Pure Appl. Chem., Vol. 81, No. 12, pp. 2157–2181, 2009.
doi:10.1351/PAC-CON-09-08-13

Supramolecular DNA nanotechnology*

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Abstract: Nature uses deoxyribonucleic acid (DNA) as the main material for the storage and transmission of life's blueprint. Today, DNA is being used as a "smart" material to help solve a number of long-standing issues facing researchers in materials science and nanotechnology. In DNA nanotechnology, DNA's powerful base-pair molecular recognition criteria are utilized to control the final structure and function of the material being generated. A sub-area of research that our group has recently termed "supramolecular DNA nanotechnology" is emerging and is extending the limits of this molecule in nanotechnology by further fine-tuning DNA's structural and functional potential. This review will discuss the fruition and fundamentals of supramolecular DNA nanotechnology, as well as its future as a viable science in a material world.

Keywords: DNA; error correction; gold; nanoparticles; nanotechnology; nanotubes; organic–inorganic; self-assembly; supramolecular; three-dimensional.

INTRODUCTION

In 1865, Mendel observed that traits are inherited according to specific laws [1], and a year later, Haeckel proposed that the factors responsible for the transmission of such traits are to be found in the nucleus [2]. Today, it is common knowledge that deoxyribonucleic acid (DNA) is the molecule responsible for the storage and transmission of genetic information—making it one of the most, if not the most, important molecules discovered to date. But is that enough? Can we ask more of DNA? Researchers in nanotechnology are starting to use DNA to help solve a number of problems, and they are succeeding. The revolution that is DNA nanotechnology was started by Seeman and co-workers in the 1980s, and many biologists, chemists, physicists, computer scientists, and engineers are currently contributing to its evolution. This field promises to address challenges in synthesis, sensing, catalysis, delivery, storage, optics, electronics, and scaffolding. A sub-area of research that our group has recently termed "supramolecular DNA nanotechnology" is emerging and is proving to be a powerful complement to some of the already established rules of structural DNA nanotechnology. In this review, we will begin by briefly discussing the fundamentals of the already well-established field of structural DNA nanotechnology, followed by an outline of some of the developmental milestones that led to the emergence of the subspecialty of supramolecular DNA nanotechnology. We will then describe how supramolecular DNA nanotechnology can be used to solve a number of long-standing problems facing researchers in DNA nanotechnology, specifically the issue of discrete nanoparticle organization and 3D DNA construction, as well as provide an unexpected solution to the problem of error prevention–correction during DNA self-assembly.

Pure Appl. Chem.* **81, 2157–2251 (2009). A collection of invited, peer-reviewed articles by the winners of the 2009 IUPAC Prize for Young Chemists.
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DNA

DNA is a masterpiece of engineering. Structurally, DNA is a long polymer made up of simple units joined together by a backbone of sugar and phosphate groups. The sugar in DNA is deoxyribose. Attached to each sugar is one of four nitrogenous bases, adenine (A), cytosine (C), guanine (G), or thymine (T). Double-stranded DNA is constructed from two anti-parallel single strands that hydrogen-bond and π-stack according to specific base-pairing recognition requirements, that is, A with T and C with G. Adenine possesses a donor–acceptor hydrogen-bonding face complementary to the acceptor–donor face of T, while C possesses a donor–acceptor–donor face complementary to the acceptor–donor–acceptor face of G. This set of hydrogen-bonding motifs is known as Watson–Crick, and is usually preferred because it tends to generate a double helix that is thermodynamically more stable than other structures—due to base-stacking, hydrogen-bonding, and minimal helix distortion [3]. B-DNA, the most common form, has a diameter of ~2 nm, a pitch of ~10.5 bases, a persistence length of ~50 nm, and a potentially addressable bit density of ~0.34 nm [3]. This, coupled with the fact that nature provides us with a toolbox of enzymes to selectively manipulate this molecule, makes DNA structurally, chemically, and functionally a superb molecule for use in materials science and nanotechnology.

DNA IN NANOTECHNOLOGY

DNA can be used to template material growth. Pioneering work by Braun and co-workers provided the first example of a DNA-templated metallic nanowire [4]. The group positioned a 16-μm-long strand of λ-DNA between two gold electrodes, electrostatically localized silver ions onto the DNA's backbone, reduced the ions to generate silver aggregates, and developed these aggregates to form 100-nm-thick silver wires (Fig. 1). DNA-templated gold, platinum, copper, and palladium wires have also been reported [5]. Braun and co-workers later developed an approach to metallize sequence-specific regions of DNA [6]. Using glutaraldehyde-functionalized DNA that localizes metal ions, and RecA proteins that

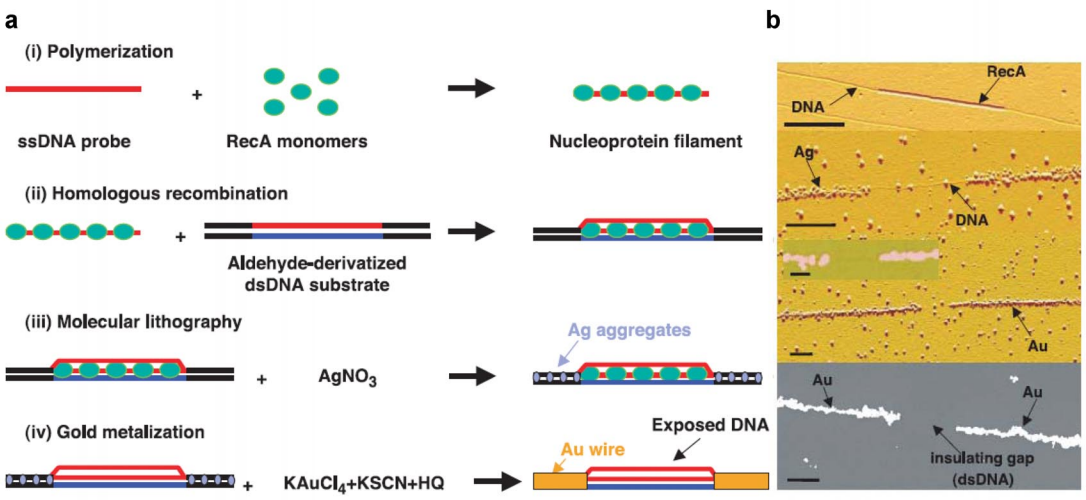

Fig. 1 (a) (i) RecA monomers bind a single-stranded DNA probe to form a filament that then (ii) binds a double-stranded substrate DNA molecule at a specific homologous sequence. (iii) Addition of $AgNO_3$ results in the formation of silver aggregates along the regions unprotected by RecA, (iv) which then serve as catalytic sites for the specific deposition of gold to convert the unprotected regions to conductive gold wires. (b) This process can be monitored in real time using atomic force microscopy (AFM) and scanning electron microscopy (SEM)—(top to bottom) double-stranded DNA protected by RecA, silver deposition, gold growth (AFM), gold growth (SEM). Reprinted with permission from [6] copyright © 2002.

bind sequence-specific regions of the DNA's backbone, the group synthesized conductive gold nanowires separated by predesigned gaps of specific length and location. Other materials have also been grown on DNA. Sargeant and co-workers reported the synthesis of DNA-templated semiconducting nanocrystals with excellent quantum efficiencies retained in the solid state [7], He and co-workers reported the synthesis of conjugated oligomers by the enzymatic polymerization of aniline monomers electrostatically bound to the DNA's backbone [8], while Schuster and co-workers covalently attached aniline monomers onto specific DNA bases and reported the sequence-specific synthesis of "conjoined" oligoaniline nanowires [9].

The true power of this molecule, however, lies in its potential for sequence-based addressability. Materials modified with single-stranded DNA molecules can be made to assemble onto specific regions of a complementary DNA template with exquisite control over their level of organization. In 1996, Alivisatos and co-workers modified gold nanoparticles with unique DNA sequences, and organized them into head-to-head and a head-to-tail dimers (Fig. 2a) [10]. The group later used this approach to organize two gold nanoparticles of different sizes into dimers and trimers with complete control over combination (Fig. 2b) [11]. In a separate contribution, Mao and co-workers used the principle of rolling circle amplification to synthesize 4-μm-long DNA templates with many repeating units, and organized gold nanoparticles modified with the complementary sequence into extended 1D nanoparticle assemblies (Fig. 2c) [12]. Niemeyer and co-workers modified proteins with DNA molecules, and presented the first example of DNA-templated protein organization, which they later adapted to construct an artificial two-enzyme complex in which the spatial proximity of the enzymes was found to be beneficial for their overall bioactivity. The group also used the biotin-streptavidin interaction as a "universal linker" to organize a number of different materials, including antibodies, enzymes, gold nanoparticles, and fluorescent molecules [13].

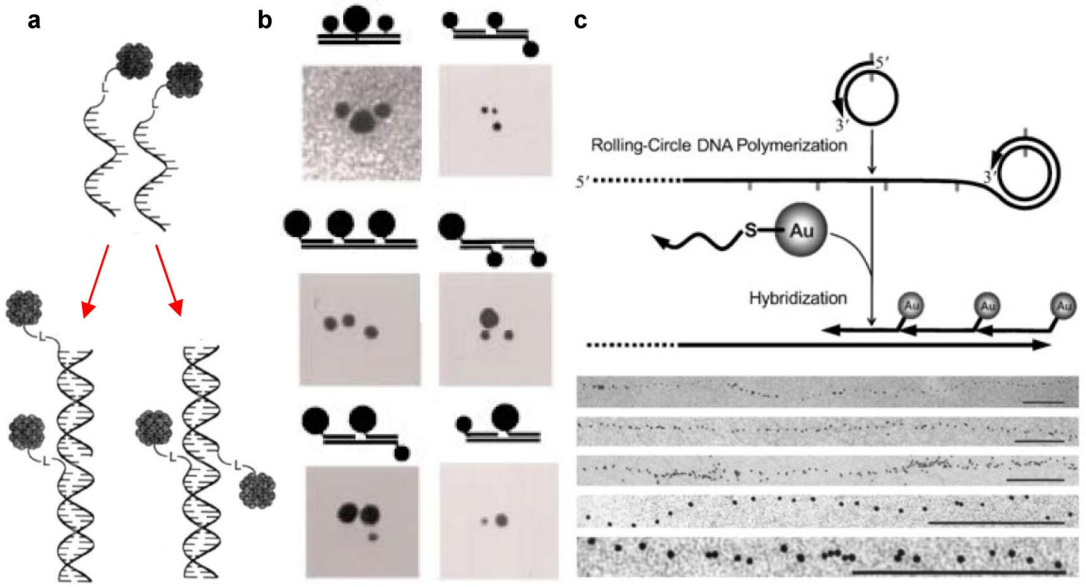

Fig. 2 (a) Two nanoparticles modified with unique single strands of DNA are organized into head-to-head and head-to-tail dimers using a complementary DNA template. (b) The same approach is used to generate discrete nanoparticle trimers, of all possible combinations. (c) Rolling circle amplification generates an "extremely long" DNA template with a repeating region, which is used to organize gold nanoparticles tagged with the complementary sequence into 1D linear assemblies. Reprinted with permission from [10] copyright © 1996, [11] copyright © 1999, and [12] copyright © 2005.

The above examples are selected to illustrate the potential of DNA in nanotechnology. If the full promise of this molecule is to be exploited, however, then rational access to non-natural two- and 3D artificial DNA motifs will need to be realized. This area of research is referred to as structural DNA nanotechnology.

STRUCTURAL DNA NANOTECHNOLOGY: BIRTH

The field of structural DNA nanotechnology utilizes DNA's powerful base-pairing molecular recognition criteria to address challenges facing researchers in materials science and nanotechnology. In it, DNA is stripped away from any of its preconceived biological roles and is treated as a powerful synthetic polymer. The initial challenge within this field was to generate a branched DNA motif. If realized, then access to 2D and 3D DNA assemblies would be feasible. In the early 1980s, Seeman and coworkers took initial inspiration from the naturally occurring branched Holliday junction, and assembled four synthetic DNA strands into a four-way branched junction (Fig. 3a) [14]. By incorporating addressable sticky ends at the periphery of this four-armed building block, the group developed the first example of a rationally designed artificial DNA module capable of constructing higher-order assemblies. This initial design, however, produced flexible junctions that could not possibly assemble into real-space structures, but that rather generated topological constructs. The level of flexibility within the branching points needs to be controlled if access to well-defined 2D and 3D DNA systems is achieved. The second challenge within this field, therefore, was to generate *well-defined* DNA building blocks. By joining two double helices with a single-strand exchange process, Seeman and co-workers constructed a well-defined double-cross-over (DX) tile with addressable sticky ends at its edges (Fig. 3b), which they used to generate well-defined 2D crystalline lattices with complete control over the size and shape of its periodicity. It is the sum of this initial work that laid the foundations for the development of structural DNA nanotechnology. These relatively simple principles of construction have since been used, adapted, and developed to generate systems with truly remarkable control over design and function.

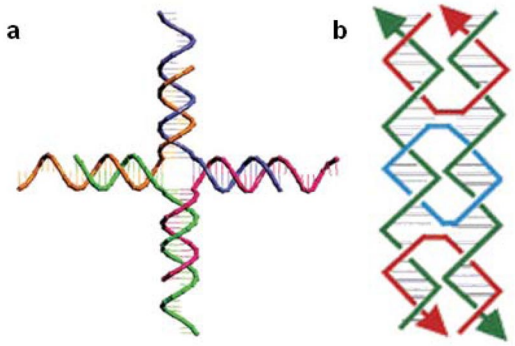

Fig. 3 (a) Four DNA strands are programmed to assemble into a four-way branched DNA building block with sticky ends at its periphery that could then be used for constructing 2D and 3D DNA assemblies. (b) Two duplexes are locked into position using a number of cross-overs to generate a structurally well-defined tile with four sticky ends (arrow head). The different colors denote different strands. Reprinted with permission from [15] copyright © 2006.

STRUCTURAL DNA NANOTECHNOLOGY: DEVELOPMENT

In addition to the four-way Holliday junction and the DX tile discussed above, a number of other branching building blocks have since been generated [15]. Most of these can be classified as being pla-

nar tiles, branched junctions, discrete building blocks, or helix bundles. (1) Planar tiles are constructed from a number of helices joined together by inter-strand cross-overs, and currently come in a number of different flavors; the number and sense (i.e., polarity) of cross-overs is what determines the type of tile produced. DXs are constructed by joining together two helixes with two cross-overs, while triple cross-overs are formed when three DNA helices are connected using four cross-over linkages (Fig. 4a, left). Four, eight, and even twelve helix tiles (Fig. 4a, left) have also been constructed. These planar tiles have been assembled into linear arrays, 2D lattices (Fig. 4a, right), and DNA nanotubes [15]. (2) Branched junctions are constructed from multiple helixes that branch from a central core, and almost always contain a number of cross-over motifs to increase rigidity (Fig. 4b). Three, four, six, eight, and twelve-arm branched DNA junctions are synthesized using this approach, and have been used to assemble 2D arrays with square, hexagonal, and compound cavities [15,16]. It should be noted that in this

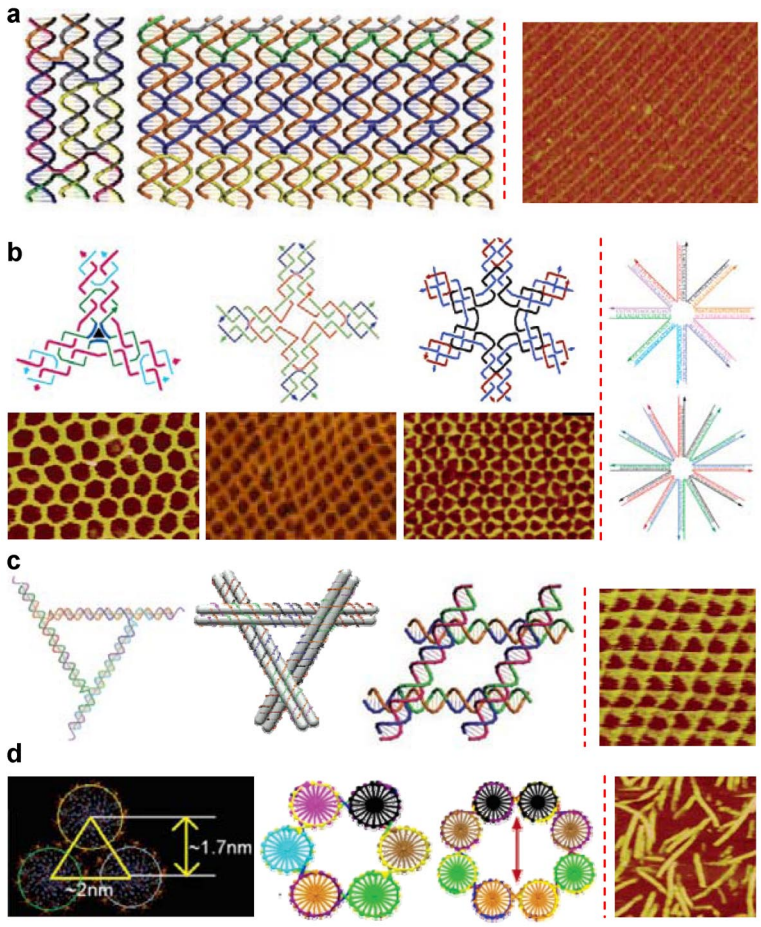

Fig. 4 (a) (*left*) A triple cross-over tile and a 12-helix cross-over tile. (*right*) An example of a 2D DNA assembly generated from a DX tile; lines represent hairpins programmed to protrude from each tile to aid in their visual detection using AFM. (b) (*left*) 3-, 4-, and 6-arm branched junctions used to generate 2D hexagonal, square, and compound lattices, respectively. (*right*) Simple 8- and 12-arm branched DNA junctions. (c) (*left*) Triangular and rhombus discrete DNA building blocks, with sticky-end overhangs. (*right*) Triangular-shaped DNA lattice generated from a triangular DNA building block (central object in left panel). (d) (*left*) 3-, 6-, and 8-membered helix bundles. (*right*) Columnar assembly generated from the three helix bundles (*left object in left panel*). Reprinted with permission from [15] copyright © 2008 and [16] copyright © 2006.

review we refer to this entire class of assemblies as branched, while conventional nomenclature typically reserves the term "branched" to Holliday-type junctions and the term "star" to the remainder of branched-type motifs. (3) Discrete building blocks are constructed from a number of DNA strands that assemble into a well-defined module with addressable sticky ends for further assembly (Fig. 4c). Examples include parallelogram- and triangular-shaped tiles that assemble into 2D arrays with square, hexagonal, or rhombic cavities [15]. (4) Helix bundles are constructed from a number of parallel DNA double strands that are linked via cross-overs (Fig. 4d). Three, six, and eight-helix bundles have been generated. These can be assembled into extended 1D nanotube or 2D periodic arrays [16].

In a recent advancement, Rothemund developed DNA origami as a new approach to generate DNA nanostructures. In DNA origami, a single continuous single-stranded DNA template is systematically folded into a number of different arbitrary shapes with the help of smaller "stapling" strands that pin together the assembly via strand-exchange cross-overs (Fig. 5) [17]. The long strand traverses the shape of the final construct, from side to side, and participates in each helix formed from each stapling strand. Using this approach, Rothemund folded the same strand of genomic DNA into squares, rectangles, stars, smiley faces, triangles with rectangular domains, and sharp triangles with trapezoidal domains and bridges between them. And because the sequence of each stapling strand is unique, the assemblies generated are also selectively addressable with a spatial resolution of ~6 nm. A number of applications utilizing DNA origami have already appeared. Yan and co-workers constructed an origami-based array for the label-free detection of RNA molecules [18], and in a separate contribution used an origami array to study the distance-dependent binding of ligands and proteins [19]. While Shih, Chou, Douglas, and co-workers used the approach of DNA origami to weave a long strand into a discrete six-helix nanotube used to align transmembrane proteins for NMR structural analysis [20].

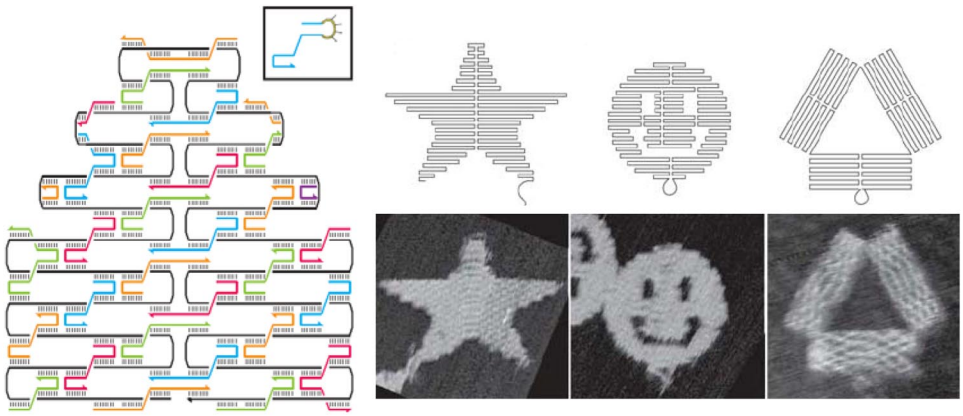

Fig. 5 (*left*) In DNA origami, a long DNA strand is folded into the desired structure, and is held into shape using many "stapling" strands (colored). Inset: Illustrates how each stapling strand could be selectively addressed, in this case using a hairpin. (*right*) This approach is used to construct a number of different 2D architectures, including a star, a smiley face, and a triangle. Reprinted with permission from [17] copyright © 2006.

STRUCTURAL DNA NANOTECHNOLOGY: APPLICATIONS

Proteins are functional molecules with applications in biosynthesis, sensing, and catalysis. Control over their organization in one, two, and three dimensions is a requirement if their full potential in DNA nanotechnology is to be exploited. Yan and co-workers were the first to demonstrate the feasibility of using the principles of DNA nanotechnology for the 1D organization of proteins. The group constructed a triple-cross-over rectangular tile capable of assembling into a 1D array, and modified each of these tiles with either one or two biotin molecules [21]. Since biotin binds strepavidin selectively, it can be used

as a tether to direct the positional organization of this specific protein. Tiles modified with a single biotin molecule have been shown to generate a linear array of Streptavidin proteins, while tiles modified with two biotin molecules produce a two-line double linear protein array. In a separate contribution, the same group used a similar triple-cross-over tile modified with DNA aptamers to direct the organization of thrombin proteins into 1D linear arrays [22]. DNA aptamers can be engineered to selectively bind a number of different target proteins, using systematic evolution of ligands by exponential enrichment (SELEX), which makes this later contribution of particular interest [23,24].

One of the initial examples of a 2D protein array was presented by Yan, LaBean, and co-workers in 2003 [25]. The group first constructed a four-way branched DNA tile capable of assembling into extended 2D square networks. By modifying the junctions of each of these tiles with a biotin molecule, Yan and co-workers organized streptavidin proteins into periodic 2D square assemblies. In a subsequent contribution, the same group demonstrated control over periodicity [26]. By generating the same 2D square array from two alternating tiles, instead of a single tile, Yan and co-workers controlled the periodicity of biotin molecules within the DNA assembly and constructed 2D streptavidin arrays of either continuous or alternating protein patterns (Fig. 6a). In 2006, Mao and co-workers modified the inner core of this same four-arm branched tile with fluorescein antigens, instead of biotin molecules, and produced 2D periodic arrays of the fluorescein antibody protein [27]. The antibody–antigen interaction is of interest to researchers in proteomics, drug discovery, and immunodiagnostic medicine, making this first example of a rationally designed antibody array of interest. Planar tiles can also be used to generate 2D protein arrays. Four different DX tiles can be programmed to assemble into an alternating array of four unique rows, each of which has the potential of being selectively addressed. By modifying one of these tiles (i.e., rows) with the *myc*-peptide, Yan, Chaput, and co-workers utilized the protein–protein interaction between the *myc*-peptide and the anti-*myc* antibody to produce rows of antibodies with

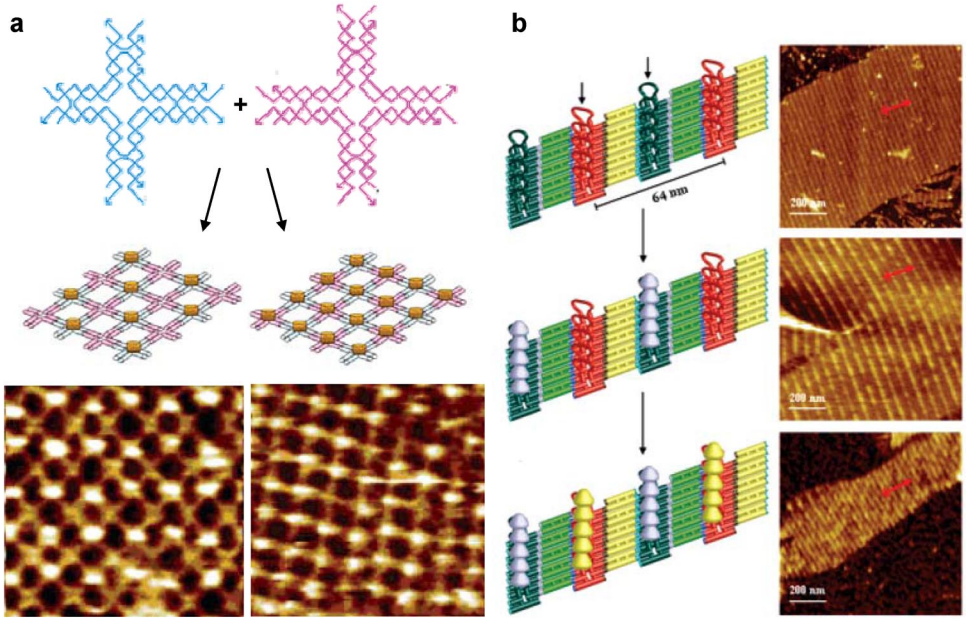

Fig. 6 (a) Two branched DNA junctions assemble to generate a square-shaped array. If one of these tiles is modified with biotin, then an alternating array of streptavidin proteins is generated (*left*), but if both tiles are modified, then a continuous protein array is produced (*right*). (b) Four tiles are assembled into an array with two unique aptamers (red and green) that organize two different proteins into alternating lines. Reprinted with permission from [26] copyright © 2005 and [27] copyright © 2006.

a 64 nm spacing [28]. In a separate contribution, Yan and co-workers modified two such tiles with two different aptamers, one specific to thrombin and the other specific to platelet-derived growth factors, and produced alternating rows of two different proteins with no unwanted cross-talk between them (Fig. 6b) [29].

Unmodified 2D DNA arrays can also template the organization of proteins. Dervan and co-workers developed a class of pyrrole-imidazole polyamides that sequence-specifically bind the minor groove of double-stranded DNA at specific sites. The group utilized this selectivity to direct the organization of proteins onto specific regions within an unmodified pre-assembled DNA array [30]. Specifically, an array from four independently addressable different planar tiles was constructed and used to subsequently organize streptavidin proteins with complete control over their overall periodicity. Turberfield and co-workers organized the protein RuvA into extended 2D arrays using unmodified DNA junctions [31]. RuvA is a DNA binding protein. The group used this interaction to bind four-armed Holliday junctions, now structurally oriented at a 90º angle, and assembled them into a well-defined square-planar array that simultaneously organizes RuvA. The assembly process occurred with a high enough fidelity to in fact allow for the protein's crystal structure to be determined with a resolution of 3.5 Å.

Nanoparticle assemblies hold great promise in nanoelectronics, sensing, catalysis, and nanophotonics. Their collective properties strongly depend on their relative arrangement within these assemblies. Our ability to organize them into well-defined systems is of great importance if their full potential is to be exploited. In 2004, Seeman and co-workers presented the first example of a DNA-templated 2D gold nanoparticle array [32]. Five-nanometer gold nanoparticles functionalized with multiple DNA strands were organized into lines on an array constructed from four unique planar tiles, one of which contained a protruding DNA capture probe complementary to the DNA sequence conjugated to the particles. By modifying a second tile with a different DNA capture probe, the group was able to later organize two different sizes of gold nanoparticles into alternating lines (Fig. 7a) [33].

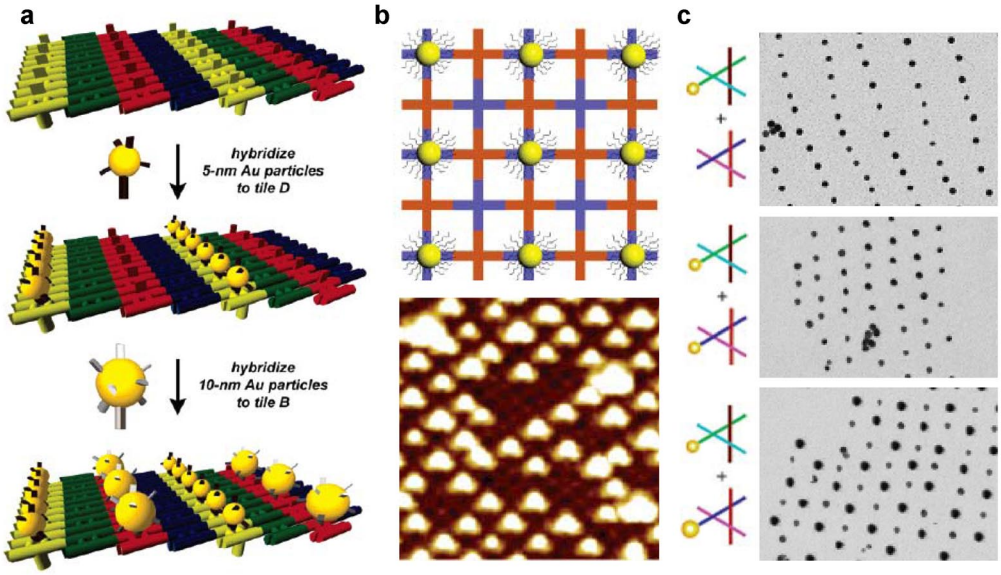

Fig. 7 (a) Four DX tiles assemble into an array with two alternating protruding capture probes. Gold nanoparticles modified with the complementary sequences are instructed to assemble into alternating lines. (b) Modifying the inner core of a single junction with a protruding DNA sequence results in an assembly that organizes gold particles into an alternating square array. (c) The modification of triangular DNA building blocks with gold nanoparticles results in a gold assembly of normal or alternating periodicity. Reprinted with permission from [33] copyright © 2005, [34] copyright © 2005, and [35] copyright © 2006.

Yan and co-workers constructed a 2D DNA array from two four-arm branched junctions, and used it to organize 5-nm gold nanoparticles into an alternating square arrangement (Fig. 7b) [34]. The approach involved modifying the core of one of these tiles with a protruding DNA capture probe complementary to the DNA strands coating the gold nanoparticles. In a second contribution, the same group directly conjugated the core of one of these tiles with a gold particle, and used a second unmodified tile to generate a number of different gold assemblies with control over periodicity and cavity size [35]. Exquisite control over the 2D organization of discrete nanoparticles was demonstrated by Seeman and co-workers [36]. The group constructed two DX triangular tiles capable of assembling into an extended rhombic lattice, which they used to organize two different sizes of gold nanoparticles into an alternating assembly (Fig. 7c). This approach involved mono-functionalizing each respective gold nanoparticle with a single DNA strand, and subsequent incorporation of this conjugate into the triangular tile prior to its use in array formation.

Although a number of well-defined 2D nanoparticle arrays have been constructed, little has been achieved in the area of well-defined discrete nanoparticle organization. The problem lies in the fact that branched DNA junctions are inherently flexible, and that the cross-over approaches developed to rigidify them typically needs to be part of an extended motif to maintain their overall structural robustness. We will discuss how the field of supramolecular DNA nanotechnology can help address this very issue.

A full summary of all other applications within DNA nanotechnology is beyond the scope of this section, however, the fields of DNA computation and DNA nanomachines merit mention. Adelman and co-workers presented a breakthrough in the area of DNA computing when they developed a simple DNA-based system capable of solving the seven-point "Hamiltonian path" problem [37]. DNA computing promises to address some of the limitations that our current silicon-based technology is starting to face with respect to miniaturization. Shapiro and co-workers engineered the first actual DNA computer with input, computation, and output modules [38]. They developed a system capable of analyzing input mRNA molecules to release a single-stranded DNA molecule that acts as a drug. Winfree and co-workers designed a set of DNA building blocks that represent Wang tiles [39]. Conceptually, Wang tiles contain a single color on each of their four sides, and assemble so that the adjacent sides of each square are of the same color—this necessarily means that each tile can only fit in a specific way within the assembly. Winfree and co-workers adapted this methodology to rectangular-shaped DNA tiles with four addressable sticky ends at each side, and demonstrated the feasibility of this algorithmic assembly using a number of DNA-based arrays [39]. Since all mathematical algorithms can be translated into Wang tiles, this work is of particular value to researchers in DNA computing.

Seeman and co-workers constructed a DNA-based nanomechanical device capable of undergoing a structural transition. This machine consists of two DX molecules connected by a double helix that undergoes a B-DNA to Z-DNA structural conversion, at high ionic strengths, and induces a nanomechanical movement of the DX tiles (Fig. 8a) [40]. DNA nanomachines are of interest because they promise to create new technologies for use in molecular sensing, intelligent drug delivery, and programmable chemical synthesis. The disadvantage of using an unspecific molecule to activate motion, such as the use of salt ions in the case of B-Z systems, is that a number of embedded devices would all respond simultaneously. Strand-displacement-based devices, however, offer a sequence-dependant mechanism for actuation and allow for the selective control of different parts within the same device. Yurke and co-workers constructed a pair of DNA tweezers with two rigid double-stranded arms connected at one end by a flexible single-stranded hinge, and sequence-selectively cycled it between a closed and an open state using "fuel" and "antifuel" DNA strands (Fig. 8b) [41]. Turberfield, Yan, Reif, and co-workers applied the same principles of strand-displacement to construct a DNA-based nanomachine with a unidirectional autonomous motor capable of "walking" across a DNA scaffold [42]. This fertile sub-area of DNA nanotechnology has been recently reviewed [43].

In structural DNA nanotechnology, DNA is used in all parts of the assembly. A number of recent publications have shown that small molecules can also be incorporated into DNA nanostructures, and that they can instill additional structural and functional advantages to the system that DNA alone can-

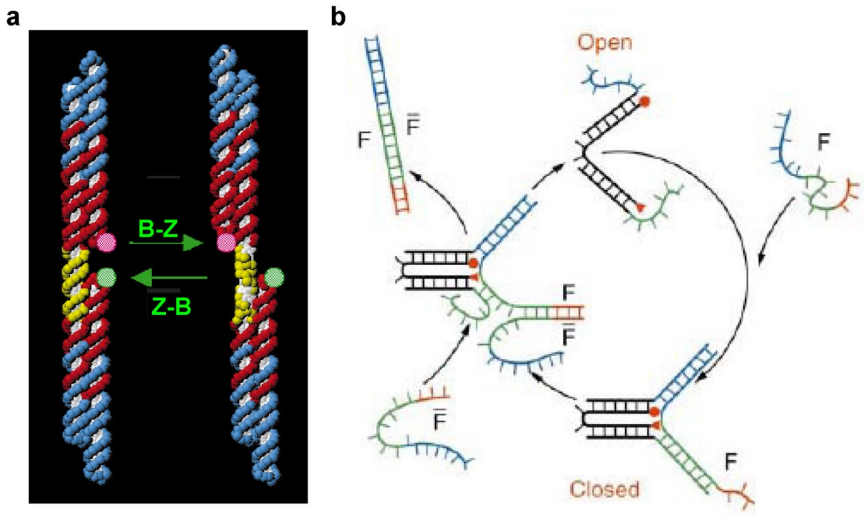

Fig. 8 (a) The B-Z DNA structural transition is monitored using fluorescence resonance energy transfer, and can in principle be used as a two-state switch. (b) Sequence-dependent actuation is demonstrated using a DNA system that contains two overhangs. In the open state, the two strands are free, addition of a fuel molecule locks the assembly into a well-defined construct, while addition of an anti-fuel molecule reopens the system. Reprinted with permission from [40] copyright © 1999 and [41] copyright © 2000.

not. Cram, Lehn, and Pedersen received the 1987 Nobel Prize in Chemistry for their work in supramolecular chemistry. This area of research deals with the study and application of noncovalent molecular interactions, such as hydrogen-bonding, metal coordination, hydrophobic effects, π–π interactions, and electrostatic forces. These rules are now being used to empower the field of DNA nanotechnology and are resulting in an emerging sub-area of research that we have recently termed "supramolecular DNA nanotechnology".

SUPRAMOLECULAR DNA NANOTECHNOLOGY: DEVELOPMENT

Molecules have structure and function. These can be exploited by DNA and can also be used to exploit DNA. In DNA nanotechnology, the entire structures are made up of DNA. In supramolecular DNA nanotechnology, molecules replace parts of these structures. Small molecules possess a number of different branching points and angles, and are relatively small, which means that they can be seamlessly incorporated into the nucleic acid assemblies.

Organic aliphatic molecules have been used to construct branched DNA building blocks with an organic core. Von Kiedrowski and co-workers synthesized a three-arm DNA building block radiating from a single aliphatic three-arm linker [44]. The group assembled these building blocks into discrete dimers, tetramers, and higher-order structures. Shchepinov and co-workers used a polyglycol-based core, constructed on the solid support, to synthesize DNA building blocks with 2, 3, 6, 9, and 27 arms [45]. Steric considerations make it difficult to access a branched 27-armed DNA building block using just DNA—the biggest being a 12-point branching point recently reported by Seeman and co-workers (Fig. 9a) [16]. In addition to organic aliphatic molecules, organic aromatic molecules can also be incorporated. Bergstrom and co-workers synthesized a self-complementary two-arm branched DNA building block with aromatic *p*-(2-hydroxyethyl)phenylethynylphenyl spacers that are attached to a single tetrahedral carbon atom, as the vertex, and assembled it into discrete structures containing 2, 4, 5, etc. units (Fig. 9b) [46].

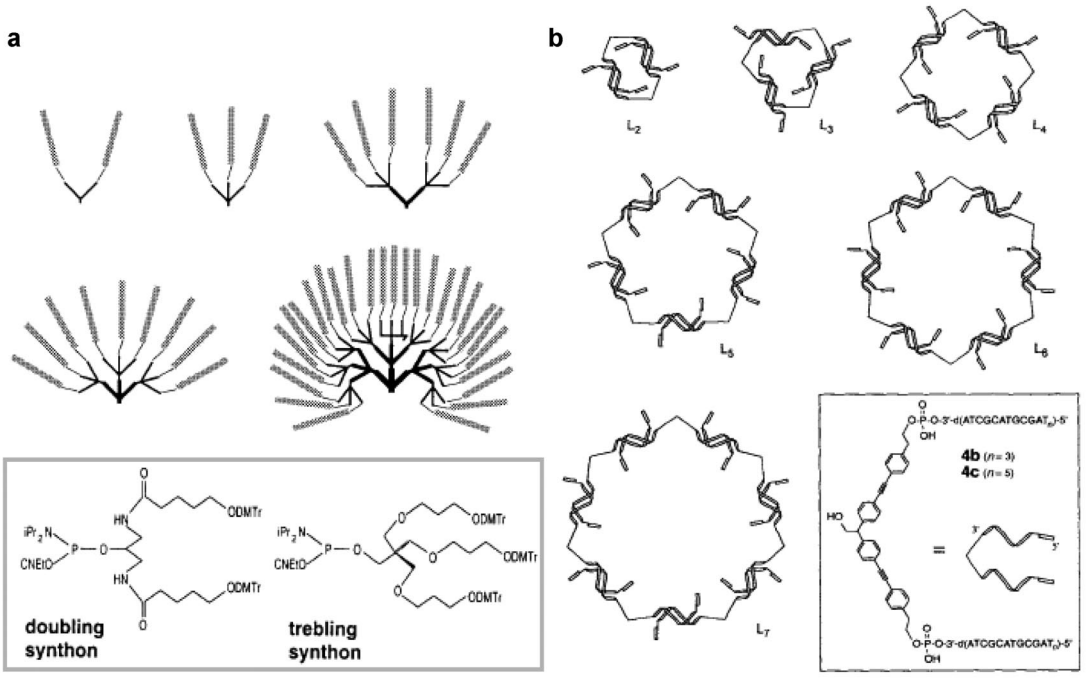

Fig. 9 (a) Branched DNA building blocks in which a number of DNA arms radiate from a central aliphatic core are constructed using two- and three-arm branching synthons (inset below). (b) Symmetrically branched DNA building block in which two arms radiate from a central aromatic core assembles into discrete assemblies of two, three, etc. building blocks. Reprinted with permission from [45] copyright © 1999 and [46] copyright © 1997.

Inorganic molecules are of particular interest because in addition to structural features, they can be used to impart functional electronic, catalytic, and optical properties to DNA. Bunz and co-workers synthesized a two-arm branched DNA building block containing a cobalt tetraphenyl-cyclobutadiene(cyclopentadienyl) vertex, and modularly assembled it into linear tapes using branched DNA building blocks with a phenyleneethynylene aromatic core [47]. Sleiman and co-workers synthesized a two-arm branched DNA building block with a ruthenium tris(bipyridine) core, which they assembled into the first example of a cyclic metal DNA nanostructure (Fig. 10a) [48,49]. McLaughlin and co-workers synthesized a two-arm ruthenium bis(terpyridine) DNA building block [50], and later presented the synthesis of a four-arm nickel cyclam [51] and a six-arm ruthenium tris(bipyridyl) branched complexes (Fig. 10b) [52]. Access to inorganic branched DNA building blocks can be synthetically limited as a consequence of the conditions used in standard automated DNA synthesis. Sleiman and Yang recently developed a synthetic approach that synergistically stabilizes both the metal environment and the DNA duplex to access metallated DNA building blocks that would otherwise be difficult to synthesize (Fig. 10c) [53].

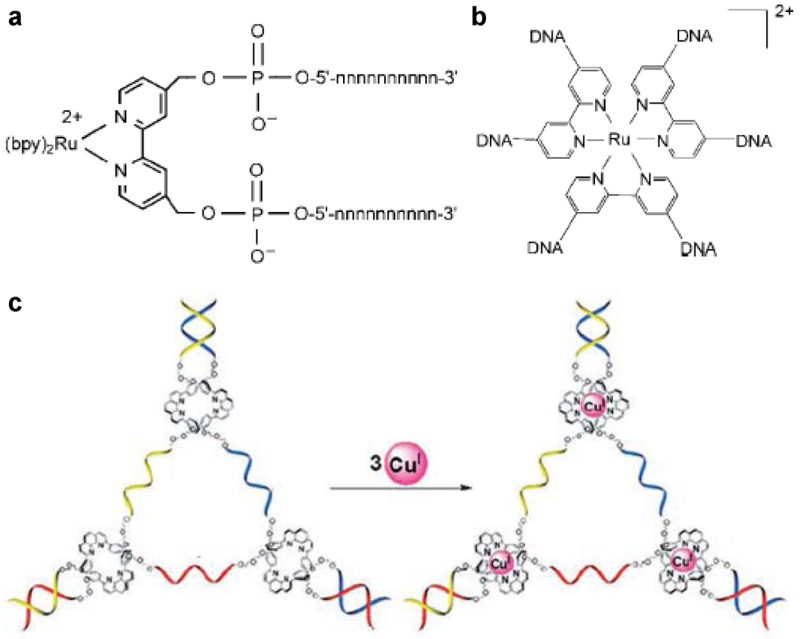

Fig. 10 (a) Two-arm branched DNA building block with an inorganic ruthenium core. (b) Six-arm branched DNA building block with an inorganic ruthenium core. (c) In this approach to accessing inorganic DNA assemblies, a construct containing metal-binding ligands is first synthesized and assembled, this is then used as a template to position metals to generate stable inorganic DNA assemblies. Reprinted with permission from [48] copyright © 2001, [52] copyright © 2004, and [53] copyright © 2008.

In classical DNA nanotechnology, the assembly outcome is dictated solely by the DNA sequence—which in fact is the power of DNA. In supramolecular DNA nanotechnology, however, the assembly process can in principle be fine-tuned as a function of both DNA sequence and supramolecular interactions, such as hydrogen-bonding, metal coordination, π–π stacking, and hydrophobic interactions. Kramer and co-workers modified the ends of a single molecule of DNA with metal binding terpyridine ligands, and used the metal–zinc interaction to induce intermolecular cyclization and override duplex formation (Fig. 11a) [54]. Li and co-workers incorporated π-conjugated molecules into DNA that assemble into π-stabilized stacks, and generated thermophilic foldable oligopolymers in which the π-conjugated stacks contributed to the final assembly process (Fig. 11b) [55]. Furthermore, Berger, Herrmann, and co-workers generated a class of DNA-polypropyleneoxide polymers—with a hydrophilic DNA region and a hydrophobic polymeric region—that microphase-separate into spherical micelles, and further showed that these assemblies can be inter-converted into rod-like micelles using an external DNA template strand as the trigger (Fig. 11c) [56].

The above examples have been selected to illustrate the major developmental milestones that led to the fruition of supramolecular DNA nanotechnology. This symbiosis was not collectively planned, but rather evolved organically in hopes of addressing a number of issues facing researchers in DNA nanotechnology, at the time. We will now show how these proof-of-concept examples provide the fundamental principles of design that can be rationally used to solve the issue of discrete nanoparticle organization, discrete and extended 3D DNA construction, as well as the long-standing problem of error prevention–correction during DNA self-assembly.

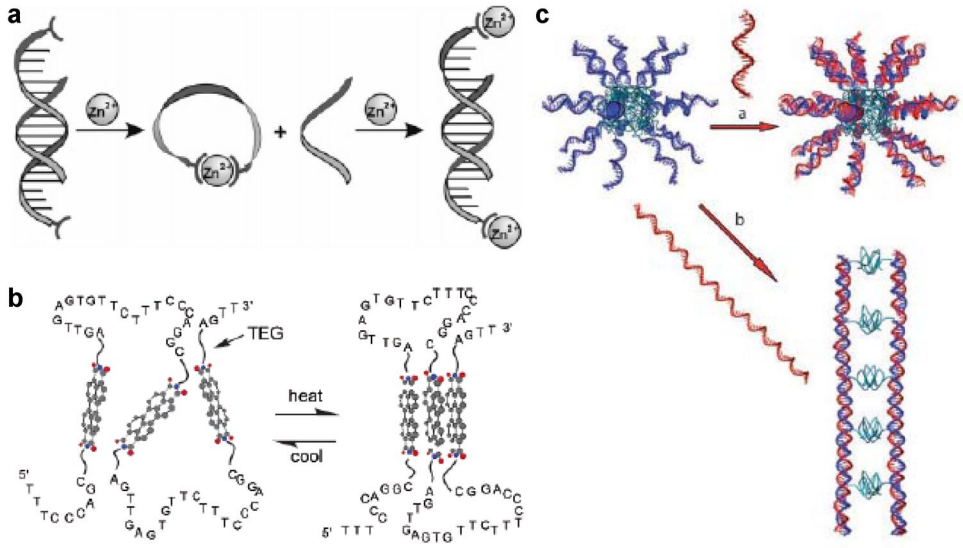

Fig. 11 (a) DNA strands that are end-modified with metal coordinating ligands can be used to bind zinc and override DNA duplex formation, and can be allowed to rehybridize to the complementary DNA strand up addition of excess zinc. (b) Extended aromatic molecules can be inserted into DNA to create folded structures through π-stacking interactions. (c) DNA strands (blue) attached to polymers (green) result in block copolymers that assemble into micelles through microphase separation of the incompatible blocks. Addition of a complementary strand of DNA (red, short) does not affect the overall morphology, while addition of a longer complementary strand of DNA (red, long) results in a change of the overall morphology. Reprinted with permission from [54] copyright © 2005, [55] copyright © 2003, and [56] copyright © 2007.

SUPRAMOLECULAR DNA NANOTECHNOLOGY: DISCRETE NANOPARTICLE ORGANIZATION

One of the central challenges of nanoscience is the ability to organize nanoparticles according to a deliberately designed pattern, and the ability to structurally and functionally control these materials at will [57–63]. Molecular responsive assemblies can provide control over the electronic and optical transport properties of nanoparticle assemblies, and could potentially contribute to the bottom-up design of nanoscale circuitry capable of performing complex functions [60–63]. Although some of the earliest work on the use of DNA in nanotechnology involved the construction of discrete nanoparticle assemblies, none of this work produced structurally well-defined discrete systems. This in fact has hampered the systematic development of model nanoparticle motifs that can be used to properly understand and exploit the full plasmonic, photonic, and electronic properties of this novel class of materials. The problem lies in the fact that DNA branching points are inherently flexible. Although a number of cross-over approaches have been developed to rigidify them, these typically need to be part of an extended system to maintain their robustness. Supramolecular chemistry can help. Instead of using DNA exclusively, corner units can be replaced with structurally well-defined organic molecules. The power of such hybrid materials lies in the fact that they are functionally programmable, due to the use of DNA, and are structurally well-defined, due to the use of well-defined corner units. Sleiman and co-workers used a simple set of six DNA building blocks with a rigid 120º organic vertex programmed to assemble into a structurally well-defined DNA hexamer (Fig. 12) [64]. They tagged six gold nanoparticles with this set of hybrid DNA molecules, and constructed the first example of a well-defined discrete gold nanoparticle hexamer.

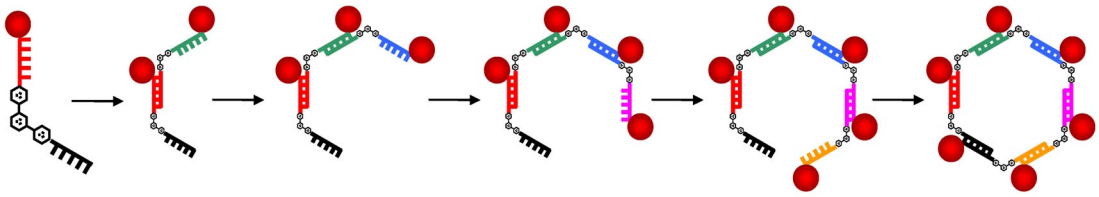

Fig. 12 Gold nanoparticles tagged with DNA building blocks containing rigid organic molecules can be sequence-programmed to assemble into a well-defined gold nanoparticle hexamer. Reprinted with permission from [64] copyright © 2006.

If the true potential of well-defined nanoparticle assemblies is to be truly exploited by nanotechnology, then access to such materials will need to be both economical and facile. To do so, the same group developed a second-generation system capable of accessing large numbers of well-defined discrete assemblies in a modular fashion, and also showed that these assemblies are structurally and functionally addressable in real time (Fig. 13) [65]. The group used a novel class of cyclic and single-stranded DNA templates embedded with rigid organic molecules as templates that are independently functional from the nanoparticles being organized. They demonstrated the overall modularity of their approach by assembling two different sizes of gold nanoparticles into all possible triangular combinations from the same single-stranded triangular template (Fig. 13b). They demonstrated the structural switching capability of their approach by using the same square-shaped DNA template to generate square, trapezoidal, and rectangular assemblies (Fig. 13c). They also demonstrated the addressability of their approach by generating a triangular construct of three gold nanoparticles, selectively removing one of these particles without affecting the connectivity between the remaining nanoparticles, and by "writing" a different sized gold nanoparticle (Fig. 13d). Their approach empowers the fields of photonics,

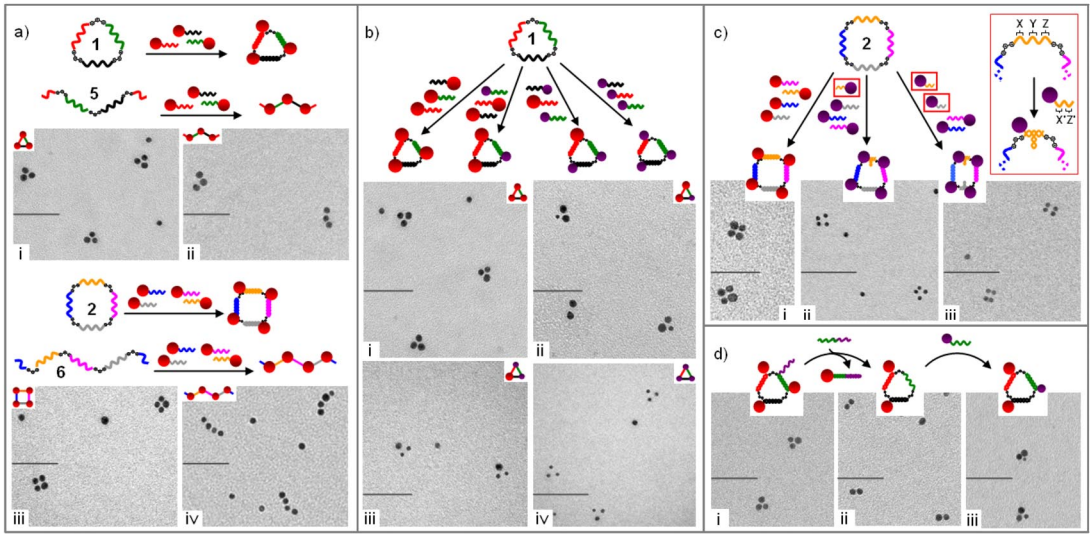

Fig. 13 (a) **1** and **2** organize gold particles into triangles and squares; **5** and **6** result in open linear assemblies of 3 and 4 particles. (b) **1** generates triangles of (i) 3 large (15-nm, red), (ii) 2 large/1 small (5-nm, purple), (iii) 1 large/2 small, and (iv) 3 small particles. (c) **2** assembles 4 gold particles into (i) squares (15-nm particles), (ii) trapezoids, and (iii) rectangles (5-nm). Inset: use of a loop shortens template's arm. (d) Write–erase function with **1** by (i) writing 3 gold particles (15-nm) into triangles, (ii) removal of a specific particle using an eraser strand, and (iii) re-writing with a 5-nm particle. Bar is 50 nm. Reprinted with permission from [65] copyright © 2007.

nanoelectronics, plasmonics, and nanooptics with the necessary tools to readily construct nanoparticle assemblies that are dynamic and addressable.

SUPRAMOLECULAR DNA NANOTECHNOLOGY: DISCRETE 3D DNA CONSTRUCTION

DNA polyhedra present tremendous potential for the encapsulation and release of drugs, regulation of protein folding and activity, and the assembly of 3D networks for catalysis and biomolecule crystallization [66]. Easy access to discrete 3D DNA assemblies, however, is not trivial. Seeman and co-workers constructed the first 3D DNA object in 1991, a cube [67]. In his approach, two quadrilaterals are ligated to form a belt-like molecule that is then purified, reconstituted, cyclized, and ligated to produce an assembly of six interconnected cyclic DNA strands with the topology of a cube in less than 1 % yield (Fig. 14a). The same group later adapted this methodology for the solid-phase synthesis of a truncated DNA octahedron with 14 interconnected cyclic DNA strands [68]. Since then, Turberfield and co-workers synthesized a DNA tetrahedron [69] (Fig. 14b) and a trigonal bipyramid [70]. The group's approach involved programming single strands of DNA so that they would necessarily assemble into the target construct, incorporating unhybridized bases into the corners units to alleviate strain, and consistently using triangular edges to insure the overall structural integrity of the final assembly. The same group later encapsulated the protein cyctochrome *c* into a DNA tetrahedron by chemically conjugating it to the inner surface of the cage [66], which is of interest to researchers in proteomics since the functional properties of proteins can in principle be modulated when encapsulated. In a separate approach, Joyce and co-workers assembled a 3D DNA object, an octahedron, by folding a long synthetic DNA template with the help of five smaller DNA strands (Fig. 14c) [71].

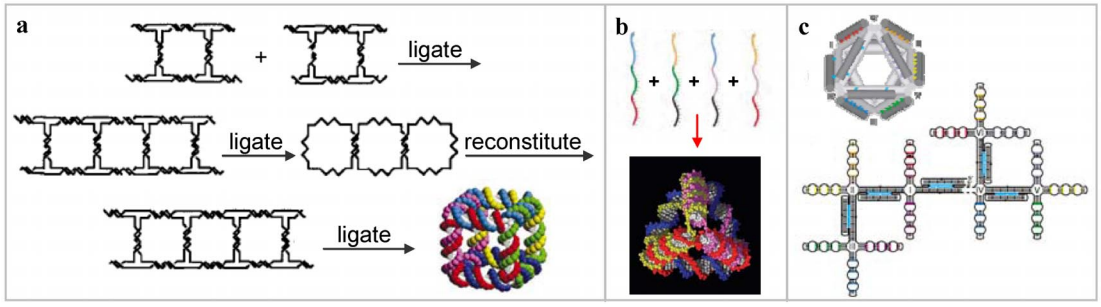

Fig. 14 (a) Two quadrilaterals are ligated to form a belt-like molecule, which is then denatured, reconstituted, cyclized, and ligated again to form an assembly with the topology of a DNA cube. (b) Four unique single strands are programmed to assemble into a DNA tetrahedron. (c) A single synthetic DNA strand is folded using five DX motifs (colored in cyan) and seven PX motifs (rainbow colors) to form a DNA octahedron. Reprinted with permission from [67] copyright © 1991, [69] copyright © 2005, and [73] copyright © 2007.

As seen above, a handful of 3D discrete DNA assemblies have emerged since the DNA cube in 1991. If the true potential of 3D DNA assemblies is to be exploited, synthetic access to such systems will need to be facile and economical. Supramolecular DNA nanotechnology can help. Sleiman and co-workers noticed that almost all platonic and non-platonic solids are composed of simple triangular, square, pentagonal, or hexagonal faces, and that a small set of geometrically simple DNA building blocks (i.e., a DNA triangle, square, pentagon, and hexagon) could in principle be used to modularly construct any of these objects [72]. The group developed a class of single-stranded and cyclic DNA building blocks with rigid organic molecules as the vertices, and used them to generate well-defined discrete nanoparticle assemblies. Using this approach, the group generated a toolbox of well-defined single-stranded triangular, square, pentagonal, and hexagonal DNA building blocks. As seen in Fig. 15, tri-

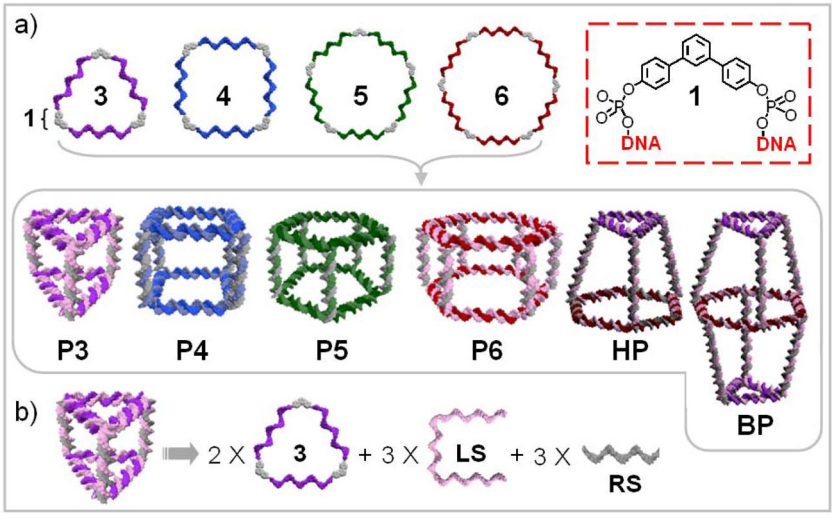

Fig. 15 (a) Single-stranded and cyclic DNA molecules containing rigid organic molecules as their corner units are used as a tool-box of building blocks to construct a number of 3D DNA assemblies. (b) The approach involves using single-stranded linking strands and rigidifying strands. Reprinted with permission from [72] copyright © 2007.

angle **3**, square **4**, pentagon **5**, and hexagon **6** are used to generate a triangular prism, a cube, a pentameric prism, a hexameric prism, and even a heteroprism and biprism in quantitative yields.

DNA building blocks that are cyclic can maintain their structural integrity in their single-stranded form, and thus, their use provides for an opportunity to generate structurally dynamic addressable assemblies. To demonstrate this, Sleiman and co-workers further constructed a triangular prism that contains single-stranded regions separating both triangular faces, and used it as a synthetic intermediate to generate three well-defined triangular prisms of different lengths (Fig. 16) [72]. Assembly of each prism is achieved using strands capable of introducing internal loops of different lengths within the single-stranded intermediate, while real-time oscillation between each structure is conducted using eraser strands. As monitored by fluorescence resonance energy transfer, the triangular prism was structurally oscillated between 5.2, 6.9, and 8.9 nm. Many applications can be anticipated for such switchable capsules, including molecule-triggered drug delivery and dynamic 3D DNA crystallization.

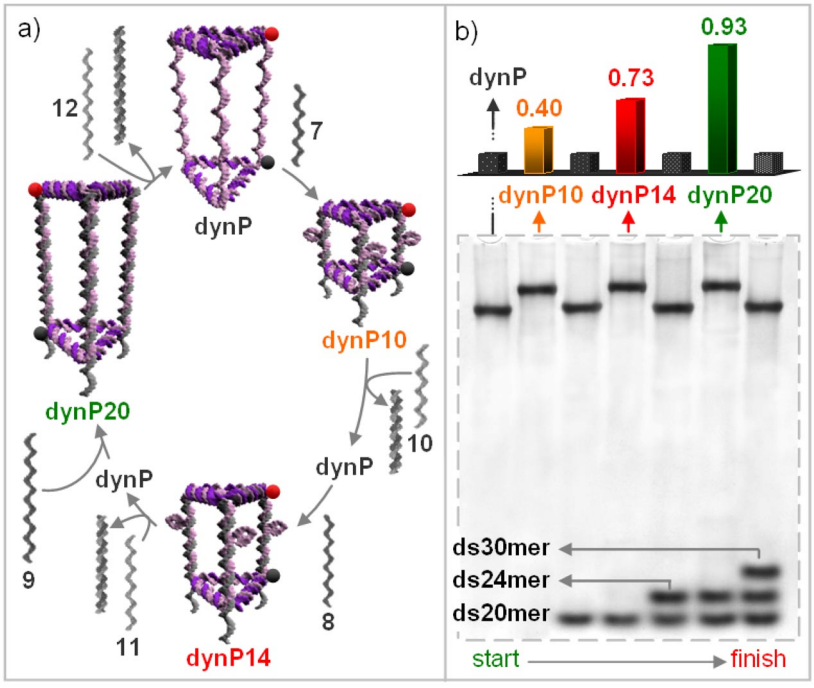

Fig. 16 (a) Strands **7**, **8**, and **9** are used to generate **dynP10**, **dynP14**, and **dynP20**, from **dynP**, with respective length of 10, 14, and 20 bases. Real-time structural oscillation between these structures is achieved by regenerating the intermediate **dynP** using strands **10**, **11**, and **12**. (b) This structural cycle is confirmed using polyacrylamide gel electrophoresis and fluorescence resonance energy transfer analysis. Reprinted with permission from [72] copyright © 2007.

SUPRAMOLECULAR DNA NANOTECHNOLOGY: EXTENDED 3D DNA CONSTRUCTION

DNA nanotubes hold great promise in applications ranging from material nanofabrication to fundamental biophysical research. For example, they can template the growth of nanowires [25], orient transmembrane proteins for structural NMR determination [20], and potentially act as stiff interconnects, tracks for molecular motors, and as drug nanocarriers [73]. DNA nanotubes are currently synthesized using one of two approaches. The first involves rolling and cyclizing a 2D DNA array with complementary sticky ends at its periphery. Arrays can be induced to cyclize by rationally programming a specific nonzero degree of curvature within each tile (Fig. 17a). Although the resulting tubes would have a preferred size, a mixture with a certain amount of variation around an optimum is typically generated. Rothemund and co-workers synthesized two such DX tiles that tessellate into a curved array, and used it to synthesize nanotubes ranging in diameter from 7 to 20 nm [74], while Turberfield and co-workers used a similar approach to fold a DNA sheet into nanotubes with alternating rings, as well as chiral nanotubes with nested helices (Fig. 17b) [75].

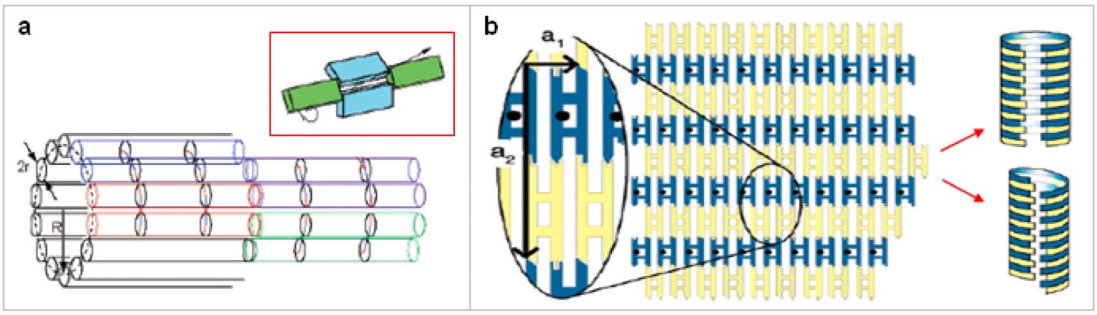

Fig. 17 (a) A non-zero degree of curvature is incorporated into rectangular DX tile assemblies (see inset), so that the generated 2D array would fold upon itself and close to generate a DNA nanotube. (b) This has been used to generate symmetrical and chiral DNA nanotubes with nested helices. Reprinted with permission from [74] copyright © 2004 and [75] copyright © 2004.

The second approach involves programming the sequence of different DNA double strands so that they would necessarily assemble into a helix bundle with a fixed number of helices within its cross-section [76]. Yan, LaBean, and co-workers linked together three DNA helices into a discrete column, and used it to construct 1D DNA columnar assemblies (Fig. 18a) [16], while Seeman and co-workers programmed a number of DNA strands to assemble into well-defined DNA nanotubes of six and eight helices (Fig. 18b) [77,78].

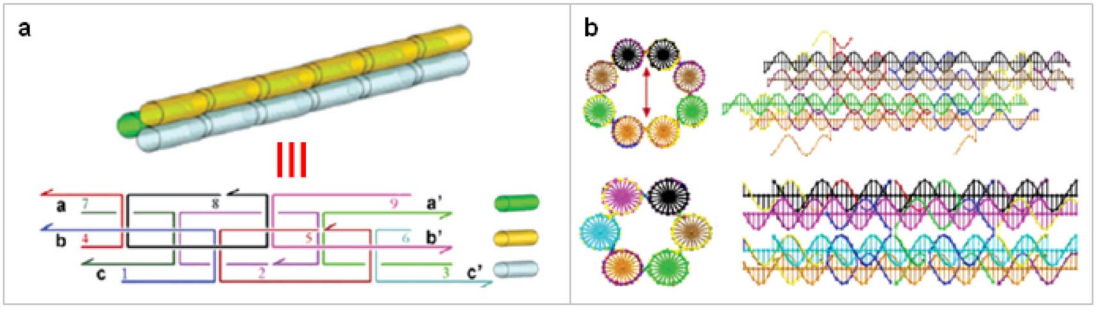

Fig. 18 (a) Nine different DNA strands are programmed to assemble into a three-helix bundle containing six crossover motifs. These units are then assembled into long 1D DNA columns. (b) The same approach is used to generate six- and eight-helix DNA nanotubes. Reprinted with permission from [16] copyright © 2005, [77] copyright © 2005, and [78] copyright © 2007.

From these selected examples, it is evident that the current approaches to DNA nanotube construction always result in cylindrical assemblies that are symmetrical and fully double-stranded. Controlling the surface topology of nanotubes provides for a new parameter that can be used to further fine-tune their resulting physical and chemical properties–function. This, in fact, is a general challenge common to all nanotube construction, including polymeric and carbon nanotubes. Supramolecular DNA nanotechnology can help. The group of Sleiman developed a class of DNA materials containing rigid organic molecules that they used for the organization of discrete gold nanoparticles and for the modular construction of dynamic 3D DNA assemblies. It is easy to envisage how this approach can be further extended into an additional dimension to address the issue of DNA nanotube construction. The group adapted their approach to construct the first example of triangular and square-shaped DNA nanotubes, as well as synthesize DNA nanotubes that can exist in a double-stranded "closed" form or a par-

tially single-stranded "open" form (Fig. 19) [79]. Their approach thus allows for the deliberate control of DNA nanotube stiffness, persistence length, and permeability, and opens the door to the possibility of using these nanotubes in their more accessible single-stranded form to allow for the loading of biomolecules–drugs, followed by their subsequent closing ensuring encapsulation.

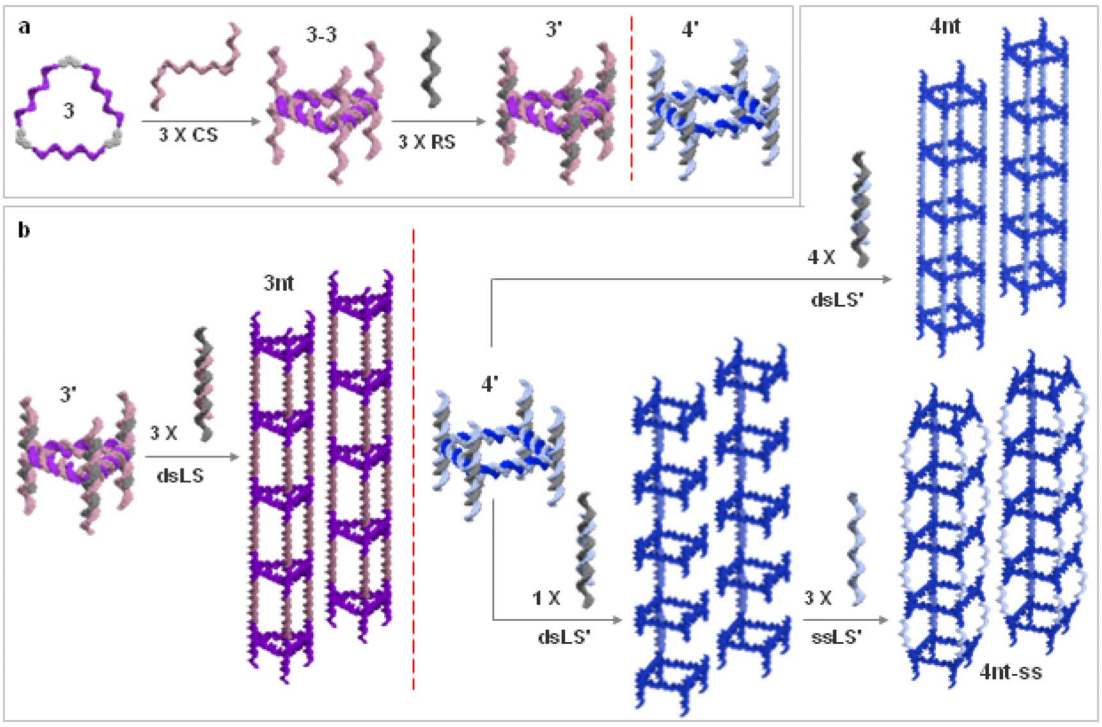

Fig. 19 (a) Single-stranded and cyclic triangular DNA building block **3** can be assembled into a well-defined triangular rung with sticky ends capable of polymerizing into a DNA nanotube. (b) This can be achieved using double-stranded linking strands. A square-shaped DNA rung can be assembled into fully double-stranded or partially single-stranded DNA nanotubes. Reprinted with permission from [79] copyright © 2009.

SUPRAMOLECULAR DNA NANOTECHNOLOGY: ERROR CORRECTION–PREVENTION DURING DNA SELF-ASSEMBLY

As it becomes necessary to design larger and more complex DNA assemblies, it inevitably becomes necessary to also incorporate degenerate DNA sequences that may assemble into a number of undesirable products. This is currently a major bottleneck facing researchers in DNA nanotechnology [80]. Errors during the self-assembly process typically occur when a DNA sequence hybridizes to an "incorrect" strand at an energetically sub-optimal configuration. One approach to address this issue would be to reduce the number of unique sequences that are used. For example, even though a four-way branched junction is structurally symmetric, it is typically constructed from nine sequence-unique strands that assemble into four unique arms (Fig. 20a, *top*). Mao and co-workers judiciously incorporated symmetry into the structurally symmetric regions of this building block, and constructed a functional four-way junction from three DNA strands instead of nine (Fig. 20a, *bottom*) [81]. The same group later synthesized a DX tile from two strands instead of four (Fig. 20b) [82], and even assembled a DNA column from a single DNA strand (Fig. 20c) [83]. Yan and co-workers applied the rules of symmetry to reduce the number of unique tiles within a DNA array of finite sizes [84].

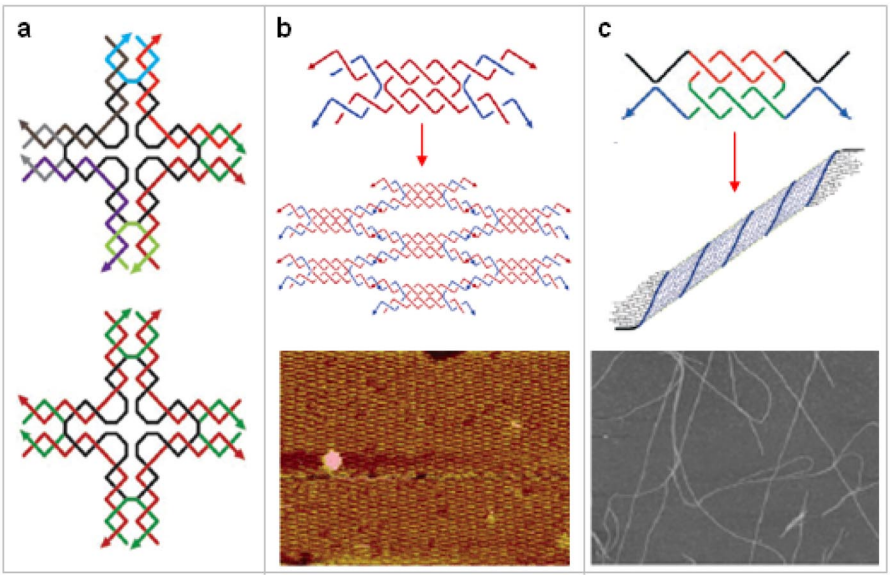

Fig. 20 (a) An asymmetric four-arm branched junction is typically constructed from nine unique strands (*top*). A symmetric four-arm branched motif is, however, constructed from three DNA strands, with judiciously programmed sequence symmetry (*bottom*), and assembles into extended 2D square DNA arrays. (b) A DX DNA tile can be constructed from only two strands, and assembles into a well-defined periodic 2D DNA array. (c) A single DNA strand can be assembled into a symmetric DNA tile capable of further generating an extended 1D DNA nanotube. Different colors represent different sequences. Reprinted with permission from [81] copyright © 2005, [82] copyright © 2005, and [83] copyright © 2006.

Another approach to reduce the necessary number of sequences incorporated into a DNA assembly is hierarchical self-assembly. In principle, if the assembly process could be conducted sequentially, then some of the sequestered sticky-end sequences could also be reused with no fear of unwanted cross-talk. Dwyer, LaBean, and co-workers used this approach to assemble a 16-tile 4 × 4 nanoarray in four steps using four unique sticky-end sequences [85].

Although symmetry considerations and hierarchical self-assembly provide mechanisms to minimize the number of sequences incorporated, it is not always feasible to use a small enough sequence-set to completely eliminate the probability of error formation. What to do when errors occur? Since mismatches are typically hybridized at an energetically sub-optimal configuration, in principle, if the system is allowed to equilibrate, then the energy landscape would be thoroughly sampled and the "correct" interactions would be favored on the bases of their thermodynamic stability. The field of DNA computation is very sensitive to imperfections that might occur during the assembly process, and has developed a number of algorithmic approaches to deal with potential mistakes. For example, Winfree and co-workers developed a system based on a 2D tile array that proofreads errors and corrects for them [86]. The tiles are programmed to stop growing when a mistake occurs unless another is made, and since the chances of another mistake occurring is relatively small, assembly halts. This pause provides the correct tile enough time to seek out and replace the thermodynamically less stable mismatched tile. Pierce and co-workers generated a number of metastable folded DNA intermediates that systematically interact with each other to assemble into a single product [87]. By programming the biochemical pathway leading to a final assembly, Pierce's approach can be used to better direct the assembly process, and is in fact an example of error prevention. Lu and co-workers presented an enzymatic approach to proofreading and correcting for errors [88]. A DNAzyme capable of cleaving DNA is used to select for errors and delete them. In the presence of the "correct" DNA strands, the DNAzyme is not properly

folded and is inactive, but in the presence of the "incorrect" DNA strands the DNAzyme is folded and proceeds to cleave and remove the errors.

Unfortunately, all of these approaches are system-dependent, and may be difficult to generalize to other DNA assemblies. Supramolecular DNA nanotechnology can help. The templated synthesis of a specific molecule from a dynamic library of possible structures has been the recent subject of intense interest [89,90]. In this approach, a template is added to a mixture of molecules in dynamic equilibrium, which re-equilibrates in favor of the member that best binds this molecule and amplifies it. Although this principle has been used to amplify the formation of small molecules, supramolecular assemblies, and macromolecules, there are no examples in which this powerful method is used in DNA nanotechnology. Sleiman's group constructed a dynamic set of discrete DNA nanostructures from symmetrically branched DNA building blocks and demonstrated the feasibility of applying the rules of host–guest supramolecular chemistry to selectively template the synthesis of a "correct" member from this library of other "incorrect" members and to convert each already formed "incorrect" member into the same "correct" assembly (Fig. 21a) [91]. The former is an example of error prevention, while the

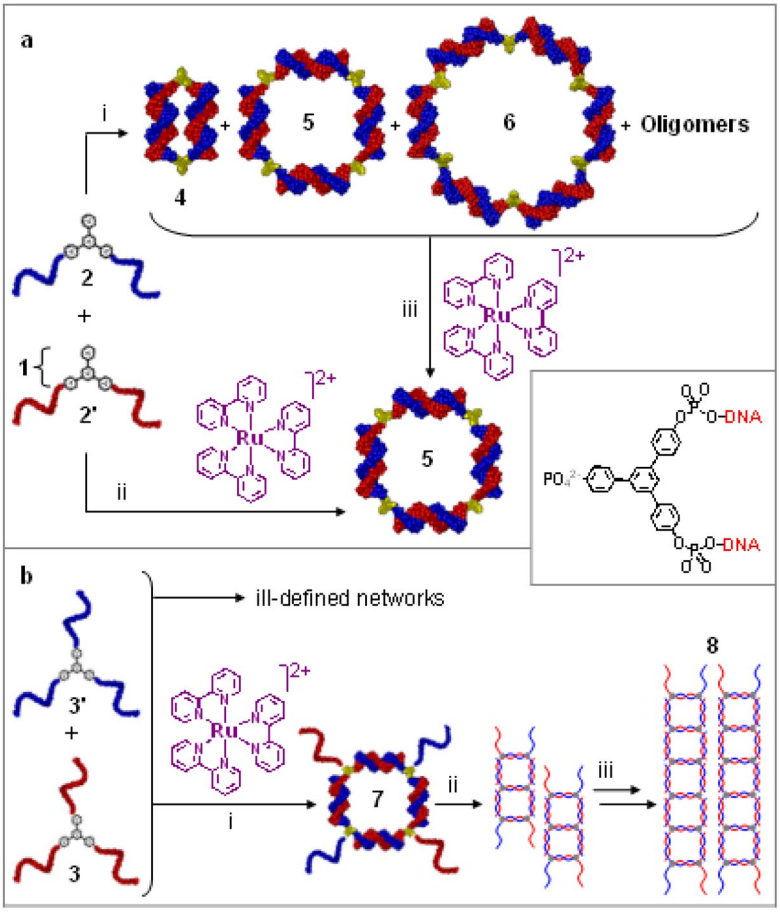

Fig. 21 (a) Complementary two-armed branched DNA building blocks generate a dynamic library of cyclic DNA nanostructures. $Ru(bpy)_3^{2+}$ can be used to template the formation of a single member, the tetramer, or to re-equilibrate the remaining members into the DNA square. (b) This can be used to generate well-defined DNA ladders extending over several microns from a three-armed DNA analog. Reprinted with permission from [91] copyright © 2007.

latter is an approach to error correction. In a direct application, the group templated the construction of uniform 1D DNA fibers from symmetrically branched three-armed DNA building blocks that would otherwise have assembled into ill-defined oligomeric networks (Fig. 21b). This work provides for a new parameter to prevent and correct for errors before and after the self-assembly and presents an opportunity to reduce the number of unique sequences incorporated when designing larger and more complex DNA systems.

OUTLOOK

DNA nanotechnology recently celebrated 25 years of fertile and active research. Today, DNA can be used to organize proteins and gold nanoparticles into a number of exquisite assemblies, and generate 1D, 2D, and 3D nanoscaled objects capable of both structural and functional addressability. DNA nanotechnology is thus poised to solve a number of long-standing problems facing researchers in nanotechnology and materials science, and has captured the imagination of many researchers worldwide. Over the past few years, however, it has become obvious that DNA alone might not be enough, and that the structural–functional power provided by organic–inorganic molecules will help. Supramolecular DNA nanotechnology combines the power of DNA nanotechnology with the well-established science of supramolecular chemistry, and has already been used to provide solutions to the problem of discrete nanoparticle organization, 3D DNA assembly, and to the issue of error correction–prevention during DNA self-assembly. The latter is of particular interest because it is a true example of what might be achieved when the power of both disciplines is combined and utilized in a calculated manner. In order to truly investigate the possibility of making practical materials for everyday life, we will need to understand what our DNA assemblies are capable of and identify the important challenges of biology, chemistry, physics, drug delivery, and engineering that they can address. It is only by taking this path that DNA nanotechnology will evolve from an academic curiosity to an applied, booming field of research. The future is promising. Supramolecular DNA nanotechnology promises to pave the path toward dynamic and functional materials that are addressable in real time, and promises to transform the way materials are made.

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