First Principles Molecular Dynamics Simulation of Solution

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Hybrid quantum mechanics/molecular mechanics (QM/MM) simulations, performed with the most advanced state of the art methods on a double-stranded DNA system in solution, provide for the first time a clear link between charge hopping and proton shift, offering a direct insight into the details of the mechanism that are not directly accessible to experimental probes. We show that at short donor-acceptor distances the coherent single step transfer of charge is mediated by the sugar-phosphate backbone.

Keywords: first principles molecular dynamics, metadynamics, QM/MM method, DNA

1. Introduction

The great interest in the charge transfer processes in DNA is due, on one hand, to the basic role of its conductivity in the oxidative damage[1] and, on the other hand, to possible applications in nanoelectronics[2]. Experiments present several technical difficulties such as the handling of single molecules or small bundles of DNA and the fine control of their contact to metallic leads and to supporting surfaces. All these elements, along with the environment in which experiments are conducted, play a non-negligible role and can deeply affect the outcome of the measurements, making hard to disentangle the fundamental properties of DNA from spurious effects induced by the experimental environment. In this respect, computer simulations able to reproduce a realistic DNA system represent a powerful tool to inspect the microscopic details of pure DNA and to work out reaction mechanisms and activation barriers that are not accessible to experimental probes.

In recent experiments charge is injected site-selectively in DNA either by intercalating an oxidizing agent or upon introduction of artificial modification in DNA. For instance, a charge sink site can be created by modifying a single G base or a GGG sequence; the net effect of such a modification is a much lower ionization potential (IP) than that of isolated native G, thus making the site an effective hole trap. The charge transport is monitored by detecting the formation of guanine radical cations G^+ that lead to selective strand cleavage[3, 4]. Basically, this shows that in DNA, the charge displacement along the strand is accompanied by a deprotonation of the G base. In order to inspect at an atomic level whether or not this is really the mechanism and to determine the corresponding free energy (activation) barriers, we performed the simulations described in the present report. This was made possible by the computational facilities available at the Earth Simulator Center during the 2005 fiscal year.

2. Results

Here we report the direct observation of charge transfer from a GGG to a G site upon deprotonation of the latter obtained by a large scale first-principles quantum mechanical (QM) coupled to a molecular mechanics (MM) simulation (QM/MM) on a fully hydrated 38-base pair B-DNA d(-ACGCACGTCGCATAATATTACGT GGGTATTATATTAGC-). This particular sequence is the same used in experiments[3, 4]. First, we equilibrated the system in solution at room temperature for 10 ns in a simulation cell of 38 × 41 × 154 $Å^3$, including 5902 water molecules and Na^+ counterions, amounting to a global system of 20265 atoms, using an AMBER classical force field. Then, QM/MM calculations were performed within the density functional theory (DFT) framework, in the local spin density formulation, as implemented in the CPMD code[5]. The QM subsystem included the sugar-phosphate backbone and amounted to 303 atoms, while the classical MM part included the remaining 19962 atoms.

In this fiscal year studies, we focused on the mechanism of the hole hopping in order to understand how a hole, which is initially localized on a stacked GGG triplet, can hop to a different isolated G, separated from the GGG by one AT bridge. It is clear that the hopping does not occur without some change in the structure or solvation of the isolated G

since the GGG triplet is a more favorable trap configuration for a hole than a single G[1]. Taking as a starting point the full QM results reported in the previous fiscal year at the Earth Simulator Center[6], where a proton coupled charge localization was observed and from the results of EPR experiments that have shown the possibility of such a proton shift[3], we studied the energetics and the related effects on the electronic structure of the deprotonation of an isolated G by means of our recently developed metadynamics method[7–9]. The principal advantages of using metadynamics rely in the fact that this approach is able to escape local minima and to overcome activation barriers, allowing to explore the free energy surface (FES) in the space of a chosen set of relevant collective variables (CVs). In this particular case, we selected two independent configurations from a 10 ns long classical MD trajectory and started two metadynamics simulations using as CVs the distance of the hydrogen chemically bound to N_1 in G base (see Figure 1 for the labeling) from the nitrogen N_3 of the C base and the coordination number (defined as in ref. 9) of hydrogen species with respect to N_3 of C. The result is summarized in Figure 1: the proton is transferred from the initial G base to the nearby paired C base and, in turn, this H^+ shift induces a charge transfer from the starting GGG site to this deprotonated G base. This provides a clear indication that the deprotonation is essential and not accessory to the charge transfer along DNA. Furthermore, as shown in panel B of Figure 1, this charge displacement occurs via a flow that passes across the backbone, that plays the role of a channel for the transfer. The free energy profile in the same figure shows that an activation barrier of 6–7 kcal/mol has to be overcome in order to complete the charge transfer and this agrees rather well with the known experimental outcome[3, 4]. Yet, experiments are not capable of catching the intimate details of the reaction and in this respect this results represent the first attempt ever to unravel the proposed mechanism.

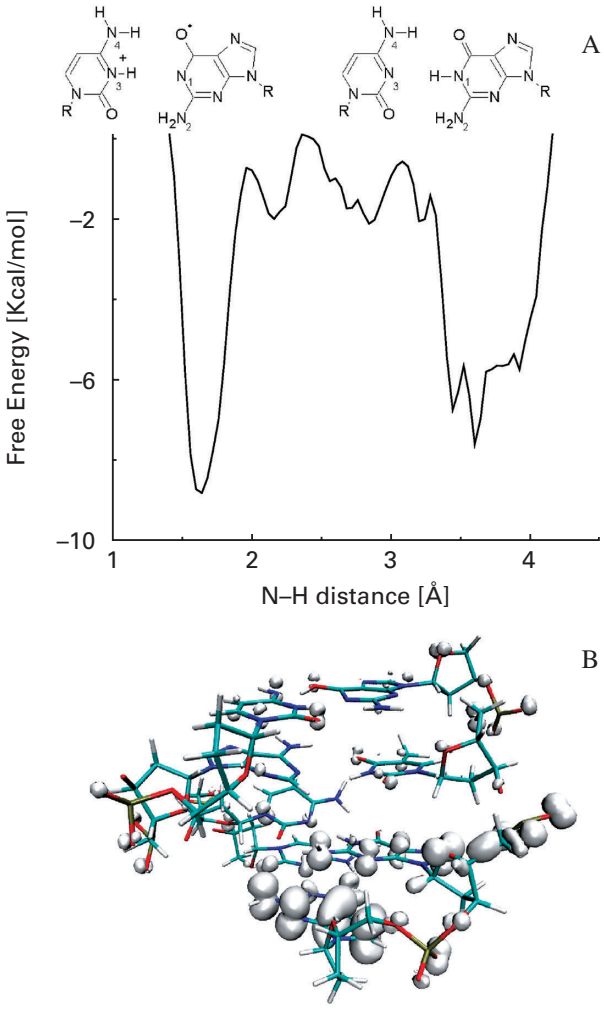

Fig. 1 Panel A shows the free energy profile relative to the distance of the hydrogen initially bound to N_1 of G from N_3 of C. With this choice of CV the minimum at 3.5 Å corresponds to the hydrogen being bound to G (upper scheme right), whereas at 1.5 Å is bound to C (upper scheme left). Panel B shows a snapshot of the QM subsystem during the radical transfer from GGG to the isolated G. The white clouds show the displacement of the spin density during the charge transfer along the DNA (details in the text). The atomic structure (sticks) is colored as follows: cyan = C, red = O, blue = N, yellow = P, white = H.

This mechanism was preserved and the pathway was substantially unchanged during different runs; this pathway is preserved even upon the use of a different collective variable, such as the coordination number or the spin density localization discussed in the report of the former fiscal year. This provides an independent check of the reaction pathway and corroborates the results obtained by assuming as a reaction coordinate the H-N_3 distance.

3. Summary

We have been able to show that a proton shift is sufficient to trigger a charge hopping from one G-site to a nearby site, supporting and complementing the most recent experiments on DNA. Our set of simulations, performed at the most advanced level in first principles methods, and made possible by the ES computational facilities, show without doubt the link between charge hopping and proton shift, providing a direct insight into the details of the mechanism that are not directly accessible to experimental probes.

Furthermore, we could show that at short donor-acceptor distances the charge transfer is mediated by the sugar-phosphate backbone.

References

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溶液の第一原理分子動力学シミュレーション

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本研究課題は、溶液内化学反応のシミュレーションに必要な技術開発を行うことにより、材料研究およびバイオロジー研究の更なる高度化をめざした共同プロジェクトである。昨年度に、QM/MM法を導入することで計算コスト低減を実現し、さらにメタダイナクスを導入し自由エネルギー面の探査を可能とした。これらの手法を用いて、今年度はB-DNAでの電荷移動過程の詳細を検討したところ、グアニン基間の電荷移動とプロトン移動が連動していることを明瞭に示す結果を得た。

キーワード：第一原理分子動力学, メタダイナミクス, QM/MM法, DNA