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Highly Efficient Recognition of Native TpT by Artificial Ditopic Hydrogen-Bonding Receptors Possessing a Conformationally Well-Defined Linkage

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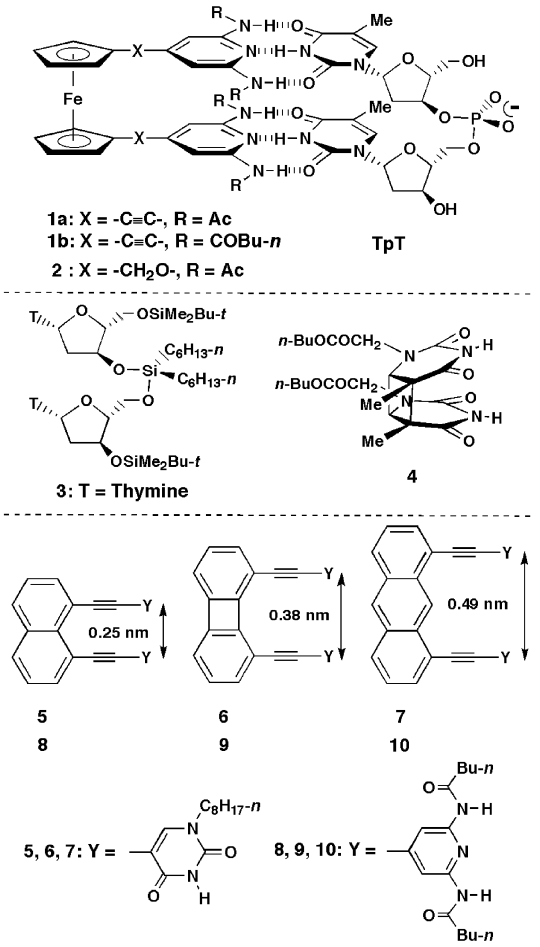
Abstract: Synthesis and binding affinity of rationally designed artificial ditopic nucleobase receptors are reported. The ditopic receptors were designed to recognize thymine−thymine dinucleotides by their two hydrogen-bonding moieties, which are connected to conformationally well-defined linkages such as ferrocene and biphenylene. The ditopic receptors exhibited a remarkably strong binding affinity for lipophilic TpT analogue in $CDCl_3$/DMSO-d_6 (85:15, v/v). The binding affinity of the ditopic receptors for the dinucleotide was so high that even native TpT was extracted by them into $CDCl_3$. Detailed comparisons for the recognition abilities of the ditopic receptors were also conducted.

Complementary hydrogen bonds arise in a very specific fashion between the purine and pyrimidine bases of the two strands of double-helical DNA in order to define the duplex architectures and regulate the biological information-transfer functions.[1] This remarkable feature of the specific and critical hydrogen-bonding interactions has inspired investigations into furnishing model systems, from which many artificial nucleobase receptors have been synthesized.[2] Among the nucleobase receptors, however, only a few of those have been effective for the recognition of dinucleotide and oligonucleotide derivatives, and much fewer examples were reported for native oligonucleotides paticularly by use of hydrogen-bonding interactions.[3] This is partly because of the entropic disadvantages due to the conformational restriction of the multitopic receptors after the recognition of the polynucleotide. In searching for an ideal linkage for connecting two recognition sites, we recently reported a novel type of ferrocene-linked artificial ditopic receptors **1** (Scheme 1).[4] The ferrocene-linked receptors **1** strongly bound thymidylyl(3′→5′)thymidine (TpT) through multipoint hydrogen bonds utilizing the pivot character of the ferrocene skeleton and the linearity of the ethynediyl spacers. However, there was no reason to believe that the combination of ferrocene and ethynediyl represented the optimal linkage, and we have examined some other systems. We now present the synthesis and binding affinities of new ditopic dinucleotide receptors possessing various conformationally well-defined linkages as well as further information for **1**.

SCHEME 1



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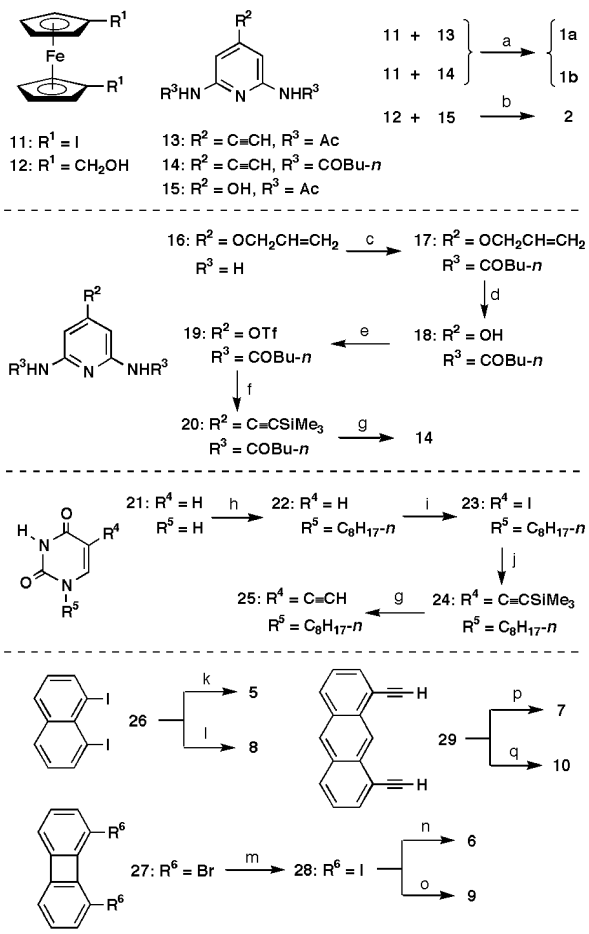
The ferrocene-linked ditopic receptors possessing an ethynediyl spacer **1a**,**b** were synthesized from 1,1′-diiodoferrocene (**11**) and 2,6-diamido-4-ethynylpyridines **13** and **14** by Sonogashira reaction,[5] respectively, while that of an oxymethylene spacer **2** from 1,1′-bis(hydroxymethyl)ferrocene (**12**) and 2,6-diacetamido-4-pyridone (**15**) was synthesized by a Tsunoda-modified Mitsunobu reaction.[6] Polynuclear aromatic-linked dinucleotide derivatives **5** and **6** were synthesized by Sonogashira reaction of 1,8-diiodonaphthalene (**26**) and 1,8-diiodobiphenylene (**28**) with 5-ethynyl-1-*n*-octyluracil (**25**), respectively, while **7** was derived from 1,8-diethynylanthracene (**29**) and 5-iodo-1-*n*-octyluracil (**23**). Polynuclear aromatic-linked ditopic receptors **8**−**10** were prepared from **26**, **28**, and **29** in a manner similar to those mentioned for **5**−**7** using **14** and **19** instead of **25** and **23**, respectively. The key intermediates **14**, **19**, **23**, and **25** for the synthesis of receptors and dinucleotide derivatives were prepared by standard synthetic methods from commercially available or known compounds (Scheme 2).

The molecular design of the ferrocene-linked ditopic receptors **1** was fully described in a previous paper.[4] The two diamidopyridine moieties (hydrogen-bonding site for thymine) were connected to the cyclopentadienyl (Cp) rings of ferrocene through linear ethynediyl spacers in order to diminish the entropic disadvantages of the receptors during the complexation. As a starting point for the development of new ditopic receptors, we investigated the influence of the spacers between ferrocene and diamidopyridine. Thus, we designed more flexible but still substantially rigid oxymethylene-connected ditopic receptor **2**. We thought that the flexible spacers, to some extent, might cause the receptors to adopt a favorable conformation for binding to dinucleotides. Of course, introducing flexibility causes a loss of entropy, but we hoped that the favorable enthalpic change resulting from the adjustability would compensate for the unfavorable entropic change.

To evaluate the hydrogen-bonding abilities of **1** and **2** for dinucleotides in detail, aprotic solvents such as $CHCl_3$ and CH_2Cl_2 must be used, so lipophilic TpT analogue **3** was chosen. The *tert*-butyldimethylsilyl groups at 5′ and 3′ ends and the di-*n*-hexylsilylene internucleotide linkage make dinucleotide **3** soluble in such solvents and prevent the deoxyribofuranoside residues of **3** from interacting with the hydrogen-bonding motif of the receptors. This allows accurate assessment for a net hydrogen-bonding interaction between the nucleobases of **3** and the recognition sites of **1** and **2**. The decision to utilize the silylene linkage was based on the similarity of the covalent bond radius of tetrahedral silicon (0.117 nm) to that of tetrahedral phosphorus (0.110 nm).[7] Unlike nucleobase residues seen in double-helical DNA in water, however, the two hydrogen-bonding sites of **3** no longer aligned in a well-defined fashion in aprotic solvents. This fact may cause technical problems for evaluating the recognition ability of **2** because flexible ditopic **3** is able to bind to the somewhat flexible **2** not only in the usual 1:1 stoichiometry but also in *m*:*m* and even *m*:*n* manners. Thus, for assessing the adjustability of the ditopic receptors to dinucleotide clearly, also synthesized were rigid thymine−thymine and uracil−uracil derivatives **4**−**7** with a different interbase distance. The interbase distances of these dinucleotides were estimated by MOPAC[8] from that of two carbon centers that were tethered to ethynediyl spacers (C-5 of uracil), although the 1,8-disubstituted naphthalene will cause the two attachments to diverge (Scheme 1).[9]

Hydrogen-bonding abilities of the ferrocene-linked ditopic receptors **1a** and **2** to dinucleotide were compared

SCHEME 2[a]



[a] Reaction conditions: (a) $(Ph_3P)_4Pd$, $Cu(OAc)_2{\cdot}H_2O$, *i*-Pr_2NH, DMF; (b) $Me_2NCON{=}NCONMe_2$, *n*-Bu_3P, THF; (c) $CH_3(CH_2)_3COCl$, Et_3N, CH_2Cl_2; (d) $(Ph_3P)_3RhCl$, DABCO, CH_3CN, EtOH, H_2O; (e) Tf_2O, pyridine; (f) $(Ph_3P)_2PdCl_2$, $Me_3SiC{\equiv}CH$, Et_3N; (g) *n*-Bu_4NF, H_2O, THF; (h) 1-bromooctane, K_2CO_3, DMSO; (i) ICl, MeOH; (j) $Me_3SiC{\equiv}CH$, $(Ph_3P)_2PdCl_2$, CuI, Et_3N; (k) **25**, $(Ph_3P)_2PdCl_2$, CuI, Et_2NH, DMF; (l) **14**, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, DMF; (m) CuI, KI, DMF; (n) **25**, $(Ph_3P)_2PdCl_2$, CuI, Et_3N; (o) **14**, $(Ph_3P)_4Pd$, $Cu(OAc)_2{\cdot}H_2O$, Et_3N, THF; (p) **23**, $(Ph_3P)_2PdCl_2$, CuI, Et_3N, CH_3CN; (q) **19**, $(Ph_3P)_2PdCl_2$, Et_3N, THF.

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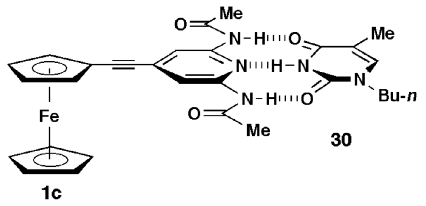
TABLE 1. Association Constants and Free Energy Changes Determined for the Binding of Receptor 1a and 2 to Dinucleotide Derivatives 3−7 in $CDCl_3$/DMSO-d_6 (85:15, v/v) at 25 °C[a]

		dinucleotide derivatives				
receptors		**3**	**4**	**5**	**6**	**7**
1a	K_a (M^{-1})	8.1×10^2	b	1.2×10^3	4.5×10^3	5.8×10^2
	$-\Delta G_{298}$ (kJ/mol)	16.5		17.6	20.8	15.8
2	K_a (M^{-1})	2.0×10^2	4.5×10	2.2×10^2	4.3×10^2	2.8×10^2
	$-\Delta G_{298}$ (kJ/mol)	13.1	9.4	13.4	15.0	14.0

[a] For details, see Experimental Section. [b] Not determined because of precipitation upon mixing.

on the basis of the association constants of the receptors for **3**−**7**. Treatment of **1a** or **2** with 1 equiv of **3**−**7** resulted in several characteristic changes of their ^{1}H NMR spectrum in $CDCl_3$. The NH protons on both receptors and dinucleotide derivatives were largely shifted downfield, reflecting the formation of a multipoint hydrogen-bonded complex. In the case of **3**, several CH protons of **3** showed substantial splits more efficiently compared to those for **3** alone, and noteworthy is that the two Me protons of thymine nuclei of **3** were distinguishable after the complexation. The splitting of the CH protons may be attributed to the increased dissymmetry between the two nucleoside residues of **3** induced by the increased conformational bias upon complexation. The 1:1 stoichiometry was confirmed by the continuous variation (Job) plots[10] that contained a maximum at a mole ratio of 0.5 in each plot for receptors and dinucleotide derivatives under conditions where [receptors] + [dinucleotide derivatives] was held constant. The binding affinity of **1a**, however, was found to be very high in pure $CDCl_3$, so $CDCl_3$/DMSO-d_6 (85:15, v/v) was used as a solvent system for the measurements of the association constants by ^{1}H NMR at 298 K. The association constants were determined by Benesi−Hildebrand analysis[11] and are summerized in Table 1. The dinucleotide derivatives not only of a shorter distance (**5**) but also of a longer one (**7**) showed lower binding affinities to **1a** than that of **6**. In **6**, the distance of 0.38 nm between the π-plane centers of two uracils is close to that between the stacked bases of native dinucleotide (the interval of aromatic bases in double-helical DNA is ca. 0.35 nm).[1] These findings indicated the strict fit of the ferrocene-modified ditopic receptor **1a** to the stacked bases of dinucleotide. Receptor **1a** also bound flexible **3** with a K_a of 8.1×10^2 M^{-1} even in such a polar medium, and thus the free energy change for the complexation ($-\Delta G_{298}$) was 16.5 kJ/mol. This value is ca. 1.8 times larger than that for monotopic counterpart **1c** and 1-*n*-butylthymine (**30**) (Scheme 3; $-\Delta G_{298}$ = 9.0 kJ/mol),[12] indicating that the entropic disadvantage of **1a** upon recognition of the dinucleotide is considerably smaller than that of the ditopic receptors thus far synthesized. The ditopic receptor bearing oxymethylene spacers **2** was also evaluated for its binding affinity. The association constants for the complexation of **2** and **3**−**7**, however, were from ca. half to one-tenth

SCHEME 3[a]



[a] **1c·30**; K_a = 38 M^{-1} ($-\Delta G_{298}$ = 9.0 kJ/mol).

of those for **1a**. Unfortunately, in the case of the ferrocene-linked ditopic receptors, entropic loss resulting from the introduction of the flexible spacer dominated the binding affinity of the receptors.[13]

Next, we examined the effect of modules for connecting two diamidopyridine moieties. The ferrocene module was selected on the basis of its restricted motions and adequate inter-ring spacing, while some polynuclear aromatics such as naphthalene, biphenylene, and anthracene also have well-defined molecular geometry. Thus, ferrocene in **1** was substituted for various polynuclear aromatics to give **8**−**10**; on the other hand, the ethynediyl spacer remained unchanged. The binding affinities of the polynuclear aromatic-linked new ditopic receptors **8**−**10** to dinucleotide derivative **3** were assessed in the same manner as those described above, i.e., ^{1}H NMR in $CDCl_3$/DMSO-d_6 (85:15, v/v). As expected, biphenylene-linked ditopic receptor **9** exhibited the highest binding constant of 1.4×10^3 M^{-1} in the new ditopic receptors ($K_a = 6.8 \times 10^2$ M^{-1} and 9.7×10^2 M^{-1} for **8·3** and **10·3**, respectively). Furthermore, **9** exceeds even ferrocene-linked **1a** in strength of binding to **3**. This remarkably strong affinity of **9** is explained from the enthalpic and entropic standpoints. The distance of the two recognition sites of **9** is just fitted for interacting with the stacked nucleobase residues of **3**, which may take advantage of the full potential of vectorial hydrogen-bonding interactions, while the highly rigid biphenylene linkage yields little entropic loss upon complexation. Native dinucleotides are completely insoluble in aprotic solvents such as $CHCl_3$ and $CDCl_3$. Thus, the extraction of native TpT into such solvents containing the receptors showed further information for the binding affinity of the receptors. In a previous paper, we demonstrated that ammonium salt of TpT was readily solubilized into $CDCl_3$ by addition of **1b** in the presence of 18-crown-6 ether, and the molar ratio of TpT/**1b** was determined to be ca. 1, as judged by integrations of the spectrum.[4] Biphe-

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(12) The association constant for the complex between **1c** and **22** was also determined under the same conditions (K_a = 19 M^{-1}; $-\Delta G_{298}$ = 7.3 kJ/mol). The value implies the similarity of the hydrogen-bonding abilities of thymine derivatives such as **30** and the uracil derivative to the diamidopyridine moiety.

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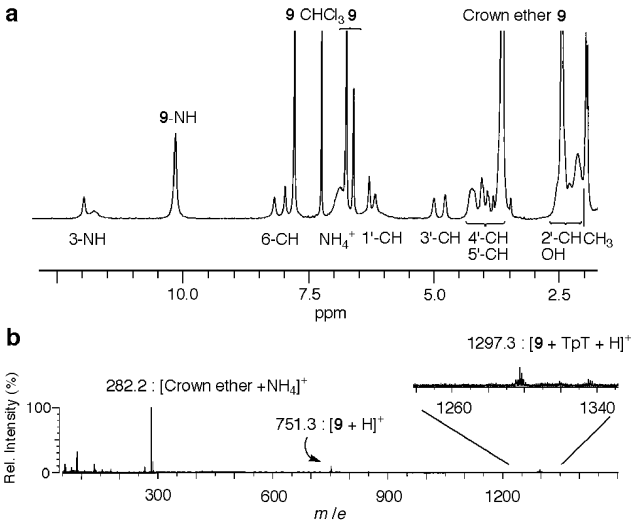

FIGURE 1. (a) ^{1}H NMR spectrum (400 MHz, $CDCl_3$, $(CH_3)_4$-Si) of the complex between TpT and **9**. Signals for receptor **9** are labeled in the spectrum. Assignment of the TpT signals (depicted below the spectrum) are based on those for **3**. (b) FAB mass spectrum (3-nitrobenzyl alcohol) of the complex.

nylene-linked receptor **9** also extracted TpT into $CDCl_3$, and the extractability of TpT by **9** was found to be almost the same as that by the ferrocene-linked **1b** (Figure 1a). The high efficiency of **9** for the extraction is attributed to its suitable ditopic hydrogen-bonding array for the recognition of even native dinucleotide. The strong affinity of **9** to TpT was further corroborated by FAB mass experiments; after the extraction experiment, the peak for the complex (m/e = 1297: **9** + TpT + H^+) appeared (Figure 1b).

In conclusion, we have developed several new ditopic dinucleotide receptors possessing a conformationally well-defined linkage. Biphenylene was found to be at least as effective as ferrocene for linking two hydrogen-bonding sites for the recognition of dinucleotides. The binding affinity of the biphenylene-linked receptor for thymine−thymine dinucleotide derivatives is very high, so native TpT was extracted by the receptors into $CDCl_3$. From this study, we were able to nominate biphenylene for an efficient module for multipoint molecular recognition. Extension of ditopic receptors to more challenging oligonucleotide recognition may necessitate various synthetic motifs of conformationally well-defined linkages as well as specific recognition sites, and such an approach is now under way.

Experimental Section

Instrumentation. ^{1}H NMR spectra were recorded at 400 or 300 MHz, and ^{13}C NMR spectra were recorded at 100 or 75 MHz. For FAB mass experiments, Xe was used as the atom beam accelerated to 8 keV. Melting points are uncorrected.

Materials. Ferrocene-linked ditopic receptor **1a**,**b**,[4] monotopic receptor **1c**,[13] thymine photodimer **4**,[14] 1,1′-diiodoferrocene (**11**),[15] 1,1′-bis(hydroxymethyl)ferrocene (**12**),[16] 2,6-diacetamido-4-ethynylpyridine (**13**),[13] 2,6-diacetamido-4-pyridone (**15**),[17] 4-allyloxy-2,6-diaminopyridine (**16**),[18] 1,8-diiodonaphthalene (**26**),[19] 1,8-dibromobiphenylene (**27**),[20] 1,8-diethynylanthracene (**29**),[21] and 1-*n*-butylthymine (**30**)[22] were prepared according to respective literature procedures. The preparation of lipophilic TpT analogue **3** was carried out from 5′-*O*-(*tert*-butyldimethylsilyl)thymidine and 3′-*O*-(*tert*-butyldimethylsilyl)thymidine by a modification of Ogilvie's methods.[23] Synthetic procedures for all new compounds are given in Supporting Information. Other starting materials were commercially available.

Methods for the Evaluation of Stoichiometry and Association Constants. All binding assays were carried out below the concentration so that the self-association of each substrates is negligible under the conditions of the measurements.

Job's plot of [complex] vs mole fraction of the receptor for the complexation of the receptor and **3**−**7**, **22**, and **30** was obtained by ^{1}H NMR (270 MHz) in $CDCl_3$/DMSO-d_6 (85:15, v/v) at 25 °C under conditions where [receptor] + [**3**−**7**, **22**, and **30**] was maintained at 0.5 or 1.0 mM.[10] The concentration of a complex in $CDCl_3$ was evaluated from $\Delta\delta_{obsd}$ for the receptor-NH according to the equation [complex] = [receptor]$_t$ ($\Delta\delta_{obsd}/\Delta\delta_{sat}$) (t = total; obsd = observed; sat = saturated).

Association constants (K_a) were determined by ^{1}H NMR under Benesi−Hildebrand conditions at 25 °C in $CDCl_3$/DMSO-d_6 (85:15, v/v).[11] The chemical shifts of the receptor-NH protons (δ_{NH}) were monitored in the presence of a 10−20-fold molar excess of **3**−**7**, **22**, and **30**. The concentration of the receptors was adjusted to obtain the appropriate complexation ratio (20−80%). In every case, the double reciprocal plots according to the equation $1/\Delta\delta_{obsd} = 1/\Delta\delta_{sat} + 1/\Delta\delta_{sat}K_a[\text{receptor}]_t$ gave good linearity with a correlation coefficient $r \geq 0.99$: [**1a**] = 0.1 (for **3** and **5**) and 0.05 (for **6** and **7**) mM; [**1c**] = 2.0 mM for **22** and **30**; [**2**] = 1.0 (for **4**), 0.2 (for **7**), 0.15 (for **3** and **5**), and 0.1 (for **6**) mM; [**8**−**10**] = 0.1 mM for **3**.

Extraction Experiments. A suspension of TpT (solid; 8.9 × 10^{-3} mmol), ditopic receptors (**1b** or **9**, 7.0 × 10^{-3} mmol), and 18-crown-6 ether (1.4 × 10^{-2} mmol) in $CDCl_3$ (0.7 mL) was stirred at 25 °C for 1 h. The suspension was filtered, and the filtrate was analyzed directly by ^{1}H NMR. The molar ratio (TpT/receptor) of the solution was determined by integrations of the spectrum.

Supporting Information Available: Experimental procedures for the synthesis and ^{1}H NMR spectra for all new compounds containing **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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