Energetics of the hole transfer in DNA duplex oligomers

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Abstract

We have studied the inner-sphere reorganization energy and interaction of the \( \pi \) orbitals in DNA. We predict an increase of the intra-strand electronic coupling in the oligomers with the increase of the number of base pairs due to the lattice packing effect. We estimate the geometry relaxation of the base pairs within the (A–T)\(_n\) and (G–C)\(_n\) oligomers \((n = 1–6)\) due to their oxidation. A decrease of the inner-sphere reorganization energy with increasing \( n \) was observed. The maximum degree of geometry relaxation is found to be located close to the oligomer center for \( n \leq 4 \).

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1. Introduction

Discovery of charge migration in DNA molecules has opened new avenues to investigate various possibilities ranging from its role in the DNA oxidative damage and repair [1] to application of DNA in nanoelectronic device developments [2]. Quite expectedly, the DNA molecule has become a subject of intense research activities both theoretically [3–7] and experimentally [8–11]. The charge migration process in the DNA molecule causes the geometry distortion of the states participating in the charge migration and the surrounding environment, which significantly contributes to the rate of charge transfer. Due to the interaction of the \( \pi \) orbitals of the nearest neighbor duplexes and small ionization potential (IP) difference between them, the holes can be distributed over several sites in the (A–T)\(_n\) and (G–C)\(_n\) oligomers. This changes the magnitudes of the geometry relaxation of the nucleobases (the inner-sphere component) and the environment contribution (the outer-sphere component). However, investigation of the transfer parameters, such as the electronic coupling and the activation energy for charge migration, i.e., the IP and the reorganization energy [3,5,12], have been reported mostly for the nucleobases and/or the base pairs.

The main purpose of our work is to estimate the electronic coupling between the two nearest nucleobases, their charge distribution and the inner-sphere reorganization energy, when they are placed within the (A–T)\(_n\) and (G–C)\(_n\) oligomer duplexes. These computations are performed using the accurate quantum-chemical methods.

2. Method of computation

Transfer of an electron in the DNA molecule is strongly dependent on the details of the donor and the acceptor energies and deviation of their geometries [11]. The charge transfer occurs due to overlapping between the \( \pi \)-electrons of the carbon and the nitrogen atoms that forms the \( \pi-\pi \) orbitals between the parallel nucleobases. Charge migration in the molecular systems with weakly interacting donors and acceptors is described by the standard high-temperature nonadiabatic electron-transfer rate

\[
k = \frac{2\pi}{h}|H_{DA}|^2(FC),
\]

where \( H_{DA} \) is the electronic donor–acceptor matrix element and FC is the Franck–Condon factor. The electronic donor–acceptor matrix element \( H_{DA} \) is defined by the coupling of the orbitals of the donor and the acceptor.
and depends on the structure of the DNA molecule. For the (A–T)\textsubscript{n} and (G–C)\textsubscript{n} oligomers, \( H_{DA} = \prod_{k=1}^{n} V_{k,k+1} \), where \( V_{k,k+1} \) is the electronic coupling of molecular orbitals belonging to the nearest base pairs \( k \) and \( k+1 \).

According to Koopman’s theorem, the electronic coupling can be estimated as half of the adiabatic state splitting \( \Delta \) between the HOMO and the HOMO-1 of the closed shell neutral system, determined in a Hartree–Fock (HF) approximation with the self-consistent field (SCF) procedure. The Koopman’s theorem for the DNA molecule is valid for a system of two stacked base pairs. For a periodic system, such as the (A–T)\textsubscript{n} and (G–C)\textsubscript{n} oligomers, where the molecular chain is a homogeneous structure and can be considered as a periodic lattice in one dimension, the electronic coupling can be derived from the tight-binding approximation in the bases of the local molecular orbitals [13]. The eigenvalues of each period \( k \) corresponding to the HOMO energies in a finite periodic system can be determined from

\[
\lambda_k = a + 2b \cos \left( \frac{kn}{n+1} \right),
\]

where \( a \) is the HOMO energy, and \( b \) is the hopping integral. Therefore, for \( n = 2 \) the electronic coupling according to Koopman’s theorem is \( V_{k,k+1} = (\lambda_1 - \lambda_2)/2 \approx 1/\Delta \). For \( n = 3 \), \( V_{k,k+1} \approx 1/\Delta /0.707 \), for \( n = 4 \), \( V_{k,k+1} \approx 1/\Delta /0.5 \), for \( n = 5 \), \( V_{k,k+1} \approx 1/\Delta /0.366 \) and for \( n = 6 \), \( V_{k,k+1} \approx 1/\Delta /0.2855 \).

In Section 3.1, we simulate the orbital splitting for the nucleobases within the (A–T)\textsubscript{n} and (G–C)\textsubscript{n} oligomers using the quantum chemistry methods with the Jaguar 6.5 program [14]. The RHF using the basis set with polarization and diffuse functions 6-31+G* was used for calculations of the orbital splitting. The 6-31+G* basis set is appropriate for our purposes. Previous investigations indicated that any further extension has little influence on the electronic coupling [5]. The geometries of the separated DNA base pairs have been optimized with the RHF/6-31+G* bases and in the following, the optimized geometries of the base pairs have been stacked with a twist angle 36° and a distance of 3.38 Å. The stacking of the preliminary optimized geometries allows us to consider the same nucleobases to be ‘in resonance’ [5] within the structures of the (A–T)\textsubscript{n} and (G–C)\textsubscript{n} oligomers.

The FC factor deals with the influence of the vibrionic interaction on the charge propagation:

\[
FC = (4ik_{\text{g}}T)^{-1} \exp \left( -\frac{(\Delta G + \lambda)^2}{4ik_{\text{g}}T} \right),
\]

where \( \Delta G \) is the free energy of the reaction, and \( \lambda = \lambda_s + \lambda_t \) is the reorganization energy. The interaction of the molecule with the solvent environment is included in the outer-sphere reorganization energy \( \lambda_s \), while the relaxation of the acceptor, the donor and the molecular bridge geometries are included in the inner-sphere reorganization energy \( \lambda_t \). According to the experimental results [8], the contribution from \( \lambda_t \) to the charge transfer process is much larger than from \( \lambda_s \). Therefore, an accurate determination of the inner-sphere component is an important issue, which is considered in our present work.

The inner-sphere reorganization energy can be estimated within the quantum chemical approach as

\[
\lambda_i = \lambda_s + \lambda_t = (E_{\text{a}}(A) - E_{\text{b}}(A)) + (E_{\text{b}}(D) - E_{\text{a}}(D)),
\]

where \( E \) is the energy of the neutral state in a neutral geometry, \( E^* \) is the energy of the neutral state in an ionic geometry, \( E_{\text{a}} \) is the energy of the ionic state in an ionic geometry, and \( E_{\text{b}} \) is the energy of the ionic state in a neutral geometry. The reorganization energy \( \lambda_s \) is the energy to remove an electron from the hole acceptor \( A \), while the reorganization energy \( \lambda_t \) is the energy to add an electron to the hole donor \( D^+ \). The vertical ionization potential is determined as \( \text{vIP} = (E^* - E) \) and differs from the adiabatic IP = \( (E_\text{a} - E) \) by the \( \lambda_s \).

The inner-sphere reorganization energy has been evaluated within the unrestricted Becke3P86/6-311+G* approximation of the DFT method. The DFT theory was found to be reasonable for this purpose based on a comparison of the results of Ref. [12]. These results show that the DFT theory with the triple-split basis set predicts the magnitude of the inner-sphere reorganization energy with a minimum error when compared to the experimental data [15–17]. Furthermore, we found a Becke3P86 approximation to be appropriate for the vertical ionization potential (vIP) calculations, while HF has significant disagreement with the experimental data [17].

3. Results and discussion

3.1. Distribution of HOMO energies

At first we consider the system of two stacked duplexes. We have estimated that delocalization of the highest occupied base orbitals (HOBs) to the phosphate backbone are really small and can be neglected. Moreover, the value of orbital splitting of the stacked bases is practically independent of the phosphate contribution. Therefore, in what follows, we consider DNA oligomers without the phosphate backbones. The results for the HOBs are presented in Table 1. In the case when the pyrimidine/pyrimidine and purine/purine bases are stacked in one strand, the HOBs of the adenine and the guanine bases have the lowest energy in comparison to the pyrimidine/purine configurations. For the (A–T)\textsubscript{2} and (G–C)\textsubscript{2} oligomers, the HOBs are delocalized over the two intrastrand nucleobases and therefore it produces a significant coupling between the \( \pi \) orbitals of the stacked pyrimidine/pyrimidine and purine/purine bases. The disagreement of the magnitude of the electronic coupling with the experimental data, where the electronic coupling is usually much smaller than 0.1 eV [8], can be related to the sensitivity of the electronic coupling to the conformation [5], that can change the magnitude of electronic coupling up to 50 times. For oligomers
where the pyrimidine and the purine bases are stacked in the same strand (A–T/T–A, G–C/C–G, A–T/C–C) or in the mixed structures (A–T/G–C and G–C/A–T), in some cases the π orbitals are delocalized, but electronic coupling is weak. For others the π orbitals are localized mostly on one nucleobase, and we can consider the weak intrastrand and interstrand coupling between the nucleobases as well. The low interstrand coupling for the cases A–T/T–A and G–C/C–G has been observed experimentally [18], while in some theoretical computations a large coupling has been determined [5].

In the (A–T)\textsubscript{n} and (G–C)\textsubscript{n} DNA oligomers, the 2\textit{n} π orbitals are delocalized over the neighboring intrastrand nucleobases. We have found that the HOMO corresponds to the central nucleobases in the (A–T)\textsubscript{n} and (G–C)\textsubscript{n} oligomers structures. Particularly, the HOBOs of the adenine and the guanine primarily belong to the nucleobase in the center of the oligomer, while the HOBO-1 belongs to the nearest neighboring nucleobase of the oligomer center. This effect is related to the coulomb potential distribution over the (A–T)\textsubscript{n} and (G–C)\textsubscript{n} oligomers in the vacuum. We have computed the electrostatic potential distribution for the (A–T)\textsubscript{n} and (G–C)\textsubscript{n} oligomers with the APBS program performing the nonlinear Poisson–Boltzmann solver [19]. The RESP procedure [20] has been applied to determine an atomic partial charge of the separated A–T and G–C base pairs. For the electrostatic simulations the atomic partial charges of the base pairs are the same for each base pair over the whole oligomer structure. We have found that for the (A–T)\textsubscript{3} structure, the electrostatic potential on the central adenine and thymine is more negative than on the nucleobases of the oligomer sides. For the (G–C)\textsubscript{3} structure, the electrostatic potential on the central guanine is more negative than on the sides, while for the cytosine the opposite is true. Therefore, a stronger localization of the HOMO density on the central nucleobase is observed for the (A–T)\textsubscript{n} oligomer, where the HOMO is mostly delocalized over three neighboring intrastrand adenines, than for the (G–C)\textsubscript{n} oligomer, where the HOMO is delocalized over four neighboring guanines. For \textit{n} = 3, the population of the HOMO is much larger for the central nucleobases than for the sides. The degree of accumulation of the negative electrostatic potential in the oligomer center decreases with the structure elongation. For \textit{n} > 3, the population of the HOMO on the central nucleobases significantly decreases due to the electrostatic potential distribution and the HOMO delocalization.

The delocalization of the orbital electron density over the oligomer structure produces a decrease of the HOBO energies with the elongation of the DNA chain. The dependence of the orbital energies of the \textit{n} HOBOs, which are the π orbitals of the nucleobases in the (A–T)\textsubscript{n} and (G–C)\textsubscript{n} oligomers, on the number of base pairs \textit{n} are presented in Fig. 1. As expected, the splitting of the HOBO and HOBO-1 decreases with the elongation of the duplex oligomer structures. The orbital splitting of the HOBO and the HOBO-1 of the nucleobases belonging to the nearest base pairs within the (A–T)\textsubscript{n} and the (G–C)\textsubscript{n} oligomers are presented in Fig. 2. As we mentioned above, the π orbitals are primarily delocalized over 3 – 4 intrastrand nucleobases. Therefore, a fast decrease of the orbital splitting for \textit{n} ≤ 4 is observed when the π orbitals have the potential to spread. For \textit{n} > 4, the splitting decreases slowly. Based on these results, we have recalculated the electronic coupling for the (A–T)\textsubscript{n} and (G–C)\textsubscript{n} oligomers according to the approximation scheme presented in Section 2 (see Eq. 2). For guanines in the DNA chain the electronic coupling is \(V_{k,k+1} = 0.155\) eV for \textit{n} = 2, \(V_{k,k+1} = 0.174\) eV for \textit{n} = 3, \(V_{k,k+1} = 0.21\) eV for \textit{n} = 4, \(V_{k,k+1} = 0.256\) eV for \textit{n} = 5 and \(V_{k,k+1} = 0.287\) eV for \textit{n} = 6. For adenines \(V_{k,k+1} = 0.086\) eV for \textit{n} = 2, \(V_{k,k+1} = 0.091\) eV for \textit{n} = 3, \(V_{k,k+1} = 0.097\) eV for \textit{n} = 4, \(V_{k,k+1} = 0.109\) eV for \textit{n} = 5 and \(V_{k,k+1} = 0.110\) eV for \textit{n} = 6. Therefore, for nucleobases the electronic coupling can increase when the number of base pairs...
in the DNA chain are increased, due to the lattice packing. The proper HOBO energies in the oligomer structure can be obtained within the tight-binding approximation as well (see Eq. 2).

### 3.2. Inner-sphere reorganization energy

The orbital overlapping and the distribution of the HOMOs over the oligomer structure directly influence the charge distribution in the DNA molecule and the inner-sphere reorganization energy, respectively. We have calculated the inner-sphere reorganization \( \lambda_{i,A} \) and \( \lambda_{i,D} \) and the vIP for the separated nucleobases and their pairs. The results are compared with the experimental data [15–17] in Table 2. From Table 2 it is clear that our calculation and the experimental results for the nucleobases are in good agreement except for cytosine. A better agreement can also be achieved within the many-body approaches including the higher orders in the perturbation theory [21]. In general, the extended basis set used here, including the polarization functions, reduces the disagreement with the experimental data in comparison to the results of Ref. [12].

<table>
<thead>
<tr>
<th>vIP</th>
<th>vIP [17]</th>
<th>( \lambda_{i,A} )</th>
<th>( \lambda_{i,D} )</th>
<th>( \lambda_{i} )</th>
<th>( \lambda_{i,A} [15–17] )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenine</td>
<td>8.874</td>
<td>8.44</td>
<td>0.200</td>
<td>0.202</td>
<td>0.402</td>
</tr>
<tr>
<td>Thymine</td>
<td>9.380</td>
<td>9.14</td>
<td>0.243</td>
<td>0.270</td>
<td>0.514</td>
</tr>
<tr>
<td>Guanine</td>
<td>8.463</td>
<td>8.24</td>
<td>0.434</td>
<td>0.439</td>
<td>0.874</td>
</tr>
<tr>
<td>Cytosine</td>
<td>9.305</td>
<td>8.94</td>
<td>0.111</td>
<td>0.112</td>
<td>0.223</td>
</tr>
<tr>
<td>(A–T)</td>
<td>8.438</td>
<td>–</td>
<td>0.149</td>
<td>0.218</td>
<td>0.368</td>
</tr>
<tr>
<td>(G–C)</td>
<td>7.833</td>
<td>–</td>
<td>0.353</td>
<td>0.368</td>
<td>0.721</td>
</tr>
<tr>
<td>( 3'-(A–T)-5' )</td>
<td>7.621</td>
<td>–</td>
<td>0.194</td>
<td>0.263</td>
<td>0.457</td>
</tr>
<tr>
<td>( 3'-(G–C)-5' )</td>
<td>6.823</td>
<td>–</td>
<td>0.446</td>
<td>0.460</td>
<td>0.906</td>
</tr>
</tbody>
</table>

All values are in eV.

For the nucleobases, the large geometry relaxation between the neutral and the oxidized states, particularly the change in C–C, C–N and C–O bond lengths, is the cause of the large magnitude of the inner-sphere reorganization energy. In the case of the pair formation, the inner-sphere reorganization energy is defined as the geometry relaxation of both nucleobases of the pair and is decreased by the flexibility of the hydrogen bonds in the neutral and ionic geometries. For the A–T pair the inner-sphere reorganization energy is found to be one-third of the sum of the reorganization energy of the separated adenine and thymine. That is a result of insignificant geometry relaxation of the nucleobases itself during the oxidation process because of the high flexibility of the two hydrogen bonds (opening translation [13]). There are three hydrogen bonds between the nucleobases in a G–C pair, which restrict the translation and rotation flexibility of the nucleobases. This causes the not so significant decrease of the inner-sphere reorganization energy for the G–C pair compared to that of the A–T pair.

We have calculated the charge distribution as the charge difference between the oxidized \( E_{+(A,D)} \) and the neutral states \( E_{(A,D)} \) with Mulliken population analysis [22]. For the (G–C) and (A–T) states with the phosphate and without the phosphate backbone ~80% of charge is localized respectively on the guanine and the adenine. Therefore, taking into account the charge distribution and the difficulties to calculate \( \lambda_{i} \) for the single purine within the DNA chain, we consider the A–T and G–C base pairs to be a single redox-active state for the following calculations of \( \lambda_{i} \). The stacking of the base pairs into the (G–C) and (A–T) oligomers leads to a decrease of the inner-sphere reorganization energy \( \lambda_{i} \) of the whole oligomer structure and a decrease of the vIP as well. The results (Fig. 3) show a decrease of \( \lambda_{i} \) due to the contribution of the rotation and translation of the base pairs relative to each other. According to our results, with elongation of the (A–T) and (G–C) oligomers, the inner-sphere reorganization energy decreases, and the vIP increases.

![Fig. 2. The dependence of Δ/2 between the HOBO and HOBO-1 for the nucleobases in the (A–T) and (G–C) duplex oligomers (RHF/6-31+G*//RHF/6-31+G*).](image)

![Fig. 3. The inner-sphere reorganization energy \( \lambda_{i} = \lambda_{i,D} + \lambda_{i,A} \) and the vIP values versus the number of pairs in a DNA duplex oligomers (A–T) and (G–C).](image)
(G–C)ₙ oligomers the twist of the base pairs mostly contributes to the decrease of the geometry relaxation of each nucleobase and in a reduction of the \( \lambda_i \). The obtained decrease of the inner-sphere reorganization energy in the DNA molecule is much stronger than for the other oligomers like oligoacenes [25]. The decrease of the inner-sphere reorganization energy (see Fig. 3) provides the decrease of the vIP.

As we mentioned above, \( \lambda_i \) depends on the charge distribution over the chain. The electrostatic potential distribution in the (G–C)ₙ and (A–T)ₙ oligomers and respectively the location of the HOMO in the oligomer centers provide the localization of the charge on the central guanines and adenines in the oxidized state. For example, the accumulation of the atomic partial charge on the edges is lower than that at the chain center by 0.06 Coul for the (A–T)₃ and by 0.25 Coul for the (G–C) sequences. For the (G–C)ₙ sequence our results are in agreement with the data in Ref. [23]. Increase of \( n \) decreases the charge accumulation in the structure center.

Therefore, charge accumulation in the oligomer centers in the oxidized state produces the maximum geometry relaxation in the center of the DNA chain. We have estimated the geometry relaxation of the separated base pairs \( \Delta_{D}^{n} \), within the optimized geometries of the (A–T)ₙ and (G–C)ₙ oligomers, where \( n = 1, \ldots, 6 \). The simulation results of \( \Delta_{D}^{n} \) for \( n = 3 \) and \( n = 5 \) are presented in Fig. 4. Clearly, for the (G–C)ₙ sequences the difference of the structure relaxation at the sides of the chain and in the center is significant than that for the (A–T)ₙ sequences. The behavior of these curves is opposite to that of the electrostatic potential distribution calculated for each base pair within the (A–T)ₙ and (G–C)ₙ oligomers, when larger \( \Delta_{D}^{n} \) corresponds to the lower value of the electrostatic potential. For the long oligomers (\( n \geq 6 \)) the electrostatic potential and correspondingly, the behavior of \( \lambda_i \) is characterized by the wavy dependencies where the values of the maximum and minimum differ slightly and are determined by the helical turn. Therefore, we can conclude that the Coulomb interaction between the base pairs within the oligomer structures defines the HOMOs, charge and the inner-sphere reorganization energy distribution over the DNA chain.

The difference between the inner-sphere reorganization energy of the (A–T)ₙ and (G–C)ₙ oligomers should provide the larger magnitude of the vibrational coupling constant for the G–C pairs than that for the A–T pairs, and larger for the guanine than that for the adenine (see Table 2). The contribution of \( \lambda_i \) to the charge migration leads to a positive shift of the free energy of next reactions G–C \( \rightarrow \) (G–C)₂ and G–C \( \rightarrow \) (G–C)₃. This statement is supported by the experimental data [24], where a significant increase of the free energy for these reactions \((-0.055 \text{ eV} \text{ and } -0.077 \text{ eV})\) in comparison to the IP difference in vacuum was observed.

4. Conclusions

We have investigated the electronic coupling and the inner-sphere reorganization energy for the (A–T)ₙ and (G–C)ₙ (\( n = 1, \ldots, 6 \)) DNA oligomers via accurate quantum-chemical methods. The electronic coupling between the two neighbor nucleobases within the same strand can increase with increasing base pair number \( n \) participating in the chain formation due to the lattice packing. A strong influence of the electrostatic interactions to the distribution of the electron density and the charge have been observed. The charge distribution in the chain determines the degree of the geometry relaxation of the base pairs during the oxidation process depending on their location within the oligomer. Therefore, the base pairs in the chain center have stronger geometry distortion during the oxidation process when \( n \leq 4 \).

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