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Quantum chemical studies on tautomerism and basicity behavior of some 1,2,4-triazole derivatives

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The acidity constants, relative stabilities, and tautomeric equilibrium constants of some 1,2,4-triazole derivatives were determined using the density functional theory (DFT) with the B3LYP method and 6-311G(d,p) basis set. The integral equation formalism version of the polarizable continuum model (IEFPCM) was used in the calculations of the aqueous phase. The calculated tautomeric equilibrium and relative stabilities values revealed that the 4H-1,2,4 triazole form for all studied molecules was favored over the 1H-1,2,4 triazole form. Protonation processes indicated the predominance of the 1H-1,2,4 triazole form over the 2H-1,2,4 triazole form. The correlation attempt between the experimental and the calculated acidity constants, pK_a values, revealed that they are quite close to the experimental values and they correlate well with a regression of around unity ($R^2 = 1$).

Key Words: 1,2,4-Triazole, proton affinity, tautomerism, acidity constant, nucleophilicity

Introduction

1,2,4-Triazole derivatives have been considered as one of the most important classes of 5-membered heterocyclic compounds. Their derivatives constitute an important class of organic compounds exhibiting diverse

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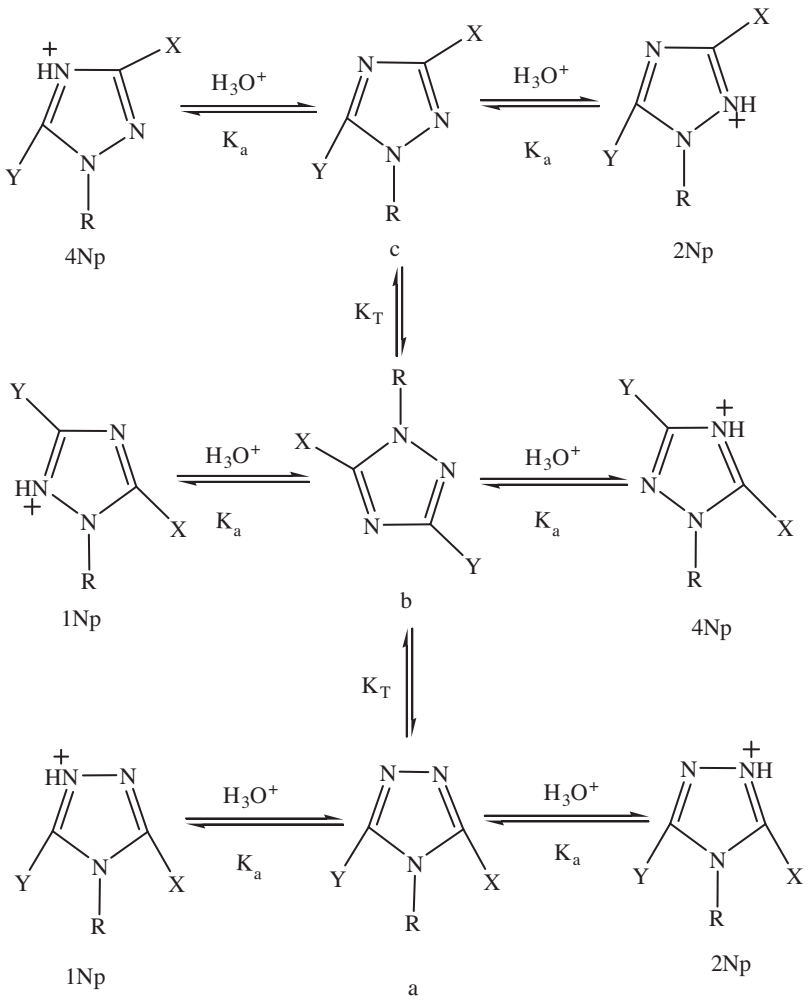
biological activities, such as anticonvulsant, antidepressant, anti-inflammatory, antitumor, analgesic, antiviral, antibacterial, and antifungicidal.[1−15] Moreover, their special structures provide them with an ability to act as biological reactive compounds and they have been used as disinfectants, pesticides, antivirals, and active reagents.[16−21] Due to the structural properties of 1,2,4-triazoles, they can also participate in several chemical reactions, and they are found to form significant intermediates in the synthesis of nitrogen atom containing heterocyclic compounds.

To elucidate the reaction mechanisms and reactivity correctly, it is important to obtain information about the tautomeric structures of heterocyclic compounds.[22] Prototautomerism exists in structures having more than one position that can locate the mobile proton. Due to this property one molecule may have more than one structure.

The acidity or basicity of a molecular site is also very important to the chemical and biological processes that may take place at that site. The acidity plays an important role in the possible hydrogen ion catalysis processes. The basicity, besides being related to the acidity, can easily be related to the nucleophilicity of the basic site. Whenever there is an application to polymers or pharmaceuticals, the understanding of acidity or basicity of a molecule is fundamental to molecular design and reaction mechanism. If the acidity and basicity of a molecule can be reliably and quickly estimated without synthesis and experimental determination, the efficiency and productivity will greatly be enhanced.[23,24] Moreover, knowledge of the pK_a values of ionizable groups is important for understanding of many areas of chemistry, both in the gas and liquid phase. They are of particular interest for elucidating reaction mechanisms, especially those involving proton transfers and for interpreting the binding of substrates or inhibitors to enzymes. However, experimental determination of individual pK_a values is difficult in complex systems. Kinetic assignments of pK_a are often complicated by uncertainties in interpreting the pH dependence of measured parameters. It is therefore useful to have reliable and accurate means of calculating relative and/or absolute pK_a values and to have an understanding of the involved factors.[23]

The recent advances in computer hardware and software have allowed us to compute several important chemical and physical properties of chemical systems in a predictive manner using various computational techniques.[25,26] Consequently, several computational approaches have been applied recently in estimating the acidities and basicities used in the interpretation of structure reactivity and structure property relations safely.[27−31]

The main purpose of the present work was to calculate the physical parameters such as acidity constants for protonation and prototautomeric equilibrium of some 1,2,4-triazole derivatives. These aqueous phase calculations were carried out by considering the solvation energies. Consequently, a DFT calculation was applied to study the protonation and tautomeric equilibrium. Prototropic annular tautomerization and protonation patterns for C–substituted and nomenclature of the investigated molecules are depicted in Scheme 1 and Table 1. The experimental acidity constant values were taken from the literature.[32] The possible correlation between the calculated and experimental acidity was examined.



X=H, CH_3, C_2H_5, C_6H_5, NO_2 ; Y = H,CH_3,C_2H_5, NO_2; R = H,CH_3 (for model compounds)

Scheme 1. Prototropic annular tautomerization and protonation patterns for C-substituted 1,2,4-triazole derivatives.

Materials and methods

Computational method

All of the geometry optimizations were performed by ab initio Hartree-Fock and density functional theory (DFT) methods which were implemented in the Gaussian03W program.[33] All geometries were taken as starting points using HF/3-21G geometry optimizations. These results were re-optimized at Becke's 3-parameter exact exchanges functional (B3) combined with gradient corrected correlation functional of Lee-Yang-Parr (LYP).[34] DFT/B3LYP methods have also been employed to optimize geometries of all tautomers by implementing the 6-311G(d,p) as triple split valence basis sets.[35]

Table 1. Nomenclature of the studied molecules.

Molecule	IUPAC name	Substituents		
		X	Y	R
1a	4H-1,2,4-triazole	H	H	H
1am	4-methyl-4H-1,2,4-triazole	H	H	CH_3
2a	3-methyl-4H-1,2,4-triazole	CH_3	H	H
2am	3,4-dimethyl-4H-1,2,4-triazole	CH_3	H	CH_3
3a	3-ethyl-4H-1,2,4-triazole	C_2H_5	H	H
3am	3-ethyl-4-methyl-4H-1,2,4-triazole	C_2H_5	H	CH_3
4a	3,5-dimethyl-4H-1,2,4-triazole	CH_3	CH_3	H
4am	3,4,5-trimethyl-4H-1,2,4-triazole	CH_3	CH_3	CH_3
5a	3,5-diethyl-4H-1,2,4-triazole	C_2H_5	C_2H_5	H
5am	3,5-diethyl-4-methyl-4H-1,2,4-triazole	C_2H_5	C_2H_5	CH_3
6a	3-phenyl-4H-1,2,4-triazole	Phenyl	H	H
6am	4-methyl-3-phenyl-4H-1,2,4-triazole	Phenyl	H	CH_3
7a	3-nitro-4H-1,2,4-triazole	NO_2	H	H
7am	4-methyl-3-nitro-4H-1,2,4-triazole	NO_2	H	CH_3
8a	3-methyl-5-nitro-4H-1,2,4-triazole	CH_3	NO_2	H
8am	3,4-dimethyl-5-nitro-4H-1,2,4-triazole	CH_3	NO_2	CH_3

For the optimized geometries, the frequencies were obtained from the second derivates of the energy computed using analytically calculated first derivates to establish the stationary points. All optimized structures were checked by analysis of harmonic vibration frequencies. The optimized structures of all investigated molecules are at the stationary points corresponding to local minima without imaginary frequency. DFT energy evaluations were carried out at molecular geometries optimized at B3LYP/6-311G(d,p) level of theory. The atomic charges have been calculated using Mulliken population analysis. Solvent effect in water was calculated by means of the IEFPCM, which is a self consistent reaction field (SCRF) method.[34,36] The solvation free energy calculations were also carried out using the B3LYP/6-311G (d,p) method. All calculations were performed at room temperature. The value of $\Delta G_s(H^+)$ was taken as -269.9 kcal mol^{-1}.[23,37–47]

Theoretical pK_a calculations

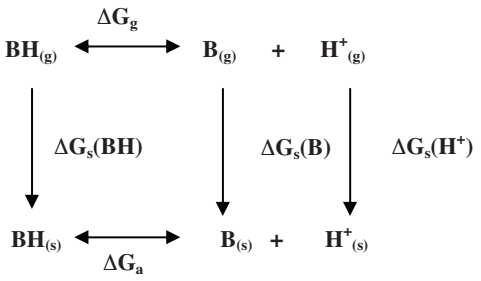
Both microscopic and macroscopic theoretical methods are now available for the estimation of solution free energies. It is possible, in principle, to determine theoretical relative or absolute acidity constants, pK_a values. Scheme 2 explains the interrelationship between the thermodynamic parameters of gas and solution phases.[23,37–47]

For protonation equilibrium of a base (Eq. 1) the following equilibrium can be written:

$$B + H^+ \overset{K_a}{\rightleftharpoons} BH^+ \tag{1}$$

$$\Delta G = G^{+}_{BH} - (G_B + G^{+}_{H}) \tag{2}$$

where K_a is the equilibrium constant of the protonation reaction (1) and ΔG is the corresponding free energies difference.



Scheme 2. Thermodynamic cycle connecting gas (g) and aqueous (s) phase for the computation of absolute pK_a.

The acidity constant, pK_a, can be computed semi-empirically by using Eq. 3,

$$\Delta G = -RT \ln K_a \tag{3}$$

and rearrangement of Eq. 3 affords Eq. 4;

$$pK_a = \Delta G / 2.303RT \tag{4}$$

Eq. 4 links the standard reaction free energy ΔG of an acid-base equilibrium with the pK_a value, where R is the gas constant ($R = 1.987 \times 10^{-3}$ kcal mol^{-1} K^{-1}) and T is the absolute temperature in Kelvin (T = 298 K).

The ab initio calculation of the absolute pK_a values can be made by using Eq. 5:

$$pK_a = [\Delta G_g + \Delta G_a] / 2.303RT \tag{5}$$

Scheme 2 illustrates the derivation of ΔG_a in a protonation or deprotonation reaction from 3 components: the reaction free energy in the vacuum (ΔG_g), the solvation free energy of educts (ΔG_s (BH)), and the solvation free energy of products (ΔG_s(B)). It indicates that for the absolute pK_a computation of the proton solvation energy $\Delta G_s(H^+)$ is required. Consequently, $\Delta G_a = \Delta G_s(B) - \Delta G_s$ (BH) + $\Delta G_s(H^+)$ can be derived from Scheme 2.

Results and discussion

The DFT calculated free energies, acidity constants, pK_a values, proton affinities, relative stabilities, and tautomeric equilibrium constants of studied 1,2,4-triazole derivates are given in Tables 2 and 3 (Supp. Inf). The nucleophilicity, HOMO and LUMO energies, charge on the N_1, N_2, and N_4 along with dipole moments values are shown in Tables 4 and 5 (Supp. Inf).

As indicated earlier to elucidate the mechanism of any chemical process, it is very important know the structure of the studied compound. Therefore, the tautomeric structures of the title compounds will be discussed first.

Tautomerism

It was stated in the literature that the **a** form (i.e. 4H-1,2,4-triazole) predominates over the **b** (i.e. 2H-1,2,4-triazole) and **c** (i.e. 1H-1,2,4-triazole) forms with K_T value of 4-10 kcal mol^{-1}.[22] The DFT calculated relative stability (RS) and tautomeric equilibrium constant values are reported in Table 2. The relative stability values indicate the stability of the **a** form (i.e. 4H-1,2,4-triazole) over the **b** form (i.e. 2H-1,2,4-triazole) and in turn predominance of the **c** form (i.e. 1H-1,2,4-triazole) over the **b** form generally (i.e. RS values have minus signs indicating the stability of the reactant). There is one exception for that and it is the RS value of -2.77 kcal mol^{-1} for 3b $\rightleftharpoons$ 3c equilibrium indicating that the **c** form of molecule **3** is predominant over the **b** form. The biggest RS value of -14.84 kcal mol^{-1} for equilibrium 3a $\rightleftharpoons$ 3b is indicative of the overwhelming predominance of the **3a** form over **3b** for molecule **3**, whereas the smallest RS value of -0.44 kcal mol^{-1} for equilibrium 6b $\rightleftharpoons$ 6c indicates the predominance of the **b** form over **c** for molecule **6** with a very small value of RS and needs to be justified by other methods. We have tried to justify this point by evaluating the K_T values of this equilibrium.

Table 2. Relative stability (RS) values for potentially tautomeric molecules by DFT (B3LYP/6-311G(d,p)) method.

Process	RS[a](Kcal mol^{-1})	K_T^b	pK_T^b	K_T^c
1a-1b	-8.19	1.00×10^{-6}	5.99	4.07×10^{-9}
2a-2b	-5.42	1.12×10^{-4}	3.95	8.31×10^{-2}
2b-2c	-2.86	83.10×10^{-4}	2.08	1.23
3a-3b	-14.84	1.47×10^{-11}	10.83	0.52
3b-3c	-2.77	104.95	-2.02	1.04
4a-4b	-4.26	7.94×10^{-4}	3.10	1.25
5a-5b	-4.83	3.01×10^{-4}	3.52	6.16×10^{-2}
6a-6b	-5.36	1.23×10^{-4}	3.91	2.29×10^{-2}
6b-6c	-0.44	0.47	0.32	0.87
7a-7b	-5.88	5.12×10^{-5}	4.29	1.14
7b-7c	-4.78	3.31×10^{-4}	3.48	0.95
8a-8b	-4.45	5.75×10^{-4}	3.24	1.23
8b-8c	-2.24	2.34×10^{-2}	1.63	0.97

[a] RS = $\Delta G_{a(1a)} - \Delta G_{a(1b)}$, minus value indicates the stability of the reactant.

[b] Calculated using the $\delta\Delta G_a = -2.303RT \log K_T$, where $\delta\Delta G_a = \Delta G_{a(1b)} - \Delta G_{a(1a)}$.

[c] pK_T = -log K_T, pK_T = p$K_{a(1am)}$ – p$K_{a(1bm)}$ Charton's equation. [22]

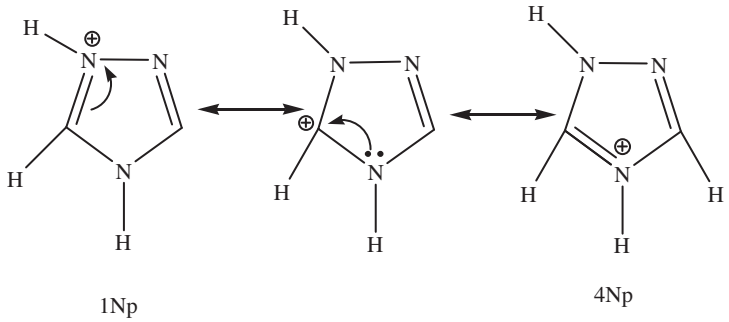
K_T values

The tautomeric equilibrium constant values, K_T, are very similar to RS values and generally support the RS values. The overwhelming predominance of **3a** over **3b** is indicated by the K_T value of 1.47×10^{-11} (i.e. pK_T = 10.83) and correlates well with the literature value, which was reported as K_T = 4-10 kcal mol^{-1}.[22] The opposite behavior of molecule **3** for 3b $\rightleftharpoons$ 3c equilibrium with a K_T value of 104.95 kcal mol^{-1} can be explained as in the case of RS values' evaluation and taking into account the substituent behavior (i.e. C_2H_5

at 3C). The steric effect may increase the stability of the **c** form for this molecule. On the other hand, the smallest K_T value of 0.47 is indicative of the coexistence of **b** and **c** forms with a low percentage.

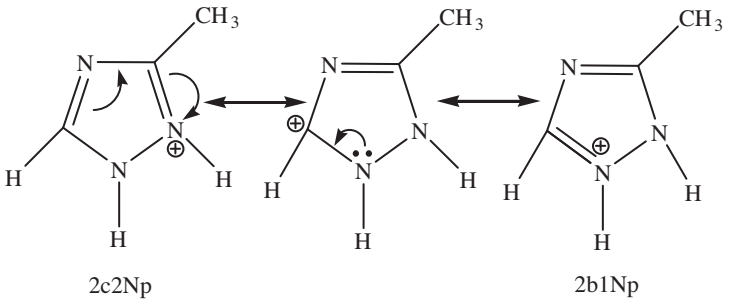
Basicity

As can be seen in Table 3 (Supp. Inf), the experimental pK_a value for protonation of molecule **1** was reported as 2.45 and the nearest calculated pK_a value was found as 4.41.[32] For the model molecule in which the mobile hydrogen atom was replaced by the methyl group **1m** the nearest calculated pK_a value was found as 2.47 for 1bm $\rightleftharpoons$ 1bm1Np and 1cm $\rightleftharpoons$ 1cm2Np equilibrium, respectively. As we can see, 1bm1Np and 1cm2Np are identical structures. The difference of 4.41 – 2.45 = 1.96 pK_a unit between the experimental and calculated pK_a values can only be explained by a change over in mechanism during the protonation. Since an increase in basicity has occurred that means molecule **1** first protonates in the **a** form then a subsequent isomerization occurs as in Scheme 3.



Scheme 3. Isomerization of protonated molecule **1**.

For molecule **2** the experimental pK_a value for protonation was reported as 3.23 and the nearest calculated pK_a value was found as 3.22 for 2c $\rightleftharpoons$ 2c2Np equilibrium.[32] On the other hand, exactly the same pK_a value of 3.23 was found for the model molecule **2m** for 2bm $\rightleftharpoons$ 2bm1Np equilibrium. Therefore, we can predict that after protonation the molecule **2c** isomerizes into the **2b** form (Scheme 4).



Scheme 4. Isomerization of protonated molecule **2.**

The experimental pK_a value for the protonation of molecule **3** was reported as 3.15 and the closest calculated pK_a value of 3.11 indicates 3a $\rightleftharpoons$ 3a1Np or 3c $\rightleftharpoons$ 3c4Np patterns for the protonation of molecule

3.[32] This is a reliable result because RS and K_T values are indicative of the formation of the **3c** form with an acceptable ratio.

For the protonation molecule **4** the experimental pK_a value of 3.79 is very close to the calculated pK_a value of 3.76 and predicts 4a $\rightleftharpoons$ 4a1Np and 4a $\rightleftharpoons$ 4a2Np pathways for protonations.[32] Both pathways can be accepted equally because the substituents are the same and the molecule is symmetrical (i.e. X=Y=CH_3). Further evidence to support this protonation equilibrium comes from the calculated pK_a value of 3.72 for equilibrium 4am $\rightleftharpoons$ 4am1Np and 4am $\rightleftharpoons$ 4am2Np. Similarly, for the protonation of molecule **5** the calculated pK_a value was found as 3.76 for 5a $\rightleftharpoons$ 5a2Np equilibrium. The protonation of model molecule **5m**, however, seems to occur with 5bm $\rightleftharpoons$ 5bm1Np and 5cm $\rightleftharpoons$ 5cm2Np equilibrium, which produces the pK_a value of 3.73. Thererfore, it seems that after protonation a subsequent isomerization occurs in this molecule as in the case of molecule **2**. For molecule **6** protonation the experimental pK_a value of 2.04 is exactly the same as the calculated one and the suggested protonation equilibrium is 6b $\rightleftharpoons$ 6b1Np.[32] For the molecule **6m** a protonation pK_a value of 2.06 was obtained, which is close enough to consider equal to 2.04.

For molecule **7** the experimental pK_a value for protonation was reported as -3.65 and the nearest calculated pK_a value was found as -3.62. For the model molecule **7m** the calculated pK_a value was found as -3.67. Therefore, we can predict that for molecule **7** the **b** form is suitable for protonation and the predicted equilibria for compound **7** and for its model **7m** will be 7b $\rightleftharpoons$ 7b1Np and 7bm $\rightleftharpoons$ 7bm4Np. Thus we can say that the parent molecule (i.e. 7b) protonates at the 1st position whereas model molecule **7bm** protonated at the 4th position, and so their protonation patterns are different.

For molecule **8** the experimental value for protonation was reported as -2.89 and the calculated pK_a value was found as -2.90 and for the model molecule **8m** the calculated pK_a value was found as -2.94.[32] Therefore, we can predict here that for the molecule **8** the **c** form is suitable for protonation and we can predict the protonation pattern for the parent compound **8** and for its model **8m** as follows: 8c $\rightleftharpoons$ 8c4Np and 8cm $\rightleftharpoons$ 8cm4Np. We can conclude that the protonation pattern of the parent molecule **8** and model **8m** is the same and it is 4N protonation.

Correlation attempts

We attempted to correlate the experimental and calculated data and in this section we comment on those results in the following manner.

Acidity constants

As can be seen in Figure, correlation between the calculated and experimental acidity constants by excluding one point (i.e. 1b1Np) is excellent with a regression of $R^2 = 1$. The slope of the correlation line is about unity. This means that the correspondence between these 2 series of data is 1 to 1.

The calculated proton affinity (PA) values indicate that the molecule **3bm** has the biggest proton affinity (i.e. 319.86). The calculated pK_a value for 3bm $\rightleftharpoons$ 3bm1Np protonation was found as 36.67, which is abnormally high. The abnormal behavior of this molecule can only be explained by geometry. When we consider the structure of molecule **3m**, we can easily see the availability of lone pair electrons on nitrogen atoms in the **3bm** molecule (Scheme 5). The lowest PA value, however, was 117.10 and it belongs to the **3cm**

molecule. Here again, it is obvious that the availability of lone pair electrons on nitrogen atoms was reduced because of the steric effects of the methyl group on 2N and the ethyl group on **3C**.

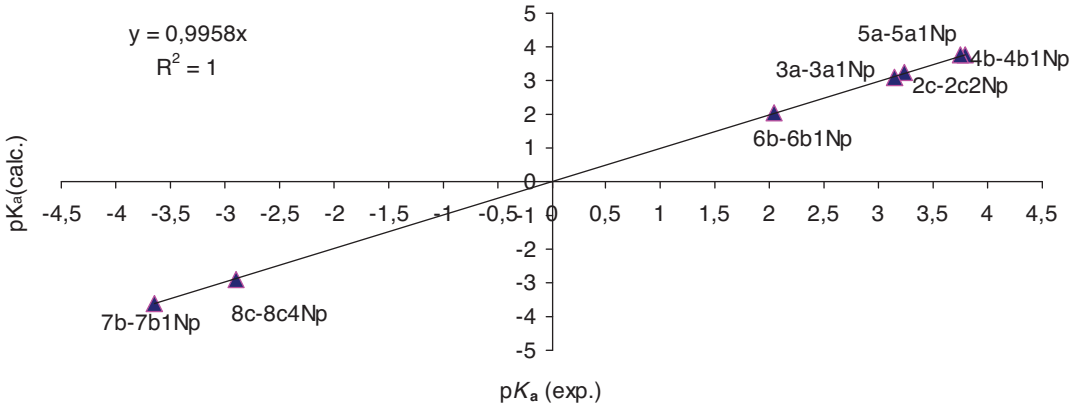
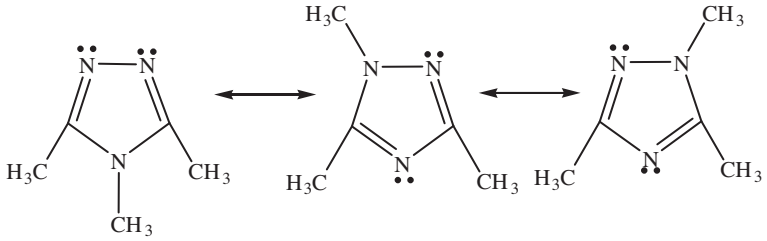


Figure. The correlation plot for experimentally determined acidity constants $\mathrm{p}K_a$ (exp.) and calculated acidity constants $\mathrm{p}K_a$ (calc.).



Scheme 5. Isomer structures of molecule **3m.**

Nucleophilicity-pK_a

There seems to be no meaningful correlation between the gas phase nucleophilicity and proton affinity values and there exists no acceptable regression between nucleophilicity, n values, and acidity constants, $\mathrm{p}K_a$ values (Tables 3 and 4) (Supp. Inf). The maximum gas phase nucleophilicity was 0.646 for molecule **7b**. The maximum aqueous phase nucleophilicity was –0.115 for molecule **8cm**.

Electronic charges-dipole moments

It seems from Table 5 (Supp. Inf) that the differences among the dipole moments are not as large as the differences in electronic charges for all molecules. The differences between aqueous phase dipole moment are calculated by

$$\Delta\mu = \mu_{\max} - \mu_{\min} = 10.13 - (3.51) = 6.62D$$

The changes in charges were found as $\Delta q_{N1} = q_{N1(max)} - q_{N1(min)} = -0.317 - (-0.190) = 0.127$ unit, for $\Delta q_{N2} = q_{N2(max)} - q_{N2(min)} = -0.318 - (-0.185) = 0.133$ unit and for $\Delta q_{N4} = q_{N4(max)} - q_{N4(min)} = -0.416 - (-0.339) = 0.075$ unit. It seems that the change observed in ΔqN_2 was larger than those of Δq_{N1}. However, the correlation between ΔqN_1 and $\Delta\mu$ values ($R^2 = 0.8094$) was larger compared to the correlation between ΔqN2 and $\Delta\mu$ values ($R^2 = 0.6286$).

Conclusion

In the present work, density functional theory at the level of B3LYP with the use of a triple split valence basis set (6-311G(d,p)) was employed in order to calculate solvation free energies, pK_a, and tautomeric equilibrium constants values for some 1,2,4-triazole derivatives.

It seems that quantum chemical calculations many allow us to predict the tautomeric and acid-base behavior of heterocyclic molecules. The protonation pathways can be deduced without elaborate laboratory measurements.

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