Highlight Review

Bio-inspired Programmable Self-assembly on DNA Templates

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Abstract

Besides the biological importance of DNA as storage of genetic information, DNA is a smart molecule to assemble functional units since it is possible to use sequences of nucleobases to encode molecularly assembled systems in a predetermined fashion over a wide range in size. This review highlights recent advance in precise control of molecular assembly on DNA templates directed towards functionalized materials.

♦ Introduction

The ultimate goal of molecular architecture is to arrange atoms and/or molecules precisely in space and to make it operate efficiently. However, dispersion of products in size and sequence is inherent in conventional synthetic approaches for polymeric system including self-assembly. On the other hand, biological system generates biopolymers such as DNA, protein, and polysaccharide without any dispersion in "number," "composition," "sequence," and "direction." These molecules organize with highly "selective" and "specific" spatial arrangement. Hence, structural motifs of biopolymers have great potential as template functions for programmable self-assembly to generate well-defined molecular architectures.

The double-helical DNA molecule is competent to serve as nanoscale materials. Diameter of DNA is about 2 nm, its helix contains coaxially stacked base pairs separated by 3.4 Å, and its helical pitch is about 3.4 nm for typical right-handed B-DNA (Figure 1a). Since chemical synthesis of DNA strands has been well established and sophisticated to give polymeric chains with designed unambiguous sequences made from nucleotides as building blocks, the basic structural motifs of DNA could be extended to encode precise molecularly assembled systems.[1–6] Automated DNA synthesizers can routinely make oligomers in length approaching 100 nucleotides, and they are applicable to incorporate unnatural building blocks as well.[7] Also, enzymatic tools developed for biotechnology can be employed to elongate and amplify DNA strands without loss of programmed information recorded as sequences of nucleobases. Most important characteristics of DNA are sequences of nucleobases and structural hierarchy. It is well understood how to work the Watson–Crick base pairing rules to assemble DNA strands into double, triple, or quadruple strands, hairpins, and branched structures. Combination of helices and junctions enable self-assembly of DNA into topologically designed structures such as sheets, cubes, and other more complex objects. Programmable molecularly assembled systems on DNA have been achieved in each hierarchical step over a range of size from 0.3 to 50 nm (Figures 1b–1e). Herein, this review highlights precise control of molecular assembly on DNA templates towards functionalized materials including our recent progress.

♦ DNA as a Hierarchical Template for Molecular Assembly

Since the pioneering work by Seeman, excellent examples of precisely controlled DNA nano-architectures have been re-

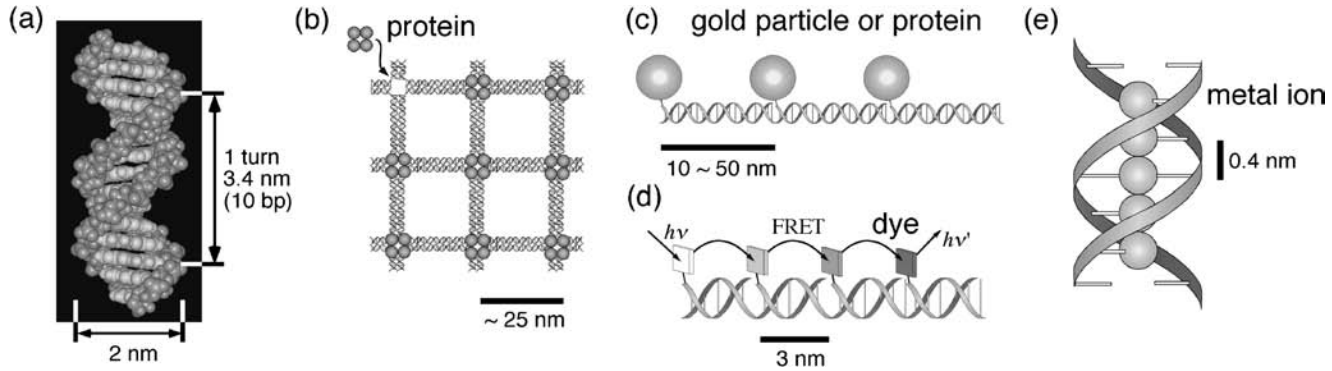

Figure 1. (a) Structure of DNA and (b)–(e) examples of precise molecular assembly on DNA templates.

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ported.[1,8] His group and others have made robust self-assembled structures with well-defined topologies of 1D tapes, 2D sheets, and 3D objects (cubes and other geometrized solids) by combining helices and junctions. Seeman has proposed initially to use DNA as a framework for the precise spatial arrangement of molecular devices. Niemeyer et al. experimentally demonstrated protein (streptavidin) arraying using covalent DNA–protein conjugates and single-stranded template DNA (Figure 1c).[2,9] Recently, LaBean et al. reported a specifically patterned protein array on a 4×4 cross tile lattice made of Seeman-type self-assembled DNA nanostructures (Figure 1b).[3,10]

Conjugation of DNA with metal, semiconductor, and polymer nanoparticles has attracted great attention in conjunction with integration of the materials for use as biosensors, nanodevices, and catalysts. For example, nanoparticles can be modified by DNA strands with encoded information for organization in analogy with the immobilization of DNA on a variety of solid surfaces (Figure 1c). Mirkin et al. and Schultz et al. reported pioneering results independently as appeared back-to-back in *Nature* in 1996.[11,12] Now, this strategy already links to practical application for biosensors, and the readers are addressed to recent excellent reviews for detailed overviews.[2c,13,14]

DNA also acts as templates for single molecular photonic wires.[15] Dye molecules with 10-base or 20-base oligoDNA can be arrayed with a 3.4 or 6.8 nm interval, respectively, on the one face of the duplex formed with complementary template DNA, because one helical pitch of DNA consists of 10 nucleotide pairs separated by 3.4 Å (Figure 1d). DNA-based unidirectional multistep FRET between spectrally different chromophores have been observed.

The smallest functional unit of DNA is a nucleotide, and therefore chemical modification of each nucleotide is directly linked to functional unit array at subnanometer resolution (Figure 1e). The modification of nucleotide is classified into subunits of a nucleotide; a phosphate linkage, a deoxyribose, and a nucleobase.[16] Among a variety of approaches to DNA-based supramolecular chemistry, the strategy of replacing DNA natural bases by alternative bases that possess distinctive shape, size, and function has allowed the modification of DNA in a highly specific and site-selective manner.[17,18]

♦ *Artificial DNA with Non-natural Bases*

Although it comes as a surprise to us that the combination of only four natural nucleobases, A, T, G, and C, organizes all genomic information with highly specific base pairing, A–T and G–C (Figure 2a), chemical and physical properties of the natural nucleobases should not vary so much when extended it as functionalized materials. Automated DNA synthesizers are applicable not only to natural nucleotides, but also to artificial building blocks that have two hydroxy groups protected with a dimethoxytrityl (DMTr) group for one and a phosphoramidite group for the other. Recently, some examples of incorporation of dye molecules or metal complexes into DNA scaffolds instead of hydrogen-bonded base pairs have been reported towards photonic or electronic wires.[19–21] Other examples of non-natural bases have also been exploited to expand genomic alphabets for information storage. For this purpose, alternative hydrogen-bonding (H-bonding) patterns (Figure 2b)[22] and the replacement of H-bonding with hydrophobic interactions (Figure 2c)[23–25] have been exploited.

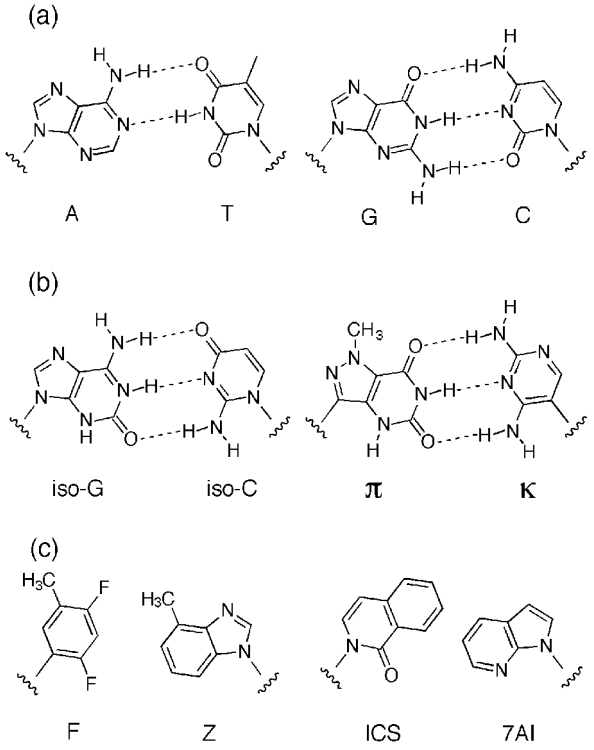

Figure 2. Examples of natural and modified DNA base pairs through (a) Watson–Crick hydrogen bonding; (b) alternative hydrogen bonding; (c) hydrophobic packing.

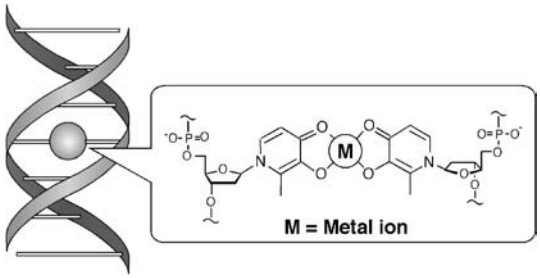

Figure 3. Artificial base pairing through metal complexation.

Alternatively, we have reported the metal-assisted base pairing, thereby creating a novel base-pairing motif in duplex DNA as an approach to the replacement of H-bonded base pairs by metal-mediated ones (Figure 3).[26–31] The basic strategy for the artificial DNA is the conversion of nucleobases into metal ligands. The artificial DNA including ligand-type nucleosides would form a duplex structure in the presence of an appropriate metal ion. Metal complexes would show a variety of characteristic features that can not be found out by organic compounds alone. Combinatorial optimization with a metal ion and a metal ligand allows fine tuning of characters of metal complexes; (1) thermodynamics and kinetics of binding and dissociation, (2) a variety of coordination numbers and geometries such as linear two coordination, tetrahedral or square-planar four coordination, octahedral six coordination, and so on, (3) physical and chemical properties such as redox-, magnetic-, optical-, and radio-activities and Lewis acidity. Consequently, DNA could be reincarnated as a new functionalized material by incorporating metal components inside.

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In 1999, we have reported the first example of a metal-mediated alternative base pair in which phenylenediamine-bearing artificial ligand-type nucleosides form a base pair through 2:1 complexation with a Pd^{2+} ion.[26] Since then, we and other groups have synthesized several types of ligand-type β-*N*- and β-*C*-nucleosides which have a monodentate **5**, bidentate **1**–**4** and **6**–**9**, tridentate **10** and **11**, hard-donor **3**, **4**, **6**, and **10** or soft-donor **11** ligand (Figure 4).[26–35]

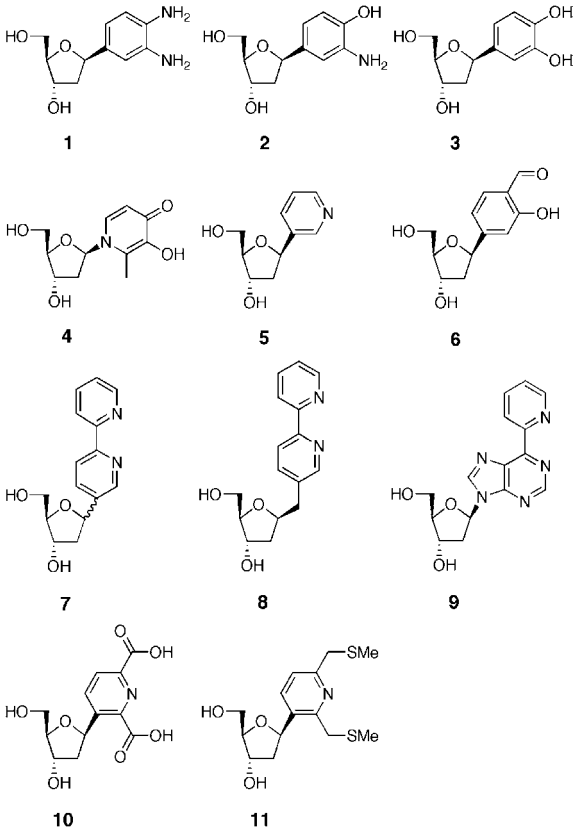


Figure 4. Examples of ligand-type nucleosides.

If individual artificial nucleobases would have a high affinity for a particular metal ion, stable metal-mediated base pairs could be incorporated into higher-order DNA structures, at pre-determined positions (Figure 5). Among these metal-mediated base pairs, a square-planar or a linear metal complex is a geometrically analogous motif of H-bonded natural base pair. So far, we have reported, in addition to the abovementioned Pd^{2+}-mediated base pairing, Pd^{2+}-mediated base pairing with 2-aminophenol,[28] Ag^{+}-assisted base pairing with pyridine (**P**–Ag^{+}–**P**),[29] and Cu^{2+}-mediated base pairing with hydroxypyridone (**H**–Cu^{2+}–**H**),[30] non-planar B^{3+}-induced base paring with catechol,[27] as alternative base pairing modes (Figure 5). Other groups have also reported metal-mediated base pairs such as a Cu^{2+}-mediated [1 + 3]-type base pair between pyridine and pyridine-2,6-dicarboxylate, an Ag^{+}-mediated one with 2,6-bis(methylthiomethyl)-pyridine bases,[32] a Cu^{2+}-mediated bipyridine nucleobase,[33] a Ni^{2+}-mediated pyridylpurine nucleobase,[34] and a covalently linked Ni–salen base pair[35] (Figure 5). The net charges and geometries of the resulting metal complexes are important factors determining distinctive property of each metal array formed in DNA.

♦ *Structural Control of DNA by Metal-mediated Base Pairing*

Bond energy of metal coordination occupies an intermediate position between those of covalent bonding and non-covalent bonding such as H-bonding. Hydroxypyridone-bearing nucleoside **4** forms a sufficiently stable base pair with a Cu^{2+} ion in a 10^{-5} M range (Scheme 1). Stability of a metal-mediated base pair is closely related to structural factors of DNA and hydrophobic environment in the duplex structure. To examine the influence of metal-mediated base pairing on the thermal stability of

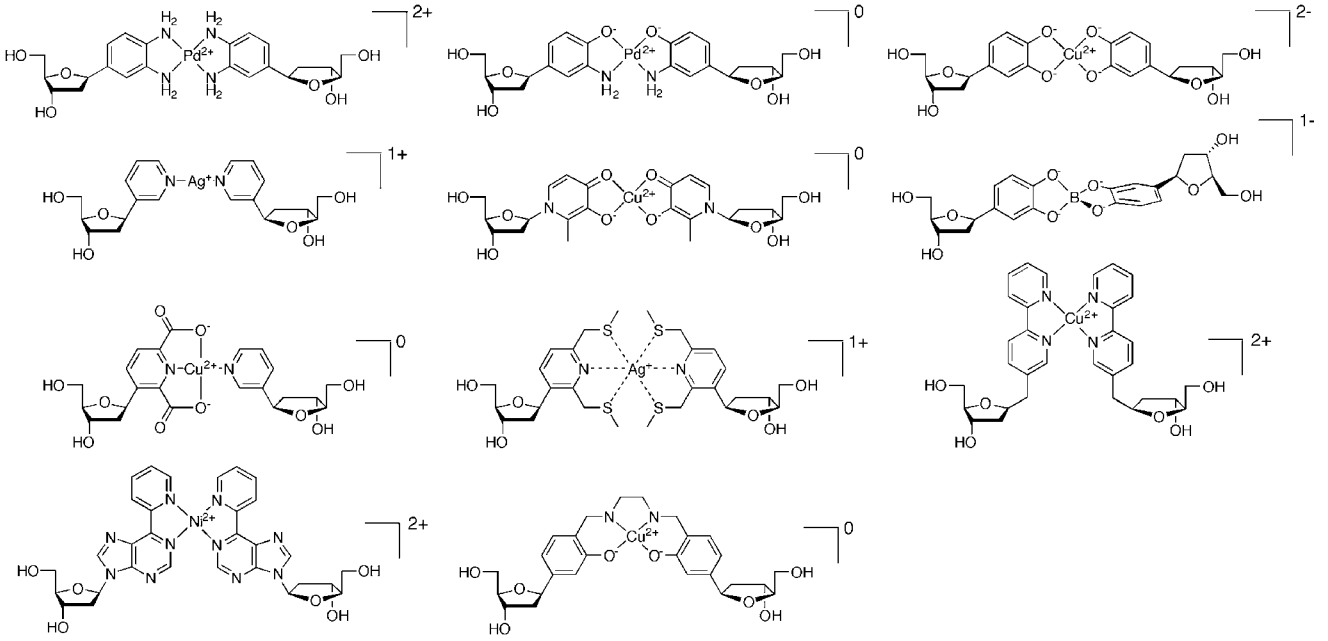
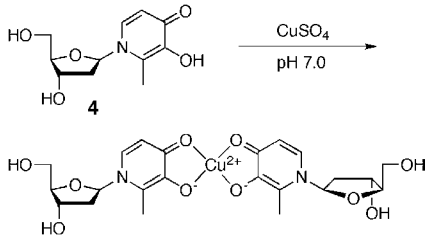


Figure 5. Metal-mediated base pairs.



Scheme 1.

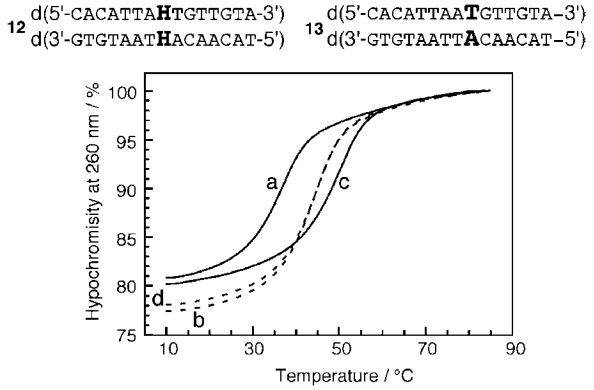
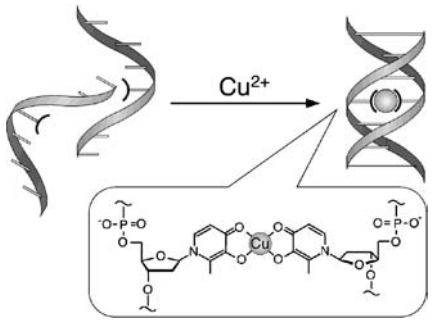
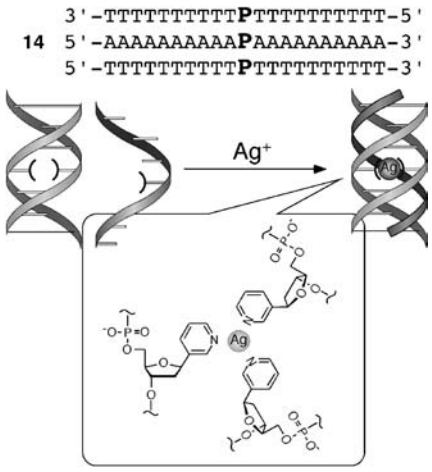


Figure 6. Melting curves of the duplexes **12** (a and c) and **13** (b and d). [**12**] = [**13**] = 2.0 μM in 10 mM Na-phosphate buffer, 50 mM NaCl (pH 7.0). [$CuSO_4$] = (a) and (b) 0 μM and (c) and (d) 2.0 μM.

a DNA double-stranded structure, an **H**–**H** pair was introduced in the middle of a 15-nucleotide DNA duplex **12**. DNA double-stranded structure thermally dissociates into a couple of single strands, and the melting temperature can be monitored by the hyperchromic shift at 260 nm. In the absence of Cu^{2+} ions, the duplex **12** showed a melting temperature of 37.0 °C (Figure 6a), whereas a natural-type oligoduplex **13**, in which the **H**–**H** base pair is replaced by an **A**–**T** base pair, melted at 44.2 °C (Figure 6b). Thus, in the absence of Cu^{2+} ions, the **H**–**H** base pair behaves as a mispair to destabilize the duplex. In contrast, addition of Cu^{2+} ions to the duplex **12** led to Cu^{2+} mediated base pairing with higher thermal stability. Thermal denaturation of **12** in the presence of equimolar Cu^{2+} ions resulted in a biphasic melting curve with a melting point of 50.1 °C (Figure 6c), which is higher than that of **12** in the absence of Cu^{2+} ions. Thus, the Cu^{2+}-assisted base pair, **H**–Cu^{2+}–**H**, stabilized the duplex by about 13 °C, whereas the



Scheme 2.



Scheme 3.

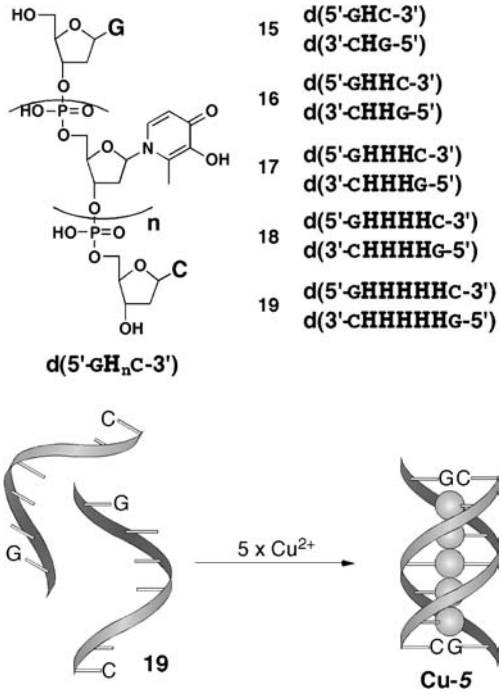
natural duplex **13** remained nearly unaffected by addition of Cu^{2+} ions (Figure 6d). Hence, transition between single strands and a double strand can be regulated by the formation of metal-mediated base pairing (Scheme 2).[30] In the case of single-site incorporation of pyridine-bearing nucleosides in the middle of the sequence of oligo(dT·dA·dA) triple strand **14**, the thermal stability of triplex **14** was significantly increased by Ag^+ complexation to form a base triplet (Scheme 3).[29]

Since the structural conversion of DNA is essentially relevant to duplication and transcription of genetic information, the strategy of the metallo-DNA would be an efficacious tool for manifestation of a gene.

♦ *Discrete Self-assembled Array of Metal Complexes in DNA*

Conventionally, crystallization is one of the most powerful methodologies to array metal complexes. However, this is not suited to control the number or the spatial arrangement of components. On the other hand, DNA has a structural basis to array functionalized building blocks without any distribution of number and sequence.

Recently, we reported the synthesis of a series of artificial oligonucleotides, d(5′-G$\mathbf{H}_n$C-3′) (n = 1–5), **15**–**19**, using hydroxypyridone nucleobases (**H**) (Scheme 4).[36,37] The changes in the UV spectra of d(5′-G$\mathbf{H}_5$C-3′)$_2$, **19**, in the presence of increasing amounts of Cu^{2+} ions are shown in Figure 7a. During the titration of Cu^{2+} ions, the absorbance at 280 nm gradually decreased while a new peak at 307 nm appeared with two isosbestic points until the ratio of [Cu^{2+}]/[duplex] reached to 5.0 equivalents (Figure 7b). This result clearly indicates five Cu^{2+} ions are arrayed into the duplex **19** via **H**–Cu^{2+}–**H** base pairing. Similar changes were observed with the other oligonucleotides, d(5′-G$\mathbf{H}_n$C-3′) (n = 1–4). Overall, the changes in absorbance at 307 nm, plotted as a function of the ratio of Cu^{2+} to d(5′-G$\mathbf{H}_n$C-3′)$_2$ (n = 1–5) (Figure 7b), strongly suggested the quantitative intermolecular complex formation of Cu-n (n = 1–5) [where Cu-n (n = 1–5) denotes $n$$Cu^{2+}$·d(5′-G$\mathbf{H}_n$C-3′)$_2$ (n = 1–5)] in which Cu^{2+}-mediated base pairs are aligned in a direct stacked manner. Cu^{2+}-assembled structures were also confirmed by electrospray ionization-time-of-flight mass spectrometry. One to five Cu^{2+}-mediated base pairs of hydroxypyridone nucleobases have been systematically incorporated into the middle of a



Scheme 4.

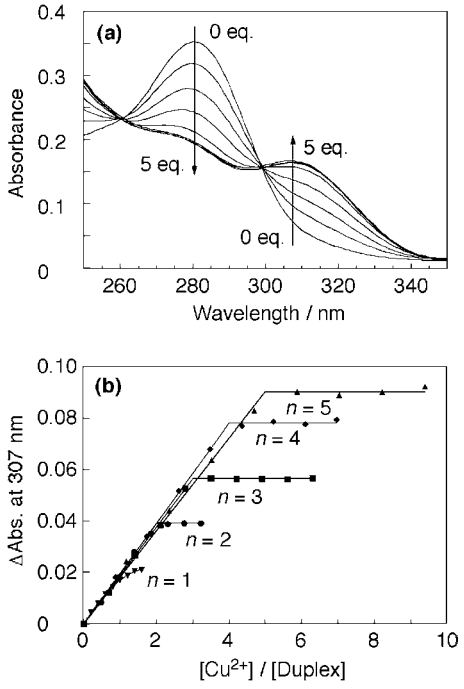


Figure 7. (a) UV absorption changes of **19** at various concentrations of Cu^{2+} at 25 °C. [**19**] = 2.0 μM in 10 mM HEPES (pH 7.0) and 50 mM NaCl. (b) Plot of absorbance at 307 nm against the ratio of Cu^{2+} to **15**–**19**.

DNA duplex, resulting in the formation of a magnetic chain by the line-up of mono- to pentanuclear Cu^{2+} complexes stacked within the DNA right-handed helix. The Cu^{2+} ions in each complex couple ferromagnetically with one another through unpaired *d* electrons. An outline of a proposed right-handed, double-stranded structure with Cu^{2+} array inside the DNA is drawn in Figure 8, where the Cu^{2+}–Cu^{2+} distance is about 3.7 Å. This strategy represents a new method for metal arrays in solution in a discrete and predictable fashion, and contrasts with the non-biological approach of others, leading to the possibility of metal-based molecular devices such as molecular magnets and wires.

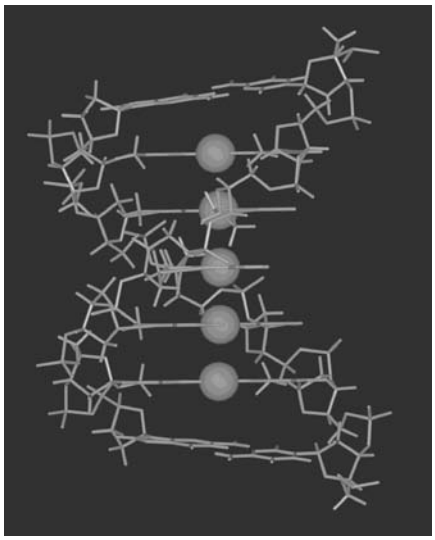


Figure 8. A plausible structure of Cu-5.

♦ *Summary and Outlook*

DNA is becoming increasingly important as a key motif for precise molecular array. The strategies discussed here are applicable to assemble ions, organic molecules, inorganic clusters, and biomolecules into subnanometer to micrometer-scale materials, because DNA contains programmable information in a simple and predictable manner. Moreover, chemists can design not only the sequences of nucleobases, but also those of nucleotides, inter- and intrastrand interactions, and interaction with matrices to give higher information contents. Hence, the possibility of programmable assembly of functional chemical components is unlimited.

Towards the next stage of the DNA-based nanotechnology, specific topics we find of particular importance and interest include; (1) more complex, (2) meso- and macroscopic precise molecular assembly without any dispersion, and (3) precise positioning of matter in 3D space using DNA templates, (4) structural and functional switching at the right time, (5) manipulation at the molecular level, and (6) conjugation with other materials of the DNA-templated assembly, (7) use of the non-biological systems for controlling genetic events.

This field is still in its early stage, but will be quickly expanded to broad research fields. We will soon eyewitness important applications of this strategy both to material sciences and biotechnologies.

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