Water induced weakly bound electrons in DNA

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We have studied the effect of humidity on the electronic properties of DNA base pairs. We found that the hydrogen links of the nucleobases with water molecules lead to a shift of the $\pi$ electron density from carbon atoms to nitrogen atoms and can change the symmetry of the wave function for some nucleobases. As a result, the orbital energies are shifted which leads to a decrease in the potential barrier for the hole transfer between the G-C and A-T pairs from 0.7 eV for the dehydrated case to 0.123 eV for the hydrated. More importantly, the $\pi$ electron density redistribution activated by hydration is enhanced by the intrastrand interactions. This leads to a modification of the nucleobase chemical structures from the covalent type to a resonance structure with separated charges, where some $\pi$ electrons are not locked up into the covalent bonds. Within the (G-C)$_2$ sequences, there is overlapping of the electronic clouds of such unlocked electrons belonging to the stacked guanines, that significantly increases the electron coupling between them to $V_{DA} = 0.095$ eV against the $V_{DA} = 0.025$ eV for the dehydrated case. Consequently, the charge transfer between two guanines within the (G-C)$_2$ sequences is increased by 250 times due to hydration. The presence of nonbonded electrons suppress the band gap up to $\sim 3.0$ eV, that allows us to consider DNA as a narrow band gap semiconductor. © 2008 American Institute of Physics. DOI: 10.1063/1.2939248

I. INTRODUCTION

The discovery of conductance in DNA has attracted considerable attention in recent years among researchers on the transport properties of DNA.$^{1-10}$ However, from available experimental data it is difficult to draw any definite conclusion. While high conductivity was reported in some experiments,$^8$ in others the DNA conductivity was very low.$^7,11$ For charge conduction through DNA, the system must contain free charge carriers at least under certain specific conditions, but the nucleobases in dry DNA are known to have the covalent structure having no free charge carriers. The weighting of the covalent structure is dominant in vacuum.$^{12}$ However, recent experimental results on DNA conductance is much more promising, where DNA conductance exhibits an exponential increase (up to $10^6$ times) with rising humidity,$^{13,14}$ which clearly indicates the important role of humidity in DNA conduction.

In this paper, we report on the influence of humidity on the electronic properties of DNA. We show that humidity and electronic interactions between stacked base pairs change the electronic properties of DNA base pairs in such a way that the covalent structures of some nucleobases are converted to structures with separated charges (ionic type), where some covalent bonds are broken and the released $\pi$ electrons are weakly coupled to the lattice. Therefore, an applied electric field and temperature can coax these electrons to contribute to DNA conductance.

II. THE DNA PAIRS IN THE SOLVENT

When DNA is placed in the solvent the base atoms are capable of making hydrogen-bonded links to water molecules.$^{13}$ Molecular dynamics simulations$^{15}$ have shown that the hydration efficiency is determined by the location of these atoms within an aromatic ring rather than on the DNA grooves. We built the crystal structures of hydrated base pairs, as shown in Fig. 1 (for details of the calculations, see Sec. IV).

The charge exchange between two stacked base pairs is determined by the overlapping of their $\pi$ orbitals. The overlapping of the highest occupied molecular orbitals (HOMOs) creates the $\pi$-pathway for the hole and the lowest unoccupied molecular orbitals (LUMOs) for electrons. Therefore, the HOMO and LUMO energies and spatial distribution of the corresponding wave functions are the most important factors that determine the charge transfer through DNA. We found that the energies of these orbitals are shifted after hydration: The HOMO shift is $-0.16$ eV for the A-T pair and $-0.708$ eV for the G-C pair. The LUMO is shifted by $-0.23$ eV for A-T and by $0.39$ eV for G-C. Therefore, hydration significantly increases the HOMO-LUMO gap for G-C and remains almost unchanged for A-T.

The interaction of molecular objects with water is known to be one of the important issues in molecular biology. In some cases, these molecule-water interactions due to the charge exchange between them leads to a change in the electronic properties of the molecules and can result in ejection of an electron from the molecule to the solvent.$^{16}$ This ionic state usually exists as a result of the stabilization potential created by the surrounding solvent. For the DNA base pairs considered here, modification of the HOMO-LUMO gap for
the A-T and G-C pairs activated by the hydration is a result of the charge exchange between the nucleobases and water, change in the electron density redistribution over the nucleobase geometries and in some cases a reversal of the symmetry (phase) occurred for the $\pi$ and $\pi^*$ orbitals. For a system of interacting nucleobases, such as the DNA pairs, if the symmetry of the $\pi$ orbital is changed for one of them, a significant shift of the orbital energies and density redistribution can occur. In the case of the A-T pair, hydration changes the symmetry of the $\pi$ and $\pi^*$ orbitals for both nucleobases, adenine and thymine, while the electron density distribution remains almost the same. As a result, we observed only an insignificant negative shift of the HOMO, HOMO-1, and LUMO energies that keeps the magnitude of the HOMO-LUMO gap practically unchanged. However, for the G-C pair the symmetry of the HOMO orbital is the same for the hydrated and dehydrated cases, as shown in Fig. 2, while the LUMO gap practically unchanged. However, for the G-C pair the symmetry of the HOMO-1 orbital is reversed by hydration, as shown here by different shades. The nucleobases are connected to each other and to the water molecules for the hydrated case by the hydrogen bonds (dotted lines).

Due to the shift of the HOMO orbital energies, the hydration is also found to change significantly the potential barrier for the hole transfer between the base pairs, which is determined as the difference of the HOMO energies between nucleobases. The interaction of the nucleobases with each other within the base pair can change the orbital correlation (symmetric and antisymmetric) of the reactants (nucleobases) that leads to the change in the symmetry for the HOMO within the base pair from that for the single nucleobase and its energetic shift. Therefore, the HOMO energies determined for the nucleobases within the base pairs can be significantly different from that for the separated nucleobases, but should be comparable to the energetics of the nucleobases within the DNA helix. The potential barrier for the charge transfer from a single guanine to a single adenine has been estimated earlier by the Hartree–Fock (HF) calculations to be 0.49 eV, while for the guanine and adenine within the corresponding canonical base pairs this barrier rises up to 0.65 eV. The experimental value within the solute DNA was 0.2 eV. We have also observed within the density functional theory (DFT) (see Sec. IV for details) that due to the base pair formation the potential barrier for hole migration between guanine and adenine is increased by up to 0.7 eV. However, hydration decreases the potential barrier for the hole transfer between G-C and A-T base pairs (G $\rightarrow$ A) to 0.123 eV. We checked the decrease of the potential barrier due to hydration when the HF/6-31+ +G** method is applied. In this case, the hydration is found to decrease the barrier from 0.69 eV [0.65 eV (Ref. 17)] to 0.175 eV, that is similar to the DFT results. The influence of the solvent on the potential barrier for the (G $\rightarrow$ A) transfer is also supported by our calculation within the Poisson–Boltzmann model, where a decrease in this barrier due to the solvent contribution by 0.244 eV was determined. However, the value of the potential barrier obtained in our present work (0.123 eV) is in better agreement with the experimental value of 0.2 eV. This makes the application of quantum chemistry methods more reliable for this purpose. The hydration is found to change the potential barrier for the G $\rightarrow$ T transfer from 1.3 to 0.83 eV and for the G $\rightarrow$ C transfer from
1.68 to 0.59 eV. For electron transfer between the G-C and A-T pairs the potential barrier is −0.37 eV in comparison to 0.24 eV for the dehydrated case.

The next issue of our work is the partial dehydration of the base pairs because the molecular dynamics simulations have shown that the water molecules remain attached to the bases for a short time [estimated to be around 100 ps (Ref. 15)]. We found that the electronic properties of the nucleobases within the hydrated base pairs can be significantly modified due to missing of even a single water molecule. First of all, the interaction of the nitrogen atoms with water molecules leads to a shift of the electron density from the carbon atoms towards the nitrogen atoms. Second, interaction with water changes the correlation of the symmetry of the reactant wave functions, that leads to the symmetry changes of the HOMOs and a shift of their energies. Therefore, we consider the influence of water on the electronic properties of the nucleobases through the alteration of the electrical dipole moments of the base pairs determined from the wave functions corresponding to the molecular orbitals. The dipole moments of the hydrated and the dehydrated A-T and G-C pairs, and also when one water molecule is missing, are presented in Fig. 4. The phase of the HOMO and HOMO-1 for A-T is switched due to hydration. If the water molecule is missing on the O2 atom, the HOMO, HOMO-1 phase, and the orbital energies remain essentially the same as those for the hydrated case and dipole moment is similar to that for the hydrated case as well. Missing of a water molecule on the O4 and N3 atoms leads to the symmetry change in the HOMO in the first case and of HOMO-1 in the second case from that for the hydrated pair. The phase switching of both the HOMO and HOMO-1 occurs when the A-T dipole moment is closer to that for the hydrated case, namely, due to dehydration of the N7 atom and N7 assembled with O3 or N3 atoms. Therefore, hydration of the N7 atom, which is not efficient [∼19% (Ref. 15)] can significantly change the electronic properties of A-T. For the G-C pair, the HOMO phase remains the same for all cases in Fig. 4, while the phase of the HOMO-1 orbital when one water molecule is missing corresponds to that for the hydrated case. However, the deviation of the HOMO and HOMO-1 energies are observed for different cases because of the change in the electron density distribution indicated by the dipole moment in Fig. 4. Despite the fact that the HOMO phase for G-C remains the same for the hydrated and the dehydrated cases, the HOMO of the partially dehydrated G-C can change the phase when its dipole moment is located somewhere in the middle between that for the hydrated and the dehydrated cases. For example, dehydration of simultaneously N2 and N7 atoms or N2 and O6 atoms leads to phase switching. The behavior of the energies and phases of the LUMO orbitals cannot however be so well systematized. Therefore, the partial dehydration significantly changes the electronic properties of the DNA base pairs because of the variation of the symmetry of the wave functions corresponding to the HOMO and LUMO orbitals and electronic density distribution.

The shift of the HOMO energies for the G-C and A-T pairs due to partial dehydration also changes the potential barrier for hole migration between these pairs. In Table I, we presented the computational results for the HOMO shift due

![FIG. 5. The chemical structures of A-T within the hydrated (A-T)₂ sequence and G-C within the hydrated (G-C)₂ sequence.](image1)

![FIG. 6. The energies for the highest and next highest bond occupied orbitals for the guanine, adenine, and cytosine within the hydrated (A-T)₂ and (G-C)₂ structures (π orbitals) and LUMO (π* orbitals).](image2)

<table>
<thead>
<tr>
<th>G-C</th>
<th>Shift (eV)</th>
<th>A-T</th>
<th>Shift (eV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydrated</td>
<td>0</td>
<td>Dehydrated</td>
<td>0.699</td>
</tr>
<tr>
<td>N3</td>
<td>0.843</td>
<td>N7</td>
<td>0.584</td>
</tr>
<tr>
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<td>O2</td>
<td>0.815</td>
</tr>
<tr>
<td>N7</td>
<td>0.442</td>
<td>N3</td>
<td>0.796</td>
</tr>
<tr>
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<td>0.676</td>
<td>O4</td>
<td>0.784</td>
</tr>
<tr>
<td>N4</td>
<td>0.677</td>
<td>N6</td>
<td>1.004</td>
</tr>
<tr>
<td>N2</td>
<td>0.817</td>
<td>⋯</td>
<td>⋯</td>
</tr>
<tr>
<td>Hydrated</td>
<td>0.708</td>
<td>Hydrated</td>
<td>0.831</td>
</tr>
</tbody>
</table>
to the partial dehydration. We found that depending on the position where a water molecule is missing the energy gap between G-C and A-T can completely disappear. Therefore, the potential profile for the hole migration through hydrated DNA molecule will vary due to the high mobility of the water molecules.

III. INTERACTION OF THE TWO STACKED PAIRS

The change in the electronic properties of the base pairs due to hydration should contribute to the charge exchange between the stacked base pairs within DNA. Moreover, the interaction of the nearest-neighbor base pairs can modify the electron density distribution over the nucleobase geometries and as a result influences the charge transfer between the base pairs. To explore that, we performed the natural bond orbital (NBO) analysis to consider the influence of hydration on the donor-acceptor charge exchange between the molecular groups within the (G-C)$_2$ and the (A-T)$_2$ sequences (see Sec. IV for details of the NBO analysis). The optimized geometries of dehydrated and hydrated base pairs were stacked with parameters characterized for the B-DNA, i.e., with a helical twist of 36° and a shift of 3.4 Å.

The amount of charge transfer $Q = Q_{DA} - Q_{AD}$ between the nucleobases varies significantly depending on hydration. The charge transfer between two guanines within the (G-C)$_2$ sequence is larger for the hydrated case by up to 250 times ($Q = 0.163e$) than that for the dehydrated case ($Q = -0.00063e$). For the rest of the nucleobases the difference is 24 times between the thymines, 3.6 times between the adenines, and 1.6 times between the cytosines. We found that 95% of the whole charge transfer between guanines is provided by the participation of the nonbonded $\pi$ electrons on the C5 ($Q_{C5-C5} = 0.151e$), which is not observed in the covalent structure of guanine (Fig. 1). We built the chemical structures for the hydrated pairs within the (G-C)$_2$ and (A-T)$_2$ sequences. The $\pi$ electron density locked into the covalent bond and belonging to the unshared pairs (nitrogen) is found to be shifted to the adjacent atoms and bonds due to the nucleobase-water and the intrastrand interactions. Thus, the interaction of the nitrogen atoms with water molecules causes a shift of the electron density of the $\pi$ electrons from the carbon atoms to the nitrogen atoms. Therefore, due to the significant shift of the density of the $\pi$ electron from C4 atoms to the N9 atom and from C5 to the N7 atom (see guanine and adenine in Fig. 1), the C4–C5 double bond is broken and C4 donates the $\pi$ electron to form a double bond with the N9 atom. As a result, the N9 atom has four bonds instead of three, while the C5 atom has three bonds instead of four. Within the system of the two stacked base pairs, the charge transfer between intrastrand nucleobases leads to a stronger charge separation between the carbon and nitrogen atoms. Therefore, the Lewis covalent structure of some nucleobases (see Fig. 1) are converted to the structures with separated charges (ionic), as presented in Fig. 5. The difference between the non-Lewis occupancy for the covalent structure of the nucleobases and for the structure with separated charges within the hydrated (G-C)$_2$ sequences is less than 0.1%. For the hydrated (A-T)$_2$ sequences the covalent structure is characterized by a higher non-Lewis occupancy (0.55%) than the ionic one. This is a borderline case meaning that both covalent and ionic structures can be accepted for the solute DNA. To convert the reference covalent structure of the A-T pair to the ionic type, the intrastrand interactions are enough, while for the G-C pair the humidity is the main factor. The reason is the low weighting of the covalent structure of adenine (~10%) in comparison to the ionic structures (~8%). Thymine has a large weighting (~30%) and therefore its structure remains covalent even within the hydrated (A-T)$_2$ sequences, where intrastrand interactions are stronger. The ionic structure of the nucleobases is stable and reproducible by different quantum chemical methods (HF or DFT), i.e., the same Lewis structure with separated charges is obtained when HF or DFT methods are applied. However, the conditions for switching of the covalent structure to the ionic type are quite sensitive to the chosen method, namely, the intrastrand distance is a factor controlling the occurrence of the ionic structure (see Sec. IV for details).

The $\pi$ electrons not tied up into the covalent bonds were found to significantly contribute to the observed huge charge exchange between the guanines within the hydrated (G-C)$_2$ sequences. We calculated the electronic coupling of the charge transfer from a guanine which becomes a donor (D) to a guanine collecting a charge (A). For the hydrated (G-C)$_2$ sequences, the electronic coupling between guanines is $V_{DA} = 0.095$ eV and between the C5–C5 atoms for the intrastrand guanines $V_{DA} = 0.041$ eV. The reverse coupling $V_{AD}$ between the nucleobases is only 0.037 eV, when the C5–C5 direct transfer is absent. For the dehydrated (G-C)$_2$ sequences, $V_{DA} = 0.025$ eV and $V_{AD} = 0.027$ eV. In the dehydrated and the hydrated (A-T)$_2$ sequences for the intrastrand adenines the charge transfer between the atoms carrying the nonbonded electrons is absent, as well for the cytosines within the (G-C)$_2$ sequences. This is the reason for an insignificant increase in the charge exchange between the adenines and the cytosines with hydration. In support of our results, the larger sensitivity of the poly(dG)-poly(dC) molecule to the relative humidity in comparison to the poly(dA)-poly(dT) molecule was indeed found in the experiment.13

Therefore, the hydration of the base pairs and the intrastrand interactions between them provide the generation of $\pi$ electrons not tied up to the covalent bond (see Fig. 5). The orbital energies for the valence nonbond $\pi$ electrons and next to that bonded $\pi$ electrons and the lowest antibond $\pi^*$ orbital are presented in Fig. 6. Clearly, the hydrated (A-T)$_2$ and (G-C)$_2$ structures are characterized by the small band gap of ~3.0 eV usually attributed to the narrow band gap semiconductors, instead of a value of over 8.0 eV obtained for the dehydrated DNA and corresponds to a wide gap semiconductor or an insulator. These results agree very well with the experimental data,20,21 where the observed optical gap was in the range of 3.0–4.0 eV and with other theoretical results,22 where the $\pi-\pi^*$ gap was 3.8 eV and found to be reduced by up to 1.28 eV due to the energy levels introduced by the solvent ions. Therefore, an applied electric field and temperature can help the $\pi$ electrons not locked up into the covalent bonds gain enough thermal energy to overcome the narrow band gap and be available for charge conduction. As
a result, the experimental observation\textsuperscript{13,14} of a significant increase of the DNA conductance with rising humidity can be explained by the occurrence of free electrons within DNA caused by the change in the Lewis structure of some nucleobases. With dehydration the electron density accumulated on the nitrogen atoms is shifted back to the carbon atoms, that subsequently changes both the symmetry of the HOMO wave functions and the potential profile for the charge migration (for details, see Sec. II), and finally leads to locking up of the nonbonded $\pi$ electrons to the covalent bonds.

IV. METHODS

The geometries of the A-T and G-C base pairs were optimized by the DFT at the B3LYP/6-31++G** level with the Jaguar program.\textsuperscript{23} To obtain the crystal structure of the hydrated DNA base pairs, the water molecule positions (see Ref. 15) were optimized with the base pair coordinate constraints that maintains the planarity of the pairs. As for the dipole moment calculations, after removing a water molecule at a certain position the positions of the water molecules have been reoptimized. The dipole moments were calculated from the wave function distribution.

The NBO analysis\textsuperscript{24} was performed based on the electron density calculated with the B3LYP/6-31++G** functional, which gives good agreement of the resonance structure weighing with the data,\textsuperscript{12} where B3LYP has been found to be a better choice for this purpose. Within the NBO analysis, the input atomic orbital basis set $\chi_i$ obtained with the DFT method is sequentially transformed into the natural localized sets, such as the natural atomic orbitals, natural hybrid orbitals, NBOs and natural localized molecular orbitals. NBOs are localized 1 or 2 center orbitals describing the local molecular bonding pattern of electron pairs. Within the NBO analysis\textsuperscript{24} the charge transfer between the nucleobases $Q_{DA}$ has been found as the sum of the charge transfer $\Omega_i \rightarrow \Omega_j^*$ between donor orbital $\Omega_i$ belonging to the one nucleobase to the acceptor orbital $\Omega_j^*$ on another nucleobase within the NBO sets as

$$Q_{DA} = \sum_{ij} Q_{ij} = \sum_{ij} q_{ij} F^2_{ij} (\epsilon_i - \epsilon_j)^2,$$

where $q_{ij}$ is the donor orbital occupancy, $\epsilon_i, \epsilon_j$ are the orbital energies, and $F^2_{ij}$ is the off-diagonal element providing the “perturbation” to convert unperturbed eigenfunctions $\Omega_i$ to final eigenfunctions. The $\Omega_i$ eigenfunctions are the NBOs describing most accurately the Lewis-like molecular bonding pattern of electron pairs. The charge transfer is considered for the case when the second-order energy $\Delta E_{ij} = -2 F^2_{ij} (\epsilon_i - \epsilon_j)$ is positive. The electronic coupling between the nucleobases has been estimated as

$$V_{DA} = \sum_{ij} V_{ij} = \sum_{ij} F^2_{ij} (\epsilon_i - \epsilon_j) = \sum_{ij} Q_{ij} (\epsilon_i - \epsilon_j)/q_{ij}. $$

For Eqs. (1) and (2) the summation runs over only $\pi$ orbitals participating in the formation of the $\pi$ pathway of the charge migration in the DNA molecule. Because $V_{DA}$ is determined as the sum of the electronic coupling between the NBOs providing the $\pi$ electrons for the formation of the $\pi$ molecular orbitals, the magnitude of $V_{DA}$ calculated here can be different from that in Refs. 5 and 6.

Because the atomic orbital basis set $\chi_i$ is used as input for the NBO analysis, the Lewis structure of the investigating molecule depends directly on the chosen initial orbitals and, therefore, on the method of their calculations. The main difference between the DFT and HF theories is in the treatment of exchange correlations\textsuperscript{25} and, therefore, the initial basis orbitals $\chi_i$ should strongly depend on the chosen methods. It was found before that for the system of two nonbonded molecular fragments\textsuperscript{26} the charge transfer from donor to acceptor is increased when correlation (DFT methods) is taken into account, that significantly changes the electron density distribution in the system. The above mentioned difference between the DFT and HF methods can crucially influence the determination of the Lewis structure of the nucleobases within the NBO analysis. We found that for the single A-T and G-C pairs the shift of electron density from the carbon atoms to the nitrogen atoms activated by hydration is much less in the HF calculation than that in the DFT calculations. In the system of two stacked pairs, because in the HF/6-31+ +G** calculations the charge transfer between the intrastand nucleobases is insignificant, the Lewis structure with separated charges appears when the intrastand distance is less than 3.0 Å. At the same time, for the B3LYP/6-31+ +G** calculations the ionic structure of nucleobases is present until the intrastrand distance is increased up to $\sim$5.0 Å. However, the observed Lewis structure with separated charges is the same for these two cases, i.e., the C5 atom carries a negative charge and the N9 atom carries a positive charge for the guanine and the adenine, while for cytosine, the N3 atom carries a negative charge and the N4 atom carries a positive charge. Moreover, a small influence of the method of calculation on the values of the nonbonded $\pi$ electrons energies (see Fig. 6) has been detected.

V. CONCLUSION

We found that different levels of humidity can significantly modify the electronic properties of the base pairs. In particular, it changes the electronic density distribution and the orbital phases, and shifts the HOMO and LUMO energies. For the hole transfer between the guanine and the adenine, the HOMO energy shift causes a drop of the potential barrier up to 0.123 eV. The hydration and electronic interactions between the stacked base pairs create specific conditions for modification of the nucleobase structures from the covalent type to the charge separated resonance structure. The above conditions contribute to the generation of weakly bound or even free charge carriers in DNA, which significantly increases the charge exchange between the base pairs and thereby the DNA conductance. Since within the hydrated (G-C)\textsubscript{5} sequences there is strong electronic coupling $V_{DA}$ = 0.041 eV between the C5 atoms of intrastand guanines, where weakly bound electrons are generated, the dehydration of such sequences will significantly decrease the conductance of the molecule, as was indeed found in the experiments.\textsuperscript{13}
ACKNOWLEDGMENTS

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20 See http://www.chem.wisc.edu/~nbo5