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Solvent effects on binding energy, stability order and hydrogen bonding of guanine–cytosine base pair

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ABSTRACT

In this study, the effect of various solvents on the stability order, binding energy and hydrogen bond (HB) strength of cytosine–guanine (C–G) complex are investigated by using the density functional theory. The results show that the stability of cytosine–guanine complex in polar solvent is higher than non-polar solutions while it is lower than solution in vacuum. The binding energy of cytosine–guanine complex in polar solvent is lower than non-polar solutions. Its HB strength in polar solvent with respect to water as natural solvent is close to each other. The natural bond orbital and frontier molecular orbital analysis have been carried out from the optimized structure. The Quantum Theory of "Atoms in Molecules" (QTAIM) of Bader is also applied here to get more details about the nature of intermolecular interactions. Finally, the chemical properties have been presented to investigate the chemical stability of cytosine–guanine complex.

1. Introduction

The polymer of DNA is composed of nucleotides which are constructed from three elements including: deoxyribose, base and phosphate group. DNA has four kinds of nucleotides named in abbreviated form as follows: A (adenine), G (guanine), C (cytosine), and T (thymine). A nucleoside is one of the four DNA bases covalently attached to the C1′ position of a sugar; the sugar in deoxynucleosides is 2′-deoxyribose. Nucleosides differ from nucleotides in that they lack phosphate groups. The DNA backbone is constructed by the covalent bond between sugar and phosphate which are called the "phosphodiester" bonds. Two DNA strands make a helical spiral structure and the two polynucleotide chains locate in opposite directions. The bases of each strand are inside of the helix. As DNA is double helix, there is another bond in DNA which maintains each polynucleotide chain near each other that would form the double strand DNA molecule. The DNA bases are classified to purine (adenine and guanine) and pyrimidine (cytosine and thymine). The hydrogen link is made between a purine base from one strand and a pyrimidine base from another strand which means it forms between A and T in one hand and C and G in the other hand. Two hydrogen bonds form between T and A on each opposite strand, and C forms three hydrogen bonds with G on the opposite strand [1]. Hydrogen bonding has an important role in DNA replication, repairing and mutation [2]. The impaired hydrogen bonds resulted to damage in DNA and genetic problems [3]. Solvents are widely used in biological research. So, it is possible they cause changes in DNA hydrogen bonds and motive in producing harm genes. Therefore, if any of them cause changes in deoxy/ribo nucleic acids, it will not be a suitable candidate in cell assays. Some of the solvents and their applications which are used in the biological research are as follows.

Ethanol and chloroform are used in manual DNA extraction method. Their safety should be proved; otherwise they cannot be led to good results of gene evaluation due to the destruction of DNA bonds. As DMSO (dimethyl sulfoxide) is used in cell freezing, therefore it should not cause any manipulation in DNA structure and bonds. Methanol and acetone are also used for cell fixation [4] and ether is used for permeabilizing of cells prior to some tests and as a constructor material of some synthetic medicinal compounds. Water, also is involved in the majority compound of the cells (70% of cell volume is water). The aim of the current study is to assess the effect of different solvents on hydrogen bonds between G and C pair by means of DFT theory to find the stability and binding energy of them in various solvents and compare their results with gas phase (solvent free).

2. Computational details

All quantum chemical calculations were performed with the Gaussian 03 [5] sets of codes. Full geometry optimization was computed at B3LYP [6] method with 6-311++G** (253 basis functions, 387 primitive Gaussians) basis set. Several different solvents (Water, methanol,

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ethanol, ether, chloroform, DMSO and acetone) to study the effect of solvent on hydrogen bonds were investigated and their effects were compared with together and also with gas phase. The computational calculations were modeled using the polarizable continuum model (PCM) [7] by the united atom cavity approach in which the cavity is created via a series of overlapping spheres. In this exploration, the estimated values of the intermolecular HB energies were calculated approximately by the Espinosa and Molins method [8]. The binding energy ($E_{binding}$) due to C–G complex formation was calculated as defined:

$$E_{binding} = E_{G-C} - (E_G + E_C). \quad (1)$$

In this formula, E_{G-C} is the total energy of cytosine–guanine formation, E_G and E_C are total energies of guanine and cytosine, respectively. Stability order of C–G complex in various solvents was also considered. The quantum theory of Bader of atom in molecule (QTAIM) basing on topological analysis of the electronic charge density was performed to find deeper understanding of the analyzed interactions. Hence, bond critical points (BCPs) [9] of the hydrogen bonds between C and G interaction were found and analyzed in terms of electron densities and their Laplacians. The QTAIM calculations was done by AIM2000 suit of program [10] using the B3LYP/6-311++G** wave functions as input. Natural bond orbital (NBO) analyses [11] to study the orbital interaction were performed using the same level.

The molecular orbital (MO) calculations such as difference between the highest occupied MO (HOMO) and lowest unoccupied MO (LUMO) were also performed with the same level of DFT theory.

3. Results and discussion

3.1. Solvent effects

Many materials are used in wide range in many aspects of laboratory trials. For example methanol, ethanol, ether, acetone and chloroform usually are used for manual DNA extraction [12] to achieve a pristine DNA sample which is the goal of DNA extraction techniques. DMSO is also used for cell cryopreservation [13]. Therefore, it is very important to know whether they can affect on DNA bonds and its structure or not. Therefore, in the present study, we chose them to evaluate their effect on DNA hydrogen bonds, DNA binding energies, DNA stability and DNA double helix. It should be noted that 70% of cell volume is occupied with water and it can change HB characters such as energy, structure and electron density [14–18]. As a result, it is expected that water has a special effect on the HB of DNA bases. So, in the present study, we also chose water as a natural compound of the cells to compare its effect with other solvents.

Structure of a full optimized cytosine–guanine and the numbering of atoms is presented in Fig. 1. As shown in Fig. 1 two kinds of hydrogen bonds exist between C–G interaction, N–H…O and N–H…N that N and O atoms are as proton donor and H atom is as proton acceptor. The configuration of C, G and C–G were fully optimized in water, methanol, ethanol, ether, chloroform, acetone and DMSO solvents using B3LYP/6-311++G** level of DFT theory to find optimized geometry and investigated intermolecular HB energy in the various solvents. The PCM method was used to calculate the effect of solvent on HB strength. According to the average of the calculated HB energies given in Table 1, it is clear that HB strength in gas phase is stronger than in solution phase. Among the solvents, HB strength decreases as follows:

$$\text{Water} \approx \text{methanol} \approx \text{ethanol} \approx \text{DMSO} \approx \text{acetone} > \text{ether} \approx \text{chloroform}$$

As seen, this order was shown that polar solvents cause stronger HB and non-polar solvents cause weaker HB strength. So, cytosine–guanine interaction in ether and chloroform solvents is weaker than other solvents. Stability of cytosine, guanine and C–G increased in polar solvents while formation energy of C–G complex decreased in these solvents (see Fig. 2). The binding energies of C–G complex have been given in Table 1. As shown, binding energy (B.E.) decreases when the dielectric constant (ε) of the solvents increases. So, according to the binding energies, formation of C–G complex in ether and chloroform, as non-polar solvents, are more favorable than other polar solvents. The dielectric constant curve in terms of binding energy is presented in Fig. 3. Stability order (S.O.) of C–G complex also changes with the dielectric constant. The smaller dielectric constant, the lower stability order will be. On the other hand, when the dielectric constant decreases, the stability also decreases. The C–G stability order values in different solvents and the change curves of dielectric constant in terms of the stability order have been shown in Table 1 and Fig. 3, respectively.

Also, there is an excellent linear correlation between stability order and binding energy with correlation coefficient (R^2) equal to 0.999 with an equation as: B.E. = −0.665 S.O.–56.01. This correlation with negative slope shows that although C–G complex has the most binding energies in ether and chloroform (as non-polar solvents), its stability in non-polar solvent is lower than others.

3.2. AIM analyses

In order to describe atomic interaction, the AIM calculation was carried out. The atomic interaction is classified in two general classes. The nature of interaction is exposed by the electron density (ρ) at bond

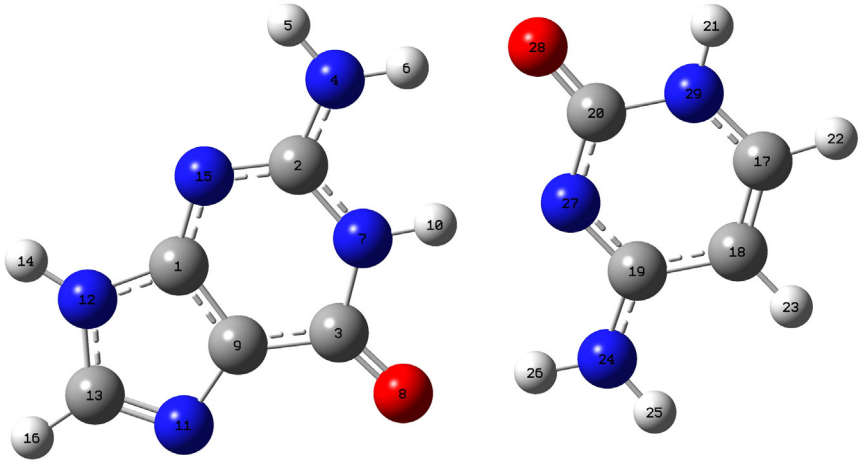

Fig. 1. The optimized structure of C–G complex and the numbering of atoms.