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THEORETICAL METHODS FOR MEASURING CHEMO-PHYSICAL PROPERTIES OF NUCLEIC ACIDS DURING THE RADICALIZATION OF DNA AND THE INCIDENCE OF CANCER

MÉTODOS TEÓRICOS PARA MEDIR LAS PROPIEDADES QUÍMICO-FÍSICAS DE LOS ÁCIDOS NUCLEICOS DURANTE LA RADICALIZACIÓN DEL ADN Y LA INCIDENCIA DEL CÁNCER

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ABSTRACT

One of cases considered for diagnosing DNA damages is diagnosing DNA probable damages against oxidizing agents, including oxidizing chemicals and various incident rays which cause the bases in the DNA to be oxidized and especially bases G in the DNA sequence which is more easily oxidized than the other bases. Therefore, the main objective of this comprehensive survey is to provide relevant information on measure physical chemical properties of nucleic acids during DNA radicalization and incidence of cancer using theoretical methods. The aim of the present study is to examine the single-stranded NBO with sequences of GG, CG, AA AG AC: AT CT GT TT followed by the levels of energy and form of orbital LUMO and HOMO obtained from Gaussian computations for above double-stranded sequences. Our results showed that form B genetic material is the most stable structure against physical and chemical agents. Only the number of molecular population and the levels of molecular dynamic vibration and molecular thermochemistry such as enthalpie and entropie are temperature independent. In addition to this, the gap between the layers and the potential and energy needed to oxidize the components in the two strands of DNA and its optimum structure will not change with temperature. Optimum conditions on DNA and its bonds are the temperature of 37 ° C and pH is 7 to 8.7. DNA has form B and the rate of physical protection is the highest.

Keywords: Cancer; Chemo-physical Properties; DNA; Gene Radicalization; Mutations; Monte Carlo.

RESUMEN

Uno de los casos considerados para diagnosticar daños en el ADN es el diagnóstico de daños probables en el ADN contra agentes oxidantes, incluidos productos químicos oxidantes y diversos rayos incidentes que hacen que las bases en el ADN se oxiden y especialmente las bases G en la secuencia del ADN que se oxida más fácilmente que las otras bases. Por lo tanto, el propósito de este trabajo es proveer información

relevante para la medición de las propiedades físico químicas de los ácidos nucleicos durante la radicalización del ADN y la incidencia de cáncer utilizando métodos teóricos. El objeto de esta investigación fue examinar la NBO de una cadena con secuencias de GG, CG, AA AG AC: AT CT GT TT seguidas de los niveles de energía y forma de LUMO orbital y HOMO obtenidos de los cálculos de Gauss para secuencias por encima de dos cadenas. Los resultados mostraron que el material genético de la forma B es la estructura más estable frente a los agentes físicos y químicos. Sólo la cantidad de población molecular y los niveles de vibración dinámica molecular y termoquímica molecular como la entalpía y la entropía son independientes de la temperatura. En adición a eso, la brecha entre las capas y el potencial y la energía necesarios para oxidar los componentes en las dos cadenas de ADN y su estructura óptima no cambiarán con la temperatura. Las condiciones óptimas en el ADN y sus enlaces son la temperatura de 37 ° C y el pH es de 7 a 8,7. EL ADN tiene la forma B y la tasa de protección física es la más alta.

Palabras clave: Cáncer; Propiedades quimio-físicas; ADN; Radicalización de genes; Mutación; Monte Carlo.

1. INTRODUCTION

The improvement of genetic knowledge in recent years and the recognition of the role of nucleic acids and DNA in various diseases, and in particular the refractory disease of cancer has caused special attention to be paid to its various applications in various fields of sciences and industry such as chemistry, biochemistry and medical, pharmaceutical industries and for the treatment of diseases. In recent years, with the help of computers and quantum methods, the achievement of the physical, chemical parameters of nucleic acids has been made possible to radicalize DNA and has been caused to know more the complex behavior of this vital component of body of living organisms.

Using chemical accounting methods and QM / MM method, it has been tried to use this extraordinary possibility in addition to filling the existing voids of experiential and experimental methods with a better knowledge of changes in the physiochemical structure of DNA, especially in conditions of radicalized and mutation agents that this knowledge will make DNA changes in cancer disease recognized and will lead to the treatment of this disease. The idea can also be a new independent opinion in the field of medical sciences which can be the basis for many future researches and studies, as well as it can be a big step for advancing scientific knowledge of scientists and researchers in molecular cell biology, biochemistry, chemistry, medicine, physiology science researchers and all subfield of the sciences above.

In a healthy living, there were always a balance between the rate of cell division and the natural death of the cell. A natural cell may be changed to a cancerous cell without any clear reason, but in most cases, the changing is made due to repeated confrontation with carcinogenic substances such as alcohol, tobacco and free radicals. The apparent form and the cancerous cells function with the normal cells have significantly different. A mutation or alteration made occurs in DNA or a genetic material of the cell. DNA is responsible for controlling and preserving apparent form and function of the cell. When the DNA of a cell changes and becomes cancerous, that cell differs from healthy cells and does not do the other tasks on the normal cells of the body. The modified cell is detached from its nearby cells and does not know when its growth should finish and die. In other words, the modified cell does not follow the instructions and internal signals that control other cells and acts independently instead of coordinating with other cells. Researchers found in their studies that non-genetic imbalances of protein lead to out-of-control growth and cancer (Zhai et al., 2012).

Previous studies showed that the two proteins Plcy1 and Grb2 were in competition with the Akt for binding during pathway while performing laboratory studies on the mice. For any reason, cells which include (instruction of mistake and error of messenger RNA of nucleic acids and DNA deficit of protein Grb2), normal growth of cell is out of control and resulting in a probability of cancer. In addition, the

protein p53 also plays vital and important role in controlling and preventing the growth of cancer cells as an inhibitor of tumor and cancer. Mutation in the gene DNA causes to a disorder in the formation or production of the protein, and in most types of cancers, mutation in the gene is obvious, and biological studies in computations method due to special attention paid to the gene in recent decades by biomedical methods that can be indicated in computations methods as a way to confront with the laboratory and research constraints in this field (Forshew et al., 2012).

There were different mutation factors in the environment that can be cause mutation and various diseases in humans such as high energy radiation, chemicals and stress. According to new analysis in scientist studies, consuming tobacco can averagely make mutation in DNA of a lung cell and make 17 types of cancer. DNA mutation can provide the potential needed for the progressive activation of cellular degeneration, and ultimately these changes will lead to cancer (Aghelan & Panjehpour 2016). One of the cases that can be considered for identifying DNA damages is identifying probable DNA damages against the oxidizing agents, including oxidizing chemicals and various incidence rays (Prat et al., 1998). DNA somewhat has ability to restore itself, but when the number of this (Bensimon et al ., 2011) the property of charges transport in DNA, in addition to creating ideal properties to identify the DNA sequencing in electrical and electrochemical biosensors, facilitates the oxidation capability of its present bases, genetic mutation and disorder in genetic process (Hall & Barton, 1996). Two mechanisms of electron transport and transport of electron hole were suggested for charge transport and oxidation transport of organic bases in two-strand. Among the present two-strand bases, guanine property for charge transporting is better than other bases, so that the percentage of base guanine present in two-strand, will have a direct effect on the charge transport property in two-strand (Gray, 2006), the tendency for electron absorbing in guanine, is lesser than other present two-strand bases, in the other hand oxidation potential, makes guanine more favorable than other bases (Grozema et al., 2008).

2. LITERATURE REVIEW

According to Larry et al., (2017) utilized computer computational methods and molecular modeling on achieving new anti-cancer drugs. Anti-cancer drugs from the factors of Cytotoxic, which were specifically destroys the DNA, by the help of computational methods affects the drugs for genetic, epigenetic disorders and more specifically tended to process of convert and development of malignant cells. Accessing to information of human genome and targeting vulnerable genes of cancer, by the use of computational modeling and prognosis, makes diagnosis and treatment of cancer possible with lesser cost and time. In recent decades, the use of computational chemistry and molecular modeling for designing drug by the help of computer attracted pharmaceutical specialists. Initially, by computational modeling method the key factors that were not attainable through examination, computed by simplifying concept of cancer to the four level of atomic, molecular, microscopic and macroscopic. The computational activity of the MTT assay showed that Atorvastatin, which is a cholesterol synthesis inhibiting, has a significant effect on inhibiting growth of HeLa's cancer cells. Molecular dynamic studies of anti-tumor activity on Nelfinavir anti-aids drug in inhibiting cellular kinase protein and inhibiting growth of cancer cell showed that, docking of Thalidomide derivatives in multiple Myeloma was evaluated and showed that, the Pomalidomide Derivate has greatest effect on inhibiting alpha-beta Tubulin Mitosis and inhibiting proliferation of cell division. Computational studies of Hydralazine, which is antihypertensive drug, showed that this compound by DNA methylation and inhibiting proliferation of growing cells has anti-cancer effect.

Effect of complex Manganese (II) and its bound to DNA and molecular docking by the using of DFT computational method and IR & UV theory studies (Yan et al., 2002). In this research, the interaction amount of related complex of metallic center to DNA by the use of CD spectroscopy methods and UV-Vis spectr|oscopy method, Electrophoresis gel, viscosity and Cyclic voltammetry were studied. The interaction of this compound with two types of DNA in Leukemia indicates excellent interaction of this compound

similar to Cisplatin anti-cancer drug. Then in the theory section, electron density theory was used to computation and optimization of geometry. Theoretical computations showed that, the complex interaction with the small DNA screws had a higher interaction. The link structure and molecular singularity surveyed between DNA and Ligands based on oxime and Palladium complexes by using DFT computational method (Bandyopadhyay, et al., 2016). They mentioned that, interaction of Palladium complex (II) with Phenyl (Pyridine-2- hydrazine) Acetaldehyde oxime (LH) and pair of two-stranded base of DNA were studied by using DFT computational method. Spectral, electrochemical and biophysics behavior of this set were evaluated. In terms of physicochemical parameters, the following binding constants were resulted. For Ligand of binding constant 3.93×10^4 and for consonant complex 1.38×10^3 M^{-1} were resulted. The formation of Mitomycin as an alkylating agent surveyed through DFT computational method (Hume et al., 2013). The mechanism of DNA complex formation with other complexes has been very successful with DFT computational method, particularly for simple models. By comparing obtained results of computations, mechanical properties were predicted with high accuracy. Reduction of one and two-electron of system strongly depends on pH.

2.1. DNA radicalization

DNA is affecting by active and reactive oxygen species (like O_2, H_2O_2 and OH). These strong oxidants are forming through ionizing rays and chemical agents that are the generators of free radical. For example, guanine oxidation leads to 7 and 8 di-hydro -8- oxo-guanine or oxoG. Oxo-guanine is highly mutagenic, because it is able to form base pair with both Adenine and Cytosine base. If form the base pair with Adenine, in the stream of base pair replication C: G will be converted to T: A. This is the most common type of mutant in human cancers. Therefore, maybe part of carcinogenicity effects of ionizing rays related to free radicals, which results in the conversion of guanine to Oxo-guanine (Steenken&Jovanovic, 1997).

Among the four organic bases present in the DNA structure, organic base of guanine has lesser oxidation potential and its oxidizing faster than other bases. The two mechanisms of electron hole transport and transport of electron to charge transport process in DNA were suggested Which both of mechanisms were presented in figure 1 (Hume et al., 2013).

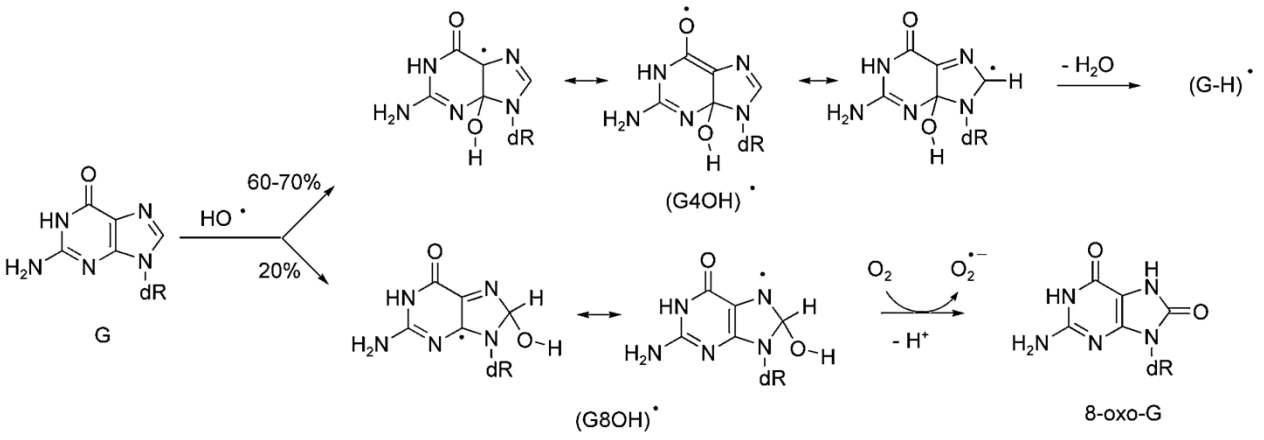

Figure 1. Radicalization and oxidation of guanine to 8-oxoguanine

Therefore, fast radicalization of guanine leads to quick and easy oxidation of it. In fact, the feature of easy radicalization of guanine has led to the conductance feature of charge to the double-stranded DNA. Interestingly, the single-stranded DNA cannot transfer the charge, which provide the role of hydrogen bond existing in double-stranded in the charge transfer of double-stranded DNA (Holmlin et al., 1997).

2.2. DNA oxidation

The property of charge transfer in the DNA, not only creates ideal properties to detect the sequence of DNA in the electrical and electrochemical biosensors, but also facilitates the oxidation capability of bases existing in it and also leads to genetic mutation and disorder in the genetic process (Hall et al.,1996).

Two mechanisms of the electron transfer and electron hole were recommended for transferring of charge and oxidation of organic bases in two strands. In transmitting the electron hole, the oxidation mechanism of the DNA, especially the base of the guanine, is intended; but in the transmission of electron, the role of transferring the charge of all the bases should be considered. Among the bases existing in double strands, the property of guanine charge transfer is better than other bases; so that the percent of guanine base existing in the double strands have a direct effect on the property of charge transfer in the double strands (Gray,2006). The tendency for electron absorption in the guanine is less than other bases existing in the double strands. On the other hand, it makes the potential of guanine oxidation more susceptible than other bases (Grozema et al., 2008).

2.3. DNA repair mechanism

In fact, the body has mechanisms for repairing damaged genome and preventing the amplification of mutant DNA, including the control gene of cell and DNA amplification which is controlling and preventing the cancer. All cells in adequate time and timely receives the signal of cell death and depression growth and amplification and their growth is prevented. In principle, the process of cell division and its amplification is known as the cell cycle process. There were control points during this cycle. Indeed, the controlling protein is responsible for the sequence accuracy of DNA or the protein of p53, that if there is mutation or defect, by examining the relevant sequence, the control point activates and the repair protein of sequence acts. In addition to the p53 gene, there are numerous other factors that control the amplification and metastasis of the tumor cells, including prostaglandin, erythropoietin and adenosine, etc. The polymerase enzymes of DNA play the role of DNA amplification and in addition, they provide additional information for control points and stop the cell cycle. In other words, if an error occurs in the amplification of genome, they stop the cell cycle until the error is repaired (Sun et al., 2015).

3. METHODOLIOGY

In this research, the Monte Carlo method was used. Monte Carlo method is a computational algorithm that uses random sampling to calculate the results. Currently, the scattering Monte Carlo method is the most available accurate calculation tool. In this type of calculations, the wave function is used to achieve the ground state of energy. The wave function consists two parts of determinant and Jastrow. The effective parameters in determining the energy depend on the wave function. In every stage, this method is used to change the parameters in such a way that the energy becomes more negative than the previous state. The calculations are performed by statistical methods so the results have some error. We tried to minimize the sources of error. The most important sources of error are slater determinant, time step and the Jastrow part of wave function. After finding the appropriate wave function, the calculation of scattering Monte Carlo method is repeated in two different time steps using CASINO computing package and the energy ground state in the zero time can be obtained by the extrapolation method. Ultimately, having energy at several points, the potential level is fitted by Morse-Rydberg potential function; and in fact, Monte Carlo methods have the applied aspect of random simulation with respect to the expansion and development of computers. These methods are accompanied by a lot of algorithms and computer calculations, where conducting the tests and theoretical calculations are very complicated or costly. Monte Carlo methods are successfully used for nonlinear complex systems with a high degree of uncertainty such as turbulence in fluids, disordered media, biological cellular structures or systems with undetermined inputs. These

methods are also employed in the mathematical calculations for calculating complex integrals in various fields of physics, chemistry, spatial explorations, crude oil exploration, cost prediction, and other fields. The most recent use of random simulation methods and specially the Monte Carlo method is trying to analyze the changes. In this study, Gaussian09w software was used.

4. RESULTS AND DISCUSSION

4.1. Stages of DNA computing using the DFT method

Examining the energy structures of bases of guanine, cytosine, thymine and adenine: First, the studied structures are drawn using Chem3D pro software and are stored as a Gaussian input file with. gjf extension and then by using POP=NBO command, the energy of forming the neutral and oxidized structure was evaluated as a positive charge.

Formation energy of thymine, guanine, cytosine and adenine: The formation energy of thymine molecule and thymine oxidized having positive charge by Gaussian, were calculated and the resulted data related to the formation energy are presented in the table 1. The formation energy data of guanine, cytosine and adenine are also presented.

Table 1: The formation energy of the molecule of thymine, guanine and cytosine and their oxidized forms

Structure	HF of formation energy (Hartree–Fock)	Dipole	Symmetry
Thymine	-454.0803993	0.72691882	C01
Positive Thimine	-453.7718013	1.1237234	C01
Guanin	-542.5229171	-0.8601835	C01
Positive Guanin	-542.2570186	-0.6031835	C01
Adenine	-467.2847005	1.402092	C01
Positive Adenine	-466.9902118	1.02872	C01
Cytosin	-394.8995662	1.3530455	C01
Cytosin Positive	-394.256412	1.1054587	C01

As it can be seen in data of formation energy table 1 guanine has the most negative formation energy in DNA's bases, and is most stable base. Guanine oxide is also more stable than other bases and in DNA, it is known as the most stable oxide, with the energy of -542.257. This stability also reduces the potential of electrochemical oxidation, so that it has the most suitable oxidation potential of about 0.6 volts in the DNA. This feature of guanine's base is used for identifying and measuring DNA in the studying environment.

Calculating the structures of bases of guanine, cytosine, thymine and adenine with NBO from # B3LY/6-311++G POP=NBO order:* First, the software was running and after opening the gift file to perform NBO order the B3LY/6-311++G* POP=NBO command was used, and then the program was run. The output file is saved in the desired part. First, bases in DNA are evaluated and then the energy changes, the degree of interaction, repulsions and orbitals of HOMO and LUMO were evaluated, which will be described in the following paragraphs. Due to importance of energy gap between HOMO and LUMO levels of bases in nucleotide, the energy level of HOMO and LUMO levels in DNA oxidation, and forming cancer it is needed to determine the characteristic of these levels and factors influencing them. For this purpose, first, these levels were examined in adenine, thymine, cytosine and guanine bases, then in relevant nucleotides and finally in single-stranded and double-stranded DNA with different sequences. At first, the examination were performed on the adenine base. Chemical structure of adenine is designed as follows, in Guassian View software, then the following NBO calculations is performed based on stated method and the results are presented below. Double-stranded DNA has a small gap between HOMO and LUMO levels, the small gap between HOMO and LUMO's orbitals caused DNAs especially those in mitochondria, be the first thing in body that are destroyed by free radicals. DNA in other parts of the cell

may also be damaged by free radicals; since DNA is the genetic materials of cells, their damage may lead to their death or mutation and make them cancerous.

4.2. Studying the effect of PH parameters on the bonds, structure and characteristic of DNA

In normal biological condition, that is 7.4 area, the DNA has the form of B. its structure changes by changing the PH. In high PHs and absence of proton in the environment and the existence of high degree of hydroxyl group, the hydrogen bonds between two strands are loosened and finally, they are separated by more increase in pH, thus the attack of radical groups to bases and the probability of mutation and oxidation in DNA is facilitated. The same phenomenon occurs in acidic pHs. It means that in very acidic pHs, the hydrogen bonds between two strands is loosened and, as a result, double-stranded DNA changes to single-stranded DNA. Single-stranded DNA is very vulnerable and due to the release of bases in it, is oxidized or affected easier by chemical factors in the environment. Therefore, blood pH changes are not appropriate for its natural value and causes mutation and physical and chemical changes proportional to it. One of the factors that changes blood pH is smoking and drinking alcohol. These factors make blood acidic, in addition to destroying DNA, will disturb the transcription and cause mutations in it.

4.3. Studying the effect of temperature parameter on bonds, structure and characteristic of DNA

As the temperature rises, the water around DNA will decrease and the amount of sodium ions around DNA will increase. Melting of double-stranded, that is the change of double-stranded to single-stranded, will be slower because in the presence of water, hydrogen bonding between single-stranded and water molecules accelerates the separation of two strands and it would be said that double-stranded melts into single-stranded. By increasing the temperature, the number of water molecules for all possible bases and sequences in the first layer of hydration increases. To compensate for the unstable DNA, due to the reduction of the water molecule, the sodium distance with these atoms decreases and the melting temperature also increases. This is more obvious in the G-C base pair, because of having three hydrogen bonds, and has less effect in A-T base pair, because of having two hydrogen bonds. In normal environments and conditions, DNA has B form. Due to the increase of the flexibility the number of DNA twists increases at higher temperatures, and gradually will be like A. therefore the probability of increased oxidation, radicalization and mutation will also increase. On the other hand, at higher temperature, the activation energy required for the chemical reactions between DNA and other chemical factors of environment is easier to provide. Another important point is the percentage of the G-C sequence in double-stranded. According to Guassian calculations, this sequence has the highest stability energy in DNA sequences. Therefore, by increasing the number and percentage of these sequences in double stranded sequences, in high temperature, the stability of double-stranded increases and more energy and temperature are required to convert double-stranded into single-stranded. However, the presence of G-C base pair in double-stranded improves the oxidation and charge transfer, so the possibility of mutation transfer caused by the oxidation will increase across double-stranded. In the following curve shows the angle of twist and stability energy of double-stranded in the temperature of 280 to 380 °K. As it can be seen, the double-stranded stability decreases by increasing the temperature and will change into single-stranded in above 360 °K area (see figure 2).

The double-stranded to single-stranded change which occurs due to temperature changes is called melting temperature. Figure 3 shows the curve of the transforming a double-stranded structure to a single-stranded as a result of increasing temperature.

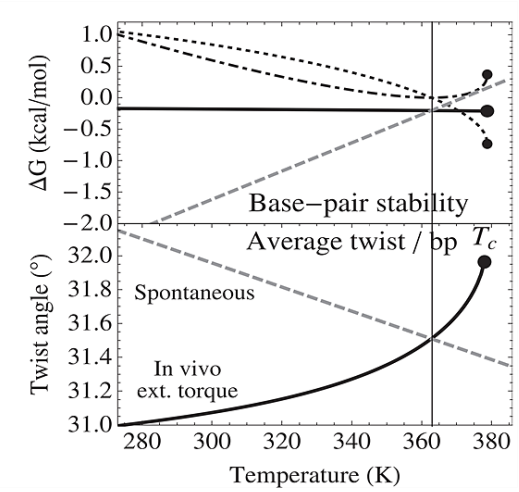

Figure 2: The decrease of the stability and twist in double-stranded due to temperature increase.

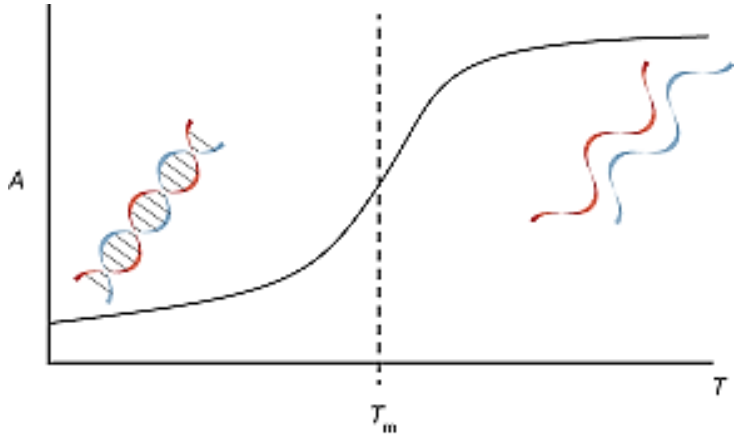

Figure 3: The curve of double-stranded to single-stranded change due to temperature change.

As the temperature rises, the structure of DNA changes form B to form Z. In another word, the amount of the twist of DNA will decrease. That means that the angle of twisting increases. Figure 4 shows this phenomenon.

According to the above-mentioned, the typical structure of DNA i.e. form B, is the most stable form and the most resistant form to the chemical and physical factors. By changing the pH and temperature relative to the normal temperature, the structure and the amount of twist in DNA and its angle will change. The change in shape and the angles will reduce its protective and resilient properties against mutagen and damaging agents.

The potential levels of electron layers are independent of temperature, and the optimal molecular structure is also independent of temperature. The only molecular population and the molecular dynamic vibration and thermochemical of molecules, including enthalpy and entropy, depend on temperature. Considering the results of the energy content of different sequences and the above-mentioned facts, it can be concluded that 37 ° C and pH of 7 to 7.8 are optimum conditions for DNA and its bonds. In this condition, DNA has Form B and maximum physical protection. Besides, the structure has the lowest G-C sequence and the highest resistance to oxidation and mutation.

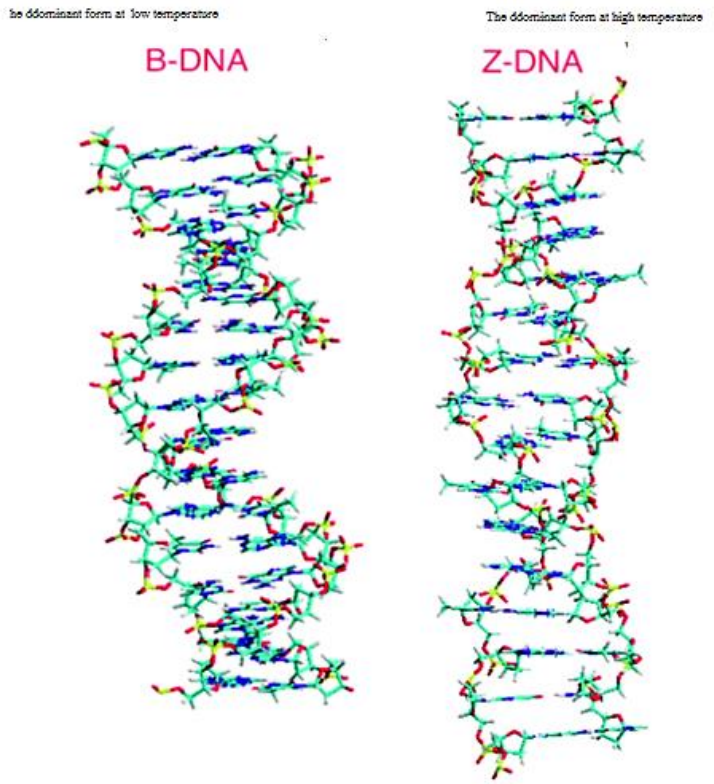

Figure 4: DNA form at normal and high temperatures and before the melting of the double-stranded.

4.4 Compare the results of this research with similar research methods

Table 2: Comparing the results of this research with similar research methods

Research team	Type of study	Research method	Results
Forster et al., 2018	The effect of oxygen on DNA degradation	Monte-Carlo	75% degradation at 0.19 eV
Baglion et al., 2008	Investigating the structure of DNA containing 42 bases	Monte-Carlo	Hexagonal structure with a diameter of 7 nm
Kino et al., 2012	Guanine destruction and oxidation	Gaussian	Stability energy of 19.9 kcal/ mol for Sp2:G and16.3 kcal/mo for Oz:G
The present study	Oxidation and radical mutation of DNA	Gaussian	GG,GC sequence with energy gap of 0.00107 eV and 0.0019 have the most possible points of mutation and oxidation

Oz: G 2,2,4-Triamino-5(2H)-oxazolone: guanine

Due to the importance of energy gap between HOMO and LUMO levels of base in nucleotides, the effect of energy levels of HOMO and LUMO orbitals on the oxidation of DNA and the development of cancer has been studied. Considering the calculations of the previous chapter and the comparison of the formation energy and HOMO and LUMO energy levels of various nucleotides, different results have been obtained that are summarized in Tables 3, 4 and 5. Table 3 reveal the formation energy and the gap

between the HOMO and LUMO energy levels of purine and pyrimidine base in DNA (adenine, guanine, cytosine and thymine). According to these results, Guanine has the most stable structure and has the lowest Gap between the HOMO and LUMO orbitals.

Table 3: Formation energy and gap between HOMO and LUMO orbitals of Adenine, Guanine, Cytosine and Thymine base

	Guanine	Adenine	Cytosine	Thymine
Formation energy	-542.5229	-467.2847	-394.8996	-454.0803
HOMO-LUMO gap	0.16046	0.17061	0.17084	0.16441

The stability and the gap have a direct relationship with each other i.e. the more stable structure has a lower gap between the HOMO and LUMO energy levels. Hence, in Adenine and Thymine whose formation energy is close to each other, there are a little difference between HOMO and LUMO energy gap.

The order of stability of formation energy: Cytosine < Thymine < Adenine < Guanine

The order of HOMO and LUMO energy gap: Cytosine > Adenine > Thymine > Guanine

According to the results, it is confirmed that among bases of DNA, Guanine has the easiest electrochemical oxidation. Among bases of DNA, Guanine has the lowest LUMO and HOMO energy gap so it needs little energy for oxidation and it is easily oxidizes. On the other hand, this base has the most stable structure in comparison with other bases in DNA. Therefore, the genetic sequences containing this base are more susceptible to damage and oxidation, resulting in mutations and cancer. The oxidation of this base results in the production of 8-hydroxy-doxy-guanosine which is separated in DNA repair processes and is excreted in the urine. The Oxidized form of 8-oxo-deoxyguanosine is observed in most types of cancers. Table 4 shows the formation energy and the gap between the HOMO and LUMO energy levels of nucleosides in DNA (adenosine monophosphate, guanosine monophosphate, cytosidine monophosphate and thymidine monophosphate). According to this results, Guanosine monophosphate has the most stable structure and the least energy gap between the HOMO and LUMO orbitals.

The order of formation energy stability is Thymidine monophosphate < cytosidine monophosphate < adenosine monophosphate < Guanosine monophosphate.

The order of energy gap between HOMO and LUMO orbitals is Thymidine monophosphate < cytosidine monophosphate < adenosine monophosphate < Guanosine monophosphate.

In Table 4, formation energy and differences in HOMO and LUMO energy levels of nucleosides in DNA are presented.

Table 4: Formation and gap between HOMO and LUMO energy levels of nucleosides in DNA

	Guanosine monophosphate	Adenosine monophosphate	Cytosidine monophosphate	Thymidine monophosphate
Formation energy	- 1603.7094	-1529.5939	-1456.7064	-1440.6536
HOMO-LUMO gap	0.06061	0.04419	0.06324	0.0424

Considering the structure and energy levels calculated by Discrete Fourier Transform (DFT), for management by objectives (MBO) of single-stranded and double-stranded DNA, Gaussian software was used. The following table shows the energy gap of HOMO and LUMO orbitals in single-stranded and double-stranded DNA with different sequences of bases. As it is shown, GG, AA, TT, CT and CT

sequences have the lowest energy gap, respectively. This indicates that they easily turn to radicals and eventually are oxidized, and the CC, AT, AC, GT and GA are respectively the most stable sequences.

Table 5: HOMO and LUMO Energy gap in different single-strands and double-strands with different sequences

The type of sequence	CT	GT	TT	AT	AC	AG	GG	CC	AA	GC
Gap between HOMO and LUMO of the single-strand	0.00937	0.01631	0.00861	0.01987	0.01986	0.01515	0.00734	0.0200	0.00737	0.01045
Gap between HOMO and LUMO of the double-strand	0.00246	0.00173	0.00256	0.0049	0.01995	0.00293	0.01085	0.01985	0.00251	0.0192

5. CONCLUSION

Genetic sequences which have guanine base are susceptible to change into radicals and consequently being oxidized which damages DNA. This genetic damage causes various diseases such as cancer. Therefore, it is necessary to find a way to prevent the occurrence of cancer and the related diseases. The typical structure of DNA, Form B, is the most stable form and the most resistant form to chemical and physical agents. By changing the pH and temperature relative to the normal temperature, the structure and the amount of twist of the DNA and its angle will change. The changes in form and angles decrease protective and resilient properties of DNA. Thus, DNA can resist against mutagenic and damaging factors.

The potential levels of electron layers and the optimal molecular structure are independent of temperature. The only molecular population, the molecular dynamic vibration and thermochemistry of molecules, including enthalpy and entropy, depend on temperature. Thus, the gap between the layers, the potential and energy needed to oxidize the components of the double-stranded DNA and its optimum structure will not change due to temperature. Optimum conditions for DNA and its bonds are the temperature of 37 ° C and pH from 7 to 8/7. In this condition, DNA has form B and is physically protected. Furthermore, the structure of DNA has the lowest G-C sequence and the highest oxidation and mutation resistance.

The results of the DFT calculations and Gaussian and NBO software have very high accuracy and the results from the calculations with this software have shown good agreement with experimental results. The computational method of QM / MM is superior to that of taking all the forces of gravity and physical, chemical and electron repulsion between atoms and their links between them, in comparison with other methods, including the Monte Carlo simulation method, and the results are in better agreement with empirical results and are more reliable. The Monte Carlo method is a mathematical computational method that does not use the forces and chemical properties of molecules.

REFERENCES

Aghelan, Z., Panjehpour, M. (2016). The role of DNA polymerase in carcinogenicity (review article). Qom University of Medical Sciences Journal, 10(5), 101- 115.

Bensimon, A., Aebersold, R., & Shiloh, Y. (2011). Beyond ATM: the protein kinase landscape of the DNA damage response. FEBS letters, 585(11), 1625-1639.

Bandyopadhyay, N., Pradhan, A. B., Das, S., Lu, L., Zhu, M., Chowdhury, S., &Naskar, J. P. (2016). Synthesis, structure, DFT calculations, electrochemistry, fluorescence, DNA binding and molecular docking aspects of a novel oxime based ligand and its palladium (II) complex. Journal of Photochemistry and Photobiology B: Biology, 160, 336-346.

Forshew, T., Murtaza, M., Parkinson, C., Gale, D., Tsui, D. W., Kaper, F., ... & Hadfield, J. (2012). Noninvasive identification and monitoring of cancer mutations by targeted deep sequencing of plasma DNA. Science translational medicine, 4(136), 136ra68.

Grozema, F. C., Tonzani, S., Berlin, Y. A., Schatz, G. C., Siebbeles, L. D., & Ratner, M. A. (2008). Effect of structural dynamics on charge transfer in DNA hairpins. Journal of the American Chemical Society, 130(15), 5157-5166.

Gray, H. B. (2006). Charge transfer in DNA: from mechanism to application. John Wiley & Sons.

Hume, P. A., Brimble, M. A., & Reynisson, J. (2013). DNA adduct formation of mitomycin C. A test case for DFT calculations on model systems. Computational and Theoretical Chemistry, 1005, 9-15.

Holmlin, R. E., Dandliker, P. J., & Barton, J. K. (1997). Charge transfer through the DNA base stack. AngewandteChemie International Edition in English, 36(24), 2714-2730.

Hall, D. B., Holmlin, R. E., & Barton, J. K. (1996). Oxidative DNA damage through long-range electron transfer. Nature, 382(6593), 731.

Lari, A., Haghkhah, M., Yazdani, M. (2016). Application of computational methods and molecular modeling in accessing new anticancer drugs.Zanko Journal of Medical Sciences / Kurdistan University of Medical Sciences.

Prat, F., Houk, K. N., & Foote, C. S. (1998). Effect of guanine stacking on the oxidation of 8-oxoguanine in B-DNA. Journal of the American Chemical Society, 120 (4), 845-846.

Steenken, S., &Jovanovic, S. V. (1997). How easily oxidizable is DNA? One-electron reduction potentials of adenosine and guanosine radicals in aqueous solution. Journal of the american chemical society, 119(3), 617-618.

Sun, Q., Li, F., Sun, F., & Niu, J. (2015). Interleukin-8 is a prognostic indicator in human hilar cholangiocarcinoma. International journal of clinical and experimental pathology, 8(7), 8376.

Yan, H., Yuan, W., Velculescu, V. E., Vogelstein, B., & Kinzler, K. W. (2002). Allelic variation in human gene expression. Science, 297(5584), 1143-1143.

Zhai, Y. F., Wirth, J. J., Welsch, C. W., &Esselman, W. J. (2012). 6. Protein tyrosine phosphatases: Cellular regulators of human breast cancer?. Mammary Tumor Cell Cycle, Differentiation, and Metastasis: Advances in Cellular and Molecular Biology of Breast Cancer, 83, 107.