Quantum Chemical Modeling of Electron Hole Transfer through π Stacks of Normal and Modified Pairs of Nucleobases

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Electron hole transfer mediated by short DNA fragments containing the Watson−Crick pairs (AT) and (GC) and their 7-deaza purine counterparts (^{z}AT) and (^{z}GC) has been modeled. On the basis of quantum-chemical results for the energetics of hole transfer and the electronic coupling of π stacks, the effective electronic coupling of hole donor and acceptor connected via short bridges has been estimated using an approximate Green function approach. The distance decay parameters β_{el} of the rate constant derived from the effective coupling has been determined at $\beta_{el} = 0.79$ Å^{-1} for $(T)_n$ and $(A)_n$ bridges, while $\beta_{el} = 0.68$ Å^{-1} resulted for $(AT)_{n/2}$ π stacks. We also considered the effects of bridging bases B on the hole transfer mediated by the duplexes TTBTT which recently have been studied experimentally. Incorporation of ^{z}G into π stacks suppresses the hole transfer. If one replaces adenine by 7-deazaadenine in TAT and TTATT, then the effective coupling increases by a factor of 2.3. A much more pronounced effect, namely, an increase by a factor of ∼70, was found for the substitution A^{z}AA → AAA. A comparison of the effective couplings of donors and acceptors mediated by π stacks TBT and ABA (B = A, ^{z}A, G, T, C) shows that the effects of B strongly depends on the neighboring nucleobases.

Introduction

DNA-mediated charge transfer (CT) currently attracts considerable interest because of its relevance for the oxidative damage and/or mutations of DNA[1,2] and its potential importance for molecular electronics[3,4] and electrochemical sequencing.[5] In this context, one of the most important questions is the distance dependence of the CT rate in DNA. The status of experimental investigations has recently been the subject of several reviews.[6−9] Several types of distance dependence were experimentally found for the electron hole transfer in DNA.[7−9] Two relevant mechanisms of charge migration have been considered:[10−13] (1) single-step superexchange which is responsible for the short-range CT and (2) a weakly distant dependent multistep hopping mechanism which controls the long-range charge transport. Note that this long-range hole migration in DNA may be presented as a series of superexchange steps between guanines (G) separated by AT pairs. Therefore, a microscopic study of the superexchange within short DNA stacks is also important for understanding the parameters used for the phenomenological description of the long-range charge transport in DNA. A variety of theoretical approaches are available for describing charge migration in DNA.[14−16] Following Marcus,[17] the rate constant of the nonadiabatic charge transfer from a donor (d) to an acceptor (a) at a distance R, is determined by the effective electronic coupling H_{da}, the free energy change ΔG and the reorganization energy λ:

$$k(R) = \frac{2\pi}{\hbar} H_{da}{}^2(R) \frac{1}{\sqrt{4\pi\lambda(R)kT}} \exp\left[\frac{-(\Delta G(R) + \lambda(R))^2}{4\lambda(R)kT}\right] \quad (1)$$

When donor and acceptor are identical, ΔG is zero and the distance dependence of the CT rate constant is determined by that of the electronic coupling H_{da} and the reorganization energy λ. Experimental studies of the distance dependence of single-step hole transfer through DNA suggest[7−9] that the corresponding rate constants exhibit an exponential decay with the donor−acceptor distance R:

$$k(R) = k_0 \exp(-\beta R) \quad (2)$$

where the decay parameter β depends on the nature of the bridge. Since the terms describing the effective electronic (el) coupling and the reorganization (r) energy terms enter as independent factors in eq 1, the parameter β of eq 2 can be expressed as a sum: $\beta = \beta_{el} + \beta_r$. Thus, within Marcus theory,[17] we can separately discuss the effect of the electronic coupling and the reorganization energy on the distance dependence of the CT rate constant.

In a recent theoretical study on the distance dependence of ΔG and λ for a heterogeneous DNA environment,[18,19] it was found that CT rates in DNA calculated with distance dependent quantities ΔG and λ differ considerably from a simple exponential behavior which one normally obtains from the electronic coupling H_{da} if one assumes ΔG and λ to be essentially independent of distance.

The first quantum chemical modeling of the effective electronic coupling in DNA has been carried out with the semiempirical method CNDO/2.[20] That study showed that although the backbone can mediate hole transfer between donor and acceptor, π stacking interactions of nucleobases play the dominant role. Most noteworthy was the conclusion that the experimentally found long-range charge migration in DNA cannot be described with the superexchange mechanism.[20] However, the characteristic decay parameter of the rate constant was determined at 1.6 Å^{-1}, a value that is twice as large as the one extracted from experiments.[9] According to our experience, established semiempirical methods significantly underestimate

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the electronic coupling of π stacking molecules at separations larger than 2.5 Å. Recently, model systems with two tetracyanoethylene molecules bridged by a π stack of several benzene rings have been analyzed with the help of ab initio calculations (Hartree−Fock/3-21G);[21] there, the exponential damping factor β_{el} was found in the range of 1.1−1.6 Å^{-1}. However, these results can hardly be extrapolated to DNA related system. In particular, the study predicts that the coupling depends only weakly on the relative orientation of the rings.[21] This is at variance with a recent investigation which demonstrates that the electronic coupling of Watson−Crick pairs is very sensitive to rather small structural changes of DNA duplexes.[22] Recently, with an approach based on an effective Hamiltonian, Olofsson and Larsson studied localized and delocalized electron hole states in DNA;[23] in particular, they found that in usual DNA strands electron holes are localized at guanine units.

In previous studies, we considered the energetics of hole and electron transfer in DNA[24,25] as well as electronic couplings of nucleobases and Watson−Crick pairs.[26,27] Also, neighboring base pairs have been shown to affect the stability of nucleobase radical cations and radical anions significantly.[24,25] It is well-known from experiment that the hole trapping by guanine is significantly affected by neighboring Watson−Crick pairs.[28,29] These results suggest that the effect of neighboring pairs on the ionization potential of bridging nucleobases has to be taken into account when modeling the hole transfer.

Recently, the modulation of DNA-mediated hole transfer for different base sequences has been experimentally studied using 29-mer duplexes 5′-AGTGT GGG TTBTT GGG-3′, where two G triplets are separated by a bridge TTBTT.[30] Here, B is one of the purine nucleobases adenine (A), 7-deazaadenine (^{z}A), guanine (G), and 7-deazaguanine (^{z}G). It was shown that the nature of B considerably affects the efficiency of the hole transfer; this effect was rationalized by differences of the ionization energy of B.[30] Yet, the ionization energy (or the oxidative potential) is not the only factor controlling the hole-transfer efficiency. Chemical modification of the bases can also produce remarkable changes in the electronic couplings between Watson−Crick pairs. However, these two factors cannot be easily separated by experiments.

Thus, motivated by these findings,[30] we extended our theoretical investigations[26,27] on the electronic coupling matrix element H_{da} to systems containing deazapurines to analyze effects of chemical modifications on the efficiency of DNA-mediated hole transfer. On the basis of the calculated energetics of hole-transfer and electronic nearest-neighbor couplings in the π stack, we employed an approach suggested by Larsson[31] to study the distance dependence of the bridge-mediated effective coupling H_{da} in π stacks of DNA and to discuss the influence of the electronic structure of the nucleobases on this coupling.

Method

Models. We examined systems where the hole donor GGG$^+$ and the acceptor GGG bracket short stacks of several Watson−Crick pairs. In our models, we considered only double stranded DNA fragments of stacked pairs of nucleobases as mediator of CT, but we neglected the sugar−phosphate backbone; this approximation seems to be quite adequate.[20] We employ an abbreviated notation; for instance, AG denotes a fragment that consists of two Watson−Crick pairs (AT) and (GC) in the standard order 5′ → 3′.

Two main factors control how bridging bases affect the charge migration through the stack: (i) the energy of the virtual state B$^+$ and (ii) the electronic coupling of B (B = A, ^{z}A, G, ^{z}G) to adjacent nucleobases. As mentioned above, the relative energies of radical cation states B$^+$ depend in an essential fashion on adjacent nucleobase pairs.[24] To take this effect into account, the ionization energy of B was estimated in the trimer duplexes 5′-TBT-3′, 5′-ABA-3′, 5′-TBA-3′, and 5′-ABT-3′ with B = A, ^{z}A, G, ^{z}G. Electronic coupling matrix elements were calculated for the duplexes 5′-TB-3′, 5′-BT-3′, 5′-AB-3′, and 5′-BA-3′.

TABLE 1: Characteristics of Hydrogen Bonds in the Nucleobase Pairs GC, ^{z}GC, AT, and ^{z}AT Calculated with the B3LYP/6-31G* Method

base pair	E(H-bond), kcal/mol	NH_2–O, Å	N_3–N_4, Å	O−NH_2, Å
GC	30.9	2.932	2.949	2.817
^{z}GC	30.1	2.953	2.949	2.812
AT	16.2	2.932	2.949	2.817
^{z}AT	16.5	2.953	2.949	2.812

TABLE 2: Electronic Coupling Matrix Elements[a] (eV) for Hole Transfer between Two Watson−Crick Pairs Using Average Experimental and Calculated Geometries of the Nucleobases

complex	expt geometry[b]	calcd geometry[c]
[(GC), (TA)]	0.026	0.025
[(TA), (GC)]	0.027	0.026
[(AT), (TA)]	0.055	0.055
[(TA), (AT)]	0.050	0.051

[a] Calculated at the HF-SCF/6-31G* level. [b] Reference 34. [c] Determined at the B3LYP/6-31G* level.

Chemical modification of the purines may induce structural changes of the corresponding nucleobase pairs. In Table 1 we compare binding energies and selected structural parameters of hydrogen bonds in natural and modified nucleobase pairs calculated at the B3LYP/6-31G* level.[32] Only minor changes result, both in the stability and the geometry of the GC pair, if one replaces G by ^{z}G. Also the pairs AT and ^{z}AT are calculated to be very similar (Table 1). On the basis of these results, one does not expect significant structural changes in DNA duplexes when the Watson−Crick pairs GC and AT are replaced by ^{z}GC and ^{z}AT, respectively. Therefore, structural models of DNA fragments containing ^{z}G and ^{z}A can be designed using the same approach as that usually employed for normal DNA. Thus, all duplexes were constructed with the program SCHNArP[33] using the step parameters of regular B-DNA (rise, 3.38 Å; twist, 36°) and the nucleobase structures obtained in B3LYP/6-31G* calculations. Note that matrix elements calculated at experimental averaged geometries of nucleobases[34] and at B3LYP/6-31G* geometries do not differ significantly; the corresponding deviations amount to at most 5% (Table 2).

Electronic Coupling. We calculated the electronic couplings for hole transfer between Watson−Crick pairs in the regular DNA structure as described previously.[27] The matrix elements were estimated as half of the minimum splitting Δ between two adiabatic states. To find the minimum splitting (where the electronic donor and acceptor levels are in resonance which permits the charge transfer), we used an external electric field along the DNA axis. Invoking Koopmans' approximation, we estimated the splitting $\Delta = E_2 - E_1$ of the cation radical states as the difference of the one-electron energies of the HOMO and HOMO-1 orbitals calculated for the corresponding neutral system, $\Delta \approx \epsilon_{HOMO-1} - \epsilon_{HOMO}$.

Hartree−Fock and B3LYP quantum chemical calculations were carried out with the program Gaussian 98 using the standard basis set 6-31G*.[32]

Energetics. Relative energies of virtual intermediate states 5′-XB$^+$Y-3′ (B = ^{z}G, ^{z}A) were estimated on the basis of calculated ionization potentials of B in triplets of regular

structure (see above). The ionization energies were determined within Koopmans' approximation using the semiempirical method NDDO-G.[35] Since only *relative* ionization energies are required, this NDDO-G based approach is expected to provide reliable estimates of the energetics of hole transfer in DNA.[24]

Effective Hamiltonian. The electronic coupling of a donor (d) and an acceptor (a) connected via a π stack can be described using an effective Hamiltonian. In this approach, a *system* $d-b_1b_2$ ...$b_{n-}a$ is described by an effective Hamiltonian determined with $(n + 2)$ basic states: two states $d^{+-}b_1b_2...b_{n-}a$ and $d-b_1b_2...b_{n-}a^+$ where the hole is localized on the donor and the acceptor, respectively, and n intermediate virtual states with the hole being one of the bridging subunits b_i ($i = 1, 2, ..., n$). In the present models, each subunit b_i corresponds to a Watson−Crick pair. The diagonal elements $\tilde{H}_{ii}$ of this effective Hamiltonian may be approximated by the relative energies of the radical cations XB^+Y; in this way, significant effects of the environment are accounted for. Off-diagonal elements $\tilde{H}_{ij} = V_{ij}$ between adjacent nucleobase pairs ($j = i \pm 1$) were approximated as the corresponding electron coupling matrix elements and neglected in other cases. The state functions are assumed to be orthonormalized so that their overlap matrix is the unit matrix. Our effective Hamitonian approach is analogous to schemes widely used for treating electron transfer in medium and large systems.[14,16] Note that here and elsewhere[23] only one state per bridge unit is taken into account. Bridge states of higher energies can play a role for the effective donor−acceptor coupling. Thus, models with one effective state per bridge unit represent an approximation; an analysis of this approximation is outside the scope of the present study.

The effective electronic coupling can be calculated using a method suggested by Larsson[31] (based on the Löwdin's partitioning technique[36]) or derived from the splitting of the donor and acceptor orbitals obtained by diagonalizing the Hamiltonian matrix. In Larsson's approach the effective d−a coupling H_{da} can be estimated as[31]

$$H_{da} = V_{d1}V_{na}\sum_{i=1}^{n}\frac{C_{1i}C_{ni}}{E-\epsilon_i} \qquad (3)$$

An alternative derivation of eq 3 can be given with the help of the Green function approach to electron transfer.[16] The energies ϵ_i and the coefficients matrix C_{ij} are determined by diagonalizing the effective Hamiltonian matrix $\tilde{H}$ of the bridge. The units b_1 and b_n are assumed to connect the bridge to the donor and the acceptor with couplings V_{d1} and V_{na}, respectively. The summation extends over all states of the bridge. The tunneling energy E is the electronic energy of the donor and acceptor in the resonant state where charge transfer occurs. The parameters for d and a correspond to guanine triplets: the electronic couplings of (GC) and (AT) pairs were used to set up the matrix elements V_{d1} and V_{na}. Because the energies of all electronic states of the system are defined relative to the ionization energy of a guanine triplet GGG which acts as donor and acceptor, the tunneling energy E is taken to be zero.

Normally, Larsson's perturbation approach[31] has a significant advantage since the effective coupling is calculated directly while diagonalization of the Hamiltonian of the whole system requires an accurate iterative search for the minimum splitting. To illustrate a limitation of the perturbation approach, we discuss a system with identical donor and acceptor moieties d = a = GGG, connected via bridge ABA. Even though donor and acceptor are identical, the states $d^{+-}ABA-a$ and $d-ABA-a^+$ are off-resonance because of the steric arrangement in DNA.

TABLE 3: Reaction Energies ΔE (eV) for the Hole Transfer from GG^+G to TBT and ABT

	ΔE			
	B = G	B = ^{z}G	B = A	B = ^{z}A
$GG^+G \rightarrow TB^+T$	0.252	0.096	0.691	0.264
GG+G f AB+A	0.134	0.246	0.587	0.019

The asymmetry is evident both from the couplings V(AB) ≠ V(BA) and the ionization energies of A in dAB and BAa.[24,27] Therefore, donor and acceptor states have to be brought into resonance to obtain the minimum splitting of the pertinent orbitals, e.g. by adjusting the relative energies of donor and acceptor. As an example, consider the system d−AAA−a, where the splitting of the donor and acceptor orbitals is 1.34×10^{-2} eV, while the corresponding minimum splitting is 9.4×10^{-6} eV. The resulting effective coupling of 4.7×10^{-6} eV is in very good agreement with the value of 4.8×10^{-6} found from eq 3. Both approaches produce also very similar results for other systems d−ABA−*a*, B = G, T, C (see Table 6). The only essential difference in the effective coupling values estimated by the two approaches was found for the bridge A^zAA; the perturbation value is about 30% larger than the value obtained by diagonalization (Table 6). The small difference between the energy of the bridge state $d-A^zA^+A-a$ and the energy of the donor and acceptor levels, 0.02 eV, puts this system at the limit of the perturbation scheme.

Results and Discussion

Energetics of ^{z}GC and ^{z}AT. The ionization potentials and thus the energetics of hole transfer are considerably affected when purines are replaced by their 7-deaza derivatives, even though this replacement induces only minor structural changes of the complementary pairs AT and GC (Table 1). The calculated reaction energies for the hole transfer $GG^+G + XBY \rightarrow GGG + XB^+Y$ with B = ^{z}G, ^{z}A are listed in Table 3. The relative energies of all possible Watson−Crick pair triplets XB^+Y of natural nucleobases have been presented previously.[24]

The fragment GGG is the strongest hole acceptor in DNA.[28] As mentioned before, neighboring nucleobases significantly affect the stabilization of a radical cation.[24] The most efficient stabilization of a cation radical B^+ has been calculated for the triplet GB^+G, while the most unfavorable environment is XB^+Y with X and Y being pyrimidines C or T. For instance, the energy of the hole transfer $GG^+G \rightarrow TG^+T$ is about 0.25 eV (6 kcal/mol; see Table 3). NDDO-G calculations on isolated species predict that 7-deaza derivatives exhibit lower ionization potentials than the corresponding natural purines. The ionization energies were calculated at 7.66 and 8.06 eV for ^{z}G and G and at 8.07 and 8.53 eV for ^{z}A and A, respectively. Thus, the calculated energy of the hole transfer between an isolated 7-deazapurine and its natural counterpart is 0.40 eV for G and 0.46 eV for A. Quite similar differences are calculated for Watson−Crick pairs: the ionization potential of (GC) is by 0.38 eV higher than that of (^{z}GC); the corresponding difference between (AT) and (^{z}AT) is determined at 0.45 eV. The differences of the ionization energies remain almost uncharged in a DNA environment. For instance, the reaction energy of $T^zG^+T + TGT \rightarrow T^zGT + TG^+T$ amounts to 0.35 eV, while it is 0.43 eV for $T^zA^+T + TAT \rightarrow T^zAT + TA^+T$. Due to its remarkably low ionization potential, ^{z}G is a better hole acceptor than GGG—even in the most unfavorable environment T^zGT (Table 3); for instance, the hole-transfer energy $GG^+G + T^zGT \rightarrow GGG + T^zG^+T$ is calculated to be −0.10 eV. Thus, the hole transfer between GGG triplets separated by a π stack

TABLE 4: Electronic Coupling (eV) of Two Watson−Crick Pairs

	XY = GC	XY = ^{z}GC	XY = AT	XY = ^{z}AT
[(XY), (TA)]	0.025	0.018	0.055	0.043
[(TA), (XY)]	0.026	0.018	0.051	0.052

TABLE 5: Effective Electronic Donor−Acceptor Coupling (eV) in d-$(X)_n$-a for Various π Stacks $(X)_n$ of Nucleobase Pairs

n	$(T)_n$	$(A)_n$	$(AT)_{n/2}$
1	8.13×10^{-4}	2.30×10^{-3}	
2	3.65×10^{-5}	1.04×10^{-4}	3.35×10^{-4}
3	1.68×10^{-6}	4.80×10^{-6}	
4	7.76×10^{-8}	2.21×10^{-7}	1.73×10^{-6}
5	3.58×10^{-9}	1.02×10^{-8}	
6	1.65×10^{-10}	4.71×10^{-10}	8.97×10^{-9}

containing ^{z}G should be quenched because of hole trapping by ^{z}G. This finding is in full agreement with the experimental results of Saito.[30] According to our estimates (Table 3), the oxidation potential of ^{z}A is similar to that of G and ^{z}A can be a strong hole acceptor in an appropriate environment G^{z}AG.

Electronic Couplings. Table 4 compares the electronic couplings calculated for dimer duplexes containing ^{z}G and ^{z}A with those of normal Waston−Crick pair dimers. The calculations show that the chemical modifications G → ^{z}G and A → ^{z}A decrease the matrix elements by up to 30%.

Distance Dependence of Electronic Couplings. Consider two systems d−b_1b_2...$b_{m-}a$ and d−b_1b_2...b_{n-}a, where donor and acceptor are separated by π stacks of lengths m and n, respectively. For charge shift processes (as opposed to charge separation), the free energy of the charge transfer is independent of the donor−acceptor separation. The rate constant k is proportional to $(H_{da})^2$, and the distance between adjacent pairs can be assumed to be 3.38 Å; therefore, the parameter β_{el} (Å^{-1}) can be estimated as

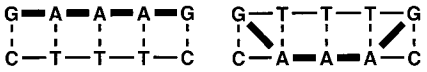
$$\beta_{el} = -\frac{2}{3.38}\frac{\ln H_{da}(n) - \ln H_{da}(m)}{n - m} \qquad (4)$$

The effective couplings $H_{da}(n)$ and $H_{da}(m)$ are calculated as described previously; see eq 3.

In the following we shall consider several DNA related systems exhibiting single-step hole transfer between two GGG triplets as donor and acceptor, mediated by different π-stacks. The effective electronic couplings calculated for the systems 5′-GGG-$(X)_p$-GGG-3′ with X = A, T ($p = n$) and X = (AT) ($p = n/2$) are given in Table 5. The nearest-neighbor coupling elements of the effective Hamiltonian were taken from our previous study[27] or from Table 4.

$(T)_n$ Bridges. Estimates of β_{el} based on the effective coupling H_{da} for bridges $(T)_n$ with $n = 1-6$ (Table 5) show that this parameter is a rather stable quantity for different values m and n in eq 4. As examples, we note the following estimates of β_{el} for various combinations (m, n): 0.80 (1, 2), 0.78 (2, 3), 0.78 (2, 3), 0.79 (2, 5), and 0.79 Å^{-1} (4, 5). Slight "initialization" effects disappear for longer π stacks (m, $n \geq 3$). The resulting β_{el} parameter is in very good agreement with a recent experimental value $\beta = 0.77$ Å^{-1} found for several systems where hole donor and acceptor are separated by AT pairs.[37] This value for a hole shift is intermediate between the values obtained previously for charge separation ($\beta = 0.7$ Å^{-1}) and charge recombination ($\beta = 0.90$ Å^{-1}).[38]

$(A)_n$ Bridges. As discussed earlier,[27] the electronic coupling between two Watson−Crick pairs is determined mainly by the interaction of purine nucleobases. It is worth noting that the electronic coupling of two pair depends on their order in a DNA fragment; for instance, the matrix elements calculated for 5′-G-A-3′ and 5′-A-G-3′ are 0.122 and 0.025 eV, respectively.[27] Thus, the difference in the effective donor−acceptor coupling mediated by $(A)_n$ and $(T)_n$ is caused by V_{d1} and V_{na}, eq 3. In the case of $(A)_n$ the *intra*strand interactions G−A and A−G, 0.089 and 0.049 eV, respectively,[27] determine the couplings between donor and bridge on one hand and bridge and acceptor on the other. At variance with this situation, in the case of the bridge $(T)_n$ the two *inter*strand matrix elements G\A and A/G (∼0.026 eV) are of importance. The difference in the CT pathways is illustrated in the following scheme; see also ref 27 for the notation.



Furthermore, neighboring nucleobase pairs affect the energy of a virtual state A^+. For instance, the relative energies of the triples AA^+G and AA^+C at the interfaces between the $(A)_n$ and $(T)_n$ bridges and the acceptor, respectively, are 0.46 and 0.74 eV, respectively.[24] The values of the coupling matrix element H_{da} for systems where donor and acceptor are separated by $(T)_3$ and $(A)_3$ are calculated at 1.7×10^{-6} and 4.8×10^{-6} eV, respectively. However, these interface effects are eliminated when β_{el} is determined from longer fragments (m, $n \geq 3$). For bridges $(A)_n$ we obtained $\beta_{el} = 0.79$ Å^{-1} which is identical to the value found for $(T)_n$. These results completely agree with the experimental finding that very similar values of β were obtained for hairpins where the guanine donor is located either in a poly-T or a poly-A strand.[9]

$(AT)_{n/2}$ Bridges. In a study on strand cleavage in systems where single-step hole transfer across an $(AT)_n$ bridge occurs, a value of $\beta = 0.7$ Å^{-1} was obtained.[8] Comparing H_{da} for d-$(AT)_n$-a ($n = 2$ and $n = 3$), we calculate a very similar value, $\beta_{el} = 0.68$ Å^{-1}. Thus, despite identical parameters $\beta_{el} = 0.79$ Å^{-1} calculated for $(A)_n$ and $(T)_n$ stacks, the decay parameter of an $(AT)_n$ stack differs notably. The difference is due to the fact that the intrastrand adenine−adenine interaction determines the coupling of intervening pairs in homogeneous bridges, whereas the interstrand A−A interaction is responsible for the coupling in $(AT)_n$ bridges.

TBT and ABA Bridges. Two characteristics of nucleobases control the electronic donor−acceptor coupling H_{da} mediated by π stacks, (i) the electronic matrix elements $V_{ij} = \tilde{H}_{ij}$ between neighboring base pairs i and j, which are very sensitive to their relative orientation, and (ii) the (relative) ionization potentials of base pairs. According to our calculations, adenine and 7-deazaadenine exhibit similar values V_{ij} (Table 4), while their relative ionization energies differ significantly (Table 3). Therefore, the chemical modification of adenine makes it possible to elucidate experimentally the effect of the ionization energy of bridging nucleobases on the CT efficiency. Experiments[30] clearly showed that the efficiency of the hole transfer between two guanine triplets GGG, separated by a bridge TTBTT, is considerably affected by the nature of the base B. In particular, the hole-transfer rate constant for B = ^{z}A is substantially larger than that of the extremely inefficient case B = A.

Before we discuss the computational results given in Table 6, it should be noted that eq 3 may be applied to estimate the donor−acceptor coupling H_{da} only if the virtual states of the bridge are not in resonance with the donor and the acceptor states. Thus, the electronic coupling between subunits of the π

TABLE 6: Effective Electronic Donor−Acceptor Coupling (eV) Mediated by Various π Stacks of Nucleobase Pairs Obtained Using Equation 3

	B = A	B = ^{z}A	B = G	B = T	B = C
TBT	4.21×10^{-6}	9.45×10^{-6}	2.31×10^{-6}	1.68×10^{-6}	1.76×10^{-6}
TTBTT	8.62×10^{-9}	19.4×10^{-8}	4.66×10^{-9}	3.58×10^{-9}	3.86×10^{-9}
ABA	4.80×10^{-6}	3.39×10^{-4}	5.43×10^{-5}	1.16×10^{-5}	6.25×10^{-6}
	$[4.68 \times 10^{-6}]^a$	$[2.63 \times 10^{-4}]$	$[5.20 \times 10^{-5}]$	$[1.14 \times 10^{-5}]$	$[6.14 \times 10^{-6}]$
AABAA	1.02×10^{-8}	7.03×10^{-7}	1.03×10^{-7}	2.46×10^{-8}	1.33×10^{-8}

[a] Values in brackets are estimated by diagonalization of the hamiltonian of the whole system (see Section Method).

stack, i.e., the off-diagonal elements V_{ij} of the effective Hamiltonian, have to be notably smaller than the energies of the hole transfer between the donor and the bridge. Otherwise, a bridge unit would trap the electron hole and the charge transfer would stop. Hence, this model cannot be applied in the case where the energy splitting between the orbitals of the bridge and the donor (or the acceptor) becomes comparable to the thermal energy (0.026 eV at room temperature) since thermal injection of holes into the bridge would occur.[15]

How does a replacement of B = A by B = ^{z}A affect the hole-transfer capability of π stacks TBT bridging two triplets GGG? The properties of the TBT bridge are determined by *inter*strand adenine−adenine coupling matrix elements. The effective donor−acceptor coupling H_{da} provided by TAT and T^{z}AT were calculated at 4.2×10^{-6} and 9.5×10^{-6} eV, respectively (Table 6). The remarkable increase of H_{da} is due to the lower ionization potential of ^{z}A since the change of the base pairs couplings acts in the opposite direction, V(AT) > V(^{z}AT) (Table 4). While the values of the effective couplings decrease exponentially with the length of the stack when bridges are extended from TBT to TTBTT, the *ratio* of the effective couplings remains unchanged in our model. This result follows directly from eq 3, if one presents the system d-TTBTT-a as d′-TBT-a′, where d′ = (d-T) and a′ = (T-a). For instance, the couplings calculated for TTATT and TT^{z}ATT are substantially smaller, 8.6×10^{-9} and 19.4×10^{-9} eV, respectively, than those of TAT and T^{z}AT given above. However, their ratio, about 2.3, remains unchanged. Thus, the effective coupling of $(T)_nA(T)_n$ stacks increases by a factor of about 2.3 when adenine is replaced by 7-deazaadenine. This result is in agreement with experiments,[30] which demonstrated that the charge transfer mediated by the bridge TTATT becomes considerably more efficient on the substitution A → ^{z}A. Unfortunately, these experimental results are not quantified,[30] preventing a more detailed comparison.

A much more pronounced effect is found for π stacks ABA, where the *intra*strand purine−purine interaction is responsible for the electronic coupling. The effective donor−acceptor couplings for AAA and A^{z}AA were calculated at 4.8×10^{-6} and 3.4×10^{-4} eV, respectively (Table 6). The considerable increase of the effective coupling H_{da} by a factor of ∼70 is caused by the small difference of the ionization potentials of A^{z}A$^+$A and GG$^+$G, 0.019 eV (see Table 3). Note that this small energy difference puts these systems at the limit of the Green function approach.[16,31]

In Table 6, we collect the calculated effective electronic couplings for all possible stacks TBT, TTBTT, ABA, and AABAA. As expected, the effects of B on the couplings provided by three- and five-membered bridges are similar. For instance, the ratio of the effective couplings for TAT and TTT as well as for TTATT and TTTTT is 2.4. Therefore, we can restrict the discussion to short bridges. As can be seen from Table 6, the effective couplings afforded by the bridges TTT and TCT are rather similar. Note that in both cases the actual coupling occurs via the complementary strands, AAA and AGA, respectively. Despite favorable energetics, the effective coupling mediated by the triplet AAA is relatively small, 0.48×10^{-5} eV, because of the weak interstrand donor−bridge and bridge−acceptor interaction as well as the small intrastrand A−A coupling, respectively.[24] In the bridge TAT, the effective coupling occurs via interstrand interactions between adenines that were calculated to be twice larger than the intrastrand coupling A−A.[24] Therefore, TAT couples donor and acceptor stronger than TTT despite the less favorable hole-transfer energetics of TAT as compared to AAA, 0.69 and 0.59 eV, respectively (Table 3).

Our calculations show (Table 6) that, for different nucleobases B, the effective donor−acceptor coupling mediated by the stacks TBT increases in the order T ≈ C < G < A < ^{z}A (Table 6), while the coupling provided by ABA bridges increases in the order A < C < T < G < ^{z}A. Thus, the effect of a nucleobase B in the bridge XBY depends considerably on X and Y because of the remarkable variation of the electronic couplings between B and neighboring Watson−Crick pairs X and Y. Furthermore, our results for both type of bridges TBT and ABA suggest that the hole-transfer efficiency increases notably if one replaces A by ^{z}A. This finding, completely in line with the experiments of Saito et al.,[30] is a consequence of two facts: (i) the ionization potential of ^{z}A is considerably lower than that of A, and (ii) adenine and 7-deazaadenine exhibit comparable electronic coupling values to neighboring nucleobases. Comparing effective couplings in TTBTT listed in Table 6 with normalized intensities of cleavage bands[30] shows a discrepancy. According to experiment, the observed efficiency changes with B as A < ^{z}A ≈ G while the calculated values of the electronic coupling vary in the order G < A < ^{z}A. This disagreement may be related to the *different* (and notable) variation of the electronic couplings *V*(AG) and *V*(AA) with the structure of the duplex. Recently, we have shown that the electronic coupling of WCPs changes significantly with structural changes due to thermal fluctuations.[22]

Conclusion

The preceding discussion shows that an approximate Green function treatment in the Larsson's model in combination with electron couplings and relative ionization energies calculated for Watson−Crick pairs and their modified analogues can be successfully used for modeling the hole transfer trough DNA π stacks. From these results and the analysis of the effective donor−acceptor couplings mediated by short DNA π stacks we conclude the following.

The calculated distance decay parameters β_{el} of the rate constant derived from the effective coupling, $\beta_{el} = 0.79$ Å^{-1} for $(T)_n$ and $(A)_n$ bridges and $\beta_{el} = 0.68$ Å^{-1} for $(AT)_{n/2}$ π stacks, agree very well with experimental attenuation parameters β obtained for the hole transfer mediated by these bridges. This suggests that the reorganization energy exhibits a weak distance dependence, characterized by β_r, to the overall decay parameter $\beta = \beta_{el} + \beta_r$. Our preliminary estimates show that β_r is about

0.1 $Å^{-1}$.[34] A previous investigation[18] yielded a considerably larger attenuation effect of reorganization energy. However, this overestimation is mainly related to the fact that very high values of the static dielectric constants, $\epsilon = 12.4$ and 20.0 for the base stack and the sugar−phosphate backbone regions, respectively, were used[18] instead of commonly assumed ϵ values in the range 2−4.

The effective electronic coupling is sensitive to relative energies of the cation radical states of intervening nucleobases. Therefore, effects of neighboring base pairs on the energetics of the hole transfer have to be taken into account when estimating the effective coupling. Especially large effects are found through a variation of the ionization energy (the oxidation potential) of guanine and adenine. The purine nucleobases exhibit relatively low oxidation potentials, and a chemical modification of these species or changes of their environment can strongly affect the efficiency of charge transfer through the corresponding bridges. According to our computational models, the effective donor−acceptor coupling of TAT units increases by about a factor of 2.3 when one replaces A by ^{z}A; thus, the CT rate constant increases by a factor of ∼5. The same substitution, A → ^{z}A, in the triplet ABA leads to substantially more pronounced effects. In other words, a decrease of the oxidation potential of a base B (due to its replacement by another base B′) in a bridge raises the hole-transfer efficiency if the couplings of B′ with their neighbors are nor considerably smaller than that of B, e.g. as in the case of A and ^{z}A. Otherwise, the π interaction between nucleobases will control the effective coupling of the donor and acceptor.

Incorporation of ^{z}G into π stacks quenches the hole transfer irrespective of its neighbors because triplets X^{z}GY (X, Y = G, A, C, T) are calculated to be better hole acceptors than GGG, in agreement with experiments[30] which showed that hole transfer between two guanine triplets was terminated by an intermediate ^{z}G. Because pyrimidine bases have considerably higher ionization energies, any (reasonable) chemical modification of thymine and cytosine will hardly produce a remarkable change of the effective donor−acceptor coupling.

Previously, we have found that the electronic couplings of the Watson−Crick pairs are very sensitive to variations of their mutual positions.[22] The electronic coupling can change considerably by thermal fluctuations of the DNA helix parameters which determine the distance between pairs along the helix axis (rise), planar displacements of the pairs (shift and slide) and DNA unwinding (twist).[22] When calculating matrix elements of the effective Hamiltonian in the present investigation, we had assumed ideal structures of the DNA fragments. Any straightforward attempt to expand the present investigation so that structural fluctuations with time and their consequences for the electronic couplings are taken into account is limited by the substantial computational effort required for an ab initio calculation of the electronic couplings along trajectories generated by the molecular dynamics of DNA fragments.

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