Electronic Coupling Mediated by Stacked [Thymine-Hg-Thymine] Base Pairs

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Very recently it has been shown that stable metal-mediated base pairs [Thymine-Hg-Thymine] can form in DNA. To estimate the effect of such pairs on the efficiency of charge transfer through DNA, we carry out quantum mechanical calculations of double-stranded π-stacks GXG, GXXG, and GXXXG, where X = [Thymine-Hg-Thymine] and stacks GT,G of canonical base pairs. The charge-transfer efficiency in short duplexes GXG and GTG is found to be similar. However, the donor—acceptor coupling in GXXG and GXXXG is stronger by a factor of 2.5–3.0 than that in GT,G (n = 2 and 3), respectively. It is shown that the valence orbitals of Hg atoms do not essentially participate in mediating the electronic coupling for hole transfer; however, they may play an important role in excess electron transfer.

Introduction

Recently, it has been found that in DNA duplexes T-T (thymine-thymine) mispairs capture Hg2+ ions and form stable neutral base pairs [T-Hg-T].1 The formation of such complexes results in stabilization of the duplex depending on the number of consecutive [T-Hg-T] pairs.1 Among various interesting effects caused by the stacked T-Hg-T pairs, one may expect remarkable modulation of the charge transfer (CT) efficiency through DNA. Electron hole transfer mediated by DNA π-stacks has received remarkable attention over last 15 years.2 A number of experimental and theoretical studies have been performed to understand mechanisms of charge migration in the double helix.3–21

It has become clear that natural DNA is a rather poor electrical conductor and the DNA conductivity must be essentially improved to be sufficient for various applications in nanoelectronics. One of the most promising approaches is the development of M-DNA, which contains the metal ions in the middle of base pairs in the duplex.22–28 It has been shown that M-DNA may operate as a better conductor than B-DNA.29–31 In such metal-mediated base pairs, the hydrogen bonds between bases are replaced by metal—nucleobase coordination bonds. The interaction of neighboring metal atoms is assumed to provide a pathway for charge conductivity. However, the change in the surface charge of DNA caused by the binding of metal ions may also play an important role in the enhancement of current with M-DNA.32

The formation of stable DNA π-stacks containing mercury-mediated thymine-thymine pairs, in which imino protons of the bases are replaced by Hg2+, suggests a new approach to the development of M-DNA.1 Still there have been no experiments on charge transfer through such π-stacks. Therefore, it is worthy to compare hole transfer in the modified and natural DNA π-stacks on the basis of computational models. Because the efficiency of nonadiabatic charge transfer is directly related to electronic coupling Vda of diabatic donor and acceptor states (the CT rate is proportional to Vda2),33,34 the calculation of Vda in short DNA stacks of similar structure provides reasonable information about the electronic effects in the charge-transfer process.3,14–16,21 Computational aspects of estimating Vda matrix elements were considered in detail.35–40

In this paper we compare the results of quantum mechanical calculations of DNA stacks containing metal-mediated [T-Hg-T] pairs and canonical AT pairs and show that the interaction of neighboring [T-Hg-T] base pairs should considerably (an order of magnitude) increase the hole transfer efficiency in a DNA π-stack.

Computational Details

The structures of the neutral [T-Hg-T] pair as well as canonical GC and AT pairs were optimized by using B3LYP calculations. The 6-31G* basis sets were used for H, C, N, and O, while for Hg we employed the LanL2DZ basis set with inner electrons substituted by effective core potentials and double-ζ quality valence functions.41 The program Gaussian03 was used.42 The calculated geometries of X, GC, and AT pairs were employed for generating a number of stacks where the hole donor and acceptor (GC) pairs are connected with one or two X and AT bridges. The mutual position of base pairs in a stack was defined by using six base-step parameters.43

For calculating electronic couplings Vda a multistate Generalized Mulliken—Hush (GMH) approach was employed. A two-state model, commonly used for estimating electronic couplings, cannot provide accurate Vda values for the DNA π-stacks because of the multistate effects.44 Recently, the dependence of the calculated couplings for hole transfer in π-stacks on the number of adiabatic states treated simultaneously within the GMH approach has been analyzed.45 It was shown that reliable estimates of Vda for thermal CT may be obtained by removing excited states of donor and acceptor from the list of adiabatic states treated within GMH and a simple scheme was suggested to select the appropriate states.45 Alternatively, the results derived within a two-state model can be considerably improved when the superexchange correction is taken into account.46

The electronic couplings were calculated within the one-electron approach based on Koopmans’ theorem. The Hartree—Fock method was used to generate molecular orbitals of the systems. This approach has recently been justified by comparison of the estimated hole-transfer couplings between stacked...
TABLE 1: Electronic Coupling $V_{da}$ (in meV) of GC Donor and Acceptor Sites in the DNA Stacks GXG, Containing Metal-Mediated Base Pairs X = [T-Hg-T] and the Natural GT$_2$G Sequences, Using the Multistate GMH Method$^{a}$

<table>
<thead>
<tr>
<th>Stack</th>
<th>Multistate Model</th>
<th>2-State Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>GXG</td>
<td>10.7 (4), 10.5 (6), 10.4 (8)</td>
<td>[2.2]$^b$</td>
</tr>
<tr>
<td>GXG</td>
<td>5.2 (6), 5.1 (8), 5.5 (10)</td>
<td>[2.0]$^b$</td>
</tr>
<tr>
<td>GXG</td>
<td>1.11 (8), 1.07 (10), 1.08(11)</td>
<td>[0.13]$^b$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stack</th>
<th>Multistate Model</th>
<th>2-State Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>GT$_2$G</td>
<td>13.7 (4), 11.7 (6), 11.2 (8)</td>
<td>[5.4]$^b$</td>
</tr>
<tr>
<td>GT$_2$G</td>
<td>2.0 (6), 2.0 (8), 2.2 (10)</td>
<td>[0.84]$^b$</td>
</tr>
<tr>
<td>GT$_2$G</td>
<td>0.29 (8), 0.35 (10), 0.31 (11)</td>
<td>[0.08]$^b$</td>
</tr>
</tbody>
</table>

$^a$ The number of states is given in parentheses. $^b$ The estimates obtained within the 2-state model [in brackets] are not accurate and are given only for comparison.

Results and Discussion

Thymine-Hg-Thymine Pair. Although the energy minimum of X corresponds to a nonplanar conformation with the nucleobases perpendicular to each other, the planar structure is found to be only 1.9 kcal/mol higher in energy. Because the stacking interaction between nucleobases is stronger than 10 kcal/mol (the reliable values of stacking interaction energies were obtained by Hobza and Sponer$^{48}$), a planar structure of X is expected to be found in π-stacks. The structure of the planar conformation of [T-Hg-T] is shown in Figure 1. The distance of 8.59 Å between the N1 atoms bound to the sugar–phosphate backbone in a DNA stack is found to be similar to N9–N1 distances in canonical AT and GC pairs. Thus, no essential structural defects are expected because of the formation of [T-Hg-T] pairs. Hg atoms lying almost in the middle of the mismatches will be near the axis of π-stacks. Different from canonical pairs, both nucleobases of the X pair are equivalent. As expected, the two first ionization potentials of an isolated [T-Hg-T] pair are very close to each other; their difference is about 0.02 eV. However, in the GXG stack, their splitting is ~0.83 eV. This remarkable difference is due to the electrostatic interaction of the thymine bases with neighboring guanine and cytosine bases. The effect of adjacent nucleobases on the stability of radical cation states in DNA stacks has already been examined in detail.$^{49}$

GXG and GT$_2$G. First, we consider the short stacks consisting of three base pairs. In these systems, the guanine donor and acceptor sites are in the same strand. Due to the interaction with bridging bases, the diabatic states are not equivalent and have slightly different energies. In the ground state of both G$_1$XG$_3$ and G$_1$TG$_3$ radical cations, the hole is mainly localized on G$_1$. The CT states in both stacks lie only ~0.05 eV higher than the ground states, and therefore are thermally accessible. Electronic couplings between G$_1$ and G$_3$ calculated within two-state and multistate approaches are presented in Table 1. As can be seen, the values found within the two-state model are considerably underestimated and cannot be used for estimating the CT efficiency. It was shown that in DNA π-stacks where donor and acceptor are separated by a bridge consisting of P base pairs, the GMH calculations, which employ (2+2P) adiabatic states, give quite reliable results.$^{45}$ In GXG and GT$_2$G, very similar values of $V_{da}$ are obtained (Table 1): the 4-state model predicts 10.7 and 13.7 meV, respectively; the values of 10.5 and 11.7 meV for GXG and GT$_2$G are calculated when taking into account 6 adiabatic states. The estimates derived within 4- and 6-state models are in good agreement. Also, further extension of the number of states leads to similar values of $V_{da}$. Thus, the couplings calculated for the GXG and GT$_2$G stacks of the regular structure are quite similar. This result is not unexpected because in both cases the donor–acceptor coupling is mainly mediated by the intrastrand interaction guanine-thymine-guanine. In GT$_2$G there are two superexchange pathways: the intrastrand coupling mediated by thymine (the energy gap is 1.30 eV) and interstrand coupling mediated by adenine (the energy gap is 0.78 eV). The corresponding contributions are about 7 and 2 meV, though the second path is energetically more feasible. In the GXG, the $V_{da}$ is almost completely mediated by intrastrand thymine (the contribution of the alternative pathway is only about 1%). In this case, the intrastrand superexchange interaction is favored by both the orbital overlap and the energy gap (the tunneling gap is 1.17 and 2.00 eV for intra- and interstrand pathways, respectively).

GXGXG and GTTG. In these stacks the distance between the hole donor and acceptor (GC pairs) is 10.14 Å. The coupling is mediated by the bridges consisting of two base pairs. The structure of the GXGXG stack is shown in Figure 2. While the $V_{da}$ values in GXG and GT$_2$G are found to be similar, the couplings in GXGXG and GTTG are remarkably different. As seen from Table 2, the estimates obtained within the two-state approach are rather unreliable. However, one arrives at consistent $V_{da}$ values when taking into account 6, 8, or 10 adiabatic states. The calculated values of $V_{da}$ are 5.2 and 2.0 meV in GXGXG and GTTG, respectively. Thus, the efficiency for hole transfer between the guanine sites in [GXGXG] should be larger than that in [GTG] by a factor of 6.

Within the superexchange model the donor acceptor coupling in GBG and GBBG can be approximately estimated as:

$$V_{da}^{SE}(GBG) = V_{G→B}/\Delta$$

$$V_{da}^{SE}(GBBG) = V_{G→B}V_{B→C}/\Delta^2 = V_{da}^{SE}(GBG)V_{B→C}/\Delta$$

where $\Delta$ is a tunneling gap (energy difference of states with a hole localized on the bridge and donor sites); only the intrastrand superexchange pathway is accounted for. Then

$$V_{da}^{SE}(GXGXG)/V_{da}^{SE}(GTG) = \frac{V_{da}^{SE}(GXGXG)/|V_{X→C}/\Delta_X|}{V_{da}^{SE}(GTG)/|V_{T→Y}/\Delta_T|}$$

Because $\Delta_X \approx \Delta_T$ and $V_{da}^{SE}(GXGXG) \approx V_{da}^{SE}(GTG)$, a stronger
interaction between [T-Hg-T] pairs, $V_{X-X}$, as compared with that of AT pairs, $V_{T-T}$, is responsible for more efficient hole transfer in the GXXG stack.

**GXXG and GTTGTG.** Let us consider systems where the donor and acceptor sites are linked with a bridge consisting of three pairs. Table 1 lists $V_{da}$ values for XXX and TTT bridges estimated by using the multistate GMH models. The $V_{da}$ value derived for GX$_2$G with use of the two-state model is an order of magnitude smaller than the couplings calculated with the number of state $\geq 8$. In the case of GT$_3$G the couplings found within the multistate and two-state models differ by a factor of about 4. When comparing the $V_{da}$ values for GX$_2$G and GT$_3$G one may suggest that the hole transfer through the modified stack should be an order of magnitude faster than that through the normal DNA stack. Thus, the X-X interaction provides a more efficient superexchange path than T-T.

On the basis of the theoretical model for hole transfer through DNA it was shown that switching from the superexchange to an alternative mechanism occurs when three or more bridging base pairs separate the d-a sites.$^{50}$ A similar conclusion was also derived from comparison of the calculated and observed hole transfer rates in several $\pi$-stacks.$^{16}$ Therefore, we do not consider bridges containing more than 3 base pairs.

**Conformational Dependence of $V_{X-X}$ and $V_{T-T}$.** Recently, it has been shown that electronic couplings in DNA strongly depend on the position of nucleobases and are very sensitive to structural fluctuations.$^{31,52}$ Therefore, the relation $|V_{X-X}/V_{T-T}| > 1$ calculated for a selected stack structure may change when other conformations are considered. Let us compare the couplings in dimers [X, X] and [(TA), (TA)] with different mutual positions of the base pairs. Figure 3 demonstrates a rather dissimilar behavior of the couplings $V_{X-X}$ and $V_{T-T}$ by conformational changes in the dimers. A mutual position of two base pairs is defined by 6 base-step parameters, three translations (slide, shift, and rise) and three rotation angles (tilt, roll, and twist). As can be seen, in several [(TA), (TA)] conformations (shift $-0.5$ Å, roll $-5^\circ$, twist $31^\circ$) the coupling is negative. This means that in the vicinity of the reference structure of the dimer there should be many configurations where the coupling is close to zero. On the contrary, the coupling of X pairs in the dimer [X, X] retains its sign in all 13 considered conformations. Also, the $V_{X-X}$ values are found to be essentially larger than the corresponding $V_{T-T}$ values. This means that both the mean value of $V_{X-X}$ and its quadratic average calculated along an MD trajectory are expected to be larger than the corresponding values for $V_{T-T}$. Thus, our conclusion that the stacked [T-Hg-T] pairs facilitate the hole transfer through DNA, which was derived for ideal $\pi$ stacks, should also hold when structural fluctuations are accounted for.

**Role of Hg–Hg Orbital Overlap.** Better conductivity of M-DNA as compared with B-DNA is often attributed to the overlap of metal orbitals. One can explore the role of the Hg orbitals in mediating the electronic coupling for hole transfer by inspecting HOMO and HOMO-1 of the [X, X] dimer. Within the one-electron approximation these orbitals describe adiabatic states of the radical cation and can be employed to calculate the electronic coupling matrix elements. The orbitals are shown in Figure 4. As can be seen, there is no essential contribution of Hg orbitals to HOMO and HOMO-1, and therefore, the metal atoms do not participate directly in the superexchange interaction. Also, other lower lying occupied MO, HOMO-I with $J = 2-6$, which describe excited states of the XX bridge do not contain any remarkable contribution of the metal orbitals. Thus, larger values of the hole-transfer coupling $V_{X-X}$ as compared with $V_{T-T}$ cannot be attributed to the metal–metal interaction, and the difference in the $V_{T-T}$ and $V_{X-X}$ magnitudes should be assigned to the changes in $\pi$-electron density caused by replacement of adenine by thymine and deprotonation of the thymine bases. However, it should be emphasized that although the metal orbitals play a minor role in mediating the hole transfer coupling, the situation will probably change in the case of excess electron transfer through $\pi$-stacks containing the XX sequence because of considerable contribution of the metal orbitals in LUMO of [T-Hg-T] (Figure 3).

**Conclusions**

On the basis of quantum mechanical calculations of double stranded $\pi$-stacks GX$_n$G, $X = [$Thymine-Hg-Thymine$]$, and GT$_n$G, $n = 1-3$, we studied the effects of substitution of X for the canonical AT pair on the hole transfer efficiency in DNA stacks. The multistate GMH method was employed to estimate the coupling matrix elements.

1. While the donor–acceptor couplings are calculated to be similar in GTG and GXG, the $V_{da}$ in GX$_n$G is found to be remarkably stronger (by a factor of 2.5–3.0) than that in GT$_n$G ($n = 2$ and 3) because of the bridge–bridge interaction.
2. Comparison of $V_\text{X-X}$ and $V_{\text{T-T}}$ in a number of conformations of $\pi$-stack dimers reveals that in all considered structures the $V_{\text{X-X}}$ values are larger than $V_{\text{T-T}}$. Therefore, one can expect that accounting for structural dynamics of the stacks will not change the conclusion about the intrinsic enhancement of the hole mobility in GX$_2$G stacks as compared with GT$_2$G.

3. No essential contribution of the metal–metal interaction to the superexchange mediated coupling for hole transfer has been found. Thus, the difference in the $V_{\text{T-T}}$ and $V_{\text{X-X}}$ electronic couplings should be attributed to structural changes in $\pi$-electron density caused by replacement of adenine by thymine and deprotonation of the thymine bases [T-Hg-T].

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References and Notes


(2) Long-Range Charge Transfer in DNA; Shuster, G. B., Ed.; Topics in Current Chemistry Series; Springer, Berlin, Germany, 2004; Vol. 236, p 237.


