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## Prototropic tautomerism of imidazolone in aqueous solution: a density functional approach using the combined discrete/self-consistent reaction field (SCRf) models

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**Abstract** A systematic investigation of the proton transfer in the keto-amino/enol tautomerization of imidazolone was undertaken. Calculations in aqueous solution were performed using both combined discrete/self-consistent reaction field (SCRf) and SCRf methods. Complexes containing one to three water molecules around the hydrophilic site of imidazolone were used for the combined discrete/SCRf calculations. The DFT results predict that the barrier height for non-water-assisted intramolecular proton transfer is very high ( $214.8 \text{ kJmol}^{-1}$ ). Hydrogen bonding between imidazolone and the water molecule(s) will dramatically lower the barrier by a concerted multiple proton transfer mechanism. The proton transfer process through a eight-member ring formed by imidazolone and two water molecules is found to be more efficient and the calculated barrier height is ca.  $61 \text{ kJmol}^{-1}$ .

**Keywords** Density functional theory · Imidazolone · Tautomerism · Water-assisted proton transfer

### Introduction

Prototropic tautomerism represents one of the most important processes involved in chemical reactions as well as in living systems. [1–3] In particular, the keto-

amino/enol isomerization, which is the most typical tautomerism, has been studied extensively both experimentally and theoretically. [4–7] Among a number of physical and chemical factors that are responsible for the tautomeric keto-amino/enol equilibrium, solvation occupies one of the most important roles, because most biochemical reactions of interest occur in solution. In the treatment of solvent effects, self-consistent reaction field (SCRf) methods [8–11], which are based on a very simple but powerful approach, allow a quantum mechanical description of the solute in the solvent continuum at a computational cost slightly higher than that required in the gas-phase calculation. However, some important electronic effects associated with specific solute–solvent interactions are neglected by the continuum approximation. One possible way to minimize the deficiency may be to employ combined discrete/SCRf models, [12–16] in which an appropriate number of solvent molecules directly interacting with specific part(s) of the solute are treated explicitly by quantum chemical methods, while other numerous solvent molecules are approximated as a continuum. Both short-range and long-range solvent polarization interactions are included in the models. Combined discrete/SCRf models have provided a reliable description of the reaction energy change and the intramolecular proton-transfer energy barrier for some amino acids, nucleic-acid bases and base pairs in solvents. For example, by adopting this model, Kassab et al. [17] obtained the free energy change and the energy barrier for the transformation between neutral and zwitterionic glycine in aqueous solution and found that the calculated results from the combined discrete/SCRf model agree with the experimental observations, better than direct SCRf methods. Leszczynski and co-workers [13] and Alemán [18] also employed this approach to examine the keto-amino/enol tautomerism of guanine and cytosine in aqueous solution. More recently, Ahn et al. [19] presented the effects of continuum water by employing the combined discrete/SCRf type model to study the isomerization of neutral/zwitterionic alanine-( $\text{H}_2\text{O}$ )<sub>n</sub>

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( $n = 1$  and  $2$ ) clusters in aqueous solution. Some of these studies reveal that involvement of water molecules in the proton-transfer transition state will reduce the barrier height and water molecules act as catalyst in the keto-amino/enol isomerization.

2-Imidazolones (**IZ**) have long been known to possess interesting biological activity [20–22], but the proton transfer over hydrogen bonds in **IZ** has received less attention from the computational community. Only one recent paper reported the direct amino/enol-keto prototropic tautomerism for bare **IZ** in vacuum and in several solutions by SCRF calculations using the PCM model [23]. In our present work, a detail theoretical investigation is undertaken for the tautomerization reaction of (**IZ**) to 2-hydroxy-imidazole (**HIZ**) in aqueous solution. One to three explicit water molecules are considered in the solvation of **IZ** and **HIZ**. The results are compared with those obtained from SCRF methods. A detailed analysis is presented for the isomerization between **IZ**·( $\text{H}_2\text{O}$ ) $_n$  and the corresponding tautomeric **HIZ**·( $\text{H}_2\text{O}$ ) $_n$  ( $n = 1$ – $3$ ) clusters as examples of solvent-mediated tautomerization. We show that the isomerization between **IZ**·( $\text{H}_2\text{O}$ ) $_n$  and **HIZ**·( $\text{H}_2\text{O}$ ) $_n$  clusters proceeds by a concerted double to quadruple proton-transfer mechanism. We also employ Tomasi's polarizable continuum model (PCM) [8], which is the most popular method for treating this kind of problem, to study the effect of bulk solvent on the infinite number of water molecules surrounding the **IZ**·( $\text{H}_2\text{O}$ ) $_n$  complexes. These calculations will provide valuable insights about the influence of the explicit water molecules in the study of tautomerism equilibria.

## Computational procedure

All calculations were performed with GAUSSIAN-98 package [24] in this study. Molecular geometries and harmonic vibrational frequencies have been determined at the B3LYP/6-31++G(d, p) level, which has been shown to provide good results for hydrogen-bonded systems [25–27]. The stationary structures were confirmed by ascertaining that all ground states have only real frequencies and all transition states have only one imaginary frequency. Thermal and entropic corrections were computed by standard statistical methods. The nature of the interaction in the reactants and transition

structures has been studied employing the natural bond orbital (NBO) analysis [28–31].

Tomasi's very useful PCM model is employed to address the effects of bulk solvent. Since the structural parameters of neutral nucleic acid bases change very little on going from the gas to solution, it is therefore a reasonable approximation to assume that all species are not affected by the presence of the bulk solvent (hereafter called direct solvent effect). However, it should be emphasized that the reoptimization in the bulk solvent is important in complex systems such as zwitterions [19]. In fact, geometry optimizations of bare **IZ** and **HIZ** at B3LYP/6-31++G(d, p) in water using the PCM method indicate that the bond lengths and angles averagely vary 0.006 Å and 0.38°, respectively.

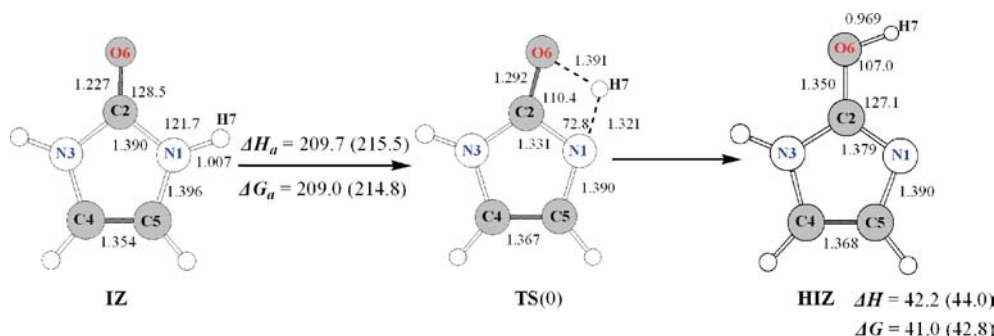
Throughout this paper, bond lengths are in angstroms and bond angles are in degrees. All relative energies are presented as enthalpy and Gibbs free energy changes at 298 K, denoted as  $\Delta H_{\text{gp}}$  and  $\Delta G_{\text{gp}}$  in the gas phase or  $\Delta H_{\text{aq}}$  and  $\Delta G_{\text{aq}}$  in aqueous solution.

## Results and discussion

### Direct tautomerism of **IZ**

As a comparison, let us start the discussion with an analysis of the structure of the **IZ** monomer and the direct tautomerism of bare **IZ**. Figure 1 shows the optimized geometries in the gas phase for two possible tautomers, keto (**IZ**) and the amino/enol (**HIZ**) monomer. Both have planar structures, which have been confirmed to be the local minima by calculating the vibrational frequencies. Our present calculations show that **IZ** is much more stable than **HIZ**. The B3LYP relative free energy of these two tautomers is 41.0 kJmol<sup>-1</sup> in the gas phase, higher than the previous theoretical value at the MP4/6-311++G\*\*//HF/6-31G\*\* level [23] by ca. 6 kJmol<sup>-1</sup>. This implies that the keto species is predominant in the gas phase. Geometries in Fig. 1 also show some important geometrical changes as the tautomerism proceeds. On going from the keto to the amino/enol monomer, the N1–C2 bond length is reduced from 1.390 to 1.308 Å, while the C2–O6 distance increases from 1.227 to 1.350 Å. This is consistent with the breaking of the

**Fig. 1** Mechanism of direct tautomerization between **IZ** and **HIZ** monomer by single proton transfer. The values in parentheses are the energetics in aqueous solution from the PCM model. All of relative energies are in kJmol<sup>-1</sup>



C=O double bond and corresponding formation of a C=N double bond.

It is clear that the O6–H7 distance plays an important role in the proton transfer reaction. In the absence of water, the **IZ** monomer cannot easily transfer the proton from N1 to O6 because the O6–H7 distance (2.685 Å) is too long. The geometry of the bare **IZ** molecule is unfavorable for the formation of an intramolecular hydrogen bond since direct proton transfer would take place through a strained four-membered ring transition structure, **TS(0)**, which contains an almost broken N1–H7 bond (1.321 Å), whereas the O6–H7 bond is still not formed (1.391 Å). This highly distorted structure leads to a very high barrier (209.0 kJmol<sup>-1</sup>), which implies that the proton transfer reaction is unlikely to occur in the gas phase.

After direct solvent effects are considered, the free energies of solvation ( $\Delta G^{\text{sol}}$ ) for the two tautomers and the transition structure determined from PCM model calculations are given in Table 1. The  $\Delta G^{\text{sol}}$  values indicate that the three species are almost equally solvated. Among them **IZ** is best solvated, while the **HIZ** and **TS(0)** are slightly less favored. As a result, the endothermicity and barrier height for the non-water-assisted proton-transfer tautomerism in aqueous solution are slightly higher than those in the gas phase by ca. 6 and 2 kJmol<sup>-1</sup>, respectively.

Tautomerization between **IZ**·(H<sub>2</sub>O)<sub>n</sub> and **HIZ**·(H<sub>2</sub>O)<sub>n</sub> ( $n = 1-3$ )

Now we investigate the tautomerization of **IZ** using the combined discrete/SCRF models. We introduce one to three water molecules in the region where proton transfer takes place to form **IZ**·(H<sub>2</sub>O)<sub>n</sub> and **HIZ**·(H<sub>2</sub>O)<sub>n</sub> complexes. For  $n = 1-2$ , the complexes give cyclic structures in which a ring of water molecules is formed linking oxygen (O6) and nitrogen (N1), denoted as **IZ**·H<sub>2</sub>O and **IZ**·(H<sub>2</sub>O)<sub>2</sub> or **HIZ**·H<sub>2</sub>O and **HIZ**·(H<sub>2</sub>O)<sub>2</sub>. For  $n = 3$ , two possible stable complexes were considered. One is similar to the structures in  $n = 1-2$ , denoted as

**IZ**·(H<sub>2</sub>O)<sub>3</sub> and **HIZ**·(H<sub>2</sub>O)<sub>3</sub>. In the alternative complexes, three water molecules are distributed around the hydrophilic region of **IZ** and **HIZ**, in which two of them are put on one side and the other is on the other side. The distribution of water molecules seems to be a better simulation for the first solvation shell of **IZ** and **HIZ**. These structures are denoted as **IZ**·(H<sub>2</sub>O)<sub>2+1</sub> and **HIZ**·(H<sub>2</sub>O)<sub>2+1</sub>.

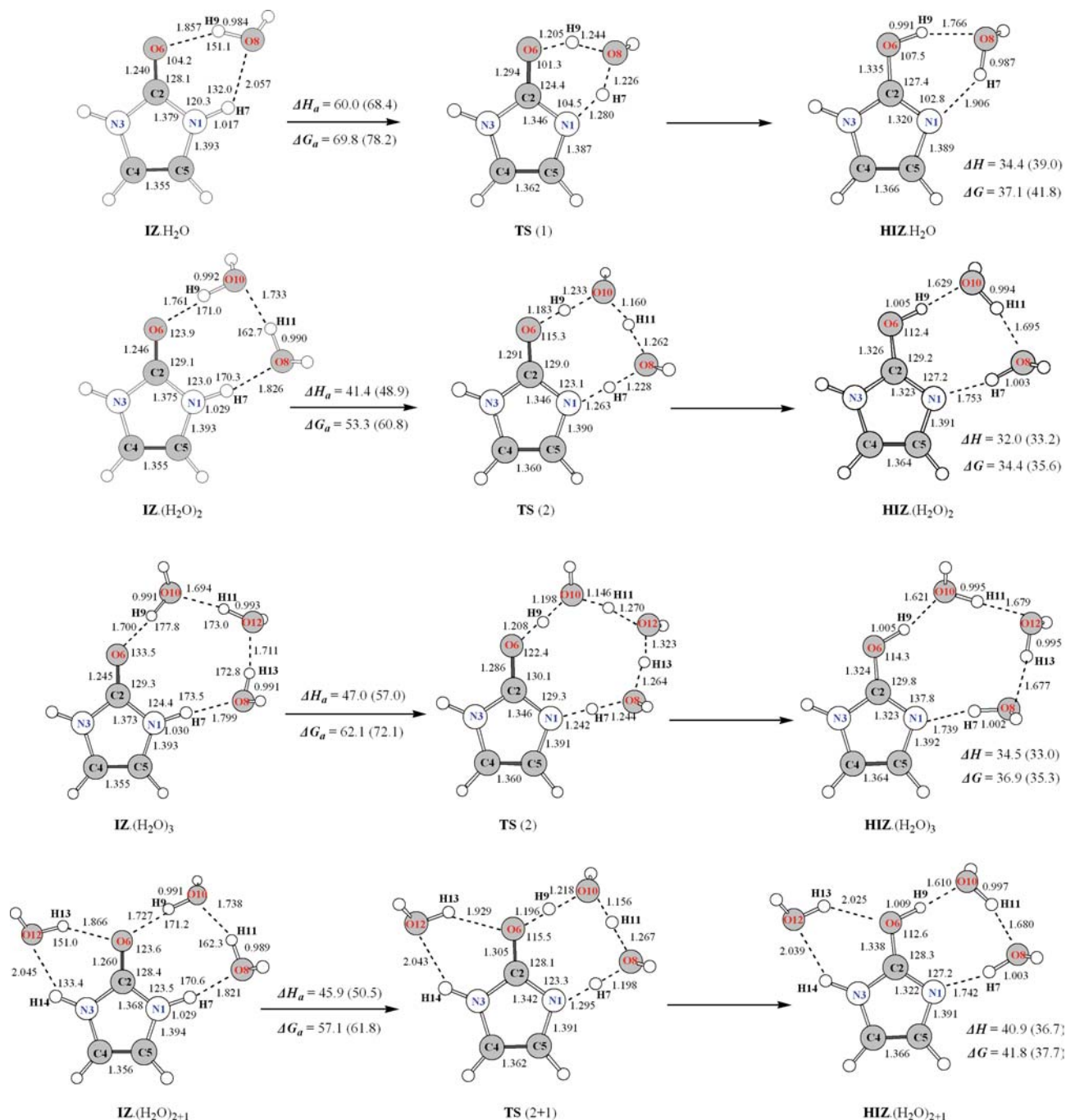
As shown in Fig. 2, two intermolecular H-bonds, O6···H9–O10 and N1–H7···O8, are formed in **IZ**·(H<sub>2</sub>O)<sub>n</sub> ( $n = 1-3$ ) with the H<sub>2</sub>O molecule(s) acting as bridge between the carbonyl oxygen (O6) atom and the NH group. The H7–O8 and O6–H9 distances in these complexes are 1.700–2.057 Å, significantly shorter than the O6–H7 distance of 2.685 Å in bare **IZ**. This shows that the proton transfer in these complexes will proceed more easily than in the **IZ** monomer.

Formation of complexes with water molecules has little influence on the structures of the **IZ** and **HIZ** units. As can be expected, the influence of the interaction with water molecules on the bond distances and angles of **IZ** tautomer manifests itself mainly in the region of intermolecular hydrogen bonding. Figure 2 shows that the C2–O6 bond length increase from 1.227 Å in **IZ** to 1.240–1.260 Å and the N1–H7 bond length from 1.007 to 1.017–1.030 Å, while the N1–C2 bond length decreases from 1.390 to 1.368–1.379 Å in **IZ**·(H<sub>2</sub>O)<sub>n</sub> ( $n = 1-3$ ) complexes. In the amino/enol complexes, **HIZ**·(H<sub>2</sub>O)<sub>n</sub>, the situation is reversed, with the C2–O6 bond length decreasing from 1.350 to 1.324–1.338 Å and N1–C2 bond length increasing from 1.308 to 1.320–1.323 Å, while the O6–H9 bond length increasing from 0.969 to 0.991–1.005 Å. These geometric changes make **IZ** more similar to its enolic tautomer, **HIZ**, and will favor the following proton transfer reaction with a lower barrier height.

It is clear from Table 2 that the formation of all complexes is energetically favorable. Interestingly, the stabilization of complexes increases almost linearly with the number of water molecules in terms of enthalpy, so that the complexes with three water molecules, **IZ**·(H<sub>2</sub>O)<sub>3</sub> and **HIZ**·(H<sub>2</sub>O)<sub>3</sub>, are almost three times more

**Table 1** Relative energies (kJmol<sup>-1</sup>), dipole moments and the free energy of solvation (kJmol<sup>-1</sup>),  $\Delta G^{\text{sol}}$ , for the stationary points corresponding to the proton-transfer reactions of **IZ** monomer and **IZ**(H<sub>2</sub>O)<sub>n</sub> complexes computed at the B3LYP/6-31++G(d,p) level

Structure	$\Delta H_{\text{gp}}$	$\Delta G_{\text{gp}}$	$\Delta G^{\text{sol}}$	$\mu(\text{D})$	$\Delta H_{\text{aq}}$	$\Delta G_{\text{aq}}$
<b>IZ</b>	0.0	0.0	-51.3	4.231	0.0	0.0
<b>TS(0)</b>	209.7	209.0	-45.5	3.518	215.5	214.8
<b>HIZ</b>	42.2	41.0	-49.5	2.260	44.0	42.8
<b>IZ</b> ·H <sub>2</sub> O	0.0	0.0	-42.5	3.400	0.0	0.0
<b>TS(1)</b>	60.0	69.8	-34.1	3.209	68.4	78.2
<b>HIZ</b> ·H <sub>2</sub> O	34.4	37.1	-37.9	2.345	39.0	41.8
<b>IZ</b> ·(H <sub>2</sub> O) <sub>2</sub>	0.0	0.0	-43.0	2.952	0.0	0.0
<b>TS(2)</b>	41.4	53.3	-35.5	2.664	48.9	60.8
<b>HIZ</b> ·(H <sub>2</sub> O) <sub>2</sub>	32.0	34.4	-41.8	1.959	33.2	35.6
<b>IZ</b> ·(H <sub>2</sub> O) <sub>3</sub>	0.0	0.0	-45.6	2.557	0.0	0.0
<b>TS(3)</b>	47.0	62.1	-35.6	2.195	57.0	72.1
<b>HIZ</b> ·(H <sub>2</sub> O) <sub>3</sub>	34.5	36.9	-47.2	2.104	33.0	35.3
<b>IZ</b> ·(H <sub>2</sub> O) <sub>2+1</sub>	0.0	0.0	-34.1	1.878	0.0	0.0
<b>TS(2+1)</b>	45.9	57.1	-29.5	1.296	36.7	37.7
<b>HIZ</b> ·(H <sub>2</sub> O) <sub>2+1</sub>	40.9	41.8	-38.3	1.520	50.5	61.8



**Fig. 2** Mechanism of water-mediated tautomerization between **IZ**·(H<sub>2</sub>O)<sub>n</sub> and **HIZ**·(H<sub>2</sub>O)<sub>n</sub> (n = 1–3) complexes by double, triple and quadruple proton transfer. The values in parentheses are the energetics in aqueous solution from the PCM model. All of relative energies are in kJmol<sup>-1</sup>

stabilized with respect to the unsolvated species than the complexes with only one water, **IZ**·H<sub>2</sub>O and **HIZ**·H<sub>2</sub>O. However, in terms of Gibbs free energy, the situation is not so favorable for the formation of highly ordered structures. It can be seen that the increase of stabilization with the size of the cluster is more modest when the entropy effect is included. The Gibbs free energies for

**IZ**·(H<sub>2</sub>O)<sub>3</sub> and **HIZ**·(H<sub>2</sub>O)<sub>3</sub> are also lower than the more ordered structures **IZ**·(H<sub>2</sub>O)<sub>2+1</sub> and **HIZ**·(H<sub>2</sub>O)<sub>2+1</sub>.

It is worth noting that all of H-bond structures formed between **HIZ** and water molecule(s), O6···H9···O10 and N1···H7···O8, have shorter distances than the corresponding H-bonds, O6···H9···O10 and N1···H7···O8 in **IZ**·(H<sub>2</sub>O)<sub>n</sub> complexes. For example, H9···O10 (1.629 Å) and N1···H7 (1.753 Å) in **HIZ**·(H<sub>2</sub>O)<sub>2</sub> are shorter than O6···H9 (1.716 Å) and H7···O8 (1.826 Å) in **IZ**·(H<sub>2</sub>O)<sub>2</sub>, respectively. Consequently, interactions with water molecule(s) will stabilize the amino/enol form by 4–6.5 kJmol<sup>-1</sup> and the tautomerization will be slightly more favorable due to the complexation with water

**Table 2** Energy (kJmol<sup>-1</sup>) for the formation of complexes in the gas phase: **IZ** + *n*H<sub>2</sub>O → **IZ**·(H<sub>2</sub>O)<sub>*n*</sub> and **HIZ** + *n*H<sub>2</sub>O → **HIZ**·(H<sub>2</sub>O)<sub>*n*</sub>

<b>IZ</b> ·(H <sub>2</sub> O) <sub><i>n</i></sub>	$\Delta H_{\text{comp}}$	$\Delta G_{\text{comp}}$	<b>HIZ</b> ·(H <sub>2</sub> O) <sub><i>n</i></sub>	$\Delta H_{\text{comp}}$	$\Delta G_{\text{comp}}$
<i>n</i> = 1	-39.72	-2.83	<i>n</i> = 1	-47.58	-6.69
<i>n</i> = 2	-87.89	-10.51	<i>n</i> = 2	-98.09	-17.08
<i>n</i> = 3	-124.29	-11.05	<i>n</i> = 3	-131.98	-5.18
<i>n</i> = 2 + 1	-125.42	-9.65	<i>n</i> = 2 + 1	-126.74	-8.81

molecule(s). These interactions can also be evaluated by the NBO analysis. The keto-H<sub>2</sub>O or amino/enol-H<sub>2</sub>O interactions were estimated using second order perturbation theory, *E*(2), and intermolecular H-bond order. The data in Table 3 show that the higher *E*(2) values between electron donor (lone pairs of oxygen) and acceptor (the O–H or N–H anti-bonding orbital), the larger value of bond order, the stronger H-bond, the more stable complex with H<sub>2</sub>O molecule(s).

After formation of the water-complexes of **IZ**, the proton transfer reactions may occur with H<sub>2</sub>O as a bridge. The situation becomes different in the kinetics of the tautomerization for **IZ**·(H<sub>2</sub>O)<sub>*n*</sub>. Upon addition of one water molecule to the process of keto↔amino/enol tautomerization, the two hydrogen atoms are transferred in the transition structure. Based on the analysis of the **TS**(1) structure, we can refer to that process as an almost synchronous double proton transfer. It can be observed from the geometry parameters that the **TS**(1) are less strained than the **TS**(0), in which the N10–H7 and O6–H9 distances become shorter due to the bridging role of water and considerably shorten the proton transferring path. The less strained transition structure

dramatically lowers the keto-amino/enol tautomeric barrier from 209.0 kJmol<sup>-1</sup> in the gas phase to 69.8 kJmol<sup>-1</sup> in terms of Gibbs free energy. In comparison with the tautomerization of the **IZ** monomer, formation of the water complex lowers the barrier by 139.2 kJmol<sup>-1</sup>, indicating that the process is enhanced by the water molecule, called water-mediated tautomerization. The binding of two water molecules may still lower the barrier to 53.3 kJmol<sup>-1</sup> for **TS**(2), catalyzing the keto↔amino/enol tautomerization by a concerted triple proton transfer mechanism. Addition of one water molecule on the other side of **IZ**·(H<sub>2</sub>O)<sub>2</sub> will just slightly raise the barrier by 3.8 kJmol<sup>-1</sup> in **TS**(2 + 1). Furthermore, we also find that three water molecules in **IZ**·(H<sub>2</sub>O)<sub>3</sub> can also catalyze the keto↔amino/enol tautomerization with higher barrier (62.1 kJmol<sup>-1</sup>) by a concerted quadruple proton transfer mechanism, which was firstly reported by Lee and co-workers [32] in the theoretical study of solvent-mediated tautomerization of purine.

We are also interested to discuss why the tautomeric energy barrier for **IZ**·(H<sub>2</sub>O)<sub>3</sub> is higher than that for **IZ**·(H<sub>2</sub>O)<sub>2</sub>. This difference seems to stem from the geometrical consideration that the proton transfer process in **TS**(3) involves a four-hydrogen-atom concerted path. This means that quite a large number of atoms must be moved from their more stable positions to a somewhat distorted geometry accompanying the elongation of B–H bond(s), in which the letter B represents O or N atom. We can define the geometric looseness of the *i*th B–H bond by %*(B–H)*<sub>*i*</sub><sup>‡</sup>, and the average geometric looseness of the B–H bonds in the transition structure by %*(B–H)*<sub>av</sub><sup>‡</sup>:

$$\%(\text{B}-\text{H})_i^{\ddagger} = 100 \left[ r_i^{\ddagger}(\text{B}-\text{H})_i - r^{\text{comp}}(\text{B}-\text{H})_i \right] / r^{\text{comp}}(\text{B}-\text{H})_i \quad (1)$$

$$\%(\text{B}-\text{H})_{\text{av}}^{\ddagger} = \sum \%(\text{B}-\text{H})_i^{\ddagger} / n \quad (2)$$

where *r*<sup>‡</sup>(B–H)<sub>*i*</sub> and *r*<sup>comp</sup>(B–H)<sub>*i*</sub> are the *i*th bond length in the transition structure and in the **IZ**·(H<sub>2</sub>O)<sub>*n*</sub> complexes, respectively. The letter *n* is the number of the hydrogen atom moved in **TS**(*n*).

Generally speaking, smaller %*(B–H)*<sub>av</sub><sup>‡</sup> values favor proton transfer. It is noted that the %*(B–H)*<sub>av</sub><sup>‡</sup> value (24.2) of **TS**(3) is slightly smaller than that (24.8) of **TS**(2), but the larger  $\sum \%(\text{B}-\text{H})_i^{\ddagger}$  value (76.0) in **TS**(3) costs more distortion energy, leading to higher barrier.

**Table 3** Selected donor–acceptor interaction energies, *E*(2), for **IZ**·(H<sub>2</sub>O)<sub>*n*</sub> and **HIZ**·(H<sub>2</sub>O)<sub>*n*</sub> (*n* = 1–3) and bond order (B.O.) for the intermolecular H-bonds

Complex	NBOLp B (donor) → H -A* (acceptor)	<i>E</i> (2) kcalmol <sup>-1</sup>	B.O. for H-bond	
<b>IZ</b> ·H <sub>2</sub> O	O6	H9–O8	14.34	0.0535
	O8	H7–N1	7.23	0.0257
<b>HIZ</b> ·H <sub>2</sub> O	O8	H9–O6	21.33	0.0751
	N1	H7–O8	14.88	0.0622
<b>IZ</b> ·(H <sub>2</sub> O) <sub>2</sub>	O6	H9–O10	25.57	0.0778
	O8	H7–N1	21.28	0.0660
<b>HIZ</b> ·(H <sub>2</sub> O) <sub>2</sub>	O10	H9–O6	37.55	0.1163
	N1	H7–O8	29.60	0.1045
<b>IZ</b> ·(H <sub>2</sub> O) <sub>3</sub>	O6	H9–O10	26.62	0.0752
	O8	H7–N1	23.46	0.0700
<b>HIZ</b> ·(H <sub>2</sub> O) <sub>3</sub>	O10	H9–O6	36.96	0.1122
	N1	H7–O8	30.39	0.1059
<b>IZ</b> ·(H <sub>2</sub> O) <sub>2+1</sub>	O6	H9–O10	22.95	0.0724
	O6	H13–O12	12.84	0.0487
	O8	H7–N1	21.61	0.0668
	O12	H14–N3	7.88	0.0271
<b>HIZ</b> ·(H <sub>2</sub> O) <sub>2+1</sub>	O10	H9–O6	39.87	0.1242
	O6	H13–O12	5.55	0.0222
	N1	H7–O8	31.12	0.1097
	O12	H14–N3	8.42	0.0269

The other reason may be attributed to the distortion of angle C2–N1–H7 from 124.4° in **IZ**·(H<sub>2</sub>O)<sub>3</sub> to 129.3° in the **TS**(3) structure. Even though there are only two hydrogen bonds in the **IZ**·H<sub>2</sub>O complex, these hydrogen bonds are nonlinear ( $\angle$ O6–H9–O8 = 151.2°,  $\angle$ N1–H7–O8 = 132.0°), which implies that some strain remains in the ring and increases the difficulty for the transfer of the hydrogen atom. The three hydrogen bonds are almost linear (162.7–171.0°) in the **IZ**·(H<sub>2</sub>O)<sub>2</sub> complex depicted in Fig. 2 and the more relaxed geometry clearly favors the triple proton transfer as compared with the strained **IZ**·H<sub>2</sub>O complex. The increment from eight-membered ring structure, **IZ**·(H<sub>2</sub>O)<sub>2</sub>, to ten-membered ring structure, **IZ**·(H<sub>2</sub>O)<sub>3</sub>, does not relax the strain in the geometry of the hydrogen bonds, so that we conclude that the eight-membered ring H-bonded structure may be a more favorable complex.

For the case of **IZ**·(H<sub>2</sub>O)<sub>2+1</sub>, there are two cycles of H-bonds that connect O6–N1 and O6–N3, respectively, forming six-membered ring and eight-membered ring H-bond structures, respectively, similar to **IZ**·H<sub>2</sub>O and **IZ**·(H<sub>2</sub>O)<sub>2</sub>. This particular geometry opens the possibility of two types of proton transfer. One involves double proton transfer as **IZ**·H<sub>2</sub>O and the other by triple proton-transfer mechanism. It is obvious that the latter is more favorable based on the above comparison between the **IZ**·(H<sub>2</sub>O) and **IZ**·(H<sub>2</sub>O)<sub>2</sub> complexes. We therefore only discuss the transition structure **TS**(2+1), in which two water molecules assist the proton transfer. In **IZ**·(H<sub>2</sub>O)<sub>2+1</sub> complex, the C2–O6 bond becomes longer than those in the other situation. This can be explained by the fact that the O6 as H acceptor forms two H-bonds, and thus results in a more polarized C2–O6 bond. The larger elongation of the C–O bond in **IZ**·(H<sub>2</sub>O)<sub>2+1</sub> makes the carbonyl oxygen atom more negative, with larger  $\%(\text{B-H})_{\text{av}}^{\delta-}$  value (25.6) and higher energy barrier (57.1 kJmol<sup>-1</sup>) than those in **IZ**·(H<sub>2</sub>O)<sub>3</sub>.

Direct solvent effects on the tautomerization reactions reported here were calculated using the PCM method. We tried to study the dynamics of the aqueous solution of **IZ** by modeling it as the **IZ**·(H<sub>2</sub>O)<sub>n</sub> complexes immersed in a water continuum. The solvation free energies ( $\Delta G^{\circ}$ ), and the thermodynamic and kinetic parameters of the proton-transfer process in aqueous solution predicted by the combined discrete/SCRF methods are summarized in Table 1. All the results indicate that the keto-form is the predominant tautomer in aqueous solution, which is different from previous theoretical predictions. [23] The influence of a polar surrounding, included in the framework of the PCM continuum model, is not so noticeable. In the process of **IZ**·(H<sub>2</sub>O)<sub>n</sub> → **HIZ**·(H<sub>2</sub>O)<sub>n</sub> ( $n=1-3$ ), all of the keto-forms are slightly more solvated than **TS**( $n$ ) ( $n=1-3$ ), increasing the activation free energy by about 5–10 kJmol<sup>-1</sup>. On the other hand, the keto forms are slightly more solvated than the amino/enol-form when  $n=1-2$ , leading to more endothermicity by 1.2–4.7 kJmol<sup>-1</sup> for the isomerization of **IZ** in aqueous solution.

## Conclusions

In this paper, we have reported a DFT investigation on the tautomeric equilibrium between the keto and amino/enol-forms of imizazolone. Calculations in aqueous solution were performed using both combined discrete/SCRF and SCRF methods. The principle conclusions from this study are as following.

1. The keto form of **IZ** is always dominant both in the gas phase and aqueous solution.
2. The binding water molecules will alter the relative thermodynamic stabilities of the keto and amino/enol tautomers and the isomerization reaction of **IZ**. The interaction of **IZ** tautomer with water molecules not only dramatically lowers the tautomeric barrier height, but also decreases the endothermicity of tautomeric reaction from **IZ** to **HIZ**.
3. In view of thermodynamics and kinetics, the proton-transfer processes with two water molecules involved are more favorable than the other situations.
4. The solvent effects on the tautomerization reaction of **IZ** by the PCM model do not significantly alter the barrier height and reaction enthalpy due to the small differences in dipole moment.

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