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The Mechanism of Long-Distance Radical Cation Transport in Duplex DNA: Ion-Gated Hopping of Polaron-Like Distortions

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Abstract The irradiation of an anthraquinone derivative that is covalently attached to duplex DNA injects a radical cation into the bases of the DNA. This radical cation can migrate hundreds of Ångstroms before it is trapped at GG steps by reaction with water. These damaged guanines result in DNA strand scissions when they are treated with piperidine. Investigation of several such DNA constructs reveals that the efficiency of radical cation migration is strongly dependent on the sequence of bases in the DNA. This observation led to the formulation of the phonon-assisted polaron hopping model for the mechanism of radical cation migration. In this model, DNA and its ionic and solvent environment are assumed to undergo motions on the timescale of the radical cation hopping. These motions lead to a distortion of the local environment around the radical cation that causes it to gain stability (the polaron). Thermal motions of the DNA and its environment (phonons) cause the radical cation to migrate adiabatically from one polaronic site to another.

Keywords Long-distance charge transport · DNA damage · Polaron hopping · Ion gated base sequence effects

1 Introduction

DNA is a chemical whose function in living cells is to store the instructions needed to maintain life. Errors introduced into those instructions generally have deleterious consequences, so there is great evolutionary pressure to prevent or correct them. At the molecular level, a reaction that changes the structure of DNA damages the instructions and introduces errors. Several reactions cause structural changes in DNA; among the most important is one-electron oxidation [1]. Oxidation of DNA can result from normal cellular metabolism, from exposure to ionizing radiation, or from interaction with light [2–5].

When DNA is oxidized, it loses an electron and a radical cation ("hole") is generated. Overwhelming evidence shows that these radical cations reside primarily on the aromatic bases that form the central core of duplex DNA. Radical cations in DNA are short-lived species that are consumed by reaction with H_2O to produce structurally modified (damaged) bases [6]. It is now widely accepted that the base initially oxidized is not necessarily the base that is eventually damaged by reaction of the radical cation with H_2O [7–9]. The radical cation migrates through the DNA duplex until it is eventually consumed by a reaction. Clearly, it is essential to understand the mechanism for long-distance migration of radical cations in DNA because that process controls the site of oxidative damage. Our findings on that topic are described in this chapter.

2 Anthraquinones as One-Electron Oxidants of DNA

Redox reactions follow well-established thermodynamic and kinetic principles. Generally, a one-electron oxidation reaction is spontaneous and rapid when its driving force ($-\Delta G_{et}$) is greater than about 5 kcal/mol (0.2 eV) and the electron donor and acceptor are at a near contact distance. Electronically excited states formed by optical excitation are often powerful oxidants. In this case, the Weller equation provides a convenient means to estimate ΔG_{et} based on the energy of the excited state (ΔE^*), the oxidation potential (E_{ox}) of the electron donor (a DNA base in the present case), the reduction potential of the electron acceptor (E_{red}), and certain electrostatic work terms [10]. Numerous organic and metallorganic compounds have been found whose

excited state meets the energetic requirement for oxidation of DNA. We have focused our attention on anthraquinone derivatives.

Anthraquinones are nearly perfect sensitizers for the one-electron oxidation of DNA. They absorb light in the near-UV spectral region (350 nm) where DNA is essentially transparent. This permits excitation of the quinone without the simultaneous absorption of light by DNA, which would confuse chemical and mechanistic analyses. Absorption of a photon by an anthraquinone molecule initially generates a singlet excited state; however, intersystem crossing is rapid and a triplet state of the anthraquinone is normally formed within a few picoseconds of excitation, see Fig. 1 [11]. Application of the Weller equation indicates that both the singlet and the triplet excited states of anthraquinones are capable of the exothermic one-electron oxidation of any of the four DNA bases to form the anthraquinone radical anion ($AQ^{-\cdot}$) and a base radical cation ($B^{+\cdot}$).

Oxidation reactions that originate with the singlet excited state of the anthraquinone (AQ^{*1}) generate a contact radical ion pair in an overall singlet

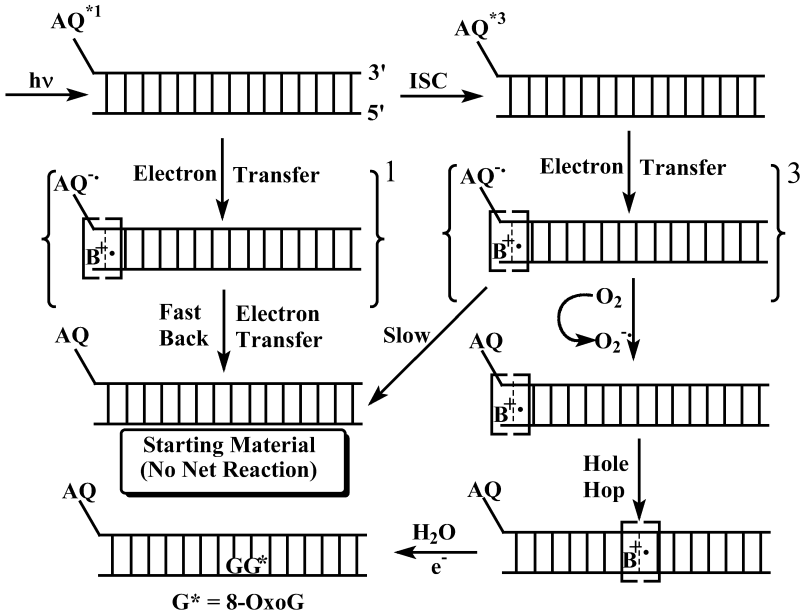

Fig. 1 Schematic mechanism for the long-distance oxidation of DNA. Irradiation of the anthraquinone (AQ) and intersystem crossing (ISC) forms the triplet excited state (AQ^{*3}), which is the species that accepts an electron from a DNA base (B) and leads to products. Electron transfer to the singlet excited state of the anthraquinone (AQ^{*1}) leads only to back electron transfer. The anthraquinone radical anion ($AQ^{-\cdot}$) formed in the electron transfer reaction is consumed by reaction with oxygen, which is reduced to superoxide. This process leaves a base radical cation ($B^{+\cdot}$, a "hole") in the DNA with no partner for annihilation, which provides time for it to hop through the DNA until it is trapped by water (usually at a GG step) to form a product, 7,8-dihydro-8-oxoguanine (8-OxoG)

spin state that can undergo rapid back electron transfer to regenerate the starting materials. Our findings indicate that this unproductive charge annihilation route dominates reactions that originate from AQ^{*1} [11].

On the other hand, oxidation of a DNA base by a triplet state of the anthraquinone (AQ^{*3}) generates a contact ion pair in an overall triplet state, and back electron transfer from this species to form ground states is prohibited by spin conservation rules. Consequently, the lifetime of the triplet radical ion pair is long enough to permit the bimolecular reaction of $AQ^{-\cdot}$ with O_2 to form superoxide ($O_2^{-\cdot}$) and regenerate the anthraquinone.

Therefore, the sequence of reactions illustrated in Fig. 1 catalytically (the anthraquinone is regenerated) "injects" a radical cation into a DNA oligonucleotide that does not simultaneously contain a radical anion. As a result, the lifetime of this radical cation is determined by its relatively slow bimolecular reaction with H_2O (or some other diffusible reagent such as $O_2^{-\cdot}$) and not by a rapid intramolecular charge annihilation reaction. This provides sufficient time for the long distance migration of the radical cation in DNA to occur.

We have examined several anthraquinone derivatives as sensitizers for oxidation of DNA. The most useful compounds for analysis of the mechanism for long distance radical cation migration are those that are covalently linked to the DNA either at a 5′-end of one strand (AQ-DNA) [12] or to the 3′-oxygen of a ribose (UAQ-DNA) [13], as shown in Fig. 2. Molecular modeling, chemical quenching studies, and spectroscopic analyses indicate that the end-linked AQ derivative is associated with the DNA by end-capping of the final base pair, as shown in Fig. 3. End-capping allows the relatively efficient oxidation of the DNA by the quinone at a known initial site without disruption of the base stacking that results from an intercalated sensitizer. Examination of the reactions of end-capped AQ show that the efficiency of

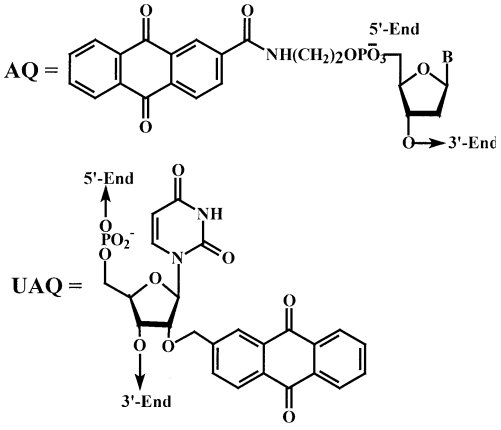

Fig. 2 Structures of the anthraquinone-linked sensitizers. AQ is covalently attached to the 5′-end of one strand. UAQ can be placed at any position, and the attached anthraquinone intercalates in duplex DNA at the 3′-side of its linked nucleotide

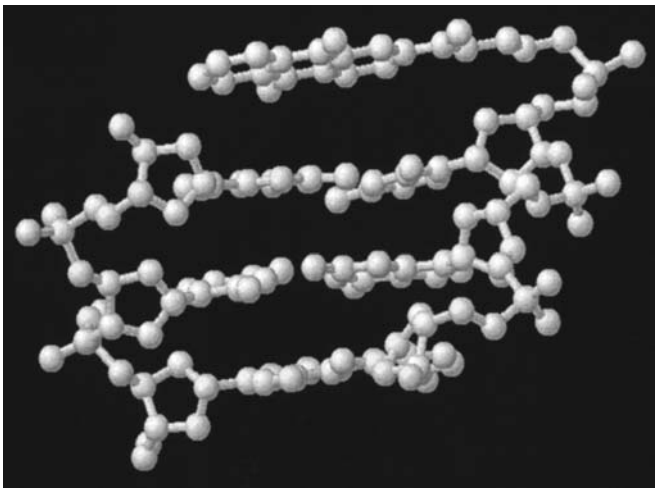

Fig. 3 Model of an end-capped anthraquinone that is covalently linked to a 5′-terminus of duplex DNA by the tether shown in Figure 2

charge injection depends on the sequence of bases near the AQ. Maximum efficiency is observed when there is no G/C base pair within the three base pairs closest to the AQ [14]. The sequence effect on charge injection efficiency is attributed to more rapid migration of the base radical cation away from the quinone radical anion when there is no nearby guanine, which acts as a shallow trap.

The anthraquinone group of the UAQ sensitizer is intercalated on the 3′-side of its linkage site [15]. Use of UAQ permits assessment of the directionality of long-range radical cation migration. Both AQ and UAQ enable the selective and efficient introduction of a radical cation in duplex DNA, whose lifetime is controlled by its relatively slow bimolecular reaction primarily with H_2O.

3
Interpretation of Radical Cation Reaction Patterns in Duplex DNA

Irradiation of an AQ-linked duplex DNA oligomer leads to selective reaction at certain base pair sequences. This reaction is detected as strand cleavage, after treatment of the irradiated sample with piperidine, by polyacrylamide gel electrophoresis (PAGE) on DNA oligomers that contain a ^{32}P radiolabel. This behavior is indicative of chemical reaction (damage) at a DNA bases rather than at a deoxyribose sugar, in which case strand cleavage generally does not require treatment with piperidine [5]. It is typically found by us and by others (using a variety of oxidants) that reaction of the radical cation usually occurs primarily at the 5′-G of GG [16, 17] steps (or at the central and 5′-G of GGG) and less frequently at the G of a 3′-AG-5′ sequence. This selectivity of reaction has been attributed to stabilization of the radical cat-

ion at GG or AG sites due to delocalization of the charge [18]. However, stabilization by GG steps does not generate a "deep trap" from which the radical cation cannot escape, since reaction is routinely observed at GG steps that are near to the AQ sensitizer (proximal) and at those further away (distal) so that the radical cation must pass through the proximal GG step to cause reaction at the distal site [12, 19].

Analysis of the relative efficiency of strand cleavage of duplex DNA provides useful information on the relative rates of charge transport, that permits analysis of the mechanism for radical cation migration. These experiments must be carried out under conditions of low conversion ("single hit") so that each DNA oligomer, on average, reacts once or not at all. Under these conditions, the competition between the rate of reaction of the radical cation with H_2O and its migration is revealed by the statistical pattern of the cleavage results. This is illustrated by considering two limiting examples.

In the first case, we presume that the rate of reaction of H_2O with the radical cation is much faster than the rate of its migration. In this case, reaction will be observed only at the GG step closest to the covalently linked AQ; the radical cation never reaches distal GG steps.

In the second limiting case, the rate of reaction with H_2O is presumed to be much slower than the rate of radical cation migration and independent of the specific base pair sequence surrounding the GG step. Under these circumstances, each GG step will be equally reactive, and just as much strand cleavage will be observed at the GG step farthest from the AQ as at the one closest to it.

In the intermediate circumstance where the rate of reaction with H_2O and the rate of radical cation migration are comparable, then the amount of reaction detected is somehow related to the distance from the AQ to the GG step.

Therefore, analysis of the efficiency and pattern of strand cleavage provides information on the relative rate of radical cation migration through different DNA sequences. This is powerful information for analysis of the charge migration mechanism.

4
The Base Sequence and Distance Dependence of Radical Cation Migration

The pattern and efficiencies of strand cleavage at GG steps in duplex DNA reflect the ability of a radical cation to migrate from its initial position through a sequence of base pairs. In an illustrative example, we consider the photochemistry of AQ-DNA(1), which is shown in Fig. 4. AQ-DNA(1) is a 20-mer that contains an AQ group linked to the 5′-end of one strand and has two GG steps in the complementary strand. The proximal GG step is eight base pairs, ca. 27 Å, from the 5′-end linked to the AQ, and the distal GG step is 13 base pairs (ca. 44 Å) away. The complementary strand is labeled with ^{32}P at its 5′-terminus (indicated by a * in Fig. 4).

Measurement of the melting temperature (T_m) and the circular dichroism (CD) spectrum of AQ-DNA(1) shows that it is a duplex at room temperature

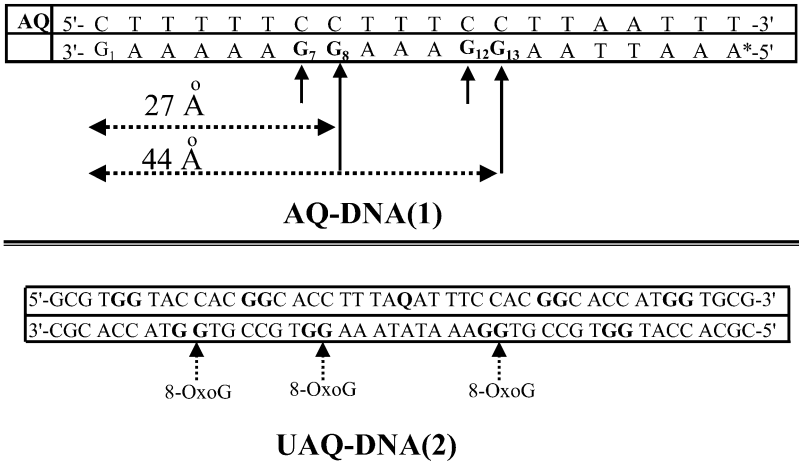

Fig. 4 Schematic representation of long-distance radical cation migration in DNA. In AQ-DNA(1), irradiation of the anthraquinone group linked at the 5′-terminus leads to reaction at GG steps that are 27 Å and 44 Å from the site of charge injection. The amount of reaction observed at each guanine is represented approximately by the length of the solid arrow. In UAQ-DNA(2), irradiation of the anthraquinone leads to reaction at each of the eight GG steps. However, replacement of a G by 7,8-dihydro-8-oxoguanine (8-OxoG) introduces a deep trap that inhibits reaction at guanines on the same side of the DNA as the trap

in 10 mM sodium phosphate buffer solution at pH 7, which are the standard conditions we use for the irradiation experiments. Irradiation of a 2.5 μM solution of duplex AQ-DNA(1) at 350 nm under the standard conditions followed by treatment of the irradiated sample with piperidine and analysis by PAGE and autoradiography (the standard analytical protocol) shows that strand cleavage occurs at both of the GG steps [12]. Control experiments confirm that this is an intramolecular reaction and is not due to the generation of a diffusible species such as singlet oxygen ($^1O_2$).

The relative amount of strand cleavage at each site of AQ-DNA(1) is indicated by the length of the solid vertical arrow shown in Fig. 4. As is often observed, the 5′-G of the GG steps react more often than do the 3′-G. In the case of AQ-DNA(1), the relative reactivity is ca. 1:3, but this ratio depends upon the specific base pair sequence surrounding a GG step, which may be an indication of radical cation delocalization to bases adjacent to the GG sequence. It is worth pointing out again that these reactions are carried out under single-hit conditions where the relative strand cleavage efficiency seen at various locations of AQ-DNA(1) reflect the statistical probability that the radical cation will be trapped by H_2O at that site.

The results from irradiation of AQ-DNA(1) show conclusively that a radical cation introduced at one site, G_1 at the 3′-terminus of the complementary strand in this case, can migrate through duplex DNA and cause reaction at remote sites. To migrate from its point of injection at G_1 to where it reacts at

GG_8, the radical cation must traverse five A/T base pairs. Electrochemical measurements in solution have shown that the purine bases (A and G) have considerably lower E_{ox} than the pyrimidines (C and T), with the E_{ox} of G estimated to be about 0.25 V below that of A [20]. It is not very likely that the E_{ox} of bases in DNA will be the same as they are in solution, but it is generally assumed that the order of E_{ox} will remain the same. Consequently, the radical cation at G_1 of AQ-DNA(1) must traverse a "bridge" of five A bases to reach GG_8. The process whereby the radical cation crosses such bridges has been a major point of debate in consideration of long distance radical cation migration mechanisms in DNA; this issue will be discussed fully below.

In AQ-DNA(1), GG_8 and GG_{13} are separated by a bridge of three A bases. If GG_8 were a deep trap for the radical cation, then no reaction would be observed at GG_{13}. If the $(A)_3$ bridge separating GG_8 and GG_{13} presented a significant barrier to charge migration, then the amount of strand cleavage at GG_{13} would be significantly less than at GG_8. The experiment reveals that the amounts of reaction at GG_8 and GG_{13} are the same within experimental error, which shows that GG steps are not deep traps and the rate of radical cation migration through an $(A)_3$ bridge is much faster than the reaction of the radical cation with H_2O at either of the two GG steps in this oligomer. More recently, Giese and coworkers have shown radical cation migration through an $(A)_{12}$ bridge [21].

A deep radical cation trap can be introduced into duplex DNA. The E_{ox} of 7,8-dihydro-8-oxoguanine (8-OxoG) is ca. 0.5 V below that of G [22]. Irradiation of an AQ-DNA(1) analog in which an 8-OxoG was substituted for G_8 essentially stops observable strand cleavage at G_7, G_{12}, and G_{13} [12]. In a related series of experiments, irradiation of UAQ-DNA(2), see Fig. 4, under the standard conditions gives strand cleavage at each of the eight GG steps of both strands. But substitution of an 8-OxoG for either of the three guanines on either side of the UAQ, as shown in Fig. 4, results in the reduction of the efficiency of strand cleavage at each G in both strands on the same side of the UAQ as the 8-OxoG [13]. This finding shows that a deep trap will inhibit charge migration both in the strand containing it and in the complementary strand, which demonstrates that the radical cation can cross from one strand of duplex DNA to its complement.

We examined long-distance charge transport in AQ-DNA(3), see Fig. 5, to obtain additional information on how base sequence affects the efficiency of radical cation migration [23]. There are four GG steps in AQ-DNA(3) that are positioned 10, 28, 46, and 55 base pairs from the site of charge injection at G_1. Significantly, there is no regularity of the sequence of bases between any of these GG steps. Irradiation of AQ-DNA(3) under the standard conditions gives detectable strand cleavage at each of the GG steps. The relative amount of strand cleavage at each GG step is indicated by the vertical arrows and is plotted as a semi-log plot against distance in Fig. 5. Remarkably, the radical cation introduced at G_1 migrates nearly 200 Å through "mixed sequence" DNA to cause reaction at G_{55}. Surprisingly, the semilog plot in Fig. 5 reveals an apparent linear relationship between the amount of reaction and the distance between the GG step and the site of charge injection, with

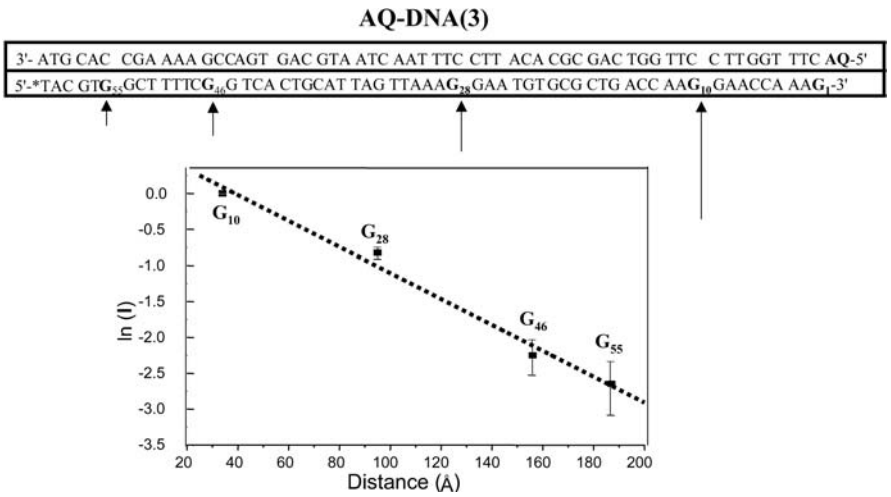

Fig. 5 Schematic representation of long distance radical cation migration in DNA. In AQ-DNA(3), irradiation of the anthraquinone group linked at the 5′-terminus leads to reaction at GG steps that are 10, 28, 46 and 55 base pairs from the charge injection site. The solid arrows indicate approximately the amount of reaction observed at each GG step. The plot shows the natural log of the normalized amount of reaction as a function of distance from the AQ. The results appear to give a linear distance dependence

an exponential distance dependence of ca. −0.02 $Å^{-1}$, a value that has also been observed with other sequences and with other sensitizers [24]. A linear dependence is unexpected because it requires that the radical cation migrate from base-to-base through both pyrimidine and purine bases or from strand-to-strand with a similar rate constant, independent of the specific order of bases it encounters. There are two reasonable explanations for this observation: either the linear dependence is an artifact; or some process is operating that causes averaging of differences in base E_{ox} that gives a distance dependence which appears to be independent of base sequence.

AQ-DNA(4), see Fig. 6, is related to AQ-DNA(1) – both have a series of GG steps separated by a number of A bases. However, in AQ-DNA(4), there are four GG steps and they are on the AQ-linked strand, which contains only purines and carries the radiolabel at its 3′-terminus. We have shown that the outcome of oxidative reactions of duplex DNA is unaffected by moving the label from one strand to its complement [25]. Irradiation of AQ-DNA(4) under the standard conditions gives the expected outcome. The amount of strand cleavage detected at GG_4 and GG_8 is nearly the same, the $(A)_8$ sequence that separates GG_8 from GG_{18} presents only a modest barrier to the migration of the radical cation: the cleavage efficiency at GG_{18} and GG_{22}, which are approximately equal, is about 40% of the amount detected at GG_4 and GG_8 [26].

The results obtained from irradiation of AQ-DNA(5) are startling in their contrast. This duplex also contains four GG steps, but the (A_8) bridge of

AQ-DNA	
4	5'AQ- A A **G G**$_4$ A A **G G**$_8$ A A A **A** A A A A **G G**$_{18}$ A A **G** **G**$_{22}$ A A A A* -3' 3'- T T C C T T C C T T T **T** T T T T C C T T C C T T T T -5'
5	5'AQ- A A **G G**$_4$ A A **G G**$_8$ A A A **T** A A A A **G G**$_{18}$ A A **G** **G**$_{22}$ A A A A* -3' 3'- T T C C T T C C T T T **A** T T T T C C T T C C T T T T -5'
6	5'AQ- A A A T G C C G G T A C C **T** C T A G G C C G T A G -3' T T T A C **G G**$_7$ C C A T **G G**$_{13}$ **A** G A T C C **G G**$_{21}$ C A T C* -5'
7	5'AQ- A A A T G C C G G T A C C **A** C T A G G C C G T A G -3' T T T A C **G G**$_7$ C C A T **G G**$_{13}$ **T** G A T C C **G G**$_{21}$ C A T C* -5'

Fig. 6 Structures of AQ-linked DNA oligomers used to assess the effect of converting an A/T base pair to a T/A base pair

AQ-DNA(4) is replaced by an $(A_3)(T)(A_4)$ sequence. In other words, one A/T base pair of AQ-DNA(4) becomes a T/A base pair in AQ-DNA(5). This simple structural change has a profound effect on the efficiency of radical cation transport across the eight-base-pair bridge. As was observed for AQ-DNA(4), GG_4 and GG_8 of AQ-DNA(5) are approximately equally reactive, but the amount of strand cleavage detected at GG_{18} and GG_{22} is reduced by ca. 95% compared with that of GG_4 and GG_8. This is surprising because AQ-DNA(3) has 13 T bases between G_{10} and G_{55} but gives the linear distance relationship that is shown in Fig. 5. Clearly, there is no general principle that requires such a linear distance dependence that is totally independent of base sequence.

In contrast to the overwhelming affect of conversion of an A/T base pair in AQ-DNA(4) to a T/A base pair in AQ-DNA(5) on radical cation transport, the identical change in AQ-DNA(6) and AQ-DNA(7) has no measurable effect on the amount of strand cleavage observed at GG_7 or GG_{21} [27]. It is apparent from consideration of these results that the effect of a change in base sequence must be considered in the context of the surrounding base pairs and not in isolation.

We probed the effect of base sequence on long-distance radical cation migration using a series of duplexes that have a regularly repeating structure of base pairs, see Fig. 7. AQ-DNA(8) can be recognized as containing an AAGG sequence that repeats six times $(AAGG)_6$. The "last" four base pairs of this duplex are $(A/T)_4$, which reduces misalignment of the duplex by slippage. Irradiation of AQ-DNA(8) under the standard conditions gives an essentially equal amount of strand cleavage at each of its six GG steps. This is precisely what is to be expected if the rate of radical cation migration is much faster than the rate of its trapping by reaction with H_2O.

A semi-log plot of the distance dependence of strand cleavage efficiency, see Fig. 8, gives a linear relationship with a slope experimentally indistinguishable from zero. DNA has occasionally been characterized as a "molecu-

AQ-DNA	
8	5'AQ- A A **G G**$_4$ A A **G G**$_8$ A A **G G**$_{12}$ A A **G G**$_{16}$ A A **G G**$_{20}$ A A **G G**$_{24}$ A A A A* -3' 3'- T T C C T T C C T T C C T T C C T T C C T T T T -5'
9	5'AQ- A T **G G**$_4$ A T **G G**$_8$ A T **G G**$_{12}$ A T **G G**$_{16}$ A T **G G**$_{20}$ A T **G G**$_{24}$ A T A T* -3' 3'- T A C C T A C C T A C C T A C C T A C C T A T A -5'
10	5'AQ- A T A **G G**$_5$ A T A **G G**$_{10}$ A T A **G G**$_{15}$ A T A **G G**$_{20}$ A T A T* -3' T A T C C T A T C C T A T C C T A T C C T A T A -5'
11	5'AQ- A T T A **G G**$_6$ A T T A **G G**$_{12}$ A T T A **G G**$_{18}$ A T T A **G G**$_{24}$ A T A T* -3' T A A T C C T A A T C C T A A T C C T A A T C C T A T A -5'

Fig. 7 Structures of AQ-linked DNA oligomers containing a regularly repeating sequence of base pairs that were used to assess the effect of base sequence effects on long-distance radical cation migration

lar wire" [28]; a phrase that lacks a precise definition. The behavior of AQ-DNA(8) is the most "wire-like" that has been reported, but this does not qualify it as a molecular wire. This point will be addressed more extensively below.

It is especially informative to compare the behavior of AQ-DNA(9) with that of AQ-DNA(4) and AQ-DNA(8). AQ-DNA(9) contains the repeating sequence $(ATGG)_6$, which can be thought of as being formed from AQ-DNA(8) by converting the A/T base pair preceding each GG step to a T/A base pair. Recall that one such change converted AQ-DNA(4) to AQ-DNA(5) and resulted in the introduction of a high barrier to radical cation migration across the $(A_3)(T)(A_4)$ bridge that this change created. In contrast, radical cation migration through the five T/A base pairs between GG_1 and GG_{24} of

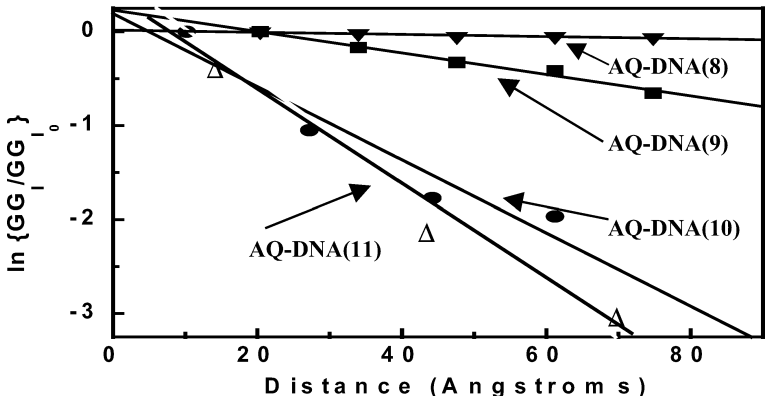

Fig. 8 Semi-log plots of the distance dependence of reaction for DNA(8-11). There is an apparent linear relationship in each case, but the slopes differ according to the specific sequence of DNA bases

AQ-DNA(9) is hardly affected. The slope of the line shown in Fig. 8 for AQ-DNA(9) is -0.008 Å^{-1}, which shows that the five T/A base pairs combined result in only a ca. 50% reduction in radical cation transport efficiency from GG_1 to GG_{24}, whereas the single T/A base pair of AQ-DNA(5) causes a 95% reduction in the efficiency of radical cation migration from GG_8 to GG_{18}. It is a similar case for AQ-DNA(10) and AQ-DNA(11), where one and two T/A base pairs are interposed between GG steps, respectively, with only a modest affect on radical cation migration from GG to GG. These observations show that the effect of base sequence on radical cation migration cannot be analyzed by considering the base pairs in isolation; base-to-base charge interaction evidently plays a key role.

5
Mechanisms of Long-Distance Charge Transport in Duplex DNA

The experiments described above, and those carried out in other laboratories, leave no doubt that a radical cation introduced at one location in DNA can migrate to and cause reaction at a remote location. The mechanism of this long-distance process has been enthusiastically debated and three broad possibilities have emerged:

a. A coherent, rapid single-step transport from donor to acceptor through a bridge of well-stacked DNA bases. In this mechanism DNA is said to behave like a "molecular wire" where the orbitals of the stacked DNA bases form a "π-way" for radical cation migration [29, 30].
b. An incoherent random-walk, multi-step hopping between initial and final states, where hops between sequential guanines (called "hole resting sites") are mediated by superexchange across intervening A/T and T/A base sequences [31–34].
c. A polaron-like hopping process where local energy-lowering dynamical structural distortions generate a self-trapped state of finite extent that is transported from one location to another by thermal (phonon) activation [7, 23, 35–37].

In order to consider and differentiate between these three mechanisms, it is necessary to understand the structure and dynamics of DNA in solution.

6
Coherent Long-Distance Radical Cation Transport

DNA is a helical polyanion built by the union of two linear polymeric strands that are composed of sugars (deoxyribose) linked by phosphates. Each sugar contains an aromatic base (G,C,A, or T) bound to C-1′ of the sugar. The two strands are normally complementary so that when they combine to form the duplex, each base on one strand forms Watson-Crick hydrogen bonds with its counterpart (G with C and A with T) on the opposite

strand. At normal physiological pH (ca. 7.4), the phosphates of the backbone polymer are fully ionized, so there must be a counterion (Na^+) for each phosphate. In fact, duplex DNA is unstable in solutions of low ionic strength because of Coulombic repulsion of the phosphate anions that is normally screened by the counterions [38].

High-resolution X-ray crystallography of DNA reveals exquisite details about its structure. In B-form DNA, the medium most commonly used for the study of long-distance radical cation transport in solution, the average distance from one base pair to the next is 3.4 Å, and each base pair is rotated around the long axis of the helix by about 36° with respect to its adjacent base pairs [39]. The regular order of stacked bases revealed by this structure led naturally to the suggestion that DNA was able to support long-distance electron transport [40]. This exciting possibility was revived and supported by measurements of apparent rapid photoinduced charge transfer over more than 40 Å between metallointercalators tethered to opposing 5′-termini of a 15 base pair DNA duplex [29, 30].

However, careful kinetic measurements on related systems showed the invalidity of wire-type behavior [41]. Furthermore, Sen and coworkers [42] recently showed that the appearance of rapid, long-distance charge transfer for metallointercalators may be an artifact caused by the formation of aggregates. Currently, there are no data that clearly support the existence of a coherent transfer process in DNA over a distance greater than one or two base pairs [43, 44].

The crystallographic structure of DNA is not a good model for consideration of the possibility that it behaves like a "molecular wire" in solution because this structure does not reveal the extent of instantaneous disorder inherent in this assembly. DNA is a dynamic molecule with motions of its constituent atoms, corresponding counterions and solvating water molecules that occur on time scales that range from femtoseconds to milliseconds or more. This is revealed clearly by consideration of careful molecular dynamics simulations [45]. It is apparent from analysis of these simulations that duplex DNA in solution has the standard B-form structure on average, but at any instant, over long distances (more than three or four base pairs) the DNA is somewhat disordered. Disorder cannot be tolerated in a coherent, single-step charge transfer process because it greatly reduces the electronic interaction that couples one base pair to the next [46]. Consequently, DNA in solution cannot be a molecular wire and this mechanistic possibility must be discarded.

7
Hopping Models: Hole-Resting-Site and Phonon-Assisted Polaron Transport

It is now clearly demonstrated that a radical cation introduced at one location in duplex DNA can migrate 200 Å or more and result in reaction at a remote GG step. Consideration of the dynamical nature of DNA in solution

led to the suggestion that this long-distance migration was the result of a radical cation hopping process [47]. In this view, the radical cation is trapped in a shallow minimum localized on a single base, or delocalized over several bases, and some process causes it to move from one location to the next until it is finally trapped irreversibly by reaction with H_2O.

In one variant of the charge-hopping mechanism, called the *hole-resting-site model*, the radical cation is localized on individual guanines and tunnels through bridges composed of A/T and T/A bases from strand-to-strand until it is trapped. Although this was considered to be a general process when it was first suggested, now it is viewed to be valid only for bridges containing three or fewer base pairs [34].

In a second possibility, the *polaron-like hopping model*, a structural distortion of the DNA stabilizes and delocalizes the radical cation over several bases. Migration of the charge occurs by thermal motions of the DNA and its environment when bases are added to or removed from the polaron [23].

The key differences between these representations is that in the hole-resting-site model, the radical cation is localized and confined to guanines, and migrates by tunneling through orbitals of the bridging A/T bases without ever residing on the bridge: the radical cation exists only virtually on the bridge. In the polaron-like hopping representation, the radical cation resides briefly as a real, measurable physical entity on the bridging bases and its hopping occurs by thermal activation.

The hole-resting-site and polaron-like hopping models can be distinguished by the distance and sequence behavior of radical cation migration. Analysis of the hole-resting-site model leads to the prediction that the efficiency of radical cation migration will drop ca. ten-fold for each A/T base pair that separates the G resting sites [33].

This possibility was explored experimentally by investigating the reactions of the DNA oligomers shown in Fig. 9 [19]. In AQ-DNA(12), the oligomer contains a series of six GG steps that are separated by TT sequences. In AQ-DNA(13) through AQ-DNA(15), the GG steps in related oligomers are separated by TTT, TTTT, and TTTTT sequences, respectively. Irradiation of

AQ-DNA	
12	5'-*$GG_7CC\ GG_6TT\ GG_5CC\ GG_4TT\ GG_3CC\ GG_2TT\ GG_1CCAAAA$-3' 3'-$CC_7GG\ CC_6\ AA\ CC_5GG\ CC_4AA\ CC_3GG\ CC_2\ AA\ CC_1GGTTTT$-AQ-5'
13	5'-*$GG_7CC\ GG_6TTT\ GG_5CC\ GG_4TTT\ GG_3CC\ GG_2TTT\ GG_1CCAAAA$-3' 3'-$CC_7GG\ CC_6\ AAA\ CC_5GG\ CC_4AAA\ CC_3GG\ CC_2\ AAA\ CC_1GGTTTT$-AQ-5'
14	5'-*$GG_7CC\ GG_6TTTT\ GG_5CC\ GG_4TTTT\ GG_3CC\ GG_2TTTT\ GG_1CCAAAA$-3' 3'-$CC_7GG\ CC_6\ AAAA\ CC_5GG\ CC_4AAAA\ CC_3GG\ CC_2\ AAAA\ CC_1GGTTTT$-AQ-5'
15	5'-*$GG_7CC\ GG_6TTTTT\ GG_5CC\ GG_4TTTTT\ GG_3CC\ GG_2TTTTT\ GG_1CCAAAA$-3' 3'-$CC_7GG\ CC_6\ AAAAA\ CC_5GG\ CC_4AAAAA\ CC_3GG\ CC_2AAAAA\ CC_1GGTTTT$-AQ5'

Fig. 9 Structures of AQ-linked DNA oligomers used to assess the effect of $(T)_n$ sequences between GG steps

these assemblies under standard conditions, and examination of the effect of sequence on strand cleavage yields at the GG steps gives in each case a semi-log plot, with a linear distance dependence having a slope within experimental error of -0.02 Å^{-1}. This value corresponds to only a ca. 10% reduction in radical cation transport efficiency for each intervening T base, which is inconsistent with the prediction of the hole resting site model. These experimental results, in part, led to the current view that tunneling from G to G cannot compete with other processes if the guanines are separated by more than three base pairs [34].

Support for the hole-resting-site model is built on the assumption that the radical cation migrates through a lattice of base pairs frozen in the standard B-form structure of DNA. However, in solution at room temperature at any given instant, only very short segments of the oligomer have their bases at precisely the B-form locations. Moreover, the magnitude of the electronic coupling interaction between adjacent bases is very strongly dependent on the details of the instantaneous structure [46]. Consequently, the factorization of the radical cation transport rate into an electronic coupling term and one due to nuclear vibrational motion (a Franck-Condon factor), employed for quantitative interpretation of the hole-resting-site model, does not apply to long distance migration of radical cations in DNA in solution.

However, such a process might operate over short distances where radical cation migration is forced to occur on a short time scale by a rapid back electron transfer reaction [43]. In such a circumstance, tunneling from G to G may occur in those DNA molecules from among the entire ensemble of molecules that happen to have structures permitting strong electronic coupling between relevant base pairs at the instant the radical cation is created. The dynamical structure of DNA in solution guarantees that such an arrangement can extend for no more than a very few base pairs, and perhaps occurs only when the DNA is constrained in a relatively rigid structure such as a hairpin [43]. On this basis, the hole-resting-site model cannot be the entire explanation for the observation of radical cation migration of 200 Å or more in duplex DNA.

The phonon-assisted polaron-like hopping model is unique because it is built upon an understanding of the dynamical nature of DNA in solution. The fundamental assumption of this model is that the introduction of a base radical cation into DNA will be accompanied by a consequent structural change that lowers the energy for the system.

A base radical cation is a highly electron-deficient species: it will be stabilized and the energy of the system will be reduced by changes in the average orientations of nearby bases, counterions and solvent molecules that provide additional electron density to the radical cation. This process, of course, will delocalize the radical cation and cause a local distortion of the DNA structure so that, on average, it is no longer in the standard B-form. This distortion may not extend over very many base pairs because the stabilization gained by delocalization must be balanced by the energy required to distort the average DNA structure. In this view, radical cations in DNA are self-trapped species that are delocalized over several base pairs contained within

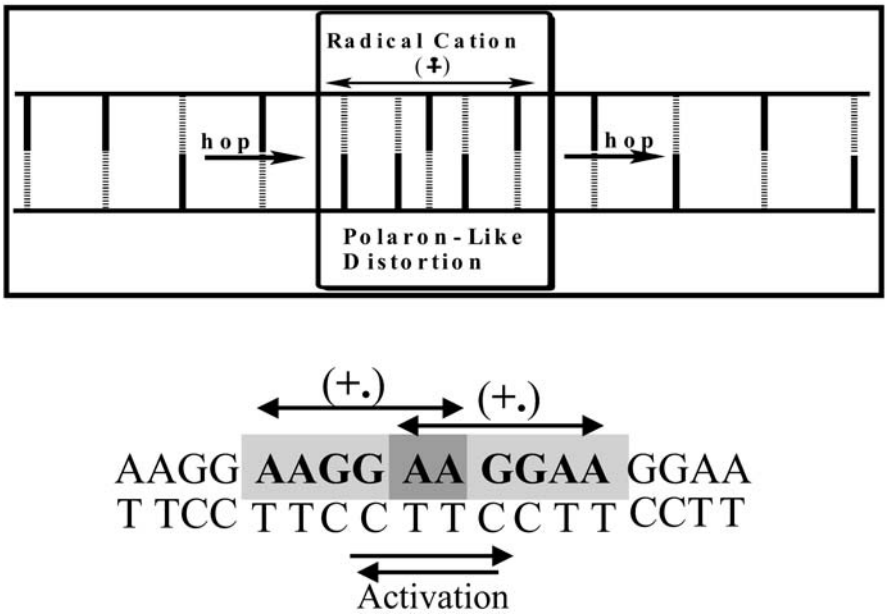

Fig. 10 Two schematic representations of a polaron-like species in DNA. In the top drawing, the base pairs of DNA are represented by the horizontal lines; the sugar diphosphate backbone is represented by the vertical lines. The polaronic distortion is enclosed in the box and extends over some number of base pairs. This is shown schematically by drawing the base-pair lines closer together. In the lower figure, a specific potential polaron is identified, AAGGAA, and the radical cation is presented as being delocalized over this sequence. Movement of the polaron from one AAGGAA sequence to the next requires thermal activation

a distorted local structure, which is the definition of a small polaron [48]. In fact, a base radical cation in DNA is more precisely referred to as a "polaron-like" species, because for most DNA oligomers the sequence of base pairs does not follow any particular repeating rule that would allow the classical polaron behavior that is observed in one-dimensional conducting polymers, for example [49].

Figure 10 shows schematic representations of possible polaron-like species in DNA. In the upper part of the Figure, the DNA bases are represented as a series of vertical lines (dashed for the purines and solid for the pyrimidines) distributed between horizontal lines that represent the sugar-diphosphate backbone. The box within this representation portrays the distortion of the polaron by placing the base pairs closer together in this region. This distortion of the DNA structure from its normal B-form average results in the delocalization of the radical cation (probably unevenly) among the bases included in the distortion. The polaron-like distortion is considered to hop through the DNA duplex, a process that may either increase or reduce the number of base pairs in the polaron; the size of the hopping step will be con-

trolled by the sequence of bases that make up the polaron and by those surrounding it.

The polaron-hopping model accommodates the experimental data obtained from long-distance radical cation migration experiments. For example, the apparent linear relationship between the log of the cleavage efficiency and distance observed for AQ-DNA(3), shown in Fig. 5, can be explained qualitatively by supposing that polaron-hopping permits two kinds of averaging that tend to reduce the effect of specific base sequence on radical cation migration efficiency. The observed linear relationship implies that the barrier for each hopping step the polaron takes is of approximately the same height, independent of specific base sequence. The height of the barrier is the difference between the energy of a polaron and the transition state that separates one polaron from the next.

The stabilization of the radical cation by forming a polaron is a trade-off between its delocalization and the energy required to distort the DNA structure. The former lowers the kinetic energy of the intrinsically quantum mechanical migrating radical cation, and the latter will be determined by factors that are independent of specific base sequence, such as the force constants of bonds in the sugar diphosphate backbone.

For example, if a strand of DNA is composed of sequential adenines or guanines (A_n or G_n), comparable stabilization of the polaron would likely involve fewer bases than in a segment having a mixed sequence of purines and pyrimidines. However, the relative energies of the two polarons could be averaged to a similar value even though they extend over a different number of bases having different sequences. The energy of the transition state that separates two polarons may also become less dependent on specific base sequence by averaging. There is no requirement that the number of bases in a hop from one location to the next be constant. If the hopping length is somehow dependent upon the identity of the bases separating the polarons, the energy of the transition state may depend less on the base sequence. Thus, the energy of the polaron is averaged over several bases and the energy of the transition state is averaged by different hopping lengths. The postulation that polaron formation accounts for the observed linear distance dependence of AQ-DNA(3) and similar experiments is qualitative. Polaron formation can be placed on a firmer footing by consideration of the experiments with AQ-DNA(4) through AQ-DNA(11).

8
Base Sequence Effects on Radical Cation Migration in DNA – A Collective Phenomenon

The linear distance dependence seen for AQ-DNA(3) is not observed to be universally independent of specific DNA base sequence. This is clearly revealed by examination of AQ-DNA(4) and AQ-DNA(5). Plots of the distance dependence of strand cleavage at the GG steps in these oligomers are shown in Fig. 11. Both show “stepped” rather than linear behavior, and the size of

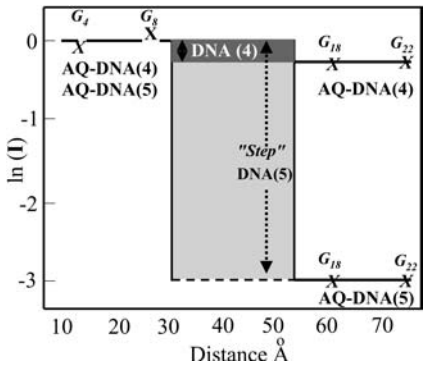

Fig. 11 Semi-log plots of the distance dependence of the reactivity of AQ-DNA(4) and AQ-DNA(5). These oligomers show "stepped" rather than linear behavior. The size of the step is strongly dependent on the details of the structure

the step is dramatically dependent on the base sequence. In both of these assemblies, the amount of strand cleavage at G_4 and G_8 is approximately equal, but amount of strand cleavage at G_{18} and G_{22} is reduced (the step), and the size of the step for AQ-DNA(4) is much less than it is for AQ-DNA(5). Clearly, averaging by polaron formation is not sufficient to give a linear distance dependence for these two sequences.

Further insight into polaron formation and sequence averaging comes from consideration of AQ-DNA(8), Fig. 7, which shows a linear distance dependence with a slope close to zero, Fig. 8. A slope of zero means that every GG step regardless of its distance from the AQ (the site of charge injection) reacts with the same efficiency. The kinetic model presented above reveals that this behavior is expected when the rate of radical cation migration is much faster than the rate of its irreversible trapping with H_2O. Since the rate of the trapping reaction is considered to be constant, a slope of zero suggests that the barriers to migration of the radical cation are significantly reduced in AQ-DNA(8) compared with AQ-DNA(3), which, for example, has a slope of -0.02 Å^{-1}. Figure 10 presents an explanation for this behavior based on the arbitrary assignment of the polaron in AQ-DNA(8) to the AAGGAA sequence.

In this formulation, the polaron is specially stabilized by the AAGGAA sequence, and identical polarons are separated by an AA sequence, which is presumed to present a relatively low-energy transition state that is easily overcome by thermal activation. This proposal is shown graphically in Fig. 12 where a potential energy surface for hopping of the {AAGGAA} polaron over an [AA] barrier ($\Delta G_8^{\neq}$) is qualitatively sketched. AQ-DNA(5) also has the AAGGAA sequence of bases and we similarly assign a specially stabilized polaron in this case. However, unlike AQ-DNA(8), the transition state between the polaron in AQ-DNA(5) centered on GG_8 and the one centered on GG_{18} contains an ATA sequence, which in this case appears to present a nearly insurmountable barrier to radical cation migration ($\Delta G_5^{\neq}$).

Having an ATA sequence between assigned polarons does not always create a high barrier for radical cation migration. In AQ-DNA(10), we assign

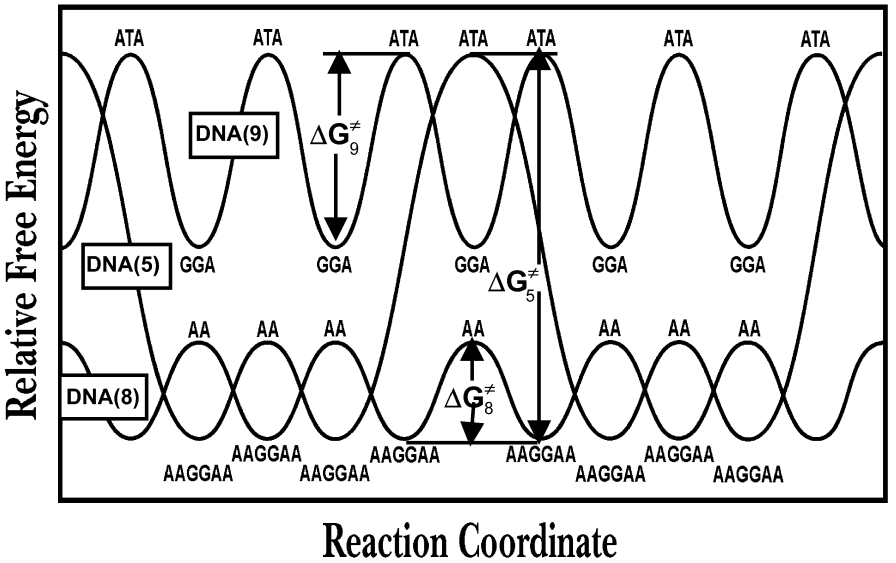

Fig. 12 A reaction coordinate diagram illustrating the emergence of sequence effects in long distance charge transport in duplex DNA. The curve representing DNA(8) shows the radical cation delocalized and stabilized in polarons; identified arbitrarily here as AAGGAA sequences in the AAGGAAGGAA segments surrounding the ATA sequence. This delocalization of the radical cation stabilizes it and results in a high barrier ($\Delta G^{\neq}_5$) at the ATA sequence; trapping of the radical cation by water occurs much faster than this barrier can be crossed. For DNA(8), the same AAGGAA polaron is identified and there are no thymines that create a high barrier for hopping from one polaron to the next, which occurs faster than trapping by water. The curve that represents DNA(9) shows an intermediate case where the polaron is assumed to be the GGA sequence, which is less delocalized and therefore higher in energy than AAGGAA. Consequently, the barrier introduced by the ATA sequence ($\Delta G^{\neq}_9$) is lower than for DNA(5) and the rate of crossing this barrier is comparable with reaction of the radical cation with water

the polaron to the {AGGA} sequence, because it is bracketed by T bases. Further, we presume that the {AAGGAA} polaron, being more delocalized, has a lower relative energy than the {AGGA} polaron. Consequently, the barrier to charge migration for the {AGGA} polaron when it encounters an [ATA] transition state ($\Delta G_9^{\neq}$)is lower than when the {AAGGAA} polaron encounters the same transition state sequence. This proposal is also illustrated in Fig. 12.

The primary conclusion that follows from the effect of base sequence on the efficiency of radical cation migration through duplex DNA is that base pairs cannot be considered in isolation. For example, the effect of placing a T in a sequence of purines depends critically on the nature and number of purines. In this regard, the effect of base sequence on radical cation transport emerges from examination of collective properties of the DNA. This is a clear indication that the charge is delocalized over several base pairs, a conclusion that is supported by extensive quantum calculations.

9
Ion-Gated Charge Transport

To consider the electronic structure of oxidized DNA properly, calculations must take account of the usual covalent bonds of the double helix as well as important ionic, hydrogen bonding, dispersion, and multipolar electrostatic interactions with its environment. The results of quantum-mechanical calculations of the duplex d(5′-$G_1A_2G_3G_4$-3′)·d(3′-$C_5T_6C_7C_8$-5′), that include neutralizing Na^+ counterions and a hydration shell, show delocalization of the radical cation over this structure [35]. This oligomer was selected because it contains the principal components considered in studies of charge transport in DNA: a G (radical cation donor) a bridge (A) and a radical cation acceptor (GG). The quantum calculations were performed on nuclear configurations selected from classical molecular dynamics (MD) simulations and distinguished from each other by the locations of the Na^+ ions and water molecules.

The MD simulations reveal rapid fluctuations in the positions of the atoms that compose the DNA, the associated Na^+ ions, and the water molecules. As expected, Na^+ ions are often located near the negatively charged phosphate groups of the backbone and near the relatively electronegative atoms (N-7 of G and A, for example) of the bases [45, 50].

Results obtained from the quantum calculations for configurations of the native and ionized duplex with the Na^+ ions near the phosphate groups are shown in Fig. 13. The highest occupied molecular orbital of the native DNA is, as expected, found to be on the G_3G_4 step. However, surprisingly, the radical cation is delocalized over this sequence with major density on G_1 and on the G_3G_4 step, and with a small amount of charge on A_2. The vertical ionization potential calculated for the d(5′-$G_1A_2G_3G_4$-3′)·d(3′-$C_5T_6C_7C_8$-5′) duplex with this configuration of Na^+ ions and solvating water molecules is 5.22 eV.

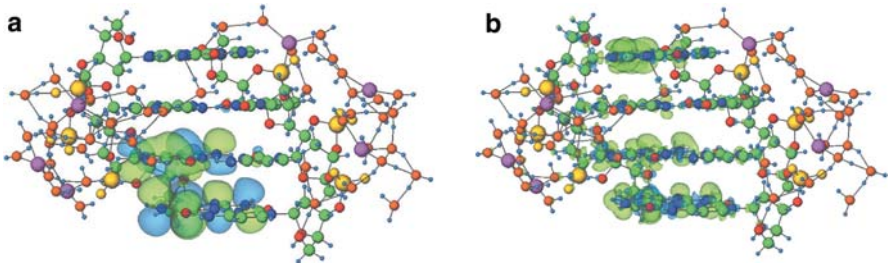

Fig. 13 Results from the quantum calculations on the duplex sequence 5′-GAGG-3′. In **a**, the sodium ions and their solvating water molecules are located at positions near the phosphate anions of the DNA backbone. In **b**, one sodium ion is moved from near a phosphate anion to N-7 of a guanine, which molecular dynamics calculations show to be a preferred site. The "balloons" represent the hole density on the GAGG sequences with the two different sodium ion orientations. The radical cation clearly changes its average location with movement of the sodium ion

Significantly, changing the position of only one Na^+ ion from near the phosphate group linking G_3 and G_4 to a favored position near N-7 of G_4 reduces the radical cation density at the G_3G_4 step, and raises the vertical ionization potential of the duplex to 5.46 eV. Even more revealing is the relocation of the Na^+ ion found at the phosphate group linking A_2 and G_1 to N-7 of G_1. In this case, movement of the single Na^+ ion causes the radical cation to localize on the G_3G_4 step and the calculated vertical ionization potential of the duplex to increase to 5.69 eV. It is important to note that the magnitude of the fluctuation in vertical ionization potential caused by the relocation of just one Na^+ ion (and its accompanying water molecules) is greater than the measured difference in ionization potential between a G (the hole donor) and an A (the "bridge"). These findings indicate that thermal fluctuations of Na^+ ions allows the system to access a configuration in which the energy of the "bridge state" is below the energy of the hole donor.

These calculations show that a radical cation in DNA is delocalized and that its motion through the duplex is controlled, at least in part, by the motions of the Na^+ ions by a process we describe as *ion-gated charge transport*. In the ion-gated transport model, a radical cation (which may extend over several DNA bases) hops from one location to another by transitions between (quantum mechanical) states that are governed by the dynamically evolving local configurations of the Na^+ ions and water molecules. This concept is represented pictorially in Fig. 14 where the energy of the radical cat-

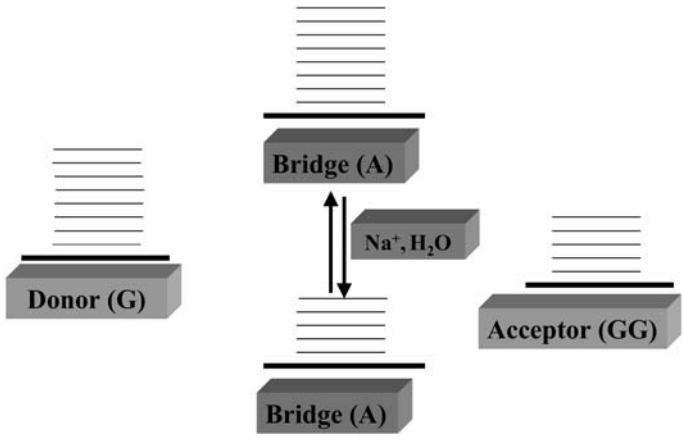

Fig. 14 Schematic representation of the ion-gated radical cation transfer postulate. A radical cation at the "donor site", identified as an isolated G, migrates to the "acceptor site", a GG step, through a bridge composed of contiguous A bases. The energy of the bridge is modulated by movements of the sodium ions and their accompanying water molecules. When the energy of the bridge comes close to the energy of the hole on the donor, the hole hops onto the bridge. Further motions result in additional energy changes that can cause the hole to migrate from the bridge to the acceptor. Of course, motions of the sodium ions can also modulate the energies of the hole donor and acceptor, but since only relative energies are relevant, these two possibilities are operationally equivalent

ion donor (G) and the radical cation acceptor (GG) are above or below the energy of the A bridge, which itself depends on the Na^+ ion configuration. In this model, there is no radical cation tunneling from G to GG through the A, and the rate determining step for the radical cation to hop is controlled by the global structure of the DNA and its environment.

In some conformations of the atoms that compose the DNA, the Na^+ ions, and the water molecules, the energy of the system with radical cation density on the bridging A is below that of configurations where the radical cation is localized on the G or GG, and it is under these conditions that the radical cation hops to the A where it resides briefly. At some nuclear configurations of the system, the energy of the radical cation on the GG step is below its energy on the bridging A or the donor G. These configurations are more likely to occur than those that stabilize the radical cation on the A or G; and consequently, the radical cation remains on the GG step for a longer time, which permits it to be trapped occasionally by H_2O.

10 Conclusions

Oxidation of DNA (loss of an electron) generates a radical cation that can migrate long distances to remote guanines in G_n steps where it is trapped by H_2O. Irradiation of anthraquinone-linked DNA oligomers is an efficient and effective method for introducing a radical cation into duplex DNA. The mechanism of long-distance radical cation migration is hopping. Of the two models currently being considered, ion-gated hopping of polaron-like distortions seems to be the most general.

References

1. Beckman KB, Ames BN (1997) J Biol Chem 272:19633
2. Cadet J (1994) In: Hemminiki K, Dipple A, Shiker DE, Kadlubar FF, Segerback D, Bartsch H (eds) IARC, Lyon
3. Sies H (1993) Mutat Res 275:367
4. Burrows CJ, Muller JG (1998) Chem Revs 98:1109
5. Pogozelski WK, Tullius TD (1998) Chem Revs 98:1089
6. Kasai H, Yamaizumi Z, Berger M, Cadet J (1992) J Am Chem Soc 114:9692
7. Schuster GB (2000) Acc Chem Res 33:253
8. Giese B, Meggers E, Wessely S, Spormann B, Biland A (2000) Chimia 54:547
9. Kelley SO, Barton JK (1999) Metal Ions Biological Syst 36:211
10. Rehm D, Weller A (1970) Israel J Chem 8:259
11. Armitage BA, Yu C, Devadoss C, Schuster GB (1994) J Am Chem Soc 116:9847
12. Gasper SM, Schuster GB (1997) J Am Chem Soc 119:12762
13. Ly D, Sanii L, Schuster GB (1999) J Am Chem Soc ??:9400
14. Sanii L, Schuster GB (2000) J Am Chem Soc 122:11545
15. Deshmukh H, Joglekar SP, Broom AD (1995) Bioconjugate Chem 6:578
16. Nakatani K, Dohno C, Saito I (1999) J Am Chem Soc 121:10854
17. Saito I, Takayama M, Sugiyama H, Nakatani K, Tsuchida A, Yamamoto M (1995) J Am Chem Soc 117:6406
18. Prat F, Houk KN, Foote CS (1998) J Am Chem Soc 120:845

19. Sartor V, Boone E, Schuster GB (2001) J Phys Chem B 105:11057
20. Steenken S, Jovanovic SV (1997) J Am Chem Soc 119:617
21. Giese B, Biland A (2002) Chem Commun ??:667
22. Hickerson RP, Prat F, Muller JG, Foote CS, Burrows CJ (1999) J Am Chem Soc 121:9423
23. Henderson PT, Jones D, Hampikian G, Kan Y, Schuster GB (1999) Proc Natl Acad Sci USA 96:8353
24. Nunez M, Hall DB, Barton JK (1999) Chemistry & Biology 6:85
25. Santhosh U, Schuster GB (2002) J Am Chem Soc 124:10986
26. Liu C-S, Schuster GB (2003) J Am Chem Soc (submitted for publication)
27. Barnett RN, Cleveland CL, Landman U, Boone E, Kanvah S, Schuster GB (2003) J Phys Chem B (in press)
28. Stemp EDA, Barton JK (1996) Metal Ions in Biol Systems 33:325
29. Murphy CJ, Arkin MR, Jenkins Y, Ghatlia ND, Bossman SH, Turro NJ, Barton JK (1993) Science 262:1025
30. Turro NJ, Barton JK (1998) J Biol Inorg Chem 3:201
31. Jortner J, Bixon M, Langenbacher T, Michel-Beyerle ME (1998) Proc Natl Acad Sci USA 95:12759
32. Bixon M, Giese B, Wessely S, Langenbacher T, Michel-Beyerle ME, Jortner J (1999) Proced Natl Acad Sci USA 96:11713
33. Bixon M, Jortner J (2000) J Phys Chem B 104:3906
34. Jortner J, Bixon M, Voityuk AA, Rosch N (2002) J Phys Chem A 106:7599
35. Barnett RN, Cleveland CL, Joy A, Landman U, Schuster GB (2001) Science 294:567
36. Rakhamanova SV, Conwell EM (2001) J Chem Phys B 105:2056
37. Conwell EM, Rakhmanova SV (2000) Proc Natl Acad Sci USA 97:4556
38. Bloomfield VA, Crothers DM, Tinoco JI (1999) Nucleic Acids: Structure, Properties, and Function. University Science Books, Sausalito
39. Dickerson RE (1992) Methods in Enzymol 211:67
40. Eley DD, Spivey DI (1962) Trans Farad Soc 58:411
41. Wan CZ, Fiebig T, Schiemann O, Barton JK, Zewail AH (2000) Proc Natl Acad Sci USA 97:14052
42. Fahlman RP, Sharma RD, Sen D (2002) J Am Chem Soc 124:ASAP (??)
43. Lewis FD, Zuo X, Hayes RT, Wasielewski MR (2002) J Am Chem Soc 124:4568
44. Shafirovich V, Dourandin A, Huang WD, Luneva NP, Geacintov NE (1999) J Phys Chem B 103:10924
45. Beveridge DL, McConnel KJ (2000) Current Opin Struct Biol 10:182
46. Troisi A, Giorgio Orlandi G (2002) J Chem Phys B 106:2093
47. Ly D, Kan Y, Armitage B, Schuster GB (1996) J Am Chem Soc 118:8747
48. Sewell GL (1962) Polarons and Excitions. Plenum Press, New York
49. Emin D (1986) Handbook of Conducting Polymers. Marcel Dekker, New York
50. McFail-Isom L, Sines CC, Williams LL (1999) Curr Opin Struct Biol 9:298