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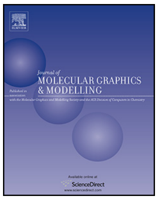

Investigation of base pairs containing oxidized guanine using *ab initio* method and ABEEM$\sigma\pi$ polarizable force field

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ABSTRACT

The integrity of the genetic information is constantly threatened by oxidizing agents. Oxidized guanines have all been linked to different types of cancers. Theoretical approaches supplement the assorted experimental techniques, and bring new sight and opportunities to investigate the underlying microscopic mechanics. Unfortunately, there is no specific force field to DNA system including oxidized guanines. Taking high level *ab initio* calculations as benchmark, we developed the ABEEM$\sigma\pi$ fluctuating charge force field, which uses multiple fluctuating charges per atom. And it was applied to study the energies, structures and mutations of base pairs containing oxidized guanines. The geometries were obtained in reference to other studies or using B3LYP/6-31+G* level optimization, which is more rational and time-saving among 24 quantum mechanical methods selected and tested by this work. The energies were determined at MP2/aug-cc-pVDZ level with BSSE corrections. Results show that the constructed potential function can accurately simulate the change of H-bond and the buckled angle formed by two base planes induced by oxidized guanine, and it provides reliable information of hydrogen bonding, stacking interaction and the mutation processes. The performance of ABEEM$\sigma\pi$ polarizable force field in predicting the bond lengths, bond angles, dipole moments *etc.* is generally better than those of the common force fields. And the accuracy of ABEEM$\sigma\pi$ PFF is close to that of the MP2 method. This shows that ABEEM$\sigma\pi$ model is a reliable choice for further research of dynamics behavior of DNA fragment including oxidized guanine.

1. Introduction

Generally, the canonical nucleic acid bases, adenine (A), thymine (T), guanine (G) and cytosine (C) exist as the main form in the double helix of DNA. The formation of specific purinepyrimidine Watson–Crick (WC) hydrogen bonds (H-bonds) is responsible for the maintenance of the genetic code. The integrity of the genetic information is constantly threatened by oxidizing agents [1–5]. Cellular DNA is constantly bombarded by reactive oxygen species (ROS) from both intra- and extracellular sources [5–7]. Of the four DNA nucleobases, guanine has the lowest redox potential [7] and is the most readily oxidized by ROS. Despite nearly a quarter of a century study, and a large number of base- and sugar-derived DNA lesions having been identified, the majority of studies have focused upon the guanine modification [8]. Oxidized guanines have all been linked to different types of cancers. For example, oxidation of guanine to 8-oxoguanine (8-oxo-G) leads to G→T transversions [1–5]. During replication of the flawed strand, oxidized guanines can be misread by polymerases as another kind of base and associated with a wrong purine or pyrimidine in the newly synthesized strand. These may lead to the introduction of a wrong genetic code [9]. The mechanism by which DNA repair enzymes such as formamidopyrimidine glycosylase (FPG/MutM) and human oGG1 enzyme (hoGG1) differentiate between 8-oxo-G and G. H-bonding and stacking interactions contribute to the stability and conformational variability of nucleic acids [10]. A proper description of these properties is useful to understand the basic principles governing the formation of the 3D nucleic acid architectures. Owing to the importance, there are numerous experimental [11–17] and computational [18–25] studies relative to the nucleotide base pairs. However, despite prolonged efforts, it remains a great challenge to understand the H-bonding and stacking interactions in oxidized guanine base pairs, and the mutagenic mechanism induced by oxidized guanine at the molecular level.

Detection and biophysical studies of modified nucleobases are challenging because they are not fluorescent and have broad electronic spectra that overlap with those of normal bases. *Ab initio* calculations supply the assorted experimental techniques, which are already capable of supplying the raw data and facts that are prerequisites for a complete understanding of the H-bonding and stacking interactions, and offered the opportunity to probe into the underlying sources of observable effects [18–21]. But, *ab initio*

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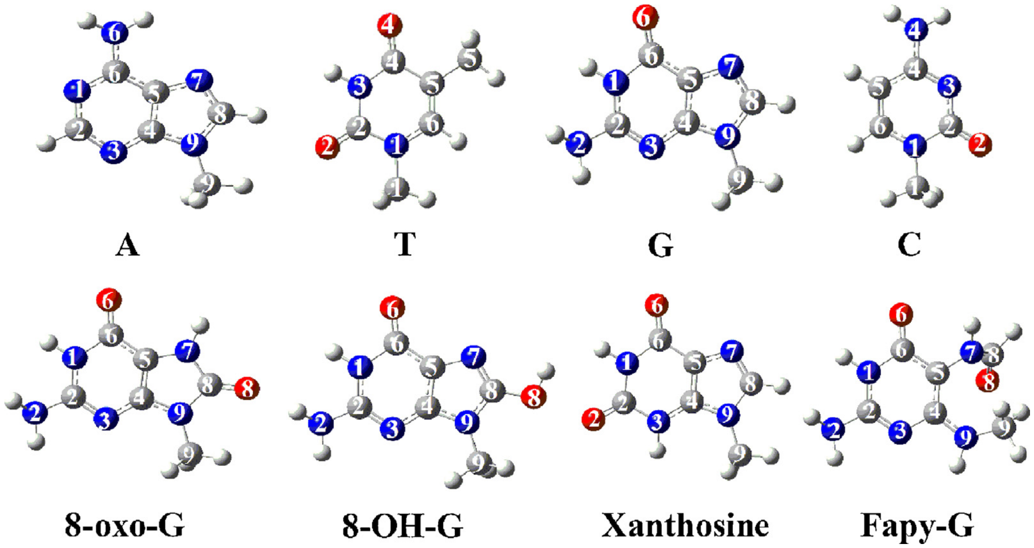

Fig. 1. The geometries and labels of canonical bases and oxidized guanines.

methods need high computational expense. Computer simulations by molecular mechanics have been a powerful tool to investigate properties of biomolecules [26,27]. The electrostatic energy makes significant contributions to the overall interaction energy of base pairs. Polarization and charge transfer effects are certainly not negligible. In view of the significance of the polarization effect, much has been achieved since the 1970s in the development and employment of the polarizable force field (PFF) for biomolecule simulation, such as AMBER [28–32], CHARMM [33–36], OPLS [37–40], NEMO [41], AMOEBA [42,43], QMPFF [44–46] *etc.* PFF mainly includes induced dipole or multipole [41–43], classical Drude oscillator [35,36] and fluctuating charge (FQ) models [33,37,47]. The computational expense of the induced dipole model is relatively high because of the iteration processes to obtain reasonable dipole, quadrupole or multipole moment. Classical Drude oscillator model introduces a massless charged particle attached to the polarizable atomic center. The positions of these “auxiliary” particles are then adjusted self-consistently to take into account the polarization. Classical Drude oscillator and induced dipole models do not consider charge transfer, which is very important for biomolecular simulation. FQ model can take charge transfer into account without iteration processes. It allows the values of partial charges to respond to the electric field of their environment. It can quickly calculate the partial charges of all the sites in the system by performing electronegativity equalization (EE) [48] or chemical potential equalization (CPE) [49] schemes in density functional theory.

ABEEM$\sigma\pi$, *i.e.*, the atom-bond electronegativity equalization method at $\sigma\pi$ level, presented by Yang and coworkers [50–52] introduces polarizability by allowing the values of partial charges to respond to their environment. It divides the single electron density of a molecule into atomic, bond (including σ and π bonds) and lone-pair regions. Recently, it was fused into molecular mechanics (MM) to establish a new generation PFF [52,53], ABEEM$\sigma\pi$ PFF or ABEEM$\sigma\pi$ fluctuating charge FF, which has been successfully applied to gas-phase water clusters and bulk water [53], aqueous ionic solutions [54–56], and biomolecules [52,57]. The results indicate that the ABEEM$\sigma\pi$ PFF is generally better than the common force fields (FFs), and its accuracy can reach or approach that of MP2 method, so it is promising to be broadly applicable. It is a well known that MP2 method coupled with large basis sets owns a much smaller error for H-bonding interactions [20,22,23], but it overestimates the binding energy of stacked dimers. Because developing the ABEEM$\sigma\pi$ fluctuating charge force field is our goal, and it was applied to study the energies, structures and mutations of base pairs containing oxidized guanines, it would be more appropriate to validate ABEEM$\sigma\pi$ results using a single *ab initio* method MP2/aug-cc-pVDZ calculation. Thus, the MP2/aug-cc-pVDZ method was selected as benchmark. In the present work, we performed theoretical investigations by *ab initio* method and ABEEM$\sigma\pi$ PFF on the stacking and H-bonding interactions of base pairs containing oxidized guanines. Then, we will summarize the structural (including geometric and electronic structure) and energetic changes caused by oxidized guanines, and further analyze the mutagenic mechanism induced by them.

2. Model molecules and methods

2.1. Model molecules

In DNA, ribose links to phosphate. In this study, we are interested in the methylated bases, oxidized guanines and their base pairs to investigate the H-bonding interaction, which have the similar chemical-bonding environment with nucleotide system. The PES of H-bonded pairs contains a small number of deep energy minima while the PES of a stacked dimer contains broad and shallow low-energy regions separated by low energy barriers. Further, as revealed by gradient geometry optimization, some stacked dimers appear to not have a minimum corresponding to a stacked arrangement, since there has been a spontaneous transition to a H-bonded structure. The bases were not methylated being kept rigid and planar, assuming MP2-optimised monomer geometries as other references [19,23]. 8-Oxo-G, 8-OH-G, Xanthosine and Fapy-G are the common forms of oxidative guanine. 8-Oxo-G results from the oxidation of guanine C8-N7 bond (an O atom in place of an H atom at C8 and an H atom at N7); 8-OH-G is an OH in place of an H atom at C8; the NH_2 at C2 is substituted with an O atom to form Xanthosine; C8-N9 bond in normal guanine is broken to form Fapy-G. These structures of canonical bases and oxidized guanines studied in this work are shown in Fig. 1. Basically, the double helix of DNA employs a Watson–Crick G:C and A:T H-bonding patterns. In Watson–Crick A:T pattern, A also has additional H-bond donor and acceptor, so it can pair with T to form Hoogsteen or reverse Hoogsteen H-bonding pattern, *i.e.* T:A:T or T:A:T(R) triplet bases, which are the fundamental constitutional units in triple helix. G also can pair with C to form Hoogsteen H-bonding pattern, where C is in the