Electronic Interactions in DNA

Environmental Fluctuations Facilitate Electron-Hole Transfer from Guanine to Adenine in DNA π Stacks**

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Long-range hole migration along the π stack of DNA currently receives much experimental and theoretical attention.[1] Charge displacements of up to 200 Å[2–5] can occur by propagating radical cation states between guanine bases (G) mediated by tunneling through intervening bridges of AT base pairs ("G-hopping"). This G-hopping mechanism[6,7] was analyzed in detail[8–10] and successfully used to interpret many experiments on charge transport through DNA.[1,11–13] A-hopping, which involves radical cation states on adenine bases (A),[14] was postulated as an additional mechanism because the G-hopping model failed to rationalize several recent experimental findings.[14–17] Yet A-hopping cannot be well described using the energetics estimated from the redox potentials of nucleobases in water,[18] which find the radical cation state G^+ on guanine more stable than the state A^+ by $\Delta = 0.4$ eV (radical states C^+ and T^+ are considerably higher in energy than G^+, with an energy gap of ≈ 1 eV,[18] and therefore are highly unlikely to accept an electron hole in DNA). Long-range hole transport over $(AT)_n$ bridges ($n > 4$) in DNA was suggested to occur[6,19] via thermally induced hole excitation from G^+ to A, followed by hole hopping to neighboring adenine bases. The Boltzmann factor

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$\exp(-\Delta/kT)$ for thermally induced hopping from G^+ to A^+, implied by the energy gap of 0.4 eV, is 10^{-7}; it is very sensitive to variations of Δ. In this work, by using results of hybrid quantum mechanics/molecular dynamics (QM/MD) modeling,[20] we studied the variation of the relative energy Δ of G^+ and A^+ radical states due to fluctuations (on a time scale of 0.3–0.4 ns) of the electrostatic interaction between DNA and its electrolyte environment, and we explored the possibility for near degeneracy of the G^+ and A^+ states.

Thus far, redox potentials of nucleobases in the interior of a DNA double helix have not been measured. Clearly, estimates derived for individual nucleosides in aqueous solution[18] disregard the possible influence of neighboring base pairs and the sugar–phosphate backbone, as well as the effect of a structured environment.

In DNA, guanine triplets $(GC)_3$ are stronger hole acceptors than single GC pairs embedded in AT runs.[5,21] This significant result demonstrated that hole trapping by guanine is significantly affected by neighboring base pairs. The stabilizing effect of neighboring pairs on radical cation states in the DNA π stacks was systematically studied using quantum-chemical calculations.[22] Hole trapping by a base B in the duplex sequence 5′-XBY-3′ was shown to be considerably affected by the subsequent base pair Y (with is relatively shifted up to 0.3 eV), whereas the effect of the preceding base pair X turned out to be rather small. In addition, recent modeling led to the conclusion that the localization and energetics of an electron-hole state in a DNA strand can be strongly affected by the configuration of neighboring sodium cations.[23,24] Therefore, among other factors, the surrounding electrolyte has to be considered as a source for changes in the electrostatic potential created in the interior of DNA that can influence the charge transfer.

Thermal structural fluctuations of DNA and its environment play an important role for charge transfer (CT) through the double helix. In particular, electronic coupling between neighboring base pairs is extremely sensitive to conformational changes in DNA.[25–27] Molecular dynamics (MD) simulations provide a detailed microscopic description of the structure and motion of DNA and its environment.[28] Here, we focus on how structural fluctuations of DNA and its surroundings affect the CT energetics between nucleobases, based on long-time ($\approx$12 ns) MD simulations[29] of various duplexes. Along the trajectories, we monitored the energetics of hole transfer in the 5′→3′ direction from G to neighboring bases A and G. For this purpose, we estimated the corresponding reaction free energy ΔG of hole transfer along the trajectories with a quantum-chemical method that takes the instantaneous atomic configuration of the environment into account (that is, snapshots at every picosecond).[34] As the estimated ΔG values correspond to an ensemble of nuclear configurations, their standard deviations include three contributions, due to: 1) the nuclear vibrations of the nucleobases, 2) the conformational changes of DNA, and 3) the fluctuations of the solvent environment.

As an example, we present results for the 14-mer duplex 5′-$TTG_3(T)_8G_{12}$TT-3′ in an aqueous solution, which includes 26 Na^+ counterions. Table 1 lists the relative energies of hole states localized on purine nucleobases. As expected, the average free energy of the A^+ hole states is positive, about 0.4 eV; guanine is a stronger hole acceptor than adenine. As the standard deviations of the ΔG values are $\approx$0.3–0.4 eV, configurations of the system should exist where a radical cation state A^+ is more stable than G^+ and, thus, hole transfer from G^+ to A is energetically feasible.[37] The nucleobases G_3 and G_{12} in the duplex have similar surroundings (however, they are not equivalent) and, therefore, the CT driving force between them is close to zero on average.

Table 1: Relative energies ΔG of radical cation states in the duplex 5′-$TTG_3T_4T_5T_6T_7T_8T_9T_{10}T_{11}G_{12}$TT-3′ and its modified neutral derivative[a] calculated for an MD trajectory of 12 ns. The occupation[b] of the states corresponding to the equilibrium distribution of hole states is also given, measured as the fraction of time (along the trajectory) where the corresponding state has the lowest energy.

	Normal DNA		Modified DNA[a]	
Base	ΔG [eV]	Occupation [%][b]	ΔG [eV]	Occupation [%][b]
G_3		50.7		36.7
A_4	0.38 ± 0.28	1.8	0.30 ± 0.23	0.8
A_5	0.43 ± 0.32	1.3	0.31 ± 0.26	0.8
A_6	0.44 ± 0.35	1.0	0.30 ± 0.29	1.0
A_7	0.45 ± 0.37	0.7	0.29 ± 0.30	1.2
A_8	0.46 ± 0.39	0.6	0.29 ± 0.32	0.9
A_9	0.44 ± 0.40	0.5	0.28 ± 0.33	1.0
A_{10}	0.41 ± 0.42	0.6	0.26 ± 0.35	1.0
A_{11}	0.40 ± 0.45	0.8	0.23 ± 0.36	1.1
G_{12}	0.06 ± 0.49	42.0	-0.12 ± 0.40	55.5

[a] Negatively charged phosphates are replaced by neutral methylphosphonate groups. [b] In view of the hole transfer from site G_3 to site G_{12}, the distribution was normalized for the whole range between the donor to the acceptor sites. Each $(TA)_2$ unit at either end of the duplex beyond the G sites would contribute about 5% (in absolute terms).

Figure 1 describes the fluctuations of the CT energy between the bases G_3 and A_6 as a function of time. The characteristic time of such relevant fluctuations is 0.3–0.4 ns.[38] Analysis of QM/MD results obtained for the present duplex and other systems[20] suggests that fluctuations of the CT driving force are mainly due to two contributions: 1) molecular vibrations of the donor and acceptor sites, and 2) correlated motion of counterions and water molecules. The conformational dynamics of DNA, that is, the relative motion of adjacent nucleobases, plays only a minor role in the CT energetics, however, it substantially affects the electronic coupling between base pairs.[25] Because the vibrations of nucleobases occur on the femtosecond time scale, they are not pertinent to the charge migration process that occurs on a time scale ranging from several tens of picoseconds to several nanoseconds.[39]

Counterions in the vicinity of nucleobases have been suggested to strongly affect the energetics of radical cation states; the consequences for electron transfer have been referred to as an "ion-gating" mechanism.[23,24] Counterions are solvated and their motion is correlated by their hydration shell, which partially screens their long-range Coulombic

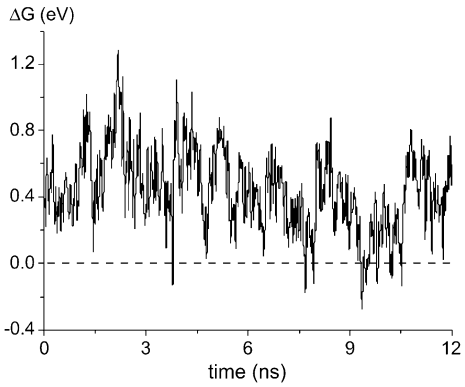

Figure 1. Fluctuations of the relative energy ΔG for hole transfer from G_3 to A_6 in the duplex 5′-$TTG_3T_4T_5T_6T_7T_8T_9T_{10}T_{11}G_{12}TT$-3′, calculated along a MD trajectory of 12 ns.

effect. To estimate directly the role of environmental fluctuations in modulating the value of ΔG for hole transfer, we considered a model system where only environmental fluctuations were accounted for, namely the rigid oligomer 5′-$(T)_5G(T)_2G(T)_5$-3′.[20] Standard deviations of ΔG for hole transfer in such a rigid system (≈ 0.15 eV) do not differ significantly from the standard deviations obtained for the corresponding system with a flexible DNA (≈ 0.19 eV), which confirms the key role of movement in the environment for modulating the hole-state energetics.

To quantify the effect of the counterions directly, we modeled a modified DNA duplex {5′-$(T)_2G(T)_8G(T)_2$-3′} where the negatively charged phosphate groups of the DNA backbone were replaced by neutral methylphosphonate groups.[23] Unlike the highly charged original duplex ($26e^-$), the modified duplex is neutral and, therefore, was modeled without counterions. The energy difference between G^+ and A^+ in modified DNA is reduced to $\Delta \approx 0.3$ eV (Table 1). Analysis of the radical ion state energies shows that on going from modified (neutral) DNA to normal DNA, the stabilization of the cations due to the phosphates is not quite compensated by the hydrated counterions, and an overall stabilization of the cation states results. Therefore, the reduced energy gap Δ of modified DNA implies that, on average, the A^+ states are better stabilized than the G^+ states. Thus, the possibility for hole hopping onto the A sites of the bridge should increase. Also, the standard deviations of the relative energies of modified DNA were calculated to be only $\approx 20\%$ smaller than for normal DNA. Apparently, the movement of the water molecules is responsible for the major contribution ($\approx 80\%$) to the energy variation of the hole states.

Changes in the energies of the hole states on different sites of a duplex were correlated. The correlation coefficients between energies of neighboring pairs of unmodified DNA (≈ 0.5) rapidly decreased with distance to 0.30, 0.11, and 0.02 for the second, third, and fourth neighbors, respectively. However, energies of states on remote sides tend to be negatively related; for instance, the correlation coefficients between hole states at G_3 on the one hand and A_8, A_{10}, and G_{12} on the other were -0.12, -0.20, and -0.31, respectively. The corresponding correlations for the modified duplex are somewhat weaker, -0.02, -0.16, and -0.29. Negative correlations are due to changes in the part of the environment between the sites; for instance, the rotation of the dipole of a water molecule directed along the DNA axis to G_3 by 180° will stabilize a hole state at G_3 and concomitantly destabilize a hole state at G_{12}. Also, the movement of counterions along DNA located between the considered sites contributes to the negative correlation.

Finally, we addressed the distribution of the hole states for CT from the donor site G_3 to the acceptor site G_{12} in the 14-mer duplex 5′-$TTG_3(T)_8G_{12}TT$-3′ and its methylphosphonate derivative (Table 1). This distribution was estimated as the fraction of time (along trajectories of 12 ns) when the corresponding hole state has the lowest energy compared to all other sites under consideration. The longest time interval for a hole resting on one of the G sites (i.e., when this hole state is lower than the cation states at all other sites) is about 100 ps, whereas this resting time is at most 12 ps on a $(TA)_8$ bridge. Non-negligible probabilities ($\approx 1\%$) were determined for events where an electron hole is localized on adenine bases. The total fractions of preferred bridge sites of unmodified and modified DNA (7–8%) are similar, but the distributions over the bridge sites differ in a characteristic way.[20] Thus, the dynamics of water molecules and counterions considerably modulates the relative redox potentials of the nucleobases. As a result, fluctuations of the environment can render hole-transfer processes from an GC base pair to an AT pair in a DNA duplex energetically feasible.

Analysis of our QM/MD simulations supports the recently proposed ion-gated mechanism for CT in DNA.[23] Note, however, that the thermal movement of the water molecules significantly dominates the variation of the hole-state energies in DNA. The fluctuations of relative energies of radical cation states are significant even in the absence of counterions, as in the case of a modified duplex with methylphosphonate groups instead of phosphates in the backbone. Our results suggest that adenine bases can also act as intermediates of electron-hole transfer. Thermal fluctuations of counterions and water molecules around DNA are responsible for configurations where the free energy of CT from a guanine to an adenine is negative. Such configurations are implied in the recently suggested A-hopping mechanism or, in a wider sense, in a domain mechanism, as recently inferred on the basis of experimental data.[14,15] Clearly, fluctuations of the CT driving force should be accounted when estimating the CT rate constants within the thermally induced hole-hopping model.[19] Further experiments probing the role of environmental fluctuations in a quantitative way are highly desirable for gaining further understanding of the CT mechanism in DNA.

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[34] The model assumes that the ensemble of radical cation states can be approximately characterized by data obtained for the corresponding non-ionized duplex; reorganization effects on the structure of DNA and its solvation shell are neglected. The driving force for hole transfer between two sites was estimated as being the difference of vertical ionization potentials calculated along MD trajectories of DNA fragments. The ionization energies were determined with the semiempirical NDDO-G method,[35] which is specially parameterized for calculating ionization and excitation energies of organic molecules. This procedure reproduces experimental ionization potentials of nucleobases in the gas phase with an average deviation of 0.09 eV,[35] and is thus well suited for estimating the value of ΔG for hole transfer between nucleobases. Because the reorganization energies connected with the formation of cation hole states of guanine and adenine bases are very similar, the corresponding contributions cancel when one estimates energy differences of such states. Thus, differences of vertical (instead of adiabatic) ionization energies can be used to estimate ΔG. The electrostatic effects of the surroundings were accounted for by approximating all atoms in the MD simulation box (26 Na^+ ions and 3936 water molecules) as point charges with values according to the force field;[31] the effective dielectric constant of the medium was chosen to be 2, which corresponds to fast electronic polarization.[36]
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[37] In line with experimental data,[1,18] radical states T^+ and C^+ lie considerably higher (1.4 and 1.2 eV, respectively) and cannot serve as hole acceptors in DNA.
[38] Characteristic times were estimated from the Fourier transform of the autocorrelation function of ΔG; they decrease from 380 ps for hole transfer $G_3 \rightarrow A_4$ to 304 ps for $G_3 \rightarrow G_{12}$.
[39] Pertinent CT time scales can be illustrated by rates for hole transfer in DNA. DNA hairpins linked by stilbene dicarboxamide imply characteristic times ranging from 30 ps to 5 ns for bridges of 1 to 3 AT base pairs.[12] Similar estimates from 10 to 200 ps were received for hole transfer from an acridine derivative as chromophore to 7-deazaguanine as acceptor, separated by one and two intermediate AT pairs.[40] Direct fluorescence probing of the dynamics of water around DNA with femtosecond resolution yielded mean residence times and reorientation times of water molecules at 3–6 ps.[41] MD simulations identified three characteristic time scales (120 ps, 280 ps, and 960 ps) for the dynamics of sodium ions near DNA.[33]
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