



# A cationic water-soluble pillar[7]arene: Synthesis and its fluorescent host–guest complex in water



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## ARTICLE INFO

### Article history:

Received 9 April 2017

Revised 26 May 2017

Accepted 31 May 2017

Available online 1 June 2017

### Keywords:

Pillararenes

Host–guest system

Hydrophobic interactions

Electrostatic interactions

Supramolecular chemistry

## ABSTRACT

The first cationic water-soluble pillar[7]arene CWP7 was prepared.  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and MALDI-TOF-MS were performed to provide converging evidences of the structure of obtained CWP7. Host–guest complexation between this novel pillar[7]arene-based host and sodium pyren-1-olate guest G was fully investigated in aqueous solution. Increased fluorescence intensity was observed during the inclusion complexation. Driven by the cooperativity of electrostatic interactions,  $\pi$ -stacking interactions and hydrophilic/hydrophobic interactions, the guest penetrated into the cavity of CWP7 to form a pseudorotaxane-type inclusion complex with relatively high binding affinity.

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Ongoing exploration of novel molecular recognition systems in supramolecular chemistry endows the syntheses of various receptor compounds vital significance.<sup>1</sup> In particular, the exploitation of efficient hosts which are able to work in water represents a research focus of current molecular recognition studies since most physiological processes take place in aqueous media. Some classical synthetic supramolecular macrocyclic hosts, including crown ethers,<sup>2</sup> cyclodextrins,<sup>3</sup> cucurbiturils,<sup>4</sup> calixarenes,<sup>5</sup> have been elaborately modified to efficiently interact with a manifold of substrates from metal ions, neutral molecules to organic cations/anions in aqueous solution. Pillararenes, made up of hydroquinone units linked by methylene bridges at the *para*-positions, have recently stimulated a tremendous upsurge of interest and have been defined as a new generation of macrocyclic host molecules in supramolecular chemistry due to their unique symmetric pillar-shaped scaffolds, facile tunable functionality, as well as intriguing host–guest binding abilities.<sup>6</sup>

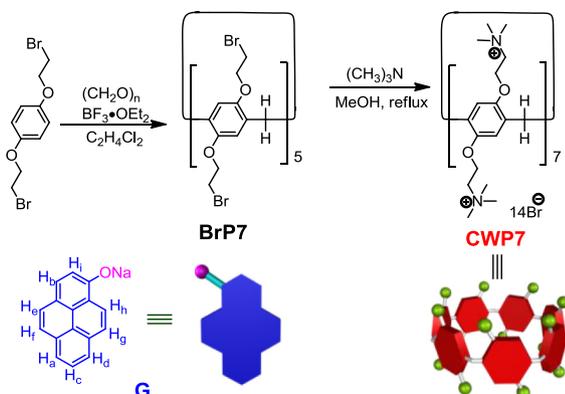
In sharp contrast to cyclodextrins and cucurbiturils, pillararenes have a poor solubility in aqueous solution. Therefore, the preparation of water-soluble pillararenes is full of importance to develop the host–guest chemistry in water. So far, several water-soluble pillararenes have been reported by introducing negatively or positively charged groups onto the cavity portals of pillararenes. The obtained water-soluble pillararenes not only enrich the host–guest recognition systems but also bring in external stimuli-responsibil-

ities for further applications in various fields, such as water-soluble supramolecular polymers, stimuli-responsive supra-amphiphiles, chemo-sensors, and some other smart materials.<sup>7</sup> Although water-soluble cationic pillar[5,6]arenes and anionic pillar[5,6,7,9,10]arenes have been synthesized, to the best of our knowledge, cationic pillar[7]arenes have not been developed heretofore.<sup>8</sup> With their enhanced cavity size, this new member of the water-soluble pillar[*n*]arenes not only can rich the pillararene-based host–guest recognition motifs but also can endow the pillararene hosts a higher selectivity for the binding of guests in water.

Herein, in this work, we report the facile synthesis of the first cationic water-soluble pillar[7]arene CWP7 functionalized with multiple trimethylammonium moieties (Scheme 1).  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) are performed to provide converging evidences of the structure of obtained CWP7. Compound CWP7 was prepared in a moderate route (Scheme 1). Neutral pillararene BrP7 with bromoethoxy groups was firstly synthesized through the cyclization of monomer with paraformaldehyde in the presence of boron trifluoride diethyl etherate as catalyst in 1, 2-dichloroethane. It's worth noting that this is a thermodynamic controlled reversible Friedel–Crafts alkylation reaction, higher reaction temperature and longer reaction time will go against the preparation of BrP7, so the real-time monitoring of the reaction is necessary. Treating BrP7 with excess amount of trimethylamine (30 equiv.) in methanol at reflux, compound CWP7 containing fourteen trimethylammonium moieties at upper and lower rims was given as a colorless solid. As expected, pillar[7]

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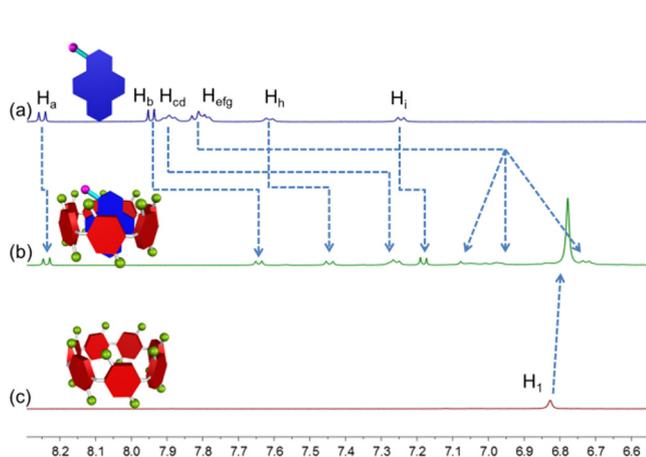


**Scheme 1.** Synthesis of the cationic water-soluble pillar[7]arene and cartoon illustration of the compounds (CWP7 and G) used here.

arene CWP7 possesses an excellent solubility in water. Furthermore, CWP7 is very hygroscopic and it will quickly turn to viscous liquids if exposed to a moist circumstance.

Due to the presence of fourteen trimethylammonium groups on the macrocyclic ring, cationic pillar[7]arene can act as a desired host for various anionic guest molecules. Considering that pillar[7]arene possesses a relatively larger cavity size (with a diameter of *ca.* 8.7 Å), which is similar to that of  $\gamma$ -cyclodextrin (*ca.* 8.3 Å) and cucurbit[8]uril (with a portal diameter of *ca.* 6.9 Å and an internal diameter of *ca.* 8.8 Å),<sup>9</sup> sodium pyren-1-olate (G) was selected as a guest to study the binding behavior of CWP7 in aqueous media. In order to investigate the size-selectivity of the host-guest complexation between CWP7 and G, the host-guest complexation between CWP6 and G was also studied.

The host-guest interaction between CWP7 and G in water was firstly studied by <sup>1</sup>H NMR spectroscopy. Fig. 1 shows the <sup>1</sup>H NMR spectra of G in D<sub>2</sub>O recorded in the absence and presence of approximately 1.0 equiv. of the host. Only one set of the peaks was observed, indicating the fast exchange complexation on the NMR timescale. Compared with the spectrum of free G (Fig. 1a), the resonance peaks related to protons H<sub>a-i</sub> of G displayed substantial upfield shifts in the presence of CWP7 (Fig. 1b) as a consequence of inclusion-induced shielding effects. On the other hand, slight upfield shift change of the aromatic protons (H<sub>1</sub>) on the framework of the pillararene host was also observed, which may be attributed to the ring current effects resulted from the  $\pi$ -stacking interactions between the pyrene ring of the guest and the ben-



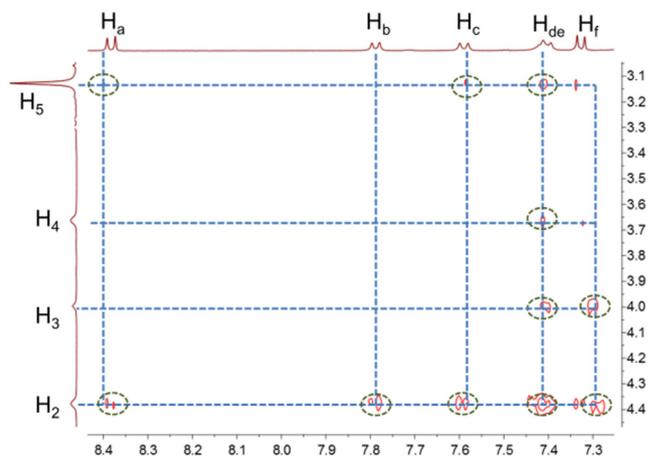
**Fig. 1.** Partial <sup>1</sup>H NMR spectra (500 MHz, D<sub>2</sub>O, 295 K): (a) G (4.00 mM); (b) CWP7 (4.00 mM) and G (4.00 mM); (c) CWP7 (4.00 mM).

zene rings of the host.<sup>10</sup> Further evidence for the formation of the inclusion complex CWP7 ⊃ G was obtained from 2D NOESY NMR study of an aqueous solution of CWP7 (10.0 mM) and G (10.0 mM). As shown in Fig. 2, nuclear overhauser effect (NOE) correlations were observed between protons H<sub>d-f</sub> on G and protons H<sub>2-5</sub> on CWP7 respectively, while no NOE was observed between protons H<sub>a</sub>, H<sub>b</sub> and H<sub>c</sub> on G and protons H<sub>3,4</sub> on CWP7, suggesting that protons H<sub>d</sub>, H<sub>e</sub> and H<sub>f</sub> were located in the cavity of CWP7.

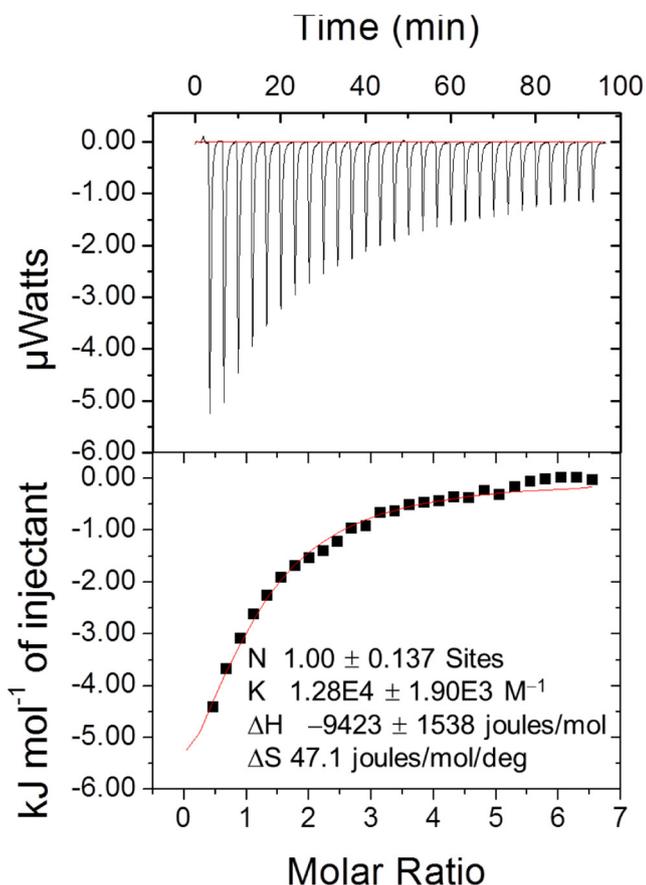
Isothermal titration calorimetry (ITC) investigation was conducted to provide thermodynamic insight into the complexation between CWP7 and G. From Fig. 3, the *K*<sub>a</sub> value of CWP7 ⊃ G was determined to be  $(1.28 \pm 0.19) \times 10^4 \text{ M}^{-1}$  in 1:1 complexation. The binding affinity of this host-guest system can be attributed to the multiple electrostatic interactions between the cationic trimethylammonium groups on the rigid pillar[7]arene platform and the anionic pyren-1-olate part,  $\pi$ -stacking interactions between the pyrene ring and the host, and hydrophilic/hydrophobic interactions. Meanwhile, the enthalpy and entropy changes were also obtained ( $\Delta H < 0$ ,  $\Delta S > 0$ ,  $|\Delta H| < |T\Delta S|$ ), indicating that this complexation was primarily driven by the entropy change with enthalpic assistance.

The host-guest interaction between CWP6 and G in water was also studied by <sup>1</sup>H NMR spectroscopy. As shown in Fig. S8, in the presence of equimolar CWP6, the resonance peaks related to protons of G also displayed upfield shifts compared to free G, indicating the existence of interactions between CWP6 and G. In order to verify if the guest G could thread into the cavity of pillararene CWP6, the 2D NOESY NMR spectroscopy was further conducted (Fig. S9). As expected, nuclear overhauser effect (NOE) correlations were observed only between protons H<sub>i</sub> on G and protons H<sub>1-3</sub> on CWP6 respectively, while no NOE was observed between other protons on G and protons on CWP6, suggesting that guest G located outside the cavity of CWP6. From the above results, the chemical shifts of the resonance peaks related to protons of G is mainly ascribed to the electrostatic interactions between CWP6 and G, while the guest molecule is too large to thread into the cavity of CWP6. Compared with the host-guest investigations between G and CWP7, the size-selectively complexation with the host molecules was clearly observed for G. In other words, host-guest inclusion complex between G and CWP7 can be formed while that between G and CWP6 can't.

Complexation of fluorescent pigments by synthetic macrocyclic hosts is a fascinating area which has attracted considerable interest in supramolecular chemistry.<sup>11</sup> Upon forming the host-guest complex, macrocyclic hosts can cause a de-aggregating effect to the

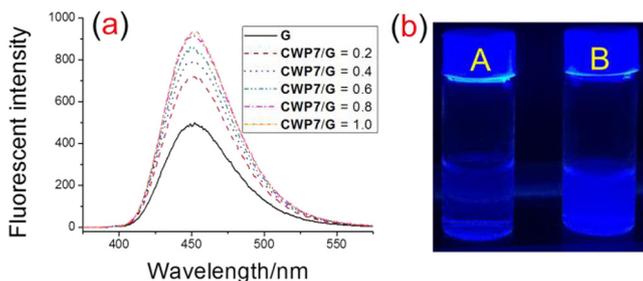


**Fig. 2.** Partial 2D NOESY NMR spectrum (500 MHz, D<sub>2</sub>O, 295 K) of a solution of CWP7 (10.0 mM) and G (10.0 mM).



**Fig. 3.** Microcalorimetric titration of G with CWP7 in water at 298.15 K. Top: raw ITC data for 22 sequential injections (10  $\mu$ L per injection) of G solution (10.0 mM) into CWP7 solution (0.500 mM); Bottom: net reaction heat obtained from the integration of the calorimetric traces.

pigments and thereby improve their water-solubility and influence their corresponding photo-physical characteristics. Most importantly, the fluorescence quantum yields and photo-stabilities of the pigments could be remarkably enhanced. Sodium pyren-1-olate, as a typical pyrene derivative, could emit blue light ( $\sim$ 450 nm) upon excitation at 365 nm, while due to the strong  $\pi$ - $\pi$  stacking interactions between the pyrene rings, the fluorescent intensity will be decreased by aggregation caused fluorescence quench effect. Therefore, the host-guest complexation induced fluorescence enhancement was observed in this system. As shown in Fig. 4a, upon gradual addition of CWP7, the fluorescent intensity of the solution of G increased and reached the maximum value when



**Fig. 4.** (a) Fluorescence spectra of G at a constant concentration upon addition of different concentrations of CWP7; (b) Photograph shows the corresponding fluorescence enhancement (A:  $1.00 \times 10^{-5}$  M G; B:  $1.00 \times 10^{-5}$  M G and  $1.00 \times 10^{-5}$  M CWP7) upon excitation at 365 nm using a UV lamp at 298 K in the presence of CWP7.

the molar ratio of CWP7/G was 1:1. Such increased fluorescence intensities can be continually observed during the inclusion complexation and mainly attributed to the changed microenvironment inside the cavities of macrocyclic hosts and to a dimensional restriction effect which can go against deactivation pathways, such as  $\pi$ - $\pi$  stacking interactions in this system. Due to the formation of host-guest inclusion complex, the  $\pi$ - $\pi$  stacking between the pyrene rings was weakened, thereby improving the dispersibility and solubility of G in water, and leading to the fluorescence enhancement.

In summary, we successfully synthesized a cationic water-soluble pillar[7]arene for the first time. The presence of fourteen positive charges on its both rims endows it great potential to act as an ideal receptor for anionic guest molecules. Furthermore, this water-soluble pillar[7]arene could bind sodium pyren-1-olate and form a [2]pseudorotaxane mainly driven by electrostatic interactions, hydrophobic/hydrophilic interactions and  $\pi$ - $\pi$  interactions in aqueous solution. Additionally, the host-guest complexation induced fluorescence enhancement of the guest was investigated. The successful preparation of this novel water-soluble macrocyclic host can provide more opportunities for researchers devoting themselves to working in the field of host-guest chemistry. This new molecular recognition motif with fluorescent enhanced property can be further applied in the construction of other functional supramolecular systems, including chemo-sensors, fluorescence imaging and drug delivery carriers.

#### Acknowledgments

This work was supported by the Fundamental Research Funds for the Central Universities.

#### A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2017.05.095>.

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