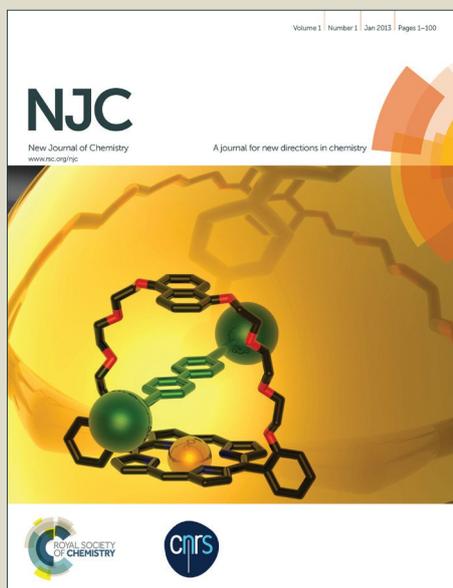


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# A water-soluble hybrid[4]arene: synthesis, host–guest complexation and application in construction of a supra-amphiphile†

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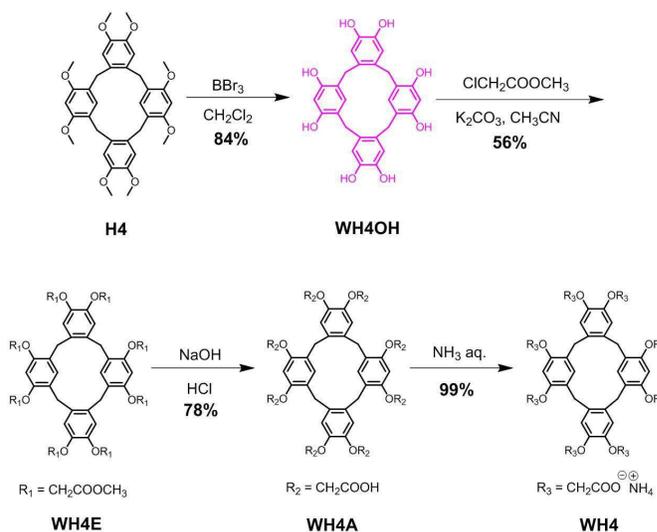
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The first water-soluble hybrid[4]arene was synthesized and its pH-responsive host–guest complexation with paraquat in water was investigated. This new host–guest recognition motif was further applied in the construction of a supra-amphiphile.

## Introduction

It has been demonstrated that the arrival of any new generation of macrocyclic hosts can not only accelerate the development of supramolecular chemistry but also provide new opportunities for materials science. Macrocycles such as crown ethers,<sup>1</sup> cyclodextrins,<sup>2</sup> calixarenes,<sup>3</sup> cucurbiturils<sup>4</sup> and pillararenes<sup>5</sup> continue to attract considerable attention because of their unique structures and superior host–guest properties. In the recent years many groups reported numerous applications of these fascinating macrocycles including supramolecular polymers,<sup>6</sup> drug delivery systems,<sup>7</sup> switches,<sup>8</sup> transmembrane channels<sup>9</sup> and fabrication of rotaxanes/pseudorotaxanes.<sup>10</sup> Such a great interest indicates that macrocycle chemistry plays a vital role in supramolecular fields.

Recently, Szumna's group reported a new series of medium-sized macrocyclic compounds called hybrid[*n*]arenes, including [2 + 2]hybrid[4]arenes, [3 + 1]hybrid[4]arenes and [3 + 2]hybrid[5]arenes.<sup>11</sup> These cyclic oligomers were obtained by a simple, one-pot, direct condensation of two different alkoxybenzenes with formaldehyde catalyzed by trifluoroacetic acid. These macrocycles exhibited interesting host–guest properties in organic solvents. However, unlike cucurbiturils and cyclodextrins, the reported hybrid[*n*]arenes modified by alkyl chains can not form stable host–guest complexes in aqueous media due to their poor solubility, limiting their further applications in various areas including biological chemistry. Thus, the preparation of water-soluble hybrid[*n*]arenes and investigation of their novel host–guest molecular recognition motifs in water is of current interest. Herein, we reported the synthesis of the first water-soluble [2 + 2] hybrid[4]arene (**WH4**, Schemes 1 and 2) and investigation of its host–guest complexation with paraquat **G** (Scheme 2). Furthermore, on the basis of this host–guest recognition motif, a supra-amphiphile<sup>17</sup> was constructed.



Scheme 1 Synthetic route to water-soluble hybrid[4]arene **WH4**.

**WH4** was prepared by introducing anionic carboxylate groups on both rims (Scheme 1), similar to the synthesis of water-soluble pillar[*n*]arenes.<sup>12</sup> **H4** was synthesized through a one-step way previously reported by Szumna's group.<sup>11</sup> Upon addition of excess  $\text{BBr}_3$ , *per*-hydroxylated hybrid[4]arene **WH4OH** was obtained. Then methoxycarbonylmethoxy-substituted hybrid[4]arene **WH4E** was prepared by etherification of **WH4OH** in acetonitrile. The following acidification after hydrolysis of **WH4E** under basic conditions afforded carboxylic acid-substituted hybrid[4]arene **WH4A**. Upon treatment with excessive ammonium hydroxide, the final product water-soluble hybrid[4]arene **WH4** was obtained.

## Experimental Sections

**Synthesis of WH4E:** To a solution of **H4** (600 mg, 1.00 mmol) in dried dichloromethane (50 mL) was added boron tribromide (3.00 g, 12.0 mmol). The mixture was stirred at room temperature for 12 h. Then the mixture was added into water. The resulting precipitated product **WH4OH** was collected by filtration, washed with water and dried under vacuum (410 mg, 84%). To a solution of **WH4OH** (410 mg, 0.84 mmol) in CH<sub>3</sub>CN (50 mL) was added methyl chloroacetate (2.00 g, 18.5 mmol) and K<sub>2</sub>CO<sub>3</sub> (2.55 g, 18.5 mmol). The mixture was heated in a flask at 80 °C under nitrogen gas protection for 12 h. Then the reaction mixture was cooled to room temperature and filtered. The filter cake was washed with dichloromethane (2 × 50 mL). Then the filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica gel with dichloromethane/methanol (20:1 v/v) as the eluent to afford product **WH4E** as a white solid (500 mg, 56%), mp: 181.3–182.2 °C. <sup>1</sup>H NMR (400 MHz, chloroform-*d*, room temperature)  $\delta$  (ppm): 6.60 (s, 4H), 5.80 (s, 2H), 5.22 (s, 2H), 4.71 (s, 8H), 4.48 (s, 8H), 3.82 (s, 12H), 3.79 (s, 12H). <sup>13</sup>C NMR (100 MHz, chloroform-*d*, room temperature)  $\delta$  (ppm): 169.82, 169.64, 153.02, 146.22, 133.06, 131.26, 121.95, 119.57, 97.09, 67.21, 66.39, 52.20, 52.03 and 31.20. HRESIMS: *m/z* calcd for [M + NH<sub>4</sub>]<sup>+</sup> C<sub>52</sub>H<sub>60</sub>O<sub>24</sub>N<sup>+</sup>, 1082.3505; found 1082.3525; error 2 ppm.

**Synthesis of WH4A:** A solution of **WH4E** (300 mg, 0.282 mmol) in methanol (20 mL) was treated with 40% aqueous sodium hydroxide (20 mL) at 70 °C for 12 h. Then the reaction mixture was evaporated under vacuum, diluted with water (30 mL) and acidified with aqueous HCl solution. The resulting precipitate was filtered, washed with water, and dried to afford product **WH4A** (210 mg, 78%) as a white powder, mp: > 300 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>, room temperature)  $\delta$  (ppm): 6.89 (s, 4H), 5.97 (s, 2H), 5.13 (s, 2H), 4.59 (s, 8H), 4.49 (s, 8H), 3.78 (s, 4H), 3.20 (s, 4H). <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>, room temperature)  $\delta$  (ppm): 170.55, 170.30, 152.54, 145.45, 131.45, 130.20, 119.94, 117.63, 65.72, 65.09 and 30.67. LRESIMS: *m/z* 951.6 [M – H]<sup>–</sup>. HRESIMS: *m/z* calcd for [M – H]<sup>–</sup> C<sub>44</sub>H<sub>39</sub>O<sub>24</sub><sup>–</sup>, 951.1831; found 951.1841; error 1 ppm.

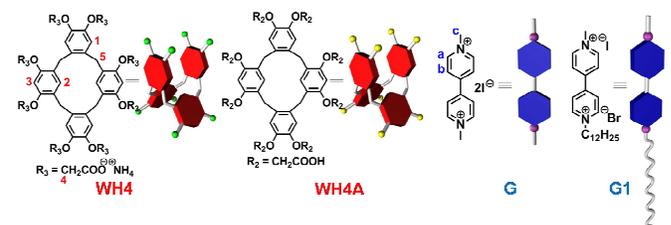
**Synthesis of WH4:** Compound **WH4A** (200 mg, 0.210 mmol) and ammonium hydroxide aqueous solution (25–28 %, 30 mL) were stirred at room temperature for 1 h. Water was removed by rotary evaporation to afford **WH4** as a white powder (226 mg, 99%), mp: > 300 °C. <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O, room temperature)  $\delta$  (ppm): 6.58 (s, 4H), 5.73 (s, 2H), 5.03 (s, 2H), 4.41 (d, *J* = 12 Hz, 4H), 4.32 (d, *J* = 12 Hz, 4H), 4.25 (d, *J* = 12 Hz, 4H), 4.20 (d, *J* = 12 Hz, 4H), 3.89 (d, *J* = 12 Hz, 4H), 3.25 (d, *J* = 12 Hz, 4H). <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O, room temperature)  $\delta$  (ppm): 179.67, 178.97, 155.79, 147.30, 135.04, 133.50, 123.34, 118.33, 70.09, 69.87 and 33.30. LRESIMS: *m/z* 974.6 [M – 7NH<sub>3</sub> + 5H]<sup>5+</sup>. HRESIMS: *m/z* calcd for [M – 5NH<sub>3</sub> + H]<sup>+</sup> C<sub>44</sub>H<sub>50</sub>O<sub>24</sub>N<sub>3</sub><sup>+</sup>, 1004.2784; found 1004.2736; error –5 ppm.

## Results and Discussion

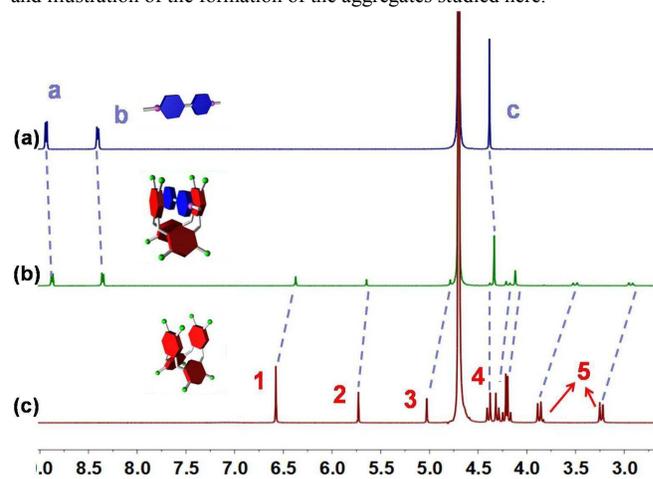
### Host–guest interactions between WH4 and G

Considering its  $\pi$ -rich tweezer-type structure and the existence of

eight carboxylate anionic groups on its two rims, **WH4** should be a suitable host for cationic guest molecules. Therefore, we used paraquat **G** as a model guest to study the host–guest chemistry of **WH4** in water. The complexation between host **WH4** and guest **G** was firstly investigated by <sup>1</sup>H NMR spectroscopy (Fig. 1). Compared with the spectrum of free **G**, upfield chemical shift changes corresponding to the proton signals of **G** occurred in the presence of **WH4** ( $\Delta\delta$  = –0.04 and –0.03 ppm for H<sub>a</sub> and H<sub>b</sub>, respectively). The reason was that these protons were shielded by the electron-rich tweezer upon the formation of the host–guest complex.<sup>13</sup> On the other hand, the resonance peaks related to protons H<sub>1–5</sub> on **WH4** also displayed slight chemical shift changes due to the host–guest interactions between **WH4** and **G**.<sup>14</sup> These phenomena provided convincing evidence for the host–guest complexation between **WH4** and **G**. Moreover, 2D NOESY NMR investigation was performed to shed light on the topological features of this complexation event (Fig. 2 and 3). The spectrum exhibits NOE cross-peaks between protons H<sub>a,b</sub> of paraquat and bridging methylene proton H<sub>5</sub>. Besides, correlation signals were also observed between protons H<sub>a,b</sub> on **G** and the aromatic proton H<sub>2</sub> on 1,3-substituted benzenes and H<sub>1</sub> on 1,2-substituted benzenes of **WH4**. These results indicated the binding mode that **WH4** acted as a molecular tweezer toward the suitable aromatic guest paraquat. The paraquat guest nestles within the wider  $\pi$ -rich cleft generated by two 1,2-substituted benzenes of **WH4** with stable host–guest complexation.<sup>21</sup>



**Scheme 2** Chemical structures and cartoon presentations of **WH4**, **G** and **G1** and illustration of the formation of the aggregates studied here.



**Fig. 1.** Partial <sup>1</sup>H NMR spectra (400 MHz, D<sub>2</sub>O, room temperature): (a) **G** (4.00 mM); (b) **WH4** (2.00 mM) and **G** (4.00 mM); (c) **WH4** (2.00 mM).

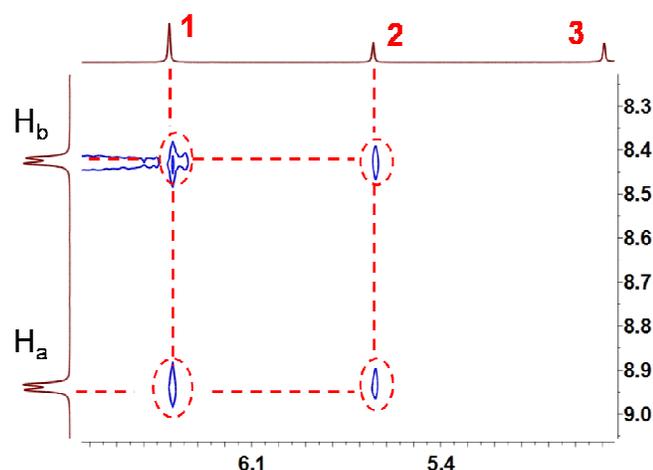


Fig. 2. Partial NOESY NMR spectrum (500 MHz, D<sub>2</sub>O, room temperature) of **WH4** (5.0 mM) and **G** (15.00 mM).

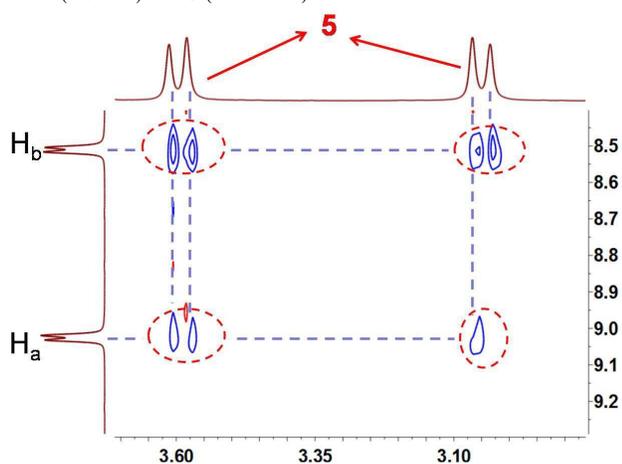


Fig. 3. Partial NOESY NMR spectrum (500 MHz, D<sub>2</sub>O, room temperature) of **WH4** (5.0 mM) and **G** (10.00 mM).

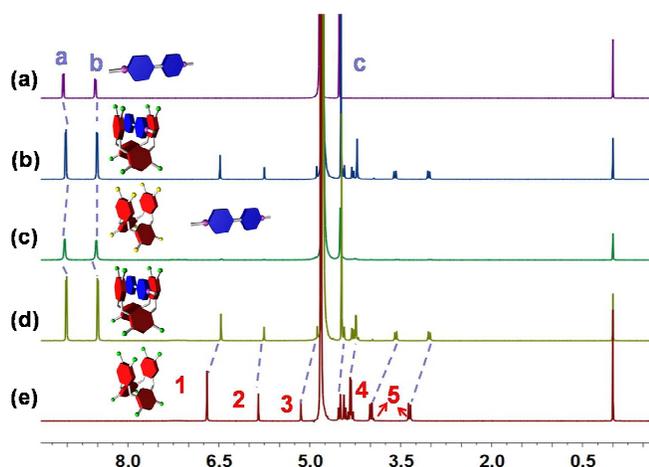


Fig. 4 <sup>1</sup>H NMR spectra (400 MHz, D<sub>2</sub>O, 293 K): (a) **G** (4.00 mM); (b) **WH4** (2.00 mM) and **G** (4.00 mM); (c) after addition of 2 μL of an aqueous DCl solution (20 wt%) to (b); (d) after addition of 1.5 μL of an aqueous NaOD solution (30 wt%) to (c); (e) **WH4** (2.00 mM).

Moreover, the complexation between **WH4** and **G** is pH-

responsive<sup>22</sup> because anionic carboxylate groups on **WH4** can be reversibly transformed into neutral carboxylic groups by adjusting the solution pH, which means the association and disassociation of the complex can be effectively controlled by sequential addition of DCl and NaOD aqueous solutions (Fig. 4). As shown in Fig. 4c, the resonance peaks related to the protons on the host disappeared upon addition of an aqueous DCl solution. Meanwhile, the signals for all protons on the guest returned to their original positions as free **G**. The reason was that the anionic carboxylate groups on **WH4** were protonated, which resulted in precipitation of the water-insoluble carboxylic acid-substituted hybrid[4]arene **WH4A** (Scheme 2), leading to the disassociation of the sandwich-type complex. Upon addition of an aqueous NaOD solution (Fig. 4d), the signals corresponding to protons on **G** shifted upfield and the peaks of protons on **WH4** appeared again, suggesting the reformation of the sandwich-type complex between **WH4** and **G**, which confirmed that the association and disassociation of this host–guest system can be controlled by changing the solution pH.

To quantitatively estimate the binding strength of **WH4** towards paraquat, isothermal titration calorimetry (ITC) was employed to determine the association constant ( $K_a$ ) and the thermodynamic parameters (enthalpy and entropy changes,  $\Delta H^\circ$  and  $\Delta S^\circ$ ) of **WH4**⊃**G**.<sup>15</sup> According to Fig. S10 (ESI†), the  $K_a$  value was measured to be  $(2.73 \pm 0.26) \times 10^4 \text{ M}^{-1}$ , showing strong binding affinity of **WH4**⊃**G**. Besides, the ITC data also showed that the stoichiometry of the host–guest complex was 1:1 and the complexation was driven by enthalpy and entropy changes ( $\Delta H^\circ < 0$ ;  $T\Delta S^\circ > 0$ ;  $|\Delta H^\circ| > |T\Delta S^\circ|$ ).

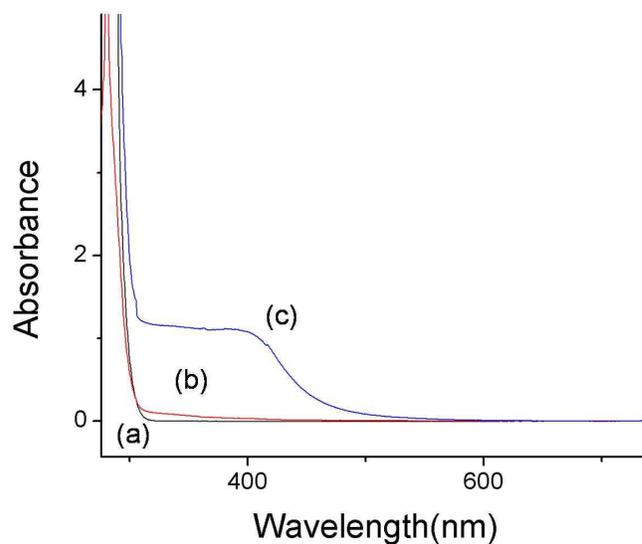
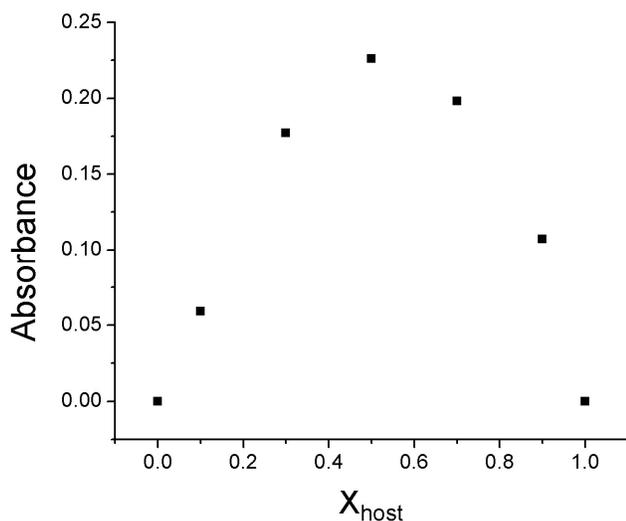


Fig. 5 UV-vis spectra of (a)  $5.00 \times 10^{-3} \text{ M G}$ , (b)  $5.00 \times 10^{-3} \text{ M WH4}$ , and (c)  $5.00 \times 10^{-3} \text{ M WH4}$  with equimolar **G** in water at room temperature.

Further evidence for the complexation between **WH4** and **G** was obtained from UV-vis absorption. The individual **WH4** or **G** in aqueous solution was colorless (Fig. S12, ESI†). However, the color of the 1:1 host–guest mixture was brown. As shown in Fig. 5, the mixture of **G** and **WH4** exhibited a clear charge transfer band, which was not observed in the spectrum of **WH4** or **G**. These phenomena revealed that this host–guest complexation was driven by charge

## COMMUNICATION

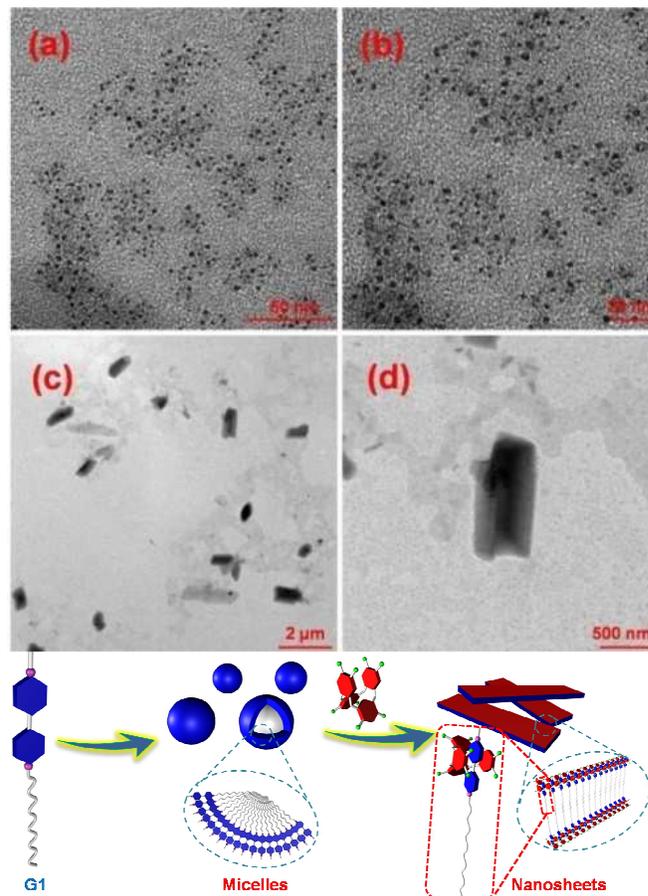
transfer interactions between electron-poor **G** and electron-rich **WH4**, while multiple cooperative electrostatic attraction forces between carboxylate anions of 1,2-dimethoxybenzene unit and dications of **G** also played an important role in the host–guest complexation.<sup>16</sup> Additionally, a Job plot (Fig. 6) for the complexation between **G** and **WH4** was made by monitoring the charge transfer band as a function of the mole fraction of **WH4**, confirming the formation of a 1:1 sandwich-type complex, in accordance with the result obtained from the ITC data.



**Fig. 6.** Job's plot showing the 1:1 stoichiometry of the complex in aqueous solution by plotting the absorbance values at  $\lambda = 425$  nm for **WH4**⊃**G** against the mole fraction of **WH4** ( $[\text{WH4}] + [\text{G}] = 5.00$  mM).

### Construction of a supra-amphiphile based on hybrid[4]arene/paraquat recognition motif

With this novel water-soluble hybrid[4]arene/paraquat recognition motif in hand, a supra-amphiphile<sup>17</sup> was constructed by employing an amphiphilic paraquat derivative **G1** as the guest molecule (Fig. 7). From previous work, we knew that the critical aggregation concentration (CAC) of **G1** was *ca.*  $1.0 \times 10^{-4}$  M.<sup>18</sup> As revealed by TEM, **G1** self-assembled into micellar aggregates with the average diameter of  $\sim 7$  nm (Fig. 7a and 7b). Upon addition of equimolar **WH4**, the CAC value was determined to be  $3.27 \times 10^{-5}$  M by using concentration-dependent conductivity (Fig. S11, ESI†). The CAC value of **G** decreases significantly by a factor of *ca.* 3 due to the generation of the stable host–guest complex between **WH4** and **G1**.<sup>19</sup> The TEM images showed that **WH4**⊃**G1** self-assembled into nanosheets in water (Fig. 7c and 7d), remarkably different from the micelles formed by **G1** alone.



**Fig. 7** TEM images: (a) **G1**; (b) enlarged image of **G1**; (c) **WH4**⊃**G1**; (d) enlarged image of **WH4**⊃**G1**.

A mechanism was proposed to explain the morphology changes of **G1** in the absence and presence of **WH4**. It's well-known that the microassembled structure of the aggregates formed by amphiphiles is determined by the curvature of the membrane.<sup>20</sup> For the amphiphilic guest **G1**, it is the balance of the electrostatic repulsion and hydrophobic effect that determine the curvature of the assemblies. As a result, micelles formed when **G1** was dissolved in water driving by electrostatic repulsion and hydrophobic effect. Accompanied with the addition of **WH4**, the hydrophilic head of **G1** slipped into the  $\pi$ -rich cleft of **WH4** through multiple electrostatic and charge transfer interactions. The charge of the guest was distracted by the host–guest interaction, which changes the balance of electrostatic repulsion and hydrophobic effect. The phenomenon led to the change of curvature of the assemblies, further resulting in the formation of different self-assembled nanosheet-type structure.

### Conclusions

In conclusion, the first water-soluble hybrid[4]arene (**WH4**) was synthesized and its pH-responsive host–guest complexation with paraquat (**G**) in water was investigated. We demonstrated that **G** located in the wider  $\pi$ -rich cleft generated by two 1,2-substituted benzenes of **WH4** to form a 1:1 host–guest complex with the association constant of  $(2.73 \pm 0.26) \times 10^4$  M<sup>-1</sup> mainly driven by electrostatic and charge transfer interactions. Furthermore, we utilized this novel recognition motif to construct a supra-amphiphile

based on **WH4** and amphiphilic **G1** in water. By adding equimolar **WH4** into a solution of **G1**, the transformation from micelles formed from **G1** to nanosheets based on **WH4**⊃**G1** was clearly observed. This novel recognition motif can be used in the construction of various functional architectures, such as supramolecular polymers, drug delivery systems, chemical sensors and nanoswitches.

## Acknowledgements

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## Notes and references

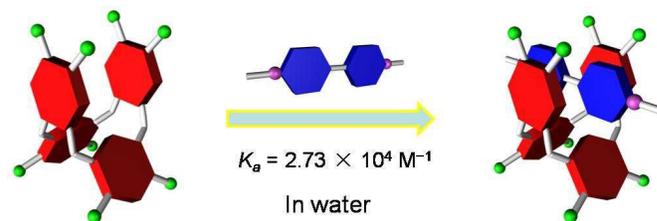
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† Electronic Supplementary Information (ESI) available: Synthetic procedures, characterizations, determination of association constants, fluorescence spectroscopy data and other materials. See DOI: 10.1039/c5xx00000x.

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## Colour Graphic:



## Text:

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