Theoretical ab Initio Study the Hydrogen Bonding Nature of the A: T Base Pair

Mohanned Jasem Al-anber

Department of Physics, College of Science,
Basrah University, Basrah, Iraq
E-mail: mohanadalnbar@yahoo.com

Abstract

The effect of applied external electric field on DNA occurs mostly at high field intensity. The results of the theoretical ab initio study on the applied electric field on A:T base pair components are reported. The geometries of the local minima were optimized at DFT level (B3LYP). The 6-31G(d, p) basis set was used. The geometrical parameters, relative stability, interaction energies and nature of hydrogen bonding energy are reported. Also, focus on the range of hydrogen bonding energy and the flexibility of the rotation angle between the A:T base pair. So that the electric field mutation may be able to be classified as multi-point mutation.

Keywords: DFT, DNA, ab initio calculation, electric field effect, mutating.

Introduction

After accurately describing the structure of DNA, Watson and Crick suggested that the effects of spontaneous mutations on DNA [1]. DNA can be damaged by many different sorts of mutagens. These include oxidizing agents, alkylating agents and also high-energy electromagnetic radiation such as ultraviolet light and X-rays. The type of DNA damage produced depends on the type of mutagen. For example, UV light mostly damages DNA by producing thymine dimers, which are cross-links between adjacent pyrimidine bases in a DNA strand [2]. On the other hand, oxidants such as free radicals or hydrogen peroxide produce multiple forms of damage, including base modifications, particularly of guanosine, as well as double-strand breaks [3]. It has been estimated that in each human cell, about 500 bases suffer oxidation damage per day [4, 5]. The most serious damage of these oxidative lesions are the double-strand breaks, as these lesions are difficult to repair and can produce point mutations, insertions and deletions from the DNA sequence, as well as chromosomal
translocations [6]. Chemically induced or exogenous methylation occurs as a result of exposure to chemical agents such as nitrosamines, di-methyl sulfate, and 1, 3-bis(2-chloroethyl)-1-nitrosourea. Recently, attention has been given to the nitrosamines, which are a principle alkaloids found in tobacco smoke (they make methylation base pairs) [7]. However, partly due to its influence on hydrogen bonding, methylation is the most pro-mutagenic methyl adducts formed and can both silence gene expression and cause point mutations [8]. Epigenetic methylation occurs at the guanine and cytosine of CpG islands in DNA and is regulated by an organism’s methyltransferases and other enzymes. These enzymes interact with DNA by flipping the target base out of the double helix and into its active site [9]. The term base flipping is commonly used to describe the rotation of single base out of the double helix as a result of attractive and repulsive forces imparted by enzyme’s active site constituents.

The aim of this theoretical investigation is to use ab initio approaches [10] to characterize the nature of changes in the interaction energy and the molecular structure in A:T base pairs under the applied external electric field. To accomplish this, we analyzed the changes in the molecular geometry and the interaction energy components [11].

**Computational details**

Theoretical calculations are used to bridge gaps in the understanding of experimental results. In many cases the results of the experimental methods are unable to describe accurately the small complex components. The molecular quantum methods can be used to investigate properties beyond the scope of the crystallographic methods. Where they allow to study the physical and chemical properties, which are not easily measured systems in the micro and nano dimensions. Also they can examine the interaction energies that are not provided by the X-ray and NMR experiments. The predictive power of the theoretical computational methods for DNA has been confirmed in the recent investigation of experiments, which concluded that the amino groups in the cytosine and the adenine are non-planar form [12]. This was postulated and predicted by the ab initio calculations over 10 years ago [13]. First geometries for all cases were optimized at Restricted Hartree-Fock (RHF) method with basis set 6-31G(d, p) and then optimized using B3LYP method to include correlation corrections with basis set 6-31G(d, p). Density functional are used, the Becke’s three-parameter hybrid functional using the LYP correlation functional which defines the exchange functional as the linear combination of Hartree-Fock, local and gradient-corrected exchange terms. The B3 hybrid functional was used in combination with the correlation functionals of Lee, Yang and Parr and non-local correlation expression provided by the LYP[l4]. Some previous calculations [15-17] suggested that the B3LYP/6-31G(d, p) results gave good agreement. All geometries for each case were performed using the Gaussian98 [18]. To examine the effect of applied electric field on the adenine, thymine, the A:T base pair and the hydrogen bonding between A:T base pair, the electric field were varied from 0.00 au to 0.002 au in step 0.0005 au. The external electric fields have been applied in x, y and z direction respectively.
Results and discussion

Stability of the adenine, thymine and the single A:T base pairs

The geometry optimized without electric field of the adenine, thymine and the single A:T base pair using B3LYP level are shown in figure 1. The change in optimized total energies ($\Delta E_t = E_t(\text{field-off}) - E_t(\text{field-on})$) of the adenine, thymine and the single A:T base pairs as a function of the considered applied electric field in this study are collected in figures 2, 3 and 4, respectively. The minimize energy calculation for the adenine, thymine and the A:T base pair (in gas phase) appeared changes in their stabilities. As the electric field increases in the x and y direction respectively the adenine stability increases with note that x direction shown more effected. While the applied electric field in the z direction, which is perpendicular to the plane of the adenine molecule, shows very low effect compared with the x and y directions, see figure 2. In figure 3 shown the effect of applied electric field on the thymine, where the y direction shows more increases in the stability of thymine compare with the case of adenine. Also the applied electric field in x direction shows more effect than the y direction, see figure 3. The results of applied electric field in the z direction for thymine appear to be the same as for the adenine. When the electric field was applied in the x direction, which is parallel to the two hydrogen bonds between the adenine and thymine in base pair, the stability of the single A:T base pair increases as the electric field increases, see figure 4. While the applied electric fields in the y direction shows the increase in the stability of the A:T base pair. The applied electric field in the z direction to the A:T base pair, which is perpendicular to the plane of A:T base pair, does not show interested effect on the its stability compared with the x and y directions. For that, the enzyme of helicase, which unwinding DNA, will response hardly in the operation of separating the double helix of DNA due to applied electric field in the x or y directions.

Figure 1: the optimized normal A:T base pair at B3LYP/6-31G(d,p) level.
Figure 2: the change in total energies of adenine as a function of the electric field in x: □, y: ◊ and z:∆ direction respectively at B3LYP/6-31G(d,p) level.

Figure 3: the change in total energies (in Kcal/mol) of thymine as a function of the electric field in x: □, y: ◊ and z:∆ direction respectively at B3LYP/6-31G(d,p) level.
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Figure 4: the change in total energies (in Kcal/mol) of A:T base pairs as a function of the electric field in x: □, y: ◊ and z:Δ direction respectively at B3LYP/6-31G(d,p) level.

Nature of Hydrogen bonding energy of the A:T base pairs
The less computationally expensive for the B3LYP/6-31G(d, p) method, which describes hydrogen bonding interactions in A:T and G:C base pairs, was in good agreement with higher-level MP2 calculations [15, 16]. In order to examine the nature of hydrogen binding between the adenine and the thymine which form the A:T base pair, we adopted only a single A:T base pair in this work. The optimized of the single A:T base pairs, without electric field, which considered in this study are shown in figure 1. The hydrogen bonding energy (HBE) in the A:T base pair, $HBE = E_{A:T} - (E_{Adenine} + E_{Thymine})$, and the change in hydrogen bonding energy, $\Delta HBE = HBE(\text{field-off}) - HBE(\text{field-on})$, as a function of applied electric field shows in figure 5. Where the applied field in the y direction is shown more lower in the hydrogen bonding energy compare with the effect of applied electric field in x direction. The applied electric field in the z direction, which is perpendicular to the plane of the two hydrogen bonds in the A:T base pair, is shown significantly different from the other two directions. It shows little decreasing in the hydrogen bonding energy and then few increasing due to field increasing. According to this result, when the electric field applied in the x or y direction may be not difficult the role of enzyme to separate the DNA sheets, which lead to be easy in the processing of the DNA copy. In general we hypothesize that the genes at the electric field may be not silenced as in the case of
G:C base pair [17], because of the ability of bases to flip out of the double helix into the active site of enzymes due to the relative lower in the hydrogen binding interactions under electric field. In order to more explore the nature of the two hydrogen bonding lengths without an applied electric field, we calculate the hydrogen bonding energy as a function of the distance between the adenine and thymine in the A:T base pair using B3LYP/6-31G(d, p), see figure 6. Whereby the distance between the adenine and thymine in the A:T base pair increase from the optimized distance, or equilibrium point, the hydrogen bonding energy shows repaid decreases beyond few angstroms, and with 3Å distance from the equilibrium point the hydrogen bonding energy finish, approximately. Also if the adenine and thymine as base pair closed once from another, then the hydrogen bonding energy exchanges into the repulsion item. The energy equal to 0.798eV enough to dispersion the hydrogen bonding energy in the A:T base pair so that each one from the adenine and thymine in the A:T base pair will be alone. To examine the nature of flexibility the two hydrogen bonds by doing rotation between the adenine and thymine in the A:T base pair with step 10°, see figure 7, using B3LYP/6-31G(d, p). It shows that the hydrogen bonding energy at the rotation angle equal to 10° will dropped to 10.9%, while at 20° the hydrogen bonding energy will dropped to 18.8%. This may be giving theoretical investigation about the limited of the rotation flexibility in arrangement 20±10°. Also, the enzyme of helicase may be need to rotating the two hydrogen bonds in the A:T base pair by angle 20±10° to flip it out of the double helix.

![Figure 5: The change in hydrogen bonding energies of A:T base pairs as a function of the electric field in x: □, y: ◊ and z:△ direction respectively at B3LYP/6-31G(d,p) level.](image-url)
**Figure 6:** the hydrogen bonding energy as a function of the change in the distance (in Å) between the A:T base pair at B3LYP/6-31G(d,p) level.

**Figure 7:** the hydrogen bonding energy as a function of the rotation angle (in degree) between the A:T base pair at B3LYP/6-31G(d,p) level.
Geometry analysis of the A:T base pairs
The change in the optimized of the two hydrogen bonds lengths between the adenine and thymine in A:T base pair, \( \Delta r = r_{\text{field-off}} - r_{\text{field-on}} \), is shown in figures 8 and 9 respectively. Calculations using B3LYP/6-31G(d, p) are made on the A:T base pair in order to see the effect of the electric field on lengths of these two hydrogen bonds between the adenine and thymine in base pair. The applied electric field in x and y directions respectively, produce compression of the hydrogen bond length \( \Delta r(H30-N7) \) as the electric field increase. Note that the effect of the field on the bond in x direction is more than the y direction. The applied electric field in z direction, which is perpendicular to the plane of A:T base pair, shown uninterested effect on the hydrogen bond lengths, see figure 8. The electric field effects on the hydrogen bond length, \( \Delta r(H14-O18) \), shown behavior, approximately, opposite to the case of \( \Delta r(H30-N7) \) under the electric field, see figure 9. Where the electric field extensions the \( \Delta r(H14-O18) \) length. At electric field in x and y directions respectively shown effects differ on the A:T base pair comparison with the case without electric field, in two ways: first, the change of the hydrogen bond length between adenine (H14) and thymine (O18) atoms, extension. Second, there is an closing of the hydrogen bond length between adenine (N7) and thymine (H30) atoms more than the normal case. This indicates an closing of the hydrogen bond at the middle site of the pair and opening at the down site. In other words, the aberrant A:T base pair under the electric field at (O18) atom, the electric field acts on the hydrogen bond so that it causing to lose its ability to participate in one of two hydrogen bonds, leaving it susceptible to mis-pairing with bases pair, which untypical for two hydrogen bonds such as A:T base pair. The effect of the electric field give the same results to that of mutagenic by methylate effect on the A:T base pair [15, 16]. From the geometrical data it should be noted that the geometrical factors of all the electric fields effects differ significantly from each other with respect to intermolecular bond lengths. The effect of the electric field on the hydrogen bond lengths is excessive when the external electric field is applied perturbs in the same directions of the plane of A:T base pair. In other words, the applied high electric field in the direction that coincident with molecule of A:T pair is significant enough to disrupt one of the two hydrogen bonds in the A:T base pair. The molecule of adenine and thymine of the A:T base pair still in the same plane of the normal A:T base pair under all fields.
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Figure 8: the change in the hydrogen bond distance (Å), $\Delta r$, as a function of the electric field in $x$: $\Box$, $y$: $\Diamond$ and $z$: $\Delta$ direction respectively at B3LYP/6-31G(d,p) level.

Figure 9: the change in the hydrogen bond distance (Å), $\Delta r$, as a function of the electric field in $x$: $\Box$, $y$: $\Diamond$ and $z$: $\Delta$ direction respectively at B3LYP/6-31G(d,p) level.
Conclusion
In summary, the results of our calculations show that the applied electric field on A:T base pairs causes significant changes in the interaction between adenine and thymine compared to the Watson-Crick hydrogen-bonding pattern. This probably is a result of inductive and steric effects. As a result of changes in the A:T hydrogen bonding energies, the energy required for base flipping may not exceed to that which is provided by the enzyme which is responsible for this process. Our results are summed up by the following:

- Based on our data, the increases in the electric field may be introducing significant changes in the geometrical parameters of the A:T base pairs. In the case of $\Delta r(H14-O18)$, which is known to cause base transitions, it is shown that one of the hydrogen bonds is lost.
- We have found that changes in interaction energies in the A:T base pairs (with applied electric field) do directly correlate to adduct pro-mutagenicity.
- Additionally, our data reveals that electrostatic contributions predominate in interactions of all investigated complexes.
- The order of stability of adenine, thymine and the A:T base pair is a function of electric field intensity and direction.
- The applied high electric field on the A:T base pair decreasing intermolecular bonding energies.
- The electric field may be able to produce the multi-point mutations.
- The range of the hydrogen bonding energy in the A:T base pair was lower than the optimized distance by $\sim 0.24\text{Å}$ and higher than by $\sim 3\text{Å}$ approximately.
- The rotation flexibility in the A:T base pair was limited as $20^\circ \pm 10^\circ$ approximately.
- Finally, some results of applied external electric field on the A:T base pair same to the results of C:G base pair and other differ [18]

References

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