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Cooperative Binding and Multiple Recognition by Bridged Bis(β-cyclodextrin)s with Functional Linkers

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ABSTRACT

Possessing two β-cyclodextrin cavities in close vicinity and a functional linker with good structural variety in a single molecule, bridged bis(β-cyclodextrin)s can significantly enhance the original binding ability and molecular selectivity of native β-cyclodextrin and thus be successfully utilized in drug carriers, solubilizers, catalysis, photochemical materials, etc. This Account describes recent developments in the intramolecular cooperative binding and multiple recognition of bridged bis(β-cyclodextrin)s with functional linkers in solution, as well as their molecular assembly behaviors through the intermolecular cooperative binding. It also gives a description of unique properties and wide applications of bis(β-cyclodextrin)s and their assemblies.

Introduction

Cyclodextrins (CDs) are a class of cyclic oligosaccharides with six−eight D-glucose units linked by α-1,4-glucose bonds. The shape of CDs, in their most symmetrical forms, resembles that of a truncated cone. The wide opening of CD is composed of C2−OH and C3−OH groups, while the narrow opening is composed of C6−OH groups (Scheme 1). Owing to a capability of encapsulating various inorganic/organic molecules within their hydrophobic cavities in both aqueous solution and the solid state, CDs are extensively studied as not only excellent receptors for molecular recognition but also functional building blocks to construct molecular devices.[1] Among various functional CDs, bridged bisCD, which comprises two CD cavities linked by a functional bridge, is a greatly promising candidate. Earlier in the 1980s, Breslow et al.,[2] Tabushi et al.,[3] Harada et al.,[4] and Fujita et al.[5] respectively reported the syntheses and inclusion complexations of bisCDs. From then on, bisCDs and their metal complexes have been extensively studied as versatile receptors for molecular recognition and building blocks for functional materials.[6−28] In comparison with native CDs and mono-modified CDs, bridged bisCDs exhibit the significantly high binding abilities and molecular selectivities through the cooperative binding of two adjacent CD units.[6] Moreover, the linker can supply a well-organized pseudo-cavity that in turns provides additional binding interactions with accommodated guest molecules. This fascinating property enables bisCDs to be successfully utilized in carriers,[8,19] catalysis,[9,10] templated synthesis,[12] photochemical materials,[13,14,26b] solubilizers,[17] enzyme mimics,[18] molecular imprinting,[27] etc.

This Account summarizes our recent endeavors and related works by other investigators on the intramolecular

Scheme 1

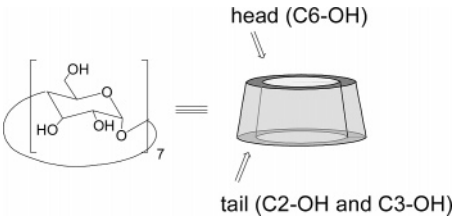

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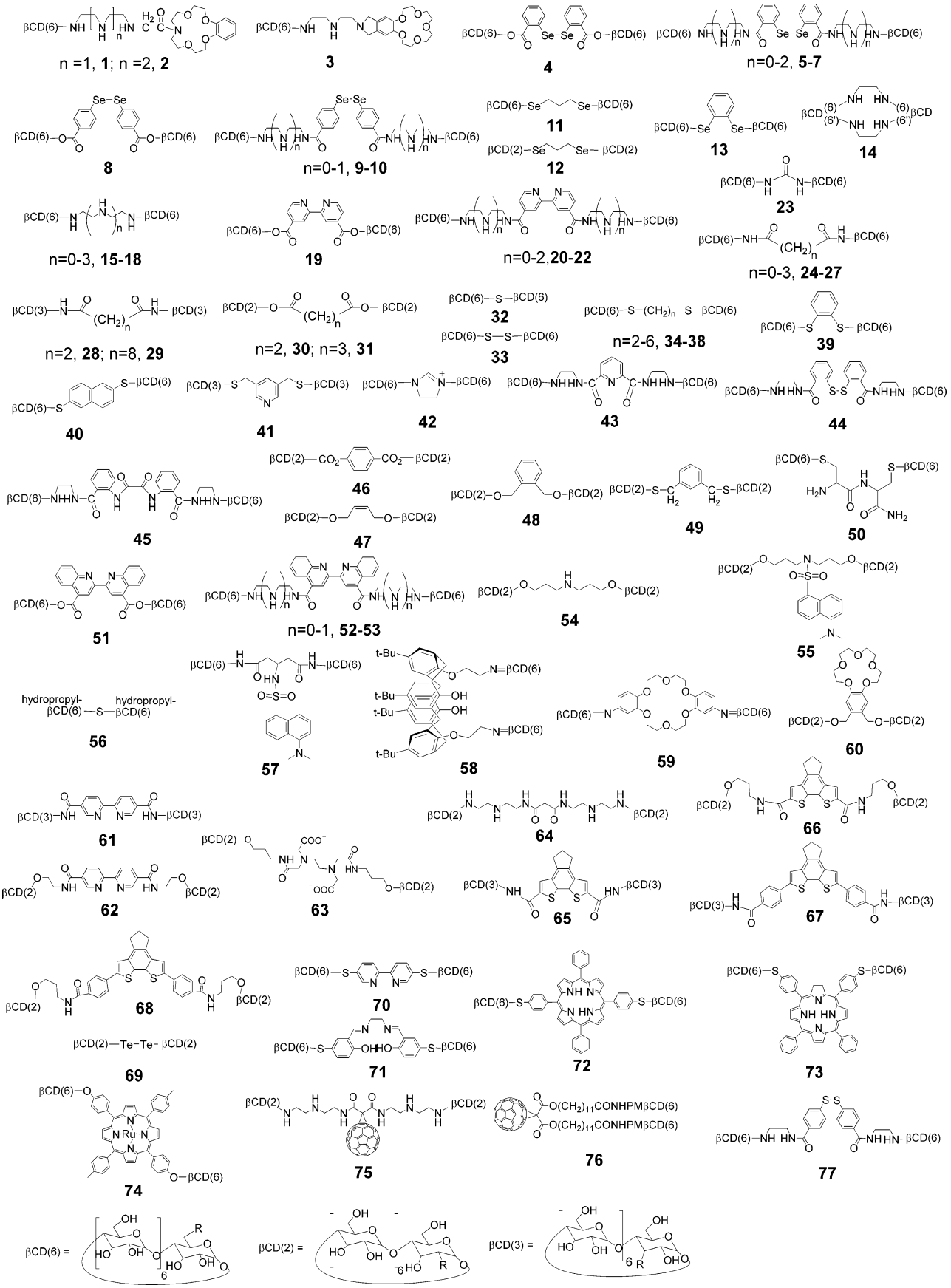
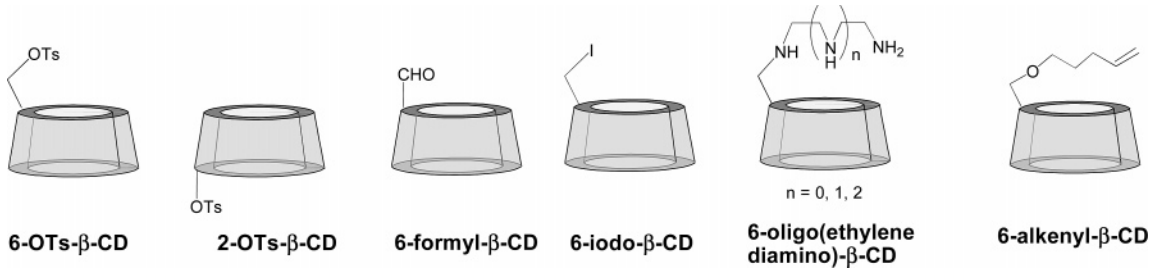
Chart 1

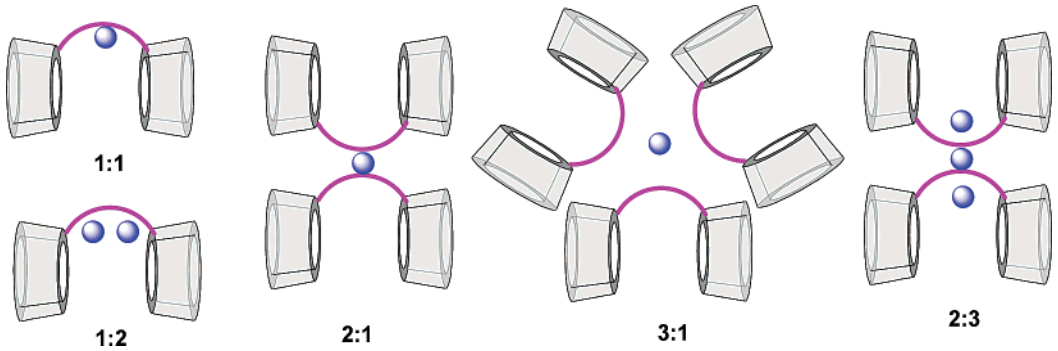


cooperative binding and multiple recognition of bridged bis(β-CD)s (**4**−**77**) with functional linkers in solution (Chart 1), as well as their molecular assembly behaviors through the intermolecular cooperative binding. It also

Scheme 2



Scheme 3



gives a description of unique properties and wide applications of bis(β-CD)s and their assemblies.

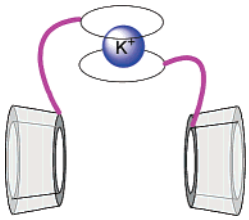
Synthesis

There are several convenient routes for the syntheses of bis(β-CD)s. The most straightforward way is through the reaction of hydroxy groups of β-CDs with required substituents, such as carboxyl or halide groups, of bridge reagents.[29] Alternatively, tosylates, halides, aldehydes, oligoethylenediamines, alkenes, and related species of β-CD[22−23,30] can be prepared as intermediates (Scheme 2) for subsequent reactions with bridge reagents through nucleophilic displacement,[31] condensation,[22−23,32] or acylation.[33] These multistep preparations initially make one site of β-CD chemically distinct from the others so that further reactions occur without the competing involvement of unreacted hydroxy groups.

The coordination of transition-metal ions to linkers of bis(β-CD)s gives metallobis(β-CD)s, and the coordination stoichiometry is mainly dependent upon the structural feature of linkers (Scheme 3). For bis(β-CD)s with seleno linkers, Pt^{IV} and Pd^{II} are appropriate metal ions and the coordination stoichiometry between bis(β-CD)s and metal ions is usually 2:1, 1:1, or 1:2.[34,35] For bis(β-CD)s with nitrogenous linkers, Cu^{II}, Ni^{II}, Ru^{II}, Zn^{II}, Co^{II}, Mn^{III}, and lanthanide cations are appropriate metal ions and the corresponding coordination stoichiometry is usually 1:1,[31] 1:2,[36] 2:1,[37] 3:1,[16] or 2:3.[37]

In situ preparation is another approach for the preparation of metallobis(β-CD)s.[38,39] Seen from Scheme 4, β-CDs **1**−**3** can spontaneously convert to bridged bis(β-CD)s in a K^+-containing solution through the sandwich complexation of two 15-crown-5 units with a K^+ ion.[40]

Scheme 4



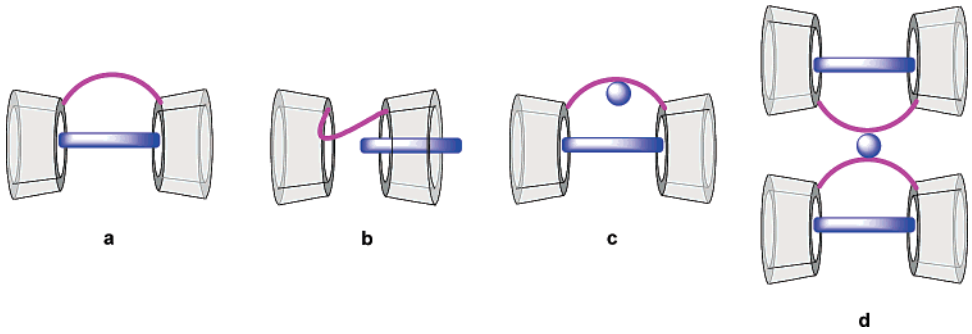
Solution Structure

The structural elucidation of bis(β-CD)s, especially their initial structure in solution, is very important to understand the molecular recognition mechanism of bis(β-CD)s. Generally, bis(β-CD) with a rigid short linker tends to adopt a self-perching conformation, where the linker is shallowly perching over the rim of β-CD cavity. Bis(β-CD) with a flexible linker in short or moderate length always adopts a self-included conformation, where the linker is embedded in the β-CD cavity. However, long-linked bis(β-CD) prefers a self-excluded conformation, where the linker is located at the exterior of the β-CD cavity, although a shallow perching model is not rigorously ruled out. Significantly, the self-included linker can move out from the β-CD cavity after coordinating with the metal ion, and this conformational change will favor the sequential penetration of the guest molecule upon inclusion complexation.[37]

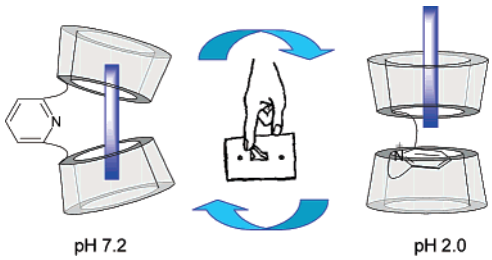
Binding Mode

The essential function of bis(β-CD)s is their cooperative binding behaviors. Extensive studies shows that there exist two cooperative binding modes for bis(β-CD)s, i.e., the intramolecular cooperative binding and the intermolecu-

Scheme 5



Scheme 6



lar cooperative binding. Generally, bis(β-CD)s form stable inclusion complexes with guest molecules through the intramolecular cooperative binding, while the intermolecular cooperative binding leads to the formation of molecular assemblies. Scheme 5 illustrates some intramolecular binding modes of bis(β-CD)s using head-to-head bis(β-CD)s as representative examples. Among them, the sandwich binding mode, which was first verified by Lawrence et al.,[20] is the most familiar one (Scheme 5a) and covers the overwhelming majority of complexations of bis(β-CD)s.[2−8,11−15,19−21,25−26,28−29,31−36] In this mode, two end groups of the guest molecule are separately included in two β-CD cavities. Meanwhile, bis(β-CD) can also supply a well-organized pseudo-cavity through the adjustment and reorientation of the linker, where the branch fragment of the T-shaped or triangular guest can be appropriately accommodated. Another binding mode of bis(β-CD)s is the host−linker−guest co-inclusion binding mode (Scheme 5b), which is observed in the complexation of bis(β-CD)s having a self-included conformation with some biological molecules such as oligopeptides or steroids.[37b,41] In this mode, the guest molecule penetrates into one β-CD cavity of bis(β-CD) and the linker is partially self-included in the other β-CD cavity. Significantly, these two modes are convertible through a smart control, e.g., by changing the pH value of the solution (Scheme 6).[41]

Binding modes of metallobis(β-CD)s are mainly dependent upon their coordination stoichiometry. Metallobis(β-CD)s with a 1:1 or 1:2 coordination stoichiometry tend to adopt a sandwich binding mode upon complexation with the guest molecule (Scheme 5c), while the pseudo-cavity formed by the linker is occupied by the coordinated metal ion in part or in whole.[31,35] However, metallobis(β-CD)s with a 2:1 or 2:3 coordination stoichiometry prefer an intramolecuar 2:2 binding mode (Scheme 5d), where each bis(β-CD) unit adopts a sandwich binding mode, upon complexation with the guest molecule.[37] Moreover, 1:2 binding modes are also observed in the cooperative binding of bis(β-CD)s and metallobis(β-CD)s.[7c,11,14,16,21b]

Molecular Recognition

Molecular recognition is one of the most important topics during the development of supramolecular chemistry. For example, functional molecules always store some specific information in their size, shape, and electronic properties, and this information can be readily read through molecular recognition. Therefore, understanding the mechanism and influencing factors of molecular recognition is of particular significance for smart control and further applications of bis(β-CD)s. This section will describe molecular recognition behaviors of bis(β-CD)s from viewpoints of cooperative binding and multiple recognition.

Cooperative Binding. It is well-documented that, among several noncovalent interactions contributing to inclusion complexations of β-CDs, the most crucial contributions are made by van der Waals and hydrophobic interactions.[42] Possessing only one β-CD cavity, native and monomodified β-CDs display limited binding abilities because of the relatively weak van der Waals and hydrophobic interactions. However, bis(β-CD)s can greatly enhance the original binding abilities of parent β-CD through the cooperative binding of two adjacent β-CD cavities and a functional linker. Furthermore, metallobis(β-CD)s can afford more stable inclusion complexes with guest molecules through the cooperative binding of two or several β-CD cavities and the additional interactions between the coordinated metal and the accommodated guest molecule.

Possessing good structural diversity and spectral sensitivity, dyes are widely used as spectral probes for the molecular recognition study of bis(β-CD)s.[2,6,8,27b] Table 1 lists the binding constants of some representative dyes with bis(β-CD)s in aqueous solution (Scheme 7). In most cases, bis(β-CD)s give obviously or slightly larger K_s values toward guest dyes than native β-CD, owing to simultaneous contributions of two hydrophobic β-CD cavities. Furthermore, metallobis(β-CD)s afford more stable complexes with guest molecules than parent bis(β-CD)s through a cooperative multisite binding mechanism. Upon inclusion complexation, metallobis(β-CD)s provide two or four hydrophobic binding sites (β-CD cavities) and one

Table 1. Binding Constants of Bis(β-CD)s with Some Dyes[a]

host	K_s (10^3 M^{-1}) G1	G2	G3	G4	G5	G6	G7	G8	G9	G10	G11	G12	G13	reference
β-CD[b]	0.1	~1.8−4.0	38	2.1	2.4	2.5	~3.0−9.0	~3.0−9.0	0.7	~2.6−3.1	0.5	~4.2−4.9	2.2	
4−**13**	~0.7−5.5	~3.6−23.8					~17.4−37.2			~2.4−24.8	~1.0−3.7	~4.5−24.7	~3.1−13.3	29a, 34, 35, 43
their Pt^{IV} complexes	~2.5−13.9	~15.3−50.2												34, 35
14−**18**	~0.7−2.4	~10.7−18.8					~3.2−34.3						~4.6−20.3	3, 31
their Cu^{II} complexes	~1.4−1.6	~21.1−23.0					~19.5−34.4						~14.3−56.7	31
19−**22**	~0.5−1.7	~4.4−10.6					~5.3−41.6			~2.7−30.8		~4.7−27.3	~3.9−8.1	33, 37a
their Cu^{II} complexes	~1.2−4.3	~11.4−29.2								~20.1−60.3		~14.3−66.9		37a
23−**27**[c]		~11.0−45.7					~25−192		~4.6−13.9					21
28−**31**		~6.7−16.7			~4.1−8.1	~3.8−6.0								4, 15b, 15c
32−**40**		~28−74	~79−8.2 × 10^3											7b, 25, 44
32[d]	0.7	87					583	2030						5
41		20	3.5 × 10^2	16			1.6 × 10^4	6.1 × 10^3						20
42			3.5 × 10^4											7d

[a] at pH ~5.9−7.2, unless noted otherwise. For 1:2 binding, K_s refers to the binding constant for the complexation of bis(β-CD) with the first guest molecule. [b] K_s values for β-CD are from refs 4, 5, 7d, 15b, 20, 21, 34, 35, and 37a. [c] at pH 9.0 and 5.5. [d] at pH 10.6.

(or several) metal center(s), which jointly contribute to the cooperative binding of metallobis(β-CD)s with guest molecules.

Some biologically important molecules, e.g., oligopeptides and steroids, are also extensively utilized as typical guest molecules for the cooperative binding of bis(β-CD)s.[16,27] In Table 2, bis(β-CD)s show moderate to strong binding abilities toward oligopeptides with a K_s range of ~10^2−10^4 M^{-1}, attributed to not only the cooperative binding of two β-CD cavities but also additional binding interactions from the linker, especially from oligo(ethylenediamino) fragments and/or coordinated metal ions in the linker. In a neutral media, −NH− units in oligo(ethylenediamino) fragments are partly protonated. Therefore, electrostatic interactions between protonated amino groups (−NH_2^+−) in the linker and the anionic carboxylate group of the oligopeptide, as well as hydrogen-bond interactions between carbonyl, carboxyl, and amino groups in oligopeptides and oligoethylenediamino fragments in the linker, jointly strengthen the host−guest inclusion complexation. For metallobis(β-CD)s, coordinated metal ions also provide additional binding interactions toward oligopeptides through heteroatom−metal chelation effects and/or electrostastic interactions. As a cumulative result of these factors, both bis(β-CD)s and metallobis(β-CD)s show good binding abilities toward oligopeptides. Similarly, bis(β-CD)s and metallobis(β-CD)s also show higher binding abilities toward steroids (K_s = ~10^3−10^6 M^{-1}) than native β-CD and monomodified β-CDs (K_s = ~10^1−10^4 M^{-1}). Through a comparison on the binding abilities of metallobis(β-CD)s and their parent bis(β-CD)s, we can find that metallobis(β-CD)s show stronger binding abilities than uncoordinated bis(β-CD)s attributed to the intramolecular 2:2 cooperative binding mode, where a metallobis(β-CD) affords four β-CD cavities and one (or three) metal center(s) jointly contributing to its cooperative binding with two guest molecules. Additionally, the coordination of the metal ion shortens the effective length of the linker to some extent and thus improves the size fit between host and guest. The cumulative result of these factors is that metallobis(β-CD)s show very strong binding abilities around ~6−4.1 × 10^3 times higher than those of native and monomodified β-CDs.[37b] Moreover, the cooperative binding of bis(β-CD)s toward macrocycles and metalated macrocycles is also reported, giving the K_s values in a range of ~1.8 × 10^3−1.7 × 10^8 M^{-1}.[13,15a,19]

Multiple Recognition. Another key function of bis(β-CD)s is their multiple recognition behaviors and the degree to which the size, shape, charge, hydrophobicity, and chirality of guest molecules match those of bis(β-CD)s has a dominant effect on stabilities of complexes formed between bis(β-CD)s and guest molecules. The role of the size-fit effect can be readily recognized by comparing binding abilities of bis(β-CD)s toward several pairs of guest molecules with structural similarities. For example, bis(β-CD)s show stronger binding affinities toward longer guest **G2** (MM2 optimized molecular length of 14.1 Å) than toward shorter guest **G1** (8.1 Å), because the longer skeleton of **G2** enables it to penetrate deeper into the β-CD

Scheme 7

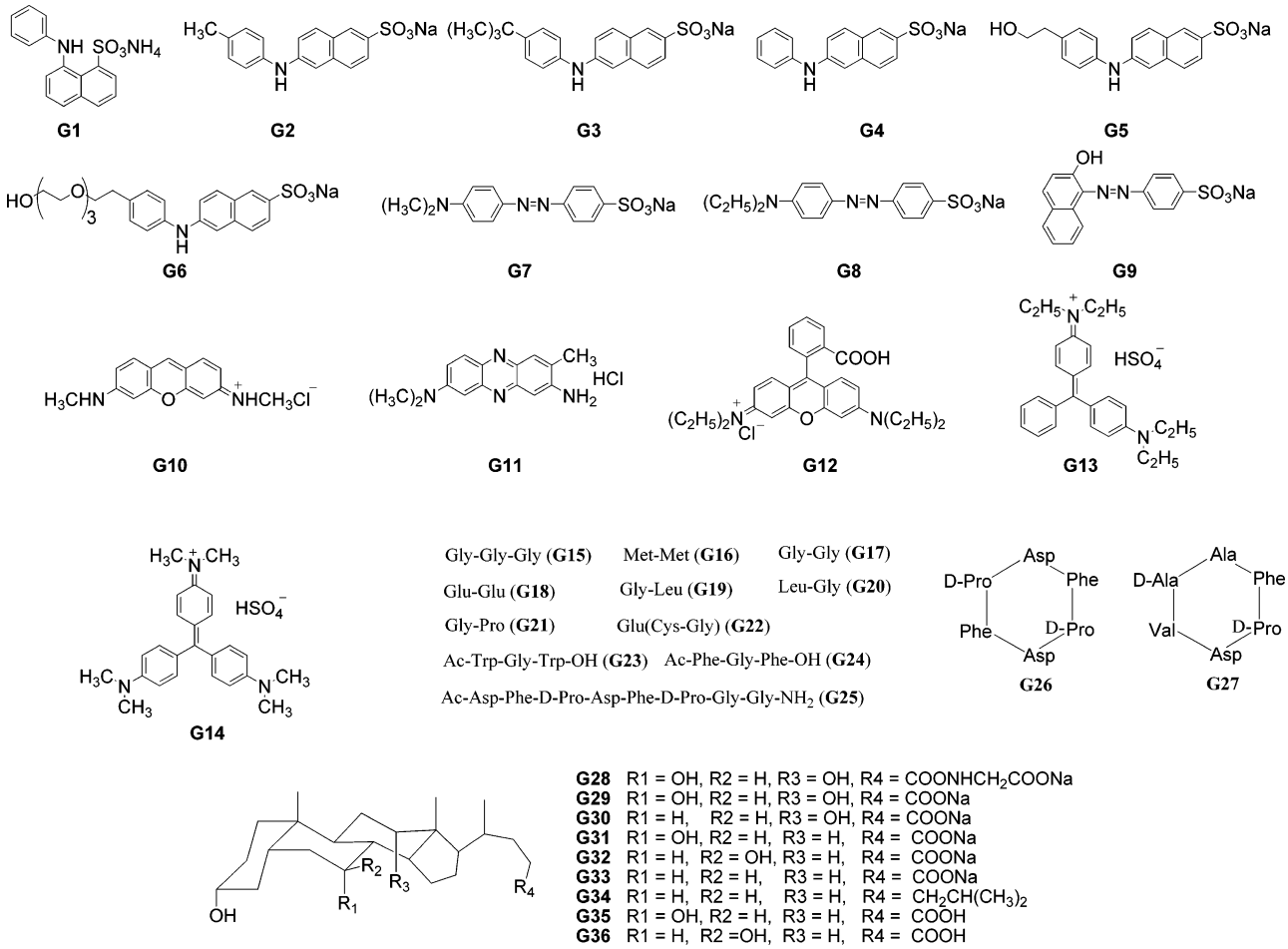


Table 2. Binding Constants of Bis(β-CD)s with Some Oligopeptides and Steroids[a]

host	guest	K_s (10^3 M^{-1})	reference
43	**G15**−**G20**	∼0.26−1.2	41
44	**G16**−**G21**	∼0.59−16.6	45
45	**G15**, **G17**−**G22**	∼0.13−6.8	36
Cu^{II} and Ni^{II} complexes of **45**	**G15**, **G17**−**G22**	∼1.3−68.2	36
33, **46**−**50**	**G23**−**G27**	∼0.08−2.6	7c
6−**7**	**G29**, **G30**	∼4.1−6.1	46
20−**22**	**G29**−**G30**	∼6.8−13.1	46
51−**53**	**G28**−**G30**	∼2.8−21.7	37b
Cu^{II} complexes of **51**−**53**	**G28**−**G30**	∼13.0−1745	37b
54−**55**	**G29**−**G33**	∼36−8.9 × 10^3	11
32, **56**	**G34**	∼147−5.54 × 10^3	7b
57	**G35**, **G36**	∼1.3−6.9	26b

[a] For 1:2 binding, K_s refers to the binding constant for the complexation of bis(β-CD) with the first guest molecule.

cavity upon complexation and thus lead to strong van der Waals and hydrophobic interactions between host and guest. For the **G10**/**G11** pair, each of which possesses a heterocycle anthracene moiety, bis(β-CD)s give higher binding abilities toward **G10** than **G11**, because smaller methylamino substituents of **G10** can be well-included in the β-CD cavity from the longitudinal direction, while **G11** only partly penetrates into the β-CD cavity because of the steric hindrance from bigger end groups. An additional example of the size-fit effect is that, for a specific guest, there is an optimum linker length for stabilizing bis(β-CD)/guest complexes that depends upon the nature of guest species, and a lengthening or a shortening of the linker will be unfavorable to the host−guest binding.[21,25]

Another important controlling factor for the multiple recognition of bis(β-CD)s is the shape-fit effect. From a comparison on binding abilities of bis(β-CD)s toward representative guests with good structural diversity, we find that T-shaped or triangular guests are better bound by long-linked bis(β-CD)s, while short-linked bis(β-CD)s show stronger binding abilities toward linear guests. For short-linked bis(β-CD)s, the linear guest can penetrate deeply into the β-CD cavity from the longitudinal direction, while the nonlinear guest only penetrates in part into the β-CD cavity because of the steric hindrance. However, long-linked bis(β-CD)s can afford preorganized pseudocavities through the adjustment and orientation of flexible linkers, where branch fragments of T-shaped or triangular guests can be appropriately accommodated, and thus exhibit stronger binding abilities for nonlinear guests.

The third controlling factor is the charge-fit effect. Its influence can be observed by examining the binding behaviors of bis(β-CD)s bearing charge recognition sites. Possessing a calix[4]arene linker as a recognition site for positive charges, bis(β-CD) **58** gives a high K_s for **G14** up to 22 300 M^{-1} and a reversed **G14**/**G13** selectivity up to

4.2 (K_s^{G14}/K_s^{G13}) versus the originally low **G14**/**G13** selectivity ($K_s^{G14}/K_s^{G13} = 0.86$) of native β-CD.[32] Crown-ether-bridged bis(β-CD)s **59**−**60** give higher binding constants for negatively charged guests **G1** and **G2** but lower binding constants for positively charged guests **G10** and **G12**, in Na_2HPO_4/NaH_2PO_4 buffer solution than in Tris-HCl buffer solution.[29b] Control experiments demonstrate that the ion strength is not the main factor for these differences in binding abilities of crown-ether-bridged bis(β-CD)s. Therefore, these unique molecular recognition behaviors may be mainly attributed to the charge-fit effect between the Na^+-coordinated crown ether unit and the charged guest molecule.

Besides size-fit, shape-fit, and charge-fit effects, there are some other controlling factors, e.g., hydrophobicity-fit, chirality-fit, and solvent effect,[7d] working in the multiple recognition of bis(β-CD)s. Through a simultaneous contribution of these factors, bis(β-CD)s exhibit exciting molecular recognition abilities superior to native and monomodified β-CDs.

Thermodynamics. Temperature-dependent spectrophotometric titrations and isothermal microcalorimetric titrations allow thermodynamic parameters for host−guest complexations to be determined. In most cases, the cooperative binding of bis(β-CD)s are mainly driven by favorable enthalpic gains, accompanied by either positive or negative entropic changes. Generally, inclusion complexations lead to not only negative enthalpic changes, which forward the equilibrium to the formation of the host−guest complex, but also negative entropic changes arising from the loss of conformational freedoms. However, unfavorable entropic losses can be compensated by the extensive desolvation effect of the host and guest to some extent. Before the complex formation, both bis(β-CD) and the guest molecule are solvated and solvent molecules around solutes are highly ordered. During the complexation process, the guest molecule loses its solvated shell and solvent molecules leave β-CD cavities. This process makes the disorder increase and leads to positive entropic changes, which overwhelm entropic losses arising from the structural freezing in part or in whole.

The enthalpy−entropy compensation effect is a general rule in many chemical and biological systems. That is, as the enthalpy becomes more favorable, the entropy becomes less so and vice versa.[47] When $T\Delta S°$ data are plotted against $\Delta H°$ values for a particular host−guest system, a good linear relationship should be obtained and the slope (α) and intercept ($T\Delta S_o$) of the $T\Delta S°-\Delta H°$ plot can be used as statistic representations for the degree of conformational change and the extent of the desolvation effect upon complexation, respectively. Using thermodynamic parameters obtained by our laboratory and others,[7e,11,13,16,33,35,46] we can obtain a $T\Delta S°-\Delta H°$ plot for the cooperative binding of bis(β-CD)s with guest molecules as shown in Figure 1.

Interestingly, the slope for bis(β-CD)s (α = 0.85) is smaller than that for monomodified β-CDs (α = 0.99) but larger than that for native β-CD (α = 0.80), while the intercept for bis(β-CD)s ($T\Delta S_o$ = 23.5 kJ mol^{-1}) is larger than that for native β-CD ($T\Delta S_o$ = 11 kJ mol^{-1}) and monomodified β-CDs ($T\Delta S_o$ = 17 kJ mol^{-1}).[47] These results demonstrate that bis(β-CD)s undergo moderate conformational changes and extensive desolvation effects upon cooperative binding with guest molecules.

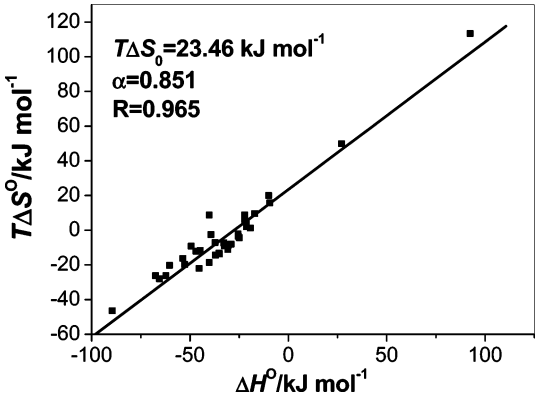


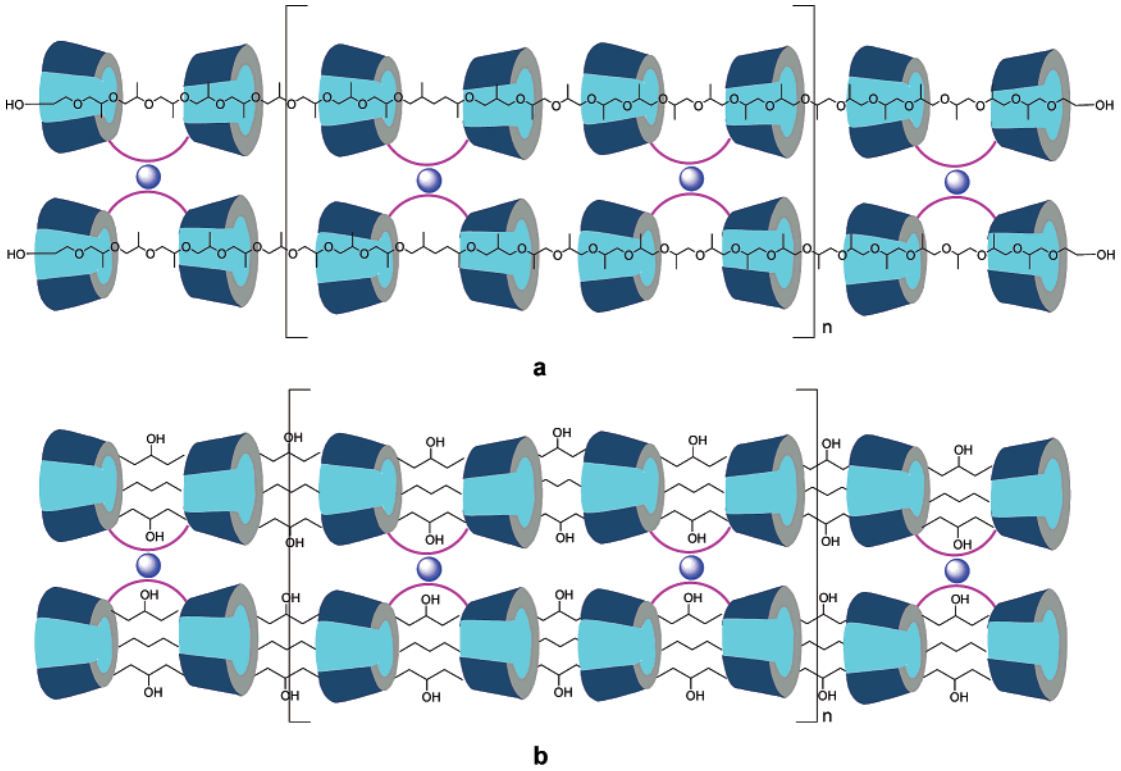
FIGURE 1. Enthalpy−entropy compensation plot for the cooperative binding of bis(β-CD)s.

Molecular Assembly

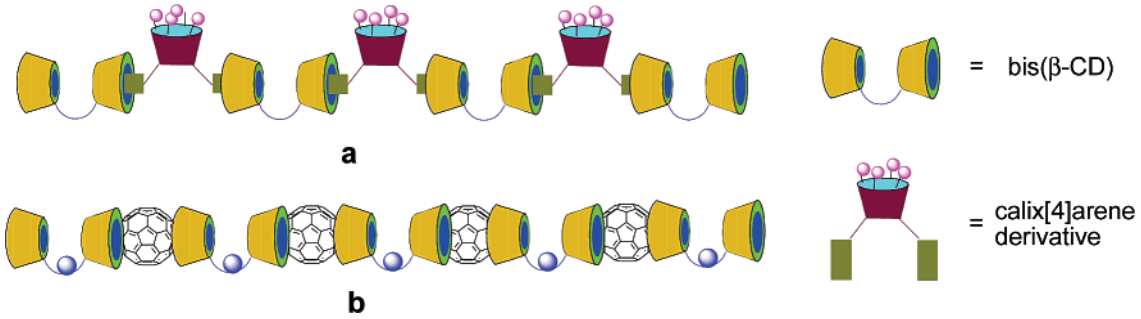
The capability of forming stable complexes with organic molecules through cooperative binding makes bis(β-CD)s attractive as building blocks for the construction of supramolecular architectures. Using a method established by Harada,[48] metallobis(β-CD)s can be threaded on two poly(propylene glycol) (PPG) chains to give bis(pseudopolyrotaxane)s possessing many coordinated metal centers (Scheme 8a),[49,50] and the number of metallobis(β-CD)s threaded on polymer chains is mainly dependent upon the length of the polymer chain. Generally, using PPG (M_w = 2000) as templates, four metallobis(β-CD)s can be threaded onto PPG chains to give bis(pseudopolyrotaxane)s in a 30% yield. Interestingly, the threading process is entirely endothermic ($\Delta H° > 0$) and gives a large entropic gain ($T\Delta S° > 0$), demonstrating that the aggregation process is driven by extensive desolvation effects of metallobis(β-CD)s and polymer chains. Bis(pseudopolyrotaxane)s obtained in this way can convert to bis(molecular tube)s by cross-linking adjacent β-CD rings with epichlorohydrin and removal of polymeric chains (Scheme 8b), which may have a potential application in nanoscience.[50]

The intermolecular *n*:*n* cooperative binding of bis(β-CD)s also leads to the formation of molecular assemblies. Through an intermolecular 2:2 cooperative binding, bis(β-CD) **61** forms double-helical assemblies with porphyrins.[15a,b] However, in most cases, the intermolecular *n*:*n* cooperative binding gives linear assemblies. For example, through the interconnective complexation of β-CDs with calix[4]arene derivatives,[51] wire-shaped aggregates in the range of ~400−900 nm are easily obtained by mixing **11** and bis(naphthoylamidoethoxy)calix[4]arenes in solution[52] (Scheme 9a). Besides calixarenes, bis(β-CD)s can also cooperatively bind other bulk molecules to form linear assemblies. Scheme 9b shows a water-soluble supramolecular fullerene assembly constructed

Scheme 8



Scheme 9



Scheme 10

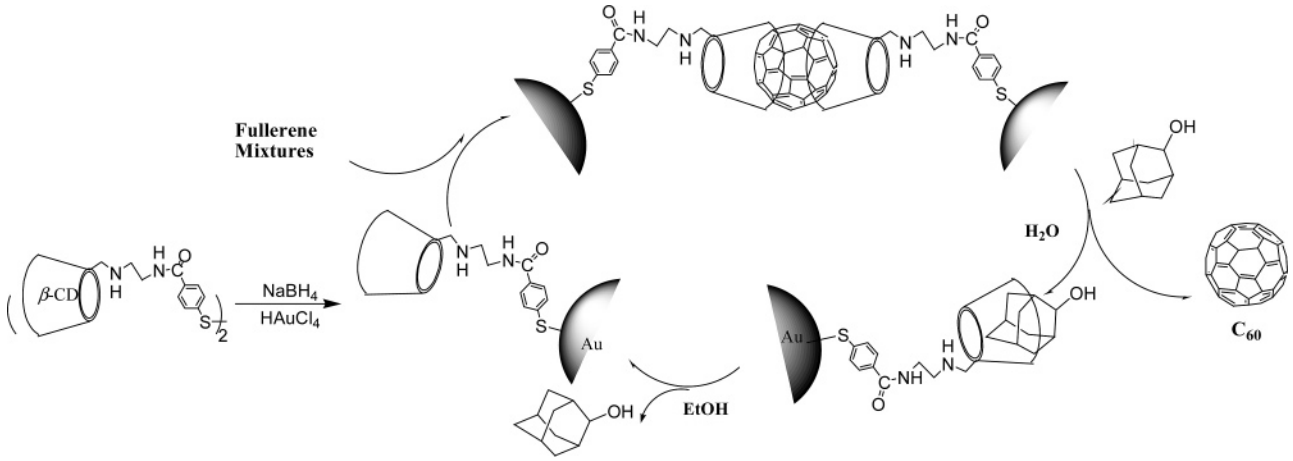
through the intermolecular cooperative binding of metallobis(β-CD)s with C_{60}s, which can serve as an efficient photodriven DNA cleaver.[53]

The intermolecular cooperative binding of bis(β-CD)s is also used in the construction of polyrotaxanes. Most reported polyrotaxanes use metal complexes or bulk organic molecules as stoppers. However, the introduction of these stoppers prevents the further assembly of polyrotaxanes to larger aggregates. Instead, using β-CDs as stoppers for polyrotaxanes, the resultant polyrotaxane-bridged bis(β-CD) can be further assembled to larger aggregates through the cooperative binding of free β-CD cavities with a wide variety of hydrophobic molecules. By this method, a short β-CD-based polyrotaxane (~15 nm) is assembled to a long linear aggregate (~600−700 nm) through the linkage of C_{60} (Scheme 10).[54]

Application

In the preceding sections, we have gained a deep insight into the cooperative binding and multiple recognition behaviors of bis(β-CD)s. The judicious application of these advantages can allow for the rational production of functional bis(β-CD)s. First, the photochemical properties of bis(β-CD)s can be addressed. For example, bis(β-CD)s **43**−**45** can be used as fluorescence sensors for oligopeptides,[36,41,45] and bis(β-CD)s **51**−**53**, **57**, and **62**$_3$·Ru/bipyridinium can be used as fluorescence sensors for ster-

Scheme 11



oids,[16,26b,37b] while **63**/*p-tert*-butylbenzoate can be used as a fluorescence sensor for lanthanide(III) cations.[14] Bis(β-CD)s also show a fluorescence sensitization ability toward some amino acids or purines. Generally, these biologically important molecules barely fluoresce in aqueous solution but emit strong fluorescence, which can be readily distinguished by the eye even at a low concentration, in the presence of bis(β-CD) **64**.[55] Significantly, bis(β-CD)s **65**−**68** can be used as photoswitchable molecules. By irradiation with light, these bis(β-CD)s are reversibly switched between a relatively flexible (open) form and a rigid (closed) form.[13]

CDs are produced from amylose and made of glucose; therefore, they are water-soluble and nontoxic. This property enables their applications in drug carriers, enzyme mimics, and photodynamic therapy.[8,44] For example, bis(β-CD) **18** can solubilize paclitaxel, an important antitumor drug, to a level of 2 mg/mL through its cooperative binding with a paclitaxel dimer, although the water solubility of parent paclitaxel is only ∼0.7−30 μg/mL (Figure 2). Biological activity experiments show that the obtained bis(β-CD)/paclitaxel complex displays a higher antitumor activity than parent paclitaxel. The high antitumor activity and satisfactory water solubility of the bis(β-CD)/paclitaxel complex suggest its potential use as an effective antitumor drug.[56] Possessing a Te−Te linker, bis(β-CD) **69** exhibits good enzymatic specificity of mimicking glutathione peroxidase and high efficiency of catalyzing the reduction of cumene peroxide and hydroperoxide in the presence of thiol substrates.[18] Bis(β-CD)s

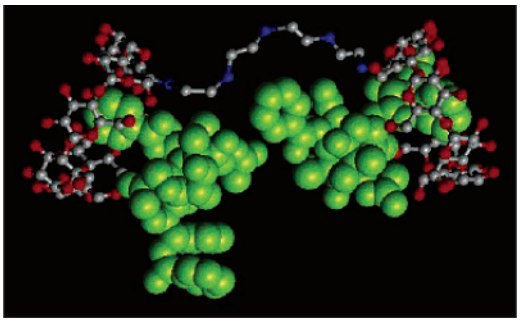


FIGURE 2. Possible structure of the bis(β-CD)/paclitaxel complex.

can also inhibit the activity of L-lactate dehydrogenase and citrate synthase at least in part by disruption of protein−protein aggregation.[7a] The irradiation of complexes formed by phthalocyanines and bis(β-CD)s with a C=C bond in the linker can cleave the olefinic linkers in complexes, resulting in precipitation of sensitizers. This process concentrates sensitizers in the light beam and has useful potential in photodynamic therapy.[8] Significantly, metal complexes of bis(β-CD)s **70**−**73** can hold the functional group of the substrate (ester carbonyl group or C=C bond) directly above a metal ion bound to the linker through the cooperative binding of the substrate with two β-CD cavities, resulting in a very fast ester hydrolysis rate and high oxidation selectivity with good turnover catalysis.[9,10] Through a similar mechanism, bis(β-CD) **74** can efficiently cleave β,β-carotene, and the product can be used as a precursor for retinol (vitamin A).[28]

In addition, bis(β-CD)s also have some other significant applications in fullerene chemistry. Bis(β-CD)s **75**−**76** can prevent the micelle-like aggregation of C_{60} in aqueous solution and thus significantly enhance the water solubility of C_{60} through the formation of intramolecular capsule-type conformers.[17,55] After bis(β-CD) **77** was attached on the surface of gold particles, the obtained bis(β-CD)-modified gold nanoparticles can be used as a recycling extractor for C_{60} (Scheme 11). In each cycle, 50 mg of bis-(β-CD)-modified gold nanoparticle can selectively capture 5 mg of C_{60} from a fullerene mixture.[57]

Conclusion

Upon complexation with guest molecules, a bis(β-CD) provides two β-CD cavities as hydrophobic binding sites and a linker as both a positive binding site for the guest and a versatile coordinating site for metal ions. Additionally, the metal ion(s) introduced in the linker not only adjusts and reorients β-CD cavities and the linker to match the size/shape of the guest molecule but also acts as an additional guest binding site(s) through coordination and/or electrostatic interactions. Therefore, bis(β-CD)s exhibit significant cooperative binding and multiple recognition abilities through simultaneous contributions of these

factors. Researches on these aspects can help us deeply understand and mimic the cooperative "multimode, multipoint" bindings often observed in biological systems. Moreover, bis(β-CD)s also actively participate in the construction of ordered nanostructure through the intermolecular cooperative binding. The past 2 decades witnessed a significant harvest in bis(β-CD) chemistry. However, we believe that exciting functions and potentials of bis(β-CD)s are only beginning to be discovered.

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