

Fluorescent Supramolecular Polymersomes Based on Pillararene/Paraquat Molecular Recognition for pH-controlled Drug Release

Run Zhao^a, Yu-Juan Zhou^a, Ke-Cheng Jie^a, Jie Yang^{b*}, Sébastien Perrier^{b,c,d*}, and Fei-He Huang^{a*}

^a State Key Laboratory of Chemical Engineering, Center for Chemistry of High-Performance & Novel Materials, Department of Chemistry, Zhejiang University, Hangzhou 310027, China

^b Department of Chemistry, The University of Warwick, Coventry CV4 7AL, UK

^c Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, 381 Royal Parade, Parkville, VIC 3052, Australia

^d Warwick Medical School, The University of Warwick, Coventry CV4 7AL, UK

Electronic Supplementary Information

Abstract Researchers have put significant efforts on developing versatile fluorescent polymeric systems due to their promising biological/biomedical labelling, tracking, monitoring, imaging, and diagnostic applications. However, complicated organic/polymeric synthesis or post-modification of these functionalized platforms is still a big obstacle for their further application and thereby provides clear motivation for exploring alternative strategies for the design and fabrication of easily available fluorescent systems. The marriage of supramolecular polymers and fluorescent imaging can provide a facile and dynamic manner instead of tedious and time-consuming synthesis due to the dynamic and reversible nature of noncovalent interactions. Herein, based on water-soluble pillararene/paraquat molecular recognition, we successfully prepare two amphiphilic polypseudorotaxanes which can self-assemble into supramolecular polymersomes in water. These polymersomes can be reversibly destroyed and reformed by tuning the solution pH. Attributed to the aggregation-induced emission of tetraphenylethylene groups, intense fluorescence can be introduced into the obtained supramolecular polymersomes. Furthermore, pH-triggered release of an encapsulated water-insoluble drug (doxorubicin) from the self-assembled fluorescent supramolecular polymersomes is also investigated.

Keywords Fluorescent polymers; Aggregation-induced emission; Host-guest interactions; Responsiveness

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INTRODUCTION

For the past decades, fluorescent labelling and imaging have fuelled the significant growth of life science and medical research due to the increasing demands on biomolecule analysing,^[1–4] biological process tracking,^[5–9] and disease and therapeutic efficacy visualizing.^[10–13] Due to the unique properties and numerous potential applications evolved from their ability to self-assemble into a plethora of morphologically diverse nanostructures such as micelles,^[14–16] polymersomes,^[17–20] cylinders,^[21–23] and others, amphiphilic copolymers with fluorescent labelling are at the focus of extensive scientific interest. However, complicated organic/polymeric synthesis or post-modifications of these functionalized polymers is still a big obstacle for the further application and provides clear motivation for exploring alternative strategies for the design and fabrica-

tion of easily available fluorescent systems.^[24,25] The marriage of supramolecular polymers and fluorescent imaging can provide a facile and dynamic manner instead of tedious and time-consuming synthesis due to the dynamic and reversible nature of noncovalent interactions, such as hydrogen bonding,^[26–28] π - π stacking,^[29–32] metal-coordination,^[33,34] and host-guest interactions.^[35–40] Furthermore, with the combination of noncovalent forces and amphiphilicity, supramolecular polymers can self-assemble into well-defined aggregates in water which can be disrupted by the destruction of non-covalent interactions, implying the potential applications in controlled drug/gene delivery.^[41,42] Among all the non-covalent interactions, host-guest interactions have successfully attracted scientists' attention owing to their abundant stimuli-responsiveness.^[43–47] Pillar[n]arenes, a new class of macrocyclic hosts, have become one of the most popular topics recently.^[48–59] Due to their rigid pillar structures, electron-donating cavities, and easy functionalization, pillar[n]arenes have shown intriguing host-guest binding properties with plenty of guest molecules,^[60–63] thereby providing a useful tool for the construction of various interesting supramolecular systems, especially the responsive supramolecular polymers and supra-amphiphiles.^[64] However, pillar-

* Corresponding authors, E-mail: J.Yang.38@warwick.ac.uk (J.Y.)

E-mail: S.Perrier@warwick.ac.uk (S.P.)

E-mail: fhuang@zju.edu.cn (F.H.H.)

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[*n*]arene-based fluorescent supramolecular polymersomes are still in their infancy.

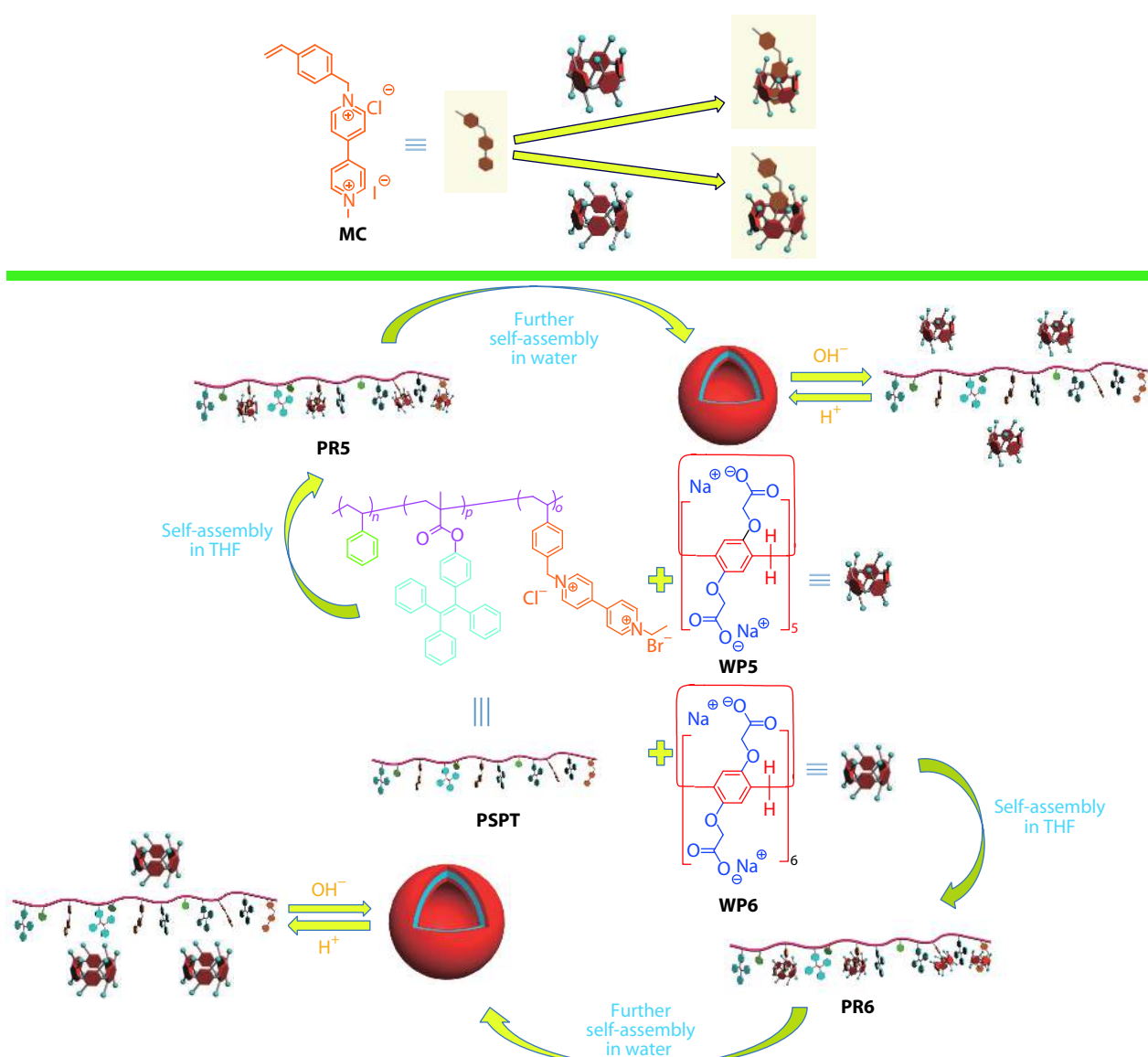
Herein, we present a novel and facile supramolecular strategy to construct fluorescent polymeric aggregates. Scheme 1 outlines our work in detail. Polymer **PSPT** is polystyrene (PS) with pendent paraquat (*N,N'*-dimethyl-4,4'-bipyridinium) units and tetraphenylethylene (TPE) groups. Unlike traditional luminescent molecules which suffer from aggregation-caused quenching (ACQ) in the condensed phase, TPE emits efficiently upon aggregation, exhibiting aggregation-induced emission (AIE),^[65–69] which makes it an ideal candidate for fabrication of fluorescent self-assembly systems in aqueous solution. Based on water-soluble pillararene/paraquat molecular recognition, we successfully prepared two amphiphilic polypseudorotaxanes, **PR5** and **PR6**, which self-assembled into supramolecular polymersomes in water. These polymer-

some were reversibly destroyed and reformed by tuning the solution pH. Attributed to the aggregation-induced emission of tetraphenylethylene groups, intense fluorescence was introduced into the obtained polymersomes. Furthermore, pH-triggered release of an encapsulated water-insoluble drug (doxorubicin) from the obtained supramolecular polymersomes was investigated.

EXPERIMENTAL

See electronic supplementary information (ESI) for more details.

Polymer **4** was prepared from styrene (compound **1**), compound **2**, and 4-vinylbenzyl chloride (compound **3**) by free radical polymerization (Chart 1). A mixture of styrene (7.80 mL, 68.1 mmol), compound **2** (950 mg, 2.28 mmol), and 4-vinylbenzyl chloride (348 mg, 2.28 mmol) in 30 mL of ben-



Scheme 1 Chemical structures of polymer **PSPT**, water-soluble pillar[5,6]arenes (**WP5** and **WP6**), and model guest **MC**, as well as the cartoon representations of host-guest complexes between **WP5** and **MC** and between **WP6** and **MC** and pH-controlled formation of supramolecular polymersomes from self-assembly of amphiphilic polypseudorotaxanes **PR5** and **PR6** in water.

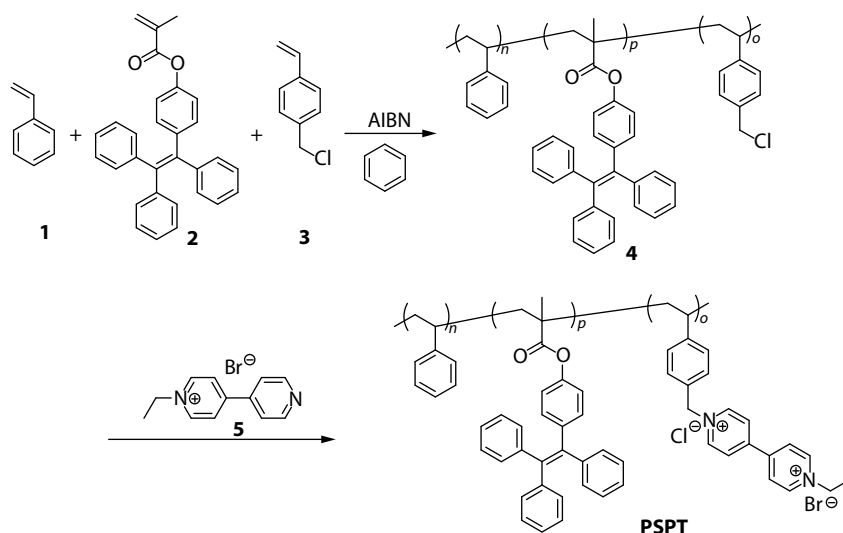


Chart 1 Synthetic route to polymer **PSPT**.

zene was stirred at room temperature. A stream of argon (Ar) was bubbled through for 30 min. In one portion was added 4.90 mg (0.0300 mmol) of azobisisobutyronitrile (AIBN) and the mixture was stirred for 10 min, sealed with a rubber septum, and heated to 70 °C for 24 h. Rapid freezing in liquid nitrogen quenched the polymerization and the solvent was removed under vacuum. The crude product was dissolved in 2 mL of CHCl_3 and precipitated into 200 mL of methanol. The precipitated solid was collected by vacuum filtration. This process was repeated three times and the collected polymer was dried in vacuum (2.13 g, 30%). The precipitate was collected by filtration and dried overnight in vacuum to give **4** as white powder ($M_{n,\text{GPC}} = 12.29$ kDa, $M_{w,\text{GPC}} = 21.14$ kDa, PDI = 1.72). $^1\text{H-NMR}$ (400 MHz, CDCl_3 , 298 K, δ , ppm): 7.24–6.80 (m, 25H, Ar), 6.78–6.28 (m, 12H, Ar), 4.52 (m, 2H, Ar– CH_2 –), 0.94–0.82 (m, 3H, CH_3).

A mixture of polymer **4** (1.00 g, 0.0814 mmol) and compound **5** (1.79 g, 6.75 mmol) in DMF (50 mL) was stirred at 80 °C overnight. The solvent was evaporated and the residue was dissolved in 2.00 mL of chloroform. Then, the solution was dropped into cold methanol (100 mL) and the precipitate was collected by filtration; this process was repeated. The solid was dried overnight in a vacuum to give brown powder (0.96 g, 74%). Fig. S3 (in ESI) is the $^1\text{H-NMR}$ spectrum (400 MHz, chloroform- d , room temperature) of **PSPT**.

RESULTS AND DISCUSSION

Polystyrene-based copolymer **PSPT** with pendent paraquat (*N,N'*-dimethyl-4,4'-bipyridinium) units and tetraphenylethylene (TPE) groups was prepared according to previous literature.^[25,70] There are about 14 paraquat moieties and 14 TPE moieties per single polymer chain for **PSPT** as calculated from proton NMR spectra and gel permeation chromatography (GPC) data (Figs. S1 and S2 in ESI). Water-soluble pillar[5]arene **WP5** and pillar[6]arene **WP6** were synthesized by the well-investigated methods reported by our group.^[49,57] Upon mixing **PSPT** with **WP5** or **WP6** in water, polypseudorotaxane **PR5** or **PR6** was obtained, in which the complexed water-soluble pillararene

molecules acted as the hydrophilic bulky groups and polymer **PSPT** served as the hydrophobic main chain (Scheme 1).

First, we investigated the host-guest complexations of model guest molecule **MC** (Scheme 1) with **WP5** and **WP6**. The proton NMR spectra of the complexes between **MC** and **WP5** and between **MC** and **WP6** were recorded (Fig. S5 in ESI). They provided convincing evidences for the formation of **WP5/WP6** and **MC** inclusion complexes. Due to the fact that the COO^- group can be converted into the neutral carboxylic acid group by adding acid, the host-guest interactions between the pillararenes and viologen moiety could be undermined. The NMR spectra (Figs. S6 and S7, ESI) also revealed the reversible **WP5/WP6** and **MC** complexations by sequential addition of DCl and NaOD aqueous solutions.

Based on the established **WP5/MC** (**WP6/MC**) molecular recognition, we constructed two amphiphilic polypseudorotaxanes **PR5** and **PR6** (Scheme 1). To investigate the self-assembly behavior of the obtained polypseudorotaxanes, aqueous solutions of 5.00×10^{-4} mol/L **PR5** and 5.00×10^{-4} mol/L **PR6** were prepared. Morphology, size, and fluorescence of the self-assembled aggregates were studied by transmission electron microscopy (TEM), dynamic light scattering (DLS), and confocal laser scanning microscopy (CLSM). At first, the self-assembly behavior of polymer **PSPT** in aqueous solutions was investigated by DLS. As shown in Fig. S7 (in ESI), the size distribution of the aggregates formed by **PSPT** itself was broad, indicating irregular self-assembly. However, the DLS data dramatically changed upon the formation of **PR5/PR6**. The average diameter of the aggregates from **PR5/PR6** was about 80/100 nm with a narrow size distribution (Figs. 1g and 1h), indicating the formation of some regular assemblies. TEM observations were further performed to confirm the DLS result through visualization of the self-assembled nanostructures. As shown in Figs. 1(c) and 1(f), **PSPT** itself self-assembled into random aggregates, which is consistent with the above mentioned DLS results. Upon the formation of polypseudorotaxanes, hollow spheres can be observed (Figs. 1a and 1b), strongly supporting the formation of vesicles rather than micelles. It is worth noting that the average ves-

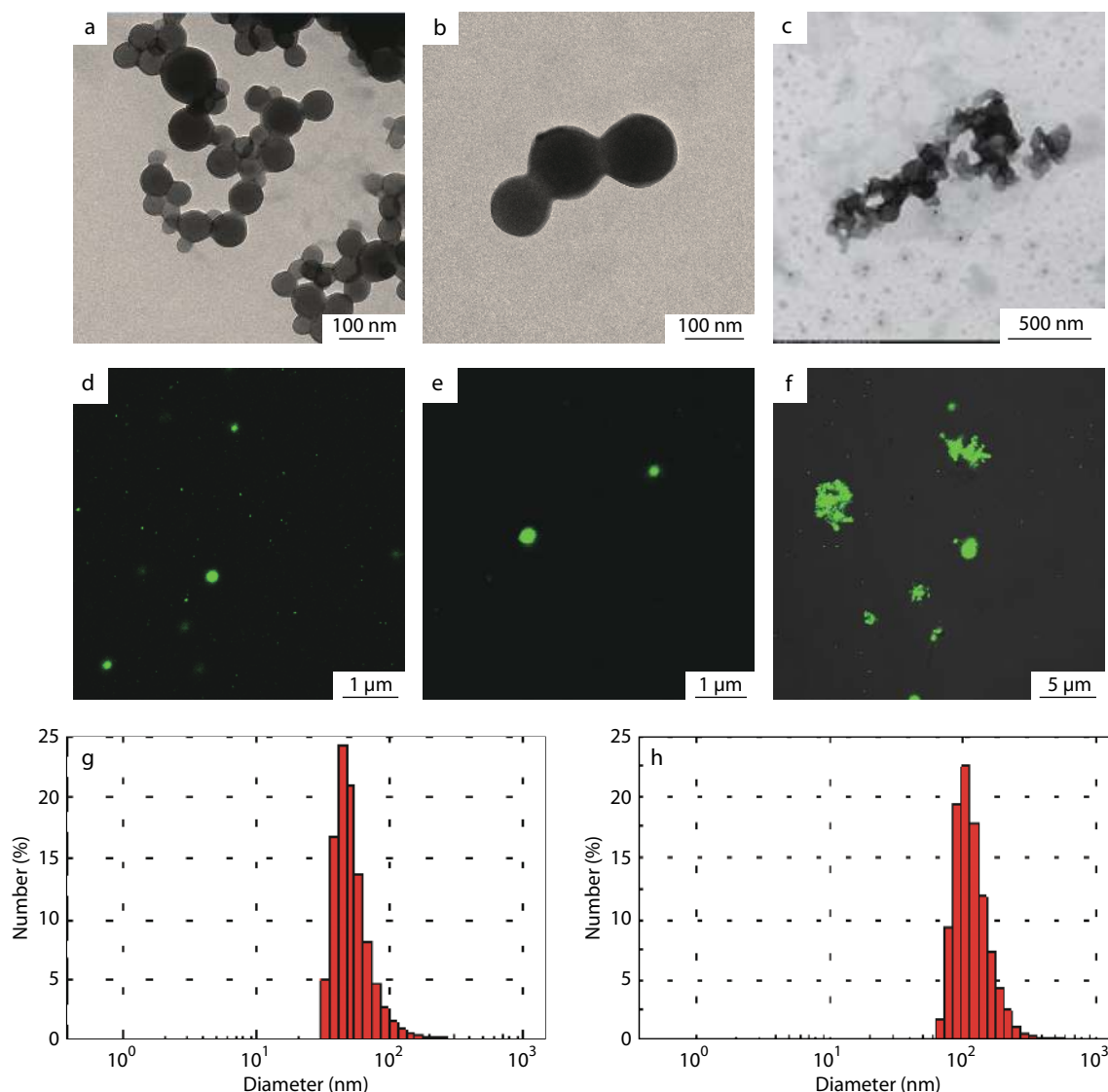


Fig. 1 TEM images of (a) **PR5** (5.00×10^{-4} mol/L), (b) **PR6** (5.00×10^{-4} mol/L), and (c) **PSPT** (5.00×10^{-4} mol/L) aggregates separated from aqueous solutions; Confocal laser microscope images of (d) **PR5** (5.00×10^{-4} mol/L), (e) **PR6** (5.00×10^{-4} mol/L), and (f) **PSPT** (5.00×10^{-4} mol/L) in aqueous solution; DLS results of (g) **PR5** (5.00×10^{-4} mol/L) and (h) **PR6** (5.00×10^{-4} mol/L) in aqueous solution.

icle size values determined by TEM were somewhat smaller than the hydrodynamic diameters obtained from DLS, since the latter technique is sensitive to both hydration and polydispersity. The larger size diameter of **PR6** is mainly attributed to the larger size of pillar[6]arene **WP6** compared to that of pillar[5]arene **WP5**.

Due to the fact that the COO^- groups of **WP5** and **WP6** can be converted into neutral carboxylic acid groups by adding acid, the host-guest interactions between pillararenes and the viologen moiety could be undermined and thereby the obtained vesicles could be destroyed. To investigate the impact of pH on the self-assembly behavior, DLS and TEM experiments were carried out. As shown in Fig. S8 (in ESI), the DLS data show that the aggregates of **PR5** had an average diameter of about 80 nm in pH 7.4 solution, while 500 nm in pH 5.5 solution, and those of **PR6** had an average diameter of about 100 nm with a narrow size distribution in pH 7.4 solu-

tion, while 550 nm in pH 5.5 solution, indicating the destruction of vesicles. Additionally, TEM directly confirmed the disassembly of vesicles formed by **PR5/PR6** in water. The spherical vesicles changed into irregular assemblies by adjusting the solution pH to 5.5 (Figs. 2a and 2c). The reason for these irregular assemblies might be that **WP5/WP6** was protonated and then detached from the main chain polymer. As expected, the vesicles can be observed again by tuning the solution pH back to 7.4 due to the reformation of **PR5/PR6** (Figs. 2b and 2d), indicating pH-controlled reversible self-assembly in water.

Besides the pH-responsive self-assembly, we are also interested in exploring the fluorescent property of this system due to the introduction of aggregation-induced emission phenomenon. As shown in Fig. S9 (in ESI), the critical aggregation concentration (CAC) of **PR5** (**PR6**) was determined to be 1.07×10^{-7} mol/L (1.37×10^{-7} mol/L) by using fluorescence spec-

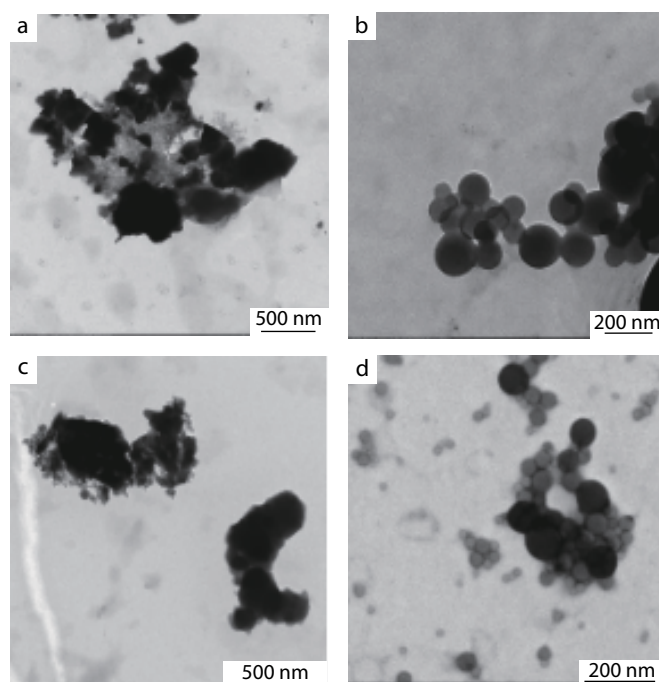


Fig. 2 TEM images of aggregates separated from dispersions: (a) **PR5** (5.00×10^{-4} mol/L) in water after adding HCl to adjust the solution pH to 5.5; (b) **PR5** (5.00×10^{-4} mol/L) in water after further adding NaOH to adjust the solution pH to 7.4; (c) **PR6** (5.00×10^{-4} mol/L) in water after adding HCl to adjust the solution pH to 5.5; (d) **PR6** (5.00×10^{-4} mol/L) in water after further adding NaOH to adjust the solution pH to 7.4.

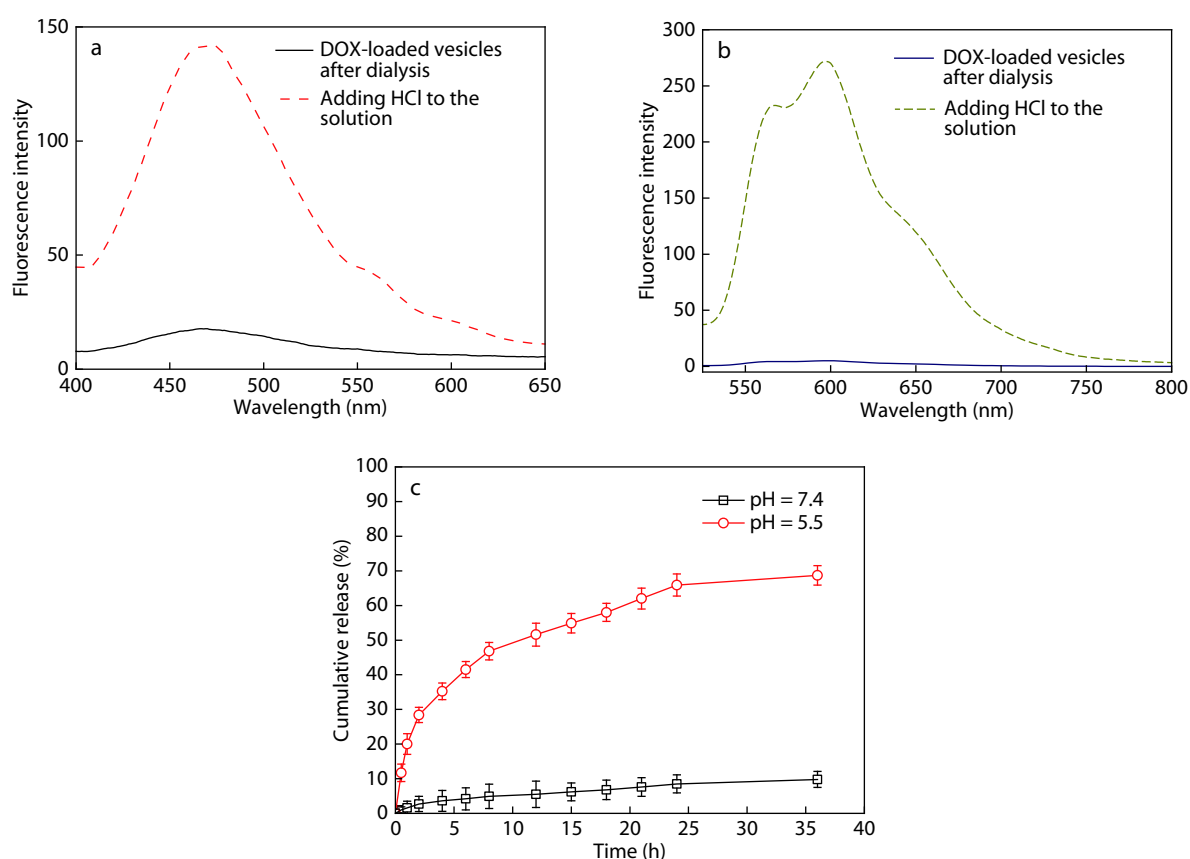


Fig. 3 (a) Fluorescence change of **PR5** (excitation wavelength is 350 nm) before/after adding HCl to the DOX-loaded **PR5** vesicle solution; (b) Fluorescence change of DOX (excitation wavelength is 485 nm) before/after adding HCl to the DOX-loaded **PR5** vesicle solution; (c) Drug release curves of DOX-loaded **PR5** under different pH values.

troscopy. The fluorescence of the solution was weak when its concentration was lower than the corresponding CAC value. However, the fluorescence intensity increased rapidly as the concentration was higher than its CAC value owing to the aggregation-induced emission effect. From CLSM image, green fluorescent vesicles self-assembled from **PR5** and **PR6** were clearly observed (Figs. 1d and 1e). These results illustrated the successful fabrication of fluorescent supramolecular polymersomes, which can provide an ideal platform for self-imaged drug delivery and thus exhibit an advantage over the non-fluorescent polymeric aggregates.

With the supramolecular polymersomes in hand, we further applied them into drug controlled release. Anticancer drug doxorubicin (DOX) was selected as a model drug. According to a previous report, DOX can be encapsulated in the hydrophobic layer of self-assembled supramolecular polymersomes, thereby establishing an artificial Förster resonance energy transfer system with dual fluorescence quenched.^[70] As shown in Fig. 3(a) and Fig. S10(a) (in ESI), **PR5** and **PR6** showed fluorescence quench when DOX molecules were stably located in the interior of the vesicles. As shown in Fig. 3(b) and Fig. S10(b) (in ESI), there was no obvious fluorescence intensity corresponding to the characteristic emission of DOX. These figures also show that the quenched fluorescence from either TPE moieties or DOX molecules was “lightened up” after adding HCl. The release behavior of DOX-loaded **PR5/PR6** vesicles was also monitored in the aqueous solution at different pH values. As shown in Fig. 3(c) and Fig. S10(c) (in ESI), by decreasing the solution pH value, DOX was effectively released from **PR5/PR6** vesicles, i.e., 63% release efficiency for **PR5** at pH 5.5 and 69% release efficiency for **PR6** at pH 5.5 within 36 h.

CONCLUSIONS

In summary, we have exploited the water-soluble pillararene/paraquat recognition in water to prepare amphiphilic polypseudorotaxanes **PR5/PR6**, which self-assembled into supramolecular polymersomes in water, and further employed them for controlled drug (DOX) release. Owing to the hydrophobicity and AIE effect of TPE moieties, the self-assembled supramolecular polymersomes were originally highly fluorescent. However, when DOX was encapsulated in **PR5/PR6**, the fluorescence from both TPE moieties and DOX molecules was quenched in the aggregation state by the Förster resonance energy transfer. By decreasing solution pH, the polymersomes could be destroyed and the loaded DOX molecules were released. As a result, the energy transfer relay between TPE moieties and DOX molecules was interrupted and the quenched fluorescence from either TPE moieties or DOX molecules “lightened up”. These polymersomes make contributions to the development of a novel strategy to fabricate smart supramolecular nanomedicines with tumor specific responsiveness and pave a new way to combine polymer science with supramolecular chemistry to construct functional materials.

Electronic Supplementary Information

Electronic supplementary information (ESI) is available free of

charge in the online version of this article at <http://dx.doi.org/10.1007/s10118-019-2305-1>.

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REFERENCES

- Yang, Z.; He, Y.; Lee, J. H.; Park, N.; Suh, M.; Chae, W. S.; Cao, J.; Peng, X.; Jung, H.; Kang, C.; Kim, J. S. A self-calibrating bipartite viscosity sensor for mitochondria. *J. Am. Chem. Soc.* **2013**, *135*, 9181–9185.
- Yu, G.; Zhang, M.; Saha, M. L.; Mao, Z.; Chen, J.; Yao, Y.; Zhou, Z.; Liu, Y.; Gao, C.; Huang, F.; Chen, X.; Stang, P. J. Antitumor activity of a unique polymer that incorporates a fluorescent self-assembled metallacycle. *J. Am. Chem. Soc.* **2017**, *139*, 15940–15949.
- Peng, H. Q.; Sun, C. L.; Niu, L. Y.; Chen, Y. Z.; Wu, L. Z.; Tung, C. H.; Yang, Q. Z. Supramolecular polymeric fluorescent nanoparticles based on quadruple hydrogen bonds. *Adv. Funct. Mater.* **2016**, *26*, 5483–5489.
- Sun, C. L.; Xu, J. F.; Chen, Y. Z.; Niu, L. Y.; Wu, L. Z.; Tung, C. H.; Yang, Q. Z. Synthesis of a disulfide-bridged bispillar[5]arene and its application in supramolecular polymers. *Polym. Chem.* **2016**, *7*, 2057–2061.
- Yang, C.; Wang, X.; Huang, S.; Wang, M. Tunable Förster resonance energy transfer in colloidal nanoparticles composed of polycaprolactone-tethered donors and acceptors: enhanced near-infrared emission and compatibility for *in vitro* and *in vivo* bioimaging. *Adv. Funct. Mater.* **2018**, *28*, 1705226–1705238.
- Jiang, N.; Ahmed, R.; Rifat, A. A.; Guo, J.; Yin, Y.; Montelongo, Y.; Butt, H.; Yetisen, A. K. Functionalized flexible soft polymer optical fibers for laser photomedicine. *Adv. Optical Mater.* **2018**, *6*, 1701118–1701127.
- Sylvie, R.; Tânia, R.; Clarisse, R.; Daniela, M. C.; José, P. S. F.; Andreia, C. G.; Carlos, B.; Senentxu, L. M. Multifunctional platform based on electroactive polymers and silica nanoparticles for tissue engineering applications. *Nanomaterials* **2018**, *8*, 933–952.
- Robert, G.; Chen, Y. C.; Lee, J. W.; Soman, P.; Zorlutuna, P.; Nichol, J. W.; Bae, H.; Chen, S.; Khademhosseini, A. Microfabrication of complex porous tissue engineering scaffolds using 3D projection stereolithography. *Biomaterials* **2012**, *33*, 3824–3834.
- Wu, C.; Hansen, S. J.; Hou, Q.; Yu, J.; Zeigler, M.; Jin, Y.; Burnham, D. R.; McNeill, J. D.; Olson, J. M.; Chiu, D. T. Design of highly emissive polymer dot bioconjugates for *in vivo* tumor targeting. *Angew. Chem. Int. Ed.* **2011**, *50*, 3430–3434.
- Feng, W.; Jin, M.; Yang, K.; Pei, Y.; Pei, Z. Supramolecular delivery systems based on pillararenes. *Chem. Commun.* **2018**, *54*, 13626–13640.
- Reisch, A.; Heimbürger, D.; Ernst, P.; Runser, A.; Didier, P.; Dujardin, D.; Klymchenko, A. S. Protein-sized dye-loaded polymer nanoparticles for free particle diffusion in cytosol. *Adv. Funct. Mater.* **2018**, *28*, 1805157–1805166.
- Lou, X. Y.; Yang, Y. W. Manipulating aggregation-induced emission with supramolecular macrocycles. *Adv. Optical Mater.* **2018**, *6*, 1800668–1800692.
- Liu, F.; Zhao, X.; Zhang, X.; Zhang, X.; Peng, J.; Yang, H.; Deng, K.; Ma, L.; Chang, C.; Wei, H. Fabrication of theranostic amphiphilic conjugated bottlebrush copolymers with alternating heterografts for cell imaging and anticancer drug delivery. *Polym. Chem.* **2018**, *9*, 4866–4874.

- 14 Liu, X.; Zhu, J.; Ouyang, K.; Yan, Q. Peroxynitrite-biosignal-responsive polymer micelles as intracellular hypersensitive nanoprobe. *Polym. Chem.* **2018**, *9*, 5075–5079.
- 15 Zhang, P.; Wang, H.; Hong, Y.; Yu, M.; Zeng, R.; Long, Y.; Chen, J. Selective visualization of endogenous hypochlorous acid in zebrafish during lipopolysaccharide-induced acute liver injury using a polymer micelles-based ratiometric fluorescent probe. *Biosens. Bioelectron.* **2018**, *99*, 318–324.
- 16 Zhao, C.; Zhang, X.; Li, K.; Zhu, S.; Guo, Z.; Zhang, L.; Wang, F.; Fei, Q.; Luo, S.; Shi, P.; Tian, H.; Zhu, W. H. Forster resonance energy transfer switchable self-assembled micellar nanoprobe: ratiometric fluorescent trapping of endogenous H₂S generation via fluvastatin-stimulated upregulation. *J. Am. Chem. Soc.* **2015**, *137*, 8490–8498.
- 17 Rideau, E.; Wurm, F. R.; Landfester, K. Giant polymersomes from non-assisted film hydration of phosphate-based block copolymers. *Polym. Chem.* **2018**, *9*, 5385–5394.
- 18 Zhang, N.; Chen, H.; Fan, Y.; Zhou, L.; Trepout, S.; Guo, J.; Li, M. H. Fluorescent polymersomes with aggregation-induced emission. *ACS Nano* **2018**, *12*, 4025–4035.
- 19 Abdelmohsen, L. K. E.; Williams, A. D. S.; Pille, J.; Ozel, S. G.; Rikken, R. S. M.; Wilson, D. A.; van Hest, J. C. M. Formation of well-defined, functional nanotubes via osmotically induced shape transformation of biodegradable polymersomes. *J. Am. Chem. Soc.* **2016**, *138*, 9353–9356.
- 20 Kulkarni, P. S.; Haldar, M. K.; Confeld, M. I.; Langaas, C. J.; Yang, X.; Qian, S. Y.; Mallik, S. Mitochondria-targeted fluorescent polymersomes for drug delivery to cancer cells. *Polym. Chem.* **2016**, *7*, 4151–4154.
- 21 Bratton, B. P.; Shaevitz, J. W.; Gitai, Z.; Morgenstein, R. M. MreB polymers and curvature localization are enhanced by RodZ and predict *E. coli*'s cylindrical uniformity. *Nat. Commun.* **2018**, *9*, 2797.
- 22 Chang, D.; Huang, A.; Olsen, B. D. Kinetic effects on self-assembly and function of protein-polymer bioconjugates in thin films prepared by flow coating. *Macromol. Rapid Commun.* **2017**, *38*, 1600449–1600454.
- 23 Thomas, C. S.; Olsen, B. D. Coil fraction-dependent phase behavior of a model globular protein-polymer diblock copolymer. *Soft Matter* **2014**, *10*, 3093–3102.
- 24 Yu, G.; Zhao, R.; Shao, L.; Zhou, J.; Yang, J.; Huang, F.; Wu, D.; Tang, G.; Zhang, F.; Chen, X. Pillar[5]arene-based amphiphilic supramolecular brush copolymers: fabrication, controllable self-assembly and application in self-imaging targeted drug delivery. *Polym. Chem.* **2016**, *7*, 6178–6188.
- 25 Jie, K.; Zhou, Y.; Ji, X. A pH-responsive amphiphilic supramolecular graft copolymer constructed by crown ether based molecular recognition. *Polym. Chem.* **2015**, *6*, 218–222.
- 26 Wang, Y.; Sukhishvili, S. A. All-aqueous nanoprecipitation: Spontaneous formation of hydrogen-bonded nanoparticles and nanocapsules mediated by phase separation of poly(*N*-isopropylacrylamide). *Macromol. Rapid Commun.* **2017**, *38*, 1700242–1700246.
- 27 Wang, H.; Ji, X.; Li, Z.; Huang, F. Fluorescent supramolecular polymeric materials. *Adv. Mater.* **2017**, *29*, 1606117–1606138.
- 28 Wang, R. F.; Peng, H. Q.; Chen, P. Z.; Niu, L. Y.; Gao, J. F.; Wu, L. Z.; Tung, C. H.; Chen, Y. Z.; Yang, Q. Z. A hydrogen-bonded-supramolecular-polymer-based nanoprobe for ratiometric oxygen sensing in living cells. *Adv. Funct. Mater.* **2016**, *26*, 5419–5425.
- 29 Wang, W.; Han, J. J.; Wang, L. Q.; Li, L. S.; Shaw, W. J.; Li, A. D. Q. Dynamic π - π stacked molecular assemblies emit from green to red colors. *Nano Lett.* **2003**, *3*, 455–458.
- 30 Lu, W.; Chan, M. C. W.; Cheung, K. K.; Che, C. M. π - π Interactions in organometallic systems. Crystal structures and spectroscopic properties of luminescent mono-, bi-, and trinuclear *trans*-cyclometalated platinum(II) complexes derived from 2,6-diphenylpyridine. *Organometallics* **2001**, *20*, 2477–2486.
- 31 Nishizawa, S.; Kato, Y.; Teramae, N. Fluorescence sensing of anions via intramolecular excimer formation in a pyrophosphate-induced self-assembly of a pyrene-functionalized guanidinium receptor. *J. Am. Chem. Soc.* **1999**, *121*, 9463–9464.
- 32 Yoshida, K.; Miyazaki, H.; Miura, Y.; Ooyama, Y.; Watanabe, S. Solid-surface fluorescence enhancement behavior of a benzofuranoquinol-type fluorescent host upon enclathration of alicyclic amines. *Chem. Lett.* **1999**, 837–838.
- 33 Ban, Q.; Du, J.; Sun, W.; Chen, J.; Wu, S.; Kong, J. Intramolecular copper-containing hyperbranched polytriazole assemblies for label-free cellular bioimaging and redox-triggered copper complex delivery. *Macromol. Rapid Commun.* **2018**, *39*, 1800171–1800176.
- 34 Wei, P.; Yan, X.; Huang, F. Supramolecular polymers constructed by orthogonal self-assembly based on host-guest and metal-ligand interactions. *Chem. Soc. Rev.* **2015**, *44*, 815–832.
- 35 Hu, J.; Liu, S. Engineering responsive polymer building blocks with host-guest molecular recognition for functional applications. *Acc. Chem. Res.* **2014**, *47*, 2084–2095.
- 36 Yang, H.; Yuan, B.; Zhang, X.; Scherman, O. A. Supramolecular chemistry at interfaces: host-guest interactions for fabricating multifunctional biointerfaces. *Acc. Chem. Res.* **2014**, *47*, 2106–2115.
- 37 Zhang, M.; Yan, X.; Huang, F.; Niu, Z.; Gibson, H. W. Stimuli-responsive host-guest systems based on the recognition of cryptands by organic guests. *Acc. Chem. Res.* **2014**, *47*, 1995–2005.
- 38 Zhang, D. W.; Zhao, X.; Li, Z. T. Aromatic amide and hydrazide foldamer-based responsive host-guest systems. *Acc. Chem. Res.* **2014**, *47*, 1961–1970.
- 39 Yang, Y. W.; Sun, Y. L.; Song, N. Switchable host-guest systems on surfaces. *Acc. Chem. Res.* **2014**, *47*, 1950–1960.
- 40 Cook, T. R.; Zheng, Y. R.; Stang, P. J. Metal-organic frameworks and self-assembled supramolecular coordination complexes: comparing and contrasting the design, synthesis, and functionality of metal-organic materials. *Chem. Rev.* **2013**, *113*, 734–777.
- 41 Servant, A.; Qiu, F.; Mazza, M.; Kostarelos, K.; Nelson, B. J. Controlled *in vivo* swimming of a swarm of bacteria-like microbotic flagella. *Adv. Mater.* **2015**, *27*, 2981–2988.
- 42 Wang, H.; Su, W.; Wang, S.; Wang, X.; Liao, Z.; Kang, C.; Han, L.; Chang, J.; Wang, G.; Pu, P. Smart multifunctional core-shell nanospheres with drug and gene co-loaded for enhancing the therapeutic effect in a rat intracranial tumor model. *Nanoscale* **2012**, *4*, 6501–6508.
- 43 Zhang, Y. M.; Li, Y. F.; Fang, H.; He, J. X.; Yong, B. R.; Yao, H.; Wei, T. B.; Lin, Q. Multi-stimuli-responsive supramolecular gel constructed by pillar[5]arene-based pseudorotaxanes for efficient detection and separation of multi-analytes in aqueous solution. *Soft Matter* **2018**, *14*, 8529–8536.
- 44 Han, Y.; Tian, Y.; Li, Z.; Wang, F. Donor-acceptor-type supramolecular polymers on the basis of preorganized molecular tweezers/guest complexation. *Chem. Soc. Rev.* **2018**, *47*, 5165–5176.
- 45 Wei, T. B.; Chen, J. F.; Cheng, X. B.; Li, H.; Han, B. B.; Yao, H.; Zhang, Y. M.; Lin, Q. Construction of stimuli-responsive supramolecular gel via bispillar[5]arene-based multiple interactions. *Polym. Chem.* **2017**, *8*, 2005–2009.
- 46 Ma, X.; Tian, H. Stimuli-responsive supramolecular polymers in aqueous solution. *Acc. Chem. Res.* **2014**, *47*, 1971–1981.
- 47 Qi, Z.; Schalley, C. A. Exploring macrocycles in functional supramolecular gels: from stimuli responsiveness to systems

- chemistry. *Acc. Chem. Res.* **2014**, 47, 2222–2233.
- 48 Ji, X. F.; Xia, D. Y.; Yan, X.; Wang, H.; Huang, F. H. Supramolecular polymer materials based on crown ether and pillararene host-guest recognition motifs. *Acta Polymerica Sinica* (in Chinese) **2017**, 9–18.
 - 49 Yang, J.; Shao, L.; Yuan, J.; Huang, F. Construction of a pillar[6]arene based water-soluble supramolecular pseudopolyrotaxane driven by cucurbit[8]uril-enhanced π - π interaction. *Chem. Commun.* **2016**, 52, 12510–12512.
 - 50 Dhinakaran, M. K.; Gong, W.; Yin, Y.; Wajahat, A.; Kuang, X.; Wang, L.; Ning, G. Configuration-independent AIE-active supramolecular polymers of cyanostilbene through the photo-stable host-guest interaction of pillar[5]arene. *Polym. Chem.* **2017**, 8, 5295–5302.
 - 51 Wang, Y.; Lv, M. Z.; Song, N.; Liu, Z. J.; Wang, C.; Yang, Y. W. Dual-stimuli-responsive fluorescent supramolecular polymer based on a diselenium-bridged pillar[5]arene dimer and an AIE-active tetraphenylethylene guest. *Macromolecules* **2017**, 50, 5759–5766.
 - 52 Hua, B.; Shao, L.; Zhang, Z.; Sun, J.; Yang, J. Pillar[6]arene/acridine orange host-guest complexes as colorimetric and fluorescence sensors for choline compounds and further application in monitoring enzymatic reactions. *Sens. Actuators B* **2018**, 255, 1430–1435.
 - 53 Hu, X.; Wu, X.; Wang, S.; Chen, D.; Xia, W.; Lin, C.; Pan, Y.; Wang, L. Pillar[5]arene-based supramolecular polypseudorotaxane polymer networks constructed by orthogonal self-assembly. *Polym. Chem.* **2013**, 4, 4292–4297.
 - 54 Li, E.; Jie, K.; Zhou, Y.; Zhao, R.; Huang, F. Post-synthetic modification of nonporous adaptive crystals of pillar[4]arene[1]quinone by capturing vaporized amines. *J. Am. Chem. Soc.* **2018**, 140, 15070–15079.
 - 55 Li, Z.; Zhang, Y.; Zhang, C.; Chen, L. J.; Wang, C.; Tan, H.; Yu, Y.; Li, X.; Yang, H. B. Cross-linked supramolecular polymer gels constructed from discrete multi-pillar[5]arene metallacycles and their multiple stimuli-responsive behavior. *J. Am. Chem. Soc.* **2014**, 136, 8577–8589.
 - 56 Xu, J. F.; Chen, Y. Z.; Wu, L. Z.; Tung, C. H.; Yang, Q. Z. Dynamic covalent bond based on reversible [4+4] photocycloaddition of anthracene for construction of double-dynamic polymers. *Org. Lett.* **2013**, 15, 6148–6151.
 - 57 Jie, K.; Zhou, Y.; Li, E.; Zhao, R.; Huang, F. Separation of aromatics/cyclic aliphatics by nonporous adaptive pillararene crystals. *Angew. Chem. Int. Ed.* **2018**, 57, 12845–12849.
 - 58 Cao, D.; Kou, Y.; Liang, J.; Chen, Z.; Wang, L.; Meier, H. A facile and efficient preparation of pillararenes and a pillarquinone. *Angew. Chem. Int. Ed.* **2009**, 48, 9721–9723.
 - 59 Ogoshi, T.; Kanai, S.; Fujinami, S.; Yamagishi, T.; Nakamoto, Y. Para-bridged symmetrical pillar[5]arenes: their Lewis acid catalyzed synthesis and host-guest property. *J. Am. Chem. Soc.* **2008**, 130, 5022–5023.
 - 60 Zhang, H.; Liu, Z.; Zhao, Y. Pillararene-based self-assembled amphiphiles. *Chem. Soc. Rev.* **2018**, 47, 5491–5528.
 - 61 Yu, G.; Yang, J.; Fu, X.; Wang, Z.; Shao, L.; Mao, Z.; Liu, Y.; Yang, Z.; Zhang, F.; Fan, W.; Song, J.; Zhou, Z.; Gao, C.; Huang, F.; Chen, X. A supramolecular hybrid material constructed from graphene oxide and a pillar[6]arene-based host-guest complex as an ultrasound and photoacoustic signal nanoamplifier. *Mater. Horiz.* **2018**, 5, 429–435.
 - 62 Jie, K.; Zhou, Y.; Li, E.; Li, Z.; Zhao, R.; Huang, F. Reversible iodine capture by nonporous pillar[6]arene crystals. *J. Am. Chem. Soc.* **2017**, 139, 15320–15323.
 - 63 Jie, K.; Liu, M.; Zhou, Y.; Little, M. A.; Bonakala, S.; S. Chong, Y.; Stephenson, A.; Chen, L.; Huang, F.; Cooper, A. I. Styrene purification by guest-induced restructuring of pillar[6]arene. *J. Am. Chem. Soc.* **2017**, 139, 2908–2911.
 - 64 Dong, R.; Zhou, Y.; Huang, X.; Zhu, X.; Lu, Y.; Shen, J. Functional supramolecular polymers for biomedical applications. *Adv. Mater.* **2015**, 27, 498–526.
 - 65 Mei, J.; Huang, Y.; Tian, H. Progress and trends in AIE-based bioprobes: a brief overview. *ACS Appl. Mater. Interfaces* **2018**, 10, 12217–12261.
 - 66 Furue, R.; Nishimoto, T.; Park, I. S.; Lee, J.; Yasuda, T. Aggregation-induced delayed fluorescence based on donor/acceptor-tethered Janus carborane triads: unique photophysical properties of nondoped OLEDs. *Angew. Chem. Int. Ed.* **2016**, 55, 7171–7175.
 - 67 Yan, X.; Wang, M.; Cook, T. R.; Zhang, M.; Saha, M. L.; Zhou, Z.; Li, X.; Huang, F.; Stang, P. J. Light-emitting superstructures with anion effect: coordination-driven self-assembly of pure tetraphenylethylene metallacycles and metallacages. *J. Am. Chem. Soc.* **2016**, 138, 4580–4588.
 - 68 Li, K.; Liu, B. Polymer-encapsulated organic nanoparticles for fluorescence and photoacoustic imaging. *Chem. Soc. Rev.* **2014**, 43, 6570–6597.
 - 69 Luo, J.; Xie, Z. J.; Lam, W. Y.; Cheng, L.; Chen, H.; Qiu, C.; Kwok, H. S.; Zhan, X.; Liu, Y.; Zhu, D.; Tang, B. Z. Aggregation-induced emission of 1-methyl-1,2,3,4,5-pentaphenylsilole. *Chem. Commun.* **2001**, 1740–1741.
 - 70 Ji, X.; Li, Y.; Wang, H.; Zhao, R.; Tang, G.; Huang, F. Facile construction of fluorescent polymeric aggregates with various morphologies by self-assembly of supramolecular amphiphilic graft copolymers. *Polym. Chem.* **2015**, 28, 5021–5025.