Long-range radical cation migration in DNA: Investigation of the mechanism

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During the past decade, long-range radical cation migration in DNA has been an area of extensive experimental and theoretical examination. The motivations for the vigorous investigation of this topic are its potential to yield a deeper understanding of the processes that cause oxidative damage of genomic DNA and the potential for use of DNA architectures in molecular electronics. This investigation has revealed the mechanisms of charge transport and the limitations of DNA as a functional element in devices. In this article we discuss various aspects of the radical cation migration process and present the plausible mechanism by which this process occurs.

Introduction

Fifty years after its structure was elucidated by Watson and Crick,[1] the DNA duplex still inspires chemists and biochemists to probe its physical and chemical properties. One fascinating property of the DNA duplex is that it can facilitate charge transfer through its hydrogen bonded base pairs over a distance of $\sim$200 Å or more.[2,3] Understanding the mechanisms of charge transfer (CT) in DNA is important since it has been implicated in aging, several types of cancer and diseases such as arteriosclerosis.[4] Progress in this field is also important for the development of new devices based on molecular electronics.[5]

Over the past decade, considerable effort has been invested in understanding the mechanism and the factors that govern charge transfer in DNA. It is now accepted that long-distance charge transfer in DNA, initiated by optical excitation of a covalently bound electron acceptor, generates a radical cation that travels through the duplex by a thermally activated hopping mechanism that results in damage primarily at the GG steps.[6–10] The termination of charge migration occurs when the radical cation reacts with water or oxygen to form oxidation products,[11] which are detected as strand cleavage when the sample is treated with piperidine.[7] Elucidation of the mechanism of radical cation migration in DNA is based mainly from the analysis of the ratios of the strand cleavage products. In this article we illustrate the factors that influence the initiation and subsequent migration of the radical cation and the likely mechanism for this fascinating process.

Abraham Joy was born in Tanzania and grew up in India. After completing his MSc (Chemistry) from the University of Hyderabad, he joined the graduate program at Tulane University. He obtained his PhD in 2000 under the guidance of Prof. V. Ramamurthy. In the fall of 2000 he joined the research group of Prof. Gary Schuster where he has been investigating the phenomenon of charge migration in DNA. His research interests are in the areas of DNA oxidative damage, detection of DNA damage lesions and DNA recognition.

Prof. Gary B. Schuster was born in New York, NY, in 1946. He received his BS degree from Clarkson College of Technology in 1968 and his PhD from the University of Rochester in 1971. Following a tour of active duty with the US 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 the Vassar Woolley Professor of Chemistry and Dean of Sciences at the Georgia Institute of Technology.

Electron acceptors (sensitizers)

Many studies have addressed the subject of sensitized oxidation reactions mediated by reactive oxygen species that form an array of DNA modifications.[12] But the sensitized one-electron oxidation of DNA is a more recent topic of interest. During the past decade, a number of compounds have been shown to initiate photoinduced one-electron oxidative damage in DNA.[13] Many such compounds intercalate between the base pairs, bind in a groove or ''cap'' a DNA terminus. Such close association with the DNA duplex facilitates the transfer of an electron from the duplex to the charge acceptor.

A number of sensitizers have been used to probe the mechanism of DNA oxidation. Barton and co-workers employ rhodium (**1**) and ruthenium (**2**) intercalators (Fig. 1) for such studies.[14] However, these may be unreliable in certain circumstances because of aggregation[15,16] and because complex electron transfer kinetics can obfuscate the results.[17,18] Lewis and Wasielewski use stilbene (**3**) linked hairpins.[19] The excited singlet state of stilbene has a short lifetime and does not intersystem cross with high efficiency. Consequently, back electron transfer occurs rapidly, which permits only short-range charge transfer to be studied. Trioxatriangulenium ion (**4**) ($TOTA^+$) is an intercalator with a preference for GC pairs (Fig. 1).[20] Irradiation of intercalated $TOTA^+$ results in the one-electron oxidation of DNA. $TOTA^+$ is a relatively inefficient sensitizer because it reacts from its singlet state.[21] Giese employs a strand cleavage reaction, which injects the radical cation into the duplex to oxidize DNA.[22]

Since the photochemistry of anthraquinone derivatives is well established,[23] we use these compounds as sensitizers. Spectroscopic and thermodynamic studies have shown that

anthraquinones such as AQC and AQS2 (Fig. 2) intercalate in DNA. Both AQC and AQS2 cause DNA strand cleavage upon irradiation and subsequent treatment with piperidine.[6] Verification that AQC damages DNA by electron transfer was provided by experiments with an anthraquinone analog (AQA) in which the amide group was modified to change the lowest excited state from an $n\pi^*$ to a $\pi\pi^*$ configuration, which is only capable of electron transfer. AQA has the same reactivity and efficiency as AQC, which shows that these sensitizers react by an electron transfer pathway.[24]

Anthraquinone derivatives covalently linked to the 5′-end of DNA (Fig. 2) provide a means to study the distance dependence of radical cation transport because the position of charge injection is defined by the structure. Molecular modeling and spectroscopic evidence indicate that the anthraquinone is ''end-capped'', which permits electronic contact with the π-electron system of the DNA but does not cause the structural distortions characteristic of intercalators.[25]

The anthraquinone excited singlet state intersystem crosses very efficiently to give a triplet state. Electron transfer to this state forms a triplet radical ion pair that is relatively long lived because back electron transfer is forbidden by spin conservation rules. The $AQ^{-\bullet}$ subsequently reacts with O_2 to give superoxide and reform the neutral anthraquinone. This allows the base radical cation to migrate through the duplex and react at guanines, which are sites of low oxidation potential. Investigation of the distribution of reaction sites in DNA oligomers provides a basis for probing the mechanism of long-range charge transfer (Fig. 3).

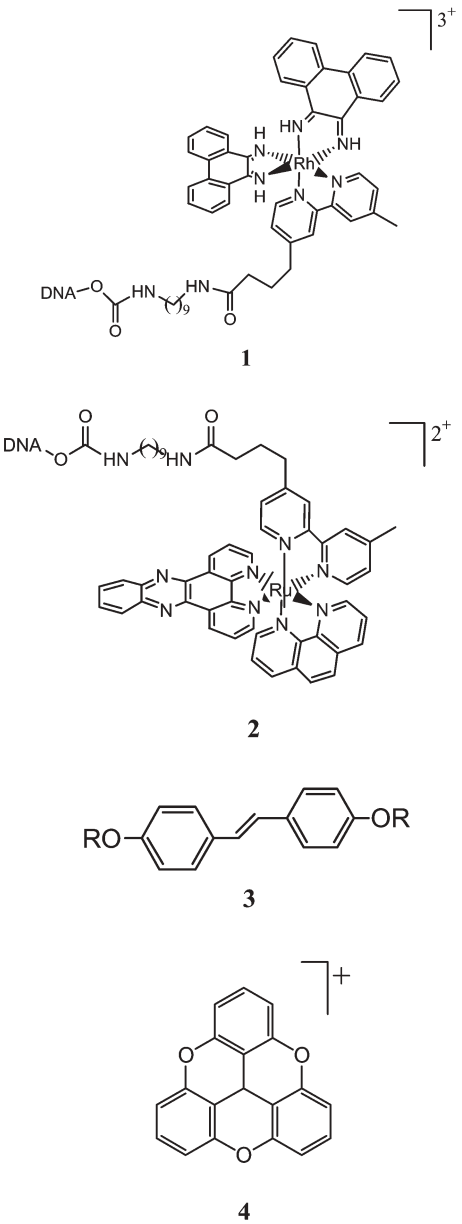

Fig. 1 Structures of some charge injectors used in studies of charge migration in DNA.

The mechanism of long-range charge migration in duplex DNA

A vigorous debate has centered on the mechanism of long-range radical cation migration in DNA. The provocative concept that DNA is a ''molecular wire'' and that long-distance charge transport from donor to acceptor through multi-base DNA bridges occurs by a coherent, rapid, single-step were advanced to explain efficient fluorescence quenching of organometallic intercalators.[26] However, this mechanism cannot account for more recent experimental observations.[27]

At least two other mechanisms have been proposed to account for the radical cation migration over long distances. The first is an incoherent random walk, multi-step hopping, where hops between sequential guanines are mediated by super-exchange across intervening A/T sequences.[28–31] The second is a polaron-like hopping process whereby local energy-lowering dynamic structural distortions generate a self-trapped state of finite extent (Fig. 4) that is transported from one location to another by thermal activation.[7,9,32,33]

A crucial difference between these two mechanisms is the process by which a radical cation centered on guanines is transported to the next guanine-containing site. In the first mechanism, it is assumed that the radical cation is localized on the guanine and that it tunnels through the A/T bridge that separates that guanine from the next. The radical cation does not ever rest on the bridge; it exists only virtually in the orbitals of the bases. In contrast, in the polaron-like hopping mechanism, the radical cation exists as a real, detectable entity on the bridge bases as it moves to the next low energy location by thermal motions of the DNA duplex and its environment. The extent of delocalization is a balance between the energy required to create a distortion and the energy gained by delocalization of the radical cation, which depends on the sequence of bases. This mechanism is supported by high-level quantum calculations that identify a central role for cationic counter ions and the tightly bound solvating water molecules.[33,34] Analysis of the effect of base sequence on the efficiency of radical cation transport provides a consistent picture of the mechanism that permits estimates of the relative rates of charge migration in a wide range of circumstances.[9]

These two mechanisms have been probed experimentally. In particular, the effect of distance is more consistent with the

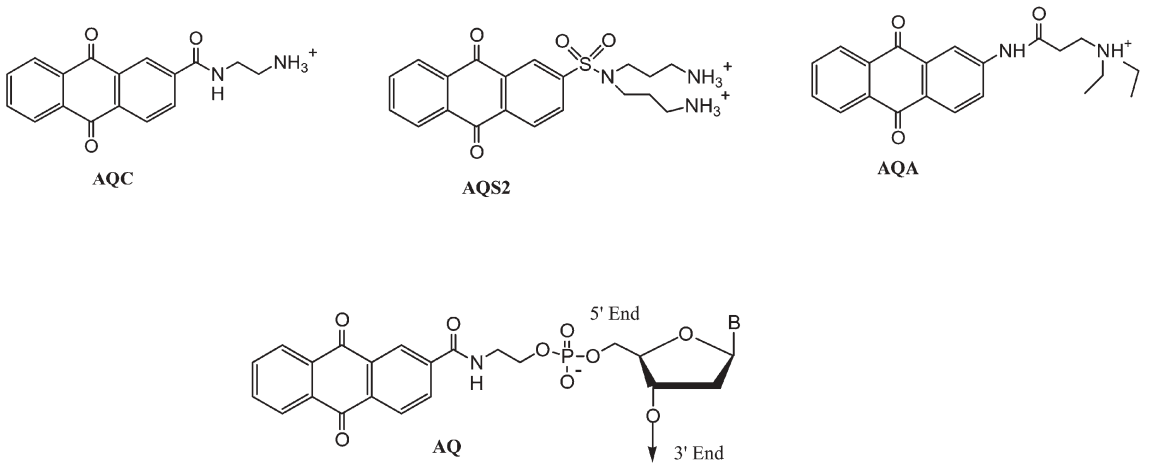

Fig. 2 Structures of anthraquinone charge injectors used in studies of charge migration in DNA.

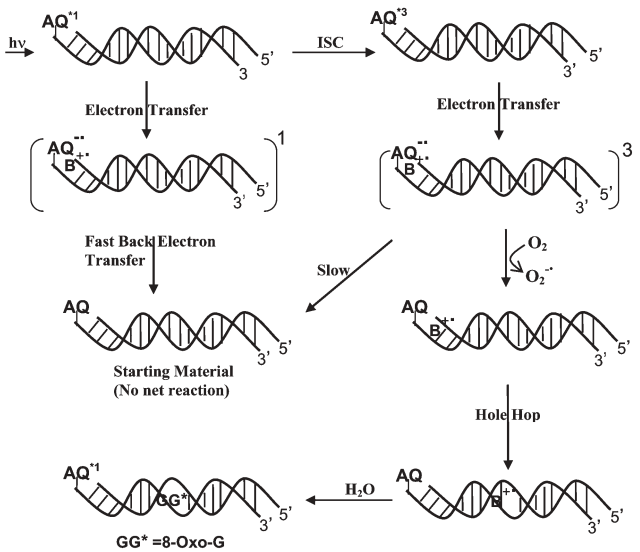

Fig. 3 Mechanism of radical cation initiation and propagation in DNA

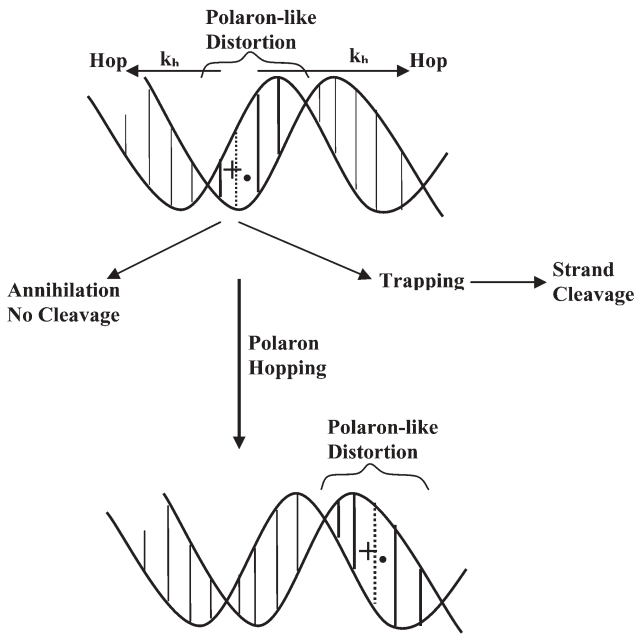

Fig. 4 Formation and propagation of a polaron in DNA.

polaron hopping mechanism for distances greater than two or three base pairs.[9,35] Also, by using N^6-cyclopropyldeoxyadenosine as a probe, it was concluded that radical cations reside long enough on the adenines in the "bridge" to cause ring opening of the cyclopropyl group.[36] This observation confirms that the radical cation is a real entity on the A/T bridge, which is consistent with the polaron hopping mechanism. Radical cation migration in DNA depends on a number of factors such as the base sequence and the motions of the hydrated counter ions that can alter the energy levels of the bridge states of the DNA.

Effect of the base sequence on charge injection efficiency

Studies have been carried out to elucidate the effect of nucleobase sequence on the efficiency of radical cation injection by anthraquinone.[37] AQ in its excited state accepts an electron from an adjacent base creating a radical ion pair. Back electron transfer regenerates the starting state whereas consumption of the AQ radical anion by oxygen provides an opportunity for the base radical cation to propagate through the duplex. The efficiency of radical cation injection into the DNA oligomer is dependent on the identity of the nucleobases near to the AQ.

Fig. 5 shows a DNA sequence that contains a variable four base sequence (N_1–N_4/X_1–X_4) next to the AQ charge injector and also contains two GG steps that serve as charge migration indicators.[37] Radical cation migration to the distal GG step is very efficient for DNA(1) in which the variable sequence is AAAT/TTTA. This is indicated by a very brief irradiation time required to cause damage at the distal GG step. In contrast, a

DNA																																
1	5’	AQ	A	A	A	T	G	C	C	**G**	**G**	T	A	C	A	A	A	C	A	T	**G**	**G**	C	C	G	T	A	C	G	3’		
	3’		T	T	T	A	C	G	G	C	C	A	T	G	T	T	T	G	T	A	C	C	G	G	C	A	T	G*	C	5’		
2	5’	AQ	T	T	T	A	G	C	C	**G**	**G**	T	A	C	A	A	A	C	A	T	**G**	**G**	C	C	G	T	A	C	G	3’		
	3’		A	A	A	T	C	G	G	C	C	A	T	G	T	T	T	G	T	A	C	C	G	G	C	A	T	G*	C	5’		
3	5’	AQ	G	A	A	T	G	C	C	**G**	**G**	T	A	C	A	A	A	C	A	T	**G**	**G**	C	C	G	T	A	C	G	3’		
	3’		C	T	T	A	C	G	G	C	C	A	T	G	T	T	T	G	T	A	C	C	G	G	C	A	T	G*	C	5’		
4	5’	AQ	C	A	A	T	G	C	C	**G**	**G**	T	A	C	A	A	A	C	A	T	**G**	**G**	C	C	G	T	A	C	G	3’		
	3’		G	T	T	A	C	G	G	C	C	A	T	G	T	T	T	G	T	A	C	C	G	G	C	A	T	G*	C	5’		

Fig. 5 DNA(1–4) used to investigate the effect of base sequence on charge injection efficiency.

far greater irradiation time for DNA(4) is required to cause equivalent damage at the distal GG steps. DNA(4) has a guanine adjacent to the AQ. When a radical cation is injected into DNA by an AQ triplet, it is localized at first on the terminal purine (N_1 or X_1). The DNA responds to this charge injection by forming a distorted structure that stabilizes the charge and spreads it over the surrounding base pairs. It is expected that back electron transfer from the anthraquinone radical anion will be slowed when the radical cation is delocalized. Delocalization of the charge is less when the base adjacent to the AQ is a guanine due to the low oxidation potential of G. Therefore, as in DNA(3,4), when the terminal base is a guanine, back electron transfer is able to compete with reaction of the radical anion with O_2 and with propagation of the radical cation and a lower efficiency of charge injection is seen in these sequences. Consequently, in order to have efficient charge injection and subsequent charge migration, guanines adjacent to the sensitizer should be avoided.

Effect of base sequence on radical cation transport

A key determinant of charge transfer efficiency in DNA is the sequence of nucleobases. In sequences that facilitate long-distance charge transfer, a radical cation injected at one end of the duplex can be detected as strand cleavage at distant GG steps. For example, in DNA(5) oxidative damage is seen at GG_{55}, which is *ca.* 185 Å from the charge-injecting AQ (Fig. 6).[32] In this case, a semilog plot of the damage to the GG steps with distance is linear with a slope of -0.02 Å^{-1}.

Similarly, for DNA(6) the strand containing AQ also contains four GG steps and an $(A/T)_8$ sequence that separates GG_8 and GG_{18} (Fig. 7). There is efficient charge transport between GG_4 and GG_8 since almost equal strand cleavage is observed at these two sites. The strand cleavage measured at GG_{18} and GG_{22} are about 40% of that detected at GG_8. In contrast DNA(7), in which a single A/T base pair in the $(AT)_8$ sequence has been switched to T/A, shows a 95% decrease in charge transfer to GG_{18} and GG_{22}.[38] In contrast to the linear behavior seen in DNA(5), these results show that distance dependence is a sensitive function of base sequence.

This dependency was revealed by examination of base sequence effects on long-distance charge transfer using DNA(8–11) (Fig. 7), which have simple, repeating sequences. For example, DNA(8) has an AAGG sequence that repeats six times. Irradiation and subsequent piperidine treatment of DNA(8) gives an equal amount of strand cleavage at each of the six GG steps, which indicates that the rate of radical cation hopping is faster than trapping and the rate of trapping at each GG step is equal. In this case, a semilog plot of the distance dependence of strand cleavage efficiency gives a linear relationship with a slope that is indistinguishable from zero. Interestingly, if the slope were actually zero then efficient charge transport could occur over an infinite distance. DNA(9) has an ATGG sequence that repeats six times and exhibits efficient charge transport to all GG steps. Importantly, in DNA(7) switching a single A/T base pair to T/A greatly reduced charge transport efficiency. These results show that the effect of base sequence on radical cation migration cannot be understood by considering the base pairs in isolation—base-

AQ C T T T G G T T C C T T G G T C A G C G C A C A T T C C T T T A A C T A A T G C A G T G A C C G A A A A G C C A C G 3
3’ G_1A A A C C A A G G_{10} A A C C A G T C G C G T G T A A G G_{28} A A A T T G A T T A C G T C A C T G G_{47} C T T T T C G G_{55} T G C 5’

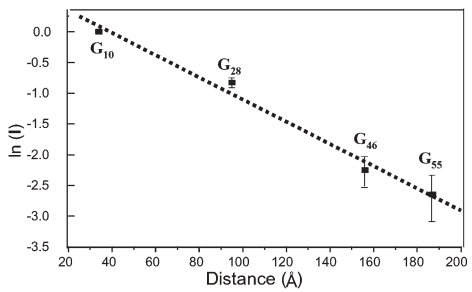

Fig. 6 Sequence of DNA(5) and the semilog plot of intensity of damage at the GG steps with distance.

DNA	
6	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'
7	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'
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 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 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' 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' 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 DNA(6–11) used to investigate the effect of base sequence on long-range charge migration.

to-base interactions must also be taken into account.[9] Theoretical studies also indicate that electronic coupling between neighboring base pairs is an important factor in the charge transport process.[39,40]

In addition to base sequence, it was suggested that the oxidation potential of the guanines is affected by the charge at the termini of DNA oligonucleotides.[41] Duplexes were prepared with $Rh(phi)_2bpy^{3+}$ as the charge injector and two GG steps were incorporated as indicators of charge migration. Machine-based synthesis of DNA strands normally gives an oligonucleotide in which both ends contain hydroxyl groups. Subsequent radiolabeling adds a phosphate group to one end. This process creates a difference in the charge distribution between the two ends of the duplex. It was reported that the ratio of damage of GG_{dist}/GG_{prox} varied depending on whether the duplex had a labeled phosphate on the 5′ end or the 3′ end. This unexpected result was attributed to static charge effects at the DNA termini.[41] This proposal was investigated by repeating the experiment with the same sequence of DNA bases but using AQ as the charge injector.[17] The result obtained showed that irrespective of whether the radiolabel was on the 5′ end or the 3′ end, the ratio of the damage of GG_{prox}/GG_{dist} is 10 ± 1. It was recently suggested that the unusual finding with $Rh(phi)_2bpy^{3+}$ may be a result of complex kinetic behavior of the sensitizer and may not be a property of the DNA.[18]

Effect of base mismatches on charge transport

Mismatches within a duplex may affect long-range charge transport in DNA since they alter stacking and hydrogen bonding between the base pairs. A report on the effect of mismatches and base deletions indicates that a single C/A mismatch reduces radical cation migration efficiency but an A/A mismatch does not have this effect.[42] Recent results indicate that charge transfer within duplexes containing an interdigitated zipper like structure of $(A/A)_n$ (where $n = 2$, 4 or 6) mismatches proceeds with an efficiency comparable to the corresponding normal duplex. However, for duplexes containing $(T/T)_n$ mismatches, which can form wobble pairs, charge migration is inhibited and depends strongly on the number of mismatched base pairs.[43] T/T mismatches do not contain a purine base. This finding among others indicates that radical cations in DNA are propagated through purines, which have lower oxidation potentials than pyrimidines.[9]

Ion-gated phonon-assisted polaron hopping

A distinguishing feature of the phonon-assisted polaron hopping model is the delocalization of the radical cation over a few contiguous purine bases. The results of quantum mechanical calculations of the model duplex d(5′-$G_1A_2G_3G_4$-3′)/d(3′-$C_5T_6C_7C_8$-5′) that include Na^+ counter ions and a hydration shell, show delocalization of the radical cation over the purine sequence (Fig. 8).[33] Most of the radical cation density is found at G_1, G_3, and G_4 with a small amount of charge on A_2. In molecular dynamics simulations, rapid fluctuations in the positions of the DNA atoms, the Na^+ ions and the water molecules are seen.[44] The Na^+ counter ions occupy positions near the negatively charged phosphates and near the electronegative atoms of the DNA bases, namely N7 of guanine and adenine. We have shown by quantum calculation that changing the position of a single Na^+ from near a phosphate to N7 of guanine can bring about a significant increase in the vertical ionization potential (vIP) of the duplex.[33] This change in vIP is larger than the difference

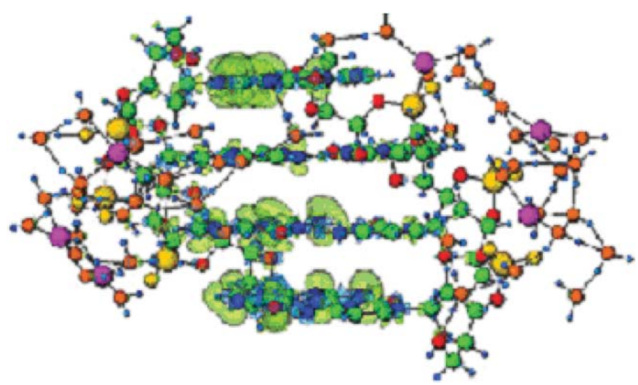

Fig. 8 Isosurface of the total electron charge density difference between the neutral and ionized duplex, depicting the spatial distribution of the hole that is found to be delocalized over the GAGG strand of the duplex. (Based on calculations performed by R. N. Barnett, C. L. Cleveland and U. Landman.)

in ionization potential of an adenine and a guanine. Therefore thermal fluctuations of Na^+ ions allows the duplex to access a configuration in which the energy of the bridge state is lower than that of the donor. In this ion-gated mechanism, transport of the radical cation is facilitated by formation of certain arrangements of the solvating water molecules and counter ions, which we defined as charger-transfer enabling configurations, that surmount the free-energy barrier associated with the radical cation transport and localization processes. Rösch recently reported results of molecular dynamics–quantum mechanical calculations that show environmental fluctuations are sufficient to reverse the normal energy order of G and A radical cation states.[45]

These studies indicate that a radical cation in DNA is delocalized and that its fate is influenced by the motion of the Na^+ ions by a mechanism we call ion-gated phonon assisted polaron hopping. The radical cation resides in a delocalized structure (the polaron) that is comprised of the DNA bases, Na^+ ions and the water molecules. Thermal fluctuations induce motions in the components of this structure that propel the radical cation from one local structure to the next. In particular, motions of the counter ions modulate the ionization potential of the bridge states, thereby facilitating hopping of the radical cation. Recently, O'Neill and Barton proposed an alternative to the ion-gated phonon-assisted polaron-hopping model that they describe as conformationally gated hopping through stacked domains.[10] However, this proposal is part of the polaron hopping mechanism[7] and indistinguishable from it when the intermediates and transition states are considered properly and it is recalled that activation energy has both enthalpy and entropy as components.

Conclusion

Long distance charge migration in DNA has been an active area of research for the past decade. The early provocative proposal that DNA behaves as a molecular wire[26] has been withdrawn.[27] It is now generally agreed that a hopping mechanism[6] prevails for distances greater than three base pairs.[22] Hopping by the ion-gated phonon-assisted polaron mechanism is consistent with the available data and is supported by theoretical calculations.

Acknowledgements

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