DOI: 10.1002/chem.200701835

Mechanism of Charge Separation in DNA by Hole Transfer through Consecutive Adenines

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Abstract: To investigate the mechanism of charge separation in DNA with consecutive adenines adjacent to a photosensitizer (Sens), a series of naphthalimide (NI) and 5-bromouracil (^{br}U)-modified DNAs were prepared, and the quantum yields of formation of the charge-separated states (Φ) upon photo-excitation of the Sens NI in DNA were measured. The Φ was modulated by the incorporation site of ^{br}U, which changes the oxidation potential of its complementary A through hydrogen bonding and the hole-transfer rates between adenines. The results were interpreted as charge separation by means of the initial charge transfer between NI in the singlet excited state and the second- and third-nearest adenine to the NI. In addition, the oxidation of the A nearest to NI leads to the rapid charge recombination within a contact ion pair. This suggests that the charge-separation process can be refined to maximize the Φ by putting a redox-inactive spacer base pair between a photosensitizer and an A–T stretch.

Keywords: charge separation · charge transfer · DNA · hole transfer · photolysis

Introduction

The efficient conversion of photon energy into chemical potentials, in the form of a long-lived charge-separated state, is highly desired in molecular-scale optoelectronics, sensor design, and other areas of nanotechnology.[1–7] To produce a long-lived charge-separated state with high quantum yield (Φ), it is important to prevent the energy-wasting charge recombination. In natural photosynthesis, long-lived charge separation is ensured by the large distance between the special pair and the final quinone acceptor, which leads to a slow charge recombination. At the same time, it also makes the single-step photoinduced electron transfer from the special pair to the final quinone very inefficient. Therefore, a high Φ is achieved by forming the final state via a series of short-range, fast hopping processes.[5]

Duplex DNA forms a one-dimensional π-stacked array of nucleobases, and intensive studies have revealed that a positive charge (hole) generated in DNA can migrate along the DNA by sequential hole transfer between nucleobases to form a long-lived charge-separated state.[8–16] Though there has been no spectroscopic evidence of the formation of the charge-separated state in DNA due to excess electron transfer, the electron has been demonstrated to move along DNA to some extent.[16–18] The photoinduced charge generation and subsequent charge-transfer process in DNA through the nucleobases is of particular interest because charge-transfer rates are highly sensitive to the presence of a mismatch, and so single nucleotide polymorphisms (SNPs) can be determined from the charge-transfer rates.[19–21] Therefore, biosensors that work on the principle of DNA charge transfer have potential application for analysis of SNPs.[22–26] Based on well-established synthetic methods, DNA can be used to assemble natural and various artificial nucleobases of different oxidation potentials within a defined double-helical structure. Therefore, DNA provides a unique system to study the mechanism of sequential charge-transfer processes during the charge separation.

DNA consists of two building blocks, adenine–thymine (A–T) and guanine–cytosine (G–C) base pairs, in which the G–C base pair has a lower oxidation potential.[27,28] Recently, we have shown that photoinduced electron transfer from an A–T base pair in consecutive A–T sequences to a photosensitizer (Sens) produces a long-lived charge-separated state in DNA,[20,21,29–35] in which the subsequent sequential hole-transfer process between the A–T base pairs helps to separate a hole from the Sens radical anion ($Sens^{\bullet-}$) before trapping at the G–C base pair to form the G radical cation ($G^{\bullet+}$). Because the charge recombination proceeds mainly

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by a single-step mechanism between Sens$^{\bullet-}$ and G$^{\bullet+}$, the charge-recombination rate significantly decreases as the number of A–T base pairs between the Sens and G nearest to it increases. Hence, a long-lived charge-separated state can be achieved for DNA having a long A–T stretch between the Sens and G.

So far, several Sens have been demonstrated to trigger the one-electron oxidation of DNA. Among these Sens, the formation of the long-lived charge-separated state was spectroscopically observed for stilbene (Lewis's group),[12,36–40] naphthaldiimide,[29,30] naphthalimide (NI),[20,21,32–35] and diphenylacetylene[31] (our group). All of these Sens can oxidize A and produce the charge-separated state based on hole transfer between the adenines. However, in most cases, the yield was not sufficiently high ($\Phi < 3.5\,\%$) due to the charge-recombination process before a hole is trapped at a hole trap, which limits the application of DNA in photoelectrochemical sensors and devices. To achieve a high Φ in DNA, it is important to further understand the dynamics of the charge-separation process.

Here, to further investigate the charge separation by hole transfer between the adenines, a series of naphthalimide (NI) and 5-bromouracil (^{br}U)-modified DNAs were synthesized. NI serves as a Sens to trigger electron transfer from A to NI upon photoirradiation and ^{br}U worked to increase the oxidation potential of its complementary base A through hydrogen bonding, that is, the oxidation potential of the A–^{br}U base pair becomes slightly higher than that of the A–T base pair. The van der Waals radius of bromine (2.00 Å) is similar to the size of a methyl group (1.95 Å). Therefore, substitution of T by ^{br}U increases the oxidation potential of its pairing A without significantly affecting the global double-helical DNA structure. An A–^{br}U base pair was expected to reduce the hole-passing through it because of the slower hole-transfer rate from A$^{\bullet+}$–T to A–^{br}U relative to that from A$^{\bullet+}$–^{br}U to A–T. Interestingly, the Φ was sensitive to the substitution position of ^{br}U and the Φ increased not only for DNA in which A–T nearest to NI is replaced by A–^{br}U, but also for DNA having A–^{br}U at the second-nearest position to NI. These results suggested that the charge-separated state is formed through the initial charge generation on the second- and third-nearest adenine to the NI instead of the oxidation of A adjacent to NI.

Results and Discussion

To gain some insight into the charge-separation process by means of hole transfer through consecutive adenines, the charge-separation process was first examined for a series of DNAs in which the oxidation potential of each A base in an A–T stretch between the Sens and a hole trap is systematically increased. For an ideal case, the DNA structure should not change upon altering the oxidation potential of A. Previously, we demonstrated that the oxidation potential of G can be controlled through hydrogen bonding by introducing a substituent on the base-pairing cytosine, and that a bromine substitution of the cytosine C5 hydrogen in the C–G base pair causes a 24-mV increase in the oxidation potential of G.[34,41] Similarly, the oxidation potential of A in the A–T base pair was expected to increase by replacing the C5 methyl group of T with a bromine group to form an A–^{br}U base pair. Because the van der Waals radius of bromine is similar to that of a methyl group, the oxidation potential of the A–^{br}U base pair can be increased from that of the A–T base pair without substantially alternating the global DNA double-helical structure. To test this hypothesis, the ionization potentials of G–C, G–^{br}C, A–T, and A–^{br}U base pairs were calculated at the 3-21G(*) level, as shown in Table 1.

Table 1. Estimated ionization potentials (IP)[a] and relative oxidation potentials (E_{rel})[b] of base pairs.

	IP [eV]	E_{rel} [mV]
G–C	7.20	0[b]
G–^{br}C	7.27	+24[b]
A–T	8.19	0[c]
A–^{br}U	8.27	+14[c]

[a] Ionization potentials were estimated by applying Koopmans' theorem. The values are the HOMO energies of 3-21G(*) single-point calculations. [b] E_{rel} for G (ref. [34]). [c] E_{rel} for A derived from the equilibrium constant (k_{-br}/k_{br}) for hole transfer between the A–T and A–^{br}U base pairs.

It was demonstrated that, similar to the results of the G–C base pair, the oxidation potential of A can be increased by introducing the electron-withdrawing group, bromine, on its base-pairing T. Hence, we synthesized a series of NI-modified DNAs in which the A–T base pair in an A–T stretch was systematically changed to the A–^{br}U base pair (Figure 1).[42]

The quantum yields of formation of the charge-separated states (Φ) in the NI- and ^{br}U-modified DNA were measured by nanosecond time-resolved transient absorption measurements. Because ^{br}U and all other nucleobases absorb below 340 nm,[17,18,43–45] it is possible to selectively excite the NI by laser irradiation at 355 nm. Laser irradiation of the NI- and ^{br}U-modified DNA leads to absorption with a peak at 400 nm assigned to NI$^{\bullet-}$ immediately after the flash, demonstrating the formation of the charge-separated state (Figure 2).[20,21,32–35] The NI$^{\bullet-}$ decayed in the timescale of tens of microseconds, consistent with a charge recombination through the single-step mechanism between G$^{\bullet+}$ and NI$^{\bullet-}$ separated by five intervening A–T base pairs. The Φ was determined from the intensity of the 400-nm band by using the transient absorption of the triplet benzophenone as an actinometer (Table 2). Interestingly, the Φ changed depending on the site of the substitution of ^{br}U. When an A–T base pair in an A–T stretch was specifically changed to an A–^{br}U base pair to increase the oxidation potential of A, the hole-transfer rates from A$^{\bullet+}$–T to A–^{br}U and A$^{\bullet+}$–^{br}U to A–T are expected to decrease and increase, respectively, compared to that between the A–T base pairs, according to the Rehm–Weller equation. Therefore, the A–^{br}U base pair works as a barrier to attenuate hole-passing through it. In particular, when the A–T base pair nearest to NI was

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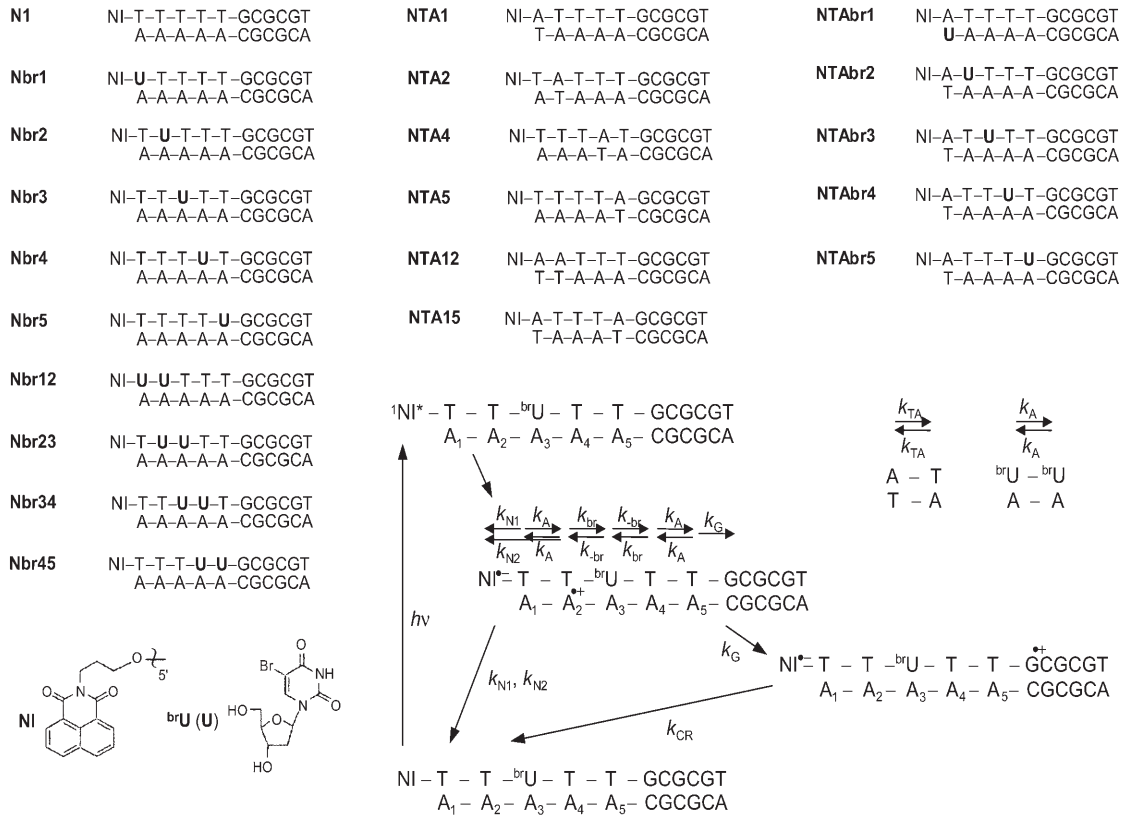

Figure 1. Structures of naphthalimide (NI), 5-bromouracil ($^{br}U = \mathbf{U}$), sequences of NI and ^{br}U-modified DNA, and kinetic scheme for photoinduced one-electron oxidation of A, hole transfer from A–T pair to A–T pair (k_A), A–T pair to A–^{br}U pair (k_{br} and k_{-br}), A–T pair to T–A pair (k_{TA}), A–^{br}U pair to A–^{br}U pair (k_A), hole trapping (k_G), and charge recombination (k_{N1}, k_{N2}, and k_{CR}) in DNA.

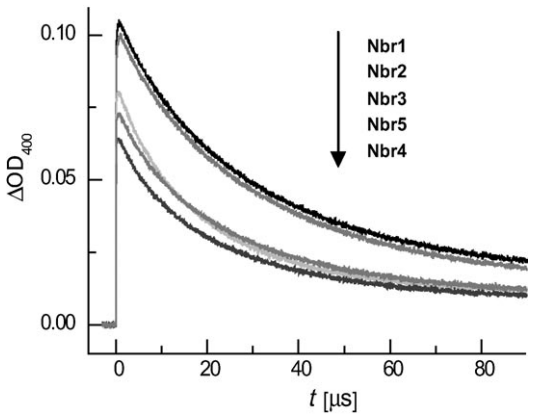

Figure 2. Time profiles of the transient absorption of $NI^{\bullet-}$ monitored at 400 nm during the 355-nm laser flash photolysis of an Ar-saturated aqueous solution of NI- and ^{br}U-modified DNA.

Table 2. Quantum yield (Φ)[a] and lifetime (τ)[b] of the charge-separated state for NI- and ^{br}U-modified DNA.

DNA	Φ[a] [10^{-2}]	τ[b] [μs]
N1	3.1	25
Nbr1	4.0	29
Nbr2	3.9	29
Nbr3	3.1	20
Nbr4	2.5	21
Nbr5	2.8	23
Nbr12	4.1	37
Nbr23	3.7	24
Nbr34	2.5	18
Nbr45	2.1	21
NTA1	4.4	106
NTA2	2.1	29
NTA4	0.2	19
NTA5	0.8	21
NTA12	1.2	65
NTA15	0.1	83
NTAbr1	5.2	143
NTAbr2	5.0	86
NTAbr3	3.3	133
NTAbr4	3.2	103
NTAbr5	3.2	122

[a] Estimated error was less than ±10%. [b] Decay lifetime of $NI^{\bullet-}$.

changed to the A–^{br}U base pair, the A–^{br}U base pair serves as a block for a hole residing on the second A (A_2), preventing it going back to the first A (A_1), therefore, the Φ of **Nbr1** is expected to increase relative to that of **N1**, which does not have an A–^{br}U base pair. Actually, the Φ value was higher for **Nbr1** than for **N1**. As for the other A–T base pairs, the change to the A–^{br}U base pair is likely to decrease the Φ value because an A–^{br}U base pair reduces the hole-passing through it. As expected, a decrease in the Φ was observed for **Nbr3**, **Nbr4**, and **Nbr5**. However, substitution of an A–^{br}U base pair at the second-nearest position to NI

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(**Nbr2**) unexpectedly resulted in an increase in the Φ value. This was also the case for DNAs containing two A–^{br}U base pairs, in which not only **Nbr12**, but also **Nbr23**, resulted in an increase in Φ, whereas a decrease in Φ was observed for **Nbr34** and **Nbr45** relative to **N1**.

To elucidate this paradox, we next prepared a series of DNAs in which each A–T base pair was inverted as a T–A base pair. Because a hole moves much faster through a consecutive A–T sequence than through an A–T/T–A repeat sequence due to the smaller distance and direct stacking between adenines,[32] the inversion of the A–T base pair in an A–T stretch was expected to decrease the Φ. Of special interest, the inversion of the A–T base pair adjacent to NI led to an increase in Φ (**NTA1**), in spite of the unfavorable decrease in the hole-transfer rate from $A_1^{\bullet+}$ to A_2. On the other hand, the inversion of the other A–T base pairs resulted in a significant decrease in Φ, as expected (**NTA2**, **NTA4**, **NTA5**, **NTA12**, and **NTA15**). These results clearly demonstrated that a decrease in the hole-transfer rate from $A_1^{\bullet+}$ to A_2 does not affect Φ, whereas a decrease in the hole-transfer rate from $A_2^{\bullet+}$ to A_1 leads to an increase in Φ. The effects of the A–T to A–^{br}U substitution on Φ was also examined for a series of DNAs in which the A–T base pair adjacent to NI was inverted to a T–A base pair (**NTAbr*n***), and a similar trend was observed for that of the **Nbr*n*** series of DNAs.[46] In particular, the Φ value was highest for **NTAbr1** with a value of $\Phi = 0.052$.

These results strongly suggest that a hole initially generated on A_1 does not contribute to the formation of the charge-separated state, that is, a hole can not escape from the charge recombination within a contact ion pair. Rather, the formation of the charge-separated state is triggered by the electron transfer between A_2, A_3, and NI in the singlet excited state (^{1}NI*). The electron-transfer rate between ^{1}NI* and A (k_{et}), or the yield of the hole initially generated on A, decreases as the distance between ^{1}NI* and the A to be oxidized (Δr) increases, according to Equation (1):

$$\ln k_{et} \propto -\beta \Delta r \qquad (1)$$

in which β takes the value between 0.4 and 0.7 Å^{-1} in DNA.[47–49] By assuming β has a value of 0.55 Å^{-1} and that 90% of the absorbed photon leads to the electron transfer between ^{1}NI* and A, a hole will be initially generated on A_1, A_2, and A_3 with a Φ value of 0.77, 0.12, and 0.018, respectively. Therefore, it is possible to explain the formation of the charge-separated state with a quantum yield of 5% or lower observed here according to the hole initially generated on A_2 and A_3.

To assess the possibility of charge separation by initial hole generation on the second and third adenine nearest to NI, kinetic modeling was performed. For example, the simultaneous differential Equations (2) for **Nbr3**, of which the kinetic model is shown in Figure 1, can be described as follows in which $[A_i\ (i=1–5)]$ corresponds to the hole population on each A site, k_A, k_{br}, k_{-br}, and k_G, are the hole-transfer rate constants from $A^{\bullet+}$–T to A–T, $A^{\bullet+}$–T to A–^{br}U, $A^{\bullet+}$–^{br}U to A–T, and $A^{\bullet+}$ to G, respectively. k_{N1} and k_{N2} are the charge-recombination rates between $NI^{\bullet-}$ and $A_1^{\bullet+}$, and $NI^{\bullet-}$ and $A_2^{\bullet+}$, respectively. k_A and k_{N1} were estimated from the experimental results of Lewis and co-workers to be 1.1×10^{10}[36] and 5×10^9,[50] respectively. k_{N2} was derived from Equation (1) based on k_{N1}. By giving the hole population on A_1, A_2, and A_3 at time = 0 s as $[A_1]=0$ (i.e., hole initially generated on A_1 leads to charge recombination), $[A_2]=0.12$, and $[A_3]=0.018$, the Φ values were determined from the hole population on G at time = 100 ns. The Φ values obtained from the numerical analysis were compared with the experimental values as shown in Figure 3. Interestingly, the Φ values derived from the kinetic modeling correlated well with the experimental results. Using the same kinetic parameter and assuming the iso-energetic charge-transfer rate between the A–^{br}U base pairs to be equal to that between the A–T base pairs (k_A), the Φ values were also calculated for the doubly ^{br}U-modified DNAs. Again, the Φ values ob-

$$\begin{aligned}
\frac{d[A_1]}{dt} &= -(k_A + k_{N1})[A_1] + k_A[A_2] \\
\frac{d[A_2]}{dt} &= k_A[A_1] - (k_A + k_{br} + k_{N2})[A_2] + k_{-br}[A_3] \\
\frac{d[A_3]}{dt} &= k_{br}[A_2] - 2k_{-br}[A_3] + k_{br}[A_4] \\
\frac{d[A_4]}{dt} &= k_{-br}[A_3] - (k_{br} + k_A)[A_4] + k_A[A_5] \\
\frac{d[A_5]}{dt} &= k_A[A_4] - (k_A + k_G)[A_5] \\
\frac{d[G]}{dt} &= k_G[A_5]
\end{aligned} \qquad (2)$$

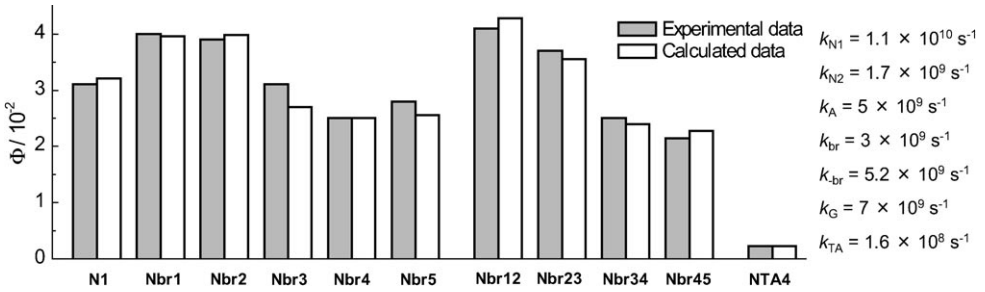

Figure 3. Comparison between the experimental and calculated charge-separated yields (Φ) for NI- and ^{br}U-modified DNA, and the kinetic parameters used for the numerical analysis.

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tained from the kinetic modeling agreed well with the experimental results. These results clearly demonstrate that the charge separation is triggered by the electron transfer between ^{1}NI* and A_2 and A_3.

Based on the numerical analysis, the relative oxidation potential of A–^{br}U to that of the A–T base pair was derived from the equilibrium constant (k_{br}/k_{-br}) to be +14 mV. This value was slightly smaller than that previously calculated for between the G–^{br}C and G–C base pairs (+24 mV).[34] The number of the hydrogen bonds between the G–C base pair is three and that between the A–T base pair is two. Therefore, the electronic substituent effects of C might be transmitted to the G partner through hydrogen bonding more effectively than that of T to A.

Similarly, the relationship between the intrastrand (k_A) and interstrand (k_{TA}) hole-transfer rates between the A–T base pairs were investigated. For this purpose, a numerical analysis was performed for **NTA4** in which the inversion of the A–T base pair affected neither the population of the initially generated hole on A_1, A_2, and A_3, nor the hole-trapping rate k_G. According to the kinetic modeling, k_A/k_{TA} was determined to be 31, showing that hole transfer through the consecutive A–T sequence is especially fast relative to that through other sequences, consistent with the importance of consecutive adenines in the formation of the charge-separated state.

Here, the effects of insertion of a hole-passing attenuator A–^{br}U and inverted A–T base pair into the A–T stretch on the charge-separation yield was evaluated with the idea of a sequential hole-transfer process between adenines, that is, a hole is localized on a single A base. On the other hand, hole delocalization in the duplex DNA, described as a polaron by Conwell[51–53] and Schuster,[9,54] was suggested by several researchers and is one of the most interesting topics remaining to be experimentally solved.[36,55–60] In particular, the experimental results reported by Giese et al.[55] and Lewis et al.[36] suggested the charge delocalization over the A-stretch. Though we have explained our results by the hole localization on a single base, the Φ values of some DNA sequences such as **Nbr3** and **Nbr5**, deviated slightly from the calculated values derived from kinetic modeling. Therefore, it would be interesting to examine our experimental results from a theoretical point of view taking into account the contribution of the charge delocalization over the A-stretch.

Conclusion

The charge-separation process in DNA possessing an A–T stretch was investigated for various series of DNAs. The experimental results were best explained by taking into account the initial charge generation on the second- and third-nearest adenine to the Sens. Furthermore, the electron transfer between a photosensitizer and adjacent A–T base pair results in a fast charge recombination within a contact ion pair. According to our results, Φ was suggested to be maximized by selective generation of a hole on the A–T base pairs second- and third-nearest to the Sens. Therefore, the charge-separation process by means of consecutive adenines can be refined to achieve a high Φ by putting a redox-inactive spacer base pair between a photosensitizer and an A–T stretch to avoid the formation of a contact ion pair that results in a rapid charge recombination.

Experimental Section

DNA synthesis: Cyanoethyl phosphoramidite of *N*-(3-hydroxypropyl)-1,8-naphthalimide and 5-bromodeoxyuridine was synthesized as previously reported.[61] All other reagents for DNA synthesis were purchased from Glen Research. The DNA used in this study was synthesized by using an Applied Biosystems 3400 DNA synthesizer with standard solid-phase techniques and purified by using a JASCO HPLC with a reverse-phase C-18 column with an acetonitrile/50-mM ammonium formate gradient. The DNAs were characterized by digestion with nuclease P1 and alkaline phosphatase (AP), and by MALDI-TOFF mass spectroscopy. Duplex solutions (20 mM sodium phosphate buffer (pH 7.0)) were prepared by mixing equimolar amounts of the desired oligodeoxynucleotide (ODN) complements and gradually annealing with cooling from 80 °C to RT.

Calculation of ionization potential: Calculations were performed at the HF/3-21G(*) level utilizing Spartan program on a Linux. Geometries of base pairs methylated at N1 (pyrimidine base) and N9 (purine base) were constructed as follows: The corresponding base pairs were constructed by using the Spartan program with standard B-form helical parameters. All the sugar backbones were removed except for the deoxyribose C1′ carbon and C1′ hydrogen. Two hydrogen atoms were then attached to the C1′ methine to complete N-methylated base pairs.[62]

Laser flash photolysis experiments: Nanosecond transient absorption measurements were performed using the LFP technique for an aqueous solution containing 40 μM DNA (strand conc.) and 20 mM pH 7.0 Na phosphate buffer.[20,21,29–35] The third-harmonic oscillation (355 nm, 20 mJ per pulse) from a Q-switched Nd/YAG laser (Continuum, Surelite II-10; 5-ns fwhm, 10 Hz) was used to excite NI selectively. A xenon flash lamp (Osram, XBO-450) was focused into the sample solution as the probe light for the transient absorption measurement. Time profiles of the transient absorption were measured by using a monochromator (Nikon, G250) equipped with a photomultiplier (Hamamatsu Photonics, R928) and digital oscilloscope (Tektronics, TDS-580D). The quantum yield of formation of the charge-separated state was determined from the transient absorption of the triplet benzophenone as an actinometer during the 355-nm laser flash photolysis. Kinetic modeling was carried out by using MatLab software.

Acknowledgements

This work was supported partly by a Grant-in-Aid for Scientific Research (Project 18750148, and others) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of the Japanese Government.

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Received: November 22, 2007
Published online: March 3, 2008

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