Density Functional Theory Studies on Guanine and Cytosine

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Abstract: DFT cluster method was employed to investigate the electronic structures of guanine and cytosine in the form of nucleobase and nucleotide. All calculations were performed at the B3LYP/6-311++G (d,p) level. From the computational study, the presence of methyl group or sugar phosphate group to the nucleic acid bases has a direct effect on the structure of the system. The planar structure of the nitrogenous base is maintained after geometry optimization procedure. No significant difference was found in the charge distribution in nucleobase and nucleotide for both guanine and cytosine. The ionization energy for guanine is found to be lower than that for cytosine. The HOMO-LUMO gap is lower for both guanine and cytosine in the nucleobase form. The calculated dipole moment shows that guanine is more polarized than cytosine.

1 INTRODUCTION

Deoxyribonucleic acid (DNA) is a versatile molecule that stores genetic information and consists of two polynucleotide chains twisted around each other in the form of a double helix. DNA is formed using sequences of four nitrogenous bases. These four bases are guanine (G), adenine (A), cytosine (C) and thymine (T), and they can be divided into two groups. Guanine and adenine belong to the purine group which is considered as a good electron donor. Cytosine and thymine on the other hand belong to the pyrimidine group which is poor electron donor as compared to the purine group. Purines and pyrimidines are considered as aromatic compounds and are electron rich in nature (Garrett and Grisham, 2002). The molecular formulas for adenine, guanine, cytosine and thymine bases are $C_5H_5N_5$, $C_5H_5N_5O$, $C_4H_5N_3O$, and $C_5H_6N_2O_2$ respectively (Kim et al. 2015). In double strand DNA, the four bases are arranged in a pair by forming hydrogen bond between the bases. Adenine on one strand will pair up with thymine base on the other strand, while guanine pair up with cytosine. These nitrogenous bases will be ordered in some ways to provide the necessary information to make proteins for building and maintaining an organism. All four nitrogenous bases have different electronic structure and chemical structure. The molecular orbital and electron distribution for all nitrogenous bases are different from one another.

DNA bases are considered as an organic molecular compound that has the ability to transport electron through (Chakraborty, 2007). In general, electron transport occurs in many important biological processes such as the storage and consumption of energy, enzyme response, and DNA UV damage repair (Klotsa et al. 2005). Electron transport along the DNA molecule and the potential application of DNA molecule has caught the attention of many chemists and physicists. DNA is a biological molecule that has potential in fabrication and construction of electronic nanodevices due to their electronic properties (Cai et al. 2000 and Kaur et al. 2011). Studies using varieties of experimental approaches show that DNA is an effective medium for charge migration (Apalkov et al. 2007). To study the electron transport or charge migration through DNA, the electronic structure of DNA bases need to be known.

There are varieties of experimental techniques that were used to determine the structure of DNA

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nitrogenous bases such as NMR spectroscopy, X-ray crystallography, and electron microscopy. The experimental results are often compared with theoretical results. Several research groups have carried out theoretical study by using isolated bases (hydrogen replace sugar phosphate) (Kilina et al. 2007) or methyl group (Mahanto et al. 2008) to replace the sugar phosphate backbone. The use of methyl group to replace sugar phosphate group that is attached to the bases can be a justifiable approximation as it can mimic the effect of sugar phosphate group through hyperconjugation effects (Mahato et al. 2008). However, methyl group is an electron donating group that could increase electron donating properties of the molecule (Pullman and Pullman, 1958). Mahanto et al. also concluded that that sugar phosphate group needs to be taken into consideration when designing a calculation model (Mahanto et al. 2008). The question on the effect of methyl group and sugar phosphate group to the electronic structure of the nitrogenous base is therefore the motivation of this study.

In this paper, we report the results of our computational investigation using DFT cluster method to study the electronic structures of one of the complementary base pairs which are guanine and cytosine. The goal of this study is to investigate the electronic structure of guanine and cytosine in two different forms.

2 METHODOLOGY

The structural data for all four structures studied in this investigation guanine nucleobase, guanine nucleotide, cytosine nucleobase and cytosine nucleotide were obtained from PubChem database (Kim et al. 2015). Figure 1 represents guanine and cytosine structures. The atoms numbering follows Sinden et al. numbering scheme (Sinden et al. 1998).

The difference between nucleobase and nucleotide structures is that for the former a methyl group is attached at the R position, whereas for the later a sugar phosphate group is attached as shown in Figure 1. The structures of the methyl group and sugar phosphate groups are shown in Figure 2. A methyl group belongs to an organic family called an alkyl group that contains one carbon atom surrounded by three hydrogen atoms. Sugar phosphate group is an important structural component that forms the backbone of nucleic acids such as DNA and RNA. A sugar phosphate group consists of deoxyribose sugar that attaches to a phosphate group.

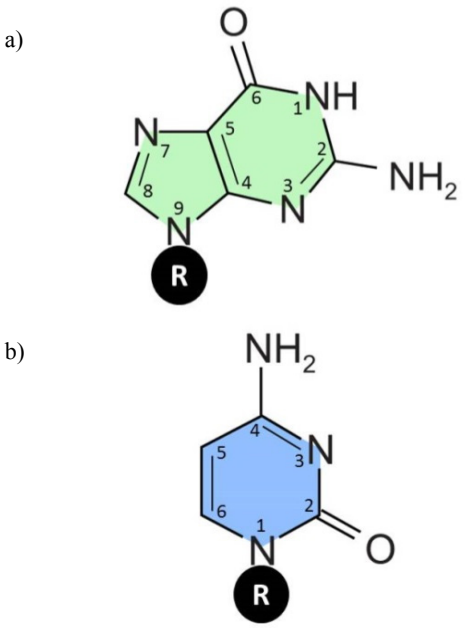

Figure 1: DNA bases structures and numbering. (a) guanine and (b) cytosine.

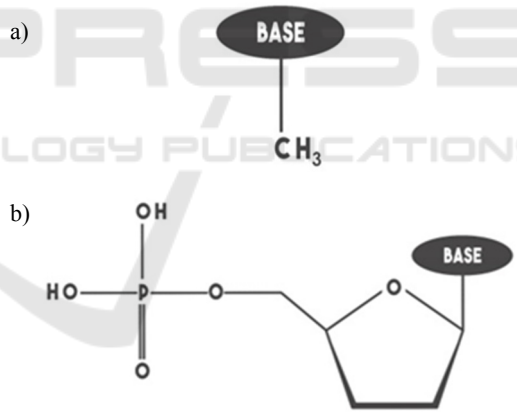

Figure 2: Methyl group and sugar phosphate structures. (a) methyl group and (b) sugar phosphate.

DFT cluster method was applied to study the electronic structures of all four structures. DFT method is an alternative *ab initio* method that is more efficient in considering correlation energy. Hybrid functional is the most popular functional used in DFT computations. One common functional is B3LYP. Hybrid functional is effective functional for organic, biochemical and large systems without requiring an excessive amount of computing time, memory and disk space (Rengifo and Murillo, 2012).

The Cluster Method was employed (Sulaiman et al. 2015) and the DFT quantum mechanical procedure at B3LYP/6-311++G (d,p) level (Izzati et al. 2011) was applied to investigate the electronic structures. The chosen basis set contains a polarization function which is important to allow the distortion of the atomic orbitals in a molecular environment. The 6-311++G basis set used in our investigation has *p*-type function added to hydrogen atom and *d*-type function added to all other atoms. The diffuse function which is also included in the 6-311++G (d,p) basis sets is to allows the electron to move further away from the nucleus in the ground state (diffuse functions were added to all atoms). The extended basis set is needed to produce a reliable result of the electronic structure and total energy (Rengifo and Murillo, 2012). The converged molecular orbitals were then used to examine the electronic structures of the systems.

Gaussian 16 (G16) computational software package installed at the RIKEN Hokusai Great Wave Supercomputing facility was used to perform the calculations. Gaussian 16 is the latest in the Gaussian series of programs and has the capabilities for electronic structure modelling (Frisch et al. 2016). There are a few types of calculation that can be done by using this computational software such as single point energy, geometry optimization, Hartee-Fock and others.

Two types of calculations were performed in this study, single point energy calculation and geometry optimization calculation. Single point energy calculations were made to compute the electronic structure of the system and provide information about the molecule such as energy, wave function and charge distribution. The calculation is performed at a single fixed geometry. On the other hand, geometry optimization calculations were conducted to determine the geometry of the molecules that is the most stable with respect to the total energy. All four structures were optimized such that the optimized geometries correspond to the systems with minimum total energy.

3 RESULT AND DISCUSSION

Following the main motivation of our computational investigation, a systematic study on the electronic structures of guanine and cytosine that are attached to a methyl group or a sugar phosphate group has been performed using the methodology presented above.

3.1 Geometrical Parameters

All optimized structures preserved the planar geometrical shape of the nitrogenous bases after atomic relaxation. Figure 3 shows the changes in the selected bond lengths of the optimized structure relative to the initial structure, while Figure 4 shows the changes in the selected bond angles. As can be seen from Figure 3 and Figure 4, the trend of the increases or decreases of the parameters are the same for most atoms in nucleobases and nucleotides form. The addition of methyl group or sugar phosphate group results in similar effects to the bond lengths and bond angles. The changes in the bond lengths and bond angles do not result in any significant modification to the planar shape of the nitrogenous bases.

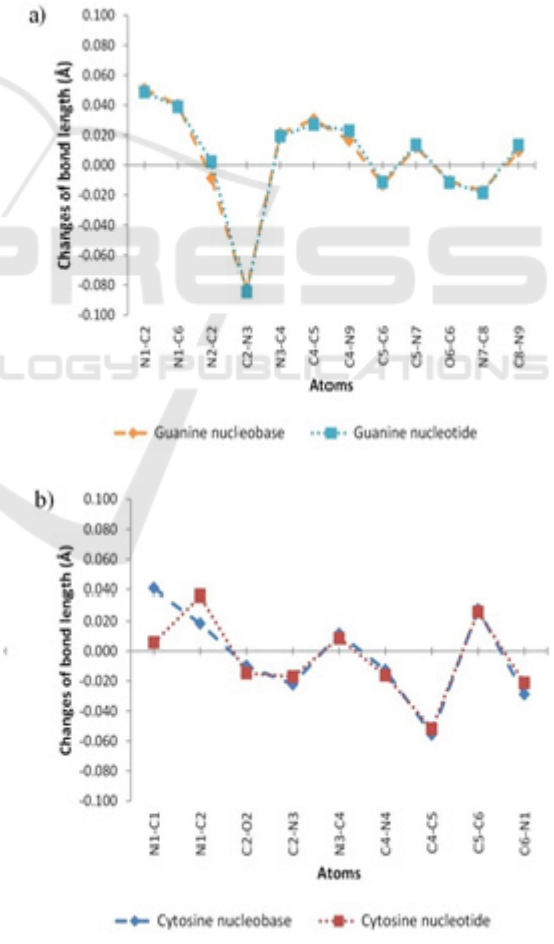

Figure 3: Bond length changes. (a) guanine and (b) cytosine.

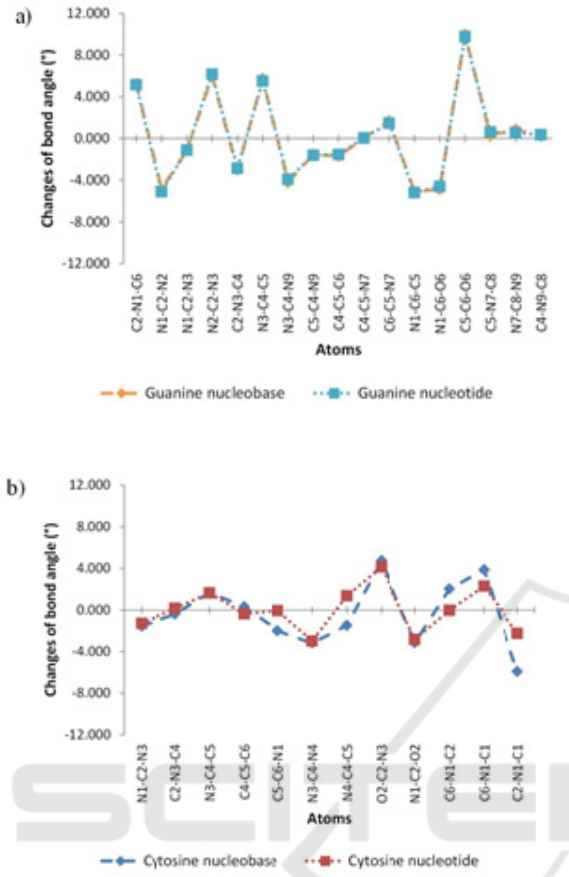

Figure 4: Bond angles change of optimized structure. (a) guanine and (b) cytosine.

3.2 Total Energy

The total energy of each molecule after geometry optimization procedure is given in Table 1. The total energy presented is relative to total energy obtained from single point energy calculation. This result indicates that the optimized structure is more stable because it has a lower energy. Nitrogenous base with attached sugar phosphate group experiences large differences in the energy after geometry optimization process. It is therefore very important to perform geometry optimization procedure before attempting to obtain the electronic structure of the system studied.

Table 1: Total energy of guanine and cytosine.

Nitrogenous base	Total energy (eV)	
	Nucleobase	Nucleotide
Guanine	- 0.584	- 1.029
Cytosine	- 0.137	- 0.634

3.3 Charge Distribution

Mulliken population analysis and natural population analysis are two population analyses that can be used to determine charge distribution in a molecule. Mulliken population analysis is the most common population analysis that has been used due to its simplicity (Šponer et al. 2001). In this study, we did not use Mulliken population analysis to determine the effective charge on the atoms because of the result is dependent of the method and basis set (Matczak, 2016). The charge distribution presented in this study is based on the natural population analysis.

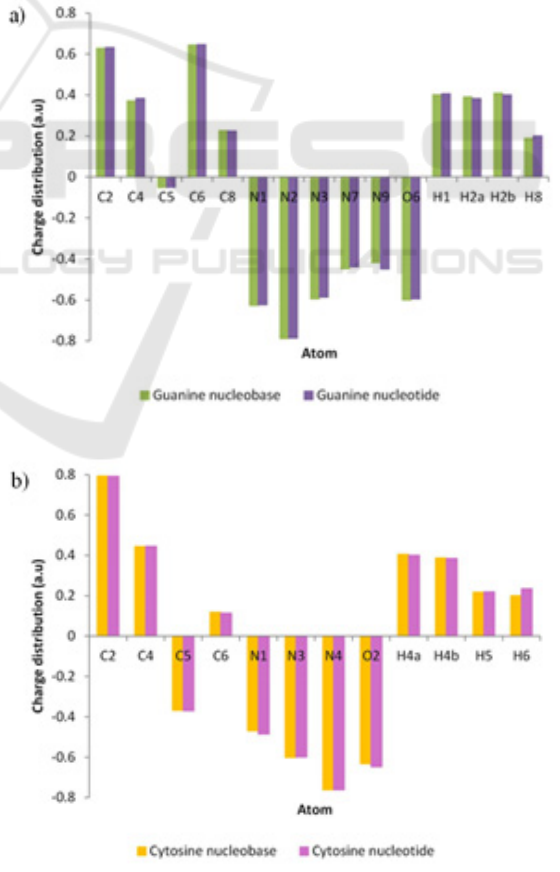

Figure 5: Atomic charge distribution. (a) guanine and (b) cytosine.

The determination of charge distribution is crucial in the study of the electronic structure of the system. Atomic charge distribution can be used to study the charge transfer in a chemical reaction. Figure 5 represents the charge distribution value of guanine and cytosine optimized structures. The existence of methyl group and sugar phosphate group does not give significant effect to the charge distribution around the nitrogenous bases ring.

3.4 Ionization Energy

The calculated ionization energies for the optimized structures are summarized in Table 2. From the result, it can be seen that the ionization energy increases by 0.364 eV when the methyl group is replaced by a sugar phosphate group. Thus, it requires more energy to remove an electron from the latter molecule. In the case of cytosine, the difference in the ionization energy between nucleobase and nucleotide is not only relatively small, but decreases, which is opposite in effect as compared to the case of guanine.

From our calculation, guanine in nucleobase and nucleotides configurations has lower ionization energies as compared to cytosine. Our results are in agreement with the statement of Senthilkumar et al. (Senthilkumar et al. 2003). Considering that guanine has a lower ionization energy, guanine base becomes the main target for oxidation to occur (Seidel et al. 1996). From biological perspective, oxidation of nitrogenous base promotes oxidative damage.

Table 2: Ionization energy of guanine and cytosine.

Nitrogenous base	Ionization energy (eV)	
	Nucleobase	Nucleotide
Guanine	5.849	6.258
Cytosine	6.462	6.459

3.5 Frontier Molecular Orbital Analysis

The transfer of charge through the molecule is affected by the electronic structure (Padmaja et al. 2009). In particular, the difference in the energy of highest occupied molecular orbital (HOMO) and lowest occupied molecular orbital (LUMO) is an important parameter that is considered to study and understand the possibilities of charge migration through DNA. The surface plot of the calculated HOMO and LUMO, and the corresponding energy level diagram are shown in Figure 6 and to Figure 7.

The molecular orbital is presented on the surface of equal amplitude of 0.020. From this plot, the positive and negative sign wave function is indicated by the red and green colour respectively. The sign of the wave function on the nitrogenous base ring in nucleobase and nucleotide configuration is opposite from each other. It is clear that methyl group and sugar phosphate groups have an impact on the attributes of the molecular orbitals.

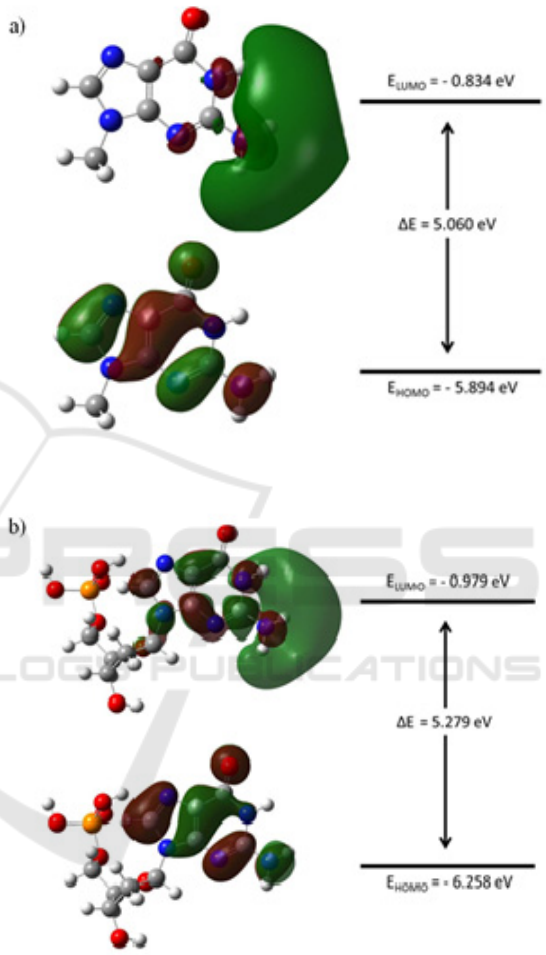

Figure 6: Molecular orbital surface plot and energy level diagram of guanine. (a) guanine nucleobase and (b) guanine nucleotide.

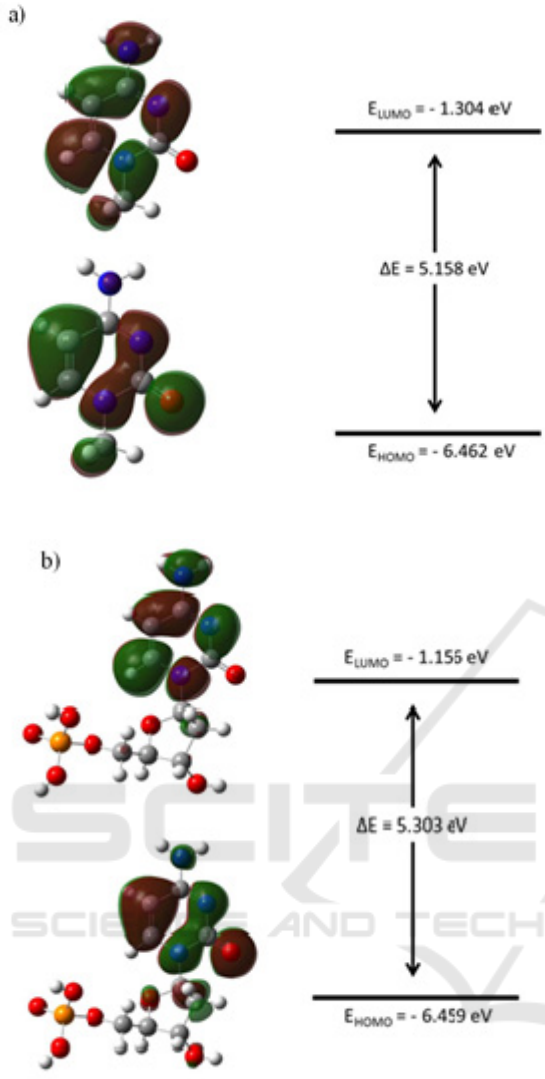

Figure 7: Molecular orbital surface plot and energy level diagram of cytosine. (a) cytosine nucleobase and (b) cytosine nucleotide.

From the molecular orbital energy diagram, it can be seen that all nucleobases and nucleotides have a HOMO-LUMO gap of more than 5 eV. The value of HOMO-LUMO gap for guanine nucleobase, guanine nucleotide, cytosine nucleobase and cytosine nucleotide are 5% lower, 9% lower, 1% lower and 2% higher than Kilina et al. findings respectively (Kilina et al. 2007). The sequence and magnitude of the HOMO-LUMO gap for all structure are guanine nucleobase < cytosine nucleobase < guanine nucleotide < cytosine nucleotide. Nucleobases structures have a lower HOMO-LUMO gap. This is more likely due to the presence of methyl group. Methyl group is an electron donating group and could decrease the HOMO-LUMO gap (Pullman and Pullman, 1958). Structure with sugar phosphate group attached to the nitrogenous base has a larger HOMO-LUMO gap. Hence, it is clear that inclusion of sugar phosphate group has an impact to the HOMO-LUMO gap. The changes in the HOMO-LUMO gap could affect the possibilities of charge transport through DNA.

3.6 Dipole Moment

The measurement of dipole moment is important in differentiating polar and non-polar molecules. Dipole moment is basically the measure of net polarity in a molecule. Polar molecule has an uneven charge distribution across the entire molecule. Moreover, the polarity is determined by the distribution of donor and acceptor functional group around the base.

Guanine and cytosine are known as polar molecules (Kilina et al. 2007). Table 3 summarizes the values of dipole moment of guanine and cytosine calculated using the optimized structures. From the calculated dipole moment, the most polar base is guanine. Cytosine has a lower dipole moment. For guanine, the dipole moment of the nucleotide is slightly larger than that for the nucleobase. However, the trend is opposite for the case of cytosine.

Table 3: Dipole moment of guanine and cytosine.

Nitrogenous base	Dipole moment (D)	
	Nucleobase	Nucleotide
Guanine	7.400	7.413
Cytosine	6.369	5.322

4 CONCLUSION

From our computational study, the presence of methyl group or sugar phosphate group to the nucleic acid bases has a direct effect on the structure of the system. Further computational investigation should be performed on adenine and thymine. A comparison between all four bases is needed so that we can have a better understanding on DNA electronic structure and properties.

The computational method that was used in this study can be employed for more complex oligomer system. This study would be extended using bigger cluster size with more bases so that the effects of neighbouring bases can be included and studied.

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