CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200601210

Hole Transfer Rates in A-Form DNA/2′-OMeRNA Hybrid

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Abstract: The hole transfer rates in the DNA/DNA B-form duplex and DNA/2′-OMeRNA A-form duplex were measured which occurred in the time range of ≈100 μs. The hole transfer rates in the A-form duplexes were slower and more strongly dependent on the temperature compared to those in the B-form duplexes, suggesting that the A-form is more rigid than the B-form duplex in this time scale.

Keywords: charge transfer · DNA structures · DNA · RNA · transient absorption

Introduction

Nucleic acids can adopt different conformations depending on the base composition, the hydration state, and its backbone type. The DNA/DNA duplex and RNA/RNA duplex form the B-form and A-form structures, respectively. The DNA/RNA hybrids, which are key intermediates in reverse transcription and antisense-based therapy,[1] take an intermediate structure between the A and B forms, but closer to the canonical A-type helix.[2] Nucleic acids are dynamic molecules that undergo both small- and large-scale fluctuations on various time scales,[3–5] and conformational dependence of such motion is of major significance in their ability to be recognized by specific proteins.[6–10] Barton and co-workers demonstrated that charge transfer through the duplex is assisted by the motion of the nucleic acids and it would be possible to access the dynamics of nucleic acids by measuring the charge transfer rates through the duplex.[11–14] The concept was followed by Fiebig[15] and supported by several theoretical groups.[16–18] In the case of the movement of a positive charge (hole) through A-form duplex, Schuster and Barton have demonstrated on the basis of a gel electrophoresis analysis that a hole can migrate along the A-form DNA/RNA hybrid.[19,20] However, there were no reports on the hole transfer rate between Gs (k_{ht}) through the A-form duplex. Recently, we have established a system to measure the k_{ht} through the B-form DNA which occurs in the time range of ns to ms depending on the length and the sequence of the DNA.[21,22] Herein, we extended this system to the DNA/2′-OMeRNA hybrid to measure the k_{ht} in A-form structure, and the difference in the k_{ht} in the A-form and B-form structures was discussed in terms of their dynamics in the time range of ns to 100 μs.

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Results and Discussion

Our method for the time-resolved transient absorption measurements of the hole transfer is shown schematically in Figure 1. Naphthalimide (NI) was attached to the A_6 sequence at one end of the duplex in order to inject a hole on G nearest to NI within the laser duration of 10 ns via fast hole hopping between A groups,[23,24] which produces a charge-separated state sufficiently long for the observation of hole-transfer between G groups through the duplex in the time range up to 1 ms.[21,22,25–28] Phenothiazine (PTZ) was attached at the other end of the duplex as a hole-trap to monitor the hole transfer through the duplex by the formation of its radical cation ($PTZ^{\bullet+}$) with a peak around 520 nm.[29] For the simplification of the system, ssDNA doubly modified with NI and PTZ at both ends (**s1**, **s2**) was synthesized in this study, so as to regulate the entire structure as the B-form and A-form by simply changing its complementary strand to DNA (**d1**, **d2**) and 2′-OMeRNA (**r1**, **r2**), respectively.[30] The melting temperature (T_m) for **s1**/**d1** and **s1**/**r1** was higher compared with their unmodified duplex **n1**/**d1** and **n1**/**r1**, respectively, which suggests the end-capping of NI and PTZ at the terminus of duplex. Since T_m values for DNA/2′-OMeRNA hybrid are relatively low at 5 μM, 20 times higher strand concentration was used for

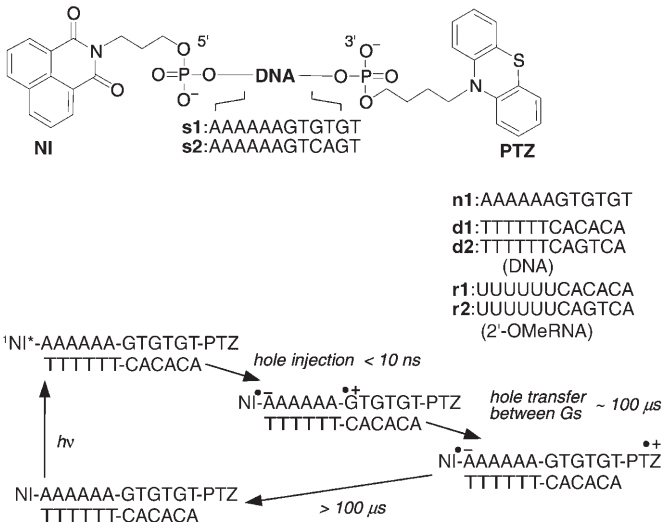


Figure 1. Sequences of NI- and PTZ-modified DNA, and kinetic scheme for hole injection and subsequent hole transfer between G bases in DNA.

transient absorption measurements to make sure that more than 90% of strands to be in the duplex form below 25°C. The conformation of the duplex was characterized by circular dichroism (CD) spectroscopy, which indicates the typical B-form for a duplex with DNA complements and the typical A-form for duplex with 2′-OMeRNA complements (Figure 2). The sequences were designed for a hole to migrate in the time scale of ≈20 μs in the B-form DNA.[21,22]

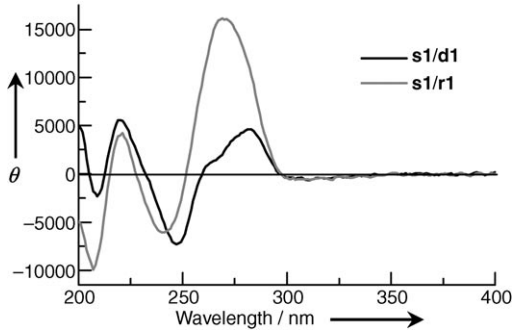


Figure 2. CD spectra of **s1/d1** and **s1/r1** (2 μM strand concentration) in 100 mM NaCl and 20 mM Na phosphate buffer (pH 7.0).

Excitation of the NI site of the NI- and PTZ-modified duplex with a 355 nm laser resulted in the formation of NI radical anion ($N^{\bullet-}$) with a peak at 400 nm immediately after the flash which remained almost constant on the time scale of the present experiments (≈100 μs) due to the slow charge recombination rate between $NI^{\bullet-}$ and $PTZ^{\bullet+}$ across six A–T base pairs (Figure 3a).[21,22,25–28] An absorption at 520 nm assigned to $PTZ^{\bullet+}$ then emerged on the time scale of several μs for the B-form duplexes **s1/d1** and **s2/d2** which was consistent with the previous reports, and on several tens of μs for the A-form duplexes **s1/r1** and **s2/r2** (Figure 3b).[31,32,33] Neither an efficient charge separation (ΔOD_{400}), nor a rise at 520 nm was observed for the single-stranded DNA **s1** (Figure 3a), clearly showing that the observed rise at 520 nm is due to the hole-transfer process through the duplex. The present results clearly showed that a hole can migrate along the A-form duplex, but its rates are three to ten times slower than that through the corresponding B-form duplex. Furthermore, the A-form duplex displayed a different sequence preference compared with the corresponding B-form duplex. A hole moved faster in the GTCAGT/CAGTCA sequence in the B-form duplex, but moved faster in the GTGTGT/CACACA sequence in the A-from duplex.

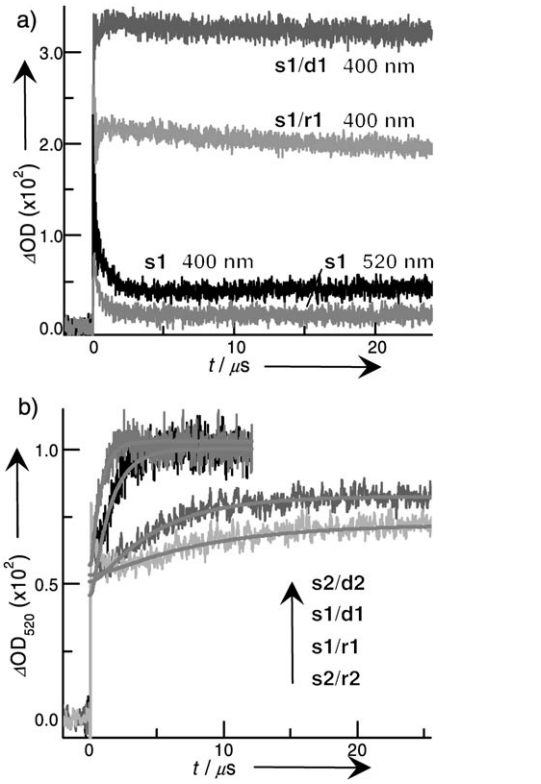


Figure 3. Time profiles of the transient absorption of $NI^{\bullet-}$ monitored at 400 nm and that of $PTZ^{\bullet+}$ at 520 nm during the 355 nm laser flash photolysis of Ar-saturated aqueous solution containing 100 mM NaCl, and 20 mM pH 7.0 Na phosphate buffer at a strand concentration of 100 μM at 10.8°C. The smooth curves superimposed on the decay curves are the fit derived from the kinetic model using k_{ht} values depicted in Table 1.

The k_{ht} in the B-form DNA depends on the distance (r) between G bases according to the following equation ($k_{ht} = A\exp(-\beta r)$) where β was determined to be 0.4–0.7 $Å^{-1}$.[34,35] Though the distance between G bases across a single A–T base pair is slightly longer in the A-form duplex than that in the B-form duplex, the observed large differences of k_{ht} in the B- and A-form duplexes cannot be solely explained by the differences in the distance, suggesting that the dynamics of duplex contributes to the k_{ht} to some extent.

To gain some insight into the effect of the dynamics of the B- and A-form duplexes on the k_{ht}, k_{ht} was measured at various temperatures. The values of k_{ht} increased with T

whereby the effect of T was more pronounced for the A-form duplexes than for the B-form duplexes (Figure 4), suggesting that the A-form duplex is more rigid than the B-form duplex in the time range of $\approx 100\,\mu s$. The activation energy (E_a) was obtained using the following semiclassical Marcus Equation in which A is the preexponential factor.

$$k_{ht}\,T^{0.5} = A\exp(-E_a/k_bT) \quad (1)$$

A plot of log ($k_{ht}T^{0.5}$) versus T^{-1} provides the E_a value for the k_{ht} (Figure 5, Table 1). The E_a values obtained for the B-form duplexes were within the range of our previous reports[22] and hole-shift reactions between the protonated 9-amino-6-chloro-2-methoxyacridine and G reported by Michel-Beyerle et al.[36,37] Of special interest, E_a for the A-form duplexes were higher than that of the corresponding sequence of the B-form duplexes and was unusually high for **s2/r2**. Orozco and co-workers demonstrated that each strand in the DNA/RNA hybrid tends to have the same nature as their intrinsic motions in the corresponding homoduplexes.[38] Therefore, k_{ht} in **s2/r2** in which a hole also migrates through the G in 2′-OMeRNA strand may strongly reflect the nature of the rigid A-form structure. The smaller k_{ht} and higher E_a values observed in the A-form duplex compared with those of the B-form duplex indicate that the A-form is more rigid than the B-form duplex in the time range of $\approx 100\,\mu s$.

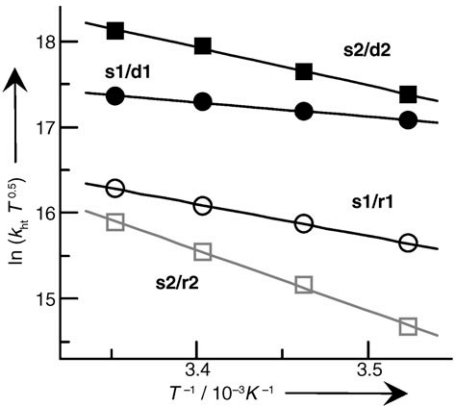


Figure 5. Plots of log ($k_{ht}T^{0.5}$) versus T^{-1}.

Table 1. Melting temperatures of duplexes (T_m), rate constants (k_{ht}) and apparent activation energy (E_a) for hole transfer between G bases.

	T_m [°C][a]	k_{ht} [$10^5 \times s^{-1}$][b]	E_a [eV][c]
n1/d1	41.2	—	—
s1/d1	46.4	19	0.14
n1/r1	25.0	—	—
s1/r1	28.2	5.6	0.32
s2/d2	45.1	36	0.38
s2/r2	31.6	3.3	0.61

[a] UV melting measurements were carried out in 100 mM NaCl and 20 mM Na phosphate buffer (pH 7.0) at a strand conc. of 5 μM. [b] Rate constants were obtained from the kinetic modeling at 20.8 °C. [c] Calculated according to Equation (1) based on the data of Figure 2d.

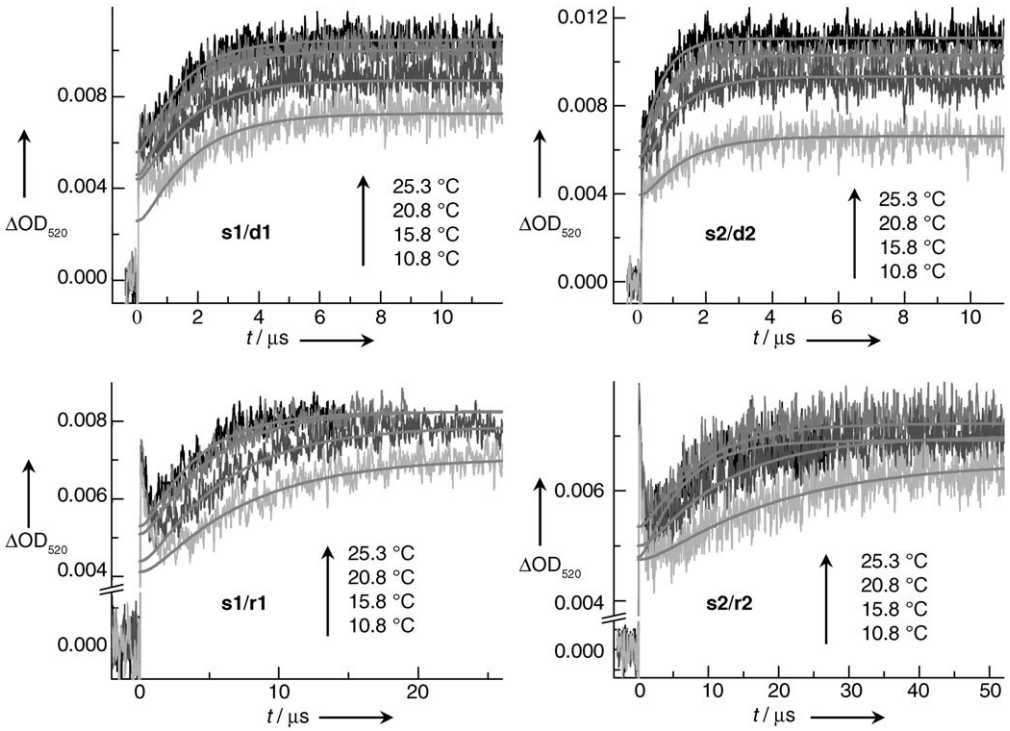


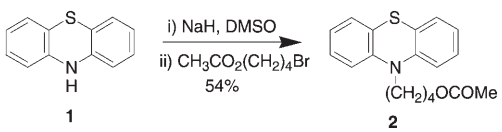
Figure 4. Time profiles of the transient absorption of $PTZ^{\cdot+}$ monitored at 520 nm during the 355 nm laser flash photolysis of Ar-saturated aqueous solution containing 100 mM NaCl, and 20 mM pH 7.0 Na phosphate buffer at a strand concentration of 100 μM at various temperatures. The smooth curves superimposed on the decay curves are the fit derived from the kinetic model.

O'Neill and Barton have shown that the photo-induced electron transfer efficiency from G to the photoexcited 2-aminopurine, which proceeds in the time range of <50 ns, is higher in the A-form DNA/RNA hybrid than that in the B-form DNA, concluding that the A-form DNA/RNA hybrid is more flexible than the B-form DNA in the time scale of <50 ns.[14] On the other hand, our results showed that a hole moves faster in B-form duplex than in A-form duplex in the time scale of 100 ns to 100 μs. Based on electron micrography, gel electrophoresis, hydrodynamic measurements or fiber diffraction, it was generally accepted that the B-form DNA is more flexible than the A-form RNA.[39,40] However, ^{1}H NMR imino proton exchange experiments have shown that the A–U base-pair lifetimes in the A-form RNA (<0.4 ms) are shorter than those of the A–T base pairs in the B-form DNA (0.5–7 ms).[41] Indeed, recent molecular dynamics (MD) simulations from MacKerell's group showed that the A-form RNA fluctuates more than the B-form DNA at the base-pair level in the time range of ≈ 5 ns.[42] Hence, it is becoming evident that for the A-form or the B-form, as to which structure is more flexible depends on the type of perturbation considered, that is, it varies depending on the time scale of interest. Therefore, the slower k_{ht} and its stronger dependence on T in the A-form duplex may suggest A-form to be more rigid than the B-form in the time scale of 100 ns to 100 μs. Although an investigation into the dynamics of the DNA and RNA at the atomic level has been greatly facilitated by theoretical approaches,[38–40,42] there are only limited experimental methods to access the dynamics of nucleic acids in the time scale of less than 1 ms.[3–5] Our system for the measurement of k_{ht} may provide a unique system to investigate the dynamic behavior of nucleic acids in the time range of ns to ms.

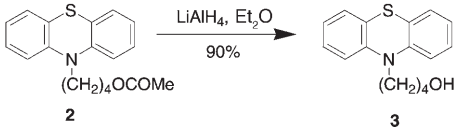
Experimental Section

Synthesis of PTZ-phosphoramidite

Synthesis of 2: Sodium hydride (50%, 2 g) was dissolved in DMSO (10 mL) and the solution was stirred for 1 h. To this solution, **1** (7.8 g) in DMSO (40 mL) was added dropwise over 1.5 h, and the reaction mixture was stirred for 1 h. Then, 4-bromobutyl acetate (8 g) in DMSO (5 mL) was added dropwise over 45 min, and the reaction mixture was stirred for over night. The reaction mixture was poured into water (250 mL), extracted with Et_2O (3×), washed with water, and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was subjected to silica gel flash chromatography (toluene) to yield **2** (6.7 g, 54% yield). ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 1.73$–1.91 (m, 4H), 1.99 (s, 3H), 3.90 (t, 2H), 4.06 (t, 2H), 6.83–6.94 (m, 4H), 7.12–7.18 ppm (m, 4H).

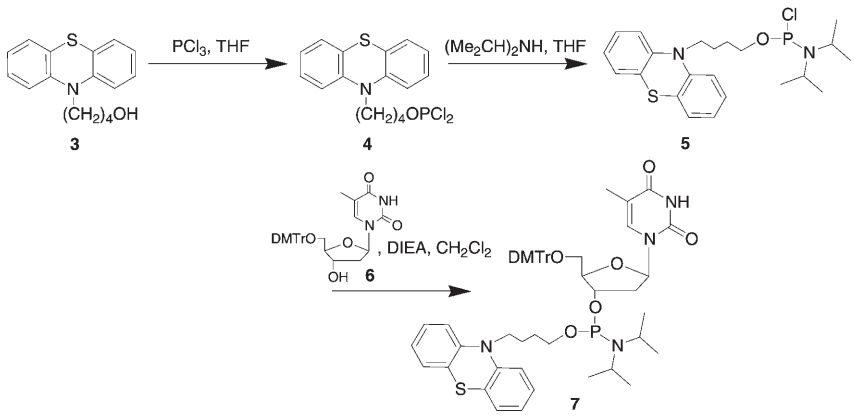


1 2



2 3

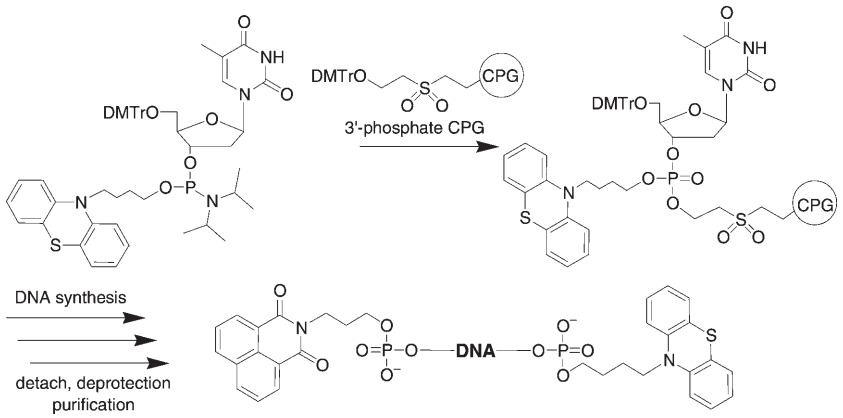
Synthesis of 3: A solution of **2** (4.6 g) in Et_2O (45 mL) was added dropwise into a solution of $LiAlH_4$ (0.88 g) in ether (15 mL), and the solution was stirred for overnight. After the addition of a small portion of water, the organic phase was washed with water, and then with brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness, and the residue was subjected to silica gel flash chromatography (ethyl acetate/hexane 1:1) to yield **3** (3.6 g, 90%). ^{1}H NMR (270 MHz, $CDCl_3$): $\delta = 1.64$–1.74 (m, 2H), 1.84–1.95 (m, 2H), 3.65 (t, 2H), 3.91 (t, 2H), 6.85–6.94 (m, 4H), 7.12–7.18 ppm (m, 4H).



3 4 5 6 7

Synthesis of 7: A solution of **3** (550 mg) in THF (20 mL) was added dropwise over 2 h into a solution of phosphorous trichloride (2 mL) in THF (10 mL) at −17 °C. The reaction mixture was warmed to room temperature over 4 h, and the solvent was evaporated to dryness. The residue was dissolved in THF (20 mL) and a solution of diisopropylamine (404 mg) in THF (5 mL) was added dropwise over 5 min at 0 °C. The reaction mixture was stirred for overnight and the solvent was evaporated to dryness. Then, the residue was dissolved in dichloromethane (20 mL) and added into a solution of **6** (436 mg) and diisopropylethylamine (1 mL) in dichloromethane (20 mL), and the reaction mixture was stirred for 5 d. After the addition of methanol (2 mL) and triethylamine (3 mL), the organic phase was washed with saturated $NaHCO_3$ aqueous solution. The organic layer was dried over anhydrous Na_2SO_4, evaporated to dryness, and the residue was subjected to silica gel flash chromatography (ethyl acetate) to yield **7** (340 mg, 18% (three-step yield)). MALDI-TOFF mass (positive ion): m/z: calcd for: 947.1, found: 946.5 $[M+H]^+$.

DNA Synthesis: 3′-Phosphate CPG (2-[2-(4,4′-dimethoxytrityoxy)ethylsulfonyl]ethyl-2-succinoyl) long chain alkylamino-CPG and all the other reagents for DNA synthesis were purchased from Glen Research. Cyanoethyl phosphoramidite of *N*-(3-hydroxypropyl)-1,8-naphthalimide was synthesized as previously reported.[43] 3′-Phosphate CPG was used as a solid support for 3′-PTZ modified DNA.[4] DNA were synthesized on an Applied Biosystems DNA synthesizer and purified by reverse phase HPLC and lyophilized. NI- and PTZ-modified DNA were characterized



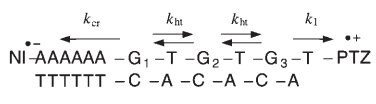
by MALDI-TOFF mass spectra. MALDI-TOFF (negative ion): *m/z*: **s1**: calcd for: 4368.1, found: 4368.0 $[M-H]^-$. **s2**: calcd for: 4337.0, found: 4337.0 $[M-H]^-$. Concentration of all DNA studied here were determined by complete digestion with nuclease P1 and AP to 2′-deoxyribonucleosides. 2′-OMeRNA was purchased from JBios. Duplex solutions (100 mM NaCl and 20 mM sodium phosphate buffer (pH 7.0)) were prepared by mixing equimolar amounts of the desired DNA complements and gradually annealing with cooling from 80 °C to room temperature.

T_m measurements: Thermal denaturation profiles were obtained with Jasco V-530 spectrophotometer equipped with a Peltier temperature controller. Absorbance of the ODN sample (5 μM duplex in 20 mM phosphate buffer (pH 7.0)) was monitored at 260 nm (A_{260}) from 10 to 65 °C with a heating rate of 1 °C min^{-1}. The T_m value was determined as the maximum in a plot of $\Delta A_{260}/\Delta T$ versus temperature.

CD spectra: CD spectra of NI- and PTZ-modified B-form and A-form duplexes were measured in aqueous solution in the presence of 100 mM NaCl, 20 mM Na phosphate buffer (pH 7.0) at a strand concentration of 2 μM at 16 °C on a JASCO CD-J720.

Laser flash photolysis: Nanosecond transient absorption measurements were performed using the laser flash photolysis technique.[21,22,25–27,44–46] Briefly, the sample cell was put in a homemade sample cell holder equipped with a circulator (DC10 K20, HAAKE) to control the temperature. The third-harmonic oscillation (355 nm, FWHM of 4 ns, 20 mJ per pulse) from a Q-switched Nd/YAG laser (Continuum, Surelight) was used for the excitation light which was expanded to a 1 cm diameter. The light from a xenon flash lamp (Osram, XBO-450) was focused into the sample solution for the transient absorption measurement. Time profiles of the transient absorption in the UV-visible region were measured with a monochromator (Nikon, G250) equipped with a photomultiplier (Hamamatsu Photonics, R928) and digital oscilloscope (Tektronics, TDS-580D).

Kinetic modeling: The rate constants of the single-step hole transfer between G bases (k_{ht}) were determined from the kinetic modelling.[21,22,26] Analysis of time profiles based on the multi-step hopping mechanism was performed with numerical analysis by using Matlab software. Kinetic model of multi-step hole transfer process is shown in Scheme 1. Charge recombination process (k_{cr}) can be ignored because the charge separated state persists over several hundred microseconds when NI and the nearest G are separated by six A–T base pairs. According to Scheme 1, simultaneous differential equations are described as Equation (1), where $[G_i$ $(i=1–3)]$ corresponds to the hole population at each G site, k_{ht} is hole transfer rate constants between G bases, and k_1 is hole transfer from $G_3^{\bullet+}$ to PTZ.



$$\frac{d[G_1]}{dt} = -k_{ht}[G_1] + k_{ht}[G_2]$$
$$\frac{d[G_2]}{dt} = k_{ht}[G_1] - 2k_{ht}[G_2] + k_{ht}[G_3]$$
$$\frac{d[G_3]}{dt} = k_{ht}[G_2] - k_{ht}[G_3] - k_1[G_3] \quad (1)$$
$$\frac{d[PTZ]}{dt} = k_1[G_3]$$

Scheme 1. Kinetic scheme for multi-step hole transfer in DNA.

Acknowledgements

This work has been partly supported by a Grant-in-Aid for Scientific Research (Project 17105005, Priority Area (417), 21st Century COE Research, and others) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japanese Government.

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Received: August 22, 2006
Published online: December 13, 2006

