Investigation of Tautomeric Equilibria of 6-Hydroxy-5-Flourocytosine and the Effect of Temperature on some equilibria

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Abstract:- Optimal molecular geometries and molecular energies were obtained for 6-Hydroxy-5-Flucytosine(OHFC) , one of the important and new metabolites of Flucytosine,an antifungal agents, with the use of the theoretical ab initio and DFT quantum mechanical calculations .The 6-31G* and 6-31G** Gussian basis sets were employed. 17 possible tautomeric forms were considered. And also thermodynamic properties ($\Delta G, \Delta E, \Delta H$) for tautomeric equilibria between different tautomers were calculated with the frequency calculations. For all calculations levels, OHFC14 form appeared to be the most stable form and it's energy is -569.406642 Hartree at the highest level and OHFC6 form is by 47.76 kcal mol^{-1} less stable than OHFC14.In any case ,30 tautomeric equilibria were considered between17 tautomers.Considering of tautomeric equilibria defines that equilibrium OHFC2 $\rightleftharpoons$OHFC5(T7) is the most stable equilibrium and it's ΔG is -26.750102 Kcal/mol .We classified these equilibria according (CN,CO,NN,NO) structural models .The effect of temperature on the stability of CO models equilibria have been investigated through the DFT level. Changes of free energy and enthalpy were obtained. We continued our investigation on heat capacity at constant pressure (C_P) and equilibrium constant (K_{eq}). It was found that in endothermic reactions, increasing in temperature causes increasing in K_{eq}. In exothermic reactions, increasing in temperature causes decreasing in K_{eq}. And also it was appeared that the values of C_P for all tautomers were increased with temperature.

Key-words: tautomerism, 6-Hydroxy-5-Flucytosine,Nucleotid bases,antifungul,mutation, exothermic, endothermic.

1 Introduction

Tautomerism as one of the possible mechanism of mutation in DNA , has extended area for studies[1]. Tautomerism of nitrogen heterocycles has long been associated in molecular biology with the natural purines and pyrimidines, and the presumed role of their rare tautomeric forms in spontaneous mutagenesis[2].Therefor different theoretical and experimental studies were performed on this process[3]. Nucleic acids are polymer molecules composed of two kinds of bases , purine , and pyrimidine [4]. The parent structure for all purine contains a 6-membered imidazol (3 carbon : 2 nitrogen). Pyrimidines are closed ring organic compounds [5]. The purines include Adenin and Guanin the pyrimidines include thymine , cytosine and uracile[6].In fact understanding of the physicochemical properties and tautomeric behavior of purine and pyrimdine bases of the nucleic acids is of fundamental importance not only in relation to qualitative concepts of chemical binding and physical chemistry but also in relation to molecular biology and the presumed role of the so-called rare tautomers in mutagenesis[7]. Cytosine is the most unstable of DNA bases,deaminating to uracil with an activation energy of $117^{+}_{-}4$ $kjmol^{-1}$ [8].there are different pyrimidine analoges used as prodrug for treatment of cancers like 5-flouroura cile (fu) and 5-flucytosine that uses as antifungal agent [9]. At first flucytosine was synthesized in 1957. It is 4-amino-5-fluoro -2(1H)-pyrimdone[9]. FC is an antifungal agent used for the treatment of severe fungal infections, particularly when combined to amphotericin

B[10]. The antifungal activity of FC results from the intrafungal formation of FU leading to the inhibition of RNA processing and DNA synthesis via FNUCt metabolites. Susceptible fungi contain cytosine deaminase the enzyme that converts FC to FU, whereas human cells lack this enzyme thus creating a theoretical absence of toxicity for FC in humans [11] .Cytosine deaminase., a pyrimidine salvage enzyme, is the only known route by which cytosine is metabolised through hydrolytic deamination to uracil and ammonia. CD also deaminates the antifungal 5-fluorocytosine (5-FC) into 5-fluorouracil (5-FU), a highly cytotoxic compound widely used as a cancer motherapeutic agent[12]. The ^{19}F NMR analysis of biofluids (plasma and urine) from patients treated with FC provided new information concerning FC metabolism in humans by FC, provided the new information about the metabolism of FC in human [13]. Two compounds involving a direct metabolism of 5-FC were found that one of them is OHFC. Ab initio calcutions were performed on the tautomers of cytosine and flucytosine. One of these calcutions was water-mediatedtutmerization of cytosine to the rare imino form that performed by geza fogarasi [14]. This investigation indicated that cytosine has 3 primery low energy forms. The amino-OXO (keto) tautomer is the canonical form, present in DNA in the gas phase , the amino –hydroxy (enol) structure dominates. The imino-oxo tautomer is considered as the rare form, calculations with CCSD(T) method give following relative energies to enol form : ΔE (keto)=1.2-1.6 kcalmol^{-1}, ΔE (imino-oxo)=1.3-2.1 kcalmol^{-1} .[15]In the present work , optimized geometries of 17 possible tautomers of OHFC will be studied with the DFT quantum calcutaions at the 6-31G*, 6-31G** basis set levels and also 30 tautomeric equiblira are considered according to The presence of 17 possible tautomers. Thermodynamic properties of these equilibria will be calculated with the frequency calculations. According to the results, the most stable and unstable tauotomers and equilibrium will be investigated and also we will invesitigat the effect of temperature on thermodynamic properties and C_P of tautomeric equilibria in CO model.

2 computational methods

In this paper for determinating of optimized geometries and energy of different tautomers of OHFC quantum calculations at HF and B3LYP levels were used with the 6-31G*, 631G** basis sets. The thermodynamic properties of tautomeric equilibria of OHFC were obtained by using of the frequency calculations HF and B3LYP levels and 6-31G* , 6-31G* basis sets. All calculations were carried out by using Gussian 98

3 Results and discussion

The 6-31G** optimized geometries and tautomeric equilibria process of OHFC are shown in Fig.2. The optimized primary form of OHFC is shown in Fig.1 According to that atom (H) is moving between which two atoms , we consider structural models of CO,CN,NN,NO that order of these models gives in Table1. We mention the tautomers, From OHFC11 to OHFC17 and the equilibria from T1 To T30. We divided these equilibria according to these models .In this modeling , CN shows methyl imine- vinyl amine case ,CO shows acetaldehyde-vinyl alcohol structure.NO shows formamide - formamidic acid case and finally NN case includ of Imin-amin model.In fact this dividing procedure is based on that part of structure which hydrogen transfer occurs is similar to which structural models(NN,NO,CN,CO).

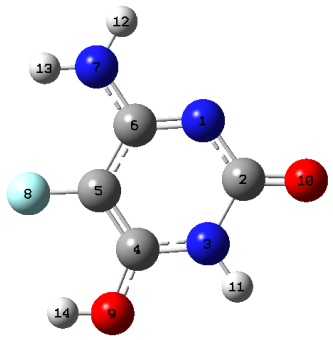

Fig.1.Optimized geometry of OHFC

Table 1:Tautomeric equilibria based onStructura models (CO,CN,NO,NN)

CO	CN		NO	NN
T5	T3	T1	T16	T8
T12	T7	T2	T18	T9
T13	T17	T23	T19	T26
T14	T22	T4	T20	T28
T15	T25	T6	T21	T30
		T10	T24	
		T11	T27	
		T29		

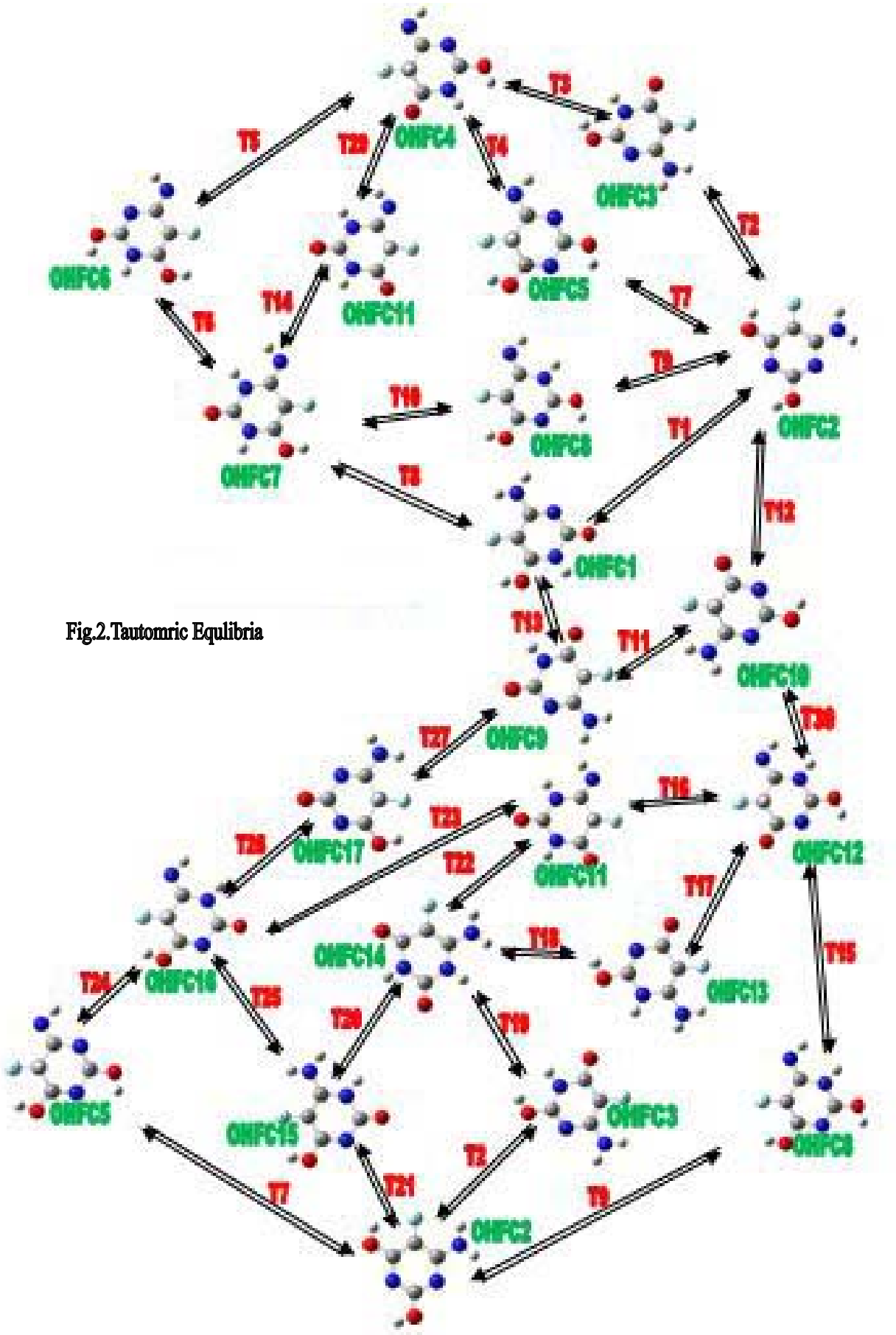

Fig.2.Tautomric Equlibria

3.1 Relative stabilities

The total energies corresponding to these structures are calculated at the HF and at the B3LYP level. Results show that the most stable tautomer is OHFC14 and its energy is-569/406642 Hatree and the most unstable tautomer is OHFC6 and it's energy is –569/34064 Hartree. Relative energies of these 17 tautomers to OHFC14 are obtained. these results

are given in Table 2.According to these amounts , the most stable tautomer to OHFC14 is OHFC9 and the most unstable tautomer to OHFC14 is OHFC6.This order is the same for two these levels.According the results of Table2.we can distinguish the order of stability for these 17 tautomers in two levels. That is following:

At HF levels:
OHFC14>OHFC9>OHFC11>OHFC2>OHFC1>
OHFC10>OHFC3>OHFC15>OHFC7>OHFC13>
OHFC12>OHFC16>OHFC17>OHFC4>OHFC8>
OHFC5>OHFC6.

At B3LYP level :

OHFC14>OHFC9>OHFC11>OHFC2>OHFC1>
OHFC3>OHFC1O>OHFC15>OHFC7>OHFC13
>OHFC16>OHFC12>OHFC17>OHFC4>OHFC8
>OHFC5>OHFC6.

As we see, the order of stability in two levels is different in some cases and its is because of effect of diffusion on DFT method and considering of the electron exchange-correlation energy in this method.

Table2. Relative stability of tautomers at HF and B3LYP levels.

Tautomer	HF/6-31G*	HF/6-31G**	B3LYP/6-31G*	B3LYP/6-31G**
OHFC1	11/13639	12/4748	12/02559	15/02006
OHFC2	7/54015	9/78036	7/21447	11/8461
OHFC3	11/9608	13/2818	17/41901	16/8084
OHFC4	28/6194	28/7186	26/36732	27/73451
OHFC5	34/0229	35/4624	33/39488	36/46834
OHFC6	41/4125	43/5736	43/16939	47/75661
OHFC7	17/3236	18/7393	17/83131	20/66828
OHFC8	28/70743	29/41702	28/773825	33/21978
OHFC9	2/51317	1/22056	0/602597	0/310617
OHFC10	15/0051	16/26379	14/20367	15/662009
OHFC11	6/5085	7/7447	2/90863	2/50941
OHFC12	23/9263	25/2991	22/309845	23/69915
OHFC13	20/7909	19/25011	20/96948	22/092720
OHFC14	0	0	0	0
OHFC15	17/32421	18/67656	17/13038	20/14117
OHFC16	23/9984	24/1996	23/29478	24/71992
OHFC17	25/6482	25/77683	26/36292	27/66062

3.2 Thermodynamic properties

Thermodynamic properties (ΔG,ΔH,ΔE) were calculated according to ε_0+G_{corr} and $\boldsymbol{\varepsilon_0+H_{corr}}$ values .In fact for calculating of (ΔG,ΔH,ΔE) of each equilibrium we take the difference of ε_0+G_{corr} and $\boldsymbol{\varepsilon_0+H_{corr}}$ of the reactant and the products of each reaction. the most ΔG and ΔH is for (T7) OHF5 ⇆ OHFC2 .The least ΔG is for T26 (OHFC16⇆OHF 17) that is – 1.26129 Kcalmol^{-1}. All quantieties at ΔG and ΔH are agree with ΔE that are given in Table 3 and Table4..The results of stability of euilibria from (ΔG,ΔH,ΔE) at two basis set levels are the same.

Table3.Thermodynamic properties for equilibria at HF level in(Kcal/mol)

Tautomerism equbliria						
T1	-2/118	-3/6132	-3/1132	-3/332	-3/215	-4/1698
T2	4/335	4/7534	4/7534	5/456	4/324	4/4244
T3	12/896	11/974	11/9735	11/176	12/809	11/641
T4	6/926	9/0493	6/9954	7/413	7/414	7/862
T5	16/402	17/684	18/2866	15/924	15/925	16/107
T6	-24/623	-26/023	-26/0261	-24/362	-24/362	-24/455
T7	-25/468	-30/745	-26/8423	-27/247	-27/2458	-26/941
T8	-6/891	-6/0743	-6/0743	-7/064	-6/1822	-6/561
T9	-21/923	-22/166	-21/5694	-20/336	-22/335	-21/415
T10	-12/9135	-12/509	-11/8819	-10/234	-10/094	-10/735
T11	-15/2452	-14/990	-14/6379	-13/618	-13/618	-13/925
T12	-4/236	-3/535	-4/21184	-7/882	-7/882	-7/428
T13	-12/335	-12/039	-11/7393	-10/1951	-10/055	-10/666
T14	-15/321	-14/707	-14/7077	-14/2765	-13/634	-14/677
T15	-5/7404	-4/894	-5/7663	-6/432	6/044	-6/251
T16	-20/924	-20/823	-20/8233	-18/782	-19/240	-19/236
T17	-2/469	-2/813	-3/2813	-3/381	-3/381	-2/623
T18	-22/364	-22/439	-22/4391	-20/714	-20/7624	-21/694
T19	15/385	15/2021	15/2021	15/835	14/263	15/269
T20	-15/648	-18/5022	-18/50221	-16/837	-16/8367	-16/970
T21	-8/259	-15/0227	-8/05345	-9/598	-7/5965	-9/142
T22	-3/038	-4/4285	-3/4285	-4/359	-4/004	-3/882
T23	-22/067	-21/966	-21/2653	-19/881	-20/137	-20/338
T24	-12/143	-11/830	-11/6972	-10/146	-10/246	-10/547
T25	6/747	5/892	5/8917	7/403	7/404	7/251
T26	2/551	2/081	2/7127	-2/706	-2/701	-2/554
T27	-24/566	-26/453	-25/0839	−24/551	−24/071	−24/186
T28	-2/275	-2/406	-3/4058	-2/550	-2/4999	-2/551
T29	-24/489	-24/747	-24/7471	-23/024	-23/0697	-23/024
T30	-7/947	-10/239	-7/8462	-7/862	-8/02145	-7/863

In Table 3 ,the results of thermodynamic properties are given at HF level, with comparison values we can classify all 30 equilibria like this:

T7>T6>T27>T29>T18>T9>T23>T16>T26>T14 >T11>T10>T13>T24>T21>T30>T12>T8>T15> T22>T1>T17>T28>T26>T2>T25>T4>T19>T5> T3.

The range of differences between energy of the most stable and the least stable equilibrium is 7.471 Kcal/mol.And like this, we can say about B3LYP levels.This process is given in Table4:

T7>T6>T27>T29>T18>T9>T16>T23>T20>T11 >T14>T24>T10>T13>T21>T30>T12>T8>T22> T17>T28>T15>T1>T26>T2>T25>T4>T19>T5> T3.

And as the same as we already said ,this range of differences between energy about equilibrium is 9.656 Kcal/mol. As we see, the most significant advantage to DFT methods is a significant increase in computational accuracy without additional increase in computing time. The effect of correlation on relative stability can be seen by comparing of Table3 and 4.

Table4.Thermodynamic properties for equilibria in B3LYP level (Kcal/mol)

Tautomerism equbliria						
T1	-2.298	-2.069	-1.486	-3.592	-3.3010`	-2.852
T2	3.105	2.863	2.122	3.6201	4.1045	3.471
T3	15.439	15.813	15.857	16.803	17.094	17.016
T4	5.742	7.026	6.479	5.804	5.75614	6.264
T5	15.278	14.622	14.657	12.794	12.059	12.136
T6	-25.462	-24.258	-24.388	-24.0889	-22.959	-23.0591
T7	-25.681	-25.796	-25.458	-26.483	-26.955	-26.750
T8	-6.264	-7.05948	-6.761	-6.193	-6.998	-6.712
T9	-19.135	-19.657	-19.234	-19.168	-19.601	-19.307
T10	-10.678	-10.528	-10.988	-9.384	-9.603	-9.7434
T11	-15.306	-14.957	-15.244	-13.747	-13.680	-13.963
T12	-6.47627	-7.389	7.184	-6.719	-7.496	-6.720
T13	-10.251	-10.266	-10.543	-8.618	-8.696	-8.947
T14	-13.505	-13.226	-13.144	-11.819	-11.672	-11.596
T15	-4.118	-4.157	-4.446	-3.526	-4.691	-4.253
T16	-19.065	-19.597	-18.933	-18.676	-18.284	-18.386
T17	-5.230	-5.729	-5.827	-5.665	-5.665	-5.844
T18	-19.251	-19.673	-19.764	-19.940	-19.771	-19.658
T19	13.282	12.706	12.925	11.816	11.631	11.519
T20	-16.597	-15.983	-16.282	-17.262	-17.624	-16.848
T21	-7.315	-7.394	-8.28403	-6.915	-7.586	-8.021
T22	-5.235	-5.835	-5.90424	-5.685	-6.50476	-6.11595
T23	-18.967	-18.671	-18.858	-17.519	-17.302	-17.491
T24	-11.263	-11.217	-11.497	-9.999	-10.028	-10.294
T25	7.603	8.437	8.481	7.529	8.343	8.458
T26	1.577	1.375	1.228	1.625	1.417	1.263
T27	-24.501	-24.148	-24.247	-23.135	-22.714	-22.813
T28	-4.011	-4.099	-4.169	-3.992	-4.122	-4.063
T29	-23.486	-22.877	-22.876	-22.115	-21.519	-21.518
T30	-9.023	-8.604	-8.605	-8.521	-8.625	-8.485

3.3 Discussing about CO model

In this work we considered on CO structure model and as we see in the Fig.3, this model includes 5 tautomeric equilibria .The 6-31G** optimized geometries of this model are given at Table 5. We consider this model as acetaldehyde - vinyl alcohol model. This consideration is based on that part of structure which hydrogen transfer occures, is similar to acetaldehyde - vinyl alcohol structure. According to Table3 and Table4 the order of stability of equilibria in this model is following:

At HF level: T14>T13>T12>T15>T5.

At B3LYP level: T14>T13>T12>T15>T5.

As we see the rout of stability for two level is the same. In the case of T13, acetaldehyde form (OHFC9) is predicated to be mor stable by 8.696 Kcal/mol at the highes level. For T12, vinyl alcohol model (OHFC2) is predicated to be more stable by 6.719 Kcal/mol at the highes level . In the case of T5, T14, T15 , acetaldehyde forms (OHFC4, OHFC11, OHFC12) are predicated to be mor stable by 12.794 , 11.819 , 3.526 Kcal/mol at the highes level , respectively. The exception to the rule, such as OHFC2, where the vinyl alcohol is the most stable tautomer , can be explained by the increasing of resonance in the enol form relative to the keto form.
The difference of stability of the most stable and the least stable equilibrium is 0.975 Kcal/mol at B3LYP level and 1.648 Kcal/mol at HF level.

Table5 .B3LYP/6-31G Optimized geometry of Tautomeric equilibria of CO structural of model .**

	CO			CO	
	a	b		a	b
	(T5)			**(T12)**	
C_4C_5	1.53119	1.3466	C_4C_5	1.5458	1.3861
C_4O_9	1.2730	1.13505	C_4O_9	1.2116	1.3472
$C_4C_5O_9$	125.65	117.3942	$C_4C_5O_9$	120.596	121.573
	(T13)			**(T14)**	
C_4C_5	1.4549	1.5308	C_4C_5	1.3509	1.5352
C_4O_9	1.2248	1.2121	C_4O_9	1.3461	1.2081
$C_4C_5O_9$	123.4916	110.855	C_5O_9	125.1048	123.45
	(T15)				
C_4C_5	1.3634	1.5472			
C_4O_9	1.3478	1.2075			
$C_4C_5O_9$	122.2936	121.2046			

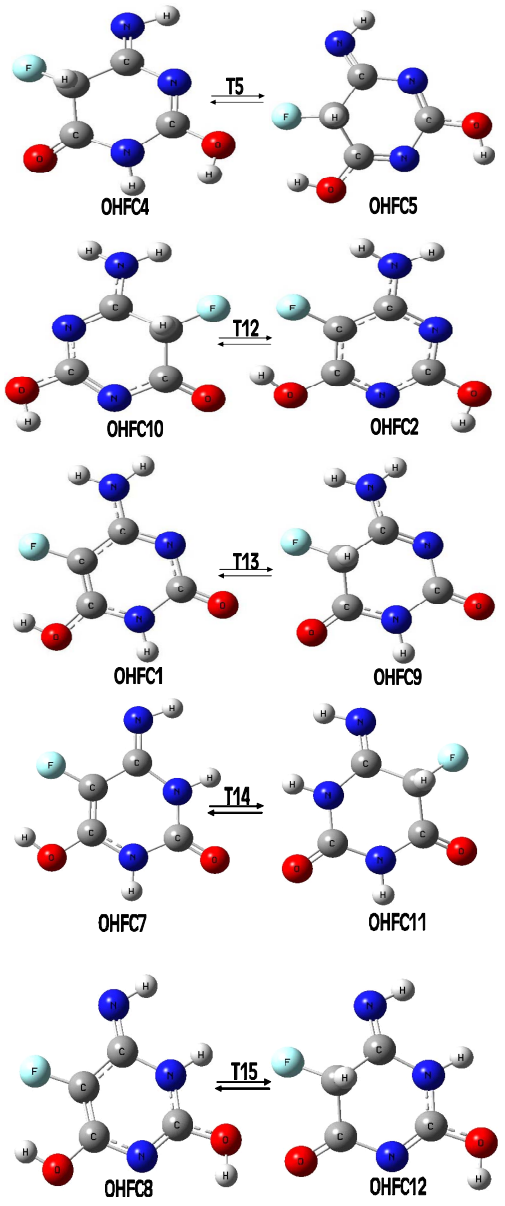

Fig.3.Tautomeric equilibria for CO model.

3.4 The effect of temperature on equilibrium

The effect of temperature on the Gibbs free energy changes or the equilibrium constant of a given reaction is calculated using either Eq. 1 or Eq. 2. [16]-[19].

$$\Delta G^\circ_T = \Delta H^\circ_T - T\Delta S^\circ_T \qquad (1)$$

or Van Hoff Equation,

$$\frac{d \ln K_{eq}}{dT} = \frac{\Delta H^\circ_T}{RT^2} \qquad (2)$$

In these equations, ΔH° and ΔS° are strictly speaking a function of temperature only. However, it is frequently assumed that these two parameters are fairly independent of temperature, especially for a narrow range of temperature, and furthermore, it is assumed that $\Delta H^\circ_T = \Delta H^\circ_{298}$ and $\Delta S^\circ_T = \Delta S^\circ_{298}$.
Chemical reaction enthalpy (heat of reaction) is defined according to the following equation :
$\Delta H = (\Delta H)$products $-(\Delta H)$reactants (3)

If H <0, then a process is *exothermic* and heat leaves the system during the process.
If H > 0, then the process is *endothermic*, and heat enters the system. It feels cold, because it draws heat from the surroundings.
If $\Delta G > 0$ reaction occurs in course of reactants formation, and if $\Delta G < 0$ reaction runs in course of products formation.
According to this results, we calculated thermodynamic data for all equilibria at B3LYP/6-31G** that here we only discusse about CO model.This data are given in Table6. As we know in CO model, T5 is endothermic and the reminder equilibrium are exothermic .
By investigating of this process we understand that ΔH° in this temperature range doesn't change so much, so we can apply Eq.4 for reactions.

$$Log\ k = \frac{-\Delta H^\circ}{٢/٣٠٣R}\ \frac{1}{T} + constant \qquad (4)$$

Table6.Influence of temperature on, enthalpy and free energy of equilibria of CO model.(Kcal/mol)

Tautomerism equbliria												
T5	12.093	12.092	12.092	12.091	12.090	12.090	12.051	12.067	12.073	12.075	12.078	12.07
T12	-8.95	-7.059	-6.99	-6.92	-6.85	-6.72	-9.65	-9.92	-9.93	-9.94	-9.98	-10.02
T13	-10.59	-7.692	-7.691	-7.691	-7.011	-6.69	-7.490	-7.692	-7.693	-7.99	-7.699	-7.69
T14	-10.59	-10.58	-10.57	10.56	-10.55	-10.54	-10.61	-10.70	-10.74	-10.78	-10.82	-10.8
T15	-3.95	-2.96	-2.95	-2.92	-2.90	-2.88	-3,95	-1.81	-1.78	-1.77	-1.75	-1.73

According data of Tabl6 ,T5 is an endothermic reaction ($\Delta H > 0$) in temperature range 298°-398° K. Free energy of consider reaction is positive as well in temperature range 298°-398° K. So the process occurs in direction of OHFC4 .(Fig.3).

T12, T13, T14, T15 are exothermic reactions ($\Delta H < 0$) in in temperature range 298°-398°K. free energy of consider reactions are negative as well in temperature range 298°-398° K. So the process of T12 occurs in direction of OHFC2 ,T13 in direction of OHFC9, T14 in direction of OHFC11,T15 in direction of OHFC12. (Fig4.T14, as an example)

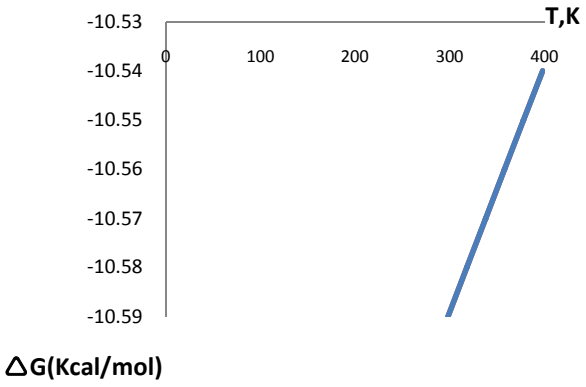

Fig.4.Effect of tempeeature on ΔG of T14 in CO model.

3.4.1 Effect on *Heat Capacity*

Most enthalpies are calculated or measured (tabulated at any rate) at 25°C. But most of the reactions we are interested in occur at higher T. We need to know how *H* changes with *T*. For this we have heat capacity.

Heat capacity is:

the amount of heat required to raise the T of 1 mole of a substance by 1 K.

.So that the heat capacity required to raise the (the amount of heat temperature) × the temperature increase is the enthalpy.

Another study that we performed, is investigation of effect of temperature on stability and heat capacity of tautomeric equilibria. For this studing, we change temperature of reaction from 298° K to 398°. Then we calculated thermodynamic properties .Here we only discusse about this effect on CO equilibria .The calculations were performed at B3LYP/6-31G** level. And also the values of C_V can obtain from gussian calculations and then with use of relation 4 , we can calculate the values of C_P by :

$C_v + R = C_P$ (4)

The C_P data in temperature range 298-398 are given in Table6. We can see for all 5 equilibria in CO model, that value of C_P of tautomers increase with increasing oftemperature.According to data we can obtain the relation between C_P and temperature(Fig.5.T14 as an example) and use these relations for each temperature

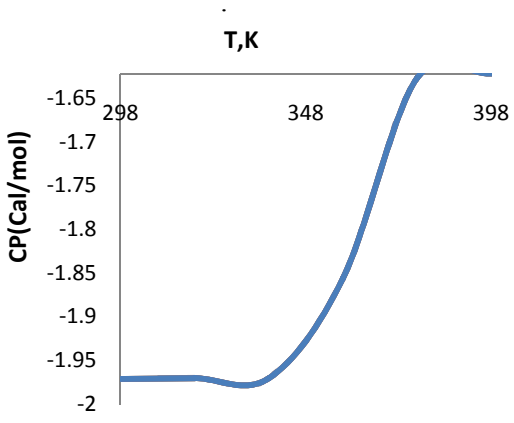

Fig.5.Effect of tempeeature on C_P of T14 in CO model.

Table7. Efect of temperature on c_p in CO model (values are in cal/mol.K)

Equilibria	298°K	318°K	338°K	58°K	378°K	398°K
T5	-0.169	-0.715	-0.663	-0.614	-1.089	-0.552
T12	-1.101	-1.754	-1.762	-1.772	- 0.216	-0.174
T13	-0.65	1.144	0.261	-0.633	0.136	0.027
T14	-1.971	-0.947	-1.907	-1.856	-1.627	-1.732
T15	-0.246	-1.259	-2.255	-1.238	-0.296	-1.185

Table8.The equations for each tautomeric equilibria of CO models according to C_P data

Equilibrium	Equation
T5	$6E\text{-}0.9T^5\text{-}1E\text{-}o.5T^4\text{-}0.07T^3\text{-}2.4T^2\text{-}420.5T\text{-}28381$
T12	$-2E\text{-}0.8E^5+3E\text{-}0.5T^4\text{-}0.021T^3+7.205T^2\text{-}1239T+8459$
T13	$-8E\text{-}o.9T^5\text{-}0.009T^3+3.001T^2\text{-}486.7T+31249$
T14	$-6E\text{-}10T^5+E\text{-}O.6T^4+0.204T^2\text{-}33.10T+2.31$
T15	$E\text{-}0.8T^5\text{-}2E\text{-}0.5T^4+0.014T^3\text{-}5.163T^2+908.2T\text{-}630.28$

3.4.2 Effect on Equilibrium Constant

Increasing of temperature can also influence on equilibrium constant (K_{eq}).Table 8 showes data for K in different temperature .According to these results we understand that in enothermic equilibria , increasing of temperature increases data of K_{eq} and in exothermic equilibria , increasing of temperature decreases these data(Fig.6)

And with assumption of that ΔH is constant we can apply Eq.4 and investigate changing of lnK with temperature.

According to the data of K_{eq} that obtain with use of Eq.4 we can say that ,T5 that is endothermic process , as temperature increases value of equilibrium constant of that reaction increases (Fig.3).In the reminder reactions (T12,T13,T14,T15) that are exothermic , as temperature increases valueof equilibrium constant of that reaction decreaces (Fig.6).

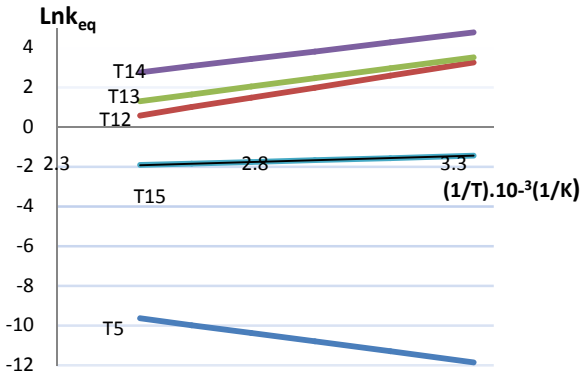

Fig.6.Effect of tempeeature on k_{eq} of T14 in CO model.

5 conclusion

All results show that OHFC14 is the most stable tautomer that has energy of -569.406642 andOHFC6 is the less stable tautomer and its energy is -569.34647 Hartree.

In (OHFC2⇆OHFC5) has the negative value for ΔG .In this study we consider different structural models an focus on effect of temperature on CO structural model.For the considered reactions thermodynamic functions ΔH and ΔG have the same sign .In other words, temperature of considered reactions become decisive factor for thermodynamic conditions. For exothermic reactions (T12,T13,T14,T15) with negative variation of enthalpy , condition that $\Delta G < 0$ will be satisfied at lower temperature.In endothermic is shown that increase of temperature causes increase of equilibrium constant of the reaction, as a result of equilibrium state proceeding in direction of products formation.For the exothermic reactions ,it is shown that increase in temperature corresponding in decrease of equilibrium constant values as result of proceeding of reactions in direction of the reactant formation.In

endothermic reaction with positive variation in enthoropy , in case of $\Delta G > 0$ proceeding of reactions occurs in direction of the product formation.

References:

[1] J. S. KwiatkowskriI., J. bartl and W. B. Person.*J. Am.Chem. Soc*. 110, 2353 (1988).

[2] J.D. Watson, F.H.C. Crick, *Nature* 171 (1953) 964–967.

[3] Thomas. L. Gilchrist. *Heterocyclic Chemistry (3rd Edition)*

[4] *Organic Syntheses*, Coll. Vol. 4, p.182 (1963); Vol. 35, p.34 (1955).

[5] *Organic Syntheses*, Coll. Vol. 4, p.336 (1963); Vol. 35, p.58 (1955).

[6] *Organic Syntheses*, Coll. Vol. 4, p.638. (1963); Vol. 35, p.80 (1955).

[7] C. Flinn, R.A. Poirier, and W.A. Sokalski. *J. Phys. Chem. A*,107, 11171 (2003).

[8] Diasio RB, Lakings DE, Bennett JE. *Evidence for conversion of 5-fluorocytosine to 5-fluorouracil in humans: possible factor in 5-fluorocytosine clinical toxicity.* Antimicrob Agents Chemother 1978;14:903–8.

[9] Polak A, Eschenhoff E, Fernex M, Scholer HJ. *Metabolic studies with 5-fluorocytosine-6-14C in mouse, rat, rabbit, dog and man*. Chemotherapy 1976;22:137–53.

[10] Polak A, Eschenhoff E, Fernex M, Scholer HJ. *Metabolic studies with 5-fluorocytosine-6-14C in mouse, rat, rabbit, dog and man*. Chemotherapy 1976;22:137–53.

[11] Chouini-Lalanne N, Malet-Martino MC, Gilard V, Ader JC, Martino R. *Structural determination of a glucuronide conjugate of flucytosine in humans*. Drug Metab Dispos 1995;23:813– 7.

[12] Reigner B, Blesch K, Weidekamm E. *Clinical pharmacokinetics of capecitabine*. Clin Pharmacokinet 2001;40:85– 104.

[13] G. Fogarasi, *J. Mol. Struct*. 413–414 (1997) 271.

[14] R. Kobayashi, *J. Phys. Chem*. 102 (1998) 10813.

[15] M.D. Topal, *J.R. Fresco,* Nature 263 (1976) 285–289.

[16] R. Zena and R. Yeager*, J. Phys. Chem.* 71, 521 (1967).

[17] D. R. Kestu and R. M. Pytkowicz, *Geochim Et. Cosmo.Acta.* 34, 1039 (1970).

[18] G. Curthoys and J. G. Mathieson, *Trans. Fat'. Soc*. 66,43 (1970).

[19] R. Derry, Miner. *Sci. Eng.* 4, 3 (1972).