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THEORETICAL AB INITIO STUDY OF THE ELECTRIC FIELD EFFECTS ON THE STRUCTURE AND STABILITY OF G:C BASE PAIR

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The effect of applied external electric field on DNA occurs mostly at high field intensity. The results of a theoretical ab initio study of effects of applied electric field on G:C base pair components are reported. The geometries of the local minima were optimized without the symmetry restrictions by the gradient procedure at density-functional level of the theory and were verified by calculations of the second derivative of energy. The standard CEP-31G basis set was used. The geometrical parameters, relative stability and interaction energies are reported. The electric field mutation could be classified as a multi-point mutation.

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1. *Introduction*

After accurately describing the structure of DNA, Watson and Crick suggested 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 adduct 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 molecular structure in G:C 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].

2. *Theoretical approach and 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 accurately describe small components of a complex biochemical. The methods of molecular quantum mechanics can be used to investigate properties beyond the scope of current crystallographic methods. The molecular quantum techniques allow us to study optical, magnetic and electronic properties which are not easily measured experimentally. The molecular quantum mechanics provides the interaction energies that are not provided by the X-ray and NMR experiments. The theoretical methods can be used to further investigate and predict the physical and chemical nature of hydrogen bonding interactions. The predictive power of computational biology for DNA has been confirmed in the recent experimental investigation which concluded that amino groups in cytosine and adenine are non-planar [12]. This was postulated and predicted by the molecular quantum calculations over 10 years ago [13]. Ab initio calculations were performed to study the G:C base pair using the Gaussian 98 program [14]. The geometries for normal (field-off) and electric field-on G:C base pairs were fully optimized at density-functional-theory (DFT) level with the CEP-31G basis set using the gradient optimization method. The applied DFT method used the B3LYP hybrid functional (a parameterized combination of Becke's exchange functional, the Lee, Yang and Parr correlation functional and the exact exchange) [15].

3. Stability of cytosine, guanine and G:C base pairs

The change in optimized total energies ($\Delta E_t = E_{\mathrm{normal}} - E_{\mathrm{field}}$), as a function of applied electric field, of guanine, cytosine and G:C base pairs considered in this study are collected in Tables 1, 2 and 3, respectively. Calculations for the guanine and cytosine alone (in gas phase) gave changes in stability of these molecules. The applied electric field in the x direction decreases the guanine stability, while its stability increases for other directions. The applied electric field in the z direction, which is perpendicular to the plane of guanine molecule, shows low effect compared with the y direction. In the case of cytosine base the applied electric field in the x and y directions decrease the stability, while the z direction field show low increases in the cytosine stability. For a weak applied electric field in the x direction, the stability of the G:C base pair decreases, but as the field increases, the stability increases. The applied electric fields in the y and z directions produces a decrease of G:C base pair stability. These two directions showed approximately the same effect. The enzyme of helicase, which is unwinding DNA, is corresponding hard in the operation of separating the double helix of DNA.

TABLE 1. The total energies (in Kcal/mol*) of guanine at different levels of the electric field in the x, y and z direction, estimated at the B3LYP/CEP-31G level.*

Electric field (a.u.)	x-direction	y-direction	z-direction
0.0001	–0.10089	0.156969	0.000205
0.0010	–1.05025	1.600899	0.008105
0.0100	–5.24153	19.22036	**0.060635**

TABLE 2. The total energies (in Kcal/mol*) of cytosine at different levels of the electric field in the x, y and z direction, estimated at the B3LYP/CEP-31G level.*

Electric field (a.u.)	x-direction	y-direction	z-direction
0.0001	–0.12064	–0.14021	8.58E-05
0.0010	–1.18499	–1.43871	0.00879
0.0100	–13.762	**–2.73721**	0.919663

TABLE 3. The total energies (in Kcal/mol*) of G:C base pairs at different levels of the electric field in the x, y and z direction, estimated at the B3LYP/CEP-31G level.*

Electric field (a.u.)	x-direction	y-direction	z-direction
0.0001	–0.16795	–0.0269	–0.00334
0.0010	1.788492	–0.20783	–0.28902
0.0100	27.27538	**–0.38876**	–20.1515

4. Hydrogen bonding energy of G:C base pairs

The less computationally expensive B3LYP/CEP-31G method describes hydrogen bonding interactions in G:C base pairing in good agreement with higher-level MP2 calculations [16]. Normal of G:C base pairs considered in this study are shown in Fig. 1. The hydrogen bonding (HB) energy of normal G:C base pair, $E^{\mathrm{HB}} = E_{\mathrm{G:C}} - [E_{\mathrm{Cytosine}} + E_{\mathrm{Guanine}}]$, without electric field, is equal to –34.05268053 Kcal/mol. The hydrogen bonding energies between the G:C base pair as a function of the electric field, are shown in Table 4. It should be noted that, for the applied electric field in the x direction of G:C base pair coincident with axes of hydrogen bonding complexes, they differ significantly from the other two directions

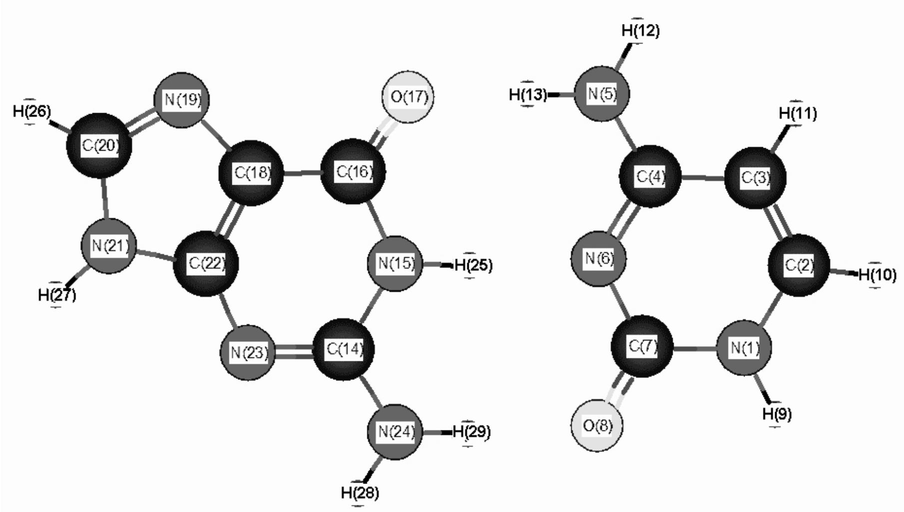

Fig. 1. The optimized normal G:C base pair at the B3LYP/CEP-31G level.

TABLE 4. The hydrogen bonding energies (in Kcal/mol*) of G:C base pairs at different levels of the electric field in the x, y and z direction, estimated at the B3LYP/CEP-31G level.*

Electric field (a.u.)	x-direction	y-direction	z-direction
0.0001	–34.1063	–34.009	–34.0491
0.0010	–38.0764	–33.6827	–33.7468
0.0100	–80.3316	–30.6528	–12.9209

with respect to intermolecular bond distances. In the former case, the hydrogen bonding energy increases, while in other two directions, the hydrogen bonding energy decreases. The applied electric field in the z direction, coincident with the normal direction to the plane of the G:C base pair, does not show large effect in this direction. The applied electric field in the direction of the hydrogen bond may interfere in the enzyme role in the separation of the DNA sheets, which may lead to errors in the processes of DNA copying. In general, we hypothesize that the genes in the electric field may be silenced, because of the inability of bases to flip out of the double helix into the active site of enzymes due to the stronger hydrogen binding interactions. In an aberrant G:C base pair in an electric field at an O_{17} atom, the electric field acts on the hydrogen bond causing it to lose its ability to participate in one of its three hydrogen bonds, leaving it susceptible to mis-pairing with bases, which is typical for two hydrogen bonds in thymine. This case may be similar to the methylation effect [16].

5. *Geometry analysis of G:C base pairs*

The changes in the optimized hydrogen bond distances as a function of applied electric field, Δr^{HB}, are collected in Table 5. The calculations were made for a normal G:C base pair in order to note the electric field effect on the hydrogen bond distances. The calculations of the effect of the electric field (equal to 0.0001 au) in x, y and z directions produce hydrogen bond distances that closely resemble those of normal G: C base pair. For the electric field equal to 0.001 au in x and y directions, the most pro-mutagenic of all fields, differences from normal G:C pairing are found in two ways. First, the change of the hydrogen bond distance between guanine (H25) and cytosine (N6) atoms is 0.164 Å. Second, there is a 0.321 Å extension of the hydrogen bond distance between guanine (O8) and cytosine (H29) atoms, more than in the above case. This indicates an opening of the hydrogen bond at the down site of the pair and

TABLE 5. The change in the hydrogen bond distances (Å) *of G:C base pair under electric field at the B3LYP/CEP-31G level.*

Electric field (a.u.)	$\Delta r(\mathrm{O}_{17} - \mathrm{H}_{13})$	$\Delta r(\mathrm{H}_{25} - \mathrm{N}_6)$	$\Delta r(\mathrm{H}_{29} - \mathrm{O}_8)$
$E_x(0.0001)$	0.001	0.001	0
$E_x(0.001)$	0.03	0.164	0.321
$E_x(0.01)$	–0.227	–0.041	0.24
$E_y(0.0001)$	0.001	0	0
$E_y(0.001)$	0.03	0.164	0.321
$E_y(0.01)$	0.016	–0.0058	–0.0079
$E_z(0.0001)$	–0.003	0.001	0
$E_z(0.001)$	–0.0117	–0.0156	–0.0176
$E_z(0.01)$	–0.227	–0.041	0.24

the middle site. The electric field effects on the G:C base pair differs from the effect of tobacco smoke, which is doing methylation in the G:C base pair, according to results of G. Forde et al. [16]. Due to the changes in the properties of regions of DAN by methylation, the third hydrogen bonding between the G:C base pair decreases, while with the electric field it does not change. From the geometrical data, it should be noted that the geometrical factors due to all electric field effects differ significantly with respect to the intermolecular bond distances. The effect of the electric field on the hydrogen bond distances is large when the external electric field is applied in the directions coincident with the plane of G:C base pair. Moreover, the applied strong electric field, in the direction that is coincident with the plane of G:C base pair, is significant enough to disrupt two of the three hydrogen bonds in the G:C base pair.

6. Conclusion

In summary, the results of our calculations show that the applied electric field on G:C base pairs causes significant changes in the interaction between guanine and cytosine compared to the Watson-Crick hydrogen-bonding pattern. This probably is a result of inductive and steric effects. As a result, the changes in G:C hydrogen bonding energies may increase the energy required for base flipping and it may exceed that what is provided by the enzyme responsible for this process. Our results are summed up by the following:

• Based on our data, the effects of high electric field may introduce significant changes in the geometrical parameters of base pairs. In the case $\Delta r_{\mathrm{H29-O8}} = 0.321$ Å, which is known to cause base transitions, it is shown that one of the hydrogen bonds is lost. As a result, DNA polymerase under the high electric field could incorporate a thymine into the daughter strand produced from a guanine.

• We have found that changes in the interaction energies in G:C base pairs (with applied electric field) do directly correlate to adduct pro-mutagenicity.

• Our data reveal that electrostatic contributions predominate in interactions of all investigated complexes.

• The order of stability of guanine, cytosine and G:C base pair is a function of electric field intensity and direction.

• The applied high electric field on G:C base pair increases intermolecular bonding energies.

• Finally, the electric field may be able to produce the multi-point mutations.

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TEORIJSKO AB INITIO PROUČAVANJE UČINAKA ELEKTRIČNOG POLJA NA GRAĐU I STABILNOST BAZNOG PARA G:C

Učinak vanjskog električnog polja na DNA javlja se najčešće za jaka polja. Izvješćujemo o ishodima proučavanja učinaka vanjskog električnog polja na sastavnice baznog para G:C polazeći od osnova teorije. Razmještaj lokalnih minimuma smo optimizirali bez ograničenja na uvjete simetrije rabeći gradijentan postupak na razini teorije funkcionala gustoće i provjerili računima drugih derivacija energije. Primijenili smo uobičajen osnovni skup CEP-31G. Izvješćujemo o promjenama razmaka, stabilnosti i energijama međudjelovanja. Mutacije električnim poljem mogle bi se razvrstati u višemjesne mutacije.