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With this Feature Article we review, for the first time, the development of DNA-host conjugates—a nascent yet rapidly growing research focus within the ambit of DNA supramolecular chemistry. Synthetic hosts (such as cyclodextrins, cucurbiturils, and calixarenes) are well-suited to be partnered with DNA, since DNA assembly and host-guest binding both thrive in aqueous media, are largely orthogonal, and exhibit controllable and input-responsive properties. The covalent braiding of these two supramolecular synthons thus leads to advanced self-assemblies and nanostructures with exciting function that range from drug delivery agents to input-triggered switches. The latter class of DNA-host conjugates have been demonstrated to precisely control protein activity, and have also been used as modulable catalysts and versatile biosensors.

1. Introduction

The biological manipulation of an organism's Deoxyribonucleic acid, DNA—the salient biomacromolecule responsible for storing and propagating genetic information—is at the forefront of a new scientific revolution.[1, 2] This revolution has vast potential ranging from the creation of more robust crops/live stocks to the elimination of genetic diseases. A prime example is the powerful gene editing technique that harnesses CRISPR-CAs9.[3, 4] A second prong of this "DNA revolution" is the use of synthetically functionalized DNA, *ex vivo*. Much of this latter aspect of DNA research has focused on exploiting the unique properties of DNA (i.e., high fidelity molecular recognition, self-assembly, and programmability) in conjunction with ancillary synthetic moieties to generate chimeras that have the combined properties of the DNA and the synthetic entity, as well as novel emergent function.[5, 6]

Indeed, various DNA-synthetic molecule conjugates have been prepared with the goal of developing well-defined assemblies, nanomaterials, biocompatible agents, and stimuli-triggered molecular machines that have applications in the triumvirate of modern research, i.e., medicine, materials, and energy. In order to create such highly functional molecules, DNA has been tethered to a number of synthetic elements, such as chromophores,[7-9] lipids,[10] organometallic complexes,[11] proteins/peptides,[12] and nanoparticles,[13, 14] to name just a few.

A group of synthetic molecules that have recently grown in interest and sophistication are synthetic hosts—macrocyclic molecules that have a defined cavity tailored for the inclusion of guest molecules.[15-20] These host molecules include, cyclodextrins, cucurbiturils, calixarenes, crown ethers, and cyclophanes. In this Feature Article we highlight recent research efforts to combine the molecular recognition abilities of key water-soluble host molecules with the unique capabilities of DNA to afford novel functional systems. We first provide a brief background into the blossoming fields of DNA supramolecular chemistry and host-guest chemistry. The next section focuses on recent advances in terms of covalent conjugation of DNA with host molecules, which will lay the foundation for the major focus of this manuscript, vis-à-vis the design, development, and exciting applications of covalently tethered DNA-host complexes.

2. Background

2.1 DNA Supramolecular Chemistry

The fact that DNA plays the preeminent role in the heredity, development, and growth of living systems is unequivocal. Besides its central foundation in biology, DNA also provides a tool for the construction of predictable, programmable, and versatile, functional synthetic systems.[21-24] It is the unique properties of DNA, such as (a) the rapid and high-fidelity association via Watson-Crick (and non-canonical) base-pairing to form defined structures (such as duplexes and quadruplexes) and (b) the ease of synthetic (established phosphoramidite chemistry) and enzymatic (i.e., using polymerases, ligases, etc.) manipulation that make DNA particularly attractive in creating synthetic self-assembling systems.

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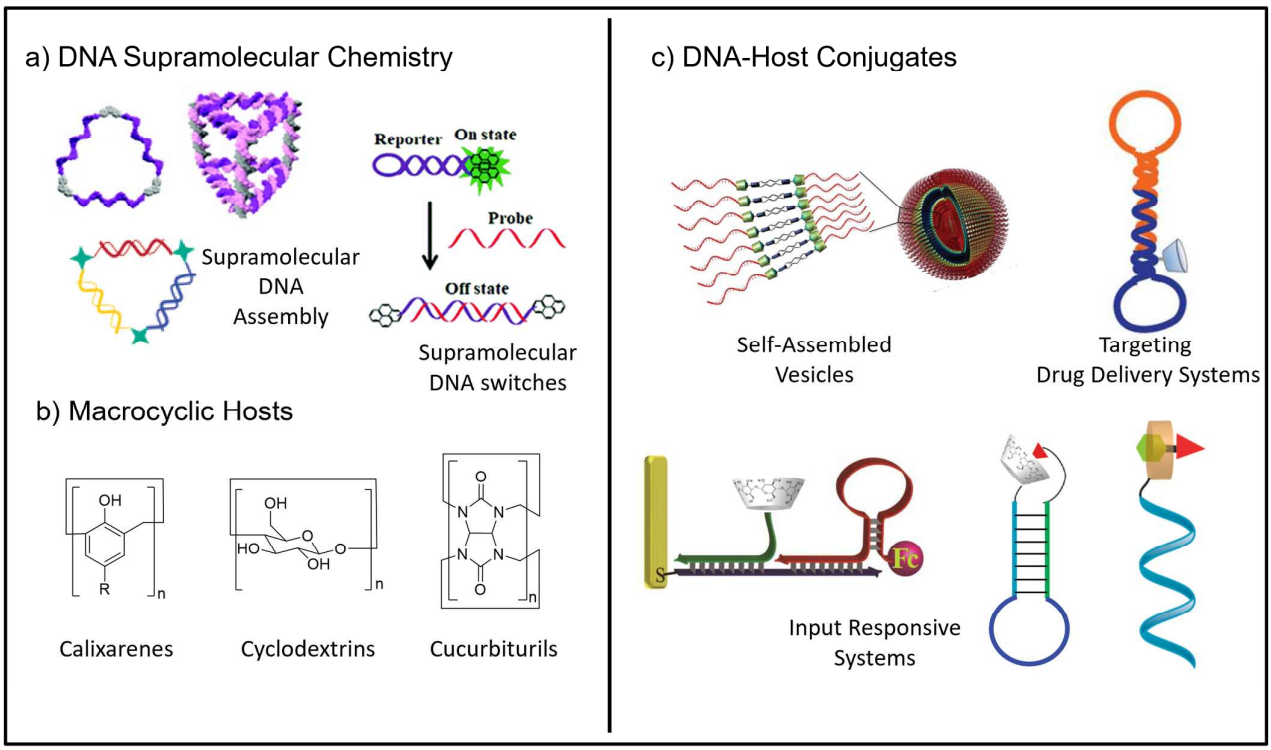


Figure 1. (a) The field of DNA supramolecular chemistry (that, *inter alia*, is composed of supramolecular DNA assembly and supramolecular DNA machines/switches) can be enriched by combining macrocyclic hosts (b) with DNA to afford DNA-host conjugates (c) that form well-defined nanomaterials and smaller supramolecular systems with diverse applications ranging from drug delivery vectors to input-responsive machines. Adapted from ref. 39, 78, and 81 with permission from the Royal Society of Chemistry. Adapted from ref. 40, 41, 71, 77, and 83 with permission from American Chemical Society.

Due to the abovementioned advantages, the field of DNA supramolecular chemistry has arisen (Figure 1a), where DNA is removed from its traditional genetic context and fused with synthetic molecules to develop diverse supramolecular architectures and functional systems.[25-30] While the term DNA supramolecular chemistry can be broadly defined, here we focus on nanostructures based on supramolecular DNA assembly[27, 28] and smaller systems based on supramolecular DNA switches[29, 30]. In this context, the DNA domain provides programmability and controllability to the otherwise mostly periodic and symmetric structures formed by purely synthetic supramolecular systems. On the other hand, the synthetic components can endow (a) interesting functionality (such photonic, electronic, catalytic, and protein-inhibition properties) and (b) orthogonal self-assembly capabilities to the DNA building blocks. Various organic,[31, 32] organometallic,[33, 34] and polymer,[35, 36] units can be used as supramolecular synthons for combining with DNA. Below, we highlight how a few exemplary synthetic organic units and ligands are utilized.

With the goal of harnessing DNA programmability to control the ordering of functional synthetic moieties, researchers have created DNA templated arrays of organic chromophores.[7-9] The position of the fluorophores can be controlled at defined sites using, single strand or double strand DNA templates, as well as higher-order DNA architectures. For example, the Sauer group assembled a unidirectional photonic wire carrying five different chromophores at well-defined positions based on a DNA duplex template.[37] Across the 13.6 nm photonic wire, a striking overall FRET efficiency of 90% was demonstrated using single-molecule fluorescence spectroscopy. Further, the appended organic chromophores can also be used to provide ancillary self-assembling interactions. For instance, Wagenknecht and colleagues have shown that the hydrophobic aromatic chromophore, perylene diimide (PDI), in conjunction with a three-way DNA junction can lead to higher-order structures. Here the PDIs serve as caps that link DNA blocks through π-stacking interactions (Figure 2a).[38]

In addition to harnessing DNA as structural scaffolds, the dynamics of DNA assembly can also be used to build functional supramolecular systems. It is established that DNA structure can be precisely controlled by various stimuli, such as pH, temperature, salt concentrations, and specific nucleic acid inputs. Thus, one can imbue these features into supramolecular DNA systems to build well-controlled machines with applications, *inter alia,* as biosensors. As an example of using DNA supramolecular switches for the detection of microRNAs, Zhang and coworkers developed a DNA hairpin that is labeled with pyrene molecules at both termini as reporter groups (Figure 2b).[39] The hairpin switch is first toggled OFF with a probe strand complementary to the hairpin. In the presence

of target microRNA Let-7a, the probe strand forms a duplex with Let-7a resulting in the hairpin being toggled back ON, providing a fluorescent signal from the pyrene excimers. Further, if a duplex-specific nuclease (DSN) is added, the probe strand is digested releasing Let-7a to bind to more probe strand and thereby providing a catalytic signal. As a combined result of the sensitivity of the pyrene excimer probe and the effective catalytic process, this system exhibits a remarkably high sensitivity with a detection limit as low as 0.58 fM.

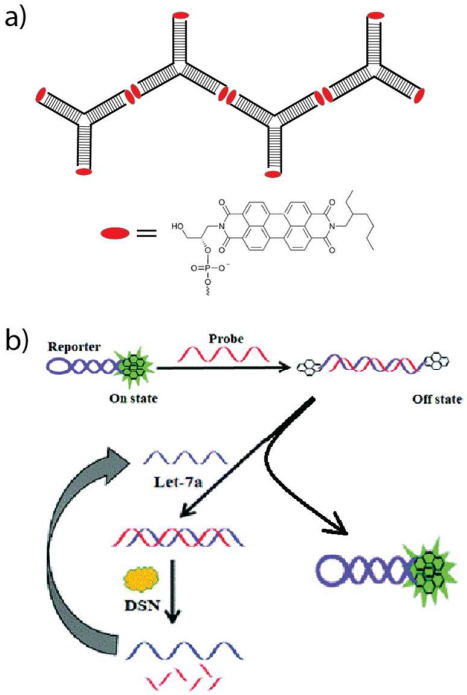


Figure 2. Examples of supramolecular systems composed of DNA tethered to chromophores. a) A higher-order assembly composed of three-way DNA junctions and perylene diimide based aromatic stacking interactions. b) A DNA switch based biosensor for microRNA detection that uses pyrene excimer formation as the signal output. Adapted from ref. 39 with permission from the Royal Society of Chemistry.

In order to enhance the traditional DNA self-assembly format and to pursue higher-order architectures, small organic molecules with specific geometries and angles can be designed and incorporated into DNA strands. These organic tethers serve as linkers and rigid vertices that assist in the formation of well-defined shapes such as DNA macrocycles and three dimensional (3D) nanocages. The Sleiman group has the led the way using this strategy. For example, the group constructed a set of single-stranded DNA polygons (Figure 3a, top) using a rigid organic linker, terphenyl **1**.[40] These two dimensional (2D) polygon building blocks were then used for facile and quantitative construction of a library of 3D DNA nanotubes (Figure 3a, bottom) with well-controlled geometry and size.

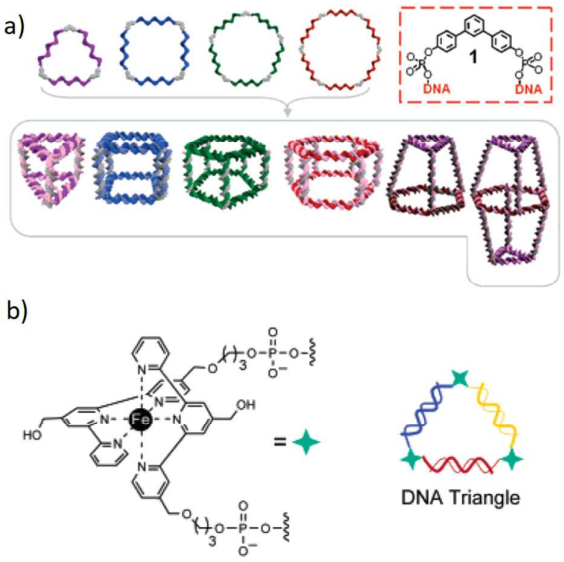


Figure 3. Examples of organic molecules used as vertices in supramolecular DNA assembly. a) Terphenyl **1** (inset) flanked on both sides with DNA sequences can be used to construct large DNA macrocycles and higher-order 3D architectures. Adapted with permission from ref. 40. Copyright 2007 American Chemical Society. b) Metal-ligand complexes can be introduced onto DNA to construct DNA triangles. Adapted with permission from ref. 41. Copyright 2004 American Chemical Society.

Supramolecular interactions that govern the self-assembly of organic ligands in water can also be harnessed to provide further diversity and functionality to DNA polygons. For instance, the group of Han has demonstrated that DNA single strands attached to a terpyridine spacer can be clipped together in the presence of Fe^{2+} via metal-ligand complex formation.[41] These organometallic complexes can serve as apexes for the assembly of DNA triangles (Figure 3b). Due to the unique coordination patterns of various metal complexes (e.g., tetrahedral, octahedral, and square planar) a variety of structures can be obtained using this approach.

2.2 Host-Guest Chemistry

As shown in the above section, orthogonal aromatic stacking or metal-ligand interactions have been interfaced effectively with DNA to create elaborate and functional supramolecular systems. Host-guest chemistry is also particularly suited to be joined with DNA self-assembly for the construction of DNA supramolecular systems (*vide infra*). Here, we provide a very brief introduction to host-guest chemistry that thrives in water. For extensive treatise on this topic, the reader is directed to the following reviews.[15-20]

Organic host molecules possess cavity structures that are able to encapsulate guests. Figure 1b provides examples of common host molecules that function effectively in water—thus are important in

interfacing with DNA. These include calixarenes (CAs),[42] cyclodextrins (CDs),[43] and cucurbiturils (CBs)[44]. Many other hosts such as crown ethers,[20] pillararenes,[45] deep-cavity cavitands,[18] and cyclophanes,[20] have also been investigated, but are less common. Hosts can bind guest molecules through a variety of non-covalent interactions including, hydrogen bonding, electrostatic, and van der Waals interactions. Further, in aqueous environments, the hydrophobic effect plays a significant role in guest encapsulation. A wide range of binding affinities from rather weak to strong can be readily dialed in depending on the host molecule of choice. Here, the CB family is particularly noteworthy since CBs can bind guests with ultra-tight binding constants[46] (a K_a of 7.2 x 10^{17} M^{-1} between CB7 and diamantine diammonium was recently reported)[47]. However, other hosts, such as CDs and especially CAs are versatile in the sense that they are more amenable for synthetic functionalization. Such host-guest systems are being widely investigated for biomedical applications due to their low toxicity in biological environments.[48, 49] Additionally, the reversibility of non-covalent host-guest binding makes it possible to design self-healing and responsive systems. The applications of host-guest systems are rapidly increasing and can be found in areas such as nanomaterials, catalysts, drug delivery platforms, protein binding and detection, and biomolecular assembly.[16, 19, 45, 48-50]

3. Synthesis of DNA-Macrocyclic Host-Conjugates

The unique functionality and self-assembly properties of DNA and host molecules and their particular application in aqueous media have provided the impetus for research into covalently tethered hybrids that compose both these species (Figure 1c). In this section, we will focus on the synthesis of covalent DNA-host conjugates. While outside the scope of this article, it should be noted that much work has also focused on the non-covalent incorporation of host molecules and DNA to form supramolecular complexes with diverse applications. Briefly, these include, dynamic gene delivery systems[51-54] and DNA binding drugs[55-59]. In addition, a variety of non-covalent complexes have been prepared for biosensing using DNA for target recognition and the hosts for sensing and signal amplification/transduction.[60-63] Furthermore, disparate applications ranging from cell immobilization[64] to nanophotonics,[65] have also been investigated by utilizing the self-assembly between hosts and DNA-guest molecule conjugates.

One traditional approach to covalently incorporate organic molecules onto oligodeoxynucleotides (ODNs) was to synthesize the corresponding phosphoramidite of the complete small molecule and use it as a monomer in solid-phase ODN synthesis. However, with the automation of DNA synthesis technology and the need for flexible DNA substrates that can be coupled to other functional elements (e.g., for life science and material science applications) a variety of modified phosphoramidite monomers that contain masked reactive functional groups became widely available. Indeed, reactive functional groups can be readily incorporated onto the 5', 3', or internal nucleobase sites and thus post-synthesis ODN conjugation is now the method of choice.

The rapid advancement of DNA-host conjugates is a consequence of the success in post-synthesis derivatization of ODNs. As a general procedure, functionalized macrocyclic hosts react with compatibly modified ODNs in either solution phase or on solid phase (where the ODN is still attached to its synthesis resin). Reactions performed on solid supports need an extra step of cleavage from the support as well as deprotection of nucleobase and phosphate protecting groups. However, the solid support also provides a facile means of removing any unreacted host starting material. After reaction, the introduction of the crude mixture to a micro-spin gel filtration chromatography column enables the removal of salts, and is typically the first step of purification. Further purifications are conducted using either reverse phase HPLC or gel electrophoresis. The pure conjugates can be dried under speed-vac or lyophilized. MALDI-TOF or ESI-MS is routinely used to confirm the successful syntheses.

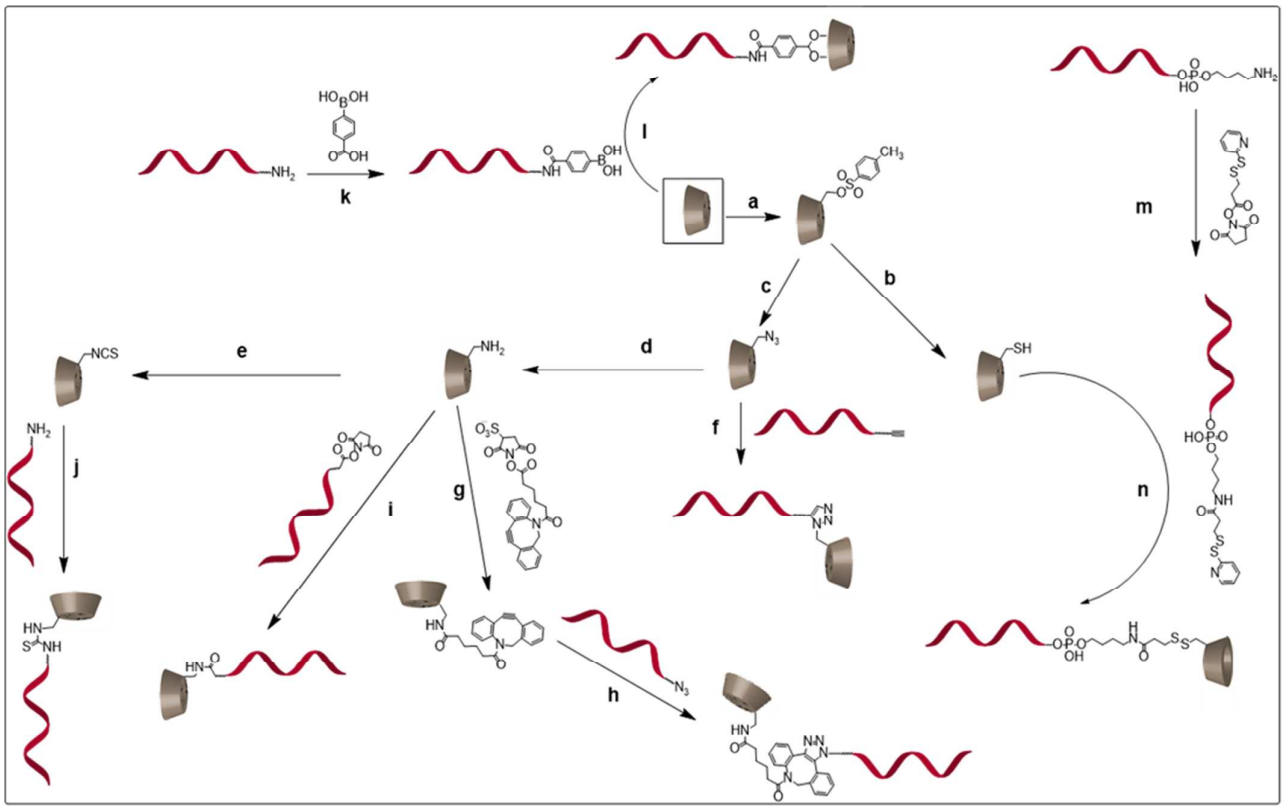
Prior to covalent conjugation of hosts with ODNs one must first choose the specific host for tethering. This choice is dependent on the application, since hosts differ in solubility, guest-selectivity, shape and size. Next, it is important to introduce a unique functional group onto the hosts that will be capable of facile reaction with ODN partners under mild conditions. Here, the orthogonality of the newly introduced reactive functional moiety is an essential feature. Since the DNA domain functions mainly in aqueous media, it is also imperative that the resultant conjugate be stable in aqueous buffers and be resistant to enzymatic cleavage (for biological applications).

The most common host family that has been tethered to ODN scaffolds is the toroid-shaped cyclodextrin family. In particular, β-cyclodextrin (β-CD, with seven repeating sugar units) and its derivatives is the leading choice for conjugation with DNA. Their low price (due to the ease of availability from the enzymatic conversion of plant starch), superior aqueous solubility, and facileness of modification (due to their multiple hydroxyl groups) make CDs highly attractive components for supramolecular chemistry in general, and DNA supramolecular chemistry, in particular. Mono-functionalization of β-CD is most often achieved via a tosylation reaction.[66] The tosylated β-CD precursor can then be converted to various reactive β-CD reagents containing for example, azido, amino, and mercapto modifications. Details of reactions involving such derivatives of β-CD undergoing copper-catalyzed azide-alkyne cycloaddition (CuAAC) (**f**) or copper-free (**h**) azide-alkyne click reactions, thiol-disulfide exchange reactions (**n**), and amine-NHS ester (**i**) or amine-isocyanate (**j**) conjugations with appropriately functionalized ODNs are shown in Scheme 1.

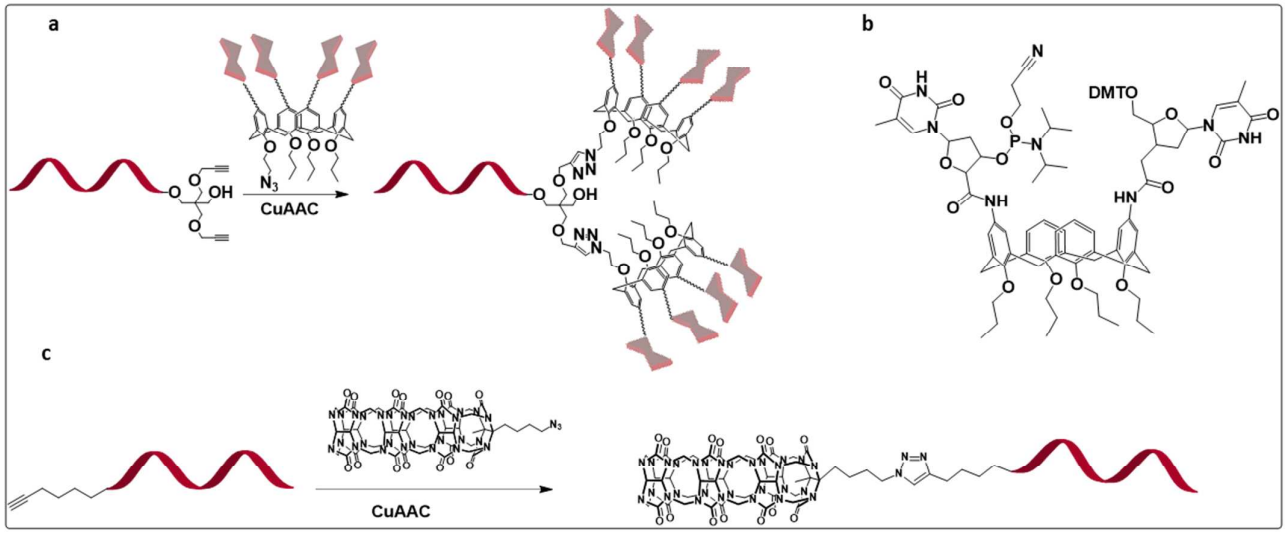
Another class of important macrocyclic compounds are calixarenes (CAs) which are synthesized by the condensation of phenols with aldehydes. The merit of this bucket-shaped host family regarding functional modification lies in the fact that the upper and lower rim can be selectively and opportunely functionalized which makes the synthetic fabrication of calixarene derivatives for DNA-based host-guest architectural design especially convenient. The utility of CAs is underexplored in terms of conjugates with ODNs. However, calix[4]arene-based glycoclusters mono-functionalized with an azide handle have been attached to alkyne modified ODNs via post-synthesis

CuAAC (Scheme 2a).[67] Interestingly, calix[4]arene has also been grafted onto ODNs using a calix[4]arene-dinucleoside phosphoramidite derivative (Scheme 2b). [68]

As much as cucurbiturils (CBs) are superior hosts in terms of binding specificity and affinity towards compatible guests, their synthetic mono-functionalization has lagged behind due to the lack of readily available handles to react from. However, recently elegant methods to mono-functionalize CBs with alcohols, amines, and azides have been reported.[69, 70] The tethering of ODNs with CBs was not successfully achieved until very recently when our group demonstrated that an azido derivative[69] of cucurbit[7]uril (CB7) can be reacted with an alkyne modified ODN via CuAAC reaction to yield a DNA-CB7 conjugate (Scheme 2c).[71] The cumbersome synthetic endeavor to obtain functionalized CBs is offset, however, by the versatility and efficiency in the host-guest chemistry involving these macrocycles. This is especially true, with species imbued with positive charge and/or an appropriately fitting shape (e.g. adamantane derivatives), where the association constants hit 10^9 M^{-1} to 10^{12} M^{-1} range, and above.



Scheme 1. Versatile approaches for DNA-cyclodextrin conjugations: **a)** mono-tosylation of β-CD with *p*-tosylchloride or *p*-tosylimidazole,[66, 72] **b)** Nucleophilic displacement of tosylate by thiourea and conversion to a thiol *via* basic work-up,[72] **c)** Nucleophilic displacement of tosylate by azide,[73] **d)** Reduction of azide to amine using Pd on carbon,[73] **e)** isothiocyanation of β-CD-NH_2 with thiophosgene,[74] **f)** conjugation of β-CD-N_3 with DNA-alkyne via CuAAC,[75] **g)** amine-NHS ester coupling to afford DBCO-functionalized β-CD,[76] **h)** β-CD-DNA conjugate synthesized via copper-free click reaction,[76] **i** and **j)** amine-NHS ester and amine-isothiocyanate coupling to yield β-CD-tethered DNA,[77] **k)** amide coupling of DNA-NH_2 with 4-carboxyphenyl boronic acid,[78] **l)** condensation of boronic acid with vicinal diols of β-CD,[78] **m)** incorporation of pyridyldithio moiety onto DNA via amine-NHS ester coupling,[72] **n)** thiol-disulfide exchange reaction to produce disulfide-linked β-CD-DNA conjugate.[72]



Scheme 2. a) Glycocluster-modified calixarene azide coupled with alkyne-functionalized ODN via the CuAAC reaction. Note: each calixarene unit is linked to four galactose residues to form a glycocluster,[67] **b)** Calixarene phosphoramidite monomer that can be used in ODN synthesis,[68] **c)** Synthesis of CB7-tethered ODN via CuAAC reaction.[71]

4. Application of DNA-Macrocyclic Host Conjugates

4.1 Building blocks and nanostructures

As discussed in the previous section, host molecules can be covalently linked to nucleic acid strands at 3' end, 5' end, or at internal positions. Since the hosts provide orthogonal self-assembly capability to the DNA building blocks, together, the DNA-host conjugates can be used to design and construct versatile, self-assemblies and nanoarchitectures. However, prior to practically building elaborate nano-assemblies, it is important to study the fundamental structure-activity relationship of the host modifications on short DNA strands. To this end, the Komiyama group tethered β-CD to the 5' end of ODNs, and evaluated the hybridization with complementary ODNs attached with guest molecules at the 3' end. The melting profiles show significant stabilization between β-CD ODN conjugates and adamantane (Ad) ODN conjugates.[79] For a 10-mer β-CD/Ad tethered duplex, the melting point (T_m) is 24.2 °C higher than the duplex without the modifications. For a shorter 7-mer duplex, the T_m increase is even more pronounced at 39.9 °C. The Inouye group covalently conjugated β-CD and Ad to the 5' ends of complementary short DNA sequences and investigated the stability of the resultant one-dimensional supramolecular oligomeric structures (Figure 4).[80] Compared with a control, non-modified, duplex (that does not form a higher-order species), the T_m of the oligomer increased by 18 °C, indicating that intermolecular host-guest interactions drive the formation of the higher-order structure. Interestingly, the melting point is substantially decreased by adding free Ad or β-CD competitors to the solution. Thus, these host-guest included DNA oligomers are both robust and easy to break with specific inputs. In lieu of intermolecular host-guest interactions, our group has investigated the stability of intramolecular Ad/β-CD interactions in a DNA hairpin scaffold (see Figure 15, molecule **11**).[77] The host-guest stabilized hairpin was found to be substantially more stable than the control hairpin, with an increase in T_m of 17 °C.

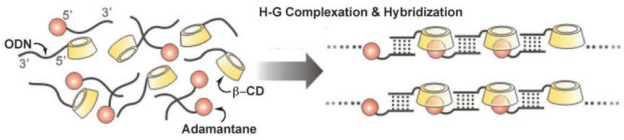


Figure 4. β-CD and Ad tethered ODNs can self-assemble to form oligomers stablized by DNA duplex and host-guest interactions. Reproduced from ref. 80 with permission from the Royal Society of Chemistry.

β-CD based host-guest interactions can not only enhance the stability of DNA self-assemblies but can also be used to build complex higher-order nanostructures. Further, the DNA-β-CD conjugates can act as simple building modules that can be "mixed and matched" with other guest linked modules of interest through host-guest interactions to afford a range of self-assemblies. For instance, the Varghese group recently reported the formation of DNA-decorated nanovesicles via the self-assembly of DNA amphiphiles (Figure 5).[81] Here, the supramolecular host-guest interactions between β-CD functionalized DNA **2** (as a hydrophilic host) and Ad modified chromophore with long alkyl chains **3** (as a hydrophobic guest) leads to the formation of DNA amphiphile **2:3** that spontaneously self-assembles to form DNA decorated nanovesicle **4**, in water. Dynamic light scattering experiments show a unimodal distribution of spherical particles with an

average diameter of 220 nm. The formation of vesicles was also confirmed by the encapsulation of calcein dye and monitoring of its emission intensity. Self-quenching of calcein fluorescence due to high concentration within the hydrophobic cavity was observed. Furthermore, the authors showed that the DNA functionalized vesicles can be annealed with 20 nm gold nanoparticles (NPs) prefunctionalized with complementrary DNA sequences to yield gold NP decorated vesicles, as well as aggregates of NP-vesicles. While the reported self-assmebled vesicles are very stable and thus cannot be readily disassembled, the authors proposed modulating the central hydrophobic modules and guests to make the system responsive with an eye towards functional applications such as drug delivery. Section 4.2 below, discusses DNA-host conjugates that have been prepared for this purpose.

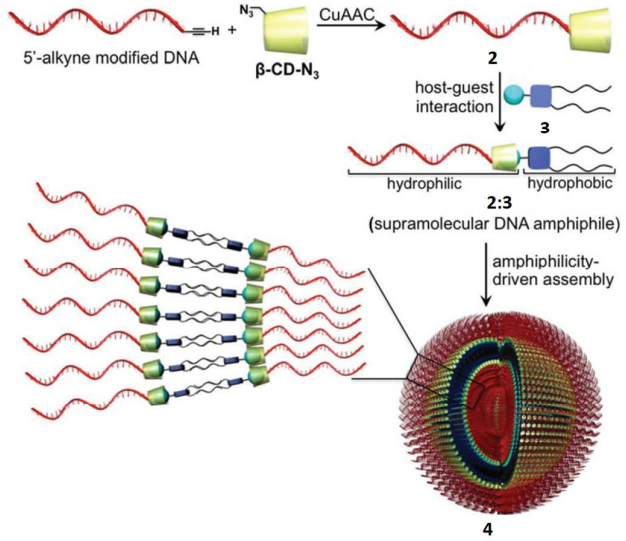


Figure 5. A DNA decorated vesicle that is self-assembled from β-CD DNA hydrophile **2** and hydrophobic moiety **3**. Adapted from ref. 81 with permission from the Royal Society of Chemistry.

In 2003, Kim and coworkers designed a group of calix[4]arene-nucleoside and calix[4]arene-ODN conjugates that form interesting DNA nanostructures.[68] Based on nucleoside linked CA[4] (molecule **5** in Figure 6), the researchers prepared a phosphoramidite (see Scheme 2b for structure) that can be inserted at internal positions of ODN strands. This internal V-shaped linker flanked by two complementary ODN regions can be used to form hairpin-type structures via intramolecular base-pairing. Further, DNA melting studies revealed that intermolecular base-paring can lead to a more thermodynamicaly favored aggregate. These uniquely shaped building blocks have potential for the development of interesting higher-order DNA architectures.

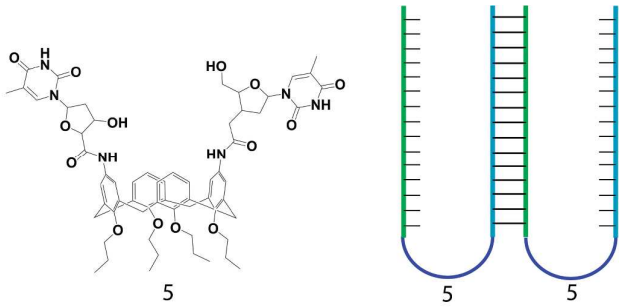


Figure 6. CA[4] dinucleoside (left) can be incorporated at internal ODN positions and hence serve as V-shaped linkers for ODN self-assembly (right).

4.2 DNA-host based structures for gene and drug delivery

Due to the significant challenge in delivering DNA/RNA into cells, much effort has focused on enhancing nucleic acid delivery with host-guest supramolecular systems. In terms of DNA-host conjugates, back in 1995, Agrawal and coworkers covalently tethered β-CD and Ad to the 3' end of DNA sequences and examined their nuclease stablility, hybridization with complementary RNAs, and cellular uptake. Although the 3' linked β-CD unit significantly increases the stability of the DNA against 3'-exonuclease, the cellular uptake of the duplex with complementary RNA was not enhanced.[82]

In order to enhance nucleic acid delivery, a cationic platform can be incorporated with host-guest/DNA systems.[51-54] While not employing covalent DNA-host conjugates per se, cationic polymers have been linked to macrocyclic hosts to enhance gene loading while decreasing the toxicity of cationic polymers. Importantly, the host molecules can also serve as sites where specific targeting groups (such as peptides or folic acid) can be bound to enhance the selectivity towards disease tissue. Further, the reversible nature of host-guest and DNA condensation chemistry can then be used to finally release the nucleic acid cargo in a stimulus responsive fashion (for example, exploiting acidic or reduced micro-environments).

With the goal of delivering small hydrophobic drugs, the Varghese group reported DNA-host conjugate based nanogels with controllable size and promising drug carrier properties (Figure 7).[75] Four ODNs functionalized at the 5' end with β-CD and sharing partial complementarity were assembled to yield four-way junction **6**. This self-assembled scaffold further underwent multivalent host-guest interactions with an adamantyl-terminated 8-arm PEG polymer in the presence of doxorubicin (DOX) to form a drug-loaded nanogel. The host-DNA conjugate based nanogel is modular, allowing the testing of multiple combinations of component modules with different Ad multivalency to succesfully afford nanogels with fine-tuned size. The delivery of the DOX cargo embedded in the DNA-nanogel manifested in excellent biocompatibility, cell permeability, and drug loading efficiency. Confocal microscopic images show that internalization of the cyanine dye-tagged nanogels occurs in both the nucleus and the cytoplasm (Figure 7b). Importantly, in a cell viability assay, a three-fold decrease in the IC_{50} was observed for the DOX included nanogel compared to DOX alone when DOX-

resistant MCF-7 cells were interrogated (Figure 7c). These studies illustrate the power of using DNA-host conjugates for nanostructure formation and as a drug delivery tool against critical diseases.

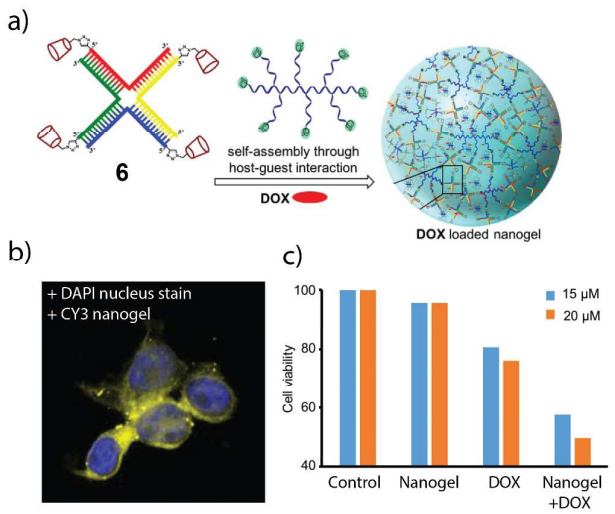


Figure 7. a) Self-assembled nanogel based on β-CD tethered four-way DNA junction **6** and an adamantane projecting PEG polymer. b) The nanogel is cell permeable as shown by confocal microscopy. c) DOX-loaded nanogel has potent cell viability effects. Adapted from ref. 75 with permission from the Royal Society of Chemistry.

Very recently, the Tan group reported a β-CD modified circular bivalent aptamer (cb-apt-CD) and its host-guest interaction with theraputics for intracelluar delivery applications (Figure 8).[83] Previously, cyclized bivalent aptamer (cb-apt) was reported for improved thermal stability, nuclease resistance, and binding affinity.[84] Here, the single-stranded sgc8 aptamer that targets protein tyrosine kinase-7 (PTK-7) was covalently modified with β-CD before being hybridized with another unit of the sgc8 aptamer via a complementary stem. The two aptamers were then covalently ligated to form a β-CD tethered complex. To demonstrate the targeting ability of the conjugate, a hydrophobic small molecule drug *N*-heterocyclic carbene gold(I) was encapsulated into the host and exposed to CEM cells, a PTK-7-positive cell line. The cb-apt-CD delivered drug shows a 5-fold increase in cytotoxity compared to a control that uses only a single aptamer delivery strategy. Furthermore, to deliver protein based theraputics, a model protein GFP and a cytotoxic protein saporin were modified with an Ad handle and assembled with cb-apt-CD. The Ad-GFP included complex is delivered into cells with an efficiency as high as 80%. Treatment of Hela cells with cb-apt-CD and Ad-functionalized saporin reduced the cell viability to 20%, while saporin alone shows no obvious cytotoxicity. This elegant work exemplifies how advanced DNA-host conjugates can be utilized effectively as a general platform for targeted delivery of small molecules and even large protein therapeutics.

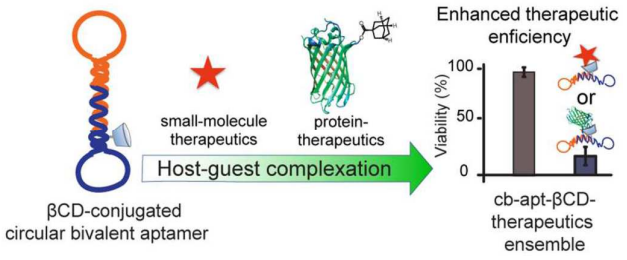


Figure 8. A β-CD conjugated circular bivalent DNA aptamer used for enhanced therapeutics delivery. Reprinted with permission from ref. 83. Copyright 2018 American Chemical Society.

4.3 Switchable structures

Besides providing orthogonal self-assembly modalities for the construction of functional supramolecular systems, the individual DNA and host components can also respond separately to stimuli. For instance, nucleic acid inputs can change the structure of a DNA assembly via complementary DNA hybridization, and likewise high-affinity guest molecules can disassemble a pre-formed host-guest interaction. Thus, the braiding of these two supramolecular synthons into DNA-host conjugates can provide a platform from which highly creative stimuli-responsive switches and nanomachines can be developed.

The Willner group, in 2013, introduced an input-responsive switch that displays electrochemical and optical signal transduction based on DNA hybridization and β-CD/guest binding (Figure 9).[78] Specifically, two separate ODN strands (**7** and **8**) assemble on adjacent footholds on another ODN strand via their complementary domains. Strand **7** is functionalized with a host (β-CD) via a boronic acid condensation reaction (see Scheme 1, **I**) and strand **8** is attached to a ferrocene (Fc) guest. The foothold strand is linked to a gold electrode via thiolation. The Fc-ODN initially has a stable hairpin loop that restricts the mobility of the DNA "arm" and thus makes the β-CD cavity on ODN **7** inaccessible to Fc. Upon addition of a fuel sequence capable of forming a more stable duplex with a portion of the Fc-ODN, the DNA arm gains partial mechanical flexibility which leads to Fc binding into β-CD. This effect was measured by differential pulse voltammetry (DPV) which reads a reduced peak anodic potential for the Fc/Fc^+ redox couple when Fc is encapsulated by β-CD. The significant change (*ca.* 100 mV) in redox potential was taken as evidence of an entirely different micro-environment surrounding the Fc moiety. The switching between ON and OFF states can be modulated by adding fuel or antifuel strands as needed.

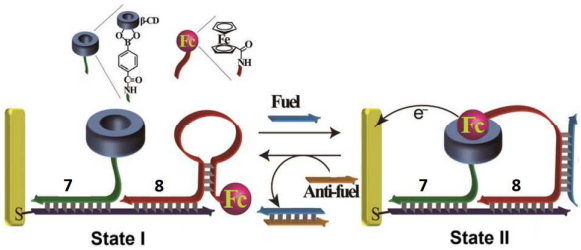


Figure 9. A mechanical DNA "arm" based on β-CD/ferrocene tethered DNA scaffolds. Adapted from ref. 78 with permission from the Royal Society of Chemistry.

These researchers also tested their system with adenosine monophosphate (AMP) as a fuel by using an aptamer that binds AMP in the Fc-ODN strand. Furthermore, addition of adenosine deaminase converts AMP to inosine monophosphate which breaks the aptamer-target affinity and reverses the system. Similarly, competitive displacement of pre-encapsulated Fc from the β-CD cavity by adamantane carboxylic acid raises the redox potential as expected. Moreover, when the gold electrode is replaced with CdSe/ZnS quantum dots (QDs), the emission from the QD at 612 nm is significantly quenched when the Fc/β-CD complex is formed. In this latter system, the charge transfer from Fc to the QD quenches the emission.

In 2016, a switchable catalytic system was reported based on whether or not the β-CD cavity can bind to *m-tert*-butylphenyl acetate for subsquent catalytic hydrolysis (Figure 10a).[76] The system again exhibits input responsive dynamism, reversibility, and hinges on the cooperation between DNA hybridization and host-guest binding. In particular, two partially complementary ODN strands are covalently linked to β-CD and Ad separately such that when the two ODNs self-assemble, the host and guest moieties are in proximity and form a favored host-guest complex. This encapsulation event shuts the β-CD cavity–an OFF state (where the hydrolysis is inhibited). In contrast, the addition of a fuel strand with a potential to form a more stable duplex kicks out the Ad-ODN strand and makes the β-CD cavity accessible to the substrate for the subsequent hydrolysis.

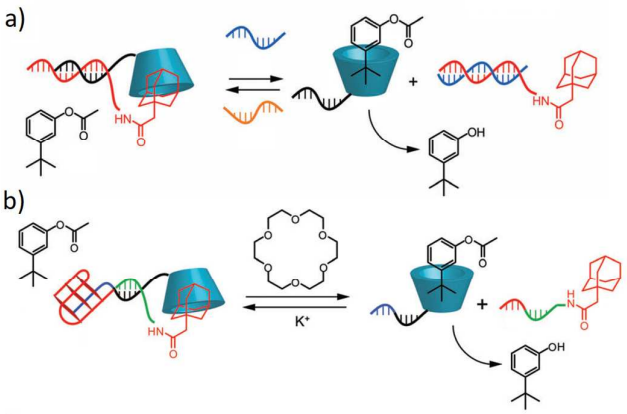


Figure 10. Supramolecular DNA switches containing DNA-β-CD conjugates with input-control over catalytic hydrolysis. Adapted from ref. 76 with permission from the Royal Society of Chemistry.

In a more complex design (Figure 10b), the host and Ad linked ODN sequences each bear two domains; a G-rich domain capable of forming a G-quadruplex and a complementary domain. When the two strands come together, an energetically favored G-quadruplex assembly "leads the charge" and cooperatively assists the hybridization of complementary domains which otherwise would not form a stable duplex to hold the two strands together. Now, this OFF state, as anticipated, prevents the hydrolysis of the substrate. Since the presence of potassium ions is a crucial factor to induce and stabilize G-quadruplex assembly, sequestration of potassium ions by 18-crown-6 ether ultimately causes the DNA strands to disassemble and leads to an ON state. Furthermore, the authors describe how such a system can be tuned for other input-driven turn-ON reactions. These systems exemplify how the interplay of multiple orthogonal non-covalent interactions (such as cation complexation, host-guest interactions, and canonical and non-canonical base-pairing) can lead to highly functional switches.

4.4 DNA-host switches for sensing

An application where switches based on DNA-host conjugates have significant potential is in biosensing. Here, the inputs are biologically relevant analytes, and the reporter groups, used for signal transduction, are often fluorescent or electrochemically active species. Using cyclodextrin as the analyte recognition moiety, Inouye's group reported a unique design for detection of fatty acids (Figure 11).[85] Their strategy is based on a pair of pyrene modified short complementary ODNs with α-CD or β-CD clicked to the opposite end of the sequences. First, the β-CD system was used to test the sensor for recognizing a bis-adamantyl guest **9**. This bifacial molecule can be encapsulated by β-CD in a 1:2 mode that brings the two ODN strands together to form a stable duplex (with an increase in T_m of 17 ^{o}C over control lacking the host). Duplex formation results in an increase in the pyrene excimer fluorescence at 500 nm while the pyrene monomer emission at 379 nm decreases. To explore the sensor's ability for fatty acid detection, stearic, oleic, elaidic and arachidonic acids were tested. Turn-ON excimer emission was observed for all three unsaturated acids but not for stearic acid.

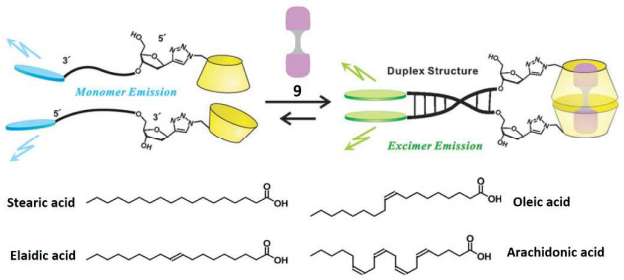


Figure 11. A fluorescent sensor for fatty acids based on duplex formation driven by 1:2 guest-host interactions. Adapted from ref. 85 with permission from the Royal Society of Chemistry.

To improve selectivity, the smaller α-CD host was conjugated to the DNA domain. When using α-CD tethered ODNs for the same set of four fatty acids, oleic acid was detected more sensitively than elaidic acid, illustrating that this sensor could differentiate cis/trans species. Arachidonic acid was not detected by the sensor since the four double bonds make its structure rigid and too big for inclusion into the α-CD cavity. This strategy is highly versatile since, in principle, various analytes can be detected by modulating the nature of the host. For instance, the same group demonstrated that when a crown ether is used as the host moiety, a sensor that can detect potassium ions is produced.[86]

In a reversal of roles, the ODN domain can be utilized for analyte binding (in particular, binding to specific nucleic acid sequences) whilst the host component can function as the signal reporter. For instance, Jyo and co-workers, in 2009, developed a multi-component cooperative system to recognize single nucleotide polymorphisms (Figure 12a).[72] In their system, a longer target DNA strand acts as a scaffold allowing a shorter β-CD-DNA conjugate strand (CyD-ODN) and another "mask" strand to undergo sequence-specific hybridization. In this ternary system, the two shorter strands are placed just one nucleobase apart

from each other, where the β-CD is oriented adjacent to the gap nucleobase of the target strand. Next, a nucleobase-specific fluorescent ligand (MNDS) (Figure 12b) is introduced to the precisely ordered ternary duplex system. MNDS is a recognition and signaling probe that consists of two parts; (a) a naphthyridine derivative complementary to guanine (AcMND), and (b) a 2,6-dansyl fluor that serves as a guest dye which displays significant fluorescence enhancement after proximity-favored inclusion into β-CD. The rationale for this elegant design is that the dye "lights up" selectively if the gap nucleobase is guanine. Indeed, fluorescent analysis showed significant enhancement in signal when guanine (see Figure 12c) is displayed in the gap position (the fold enhancement in signal for a G gap residue is 13.3, 25.6, and 23.8 versus A, C, and T, respectively).

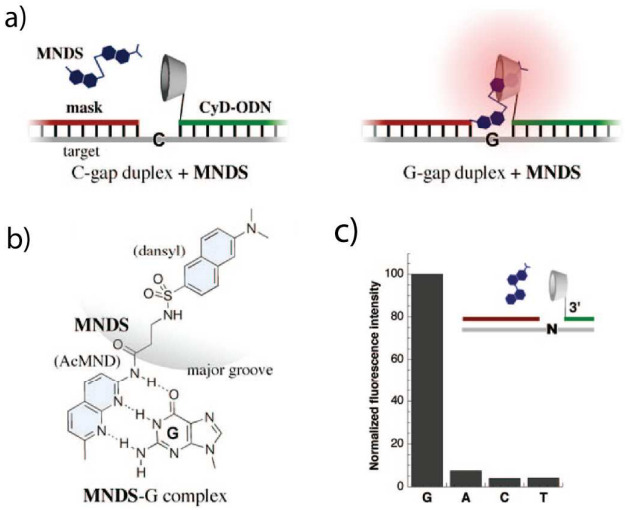


Figure 12. A β-CD-DNA conjugate based fluorescent sensor system for detecting single nucleotide polymorphisms. a) Sensor design in the OFF state (left) where the gap nucleobase is C and in the ON state (right) where the gap nucleobase is G. b) Base-pairing mode of MNDS with G. c) Fluorescence data illustrating the large enhancement in fluorescence for G. Adapted with permission from ref. 72. Copyright 2009 American Chemical Society.

By introducing DNA aptamers into the design of DNA-host based biosensors, the types of analytes recognized by the DNA domain can be expanded from nucleic acid sequences to almost any target that an aptamer can be selected for. For example, the Peyrin group designed a complex for sensing adenosine via fluorescent signal transduction of a dansyl dye (Figure 13).[87] Here, the authors split an adenosine binding aptamer into two sequences, CD-H1-CD and dansyl-H2-dansyl. The former sequence is modified at both ends with β-CDs while the latter is functionalized with dansyl dyes. Introduction of adenosine into the system, as the aptamer target, results in a sandwich-like sensor where the two strands form a duplex-type structure stabilized by two adenosines and flanking host-guest interactions (between the β-CD and dansyl arms). A significant enhancement of the fluorescent signal of the dansyl dye (at 443 nm) and the concomitant increase in the T_m of the DNA architecture (by 6.5 °C) provided evidence for the formation of the adenosine-induced complex.

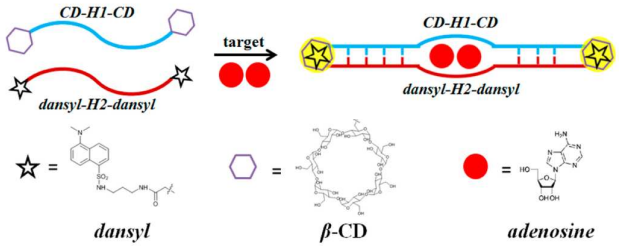


Figure 13. A fluorescent split aptamer-based biosensor for adenosine with host-guest interactions providing the signaling mechanism. Reprinted with permission from ref. 87. Copyright 2015 American Chemical Society.

4.5 DNA-host switches for protein activity control

Since proteins are critical regulators of most biological and pathological processes, the precise control of protein activity is a salient goal in a number of scientific fields, including chemical biology, medicinal chemistry, and supramolecular chemistry. DNA-based switches are particularly well-suited for controlling protein function in a spatio-temporal manner due to their versatile molecular recognition and input-responsive capacities.[88-90] For example, template single-stranded ODNs can be covalently fastened onto proteins (Figure 14a).[91] Subsequently, the addition of complementary ODN strands bearing small molecule inhibitors can facilitate input-responsive protein inhibition. While such strategies have applications in logic gates and biosensors, it is not a practical approach to control protein activity in native biological milieu, since the proteins must first be linked covalently to the template ODN.

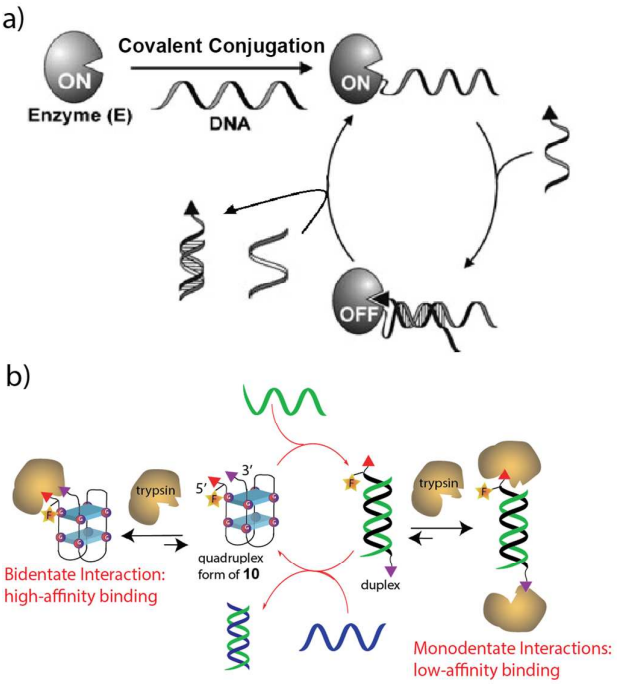


Figure 14. DNA-small molecule conjugates for protein activity control. a) Input responsive enzyme inhibition based on covalent conjugation of a protein with a template ODN. Subsequent fuel and

antifuel strands can turn OFF and turn ON enzyme activity, respectively. Adapted with permission from ref. 91. Copyright 2007 John Wiley and Sons. b) Input-controllable protein binding based on a DNA switch conjugated to two small molecule protein binders.

We have focused our efforts on developing mechanisms and design strategies towards input-triggered DNA-based protein binders that function without the need for prior protein labeling.[92, 93] For example, we have shown that DNA inputs can be used to toggle a synthetic DNA switch **10** between bivalent and monovalent thrombin-binding states (Figure 14b).[94] The DNA switch **10** is based on a core G-rich ODN domain flanked by two thrombin binding small molecules. An intramolecular quadruplex state of **10** leads to a bidentate (i.e., high-affinity) protein binding mode whilst a pseudo-complementary DNA input can convert the quadruplex to a duplex that can only bind to thrombin via a monodentate (low-affinity) conformation. Importantly, a second ODN input reverts the structure back to the high-affinity form.

The scope of supramolecular mechanisms that can be used to achieve input-controlled protein function can be greatly enhanced by using DNA-host conjugates. In 2011, our group reported a β-CD and Ad conjugated DNA hairpin structure **11** with turn-ON protein binding activity (Figure 15).[77] The core hairpin forming ODN domain of **11** is attached to an Ad head-group (at the 5′ end) which serves as a prototypical hydrophobic unit that binds β-lactoglobulin. Further, the 3′ terminus is tethered to β-CD. A robust hairpin structure is formed when ODN **11** self-folds as a result of the additional stabilizing intramolecular host-guest interaction. Further, since the Ad head group is bound into the host cavity, β-lactoglobulin is not appreciably bound by the hairpin state of **11** (K_a << 3.0 × 10^3 M^{-1} as observed by fluorescence anisotropy studies). In contrast, by introducing a perfect complementary sequence, the hairpin is conformationally switched to a duplex state with the Ad head group unsheathed. This activated state of **11** is a much stronger binder of β-lactoglobulin (K_a = 7.8 × 10^3 M^{-1}). Moreover, input sequences containing one or two base-pair mismatches are unable to effectively switch the hairpin state to the duplex form, indicating that the system is selective in terms of input sequences.

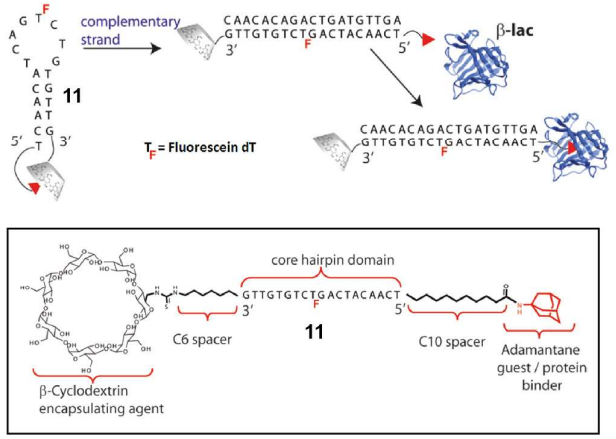


Figure 15. A DNA hairpin based host-guest system that binds a protein target in response to an ODN trigger. Adapted with permission from ref. 77. Copyright 2011 American Chemical Society.

As should be evident from this review, to date, the vast majority of DNA-host conjugates have been prepared using β-CDs as the host unit. In an effort to expand the scope of DNA-host systems and to use the particularly strong host-encapsulation properties of CBs, our group recently reported the synthesis and protein inhibition activity of a CB7-DNA tranducer (Figure 16).[71] This hybrid molecule is capable of converting a chosen biological input (adenosine triphosphate) into the release of a small molecule protein inhibitor.

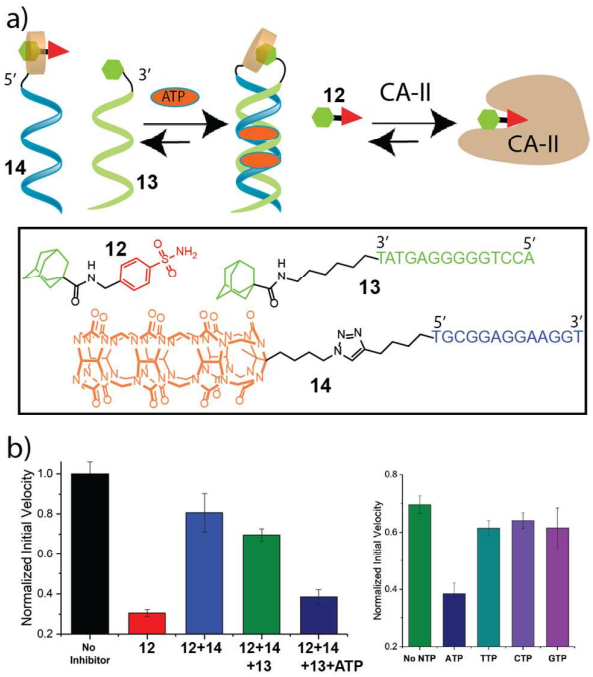


Figure 16. A host-guest tethered DNA transducer for responsive protein inhibition. a) Scheme for ATP induced release of a sequestered CA-II inhibitor. b) CA-II inhibition assays. Adapted with permission from ref. 71. Copyright 2017 American Chemical Society.

In our design (Figure 16a), one half of a split ATP-binding aptamer is tethered to a CB7 headgroup at the 5′ position (ODN **14**), while the other half of the aptamer is attached to Ad at the 3′ position (ODN **13**). The CB7 head-group of **14** is capable of forming a strong (K_a = 1.9 × 10^9 M^{-1}) host-guest complex with Janus molecule **12** that contains an Ad tail and a benzenesulfonamide moiety (a carbonic anhydrase II, CA-II, inhibitor). As a result, the Ad moiety of **12** is included into the CB7 headgroup and the benzenesulfonamide moiety of **12** is too sterically hindered for optimal CA-II binding and inhibition. Addition of the Ad-DNA conjugate **13** does not significantly affect the former complex since **13** is not complementary to the CB7 tethered sequence **14**. However, in the presense of ATP as a stimulus, the two conjugates form an ATP templated non-canonial duplex structure with the Ad moiety close to the CB7 moiety. A strong "intramolecular" host-guest interaction between the CB7 and Ad moieties leads to the eviction of **12**. Thus, this ATP triggered conformational switch results in non-sequestered **12**, affording effective CA-II inhibition. Enzyme inhibition assays illustrate the ATP induced OFF-ON switch (Figure 16b). Importantly, control experiments with other nucleotide triphosphates (NTPs) show that the tranducer is selectively triggered by ATP.

5. Conclusion

The past decade has seen a rapid increase in examples of systems that utilize DNA-host conjugates—the judicious covalent combination of water-soluble hosts with DNA. Separately, these two supramolecular synthons are unique in that they allow for programmed self-assembly, molecular recognition, and input-responsive properties in highly competitive aqueous environments—an important media where many synthetic self-assembling molecules fail due to insolubility and competing interactions with water. The recent advances in DNA-host conjugates have been propelled by straightforward post-synthesis DNA conjugation methodologies and elegant host functionalization chemistry. The incorporation of DNA with host molecules not only enhances the stability of the resultant DNA supramolecular structures via orthogonal molecular recognition elements, but also enables researchers to develop an array of "smart" functional nanostructures and assemblies with promising applications. These hybrid DNA-host systems include (a) versatile nanocarriers that can serve as delivery vehicles for small drug molecules or large proteins, (b) supramolecular catalysts that can be turned ON or OFF on demand, (c) sensors capable of detecting small biomolecules and even larger nucleic acid sequences (with single nucleotide polymorphism detection capability), and (d) synthetic transducers that are capable of controlling protein activity via biologically relevant inputs.

While the creative systems discussed in this review have already provided new directions and vigor to the field of DNA supramolecular chemistry, the full scope of applications that DNA-host conjugates can bring to bear still remains to be explored. Indeed, the majority of DNA-host systems have focused on using β-CDs as the host molecule with only a couple of examples using CAs and CBs. As these latter hosts continue to be developed and fused with DNA, more elaborate supramolecular systems are expected (e.g., CBs will bring higher affinity while CAs can be readily tailored with specific functional groups). Further, a number of other hosts that function in water (e.g., deep-cavity cavitands and pillararenes) remain to be incorporated with DNA. Another area of research where DNA-host conjugates is expected to play a leading role is in nanophotonics where dyes can be precisely arranged using DNA programmablility[95] and have enhanced photophysical properties due to sequestration by hosts.[96, 97]

From the nucleic acid perspective, the development of functional covalent RNA-host conjugates is an open challenge. RNA is being increasingly recognized as a potential construction material with distinct advantages such as the ability to (a) be genetically encoded and expressed in cells, and (b) access a diverse array of structures and functionality (e.g, enzymatic catalysis) not possible with DNA.[98, 99] In summary, the conjugation of hosts with oligonucleotides is still in its infancy and it is anticipated that much exciting research directions and real world applications will follow in the future.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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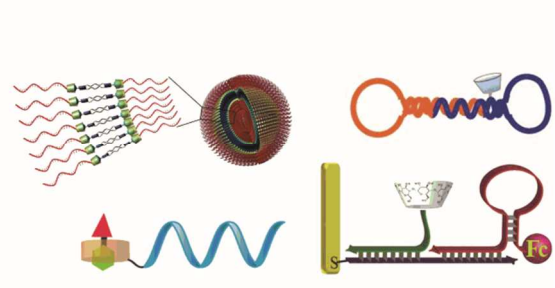

This review discusses the nascent field of DNA-host conjugates and their applications in advanced self-assemblies, nanostructures, and input-triggered switches.