Terpyridyl Derivative Useful for Synthesis of DNA Crystal

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The construction of highly ordered multidimensional networks *via* predictable assembly of molecules attracts great attention due to their potential as fabricated crystals.[1,2] In particular, DNA crystals assembled from oligonucleotides offer considerable advantages over supramolecular frameworks derived from commonly employed organic and metal-ligand building blocks in that they can further template spatial arrangement of molecular components tethered to DNA binding molecules or DNA itself in a programmable manner.[3-5] However, the self-assembly process driven only by hydrogen bonding of complementary oligonucleotides has a fundamental limitation of incorporating vertices into branch points at which a linear DNA double helix in a DNA crystal is held together.[3] Here, we report the design and synthesis of a terpyridyl derivative **1** that can be site-specifically linked to oligonucleotides (Figure 1 and Scheme 1). Oligonucleotides equipped with the metal chelator terpyridine can serve as a key building block in the design of supramolecular polygons and ultimately of DNA crystals since oligonucleotide and terpyridine moieties create a line segment and a vertice upon DNA double helix and dimeric terpyridine metal complex formations, respectively (Figure 1).

A terpyridyl derivative **1** was synthesized as shown in Scheme 1. α-Oxoketene dithioacetal **3**[6,7] underwent 1,4-addition with the potassium enolate of 2-acetyl-4-methylpyridine **2**[8,9] followed by elimination of methanethiolate to provide 1,5-enediones. This intermediate is converted into a terpyridyl derivative **4** by treatment with ammonium acetate and acetic acid.[6,7] Oxidation of **4** with molecular oxygen in the presence of potassium *t*-butoxide afforded **5**.[10] Subsequent esterification of **5** with thionyl chloride in refluxing methanol followed by complete reduction using $NaBH_4$ provided the desired product **7**. A coupling reaction between **7**

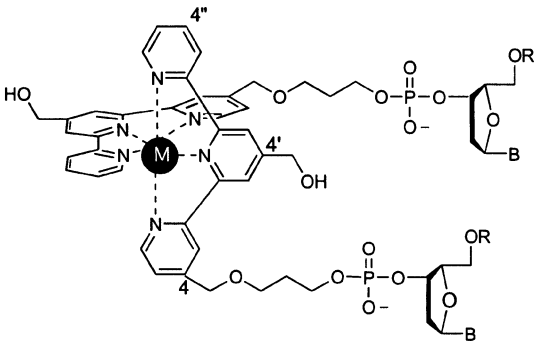
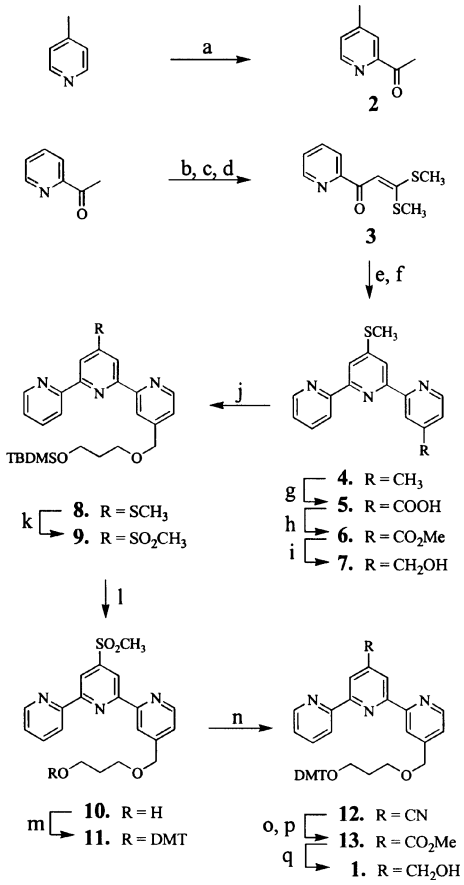


Figure 1. The structure of a dimeric oligonucleotide-terpyridine where the metal ion is octahedrally coordinated to terpyridyl ligands. The 4′-substituted terpyridine orients two oligonucleotides at a 90° angle.



Scheme 1. Reagents and conditions: (a) paraldehyde, *t*-BuOOH, CF_3CO_2H, $FeSO_4{\cdot}7H_2O$, CH_3CN, reflux, 20%; (b) *t*-BuOK, THF; (c) CS_2; (d) CH_3I, 68% for b-d; (e) **2**, *t*-BuOK, THF; (f) NH_4OAc, HOAc, reflux, 77% for e-f; (g) *t*-BuOK, O_2, DMF, 81%; (h) $SOCl_2$, MeOH, reflux, 70%; (i) $NaBH_4$, THF/EtOH (10:1), reflux, 88%; (j) $Br(CH_2)_3OTBDMS$, NaH, 4-DMAP, DMF, 98%; (k) *m*-CPBA, CH_2Cl_2, 82%; (l) Bu_4NF, THF, 67%; (m) 4′,4-dimethoxytrityl chloride (DMT·Cl), 4-DMAP, pyridine, 94%; (n) KCN, DMF, 100 °C, 52%; (o) NaOH, H_2O/MeOH/ethylene glycol, 85 °C; (p) CH_3I, DMF, 46% for o-p; (q) $NaBH_4$, THF/EtOH (10:1), 85 °C, 73%.

and 3-bromo-*tert*-butyldimethylsilyloxy propane using NaH afforded **8**, which was then oxidized to methyl sulfone **9** with *m*-chloroperoxybenzoic acid. After converting the TBDMS to DMT group, the methylsulfonyl group of **11** was displaced by cyanide ion to give **12**. Basic hydrolysis and methyl iodide treatment[11] of **12** afforded **13**, which was subsequently reduced to the final product **1** by use of $NaBH_4$.[12]

In conclusion, we described a synthetic pathway to the terpyridyl derivative whereby a metal complex can be conjugated to oligonucleotides. Further study for the preparation of oligonucleotides functionalized with this derivative using

solid-phase DNA synthesis is in progress and will be reported in due course.

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12. **1**: TLC (EtOAc : hexane : NH_4OH = 5 : 1 : 0.2) R_f = 0.40; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, *J*=4.8 Hz, 1H, $C_{6''}$-H), 8.62 (d, *J*=4.8, 1H, C_6-H), 8.55 (d, *J*=8.1, 1H, $C_{3''}$-H), 8.47 (s, 1H, C_3-H), 8.43 (s, 2H, $C_{3'}$-H and $C_{5'}$-H), 7.79 (dt, 1H, *J*=1.8, 7.7, $C_{4''}$-H), 7.43 (d, *J*=7.2, 1H, $C_{5''}$-H), 7.33-7.20 (bm, 9H, DMT), 7.18 (d, *J*=7.2, 1H, C_5-H), 6.78 (d, *J*=8.7, 4H, DMT), 4.88 (s, 2H, py′-CH_2-), 4.63 (s, 2H, py-CH_2-), 3.74 (s, 8H, -CH_2O- and DMT), 3.24 (t, *J*=6.0, 2H, -OCH_2-), 1.97 (m, 3H, -CH_2-, -OH); ^{13}C NMR (300 MHz, $CDCl_3$) δ 158.2 (DMT), 156.0 (2 carbons), 155.4 (2 carbons), 152.3 ($C_{4'}$), 149.1, 149.0, 148.8 (C_4), 145.1 (DMT), 136.9, 136.4 (DMT), 129.9 (DMT), 128.1 (DMT), 127.7 (DMT), 126.6 (DMT), 123.8, 121.9, 121.4, 119.3, 118.6, 118.4, 112.9 (DMT), 85.8 (DMT), 71.4 (py-CH_2-), 68.1 (-CH_2O-), 63.8 (py′-CH_2OH), 59.9 (-OCH_2-), 55.2 (DMT), 30.4 (-CH_2-).