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Encapsulation Enhanced Dimerization of a Series of 4-Aryl-*N*-Methylpyridinium Derivatives in Water: New Building Blocks for Self-Assembly in Aqueous Media

Ying Zhang,[a] Tian-You Zhou,[a] Kang-Da Zhang,[a] Jin-Ling Dai,[a] Yuan-Yuan Zhu,[b] and Xin Zhao*[a]

Abstract: The construction of supramolecular systems in aqueous media is still a great challenge owing to the limited sources of building blocks. In this study, a series of 4-aryl-*N*-methylpyridinium derivatives have been synthesized. They formed very stable host–guest (1:2) complexes with CB[8] in water (binding constants up to $10^{14}\,M^{-2}$) with the two guest molecules arranged in a head-to-tail manner and the complexes showed high thermostability, which was revealed by ^{1}H NMR and UV/Vis spectroscopic studies, ITC, and crystallographic analysis.

Molecular self-assembly is a powerful tool in constructing well-defined aggregates that are the basis for fabricating functional materials.[1] To apply this approach, supramolecular building blocks (also known as supramolecular tectons) must first be rationally designed and then synthesized. Driven by noncovalent interactions, those building blocks can spontaneously aggregate to form well-ordered supramolecular systems under certain conditions.[2] In this context, a supramolecular tecton is the most fundamental unit, which determines the final structure of a self-assembled architecture. For this reason, developing new building blocks is regarded as one of the most important themes in supramolecular chemistry. In the past few decades, a myriad of supramolecular tectons have been synthesized with different noncovalent interactions such as hydrogen-bonding,[3] coordination,[4] static interactions,[5] aromatic stacking,[6] donor–acceptor,[7] cation···π,[8] anion···π,[9] and C–H···π interactions.[10] However, building blocks that can be used to construct supramolecular architectures in the aqueous phase are still limited. In addition, supramolecular systems usually show low thermostability because noncovalent interactions (except metal–ligand interactions) are weak. This low stability dramatically limits their application. In this regard, building blocks that are stable at elevated temperatures should be very useful for the construction of thermostable supramolecular architectures.

Aromatic stacking, which is also known as π–π stacking, is one of the most widely used types of noncovalent interactions in self-assembly. Although in highly polar solvents it has advantages over hydrogen-bonding, which is dramatically weakened owing to the competition of solvent molecules, aromatic stacking usually suffers from weak interactions and the lack of direction. In 2001, Kim et al. found that the bonding strength between electron-deficient viologens and electron-rich species such as 1,4-dihydroxybenzene could be considerably enhanced by being encapsulated in the cavity of cucurbit[8]uril (CB[8]) to form a 1:1:1 ternary complex.[11] Since then this type of host-stabilized donor–acceptor interaction has been widely employed to construct sophisticated supramolecular systems in aqueous media.[12] Very recently, Zhang and co-workers reported that this strategy could also be applied to enhance π–π interactions.[13] Despite the progress that has been achieved, controlling the arrangement of guests in the cavity of CB[8] in an accurate way remains challenging in these systems. In this study, we constructed a series of 4-aryl-*N*-methylpyridinium derivatives **T1–T6** to develop an efficient strategy to control the bonding direction of guest molecules in host CB[8] (Scheme 1).[14,15] We anticipated that a head-to-tail arrangement of the molecules must be adopted when they are stacked because a head-to-head arrangement might result in strong electrostatic repulsion between the pyridinium units. We found that these molecules dimerized in the cavity of CB[8] to form extremely stable host–guest complexes in aqueous solution, in which the guest molecules aligned in a head-to-tail manner. Furthermore, unusually high thermostability was also observed for these complexes.

A ^{1}H NMR spectroscopy dilution experiment was first carried out for compound **T1** in D_2O. All the protons of **T1** showed very small downfield shifts (<0.03 ppm) when the

[a] Y. Zhang, T.-Y. Zhou, Dr. K.-D. Zhang, J.-L. Dai, Prof. X. Zhao
Laboratory of Materials Science
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (China)
Fax: (+86) 21-64166128
E-mail: xzhao@mail.sioc.ac.cn

[b] Prof. Y.-Y. Zhu
Anhui Key Laboratory of Advanced Functional Materials and Devices
School of Chemical Engineering
Hefei University of Technology
Anhui, 230009 (China)

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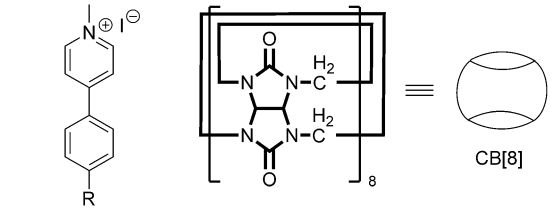

T1: R = OCH_3 **T4**: R = Cl
T2: R = SCH_3 **T5**: R = Br
T3: R = H **T6**: R = NO_2

Scheme 1. Chemical structures of **T1–T6** and CB[8].

concentration was reduced from 12.8 mM to 0.3 mM (Figure S1, see the Supporting Information), thus suggesting that the aggregation of **T1**, if any, is very weak. We thus examined its aggregation in the presence of CB[8] by ^{1}H NMR titration. As shown in Figure 1, following the addition of CB[8], a new set of signals appeared, accompanied by a decrease in the intensities of the peaks that correspond to free **T1**. The new set of signals could be attributed to a complex formed from **T1** and CB[8] under a very slow exchange between complexed **T1** and free **T1** on the NMR time scale. Compared with that of free **T1**, all of the protons of **T1** showed a pronounced upfield shift after complexing with CB[8] with the exception of the NMe group. The titration experiment also revealed that the signals of free **T1** were significantly diminished after 0.5 equivalents of CB[8] was added and further addition of CB[8] (0.6 equiv)[16] did not result in any change in the signals, thereby indicating a 2:1 binding stoichiometry for **T1** and CB[8]. The 2:1 binding stoichiometry was further corroborated by a Job's plot, which displayed the maximum change in UV/Vis absorbance of **T1** at 66.7% of free **T1** in a mixture of **T1** and CB[8] (Figure 2). A UV/Vis study revealed that the maximum absorbance of **T1** decreased by approximately 34% and the corresponding peak was red-shifted by 8 nm upon the addition of 0.5 equivalents of CB[8] (Figure 2). Such phenomena could be attributed to the hypochromic effect that results from the π–π stacking and J-type arrangement of the two molecules of **T1** in the cavity of CB[8].[17] Furthermore, it was found that the fluorescence emission of **T1** was considerably enhanced and displayed a bathochromic shift after being encapsulated, which is in agreement with the J-type arrangement of **T1** in the cavity of CB[8] (Figure S2, see the Supporting Information).[18]

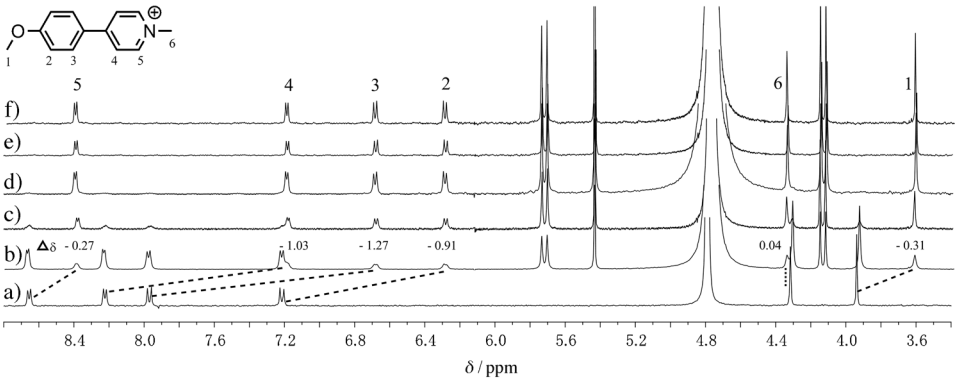

Figure 1. ^{1}H NMR spectra (500 MHz) of (a) **T1** (1.0 mM), (b) **T1**–CB[8] (0.15 equiv), (c) **T1**–CB[8] (0.2 equiv), (d) **T1**–CB[8] (0.4 equiv), (e) **T1**–CB[8] (0.5 equiv), and (f) **T1**–CB[8] (0.6 equiv) in D_2O at 25 °C.

The binding behavior between CB[8] and **T2–T6** was then investigated by using ^{1}H NMR titration, UV/Vis, and fluorescence spectroscopy experiments under the same conditions used for **T1. T2–T6** showed similar changes in both chemical shift and absorption to that of **T1** upon the addition of CB[8] (Figure S3–S7, see the Supporting Information), and this suggested a similar binding model to that of **T1**. The binding stoichiometries were confirmed by Job's plots to be 2:1 for **T3–T6** and CB[8] (Figure S8–S11, Supporting Information), respectively. Under similar conditions, free **T2** and **T2**–CB[8] showed very weak UV/Vis absorbance. Although a satisfactory Job's plot could not be generated for the **T2**–CB[8] complex owing to its weak UV/Vis absorption, the binding stoichiometry between **T2** and CB[8] could still be confirmed to be 2:1 by ^{1}H NMR titration experiments. Similar to **T1**, the fluorescence emissions of **T3**, **T4**, and **T5** were enhanced after being encapsulated in CB[8] (Figure S12–S14, see the Supporting Information). In contrast, the **T2**–CB[8] and **T6**–CB[8] complexes were not fluorescent under similar conditions.

Reducing the concentration of an aqueous solution of complex **T1**–CB[8] from 0.39 mM to 0.02 mM did not result in any shift of the signals in the ^{1}H NMR spectra (Figure S15, see the Supporting Information), thereby revealing that the complex was highly stable in aqueous media. The binding constants between CB[8] and **T1–T6** were estimated by isothermal titration calorimetry (ITC) experiments (see Figures S16–S21 in the Supporting Information for the ITC data and thermodynamic binding data). The ITC results also indicated a stoichiometry of 2:1 for **T1**(-**T6**)–CB[8]. The data were fitted by using a sequential binding model to give the binding constants and the results are provided in Table 1. The values indicate that these complexes are highly stable, with **T5**–CB[8] exhibiting the largest binding constant ($1.3\times10^{14}\,M^{-2}$), while **T6**–CB[8] showed the lowest value

Table 1. Binding constants for the complexes formed between **T1–T6** and CB[8].

Complex	**T1**–CB[8]	**T2**–CB[8]	**T3**–CB[8]	**T4**–CB[8]	**T5**–CB[8]	**T6**–CB[8]
Binding constant [M^{-2}]	3.4 $(\pm0.9)\times10^{12}$	3.5 $(\pm0.8)\times10^{12}$	4.4 $(\pm0.6)\times10^{13}$	3.0 $(\pm1.3)\times10^{13}$	1.3 $(\pm0.4)\times10^{14}$	2.0 $(\pm0.5)\times10^{12}$

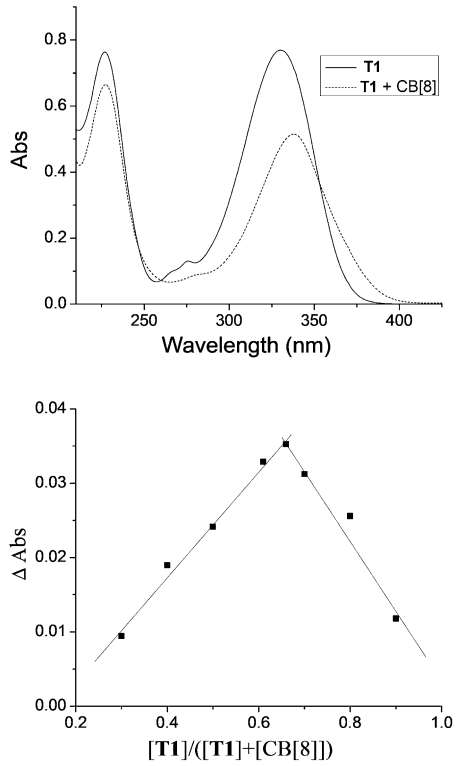

Figure 2. UV/Vis spectra of **T1** (37.5 μM) without and with CB[8] (18.8 μM) in a sodium phosphate buffer (0.1 M, pH 7.0) at 25 °C (top), and Job's plot indicating a 2:1 stoichiometry for **T1** and CB[8] (bottom). The total concentration used for generating the Job's plot was 10 μM.

(2.0×10^{12} M^{-2}). The difference might be attributed to their different hydrophobic features.

To obtain detailed information about the arrangement of the molecules in the cavity of CB[8], single crystals of complex **T1**–CB[8], suitable for crystallographic analysis, were grown by slow evaporation of an aqueous solution of **T1** and CB[8] (2:1) at 25 °C.[17] The crystal structure clearly reveals that two molecules of **T1** are encapsulated inside one CB[8] molecule (Figure 3). The anisole unit and the pyridinium segment of the molecule are almost coplanar (the dihedral angel between anisole unit and pyridinium segment is 6.4°). Furthermore, the two encapsulated molecules are antiparallel to each other and adopt a head-to-tail offset stacking with a mean distance of 3.8 Å, a typical distance for aromatic stacking. Single crystals of complex **T2**–CB[8] were also grown in a similar way and elucidated;[19] this revealed that compound **T2** adopted almost the same arrangement in the cavity of CB[8] as that of compound **T1** (Figure 3).

Variable-temperature ^{1}H NMR experiments revealed that these 2:1 complexes had high thermostability. Figure 4 shows the ^{1}H NMR spectra of complex **T1**–CB[8] and free **T1** at different temperatures. It was found that both the signals that correspond to complex **T1**–CB[8] and free **T1** shifted downfield with increasing temperature; this is attributed to the inherent effect upon raising the temperature. No signals of the free **T1** were observed for the solution of **T1**–

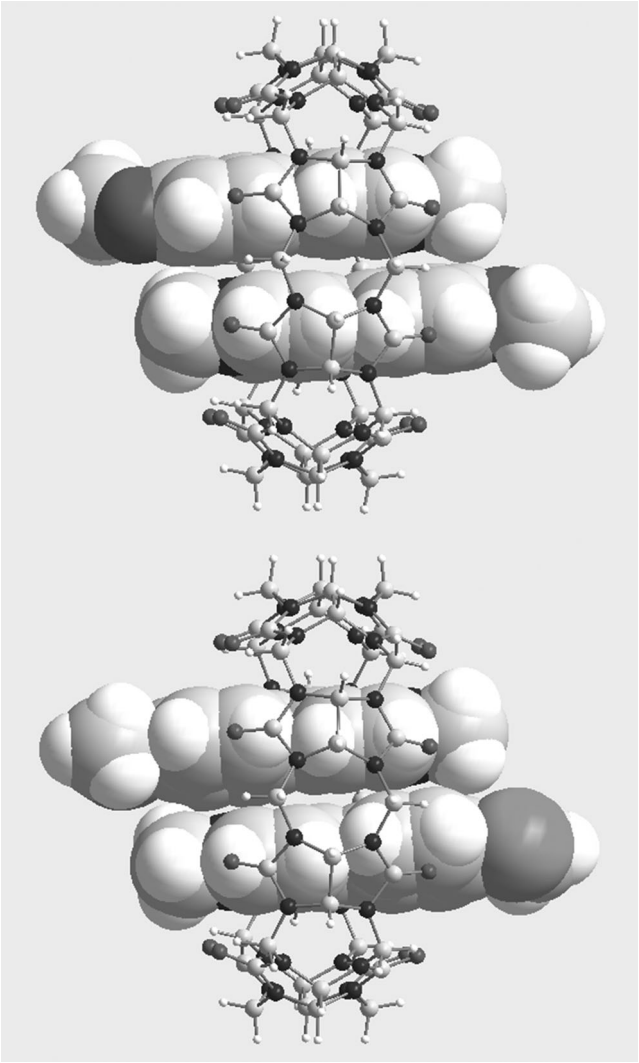

Figure 3. Crystal structures of complexes **T1**–CB[8] (top) and **T2**–CB[8] (bottom) indicate the head-to-tail offset stacking of a pair of **T1** or **T2** in the cavity of CB[8].

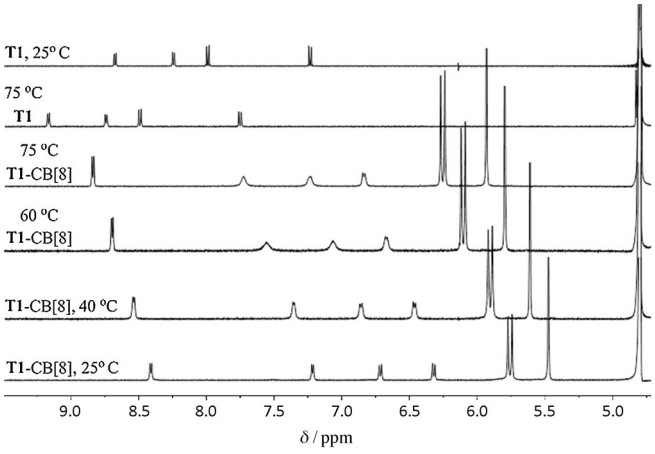

Figure 4. Partial ^{1}H NMR spectra of **T1**–CB[8] (2:1) and **T1** in D_2O at different temperatures. The concentration of **T1** was 1.0 mM.

CB[8] (2:1) even at 75 °C,[20] thus indicating that **T1** was still encapsulated in the cavity of CB[8] at this temperature. A rapid exchange between the free **T1** and encapsulated **T1** at elevated temperatures could be considered, but this was ruled out by variable-temperature ^{1}H NMR experiments that were carried out for a mixture of **T1** and CB[8] (2:0.6), in which both the bound **T1** and free **T1** coexisted and displayed distinct peaks. With increasing temperature, the two sets of signals that correspond to bound **T1** and free **T1** shifted downfield, respectively, but no merging of the two sets of signals was observed even at 60 °C (Figure S22, see the Supporting Information). This result suggests that the complex **T1**–CB[8] and free **T1** exist in the aqueous solution independently at elevated temperatures (60 °C), thus indicating the high thermostability of complex **T1**–CB[8]. It should be noted that at 75 °C all the aromatic peaks became very broad, thus suggesting that at this temperature, exchange between complex **T1**–CB[8] and excess **T1** occurs at a rate comparable to the ^{1}H NMR time scale. Other complexes also showed a high thermostability, as revealed by the variable-temperature ^{1}H NMR experiments (Figure S23–S27, see the Supporting Information).

In summary, a new model for encapsulation-enhanced aromatic stacking has been developed. These 4-aryl-*N*-methylpyridinium derivatives spontaneously dimerize in the cavity of CB[8] and the resulting host–guest complexes have very high stability in aqueous media. Their high thermostability should be very useful in fabricating supramolecular systems that can survive at elevated temperatures in aqueous media. The head-to-tail arrangement of the dimers provides excellent direction control when the two building blocks are bound together. Further studies on using these novel building blocks to construct complicated supramolecular systems such as supramolecular polymers[21] are now in progress.

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Keywords: cucurbit[8]uril · dimerization · head-to-tail · host–guest systems · self-assembly

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