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Hydrophobic interactions in the pillar[5]arene-based host–guest complexation and their application in the inhibition of acetylcholine hydrolysis

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ABSTRACT

The host–guest complexations between a water-soluble pillar[5]arenes (**WP5**) and choline derivatives with different alkyl chain lengths were investigated. The hydrophobic interactions played a significant role in these pillar[5]arene-based host–guest complexations. By taking advantage of hydrophobic interactions, the cavity of **WP5** could be further employed to inhibit the hydrolysis of acetylcholine in the presence of acetylcholinesterase.

The arrival of any novel macrocycles can drive the development of supramolecular chemistry.[1] Host–guest systems based on pillar[*n*]arenes have attracted remarkable interest from researchers since its first synthesis in 2008.[2a] On account of their unique symmetrical structures and easy functionalization, pillar[*n*]arenes, mainly including pillar[5]arenes[2] and pillar[6]arenes,[3] have exhibited fantastic prospects for extensive applications in various supramolecular systems, such as drug delivery systems,[4] cyclic dimers,[5] chemosensors,[6] cell glue,[7] transmembrane channels,[8] and supramolecular polymers.[9] Although the electron-donating cavity and the rigid architecture afford pillar[*n*]arenes superior host–guest properties, one original question is still in debate whether the cavity of pillar[*n*]arenes is hydrophobic or hydrophilic. Unlike other macrocyclic hosts, such as cyclodextrins,[10] calixarenes[11], and cucurbiturils,[12] which have been convincingly demonstrated to possess hydrophobic cavities. However, Hou and co-workers found that water molecules were induced into the cavity of pillar[5]arene to form ordered water wires.[8a] Therefore, it is of significant importance to verify the cavity property of pillar[*n*]arenes for further studies.

Herein, we chose choline iodide derivatives with different alkyl chain lengths in tails (**G1**–**G6**) as guests to demonstrate that the cavity of a water soluble pillar[5]arene (**WP5**) was more likely hydrophobic, and the hydrophobic interactions between **WP5** and the guests played a significant role in their host–guest complexations (Scheme 1). By increasing the hydrophobicity of the guest, the binding affinity was enhanced effectively between **WP5** and the corresponding guest. More importantly, the hydrophobic cavity of **WP5** could be utilized to inhibit the hydrolysis of acetylcholine in the presence of acetylcholinesterase (AChE).

The complexations between **WP5** and **G1**–**G6** were firstly studied by ^{1}H NMR (Figs. 1a, S1, S3, S6, S11, and S14). Partial proton NMR spectra of **G4**, **WP5**, and a mixture of **G4** and **WP5** are displayed in Figure 1a. Compared with the spectrum of free **G4**, significant upfield shift changes corresponding to the proton signals of **G4** occurred in the presence of 1 equiv of **WP5** ($\Delta\delta$ = −2.27, −3.01, −2.64, −0.14, and −0.12 ppm for H_{4a}, H_{4b}, H_{4c}, H_{4d}, and H_{4e}, respectively), which was caused by shielding effect of the electron-rich cavity upon formation of a threaded structure.[13] The peak related to protons H_{4f} also showed a slight downfield shift due to the electrostatic interactions between the negative carboxylate anions and cationic trimethylamine.[2j] Therefore, we speculated that the alkyl chain of **G4** was deeply penetrated into the cavity of **WP5** and the cationic trimethylamine group appended on the rim of the host. On the other hand, the resonances of protons H_1, H_2, and H_3 also exhibited remarkable chemical shift changes, which were ascribed to the host–guest interactions. The peaks related to protons H_1 on the benzene rings and H_3 on the methylene bridges shifted downfield ($\Delta\delta$ = 0.17 and 0.04 ppm for H_1 and H_3, respectively) due to deshielding effects. Notably, the signal of methylene protons H_2 was observed to split into two overlapped

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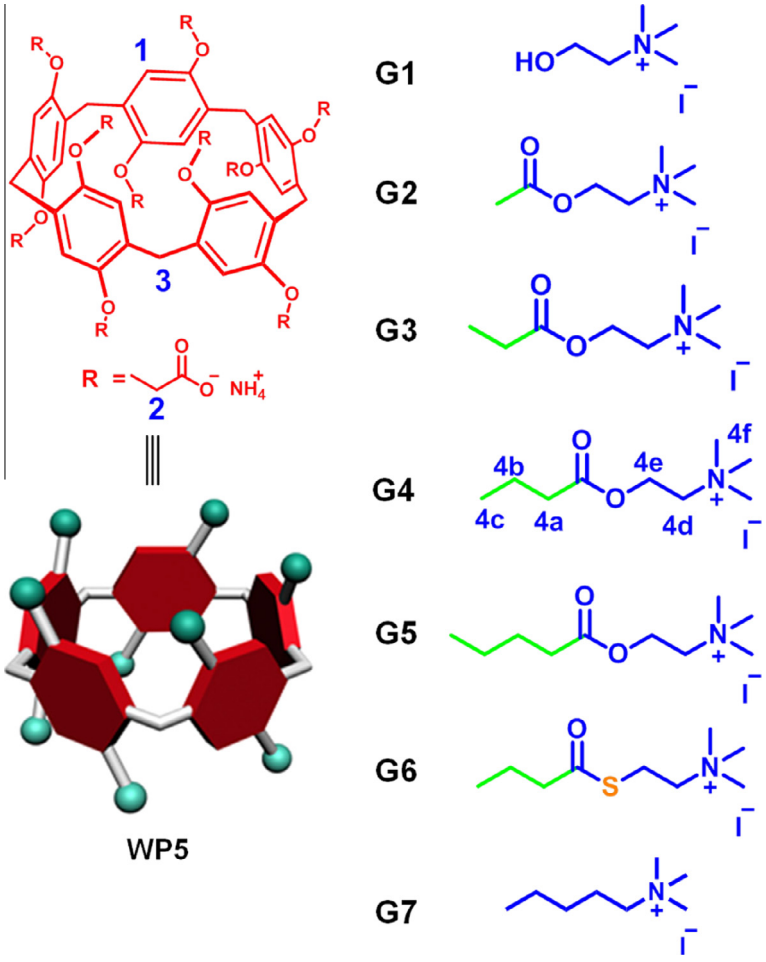

Scheme 1. Chemical structures of the guests (**G1**–**G7**) and a water-soluble pillar[5]arene **WP5**.

doublets (B, C in Fig. 1a) as a result of the desymmetrization induced by the inclusion of a non-symmetrical guest.[14]

In order to investigate the relative positions of the components in the inclusion complexes, 2D NOESY NMR experiments were conducted (Figs. 1b, S4, S7, and S12). For example, strong correlations (A–L) were observed between protons H_{4b}, H_{4c}, and H_{4a} on **G4** and protons H_1, H_2, and H_3 on **WP5** (Fig. 1b), while no NOE correlation signals could be observed for protons H_{4e}, H_{4d}, and H_{4f}, indicating that protons H_{4a}, H_{4b}, and H_{4c} threaded deeply into the cavity of **WP5**, in accord with the conclusion obtained from ^{1}H NMR.[15]

Isothermal titration calorimetry (ITC) is a useful tool to explore the inclusion complexation, which not only provides the association constant (K_a) but also yields their thermodynamic parameters (enthalpy $\Delta H°$ and entropy changes $\Delta S°$). From Table 1, the K_a values for **WP5**⊃**G** (**G2**–**G5**) were measured to be $(1.97 \pm 0.55) \times 10^4\ M^{-1}$, $(2.18 \pm 0.32) \times 10^4\ M^{-1}$, $(9.31 \pm 0.19) \times 10^4\ M^{-1}$, $(4.92 \pm 0.11) \times 10^5\ M^{-1}$, respectively. As the alkyl chain became longer, the association constants increased gradually. It should be emphasized that the association constant between **G1** and **WP5** was too weak to be calculated due to the shortage of hydrophobic interactions (Fig. S2). These data confirmed that the hydrophobic interactions played a significant role in these host–guest complexations. Moreover, the K_a value of **WP5**⊃**G6** was calculated to be $(1.72 \pm 0.06) \times 10^6\ M^{-1}$, which was about 20 times higher than that of **WP5**⊃**G4**. The reason was that the sulfur atom exhibits stronger hydrophobicity than that of the oxygen atom, thus resulting in the achievement of hydrophobic interactions with **WP5** more effectively. It should be noted that the values of $\Delta S°$ for the host–guest systems decreased gradually and turn from positive to negative associated with the increase of the alkyl chain length of the guests. The reason was that the guest with a longer alkyl chain exhibited stronger binding affinity. As a consequence, the alkyl chain was fixed more tightly in the cavity of **WP5**, thus resulting in the reduction of the degrees of freedom for the corresponding guest. In order to further demonstrate the importance of hydrophobic interactions in these host–guest systems, **G7** without the ester group was chosen as a model compound. In comparison with that of **WP5**⊃**G2**, the K_a value of **WP5**⊃**G7** was improved significantly by a factor of ca. 78. The reason was that the hydrophobicity of **G7** enhanced remarkably by replacing the ester group by the alkyl chain, thus resulting in the improvement of the hydrophobic interactions between **WP5** and **G7**, which further provided convincing evidence for the importance of the hydrophobic interactions in these pillar[5]arene-based host–guest complexations.

We wandered whether **WP5** can be employed as a supramolecular container to inhibit the hydrolysis of acetylcholine analogue by taking advantage of the hydrophobic interactions. Herein, we studied the hydrolysis behavior of acetylcholine iodide (**G2**) in the absence and presence of **WP5** by culturing with AChE. ^{1}H NMR experiments were performed to detect the hydrolysis percentage of **G2** in the absence and presence of **WP5** (Figs. S17 and S18). As shown in Figure 2, **G2** was hydrolyzed rapidly into choline and acetic acid. It took about 1 h to completely hydrolyze **G2** by culturing the solution of **G2** (30 mM) with AChE (1 U/mL) at 37 °C. In contrast, the hydrolysis rate of **G2** slowed down significantly and the percentage of hydrolyzed **G2** was 70.0% in the

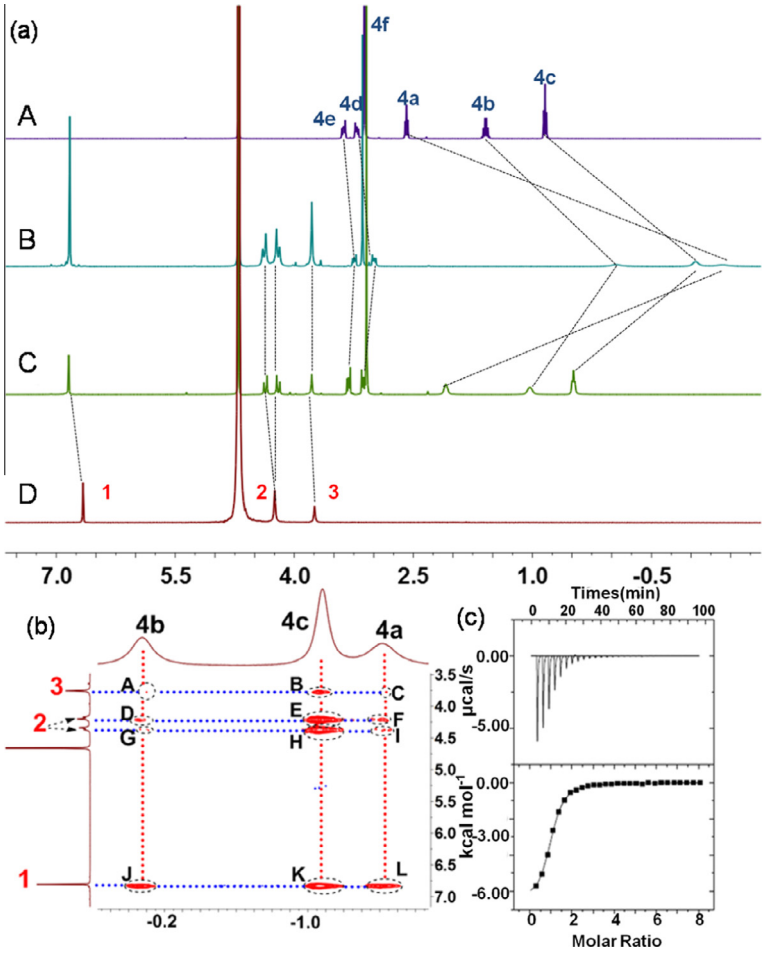

Figure 1. (a) Partial ^{1}H NMR spectra (400 MHz, D_2O, 295 K): A, **G4** (2.00 mM); B, **WP5** (2.00 mM) and **G4** (2.00 mM); C, **WP5** (2.00 mM) and **G4** (6.00 mM); D, **WP5** (2.00 mM). (b) Partial NOESY NMR spectrum (500 MHz, D_2O, 295 K) of 10.0 mM **WP5** and **G4**. (c) Microcalorimetric titration of **G4** with **WP5** in water at 298.15 K. (Top) Raw ITC data for 29 sequential injections (10 μL per injection) of a **G4** solution (2.00 mM) into a **WP5** solution (0.100 mM). (Bottom) Net reaction heat obtained from the integration of the calorimetric traces.

Table 1
Association constants (K_a), enthalpy changes ($\Delta H°$) and entropy changes ($\Delta S°$) obtained from ITC experiments for the 1:1 complexes of **WP5** with the guests (**G2**–**G7**)[a]

	K_a (M^{-1})	$\Delta H°$ (cal/mol)	$\Delta S°$ (cal/mol/deg)
G2	(1.97 ± 0.55)E4	−(2.229 ± 0.287)E2	18.9
G3	(2.18 ± 0.32)E4	−(2.027 ± 0.222)E3	13.1
G4	(9.31 ± 0.19)E4	−(6.646 ± 0.035)E3	0.444
G5	(4.92 ± 0.11)E5	−(1.181 ± 0.003)E4	−13.6
G6	(1.72 ± 0.06)E6	−(1.266 ± 0.003)E4	−13.2
G7	(1.54 ± 0.04)E6	−(3.216 ± 0.003)E4	−79.5

[a] Microcalorimetric titration experiments were conducted in water at 303.15 K.

presence of **WP5** (30 mM) for 1 h under the same conditions as the free **G5**. The reason was that there was a dynamic equilibrium between the complexed and uncomplexed states of **G2**, and AChE only attacked the free **G2**,[16] demonstrating that the rigid macrocycle could be utilized to hinder the hydrolysis of **G2**. Acetylcholine is an organic molecule that acts as a neurotransmitter in many organisms. The lack of acetylcholine in the brain has been proven to be related to the memory deficits associated with Alzheimer's disease.[17] Therefore, it really matters how to maintain the normal level of acetylcholine to keep our brains healthy. This supramolecular complex-induced inhibition of acetylcholine could be potentially applied in the treatment of Alzheimer's disease.

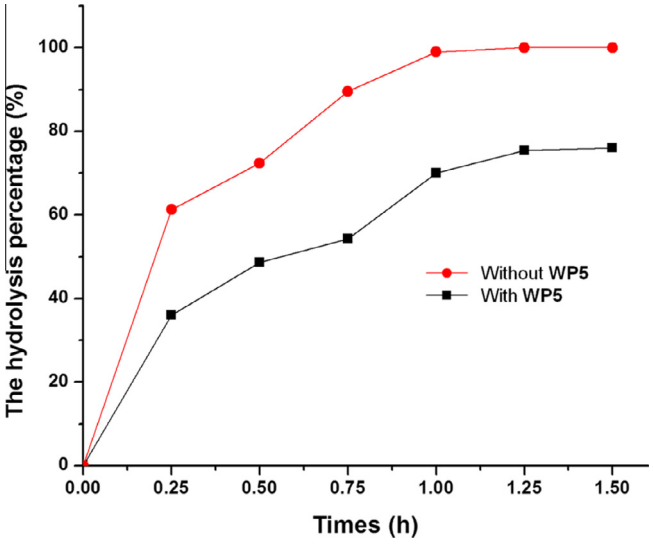

Figure 2. Hydrolysis percentage of **G2** in the absence and presence of **WP5** by culturing with AChE at 37 °C.

In conclusion, the host–guest complexations between **WP5** and choline derivatives with different alkyl chain lengths were investigated. As the alkyl chain length of the guest increased, the binding

affinity of the host–guest complex was enhanced effectively, confirming that the cavity of **WP5** was hydrophobic. Furthermore, **WP5** could be used as a supramolecular container to inhibit the hydrolysis of acetylcholine successfully by taking advantage of hydrophobic interactions. These results not only exemplify the enormous potential application of hydrophobic interactions in the construction of mechanically interlocked molecules, such as pseudorotaxanes, rotaxanes, and catenanes, but also exhibit fantastic prospect for pillar[*n*]arenes to fabricate functional biomaterials.

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Supplementary data

Supplementary (^{1}H NMR, 2D NOESY spectra, and ESI mass spectra) data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.01.064.

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