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A water-soluble biphen[3]arene: synthesis, host-guest complexation, and application in controllable self-assembly and controlled release[†]

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The first water-soluble biphen[3]arene has been synthesized. Its pH-responsive host-guest complexation with secondary ammonium salts in water and application in controllable self-assembly and controlled release have been investigated.

The coming of any new generation of macrocycles can speed up the development of supramolecular chemistry.¹ It can supply many opportunities for building different kinds of supramolecular systems, such as molecular machines,² chemosensors,³ liquid crystals,⁴ supramolecular polymers,⁵ drug delivery systems⁶ and other advanced functional materials.⁷ Crown ethers,⁸ cyclodextrins,⁹ calixarenes,¹⁰ cucurbiturils¹¹ and pillararenes,¹² five important classes of macrocyclic hosts, have been widely studied in supramolecular chemistry.

Biphenarenes,¹³ including biphen[3]arenes and biphen[4]arenes, are a new family of macrocyclic hosts first reported by Li and coworkers. Their repeating units, 4,4'-biphenol or 4,4'-biphenol ether, are connected by methylene bridges at the 3- and 3'-positions, which are different from most of the other macrocyclic hosts with substituted mono-benzene and mono-heterocycle units. The unique structure and easy functionalization of biphenarenes can afford them outstanding abilities to selectively bind different kinds of guests and provide a useful platform for constructing various interesting supramolecular systems.

Herein, we synthesized the first water-soluble biphen[3]arene (**WB3**) through four steps totally in our method (Scheme 1). Compound **EtBP3** was made by a one-step method previously reported by Li's group.¹³ Firstly, *per*-hydroxylated biphen[3]arene **1** was obtained *via* dealkylation of **EtBP3** by using excess BBr₃. Compound **1** was then processed with excess methyl chloroacetate in acetonitrile to gain methoxycarbonylmethoxy-substituted biphen[3]arene **2**. Acidification, after hydrolysis of **2** under basic conditions, afforded



carboxylic acid-substituted biphen[3]arene 3. Through treating with excessive ammonium hydroxide, water-soluble biphen[3]arene **WB3** was obtained.

The complexation between host **WB3** and guest **G** was investigated by ¹H NMR spectroscopy. Due to the relatively poor solubility of **G** in aqueous solution, 1-dihexylammonium chloride (**G**') was used as a model compound. Upon addition of **WB3**, chemical shift changes of the protons on **G**' appeared (Fig. 1), providing strong evidence for the interactions between **WB3** and **G**'. The signals corresponding to protons H₁ and H₂ of **G**' displayed upfield shifts ($\Delta \delta = -0.15$, -0.10 ppm for H₁ and

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(1.00 mM) and \mathbf{G}' (5.00 mM); (c) after addition of 2 μ L of aqueous DCl solution (35 wt%) to (b); (d) after addition of 3.5 μ L of aqueous NaOD solution (30 wt%) to (c); (e) **WB3** (1.00 mM).

 H_2 , respectively). The resonance peaks related to protons $H_{3,4,5}$ and H₆ all shifted upfield as well. The reason is that these protons are immersed into the cavity of WB3 and shielded by the electron-rich cyclic structure, forming a threaded structure between WB3 and G'. In addition, protons on WB3 also exhibited slight chemical shift changes. The peak related to proton H_b on the biphenyl rings shifted downfield from 7.40 to 7.46 ppm due to the interactions between WB3 and G'. These phenomena presented the obvious evidence for the host-guest complexation between WB3 and G'. Moreover, 2D NOESY NMR investigation of an aqueous solution of WB3 (5.00 mM) and G' (25.0 mM) was performed to investigate the relative spatial positions of such an inclusion complex. As shown in Fig. 2, NOE correlation signals were clearly observed between protons H_{a-e} of WB3 and protons H_{1-6} of G', indicating that G' penetrated through the cavity of macrocyclic host WB3. Therefore, according to the ¹H NMR and 2D NOESY investigations, we can draw a conclusion that the model compound G', as an axis, was threaded through the cavity of the cyclic host WB3 to form an inclusion complex.



Fig. 2 2D NOESY NMR (500 MHz, D_2O , 293 K) spectrum of a solution of **WB3** (5.00 mM) and **G**' (25.0 mM).

Subsequently, isothermal titration calorimetry (ITC), a powerful tool for studying host–guest interactions, was applied to determine the association constant (K_a) and the thermodynamic parameters (enthalpy and entropy changes ΔH° and ΔS°) of **WB3** \supset **G**'.¹⁴ On the basis of the ITC data (Fig. S13, ESI†), K_a for the formation of the **WB3** \supset **G**' complex was calculated to be (2.57 ± 0.80) × 10⁴ M⁻¹. Moreover, from the ITC data, the 1:1 complexation between **WB3** and **G**' could be obtained, which was driven by a favorable entropy change ($T\Delta S^{\circ} = 5.754 \text{ kJ mol}^{-1}$), accompanied by a favorable enthalpy change ($\Delta H^{\circ} = -248.4 \text{ J mol}^{-1}$).

To investigate the pH-responsiveness of WB3, fluorescent titration experiments were utilized. The fluorescence intensity at 353 nm corresponding to the characteristic peak for WB3 changed little when the solution pH changed from 11.37 to 5.59, but decreased rapidly when the solution pH changed from 5.59 to 4.30. On the other hand, almost no significant intensity changes were observed when the pH decreased from 4.30 to 2.63 (Fig. S14, ESI[†]). The opposite phenomena were observed when the pH increased from 2.57 to 11.21 (Fig. S15, ESI⁺). The pH-controlled solubility of WB3 was confirmed by the ¹H NMR spectroscopy investigation. When the water-soluble biphen[3]arene precipitated from D₂O after acidification of the solution by adding an aqueous DCl solution, the signals for all protons on the host WB3 disappeared accompanied by the resonance peaks related to protons on the model compound G' returning to their original positions just as free G' (Fig. 1c). These indicated that no interactions existed between WB3 and G' after WB3 was acidified because the anionic carboxylate groups on WB3 were protonated to neutral carboxylic acid groups. The protonated host precipitated from the solution associated with the disassembly of the inclusion complex, whereas the water-soluble model compound G' kept dissolved in D2O. Upon addition of NaOD, the insoluble carboxylic acid groups were deprotonated, so the macrocyclic host would become soluble in water again. Accordingly, the peaks corresponding to protons H1-6 on G' all shifted upfield and became broad again as shown in the ¹H NMR spectra (Fig. 1, spectrum d). These results demonstrated that the host-guest complexation between **WB3** and G' could be easily controlled by changing the solution pH. With this novel water-soluble biphen[3]arene/ secondary ammonium salt molecular recognition motif in hand, a supra-amphiphile¹⁵ was fabricated by employing the amphiphilic guest G with the alkyl chain as the hydrophobic part and the secondary ammonium salt as the hydrophilic head, and further utilized in controllable self-assembly in water. The aggregation behavior of this supra-amphiphile was studied by fluorescence spectroscopy of the solutions containing pyrene probe molecules (1.00 µM). The fluorescence intensity related to pyrene dramatically decreased by the gradual addition of G into a solution containing WB3 (Fig. S16, ESI⁺), because nonpolar pyrene was solubilized near the Stern region in aggregates, which was ascribed to the formation of the aggregates in water.16

Since it was observed that the addition of different amounts of **G** led to obvious changes in the pyrene intensity in aqueous solution, it is necessary to determine the best molar ratio between **WB3** and **G** for constructing supramolecular aggregates. The fluorescence emission spectra of pyrene and its plot of fluorescent intensity at 379 nm as a function of the concentration of **WB3** added to the fixed 80.0 μ M G solution are shown in Fig. S17 (ESI[†]). Upon gradual addition of **WB3**, the fluorescent intensity of pyrene at 379 nm underwent a sharp decrease until the minimum was reached at a **WB3/G** ratio of 0.05 and then an inverse increase was observed upon further addition of **WB3**. This initially rapid decrease of the fluorescent intensity of pyrene indicated the formation of a higher-order complex between **WB3** and **G** with a tendency toward a supramolecular amphiphilic assembly, which was then disassembled upon further addition of **WB3** to gradually afford a simple 1:1 inclusion complex. The inflection was observed at the **WB3/G** molar ratio of 0.05, which means that, in the present **WB3-G** system, the best molar ratio for the amphiphilic assembly is 1:20 (**WB3:G**).

Based on this best molar ratio, the critical aggregation concentration (CAC) of **G** was calculated to be about 5.65×10^{-5} M using concentration-dependent conductivity (Fig. S18, ESI⁺). Excitingly, the critical aggregation concentration of G in the presence of WB3 was decreased to about 5.20×10^{-6} M (Fig. S19, ESI⁺). The CAC value of G decreases pronouncedly by a factor of ca. 10.9 due to the formation of a stable host-guest complex with WB3.17 As shown in Fig. 3a, the solution of WB3 and G in the best molar ratio for amphiphilic assembly in water exhibits a distinct Tyndall effect, indicating the existence of abundant aggregates.^{6a} Transmission electron microscopy (TEM) and dynamic laser scattering (DLS) experiments assisted in the identification of the self-assembly sizes and morphologies of G and WB3 \supset G. Solid spheres formed by G alone with an average diameter of about 4 nm were observed when the concentration was higher than its CAC value (Fig. S20, ESI⁺). The diameter is near to the length of two G molecules (Fig. S21, ESI⁺), confirming the formation of micelles. Upon addition of WB3, a supraamphiphile formed on the basis of the novel host-guest recognition motif, resulting in the significant changes in the aggregation structures. The DLS results showed that the average diameter of aggregates formed by WB3 \supset G was around 130 nm (Fig. 3a), and TEM images showed the formation of hollow spherical aggregates with an average diameter of ~125 nm, convincingly indicating the formation of a vesicular structure (Fig. 3b). The diameter of vesicles found by DLS was slightly larger than that measured by TEM, which is reasonable, because DLS and TEM showed swollen and solid vesicles,



Fig. 3 (a) DLS data of the $WB3 \supset G$ aggregates. Inset: photo showing the Tyndall effect of a solution containing $WB3 \supset G$. TEM images: (b) $WB3 \supset G$ aggregates (scale bar = 200 nm); (c) $WB3 \supset G$ aggregates after the solution pH was adjusted to 4.0 (scale bar = 200 nm); (d) illustration of the formation of the aggregates and the process of pH-responsive release of pyrene molecules.

respectively.¹⁸ The wall thickness of the hollow vesicles was calculated to be about 8 nm from the TEM image (Fig. 3b), close to the extended length of two **WB3** \supset **G**, suggesting that the vesicles have a bilayer wall.^{16a}

It is well-known that the micro-assembled structure of the aggregates formed by an amphiphile is determined by the curvature of the membrane.16a When this amphiphilic guest was dissolved in water, the hydrophobic part tended to aggregate while the hydrophilic part favored pointing into the polar aqueous medium, which resulted in the generation of micelles. Accompanied by the addition of WB3, the hydrophilic head of G containing the water-soluble cationic secondary ammonium salt unit threaded into the cavity of WB3 driven by electrostatic and hydrophobic interactions, forming a supra-amphiphile. Due to the steric hindrance and the electrostatic repulsion generated upon insertion of the WB3 molecules, a vesicular structure with low curvature is obtained. When the solution pH was adjusted to 4.0, WB3 precipitated from the solution, resulting in the damage of the complexation between the hydrophilic head on G and WB3 (Fig. 3c). Therefore, the selfassembly of this host-guest system could be controlled between micelles and vesicles by simply changing the solution pH.

This pH-responsive host–guest system could be potentially applied in control release. With this in mind, pyrene as a model guest was loaded in the hydrophobic layer of vesicles. Release of pyrene from the walls of the vesicles was accompanied by an increase in fluorescence emission. As shown in Fig. S22 (ESI[†]), the release of pyrene molecules from the walls of vesicles was achieved by increasing the acidity of solution, which resulted from the collapse of the vesicles (Fig. 3d).

In conclusion, we synthesized the first water-soluble biphen[3]arene (WB3) and investigated its pH-controlled complexation with 1-cetylethylammonium chloride (G) in water. We demonstrated that the model compound 1-bishexylamine chloride (\mathbf{G}') , as an axis, was threaded through the cavity of the cyclic host WB3 to form a 1:1 inclusion complex with the association constant of (2.57 \pm 0.80) \times 10⁴ M⁻¹ mainly driven by electrostatic and hydrophobic interactions. Furthermore, we used this novel recognition motif to construct a supra-amphiphile based on WB3 and amphiphilic G in water. By adjusting the solution pH, the transformations between micelles formed by G and vesicles based on WB3 \supset G were realized. This novel recognition motif based on the water-soluble biphen[3]arene in aqueous media will be helpful for the fabrication of functional architectures and definitely bring about many promising applications, such as supramolecular polymers, sensors, nanoelectronics, drug delivery and controlled release.

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