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Controllable Fabrication of Various Supramolecular Nanostructures Based on Nonamphiphilic Azobenzene Derivatives and Pillar[6]arene

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Various novel types of supramolecular nanostructures formed by nonamphiphilic azobenzene derivatives, **G1** or **G2** have been successfully fabricated, where **G2** is structurally similar with **G1** but an extra phenoxy group is connected with the azobenzene motif . Micellar structures can be obtained from the self-assembly of **G1**, which further transform to large-sized spindle structures; while nanorods can be initially formed by **G2**, which will gradually aggregate to form layered structures with much larger size. Moreover, it is found that upon addition of **WP6**, which can form inclusion-complex with **G1** or **G2**, separately, the nonamphiphilic **G1** and **G2** thus converse to supramolecular amphiphiles **WP6⊃G1** and **WP6⊃G2**, respectively. Consequently, both of the above **WP6⊃G1** and **WP6⊃G2** complexes can further assemble to form supramolecular binary vesicles, which will gradually transform to nanotubes (**WP6⊃G1**) or well-ordered nanosheets (**WP6⊃G2**).

Keywords nanostructure, azobenzene derivatives, pillararene, self-assembly, UV-responsiveness

Introduction

Molecular self-assembly is an attractive and powerful strategy for the fabrication of sophisticated and functional supramolecular architectures.[1] Based on this concept, various functional nanoscale structures which can be used in the fields of drug delivery,[2] controlled release,[3] nanoreactors,[4] supramolecular polymers,[5] and detection[6] can be precisely constructed and manipulated by rational design and modification of the self-assembling building blocks at the molecular level. Over the past decade, supramolecular nanostructures formed by the self-assembly of supramolecular amphiphiles bearing both hydrophilic and hydrophobic segments have attracted much attention because they can not only spontaneously aggregate to form different assemblies depending on the repelling and coordinating forces between their hydrophilic and hydrophobic parts of the component molecules and the surrounding medium,[7] but also undergo structure transitions in response to numerous stimuli, such as pH, temperature, redox, and light.[2c,8] However, to the best of our knowledge, although a variety of nanostructures with various sizes and functions have been reported based on supramolecular amphiphiles,[7,9] the investigation on nanoscale structures formed by nonamphiphilic molecules in aqueous solution, which can also assemble into various well-defined architectures and may find analogous potential applications in encapsulation and controlled release, has rarely been studied and is far from satisfactory. Therefore, the exploration of nonamphiphilic molecules that can spontaneously form well-defined nanostructures such as micells, vesicles, nanorods, and nanosheets in aqueous solution will increase our understanding and broaden the applications of these well-ordered nanoaggregates in the field of biotechnology and biomedicine, particularly for drug delivery.

During our investigation about the construction of stimuli-responsive supramolecular vesicles based on supramolecular amphiphiles for controlled drug delivery,[10] we surprisingly found that a kind of nonamphiphilic azobenzene derivatives bearing long alkyl chains at one end could also spontaneously aggregate to form well-defined nanoscale structures. Moreover, with the addition of water-soluble pillar[6]arene (**WP6**), such nonamphiphilic molecules could transform to supramolecular amphiphiles *via* pillaraene-based host-guest interaction,[11] which could further assemble to form nanostructures with completely different morphology compared with that of the nonamphiphilic ones. This finding may help us to have a better understanding on the self-assembly of nonamphiphilic molecules.

Herein, we report the successful fabrication of vari-

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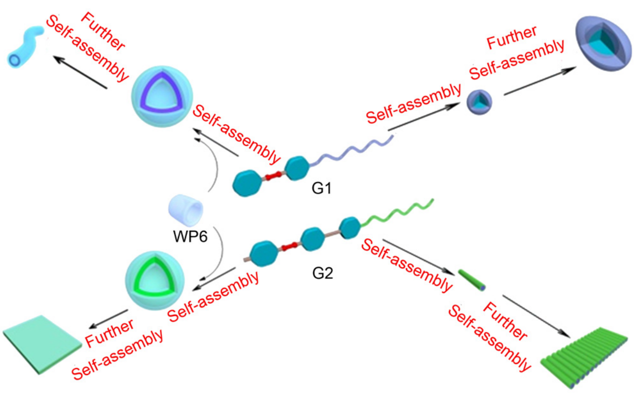
ous novel types of supramolecular nanostructures formed by nonamphiphilic azobenzene derivatives, **G1** or **G2**, where **G2** is structurally similar with **G1** but an extra phenoxy group is connected with the azobenzene motif (Scheme 1). It was found that micellar structures could be obtained from the self-assembly of **G1**, which would further transform to large-sized spindle structures; whereas, nanorods could be initially formed by **G2**, which would gradually aggregate to form layered structures with much larger sizes. Moreover, with the addition of **WP6**, supramolecular amphiphiles **WP6⊃G1** and **WP6⊃G2** could be obtained *via* the pillararene-based host-guest interaction, leading to the formation of supramolecular binary vesicles, which would gradually transform to nanotubes (**WP6⊃G1**) or well-ordered nanosheets (**WP6⊃G2**) through further self-assembly process.

Scheme 1 Cartoon illustration of the self-assembly of nonamphiphilic azobenzene derivatives



Results and Discussion

Initially, two azobenzene-based nonamphiphilic molecules **G1** and **G2** were designed, where **G2** is structurally similar with **G1** but an extra phenoxy group is connected with the azobenzene motif. As expected, both of them exhibited good photoresponsive properties as investigated by the UV-vis spectroscopy (Figure 1). As shown in Figure 1, upon irradiation of the **G1** or **G2** solution with UV light at 365 nm for 10 min, the absorption band at around 350 nm decreased remarkably, meanwhile, the absorption band at around 445 nm increased slightly. The absorption bands of the azobenzene group at 350 nm and 445 nm are ascribed to π-π* and n-π* transitions, respectively.[8d] Such changes of the absorption bands induced by UV irradiation suggested the photoisomerization of the azobenzene motif in **G1** or **G2** from the *trans*-state to the *cis*-state. On the contrary, upon further irradiation of the above solution with visible light at 435 nm for 10 min, the absorption band at around 350 nm attributed to the *trans*-state of **G1** or **G2** increased almost to its original intensity, while the absorption peak at 445 nm attributed to the corresponding *cis*-state decreased slightly, indicating the reversible change from the *cis*- to the *trans*-state of **G1** or **G2**. All the above results clearly demonstrated that such azobenzene-based nonamphiphilic molecules **G1** and **G2** exhibited good UV-responsiveness.

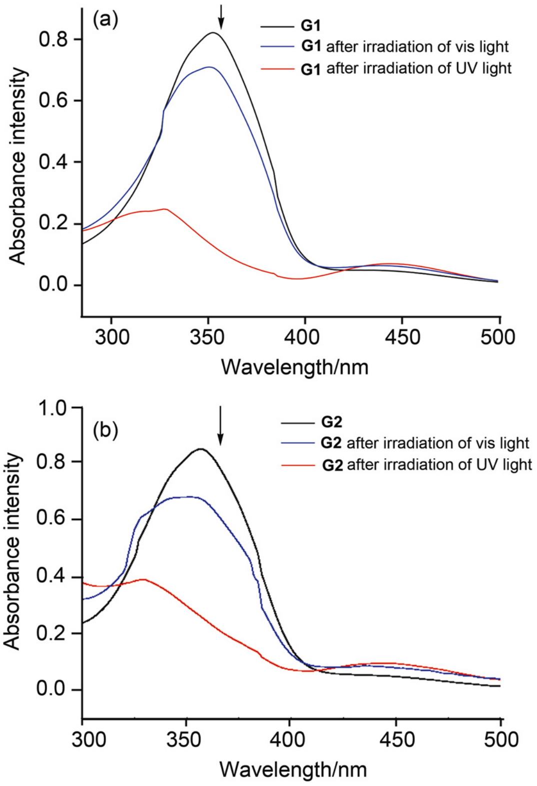


Figure 1 UV-vis absorption spectra of guests (**G1** and **G2**) in ethanol under UV irradiation at 365 nm for 10 min, and then after further irradiation with visible light at 435 nm for 10 min. (a) **G1** (6×10^{-5} mol/L); (b) **G2** (6×10^{-5} mol/L).

Subsequently, an interesting phenomenon was found that when we injected **G1** or **G2** (0.0025 mmol, dissolved in 0.5 mL of THF) into 49.5 mL of deionized (DI) water, a white opalescent phenomenon was obviously observed from the aqueous solution of **G1** or **G2**, indicating the formation of microaggregates. Then the sizes and morphologies of these nanostructural aggregates formed by nonamphiphilic molecule **G1** or **G2** in aqueous solution were investigated *via* transmission electron microscopy (TEM) and dynamic light scattering (DLS) experiments. As shown in Figure 2 and Figure 3, DLS result showed that the freshly prepared **G1** solution formed aggregates with a narrow size distribution, giving an average diameter of 37 nm (Figure 3a), and TEM images indicated the solid spherical morphology with a diameter ranging from 20 to 50 nm, convincingly indicating the formation of micellar structure. Surprisingly, we found an interesting phenomenon that such micellar structures would gradually transform to large-sized spindle structures with increasing incubation time. Figure 2b showed the TEM image of the freshly prepared micellar structures after an incubation time of one week, in which a large number of beaded structure and some larger micells could be seen. And after 2 weeks, almost all of these structures had been transformed to large-sized spindle structures (Figure 2c). Moreover, DLS results also confirmed such gradually size-increasing phenomenon of freshly prepared small micellar structures to spindle aggregates with much larger size (Figure 3b). With respect to the azobenzene derivative **G2**, it was found that nanorods with an average diameter of about 0.35 μm could be observed from its freshly prepared solution based on the TEM and DLS results (Figures 2d, 2e, and Figure 3c). However, after two weeks, the morphology of these nanorods transformed into large-sized disordered layered structures with an average diameter of 0.85 μm (Figure 2f and Figure 3d). The different morphologies of the nanostructures formed from **G1** or **G2** may be associated with the presence of an extra phenoxy group in **G2**, where the cooperative intermolecular hydrogen bonding and π-π interactions within the azobenzene and benzamido motifs of **G2**, make it more easily to assemble into layer-like structures by π-π stacking.

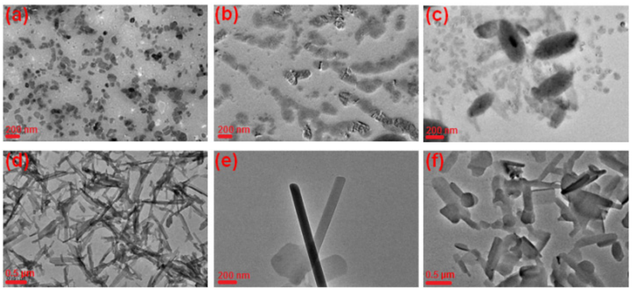


Figure 2 TEM images: (a) **G1** aggregates in water (1% THF was added to improve the solubility of **G1**); (b) **G1** aggregates after standing for one week; (c) **G1** aggregates after standing for two weeks; (d) **G2** aggregates in water (1% THF was added to improve the solubility of **G2**); (e) enlarged image of (d); (f) **G1** aggregates after standing for two weeks. $[\mathbf{G1}]=5\times10^{-5}$ mol/L, $[\mathbf{G2}]=5\times10^{-5}$ mol/L.

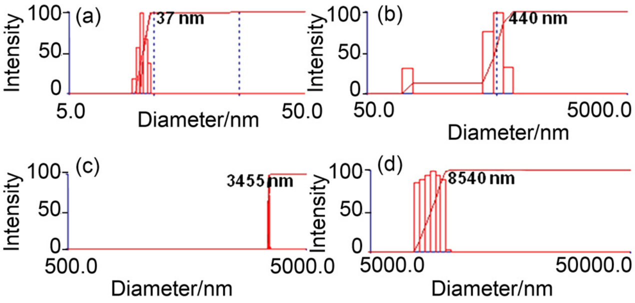


Figure 3 DLS data of the aggregates formed from **G1** or **G2**: (a) DLS results of Figure 2a; (b) DLS results of Figure 2c; (c) DLS results of Figure 2d; (d) DLS results of Figure 2f.

Since we know that water-soluble pillar[6]arenes (**WP6**)[12] have been demonstrated to have a strong binding affinity with azobenzene derivatives in water driven by hydrophobic and electrostatic interactions,[12a,13] we envision that such nonamphiphilic **G1** or **G2** would be transformed to supramolecular amphiphiles **WP6**$\supset$**G1** and **WP6**$\supset$**G2**, respectively *via* pillaraene-based host-guest interaction, and the obtained supramolecular amphiphiles would be possibly able to form supramolecular nanoaggregates in water by self-assembly. Subsequently, UV-vis absorption spectroscopy was used to study the host-guest complexation between **WP6** and azobenzene derivative **G1** or **G2**. As shown in Figure 4, upon the addition of **WP6** into guests **G1** and **G2**, respectively, the absorption band around 290 nm ascribed to the characteristic absorption of **WP6** increased dramatically compared with its original absorption; meanwhile, the absorption peak around 340 nm assigned to the characteristic absorption of the azobenzene guest (**G1** or **G2**) also increased remarkably together with a slightly hypochromatic shift (Figures 4a, 4b). The above observations clearly indicated the formation of supramolecular complexes between **WP6** and guests (**G1**, **G2**), mainly driven by the hydrophobic interactions. With the presence of **WP6**, the *trans*-azobenzene motif of the guests **G1** or **G2** could thread into the cavity of **WP6** to form supramolecular amphiphiles **WP6**$\supset$**G1** and **WP6**$\supset$**G2,** resulting in the changes of the absorbance intensity at 290 nm and 334 nm.

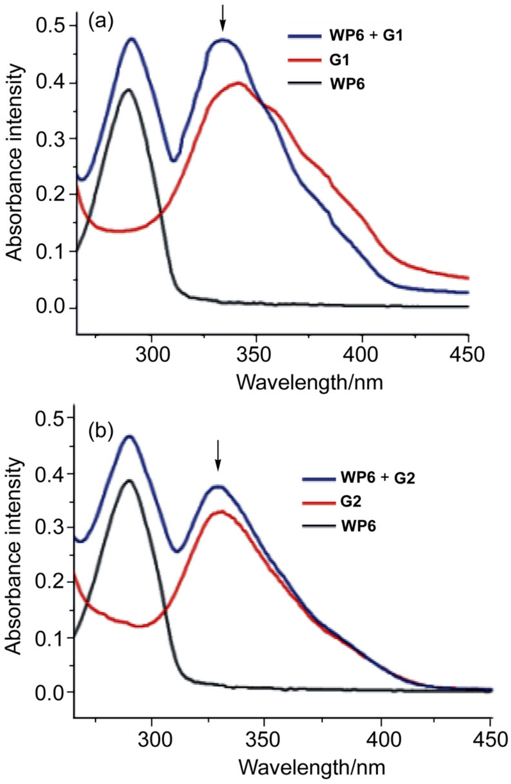


Figure 4 UV-vis absorption spectra of **WP6** with azobenzene guests (**G1** or **G2**): (a) **WP6** (2.5×10^{-5} mol/L) in water (black line), **G1** (2.5×10^{-5} mol/L) in water (red line, 1% EtOH was added to improve the solubility of **G1**), a mixture of **WP6** and **G1** (blue line, molar ratio, 1∶1); (b) **WP6** (2.5×10^{-5} mol/L) in water (black line), **G2** (2.5×10^{-5} mol/L) in water (red line, 1% EtOH was added to improve the solubility of **G2**), a mixture of **WP6** and **G2** (blue line, molar ratio, 1∶1).

Encouraged by the above-mentioned results, we speculated that the obtained supramolecular amphiphiles **WP6⊃G1** and **WP6⊃G2** might exhibit different self-assembly behaviors. Then, we investigated the morphology and size of these aggregates formed by **WP6⊃G1** and **WP6⊃G2** supramolecular amphiphiles, respectively in aqueous solution *via* TEM and DLS measurement. As shown in Figure 5, **WP6⊃G1** formed supramolecular binary vesicles (Figure 5a) with an average diameter of 82 nm (Figure 5e). Interestingly, after two weeks, it was found that such vesicular structures further transformed into large-sized nanotubes (Figure 5b) with an average diameter of 340 nm (Figure 5f). With respect to the **WP6⊃G2** supramolecular amphiphile, it could also assemble into small-sized supramolecular vesicles (Figure 5c) with an average diameter of 117 nm (Figure 5g). However, after two weeks, the obtained **WP6⊃G2** vesicles further aggregated to form well-ordered nanosheets (Figure 5d) with much larger size (*ca*. 9949 nm, Figure 5h).

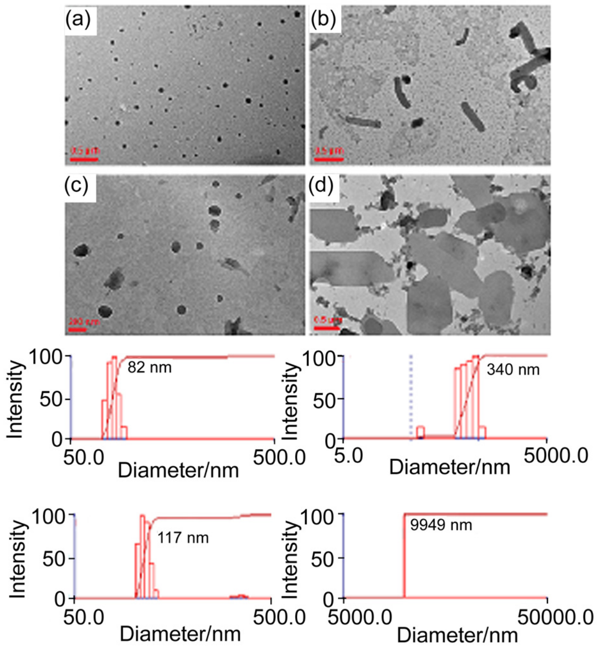


Figure 5 (A) TEM images: (a) freshly prepared **WP6⊃G1** aggregates; (b) **WP6⊃G1** aggregates after standing for two weeks; (c) freshly prepared **WP6⊃G2** aggregates; (d) **WP6⊃G2** aggregates after standing for two weeks. (B) DLS data of the aggregates formed from **WP6** with **G1** or **G2**: (e) DLS results of Figure 5a; (f) DLS results of Figure 5b; (g) DLS results of Figure 5c; (h) DLS results of Figure 5d.

For some supramolecular amphiphilic complex[14] based on the host-guest recognition of pillar[6]arene host and azobenzene-containing guest, it has been reported that the photo-controllable threading-dethreading switch can be obtained due to the photoisomeration of the azobenzene motif.[13,15] However, such reversible switch could not be achieved for our amphiphilic supramolecular self-assembly system. As shown in Figure 6, upon irradiation of the **WP6⊃G1** or **WP6⊃G2** solution with UV light at 365 nm for 0.5 h, the absorption bands at around 290 and 340 nm almost had no change; meanwhile, upon further irradiation with visible light at 435 nm for 0.5 h, nearly no change could be observed. For such phenomenon, we speculated that since the two azobenzene guests were nonamphiphilic, the strong hydrophobic effect in aqueous solution may make the *trans*-azobenzene derivative **G1** or **G2** which fits well with the **WP6** cavity hardly to dethread from the cavity of **WP6**, resulting in the non-photoresponsive property of such azobenzene-based supramolecular amphiphiles.

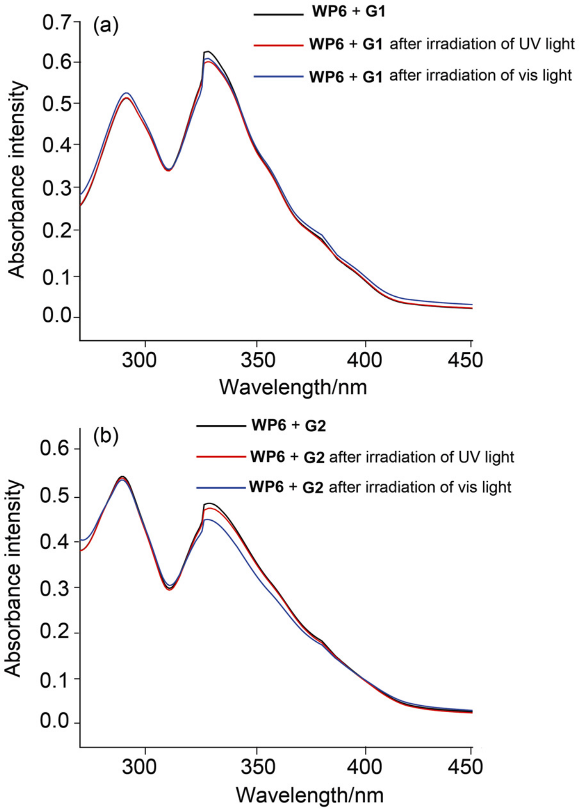


Figure 6 UV-vis absorption spectra of the **WP6⊃G1** and **WP6⊃G2** complexes in water (1% EtOH was added to improve the solubility of the guests) under UV irradiation at 365 nm for 30 min, and then after further irradiation with visible light at 435 nm for 30 min: (a) **WP6⊃G1** complex (**WP6**=3×10^{-5} mol/L, **G1**=3×10^{-5} mol/L); (b) **WP6⊃G2** complex (**WP6**=3×10^{-5} mol/L, **G2**=3×10^{-5} mol/L).

Conclusions

In summary, the self-assembly behaviors of nonamphiphilic azobenzene derivatives **G1** and **G2** were investigated in aqueous solution, and various novel types of supramolecular nanostructures could be obtained based on their self-assembly process. **G1** itself initially self-assembled into small spherical micells, which would gradually convert to large-sized spindle structures with increasing incubation time. Compared with **G1**, azobenzene derivative **G2** that has an extra phenoxy group connected with the azobenzene motif could form nanorod-like aggregates, which would then transform into disordered layered structures probably due to the presence of cooperative intermolecular hydrogen bonding and π-π interactions within the azobenzene and benzamido motifs of **G2**. Significantly, it was found that upon addition of **WP6**, which could form inclusion-complex with **G1** or **G2**, separately, the nonamphiphilic **G1** and **G2** thus converse to supramolecular amphiphiles **WP6⊃G1** and **WP6⊃G2**, respectively. Consequently, both of the above **WP6⊃G1** and **WP6⊃G2** complexes could assemble to form supramolecular binary vesicles, which will gradually transform to nanotubes (**WP6⊃G1**) or well-ordered nanosheets (**WP6⊃G2**). The present study provides a novel strategy for the controllable fabrication of well-defined nanostructures.

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