DFT explorations of tautomerism of 2-mercaptoimidazole in aqueous solution

Hua-Jie Zhu[a], Yi Ren[b,*], Jie Ren[a], San-Yan Chu[c]

[a]State Key Lab of Phytochemistry and Plant Resources in West China, CAS, Kunming, 650200, People's Republic of China
[b]College of Chemistry, Sichuan University, Chengdu 610064, People's Republic of China
[c]Department of Chemistry, National Tsing Hua University, Hsinchu 30013, Taiwan, ROC

Abstract

A systematic investigation of the proton transfer in the tautomerization of 2-mercaptoimidazole was undertaken. Calculations in aqueous solution were performed using the combined supramolecular/continuum and the direct continuum models, respectively. Complexes containing one and two water molecules around the hydrophilic site of 2-mercaptoimidazole were used for the combined supramolecular/continuum calculation. DFT results predict that the barrier height for non-water-assisted intramolecular proton transfer is very high (175.8 kJ/mol). Hydrogen bonding between 2-mercaptoimidazole and the water molecule(s) will dramatically lower the barrier by the concerted multiple proton transfer mechanism. The proton transfer process through a eight-member ring formed by 2-mercaptoimidazole and two water molecules is found to be more efficient one and the calculated barrier height is reduced to ca. 72 kJ/mol.
© 2005 Elsevier B.V. All rights reserved.

Keywords: DFT; 2-Mercaptoimidazole; Tautomerism; Water-assisted proton transfer

1. Introduction

The prototropic tautomerism represents one of the most important processes involved in chemistry reaction as well as in living system [1–3]. In particular, the thione/thiol tautomeric equilibrium, although less studied than their oxygen analogues, has attracted great experimental and theoretical interests [4–7].

keto (X=O)   enol (X=O)
thione (X=S)   thiol (X=S)
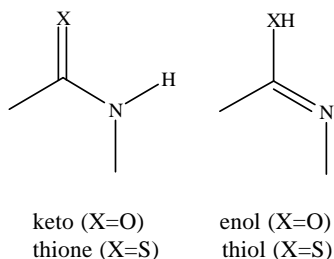
1

Among a number of physical and chemical factors that are responsible for the tautomeric equilibrium, solvation occupies one of the most important roles, because most biochemical reactions of interest occur in solution phase. In the treatment of solvent effect, 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 the combined supramolecular/continuum models [7,12–18], 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 continuum. In this way, both short-range and long-range solvent polarization interactions are included. The combined models have provided a reliable description of the reaction energy change and the proton-transfer energy barrier for some amino acids, nucleic acid bases and base pairs in

* Corresponding author. Tel.: +86 28 85412800; fax: +86 28 85257397.
E-mail address: yiren57@hotmail.com (Y. Ren).

solvents. For example, by adopting this model, Kassab et al. [13] 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 model agree with the experimental observation, better than the direct SCRF methods. Leszczynski et al. [17] and Alemán [18] also employed this approach to examine the keto/enol tautomerism of guanine and cytosine in aqueous solution. Ahn et al. [19] presented the effects of continuum water to study the isomerization of neutral/zwitterionic alanine-nW ($n=1$ and 2) cluster in aqueous solution. More recently, Yan et al. [7] presented the effects of continuum ethanol by employing the combined model to study the thione/thiol tautomeric equilibrium of 3-hydroxy-2-mercaptopyridine in ethanol. Some of studies reveal that involvement of solvent molecules in the proton-transfer transition state will reduce the barrier height and solvent molecules act as catalyst in the tautomerization.

2-Imidazolones (**IZ**) has long been known to possess some interesting biological activities [20,21]. Its sulfur analogue, 2-mercaptoimidazole (**MIZ**), was also studied to compare the effect of replacing oxygen by sulfur on the thermodynamics of both molecular systems. **MIZ** has been suggested as a chemical precursor of some oxo compound found in a group of marine alkaloids such as aplysinopsin and polyandrocarpine [22]. Recently, some new **MIZ** derivatives were synthesized [23].These new compounds show considerable antimicrobial activity against bacteria, yeast, and fungi.

The proton transfer over hydrogen bonds in **MIZ** has received less attention from the computational community. Only one recent paper reported the direct prototropic tautomerism for bare **MIZ** in vacuum and in several solutions by the direct SCRF calculations using the PCM model [24]. In our present work, a detail theoretical investigation is undertaken for the tautomerism of **MIZ** in aqueous solution. One and two explicit water molecules are considered in the solvation of thione and thiol. A detailed analysis is presented for the isomerization between two tautomers of hydrated **MIZ**, thione.nW and thiol.nW ($n=$ 1–2), as examples of solvent-assisted tautomerization. It is shown that the isomerization between thione.nW and thiol.nW clusters proceeds by the concerted double and triple proton-transfer mechanism. As a important part of the combined supramolecular/continuum model, Tomasi's polarizable continuum (PCM) [8] model will be applied to study the effect of bulk solvent on the infinite number of water molecules surrounding the **MIZ**·nW complexes. Our results are also compared with the estimations obtained from the direct continuum model at the same level. These calculations will provide valuable insights about the influence of the explicit solvent molecules in the study of tautomeric equilibria and may guide future experimental efforts.

2. Computational details

All calculations were performed with GAUSSIAN-98 packages [25] in this work. Molecular geometries and harmonic vibrational frequencies have been determined at the level of B3LYP/6-31++G(d,p), which has been shown to provide good results for hydrogen-bonded systems [26–28]. The stationary structures are 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. Specific solute–solvent interactions between **MIZ** and water molecule(s) were studied using natural bond orbital (NBO) analysis [29].

The PCM model, which is the most popular method for treating this kind of problem, is employed to address the effects of bulk solvent. Since the structural parameters of **MIZ** change very little on going from the gas phase to solution, therefore, it is 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 re-optimization in the bulk solvent is important in complex systems such as zwitterions [19]. In fact, geometry optimizations of the bare thione and thiol at B3LYP/6-31++G(d,p) in water using 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 degree. All relative energies are computed using the enthalpy and Gibbs free energy at 298 K, denoted as ΔH_{gp} and ΔG_{gp} in the gas phase or ΔH_{aq} and ΔG_{aq} in aqueous solution.

3. Results and discussion

3.1. Direct tautomerism of bare thione

As a comparison, let us start the discussion with an analysis of the optimized structure of the bare thione and thiol tautomers of **MIZ**. As shown in Fig. 1, both of them have planar structures, which have been confirmed to be the minima by the vibrational analysis. The thione is theoretically predicted to be the most stable form of **MIZ**. The DFT energy favors the thione tautomer and the enthalpy difference, ΔH_{gp} (thiol–thione), calculated in the present work is 36.4 kJ/mol (Table 3), that implies that the thione form of **MIZ** is predominant in the gas phase. It is worth noticing than both tautomers, thione and thiol, can act as simultaneously as hydrogen bond donor and acceptors (Scheme 1), which have in common the protonated and deprotonated species, and thus, the less stable one shows simultaneously the larger basicity and acidity. The characteristic of tautomeric structures is known as the Gustafsson paradox [30]. Our calculated results (Table 1) are consistent with the paradox. Geometries in Fig. 1 show
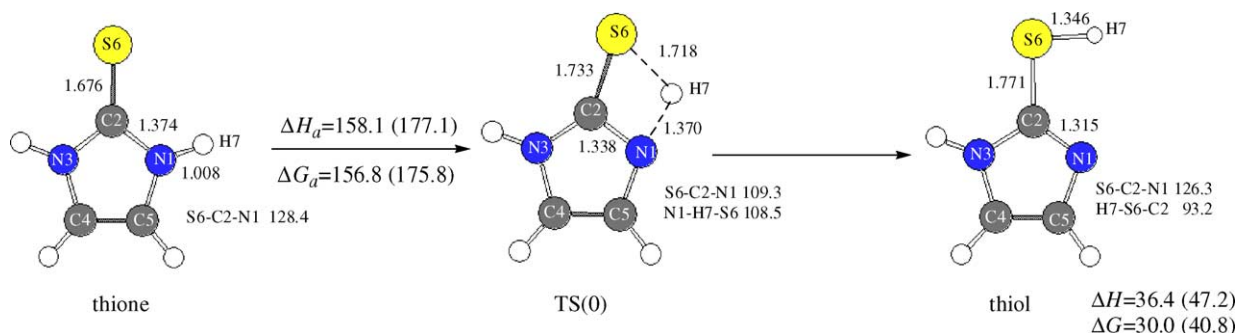
Fig. 1. Mechanism of direct tautomerization between bare thione and thiol monomer by single proton transfer. The values in parentheses are the energetics (in kJ/mol) in aqueous solution from the PCM model.

some important geometrical change as the tautomerism proceeds. When going from the thione to thiol tautomer, the N1–C2 bond length is reduced from 1.374 to 1.315 Å, while the C2–S6 distance increases from 1.676 to 1.771 Å. This is consistent with the breaking of the S=O double bond and corresponding formation of C=N double bond. It is clear that the S6–H7 distance play an important role in the intramolecular proton transfer reaction. In absence of water, the thione form cannot easily transfer the proton from the N1 to S6, because of a too long S6–H7 distance (2.974 Å). The geometry of the bare thione tautomer is unfavorable for the formation of an intramolecular hydrogen bond. The direct proton transfer would take place through a quite tense four-member ring transition structure, TS(0), which contains an almost broken N1–H7 bond (1.370 Å) whereas the S6–H7 bond is still not formed (1.718 Å). This highly distorted structure would lead to a very high barrier, (see Table 3, $\Delta H_{gp}^{\neq} = 158.1$ kJ/mol, $\Delta G_{gp}^{\neq} = 156.8$ kJ/mol), indicating that the direct proton transfer in MIZ monomer is unlikely to occur in the gas phase.

The direct solvent effects determined form PCM model for two tautomers of MIZ and TS structure, TS(0), are given in Table 3. The ΔG^{sol} values indicate that the thione form is the best solvated, while the thiol form and TS(0) are less

favored. As a result, the barrier height and endothermicity for the non-water-assisted proton-transfer tautomerism in aqueous solution is higher than those in the gas phase by ca. 19 and 11 kJ/mol, respectively.

3.2. Tautomerization between thione.nW and thio.nW (n=1–2)

Now we investigate the tautomerization of MIZ using the combined supramolecular/continuum models. We introduce one and two water molecules in the region where proton transfer takes place to form thione.nW and thiol.nW complexes. For $n=1$, the complexes present six-member cyclic structures in which a ring of water molecules is formed linking sulfur (S6) and nitrogen atom (N1), denoted as thione.W and thiol.W. For $n=2$, two possible stable structures are considered. One is similar to the ones in $n=1$, labelled as thione·2W and thiol·2W, in which both of water molecules are put on one side and eight-member ring hydrogen bond structures are formed. In the alternative complexes, two water molecules are distributed around the hydrophilic region of thione and thiol form of MIZ, in which one of them is put on one side and the other is on
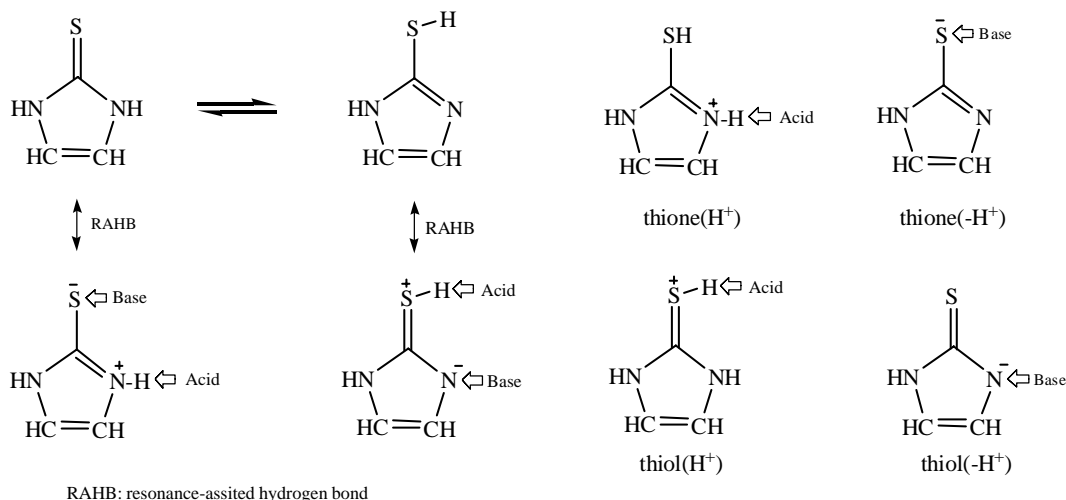
Scheme 1.

Table 1
The enthalpies for protonation and deprotonation reactions of **MIZ** tautomers in the gas phase

	Reaction	ΔH_{gp} (kJ/mol)
Protonation	thione + H$^+$ → thione(H$^+$)	−908.2
Deprotonation	thione → thione(−H$^+$) + H$^+$	1429.9
Protonation	thiol + H$^+$ → thiol(H$^+$)	−944.7
Deprotonation	thiol → thiol(−H$^+$) + H$^+$	1393.5

the other side. These structures are denoted as thione.$(1+1)$W and thiol.$(1+1)$W.

Formation of complexes with water molecules will affect the structures of the thione and thiol units. As can be expected, the influence of the interaction with water molecules on the bond distances and angles of thione and thiol tautomer manifests themself mainly in the region of intermolecular hydrogen bondings. Fig. 2 shows that the C2–S6 bond length increase from 1.676 Å in the bare thione

to 1.693–1.709 Å and the N1–H7 bond length from 1.008 Å to 1.024–1.033 Å, while the N1–C2 bond length decreases from 1.374 Å to about 1.360 Å in the thione·nW ($n=1$–2) complexes. These geometric changes will favor the following proton transfer reaction with lower barrier heights. In the complexes, thiol.nW ($n=1$–2), the situation is different, with the C2–S6 bond length a little bit changing from 1.771 Å to about 1.770 Å and N1–C2 bond length increasing from 1.315 Å to about 1.325 Å, while the S6–H9 bond length increasing from 1.346 Å to 1.360–1.370 Å.

It can be observed from Fig. 2 that the H-bonds, S6–H9···O10, in thiol.nW, are shorter (1.854–2.002 Å) than the corresponding S6···H9–O10 H-bonds (2.250–2.363 Å) in thione.nW complexes, but the data in Table 3 show that the complexing with water molecule(s) makes the thione from more stable than the thiol form. The interactions with water molecule(s) favor the thione form by 10–23 kJ/mol, implying that the tautomerization from the thione to thiol
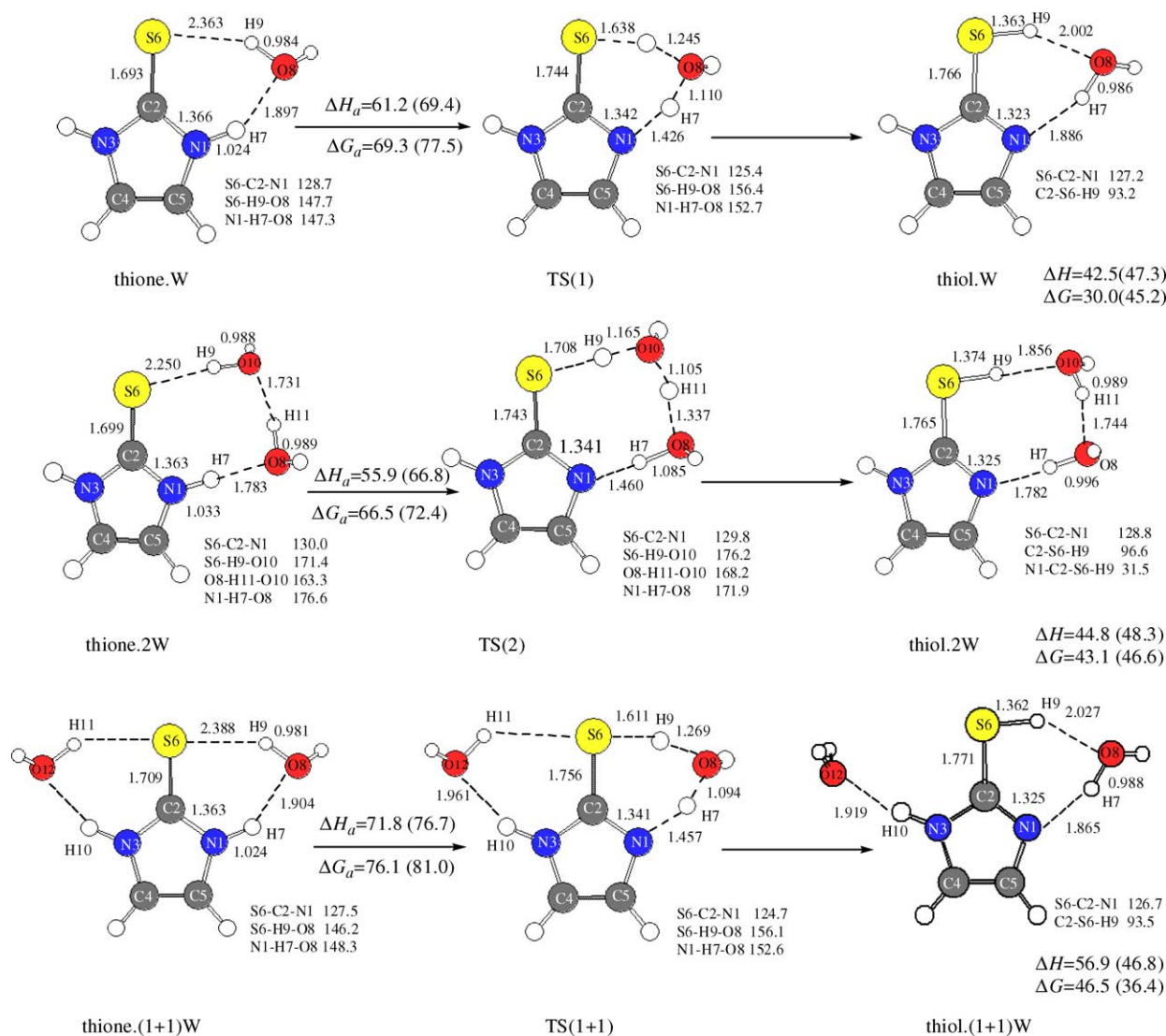

Fig. 2. Mechanism of water-assisted tautomerization between thione.nW and thiol.nW ($n=1$–2) complexes by double and triple proton transfer. The values in parentheses are the energetics (in kJ/mol) in aqueous solution from the PCM model.

form will be more thermodynamically unfavorable. That can be explained by two reasons, one is from more acidity of the hydrogen atom in S6···H9–O10 than in S6–H9···O10, the other reason may from the deviation of H10 atom in thiol.nW from planar structure of bare thiol form, due to the complexing with water molecules. Comparison between the complex thione.2W and thione.$(1+1)$W shows that the former is more stable and DFT Gibbs free energies favor thione.2W by 3.0 kJ/mol. These interactions between **MIZ** tautomers with water molecules can also be evaluated using the charge transfer energy, ΔE_{CT} (B→A–H*), from the basic atoms, B=N(O or S), into the A–H*(A=N or O,S) anti-bonding orbitals and intermolecular H-bond bond order in NBO analysis(Table 2). The charge transfer is a measure of the electron donating ability, that is, basicity, of the basic atom N (O or S) within a given complex, as well as the strength of the intramolecular hydrogen bond. The higher charge transfer energy, the stronger H-bond, the larger value of bond order, the more stable complex with water molecule(s).

After formation of the mono- and di-hydrated tautomers of **MIZ**, the proton transfer reactions may occur with water molecule(s) as a bridge. As shown in Fig. 2, two intermolecular H-bonds, S6···H9–O10 and N1–H7···O8, are formed in thione.nW ($n = 1$–2) with the H_2O molecule(s) acting as bridge between the sulfur atom (S6) and the NH group. The H7–O8 and S6–H9 distances in these complexes are 1.783–2.388 Å, significantly shorter than the S6–H7 distance of 2.974 Å in the bare thione. This shows that the proton transfer in these complexes will be more easily than in the bare thione form.

Table 2
The selected charge transfer energies, (in kJ/mol) and bond orders (B.O.) of the Intramolecular Hydrogen Bondings in the thione.nW and thiol.nW ($n = 1$–2) tautomers

Complex	Donor → acceptor, B_{Lp}→A–H*		ΔE_{CT} (B→A–H*) kJ/mol	B.O. for H-bond
Thione.W	S6	H9–O8	51.34	0.0682
	O8	H7–N1	63.09	0.0483
Thiol.W	O8	H9–S6	44.06	0.0455
	N1	H7–O8	69.75	0.0637
Thione.2W	S6	H9–O10	86.19	0.093
	O10	H11–O8	98.87	0.0754
	O8	H7–N1	105.94	0.0763
Thiol.2W	O10	H9–S6	76.32	0.0685
	O8	H11–O10	96.61	0.075
	N1	H7–O8	107.74	0.091
Thione.$(1+1)$W	S6	H9–O8	47.03	0.0555
	S6	H11–O10	46.90	0.0553
	O8	H7–N1	62.59	0.0476
	O12	H10–N3	62.63	0.0476
Thiol.$(1+1)$W	O8	H9–S6	40.12	0.0423
	N1	H7–O8	76.19	0.0696
	O12	H10–N3	64.52	0.0411

Upon addition of one water molecule in the process of thione.nW ↔ thiol.nW tautomerization, the two hydrogen atoms will be transferred in the transition structure, TS(1). We can refer to that process as an almost synchronous double proton transfer based on the analysis of TS(1). It can be observed from the geometrical parameters that the TS(1) is less tense than the TS(0), in which the N10–H7 and S6–H9 distances become shorter due to the bridging role of water and considerably reduce the proton transferring path. The less tense transition structure dramatically lowers the tautomeric barrier from 156.8 to 69.3 kJ/mol in terms of $\Delta G_{gp}^{\neq}$. In comparison with the tautomerization of the thione monomer, formation of the water complex lowers the barrier by 87.5 kJ/mol, indicating that the tautomeric process is enhanced by the water molecule, called water-assisted tautomerization.

The binding of two water molecules in thione.2W may still lower the barrier to 66.5 kJ/mol for TS(2), catalyzing the thione↔thiol tautomerization by the concerted triple proton transfer mechanism. Addition of one water molecule on the other side of thione.W will raise tautomeric barrier by 6.8 kJ/mol in TS$(1+1)$. That means tautomerism between thione.$(1+1)$W ↔ thiol.$(1+1)$W is unfavorable in views of kinetics.

We are also interested to compare the tautomeric energy barrier for thione.W, thione.2W and thione·$(1+1)$W. This difference seems to stem from geometrical consideration. There are two hydrogen bonds in the complexes thione.W, in which the angles are about 147°. The non-linear H-bond angles will increase the repulsion between two heavy atoms with higher electronegativity and implies that some strain remains in the six-member ring structures, so that increases the difficulty for the transfer of the hydrogen atom. The three hydrogen bonds are more linear (H-bond angles from 163.3 to 176.6°) in the thione.2W complex depicted in Fig. 2 and the more relaxed geometry clearly favors the triple proton transfer as compared with the strained thione.W and thione.$(1+1)$W complexes, leading the tautomeric barrier for thione.2W lower than that for thione.W and thione.$(1+1)$W. So we conclude that the eight-member ring H-bonded structure may be a more favorable complex. For the case of thione.$(1+1)$W, there are two cycles of H-bonds that connect S6, N1 and S6, N3, respectively, forming two six-member ring H-bonds structures, respectively, similar to the thione.W, involving the double proton transfer as TS(1). In thione.$(1+1)$W, the C2–S6 bond becomes longer than thione.W, due to the fact that the S6 as proton acceptor forms two H-bonds, and thus results in a more polarized C2–S6 bond. The more elongation of the C–S bond in thione.$(1+1)$W makes the sulfur atom more negative, with more elongation of N–H bond and higher energy barrier (76.1 kJ/mol) than those in thione.W.

The 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 thione by modeling it as the thione.nW complexes immersed in

Table 3
Relative energies (in kJ/mol), dipole moments and the free energy of solvation (in kJ/mol), ΔG^{sol}, for the stationary points corresponding to the proton-transfer reaction of thione monomer and thione.nW ($n=1$–2) complexes computed at the B3LYP/6-31$++$G(d, p) level

Species	ΔH_{gp}	ΔG_{gp}	ΔG^{sol}	μ_{gp}(D)	ΔH_{aq}	ΔG_{aq}
Thione	0.0	0.0	-47.8	5.7493	0.0	0.0
TS(0)	158.1	156.8	-28.8	4.1622	177.1	175.8
Thiol	36.4	30.0	-37.0	2.7021	47.2	40.8
Thione.W	0.0	0.0	-40.0	4.5803	0.0	0.0
TS(1)	61.2	69.3	-31.8	3.1718	69.4	77.5
Thiol.W	42.5	40.5	-35.3	3.5773	47.3	45.2
Thione.2W	0.0	0.0	-42.5	4.1297	0.0	0.0
TS(2)	55.9	66.5	-36.7	2.2030	61.8	72.4
Thiol.2W	44.8	43.1	-39.0	3.5901	48.3	46.6
Thione.(1$+$1)W	0.0	0.0	-32.0	3.0289	0.0	0.0
TS(1$+$1)	71.8	76.1	-27.1	1.3260	76.7	81.0
Thiol.(1$+$1)W	56.9	46.5	-42.1	4.6492	46.8	36.4

the continuum water. The solvation free energies (ΔG^{sol}), and the thermodynamic and kinetic parameters of the proton-transfer process in aqueous solution predicted by the combined supramolecular/continuum methods are summarized in Table 3. All the results indicate that the thione form is be more predominant in aqueous solution, which is different from previous theoretical prediction [24]. The influence of a polar surrounding, included in the framework of the PCM continuum model, is not so noticeable for the thione.nW $\leftrightarrow$ thiol.nW ($n=1$–2) tautomeric equilibrium in aqueous solution. The thione monomer, thione.W and thione.2W complexes are slightly more solvated than corresponding TS structures, TS(1) and TS(2), and the thiol tautomers, leading the increase of the activation energy by about 6–8 kJ/mol and endothermicity of the reaction by about 3–5 kJ/mol, that indicate the isomerization of **MIZ** from thion to thiol form is more difficult in aqueous solution.

3.3. Electron delocalization on the thione.nW and thiol.nW(n=0–2)

The relative stability of the various species in the tautomerization between thione.nW and thiol.nW can also be further discussed by considering the electron delocalization on the MIZ moiety. This can be clearly evidenced by comparing the bond lengths (Figs. 1 and 2) or, better,

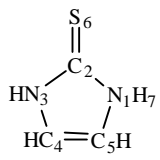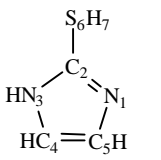the Wiberg's bond indices from the NBO analysis of bonds N1–C2 and C2–S6 (Table 4).

As shown in Figs. 1 and 2, the thione/thiol tautomerism is accompanied only by significant changes of the two bonds, N1–C2 and C2–S6. So we can estimate the electron delocalization on the **MIZ** moiety in the complexes **MIZ**.nW ($n=0$–2) using the standard deviation(STD) for the N1–C2 and C2–S6 bond lengths. The tautomer with smaller STD value will be more stable. It can be found there is a reasonable correlation between the enthalpies for the thione.nW $\rightarrow$ thiol.nW($n=0$–2) reactions and the differences of STD ($R^2=0.927$), which indicates the better electron delocalization in the thione moiety would stabilize the thione.nW form and lead to more endothermicity of the tautomeric reactions. Consequently, some general features are noticed: the thione structures are more stable than the corresponding thiol ones. Similar discussions were made in the study of push–pull conjugated molecules [31].

4. Conclusions

In this paper, we have reported a systematic DFT investigation on the thion/thiol tautomeric equilibrium of 2-mercaptoimidazole(MIZ) in aqueous solution, employing the combined supramolecular/continuum and direct

Table 4
Selected Wiberg bond index of **MIZ** moiety in **MIZ**.nW($n=0$–2)

thione   thiol

Bond	Thione	Thiol	Thione.W	Thiol.W	Thione.2W	Thiol.2W	Thione.(1$+$1)W	Thiol.(1$+$1)W
N1–C2	1.163	1.528	1.205	1.485	1.372	1.474	1.222	1.478
C2–S6	1.484	1.070	1.403	1.093	1.222	1.093	1.336	1.083
STD	0.227	0.324	0.140	0.277	0.106	0.269	0.081	0.279

continuum models. The principle conclusions from this study are as following:

1. The thione form of **MIZ** is always dominant both in the gas phase and in aqueous solution.
2. The binding water molecules will alter the relative thermodynamics stability of the thione/thiol tautomers and the isomerization reaction of thione. The interaction of thione tautomer with water molecules would dramatically lowers the tautomeric barrier height, but will increase the endothermicity of tautomeric reaction from thione to thiol.
3. Our DFT computations support two water molecules involved in the tautomeric equilibrium in aqueous solution and eight-member ring structure formed by **MIZ** and two water molecules is found to be more efficient.
4. The solvent effects on the tautomerization reaction of thione by the PCM model do not significantly alter the barrier height and reaction enthalpy due to the small differences in dipole moment.

Acknowledgements

References

[1] A. Douhal, F. Lahmani, A.H. Zewail, Chem. Phys. 207 (1996) 477 (and references therein).
[2] H.H. Limbach, J. Manz, Special issue on hydrogen transfer: experiment and theory, Ber. Bunsenges Phys. Chem. 102 (1998) 289 (editorial).
[3] N. Agmon, Isr. J. Chem. 39 (1999) 493.
[4] P. Beak, F.S. Fry, J. Lee Jr., F. Steele, J. Am. Chem. Soc. 98 (1976) 171.
[5] D. Moran, K. Sukcharoenphon, R. Puchta, H.F. Schaefer III, P.v.R. Schleyer, C.D. Hoff, J. Org. Chem. 67 (2002) 9061.
[6] R. Martos-Calvente, V.A. de la Peña O'Shea, J.M Campos-Martin, J.L.G. Fierro, J. Phys. Chem. A 107 (2003) 7490.
[7] W.Z. Yan, Y. Xue, H. Zhu, J. Zeng, D.Q. Xie, J. Comput. Chem. 25 (2004) 1833.
[8] J. Tomasi, M. Persico, Chem. Rev. 94 (1994) 2027.
[9] C.J. Cramer, D.G. Truhlar, Chem. Rev. 99 (1999) 2161.
[10] V. Barone, M. Cossi, B. Mennucci, J. Tomasi, J. Chem. Phys. 107 (1997) 3210.
[11] S. Miertus, E. Scrocco, J. Tomasi, Chem. Phys. 55 (1981) 117.
[12] A. Fernandez-Ramos, Z. Smedarchina, W. Siebrand, M.Z. Zgierski, J. Chem. Phys. 113 (2000) 9714.
[13] E. Kassab, J. Langlet, E. Evieth, Y. Akacem, J. Mol. Struct. (Theochem) 531 (2000) 267.
[14] I. Tunon, E. Silla, C. Millot, M.T.C. Martins-Costa, M.F. Ruiz-Lopez, J. Phys. Chem. A 102 (1998) 8673.
[15] L. Gontrani, B. Mennucci, J. Tomasi, J. Mol. Struct. (Theochem) 500 (2000) 113.
[16] K.J. Jalkanen, R.M. Nieminen, K. Frimand, J. Bohr, H. Bohr, R.C. Wade, E. ajkhorshid, S. Suhai, Chem. Phys. 265 (2001) 125.
[17] Z. Smedarchina, W. Siebrand, A. Femandez-Ramos, L. Gorb, J. Leszczynski, J. Chem. Phys. 112 (2000) 566.
[18] C. Alemán, Chem. Phys. 253 (2000) 13.
[19] D.S. Ahn, S.W. Park, I.S. Jeon, M.K. Lee, N.H. Kim, Y.H. Han, S. Lee, J. Phys. Chem. B 107 (2003) 14019.
[20] S.J. Dominianni, T.T. Yen, J. Med. Chem. 32 (1989) 2301; M.W. Moon, C.G. Chidester, R.F. Heier, J.K. Morris, R.J. Collins, J. Med. Chem. 34 (1991) 2314.
[21] E.M. Naylor, E.R. Parmee, V.J. Colandrea, L. Perkins, L. Brockunier, M.R. Candelore, M.A. Cascieri, L.F. Colwell Jr., L. Deng, W.P. Feeney, M.J. Forrest, G.P. Hom, D.E. MacIntyre, C.D. Stroder, L. Tota, P.-R. Wang, M.J. Wyvratt, M.H. Fisher, A.E. Weber, Bioorg. Med. Chem. Lett. 9 (1999) 755.
[22] I. Manani, G. Guella, C. Delcitus, D. Duhet, F. Pietra, Helv. Chim. Acta 77 (1994) 1886.
[23] M.A. Salama, L.A. Almotabacani, Phosphorus Sulfur 179 (2004) 305.
[24] J.G. Contreras, S.T. Madariaga, J. Phys. Org. Chem. 16 (2003) 47.
[25] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, V.G. Zakrzewski, J.A. Montgomery, R.E. Stratmann Jr., J.C. Burant, S. Dapprich, J.M. Millam, A.D. Daniels, K.N. Kudin, M.C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G.A. Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. Cioslowski, J.V. Ortiz, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, J.L. Andres, C. Gonzalez, M. Head-Gordon, E.S. Replogle, J.A. Pople, GAUSSIAN 98, Revision A.9, Gaussian, Inc.: Pittsburgh, PA, 1998.
[26] O.V. Shishkin, L. Gorb, J. Leszczynski, J. Phys. Chem. B 104 (2000) 5357.
[27] A.T. Dubis, S.J. Grabowski, D.B. Romanowska, T. Misiaszek, J. Leszczynski, J. Phys. Chem. A 106 (2002) 10613.
[28] O. Lukin, J. Leszczynski, J. Phys. Chem. A 106 (2002) 6775.
[29] A.E. Reed, R.B. Weinstock, F. Weinhold, J. Chem. Phys. 83 (1985) 735; J.P. Foster, F. Weinhold, J. Am. Chem. Soc. 102 (1980) 7211; A.E. Reed, F. Weinhold, J. Chem. Phys. 78 (1983) 4066; A.E. Reed, L.A. Curtiss, F. Weinhold, Chem. Rev. 88 (1988) 899.
[30] J. Elguero, C. Marzin, A.R. Katritzky, P. Linda, The Tautomerism of Heterocycles, Academic Press, New York, 1976.
[31] A. Bouchy, D. Rinaldi, J.L. Rivail, Int. J. Quantum Chem. 96 (2004) 273.