Journal of Molecular Graphics and Modelling 49 (2014) 47–54

Contents lists available at ScienceDirect

Journal of Molecular Graphics and Modelling

journal homepage: www.elsevier.com/locate/JMGM

# Tautomerism in pyridazin-3(2H)-one: A theoretical study using implicit/explicit solvation models

Saeed Reza Emamian[a,*], Luis Ramón Domingo[b], Sayyed Faramarz Tayyari[a]

[a] Chemistry Department, Shahrood Branch, Islamic Azad University, Shahrood, Iran
[b] Departamento de Química Orgánica, Universidad de Valencia, Dr. Moliner 50, E-46100 Burjassot, Valencia, Spain

ARTICLE INFO

*Article history:*
Received 3 October 2013
Received in revised form
25 December 2013
Accepted 20 January 2014
Available online 28 January 2014

*Keywords:*
Tautomerism
Pyridazinone
DFT calculations
Solvent effects
Explicit and implicit solvation models

ABSTRACT

The tautomeric conversion of pyridazin-3(2H)-one **1** into pyridazin-3-ol **2** has been theoretically studied using density functional theory (DFT) methods at the B3LYP/6-311++G** level. Two mechanisms have been considered for this process: (i) one in which the hydrogen is directly transferred through **TS12**; and (ii) another one in which a double hydrogen transfer takes place via **TS1122** upon formation of the corresponding dimer. The former requires a very high activation energy of 42.64 kcal/mol as a consequence of the strain associated with the formation of the four-membered **TS12**, while the latter requires a much lower activation energy, 14.66 kcal/mol. Implicit, explicit, and a combination of both implicit and explicit solvation models, using both protic and aprotic polar solvents, have been considered for the first mechanism. This study allows the establishment of the requirement to use protic polar solvents in order to reduce the high activation energy associated with **TS12**.



## 1. Introduction

Tautomerism, because of its importance in organic chemistry, has been the subject of enormous theoretical and experimental studies. It is well known that properties, activities, and functions of many biologically and pharmaceutically important substances can be considerably affected by tautomerism [1]. The concept of tautomerizations is called tautomerism, which results in the formal migration of a hydrogen atom or proton, accompanied by a switch of a single bond and its adjacent double bond (see Chart 1) [2–4]. β-Ketoamides are versatile intermediates for the synthesis of many heterocyclic compounds and antibiotics [5]. It has been found that the reactivity of these compounds is related to their tautomeric equilibria [6]. Hydroxamic acids are used as metal chelating agents [7], corrosion inhibitors [8], and antioxidants [9]. Tautomerism can affect the chemical and biological activities and, especially, the chelating properties of hydroxamic acids [10]. Keto-enol tautomerism of p-hydroxyphenylpyruvic acid, whose level in blood and urine can be used for the diagnosis of the congenital metabolic defect known as tyrosinemia, is also widely studied [1,11].

Two different mechanisms for the hydrogen transfer process have been proposed for tautomerization processes (see Scheme 1): (i) a one-step mechanism, which involves direct intramolecular hydrogen transfer process; and (ii) an intermolecular process involving the participation of an acid/base catalyst species. In the latter, different basic/acid species can participate as proton acceptor and/or donor, and experimental data seem compelling to reach such a conclusion [8,12].

An earlier study of the intramolecular tautomerization in acetaldehyde/vinyl alcohol, X = O, and acetaldimine/vinylamine, X = NH, systems using different computational levels showed that the tautomerization process via the direct intramolecular hydrogen transfer presents a very high activation barrier, 71–94 kcal/mol for X = O and 62–85 kcal/mol for X = NH, as a consequence of the strain associated with the formation of the four-membered transition state structures (TSs) required in this one-step hydrogen transfer process [13].

Tautomerism can occur in gas phase, solution, and in the crystalline state, although in the latter case harder conditions such as high temperatures need to be considered [1,12,14]. The ratio of tautomers can strongly be modified by the use of an adequate solvent [12,15]. In order to investigate the solvent effect on tautomerization reactions many theoretical studies [16–21], in addition to the experimental works, have been performed using *self-consistent reaction field (SCRF)* [22–25] approaches. In these simple but powerful methods, solvents are modelled by a continuum of a uniform dielectric constant ($\varepsilon$), namely the reaction field, and the solute

* Corresponding author. Tel.: +98 912 1735085; fax: +98 273 3390537.
*E-mail addresses:* saeedreza_em@yahoo.com, s_emamian@iau-shahrood.ac.ir (S.R. Emamian).

1093-3263/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jmgm.2014.01.006

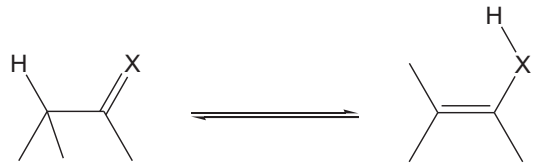
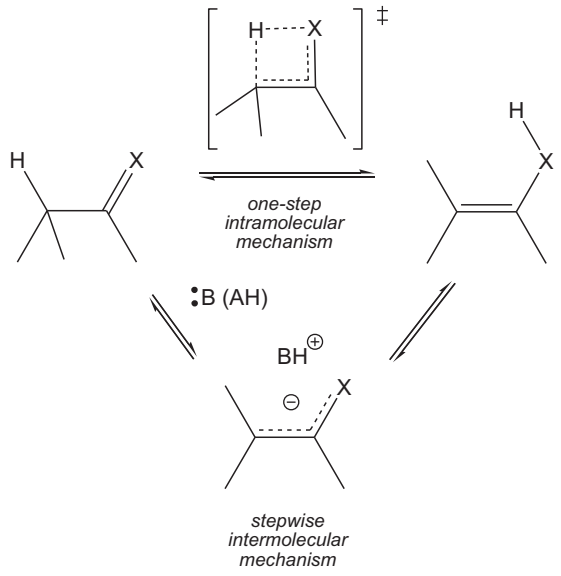
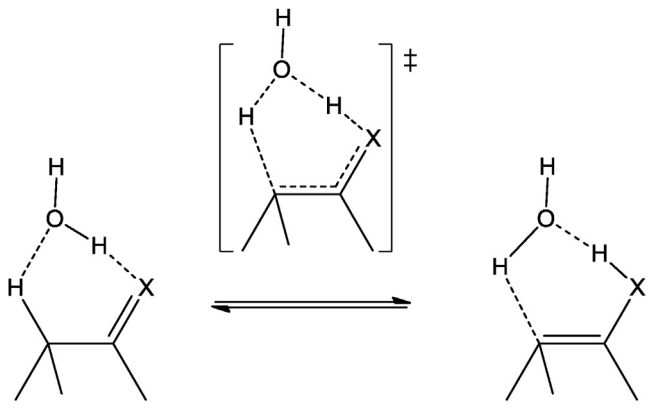


**Chart 1.** Tautomerism.

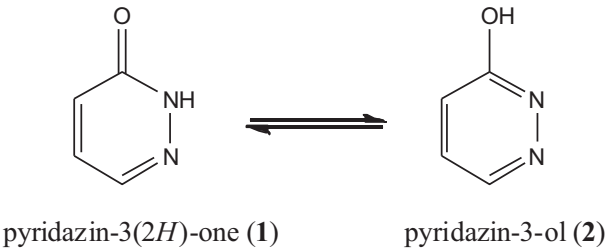
is placed into a cavity within the solvent. SCRF approaches differ in how they define the cavity and the reaction field [26]. In SCRF methods long range solute–solvent interactions are considered; that is, some important electronic effects associated with specific solute–solvent interactions, such as hydrogen bonding (HB), cannot be considered. Consequently, when the solute is placed in a solvent which can form hydrogen bonds, especially with the hydrogen involved in the tautomerization process, using SCRF methods may lead to a high degree of error in both geometries and energies. One way to overcome this deficiency of SCRF approaches is considering an appropriate number of solvent molecules directly interacting with the solute, especially at the reaction site (see Scheme 2). In other words, combined supermolecular/continuum models, which is usually known as the *explicit solvation model*, is a reasonable strategy in which specific solute–solvent interactions are taken into account [27].



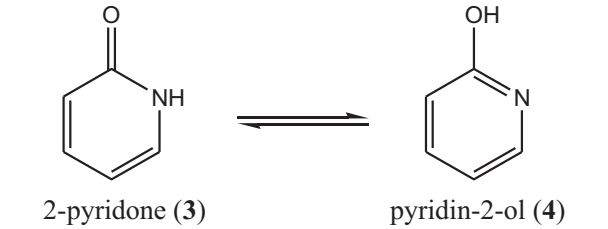

**Scheme 1.**



**Scheme 2.**




**Scheme 3.** The tautomeric equilibrium investigated in this work.




**Scheme 4.** The tautomeric equilibrium investigated by Fu et al. [36].

In the vast majority of theoretical works, the explicit solvation model is used when a solvent with HB accepting/donating capability such as water or methanol is involved [28–34], while in the case of other solvents which behave as HB acceptors such as tetrahydrofuran (THF), acetone, dimethylsulfoxide (DMSO), etc., the explicit solvation model is not considered.

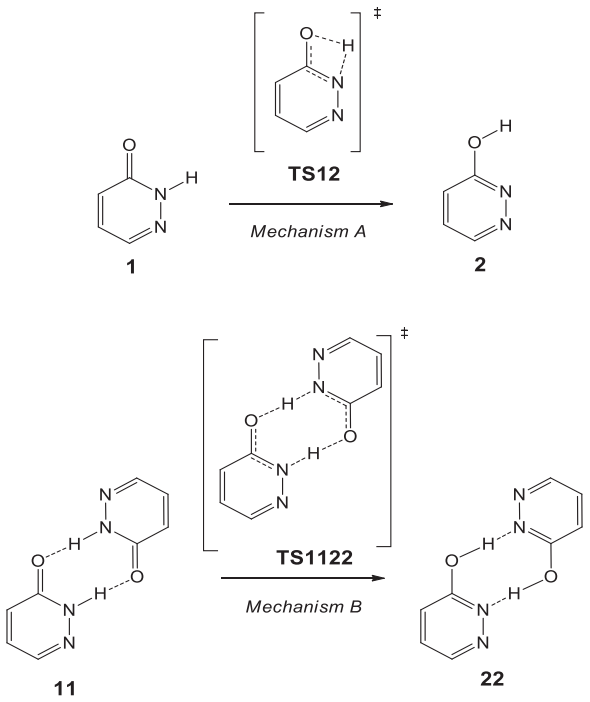
Pyridazin-3(2H)-one (pyridazinone, **1**) is the main skeleton of pyridazinone derivatives, well known for their pronounced analgesic, anti-inflammatory, antinociceptive, and antiulcer activities. Pyridazinones have been used as anticonvulsant, antiasthmatic, antidiabetic, and antimicrobial agents [35]. The main goal of present work is to exactly address the effects of protic polar solvents such as water and methanol, and aprotic polar solvents such as THF or DMSO on tautomerization reactions using a combined explicit and/or implicit solvation model. In line with this goal, the tautomerization of the simplest pyridazinone, which can exist in the pyridazinone **1** and pyridazin-3-ol (pyridazinol **2**) tautomeric forms, is studied (Scheme 3).

In 2005, Fu et al. studied the tautomerization of 2-pyridone **3** into pyridin-2-ol **4** in the absence and the explicit presence of water molecules, as well as the self-assisted dimer reaction using B3LYP and BH-LYP hybrid density functional methods at the 6-311++G(2d,2p) basis set level (see Scheme 4) [36]. They found that the barrier heights for both water-assisted and self-assisted reactions are significantly lower than that of the tautomerization reaction for isolated 2-pyridone **3**. When long-range solvent effects were considered by using a continuum model for water, both barrier heights and reaction energies increased, indicating that the tautomerization of 2-pyridone becomes less favourable in the polar solvent.

Herein, we report a theoretical study of the solvent effects on the tautomerization process of the simplest pyridazinone **1** into pyridazol **2,** using DFT methods at the B3LYP/6-311++G** level of theory (see Scheme 3). A combined explicit and implicit solvation model for protic and aprotic polar solvents is used in order to analyze the solvent effects on the tautomerization.

## 2. Computational details

The geometries of monomers, dimers, and TSs investigated in this work, in both gas phase and in the presence of polar solvents, were fully optimized at the DFT-B3LYP [37] level combined with the 6-311++G** basis set, using the Gaussian 09 software package




**Scheme 5.** Direct hydrogen transfer, mechanism A, and indirect hydrogen transfer, mechanism B, involved in the gas phase tautomerization of pyridazinone **1** into pyridazol 2.

[38]. The accuracy of the B3LYP method for studying systems with HB interactions and proton transfer has previously been proved [36,39,40]. In order to verify the nature of each stationary point, frequency calculations were performed at the same level used for optimizations; TSs were characterized by one and only one imaginary frequency. The IRC paths [41] were traced in order to check the energy profiles connecting each TS to both associated minima of the proposed mechanism using the second order González-Schlegel integration method [42]. Tomasi's PCM model [22] was employed to address the solvent effect on the investigated tautomerization. The steric repulsion energy between the lone-pair electrons of the adjacent $sp^2$ nitrogen atoms in pyridazol **2** was calculated using the NBO 5.0 program [43] and it is graphically represented using NBOView 1.1.

## 3. Results and discussion

### 3.1. Tautomerism in gas phase

Two mechanisms, as sketched in Scheme 5, have been considered for the tautomerism process in the gas phase; (i) one via a direct hydrogen transfer process, mechanism A; and (ii) the other via an indirect (by dimerization) hydrogen transfer process, mechanism B. The total and relative electronic energies for reactants (R), TSs, and products (P) involved in the two mechanisms are displayed in Table 1. The geometries of the TSs associated with the two mechanisms, including corresponding imaginary frequencies, can also be observed in Fig. 1.

Tautomerization of pyridazinone **1** into pyridazol **2** is an endothermic process of 8.66 kcal/mol; i.e. pyridazinone **1** is more stable than pyridazol **2**. At a glance, it seems that pyridazol **2** should be more stable than pyridazinone **1** due to its expected high aromatic character. The resonance stabilization energy (RSE) corresponding to pyridazinone **1** and pyridazol **2** can easily be evaluated using the isodesmic reactions presented in Scheme 6.

The isodesmic reactions given in Scheme 6 show that pyridazinone **1** has a high RSE, 13.91 kcal/mol, however, it is lower than that computed for pyridazol **2**, 23.49 kcal/mol. Although the RSE of pyridazol **2** is lower than that computed for benzene, 37.08 kcal/mol, the high RSE found in pyridazol **2** can be associated with some aromatic character of this species. However, in spite of the high RSE of pyridazol **2**, which is 9.49 kcal/mol higher than that of pyridazinone **1**, pyridazinone **1** is 8.66 kcal/mol more stable than pyridazol **2**. Indeed, in order to explain the relative stability of these two tautomers, other factors, besides aromaticity, should be considered. In pyridazinone **1** a carbonyl group, a high stabilizing functional group, is present, while this functional group is absent in pyridazol **2**. On the other hand, the steric repulsion (8.77 kcal/mol) between the lone-pair electrons of the adjacent $sp^2$ nitrogen atoms, see Fig. 2, should be considered as an important destabilizing factor in pyridazol **2** with respect to pyridazinone **1**. Based on these three factors, it can be understood why pyridazol **2** is less stable than pyridazinone **1** in spite of its higher aromatic character.

According to the direct mechanism A, as presented in Scheme 5, tautomerism takes place through the four-membered **TS12**. As mentioned before, the high activation energy associated with **TS12**, 42.64 kcal/mol, can be related to the high strain caused by the formation of four-membered cycle. This activation energy is 4.94 kal/mol higher than that found for tautomerizartion of 2-pyridone **3** [36]. In mechanism B, a double tautomerization takes place via the eight-membered **TS1122**, without strain. Consequently, the activation energy for double tautomerization via **TS1122** presents a very low value, 14.66 kcal/mol, when it is compared with that obtained for **TS12**. A similar results was found by Fu on the tautomerization of the dimer of 2-pyridone **3**; 9.57 kcal/mol [36]. It is clear that the indirect mechanism B is the kinetically preferred mechanism in the gas phase. Similar to the case of the direct mechanism A, tautomerization via mechanism B is endothermic by 12.20 kcal/mol, indicating lower stability for dimer **22** than dimer **11**. However, the endothermic character of mechanism B is 5.12 kcal/mol less unfavourable than twice the direct mechanism A, probably as a consequence of a stronger HB formation in dimer **22** than in dimer **11**.

The geometries of **TS12** and **TS1122** are given in Fig. 1. At the four-membered **TS12**, the length of the N-H breaking bond is 1.318 Å, while the length of the O-H forming bond is 1.361 Å. At the dimeric **TS1122**, the length of N—H breaking bond is 1.336 Å, while the length of the O—H forming bond is 1.162 Å.

### 3.2. Solvent effects on tautomerism

Solvent effects on tautomerism have been considered using three computational models: (i) long range interactions between solute and solvent, modelled through the use of the SCRF method (implicit solvation model) in the gas phase mechanisms A and B; (ii) short range interactions between solute and solvent molecules in the gas phase mechanism A, modelled by considering the *explicit* participation of one molecule of various polar protic and aprotic solvents. The explicit solvation model in mechanism B has not been considered; and (iii) a combination of both long and short range interactions is considered by using both implicit and explicit solvation models.

#### 3.2.1. Implicit solvent effects on tautomerism via the mechanisms A and B using the SCRF method

In order to establish the implicit solvent effects on the kinetics and thermodynamics of the tautomerization reaction, the gas phase stationary points involved in the mechanisms A and B were optimized using the SCRF/PCM method for several polar solvents of different dielectric constants. The total and relative electronic energies for the species involved in both mechanisms are dsiplayed

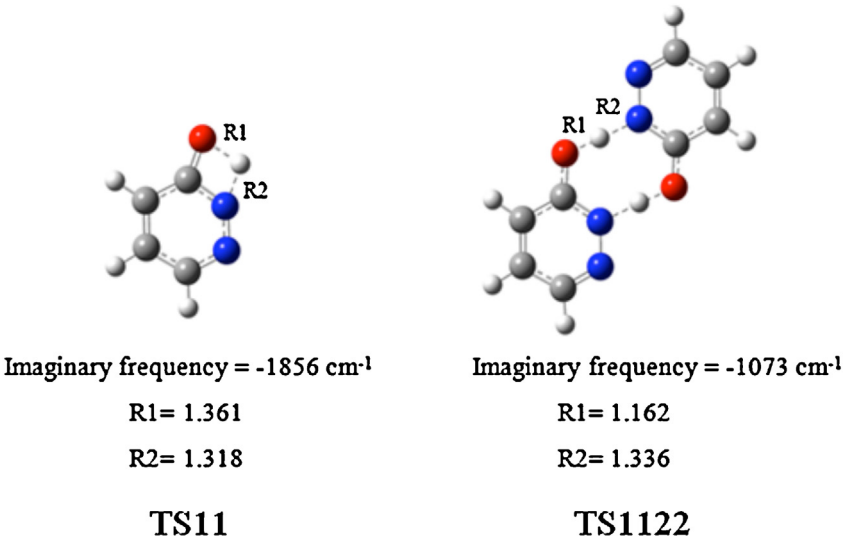
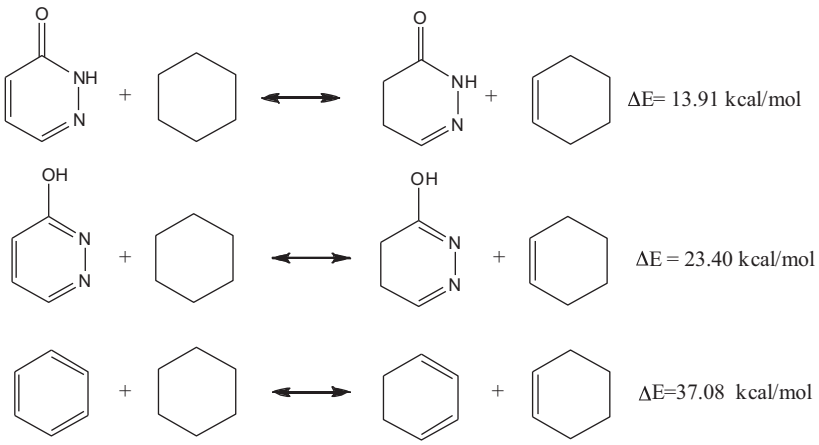



**Fig. 1.** Optimized structures of TSs associated with mechanism of path A (left) and B (right) including the corresponding imaginary frequencies. R1 and R2 are given in Å.




**Scheme 6.** Isodesmic reactions considered for the evaluation of RSE of pyridazinone **1** (top), pyridazol **2** (medium) and benzene (bottom) as reference. Isodesmic energies, ΔE, were calculated at the B3LYP/6-311++G** level.

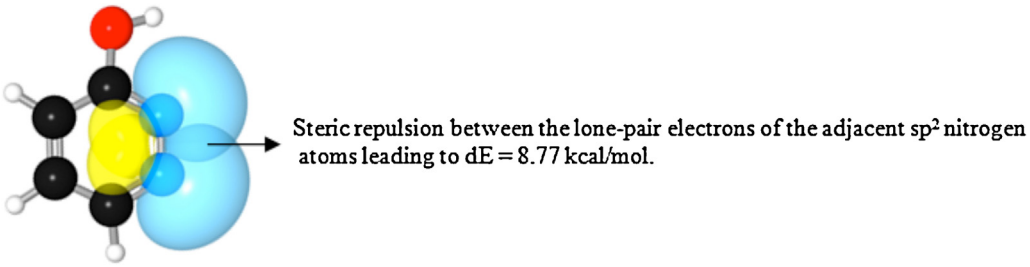



**Fig. 2.** Graphic representation of pairwise steric exchange energy, dE = 8.77 kcal/mol, between the lone-pair electrons of the adjacent $sp^2$ nitrogen atoms in pyridazol **2**.

in Tables 2 and 3. In order to have a clear comparison, the gas phase (vacuum) results are also included in the first row of these tables. As can be seen, in comparison with the gas phase, even though the electronic energies of the species involved in both mechanisms are affected by solvents, the energy changes along tautomerization are very small among various solvents especially for those having a dielectric constant at above 20. In mechanism A, both activation and reaction energies are increased with increasing the medium

**Table 1**
Total electronic energy ($E$) for species involved in mechanism A and B including corresponding activation ($\Delta E^{\neq}$) and reaction ($\Delta E_r$) energies.

| Mechanism | $E$ (a.u.) | | | $\Delta E^{\neq}$ (kcal/mol) | $\Delta E_r$ (kcal/mol) |
|---|---|---|---|---|---|
| | $R$ | TS | $P$ | | |
| A | −339.63245992 | −339.56450080 | −339.61864791 | 42.64 | 8.66 |
| B | −679.28778415 | −679.26441430 | −679.26832951 | 14.66 | 12.20 |

**Table 2**
Total electronic energy ($E$) for species involved in mechanism A including corresponding activation ($\Delta E^{\neq}$) and reaction ($\Delta E_r$) energies in various media.

| Medium | Dielectric constant ($\varepsilon$) | $E$ (a.u.) | | | $\Delta E^{\neq}$ (kcal/mol) | $\Delta E_r$ (kcal/mol) |
|---|---|---|---|---|---|---|
| | | $R$ | TS | $P$ | | |
| Vacuum | 1.00 | −339.63245992 | −339.56450080 | −339.61864791 | 42.64 | 8.66 |
| THF | 7.42 | −339.64206936 | −339.57179600 | −339.62709979 | 44.09 | 9.39 |
| Acetone | 20.49 | −339.64358235 | −339.57297652 | −339.62848423 | 44.30 | 9.47 |
| Methanol | 32.61 | −339.64392357 | −339.57324383 | −339.62879840 | 44.35 | 9.49 |
| DMSO | 46.82 | −339.64410188 | −339.57338366 | −339.62896285 | 44.37 | 9.49 |
| Formic acid | 51.10 | −339.64413636 | −339.57341070 | −339.62899466 | 44.38 | 9.50 |
| Water | 78.35 | −339.64426849 | −339.57351440 | −339.62911668 | 44.39 | 9.50 |

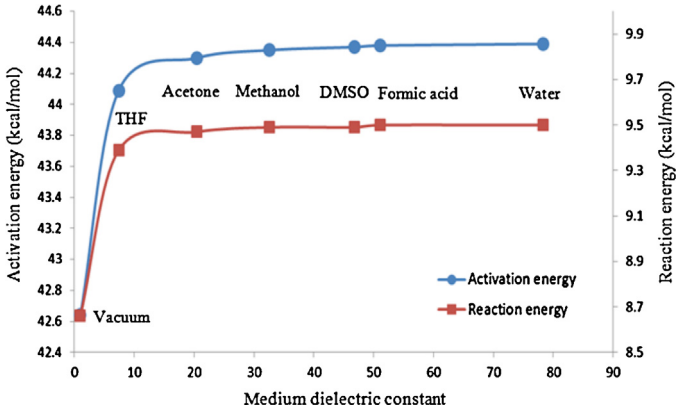



**Fig. 3.** Variations of activation and reaction energies for mechanism A with a medium dielectric constant.

polarity, which indicates that in the presence of the solvent the reactant is more stabilized than the TS and product. Variations of activation and reaction energies of mechanism A with a medium dielectric constant are presented in Fig. 3. As shown in Fig. 3, the activation and reaction energies increase nonlinearly with an increase in the medium dielectric constant. Fig. 3 also shows that both activation and reaction energies are approximately insensitive to the polarity of solvents with dielectric constants at above 20. Table 3 clearly shows that both activation and reaction energies associated with mechanism B remain relatively unchanged in the presence of a polar solvent; that is, the magnitude of stabilization for the reactant, TS, and product are almost equal in the presence of a solvent. Indeed, the solvent has no significant effect on the activation and reaction energies associated with mechanism B, even though the species involved in this mechanism can be considerably affected by a solvent.

### 3.2.2. Gas phase explicit solvent effects on tautomerism

Polar solvents considered in this work can be classified into two different types: (i) protic solvents such as water, methanol, and formic acid with a relatively acidic hydrogen atom, capable of accepting and donating a proton; and (ii) aprotic solvents such as acetone, DMSO, and THF, capable of accepting a proton. In order to establish the explicit solvent effects of polar solvents on the kinetics and thermodynamics of tautomerism, geometry optimizations were carried out on the monomeric mechanism A including one solvent molecule (see Fig. 4). While protic solvents, which have an acid/base character, can participate in tautomerism involving the acidic hydrogen atom of the solvent, aprotic solvents can only participate in the reaction as a basic species, favouring the proton abstraction of the tautomeric species. The total and relative electronic energies of the species involved in mechanism A, explicitly assisted by one molecule of various solvents in gas phase, are presented in Table 4. As can be seen, the activation energy of tautomerization is markedly reduced in the presence of one solvent molecule. This reduction is more evident for protic solvents, which can act as a proton donor/acceptor species. In order to explain the explicit solvent effects, both the proton accepting as well as the proton donating capability of solvent should be taken into account. This goal can be reached by definition of the index $\Sigma\Delta$ ($\Sigma\Delta = (R_{1\ \text{in GS}} - R_{1\ \text{in TS}}) + (R_{2\ \text{in GS}} - R_{2\ \text{in TS}})$) describing bond distance changes on moving from the ground state (GS) to TS. Some selected bond distances between solvents and pyridazinone **1** in ground states and in their corresponding TSs including $\Sigma\Delta$ index are presented in Fig. 4. In protic solvents, $R_1$ and $R_2$ values can be related to the proton accepting and proton donating capability of solvent, respectively. In fact, lower values of $R_1$ and $R_2$ indicate a greater tendency of the solvent to accept and to donate proton, respectively. A smaller value of the $\Sigma\Delta$ index reveals more similarity between the GS and the corresponding TS structures; that is, tautomerization can take place via a shorter pathway leading to a smaller activation energy value. The resulted trend for values of $\Sigma\Delta$ index for protic solvents is: water (1.458 Å) > methanol (1.430 Å) > formic acid (1.167 Å), which is in excellent agreement with the resulting trend for calculated activation energies: water (19.01 kcal/mol) > methanol (18.11 kcal/mol) > formic acid (9.59 kcal/mol). In the case of aprotic solvents, while $R_1$ has the meaning similar to the protic solvents, $R_2$ can be considered as the tendency of proton to runaway from the solvent. Here also, again, a smaller value of $\Sigma\Delta$ index shows a greater similarity between GS and corresponding TS structures leading to a smaller activation energy value. The resultant trend for values of $\Sigma\Delta$ index is: acetone (1.560 Å) > THF (1.454 Å) > DMSO (1.311 Å) which is in excellent agreement with the resulting trend of the calculated activation energies: acetone (41.14 kcal/mol) > THF (35.46 kcal/mol) > DMSO (28.43 kcal/mol). As can be seen, short range interactions are more

**Table 3**
Total electronic energy ($E$) for species involved in mechanism A including corresponding activation ($\Delta E^{\neq}$) and reaction ($\Delta E_r$) energies in various media.

| Medium | Dielectric constant ($\varepsilon$) | $E$ (a.u.) | | | $\Delta E^{\neq}$ (kcal/mol) | $\Delta E_r$ (kcal/mol) |
|---|---|---|---|---|---|---|
| | | $R$ | TS | $P$ | | |
| Vacuum | 1.00 | −679.28778415 | −679.26441430 | −679.26832951 | 14.66 | 12.20 |
| THF | 7.42 | −679.29974804 | −679.27598705 | −679.27946811 | 14.91 | 12.72 |
| Acetone | 20.49 | −679.30184746 | −679.27802404 | −679.28141487 | 14.94 | 12.82 |
| Methanol | 32.61 | −679.30233134 | −679.27849279 | −679.28186236 | 14.95 | 12.84 |
| DMSO | 46.82 | −679.30258581 | −679.27873915 | −679.28209747 | 14.96 | 12.85 |
| Formic acid | 51.10 | −679.30263513 | −679.27878689 | −679.28214303 | 14.96 | 12.86 |
| Water | 78.35 | −679.30282458 | −679.27897022 | −679.28231795 | 14.97 | 12.86 |

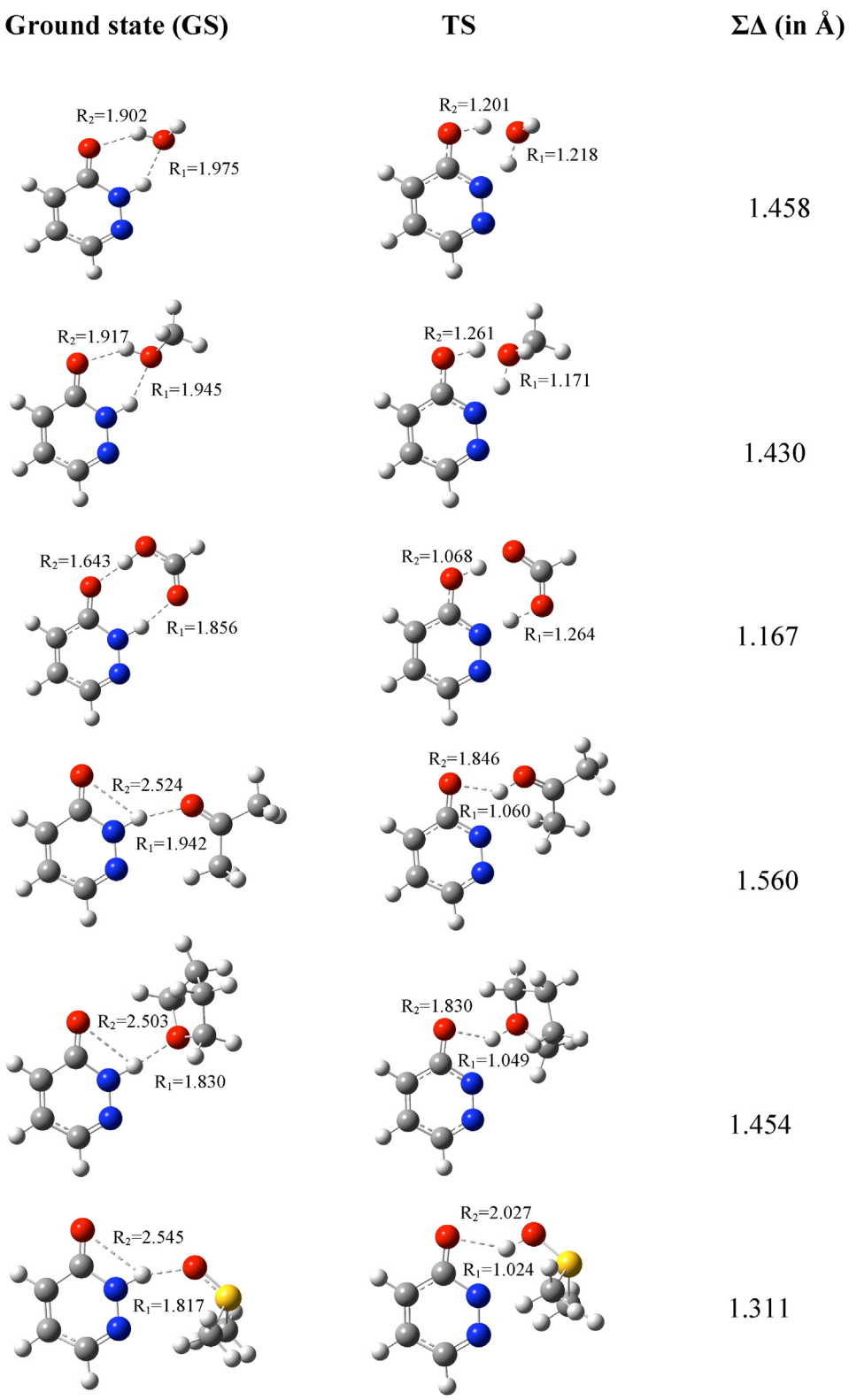



**Fig. 4.** Some selected bond distances ($R_1$ and $R_2$ in Å) between solvents and pyridazinone **1** in GS and in its corresponding TS. $\Sigma\Delta = (R_{1\ in\ GS} - R_{1\ in\ TS}) + (R_{2\ in\ GS} - R_{2\ in\ TS})$.

significant in the case of protic solvents so that the activation energies are more reduced in the presence of these kinds of solvents.

### 3.2.3. *Joint implicit/explicit solvent effects on tautomerism*

In this section, in order to consider both short and long range interactions between the solute and solvent on tautomerism, we attempt to study the solvent polarity effect on the solvent-assisted tautomerization via mechanism A, described in section 3.2.2 by using the SCRF method. The total and relative electronic energies for the species involved in mechanism A explicitly assisted by one molecule of various solvents using the SCRF/PCM method are displayed in Table 5. As mentioned previously, the

**Table 4**
Total electronic energy ($E$) for species involved in mechanism B including corresponding activation ($\Delta E^{\neq}$) and reaction ($\Delta E_r$) energies in various media.

| Solvent molecule | $E$ (a.u.) | | | $\Delta E^{\neq}$ (kcal/mol) | $\Delta E_r$ (kcal/mol) |
|---|---|---|---|---|---|
| | $R$ | TS | $P$ | | |
| Water | −416.10686717 | −416.07657562 | −416.09557365 | 19.01 | 7.09 |
| Methanol | −455.41327279 | −455.38442016 | −455.40240787 | 18.11 | 6.82 |
| Formic acid | −529.48499707 | −529.46971377 | −529.47448646 | 9.59 | 6.60 |
| Acetone | −532.85967969 | −532.79411123 | −532.85076987 | 41.14 | 5.59 |
| THF | −572.16347371 | −572.10696404 | −572.15272091 | 35.46 | 6.75 |
| DMSO | −892.91451674 | −892.86921516 | −892.91004204 | 28.43 | 2.81 |

**Table 5**
Total electronic energy ($E$) for species involved in mechanism A explicitly assisted by one molecule of various solvents using SCRF method including corresponding activation ($\Delta E^{\neq}$) and reaction ($\Delta E_r$) energies.

| Medium | Dielectric constant ($\varepsilon$) | $E$ (a.u.) | | | $\Delta E^{\neq}$ (kcal/mol) | $\Delta E_r$ (kcal/mol) |
|---|---|---|---|---|---|---|
| | | $R$ | TS | $P$ | | |
| THF | 7.42 | −572.17298052 | −572.12304090 | −572.16112856 | 31.34 | 7.44 |
| Acetone | 20.49 | −532.87507662 | −532.82014326 | −532.86261197 | 34.47 | 7.82 |
| Methanol | 32.61 | −455.42320933 | −455.39367824 | −455.41139128 | 18.53 | 7.42 |
| DMSO | 46.82 | −892.93577640 | −892.89649612 | −892.92493603 | 24.65 | 6.80 |
| Formic acid | 51.10 | −529.49635966 | −529.48331984 | −529.48519720 | 8.18 | 7.00 |
| Water | 78.35 | −416.11879043 | −416.08806922 | −416.10643912 | 19.28 | 7.75 |

gas phase activation energy associated with tautomerism via mechanism A is 42.64 kcal/mol. When only long range interactions are considered, in comparison with the gas phase, the activation energy remains relatively unchanged in different solvent types (see Table 2); that is, long range interactions are of a smaller importance. On the other hand, when just short range interactions are taken into account, the activation energies are considerably reduced in comparison with the gas phase as: acetone (41.14 kcal/mol) > THF (35.46 kcal/mol) > DMSO (28.43 kcal/mol) > water (19.01 kcal/mol) > methanol (18.11 kcal/mol) > formic acid (9.59 kcal/mol) (see Table 4). This result clearly shows that short range interactions, even in aprotic solvents, are more important than long range interactions. Finally, when implicit/explicit solvent effects are considered, the activation energies are reduced, following the same trend than that observed for short range interactions, emphasizing again, the importance of explicit solute/solvent interactions on the reduction of the activation energies: acetone (34.47 kcal/mol) > THF (31.43 kcal/mol) > DMSO (24.65 kcal/mol) > water (19.28 kcal/mol) > methanol (18.53 kcal/mol) > formic acid (8.18 kcal/mol) (see Table 5).

These results can be understood considering two kinds of behaviour of the tautomerization of pyridazinone **1** via mechanism A: (i) the high activation energy found in the tautomerization of pyridazinone **1** into pyridazol **2**, via **TS12**, is mainly a consequence of the strain associated with the formation of four-membered TS of the intramolecular hydrogen transfer process. Any acid/base solvent molecule capable to perform this hydrogen transfer via a less strained process can markedly favour the tautomerization process. In this way, polar protic solvents, which concurrently have acid/bases properties, are more efficient than aprotic polar solvents, which only act as bases. Since the former can favour the hydrogen transfer via a six or higher membered TSs, the corresponding strain is significantly reduced; and (ii) because both reagents and TSs present similar polarity, consequently, implicit solvent effects have a low incidence in kinetic parameters since all species involved in the tautomerization are similarly solvated.

## 4. Conclusion

The tautomerization of the simplest pyridazinone **1** into pyridazol **2** has been theoretically studied using DFT methods at the B3LYP/6-311++G** level. In the gas phase two mechanisms for the hydrogen transfer have been investigated. Along mechanism A, the hydrogen is directly transferred from the nitrogen to the oxygen atom through the synchronous **TS12**, whereas along mechanism B a double hydrogen transfer via **TS1122** takes place upon the formation of the corresponding dimer. Mechanism A presents a very high activation energy of 42.64 kcal/mol as a consequence of the strain associated with the formation of the four membered **TS12**. On the other hand, tautomerization via mechanism B presents a relatively low activation energy of 15.66 kcal/mol due to the absence of strain at the eight-membered **TS1122**. Solvent effects on mechanism A have been considered by using three computational models. In the first model, the implicit solvation of protic and aprotic polar solvents has been considered using the SCRF/PCM method. In the second model, the gas phase optimizations including one molecule of protic and aprotic polar solvents were performed in order to establish explicit solvent effects. Finally, in the third model, implicit and explicit solvent effects were studied by combining the first two approaches. By this comparative study it is possible to conclude that while the implicit solvent effects of polar solvents do not substantially modify the gas phase energies found along mechanism A, the explicit inclusion of one solvent molecule favours the reaction to take place via a less strained TS. In this way, protic polar solvents are very efficient since their acid/base character allows the hydrogen to be transferred via a six or higher membered TSs. Finally, the similar polarity of reagent and TS involved in the non-solvent assisted process, which produces a closer solvation of these species, accounts for the low solvent effects found along the SCRF calculations.

## References

[1] Z. Wojnarowska, P. Wlodarczyk, K. Kaminski, K. Grzybowska, L. Haewlek, M. Paluch, On the kinetics of tautomerism in drugs: new application of broadband dielectric spectroscopy, J. Chem. Phys. 133 (2010) 094507–094515.
[2] M.B. Smith, J. March, Advanced Organic Chemistry, fifth ed., Wiley Interscience, New York, 2001.
[3] C.C. Wu, M.H. Lien, Ab initio study on the substituent effect in the transition state of keto-enol tautomerism of acetyl derivatives, J. Phys. Chem. 100 (1996) 594–600.
[4] B. Chahkandi, S.F. Tayyari, M. Bakhshaei, M. Chahkandi, Investigation of simple and water assisted tautomerism in a derivative of 1,3,4-oxadiazole: A DFT study, J. Mol. Graph. Model. 44 (2013) 120–128.
[5] L. Lázár, F. Fülöp, Recent developments in the ring-chain tautomerism of 1,3-heterocycles, Eur. J. Org. Chem. 2003 (2003) 3025–3042.

[6] S. Laurella, M.G. Sierra, J. Furlong, P. Allegretti, Analysis of tautomerism in b-ketobuanamides by nuclear magnetic resonance: substituent temperature and solvent effects, J. Appl. Solut. Chem. Model. 1 (2012) 6–12.
[7] A. Isha, N.A. Yusof, M. Ahmad, D. Suhendra, W.M.Z. WanYunus, Z. Zainal, Optical fibre chemical sensor for trace vanadium(V) determination based on newly synthesized palm based fatty hydroxamic acid immobilized in polyvinyl chloride membrane, Spectrochim. Acta A – Mol. Biol. 67 (2007) 1398–1402.
[8] H. Deng, H. Nanjo, P. Qian, Z. Xia, I. Ishikawa, T.M. Suzuki, Corrosion prevention of iron with novel organic inhibitor of hydroxamic acid and UV irradiation, Electrochim. Acta 53 (2008) 2972–2983.
[9] Y.H. Liu, S.Y. Chuang Lin, C.C. Lee, W.C. Hou, Antioxidant and nitric oxide production inhibitory activities of galacturonyl hydroxamic acid, Food Chem. 109 (2008) 159–166.
[10] H. Tavakol, Computational study of simple and water-assisted tautomerism of hydroxamic acids, J. Mol. Struct. (THEOCHEM) 916 (2009) 172–179.
[11] L. Huang, Y. Huang, Y. Chi, J. Lin, L. Yu, L. Xu, G. Chen, Study on the kinetics of keto-enol tautomerism of p-hydroxyphenylpyruvic acid using capillary electrophoresis, J. Choromatogr. A 1175 (2007) 283–288.
[12] O. Godsi, B. Turner, K. Suwinska, U. Peskin, Y. Eichen, Enol-enamine tautomerism in crystals of 1,3-bis(pyridin-2-yl) propan-2-one: a combined crystallographic and quantum-chemical investigation of the effect of packing on tautomerization processes, J. Am. Chem. Soc. 126 (2004) 13519–13525.
[13] J. Andrés, L.R. Domingo, M.T. Picher, V.S. Safont, Comparative theoretical study of transition structures, barrier heights, and reaction energies for the intramolecular tautomerization in acetaldehyde/vinyl alcohol and acetaldimine/vinylamine systems, Int. J. Quant. Chem. 66 (1998) 9–24.
[14] E. Tombari, C. Ferrari, G. Salvetti, G.P. Johari, Spontaneous liquifaction of isomerizable molecular crystals, J. Chem. Phys. 126 (2007) 021107–021110.
[15] A.R. Katritzky, J. Elguero, The Tautomerism of Heterocycles, Academic, New York, 1976.
[16] E.D. Jemmis, K.T. Giju, J. Leszczynski, Tautomeric rearrangements in mono- and dichalcogenide analogs of formic acid, HC(X)YH (X, Y = O, S, Se Te): a theoretical study, J. Phys. Chem. A 101 (1997) 7389–7395.
[17] Y.H. Wang, J.W. Zou, B. Zhang, Y.X. Lu, H.X. Jin, Q.S. Yu, Enone-dienol tautomerism of but-2-enal and substituent effect: a theoretical study, J. Mol. Struct. (THEOCHEM) 755 (2005) 31–37.
[18] A.M. El-Nahas, K. Hirao, A theoretical study on 2-hydroxypyrazine and 2,3-dihydroxypyrazine: tautomerism, intramolecular hydrogen bond, solvent effects, J. Mol. Struct. (THEOCHEM) 459 (1999) 229–237.
[19] K. Anandan, P. Kolandaivel, R. Kumaresan, Ab initio and DFT studies on tautomerism of indazole in gaseous and aqueous phases, J. Mol. Struct. (THEOCHEM) 686 (2004) 83–89.
[20] S.X. Tian, K.Z. Xu, A density functional approach of prototropic tautomerism of guanine, Chem. Phys. 264 (2001) 187–196.
[21] A.P. Mazurek, N.S. Sosnowska, Studies on tautomerism in tetrazole: comparison of Hartree–Fock and density functional theory quantum chemical methods, Chem. Phys. Lett. 330 (2000) 212–218.
[22] J. Tomasi, M. Persico, Molecular interactions in solution: an overview of methods based on continuous distributions of the solvent, Chem. Rev. 94 (1994) 2027–2094.
[23] C.J. Cramer, D.G. Truhlar, Implicit solvation models: equilibria, structure, spectra, and dynamics, Chem. Rev. 99 (1999) 2161–2200.
[24] V. Barone, M. Cossi, B. Mennucci, J. Tomasi, A new definition of cavities for the computation of solvation free energies by the polarizable continuum model, J. Chem. Phys. 107 (1997) 3210–3221.
[25] S. Miertus, E. Scrocco, J. Tomasi, Electrostatic interaction of a solute with a continuum A direct utilization of AB initio molecular potentials for the prevision of solvent effects, Chem. Phys. 55 (1981) 117–129.
[26] J.B. Foresman, A. Frisch, Exploring Chemistry with Electronic Structure Methods, Gaussian, Inc., Pittsburgh, PA, 1996.
[27] Q.G. Li, G.M. Liang, X. Wang, S.Y. CHU, Y. Ren, Ab initio computational modeling on the tautomerism of monochalcogenocarboxylic acids $CH_3C(=O)XH$ (X = S, Se, and Te) in the polar and aprotic solution, Int. J. Quantum Chem. 107 (2007) 921–929.
[28] D. Mazzuca, T. Marino, N. Russo, M. Toscano, A theoretical study on tautomerization processes of dehydrated and monohydrated cytosine, J. Mol. Struct. (THEOCHEM) 811 (2007) 161–167.
[29] H.S. Kim, D.S. Ahn, S.Y. Chung, S.K. Kim, S. Lee, Tautomerization of adenine facilitated by water: computational study of microsolvation, J. Phys. Chem. A 111 (2007) 8007–8012.
[30] A. Fu, H. Li, D. Du, Thiol-thione tautomerism in 2-pyridinethione: effect of hydration, J. Mol. Struct. (THEOCHEM) 767 (2006) 51–60.
[31] S. Abdalla, M. Springborg, Theoretical study of tautomerization and isomerization of methylamino- and phenylamino-substituted cyclic azaphospholines, oxaphospholines and thiaphospholines in gas and aqueous phases, J. Mol. Struct. (THEOCHEM) 962 (2010) 101–107.
[32] S. Yamabe, T. Fukuda, S. Yamazaki, Proton transfers along hydrogen bonds in the tautomerization of purine, J. Phys. Chem. A 116 (2012) 1289–1297.
[33] Q.G. Li, Y. Xue, G.S. Yan, Water-assisted enol-to-keto tautomerism of a simple peptide model: a computational investigation, J. Mol. Struct. (THEOCHEM) 868 (2008) 55–64.
[34] N. Mora-Diez, M.L. Senent, B. Garcia, Ab initio study of solvent effects on the acetohydroxamic acid deprotonation processes, Chem. Phys. 324 (2006) 350–358.
[35] R. Bansal, S. Thota, Pyridazin-3(2*H*)-ones: the versatile pharmacophore of medicinal significance, Med. Chem. Res. 22 (2013) 2539–2552.
[36] A. Fu, H. Li, D. Du, Z. Zhou, Density functional study on the reaction mechanism of proton transfer in 2-pyridone: effect of hydration and self-association, J. Phys. Chem. A 109 (2005) 1468–1477.
[37] A.D. Becke, Density-functional thermochemistry III. The role of exact exchange, J. Chem. Phys. 98 (1993) 5648–5652.
[38] M.J. Frisch, et al., Gaussian 09, Revision A.02-SMP, Gaussian, Inc, Wallingford, CT, 2009.
[39] J.J. Novoa, C.J. Sosa, Evaluation of the density functional approximation on the computation of hydrogen bond interactions, J. Phys. Chem. 99 (1995) 15837–15845.
[40] S.F. Tayyari, M. Zahedi-Tabrizi, H. Rahemi, H.A. Mirshahi, J.S. Emampour, M. Rajabi, F. Milani-Nejad, A two-dimensional potential function for bent hydrogen bonded systems II-6-hydroxy-2-formylfulvene, J. Mol. Struct. (THEOCHEM) 730 (2005) 17–21.
[41] K. Fukui, Formulation of the reaction coordinate, J. Phys. Chem. 74 (1970) 4161–4163.
[42] (a) C. González, H.B. Schlegel, Reaction path following in mass-weighted internal coordinates, J. Phys. Chem. 94 (1990) 5523–5527;
(b) C. González, H.B. Schlegel, Improved algorithms for reaction path following: higher-order implicit algorithms, J. Chem. Phys. 95 (1991) 5853–5860.
[43] E.D. Glendening, J.K. Badenhoop, A.E. Reed, J.E. Carpenter, J.A. Bohmann, C.M. Morales, F. Weinhold, Theoretical Chemistry Institute, University of Wisconsin, Madison, WI, 2001 http://www.chem.wisc.edu/~nbo5