Communication

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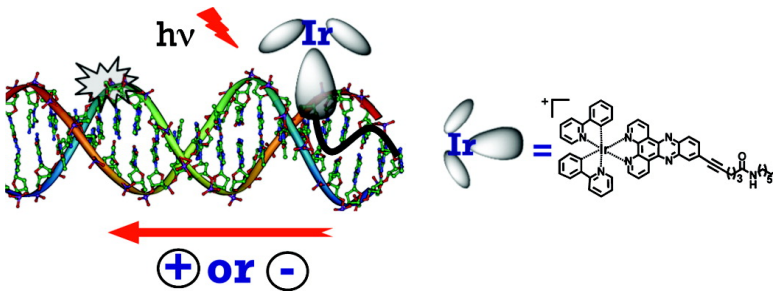

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Charge Migration along the DNA Duplex: Hole versus Electron Transport

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DNA-mediated charge transport (CT) to promote oxidative or reductive chemistry from a distance is currently of great interest.[1] This process has been characterized through many experiments, from time-resolved spectroscopic measurements[2] to biochemical assays.[3] For DNA-mediated CT, the nature of the charge donor and acceptor, their coupling to the base stack and energetics, as well as the integrity of the intervening base stack have been found to be critical.[4] As a result, DNA-mediated CT provides a means to detect perturbations in base pair stacking as arise with base mismatches, lesions, and protein binding.[5] In fact, this sensitivity in DNA CT to stacking has led to the proposal that DNA CT may play a role in detecting DNA damage within the cell.[6]

While oxidative DNA damage through DNA CT has been studied extensively, less attention has been devoted to studies of DNA reduction.[1,7] Recently, incorporating modified bases as kinetically fast electron traps in DNA assemblies with varied organic photoreductants has been advantageous in characterizing the reductive chemistry in solution.[7] A hopping mechanism involving pyrimidines, the bases considered easiest to reduce,[8] has been proposed.[7,9] DNA-mediated reductions have also been examined electrochemically, in ground state reactions on DNA-modified electrodes containing well-stacked redox probes.[5,10] These studies, like those of DNA-mediated photooxidations in solution, show that DNA electron transport occurs with a very shallow distance dependence and is sensitive to perturbations in base stacking as well as the coupling of the redox probe into the stack.

Here we compare directly the distance dependence of hole and electron migration through DNA using a tethered Ir intercalator that functions both as a photooxidant and reductant. Recently we have shown that bis(cyclometalated) complexes of Ir(III), tethered to DNA through a functionalized dipyrido[3,2-a:2,3-c]phenazine (dppz), can trigger both photooxidative and photoreductive damage in DNA from a distance.[11] Thus, in these oxidative and reductive reactions, coupling of the hole and electron donor with DNA is conserved. These photoredox processes have been characterized through spectroscopic and photolysis measurements using cyclopropylamine-substituted bases as electron and hole traps. Indeed, these traps report transient hole or electron occupancy very efficiently owing to their fast ring opening reactions (10^{-11} s)[12] upon one electron oxidation or reduction.[13]

To monitor hole transport, we designed a series of Ir−DNA conjugates containing a cyclopropylamine-substituted adenine (N^6-cyclopropyladenine; ^{CP}A) incorporated at different positions in the purine stack of a nine AT base pair tract (Figure 1, series **1**). For electron transport, we prepared two sets of assemblies. Series **2** resembles series **1** but with a modified pyrimidine as a reductive trap, while series **3** also contains the reductive trap but has the A-tract and T-tract flipped. For all assemblies the duplex terminus is similarly functionalized with Ir as well as an identical 4-base sequence for Ir intercalation.[14,15] Although ^{CP}C (N^4-cyclopropylcytosine) had been previously used to report on DNA electron transport,[11,16] here we use 5-bromouridine (^{Br}U) incorporated either

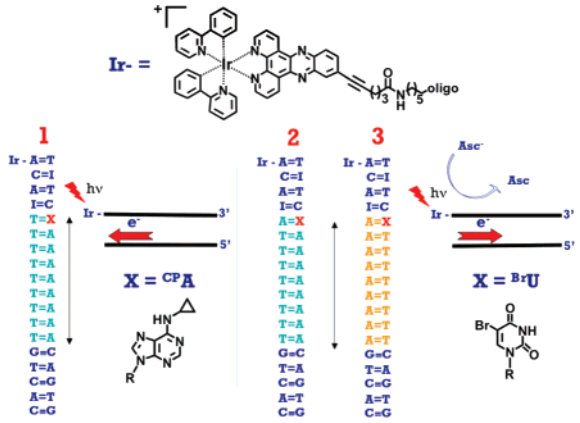

Figure 1. Schematic illustration of the different 18-mer Ir-DNA conjugates used for the distance dependence study of hole transport (**1**) and electron transport (**2** and **3**).

in the purine (series **2**) or the pyrimidine stack (series **3**). ^{CP}C is known to undergo a ring-opening reaction upon both oxidation and reduction, whereas ^{Br}U decomposes exclusively with one-electron reduction (10^{-9} s).[17] Also, since the excited state of the Ir(III) complex in water ($\tau < 10$ ns) is not sufficiently energetic or long-lived to photoreduce ^{Br}U efficiently,[11] for electron transport studies, we used the flash−quench technique[18] with sodium ascorbate as an external reducing agent to generate a ground-state reductant upon photolysis of the complex.[19] After irradiation and subsequent digestion of each Ir−DNA conjugate by phosphodiesterase I and alkaline phosphatase, the relative percentage of decomposed ^{Br}U or ^{CP}A resulting from the reduction or oxidation process was obtained by HPLC analysis.[20]

For each series of DNA conjugates, the efficiency of base decomposition, Y, as a function of distance intervening between the intercalated Ir and the modified base in the A tract is shown (Figure 2). Significantly, both hole and electron transport display a shallow dependence on distance. The inherent resistivity of a sequence can be gauged using the parameter β, representing the exponential decay in yield with distance. Here, hole transport is characterized by a β value of 0.05 Å^{-1} and electron transport, a β value of 0.10−0.12 Å^{-1}.[21] These results are comparable both to studies of hole transport across A tracts and to studies of electron transport.[22] However, our Ir-DNA conjugates allow a direct comparison of these processes triggered by the same injector with identical coupling to the base stack within equivalent sequences. Electron transport is found to proceed similarly to hole migration.[23]

Perturbations in the intervening base stack also lead to significant changes in decomposition efficiency. Figure 3 depicts efficiencies of decomposition for different assemblies with an intervening mismatched base pair (AC) or an abasic site (A-Ab) at the beginning of the AT tract. Both for the abasic and mismatched base pair, a significant attenuation is evident, and, strikingly, it is the same for hole and electron transport. Thus, the attenuation must not be a function of varying redox potential within the DNA bridge

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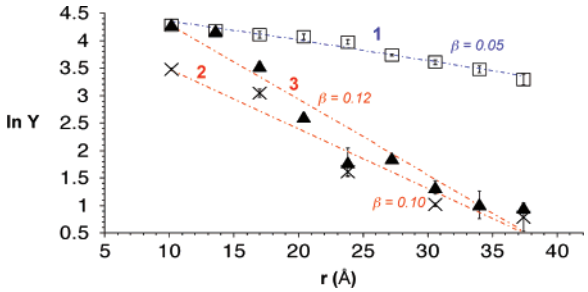

Figure 2. Percent decomposition, *Y*, of ^{CP}A (hole transport; squares, series **1**, blue line) and ^{Br}U (electron transport; crosses, series **2**, and triangles, series **3**, red lines) as a function of *r* (in Å), where *r* is the distance between the intercalation site of the Ir(III) complex[14] and the modified base. Experimental conditions: $\lambda_{irr} = 365$ nm (Hg−Xe lamp, 1000 W), irradiation time = 30 min, [DNA−Ir] = 10 μM, 50 mM TRIS−HCl pH = 7.0. For ^{Br}U strands, [Na ascorbate] = 200 mM. Error bars are also given.

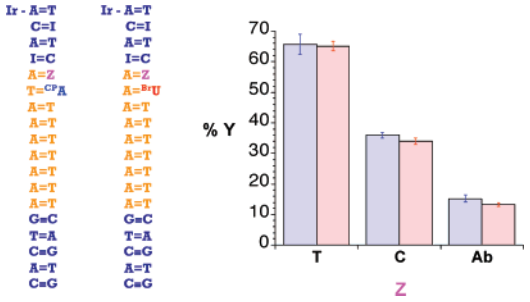

Figure 3. Percent decomposition, *Y*, for a ^{CP}A (blue) or ^{Br}U (red) in position 2 upon modification of the sequence. The experimental conditions are the same as described in Figure 2.

associated with the substitution, but, instead, the result of perturbations in the base pair stack. This sensitivity to base stacking has been extensively studied for hole transport and, on the basis of this result, appears to be a characteristic of electron transport as well. Hence, DNA CT appears to be a general reporter of sequence-dependent structure and dynamics, irrespective of the oxidative or reductive probe.

From these studies of DNA-mediated CT with a combined hole and electron donor, we are therefore able to compare the efficiency of the hole and electron migration process within the same assembly and establish that both processes share similar characteristics. Both show a remarkably shallow distance dependence in their reactions as well as equal sensitivity to the stacking of the intervening DNA bridge.

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(13) Because ring-opening is rapid, competition with recombination can also be eliminated, increasing the overall efficiency of the reaction.

(14) On the basis of modeling, melting temperatures, and hypochromicity, we assume the Ir complex intercalates two bases in from the terminus.

(15) DNA strands with tethered Ir or with ^{CP}A were synthesized as described.[11] Strands containing ^{Br}U were prepared using standard phosphoramidite chemistry with 5-bromouridine at the target site.

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(20) The % base decomposition (*Y*), i.e., the amount of decomposed ^{CP}A or ^{Br}U, was determined by subtracting the ratio of the area under the peak of the undecomposed base in an irradiated sample over that in a non-irradiated sample from one, with adenine or inosine as an internal HPLC standard. Irradiations were repeated three times and the results averaged.

(21) It should also be noted that, for short distances, the efficiency of CT for series **2** is lower than for series **3**, which may reflect the difference in redox potential of the two strands for electron migration.

(22) For hole transport, with naphthaldiimide as donor and phenothiazine as acceptor, $\beta = 0.08$ Å^{-1} [2b]; with Rh(III) as donor and ^{CP}A as acceptor, $\beta = 0.001$ Å^{-1}, see: Augustyn, K. E.; Genereux, J. C.; Barton, J. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 5731. For electron migration from a reduced flavin to a thymine dimer, $\beta = 0.11$ Å^{-1}, see: Behrens, C.; Burgdorf, L. T.; Schwögler, A.; Carell, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1763.

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