CHEMCOMM Communication
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Ferrocene-modified bis(spiropyridopyran)s as synthetic signaling receptors for guanine–guanine dinucleoside derivatives

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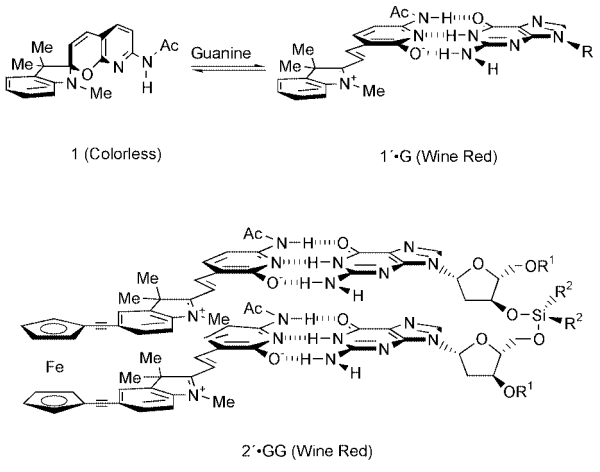
Received (in Cambridge, UK) 13th August 2001, Accepted 16th October 2001
First published as an Advance Article on the web 30th October 2001

A ferrocene-linked bis(spiropyridopyran) was designed and synthesized, that recognized guanine–guanine dinucleoside derivatives *via* complementary hydrogen bonds in CH_2Cl_2, resulting in the isomerization of the colorless spiropyridopyran as self-indicating receptors.

The recognition and selective binding of nucleobases play essential roles in entire living systems. For example, complementary hydrogen bonds arise in a very specific fashion between purine and pyrimidine bases of the two strands of double-helical DNA in order to store genetic information.[1] Thus, the synthetic models that recognize specific nucleobases and that read-out the recognition event are attracting much attention from the viewpoint of their uses in biological sciences.[2] In this connection, we have reported spiropyridopyrans **1**,[3] isomerization of which to the colored merocyanines **1′** was induced by recognition of guanosine derivatives.[4] To extend this approach to more challenging projects, we focused on the recognition of oligonucleotides. Here we describe the molecular recognition ability and its recognition-induced coloration of a ferrocene-modified bis(spiropyridopyran) **2** for guanine–guanine dinucleosides (Scheme 1).

The choice of ferrocene as a linker was based on the inter-ring spacing of the two Cp rings (0.33 nm),[5] which is near to the spacing between the stacked base pairs.[6] Another advantageous point of the ferrocene skeleton is its restricted conformational flexibility. This may result in the decrease of the entropy loss of **2** upon complexation with dinucleotides.[7] To evaluate the recognition abilities of **2** for dinucleotides in less-polar solvents, lipophilic dinucleoside derivatives were chosen (Fig. 1b). The bulky silyl groups at the 5′ and 3′ ends and the di-*n*-hexylsilylene internucleoside linkage make the dinucleoside soluble in such solvents and prevent their deoxyribofuranoside residues from interacting with the hydrogen-bonding motif of **2**. The decision for utilizing the silylene linkage was based on the similarity of covalent bond radius of tetrahedral silicon (0.117 nm) to that of tetrahedral phosphorus (0.110 nm).[8]



Scheme 1

The 3*H*-indole derivative bearing ethynyl groups at the 5 position was prepared from 4-bromophenylhydrazine by using the Fischer-indole synthesis followed by Sonogashira reaction.[9] Further Sonogashira reaction of the indole with 1,1′-diiodoferrocene[10] gave ferrocene-linked bis(3*H*-indole),[7c] which was methylated at the nitrogen and condensed with 6-acetamido-2-pyridone-3-carbaldehyde[4a] to yield desired bis(spiropyridopyran) **2** (Scheme 2).† The lipophilic dinucleoside derivatives were prepared according to a literature procedure.[8]

The ferrocene-linked bis(spiropyridopyran) **2** showed wine-red color in CH_2Cl_2, indicating that it exists at least partly as the open merocyanine form. This was demonstrated by the ^{1}H NMR spectrum of **2**, in which 10% or less of **2** is present as **2′** on the basis of the integration of the spectrum.‡ Futhermore, the UV-vis spectrum of **2** revealed an absorption maximum around 580 nm ($\varepsilon = 6.9 \times 10^3$) that is unambiguously attributed to the merocyanine chromophore (Fig. 1a; a line of 'none').[4a] In CH_2Cl_2, addition of the guanine–guanine dinucleoside derivative **GG** (10 equiv.) to **2** produced changes in the absorption spectra, and strong absorption bands appeared ($\lambda_{max} = 575$ nm, $\varepsilon = 3.8 \times 10^4$). The change was clearly seen visually, as the wine-red color of **2** dramatically darkened. Unfortunately, the ^{1}H NMR spectrum of the mixture of **2** and **GG** in $CDCl_3$ gave no useful information for the increment of the merocyanine

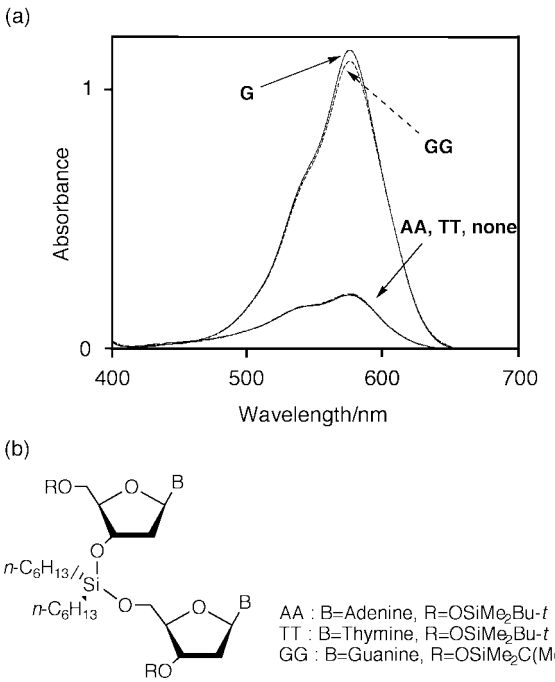
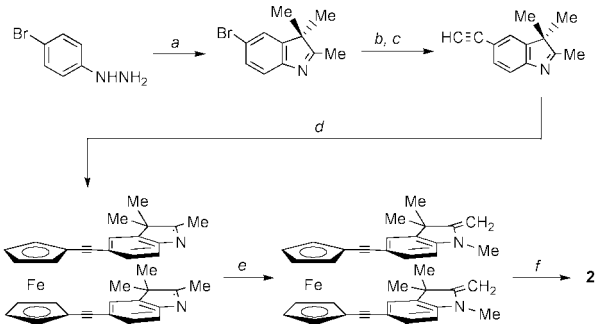


Fig. 1 (a) Electronic absorption spectra of **2** (3.0×10^{-2} mM) in the presence of the lipophilic nucleoside derivatives (3.0×10^{-1} mM) in CH_2Cl_2 at 25 °C. (b) The structures of the dinucleoside derivatives. The guanine–guanine dinucleoside (**GG**) was used as a mixture with 3′–3′ and 5′–5′ homo-coupling dimers. The guanine mononucleoside (**G**) is 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)deoxyguanosine.

 DOI: 10.1039/b107306k



Scheme 2 *Reagents*: (*a*) butan-2-one, AcOH; (*b*) 2-methylbut-3-yn-2-ol, $(Ph_3P)_2PdCl_2$, CuI, Et_2NH; (*c*) NaOH, toluene; (*d*) 1,1′-diiodoferrocene,[10] $(Ph_3P)_2PdCl_2$, $Cu(OAc)_2$, *i*-Pr_2NH; (*e*) MeI, MeCN, then NaOH, H_2O; (*f*) 6-acetamido-2-pyridone-3-carbaldehyde,[4a] EtOH.

form **2′** because of much overlap of the peaks between **2′** and **GG**. The guanine mononucleoside **G** resulted in similar changes to the absorption spectrum, while other mononucleoside (**A**, **T**, **C**) and dinucleoside (**AA** and **TT**) derivatives had absolutely no influence on it (Fig. 1a). These findings indicated that the complementary triple hydrogen bond between the acetamidopyridone anion part of **2′** and guanine bases is critical for selective coloration.

The binding constants were estimated by UV titration at 25 °C using an iterative least-squares curve-fitting with weighting of data points according to the error analysis of Deranleau.[11] The absorbances of the merocyanine forms (575 nm) were monitored as a function of the concentration of guanosine derivatives assuming that all the complexed-spiropyrans exist as merocyanine forms. The association constant between **1′** and **G** displayed 2.4×10^4 M^{-1} ($-\Delta G_{298}$ = 25.0 kJ mol^{-1}), while that of **2′** and **GG** was 4.2×10^5 M^{-1} ($-\Delta G_{298}$ = 32.0 kJ mol^{-1}). The increment of the binding energy was lower than that predicted by the doubled recognition sites; this may partly result from the electrostatic repulsion between the two zwitterionic merocyanines.

In summary, a ferrocene-modified bis(spiropyridopyran) was developed as a synthetic signaling receptor for guanine–guanine dinucleoside derivatives. The high selectivity for the coloration of the receptor is governed by the hydrogen-bonding complementarity between them. In the future, design and synthesis of the receptors that bind native nucleotides will be expected to show significant practical value.

Notes and references

† **2**: ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 1.18 (s, 6 H, $C(CH_3)_2$), 1.33 (s, 6 H, $C(CH_3)_2$), 2.12 (s, 6 H, $COCH_3$), 2.77 (s, 6 H, NCH_3), 4.31 (s, 4 H, Cp-CH), 4.53 (s, 4 H, Cp-CH), 5.67 (d, J = 10.0 Hz, 2 H, pyrane-CH), 6.45 (d, J = 8.0 Hz, 2 H, benzene-CH), 6.83 (d, J = 10.0 Hz, 2 H, pyrane-CH), 7.18 (s, 2 H, benzene-CH), 7.30 (d, J = 8.0 Hz, 2 H, benzene-CH), 7.41 (d, J = 8.0 Hz, 2 H, pyridine-CH), 7.71 (br s, 2 H, NH), 7.72 (d, J = 8.0 Hz, 2 H, pyridine-CH).

‡ **2′** (diagnostic peaks in ^{1}H NMR): 1.73 (s, $C(CH_3)_2$), 2.31 (s, $COCH_3$), 3.62 (s, N^+CH_3). Assignments of the peaks of **2** and **2′** were based on those for **1** and **1′**.[4a]

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