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Emergent Functionality of Nucleobase Radical Cations in Duplex DNA: Prediction of Reactivity Using Qualitative Potential Energy Landscapes

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Abstract: The one-electron oxidation of a series of DNA oligonucleotides was examined. Each oligomer contains a covalently linked anthraquinone (AQ) group. Irradiation of the AQ group with near-UV light results in a one-electron oxidation of the DNA that generates a radical cation (electron "hole"). The radical cation migrates through the DNA by a hopping mechanism and is trapped by reaction with water or molecular oxygen, which results in chemical reaction at particular nucleobases. This reaction is revealed as strand cleavage when the irradiated oligonucleotide is treated with piperidine. The specific oligomers examined reveal the existence of three categories of nucleobase sequences: charge shuttles, charge traps, and barriers to charge migration. The characterization of a sequence is not independent of the identity of other sequences in the oligonucleotide, and for this reason, the function of a particular sequence emerges from an analysis of the entire structure. Qualitative potential energy landscapes are introduced as a tool to assist in the rationalization and prediction of the reactions of nucleobases in oxidized DNA.

The one-electron oxidation of DNA is an important biological process because it leads to nucleobase damage and to possible mutations.[1] Numerous investigations over the past decade have revealed that the radical cation ("hole") formed by electron loss from DNA can migrate long distances through the duplex by a hopping mechanism.[2−4] Eventually, the migrating radical cation is consumed at traps in an irreversible reaction with water or molecular oxygen.[5,6] The efficiency of this long-distance charge migration is determined by the specific sequence of nucleobases in the DNA oligomer. In some cases, the trapping reaction at a particular nucleobase (k_{trap}) is much faster than hopping from base to base (k_{hop}), and transport proceeds from the point of charge injection through just a few base pairs. For other sequences of nucleobases, hopping is much faster than trapping, and radical cation migration over very long distances is observed.[7] These charge transport properties of DNA and its ability to self-assemble have led to suggestions that it may be useful in the construction of molecular electronic devices.[8,9]

In a seminal discovery, Kawanishi and co-workers showed that the reaction of radical cations in duplex DNA normally occurs primarily at GG steps.[10] This finding is currently understood on the basis of oxidation potentials. Guanines are the most easily oxidized of the four DNA nucleobases, and both calculations[11] and kinetic measurements[12] indicate that GG sequences have a lower oxidation potential than an "isolated" guanine. These relatively low oxidation potential sites serve as shallow traps where the radical cation pauses long enough to permit irreversible reaction with water or molecular oxygen to occur. These conclusions have been expanded on the basis of calculations that identify the nucleobases on the 3′-side of a guanine as the primary determinant of the extent of oxidative damage.[13,14] Purines lower the oxidation potential of the guanine more than pyrimidines do, and this accounts for the GG effect as well as for the observation that a guanine with an adenine on its 3′-side is also an especially reactive site.[15] Consistent with this view, Giese and co-workers have observed that radical cations are transported efficiently through TGT sequences, and that the relative reactivity of those "isolated" guanines is much lower than it is for those in G_n ($n > 1$) sequences.[16,17]

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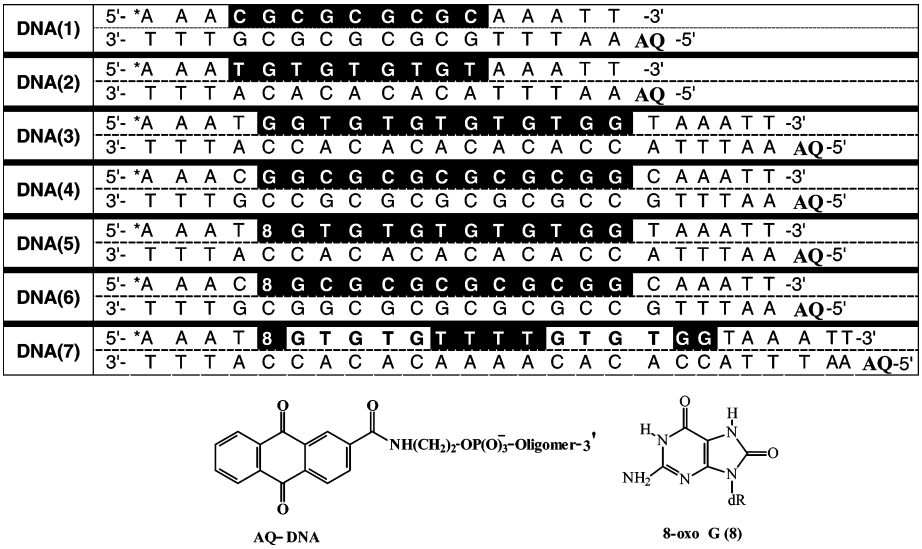

Figure 1. Structures of the DNA oligomers used in this work.

We report here the results of a systematic study of radical cation transport in DNA oligomers containing TGT and CGC sequences. We analyzed the reactivity of radical cations in oligomers containing only such isolated guanines and compared that with similar constructs that also contain GG steps or an 8-oxo-7,8-dihydroguanine (8-oxoG), which due to its low E_{ox} is a deep trap.[18,19] The results show that the reactivity of a particular nucleobase in a DNA oligonucleotide is not determined exclusively by its oxidation potential. Specific reactivity can be understood only by considering the set and sequence of bases in the entire oligonucleotide. In this regard, the properties of nucleobase radical cations are complex functions whose values emerge from consideration of the interactions of all nucleobases of the DNA oligomer among themselves.

Materials and Methods

[γ-^{32}P]ATP radioactive isotopes and T4 polynucleotide kinase were purchased from New England Biolab and stored at −20 °C. Unmodified DNA oligomers and AQ containing complementary oligomers (HPLC grades) were synthesized as described elsewhere on an Applied Biosystems DNA synthesizer.[20] The extinction coefficients of the oligomers were calculated using the Online Biopolymer Calculator, and the absorbance was measured at 260 nm. Reverse-phase HPLC was performed on a Hitachi system using a Microsorb-MV C18 reversed-phase column (4.6 mm i.d. × 25 cm length, 300 Å) from Rainin with an oven temperature maintained at 65 °C. The oligonucleotides gave the expected mass spectra. UV melting and cooling curves were recorded on a Cary 1 E spectrophotometer equipped with a multicell block, temperature controller, and sample transport accessory. CD spectrum was recorded in JASCO J-720 spectropolarimeter.

Cleavage Analysis by Radiolabeling and Polyacrylamide Gel Electrophoresis (PAGE). DNA oligonucleotides were radiolabeled at the 5′-end with [γ-^{32}P]ATP and bacterial T4 polynucleotide kinase. The radiolabeled DNA was purified by 20% PAGE. Samples for irradiation were prepared by hybridizing a mixture of "cold" and radiolabeled (10 000 cpm) oligonucleotides with AQ or non-AQ complementary strands in sodium phosphate buffer (pH = 7.0) and water (to a total volume of 20 μL). Hybridization was achieved by heating the samples at 90 °C for 10 min, followed by slow cooling to room temperature overnight. Samples were irradiated in microcentrifuge tubes in a Rayonet photoreactor (Southern New England Ultraviolet Company, Barnsford, CT) equipped with 8 × 350 nm lamps at ca. 30 °C. After irradiation, the samples were precipitated once with cold ethanol (100 μL) in the presence of glycogen, washed with 80% ethanol (100 μL), dried (speedvac, low heat), and treated with piperidine (100 mL, 1 M solution) at 90 °C for 30 min. After evaporation of the piperidine (speedvac, medium heat), lypholization twice with water (20 μL), and suspension in denaturing loading buffer, the samples (3000 cpm) were electrophoresed on a 20% 19:1 acrylamide:bisacrylamide gel containing urea (7 M) at 70 W for 90 min. The gels were dried, and the cleavage sites were visualized by autoradiography. Quantization of cleavage bands was performed on a phosphorimager.

Results

The seven duplex DNA oligonucleotides examined in this study, shown in Figure 1, were prepared, purified, and characterized by standard procedures.[20] Each duplex contains an anthraquinone group (AQ) linked to a 5′-terminus and a ^{32}P radiolabel (∗ in Figure 1) at the 5′-terminus of the complementary strand for analysis of strand cleavage reactions by autoradiography. DNA(1) contains the nine base pair sequence 5′-CGCGCGCGC-3′ in the central region of the labeled strand delimited on both flanks by sequences that do not contain guanines. Each G has a C on both its 5′- and 3′-sides in this central region of DNA(1). DNA(2) is constructed similarly except that it contains a nine base pair 5′-TGTGTGTGT-3′ sequence central region in which each G has a T on both its 5′- and 3′-sides. In contrast, the central 5′-TGTGTGTGT-3′ sequence of DNA(3) is flanked at both ends by GG steps; similarly for DNA(4), GG steps flank its 5′-CGCGCGCGC-3′ central sequence. In DNA(5), the 5′-GTGTGTGT-3′ central sequence is flanked by a GG step on its 3′-side and an 8-oxoG on its 5′-side (**8** in Figure 1), and similarly for DNA(6), a GG step and an 8-oxoG flank the 5′-CGCGCGCGCG-3′ central sequence. DNA(7) is unique, its central 5′-TGTG(T)$_4$GTGT-3′ sequence of TGT nucleobases contains a (T)$_4$ segment in the middle, and it is flanked on the 5′-side by an 8-oxoG and on the 3′-side by a GG step.

Irradiation of an AQ-linked duplex DNA oligomer at 350 nm, where only the AQ absorbs, injects a radical cation into

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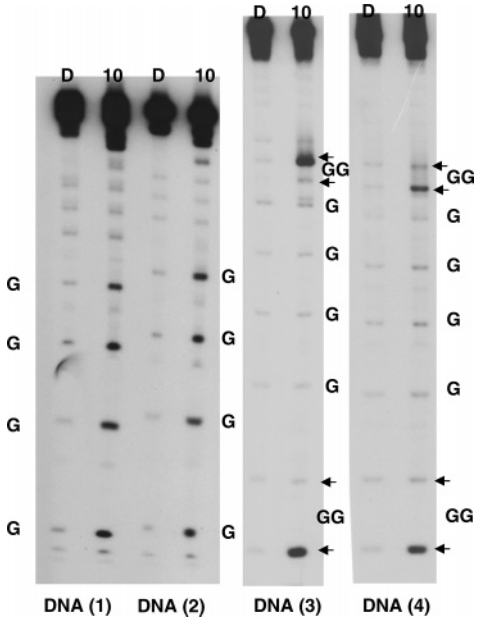

Figure 2. Autoradiograms from the irradiation of DNA(1) through DNA-(4). The lanes labeled D are the dark controls, no irradiation. The samples in lanes labeled 10 were irradiated for 10 min (8 lamps, 350 nm) and then treated with 1 M piperidine, which causes strand cleavage at highly oxidized guanines, before gel electrophoresis. The ^{32}P is at the 5′-terminus of the labeled oligomer. The guanines are indicated by a G, and the guanines that are part of a GG step are indicated with arrows.

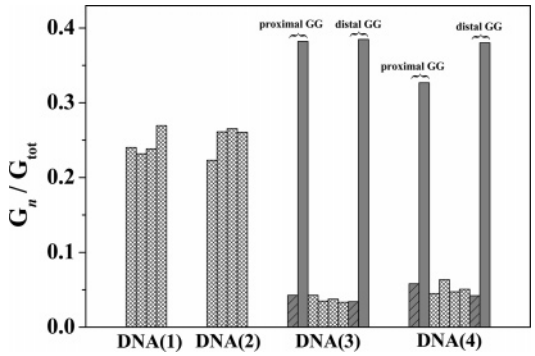

Figure 3. The ratio of the strand cleavage at a particular guanine (G_n) to the total amount of strand cleavage at all guanines in the oligomer (G_{tot}) determined by phosphorimagery of oligomers DNA(1) through DNA(4). The speckled bars represent the isolated guanines in the central region, whereas the solid gray bars represent the 5′-G of the GG steps, and the crosshatched solid gray bars are the 3′-G of the GG steps.

the DNA that migrates through the oligomer by hopping until it is irreversibly trapped by reaction with H_2O or O_2 to create an oxidatively "damaged" DNA nucleobase.[21] Subsequent treatment of the irradiated oligomer with piperidine results in strand cleavage at highly oxidized damage sites.[22] The amount of strand cleavage at a particular nucleobase at low conversion (single-hit conditions) is directly proportional to the relative reactivity of that base in the duplex oligonucleotide.

Irradiation of DNA(1) and its subsequent piperidine treatment results in strand cleavage at each of the four guanines in the labeled strand of this compound (see Figure 2). The results of quantitative phosphorimagery (Figure 3) show that within experimental error the amount of cleavage is the same at each of the four guanines in the central region of DNA(1), which indicates that for this sequence of nucleobases k_{hop} from G to G across a C bridge is much faster than k_{trap}. Consequently, trapping of the radical cation occurs with equal probability at each of the four essentially equivalent guanines in this oligonucleotide. Similarly for DNA(2), where the single base bridge between guanines is a T, irradiation and piperidine treatment results in equal cleavage at all four guanines (see Figure 2 and Figure 3), which indicates in this case too that k_{hop} is much greater than k_{trap}. From these findings, it would appear appropriate to conclude that the one-electron oxidation of duplex DNA will lead to extensive reaction at guanines in CGC or TGT sequences. However, examination of DNA(3) through DNA-(7) shows that this will not always be the case.

The central region of DNA(3) contains the same set of TGT nucleobases as DNA(2) except that it is flanked by GG steps on both sides. Figure 2 shows the results of irradiation of DNA-(3) after its subsequent treatment with piperidine. Strand cleavage occurs predominantly at the 5′-guanines of the two GG steps. The reactivity at the 5′-G of the GG step is approximately 10 times greater than that of a guanine embedded in the TGTGTGTGT sequence as shown by quantitative phosphorimagery in Figure 3. It is important to note that the amount of strand cleavage observed at the distal GG step (the one farthest from where the radical cation is injected at the AQ) is the same as the proximal GG step (closest to the AQ), which shows that for this oligomer k_{hop} is greater than k_{trap} and that thermodynamic considerations control the reaction's outcome. A nearly identical result is obtained from the irradiation of DNA-(4). In this case too, strand cleavage is dominant at the 5′-guanines of the GG steps that flank the central CGCGCGCGC sequence. In both of these examples, introduction of "remote" GG steps modulates the reactivity of the isolated guanines, and it would appear appropriate to conclude that the one-electron oxidation of DNA will always cause extensive reaction at GG steps. However, the examination of DNA(5) and DNA(6) shows that this is not the case.

Both DNA(5) and DNA(6) have GG steps preceding the central regions that contain the TGT and CGC sequences, respectively, and the central regions are followed by an 8-oxoG. The results of their irradiation and piperidine treatment are shown in Figures 4 and 5. There is virtually no strand cleavage at the GG step or at any guanine in the central region. All of the measurable light-induced reaction occurs at the 8-oxoG even though it is 19 base pairs (ca. 65 Å) from the site of charge injection adjacent to the AQ. Clearly the radical cation must pass through the GG step and the intervening isolated guanines before it arrives at the 8-oxoG, but the introduction of this remote deep trap inhibits reaction at these "normally" reactive sites. In this example, introduction of 8-oxoG quenches the reaction of isolated guanines and of GG steps. Thus it seems that the one-electron oxidation of duplex DNA should always lead to extensive reaction at an 8-oxoG. However, the examination of DNA(7) shows that this is not the case.

The results of irradiation and subsequent piperidine treatment of DNA(7) are shown in Figures 4 and 5. Surprisingly, there is essentially no strand cleavage above the background amount at the 8-oxoG. Instead, the majority of the reaction is observed to occur at the GG step closest to the AQ. In this case, the $(T)_4$

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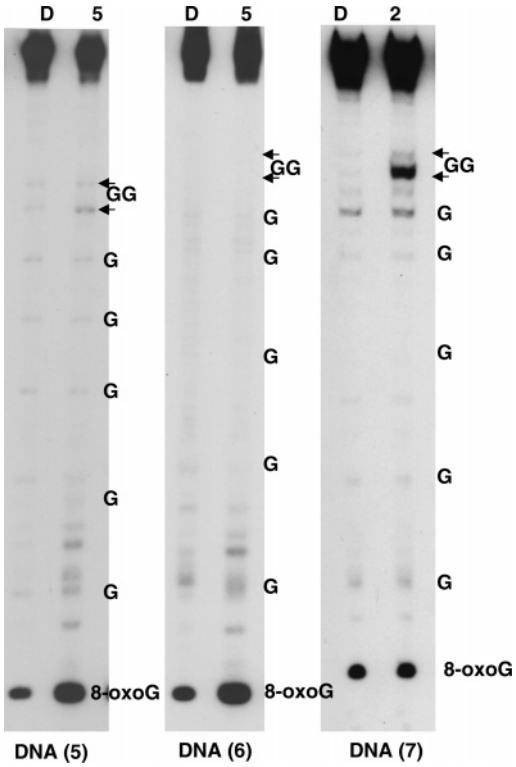

Figure 4. Autoradiograms from the irradiation of DNA(5) through DNA-(7). The lanes labeled D are the dark controls, no irradiation. The samples in lanes labeled 5 and 2 were irradiated for 5 and 2 min, respectively (4 lamps, 350 nm), and then treated with 1 M piperidine, which causes strand cleavage at highly oxidized guanines, before gel electrophoresis. The ^{32}P is at the 5′-terminus of the labeled oligomer. The guanines are indicated by a G, and the guanines that are part of a GG step are indicated with arrows. The 8-oxoG is indicated, and the strand cleavage seen in the dark control lanes at this site is due to oxidation during piperidine treatment.

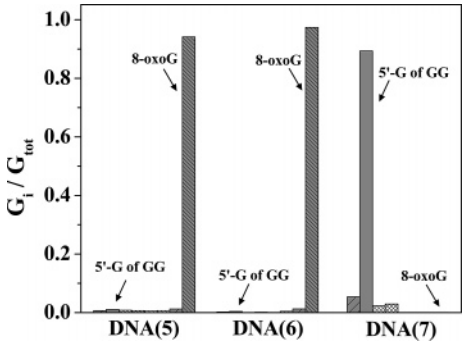

Figure 5. The ratio of the strand cleavage at a particular guanine (G_i) to the total amount of strand cleavage at all guanines in the oligomer (G_{tot}) determined by phosphorimagery of oligomers DNA(5) through DNA(7). The amount of reaction at 8-oxo-2′-deoxyguanine (8-oxoG) is indicated. The speckled bars represent the isolated guanines in the central region, whereas the solid gray bars represent the 5′-G of the GG steps, and the crosshatched solid gray bars are for reaction at the 8-oxoG.

segment essentially divides the DNA duplex into two parts, and the radical cation cannot get from one part to the other. Since the initial one-electron oxidation occurs at a nucleobase adjacent to the AQ, the 8-oxoG is in the part of the duplex that is inaccessible to the radical cation. In essence, the $(T)_4$ sequence introduces a sufficiently high barrier to hopping that the radical cation is trapped at the available GG step much more often than it can cross that barrier, which prevents it from falling into the deep 8-oxoG trap.

Discussion

We have previously shown that the distribution of oxidative damage following electron loss from DNA oligomers comprised of regularly repeating sequences of DNA can be understood simply by consideration of the relative magnitudes of the rates of charge hopping and charge trapping.[7] For example, hopping is much faster than trapping in an oligomer composed of (AAGG) repeats, and the amount of reaction at each GG step is essentially the same, but trapping is faster than hopping for DNA composed of (ATTAGG) repeats, and in this case, GG steps react with much greater efficiency if they are closer to the site of one-electron oxidation adjacent to the AQ. In these sequences, a semilog plot of the amount of reaction at a particular site is linear with its distance from the point of charge injection. The DNA sequences examined in this work are not highly regular, and the experimental results show clearly that in this circumstance the reactivity of a specific nucleobase radical cation must be understood by consideration of all of the bases in the oligomer. The reactivity of a particular nucleobase depends on the identity and sequence of the other bases in the oligomer, and the semilog plot of reactivity and distance is not a simple linear function.[23] The complex relationship between reactivity and sequence can be simplified by consideration of relative potential energy "landscapes" as shown in Figure 6.

Consider first the division of segments along the DNA oligomers into three broad qualitative categories: charge shuttles, charge traps, and hopping barriers. A trap is a sequence of bases, or single nucleobase, where a radical cation will react with high probability; a shuttle is a sequence of bases where the charge hops efficiently but there is a low likelihood that the radical cation will react; and a barrier is a sequence of nucleobases that prevents charge migration. For example, in DNA(1) and DNA(2), the central CGCGCGCGC and TGTGTGTGT segments are traps because the radical cation reacts there, and the A/T sequences that precede and follow these central segments are charge shuttles; the radical cation passes through but rarely reacts there. DNA(1) does not contain a hopping barrier. A complexity is that the characterization of a sequence as a shuttle, trap, or barrier is context dependent. Consider the results from irradiation of DNA(3) and DNA(4). Just as in DNA-(1) and DNA(2), they contain central regions composed of TGTGTGTGT and CGCGCGCGC segments. In DNA(1) and DNA(2), these segments are traps, but in DNA(3) and DNA-(4), they are charge shuttles because little reaction is observed there. Instead, reaction occurs predominantly at the GG steps of DNA(3) and DNA(4) that are charge traps. This distinction is shown pictorially in Figure 6A and 6B.

Figure 6A shows the central regions of DNA(1) and DNA-(2) as a two-dimensional potential energy landscape with "valleys" representing the guanines and "hills" representing the T or C nucleobases. The shading in the figure is proportional to the amount of strand cleavage resulting from reaction of the radical cation at each site. The amount of reaction observed at each G of DNA(1) and DNA(2) is the same. The radical cation is equally distributed, or delocalized,[3,24] over the four essentially equivalent guanines, and the reaction is controlled by thermo-

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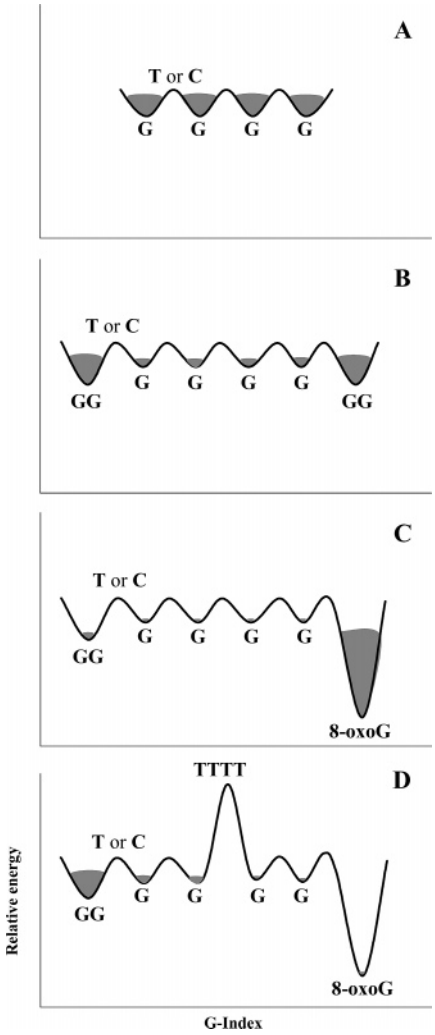

Figure 6. A schematic representation of the potential energy landscapes for DNA oligomers. A "G" represents an "isolated" guanine in a TGT or CGC sequence. A "GG" represents two adjacent guanines in a GG step. The "T" or "C" represents thymine or cytosine nucleobases that separate G or GG steps from one and other. 8-oxoG stands for 8-oxo-2′-deoxyguanine. And "TTTT" represents four thymines. The shading represents the relative amount of strand cleavage observed at each site after irradiation of a piperidine treatment. The *X*-axis (G-index) is not drawn to scale and represents the position of guanines, GG steps, and 8-oxoG along the DNA oligomer; the intervening barriers may be one base pair or several.

dynamic considerations. This is essentially equivalent to saying that hopping is much faster than trapping throughout the entire sequence of nucleobases in DNA(1) and DNA(2). The situation is only slightly different for DNA(3) and DNA(4) as depicted in Figure 6B. Because they have slightly lower oxidation potentials, the valleys representing the GG steps are somewhat deeper than those for the isolated guanines, and as a consequence, the thermodynamic distribution of the radical cation favors the GG steps. Significantly, the amount of reaction at the two GG steps, one before and one after the central sequence, is essentially the same, which shows that hopping is faster than trapping and the reaction outcome is determined solely by thermodynamic considerations.

The properties of DNA(5) and DNA(6), depicted in Figure 6C, can also be understood using the landscape model. These oligomers contain an 8-oxoG, which functions as an irreversibly deep trap.[19] The E_{ox} of 8-oxoG is so much lower than that of the other DNA nucleobases that its conversion to a radical cation essentially always results in reaction and trapping at that site; the radical cation cannot escape by hopping away. This is shown in Figure 6C as a very deep valley for the 8-oxoG. In these cases, the GG step and the TGT or CGC segments behave as charge shuttles, little reaction of the radical cation occurs there, and the 8-oxoG is the sole charge trap. As in the previous examples, the outcome of the reaction is controlled primarily by thermodynamic considerations: charge hopping is fast (except for the 8-oxoG) and relative reactivity is determined by relative oxidation potential. This pattern is broken with DNA-(7), which contains a hopping barrier.

The labeled strand of DNA(7) is divided by a $(T)_4$ segment, which in this case creates an essentially insurmountable barrier to radical cation hopping that is represented as a high hill in Figure 6D. A radical cation introduced into the DNA on either side of this barrier cannot hop to the other side. That is why there is no significant reaction at the 8-oxoG of DNA(7); the radical cation is consumed by reaction before it reaches that site. In this case, thermodynamic considerations alone are not sufficient to explain the pattern of reactivity; the kinetics of charge hopping play a key role in determining the outcome of reaction because hopping through the $(T)_4$ segment is much slower than trapping.

Conclusions

The construction of potential energy landscapes comprised of shuttles, traps, and barriers for radical cations in DNA oligomers is sufficient to permit a qualitative prediction of reactivity. The key to the application of this approach is the realization that the characterization of a particular nucleobase, or sequence of bases, cannot be understood without consideration of that sequence in the context of the entire oligonucleotide; that is, interactions between the bases play the determining role in controlling the end point of the process. For example, in some circumstances, a $(TG)_n$ sequence is a shuttle, in others it is a trap. Similarly, on one side of a barrier, an 8-oxoG is uniquely reactive, on the opposite side, it is unreactive. Likewise, the character of an $(ATTAGG)_n$ sequence changes with the value of *n*. If *n* is small, this sequence behaves like a trap or a shuttle, but if *n* is large, it is a barrier. The nucleobases of DNA are themselves individual entities that function collectively in the environment of the oxidized oligomer to create complex behavior that is not a property of a single entity. This phenomenon is characteristic of systems exhibiting emergent functionality.[25] Each nucleobase or sequence of bases in an oxidized oligomer has a set of fixed properties and a set of side effects. The fixed properties include its oxidation potential and the proclivity of its radical cation to react with H_2O or O_2. The side effects influence the properties of other bases in the oligomer. This understanding permits the prediction of reactivity for one-electron-oxidized DNA oligomers using qualitative potential energy landscapes that goes beyond the previous understanding that reactivity is controlled by oxidation potential.

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