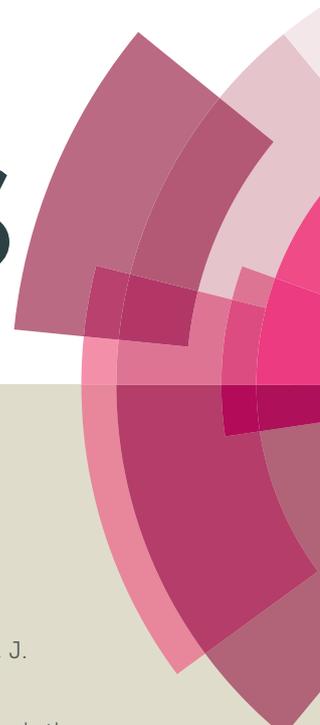


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Diols-responsive triple-component supra-amphiphile constructed from pillar[5]arene-based recognition†

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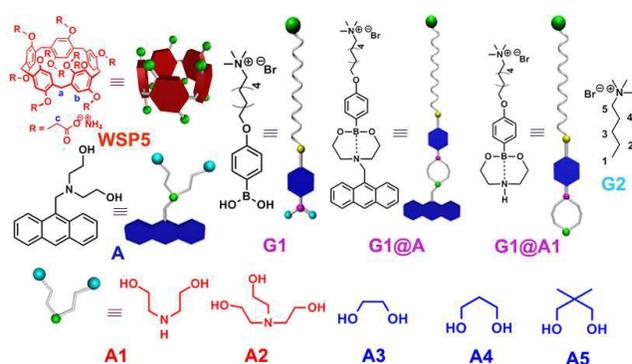
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A triple-component supra-amphiphile WSP5>G1@A is constructed based on phenylboronic acid/diols dynamic covalent chemistry and water-soluble pillararenes/trimethylamine host-guest recognition. The ternary complex WSP5>G1@A self-assembles into nanoparticles in aqueous solution and exhibits appealing diols-responsive behavior: upon concomitant addition of diols, the self-assembled nanoparticles transforms into regular nanosheets and simultaneously experiences a pronounced fluorescence decrease in aqueous solution.

Stimuli-responsive self-assembled materials have become a hot topic in the supramolecular community because it can be applied in the areas of controlled release,¹ drug delivery² and supramolecular polymers.³ Numerous external stimuli including gases, temperature, enzymes, redox and pH, have been applied in the construction of stimuli-responsive supramolecular materials.⁴ Notably, diols-responsive self-assembly is especially attractive because several diols are of biological and environmental relevance, such as carbohydrates and nucleic acid derivatives,⁵ possessing excellent biocompatibility and biodegradability. These diols-responsive self-assembled nanomaterials show great promise for the applications in drug delivery and controlled release. Therefore, it is urgently necessary to develop diols-responsive self-assembled functional materials.

Supra-amphiphiles,⁶ a class of charming molecules bearing both hydrophilic and hydrophobic part, can self-assemble in water or organic solvents to generate specific nanostructures depending on noncovalent interactions, such as hydrogen bonding, π - π stacking interactions, electrostatic interactions and charge-transfer interactions. Supra-amphiphiles with different chemical structures can self-assemble into form various fascinating nanostructures, which provide a facile platform to fabricate diverse advanced materials. As a class of fascinating macrocyclic hosts next to crown ethers,⁷ cyclodextrins,⁸ calixarenes⁹ and cucurbiturils,¹⁰ pillar[*n*]arenes¹¹ have gradually become a new driving force to

stimulate the development of supramolecular chemistry since its first report. The self-assembly behaviors of the supra-amphiphiles based on pillar[*n*]arenes have been widely studied so far.¹² However, compared with ubiquitous binary supra-amphiphiles system, multi-component self-assembly based on water-soluble pillar[*n*]arenes has been rarely investigated.¹³ Herein, we utilize dynamic covalence and host-guest chemistry to fabricate a novel ternary supra-amphiphile, which self-assembles into the nanoparticles in water (Scheme 2). Interestingly, the obtained ternary supra-amphiphile possesses unique diols-responsive behavior. In the presence of diols, the nanoparticles transform into regular nanosheets, while simultaneously experience a pronounced fluorescence decrease in aqueous solution.

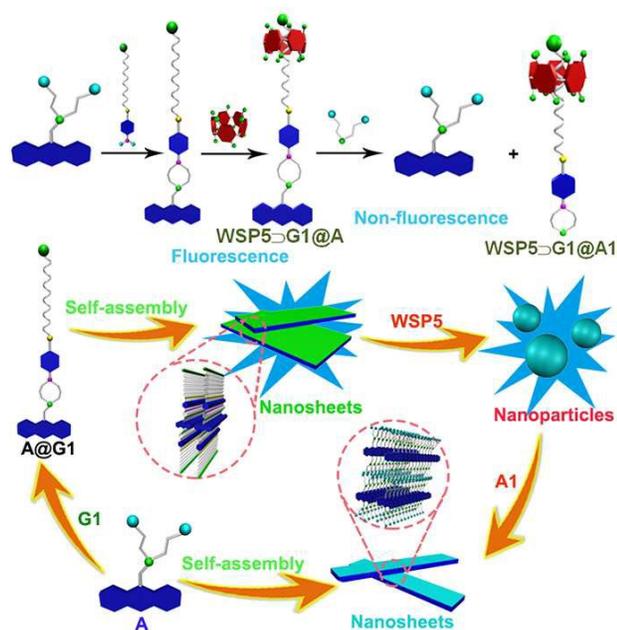


Scheme 1 Chemical structures of the compounds used in this article.

The triple-component supra-amphiphile **WSP5>G1@A** was constructed as shown in Scheme 1 and Scheme 2. The amphiphilic molecule (**G1**) possesses a phenylboronic acid group and a cationic trimethylamine, where the phenylboronic acid group can rapidly react with diethanol part of **A** *via* dynamic covalent chemistry, resulting in the generation of two five-membered rings. On the other hand, host-guest complexation occurred between a water-soluble pillar[5]arene

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(WSP5) bearing five carboxylate anionic groups on both rims and the cationic trimethylamine moiety of G1, resulting in the formation of a stable host-guest complex mainly driven by electrostatic interactions. In this ternary supra-amphiphile, the host-guest complex acts as the hydrophilic section, while the alkyl chain and anthracene ring linked by the dynamic covalent.



Scheme 2 Schematic representation of triple-component self-assembly and its fluorescence behavior in water.

The host-guest complexation was first investigated by using a model compound G2 through ^1H NMR spectroscopy due to the relatively poor water-solubility of G1 in water. Compared with the spectrum of free guest G2 (Fig. 1a), remarkable upfield shift changes were observed corresponding to the proton signals of G2 upon addition of an equimolar amount of WSP5 ($\Delta\delta = -0.89, -2.04, -2.62, -2.12$ and -1.34 ppm for H₁, H₂, H₃, H₄ and H₅, respectively), which was ascribed to the shielding effect of the electron-rich cavity upon formation of a threaded structure.¹⁴ As shown in Fig. 1c, the signals related to the protons on WSP5 shifted downfield slightly, which was induced by the deshielding effect after the achievement of host-guest complexation between WSP5 and G2. Meanwhile, extensive broadening effect occurred caused by the complexation dynamic.¹⁵ 2D NOESY NMR spectroscopy also provided a convincing evidence for the formation of an inclusion complex (Fig. S5).¹⁶ Strong nuclear overhauser effect (NOE) correlations were observed between the signals related to the protons H_{a-c} on WSP5 and the protons H₁₋₅ on G2, verifying the alkyl chain on G2 deeply threaded into the cavity of WSP5, in accordance with the conclusion obtained from ^1H NMR studies. Furthermore, the association constant was calculated to be $(2.06 \pm 0.04) \times 10^5 \text{ M}^{-1}$ for WSP5>G2 in 1:1 complexation by isothermal titration calorimetry (ITC) experiment,¹⁷ confirming strong interactions in this host-guest system (Fig. S6). Additionally, the ITC data

also indicated that the complexation was mainly driven by enthalpy changes ($\Delta H^\circ < 0$; $T\Delta S^\circ < 0$; $|\Delta H^\circ| > |T\Delta S^\circ|$).

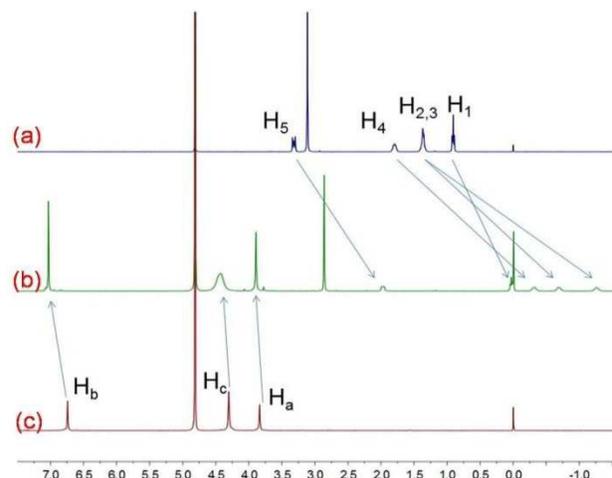


Fig. 1 Partial ^1H NMR spectra (400 MHz, D₂O, 295 K): (a) G2 (2.00 mM); (b) WSP5 (2.00 mM) and G2 (2.00 mM); (c) WSP5 (2.00 mM).

After the establishment of the recognition motif between WSP5 and G2 in water, a supra-amphiphile was constructed by using G1 as a guest. The critical aggregation concentration (CAC) of A in water was calculated to be $5.49 \times 10^{-7} \text{ M}$ by using concentration-dependent conductivity (Fig. S7).¹⁸ As shown in TEM image, A self-assembled into nanosheets in water (Fig. 2a). The thickness of A aggregates was measured to be $2 \mu\text{m}$ by scanning electron microscope because their packing structure was in a multi-layered antiparallel pattern (Figure S18). The main driving forces of the formation of nanosheets were the π - π stacking interactions between anthracene groups and the intermolecular hydrogen bonds between the diethanol groups.¹⁹ Upon formation of complex G1@A linked by dynamic covalent bond, the CAC value was enhanced to be $7.95 \times 10^{-6} \text{ M}$ (Fig. S8), arising from the introduction of the water-soluble cationic trimethylamine group into the amphiphilic system. The nanosheets self-assembled from A became thinner upon addition of G1 into the solution of A (Fig. 2b) and its thickness was calculated to be 4 nm (Figure S19). The main reason was that the introduction of electrostatic repulsion destroyed the intermolecular hydrogen bonds between the layers due to the formation of boronate G1@A. Interestingly, the CAC value of G1@A in the presence of WSP5 was further increased to $4.74 \times 10^{-5} \text{ M}$ (Fig. S9). The enhancement of the CAC value was attributed to stable host-guest complexation between WSP5 and G1@A.²⁰ Upon addition of WSP5, the nanosheets of G1@A disappeared, while nanoparticles with the average diameter about 150 nm were observed (Fig. 2c and 2d). Besides, the dynamic light scattering (DLS) experiment showed the main diameter distribution of these nanoparticles was 150 nm (Fig. S10), which was in good agreement with TEM images.

A reliable mechanism was proposed to elucidate the morphology changes of G1@A upon titration of WSP5. It's well-known that the microassembled structure of the aggregates formed by amphiphiles is determined by the curvature of the

membrane.^{6a} Upon addition of **WSP5**, the hydrophilic head of **G1@A** bearing the cationic trimethylamine moiety threaded into the π -rich cavity of **WSP5** mainly driven by electrostatic and hydrophobic interactions, forming a novel supra-amphiphile **WSP5** \supset **G1@A**. **WSP5** \supset **G1@A** self-assembled into small micelles with low curvature in water and the small micelles further aggregated together to form large multimolecular nanoparticles. In other words, the large nanoparticles were a type of multimicelle aggregates with the basic building units²³ (Fig. S20).

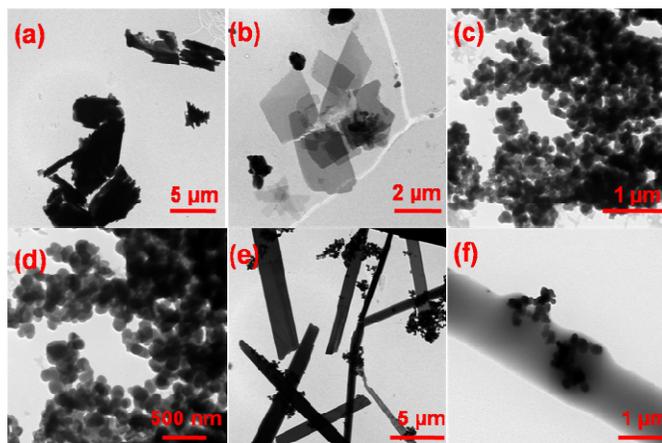


Fig. 2. TEM images of (a) **A** aggregates, (b) **G1@A** aggregates, (c) **WSP5** \supset **G1@A** aggregates, (d) enlarged image of **WSP5** \supset **G1@A** aggregates, (e) **WSP5** \supset **G1@A** aggregates upon addition of 1 equiv of **A1** and (f) enlarged image of (e).

Due to the dynamic nature of boronate, the diol **A1** can replace molecule **A** of the complex **WSP5** \supset **G1@A** to form a new ternary complex **WSP5** \supset **G1@A1**. This competitive process was observed by TEM (Fig. 2e and 2f). Upon addition of **A1** (1 equiv.) into the solution of **WSP5** \supset **G1@A**, the nanoparticles formed from **WSP5** \supset **G1@A** disappeared, while the multi-layered nanosheets self-assembled from **A** appeared again. The phenomena confirmed the occurrence of the competitive process. Notably, **A** was a typical fluorescence-quenched molecule caused by photoinduced electron transfer (PET) effect and π - π stacking.²¹ When **G1** bound to the diethanolamine part of **A**, the quenched fluorescence of the anthracene group recovered because the PET effect and the π - π stacking were effectively inhibited. Accompanied with addition of the competitive diol **A1** in water, **A** was disassociated from **WSP5** \supset **G1@A** and the fluorescence was quenched again. Hence, the diols-responsive behavior of ternary supra-amphiphile can be monitored by fluorescence spectroscopy.

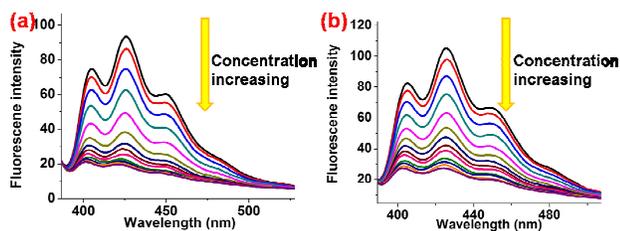


Fig. 3. The changes in fluorescence intensity of **WSP5** \supset **G1@A** (0.100 mM) upon gradual addition of (a) **A1** and (b) **A2** (0, 0.100, 0.300, 0.600, 1.00, 1.50, 2.00, 2.50, 3.00, 4.00, 5.00, 6.00 and 7.00 equiv.) in water ($\lambda_{\text{ex}} = 370$ nm).

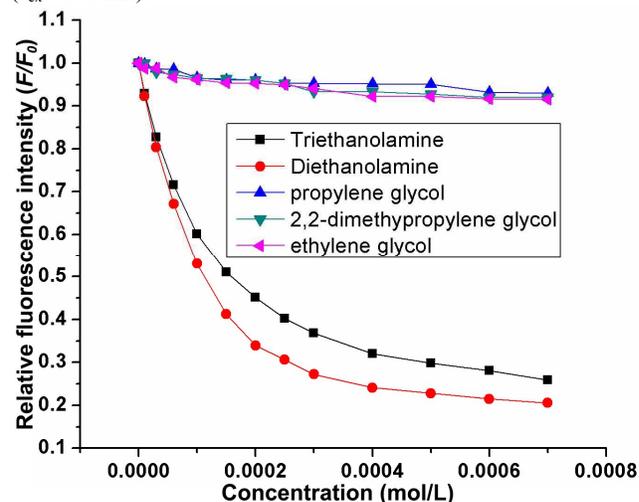


Fig. 4. Relative fluorescence intensity of **WSP5** \supset **G1@A** (0.1 mM) with different concentrations of diols or triols ($0-7.00 \times 10^{-4}$ mol/L) in water ($\lambda_{\text{ex}} = 370$ nm, F represented the fluorescence intensity at 427 nm).

To further investigate the fluorescence property of our ternary complex **WSP5** \supset **G1@A**, the fluorescence titrations of **WSP5** \supset **G1@A** in the presence of different diols were carried out in water (Fig. 3 and Fig. S11–S15). As shown in Fig. 3, the fluorescence intensity decreased gradually by increasing the concentration of diethanolamine or triethanolamine (**A2**). The fluorescence intensity changes indicated that the addition of these diols stimulated the disassociation of **G1@A** instead by the formation of new complexes (**A@A1** and **A@A2**). From Fig. 4, we found that the ternary supra-amphiphile exhibited higher selectivity towards diethanolamine than triethanolamine. However, **A3**, **A4** and **A5** were not able to quench the fluorescence of **WSP5** \supset **G1@A** effectively, indicating these diols were not able to substitute **A** from complex **WSP5** \supset **G1@A** in aqueous phase. The reason was that the existence of B-N bond played a vital role in the stabilization of boronate in aqueous solution.²² The results obtained from fluorescence titration demonstrated that the ternary supra-molecular systems possessed highly selective diols-responsiveness, in line with the TEM investigations.

In conclusion, we designed and synthesized an amphiphilic molecule **G1**, which assembled to form a triple-component supra-amphiphile **WSP5** \supset **G1@A** based on phenylboronic acid/diols dynamic covalent chemistry and pillararene/trimethylamine host-guest complexation. The ternary complex **WSP5** \supset **G1@A** self-assembled into nanoparticles in aqueous solution and showed appealing diols-responsive behavior: upon concomitant addition of diols, the nanoparticles transformed into regular nanosheets and simultaneously experienced a pronounced fluorescence decrease in aqueous solution. These interesting phenomena suggested the triple-component supra-amphiphile showed great

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potential for application in the biologically and environmentally relevant fields, such as controlled release and drug delivery.

Acknowledgements

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Notes and references

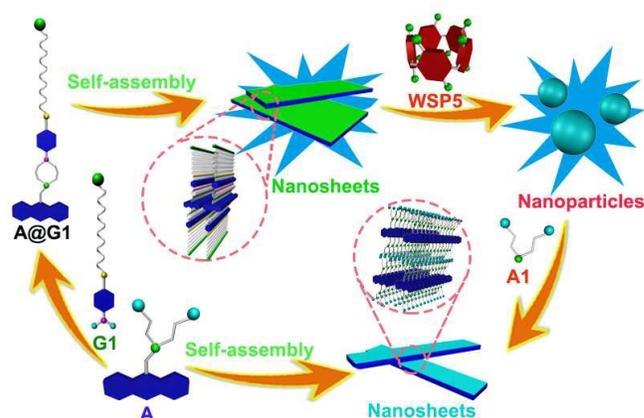
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† Electronic Supplementary Information (ESI) available: Synthetic procedures, characterizations, determination of association constants, fluorescence spectroscopy data and other materials. See DOI: 10.1039/c6xx00000x.

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