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Long-Range Charge Transfer in DNA: Transient Structural Distortions Control the Distance Dependence

GARY B. SCHUSTER
School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

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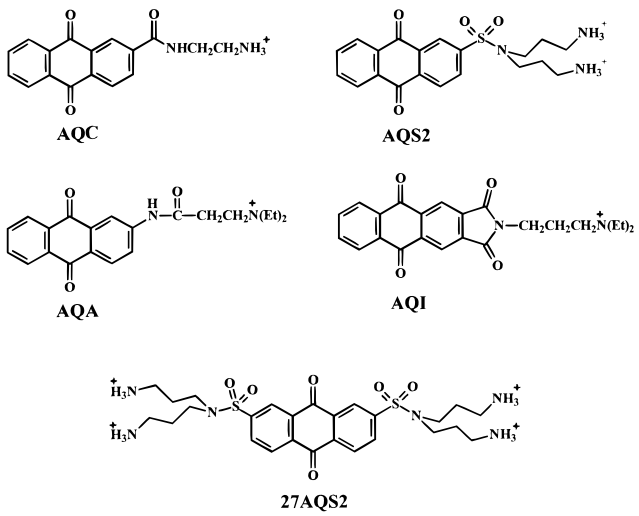
ABSTRACT
Damage to DNA is often caused by oxidative reactions. In one such process, an electron is lost from a base, forming its radical cation. Further reaction of the radical cation can lead to permanent change, which results in mutation. This Account is a report on oxidative damage to DNA caused by irradiation of anthraquinone derivatives, which are either randomly bound to the DNA or attached to it covalently at specific locations. Radical cations introduced in the DNA by the excited quinone cause damage both near to it and far away. We describe a mechanism for long-range charge transport in DNA that depends on its spontaneous structural distortion, which we call phonon-assisted polaron hopping. This mechanism, and its extension, provides a framework for understanding the reactions and charge-transport properties of DNA.

Introduction

DNA has fascinated generations of biological, chemical, and physical scientists. Its greatest role, of course, is as the vehicle for inheritance in cellular life, and for this reason understanding the processes that damage DNA and cause mutations takes on great importance. Oxidation of DNA, a major source of damage, may be initiated by reaction with singlet oxygen, $^1O_2$,[1] by hydrogen atom abstraction from a deoxyribose to form an intermediate free radical,[2] or by the loss of an electron from an aromatic base,[3] which forms an intermediate radical cation. Aspects of the latter two processes are topics of this Account. However, interest in DNA today goes beyond its role in biology. Its myriad self-organizing structural motifs are being manipulated to construct switchable molecular nanomachines.[4] And 600-nm-long "ropes" of desiccated DNA are claimed to be efficient electrical conductors, which have been identified as potential one-dimensional quantum wires for mesoscopic devices.[5,6] Electrical conduction and long-range oxidative damage of DNA may depend on common properties, since both require electronic interaction between base pairs. The nature of this electronic interaction is vigorously debated,[7−9] and this subject is a major part of this Account.

Gary B. Schuster was born in New York, NY, in 1946. He received his B.S. degree from Clarkson College of Technology in 1968 and his Ph.D. from the University of Rochester in 1971. Following a tour of active duty with the U.S. Army and a postdoctoral appointment at Columbia University with N. J. Turro, he joined the faculty of the University of Illinois−Urbana/Champaign in 1975, where he remained until 1994. He is currently Professor of Chemistry and Dean of Sciences at Georgia Institute of Technology.

Chart 1. Structures of the Anthraquinone Derivatives



Our study of DNA chemistry arose through collaboration with the late Professor Ole Buchardt of the University of Copenhagen. Troels Koch, a Ph.D. student with Buchardt, joined my laboratory to explore the photo-cross-linking of DNA to molecular probes. We concentrated our investigation on a series of anthraquinone derivatives, since their photochemistry appeared to be well understood, and they seemed promising for this application. However, we soon discovered that irradiation of anthraquinones caused DNA strand cleavage, not cross-links, and that observation changed our research objective. Experiments with anthraquinones of diverse structures bound to DNA by various means have revealed light-induced oxidative damage occurring both near to the quinone and far from it. Our research focused on defining the mechanism that causes damage and on determining the distance and sequence dependence of the long-range reaction.

Anthraquinones and DNA: Binding and Reactions

Intercalation and binding in the minor groove are two well-defined modes of strong association for small molecules with DNA.[10] Anthraquinones such as AQC and AQS2 (see Chart 1) are expected to intercalate because their planar aromatic, three-ring structures stack well with base pairs and because they efficiently fill the available intercalation space. Spectroscopic and thermodynamic studies of AQC strongly suggest its binding to duplex DNA by intercalation with little or no base sequence selectivity.[11] The chemical and spectroscopic interactions of AQS2 and AQC with DNA are essentially identical, and AQS2 forms a crystalline complex with the self-complementary sequence d(CGTACG). The 1.8-Å X-ray structure of this complex confirms intercalation of anthraquinone at the CG steps, with the alkylammonium tail located in the major groove.[12]

Irradiation of AQC complexed with DNA at 350 nm, where only the anthraquinone group absorbs, damages

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the DNA. Although intercalation is random, the damage, revealed as strand cleavage following piperidine treatment, is not. Most of the strand cleavage occurs at the 5′-G of GG steps, with lesser amounts at the 3′-G of this sequence and at the G of 5′-GA-3′ sequences.[13] This pattern has come to be associated with the one-electron oxidation of DNA. It may be the result of thermodynamic factors,[14,15] since G has the lowest oxidation potential (E_{ox}) of the four common DNA bases,[16] or of kinetic factors resulting from sequence-dependent activation energies.[12]

The excited state of AQC has an nπ* configuration which is capable of either abstracting a hydrogen atom from a deoxyribose (RH) or oxidizing a base to form the anthraquinone radical anion ($AQ^{-\bullet}$) and a base radical cation ($BH^{+\bullet}$). Time-resolved absorption spectroscopy reveals formation of $AQ^{-\bullet}$ within the 20-ps resolution of the experiment, but this does not settle the issue.[11] The pK_a of the semiquinone radical ($AQH^{\bullet}$) formed in the hydrogen abstraction is below the pH of the solution, and its deprotonation will give $AQ^{-\bullet}$ by a two-step route: $AQ^{*} + RH \rightarrow AQH^{\bullet} + R^{\bullet} \rightarrow AQ^{-\bullet} + H^{+}$.

Verification that electron transfer is the primary cause of DNA damage was provided by experiments with AQA, which also intercalates in DNA.[17] The structures of AQC and AQA differ in the "orientation" of the amide that links the anthraquinone and alkylammonium groups. In AQC, the amide carbonyl group is bonded to the anthraquinone; for AQA, the bond to the quinone is from the amide's nitrogen atom. This switch converts the lowest excited state of AQA to a $\pi\pi$* configuration, which is capable of electron transfer but not hydrogen atom abstraction. Irradiation of intercalated AQA cleaves DNA with the same 5′-G selectivity and same efficiency as observed for AQC: a result that is possible only if both AQC and AQA react by electron transfer.

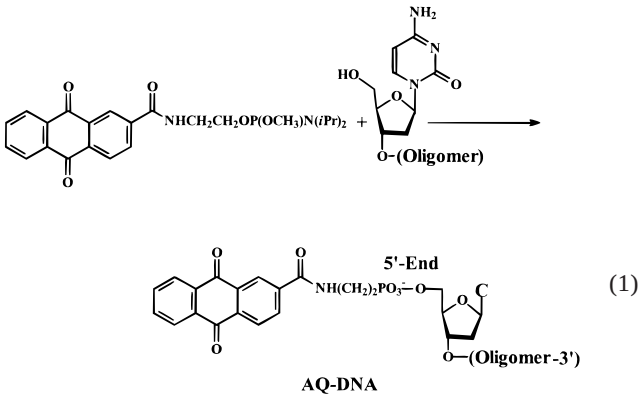
The fate of the $AQ^{-\bullet}$ formed in the one-electron oxidation of DNA plays an important part in the reaction mechanism.[11] Photointiated electron transfer gives radical ion pairs that may undergo rapid back electron transfer, which simply regenerates the starting materials. The anthraquinone excited singlet state formed by light absorption intersystem-crosses very rapidly to give a triplet state. Electron transfer to this state forms a triplet radical ion pair $[(AQ^{-\bullet})(BH^{+\bullet})]^3$, which is relatively long-lived because back electron transfer is forbidden by spin conservation rules. The increased lifetime of $AQ^{-\bullet}$ in the triplet ion pair allows it to react with O_2 to give superoxide ($O_2^{-\bullet}$), which we detect by its reduction of cytochrome *c*. This reaction re-forms the anthraquinone and leaves the DNA base radical cation with no partner in the DNA for annihilation: $[(AQ^{-\bullet})(BH^{+\cdot})]^3 + O_2 \rightarrow AQ + BH^{+\cdot} + O_2^{-\bullet}$. The net result of this reaction sequence is regeneration of the anthraquinone and injection of a radical cation into DNA. The strand cleavage at GG steps caused by irradiation of intercalated AQC comes from reactions of this radical cation. Identification of the mechanism for migration of the radical cation from its point of injection to the site of its reaction has captivated scientists worldwide.[18−20] This issue is addressed below, but first we consider briefly anthraquinone derivatives that do not bind to DNA by intercalation.

The physical and chemical interactions of 27AQS2 and AQI with DNA are markedly different from those of AQC.[21−23] Extensive analysis by 2D-NMR spectroscopy of the complex formed with the self-complementary sequence d(CGCGAATTCGCG) shows that 27AQS2 does not intercalate but binds in the minor groove primarily at the central AATT sequence. With hairpin-forming d(5′-CACTGGTCTCTACCAGTG-3′), where the underlined bases form a duplex stem that is capped by the single-stranded CTCT loop, 27AQS2 binds at the loop and at the stem−loop junction. Intercalation by 27AQS2 is inhibited because both "ends" of the anthraquinone group have large out-of-plane substituents. Spectroscopic analysis and scanning force microscopy show that AQI also does not bind by intercalation. Irradiation of these non-intercalated anthraquinone complexes does not give the efficient GG-selective cleavage that is characteristic of radical cation injection into DNA. Instead, the results depend on the precise binding mode and on the specific base sequence. Both the hydrogen atom abstraction and electron-transfer mechanisms operate, but base damage is controlled primarily by secondary structure and solvent (H_2O) exposure. Evidently, efficient charge injection requires good π-electron overlap of the anthraquinone with the DNA bases.[24]

Long-Distance Charge Transport in DNA

The illusory static regularity of DNA's canonical double helix has repeatedly provided inspiration for suggestions that it possesses extraordinary physical properties.[25] Barton and co-workers first attributed charge transport over more than 40 Å in less than 1 ns to superexchange through a bridge orbital of well-stacked bases they called a "π-way".[8,26] Later, they suggested that the ability of DNA to transport charge is gated by dynamical disruption of stacking.[27] Indeed, radical cations randomly injected into DNA by γ-irradiation of frozen samples are known to migrate,[28] but the rate and mechanism are unclear.[29] The anthraquinone derivatives provide a means to inject a radical cation into the DNA helix and study its migration. However, a clearly defined point of charge injection is essential to their utilization as probes of the charge-transport mechanism. This was accomplished by covalently linking an anthraquinone to a 5′-end of duplex DNA.[30]

The synthesis of DNA oligomers containing a linked anthraquinone group proceeds smoothly from the phosphoramidite using solid-phase methods (eq 1). The four-atom tether linking the 5′-end of the DNA to the quinone is too short to permit intercalation. The application of chemical and physical probes led us to conclude that the linked quinone is associated with the DNA terminus by end-capping.[30] The anthraquinone is hydrophobic and electron deficient relative to the DNA bases. Together, these factors encourage π-electron overlap between the



(1)

AQ-DNA

quinone and the DNA.[31] Figure 1 shows a model illustrating an end-capped duplex. Excitation of the quinone in this configuration results in transfer of one electron and injection of a radical cation into the DNA at a well-defined location.

Chart 2 shows two AQ-linked duplex oligonucleotides designed to address questions of radical cation transport and reaction in DNA. AQ-DNA(1) is a 60-mer with an anthraquinone group linked to its 5′-terminus.[9] Its complement, DNA(2), contains four GG steps located various distances from its 3′-end. In duplex AQ-DNA(1)/DNA(2), there are nine base pairs between the AQ and G_{10}, which is the 5′-G of the first GG step a migrating radical cation will encounter. The most distant 5′-G is G_{55}, which is 185 Å from the AQ. There is no regularity in the base sequences between the four GG steps of DNA(2). In particular, there are three adjacent T bases before G_{10}, and there are five contiguous A or T bases between G_{28} and G_{46}. Runs of A and T bases have been proposed to be barriers for radical cation migration.[19]

Irradiation of AQ-DNA(1)/DNA(2) at 350 nm leads to damage at each of the four GG steps, which is revealed as strand cleavage after treatment with piperidine or formamidopyrimidine glycoslyase (Fpg). Control experiments confirm that this is an intramolecular reaction, which occurs by migration of a radical cation. The reaction efficiency decreases with increasing distance between the AQ group and the GG step. Figure 2 reveals a linear relationship between the log of reaction efficiency and distance that falls off with a slope of -0.02 Å^{-1}. This very long-range reaction has now been generally observed. It is found for other AQ-containing systems,[32] and Barton and co-workers recently reported guanine oxidation by photoexcitation of a covalently linked Rh(III) derivative over a distance of 200 Å.[33] The linear relationship between efficiency and distance revealed in Figure 2 clearly indicates the operation of a charge-transport process that averages differences in the base sequence between GG steps. This fact plays a key role in defining the possible mechanisms for long-distance charge transport.

A radical cation injected into AQ-DNA(1)/DNA(2) must pass through a nearby GG step to damage one that is farther away. GG-containing sequences have calculated ionization potentials below single guanines,[14] but the depth of this "trap" evidently is not great enough to stop the migrating charge. The oxidation potential of 7,8-dihydro-8-oxoguanine (8-OxoG) is ca. 0.5 eV below that of G,[34] and its incorporation in DNA does not cause significant structural distortion.[35] We found that charge transport to a distant GG step is inhibited when the 5′-G of a nearer GG step is replaced by 8-OxoG.[30] The radical cation transport is retarded by the deeper, more reactive trap, and this provides a powerful tool for mapping the migration path.

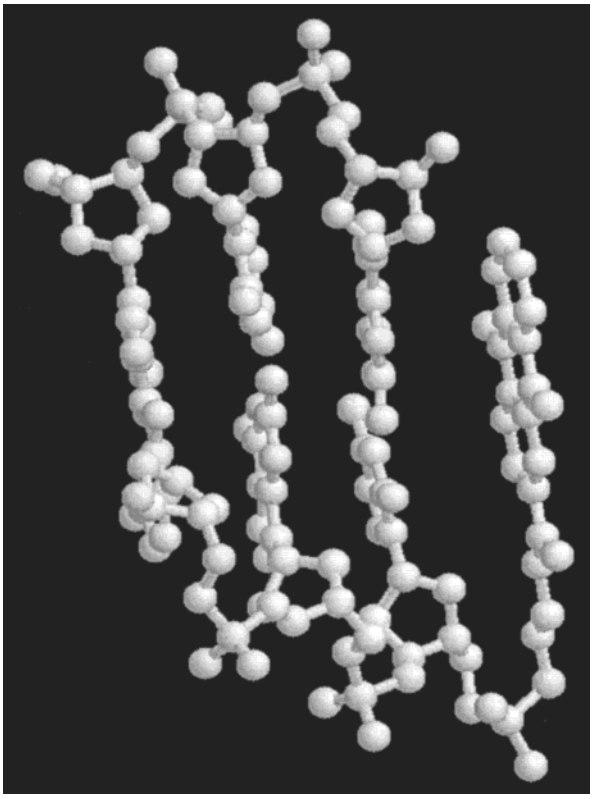
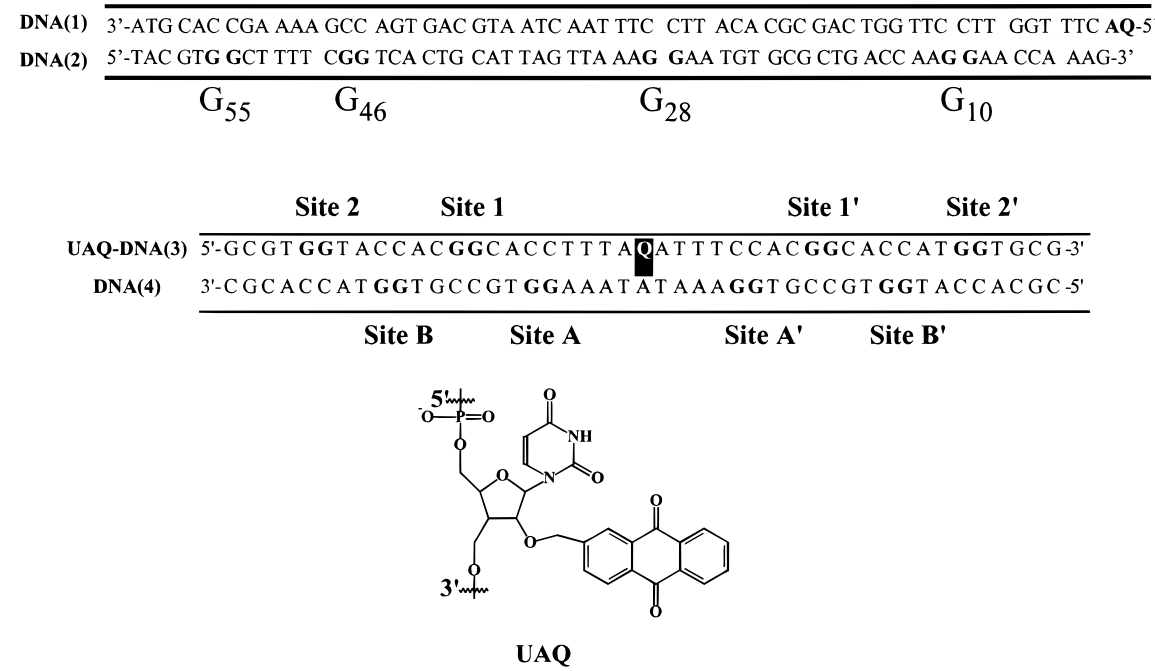


FIGURE 1. Model illustrating end-capping of the DNA duplex by the covalently attached anthraquinone. The covalent linkage is that shown in eq 1. The DNA coordinates used in this model were taken from the Protein Data Bank. The three base pairs shown, d(5′-CGC-3′), were removed from the end of the sequence. The model structure was created in Biosym by forming a bond between the anthraquinone and the 5′-OH of the DNA, followed by manipulation of the linker torsion angles to place the anthraquinone over the terminal CG base pair.

UAQ-DNA(3) contains an anthraquinone derivative linked to the ribose 2′-oxygen atom of a uridine located at the central position of a symmetrical oligomer (Chart 2). Physical and spectroscopic experiments suggest that the quinone group intercalates at the 3′-side of the UAQ-DNA/DNA(3) duplex.[36,37] UAQ-DNA contains four GG steps, two on each side of the UAQ, and its complement, DNA(3), also has four symmetrically disposed GG steps. The path for migration of radical cations injected at the UAQ intercalation site was mapped by substitution of 8-OxoG for 5′-G at GG steps in DNA(4).[32] These experiments show that 8-OxoG effectively stops migration to GG steps when the radical cation must pass through it: an 8-OxoG at site A stops reaction at site B. But 8-OxoG substitution does not inhibit damage to GG steps on the opposite side of the UAQ: an 8-OxoG at sites A or B does not affect damage at sites A′ or B′ (and vice versa).

Chart 2. Structures of AQ-Linked DNA Oligomers Used for Probing the Distance Dependence of Charge Transport (Q stands for UAQ)



Significantly, radical cations can cross from strand to strand but, in this case, not as effectively as they migrate on one strand of the duplex: an 8-OxoG at site A inhibits reaction at sites 1 and 2, but not as much as at site B.

The findings from examination of AQ-DNA(1)/DNA(2) and UAQ-DNA(3)/DNA(4) help to reveal the mechanism for long-range radical cation migration in DNA. In particular, interpretation of the significance and magnitude of the distance dependence for long-range charge transfer in DNA (the slope in Figure 2) has sparked an intensive debate.[7,8,38,39] Its characterization as β, a measure of the distance dependence for electronic coupling, has been vigorously challenged. This has prompted an alternative, phenomenological characterization of the slope as γ,[40] and the introduction of time-dependent disruptions to base stacking as another parameter, which controls long-range electron transfer.[27] Our findings support a kinetic model for γ, which supports a multistep charge-transport mechanism.[9,18]

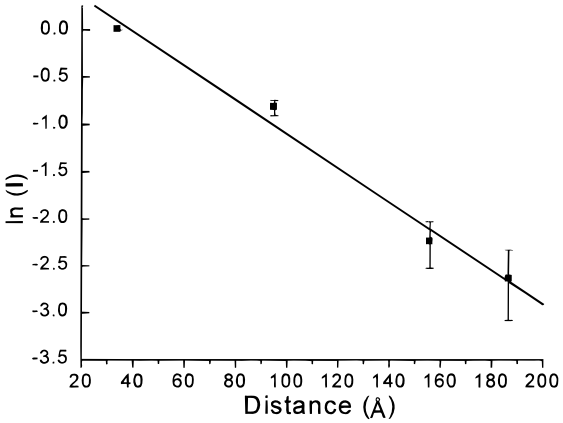


FIGURE 2. Semilog plot of the cleavage intensity after piperidine treatment of irradiated DNA(1)/5′-^{32}P-DNA(2), determined by counting the radioactivity with a β-detector. The measured counts in each band were normalized so that $G_{10} \equiv 1.0$. The distance scale was calculated assuming an average distance of 3.4 Å between base pairs. The error bars represent standard deviations calculated from four independent experiments.

A Mechanism for Charge Transport: Phonon-Assisted Polaron-Like Hopping

Two limiting mechanisms of charge transport in DNA may be considered. In the first, DNA behaves like a wire having a continuous, delocalized molecular orbital. In this orbital, each base pair is in electronic contact with every other, and charge transport occurs by superexchange.[8] The second model is discrete hopping, which presumes that the radical cation is localized on one base and has no significant electronic overlap with adjacent bases. The localized radical cation migrates (hops) by a thermally activated process to adjacent bases.[13] Jortner and coworkers advanced arguments that superexchange and multistep charge transport will operate in separate energetic regimes.[18] Our findings and those recently reported by others[41] suggest that charge transport requires a structural distortion of the DNA in both the superexchange and hopping regimes.

DNA is dynamic: sugar and base motions occur with periods as short as 30 ps.[42] Injection of charge into DNA will cause its structure to change. Base radical cations are electron deficient, and DNA will rapidly distort its local structure to relieve this deficiency. The radical cation will be stabilized by its delocalization onto adjacent bases. Delocalization may be accomplished by a change in the normal inclination angle of neighboring bases, which will bring them closer to the radical cation, thus delocalizing and stabilizing it. Also, unwinding of the DNA may delocalize the radical cation by increasing the π-electron overlap with neighboring bases.[43] Base radical cations are

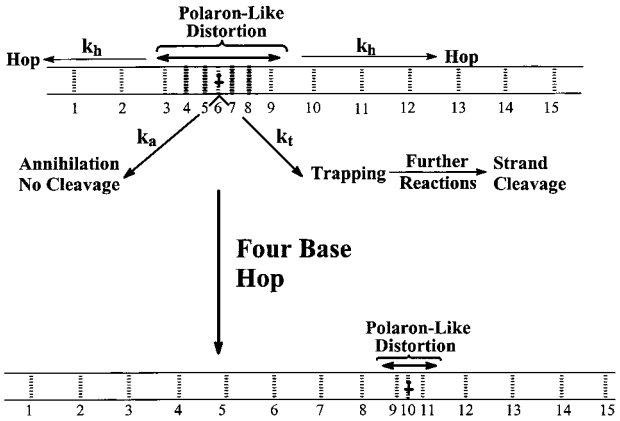


FIGURE 3. Schematic representation of DNA where the vertical lines represent the base pairs and the horizontal lines stand for the sugar−phosphate backbone. The upper structure shows a 15-mer containing a radical cation delocalized as a polaron distortion over seven base pairs (3−9). The polaron may be consumed by annihilation (k_a), by reaction leading to strand cleavage (k_t), or by (phonon-assisted) hopping (k_h). A four-base hop is depicted in the figure, with the lower structure showing a polaron delocalized over three base pairs (9−11) of the 15-mer

more acidic than their uncharged forms,[44] and the partially charged bases of a delocalized radical cation will certainly respond similarly. Consequently, shifts of proton location in the hydrogen bonds forming the base pairs are another likely structural distortion caused by radical cation injection.

A polaron is defined as a radical ion self-trapped by structural distortion of its containing medium.[45] The distorted section of duplex DNA surrounding a base radical cation may be considered a polaron-like species (Figure 3).[18] The detailed properties of the distortion will depend on base sequence, and for this reason it is not strictly a polaron. The polaron will not extend indefinitely through the DNA oligomer. At some point the energy required to distort the DNA will just balance the stabilization, and then extension of the polaron will stop.

The formation of a polaron provides a means for averaging the differences in base sequences required by the data in Figure 2. Thermodynamic values of E_{ox} for bases in DNA are not available. However, evidence for averaging is revealed in Saito's calculation of ionization potentials (I_p).[14] For example, the calculated I_p of guanine in a GC pair is 7.34 eV,[15,46] but the I_p values for the 5-mer duplex sequences TAGAT and TTGTT in their standard B-forms are estimated to be only 6.73 and 6.96 eV, respectively. Stabilization of the radical cation will increase when the normal DNA geometry relaxes to accommodate the charge and forms a polaron. It thus seems certain that the differences between E_{ox} of the DNA bases will be reduced when they are in duplex DNA, since those bases that are more difficult to oxidize will benefit most from delocalization.

Radical cation strand crossover, revealed by Giese's experiments[19] and examination of UAQ-DNA(3)/DNA(4), also attenuates base sequence differences. Increased electronic overlap of a partially charged pyrimidine (C and T have high E_{ox}) with a purine (A and G have lower E_{ox}) in the distorted structure may facilitate crossover and reduce the effect of base sequence differences on the efficiency of charge transport.

Movement of the polaron provides a mechanism that explains long-range radical cation migration in DNA.[9,18,32] Thermal (phonon) activation will cause base pairs in and near the structural distortion to leave or join the polaron. In simple terms, this may be thought of as analogous to the movement of a compression through a coiled spring. We designate it phonon-assisted polaron hopping.

The number of base pairs in the polaron hop will depend on the sequence, and this is a second mechanism for averaging sequence differences. For example, the 3-mer CGC and the 5-mer TTGTT both have calculated $I_p = 6.96$ eV.[14] Thus, to the extent that the calculations reflect reality for the distorted structures, the four-base hop $[CGC]^{+\bullet} \rightleftarrows [TTGTT]^{+\bullet}$ in the sequence $d(CGC_1T_2T_3G_4TT)$ can occur with $\Delta G^\circ = 0$. In general, we suppose that the size of each hop the polaron takes will be determined by the number of bases required to minimize the free energy change.

The phonon-assisted polaron hopping model for long-distance charge transport in DNA is accommodated within the bounds of Marcus theory for electron-transfer reactions.[47,48] Transition-state theory identifies the transmission coefficient, κ, and the activation energy, $\Delta G^\ddagger$, as the electronic and nuclear factors that determine rate constants for reactions: $k_{et} = (\kappa kT/h)e^{-\Delta G^\ddagger/RT}$. The $\Delta G^\ddagger$ for electron transfer depends quadratically on the sum of the reorganization energy (λ) and ΔG° according to $\Delta G^\ddagger = (\lambda + \Delta G^\circ)^2/4\lambda$. Polaron formation and variable hop length provide a means for the minimization of ΔG°. Phonon-driven motions of the bases in and near the polaron provide the activation energy required to raise the system to its transition state. If the electron donor and acceptor are close together ($r = r_o$), the electronic factor is relatively large, but κ decreases exponentially with distance when they are far apart ($r > r_o$) according to $\kappa = A \exp[-\beta(r - r_o)]$, where A is related to vibrational frequency. Experimentally, systematic variation of the separation between an electron donor and acceptor reveals the distance dependence, which, depending on the mechanism, may be controlled by either the nuclear or electronic factor. The slope of Figure 2, γ, is a measure of the distance dependence for radical cation migration in DNA. Its value is far too small for it to be β, which is expected to be $\approx$1.2 Å^{-1}.[38] In the phonon-assisted polaron hopping mechanism, we assume that κ is large, and that a kinetic model identifies γ as a measure of relative reaction rates.

A Kinetic Model for γ

For clarity and simplicity, we limit the polaron in DNA to the three reactions that are outlined in Figure 3. It can hop, a process we symbolize with the first-order rate constant k_h. We presume that k_h is independent of sequence, which implies that, after the first step, migration in either direction is equally likely. This is a hypothesis that we are currently testing with further experiments. A

second reaction is annihilation, assigned rate constant k_a, which results in consumption of the polaron but does not generate strand cleavage. The third reaction is trapping of the polaron at a GG step, symbolized by k_t. Trapping of the polaron yields a chemical product that is revealed as strand cleavage. Both k_a and k_t are treated as first-order process by assuming a constant reagent concentration.

$$P_c = P_f P_t [e^{(n-2)\log(P_h)}] \quad (2)$$

$$P_t = \frac{k_t}{k_t + k_a + 2k_h} \quad (3)$$

$$P_f = \frac{k_h}{k_t + k_a + k_h} \quad (4)$$

$$P_h = \frac{2k_h}{k_t + k_a + 2k_h} \quad (5)$$

Application of probability theory to this kinetic model yields eq 2 as a description of the radical cation migration process. In eq 2, P_c is the amount of strand cleavage observed at a particular base and is directly proportional to the experimental value **I** in Figure 2, n ($\geq$ 2) is the number of hopping steps between the cleavage site and the point of charge injection, P_t is the probability of trapping the polaron, P_f is the probability that the first, unique step will occur, and P_h is the probability that the polaron will hop before it is annihilated or trapped. Within this model, the slope, γ, in Figure 2 is proportional to log (P_h).

The delocalized polaron kinetic model for long-distance charge transport in DNA contains features of both the instantaneous delocalization and the discrete hopping models that are identified above as mechanistic extremes. Fundamentally, charge moves through the DNA by distinct hops, but it is not hopping of a radical cation that is localized on one base. Instead, the charge is delocalized in a distorted segment of the DNA containing several base pairs (the polaron). Thermal motions (phonons), which distort adjacent segments of the DNA, cause the polaron to hop one or several base pairs. Significantly, this model may be extended to cases where charge is not injected and the distance dependence of charge transfer has been identified as a measure of β.[8,26,40,49−55]

In these experiments, the DNA is modified so that it contains a covalently linked, fluorescent electron acceptor and an electron donor situated some variable distance from the fluorescer. The effect of this separation distance on the fluorescence intensity or lifetime is then taken as a measure of β. Unlike the anthraquinone irradiation experiments, in these cases there is no injected radical cation whose electron deficiency distorts the DNA structure. However, the kinetic model suggests an alternative interpretation of these experiments, which has received some experimental support.[41]

Structural fluctuations occur spontaneously in DNA. It is clear now that the π-electron overlap of bases in canonical B-form DNA is insufficient to create a π-way as it was originally conceived.[26] However, some transitory distorted structures among the entire population of DNA conformations may contain such a pathway. The instantaneous concentration of these structures is defined by the kinetic steady-state hypothesis as a ratio of the rates for their formation and disappearance. Rapid (less than 1 ps) quenching of fluorescence can occur in those conformations when the distortion creates a continuously overlapped π-orbital that extends all the way from the fluorescer to the quencher. In this view, the experimentally observed distance dependence for electron transfer is not a measure of β; instead, it reflects the effect of distance on the probability of forming suitable π-way-containing distortions.

The polaron hopping model and its extension to include spontaneous structural distortion provides a framework for interpretation of long-distance charge transfer in DNA that extends the mechanistic duality on the basis of energetic criteria.[18] It seems that spontaneous distortions of the B-form DNA structure can cause transient π-electron overlap of three or four base pairs (a distance of 10 or 15 Å) that is sufficient to allow electron transfer by superexchange when that is required by energetic considerations.[32,41] This is the extent to which DNA may be considered to behave like a molecular wire. In contrast, a radical cation injected in DNA may migrate 50 or 60 base pairs (a few hundred angstroms) by formation of a multibase polaron, which hops through the DNA.[9,33] Finally, conductivity measurements seem to show that some degree of electronic overlap can extend for thousands of base pairs in certain ill-defined DNA structures.[5,6] These observations suggest the exciting possibility that among the myriad stable forms of DNA, some may prove to be more suitable for electron transfer than the B-form.

The Future: DNA from A to Z

The heading for this section is taken from the title of a review article detailing the variety of structural forms found and created in DNA oligomers.[56] The global structure of DNA can be manipulated by selecting particular base sequences, by chemical modification to the natural bases, by creating structures with other than two strands, by replacing some of the deoxyriboses with riboses, by changing the group linking the deoxyriboses, by changing the phosphate's counterions, or by changing the ionic strength of the solvent. The point, of course, is that each of the unique structural forms will have its own characteristic π-electron overlap and its own sets of k_h, k_a, and k_t. We have begun the investigation of the effect of structural modification on the reactions of radical cations and long-range charge transport in DNA with some surprising results which can be summed up in a simple phrase: structure matters. For example, DNA triplexes and structures having single-stranded regions transport charge but behave differently than duplex DNA. In truth, the investigation of charge transport and reaction in DNA is still at an early stage. It seems certain, however, that future

research will reveal additional interesting and important aspects of this fascinating topic.

I am deeply indebted to all of the students and co-workers who have contributed to the work described in this Account. It is because of their insight and hard work that this effort has been productive. We are grateful to the National Science Foundation and to the National Institutes of Health for financial support.

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