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Amide naphthotubes: Biomimetic macrocycles for selective molecular recognition

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ABSTRACT

Selective molecular recognition in water is routine for bioreceptors, but remains challenging for synthetic hosts. This is principally because noncovalent interactions are usually less efficient in aqueous environments. By mimicking the cavity feature of bioreceptors, Prof. Wei Jiang proposed and clarified the concept of "endo-functionalized cavity". Through situating polar binding sites into a deep hydrophobic cavity, we designed and synthesized several macrocyclic hosts, among which amide naphthotubes are the most representative. The hosts can selectively recognize various polar molecules including organic micropollutants, drug molecules, and chiral molecules in water by employing the hydrophobic effect and shielded hydrogen bonding. In addition, these biomimetic hosts have been applied in spectroscopic analysis, adsorptive separation and self-assembly. In this review, we provide an overview of recent advances on amide naphthotubes with special emphasis on the efforts of Jiang's group. We are convinced that these biomimetic macrocycles will make further contributions to supramolecular chemistry and beyond.

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1. Introduction

Selective molecular recognition in water is ubiquitous in nature and responsible for almost all biological functions [1]. However, it remains challenging for artificial hosts to realize satisfactory selective recognition in water, as it is difficult for them to recognize the polar functional groups of the guest molecules by using non-covalent bonds [2–4]. The reasons are as follows: (a) Non-covalent binding sites are exposed to the solvent and competed by water molecules in aqueous media; (b) The high polar environment will seriously weaken the non-covalent bonds such as hydrogen-bonding interactions between the host cavity and guest molecules; (c) Polar functional groups are highly solvated in water, requiring high energy to compensate for the desolvation process [5]. Herein, it is usually difficult for synthetic hosts to achieve precisely binding polar organic molecules or functional groups in water. This seriously impedes the application of artificial molecular recognition in chemical biology, environmental science, biomedicine and other fields.

In contrast, biological receptors can effectively utilize polar non-covalent bonds including hydrogen bonding interactions in water to differentiate distinct functional groups of substrate molecules [6]. This is primarily because their deep binding cavities are highly hydrophobic and contain polar binding sites like hydrogen-bonding sites. The interior of the bioreceptor cavity has a low dielectric constant and is relatively isolated from the external environment. Therefore, non-covalent interactions like hydrogen bonding can effectively operate within the binding pockets, allowing for selective molecular recognition when combined with the hydrophobic effect [7]. To mimic the binding pockets of bioreceptors, Prof. Jiang proposed the concept of "endo-functionalized cavity" [8,9], which involves implanting hydrogen bonding sites into a deep hydrophobic cavity for the construction of endo-functionalized macrocyclic hosts (Fig. 1). In this way, the hydrophobic cavity provides a relatively non-polar environment for hydrogen bonding interaction and avoids the competition of water molecules, thus the synergistic effect between hydrophobic effect and hydrogen bonding interactions will greatly enhance the affinity and selectivity between host and guest molecules.

To construct a deep hydrophobic cavity in water, a rigid curved skeleton is required. The bis-naphthalene cleft (Scheme 1a), initially introduced by Whitesides in 1982 [10], is ideal for constructing macrocyclic hosts due to its rigid and well-defined curvature. By covalently linking the two curved skeletons, a macrocyclic host

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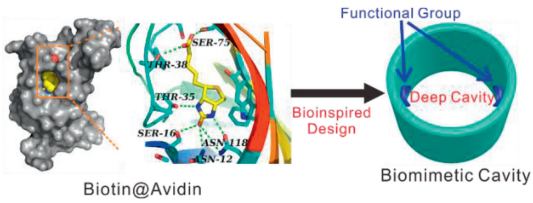
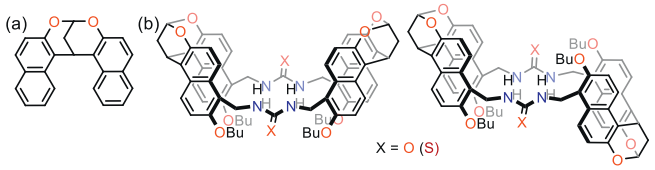


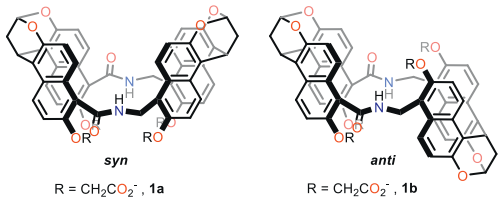
Fig. 1. Bio-inspired concept: *endo*-functionalized cavity. Reproduced with permission [13]. Copyright 2020, American Chemical Society.



Scheme 1. Chemical structures of bis-naphthalene cleft (a) and (thio)urea naphthotubes (b).

featuring a deep hydrophobic cavity can be constructed. Jiang and co-workers first developed some macrocyclic hosts with inward-pointed hydrogen bonding sites like urea or thiourea (Scheme 1b), and realized selective recognition of neutral molecules in the organic solvent [8,9,11]. These hosts share tube-like structures and are constructed from naphthols, we thus call them "naphthotube" [12,13]. However, efforts to synthesize water-soluble (thio)urea naphthotube are unavailing as they tend to aggregate in aqueous media, which limits the further investigation of their recognition abilities in aqueous solution.

Actually, Glass and colleagues synthesized a pair of macrocycles using bis-naphthalene in 2004, they possess good water solubility and can be used for fluorescent sensing of lipids in water (Scheme 2) [14]. However, the inward-directed amide protons were proved to be adverse for the recognition and were optimized to allyl groups to reduce conformational freedom [15]. We think that Glass receptors are exactly fitting with our conception of "endo-functionalized cavity" and classed as amide naphthotubes, the inward-directed amide protons would play an active role in recognizing functional organic molecules, we thus further investigated their molecular recognition behaviors [16]. They are truly able to achieve selective recognition of various polar molecules including chiral compounds [17], drug molecules [18], fluorescent dyes [19], and polar organic pollutants [20] in water. Moreover, the synthetic hosts have been applied in various areas such as spectroscopic analysis, adsorptive separation, water treatment and self-assembly, which significantly expands the application scope of artificial molecular recognition. In this review, we provide a summary about recent research efforts on amide naphthotubes, their unique molecular recognition behavior and wide applications are reviewed, and the lessons and experience learned from these biomimetic macrocycles are discussed as well.

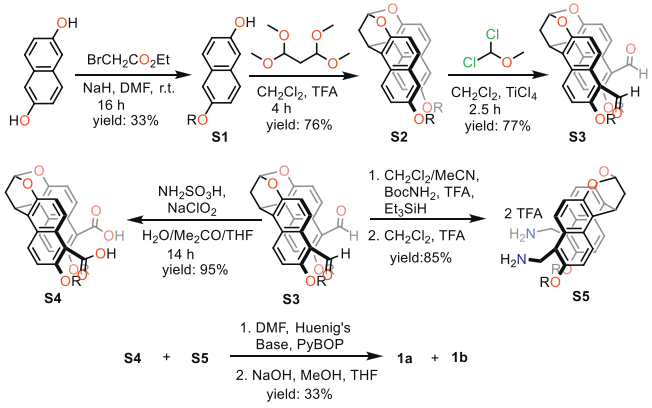


Scheme 2. Chemical structures of amide naphthotubes **1a** and **1b**.

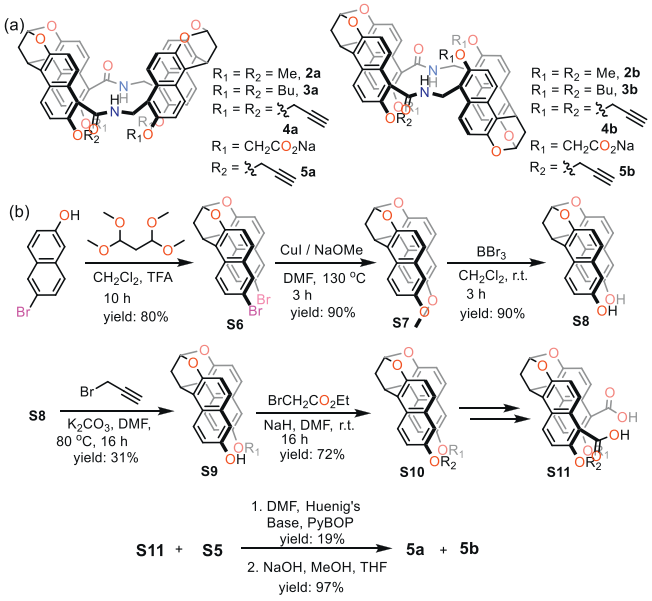
2. Synthesis

Amide naphthotubes were initially prepared with 2,6-naphthalenediol as the starting material (Scheme 3) [14]. The successful application of the bis-naphthalene cleft in the construction of a macrocycle depends on the introduction of an alkoxyl group to the bis-naphthalene cleft which can activate the α-position on each naphthalene moiety, thereby facilitating the production of dialdehyde **S3** through electrophilic formylation of bis-naphthalene **S2**. Then diacid **S4** and diamine **S5** can be obtained by oxidation or reductive amination of **S3**. For the macrocyclization processes, two configurational isomers were obtained which were further separated and purified by column chromatography. However, the polarities of the two isomers are very near, and column chromatography is inefficient and not suitable for large-scale preparation. We later optimized the separation methods for the diastereomers, effectively achieving separation by washing the mixture with different solvents [21].

With this improved separation method in hand, amide naphthotubes can be prepared in gram-scale, and we further synthesized amide naphthotubes with various side chains (Scheme 4a) [20,22], which provides the material foundation for further inves-



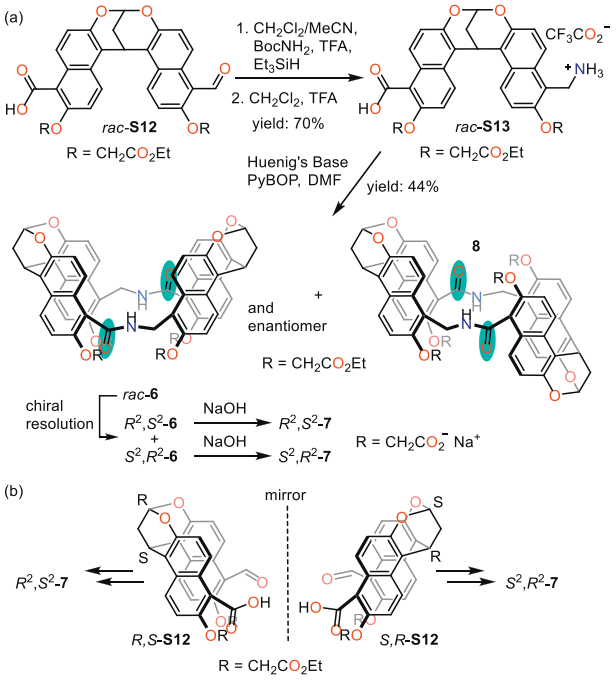
Scheme 3. Synthetic procedures for amide naphthotubes **1a** and **1b**.



Scheme 4. (a) Chemical structures of amide naphthotubes **2**–**5**. (b) Synthetic route for mono-functionalized amide naphthotubes.

tigating the recognition behavior and expanding their applications. Moreover, the starting material 2,6-dihydroxynaphthalene is prohibitively expensive. We thus investigated and found that the more affordable 6–bromo-2-naphthol can be used as a substitute for producing amide naphthotubes [23]. The synthetic procedure from 6–bromo-2-naphthol is depicted in Scheme 4b. With this more economical starting material, we synthesized mono-alkyne functionalized amide naphthotubes (**5a**, **5b**), allowing the introduction of functional groups for further applications.

For *syn* configurational amide naphthotube isomer **1a**, it is possible to generate its chiral analogue by relocating one carbonyl group from one bis-naphthalene to another, as this adjustment causes the quaternary carbon centers on the acetal bridges to become chiral. We developed two strategies for constructing the chiral hosts: "chiral separation" strategy and "chirality-directed macrocyclization" strategy (Scheme 5) [24]. *Rac*-**S12**, a racemic mixture containing one carboxylic acid and one aldehyde group, is a key intermediate for both strategies. For the first approach, *rac*-**S12** was directly converted to *rac*-**S13**, which contains one carboxylic group and one protonated aminomethyl group. Self-macrocyclization of *rac*-**S13** under pseudo-dilution condition results in the formation of two isomers with different configurations: *rac*-**6** and **8**. Chiral separation of *rac*-**6** by chiral HPLC affords enantiopure R^2,S^2–**6** and S^2,R^2–**6**. However, a large amount (26%) of unwanted achiral isomer **8** was yielded for this method. Fortunately, the formation of achiral **8** can be totally avoided through a "chirality-directed macrocyclization" strategy. During this strategy, *rac*-**13** was firstly separated by chiral HPLC, and then the enantiopure compounds were converted to the corresponding *R,S*-**13** or *S,R*-**13**. Then self-macrocyclization of each isomer gives enantiopure *syn*-configurational isomers R^2,S^2–**6** or S^2,R^2–**6** with single chirality. Hydrolysis of R^2,S^2–**6** and S^2,R^2–**6** gives the corresponding water-soluble naphthotube R^2,S^2–**7** and S^2,R^2–**7**.



Scheme 5. Synthetic route for chiral amide naphthotubes R^2,S^2–**7** and S^2,R^2–**7** by "chiral separation" strategy (a) or "chirality-directed macrocyclization" strategy (b). This figure has been published in CCS Chemistry [2020], [Enantioselective Recognition of Neutral Molecules in Water by a Pair of Chiral Biomimetic Macrocyclic Receptors] is available online at [DOI: 10.31635/ccschem.020.202000160].

3. Molecular recognition

Hydrophilic molecules are seriously solvated in aqueous media, and the recognition of hydrophilic molecules needs to compensate for high desolvation energy. Therefore, the precise recognition of hydrophilic chemicals in water is a recognized challenging problem in supramolecular chemistry. It is revealed that amide naphthotubes can effectively bind hydrophilic solvents such as 1,4-dioxane, DMF, DMSO, and THF in aqueous media, exhibiting high association affinity and selectivity [16]. For example, the binding constant of **1b** to 1,4-dioxane is as high as 10^4 L/mol, compared to only 210 L/mol for 1,3-dioxane and 68 L/mol for the more hydrophobic tetrahydropyran. These findings suggest that the amide naphthotubes with biomimetic cavities exhibit bioreceptor-like recognition properties, enabling them to "read" the position information of functional groups of guest molecules and distinguish subtle differences in molecular structure in water.

The binding thermodynamics and driving forces exhibited by amide naphthotubes are quite unique [13,25]. The binding process is mainly driven by enthalpic contribution while the contribution of entropy is relatively small, accompanied by a weak enthalpy-entropy compensation. The main driving forces are the shielded hydrogen bonding interactions and the hydrophobic effect that releases "high energy water" from the cavity. Direct evidence of the hydrogen bonding interactions comes from the single crystal structure analysis, which showed that two hydrogen bonds formed between 1,4-dioxane and amide naphthotubes (Fig. 2a). ^{1}H NMR experiments conducted in H_2O:D_2O (9:1) also reveal the formation of hydrogen-bonds between the host and the guest. Additionally, the binding constant in chloroform is significantly lower than that in water, indicating the essential role of the hydrophobic effect. Molecular dynamics simulations (Fig. 2b) revealed that free host **1b** can hold 3–4 water molecules, with an average number of 2.67 hydrogen bonds per one water molecule, which is lower than that in bulk water (3.62). Host-guest binding leads to the release of "high-energy water" from the hosts, enabling the formation of more hydrogen bonds, thus facilitating bonding. Furthermore, we also investigated the effect of high pressure on this biomimetic molecular recognition system, which showed that pressure increased the binding constant of **1a** but decreased that of **1b**, and the hydrogen bond between host and guest was more difficult to compress than the hydrogen bond between solvent and water [26].

Organic molecules often contain both hydrophobic and polar functional groups, making it challenging to fully recognize them. We thus used organic molecules with phenyl and polar functional groups to compare the recognition properties of cucurbit[7]uril (CB7), β-cyclodextrin (β-CD) and amide naphthotubes [18]. The study revealed that amide naphthotubes can effectively bind these neutral molecules with higher binding strength compared to the other two hosts. β-CD showed low binding constants and selectiv-

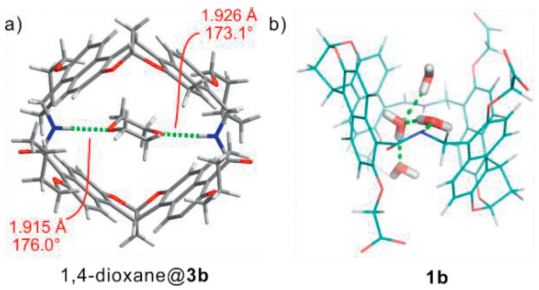


Fig. 2. (a) X-ray single-crystal structure of 1,4-dioxane@**3b**. (b) Representative molecular dynamics snapshot of **1b** in water. Reproduced with permission [13]. Copyright 2020, American Chemical Society.

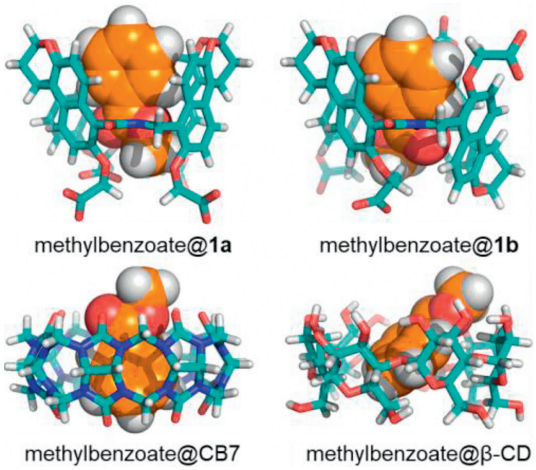


Fig. 3. Energy-minimized structures of complexes of **1a**, **1b**, CB7 and β-CD with methylbenzoate calculated by the DFT in water at 298 K. This figure has been published in CCS Chemistry [2020], [Biomimetic Recognition of Organic Drug Molecules in Water by Amide Naphthotubes] is available online at [DOI: 10.31635/ccschem.020.202000288].

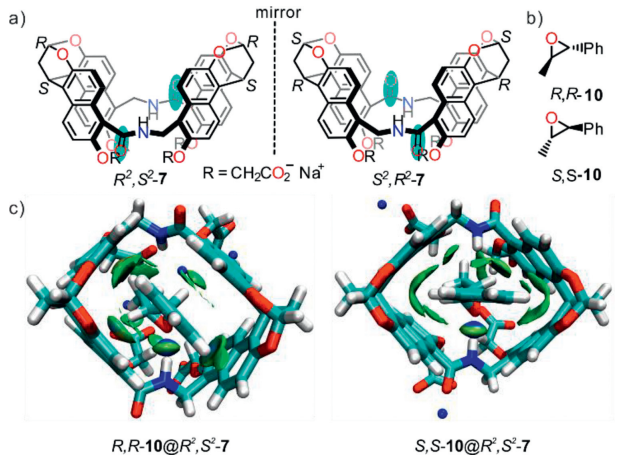


Fig. 5. Chemical structures of (a) chiral amide naphthotubes R^2,S^2–**7** and S^2,R^2–**7** and (b) the chiral guest *R,R*-**10** and *S,S*-**10**. (c) Independent gradient models of optimized structures of *R,R*-**10**@R^2,S^2–**7** and *S,S*-**10**@R^2,S^2–**7** in H_2O. This figure has been published in CCS Chemistry [2020], [Enantioselective Recognition of Neutral Molecules in Water by a Pair of Chiral Biomimetic Macrocyclic Receptors] is available online at [DOI: 10.31635/ccschem.020.202000160].

ity as it only binds hydrophobic phenyl. CB7 exhibited intermediate binding strength and selectivity mainly depends on hydration energy of the guest. The calculated results reveal that β-CD only binds hydrophobic phenyl groups, while CB7 can partly accommodate polar functional groups but lacks the capability to form effective non-covalent interactions with them. In contrast, amide naphthotubes can entirely recognize these guests and hydrogen bonding interactions with functional groups of guest molecules are formed (Fig. 3). Therefore, it can be concluded that guest molecules preferentially recognized by amide naphthotubes typically have the following characteristics: they are either hydrophilic small molecules that well-match the hydrogen bonding sites of the host, or organic molecules with hydrophobic phenyl groups and additional hydrogen bonding receptor sites, these organic molecules generally possess small or slender structures that fit the cavity of amide naphthotubes. Some drug molecules share these characteristics and can be well recognized by amide naphthotubes with the highest binding constant up to 10^6 L/mol.

The development of water-soluble hosts with pH-responsive characteristic is a challenging yet important task [27]. Recently, Jiang designed and synthesized a pair of pH-responsive water-soluble naphthotubes that contain amide and amine groups inside their cavity [28]. The amine group can be either protonated or deprotonated (Fig. 4a), modifying the cavity's features

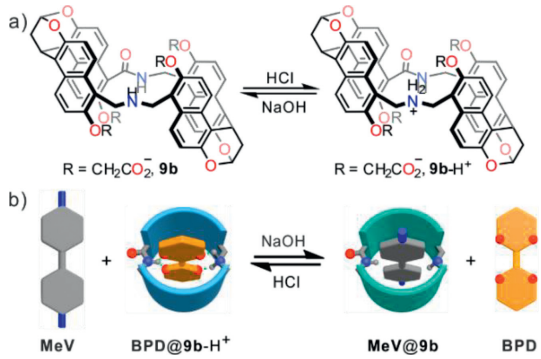


Fig. 4. (a) pH-induced protonated and deprotonated interconversion of **9b**. (b) Schematic illustration of switchable molecular recognition. Reproduced with permission [28]. Copyright 2022, Springer Nature.

and guest-binding preferences in water. These naphthotubes exhibit significantly different binding behavior toward guests at different pH values, which can be easily adjusted by controlling the pH value in the mixture. The pH-responsive characteristics of these hosts can be demonstrated in a ternary mixture, in which two guests 2,2′-bipyrimidine (BDP) and methyl viologen (MeV) can selectively enter the host's cavity by adjusting the pH value because of the differences in charge effect, hydrogen bonding and hydrophobicity of the two host states (Fig. 4b). These bio-inspired hosts with controllable and selective recognition behaviors at different pH values have promising applications in areas such as controlled assembly materials and water-soluble molecular machines.

Enantioselective recognition is a key feature of biomolecule recognition. Bio-receptors typically have binding sites with a chiral environment, leading to high recognition selectivity for chiral substrates. However, synthetic receptors still face significant challenges in achieving aqueous chiral recognition [29]. By introducing the chiral environment into amide naphthotube, we synthesized a pair of chiral hosts (R^2,S^2-**7** and S^2,R^2-**7**) that can achieve chiral molecular recognition in water with good selectivity (Fig. 5a) [24]. They can selectively recognize small chiral molecules, such as epoxy (for example, *R,R*-**10** and *S,S*-**10**), acetal, and oxazoline, in water (Fig. 5b). The study of solvent effects revealed that the hydrophobic effect has a very low impact on chiral recognition. DFT calculations supported the "three-point contact" model, which identified the difference between C–H$\cdots\pi$ and hydrogen bonding interactions are the main driving force for the enantioselective recognition (Fig. 5c). This chiral recognition system demonstrates that the concept of "endo-functionalized cavity" can also be used for enantioselective recognition in water, providing an important reference for the development of more selective chiral recognition systems.

4. Applications

4.1. Spectroscopic analysis

With four naphthalenes as backbones, amide naphthotubes exhibit fluorescence and often display enhanced fluorescence upon guest complexation (Fig. 6a). We have demonstrated that **1b** is an effective fluorescent sensor for detecting various environmental

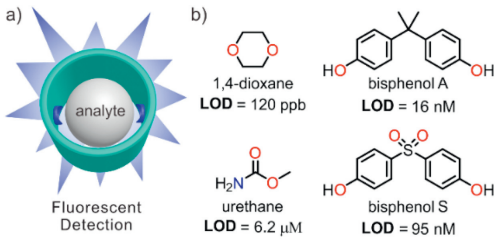


Fig. 6. (a) Fluorescent detection of organic pollutants with naphthotubes in water. (b) selected pollutants and the corresponding LOD values. Reproduced with permission [13]. Copyright 2020, American Chemical Society.

contaminants in water (Fig. 6b). For instance, 1,4-dioxane, a common solvent in the chemical industry, is a persistent groundwater pollutant and a Group 2B carcinogen [30]. We have confirmed that host **1b** can selectively detect 1,4-dioxane in water, even in the presence of other structurally similar interfering molecules [16]. The detection limit was measured to be 120 ppb, and this is close to the WHO guideline value (50 ppb). Additionally, **1b** is an effective fluorescent sensor for the detection of Group 2A carcinogen urethane [31] in water (detection range: 6.2–60 μmol/L) and beer (detection range: 22.9–60 μmol/L) [32]. Bisphenol A and bisphenol S are widely-used raw materials in fine chemicals and are common endocrine-disrupting compounds that can disrupt the endocrine system [33]. The fluorescence intensity of **1b** is greatly enhanced upon the addition of bisphenol A or bisphenol S, and thus a fluorescence detection method was established [20]. The established LOD value for bisphenol A was 3.6 ng/mL (16 nmol/L), and the detection range was 16 nmol/L – 2.2 μmol/L. The LOD value is lower than the guideline value of bisphenol A in drinking water in China (10 ng/mL, GB 5749–2006). Similarly, the LOD for bisphenol S was calculated to be 95 nmol/L and the detection range were 95 nmol/L–1.0 μmol/L.

Furthermore, fluorescence monitoring of the hydrolysis kinetics of non-fluorescent ester molecules was also achieved by utilizing amide naphthotube **1b** [34]. The basic principle is that **1b** is capable of binding to esters, resulting in a significant increase in fluorescence intensity. However, upon hydrolysis of the esters, the equilibrium is disturbed, leading to a decrease in fluorescent intensity. The correlation between time and observed fluorescence intensity can be deduced, and the rate constants were determined through nonlinear fitting. Unlike cucurbit[8]uril-based indicator displacement assays which require fluorescent indicators [35], the system involves a much simpler equilibrium own to the intrinsic fluorescence of the host.

The fast measurement of absolute configuration and optical purity of chiral samples is crucial in asymmetric synthesis. Compared with chiral chromatographic techniques, optical chirality sensing is more cost-effective and applicable to high-throughput screening [36,37]. Common chiral molecules typically exhibit weak or negligible absorption in the UV–vis region, and amide naphthotubes are achiral, so both of them display weak or no circular dichroism (CD) signals. However, when a chiral guest molecule binds to the amide naphthotube, the hydrogen bonding between them can transfer chirality from the guest to the naphthotube, inducing a strong CD spectral signal (Fig. 7a). We found that achiral naphthotube are good CD probes of chiral molecules in water [17]. This method is suitable for the configuration analysis and *ee* measurement of small chiral organic molecules (Fig. 7b), such as asymmetric catalytic products, chiral drug molecules, and natural products [38]. This technique boasts several advantages such as wide applicable scope, fast response, environmentally-friendly nature, and promising potential for future applications.

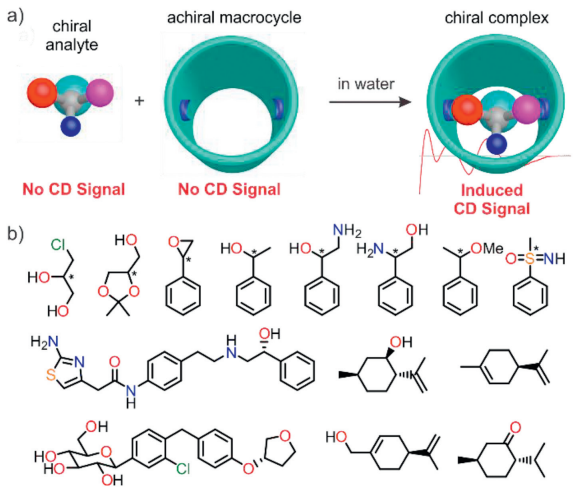


Fig. 7. (a) Schematic representation of chiroptical sensing with amide naphthotube in water. (b) Chemical structures of chiral molecules for optical chirality sensing based on amide naphthotube. Reproduced with permission [38]. Copyright 2020, Wiley-VCH.

4.2. Adsorptive separation

The separation and purification of petrochemical products is one of the research focuses in chemical industry. In recent years, macrocycle-based nonporous adaptive crystals (NACs) have been widely used to separate organic chemicals with similar structures [39,40]. Benzene hydrogenation is a significant process for the production of cyclohexane and cyclohexene, which requires the separation of the mixture of benzene, cyclohexene, and cyclohexane to achieve high-purity target chemicals [41]. However, previous adsorption methods could only separate binary mixtures, and the separation of ternary mixtures had not been achieved. We successfully achieved the selective adsorption ternary mixture of benzene, cyclohexene, and cyclohexane by using amide naphthotube **1b** through the concept of NACs (Fig. 8) [22]. The amide naphthotube demonstrated high adsorption selectivity, with selectivities of 91.3% and 97.1% for benzene over cyclohexene and cyclohexane, respectively. In ternary mixtures, the selectivity of benzene could reach 90.2%. The single crystal structure and calculated structure showed that the N–H···π interaction of the host and guest played a decisive effect in the selectivity. Compared with other NACs, amide naphthotube presents various advantages, including quick adsorption rate, significant adsorption capacity, and high selectivity.

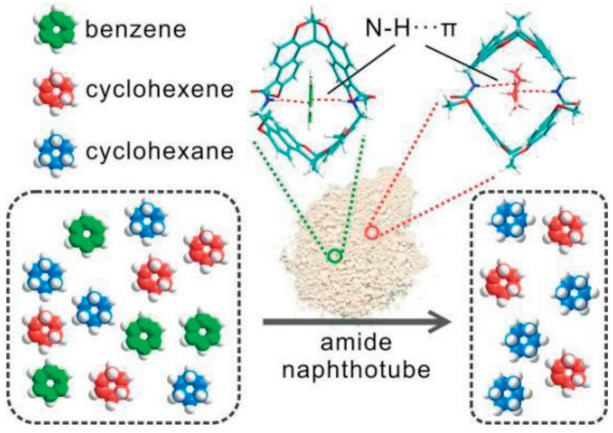


Fig. 8. Adsorptive separation of benzene, cyclohexene, and cyclohexane by amide naphthotubes. Copied with permission [22]. Copyright 2021, Wiley-VCH.

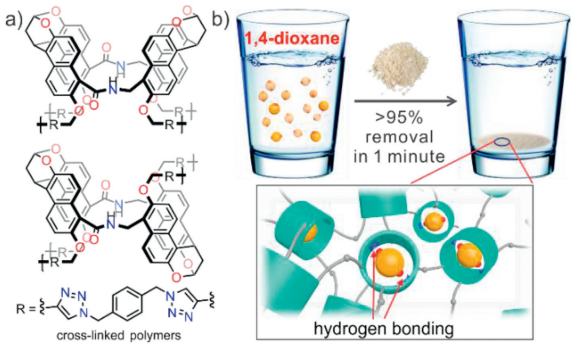


Fig. 9. (a) Chemical structures of polymerized amide naphthotube. (b) Schematic illustration of removal of micropollutants from water by polymerized amide naphthotube. Reproduced with permission [20]. Copyright 2021, Wiley-VCH.

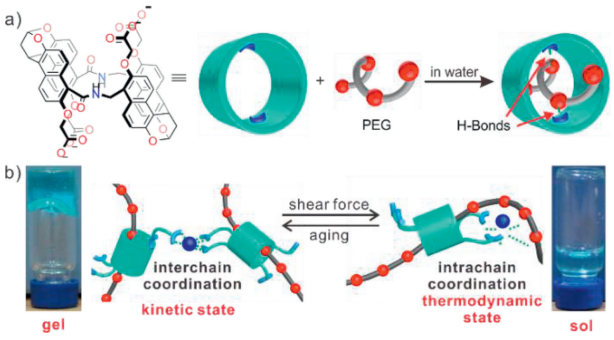


Fig. 10. (a) Schematic illustration of recognition of PEG chain by amide naphthotube. (b) Stimuli-responsive properties of the shear-induced hydrogel and proposed mechanism for the reversible process. Reproduced with permission [21]. Copyright 2019, Springer Nature.

Organic pollutants in water are crucially important for human health and the safety of aquatic environments since they are widely sourced and highly toxic [42]. In recent years, macrocycle-cross-linked polymers have emerged as adsorbents for adsorbing organic micro-pollutants from water [43–46]. The adsorption performance of these materials mainly depends on the binding strength between pollutants and macrocyclic hosts. Nevertheless, it remains challenging for the removal of polar organic pollutants ($\log K_{OW} < 3.0$) from water due to the limited binding capability of common macrocyclic hosts towards such pollutants in water [4]. Amide naphthotube is highly effective in binding polar organic pollutants ($\log K_{OW} < 3.0$) in water, with binding constants ranging from 10^3 L/mol to 10^6 L/mol, the affinities are obviously higher than that of β-cyclodextrin. By employing cross-linked polymers containing amide naphthotube (Fig. 9a), efficient adsorption and removal of 18 different polar organic pollutants, including highly hydrophilic and polar pollutants such as 1,4-dioxane, can be achieved (Fig. 9b) [20]. The materials showed rapid adsorption kinetics and large adsorption capacity, significantly outperforming other commercial adsorption materials. The cross-linked polymers demonstrate exceptional performance even when treating a mixing solution with 18 distinct organic pollutants. Moreover, it can be easily recycled by washing with methanol or ethanol.

4.3. Hydrogels

Dissipative self-assembly is a crucial process for complex life functions, maintaining non-equilibrium assembly structures by consuming "fuel". Existing artificial dissipative self-assembly systems are always powered by chemicals, light or electricity [47], while non-covalent interactions-mediated dissipative self-assembly has rarely been reported. We found that **1b** can bind highly hydrophilic polyethylene glycol in water, forming a pseudorotaxane structure that resembles a necklace (Fig. 10a) [21]. In the presence of Cu^{2+}, the carboxylate ions on the host can be cross-linked through coordination bonds, resulting in a hydrogel structure (Fig. 10b). However, this hydrogel is unstable and gradually transforms into a solution state. Further studies have shown that shaking or oscillator can transform the solution into a gel state again, and this process can be cycled multiple times. This is a shear force-driven dissipative self-assembly system, with the hydrogel in a kinetic non-equilibrium state, while the sol is in a thermodynamic equilibrium state. The study shows that shear force induces Cu^{2+} transformation from intra-chain coordination to inter-chain coordination, leading to hydrogel formation. In the process of energy dissipation, the coordination mode is slowly transformed from inter-chain to intra-chain, thus forming a thermodynamically stable solution state. The transient hydrogel exhibits excellent extensibility and can be stretched up to 30 times its original length. The host "slides" on the polyethylene glycol polymer chain during the stretching process, and this "molecular pulley" structure dissipates tensile stress, resulting in highly stretchable properties. In addition, the hydrogel can achieve rapid self-healing under shaking conditions. The uniqueness of molecular recognition of endo-functionalized cavity in water forms the basis of the performance of the assembly system.

Recently, we utilized amide naphthotubes' binding capacity to polyethylene glycol in water again to create a muscle-inspired hydrogel containing polyrotaxanes [48]. This hydrogel can be mechanically enhanced through training, similar to muscles. As external forces are applied for training, the hydrogel redirects the polymer chains to form anisotropic structures. The hosts on the PEG chain induce the contraction of adjacent polymer chains due to their multiple hydrogen bonding sites and mobile nature. This process results in the formation of dense anisotropic nanocrystalline domains through a hydrogen bonding network. The trained hydrogel exhibits an impressive ~10-fold improvement in tensile stress, achieving a remarkable tensile stress enhancement of approximately 110 kPa compared to its initial state. This research presents a novel strategy for enhancing the mechanical properties of soft materials.

4.4. Biomedical applications

Amide naphthotubes display a limited capacity to form complexes with anions, cations, amino acids, nucleosides, sugars, and other biomolecules in water [49]. Moreover, elevated salt concentration does not compromise their ability to interact with neutral guest molecules. This notion is reinforced by the similarity in binding constants between amide naphthotubes and 2-phenyl pyrimidine across various complex biological media, including water, PBS buffer and bovine serum, thus this binding pair is very selective to each other [50]. By incorporating tetraphenyl ethylene (TPE) as an anchor (Fig. 11a), the modified amide naphthotube can be fixed into the cell membrane, and the negatively charged host cavity remains accessible on the cell surfaces, facilitating the binding of a guest molecule. Through cell experiments, it has been demonstrated that this bioorthogonal host-guest pair effectively recognizes mutually on cell surfaces, leading to enhanced cell-cell interactions. Furthermore, these artificial receptors serve as targeting positions, greatly improving the targeting efficiency of guest species and guest-modified liposomes in living animals (Fig 11b). It should be mentioned that the binding constant of the guest (PEG-2000: 10^4 L/mol; 2-phenyl pyrimidine: 7.0×10^5 L/mol) to amide naphthotube is typically considered inadequate for biological applications. This result suggests the bioorthogonal nature of the amide naphthotube-based recognition. The research introduces

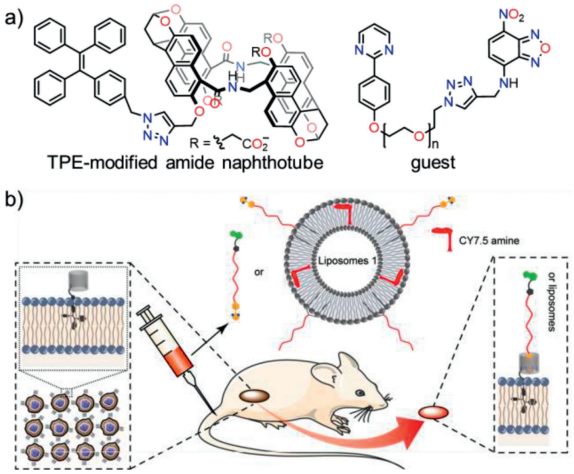


Fig. 11. (a) Chemical structures of TPE-modified amide naphthotube and guest. (b) Scheme showing cell membrane anchoring and bioorthogonal molecular recognition. This figure has been published in CCS Chemistry [2022], [Biomimetic recognition-based bioorthogonal host–guest pairs for cell targeting and tissue imaging in living animals] is available online at [DOI: 10.31635/ccschem.021.202101178].

a novel supramolecular bioconjugation method and establishes a new conceptual framework for the design of bioorthogonal recognition system with broad implications in biological applications.

Organophosphorus compounds are always high-toxic and utilized as pesticides and nerve agents [51]. Amide naphthotubes have been demonstrated to bind organophosphorus compounds with higher affinity than other hosts like molecular baskets and cyclodextrins, making naphthotube **1b** an effective inhibitor for reducing the toxicity of paraoxon to acetylcholinesterase [52]. Furthermore, naphthotube **1b** exhibits selective binding towards the colorless, closed-ring isomer of spiropyran rather than its merocyanine isomer [53]. This binding causes a noticeable color change in the spiropyran solution, allowing the preparation of a test strip for the detection of toxic paraoxon with the naked eye.

4.5. Stabilization of reaction intermediates

Capturing reaction intermediates is challenging yet crucial for understanding and guiding reactions in water. For instance, stabilizing labile imine and relevant hemiaminal intermediates in water is valuable for understanding the aldol mechanism and offers strategies for conducting organic chemical reactions in water [54]. Recently, Jiang and co-workers constructed a mono-modified amide naphthotubes derivative capable of capturing water-sensitive imine and hemiaminals intermediates at room temperature in water [55]. By utilizing a "click" reaction, a primary amine group was connected to the amide naphthotube (Fig. 12a). 2D NMR spectra showed that the primary amine tail chain bent into the cavity in water, forming a self-contained structure. The amide naphthotube was able to form imines with aliphatic aldehydes or aromatic benzaldehydes in water (Fig. 12b). The imine was wrapped by the hydrophobic cavity and formed hydrogen bonds with inward-directed amide proton, rendering it stable under various conditions such as heating, alkalinity, nucleophilic reagents, and electrophilic reagents. Furthermore, they also successfully captured the active tetrahedral intermediate hemiaminals during the reaction process through NMR and mass spectrometry. The active intermediate was stabilized by the hydrogen bonding site provided by the acylamide of the host and hydrophobic effect, and the binding cavity tightly wrapped the hemiaminals, isolating it from the outside world (Fig. 12c). The interior of the pocket contains hydrogen bonding donor sites and amine groups, which have a similar structure to biological receptors. The biomimetic strategy used here provides a solution to the challenge of stabilizing enzyme-catalyzed reaction intermediates.

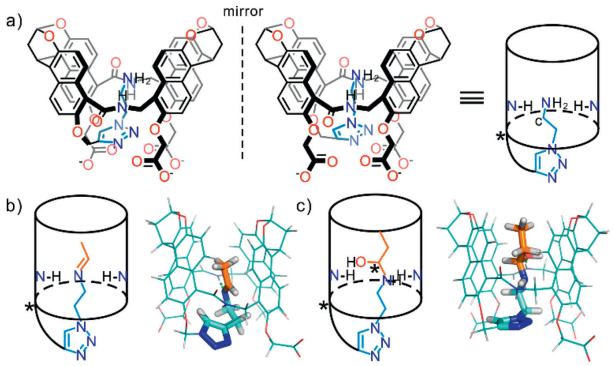


Fig. 12. (a) Chemical structures of mono-functionalized naphthotube featuring a primary amine group. (b) Schematic representation and optimized structure of imine reaction product of naphthotube with acetaldehyde in water. (c) Schematic representation and optimized structure of hemiaminal during the reaction of naphthotube with propanal in water. Reproduced with permission [55]. Copyright 2022, Wiley-VCH.

5. Conclusion and outlook

By imitating the binding cavities of biological receptors, Jiang proposed the concept of "endo-functionalized cavity" for designing macrocyclic hosts, which provides a solution for addressing the generally accepted challenge of "selective molecular recognition using hydrogen bonds in water". As a macrocyclic host exactly with endo-functionalized cavity, amide naphthotubes possess deep hydrophobic cavity featuring buried hydrogen-bonding sites. The shielded hydrogen bonds and hydrophobic effects together achieve the selective recognition of organic molecules such as hydrophilic molecules, chiral molecules and drug molecules, demonstrating the effectiveness and uniqueness of the "endo-functionalized cavity" in molecular recognition in water. The aqueous molecular recognition ability of these amide naphthotubes also provides a novel tool for research on chiral spectroscopic analysis, pollutant sensing and removal, dissipative self-assembly, bioorthogonal molecular recognition, and the stabilization of chemical reaction intermediates. Generally, amide naphthotubes were highly complementary to other macrocyclic hosts, both in terms of structure and function, jointly advancing the development and expanding the application spectrum of supramolecular chemistry [56–61]. In the future, we anticipate further exploration of the utilization of amide naphthotube in areas such as chemical biology and medical science [62].

Besides amide naphthotubes, the concept of the "endo-functionalized cavity" has also been applied to synthesizing other biomimetic macrocyclic hosts [63–71]. For instance, the protonated amine naphthotubes exhibit selective recognition of organic carboxylic acids in water through the hydrophobic effect and shielded salt bridge [67]. By using bent anthracene dimer as a building block, a biomimetic host for selectively recognizing quinones was also synthesized [68]. Nevertheless, in view of the constant emergence of new macrocyclic hosts in recent years [72–78], these with endo-functionalized cavities remain rare [79–84]. Considering the unique advantages of this concept in molecular recognition, we believe that it has the potential to solve even more challenging problems in molecular recognition. For example, amide naphthotubes are appropriate for binding medium-sized organic molecules with slender structures, but it exhibits weaker binding with smaller and larger organic molecules or ions, many of which are important biologically functional compounds or drugs. Therefore, designing and synthesizing water-soluble macrocycles with smaller and

larger endo-functionalized cavities is highly significant, although it is more challenging. Additionally, it is still challenging to achieve highly selective chiral recognition in water. Our previous studies have demonstrated that endo-functionalized cavity is effective in chiral recognition, but the selectivity is far from pretty. By increasing polar interactions such as hydrogen bonding, it should be able to further enhance chiral selectivity. Moreover, selective molecular recognition in the complex biological environment remains a significant challenge. Following this concept, it may be possible to construct host-guest pairs with higher binding affinity and selectivity, allowing for applications in complex environments. Overall, we are convinced that the emergence of biomimetic hosts like amide naphthotubes will pave the way for more practical and effective resolutions to the persistent issues faced in various domains, such as analytical, biomedical, and materials science.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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