

DFT and MP2 study of low barrier proton transfer in hydrazide schiff base tautomers via water bridges and in the gas

Hossein Tavakol · Hossein Farrokhpour

Received: 31 January 2013 / Accepted: 5 May 2013 / Published online: 25 May 2013
© Springer-Verlag Berlin Heidelberg 2013

Abstract MP2 and DFT studies were performed on the tautomers of N'-ethylideneacetohydrazide in different environments including gas phase, continuum solvent and microhydrated environment. The ground electronic state structures of the tautomers were optimized at the MP2 and B3LYP levels of theory using 6-311++G(d,p), separately. The optimized geometries of the transition states of different tautomerism processes, which occur through the proton transfer (PT) reaction, were determined using the QST3 approach at the same levels of theory. The same stability order as T1Z) T1E) T2ZE) T2ZZ) T2EE) T2EZ) T6) T4E was found for the tautomers in the gas phase, continuum solvent and microhydrated environment for both B3LYP and MP2 levels of theory. In addition, the variations of the Gibbs free energies of tautomeric processes, the activation Gibbs free energies of the forward and reverse tautomeric processes with the polarity of the solvent (in continuum solvent model) and the number of water molecules (in microhydrated environment) were investigated. It was found that the reverse tautomeric process is more favorable in all considered environments thermodynamically and kinetically. In addition, it was shown that the rate constants of the reverse and forward considered tautomeric processes decrease with the solvent polarity in the continuum solvent model and the process becomes more difficult than the gas phase. The opposite trend is seen in the microhydrated environment.

Keywords N'-ethylideneacetohydrazide · Proton transfer · Solvent effect · Tautomer · Water influence

Electronic supplementary material The online version of this article (doi:10.1007/s00894-013-1883-z) contains supplementary material, which is available to authorized users.

H. Tavakol (✉) · H. Farrokhpour
Department of Chemistry, Isfahan University of Technology,
Isfahan 84156-83111, Iran
e-mail: H_TAVAKOL@cc.iut.ac.ir

Introduction

Tautomerism is an important part in several chemical and biological processes. Understanding tautomeric processes is very essential in biological processes and has been provided a strong interest for quantum computational studies especially when the effect of the solvent is studied. The interaction of solvent with the solute molecule changes the molecular properties of solute and therefore, it is necessary to investigate the solvent effect [1]. For example, the polarity of solvent plays a major role in tautomeric process so that it changes the thermodynamic and kinetic parameters of the happening proton transfer (PT) reaction making it more easy or hard compared to the gas phase.

It has also been known that sometimes the solvent is a direct participant in the biological reactions instead of a simple passive dielectric medium [2, 3]. In this case, solvent assisted reactions are important for the efficiency of biological reactions. Because of the importance of water in biology, the microscopic roles of water in chemical reactions have been of great interest. Catalytic action of water has been implied in a variety of PT reactions such as acid–base reactions, prototropic tautomerization, and proton pump in biological systems. For example, the PT along peptides is an important biological process. In this case, the proton moves from one atom to the other through water bridge (multi-water assistance) [3]. Considering the above explanations, studying the tautomeric processes in the microhydrated environment (considering different number of water molecules) can provide worthwhile information about the functionality of water in catalyzing the biological reactions.

Hydrazides are a class of compounds with wide applications especially as a ligand in preparation of new complexes [4]. These compounds are used in pharmaceutical chemistry [5], synthesis of novel heterocyclic compounds [6], preparation of inhibitors (against *Trypanosoma brucei*) [7] and photochemical reactions [8]. Moreover, their schiff base

derivatives (hydrazone Schiff bases) are of great interest for scientists, especially in preparation various complexes such as Ortho-metallated ruthenium(III) [9], zinc [10], Oxomolybdenum(V) [11] and Ruthenium II/III [12] complexes. These compounds also show Antioxidant [13] and magnetic properties [14].

In this work, we focus on the theoretical study of tautomerism of *N'*-ethylideneacetohydrazide in the gas phase and different continuum solvents. The reason for this study is that the isomerization in the hydrazone Schiff bases affects their complexation properties [15]. Therefore, it is worthwhile to obtain information about the complete scheme of tautomerism in acyl hydrazides. In addition, theoretical study on the intramolecular PT in the tautomers of *N'*-ethylideneacetohydrazide assisted by water is also performed. To do this, the calculations are performed in microhydrated environment including different numbers of water molecules (up to three water molecules). This work is a continuing of our interest on the theoretical study of tautomerism in organic compounds [16, 17].

Computational details

All geometry optimization and frequency calculations were performed using Gaussian 09 computational Package program [18]. All of the calculations were performed at two different levels of theory including MP2 and B3LYP using 6-311++G(d,p) basis set. The minima (number of imaginary frequencies, (NIMAG) = 0) and transition states (NIMAG = 1) were confirmed by calculating the harmonic vibrational frequencies. Frequency calculations were also used to obtain the zero point energy (ZPE) of each molecule. The frequency calculations were performed at the standard conditions (temperature = 298 K and pressure = 1 atm). The geometry optimization of the transition states in the gas phase, different continuum solvents and microhydrated environment were determined using QST3 method at the MP2 and B3LYP levels of theory, separately. The solvent effects were taken into account by means of the self-consistent reaction field model [19] based on the polarizable continuum model (PCM) [20, 21] Gaussian 09 package uses UFF atomic radii for constructing the solvent cavity. Four different solvents including cyclohexane, CHCl₃, acetone and water were selected to study the dielectric effect of the solvent on the tautomerism. All rate constants and reaction dynamics have been calculated by canonical transition state theory using Eyring equation [22]. Moreover, to import the tunneling effect in the rate constants, Wigner coefficient (w_f) was obtained using Eq. 1 and all rate constants were corrected with this coefficient. In this equation, ν is the imaginary frequency of the transition state related to the corresponding tautomeric process, k is the Boltzmann constant, h is the

Planck constant and T is the temperature (room temperature were used) [23–25].

$$w_f = \left(1 + \frac{1}{24} \left(\frac{h\nu}{kT} \right)^2 \right) \quad (1)$$

Results and discussion

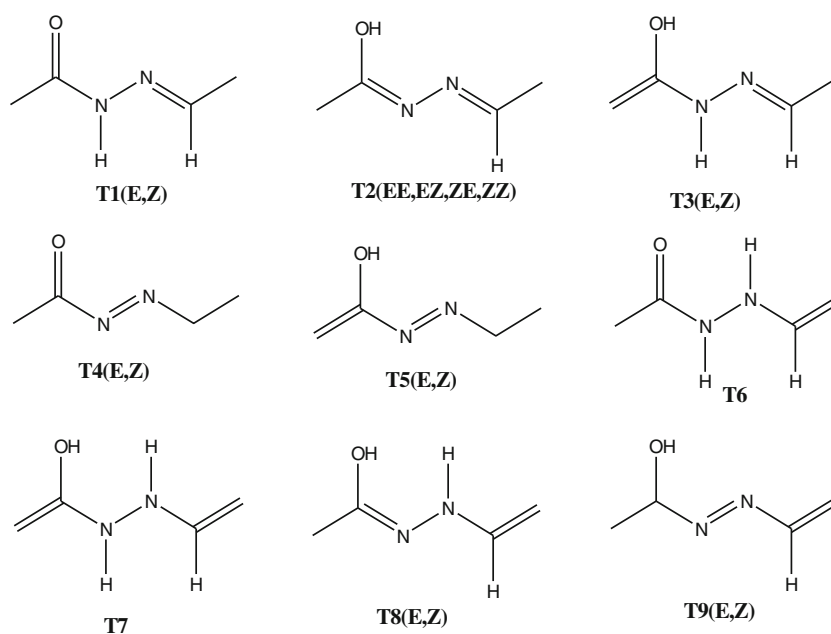
Stability of the tautomers in gas phase

The structures of possible tautomers of *N'*-ethylideneacetohydrazide have been shown in Fig. 1. Figure 2 also shows the numbering scheme used in the present study for definition of the parameters of the *N'*-ethylideneacetohydrazide tautomers. As shown in Fig. 1, there are nine different tautomers for *N'*-ethylideneacetohydrazide and some of them have *E* and *Z* isomers. The geometry of the considered isomers were fully optimized at the MP2/6-311++G(d,p) and B3LYP/6-311++G(d,p) levels of theory, separately. The different bond lengths of the optimized structures of all isomers, calculated at the MP2 level of theory, have been tabulated in Table S2 (in Supplementary information). To the best of our knowledge, there is no experimental report on the geometry of these compounds in the literature for comparison. In addition, Fig. 3 shows the structures of the eight most stable isomers of T1, T2 and T4 tautomers optimized at the MP2/6-311++G(d,p) level of theory.

The relative enthalpy, Gibbs free energies and dipole moments of all isomers of *N'*-ethylideneacetohydrazide, shown in Fig. 1, have been reported in Table 1. It is seen that, the stability order of the eight most stable isomers of *N'*-ethylideneacetohydrazide is T1Z > T1E > T2ZE > T2ZZ > T2EE > T2EZ > T6 > T4E for both B3LYP and MP2 calculations. It should be mentioned that the instability of the isomers relative to T1Z, calculated at the MP2 level of theory, is more than B3LYP method. For example, the relative enthalpy of T1E isomer, at the B3LYP level of theory, is 2.84 kcal mol⁻¹ while, the corresponding value at the MP2 level of theory is 3.36 kcal mol⁻¹. The most stable isomer is T1Z which has keto form and it is the most common tautomer of this compound. A previous report about energy profile of acetyl hydrazide tautomers (with similar structure) confirmed that the common tautomers were the most stable tautomers obtained from the calculations [17].

Table 1 also reports the values of the dipole moments of the optimized isomers of each tautomer in the gas phase. It is seen that the isomers of each tautomer have different values of dipole moments. Among the isomers of the most stable tautomers, T1E has the maximum value of dipole moment (5.23 Debye at the B3LYP level of theory) and

Fig. 1 Structures of possible tautomers of N'-ethylideneacetohydrazide



T2EZ has the lowest value of dipole moment (0.8 Debye). The decrease of the dipole moment from T1 to T2 tautomer is related to the increase in the symmetry of the molecule. The lowest value of dipole moment, among the isomers of the considered tautomers, is related to the T8Z isomer of T8 tautomer (0.71 Debye). Generally, there is a direct relationship between the amount of the dipole moment of molecule and the stability of molecule in the solvent. The stability of a molecule, which has dipole moment, in a polar solvent, is more than that in the gas phase because of the solvent effects.

Tautomeric processes in the gas phase

In this part, the PT reaction for the inter-conversion of isomers in the gas phase is investigated. As shown in Fig. 4, T1 tautomer can be converted to T2, T3, T4 and T6 tautomers through the PT reaction and T2 tautomer can only be converted to T4 and T5 tautomers. The optimized structures of the transition states (TS-1-2, TS-1-3, TS-1-4, TS-1-6, TS-2-4 and TS-2-5) of the considered tautomerism processes have also been shown in Fig. 4. The optimized structural parameters, relative energies and dipole moment of the relevant transition states have also been reported in Tables S2 (in Supplementary information) and 1, respectively. Table 2 tabulates the Gibbs free energy change (ΔG), equilibrium constant (K_{eq}), Gibbs free activation energy for the

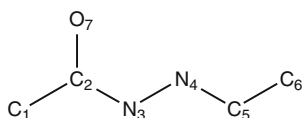


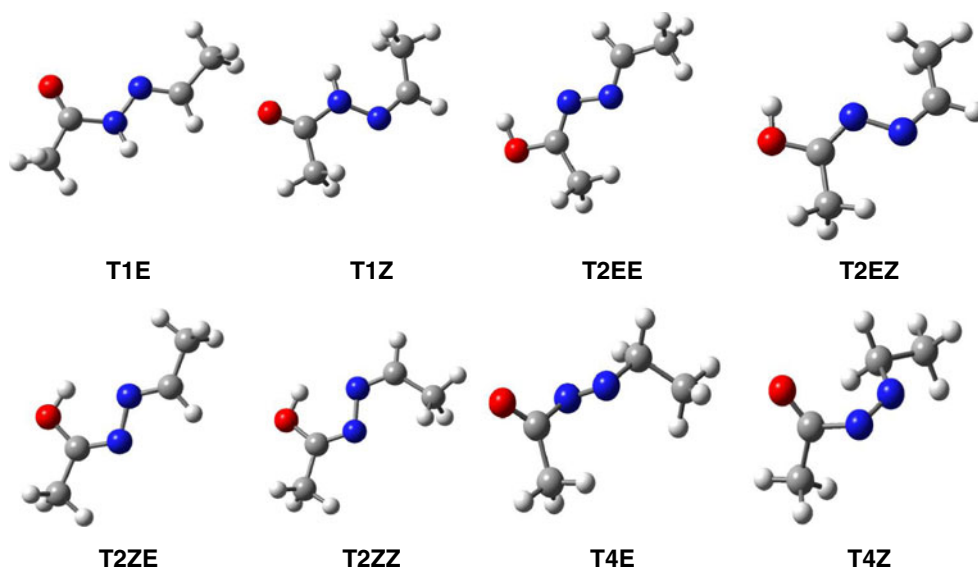
Fig. 2 The numbering scheme for N'-ethylideneacetohydrazide (used for definition of parameters)

forward (ΔG_{fwd}^\ddagger) and reverse (ΔG_{rev}^\ddagger) tautomerism processes, the rate constants of the forward (k_{fwd}) and reverse (k_{rev}) of possible tautomerism interconversions and the imaginary vibrational frequency of their corresponding transition states. To calculate the Gibbs free activation energies, the QST3 method was used at the MP2/6-311++G(d,p) and B3LYP/6-311++G(d,p) levels of theory, separately.

T1Z isomer can be converted to the most stable isomer of tautomer T2 (T2ZE) by transferring the proton from N3 site to O7 site in T1Z (see Fig. 2). The value of N3-H distance in the T1Z and TS1-2 is 1.017 and 1.350 Å, respectively that confirms that an intramolecular PT has been occurred. Meanwhile, the C2-O7 bond distance of T1Z isomer changes from 1.221 Å to 1.344 Å confirming that the C2-O7 in T2ZE isomer is a single bond. The distance between the transferring hydrogen and the N3 and O7 is 1.350 and 1.345 Å, respectively. The calculated values of ΔG_{fwd}^\ddagger and ΔG_{rev}^\ddagger for the T1→T2 process, calculated at the B3LYP level of theory, are 36.58 and 31.54 kcal mol⁻¹, respectively (see Table 2). The corresponding values calculated at the MP2 level of theory are 35.60 and 32.58 kcal mol⁻¹. It is evident that the reverse tautomeric process for the inter-conversion of T1Z to T2ZE is more favorable than the forward conversion. In addition, the conversion of T1→T2 is more favorable at the MP2 level of theory than the B3LYP method from the thermodynamically and kinetically point of view. The imaginary vibrational frequency of the transition state of T1→T2 process, calculated at the B3LYP and MP2 levels of theory, is -1784 and -1710 cm⁻¹, respectively.

Transferring the hydrogen from the methyl group (C1) to O7 converts T1Z isomer to T3E isomer. The relevant transition state has been shown in Fig. 4. The distance between the transferring hydrogen and C1; and O7 is nearly equal to

Fig. 3 Graphical representation of MP2 optimized structures of eight more stable isomers of N'-ethylideneacetohydrazide (from three more stable tautomers)



each other ($\approx 1.350 \text{ \AA}$). Comparison of the value of ΔG for T1→T3 process ($24.45 \text{ kcal mol}^{-1}$ at B3LYP; $25.20 \text{ kcal mol}^{-1}$ at MP2) with the corresponding values calculated for T1→T2 process (5.04 ; $3.02 \text{ kcal mol}^{-1}$) shows that the T1→T3 process is not favorable in comparison with

T1→T2 process, thermodynamically. The values of $\Delta G_{\text{fwd}}^{\ddagger}$ and $\Delta G_{\text{rev}}^{\ddagger}$ for the T1→T3 process, calculated at the MP2 level of theory, are 66.33 and $41.88 \text{ kcal mol}^{-1}$, respectively. Again, it is seen that the reverse process is more favorable. Moreover, it is seen that the values of the

Table 1 Relative enthalpies, Gibbs free energies (in kcal mol^{-1}) and dipole moments (in Debye) of all isomers and transition states

Molecule	B3LYP			MP2		
	Relative H	Relative G	Dipole moment	Relative H	Relative G	Dipole moment
T1E	2.84	2.29	5.23	3.36	2.83	5.84
T1Z	0.00	0.00	3.84	0.00	0.00	4.38
T2EE	8.76	9.51	0.90	6.35	4.62	1.13
T2EZ	9.26	10.03	0.80	8.05	7.52	1.10
T2ZE	4.47	5.04	1.25	2.85	3.02	1.40
T2ZZ	5.53	6.87	1.09	4.15	3.63	1.30
T3E	24.57	24.45	1.63	25.45	25.20	2.06
T3Z	25.57	25.12	2.00	25.92	26.00	2.17
T4E	19.11	22.01	3.65	13.62	13.17	4.07
T4Z	24.79	23.96	3.23	21.60	21.09	3.54
T5E	31.15	33.64	2.23	29.34	29.49	2.75
T5Z	42.77	42.94	3.59	39.76	40.43	3.82
T6	12.44	12.14	3.06	13.22	13.24	3.87
T7	36.28	36.69	0.65	37.87	38.26	0.80
T8E	21.24	20.99	1.59	21.93	21.96	1.69
T8Z	19.94	20.37	0.71	18.87	19.22	0.56
T9E	31.46	31.77	2.06	28.15	28.41	2.10
T9Z	43.56	44.07	1.78	40.11	40.62	1.85
TS-1-2	36.35	36.58	2.45	36.08	35.60	2.92
TS-1-3	65.43	66.33	5.15	66.76	67.32	5.64
TS-1-4	64.94	66.31	3.15	71.23	70.91	2.19
TS-1-6	86.62	88.26	4.92	90.95	92.12	6.41
TS-2-4	48.81	50.12	1.54	101.70	103.92	2.79
TS-2-5	63.20	65.42	2.55	57.26	59.54	2.61

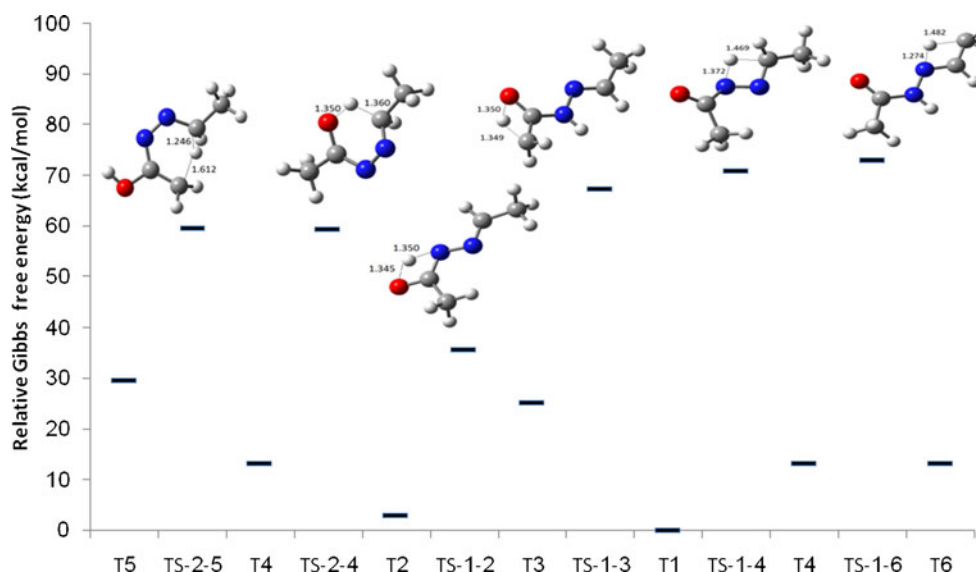


Fig. 4 A simple graphical representation of the Gibbs free energy levels for tautomerism interconversions in the gas phase obtained from the MP2 calculations. The structure of each transition state was placed on the top of its name (and also its energy level) on the horizontal axis

Gibbs free activation energies of the reverse and forward reaction of T1→T3 process are higher than those for the T1→T2 process. It can be concluded that the T1→T3 process is more difficult than the T1→T2 process. Comparison of $\Delta G_{\text{fwd}}^{\ddagger}$ of T1→T3 with that of T1→T2 process shows that the energy of the transition state of T1→T3 process is higher than that of T1→T2. This may be attributed to the amount of positive charge on the transmitted hydrogen before shifting (the atomic charges were calculated and can be found in Table S3, in Supplementary information). The hydrogen in T1→T2 process has more positive charge than that in T1→T3 process before shifting because of the connection with the nitrogen atom of T1Z isomer. Therefore, the proton on the nitrogen can be transferred to oxygen atom more easily in T1→T2 process than the proton

connected to carbon atom in T1→T3 process. The values of vibrational imaginary frequencies of the transition state of T1→T3 process, calculated at the B3LYP and MP2 levels of theory, are -1905 and -1869 cm^{-1} , respectively.

In the case of T1→T4 (T4E) and T1→T6 interconversions, the hydrogen transfers from N3 to C5 and; C6 to N4, respectively. The values of Gibbs free activation energies (for both forward and reverse reaction) of T1→T4 process are nearly equal to those of T1→T3 process. This reflects the similarity of the transition states of these two tautomeric processes. For example, the transmitted proton is located between nitrogen and carbon atom in TS-1-4 and; carbon and oxygen in TS-1-3. The electronegativity of nitrogen (3.04) is nearly equal to that of oxygen (3.44). It should be noticed that the T1→T6 inter-conversion has the

Table 2 The calculated thermodynamic^a and kinetic parameters^b for the possible tautomerism interconversions considered in this work. Rate constants were corrected by Wigner coefficient

	B3LYP	ΔG	Keq	$DG_{\text{fwd}}^{\ddagger}$	$DG_{\text{rev}}^{\ddagger}$	Imag. freq	W_f^c	k_{fwd}	k_{rev}
T1-T2		5.04	2.02E-04	36.58	31.54	-1784.1	4.10	3.91E-14	1.93E-10
T1-T3		24.45	1.21E-18	66.33	41.88	-1904.7	4.53	6.74E-36	5.59E-18
T1-T4		22.01	7.33E-17	66.31	44.30	-1035.1	2.04	3.15E-36	4.30E-20
T1-T6		12.14	1.27E-09	75.71	63.57	-1167.6	2.33	4.64E-43	3.65E-34
T2-T4		16.97	3.64E-13	45.08	28.11	-1545.3	3.32	1.86E-20	5.13E-08
T2-T5		28.60	1.09E-21	60.38	31.78	-1288.8	2.62	8.95E-32	8.24E-11
MP2									
T1-T2		3.02	6.11E-03	35.60	32.58	-1710.3	3.85	1.92E-13	3.14E-11
T1-T3		25.20	3.37E-19	67.32	42.12	-1869.5	4.40	1.23E-36	3.65E-18
T1-T4		13.17	2.22E-10	70.91	57.74	-2031.1	5.01	3.28E-39	1.48E-29
T1-T6		13.24	1.97E-10	72.97	59.73	-1573.7	3.41	6.84E-41	3.47E-31
T2-T4		10.15	3.63E-08	56.35	46.20	-1231.2	2.47	7.61E-29	2.10E-21
T2-T5		26.47	3.96E-20	56.52	30.05	-969.0	1.91	4.42E-29	1.12E-09

^aEnergy values are reported in kcal mol^{-1}

^brate constants are reported in sec^{-1}

^c w_f is Wigner coefficient

Table 3 The thermodynamic^a and kinetic parameters^b for the possible tautomerism interconversions in four different solvents. All rate constants were corrected by Wigner coefficient

		ΔG	K_{eq}	$\Delta G_{\text{fwd}}^{\#}$	$\Delta G_{\text{rev}}^{\#}$	k_{fwd}	k_{rev}
T1-T2	Cyclohexane	4.73	3.39E-04	37.84	33.10	4.41E-15	1.30E-11
	CHCl ₃	8.13	1.10E-06	42.30	34.17	2.36E-18	2.15E-12
	Acetone	12.22	1.11E-09	47.85	35.63	2.01E-22	1.82E-13
	Water	13.67	9.56E-11	50.14	36.47	4.19E-24	4.39E-14
T1-T3	Cyclohexane	24.67	8.26E-19	67.72	43.05	6.23E-37	7.54E-19
	CHCl ₃	25.44	2.23E-19	70.28	44.84	8.29E-39	3.71E-20
	Acetone	27.61	5.73E-21	74.12	46.51	1.27E-41	2.21E-21
	Water	28.19	2.15E-21	75.94	47.75	5.88E-43	2.73E-22
T1-T4	Cyclohexane	14.49	2.38E-11	73.00	58.51	9.64E-41	4.04E-30
	CHCl ₃	17.77	9.47E-14	77.35	59.58	6.24E-44	6.59E-31
	Acetone	22.37	4.02E-17	82.83	60.46	6.04E-48	1.50E-31
	Water	24.31	1.52E-18	85.10	60.79	1.30E-49	8.54E-32
T1-T6	Cyclohexane	11.75	2.43E-09	72.84	61.09	8.53E-41	3.51E-32
	CHCl ₃	12.06	1.45E-09	75.00	62.94	2.23E-42	1.54E-33
	Acetone	14.47	2.48E-11	78.57	64.10	5.41E-45	2.18E-34
	Water	15.68	3.22E-12	80.32	64.65	2.80E-46	8.69E-35
T2-T4	Cyclohexane	9.76	7.03E-08	56.48	46.72	6.15E-29	8.75E-22
	CHCl ₃	9.64	8.61E-08	57.12	47.48	2.07E-29	2.41E-22
	Acetone	10.15	3.64E-08	58.21	48.06	3.32E-30	9.13E-23
	Water	10.64	1.59E-08	58.94	48.30	9.57E-31	6.01E-23
T2-T5	Cyclohexane	25.92	1.01E-19	57.69	31.78	6.12E-30	6.08E-11
	CHCl ₃	25.44	2.27E-19	58.40	32.97	1.84E-30	8.12E-12
	Acetone	25.60	1.73E-19	59.53	33.93	2.77E-31	1.60E-12
	Water	25.84	1.15E-19	60.27	34.44	7.85E-32	6.80E-13

^aEnergy values are reported in kcal mol⁻¹

^brate constants are reported in sec⁻¹

highest $\Delta G_{\text{fwd}}^{\#}$ (75.71 kcal mol⁻¹) among the tautomerism processes originated from T1 isomer. The distance between the hydrogen and nitrogen in TS1-4 and TS1-6 is lower than the distance with carbon atom because of the higher electronegativity of nitrogen relative to carbon. Again, it can be seen that the reverse tautomeric process is more favorable than the forward process for T1→T4 (T4E) and T1→T6 interconversions, both thermodynamically and kinetically.

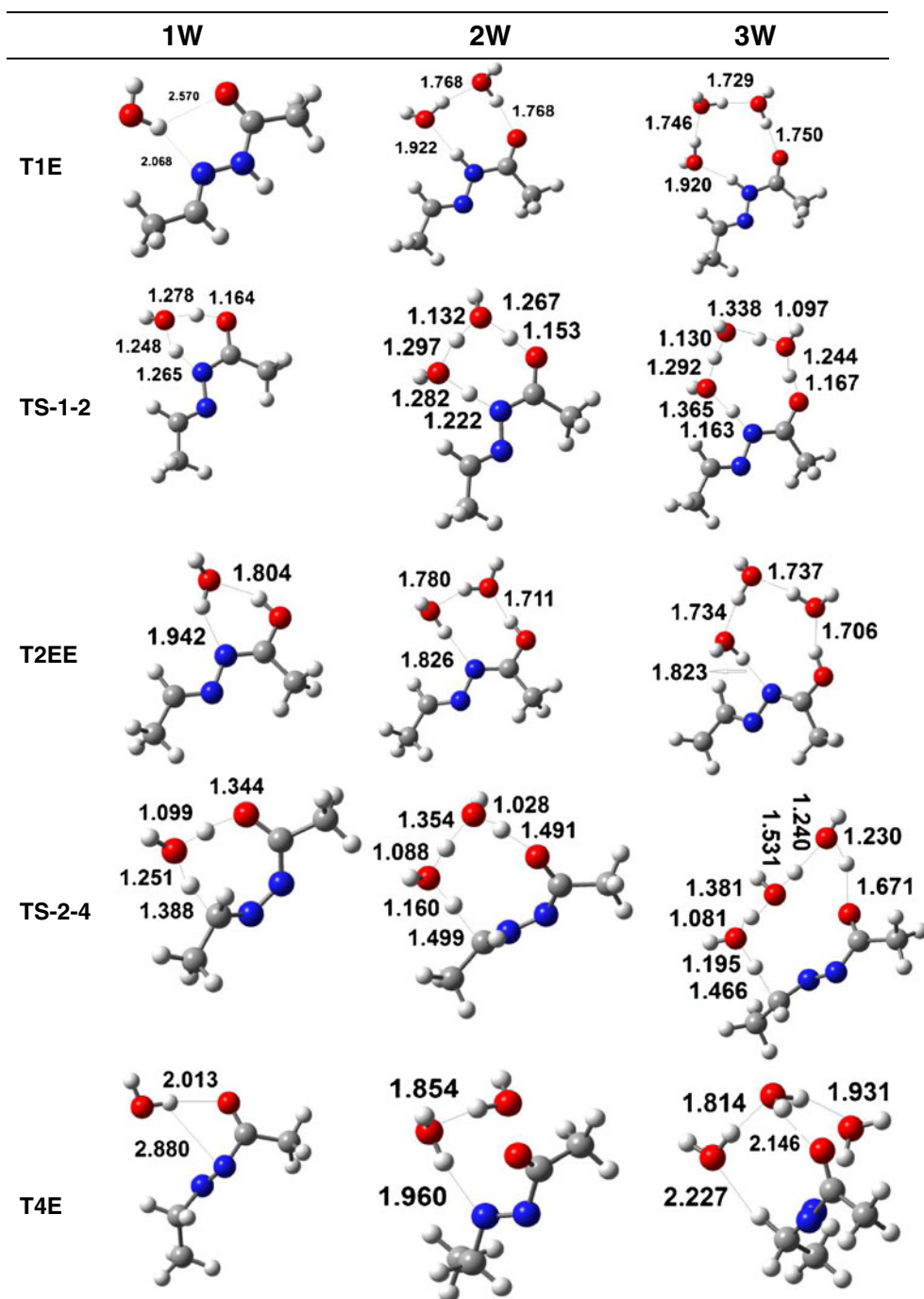
T2→T4 process is related to the transfer of proton from O7 to C5 and T2→T5 process is relevant to the shift of proton from C1 to C5. The reverse tautomeric process is more favorable than the forward process for both T2→T4 and T2→T5 processes. The value of $\Delta G_{\text{fwd}}^{\#}$ of T2→T5 process is higher than that of T2→T4 process at the B3LYP level of theory while they are equal to each other at the MP2 level of theory. As a result, it was found that in the gas phase and without microsolvation, all energy barriers are high and their values are between 28.11 kcal mol⁻¹ and 75.71 kcal mol⁻¹ using B3LYP/6-311++G** level of theory. These values are comparable with previous reports about energy barrier of gas phase tautomerism in N-hydroxy amidines [16], acetyl hydrazides [17] and amidrazones [26] in that their energy barriers are respectively in the range of 33.4–71.3 kcal mol⁻¹, 24.53–77.91 kcal mol⁻¹ and 43.67–75.30 kcal mol⁻¹ at the same level of theory.

Tautomeric processes in the solvent

The effect of solvent on the tautomeric process of N'-ethylideneacetohydrazide is investigated using two different approaches. In the first approach, the effect of solvent is approximated by using the self-consistent reaction field method based on the PCM model. In this case, the effect of the polarity of solvent on the thermodynamic and kinetics of the considered tautomeric process is studied. In the second approach, the effect of solvent through the micro hydration model is investigated. In this case, the assistance role of water molecules, inserted as a bridge between two adjacent or non-adjacent atoms is studied.

Table 3 tabulated the thermodynamic and kinetic parameters for the considered tautomeric processes at different solvents including cyclohexane, CHCl₃, acetone and water by using PCM model. It can be seen that the values of ΔG for the conversion of T1 tautomer to T2, T3, T4 and T6 tautomers increase with the polarity of solvent and this means that the tautomeric process will be thermodynamically more difficult in the solvent than gas phase. For example, the values of ΔG for T1→T2 process are 4.73, 8.13, 12.22 and 13.67 kcal mol⁻¹ at cyclohexane, CHCl₃, acetone and water, respectively. This means that the T1 tautomer is

Fig. 5 Optimized structures of T1, T2 and T4 and transition states between them in the presence of 1–3 molecules of water



stabilized in the polar solvent more than the T2, T3, T4 and T6 tautomers. We calculated the MP2 and B3LYP dipole moments of all compound (shown in Table 1) and we found that this stability could be attributed to the higher value of dipole moment of T1 tautomer compared to the other tautomers. From the MP2 calculations, the value of T1 dipole moments is 5.84 Debye while dipole moments of the other tautomers are between 0.56–4.07 Debye.

Interestingly, it is seen that the values of the ΔG for the conversion of T2 to T4 and T5 are nearly independent of the kind of solvent and they are close to those calculated in the

gas phase. In addition, it is evident that by increasing the polarity of solvent, the values of $\Delta G_{\text{fwd}}^{\#}$ increases while the value of the $\Delta G_{\text{rev}}^{\#}$ is nearly independent from the kind of solvent for inter-conversion of T1 tautomer to T2, T3, T4 and T6 tautomers. For T2→T4 and T2→T5 processes, both $\Delta G_{\text{fwd}}^{\#}$ and $\Delta G_{\text{rev}}^{\#}$ are independent of the kind of solvent.

Table 3 also reports the rate constants for the forward and reverse tautomeric processes at different solvents. It is evident that the k_{rev} is higher than k_{fwd} for all tautomeric processes, which means that the reverse process is more favorable. This conclusion is in agreement with the results

Table 4 Thermodynamic^a and kinetic parameters^b for intramolecular PT in the presence of 1–3 molecules of water. All rate constants were corrected by Wigner coefficient

	ΔG	Keq	$\Delta G_{\text{fwd}}^{\ddagger}$	$\Delta G_{\text{rev}}^{\ddagger}$	Imag. Freq	W_f^c	k_{fwd}	k_{rev}
Gas	3.02	6.11E-03	35.60	32.58	-1710	3.85	1.92E-13	3.14E-11
1 W	4.93	2.45E-04	13.32	8.40	-1485	3.15	3.37E+03	1.37E+07
2 W	10.60	1.71E-08	18.62	8.03	-1279	2.59	3.59E-01	2.10E+07
3 W	10.28	2.92E-08	21.26	10.98	-1067	2.11	3.40E-03	1.16E+05
Gas	10.15	3.63E-08	56.35	46.20	-1231	2.47	7.61E-29	2.10E-21
1 W	11.12	7.08E-09	46.30	35.18	-1184	2.36	1.70E-21	2.40E-13
2 W	13.23	2.00E-10	49.09	35.86	-1015	2.00	1.29E-23	6.45E-14
3 W	16.22	1.30E-12	40.16	23.94	-938	1.86	4.24E-17	3.27E-05

^aEnergy values are reported in kcal mol⁻¹

^brate constants are reported in sec⁻¹

^c w_f is Wigner coefficient

obtained from the thermodynamic study. It can also be seen that by increasing the polarity of solvent both k_{rev} and k_{fwd} decreases which means that the tautomeric process will be more difficult.

Water assisted proton transfer

The solvents can form hydrogen bonding such as water or alcohols can accept a proton from the donor site of the solute molecule and release another proton back to the proper site of the solute, which leads to the proton migrating along the solute molecule. In this case, the water molecules are inserted as a bridge between the two sites of the molecule. We employed this structure and found that the presence of water molecules lowers the free energy barrier in the related PT reaction [27, 28]. In this part the thermodynamic and kinetic of intramolecular PT in the N'-ethylideneacetohydrazide at the presence of one to three water molecules is discussed.

Typically, the inter-conversion of T1E→T2EE and T2EE→T4E are considered for studying the mechanism of water-assisted PT reaction. Figure 5 shows the optimized microsolvated structures of T1E, T2EE and T4E isomers and related transition states (in the presence of one, two and three waters molecules), at the MP2/6-311++G(d,p) level of theory. In addition, the calculated thermodynamic and kinetic parameters of these water-assisted PT reactions have also been reported in Table 4. Figure 5 also shows some important geometrical parameters of the optimized structures of tautomers in the microhydrated environment.

It is evident from Table 4 that the relative stability order of T1E, T2EE and T4E isomers in the microhydrated environment is the same as that in the gas phase. Comparison of the values of ΔG for the conversion of T1 to T2 and T2 to T4 in the microhydrated environment with the corresponding calculated values in the gas phase shows that the forward tautomeric process is more difficult in the microhydrated environment. In addition, it can be seen that by increasing the number of water molecules the value ΔG , for inter-conversion of T1 to T2 and T2 to T4, increases (more positive) with the increase in the number of water

molecules. This behavior is similar to the trend seen in the solvent, in that the value of ΔG increases with the polarity of solvent. The values of ΔG show that the reverse conversion is thermodynamically more favorable than the forward process.

The value of $\Delta G_{\text{fwd}}^{\ddagger}$ and $\Delta G_{\text{rev}}^{\ddagger}$, reported in Table 4, can be used for evaluating the effect of water molecules on the kinetics of PT reaction. The value of $\Delta G_{\text{fwd}}^{\ddagger}$ decreases from 35.6 kcal mol⁻¹ to 13.32 kcal mol⁻¹ going from gas phase to microhydrated environment including one water molecule for T1→T2 conversion. It can be seen that the value of $\Delta G_{\text{fwd}}^{\ddagger}$ increases with the number of water molecules for T1→T2 conversion. Similar trend can be seen for the $\Delta G_{\text{rev}}^{\ddagger}$ of T1→T2 conversion.

Again, it can be seen that the values of $\Delta G_{\text{fwd}}^{\ddagger}$ and $\Delta G_{\text{rev}}^{\ddagger}$, for T2→T4 conversion, are lower than that in the gas phase. The value of $\Delta G_{\text{fwd}}^{\ddagger}$ increases with the number of water molecules but suddenly decreases in the microhydrated environment including three water molecules. Finally, microsolvation with water strongly enhances the rate constants of tautomerisms. This enhancement was previously observed in related systems such as tautomerism in N-hydroxy amidines [16], acetyl hydrazides [17] and amidrazones [26] in that their rate constants are respectively $7.10 \times 10^2 \text{ s}^{-1}$, $2.7 \times 10^4 \text{ s}^{-1}$ and $1.52 \times 10^1 \text{ s}^{-1}$ in comparison with $3.37 \times 10^3 \text{ s}^{-1}$ in this report (using one molecule of water in all cases). These values confirm the important role of direct insertion of water into the tautomerism, which leads to a great increase in rate constant because water makes a proton bridge to facilitate PT.

Conclusions

This work represents the study of tautomerism of N'-ethylideneacetohydrazide compound in the gas phase, continuum solvent and microhydrated environment. The calculations showed that the T1Z isomer is the most stable isomer in the gas phase. The stability order of isomers in the gas phase is: T1Z > T1E > T2ZE > T2ZZ > T2EE > T2EZ > T6 > T4E. The thermodynamic and kinetic parameters of the

considered tautomeric process were calculated at different environments. It was found that the value of ΔG for $T1 \rightarrow T2$, $T1 \rightarrow T3$, $T1 \rightarrow T4$ and $T1 \rightarrow T6$ tautomeric process increases (more positive) when the polarity of solvent increases while for $T2 \rightarrow T4$ and $T2 \rightarrow T5$ processes this value is nearly independent from the polarity of solvent. Similar trends were seen for the variation of $\Delta G_{\text{fwd}}^{\#}$ and $\Delta G_{\text{rev}}^{\#}$ with the change in the polarity of solvent. Two tautomeric processes including $T1 \rightarrow T2$ and $T2 \rightarrow T4$ were considered for the investigation of the role of water molecules on the tautomeric process. Similar to the effect of solvent, it was seen that the tautomeric process would be more difficult when the number of molecules increases. Generally, it was found that the reverse tautomeric process is thermodynamically and kinetically more favorable than the forward process.

References

1. Reichardt C (2003) Solvent and solvent effects in organic chemistry, 3rd edn. Wiley-VCH, Weinheim
2. Agmon N (1995) Chem Phys Lett 244:456–472
3. Chen PT, Wang CC, Jiang JC, Wang HK, Hayashi M (2011) J Phys Chem B 115:1485–1491
4. Fujino M, Shinagawa S, Kawai K, Ishii H (1979) Naturwissenschaften 66:625–630
5. Xu G, Zhang L, Liu L, Liu G, Jia D (2008) Polyhedron 27:12–19
6. Burbuliene MM, Bobrovos O, Vainilavicius P (2006) J Heterocycl Chem 43:43–48
7. Ceffrey CR, Schanz M, Nkemngu NJ, Brush M, Hansel E, Cohen FE, Flaherty TM, McKerrow JH, Steverding D (2005) Int J Antimicrob Agents 26:100–112
8. Chao CS, Cheng CK, Li SH, Chen KM (2009) Tetrahedron Lett 50:333–339
9. Raveendran R, Pal SJ (2007) Organomet Chem 692:824–832
10. Singha AK, Kumaria S, Kumarb KR, Sridharb B, Rao TR (2008) Polyhedron 27:1937–1945
11. Harikumar-Nair ML, Thankamani Russ D (2010) J Coord Chem 36:259–265
12. Nehru K, Attaphan P (2001) Transit Met Chem 26:652–658
13. Gwaram NS, Ali HM, Abdulla MA, Buckle MJC, Sukumaran SD, Chung LY, Othman R, Alhadi AA, Yehye WA, Hadi AHA, Hassandarvish P, Khaledi H, Ibrahim S (2012) Molecules 17:2408–2413
14. Lin P, Gorelsky S, Savard DT, Burchell J, Wernsdorfer C, Murugesu WRM (2010) Dalton Trans 39:7650–7657
15. Pytaa K, Przybylskia P, Huczyńska A, Hoserb A, Woźniakb K, Schilfc W, Kamięńskic B, Grechd E, Brzezinski B (2010) J Mol Struct 970:147–154
16. Tavakol H, Arshadi S (2009) J Mol Model 15:807–816
17. Tavakol H (2011) Int J Quantum Chem 111:3717–3724
18. Frisch MJ et al. (2009) Gaussian 09 Revision A1 Gaussian Inc, Wallingford CT
19. Tomasi J, Persico M (1994) Chem Rev 94:2027–2035
20. Cancas E, Mennucci B, Tomasi J (1997) J Chem Phys 107:3032–3039
21. Barone V, Cossi M, Tomasi J (1998) J Comput Chem 19:404–412
22. Masel RI (2001) Chemical kinetics and catalysis. Wiley, New York
23. Wigner EZ (1941) Phys Chem 19:203–216
24. Jolibois F, Grand A, Cadet J, Adamo C, Barone V (1999) Chem Phys Lett 301:255–562
25. Di Labio GA, Johanson ER (2007) J Am Chem Soc 129:6199–6203
26. Tavakol H (2011) Struct Chem 22:1165–1177
27. Markova N, Enchev V, Timtcheva I (2005) J Phys Chem A 109:1981–1989
28. Kyrtychenko A, Waluk J (2006) J Phys Chem A 110:11958–11965