



Review Article

Interaction of thiourea and urea with maleimide: comparative theoretical DFT study



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ABSTRACT

A gas-phase mechanism reaction of maleimide with urea or thiourea was studied by DFT method. A comparison between atomic charges, Fukui index evaluation and Frontier orbitals theory was carried out. The involvement of pre- and post-reactive complexes was examined as the reaction profiles are modelled. For each mechanism, two approaches have been proposed through nitrogen and sulfur (for thiourea), or oxygen and nitrogen (for urea) attack. The results indicate that the carbon double bonded of maleimide is the electrophilic site and chalcogen atom of chalcogenourea is the nucleophilic one. The obtained activation free energies predict suitable specie that could be generated after an opening-cycle and new bonds formation. Consequently, the sulfur attack of thiourea was promoted on oxygen (urea) which is in accordance with the experiments.

1. Introduction

Compounds containing heterocyclic ring system with several alkaline centers, nitrogen, oxygen and sulfur atoms have a great interest as they belong to class of compounds in medicinal chemistry and biochemical applications. Because of their varied biological activities, thiazolidines, thiazolidinones and their derivatives have attracted a great attention of organic chemists in recent years. These classes of compounds displayed a broad spectrum of biological activities including antitumor [1, 2], anticancer [3], anti-inflammatory [4], antimicrobial [5, 6, 7, 8], antioxidant [9] and antiproliferative [10]. Consequently, chemists still enthusiastically pursue the syntheses and activity evaluation of thiazolidine or thiazolidinone derivatives [11, 12]. Thiazolidinone derivatives were investigated using both theoretical and experimental tools, due to their chemical reactivity.

New structures were obtained from the maleimide and thiourea mechanism tested by Kolli and collaborators [13]. The synthetic

derivative was obtained and analyzed using analytical techniques such as ¹H and ¹³C NMR, IR elemental analysis. In this paper, two approaches were considered; the first one consists on the attack of maleimide's double bond by thiourea's sulfur. However, in the second one, thiourea's ones pairs of the two nitrogens can play a role of electron donor and react with maleimide. The same mechanism was involved in the case of urea's oxygen. The aim of this work is to have an insight from the famous Density Functional Theory (DFT) on the reaction mechanisms occurred between the maleimide and the thiourea or the urea (Scheme 1).

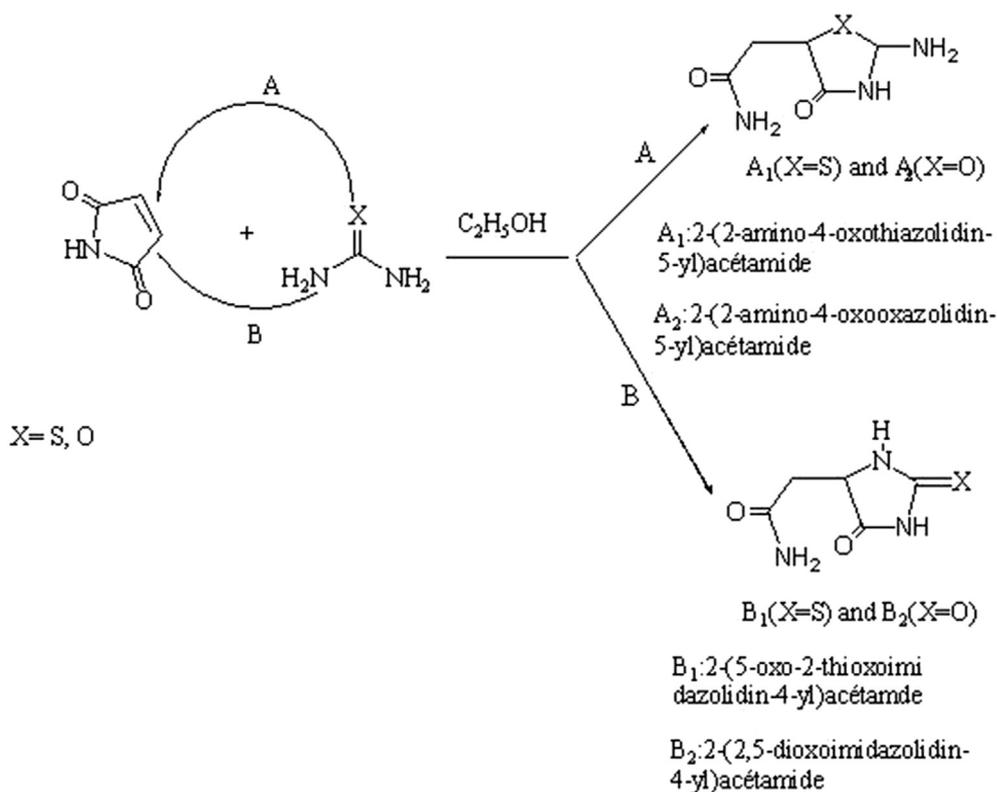
2. Main text

2.1. Computational details

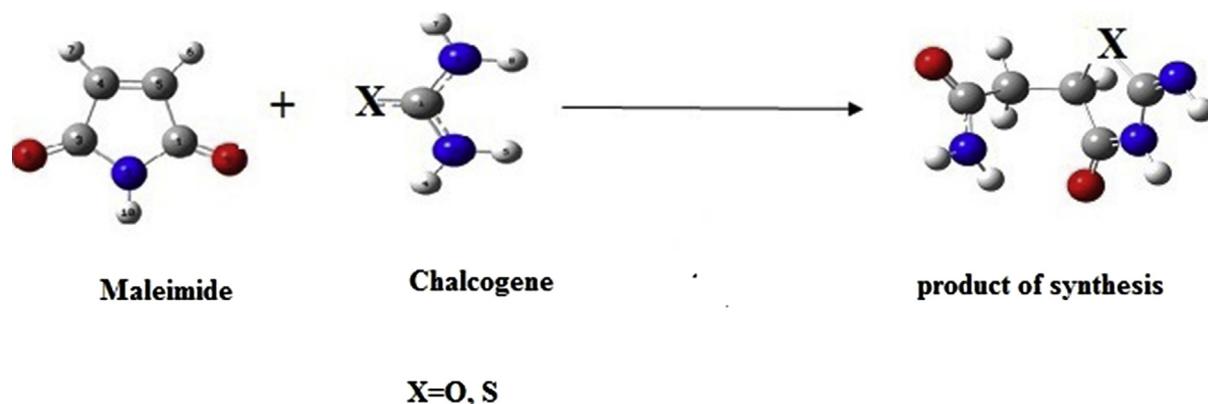
Calculations were based on DFT method using the B3LYP and CAM-B3LYP functionals [14, 15] with the 6-31G (d) and 6-311++G (d,p) basis sets respectively. Optimization of geometries (Scheme 2) was

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Scheme 1. Representation of the studied mechanism.



Scheme 2. Optimized structures of maleimide, chalcogene and products of synthesis.

Table 1
Atomic charges of maleimide.

Atoms	Charges			
	B3LYP/6-31G(d)		CAM-B3LYP/6-311++G(d,p)	
	MPA	NPA	MPA	NPA
C ₁	0.598	0.667	-0.030	0.669
N ₂	-0.662	-0.695	-0.230	-0.685
C ₄	-0.162	-0.266	0.050	-0.229
O ₈	-0.459	-0.538	-0.304	-0.543

performed by the Berny gradient analysis method [16] and the stationary points were characterized by frequency calculation.

Transition states were performed by QSTn (n = 2, 3) [17] and scan methods [18]. A single imaginary frequency may confirm the determined transition state. The IRC (Intrinsic Reaction Coordinate) calculation [19] has been performed to confirm the smooth transition from the reactants to product through the respective transition state. Therefore, the energetic profile of each elementary step could be plotted and the transition state for both minima could be checked. In order to predict the most favorable attack sites (i.e. electrophilic and nucleophilic), Mulliken (MPA) [20] and Natural Population Analysis

Table 2Atomic charges (q_i) of thiourea and urea.

	B3LYP/6-31G(d)				CAM-B3LYP/6-311++G(d,p)			
	Urea (X = O)		Thiourea (X = S)		Urea (X = O)		Thiourea (X = S)	
	MPA	NPA	MPA	NPA	MPA	NPA	MPA	NPA
q_X	-0.500	-0.644	-0.327	-0.277	-0.396	-0.657	-0.451	-0.263
q_N	-0.743	-0.898	-0.722	-0.826	-0.389	-0.851	-0.267	-0.802

Table 3Reactivity indices f_i^+ of maleimide and f_i^- of thiourea/urea.

Maleimide								
	B3LYP/6-31G(d)				CAM-B3LYP/6-311++G(d,p)			
	MPA	NPA	MPA	NPA	MPA	NPA	MPA	NPA
$f_{C_2}^+$	0.094	0.086	0.026	0.081				
$f_{C_3}^+$	0.077	0.153	0.136	0.173				
	B3LYP/6-31G(d)				CAM-B3LYP/6-311++G(d,p)			
	Urea (X = O)		Thiourea (X = S)		Urea (X = O)		Thiourea (X = S)	
	MPA	NPA	MPA	NPA	MPA	NPA	MPA	NPA
f_X^-	0.356	0.501	0.673	0.734	0.472	0.563	0.595	0.749
f_N^-	0.106	0.169	0.049	0.075	0.133	0.161	0.024	0.079
f_N^-	0.106	0.169	0.049	0.075	0.134	0.161	0.024	0.079

$$f_i^+ = q_i(N+1) - q_i(N)$$

$$f_i^- = q_i(N) - q_i(N-1)$$

$q(N)$: charge of neutral species.

$q(N-1)$ and $q(N+1)$: charge of cationic and anionic species respectively.

(NPA) [21] charge calculations were carried out together with the Fukui indices [22, 23]. All calculations were performed with Gaussian package [24] and all the structures represented have been mapped using GaussView [25].

2.2. Results and discussion

Theoretical atomic charges and Fukui functions have been calculated for each atom in the molecule and they provided an insight in directing the incoming nucleophiles for the attack of electrophiles.

2.2.1. Atomic charges

The atomic charges derived from Mulliken population analysis (MPA) and Natural population analysis (NPA) are reported in Table 1 for selected atoms of maleimide, and in Table 2 for heteroatoms of urea and thiourea. Table 1 shows that both MPA and NPA charges have negative values for N_2 , C_4 and O_8 atoms, whereas, NPA charges of C_1 are positive, it is an electrophilic site and undergoes nucleophilic attack. However, it has been experimentally observed that in most cases, the nucleophilic attack takes place at the double bonded carbon. Hence, it is difficult to predict from atomic charge values, which are the reactive sites of this compound. The C_1 atom has a negative value of MPA charge with CAM-B3LYP/6-311++G (d,p), showing that Mulliken population analysis has a problem concerning the relatively large basis set and methods dependence.

Nitrogen atom is more negative than oxygen and sulfur atoms for both urea and thiourea (Table 2). The chalcogens atoms are less nucleophile

than the nitrogen one because N is characterized by the largest negative charge value.

2.2.2. Fukui function

The absolute values of condensed Fukui function values for electrophilic attack calculated at B3LYP/6-31G(d) and CAM-B3LYP/6-311++G(d,p) levels of theory are shown for relevant atoms in urea and thiourea (Table 3). The highest value belongs to chalcogens atoms. In addition, Fukui values obtained with both levels illustrate the same tendencies. This means that X atom (X = O, S) should be the nucleophilic site. Moreover, the sulfur atom is mostly a reactive site towards an electrophilic attack. The highest values of Fukui functions are located on NPA. It is noticeable that the MPA and NPA derived Fukui functions predict the same trend.

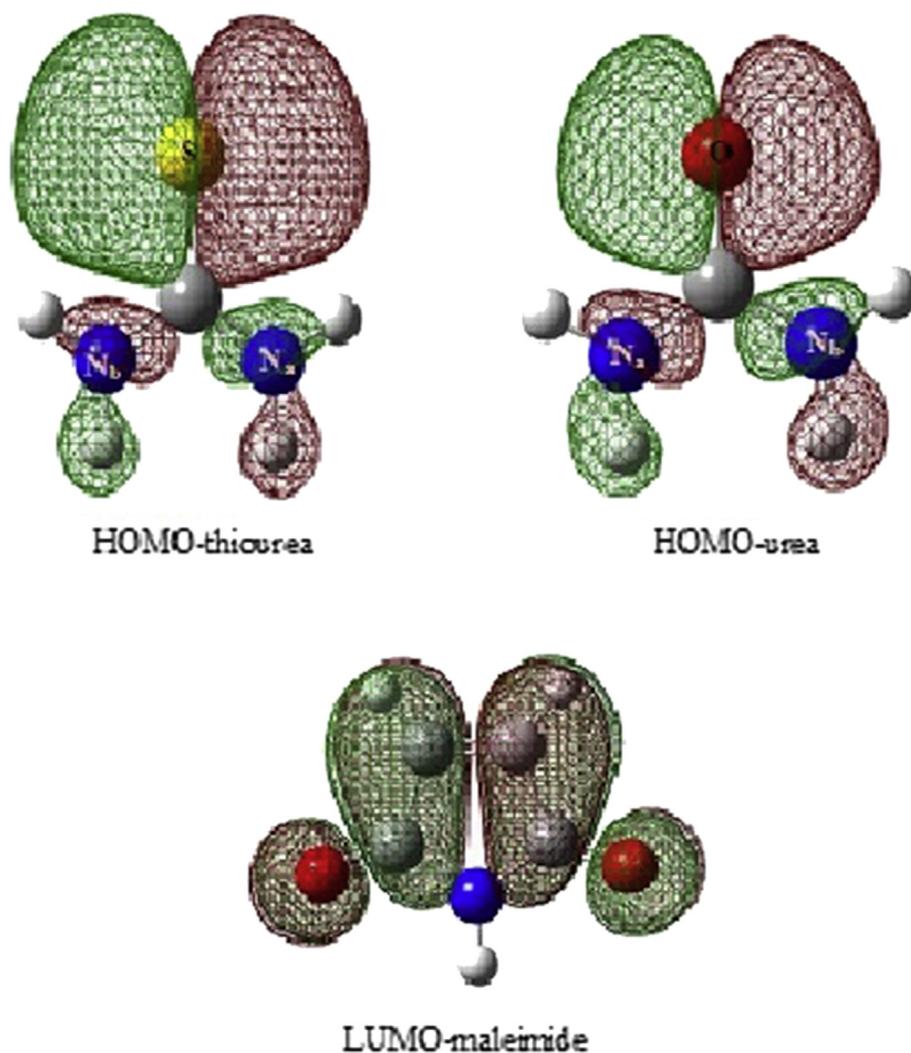
2.2.3. Molecular orbitals

The frontier molecular orbitals of maleimide, urea and thiourea are analyzed. The HOMO of urea and thiourea, and the LUMO of maleimide are illustrated in Scheme 3. For the maleimide, π molecular orbitals are localized on C_1 - C_5 and C_3 - C_4 accordingly to the LUMO shape. However, for both urea and thiourea, the weight of HOMO in chalcogen atom is more important than nitrogen atom. It is noticeable that the greatest extension value of HOMO is observed for sulfur atom. According to the molecular orbital analysis, the relative reactivity can be explained. The π molecular orbital delocalization agrees well with the reactivity behavior of maleimide. The weight of the chalcogen atom in the HOMO shape on sulfur atom suggests its exceptional reactivity in electrophilic reactions.

The HOMO-LUMO energy gaps were calculated for maleimide, urea and thiourea (Table 4). The obtained results indicate that the energy gap of thiourea/maleimide is relatively lower than urea/maleimide. All these data arising from frontier orbitals analysis, energy gaps and Fukui indices specify that the reaction is carried out with chalcogen atom of chalcogenourea and double bonded carbon of maleimide. Moreover, the reaction between thiourea and maleimide is promoted, which is in accordance with the experimental observations [26, 27]. In our recent studies in gas phase and in solution [28], sulfur atom appears to be more reactive than oxygen and the reactivity of oxygen atom in solution becomes very low.

2.2.4. Chalcogenourea on maleimide

2.2.4.1. Thiourea mechanism on maleimide by sulfur attack. The thiourea mechanism on the maleimide involves three basic steps. The transition state TS is defined in each step through a single imaginary frequency. Each elementary stage is characterized by an initial state denoted (IS), a transition state (TS) and a final state (FS). In the first elementary step, the approach is made by the sulfur atom of thiourea on one of the carbon atoms of the maleimide. A transition state was also determined and noted TS₁. An imaginary frequency about i223



Scheme 3. Representation of the density of reagents.

Table 4

 E_{HOMO} , E_{LUMO} and Gap energies in eV.

Compounds	B3LYP/6-31G(d)		CAM-B3LYP/6-311++G(d,p)	
	E_{HOMO}	E_{LUMO}	E_{HOMO}	E_{LUMO}
Maleimide	-7.3	-3.1	-9.8	-1.9
Thiourea	-5.7	-1.9	-7.62	-0.8
Urea	-6.8	-0.9	-8.9	-0.1
Gap1(Thiourea/Maleimide)	2.6		5.7	
Gap2 (Urea/Maleimide)	3.7		7.1	

Where:

$$\text{Gap1} = |E_{\text{HOMO}}(\text{Thiourea}) - E_{\text{LUMO}}(\text{Maleimide})|$$

$$\text{Gap2} = |E_{\text{HOMO}}(\text{Urea}) - E_{\text{LUMO}}(\text{Maleimide})|$$

cm^{-1} and $i259 \text{ cm}^{-1}$ was obtained with B3LYP/6-31G(d) and CAM-B3LYP/6-311++G(d,p) respectively. This step is characterized by the formation of a stable compound following S–C bond formation. The second stage is characterized by the formation of a new five-membered ring. A bond is formed between the nitrogen atom N_{12} and the carbon atom C_5 , followed by the migration of hydrogen H_{13} to bind to oxygen O_6 , leading to an alcohol function. A transition state

denoted TS_2 was localized with an imaginary frequency about $i1064 \text{ cm}^{-1}$ and $i1034 \text{ cm}^{-1}$ respectively with B3LYP/6-31G(d) and CAM-B3LYP/6-311++G(d,p). The final compound of the second elementary step is unstable; this last stage requires an opening of the cycle at the $\text{C}_5\text{--N}_7$ bond. A TS_3 transition state was easily determined, characterized by an imaginary frequency equal to $i112 \text{ cm}^{-1}$ with B3LYP/6-31G(d) and to $i1045 \text{ cm}^{-1}$ with CAM-B3LYP/6-311++G(d,p).

Fig. 1 illustrates the energetic profiles of three elementary stages of the sulfur's thiourea attack on one of the double bonded carbons of the maleimide. It is noticeable that the first stage of the mechanism is characterized by relatively low energy barrier in both methods. The reaction coordinate obtained by CAM-B3LYP is closer to the experimental value. The structure of the transition state is similar to the initial state, according to the Hammond postulate [29]. The second step gives a higher value of activation enthalpy compared to the first step, and is considered as the rate determining step. Thus, the bond lengths are similar to both methods. The final product of the second stage is very unstable due to the ring tension. The third step of the mechanism provides an opening at the N–C bond, which is characterized by relatively weak activation enthalpy compared to the second step.

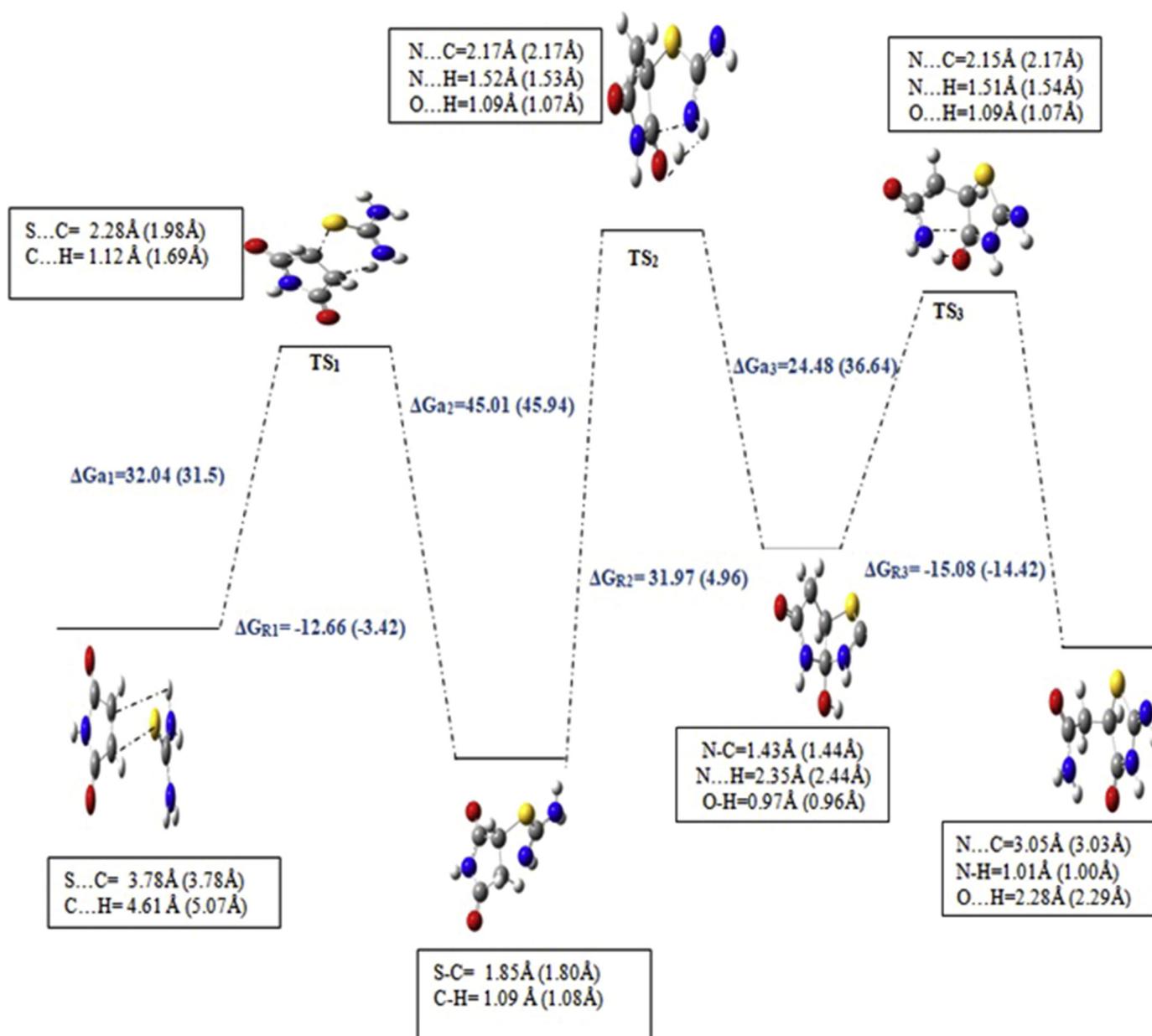


Fig. 1. Energetic diagram with thiourea mechanism (ΔG in kcal/mol) values issued from B3LYP/6-31G(d) (CAM-B3LYP/6-311++G(d,p)).

2.2.4.2. Urea mechanism on the maleimide by oxygen attack. To release a comparative theoretical study between thiourea and urea, calculations using B3LYP/6-31G(d) and CAM-B3LYP/6-311++G(d,p) were performed in order to study the urea mechanism on the maleimide, by oxygen attack. For this purpose, three basic steps have been carried out, where each species has been optimized. Similarly to thiourea mechanism, the urea attack can be described by three steps. In the first step, a C–O bond formation followed the approach of both reagents, namely the oxygen atom of urea with one of the double bonded carbons of maleimide. A TS₄ transition state was localized and characterized by an imaginary frequency equal to $i261\text{ cm}^{-1}$ and $i411\text{ cm}^{-1}$ respectively with B3LYP/6-31G(d) and CAM-B3LYP/6-311++G(d,p). The new bond formed between N₁₆ nitrogen atom and C₅ carbon atom was generated during the formation of a second ring. Hydrogen H₁₅ will migrate to the oxygen atom O₆ in order to form an alcohol function and obtain a five-

membered ring. A transition state TS₅ is assigned to an elongation mode characterized by an imaginary frequency equal to $i1447\text{ cm}^{-1}$ and $i1539\text{ cm}^{-1}$ through B3LYP/6-31G(d) and CAM-B3LYP/6-311++G(d,p) method respectively. In the last step of the urea mechanism on the maleimide by oxygen attack, the cycle-opening at the bond C₅–N₇ is due to the high cycle tension. This step is characterized by a transition state TS₆ for which an imaginary frequency is obtained at $i896\text{ cm}^{-1}$ with B3LYP/6-31G(d) and $i971\text{ cm}^{-1}$ with CAM-B3LYP/6-311++G(d,p).

The energetic profile of the urea mechanism by the oxygen attack on the maleimide is shown in Fig. 2. Unlike thiourea mechanism, the first elementary step of the urea mechanism gives relatively high activation energy. It is noticeable that the approach of urea oxygen to the carbons double bond of maleimide requires high energy. However, the second stage is characterized by a bonding formation, which led to a new ring. This step is decisive because the energy barrier is quite important and the

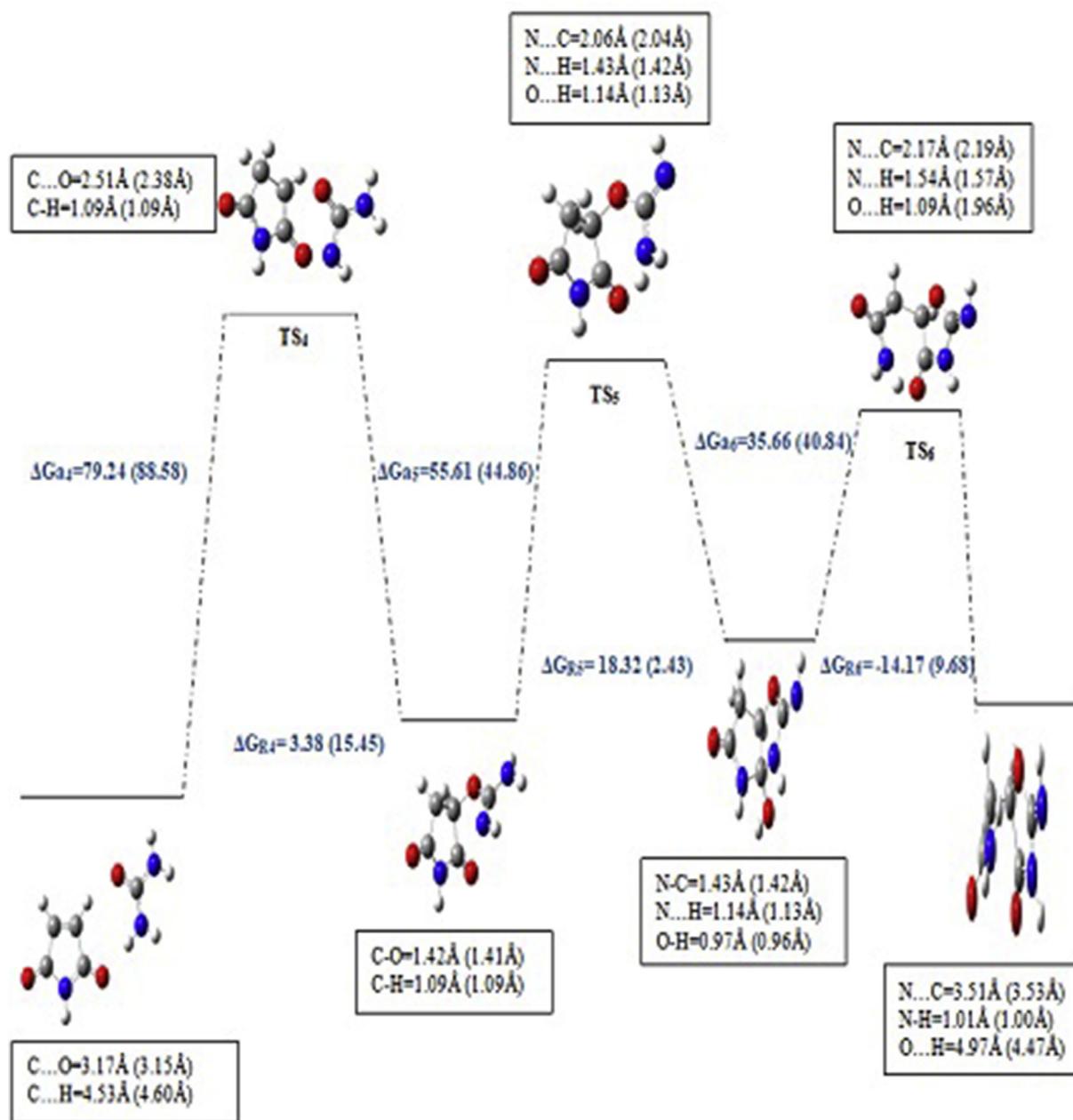


Fig. 2. Energetic diagram with urea mechanism (ΔG in kcal/mol) values issued from B3LYP/6-31G(d) (CAM-B3LYP/6-311++G(d,p)).

Table 5

Gibbs free activation (ΔG_a) and reaction (ΔG_R) energies (in kcal/mol). for both mechanisms.

	B3LYP/6-31G(d)		CAM-B3LYP/6-311++G(d,p)	
	ΔG_a	ΔG_R	ΔG_a	ΔG_R
Thiourea mechanism	32.0	-12.7	31.5	-3.4
	45.0	31.9	45.9	4.9
	24.5	-15.1	36.7	-14.4
Urea mechanism	79.2	3.4	88.6	15.5
	55.6	18.3	44.9	2.4
	35.7	-14.2	40.8	-9.7

Table 6

Gibbs free activation (ΔG_a) and reaction (ΔG_R) energies (in kcal/mol) for both mechanisms.

Methods	B3LYP/6-31G(d)		CAM-B3LYP/6-311++G(d,p)	
	ΔG_a	ΔG_R	ΔG_a	ΔG_R
Thiourea mechanism with nitrogen approach	61.7	-7.3	60.0	-5.8
	64.1	49.5	48.8	17.7
	53.5	-15.0	73.0	-11.9
Urea mechanism with nitrogen approach	32.3	-8.10	59.5	-6.9
	70.9	35.1	72.4	28.0
	33.8	-39.4	39.0	-36.0

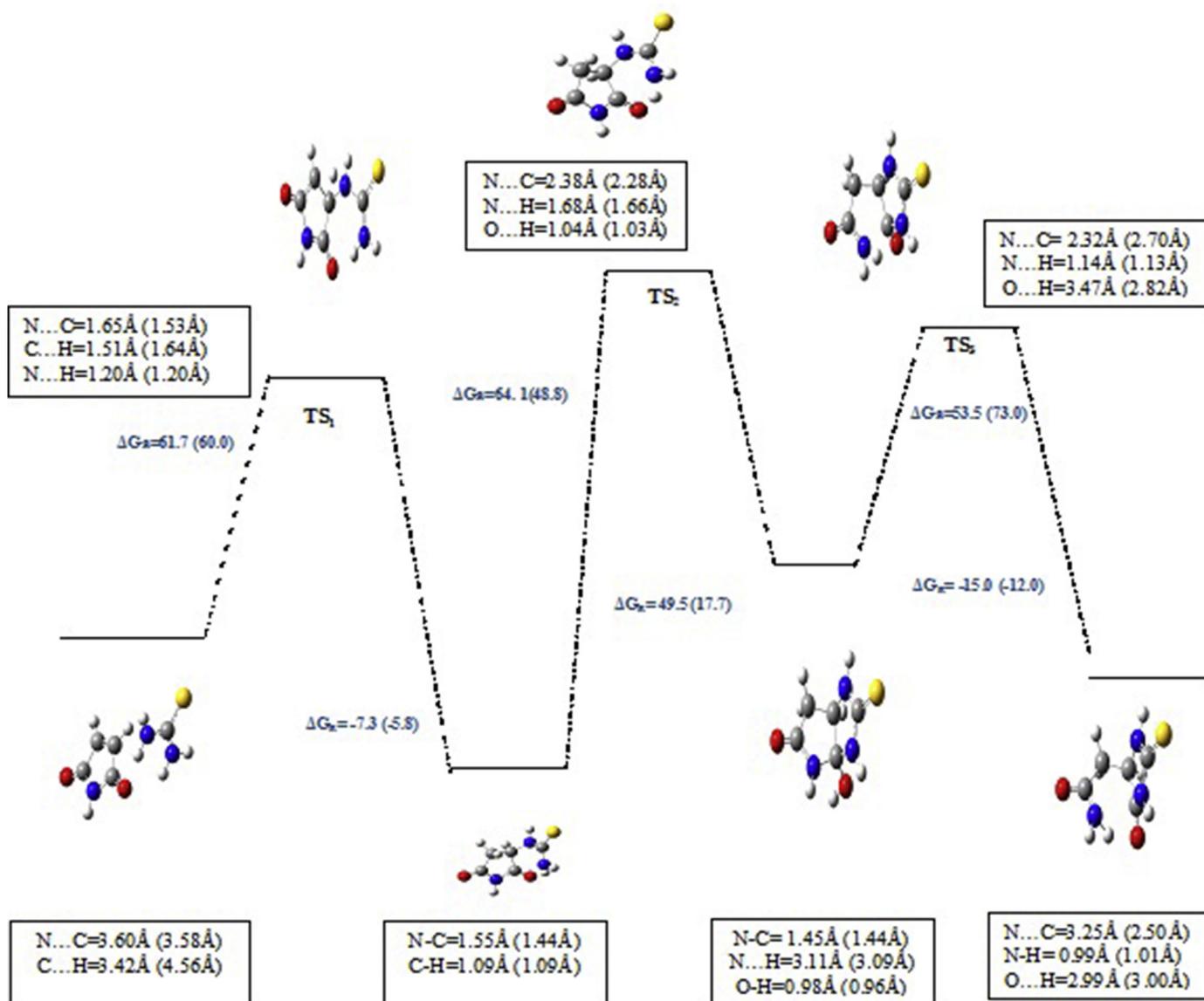


Fig. 3. Energetic diagram with thiourea mechanism by nitrogen approach (ΔG in kcal/mol) values issued from B3LYP/6-31G(d) (CAM-B3LYP/6-311++G(d,p)).

coordinate reaction is similar on both methods. The cycle tension makes the final compound of the second step very unstable, which leads to C–N bond breaking. This step is exothermic and relatively fast since it requires less energy.

Fig. 2. All activation and reaction energies of both reactions of thiourea and urea on maleimide are summarized in Table 5.

The results for pathway B, the nitrogen attack in thiourea and urea, are summarized in Table 6.

On the basis of the results obtained by considering track B, that the energy barriers are relatively high compared with those obtained with track A.

Energy barriers are presented in Figs. 3 and 4 respectively.

3. Conclusion

A theoretical study of reactivity was carried out using the density functional theory (DFT) for maleimide. Reactivity indexes derived from DFT have been successfully applied in understanding of chemical reactivity. Global and local descriptors such as frontier

molecular orbital shapes and energy gaps, atomic charges and Fukui indexes were determined and used to identify the differences in the reactivity of compounds. Two approaches have been proposed for thiourea and urea mechanism on the maleimide through sulfur and nitrogen attack for thiourea mechanism. However, for urea mechanism, the attack is rather realized by oxygen and nitrogen on one of the double bonded carbons of the maleimide. It should be concluded that:

1. The obtained Fukui values with two levels illustrate the same tendencies. This means that chalcogen atom ($X = O, S$) of urea or thiourea should be a nucleophilic site and the double bonded carbon of maleimide is an electrophilic one.
2. Maleimide molecular orbital shapes present the π molecular orbitals, which are localized on C_1 – C_5 and C_3 – C_4 . Moreover, the highest occupied molecular orbital is localized on chalcogen atom with a highest extension value.

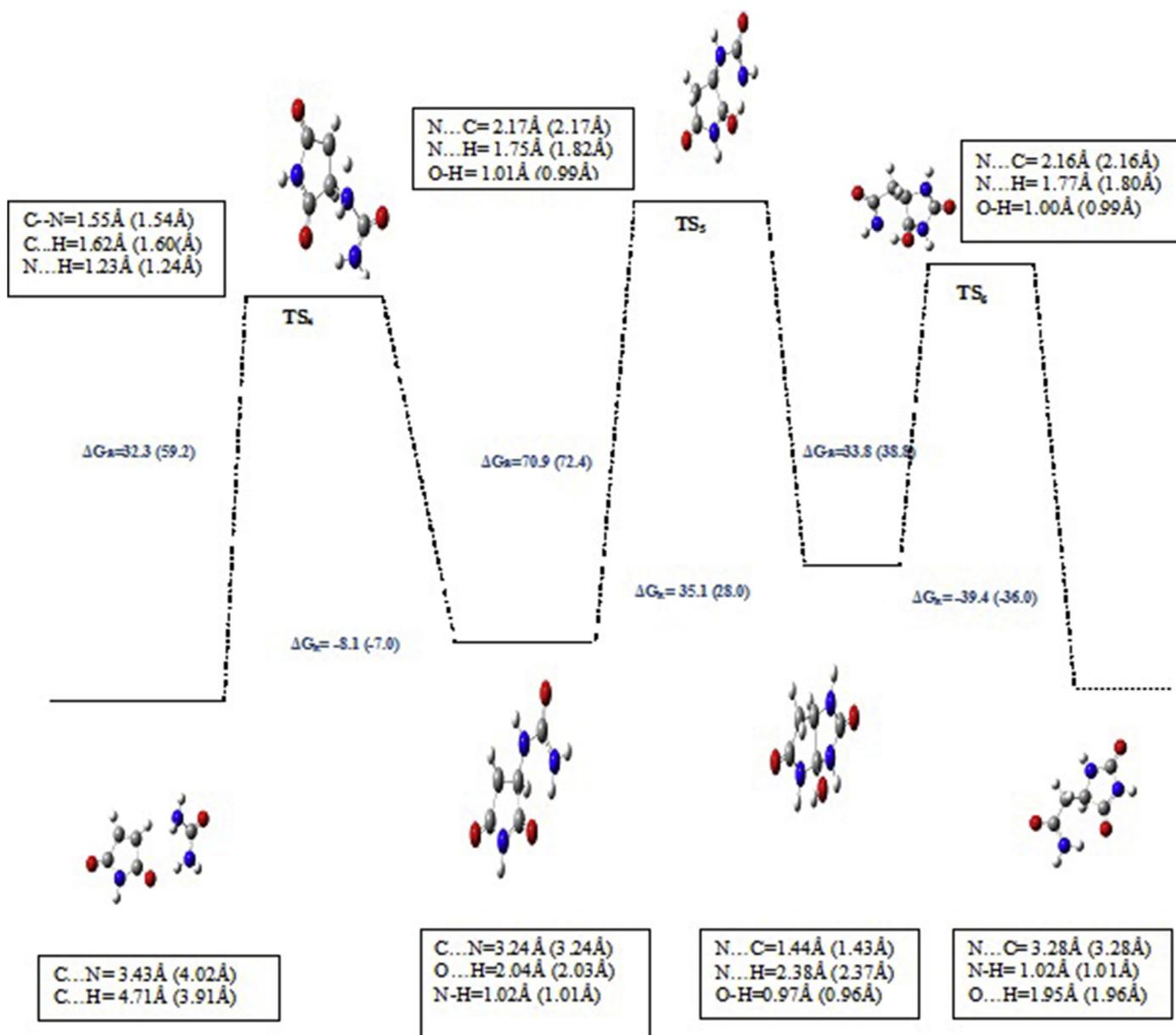


Fig. 4. Energetic diagram with urea mechanism by nitrogen approach (ΔG in kcal/mol) values issued from B3LYP/6-31G(d) (CAM-B3LYP/6-311++G(d,p)).

- The reaction is carried out with chalcogen atom of chalcogenourea and double bonded carbon of maleimide.
- The determined step is considered as the second step, where the activation free energy is the highest and it being rate-determining step.
- The values of both Gibbs free energy of activation and reaction for the thiourea mechanism on the maleimide are lower than those obtained for the urea mechanism on maleimide.
- Mechanism obtained by the sulfur approach with both methods is favored.

Declarations

Author contribution statement

Yamina Akacem, Bellara Nedjar-Kolli: Conceived and designed the experiments.

Dalila Hammoutene: Analyzed and interpreted the data; Wrote the

paper.

Karima Zaioua, Nabila Achoui: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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