

## The mechanism of proton transfer and tautomerism in barbituric acid: A theoretical study

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### Abstract

Intermolecular proton transfer in barbituric acid (BA), both in the gas phase and in the presence of water molecule, was investigated using B3LYP method with aug-cc-pVDZ basis set. The overall process involves keto-enol and lactam-lactim tautomerism. The most stable form of barbituric acid turns into the intermediates with three step proton transfer at three different positions of the structure of this compound. Then, these intermediates become the final products passing from two competing processes. In order to determine the priority of each competitive process, energy changes of all possible tautomeric forms were investigated along the role of solvent molecules in multiple routes. Also, transposition in the proton-transfer process makes changes in the electron-transfer energy which was investigated both in the gas phase and in the presence of water molecules. Frequency calculations were performed to characterize ground and transition states and calculation of zero point energies. Natural bond orbital analysis and topological property of electron density were investigated using natural bond orbital (NBO) and atoms in molecules (AIM) analysis. From the results, all proton transfer processes in the gas phase and in the presence of the solvent molecule (water) is exothermic and non-spontaneous. In the gas phase and in the water assisted condition, the route 1b is kinetically more preferred. Despite the increase of the ring resonance of stronger hydrogen bonds in the product as compared to the reactant, the products are more unstable than the reactant. Therefore, the only factor that can make the product unstable is the severe decrease of LP (N)  $\rightarrow$   $\sigma^*$  (C-O) electron-transfer energy.

**Keywords:** Barbituric acid; tautomerism; proton transfer; charge transfer; stability.

### Introduction

Barbituric acid (BA) which structurally belongs to the 2,4-pyrimidinone derivatives plays an important role in the environment, industry, and pharmacy. Therefore, barbituric acid and its derivatives have widely been considered. The wide varieties of the

experimental research conducted about this compound and its derivatives show the significance of this structure [1]. This compound has widely been used in the preparation of colors and dyes [2], drugs [3], cloth [5], vitamin B2 (riboflavin) [6], and polymerization [7], and also employed as an intermediate in

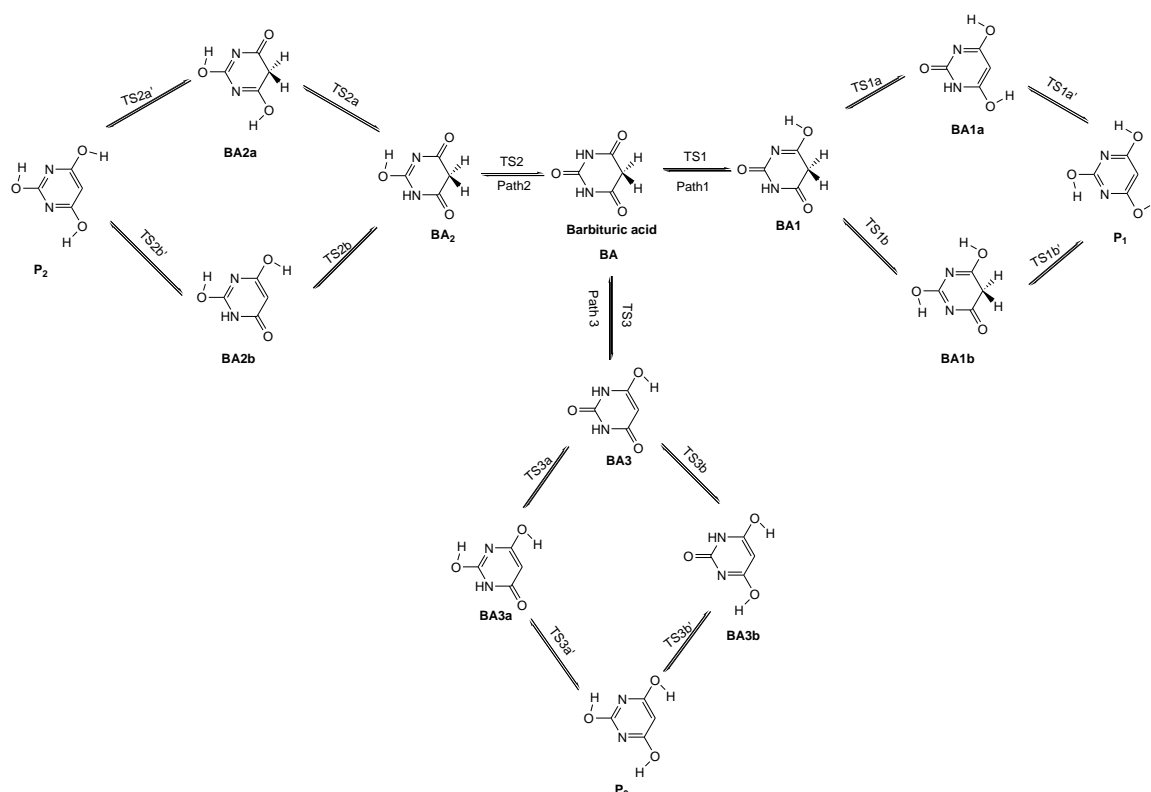
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some processes [8]. Barbituric acid has also been applied as a precursor for the derivatives, which exhibit antibacterial and tumor inhibitor activities [9]. Barbituric acid was firstly synthesized by Adolf von Baeyer, a German chemist, in December 6, 1864. This compound was obtained by the concentration of urea (a dung byproduct) with malonic acid (present in the apple) *via* the condensation method [10]. Barbituric acid is a pyrimidine heterocyclic compound which has some functional groups containing nitrogen. In the barbituric acid, the hydrogen atoms have higher mobility so this structure has the various tautomer forms. The most common tautomer form is the three-keto form. The acidic nature of

hydrogen atoms in the barbituric acid (pH = 4.8) is related to the lactam-lactim tautomer form of this structure. This compound has three lactam groups, and one, two or three groups attract hydrogen atom to produce the lactim form [11]. In this research, the intramolecular proton-transfer process in the barbituric acid has been investigated in the gas phase and in the presence of water molecules (Fig. 1). This proton transfer contains keto-enol and lactam-lactim tautomer processes which occur with the precedence. Thus, in this study, the energy changes of all possible tautomeric forms along with the role of solvent molecules in the proton transfer multistep have been investigated.



**Figure 1.** The different keto-enol and lactam-lactim tautomeric forms in the barbituric acid (**BA**)

As illustrated in Figure 1, the most stable form of barbituric acid (**BA**) is transformed into the intermediate structures during the three steps of

proton transfer in three different positions, and finally produced the final product during two competitive paths. Determining the priority of each

competitive paths can show the valuable facts about the determination of a preferred proton transfer route in this structure.

### Computational methods

All the structures in this work were optimized with B3LYP/aug-cc-pVDZ level using Gaussian 09 and Gamess suite software package [12, 13]. Vibrational frequencies were obtained at the same level for characterization of stationary points and thermal zero-point energy corrections. Intrinsic reaction coordinate (IRC) approach [14-17] was performed to ensure that the given transition state connects with the corresponding reactants and products. The natural bond orbital (NBO) analysis was carried out using version 3.1 of NBO package [18]. In addition, topological properties have been calculated using AIM methodology on the wave functions obtained at aug-cc-pVDZ level [19].

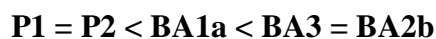
### Results and discussion

#### *The energies and structural parameters*

As can be seen in Figure 1, in the route **1**, the **BA** compound is transformed to the **BA1** intermediate *via* a proton transfer step after passing the **TS1** transition state. During two competitive paths, this intermediate is transformed to the **BA1a** and **BA1b** intermediates by passing the **TS1a** and **TS1b** transition states, respectively, and then changed to the **P1** final product by passing the **TS1a'** and **TS1b'**. Also, the **BA1** intermediate can be transferred into the different **BA1c** product during a proton transfer step after passing the **TS1c** intermediate. In the route **2**, the **BA** compound is transformed to the **BA2** intermediate by passing the **TS2** transition state, and then transferred into the **P2** final product *via* two proton transfer steps in two competitive paths. In the route **3**, the **BA** compound passes

the **TS3** state to produce the **BA3** intermediate. This structure is transformed into the final **P3** product during two proton transfer steps in two different competitive paths. It should be mentioned that the **P1**, **P2**, and **P3** products are completely identical, and presented by **1**, **2** and **3** numbers due to their formation in three different routes. All structures optimized in the gas phase (isolated) has been depicted in Figure 2.

The keto-enol tautomer process in the barbituric acid (**BA**) includes the transfer of H7 to O9 or O10 which are completely identical regarding the energy level and due to the structural symmetry of **BA**. It is obvious that in all these transformations, the C-C bond length decreases while the C-O bond length increases. The order of C-C bond length decrease in these structures is as follows:



The amount of C-C bond length decrease in these structures is as follows: 0.137, 0.145, and 0.156 Å, and also the C-O bond length rises in these transformations. The order of changes in these structures is as follows:

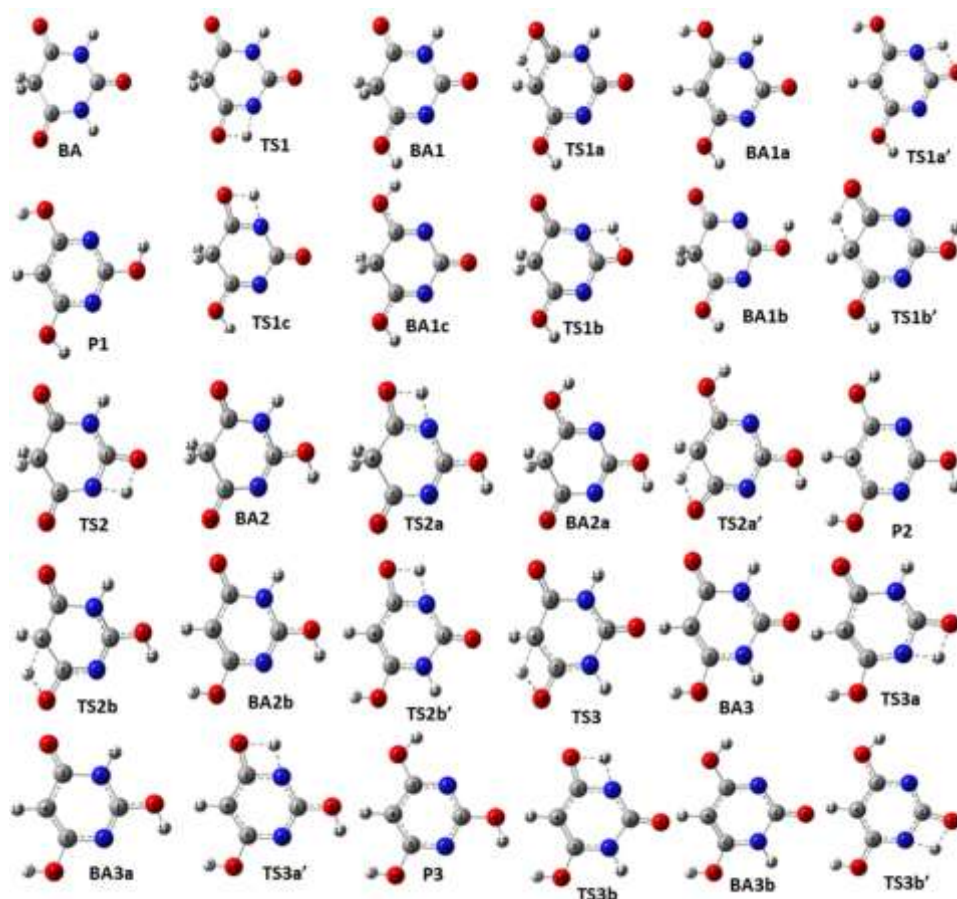


The amount of these changes is 0.138, 0.137, 0.136, and 0.135 Å.

In the lactam-lactim tautomeric form, the highest and the lowest reduction in the N-C bond length are related to the **BA1b** and **BA3a** structures, respectively (0.109 and 0.094 Å). Also, the highest and the lowest increase of the C-O bond length are related to the **BA1c** and **BA2a** structures, respectively (0.127 and 0.121 Å). It is indicated that in all structures, the amount of these changes in the bonds participating in the keto-enol tautomeric form is more than the lactam-lactim tautomeric form. In the **BA** compound, the different proton

transfer routes pass from 15 transition state structures. The unique negative frequency in these structures is related to the vibration of H atom between C and O atoms or N and O atoms. All transition state structures related to the lactam-lactim tautomerism in the gas phase contains an O-H-N-C four-

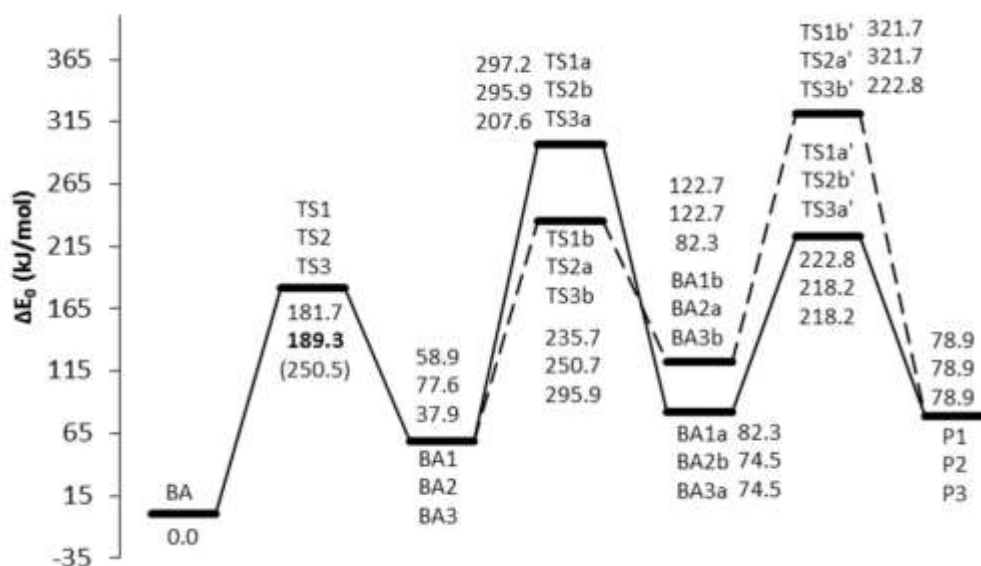
membered ring, and the proton transfer takes place on the sheet. However, in the keto-enol tautomerism, all transition state structures in the gas phase include an O-H-C-C four-membered ring, and the proton transfer takes place out of the sheet (Figure 2).



**Figure 2.** The Optimized structures in the gas phase

The diagram of the potential energy surface related to the structures participating in the proton-transfer process along with the zero-point electronic energies ( $\Delta E_0$ ) have been shown in Figure 3. The obtained results depicted that in the proton-transfer process in the gas phase, the **BA** and **BA1c** compounds have the most stable and the least stable structures,

respectively, among all ground state structures. In the route **1**, after one proton transfer step, the **BA1** intermediate is produced, and then the reaction proceeds through two competitive pathways. Two competitive paths **1a** and **1b** resulting the **P1** product during two proton transfer steps.



**Figure 3.** The diagram of potential energy surface for the proton transfer in the gas phase

The activation energies for the first and second steps of proton transfer in the path **1a** are 283.3 and 140.5 kJ/mol, respectively, while in the path **1b**, these energies are 176.5 and 199.0 kJ/mol, respectively. Both competitive paths **1a** and **1b** have an identical nature and the transposition of two proton-transfer steps only make these two pathways different and are led to the joint **P1** product. The first step of proton-transfer in the route **1a** and the second step of proton transfer in the route **1b** are related to the keto-enol tautomerism under an identical position of **BA** compound. The activation energy difference of these two steps is 39.3 kJ/mol. The second step of proton transfer in the route **1a** and the first step of proton transfer in the route **1b** are related to the lactam-lactim tautomerism under an identical position of **BA** compound. The activation energy difference of these two steps is 36.3 kJ/mol. These considerable differences in the activation energies can perfectly show the precedence of proton-transfer steps. In the route **1a**, the energy consumed in passing the activation energies of two proton-

transfer steps is 3 kJ/mol more than the route **1b**. Also, in the route **1a**, the highest activation energy is related to the first proton transfer step, while in the route **1b**, this energy is considered for the second proton transfer step which chosen as a rate-determining step. The energy difference between the rate-determining steps of these two routes is 39.3 kJ/mol which shows that the route **1a** is kinetically more stable than the route **1b**.

The first proton transfer step is an endothermic process ( $\Delta H = 77.5$  kJ/mol) so the first step of proton transfer in the routes **1a**, **1b**, and **1c** are endothermic and non-spontaneous processes. The second steps of proton transfer in the competitive routes **1a** and **1b** are exothermic and spontaneous processes. Although the second proton transfer in the route **1b** has the high activation energy (199.0 kJ/mol) in comparison with the route **1a** (140.5 kJ/mol), but it is more spontaneous than the route **1a** ( $\Delta G = -47$  kJ/mol). The total reaction is endothermic and non-spontaneous ( $\Delta G = 83.5$  kJ/mol and  $\Delta H = 77.8$  kJ/mol). Since in all three routes **1**, **2**, and **3** the reactant and the product



are identical and have the same potential energy surface, no thermodynamic precedence or priority has been seen. Therefore, the kinetic stability only plays an important role in three routes **1**, **2**, and **3**. However, the kinetic and thermodynamic stability can be discussed in different steps of each route.

In the route **2**, the **BA** compound is transformed to the **BA2** after passing a proton transfer step (**Ts2**). Then, during two competitive pathways **2a** and **2b**, it is transferred into the stable product **P2**. The **BA** compound passes the activation energy (**TS2**) which is 7.6 kJ/mol more than the similar case (**TS1**) in the route **1** to produce the intermediate **BA2** which is 18.7 kJ/mol less stable than the **BA1**. The first step of the competitive path **2a** and the second step of the competitive path **2b** contain a lactam-lactim tautomerization in which the activation energy difference of proton transfer is 29.5 kJ/mol. The second step of the competitive path **2a** and the first step of the competitive path **2b** include a keto-enol tautomerization in which the activation energy difference of proton transfer is 19.2 kJ/mol. The considerable difference between the activation energies clearly illustrates the role of precedence in the proton transfer process. The keto-enol proton transfer steps take place in two competitive pathways and due to having higher activation energy in comparison with the lactam-lactim proton transfer steps, they are considered as the rate-determining step in each pathway. As mentioned before, the activation energy of this proton transfer in the path **2b** is 19.2 kJ/mol lower than the path **2a**, which shows the kinetic stability of the competitive path **2b** in comparison with the competitive path **2a**. Also, due to lower

energy consumption in the path **2b** (361.9 kJ/mol) compared to the competitive pathway **2a** (372.9 kJ/mol), it not only depicts the importance of precedence in the tautomeric forms, but also it proves the priority of the competitive pathway **2b** in comparison with the competitive path **2a**. The first proton transfer step in this route is endothermic ( $\Delta H = 189$  kJ/mol). The **BA2a** intermediate has the kinetic stability, but the intermediate **BA2b** has the thermodynamic stability.

The first proton transfer step in the path **2a** is endothermic and non-spontaneous, while the second proton transfer step in the path **2a** is exothermic and spontaneous. In this step, the product **P2** is thermodynamically stable. In the pathway **2b**, the second proton transfer step is endothermic and non-spontaneous. In this step, the product is kinetically stable.

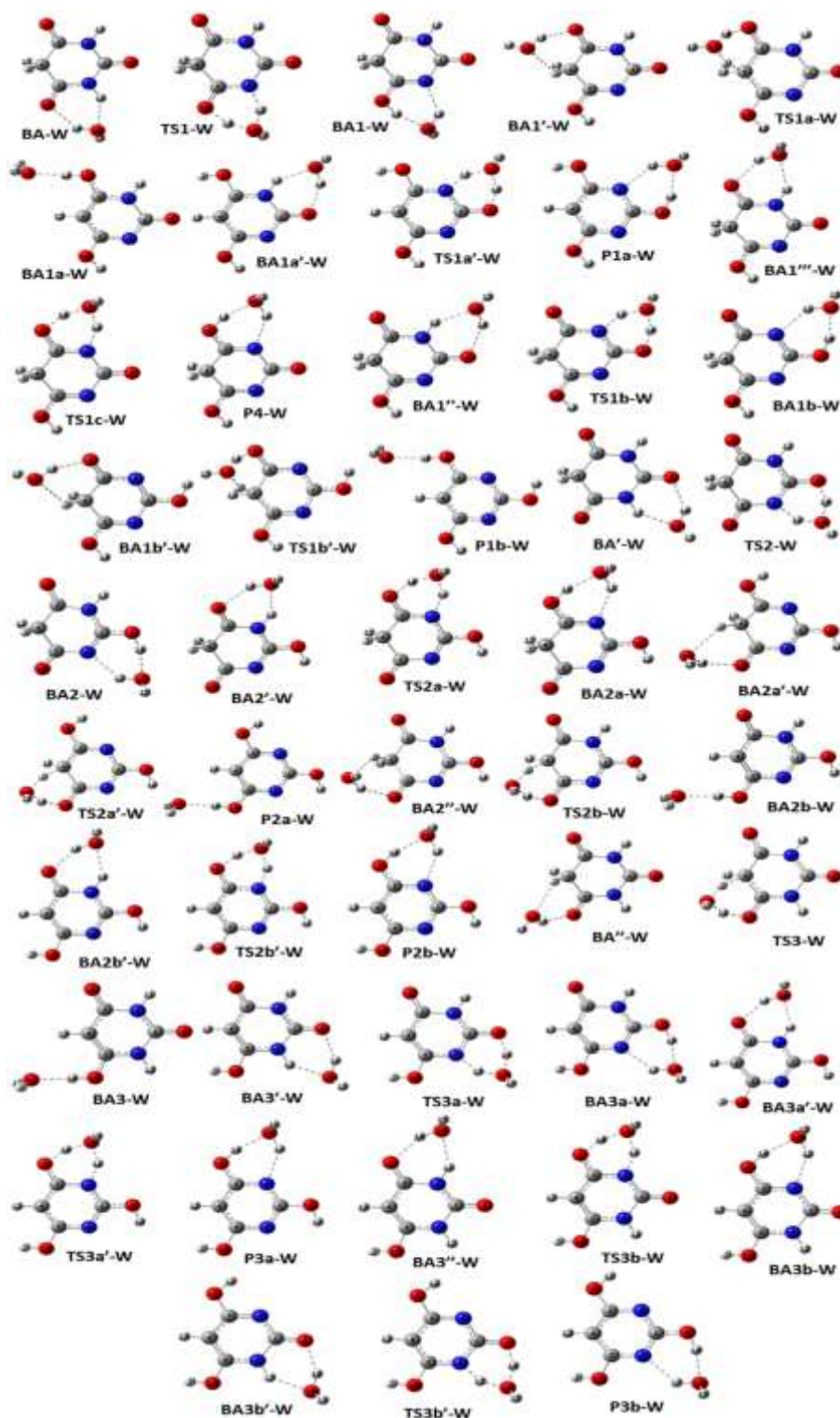
In the route **3**, the **BA** compound is transferred to the **BA3** via a keto-enol tautomerism. The **BA3** compound is transformed into the stable product **P3** during two proton transfer steps (lactam-lactim tautomer) in two competitive pathways **3a** and **3b**. In the first step, the keto-enol tautomerization has the highest activation energy (250.5 kJ/mol) which is chosen as a rate-determining step. The highest activation energy in the route **3a** is 169.8 kJ/mol which is 26.1 kJ/mol more stable than the highest activation energy in the route **3b** (143.7 kJ/mol) representing the kinetic priority of pathway **3a**. The route **3b**, which consumes 304.7 kJ/mol energy in comparison with the energy consumed in the route **3a** (313.4 kJ/mol), has the precedence. The lactam-lactim tautomerism in the first step of the competitive pathway **3a** and the second step of the competitive pathway **3b**

takes place under an identical position of the compound **BA**. The activation energy of these two proton transfer processes, in spite of having an identical nature, has a 20.6 kJ/mol difference. A 29.3 kJ/mol difference exists between the activation energies in the second step of the competitive pathway **3a** and the first step of the competitive path **3b**. In this pathway, except the second step of the competitive route **3b**, all proton transfer steps are endothermic and non-spontaneous. The effects of the solvent molecule, the water assisted proton transfer process have also been studied. The optimized structures has been shown in Figure 4. The keto-enol proton transfer process in the presence of water molecule contains the transfer of H7 or H13 atom to the O16 of water molecule along with the transformation of H14 of the water molecule into the O10 or O9 atoms. In the lactam-lactim tautomerism, the H11 or H12 atoms are transformed to the O16 atom of the water molecule. Indeed, the water molecule as a bridge assist the proton transfer process. In the lactam-lactim tautomerization, the transition state structures include an O-H-O-H-N-C six-membered ring, and the proton transfer take places in the sheet. The diagram of the potential energy surface related to the different structures participating in the proton transfer process in the presence of water molecule along with the zero-point electronic energies ( $\Delta E_0$ ) have been depicted in Figure 5.

In the route **1**, the activation energy of the first proton transfer step in the presence of water molecule (68.3 kJ/Mol) decreases in the amount of 113.4 kJ/Mol. The complexation energy

makes the compound **BA1-W** more stable than the **BA1** in the amount of 24.8 kJ/mol. Also, the complexation energy raises the stability of **P1a-W** and **P1b-W** products about 31.8 and 24.7 kJ/mol, respectively, but, the total process is endothermic and non-spontaneous. Although in the first step, the proton transfer of the competitive pathways **1a** and **1b** are endothermic similar to the gas phase, but the activation energy of the proton transfer shows the decrease of 128.4 and 106.2 kJ/mol, respectively. In the second step of pathways **1a** and **1b**, the proton transfer processes are exothermic and spontaneous similar to the gas phase, while the activation energy illustrates the 100.2 and 113.8 kJ/mol decrease, respectively. Although in the pathway **1b** the highest activation energy is 24.7 kJ/mol lower than the highest activation energy in the route 1a, it has the kinetic priority. The route 1a has the thermodynamic stability due to the formation of more stable product **P1a-W**, and has the priority regarding to lower energy consumption.

In the route **2**, the activation energy of the first proton transfer step in the presence of the water molecule is 114.4 kJ/mol lower than the gas phase. The first step of the competitive pathway **2a** is a rate-determining step. The complexation energy in the product **BA-W** is -24.9 kJ/mol. In this condition, similar to the gas phase, the route **2a** has the kinetic precedence, but the competitive pathway **2b** has the thermodynamic stability. In the route **2a**, the activation energy of the first and second steps shows 110.7 and 117.4 kJ/mol decrease, respectively, while in the route **2b**, it depicts 118.1 and 101.8 kJ/mol reduction, respectively.

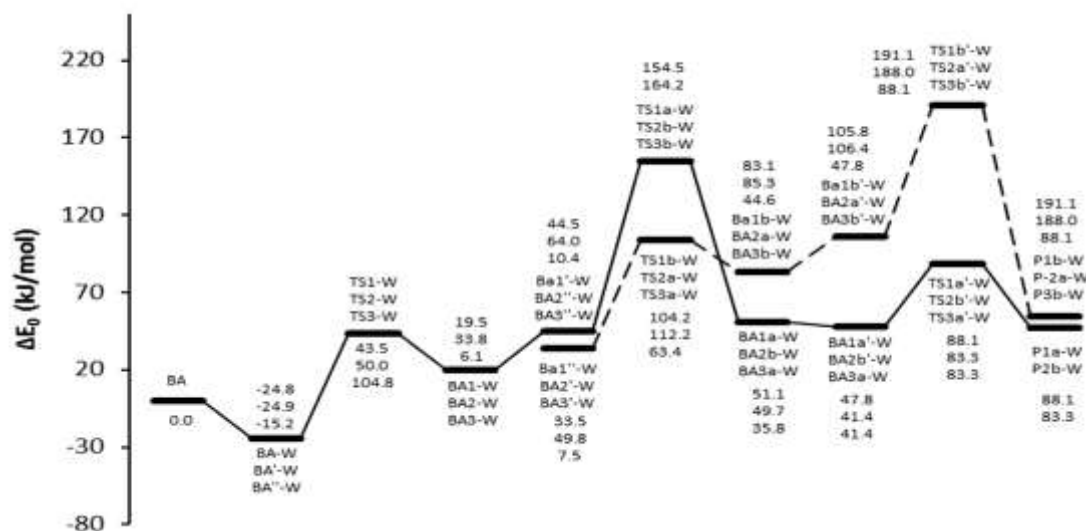


**Figure 4.** The optimized structures in the presence of the water molecule

The routes **2a** and **2b** does not represent a special energy priority due to the consumption of 144.1 and 142.1 kJ/mol energies, respectively. The **P2a-**

**W** and **P2b-W** products like the reactants have the considerable stability of -24.7 and 33.16 kJ/mol, respectively, in comparison with the gas phase.





**Figure 5.** The diagram of potential energy surface of the proton transfer process in the presence of one water molecule

In the route **3**, the complexation energy of **BA-W** compound is slightly lower than the routes **1** and **2** (-15.21 kJ/mol). The first proton transfer step, which is a rate-determining step, considerably depicts a decrease of 130.5 kJ/mol compared to the gas phase. Although the activation energies of the first and second step of the competitive pathways **3a** and **3b** decrease in comparison with the gas phase, no significant differences have been observed between the activation energies of the first and second steps of these pathways. It can be due to the identical nature of the proton transfer process (lactam-lactim) in these competitive routes. The products **P3a-W** and **P3b-W** have the stability of 33.2 and 31.8 kJ/mol compared to the gas phase, while they do not have a considerable difference in term of stability. Although the activation energy of the first and second proton transfer steps in the routes **3a** and **3b** does not show any significant differences, they considerably decrease compared to the gas phase. In the gas phase, the route **3b** is more preferred but in the presence of the water molecule, the pathway **3a** is preferred.

### Analysis of natural bonding orbital (NBO)

Analyzing the charges of the atoms participating in the proton transfer process along with the occupation number and the main charge transitions between the bonds participating in the proton transfer in the gas phase have been presented in Table **S1**. The charge analysis shows that in the proton transfer process and in the keto-enol and lactam-lactim tautomeric forms in all three pathways, the charge is transferred to the H atom, and the charge of the proton donor atoms (C or N) decreases, while the charge of the proton acceptor atoms (O) increases. In the lactam-lactim proton transfer process, the charge changes on the H atom are about 0.0591-0.068 a.u but in the keto-enol proton transfer process, the charge changes on the H atom are more (0.206-0.221 a.u) due to the electronegative difference between two atoms of C and O. The precedence of proton transfer processes affects the atomic charge changes. For instance, the atomic charge changes on the H atom in the proton transfer process have been investigated. In the route **1**, in the first step of the competitive pathway **1a**

and the second step of the competitive route **1b**, the atomic charge changes on the H atom are 0.221 and 0.206 a.u., respectively. In the route **2**, the atomic charge changes on the H atom in the second step of the competitive pathway **2a** and the first step of the competitive route **2b** are 0.206 and 0.221 a.u. In the route **3** and in the first proton transfer step, the atomic charge change on the H atom is 0.219 a.u. Investigating the occupation number depicts that in all proton transfer steps, the occupation number of C-O bonds increases, whereas the occupation number of C-N or C-C bonds decreases. In all cases, the decrease of C-C bond occupation number is lower than the C-N bond. The precedence of the proton transfer process affects the occupation number of anti-bonding orbitals ( $\sigma^*$ ). For instance, the occupation number changes of anti-bonding orbitals in the C-O bond are not equal in any competitive pathways. Therefore, the charge transfer energy ( $E^{(n)}$ ) in these systems has been studied. The charge transfer energy ( $E^{(n)}$ ) shows the electron delocalization from the bond donor to the bond acceptor. The high amount of  $E^{(2)}$  indicates the strong interaction between two bonds. In the lactam-lactim tautomerization process, there are two main electron transfer as follows: LP (N)  $\rightarrow \sigma^*$  (C-O) and LP (O)  $\rightarrow \sigma^*$  (C-N). In the lactim forms, the LP (N)  $\rightarrow \sigma^*$  (C-O) transfer energy considerably decreases, while the LP (O)  $\rightarrow \sigma^*$  (C-N) transfer energy raises. Also, in the lactim forms, another LP (O)  $\rightarrow \sigma^*$  (C-N) transfer exists.

In the keto-enol tautomerization processes, the keto and enol forms have a LP (O)  $\rightarrow \sigma^*$  (C-C) transfer. The energy of this electron transfer considerably increases in the enol forms compared to the keto forms. The first proton transfer steps in the routes **1**

and **2** are related to the lactal-lactim proton transfer in the different positions of **BA** compound. The LP (N)  $\rightarrow \sigma^*$  (C-O) transfer energy decreases about 45.6 kJ/mol in the **BA** $\rightarrow$ **BA2** transformation, whereas the decrease of this energy transfer is about 20.1 kJ/mol in the **BA** $\rightarrow$ **BA1** transformation. These results show that the proton transfers in the different conditions affect the transfer energies. The precedence of proton transfer process can more affect the proton transfer energies. For example, in the route **1**, the LP (O)  $\rightarrow \sigma^*$  (C-C) transfer energy increases about 19.8 kcal/mol in the first proton transfer process of the competitive pathway **1a**, while this increase is 18.2 kcal/mol in the second step of the competitive pathway **1b**. Also, in the second step of the competitive route **1a**, the LP (N)  $\rightarrow \sigma^*$  (C-O) transfer decreases about 38.2 kcal/mol, however, the LP (O)  $\rightarrow \sigma^*$  (C-N) transfers increases about 15.3 kcal/mol. In the first step of the competitive pathway **1b**, the amounts of this decrease and increase are 42.1 and 21.6 kcal/mol, respectively.

#### Analysis of atoms in molecules (AIM)

Quantum theory of atoms in molecules (QTAIM) is an appropriate tool for investigating hydrogen bonds [20-22]. To gain more concise information about the power and nature of hydrogen bonds, the analysis of electron density at the bond critical points  $\rho(r)$ , laplacian of electron density at the bond critical points ( $\nabla^2\rho(r)$ ), total electron density  $H(r)$ , electron potential energy density  $V(r)$ , and the electron kinetic energy density  $G(r)$  at the bond critical points (BCPs) have been carried out using the atoms in molecules theory.

As shown in Table S2, investigating the ring density illustrates that in each step of proton-transfer from **BA** to **P**, the electron-density at the ring critical point (RCP) gradually increases. The increase of LP (O)  $\rightarrow\sigma^*$  (C-N) and LP (O)  $\rightarrow\sigma^*$  (C-C) transfer energies causes an increase of the ring electron density in the compound **BA**. Actually, the increase of ring electron density must naturally raise the ring resonance and makes the ring stable. Via investigating the stability of the structures, it is indicated that all three pathways lead to the more unstable products (**P1**, **P2**, or **P3**) compared to the reactant **BA**. The increase of resonance is not the reason of stability of the product, but it can be due to the severe reduction of LP (N)  $\rightarrow\sigma^*$  (C-O) transfer energy, which depicts to be more prevalent than the resonance effect. The amount of electron density ( $\rho(r)$ ) at the ring critical point (**R1**) increases from 0.018 in reactant **BA** to 0.026 in product **P**. The precedence of proton transfer affects the electron density. In the transition state structures, there is another ring critical point (**R2**) which is considered as a result of the simultaneous interaction of H with N and O in the four-membered ring. The electron density of this ring does not show the similar changes in different competitive pathways. The values of  $\nabla^2\rho(r)$  and  $H(r)$  at the BCP of X...H bonds (X=C, N, O) involved in the hydrogen bond in ground and transition state structures are negative (with the exception of **TS1b'** and **TS2a'** structures), indicate that X...H bonds have covalent character. The values of

$\nabla^2\rho(r)$  and  $H(r)$  at the BCP of O...H bond in **TS1b'** and **TS2a'** structures are positive and negative, respectively. These values reveal the partial covalent nature of O...H bond in these structures. It can be concluded that O...H bond in **TS1b'** and **TS2a'** structures are weaker than other transition state structures. Analysis of BCP data reveals that the covalent nature of the X...H bond decreases on going from ground states to transition states.

### Conclusion

The mechanism of intramolecular proton-transfer in the barbituric acid (**BA**) in the gas phase and in the presence of the water molecule has been investigated. The results are as follows:

1. In the gas phase and in the presence of the water molecule, the transposition of proton-transfer processes causes some changes in the electron-transfer energies and also stability energies of the structures.
2. All proton-transfer processes in the gas phase and in the presence of the solvent molecule (water) are exothermic and non-spontaneous.
3. In the presence of water molecules, the potential energy surfaces and the transition barriers considerably decrease as compared to the gas phase.
4. In the gas phase and in the water assisted condition, the route **1b** is kinetically more preferred.
5. Although the steric effect and ring resonance can be effective factors in the stability of the complexes, the results show that the electron-transfers play an important role in the complex stability.
6. The increase of ring resonance has no role in the structural stability, due to the severe reduction of LP (N)  $\rightarrow\sigma^*$  (C-O) transfer energy.

7. The results are presented that although the evidence proves the presence of stronger hydrogen bonds in the product as compared to the reactant, in all pathways, the products are more unstable than the reactant. Therefore, the only factor that can make the product unstable is the severe decrease of LP (N)  $\rightarrow\sigma^*$  (C-O) electron transfer energy.

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