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Review

DNA modified with metal complexes: Applications in the construction of higher order metal–DNA nanostructures

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ABSTRACT

DNA has recently emerged as a useful building block for higher order nanostructures, such as extended two-dimensional surfaces and discrete two- and three-dimensional structures. Transition metal complexes can introduce functionality to these otherwise passive nanostructures. This review examines the synthetic strategies used to introduce metals in a site-specific manner to DNA: either by attaching preformed metal complexes to DNA, or by metal coordination to unmodified or modified DNA. The applications of metal–DNA complexes in building higher order nanostructures and the utility of attaching luminescent or electrochemical labels are discussed.

1. DNA nanotechnology

In the "bottom-up" approach to nanoscale construction, one of the ultimate goals is to precisely position building blocks in a predetermined manner so that each component can be individually addressed in the final assembly. In recent years, DNA has emerged as a useful scaffold to organize molecules and materials into one-, two- and three-dimensional structures. DNA possesses several physical attributes that make it a unique construction material, including high fidelity of hybridization, a simple A–T, G–C four letter code, predictable secondary structures, well-known nanoscale dimensions of the double-stranded helix, ease of automated synthesis, and availability of enzymes that can further modify DNA strands [1].

Researchers have constructed remarkably complex metal-free two-dimensional (2D) and three-dimensional (3D) DNA structures (Fig. 1). Extended 2D surfaces based on crossover DNA junctions were assembled in pioneering work by Seeman and co-workers [2]. These DNA 2D surfaces have been used to organize proteins and gold nanoparticles [3]. Rothemund reported an 'origami' method, in which a long DNA strand can be folded using small 'staple strands' to make discrete objects that are visible by AFM, such as a 'smiley face' or a map of the Americas [4]. By attaching aptamers to DNA origami tiles, DNA chips have been made to recognize specific proteins [5].

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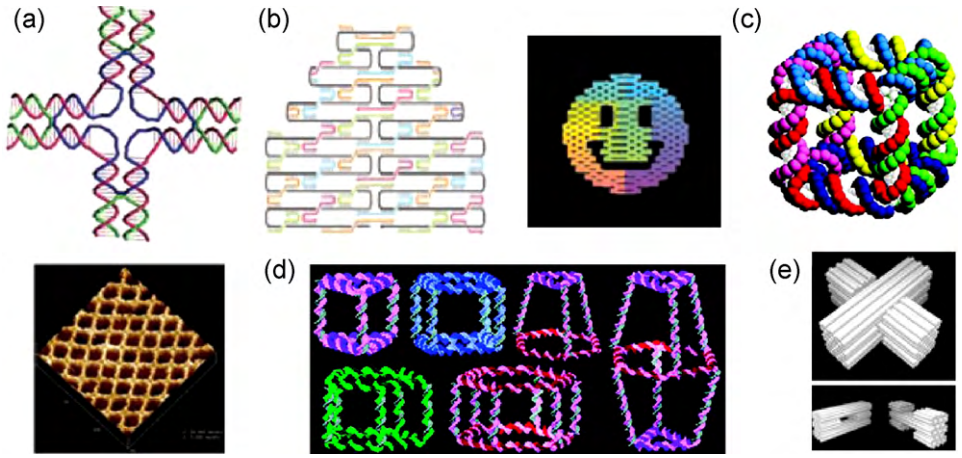

Fig. 1. DNA 2D and 3D objects. (a) Extended 2D sheets with controlled size [2]. (b) Origami method to make 2D discrete objects [4]. (c) Topological cube [6]. (d) Face-centered polyhedra [9]. 3D DNA origami [12].

Three-dimensional DNA structures have been objects of intense focus over the past few years (Fig. 1c–e). They are of interest not only for the fundamental investigation of the assembly mechanism of higher order structures, but also because they have potential as nanocontainers, with deliberately controlled pore size, geometry and addressability, for guest molecules. The groups of Seeman [6], Joyce [7], Turberfield [8], Sleiman [9], Mao [10], Gothelf [11] and Shih [12] have used a variety of strategies to construct different discrete 3D structures, nanotubes and extended 3D structures.

2. Incorporation of metals into DNA

In nature, numerous chemical reactions are facilitated by metal complexes that are embedded within biomolecules, such as metalloproteins and other metal-binding small molecules [13]. The precise arrangement of metals at the nanoscale would have significant implications in the development of devices for catalysis, nanoelectronics, and artificial photosynthesis. With the recent advancements in DNA assembly and manipulation, DNA has proven to be an extremely valuable building material for the construction of nanoscale structures.

The incorporation of transition metal complexes into DNA could result in a new class of materials in which the programmability and nanoscale rigidity of DNA and the desired functionality and properties of metal complexes are combined. For example, in terms of DNA assembly, metal complexes have a variety of defined geometries, and these may be used to build branching DNA junctions with different spatial arrangements that would be otherwise difficult to achieve. The metal complexes bound to DNA double helices can also modulate the stability of DNA, affecting the reversibility and robustness of the DNA structures for nanomaterials. The metal complexes can possess electronic, catalytic or photochemical properties, and this may be relevant for materials science and biotechnology applications. For the arrangement of metals, DNA can act as a scaffold in the creation of asymmetric structures where different transition metals are site-specifically positioned into 2D and 3D patterns. Furthermore, the DNA assemblies can be reversible or switchable; the controlled manipulation of metal–metal distances within nanoscale structures could directly affect metal–metal interactions and be useful for applications such as detection assays and catalysis.

While the combination of metal complexes and DNA scaffolds suggests exciting possibilities, the synthesis of the final materials is not straightforward. Some of the challenges include the non-specific binding of metals with the DNA bases or the phosphate backbone, the activity of some metal complexes towards DNA degradation, the decomposition of metal complexes in the aqueous DNA environment or during solid-phase DNA synthesis, and, due to the complexity of DNA, the difficult characterization of metal–DNA complexes.

The methods to site-specifically incorporate metals to DNA can be divided to three categories (Fig. 2). The first is the direct metal binding to natural DNA. The second involves the synthesis of a metal complex, followed by attachment of this complex to DNA. The third approach involves the attachment of a metal-binding ligand to DNA, either through base- or phosphate backbone modifications, followed by the binding of the metal to the ligand-modified DNA. In this review, the three approaches will be discussed separately.

3. Site-specific metal binding to unmodified DNA

It has been long known that metal ions can interact with the DNA backbone or they can replace a hydrogen in the H-bonding

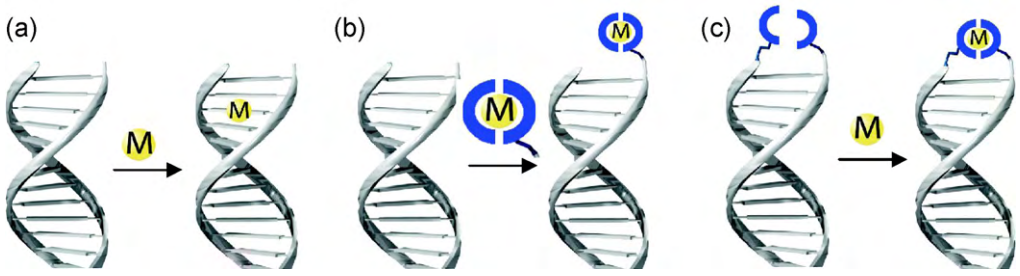

Fig. 2. Methods to site-specifically incorporate metals into DNA. (a) Metal binding to unmodified DNA. (b) Attachment of metal complexes to DNA. (c) Metal binding to ligand-modified DNA.

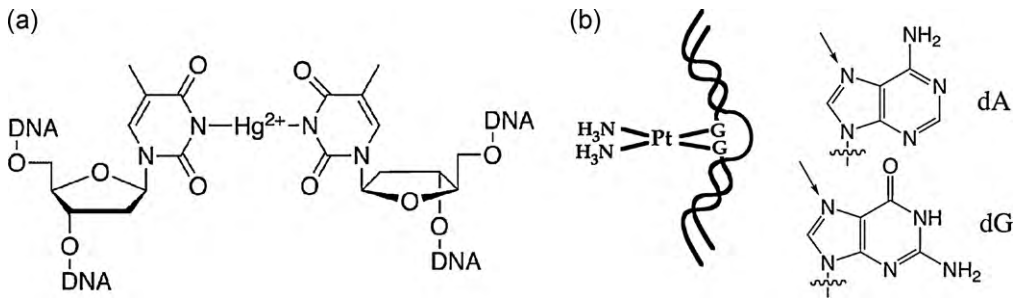

Fig. 3. Metal binding to unmodified DNA. (a) Hg^{2+} coordination to a T–T mismatch in the DNA duplex [17]. (b) Cisplatin binds to DNA on N-7 of purines [19].

Watson–Crick base pairs in unmodified DNA [14]. This type of interaction is generally not base selective. For example, divalent metal ions (Zn^{2+}, Ni^{2+} and Co^{2+}) were reported by the Lee group to form complexes with unmodified DNA at high pH conditions [14]. Upon adding these metal ions to B-DNA at pH 8.5, a pH decrease and NMR results were consistent with replacement of the imino proton in each base pair of the duplex by a metal ion. Such metal–DNA complexes were named M-DNA and can be more conductive than DNA, with potential for the development of molecular wires. However, the exact structure and the electronic properties of M-DNA are still controversial [15,16]. For instance, AFM study of M-DNA duplexes showed that they have a very condensed structure compared to B-DNA duplexes that has yet to be explained [15].

The more site-specific incorporation of metals into unmodified DNA has been previously reported. Studies from a number of groups have confirmed that Hg^{2+} can coordinate to the nitrogens between T–T mismatches (Fig. 3a) [17]. Using ^{15}N substituted T–T mismatches, the Ono group studied the ^{15}N NMR of the interaction between Hg^{2+} and T–T and found strong evidence of the structure of T–Hg–T. As determined by ESI-MS spectroscopy, up to five Hg^{2+} can stack in a row between T–T base pairs [17]. Specific interactions between Ag^{I} and C–C mismatches in a DNA duplex were also reported [18].

A well-known example of metal complexes binding to unmodified DNA involves the cisplatin family of anticancer drugs. These Pt^{2+} complexes bind with the N-7 of purines that is not used for hydrogen bonding in the DNA duplex (Fig. 3b). Two adjacent guanine residues can replace the chlorines on cisplatin and generate a stable species. This is one of the crucial steps in the action of cisplatin as an anticancer drug. For an excellent review of this class of complexes, see ref. [19].

4. DNA modified with metal complexes

With unmodified DNA, it is difficult to achieve site-specific metalation with a broad range of metals. To obtain a well-defined metal–DNA structure, a more general method is to attach stable metal complexes to DNA. The metal complexes can serve as luminescent or electrochemical labels or junctions for the assembly of higher order DNA structures. There are two different synthetic approaches. The first one involves the conjugation of the metal complex to the end of purified oligonucleotides, usually through a primary amine or sulfhydryl group on the 5′ end of DNA. The second approach couples a phosphoramidite derivative of the metal complex to DNA during standard automated DNA synthesis. These metal complexes must be inert. Especially for the second approach, they must also resist standard DNA synthesis steps such as oxidation and treatment with acid and base.

4.1. Metal complex-modified DNA as luminescent labels and charge donors and acceptors for DNA charge transport studies

One application of DNA modified with metal complexes is as luminescent labels for biosensors. Metal complexes as luminescent labels have advantages over organic dyes such as longer excited-state lifetimes, larger Stokes shifts, reduced self-quenching, tunable ground-state and excited-state energies and their sensitivity to the local environment which make them interesting as biosensors [20]. DNA labelled with luminescent or electrochemically active metal complexes has been studied since the early nineties. Many examples have been reported that incorporate Ru–, Rh–, Os–, Ir– or Fe–DNA complexes.

Metallo-intercalators for DNA have been well-studied, such as Rh(III) complexes that can recognize and specifically react with DNA base mismatched sites. There are a number of examples in which metal complexes are not covalently attached to DNA; these will not be included in this review [21].

Ruthenium bipyridine derivatives are among the most extensively studied metal luminescent labels. They can be tagged as a phosphoramidite derivative to the DNA backbone [22], as a base modification [23], or as a deoxyribose modification [24] to obtain different luminescent properties. Ru complexes have also been attached to DNA using post-modification methods, as reported by the Barton and Mesmaeker groups [25]. In many of these complexes, the photophysical properties are sensitive to the DNA environment. As shown in Fig. 4a, the DNA strand labelled with a

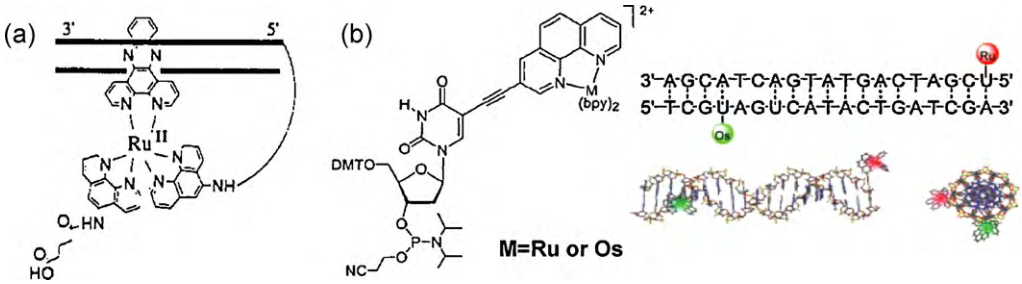

Fig. 4. DNA modified with luminescent metal complexes. (a) An example of a Ru complex as a luminescent label for DNA, which is sensitive to the DNA being single-stranded or double-stranded [25]. (b) DNA modified with Os and Ru complexes. When the Os center is close to the Ru center, the Ru emission is quenched [27].

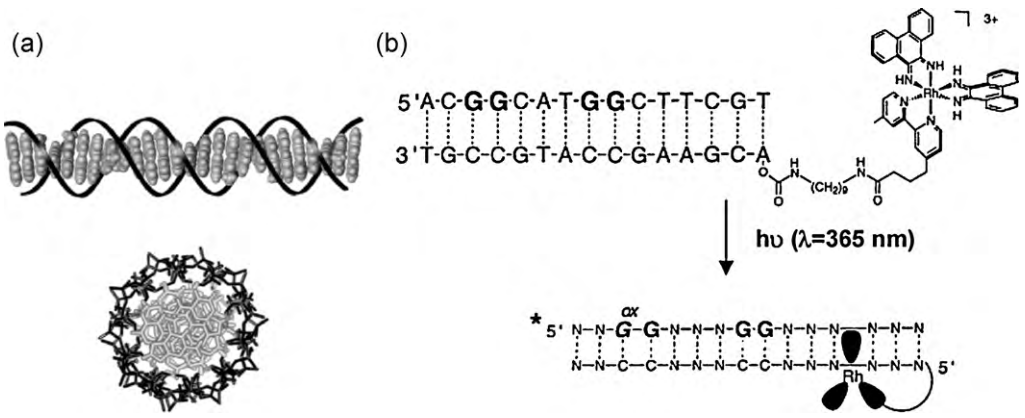

Fig. 5. DNA charge transport with metal complexes as probes. (a) DNA bases stack as a long aromatic column, side view and top view [28]. (b) Rh complex as a photooxidant attached to DNA. Upon UV irradiation, the Rh intercalator tagged on DNA can cause oxidative damage to a GG site over a distance [32].

Ru dipyridophenazine complex is intensely luminescent only when it is hybridized with its complementary strand. Such metal–DNA complexes have been used as photochemically activated specific nucleases [26], as probes of energy- and electron transfer within the DNA backbone [28–37], as DNA mismatch detection tools and as DNA sensors [29,38].

Tor's group coupled Ru(II) and Os(II) complexes to a modified deoxyuridine (Fig. 4b) [27]. By controlling where the metal complexes are placed along each DNA strand, the distance between the Ru and Os metal centers is varied. As the distance becomes smaller, the ^{3}MLCT of the Ru emission is quenched by Os. This study has contributed to the characterization of the distance dependence of energy transfer through DNA.

In work pioneered by the Barton group, DNA has been demonstrated as a medium for long-range charge transport (CT) both in solution [28] and on DNA-modified surfaces [29]. The DNA helix can be considered as a column of stacked aromatic base pairs (Fig. 5a). Electron- or hole transport has been postulated to occur through the π-stack over long distances. Different photochemical or electrochemical assays were developed to examine the CT through the DNA duplex. In these studies, Rh, Ru or Os complexes that have large π-surfaces that can intercalate with DNA were used as electron donors or acceptors. The luminescent metals are not only the reactants but also provide the binding information.

The electron donors and acceptors were tethered to DNA strands to allow the precise control of the location of these probes. The first example involving tethered metallo-intercalators was reported in 1993 [30]. A ruthenium complex served as a photoexcited donor and a rhodium complex was the acceptor. They were attached to a DNA duplex on the opposite ends. The luminescence of the Ru complex was quenched by the Rh complex over a distance of 4 nm. Another study using an ethidium derivative instead of Ru as the photoexcited donor showed luminescent quenching over 2–3 nm [31].

More interestingly, a DNA base itself can be the electron donor, which could be related to the oxidative damage of DNA *in vivo*. Base oxidative damage over a long range was first studied on sequences containing GG steps that were spatially separated from the oxidant (Fig. 5b) [32]. A Rh complex was tethered to the 5′ end of DNA. This complex intercalates into the DNA duplexes and serves as a photooxidant to cause oxidative damage to 5′ G of the GG doublets. This damage could happen over a distance of 20 nm or more by long-range charge migration [33]. Using different organic photooxidants, such as naphthalene diimide (NDI), ethidium and modified anthraquinones, the same phenomenon—5′G of GG duplex was oxidized over a long range—was observed [34]. This means the CT is associated with the nature of DNA, not the probes.

Using organic photooxidants or metallophotooxidants does make a difference in the case of the study of CT of DNA/RNA hybrids. Such a hybrid is more A-form-like and the major groove is narrower. As a result, metallophotooxidants cannot intercalate into the π-stack and therefore CT does not occur. This emphasizes the importance of π-stacking of the donors and the acceptors with the DNA duplex for CT [35,36].

The charge transport of DNA is sensitive to the dynamic structure and stacking within the DNA duplex. When there is a base bulge, mismatch or a DNA-binding protein, the base stacking is disturbed and therefore the CT efficiency decreases [37].

An immediate application of this structural dependence of CT is DNA-based biosensors for mutation analysis. Electrochemical assays based on DNA charge transport at self-assembled DNA monolayers can use transition metal complexes to generate detection signals, as demonstrated in Barton's work regarding CT on Au and graphite surfaces [29,38]. Inouye's group reported the immobilization of a DNA strand end-modified with a nucleoside analogue of a π-conjugated ferrocene on a Au surface (Fig. 6) [38]. The electrochemical signal is very different when the DNA is hybridized with its fully complementary sequence than with a mismatched sequence with single nucleotide polymorphism. This can be potentially used as a diagnostic tool.

In the biological context, recent research suggests that DNA CT may be important in the DNA damage process in funnelling the oxidative damage to specific sites [39]. DNA charge transport and its applications are a well-developed research field and full coverage is beyond the scope of this review. The reader is referred to some excellent reviews [28,29,36,40].

4.2. DNA modified with metal complexes as building blocks for higher order DNA structures

The Sleiman group published one of the early reports on the synthesis of DNA junctions modified with transition metal complexes and their application to nanostructure assembly [41]. After growing DNA strands on a solid support in a DNA synthesizer, a Ru complex was coupled to two DNA arms with the same sequence and polarity in a convergent approach (Fig. 7). Two of these building blocks with complementary sequences can hybridize to form a discrete cyclic structure, facilitated by the proper orientation of the arms which is defined by the Ru center. It is interesting that DNA strands with bipyridine vertices but without metals undergo less selective hybridization, which illustrates the role of metal in this process.

The McLaughlin group reported the synthesis of a ruthenium complex with six DNA arms having the same polarity (Fig. 8) [42].

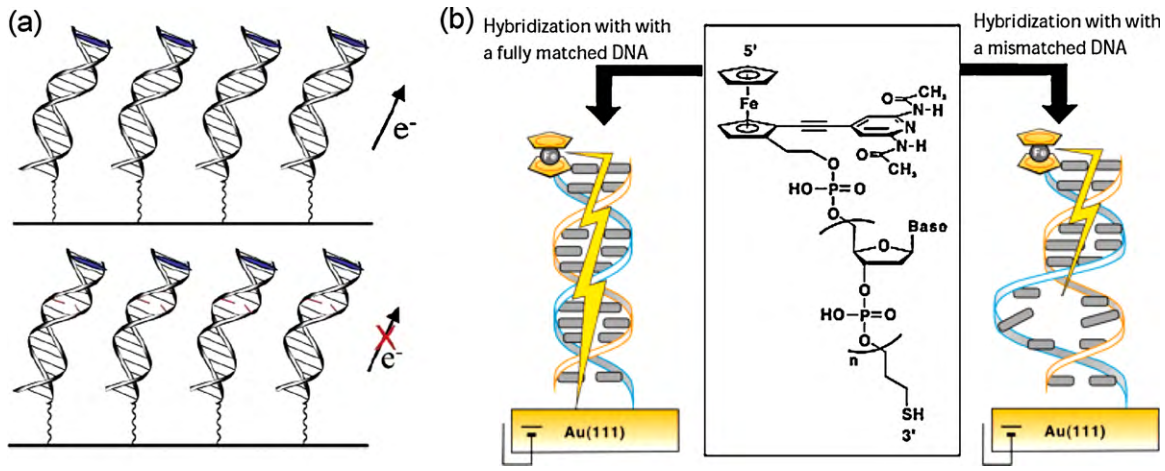

Fig. 6. DNA charge transport on surfaces. (a) Schematic illustration of using DNA CT to monitor the base perturbation [36]. (b) DNA modified with a ferrocene complex can be immobilized on a Au surface for single nucleotide polymorphism detection via its electrochemical signals [38].

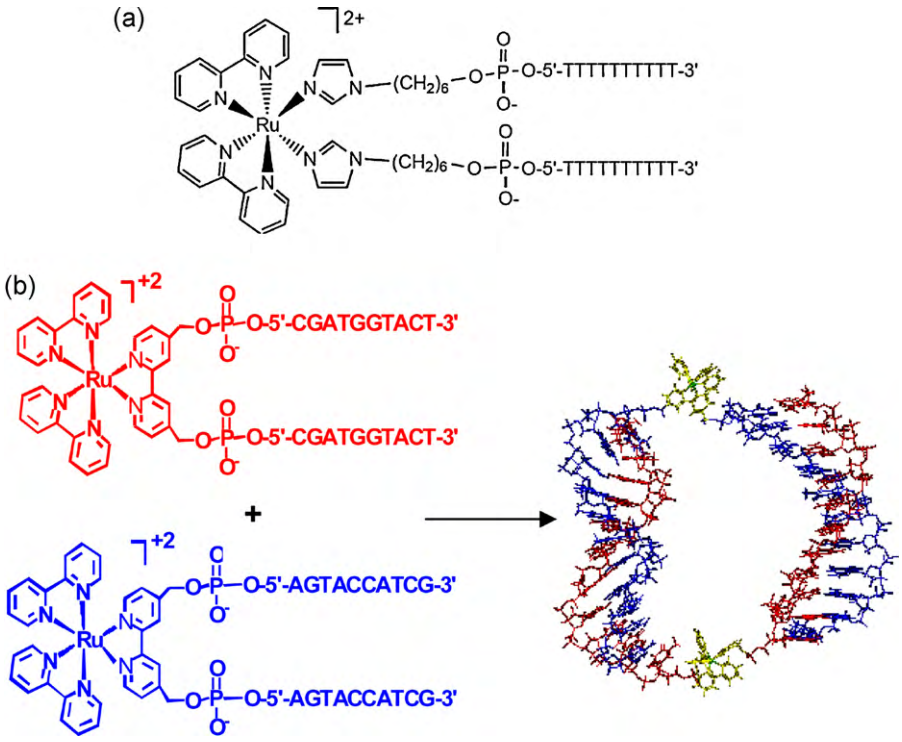

Fig. 7. Ru complexes conjugated with symmetric DNA arms and their self-assembly to a discrete cyclic structure. (a) First generation symmetric Ru DNA complex with labile ligands. (b) Second generation symmetric Ru DNA complex and the formation of a cyclic structure [41].

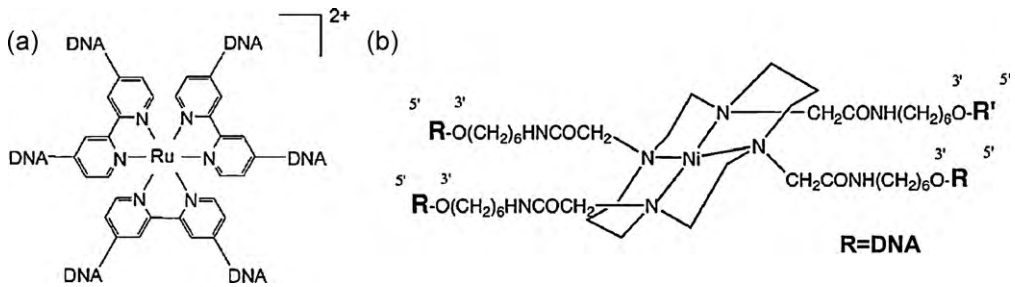

Fig. 8. Metal DNA branch junctions with multiple arms. (a) Ru complex with six DNA arms. (b) Ni complex with four DNA arms, which can hybridize to four other four-armed DNA Ni complexes [42,43].

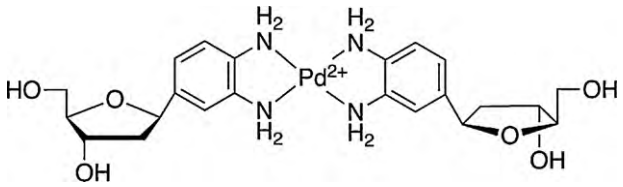

Fig. 9. The first metal-mediated artificial base pair: a Pd complex, by the Shionoya group [44].

With a combination of standard solid state DNA synthesis and reverse synthesis, branched Ru–DNA complexes were synthesized. The product has a ruthenium tris(bipyridine) center with six DNA arms that can either be all of the same sequence or where one has a different sequence from the others. A Ni^{II} complex with four DNA arms made by a similar approach and its assembly to higher order structures were reported from the same group [43]. These junctions can potentially be used to construct 3D DNA assemblies.

5. DNA modified with ligands and its metal coordination

While metals have been incorporated into DNA either by binding the metal ion directly to the unmodified DNA or through attaching a full metal–ligand complex to DNA, it can be advantageous to first attach a ligand to DNA, and then coordinate the metal. One advantage of attaching ligands to DNA instead of a complete metal complex is that the individual ligand is usually more compatible with DNA synthesis methods. This would then allow the incorporation of numerous kinetically labile metals into DNA structures. Ligands can be easily incorporated into any position of a DNA sequence using their phosphoramidite derivatives. In addition, they can be very different from the DNA bases so the metal can bind with the ligands selectively. The main methods to incorporate ligands into DNA for the coordination of metal ions involve either the synthesis of artificial bases or the attachment of the ligand to the DNA backbone.

5.1. Metal base pairs in DNA

One approach to incorporate metals into DNA involves the replacement of the hydrogen-bonded DNA base pairs with metal complexes in the interior of the DNA duplexes to create a 'metal base pair'. This approach provides close contact between the DNA duplex and the metal complex while the structural features of DNA remain undisturbed.

Shionoya and co-workers reported the first metal-mediated artificial base pair in 1999: a Pd^{2+} ion coordinated to a pair of amine-modified artificial bases (Fig. 9) [44]. Since then, Shionoya, Schultz, Meggers, Tor, Carell and others have reported other metal base pairs, including metal complexes formed with Cu^{2+}, Ag^{+}, Ni^{2+}, Co^{2+} or Mn^{3+} [45]. Selected examples of metal base pairs will be discussed here, particularly Cu^{2+} and Ag^{+} metal base pairs and incorporation of multiple metal centers to DNA duplexes.

Cu^{2+} is among the most commonly used metals for metal base pair studies. It has little interaction with the DNA backbone and can easily be introduced to water-based buffer solution. Schultz reported the incorporation of a metal base pair into DNA strands (Fig. 10) [46]. This Cu^{2+} DNA complex was characterized with thermal denaturation experiments, EPR (electron paramagnetic resonance) spectroscopy, CD (circular dichroism) experiments with different sequences and salt concentrations and particularly, its X-ray structure was resolved. These studies used DNA with a high GC content, which forms Z-DNA at high salt concentrations. The DNA duplex modified with this metal base pair has similar thermal stability as a DNA duplex in which the metal base pair is replaced with an A–T base pair. The X-ray structure for such an artificial DNA duplex reveals a Z-DNA structure with a slightly distorted base plane and axial coordination from neighbouring nucleotides (Fig. 10). A solution CD study confirmed that this metal base pair induces Z-DNA conformation with sequences that contain high alternating CG content, even at low salt concentrations; with normal DNA sequences, the metal–DNA duplex remains in a B-DNA conformation. It was suggested that square planar coordination may eliminate the distortion and the coordination from neighbouring nucleotides, causing less disturbance to the B-DNA structure.

The Tor group reported a bipyridine derivative as an artificial base. This complex binds to Cu^{2+}, resulting in a slight thermal denaturation temperature (T_m) increase upon metal binding (3.5 °C, Fig. 11a) [47]. Switzer and co-workers reported two other artificial bases with bipyridine derivatives. They found that for both of these modifications, Ni^{2+} gives a T_m increase of 4.4–9.4 °C compared to an A–T pair at the same site, which is higher than the other metals studied, including Cu^{2+}, Fe^{2+}, Mn^{2+}, Co^{2+} and Zn^{2+} [48].

Steric perturbation caused by base modification to the DNA base stack can be a general problem when designing stable metal base pairs. By introducing flexibility to the artificial DNA duplex, a more stable metal–ligand species can be generated. Work on a Cu^{2+} metal base pair published by Meggers and co-workers investigated base- and backbone modifications to a DNA duplex (Fig. 11b) [49]. They used a simple C3 backbone attached to a bicyclic bidentate hydrophobic ligand. Cu^{2+} can bind quantitatively with DNA duplexes with such ligands on opposite sites, resulting in an increase of the T_m by 29 °C.

Ag^{+} is another well-studied ion for metal base pairs. It is a soft metal that is compatible with water and is not normally active for non-specific binding or degradation of DNA. The Schultz group reported a sulfur-modified six-coordinate base pair, which could coordinate to a soft metal such as Ag^{+}, resulting in an increase of the DNA duplex stability (3.4 °C higher than DNA with an A–T pair at the same site in the duplex, Fig. 12a, *left*) [50]. They also synthesized

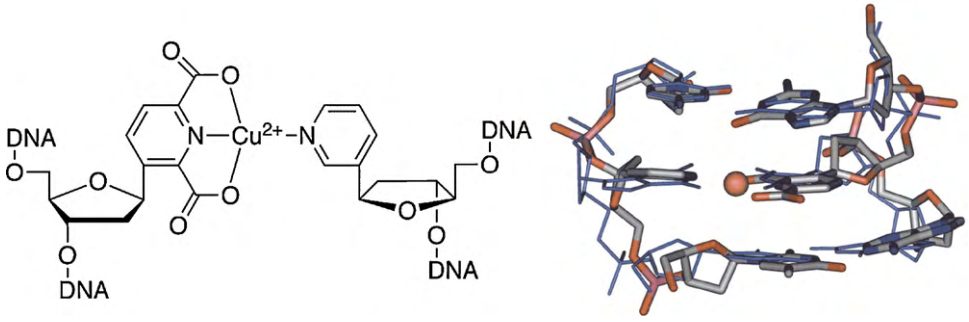

Fig. 10. Structure of Schultz's Cu^{II} DNA complex. Chemical scheme (*left*), X-ray structure showing slightly distorted Cu^{II} coordination with artificial bases and neighbouring nucleotides (*right*) [46].

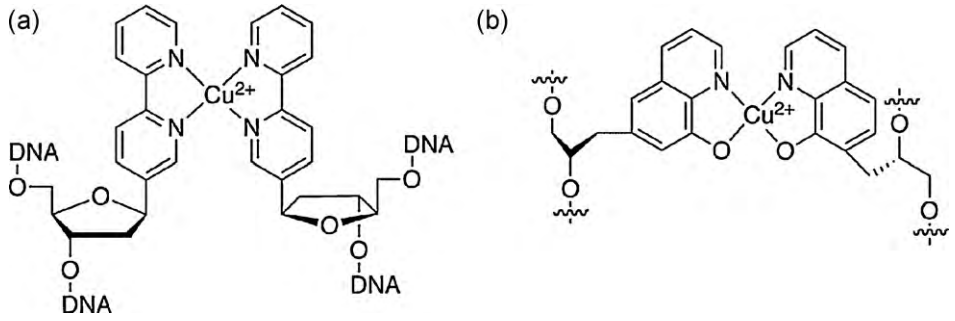

Fig. 11. Structures of Cu^{II} coordinated metal base pairs. (a) Bipyridine-modified nucleotide with a slight thermal stability increase upon Cu^{II} binding. (b) Artificial base with C3 backbone modification, which shows high thermal stability upon Cu^{II} binding [47,49].

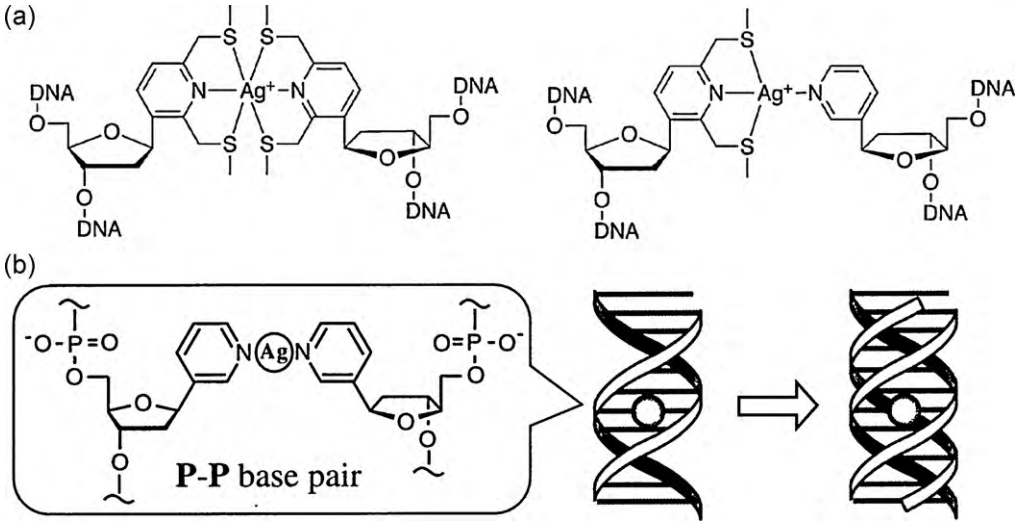

Fig. 12. Structure of Ag^{I} coordinated metal base pairs. (a) Schultz's sulfur-modified DNA bases coordinated to Ag^{I}. (b) Shionoya's pyridine-modified base can induce the formation of an Ag–DNA triplex structure [50,51].

a four coordinate Ag^{+} complex, for which the melting temperature decreased 4.4 °C compared to an A–T pair at the same site (Fig. 12a, *right*). Linear Ag^{+} coordination into pyridine-modified base pairs was reported by Shionoya. This Ag^{+}-pyridine modification could also be incorporated into a DNA triplex (Fig. 12b) [51].

A significant advance involves the incorporation of multiple highly stable metal base pairs into DNA duplexes in a stack. The metal centers are in close contact with each other, and can exhibit electronic or magnetic interactions.

Shionoya et al. chose a square planar Cu^{2+} complex, copper-hydroxypyridone, as the metal base pair, in which the metal binds quantitatively and significantly stabilizes the DNA duplex (T_m increase of 5.9 °C compared to an A–T base pair at the same site, Fig. 13) [52]. Up to five of these Cu^{2+} complexes can be incorporated in a row into DNA strands, with only one C–G pair at each end of the duplex [53]. The Cu^{2+} metals can couple with one another ferromagnetically through their unpaired d electrons. This approach allows the organization of metal ions in solution in a discrete and predictable manner. The linear alignment of metal ions in a well-defined order may be important in the design of molecular magnets and wires.

Carell's group incorporated metal salen (N,N′-ethylenebis (salicylimine)) complexes as DNA–metal base pairs. Two salicylic aldehyde-modified nucleotides on opposite positions in a DNA duplex are covalently linked by ethylenediamine and coordinated to a metal, making the DNA duplex highly stable, especially when the metal ion is Cu^{2+} or Mn^{3+} (e.g., the T_m increase is 32.3 °C for the Cu^{2+} complex compared to an A–T pair at the same site (Fig. 14a)

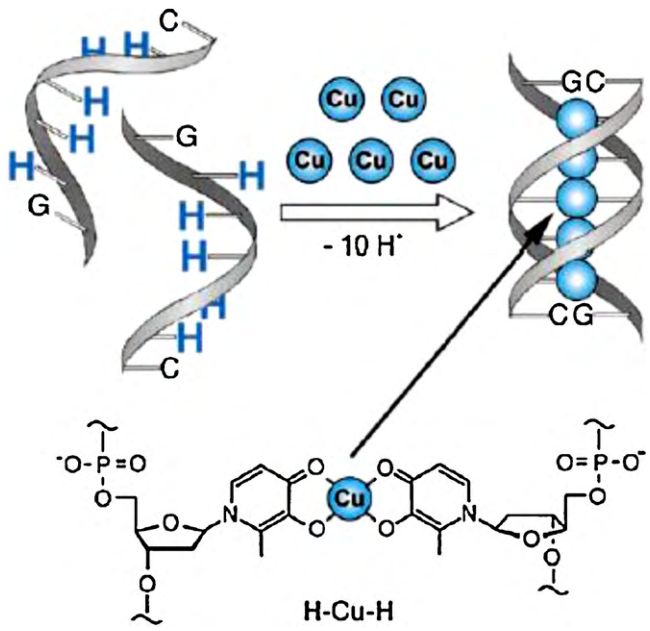

Fig. 13. Structure of Cu^{II} hydroxypyridone base pairs and their stacking within a DNA duplex, reported by the Shionoya group [52,53].

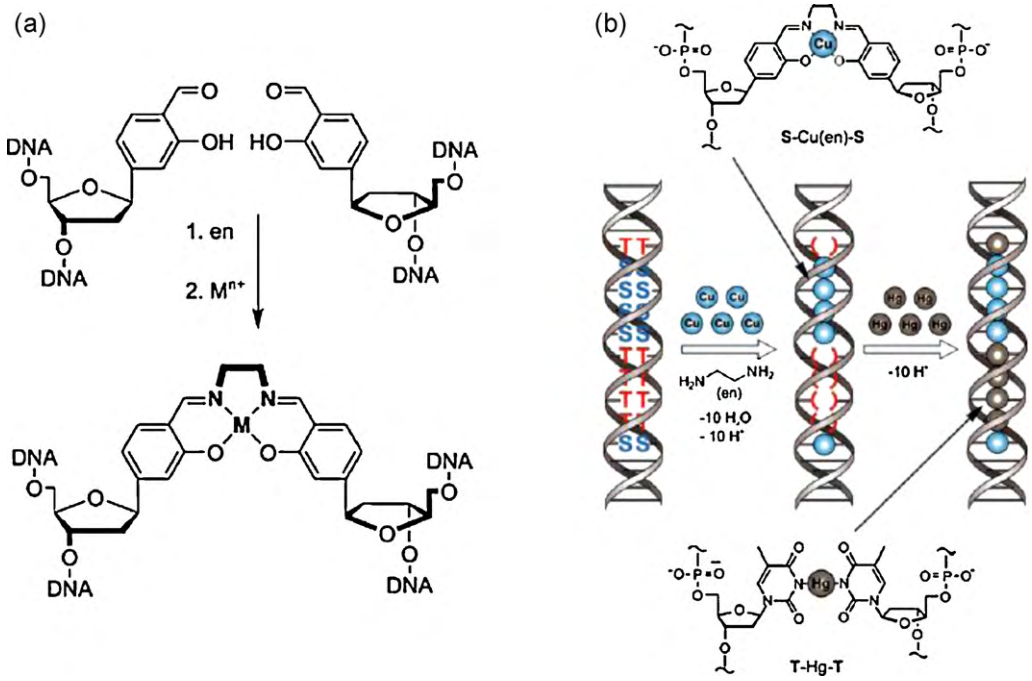

Fig. 14. Incorporation of salen metal complexes into a DNA duplex. (a) The formation of a salen metal complex from salicylic aldehyde. (b) Incorporation of multiple Cu^{2+} and Hg^{2+} complexes into the DNA duplex in a stack [54,56].

[54]. Up to 10 of the salen-Mn^{3+} or Cu^{2+} metal base pairs can be stacked in a row in a DNA duplex [55]. Shionoya and Carell combined this system with the preferential coordination of Hg^{2+} between T–T pairs (Section 3). They reported that Hg^{2+} and Cu^{2+} can be placed in the same DNA duplex with up to 10 mixed metal complexes stacked in a row (Fig. 14b), as determined by CD titration and ESI-MS (electrospray ionization mass spectrometry) [56]. This is so far the only example in which multiple different metals can be programmed into the same DNA structure.

When metals are incorporated into DNA, either as metal base pairs or as complexes attached to the DNA backbone, the thermal denaturation temperature (T_m) is commonly used as an indicator of the change in stability of the DNA as a result of metal binding. There are, however, some precautions to consider before using T_m data to compare the stabilities of different metal DNA systems. First, the T_m of a DNA system depends not only on the stability of the metal–DNA conjugate, but also on the base sequence, the DNA concentration, and the buffer. Comparisons between different systems are truly valid only when the experimental conditions are very similar. The second important factor to consider is the thermal stability of the metal complex itself. If the metal complex is not thermally stable, it may dissociate before reaching the T_m of the DNA duplex, and the T_m results will not be indicative of the stability of the metal–DNA interaction. When the T_m of the DNA duplex and the thermal dissociation of the metal complex occur at similar temperature, T_m is a better reflection of the contribution of the metal to the stability of the DNA duplex. If, on the other hand, the metal complex is thermally stable throughout the thermal denaturation process of the DNA duplex, the position of the metal-binding site along the duplex may significantly affect the T_m of the system. For example, when the metal-binding site is at the end of the DNA duplex, the structure may be more similar to a DNA hairpin than to a DNA duplex. In this case, the entropic gain for the thermal denaturation process is significantly reduced, thus raising the thermal denaturation temperature as a result. To accurately compare different metal–DNA systems, the base sequences used, the specific experimental conditions, thermal stability of the individual metal complexes, and their positioning along the DNA duplex must all be considered.

5.2. Metal coordination to DNA in which the backbone is modified with ligands

Metal base pairs provide a very interesting method to incorporate metals into double-stranded DNA, and there is strong potential for such systems to be developed as molecular wires and magnets. There are some limitations of this approach, however. A general concern about the design of a metal base pair is the coordination geometry [57]. In most examples of metal base pairs, the coordination number is either 2 or 4, with linear or square planar geometry. This is required to promote π-stacking and maintain the B-DNA-like structure; metals that require binding of the ligands perpendicular to the base pair may either cause distortion of the double-helix structure or may not bind at all. To obtain a stable structure, the size and shape of the modified bases also have to fit in the interior of the DNA duplex, and moreover, the metal complex needs to display some planarity, in order to π-stack with the DNA base pairs. This inevitably limits the range of metal complexes that can be incorporated into DNA using this otherwise powerful method.

An alternative method is to modify the DNA backbone itself with ligands for metal coordination. This approach allows a broad range of ligands to be incorporated into the DNA structure. It is synthetically less challenging than artificial nucleoside synthesis, and it could be easily adapted to make higher order structures.

5.2.1. DNA modified with terpyridine, bipyridine and phenanthroline

Terpyridine, bipyridine and phenanthroline have been conjugated to the DNA backbone to coordinate different metals. Han's group studied the metal binding to DNA strands modified at their ends with terpyridine. They added Fe^{II} to two such strands with different sequences and length, giving a mixture of homodimers and a heterodimer (Fig. 15a). The heterodimer was separated by gel electrophoresis. They programmed the sequences so that three of these heterodimers can hybridize with one another to form a discrete triangle structure [58]. This work was the first example in which a higher order DNA structure was generated using building blocks

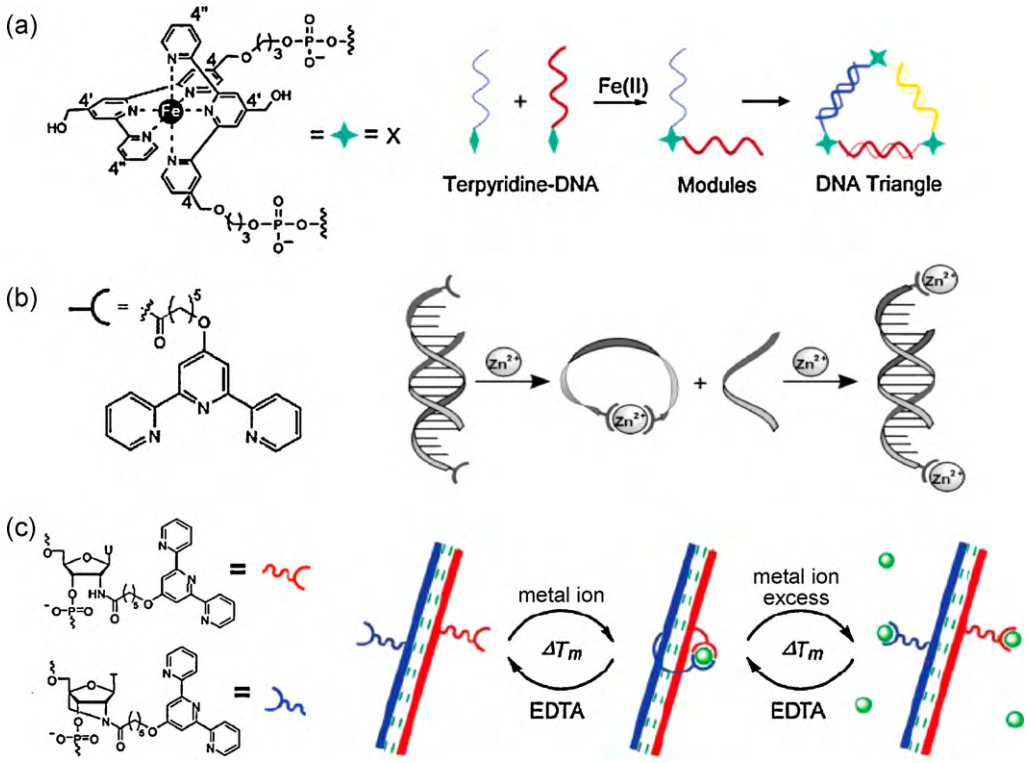

Fig. 15. DNA complexes modified with terpyridine. (a) Using Fe^{II} terpyridine DNA junction to assemble a DNA triangle [58]. (b) Zn^{II} can close and open a cyclic DNA with terpyridine modifications at both ends [59]. (c) 2′-Amino-DNA and 2′-amino-LNA modified by terpyridine and the metal binding [60].

that were synthesized by metal coordination to ligand-modified DNA.

The reversible nature of some metal coordination reactions can be used to build dynamic DNA structures. Kramer reported that terpyridine modification at both ends of one DNA strand can induce the formation of a cyclic structure upon metalation even when this DNA is hybridized to a partially complementary strand (Fig. 15b) [59]. When the metal is Zn^{2+}, this cyclic structure can be reopened with excess metal, but not if the metal is the more inert Fe^{2+}. This is an example of a metal being used to switch the structure of DNA.

The Wengel group reported the reversible switching between one bis(terpyridine) metal complex and two mono(terpyridine) metal complexes in a DNA structure. They positioned terpyridine-modified 2′-amino-DNA and terpyridine-modified 2′-amino-LNA (locked nucleic acid) on the opposite strands of a DNA duplex. Both of the modifications are on the 2′ position of the nucleotides (Fig. 15c) [60]. Interestingly, the T_m increase upon metal binding varies with the placement of the modifications along a DNA duplex. When these artificial nucleotides bind at the minor groove position with a Ni^{2+}, the T_m increase is the greatest (49 °C). In these studies, the CD spectra of these metal complexes are very similar to B-DNA with little induced chirality in the metal complex or ligand region, likely because the ligands are not in close contact with the DNA duplex.

Bipyridine was also incorporated into the backbone of one strand in a DNA duplex with a dC on the opposite site. Pt^{2+} coordination can increase the stability of such a duplex [61]. Interesting work published by Sugimoto demonstrated the use of metals to assemble higher order structures [62]. They used bipyridine-modified G-quadruplexes as the building blocks and Ni^{2+} ions to connect the building blocks. In this work, bipyridine replaced thymines in the main chain of $d(G_4T_4G_4)$ (Fig. 16a). Upon binding to Ni^{2+},

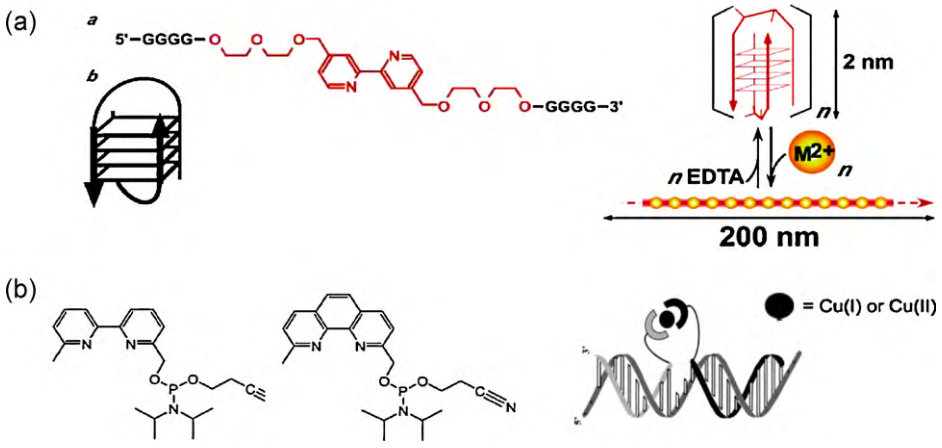

Fig. 16. Metal DNA complexes modified with bipyridine or phenanthroline [62]. (a) Bipyridine-modified DNA folds to a G-quadruplex, which binds Ni^{II} to form a 'G-wire'. (b) Cu^{I} and Cu^{II} binding to bipyridine- and phenanthroline-modified DNA [63].

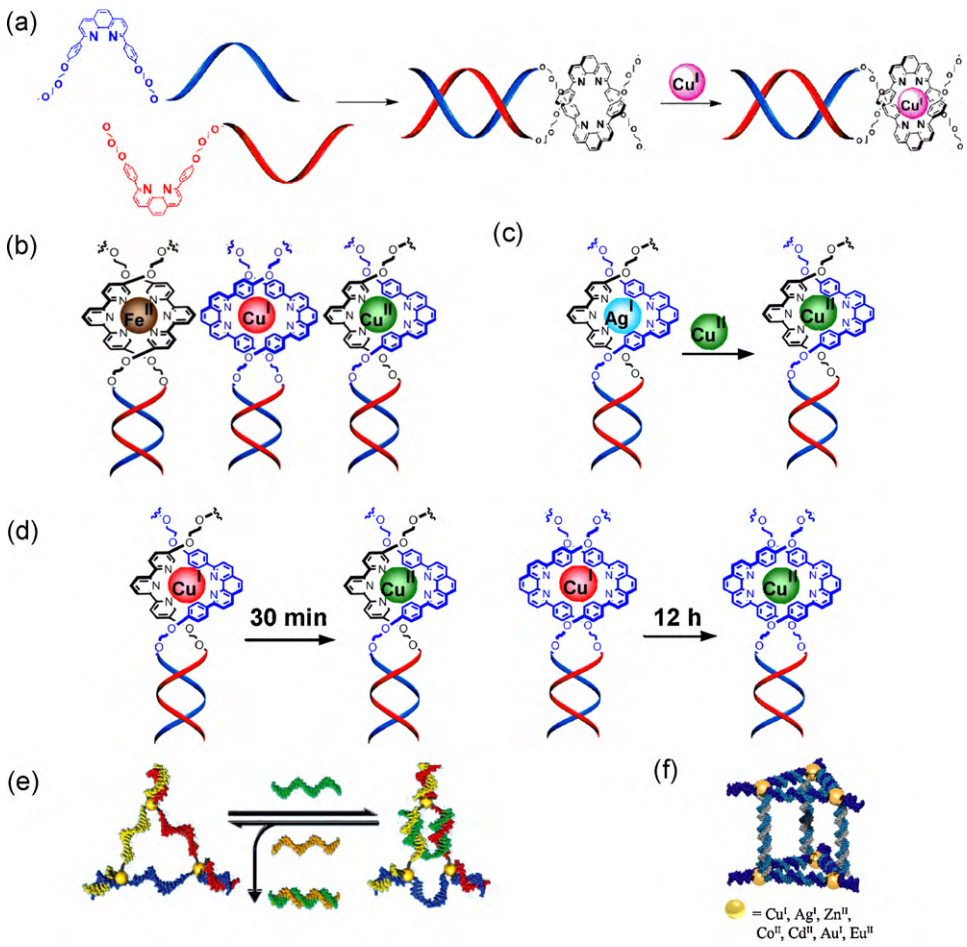

Fig. 17. Metal DNA complexes with chiral metal centers and the construction to 2D and 3D metal–DNA structures. (a) Incorporation of diphenylphenanthroline (dpp) modifications to DNA and the metal binding to form highly stable duplexes [64]. (b) DNA ligand environments that are selective for preferred metals [65]. (c) Displacement of unfavoured metal [65]. (d) Spontaneous change in the oxidation state to generate a more stable species [65]. (e) Dynamic switchable metal–DNA triangle [64]. (f) Metal–DNA cage structure [67].

the antiparallel structure of this bipyridine-modified G-quadruplex changes to a parallel structure; these can be connected intermolecularly into a 'G-wire'. This metal-mediated supramolecular assembly of G-quadruplexes is reversible with the addition of EDTA.

Haner reported work in which bipyridine- or phenanthroline-modified DNA strands were placed in juxtaposed positions after hybridization to a common target strand (Fig. 16b). The duplex was stabilized by the addition of Cu^{I} or Cu^{II} through the formation of a metal complex in which the two short sequences are linked through $Cu(bpy)_2$, $Cu(phen)_2$, or Cu(bpy)(phen) domains [63].

The Sleiman group reported a template strategy to stably incorporate different metals into DNA. They first constructed two complementary DNA strands, modified at their 3′- and 5′-ends with bidentate 2,9-diphenyl-1,10-N,N-phenanthroline (dpp) ligands (Fig. 17a). Hybridization of these two strands brings the two phenanthroline ligands in close proximity, and in a π-stacked arrangement to the DNA duplex base pairs. When a metal binds to the DNA-bound ligands, the right-handed helical chirality is transferred from DNA to the metal–ligand complex as a result of the close contact between the complex and the DNA base stack. In this structure, the metal complex and the DNA synergetically stabilize each other, resulting in highly stable DNA–metal assemblies (Fig. 17a) [64]. Without metal, the dpp-modified DNA duplex has a T_m increase of 9 °C compared to natural DNA. This is because the ligands π–π stack with the bases in the duplex. Upon binding to metals such as Ag^{I} or Cu^{I}, the T_m increases dramatically by 21 and 37 °C, respectively. In this approach, the combination of a ligand environment that easily follows the helicity of the DNA duplex, π–π stacking between the ligands and the bases, and the metal coordination allows the addition of metal ions that would not otherwise be compatible with DNA, including labile and reactive metals.

While this approach allows a variety of metals to be incorporated into DNA strands, the real potential of DNA is to organize different metals in the same structure in a site-specific manner. Towards this goal, three different ligand environments were created by introducing terpyridine (tpy)-modified DNA: $(dpp)_2$, $(tpy)_2$ and tpy:dpp (Fig. 17b) [65]. Thermal denaturation studies of the binding of Cu^{I}, Ag^{I}, Cu^{II}, Co^{II}, and Fe^{II} with these ligand–DNA duplexes demonstrated that each of these ligand environments has its preferred metal: $(dpp)_2$-DNA binds strongest with Cu^{I}, $(tpy)_2$-DNA binds strongest with Fe^{II}, and the mixed ligand environment tpy:dpp prefers Cu^{II}. The Fe^{II}-$(tpy)_2$-DNA gives a T_m increase of 40 °C, and this is one of the highest reported T_m increases for metal complex modification of a DNA duplex.

More interestingly, when a metal was placed in the 'incorrect' environment, 'error-checking' occurs [65]. The system can adjust by displacing the unfavoured metal (Fig. 17c), changing the metal oxidation state, or reorganizing the ligand environment to generate a more stable species. For instance, when Cu^{I} is added to the tpy:dpp:DNA structure, it undergoes spontaneous oxidation to Cu^{II}, which is the preferred metal for this coordination environment (Fig. 17d). On the other hand, when Cu^{II} is added to the $(dpp)_2$:DNA structure, it undergoes spontaneous reduction to Cu^{I}, which is the

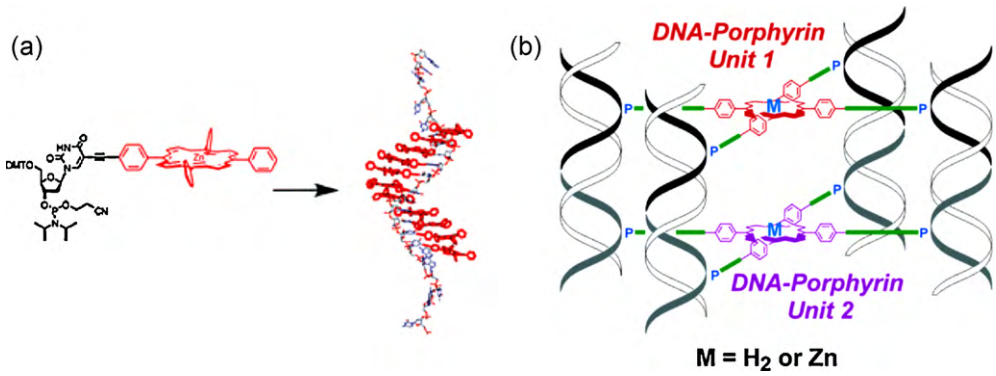

Fig. 18. Metal DNA complexes modified with porphyrin. (a) Eleven Zn^{II} porphyrin complexes incorporated to a DNA single strand can form a helical conformation along DNA [69]. (b) A porphyrin derivative conjugates to four DNA strands. Two different porphyrin units assembled together [70].

favoured metal for this ligand environment (Fig. 17d). This binding specificity provides the opportunity to use DNA's programmable character to position different metals into deliberately designed patterns, which is currently a difficult goal to achieve using conventional supramolecular chemistry.

Using this strategy, higher order 2D and 3D DNA structures were assembled with the $(dpp)_2$–metal–DNA junctions. First, a cyclic triangle structure was quantitatively constructed with one Cu^{I}–$(dpp)_2$ at each corner (Fig. 17e) [64]. The single-stranded sides of this triangle allowed the structure to be reversibly switched by hybridization with specific DNA strands in this dynamic metal–DNA structure. The controlled tuning of the metal–metal distance in these assemblies is a defining feature of metal–metal communication.

Three-dimensional DNA structures have been the subject of active research in recent years. As found in a number of synthetic (metal-organic frameworks) and natural (metalloproteins) systems, the precise positioning of metal complexes in 3D structures could lead to multi-component catalytic or photosynthetic assemblies [66]. Towards this end, two DNA triangles with programmed $(dpp)_2$ ligand pockets were quantitatively linked together into a 3D DNA prismatic structure, containing six ligand pockets (Fig. 17f) [67]. Exactly six metal ions were found to site-specifically bind to these ligand pockets. This work presented the first example of 3D metal–DNA cages, allowing the use of DNA to programmably tune pore size, geometry and addressability in these biometallic host systems.

5.2.2. *DNA modified with porphyrin*

Another interesting family of metal-binding artificial DNA is porphyrin-modified DNA, where porphyrins can coordinate to a variety of metals and display unique electronic and photophysical properties [68–70].

Stulz published a report in which DNA was used as a supramolecular scaffold for the arrangement of Zn^{II} porphyrin complexes (Fig. 18a) [69]. Up to 11 porphyrin moieties, each π-conjugated to a modified base, were incorporated into DNA, forming an array along the DNA strand. The single-stranded Zn^{II}

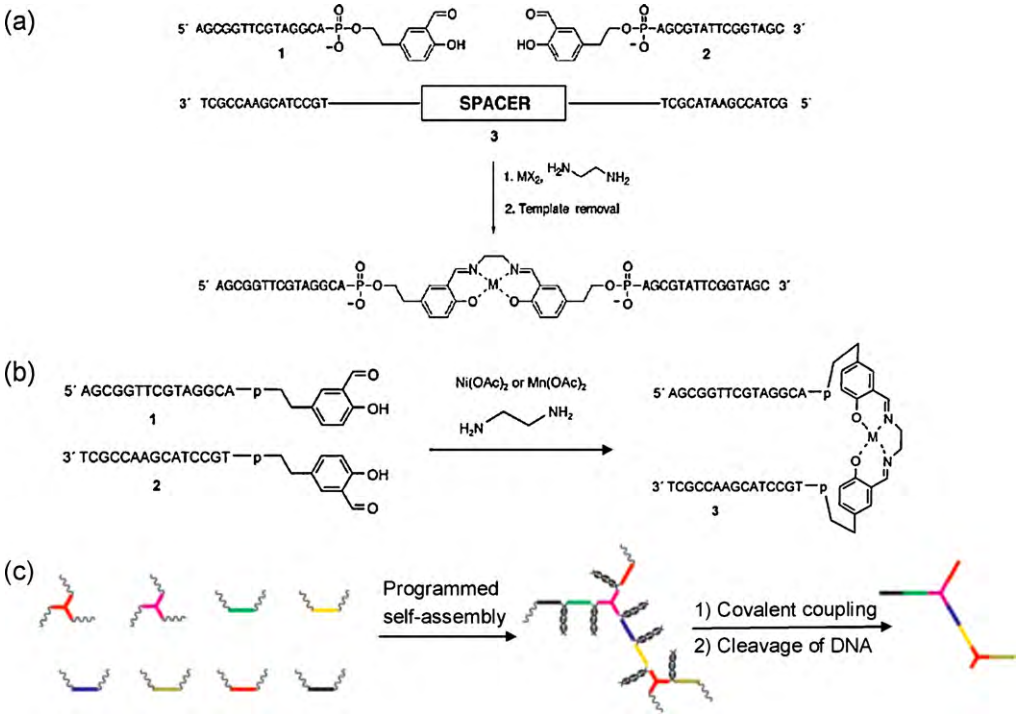

Fig. 19. Salen DNA–metal complexes. (a) Using a template DNA to connect two salicylic aldehyde-modified DNA by reaction with diethylamine and metal ion [72]. (b) Two complementary salicylic aldehyde-modified DNA form a hairpin structure [73]. (c) Using the salen complexation to modulate the programmed synthesis of functional groups [74].

DNA–porphyrin complex orders itself into a stacked α-helical conformation. This is an example in which DNA is used to induce the alignment of multiple electro- and photoactive molecules into a helical stack.

Majima reported that one porphyrin can be attached to the middle of four identical DNA strands (Fig. 18b) [70]. Two such porphyrin–DNA conjugates can be connected by their complementary strands, forming a four double-helix bundle connected by two porphyrin units. In this example, one porphyrin was uncoordinated and the second porphyrin was bound to Zn^{II}. Seeman and Majima reported a four-armed DNA branching from a porphyrin center that can induce the formation of a DNA nanotube that would otherwise be an extended 2D structure [71].

5.2.3. DNA modified with salen metal complex

Sheppard reported the first example of the templated synthesis of salen metal–DNA complexes from salicylic aldehyde-modified DNA (Fig. 19a) [72]. Using one DNA strand as a template, two salicylic aldehyde-modified DNA strands can be covalently linked and coordinate a metal ion, resulting in a very stable structure that resists chemical denaturation. The same group also reported that two complementary DNA strands with salicylic aldehyde modifications at the ends can also template the formation of a salen metal complex (Fig. 19b) [73]. The covalently linked product has slightly higher stability than a DNA hairpin. Gothelf reported a series of studies on using DNA hybridization and metal complexation to join organic functional groups together to make macromolecular nanostructures [74]. The idea is that DNA can direct the assembly of the functional groups so that they are located at desired positions. They can then be connected together using metal salen complex formation and the macromolecular product can be cleaved from the DNA (Fig. 19c).

6. Conclusions and future work

The precise arrangement of metals on the nanoscale represents an important step in the development of devices for nanoelectronics, artificial photosynthesis and catalysis applications. Developments in our ability to manipulate DNA into well-defined assemblies have led to exciting possibilities for the construction of functional nanoscale devices, especially as researchers have learned how to incorporate metals into these scaffolds. We have discussed here the three main approaches commonly used to attach metals to DNA. Metal ions can be added to unmodified "natural" DNA, full metal complexes can be incorporated into DNA strands, or free ligands can be introduced into DNA, followed by metal incorporation to form metallated DNA.

The combination of DNA and functional metal complexes can introduce significant advantages to both the metals and the DNA structures. To the DNA scaffolds, the metal complexes can impart numerous coordination geometries for further assembly, and they can modify the stability of the DNA duplex for applications in materials science and biotechnology. The metals can possess electronic, photochemical, or reactive properties that can render the DNA assembly functional. For the metal complexes, DNA presents a way to pattern metals in precise positions and in a programmable manner, and it is also possible to generate dynamic, switchable and molecule-responsive structures. Under specific conditions, DNA can also serve as an effective mediator for charge transport.

While the introduction of functional metal complexes into DNA assemblies is exciting, there are still some important issues to be addressed. For example, robust devices that allow the direct measurement of charge transport or magnetic interactions in these metal–DNA structures need to be developed. In addition, although some metals can be precisely positioned into DNA constructs, the incorporation of multiple *different* metals is still challenging. The ability of researchers to overcome these challenges will have important implications in the development of nanoscale devices for many applications. The understanding of magnetic or electronic interactions between carefully arranged metal complexes could directly benefit devices for circuits or data storage. The judicious arrangement of the proper metal complexes on the nanoscale could be important for the development of artificial photosynthesis systems and multi-component catalysts that perform multiple transformations in a cooperative manner.

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