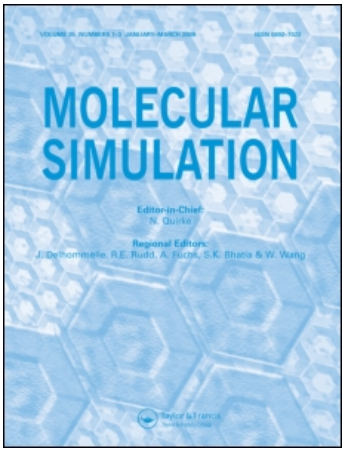

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Charge localisation and hopping in DNA

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Charge localisation and hopping in DNA

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This paper is dedicated to the memory of Professor Shuichi Nosé

A set of full quantum and hybrid quantum mechanics/molecular mechanics simulations, performed on double-stranded DNA systems fully solvated, has provided for the first time a clear link between charge hopping and proton shift, offering a direct insight into the fundamental charge transfer process suggested by experiments.

Keywords: DNA; Charge transport; Molecular dynamics; Car–Parrinello

1. Introduction

Charge localisation and transfer in native and synthetic DNA represent a forefront research topic whose increasing interest is due, on one hand, to the basic role of the conductivity of DNA in the oxidative damage [1] and, on the other hand, to possible nanoelectronic applications [2]. Recent experiments have provided new insights into this class of phenomena: the general picture that emerges is that in DNA, the charge displacement along the strand is accompanied by a deprotonation of the G base [3,4]. This motivated our present study, aiming at giving an insight at an atomic level into this proton shift mechanism and the related charge migration.

The general understanding is that two mechanisms can in principle explain the long range transport of positive (*hole*) charge in double stranded DNA. In the first picture a coherent single step from donor to acceptor occurs; however this requires a well ordered system with very little or no randomness induced by different base-pair sequences [5]. This can be the case of synthetic DNA fibers like the Z-DNA poly-GC biopolymer discussed in this work. In the second picture, a hopping mechanism is expected to occur where the excess of positive charge, initially localised on one or more bases, moves to a different location along the DNA, provided that a suitable triggering operates [6]. This second mechanism has the advantage to be applicable also when distortions and chemical randomness due to different bases sequences are present.

The processes that induce the charge localisation have already been discussed extensively in the literature [1–7]. In this work, we focus in particular on the most recent and accredited scenario in which the charge hopping and localisation from one G site to another one is coupled to the transfer of a proton from a G base to the neighbour hydrogen bonded C base [3]. Full quantum simulations within the Car–Parrinello Molecular Dynamics (CPMD) approach were performed on a double stranded poly-GC Z-DNA radical cation system fully hydrated. This allows for the disentangling of the disorder induced by random sequences, but at the same time preserves all the features of an active DNA. These simulations have provided a clear evidence for a remarkable increase in the charge localisation upon displacement of a proton from G to C [7]. On the other hand, hybrid quantum mechanics (QM)/molecular mechanics (MM) simulations (QM/MM) were performed on a hydrated 38-base pair B-DNA, allowing to tackle the complexity induced by the presence of interposed A:T base pairs in between G:C and to work out the free energy profile characterising the proposed mechanism.

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2. Simulation methodology

We performed first-principles quantum mechanical (QM) Car–Parrinello calculations [8,9] on a polyd(GpCp) Z-DNA system and hybrid QM coupled to molecular mechanics (QM/MM) [10] reactive CPMD [11] simulations on B-DNA, both fully solvated. In the first case the simulation box is a triclinic supercell with sizes $18.100 \times 18.100 \times 43.098\,\text{Å}^3$ and $\angle ab = 120°$ including 12 G–C base pairs plus six H_2O molecules and one Na^+ counterion per nucleotide, $C_{228}N_{96}O_{144}P_{24}Na_{24}H_{264} * 138(H_2O)$. In the second case we used a fully hydrated 38 base-pair B-DNA amounting to 20,265 MM atoms, including 5902 solvent water molecules, and 238 QM atoms plus four capping monovalent link atoms to compensate the cut bonds. The whole orthorhombic QM/MM simulation cell has a size of $38.0 \times 49.0 \times 154.0\,\text{Å}^3$, while the QM subsystem cell is $22.6 \times 48.6 \times 38.5\,\text{Å}^3$ and contains five base pairs corresponding to the segment d(5′-GTGGG-3′). The MM part is treated via a classical AMBER99 force field [12]. The QM part, instead, is computed in both cases within the density functional theory (DFT) framework in the local spin density approximation, in terms of Car–Parrinello molecular dynamics [9]. HCTH gradient corrections on the exchange and correlation functional were included [13,14] in an unrestricted spin approach. The interaction between core and valence electrons was described by Martins–Troullier pseudopotentials [15] and valence orbitals were expanded in a plane wave (PW) basis set with an energy cut-off of 70 Ry. The Brillouin zone was sampled at the Γ point only.

All the CPMD runs were performed at 300 K and the temperature was controlled via a Nosé–Hoover [16–18] chain thermostat on the ionic degrees of freedom.

The reaction path was sampled via the metadynamics approach by adding to the Car–Parrinello Lagrangean the degrees of freedom of selected collective variables plus a history dependent Gaussian potential [11,14]. The specific collective variables adopted in each simulation will be given in the forthcoming paragraph, as a support to the discussion.

3. Simulations results and discussion

In the case of the Z-DNA radical cation, we performed canonical (*N*,*V*,*T*) Car–Parrinello molecular dynamics simulations at $T = 300$ K starting from a configuration previously equilibrated with a classical force field [12]. This simulation has shown that the thermal fluctuations induce a breaking of the intrinsic symmetry of the double stranded poly-GC structure and, as a consequence, the excess charge, represented by the net spin density $\rho_s(\mathbf{x}) = \rho_\alpha(\mathbf{x}) - \rho_\beta(\mathbf{x})$ (α = up, β = down), tends to localise on those particular G site that are mostly affected by these structural modifications. More specifically, a tilt of the base turns out to be responsible for an excess of charge localisation on this site, as shown in panel (a) of figure 1.

The amount of localisation can be made more quantitative by projecting the total spin density along the *z*-axis of the Z-DNA as

$$\rho_s(z) = \iint \rho_s(\mathbf{x})\mathrm{d}x\mathrm{d}y \tag{1}$$

and the result is shown by the dashed curve in panel (c) of figure 1. As it can be noticed, beside a relatively large contribution on a peculiar G, corresponding to $z \approx 25$ Å, the presence of other satellite peaks, with non-negligible amplitudes, indicates that the charge spreads also on

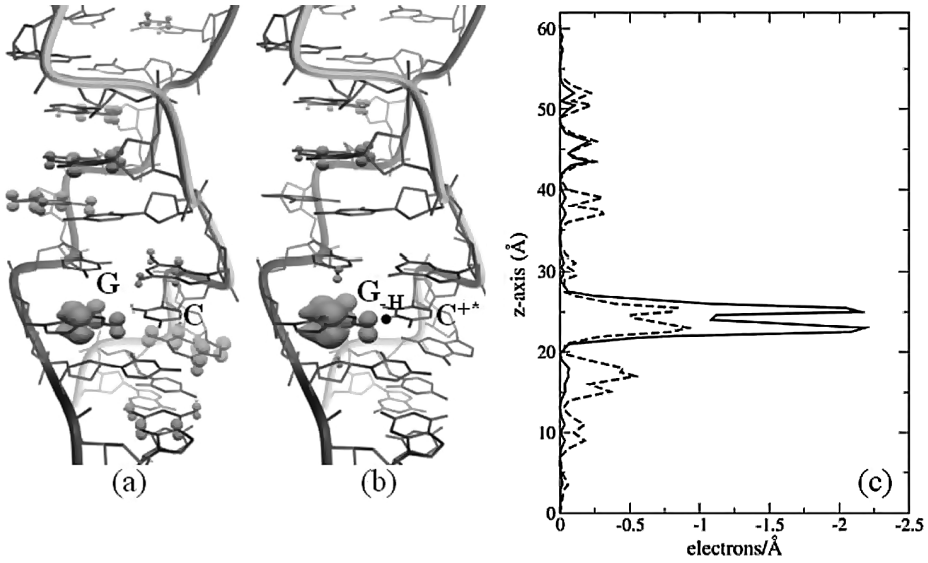

Figure 1. Three dimensional snapshots of the polyd(GpCp) Z-DNA before the proton transfer (a) and after the proton shift from G to C (b). The transferred proton is shown as a black ball and grey coloured clouds represent the spin density at an isosurface value of $10^{-3}\,e/\text{Å}^3$. The right panel (c) shows the projection of the spin density along the *z*-axis before the proton transfer (dashed line) and after it (solid line).

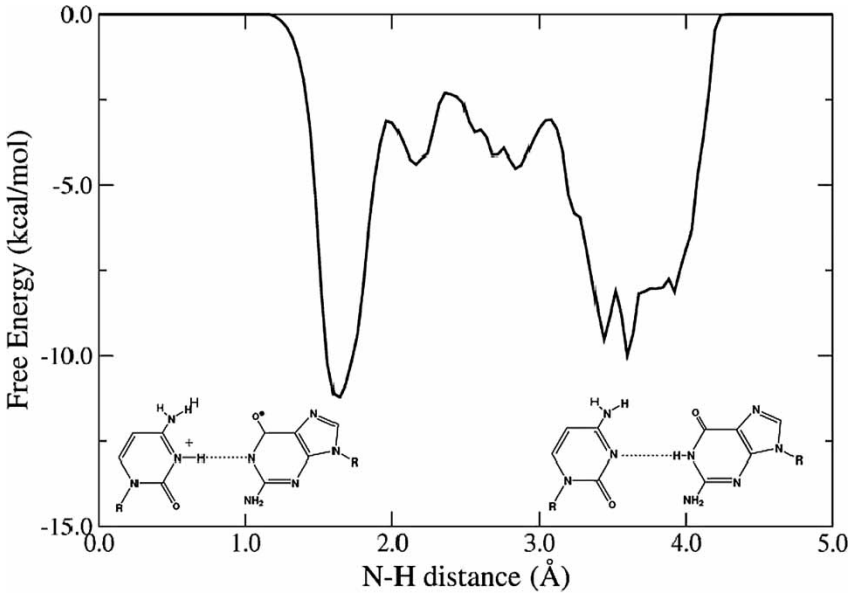

Figure 2. Free energy profile for the proton shift reaction as obtained from metadynamics on B-DNA by using as a reaction coordinate the N—H distance. The left and right panels show schematically the final and initial G–C state, respectively.

several other G bases. On top of that, it is clearly difficult to control fluctuations and structural changes in DNA in such a fine way that the excess charge is trapped exactly at the site that one would wish. This was one—although not the only one—of the ingredients that led to the idea of the possibility of a proton-coupled charge transfer [3]. Indeed, controlling charge defects, although difficult in soft matter, is certainly less problematic than controlling random thermal fluctuations.

In order to inspect the possibility of a proton-coupled charge transfer mechanism and to understand the implications of a proton displacement on the extent of localisation of the spin density, we dislodged a proton from the N1 site of G to the nitrogen site N_3 of the hydrogen-bonded neighbour C base. In a first simulation, this was done by selecting the G:C base pair that showed already the maximum amount of localisation as explained above and illustrated in figure 1. By allowing the structure to relax, we got the result illustrated in panel (b) and by the solid line of panel (c) in figure 1. Namely, the projected spin density increases by more than a factor two on the deprotonated G site (G_{-H}), whereas satellite peaks are remarkably suppressed. This is a clear signature of a strict relationship between proton transfer and charge localisation, that found a further confirmation when we repeated a similar calculation by selecting a different G:C base pair where the spin density was not maximally localised at the beginning. Also in this case, upon proton shifting, the localisation show a clear increase on the deprotonated G.

Of course, the reaction pathway and the related free energy profile relative to the proton transfer are not provided by the former calculations, which refer only to the initial (G:C) and final (G_{-H}:C^+) states of the whole process. In an attempt at unraveling this issue, we performed reactive Car–Parrinello simulations [11] on a full B-DNA including also A:T base pairs. In this case, we adopted a hybrid QM/MM approach, as explained in the previous paragraph, and selected as a collective variable (reaction coordinate) the distance N—H between the H atom of the G base that is expected to be deprotonated and the N atom of the C base forming a hydrogen bonded pair with this G. The free energy profile that we obtained is shown in figure 2 along with the schemes of the initial and final configurations of the base pair involved in the reaction.

This shows that the displacement of the proton from G to the neighbour C occurs by overcoming a rather modest free energy barrier amounting to about 6 kcal/mol and that the final protonated C^+ and deprotonated G_{-H} represent a stable minimum of the free energy surface (FES). A second metadynamics simulation was then performed, in which the adopted collective variable was the coordination number of the N atom of the C base that is expected to be protonated with the H atomic species. In this way, no particular H atom is selected, thus such a simulation does indeed provide an independent verification of the result obtained by constraining a distance between two pre-assigned atoms. Also in this second case the deprotonated state is found to be a stable local minimum of the FES (figure 3) and the proton that jumps from G to C turned out to be exactly the one selected in the former simulation. The free energy difference between the initial configuration and the transition state, located at a value of the coordination number of about 0.4 (local maximum) is in rather good agreement with the former result.

In terms of spin density, we remark that initially $\rho_s(\mathbf{x})$ is localised on a G:C site which is labeled by the letters "G" and "C" in figure 4 and is separated by the final G_{-H}:C^+ site by three base pairs, one of which is A:T.

Upon deprotonation of a G base different from the initial one carrying the excess spin, the charge flows along the

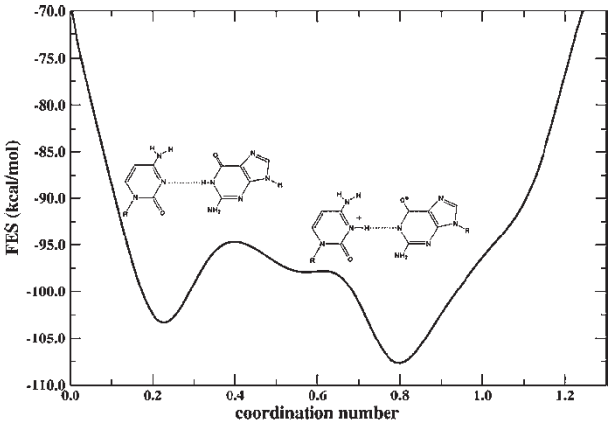

Figure 3. Free energy profile obtained by using as a collective variable the coordination number of the N citosin base undergoing the reaction with any H species. The two schemes included show the initial (left panel) and final (right panel) configurations.

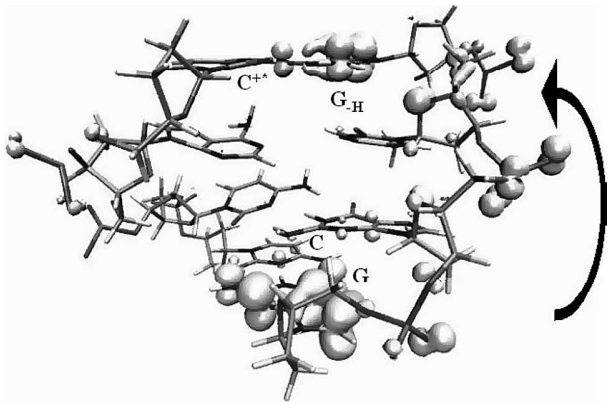

Figure 4. Snapshot of the QM subsystem showing the charge flow across the phosphate backbone. The charge is initially located at the bottom G:C pair site and displaces on G_{-H}:C^{+} upon deprotonation of G.

sugar-phosphate backbone (figure 4) and becomes trapped at the G_{-H}:C^{+} site. Charge displacements have been observed also in cases in which the backbone is known to be broken, so this mechanism may not be the only one active. Nevertheless, the main issue that charge goes localising on sites where the proton shift occurs seems to be a rather clear outcome of the present set of simulations that, in this respect, are consistent with a wealth of experimental data [3,4,19]. Furthermore, these G-to-C proton transfer results allow for the comprehension of a phenomenon that cannot be rationalised solely in terms of structural distortions or ion-gated charge hopping triggered by partial desolvation or drying of the Na^{+} counterions [7].

4. Final remarks

The general picture provided by the simulations presented in this work shows rather clearly how a proton transfer from a G to a C base can induce a strong spin localisation on the G bases in the case of the poly-GC Z-DNA radical cation. This picture holds also in the case of B-DNA, where a proton shift turns out to be sufficient to trigger a charge hopping from one G-site to another G-site site, supporting and complementing the experimental evidence coming from H/D substitution and electron paramagnetic resonance measurements [4,19]. Furthermore, we provide a microscopic insight into the link between charge hopping and proton shift and show how at short donor–acceptor distances the charge transfer could be mediated by the sugar–phosphate backbone.

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