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Charge Transport in DNA Via Thermally Induced Hopping

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Abstract: In this contribution we advance and explore the thermally induced hopping (TIH) mechanism for long-range charge transport (CT) in DNA and in large-scale chemical systems. TIH occurs in donor−bridge−acceptor systems, which are characterized by off-resonance donor−bridge interactions (energy gap $\Delta E > 0$), involving thermally activated donor−bridge charge injection followed by intrabridge charge hopping. We observe a "transition" from superexchange to TIH with increasing the bridge length (i.e., the number N of the bridge constituents), which is manifested by crossing from the exponential N-dependent donor−acceptor CT rate at low N ($< N^{\mathrm{X}}$) to a weakly (algebraic) N-dependent CT rate at high N ($> N_{\mathrm{X}}$). The "critical" bridge size N_{X} is determined by the energy gap, the nearest-neighbor electronic couplings, and the temperature. Experimental evidence for the TIH mechanism was inferred from our analysis of the chemical yields for the distal/proximal guanine (G) triplets in the $(\mathrm{GGG})^{+}$TTXTT(GGG) duplex (X = G, azadine ($^{\mathrm{z}}$A), and adenine (A)) studied by Nakatani, Dohno and Saito [*J. Am. Chem. Soc.* **2000**, *122*, 5893]. The TIH sequential model, which involves hole hopping between (GGG) and X, is analyzed in terms of a sequential process in conjunction with parallel reactions of $(\mathrm{GGG})^{+}$ with water, and provides a scale of (free) energy gaps (relative to $(\mathrm{GGG})^{+}$) of $\Delta = 0.21-0.24$ eV for X = A, $\Delta = 0.10-0.14$ eV for X = $^{\mathrm{z}}$A, and $\Delta = 0.05-0.10$ eV for X = G. We further investigated the chemical yields for long-range TIH in $(\mathrm{G})_l^{+}\mathrm{X}_n(\mathrm{G})_l$ ($l = 1-3$) duplexes, establishing the energetic constraints (i.e., the donor $(\mathrm{G})_l^{+}$ − bridge base (X) energy gap Δ), the bridge structural constraints (i.e., the intrabridge X−X hopping rates k_{m}), and the kinetic constraints (i.e., the rate k_{d} for the reaction of $(\mathrm{G})_l^{+}$ with water). Effective TIH is expected to prevail for $\Delta \lesssim 0.20$ eV with a "fast" water reaction ($k_{\mathrm{d}}/k_{\mathrm{m}} \simeq 10^{-3}$) and for $\Delta < 0.30$ eV with a "slow" water reaction ($k_{\mathrm{d}}/k_{\mathrm{m}} \simeq 10^{-5}$). We conclude that $(\mathrm{T})_n$ bridges (for which $\Delta \simeq 0.6$ eV) cannot act in TIH of holes. From an analysis based on the energetics of the electronic coupling matrix elements in $\mathrm{G}^{+}(\mathrm{T-A})_n(\mathrm{GGG})$ duplexes we conclude that the superexchange mechanism is expected to dominate for $n = 1-4$. For long $(\mathrm{A})_n$ bridges ($n \gtrsim 4$) the TIH prevails, provided that the water side reaction is slow, raising the issue of chemical control of TIH through long $(\mathrm{A})_n$ bridges in DNA attained by changing the solution composition.

I. Prologue

Apart from the fundamental interest in the electronic properties of DNA in the context of radiation damage and repair,[1,2] novel research areas of the dynamics, response, and function of nanostructures and biosensors are emerging.[3] DNA-based molecular electronic devices are expected to utilize the unique features of recognition, assembly, and specific binding properties of the nucleobases. The DNA duplexes may serve as conducting building blocks or as insulating (or conducting) templates for the assembly of other electrically active nanoelements, for example, semiconducting or metal clusters. While presently nanoelectronic DNA-based systems still constitute "theoreticians' dreams", the elucidation of the mechanism and dynamics of charge transport/transfer in DNA is of central importance.

The majority of the experimental information on charge transport in DNA pertains to the positive charge (hole) migration, that is, the propagation of the radical cation along the duplex.[4−13] In view of the hierarchy of the oxidation potentials of single nucleobases in solution[14] and of the ionization

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potentials of single nucleobases[15−17] and of nucleobases in duplexes[17] (G < A < C,T), it is inferred that hole hopping occurs between guanine (G) nucleobases. Computational results[16−18] show that G nucleobases act as "resting" lowest-energy states for holes in DNA duplexes, while GG and GGG fragments act as hole traps in DNA, in accord with the experimental data.[5,6,8,9] Experimental evidence for long-range (distance scale 50−300 Å) hole transport in DNA stems from chemical yield data induced by hole shift or injection, as reported by Barton et al.,[5] Giese and Michel-Beyerle et al.,[8] and Schuster et al.,[9] triggering "chemistry at a distance". The interrogation of individual elementary steps of charge injection, trapping, hopping, and recombination, and their lifetimes in (intercolated, substituted, or capped) DNA was accomplished utilizing the arsenal of (nanosecond to femtosecond) time-resolved spectroscopy, as reported by Wasielewski and Lewis,[6] Zewail and Barton,[19] and Michel-Beyerle[20] and their colleagues.

On the theoretical front,[11−13,21−23] the concept of (donor−bridge) energetic control in DNA, advanced in 1998,[11] provided a unified description of the "transition′ from off-resonance, superexchange induced, short-range unistep charge transfer, to resonance coupled, long-range multistep charge-hopping transport. The quantitative analysis of long-range charge hopping predicted the breakdown of the conventional unistep charge-transfer rate $k_{CT} \propto \exp(-\beta R)$ (where R is the donor−acceptor separation) being replaced by an algebraic relation $k_{CT} = kN^{-\eta}$ (where N is the number of the bridge constituents, $\eta \simeq 1-2$, and k the interbase hopping rate). This picture is in accord with experimental results for charge transfer in organized molecular systems[24] and hole shift in the GTTGTT···GGG DNA duplexes.[8] The theoretical description of hole transport brought together superexchange mediation and hopping, with the individual hopping rates between the guanine sites in GXY···G (with X, Y = T, A) being superexchange-mediated through the bridging of (T−A) groups. The hopping rates were described in terms of the nonadiabatic charge-transfer theory,[11] which is determined by electronic couplings and nuclear Franck−Condon factors. The contributions of intermolecular nuclear distortions to the Franck−Condon factor in a one-dimensional model correspond to the polaron picture invoked for charge transfer in DNA.[23] Both intrastrand hole hopping (in the 5′-GXY/···G-3′ duplex) or interstrand hole hopping (in the 5′-GXY···G-5′ duplex, induced by the zigzagging mechanism)[11] can prevail. Analytical kinetic models based on the superexchange-mediated hopping picture were utilized[12] to account quantitatively for the bridge-size dependence of the chemical quantum yields for long-range hole shift in the $G^+[(T)_mG]_n(T)_mGGG$ duplex over the G^+···GGG distance scale of 10−40 Å ($m = 2$, $n = 0-3$). A theoretical framework for the quantum mechanical rate expression was advanced to describe the elementary rates for hole injection/shift/hopping/trapping involving G nucleobases (separated by T−A groups) in DNA. Individual steps of hole transfer, hopping, and trapping were quantified by the calculation of

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(18) In view of recent theoretical calculations of the ionization potentials of nucleobases and trimer duplexes,[16,17] the energies of the ionic states reported by Saito et al.[16] seem to be too large. The energies relative to $(GGG)^+$ calculated by Voityuk et al.[17] are: $[E(TG^+T) = E((GGG)^+)] = 0.29$ eV (as compared to 0.76 eV[16]) and $[E(TA^+T) = E((GGG)^+)] = 0.75$ eV (as compared to 1.48 eV[16]). These gas-phase energetic values[17] should be corrected for solvation and entropy effects. Note that the difference between the calculated gas-phase ionization potentials of G and A is 0.46 eV,[17] being close to the difference of 0.4 eV between the redox potentials of the two nucleosides in a solution.[14] Regarding the energetics of hole trapping by G doublets and triplets, the recent theoretical calculations[17] give for the energy gap between 5′-AG$^+$A-3′ and 5′-AG$^+$G-3′, $\Delta E = 0.13$ eV, while between 3′-AG$^+$A-5′ and 3′-G$^+$GA-5′, $\Delta E = 0.1$ eV. The difference between these two ΔE values manifests directional asymmetry. The kinetic analysis based on the rates of hole trapping/detrapping in the

$$AG^+AGG \underset{k_{-t}}{\overset{k_t}{\rightleftharpoons}} GA(GG)^+$$

system[6f] gives for the free energy for hole trapping by GG the value $\Delta G = k_BT \ln(k_t/k_{-t}) = 0.053$ eV. For hole trapping/detrapping in the

$$G^+A(GGG) \underset{k_{-t}}{\overset{k_t}{\rightleftharpoons}} GA(GGG)^+$$

system, a kinetic analysis gives $\Delta G = 0.077$ eV, while an analysis of quantum yield date[12c] resulted in $\Delta G = 0.062$ eV. For hole trapping/detrapping in the

$$G^+T(GGG) \underset{k_{-t}}{\overset{k_t}{\rightleftharpoons}} GT(GGG)^+$$

system, quantum yield data result in $\Delta G = 0.096$ eV. These values of ΔG are lower than the calculated gas phase energetic ΔE data,[17] but exhibit the same bridge specificity on the energetics. In any case, GG and GGG involve shallow hole traps.

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electronic coupling matrix elements between nearest-neighbor nucleic bases.[22]

The concept of energetic control is strictly valid only at sufficiently low temperatures. The issue of the "transition" between superexchange ($\Delta E > 0$) and sequential ($\Delta E < 0$) charge transfer was addressed for localized charge transport in small energy gap model systems[25a−c] and for quasifree electron tunneling in hydrocarbons.[25d] For off-resonance donor−bridge coupling in DNA ($\Delta E > 0$), thermally activated charge injection from G^+, $(GG)^+$, or $(GGG)^+$ into some nucleobases of the bridge (which are characterized by a higher oxidation potential), followed by multistep hopping among the bridge constituents, can occur at finite temperatures. The mechanism of thermal donor−bridge excitation followed by hopping within the bridge in DNA was introduced by us.[12b] Giese and Spichty[26] proposed that thermally induced hole injection from G^+ to A might occur. The thermally induced hopping (TIH) process occurs from the vibronic levels of the hole donor manifold at energies $E \geq \Delta E$. The TIH occurs in parallel with the unistep superexchange tunneling (from the lowest vibronic levels $E < \Delta E$ of the hole donor manifold) through the bridge to the final hole acceptor. The dominance of either TIH or of superexchange will be determined by the nature of the bridge, that is, the energetics, the electronic couplings, the elementary hopping rates, and the number of constituents. The features of TIH are general, being applicable not only for DNA, but also for charge migration in large-scale chemical systems, for example, the donor−acceptor bound by polymers, such as oligoproline donor−acceptor complexes,[27] and in biological systems[28,29]

In this contribution we advance and explore the TIH mechanism and its implications for charge transport in DNA and large-scale chemical systems. The general characteristics of the competition between TIH and superexchange are presented in section II. Our analysis reveals the crossing between unistep superexchange mediated charge transfer and multistep TIH at a "critical" value of the bridge size. In the case of hole migration in DNA the semiquantitative model for the competition between superexchange and TIH has to be supplemented by the role of the parallel side reactions of G^+ and $(GGG)^+$ radical cations with water,[5,8,9,30,31] which involve a major depletion channel for the hole charge carriers in DNA. Experimental evidence for TIH in DNA duplexes is obtained from our analysis presented in section III of the recent experimental results of Nakatani, Dohno, and Saito[31] on hole transfer in the duplex 5′-GGG-TTXTTGG-3′, where X = guanine (G), azaguanine (^zG), aza-adenine (^zA), and adenine (A). In this well-characterized system, Nakatani et al.[31] have found that when X constitutes a low-oxidation potential base, the rate of hole exchange between the two GGG triplets is enhanced. We propose that in this system with X = G, ^zA, A,[31] TIH occurs and X^+ constitutes a real chemical intermediate, reached by thermally activated hole hopping from $(GGG)^+$. We present a kinetic analysis of hole hopping in the GGGTTXTTGGG system, where we consider the competition between unistep superexchange and TIH and establish the conditions for the dominance of the TIH. Model calculations of hole hopping in $(G)_l^+X_n(G)_l$, $(G)_l^+(TX)_nTX(G)_l$, and $(G)_l^+(TTX)_nTTX(G)_l$ duplexes ($l = 1-3$) and their dependence on the G−X energy gap and the reaction rate of G^+ with water (section IV) establish the conditions for long-range TIH in DNA, with possible applications for the role of A nucleobases as hole carriers in a thermally activated process.

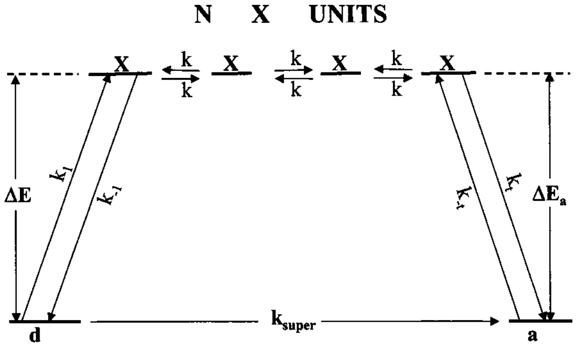

Figure 1. A kinetic-energetic scheme for the TIH mechanism in the donor−X_N−bridge acceptor system. Horizontal lines depict energy levels with donor−bridge energy gap ΔE and the bridge−acceptor energy gap ΔE_a. The arrows represent individual rates for charge injection (k_1), recombination (k_{-1}), hopping (k), trapping (k_t), and detrapping (k_{-t}). The unistep donor−acceptor superexchange rate is denoted by k_{super}.

II. The Crossing from Superexchange To Thermally Induced Hopping

The concept of energetic control for the donor−bridge energy gap ΔE, which implies the occurrence of unistep superexchange for $\Delta E > 0$, has to be extended at a finite (room) temperature, when $\Delta E > k_BT$ and when the number N of the nucleobases in the bridge is sufficiently large. Under these circumstances the superexchange rate $k_{super} \propto \exp(-\bar{\beta}n)$ (where $\bar{\beta} = \beta R_0$ with R_0 being the intrabase distance) is overcome by donor−bridge thermal excitation followed by hopping via the bridge. We shall now establish the energetic and bridge specificity constraints for the prevalence of the thermal-excitation/hopping scenario, which is referred to as the TIH mechanism. For the case of a cursory analysis we present a unified picture for both electron (or hole) transfer/transport in a large-scale chemical model system $d(X)_na$, where d, a, and X represent the donor, acceptor, and bridge molecular elements and $\Delta E > 0$. In these systems thermally induced hole injection from d to the bridge can occur in parallel to superexchange (Figure 1).

Consider first the TIH process. The rates of thermally induced charge injection (shift) k_1 and charge recombination (backshift) k_{-1} are related by a detailed balance

$$K = k_1/k_{-1} = \exp(-\Delta E/k_BT) \tag{1}$$

These reactions are followed by hole hopping (with symmetric rates k), hole trapping (rate k_t), and detrapping (rate k_{-t}). The TIH process from d to a can be characterized by the overall rate

$$k_{TIH} \simeq T\frac{Kk}{N(k/k_t + N/2)} \tag{2}$$

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Equation 2 holds under the conditions $N > 1$ and $k_t/k_{-t} = e^{\Delta E_a/k_BT} \gg 1$, where ΔE_a is the bridge−acceptor energy gap (Figure 1). The ratio of the rate constants in eq 2 is taken as $k/k_t = \exp(-\Delta E_a/2k_BT)$. Equation 2 exhibits an algebraic N dependence. For an effective sink, that is, $k/k_t < N/2$, $k_{TIH} \propto 1/N^2$, manifesting diffusive motion.[11] Equation 2 is recast in the form

$$k_{TIH}/k = \exp(-\Delta E/k_BT)/(N^2/2) \tag{2a}$$

Making contact with quantum mechanical expressions for the hopping rates, k, we get

$$k = (2\pi/\hbar)|V(X - X)|^2F \tag{3}$$

where $V(X - X)$ is the electronic matrix element for nearest-neighbor charge transfer between adjacent X molecular elements and F is the nuclear Franck−Condon factor for symmetric hopping.

The unistep superexchange mechanism operates in parallel to the TIH. The superexchange rate is

$$k_{super} = (2\pi/\hbar)\left(\frac{V(d - X)V(X - a)}{\Delta E}\right)^2 r^{N-1}F', \ (N \geq 2) \tag{4}$$

$V(d - X)$ and $V(X - a)$ are the nearest-neighbor electronic matrix elements between d − X and X − a, respectively. r represents the reduction factor of the rate upon the addition of an extra group to the bridge, which is given by

$$r = |V(X - X)/\Delta E|^2 \tag{5}$$

and ΔE is the X − d energy gap. Finally, F' in eq 4 is the nuclear Franck−Condon factor for the superexchange process, which can be approximated by $F' = F$. For model calculations we take an average electronic matrix element, that is, $V(d - X) \simeq V(X - a) \simeq V(X - X) \simeq \langle V\rangle$. The magnitude of these matrix elements falls in the range calculated for the nearest-neighbor intrastrand electronic couplings in DNA.[22,23] Thus we obtain from eqs 3−5 the simple relation

$$k_{super}/k \simeq r^N \tag{6}$$

where $r = (\langle V\rangle/\Delta E)^2$. In Figure 2 we compare the exponential N dependence of k_{super}/k, eq 6, with the algebraic N dependence of k_{TIH}/k, eq 2a. The crossing between superexchange and thermally induced hopping will occur at $N = N_X$. N_X is given, using eqs 2 and 6, from the relation

$$N_X = -\Delta E/k_BT \ln r - \ln(N_X^2/2)/\ln r \tag{7}$$

Equation 7, which should be solved numerically, determines the dependence of N_X on the donor−bridge energy gap (ΔE), on the electronic coupling ($\langle V\rangle$) and on the temperature, with N_X increasing with decreasing T.

The general features of charge transfer/transport in organized chemical systems,[27] in biophysical systems[28,29] and in DNA, which emerge from this analysis, involve an exponential N dependent superexchange rate at lower N ($\leq N_X$), a break at $N \simeq N_X$, followed by a weakly N-dependent TIH rate for $N \geq N_X$ (Figure 2). Such a behavior is indicated for charge transfer in long polymer systems.[27] It will be instructive to estimate the dependence of N_X on the energetic and coupling parameters ΔE and $\langle V\rangle$. From the model calculations of Figure 2 we note that for a fixed value of $\langle V\rangle$, N_X exhibits only a weak dependence on ΔE (e.g., for $\langle V\rangle = 0.05$ eV, $N_X = 4-6$ for $\Delta E = 0.1-0.4$ eV). This pattern reveals a mutual cancellation due to the lowering of both superexchange and TIH contributions with increasing ΔE. On the other hand, N_X reveals a strong dependence on $\langle V\rangle$ (insert to Figure 2), manifesting the enhancement of the superexchange contribution with increasing $\langle V\rangle$.

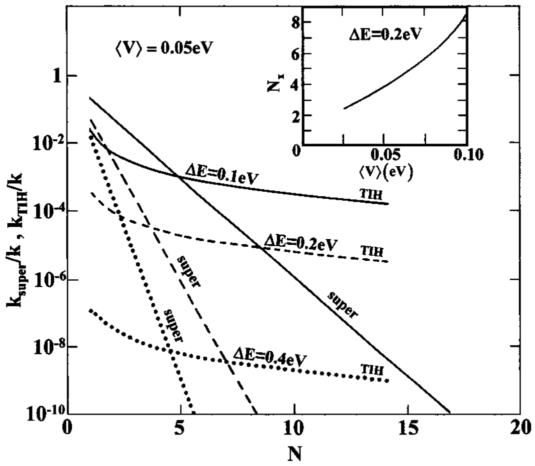


Figure 2. The crossing of the donor−acceptor charge-transfer rate from superexchange to TIH in donor−X_N−acceptor systems with increasing the bridge size. The lines marked by super represent k_{super}/k, while those marked by TIH represent k_{TIH}/k. The energy gaps are: (···) $\Delta E = 0.4$ eV, (- - -) $\Delta E = 0.2$ eV and (−) $\Delta E = 0.1$ eV. The nearest neighbor electronic couplings are $\langle V\rangle = 0.05$ eV. The "transition" at $N = N_X$ occurs at the crossing of the two lines for fixed values of ΔE and $\langle V\rangle$. The insert shows the dependence of N_X on $\langle V\rangle$ at $\Delta E = 0.2$ eV.

The foregoing discussion of the donor−acceptor charge-transfer rates does not provide complete information on the realization of long-range charge hopping in DNA. The efficiency of long-range charge migration is determined by the competition between the charge hopping/trapping rates between the appropriate nucleobases and the side reactions, which terminate the processes. Without such side reactions there is no limit for the spatial range of the charge-transfer processes. For the case of hole transfer/transport in DNA the side reactions involve the reaction of the guanine radical cations G^+, $(G)_l^+$ ($l = 2, 3$)[5,8,9,30,31] and possibly also of A^+ [8b] with water. Quantitative information on the relative rate for the reaction of G^+ and $(GGG)^+$ with water was inferred from the analysis[12] of chemical yield data for hole hopping in G^+TTGTT···GGG duplexes,[8] which will be utilized in the subsequent analysis. All the current experimental studies[5,8,9,30,31] of long-range hole transport in DNA are based on the measurement of the chemical yields for the side reaction.

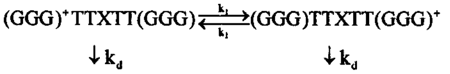
III. Thermally Induced Hopping in DNA Duplexes

Experimental evidence for the TIH mechanism in DNA duplexes emerges from the experiments of Nakatani et al.[31] They reported the ratios of yields between cleavage on the distal/proximal G triplets in the

$$(GGG)^+TTXTT(GGG) \text{ duplex} \tag{I}$$

as 0.05 for X = A, 0.42 for X = ^zA, and 0.59 for X = G and interpreted their significant experimental results in terms of a unistep superexchange mechanism. On the basis of the comparison of the experimental results of Nakatani et al.[31] with those of Giese et al.,[8] it appears that the unistep superexchange model is inapplicable in the former case. The superexchange rate through a five-unit bridge, even if the middle base has a relatively low oxidation potential, should be lower than that for a four-membered bridge composed of T and A bases. According to the experimental data of Giese et al.,[8] the relative yield for hole trapping in the $\mathrm{G}^{+}(\mathrm{T{-}A})_{4}\mathrm{GGG}$ duplex is 0.03, and the yield decreases by an order of magnitude upon the addition of each (T−A) bridge element, in accordance with theoretical estimates[22] of the reduction factor $r_{\mathrm{T}} = 7 \times 10^{-2}$ for the rates of intrastrand (superexchange-mediated) hole trapping (or hopping) upon the addition of a T (or A) base. Accordingly, the relative yield for duplex (I) (with X = T or A) is expected to be about 2×10^{-3}, which constitutes an extremely low relative yield. This low yield precludes the unistep superexchange mechanism[31] for this system, and the experimental results should be interpreted within the framework of a TIH.

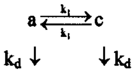
III.a. Superexchange. The argument concerning the inapplicability of the superexchange model proposed by Nakataini et al.[31] for hole transfer between the initial and terminal (GGG) groups in duplex (I) can be quantified in terms of a kinetic scheme for the superexchange model for hole transfer in the system, which is given by



$$\begin{tikzcd}(\mathrm{GGG})^{+}\mathrm{TTXTT(GGG)} \arrow[r, shift left, "k_1"] \arrow[d, "k_d"] & (\mathrm{GGG})\mathrm{TTXTT}(\mathrm{GGG})^{+} \arrow[l, shift left, "k_1"] \arrow[d, "k_d"] \\ {} & {}\end{tikzcd}$$

(8)

This scheme will be recast in the form



$$\begin{tikzcd}\mathrm{a} \arrow[r, shift left, "k_1"] \arrow[d, "k_d"] & \mathrm{c} \arrow[l, shift left, "k_1"] \arrow[d, "k_d"] \\ {} & {}\end{tikzcd}$$

(8a)

where a = $(\mathrm{GGG})^{+}\mathrm{TTXTT(GGG)}$ represents the cation radical of the proximal G triplet and b = $(\mathrm{GGG})\mathrm{TTXTT}(\mathrm{GGG})^{+}$ represents the cation radical of the distal G triplet. Here k_1 is the rate constant for the superexchange in system (I) through the five-base TTXTT bridge. The initial and the final states in eq 8 are taken to be isoenergetic, so that the forward and backward rates are taken as equal. It will be useful to express k_1 in terms of the (superexchange mediated) hole-hopping rate k in the system $\mathrm{G}^{+}\mathrm{TTG}$, which was studied and analyzed by Giese et al.[8] and by Bixon et al.,[12] taking the ratio $\alpha = k_1/k$. We expect that $k_1/k \ll 1$, due to the presence of three extra base pairs, of which only one has a low ionization potential. In this and in the following discussion the triple guanine (GGG) is treated as a single entity. This approach is discussed and justified in Appendix A. k_d in eq 8 is the rate for the reaction of $(\mathrm{GGG})^{+}$ with water. From a previous analysis[12] we infer that $\xi = k_d/k = 0.08$.

The unistep superexchange kinetics is described by the rate constant matrix **K** (Appendix A), from which we obtain the chemical yields for the initial and final states

$$Y_{\mathrm{a}} = \frac{\alpha + \xi}{2\alpha + \xi} \tag{9}$$

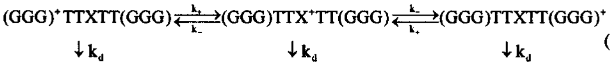
$$Y_{\mathrm{c}} = \frac{\alpha}{2\alpha + \xi} \tag{10}$$

The yield ratio for distal/terminal oxidation products is

$$Y_{\mathrm{c}}/Y_{\mathrm{a}} = \frac{1}{1 + (\xi/\alpha)} \tag{11}$$

Consider first the situation for X = ^{z}A and G. For these low-oxidation potential constituents we expect that the superexchange rate k_1 is lower than the corresponding rate for the TTTT bridge. From the experimental data[8] and the theoretical analysis,[12] the reduction factor for the $\mathrm{G}^{+}\cdots\mathrm{G}$ superexchange rate upon the addition of one (T−A) element is $r_{\mathrm{T}} \approx 0.1{-}0.06$. Accordingly, we expect that $k_1 < k(r_{\mathrm{T}})^2$ and $\alpha = k_1/k < 10^{-2}$. Thus, the yields ratio, eq 9, is bound by $\mathrm{Y_c/Y_a} < (1 + \xi/r_{\mathrm{r}}^{2})^{-1} = 0.11$. This upper limit is considerably lower than the experimental values of $Y_{\mathrm{c}}/Y_{\mathrm{a}} = 0.42$ for X = ^{z}A and $Y_{\mathrm{c}}/Y_{\mathrm{a}} = 0.59$ for X = G. Next, we consider the situation for X = A, where the donor and acceptor (GGG) groups are separated by five (T−A) units, whereupon $k_1 \cong k(r_{\mathrm{T}})^3$. Thus $\alpha = k_1/k \simeq 10^{-3}$ and $Y_{\mathrm{c}}/Y_{\mathrm{a}} = (1 + \xi/\alpha)^{-1} = 0.012$. This value is lower than the experimental result[31] $Y_{\mathrm{c}}/Y_{\mathrm{a}} = 0.05$ for X = A. We infer that the superexchange channel contributes about 25% to the charge transport, although the branching ratio can be somewhat higher, due to uncertainties in the input data. From the foregoing analysis we conclude that the unistep superexchange mechanism cannot account for the experimental data in system (I), with X = ^{z}A and G, and may make a substantial contribution to the charge transport for this system for X = A. An alternative TIH model for charge migration in this system will now be advanced.

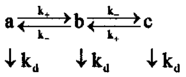
III.b. The TIH Model. The experimental data of Nakatani et al.[31] are interpreted by us in terms of a TIH sequential model involving hole hopping between the (GGG) triplets and X, with X^{+} appearing as a real intermediate in the charge-transport process. In the case of X = ^{z}G, the hole was trapped mainly on ^{z}G,[31] which was proposed[31] to act as a differential hole trap, which implies a sequential mechanism rather than superexchange and requires a very effective internal loss process in $^{z}\mathrm{G}^{+}$ relative to G^{+}. We propose that $^{z}\mathrm{G}^{+}$ constitutes a genuine chemical intermediate. A plausible interpretation of the experimental results[31] is that the (free) energy of $^{z}\mathrm{G}^{+}$ is close to that of $(\mathrm{GGG})^{+}$. On the basis of the foregoing analysis in this section, we infer that the corresponding energy differences are $E(\mathrm{T}^{z}\mathrm{G}^{+}\mathrm{T}) - E((\mathrm{GGG})^{+}) \approx 0$ to -0.05 eV and $E(\mathrm{TG}^{+}\mathrm{T}) - E(\mathrm{T}^{z}\mathrm{G}^{+}\mathrm{T}) \approx 0.05{-}0.1$ eV. For X = G, A^{z} (and also for A) the energy gap between $(\mathrm{GGG})^{+}$ and X is positive, and thermally induced hole injection between the proximal $(\mathrm{GGG})^{+}$ to X occurs, followed by trapping from X^{+} to the distal GGG. In addition, back reactions take place. In parallel, the radical cations react with water. The kinetic scheme for TIH in this system is



$$\begin{tikzcd}(\mathrm{GGG})^{+}\mathrm{TTXTT(GGG)} \arrow[r, shift left, "k_+"] \arrow[d, "k_d"] & (\mathrm{GGG})\mathrm{TTX}^{+}\mathrm{TT(GGG)} \arrow[l, shift left, "k_-"] \arrow[r, shift left, "k_-"] \arrow[d, "k_d"] & (\mathrm{GGG})\mathrm{TTXTT}(\mathrm{GGG})^{+} \arrow[l, shift left, "k_+"] \arrow[d, "k_d"] \\ {} & {} & {}\end{tikzcd}$$

(11)

or in a concise form,



$$\begin{tikzcd}\mathrm{a} \arrow[r, shift left, "k_+"] \arrow[d, "k_d"] & \mathrm{b} \arrow[l, shift left, "k_-"] \arrow[r, shift left, "k_-"] \arrow[d, "k_d"] & \mathrm{c} \arrow[l, shift left, "k_+"] \arrow[d, "k_d"] \\ {} & {} & {}\end{tikzcd}$$

(11a)

where a and c represent the proximal and distal ion radicals of the G triplets, respectively (section II), while b = (GGG)-$\mathrm{TTX}^{+}\mathrm{TT(GGG)}$ represents the cation radical of X.

The unistep hole-transfer reactions between $(\mathrm{GGG})^{+}$ and X are characterized by forward (injection) and backward (back transfer) hopping rates, k_+ and k_- in eq 11, with their ratios being given by the equilibrium constant

$$K = k_+/k_- = \exp(-\Delta/k_{\mathrm{B}}T) \tag{12}$$

where Δ is the (free) energy gap between states b and a. The injection rate k_+ into the X base of the bridge (mediated by superexchange via two T bases) can be readily evaluated for the "normal" Marcus region when $\Delta \ll \lambda$, where λ is the medium reorganization energy. Then a rough estimate gives

$$k_+ = C\exp[-(\lambda + \Delta)^2/4k_{\mathrm{B}}T] \approx k\exp(-\Delta/2k_{\mathrm{B}}T) \tag{13}$$

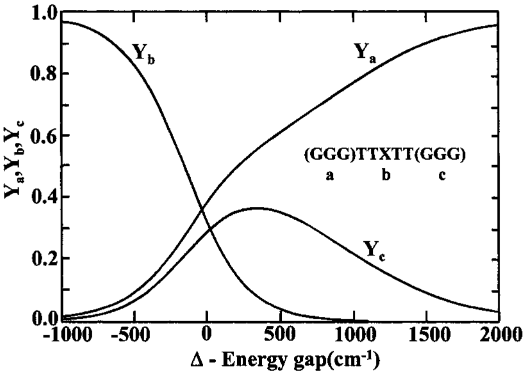


Figure 3. The dependence of the chemical yields Y_a, Y_b, and Y_c for TIH in the $(GGG)^+TTXTT(GGG)$ duplex on the energy gap of TX^+T relative to $(GGG)^+$.

where C is a numerical constant, which contains also the contribution of high-frequency nuclear modes and $k = C \exp(-\lambda/4k_BT)$ is the symmetric hopping rate (for $\Delta = 0$). The recombination rate k_- is given from eqs 12 and 13 by

$$k_- = k \exp(\Delta/2k_BT) \tag{14}$$

Equations 3 and 14 express the injection and recombination rates in duplex (I) in terms of the symmetric hopping rate k in the G^+TTG duplex over a bridge consisting of two T bases.

The final termination of the sequential process takes place by a reaction of the radical cations with the water solvent, which removes the charge from the DNA molecule. Previous analysis[12] resulted in $k_d/k = 0.08-0.10$. In our "minimal" model, eq 11, we assume that the rate constant for this water reaction has the same value, k_d, for the three ionic sites a, b, and c. This assumption is adequate for the proximal and distal $(GGG)^+$ groups in the system, but not necessarily for X^+. Our model calculations show that the results for the relevant chemical yield ratios are not sensitive to the value of k_d/k for X^+ (for $\Delta > 0$). Taking $k_d/k = 0.08-0.10$ for the a and c groups and $k_d = 0$ for X^+, we find that the ratio Y_c/Y_a varied by 5% for $\Delta = 0$ and by less than 0.1% for $\Delta \geq 500$ cm^{-1} as compared to the results of the "minimal" model.

The kinetic analysis of eq 11 (Appendix A) provides the ratio Y_c/Y_a of the chemical yields on the distal/proximal G triplets in the following transparent form

$$Y_c/Y_a = [1 + 2\xi \exp(\Delta/2k_BT) + \xi \exp(-\Delta/2k_BT) + \xi^2]^{-1} \tag{15}$$

where $\xi = k_d/k$.

The dependence of the chemical yields, eqs A6, A7, and A8, on the energy gap Δ for system (I) is displayed in Figure 3. From these data we can infer that the experimental results for $X = {}^zG$[31] are consistent with $\Delta = -500$ cm^{-1} (-0.062 eV) for which $Y_b = 0.85$, $Y_a \simeq 0.05$, and $Y_c \simeq 0.1$, with the population of the mediating TT^zG^+TT system being dominant. In this system with $\Delta < 0$ trapping by ${}^zG$ with reverse TIH from ${}^zG^+$ to GGG does occur. Nakatani et al.[31] provided an alternative explanation of their experiment with $X = {}^zG$ in terms of differential hole trapping, involving relaxation within a ${}^zG^{\bullet+}$ intermediate, whose reaction with water is considerably faster than the water reaction with $(GGG)^+$. Further experimental and theoretical work is required to establish whether hole trapping by ${}^zG$ involves the Nakatani[31] differential trapping mechanism (with a positive value of Δ) or whether the role of ${}^zG$ was a thermodynamic hole sink (with $\Delta < 0$), as obtained from our analysis. From Figure 3 we infer that the population of the intermediate TTX^+TT state becomes low (i.e., $Y_c < 0.1$) for $\Delta > 200$ cm^{-1}. Thus, while the sequential TIH mechanism is operative for $\Delta > 0$ at room temperature, the population of the intermediate X^+ remains low for this mechanism.

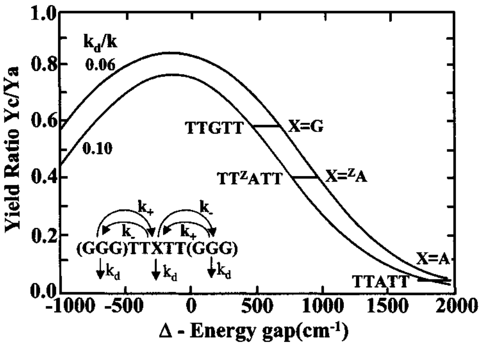


Figure 4. The ratios of the chemical yields for the distal/proximal GGG cleavage in the $(GGG)^+TTXTT(GGG)$ duplex over the range of the energy gap $\Delta = -1000$ cm^{-1} to 2000 cm^{-1}. The two curves correspond to the water reaction rates $k_d/k = 0.1$ and $k_d/k = 0.06$, as marked. The energy gaps of TX^+T relative to $(GGG)^+$, which are inferred from the experimental results of ref 31, are marked by horizontal lines.

The ratios of the chemical yields for the cleavage on the distal G triplet to the proximal G triplet, calculated from eq 15, are presented in Figure 4. The experimental data for X = A, ${}^zA$, and G can now be analyzed in terms of these calculations for the sequential model (Figure 2), with the realistic values $\xi = k_d/k = 0.1-0.06$, to give the following (free) energy gap ranges (all relative to $(GGG)^+$):

$$E(TA^+T) = 1700-1900\ \text{cm}^{-1} = 0.21-0.24\ \text{eV}$$

$$E(T^zA^+T) = 800-1100\ \text{cm}^{-1} = 0.10-0.14\ \text{eV}$$

$$E(TG^+T) = 400-800\ \text{cm}^{-1} = 0.05-0.1\ \text{eV}$$

These energetic estimates are marked on Figure 4.

From this analysis we conclude that the TIH at room temperature constitutes an effective process in duplex (I) for thermally induced hole hopping from $(GGG)^+TTXTT\cdots$ to $(GGG)TTX^+TT\cdots$ ($X = {}^zA$, and G). For these bridges, containing ${}^zA$ or G, the chemical yields are sufficiently high to warrant the contribution of the superexchange channel to be minor. These hole acceptors X are characterized by a positive (free) energy gap (relative to $(GGG)^+$) in the range $\Delta = 0.05-0.14$ eV and are reached from the initial $(GGG)^+$ by an activated process with a rate given by eq 13. The genuine X^+ intermediate is subsequently depleted by an effective hole transfer to the terminal GGG or back to the proximal GGG, so that its yield is low (<0.05). The elementary TIH rates k_+ and k_- represent (GGG)$-$X superexchange through two T bases. The TIH via $X = G$ provides new information on the energetics of hole trapping via a G triplet. (GGG) constitutes a shallow hole trap from G^+ ($\Delta = 0.05-0.1$ eV). This (free) energy gap for TG^+T, relative to $(GGG)^+$, is close to the (free) energy gap $E(AG^+A(GGG) - E(AGA(GGG)^+) = 0.077$ eV estimated from the kinetic data of Lewis et al.[6f] and 0.062 eV inferred[12c] by us from chemical yield data[8c,d] in the AG^+AGGA duplex and to the energy gap $E(TG^+TGGG) - E(TGT(GGG)^+) = 0.096$ eV estimated[12c] from chemical yield data.[8c,d]

We now refer to hole transfer/transport in duplex (I) with X = A, where the TIH sequential mechanism resulted in the

2value of $\Delta = 0.21-0.24$ eV for (GGG)TTA$^+$TT(GGG), relative to (GGG)$^+$TTATT(GGG). While early estimates of the energy gap $E(\mathrm{G^+A}) - E(\mathrm{GA^+})$, based on redox potential data in vitro, resulted in a higher value of 0.4 eV,[11] the present estimate of $\Delta = 0.21-0.24$ eV and $E(\mathrm{TA^+T}) - E(\mathrm{TG^+T}) \simeq 0.20$ eV constitutes a reliable estimate of the energy gap between G$^+$A and GA$^+$ in DNA. This result is of considerable interest to assess the feasibility of the mechanism of TIH (sections IV and V). The low experimental value of $Y_c/Y_a = 0.05$[31] may require the incorporation of the superexchange channel in parallel to TIH. Our rough estimates (section III.a) give a superexchange contribution to the relative yield of 10^{-2} for the TTATT bridge, whereupon the branching ratio for the superexchange channel is ~25% in this system.

IV. Long-Range Hole Hopping

We explored the dependence of the relative chemical yields

$$\psi = (\mathrm{G})_l^+(\mathrm{distal})/(\mathrm{G})_l^+(\mathrm{proximal}) \qquad (16)$$

in the duplex $(\mathrm{G})_l^+(\mathrm{T}_m\mathrm{X})_n\,\mathrm{T}_m(\mathrm{G})_l$ (with $m = 2$, 1, and 0 and $l = 1-3$) on the bridge length in long DNA duplexes. The proximal $(\mathrm{G})_l^+$ and distal $(\mathrm{G})_l$ constitute the primary hole donor and acceptor, respectively. The X bases (with a lower redox potential than that of T, but higher than that of $(\mathrm{G})_l$) act as hole carriers via TIH. The bridge length was specified in terms of the total number of the bridge bases $[(m + 1)n + n]$, and the energetics of the $\mathrm{T}_m\mathrm{X}^+\mathrm{T}_m$ subunits relative to G$^+$ was characterized by the energy gap Δ (>0). The kinetic scheme is

$$\begin{array}{ccccccccc} \mathrm{G^+} & \underset{k_-}{\overset{k_+}{\rightleftarrows}} & \mathrm{T_mX^+_{(1)}T_m} & \underset{k_m}{\overset{k_m}{\rightleftarrows}} & \mathrm{T_mX^+_{(2)}T_m} & \underset{k_m}{\overset{k_m}{\rightleftarrows}} \cdots & \mathrm{T_mX^+_{(n)}T_m} & \underset{k_+}{\overset{k_-}{\rightleftarrows}} & (\mathrm{G})_l^+ \\ \downarrow k_d & & \downarrow k_d' & & \downarrow k_d' & & \downarrow k_d' & & \downarrow k_d \end{array} \qquad (17)$$

The individual hole-hopping rates k_m between $\mathrm{X}_{(j)}\cdots\mathrm{X}_{(j+1)}$ adjacent bases ($j = 1\cdots(n-1)$), separated by m T bases, exhibit the segment length dependence $k_m = kr^{m-2}$, where $r \simeq 0.1$ is the reduction factor of the rate upon adding one T base between a pair of adjacent X bases, and k ($= k_{m=2}$) corresponds to the hopping rate over two T bases (discussed in section III). The case of the bridge $(\mathrm{X})_n$ ($m = 0$), where the nearest-neighbor intrastrand electronic coupling matrix elements are large (~0.03−0.15 eV[22,23]), will be treated in terms of the strong scattering/hopping picture, rather than by the band motion.[32,33] For the bridge elements with $m = 1$, 2, the (superexchange-mediated) electronic couplings between X groups are sufficiently small (~$10^{-3}-10^{-4}$ eV) to warrant the applicability of the strong-scattering incoherent charge-hopping picture.[32,33] The hole injection rate k_+ and trapping rate k_- are expressed, following the analysis in section (III.b), in the form: $k_+ = k_m \exp(-\Delta/2k_BT)$ and $k_- = k_m \exp(\Delta/2k_BT)$, with $k_+/k_- = \exp(-\Delta/k_BT)$. Additional required information pertains to the chemical rate constants k_d and k_d' for the reaction of G$^+$ and of X$^+$ with water, respectively, which are local properties, being independent of the length of the T_m segment separating the nearest-neighbor G···X and X···X bases. On the basis of experimental information for $m = 2$,[8] the relative chemical rates k_d/k_m are taken as 0.1 for $m = 2$ ($(\mathrm{G})_l^+$TTXTT···TT$(\mathrm{G})_l$), 0.01 for $m = 1$ ($(\mathrm{G})_l^+$TXTX···XT(G)), and 0.001 for $m = 0$ ($(\mathrm{G})_l^+\mathrm{X}_n(\mathrm{G})_l$). In the absence of information on the rates k_d', we shall first take $k_d' = k_d$ and subsequently refer to the sensitivity of the results to the variation of k_d'. In this simple model (described by eq 17 with $k_d = k_d'$) we need only the energy gap Δ and the relative rate k_d/k_m to express the relative yields. In Figure 5 we present the bridge length dependence of the relative chemical yields ψ for the regular structural duplexes, with $m = 0-2$, and for energy gaps in the range $\Delta = 300-1800$ cm^{-1} (0.04−0.24 eV). The efficiency (measured in terms of ψ) of the long-range transport by TIH decreases with increasing Δ (Figure 5), reflecting on the inhibition of TIH at large gaps. The dependence of ψ on the structure of the bridge (Figure 5) reflects a major enhancement with decreasing the number m of the mediating T bases (and decreasing of k_2/k_m), with the most efficient TIH being manifested for the neat X_n bridge.

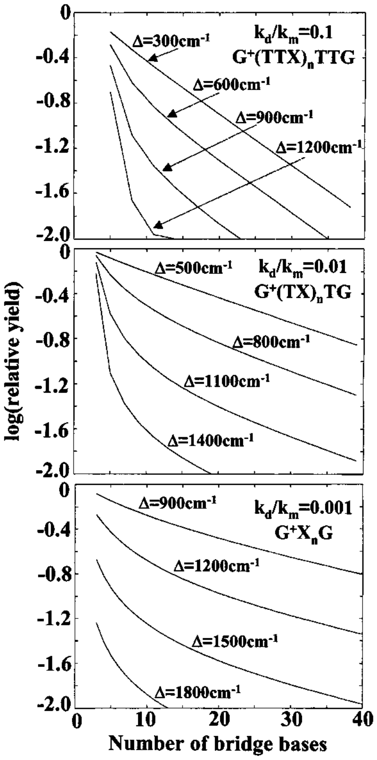


Figure 5. Model calculations for the dependence of the relative chemical yields ψ via TIH for the distal/proximal $(\mathrm{G})_l^+$ ($l = 1-3$) in the duplex $(\mathrm{G})_l^+(\mathrm{T}_n\mathrm{X})_n\mathrm{T}_m(\mathrm{G})_l$ ($m = 1$, 2) on the bridge length (total number of bridge bases $[(m + 1)n + n]$. The three panels correspond to different rates of G$^+$ with water specified by $k_d/k_{m=2} = 0.1$ (from ref 12), $k_d/k_{m=1} = 0.01$ and $k_d/k_{m=0} = 0.001$. The energy gaps are marked on the curves.

The model calculations of Figure 5 demonstrate the prevalence of long-range hole transport via TIH over tens to hundreds of base pairs in regular structures for X−G energy gaps lower than $\Delta < 1800$ cm^{-1} (0.23 eV). To quantify the range of hole transport in these model duplexes we take somewhat arbitrarily the number $\bar{N}(\psi)$ of the bridge bases where ψ is in the range $\psi = 0.1-0.01$. In Figure 6 we portray the $\bar{N}(0.05)$ values for relative yields of 5%, which are readily amenable to experimental observation.[5,8,9,30,31] Long-range transport over 10 bases is accomplished for mediators X with $\Delta = 900$ cm^{-1} for $m = 2$, $\Delta = 1300$ cm^{-1} for $m = 1$, and $\Delta = 1500$ cm^{-1} for $m = 0$. The effectiveness of the neat X_n bridge ($m = 0$) is reflected in Figure 7, where the values of $\bar{N}$ for relative yields of 1 and 10% are presented for the $(\mathrm{G})_l^+\mathrm{X}_n(\mathrm{G})_l$ duplex. TIH (with $\psi = 0.01$) can be accomplished over 100 nucleobases for the energy gap of $\Delta = 1000$ cm^{-1} (corresponding to ^{z}A bridge elements according to the analysis of section III.b), and over 13 nucleo-

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[32] Katz, J. L.; Rice, S. A.; Choi, S. I.; Jortner, J. *J. Chem. Phys.* **1963**, *39*, 1683−1697.

[33] *Molecular Electronics*; Jortner, J., Ratner, M. A., Eds.; Blackwell Science: Cambridge, MA, 1998; pp 5−72.

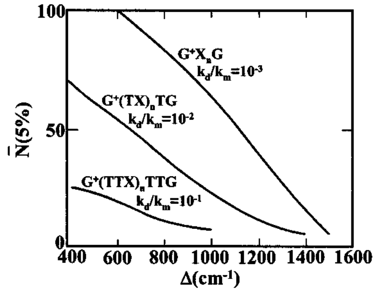

Figure 6. The energy gap dependence of the number $\bar{N}(\psi = 0.05)$ of bridge bases required for the attainment of the relative chemical yield $\psi = 0.05$ for TIH in $G^+(T_mX)_nT_mG$ duplexes ($m = 2, 1, 0$). Parameters for k_d/k_m as in Figure 5.

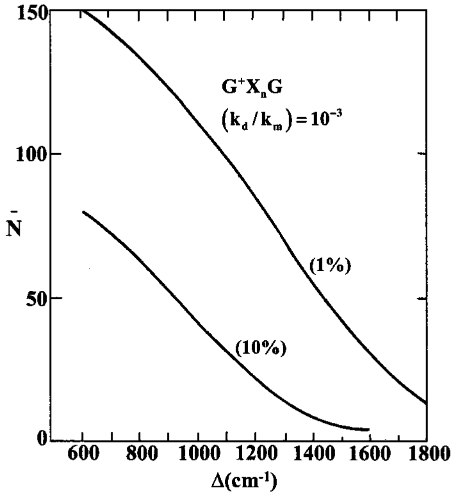

Figure 7. The energy gap dependence of the number $\bar{N}(\psi)$ of X bridge bases for TIH in G^+X_nG duplexes for $\psi = 0.01$ (marked 1%) and for $\psi = 0.1$ (marked 10%).

bases for the energy gap $\Delta = 1800$ cm^{-1} (corresponding to the A bridge elements according to section III.b). This analysis demonstrates the energetic constraints for the applicability of the TIH mechanism under the conditions of the effective reaction with water, for example, $k_d/k_m = 10^{-3}$ and $k'_d = k_d$ for the $(G)_lX_n(G)_l$ duplex.

It is instructive to go beyond the "minimal" model employed herein (i.e., the water reaction rate being equal for G^+ and X^+, that is, $k_d = k'_d$) and consider the situation where the bridge radical cations do not react with water (i.e., $k'_d = 0$). From model calculations for the kinetic scheme (eq 17), we infer that for large energy gaps $\Delta \geq 1000$ cm^{-1} and ψ is practically independent of the value of k'_d (in the range $0 \leq k'_d \leq k_d$, while $k_d/k_m = 10^{-2}$–10^{-5}). This result is due to a very small population of the bridge X^+ cations. Thus, for $(G)_lX_n(G)_l$ duplexes with azaadenine bridging bases $X = {}^zA$, for which $\Delta \cong 1000$ cm^{-1}, and with adenine-bridging bases X = A, for which $\Delta \cong 1800$ cm^{-1} (section III.b), the reaction of the X^+ radical cations with water is of minor importance and will not be experimentally observed. On the other hand, when the bridge contains G bases, the energy gap is small ($\Delta \cong 500$ cm^{-1}) and water reactions of the mediating G^+ bridge groups have to be incorporated in the kinetic analysis (Figures 5–7).

Of considerable interest is the possibility of the modification of the rate k_d for the reactions of the proximal and the terminal G^+ cations with water. The chemical rates k_d may depend on the solvent composition and on the pH of the solution.[26] In Figure 8 we portray kinetic simulations for ψ in the model system of a G^+X_nG duplex, where the reactivity of the proximal and terminal G^+ varies in the range $k_d/k_{m=0} = 10^{-2}$–10^{-5} and $k'_d = 0$. The calculations were performed for large energy gaps ($\Delta = 1000$–2000 cm^{-1}) where ψ is independent of the value of k'_d, and for smaller energy gaps ($\Delta = 500$ cm^{-1}) where ψ exhibits a dependence on k'_d (Figure 8). In general, ψ increases with decreasing k_d/k_m, manifesting the slowing down of the parallel terminating chemical reaction.

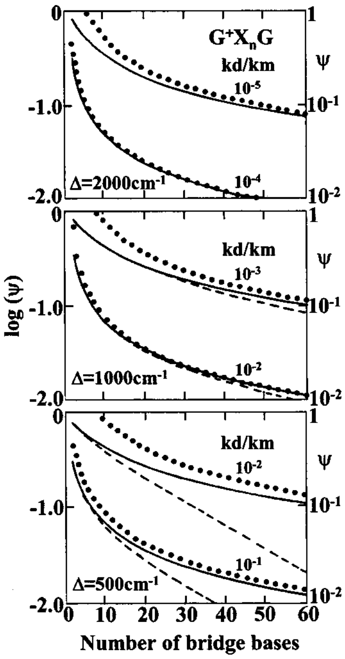

Figure 8. The effects of the chemical control of the distal/proximal G^+ chemical yields ratio ψ for TIH in G^+X_nG duplexes. Model calculations for the dependence of ψ on the number n of the bridge bases are presented for the $G^+X - GX^+$ energy gap ($\Delta = 2000$ cm^{-1} (upper panel), $\Delta = 1000$ cm^{-1} (middle panel) and $\Delta = 500$ cm^{-1} (lower panel), with the ratios k_d/k_m marked on the curves. Upper panel: (—) both $k'_d = k_d$ and for $k'_d = 0$. Middle and lower panel: (—) $k'_d = 0$, (- - -) $k'_d = 0$. The dotted curves (···) represent the approximate relation for ψ, eq 18.

A very useful approximate expression for the relative chemical yield is given by

$$\psi = \exp(-\Delta/k_BT)/(k_d/k_m)\bar{N}(\psi) \qquad (18)$$

As is evident from Figure 8, eq 18 constitutes a good description of ψ over a broad range of k_d values (with $k'_d = k_d$ or 0 for $\Delta \geq 1000$ cm^{-1} and $k'_d = 0$ for $\Delta < 1000$ cm^{-1}) in the range $\psi \leq 0.25$. Choosing again $\psi = 0.1$ to specify the spatial range of TIH, the dependence of $\bar{N}(0.1)$ on the relevant parameters Δ and k_d/k_m is given from eq 18 by the simple expression

$$\bar{N}(0.1) = [10/(k_d/k_m)]\exp(-\Delta/k_BT) \qquad (19)$$

Equation 19 implies an exponential dependence of $\bar{N}$ on the energy gaps (Δ/k_BT) and an algebraic linear dependence on k_d (reciprocal) and on k_m (proportional). Most interesting is the increase of the range for TIH provided that the ratio k_d/k_m is sufficiently small. For a large energy gap $\Delta = 2000$ cm^{-1}, eq 19 gives for the range for hole TIH the values $\bar{N}(0.1) = 5$ for $k_d/k_m = 10^{-4}$, and $\bar{N}(0.1) \simeq 45$ for $k_d/k_m = 10^{-5}$. From the model calculations for hole TIH in $(G)_l^+(T_mX)_nT_m(G)_l$ ($m = 0$, 1, 2, $l = 1$–3) duplexes at 300 K, the following conclusions emerge:

(1) Energetic constraints for TIH. The TIH mechanism provides an effective route for efficient long-range hole transport between G bases separated by an n-component bridge. From eq 18 we infer that the energetic onset for TIH (i.e., $\psi = 0.1$ for $n \geq 5$) is $\Delta \lesssim k_B T\ ln(2k_m/k_d)$. Accordingly, for the "fast" water reaction of G^+, i.e., $k_d/k_m = 10^{-3}$, TIH will be exhibited for $\Delta < 1500\ cm^{-1}$, while for the "slow" water reaction, that is, $k_d/k_m = 10^{-4}$, TIH prevails for $\Delta < 2000\ cm^{-1}$.

(2) Bridge structural constraints for TIH. The increase of the individual hopping rates k_m between the X bases in the bridge (keeping Δ and k_d fixed) results in the increase of TIH in the form $\bar{N}(0.1) \propto k_m$. This relation is adequate for large energy gaps ($\Delta > 1000\ cm^{-1}$) and also for a larger range of $\Delta > 300\ cm^{-1}$ when $k'_d = 0$. For smaller energy gaps ($\Delta < 1000\ cm^{-1}$) and $k_d = k'_d$, the qualitative behavior is similar, but numerical kinetic calculations are required.

(3) Kinetic constraints on TIH. The range of hole transport via TIH increases with decreasing the rate of the water reaction with the G^+ cations. For large values of Δ (>1000 cm^{-1}), $\bar{N} \propto k_d^{-1}$. This result opens an avenue for the chemical control of the range of TIH by modifying k_d through changes of the solution composition.[26]

On the basis of the energetic and bridge structural constraints we assert that effective bridge elements for TIH of holes in $(G^+)_l X_n (G)_l$ duplexes ($l = 1-3$) will involve X bases with $\Delta < 0.25$ eV at $T = 300$ K. Obviously, T nucleobases, which are characterized by very high values of Δ (0.6 eV as inferred from redox potential solution data[16]), are precluded to act as effective X bridge elements in TIH of holes. These can be present as bridge structural elements separating the active X bases. The active X bases can be G bases scattered among T nucleobases with the hole donor/acceptor consisting of (GGG) or (GG) shallow hole traps (as discussed for duplex (I) in section III). The X elements can be substituted nucleobases, that is, azoadenine ^zA (with $\Delta \simeq 0.1$ eV according to section III), which can induce long-range hole TIH over bridges containing ~10 bases (for $G^+TT^zATT\cdots G$) to ~100 bases (for $G^+(^zA)_nG$), which will be of interest for the response of synthetic nanostructures. The role of the adenine A bases as bridge elements for TIH constitutes a borderline case. On the basis of redox potential data of a single nucleobase in a polar solvent,[16] an estimate of the G^+-A energy gap of $\Delta = 0.4$ eV was obtained, which is close to the value of $\Delta \simeq 0.45$ eV inferred by Lewis et al.[6g] for free energy relationships for the hole-injection rates from hairpinned diphenylacetylene dicarboxyanide to nucleobases. These values of $\Delta = 0.40-0.45$ eV are too high to allow for effective involvement of A in TIH. The energy gap for A estimated from the polar solvent redox potential data for the single nucleobase,[14] which is also used for the free energy relationships,[6g] may be overestimated as they do not include interbase and phosphate stabilization effects. Our analysis for the GGGTTATTGGG duplex (section III) resulted in a lower energy gap of $\Delta = 0.21-0.24$ eV. The energy gaps inferred from the analysis of section III are 0.20−0.23 eV for G^+A and 0.21−0.24 eV for $(GGG)^+A$. These lower energy gaps constitute the upper limits to ensure the occurrence of TIH.

V. Discussion

The TIH mechanism explored herein generalizes the concept of energetic control (for $\Delta E > 0$). Long-range charge transport can be induced via thermally activated charge injection from the donor to the bridge, which is followed by charge hopping within the bridge. Thus, the TIH essentially involves an endothermic charge transfer to the bridge. The multistep TIH (induced from higher vibronic levels at energies $E \geq \Delta E$ of the donor manifold) occurs in parallel with unistep superexchange (occurring from lower vibronic levels at energies $E \leq \Delta E$ of the donor manifold). Thermal excitations result in a parallel superexchange − TIH mechanism, with one of the channels being dominant. Such a parallel mechanism is general for DNA, for large-scale chemical systems,[27] for biological systems,[28] as well as for the (sequential-superexchange) primary charge separation in chemically or mutagenetically modified photosynthetic reaction centers.[29,34]

The major implications of the TIH mechanism are

(1) The "transition" from unistep superexchange to TIH in a donor−bridge−acceptor system ($\Delta E > 0$) with increasing the length (N) of the bridge. The crossing between the superexchange, exponentially N dependent rate for $N < N_X$ to an algebraic weakly N-dependent TIH rate at $N > N_X$ will be exhibited, with the "critical" bridge size N_X being determined by the strength of the electronic couplings, by the donor−bridge energy gap, and by the temperature.

(2) In composite bridges of DNA duplexes, for example, (GGG)TTXTT(GGG) (X = G, ^zA, and A),[31] hole TIH between the proximal and the distal (GGG) groups occurs, with X^+ constituting a genuine kinetic intermediate. It is gratifying that the experimental results of Nakatani et al.[31] for hole transfer in this duplex provide the first experimental evidence for the applicability of the TIH mechanism. For X = G and ^zA the TIH channel dominates, while for X = A some contribution (~25%) of the superexchange channel prevails.

(3) The range of long-range hole hopping via TIH between G bases in $(G)_l^+ X_n (G)_l$ ($l = 1-3$) DNA duplexes is determined by energetic constraints (i.e., the donor $(G)_l$ − bridge (X) energy gap Δ), by bridge structural constraints (i.e., the intrabridge X−X hopping rates k_m) and by kinetic constraints (i.e., the rate k_d for the reaction of the G^+ radical cations with water).

The TIH mechanism was subjected to a detailed kinetic analysis. Our model calculations for TIH in DNA (sections III and IV) adopted a "minimal" model, neglecting the effects of directional asymmetry[11,22] on the electronic couplings and the hopping rates in the 3′−5′ and 5′−3′ directions within the duplex. Furthermore, we have taken the electronic matrix elements for hole-transfer nearest-neighbor G−X and X−X bases to be equal, while detailed information was obtained for base pair specificity for both intrastrand and interstrand electronic coupling matrix elements.[22] These simplifications result in a kinetic scheme where the relative yields ψ are expressed in terms of just two parameters, the energy gap Δ and the ratio of the rates k_d/k_m. More elaborate kinetic calculations, relaxing these approximations, are straightforward and will be conducted when more detailed experimental information will become available.

The TIH mechanism in $(G)_l^+ X_n (G)_l$ ($l = 1-3$) duplexes may be operative for long-range hole transport between $(G)_l$ groups separated by long X_n bridges, whose elements satisfy the appropriate energetic and kinetic constraints. Our model calculations in section IV imply that for a "fast" water reaction ($k_d/k_m = 10^{-3}$) $\Delta < 0.20$ eV, while for a "slow" water reaction ($k_d/k_{m=0} \simeq 10^{-5}$) the energetic onset is $\Delta < 0.30$ eV. From these estimates of Δ it appears that $(T)_n$ bridges in $(G)_l^+ T_n (G)_l$ duplexes (with $\Delta = 0.6$ eV[11,14]) cannot act in TIH of holes, and only the unistep superexchange mechanism will be operative for short bridges. A short ($n = 1-4$) adenine bridge element in

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(34) Bixon, M.; Jortner, J.; Michel-Beyerle, M. E. *Chem. Phys.* **1995**, *197*, 389−404.

Table 1. Crossing from Superexchange to TIH in DNA Duplexes

duplex	$\Delta(\mathrm{G}-\mathrm{X}_{(1)})$ (eV)	$\lvert V_{\mathrm{super}}\rvert^2$ (eV^2)	$\lvert V(\mathrm{X}_{(2)}-\mathrm{X}_{(1)})\rvert^2 \exp[-\Delta(\mathrm{G}-\mathrm{X}_{(1)})/k_{\mathrm{B}}T]/(n^2/2)$ (eV^2)
$\mathrm{G^+TG}$	0.6	3.8×10^{-4}	4.6×10^{-17}
$\mathrm{G^+TTG}$	0.6	2.6×10^{-5}	2.3×10^{-17}
$\mathrm{G^+ATG}$	0.22	3.3×10^{-5}	3.7×10^{-7}
$\mathrm{G^+ATTG}$	0.22	2.3×10^{-6}	1.6×10^{-7}
$\mathrm{G^+ATATG}$	0.22	1.7×10^{-7}	9.2×10^{-8}
$\mathrm{G^+AG}$	0.22	3.9×10^{-4}	7.4×10^{-7}
$\mathrm{G^+AAG}$	0.22	1.9×10^{-5}	3.7×10^{-7}
$\mathrm{G^+(A)_3G}$	0.22	9.0×10^{-7}	1.6×10^{-7}
$\mathrm{G^+(A)_4G}$	0.22	4.3×10^{-8}	9.2×10^{-8}
$\mathrm{G^+(A)_5G}$	0.22	2.1×10^{-9}	5.9×10^{-8}

$(\mathrm{G})_l^+(\mathrm{T}-\mathrm{A})_n(\mathrm{G})_{l'}$ ($l, l' = 1-3$) duplexes is expected to act as a superexchange mediator, while for longer ($n \gtrsim 4$) adenine bridges the TIH may prevail.

Following the analysis of section II, a more detailed analysis will be provided for the crossing from the superexchange mechanism to the TIH with increasing the TIH bridge. In this treatment the electronic coupling matrix elements between neighboring nucleobases[22] are kept constant, and the effects of configurational fluctuations[22,35] are neglected. The energy gaps are taken from the analysis of sections III and IV. On the basis of model quantum mechanical calculations[17] and the analysis of experimental data,[18,12c] it appears that changes in the energy gaps for DNA duplexes due to bridge specificity are in the range of 0.05 eV. The (constant) electronic matrix elements and the (approximate) energy gaps account for gross features of sequence specificity of the superexchange hopping rates and of the thermal injection rates in TIH. Regarding the mechanism of side reactions, we do not consider explicitly the possibility of hole trapping via proton transfer[36] as a distinct process for the general reaction with water, which may depend on proton concentration. Considering parallel superexchange and TIH, we assert that the dominance of the superexchange contribution will be determined by the condition

$$|V_{\mathrm{super}}|^2 > |V(\mathrm{X}_{(2)} - \mathrm{X}_{(1)})|^2 \exp[-\Delta(\mathrm{G} - \mathrm{X}_{(1)})/k_{\mathrm{B}}T]/(n^2/2) \tag{20}$$

where the G···G superexchange electronic coupling is

$$V_{\mathrm{super}} = \frac{V(\mathrm{G} - \mathrm{X}_{(1)})V(\mathrm{X}_{(n)} - \mathrm{G})}{\Delta(\mathrm{G} - \mathrm{X}_{(1)})} \prod_{j=1}^{n-1} \frac{V(\mathrm{X}_{(j)} - \mathrm{X}_{(j+1)})}{\Delta(\mathrm{G} - \mathrm{X}_{(j)})} \tag{21}$$

where $V(\mathrm{G} - \mathrm{X}_{(1)})$, $V(\mathrm{X}_{(j)} - \mathrm{X}_{(j+1)})$ and $V(\mathrm{X}_{(n)} - \mathrm{G})$ are the nearest-neighbor matrix elements in the duplex $\mathrm{G^+X_{(1)}X_{(2)}X_{(5)}\cdots X_{(n)}G}$, which were calculated by Voityuk et al.[22] The energy gaps $\Delta(\mathrm{G} - \mathrm{X}_{(1)})$, with $\mathrm{X}_{(1)} = \mathrm{T}$ or A, are taken as $\Delta(\mathrm{G}-\mathrm{T}) = 0.6$ eV (from redox potential data) and $\Delta(\mathrm{G} - \mathrm{A}) = 0.22$ eV (following the analysis of section III). From Table 1 we conclude that the superexchange mechanism dominates, according to eq 20, for the $\mathrm{G^+(T-A)_nGGG}$ duplexes ($n = 1-4$) studied by Giese et al.[8] For these systems the superexchange coupling $|V_{\mathrm{super}}|^2$ exhibits an exponential dependence on the bridge length n ($= 1-4$) and on the G···G distance (Table 1 for $|V_{\mathrm{super}}|^2$) in accord with the experimental results.[6,8] The analysis of Table 1, which solely considered intrastrand coupling, should be extended for G···G superexchange-mediated interstrand coupling[5h,11,22] via short bridges. Time-resolved experimental data for hole transport, in the presence of a site-specifically bound methyltransferase M•HhaIQ237W mutant,[5i] revealed that the observed hole-transport rate ($k = 5 \times 10^6$ s^{-1}) between the initial and the terminal G is higher by 2 orders of magnitude than that inferred from sequential intrastrand G···G hopping steps for superexchange in this system.[5i,37] These interesting experimental results[5i] are compatible with a sequential multistep interstrand hopping mechanism[37] with the rate-determining superexchange rates being $k \simeq 1.2 \times 10^6$ and 2×10^6 s^{-1},[37] in reasonable agreement with experiment. Thus, for short $(\mathrm{T-A})_n$ ($n \leq 4$) bridges intrastrand or interstrand superexchange prevails. For longer $\mathrm{G^+(A)_nG}$ ($n \gtrsim 3$) and $\mathrm{G^+ATAT}$- -G duplexes ($n \gtrsim 4$) the TIH mechanism will set in (Table 1), provided that the relative chemical yield is sufficiently high. For the $\mathrm{G^+ATATG}$ duplex, where the chemical yield is 3%,[8] about 35% of the transport will occur via TIH. Bridge specificity for TIH is manifested by a marked difference between long $\mathrm{G^+ATAT\cdots G}$ and $\mathrm{G^+TATA\cdots G}$ duplexes. While for the $\mathrm{G^+ATATGGG}$ duplex[8] the TIH is effective, for the $\mathrm{G^+TATATAGGG}$ duplex[30b] less effective TIH involves intrastrand $\mathrm{G^+A}$ hole injection mediated by a T nucleobase or interstrand direct $\mathrm{G^+A}$ injection.

The experimental implications of the TIH mechanism advanced and analyzed herein are of considerable interest. While for the short $\mathrm{G^+(T-A)_nG}$ ($n < 4$) duplexes hole superexchange between guanines prevails in accord[12,13] with the experimental

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[35] Cheatham, T. E., III; Kollman, P. A. *Annu. Rev. Phys. Chem.* **2000**, *51*, 435−471.

[36] Steenken, S. F. *Free Radical Res. Commun.* **1992**, *16*, 349−356.

[37] Although intrastrand electronic coupling in DNA duplexes dominates the superexchange interactions,[22] eq 21, interstrand superexchange (or direct) electronic coupling can be sufficiently strong to warrant interstrand G···G hole hopping.[22] The recent experimental results of Barton et al.[5i] provide evidence for sequential, interstrand hole transport. Time-resolved hole transport via guanines in the presence of a site-specifically bound M•HhaIQ237W mutant was studied in the duplexes[5i]

$$\begin{matrix} 3'\text{–}\mathrm{G_{(1)}} & \mathrm{C} & \mathrm{T} \\ 5'\text{–}\mathrm{C} & \mathrm{G_{(2)}} & \mathrm{A} \end{matrix} \begin{pmatrix} \mathrm{G_{(3)}A} & \mathrm{C} & \mathrm{T} \\ \mathrm{C} & \mathrm{TG_{(4)}} & \mathrm{A} \end{pmatrix}_{n} \begin{matrix} \mathrm{C} & \mathrm{G_{(6)}} & \mathrm{XG} \\ \mathrm{G_{(5)}C} & & \mathrm{GC} \end{matrix} \qquad (n = 0,1,2)$$

(where the G nucleobases were labeled consecutively). As noted by Barton et al.,[5i] their experimental rates $k = 5 \times 10^6$ s^{-1} (for $n = 0-2$) cannot be reconciled with the intrastrand, sequential, superexchange hopping rates, e.g.,

$$\mathrm{G}_1^+ \xrightarrow{k_{13}} \mathrm{G}_3$$

and

$$\mathrm{G}_3^+ \xrightarrow{k_{36}} \mathrm{G}_6$$

for $n = 1$. According to the time-resolved data of Lewis et al.[6e,f] and their distance dependence[6e,f] the rate-determining step is expected to be $k_{36} = 5 \times 10^4$ s^{-1}, which is by 2 orders of magnitude lower than k. These experimental results[5i] are compatible with a sequential G−G nearest-neighbor, interstrand hopping mechanism. For the duplex given above[5i] (with $n = 1$) the superexchange (or direct) electronic couplings V for the individual hole-hopping steps were calculated using the matrix elements computed by Voityuk et al.,[22] being given by: (a) $\mathrm{G}_1^+ \rightarrow \mathrm{G}_2$, $|V| = 4 \times 10^{-2}$ eV; (b) $\mathrm{G}_2^+ \rightarrow \mathrm{G}_3$, $|V| = 3.8 \times 10^{-3}$ eV; (c) $\mathrm{G}_3^+ \rightarrow \mathrm{G}_4$, $|V| = 2.9 \times 10^{-3}$ eV; (d) $\mathrm{G}_4^+ \rightarrow \mathrm{G}_5$, $|V| = 1.9 \times 10^{-2}$ eV. As $k_{(\alpha)} \propto V^2$ (α = a, b, c, d), we infer that the direct interstrand hole-transfer rate, reaction a, is the largest, being higher (by a numerical factor of ∼4) than the rate for the intrastrand transfer rate, reaction d. The rate-determining steps involve the interstrand hopping reactions b and c. The rates for these two slowest reactions were estimated from the experimental result of Lewis et al.[5e,f] $k_{(\mathrm{d})} = 5 \times 10^7$ s^{-1} scaled by the ratio of the corresponding $|V|^2$ values, which result in $k_{(\mathrm{b})} = 2 \times 10^6$ s^{-1} and $k_{(\mathrm{c})} = 1.2 \times 10^6$ s^{-1}. Accordingly, the composite interstrand hopping mechanism accounts well for the experimental data,[5i] providing rate-determining rates in reasonable agreement with experiment and accounting for the weak distance (n) dependence of the rates.[5i] From the point of view of general methodology, the calculations of the electronic superexchange coupling for the individual rates given above, result in relatively high values (∼1/25−1/35) for the "penalty factor"[5i] for interstrand hole crossing for the $\mathrm{G_{(2)}\cdots G_{(3)}}$ and for the $\mathrm{G_{(3)}\cdots G_{(4)}}$ superexchange coupling, while for the direct interstand $\mathrm{G_{(1)}\cdots\ G_{(2)}}$ coupling no penalty exists.

data,[8,30] for longer $(T-A)_n$ bridges ($n \gtrsim 4$) the TIH process may take over. We now distinguish between $G^+\cdots G$ long-range transport induced by hopping superexchange steps through moderately short $(T-A)_n$ ($n < 4$) bridges,[5-9,12,13,20,30] and very long-range transport induced by TIH via long $(A)_n$ ($n \gtrsim 4$) chains considered in the present work. In view of the moderate G$-$A energy gap ($\Delta = 0.21-0.24$ eV inferred in section III) the TIH process for $(A)_n$ bridges will be effective, if the reaction with water is sufficiently slow. This conclusion is in accord with the experimental data of Schuster et al.[9c-f] and with the experimental results of Barton et al.[5g-h] for which hole transfer between $(G)_l$ bases separated by very long $(T-A)_n$ bridges ($n = 5-10$) were reported. A careful examination is required to assess whether these experimental data[5,9] are due to TIH via A bases. Three questions arise in the context of the involvement of A bases in TIH (with endothermic hole injection from G to A) in $G^+(A)_nG$ duplexes. First, what is the interplay between superexchange through short $(A)_n$ bridges, and TIH through long $(A)_n$ bridges? Second, what are the mechanistic issues of bridge specificity for TIH through long $(A)_n$ bridges? Third, is TIH induced through long $(A)_n$ bridges amenable for experimental observation? Following the analysis based on eqs 20 and 21 regarding the "transition" from superexchange to TIH we infer from the data in Table 1 for $G^+(A)_nG$ duplexes that the TIH mechanism may set in for $n > 3-4$. In the context of mechanistic issues of bridge specificity for TIH via $(A)_n$ bridges in $(T-A)_n$ duplexes ($n \gtrsim 4$), we have to consider both intrastrand and interstrand electronic coupling and hopping between nearest-neighbor A nucleobases. Quantum mechanical calculations of the electronic coupling matrix elements[22] reveal that the A$-$A couplings are unique in the sense that the intrastrand and interstrand couplings are about equal.[22] We infer that effective zigzagging,[11] that is, switching between A nucleobases in the two strands in long $(T-A)_n$ duplexes may occur, with the overall TIH via the $(A)_n$ bridge being nearly invariant with respect to the base ordering within the $(T-A)_n$ duplex. As every Watson$-$Crick pair contains either a G or an A nucleobase, a marked erosion of sequence specificity for hole transport via TIH in large $(A)_n$ chains is expected. Concerning the realization of an effective TIH mechanism for long $(A)_n$ bridges, the water reaction should be relatively slow. Relying on eq 19 we conclude that this situation will be realized for the energetic parameter $\Delta = 0.21$ eV (section III) for $k_d/k_m < 2 \times 10^{-4}$. The required value of the chemical reaction rate is rather low, being lower than the value of $k_d/k_m \cong 10^{-3}$ deduced from the analysis of Giese's data (at pH = 7). Raising the solution pH may change k_d,[26] rendering an effective TIH process through the long A bridge. In view of quantitative differences between the chemical yield data reported by Giese et al. under different experimental conditions,[8,26] and between the data of Giese[8,26] on one hand, and those of Barton,[5g-h] and of Schuster,[9c-f] on the other hand, there is a distinct possibility of chemical control of the reaction of G^+ with water, as well as of the modification of the energy gap Δ for TIH. We note two possible elements of chemical control which may enhance TIH via long ($n > 4$) $(A)_n$ bridges: (i) lowering the energy gap Δ by changing the solution composition, for example, the ionic strength; (ii) decreasing the reaction rate k_d of the parallel reaction with water by changing the solution composition, for example, the pH. The issue of the chemical control of TIH through long $(A)_n$ bridges by changing the solution composition is of considerable interest and should be subjected to experimental scrutiny.

The confrontation of our analysis of TIH via $(A)_n$ bridges with the experimental reality of hole transport in DNA duplexes in water[5-12,19,20] is now in order. In the long-range hole transport experiments of Schuster et al.[9] most of the duplexes studied involve a GG donor and acceptor separated by $G(T-A)_mG(T-A)_{m'}G(T-A)_{m''}$ bridges where $m, m', m'' \leq 4$, so that there are enough closely spaced G bases for superexchange mediation of the individual $G\cdots G$ hopping steps. An interesting exception is the effective transport through the (GG)AAATTGATTA(GG) segments,[9c-f] where the five-membered AAATT bridge is ineffective for superexchange and may be operative by TIH, provided that the chemical constraints are adequate. In the recent experiments of Barton et al.[5g,h] long-range hole transport through long adenine bridges in $G^+(A)_nG$ duplexes ($n = 4-10$) was reported, revealing that for these long adenine chains the superexchange mechanism is inapplicable, both quantitatively (i.e., the observation of high chemical yields at the distal site) and quantitatively (i.e., a weak $(A)_n$ bridge length dependence of the relative chemical yields).[5h] The shallow distance dependence of the guanines' oxidation ratio led Barton et al.[5h] to propose hole hopping through all the bases (in the duplex). The TIH process advanced and analyzed herein provides the mechanism for the long-range, weakly distance-dependent hole transport over long ($n \gtrsim 4$) adenine chains, in accord with the experimental observation and interpretation of Barton et al.[5h] The fingerprint of the TIH mechanism is the weak distance dependence of the hole-transport rates and of the relative chemical yields. The analysis of the TIH rates (section II) provides an algebraic diffusive type (n^{-2}) distance dependence of k_{TIH}. An analysis of the distal/proximal G^+ yields (ψ) in $G^+(A)_nG$ and $G^+(A)_nGGG$ duplexes (to be published elsewhere) results in a very weak distance dependence $\psi \propto n^{-\alpha}$ ($0 \leq \alpha \leq 1$). This predicted shallow distance dependence for TIH provides an overall picture, which is in qualitative agreement with the experimental results.[5h] Details of variations of ψ with sequence $(A)_n$ bridge and length were attributed[5h] to conformational dynamics,[5h,22,35] which may modify electronic couplings,[22] energy gaps,[12c,17,18] and nuclear Franck$-$Condon factors, and which deserve further theoretical and experimental explorations.

Another interesting distinct aspect of charge transport in DNA pertains to "one-dimensional" conductivity in the double helix. Measurements on small clusters of duplexes using tungsten tips[3h] and nanoelectrode assembly,[3i] as well as studies of conductivity in λ DNA,[38] fail to give consistent results. What is interesting in the context of our analysis of TIH is the possibility of thermally activated hole-hopping conductivity from G^+ to A_n chains, which will be characterized by an activation energy of $\Delta \simeq 0.25$ eV. This small energy gap is considerably lower than the valence-conduction HOMO$-$LUMO electronic band gap of 5$-$6 eV expected in proteins and in DNA.[38a,39] Recent experimental data on the temperature dependence of microwave electrodeless conductivity in DNA[38a] report an energy gap for hopping transport in λ-DNA in the range 0.30$-$0.33 eV, which is close to the $G^+ - A$ energy gap for TIH inferred by us. However, we still have to reserve judgment concerning the applicability of our theoretical framework for the interpretation of these conductivity experiments.

We made progress in the characterization of a new TIH long-range transport regime and in the specification of the conditions for its realization in real life, which calls for further experimental and theoretical work in this fascinating field.

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Note Added in Proof

After this paper was submitted for publication, Giese et al. [*Nature* **2001**, *142*, 318−320] studied hole shift in $G^+(T-A)_n$-GGG ($n = 1-16$) duplexes, providing compelling experimental evidence for the "transition" between the superexchange ($n = 1-3$) and the TIH ($n = 4$) mechanisms, which was theoretically modeled herein.

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Appendix A: Kinetic Schemes for the Superexchange and for the Sequential Mechanism

The kinetic matrix of the rate constants for the superexchange unistep process, eq 8a, is given by

$$\mathbf{K} = \begin{pmatrix} -(k_1 + k_d) & k_1 \\ k_1 & -(k_1 + k_d) \end{pmatrix} \qquad \text{(A1)}$$

The concentration of the two species a and b, represented by the vector

$$\mathbf{v} = \begin{pmatrix} \mathrm{a}(t) \\ \mathrm{b}(t) \end{pmatrix}$$

obeys the relation

$$\mathrm{d}v/\mathrm{d}t = \mathbf{K}v \qquad \text{(A2)}$$

with the initial condition $\mathrm{a}(t = 0) = 1$. The yields of the water reaction for the species a and c are given by

$$Y_\mathrm{a} = k_\mathrm{d}\int_0^\infty \mathrm{a}(t)\mathrm{d}t = k_\mathrm{d}[\int_0^\infty \exp\{\mathbf{K}t\}\ \mathrm{d}t]_{1,1} = k_d\mathbf{K}^{-1}_{1,1}$$

$$Y_\mathrm{c} = k_\mathrm{d}\int_0^\infty \mathrm{c}(t)\mathrm{d}t = k_\mathrm{d}[\int_0^\infty \exp\{\mathbf{K}t\}\mathrm{d}t]_{1,2} = k_\mathrm{d}\mathbf{K}^{-1}_{1,2} \qquad \text{(A3)}$$

From eq A3 we obtain by inversion the chemical yields Y_a and Y_c, eq 9.

The kinetic matrix for the sequential mechanism, eq 11a is given by

$$\mathbf{K} = \begin{pmatrix} -(k_+ + k_\mathrm{d}) & k_- & 0 \\ k_+ & -(2k_- + k_\mathrm{d}) & k_+ \\ 0 & k_- & -(k_+ + k_\mathrm{d}) \end{pmatrix} \qquad \text{(B2)}$$

We refer to the concentrations of three species, by a, b, and c, represented by the vector

$$\mathbf{w} = \begin{pmatrix} \mathrm{a}(t) \\ \mathrm{b}(t) \\ \mathrm{c}(t) \end{pmatrix}$$

which obeys the equation

$$\frac{\mathrm{d}w}{\mathrm{d}t} = \mathbf{K}w \qquad \text{(A5)}$$

with the initial condition $\mathrm{a}(t = 0) = 1$.

The yields of the water reaction for the species a, b, and c are given by by eq A3 for Y_a and Y_c and by a similar equation for the yield Y_b for the species b,

$$Y_\mathrm{a} = \frac{k_+k_- + 2k_-k_\mathrm{d} + k_+k_\mathrm{d} + k_\mathrm{d}^2}{2k_+k_- + 2k_-k_\mathrm{d} + 2k_+k_\mathrm{d} + k_+^2 + k_\mathrm{d}^2} \qquad \text{(A6)}$$

$$Y_\mathrm{b} = \frac{k_+}{k_+ + 2k_- + k_\mathrm{d}} \qquad \text{(A7)}$$

$$Y_\mathrm{c} = \frac{k^2}{2k^2 + 2k_-k_\mathrm{d} + 2k_+k_\mathrm{d} + k_+^2 + {k_\mathrm{d}}^2} \qquad \text{(A8)}$$

The ratio $Y_\mathrm{c}/Y_\mathrm{a}$ between the yields of the terminal and the initial GGG groups is then obtained by eq 15. In this simplified scheme the ratio $Y_\mathrm{c}/Y_\mathrm{a}$ depends only on two parameters: $\xi = k_\mathrm{d}/k$ and the energy gap Δ.

Finally, we consider the kinetic treatment of the proximal and distal GGG triplets in duplex (I). The triple guanine 5′-$G_1G_2G_3$-3′ was treated as one entity. This is possible if fast equilibration between the three G radical cations prevails. Let us assume that the oxidation potentials of G_1 and G_2 are the same but that of G_3 is higher by the energy δ. This is in accord with quantum mechanical calculations[17] which show that the energies of the triplet G constituents in the 5′−3′ direction are 0.03−0.001 eV for G_1^+, 0 eV for G_2^+, and 0.13−0.27 eV for G_3^+. Assuming a thermal equilibrium between the three G and writing $[GGG^+]$ for the total concentration, we get for the concentration of G_3

$$[G_3^+] = \frac{\exp\left\{-\dfrac{\delta}{k_\mathrm{B}T}\right\}}{2 + \exp\left\{-\dfrac{\delta}{k_\mathrm{B}T}\right\}}[GGG^{\,+}] \qquad \text{(A9)}$$

The rate from G_3^+ to the intermediate is written as $k_\mathrm{p}[G_3^+]$ which, when written in terms of the total concentration, is

$$k_\mathrm{p}[G_3^+] = k_\mathrm{p}\frac{\exp\left\{-\dfrac{\delta}{k_\mathrm{B}T}\right\}}{2 + \exp\left\{-\dfrac{\delta}{k_\mathrm{B}T}\right\}}[GGG^{\,+}] = k_+[GGG^{\,+}] \qquad \text{(A10)}$$

The rate from the intermediate back to the triple (or, equivalently, to G_3^+) is $k_-[X^+]$. The ratio $k_\mathrm{p}/k_- = \exp\{-(\Delta - \delta)/k_\mathrm{B}T\}$, and therefore the ratio between the effective rate constants, is

$$\frac{k_+}{k_-} = \frac{\exp\left\{-\dfrac{\Delta}{k_\mathrm{B}T}\right\}}{2 + \exp\left\{-\dfrac{\delta}{k_\mathrm{B}T}\right\}} \qquad \text{(A11)}$$

In the terminal $(GGG)^+$ the closest G^+ has the lowest energy (being on the 5′ side). Its concentration is $1/(2 + \exp\{-\delta/k_\mathrm{B}T\})$; therefore, also for the last part of the reaction scheme the effective rate constants ratio is the same as before in eq A11. In principle, all the details can be lumped together into an effective free energy gap. Of course, we have to assume that the electronic couplings are not affected by directional asymmetry effects.

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