CHAPTER 1

Charge Transport in DNA

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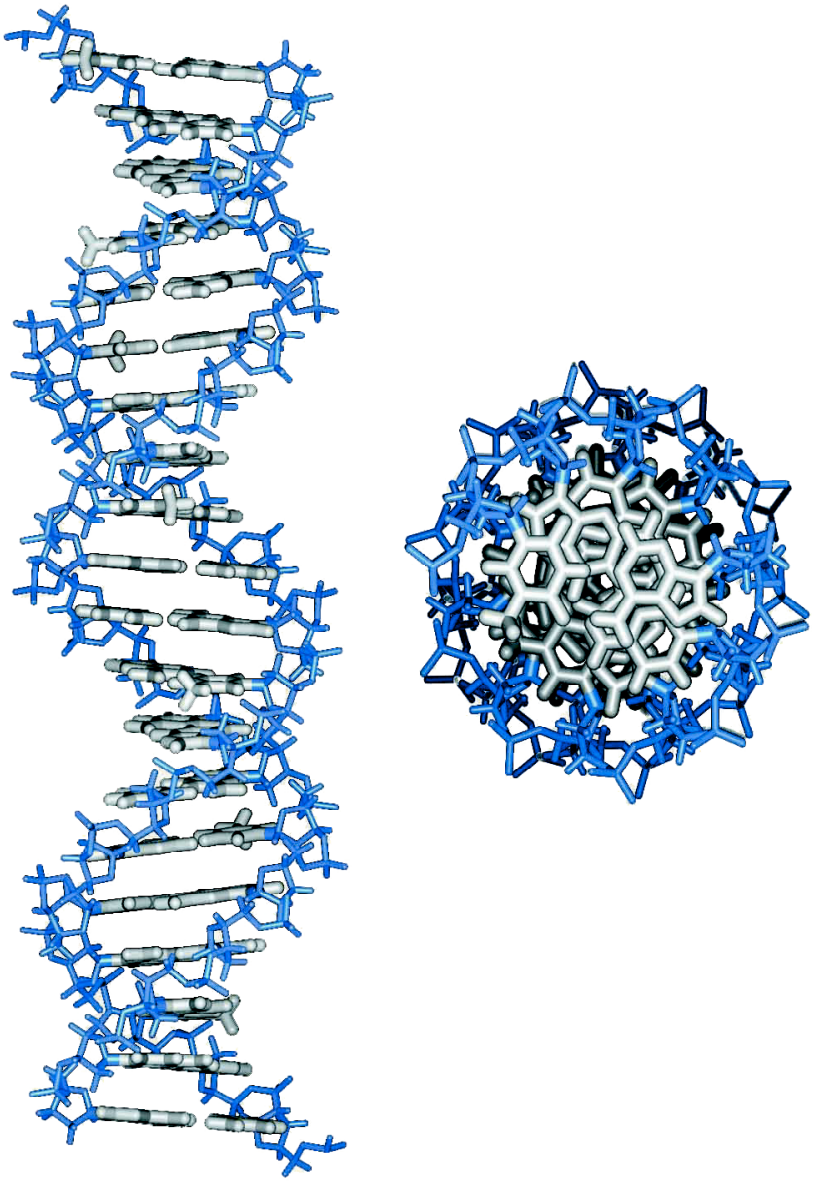
INTRODUCTION

Using a full range of physical and biochemical methods, studies have now established double helical DNA (Figure 1.1) as a medium for the efficient transport of electrons and electron holes. As a result, the focus of the field has shifted from asking whether DNA can mediate long range charge transport (CT) to questioning how it works. How do DNA structure and sequence affect this reaction, and is DNA-mediated charge transport physiologically important? Recent experiments in which charge transport through the π-stacked DNA base pairs has been demonstrated, and through which critical parameters have been established, are discussed here. These experiments have underscored not only that the DNA base pair stack can mediate hole and electron transport chemistry, but also the exquisite sensitivity of DNA charge transport through the π-stack to DNA structure and dynamics.

EXPERIMENTAL APPROACHES TO STUDYING DNA-MEDIATED CHARGE TRANSPORT

A variety of experimental approaches to probe DNA charge transport have been utilized. The earliest studies involved physical measurements of current flow in DNA fibers and these studies led to a mixture of conclusions, some suggesting high electron mobility through DNA, others indicating no conductivity (1,2). Electron conductivity was clearly demonstrated in recent experiments on aligned DNA films, and this conductivity was found only

Figure 1.1. Structure of the DNA double helix. The sugar phosphate backbone is shown in blue and the heterocyclic, aromatic base pairs are shown in gray. The base pairs of DNA are stacked parallel to one another with significant overlap of their π-orbitals down the helical axis. This π-stack is the path of DNA-mediated charge transport.



along the direction parallel to the helical axis (3). Sophisticated methods have also recently been used by physicists to examine electrical transport in single molecules or small collections of molecules at low temperatures (4,5). Here DNA was found to have the characteristics of a semiconductor, but whether wide gap or narrow gap also varied with the experiment. In fact, one experiment even pointed to DNA as a superconductor (6). These physical studies have not yet been reconciled one with another. Likely the variations seen depend heavily upon the connections between DNA and electrodes used as well as upon the integrity of the DNA itself in the absence of water and exposed to very high voltages.

Chemists have instead focused primarily on photochemical and photophysical studies of well defined oligonucleotide assemblies in solution. Assemblies were first prepared containing pendant donors and acceptors, and electron transfer was measured through fluorescence quenching as a function of distance (7-10). These studies also yielded a mixture of conclusions, and here, too, likely the variation depends upon the connections, or coupling, of donor and acceptor into the base pair stack. Effective quenching with a shallow distance dependence was seen with donors and acceptors that were well coupled with the base pair stack through intercalation.

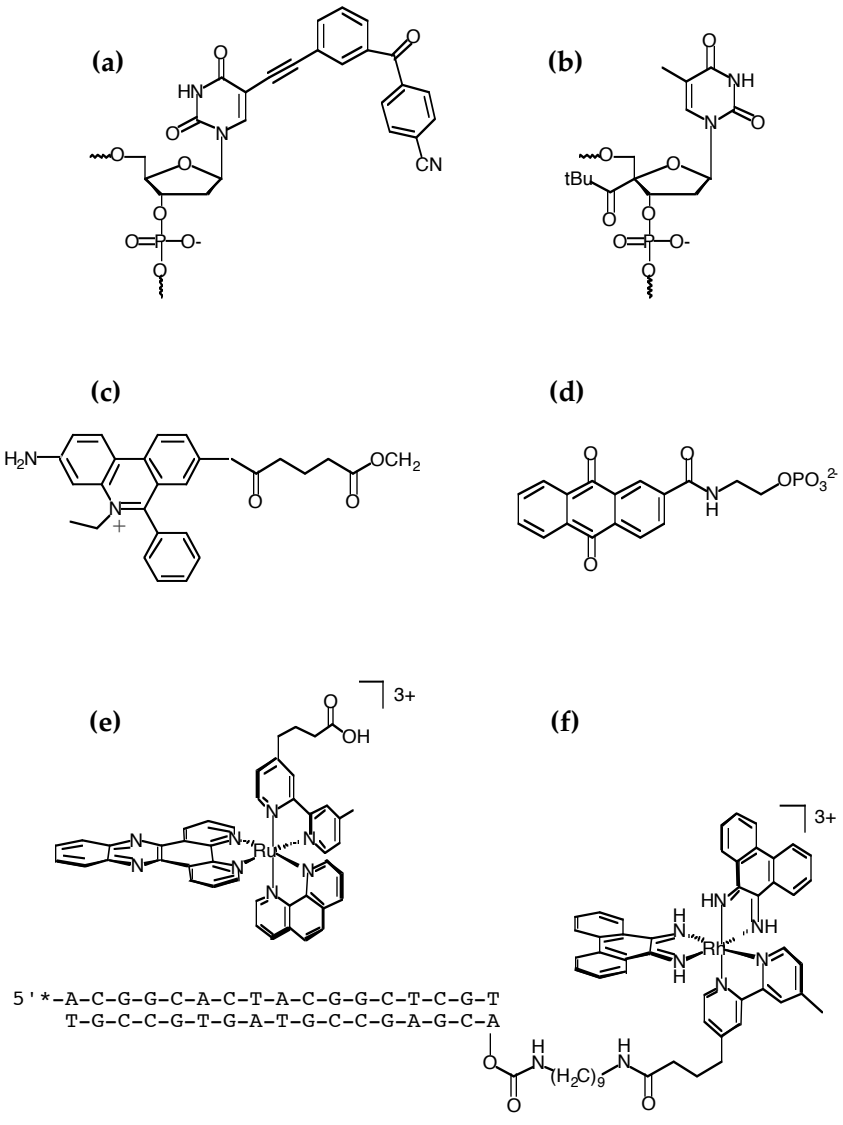
Biochemical studies of DNA charge transport have perhaps been most fruitful, first in identifying that DNA charge transport can proceed over long molecular distances (~ 200 Å) (11,12) and also in raising the possibility that such transport may be a factor leading to DNA damage within the cell (13).

In these studies, photooxidants are appended to a DNA duplex at a given site spatially separated from guanine doublet or triplet sites, the targets for oxidative damage; the yield of oxidative damage can then be analyzed as strand breaks using gel electrophoresis. Some examples of the different photooxidants utilized (12,14-18) are given in Figure 1.2. Also shown is the first assembly in which oxidative damage to DNA was demonstrated (14). Using the pendant rhodium intercalator as photooxidant, damage was observed at the guanine doublet sites 17 Å and 34 Å away from the site of rhodium intercalation. These studies laid the foundation for much of the work that followed, in which variations in distance, sequence, and structure were explored, and through which mechanistic proposals were tested.

MECHANISTIC CONSIDERATIONS

Two theories have been described to explain the mechanism by which charge is transported from donor to acceptor through DNA duplexes. These theories are superexchange, or tunneling, through the DNA bridge between the bound donor and acceptor, and charge hopping between discrete base orbitals (Figure 1.3). Tunneling mechanisms predict that the rate of the charge transport will decrease exponentially with distance between donor and acceptor, while in an incoherent hopping mechanism, the distance dependence is expected to be much more shallow (19,20). Experimentally, rates of electron transfer were measured over short distances with a range of

Figure 1.2. Chemical structures of some of the photooxidants that have been used in DNA charge transport studies: (a) cyanobenzene-modified deoxyuridine (17); (b) 4′-pivaloyl-modified deoxythymine (18); (c) ethidium′ (16); (d) modified anthraquinone (46); (e) $Ru(phen)(bpy')(dppz)^{3+}$ (15). Also shown (f) is a typical assembly used to promote long range guanine oxidation in our laboratory using $Rh(phi_2)(bpy')^{3+}$ (14). This is the first assembly in which oxidative damage to guanine bases was observed using an appended photooxidant.



distance dependencies observed (21-26); recent data have pointed generally to an intermediate distance dependence through DNA, more shallow than for proteins, but not sufficient for "wire"-like behavior over long range. Biochemical measurements of yields of oxidative damage have also been used indirectly to assign relative rates, and these studies have prompted most mechanistic proposals concerning long range charge transport (27).

Based upon these seemingly contradictory data, theoretical proposals have sought to combine tunneling and hopping regimes in efforts to describe charge transport over various distance and energetic constraints (28,29). One interesting proposal focused on the sequence dependence of DNA charge transport (30). It was proposed that charge transport occurs by hopping between guanine bases and tunneling through intervening TA steps. Giese, Jortner, and coworkers had observed that yields of guanine oxidation decrease dramatically with increasing separation between guanine "stepping stones" by TA steps. However 5'-TA-3' steps tend to be more flexible, and this flexibility, in decreasing coupling within the base stack, could also account for the results.

To test the notion that tunneling, rather than hopping, occurred on AT tracts, Williams et al. systematically varied the length of TT, AA, and AT intervening segments in biochemical measurements of long range oxidative damage (31). Guanine oxidation was observed over separations of up to 10 TA steps with no loss of yield over that distance, and, in fact, the introduction of a GC base pair within a long TA stretch decreased the oxidative damage yield. Thus, a simple guanine hopping model was not sufficient to describe charge transport through long sequences of DNA.

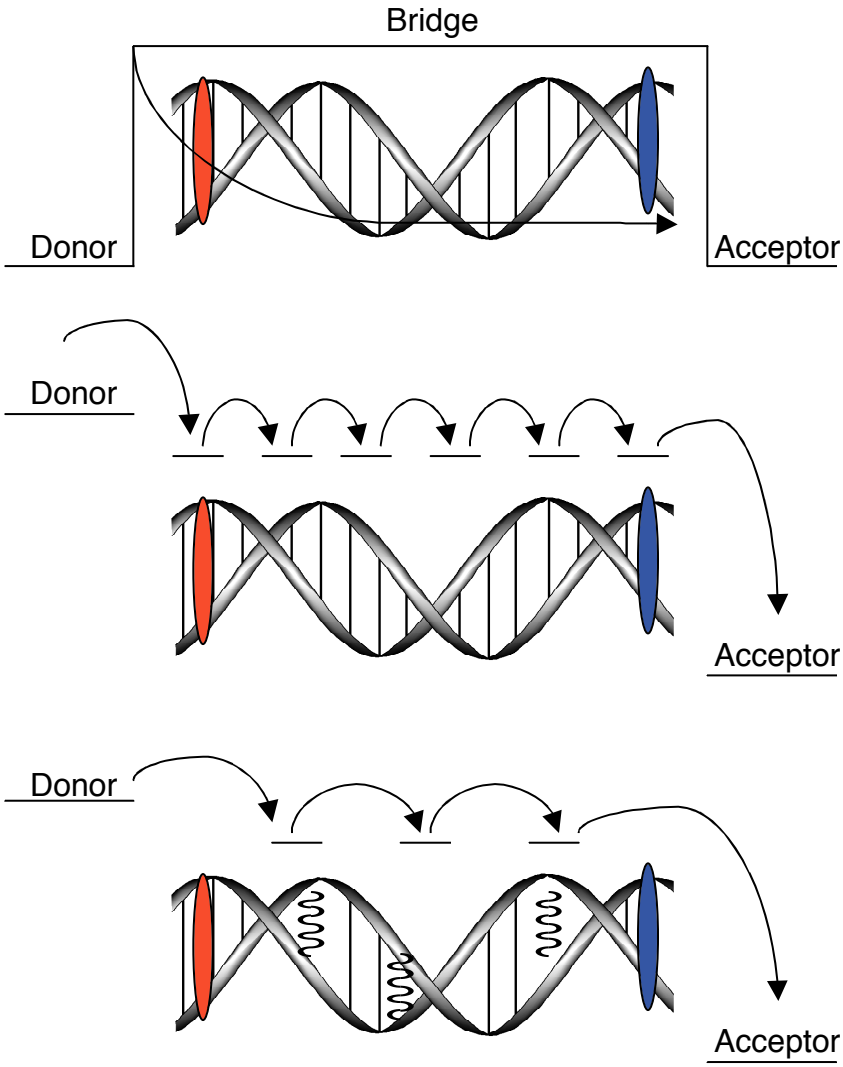
More experiments were carried out particularly to reconcile the variations in observations for long versus short range charge transport. Experiments in which the radical cation was formed first on the sugar, followed by hole transport to a neighboring guanine, showed that the yield of guanine oxidation decreased steeply only if guanines stepping stones were separated by less than three TA steps; if more bridging base pairs were present, oxidation yields exhibited a far more shallow distance dependence (32). This change in damage yield was attributed to a shift in mechanism from superexchange at short distances (less than three base pairs) to a mechanism mediated by thermally induced hopping of charge between adenine bases at long distances.

Schuster and coworkers have proposed phonon-assisted polaron hopping between guanine residues (33) as a mechanism for charge migration in DNA, also based on measurements of oxidative damage yields. In this model, upon hole injection a transient polaron is formed, and the sequence dependent conformational dynamics of DNA are expected to aid in charge transport of this polaron; charge is then transported along the DNA by polaron hopping assisted by phonons. Polaron formation and propagation are expected to be sensitively modulated by the changing counter ion distribution (34). In a different study, charge transport was seen to be quite sensitive to the placement of static charges, e.g., the introduction of phosphate termini on the 3′- or 5′-end of the oligomer (35). From these experiments, a high longitudinal polarizability for DNA was inferred, another characteristic that could enhance charge transport within the DNA interior (36).

The critical importance of DNA dynamics was underscored by ultrafast spectroscopy experiments (24) using tethered ethidium as the photoexcited DNA oxidant and 7-deazaguanine (Z) as the electron donor. Charge transport in these assemblies, which was observed with femtosecond resolution, was independent of ethidium and Z separation, but the kinetics of the process had two time constants, a 5 ps and a 75 ps component. These components were assigned, respectively, as the inherent rate of charge transport, and the motional time of the ethidium intercalator within its binding site to align for an orientation allowing charge transport. These data suggest that dynamical motions within the base pair assembly gate DNA-mediated charge transport. These data also suggested that hole injection into the DNA bridge was rate determining, which indicates that the DNA orbitals between the electron donor and acceptor participate in the reaction directly, not merely as a virtual bridge as would be expected with superexchange.

Based on these and other results that reflect the high sensitivity of the reaction to sequence dependent conformation, Barton and coworkers have proposed that charge transport over long molecular distances might best be considered as *domain* hopping (11,31) (Figure 1.3). Charge is transiently delocalized over domains depending upon their sequence and dynamical motions. Charge hopping and propagation are gated by sequence dependent DNA flexibility, allowing charge transport from one delocalized domain to the next.

Figure 1.3. Schematic representations of several possible mechanisms for charge transport through DNA. (a) Superexchange: charge tunnels form the donor to the acceptor through the bridge in a nonadiabatic process. An exponential decrease in rate with increasing length of bridge is predicted. (b) Hopping: charge occupies the bridge in traveling from donor to acceptor by hopping between discrete molecular orbitals on the bridge. If the rate of charge migration is faster than trapping, the charge should be able to migrate over long distances before getting trapped. (c) Domain Hopping: charge occupies the bridge by delocalizing over several bases, or a domain. This domain hops along the bridge to travel from donor to acceptor. As in a pure hopping mechanism, the charge should be able to travel long distances before getting trapped.



SENSITIVITY TO DYNAMICAL STRUCTURE

Irrespective of the mechanisms used to describe the process, it has become apparent that these reactions are extremely sensitive to DNA base pair stacking (7,8,12,23,37-48). Indeed charge transport studies may be able to provide a measure of the sequence dependent conformational dynamics in DNA. The details of how the electron donor and acceptor bind to DNA, as well as the DNA base sequence, conformational dynamics, and local flexibility all contribute to coupling within the base pair π-stacked array, and therefore to the efficiency of the DNA-mediated charge transport reaction.

The importance of the stacking of the electron donor and acceptor within the DNA base stack was highlighted in experiments measuring base-base electron transfer (37). Charge transport between guanine and modified fluorescent adenine derivatives was measured in fluorescence quenching studies on DNA duplexes. Depending on how well the unnatural adenine base was stacked within the DNA duplex, the DNA helices displayed charge transport efficiencies ranging from insulating to "wire"-like. Base-base electron transfer also established that in B-DNA duplexes the rate of intrastrand electron transfer is ~100 times faster than interstrand transfer. The preference for intrastrand transfer is understandable based upon the structural constraint of intrastrand but not interstrand base stacking in B-DNA.

Biochemical experiments have also underscored the remarkable sensitivity of DNA-mediated charge transport to the stacking of the base

pairs intervening between the donor and acceptor (7,8,12,23,37-42). Base bulges (38), flexible sequences (11,31), and protein-induced distortions (40,41) all greatly influence the efficacy of long range DNA-mediated electron transfer. Some illustrations of the distortions examined are illustrated in Figure 1.4. Long range oxidative damage has also been examined in DNA/RNA hybrids (42,43), DNA triplexes (44,45), and in multiple stranded assemblies (39).

Mismatches are generally stacked in a DNA duplex but undergo greater dynamical motion than Watson-Crick paired bases (49-51). DNA charge transport was also found to be very sensitive to these motions (Figure 1.5). For example, a single CA mismatch inserted into a DNA duplex between a covalently attached photoinduced electron donor (ethidium) and a covalently attached intercalating acceptor ($Rh(phi)_2bpy'^{3+}$), significantly inhibits electron transfer based on the results of fluorescence quenching experiments (8). The ability of DNA duplexes to support charge transport through base mismatches was then systematically examined in assemblies using guanine oxidation ratios as a measurement of charge transport efficiency (52). These results indicated that charge transport through a mismatch site is closely correlated to the base pair lifetime of that mismatch, as measured by ^1H NMR imino proton exchange rates. These results again implicate base dynamics in modulating long range charge transport through DNA.

Many proteins, in binding to the double helix, cause distortions in the base pair stack. Guanine oxidation ratios as measures of charge transport efficiency have also been used to probe DNA-protein interactions (40,41).

Figure 1.4. Schematic illustrations of some of the base stacking perturbations we have studied using guanine oxidation ratios: (a) base bulges, (b) protein induced distortions, and (c) single base mismatches. DNA-mediated charge transport chemistry is exquisitely sensitive to such stacking perturbations, and with a stacking perturbation intervening between two guanine doublets, the ratio of oxidation at the distal site versus proximal site is significantly diminished.

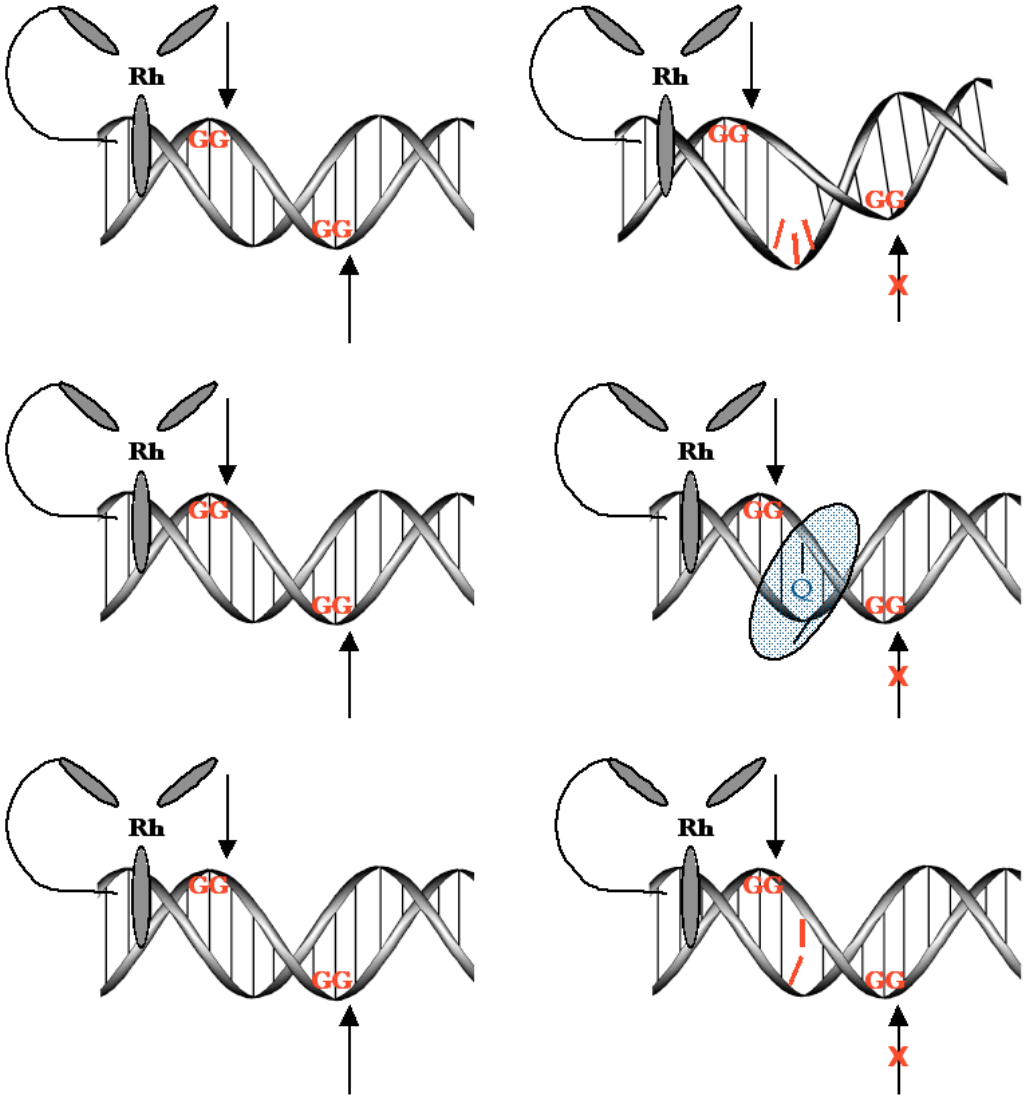
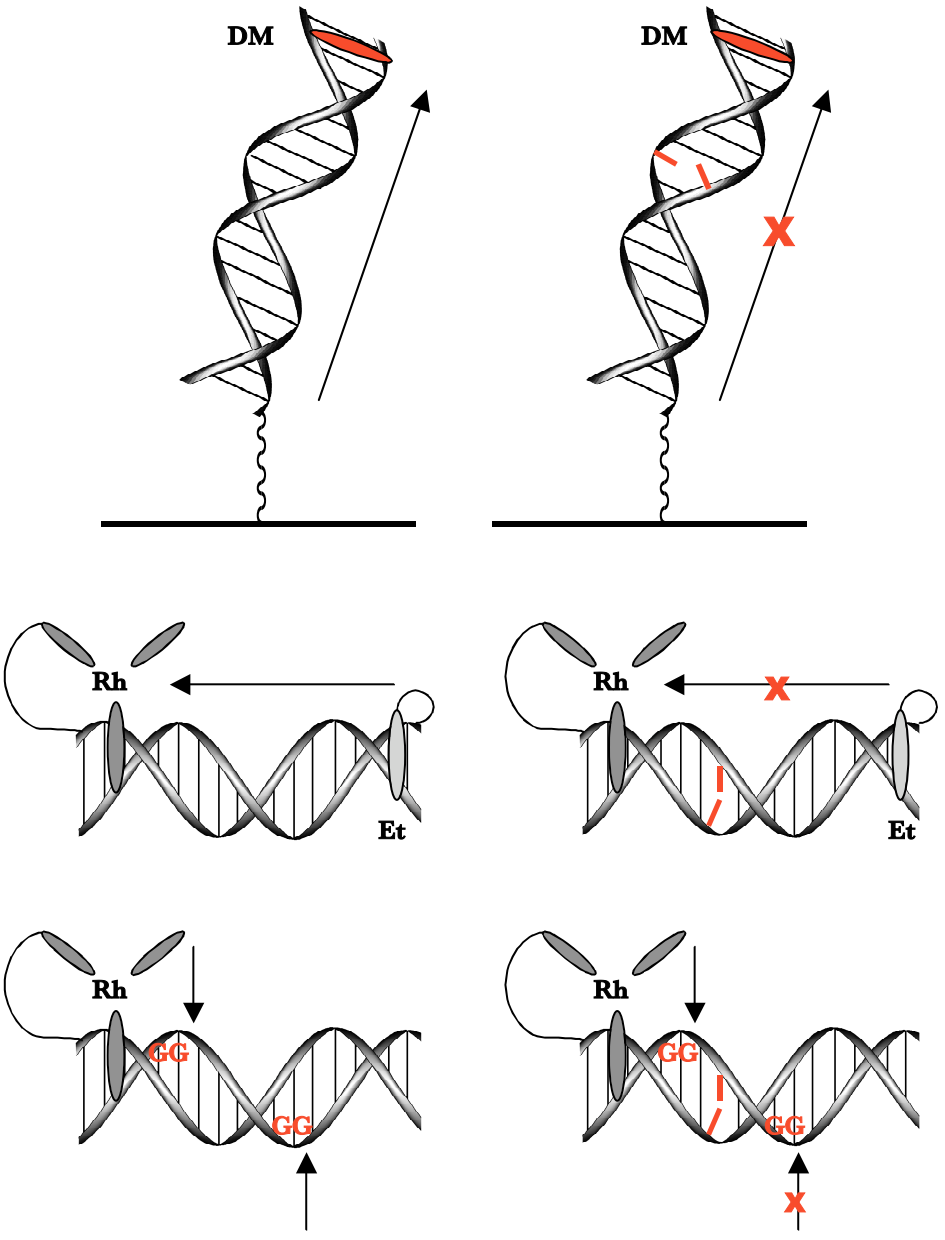


Figure 1.5. Schematic illustrations of different experiments for mismatch detection based on DNA charge transport. The diminution in efficiency of DNA-mediated charge transport chemistry upon introduction of a single mismatch into the intervening base stack can be detected using (a) electrochemistry through DNA films to an intercalator (DM = daunomycin), (b) fluorescence quenching, and (c) guanine oxidation yield. These results illustrate both that base stacking is a general principle that governs charge flow in DNA and how remarkably sensitive this chemistry is even to very small structural perturbations such as single base mismatches.



This methodology, for example, was used to examine base flipping by the methyltransferase *Hha*I. In vivo, M.*HhaI* methylates each cytosine in 5'-GCGC-3' sequences by flipping the cytosine into its active site pocket and inserting Gln237 in its place, effectively creating a hydrophobic plug within the base stack of the DNA. When the binding site for M.*Hha*I was placed between two guanine doublets, and long range hole transport from the appended rhodium photooxidant was determined, guanine oxidation at the site distal to protein binding was greatly diminished. In identical experiments using a mutant enzyme that inserts the aromatic, heterocyclic residue tryptophan instead of glutamine, distal damage was restored. Furthermore, using the tryptophan mutant enzyme bound to DNA tethered to a ruthenium photooxidant, a transient tryptophan radical was observed in spectroscopic experiments of DNA-mediated charge transport (53,54). This protein-dependent charge transport was observed over 50 Å, and over this distance range, charge transport was not rate limiting, occurring at a rate $\geq 10^7\ s^{-1}$.

APPLICATIONS IN SENSING

This sensitivity to base stacking provides the basis for sensor applications based on DNA-mediated charge transport. We have focused on electrochemistry experiments on DNA-modified surfaces (55-60). In these experiments, DNA oligonucleotide duplexes containing a thiol linker are

attached to a gold surface by self-assembly, and reduction of a redox active intercalator bound to the close packed DNA film is monitored (Figure 1.6). This thesis work has focused on elucidating and optimizing this sensor technology.

We first examined DNA films containing daunomycin covalently bound to guanine sites on the duplex and found that current flow to daunomycin was independent of its position in the film (58). We then tested current flow in the presence of an intervening CA mismatch (Figure 1.5). Remarkably, the mismatch shut off the reduction of the daunomycin adduct. This experiment established again that the path for charge transport was through the base pair stack. Importantly, given the sensitivity of charge transport to base pair stacking, the experiment also established that a single base mismatch in DNA could be detected electrochemically.

Subsequent experiments established the sensitivity of the reaction to all intervening base mismatches in DNA. Interestingly, using noncovalent daunomycin as a redox reporter bound near the top of the densely packed film, results (59) were found to correlate with long range oxidative damage studies on assemblies containing intervening mismatches (52). Thus, sensitivity to structure was evident both with oxidation chemistry (of the DNA base) and reduction chemistry (of the DNA-bound daunomycin).

The ability to detect single base mismatches by DNA-mediated charge transport that is now being exploited for mutational analysis in electrochemistry based assays is described in Chapters 2 and 3. This assay was increased in mismatch discrimination and signal/noise using electrocatalysis and, as a result, provides a completely new technology for the

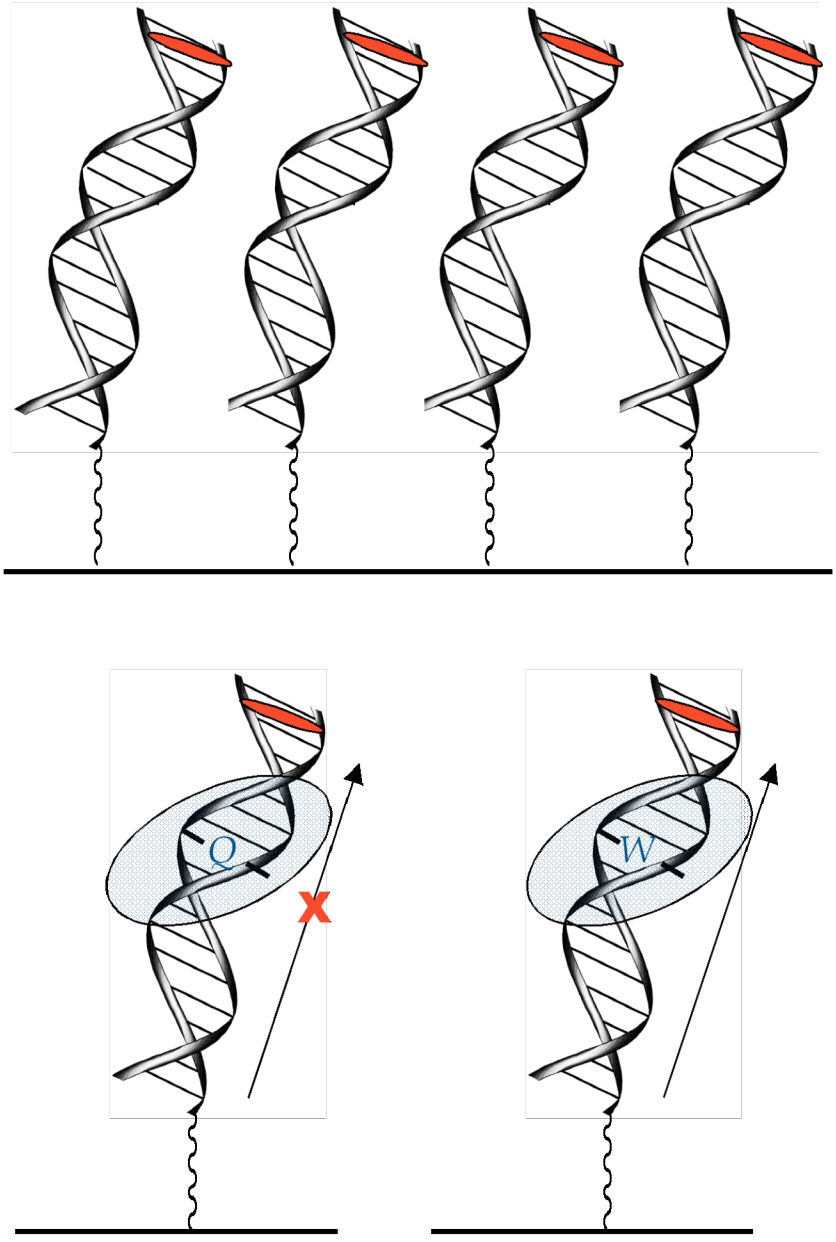
rapid detection of single nucleotide polymorphisms. As a result, this assay may offer significant advantages in accuracy and sensitivity over current technologies for DNA based diagnosis.

Chapters 4-6 provide further characterization of our DNA-modified surfaces and the kinetics and mechanism of this charge transport chemistry through DNA films. Chapter 4 fundamentally examines the pathway of charge transport at DNA-modified electrodes, and Chapter 5 provides an analysis of the kinetics of our electrocatalytic assay. Chapter 6 offers characterization of the importance of the length, orientation and flexibility of the alkanethiol tether used to self-assemble the DNA duplexes in forming densely packed DNA films.

Chapters 7 and 8 demonstrate examples of the value of electrochemistry at DNA-modified surfaces in biosensing. The utility of DNA-mediated charge transport at DNA-modified surfaces as an assay for directly probing base stacking within DNA duplexes is emphasized. Chapter 7 describes an application of this methodology to probe the preferred base stacking orientation of a conformationally constrained nucleotide (3'-endo locked) within DNA/DNA and DNA/RNA duplexes. The conformation of the sugar is seen to sensitively determine the local stacking of the duplex.

The electrochemical reduction of DNA-bound intercalators is also effective in developing an assay for protein-induced changes in DNA structure (Figure 1.6) (61). This novel probe of protein-DNA interactions is described in Chapter 8. This assay could be useful in screening for inhibitors

Figure 1.6. An illustration of applications for DNA-mediated charge transport chemistry using DNA based array technology. (a) DNA-mediated charge transport is monitored electrochemically at DNA-modified electrode surfaces using intercalators bound to the film as the redox probe. The efficiency of reduction of the intercalator bound near the top of the film provides a measure of the intervening DNA stack. (b) DNA films can also be used to monitor stacking perturbations as associated with DNA binding proteins.



of protein-DNA interactions and perhaps also in monitoring real time perturbations in DNA structure associated with protein binding and reaction.

BIOLOGICAL CONSIDERATIONS

Experiments from many different laboratories have now confirmed that oxidative damage to DNA can proceed over long molecular distances and the reaction is sensitive to sequence as well as sequence dependent structure. These findings prompt the question of whether long range charge transport similarly promotes chemistry at long range within the cell. Are some sites, for example, necessarily insulated from charge transport damage, while others represent hot spots to which damage is funneled? Given that both activation and inhibition of charge transport by DNA-binding proteins have been seen in the test tube, do DNA-binding proteins similarly modulate charge transport chemistry in the nucleus?

In considering these possibilities, it is important first to establish that DNA-mediated charge transport does proceed in the cell. Using photoactivated rhodium intercalators, DNA charge transport within cell nuclei has begun to be probed (62). *Hela* cell nuclei were incubated with the rhodium photooxidant, irradiated, and then the genomic DNA was isolated and examined. The analysis revealed base damage preferentially at the 5′-guanine of 5′-GG-3′ sites, a hallmark of base damage by DNA-mediated charge transfer chemistry. Moreover, on transcriptionally active DNA within

the nucleus, oxidative damage was found at protein-bound sites that were inaccessible to rhodium, as established by photofootprinting. Thus, within the nucleus, DNA-mediated charge transport can lead to base damage from a distance. Direct interaction of an oxidant is not necessary to generate a base lesion at a specific site.

Reactions on DNA through charge transport chemistry, furthermore, are not restricted to oxidative base damage. We have found that the repair of thymine dimers in DNA may be triggered oxidatively from a distance (65-67), and thymine dimer repair has also been demonstrated reductively with bound flavins (68,69). Our electrochemistry experiments to sense mismatches and lesions in DNA also suggest that this chemistry might be valuable as a sensing device within the cell (Chapter 3), although this application in vivo has yet to be demonstrated. Certainly, however, charge transport chemistry mediated by DNA offers opportunities to carry out a range of reactions from a distant position on the DNA helix.

Various proposals are now being made concerning the biological ramifications of this chemistry and how it may be exploited physiologically. It has been proposed, for example, that regions containing a disproportionate frequency of guanines, as found in CpG islands and telomeres, may represent hot spots for damage (63). Our studies of long range damage on restriction fragments (44) suggest that the physiological range for charge migration may be on the order of a 100 Å, but likely not longer. This range does however represent the size range for nucleosomes, in which DNA is packaged within the cell, and efficient oxidative damage from a distance has been demonstrated in the nucleosome core particle (64).

In vitro, DNA-mediated charge transport is modulated by bound proteins (40,41) and in vivo, proteins are nearly always associated with DNA; this observation has prompted questions in our lab about whether or not protein to DNA charge transport is physiologically relevant. Particularly intriguing for investigation of charge transport between DNA and proteins are DNA-binding proteins that contain redox active cofactors such as FeS clusters. There are now many examples of FeS cluster containing DNA-binding proteins including MutY, endonuclease III, SoxR (17), FNR, spore photoproduct lyase, and a uracil DNA glycosylase, among others (70).

In Chapters 9 and 10 of this thesis, we examine the base excision repair enzyme MutY. MutY is an *E. coli* DNA repair enzyme that binds to 8-oxo-G:A and G:A mismatches and catalyzes the deglycosylation of the mismatched 2'deoxyadenosine. Interestingly, MutY contains a 4Fe4S cluster cofactor, the function of which is not known. Perhaps MutY utilizes this cluster for DNA-mediated charge transport, taking advantage of the sensitivity of this chemistry to stacking perturbations, to facilitate location of its mismatched binding site. Chapter 9 offers spectroscopic and electrochemical characterization of MutY in complex with DNA as an early foundation for probing protein-DNA charge transport chemistry in these complexes. In Chapter 10 we have applied DNA-mediated charge transport to probe the interaction of MutY with its DNA substrate in solution. The results expand studies using oxidation promoted from a distance with a tethered rhodium intercalator, provide further insight into the catalytically active MutY-DNA complex, and extend the methodology for examination of DNA-protein interactions using DNA-mediated charge transport.

SUMMARY

DNA charge transport chemistry is a remarkable characteristic of double helical DNA. Oxidative DNA damage mediated by the base pair stack can occur over 200 Å away from the position of the oxidant and in a reaction that is modulated by intervening sequence, structure and dynamics. Proteins in binding to DNA can also modulate long range charge transport, both positively and negatively. Indeed, given the sensitivity of this chemistry to base pair stacking, DNA charge transport is being harnessed as a sensor of perturbations in the base pair stack. This thesis describes our work to fully explore this sensor technology. The applications of this technology both practically and perhaps also in the context of chemotherapy are exciting to consider. More intriguing still and a challenge for biochemists today is the consideration of the consequences and opportunities for charge transport through the DNA base pair stack within the cell. Here begin to explore this possibility with the FeS cluster containing, base excision repair enzyme MutY.

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