Quantum mechanical calculations related to ionization and charge transfer in DNA

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Abstract. Ionization and charge migration in DNA play crucial roles in mechanisms of DNA damage caused by ionizing radiation, oxidizing agents and photo-irradiation. Therefore, an evaluation of the ionization properties of the DNA bases is central to the full interpretation and understanding of the elementary reactive processes that occur at the molecular level during the initial exposure and afterwards. Ab initio quantum mechanical (QM) methods have been successful in providing highly accurate evaluations of key parameters, such as ionization energies (IE) of DNA bases. Hence, in this study, we performed high-level QM calculations to characterize the molecular energy levels and potential energy surfaces, which shed light on ionization and charge migration between DNA bases. In particular, we examined the IEs of guanine, the most easily oxidized base, isolated and embedded in base clusters, and investigated the mechanism of charge migration over two and three stacked guanines. The IE of guanine in the human telomere sequence has also been evaluated. We report a simple molecular orbital analysis to explain how modifications in the base sequence are expected to change the efficiency of the sequence as a hole trap. Finally, the application of a hybrid approach combining quantum mechanics with molecular mechanics brings an interesting discussion as to how the native aqueous DNA environment affects the IE threshold of nucleobases.

1. Introduction
Ionization via high-energy radiation of the components of DNA and charge transfer in DNA are key processes in the propagation and detection of DNA radiation damage occurring in the cells of human beings [1]. As we know now, DNA radiation damage is responsible for many neurological diseases and plays an important role in aging and many forms of human cancer. Each portion of the DNA molecule and its environment such as the nucleobases, the sugar-phosphate backbone and the water molecules of hydration are ionized in a near random fashion. However, owing to charge transfer, the chemical damage in irradiated DNA often occurs at sites other than where the original ionization takes place. For these reasons, the evaluation of the ionization properties of the components of DNA as well as the elucidation of the mechanisms responsible for the charge transfer phenomena in DNA are a great challenge in the current research on the oxidative damage of DNA. This challenging problem is also essential in the nanoscience theme area [2]. In particular, the ability of DNA to serve as a medium...
for long-range charge transfer has stimulated interest in the possibility to exploit this molecule in nanoscale electronics and in electrochemical biosensor electronics.

The improvement of quantum calculation techniques, together with the increase of computing power, makes the quantum approach particularly suitable to study, on the molecular scale, elementary mechanisms related to the DNA damage process [3]. Thus, the aim of our study was to apply high level methods of quantum chemistry in a complementary way investigating several aspects of this problem such as the ionization of the DNA bases, isolated and embedded in base clusters, the sensitivity of the sequence, in particular the human telomere overhang sequence, to oxidation and the role of structural variations in the efficiency of charge transport in DNA. In addition, particular attention has been given to the effects of the DNA environment structure and dynamics on the energetic of the ionization process generated in DNA.

2. Computational Methods

Various sophisticated “post Hartree-Fock” methods considering explicitly that electron motions are correlated, have been used in this work. These methods are based on the three main wave function based approaches for calculating electron correlation: Many Body Perturbation Theory (MBPT), Coupled Cluster (CC) and Configuration Interaction (CI). The Density Functional Theory (DFT), the alternative quantum mechanical electron correlation method in which the total energy is expressed in terms of the total electron density rather than the wave function, has also been used. Concerning the choice of the basis set, the 6-31G(2d(0.8,0.2),p) basis set, proposed by our group [4], which corresponds to the standard 6-31G(d,p) basis set augmented by diffuse polarization functions (exponent $\alpha_d = 0.2$) on the heavy atoms, has mainly been exploited for investigating ionization of large systems involving the DNA bases. Indeed, it has been demonstrated that this basis set can be used to predict the H-bond and $\pi-\pi$ energies and to compute the energy differences related to ionization as well as larger polarized and/or augmented basis sets of the literature but at lower computer costs. Thanks to this optimized basis set, the study of large ionized clusters related to DNA has been made possible.

3. Results and Discussion

3.1. Ionization energy of stacked DNA bases

While the ionization of isolated DNA bases has been studied extensively, only a few ab initio ionization energy (IE) calculations on $\pi$-stacked bases have been reported. Indeed, whereas the qualitative features of ionization of stacked systems, i.e. the lowering of IE and the dependence of hole delocalization on the relative orientation of the fragments, can be easily explained by an electrostatic model and simple molecular orbital analysis [5], the quantitative predictions are much more challenging. In our study, the influence of stacking interactions on IE of guanine (G), guanine being the most easily oxidized nucleic acid base, has been examined by employing pure guanine single-stranded model systems [6]. These consist of stacked bases in orientations that occur in the standard B form of DNA. In this case, the geometries of the stacked systems were not optimized and the calculated values are vertical IEs. Table 1 summarizes the results, which include MP2 IE estimates using the 6-31G(2d(0.8,0.2),p) basis set. Stacking interactions in the GG and GGG sequences are found to reduce the vertical IE by 0.4-0.5 eV. The IE lowering by stacking interactions is further confirmed for four, five and six stacked guanines, in which the IE gradually drops with increasing number of nucleobases.
3.2. Human telomere sequence

The hypothetical protection of genes from oxidative damage provided by the G-rich telomeric overhangs located at the end of chromosomes, which consist, in humans, of single strands of TTAGGG sequence repeats, has been investigated [6]. First principle MP2 calculations reveal that the TTAGGG human telomere sequence is particularly prone to oxidation (IE=6.76 eV) and can act as a profound hole trap as deep as a sequence of five consecutive guanines (see table 1). In addition, IEs were estimated, at the same level of calculation, for TTGGGG (7.30 eV), GGGATT (7.48 eV) and GGGGGTT (7.39 eV) sequences. These show that the sequence dependence is very important and that modifications in the human telomeric sequence can induce crucial changes in the electronic structure of the sequence, with concomitant increase of the ionization energy. Interestingly, the expected most electron-releasing 5’ side G in the TTGGGG sequence is not susceptible to oxidation in contrast to the human telomeric sequence TTAGGG in which the 5’ side G is found to be efficiently oxidized (see figure 1). According to our calculations, this is caused by the fact that the molecular orbitals which are localized on the 5’ side G are largely stabilized in the cationic state of TTGGGG due to an orbital mixing with the orbitals from the thymine bases. The molecular orbitals of the cationic state of the human telomeric sequence, however, show that no orbital mixing appears due to the presence of A.

Table 1. Vertical IEs (in eV) of the B-form stacked contiguous guanines. Adapted from Cauet [6].

| 5’-Base(s)-3’ | MP2/6-31G(2d,p) |
|--------------|-----------------|
| G            | 8.07            |
| GG           | 7.67            |
| GGG          | 7.54            |
| GGGG         | 6.92            |
| GGGGG        | 6.81            |
| GGGGGG       | 6.57            |

Figure 1. Isosurfaces of the π-like HOMO and singly occupied HOMO (SOMO) orbitals of the neutral and ionized species, respectively, calculated at the HF/6-31G(0.8,0.2), p) level, for the 5’-TTAGGG-3’ and 5’-TTGGGG-3’ sequences. The two different colours of the isosurfaces correspond to the different signs of the wave function. Adapted from Cauet [6].
3.3. Charge Transfer in π-stacked guanine clusters

High-level multiconfigurational methods have been applied to determine the reaction path describing the charge transfer between two consecutive stacked guanines [7]. From these calculations, the most important conformational changes that accompany the charge transfer process have been identified as a slide and a shift of one base with respect to the other. Figure 2 presents the topology of the ground-state potential energy surface of a radical cation (G₅'-G₃')⁺ calculated at the RASSCF/RASPT2/6-31G(d(0.2)) level of theory as a function of the parameters q and l describing translation motions of G₅' along the axes q (slide) and l (shift), respectively. The topology shows five stationary points: three minima, denoted M1, M2 and M3, and two saddle points, S1 and S2. The minimum M1, in which most of the positive charge is on G₅', is more stable by 3.84 kcal/mol than M3 where most of the charge is on G₃'. The intermediate minimum M2, where the positive charge is almost equally distributed between the two guanines, is destabilized by 2.13 kcal/mol relative to M1. Furthermore, our study has been extended to a stacked sequence of three guanines. The results of the calculations performed on these trimer geometries are promising and exciting as they show that the charge transfer proceeds in a multi-step fashion, from one base to another, across the trimer following the mechanism we have predicted from the dimer study.

![Figure 2. Energy map for the ground state calculated at the RASSCF/RASPT2/6-31G(d(0.2)) level for the radical cation (G₅'-G₃')⁺ as a function of the parameters q and l. The vertical separation between the two stacked guanines is kept fixed equal to 3.3 Å. Five stationary points have been localized (M for minimum, S for saddle point). The point (0,0) corresponds to the reference crystal structure 1TC3. Adapted from Cauët et al. [7].](image)

3.4. Influence of the native DNA environment

As described in the earlier sections, quantum mechanics calculations may be applied for systems where no relevant experiments exist, such as stacked and H-bonded nucleic acid bases. However, it is important to recognize that in physiological surroundings the nucleobases interact with solvent, counterions and the sugar-phosphate backbone of the double-stranded DNA helix. All these effects can cause important changes in the electronic structure of the DNA bases and the next step is thus to ask what are the IEs of DNA bases if we take these into account. We have recently applied a hybrid quantum mechanics/molecular mechanics (QM/MM) methodology at the CCSD(T)/aug-cc-pVDZ level of theory to estimate the vertical IEs of the four individual DNA bases embedded in a 12-mer fragment of B-DNA neutralized by 22 sodium cations and solvated with 5760 water molecules [8]. The results are collected in table 2 where they are compared to the gas-phase IE values computed at the same level. The large increase of the vertical IEs in the hydrated DNA environment may, at first, seem surprising given the fact that hydration is expected to screen electrostatic interactions and thus stabilize the cationic species whereas the opposite is observed here. However, the latter notion is for bulk and it does not apply to the special hydration process of DNA. Indeed, the solvent structure created by the anionic phosphates and counterions intensifies the attractive interaction between the electrons and the dipolar charge distribution of the water molecules increasing thus the energy necessary to ionize the bases.
Table 2. Results of gas-phase and QM/MM calculations of vertical ionization energies (in eV) of guanine, adenine, cytosine and thymine. Energies (Δ) of QM/MM results relative to the calculated gas-phase values are included. Adapted from Cauët et al. [8].

|               | CCSD(T)/aug-cc-pVDZ | Gua | Ade | Cyt | Thy |
|---------------|---------------------|-----|-----|-----|-----|
| Gas phase     |                     | 7.93| 8.23| 8.65| 8.98|
| QM/MM         |                     | 11.09| 11.55| 11.98| 12.33|
| Δ             |                     | 3.16| 3.32| 3.33| 3.35|

4. Conclusions
The present findings point to interesting phenomena in which stacking interactions and long-range modulation of the solvent structure strongly affect the IEs of DNA bases. Despite these considerable efforts, continuous work to provide accurate theoretical values of the IEs of the DNA bases with reliable methods and proper environment representation is still required. Several important issues remain to be further explored such as the sequence dependence of IE and the influence of geometry relaxation. Indeed, consideration of geometry relaxation of a stacked cluster may be expected to induce changes of the IE of the stack that are of the same order of magnitude as the ones discussed in this work and would allow for a more quantitative treatment of the ionization of these complexes.

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