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Four-Way-Branched DNA−Porphyrin Conjugates for Construction of Four Double-Helix-DNA Assembled Structures

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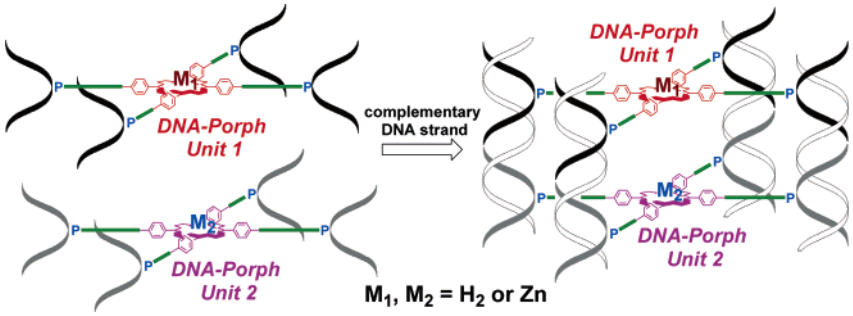

DNA−porphyrin conjugates having four DNA strands were designed and synthesized. Four double helices were assembled using two DNA−porphyrin conjugates and their complementary strands, and the formation of the four double-helix assembled structures with the two DNA−porphyrin units was examined by gel electrophoresis and spectroscopic analysis. The interaction between two porphyrin chromophores in the complex was investigated by measurement of fluorescence lifetimes, and the singlet energy transfer between the two different phorphyrin units (Zn-porphyrin and H_2-porphyrin) was observed. These results indicate that multiple and different porphyrin chromophores can be integrated into the DNA structures by programming the sequences of the DNA strands.

Introduction

Programmed molecular assembly for creating the desired materials from specific components is one of the most crucial issues in the fields of supramolecular chemistry, materials science, and nanotechnology.[1−3] For the desired arrangment of the functional molecules, molecular components having reliable recognition ability and well-defined structure are required. Oligodeoxyribonucleotide (DNA) is a good candidate for this purpose, because it can control the precise and periodical molecular assembly with various combinations of the sequences. Precise and programmed assembly of DNA makes it possible to regulate selective and multiple organic and inorganic reactions which proceed by stepwise recognition of DNA and subsequent chemical reactions.[4] In terms of the structural feature of double-helix DNA, the studies aiming at construction of one-dimensional and multidimensional nanostructures have been done by employing structurally controlled DNA[5,6] and chemically modified DNA.[7,8] Therefore, the selective and geometrical assembly of the functional molecules using the assistance of DNA can be a promising approach for

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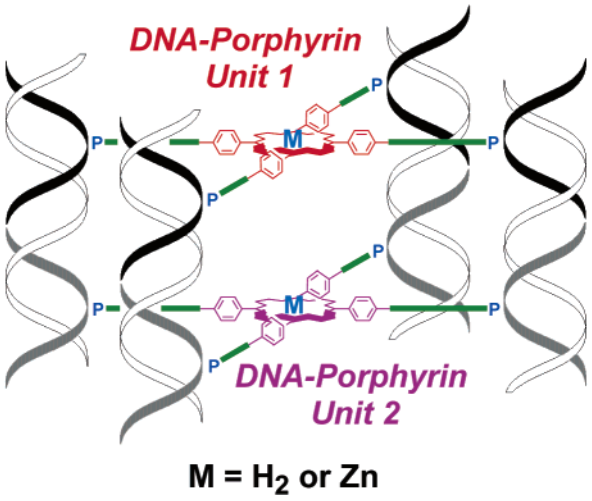

FIGURE 1. Four-DNA double-helix assembled structure containing two porphyrin derivatives. Free base porphyrin (H_2-Porph) and zinc porphyrin (Zn-Porph) derivatives were incorporated into the DNA structures.

creation of periodic arrays of functional molecules in the supramolecular DNA structures.

In this report, we designed and synthesized DNA−porphyrin conjugates in which four DNA strands are connected by a porphyrin derivative and characterized the four double-helix assembled DNA structures, which consisted of two DNA−porphyrin conjugates and four complementary strands (Figure 1). We employed a tetraphenylporphyrin derivative as a connector for assembling four double-helix DNA strands (Scheme 1). Two different porphyrins such as free base (H_2-Porph) and Zn-porphyrin (Zn-Porph) that show different photochemical properties were incorporated into the DNA structure. The four double-helix assembled DNA structures containing the heterogeneous porphyrin dimer were constructed, and the arrangements of these porphyrins were programmed by the sequence of the complementary strand.

Results and Discussion

Synthesis of DNA−Porphyrin Conjugates. To construct the four DNA double-helix assembled structure, a DNA−porphyrin conjugate DNA−H_2-Porph was synthesized (Scheme 1). We employed 10-mer DNA strands for the DNA−porphyrin conjugates, and the linker of the porphyrin derivative was connected to the central phosphorus atom of the 10-mer strand. Because the spacing of 10 bases between the two linkers of the porphyrin connectors corresponds to one helical turn, the linkers can be placed on the same side of the duplex for alignment. A cystamine tether was introduced via a phosphoramidate linkage according to the reported method.[7b−d,9] Two adjacent diastereomer peaks appeared on HPLC, and the faster and slower eluting diastereomers are denoted as diastereomers A and B, respectively (Figure S2, Supporting Information).[7b−d] The sequences of the synthetic oligonucleotides are CGGCTpACTCC (**1**) and GTGCTpAGCGG (**2**), with p denoting the position of a phosphoramidate where a linker of the porphyrin derivative is attached.

The synthetic route for the DNA−porphyrin conjugates with four DNA strands (DNA−H_2-Porph and DNA−Zn-Porph) is shown in Scheme 1. Synthesis of a porphyrin-maleimide derivative is described in Supporting Information. We employed a two-step synthesis for the preparation of DNA−H_2-Porph. Because of the low solubility of the porphyrin-maleimide derivative in the DMSO−water solvent, it was difficult to control the ratio of the porphyrin-maleimide and DNA in the suspension of the reaction mixture. Therefore, a DNA−porphyrin conjugate with one single-strand DNA (Porph−DNA_1) was first synthesized using excess porphyrin-maleimide, and the remaining DNA was then introduced into it for preparation of the DNA−porphyrin conjugate with four DNA strands (Porph−DNA_4; DNA−H_2-Porph).

The diastereochemically pure oligonucleotides (DNA−cystamine) were treated with DTT for the preparation of thiol-tethered DNA (DNA−SH). Excess porphyrin-maleimide derivative was added to the DNA−SH for linking the DNA strand to give Porph−DNA_1 (Scheme 1). After HPLC purification, the Porph−DNA_1 was treated with 3 equiv of DNA−SH to give Porph−DNA_4 (DNA−H_2-Porph). The molecular weights of the HPLC-purified DNA−H_2-Porph conjugates were directly identified by MALDI-TOF mass spectroscopy. The DNA−H_2-Porph conjugates were also characterized by polyacrylamide gel electrophoresis (PAGE) and UV−vis spectroscopy. According to a denaturing PAGE analysis, all the purified DNA−H_2-Porph conjugates had a mobility similar to that of 40-mer single-strand DNA, and a red fluorescence emission was observed with photoirradiation at 365 nm by a transilluminator (Figure S3, Supporting Information). The number of DNA strands attached to the porphyrin derivative in the first step was also identified by comparing the absorbances of the Soret bands and DNA (260 nm) with those of Porph−DNA_4 (Porph−DNA_4) (Figure S3). When the Soret bands were normalized, the absorbance at 260 nm of the DNA−porphyrin conjugates in the first step was one-fourth that of DNA−H_2-Porph. We identified the DNA−porphyrin conjugate purified in the first step as a conjugate having one DNA strand (Porph−DNA_1). Incorporation of Zn into porphyrin-maleimide derivative was easily achieved using $Zn(OAc)_2$ (Supporting Information). Using the same method, excess $Zn(OAc)_2$ was added to the DNA−H_2-Porph, and the product was purified by reversed-phase HPLC. The product was identified by the characteristic Q-bands of the porphyrin moiety similar to that of the Zn−porphyrin-maleimide (Figure 2 and S1, Supporting Information).

Complex Formation. The complex formation of the DNA−porphyrin conjugates (units) with their complementary strands was characterized by stoichiometric analysis and nondenaturing PAGE analysis. The sequence of the 20-mer DNA strand complementary to strands **1** and **2** used here is 5′-GGAGTAGCCGC-

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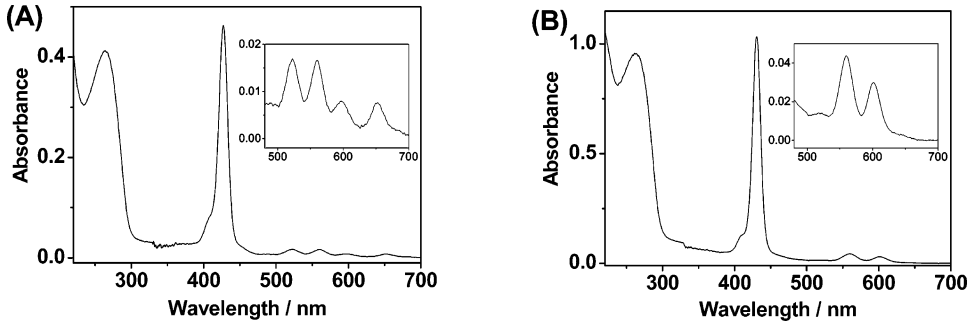

FIGURE 2. UV−vis spectra of **1A−H_2-Porph** (A) and **1A−Zn-Porph** (B) in 10 mM Tris-HCl (pH 7.6). Insets are expanded regions of Q-bands.

CGCTAGCAC-3′. First, to determine the stoichiometry of the complex formation, the molar ratio of the two DNA−porphyrin units and their complementary strand was examined by monitoring the absorption changes at 260 nm by changing the ratio of the DNA−H_2-Porph and the complementary strand. When 4 equiv of the 20-mer complementary strand were added to **1-H_2−Porph** and **2-H_2−Porph**, the absorption of the complex reached a minimum (Figure S5, Supporting Information), indicating that two DNA−porphyrin units form a complex with the four equivalent complementary strands. Second, the complex formation of the two DNA−porphyrin units with the complementary strand was examined by nondenaturing PAGE analysis (Figure 3). When the complementary strand was added to one DNA−H_2-Porph unit, a slight complex formation was detected (lanes 2 and 4). In contrast, when two DNA−porphyrin units were annealed with the complementary strand, the complexes appeared clearly and migrated slower than a 100-mer duplex DNA marker (lanes 3 and 5). These complexes contain a total of 80 base pairs and are expected to form columnar structures of 6.8 nm height and of 10 nm diameter. These noncanonical DNA structures would decrease the mobility on the gel as compared to a linear DNA marker of 80 base pairs. The relatively large distribution of the complex on the gel (lanes 3 and 5) may be attributed to the flexible structure and the isomers generated from the thiol−maleimide coupling.

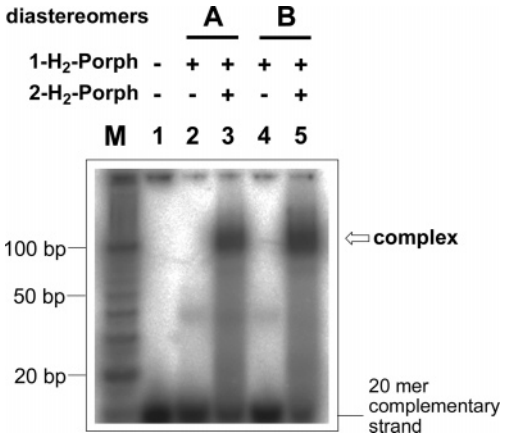

FIGURE 3. Nondenaturing PAGE (10%) of the complexes containing the DNA−porphyrin units and their complementary strand in a pH 7.6 solution containing 0.1 M NaCl. The 5′ terminal of the 20-mer complementary strand was ^{32}P-labeled.

Characterization of the DNA Structures. The stabilities of the DNA structures were examined by melting temperature (T_m) measurements (Table 1). Complexes with one DNA−porphyrin unit and 4 equiv of a complementary strand showed low T_m values compared to the native duplex. Similar results were also observed for the T_m values of the cross-linked DNAs in which two

SCHEME 1. Synthesis of DNA−Porphyrin Conjugates DNA−H_2-Porph and DNA−Zn-Porph

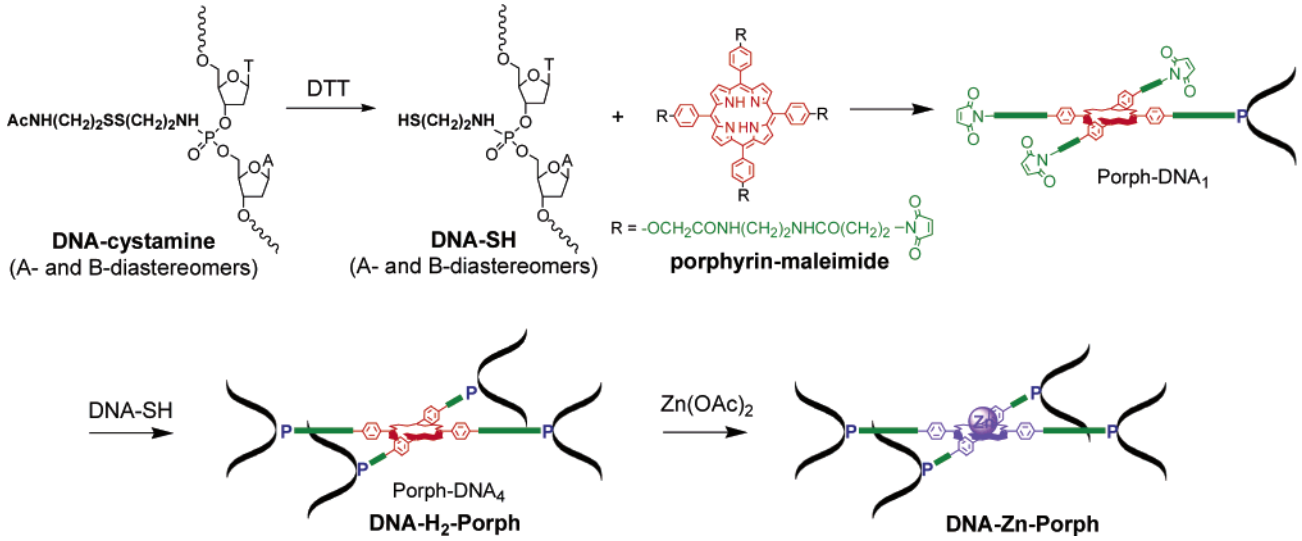

TABLE 1. Stabilities of the DNA Structures Containing One or Two DNA−Phorphyrin Units and Their Complementary Strand[a]

DNA	0.1 M NaCl		1.0 M NaCl	
	T_m (°C)	ΔT_m (°C)	T_m (°C)	ΔT_m (°C)
1A−H$_2$-Porph	24.3	−23.1	35.5	−16.8
1B−H$_2$-Porph	30.3	−17.1	37.5	−14.8
1 (native)	47.4		52.3	
1A−H$_2$-Porph + 2A−H$_2$-Porph	38.5	−6.5	49.2	−7.2
1B−H$_2$-Porph + 2B−H$_2$-Porph	42.0	−3.0	50.9	−5.5
1 + 2 (native)	45.0		56.4	

[a] Melting temperatures (T_m (°C)) were obtained with different concentrations of NaCl (0.1 and 1.0 M). Conditions: 0.5 μM DNA−porphyrin units, 2.0 μM complementary DNA, 10 mM Tris-HCl (pH7.6), and 0.1 or 1.0 M NaCl.

DNA strands were connected by disulfide and maleimide linkers.[7b,c] The assembly of the double-helix DNAs using one DNA−porphyrin unit would be entropically unfavorable because the assembled double helixes can freely rotate around the linkers of the porphyrin connector. In contrast, in the cases of the complexes containing two DNA−porphyrin units, the complexes were largely stabilized compared to those with one DNA−porphyrin unit, indicating that the two DNA−porphyrin units cooperatively function to stabilize the DNA structures. In addition, the stereochemical effects of the phosphoramidates were observed, and the complexes containing diastereomer B were thermally more stable than those with diastereomers A.[7b,c]

The backbones of the DNA structures were characterized by circular dichroism (CD) spectroscopy (Figure S7, Supporting Information). Both the DNA structures containing two DNA−porphyrin units with diastereomer A or B formed typical B-form double-helix structures.[10] In the DNA structure with diastereomer A, the intensities of the positive and negative bands (280 and 260 nm, respectively), which are characteristic for a double-helix structure, were almost the same as those of the native duplex structures. In the case of the diastereomer B, the intensity of the negative band was slightly decreased compared to that of the native duplex, indicating that diastereomer B would alter the B-form DNA structures. An induced CD band originating from the porphyrin was also observed around 420 nm in both DNA structures.

Photochemical Properties of Porphyrin Derivatives in the DNA Structures. To characterize the relative conformations of the porphyrin chromophores in the DNA structures, we measured UV−vis spectra of the two DNA−porphyrin conjugates with a 20-mer complementary strand (Figure S8, Supporting Information). The wavelength shifts of the Soret band and Q-bands were modest (within 1 nm) when the complementary strand was added, indicating that the interactions between duplex DNA and porphyrin and between two porphyrin chromophores are very weak.[11]

To examine the details of the interaction between the porphyrin chromophores, the DNA−Zn-Porph unit was incorporated into the DNA structures. We measured the fluorescence lifetimes[12] of the porphyrin derivatives in the DNA structures containing **1−H$_2$-Porph/2−H$_2$-Porph**, **1−Zn-Porph/2−H$_2$-Porph**, and **1−Zn-Porph/2−Zn-Porph** (Table 2). The fluorescence lifetimes of Zn-porphyrin in the **1−Zn-Porph/2−H$_2$-Porph** complex and that of Zn-porphyrin in the **1−Zn-Porph/2−Zn-Porph** complex were compared. From these analyses, singlet energy transfer from ^{1}**1−Zn-Porph*** to **2−H$_2$-Porph** was observed, and the singlet energy transfer rate constants were calculated to be 1.3×10^8 s^{-1} for both DNA structures containing **1A−Zn-Porph/2A−H$_2$-Porph** and **1B−Zn-Porph/2B−H$_2$-Porph**.[12] These results indicate that the two heterogeneous porphyrin molecules (H$_2$-Porph and Zn-Porph) are integrated into the DNA structures. The rate of the energy transfer obtained here is large if two porphyrin derivatives are separated by 3.4 nm, which corresponds to the distance of 10 base pairs between two phosphoramidate linkages in the duplex DNA.[12] Although the linkers connecting porphyrin and DNA are long enough for two porphyrin chromophores to approach by less than 3.4 nm, the distance between the two porphyrins remains unclear in the present study. Singlet oxygen formation by excitation of the Zn-porphyrin may be considered. No detectable decomposition of DNA was observed on HPLC under the fluorescence lifetime measurements here.

TABLE 2. Fluorescence Lifetimes (τ) for Various DNA Structures Containing H$_2$-Porphyrin and Zn-Porphyrin Units

DNA	τ (ns)
1A−H$_2$-Porph + 2A−H$_2$-Porph	6.8
1B−H$_2$-Porph + 2B−H$_2$-Porph	6.3
1A−Zn-Porph + 2A−H$_2$-Porph	1.4
1B−Zn-Porph + 2B−H$_2$-Porph	1.4
1A−Zn-Porph + 2A−Zn-Porph	1.7
1B−Zn-Porph + 2B−Zn-Porph	1.7

Conclusion

We synthesized DNA−porphyrin conjugates with diastereochemically pure phosphoramidates and characterized the formation of four double-helix assembled structures with the DNA−porphyrin units. Two porphyrin units (both homogeneous and heterogeneous combinations) are integrated in the DNA structures by following the DNA sequences. The cofacial porphyrin dimers[12−17] can be a host for various guests such as bispyridine

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derivatives,[14] amino acids,[15] viologen,[16] and fullerene.[17] The DNA structures we created here provide a scaffold for a host−guest system using these kinds of guests, and the structures may be expanded using multiple DNA−porphyrin conjugate units and complementary DNA strands.

Experimental Section

Synthesis of DNA−Porphyrin Conjugates (DNA−H_2-Porph) and DNA−Zn-Porphyrin Conjugates (DNA−Zn-Porph). A disulfide tether was introduced via a phosphoramidate linkage in the center of the 10-mer single-strand DNA according to the previously reported method.[7b,c,9] Two adjacent diastereomer peaks (diastereomers A and B) were separated on reversed-phase HPLC [linear gradient using 2−15% acetonitrile/water (20 min) containing 50 mM ammonium formate, C18 reversed-phase column (7.5 × 150 mm), 2.0 mL/min, 260 nm]. The purified diastereochemically pure oligonucleotide (10 nmol) was reduced in a solution containing 50 mM Tris-HCl (pH 8.0) and 10 mM DTT at 50 °C for 30 min. The thiol-attached DNA (DNA−SH) was purified by reversed-phase HPLC (the same conditions as described above). The DNA−SH was treated with excess porphyrin-maleimide derivative (Supporting Information) in a 20% DMSO/water solution containing 40 mM ammonium formate (pH 6.5) at 50 °C for 2 h. A DNA−porphyrin conjugate with one DNA strand (Porph−DNA_1) was purified by HPLC [the same conditions as described above except for a linear gradient using 2−50% acetonitrile/water (20 min)]. MALDI-TOF-MS: calcd for Porph−DNA_1 (**1A**), 4705 $[M + H]^+$; found, 4706. The purified Porph−DNA_1 was treated with 3 equiv of DNA−SH in 50 mM ammnomium formate (pH 6.5) at 37 °C overnight. A DNA−porphyrin conjugate with four DNA strands (Porph−DNA_4; DNA−H_2-Porph) was purified by HPLC [a linear gradient using 2−50% acetonitrile/water (20 min)] and finally lyophilized. MALDI-TOF-MS: calcd for **1-H_2-Porph**, 13 776; found for **1A−H_2-Porph**, 13 782; **1B−H_2-Porph**, 13 787; calcd for **2-H_2-Porph**, 14 256; found for **2A−H_2-Porph**, 14 260; **2B−H_2-Porph**, 14 273.

Introduction of zinc ion into the center of the DNA−porphyrin conjugates was carried out in a 100 μL solution containing DNA−Porph conjugate (2 nmol), 0.1 mM of Zn-$(OAc)_2$, and 10 mM Tris-HCl (pH 7.6). After incubation at room temperature for 1 h, the excess $Zn(OAc)_2$ was removed by HPLC [a linear gradient using 2−50% acetonitrile/water (20 min)]. The purified DNA−Zn-Porph was lyophilized, and incorporation of Zn ion was confirmed by UV−vis spectroscopy.

Nondenaturing Polyacrylamide Gel Electrophoresis. Samples (20 μL) containing 0.5 μM of DNA−Porph, 2 μM of ^{32}P-labeled 20-mer complementary strand, 10 mM Tris-HCl (pH 7.6), and 0.1 M NaCl were annealed by a thermal cycler from 85 to 15 °C at a rate of −0.2 °C/min. Glycerol (40%, 4 μL) was added to the samples, and the samples were loaded onto a 10% nondenaturing polyacrylamide gel. After the electrophoresis, the gel was visualized by an imaging analyzer.

Melting Temperature (T_m) Measurements. Thermal denaturation profiles were obtained on a UV−vis spectrophotometer equipped with a temperature controller. A solution containing 0.25 μM porphyrin−DNA, 1.0 μM complementary DNA, 10 mM Tris-HCl (pH 7.6), and 0.1 or 1.0 M NaCl was heated at 85 °C in a quartz cell and then cooled to 10 °C at a rate of −1.0 °C/min. Measurements were carried out by heating from 10 to 80 °C at a rate of 1.0 °C/min, and the absorption change of DNA was monitored at 260 nm. The first derivative calculated from the melting profile was used to determine the T_m value.

Fluorescence Lifetime Measurements. Fluorescence decays were acquired by the single-photon counting method using a streak scope (Hamamatsu Photonics, C4334-01). Samples were excited with a second harmonic generation (430 nm) of a Ti:Sapphire laser (Spectra Physics, Tsunami 3941-M1BB) (fwhm 100 fs). Measurements were carried out at 0 °C in a solution containing 0.5 μM DNA−Porph units, 2.0 μM complementary DNA, 10 mM Tris-HCl (pH 7.6), and 1.0 M NaCl. Singlet energy transfer rates (k_{ET}) were calculated using the equation, $k_{ET} = (1/\tau_F - 1/\tau_{F0})$, where τ_F is the fluorescence lifetime of the Zn−Porph in the Zn−Porph/H_2−Porph complex and τ_{F0} is the fluorescence lifetime of the Zn−Porph in the Zn−Porph/Zn−Porph complex.

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Supporting Information Available: Experimental procedure of synthesis and characterization of porphyrin derivatives and DNA−porphyrin conjugates, stoichiometric analysis, melting profiles, CD spectra, and UV−vis spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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