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Thermodynamic and reactivity descriptors Studies on the interaction of Flutamide anticancer drug with nucleobases: A computational view

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ABSTRACT

In this work, the interaction between Flutamide (FLU) anticancer drug with nucleobases such as cytosine, thymine, uracil and adenine was studied by density functional theory (DFT) methods from a thermodynamic point of view. The Gibbs free energy (ΔG) and enthalpy (ΔH) of C-FLU, T-FLU, U-FLU and A-FLU complexes were computed and demonstrate that the stronger interaction between cytosine and FLU and the adsorption of the drug on the bases proceeds spontaneously. The negative value of ΔH indicates that the adsorption of FLU drug on the cytosine, thymine and uracil bases are exothermic, these results confirmed ΔE results. During the interaction of Flutamide drug with nucleobases, the energy levels of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) were significantly changed. The values of the energy gap (E_g) reduced during the adsorption of the FLU drug onto bases which confirmed that the reactivity of the resulted complex increase upon adsorption. On the other hand, as a result of theoretical calculations, the values of the Eg for the Base-FLU structures in water solution are decreased in comparison to the corresponding values in the gas phase, indicating more the reactivity of the studied complexes in the aqueous medium.

1. Introduction

Study on the interaction between drugs and DNA [1-3] represents a great interest in many aspects of today biochemical research not only in understanding the mechanism of action of the drug, but also for the design of new drugs [4]. However, mechanism of interactions between drug molecules and DNA is still relatively little known. It is necessary to introduce more simple methods for investigating the mechanism of DNA-drug interaction. The understanding of the mechanism of interaction will promote designing of new DNA-targeted drugs.

In recent years there is a growing interest in the investigation of interaction between anticancer drugs and DNA targeted molecules. This research is currently under intense investigation owing to their therapeutic value as anti-cancer agents [5,6]. Cancer, in which cells grow and divide abnormally, is one of the primary diseases with regards to how it responds to drug delivery [7].

Flutamide (4-nitro-3-trifluoromethylisobutylanilide) a synthetic antiandrogenic compound with therapeutic use in prostatic cancer has been electrochemically studied to propose a new electroanalytical alternative for its quantitative determination in pharmaceutical forms [8]. Flutamide is used as antineoplastic and antiandrogen drug. It is a powerful nonsteroidal androgen antagonist [9] which is used to treat prostate cancer and is believed to block androgen receptor sites. Vargas et al. [10] have investigated photochemistry and phototoxicity studies of Flutamide, a phototoxic anti-cancer drug. Payen et al. [11] studied synthesis and biological activity of ferrocenyl derivatives of the non-steroidal antiandrogens Flutamide and bicalutamide.

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Previously, we investigated the interaction of Flutamide (FLU) anticancer drug molecule with the four nucleobases i.e. cytosine (C), thymine (T), uracil (U) and guanine (G) at different levels of density functional theory [10]. The DFT results exhibit that interaction of the drug molecule and the nucleobases is favorable and all of the designed complexes are stable. Furthermore, among the four kind of the nucleobases used in this study, cytosine forms the most stable complexes with FLU drug in the both at the M06-2X and CAM-B3LYP levels. Examinations related to the binding energy values, topological analysis and NBO analysis display the physical nature of the formed complexes between the FLU molecule and the bases. It should be noted that, the results of our previous theoretical calculations show that M06-2X is lower than its corresponding values in CAMB3LYP approach.

The objective of the present study was to perform density functional theory (DFT) calculations to investigate the effect of cytosine, thymine, uracil and adenine bases interaction with FLU drug molecule in terms of variation in HOMO–LUMO energy gap, and global reactivity descriptors; frontier orbital contribution to the electronic charge distribution in the Base-drug system. The frontier molecular orbitals (FMO) analysis provides precise and valuable information about the reactivity of a drug complex system. Thus, in the present work, we select the most stable complexes among DNA and Flutamide drug from previous study [12] and are studied thermodynamic point of view. Moreover, it is necessary to understand these properties of the considered complexes in order to perform further pharmacological studies.

2. Computational methods

The DFT calculations were carried out using the Gaussian 03 program [13]. The M06-2X functional was used in combination with the 6-311++G** basis sets. [14, 15]. M06-2X level is a powerful method which has been able to successfully predict the geometry and its related properties. All studied complexes were optimized without any constrain. The frequency calculations were performed to ensure the minima structure for all geometries and revealed that they are energetically minimum in structure. The zero-point vibration energy (ZPVE) correction was considered in the calculations of the binding energy (ΔE). Tomasi's polarized continuum (PCM) model [16,17] has been employed for the solvent effect of water calculation. Different quantum molecular descriptor (QMD) of all studied compounds such as the ionization potential ($I= -E_{HOMO}$), the electron affinity of the molecule ($A = -E_{LUMO}$), the chemical potential of the system ($\mu = - (I + A)/2$), hardness ($\eta= (I – A)/2$), softness ($S = 1/(2\eta)$), the Fermi level ($E_F = (E_{HOMO} + E_{LUMO})/2$), the electrophilicity ($\omega= \mu^2/2\eta$) and nucleophilicity index (N) and were studied [16] to obtain chemical reactivity and stability. The N nucleophilicity index for a given system, was therefore defined [17,18] as $N=E_{HOMO(Nu)} - E_{HOMO(TCE)}$ (in eV units) where $E_{HOMO(Nu)}$ is the HOMO energy of the nucleophile and $E_{HOMO(TCE)}$ corresponds to the HOMO energy of the tetracyanoethylene (TCE) taken as reference. A molecule with a small frontier orbital gap is more polarizable and is generally associated with a high chemical reactivity, low kinetic stability [19, 20].

The role of the chemical potential in chemistry has been analyzed by Parr and Pearson [21-23]. They suggested that the chemical potential plays an important role in explaining chemical reactions through the charge transfer process.

In order to explore the direction of the electron transfer between the FLU molecule and base in the adsorption process, the parameter ΔN, which determines the fractional number of electrons transferred from a system A (acceptor) to system B (donor) is defined as [24,25]:

$$\Delta N= (\mu_B - \mu_A) / (\eta_A + \eta_B) \quad (1)$$

Where μ and η are the chemical potential and the chemical hardness of donor (B) and acceptor (A), respectively. The positive value of ΔN reveals that electron flows spontaneously from B to A or otherwise it is in the reverse direction.

Additionally, the reactivity descriptors such as the overall stabilization energy ($\Delta E_{SE(AB)}$), the individual energy change of acceptor ($\Delta E_{A(B)}$) and the individual energy change of donor ($\Delta E_{B(A)}$) are applied to understand the stability of the resultant compounds as follows [23,26]:

$$\Delta E_{SE(AB)} =\Delta E_{A(B)}+\Delta E_{B(A)}= -(\mu_B - \mu_A)^2 /2(\eta_A + \eta_B) \quad (2)$$

$$\Delta E_{A(B)} = \Delta N (-\mu_A + ½ \eta_A \Delta N) \quad (3)$$

$$\Delta E_{B(A)} = \Delta N (-\mu_B + ½ \eta_B \Delta N) \quad (4)$$

Argued further, it was also shown how $\Delta E_{B(A)}$ can be used to study the kinetics, whereas $\Delta E_{A(B)}$ is for thermodynamics of chemical reactions [27]. The electron transfers values (i.e., ΔN) are used to explain both the rate of interaction as well as stability of the adducts as it is formally linked to all the kinetic and thermodynamic descriptors as shown by eqs 2-4. Moreover, to study the effects of the FLU attachment to the nucleobases on its electronic properties, the density of state (DOS) analysis is carried out [28-31].

3. Results and discussion

According to the obtained results from previous study [10], it is found that the most negative binding energy value belongs to the C-FLU, T-FLU, U-FLU and A-FLU complexes with equilibrium distances and binding energies of 1.805 Å and -76.96 kJ/mol, 2.303 Å and -38.00 kJ/mol, 2.323 Å and -40.75 kJ/mol, and 1.910 Å and -26.55 kJ/mol respectively, as displayed in Figure 1. The results of binding energies show the studied complexes are stable and the intermolecular interaction of FLU drug with bases is exothermic.

3.1. Thermodynamic Parameter

In order to study the feasibility of the adsorption process, the thermodynamic parameters were calculated [32]. Table 1 shows the Gibbs free energy (ΔG), enthalpy (ΔH) and entropy (ΔS) of interaction of the drug on the bases. The order of ΔG and ΔH (absolute values) for adsorption of drug on the bases is as follows: C-FLU > T-FLU > U-FLU > A-FLU.

Table 1. Calculated binding (ΔE) energy (in kJ/mol) and at M06-2X level in the gas phase (Values in parentheses refer to calculation in the water phase).

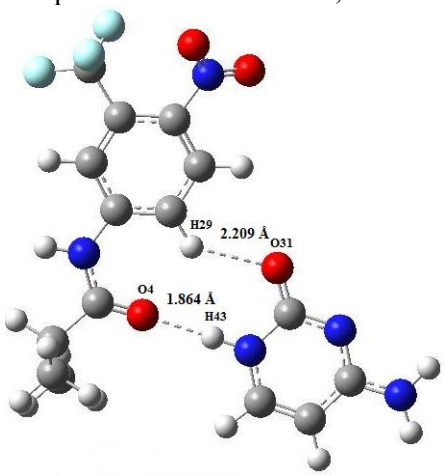
model	ΔE	ΔG	ΔH	ΔS
C1-FLU	-72.32 (-21.15)	-65.96 (21.19)	-110.75 (-18.49)	-0.13 (-0.13)
C2-FLU	-76.96 (-37.7)	-68.12 (9.24)	-107.44 (-37.72)	-0.15 (-0.16)
T1-FLU	-37.82 (-20.66)	-21.15 (20.26)	-75.54 (-17.93)	-0.18 (-0.13)
T2-FLU	-38.00 (-21.66)	-28.40 (22.42)	-74.12 (-21.24)	-0.15 (-0.15)
U1-FLU	-37.88 (-21.73)	8.50 (23.56)	-35.59 (-20.77)	-0.15 (-0.15)
U2-FLU	-40.75 (-22.93)	1.66 (20.31)	-38.40 (-20.32)	-0.13 (-0.14)
A1-FLU	-22.93 (-10.61)	19.24 (32.56)	-19.17 (-6.84)	-0.13 (-0.14)
A2-FLU	-26.55 (-12.68)	18.03 (28.80)	-24.00 (-11.47)	-0.14 (-0.13)

This could be related to the stronger interaction between cytosine and FLU. The negative value of ΔH indicates that the adsorption of FLU drug on the cytosine, thymine, uracil and adenine bases are exothermic, these results confirmed ΔE results. Also, the negative values of ΔG indicate that the adsorption of drug on the bases proceeds spontaneously. The calculated ΔG values are less negative compared to the ΔH values, indicating an entropy reduction. The value of ΔS decreases during the adsorption process, which is due to decrease of the degree of freedom translation.

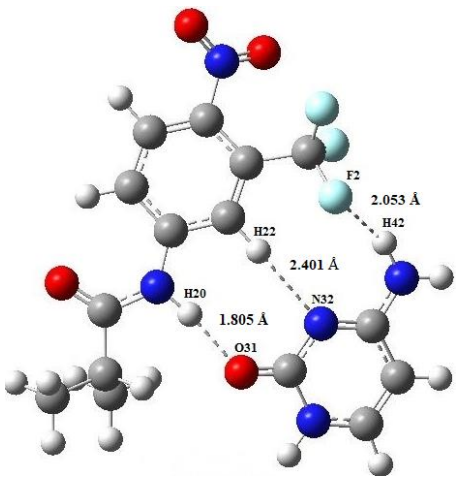
The kinetic aspects of the interaction between the bases and FLU drug molecule are investigated by using $\Delta E_{B(A)}$, whereas $\Delta E_{A(B)}$ and $\Delta E_{SE(AB)}$ are exploited to understand the thermodynamic stability of the studied complexes. By considering the calculated theoretical results, it can be concluded that the nucleobase is B (i.e., donor) and the FLU is A (i.e., acceptor). It is worth mentioning that the numerical value of ΔN easily defines the donor and the acceptor involved in the process of interaction. The values of ΔN and $\Delta E_{B(A)}$ are positive which indicate that the electron flow is spontaneous from the base to FLU (see Table 2). The interaction is 'normal electron demand' (NED) reaction due to the direction of electron flow from the donor B to the acceptor A. Furthermore, the negative value of $\Delta E_{A(B)}$ confirms that the Base-FLU complex is energetically stable. Also, the $\Delta E_{SE(AB)}$ value is negative for the favorable intermolecular interaction between the drug molecule and the nucleobases (see Table 2).

Table 2. The values of the overall stabilization energy ($\Delta E_{SE(AB)}$), the individual energy change of acceptor ($\Delta E_{A(B)}$) and the individual energy change of donor ($\Delta E_{B(A)}$) (all in eV) and charge transfer (ΔN) within the reacting FLU drug molecule and the nucleotide basses

	$\Delta E_{SE(AB)}$	$\Delta E_{A(B)}$	$\Delta E_{B(A)}$	ΔN
cytosine	-0.002 (-0.002)	-0.025 (-0.025)	0.020 (0.020)	0.135 (0.134)
thymine	-0.002 (-0.002)	-0.021 (-0.023)	0.019 (0.021)	0.112 (0.126)
uracil	-0.001 (-0.001)	-0.015 (-0.018)	0.014 (0.016)	0.078 (0.096)
adenine	-0.004 (-0.004)	-0.032 (-0.032)	0.028 (0.028)	0.181 (0.180)



C1-FLU



C2-FLU

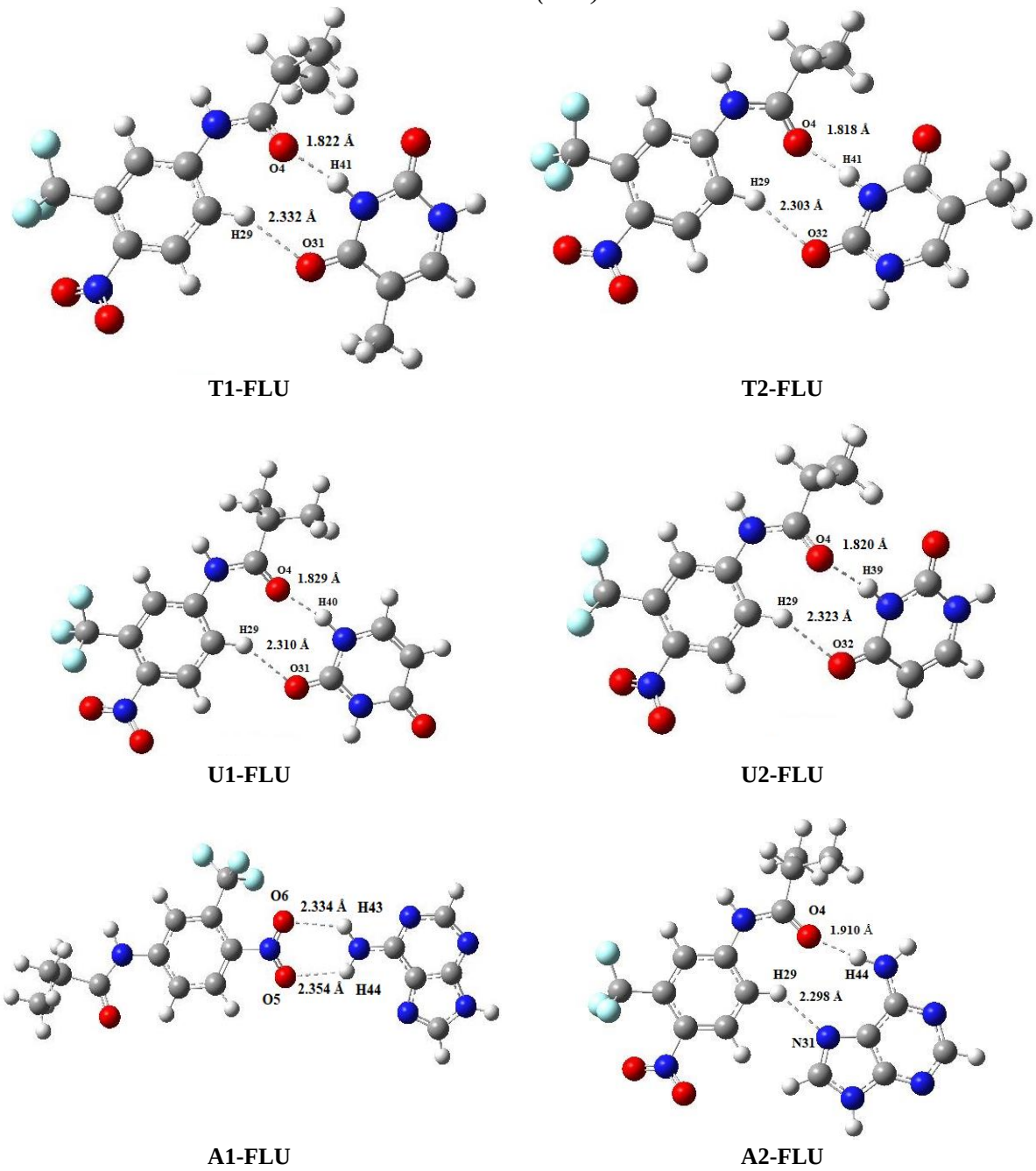


Figure 1. The most stable structures of Flutamide and cytosine (C-FLU), Flutamide and thymine (T-FLU), Flutamide and uracil (U-FLU) and Flutamide and adenine (A-FLU) complexes

3.2. *Dipole Moment and Molecular Electrostatic Potential*

The dipole moment is the first derivative of the energy with respect to an applied electric field as a measure of asymmetry in the molecular charge distribution [33]. After adsorption of FLU, μ° changes in the range of 9.32 Debye to 12.99 Debye. This enhancement of μ°clearly proves that the significant amounts of charges are transferred between adsorbate and adsorbent. The values of μ°are increased into 12.99 Debye when FLU adsorbed in cytosine; 9.32 Debye in case of thymine, 11.85 Debye for uracil and 10.85 Debye for adenine base as shown in Table 3. The value of dipole moment of C-FLU complex is larger than that of T-FLU, U-FLU and A-FLU complexes. As can be seen from Table 3, the dipole moments of the selected complexes enhance by changing the gas phase to the solution medium. Also, the enhancement polarity suggests the possible solubility of these complexes in the presence of the water solvent. Moreover, it is observed that greater dipole moment is associated with higher absolute values of the adsorption energy (see Table 1). Indeed, the high dipole moment illustrates the great reactivity and suggests the contribution from resonance.

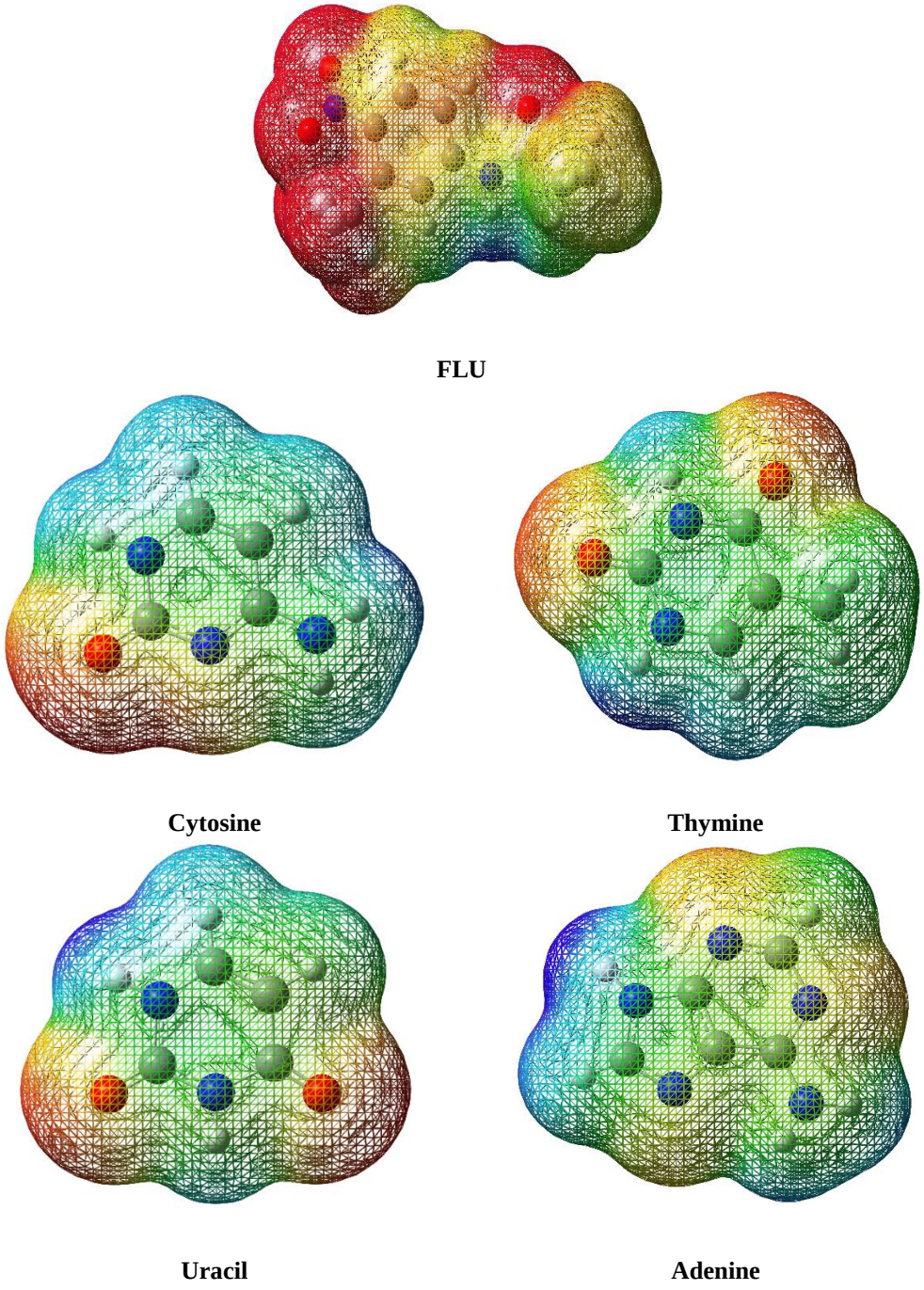


Figure 2. The molecular electrostatic potential surface of the FLU drug, cytosine, thymine, uracil and adenine

The molecular electrostatic potential (MEP) [34] as a helpful criterion in research of molecular structure with its physiochemical property relationship is evaluated based on the potentials created in the space around a molecule by its nuclei and electrons. The MEP surfaces of the single pyrimidine bases and drug molecule are shown in Figure 2. It is obvious that there is an extensive region of negative electrostatic potential around the oxygen atoms of the bases, whereas the regions around hydrogen atoms in the case of the considered bases have positive electrostatic potential (see Figure 2).

On the other hand, as shown by the MEP plot in Figure 2, in FLU molecule, the oxygen atoms are negatively charged (red colors), while the hydrogen atoms are positively charged (blue colors). The negative regions of MEP shown in red correspond to the electrophilic reactivity and the positive regions shown in blue are responsible for nucleophilic reactivity. Therefore, hydrogen bonding in complexes formed between nucleobases and FLU drug is expectable. There are no any significant changes occurred in bases and FLU drug structures, when we re-optimized them in the water phase.

Table 3. The values of the highest occupied molecular orbital energies (E_{HOMO}) and the lowest unoccupied molecular orbital energies (E_{LUMO}), energy gap (E_g), Fermi level (E_F), dipole moment (μ°), ionization potential (I), the electron affinity of the molecule (A),chemical potential (μ), global hardness (η), softness (S), electrophilicity (ω) and nucleophilicity (N) index (all in eV) for FLU, the nucleotides bases, and different models at M06-2X level in the gas phase (Values in parentheses refer to calculation in the water phase).

Property	cytosine	thymine	uracil	adenine	Flutamide	C2-FLU	T2-FLU	U2-FLU	A2-FLU
E_{LUMO}	-0.45 (-0.25)	-0.46 (-0.36)	-0.58 (-0.44)	-0.24 (-0.07)	-1.76 (-1.93)	-1.35 (-1.87)	-1.63 (-1.94)	-1.61 (-1.95)	-2.20 (-2.08)
E_{HOMO}	-8.03 (-8.19)	-8.33 (-8.20)	-8.70 (-8.54)	-7.62 (-7.74)	-8.68 (-8.44)	-7.89 (-8.18)	-8.32 (-8.13)	-8.61 (-8.47)	-7.60 (-8.12)
E_g	7.58 (7.94)	7.86 (7.84)	8.12 (8.10)	7.38 (7.67)	6.92 (6.51)	6.54 (6.32)	6.70 (6.19)	6.89 (6.48)	5.40 (6.04)
E_F	-4.24 (-4.21)	-4.39 (-4.28)	-4.64 (-4.49)	-3.93 (-3.91)	-5.22 (-5.19)	-4.62 (-5.02)	-4.98 (-5.03)	-5.11 (-5.21)	-4.90 (-5.10)
μ°	6.79 (9.56)	4.47 (6.09)	4.54 (6.13)	2.49 (3.42)	7.78 (9.94)	12.99 (18.16)	9.32 (12.30)	11.85 (16.02)	10.85 (17.16)
I	8.03 (8.19)	8.32 (8.20)	8.70 (8.54)	7.62 (7.74)	8.68 (8.44)	7.89 (8.18)	8.33 (8.13)	8.61 (8.47)	7.60 (8.12)
A	0.45 (0.25)	0.46 (0.36)	0.58 (0.44)	0.24 (0.07)	1.76 (1.93)	1.35 (1.87)	1.63 (1.94)	1.61 (1.95)	2.20 (2.08)
μ	-4.24 (-4.22)	-4.39 (-4.28)	-4.64 (-4.49)	-3.93 (-3.91)	-5.22 (-5.19)	-4.62 (-5.02)	-4.98 (-5.04)	-5.11 (-5.21)	-4.90 (-5.10)
η	3.79 (3.97)	3.93 (3.92)	4.06 (4.05)	3.69 (3.83)	3.46 (3.26)	3.27 (3.16)	3.35 (3.09)	3.40 (3.21)	2.70 (3.02)
S	0.13 (0.13)	0.13 (0.13)	0.12 (0.12)	0.14 (0.13)	0.14 (0.15)	0.15 (0.16)	0.15 (0.16)	0.14 (0.15)	0.19 (0.17)
ω	0.09 (0.08)	0.09 (0.08)	0.10 (0.09)	0.08 (0.07)	0.14 (0.13)	0.16 (0.14)	0.15 (0.14)	0.15 (0.13)	0.16 (0.16)
N	1.08 (0.93)	0.80 (0.92)	0.41 (0.58)	1.50 (1.37)	0.43 (0.67)	1.22 (0.93)	0.78 (0.98)	0.65 (0.70)	1.52 (0.99)

3.3. Frontier molecular orbitals and global properties of bases and FLU molecule

The HOMO and LUMO molecular orbitals were known as Frontiers, which played an important role for evaluating the molecular chemical stability and reactivity [35,36]. In order to illustrate the ability to donate or obtaining electron, HOMO and LUMO profiles of the desired structures i.e., FLU molecule, pristine cytosine, thymine, uracil have been shown in Figure 3. As it is illustrated in this figure, the distributions of HOMO and LUMO orbitals of the FLU molecule is not located on CH3 and CF3 groups; but, they cover the other parts of the drug molecule. This kind of profile implies that C=O and N-H terminals of the drug molecule are more reactive in comparison with CH3 and CF3 groups. Moreover, close inspection of Figure 3 shows that the frontier orbital plots of the pristine bases are distributed in the uniform states.

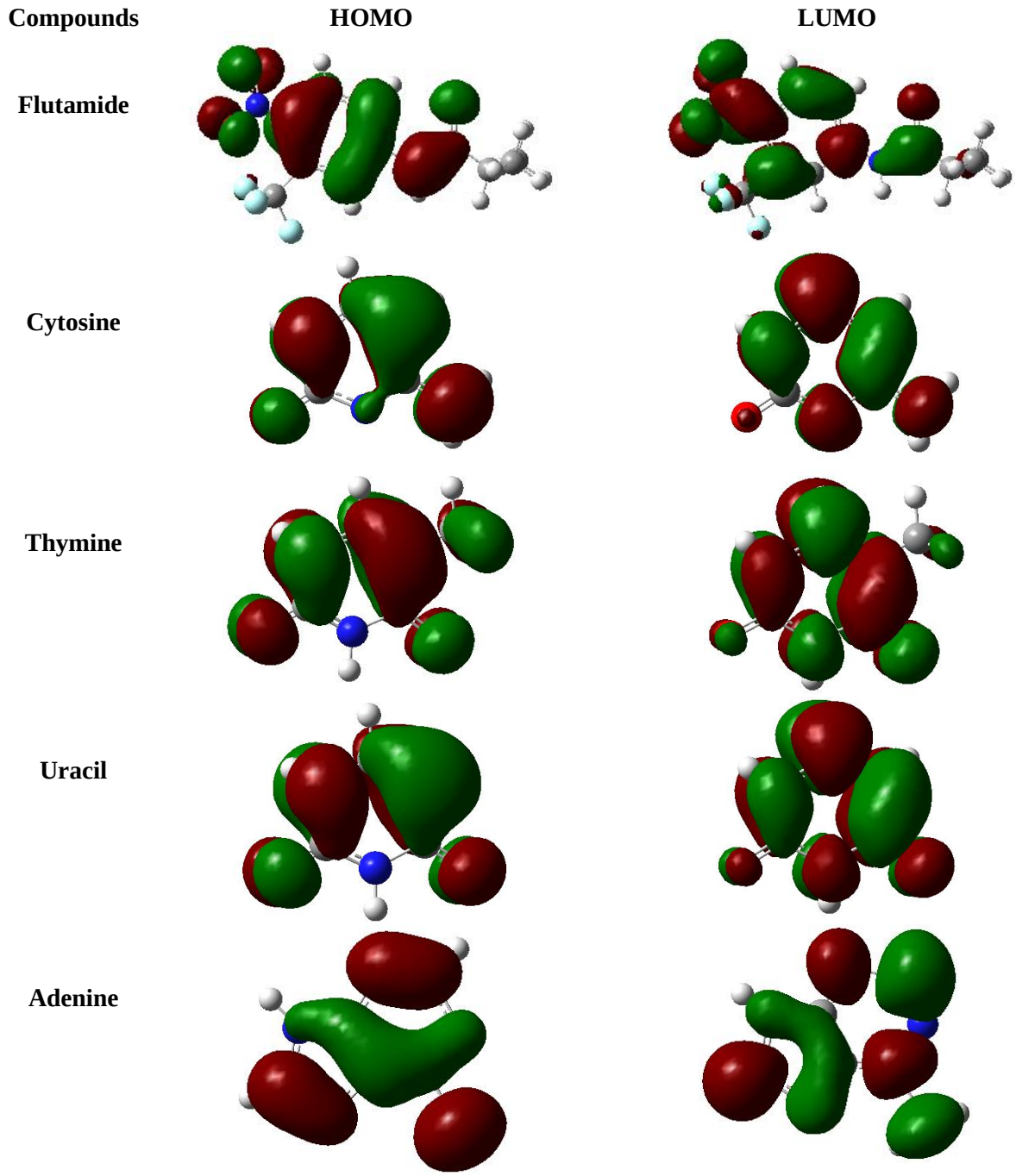


Figure 3. HOMO and LUMO distributions of FLU, cytosine, thymine, uracil and adenine

3.4. Frontier molecular orbitals, global properties and the partial electronic density of states of C-FLU, T-FLU, U-FLU and A-FLU most stable complexes

We made a comparison between the global properties of all structures before and after adsorption to show the effect of adsorption of FLU molecule on the bases. Also, to show the reactivity and stability of all structures before and after adsorption. Table 3 display the values of HOMO, LUMO, energy gap (E_g), Fermi level (E_F), ionization potential (I), the electron affinity of the molecule (A), the chemical potential of the system (l), hardness (η), softness (S), and the electrophilicity index (ω) of the complexed forms of C-FLU, T-FLU, U-FLU and A-FLU complexes. Hardness is defined as the measure of resistance to the deformation of a chemical structure in an external electric field and the enhancement of η defines the greater stability of a structure and this parameter signifies the opposite behavior of softness. As shown in Table 3, the values of hardness reduced during the adsorption of the FLU drug onto bases which confirmed that the reactivity of the resulted complex

was more compared to pristine bases and therefore further FLU molecule could be adsorbed on base. In other words, the reduction of hardness indicates the reduction of chemical stability as well as the enhancement of chemical activity. The values of softness increase during the adsorption of the FLU drug onto bases which confirmed that the reactivity of the resulted complex increase upon adsorption. Besides, softer compounds have a lower E_g. The softness of cytosine (0.13 eV^{-1}) declines to 0.15 eV^{-1} (C2-FLU) owing to the smaller energy gap of the system. Moreover, considering the amount of chemical potential values of Table 3 confirms that electrons will flow from a particular occupied orbital in base into a definite empty orbital in FLU molecule. Indeed, the electron is transferred from higher chemical potential (Base) to the lower electronic chemical potential (FLU), until the electronic chemical potentials become identical [37]. It is observed that when FLU drug adsorbs on base, the electronic chemical potential values of the most considered configurations are decreased, which indicated that the reactivity of these systems is increased (see Table 3). Finally, the electrophilicity index shows the ability of the fragments to accept electrons. With adsorption of FLU drug on the surface of cytosine, thymine, and uracil bases, the values of electrophilicity index increased during the adsorption of the FLU drug onto bases which confirmed that complexes with more tendency to accept electron compared to the corresponding pure systems. The reduction of the value of E_g and η along with the enhancement of the value of ω and S is higher for the interaction of FLU drug with cytosine compared with the interaction of FLU with other two bases claims the greater interaction ability of FLU with cytosine base as discussed before.

Also, the HOMO and LUMO distributions of C-FLU, T-FLU, U-FLU and A-FLU complexes are depicted in Figure 4. The LUMO plots of the complexes focused on the FLU drug. While, HOMO plots focused on the bases demonstrated more density of electron around the N and O atoms. This suggests a charge transfer from the HOMO to the LUMO. So, the adsorption of FLU drug onto bases, causes some minor changes in the values of HOMO and LUMO energies as shown in Table 3.

As a result, the E_g values of all C-FLU, T-FLU, U-FLU and A-FLU complexes were reduced. The E_g values in cytosine reduced from 7.58 eV (C) to 6.54 eV (C2), while in thymine reduced from 7.86 eV (T) to 6.70 eV (T2), in uracil reduced from 8.12 eV (U) to 6.89 eV (U2) and in adenine reduced from 7.38 eV (U) to 5.40 eV (U2).

The E_g values show reactivity and sensitivity and the lower values indicate higher sensitivity and reactivity [38-41]. The reduction of the value of E_g and η along with the enhancement of the value of ω is higher for the interaction of FLU with cytosine compared with the interaction of FLU with other two bases claims the greater interaction ability of FLU with cytosine base as discussed before. Therefore, it is clear that the FLU-C in state C2 is more sensitive rather than other configurations.

In addition, in order to study the effect of FLU adsorption on the electronic properties of the base, the total electronic density of states (DOS) have been measured. The electronic density of states of isolated bases, and C-FLU, T-FLU, U-FLU and A-FLU complexes were illustrated in Figure 5. The comparison between the DOS plots of pure bases versus their complex forms demonstrated the changes in the electronic properties of the bases upon adsorption process that can be used to determine the sensitivity of the stated bases towards Flutamide drug. Upon interaction of each base with FLU, it can be concluded from Figure 5 that some new energy states appeared around the Fermi level, which resulted in lessening in the E_g values. Decrease in the E_g exponentially increases the population of conduction electrons, thereby, increasing the electrical conductivity which can be converted to an electrical signal. This signal is connected to the presence of chemicals in the environment. Herein, it can be decided that the presence of the FLU can be recognized by C, T and U bases via generating an electrical noise. Therefore, we deduced that that the C, T and U bases are sensitivity toward the FLU drug. Moreover, it is found that the values of E_{HOMO}, E_{LUMO}, and HOMO–LUMO energy gap of the studied configurations in solvent phase have less deviation with respect to those corresponding values in the gas phase (see Table 3).

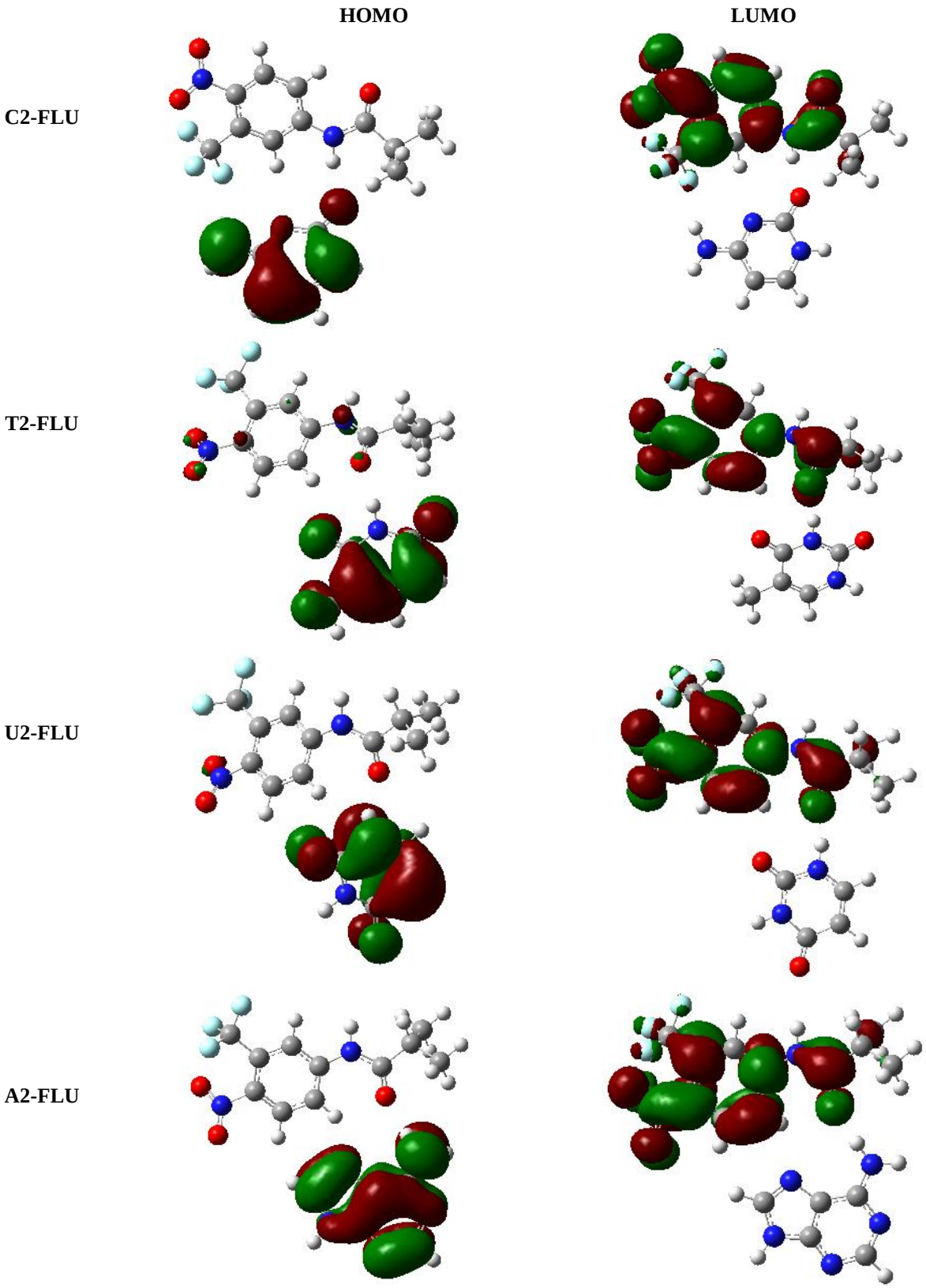


Figure 4. HOMO and LUMO distributions of C-FLU, T-FLU, U-FLU and A-FLU complexes.

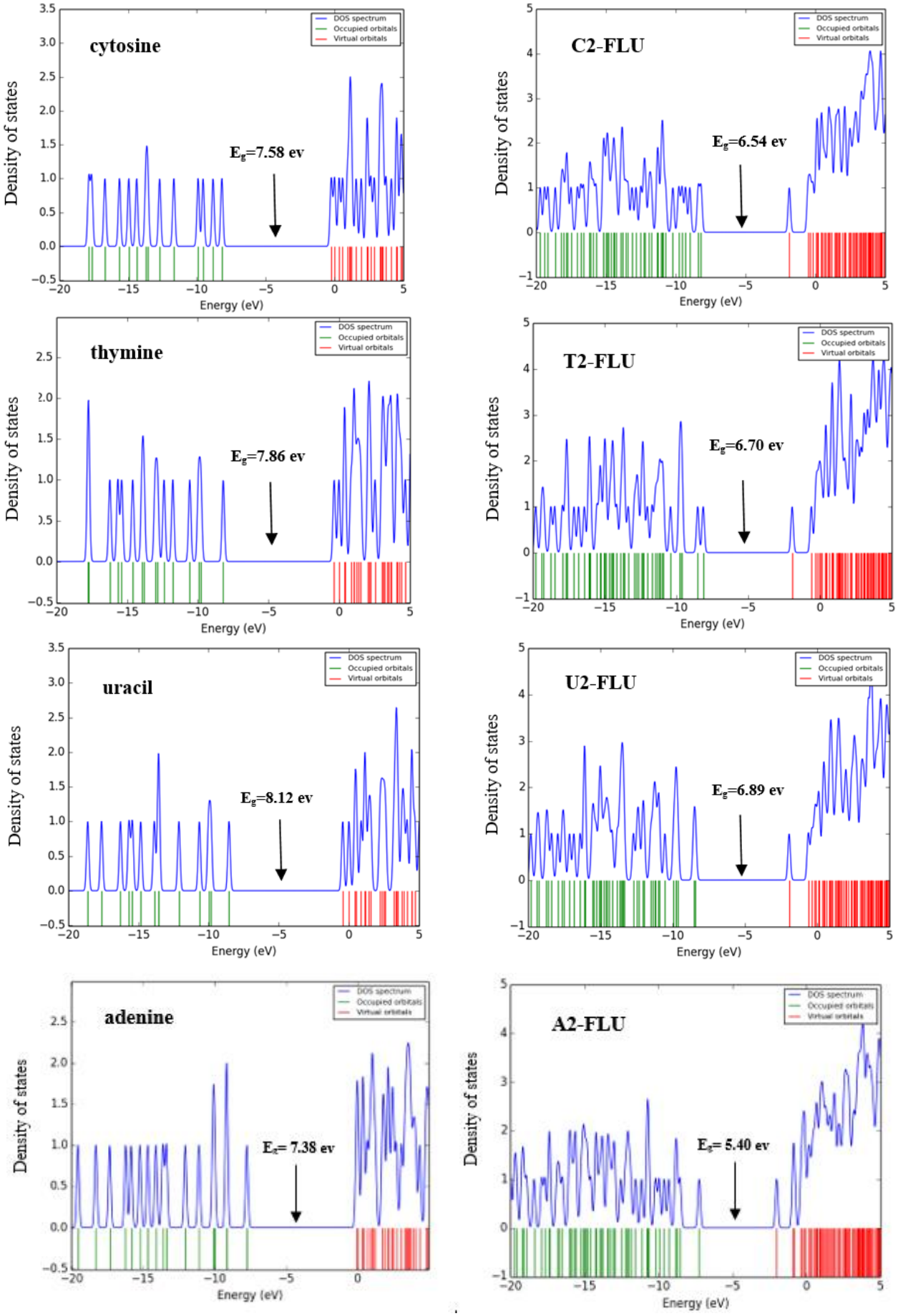


Figure 5. DOSs of pure C, T, U and A bases and the most stable complexes with FLU drug

4. Conclusion

The electronic characteristics and thermodynamic stability of Base-FLU are studied. The calculations indicated weak adsorption energy and sensitivity after FLU drug adsorbed on the cytosine, thymine and uracil bases. The cytosine facilitates the interaction of the FLU compared to the thymine and uracil. Thermodynamic calculations were indicated interaction of FLU with cytosine, thymine and uracil are exothermic and spontaneous. The magnitude of the Gibbs free energy and enthalpy values for the interaction of FLU drug with the cytosine base are more than that for thymine and uracil bases. Furthermore, the QMD such as electrophilicity, chemical hardness and electronic chemical potential of these drugs are explored. The calculation results of quantum molecular descriptors show that the interaction of drug on bases increases the chemical reactivity. Also, the values of the energy gap (E_g) reduced during the adsorption of the FLU drug onto bases which confirmed that the reactivity of the resulted complex increase upon adsorption. On the other hand, as a result of theoretical calculations, the values of the E_g for the Base-FLU structures in water solution are decreased in comparison to the corresponding values in the gas phase, indicating more the reactivity of the studied complexes in the aqueous medium. The results of DOS plot and E_g were indicated that the cytosine base has greater sensitivity to the FLU drug than the other studied bases. The obtained results are in with line DFT results in previous work and confirm that the interaction of the drug molecule with cytosine is stronger than the other base molecules. Our findings indicate that quantum mechanical calculations can be successfully employed to interpret the electronic and thermodynamic point of the interaction between the drug and bases.

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