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A comparative study of Direct and Water-mediated Thione-thiol Tautomerisation processes in 4-amino-1,2,4-triazole-5-thiones

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Abstract
Theoretical studies of the thione-thiol tautomerism in 4-amino-1,2,4-triazole-5-thiones at the DFT (B3LYP/6-31+G(d,p)) level reveal that in the gas phase, thiones are more stable than thiols by ~15 kcal mol^{-1} and are separated by a high energy barrier of ~44 kcal mol^{-1}. However, in the water-mediated process, thiones first combine with a molecule of water to form a reactant complex in which H_2O molecule forms a bridge between N1-H and sulfur atom of the thione group. It is followed by the transfer of the proton to the sulfur atom which is the rate determining step. The reaction leads initially to the product complex which finally releases the product molecule accompanied by the loss of the H_2O molecule.

Keywords*: DFT, 4-amino-1,2,4-triazole-5-thiones, thione-thiol tautomerism, water-mediated proton transfer, reactant complex, product complex.*

Introduction

The keto-enol tautomerism involving intramolecular and intermolecular proton transfer is one of the simplest but most important processes in chemistry and bio-systems[1-7]. The mercapto and thione substituted 1,2,4-triazole ring systems have been associated with antibacterial[8], antifungal[9], antitubercular[10], anticancer[11], hypoglycemic[12] and diuretic[13] bioactivities. The importance of the thione-thiol tautomerism on the inhibition of peroxidase-catalysed reactions has been studied by using N,N-disubstituted thiones and selones. These studies indicate that the presence of a free N-H moiety in the sulfur-based compound is essential for an efficient inhibition[13].

Some theoretical studies of thione-thiol tautomeric equilibrium of heterocyclic thione derivatives have been reported and it has been found that in the gas phase, these systems exist predominantly as thiones[14-17]. Prototropic shift in 1,2,4-triazole-5-thione and its various disubstituted derivatives has been investigated at the DFT and *ab initio* levels and it has been shown that at all different levels of theory, thione form is the most stable tautomer[18]. Furthermore, on comparing various theory levels, it has been concluded that B3LYP/6-31G(d,p) level is quite well suited and reliable to study these types of tautomerism[18].

In this context, it has been found that although energy barriers for the direct proton transfer in the tautomeric

process are significantly high, these are remarkably lowered in H_2O-assisted[19-20] or EtOH-mediated[21]process.

In the DNA and RNA duplexes, water-assisted proton transfer reactions constitute an important dynamic event[22,23]. Theoretical quantum chemical study of the tautomerism and proton transfer in 6,8-dithioguanine revealed that water-assisted proton transfer reactions considerably decrease the energy barrier as compared to that in the gas phase[24]. No theoretical studies of water-mediated proton transfer in 4-amino-1,2,4-triazole-5-thiones have been done so far. In view of this, it was considered interesting to make a comparative study of the thione-thiol tautomerism in 4-amino-1,2,4-triazole-5-thiones without the assistance of water and water-mediated process. We succeeded in locating the reactant complex and the product complex on the potential energy surface (PES) of water-mediated tautomerisation for the first time. The results are presented in this paper.

Computational Details

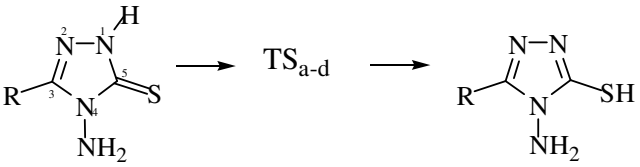
Gaussian 03 package of programs[25] was used for all calculations. The geometries of thiones and thiols and the corresponding transition structures involved in the tautomerisation were optimized at the restricted Becke's three parameter hybrid functional[26] in conjunction with the correlation functional of Lee, Yang and Parr[27], known as B3LYP level with 6-31+G(d,p) basis set. Vibrational frequencies were also calculated at the same level. All minima and transition structures were confirmed to have none or one imaginary frequency respectively. Total energies were calculated by adding unscaled zero point energy (ZPE) from B3LYP/6-31+G(d,p) level to the single point energies obtained at the same level. The inter-relation between the respective thiones, thiols and the transition structures was confirmed by carrying out intrinsic reaction coordinate (IRC) calculations[28].

Natural bond orbital (NBO) analysis[29] was done for determining the bond order (Wiberg bond indices)[30]. The solvent effect has been studied by calculating single point energy of the B3LYP/6-31+G(d,p) gas phase optimized stationary points at the same level using self consistent reaction field [SCRF] method[31] based on Tomasi's polarisable continuum model (PCM) [32].

Results and Discussion

Direct Thione-Thiol Tautomerisation

In order to determine the energy barriers for direct thione-thiol tautomerism in 4-amino-1,2,4-triazole-5-thiones and the effect of the substituent group on it, the following four systems were computed as shown in Scheme 1.



1$_{a-d}$ **2**$_{a-d}$

Reaction no./1,2	1/a	2/b	3/c	4/d
R	H	Me	Et	Ph

Scheme 1*: Thione-thiol taumerisation in 4-amino-1,2,4-triazole-5-thiones.*

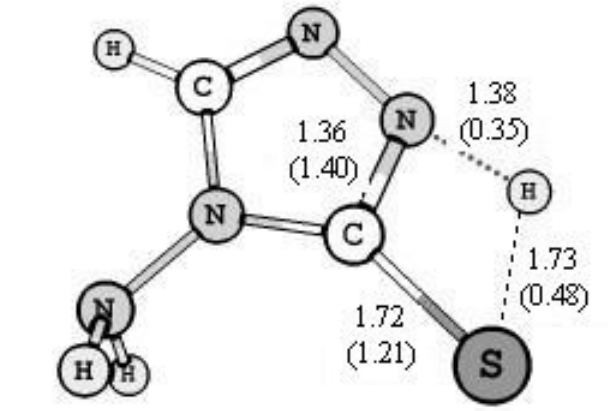
The relative thione-thiol tautomerisation activation barriers and the tautomerisation energies of the four model systems in the gas phase and in solvents are given in Table 1.

Table 1: Relative activation energies and tautomerisation energies of thione-thiol tautomerism in 4-amino-1,2,4-triazole-5-thiones.[a]

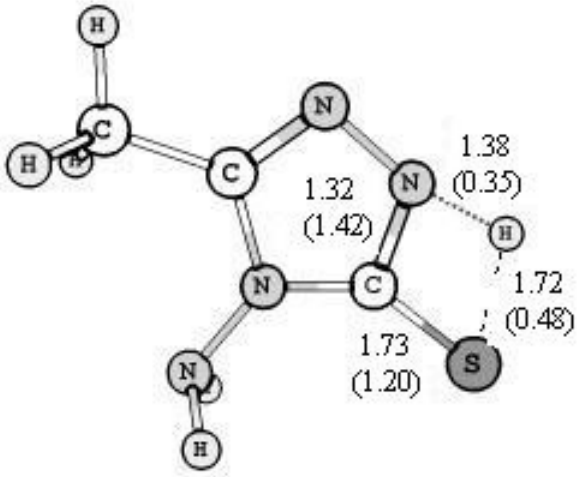
Reaction no.	Relative activation energy			Relative tautomerisation energy		
	Gas phase	Water	Ethanol	Gas phase	Water	Ethanol
1	44.14	46.20	47.56	15.01	13.84	13.53
2	44.70	46.49	46.41	15.90	14.52	14.60
3	44.70	46.48	46.40	15.81	14.38	14.50
4	44.30	46.06	45.97	15.17	13.91	14.02

[a] Energy units in kcal mol^{-1}.

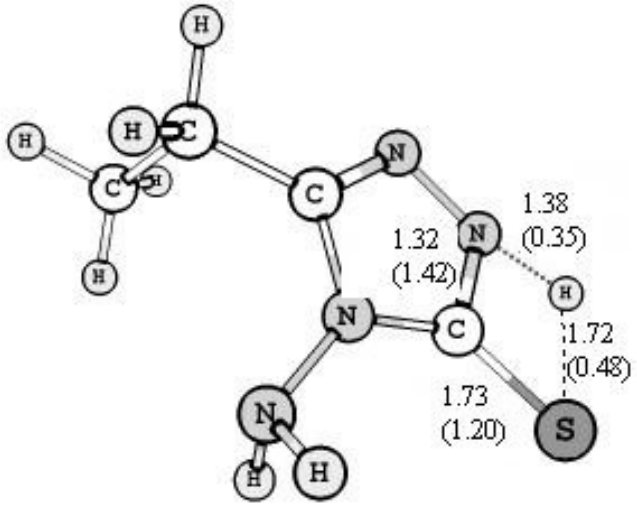
The transition structures (TS_{a-d}) involved in thione-thiol tautomerisation in the reactions 1-4 along with the lengths of the N-H and S-H bonds and their Wiberg bond indices (in parentheses) are shown in Fig.1.



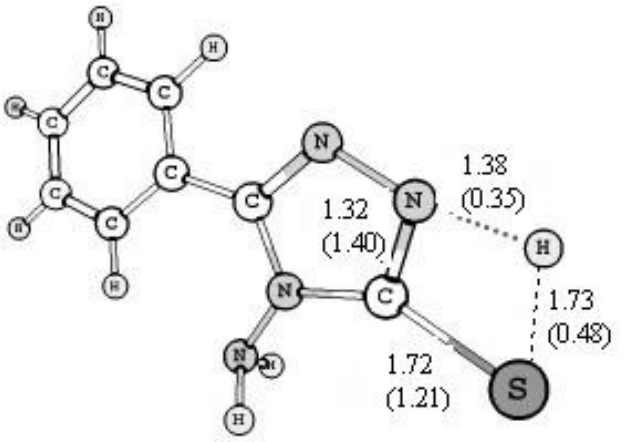
TS_a



TS_b



TS_c



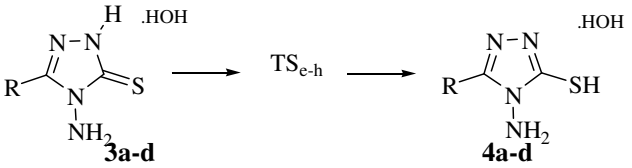
TS_d

Fig. 1 Structures of the transition states (TS_{a-d}) involved in the thione-thiol tautomerisation of 4-amino-1,2,4-triazole-5-thiones along with the N-H and S-H bond lengths (in Å) and the corresponding Wiberg bond indices (in parentheses).

It may be noted from Table 1 that in the gas phase, the thione forms of 4-amino-1,2,4-triazoles are more stable than the corresponding thiol forms by about 15 kcal mol^{-1} and this scenario remains almost unaffected by the presence and nature of a substituent group at 3-position. The energy barrier for the change of thione form into the thiol form in the gas phase is prohibitively high, ~44 kcal mol^{-1} which increases further by ~2 kcal mol^{-1} in water or ethanol, although the stability of the thiol form in this solvent, as expected, increases by ~1 kcal mol^{-1} as compared to that in the gas phase.

Water-Mediated Thione -Thiol Tautomerisation

As mentioned earlier, energy barriers for the proton transfer in the H_2O-mediated process are lowered remarkably[19–21]. In order to study this effect theoretically in the case of 4-amino-1,2,4-triazole-5-thiones, we computed following representative reactions mediated by H_2O molecule as illustrated in Scheme 2.



3a-d **4a-d**

Reaction no./3,4	5/a	6/b	7/c	8/d
R	H	Me	Et	Ph

Scheme 2 H_2O-mediated thione-thiol tautomerisation in 4-amino-1,2,4-triazol-5-thiones.

Yoshizawa and co-workers[33] while studying the reaction pathway for direct benzene hydroxylation by FeO^+ species theoretically, detected the existence of the reactant complex and the product complex on the potential energy surface (PES) of the reaction. In some other cases also, involvement of these species has been established[35-37]. Formation of such complexes is accompanied by lowering of the energy, termed as the binding energy. In view of this, we scanned the PES of the tautomerisation processes of the 4-amino-1,2,4-triazole molecule in the presence of water for the existence of the reactant and product complexes and could locate both types of species. Optimized geometries of the four reactant complexes (3a-d) formed from the association of 1a-d with a molecule of H_2O as also of the corresponding product complexes (4a-d) are given in Fig. 2.

Formation of the reactant and product complexes is accompanied by the release of the energy shown as binding energies in Table 2.

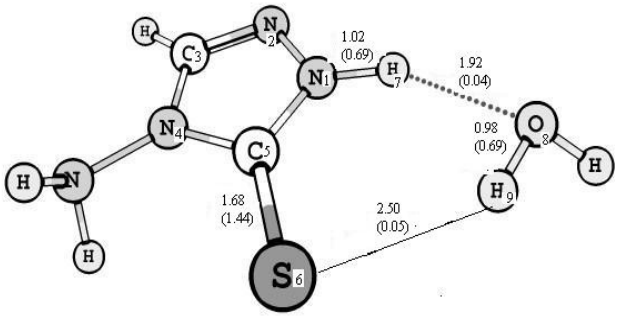
Table 2 Binding energies in the reactant and product complexes in H_2O-mediated proton transfer in 4-amino-1,2,4-triazole-5-thiones.[a]

Reaction No.	Binding energy in the reactant complex		Binding energy in the product complex	
	Gas	Water	Gas	Water
5	-4.96	-12.95	-5.32	-14.06
6	-4.83	-12.96	-5.48	-14.24
7	-4.95	-9 58	-5.41	-13.93
8	-4.98	-6.16	-5.36	-14.16

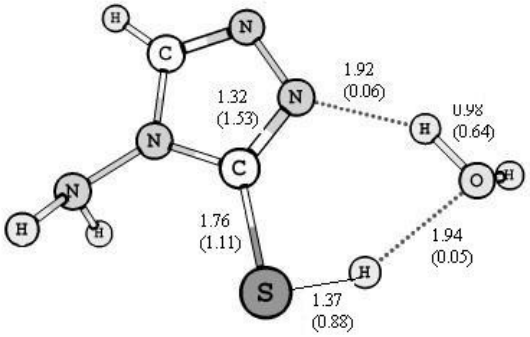
[a] Energy units in kcal mol^{-1}

In the case of FeO^+ activated benzene hydroxylation, reactant complex induced C-H activation of benzene followed by abstraction of the H atom. In the present case also, a similar process appears to occur. As can be seen in Fig. 2, in **3a-d,** H_2O molecule forms a bridge between N1-H and sulfur atom of the thione group thus facilitating the transfer of the proton from the former to the latter. Formation of the hydrogen bond between H2 and oxygen atom of the water molecule weakens N3-H2 bond on the one hand and induced interaction between hydrogen atom of the water molecule and sulfur atom helps in the transfer of the proton on the other hand. NBO studies confirm these interactions and their resulting effects. For example, the presence of 0.04 e in the σ^*_{N3-H2} orbital results in the weakening of the N3-H2 bond, whereas generation of -0.28 charge on the sulfur atom helps inducing its interaction with the hydrogen atom of the OH group of water molecule. Furthermore, in the reactant complexes, the Wiberg indices of the C4-S5 and S5-H6 bonds are 1.44 and .05 respectively revealing weakening of the C=S bond with simultaneous formation of the S-H bond.

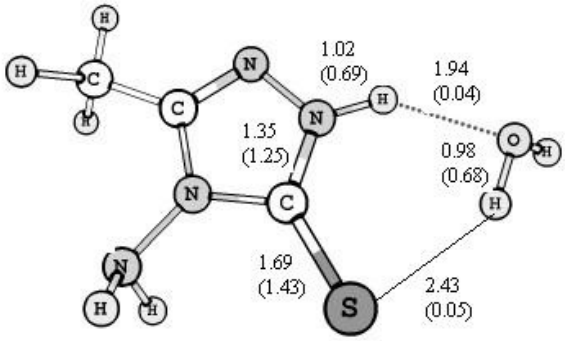
The reactant complex subsequently leads to the transition structure complex. Optimized geometries of the transition structures involved in the H_2O-mediated proton transfer process (TS_{e-h}) are given in Fig.3.



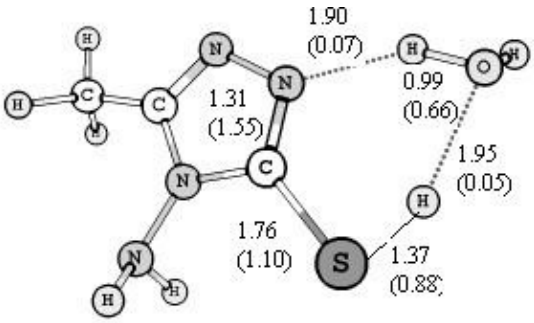
3a



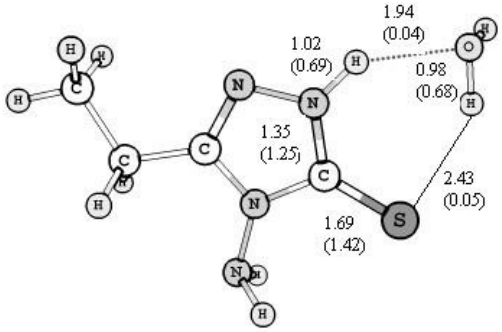
4a



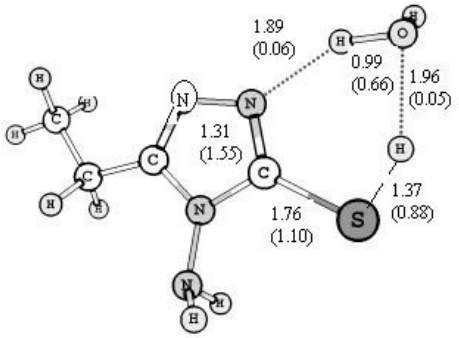
3b



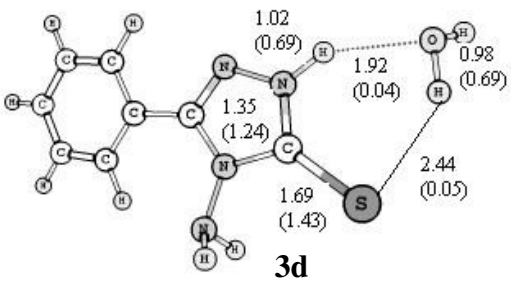
4b



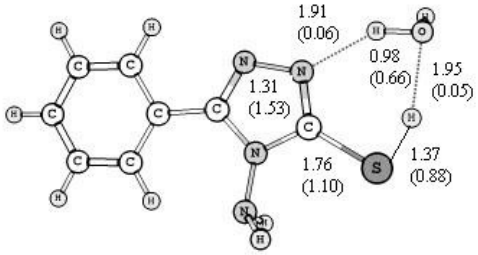
3c



4c



3d



4d

Figure 2 Optimized geometries of the reactant complexes (3a-d) and product complexes (4a-d) at the B3LYP/6-31+G(d,p) level along with the bond distances (in Å) and Wiberg bond indices (in parentheses).

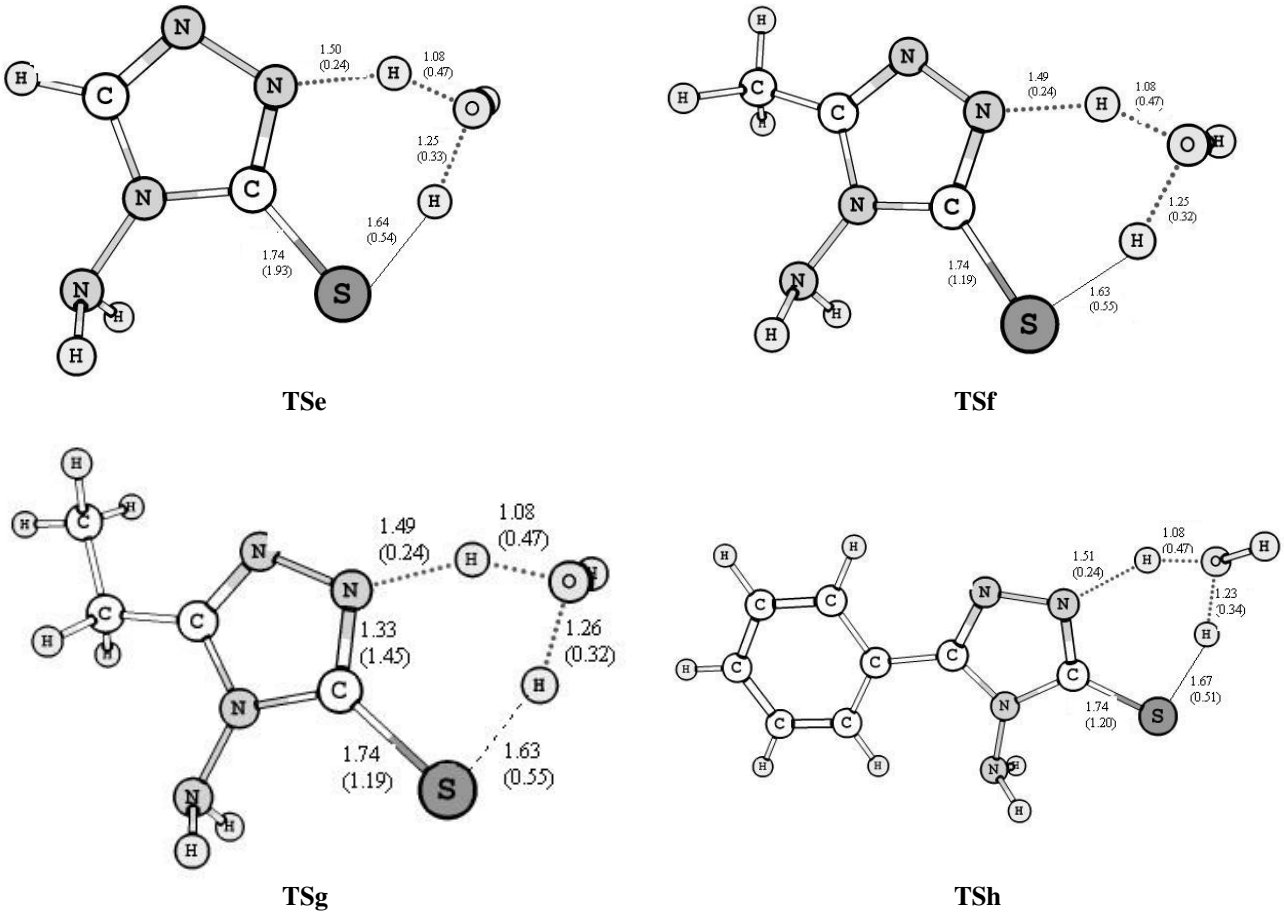


Figure 3 Optimized geometries of the transition structures complexes (TS_{e-h}) involved in the H_2O-mediated proton transfer process at the B3LYP/6-31+G(d,p) level along with the bond distances (in Å) and Wiberg bond indices (in parentheses).

The relative activation energies and tautomerisation energies of H_2O-mediated proton transfer in 4-amino-1,2,4-triazole-5-thiones are given in Table 3.

Table 3: The relative activation energies and tautomerisation energies of H_2O-mediated proton transfer in 4-amino-1,2,4-triazole-5-thiones.[a]

Reaction No.	Relative activation energy		Relative tautomerisation energy	
	Gas	Water	Gas	Water
5	18.68	18.12	14.65	12.73
6	19.26	18.69	15.24	13.24
7	19.32	14.41	15.34	9.03
8	18.82	11.54	14.79	5.91

[a] Energy units in kcal mol^{-1}.

It may be noted from Table 3 that the activation barriers for the H_2O-mediated proton transfer are remarkably lowered as compared to those for the unassisted process.

NBO studies of the transition structures TS_{e-h} in relation to the corresponding transition structures $TS_{a,b}$ involved in the unassisted proton transfer reveal that formation of the S-H bond in the former (σ_{S-H}, occupancy ~ 1.95 e) is much more advanced than in the latter. Moreover, stronger perturbative interactions in the TS_{e-h} help in lowering their energies as compared to those of the $TS_{a,b}$.

As mentioned earlier, the H_2O-mediated proton transfers lead to the product complexes which are 4-amino-1,2,4-

triazole-5-thiol molecules associated with a H_2O molecule. The optimized geometries of the product complexes (4a-d) are shown in Fig. 2. It may be noted that product complexes have strong hydrogen bonding between S-H and oxygen atom of the water molecule which makes them more stable than the unassociated product molecules. These energies, shown as the product complex binding energies, are given in Table 2. The product complex finally liberates the unassociated product molecule by eliminating a water molecule.

Like the unassisted processes, H_2O-mediated process is also endothermic indicating that even in water, thiones are more stable than the corresponding thiol molecules. It may be attributed to the presence of strong hydrogen bonding between N1-H and H_2O in 4-amino-1,2,4-triazole-5-thiones.

A comparison of the activation barriers for the H_2O-mediated proton transfer with that for the direct thione-thiol tautomerisation in 1a has been depicted graphically in Fig. 4.

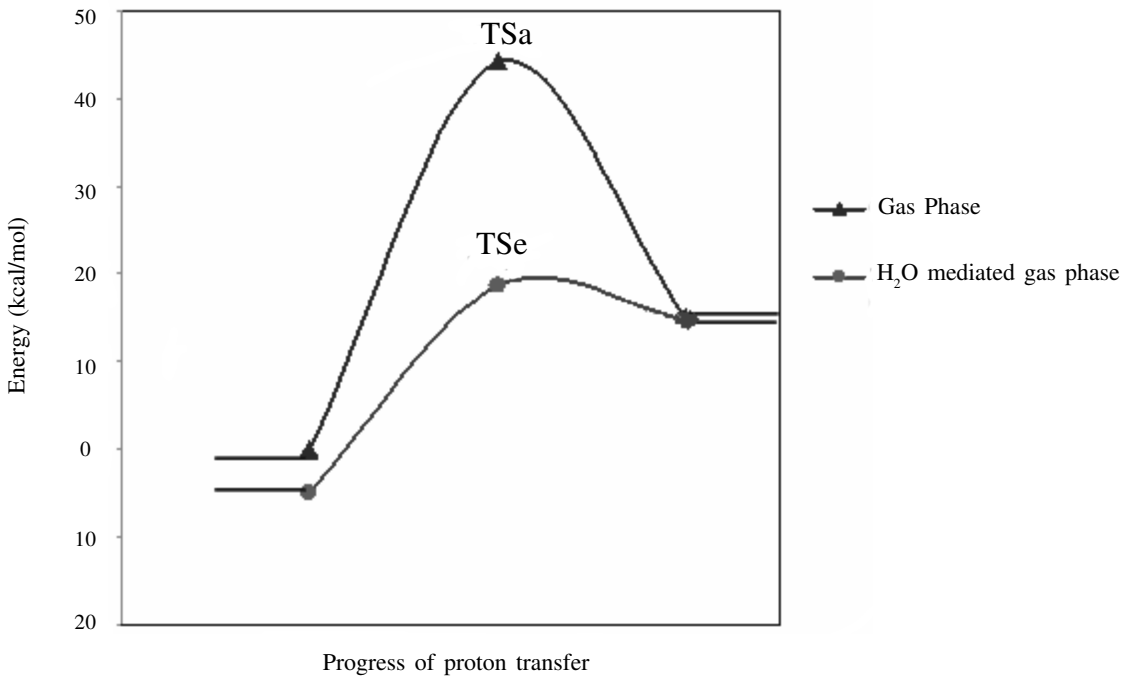


Fig. 4: Activation barrier for thione-thiol tautomerism of 1a by direct process and through H_2O-mediated process in the gas phase.

Conclusions

The activation barrier for the thione-thiol tautomerism in 4-amino-1,2,4-triazole-5-thiones in the gas phase is prohibitively high, ~44 kcal mol^{-1} which is not affected by the nature of the substituent group at 3-position. However, there is a remarkable lowering of the activation barrier for the H_2O-mediated proton transfer and it lies in the range ~19 kcal mol^{-1}. In the H_2O-mediated proton transfer, first a reactant complex is generated, in which H_2O molecule forms a bridge between N1-H and sulfur atom of the thione group thus facilitating the transfer of the proton from the former to the latter. Transfer of the proton to the sulfur atom in the reactant complex is the rate determining step. The reaction first leads to the product complex which subsequently liberates thiol molecule by the loss of water molecule. In both cases, namely the direct proton transfer or the H_2O-mediated one, the thione-thiol tautomerism in 4-amino-1,2,4-triazole-5-thiones is endothermic.

Acknowledgements

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