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Molecular recognition and biological application of modified β-cyclodextrins

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The molecular recognition based on cyclodextrins (CDs) has become a focus of interest in modern supramolecular chemistry. CDs are known to encapsulate various ions and organic/inorganic molecules in their hydrophobic cavities and form stable inclusion complexes through cooperative noncovalent interactions. During the past few decades, a large variety of modified CDs have been elaborately designed and synthesized, which significantly promotes our molecular-level understanding of the structure–function relationship in many supramolecular systems. Through the accurate analysis on the molecular binding behaviors, one can create a library of CD-based nanoassemblies with controlled physicochemical properties. In this review, we will focus on the stability constant-directed molecular recognition and the biological activities of β-CDs toward some representative bioactive substrates, including metal ions, steroids, porphyrins, amino acids and oligopeptides, as well as drug molecules, with the final goal of promoting their practical applications in the biomedical field.

Host-guest chemistry, molecular recognition, cyclodextrin, biological function

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1 Introduction

As a class of torus-shaped cyclic oligosaccharides typically possessing 6–8 D-glucose units, cyclodextrins (CDs) can form inclusion complexes with diverse bioactive molecules in their hydrophobic cavities and have been actively involved in a wide range from fundamental research to industrial application, including pharmacy, food, cosmetics, and environment (Figure 1) [1]. In the academic field, the native and chemically modified CDs, in conjunction with crown ethers, calixarenes, cucurbiturils, and pillararenes, are treated as the most common cavity-bearing synthetic macrocycles in the construction of controllable supramolecular assemblies [2]. In addition, many fascinating properties can stem from the CD-based topologically interesting nanoaggregates, such as (pseudo)rotaxanes, supramolecular polymers, cross-linked hydrogels, and functionalized nanoparticles [3].

Structurally, CDs possess multiple hydroxyl groups on their primary and secondary faces, which can be conveniently converted into various functional substituents to improve their molecular binding affinity and selectivity. For example, recently, the site-selective hexa-hetero-functionalization of α-CD was achieved by a site-directing method [4]. This synthetic strategy was further applied to construct a bridging β-CD that could prevent self-inclusion and eventually promote the nucleic acid condensation in a supramolecularly polymeric manner [5]. Thermodynamically, the CD-involved molecular recognition processes are usually governed in a favorable way through a combination of van der Waals and hydrophobic interactions as the major driving forces [6]. Moreover, as a good supplement to the existing

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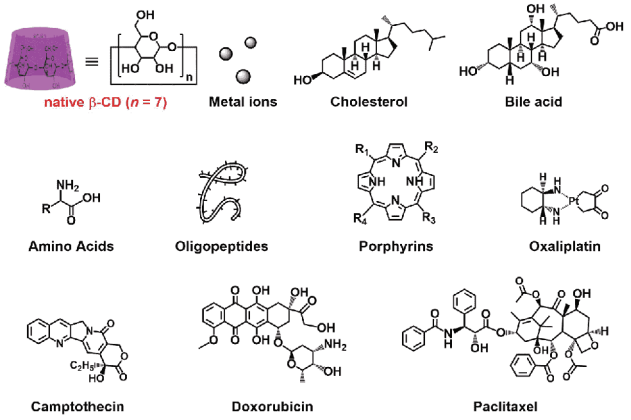

Figure 1 Molecular structures of native β-CD (n=7) and the typical guest ions/molecules applied in the CD-based molecular recognition (color online).

well-known hydrophobic effect, the latest studies have demonstrated that the chaotropic effect also plays an important role in the CD-based molecular binding process, especially toward the large-sized anions [7].

The native CDs can be classified as α- (n=6), β- (n=7), and γ-CDs (n=8). Among all the frequented encountered CDs, β-CD and its derivatives have immense advantages for the macrocycle-involved molecular recognition, mainly due to their lowest price, moderate water solubility, and suitable cavity size that are compatible with many types of organic and inorganic guest molecules (Figure 1) [8]. Meanwhile, many poly-substituted β-CD derivatives, such as hydroxypropyl β-CD, randomly methylated β-CD, and sulfobutylether β-CD, have been clinically approved and widely applied as active ingredients in the pharmaceutical field [9]. Generally, most of hydrophobic substrates with appropriate molecular size can be utilized as guest molecules in the CD chemistry, such as organometallic complexes, fluorescent dyes, and even biomacromolecules. Due to the huge amount of guest molecules reported in publications, it is impossible for us to review all of them; thus, we only selected the related and representative works by our group and other investigators on the cooperative binding behaviors and concomitant biological functions on the basis of their stability constants (K_S) between the modified β-CDs and some biologically relevant substrates. With the revolutionary advances in supramolecular chemistry, we believe that the expanded use of newly synthesized and known CD derivatives will continue to energize the translational development of CD-based nanoarchitectures in the biomedical field.

2 Molecular recognition with metal ions

In general, the internal binding inside the CD's cavities can greatly improve the catalytic, sensing, and magnetic properties of organometallic guests. Meanwhile, the external binding of alkali, transition, and lanthanide ions outside the CD's cavities can not only create numerous topologically interesting structures, but also endow the CD's supramolecular nanoassemblies with desirable photophysical behaviors for wider biological applications. In particular, the metal coordination complexes/clusters (e.g. polyoxometalate) have been exploited as a new type of building blocks in the construction of CD-based multicomponent assemblies in the past few years [10]. Recently, Huang *et al*. [11] comprehensively reviewed the polymeric supramolecular nanoassemblies constructed by the orthogonal host-guest and metal-ligand interactions. Lewiński *et al*. [12] gave an excellent review about the interactions and applications of native CDs with metal ions and inorganic particles in chemistry and material science. In the following section, we will discuss the molecular binding behaviors and biological functions of some metal ions in the β-CD-involved nanosystems.

2.1 Transition metal ions

Although CDs as anion-receptor hosts are less prone to directly encapsulate inorganic cations or positively charged guests inside their cavities, the hydroxyl groups located at the CD's primary and secondary faces provide multiple anchoring points to coordinate with metal ions. For instance, the binuclear complexes could be readily formed between α-, β-CDs and Cu(II) under strong basic condition, which gave enhanced binding abilities toward aromatic amino acids and organic dyes, mainly due to the favorable electrostatic interaction [13]. Moreover, in enzyme mimics, it is found that the Cu(II)-pyridine-bridged bis(β-CD) complex could be used as an artificial catalyst to promote the enantioselective hydrolysis of amino acid esters at the neutral pH [14].

In most cases, the chemical modification of metal ligands onto the β-CD's skeleton is a direct and effective strategy to attain the CD-based supramolecular biosensing systems for metal ions. Of these, the Zn(II) fluorescence probes are extensively studied, because Zn(II) is one of the most abundant elements in living cells and plays a vital role in a variety of biological processes [15]. It has been reported that the water-soluble β-CD derivative possessing *N*-(8-quinolyl)-*p*-aminobenzenesulfonamide (HQAS) moiety showed strong green fluorescence response to Zn(II) as compared to other interfering ions under physiological conditions, which could be further utilized as an imaging agent to stain yeast cells [16]. Moreover, after validating its binding ability to the loose bilayer membranes, the HQAS-modified β-CD was further found to act as an efficient cell-impermeable probe in the discrimination of the Zn(II)-containing damaged cells from the normal ones (Figure 2(b)) [17]. In the subsequent work, the methyl group-substituted HQAS, 4-amino-*N*-(2-methylquinolin-8-yl)-benzenesulfonamide (MQAS), was in-

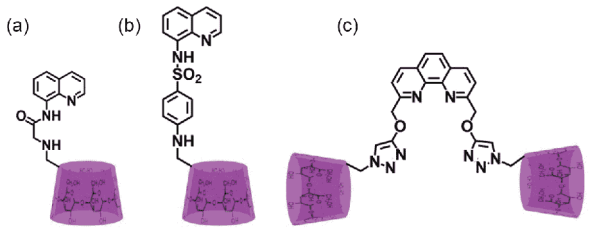

Figure 2 Molecular structures of β-CDs modified by (a) 8-aminoquinoline, (b) *N*-(8-quinolyl)-*p*-aminobenzenesulfonamide (HQAS), and (c) 1,10-phenanthroline for the detection of Zn^{2+} in water (color online).

troduced to the skeleton of permethyl β-CD (PMCD), concurrently exhibiting the stoichiometric 2:1 coordination of Zn(II) with MQAS moiety and the strong inclusion complexation with sulfonated porphyrin [18]. This metal ion-mediated supramolecular triad showed very interesting transmembrane dissociation behaviors upon incubation with yeast cells. That is, the cell staining experiments demonstrated that only the released porphyrins could enter the cells, leaving the Zn(II)/MQAS-PMCD coordination complexes in the cell membrane. It is believed that this work provided an alternative method to selectively visualize and transport bioactive molecules at different cellular sites.

The biocompatible switch-on fluorescent probes can be also obtained through a CD/guest/metal ion triple recognition mode [19]. For example, a water-soluble β-CD derivative modified by both 1,10-phenanthroline and triazole moieties could exhibit dramatic fluorescent enhancement upon chelation with Zn(II), mainly due to the inhibition of intramolecular photo-induced electron transfer process (Figure 2(c)) [20]. Moreover, this fluorescence sensing ability towards Zn(II) could be further enhanced after complexation with 1-adamantanecarboxylic acid sodium. Benefiting from the cooperative coordination with phenanthroline and triazole groups, as well as the extra carboxylic group from adamantyl guest, the binding constant ($\log K_S$) greatly increased from 5.95 to 7.74 with a relatively lower limit of detection down to 10^{-7} M. In addition, the association rate of host compound to Zn(II) was much faster in the presence of 1-adamantanecarboxylic acid sodium, thus leading to a visual and rapid florescence sensing in the cellular environment.

Furthermore, the ruthenium polypyridyl complexes have been also extensively applied in the CD-based nanosystems. For example, a series of metallo-glycodendrimers were constructed by the inclusion complexation between the mannose-capped β-CDs and adamantane-grafted chiral Ru (II) complex (Figure 3(a)) [21]. These obtained supramolecular Ru(II)-glyconanoclusters could exhibit the enantioselective binding abilities with lectins, thus providing us with an optimized model to deeply understand the carbohydrate-protein interactions. In addition, Liu *et al*. [22] previously investigated that the Ru(II)-coordinated phenanthroline-modified β-CD could induce the originally circular DNA to the uniformly sized spherical nanoparticles (Figure 3(b)). Meanwhile, this host compound could be used as an efficient inhibitor for DNA topoisomerase and DNA cleavage enzymes, which was attributed to its good DNA condensation ability. Moreover, benefiting from the strong fluorescence emission at around 580 nm, this water-soluble luminescent probe could trace the translocation of DNA into the naturally cultured cells with preferential localization in the cytoplasm. In a recent study, the same group reported a hexa-β-CD appended ruthenium polypyridyl complex, which could exhibit enhanced DNA binding and photocleavage abilities upon the host-guest inclusion complexation with adamantane-modified anthracene (Figure 4) [23]. The superb DNA binding ability was achieved by the targeted intercalation of peripheral anthracenes into DNA helix, accompanied by the dramatic fluorescence quenching of anthryl group and the significant change in the conformation of double helical DNA. Meanwhile, with the assistance of supramolecular complexes, the supercoiled DNA was completely photocleaved in a concentration-dependent manner, which was attributed to the generation of reactive oxygen species under light irradiation. More gratifyingly, colocalization assays further revealed that the supramolecular complexes were specifically accumulated within the cell nucleus, thus leading to a much better photo-activated anticancer activity in cancer cells than some commercial reagents and ruthenium-containing photosensitizers. This work may provide a new perspective in exploring more effective cancer treatments by supramolecular photodynamic therapy.

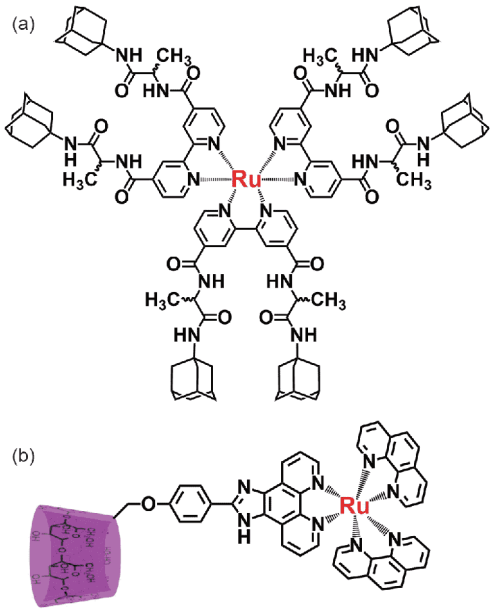

Figure 3 Molecular structures of (a) adamantane-grafted chiral Ru(II) complex for the enantioselective binding with lectins; and (b) Ru(II)-coordinated phenanthroline-modified β-CD for DNA condensation, enzyme inhibition, and translocation tracing (color online).

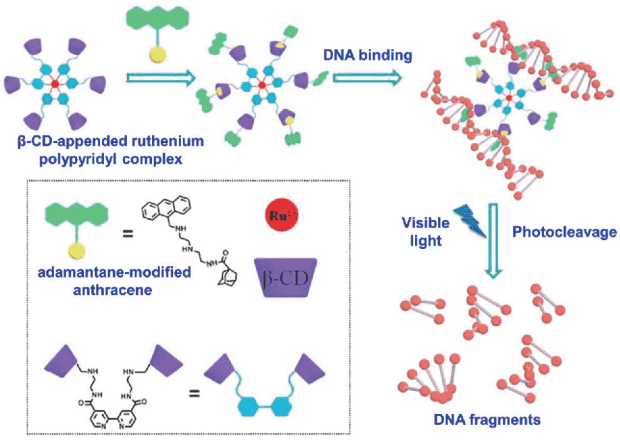

Figure 4 Enhanced DNA binding and photocleavage by the noncovalent conjugation of hexa-β-CD appended ruthenium polypyridyl complex and adamantane-modified anthracene [23] (color online).

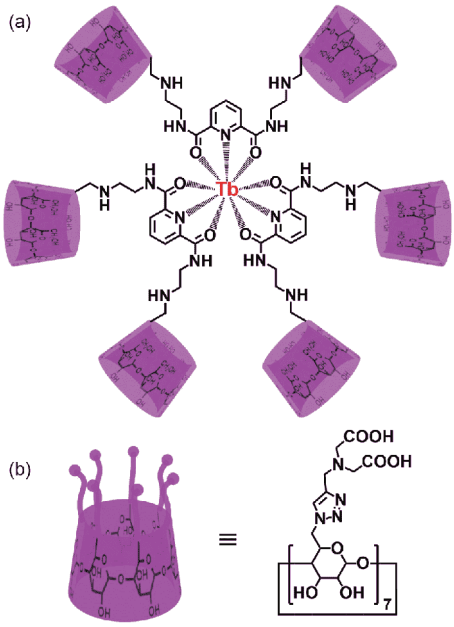

Figure 5 Molecular structures of (a) Tb(III)-coordinated pyridine-2,6-dicarboxylic acid-bridged bis(β-CD) for the energy transfer with C_{60}; and (b) β-CD derivative with multiple 1,2,3-triazole and carboxyl groups as a potential magnetic resonance imaging probe (color online).

2.2 Lanthanide ions

The complexation with lanthanide ions, especially via the polypyridine-metal coordination, can be considered as a facile procedure of rendering the CD-based nanostructures broadly luminescent in the fabrication of supramolecular photoactive materials with tunable photophysical properties. Moreover, owing to the intrinsically positive charges and the compelling luminescence properties, the CD-based biological nanosystems mediated by lanthanide ions have also been successfully developed for bioimaging and theranostic applications [24]. In one case, by virtue of the extraordinarily high affinity between Tb(III) and the pyridine-2,6-dicarboxylic acid in 1:3 binding stoichiometry, a bundle-shaped linear nanoassembly was constructed through the hydrophobic encapsulation of C_{60} with the β-CD–Tb(III) luminescent complex (Figure 5(a)) [25]. Spectral analyses further demonstrated that a two-step 'pyridine → Tb(III) → C_{60}' intermolecular energy transfer process could be efficiently operative with the quenched lanthanide luminescence under UV light irradiation. In the other case, Gouhier and Ling *et al.* [26] synthesized a novel polyaminocarboxylate-bearing β-CD scaffold via Cu(I)-catalyzed 1,3-dipolar cycloaddition, which could form multinuclear complexes with Gd(III) in an octavalent coordination spherical conformation (Figure 5(b)). More significantly, this β-CD-based Gd(III) ligand showed much better ability to alter the relaxation time of coordinated water than other frequently encountered linear and cyclic ligands, which may be developed as a promising contrast agent for magnetic resonance imaging in clinical use.

2.3 β-CD-based metal-organic frameworks

Generally, the CD-based metal-organic frameworks can be conveniently obtained by the bottom-up fabrication of native and modified CDs with metal ions (i.e. alkali and alkaline earth metal cations). In the past decade, this new type of organic-inorganic hybrid nanoarchitectures have been rapidly developed and extensively exploited in miscellaneous fields, such as pollutant absorption [27], gas binding and sensing [28], (petro)chemical purification and separation [29], as well as drug loading and delivery [30].

Furthermore, in view of facile synthesis, well-defined chemical structures, tunable porous sizes and improved biocompatibility, the synergistic combination of macrocyclic receptors and metal-organic frameworks may hold great promise in the ultrasensitive bioassay and efficient delivery of therapeutic agents [31]. For example, a metal-organic nanotube was fabricated via the metal coordination of Pb(II) with β-CD, thus exhibiting a coplanar metallamacrocycle surrounded by two β-CD units [32]. More gratifyingly, this nanotubular metal-coordination complex could be utilized as a turn-on fluorescent probe to detect H_2S in the living cells, which was attributed to the high affinity between Pb(II) and H_2S as an auxochromic group. In the subsequent work, this team implemented the same strategy to selectively and sensitively detect uric acid through the host-guest interaction with Pb(II)-β-CD meta-organic nanotube [33]. In another case, an electrochemiluminescent system was smartly designed and constructed by using the Pb(II)-β-CD metal-organic framework as the sensing platform and the limit of detection of such immunosensor for insulin was determined as 0.042 pg mL^{-1} [34].

As for the controlled capture and release of cargo molecules, Zhang and Deng *et al.* [35] reported a drug delivery

system by the post-synthetic surface modification of β-CD with metal-organic framework via click reaction. Benefiting from the β-CD surface coating, the undesired premature drug release was largely eliminated and more significantly, the targeted drug delivery and improved anticancer activity were concurrently achieved by the introduction of pH-sensitive benzoic imine bonds and redox-sensitive disulfide bonds onto the outer surface of Fe(III)-involved hybrid nanostructure. Moreover, Wang and co-workers [36] fabricated a mechanized azobenzene-functionalized Zr(IV) metal-organic framework, in which the fluorescent dyes could be on-demand captured and released upon the photoisomeric complexation between β-CDs and the pendant azobenzenes.

3 Molecular recognition with steroids

Steroids, one of the most important bioactive substrates, are considered as the ideal type of guest molecules in the CD-based molecular recognition systems mainly because of their appropriate molecular sizes that can be well-fitted in the β-CD's cavity. In addition to the high binding affinity with CDs, steroids can also form stable inclusion complexes with many molecular containers, such as cyclic and acyclic cucurbituril-type receptors [37]. In this section, we will discuss the biological functions of β-CD-involved complexation with cholesterol and bile acids, which are two frequently encountered steroids with sufficient biological functions.

3.1 Cholesterol

The disorder of cholesterol metabolism is closely linked to many severe pathological processes and the strong complexation of cholesterol with functionalized CDs has been developed as an emerging therapeutic tool in preventing and reversing cardiovascular and neurodegenerative diseases. Recently, Coisne *et al*. [38] gave a comprehensive discussion on the CD-based therapies and their related clinical trials in the treatment of cholesterol-associated diseases. In one case, atherosclerosis is an inflammatory disease that can induce the elevated concentration and abnormal accumulation of cholesterol in blood. It has been known that native, methylated, 2-hydroxypropyl β-CDs are all promising candidates capable of promoting atherosclerosis regression. For example, Latz *et al*. [39] reported that 2-hydroxypropyl β-CD as the cholesterol-sequestrating agent could exert anti-inflammatory effect in the prevention of atherosclerosis, which was jointly attributed to the solubilization effect and the removal capacity of macrophages toward cholesterol. In the other case, the administration of 2-hydroxypropyl-β-CD was found to greatly reduce the hepatic cholesterol and has been approved in clinical trials for the treatment of Niemann-Pick type C disease, a type of neurological disorders that display the abnormal storage of unesterified cholesterol in cells. In addition, it is also found that methylated β-CD is more potent than 2-hydroxypropyl β-CD in the reduction of cholesterol accumulation [40]. More interestingly, Yui and co-workers [41] have constructed a reduction-cleavable polyrotaxane bearing terminal disulfide-bond linkage, in which 2-hydroxypropyl β-CDs were threaded onto the pluronic backbone. The obtained polyrotaxanes were specifically disassembled under the reducing environment of lysosomes and the released β-CDs could efficiently remove the excessive endogenous cholesterol from the disease-derived cells. This finding provided a novel therapeutic method for Niemann-Pick type C disease.

3.2 Bile acids

As a group of biologically important steroids, bile acids are actively involved in various physiological and pathological processes. Meanwhile, as the water-soluble derivatives of steroids, bile acids have shown the superior host-guest complexation properties with various CDs. In 2012, Liu *et al*. [42] systematically reviewed the molecular binding behaviors of bile acids with native, mono-modified, and bridged β-CDs, demonstrating that the hydrophobic interaction with CD's cavities and the electrostatic attraction with positively charged centers are two decisive factors to enhance the binding strength with bile acids. For instance, compared with native β-CD, the binding stability of D-tyrosine-modified β-CD toward cholic acid and deoxycholic acid (DCA) largely increased to ca. 9000 M^{-1} in aqueous buffer solution, while this value of L-tyrosine-modified β-CD toward the same bile acids sharply decreased to ca. 1000 M^{-1} under the same experimental condition [43]. These strikingly distinctive molecular binding behaviors were mainly attributed to a more favorable conformational change upon complexation with D-tyrosine-modified β-CD; that is, the carboxylate groups in D-tyrosine and bile acids were located far away from each other, thus avoiding the undesired electrostatic repulsion and leading to a more deep penetration into the β-CD's cavity in the molecular recognition process.

Furthermore, despite the fact that numerous thermodynamic parameters have been quantitatively determined by means of isothermal calorimetric and spectroscopic titrations in the past decades, the biomedical application of bile acid-CD supramolecular systems is rarely explored. After realizing the potential cytotoxicity of endogenous bile acids, Liu and co-workers [44] synthesized the tyramine-modified β-CD and found that the molecular binding strength could be largely improved when tyrosine was decarboxylated to tyramine (Figure 6(a, b)). That is, the K_S value between tyramine-modified β-CD and DCA was calculated as 1.57×10^4 M^{-1} in DMSO-phosphate buffer solution, while

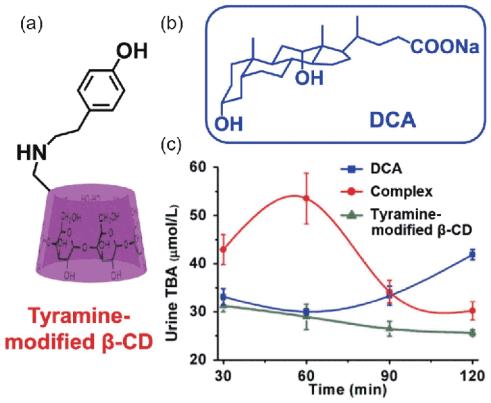

Figure 6 Molecular structures of (a) tyramine-modified β-CD, (b) deoxycholic acid (DCA), and (c) total bile acid data of mice urine after injection with free DCA, tyramine-modified β-CD, and their inclusion complex, respectively, in 120 min, showing that the excess DCA could be rapidly removed via urinary system [44] (color online).

this value was only 627 M^{-1} for L-tyrosine-modified β-CD under the same experimental condition. Mechanismically, potentiometric titration demonstrated that nearly 92% amino group was protonated in the tyramine-modified β-CD at pH 7.2 and therefore, the electrostatic attraction was promoted as a predominant driving force to tightly bind DCA. More significantly, the biocompatible tyramine-modified β-CD could largely eliminate the cytotoxicity induced by DCA at the cellular level. In an animal model, the excess DCA could be rapidly cleared from the mouse blood via urinary excretion (Figure 6(c)). This study definitely provided a supramolecular method in the treatment of bile-acid related diseases, such as cholestasis and hepatocellular carcinoma.

4 Molecular recognition of permethyl β-CD with porphyrins

The binding of CDs and porphyrinoids through covalent linking and inclusion complexation has been extensively studied in enzyme and hemoglobin mimicking, light-harvesting systems, and photodynamic therapy [45]. Among all the frequently used β-CDs, permethyl β-CD is one of the optimal choices in the formation of stable inclusion complexes with negatively charged porphyrins, such as carboxylated and sulfonated porphyrins, in aqueous solution. Moreover, a recent study showed that the photodynamic activities toward cancer cells could be greatly enhanced upon complexation of permethyl β-CD with aniline- and phenol-substituted porphyrins, mainly due to their efficient intracellular uptake by tumor cells [46]. Previously, Kano *et al.* [47] systematically investigated the molecular binding behaviors of permethyl β-CDs with different types of water-soluble tetraarylporphyrins, revealing that they could exclusively form stable 2:1 host-guest complexes with an extremely high stability constant up to 10^8 M^{-2} order of magnitude mainly through the strong van der Waals interaction. Consequently, numerous efforts have been devoted to exploring the biological functions based on the porphyrin-permethyl β-CD complexation.

In this context, Kano and co-workers [48] have made pioneering contribution on the permethyl β-CD-involved biomimetic nanosystems. They found that the inclusion complexation of pyridine-bridged bis(permethyl β-CD) with Fe(II) porphyrin could be developed as a simple model system of myoglobin, by which dioxygen (O_2) could be reversibly entrapped to form six-coordinate stable adduct in aqueous solution. In addition to O_2, this supramolecular receptor could be also capable of binding other diatomic molecules, such as carbon monoxide (CO) and nitric oxide (NO) [49]. Interestingly, the autoxidation of NO-bound supramolecular species would occur in the presence of O_2, thus leading to the formation of oxidized Fe(III) porphyrin and NO^{3-} anion inside the permethyl β-CD's cavity. Moreover, benefitting from the selective capture and excretion of CO under physiological condition, this supramolecular ferric porphyrin was further implemented in the removal of endogenous CO from the rat body [50] and in the maintenance of ferrous/ferric balance of hemoglobin in the blood [51]. In a very recent study, the CO-removal efficiency was greatly improved when the porphyrin-permethyl β-CD complex was equipped by a targeting peptide (Figure 7(a)) [52]. The introduction of octaarginine peptide onto porphyrin backbone could endow the resultant inclusion complex with the desired cell-permeable ability. As a result, the increased level of reactive oxygen species and the inhibition of anti-inflammatory effect were observed in macrophages after the removal of CO was realized by the host-guest inclusion complex. Overall, the porphyrin-permethyl β-CD supramolecular nanosystem provides us with a powerful and sim-

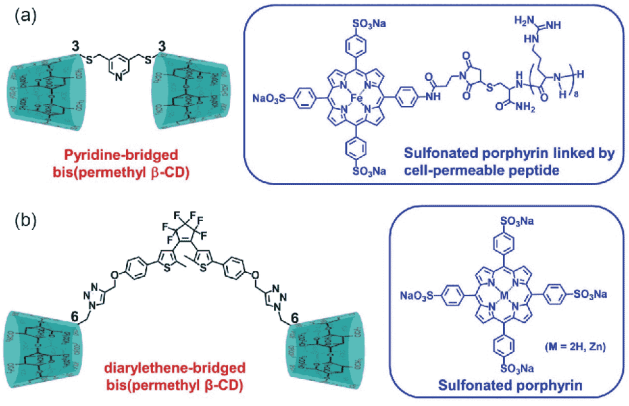

Figure 7 (a) Supramolecular complex formed by pyridine-bridged bis (permethyl β-CD) and cell-permeable peptide-containing sulfonated porphyrin for the detection and removal of endogenous CO in cells; (b) linear supramolecular assembly constructed by diarylethene-bridged bis(permethyl β-CD) and sulfonated porphyrin for the photo-controlled $^1O_2$ generation in aqueous media (color online).

plified model complex in deeply understanding the regulatory role and biological significance of many gaseous signaling molecules.

Furthermore, many fascinating physicochemical properties can stem from the unique combination of permethyl β-CD and anionic porphyrins, such as the photo-controlled morphological interconversion [53], and the photo-induced electron [54] and energy transfer [55]. As for the biological applications, Liu *et al*. [56] designed a diarylethene-bridged bis(permethyl β-CD), by which the fluorescence emission of included porphyrin could be reversibly controlled upon alternating UV and visible-light irradiation (Figure 7(b)). More remarkably, the generation of singlet oxygen ($^1O_2$) could be also efficiently regulated by the photochromic reaction of diarylethene core between the ring-open and ring-closed states. To be envisaged, this biocompatible photoswitchable nanosystem may hold great promise in the selective fluorescence visualization and imaging-guided photodynamic therapy. Moreover, the supramolecular assemblies based on the porphyrin-permethyl β-CD complexation have been successfully implemented in combinational cancer therapy. For instance, a versatile theranostic nanoplatform constructed by the tirapazamine-loaded mesoporous silica nanoparticles was obtained, followed by the sequential decoration of permethyl CD-grafted hyaluronic acid and Gd (III)-chelated anionic porphyrin through host-guest interaction [57]. Benefiting from the hyaluronic acid-mediated internalization process, the obtained nanoparticles could be specifically recognized by cancer cells and then disassembled by over-expressed hyaluronidase. Consequently, the near-infrared fluorescence, magnetic resonance imaging, and combined photodynamic-chemotherapy were concurrently achieved for tumor-targeted diagnosis and treatment.

5 Molecular recognition with amino acids and oligopeptides

As biologically important molecules, amino acids and oligopeptides are extensively utilized as typical guest molecules in the β-CD-involved molecular recognition process. However, the direct complexation of native β-CD with amino acids and oligopeptides is not an effective way to obtain large K_S values. Therefore, the chemical modification of their molecular skeletons is believed as one of the most popular methods to enhance the molecular binding affinity with oligopeptides and thus improve their concomitant biological properties.

5.1 Amino acids

The introduction of cationic and chiral substituents onto the β-CD's skeleton can greatly enhance the enantioselective sensing ability toward amino acids. In an early study, the fluorescent β-CD derivative containing L-phenylalanine and dansyl groups was found to be more enantioselective than its analogous compound containing D-phenylalanine in the molecular recognition toward amino acids [58]. The authors attributed this phenomenon to the self-inclusion of dansyl group into the β-CD's cavity, which could increase the chiral discrimination ability to a large extent. More recently, by introducing an enantiomeric helicene to the β-CD's primary face, Yang *et al*. [59] reported the chirality sensing of the (*P*)- and (*M*)-3-azonia[6]helicenyl β-CD toward the underivatized amino acids in water (Figure 8). Benefiting from both the inherent chirality of helical substituent and the hydrophobic cavity of β-CD, the high L/D selectivity and *P*/*M* preference were concurrently obtained in the leucine group as 12.4 and 28.2, respectively, in the neutral aqueous solution. This work demonstrated a dual chiral approach in differentiating proteinogenic amino acids based on the rigidified chiral substituent of 3-aza[6]helicene and inherently chiral receptor of β-CD.

Moreover, in addition to the mono-modified β-CDs, the enantiomer separation behaviors of many β-CD-based nanostructures toward amino acids have also been extensively studied, such as the β-CD-functionalized gold nanoparticle for tyrosine [60], the graphene-involved nanocomposite for phenylalanine [61] and tryptophan [62], the supramolecular dye aggregate assembly for lysine and arginine [63], as well as the β-CD-imbedded protein nanopore for natural aromatic amino acids [64]. As shown in these reported results, the chiral discrimination by monovalent amino acid-CD association cannot meet the high criteria of sensing systems and precision medicines for diagnostic and therapeutic purposes. However, with the rapid development of supramolecular nano- and bio-technology, it is believed that more highly sensitive and selective enantiomeric platforms and devices toward the rapid screening and detection of amino acids can be created by β-CD-based nanoassemblies.

5.2 Oligopeptides

Although the host-guest binding behaviors between β-CD and oligopeptides have been widely reported during the past few decades, their stability constants are fairly low with native and neutral β-CD derivatives. For example, the K_S values between the aliphatic oligopeptides and the pyridine-bridged bis(β-CD) rarely exceeded 10^3 M^{-1} in aqueous buffer solution [65]. These results are probably attributed to the hydrophilicity and flexible skeleton of most oligopeptides that cannot form stable inclusion complexes in the β-CD's cavity. However, similar to the molecular binding behaviors toward anionic molecules, the introduction of positively charged centers can largely enhance the complex stability of

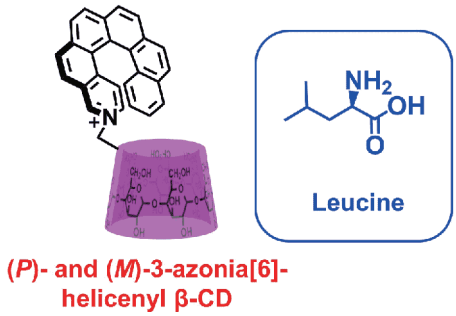

Figure 8 Chirality sensing of leucine by (*P*)- and (*M*)-3-azonia[6]helicenyl β-CD (color online).

β-CDs with dipeptides and tripeptides. Through the synergistic binding of two CD cavities and the chelation effect of coordinated metal centers, the obtained K_S values could be substantially increased up to 10^4 M^{-1} order of magnitude in the case of metallobridged bis(β-CD)s [66].

Alternatively, the covalent modification of oligopeptides with functional groups can offer another effective method to enhance the intermolecular binding strength with β-CD. Owing to the high binding affinity with the β-CD's cavity, adamantyl moiety is frequently anchored to the peptide skeleton by amide condensation, and this strategy has been successfully implemented in the cell-specific sequential surface functionalization [67], enhancement of neural differentiation [68], tumor-targeting metalloanticancer therapeutics [69], cell culture and cell recovery postculture [70], as well as proteolytically degradable hydrogels [71]. Moreover, as for the controlled morphological conversion, in one case, an amphiphilic β-CD possessing polyether head and alkyl tail could spontaneously form vesicular structure in neutral aqueous solution and the adamantane-modified octapeptide adopted a random coil conformation to uniformly reside in the β-CD's cavity [72]. In contrast, this peptide guest rearranged into a β-sheet conformation upon acidification at pH 5.0, thus showing a morphological change from spherical to fibrous structures. In the other case, it is found that the adamantane-pendant diphenylalanine could exclusively form one-dimensional nanofibers with a twisted β-sheet structure, while the well-defined planar nanosheets were obtained in the presence of *trans*-azobenzene-bridged bis(β-CD) (Figure 9) [73]. Interestingly, the inclusion complexation between the *cis*-isomer of host molecule and the same guest molecule gave the open-ended, curved tubular structures. The lamellar and tubular structures could interconvert into each other via UV-Vis light irradiation, further resulting in the different absorption and fluorescence enhancement abilities toward organic dyes. This work further emphasizes the power of CD-based supramolecular systems in the fabrication of biocompatible stimuli-responsive nanomaterials.

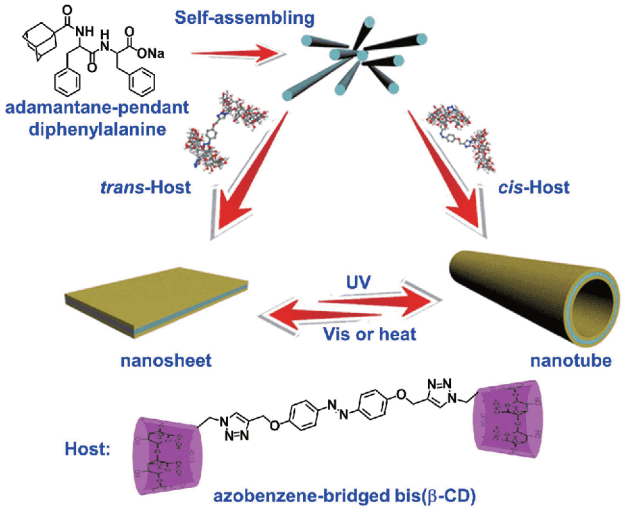

Figure 9 Photo-induced morphological conversion of adamantane-pendant diphenylalanine by the inclusion complexation with azobenzene-bridged bis(β-CD) under UV-Vis light irradiation [73] (color online).

6 Molecular recognition with drug molecules

As a type of macrocyclic receptors possessing hydrophobic cavities, CDs have been actively engaged in the biomedical and pharmaceutical fields. More significantly, it is noteworthy that many CD-based formulations, including the chemically modified CDs and the inclusion complexes with conventional chemotherapeutic drugs, have received approval for clinical use [74]. There are two intriguing examples about the CD-based drug formulations. One is Opalmon® (Limaprost alfadex), an inclusion complex consisting of α-CD as an excipient material that can largely improve the stability and bioavailability of alprostadil [75]. The K_S value between α-CD and alprostadil was determined as ca. 550 M^{-1} at 37 °C by conductometry [76]. The other one is Bridion® (Sugammadex), the brand name of a carboxylated γ-CD that can be clinically used in reversing neuromuscular block by chemical encapsulation of rocuronium bromide, because the binding stability in this host-guest complexation can reach up to 10^7 M^{-1} under physiological conditions in a thermodynamically favorable way [77].

Furthermore, a large number of therapeutically important pharmaceuticals have been employed as the guest molecules in the β-CD-based molecular recognition process, including cinchona alkaloids [78], curcumin and its derivatives [79], as well as the anticancer drugs of cisplatin, doxorubicin and paclitaxel [80]. Meanwhile, a variety of newly synthesized β-CD derivatives, such as amphiphilic β-CDs, multiply charged β-CDs, and β-CD-containing polymers, have been widely investigated for their unique molecular binding abilities with different drug molecules [81]. In particular, ionizable β-CDs can induce oppositely charged guests to

form stable complexes and assemblies [82]. For instance, Liu *et al*. [83] reported that the hepta-carboxyl-β-CD could form stable inclusion complex with amantadine, a drug for anti-Parkinson and antiviral. In addition, their K_S value was accordingly calculated as 2.3×10^4 M^{-1} in D_2O by ^1H NMR titration method (Figure 10). Moreover, the well-defined spherical nanoparticles could be readily obtained between the same host and an amphiphilic ammonium salt in water, thus exhibiting the controlled capture and release behaviors toward the pyrene-derived fluorescent dye as a model drug. In the subsequent work, the authors found that compared to the native and mono-modified β-CDs, the polyanionic β-CDs possessing multiple carboxylic groups with different alkyl linkers in length showed more affinitive binding abilities towards irinotecan, topotecan, and doxorubicin [84]. Interestingly, these polyanionic β-CDs also showed the pH-controlled drug release behaviors, which would make them the promising candidates in the delivery of anticancer drugs.

As for the β-CD-containing polymers, Kim and co-workers [85] constructed a nanoparticulate drug delivery system, which was formed by the polymeric β-CDs and paclitaxels through multivalent inclusion complexation. The competition titration with fluorescent probe revealed that the K_S value in the complexation of polymeric β-CDs and paclitaxels was 10^4-fold higher than that of monovalent paclitaxel-β-CD complex. As a result, the robust nano-assembly exhibited high stability in the blood and long-term *in vivo* antitumor activity. This work further demonstrated that the orthogonal and multivalent interactions could be utilized as an effective strategy to enhance the molecular binding affinity and selectivity in the CD-based molecular recognition process. More gratifyingly, during the past few years, β-CD-grafted hyaluronic acid (HACD), a novel type of biocompatible and biodegradable polysaccharides, has been emerged as a versatile nanocarrier to specifically transport nucleic acids [86], inorganic nanoparticles [87], targeting peptides [88], photosensitizers [89], and various anticancer drugs into tumor cells [90]. A good and representative example of β-CD-grafted hyaluronic acid is a supramolecular conjugate constructed by the noncovalent encapsulation with adamplatin prodrug (Figure 11) [91]. ^1H NMR titration experiments indicated the K_S value between native β-CD and adamplatin was 4.1×10^3 M^{-1} in 1:1 binding stoichiometry, thus allowing the formation of stable core-shell nanostructures under physiological conditions. Both cell-proliferation and tumor-growth inhibition experiments jointly demonstrated that the obtained supramolecular polysaccharide nanoparticles possessed high activity and low toxicity in the cancer treatment.

Meanwhile, many structurally interesting β-CD-based nanoassemblies, including micelles, vesicles, (pseudo)rotaxanes, supramolecular polymers, and hydrogels, can offer an alternative or even powerful method to delivery drug

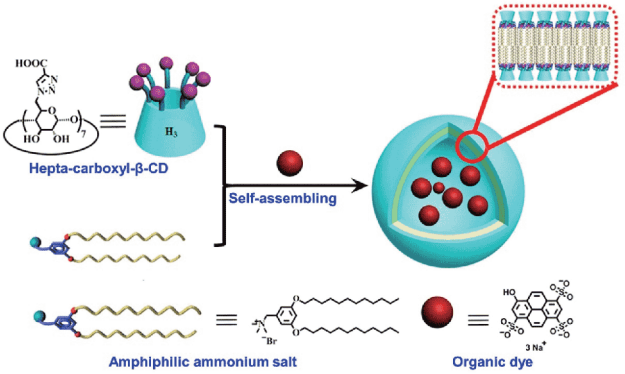

Figure 10 Supramolecular nanoparticles constructed by hepta-carboxyl-β-CD and amphiphilic ammonium salt for the controlled capture and release of fluorescent dye [83] (color online).

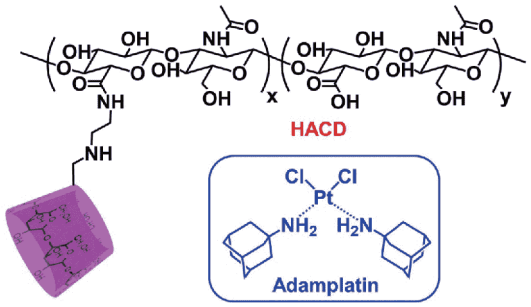

Figure 11 Polysaccharide nanoparticles constructed by β-CD-grafted hyaluronic acid (HACD) and adamplatin (color online).

molecules at their site of action [92]. The introduction of β-CD moieties can not only solubilize the entrapped drug molecules but also endow the obtained nanostructures with highly desired biocompatibility, cell-targeting ability, and curative effect. Recently, a glutathione-responsive supramolecular polymer was successfully constructed by the self-exclusion of camptothecin-modified β-CDs with a disulfide linker (Figure 12) [93]. Benefiting from the large K_S value between β-CD and camptothecin (ca. 1.4×10^4 M^{-1}), the formation of stable one-dimensional nanoarchitectures could dramatically increase the water-solubility of pristine camptothecin by a factor of 232 under physiological condition. After introducing the cell-targeting and radio-labeling agents into the vacant β-CD's cavities at the end of the supramolecular polymers, the supramolecular theranostic nanoparticles could be conveniently obtained via π-π stacking, host-guest complexation, and multiple hydrogen-bonding interconnections, eventually achieving the enhanced anticancer efficacy, anti-metastasis effect, and non-immunotoxicity in a mouse tumor model at the same time.

7 Conclusions and outlook

In this review, the molecular binding behaviors and biolo-

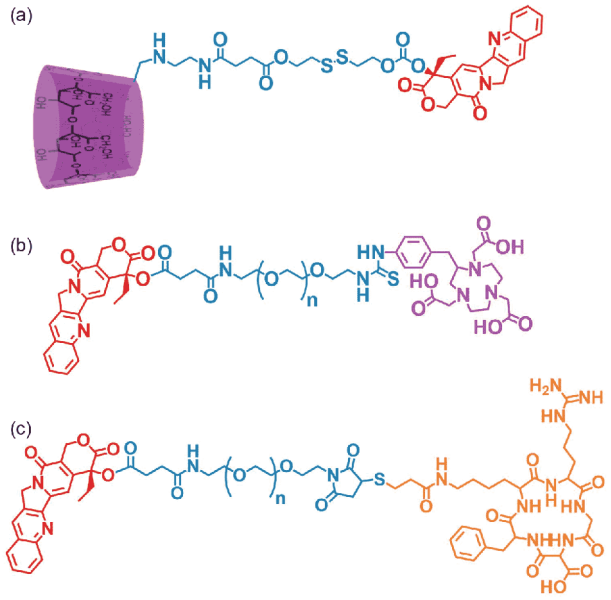

Figure 12 Supramolecular theranostic nanoparticles constructed by (a) the self-exclusion of camptothecin-modified β-CD containing disulfide linker and then equipped with (b) radio-labeling and (c) cell-targeting agents (color online).

gical characteristics of some modified β-CDs were introduced and summarized. From these aforementioned examples, it is apparent to see that the highly affinitive and selective molecular binding abilities of β-CD derivatives can synergistically contribute to various noncovalent interactions, thus exhibiting many fascinating biological properties and practical applications in the fabrication of chemical sensors, artificial nanodevices, and biocompatible materials. It has been shown that there are many successful examples of β-CD-based supramolecular systems with tunable morphological conversion, detection and separation abilities, gene/drug delivery behaviors, and removal capacity toward toxic substances and hazardous waste. In our opinion, apart from the commonly employed adamantane, azobenzene, and ferrocene, more new functional guest molecules with sufficient biological implications and adaptive capacity to macrocyclic hosts should be continuously exploited to enrich the CD-based supramolecular nanosystems. Meanwhile, a great deal of effort in conceptual and theoretical guidance should be required to master the structure-function relationship and promote the practical uses of CDs in clinic.

The past decades have witnessed the rapid development of CD chemistry from mono-, di-, per-, bridged-modification to site-selective poly-hetero-functionalization; from monovalent inclusion complexation to multivalent supramolecular aggregation; from simple encapsulation to stimuli-responsive capture and release of biological targets in the treatment of many life-threatening diseases. With the close collaboration of researchers in multidisciplinary fronts, we believe that more exciting findings and potentials of β-CD-involved supramolecular systems with interesting and important biological applications can be anticipated in the near future.

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Conflict of interest The authors declare that they have no conflict of interest.

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