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Supramolecular Polymerization with Dynamic Self-Sorting Sequence Control

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Supporting Information Placeholder

ABSTRACT: Synthetic polymerization and supramolecular polymerization with sequence control is far from an easy task. Herein, a narcissistic self-sorting supramolecular polymer is prepared with a sequence of $(-AA-BB-)_n$ by using cucurbit[8]uril (CB[8])-based ternary complexes as supramolecular monomers, which are spontaneously formed from starting materials of heteroditopic AB-type guest and CB[8]. The process of supramolecular polymerization and their structural changes at each stage of polymerization have been successfully demonstrated by NMR, UV-Vis and fluorescence spectra. The self-sorting starts from the second step of polymerization after the formation of different ternary complexes as supramonomers. The dynamic supramolecular interactions and the thermodynamic stability of the host-guest complexes are found to be the crucial factors to drive the sequence control of the supramolecular polymers. Furthermore, the water-soluble supramolecular polymer is red-emissive, which can serve as fluorescent sensor to detect morphine in artificial urine with considerable stability, sensitivity and accuracy. And it can also distinguish heroin and morphine, which are two kinds of opioids with similar structures.

Sequence control plays an important role in biology and is a prerequisite for crucial features of life, such as the sequence control in DNA and protein structure. The sequence of DNA double helix formed from the self-sorting of adenine-thymine (A-T) and guanine-cytosine (G-C) base pairs is the molecular basis for the storage, replication, and transcription of genetic information. Errors in base pairs can lead to serious genetic diseases. Generally speaking, DNA template controls the DNA sequence and DNA polymerase checks and corrects wrong nucleotide.¹ In recent years, synthetic polymer with controlled polymer sequence has attracted much attention due to its potential applications.² Compared with the sequence control of DNA, it seems much easier for synthetic polymers. However, sequence control for covalent polymerization is still a big challenge. The general method for preparing

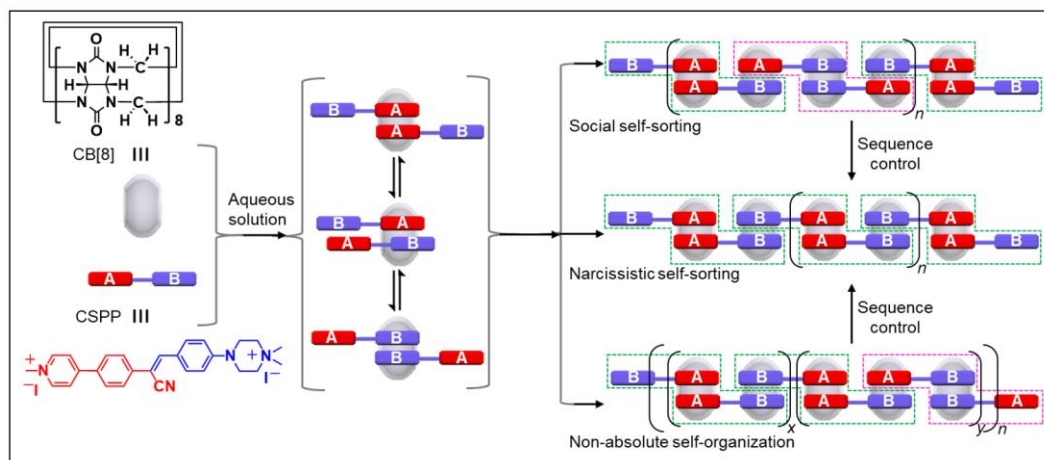
sequence-defined polymers is to connect monomers one by one by using iterative chemical steps or sequential monomer addition technique,² such as solid-phase support for the synthesis of oligopeptides³ or step-growth radical polymerization⁴. However, it is a tedious process and requires very high reaction yields to get rid of impurities with error structures, and it also lacks of control on molecular weight. Supramolecular polymers have attracted great interest in recent decades because the non-covalent interactions that bind them together endow the materials with dynamic, reversible and degradable characteristics.⁵⁻⁹ A variety of noncovalent interactions, such as hydrogen bonding, metal coordination, host-guest interactions and aromatic stacking have been utilized to construct supramolecular polymers with high fidelity, high molecular weight and wonderful applications.⁵⁻¹¹

However, sequence control is also a huge challenge to supramolecular polymerization. According to Zhang's classification,⁵ supramolecular monomers have five major types: AA type, AB type, AA/BB type, ABBA type and aromatic-stacking type. Among them, AB type,¹²⁻¹⁴ AA/BB type¹⁵⁻²⁰ and ABBA type^{14,21,22} can polymerize to generate $(-AB-AB-)_n$ alternating block copolymers. Moreover, by introducing self-sorting into the supramolecular polymerization, more complicated and programmed polymer sequence can be achieved. Self-sorting is a self-assembly process in which molecules are endowed with the ability to selectively and specifically form complexes with their mutual counterparts within a complex mixture.²³⁻²⁹ Huang and coworkers used two heteroditopic monomers to produce $(-AD-CB-)_n$ alternating copolymer based on crown size-dependent social self-sorting.³⁰ Haino and coworkers employed three heteroditopic monomers to produce $(-AE-FC-DB-)_n$ sequence-controlled supramolecular terpolymer via a self-sorting behavior based on two kinds of host-guest interactions of biscalix[5]arene-C60 and bisporphyrin-TNF, and Hamilton's hydrogen-bonding complex.³¹ Although it is very easy to construct many kinds of supramolecular polymers with different sequences based on host size-dependent social self-sorting or the self-sorting between different kinds of noncovalent interactions. However, the self-sorting supramolecular polymerization by using merely cucurbiturils (CBs) and their guests is very hard to achieve due to the difficulties in the modification of CBs.

Among the most common macrocyclic hosts (cyclodextrins, CBs, calixarenes and pillararenes), CBs can bind a variety of neutral or positively charged guests with very high binding constants,³² which have been widely utilized for the development of new supramolecular polymers.^{5,33} Given the difficulties in the modification of CBs, CB[8] is the most potential host to fabricate supramolecular polymers because it's like an interlock to connect two guests in its relatively large cavity.^{5,33,34} Classical host-guest supramolecular polymers of CB[8] are usually constructed

based on either the host-stabilized charge transfer (HSCT) interaction³⁴⁻³⁶ or the host-enhanced π - π interaction^{27,37-40} between the functional groups of guests that are included simultaneously inside host cavity. Currently, the popular guest pairs are methylene-bridged dipyridyliumethylene-naphthalene HSCT pair,⁴¹ methyl viologen-naphthol HSCT pair,⁴² methyl viologen-anthracene HSCT pair,²¹ methyl viologen-azobenzene HSCT pair,¹⁴ and so on. Those HSCT pairs often generate programmed and indubitable sequence of supramolecular polymers. But for heteroditopic AB-type guest or AA/BB-type guest with more host-enhanced π - π interaction than host-stabilized charge transfer interaction, the results are sometimes complicated and unpredictable. The difficulty lies in two aspects: 1) The selective complexation between different ternary complexes (AA-CB[8], BB-CB[8] and AB-CB[8] complex) may not be strong enough for self-sorting; 2) It's hard to characterize the structure and ratio of different ternary complexes. Therefore, most researches just simply use homoditopic guests^{38-40,43-45} or the classical HSCT pairs³⁴⁻³⁶ to produce host-guest supramolecular polymers. To explore new possibilities of host-guest supramolecular polymers, new AB-type guests are highly required. Recently, Masson et. al. reported a mixed oligomer formed by a positive ditopic Ir(III) bisterpyridine guest (AA-type) and a negative ditopic Fe(II) bisterpyridine guest flanked by four butyrate side chains (BB-type) with CB[8], generating a mixed sequence of $(-BA-AB-BB-)_n$, namely, $(Fe-Ir-Ir-)_n$ sequence.⁴⁶ Using orthogonal self-assembly based on host-guest interactions or with metal-ligand interactions, it indeed can prepare a supramolecular polymer with $(-AA-BB-)_n$ sequence from heteroditopic monomers.^{47,48} However, to the best of our knowledge, supramolecular polymers merely based on heteroditopic AB-type guest and CB[8] with a narcissistic self-sorting sequence of $(-AA-BB-)_n$ rather than $(-AB-AB-)_n$ sequence have not been reported yet.

Scheme 1. The cartoon representation of the dynamic self-sorting sequence control of the supramolecular polymerization of CB[8] and CSPP. The double-headed arrow means the shuttle motion of guest and host. AA and BB monomers are framed by green dotted line and purple dotted line, respectively. To make the scheme simple, only polymer formed by AA monomers is drawn in the narcissistic self-sorting, which may also be formed by BB monomers.



In this work, we have designed a heteroditopic AB-type guest called CSPP, in which the 1-methyl-4-phenylpyridinium section was denoted as A (red color) and the 1,1-dimethyl-4-phenylpiperazinium section was denoted as B (blue color), as shown in Scheme 1. The synthesis of CSPP molecule have been reported in our previous work.⁴⁹ Other works based on CB[8] and homoditopic guests with cyanostilbene backbone have successfully synthesized fluorescent water-soluble supramolecular polymer and found their good applications.^{38,44} Herein, the cyanostilbene-based guest, CSPP, has nonsymmetric two sides. From a statistical point of view, three kinds of supramolecular polymers can be formed with a sequence of $(-AB-AB-)_n$ made by hetero-ternary complexes or a sequence of $(-AA-BB-)_n$ made by homo-ternary complexes or a sequence of $[(AA-BB)_x(-AB-AB)_y]_n$ made by both homo-ternary and hetero-ternary complexes as illustrated in Scheme S1 in Supporting Information. In fact, the complexation of CSPP and CB[8] generates supramolecular polymer with merely a sequence of $(-AA-BB-)_n$. This phenomenon is attributed to the self-sorting and error correction during the supramolecular polymerization. We found that there are two steps during polymerization (see Scheme 1). The first step is the formation of homoditopic AA and BB ternary complexes, which act as supra-monomers. The second step is the formation of supramolecular polymers by supra-monomers through self-sorting. Interestingly, the results

indicate that AB complexes are formed during the supramolecular polymerization, but it can be corrected to AA or BB units along with the supramolecular polymerization, and ultimately leading to the formation of a polymer with $(-AA-BB-)_n$ sequence.

RESULTS AND DISCUSSION

Supramolecular polymerization studied by ^1H NMR and ^1H - ^1H NMR spectra. The interaction between CSPP and CB[8] was firstly investigated by ^1H NMR titration. Before doing the NMR titration experiment, the protons in CSPP were clearly assigned based on the results of ^1H - ^1H COSY (correlation spectroscopy) and ^1H - ^1H ROESY (rotating frame nuclear overhauser effect spectroscopy) (Figure S1 and S2). After titration of 0.15 equiv. CB[8] into CSPP, a new set of sharp peaks appeared (Figure 1). All the protons of the conjugated structure (from H_b' to H_k') shifted upfield by ~ 0.5 ppm, which was attributed to the shielding effect of the CB[8] cavity (see the Table in Figure 1). The methyl protons of the pyridinium shifted upfield by only 0.12 ppm, indicating that they were included near the CB[8] portal. Nevertheless, the protons of the piperazinium unit (H_i' , H_j' and H_k') shifted downfield by less than 0.1 ppm, indicating that they were in a location near the portal yet outside the CB[8] cavity. When 0.55 equiv. CB[8] was added, the peak of free CSPP disappeared completely. Furthermore, nearly all the guest protons on the aromatic rings revealed an upfield

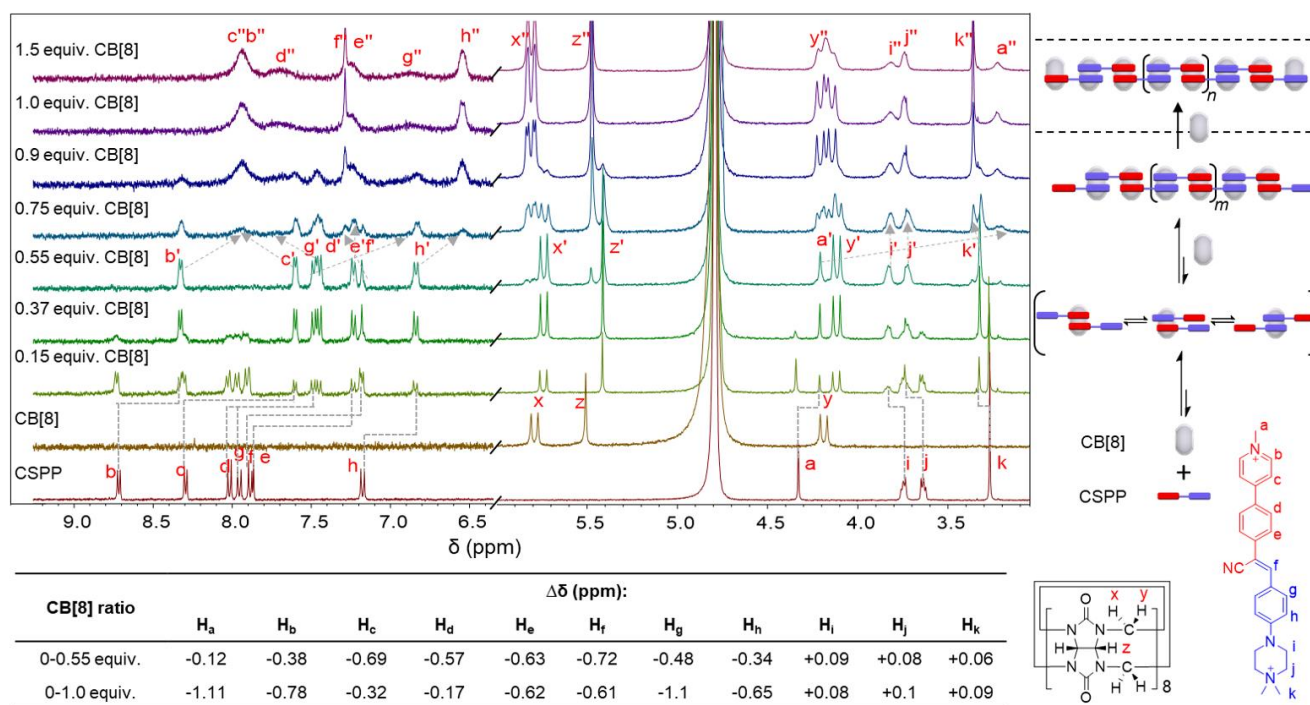


Figure 1. Titration of CB[8] to 0.8 mM CSPP monitored by ^1H NMR spectra. The scheme on the right side reflected the dynamic processes involved in the titration. There are two slow exchanges during the supramolecular polymer formation: first, ternary complexes are formed from free CSPP and CB[8]; second, supramolecular polymers are formed from ternary complexes. Slow exchange refers to slow inter-molecular association and dissociation. In addition, ternary complexes undergo fast intra-conversion between different ternary complexes resulted from the shuttle motion of both host and guest. Table showed the chemical shift of protons in CSPP during CB[8] titration.

chemical shift of ~ 0.5 ppm, indicating that the proton chemical shift of the guests were the averaged signals arising from a partial inclusion and partial exclusion by the CB[8] cavity.⁵⁰ At the same time, the charge distribution on the CB[8] portal was also averaged leading to no splitting of its peaks. In these contexts, we speculate that different ternary complexes formed between CSPP and CB[8] resemble molecular shuttles so that they can be converted into each other. In other words, there is a shuttle motion performed by CB[8] on the guests and a high-frequency intramolecular transformation of different overlapping configurations between the two inclusion guests (see the Scheme in Figure 2). These motions are so fast on the NMR time scale that the signals from different configurations of ternary complexes are averaged into merely one set of NMR peaks. To seek more detailed information on the ternary complexes, 2D NMR spectra including ^1H - ^1H COSY, ^1H - ^1H NOESY (nuclear overhauser effect spectroscopy) and ^1H - ^1H ROESY of CSPP solution containing 0.55 equiv. CB[8] were measured. The ^1H - ^1H COSY spectrum proved the assignment of ^1H NMR peaks of the ternary complexes (Figure S3). The ^1H - ^1H NOESY and ^1H - ^1H ROESY spectra confirmed the packing modes of the guests inside the CB[8] cavity (Figure 2a, Figure S4 and S5). The NOE correlation of H_f' - H_a demonstrated the inclusion of the guests inside the CB[8] cavity (Figure 2a). The NOE correlations (H_b' - H_e , H_c' - H_e , H_c' - H_g , H_d' - H_f , H_h' - H_i , H_h' - H_j) and the ROE signals (H_c' - H_e , H_b' - H_e , H_d' - H_f , H_h' - H_i , H_h' - H_j) implied that there were possibly four kinds of packing modes of guests: AA, BB, AB¹ and AB² (see Figure S6). The packing types of AA, AB¹ and BB (two guest molecules are arranged oppositely) are interconvertible due to the fast-molecular shuttle motions by guest and host, so that the whole system is in the state with the lowest energy. It may contain small amount of AB² packing (two guest molecules are arranged in the same direction). But AB² cannot directly transform into the configurations of the other three. Therefore, the ternary complexes of AA, AB¹ and BB are the primary components when the ratio of CB[8] to CSPP is 0.5.

When the ratio of CB[8] to CSPP is more than 0.5, the proton peaks of the ternary complexes still existed and a new set of broad peaks appeared. After addition of 1.0 equiv. CB[8], only very broad and weak peaks of the guests were left, suggesting the formation of high-molecular-weight supramolecular polymer aggregates.^{14,22,30,51} After the peak assignment of the protons of polymers (see the discussion listed above Figure S7 in Supporting Information), we continue to check the process of polymer formation during ^1H NMR titration as shown in Figure 1. The H_a'' of polymer displayed a very large upfield shift (1.11 ppm) relative to the H_a of free guest. H_b'' , H_g'' and H_h'' also revealed an upfield shift of about 0.78, 1.1 and 0.65 ppm, respectively, compared to those of free guest (see the Table in Figure 1). This result suggested that these protons were further wrapped deeply in the cavity of CB[8] during the polymer formation. The ^1H - ^1H NOESY spectrum of the supramolecular polymer (with 1.0 equiv. CB[8]) showed NOE correlations: H_b'' - H_d'' , H_c'' - H_e'' ,

H_h'' - H_j'' , H_h'' - H_i'' , H_k'' - H_a'' (see Figure 2b and Figure S9). The spatial correlation between H_k'' and H_a'' suggested that the distance between them was within 5 Å. So, it can be deduced that the guests were sequentially arranged in a head-to-tail manner and connected by CB[8] to form a supramolecular polymer. Other NOE correlations proved the packing modes of AA and BB units in the supramolecular polymer, but without the AB packing (see Figure 2b). The spatial correlations of H_c'' - H_e'' and H_b'' - H_d'' illustrated two kinds of AA packings. The former one is similar to the AA packing in the ternary complexes, while, in the latter AA packing, one A moved deeply into the cavity until H_a'' and H_b'' were completely wrapped by CB[8]. This configuration is consistent with the large upfield chemical shift of both H_a'' and H_b'' (see the Table in Figure 1). In addition, we simulated the possible structures of supramolecular polymers with the lowest energy through Gaussian molecular simulation (see Figure 2c). The simulated AA packing is just similar to the AA packing deduced by the spatial correlation of H_b'' - H_d'' . This AA packing slightly separates the distance between the two guests compared with the AA packing deduced by the spatial correlation of H_c'' - H_e'' in order to reduce the rigidity and the repulsion force of supramolecular polymer chains. The simulated BB packing is exactly the same as the packing proved by the NOE correlation. Therefore, the possible structure of the supramolecular polymer was inferred as shown in Figure 2b. After the formation of supramolecular polymer, the molecular shuttle motion is restricted to some extent. So, the portals of CB[8] with different charge density led to the splitting of both H_x and H_y in the ^1H NMR spectrum (see Figure 1).

The chemical exchange during supramolecular polymerization. When the CB[8] content was between 0.55 equiv. and 1.0 equiv., there were two sets of well-defined ^1H NMR signals corresponding to ternary complexes and supramolecular polymers, respectively. With the addition of CB[8], the signals from ternary complexes gradually decreased, while the signals from supramolecular polymers increased, indicating that the ternary complexes acted as supra-monomers to propagate into supramolecular polymers. In the ^1H - ^1H NOESY spectrum of CSPP-0.75 equiv. CB[8] (Figure 3 and Figure S12), not only the NOE correlations from the three ternary complexes (H_c' - H_e , H_c' - H_g , H_d' - H_f , H_h' - H_i , H_h' - H_j) and the NOE correlations from the supramolecular polymer (H_h'' - H_i'' , H_h'' - H_j'') were observed, but also the exchange-mediated NOE correlations (H_b'' - H_e'' , H_c'' - H_e , H_b'' - H_d , H_d' - H_f , H_c' - H_g) were found. The appearance of exchange-mediated NOE correlations means that the overhauser effect and the chemical exchange occur simultaneously. Therefore, the ternary complexes and the supramolecular polymers can undergo slow chemical exchange. Moreover, among the ternary complexes, AB¹ could not directly connect to the supramolecular polymer. It was converted to AA and BB through molecular shuttle motion, the latter two then acted as supra-monomers (see the Scheme in Figure 3). Generally speaking, the AA and BB monomers are able to randomly combine with themselves or each other during

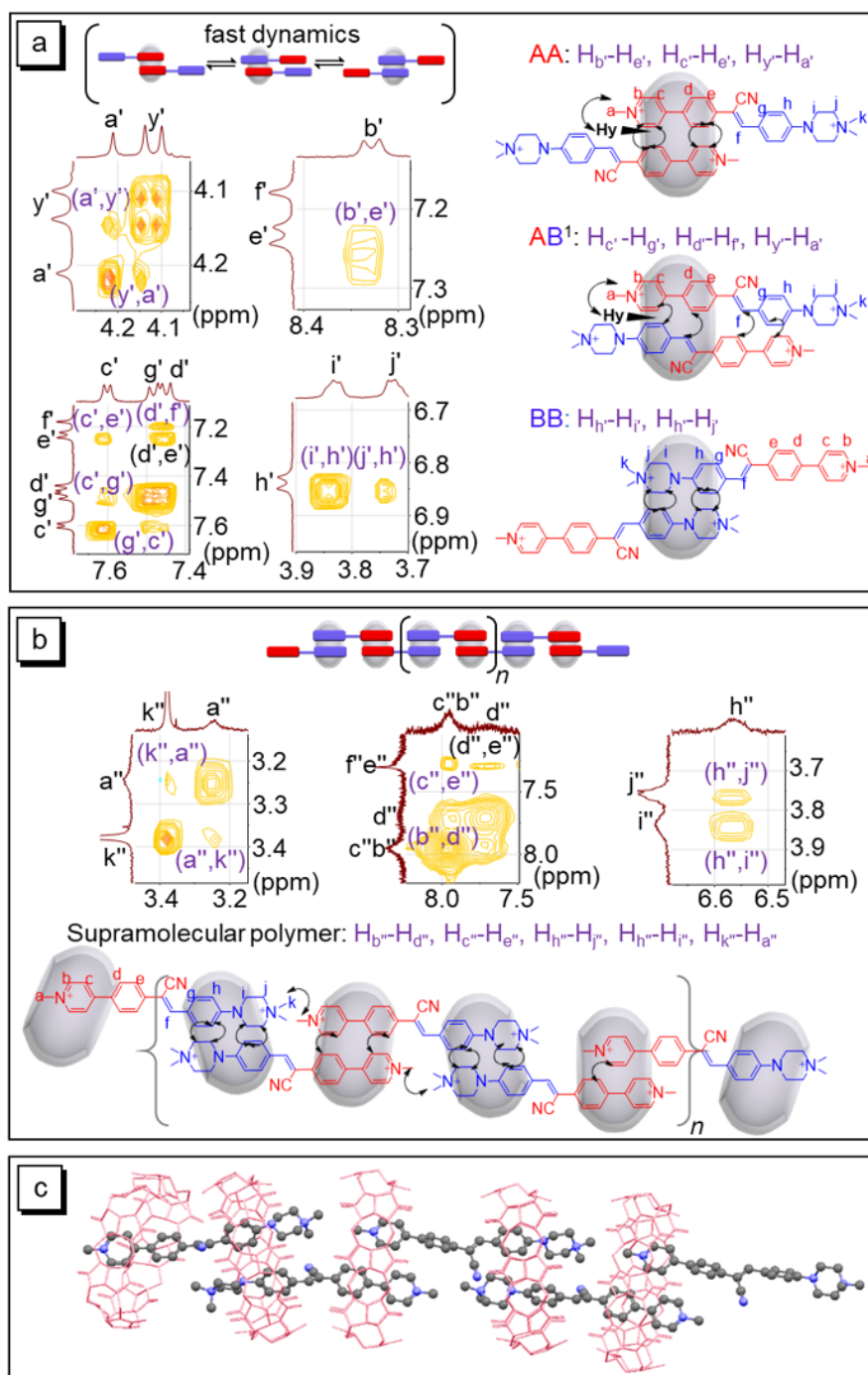


Figure 2. ^1H - ^1H NOESY studies for CSPP-CB[8] complexation in D_2O . (a) The schematic plot of the fast intra-conversion between different ternary complexes, parts of NOESY spectra, and the deduced inter-molecular packing of guests inside the CB[8] cavity when the ratio of CB[8] to CSPP is 0.5. (b) The schematic plot of supramolecular polymer, parts of NOESY spectra and the deduced inter-molecular packing of guests in supramolecular polymer when the ratio of CB[8] to CSPP is 1.0. The concentration of CSPP is 0.8 mM. H-H spatial correlations are indicated with double-headed arrows in the structures. The spatial correlations resulted from molecular packing are marked in purple. (c) Molecular modeling of the CSPP-CB[8] oligomer, where the color of CB[8] is shown in light red for clarity. The geometry was optimized by using the universal force field in Gaussian 09 package.

the supramolecular polymerization. When they bind with themselves, narcissistic self-sorting polymer will be formed. When they bind with each other, social self-sorting polymer will be produced. When they bind with

both themselves and each other, non-absolute self-organized polymer (according to Stang's categorization⁵³) will be formed. Therefore, statistically, three kinds of polymers can be produced (see the Scheme in Figure 3).

However, the ultimately formed polymer only exhibited a sequence of $(-AA-BB-)_n$ (narcissistic self-sorting polymer) when 1.0 equiv. CB[8] was added, as proved in the former part. Actually, the essential structural difference between narcissistic self-sorting polymer and the other two is whether the AB unit exists in the polymer chain or not. To find the reason, the ^1H - ^1H NOESY spectra of CSPP-0.75 equiv. CB[8] and CSPP-0.95 equiv. CB[8] were compared. We found that the related correlation signals of AB packing, such as $\text{H}_c\text{-H}_g$, $\text{H}_c\text{-H}_g''$, $\text{H}_d\text{-H}_f$ and $\text{H}_d\text{-H}_f''$ appeared in the former spectrum but vanished in the latter one (Figure 3, Figure S12 and Figure S14). This result suggested that AB packings were reduced along with the addition of CB[8], which was mainly caused by the consumption of AB^1 ternary complex induced by supramolecular

polymerization. Besides, among the signals, the exchange-mediated NOE correlation of $\text{H}_c\text{-H}_g''$ might come from two ways. It can be derived from the newly formed AB^2 unit in the polymer chain after polymerization by ternary complexes (error in the polymer chain, Figure 3). It can also be derived from the newly formed AB^1 ternary complex after the molecular shuttle motion following the dissociation of a polymer unit (Figure 3). Therefore, the disappearance of $\text{H}_c\text{-H}_g$ correlation indicated that error correction in the polymer chain may occur to some extent.

The mechanism of the self-sorting sequence control of supramolecular polymerization. Why the AB unit disappeared in the final sequence of the supramolecular polymers $(-AA-BB-)_n$? Studies by Isaacs⁵³ and Schalley⁵⁴ showed that the self-sorting systems

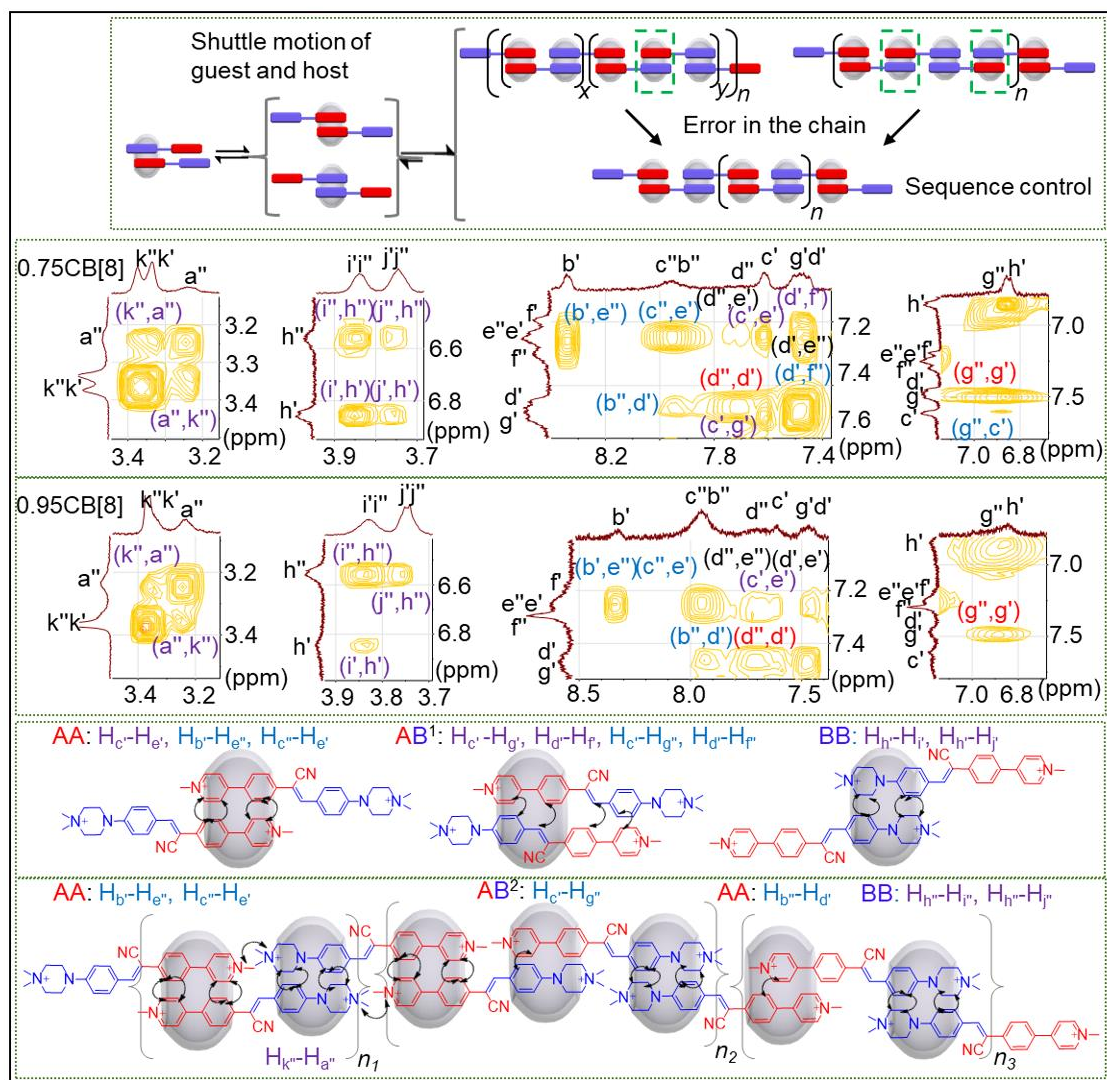


Figure 3. The sequence control during the supramolecular polymerization of CSPP-CB[8] complexes in D_2O studied by ^1H - ^1H NOESY. The schematic plot showing the slow exchange between ternary complexes and supramolecular polymers, and the proposed error corrections of the polymer sequence. Parts of NOESY spectra of CSPP with 0.75 equiv. CB[8] and with 0.95 equiv. CB[8], and the inter-molecular packing of guests in both ternary complexes and supramolecular polymers. The concentration of CSPP is 0.8 mM. H-H spatial correlations are indicated with double-headed arrows in the structures. The spatial correlations resulted from molecular packing are marked in purple, the spatial correlations after chemical exchange are marked in blue and the chemical exchange are marked in red.

evolved into equilibrium where the outcome was thermodynamically controlled. Based on this, we speculate that as the supramolecular polymerization proceeds, the relatively unstable AB² units on the chains probably break up and gradually transform into more stable AA or BB units due to the ever-growing chain rigidity and unfavorable entropy reduction. To figure out the self-sorting between different ternary complexes when forming supramolecular polymers, we try to understand the thermodynamics of the self-sorting systems by using separated A and B as model compounds. Two model compounds, 1-methyl-4-phenylpyridin-1-ium iodide (MPP, denoted as A) and 4-(4-formylphenyl)-1,1-dimethylpiperazin-1-ium iodide (FDPP, denoted as B) were synthesized. The ¹H NMR titration, ¹H-¹H COSY and ¹H-¹H NOESY spectra proved the complexation of the model compounds with CB[8] (Detailed characterization from Figure S16 to Figure S24 were listed in Supporting Information, and the discussion was put under Figure S20). Fortunately, the protons of guests resonated at different frequencies in NMR spectrum when comparing homo-ternary complexes with hetero-ternary complexes. This makes it easy to decipher the self-sorting patterns between model compounds and CB[8]. Remarkably, when the ratio of MPP: FDPP: CB[8] was 1:1:1, the formed CB[8]-based ternary complexes of AA, BB and AB were determined to be 45%, 46% and 9%, respectively (Figure S21b). The amount of AB complex was albeit much less than the AA and BB complexes, but was still considerable. In addition, the ¹H-¹H NOESY spectrum implied that there were two kinds of AB packings: two guests arranged with positive charge on the opposite side or on the same side of CB[8] (Figure S23 and S24). The results of the four kinds of complexation between model compounds and CB[8] confirmed our hypothesis in the previous section that the two supra-monomers (AA and BB) can randomly combine with themselves or each other during the supramolecular polymerization. After the

NMR experiments, we performed the isothermal titration calorimetry (ITC) experiments (Figure S25 and S26). The thermodynamic parameters of the complexation between model compounds and CB[8] were listed in Table 1. According to the research on cooperativity by Prof. Anderson⁵⁵ and Prof. Zhang⁵⁶, it was easy to know that the formation of 2:1 AA-CB[8] complex was non-cooperative ($-0.5 < \log \alpha = 0.23 < 0.5$), while 2:1 BB-CB[8] complex displayed a slightly negative cooperativity ($\log \alpha = -1.05 < -0.5$). Because model compound FPDP (B) carries hydrophobic and bulky side groups (*N,N*-dimethylpiperazium), it released more high-energy water in the cavity and also offered entropy compensation during the first guest binding, leading to higher binding affinity than that of MPP (A) in the first binding (the K_{a1} for BB-CB[8] was $7.81 \times 10^5 \text{ M}^{-1}$, and the K_{a1} for AA-CB[8] was $1.65 \times 10^6 \text{ M}^{-1}$). However, when 1:1 complex continued to form 2:1 ternary complex, it generated a large entropy penalty ($-\Delta S_2 = 16.95 \text{ kJ/mol}$) induced by the first guest B inside cavity, which suppressed the association of the second guest B and also decreased the binding affinity (the K_{a2} for BB-CB[8] was $1.76 \times 10^5 \text{ M}^{-1}$, and the K_{a2} for AA-CB[8] was $6.98 \times 10^5 \text{ M}^{-1}$). When the 1:1 mixture of A and B associated with CB[8] to form 2:1 complex, it showed a negative cooperativity ($\log \alpha = -2.29$), an even larger entropy penalty ($-\Delta S_2 = 32.99 \text{ kJ/mol}$) and a much smaller binding affinity ($K_{a2} = 1.00 \times 10^3 \text{ M}^{-1}$) for the second binding compared to that of 2:1 BB-CB[8] complex. Since the complexation between the mixture (A:B = 1:1) and CB[8] was able to form AA-, BB- and AB-type ternary complexes as proved by the NMR experiments, so the overall thermodynamic parameters were determined by the three-part contribution. Therefore, it is reasonable to speculate that the binding affinity of AB-type ternary complex is substantially weaker than that of AA-type and BB-type ternary complexes. In view of the slightest reduction of Gibbs free energy for AB-type ternary complexes during the second

Table 1. Thermodynamic parameters of the host-guest complexation between model compounds and CB[8] acquired from ITC experiments.

Model complexes	$\log \alpha^a$	$K_{a1} (10^5 \text{ M}^{-1})^b$	$K_{a2} (10^5 \text{ M}^{-1})^b$	ΔH_1 (kJ/mol) b	$-\Delta S_1$ (kJ/mol) b	ΔG_1 (kJ/mol) b	ΔH_2 (kJ/mol) b	$-\Delta S_2$ (kJ/mol) b	ΔG_2 (kJ/mol) b
AA-CB[8]	0.23	16.52	6.98	-27.93	-7.55	-35.48	-30.82	-2.54	-33.36
BB-CB[8]	-1.05	78.13	1.76	-32.97	-6.37	-39.34	-46.90	16.95	-29.95
A:B = 1:1 with CB[8]	-2.29	7.78	0.01	-42.19	8.56	-33.63	-50.14	32.99	-17.15

^a Interaction parameter ($\log \alpha$) is calculated on the basis of $\alpha = 4K_2/K_1$ to describe the cooperativity in a quantitative manner.^{55,56} When $\log \alpha > 0.5$, the system displays positive cooperativity; When $\log \alpha < -0.5$, the system displays negative cooperativity; When $0.5 > \log \alpha > -0.5$, the system is noncooperative. ^b K_{a1} and K_{a2} are macroscopic stepwise binding constants. ΔH_1 , ΔS_1 and ΔG_1 are the binding enthalpy, binding entropy and the Gibbs free energy change for the first step. ΔH_2 , ΔS_2 and ΔG_2 are the binding enthalpy, binding entropy and the Gibbs free energy change for the second step. ΔG is calculated through the equation: $\Delta G = \Delta H - T\Delta S$.

binding (Table 1), it can also be inferred that the thermodynamic stability of AB-type ternary complexes is much less than that of AA-type and BB-type ternary complexes. In addition, when the 1:1 mixture of A and B interacted with CB[8], it still had 9% possibility to produce AB hetero-complexes as proved previously, but the supramolecular polymerization decreased the possibility of the formation of AB hetero-complex unit in the final polymer chain to nearly zero (below the resolution of NMR). Hence, it suggests that the supramolecular polymerization promotes error correction during the process of polymerization.

In addition, the ITC titration experiment of CSPP and CB[8] was also measured as shown in Figure S27. The supramolecular polymerization was unfavorable in entropy with an entropic change of -96.2 J/mol·K. And the overall binding enthalpy was -64 kJ/mol, which is consistent with that of reported ternary complexes and the computational enthalpy changes when two guests occupy the cavity of CB[8] to completely dehydrate the cavity.⁵⁰ Except that, it showed a stoichiometry ratio of 1:1 and a high binding affinity (1.39×10^6 M⁻¹).

Therefore, the mechanism behind the self-sorting sequence control is elucidated by ITC experiments. As the increase of the molecular weight and the chain rigidity of supramolecular polymers, the ever-growing unfavorable entropy reduction during the polymer propagation leads

to the breakage of the polymer chain at the relatively unstable AB² unit due to the dynamic nature of host-guest interactions. Then, the disconnected position becomes a chain end or re-polymerizes to form an AA or BB unit in the polymer chain (see the Scheme in Figure 3). Therefore, through the dynamic supramolecular breaking and binding, the thermodynamic corrects the assembly errors during the polymerization process. As a result, the sequence control of supramolecular polymer is smartly achieved.

Supramolecular polymerization studied by UV-Vis and fluorescence spectroscopy. The supramolecular polymerization process was further evaluated by UV-Vis and fluorescence spectroscopy (Figure 4). The fluorescence spectra showed that with the addition of CB[8], the fluorescence intensity gradually increased and two inflection points appeared (Figure 4a and 4c). The first inflection point was around 0.5, indicating the formation of the ternary complexes of CSPP and CB[8]. After addition of more than 0.5 equiv. CB[8], supramolecular polymer began to produce. Since both ends of the AIEgens were encapsulated by CB[8] in the polymer chain, the molecular motion was greatly restricted, leading to the large suppression of nonradiative decay. Thus, the AIE property of supramolecular polymer was more obvious than that of supra-monomers to result in greatly enhanced fluorescence. Then, the emission intensity went to an equilibrium after ~ 1.0 ratio, meaning that the supramolecular polymer was completely formed. In addition, the absorption

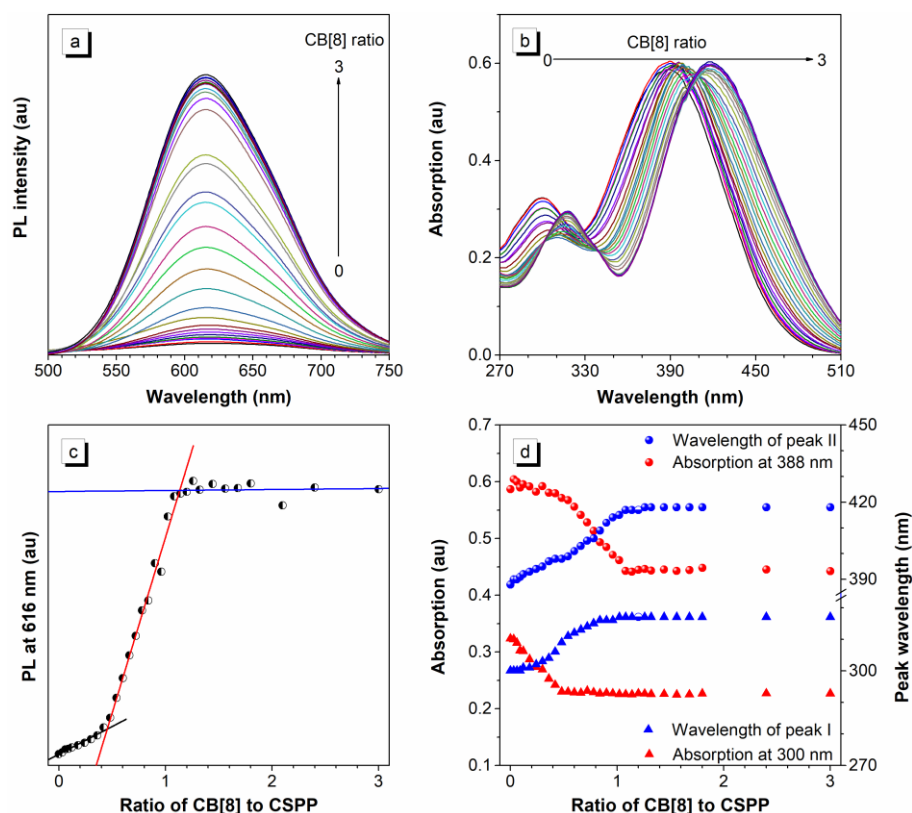


Figure 4. (a) Fluorescence emission and (b) UV-Vis absorption spectra of CSPP (20 μ M) upon increasing the concentration of CB[8] in aqueous solution, $\lambda_{\text{ex}} = 405$ nm. (c) The change of PL intensity at 616 nm as the increase of CB[8] ratio. (d) The absorption change of CSPP at 300 nm (peak I, red triangle) and at 388 nm (peak II, red circle) and the maximum wavelength change of peak I (blue triangle) and peak II (blue circle) as the increase of CB[8] ratio. “PL” is short for “photoluminescence”.

curves of both CSPP and supramolecular polymer showed two peaks (Figure 4b). With the progress of supramolecular polymerization, the absorbance of both the peak I (at 300 nm) and the peak II (at 388 nm) of CSPP decreased gradually. And the absorbance of peak I reached to an equilibrium after ~ 0.5 ratio, but the absorbance of peak II reached to an equilibrium after ~ 1.0 ratio as shown in Figure 4d. Besides, along with the supramolecular polymerization, the maximum absorption wavelength of peak I gradually redshifted from 300 nm to 317 nm, and that of peak II redshifted from 388 nm to 418 nm. Both peak wavelength remained unchanged after CB[8] ratio was above ~ 1.0 (Figure 4d). The absorption redshift is due to the host-enhanced π - π interaction during the supramolecular polymerization. However, the change of the maximum emission wavelength during the supramolecular polymerization was very small, and it just blue-shifted from 622 nm of pure CSPP to 616 nm (Figure 4a). This is because the supramolecular polymerization extends π - π conjugation to induce emission red-shift. At the same time, the guests are wrapped by the hydrophobic cavity of CB[8] to lead to emission blue-shift. Besides, the emission peak is very broad, making the small emission shift imperceptible. In a word, the change of the emission wavelength caused by the two opposite factors is not obvious when the emission peak is very broad.

In addition, we also reduced the concentration of the supramolecular polymer to check whether the inflection points would change or not (Figure S28). As expected, it also exhibited the same results of UV-Vis and fluorescence spectra as that of the concentration used here.

Supramolecular polymerization studied by other techniques. We also performed other experiments to further confirm the successful formation of supramolecular polymers. The diffusion-ordered NMR spectroscopy (DOSY) experiments showed that the diffusion coefficient

of the supramolecular polymer ($1.93 \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$) decreased compared with that of the pure guest ($3.79 \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$) and that of the ternary complexes ($2.64 \times 10^{-10} \text{ m}^2 \cdot \text{s}^{-1}$), suggesting that the enlarged particle size was resulted from the formation of supramolecular polymers (Table S1, Figure S29, S30 and S31). And the diffusion coefficient of the supramolecular polymer is similar to that of other CB[8]-based supramolecular polymers in references.^{14,51,57} Dynamic light scattering (DLS) was applied to measure the hydrodynamic diameter of the supramolecular polymer at different concentrations. Results showed that when the concentration of the supramolecular polymer increased, the hydrodynamic diameter gradually increased due to the increase of polymerization (Figure S32). An equilibrium was reached at $\geq 200 \mu\text{M}$ and the particle size was close to 300 nm, confirming the formation of high-molecular-weight supramolecular polymers. The weight molecular weight of 0.5 mM of 1:1 CSPP-CB[8] complexes in 50 mM sodium acetate buffer (pH 4.75) was 43.4 ± 17.3 kDa with a radius of gyration of 182 nm measured by static light scattering. The self-assemblies of CSPP-CB[8] polymer were characterized by SEM, TEM and fluorescence microscopy. TEM image (Figure 5c) displayed small rectangular strips with a length of 20–50 nm. SEM (Figure 5a and 5b), fluorescence (Figure 5d) and brightfield (Figure 5e) images exhibited red-emissive large strips around 5–20- μm 's long, which were not rectangular at both ends. This may be resulted from the heterogeneous growth of larger self-assembly. The grazing incidence wide-angle X-ray scattering (GIWAXS) measurements provided essential information about the structure stacking of CSPP-CB[8] self-assembly (Figure 5f). Several diffraction peaks were observed, giving a d spacing of 17.92, 13.66, 12.37, 10.07, 8.48, 6.86, 6.17, 4.70 and 3.66 Å, which indicated the presence of periodic structure stackings. In particular, the peak observed at 17.92 Å corresponded to the distance between two neighboring polymer chains as

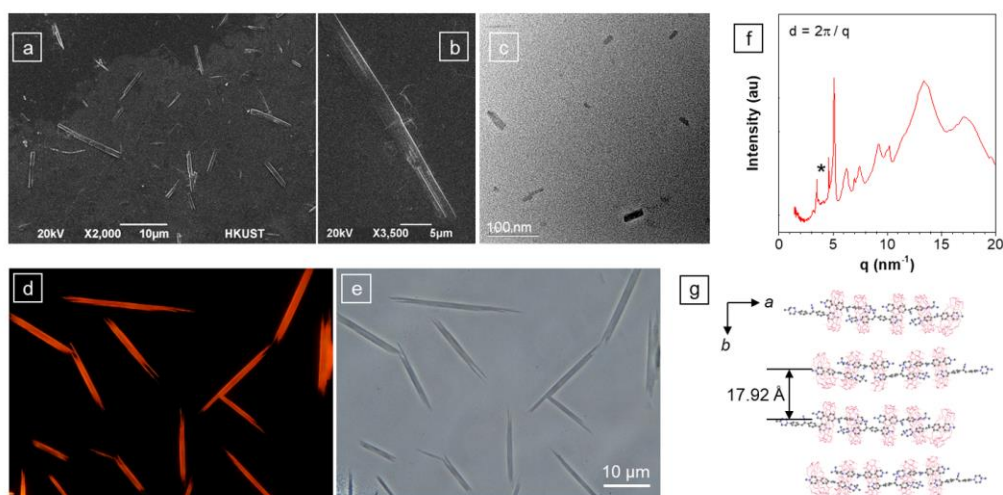


Figure 5. (a, b) The SEM images, (c) TEM image, (d) fluorescence image and (e) bright-field image of CSPP-CB[8] self-assemblies from 10 μM (1:1 molar ratio) aqueous solution. (f) Grazing incidence wide-angle X-ray scattering profile of the CSPP-CB[8] self-assemblies. The peak marked with an asterisk gives a spacing d of 17.92 Å. (g) Schematic representation of proposed parallel stacking layer of supramolecular polymers (on ab plane).

shown in the representative 2D stacking pattern of the linear supramolecular polymers (Figure 5g). The distance was very close to those found in other CB[8]-based linear supramolecular polymers.^{14,58} Therefore, we can conclude that the self-assembly of CSPP-CB[8] polymers is red-emissive 3D strips made by parallel stacking of the linear supramolecular polymers.⁵⁹ On the contrary, the self-assembly of CSPP was orange-emissive long fibers (Figure S33). Furthermore, we measured the fluorescence lifetime of the lyophilized supramolecular polymer powder. The fluorescence lifetime was 3.0 ns for the supramolecular polymer, while only 0.6 ns for pure CSPP (Table S2 and Figure S34). The fluorescence quantum yield of the supramolecular polymer in an aqueous solution of 10 μM was 2.6%, which was 3.7 times of that of CSPP solution (Table S2). The fluorescence quantum yield of the supramolecular polymer powder was 16.9%, which was 4.8 times of that of CSPP powder (Table S2 and Figure S34). Therefore, those techniques for studying the supramolecular polymerization have further confirmed the successful formation of supramolecular polymers.

Drug detection by using the supramolecular polymers. Thanks to the AIE property of the guest, it showed higher emission after being polymerized with CB[8] in aqueous solution than the emission when mo-

lecularly dissolved. So, it's very suitable to be used in molecular detection. Then, we try to explore its applications in drug detection. Conventional chromatographic techniques, mass spectrometry, Raman and FTIR spectrometry are very time-consuming, expensive and not applicable to on-site monitoring, as well as require many clean-up steps and trained personnel.^{60,61} However, fluorescence method is simple, rapid, sensitive, convenient to carry and suitable for on-site detection. Heroin and morphine are well-known narcotic drugs that belong to a class of drugs known as opioids.⁶² As illustrated in Figure 6a, the fluorescent indicator displacement assay was applied to measure the dissociation constants of drug with CB[8] and also to detect the drug. The association constants of morphine and heroin with CB[8] were equal to $3.85 \times 10^6 \text{ M}^{-1}$ and $1.16 \times 10^5 \text{ M}^{-1}$, respectively (Figure 6b). Although their structures are very similar, the association constant of morphine with CB[8] is 32-times larger. Because the association constant of the supramolecular polymer is exactly between those of the two drugs with CB[8], the two similar structures can be distinguished in a low concentration range (less than 10 μM of drug). Since morphine is the primary metabolite of heroin and codeine, so the presence of morphine in urine indicates the exposure to morphine, heroin, or codeine within 2 to 3 days.⁶³ Hu-

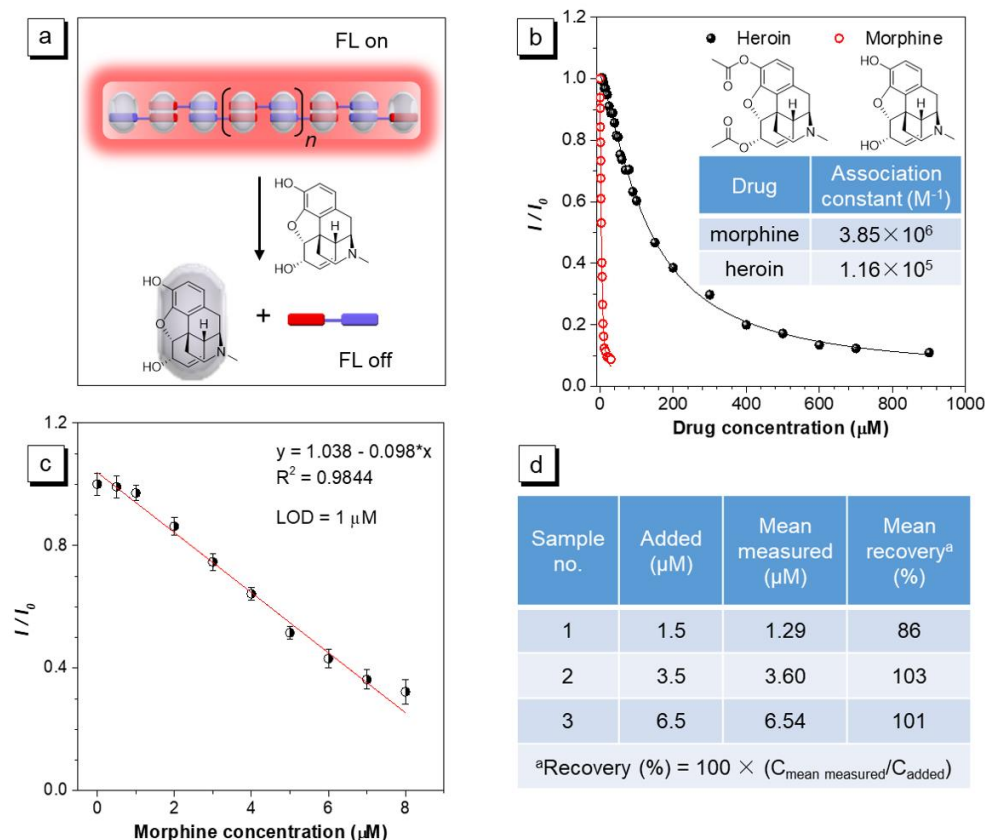


Figure 6. (a) Scheme of fluorescent indicator displacement assay for drug detection. Herein, morphine is used as an example. “FL” is short for “fluorescence”. (b) The relative fluorescence intensity change of CSPP-CB[8] complexes in water at 616 nm upon morphine competition or heroin competition for CB[8]. The structures of morphine and heroin and their association constants measured by fluorescence method are listed. (c) Calibration curve for morphine detection in 10% artificial urine; (d) The table for the detection of morphine spiked in artificial urine samples ($n = 3$). The practical application of this method in complex biological matrix was studied by determining the recovery of target morphine spiked in 10% diluted artificial urine samples. The concentration of CSPP and CB[8] are both 10 μM .

man urine is a complex medium comprising electrolytes, small molecules and up to 1500 different proteins, which can make the analysis less effective. Therefore, developing a stable red-emissive supramolecular probe for detection of morphine in urine is highly demanded. Our probe gave a maximum emission at 616 nm when being excited at 405 nm. The emission of the supramolecular probe excellently ruled out the influence of the autofluorescence of proteins (BSA and FBS) with a maximum emission of 464 nm (Figure S35). To study the stability of the supramolecular probe, we tested whether the probe can detect morphine in the presence of PBS, urea, uric acid, artificial urine, creatinine or BSA (Figure S36). The results showed that in the presence of these interfering substances, the addition of morphine into the supramolecular probe still caused more than 70% changes of fluorescent signal. Then, we measured the standard curve of morphine in 10% artificial urine solution (Figure 6c), which showed a LOD of 1 μ M. And the measured concentration was between 86% and 103% of the actual concentration (see the Table in Figure 6d). So, the supramolecular probe has considerable stability, sensitivity and accuracy.

CONCLUSION

In summary, we have successfully prepared a narcissistic self-sorting supramolecular polymer with a sequence of $(-AA-BB-)_n$ by using CB[8]-based ternary complexes as supra-monomers, which were spontaneously formed from starting materials of heteroditopic AB-type guest and CB[8]. There are two steps for the supramolecular polymerization along with the addition of CB[8] as demonstrated by the ^1H NMR, UV-Vis and fluorescence titration experiments. The structural changes at each stage of polymerization are clearly demonstrated by the ^1H - ^1H COSY, ^1H - ^1H NOESY and ^1H - ^1H ROESY spectra. The first step is the formation of ternary complexes, among which the homoditopic AA and BB ternary complexes are further employed as supra-monomers. The second step is the supramolecular polymerization by using supra-monomers. The formation of supramolecular polymers is further confirmed by the results of DOSY, DLS, SLS and the self-assembly of CSPP-CB[8] complexes. The mechanism behind the self-sorting sequence control is elucidated by ITC experiments. And it proved that the binding affinity and the thermodynamic stability of AB unit is much less than that of AA and BB unit. During the supramolecular polymerization, AB unit appears to some extent, but it is broken up and transformed into stable AA and BB units as the increase of chain rigidity and unfavorable entropy reduction of supramolecular polymers, finally leading to the formation of narcissistic self-sorting supramolecular polymers with a sequence of $(-AA-BB-)_n$. Therefore, the sequence control is attributed to the dynamic supramolecular interactions and the thermodynamic stability. This supramolecular polymerization provides an innovative way for designing sequence-controllable supramolecular polymers using heteroditopic AB-type guests and CB[8]. And the method is anticipated to shed light on the construction of more kinds of supra-

molecular polymers in the future, such as constructing highly emissive supramolecular polymers, dendrimers or hydrogels with long emission wavelength. In addition, the supramolecular polymer as a probe can distinguish heroin and morphine (opioids with similar structures). And it can detect morphine in artificial urine with considerable stability, detection sensitivity and accuracy. Hence, the red-emissive supramolecular polymer enriches the library of the luminescent guests of CB[8] in the field of small molecule detection.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.

Materials and Methods; Associated NMR spectra, ITC data, fluorescence and UV-Vis supplemented data, DOSY data, DLS data, fluorescence quantum yield and fluorescence lifetime, supplemented data for drug detection. (PDF)

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Notes

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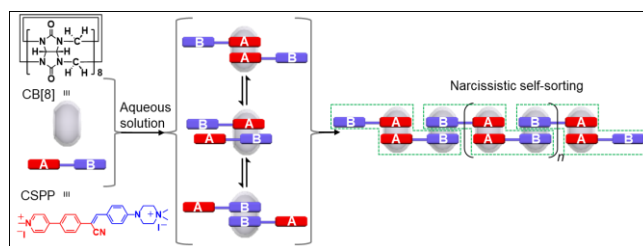
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