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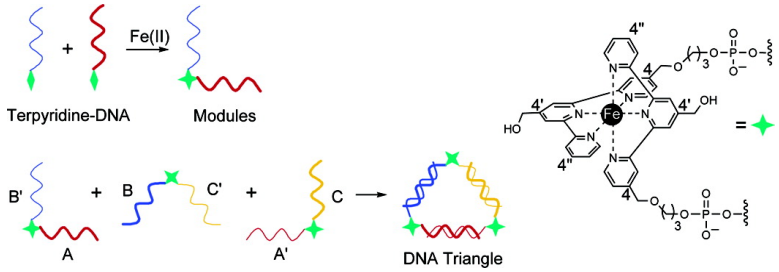

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Synthesis of DNA Triangles with Vertexes of Bis(terpyridine)iron(II) Complexes

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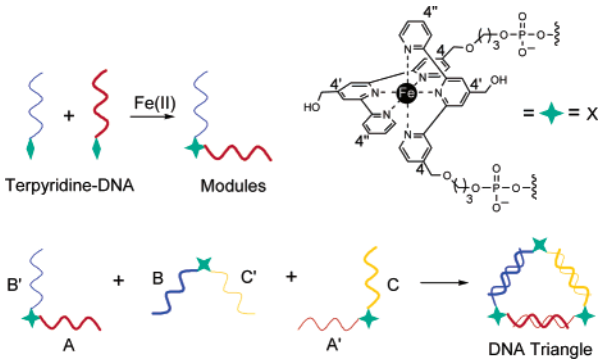
Molecular self-assembly offers a powerful means of fabricating well-defined and complex structures from simple components in a programmable manner.[1] Recently, DNA molecules have been used to create DNA-based nanostructures and to direct the assembly of other functional molecules.[2,3] DNA nanotechnology takes advantage of the ability of DNA to form the double helix and unusual structural motifs through Watson−Crick base pairing. In particular, immobile analogues of the Holliday junction serve as a stable, branched junction with four double helical arms. However, the limited number of available DNA motifs applicable to the self-assembly of DNA restricts the possible construction of geometric DNA objects in more diverse and sophisticated arrangements. The development of novel versatile junctions would therefore greatly assist the further extension of the DNA role in a material world.

Here, we report the synthesis of the terpyridine derivative whose dimeric metal complex can be used as an alternative to the Holliday junction (Scheme 1). This terpyridine derivative allowed the preparation of terpyridine−DNA conjugates that formed two-way branched metal−organic modules upon dimerization of terpyridine ligands in the presence of Fe(II) ions. These modules self-assembled into DNA triangles in which each vertex and side consist of a bis(terpyridine)Fe(II) complex and a DNA duplex, respectively.

The terpyridine derivative **1** was synthesized as shown in Scheme 2.[4] Oxidation of compound **2**[4a−d] with molecular oxygen in the presence of potassium *tert*-butoxide afforded **3**.[4e] Subsequent esterification of **3** with thionyl chloride in refluxing methanol followed by complete reduction using $NaBH_4$ provided **5**. A coupling reaction between **5** and (3-bromopropoxy)-*tert*-butyldimethylsilane using NaH afforded **6**, which was then oxidized to methyl sulfone **7** with 3-chloroperoxybenzoic acid. After converting the TBDMS to the DMT group, the methylsulfonyl group of **9** was displaced by cyanide ion to give **10**. Basic hydrolysis and iodomethane treatment[4f] of **10** afforded **11**, which was subsequently reduced to the final product **1** by use of $NaBH_4$. A CPG-coupled terpyridine derivative **12** was prepared by succinylation of the 4′-hydroxyl group of **1** followed by coupling to LCAA-CPG beads with HOBt/BOP coupling reagents.[5] Subsequent capping of unreacted free amines on the CPG with acetic anhydride was performed to prevent nonspecific coupling of bases to the support during oligonucleotide synthesis. Spectrophotometric analysis (A_{504}) of DMT cations released upon treatment of **12** with trichloroacetic acid/CH_2Cl_2 (5:95) confirmed 28 μmol/g loading of **1** onto the CPG support.

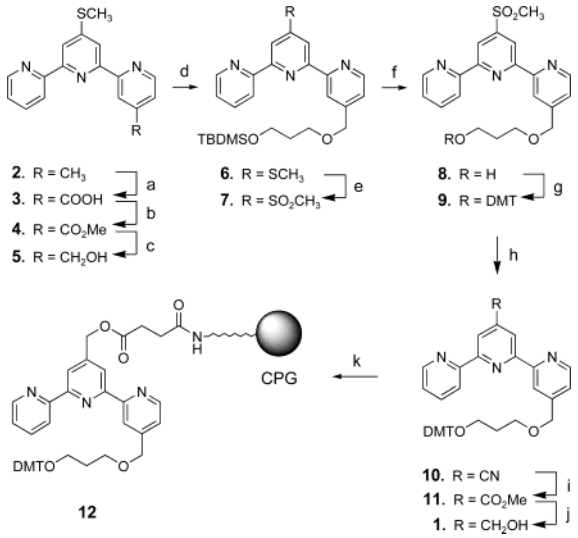
With **12** in hand, we set out to synthesize terpyridine−DNA conjugates using automated methods. Each of these conjugates contains a DNA strand tethered by its 3′-end to the 4-position of terpyridine. Two-way branched metal−organic modules **13**−**17** were prepared by adding two equivalents of Fe(II) ions to an

Scheme 1. Use of Terpyridine−DNA Conjugates for the Preparation of Two-Way Branched Metal−Organic Modules Capable of Self-Assembling into DNA Triangles[a]



[a] Modules contain a bis(terpyridine)Fe(II) complex X tethered by its 4-positions to the 3′-end of two oligonucleotides. The 4-substituted bis(terpyridine)Fe(II) complex orients two oligonucleotides at a 90° angle. DNA strands A, B, and C are complementary to A′, B′, and C′, respectively. The terpyridine and bis(terpyridine)Fe(II) complex X are shown in green, and DNA strands are shown in red, yellow, and blue, respectively.

Scheme 2 [a]



[a] Reagents and conditions: (a) *t*-BuOK, O_2, DMF, rt, 82%; (b) $SOCl_2$, MeOH, reflux, 77%; (c) $NaBH_4$, THF/EtOH (10:1), 80 °C, 87%; (d) $Br(CH_2)_3OTBDMS$, NaH, DMF, rt, 98%; (e) *m*-CPBA, CH_2Cl_2, rt, 83%; (f) Bu_4NF, THF, rt, 98%; (g) DMT-Cl, DMAP, pyridine, rt, 91%; (h) KCN, DMF, 100 °C, 89%; (i) NaOH, H_2O/MeOH/ethylene glycol, 85 °C, then MeI, DMF, rt, 48%; (j) $NaBH_4$, THF/EtOH (10:1), 85 °C, 70%; (k) (*i*) succinic anhydride, DMAP, pyridine, rt, (*ii*) LCAA-CPG, HOBt, BOP, DIEA, DMF, rt, then (*iii*) Ac_2O, DMAP, CH_2Cl_2, rt, 28 μmol/g.

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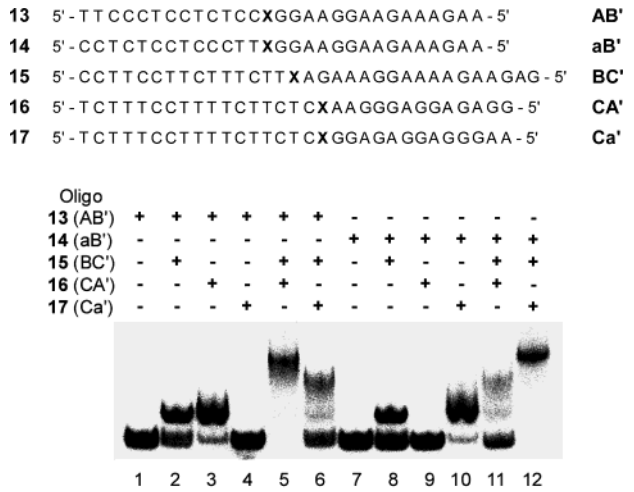

Figure 1. (Upper) Sequences of DNA strands A, B, and C and their complementary oligonucleotides A′, B′, and C′ respectively linked to a central bis(terpyridine)Fe(II) complex X in the modules **13**−**17**. Two complementary DNA strands a and a′ contain the reverse sequences of A and A′, respectively. (Lower) Gel-shift analysis of the formation of DNA triangles by PAGE on a 15% nondenaturing polyacrylamide gel.[6] The modules **13** and **14** were labeled with ^{32}P at the 5′-end of DNA strands. Each lane contains an equimolar mixture of component modules indicated at the top.

equimolar mixture of two different terpyridine−DNA conjugates in H_2O (Figure 1, Upper). Each of these modules contains a central bis(terpyridine)Fe(II) complex X flanking two single-stranded DNAs that differ in sequence and length. The sequences of DNA strands A, B, and C in the modules are complementary to those of A′, B′, and C′, respectively. As controls, two complementary DNA strands a and a′ with reverse sequences of A and A′, respectively were also synthesized. The length difference between two DNA strands attached to a bis(terpyridine)Fe(II) complex allowed facile separation of heterodimeric modules from homodimeric ones using PAGE on a 20% denaturing polyacrylamide gel after they were formed upon complexation of an Fe(II) metal ion by two terpyridine−DNA conjugates.[6] The relative orientation of two single-stranded DNAs in each module is constrained at a 90° angle due to their positioning on a bis(terpyridine)Fe(II) complex.

Triangular assembly of modules **13**−**17** was initiated simply by annealing an equimolar mixture of the component modules in TE buffer and thereby allowing intermodular DNA duplex formation (Figure 1, Lower). Proper formation of DNA triangles was confirmed by comparison with a control series of linear assemblies on a 15% nondenaturing polyacrylamide gel.[6] DNA triangles were formed only when three modules were annealed such that the sequence of each DNA strand in one module was complementary to that in the other in a cyclic way (Figure 1, Lower, lanes 5 and 12). DNA triangles migrated more slowly than linear assemblies despite the same length and sequence composition (Figure 1, Lower, lanes 5, 12 vs 6, 11, respectively). DNA triangles appeared as a single band, indicating that their structure is not destabilized by the presence of bis(terpyridine)Fe(II) complex junctions. Formation of significant quantities (>99%) of DNA triangles precluded the presence of higher cyclic species. It is noteworthy that these junctions are flexible enough to accommodate the inner angles of about 48°, 58°, and 74° and side lengths of 17, 15, and 13 base pairs in DNA triangles. Thus, DNA precisely placed three bis(terpyridine)Fe(II) complexes at nanoscale distances in triangular arrays.

In conclusion, we describe the synthesis of a terpyridine derivative that can be site-specifically linked to an oligonucleotide. This derivative affords terpyridine−DNA conjugates that serve as a key building block to create molecular modules. These molecular modules are easily generated by mixing terpyridine−DNA conjugates with metals and are successfully employed for the construction of DNA triangles. Taken together, a bis(terpyridine)Fe(II) complex demonstrates its potential for an alternative to the Holliday junction in DNA-based self-assembly. Further study for the preparation of terpyridine derivatives functionalizable with multiple oligonucleotides in a geometrically distinct way using solid-phase DNA synthesis is in progress.

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Supporting Information Available: Detailed synthetic procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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