Comprehensive Research and Reviews in
Chemistry and Pharmacy
Journal homepage: https://crrjournals.com/crrcp/
ISSN: 2961-3604 (Online)

(RESEARCH ARTICLE)

Check for updates

Nucleic nitrogenous bases complementary: A DFT investigation

Mustapha Cherkaoui and EL Hassane Mourid *

Interdisciplinary Laboratory for Research in Bio-resources, Environment and Materials, Cadi Ayyad University, Marrakech, Morocco.

Comprehensive Research and Reviews in Chemistry and Pharmacy, 2022, 01(01), 041–050

Publication history: Received on 09 August 2022; revised on 16 September 2022; accepted on 19 September 2022

Article DOI: https://doi.org/10.57219/crrcp.2022.1.1.0005

Abstract

In DNA, the complementarity of the two strands or bases is based on Watson-Crick principle. This associates a complementary base with each base. Thus, to each base A (Adenine) of a strand is associated with a base T (Thymine) of the complementary strand, and vice versa. Moreover, to each C (Cytosine) base of a strand is associated with a G (Guanine) base of the complementary strand, and vice versa. Moreover, the double helix assembly requires an opposite orientation of the two complementary strands, for the reason it can be said that the double helix took an antiparallel orientation. All the heterogeneous combinations of the different DNA bases have been studied theoretically at B3LYP/6–311G (d,p) level of calculation. The results obtained confirm the experimental observations, namely the specific affinity of the following pairs (A/T) and (G/C). The phenomenon of denaturation was also raised by the study. It can be noticed that Adenine and Guanine are purines, while that Cytosine, Thymine and Uracil are pyrimidines.

Keywords: DNA; Denaturation; DFT; Hydrogen bond; Nitrogenous bases

1 Introduction

The phenomena of replication, repair, transcription and translation use what is called base complementarity [1, 2]. During these processes, base pairs are formed. Among the studies that are interested in the cell, we can highlight the study of its genetic material located in the cell nucleus, that is to say the study of the structure of the acid nucleic and then that of proteins. Within the cell nucleus are all the genes contained in a double helix-shaped macromolecule, DNA that occupies a critical role in cells, because it is the source of all intrinsic genetic information. DNA contains all information allowing an organism to live and develop. The three constituent and fundamental entities of DNA are the deoxyribose, nitrogenous bases and phosphate groups. Mastery of knowledge about these entities, from a structure, interaction and reactivity, allows to run smoothly cancer chemotherapy [3, 4].

Therefore, this chemotherapy can lead to halt or slow down the progression of proliferation tumor cells by acting on the DNA, RNA, or proteins [5, 6]. DNA and RNA are the most important biological molecules with a diverse set of biological functions [7]. However, what catches our attention and our motivation is the specific complementarity noted for two pairs of nitrogenous bases in DNA. The complementary of nitrogenous bases (A/T and G/C) are always observed together using a Watson-Crick complementarity [8]. This complementarity allows planar molecules to fit together and establish hydrogen bonds between them, forming the bars of the structure of the DNA double helix [9-12].

It is widely noted that a reversible association is established between the pairs of nitrogenous bases A/T and G/C at the DNA double helix [13, 14]. This association has particular characteristics such as Adenine does not associate with Guanine. Generally, the canonical nucleic acid bases, adenine, thymine, guanine and cytosine exist as the main form in the double helix of DNA. The formation of specific purine pyrimidine Watson–Crick (WC) hydrogen bonds (H-bonds) is responsible for the maintenance of the genetic code. The two strands of DNA or RNA are complementary that is to say

* Corresponding author: EL Hassane Mourid

a pairing is formed between the two strands of two nucleic bases forming a pair of compatible bases A/T and G/C. The reversible association between base pairs is ensured via hydrogen bonds [15]. It is recalled here that a hydrogen bond is an intermolecular bond involving a labile hydrogen atom and an electronegative atom like oxygen, nitrogen and fluorine. The intensity of hydrogen bond is intermediate between that of a covalent bond and that of the forces of Van deer Waals. It is a system that is similar to a key lock mechanism. Adenine and thymine can bind to each other but not with guanine or cytosine; likewise, guanine and cytosine can bind to each other but not with adenine or thymine. This fact comes down to the three-dimensional structure of each of these four nucleic bases A, T, G and C [16].

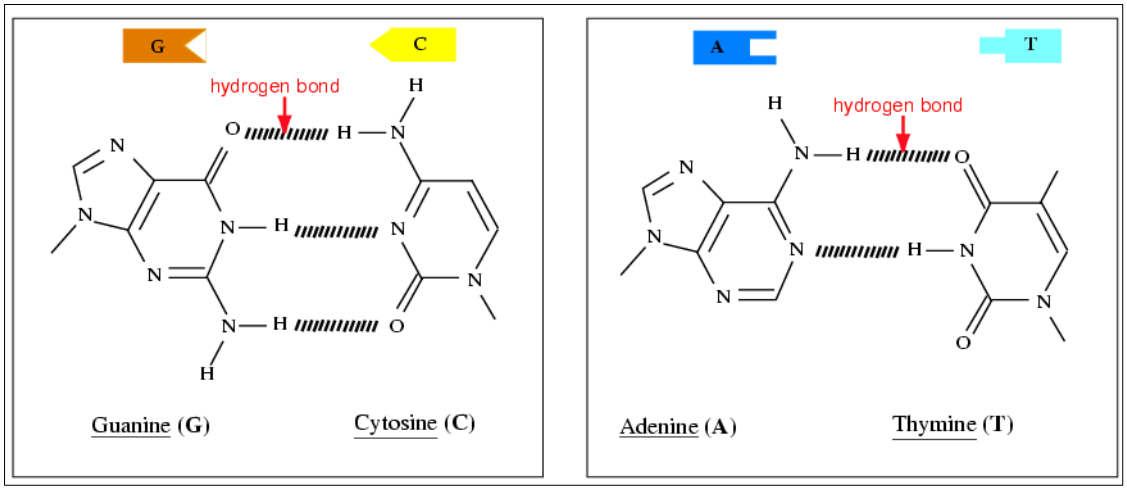

Figure 1 Hydrogen bond ensuring nitrogenous bases complementarity in G/C and A/T couples

For each pair of compatible bases (A, T) or (C, G), we can notice the association (bicyclic molecule, molecule monocyclic) with:

$$(\text{Adenine A, Thymine T}) \equiv \begin{pmatrix} \text{bicyclic molecule} \\ \text{with 2 arms} \end{pmatrix}, \begin{pmatrix} \text{monocyclic molecule} \\ \text{with 2 arms} \end{pmatrix}$$

$$(\text{Guanine G, Cytosine C}) \equiv \begin{pmatrix} \text{bicyclic molecule} \\ \text{with 3 arms} \end{pmatrix}, \begin{pmatrix} \text{monocyclic molecule} \\ \text{with 3 arms} \end{pmatrix}$$

Each of the arms of a molecule can bind to the other bra among those of the other compatible molecule to form a stable pairing. The two molecules are linked by their arm by means of specific links known as links hydrogen; and constitute stable bridges between molecules [17].

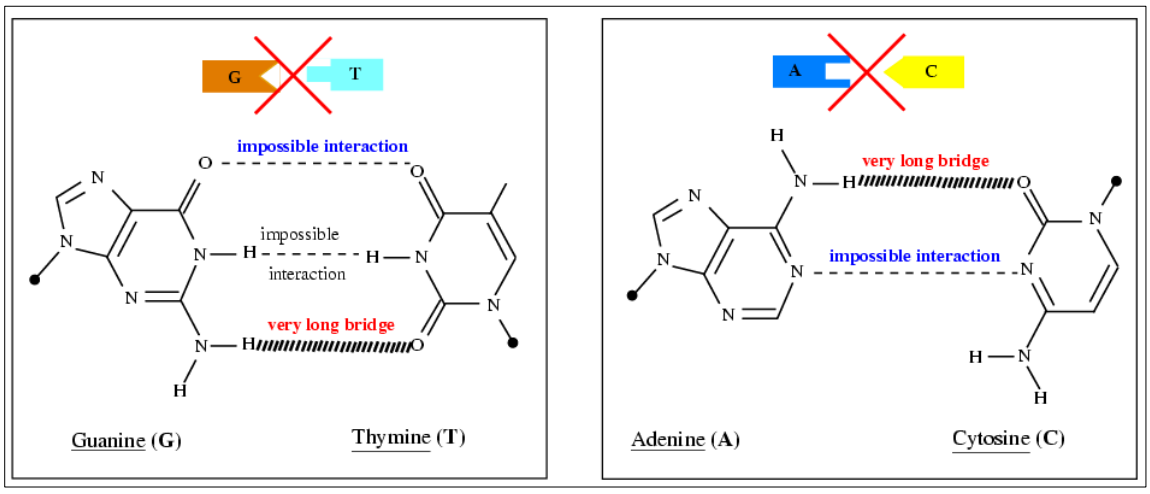

Figure 2 Unfavorable coupling to nitrogenous bases complementarity in G/T and A/C couples

One might think that a molecule with three arms (G or C) can bind twice with a two-armed molecule (T or A). However, such a configuration would give a very uncomfortable structure of DNA, because the length of the bridges formed would make the DNA unstable. For example, the link between A and G would produce a very long (two molecules with two rings), while the bond between T and C would produce a very short bridge (two single ring molecules). Likewise, the connection between A and C would produce an unnecessary arm (carried by C), in the same way as the connection between T and G (arm useless carried by G).

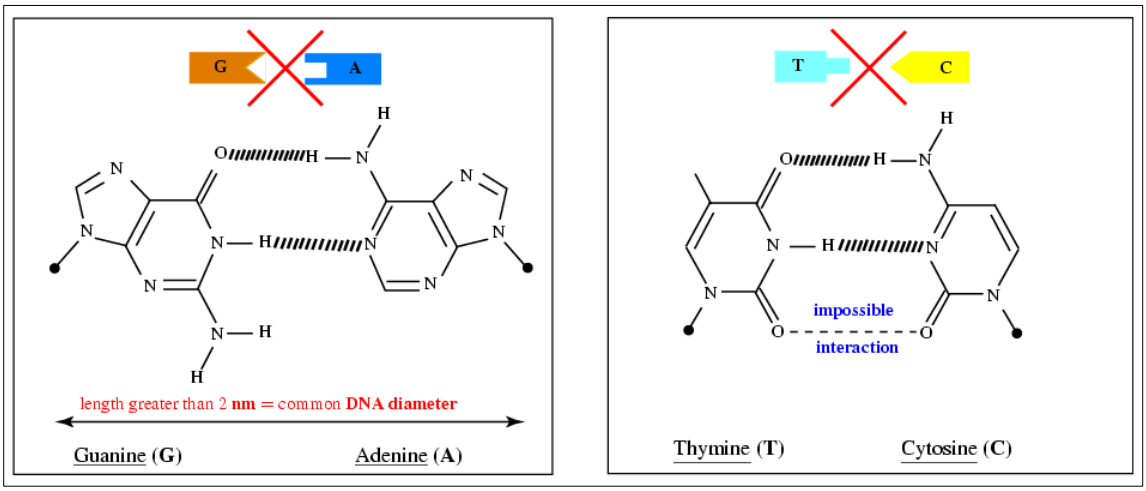

Figure 3 Unfavorable coupling to nitrogenous bases complementarity in G/A and T/C couples

This work aims to confirm or refute this finding based on theoretical investigation. We will also be interested in the phenomenon of hyperchromicity or the hyperchromic effect. It is about the property of biological polymers, and in particular DNA and RNA [18, 19]. To see their absorption in UV increase when they undergo denaturation, that is to say a loss of their secondary structure [20]. This property is commonly used in biology to analyze the structuring by spectrophotometry of nucleic acids into function of physical and chemical parameters (temperature, pH, ions ...). The combinations, subjects of study, are listed in the following table:

Table 1 Combinations of DNA nitrogenous bases subjects of study

	A	**C**	**G**	**T**	**U**
A		*	*	*	*
C	*		*	*	*
G	*	*		*	*
T	*	*	*		*
U	*	*	*	*	

In this work, the only nitrogenous basescombinations concerned by the study are with chelated N-H…O, C-H…O and N-H…N, via hydrogen bonds.

2 Computational methods of calculation

The geometry optimizations have been carried out at B3LYP/6–311G(d,p) level. The nature of all stationary point structures were determined by analytical frequency analysis, which also provided a zero–point vibrational energies (ZPEs) [21]. ZPEs were scaled by the factor 0.9153 [22]. All structures reported here are minima on the potential energy surface (only positive eigenvalues of the Hessian matrix). Final energies were calculated at the B3LYP/6–311G(d,p)+ZPEs level. The basis set superposition error (BSSE) correction was evaluated using the counterpoise method [23]. The electronic structure has been done using the natural bond orbital (NBO) partitioning analysis [24]. We adopted the following three steps, which are generally needed in the following order: geometry optimization and calculation of frequencies for the initial state, then after geometry optimization and calculation of the frequencies for

the finalstate and finally generation of the vibrationally-resolved UV-Vis absorption spectra. The calculations were performed using the GAUSSIAN 09 suite of programs [25, 26].

3 Results and discussion

3.1 Geometric parameters

The geometric parameters of the nitrogenous bases were showed in the Figures 4 and 5:

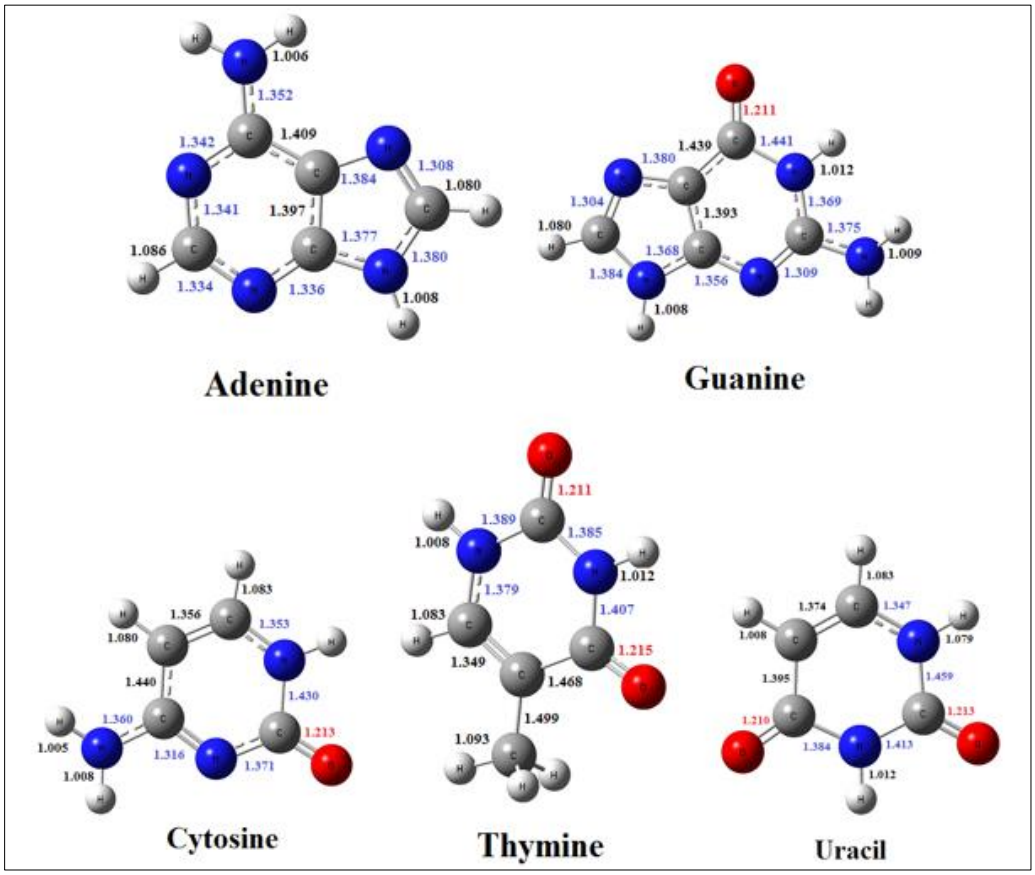

Figure 4 Optimized geometries of nitrogenous bases with bond lengths obtained at B3LYP/6–311G(d,p)

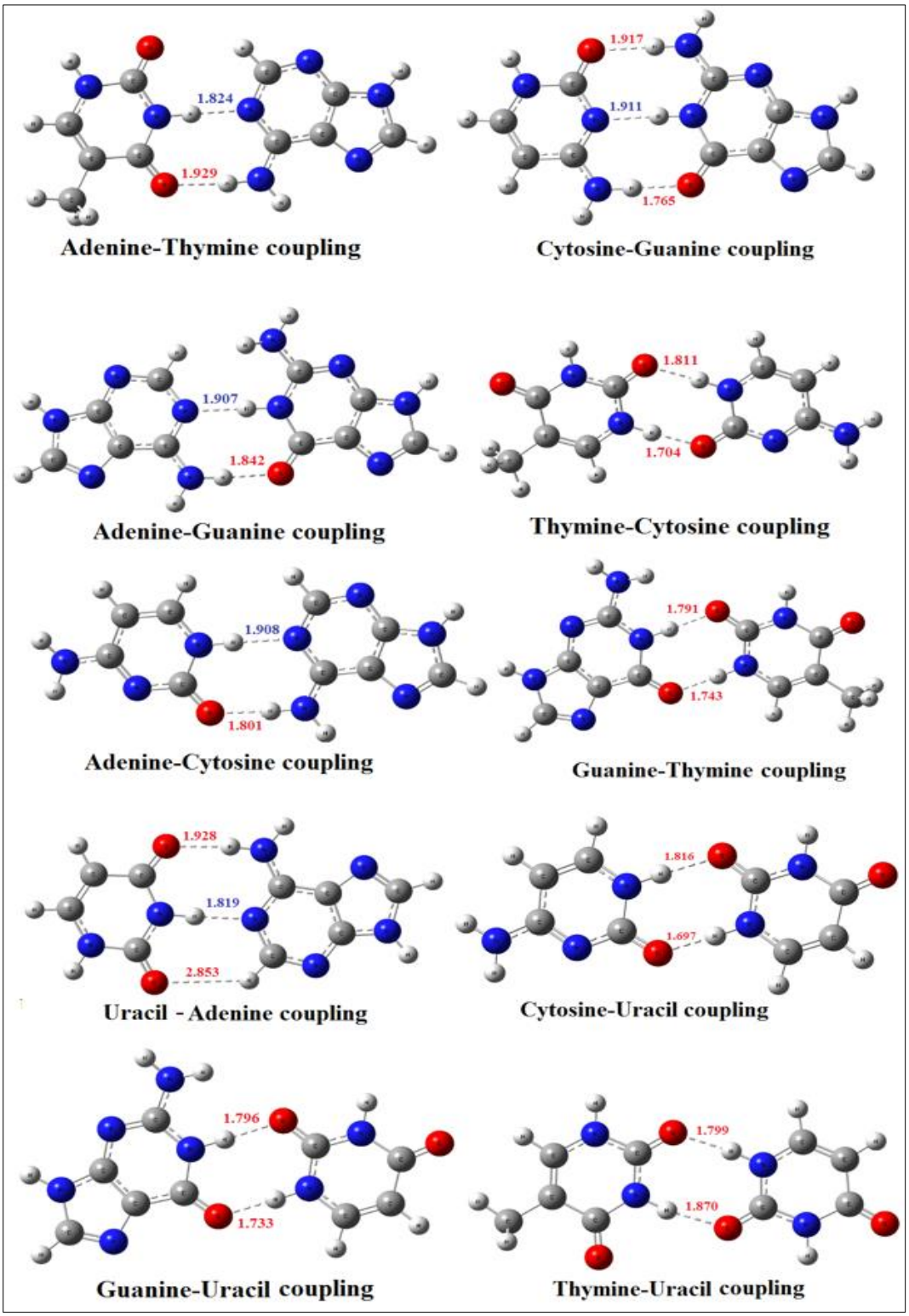

Figure 5 Optimized geometries of nitrogenous bases with hydrogen bond lengths obtained at B3LYP/6–311G (d,p)

The hydrogen bond causes an elongation of the X-H bond due to charge transfer, resulting in weakening and shifting to low frequencies of the vibration as shown by the following results:

Table 2 Nitrogenous bases coupling effect on N-H bond vibration frequency

f(N-H)	A	C	A (in AC)	C (in AC)
	3606.86	3598.36	3269.57	3133.62
f(N-H)	A	G	A (in AG)	G (in AG)
	3606.86	3589.72	3308.32	3120.81
f(N-H)	A	T	A (in AT)	T (in AT)
	3606.86	3600.43	3408.27	2989.08
f(N-H)	A	U	A (in AU)	U (in AU)
	3606.86	3641.37	3408.08	2975.28
f(N-H)	C	T	C (in CT)	T (in CT)
	3598.36	3600.43	3259.85	3071.3
f(N-H)	C	U	C (in CU)	U (in CU)
	3598.36	3641.37	3272.21	3048.77
f(N-H)	C	G	C (in CG)	G (in CG)
	3598.36	3589.72	3142.03	3216.89
f(N-H)	G	T	G (in GT)	T (in GT)
	3589.72	3600.43	3251.96	3103.27
f(N-H)	G	U	G (in GU)	U (in GU)
	3589.72	3641.37	3261.27	3082.27
f(N-H)	T	U	T (in TU)	U (in TU)
	3600.43	3641.37	3313.35	3313.35

The engagement in the hydrogen bond of the H atom of the N-H bond of the coupled nitrogenous bases causes a restriction in the vibrational movement of the N-H bond, which experiences a low elongation, which decreases the bond order, and therefore the associated vibration frequency f (N-H) decreases.

On the other hand, the establishment of the hydrogen bond between labile hydrogen and (Nx) or (Oy) heteroatom also leads to the increase in the electron density around the heteroatom. As shown by the charge transfer obtained through the NBO calculation; as gathered in the following table knowing that x and y are the heteroatom numbers in the nitrogenous base' structure under consideration:

Table 3 Charge transfer Q_t (electron)

	AC	**AG**	**AT**	**AU**	**CG**	**CT**	**CU**	**GT**	**GU**	**TU**
Q_t (N7)	-0.065	-0.075	-0.059	-0.06						
Q_t (N25)					-0.06					
Q_t (O2)										-0.076
Q_t (O3)						-0.076	-0.077			
Q_t (O7)					-0.087			-0.08	-0.081	
Q_t (O10)										-0.057
Q_t (O12)						-0.077	-0.077			
Q_t (O15)	-0.062		-0.013	-0.013						
Q_t (O18)		-0.062								
Q_t (O21)			-0.061	-0.062	-0.063			-0.089	-0.088	
Q_t (O25)										

3.2 Energies

The energy part of the work led to the results, which appear in table 4 as follows:

Table 4 B3LYP/6–311G(d,p) + ZPE coupling energies without and with BSSE and Hydrogen bonds O---H/N---H for different cases of nitrogenous bases coupling

	$E_{coupling}$ without BSSE (kcal/mol)	**$E_{coupling}$ with BSSE (kcal/mol)**	**Hydrogen bond O---H**	**Hydrogen bond N---H**
AC	-16.86	-14.10	1.801	1.908
AG	-15.69	-12.54	1.842	1.907
AT	**-20.63**	**-17.69**	1.929	1.824
AU	-14.18	-10.94	1.928/2.853	1.819
CG	**-27.07**	**-23.29**	1.765/1.917	1.911
CT	-19.95	-16.97	1.704/1.811	-
CU	-20.30	-17.13	1.733/1.796	-
GT	-20.57	-17.60	1.743/1.791	-
GU	**-13.98**	**-10.78**	1.733/1.796	-
TU	-14.14	-8.50	1.870/1.799	-

From Table 4, we can see thatthe relatively strongest coupling is that established between the two nitrogenous bases C and G known to be complementary to each other. This is true taking into account or not the BSSE quantity. In the second row of coupling strength comes the case of nitrogenous bases A and T noting a small singularity in the case of the TU combination, which represents the least stable coupling when taking into account the BSSE in the energy. This result is in agreement with the complementarity of the two strands based on the principle of complementarity of Watson-Crick [8]. This associates a complementary base with each base. Furthermore, at each base A of a strand is associated with a base T of the complementary strand, and vice versa. Moreover, to each base C of a strand is associated with a base G of the complementary strand, and vice versa. In addition, the double helix assembly requires an opposite orientation of the two complete strands, and the double helix is therefore said to be antiparallel [27].

3.3 Denaturation

The stability of the DNA double helix, i.e. its resistance to denaturation, depends on the sequence: the sequences rich in C and G have greater stability than those rich in A and T, because the G and C base pair is linked by a triple hydrogen bond, while A and T only involves two hydrogen bridges [28].

In DNA, bases are stacked (π-stacking) within the double helix, which leads to a decrease in their absorption in the UV. When the base pairing is broken, for example when heating a DNA solution, the two strands separate, the bases are exposed to the aqueous solvent and their absorbance increases by 20-40 % compared to the duplex paired state. By following the evolution of the absorbance of a DNA solution as a function of temperature, it is thus possible to determine a temperature of melting of the double helix noted T_m bridges [29]. This temperature T_m corresponds to the temperature for which half DNA is denatured; either let us to say that when the nitrogenous bases decouple, they see the absorbance of the new system increases compared to the initial system.

To ensure denaturation phenomenon according to a theoretical investigation, we proceed to determine the absorption spectra of the nitrogenous bases in both free states and coupled ones by generation of the vibrationally resolved UV-Vis absorption spectra. The results obtained at the maximum absorption of different entities at λ_{max} = 238 nm wavelength, are listed as follows:

Table 5 Absorbance of nitrogenous bases without and with coupling

	Absorbance (A/k=Ɛ)		**Absorbance (A/k=Ɛ)**	**ΔA/k**
A	8537.2	**AT**	13539.4	-49.8
T	5052.0	**AC**	12408.5	-3862.5
C	7733.8	**AG**	13790.6	-5686.4
G	10939.8	**AU**	12392.7	-1127.9
U	4983.4	**CG**	15172.7	-3500.9
		CT	11227.6	-1558.2
		CU	12392.6	-324.6
		GT	13665.0	-2326.8
		GU	13091.7	-2831.5
		TU	9937.1	-98.3

The variation of the absorbance during the denaturation of the coupled bases into free bases is given by:

$$\Delta A = A(\text{coupled bases}) - A(\text{base1}) - A(\text{base2})$$

DNA denaturation is a process of separating the two complementary strands of a DNA molecule by exposing it to high temperature or pH. It is the breaking of the hydrogen bonds between the bases that causes this separation. Consequently, the electron density of the free unsaturated rings no longer participates in the various hydrogen bonds, which allows an increase in their absorbance as confirmed by the results of table 5 thus showing a compatibility between experimental observation and theoretical investigation [30, 31].

4 Conclusion

This study can be useful and constitute a support to approach the subject of the cell and very specifically its genetic relationship located in the cell nucleus, that is to say the study of the structure of the nucleic acid then that of the proteins. Within the cell nucleus, there are all the genes contained in a double helix of DNA macromolecule, the latter that develops by the phenomenon of denaturation, which will involve the breaking of the hydrogen bonds between the bases and causes the separation. Subsequently, each entity contains an electron density. It has been found that free unsaturated rings in bases do not participate in the various hydrogen bonds. After the formation of DNA, this macromolecule contains all the information allowing an organism to live and develop, which is possible thanks to the

three constituent and fundamental entities of DNA: deoxyribose, phosphate groups and nitrogenous bases. Even if our study focused on the nitrogenous bases, the mastery of knowledge on these three entities, from the point of view of the structure, the interaction and the reactivity, this study makes it possible to go well in chemotherapy, in particular in cancer chemotherapy.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

References

[1] Tretyakova NY, Groehler A, Ji S. DNA-Protein Cross-Links: Formation, Structural Identities, and Biological Outcomes. Acc Chem Res. 2015; 48: 1631–1644.

[2] Vaz B, Popovic M, Ramadan K. DNA-Protein Crosslink Proteolysis Repair. Trends Biochem Sci. 2017, 42: 483–495.

[3] Penn I. Cancer in the immunosuppressed organ recipient. Transplant Proc; 1991, 23:1771–1772.

[4] Euvrard S, Kanitakis J, Claudy A, Skin cancers after organ transplantation. N Engl J Med. 2003, 348: 1681–1691.

[5] Brem R, Li F, Montaner B, et al., DNA breakage and cell cycle checkpoint abrogation induced by a therapeutic thiopurine and UVA radiation. Oncogene, 2010, 29:3953–3963.

[6] Gueranger Q, Kia A, Frith D, et al, Crosslinking of DNA repair and replication proteins to DNA in cells treated with 6-thioguanine and UVA. Nucleic Acids Res. 2011, 39:5057-5066.

[7] Doudna JA, Cech TR. The chemical repertoire of natural ribozymes. Nature, 2002, 418:222–228.

[8] Watson JD, Crick FHC. Genetical implications of the structure of deoxyribonucleic acid. Nature, 1993, 269:1967-1969.

[9] Daniels DS, Mol CD, Arvai AS, et al, Active and alkylated human AGT structures: a novel zinc site, inhibitor and extrahelical base binding. EMBO J. 2000, 19:1719–1730.

[10] Harding SE, Channell G, Phillips-Jones MK (2018) The discovery of hydrogen bonds in DNA and a re-evaluation of the 1948 Creeth two-chain model for its structure. Biochem Soc Trans 46:1171-1182.

[11] Feng B, Sosa RP, Mårtensson AK, et al (2019) Hydrophobic catalysis and a potential biological role of DNA unstacking induced by environment effects. Proc Natl Acad Sci 116:17169-17174.

[12] Kohagen M, Uhlig F, Smiatek J (2019) On the nature of ion-stabilized cytosine pairs in DNA i-motifs: the importance of charge transfer processes. Int J Quantum Chem 119:e25933.

[13] Dylawerska A, Barczak W, Wegner A, et al (2017) Association of DNA repair genes polymorphisms and mutations with increased risk of head and neck cancer: a review. Med Oncol 34: 197.

[14] Tolosa S, Sansón JA, Hidalgo A (2020) Mechanisms of the T-A to C-G transition studied by SMD simulations: Deamination vs tautomerisation. J Mol Liq 308:113036.

[15] Wang SR, Wang JQ, Fu BS, et al (2018) Supramolecular coordination-directed reversible regulation of protein activities at epigenetic DNA marks. J Am Chem Soc 140:15842-15849.

[16] Qi Y, Chen Y, He J, Xiu F (2020) A colorimetric sensor for DNA detection: Combination of synergistic coupling catalysis and significant distinction in the dimensional structure of DNA. Microchem J 159:105546.

[17] Sharma S, Lafontaine DL (2015) 'View from a bridge': a new perspective on eukaryotic rRNA base modification. Trends Biochem Sci 40:560-575.

[18] D'Abramo M, Castellazzi CL, Orozco M, et al (2013) On the nature of DNA hyperchromic effect. J Phys Chem 117:8697-8704.

[19] Wang X, Son A (2013) Effects of pretreatment on the denaturation and fragmentation of genomic DNA for DNA hybridization. Environ Sci Process Impact 15:2204-2212.

[20] Leonard AC, Méchali M (2013) DNA replication origins. Cold Spring Harb Perspect Biol 5:a010116.

[21] Carnimeo I, Biczysko M, Bloino J, Barone V (2011) Reliable structural, thermodynamic, and spectroscopic properties of organic molecules adsorbed on silicon surfaces from computational modeling: the case of glycine@ Si (100). Phys Chem Chem Phys 13:16713-16727.

[22] Cherkaoui M, Boutalib A (2012) A Theoretical investigation of furan-AlX3, pyrrole-AlX3 and thiophene-AlX3 (X= H, F, Cl, Br) interactions. Orbital: Electron J Chem 4:235-244.

[23] Alkorta I, Trujillo C, Elguero J, Solimannejad M (2011) A theoretical study of the hydrogen bonding properties of H2B=NH2: Some considerations on the basis set superposition error issue. Comput Theor Chem 967:147-151.

[24] Balachandran V, Lakshmi A, Janaki A (2011) Ab initio, DFT, HOMO–LUMO and Natural Bond Orbital analyses of the electronic structure of 2-mercapto-1-methylimidazole. J Mol Struct 1006:395-401.

[25] Frisch MJ, Trucks GW, Schlegel HB, et al (2009). Eds Gaussian Inc: Wallingford, CT, USA.

[26] Karthikeyan N, Prince JJ, Ramalingam S, et al (2015) Electronic [UV–Visible] and vibrational [FT-IR, FT-Raman] investigation and NMR–mass spectroscopic analysis of terephthalic acid using quantum Gaussian calculations. Spectrochim Acta A Mol Biomol Spectrosc 139:229-242.

[27] Chen X, Cui Y, Best RB, et al (2020) Cutting antiparallel DNA strands in a single active site. Nat Struct Mol Biol 27:119-126.

[28] Villani G (2005) Theoretical investigation of hydrogen transfer mechanism in the adenine–thymine base pair. Chem Phys 316:1-8.

[29] Vologodskii A, Frank-Kamenetskii MD (2018) DNA melting and energetics of the double helix. Phys Life Rev 25:1-21.

[30] Matta CF, Castillo N, Boyd RJ (2006) Extended Weak Bonding Interactions in DNA: π-Stacking (Base–Base), Base–Backbone, and Backbone–Backbone Interactions. J Phys Chem 110:563-578.

[31] Spiegel M, Andruniów T, Sroka Z (2020) Flavones' and Flavonols' Antiradical Structure–Activity Relationship—A Quantum Chemical Study. Antioxidants 9:461