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Using Implicit/Explicit Salvation Models to Theoretical Study Tautomerism in 7H-purine-2, 6-diamine

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ABSTRACT

A theoretical study at the B3LYP/6-31++G(d,p) level was performed on the tatumerization of 7H-purine-2, 6-diamine into 9H-purine-2, 6-diamine. Such a tautomerism can take place *via* three different pathways namely A, B, and C. The energetic results associated with the gas phase reveal that pathways A, B, and C display a very high activation Gibbs free energy of 45.1, 68.6 and 48.9 kcal/mol, respectively, indicating this process cannot take place in the gas phase. When solvent effects of water are taken into account through a continuum of a uniform dielectric constant, the gas phase activation Gibbs free energies increase to 58.8, 70.6, and 52.4 kcal/mol along pathway A, B, and C, respectively, emphasizing long range solute-solvent interactions do not play a key role in the considered tautomerization. The studied process can easily take place by inclusion of three molecules of water in which a significantly reduced activation Gibbs free energy of 24.8 kcal/mol indicates the predominance of short range solute-solvent interactions over the long range ones. Combination of short range and long range solute-solvent interactions lead to an activation Gibbs free energy of 23.5 kcal/mol for tatumerization of 7H-purine-2, 6-diamine into 9H-purine-2, 6-diamine. This value clearly points out that employing a polar and protic solvent is able to noticeably reduce the barrier of tatomerization.

Keywords: Tautomerism; purines; DFT; Explicit and implicit solvation models

1. INTRODUCTION

The vast majority pharmaceutical molecules (drugs) contain heteroaromatic systems with 4, 5 or 6 membered rings and many of these molecules are capable of existing as two or more tautomeric structuers that usually involve migration of a proton (prototropy) from one site to another site of molecule. In DNA, Adenine normally pairs with Thymine but the imino form of Adenine pairs with Cytosine (fig.1). Clearly therefore, it is important to recognize the potential for tautomerization in heteroatomic systems and to assess the role of individual tautomers in biological activity [1].

The tetrazole ring appears in a number drugs affording N1 to N2 tautomerism. For example in Doivan (1), [2] Benicar (2), [3] Avapro(3) [4]. Atacand(4) [5] and Hyzaar(5) [6] high-resolution NMR in ^{15}N experiment showed that at room temperature (295K), the four tetrazole

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nitrogen atoms gave a very broad single compared to imidazole signals, but became sharp in 153K. These findings are consistent with fast prototropic exchange as proposed by Harris in ref 7.

2,6-substituted purines, obtain clinically useful tools for the potentiating of cancer chemotherapy and for the mechanistic studies of DNA damage recognition[8,9].

7H-purine-2, 6-diamine,7(H),exists in different tautomeric forms and the proton transfer can occur in both rings of this molecule.The proton transfer in imidazole ring of 7(H) leading to generation of 9H-purine-2, 6-diamine,9(H), tautomer is depicted in Fig.3.In the present work, this tautomerization is theoretically investigated to determine the barriers of process and to elucidate how much barriers are affected by the short and long range interactions with a polar and protic solvent such as water.

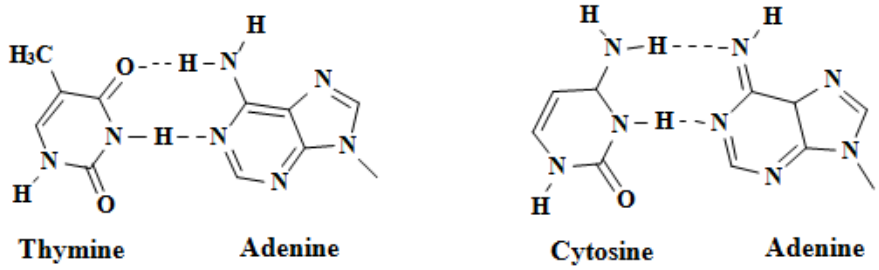

Fig. 1. Base pairing in nucleic acids: Differences between its normal amino and rare imino.

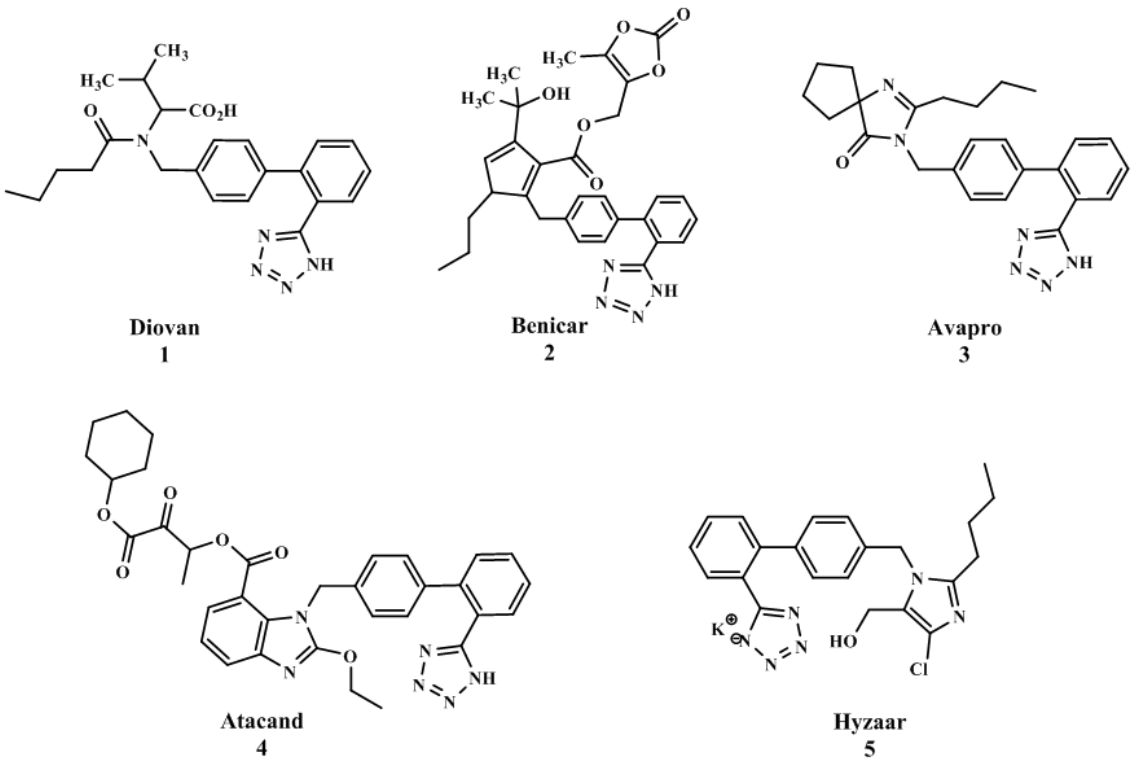

Fig. 2. Structure of drugs 5-9.

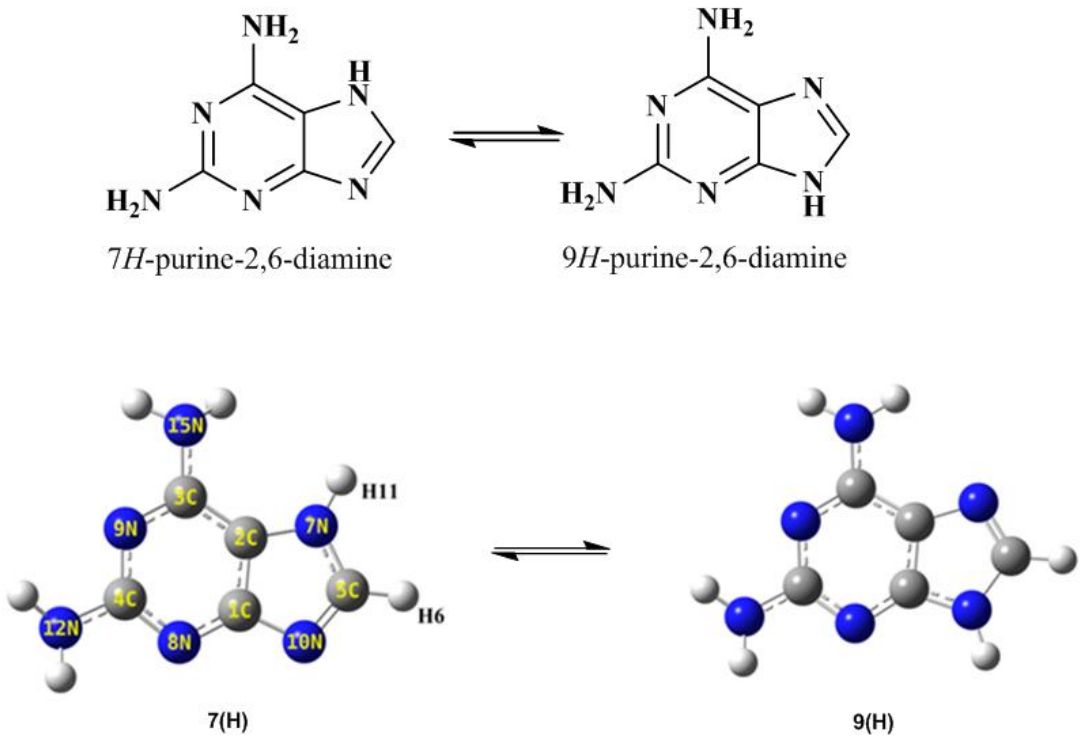

Fig. 3.7(H) and 9(H)tautomers including atom numbering.

2. THEORETICAL Method

The geometries of reactant, transition states (TSs), intermediates and products in both gas phase and solvent, were optimized at the DFT-B3LYP [10] level combined with The 6-311++G(d,p) basis set, using the Gaussian 09 software package[11]. The validity of the B3LYP method for studying systems with hydrogen bonding (HB) Interactions and proton transfer has previously been proved [12-14].

Frequency calculations were performed at the same level used for optimizations to determine the harmonic vibrational frequencies, thermochemical functions and, the structure being a minimum or a transition state; transition states were designated by one and only one imaginary frequency. The intrinsic reaction coordinates (IRC) paths [15] for both forward and reverse directions started at each TS were also traced to verify the correct connections. Tomasi's PCM model [16] in the framework of self-consistent reaction field (SCRF) method was employed to address the solvent effects on the studiedtautomerization through re-optimization of the gas phase stationary points in the presence of solvent.

3. RESULTS AND DISCUSSION

Three pathways are proposed for transformation of the H11 from N7 to N10 in 7(H) in gas phase and in water to establish the implicit solvent effect using the SCRF/PCM method. Also explicit three water molecules effects in gas phase and in water are examined to clarify the effect of solvent polarity along the water assisted tautomerization process by using the SCRF/PCM method.Geometries of the species in these pathways are shown in Figs. 4–7, which involve 4 intermediates and 7 TSs. The thermal energies, U,

standard enthalpies, H, and the Gibbs free energies, G, at 298.15K of the species as well as the imaginary vibrational frequency of the corresponding transition states are listed in Table 1.

While calculated activation enthalpies, $\Delta H^{\#}$, reaction enthalpies, ΔH, activation Gibbs free energies, $\Delta G^{\#}$and reaction Gibbs free energies,ΔG, are given in Table 2, transition state theory based reaction rate constant, $k_{T.S.T}$[17], the Wigner tunneling coefficient, χ[18],corrected activation energies, Ea_{corr}[17], and corrected reaction rate constant,k_{Corr},were calculated according to the equations 1-4 and corresponding values are presented in Table 2 as well.

$$k_{T.S.T} = \frac{k_B.T}{h} e^{\frac{-\Delta G^{0\neq}}{RT}} \quad (1)$$

$$\chi = 1 + \frac{1}{24}\left(\frac{h.c.\bar{\vartheta}_{im}}{k_B.T}\right)^2 \quad (2)$$

$$Ea_{corr} = \Delta H^{0\neq} + RT[1 + 2\left(\frac{\chi-1}{\chi}\right)] \quad (3)$$

$$k_{corr} = \chi.k_{T.S.T} \quad (4)$$

Table 1. B3LYP/6-311G++(d,p) calculated thermal energy, U in a.u., enthalpy, H in a.u., Gibbs free energy, G in a.u.,and imaginary frequency forTSs at 298.15 K of the species involved in the intramolecular proton transfer reaction of 7(H) in gas phase and in water (given in the parentheses)using the SCRF/PCM method

Species	U	H	G	Imaginary frequency
7(H)	-522.6932 86	-522.692342	-522.735320	-
	(-522.718192)	(-522.717247)	(-522.760128)	-
9(H)	-522.706717	-522.705772	-522.74884	-
	(-522.723093)	(-522.722149)	(-522.765241)	-
IM1	-522.6630300	-522.662059	-522.706280	-
	(-522.682373)	(-522.681429)	(-522.725108)	-
IM2	-522.659317	-522.658372	-522.701306	-
	(-522.680095)	(-522.679150)	(-522.722178)	-
IM3	-522.660207	-522.659263	-522.701937	-
	(-522.681582)	(-522.680638)	(-522.723379)	-
IM4	-522.631316	-522.630371	-522.673708	-
	(-522.649665)	(-522.648721)	(-522.692218)	-
TS1	-522.621494	-522.620549	-522.663465	1490.73 i
	(-522.640392)	(-522.639428)	(-522.682642)	(1500.96 i)
TS2	-522.618414	-522.617470	-522.660546	1526.76 i
	(-522.635062)	(-522.634118)	(-522.677040)	(1551.14 i)
TS3	-522.583985	-522.583041	-522.626001	1711.13 i
	(-522.605624)	(-522.604680)	(-522.647723)	(1705.35 i)
TS4	-522.599865	-522.598921	-522.641978	1617.96 i
	(-522.616240)	(-522.615296)	(-522.659004)	(1611.09 i)
TS5	-522.615683	-522.614739	-522.657340	1548.95 i
	(-522.634714)	(-522.633770)	(-522.676759)	(1584.34 i)
TS6	-522.613034	-522.612090	-522.654532	1044.43 i
	(-522.632625)	(-522.631681)	(-522.674136)	(1026.35 i)
TS7	-522.608752	-522.607808	-522.650678	1327.22 i
	(-522.624525)	(-522.623581)	(-522.666531)	(1364.67 i)

In the above mentioned equations while k_B, T, h, and R denote Boltzmann constant, temperature, and universal gas constant in the appropriate units, respectively, c and $\bar{\vartheta}_{im}$ indicate light velocity and imaginary frequency of corresponding TS. Inclusion of χ in equations (3) and (4) corrects activation energy and transition state theory based reaction rate constant, respectively, considering quantum tunneling effect which is highly important in the reactions involving a light-atom transferring such as proton.

3.1. Intramulecol Proton Transfer

Pathway-A (P(A)). P (A), as shown in Fig. 4, includes two-step proton transfer path in which the C5 carbon atom is mainly involved. In the first step, the hydrogen atom (H11) linking N7 directly drifts to the C5 atom via TS1 with an energy barrier of 45.6 kcal/mol to form an intermediate (IM1). In TS1, the H11 atom is out of the plane of the imidazole ring above N7–C5 bond where the N7–H11 bond length is expanded from 1.006 to 1.340 Å and the C5–H11 distance is briefed from 2.122 to 1.285 Å. It denotes that the C5–H11 bond is being formed and the N7–H11 is being broken. C5 in IM1 has thus been saturated with sp^3-type hybridized bonds (i.e., two C–H and two C–N single bonds). This step of the reaction is endergonic by 18.2 kcal/mol. In the second step, the hydrogen atom H11 is transferred to the N10 atom via TS2 with an energy barrier of 28.7kcal/mol. In TS2, the C5–H11 bond length is expanded from 1.097 to 1.252 Å and the C5–H6 distance is slightly briefed from 1.097 to 1.082 Å. The product 9(H) is a planar structure, in which C5 reaches a sp^2 hybridization just like in the reactant 7(H). This step is exergonic by 26.7 kcal/mol. The results show that it is unthinkable to occur tautomerization reaction through this pathway due to the high barrier, 45.1 kcal/mol, in the rate-determining step.

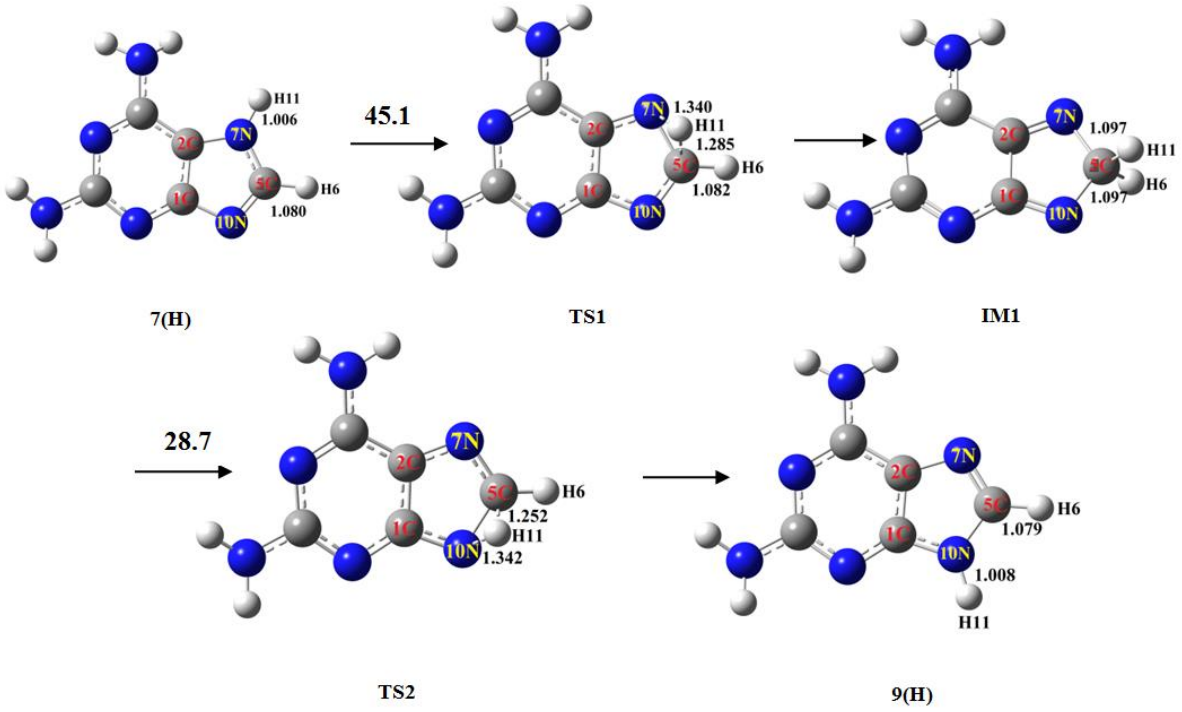

Fig. 4. Intramolecular proton transfer in compound 7(H) *via* pathway-A. B3LYP/6-311++G (d,p) activation Gibbs free energies, in kcal/mol, are given above arrows and bond distances are in angstrom.

Pathway-B(P(B)). P (B), as shown in Fig. 5, also contains a two steps proton transfer process associated again with the C5 atom to form intermediate IM2. The hydrogen atom H6 on C5 in 7(H) is firstly transferred onto the N10 atom via TS3 with an energy barrier of 68.6 kcal/mol and leaves C5 to form a carbenenoide structure in IM2. In TS3, the H6 is above the C5–N10 bond and the C5–H6 bond length is expanded from 1.080 to 1.291 Å and the N9–H6 distance is shortened from 2.121 to 1.269 Å. This step is endergonic by 21.3 kcal/mol as shown in Table 2 and Fig. 5. In the next step the hydrogen atom H11 on N7 atom in IM2 transfers into C5 via TS4 with an energy barrier of 37.2 kcal/mol to form the tautomer 9(H). In TS4, the H11 atom is above the N7–C5 bond where the N7–H11 bond length is enlarged from 1.006 to 1.261 Å and the C5–H11 distance is shortened from 2.122 to 1.308 Å. This step is exergonic by 29.8 kcal/mol. The activation energy, (67.2 kcal/mol), in the first step is higher than that in P (A), so the tautomerization reaction of Pathway P (B) is believed infeasible.

Pathway-C (P (C)). P (C) is displayed in Fig. 6, involves a three-step proton transfer process via the sp^3 hybridized C2 and C1 atoms. At the first, the hydrogen atom H11 on N7 in 7(H) is transferred onto the C2 atom via TS5 with an energy barrier of 48.9 kcal/mol to form an intermediate IM3. In TS5, the H11 is above the C2–N7 bond and the N7–H11 distance is expanded from 1.006 to 1.293 Å while the C2–H11 bond length is briefed from 2.160 to 1.263 Å. In IM3, the C2 atom is a typical tetrahedral (sp^3) bonding corresponded to H11–C2–C1, H11–C2–N7 and H11–C2–C3 angles of 105.9°, 108.1° and 108.6°. This step

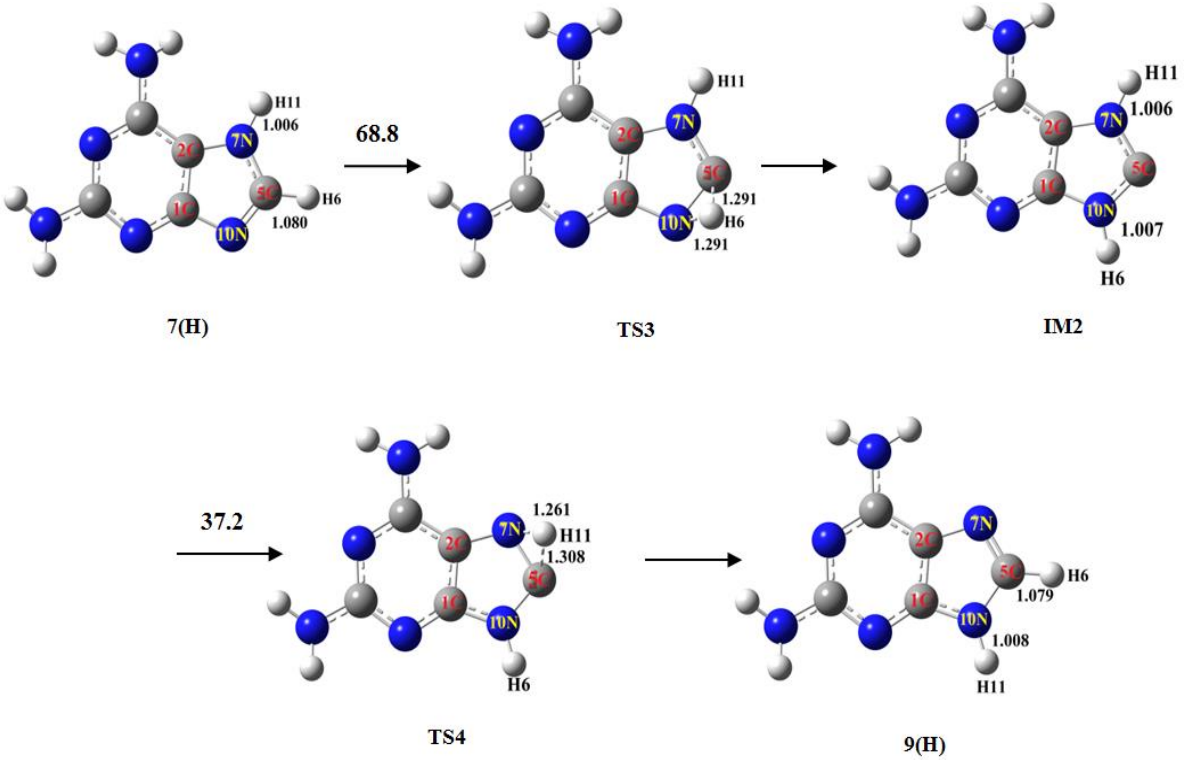

Fig. 5. Intramolecular proton transfer in compound 7(H) *via* pathway-B. B3LYP/6-311++G (d,p) activation Gibbs free energies, in kcal/mol, are given above arrows and bond distances are in angstrom.

of the reaction is endergonic by 20.9 kcal/mol with respect to the reactant 7(H). The H11 in IM3 may walk onto the C1 atom via TS6 with an energy barrier of 29.7 kcal/mol to form an intermediate IM4. In TS6, the C2–H11 distance is expanded from 1.101 to 1.426 Å and the C1–H11 bond length is shortened from 2.135 to 1.262 Å. The H11–C2–C1 angle is decreased to 51.6° from 108.6°. The intermediate IM4 with the C1 atom is formed as a typical tetrahedral bonding, where the H11–C1–C2, H11–C1–N8 and H11–C1–N10 angles are 107.3°, 102.7° and 108.5°, respectively. This step is endergonic by 17.7 kcal/mol with respect to IM3. Finally, the hydrogen atom H11 on C1 in IM4 places onto the N10 atom via TS7 with an energy barrier of 14.5 kcal/mol to produce the product 9(H). This step is exergonic by 47.1 kcal/mol with respect to the IM4.

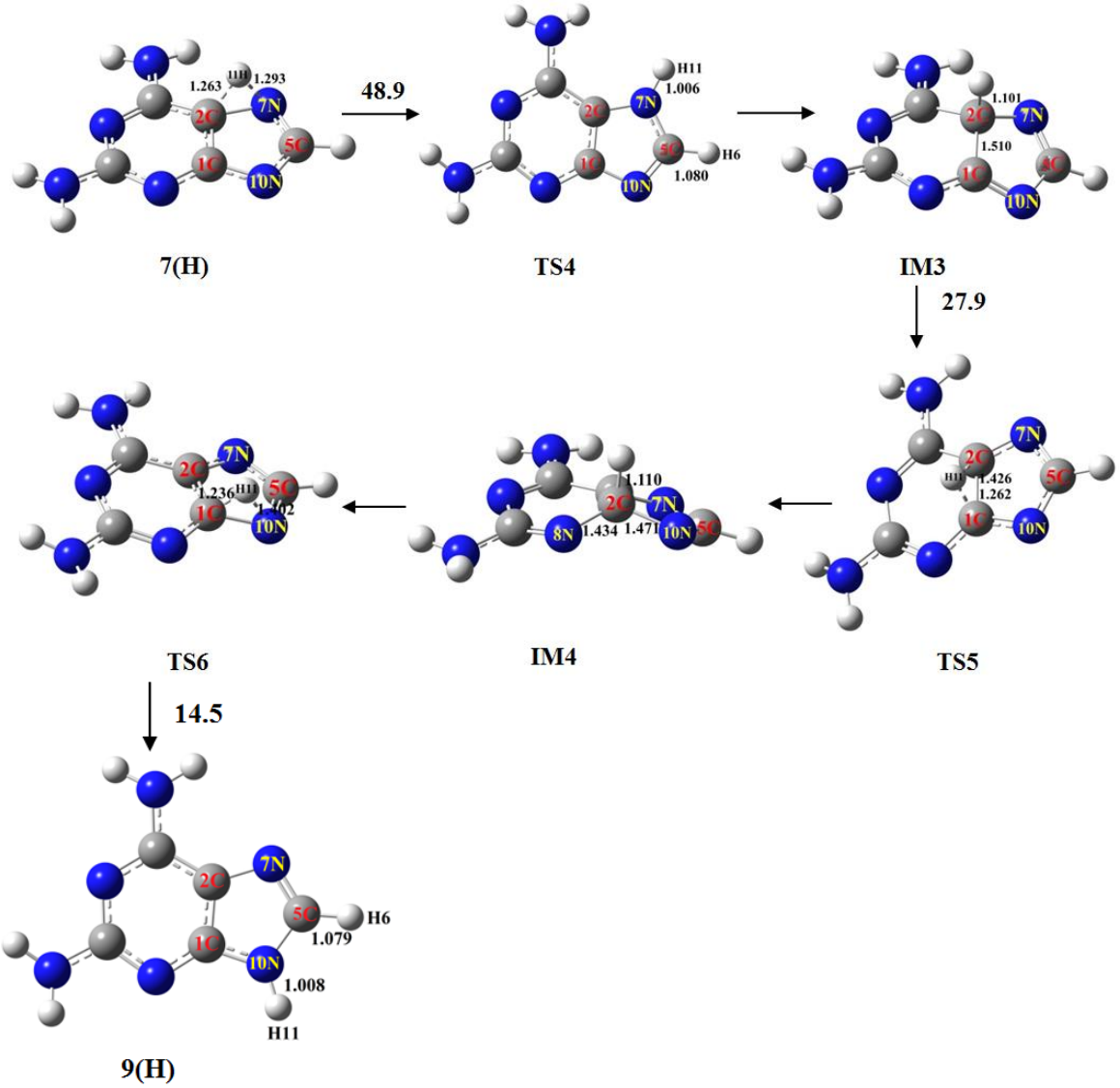

Fig. 6. Intramolecular proton transfer in compound 7(H) *via* pathway-C. B3LYP/6-311++G (d,p) activation Gibbs free energies, in kcal/mol, are given above arrows and bond distances are in angstrom.

The activation Gibbs free energies in P (A), P (B) and P (C) are 45.1, 68.6 and 48.9 kcal/mol, respectively. The highest barrier is corresponded to P (B) which originates from the large demand energy to form a sp^2 configuration carbenoide in C5. Unlike P(B), in both of P (A) and P (C) rate determinate step, step1, is a [1,5] hydrogen shift which is allowed to proceed suprafacially *via* a Huckel-topology transition state and, hence, the barrier becomes lower.

The energy barriers obtained in water using the SCRF/PCM method in P (A), P (B) and P (C) are 48.6, 70.5 and 52.3 kcal/mol, respectively. These results show that long range solute-solvent interactions cannot decrease energy barrier in P (1), P (2) or P (3) (Tables 2) since the reactants are more stabilized than TSs by long-range solute-solvent interactions in the considered tautomerization.

3.2. Tautomerizatin Consdering Expicit Solvent Effects

In order to establish the explicit effects of a polar and protic solvent such as water on the kinetic and thermodynamic of the studied tautomerization a mechanism including three water molecules is proposed, having relatively acidic hydrogen atoms, can act as accepting and donating a proton (Fig. 7).

Table 2. Activation and reaction enthalpies, Gibbs free energies, corrected activation energies, in kcal/mol, and the corrected reaction rate constant, in s^{-1}, for the transitionsby which 7(H) is transferred into 9(H) in the gas phase and in water (given in parentheses) using the SCRF/PCM method

Transition	TS	$\Delta H^{\#}$	ΔH_r	$\Delta G^{\#}$	ΔG_r	Ea_{corr}	k_{Corr}
7(H) → IM1	TS1	45. 1	19.0	45.1	18.2	44.8	5.509×10^{-21}
		(48.8)	(22.5)	(48.6)	(22.0)	(48.5)	(1.413×10^{-23})
IM1 → 9(H)	TS2	28. 0	-27.4	28.7	-26.7	27.7	5.719×10^{-9}
		(29.7)	(-25.6)	(30.2)	(-25.2)	(29.4)	(4.423×10^{-10})
7(H) → IM2	TS3	68. 6	21.3	68.6	21.3	68.3	3.2131×10^{-38}
		(70.6)	(23.9)	(70.5)	(23.8)	(70.3)	(1.223×10^{-39})
IM2 → 9(H)	TS4	37.3	-29.7	37.2	-29.8	37.0	3.1902×10^{-15}
		(40.1)	(-27.0)	(39.6)	(-27.0)	(39.4)	(5.640×10^{-17})
7(H) → IM3	TS5	48.7	20.8	48.9	20.9	48.4	8.385×10^{-24}
		(52.4)	(23.0)	(52.3)	(23.1)	(52.1)	(2.732×10^{-26})
IM3 → IM4	TS6	29.6	18.1	29.7	17.7	29.5	9.742×10^{-10}
		(30.7)	(20.0)	(30.9)	(19.6)	(30.6)	(1.356×10^{-10})
IM4 → 9(H)	TS7	14.2	-47.3	14.5	-47.1	14.0	159.096
		(-15.8)	(-46.1)	(16.1)	(-45.8)	(15.6)	(9.7140)

In this Pathway three molecules of water are arranged above imidazole ring in desired distance from N7 to N10 so that each molecule of water can act as accepting and donating a proton (TS8). In TS8, the H11 is above the N10 atom and the N7–H11 bond length is expanded from 1.017 to 1.556Å and the N10–HOH distance is shortened from 1.906 to 1.622 Å and the energy barrier is decreased to 24.8 kcal/mol (Fig. 2). Also to investigate both short- and long-range interactions

between the solute and solventon the considered tautomerization, we carried out the study of solvent polarity effect on the water assisted tautomerization, by using the SCRF/PCM method. In this case the energy barrier is decreased to 23.6 kcal/mol.The corresponding activation enthalpies, $\Delta H^{\#}$, reaction enthalpies, ΔH, activation Gibbs free energies, $\Delta G^{\#}$, reaction Gibbs free energies, ΔG, corrected activation energies, Ea, and the corrected rate constantreaction, k_{corr}, are listed in Table 3. The results show that a combination of short- and long-range interactions between the solute and solvent decrease the energy barrier for the intramolecular tautomerization reaction within the imidazole ring (Table 3). It is arising from the lesser angel and torsion strains in TS8 leading to a much lower energy barrier. A comparison of the energy barriers for proposed pathways are depicted in Fig. 8.

4. CONCLUSION

Tatumerization of 7H-purine-2, 6-diamine, **7(H)**, into 9H-purine-2, 6-diamine, **9(H)**, was theoretically studied at the B3LYP/6-31++G(d, p) level proposing three different pathways A, B, C.The gas phase energetic results imply that the proposed pathways present a very high activation Gibbs free energy of 45.1, 68.6, and 48.9 kcal/mol, respectively, demonstrating such tautomerizationis not allowed to take place in the gas phase. When solvent effects of water are taken into consideration through a continuum of a uniform dielectric constant, the gas phase activation Gibbs free energies increase to 48.6, 70.5, and 52.3 kcal/mol along pathway A, B, and C, respectively, high lighting long- range solute-solvent interactions do not play a key role in the investigated tautomerization. On the other hand, the proton transfer can easily take place when this reaction is explicitly assisted by three molecules of water in which a significantly lower activation Gibbs free energy of 24.8 kcal/mol implies the predominance of short-range solute-solvent interactions over the long-range ones. Combination of short- and long-range solute-solvent interactions lead to an activation Gibbs free energy of 23.6 kcal/mol for tatumerization of **7(H)** into **9(H)**. This value evidently reveals that employing a polar and protic solvent is capable to noticeably reduce the barrier of tatomerization.

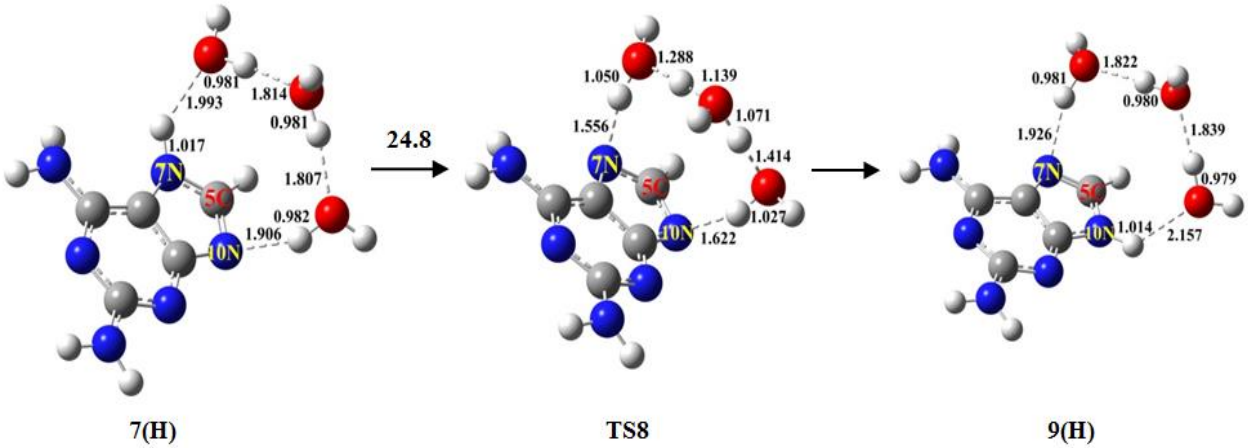

Fig. 7. Reaction pathway for the intramolecular tautomerization processes of 7(H) explicitly assisted by three molecules of water in gas phase displaying an activation Gibbs free energy of 24.8 kcal/mol calculated at the 298.15 K and B3LYP/6-311++G (d,p) level. Bond distances are in angstrom.

Table 3. Activation and reaction enthalpies, Gibbs free energies, corrected activation energies, in kcal/mol, and the corrected reaction rate constant, in s^{-1}, for the mechanisms involved in the studied intramolecular proton transfer reaction at 298.15 K

Mechanism	$\Delta H^{\#}$	ΔH_r	$\Delta G^{\#}$	ΔG_r	Ea	k_{Corr}
gas phase explicitly assisted by water	20.1	-4.6	24.8	-5.1	20.5	4.451×10^{-6}
gas phase explicitly assisted by water in combination with SCRF/PCM	17.2	-0.4	23.6	0.6	17.7	2.862×10^{-5}

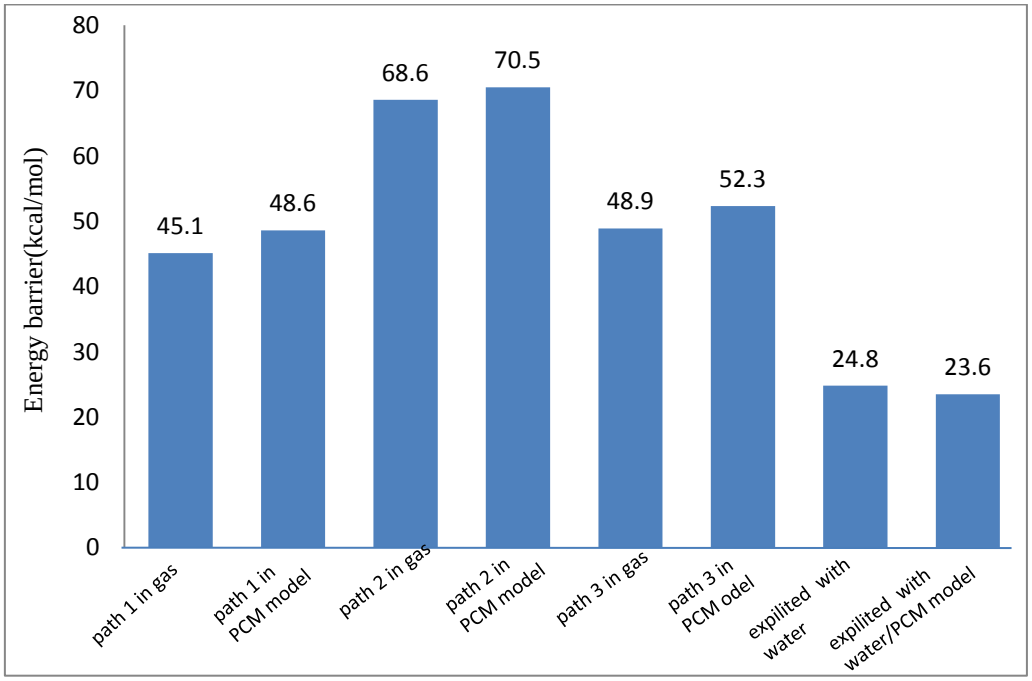

Fig. 8. The energy barriers for the intramolecular tautomerization processes of 7(H) through proposed pathways A, B, and C.

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