Electronic parameters for the hole transfer in DNA duplex oligomers.

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We report on our calculations of the inner-sphere reorganization energy and the interaction of the $\pi$ orbitals within DNA oligomers. The exponential decrease of the electronic coupling between the highest and second highest occupied base orbitals of the intrastrand nucleobases in the (A-T)$_n$ and (G-C)$_n$ oligomers have been found with an increase of the sequence number $n$ in the DNA structure. We conclude that for realistic estimation of the electronic coupling values between the nucleobases within the DNA molecule, a DNA chain containing at least four base pairs is required. 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. The decrease of the inner-sphere reorganization energy with elongation of the oligomer structure participating in the oxidation process have been observed. The maximum degree of geometry relaxation of the nucleobase structures and correspondingly the higher charge density in the oxidized state are found to be located close to the oligomer center.

I. 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]. In fact, DNA-based molecular electronic devices are expected to operate within the picoseconds range [3, 4] that can exceed the potential of the present solid state devices. Quite expectedly, the DNA molecule has become a subject of intense research activities both theoretically [5, 6, 8, 9, 10, 11, 12] and experimentally [7, 12, 13, 16].

From all these studies of charge migration in the DNA molecule reported as yet, it is clear that there are two mechanisms for transfer of charge depending on the DNA structure and transfer parameters: a superexchange charge transfer and the incoherent hopping [7]. The charge migration leads to the geometry changes in the nucleotides and the surrounding environment, which significantly contribute to the charge migration process. Due to the interaction of the $\pi$ orbitals of the nearest neighbor duplexes and insignificant IP difference between them, hole can be distributed over several sites in the (A-T)$_n$ and (G-C)$_n$ oligomers. This significantly changes the magnitudes of the geometry relaxation of the nucleobases – inner-sphere component and environment contribution – outer-sphere component. However, the investigation of the transfer parameters, such as orbital overlapping [9, 10, 17] and activation energy for charge migration i.e., the IP and the reorganization energy [3, 4, 8, 10, 17, 18, 19, 21], have been performed mostly for the nucleobases or base pairs.

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

II. METHOD OF COMPUTATION

The relatively small reaction free energy in the DNA molecule makes the DNA hole transfer mechanism qualitatively different from that in most proteins [22]. The electron transfer in the DNA molecule was found to be strongly dependent on the details of the donor and acceptor energies and deviation of their geometries [16].

The charge transfer in a DNA molecule occurs due to the 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, such as between the base pairs in the DNA molecule, is described by the standard high-temperature nonadiabatic electron-transfer rate

$$k = \frac{2\pi}{\hbar} |H_{DA}|^2(FC),$$

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)$_n$ and (G-C)$_n$ oligomers the simple expressions for the deviation of the electronic coupling on the sequence number $n$ have been generated [23]. According to these expressions, the value of the electronic coupling decreases with elongation of the oligomers [23]. In Sect. III A, we simulate the electronic coupling of the nucleobases within the (A-T)$_n$ and (G-C)$_n$ oligomers using the quantum chemistry methods with the Jaguar 6.5 program [24]. According to the Koopmans’ theorem, the electronic coupling can be estimated as half of the adiabatic state splitting between the HOMO and the HOMO-1 of the closed shell neutral system, determined in a...
where $\Delta G$ is the reorganization energy and $E^*$ is the energy of the neutral state in an ionic geometry, $E_+$ is the energy of the ionic state in an ionic geometry, and $E^*_+ = E_+ - E_0$ is the energy of the ionic state in a neutral geometry. The reorganization energy $\lambda_{i,A}$ is the energy to remove an electron from the hole acceptor $A$, while the reorganization energy $\lambda_{i,D}$ is the energy to add an electron to the hole donor $D^+$. The scheme for calculation of the reorganization energy is presented in Figure 1. Clearly, the vibronic interactions stabilize the geometry of the donor and the acceptor from a non-equilibrium state $(E^+_A, E^*_D)$ to the equilibrium state $(E^*_A, E^*_D)$. The vertical ionization potential is determined as $\text{vIP} = (E^*_A - E)$ and differ from the adiabatic IP = $(E^-_A - E)$ by the inner-sphere reorganization energy.

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. [21]. These results show that the DFT theory predicts the magnitude of the inner-sphere reorganization energy with a minimum error when compared to the experimental data [22, 20, 27]. Furthermore, we have also tested the application of the HF method and the DFT theory for the vertical ionization potential (vIP) calculations and have found significant qualitative and quantitative disagreement of the HF with the experimental data [22], while the Becke3P86 approximation is appropriate for this purpose.

III. RESULTS AND DISCUSSION

A. High occupied orbital distribution

At first we consider the system of two stacked duplexes. The results for the highest occupied base orbital (HOBO) are presented in Table I. In the case when the pyrimidine/pyrimidine and purine/purine bases are stacked in one strand, the HOBOs of the adenine and guanine bases have lowest energy in comparison to the pyrimidine/purine configurations. For the (A-T)$_2$ and (G-C)$_2$ oligomers the HOBOs 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. 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), for some cases the $\pi$ orbitals are delocalized, but electronic coupling is weak. For others the $\pi$ 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 [22].

In the (A-T)$_n$ and (G-C)$_n$ DNA oligomers, the $2n \pi$ orbitals are delocalized over the neighboring intrastrand nucleobases. We have found that the HOMO corresponds to the central nucleobases in the (A-T)$_n$ and (G-
TABLE I: The HOBO within the system of two stacked base pairs estimated with RHF/6-31+G*//RHF/6-31+G*, in the case when the orbital is localized (l) on a single nucleobase, or delocalized (d). All values are in eV.

|   | A A | A T | G G | G C | A G | G A | A C |
|---|-----|-----|-----|-----|-----|-----|-----|
| T T | T A | C C | C G | T C | C T | T G |
| adenine | 8.10(d),8.38(d) | 8.17(d),8.33(d) | - | - | 7.96(l) | 8.24(l) | 8.32(l) |
| thymine | 9.24(d),9.71(d) | 9.01(l),9.35(l) | - | - | 9.38(d) | 9.48(d) | 8.69(l) |
| guanine | - | - | 7.17(d),7.48(d) | 7.46(l),7.77(l) | 7.39(l) | 7.34(l) | 7.44(l) |
| cytosine | - | - | 9.69(d),10.08(d) | 9.33(l),9.36(l) | 9.71(d) | 9.81(d) | 9.65(l) |

Cₙ oligomers structures. Particularly, the HOBOs of the adenine and guanine primarily belongs to the nucleobase in the center of the oligomer, while HOBO-1 belongs to the nearest neighboring nucleobase to that in the oligomer center. Similarly, the HOMO resides primarily on the central guanine have been observed for the 5’-(G-C)ₙ structures. This effect is related to the electrostatic potential distribution over the (A-T)ₙ and (G-C)ₙ oligomers in the vacuum. We have computed the electrostatic potential distribution in the (A-T)ₙ and (G-C)ₙ oligomers with the the APBS program performing the nonlinear Poisson-Boltzmann solver. The RESP procedure has been applied to determine an atomic partial charge of the A-T and G-C base pairs. The atomic partial charges of the base pairs have been the same for each base pair in the oligomer structures. We have found that for the (A-T)ₙ structure, the the electrostatic potential on the central adenine and thymine is more negative than on the nucleobases of the oligomer sides. For the (G-C)ₙ structure, the electrostatic potential on central guanine is more negative than on the sides, while for the cytosine the opposite effect takes place. Therefore, the stronger localization of the HOMO density on the central nucleobase is observed for the (A-T)ₙ oligomer, where the HOMO is mostly delocalized over three neighboring intrastrand adenines, than for the (G-C)ₙ oligomer, where the HOMO is delocalized over four neighboring guanines. The HOMO electronic density for the (A-T)₅ DNA sequence are presented in Figure 2. It has been found, that for the n=3 the population of the HOMO is much larger for the central nucleobases than for the sides. For the n > 3 the population of the HOMO on the central nucleobases decreases due to the HOMO delocalization.

The delocalization of the orbital electron density over the oligomer structure produces a decrease of the HOBO energies with elongation of the DNA chain. The dependence of the orbital energies of the n HOBOs, which are π orbitals of the nucleobases, in the (A-T)ₙ and (G-C)ₙ oligomers on the sequence number n are presented in Figure 3. As we see from the results, the splitting of the HOBO and HOBO-1 decreases with elongation of the duplex oligomer structures. We conclude that the electronic coupling between the HOBO and HOBO-1 belonging to the nearest intrastrand nucleobases decreases as well due to the spreading of the electron density of the molecular π orbitals over the larger sequence number. Therefore, the maximum value of the electronic coupling is observed for the structures of the two stacked base pairs, where the HOBO can spread only over two nucleobases. The electronic coupling between the two HOBO and HOBO-1 for the different nucleobases within the (A-T)ₙ and (G-C)ₙ oligomers are presented in Figure 4. As we mentioned above, the π orbitals are primarily delocalized over 3-4 intrastrand nucleobases. Therefore, a fast decrease of the electron coupling for n ≤ 4 is observed when the π orbitals have the potential to spread (see Figure 2). For n > 4 the electronic coupling decreases slowly. For n=6, the electronic coupling magnitude is less than half of that for n=2. According to the performed extrapolation procedure in Figure 4 for n ≥ 8 the coupling is practically independent of the sequence number.

The observed decrease of electronic coupling in the (A-T)ₙ and (G-C)ₙ oligomers is in good agreement with the approximation in Ref. 22, where for n=4 the electronic coupling is half of that for n=2. Moreover, it can explain the disagreement of the earlier theoretical results and experiments, where the electronic coupling is usually much smaller than 0.1 eV. Based on these results we conclude that the electronic coupling calcu-
FIG. 3: The π orbitals of the nucleobases within the (A-T)$_n$ and the (G-C)$_n$ oligomers, where $n$ is number of the DNA base pair (RHF/6-31$^+$G$^*$ // RHF/6-31$^+$G$^*$).

FIG. 4: The electronic coupling between the HOBO and HOBO-1 for the nucleobases in the (A-T)$_n$ and the (G-C)$_n$ duplex oligomers (RHF/6-31$^+$G$^*$ // RHF/6-31$^+$G$^*$). The dotted lines correspond to the extrapolated results.

B. 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 energy and the vIP for the separated nucleobases and their pairs. The results are compared with the experimental data in Table II. From Table II it is clear that our calculations and the experimental results for the nucleobases are in good agreement except for cytosine. Unfortunately, the experimental values were defined as the difference between the vertical ionization potential and the adiabatic ionization potential, with values extracted from different sources [22, 26, 27]. As a result, in general the final values can be inaccurate due to the use of different experimental techniques and agreement of the theoretical data with the experiment is not completely reliable. For the nucleobases, the large geometry relaxation between the neutral and 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. The unit charge, spread between the two nucleobases in the pair instead of one, decreases the geometry relaxation of each nucleobase as well. 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 [23]). 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.

Further, the hydrogen bonds are the channels for charge transfer between the nucleobases. In the oxidized state the hydrogen bonds participate in the charge transfer between the nucleobases to bring the pairs from the nonequilibrium state, where the charge is localized only on the nucleobase with a lower IP, to the equilibrium state.

TABLE II: The inner-sphere reorganization energy and the values of vIP for the nucleobases and pairs estimated with UB3P86/6-311$^+$G$^*$. All values are in eV.

|        | vIP   | vIP$^a$ | $\lambda_{i,A}$ | $\lambda_{i,D}$ | $\lambda_i$ | $\lambda_{i,A}^b$ |
|--------|-------|---------|------------------|------------------|-------------|------------------|
| adenine| 8.8740| 8.44    | 0.1999           | 0.2020           | 0.4019      | 0.18             |
| thymine| 9.3797| 9.14    | 0.2432           | 0.2703           | 0.5135      | 0.27             |
| guanine| 8.4626| 8.24    | 0.4344           | 0.4392           | 0.8737      | 0.47             |
| cytosine| 9.3049| 8.94    | 0.1107           | 0.1120           | 0.2227      | 0.26             |
| A-T    | 8.4381| -       | 0.1492           | 0.2184           | 0.3676      | -                |
| G-C    | 7.8326| -       | 0.3526           | 0.3679           | 0.7205      | -                |

$^a$Experimental data [22]

$^b$Experimental data [22, 26, 27]
where the charge is spread over the base pair \(^{32}\). We consider the A-T and G-C base pairs as a single state for the following calculations of \(\lambda_i\). The stacking of the base pairs into the (G-C)\(_n\) and (A-T)\(_n\) oligomers leads to a decrease of the inner-sphere reorganization energy \(\lambda_i\) and a decrease of the vIP as well. The results are presented in Figure 5 where the decrease of \(\lambda_i\) is seen to occur due to the contribution of the rotation and translation of the base pairs relative to each other and to the spreading of the charge between the pairs. According to our data, with elongation of the (A-T)\(_n\) and (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 decrease of the energies of the adiabatic IP (see Fig. 3) and the inner-sphere reorganization energy (see Fig. 5) provide the decrease of the vIP, which is the sum of above two components.

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 residence of the HOMO in the oligomer centers provides the localization of the charge on the central guanines and adenines in the oxidized state. We have calculated the charge distribution as the difference between oxidized \(E_{+1}^{(A,D)}\) and neutral states \(E_{0}^{(A,D)}\) with Mulliken population analysis \(^{32}\). In the (G-C)\(_n\) and (A-T)\(_n\) sequences the charge is distributed along the chain and is characterized by the low charge density at the DNA molecule sides. For example, the density of the atomic partial charge localized on the \(n=1\) site is lower than that at the chain center by 0.06 coul for the (A-T)\(_n\), and by 0.25 coul for the (G-C)\(_n\) sequences. For the (G-C)\(_4\) sequence our results are in agreement with the data in Ref. \(^{34}\).

Therefore, the charge accumulation in the oligomer centers in the oxidized state produces the maximum geometry relaxation in the center of the DNA chain. We have performed an estimation of the geometry relaxation of the separated base pairs \(\lambda^n_{i,D}\) within the optimized geometries of the (A-T)\(_n\) and (G-C)\(_n\) oligomers, where \(n = 1\ldots6\). The simulation results of \(\lambda^n_{i,D}\) for \(n=3\) and \(n=5\) are presented in Figure 6. 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 repeats primarily the charge distribution in the (A-T)\(_n\) and (G-C)\(_n\) sequences.

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 III).

IV. CONCLUSIONS

We have performed accurate quantum-chemical calculations to determine the electron coupling and the inner-sphere reorganization energy for the (A-T)\(_n\) and (G-C)\(_n\) DNA oligomers, where \(n = 1\ldots6\). The electronic coupling between the two neighbor nucleobases within the same strand decreases exponentially with increasing of the base pairs number \(n\) participating in the chain formation. The \(n\geq4\) is the sequence number required for an accurate evaluation of the electron coupling in the DNA molecule. The orbital distribution in oligomers

FIG. 5: The inner-sphere reorganization energy \(\lambda_i\) and the vIP values versus the number of pairs in a DNA duplex oligomers (A-T)\(_n\) and (G-C)\(_n\) performed with UB3P86/6-311\(^+\)G*.

FIG. 6: The inner-sphere reorganization energy \(\lambda_{i,D}\) corresponding to the single base pairs within the (A-T)\(_n\) and the (G-C)\(_n\) oligomers, where \(n = 3\) and \(n=5\) are calculated with UB3P86/6-311\(^+\)G*. 
with the HOBO residing on the central nucleobase have been found to be the main reason for charge accumulation on the base pair located close to the chain center. The charge distribution in the chain determines degree of the geometry relaxation of the base pair during the oxidation process in dependence on their location within the oligomer. Therefore, the base pairs in the chain center have stronger geometry distortion during the oxidation process. Such results are in good agreement with the theory of polaron formation in the DNA molecule, where the maximum structure distortion occurs in the polaron center [35].

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VI. REFERENCES

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