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Metal-Complex/DNA Conjugates: A Versatile Building Block for DNA Nanoarrays

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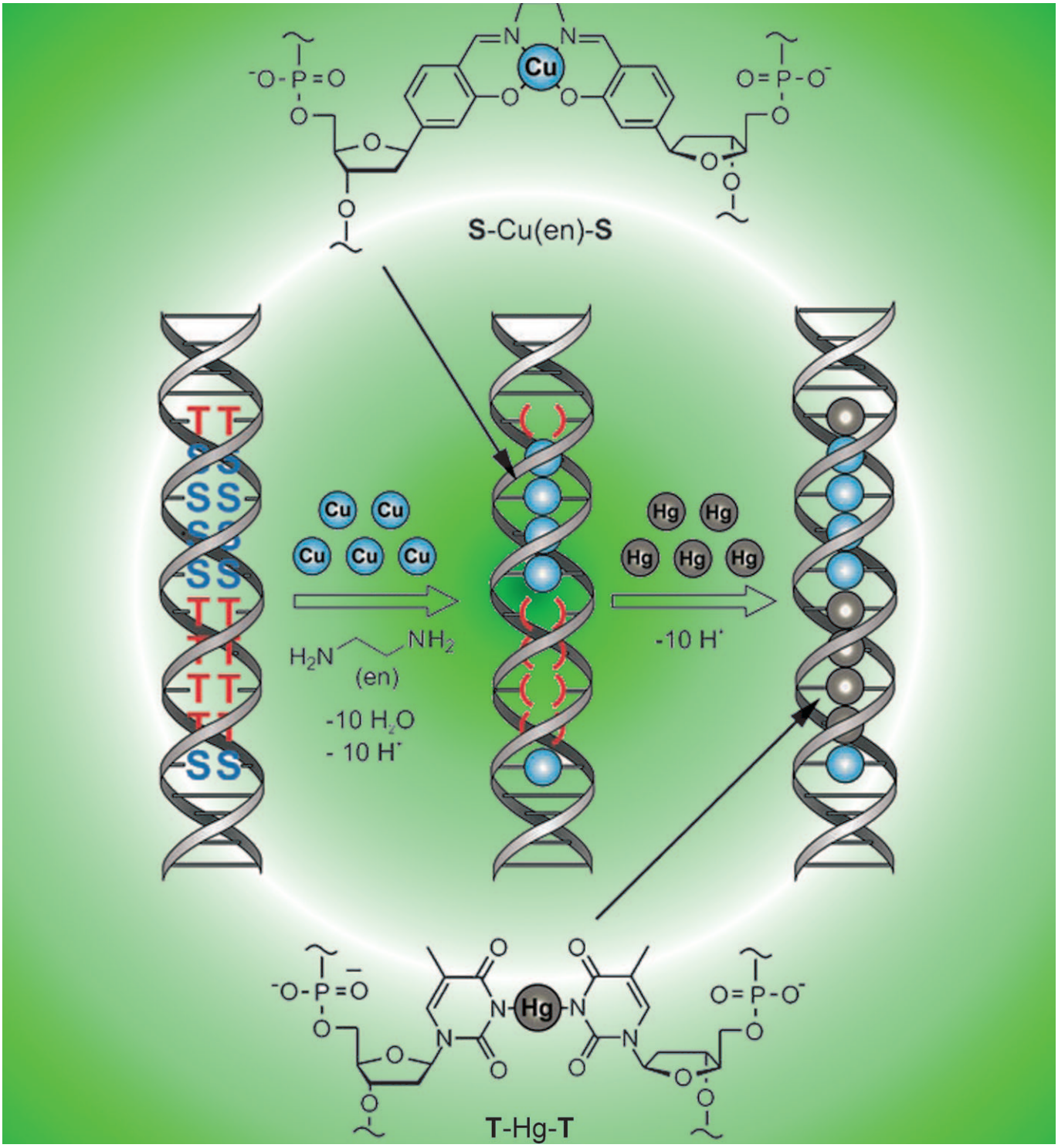

Abstract: The use of DNA networks as templates for forming nanoarrays of metallic centres shows an exciting potential to generate addressable nanostructures. Inorganic units can be photoactive, electroactive and/or can possess magnetic and catalytic properties and can adopt different spatial arrangements due to their varied coordination nature. All these properties influence both the structure and function of passive DNA scaffolds and provide DNA nanostructures as a new platform for new materials in emerging technologies, such as nanotechnology, biosensing or biocomputing.

Keywords: DNA · metalation · nanostructures · nanoarrays · oligonucleotides · self-assembly

Introduction

Chemistry is the science of matter and was considered for a long time as the science for discovering and preparing substances and studying the transformation of one product to another one. An important break down was initiated by the concept of supramolecular chemistry, which has dramatically changed the perception of chemistry.[1] Supramolecular chemistry focuses on the design of chemical system built up from the assembly of molecular subunits. During the last decades, more sophisticated supramolecular chemistry has emerged with the development of various molecular devices and machines with applications in molecular electronics, photonics, and chemionics.[2] It is worth noting that most of the bottom-up approaches to nanotechnology are currently based on supramolecular chemistry concept.

In this context, biological systems are a source of inspiration for designing two- and three-dimensional nanostructures of increasing complexity. Among all biological macromolecules, DNA is certainly the most promising candidate. This is mainly due to its nanometric dimension, relatively high physicochemical stability and specific noncovalent hydrogen-bonding, so-called "Watson–Crick" base-pairing properties, that can act as programmable assemblers for the fabrication of complex networks.[3] Moreover the ability to synthesise DNA with arbitrary base sequences permits programming of intra- and intermolecular associations and thus able to build up artificially engineered supramolecular networks. Therefore DNA is regarded as the "silicon of the nanoworld". Another very attractive feature of DNA is the great mechanical rigidity of short double helices, such that they behave effectively like a rigid rod. According to Seeman, for the past half century research on DNA was only confined to the biologists and biologically oriented physical scientists, but during next 50 years, it would be the promising subject of research to all material scientists, nanotechnologists and computer engineers.[4]

During the last two decades, different strategies have been developed to fabricate periodic 2D or sophisticated 3D DNA architectures exploiting both base complementarities of single-stranded DNA and ligation of "sticky" DNA ends through hybridisation.[5] More recently, a different approach, namely a "DNA origami technique" based on the intramolecular folding of a long DNA strand, has revealed an interesting alternative procedure.[6] Novel methods are currently explored for organising, in a programmable manner, multiple functionalised DNA origami for the construction of even more sophisticated mesoscale DNA assemblies.[7] Such different patterned 2D- or 3D-DNA arrays might help to organise different materials (e.g., proteins, aptamers, nanoparticles, metal complexes and DNA-binding small molecules) sequentially or periodically to form promising components for functional devices. In this context, DNA nanostructures sustaining metal complexes into its vertices have been much less explored. Nevertheless, DNA-programmed assemblies of metal-complex building blocks are relevant for photochemical and electrochemical devices, because DNA can act as a template to organise the inorganic molecular units to provide nanometer-scale features and patterns to the system. Incorporation of transition metals or metal complexes into DNA can dramatically influence both the structure and function of DNA nanoassembly thus form new paradigms of "structural DNA nanotechnology".[8] Nanometric dimension of metal ions and their geometrical preference of coordinating with different ligands allow DNA assembly to form diverse structures ranging from a simple tetrahedral motif to complex octahedral forms. Furthermore metal complex can be photoactive, electroactive and/or can possess magnetic and catalytic properties that allow wide range of functions to the DNA self-assembly. In this concept article we describe the development and synthesis of different metal-complex/ODN (oligodeoxyribonucleotide) conjugates to form rigid structural scaffolds for achieving various types of 2D or 3D supramolecular DNA nanoassemblies and their few applications in biotechnology and material sciences.

It should be noted that metallic nanoparticles (Au, Ag, CdS etc.) have also been anchored to ODNs in order to generate functional DNA nano-assemblies. This approach (i.e., use of nanoparticles-DNA conjugates) is evidently of interest and many promising applications are currently devel-

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oped. However, it is out of the scope of this article but we refer the reader to some recent reviews.[9]

Synthetic Approaches to Form Metal-ODN Supramolecular Assemblies

Two major approaches have been explored to combine either metal ions or metal complexes with ODNs, one is the substitution of canonical Watson–Crick base pairing by a coordinative metal–base pairing and the other one involves the covalent attachment of the metal complexes to ODNs.

Replacement of DNA base pairs by a metallic complex—metal-mediated base pairing: Replacement of noncovalent hydrogen-bonding interactions between natural DNA base pairs (i.e., canonical Watson–Crick base pairing) by noncovalent metal complexation is one of the approaches to form metal–DNA-based nanostructures (Figure 1A). For this purpose, unnatural nucleobases have been designed to form complexes with transition metals and incorporated into DNA sequence. Such metal ions stabilise the duplex by means of coordination forces instead of classical Watson–Crick hydrogen bonding. Since metal coordinative bond energy is intermediate between that of covalent and non-covalent bonds, the metal ions incorporation would stabilise high-order DNA structures (duplex, triplex, etc.) as well as allow the formation of one-dimensional metal arrays along the DNA helix axis. A number of artificial nucleosides with mono- or tetradentate ligands, which form complexes with transition metal ions to give linear, trigonal planar, square planar, or tetrahedral geometry and hence are most likely replace a flat, hydrogen-bonded base pair, have been reported (Figure 1B). Here we have described a succinct overview of "metal–base pairing" approach, but to obtain detailed information on this approach we refer the reader to the recent excellent review from Carell and Coll.[10]

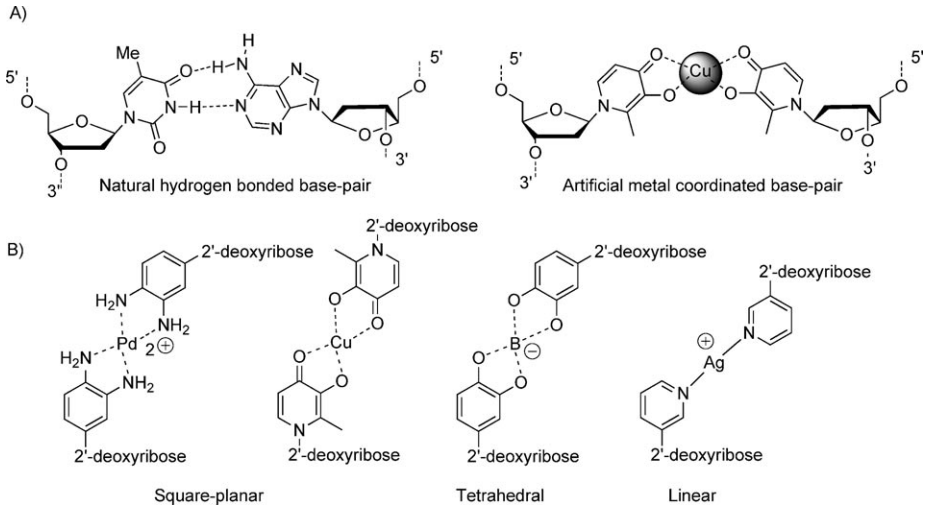

Figure 1. A) Schematic representations of Watson–Crick base-pairing and Cu^{2+} mediated base pairing. B) Examples of some metal-coordinating artificial nucleoside analogues, which on complexation with metals form either square planar, tetrahedral or linear geometries.

For the first-generation of metal–base pairs, the following artificial ligands have been used: *o*-phenylenediamine, pyridine-2,6-dicarboxylate, pyridine, bis(methylthiomethyl)pyridine, 2,2′-bipyridine, 8-hydroxyquinoline and hydroxypyridone. Later five consecutive copper–hydroxypyridone base pairs were incorporated into a double-stranded DNA in which efficient interaction between the metallic centres was observed.[11] Each of these Cu^{2+} ions is coupled with another one through d electrons, resulting in a magnetic DNA wire with ferromagnetic properties.

Another interesting way to generate metal–base pair analogue is to attach a *N*,*N*′-bis(salicylidene)ethylenediamine (salen) ligand to ribose as a C-nucleoside. In contrast to all other metal–base pairs, the formation of the metal–salen base pair in DNA requires ethylene diamine (en), which reacts with both the chelating ligand and a metal ion (Cu^{2+}, Mn^{3+}, VO^{2+}, Fe^{3+} and Ni^{2+}).[12] Using Cu^{2+}–salen and Hg^{2+}–thymidine base pairing, heterogeneous assembly of both Cu^{2+} and Hg^{2+} ions into an artificial duplex structure could be achieved (Figure 2A).[13] This can afford a potential linear metal ion array with precise control of the sequence and the distance between the individual ions. In another strategy the metal coordination to unmodified DNA bases have also been investigated leading to the formation of M–DNA (Figure 2B).[14]

Conjugation of the metal complex to the oligonucleotide: Covalent conjugation of ODNs with metal complexes has mainly been achieved for electron-transfer studies, designing synthetic nucleases, photoprobes and more recently has been applied for building complex nanostructures.

There are mainly three approaches available for the synthesis of metal-complex/DNA conjugates.[15] The first one involves covalent attachment of a ligand at either terminus or at internal position of the ODN sequence. The ligand, usually containing a short linker, is converted to a phosphoramidite derivative for incorporation into ODN by automated DNA synthesis.[8b] Similarly a base residue, usually thymidine, is functionalised (generally at C-5 position) with a linker containing ligand to incorporate the metal complex in the middle of the probe sequence.[16] Regardless of the site of ligand attachment to the oligonucleotide, the metal ion can be complexed to the tethered ligand by post-synthetic

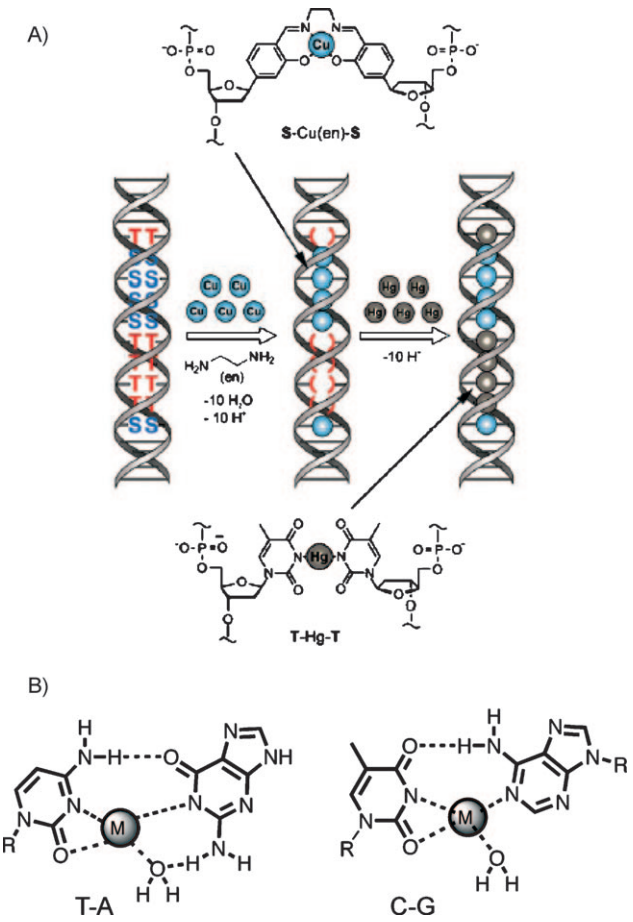

Figure 2. A) Schematic representations of Cu^{2+} and Hg^{2+} mediated duplex formation in which five Cu^{2+} ions and five Hg^{2+} ions are aligned along the helical axis within the DNA. Here "S" represents salicyldehyde which is involved in forming a salen complex with Cu^{2+} in presence of ethylene diamine (en) and thymine base (T) involved in forming imino complex with Hg^{2+} ion (taken with permission from reference [10]); B) Base pairing of M-DNA in which metal ions form imino complex with thymine and cytosine in T-A and C-G base pairing respectively.

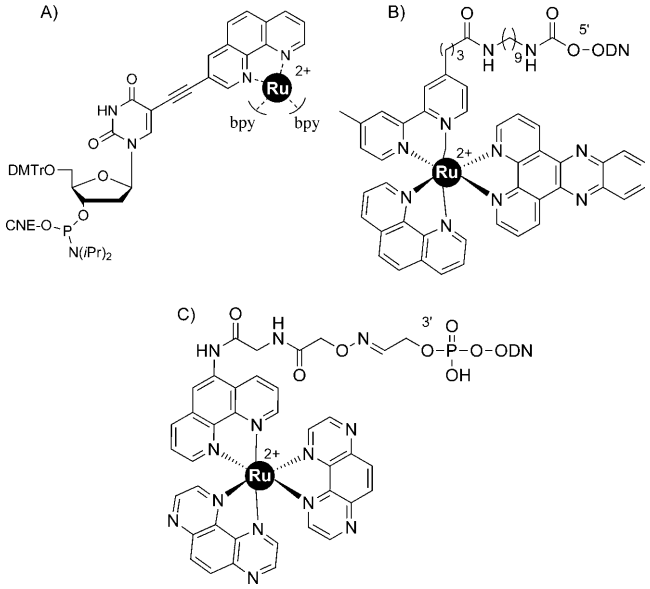

Figure 3. Conjugation of metal complexes to oligonucleotides. A) Ruthenium metal complex containing phosphoramidite; B) metal-complex/ODN conjugate obtained through post-functionalisation on support using activated ester of the metal complex; C) metal-complex/ODN conjugate obtained through post-functionalisation in solution through oxime bond ligation.

procedure. In this procedure excess metal salt solution can be used to occupy all ligand coordination sites. At the end, a scavenging ligand can be used to trap both excess metal ions in solution and to remove non-specifically bound metals from the complex. It should be noted that this approach is tedious and inefficient.

In a second approach the metal can be complexed to the desired ligand and then the metal-complex-derivatised phosphoramidite is incorporated into the nucleic acid strand during solid-phase synthesis protocol. In this case, the metal complex must survive the conditions of DNA assembly, deprotection and isolation stages, which represents a serious limitation of this approach. Nevertheless, Ru^{2+}-derivatised phosphoramidites (see as an example Figure 3A) have been used in an automated DNA synthesiser with enormous flexibility for rapid and straightforward introduction of the Ru^{2+} complex at various sites of ODN.[17]

The third approach consists of a post-functionalisation strategy and involves the separate synthesis and purification of ODNs and the metal complexes incorporating mutually reactive functional moieties, followed by their coupling reaction, on-support or in solution, leading to the formation of reversible covalent bonds. In the context of studies concerning DNA-mediated charge-transport processes, Barton's group has prepared metal-complex/ODN conjugates with metals like ruthenium, osmium, and iridium using on-support coupling reactions between amine-modified ODNs and the activated ester of the metal complexes leading to an amide linkage (Figure 3B).[18] The key concern while using the on-support coupling procedures is the stability of the metal complexes during ammonia treatment used for the deprotection of nucleobases and cleavage of ODN sequence from the solid support. In some cases, the metal complexes are not stable enough for direct incorporation by using automated ODN synthesis, and therefore solution-phase coupling reaction strategies must be used. For efficient coupling, reactions based on the click-chemistry concept are preferred; for example, oxime bond formation between aldehyde-containing ODNs and aminooxy-modified metal complexes has been used for the preparation of covalent metal-complex/oligonucleotide conjugates containing base-sensitive complexes such as $[Ru(TAP)_2Phen]$ at the 3′- or the 5′-extremity (Figure 3C). These kinds of conjugates are useful as photoprobes, and can give rise to DNA damage by photo-crosslinking.[19]

These advances for the efficient synthesis of metal-complex/oligonucleotide conjugates have thus permitted to obtain various building blocks for the design of nanostructures upon appropriate self-assembly process. In the next

paragraph, we describe the different architectures that have been achieved by using such suitable building-blocks.

Structural Diversity of Metal-Complex/ODN Conjugates

For nanostructures based on metal-complex/ODN conjugates, the metal complex plays the role of nodes (junction) and ODNs the arms, which self-assemble upon hybridisation with appropriate ODNs partners. The metal-complex/ODN building blocks should indeed influence the structure of the DNA nano-assemblies due to their varied coordination nature (tetrahedral, octahedral, square-planar and trigonal-bipyramidal structures). Moreover, the metal complex can bear one, two or more ODNs to generate structurally diverse metal/ODN hybrids. In this context, different metal complexes with various geometries have been tethered to oligonucleotides to prepare self-assembled nanostructures upon hybridisation with their appropriate complementary sequences. Some interesting examples of those types of assemblies are showed in the following part (Figure 4).

Linear DNA arrays: Preparation of linear DNA arrays has been achieved by using metal-complex/ODN conjugates based on the terpyridine ligand. In a pioneering work, Stewart and McLaughlin designed a bis(terpyridine)Ru^{II} complex bearing two ODN sequences (Figure 4A). A pair of such conjugate was prepared such that the DNA sequence of one (A complex) is complementary to the second (B complex). The ratio of A:B and B:A mainly dictate the structure of assembly upon hybridisation. For example a ratio of A:B or B:A of 2:1 results in A_2B or B_2A trimer as the major component and a longer linear array is formed when the ratio of complexes approaches to 1:1.[20] By using a more versatile synthetic strategy, we were able to prepare symmetrical homoleptic metal-complex/ODN building block (i.e., with one DNA strand on each ligand such as A or B in Figure 4A). Hybridisation between these building blocks gives rise to a linear 2D-network, which was studied by CD spectroscopy, thermal denaturation experiments and non-denaturing gel electrophoresis studies. Some evidence of the formation of a long, linear network were also obtained by transmission electron microscopy.[21] However, it should be noted that it is quite difficult to control the length (i.e. the number of involved strands) of the linear DNA networks.

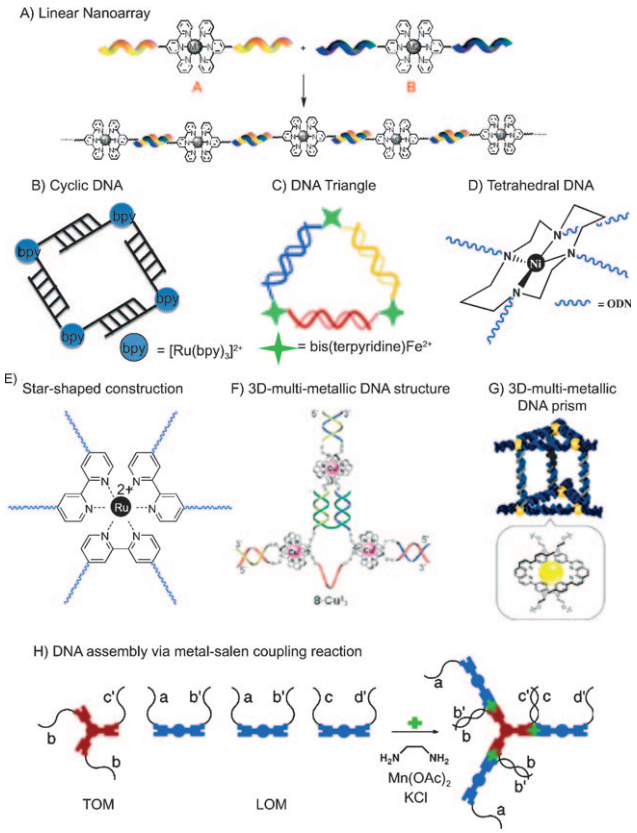

Figure 4. Examples of structural diversity of metal-complex/ODN conjugates upon different tethering approaches of ODNs to different metal complexes (taken with permission from references [20–27]).

Cyclic DNA arrays: Sleiman and co-workers have reported the formation of cyclic self-assembly of DNA using tris(bipyridine)ruthenium-branched oligonucleotides. The cyclic supramolecular structure was formed when two parallel DNA strands are linked to one of the bipyridine ligand of the rigid tris(bipyridine)Ru^{II} complex and hybridise with the complementary ODN strand of the similar kind of tris(bipyridine)Ru^{II} complex (Figure 4B).[22] From a gel electrophoresis study it was noted that the cyclic product is formed along with small amounts of polymeric species of high molecular weight. In a related approach, Han and co-workers reported the self-assembly into "DNA triangles" in which each vertex and side consist of a bis(terpyridine)Fe^{II} complex and a DNA duplex, respectively (Figure 4C).[23] Very interestingly no higher cyclic species is observed: only DNA triangles are formed. Thus DNA arms precisely locate the three bis(terpyridine)Fe^{II} complexes at nanoscale distance in a triangular array.

3D nanostructures: Stewart and McLaughlin have reported the preparation of multi-armed metal-centred ODN conjugates for the construction of 3D supramolecular assemblies. In one case, four single-strand (ss) ODNs were attached at four sites of an N-based 1,4,8,11-tetraazacyclotetradecane (cyclam) ligand, which on complexation with Ni^{II} ions forms a tetrahedral assembly (Figure 4D). The ss-ODN overlap in four directions and are ready to hybridise with the complementary ODNs; they are thus able to form an Ni^{II}-based tetrahedral supramolecular DNA assembly.[24] In another example, a star-shaped construct based on a six-oligonucleotide-armed tris(bipyridyl)Ru^{II} complex was designed (Figure 4E). Hybridisation of two complementary system was performed leading to high-molecular-weight assemblies as revealed by PAGE but the exact geometry of the assembly could not be determined.[25]

More recently, Yang and Sleiman described an elegant DNA-templated method for the generation of 3D multimetallic structures in which three metal complexes were present at the corners, single-stranded DNA as the sides and multiple DNA double strands at the periphery (Figure 4F).[8b] Using this methodology both DNA duplexes and transition metal complexes synergistically stabilise each other. Another new class of 3D metal/nucleic acid cages has been recently reported in which transition-metal-coordinated DNA triangles were assembled into a DNA prism (Figure 4G). They can be used as suitable encapsulated cargo for release of biomaterials.[26]

In a molecular engineering strategy, Gothelf and co-workers reported the use of manganese–salen formation between two salicylaldehyde groups for linking together different ODN units. Linear oligonucleotide-functionalised modules (named LOM) and tripodal oligonucleotide-functionalised modules (TOM) bearing salicylaldehyde moieties at each extremity were synthesised (Figure 4H). The assembly of LOMs and TOMs through metal–salen coupling reactions afforded a variety of predetermined nanostructures.[27] The metal link in between the structure can act as a potential conductor for designing molecular electronic circuits.

Characterisation of Metal-Unit/DNA Nanoassemblies

The preliminary binding environment, that is, the selectivity and binding strength of various metal ions to a given ODN, could be evaluated by thermal denaturation, and UV/Vis and circular dichroism spectroscopy. Most of the cases the incorporation of metal ions into duplex motif stabilises the resultant structure with respect to unmodified one. The formation of nanoassemblies upon hybridisation of ODNs can be studied by polyacrylamide gel electrophoresis (PAGE) analysis in nondenaturing conditions. Indeed, the formation of high-molecular-weight DNA self-assemblies formed by solution annealing give rise to bands with low electrophoretic mobility. By using a molecular-weight marker ladder, the number of strands involved in the nanoassembly and approximate length and molecular weight can be predicted. However, the determination of the structure of the DNA assemblies by using PAGE analysis is more tricky. It should be noted that DNA assemblies are soft and fragile, which is why they are difficult to handle in liquid. In this regard it is safe to directly perform DNA self-assembly onto solid surfaces like gold, conductive polymers, or silica or carbon surfaces.

Transmission electron microscopy (TEM) and high-resolution scanning transmission electron microscopy (HR-STEM) as well as atomic force microscopy (AFM) are generally used to image such complex DNA architectures. For example, Carell and co-workers have employed HR-STEM to visualise DNA/silver-cluster nanostructures.[28] AFM is another powerful technique for imaging nanostructures from simple triangular, tetrahedral to complex hexagonal DNA architectures. Moreover, AFM has been exploited to evaluate the rigidity of DNA nanostructure.[29] Nevertheless, caution should be taken when using AFM analysis, as a number of experiments have been carried out after drying the samples on the surface that have lead to mistakes in the interpretation. More accurate analysis should be obtained with solution AFM techniques.

Applications of DNA Nanoarrays Compose of Metal-Complex/DNA Conjugates

DNA nanoarrays built from repeating DNA motifs have significant power to organise different biomolecules, such as peptides, antibodies, inorganic materials, nanoparticles, metal complexes, and so forth, in a precisely defined manner through specific covalent and noncovalent interactions. Incorporation of metal centres into nucleic acids provides exceptional opportunities to create new type of materials due to their characteristics electronic, magnetic, catalytic and optical properties. Although very promising, there are still few applications of DNA nanoarray comprising with DNA-metal complex: in the following, we report some examples.

Applications for diagnostics: Redox-active ferrocenyl–DNA was used as an efficient probe for rapid and user-friendly electrochemical detection of nucleic acids.[30] Charge transport from ferrocene to Au or graphite surface through DNA double helix is the key event for such an electrochemical-based DNA detection assay. Using this method, the target DNA can be detected at concentrations as low as 500 femtomolar with a point mutation selectivity factor of $\approx$100 000:1. This redox-active DNA strand might activate other bioelectrocatalytic cascades to amplify DNA detection process. Thus DNA has been used as bioelectrocatalysts for amperometric detection of nucleic acid.

Metal-complex/ODN conjugates has been known for many years and applied in many chemical and photochemical reactions at particular sequences in DNA so as to probe and/or chemically modify biologically relevant sequences. Especially polypyridyl-ligand-containing d^6 metal complexes of Ir^{III}, Re^{I} and Ru^{II} and certain 4f elements are successful luminescent probes of nucleic acids.[31] In this context, a number of nanostructure based on these metal complexes have been designed, but to our knowledge, no application for diagnostic has been reported to date.

Metal-complex-induced DNA conductivity—applications in nano-electronics: The miniaturisation of transistors by the commonly used lithography technology is limited and therefore alternative methods are required for overcoming this barrier. In this context, a bottom-up approach by using DNA nanostructures as building blocks for the design of nanocircuitry has been explored. However, the low intrinsic conductance of DNA seems to be a serious obstacle for the use of its unique self-assembly capabilities in nano-electron-

ics. The addition of metal atoms to the structure of DNA turned out to be a promising way to decrease the resistance significantly. Thus, the development of methods to assemble metals or semiconductors on DNA is a basic prerequisite for the construction of nanocircuits and nanodevices. This has been done mainly by introduction of either metallo-base pairs or metallisation along DNA helix.

One fascinating way for enhancing the DNA conductivity has been achieved by converting normal B-DNA into M-DNA. The increased conductivity of M-DNA is attributed to the regular array of metal ions bound in an asymmetric ligand field and the helical twist of DNA ensures that adjacent metal ions experience a different structural environment upon addition of the gate voltage. Thus M-DNA can be used as an active element of a field-effect transistor[32] and has a tremendous advantage in the design of molecular electronics.

Metallisation along the DNA helix by Pd, Pt, Au and Ag, transforms them into a conductive nanowire with good conductivity approaching that of polycrystalline gold. In this process accumulated metal ions on DNA surface were reduced by using light or basic hydroquinone solution to form metal aggregates bound to the DNA by metal–polyelectrolyte interactions. These nanowires are considered as building blocks for the self-assembly of logic and memory circuits in future nanoelectronic devices.[33] Another interesting way for creating nanowires is based on self-assembling of G-quartets.[34]

Nevertheless, the fabrication of operational DNA-based nanocircuitry is a great challenge. Many problems such as the development of efficient synthetic route for the preparation of high quantities of metallic DNA material and the connection of the nanowires to the external world have to be overcome.

Metal-ion-induced DNA nanomachines: Metal ions help in building nanomolecular machines by DNA. There is currently great interest in the design of such nanodevices as they are capable of performing linear and rotary movements. Metal ions are responsible for electrostatic switching of DNA devices. For example the presence of $[CoCl_3(NH_3)_6]$ triggers the conformational change of the double helix from a right-handed B-helix to a left-handed Z-helix (Figure 5 A).[35] A simple and robust nanomachine can be created by changing DNA morphology from duplex to quadruplex or vice versa.[36] It has been found that Li^+ ions help in converting the duplex to quadruplex, whereas bivalent Mg^{2+} ions stabilise the duplex structure and switches the nanodevice to form duplex structure (Figure 5 B).

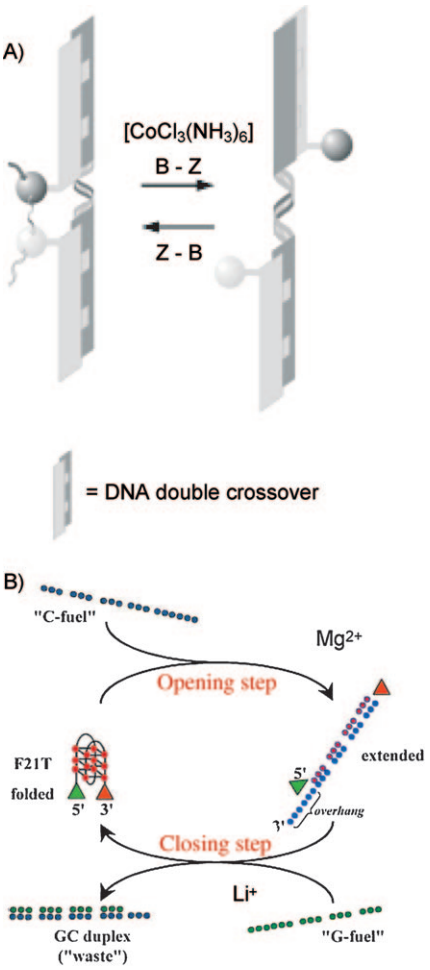

Figure 5. DNA nanomechanical devices. A) Electrostatic switching of double helix from a right-handed B-helix to a left-handed Z-helix by $[CoCl_3(NH_3)_6]$. The rotational movement was detected by the interruption of the FRET signal occurring between two fluorophores. B) Switching between an intramolecular quadruplex (left) and a duplex (right) in presence of appropriate metal ions (taken with permission from references [35 and 36]).

Conclusion and Future Prospects

Bio-inspired materials take advantage of the knowledge that nature has been optimising over millions of years. Scientists can now take inspiration from complex, naturally organised, chemical and biological structures to generate new materials with unique structural and functional properties. In this context, DNA emerges as a promising candidate for designing nano-architectures, because of its unique and selective self-assembly and ready programmability, based on hybridisation properties as well as its facile chemical or biological synthesis. The incorporation of metallic units into the DNA scaffold is one of the approaches that may control the structure and function of the corresponding nanostructure. A large driving force for research in this area stems from their already-known applications as electrochemical sensors, artificial nucleases, luminescent probes and study of electron transfer through DNA. This has contributed to great efforts for the facile and versatile preparation of metal-complex/DNA conjugates. At present, efforts are focused on designing metal complexes based nanostructures for molecular electronic, chemical sensors, molecular medicine and diagnostic applications. Evidently, new strategies that are being developed have to focus on the electrochemical or photo-

physical properties (i.e., the communication ability between metallic nodes) of these DNA nanomaterials. Nevertheless, it is a real challenge to create heterometal arrays with unique functions, leading to chemical communication between different kinds of metals triggered by external stimuli. These multimetallic–DNA assemblies might be applied in nanoelectronics, nanooptics, artificial photosynthesis, high-density data storage and catalysis.[37]

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