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Direct simulation of electron transfer reactions in DNA radical cations

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Abstract

The electron transfer properties of DNA radical cations are important in DNA damage and repair processes. Fast long-range charge transfer has been demonstrated experimentally, but the subtle influences that experimental conditions as well as DNA sequences and geometries have on the details of electron transfer parameters are still poorly understood. In this work, we employ an atomistic QM/MM approach, based on a one-electron tight binding Hamiltonian and a classical molecular mechanics forcefield, to conduct nanosecond length MD simulations of electron holes in DNA oligomers. Multiple spontaneous electron transfer events were observed in 100 ns simulations with neighbouring adenine or guanine bases. Marcus parameters of charge transfer could be extracted directly from the simulations. The reorganisation energy λ for hopping between neighbouring bases was found to be ca. 25 kcal/mol and charge transfer rates of $4.1 \times 10^9 \text{ s}^{-1}$ for AA hopping and $1.3 \times 10^9 \text{ s}^{-1}$ for GG hopping were obtained.

Introduction

The conductive properties of DNA have attracted much study since Eley et al. first suggested that the interacting π -systems of the stacked bases might facilitate electron transfer along the hydrophobic core of DNA double strands.¹ Charge transfer phenomena are of particular interest for their role in naturally occurring oxidative DNA damage and repair^{2–6} and due to the possible use of manufactured DNA constructs as self-assembling ‘molecular wires’ in the emerging discipline of nano-electronics⁷. The unusual structure of the double helix and the complex energetic interplay of the nucleobases, DNA backbone and aqueous environment make this a challenging system for theoreticians to describe and a formidable test bed for the methods of computational chemistry.

Neutral DNA is expected to be an insulating or semiconducting substance (with a band gap in the range of 2.0 eV)⁸ but early experiments proposed a variety of different conductivity regimes for DNA: from metallic or semi-conducting to insulating behaviour^{9–12}. Direct measurement of current through individual DNA molecules with nanoscopic setups have been conducted, but the extraordinary technical difficulties in conducting these types of experiments make an interpretation of the measured currents difficult¹¹.

The main body of experimental data concerns itself with the movement of artificially induced electron holes, generated via chemical or photochemical oxidants.^{2,13–16} The important findings here are that charges are very mobile (able to move more than 200 Å along a DNA strand before trapping reactions with solvent occur), primarily located on guanine residues (due to their lower redox potential) and that charge transfer rates are strongly dependent on DNA sequence, geometries and experimental conditions. A positive excess charge in DNA is likely to be confined to the π -system of one nucleobase, as static and thermally induced disorder in the DNA structure prevent long range delocalisation and contribute to the formation of a

polaron¹⁷. These findings are combined in the so called thermally activated hopping model for charge transport.^{18,19} In this model one or more consecutive guanine bases form low energy sites on which a positive charge localises. Charge transport along a DNA strand is accomplished by fast movement of an electron hole past the nucleobases of higher redox potential separating these resting places. Depending on the distance of two guanine clusters, two different charge transport mechanisms are postulated (Figure 1). In the first an electron hole moves between guanine bases in a direct superexchange process, tunnelling through intermediate bases that act as a bridge without becoming charged themselves. The rate of this process is strongly distance dependent and it is the main mode of charge transport only if no more than three bases lie in between the guanines.²⁰ For transfer over longer stretches of non-guanine bases, a thermally activated hopping process becomes dominant, featuring a polynomial distance dependency. Here, in a rate limiting step, electron transfer from a guanine base to a neighbouring adenine base occurs first, overcoming a ca. 0.4 eV energy barrier, followed by rapid movement of the positive charge along a stretch of adenine bases until it reaches the next cluster of guanines. It is unclear to what extent an electron hole can jump between the two complementary base strands while moving along the DNA duplex.²¹

There have been various theoretical studies of charge transfer in DNA, many of them aimed at the calculation of charge transfer parameters conforming to the Marcus model of two-site charge transfer. Quantum mechanical calculations using static structural models of DNA, in which solvent or the DNA backbone atoms often had to be removed due to the sheer size of the systems, have been conducted,^{22–25} but in recent times, the use of implicit solvent models or multiple conformations, e.g. from MD simulations, to better simulate the dynamic environment of DNA oligomers has gained popularity.^{26–31} While these efforts have greatly enhanced our understanding of charge transport in DNA, to our knowledge there has not been a theoretical study that simulates such electron transfer phenomena using a single unified QM/MM model that explicitly considers solvent interactions for charge trapping, full conformational flexibility of the DNA molecule and the polarisation of the surrounding environment by the positive charge on a nucleobase.

In this work we use a model of DNA oligomers in explicit saltwater solution, treated by a QM/MM mixed potential function. The quantum part of the system will be described on an atomistic tight binding level, carefully parameterised according to *ab initio* DFT calculations. This approach has been employed successfully in the description of DNA charge transfer before.³² The classical part of the system will be represented by the Amber force field. The novel part of our approach is that we conduct nanosecond length MD simulations of DNA radical cations, allowing full coupling between the quantum and classical parts of the system. This represents a major improvement over previous studies, which used snapshots of classical MD simulations of neutral systems as a starting point for subsequent quantum mechanical calculations. During our simulations, we observed many spontaneous charge transfer events on a nanosecond timescale, showing that a chemically specific and qualitatively accurate description of electron transfer events in solvated nucleic acid oligomers is possible with our simple one-electron model. Our method is fast, transparent and easily extendable to unusual DNA conformations or artificial DNA bases.

Models and Methods

All computer simulations were performed using the Amber 10 molecular modelling package with added modifications to allow the use of a tight binding QM/MM potential, as recently introduced in our previous work.³³ Our approach is based on an approximate separation of the σ and π electronic subsystems where the π -electrons are described quantum mechanically and the remainder of the system is subject to an empirical force field potential. Only the p_z atomic orbitals of the four nucleobases form the quantum part of the system, while their σ -bond

framework belongs to the classical part of the system together with the DNA backbone and solvent atoms (Figure 2). The classical part of the system is described by the Amber force field equation containing harmonic bond and angle terms and trigonometric dihedral terms for bonded atoms as well as Lennard-Jones and Coulombic two-body interactions for non-bonded atoms:³⁴

$$V_{MM} = \sum_{\text{bonds}} K_B (r - r_0)^2 + \sum_{\text{angles}} K_\varphi (\varphi - \varphi_0)^2 + \sum_{\text{dihedrals}} \frac{K_D}{2} [1 + \cos(n\phi + \gamma)] + \sum_{i,j < l} \left[\frac{A}{r^{12}} - \frac{B}{r^6} + \frac{q_i q_j}{r} \right] \quad (1)$$

The various parameters supplied by the force field are: the force constants K , the equilibrium values for bond lengths and angles r_0 , φ_0 , the phases of dihedral angles γ , the repulsive and attractive Lennard Jones parameters A and B and the atomic partial charges q .

The quantum part of the system is treated with a fast one electron method, using an empirical tight binding Hamiltonian successfully employed by Utz and coworkers:³⁵

$$\hat{H} = \sum_i (\varepsilon_i + V_i) n_i + \sum_{ij} \Delta_{ij} a_i^\dagger a_j \quad (2)$$

Here, i and j run over all atoms in the quantum part of the system, ε_i is the site energy and V_i the electrostatic potential due to the classical part of the system. The Δ_{ij} are tight binding hopping matrix elements, which are non-zero only for atoms bonded to each other. Tight-binding parameters from the previous work of Cramer et al. were used in this study (Table 1),³⁶ together with their description of base stacking interactions based on empirical functions for the overlap of p_z-orbitals in arbitrary spatial relationships.²⁶

The coupling between the quantum mechanical and classical subsystems is electrostatic: the potential on each atom i in the quantum region is computed as the combined screened Coulomb potential of every classical atom k :

$$V_i = - \frac{e^2}{4\pi\epsilon_0} \sum_{k(MM)} \frac{z_k}{r_{ik} + r_{MN}} \quad (3)$$

Classical atoms bonded to atoms in the quantum part of the system were excluded from the potential calculation; (this only affects the nucleobase hydrogens, thymine methyl group and ribose C1' carbon atoms). A simplified Mataga-Nishimoto approximation,³⁷ resulting in the additional constant r_{MN} , was used to prevent overpolarization of the QM system by nearby classical point charges, with a value of 1.45 Bohr used for the screening constant throughout.

To account for the effect of a quasi-infinite solvation shell around the solute of interest, periodic boundary conditions³⁸ were applied in our simulations. The electrostatic potential is then computed (using the Ewald procedure) as the sum of two terms, a direct sum according to (3), multiplied by a switching function that smoothly brings it to zero at a given cutoff distance and a reciprocal sum computed by a fast grid-based particle mesh Ewald calculation.³⁹ The screening constant r_{MN} was only applied for the direct sum calculation. The reciprocal term is not pairwise decomposable, preventing the separation of potential contributions from the quantum mechanical and classical atoms. Therefore, a two-stage process was employed to compute the potential, similar to the approach used by Walker et al.⁴⁰ At the start of each MD step, the atomic partial charges on all atoms of the quantum system were set to zero and the electrostatic potential according to this modified charge distribution was computed. This potential was included in the Hamilton matrix and the solution of the corresponding eigenvalue problem yielded new partial charges for each atom in the quantum part of the system. With the

new charges the electrostatic energies and forces were computed a second time and used to propagate the system for the MD timestep.

To prevent overpolarization of the QM system by nearby charges, the sum in (3) excludes the electrostatic potential of all atoms bonded to a QM atom. The charges on these atoms are also set to zero in the first calculation of the reciprocal contribution to the electrostatic potential described above (but are of course restored for the second one in which the electrostatic energy and forces are computed). Since the tight binding scheme involves only p_z -orbitals and leaves the classical σ -bonds in place, no link atoms or similar approaches were needed to treat the QM/MM boundary.

Two ways to compute the variable atomic partial charges on the quantum atoms were tested: In the first, partial charges were computed by combining Mulliken charges from the MO-coefficients with a fixed basis charge for every atom:

$$q_i^{QM} = q_i^{Basis} + ne - \sum_{occ.MO} c_i^2 \quad (4)$$

In (4), n is the number of electrons an atom contributes to the π -system. The basis charges q_i^{Basis} were derived so that combining them with Mulliken charges computed for the neutral DNA bases in vacuum yielded the original atomic partial charges from the forcefield.

The second way to compute partial charges used only the highest occupied molecular orbital and assumes the π -system to be a radical cation:

$$q_i^{QM} = q_i^0 + c_{i,HOMO}^2 \quad (5)$$

Here, the q^0 are the unmodified atomic partial charges from the forcefield.

Both methods for deriving the charge distribution in DNA radical cations were tested in this work and gave comparable answers (See chapter 1 of the results below). The majority of simulations (results chapters II to V) used Eq. 5 only, in which the eigenvector corresponding to the highest occupied molecular orbital is used to derive the location of the positive excess charge. While the Mulliken charges derived via Eq. 4 are a more broadly applicable way of computing the distribution of π -charges in arbitrarily charged systems (in contrast to Eq. 5 which is limited to radical cations), their application to larger quantum systems in test simulations lead to the accumulation of more than a full electron charge on one nucleobase. This behaviour can be interpreted as an artefact from the tight binding method used here, in which the disregard of electron-electron repulsion necessary to preserve to one-electron character of the Hamiltonian allows for an unrealistically large overpolarization of the quantum system. However for small quantum system, the two charge derivation methods yielded comparable results. An additional reason why Eq. 5 was preferably used in this work is that it better preserves the amber charge model, because the quantum mechanical part of the calculation only results in a correction of the classical amber partial charges. In comparison, charge derivation according to Eq. 4 computes partial charges for the QM system by a different model (Mulliken charges) than the one used for the classical part of the system (were unchanging RESP charges are used).

Starting geometries were generated as ideal B-DNA geometries using *nab*.⁴¹ The Amber ff99 forcefield with additional corrections for DNA geometries (using the parmbsc0 forcefield modifications) was used for the classical part of the system.^{42,43} The additional forcefield corrections were developed especially for long MD simulations of DNA duplexes and provide a good description of DNA conformations on a multi-nanosecond timescale. The TIP3P water model⁴⁴ was used to embed the DNA oligomers in a solvent simulation box so that no solute atom was closer than 14 Å to any box side. Sodium ions were used to neutralize the DNA

molecules. The final models consisted of ca. 16,000 atoms, most of them belonging to the solvent.

All systems studied were subjected to an equilibration procedure before data collection from the simulation started: First, a 100 steps steepest descent minimization was conducted to remove bad van-der-Waals contacts. This was followed by a 5 ps NVT simulation in which the system temperature was quickly raised to 298 K by means of a Langevin thermostat using a collision frequency of 10 ps^{-1} . For the following 1 ns length density equilibration phase in the NPT ensemble, the thermostat collision frequency was lowered to 2 ps^{-1} . The SHAKE⁴⁵ algorithm was used to constrain bonds involving hydrogen atoms and an integration timestep of 2 fs was used. After equilibration, the rectangular simulation boxes had dimensions of ca. $50 \times 50 \times 60 \text{ \AA}$, corresponding to a density of ca. 1.02 g/cm^3 .

To check for conformational changes of the studied DNA oligomers, their all-atom rmsd was calculated. Disruptions of the hydrogen bonding pattern and nucleobase geometries deviating from ideal B-DNA structure were observed for the terminal residues of the oligomers. Therefore, the two residues closest to the 3' or 5' end of either strand were excluded from the rmsd calculation. To give an example for two of the systems simulated below, stable rmsd values in the range of $1.81 \pm 0.24 \text{ \AA}$ for the $A_4G_2A_4$ system and $1.69 \pm 0.26 \text{ \AA}$ for the A_{10} system (see below for details) were found, indicating stable oligomer geometries during the course of the simulation. Rmsd values very similar to those reported above were found in all MD simulations described in this work, with stable double helical geometries close to the ideal B-DNA form. No major structural changes of the DNA duplex were found when comparing QM/MM simulations with classical MD simulations of DNA oligomers.

The charge in DNA radical cations is predominantly localized on guanine bases, due to their lower redox potential E^0 . While no experimental values for the E^0 of nucleobases incorporated in double stranded DNA exist, values for guanine and adenine nucleosides in aqueous solution are available. To test if our model adequately describes the relative redox potential of these two nucleobases, guanosine and adenosine molecules in explicit water were built and equilibrated. Average values for the HOMO energies were computed from 100 ps long simulations at 300 K under NPT conditions. The nucleosides were simulated as radical cations to include solvent stabilization of the positive ions. HOMO energies fluctuated by 0.25 eV for both molecules and the difference in average energy $E_{(Gua)} - E_{(Ade)}$ was found to be 0.46 eV. The experimental values of 1.58 V and 2.03 V for guanine and adenine show a difference of 0.45 eV,⁴⁶ suggesting that no further adjustment of MO energies needed to be introduced into our model.

Our tight binding model is very fast compared to other quantum mechanical methods. For the 10 base-pair duplex systems studied here, when two bases are treated quantum mechanically, the quantum part of the calculation uses only ca. 14% of the total CPU time. The major part of this is the calculation of the electrostatic potential on each QM atom with a negligible time spent on matrix diagonalization. This made our approach easily parallelisable and our calculations yielded a one nanosecond length trajectory in about 14 hours on four Intel Xeon 2.33 GHz processors.

Results

1) Electrostatic potential fluctuations and charge distributions at a single DNA base

We will first focus on DNA oligomers in which only a single base was treated quantum mechanically, to analyse the effect of the surrounding medium, before turning to simulations of systems where charge transfer can occur. Solvated DNA double strand decamers were built and equilibrated with the sequences A_{10} and A_4GA_5 and the adenine or guanine base at position

5 was treated quantum mechanically and the paired complementary strand pyrimidine base was part of the classical system. For convenience, DNA sequences will always be given as single-strand sequences in the 5'→3' direction, with the second strand of matching bases always implied (e.g. A₄GA₅ means that the system contained twenty nucleobases total, namely a 5' AAAAGAAAAA3' and a complementary 5'TTTTCTTTT3' decamer). Single cytosine and thymine base quantum systems were not simulated, since they are not likely to be charge carriers due to their higher redox potentials.

Two one nanosecond length simulations were run for each system, one in which the DNA base was considered neutral and one in which it carried a positive charge. For the radical cation systems, the variable atomic point charges of the QM system were computed according to Eq. 4. The charge and electrostatic potential due to the environment at each QM atom was recorded every picosecond and average values were calculated from the resulting 1000 snapshots. In all simulations, the computed partial charges did not vary significantly over the course of the simulations, with standard deviations in the range of 0.01 to 0.03 e. For the neutral bases, computed atomic partial charges similar to the fixed forcefield charges were found, with average deviations of 0.03 e for adenine and 0.07 e for guanine. For the radical cationic bases, the distribution of the positive charge caused by removing one electron from the π -systems is depicted in Figure 2.

The electrostatic potential on the QM atoms was found to be strongly fluctuating (see Figure 3). The electrostatic potential averaged over all QM atoms was 0.87 ± 0.31 V and 1.03 ± 0.40 V in the simulations of neutral adenine and guanine, respectively. For positively charged bases, the potential dropped drastically due to stabilisation of the charge by its surroundings, to -2.17 ± 0.30 V for adenine and -2.37 ± 0.34 V for guanine. This shows that a positive charge on both types of purine bases is comparably well stabilized and conformational changes of the DNA molecule, solvent and counter ions induce a drop of the electrostatic potential of about 3 V (or 3.4 V for guanine) at the site of the base. The big variations of the potential both for the neutral and cationic cases give a good first indication how thermal fluctuations of the environment could easily drive charge transfer events between DNA bases. Potential fluctuations of a similar magnitude have been reported before²⁸, although not directly extracted from a QM/MM MD simulation. The autocorrelation functions for these fluctuations (bottom of Figure 3) show rapid initial decays on the order of 18 fs for adenine and 20 fs on a guanine, suggesting that DNA vibrational motion influences the electrostatic potential at the base sites. This initial rapid decay is followed by a slower process (on the order of picoseconds) that probably reflects solvent and backbone reorganization.

The simulations of the radical cations were repeated with the different charge derivation method described in Eq. 5 and very similar results were obtained. The charge distribution for the cations differed on average by 0.04 e for adenine and 0.06 e for guanine. Only small changes in the range of ca. 0.1–0.2 V were found for the average potential at each atom. For all further simulations, the quantum mechanical charges were computed according to Eq. 5.

II) Influence of complementary strand pyrimidine bases

In all simulations discussed in this work, the pyrimidine bases paired with the purine bases that make up the quantum system were treated classically and not as part of the quantum region. This is justifiable by their much higher redox potential, making them very unlikely to carry a charge in DNA radical cations. To test if our model captures this essential property of charge localisation in DNA, simulations of the A₁₀ and A₄GA₅ DNA double strand radical cation models were conducted in which the full AT or GC basepair at position 5 was treated quantum mechanically. During 1 nanosecond length MD simulations of the preequilibrated systems, >99% of the positive charge was always found on the respective purine base. Comparing the average charges computed for each QM atom of the purine base both for quantum mechanical

and classical treatment of the paired pyrimidine base, only small changes were found, with average deviations of 0.01 e and 0.03 e for adenine and guanine respectively (on the pyrimidine bases, the quantum mechanical treatment did not change the partial charges). The computed average electrostatic potential also did not significantly change when a full basepair was simulated. The average electrostatic potential on the pyrimidine base was found to be 0.87 V more positive on T than on A and 1.52 V more positive on C than on G. The robustness of our results with respect to including pyrimidine bases into the quantum system lead us to treating all cytosine and thymine bases as classical in the following, in order to keep the quantum systems as small as possible.

III) Nearest neighbour charge transfer between identical DNA bases

To test how thermal fluctuations in the environment drive charge transfer between different purine bases, we now turn to simulations of DNA oligomers in which neighbouring stacked nucleobases are treated quantum mechanically. Since in our model the electron ‘jumps’ whenever the acceptor has a lower energy than the donor, we limit our simulation to superexchange between bases in van der Waals contact. The electronic coupling between neighbouring bases (in the range of 0.1 eV⁴⁷) is large enough to assume (as our model does) strongly coupled electron transfer; direct hopping between more distant base pairs would need a more complex theory that explicitly considers the transition matrix element between donor and acceptor.

First, DNA double strand decamers of the sequences A₁₀ and A₄G₂A₄ were built and equilibrated. The two central (residues 5 and 6) purine bases formed the quantum system and a single positive charge was placed on them, forming a radical cation. Then for both systems, unrestrained MD simulations of 10 ns length were conducted and the charge distribution between the two central bases was monitored. In both simulations, the positive excess charge was strongly localized on only one base. This was the case in 97% of MD snapshots for the dual adenine system and in 99% of snapshots for the dual guanine system (here, a measure of 0.98 e of positive charge on one base computed according to Eq. 5 was adopted to define localisation). However, the actual base carrying the charge changed several times during 10 ns, allowing the observation of spontaneous, environment-driven electron transfer events during the course of the simulations. These electron ‘jumps’ were caused by thermal fluctuations in the environment, mainly from changes of the relative electrostatic potential on the bases. The stabilisation of a charge on a nucleobase was subject to rapid fluctuations. The electrostatic potential varied on average by 0.28 V on an adenine base and 0.30 V on a guanine base during 10 ns.

Interestingly, a different residue was preferred as the location for the positive charge in the two simulations, with the adenine base closer to the 5′ end of its strand carrying the positive charge 93.6 % of the time in the A₁₀ system, while for the A₄G₂A₄ system the guanine base closer to the 3′ end of its strand carried the charge in >99% of the MD snapshots. For the adenine case, 42 times during the simulation, an electron transfer event was observed (we define a transfer event as a sign change in the charge difference between the two central nucleobases) but in only 18 of these cases the new charge distribution was stable for more than 1 ps; in the other cases, rapid transfer back to the previous charge distribution occurred (Figure 4). Transfer events were strongly correlated, with 40% of electron jumps occurring within 100 fs of a previous jump. For the A₄G₂A₄ system, the charge was located on residue 5 (the central base closer to the 5′ end of the strand) only for two continuous stretches at ca. 2.5 ns simulation time, one of only 8 fs length, which after 0.8 ps is followed by a second stretch of 2.1 ps length. Only four charge transfer events in 10 ns simulation time were observed between the guanine bases.

For the A₁₀ system, the positive charge was better stabilised on residue 5, while for the A₄G₂A₄ system, the stabilisation was greater on residue 6 (Table 2). The difference was smaller for the former system, where the average potential on residue 5 was 0.05 V lower than on residue 6, while for the latter, the potential was 0.45 V more negative on residue 6 than on residue 5. For both systems, the electrostatic potential at a base became more negative by ca. 1 V while the positive charge was localized on it. From the occupancy of the two possible charge localisation states, charge localisation on the base closer to the 5' end of the DNA oligomer appears to be energetically more favourable in our model by 1.6 kcal/mol if the two central bases are adenines, while the base closer to the 3' end is energetically favoured by 5.0 kcal/mol when the two central bases are guanines.

A preferred localisation of a charge on one side of short guanine repeats has been suggested in the literature,^{22,48} similar to the result found here. The better stabilisation of a polaron on one of two identical nucleobases in a homogeneous piece of DNA could nevertheless be a simulation artefact stemming from either the short length of studied DNA oligomers or the artificially introduced QM/MM boundary between the charged bases making up the QM system and those stacked next to them. We have performed various additional simulations to address these questions:

(A) DNA twelve- and fourteenmers A₁₂ and A₁₄ were built, solvated, neutralized and equilibrated as described above. Unrestrained MD simulations of 10 ns length were conducted in which the central two adenine bases (residues 6/7 and 7/8 respectively) were treated quantum mechanically and as radical cations. Both for the A₁₂ and A₁₄ systems, charge distributions very similar to those for the A₁₀ system described above were found, with a localized charge predominantly (in 90.0% and 98.1% of MD snapshots, respectively) located on the adenine base closer to the 5' end of its strand

(B) To test if the location of the QM/MM boundary strongly affects the observed preferred charge localisation, the A₄G₂A₄ system was reequilibrated as a radical cation with a larger quantum region encompassing the four central purine bases (guanine bases 5 and 6 plus adenine bases 4 and 7). The higher redox potential of the adenine bases is expected to mostly prevent charge localisation on them, so the charge distribution should be similar to that of the previous simulation with the smaller quantum region. A 1 ns length MD simulation with the extended QM system was conducted and the positive charge was found to be located on the guanine base at position 6 in the DNA strand, as in the simulation with a smaller quantum system above.

(C) In all simulations presented so far, the oligomers consisted of a strand of DNA containing only purine bases paired with a strand containing the matching pyrimidine bases. To test a different pattern, we prepared DNA oligomers of the sequences T₄A₂T₄ and T₄G₂T₄, equivalent to the A₁₀ and A₄G₂A₄ systems described above, with only the two central bases moved to the complementary strand. MD simulations were run for 10 ns for both systems with the central two purine nucleobases forming the quantum system and the charge set to a radical cation. As in the previous simulations, charges were found to be localized preferably on one of the two central bases, namely the one closer to the 5' end of its strand for the adenine base in the sequence T₄A₂T₄ and the one closer to the 3' end of its strand for the guanine base in the sequence T₄G₂T₄.

These results support the notion that the preferred localisation of a positive excess charge on one side of the quantum region is not caused by the short lengths of the simulated oligomers or artificial QM/MM boundary effects of our simulation setup.

IV) Free energy profiles and derivation of the Marcus parameters

In the simulations described so far, too few charge transfer events were observed to derive a good description of the kinetics. To gain better statistics, we performed an additional 100 ns of MD simulations both for the A₁₀ and the A₄G₂A₄ system. These were broken down into 10 pairs of 10 ns length simulations each, starting from equilibrated random coordinate snapshots for the radical cation systems taken from the simulations described in the previous chapter. The two central purine bases again made up the quantum part of the system, but an additional biasing potential was applied to approximately equalize the charge distribution between the two bases, to facilitate more charge transfer events. A biasing potential of 0.07 V on residue 5 of the A₁₀ system and 0.22 V on residue 6 of the A₄G₂A₄ system resulted in a more uniform charge distribution between the two residues: For the A₁₀ system, a probability of 40% was found for the charge to be located on residue 5 (compared to 93.6% without the biasing potential), with 411 charge transfer events observed during the 100 ns of total simulation time. For the A₄G₂A₄ system, the probability of finding the charge on the guanine residue 5 rose to 1.7 % when the biasing potential was used (compared to less than 0.1% without it) and 126 electron transfer events were observed. Again, electron jumps were correlated, with 131 and 30 transfers (for the A₁₀ and the A₄G₂A₄ system, respectively) being followed by a backtransfer within 100 fs or less, and with the new charge distribution after a transfer event stable for more than 100 ps in only 170 and 43 cases, respectively (see Figure 5). A simple counting of the number of charge transfer events observed in 100 ns of simulation time gives rate constants of $4.1 \times 10^9 \text{ s}^{-1}$ for hopping between adenine bases and $1.3 \times 10^9 \text{ s}^{-1}$ for hopping between guanine bases. If we take into account that all transfers occurring in clusters of consecutive electron hops with an even number of jumps result in an unchanged charge distribution, and all other clusters only result in one net electron transfer, only 175 *effective* jumps are observed for adenine bases and 65 for guanines, corresponding to rates of $1.75 \times 10^9 \text{ s}^{-1}$ and $6.5 \times 10^8 \text{ s}^{-1}$, respectively. From the absolute vs. the effective number of electron jumps, a transmission factor χ of 43% for adenine hopping and 52% for guanine hopping can be calculated, indicating that only about every second charge transfer event actually results in a different charge distribution, with the rest cancelled out by retransfers.

Deriving rates by simply counting electron transfer events as described above suffers from sampling uncertainties because events are unevenly distributed during the simulations. When the number of transfer events during each of the ten sets of 10 ns length simulations are counted separately, 12 to 62 jumps are found for the A₁₀ system (with a standard deviation of 15) and zero to 30 for the A₄G₂A₄ system (with a standard deviation of 9). Taking into account the ten different ‘measurements’, statistical errors of 11% and 22% are found for the two systems, respectively.

From these simulations, a free energy profile for charge transfer between two neighbouring purine bases was constructed (Figure 6). As a reaction coordinate, the difference in the average electrostatic potential between the two DNA bases, ΔV^{EL} , was chosen. This reaction coordinate incorporates all nuclear degrees of freedom both in the DNA and in the solvent which are involved in stabilising a positive charge on one or the other base. The RC was divided into 66 histogram bins 0.06 V wide, ranging from -2 to +2 V. Values of ΔV^{EL} outside that range occasionally occurred in the simulations but represent high energy states not relevant for charge transfer and were not further analysed. The histograms contain information from thousands of MD snapshots in the most sparsely populated bins close to the transition state and millions of MD snapshots close to the energy minima. A comparison of the free energy profile of the ground and first excited state of the two reactions with the Marcus model of two-site charge transfer (Figure 6, top) allows a straightforward evaluation of the Marcus parameters reorganisation energy λ , free energy of reaction ΔG , activation barrier E_A and electronic coupling element t from our simulations (Table 3). The ground state free energy profile with

respect to an arbitrary zero was computed from the probability P of finding the system at point x of the reaction coordinate according to

$$G(x) = -RT \ln(P(x)) \quad (6)$$

If the free energy curve calculated according to Eq. 6 is replaced with a plot of the total system energy, as computed by the MD forcefield, a very noisy curve with a comparable barrier height, high fluctuations of the total energy average and no clearly defined minima resulted. As first excited state of the systems, an electron configuration containing a doubly occupied HOMO ϕ_i and a singly occupied second highest MO $\phi_{(i-1)}$ was used.

The Marcus parameters obtained are characteristic for charge transfer between two strongly coupled sites, with electronic coupling elements in the range of 2 kcal/mol. The computed reorganisation energies of ca. 25 kcal/mol are about a factor of two larger than results from some previous computational studies^{36,49}, but are in good agreement with newer reported values.⁵⁰ The slightly larger reorganisation energy and smaller electronic coupling for transfer between guanine bases when compared to adenines is in good agreement with their lower observed rate of electron jumps in our simulations. Since the two DNA bases in both systems lie at different energy levels, two activation barriers, differing by ΔG , can be computed and consequently two rates, one for exothermic and one for endothermic transfer, can be calculated from the Marcus formula:

$$k_r = \frac{t^2}{\hbar} \sqrt{\frac{\pi}{\lambda k_b T}} \exp\left(-\frac{E_A}{k_b T}\right) \quad (7)$$

in which the transfer rate k_r depends on the electronic coupling between the two states t , the reorganisation energy λ and of the activation barrier E_A . From Eq. 7 we obtain charge transfer rates (endothermic and exothermic, respectively) of 1.5×10^{11} and $2.0 \times 10^{11} \text{ s}^{-1}$ for adenine-adenine or 1.1×10^{10} and $6.1 \times 10^{11} \text{ s}^{-1}$ for guanine-guanine hopping. These rates are much higher than the ones observed in the simulations (which were on the order of 10^9 s^{-1}), and indicate that the assumption in Eq. (7) of weak electronic coupling is not valid here. Judging from the free energy plots and comparatively large values of t , we are in the adiabatic regime of charge transfer and need to calculate rates using the conventional Arrhenius model for activated hopping⁵¹. In this theory, the charge transfer rate is determined by:

$$k_r = k^0 \chi \Gamma \exp\left(-\frac{E^A}{k_b T}\right) \quad (8)$$

where k^0 denotes the effective frequency for motion along the reaction coordinate, which is $k_b T / \hbar$ in classical transition state theory. χ is the electronic transmission factor and Γ the nuclear tunnelling factor which was set to unity here. Using the transmission factors estimated above, we obtain rates for exothermic electron transfer of $2.27 \times 10^9 \text{ s}^{-1}$ for adenine-adenine hopping and $4.47 \times 10^8 \text{ s}^{-1}$ for guanine-guanine hopping from Eq. 8, close to the result from direct counting of the effective electron transfer events. (Alternatively, rates of $5.4 \times 10^9 \text{ s}^{-1}$ for adenine-adenine hopping and $8.6 \times 10^8 \text{ s}^{-1}$ for guanine-guanine hopping are calculated when χ is set to one, close to the rates obtained when every electron transfer event is counted).

V) Charge localisation on guanine in an AG dimer

A critical step in the hopping mechanism is the thermally activated transfer of an electron hole from a guanine base to a neighbouring adenine base. This is proposed to be the rate-limiting step for charge transport between guanine bases separated in sequence by more than 3 adenine bases. To study this, we examined DNA oligomers of the sequences A_5GA_4 and A_4GA_5 , where the central adenine and guanine bases were treated quantum mechanically. Here, the first sequence has A in the 5' position of the central base-stack, and the second has G at the 5'

position. MD simulations of 10 ns length for both systems were performed. For the A₅GA₄ system, the positive charge was located on guanine residue 6 throughout the whole simulation, but for the A₄GA₅ oligomer, a single 1.13 ps episode during 10 ns of simulation time was observed in which the positive charge localized on the adenine base part of the QM system. The average electrostatic potential on the two central bases showed a slightly preferable stabilisation on the adenine site: While the positive charge was localized on the guanine base, an average potential of -2.08 V was computed for its atoms, with a potential of -1.21 V on the neighbouring adenine base. While the charge was localized on the adenine base, the average electrostatic potential on its atoms was found to be -2.24 V vs. -1.30 V for the guanine base. The relative electrostatic stabilisation of the charge carrying base compared to its next neighbour therefore were similar but with a slightly higher value of 0.94 V for adenine, compared to 0.87 V for guanine.

Discussion

Results from our model faithfully reproduce several key predictions from the current ideas about charge localisation in DNA radical cations: (1) The chemical differences of the four DNA bases could be described without any additional base-specific parameterisation. Specifically, the experimentally determined redox potentials of adenine and guanine nucleosides in aqueous solution are quantitatively reproduced in our calculation.

(2) When full base pairs were treated quantum mechanically, the pyrimidine bases did not influence the charge distribution significantly and could be left out of further calculations. This is in good accordance with the negligible role that pyrimidine bases are thought to have in DNA charge transport.

(3) In our simulations of a stacked adenine-guanine pair, we found the charge to be almost exclusively located on the guanine base, which has a redox potential ca. 0.4 eV lower than adenine for the isolated bases. A very small part of MD snapshots showed the electron hole situated on the adenine base. This can be thought of representing the rate limiting first step in the hopping model, in which the small, but nonzero chance to move the electron hole to an energetically less favourable position via thermal activation initiates long range electron transport to a neighbouring guanine cluster.

In all our simulations, strong charge trapping to a single nucleobase occurs. Our explicit classical treatment of all the nuclear degrees of freedom in the solvated DNA system allows conformational adjustments that result in electrostatic potentials at the site of a nucleobase that are several Volts more negative in the presence of a positive charge than without it. However, in rare cases during our MD simulations, conformations exist in which the charge is delocalized over the π -system of more than one base. These events are accompanied by electron transfer. This can be interpreted in terms of an activated mode of transport: the most probable DNA geometries are unfavourable in terms of their electron transfer parameters but thermal fluctuations generate a small population of conformations in which charge transfer is efficient and likely.²⁹

We find that charge localisation exists even for simulations of exchange between identical purine bases, such that the positive charge is slightly more likely to reside on the 5' side of two neighbouring adenines and is significantly more likely to localize on the 3' side of a pair of guanines. Previous computational work predicted 5'-localisation of the HOMO in stacked GG bases which is not in agreement with our results.²² A major difference between our study and previous work is the full incorporation of the electrostatic effects of the surrounding medium on our simulations. There is experimental evidence that the 5'-guanine in a GG cluster is the preferred site of double strand cleavage⁴⁸ after irradiation and piperidine treatment, but this

5'-preference can be expected to depend on the specific base sequence surrounding the GG cluster, and due to the unknown reaction mechanism by which piperidine-induced DNA strand cleavage occurs no unambiguous conclusion from preferred cleavage site to preferred charge localisation site can be drawn.

The reorganisation energy λ , according to Marcus' theory, gives the relative stabilisation energy a charge possesses when it is localized at the donor site compared to a state with identical nuclear coordinates but with the charge localized at the acceptor site. In a linear response model, it should be identical to minus an electron charge times the quantity Δ in Table 2, which gives the drop in electrostatic potential when a base is carrying a charge, compared to when the neighbouring base carries a charge. When the Δ values for residues 5 and 6 are averaged, a λ of 22.9 kcal/mol for the A₁₀ system and a λ of 24.8 kcal/mol for the A₄G₂A₄ system are calculated from Table 2. These values are in good agreement with the reorganisation energies determined from the free energy curves (Figure 6 and Table 3) and reproduce the trend of a slightly higher λ for guanine-guanine than for adenine-adenine transfers.

Concerning the mobility of a charge hopping along a DNA strand, a naive counting of charge transfer events lead us to an electron transfer rate of $4.1 \times 10^9 \text{ s}^{-1}$ for hopping between adenine bases and $1.3 \times 10^9 \text{ s}^{-1}$ for hopping between guanine bases. This places our result within an order of magnitude to experimentally determined values for adenine-adenine hopping⁵² and finds direct guanine-guanine transfer to be slower than transfer between adenines. The rates given here were computed from simulations in which an additional biasing potential was used to equilibrate the average potential between the two nucleobases. Judging from the number of electron transfer events found in the shorter, unbiased simulations, the biasing potential seems not to have affected the transfer rate between adenines significantly, while raising the rate of charge transfers by a factor of about 3 for guanine-guanine hopping

Apart from rates derived by simply counting the numbers of charge transfer events, from a simple statistical analysis (see Figure 6) of our simulations, free energy curves and the Marcus parameters could be determined directly. Hence, the important kinetic and thermodynamic parameters can be extracted from a single, dynamical and unified QM/MM description of the system, without any need for additional parameters or high level QM postprocessing. Charge transfer rates for both adenine-adenine and guanine-guanine hopping were calculated that are close to the observed rates from counting electron jumps and which are in good agreement with experimental estimates for those rates.

Both direct observation and analytical derivation of charge transfer rates from our simulations yielded values that serve as an excellent qualitative description of the link between microscopic conformational and electronic state changes and the macroscopic phenomenology of charge transfer kinetics. For future studies, we plan to conduct simulations of DNA in a biochemically more relevant environment like DNA-protein complexes. Alternatively, modified DNA geometries can be build to study the effect that e.g. DNA bending or introducing artificially modified DNA bases have on the charge transfer properties. The atomistic nature of our model and our explicit treatment of conformational flexibility allows for an easy extension of our simulations to more complex systems without the need for deriving additional parameters.

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Figure 1.

The hopping model for thermally activated charge transport in DNA. There are two competing mechanisms by which the positive charge can pass the adenine bridge. The first involves direct superexchange between guanine bases. The rate of this process (k_{SE}) exhibits an exponential distance-dependence, and for more than three intervening non-guanine bases a second mechanism becomes dominant. In this, the charge is first transferred to a neighbouring adenine base by a slow, thermally activated process (k_T), then rapidly travels along intervening adenines (k_{AA}) until it reaches the next cluster of guanine bases in sequence. The rate of the later process is less strongly influenced by the distance of the two guanine sites and accounts for the ability of electron holes to travel long distances in DNA.

Figure 2.

The four nucleobases correspond to π -systems with 10–14 electrons. Our model distinguishes two types of nitrogen atoms, those that contribute 2 π -electrons are marked with two dots. Note that the methyl group in thymine is not included in the quantum part of the system. For the purine bases, the change of the partial charge upon removal of a π -electron is depicted.

Figure 3.

Potential energy fluctuations and relaxation at the site of adenine 5 in an A_{10} decamer (left) and the guanine in an A_4GA_5 decamer (right). Only one base was treated quantum mechanically. E gives the average electrostatic potential at each QM atom. The electrostatic potential during 1 ns of unrestrained MD simulations shows large and fast fluctuations in the range of 0.3 V. Below each graph, the corresponding autocorrelation functions is plotted. The ACF has a halftime in the range of 10–20 fs, but is modulated with an oscillation in the frequency range of molecular vibrations.

Figure 4. Charge distribution between the central two purine bases in DNA decamers. Both plots show the amount of positive excess charge on the base closer to the 5' end and the difference in electrostatic potential between the two bases (upper curve and lower curve in both plots, respectively). A negative value for the potential difference means that a positive charge is energetically more favourable on the base closer to the 5' end. Top: During 10 ns of MD simulation time for the A_{10} system, the positive charge is localized on one adenine nucleobase, predominantly on residue 5. Several charge transfer events, often accompanied by fast retransfers can be observed. The electrostatic potential quickly readjusts after a transfer event to stabilize the new charge distribution. Bottom: A representative 2 ps cutout of the $A_4G_2A_4$ system simulation showing two typical transfer events: At about 2487 ps, the potential difference approaches zero, and the charge starts to be slightly more delocalized (A). Then the potential difference crosses zero and charge transfer occurs, moving the majority of positive charge onto residue 5 (B), followed by quick retransfer and a second zero crossing of the

electrostatic potential. At 2487.8 ps, another charge transfer event occurs (C), but this time the potential readjusts to favour localization on residue 5 and the new charge distribution persists.

Figure 5.

The observed charge transfer events are highly correlated. Plotted are two histograms of electron jumps for the A_{10} system. Above: Frequency of backtransfers immediately after an electron transfer event. The bars indicate how often backtransfer occurred within the first ten 10 fs time intervals after a previous transfer. Backtransfer is most likely in the first 40 fs and frequently occurs within 100 fs after a transfer event. The histogram contains 131 of the 411 total charge transfer events observed, i.e. only 280 transfer events lay outside the scale of the plot and occurred after a charge localisation was stable for more than 100 fs. Below: Clustering of electron transfer events. A cluster of events is defined here as a series of charge transfers that occur with less than one picosecond between them. The bars indicate how often clusters of a given number of transfer events occur, i.e. ten clusters of four immediately consecutive charge transfer events were observed. 156 charge transfer events occurred in clusters of one, i.e. individually. It should be noted that clusters containing an even number of charge transfer

events return the system to the initial charge distribution and would not be measurable in most experimental settings.

A Marcus model of two-site charge transfer **B** Free energy profile for A-A hopping **C** Free energy profile for G-G hopping **Figure 6.**

A, top Marcus model for adiabatic electron transfer between two nonidentical sites in arbitrary units. A reaction coordinate summing over appropriate nuclear motions is assumed. The relation of the Marcus parameters free energy of reaction ΔG , reorganisation energy λ and activation barrier E_A to the curves is shown. The electronic coupling between donor and acceptor t can be calculated from the minimum energetic distance between ground and first excited state at the transition state, which amounts to $2t$ (dashed line). In diabatic electron transfer t is very small compared to E_A , but it is clearly visible in the adiabatic charge transfer curve shown here. *Middle and bottom:* Free energy profiles with respect to an arbitrary zero for the charge transfer between the two central purine bases in two DNA decamers, with

sequences A_{10} (*B, middle*) and $A_4G_2A_4$ (*C, bottom*). The reaction coordinate is defined as the difference in average electrostatic potential on the two bases, ΔV^{EL} . Histogram bins of 0.06 V widths were used in constructing the free energy curve. The free energy was calculated from the probability of finding the system at a given point of the RC. The ground state-excited state energy gap was computed from the energy difference of the HOMO and the second highest MO $\phi_{(i-1)}$. See Table 3 for the Marcus parameters derived from these plots.

Table 1**Tight-binding parameters for DNA bases**

ε gives the site energies relative to carbon, Δ the nearest neighbour hopping matrix elements. Two different types of nitrogen atoms are distinguished: Aromatic nitrogens contribute one electron to the π -system, trigonally coordinated nitrogens contribute two.

$\varepsilon(N_{\text{arom}})$	-1.50 eV	Δ_{CC}	-3.20 eV
$\varepsilon(N_{\text{trig}})$	-4.50 eV	Δ_{CN}	-2.56 eV
$\varepsilon(\text{O})$	-1.50 eV	Δ_{CO}	-3.20 eV

Table 2

Different average electrostatic potentials on the two quantum mechanically treated central purine bases for two different DNA oligomers from 10 ns length MD simulations. Δ give one possible measure of the reorganisation energy, i.e. the drop in electrostatic potential when a base is carrying a positive charge, compared to the case when the neighbouring base carries a positive charge.

Charge located on residue	5	6	Δ
A ₁₀ oligomer			
E _{AVG} [V] (Residue 5)	-1.90	-0.95	0.95
E _{AVG} [V] (Residue 6)	-0.81	-1.85	1.04
A ₄ G ₂ A ₄ oligomer			
E _{AVG} [V] (Residue 5)	-1.78	-0.70	1.08
E _{AVG} [V] (Residue 6)	-1.14	-2.23	1.07

Table 3

Marcus parameters of electron transfer for nearest neighbour charge transfer between adenine or guanine bases. See figure 6 and text for explanation of the parameters. Since the two sites are not energetically equal in our simulations, two activation barriers can be calculated, one with respect to the left and right minimum respectively. Reorganisation energies were also determined at both sides of the plot and then averaged for the final result (The reorganisation energies measured at either minimum should be identical according to the Marcus theory, but differ slightly due to deviations of the energy profile from the ideal parabolas in real systems). All energy values are given in kcal/mol.

System:	A ₁₀	A ₄ G ₂ A ₄
ΔG	0.17	2.38
t	2.39	1.64
λ	24.93	26.56
E _A (left)	4.00	2.88
E _A (right)	4.17	5.26