Energy contribution of the solvent to the charge migration in DNA

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The authors have investigated the interactions of the reaction centers, participating in the charge transfer reaction within the DNA molecule with the phosphate backbones and the solvent molecules, and have estimated the contribution of these interactions into the charge migration in DNA. They have determined the unequal shift of the energy surfaces of the initial and final transition states of the transfer reaction along the energy axis and the dependence of the magnitude of the energy shift on the nature of the reaction centers and the surrounding environment. The nonuniform distribution of the negative charge in the DNA phosphate backbones results in an increase of the positive shift of the energy surface of the DNA base pairs in the center of the structure, where the maximum density of the negative charge is concentrated. Localization of the positive charge on the guanine and the adenine in the DNA base pairs in the oxidized state results in a dependence of the free energy of reaction in the solvent on the pair sequences and their arrangement in the DNA chain. As an example, for the G-C/A-T configuration the positive charges are localized on the same strand that results in a decrease of the free energy of reaction in the solvent for charge migration from G-C to A-T pair by 0.125 eV. © 2007 American Institute of Physics. [DOI: 10.1063/1.2428304]

I. INTRODUCTION

Charge migration in double-helical DNA has been the topic of intense current interest, both theoretically and experimentally.1–10 Recent investigation of the distance-dependent charge transfer rates in DNA has revealed that in addition to the electron overlapping of the orbitals,2–4,6 the dynamics of charge migration is also essential for the interaction of the reaction centers with the surrounding environment, which is usually included in the solvent reorganization energy.7,8,10–12 The general concept of the reorganization energy was first developed in the 1950s by Marcus.13 It has been described as an energy shift due to restructuring of the molecular environment during the transfer reaction. Here one assumes that the transfer reaction in a molecule is activated by thermal reorientation of a polarized solvent molecule. A theoretical framework for calculation of the solvent reorganization energy was developed for spherically symmetric cavities of charges in a homogeneous dielectric medium.13

Despite significant developments in the theoretical work on charge migration in DNA,1 evaluation of the reorganization energy in DNA has been reported only in a few publications.14–17 However, not only that there are serious disagreements between the results of these calculations and some experimental data12,18 (except in Ref. 19), the distance dependence found in many of these works were often contradictory. In particular, in Refs. 14–17 the reorganization energy was predicted to increase with increasing distances between a donor and an acceptor, while in some experiments12,18 the opposite, or a practically distance-independent behavior was found. Proper evaluation of the contribution of the solvent to the charge transfer reaction is rather crucial for a better understanding of the long-range electron transfer in DNA and is the topic of this work.

Here we present a theoretical approach where the contributions of the molecular environment and the solvent surrounding the reaction centers are estimated as an energy shift to transfer the molecule segments participating in the charge transfer reaction from the vacuum into the solute. In our calculations we have included the electrostatic interaction of the molecule segments, participating in the charge transfer reaction with the molecular environment and the surrounding solvent, via the continuum electrostatic approach based on the Poisson-Boltzmann solver. Within this approach a molecule is represented by individual atomic charges, while the solvent is a continuous dielectric medium. A major drawback of all previous investigations of the solvent reorganization energy within the Marcus theory14–17 was the total disregard of the charge distribution inside the DNA base pairs and interaction of the reaction centers with the molecular environment, which is now properly included in the present approach.

II. THEORY

The elementary step of the hole transfer between the donor (D) and the acceptor (A) in the molecular environment is the exchange reaction \( D^+ + A + A^- \rightarrow A^+ + D \), which is typical for the charge transfer in a DNA molecule, where

\[
\Delta G = \Delta G_g + \Delta G_{s-m}.
\]

In Eq. (1), \( \Delta G_g \) is the free energy of the reaction in the gas phase, which can be estimated as the difference between the ionization potentials of \( D \) and \( A \), plus the inner-sphere reorganization energy \( \lambda \), accounting for the geometry relaxation of the molecular segments participating in the reaction. The
free energy of reaction in the solvent differs from that in the vacuum. The distinction is related to the different accessibility of the donor and acceptor to the solvent. Therefore, the energy term \(\Delta G^{g-m}\) in Eq. (1) is used to relate the influence of the molecular environment on the charge transfer between the donor and acceptor. In the solvent, we have estimated the energy \(\Delta G^{g-m}\) as the energy required to transfer the reaction centers from the vacuum to the change of the potential surfaces of the donor and acceptor in the surrounding solvent has to be taken into account. Contributions from all these interactions are included into three energy terms. 21 The Born-solvation energy \(G_{\mu}^{\text{Born}}\), the interaction of this group with other polar groups of the molecule and with the ions in the surrounding solvent has to be taken into account. Contributions from all these interactions are included into three energy terms. 21

\[
\Delta G^{g-m} = G_{D}^{g-m} - G_{A}^{g-m} = (E_{D}^{g-m} - E_{A}^{g-m}) - (E_{D}^{s} - E_{A}^{s}).
\]

Here \(G_{\mu}^{g-m}\) is the energy shift generated if a molecular group \(\mu = A\) or \(\mu = D\) is transferred from the vacuum into the molecular environment. The contribution of the electronic polarization in the energy shift \(G_{\mu}^{g-m}\) is significant in comparison to the dipole and atomic polarizations, while the dipole polarizations still prevail over the atomic part. This has been confirmed in the experimental investigation of polynucleotide macromolecules. 20

The methodology to calculate the shift of the free energy of reaction when a molecular group is transferred from the gas phase into the molecular environment was developed earlier for titration of the base and acid groups in proteins. 21,22 This approach allows us to investigate the influence of the electronic polarization inside the redox-active group on the surrounding environment, particularly the orientation of the solvent molecules in the electric field of the charges of the redox-active group. It includes two steps: transfer of the redox reactions from the gas phase into the aqueous phase and from the aqueous phase into the molecular environment \(\Delta G^{g-m} = \Delta G^{g-\nu} + \Delta G^{m-\mu}\). For a single titratable or redox-active group \(\mu\) the energy shift \(G_{\mu}^{g-m} = E_{\nu}^{g-m} - E_{\nu}^{s}\), where \(E_{\nu}\) is the solvation energy, i.e., the energy required to transfer the group \(\mu\) from vacuum into the aqueous phase. To transfer the redox-active group \(\mu\) from the aqueous phase to a molecular environment \(G_{\mu}^{m-\mu}\), the interaction of this group with other polar groups of the molecule and with the ions in the surrounding solvent has to be taken into account. Contributions from all these interactions are included into three energy terms. 21

The first term is the Born-solvation energy \(G_{\mu}^{\text{Born}}\), which describes the interaction of the redox-active group \(\mu\) with its reaction field. Due to the transfer reaction, the charge state of the redox-active group is changed, which leads to reorientation of the solvent polar molecules in the electric field of the charged group \(\mu\). The \(x_{\mu}^{n}\) represents the case if the redox-active group \(\mu\) is charged \(x_{\mu}^{n} = 1\) or uncharged \(x_{\mu}^{n} = 0\). The resulting electric field is the reaction field of \(\mu\). The second term is the energy \(G_{\mu}^{\text{back}}\), which includes contributions from the interaction of \(\mu\) with the background charges of the polar solute. 21

The changes of atoms in the nonactive redox groups of a molecule and of atoms in all active groups \(\nu\) in their uncharged form are regarded as background charges. The redox behavior of the redox-active group depends strongly on the neighboring charges, in particular, if several redox groups within the molecule are in their charged form. In the third term the interaction of the redox-active groups \(\mu\) with all the other redox-active groups or titratable groups \(\nu\) is included in the form of a \(W\) matrix. 22 Finally, using the energy terms \(G_{\mu}^{\text{Born}}, G_{\mu}^{\text{back}}, W_{\mu,\nu}\), we can compute the energy shift when the redox groups are placed from the vacuum to a molecular environment

\[
G_{\mu}^{g-m} = (E_{\nu} - E_{\nu}^{s}) + [G_{\mu}^{\text{Born}} + G_{\mu}^{\text{back}}] + \frac{1}{2} \sum_{i=1}^{N_{\nu}} W_{\mu,\nu} x_{\mu}^{n} x_{\nu}^{n}. \tag{3}
\]

The last term in Eq. (3) appears only when both groups \(\mu\) and \(\nu\) are in their charged states \((x_{\mu}^{n} = 1, x_{\nu}^{n} = 1)\) and accounts for the probability of oxidation of the redox-active group \(\mu\) in the molecule under the condition that the group \(\nu\) is already in the oxidized state. In Eq. (3) the summation runs over the number of redox-active groups \(\nu\) in the molecule.

III. RESULTS

We have used a two-step approach to evaluate the energy \(\Delta G^{g-m}\). First, a quantum chemical computation is performed in vacuum to determine the optimized neutral and ionic geometries of the redox-active groups and their atomic partial charge distribution. It is well known that the energy of the hydrogen bonds between nucleotides in the base pairs is strong, 24 which allows us to define the A-T and G-C pairs in a DNA molecule as redox-active groups. A geometry optimization is performed for the neutral and oxidized redox-active groups in the JAGUAR 6.5 program 25 within the Becke3P86/6-311G* approximation of the density functional theory method. Evaluation of the inner-sphere reorganization energy \(\lambda\), gives the values of 0.3676 and 0.7205 eV for the A-T and G-C pairs, respectively, which are in good agreement with the experimental results. 12 This can be regarded as a confirmation of the participation of the DNA pairs in the transfer reaction as redox-active groups. The restrained electrostatic potential (RESP) procedure 26 has been applied for the optimized neutral and ionic geometries to determine the atomic partial charge of the redox-active groups. The charge within such a redox-active group has a nonuniform distribution. The results show that in the nucleotide pairs in the oxidized state, the charge is mostly localized on the adenine and the guanine. The charge distribution has been calculated as a difference between the atomic partial charge in the oxidized and in the neutral states. In the A-T pair, 78% of the charge is localized on the adenine and 22% on the thymine, while in the G-C pair 88% of the charge is localized on the guanine and 12% on the cytosine.

In the second step, the optimized geometries of the redox-active groups in the neutral state were used for construction of the various sequences of a DNA molecule within the CHARMM27 program. The atomic partial charge of the reaction centers in the X and Xt states defined within the quantum chemical calculation were used for electrostatic calculations. The entire DNA molecule was described explicitly.
by the atomic partial charge and the van der Waals radii of atoms, which are available in Ref. 27. The energy $\Delta G^{\text{vacuum}}$ has been defined by the energy shifts of the redox-active groups $G_{\mu}^{\text{redox}}$ and $G_{\mu}^{\text{ox}}$. The APBS program with a nonlinear Poisson-Boltzmann solver was employed to evaluate the electrostatic potential of the solute molecule.28 This program has been improved to perform the $G_{\mu}^{\text{Born}}$, $G_{\mu}^{\text{back}}$, and $W_{\mu \nu}$ energy calculations and has also been adapted for the inhomogeneous dielectric medium calculations. We use the following dielectric constants for our calculations:29 $\varepsilon_1=3.4$ for the bases, $\varepsilon_2=2.0$ for sugar, $\varepsilon_3=20.6$ for the phosphate, $\varepsilon_4=40.0$ for the “bound water” region around molecular surface <3 Å, and $\varepsilon_5=78.3$ for the bulk water. In the bound water zone, the deviations of the local dielectric constant from the bulk value as a result of the lower mobility of the water molecules interacting with the charged and the polar group of the DNA molecule were simulated with the harmonic average smoothing method.

Our results for the salvation free energy $E_s$ and the energy shift $G_{\mu}^{\text{ox}}-G_{\mu}^{\text{redox}}$ are presented in Table I. Our calculated values of the solvation energy are in good agreement with the experimental results30 and with the results from other theoretical groups.31 Although it is not possible to compare our results for $G_{\mu}^{\text{ox}}-G_{\mu}^{\text{redox}}$ with any experimental data, from the agreement between our solvation energy and the other published results, the $G_{\mu}^{\text{ox}}-G_{\mu}^{\text{redox}}$ values can also be regarded as a reliable estimate. The energy $\Delta G^{\text{ox}}=G_{\mu}^{\text{ox}(\text{G-C})}-G_{\mu}^{\text{ox}(\text{A-T})}$ for charge migration from the G-C base pair to the A-T pair due to the solvent environment contribution is found to be $-0.075$ eV. The different accessibility of these redox-active groups to the solvent provides the decrease of the potential barriers between the G-C and A-T pairs in the aqueous phase [see Eq. (1)] in comparison to its value in vacuum $\Delta G^{\text{vacuum}}=0.34$ eV.

Calculations of the energy shift $G_{\mu}^{\text{ox}}-G_{\mu}^{\text{redox}}$ to transfer the redox-active groups from the solvent to a molecular environment were performed within the electrostatic approach [Eq. (3)]. Let us first explain the set of calculations for the 5′−(G−C)$_n$−3′ and 5′−(A−T)$_n$−3′ DNA sequences. Results for $G_{\mu}^{\text{ox}}-G_{\mu}^{\text{redox}}$ versus the dinucleotide number $n$ in the DNA sequences are presented in Fig. 1, where $n=6,10,16$. The energy $\Delta G^{\text{ox}}=G_{\mu}^{\text{ox}}-G_{\mu}^{\text{redox}}$ is negative for charge migration from the molecule sides to the n/2 nucleotide site, and positive for migration from n/2 to the molecule sides (Fig. 1). Such a behavior is found to be related to the nonuniform charge distribution along the negatively charged phosphate backbones because of a lower density of the negative charge at the termination sides 5′ and 3′. This leads to an increase of $G_{\mu}^{\text{ox}}-G_{\mu}^{\text{redox}}$ in the molecule center ($G_{\mu}^{\text{ox}(\text{G-C})}$). An increase of the sequence number $n$ in the DNA chain leads to a strong growth of $G_{\mu}^{\text{ox}(\text{G-C})}$ and its saturation is observed for the DNA sequences with $n=16$. The magnitude of the energy $\Delta G^{\text{ox}}$ is found to be maximum for $n=16$, particularly $\Delta G^{\text{ox}}=0.12$ eV for charge migration from the donor to the n/2 sequence.

The other sets of calculations were performed for the 5′−(G−(T)$_n$−(G)$_{5−n}$−3′ and 5′−(A−(T)$_n$−(G)$_{5−n}$−3′ DNA chains (Fig. 2). The nonuniform charge distribution in the oxidized state within the DNA pairs is the reason for the dependence of the energy shifts $E_{\mu}^{\text{ox}}$ on the DNA sequence combination. The nucleotides with high localization of the positive charge (adenine and guanine) can be stacked in opposite strands or within one strand. Stacking of guanine and adenine in the opposite DNA strands leads to a positive value of $\Delta G^{\text{ox}}=G_{\mu}^{\text{ox}(\text{G-C})}$, $G_{\mu}^{\text{ox}(\text{T-A})}$ for charge migration from G-C to T-A [Fig. 2(a)], despite the fact that $\Delta G^{\text{ox}}=0.075$ eV (Table I) is included in $\Delta G^{\text{ox}}$. The $\Delta G^{\text{ox}}$ for such sequences is $\sim0.08$ eV depending on the neighboring pairs. Therefore, for the charge migration from the first G-C to any of the T-A pairs in the 5′−(G−(T)$_n$−(G)$_{5−n}$−3′ sequence the energy $\Delta G^{\text{ox}}$ is positive ($\sim0.02$ eV). When the guanine and adenine are stacked within the same DNA strand an opposite effect takes place, namely, a negative value of $\Delta G^{\text{ox}}=G_{\mu}^{\text{ox}(\text{G-C})}$, $G_{\mu}^{\text{ox}(\text{T-A})}$ is observed [Fig. 2(b)]. The contributions of both the energies $\Delta G^{\text{ox}}=0.075$ eV and $\Delta G^{\text{ox}}=0.05$ eV are negative and significantly decrease the potential barriers between the G-C and A-T pairs (by 0.125 eV) that allows a hole to migrate easily toward the A-T pairs in the solvent than in the vacuum.

A similar behavior is also observed for the 5′−(G−(T)$_n$−(G)$_{5−n}$−3′ and the 5′−(A−(T)$_n$−(G)$_{5−n}$−3′ DNA sequences (Fig. 3). In the first case [Fig. 3(a)], the $\Delta G^{\text{ox}}$ for the hole migration from the donor G-C pair to the next G-C pair is negative. This value changes into the positive only when the distance between the two G-C pairs exceeds three T-A pairs and the influence of the negative charge distribution along the backbone becomes dominant [see the last se-

<table>
<thead>
<tr>
<th>$G_{\mu}^{\text{ox}}-G_{\mu}^{\text{redox}}$</th>
<th>$E_s$ (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenine</td>
<td>−0.37</td>
</tr>
<tr>
<td>Thymine</td>
<td>−0.39</td>
</tr>
<tr>
<td>Guanine</td>
<td>−0.63</td>
</tr>
<tr>
<td>Cytosine</td>
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</tr>
<tr>
<td>A-T</td>
<td>−0.49</td>
</tr>
<tr>
<td>G-C</td>
<td>−0.73</td>
</tr>
</tbody>
</table>

Table I. The solvation free energy $E_s$ and the energy shift $G_{\mu}^{\text{ox}}-G_{\mu}^{\text{redox}}$. All values are in eV.
quences in Fig. 3(a)]. The $\Delta G_{\mu}^{\pm-m}$ for the hole migration from the donor G-C pair to the T-A pair is almost everywhere positive. For the $5'-G-(A)_n-G-(A)_{4-n}-3'$ DNA sequences [Fig. 3(b)] the energy $\Delta G_{\mu}^{\pm-m}$ remains negative over the whole chain for charge migration from G-C pair to any A-T pair due to the negative contribution of both components $G_{\mu}^{\pm}$ and $G_{\mu}^{\pm-m}$.

Finally, for charge migration from the G-C to the A-T pair within the molecular environment the potential barrier was found to be decreased by 0.125 eV in comparison to that in the vacuum ($\Delta G_{\text{vacuum}}=0.34$ eV). The influence of the molecular environment for charge migration from the G-C to the T-A pair is not strong and leads to an increase of the potential barrier by 0.02 eV. These results are in good agreement with the theoretical simulations of charge transport in the DNA molecule within the polaron model. The contribution of the solvent environment was found to be responsible for a decrease of the potential barriers between the G-C and the A-T pairs.

The value of the dielectric constant determines the degree of mobility of the molecule segments, namely, a lower dielectric constant corresponds to a lower relaxation of the molecule segments during the transfer reaction. We have investigated the influence of $\varepsilon_{s}$ in the “bound water” region on the energy shift $G_{\mu}^{\pm-m}$. A decrease of $\varepsilon_{s}$ from 40 to 5 provides a fast increase of about 0.15 eV ($n=10$) for the $G_{\mu}^{\pm-m}$ in the center of the molecular chain. Qualitatively, the same dependence is seen for the dielectric constant of the phosphate backbone $\varepsilon_{g}$.

The oxidation potential of the redox-active group at the donor side of a molecular chain $\mu=1$ depends both on the molecular environment and on the charge state of other redox-active groups $\nu$. The Coulomb interaction between charges of the two redox-active groups $\mu$ and $\nu$ in their oxidized state is included in the $W$ matrix [Eq. (3)]. Our results show that the oxidation potential $E_{\mu}^{\pm-m} = E_{\mu}^{\pm-m} - E_{\nu}^{\pm-m}$ of the group $\mu$ at the donor side changes slightly if another group $\nu$ is in its oxidized state ($\frac{1}{2}W_{\mu=1,n=2}=0.1$ eV if the second charge is localized on the neighboring pairs). The $W$ matrix can be expressed as $\frac{1}{2}W_{\mu,n}=0.6 \exp(-N_{\mu}eV)$, where $N_{\mu}$ is the order number of the second charged group $\nu$ in the DNA chain. Such a dependence of the oxidation potential on radical localization along the DNA chain allows us to assume that several holes can migrate through the DNA molecule simultaneously due to the weak Coulomb interaction between two charges localized on the neighboring base pairs.

IV. CONCLUSIONS

In our present approach it has been shown that the contribution of the interactions of the reaction centers with the surrounding environment $\Delta G_{\mu}^{\pm-m}$ into the charge transfer re-
action in the DNA molecule changes the potential energy surfaces of the initial and the final transition states. In particular, these surfaces are shifted along the energy axis depending on the accessibility of the reaction centers to the solvent environment. The contribution of the molecular environment and the charge distribution inside the DNA pairs provides an unequal shift of the initial and final states, which can increase or decrease the free energy of reaction in the solvent depending upon the $\Delta G^{\ddagger m}$ being positive or negative. Prior to our present work, this fact was not properly taken into account. The decrease of the potential barrier by 0.125 eV for charge migration between the G-C and A-T pairs and an increase by 0.02 eV between the G-C and the T-A pairs inside the DNA molecule have been established. An important point to note here is that, due to the contribution from a nonuniform distribution of the negative charge of the phosphate backbones and the nonuniform charge distribution between the nucleotides in a DNA pair, no strong distance dependence of the energy shift $\Delta G^{\ddagger m}$ is present in our results, which agrees with some of the experimental results. Furthermore, the dependence of $\Delta G^{\ddagger m}$ on the site position in the DNA chain (Fig. 1) can be a reason for the experimentally observed contradictory distance dependences of the solvent reorganization energy.  

**ACKNOWLEDGMENTS**

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1. Long-range Charge Transfer in DNA, edited by G. B. Schuster (Springer-Verlag, Heidelberg, 2004) and references therein.
22. For details about the formalism, see Ref. 21.