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Efficient Charge Transport via DNA G-Quadruplexes

Arun K. Thazhathveetil, Michelle A. Harris, Ryan M. Young, Michael R. Wasielewski,* and Frederick D. Lewis*

Department of Chemistry and Argonne-Northwestern Solar Energy Research (ANSER) Center, Northwestern University, Evanston, Illinois 60208-3113, United States

Supporting Information

ABSTRACT: The dynamics and efficiency of photoinduced charge transport has been investigated in DNA capped hairpins possessing a stilbenedicarboxamide (Sa) hole donor and stilbenediether (Sd) hole acceptor separated by DNA G-quadruplex structures possessing 2- to-4 tetrads by means of femtosecond and nanosecond transient absorption spectroscopy with global analysis. The results for the quadruplex structures are compared with those for the corresponding duplex structures having G-C base pairs in place of the G-tetrads. Following photoinduced charge separation to form a contact radical ion pair, hole transport to form the $Sa^{-\bullet}/Sd^{+\bullet}$ charge-separated state is slower but more efficient for the quadruplex vs duplex structures. Thus, the G-quadruplex serves as an effective conduit for positive charge rather than as a hole trap when inserted into a duplex, as previously postulated.

The DNA G-quadruplex continues to attract attention both for its potential role in regulating DNA-based cellular processes[1] and as a potential building block for conductive devices.[2] The quadruplex can be constructed from two or more tetrads containing four guanines by parallel or antiparallel assembly of four independent strands, dimerization of two hairpins, intramolecular folding of oligomers possessing four or more G-rich regions, or some combination of these or other approaches.[3] G-Quadruplexes are notoriously polymorphic, often adopting more than one structure or incorporating bases other than G.[4] For example, a duplex containing two G_4 mismatch regions fails to form a quadruplex in the presence of Li^+ and forms two different quadruplex structures in the presence of added Na^+ or Sr^{2+}.[5] Recently, left and right handed structures have been reported for the same quadruplex-forming sequence.[6]

Measurement of charge transport through an intramolecular three-layer quadruplex using the break-junction technique found good conductivity.[7] However, no comparisons were made with duplex conductivity or with quadruplexes possessing different numbers of tetrads. Voltage-dependent measurements of current across G-quadruplexes (but not duplexes) as long as 100 nm deposited on mica have been reported.[8] There have been several studies of photoinduced charge transport in G-quadruplexes. Most of these have employed strand cleavage at guanine to probe guanine oxidation at sites remote from the locus of hole injection. Initial studies established that positive charge (holes) could move from duplex base pair domains into quadruplexes[5,9,10] or from one side of a quadruplex formed from a hairpin dimer to the other side.[11] These studies led to the conclusion that quadruplexes are more readily oxidized than G-tracts within duplex domains and thus served as hole traps for migrating charge. Sen and co-workers concluded that G-quadruplexes may protect duplex sites from oxidative damage by acting as a sink to draw holes away from duplex sites.[10] Majima and co-workers reached a similar conclusion based on their laser flash photolysis study of hole transport from singlet riboflavin covalently attached to one G-quadruplex forming sequence and a pulse radiolysis study of a second sequence.[12] The occurrence of electron (negative charge) transport in G-quadruplexes has also been reported.[13] The behavior of G-quadruplex excited states has also been subject to recent investigation.[14]

Whereas strand cleavage studies can provide a convenient method of establishing the occurrence of hole transport in DNA, they do not provide information about the dynamics and efficiency or distance-dependence of the transport process or allow for a direct comparison of hole transport in duplex and quadruplex structures. We report here the direct measurement of the dynamics and efficiency of hole transport in donor-bridge-acceptor systems having a stilbenedicarboxamide (Sa) singlet excited hole donor and stilbenediether (Sd) hole acceptor separated by bridges containing either G-C base pairs or G-tetrads (Chart 1, Sa and Sd omitted from structure names throughout text for sake of brevity).

A combination of femtosecond and nanosecond transient absorption spectroscopy (fsTA and nsTA, respectively) has been used to characterize the $Sa^{-\bullet}$ and $Sd^{+\bullet}$ radical ions and determine the quantum yield for charge separation and dynamics for hole injection, charge separation and charge recombination. G-Quadruplex bridges were modeled on intramolecular G-quadruplexes of known solution structures by replacement of oligonucleotide linkers with Sa and Sd linkers (Figure 1) and their structures confirmed by comparison of their circular dichroism (CD) spectra with those of the sequences possessing oligo linkers. Hole transport via G-quadruplex structures is found to be slower but more efficient than hole transport via duplexes having the same number of G-C base pairs vs tetrads. Furthermore, the rate constants for hole transport are found to increase as the number of tetrad layers in the G-quadruplex increases, counter to the normal distance dependence expected for hole transport in DNA.

We have previously employed Sa/Sd donor-bridge-acceptor systems to investigate hole transport dynamics in systems having

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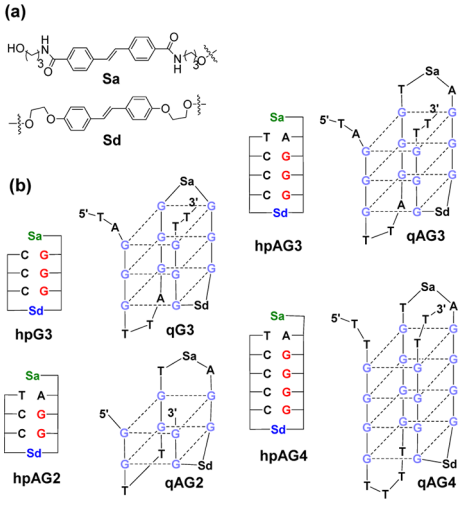
Chart 1. Structures of (a) Sa and Sd Hairpin and Quadruplex Linkers and Capping Groups and (b) Sa/Sd Hairpins and G-Quadruplexes



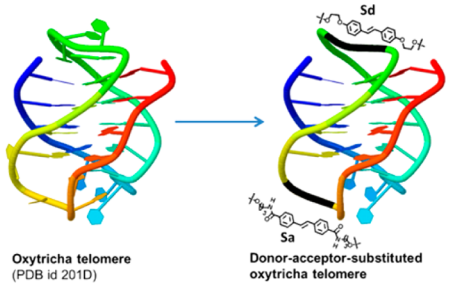


Figure 1. Intramolecular G-quadruplex (PDB id 201D) showing loop sequences in black replaced with stilbene acceptor and donor linkers.

duplex[15] and triplex bridges[16] and three-way junctions capped with stilbene chromophores.[17,18] The differences in ground state spectra and excited state and radical ion transient spectra make it possible to determine the kinetics and efficiency of hole transport from Sa* to Sd by means of a combination of fs- and nsTA spectroscopy. In view of the known tendency toward polymorphism on the part of G-quadruplex structures, we have based our bridge structures on the intramolecular sequences shown in Chart 1 and Chart S1 whose solution structures are related to structures that are well-characterized by NMR spectroscopy (as well as solid state X-ray crystallography).[19] The Sa and Sd chromophores are introduced by replacing the bases in the internal loop regions of the quadruplexes with the stilbene linkers shown in Chart 1a. A dinucleotide was also appended to the 5′G in some cases to discourage formation of intermolecular G-aggregates. The modified quadruplexes were synthesized, purified, and characterized as described in Supporting Information. The reference duplex systems shown in Chart 1 (with the exception of **hpAG$_4$**) have previously been synthesized[20] but were all resynthesized for this study.

The UV and CD spectra of the Sa/Sd **hpAG4**, **qAG4**, and the parent G-quadruplex are shown in Figure 2. The spectra of the other hairpins and quadruplexes are shown in Figure S1, Supporting Information. The UV spectra of the Sa/Sd hairpins and quadruplexes have maxima near 330 nm assigned to the stilbene chromophores, shoulders near 290 assigned to the G-quadruplex, and maxima near 260 nm assigned to the overlapping absorption of the nucleobases and stilbenes.

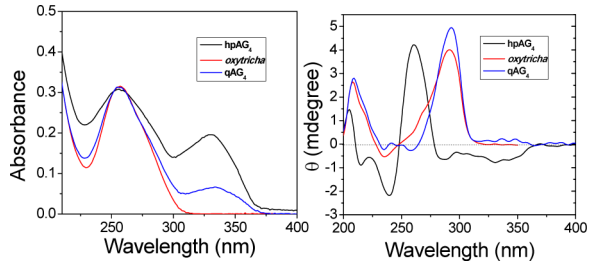


Figure 2. UV and circular dichroism spectra of **hpAG4**, **qAG4**, and *oxytricha telomere* sequence $(\mathbf{G_4T_4})_3\mathbf{G_4}$ in 10 mM potassium phosphate buffer (0.1 M KCl, pH ~ 7.2).

Thermal dissociation profiles for the Sa/Sd G-quadruplexes in 10 mM potassium phosphate buffer, pH ~ 7.2 (100 mM KCl) are shown in Figure S2. Quadruplex qAG2 displays a melting transition above 40 °C and the other quadruplexes are significantly more stable, in accord with their possession of three or four tetrads. The CD spectrum of **hpAG4** has maxima and minima at 265 and 240 nm characteristic of duplex DNA; whereas the spectrum of **qAG4** has maxima and minima at 280 and 265 nm, similar to those of the unmodified G-quadruplex.[21] The hairpin also has long-wavelength minima and maxima at 340 and 300 nm assigned to exciton coupling between the electronic transition dipoles of the two stilbenes which are positioned approximately coplanar with each other by the helical duplex scaffold.[22] The long-wavelength CD bands for the quadruplex are much weaker, presumably as a consequence of the non-co-planar alignment of the two stilbenes.[23]

The dynamics of charge separation and charge recombination were investigated by a combination of fsTA and nsTA using the methods previously described for our studies of Sa/Sd hairpins having AT base pair bridges and three-way junctions having Sa and Sd linkers and capping groups (see Supporting Information).[17,24] Typical transient absorption spectra are shown in Figure 3 for **hpAG4** and **qAG4** along with their normalized 575 and 535 nm single wavelength decays. fsTA and nsTA spectra for the other hairpins and quadruplexes in Chart 1 are shown in Supporting Information (Figures S3–S7). The excited state

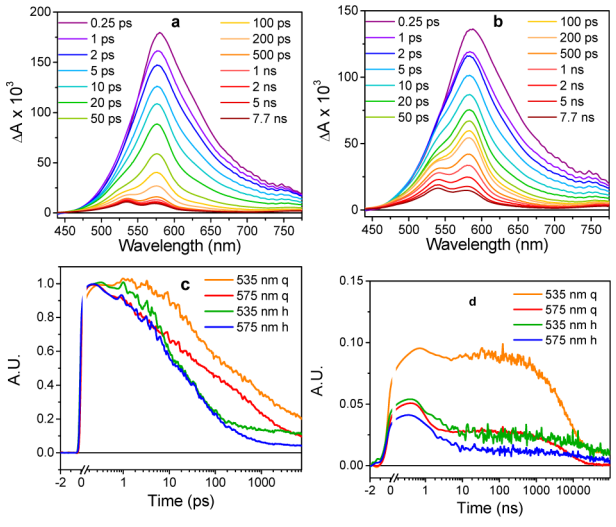


Figure 3. Transient absorption spectra of **hpAG3** (a) and **qAG3** (b) in 10 mM potassium phosphate buffer (0.1 M KCl, pH ~ 7.2) and ps (c) (normalized to maximum value of transient absorption) and ns (d) 575 and 535 nm single wavelength decays for **hpAG3** and **qAG3**.

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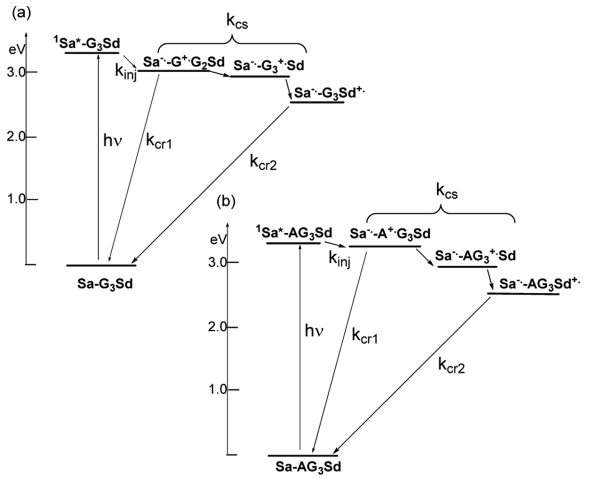
dynamics of **hpG3** and **qG3**, which possess a guanine base adjacent to Sa, are analyzed using the mechanism shown in Scheme 1a; whereas the other hairpins and quadruplexes, which possess an adenine base adjacent to Sa, are analyzed using the mechanism shown in Scheme 1b.

Scheme 1. Mechanism and Energetics for Charge Separation and Charge Recombination in Hairpin and Quadruplex Systems Having (a) G_3 Purine Sequences (hpG3 or qG3) and (b) AG_3 Purine Sequences (hpAG3 or qAG3) Separating the Sa Hole Donor and Sd Hole Acceptor



Following excitation of the Sa chromophore during the laser pulse, the initial step in the charge separation process is hole injection to the neighboring purine base, either G or A (k_{inj}, Scheme 1a,b). Hole injection is accompanied by reduction of ^{1}Sa* to Sa$^{-\bullet}$ and results in the formation of a shoulder on the blue edge of the ^{1}Sa* transient absorption spectrum. In the case of the hairpin **hpG3** and quadruplex **qG3**, this occurs within the first ps following the laser pump pulse. Values of k_{inj} are 1 order of magnitude slower for the **hpAGn** hairpins as previously observed for hairpins having a single A preceding a G-tract.[20] Values of k_{inj} are somewhat faster for the corresponding quadruplexes, consistent with a lower oxidation potential for a G-quadruplex than for a G-tract.[12]

Following hole injection, hole transport to Sd and trapping as Sd$^{+\bullet}$ complete the charge separation process (k_{cs}, Scheme 1). Charge recombination (k_{cr1}) from the oxidized duplex or quadruplex to Sa$^{-\bullet}$ prior to hole trapping by Sd competes with hole transport, reducing the efficiency of charge separation (Φ_{cs}). Values of k_{cr1}, where available,[25] are reported in Table 1. In the case of **hpAG4** and **qAG4**, the values of k_{cr1} are similar. The charge separation process is considered to be complete when the transient absorption band at 535 nm (attributed to the sum of the Sd$^{+\bullet}$ band and the Sa$^{-\bullet}$ shoulder) is larger than the 575 nm Sa$^{-\bullet}$ band. The values of k_{cs} can be determined either by means of global analysis (as reported in Table 1) or by plotting the ratio of the 525/575 nm band intensity ratio and determining its rise time.[20] Similar values are obtained by either method.

The values of k_{cs} obtained for the **hpAGn** hairpins by means of global analysis increase as the number of base pairs decreases, as previously observed.[20] However, the values of k_{cs} for the **qAGn** quadruplexes increase slightly as the number of tetrads increases. This unusual acceleration in hole transport may reflect changes in electronic coupling within the **qAGn** quadruplex as the number of stacked tetrads increases from two to four. Lech et al. have

Table 1. Dynamics and Efficiency of Charge Injection, Charge Separation, and Charge Recombination in Hairpin and Quadruplex Systems[a]

structure[b]	k_{inj} (ns^{-1})	k_{CR1} (ns^{-1})	k_{CS} (ns^{-1})	k_{CR2} (ms^{-1})[c]	Φ_{cs}[d]
hpG3	1200 ± 50	68 ± 0.7	4800	0.07	
qG3	1300 ± 100	44 ± 0.5	2.0 ± 0.2	4500	0.27
hpAG2	120 ± 9.0	11 ± 0.4	4600	0.21	
qAG2	400 ± 20	16 ± 0.3	0.70 ± 0.01	5400	0.28
hpAG3	120 ± 10	9.5 ± 1	210	0.18	
qAG3	330 ± 100	29 ± 10	0.90 ± 0.08	170	0.31
hpAG4	140 ± 50	22 ± 0.4	2.7 ± 0.03	150	0.14
qAG4	560 ± 100	27 ± 3	1.2 ± 0.09	67	0.26

[a]Kinetic parameters defined in Scheme 1. [b]See Chart 1 for hairpin and quadruplex structures. [c]See Scheme 1 for kinetics. [d]Errors ≤ 10%.

estimated rate constants for hole transport between adjacent stacked G-tetrads k_{cs} using a combined quantum mechanics, molecular dynamics approach.[26] Their estimated values for antiparallel G-quadruplex stacking are ca. 100 ± 50 ns^{-1}, depending on the stacking geometry, appreciably slower than our charge separation rate constants (Table 1). They estimated even slower rates for parallel quadruplexes. It is possible that photoinitiated hole transport in our antiparallel G-quadruplex structures occurs via a conduction channel[27] that is delocalized over both stacked and adjacent guanines, rather than a hopping mechanism involving only stacked guanines,[26] thus accounting for the fast charge separation rate constants.

Quantum yields of charge separation (Φ_{cs}) for the hairpin and quadruplex structures in Chart 1 obtained as described in Supporting Information are reported in Table 1. The values for the quadruplexes are consistently larger than those for the hairpins having the same purine sequence between Sa and Sd. This difference is most pronounced for the G3 purine sequence for which inefficient hairpin hole transport has been attributed to fast charge recombination of the Sa$^{-\bullet}$G$_3^{+\bullet}$ radical ion pair.[20] Plausibly, charge delocalization in the G-quadruplex of **qG3** is sufficiently rapid to compete with charge recombination. Charge recombination for Sa$^{-\bullet}$A$^{+\bullet}$ is slower than for the Sa$^{-\bullet}$G$^{+\bullet}$ contact radical ion pair in DNA hairpins as a consequence of the larger energy gap for charge recombination (k_{cr1}, Scheme 1).[20] Thus, the presence of an AT base pair between Sa and the GC base pairs in the **hpAGn** vs **qAGn** structures serves to attenuate the difference in Φ_{cs} for these structures. Still, rather than serving as a sink, it is clear that the G-quadruplex serves as a conduit for more efficient transport of charge than does the GC duplex. Efficient hole trapping presumably requires the presence of a hole trap, in this case Sd, with a oxidation potential less positive than that the G-quadruplex, adjacent to the quadruplex. Endergonic hole transport from a G-quadruplex to a duplex base-pair domain has been reported;[10] however, its efficiency remains to be investigated.

Following charge separation, the Sa$^{-\bullet}$/Sd$^{+\bullet}$ charge-separated states undergo charge recombination to the ground state with a rate constant k_{cr2} (Scheme 1). The values of k_{cr2} are similar for the shorter hairpins and quadruplex but diverge as the bridges become longer, the quadruplexes having somewhat slower rate constants than the hairpins. This may reflect differences in the orientation of the Sa/Sd chromophores in the duplex vs quadruplex structures as reflected in their CD spectra (Figures 2 and S1). Unlike charge separation, which occurs via a multistep mechanism (Scheme 1), charge recombination may occur via a

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single step tunneling mechanism that is dependent upon the electronic coupling between the hole donor and acceptor.[28] Lacking precise structural information about the orientation of the hairpin linkers with respect to the quadruplex core, we hesitate to speculate further about the factors that may influence charge recombination dynamics in these donor-bridge-acceptor systems.

In summary, the dynamics and efficiency of photoinduced charge separation has been investigated in four Sa/Sd donor-bridge-acceptor systems possessing G-quadruplex bridges by means of fsTA and nsTA spectroscopy and the results compared with those for systems with duplex bridges (Chart 1). Charge separation times for the quadruplex systems are slower than those for the duplex systems with similar numbers of tetrads vs base pairs separating Sa and Sd by factors ranging from 2.4 to 34. However, the efficiency of charge separation is larger for the quadruplex systems in all cases by factors ranging from 1.3 to 2.8. Efficient charge transport is consistent with previous results obtained by means of conductance measurements using break junctions and long G-quadruplexes deposited on mica.[7,8] The slower rates but higher efficiencies suggest that the quadruplex can act as an effective reservoir for holes, delaying charge recombination with $Sa^{-\bullet}$ until hole trapping by Sd occurs (Scheme 1).

Having established that G-quadruplex structures containing 2−4 tetrads can be used to transport holes with moderate efficiency, it remains a significant challenge to design prototype quadruplex-based devices for molecular electronics that have either two inputs and one output (combiners) or one input and two outputs (splitters). The use of intramolecular systems similar to the ones used in this study (Chart 1) having three or more chromophores that can be addressed individually would present a significant synthetic challenge. However, the construction of quadruplexes from the assembly of two hairpins or four single strands also has potential problems including the control of quadruplex polarity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b10265.

Materials and methods section including mass spectral data, UV and CD spectra, and additional ps and ns transient absorption spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*m-wasielewski@northwestern.edu

*fdl@northwestern.edu

ORCID

Michael R. Wasielewski: 0000-0003-2920-5440

Frederick D. Lewis: 0000-0002-3669-2796

Notes

The authors declare no competing financial interest.

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