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Theoretical study of the reactivity of urea, thiourea and some of their hydroxylated derivatives towards free radicals

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Abstract
Urea is an organic compound with the chemical formula $CO(NH_2)_2$. It is similar to thiourea of formula $CS(NH_2)_2$, except that the oxygen atom is replaced by a sulfur atom. It has been shown that urea and thiourea, have derivatives such as: Enolurea, hydroxyurea, hydroxyhiourea, enolthiourea.

Indeed, since the discovery of these different compounds, the results of *in vitro* tests have shown the capacity of each of them to participate in the antioxidant defence of the body by trapping free radicals.

In the present work, a comparative study of the antioxidant properties of urea, enolurea, thiourea, 1-hydroxyurea, hydroxythiourea and enolthiourea was carried out by DFT method M06-2X/6-311++G (d, p).

The results of the various calculations allowed to:

- Identify the oxygen atoms of the O-H groups, O-H^9, O-H^7 and O-H^8, as the most important sites for the manifestation of the antioxidant activity of hydroxythiourea, hydroxyurea, enolthiourea and Enolurea respectively.
- It was found that thiourea and hydroxythiourea are the most antioxidant of the six molecules.
- to note that the replacement of the oxygen atom by that of sulfur considerably modifies the antioxidant properties of the urea molecule to note that the mechanism passing by the elimination of atomic hydrogen by homolytic rupture of bond (HAT), as the most probable for the trapping of a radical by each of the molecules.

Keywords: DFT, antioxidant, urea, thiourea

Introduction

Urea is an organic compound with the chemical formula $CO(NH_2)_2$. It is a small polar molecule with three resonance structures. It is generally synthesized in the liver and then transported by the blood to the kidneys. Experimental work published in the literature has shown that urea is also obtained by conversion of ammonia [1].

The kinetics of urea production, excretion and hydrolysis have been extensively studied in humans [2]. However, very little research has been devoted to the roles of urea in the body [3]. Traditionally, urea has played a passive role in the body. One of its functions is related to the fact that it is an osmotically active substance. Thus, changes in its concentration can contribute to osmoregulation in the kidneys [4]. Other studies have shown that it also stimulates transcription and expression of immediate early genes [5]. It is used in many fields, such as agricultural, pharmaceutical, chemical and medical industries [6].

On the experimental level, the capacity of urea to trap radical species has been reported in the literature. Indeed, the results of *in vitro* tests have shown the capacity of urea to trap free radicals, thus proving its participation in the antioxidant defence of the body. Moreover, an increase in the antioxidant capacity of serum has been observed in patients suffering from kidney disease. This increase would be entirely due to the relatively high serum urea present in the patients examined. In contrast, after hemodialysis when the serum urea concentration was significantly decreased, the antioxidant capacity of serum was significantly reduced [7]. Some works have also shown that due to its low molecular weight, urea seems to be more mobile compared to macromolecular antioxidants such as superoxide dismutase (SOD), catalase (CAT) and ceruloplasmin (CP), whose total antioxidant capacity seems to be confined by their limited mobility and for some, their compartmentalized distribution [8].

On the theoretical level, several works published in the literature have shown that urea has antioxidant properties, for example, by DFT / BHHLYP and DFT/ωB97X-D methods, it was shown that the direct H-atom abstraction mechanism is kinetically preferred to the OH radical addition reaction [9]. In the same year, a M06-2X/6-311++G (d, p) study found that the superoxide radical anion can effectively abstract a hydrogen atom from one of the amino groups of urea and thiourea in aqueous media. They therefore concluded that these two compounds would both serve as very efficient scavengers of superoxide radical anion [10].

In addition, it has been shown experimentally in the literature, that urea has derivatives such as: Enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea. The latter are recognized as antioxidants due to their ability to trap radical species and reduce hydrogen peroxide. They are involved in the protection of cardiac rhythm and coronary flow [11].

Thiourea is a sulfur derivative of urea with the formula $CH_4 N_2 S$. It is similar to urea, except that the oxygen atom is replaced by a sulfur atom. They present all of them, two (02) tautomeric forms. The properties of urea and thiourea differ considerably due to the relative electronegativities of sulfur and oxygen [12]. Various experimental studies published in the literature have shown that thiourea has antiviral [13] and antifungal properties [14]. Hydroxyurea ($CH_4 N_2 0_2$) differs from urea by the presence of a hydroxyl group on one of the nitrogen atoms [15]. This molecule is recognized as a non-alkylating antineoplastic and antiviral agent used in hematology, oncology, infectious diseases and dermatology [16].

From all the above, it should be noted that to our knowledge, no theoretical or experimental work has compared the antioxidant powers of urea, enolurea, thiourea, hydroxyurea and hydroxythiourea. The objective of the present work is to determine the best antioxidant among these compounds by the methods of theoretical chemistry. The reactivities of the different compounds will be compared between them, in order to deduce the most antioxidant of these molecules.

To achieve this objective, different electronic and spectroscopic parameters will be calculated and the results will allow to deduce a ranking order of the antioxidant powers of each compound.

Materials

The chemical systems object of our study were: urea, enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea

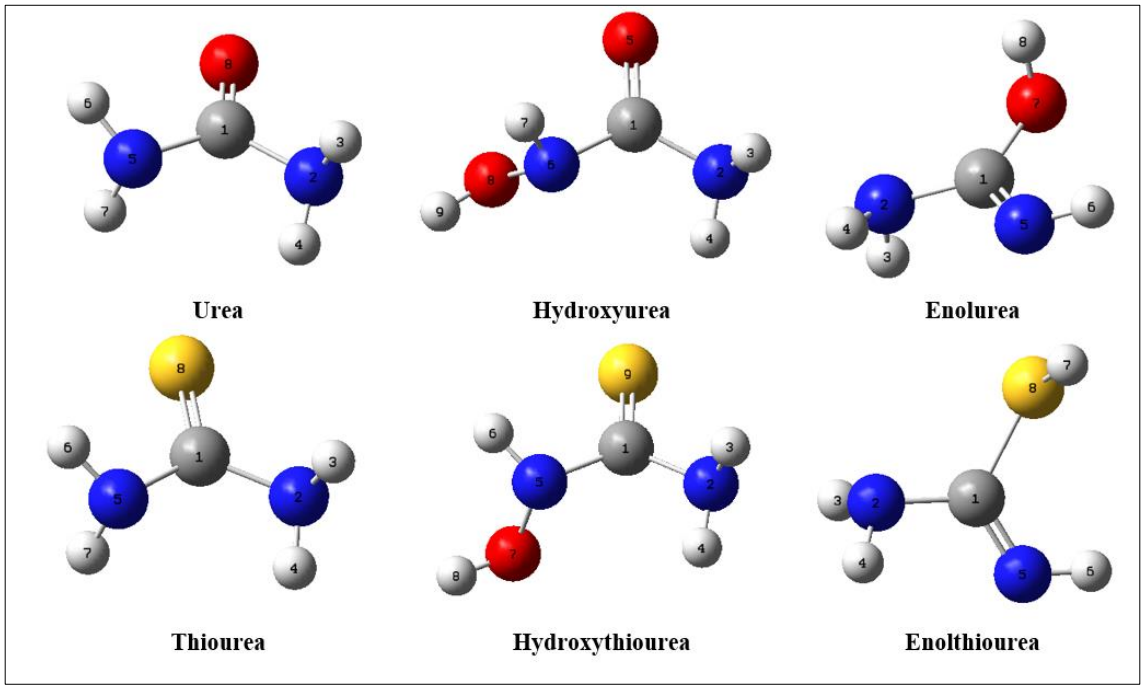


Fig 1: Optimized form of each compound

Methodology

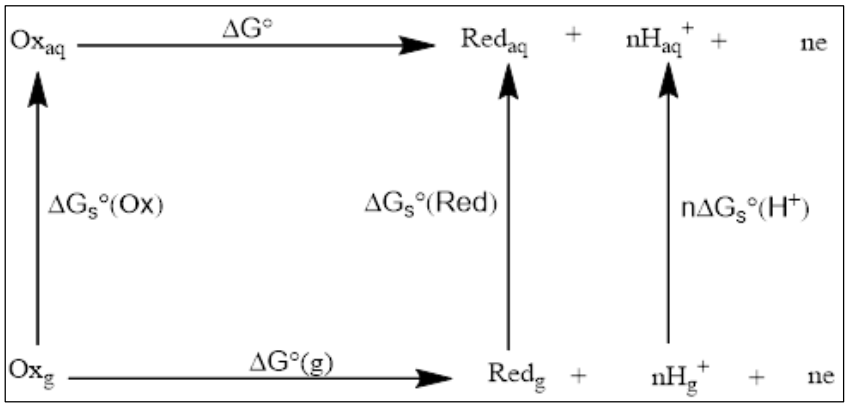
For urea, Enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea, the calculated parameters were:

- **Electronic parameters**
- The Energy *Gap* $_{(HOMO\text{-}LUMO)} = E_{LUMO} - E_{HOMO}$ which is all the lower that the molecule has a high antioxidant power
- The electronic affinity (*AE*): $AE=-E_{LUMO}$; the ionization energy $EI = -E_{HOMO}$ [17].
- The dipole moment (*M*) which accounts for the greater or lesser polarity of a molecule
- The hardness (η) which expresses the resistance of a molecule to the change of its electron number or charge transfer [18]. The stronger the hardness, the less reactive the molecule: $\eta = \frac{(ELUMO - EHOMO)}{2}$
- The electronegativity (χ) which measures the tendency of a chemical species to attract electrons [18]: $\chi = \frac{-(ELUMO + EHOMO)}{2}$
- The electrophilic index (ω) which is the stabilization energy of a molecule saturated by electrons from its surroundings [18]: $\omega = \frac{\chi^2}{2\eta}$
- The redox potential E^0 of the molecules, given by the relation of Nerst.

$E^0 = \frac{-\Delta G^o}{nF}$

With ΔG^o the Gibbs energy related to the reaction $Ox \rightarrow +nH_{❑}^{++ne}$ n the number of transferred electron and F the Faraday constant.

The lower the redox potential of a molecule, the higher its antioxidant activity [19]. Since the redox potential is measured in the aqueous phase, the calculation of ΔG^o requires the use of the Born-Haber cycle.



Scheme 1: Born-Haber cycle for obtaining ΔG^0 from $\Delta G°(g)$

$\Delta G_s^o(H+) = -1104.6\ kJ.mol^{-1}$

On the basis of this cycle we can establish:

$\Delta G^0 = \Delta G_s^\circ + \Delta G^\circ(g) + n\,\Delta G_s^\circ(H^+) - \Delta G_s^\circ(Ox)$

- Spectroscopic parameters such as infrared and UV-visible spectra were calculated by the TD-DFT method. These parameters will allow on the one hand to find the influence of antioxidant properties on the variation of the chemical function and on the other hand to compare the antioxidant properties of the compounds.
- Studies of the mechanisms of antioxidant activity of molecules in the present work, it was considered to determine the most probable routes of the reactions that take place between the studied molecules. For this purpose, three different types of ways of manifestation of the antiradical activity of the molecules have been examined.
  - The elimination of an electron ($ArOH \rightarrow ArOH^{\circ+}+e^-$), followed by that of a proton), (Single-Electron Transfer - Proton Transfer (SET-PT)). For this purpose, the formula: SETPT = $\Delta H(ArO^\bullet)$ ΔH) - ΔH)
  - The elimination of a proton ($ArOH \rightarrow ArO^{-}+H^+$), followed by that of an electron), (Sequential Proton Loss Electron Transfer (SPLET)); then trapping of free radicals. For this purpose the affinity formula :

SPLET = $\Delta H(ArO^\bullet)$ + ΔH**)** + $\Delta H(e)$ - $\Delta H(ArOH^{❑})$

The elimination of a hydrogen atom by homolytic OH) and then trapping of free radicals. For this purpose the BDE (Bond Dissociation Energy) has been calculated:

$BDE = \Delta H(ArO^\bullet) + \Delta H(H^\cdot) - \Delta H(ArOH^{❑})$

For each of these three reaction paths, an energy balance has been made. The lower the total energy released on a reaction pathway, the more likely this pathway will be. On the basis of such an energy balance, we can then propose the most probable mechanism of manifestation of the antiradical activity of the studied molecules, and determine the hydroxyl sites most favorable to this manifestation.

H(ArOH): Enthalpy of the ArOH molecule; H (ArO•): Enthalpy of the ArO radical**•;**
H (ArOH• +): Enthalpy of the cation radical $ArOH^{\circ+}$H (ArO-): Enthalpy of the anion ArO^{-}**;**
H(e-): Enthalpy of the electron (0.752 Kcal/mol) [20];
H (H+): Enthalpy of the proton (1.482 Kcal/mol) [20];

Representation of molecular electrostatic potentials in three dimensions (3D)

The electrostatic potential gives information about the nuclear and electronic charge distribution of molecules. It is an indispensable tool for the interpretation and prediction of chemical reactivity. It is widely used as a molecular reactivity map because it displays the most probable regions for nucleophilic and electrophilic attacks. Indeed, in the potential energy surface, the red color refers to an electron-rich (negative) region, the blue color refers to an electron-poor (positive) region and the green color means a zero electrostatic potential. In most surface energy surfaces, the negative region is the preferred site for electrophilic attack and the positive region is preferred for nucleophilic attack [22].

Results and Discussions

Analysis of the electronic parameters of urea, Enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea

The calculated values of the electronic parameters, at the M06-2X approximation level of each of the six molecules are recorded in the following Table 1:

Table 1: Calculated values (kJ/mol) of *the* electronic parameters of urea, enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea

	E_{Gap}	AE	EI	μ	ω	η	χ
Urea	204.54	8.15	212.72	3.79	59.62	102.27	110.43
Enolurea	193.9	8.78	202.68	3.01	57.65	96.95	105.73
Hydroxyurea	203.94	8.15	212.09	3.94	59.49	101.97	110.12
Thiourea	156.87	11.92	168.79	5.07	52.04	78.43	90.35
Enolthour	191.39	5.64	197.03	2.28	53.65	95.69	101.33
Hydroxythiourea	161.27	11.92	173.19	4.61	53.11	80.63	92.55

The results in Table 1 show that:

The six molecules, thiourea gave the lowest Gap value (HOMO-LUMO) followed by hydroxythiourea. This result in agreement with experimental data published in the literature, means that thiourea and hydroxythiourea are much less stable and therefore more antioxidant than urea, enolurea, hydroxyurea and enolthiourea [23].

Overall, the Gaps ranking order of the six molecules would be: thiourea < hydroxythiourea < enolthiourea < hydroxyurea < urea by decreasing order of the antioxidant activity; we have thus thiourea - hydroxythiourea - enolthiourea - hydroxyurea - urea. The thiourea would be the most antioxidant of the six molecules.

- The six compounds, the lowest values of hardness (η), electronegativity (χ) and electrophilic index (ω) on the one hand, the highest value of dipole moment (μ) on the other hand were obtained respectively by thiourea and hydroxythiourea. These series of results show more that thiourea followed by hydroxythiourea are the most antioxidant of the molecules. Also, the values obtained of the dipole moment reveal that thiourea and hydroxythiourea are more polar than enolthiourea, hydroxyurea and urea.
- It appears from these analyses that thiourea and hydroxythiourea are more antioxidant than enolthiourea, Enolurea, hydroxyurea and urea.

Calculation of the redox potentials of molecules

The redox potentials (**E°)** of the six molecules, calculated by the M06-2X functional method in bases 6-311++G (d, p) are reported in Table 2.

Table 2: Calculated values (in volt) of the redox potential *of* urea, enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea

	M06-2X / 6-311++G (d,p)
Urea	-0.47
Enolurea	-0.61
Hydroxyurea	-0.49
Thiourea	-0.83
Enolthour	-0.67
Hydroxythiourea	-0.75

From the analysis of the results in Table 2, it appears that the lowest values of redox potentials obtained in the order: Thiourea < hydroxythiourea < enolthiourea < hydroxyurea < urea.

This result further indicates that thiourea followed by hydroxythiourea are the most antioxidant of the six (06).

Determination of the probable hydroxyl sites of antioxidant activity of the molecules

For the different O-H bonds found in urea, Enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea molecules, the values of the bond breaking enthalpies (BDE) were calculated at the M06-2X approximation levels. The results obtained are reported in Table 3.

Table 3: Values (in kcal/mol) of O-H bond breaking enthalpies (BDE) calculated at the M06-2X approximation levels for urea, enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea

Links		**M06-2X/6-311++G (d,p)**
Urea	O-H[4]	116.08
	O-H[6]	109.18
Enolurea	O-H[4]	106.675
	O-H[8]	97.26
Thiourea	O-H[4]	46.43
	O-H[9]	84.71
Hydroxyurea	O-H[7]	90.98
	O-H[4]	116.71
	O-H[8]	79.06
Hydroxythiourea	O-H[6]	94.75
	O-H[4]	109.185
	O-H[6]	104.16
Enolthiourea	O-H[4]	109.81
	O-H[7]	89.105

The results in Table 3 show that:

- Of the six molecules, the lowest values of dissociation enthalpy by homolytic OH bond breaking (BDE) was obtained by thiourea. This result further confirms that thiourea is the most antioxidant of the six molecules.
- For hydroxythiourea, hydroxyurea, enolthiourea and Enolurea, the lowest enthalpy values are mainly obtained for the bonds

O-H[8], O-H[9], O-H[7] and O-H[8] respectively. These results indicate that the hydrogen atoms H[8], H[9], H[7] and H[8] can easily dissociate from each of the four molecules to release radicals that can scavenge free radicals. Thus, the O-H[8], O-H[9], O-H[7] and O-H[8] sites appear to be the most important for the manifestation of antioxidant activity of hydroxythiourea, hydroxyurea, enolthiourea and Enolurea respectively.

- Overall, the BDE values given for each of the molecules are ranked in order: Thiourea < hydroxythiourea < enolthiourea < hydroxyurea < Enolurea < urea.

The antioxidant activity of thiourea would thus be more important than that of the other six molecules

Mechanisms and sites of manifestation of antiradical activity of molecules

For the different O-H bonds found in each of the molecules, the calculated values of the different energy parameters (HAT SETPT and SPLET), relative to the three reaction paths considered, are recorded in Table 5.

Table 5: Calculated values (in kcal/mol) of the energy parameters of urea, Enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea

	Urea	Enolurea	Thiourea	Enolthiourea	Hydroxyurea	Hydroxythiourea
HAT	116.08	97.26	46.43	89.105	84.71	79.06
SETPT	430.06	411.23	360.41	403.08	404.96	393.04
SPLET	430.81	411.98	361.16	403.83	405.71	393.79

The results obtained for urea, Enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea show that the reaction pathway passing through the elimination of a hydrogen atom by homolytic rupture of the O-H bond required the lowest energy values. This means that the manifestation of the antiradical activity of each of the six molecules, would probably pass by this last reaction path (elimination of a hydrogen atom by homolytic rupture of OH bond then scavenging of the free radicals).

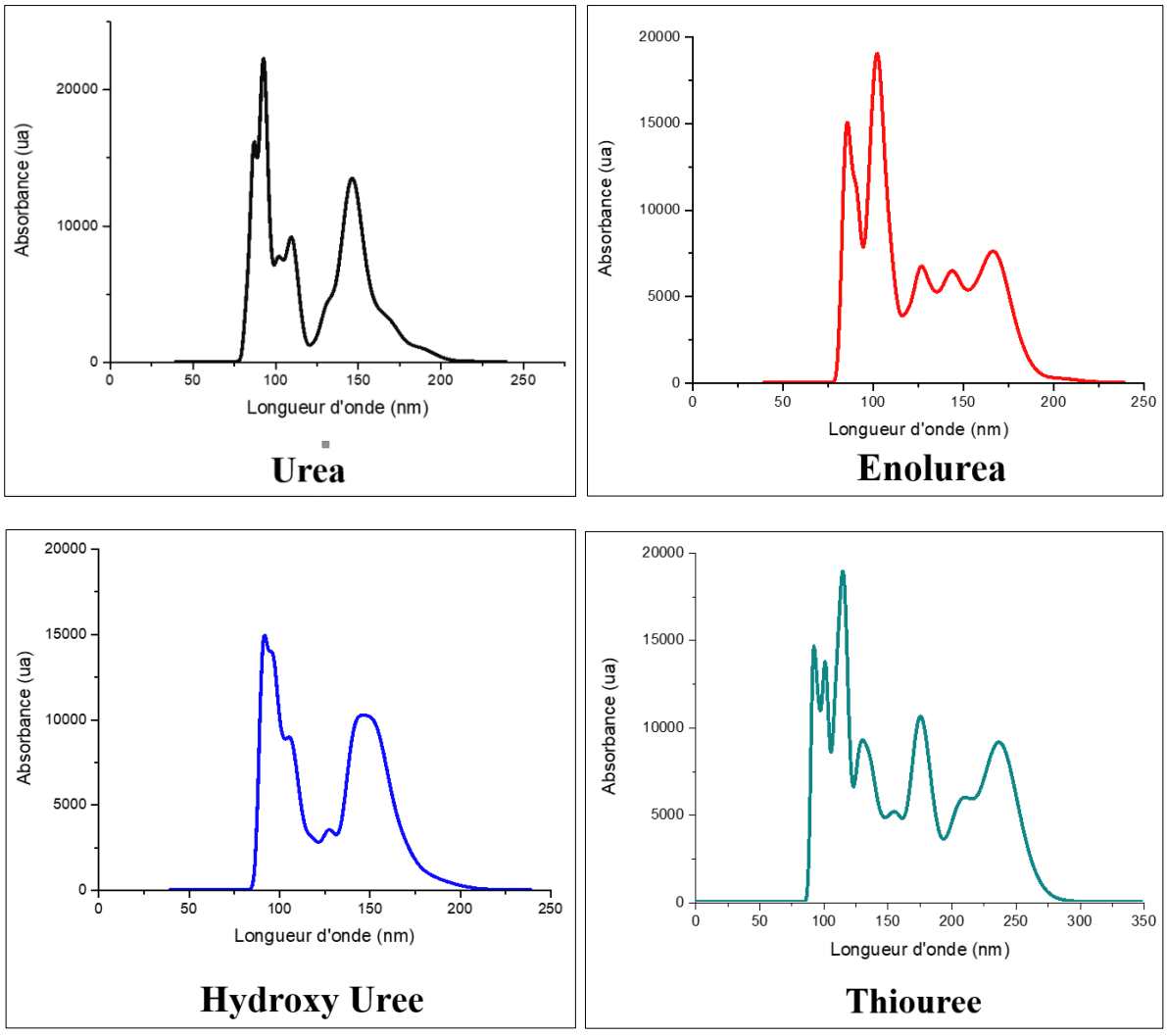
Study of the uv-visible spectra of urea, Enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea

The absorption curves of the UV-Visible spectrum of each of the six molecules were calculated and represented at the level M06-2X/6-311++G (d, p) (Figure 2).

From the analysis of the different absorption curves it appears that:

- Urea, Enolurea and hydroxyurea have respectively 3, 5, 2 peaks of UV-vis absorption whose band width varies between 50 nm and 230 nm. Regarding thiourea, hydroxythiourea and enolthiourea they present 8, 7 and 4 peaks respectively whose absorption band is between 300 nm and 350 nm. It follows from these results that thiourea, hydroxythiourea and enolthiourea appear more antioxidant than urea, Enolurea and hydroxyurea. These last molecules having presented a range of absorption band less broad than thiourea, hydroxythiourea and enolthiourea. Indeed, according to the experimental work published in the literature by [24], the molecules presenting a broad range of UV-vis spectra facilitate more the electronic delocalization and present a strong antioxidant character.
- The comparison between the UV-visible absorption spectra of urea, Enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea showed that thiourea and hydroxythiourea had the widest absorption bands. This means that thiourea and hydroxythiourea have the strongest antioxidant powers of the six molecules.

From all the above, it should be said that thiourea and hydroxythiourea are antioxidant than urea, enolurea, hydroxyurea and enolthiourea.



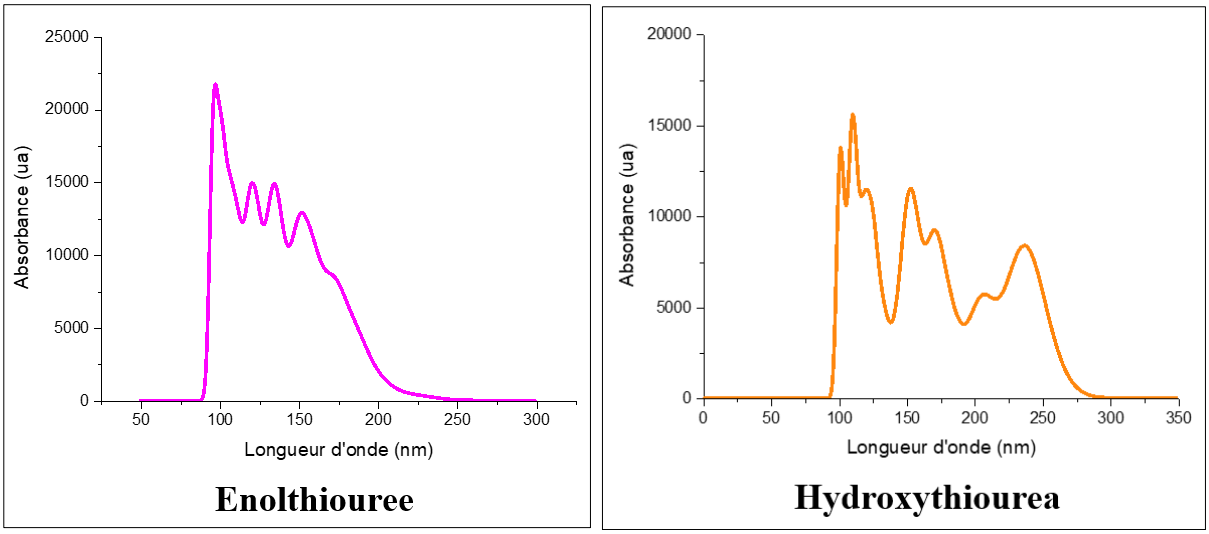


Fig 2: Uv-visible spectra of urea, Enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea

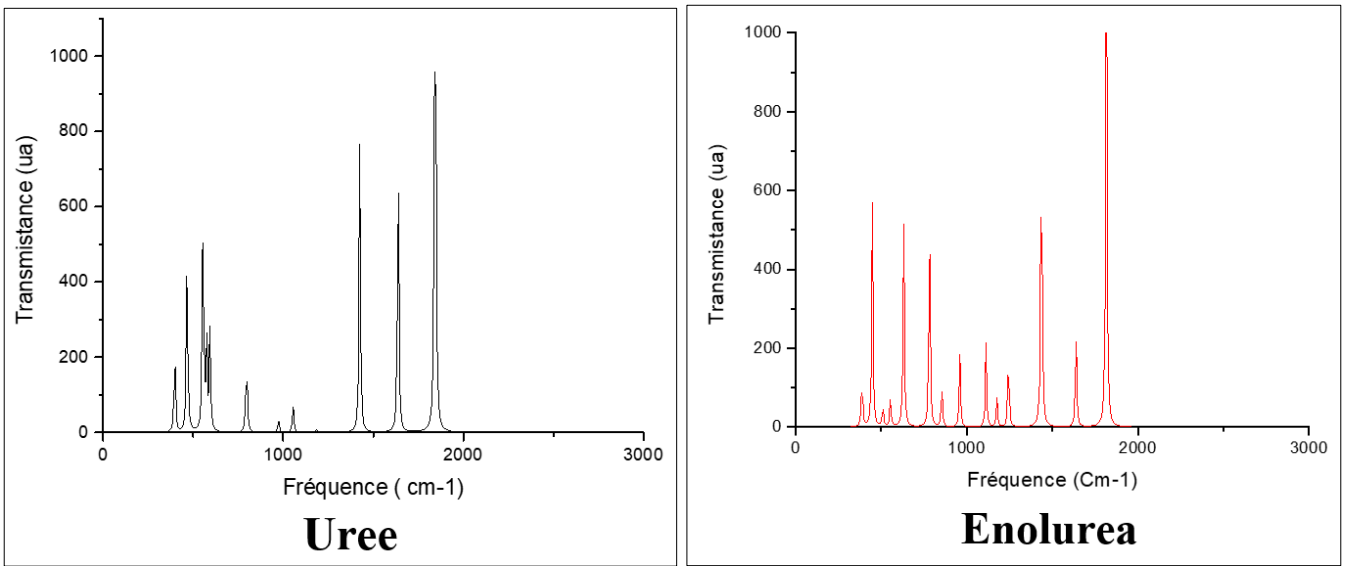
Analysis of the Infra-Red spectra of urea, Enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea

The IR spectra of urea, Enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea are shown in Figure 3.

From the analysis of the different spectra, it appears that:

- Infrared spectra of urea, Enolurea and hydroxyurea are dominated by intense bands located in the spectral range 0 to 2000 cm^{-1}. For thiourea, hydroxythiourea and enolthiourea less intense IR spectral bands between 0 cm^{-1} and 1800 cm^{-1} were observed. From these observations, it appears that thiourea, hydroxythiourea and enolthiourea appear to be more stable than urea, Enolurea and hydroxyurea
- IR spectra of urea, Enolurea and hydroxyurea gave much less intense bands than those of thiourea, hydroxythiourea and enolthiourea. This result indicates that electron delocalization would be more important in urea, Enolurea and hydroxyurea than in thiourea, hydroxythiourea and enolthiourea. This implies a greater weakening of the hydroxyl (O-H) and (N-H) bonds in each of the urea derivatives than in the thiourea derivatives. These results further show that thiourea and hydroxythiourea are the most antioxidant of the six molecules

From these analyses, it appears that the replacement of the oxygen atom by that of sulfur considerably modifies the antioxidant properties of the urea molecule



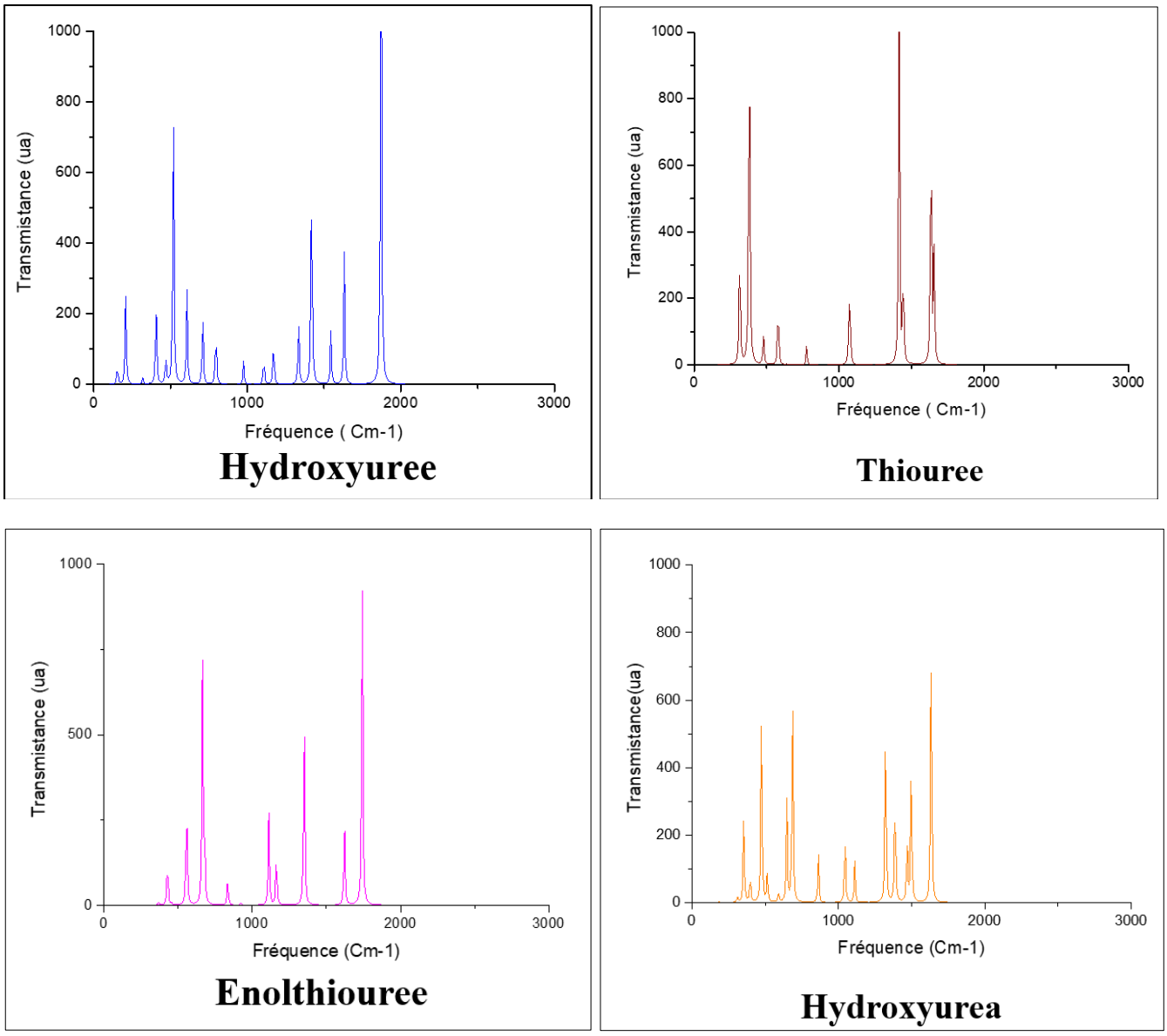


Fig 3: Infrared spectra of urea, Enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea

Representation of the molecular electrostatic potentials in three dimensions (3D) of each molecule

The electron populations at the potential energy surface are indicated by different colors. The 3D representation of the potential energy surfaces of urea, Enolurea, thiourea, 1-hydroxyurea, hydroxythiourea and enolthiourea were shown (Figure 4). The analysis of the different surfaces showed that the electron density values increase in the following order: Red > Orange > Yellow > Black > Blue

For urea, Enolurea, hydroxyurea, the electron density is in the regions between [-3.780 ua; 3.780 ua], [-3.560 ua; 3.460 ua] and [-4.700 ua; 3.500 ua] respectively. The analysis of the molecular electrostatic potentials (MEP) of each of these three molecules shows that they possess more electron-rich partial negative charges (electrophilic site) than electron-deficient charges (nucleophilic site); which means that these three molecules are good antioxidant candidates. Moreover, of the three molecules, enolthiourea presents a stronger electronic delocalization; this molecule thus appears to be the most antioxidant of the three molecules.

For thiourea, hydroxythiourea and enolthiourea, the electron density is in the regions between [-3,800 ua; 3,800 ua], [-3,820 ua; 3,450 ua] and [-5,020 ua; 3,120 ua] respectively. The analysis of the molecular electrostatic potentials (MEP) of each of these three molecules shows that there is more electrophilic site than nucleophilic site; which means that these three molecules are good antioxidant candidates. Moreover, thiourea and hydroxythiourea presented more electrophilic sites. This result indicates that these two molecules are the most antioxidant.

A comparative study of the isoelectric surfaces shows that among the six molecules (urea, Enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea), thiourea and hydroxythiourea have presented the highest electronic populations. From this analysis, it appears that thiourea and hydroxythiourea are the most antioxidant of the six molecules.

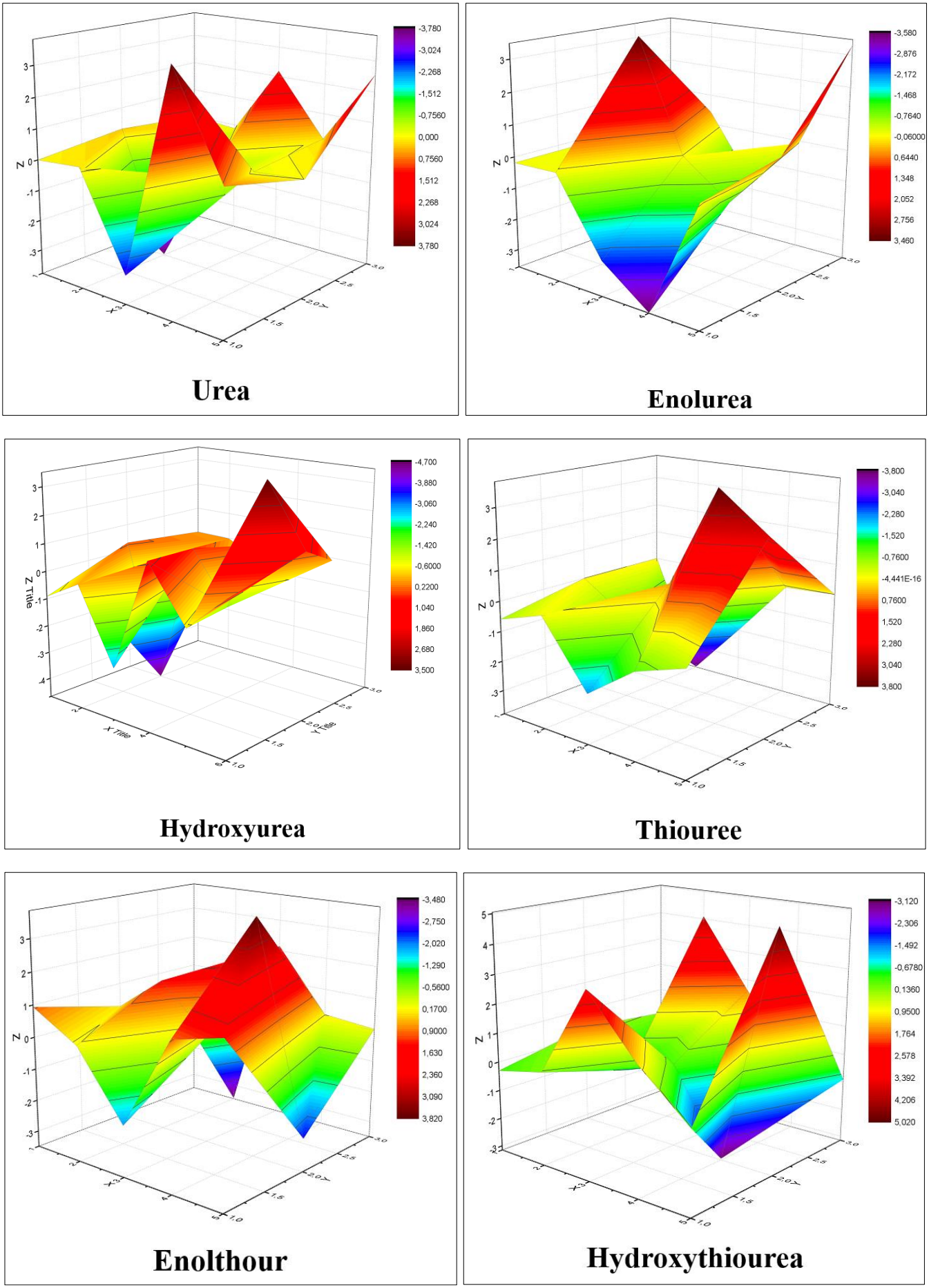


Fig 4: representation of the molecular electrostatic potentials at the 3D level of urea, Enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea

Conclusion

A theoretical study of the chemical reactivities of urea, Enolurea, thiourea, hydroxyurea, hydroxythiourea and enolthiourea, by the method M06-2X/6-311++G (d, p). The comparison between the calculated values of the different electronic, thermodynamic and spectroscopic parameters allowed:

- To identify the oxygen atoms of the O-H groups[8], O-H[9], O-H[7] and O-H[8], as the most important sites for the manifestation of the antioxidant activity of hydroxythiourea, hydroxyurea, enolthiourea and Enolurea respectively.
- That thiourea and hydroxythiourea are the most antioxidant of the six molecules.
- to note that the replacement of the oxygen atom by that of sulfur considerably modifies the antioxidant properties of the urea molecule.
- to note that the mechanism passing by the elimination of atomic hydrogen by homolytic rupture of bond (HAT), as the most probable for the trapping of a radical by each of the molecules.

Regarding the prediction of the antioxidant properties of the molecule and the studied complexes, the theoretical results are in agreement with the experimental data published in the literature.

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