10^{-3} \text{ s}^{-1}$ and

$13.40 \times 10^{-3} \text{ s}^{-1}$, respectively. The finding that the latter value significantly exceeds the former might be attributed to a decrease of the space barriers of the compact stacking structure of *trans*-AZO by host-guest interaction with TBTQ-C₆, resulting in a faster *trans*-*cis* conversion. The pH-responsive behaviour of the H \supset *trans*-AZO complex was studied by ¹H NMR spectroscopy using the model compound G. When the pH of the solution of H \supset G was changed from 7.4 to 5.0, the proton signals were slightly shifted and enhanced due to the decomposition of the host-guest complex (Figure S15). In turn, when the pH of the solution was readjusted to 7.4, the proton signals of TBTQ-C₆ and G tended to shift back to the original resonance. These observations corroborate the reversible pH-responsive complexation between TBTQ-C₆ and G.

In conclusion, we have successfully constructed a photo and pH dual-responsive supramolecular vesicle system based on supra-amphiphiles formed by the host-guest interaction between the tribenzotriquinacene-based hexacarboxylate TBTQ-C₆ and the photo- and acid-sensitive guest *trans*-AZO. The host-guest complexation takes place in a 1:1 molar ratio with an association constant of $K_a = (1.68 \pm 0.27) \times 10^5 \text{ M}^{-1}$. The guest *trans*-AZO on its own was found to form micelles but, in the presence of one equivalent of TBTQ-C₆, the two components accrete to uniform vesicles with a diameter of ~ 172 nm. Reversible conversion between the vesicles and micelles was observed and found to be controllable by both UV and visible light irradiation and pH adjustment. These photo and pH dual-responsive supramolecular vesicles may have potential for the development of novel versatile supramolecular materials such as controlled drug delivery systems.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: tribenzotriquinacene · host-guest systems · supra-amphiphile · supramolecular vesicle · stimulus responsiveness

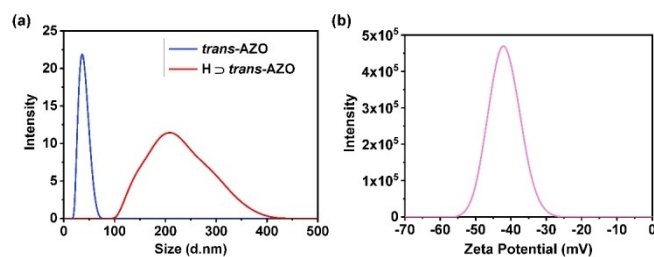


Figure 4. (a) DLS results of *trans*-AZO and H \supset *trans*-AZO; (b) ζ -potential of H \supset *trans*-AZO.

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