Charge Hopping in DNA

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Abstract: The efficiency of charge migration through stacked Watson−Crick base pairs is analyzed for coherent hole motion interrupted by localization on guanine (G) bases. Our analysis rests on recent experiments, which demonstrate the competition of hole hopping transitions between nearest neighbor G bases and a chemical reaction of the cation G^+ with water. In addition, it has been assumed that the presence of units with several adjacent stacked G bases on the same strand leads to the additional vibronic relaxation process $(G^+G...G) \rightarrow (GG...G)^+$. The latter may also compete with the hole transfer from $(G^+G...G)$ to a single G site, depending on the relative positions of energy levels for G^+ and $(G^+G...G)$. A hopping model is proposed to take the competition of these three rate steps into account. It is shown that the model includes two important limits. One corresponds to the situation where the charge relaxation inside a multiple guanine unit is faster than hopping. In this case hopping is terminated by several adjacent G bases located on the same strand, as has been observed for the GGG triple. In the opposite, slow relaxation limit the GG...G unit allows a hole to migrate further in accord with experiments on strand cleavage exploiting GG pairs. We demonstrate that for base pair sequences with only the GGG triple, the fast relaxation limit of our model yields practically the same sequence- and distance dependencies as measurements, without invoking adjustable parameters. For sequences with a certain number of repeating adenine:thymine pairs between neighboring G bases, our analysis predicts that the hole transfer efficiency varies in inverse proportion to the sequence length for short sequences, with change to slow exponential decay for longer sequences. Calculations performed within the slow relaxation limit enable us to specify parameters that provide a reasonable fit of our numerical results to the hole migration efficiency deduced from experiments with sequences containing GG pairs. The relation of the results obtained to other theoretical and experimental studies of charge transfer in DNA is discussed. We propose experiments to gain a deeper insight into complicated kinetics of charge-transfer hopping in DNA.

Introduction

Charge migration phenomena in DNA have attracted much interest because of relevance to the generation of damage[1] and mutations.[2] In addition to biological implications, the understanding of this phenomenon is central for further development of DNA-based molecular technologies, especially for electrochemical sequencing techniques.[3] Experimental and theoretical studies of charge migration in DNA have also been triggered by the idea of doing "chemistry at a distance" [4] and by potential application of DNA as a molecular wire in mesoscopic electronic devices.[5]

Unlike such proteins as cytochromes or the photosynthetic reaction center, DNA is not primary an electron-transfer species.[6] Nevertheless, the ordered π-electron system of the common DNA bases in duplex B-form DNA (referred to here simply as DNA) provides an appropriate pathway for the motion of excess charges once generated on extended and well-defined stacks of base pairs. The latter condition is fulfilled under exposure of DNA to ionizing radiation,[7,8] in the case of certain light driven processes,[5d,9−11] and for specially constructed DNA analogues

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with functional groups that allow the formation of radical cations upon activation.[12−14]

The subsequent motion of charges generated in DNA by these physical and chemical means is a controversial matter that has been probed by different experimental techniques. These include pulse-radiolysis time-resolved microwave conductivity,[6] direct measurements of electrical current as a function of the potential applied across a few DNA molecules,[5g,h] fluorescent quenching,[15] and femtosecond transient absorption measurements.[16] Various experiments exploit pendant or intercalated donors and acceptors,[17−19] fluorescent analogues of adenine chemically incorporated in base pair sequences[20] and a photocleavage reaction for a site-selective generation of charge on a guanine base using an exogenous hole donor.[12,14,21] The discussion of results obtained using these different systems and methodologies[4,19d,22] has been centered around the dependence of charge-transfer efficiency on the length of a π-pathway serving as a bridge between primary donor and acceptor sites. The observed far reaching translocation of charge[12,14,17b,19b,20,21,23] (up to ∼200 Å) was found to be in dramatic conflict with the conventional tunneling mechanism of unistep superexchange-mediated electron transfer.[24] Quantum mechanical calculation shows that this coherent superexchange mechanism should lead to the reduction of the charge-transfer efficiency by roughly a factor of 10 for every base pair extension of the DNA bridge. To resolve the contradiction, recent studies[12,14,20,22d,e,26−29] suggest that the long-range charge migration in DNA can be viewed as a series of short-range hops between energetically appropriate guanine bases.

In this paper we present a hopping model for charge migration in DNA and apply it to the kinetic analysis of two distinct sets of strand cleavage data used to obtain information about the efficiency of hole migration in DNA. One set involves the data on the relative reactivity of a guanine (G) radical cation G^+ and of charge trapped by a distant triple guanine unit (GGG) within one of the strands of the helix.[12,14] Another includes strand cleavage intensities measured at different positions of guanine pairs GG in base pair sequences.[21,23] We demonstrate that these two sets of experimental data can be described within two important limits of the proposed model. The first limit corresponds to the case where the relaxation of the positive charge inside a multiple guanine unit, that is, the process $(G^+G...G) \rightarrow (GG...G)^+$, is faster than hopping.[30] We show that in this fast relaxation limit the GG...G unit terminates hole hopping as has been found for sequences containing a GGG triple.[12,14] Such a strong kinetic restriction does not exist in the second limit of our model, where hopping is faster than charge relaxation. As a consequence, the GG...G unit allows a hole to migrate further in accord with experiments on strand cleavage exploiting GG pairs.[21,23] The sequence and distance dependencies of the hole migration efficiency derived within fast and slow relaxation limits are in reasonable agreement with those deduced from the relative reactivity[12,14] and the cleavage intensity data.[21,23] Nevertheless, we conclude that certain aspects of the hopping mechanism of charge migration in DNA should be clarified in more detail. Experiments suited for this purpose are proposed and briefly discussed.

Model

1. Qualitative Consideration. Most of the available experimental data on charge transfer in DNA pertains to hole (positive ion) transfer and/or transport in solution.[12,14−16,19b,c,e,21,23,26,27,31,32] This corresponds to the case where an electron undergoes a transition from the hole acceptor to the electronically excited or positively charged hole donor. According to earlier theoretical analysis,[22d,h,28,29,33] two extremes for

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(30) Hereinafter GG...G stands for the sequence fragment consisting of a finite number of G bases stacked on the same strand. Using the standard notation, an example of sequences containing this fragment can be written in general form as 5′-X_1TGX_2(GG...G)TX_3-3′, where X_1 and X_3 are sequence segments containing individual A, T, and G bases, while X_2 is the segment containing only A or T bases. Correspondingly, the notation $(G^+G...G)$ signifies the intermediate state of the GG...G fragment formed as a result of the hole transfer to the G base nearest to the single G site previously occupied by a hole. The lowest energy radical cation state of the GG...G fragment is denoted by $(GG...G)^+$.

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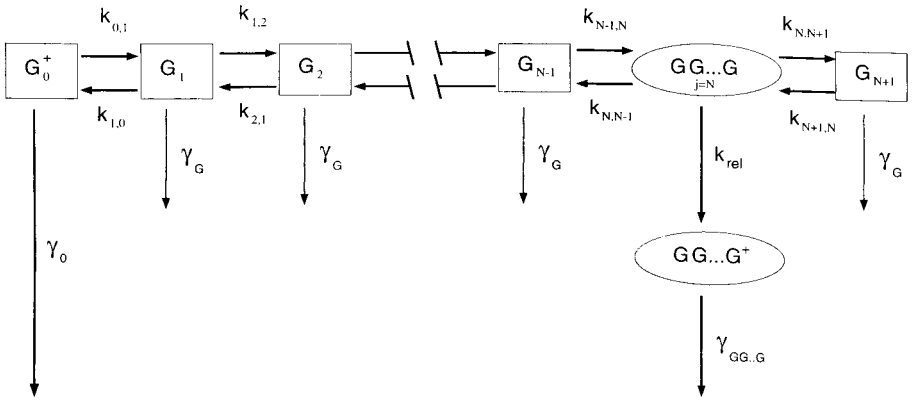

Figure 1. Schematic picture of rate processes for hole motion along base pair sequences. Fragments between G sites that are not shown in the scheme consist of AT base pairs only. Notations are given in the text.

the mechanism of hole migration in DNA should be considered. One extreme is the unistep superexchange-mediated tunneling.[24] This coherent mechanism yields a charge-transfer rate k_{CT} depending exponentially on the length of the bridge, R,

$$k_{CT} = k_0 \exp(-\beta R) \qquad (1)$$

where k_0 is the preexponential factor and β is the falloff parameter, expected to be of the order of 1 Å^{-1}, see, for example, refs 22d and 25. The other mechanism involves incoherent hopping between adjacent nucleobases with similar energetics appropriate for temporary localization of a moving charge.

There is no dichotomy between coherent and incoherent mechanisms of charge migration in donor−bridge−acceptor systems. On the contrary, each can contribute to the mechanism of the process. The contribution depends on what is measured and particularly on the specific relative energies of the charge donor, the acceptor, and the bridge.[33] If the "bridging states" of nucleobases are very high in energy compared with that in the donor and the acceptor, the coherent mechanism will dominate. Otherwise, charge migration will mainly proceed by incoherent hopping.[34] Note, however, that resonance coupling between the hole donor and certain nucleobases in the DNA bridge provided conditions wherein both limiting extremes are operative: The superexchange-mediated tunneling controls the rate of the elementary jump between proximate nucleobases with the same redox potentials, while hopping is responsible for the long-range migration of charge along the bridge. There are reasons to believe[22d,h,28,29] that this mechanistic picture is applicable to the description of the ground-state hole transfer from a guanine (G) radical cation G^+ (a hole donor) to the hole trap triple GGG (an acceptor) through the bridge of stacked Watson−Crick base pairs. Indeed, the data on one-electron redox potentials of nucleobases in solution,[35] experimental values of their ionization potentials in vapors,[36] and computational results[37−39] show that the energy of the hole when residing on adenine (A), cytosine (C), or thymine (T) bases is higher than when on G by 0.5−0.7 eV. The lower energy of G^+ in comparison with that of A^+ also follows from the data on the oxidation potential of nucleobases.[40] If this trend is maintained in DNA, the coupling between the adjacent G and G^+ has to be considered as resonant, and hole migration will occur between the primary guanine cation G^+ and GGG via hopping through the G bases. By contrast, only off-resonant coupling should be expected for the nearest-neighbor G^+T, G^+C and G^+A bases. As a consequence, a hole is unable to hop from G^+ to T, A and C, which mediate the resonant $G \leftrightarrow G^+$ interaction via superexchange.

Thus, the motion of "electronic" holes along the DNA bridge can be treated as a series of linked hops between G sites. The fast exponential decrease of the tunneling rate with bridge length, see eq 1, makes direct long-range superexchange transfer much less effective than the multistep hopping process between the G bases, where each individual step contributes to the overall rate according to eq 1.

In what follows we exploit this picture for the analysis of the hole-transfer efficiency along sequences of stacked nucleobases with different arrangements and numbers of AT and GC base pairs. To be in contact with experiment, particular emphasis will be placed on the sequences containing either a single triple GGG[12,14] or several GG pairs.[21] As follows from ab initio calculations of ionization potentials,[10,38,39] the energy of holes on GGG and GG molecular units is lower than the energy of G^+ by about 0.7 and 0.5 eV, respectively. Therefore the triple GGG and the pair GG, as opposed to the single G base, are able to interrupt the hopping motion of hole.

2. Mathematical Formulation. On the basis of the hopping model[28,29] and recent experimental findings[12,14,21] the rate processes involved in the hole migration along these stacks of AT and GC base pairs can be depicted by the scheme shown in Figure 1. Following experiments,[12,14,21] we assume that initially a hole is site-selectively generated on the certain guanine site, G_0, for instance by a charge shift from an adjacent desoxyribose cation.[12,14] Thereafter, the primary radical cation G_0^+ is able to lose its positive charge in two competitive

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processes, namely hole transfer to the nearest-neighbor guanine base, G_1, and side reactions with water.[41] The rates of these processes are symbolized by $k_{0,1}$ and γ_0, respectively. Similar competitive decay channels exist for a positive charge on other sites containing a single G base: a hole can undergo the transition between neighboring single G sites with a hopping rate $k_{j,j\pm1}$ or can disappear in the side reaction with a decay rate γ_G. The situation remains unchanged until a hole has reached the GG...G site with G bases located on the same strand. It is assumed that at the GG...G step an intermediate state (G^+G...G) can first be formed, since a positive charge is transferred to the G base nearest to the single G site currently occupied by a hole. As a next step from this intermediate state, two possibilities exist: (i) the relaxation to the lowest-energy state $(GG...G)^+$ followed by the reaction with water and (ii) charge transfer to the adjacent single G sites through a segment consisting of AT base pairs only.

The above assumption about the charge behavior at the GG...G step makes the present model different from those proposed earlier.[22d,28,29] Those models suggest a direct transition of a hole to the state corresponding to $(GG...G)^+$. This suggestion appears to be incompatible with experimental results,[42] which demonstrate that the rates of charge transfer between two single G bases and between a single G and a GG pair are almost the same. Furthermore, the direct transition of a hole to the state corresponding to the radical cation $(GG)^+$ should be irreversible due to the large energy difference between G^+ and $(GG)^+$, while experimental results of Schuster and co-workers[21,23] imply that holes can continue their motion after visiting GG units.

To analyze recent experiments on hole transfer along stacks of AT and GC base pairs,[12,14] we introduce the probability, $P_j(t)$, of finding a hole on the j-th G site at time t. In the case of the unbiased hopping $k_{j,j\pm1} = k_{j\pm1,j}$ for all j, and therefore the scheme presented in Figure 1 leads to the following kinetic equation for $P_j(t)$

$$\frac{dP_j(t)}{dt} = -\gamma_0 P_j(t)\delta_{j,0} - \gamma_j P_j(t)(1-\delta_{j,0}) - k_{j,j+1}(P_j(t) - P_{j+1}(t)) - k_{j-1,j}(P_j(t) - P_{j-1}(t))(1-\delta_{j,0}) \quad (2)$$

where $\delta_{s,q}$ is the Kronecker symbol and γ_j is equal to the relaxation rate k_{rel} for each of GG...G sites and coincides with γ_G otherwise. Since at $t = 0$ a hole was site-selectively generated at the G site with $j = 0$, the initial condition is given by

$$P_0(t=0) = 1,\ P_{j\neq0}(t=0) = 0 \quad (3)$$

Two limiting cases become evident from eq 2 under the steady-state condition. The GG...G unit separated from the primarily oxidized G by a sequence without stacked guanines, such as a site with $j = N$ in Figure 1, can act as an irreversible sink for moving holes. This limit corresponds to the fast relaxation of charge within GG...G, that is, to the situation where a rate k_{rel} of the process (G^+G...G) → $(GG...G)^+$ is much larger than the rate of backward charge transfer (G^+G...G) → G^+. As a consequence, the process of reversible hopping is terminated at the GG...G step with a rate $k_{N-1,N}$. Such a hopping-controlled trapping mechanism concurs with experiments,[12,14] which explore hole transport from site-selectively generated G^+ to the triple GGG. Another situation arises if the relaxation is slow in comparison with charge transfer. Now "electronic" holes can either be trapped at the GG...G step with the effective rate $k_{rel}k_{N-1,N}/(k_{N-1,N} + k_{N+1,N} + k_{rel})$ or reach the next single G site $j = N + 1$ with the rate $k_{N-1,N}k_{N+1,N}/(k_{N-1,N} + k_{N+1,N} + k_{rel})$. Thus, the trapping process in the limit of slow relaxation is controlled by hopping to a smaller extent as compared to the fast relaxation limit. This partially hopping-controlled trapping may occur in the case of GG pairs, which do not terminate the hopping process and therefore allow holes to travel larger distances than the hole trap triple GGG. Accordingly, a GG pair does not necessarily function as a true hole trap. The same conclusion follows from direct measurements of the photoinduced charge separation rates in synthetic DNA hairpins, which contain two adjacent GC base pairs at varying position in the hairpin stem.[42]

(41) In addition to the reaction with water, radical cations G^+ can also undergo deprotonation with subsequent H-abstraction, see Steenken, S. *Biol. Chem.* **1997**, *378*, 1293−1297. However, according to ref 12 the contribution of this process to the measured relative yield is small. If one nevertheless assumes that proton transfer is a kinetic competitor for hole transfer, the upper limit for hole migration distances estimated by Steenken will be 17 Å. This value is much less than migration distances observed in experiments.[12,14,17b,19b,20,21,23] On the basis of these circumstances, we will not consider the protonation state of G^+ in our analysis.

(42) Lewis F. D.; Wu, T.; Liu, X.; Letsinger, R. L.; Greenfield, S. R.; Miller, S. E.; Wasielewski, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 2889−2902.

Calculation of Observables and Comparison with Experiment

1. Sequences with the GGG Triple. Earlier kinetic analysis motivated by experimental studies[12,14] has shown that the efficiency of hole transfer in these systems can be deduced from the measurements of the time-independent yields $Y_j (j = 0, ..., N-1)$ and Y_{GGG} for the products formed in the reactions of water with G_j^+ and $(GGG)^+$, respectively. The experimental yield data[12,14] are given in terms of the total damage ratio

$$\phi = \frac{Y_{GGG}}{\sum_{j=0}^{N-1} Y_j} \quad (4)$$

or, alternatively, in the form

$$\phi' = Y_{GGG}/Y_0 \quad (5)$$

To calculate the ratios ϕ and ϕ' within the framework of the hopping model, it is instructive to note that in the case of the hopping-controlled hole trapping at the GGG step eq 2 can be rewritten as

$$\frac{dP_j(t)}{dt} = -\gamma_0 P_j(t)\delta_{j,0} - \gamma_G P_j(t)(1-\delta_{j,0}) - k_{j,j+1}(P_j(t) - P_{j+1}(t))(1-\delta_{j+1,N}) - k_{j,j-1}(P_j(t) - P_{j-1}(t))(1-\delta_{j,0}) - k_{j,j+1}P_j(t)\delta_{j,N-1}, \quad j = 0,1, ..., N-1 \quad (6)$$

Once the solution of eq 6 is known for all j, the ratios ϕ and ϕ' can be obtained by substituting $P_j(t)$ into expressions

$$\phi = \frac{\int_0^\infty k_{N-1,N}P_{N-1}(t)dt}{\int_0^\infty (\gamma_0 P_0(t) + \gamma_G \sum_{j=1}^{N-1} P_j(t))dt} \quad (7)$$

$$\phi' = \frac{\int_0^\infty k_{N-1,N}P_{N-1}(t)dt}{\gamma_0 \int_0^\infty P_0(t)dt} \quad (8)$$

The above procedure provides the basis for kinetic analysis of the efficiency of hole migration along various base pair sequences with the GGG triple and offers exact analytical results for several important cases. In particular, if $\gamma_G = 0$, so that the main contribution to the total damage ratio comes from the reactions of water with the primary radical cation G_0^+ and with $(GGG)^+$, our calculations give

$$\phi = \phi' = \frac{k_{N-1,N}\int_0^\infty P_{N-1}(t)dt}{\gamma_0 \int_0^\infty P_0(t)dt} = \frac{1}{\gamma_0}\cdot\frac{1}{\left(\frac{1}{k_{0,1}} + \frac{1}{k_{1,2}} + \frac{1}{k_{N-1,N}}\right)} \quad (9)$$

Table 1. Efficiency of Hole Migration through Base Pair Sequences Bridging the Primarily Oxidized G Site and the GGG Triple[a]

	Sequence	efficiency expressed in terms of damage ratios			
		ϕ'		ϕ	
		exp.	theor.	exp.	theor.
I	T / A	30±6[12]		30±6[12]	
II	T T / A A	8.9±1.9[14]		8.9±1.9[14]	
III	T A / A T	3.2±0.6[12]		3.2±0.6[12]	
IV	T G T A / A C A T	3.4±0.7[12]	2.8±0.6	3.0±0.7[12]	2.6±0.6
V	T A C A / A T G T	3.8±0.8[12]	2.8±0.6		1.4±0.6
VI	T T G T T / A A C A A		4.2±0.9	2.8±0.4[14]	2.8±0.6
VII	T T G T T G T T G T T / A A C A A C A A C A A		1.7±0.7	0.9±0.1[14]	0.8±0.3
VIII	T C A G C T C A G T C T G C A / A G T C G A G T C A G A C G T	3.4±0.7[12]	3.15±0.8		0.7±0.2
IX	T A T A / A T A T	0.03±0.015[12]	0.036±0.02		

[a] Theoretical predictions concerning the efficiency of hole migration were based on calculations of the damage ratios from the experimental data of refs 12 and 14 for sequences **I**, **II**, and **III**. Theoretical λ values in eq 12 were obtained from the solution of eq 6. Errors in theoretical values were estimated by using experimental errors.

Note that the rates $k_{j,j+1}$ in this equation depend on the lengths, $L_{j,j+1}$, of the sequence segments which connect adjacent G sites and consist of AT base pairs only.

The expression derived for ϕ' reduces to that obtained by Bixon et al.[28] as long as all the local G ↔ G rates are the same, $k_{0,1} = ... = k_{N-2,N-1}$. The latter condition is satisfied for the sequences with m repeating AT pairs between G bases ($m = 1$, 2, ...). By virtue of eq 1 each hopping step in such regular sequences proceeds with the rate $k_m \propto \exp[-\beta (m + 1)l]$, where l is the mean plane-to-plane distance between base pairs. The same rate is expected for charge trapping at the GGG step, because in the fast relaxation limit this process is controlled by hole transfer from G^+_{N-1} to the nearest-neighboring G bases of the GGG triple. Hence, for regular sequences eq 9 can be rewritten as

$$\phi = \phi' = l(m+1)\frac{k_m}{\gamma_0 R_b} \qquad (10)$$

with R_b being the length of the bridge between the primary radical cation G_0^+ and the hole trap triple GGG.

The above results make evident that the efficiency of hole migration along a DNA bridge of given length should be strongly affected by the arrangement and number of G bases. This prediction of the hopping model is strongly supported by recent measurements[12] of the damage ratios for different polynucleotide sequences. Furthermore, eqs 6, 7, and 8 can be used for quantitative interpretation of the observed sequence-dependent charge transfer, if information about the jump rates for each step of hopping motion is available. The necessary information is provided by theoretical and experimental studies of hole transfer from G^+ to GGG through one and two AT base pairs.[12,14,33] As has been found, the jump rate decreases by about a factor of 0.3 for each intervening AT base pair linked directly to the previous pair[14] (like $\frac{AA}{TT}$) or about an order of magnitude for cross linked pairs[12] (like $\frac{AT}{TA}$). This permits the use of eq 8 to predict the damage ratio ϕ and, hence, the efficiency of charge transfer for the DNA bridge with arbitrarily complicated sequences of AT and GC pairs (see Table 1).

As follows from eqs 6 and 9, the values of ϕ and ϕ' for the irregular sequences **IV**−**VI** are determined by the rates for the homogeneous sequences **I**, **II**, and **III** given by the ratios of the corresponding transfer rate and the rate of the G^+ reaction. The direct use of experimental values[12,14] of these ratios in eq 6 gives ϕ and ϕ' for the polynucleotide sequences **IV**−**VIII** without additional fitting parameters, if γ_0 is assumed to be equal to γ_G. The validity of the latter assumption was verified by the best-fit procedure applied to experimental data reported for regular sequences **II**, **VI**, and **VII**.[14] The sequence **IX** has been described as the continuation of the results for sequences **I** and **III** using eq 1. Theoretical results obtained (Table 1) are seen to be in agreement with observations[12,14] within the experimental error. In Figure 2 the data of ref 12 are shown together with the theoretical prediction obtained according to the rules formulated above. The nonmonotonic behavior of the charge-transfer efficiency (expressed in terms of the damage ratios ϕ' and ϕ) as a function of the bridge length is described satisfactorily within the hopping model.

The analysis performed above is easily applicable to other important aspects of charge transfer in DNA. In particular, eq 6 can be exploited for specifying the dependence of the relative ground-state charge-transfer rate on the bridge length R. The solution of eq 6 shows (see Table 1) that the sequence effect strongly suppresses the length dependence of ϕ' for irregular bridges with AT and GC base pairs. This becomes evident from the fact that ϕ' are almost equal for bridges composed of sequences **IV** and **VIII** with lengths $R = 17$ and 54 Å, respectively. Therefore, experiments with irregular DNA bridges of distinct lengths do not provide unambiguous results. Our theoretical analysis, however, enables us to clarify the situations where measurements on the distance dependence do make sense. One case involves experiments with the bridges consisting of homogeneous AT sequences. These systems are known to exhibit exponential distance dependence.[12,15] Alternative measurements[14] explore sequences with regularly arranged G bases separated by m repeating AT pairs. For these sequences, the extension of eq 10 to the case $\gamma_0 = \gamma_G = \gamma$ yields

$$\phi = \frac{k_m}{\gamma}\frac{2\sinh(\lambda)\sinh(\lambda/2)}{\cosh(\lambda(N-1/2)) - \cosh(\lambda/2)}, \qquad \phi' = \frac{k_m}{\gamma}\frac{\sinh(\lambda)}{\sinh((N-1)\lambda)} \qquad (11)$$

where N is the number of G sites (see Figure 1), $N - 1$ is the number of AT fragments and λ is the decrement given by

$$\lambda = \ln\left(1 + \frac{\gamma}{k_m} + \sqrt{\frac{\gamma}{k_m} + \frac{\gamma^2}{4k_m^2}}\right) \approx \sqrt{\gamma/k_m} \qquad (12)$$

We have defined k_m as the jump rate through the sequence fragment with m repeating AT units between the G bases. The approximate expression (eq 12) for λ corresponds to the experimental situation where k_m is faster than the reaction rate γ. Then for sufficiently short alternating sequences with $N < k_m/\gamma^{1/2}$ the dependence of the relative transfer rates on the bridge

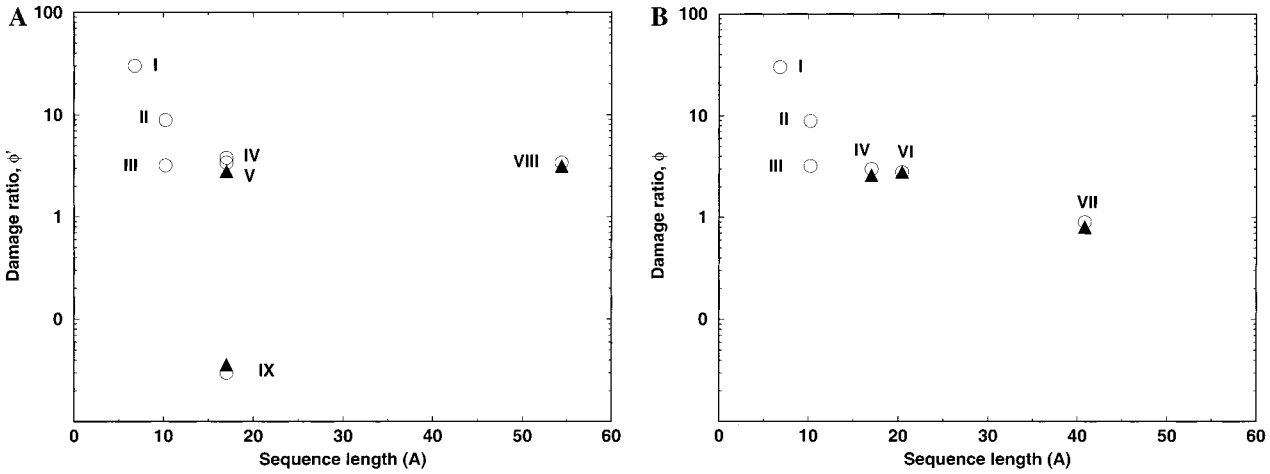

Figure 2. Dependence of the damage ratios ϕ' (panel A) and ϕ (panel B) on the length of sequences listed in Table 1. Experimental data[12,14] and results of our calculations are shown by open circles and filled triangles, respectively. Legends near points identify sequences listed in Table 1.

Duplex A

DNA(1) 3'-ATG CAC CGA AAA GCC AGT GAC GTA ATC AAT TTC CTT ACA CGC GAC TGG TTC CTT GGT TTC **AQ**-5

DNA(2) 5'-TAC GT**G G**CT TTT C**GG** TCA CTG CAT TAG TTA AA**G G**AA TGT GCG CTG ACC AA**G G**AA CCA AAG-3'

Duplex B

DNA(1) 3'-**AQ** ATT TCC GGC ATG CGA CCA GTA CAC CAA GTC ACC ACT GAA CCA ACG TAC CAT GCA GGC-5'

DNA(2) 5'-TAA A**GG** CCG TAC GCT **GG**T CAT GT**G G**TT CAG T**GG** TGA CTT **GG**T TGC ATG **G**TA CGT CCG-3'

Figure 3. Duplex DNA oligomers with two strands DNA(1) and DNA(2) studied experimentally by Schuster and co-workers.[21,23] Anthraquinone derivatives (AQ) which are covalently linked to a DNA(1) strand allow the site-selective generation of holes due to electron transfer from the G base to the photoexcited AQ. The DNA(2) strand which is complementary to DNA(1) provides the sequence of nucleobases with several isolated GG pairs.

length R_b (of regular alternating bridges) is given by the power laws

$$\phi' \approx \frac{l(m+1)}{R_b} \text{ and } \phi \approx \frac{l(m+1)}{R_b\left(\frac{R_b}{l(m+1)}+1\right)} \qquad (13)$$

In the opposite case of a long bridge eq 11 leads to exponential decrease of both ratios

$$\phi,\phi' \approx \exp(-\eta R_b) \qquad (14)$$

with

$$\eta = \frac{1}{l(m+1)}\left(\frac{\gamma}{k_m}\right)^{1/2}$$

The bridges investigated in ref 14 are examples of regular alternating bridges. The agreement of the experimental length dependence and the predictions of eq 11 for the damage ratio are demonstrated in Table 1 for sequences **II**, **VI**, and **VII**. As follows from eqs 6 and 9 (see sequence **II** in the Table 1) $k_m/\gamma \approx 8.9$. Accordingly the reciprocal of the decay length for the damage ratios, η, is equal to 0.03 Å^{-1} for the typical value $l =$ 3.4 Å reported for of the mean plane-to-plane distance between stacked base pairs.[19a,15] This η value is determined largely by the reaction rate γ, and is much less than the falloff parameter $\beta \approx 1$ Å^{-1} calculated for the conventional tunneling mechanism of unistep superexchange mediated charge transfer in DNA.[25]

Thus, for sufficiently long bridges the hopping mechanism of charge transfer along DNA bridges with regular base pair sequences exhibits an exponential distance dependence, as does unistep superexchange-mediated tunneling, cf. eq 1. The R_b parameter is equal to the total length R. The falloff parameters for these two mechanisms are, however, distinct. While the falloff parameter β in eq 1 is a measure of electronic coupling between donor and acceptor sites, the falloff parameter η for the distance dependence of the damage ratios ϕ and ϕ' reflects both the hopping rate and the ability of the hole to react with water during the hopping motion along the bridge.

2. Sequences with Several GG Pairs. Hole transfer along these sequences manifests itself in the long-range oxidation of GG sites in DNA first demonstrated by Barton and her colleagues.[11a] A representative example of such systems is the set of anthraquinone (AQ)-linked duplex DNA oligomers studied by Schuster and co-workers[21,23] (see Figure 3). Experiments[11,21] show that "electronic" holes are able to migrate along the stack of base pairs, causing reaction at GG steps revealed as strand breaks. It is remarkable that the strand cleavage was observed not only at the GG step closest to the primarily oxidized G site, but also at more remote GG steps.[21,23] Hence, charge motion is not terminated by GG pairs. The latter conclusion is consistent with recent experimental data on charge separation and recombination rates in synthetic DNA hairpins[42] which show that contrary to the GGG triple, the GG pair does not act as an irreversible sink for moving holes. According to our model, this suggests that hole trapping at GG steps proceeds in the partially

hopping-controlled regime that enables holes to escape trapping at a GG step and to continue their motion along the stack of base pairs.

Since GG pairs do not absorb all holes, the experimental data on the strand cleavage yield X_i at each GG step ($i = 1, 2, 3, 4$) allow conclusions concerning the efficiency of hole migration through the (AQ)-linked duplex DNA oligomer. The results are usually reported in terms of the cleavage ratio

$$\varphi_i = \frac{X_i}{X_1} \tag{15}$$

where the subscript $i = 1$ labels the GG pair closest to the position of the first oxidized G base.

To estimate the efficiency of hole migration theoretically, we express X_i in terms of the population probability for the i-th pair GG, $P_i(t)$. On the assumption that the rate of the cleavage process is independent of i, this yields

$$\varphi_i = \frac{\int_0^\infty P_i(t)\mathrm{d}t}{\int_0^\infty P_1(t)\mathrm{d}t} \tag{16}$$

Now the calculation of φ_i is straightforward. All we need to do is to solve eq 2 and to substitute the result into eq 16. For long sequences such as shown in Figure 3, the integrals in eq 16 cannot be evaluated analytically, while the numerical procedure requires knowledge of the parameters γ_0, γ_G, k_{rel}, and the hopping rates $k_{j,j\pm1}$ between neighboring G sites.

The dominant strand cleavage at the GG step observed in experiments with sequences containing GG pairs suggests that the chemical rates γ_0 and γ_G are small in comparison with other kinetic parameters and therefore can be neglected. The necessary information about the hopping rate between a single G base and a GG pair separated exclusively by AT base pairs can be deduced from measurements of cleavage efficiencies performed by Saito and co-workers[43] (Table 2). For this purpose, we extend eq 2 to the case studied in ref 43, where G is oxidized to G_0^+ via electron transfer to the adjacent photoexcited cyanobenzophenone-substituted uridine (U) incorporated in the B-form duplex without perturbing the base stacks. Assuming that the initially formed G_0^+ is quenched by back electron transfer from the U radical anion with the rate k_q, it can be verified that the cleavage band intensity, I, at the GG step is given by

$$I \sim \frac{1}{k_{\mathrm{rel}} + \left(1 + \dfrac{k_{\mathrm{rel}}}{k(R_{\mathrm{b}}')}\right)(k_q + \gamma)\exp\left(\dfrac{e^2}{\epsilon k_{\mathrm{B}} TL}(1 - L/R_{\mathrm{b}}')\right)} \tag{17}$$

Here $k(R_{\mathrm{b}}')$ is the rate of the hole transition from the initially oxidized G_0^+ to the GG pair connected by the AT bridge of the length R_{b}', k_{B} is the Boltzmann constant, T is temperature, ϵ is the dielectric constant of the water surroundings, L is the distance between U and the adjacent G base, and γ is the rate of the reaction between a hole and the surroundings leading to the cleavage at the GG step. Equation 17 provides the expression for the relative cleavage efficiency Φ_{rel} defined as the intensity I normalized to its value obtained for the sequence **I d**. In the slow relaxation limit, where $k_{\mathrm{rel}} < (k_q + \gamma)$, the result follows

(43) Nakatani, K.; Dohno, C.; Saito, I. *J. Am. Chem. Soc.* **1999**, *121*, 10854−10855.

Table 2. Relative Cleavage Efficiencies Φ_{Rel} for Various Sequences of AT Base Pairs Bridging the Primarily Oxidized G Site and the GG Pair[a]

	Sequence	Φ_{rel}	
		exp.	theor.
I d	T A	1.0	1.0
II d	T T A A	0.78	0.71
III d	T T T A A A	0.30	0.43
IV d	T T T T A A A A	0.16±0.04	0.21
V d	T T T T T A A A A A	0.14±0.02	0.11

[a] Experimental values were taken from the work of Saito and co-workers.[43] Theoretical values were obtained from fitting eq 18 to the experimental data.

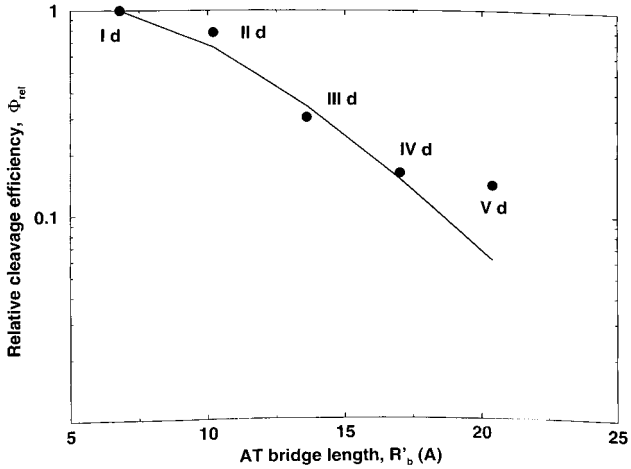

Figure 4. Dependence of the relative cleavage efficience Φ_{rel} vs the length of AT bridges, R_b', between the primarily oxidized G site and the GG pair. Legends near points identify sequences listed in Table 2. Points are experimental data from ref 43. Solid line was obtained from eq 18 taking $L = 3.4$ Å, and fitting to the first four points (see text).

from eqs 1 and 17

$$\Phi_{rel} = \frac{1 + c}{1 + c\exp(\beta(R_{\mathrm{b}}' - L))} \tag{18}$$

where the constant c turns out to be independent of R_{b}'. As follows from Figure 4, the dependence Φ_{rel} versus R_{b}' predicted by eq 18 fits four experimental points reasonably well if the falloff parameter β is taken to be 0.29 Å^{-1}. The discrepancy between numerical and experimental results is within the accuracy of measurements. The fifth point corresponding to the bridge with 5 AT base pairs (sequence **V d** in Table 2) was not taken into account in the fitting procedure. According to our estimations, in this case charge transport becomes incoherent and involves thermally activated injection of holes from the initially oxidized G_0^+ to the bridge. The contribution of the latter mechanism[34d,f] increases with the bridge length and may become dominant for bridges with five AT base pairs (sequence **V d**).

The β value obtained above for the transition $G^+ \rightarrow (G^+G)$ together with the data on the rates of other steps taken from the data in Table 1 (sequences **I**−**III**) allow us to describe the experimental data of Schuster and co-workers[21,23] in terms of

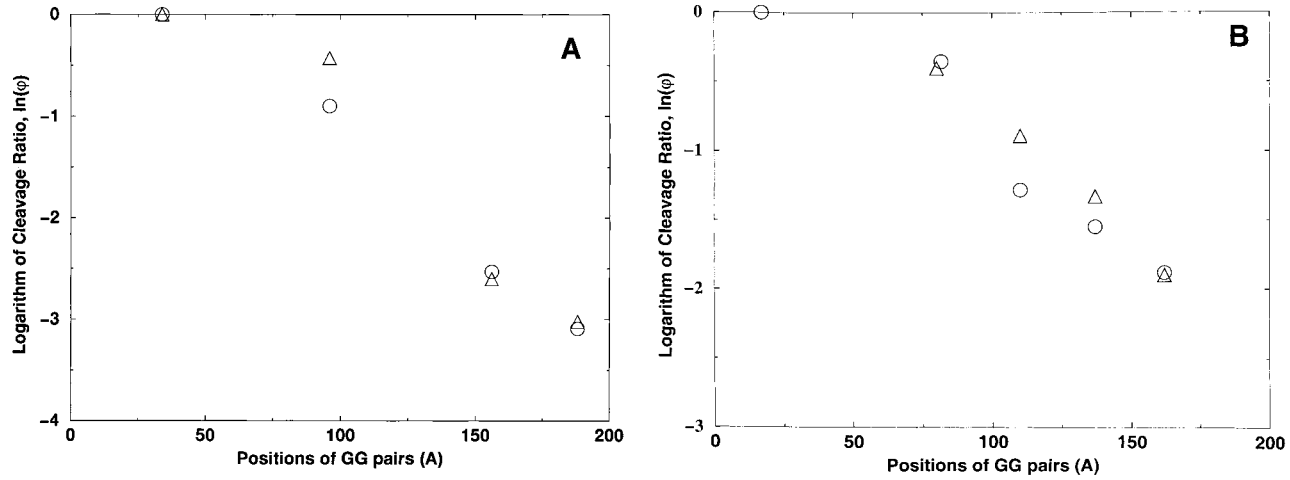

Figure 5. Cleavage ratio φ at GG steps vs the position of GG pairs on the strand DNA(2). Experimental results for duplex A and duplex B in Figure 3 are taken from refs 21 and 23. These results are plotted in panels A and B, respectively. Circles correspond to experimental data. Triangles are theoretical values of the cleavage ratio calculated from eqs 2 and 16.

the hopping model by treating the relaxation rate k_{rel} as the only adjustable parameter. As follows from Figure 5, the calculated cleavage ratio φ agrees with the measured values if k_{rel} is taken to be about 1/30 of the rate for hole transfer through a single AT base pair. The agreement can be considered as reasonable in view of the low precision of the method used to measure the cleavage efficiency.

Discussion and Conclusions

We propose a phenomenological description of charge motion in DNA in terms of a hopping model. The model suggests that the long-range migration of "electronic" holes consists of a series of short-range transitions between G bases separated by AT pairs.[12,14,22d,h,28,29] This mechanistic picture allows predictions of the charge migration efficiency for arbitrarily complicated base pair sequences if the information about the rate of each transition is available.

To deduce the required information, we use experimental data[12,14] on the relative rate of hole transfer from the primary radical cation G^+ to the triple GGG through bridges consisting of AT base pairs only. This rate is assumed to coincide with the relative rate of the hole jump between two neighboring G bases with the same separation distance. The latter assumption is valid only for the two-stage mechanism of hole transfer from G^+ to GG...G. The mechanism includes (i) a hole jump to the G base nearest to the primary radical cation $G^+ \rightarrow (G^+G...G)$ and (ii) a subsequent relaxation of charge $(G^+GG) \rightarrow (GG...G)^+$ within the GG...G unit. Ab initio quantum mechanical studies of the GGG triple[44] support the existence of the step (i), while the difference in the ionization potentials of a single G and GGG[10,38,39] provides arguments in favor of the step (ii). If the relaxation is much faster than the charge-transfer step (i), the rate of the process $G^+ \rightarrow (GG...G)^+$ will be mainly determined by the number of AT pairs separating the primary radical cation and the nearest neighboring G within the GGG triple. This justifies the choice of the parameter for calculations of the hole transfer efficiency in sequences with different number and position of AT and GC base pairs.

The fast relaxation limit discussed above corresponds to the situation where GG...G units act as irreversible traps for moving holes. Therefore, a GGG triple should terminate hole hopping, as has been observed in experiments with sequences consisting of AT, GC, and a single GGG unit.[12,14] In this situation we actually deal with the donor-bridge-acceptor system, in which the primary radical cation G^+ operates as a hole donor, the base pair sequence functions as a bridge, and the GGG triple serves as a hole acceptor (sink).[45] In our analysis of charge transfer in this system, we have followed the experimental literature in defining the efficiency of hole migration in terms of damage ratios, ϕ' and ϕ. This is the actual measured result for ground-state hole migration. The hopping model predicts that for bridges with a certain number of repeating AT base pairs between multiple G bases, the hole transfer efficiency should vary in inverse proportion to the bridge length R_b for short $(^{G}_{C})\cdots(^{G}_{C})\cdots(^{G}_{C})\cdots$ bridges, with change to slow exponential decay for longer bridges. To calculate the actual rate constant k_{CM} for hole migration, it is instructive to recognize that in contrast to the damage yield, k_{CM} is defined by the current to the GGG site rather than by the ratio of hole currents to two sinks corresponding to the acceptor and the donor. This leads to different distance dependencies of k_{CM} and ϕ' for sequences with regularly alternating AT and GC base pairs: While $\phi' \sim 1/R_b$,

(44) Yoshioka, Y.; Kitagawa, Y.; Takano, Y.; Yamagushi, K.; Nakamura, T.; Saito, I. *J. Am. Chem. Soc.* **1999**, *121*, 8712−8719.

(45) Recently it has been reported that a hole can be transferred between two GGG triplets connected by the sequence TTGTT, while the replacement of the G base by A suppresses the process, see: Nakatani, K.; Dohno, C.; Saito, I. *J. Am. Chem. Soc.* **2000**, *122*, 5893−5894. This experimental result is not in contradiction with our treatment of the GGG triple as an irreversible trap (a sink) in base pair sequences with the *only* GGG unit. In the latter case, which is studied in detail in this paper, the hole transfer from GGG to the neighboring single G is precluded by the large difference in energies of GGG^+ and G^+. By contrast, for sequences with several GGG units the hole transfer between two triples does not require an energy expenditure and can proceed, mediated by the GC base pair that possesses proper energetics. It should be stressed that our treatment of the GGG triple as an irreversible trap (a sink) refers *only* to the situation where hole generation and transport are not constrained by Coulomb attraction within the primary radical pair, as it occurs in experiments of Meggers and co-workers[12] and Giese et al.[14] In their experiments analyzed in the present work the hole injection proceeds via the charge shift from an adjacent deoxyribose cation to G_0 (see Figure 1) to minimize a Coulomb barrier. This is not a case in other experiments with a single GGG, see e.g.: Lewis, F. D.; Liu, X. Y.; Liu J. Q.; Miller S. E.; Hayes, R. T.; Wasielewski, M. R. *Nature* **2000**, *406*, 51 and Lewis, F. D.; Liu, X. Y.; Liu J. Q.; Hayes, R. T.; Wasielewski, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 12037−12038. As follows from our estimations, a strong Coulombic interaction between a hole and a negative ion of the electron acceptor (singlet stilbene-4, 4′-dicarboxamide in experimental studies of Lewis et al.) can significantly reduce free energy changes ΔG for hole transfer from G to GGG. Furthemore, the estimated ΔG values were found to be much less than the differences in the ionization potentials of the single G and GGG triplet[38a] in agreement with experimental findings of Lewis et al.

the absolute rate k_{CM} decreases with the bridge length approximately as $1/R_b^2$ in agreement with the earlier theoretical result.[22d] In view of the inverse proportionality between k_{CM} and R_b^2, we expect that the absolute migration rate for sequences **I** and **VIII** (Table 1) will differ by a factor of 50.

In the opposite case of slow relaxation, the hopping model requires that GG...G units should behave as shallow traps, which allow holes to continue their motion along the sequence. Such behavior is typical for GG pairs as is evidenced by the strand cleavage in oligomer DNA duplexes containing several sites with two G bases stacked on the same strand.[21,23,43] The same conclusion follows from the recent study of photoinduced charge separation in synthetic DNA hairpins.[42] The numerical results obtained within the slow relaxation limit indeed concur with experimental data on the efficiency of hole migration in duplex DNA oligomers with several GG pairs.[21,23,43] Thus, the relaxation is always fast on GGG, but may be slow on GG. The agreement between theory and experiment suggests that the charge relaxation at each GG step should be almost 30 times slower than the rate for the hole transfer through a single AT base pair. This implies that a positive charge relaxes at the GGG step faster than at the GG step at least by 2 orders of magnitude. The physical reason for the dramatic difference in time scales of the relaxation process within GG and GGG units currently remains unclear. Formation of radical cations $(GG)^+$ and $(GGG)^+$ is accompanied by the change in GG and GGG geometries, as is observed for aromatic hydrocarbon dimer cation radicals.[46] Therefore polaron effects similar to those proposed by Schuster[23] and Conwell[47] will be important for the description of the relaxation process.

It is also interesting to compare the values of the falloff parameters β for hole transfer from the primary oxidized G site to the GG pair and GGG triple through identical bridges composed of AT base pairs only. The application of the hopping model to experimental results of Saito and co-workers[43] gives $\beta = 0.29$ Å^{-1} if a hole acceptor is a GG pair. Within the limits of experimental error, the obtained value coincides with $\beta = 0.35 \pm 0.12$ Å^{-1} evaluated from the chemical yield data for hole transfer to the GGG triple[12,14] (cf. data for sequences **I** and **II** in Table 1). The close agreement between the β values for two hole acceptors is consistent with the assumption that in both cases a positive charge is transferred to the G base nearest to the primary radical cation G^+. If, however, the AT bridge contains two neighboring A bases on different strands, the falloff parameter increases by a factor of 2.[12] This indicates that the arrangements of AT bases in the duplex affect the electronic coupling between the donor and acceptor.

The small values of the falloff parameter β for hole transfer through AT bridges can be understood if the hole motion within the structural unit G...G...G is considered as the motion of charge carriers in the impurity band of doped semiconductor with the width determined by the hole transfer integral b. In this case the tight-binding approximation[24a,33] enables one to express β in terms of b, the mean plane-to-plane distance between bases l, and the difference in energies of the hole when residing on the AT bridge and on the G base, Δ, as[48]

$$\beta = \frac{2}{l} \ln\left[\frac{\Delta}{2b} + \left(1 + \frac{\Delta^2}{4b^2}\right)^{1/2}\right]$$

According to ab initio molecular orbital calculations of Sugiyama and Saito,[38a] $b \approx 0.4$ eV if l is taken to be 3.4 Å, while Δ is equal to 0.5 eV.[35] With these values of parameters, the above equation yields $\beta = 0.35$ Å^{-1} in reasonable agreement with the results of the fitting procedure.

The above findings call for further experimental and theoretical investigations. In particular, it might be useful to perform experimental studies of hole migration to a GG pair and a GGG triple employing the same sequences and the same method for the site-selective generation of charges. These studies would enable one to obtain more accurate data for comparison of GG and GGG units as hole traps. Another interesting possibility is a measurement of the strand cleavage efficiencies in long sequences, which contain single GGG triples in different well-defined positions between GG pairs. Such experiments can prove that π-stacking of base pairs provides the only pathway for charge transport in sequences with the length of several hundred angstroms.

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