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# Theoretical Study of Stability, Tautomerism, Equilibrium Constants ( $pK_T$ ) of 2-Thiouracil in Gas Phase and Different Solvents (Water and Acetonitrile) by the Density Functional Theory Method

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## *Author's contribution*

*The only author NSB performed the whole research work. Author NSB wrote the first draft of the paper. Author NSB read and approved the final manuscript.*

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## ABSTRACT

A density functional theory (DFT) calculations were carried out to investigate the relative energies, equilibrium constants and dipole moments of 2-thiouracil in the gas phase and in solutions with different polarities. Solvent effects were examined by means of the self-consistent reaction field (SCRF) method. All possible tautomers are optimized at the B3LYP/6-311++G (d,p). All calculations indicate that the most stable tautomer for both species, in the gas phase as well as in solution, has the 2TU1 form. In addition to calculate the thermodynamic properties and the inter conversion equilibrium constants for all tautomers. The molar transfer Gibbs energies of  $\Delta\Delta G_t^0$  (solvent1- solvent 2), determines the solvent effect on the position of the equilibrium.

**Keywords:** 2-Thiouracil; DFT method; tautomerism; relative stabilities; equilibrium constants; solvent effects.

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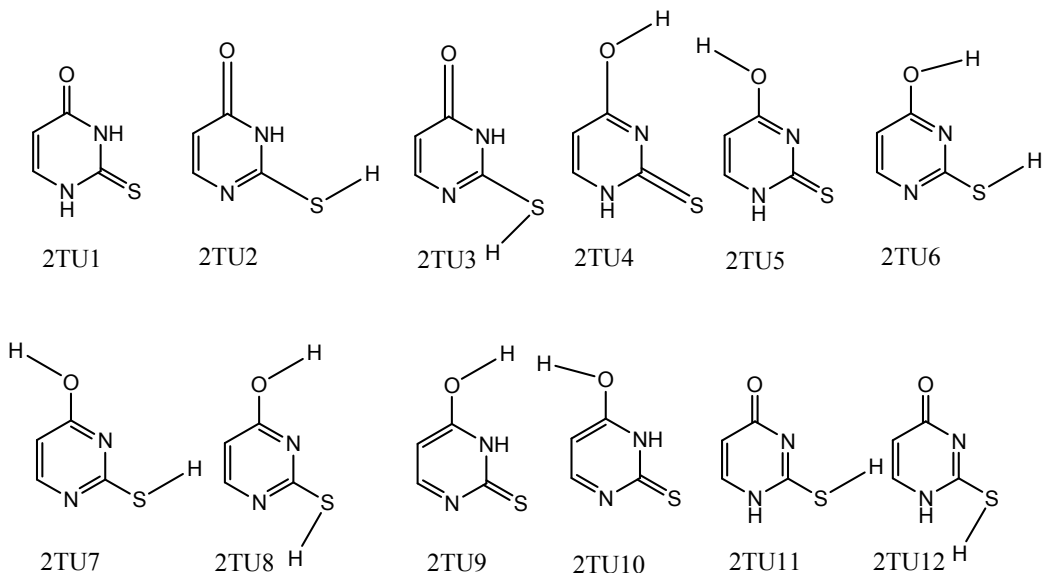
## 1. INTRODUCTION

Tautomerism interconversions [1] have been investigated by chemists during last decades. Recently, study of tautomerism received renewed attention due to its importance on determination of compounds' properties and their area of applications. The importance of tautomerism is revealed more since in recent years the investigation about tautomerism has been the major topic in theoretical chemistry. For example, tautomerisms in keto-enol [2], imine-enamine [3] and many other systems [4] have been studied during past decades. Tautomerism and proton transfer of the keto-enol tautomer of heterocyclic systems with several basic centers, N, O and S atoms, are of great interest to medicinal and biochemical applications. Also, understanding of the relative stabilities of heterocyclic tautomers and any subsequent conversions between tautomeric forms is very vital for both structural chemists and biologists [5]. Along this line, relative stabilities of various tautomeric structures of five-, six- and seven-member heterocyclic rings were investigated using both theoretical and experimental tools [6].

In recent years, uracil and its thio derivatives have already become the intense focus of research due to their biological, pharmacological, and spectroscopic activities. For example, a series of thiouracils, such as 2-thiouracil, 4-thiouracil, and 2,4-dithiouracil, have been identified as minor components of t-RNA and peptide nucleic acids, where the former two thiouracils have also been used as anticancer and antithyroid drugs and for the treatment of heart disease [7–11]. The in appropriate replacement of uracil by a thiouracil can be responsible for the misrecognition in m-RNA [12]. Moreover, their various tautomeric forms seem to be important for explaining the mutation occurring during DNA duplication. Meanwhile, the complexes of thiouracil derivatives with transition metal ions of biological importance have been shown to exhibit anticancer and antimicrobial activity [13]. Additionally, thiouracils have also been proposed to be efficient metal corrosion inhibitors [14]. Thus, the properties and characteristics of thiouracils are of great interest in pharmaceutical researches and applications. In the present paper, the geometries, dipole moments, Mullikan charges and relative energies have been calculated, using the DFT method.

## 2. COMPUTATIONAL METHOD DETAILS

2-thiouracil has 6 keto– enol and enol–enol tautomeric forms altogether. Considering the orientation of the hydroxyl hydrogen and thio hydrogen (it is in the same or opposite direction with the C=N bond of the enol), the number of the tautomers ascends to 12, Fig. 1, illustrates the 12 tautomers. All the geometries of the tautomers have been fully optimized using the B3LYP method within the framework of density functional theory (DFT) in conjunction with the 6-311++G (d,p) basis set, i.e., Becke's three parameter non-local hybrid exchange potential with the non-local correlation functional of Lee, Yang, and Parr [15,16]. The B3LYP method has been shown to yield reliable geometries for a wide variety of systems also including the relevant uracil species [17-19]. Following the geometry optimizations, analytical frequency calculations were proceeded at the DFT/6-311++G (d,p) level, using following standard procedures, to obtain the thermochemical properties. Solvent effect was considered when calculating the equilibrium constant. All these calculations were carried out on a Pentium V personal computer by means of GAUSSIAN09 program package and for our computations [20].



**Fig. 1. Tautomers of 2-thiouracil**

Thermodynamic properties such as: the enthalpy, the Gibbs free energy and the entropy were given according to the formulas [21]

$$H = E + RT \quad (1)$$

$$G = H - TS \quad (2)$$

E is the thermal energy.

H is the enthalpy.

G is the Gibbs free energy.

In order to determine the kinetic parameters of the transformations, we calculated their tautomeric equilibrium constants by using the following relations [22].

$$K_T = \exp(-\Delta G/RT) \quad (3)$$

Where  $K_T$  is the equilibrium constant between the tautomers, the gas constant is R is  $1.987 \times 10^{-3}$  kcal.mol<sup>-3</sup> and the temperature T is 298.15K. The quantity  $\Delta G$  is the difference between the Gibbs free energies of the given tautomer with respect to stable one. The  $pK_T$  values of the studied molecules were calculated by the following equation [21]:

$$pK_T = -\log K_T \quad (4)$$

Calculated total energies (a.u), thermal Enthalpy (H) (a.u), thermal free energy (G) (a.u), dipole moment ( $\mu$ ) ( debye ), enthalpy change ( $\Delta H^0$ ), free energy change ( $\Delta G^0$ ), entropy change ( $\Delta S^0$ ) equilibrium constants (K) and  $pK_T$  for various tautomers. These thermochemical parameters were obtained through the frequency calculation at DFT/6-311++G (d,p) level. The solvents (acetonitrile and water) effect on the tautomerism processes of 2-thiouracil was investigated by self-consistent reaction field (SCRf) method based on Onsager's reaction field theory.

### 3. RESULTS AND DISCUSSION

#### 3.1 Energies and Relative Stability

The total and relative energies (at DFT/6-311++G(d,p) level) of 12 tautomers of 2-thiouracil are presented in Table 1, among the 12 tautomers, four are (2TU2, 2TU3, 2TU11 and 2TU12) thio-enols, four are (2TU4, 2TU5, 2TU9 and 2TU10) keto-enols, three are di-enols (keto-enol and thio-enol) and one is keto tautomer (2TU1). The most stable 2TU1 is taken as reference to obtain the relative energetic stability of other tautomers. It can be seen from the results that among four mono-enol tautomers two are thio-enol(2TU11 & 2TU12) and two are keto-enol (2TU9 & 2TU10) tautomers have highest energy, with relative energy about 20-25 kcal mol<sup>-1</sup>, because of the possibility of migration of hydrogen atoms, and eliminating the simultaneous transfers little likely of more than atom, only the exchange of hydrogen atom between heteroatom spatially close and separate by more than two atoms can be carried out. From the Table 1 shows that the mono-enol tautomers of thio-enol(2TU11 & 2TU12) and keto-enol (2TU9 & 2TU10) tautomers have highest energy, with relative energy about 20-25 kcal mol<sup>-1</sup>. Because of the possibility of migration of hydrogen atoms, and eliminating the simultaneous transfers little likely of more than atom, only the exchange of hydrogen atom between heteroatom spatially close and separate by more than two atoms can be carried out.

**Table 1. The energies of tautomers(a.u) at DFT/6-311++G(d,p) level in different media and the relative energies compared to the most stable isomer 2TU1. The relative energies in brackets in kcal mol<sup>-1</sup> (in brackets Kcal/mole)**

Isomers	$\Delta E(\text{gas})$	$\Delta E(\text{water})$	$\Delta E(\text{Acetonitrile})$
2TU1	-737.899473020 (0.0000)	-737.916336580(0.0000)	-737.915900370(0.0000)
2TU2	-737.88090388(11.6523)	-737.89353095(14.3107)	-737.89321425(14.2358)
2TU3	-737.87768488(13.6723)	-737.89233375(15.0620)	-737.89229300(14.8138)
2TU4	-737.87925325(12.6881)	-737.89911925(10.8040)	-737.86856173(29.7054)
2TU5	-737.86747854(20.0768)	-737.89378865(14.1490)	-737.89418033(13.6295)
2TU6	-737.88025401(12.0601)	-737.88803863(17.7572)	-737.88784348(17.6060)
2TU7	-737.87957496(12.4862)	-737.88785780(17.8707)	-737.88773617(17.6733)
2TU8	-737.87169145(17.4332)	-737.88478499(19.7989)	-737.88454688(19.6746)
2TU9	-737.86363640(22.4878)	-737.88764167(18.0063)	-737.88693953(18.1732)
2TU10	-737.85926764(25.2293)	-737.88308063(20.8684)	-737.88366617(20.2273)
2TU11	-737.86186485(23.5995)	-737.88792579(17.8280)	-737.88715114(18.0404)
2TU12	-737.86670631(20.5614)	-737.88899187(17.1591)	-737.88836509(17.2786)

Other mono and di-enol tautomers are less relative energy, except the tautomer 2TU5 (20.07kcal/mole), with relative energy about 11–18 kcal mol<sup>-1</sup>. The energy difference of the tautomers of same tautomeric form that differs in the orientations of hydroxyl hydrogens, varies for specific systems. The order of relative stabilities for tautomer in gas phase with respect to stable tautomer: 2TU2 > 2TU6 > 2TU7 > 2TU4 > 2TU3 > 2TU8 > 2TU5 > 2TU12 > 2TU9 > 2TU11 > 2TU10.

Solvent effects are relevant in tautomers stability phenomena, since polarity differences among tautomers can induce significant changes in their relative energies in solution. SCRF/B3LYP calculations were used to analyze the solvent effects on tautomerism of 2-thiouracil. The data presented in Table 1 show that polar solvents increase the stability of all

2-thiouracil tautomers in compare to gas phase. The difference between the total energies of 2-thiouracil and the other forms do not show a regular trend when changing from gas phase to most polar solvents (water). The solvent interactions have pronounced effect on the order of stability of the tautomers in the gas phase. The order of stability of 2-thiouracil in acetonitrile: 2TU5> 2TU2 > 2TU3 > 2TU12 > 2TU6 > 2TU7 > 2TU11 > 2TU9 > 2TU8 > 2TU10 > 2TU4 and The order of stability in water: 2TU4> 2TU5 > 2TU2 > 2TU3 > 2TU12 > 2TU6> 2TU11 > 2TU7 > 2TU9 > 2TU8 > 2TU10.

The dipole moment ( $\mu$ ) has been calculated in different media, at the same basis set level and presented in Table 2. It seems that the dipole moments ( $\mu$ ) increases by changing the gas phase to the solution as well as by increasing the solvent polarity. On going from gas phase to solution, dipole moments of all isomers are increased, as the solvent becomes much more polar. The increase in dipole moments implies that charges around the molecule are probably more developed due to the polarization induced by solvents.

**Table 2. The zero dipole moments ( $\mu$ ) in Debye units, for the tautomers at DFT/6-311++G(d,p) level in different media**

Isomers	Gas	Water	Acetonitrile
2TU1	4.7462	6.6964	6.6414
2TU2	2.9654	4.1644	4.1331
2TU3	2.1055	2.8698	3.0960
2TU4	5.7112	9.0025	8.9053
2TU5	8.5147	12.0860	12.6761
2TU6	1.3385	1.9524	1.9356
2TU7	2.1036	2.8607	2.9737
2TU8	4.1486	5.5645	5.6054
2TU9	8.1244	12.6227	12.4880
2TU10	6.5580	9.5422	10.3299
2TU11	8.3876	12.3290	12.2103
2TU12	6.7169	9.9378	9.8397

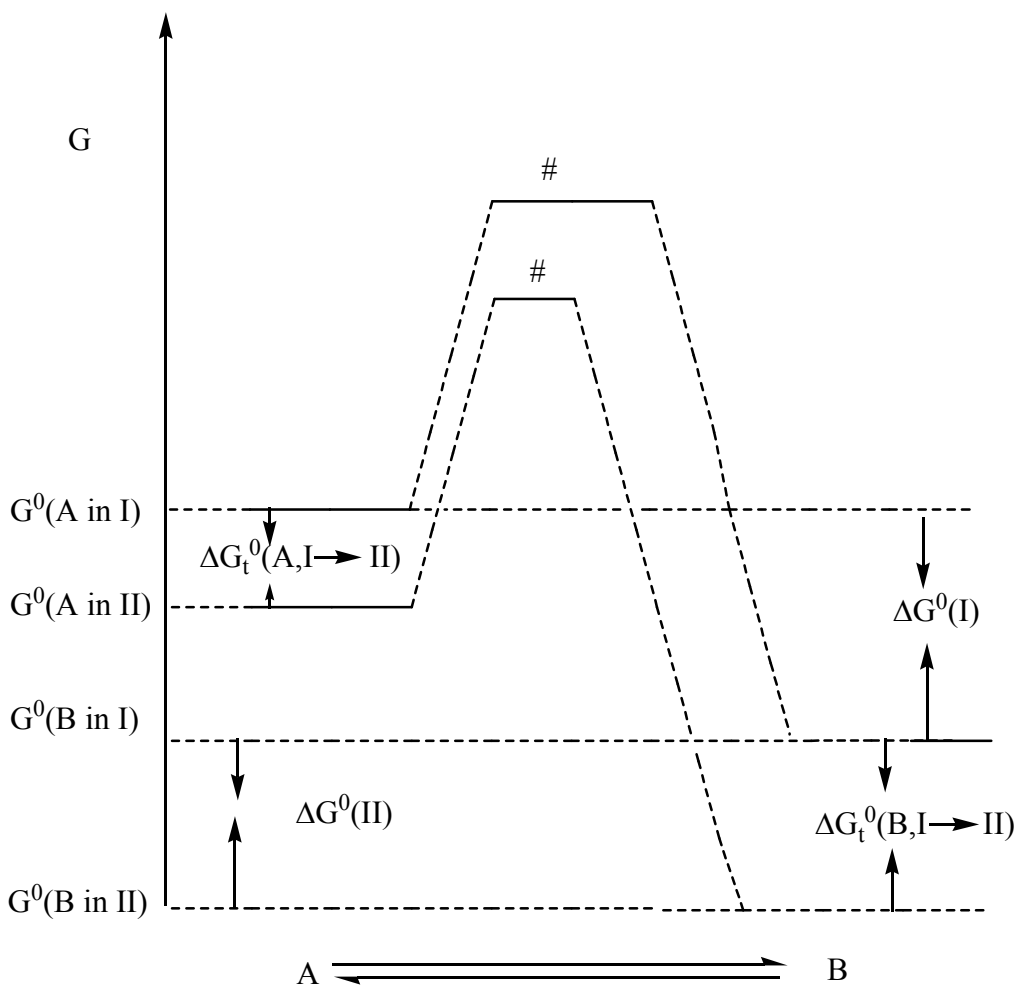
### 3.2 The Thermodynamic Parameters

The thermodynamic parameters are presented in Table 3 in different media, the  $\Delta H$ ,  $\Delta G$  and  $\Delta S$  values are all positive for different solvents except 2TU1 $\leftrightarrow$ 2TU4 has negative  $\Delta S$  value in all solvents.  $\Delta H$  values are all positive, i.e endothermic reaction,  $\Delta S$  usually is relatively small, indicate that with no ring formation or other unusual changes in the constraints between the products and reactants.

**Table 3. The enthalpy ( $\Delta H$ ), Gibbs free energy ( $\Delta G$ ) values in kcal/mol and entropy ( $\Delta S$ ) in kcal/mol Kelvin, for the tautomers at DFT/6-311++G(d,p) level in different media**

Isomers	Gas			Water			Acetonitrile		
	$\Delta H$	$\Delta G$	$\Delta S$	$\Delta H$	$\Delta G$	$\Delta S$	$\Delta H$	$\Delta G$	$\Delta S$
2TU1 $\leftrightarrow$ 2TU2	9.3618	8.9859	0.00126	11.9327	11.5054	0.00143	11.8606	11.4357	0.0013
2TU1 $\leftrightarrow$ 2TU3	11.3435	10.5886	0.00253	12.6688	12.0865	0.00195	12.4611	11.8744	0.0025
2TU1 $\leftrightarrow$ 2TU4	12.4598	12.5471	-0.00029	10.5685	10.6438	-0.00025	10.6444	10.7210	-0.0003
2TU1 $\leftrightarrow$ 2TU5	19.5827	19.4214	0.00054	13.7230	13.5818	0.00047	13.3214	13.2907	0.0005
2TU1 $\leftrightarrow$ 2TU6	9.7885	9.7440	0.00015	15.2704	15.0182	0.00085	15.1249	14.8789	0.0001
2TU1 $\leftrightarrow$ 2TU7	10.1977	10.1236	0.00025	15.4204	15.1575	0.00088	15.1914	14.9404	0.0002
2TU1 $\leftrightarrow$ 2TU8	15.0006	14.8387	0.00054	17.2935	16.9290	0.00122	17.1567	16.8430	0.0005
2TU1 $\leftrightarrow$ 2TU9	21.8235	21.6641	0.00053	17.4843	17.3833	0.00034	17.6525	17.5571	0.0005
2TU1 $\leftrightarrow$ 2TU10	24.3863	23.9621	0.00142	20.2209	19.9636	0.00086	19.7929	19.7709	0.0014
2TU1 $\leftrightarrow$ 2TU11	21.0642	19.9109	0.00387	15.4876	14.7527	0.00246	15.6946	14.9410	0.0039
2TU1 $\leftrightarrow$ 2TU12	18.1168	17.3136	0.00269	14.8713	14.2871	0.00196	14.9868	14.3938	0.0027

The effect of the medium on the position of equilibrium can be considered from two points of view: (a) comparison of the gas-phase and solution equilibrium constants, and (b) comparison of the equilibrium constants for different solvents. These are primarily non-ionic reactions where the interaction between reacting molecules and solvent is relatively small. Let us consider a simple isomerization reaction  $A \leftrightarrow B$  in the solvents I and II, whose abilities to solvate A and B are different. This corresponds to the Gibbs energy diagram shown in Fig. 2 [23]. From Fig. 2, Eq. (5) can be immediately derived,



**Fig. 2. One-dimensional Gibbs energy diagram for an equilibrium reaction  $A \leftrightarrow B$  in the solvents I and II. Ordinate: standard molar Gibbs energies of the reactants A and B in solvents I and II; Abscissa: not defined.  $\Delta G_{\text{t}}^{\circ}(\text{I})$  and  $\Delta G_{\text{t}}^{\circ}(\text{II})$ : standard molar Gibbs energies of reaction in solvents I and II, respectively;  $\Delta G_{\text{t}}^{\circ}(\text{A}, \text{I} \rightarrow \text{II})$  and  $\Delta G_{\text{t}}^{\circ}(\text{B}, \text{I} \rightarrow \text{II})$ : standard molar Gibbs energies of transfer of the solutes A and B from solvent I to solvent II, respectively [ $\Delta G_{\text{t}}^{\circ}(\text{A}, \text{I} \rightarrow \text{II}) = G^{\circ}(\text{A in I}) - G^{\circ}(\text{A in II})$ , and [ $\Delta G_{\text{t}}^{\circ}(\text{B}, \text{I} \rightarrow \text{II}) = G^{\circ}(\text{B in I}) - G^{\circ}(\text{B in II})$ ], # = transition state**

$$\Delta G^0(\text{II}) + \Delta G^0_{\text{t}}(\text{A}, \text{I} \rightarrow \text{II}) = \Delta G^0_{\text{t}}(\text{B}, \text{I} \rightarrow \text{II}) = \Delta G^0_{\text{t}}(\text{B}, \text{I} \rightarrow \text{II}) + \Delta G^0(\text{I}) \quad (5)$$

which, on rearrangement, leads to Eq.6

$$\begin{aligned} \Delta G^0(\text{II}) - \Delta G^0(\text{I}) &= \Delta G^0_{\text{t}}(\text{B}, \text{I} \rightarrow \text{II}) - \Delta G^0_{\text{t}}(\text{B}, \text{I} \rightarrow \text{II}) \\ &= \Delta \Delta G^0(\text{I} \rightarrow \text{II}) \end{aligned} \quad (6)$$

Since, for equilibria, the logarithm of the equilibrium constant is proportional to the standard molar Gibbs energy change,  $\Delta G^0$ , according to Eq. (7),

$$\Delta G^0 = -RT \ln K \quad (7)$$

It follows from Eqs. (6) and (7) that the difference in the molar transfer Gibbs energies of reactant A and product B,  $\Delta \Delta G^0_{\text{t}}(\text{I} \rightarrow \text{II})$ , determines the solvent effect on the position of this equilibrium. In studying solvent effects on equilibria, it is, in principle, not sufficient to investigate the  $\Delta G^0$  changes alone, because this term is determined by both an enthalpy and an entropy term according to Eq. (8).

$$\Delta G^0 = \Delta H^0 - T\Delta S^0 \quad (8)$$

Transfer functions can also be defined for the thermodynamic state functions  $\Delta H^0$  and  $\Delta S^0$  if both transfer Gibbs energies and transfer enthalpies are available, it should be possible to achieve a complete dissection of the effect of solvents on the various thermodynamic parameters. The values of  $\Delta \Delta H^0$  and  $T \Delta \Delta S^0$  were presented in Table 4 in all the solvents. From the table four types of reaction control can be recognized:

(a) Cooperative effects, with  $\Delta \Delta H^0$  and  $T\Delta \Delta S^0$  having opposite signs. Then these two terms will be additive; (b) Enthalpy-controlled effects, in which the two terms are opposed, but the enthalpy term is larger; (c) Entropy-controlled effects, in which the two terms are opposite but the  $\Delta \Delta S^0$  is larger; and (d) Compensating effects, in which the two terms are opposed but nearly equal.



**Table 4.  $\Delta\Delta H^0$  (solvent 1- solvent 2), and  $T\Delta\Delta S^0$ (solvent 1- solvent 2), values in kcal/mole for the tautomers at DFT/6-311++G(d,p) level in different media**

Isomers	$\Delta\Delta H^0(\text{G}\rightarrow\text{W})$	$T\Delta\Delta S^0(\text{G}\rightarrow\text{W})$	$\Delta\Delta H^0(\text{G}\rightarrow\text{A})$	$T\Delta\Delta S^0(\text{G}\rightarrow\text{A})$	$\Delta\Delta H^0(\text{A}\rightarrow\text{W})$	$T\Delta\Delta S^0(\text{A}\rightarrow\text{W})$
2TU1 $\leftrightarrow$ 2TU2	-2.5709	-0.0506	-2.4988	-0.0119	-0.0721	-0.0387
2TU1 $\leftrightarrow$ 2TU3	-1.3253	0.1729	-1.1176	0.0089	-0.2077	0.1639
2TU1 $\leftrightarrow$ 2TU4	1.8913	-0.0119	1.8154	0.0029	0.0759	-0.0149
2TU1 $\leftrightarrow$ 2TU5	5.8597	0.0208	6.2613	0.0119	-0.4016	0.0089
2TU1 $\leftrightarrow$ 2TU6	-5.4819	-0.2087	-5.3364	0.0149	-0.1455	-0.2236
2TU1 $\leftrightarrow$ 2TU7	-5.2227	-0.1878	-4.9937	0.0149	-0.229	-0.2027
2TU1 $\leftrightarrow$ 2TU8	-2.2929	-0.2027	-2.1561	0.0119	-0.1368	-0.2146
2TU1 $\leftrightarrow$ 2TU9	4.3392	0.0566	4.1710	0.0089	0.1682	0.0477
2TU1 $\leftrightarrow$ 2TU10	4.1654	0.1669	4.5934	0.0059	-0.428	0.1610
2TU1 $\leftrightarrow$ 2TU11	5.5766	0.4203	5.3696	-0.0089	0.2070	0.4293
2TU1 $\leftrightarrow$ 2TU12	3.2455	0.2176	3.1300	-0.0029	0.1155	0.2206

### 3.3 Equilibrium Constants

In order to determine the kinetic parameters of the transformations, we calculated their tautomeric equilibrium constants by using the relation [21]. The constants were calculated by considering that all the tautomers can be in the equilibrium with the most stable tautomer. Table 5 contained the equilibrium constants (K) and the  $pK_T$  values in different solvents, calculated from tautomeric most stable which was 2TU1. All  $pK_T$  values in gas phase and the two solvents were positive and this confirmed the fact that 2TU1 tautomer is most stable.

Calculated values for the equilibrium between the tautomers of 2-thiouracil show that the 2TU1 is more dominant than the 2TU2, for both the gas and solutions (water and acetonitrile) with  $pK_T$  value of 6.5874, 8.4344 and 8.3833, respectively. The 2TU1 form is also a more dominant tautomer than the 2TU6 form, 2TU7 form, 2TU3 form and the 2TU4 form. Tautomers 5, 8, 9, 10, 11 and 12 are not present in detectable amounts. In the gas phase the order of the stability of 2-thiouracil tautomers is  $1 > 6 > 7 > 3 > 4$  while tautomers 5, 8, 9, 10, 11 and 12 are not detected. However, we predict the order of stability in aqueous and acetonitrile solutions are same, to be  $1 > 4 > 2 > 3 > 5$ .

We can return to our diagram of interconversion, to evaluate in a more realistic way the constants of equilibrium as presented in Fig 3. Table 6 contained the  $pK_T$  of the equilibrium constants calculated from the general outline of interconversion. Some  $pK_T$  were positive and other negative; that determine the privileged direction of equilibrium. If the  $pK_T$  was positive, equilibrium moved from right towards the left and when it was negative, equilibrium moved from left towards the right.

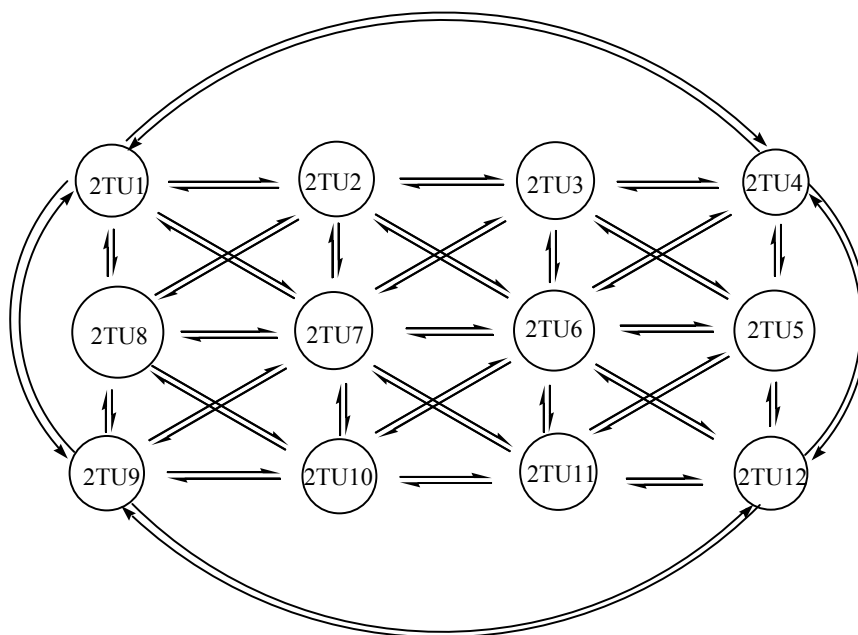


Fig. 3. Diagram of interconversion of 2-thiouracil

**Table 5.** The equilibrium constants (K) and  $p^K_T$  values for the tautomers at DFT/6-311++G(d,p) level in different media

Isomers	Gas		Water		Acetonitrile	
	K	$p^K_T$	K	$p^K_T$	K	$p^K_T$
2TU1↔ 2TU2	$2.58590 \times 10^{-7}$	6.5874	$3.67804 \times 10^{-9}$	8.4344	$4.13702 \times 10^{-9}$	8.3833
2TU1↔ 2TU3	$1.72864 \times 10^{-8}$	7.7623	$1.37919 \times 10^{-9}$	8.8604	$1.97305 \times 10^{-9}$	8.7049
2TU1↔ 2TU4	$6.33821 \times 10^{-10}$	9.1980	$1.57485 \times 10^{-8}$	7.8028	$1.38244 \times 10^{-8}$	7.8594
2TU1↔ 2TU5	$5.78831 \times 10^{-15}$	14.2374	$1.10522 \times 10^{-10}$	9.9566	$1.80669 \times 10^{-10}$	9.7431
2TU1↔ 2TU6	$7.19224 \times 10^{-8}$	7.1431	$9.78253 \times 10^{-12}$	11.0095	$1.23762 \times 10^{-11}$	10.9074
2TU1↔ 2TU7	$3.78954 \times 10^{-8}$	7.4214	$7.73274 \times 10^{-12}$	11.1117	$1.11559 \times 10^{-11}$	10.9525
2TU1↔ 2TU8	$1.32446 \times 10^{-11}$	10.8780	$3.88760 \times 10^{-13}$	12.4103	$4.49510 \times 10^{-13}$	12.3473
2TU1↔ 2TU9	$1.31363 \times 10^{-16}$	15.8815	$1.80569 \times 10^{-13}$	12.7434	$1.34661 \times 10^{-13}$	12.8708
2TU1↔ 2TU10	$2.71552 \times 10^{-18}$	17.5661	$2.31780 \times 10^{-15}$	14.6349	$3.20855 \times 10^{-15}$	14.4937
2TU1↔ 2TU11	$2.53343 \times 10^{-15}$	14.5963	$1.53138 \times 10^{-11}$	10.8149	$1.11441 \times 10^{-11}$	10.9530
2TU1↔ 2TU12	$2.03113 \times 10^{-13}$	12.6923	$3.36052 \times 10^{-11}$	10.4736	$2.80658 \times 10^{-11}$	10.5518

**Table 6. The inter conversion equilibrium constants (K) and  $p^K_T$  values for tautomers at DFT/6-311++G(d,p) level in different media**

Isomers	Gas		Water		Acetonitrile	
	K	$p^K_T$	K	$p^K_T$	K	$p^K_T$
2TU1↔ 2TU2	2.5857 x10 <sup>-7</sup>	6.5874	3.6781x10 <sup>-9</sup>	8.4344	4.1370x10 <sup>-9</sup>	8.3833
2TU2↔ 2TU3	6.6853x10 <sup>-2</sup>	1.1749	3.7500x10 <sup>-1</sup>	0.4259	4.7692 x10 <sup>-1</sup>	0.3215
2TU3↔ 2TU4	3.6669x10 <sup>-2</sup>	1.4357	1.1418x10 <sup>1</sup>	-1.0576	0.7006 x10 <sup>-1</sup>	-0.8455
2TU4↔ 2TU5	9.1314x10 <sup>-6</sup>	5.0395	7.0179x10 <sup>-3</sup>	2.1538	1.3069x10 <sup>-2</sup>	1.8838
2TU5↔ 2TU6	1.2427x10 <sup>7</sup>	-7.0944	8.8517x10 <sup>-2</sup>	1.0530	6.8502x10 <sup>-2</sup>	1.1643
2TU6↔ 2TU7	5.2685x10 <sup>-1</sup>	0.2783	7.9045x10 <sup>-1</sup>	0.1021	9.0140x10 <sup>-1</sup>	0.0450
2TU7↔ 2TU8	3.4950x10 <sup>-4</sup>	3.4566	5.0278x10 <sup>-2</sup>	1.2986	4.0293x10 <sup>-2</sup>	1.3948
2TU8↔ 2TU9	9.9178x10 <sup>-6</sup>	5.0036	4.6446x10 <sup>-1</sup>	0.3330	2.9957x10 <sup>-1</sup>	0.5235
2TU9↔ 2TU10	2.0674x10 <sup>-2</sup>	1.6846	1.2836x10 <sup>-2</sup>	1.8916	2.3827x10 <sup>-2</sup>	1.6229
2TU10↔ 2TU11	9.3295x10 <sup>-2</sup>	-2.9699	6.6064x10 <sup>3</sup>	-3.8200	3.4732x10 <sup>3</sup>	-3.5407
2TU11↔ 2TU12	8.0168x10 <sup>1</sup>	-1.9040	0.2194x10 <sup>-1</sup>	-0.3413	0.2518 x10 <sup>-1</sup>	-0.4011
2TU1↔ 2TU8	1.3244x10 <sup>-11</sup>	10.878	3.8879x10 <sup>-13</sup>	12.4100	4.4951x10 <sup>-13</sup>	12.347
2TU8↔ 2TU9	9.9178x10 <sup>-6</sup>	5.0036	4.6446x10 <sup>-1</sup>	0.3330	2.9957x10 <sup>-1</sup>	0.5235
2TU1↔ 2TU7	3.7895x10 <sup>-8</sup>	7.4214	7.7328x10 <sup>-12</sup>	11.112	1.1156x10 <sup>-11</sup>	10.952
2TU8↔ 2TU6	5.4308x10 <sup>-3</sup>	-3.7349	2.5162x10 <sup>1</sup>	-1.4007	2.7533x10 <sup>1</sup>	-1.4398
2TU2↔ 2TU6	2.7816x10 <sup>-1</sup>	0.5557	2.6597x10 <sup>-3</sup>	2.5752	2.9916x10 <sup>-3</sup>	2.5241
2TU7↔ 2TU3	4.5617x10 <sup>-1</sup>	0.3408	1.7837x10 <sup>2</sup>	-2.2513	1.7686x10 <sup>2</sup>	-2.2476
2TU3↔ 2TU5	3.3483x10 <sup>-7</sup>	6.4752	8.0128x10 <sup>-2</sup>	1.0962	9.1569x10 <sup>-2</sup>	1.0383
2TU6↔ 2TU4	8.8128x10 <sup>-3</sup>	2.0549	1.6098x10 <sup>3</sup>	-3.2068	1.1170x10 <sup>3</sup>	-3.0481
2TU6↔ 2TU12	2.8238x10 <sup>-6</sup>	5.5492	0.3434 x10 <sup>-1</sup>	-0.5359	0.2267 x10 <sup>-1</sup>	-0.3555
2TU11↔ 2TU5	0.2284 x10 <sup>-1</sup>	-0.35881	0.7217x10 <sup>-1</sup>	-0.8583	1.6212x10 <sup>1</sup>	-1.2098
2TU7↔ 2TU11	6.6857x10 <sup>-8</sup>	7.1749	0.1980x10 <sup>-1</sup>	-0.2967	9.9894x10 <sup>-1</sup>	0.4600
2TU10↔ 2TU6	2.6486x10 <sup>10</sup>	-10.423	4.2206x10 <sup>3</sup>	-3.6254	3.8572x10 <sup>3</sup>	-3.5863
2TU8↔ 2TU10	2.0504x10 <sup>-7</sup>	6.6882	5.9617x10 <sup>-3</sup>	2.2246	7.1379x10 <sup>-3</sup>	2.1464
2TU9↔ 2TU7	2.8849x10 <sup>8</sup>	-8.4601	4.2823x10 <sup>1</sup>	-1.6317	8.2844x10 <sup>1</sup>	-1.9183
2TU1↔ 2TU9	1.3135x10 <sup>-16</sup>	15.882	1.8058x10 <sup>-13</sup>	12.743	1.3466x10 <sup>-13</sup>	12.871
2TU4↔ 2TU12	3.2043x10 <sup>-4</sup>	3.4943	2.1338x10 <sup>-3</sup>	2.6708	2.0302x10 <sup>-3</sup>	2.6925
2TU1↔ 2TU4	6.3387x10 <sup>-10</sup>	9.1980	1.5748x10 <sup>-8</sup>	7.8028	1.3824x10 <sup>-8</sup>	7.8594
2TU9↔ 2TU12	1.5463x10 <sup>3</sup>	-3.1893	1.8609x10 <sup>2</sup>	-2.2697	2.0842x10 <sup>2</sup>	-2.3189
2TU2↔ 2TU7	1.4655x10 <sup>-1</sup>	0.8340	2.1024x10 <sup>-3</sup>	2.6773	2.6966x10 <sup>-3</sup>	2.5692
2TU7↔ 2TU10	7.1662x10 <sup>-11</sup>	10.1450	2.9974x10 <sup>-4</sup>	3.5233	2.8761x10 <sup>-4</sup>	3.5412
2TU3↔ 2TU6	0.41608x10 <sup>-1</sup>	-0.6191	7.0927x10 <sup>-3</sup>	2.1492	6.2726x10 <sup>-3</sup>	2.2026
2TU6↔ 2TU11	3.5224x10 <sup>-8</sup>	7.4532	0.1565 x10 <sup>-1</sup>	-0.1945	9.0045x10 <sup>-1</sup>	0.4554

#### 4. CONCLUSION

For 2-thiouracil, tautomerization in gas phase and solution was studied using DFT at the B3LYP/6-311++G(d,p) basis set. In this work we calculated relative stability, the constants of equilibrium for different tautomers of 2-thiouracil. According to our calculations, the most stable form is di ketone form (2TU1) and the order of energies; acetonitrile > water > gas, the dipole moments are order: Gas > acetonitrile > water, because of polarity increasing. In addition the equilibrium constants and inter conversion equilibrium constants also calculated. From this we observed some  $pK_T$  were positive and other negative; that determine the privileged direction of equilibrium.

#### COMPETING INTERESTS

Author has declared that no competing interests exist.

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