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RESEARCH ARTICLE

Applying density functional theory on tautomerism in 3,4-dihydropyrimidin-2(1*H*)-ones

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In the present study, the density functional theory (DFT) and Gibbs free energy calculations were performed to investigate the stability and tautomerism of C4-substituted-3,4-dihydropyrimidin-2(1*H*)-ones. Three different forms are possible for the ethyl 3,4-dihydropyrimidinones (ethyl 4-aryl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylates, ethyl 4-aryl-2-hydroxy-6-methyl-1,4-dihydropyrimidine-5-carboxylates and ethyl 4-aryl-2-hydroxy-6-methyl-3,4-dihydropyrimidine-5-carboxylates) forms that the most stable form is ethyl 4-aryl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylates (keto-form). The obtained data showed that the substitution on the C4-substitut position can be effective on the equilibrium constant (K_{eq}).

Keywords Gibbs free energy, density functional theory (DFT), tautomerism, dihydropyrimidin-2(1*H*)-ones, Keto-Form

1 Introduction

In 1893, the Italian chemist Pietero Bigginelli reported a condensation reaction between ethyl acetoacetate, benzaldehyde and urea to obtain a heterocyclic system of 3, 4-dihydropyrimidinone (DHPM), which is known as Biginelli reaction [1].

The 3,4-dihydropyrimidinones (DHPMs) compounds have aroused much interest in recent years due to their wide spectra of biologic activities and medicinal application as calcium channel blockers, antihypertensive, antibacterial, antitumor and anti-inflammatory agents [2–6].

Recently, computational methods have begun to be employed in studying the geometry of the 3,4-dihydropyrimidinones [7–9]. Furthermore, they used the details obtained from the optimization of the DHPMs as very useful substrate in the mechanistic studies of the oxidation reactions [7–9]. However a vast amount of information on these DHPMs is available including determination of the crystal structures of these compounds [10–13].

Heterocycles often display tautomerism as a result of the transfer of a proton, such as keto-enol, amine-enol and imine-amine equilibrium. However, several theoretical and experimental papers were published about the tautomerism of these compounds [14–16]. In all these experimental studies, the keto form of DHPMs are confirmed [11,17–19], but the aim of this study is to carry out systematic theoretical investigation of the keto-iminol form of these compounds.

2 Calculation methods

The quantum chemical calculations were performed with GAUSSIAN 98 suite of programs [20]. Full geometry optimizations were carried out using the density functional theory (DFT) calculations with the B3LYP/6-31 + + G** and B3LYP/6-31G** levels.

3 Results and discussion

Considering the importance of the configuration of the aryl group at the C4-position of heterocyclic ring on the biologic and pharmacological activities of DHPMs, in the present study, we used B3LYP/6-31 + + G** computations to study the structure of the keto-iminol form of these compounds. To obtain enthalpies, free energies and calculation of the gas phase equilibrium constant reactions of DHPMs, a vibrational analysis seemed necessary.

We studied the general structures of the DHPMs with aryl-up (antagonist) conformation in previous paper [9]. The data obtained from optimization of ethyl 4-aryl-2-hydroxy-6-methyl-1,4-dihydropyrimidine-5-carboxylates show that the structures of these compounds are similar to ethyl 4-aryl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylates. The general structure of these compounds is shown in Fig. 1.

The geometries of 1,4-dihydropyrimidines were optimized using DFT B3LYP method with 6-31 + + G** basis set. The analysis of the optimized structures of dihydropyrimidines shows that the six-member ring adopt a boat conformation, flatted at N_1 toward an envelope conformation, with a *pseudo-axial* orientation of the C4-substituent, i.e., in all derivatives, the C4-substitution adopts the *up* orientation with respect to the heterocyclic ring boat plane. Furthermore, the conformation of the carboethoxy group ($C_7 = O_8$) can be considered approximately as *s-trans* with respect to their adjacent $C_5 = C_6$ bonds of the 1,4-dihydropyrimidines ring.

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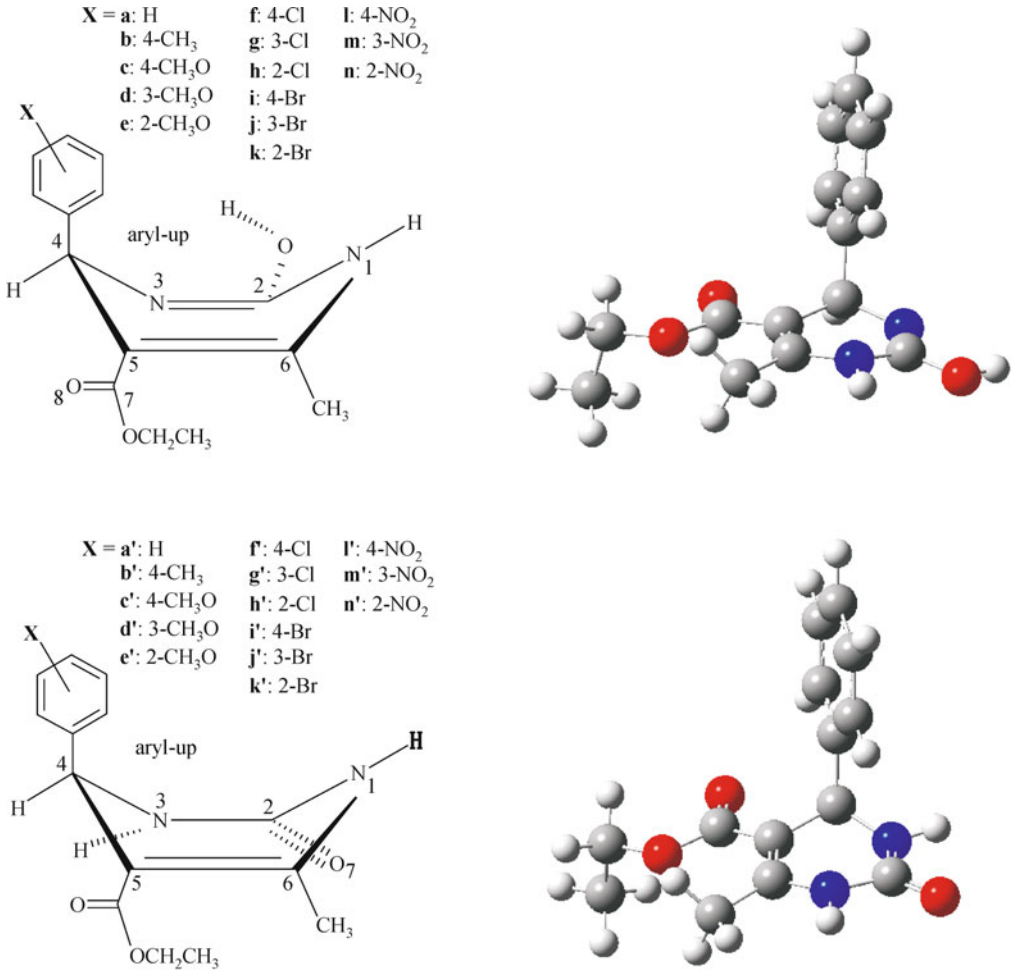

Figure 1 General structure of the ethyl ester forms of 1,4-dihydropyrimidines and 3,4-dihydropyrimidin-2(1*H*)-ones with aryl-up conformation and the numbering scheme used in this work.

4 Thermochemical analysis

The enthalpies (ΔH_f°) and Gibbs free energies (ΔG°) of the tautomerism reaction of 1,4-dihydropyrimidines are calculated based on the equilibrium reaction given in Fig. 2 using the B3LYP hybrid functional with geometry optimization and frequencies at the B3LYP/6-31G** level. These parameters are calculated for the three forms of ethyl 4-aryl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (**I**), ethyl 4-aryl-2-hydroxy-6-methyl-1,4-dihydropyrimidinone-5-carboxylate (**II**)and ethyl 4-aryl-2-hydroxy-6-methyl-3,4-dihydropyrimidinone-5-carboxylate (**II**).

The results of these calculations of the enthalpies (formation and the equilibrium reaction, $\Delta H_f^\circ, \Delta H_{eq}^\circ$)) and Gibbs free energies (formation and the equilibrium reaction, $(\Delta G_f^\circ, \Delta G_{eq}^\circ)$) of these compounds are reported in the Tables 1 and 2.

The analysis of the data reported in Table 1 shows that the

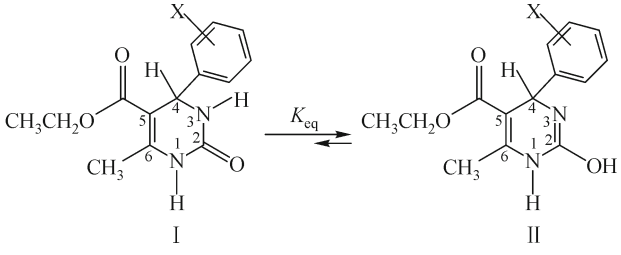

Figure 2 Tautomerism between ethyl 6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (**I**) and ethyl 2-hydroxy-6-methyl-4-phenyl-3,4-dihydropyrimidinone-5-carboxylate (**II**)

formation enthalpies (ΔH_f°) (of 3,4-dihyropyrimidi-2(1*H*)-ones are larger than the 1,4-dihydropyrimidines because the energy of $C_2 = O_7$ bond is more than that of the $C_2 = N_3$ bond and the bond length of carbonyl group is smaller than that of the imine group. (The bond lengths for **a′** and **a** compounds are 1.22670 Å, 1.26695 Å respectively).

Table 1 The formation and the equilibrium reaction enthalpies ΔH_f°,ΔH_{eq}° of some 3,4-dihyropyrimidi-2(1*H*)-ones and 1,4-dihydropyrimidines calculated based on the B3LYP/6-31G**.

$\Delta H_f^\circ/(\mathrm{kJ\cdot mol^{-1}})$				$\Delta H_{eq}^\circ/(\mathrm{kJ\cdot mol^{-1}})$
Comp.	3,4-dihyropyrimidiones	Comp.	1,4-dihydropyrimidines	Equilibrium reaction
a′	−629.9	**a**	−555.9	74.0
b′	−706.8	**b**	−632.3	74.5
c′	−815.0	**c**	−740.0	75.0
d′	−813.2	**d**	−739.6	73.6
e′	−816.2	**e**	−734.9	81.3
f′	−630.2	**f**	−558.1	72.1
g′	−629.7	**g**	−558.6	71.1
h′	−615.3	**h**	−545.4	70.0
i′	−539.2	**i**	−466.9	72.2
j′	−538.9	**j**	−468.1	70.9
k′	−531.5	**k**	−461.6	69.9
l′	−605.6	**l**	−536.0	69.5
M′	−604.2	**m**	−536.8	67.3
n′	−572.4	**n**	−504.1	68.2

According to the equilibrium reaction enthalpies data reported in the Table 1 for 3,4-dihyropyrimidin-2(1*H*)-ones and 1,4-dihydropyrimidines, we confirm the dynamic nature of 3,4-dihyropyrimidin-2(1*H*)-ones.

The calculations of the formation Gibbs free energies of 3,4-dihyropyrimidin-2(1*H*)-ones and 1,4-dihydropyrimidines compounds show that the keto forms of dihydropyrimidinones are more stable than iminol forms of these compounds. For example, the formation Gibbs free energies (ΔG_f°) of **b′** and **b** compounds are −2407778 and −2407704 KJ/mol respectively. It appears that ethyl 4-(4-methylphenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate is more stable than the ethyl 4-(4-methylphenyl)-2-hydroxy-6-methyl-1,4-dihydropyrimidin-5-carboxylate. Furthermore, the analysis of the equilibrium constant (K_{eq}) data reported in Table 2 shows that the value of 1,4-dihydropyrimidine compounds is less than that of the 3,4-dihydropyrimidin-2(1*H*)-one compounds. For example, the K_{eq} for **f′** and **f** is 3.49×10^{-13}. However, the analysis of the data in Table 2 shows that K_{eq} also depends on the type and position of the substituent on the aryl ring. For example, K_{eq} for 4-methyl aryl (**b**) is larger than K_{eq} for 4-methoxy aryl (**c**) ring. (K_{eq} for these compounds are 1.45×10^{-13}, 7.90×10^{-14} respectively).

According to the K_{eq} data shown in Table 2, the compounds with donating electron substituent on the aryl ring have the least K_{eq} compared with the compounds with acceptor electron substituent on aryl ring. For example, K_{eq} for 4-methoxy (**c**) and 4-nitro (**l**) substituent on the aryl ring are 7.90

Table 2 The formation and the equilibrium reaction Gibbs free energies $(\Delta G_f^\circ,\Delta G_{eq}^\circ)$ and equilibrium constant of some 3,4-dihyropyrimidi-2(1*H*)-ones and 1,4-dihydropyrimidines calculated based on the B3LYP/6-31G**.

$\Delta G_f^\circ/(\mathrm{kJ\cdot mol^{-1}})$				$\Delta G_{eq}^\circ/(\mathrm{kJ\cdot mol^{-1}})$	Equilibrium constant
Comp.	3,4-dihyropyrimidiones	Comp.	1,4-dihydropyrimidines	Equilibrium reaction	K_{eq}
a′	−2304645	a	−2304572	73.5	1.33×10^{-13}
b′	−2407778	b	−2407704	73.2	1.45×10^{-13}
c′	−2605141	c	−2605066	74.7	7.90×10^{-14}
d′	−2605140	d	−2605065	74.5	8.67×10^{-14}
e′	−2605141	e	−2605058	82.9	2.97×10^{-15}
f′	−3510883	f	−3510812	71.1	3.49×10^{-13}
g′	−3510884	g	−3510815	69.6	6.22×10^{-13}
h′	−3510867	h	−3510797	69.4	6.78×10^{-13}
i′	−9052542	i	−9052471	70.9	3.76×10^{-13}
j′	−9052543	j	−9052472	71.4	2.99×10^{-13}
k′	−9052532	k	−9052461	70.2	4.91×10^{-13}
l′	−2841361	l	−2841293	68.6	9.35×10^{-13}
m′	−2841360	m	−2841294	66.7	2.01×10^{-12}
n′	−2841326	n	−2841260	66.9	1.85×10^{-12}

$\times 10^{-14}$ and 9.35×10^{-13} respectively. This can be attributed to the charge density on the N3-*H* atom. For example, the charge density on the N3-*H* atom in the **c** and **l** compounds are + 0.247 and + 0.280 respectively. It seems that increasing the acidity of N3-*H* atom cases makes the iminol form increase as well.

Furthermore, in this paper we investigate the tautomerism between **I** and **III** compounds. Figure 3 shows that the formation enthalpy $\left(\Delta H_f^\circ\right)$ of ethyl 2-hydroxy-6-methyl-4-phenyl-3, 4-dihydropyrimidine-5-carboxylate (**III**) is − 570.9 kJ/mol. However, the formation enthalpy of tautomerism reaction is 59.0 KJ/mol. The data obtained from the formation and the equilibrium reaction Gibbs free energies $\left(\Delta G_f^\circ, \Delta G_{eq}^\circ\right)$ are − 2304587 and 58.5 kJ/mol respectively. Based on these data, the equilibrium constant for this reaction is 5.52×10^{-11}.

The obtained data suggest that the keto form (**I**) is more stable than the iminol form (**III**). The comparison of the thermodaynatic data of ethyl 2-hydroxy-6-methyl-4-phenyl-3,4-dihydropyrimidine-5-carboxylate (**III**) and ethyl 2-hydroxy-6-methyl-4-phenyl-1,4-dihydropyrimidine-5-carboxylate (**II**) shows that the tautomeric form **III** is more stable than form **II**. In the previous paper [9], we reported the charge density of the N_1 and N_3 atoms for some 3,4-dihydropyrimidinones. The data showed that the charge density on the N_3 atom is slightly higher than that on the N_1 atom. However, generation of the tautomeric form **II** is more likely than the tautomeric form **II**.

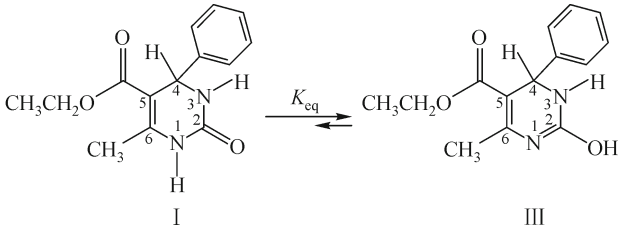

Figure 3 Tautomerism between ethyl 6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one-5-carboxylate (**I**) and ethyl 2-hydroxy-6-methyl-4-phenyl-3,4-dihydropyrimidine-5-carboxylate (**III**)

5 Conclusion

The B3LYP/6-31 + + G(d,p) optimized structures show that in all 1,4-dihydropyrimidines, the heterocyclic ring has a flat boat conformation, and the aryl ring prefers a *pseudo-axial* position on C_4. Furthermore, in the B3LYP optimized structures, the carbonyl group at C5-position is oriented *s-trans* with respect to the $C_5 = C_6$ bond of the 1,4-dihydropyrimidine ring. On the other hand, the structures of these compounds are quite similar to 3,4-dihydropyrimidinones. The present calculations show that the 3,4-dihydropyrimidin-2(1*H*)-one form (**I**) (keto form) is more stable than the 1,4-dihydropyrimidine (**II**) and 3,4-dihydropyrimidine (**III**) forms (iminol form). Based on the results of the present work, we have confirmed that the generation of the 1,4-dihydropyrimidine (**I**) form is more likely than 3,4-dihydropyrimidine (**II**) form because the charge density on the N_3 atom is slightly higher than that on the N_1 atom.

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