# Theoretical Rate Constants of Super-Exchange Hole Transfer and Thermally Induced Hopping in DNA

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Recently, the electronic properties of DNA have been extensively studied, because its conductivity is important not only to the study of fundamental biological problems, but also in the development of molecular-sized electronics and biosensors. We have studied theoretically the reorganization energies, the activation energies, the electronic coupling matrix elements, and the rate constants of hole transfer in B-form double-helix DNA in water. To accommodate the effects of DNA nuclear motions, a subset of reaction coordinates for hole transfer was extracted from classical molecular dynamics (MD) trajectories of DNA in water and then used for ab initio quantum chemical calculations of electron coupling constants based on the generalized Mulliken−Hush model. A molecular mechanics (MM) method was used to determine the nuclear Franck−Condon factor. The rate constants for two types of mechanisms of hole transfer—the thermally induced hopping (TIH) and the super-exchange mechanisms—were determined based on Marcus theory. We found that the calculated matrix elements are strongly dependent on the conformations of the nucleobase pairs of hole-transferable DNA and extend over a wide range of values for the "rise" base-step parameter but cluster around a particular value for the "twist" parameter. The calculated activation energies are in good agreement with experimental results. Whereas the rate constant for the TIH mechanism is not dependent on the number of A−T nucleobase pairs that act as a bridge, the rate constant for the super-exchange process rapidly decreases when the length of the bridge increases. These characteristic trends in the calculated rate constants effectively reproduce those in the experimental data of Giese et al. [*Nature* **2001**, *412*, 318]. The calculated rate constants were also compared with the experimental results of Lewis et al. [*Nature* **2000**, *406*, 51].

## I. Introduction

The properties and dynamic behavior of DNA carrying electronic charges are basic and elemental biological problems. In particular, hole transfer between DNA nucleobase pairs is an interesting phenomenon, because the migration of a hole induced by ultraviolet (UV) light at a guanine nucleobase site is an important process in the repair mechanism for damaged DNA.[1,2] Even disregarding these biological issues, charge migration in DNA is still an interesting phenomenon. If DNA can conduct an electronic current, it can be used to connect molecular devices in nanoscale electronics.[3] Biosensors in which DNA acts as a nanowire have already been studied and developed.[4] Furthermore, various properties of DNA are useful in the assembly of molecular-sized electronic circuits. These include the self-assembly of highly advanced structures, such as the double helix, and complementarity-based recognition of a nucleobase pair. There have been several experimental studies of DNA conductance from these perspectives. In early experiments, it was reported that DNA connecting two electrodes under vacuum can conduct an electronic current like a conductor,[5] whereas other experiments report DNA behaving as an insulator.[6] Yet other experiments have shown that DNA acts a semiconductor with a wide band gap.[7,8] The experimental difficulties in connecting electrodes with DNA have been a significant barrier to the clarification of the electronic properties of DNA.

Despite many experimental studies, it is still unclear whether DNA carries electricity, as predicted. Recently, however, Giese et al. have clearly shown that a hole (positive charge) induced at a guanine base site can migrate between nucleobase pairs in DNA in solution.[9,10] They prepared DNA samples with the $G^+(A-T)_nGGG$ nucleobase sequence and measured the relative chemical yield, to estimate the efficiency of hole transfer from the guanine nucleobase site to the GGG triplet separated by the $(A-T)_n$ bridge (see Figure 1). These experiments showed that the yield ratio rapidly decreased as the length of the bridge increased but the values in the region of $n > 4$ did not change significantly. These data suggested that there are two types of mechanisms in the hole-transfer process: the thermal-induced hopping (TIH) mechanism and the super-exchange mechanism. The super-exchange mechanism is a coherent (tunneling) and short-distance charge-transfer process between a localized donor and an acceptor. On the other hand, the TIH mechanism is a multistep charge-transfer process via adenine nucleobases that act as bridges, and this mechanism allows long-distance charge transfer. Figure 1 shows that the super-exchange mechanism mainly transports holes in the region of $n < 4$, whereas the TIH mechanism acts in long-distance hole migration ($n > 4$). Lewis et al. have successfully measured the rate constants for hole transfer in DNA directly.[11,12]

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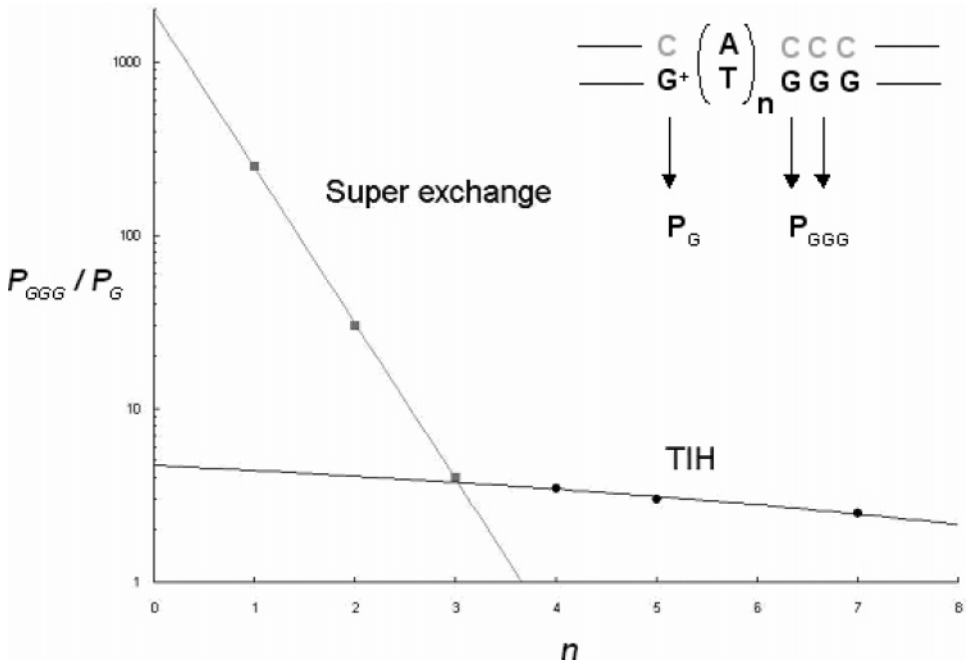


**Figure 1.** Plot of the yield ratios $P_{GGG}/P_G$ against the number ($n$) of A−T nucleobase pairs measured by Giese et al.[10] for hole transfer between a guanine radical cation and a GGG sequence separated by the $(A-T)_n$ bridge. The efficiency of hole transfer was measured by the ratio of the products $P_{GGG}/P_G$.

Compound **1**.

5'- $A_1$ $A_2$ $A_3$ $C_4$ $C_5$ $C_6$ **$A_7$** $C_8$ $G_9$ $T_{10}$ $T_{11}$ $T_{12}$ -3'

3'- $T_{24}$ $T_{23}$ $T_{22}$ **$G_{21}$** **$G_{20}$** **$G_{19}$** $T_{18}$ **$G_{17}$** $C_{16}$ $A_{15}$ $A_{14}$ $A_{13}$ -5'

Compound **2**.

5'- $A_1$ $A_2$ $A_3$ $C_4$ $C_5$ $C_6$ **$A_7$** **$A_8$** $C_9$ $G_{10}$ $T_{11}$ $T_{12}$ $T_{13}$ -3'

3'- $T_{26}$ $T_{25}$ $T_{24}$ **$G_{23}$** **$G_{22}$** **$G_{21}$** $T_{20}$ $T_{19}$ **$G_{18}$** $C_{17}$ $A_{16}$ $A_{15}$ $A_{14}$ -5'

Compound **3**.

5'- $A_1$ $A_2$ $A_3$ $C_4$ $C_5$ $C_6$ **$A_7$** **$A_8$** **$A_9$** $C_{10}$ $G_{11}$ $T_{12}$ $T_{13}$ $T_{14}$ -3'

3'- $T_{28}$ $T_{27}$ $T_{26}$ **$G_{25}$** **$G_{24}$** **$G_{23}$** $T_{22}$ $T_{21}$ $T_{20}$ **$G_{19}$** $C_{18}$ $A_{17}$ $A_{16}$ $A_{15}$ -5'

Compound **4**.

5'- $A_1$ $A_2$ $A_3$ $C_4$ $C_5$ $C_6$ **$A_7$** **$A_8$** **$A_9$** **$A_{10}$** $C_{11}$ $G_{12}$ $T_{13}$ $T_{14}$ $T_{15}$ -3'

3'- $T_{30}$ $T_{29}$ $T_{28}$ **$G_{27}$** **$G_{26}$** **$G_{25}$** $T_{24}$ $T_{23}$ $T_{22}$ $T_{21}$ **$G_{20}$** $C_{19}$ $A_{18}$ $A_{17}$ $A_{16}$ -5'

**Figure 2.** Sequences of the model DNAs used for simulations.

Experimental studies have clarified the phenomenon of hole transfer in DNA in solution. Theoretical studies have also investigated the electronic conductance of the DNA molecule based on Green's function method,[13] Landauer formalism,[14] and the Louisville equation.[15] A kinetic-quantum model of the mechanism of hole transfer in DNA was suggested by Bixon and Jortner.[16,17] They estimated the electronic coupling matrix elements of the super-exchange and TIH mechanisms and calculated the rate constants for hole transfer in DNA on the basis of Marcus theory.[18] However, the Franck−Condon factors were treated as parameters in their estimations. In this paper, we report a method of calculating the rate constants for hole transfer in DNA without those parameters.

The hole-transfer process includes two characteristic factors: the nuclear Franck−Condon factor and the electronic coupling between DNA nucleobases. The Franck−Condon factor represents the nuclear motions of both intramolecular vibrations and the medium, and electronic coupling represents the electronic factor in the hole-transfer process. We calculated the Franck−Condon factor based on molecular mechanics (MM) methods and force fields, without referencing any specific experimental results. We determined the electronic coupling matrix elements based on ab initio quantum chemical methods, considering the nuclear motions of DNA in the hole-transfer process.[19] Many other theoretical studies have used the stable B-form DNA structure in the calculation of electronic couplings; however, hole transfer does not always occur in that structure. Because DNA is not a rigid crystal, DNA structures in water should change flexibly, similar to those of soft molecules. Therefore, the electronic coupling matrix elements of hole transfer in the DNA may be strongly dependent on the nuclear parameters of DNA at the time of hole migration and should be determined with consideration of the nuclear motion of the DNA. We use classical molecular dynamics (MD) methods to describe the DNA conformation in water. A subset of DNA coordinates was extracted from MD trajectories and used in electron coupling calculations. To extract this subset, we monitored the difference between the energy calculated for the geometries of the MD trajectories and the energy of the hole-transported systems. This method is adequate in terms of the Franck−Condon principle and the principle of energy conservation. The electronic coupling matrix elements for the extracted geometries were calculated using ab initio quantum chemical methods. We also report the rate constants for hole transfer, based on Marcus theory,[18] and compare them with experimental results.

## II. Calculation of Rate Constants

**1. Nuclear Franck−Condon Factor.** In charge-transfer processes, the migration of a charge is completed quickly, compared with nuclear motion (the Franck−Condon principle). After the charge is transported, the excess energy of the system slowly dissipates through a reorganization of the molecule and the medium. This relaxation process can be described as the "reorganization energy" in Marcus theory.[18] The reorganization energy of hole transfer in DNA has been calculated by several techniques, for example, by solving the Poisson−Boltzmann equation by finite difference methods or using correlation functions in classical MD simulations.[20−22] Because these methods require significant computational time to achieve results, we used a technique to calculate the reorganization energy based on MM methods.

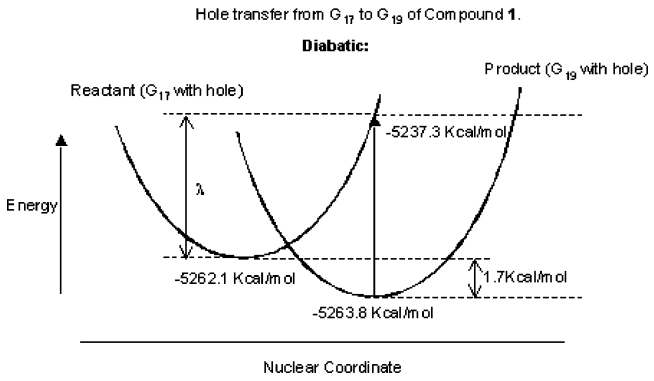


**Figure 3.** Scheme of hole transfer from $G_{17}$ to $G_{19}$ in compound **1**.

**TABLE 1: Optimized Energy of Model DNAs (see Figure 2)**

| | optimized energy (kcal/mol)[a] | energy of hole-transported system (kcal/mol)[a] |
|---|---|---|
| | Compound **1** | |
| DNA base with hole | | |
| $G_{17}$ | −5262.1 | |
| $A_7$ | −5243.2 | |
| $G_{19}$ | −5263.8 | |
| hole transfer | | |
| $A_7$ to $G_{17}$ | | −5243.1 |
| $G_{19}$ to $G_{17}$ | | −5237.3 |
| | Compound **2** | |
| DNA base with hole | | |
| $G_{18}$ | −5659.3 | |
| $A_8$ | −5639.8 | |
| $A_7$ | −5640.6 | |
| $G_{21}$ | −5660.4 | |
| hole transfer | | |
| $G_{21}$ to $G_{18}$ | | −5634.7 |
| $A_7$ to $A_8$ | | −5629.2 |
| | Compound **3** | |
| DNA base with hole | | |
| $G_{19}$ | −6055.4 | |
| $A_9$ | −6035.8 | |
| $A_8$ | −6036.5 | |
| $G_{23}$ | −6058.2 | |
| hole transfer | | |
| $G_{23}$ to $G_{18}$ | | −6032.2 |
| $A_8$ to $A_9$ | | −6025.9 |
| | Compound **4** | |
| DNA base with hole | | |
| $G_{20}$ | −6443.5 | |
| $A_{10}$ | −6423.7 | |
| $A_9$ | −6423.4 | |
| $G_{25}$ | −6442.3 | |
| hole transfer | | |
| $G_{25}$ to $G_{20}$ | | −6416.7 |
| $A_9$ to $A_{10}$ | | −6412.9 |

[a] Corrections by ab initio quantum chemical calculations are included.

For MM simulations, we used the B-form double-helix DNA structure with the base sequence shown in Figure 2 and the Amber program (version 7) with the Amber force field (parm99).[23] The generalized Born model was used to accommodate solvent effects.[24,25] The partial charges on the guanine and adenine nucleobases with holes were determined by the restrained electrostatic potential (RESP) method.[26,27] Electrical static potentials, which are required to determine the RESP partial charges, were calculated at the level of UHF/6-31G*, using the Gaussian98 program.[28]

Figure 3 shows the scheme that we used to calculate the reorganization energy ($\lambda$) and the energy gap ($\Delta E$) for the hole transfer from $G_{17}$ to $G_{19}$ of compound **1**. We first determined

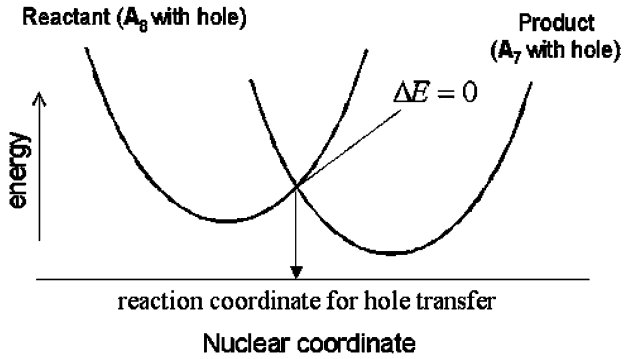


**Figure 4.** Reaction coordinate for hole transfer. A hole migrates to the nearest-neighbor nucleobase pair when the system is at the conformation where $\Delta E = 0$.

**TABLE 2: Reorganization Energy ($\lambda$), Activation Energy ($\Delta G^*$), and Franck−Condon Factor (FC) for Model DNAs Depicted in Figure 2**

| hole transfer | $\lambda$ (kcal/mol) | $\Delta G^*$ (kcal/mol) | FC[a] |
|---|---|---|---|
| | Compound **1** | | |
| $G_{17}$ to $A_8$ | 19.03 | 18.92 | $3.10 \times 10^{-14}$ |
| $G_{17}$ to $G_{19}$ | 24.82 | 5.39 | $2.00 \times 10^{-4}$ |
| | Compound **2** | | |
| $G_{18}$ to $A_8$ | 19.92 | 19.92 | $5.67 \times 10^{-15}$ |
| $G_{18}$ to $G_{21}$ | 21.32 | 4.80 | $5.82 \times 10^{-4}$ |
| $A_8$ to $A_7$ | 20.89 | 4.83 | $5.55 \times 10^{-4}$ |
| | Compound **3** | | |
| $G_{19}$ to $A_9$ | 20.12 | 20.12 | $4.03 \times 10^{-15}$ |
| $G_{19}$ to $G_{23}$ | 23.22 | 4.49 | $9.30 \times 10^{-4}$ |
| $A_9$ to $A_8$ | 20.49 | 4.78 | $6.10 \times 10^{-4}$ |
| | Compound **4** | | |
| $G_{20}$ to $A_{10}$ | 20.07 | 20.07 | $4.39 \times 10^{-15}$ |
| $G_{20}$ to $G_{25}$ | 26.82 | 7.32 | $7.50 \times 10^{-6}$ |
| $A_{10}$ to $A_9$ | 21.09 | 5.42 | $2.04 \times 10^{-4}$ |

[a] At 300 K.

the optimized structure and the energy of the DNA with $G^+$ or $A^+$ in solvent, using the MM method. The difference between the optimized energies corresponds to the energy gap $\Delta E$. The reorganization energies were calculated from the optimized energies and the energy of the hole-transported system in Figure 2. In these calculations, the energy gap and the reorganization energy were corrected for the energy of the nucleobase, which was calculated by ab initio quantum chemical calculations at the level of UHF/6-31G*, because the energy of a nucleobase with a hole calculated by the MM method is insufficiently accurate. The optimized energies calculated for the model DNAs in Figure 2 are summarized in Table 1. Note that the GGG triplet with a hole is more stable than the single guanine nucleobase with a hole in all model DNAs except compound **4**. MM calculations confirmed the features observed in the experimental measurement of the ionized energy of the nucleobases with ab initio quantum chemical calculations.[29,30]

Finally, the activation energy was calculated based on Marcus theory:[18]

$$\Delta G^* = \frac{(\lambda + \Delta E)^2}{4\lambda} \quad (1)$$

where $\lambda$ is the reorganization energy, $\Delta E$ the energy gap, and $\Delta G^*$ the activation energy. The reorganization energy and the activation energy calculated for guanine, the GGG triplet, and adenine in the A−T bridge, with a hole, are summarized in

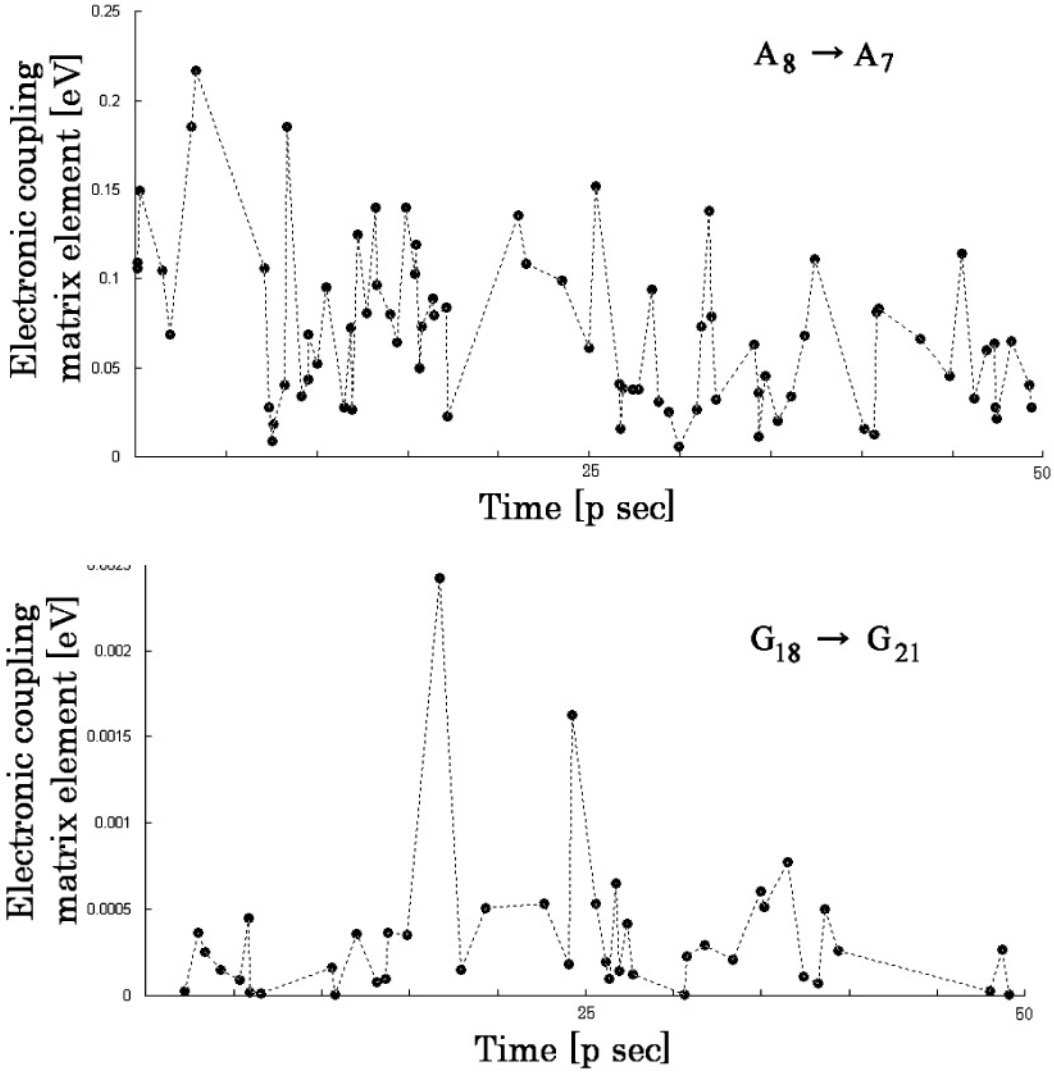


**Figure 5.** Electronic coupling matrix elements calculated at molecular dynamics (MD) time points.

Table 2. The Franck−Condon factor (*FC*) at 300 K was then calculated with the following equation:

$$FC = \frac{1}{(4\pi\lambda k_B T)^{1/2}} \exp\left[-\frac{\Delta G^*}{k_B T}\right] \quad (2)$$

The calculated activation energy, for example, for a hole transfer from $G_{17}$ to $A_7$ in compound **1** (0.2365 eV) is in good agreement with the experimental value reported by Davis et al. of 0.20 ± 0.04 eV,[31,32] although the sequence of our model DNA is slightly different from the DNA that they used. They also modified the DNA with specific chemical compounds to measure the activation energy experimentally.

**2. Electronic Coupling Matrix Element.** To calculate the rate constants, the electronic factor in the hole-transfer process must be evaluated, in addition to the Franck−Condon factor. The most elemental electronic factor in the charge-transfer process is electronic coupling. Electronic coupling is related to the overlap of molecular orbitals between a donor and an acceptor. If the molecular orbitals have significant overlap, the probability of charge transfer should increase as the distance between the donor and acceptor becomes shorter. Although there are many techniques to determine the electron coupling matrix element *V*,[33−40] we estimated it using the generalized Mulliken−Hush model that was proposed by Cave and Newton:[41,42]

$$|V| = \frac{\Delta E_{12}|\mu_{12}|}{\sqrt{(\mu_1 - \mu_2)^2 + 4(\mu_{12})^2}} \quad (3)$$

Here, $\Delta E_{12}$ is the vertical excitation energy, $\mu_1 - \mu_2$ the difference in adiabatic dipole moments, and $\mu_{12}$ the adiabatic transition dipole moment.

To calculate the matrix elements, the DNA structure in which a hole migrates must be known. Many theoretical calculations of the matrix elements have been based on the stable B-form DNA structure; however, DNA, especially in water, assumes various conformations in the process. To accommodate such effects, some studies used DNA conformations obtained from classical MD trajectories at a given time interval.[43−45] However, the matrix elements are desirable to calculate at DNA conformations where a hole can migrate from a donor to an acceptor. To find reaction DNA coordinates for hole transfer, we used classical MD methods and calculated the electronic coupling matrix elements at the coordinates. The reaction coordinates for hole transfer were determined by monitoring the energy difference between the energy $E_{react}(\vec{R})$ calculated for a series of geometries, $\vec{R}$ at every time point of an MD trajectory, and

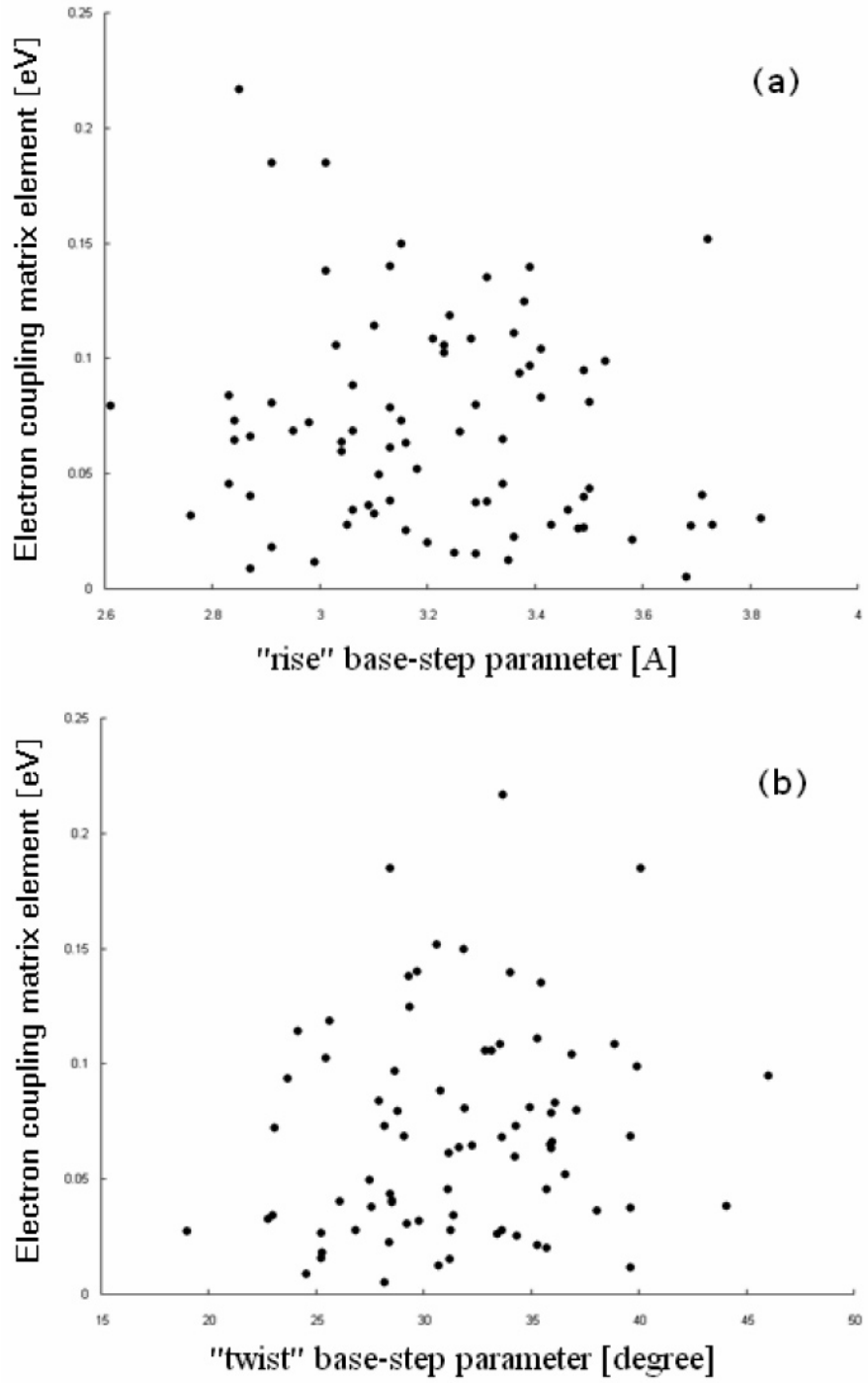


**Figure 6.** Electronic coupling matrix elements plotted with respect to the (a) "rise" and (b) "twist" base-step parameters.

the energy $E^{\text{virtual}}_{\text{product}}(\vec{R})$ of the hole-transferred system. Here, the system includes both DNA and solvent. Note that $\vec{R}$ of $E^{\text{virtual}}_{\text{product}}(\vec{R})$ is the same as that of $E_{\text{react}}(\vec{R})$. A hole is assumed to migrate between nearest-neighbor nucleobases with geometries such that the energy difference

$$\Delta E = E^{\text{virtual}}_{\text{product}}(\vec{R}) - E_{\text{react}}(\vec{R}) \tag{4}$$

becomes zero (see Figure 4). In other words, when the system is in reaction coordinates for hole transfer, the energy of the system does not change, even when a hole migrates. Therefore, nuclear motion is very slow, compared with the rate of hole transfer, and a hole can migrate without violating the principle of energy conservation.

Classical MD simulations were performed with the same procedure used for the MM simulations described in the pre-

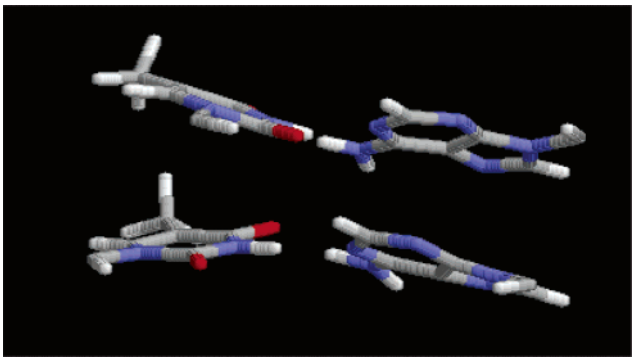

**Figure 7.** Snapshot of a nucleobase pair of a hole-transferable conformation on a classical MD trajectory, with a "rise" of 2.84 Å and a "twist" of 34.3°.

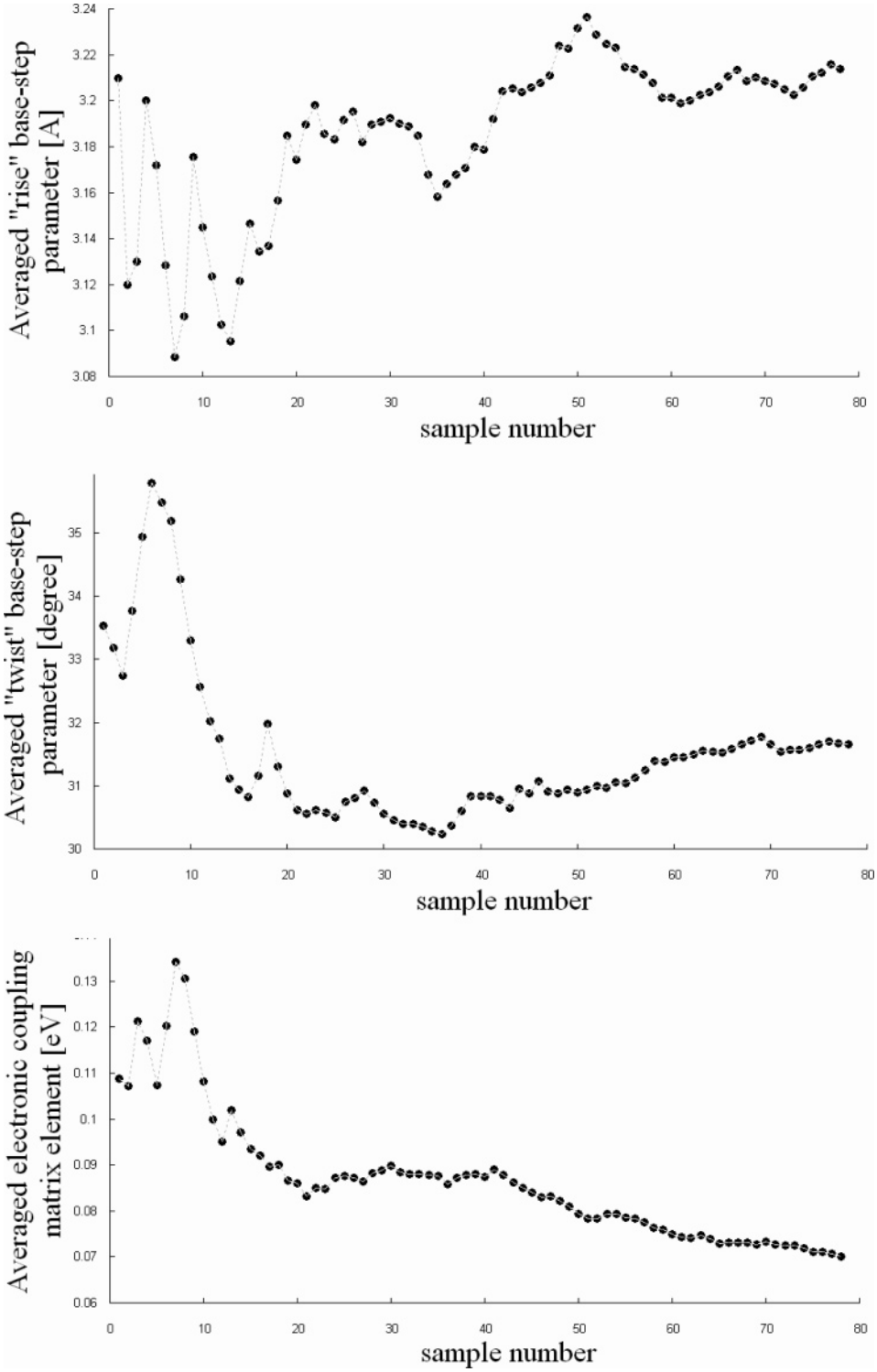


**Figure 8.** Change of average "rise" base-step parameter, "twist" base-step parameter, and electronic coupling matrix elements when the sample number increases.

vious section. The simulation temperature was set at 300 K.[46] For HF/6-31G* calculations of $V$, the part of the nucleobases that participates in hole transfer was removed from the entire DNA geometry, which gives $\Delta E = 0$. These parts of the nucleobases include the C1′ carbon, the H1′ hydrogen atoms of the ribose ring, and the two hydrogen atoms that are attached to C1′.

Figure 5 shows the calculated electronic coupling matrix elements at MD time points when a hole transfers from $A_8$ to $A_7$ and from $G_{19}$ to $G_{23}$ in compound **2**; here, we used eq 6 in the next subsection to calculate matrix elements for hole transfer from $G_{19}$ to $G_{23}$. Even if the systems are in the reaction coordinate for hole transfer, the hole-transfer probability is not constant and is strongly dependent on the details of the DNA conformation sampled by the MD calculations. To understand whether there is any uniform relationship between the hole-transferable coordinates and electronic couplings, we analyzed the results on the basis of the base-step parameters (twist, roll, tilt, slide, shift, and rise) introduced by Lu et al.[47] These base-step parameters describe the relative geometries of nucleobase pairs and can be used to rebuild the nucleic acid structures. Of these parameters, "rise" and "twist" represent the distance and

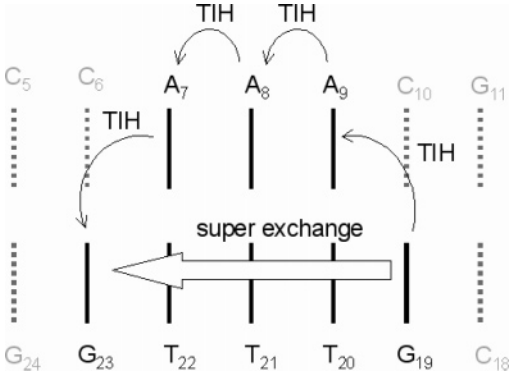


**Figure 9.** Hole-transfer process in compound **3**: (top) the TIH mechanism and (bottom) the super-exchange mechanism.

**TABLE 3: Rate Constant of Hole Transfer in Model DNAs in Figure 2**

| hole transfer | electronic coupling (eV) | FC[a] | rate constant ($s^{-1}$) |
|---|---|---|---|
| | Compound **1** | | |
| $G_{17}$ to $A_7$ | $2.1218 \times 10^{-2}$ | $3.10 \times 10^{-14}$ | $1.33 \times 10^{-1}$ |
| $G_{17}$ to $G_{19}$ | $4.635 \times 10^{-3}$ | $2.00 \times 10^{-4}$ | $4.11 \times 10^{+7}$ |
| | Compound **2** | | |
| $G_{18}$ to $A_8$ | $2.1218 \times 10^{-2b}$ | $5.67 \times 10^{-15}$ | $2.44 \times 10^{-2}$ |
| $G_{18}$ to $G_{21}$ | $5.51 \times 10^{-4}$ | $5.82 \times 10^{-4}$ | $1.68 \times 10^{+6}$ |
| $A_8$ to $A_7$ | $8.3501 \times 10^{-2c}$ | $5.55 \times 10^{-4}$ | $3.69 \times 10^{+10}$ |
| | Compound **3** | | |
| $G_{19}$ to $A_9$ | $2.1218 \times 10^{-2b}$ | $4.03 \times 10^{-15}$ | $1.73 \times 10^{-2}$ |
| $G_{19}$ to $G_{23}$ | $1.33748 \times 10^{-5}$ | $9.30 \times 10^{-4}$ | $1.59 \times 10^{+3}$ |
| $A_9$ to $A_8$ | $8.3501 \times 10^{-2c}$ | $6.10 \times 10^{-4}$ | $4.06 \times 10^{+10}$ |
| | Compound **4** | | |
| $G_{20}$ to $A_{10}$ | $2.1218 \times 10^{-2b}$ | $4.39 \times 10^{-15}$ | $1.89 \times 10^{-2}$ |
| $G_{20}$ to $G_{25}$ | $1.20834 \times 10^{-6}$ | $7.50 \times 10^{-6}$ | $1.05 \times 10^{-1}$ |
| $A_{10}$ to $A_9$ | $8.3501 \times 10^{-2c}$ | $2.04 \times 10^{-4}$ | $1.36 \times 10^{+10}$ |

[a] Nuclear Franck−Condon factor at 300 K. [b] The matrix element of compound **1** is used. [c] The matrix element of compound **2** is used.

the twisted angle of the nucleobase pair, respectively. Figure 6 shows the correlation of electronic couplings with the (a) "rise" and (b) "twist" base-step parameters in the case of hole transfer from $A_8$ to $A_7$. In principle, electronic coupling may be dependent on the distance between the nucleobase pair; therefore, it is reasonable to expect that electronic couplings become large when the "rise" base-step parameter is small. However, Figure 6a indicates only a small correlation between the "rise" base-step parameter and the matrix element. This may be due to the fact that matrix element is not determined by only the "rise" parameter; other parameters, including "twist", are also important. In addition, some technical problems probably cause the weak correlation; that is, the base-step parameters are defined for planar nucleobase pairs and the "rise" parameter does not directly correspond to the distances between nucleobase pairs when DNA reaction coordinate for hole transfer are significantly distorted from planar. For example, the electronic coupling of a nucleobase pair participating in hole transfer with a "rise" of 2.84 Å and a "twist" of 34.3°, shown in Figure 7, which is strongly distorted and actually not planar, is calculated to be 0.07 eV.

When we determine the rate constants for hole transfer, all the calculated electronic coupling matrix elements are taken into consideration by eq 5:

$$V^2 = \frac{V_1^2 + V_2^2 + V_3^2 + ... + V_N^2}{N} \quad (5)$$

The averaged electronic coupling matrix elements of the hole-transferable conformations sampled by MD calculations were calculated to be 0.084 eV. This averaged value is twice as large as the value for the optimized DNA structure ("rise" = 3.23 Å and "twist" = 37.8°) and that calculated by Voityuk et al.[37] for standard stable B-form DNA ("rise" = 3.38 Å and "twist" = 36.0°) of 0.046 and 0.03 eV, respectively. The averaged values for the "rise" and "twist" parameters of hole-transferable DNA conformations were calculated to be 3.21 Å and 31.7°, respectively. This indicates that the average hole-transferable conformation sampled by MD calculations corresponds to a DNA conformation of a slightly closer and less-twisted nucleobase pair, compared with the optimized and stable B-form structures, and that there is greater electronic coupling in this conformation. We also calculated the changes of averaged "rise" and "twist" base-step parameters and averaged electronic coupling matrix element of reaction coordinate for hole transfer when the number of sample increases in Figure 8, to statistically confirm the aforementioned discussions. Therefore, we may conclude that the hole-transferable conformations are spread over a wide range of the "rise" base-step parameter while being spread around a "twist" of 32°, which is smaller than that of the stable B-form DNA. This result may suggest that not stretching but rather twisting motions in DNA mainly transport a hole to a neighbor nucleobase.

**3. Super-Exchange Mechanism.** There are two types of mechanisms in the hole-transfer process in DNA: the TIH mechanism and the super-exchange mechanism. In the TIH mechanism, a hole that is injected at the guanine nucleobase site hops thermally to the adenine nucleobase site in the A−T bridge, and sequential thermal hopping finally transports the hole to the stable GGG triplet. On the other hand, the super-exchange mechanism transports a hole from the donor to the acceptor directly and coherently (see Figure 9). When a hole is transferred by the super-exchange mechanism, the Franck−Condon principle must be satisfied, as is also the case with the TIH mechanism. Therefore, we can determine the hole-transferable coordinates by the same method discussed in the previous section.

We calculated the matrix elements for the super-exchange mechanism based on the following equation, when the system is in reaction coordinates for hole transfer:[17]

$$V = \sum_{\text{routes}} \frac{V(G - X_{(1)})V(X_{(n)} - G)}{\Delta(G - X_{(1)})} \times \prod_{j=1}^{n-1} \frac{V(X_{(j)} - X_{(j+1)})}{\Delta(G - X_{(j+1)})} \quad (6)$$

We took into consideration a particular route, that is, the hole was exchanged through the highest occupied molecular orbitals (HOMOs) of thymine nucleobases in the bridge. $V(G - X_{(1)})$, $V(X_{(n)} - G)$, and $V(X_{(j)} - X_{(j+1)})$ are the matrix elements between the neighborhood nucleobases into a $G^+X_{(1)}X_{(2)}X_{(3)}... X_{(n)}G$ sequence, where $X_{(j)}$ represents thymine nucleobases. $\Delta(G - X_{(j)})$ is the difference in ionized energy between G and T. To determine the electronic couplings, ab initio quantum chemical calculations at the level of HF/6-31G* were performed for the nucleobases that are removed from the entire DNA, as discussed in the previous section.

**4. Rate Constant.** The elementary rate constants for hole transfer were finally estimated based on Marcus theory,[18,48−50] using the reorganization energies, the activation energies, and the electronic coupling matrix elements that were calculated in the previous sections:

$$k = \frac{2\pi}{\hbar} V^2 \frac{1}{(4\pi\lambda k_B T)^{1/2}} \exp\left[-\frac{\Delta G^*}{k_B T}\right] \quad (7)$$

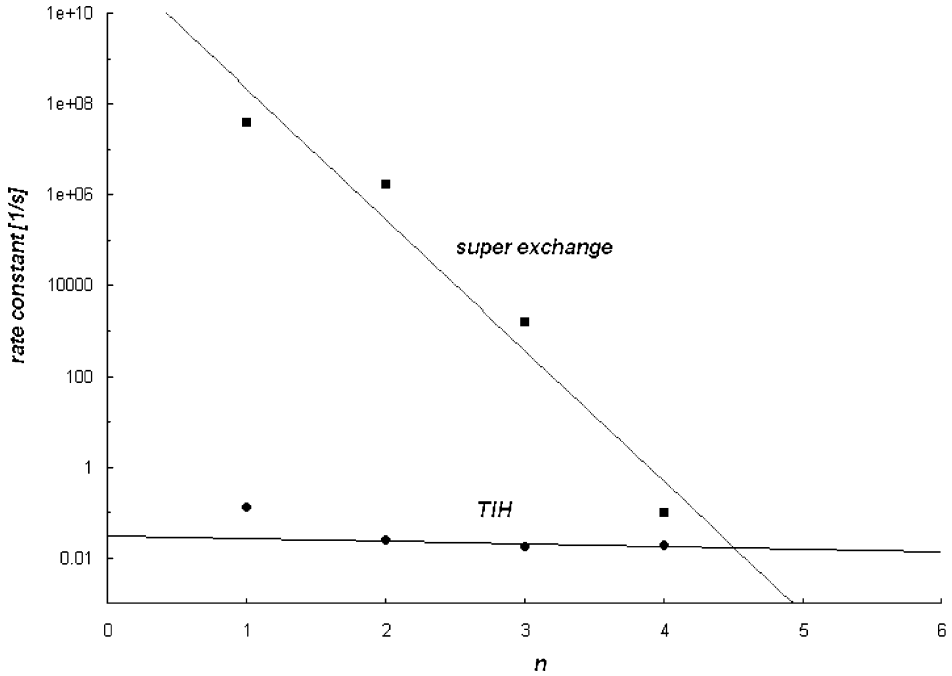


**Figure 10.** Calculated rate constants against the number ($n$) of A−T nucleobase pairs.

where $\Delta G^*$ is the activation energy, $\lambda$ the reorganization energy, $k_B$ the Boltzmann constant, $T$ the temperature, and $V$ the electronic coupling matrix element. Table 3 summarizes the calculated rate constants, and Figure 10 shows the relationship between the calculated rate constants and the number of A−T nucleobase pairs. Here, although precise models are proposed for the TIH mechanism by Berlin el al.[51−53] and Bixon and Jortner,[17] we adopted the elementary rate constants from G to A as the rate constants for the TIH mechanism to easily estimate them, because the elementary process is dominant in the TIH mechanism, as mentioned below. The calculations indicate that the rate constants for the super-exchange mechanism are strongly dependent on the number of A−T base pairs between the donor and the acceptor; when the number of bridge elements increases, the calculated rate constants decrease rapidly, because the electronic couplings for the super-exchange mechanism diminish rapidly. However, if we compare the rate constants for the super-exchange mechanism with those for the TIH mechanism, the super-exchange is still the faster process in the region of $n \leq 4$, because the Franck−Condon factor is larger. We found that the process of hole transfer from A to A is faster than the process of hole transfer from G to A with the TIH mechanism, because the rate constants for the transfer from G to A are smaller than those for the transfer from A to A. For example, the rate constant from A to A is calculated to be $3.69 \times 10^{10}$ s$^{-1}$ in compound **2**, whereas the rate constant from G to A is $2.44 \times 10^{-2}$ s$^{-1}$. In other words, when a hole migrates from G as a donor to the GGG triplet as an acceptor, the process from G to A is dominant in the TIH mechanism. Therefore, the rate constant of the TIH mechanism is not dependent on the length of the bridge.

The rate constants calculated have the same characteristics as those observed in the experiments of Giese et al.[10] (see Figure 1). Although the samples measured in the experiments are not exactly the same as those in our simulation model, our theoretical rate constant ($4.11 \times 10^7$ s$^{-1}$) is in good agreement with the experimental results of Lewis and co-workers ($8.7 \pm 1 \times 10^7$ s$^{-1}$).[11,12] The rate constants based on the super-exchange mechanism were calculated by Tang et al.[36] for GC/(AT)$_n$/GC, which corresponds to the DNA sequence examined by Lewis and co-workers.[11,12] Their results produced essentially the same trend for the bridge-size dependence of the rate constant as our results.

## III. Conclusion

We calculated the reorganization energies, the activation energies, the electronic coupling matrix elements, and the rate constants for hole transfers in DNA. The classical molecular mechanics (MM) method was used to determine the nuclear Franck−Condon factor of a system involving both DNA and solvent. We extracted the reaction coordinates for hole transfer from classical molecular dynamics (MD) simulations by monitoring the energy difference between the energy of the system and the energy of the hole-transported system, to accommodate nuclear motions in ab initio quantum chemical calculations of the electronic couplings, based on the generalized Mulliken−Hush model.[40] There are two types of mechanisms in the hole-transfer process, and we determined the rate constants for both the thermally induced hopping (TIH) mechanism and the super-exchange mechanism based on Marcus theory.[18] The activation energies that have been calculated are in good agreement with experimental results. The calculated matrix elements are strongly dependent on the conformation of the DNA nucleobase pairs when a hole migrates, and they extend over a wide range of values for the "rise" base-step parameter, whereas they cluster around a particular value for the "twist" parameter. Although the rate constants for the TIH mechanism are not dependent on the number of A−T nucleobase pairs, those for the super-exchange process rapidly decrease when the length of the bridge increases. These rate constant characteristics are identical to the experimental data of Giese et al.[10] and are in good agreement with the measurements made by Lewis and co-workers.[11,12]

The techniques that we used to calculate the rate constants can also be applied to A-form DNA, DNA analogues with modified bases or a modified sugar−phosphate backbone, and proteins such as cytochrome complexes,[54,55] because no specific properties of DNA or experimental parameters are included. Theoretical studies of these systems are in progress.

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