Construction and Functions of Cyclodextrin-Based 1D Supramolecular Strands and their Secondary Assemblies

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Cyclodextrins (CDs), a class of cyclic oligosaccharides, are water-soluble, nontoxic, and commercial available with a low price, and their well-defined hydrophobic cavity can bind various organic/biological substrates. Through their molecular assembly mediated by organic, inorganic, or polymeric molecules as templates, CDs and their functional derivatives can be assembled to 1D supramolecular strands, wherein the functional groups of the CDs are closely located in a highly ordered manner. This structural feature greatly favors the cooperative effect of numerous functional groups in the supramolecular strand, as well as the interactions of the supramolecular strands with the multiple binding sites of substrates, especially biological substrates. Therefore, CD-based 1D supramolecular strands exhibit many material, biological, and catalytic functions, and these properties can be further improved through their secondary assembly. An overview of recent advances in the development of the construction and functions of CD-based 1D supramolecular strands and their secondary assemblies is given here. It is expected that the representative contributions described can inspire future investigations and lead to discoveries that promote the research of CD-based functional materials.

1. Introduction

Cyclodextrins (CDs) are a class of torus-shaped cyclic oligosaccharides mainly with six to eight D-glucose units linked by α-1,4-glucose bonds (**Figure 1**a). Because CDs are obtained from the enzymatic degradation of one of the most essential polysaccharides, starch, they are nontoxic and commercial available with a low price. Importantly, CD possesses a hydrophobic cavity that can bind various inorganic/organic/biological molecules and ions in both aqueous solution and the solid state. These properties, along with the satisfactory water solubility, jointly enable the wide application of CDs not only as excellent receptors for molecular recognition but also as convenient building blocks to construct nanostructured functional materials, especially bioactive materials.[1] During the period from the 1970s to the 1990s, many successful studies on natural and simply modified CDs as artificial enzyme models,[2] enzymes synergists,[3] drug carriers,[4,5] and biological molecules sensors[6] were widely reported, and all these properties are closely related to the encapsulation of model substrates in the hydrophobic cavity of CDs. After the end of 1990s, more and more attention was paid to the design and construction of CD-based supramolecular assemblies,[7] a class of CD aggregates of nanometer size, because the limited inclusion-complexation abilities of natural CDs and simple modification were found inevitably unfavorable to the bioavailability and bioactivity of CDs. Among the various CD-based supramolecular assemblies, 1D supramolecular strands have attracted increasing interest. As compared with natural CDs and simply modified CDs, CD-based 1D supramolecular strands possess several inherent advantages. Firstly, CD-based 1D supramolecular strands gather multiple CD cavities with functional substituents in a highly ordered manner with a single growth direction, which is favorable for efficient association with the substrates through cooperative binding. Secondly, the close location between the functional groups in the 1D supramolecular strands and the substrate enables simultaneous interaction of numerous functional groups of CD-based 1D supramolecular strands with multiple sites of substrates through an integrative effect of a number of non-covalent interactions. As a joint result of these factors, CD-based 1D supramolecular strands can be regarded as an ideal model to mimic the cooperative "multimode, multipoint" binding often observed in biological systems, and is thus expected to exhibit a number of fascinating biomaterial functions. This Research News article summarizes our recent endeavors and related work by other investigators on CD-based 1D supramolecular strands and their secondary assemblies, with a special emphasis on their construction and their function as biological sensors, DNA cleavers, and drug/gene carriers, for example.

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2. CD-Based 1D Supramolecular Strands with Covalent Polymer as Core

1D supramolecular strands composed of one or two covalent polymers as the axle component and several or more CD

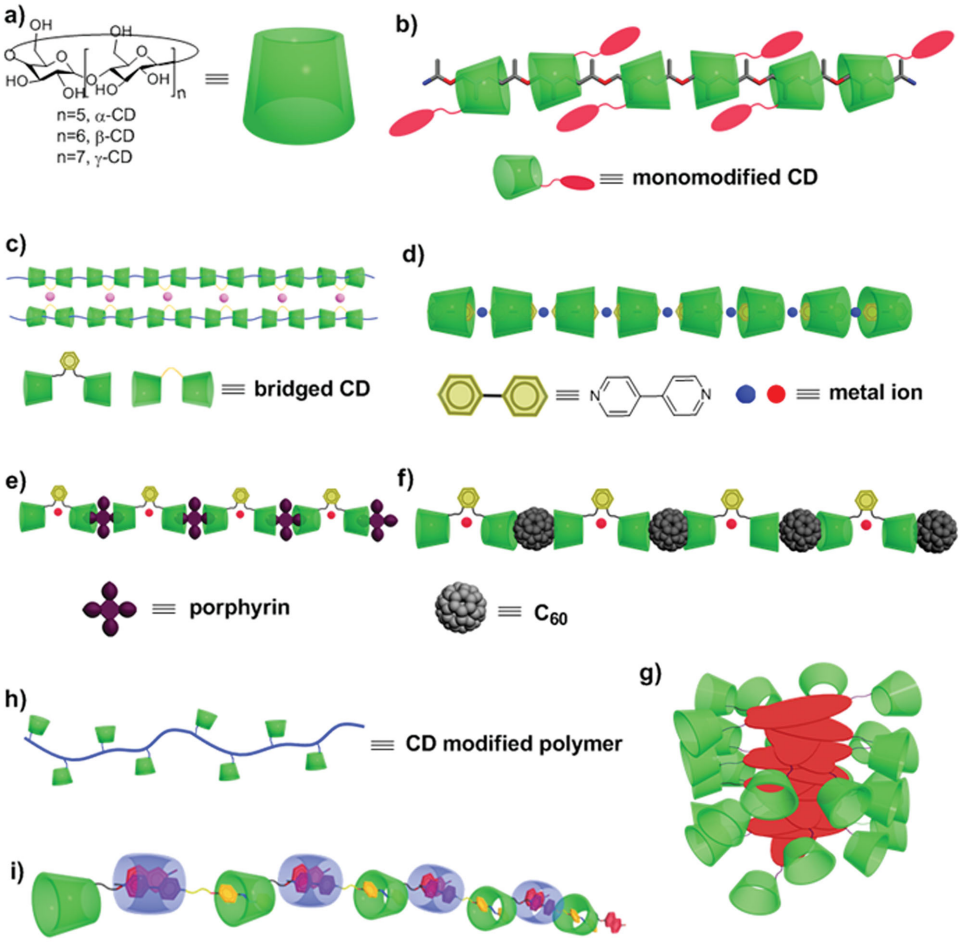

Figure 1. Schematic illustration of: a) CDs; b,c) CD-based 1D supramolecular strand with covalent polymer as the core; d) CD-based 1D strand with coordinated polymer as core; e) CD-based 1D strand with polyporphyrin as the core; f) CD-based 1D strand with polyfullerene as the core; g,h) self-assembled 1D supramolecular strand, and i) 1D supramolecular strand with CD grafts.

cavities as the wheel component are named pseudopolyrotaxane or polyrotaxane.[8] Generally, CD-based pseudopolyrotaxane can be conveniently constructed using the method established by Harada,[9] where several CD cavities are threaded onto a covalent polymer axis. After introducing big terminal groups at the chain ends as stoppers to prevent the de-threading of the CDs, the CD-based pseudopolyrotaxane can convert to CD-based polyrotaxane. Significantly, in a pseudopolyrotaxane or polyrotaxane, the functional substituents of the building blocks are closely located in a limited space, which enables them to interact simultaneously with the multiple binding sites of a substrate, especially biological molecules, and thus greatly enhances the functions of the building blocks. For example, anthryl-modified β-CD gives a moderate affinity toward DNA because the anthryl group can only intercalate in the minor DNA groove. However, when assembling anthryl-modified β-CDs to a supramolecular strand, the anthryl groups in the supramolecular strand can intercalate in both the minor and major DNA grooves. As a result, the supramolecular strand presents good abilities of sensing DNA and condensing the originally loose free DNA to solid particles with an average diameter of ca. 100 nm, and thus is expected to have many exciting applications as a sensitive analytical tool in DNA chemistry with a promising potential to control gene expression and delivery (Figure 1b).[10]

The threading of metallo-bis(β-CD)s, such as the stoichiometric 2:1 organoselenium-bridged bis(β-CD)-Pt(IV) complexes, 2,2′-bipyridine-4,4′-dicarboxy-bridged bis(β-CD)–Cu(II) complexes or N,N′-bis(2-aminoethyl)-2,2′-biquinoline-4,4′-dicarboxamide-bridged bis(β-CD)–Ni(II) complexes, on two covalent polymer chains can generate the 1D supramolecular bis-strand with many coordinated metal centers (Figure 1c).[11] Based on scanning tunneling microscopy (STM) images and molecular model study, it can be found that this type of bis-strand exists as a preorganized porous structure, where the size of the hole between two adjacent metallo-bridged bis(β-CD) units is calculated to be suitable to accommodate a C_{60} or C_{70} molecule. Therefore, these supramolecular bis-strands present the capability of capturing fullerenes within the ordered holes formed by two adjacent metallo-bridged bis(β-CD) units and enhancing the solubility of fullerenes in water. In a typical example, C_{60} can associate with 53% of the ordered holes in a supramolecular bis-strand constructed from N,N′-bis(2-aminoethyl)-2,2′-biquinoline-4,4′-dicarboxamide-bridged bis(β-CD)–Ni(II) complexes.[11c]

Besides the threading reaction, another convenient strategy is the polycondensation reaction of CD inclusion complexes, and this strategy always leads to the formation of a CD-based 1D supramolecular strand with conjugated polymer as the core.[12] The polycondensation reaction of permethyl-β-CD/aniline complexes gives a supramolecular strand with polyaniline as the core and permethyl-β-CDs as the envelope, where ca. 5 phenyl units of polyaniline chain can thread a permethyl-β-CD unit due to the inevitable de-threading of permethyl-β-CDs during the polycondensation reaction. Electron paramagnetic resonance (EPR) experiments show that the permethyl-β-CD/polyaniline supramolecular strand exhibits a much slower attenuation speed and a much smaller attenuation ratio of the signal intensity than those of polyaniline. The more-negative first anodic peak of the permethyl-β-CD/polyaniline supramolecular strand in the cyclic voltammetry (CV) curves also confirms that the formation of radical cations in the supramolecular strand is easier than in free polyaniline. These results jointly demonstrate that the enveloping of permethyl-β-CDs on a polyaniline chain not only enhances the water solubility of the polyaniline but also stabilizes the radical cations existing in the emeraldine state, i.e. the conductive doped form, of polyaniline, which is greatly favorable for the stability and conductivity of polyaniline.[12b]

3. CD-Based 1D Strands with Coordinated Polymer as Core

The metal coordination linkage of CD/ligand inclusion complexes is another convenient way to construct CD-based 1D supramolecular strands (Figure 1d). In this strategy, CD firstly associates with organic ligands, especially ditopic aromatic heterocyclic ligands such as dipyridine, to form CD/ligand inclusion complexes with a 1:1 or 1:2 stoichiometry. Then, the coordination of CD/ligand inclusion complexes with equivalent transition metal ions or metallo-organic groups gives a 1D supramolecular strand in aqueous solution. Herein, the fine structure of the supramolecular strand mainly depends on the coordination geometry of the metal center, while the length of the supramolecular strand decreases with the enlargement of the CD cavity. For example, either α-CD or β-CD can form a stoichiometric 1:1 inclusion complex with 4,4′-dipyridine, which further coordinates with Ni(II) ions with an octahedral coordination geometry to produce a linear supramolecular strand, with a length of ca. 1600 nm for the supramolecular strand constructed from α-CD/4,4′-dipyridine or ca. 450 nm for that constructed from β-CD/4,4′-dipyridine, respectively. When using the stoichiometric 1:2 γ-CD/4,4′-dipyridine complex and Cu(II) ions with a square-planar coordination geometry as building blocks, the length of the resultant linear supramolecular strand decreases to ca. 200 nm.[13] Alternatively, when using the β-CD/4,4′-dipyridine complex as the building blocks and Ru(2,2′-dipyridine)$_2$ groups as linker components, the resultant supramolecular strand shows a 1D zig-zag morphology because two adjacent β-CD/4,4′-dipyridine complexes are coplanar and located perpendicular to each other around the octahedron-coordinated Ru center.[14] It is noteworthy that this supramolecular strand exhibits good photophysical properties in both aqueous solution and the solid state.

4. CD-Based 1D Strands with Polyporphyrin as Core

CDs, especially permethylated CDs, can form very stable 2:1 inclusion complexes with anionic porphyrins in water.[15] Therefore, a CD-based 1D strand with polyporphyrin as the core can be easily prepared in situ by simply mixing the aqueous solutions of bridged permethyl-CD dimers and anionic porphyrins (Figure 1e),[16] and the linear array of such a supramolecular strand can convert to a periodic porous array by using permethyl-CD tetramers or octamers instead of permethyl-CD dimers as building blocks.[17] Owing to the attractive electronic, photochemical, and photophysical properties of porphyrins, the polyporphyrin cores can interact with the linkers of bridged permethyl-CD oligomers, leading to good electron transfer, energy transfer, and DNA cleavage properties.[16a,c17b], For example, the photoinduced electron transfer (PET) within supramolecular strands constructed from C_{60}-bridged permethyl-CD dimers and [5,10,15,20-tetrakis(4-sulfonatophenyl) porphinato]zinc(II)s can quench 96% of the fluorescence intensity of [5,10,15,20-tetrakis(4-sulfonatophenyl)porphinato]zinc(II), giving a rate of charge separation of up to $9.06 \times 108\ s^{-1}$.[16a] In addition, supramolecular strands constructed from BODIPY-bridged permethyl-CD dimers (BODIPY = 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (boron-dipyrromethene)) and 5,10,15,20-tetrakis(4-sulfonatophenyl) porphyrin gives a fairly high energy-transfer quantum yield up to 94% for the fluorescence resonance energy transfer (FRET) from the BODIPY spacers to the polyporphyrin core.[16c] Interestingly, this type of supramolecular strand can be disrupted when interacting with a cell membrane to release the porphyrin components into the cell, but the bridged permethyl-CD dimers remain in the cell membrane. This transmembrane dissociation property of the supramolecular strands will enable their application in the delivery of biological and drug molecules containing an anionic porphyrin skeleton such as β-octaphenyl-meso-tetra(4-carboxyl)-phenylporphyrin.[16d]

5. CD-Based 1D Strands with Polyfullerene as Core

C_{60} has also been reported able to form stoichiometric 1:2 inclusion complexes with CDs,[18] and this property was then successfully employed in the construction of a 1D strand with polyfullerene as the core through end-to-end intermolecular cooperative binding of C_{60}s by CD oligomers. In the first reported example of such an assembly, stirring an equimolar mixture of Pt-coordinated organo-selenium bridged bis(β-CD)s with C_{60} in a toluene/DMF solution (v/v = 4:6) results in the formation of an 1D supramolecular strand (Figure 1f).[19] Interestingly, this supramolecular strand can cleave the closed supercoiled form of DNA into the nicked circular form by incubation under visible-light irradiation but shows no cleavage ability in the dark through a singlet oxygen mechanism. Herein, the C_{60}

moieties in the supramolecular strand are located close to the guanosine positions of the DNA. Under visible-light irradiation, the singlet oxygen ($^1O_2$) is sensitized by the photoexcitation of C_{60}. Then, the sensitized singlet oxygen reacts with the guanosines in the DNA by either [4 + 2] or [2 + 2] cycloaddition to the five-membered imidazole ring of the purine base, thus cleaving the DNA. In addition to the DNA cleavage, the C_{60} moieties in the supramolecular strand can also act as a good acceptor in the energy-transfer process. For example, the intermolecular binding of a stoichiometric 3:1 pyridine-2,6-dicarboxamide-bridge bis(β-CD)/Tb^{3+} complex with three equivalents of C_{60} can form a trefoil-bundle-shaped supramolecular strand.[20] In this supramolecular strand, the incoming UV light is absorbed by the pyridine-2,6-dicarboxamide group, and then the coordinated Tb is excited and luminesces. Subsequently, most of the luminescence is absorbed by the C_{60} accommodated in the CD cavities, and the pyridine → Tb → C_{60} energy-transfer process leads to quenched luminescence.

6. Other CD-Based 1D Strands

Generally, CD derivatives bearing hydrophobic substituents, especially aromatic or bulky aliphatic groups that well match the size/shape of a CD cavity, tend to form self-assembled supramolecular strands with a helical or channel topology in the solid state.[7b] However, similar supramolecular strands formed in water are fairly rare because the self-aggregation degree of CD derivatives in water is usually low. Interestingly, when introducing a big aromatic substituent that has a strong tendency of π-stacking in water to the parent CD, the obtained CD derivatives are readily self-assembled to a 1D supramolecular strand in aqueous solution. In a typical example, perylenebisimide is attached onto the permethyl-β-CD rim, and further self-assembly of the resultant perylenebisimide-CD conjugate via π–π stacking interactions produces a 1D helical supramolecular strand (Figure 1g). In this supramolecular strand, the perylenebisimide units act as fluorescence probes due to their strong solid-state fluorescence, photochemical stability, and low quantum yield of intersystem crossing, while permethyl-β-CDs acts as molecular receptors that provide the binding sites for the analytes. Fluorescence-sensing experiments show that this supramolecular strand can be used as a highly sensitive vapor-detecting material for several kinds of volatile organic compounds, especially organic amines.[21] That is, the inclusion complexation of gaseous organic compounds with a CD cavity may change the distance between the perylene backbones and then induce the fluorescence quenching of perylenebisimide chromophores. In addition, the guest/substituent-induced self-sorting assembly of β-CDs with other macrocycles including α-CDs,[22] calixarenes,[23] and cucurbiturils[24] have also been successfully employed in 1D supramolecular strands with an alternating β-CD·macrocycle·β-CD·macrocycle··· order in solution (Figure 1h).

Besides being located in the main chain of a supramolecular strand, CD cavities can be also grafted to a functional polymer as side-chain branches. Subsequently, the grafted CD cavities further associate with the model substrates to form 1D supramolecular strands (Figure 1i). In a typical example of such a supramolecular strand, the CD cavities are linked to a targeting polysaccharide, namely hyaluronic acid. Then, as a consequence of the encapsulation of the hydrophobic moiety of the drug into the CD cavity, anticancer drugs or prodrugs such as adamplatin, are non-covalently bound to the CD-grafted hyaluronic acid to produce a supramolecular strand. The supramolecular strand thus prepared is biocompatible, biodegradable, and is well-recognized by the hyaluronic acid receptors that are over-expressed on the surface of cancer cells, exhibiting anticancer activities comparable to the commercial anticancer drug, cisplatin, toward MCF-7 human breast cancer cells and SKOV-3 human ovarian cancer cells but with lower side effects both in vitro and in vivo. This property consequently enables the potential application of this supramolecular strand as an efficient targeted-delivery system for anticancer drugs.[25]

7. Secondary Assemblies of CD-Based 1D Strands

Through their judicious design, CD-based 1D strands can be extended to enlarged 1D, 2D, and 3D secondary assemblies, accompanied by the improvement of properties. Generally, the length of the pseudopolyrotaxane or polyrotaxane constructed via the threading of CDs on the covalent polymer is mainly dependent on the length of the polymer template, which makes the construction of a long supramolecular strand difficult. However, a secondary assembly of pseudopolyrotaxane or polyrotaxane along its main chain direction can address this limitation. After introducing two free β-CD cavities as stoppers to the terminals of a CD-based pseudopolyrotaxane, the resultant polyrotaxane can further assemble with C_{60} through 2:1 β-CD/C_{60} inclusion complexation, resulting in the elongation of the original polyrotaxane by 13 times (**Figure 2**a).[26] In addition, the CD-based polyrotaxane with nine anthracene groups as stoppers can also be elongated by 2–50 times through the photoinduced intermolecular dimerization of anthracene in solution.[27] Significantly, after one stopper group of a CD-based polyrotaxane with a conjugated polymer as core is connected to the electrode, the secondary assembly of the two polyrotaxanes attached to the electrode, through the reaction of the other stopper group of the polyrotaxane with stilbene or diarylethene, leads to the formation of long molecular wires between the two electrodes.[28]

Besides along the main-chain direction, the secondary assembly of supramolecular strands can also take place along a direction perpendicular to the main chain. The supramolecular strand constructed from the threading of polycationic β-CDs onto a covalent polymer chain shows the gene transfection ability with and without serum, comparable to that of branched PEI (weight-average molecular weight 25 000 g mol^{-1}), one of the most effective gene-delivery polymers studied to date,[29] and its DNA condensation ability can be controlled at a level of moderate to high through adjusting the secondary-assembly degree of cucurbit[6]uril on the side chains of the supramolecular strand, giving the highest DNA condensation efficiency when 70% of the polycationic β-CDs in the supramolecular strand associate with the cucurbit[6]urils (Figure 2b).[30] In another typical example, a supramolecular strand with polyporphyrin as the core, constructed from

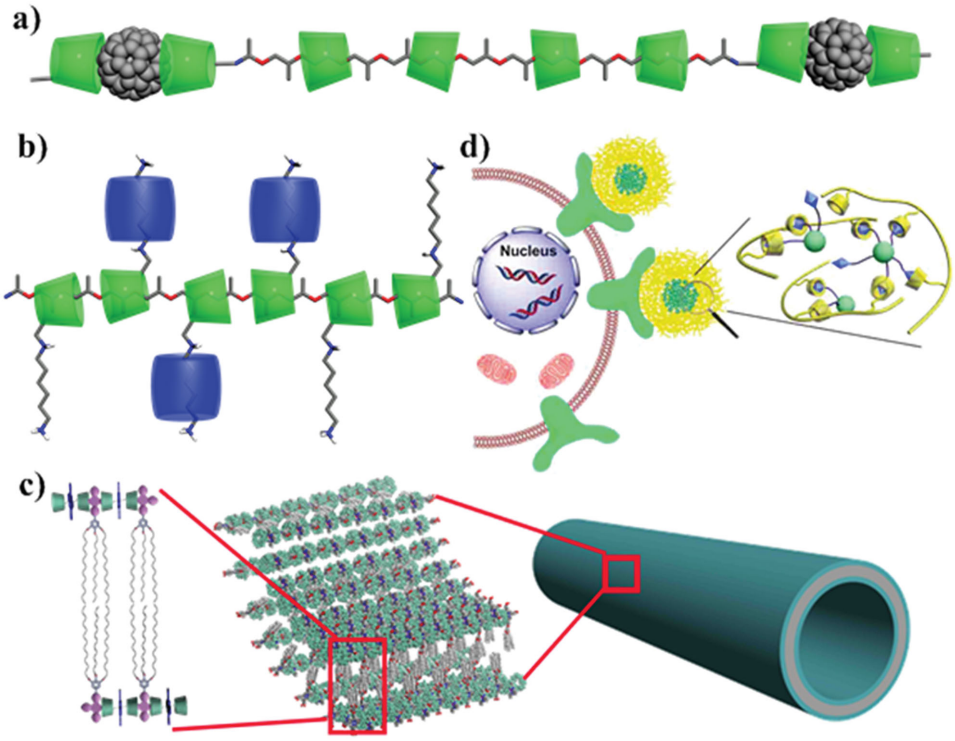

Figure 2. Schematic illustration of some secondary assemblies: a) from polyrotaxane and C_{60}, b) from supramolecular strands with side chains and cucurbit[6]uril, c) from supramolecular strands with polyporphyrin bearing hydrophobic tails, d) from supramolecular strands on gold nanoparticles.

phthalocyanine-bridged bis(permethyl-β-CD)s and anionic porphyrins with long hydrophobic alkyl tails, undergoes a secondary assembly to form a hollow tubular nanostructure (Figure 2c). The interior and exterior surfaces of this nanotube are composed of highly stable permethyl-β-CD/porphyrin-associated units with rigid phthalocyanine spacers, whereas the hydrophobic alkyl chains interlace with each other in the middle of the tubular walls. Importantly, the resulting nanotube not only provides numerous anionic porphyrins as the anchoring sites for catalytic centers, such as Pd^{2+}, but also offers a hydrophobic microenvironment, i.e. the hydrophobic domains of the alkyl chain interlayers, to readily accommodate the hydrophobic reactant at a location close to the catalytic centers. As a result, this tubular nanostructure can promote highly efficient catalytic reactions under environmentally benign conditions, giving good isolated yields (93–99%) for Suzuki–Miyaura coupling reactions between aryl halides and phenylboronic acid derivatives in one hour at room temperature, and can be easily recovered and reused for many catalytic cycles without any loss of reactivity and conversion ratio.[31]

The secondary assembly of CD-based 1D supramolecular strands on some inorganic or organic nanostructures, such as gold nanoparticles or carbon nanotubes, can produce 3D architectures with fascinating properties. For example, no gold nanoparticle, thioCD-based pseudopolyrotaxane or L-Try-CD-based pseudopolyrotaxane shows any capability of cleaving DNA or capturing fullerene. However, the secondary assembly of thioCD-based pseudopolyrotaxane on gold nanoparticles presents the ability of cleaving 75% of the closed supercoiled DNA to nicked DNA under visible-light irradiation, owing to the cooperative contribution of the sulfur-to-gold charge-transfer band and the gold d–d band excitations, as well as the subsequent transfer of excitation energy to the ground-state oxygen molecules to produce a singlet oxygen that cleaves the DNA.[32] Similarly, the secondary assembly of L-Try-CD-based pseudopolyrotaxanes on gold nanoparticles shows the capability of capturing and enriching fullerenes in solution, which does not belong to any of its components. Therein, the well preorganized porous structure and the presence of numerous electron donors (L-Try residues) in this secondary assembly is responsible for the fullerene-capturing ability through electron-transfer interactions between L-Try residues and fullerenes. In a quantitative analysis, 1 mg of secondary assembly (in 1 mL of water) can capture 1.83 mg of C_{60} in water.[33] In another example, a CD-grafted hyaluronic acid supramolecular strand shows special targeted-delivery ability for adamplatin prodrug due to the strong binding of the β-CD cavity with adamantyl groups.[25] Significantly, further assembly of this supramolecular strand on gold nanoparticles bearing adamantane moieties produces its secondary assembly as a 3D porous nanostructure (Figure 2d). Superior to its CD–hyaluronic acid precursor, this secondary assembly can serve as a versatile and biocompatible platform for the loading and delivery of various hydrophobic and hydrophilic anticancer drugs, including doxorubicin hydrochloride, paclitaxel, camptothecin, irinotecan hydrochloride, and topotecan hydrochloride, by taking advantage of the controlled association/dissociation of drug molecules from the cavities formed by the CD–hyaluronic acid skeletons and gold nanoparticles, as well as by harnessing the efficient targeting of cancer cells by hyaluronic acid. It is also noteworthy that the release of anticancer drugs from the secondary assembly is

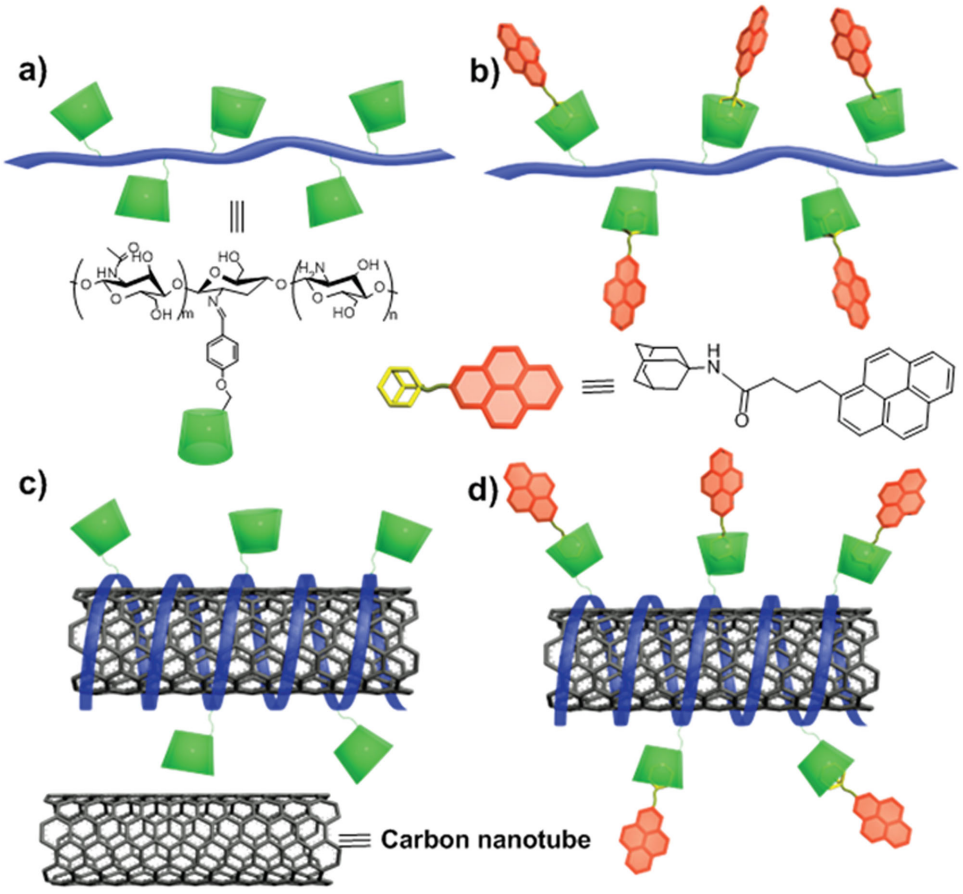

Figure 3. Secondary assemblies of CD-grafted chitosan/adamantanyl pyrene with carbon nanotubes in different sequences: a) CD-grafted chitosan, b) CD-grafted chitosan/adamantanyl pyrene dyad assemblies, c) CD-grafted chitosan/carbon nanotube dyad assemblies, d) CD-grafted chitosan/carbon nanotube/adamantanyl pyrene triad assemblies.

pH-responsive, with more-efficient release occurring under a mildly acidic environment, such as that in a cancer cell.[34]

In addition to gold nanoparticles, carbon nanotubes are also widely used as a template in the secondary assembly of CD-based 1D supramolecular strands. In such a system, CD-grafted chitosan (**Figure** 3a) assembles with adamantanyl pyrene and carbon nanotubes in different sequences to produce three different hierarchical assemblies, i.e., CD-grafted chitosan/adamantanyl pyrene dyad assemblies (Figure 3b), CD-grafted chitosan/carbon nanotube dyad assemblies (Figure 3c), and CD-grafted chitosan/carbon nanotube/adamantanyl pyrene triad assemblies (Figure 3d). Interestingly, these four assemblies exhibit different DNA condensation abilities. That is, CD-grafted chitosan shows a moderate DNA condensation ability and can only condense free DNA chains to uniform hollow loops. However, its hierarchical assemblies are much more effective in condensing DNA, and the free DNA chains can be condensed to infarctate or compact particles with an average diameter of ca. 200 nm, ca. 80 nm and ca. 160 nm by CD-grafted chitosan/ adamantanyl pyrene dyad, CD-grafted chitosan/carbon nanotube dyad, and CD-grafted chitosan/carbon nanotube/adamantanyl pyrene triad assemblies, respectively, owing to the cooperative contribution of aromatic pyrenes and inherent $-NH_3^+$ cations on the chitosan, as well as the rearrangement of CD-grafted chitosan on the surface of the carbon nanotubes as the highly dispersed polymers.[35] On the other hand, the secondary assembly of permethyl-β-CD/polyaniline supramolecular strands on carbon nanotubes is able to enhance the conductivity of the original supramolecular strand by 25 times.[12b]

8. Conclusion

It is clear that, with several classes of organic, inorganic, and polymeric molecules as mediators, CD-based 1D supramolecular strands and their secondary assemblies bearing numerous functional groups that are closely located in an ordered manner can be readily constructed through non-covalent fabrication. As a result, the 1D or multi-dimensional supramolecular systems thus obtained always exhibit fascinating properties, which enable many successful material, biological, and catalytic applications. In this Research News article, it has been shown that there are many successful examples of functional CD-based supramolecular strands and their secondary assembly in aqueous environment, and their structure and properties can

be smartly controlled. This finding, along with the non-covalent nature and multi-stimulus-responsive property, will promote not only convenient, detachable and dynamic construction, but also intelligent control of the CD-based supramolecular systems. Past studies have witnessed a significant harvest in CD-based supramolecular strands and their secondary assembly, and the need for functional materials provides timely opportunities for the application of these CD-based supramolecular systems. Therefore, we believe that exciting findings and potentials of CD-based supramolecular strands and their secondary assemblies are only beginning to be discovered.

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